believed to act by reducing the deposition and/or load of amyloid in the brain through its binding to soluble Aβ peptide. For increasing the therapeutic effectiveness of 3APS, it would be desirable to increase bioavailability, stability and/or crossing the blood brain barrier of 3APS. These and other needs can be satisfied by the disclosure herein of a prodrug form of 3-amino-1 -propanesulfonic acid (3APS), pharmaceutical compositions and uses thereof to treat various medical disorders.

Previous metabolic stability studies had demonstrated that there was no *in vitro* metabolism of 3APS. Those studies include: 3APS metabolic stability in pooled human hepatocytes, human, rat and dog liver microsomes, human intestinal microflora, pooled human liver cytosol, and human arylamine N-acetyltransferase (See Examples 4 and 5).

a. PCT publication number WO2004/112375 discloses phenylalanyl and phenylalanyl-phenylalanyl substituted 3-amino-1-propanesulfonic acid for use in inhibition amyloid deposition. PCT publication number WO2002/096937 discloses all-D peptides which include 3-amino-1-propane sulfonic acid as potential vaccines against amyloid-beta related diseases.

b. Varga and co-workers in *Neurochem. Res.* (1988), 13(11), pages 1027-1034, described a gamma-glutamyl derivative of 3-amino-1-propanesulfonic acid active in neurotransmission assays.

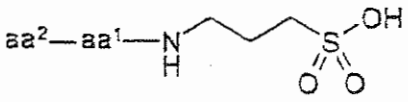
c. A 3-APS derivative of carbobenzoxy-tryptophan was described in U.S. Patent No. 5-776,970 (Shechter et al.) as a treatment for neoplasms, where the tryptophan moiety is the core structure and the CBz group acts as a lipophilic group to help cell penetration.

Summary of the Invention

Surprisingly, it has now been found that 3APS is metabolized both *in vitro* and *in vivo*. Indeed, as described in more detail hereinafter, recent in vivo studies indicate extensive metabolism, particularly first-pass and/or systemic metabolism of 3APS. Three potential metabolites were identified from at least one type of biological species: 2-carboxyethanesulfonic acid, 3-hydroxy-1 -propanesulfonic acid and 3-acetylamino-1-propanesulfonic acid. Further studies demonstrated that 2-carboxyethanesulfonic acid was the only major metabolite of 3APS in mice, rats, dogs and humans.

that the conversion of 3APS to 2-carboxyethanesulfonic acid in primary neuron culture media was significantly inhibited by vigabatrin, a classic GABA transaminase inhibitor. Nialamide, a monoamine oxidase inhibitor, also reduced the formation of 2-carboxyethanesulfonic acid (from 3APS) but to a lesser extent.

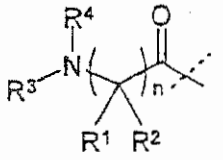
In a first aspect of the present disclosure, there is provided a compound of Formula IV, or a pharmaceutically acceptable salt or solvate thereof:



(IV)

wherein:

aa^1 is a natural or unnatural amino acid residue;
aa^2 is a natural or unnatural amino acid residue, or is absent;
wherein said aa^1, and aa^2, are each independently amino acid residues of Formula VI:



(VI)

wherein:

R^1 is selected from the group consisting of a substituted or unsubstituted group selected from C_1-C_{12}alkyl, C_2-C_{12}alkenyl, C_2-C_{12}alkynyl, C_3-C_{15}cycloalkyl;
R^2 is hydrogen
R^3 is hydrogen; or R^3 is a bond between two amino acid residues, when two amino acid residues are present;
R^4 is selected from the group consisting of H and a substituted or unsubstituted group selected from C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl; and
n is 1, 2 or 3;
wherein the term substituted when in association with any of the foregoing groups refers to a group substituted at one or more position with substituents selected from amino selected from simple amino, mono and dialkylamino, mono and diarylamino, and alkylarylamino, acylamino including carbamoyl, and ureido, aminocarbonyl, mono and dialkylaminocarbonyl, cyano, azido, halogen, hydroxyl, nitro, trifluoromethyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6 alkoxy, aryloxy, benzyloxy, benzyl, guanidine, imino, and formyl;
provided that when R^2 is H and R^3 is H or a bond, then R^1 is not a -CH_2phenyl group.

In a second aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound as defined above together with a pharmaceutically acceptable carrier.

In a third aspect of the present disclosure, there is provided a prodrug of 3-amino-1-propanesulfonic acid, wherein said prodrug is a compound as defined above.

In a fourth aspect of the present disclosure, there is provided a compound as defined above, for use in the treatment or prevention of a disease or condition selected

from Alzheimer's disease, mild cognitive impairment, Down's syndrome, Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, cerebral amyloid angiopathy, Parkinson's disease, a degenerative dementia, a dementia of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, or diffuse Lewy body type of Alzheimer's disease.

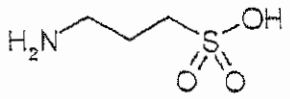
In a fifth aspect of the present disclosure, there is provided the compound as defined above, for use in providing neuroprotection to a subject having an amyloid-β related disease.

In a sixth aspect of the present disclosure, there is provided a compound as defined above, for use in delivering 3-amino-1-propanesulfonic acid (3APS) by contacting said compound with an enzyme which metabolizes said compound to 3APS *in vitro or in vivo*.

In a seventh aspect of the present disclosure, there is provided the compound as defined above, for use in inhibiting neuronal cell death.

Accordingly, ~~an aspect of~~ the ~~invention~~present disclosure concerns compounds and compositions that can deliver 3APS by minimizing the metabolism, e.g., first-pass metabolism, associated with that drug, and more particularly compounds that would block or protect the amino group of 3APS such that it avoids metabolism, e.g., by transaminases and/or monoamine oxidases.

The ~~invention~~present disclosure includes methods, compounds, compositions and vehicles for delivering in a subject, preferably a human subject, 3-amino-1-propanesulfonic acid, or salts thereof. 3-Amino-1-propanesulfonic acid (also named 3APS, Tramiprosate, Alzhemed™) has the structure:



3APS

T~~According to an aspect, t~~he present ~~invention~~disclosure relates to compounds or compositions that will yield or generate 3APS after administered in a subject. In one embodiment, the compound that will yield or generate 3APS is an amino acid prodrug of 3APS. In another embodiment, the compound that will yield or generate 3APS is a carbamate prodrug of 3APS. In another embodiment, the compound that will yield or generate 3APS is an amide prodrug of 3APS. In another embodiment, the compound that will yield or generate 3APS is a carbohydrate-derived prodrug of 3APS. In another embodiment, the compound that will yield or generate 3APS is a N-hydroxy prodrug. In another embodiment, the compound that will yield or generate 3APS is a cyclic double-protected prodrug. In further embodiment, the compound that yields or generates 3APS is a 3APS polymer (e.g. a molecule composed of two or more molecules of 3APS linked together). In further embodiment, the compound that yields or generates 3APS is a gemini dimer of 3APS. In certain embodiments, the amino acid prodrugs of 3APS that are capable of yielding or generating, either in *vitro* or in *vivo*, 3APS have one of the general or specific formulae or structures disclosed herein. The present ~~invention~~disclosure encompasses these compounds, pharmaceutical compositions containing these compounds, and methods employing such compounds or compositions in the treatment of various medical disorders such as Alzheimer's disease.

The present ~~invention~~disclosure also relates to pharmaceutical compositions comprising a compound of the present ~~invention~~disclosure.

The present ~~invention~~disclosure further relates to a method for increasing the therapeutic effectiveness of 3APS comprising administering to a subject, preferably a human subject, an effective amount of a prodrug of the present ~~invention~~disclosure.

The present ~~invention~~disclosure also provides processes for converting compounds of the ~~invention~~present disclosure to 3APS. The conversion and/or generation of 3APS involves contacting any of the compounds of the ~~invention~~present disclosure, e.g., with blood, plasma and/or brain cells. The conversion can occur *in vitro or in vivo*. The conversion may also occur in the presence of enzymes capable of cleaving amine bonds, such as peptidases, or other enzymes appropriate for other structures herein, including those found in the blood, plasma and/or brain.

The ~~invention~~present disclosure also provides the use of a compound according to the ~~invention~~present disclosure for the manufacture of a medicament. The ~~invention~~present disclosure also provides the use of a compound of the ~~invention~~present disclosure for the treatment or prevention of Alzheimer's disease, mild cognitive impairment, Down's syndrome, Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, cerebral amyloid angiopathy, other degenerative dementias, dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, or diffuse Lewy body type of Alzheimer's disease. The ~~invention~~present disclosure also provides methods for the treatment or prevention of the aforementioned diseases comprising administration of a therapeutically effective amount of a compound of the ~~invention~~present disclosure or a composition comprising the same, to a subject, preferably a human subject, in need thereof. More preferably, the disease is Alzheimer's disease. Accordingly, a related ~~aspect~~embodiment of the ~~invention~~present disclosure relates to the prevention and/or treatment of Alzheimer's disease in a human subject by administering an effective amount of a compound or composition of the present ~~invention~~disclosure to a human subject in need thereof.

In a further embodiment the ~~invention~~present disclosure includes administration of 3APS via or under the mucous membranes, the nose (intranasally), mouth, or eye, e.g., by nasal spray, chewing gum, or eye drops, via the ear, e.g., by eardrops, by the use of an implant, rectally, e.g., by a suppository or enema, vaginally, e.g., by a cream or lotion, or by the respiratory system, e.g., by inhalation, intranasally or intratracheally.

The ~~invention~~present disclosure in further ~~aspects~~embodiments includes the administration of compounds of the ~~invention~~present disclosure via any mode and/or vehicle, including all modes and/or vehicles disclosed herein, e.g., the administration of the prodrugs of 3APS via the nose, mucous membranes, transdermally, via a patch, etc.

This ~~invention~~present disclosure in various ~~aspects~~embodiments relates to the following numbered ~~aspects~~embodiments:

~~Aspect~~Embodiment 1. A compound of the Formula I:

$$B-L-A \qquad (I)$$

wherein

B is a pharmacokinetic modulating moiety, which is optionally also bonded to A directly or indirectly through a further linking group L;

A is a 3-amino-1-propanesulfonic acid moiety (i.e., 3APS bound to L-B), and

L is a cleavable linkage for covalently and dissociably coupling B to A (preferably and typically via the NH_2 group), or is absent, whereby L can be a direct bond or additional chemical structure providing a cleavable linkage,

or a pharmaceutically acceptable salt or solvate thereof.

~~Aspect~~Embodiment 2. The compound according to ~~aspect~~embodiment 1, wherein L is a linkage that when metabolized or hydrolyzed either in *vitro* or in *vivo* produces 3APS, and/or

B is a moiety that increases the therapeutic bio-distribution of 3APS upon administration of the compound of formula I to a human subject.

~~Aspect~~Embodiment 3. The compound according to ~~aspect~~embodiment 1, wherein B is a 3-amino-1-propanesulfonic acid moiety.

~~Aspect~~Embodiment 4. A compound according to ~~aspect~~embodiment 1, wherein B is an amino acid or a peptide, and

and L is a hydrolyzable linkage.

~~Aspect~~Embodiment 5. A compound according to ~~aspect~~embodiment 1, which is a compound of formula (I), (I-A), (I-C), (I-D), (I-E), (I-P), (I-P2), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), (XII), (XII-A) or (XIII), which are set forth hereinafter, or a pharmaceutically acceptable salt thereof.

~~Aspect~~Embodiment 6. A pharmaceutical composition comprising a compound of ~~aspect~~embodiment 1 and a pharmaceutically acceptable vehicle.

~~Aspect~~Embodiment 7. A method for treating or preventing Alzheimer's disease, mild cognitive impairment Down's syndrome, Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, cerebral amyloid angiopathy, a degenerative dementia, a dementia of mixed

vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, or diffuse Lewy body type of Alzheimer's disease comprising administering a therapeutically effective amount of a compound of ~~aspect~~embodiment 1 to a human subject in need thereof.

~~Aspect~~Embodiment 8. A process for converting a compound of ~~aspect~~embodiment 1 to 3APS comprising contacting said compound with an enzyme which metabolizes said compound to 3APS *in vitro or in vivo*.

~~Aspect~~Embodiment 9. A process according to ~~aspect~~embodiment 8, comprising contacting said compound with plasma, blood and/or brain cells.

~~Aspect~~Embodiment 10. A method for increasing the therapeutic bio-distribution of 3APS in a human subject, comprising lessening metabolism of 3APS, e.g., first pass metabolism, which occurs when 3APS is administered to a human subject.

~~Aspect~~Embodiment 11. A method for reducing side effects of 3APS in a human subject (e.g., reducing or preventing gastrointestinal intolerance), comprising lessening metabolism of 3APS, e.g., first pass metabolism, which occurs when 3APS is administered to a human subject.

~~Aspect~~Embodiment 12. A method according to ~~aspect~~embodiment 10, wherein 3APS is administered in the form of a prodrug of 3APS which yields or generates 3APS after being administered to said human subject.

~~Aspect~~Embodiment 13. A method according to ~~aspect~~embodiment 10, wherein the prodrug is a compound of the Formula I:

$$B-L-A \qquad (I)$$

wherein

B is a pharmacokinetic modulating moiety, which is optionally also bonded to A directly or indirectly through a further linking group L;

A is a 3-amino-1-propanesulfonic acid moiety (i.e., 3APS bound to L-B), and

L is a cleavable linkage for covalently and dissociably coupling B to A (preferably and typically via the NH_2 group), or is absent, whereby L can be a direct bond or additional chemical structure providing a cleavable linkage,

or a pharmaceutically acceptable salt or solvate thereof.

~~Aspect~~Embodiment 14. A method according to ~~aspect~~embodiment 10, wherein 3APS is administered through the respiratory system, intratracheally, intranasally, via or under a mucous membrane, via the ear, rectally, or vaginally, or by an implant, spray, nasal spray, chewing gum, eye drop, eardrop, suppository, enema, or vaginal cream or lotion.

~~Aspect~~Embodiment 15. The method of ~~aspect~~embodiment 10, wherein the bioavailability of 3APS, AUC of 3APS, brain levels of 3APS, CSF levels of 3APS, C_{max} of 3APS, T_{max} of 3APS, and/or bio-absorption of 3APS is increased.

~~Aspect~~Embodiment 16. A method according to ~~aspect~~embodiment 10, wherein Alzheimer's disease is treated or prevented.

~~Aspect~~Embodiment 17. A method according to ~~aspect~~embodiment 10, wherein the effective therapeutic level of 3APS in a selected human tissue is increased.

~~Aspect~~Embodiment 18. A method according to ~~aspect~~embodiment 17, which increases the level of 3APS in the brain of said human subject.

~~Aspect~~Embodiment 19. A method according to ~~aspect~~embodiment 10, which increases the therapeutic effectiveness of 3APS.

~~Aspect~~Embodiment 20. A method according to ~~aspect~~embodiment 10, which lessens the first pass metabolism of 3APS.

~~Aspect~~Embodiment 21. A method according to ~~aspect~~embodiment 10, which reduces the side effects of 3APS.

~~Aspect~~Embodiment 22. A method according to ~~aspect~~embodiment 10, wherein the oral AUC of 3APS is increased by at least 20%.

~~Aspect~~Embodiment 23. A method for increasing the therapeutic bio-distribution of 3APS in a human subject, comprising administering 3APS in the form of a prodrug or in the form of a gemini dimer of 3APS.

~~Aspect~~Embodiment 24. A method for increasing the therapeutic bio-distribution of 3APS in a human subject, comprising administering 3APS non-orally or non-enterally.

~~Aspect~~Embodiment 25. A method according to ~~aspect~~embodiment 10, wherein 3APS is delivered using a route (transdermally, S.C., intranasally, etc.) or vehicle (patch, implant, spray, formulation, etc.) which minimizes hepatic first-pass metabolism of 3APS.

~~Aspect~~Embodiment 26. A compound according to ~~aspect~~embodiment 1, wherein said cleavable linkage is selected for yielding or generating 3APS or a derivative of 3APS, either in *vitro* or in *vivo*, e.g., wherein the linkage is cleavable hydrolytically or enzymatically.

~~Aspect~~Embodiment 27. A compound according to ~~aspect~~embodiment 1, wherein said pharmacokinetic modulating moiety is selected for increasing the therapeutic bio-distribution of 3APS upon administration of the compound of formula I to a human subject.

~~Aspect~~Embodiment 28. A prodrug of the Formula I:

B— L — A (I)

wherein

B is a pharmacokinetic modulating moiety, which is optionally also bonded to A directly or indirectly through a further linking group L;

A is a 3-amino-1-propanesulfonic acid moiety (i.e., 3APS bound to L-B), and

L is a cleavable linkage for covalently and dissociably coupling B to A (preferably and typically via the NH_2 group), or is absent, whereby L can be a direct bond or additional chemical structure providing a cleavable linkage,

or a pharmaceutically acceptable salt, metabolite or solvate thereof,

wherein the metabolite of said prodrug can be 3APS and/or other metabolites, including, but not limited to, metabolites identified elsewhere herein, e.g., the examples.

Additional objects, advantages and features of the present ~~invention~~disclosure will become more apparent upon reading of the following non-restrictive description of preferred embodiments which are exemplary and should not be interpreted as limiting the scope of the ~~invention~~present disclosure.

CLAIMS

1. A compound selected from the group consisting of, or a pharmaceutically acceptable salt or solvate thereof:

a) a compound of Formula I:

$$B-L-A \qquad (I)$$

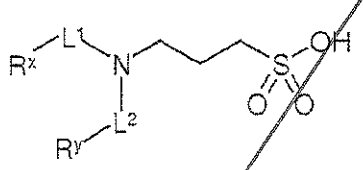
wherein

B is a pharmacokinetic modulating moiety, which is optionally also bonded to A directly or indirectly through a further linking group L;

A is a 3-amino-1-propanesulfonic acid moiety; and

L is a cleavable linkage for covalently and dissociably coupling B to A via the NH_2 group, whereby L can be a direct bond or additional chemical structure providing a cleavable linkage;

b) a compound of Formula I-A:



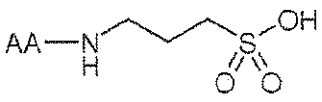
(I-A)

wherein,

R^x and R^y are independently selected from hydrogen and a protecting group, wherein R^x and R^y are not both hydrogen; and

L^1 and L^2 are each a cleavable linkage; wherein when R^x is H, L^1 is absent, and when R^y is H, then L^2 is absent;

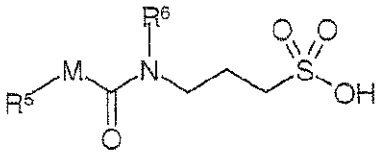
c) a compound of Formula II:



(II)

wherein AA is a natural or unnatural amino acid residue or a peptide comprising 2, 3 or more natural or unnatural amino acid residues;

d) a compound of Formula VII:



(VII)

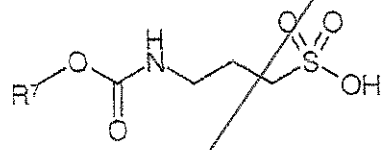
wherein,

R^5 is a substituted or unsubstituted group selected from C_1-C_{12}alkyl, C_2-C_{12}alkenyl, C_2-C_{12}alkynyl, C_3-C_{15}cycloalkyl, C_3-C_{15}heterocycloalkyl, C_6-C_{15}aryl, C_5-C_{15}heteroaryl, $NH(C_1$-C_6alkyl), $N(C_1$-C_6alkyl)$_2$, and $C(O)(C_1$-C_6alkyl);

R^6 is a hydrogen or a substituted or unsubstituted group selected from $C(O)NH_2$, $C(O)NH(C_1$-C_6alkyl), $C(O)N(C_1$-C_6alkyl)$_2$, and $C(O)(C_1$-C_6alkyl); or R^5 and R^6 are taken together with the adjacent carbon atom to form a substituted or unsubstituted C_3-C_{12}heterocycloalkyl;

M is selected from the group consisting of oxygen, sulfur, nitrogen or absent;

e) a compound of Formula VIII:

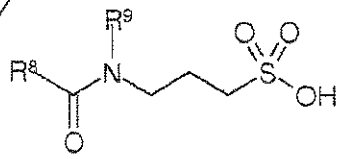


(VIII)

wherein,

R^7 is a substituted or unsubstituted group selected from C_1-C_{12}alkyl, C_2-C_{12}alkenyl, C_2-C_{12}alkynyl, C_3-C_{15}cycloalkyl, C_3-C_{15}heterocycloalkyl, C_6-C_{15}aryl, C_5-C_{15}heteroaryl, C_7-C_{12}arylalkyl, C_7-C_{12}heteroarylalkyl, and combinations thereof;

f) a compound of Formula IX:



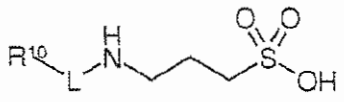
(IX)

wherein,

R^8 is a substituted or unsubstituted group selected from C_1-C_{12}alkyl, C_2-C_{12}alkenyl, C_2-C_{12}alkynyl, C_3-C_{15}cycloalkyl, C_3-C_{15}heterocycloalkyl, C_6-C_{15}aryl, C_5-C_{15}heteroaryl; and

R^9 is a hydrogen or a substituted or unsubstituted C(O)(C_1-C_6alkyl), C(O)NH_2, C(O)NH(C_1-C_6alkyl), or C(O)N(C_1-C_6alkyl)$_2$; or R^8 and R^9 are taken together with the adjacent carbon atom to form a substituted or unsubstituted C_3-C_{12}heterocycloalkyl;

g) a compound of Formula X:



(X)

wherein,

R^{10} is a residue of a carbohydrate, a carbohydrate derivative or a carbohydrate-derived polyol, e.g., a C_{5-6} saturated or partially or completely unsaturated cycloalkyl group, optionally and preferably containing an -O- group, which is substituted by 3 to 5 substituents, each independently selected from –OH, -OAc, -CH_2OH, -OCH_3, -CH_2OAc and =O.

L is a linking moiety or is absent, e.g., an alkyl group, which may be saturated or unsaturated, preferably a lower alkyl group, which is optionally interrupted by one or more -O- and/or -NH- groups, and is optionally substituted by one or more =O, -OH, and/or –NH_2 groups;

h) a compound of Formula XI:



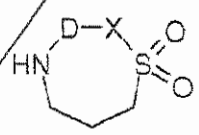
(XI)

wherein,

R^{11} is a hydrogen or a substituted or unsubstituted group selected from C_1-C_{12}alkyl, C_2-C_{12}alkenyl, C_2-C_{12}alkynyl, C_3-C_{15}cycloalkyl, C_3-C_{15}heterocycloalkyl, C_6-C_{15}aryl, C_5-C_{15}heteroaryl, C(O)R^{12}, and C(O)OR^{13}; and

R^{12} and R^{13} are independently selected from substituted or unsubstituted C_1-C_{12}alkyl, C_2-C_{12}alkenyl, C_2-C_{12}alkynyl, C_3-C_{15}cycloalkyl, C_3-C_{15}heterocycloalkyl, C_6-C_{15}aryl, and C_5-C_{15}heteroaryl;

i) a compound of Formula XII:



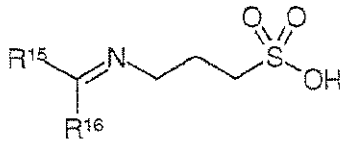
(XII)

wherein,

D is a carbonyl, an amino acid residue, or a substituted methylene group; and

X is selected from O, NH, and S;

j) a compound of Formula XIII:



(XIII)

wherein,

R^{15} and R^{16} are independently selected from a hydrogen or a substituted or unsubstituted group selected from C_1-C_{12}alkyl, C_2-C_{12}alkenyl, C_2-C_{12}alkynyl, C_3-C_{15}cycloalkyl, C_3-C_{15}heterocycloalkyl, C_6-C_{15}aryl, and C_5-C_{15}heteroaryl; and

k) a compound of Formula I-P:

$$\mathbf{A}-(\mathbf{L}^{x}-\mathbf{A})_{p}-\mathbf{L}^{x}-\mathbf{A} \qquad \text{(I-P)}$$

wherein:

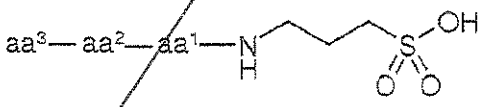
A is 3-amino-1-propanesulfonic acid moiety;

L^x is a cleavable linkage for covalently and dissociably coupling together two adjacent 3APS moieties, and

p is 0, or an integer number which may vary from 1 to 5, e.g. 2, 3, 4, or 5; or a pharmaceutically acceptable salt or solvate thereof.

2. The compound of claim 1, wherein said compound of Formula II is selected from the group consisting of:

a) a compound of Formula III:



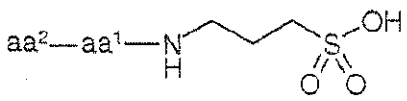
(III)

wherein:

aa^1 is a natural or unnatural amino acid residue;

aa^2 and aa^3 are each independently a natural or unnatural amino acid residue or absent, or a pharmaceutically acceptable salt or solvate thereof;

b) a compound of Formula IV:



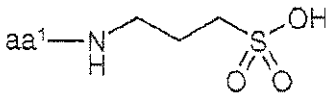
(IV)

wherein:

aa^1 is a natural or unnatural amino acid residue;

aa^2 is a natural or unnatural amino acid residue, or is absent, or a pharmaceutically acceptable salt or solvate thereof;

c) a compound of Formula V:

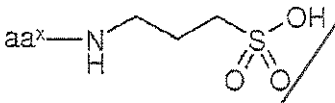


(V)

wherein

aa^1 is a natural or unnatural amino acid, or a pharmaceutically acceptable salt or solvate thereof; and

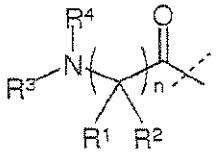
d) a compound of Formula V-A:



(V-A)

wherein aa^x is an amino acid residue selected from valine, proline, lysine, leucine, methionine, D-methionine, serine, alanine, D-alanine, glycine, isoleucine, histidine, aminoisobutyric acid, phenylglycine, tryptophan, tyrosine, *O*-benzylserine, *O*-benzylglutamine, and γ-aminobutyric acid, or a pharmaceutically acceptable salt of solvate thereof.

3. The compound of claim 2, wherein said aa^1, aa^2, and aa^3, are amino acid residues of Formula VI:



(VI)

wherein:

R^1 and R^2 are each independently selected from the group consisting of H and a substituted or unsubstituted group selected from C_1-C_{12}alkyl, C_2-C_{12}alkenyl, C_2-C_{12}alkynyl, C_3-C_{15}cycloalkyl, C_3-C_{15}heterocycloalkyl, C_6-C_{15}aryl, C_5-C_{15}heteroaryl, NH(C_1-C_6alkyl), N(C_1-

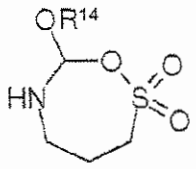
C_6alkyl)$_2$, and C(O)(C_1-C_6alkyl); or R^1 and R^2 are taken together with the adjacent carbon atom to form a substituted or unsubstituted C_3-C_{12}heterocycloalkyl;

R^3 is selected from the group consisting of H and a substituted or unsubstituted group selected from C_1-C_{12}alkyl, C_2-C_{12}alkenyl, C_2-C_{12}alkynyl, C_3-C_{15}cycloalkyl, C_3-C_{15}heterocycloalkyl, C_5-C_{15}aryl, C_5-C_{15}heteroaryl, C(O)(C_1-C_6alkyl), and C(O)(C_6-C_{15}aryl); or R^3 is a bond between two amino acid residues, when at least two amino acid residues are present;

R^4 is selected from the group consisting of H and a substituted or unsubstituted group selected from C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl; or R^1 and R^4 are taken together with the adjacent carbon and nitrogen atoms to form a C_3-C_{10}heterocycloalkyl; and

n is an integer selected from 1 to 10.

4. The compound claim 1, wherein said compound of Formula XII is a compound of Formula XII-A:



(XII-A)

wherein,

R^{14} is a substituted or unsubstituted group selected from C_1-C_{12}alkyl, C_2-C_{12}alkenyl, C_2-C_{12}alkynyl, C_3-C_{15}cycloalkyl, C_3-C_{15}heterocycloalkyl, C_5-C_{15}aryl, C_5-C_{15}heteroaryl, or a pharmaceutically acceptable salt or solvate thereof.

5. The compound of claim 1, wherein said compound of Formula I-P is selected from the group consisting of:

a) a compound of Formula I-P2:

$$L^y(A)_m \qquad \text{(I-P2)}$$

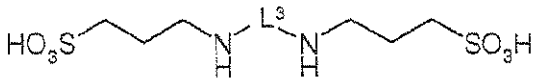
and pharmaceutically acceptable salts, esters, and solvates thereof, where:

m is an integer from 2 to 5;

A is 3-amino-1-propanesulfonic acid moiety;

L^y is a multivalent carrier moiety for covalently and dissociably coupling from two to five A moieties, either at the amino or sulfonic acid end of A, or a pharmaceutically acceptable salt or solvate thereof;

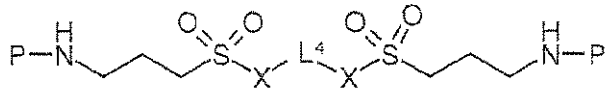
b) a compound of Formula I-C:



(I-C)

wherein, L^3 is bivalent linker which connects two molecules of 3APS at their amino groups either using the same or different linkages as defined herein, including, but not limited to, amide linkage and carbamate linkage, or a pharmaceutically acceptable salt or solvate thereof;

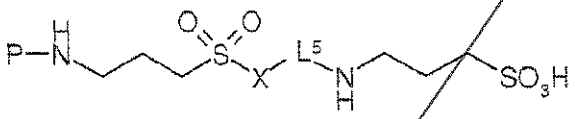
c) a compound of Formula I-D:



(I-D)

wherein, L^4 is a bivalent linker which connects two molecules of 3APS at their sulfonic acid groups either using the same or different linkages as defined herein, including, but not limited to, ester linkage or anhydride linkage where X is oxygen, or sulfonamide linkage where X is nitrogen (NH, or NR), or thiosulfonate linkage where X is sulfur, P is hydrogen or a N-protecting group, or a pharmaceutically acceptable salt or solvate thereof; and

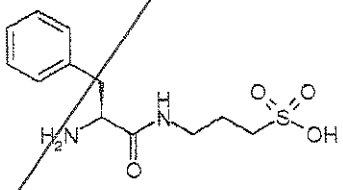
d) a compound of Formula I-E:

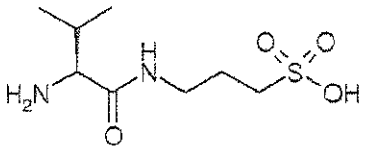


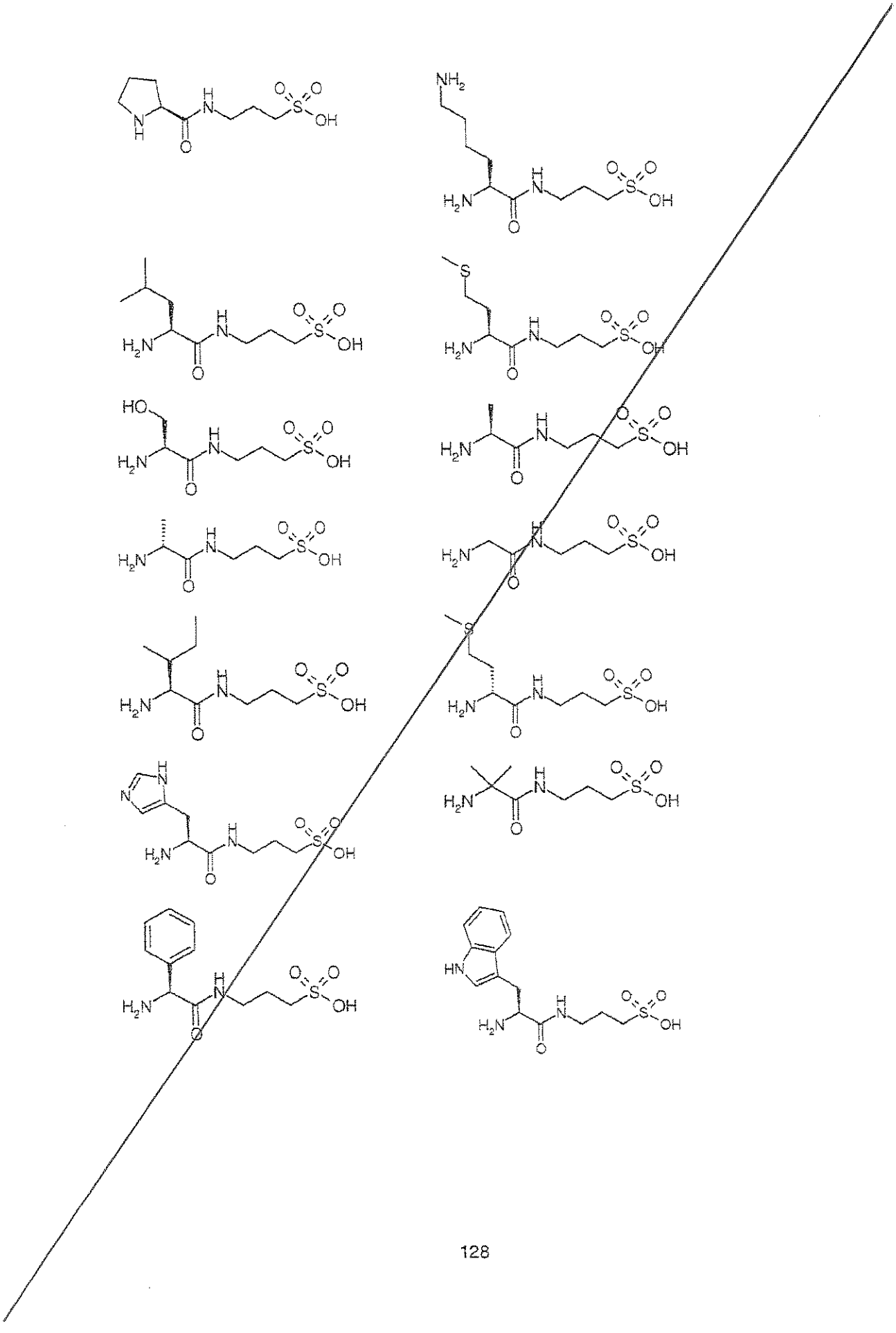
(I-E)

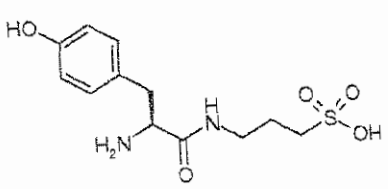
wherein, L^5 is a bivalent linker which connects two molecules of 3APS, at amino group in one 3APS using a linkage as defined in Formula I-C, and at sulfonic acid group in the other 3APS using a linkage as defined in Formula I-D, P is hydrogen or a N-protecting group as defined herein, or a pharmaceutically acceptable salt or solvate thereof.

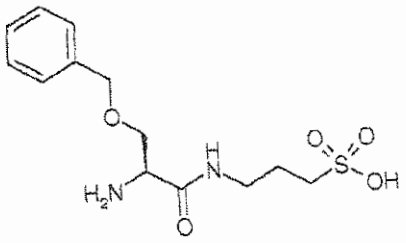
6. The compound of claim 1, wherein said compound is selected from the group consisting of:

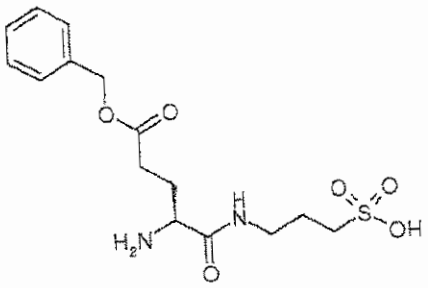


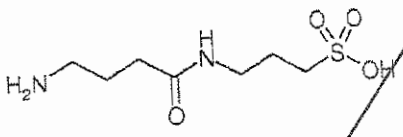


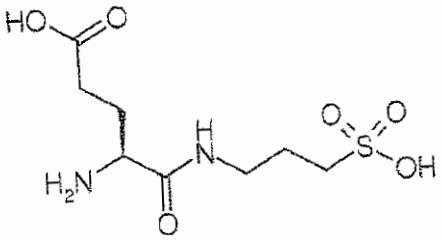


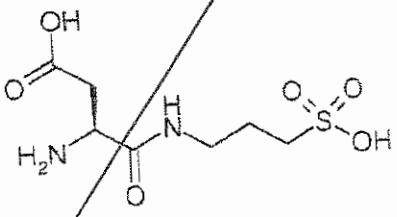


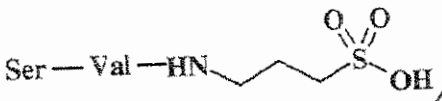


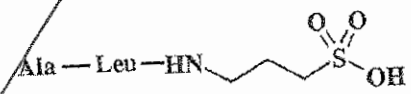


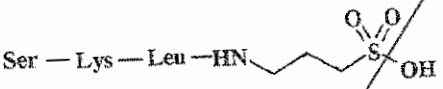


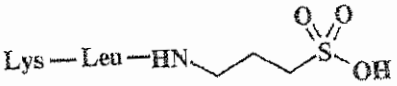


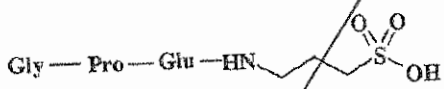


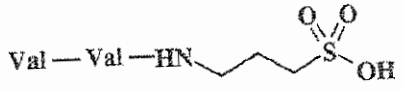




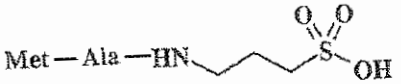


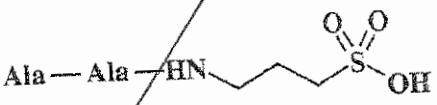


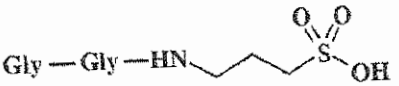


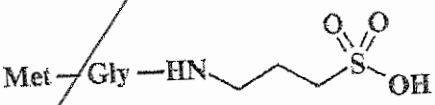


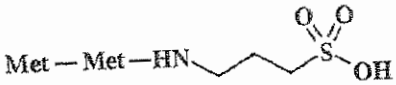


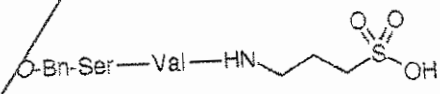


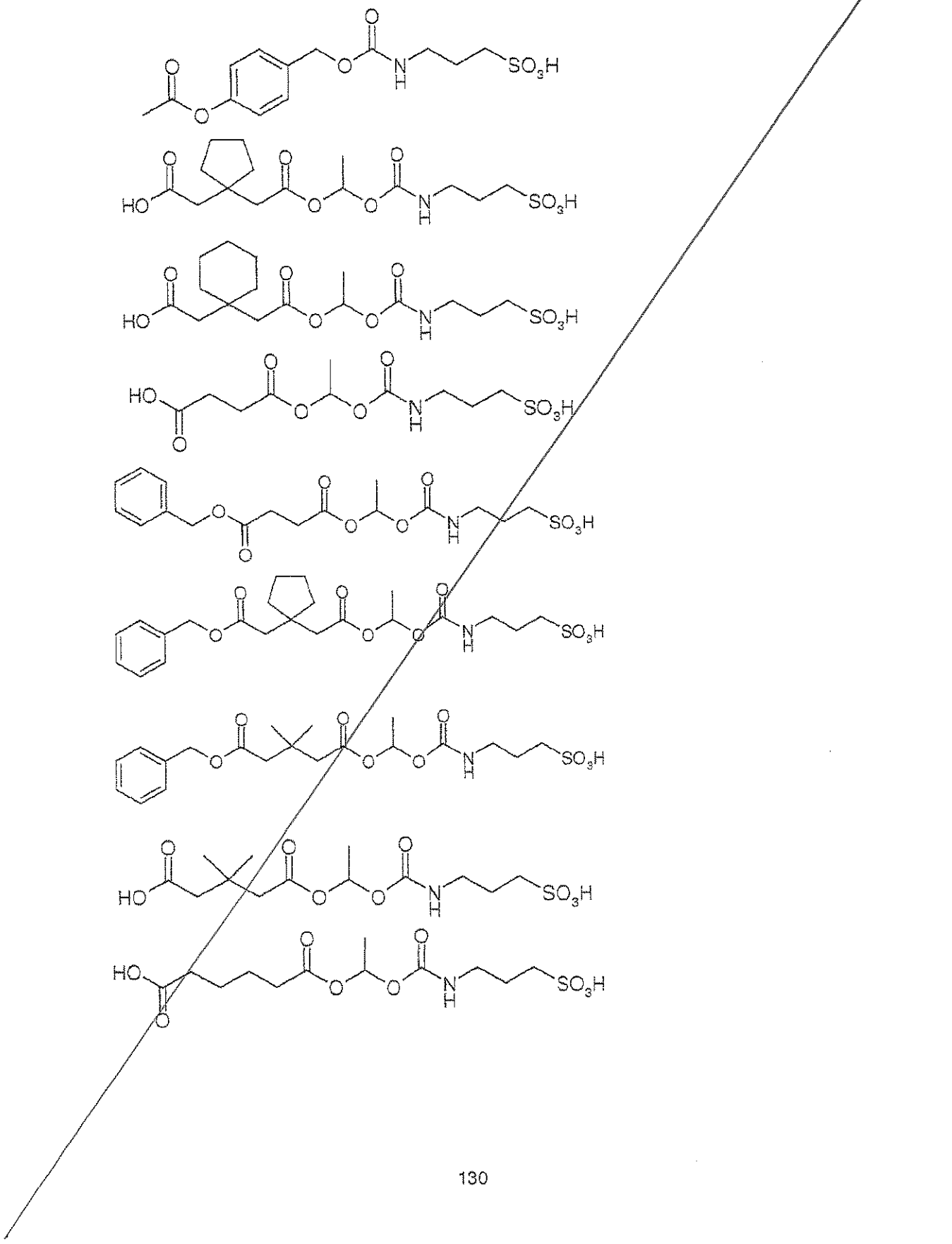


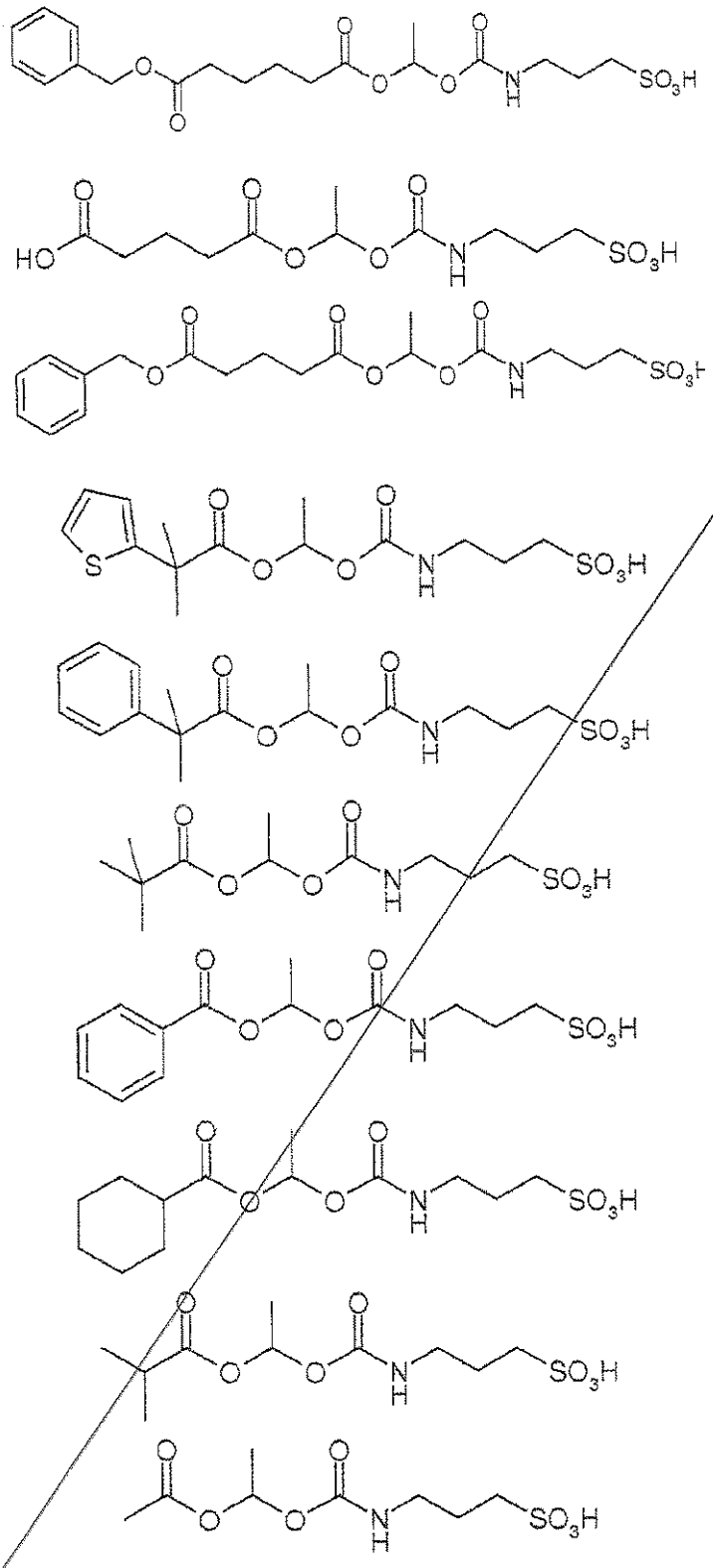


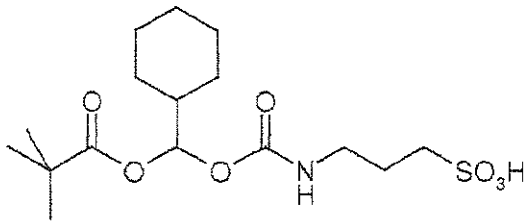


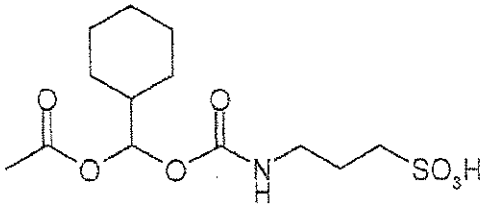


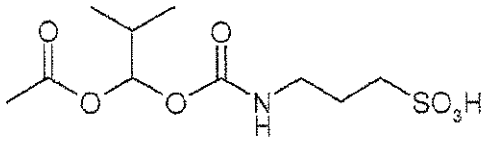


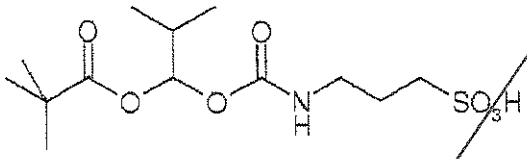


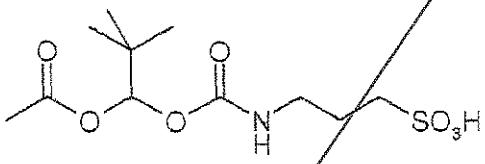


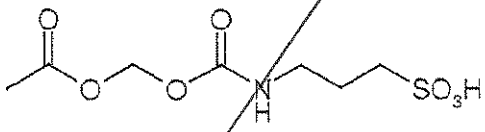


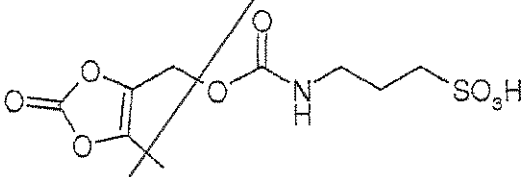


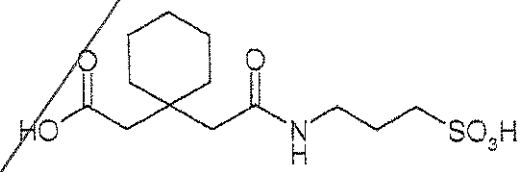


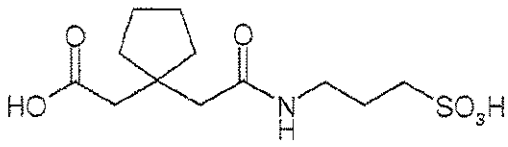


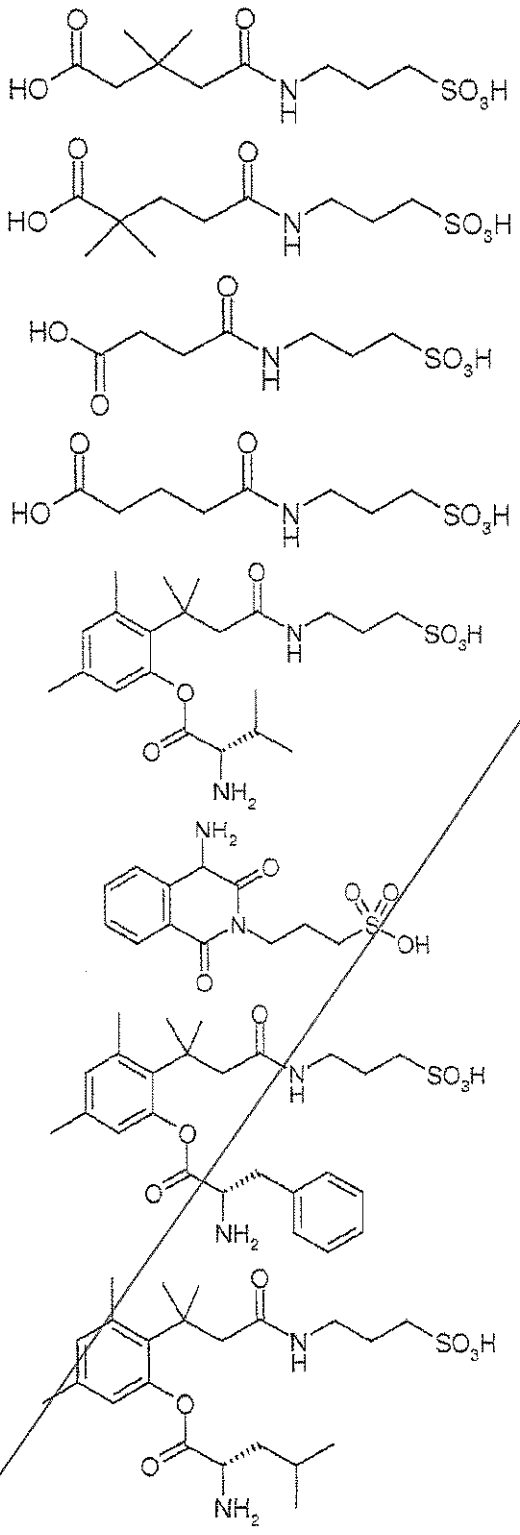


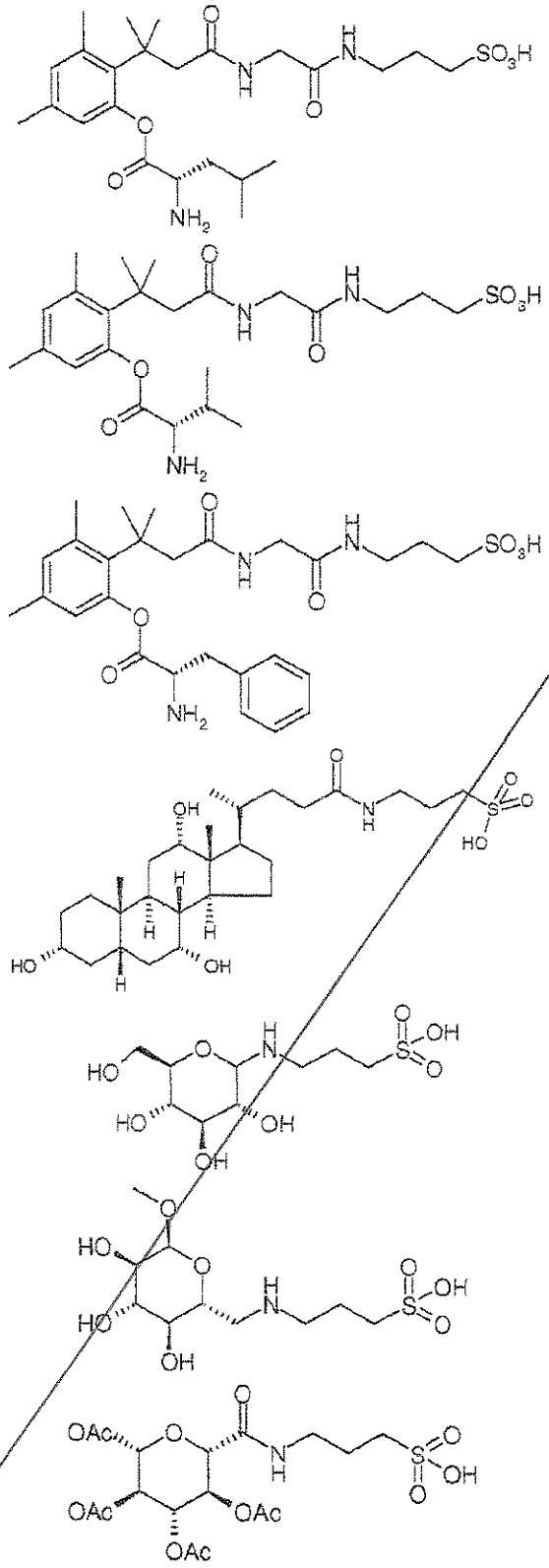


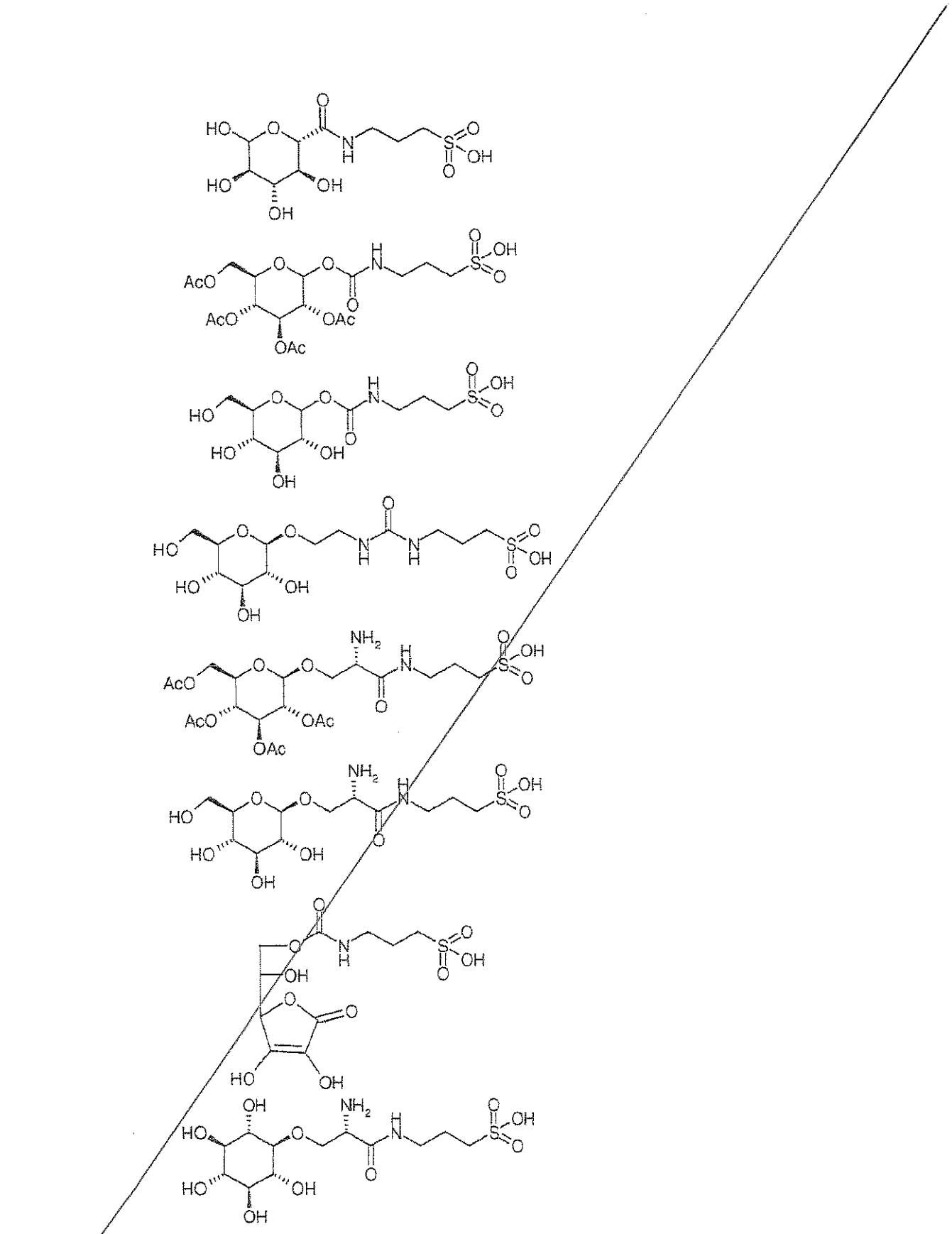


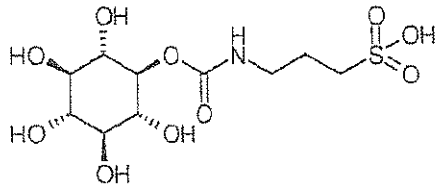


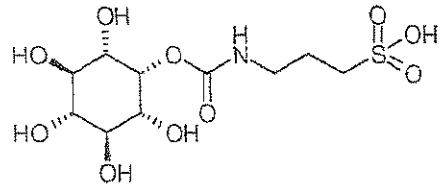


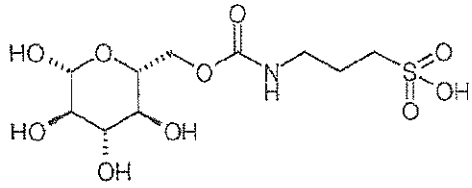


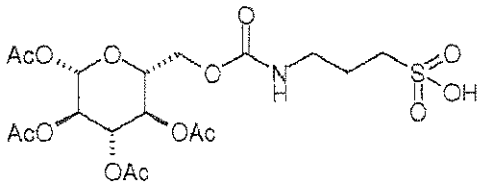


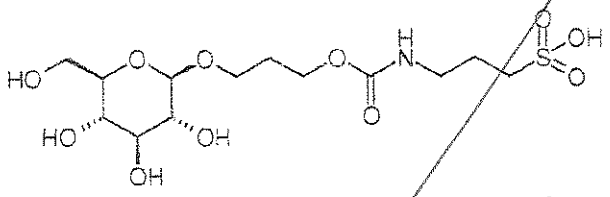


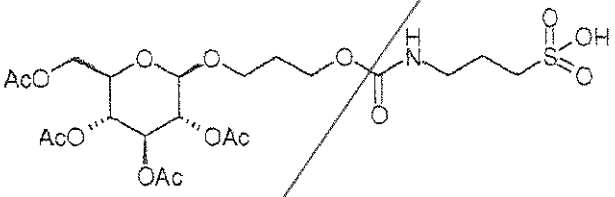




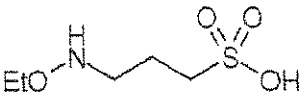


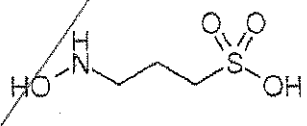


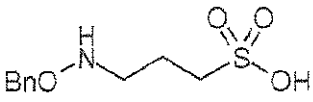




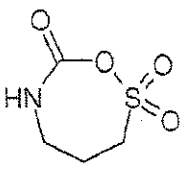


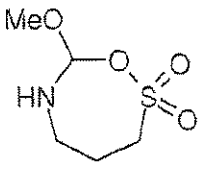


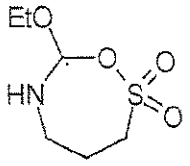


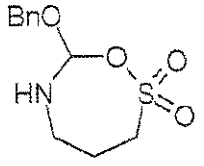


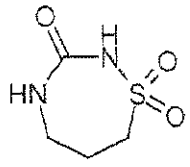
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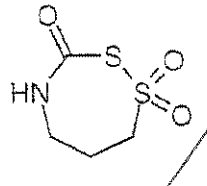


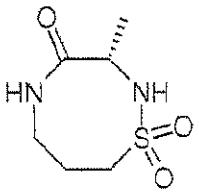


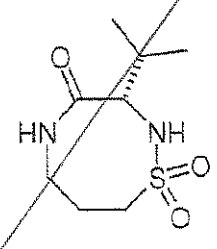




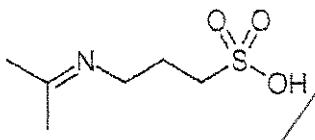


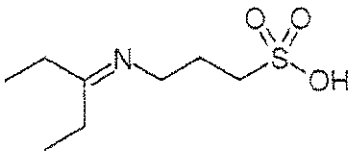




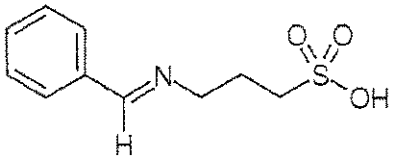


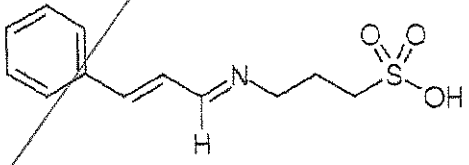
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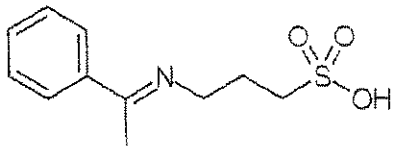


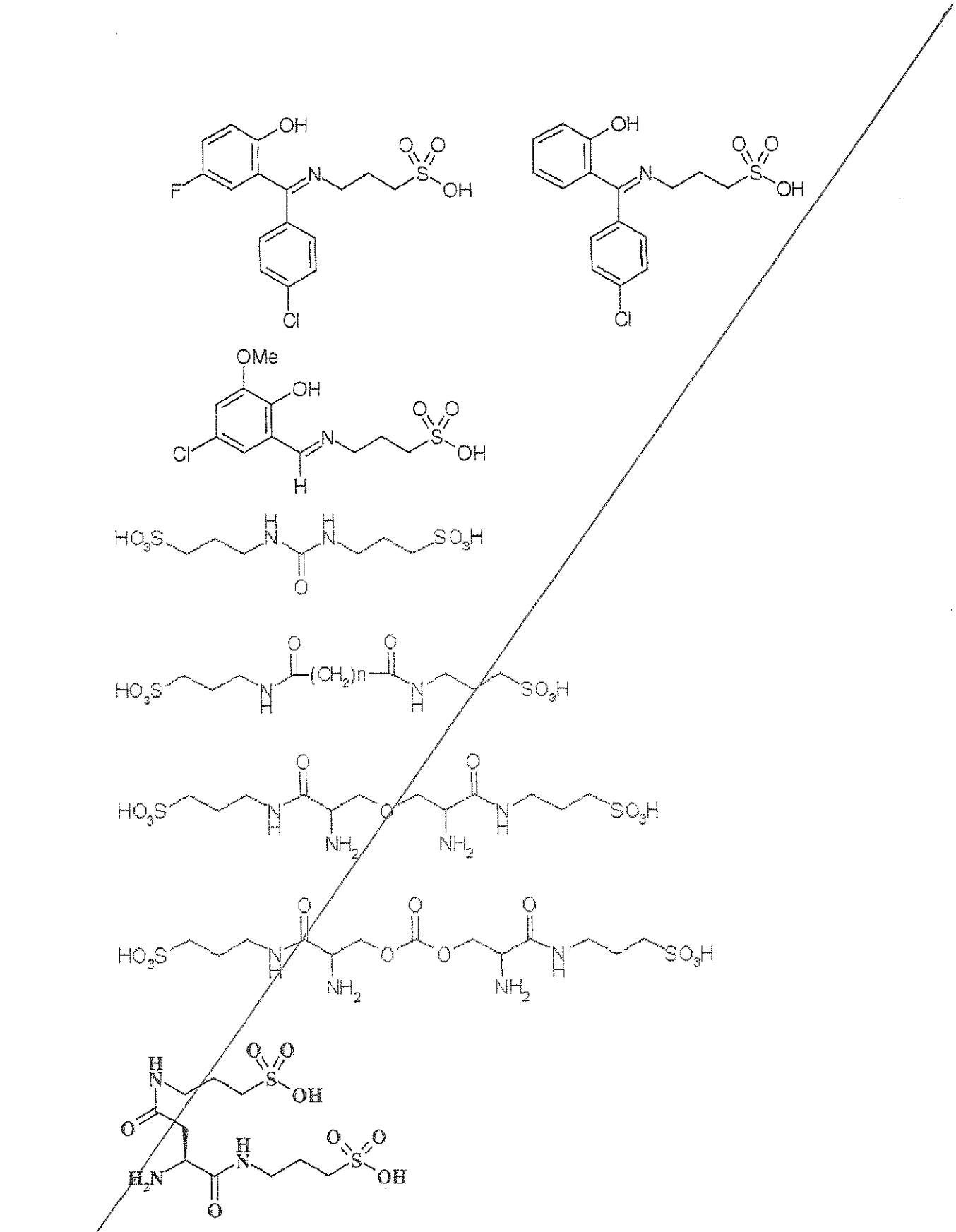


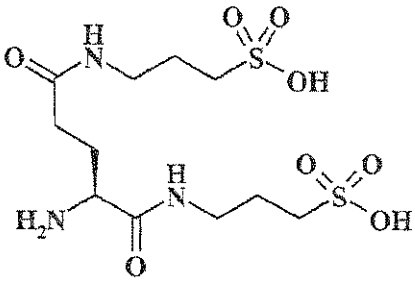


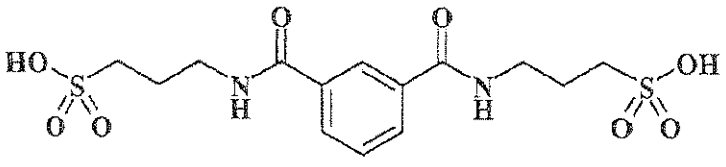


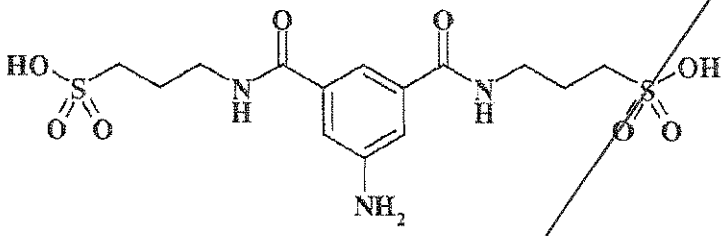


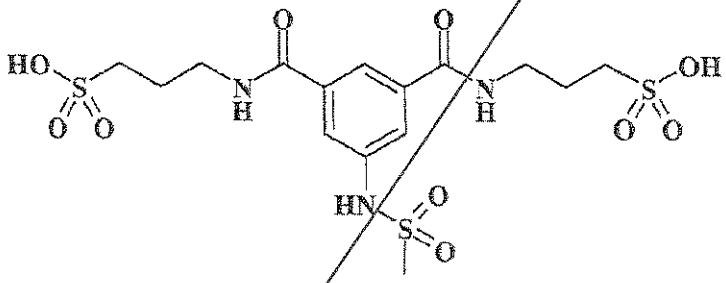


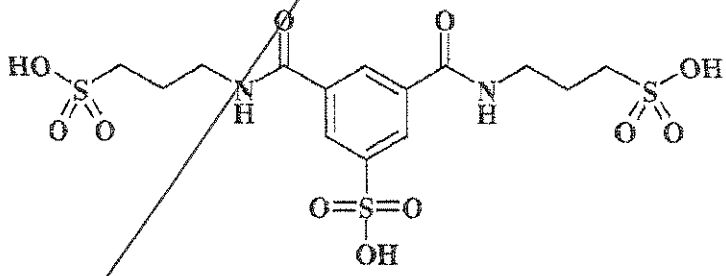




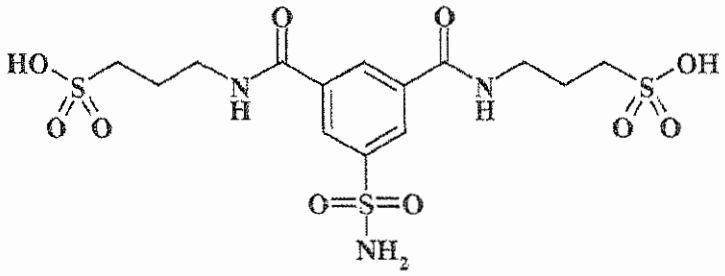






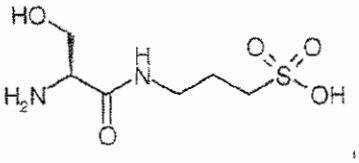


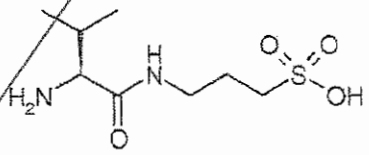
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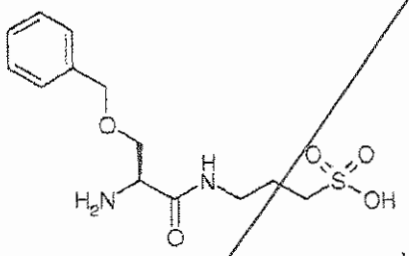


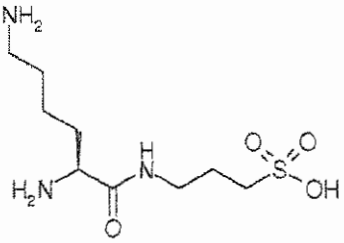
7. A pharmaceutical composition comprising a compound of claim 1 together with a pharmaceutically acceptable carrier.

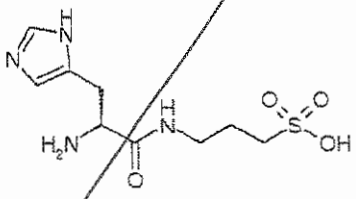
8. The pharmaceutical composition of claim 7, wherein said compound is selected from the group consisting of:



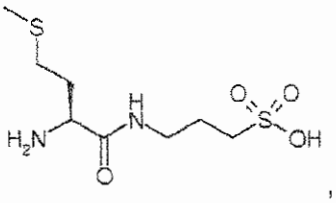








, and



or a pharmaceutically acceptable salt or solvate thereof.

9. A prodrug of 3-amino-1-propanesulfonic acid, wherein said prodrug is a compound of claim 1.

10. A method for treating or preventing Alzheimer's disease, mild cognitive impairment Down's syndrome, Hereditary Cerebral Hemorrhage with Amyloidosis of the

Dutch-Type, cerebral amyloid angiopathy, a degenerative dementia, a dementia of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, or diffuse Lewy body type of Alzheimer's disease comprising administering a therapeutically effective amount of a compound of claim 1 to a human subject in need thereof.

11. A process for converting a compound of claim 1 to 3-amino-1-propanesulfonic acid comprising contacting said compound with an enzyme which metabolizes said compound to 3APS *in vitro* or *in vivo*.

12. The process of claim 11, comprising contacting said compound with plasma, blood and/or brain cells.

13. A method for increasing the therapeutic bio-distribution of 3APS in a human subject, comprising lessening metabolism of 3APS, which occurs when 3APS is administered to a human subject.

14. The method of claim 13, wherein said metabolism is first pass metabolism.

15. A method for reducing or preventing gastrointestinal intolerance side effects of 3APS in a human subject, comprising lessening metabolism of 3APS, which occurs when 3APS is administered to a human subject.

16. The method of claim 15, wherein 3APS is administered in the form of a prodrug of 3APS which yields or generates 3APS after being administered to said human subject.

17. The method of claim 16, wherein said prodrug is a prodrug of claim 10.

18. The method of claim 13, wherein 3APS is administered through the respiratory system, intratracheally, intranasally, via or under a mucous membrane, via the ear, rectally, or vaginally, or by an implant, spray, nasal spray, chewing gum, eye drop, eardrop, suppository, enema, or vaginal cream or lotion.

19. The method of claim 13, wherein at least one of bioavailability of 3APS, AUC of 3APS, brain levels of 3APS, CSF levels of 3APS, C_{max} of 3APS, T_{max} of 3APS, or bio-absorption of 3APS is increased.

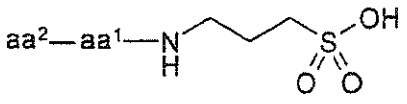
20. The method of claim 13, wherein Alzheimer's disease is treated or prevented.

21. The method of claim 13, which increases the level of 3APS in the brain of said human subject.

22. The method of claim 19, wherein the oral AUC of 3APS is increased by at least 20%.

Claims

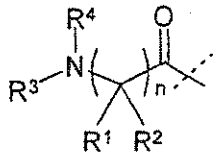
1. A compound of Formula IV, or a pharmaceutically acceptable salt or solvate thereof:



(IV)

wherein:

aa^1 is a natural or unnatural amino acid residue;
aa^2 is a natural or unnatural amino acid residue, or is absent;
wherein said aa^1, and aa^2, are each independently amino acid residues of Formula VI:

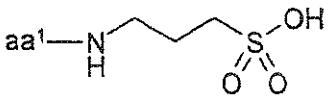


(VI)

wherein:

R^1 is selected from the group consisting of a substituted or unsubstituted group selected from C_1-C_{12}alkyl, C_2-C_{12}alkenyl, C_2-C_{12}alkynyl, C_3-C_{15}cycloalkyl;
R^2 is hydrogen
R^3 is hydrogen; or R^3 is a bond between two amino acid residues, when two amino acid residues are present;
R^4 is selected from the group consisting of H and a substituted or unsubstituted group selected from C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl; and
n is 1, 2 or 3;
wherein the term substituted when in association with any of the foregoing groups refers to a group substituted at one or more position with substituents selected from amino selected from simple amino, mono and dialkylamino, mono and diarylamino, and alkylarylamino, acylamino including carbamoyl, and ureido, aminocarbonyl, mono and dialkylaminocarbonyl, cyano, azido, halogen, hydroxyl, nitro, trifluoromethyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6 alkoxy, aryloxy, benzyloxy, benzyl, guanidine, imino, and formyl;
provided that when R^2 is H and R^3 is H or a bond, then R^1 is not a -CH_2phenyl group.

2. The compound of claim 1, wherein said compound is a compound of Formula V, or a pharmaceutically acceptable salt or solvate thereof:



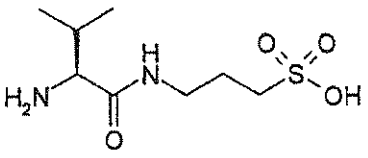
(V)

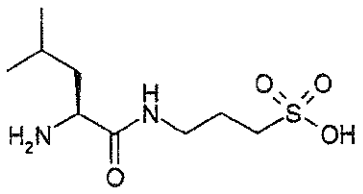
wherein:

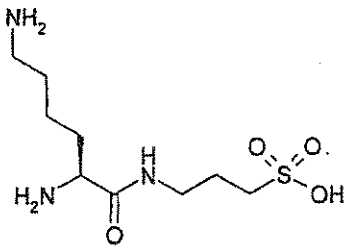
aa^1 is a natural or unnatural amino acid as defined in claim 1.

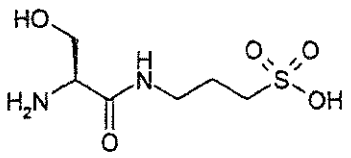
3. The compound of claim 2, wherein aa^1 is selected from amino acid residues of valine, lysine, leucine, serine, alanine, isoleucine, histidine, and O-benzylserine.

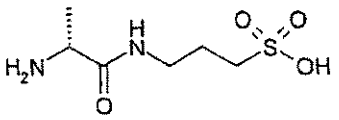
4. The compound of claim 1 or 2, wherein said compound is selected from the group consisting of:

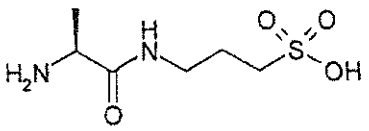


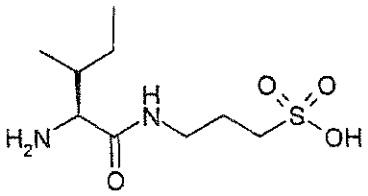


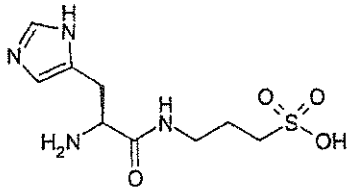


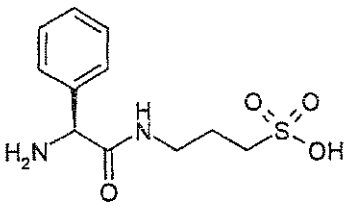


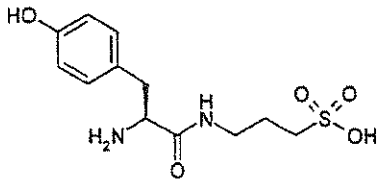


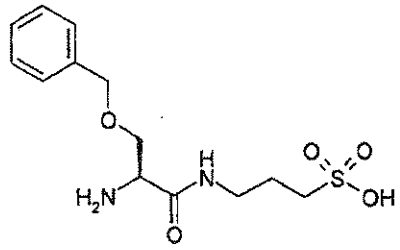


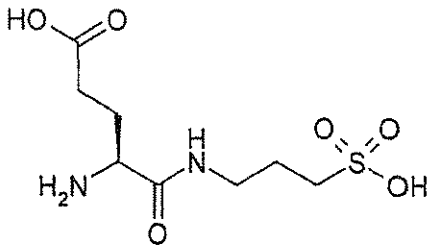


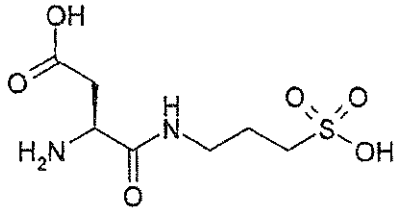


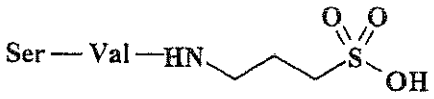


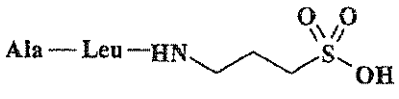


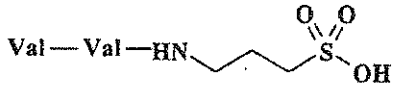


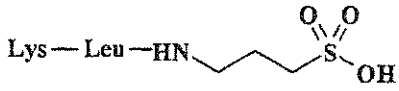


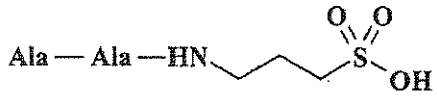


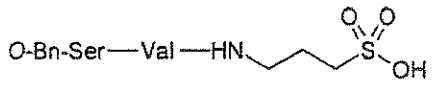






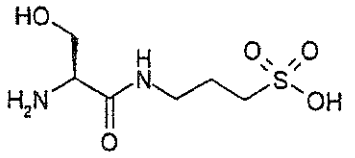


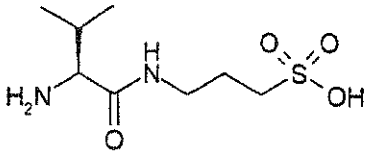


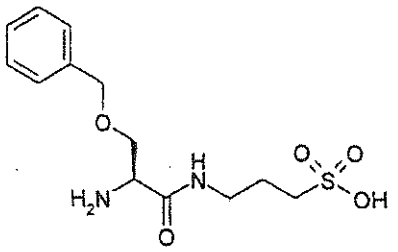


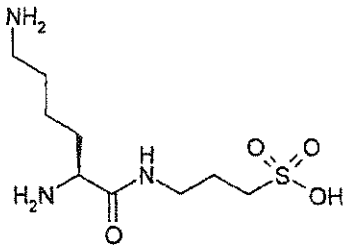
or a pharmaceutically acceptable salt or solvate thereof.

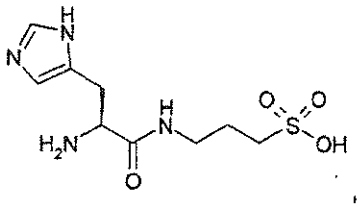
5. The compound of claim 4, wherein said compound is selected from:





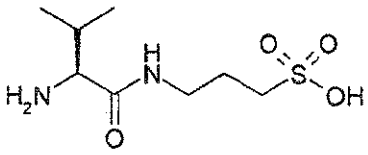






and pharmaceutically acceptable salt or solvates thereof.

6. The compound claim 5, wherein said compound is:



or a pharmaceutically acceptable salt or solvate thereof.

7. A pharmaceutical composition comprising a compound of any one of claims 1 to 6 together with a pharmaceutically acceptable carrier.

8. A prodrug of 3-amino-1-propanesulfonic acid, wherein said prodrug is a compound of any one of claims 1 to 6.

9. A compound of any one of claims 1 to 6, for use in the treatment or prevention of a disease or condition selected from Alzheimer's disease, mild cognitive impairment, Down's syndrome, Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, cerebral amyloid angiopathy, Parkinson's disease, a degenerative dementia, a dementia of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, or diffuse Lewy body type of Alzheimer's disease.

10. The compound for use according to claim 9, wherein said disease or condition is selected from Alzheimer's disease, mild cognitive impairment, cerebral amyloid angiopathy, and degenerative dementia.

11. The compound for use according to claim 10, wherein said disease or condition is Alzheimer's disease.

12. The compound of any one of claims 1 to 6, for use in providing neuroprotection to a subject having an amyloid-β related disease.

13. A compound of any one of claims 1 to 5, for use in delivering 3-amino-1-propanesulfonic acid (3APS) by contacting said compound with an enzyme which metabolizes said compound to 3APS *in vitro* or *in vivo*.

14. The compound of claim 13, wherein 3APS is delivered when said compound is contacted with plasma, blood and/or brain cells.

15. The compound of any one of claims 1 to 5, for use in inhibiting neuronal cell death.