skin is dependent on their ionic form, wherein non-ionized species generally have higher permeability coefficients in comparison to ionized species and further, cations generally have higher permeability coefficients than anions.

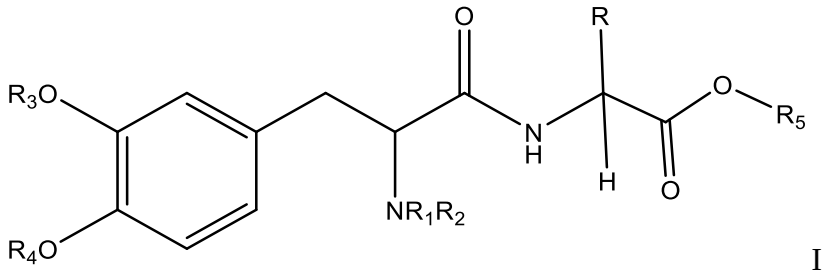
[0009] US 3,803,120, US 4,035,507, US 5,686,423 and US 2002/099013 disclose certain levodopa amino acid and levodopa peptide conjugates; however, details regarding formulations are not provided therein, and when provided, only solid oral formulations are contemplated. The theoretical option of preparing liquid compositions is briefly mentioned in US 3,803,120 (US '120, column 3, lines 49-53); however, no such compositions were prepared and moreover, it is erroneously disclosed that the conjugates are soluble (column 3, lines 65-66).

[0010] As detailed above, there is still a need to effective formulations, and particularly liquid formulations, for treating disorders such as Parkinson's disease.

SUMMARY

[0010a] In an aspect of the present disclosure, there is provided a liquid pharmaceutical composition comprising:

a levodopa amino acid conjugate (LDAA) of the general formula (I):



I

an enantiomer, diastereomer, racemate, ion, zwitterion, pharmaceutically acceptable salt thereof, or any combination thereof, wherein:

R is an amino acid side chain;

R_1 and R_2 are each independently selected from the group consisting of H, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, C_3-C_6cycloalkyl, phenyl, -O-C(=O)-R', -C(=O)-OR', -C(=O)-R', -C(=S)-R', -O-C(=O)-NR'R', -O-C(=S)-NR'R', and -O-C(=O)-R'';

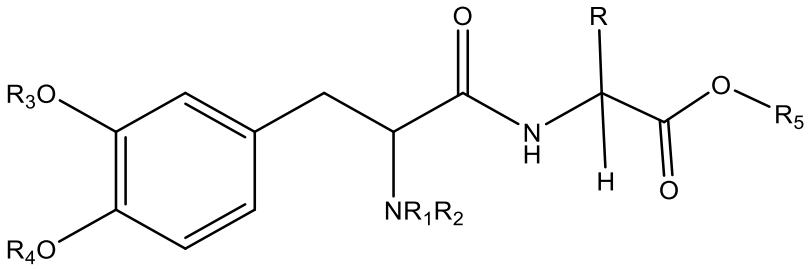
R_3 and R_4 are each independently selected from the group consisting of H, (C_1-C_3)alkyl, C_3-C_6cycloalkyl, phenyl, and-P(=O)(OR')$_2$;

R_5 is selected from the group consisting of H, (C_1- C_3)alkyl, C_3-C_6cycloalkyl and phenyl; R' is independently selected, for each occurrence, from the group consisting of H, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, C_3-C_6cycloalkyl , phenyl, and heteroaryl bonded to the nitrogen through a ring carbon; and

R'' is independently selected, for each occurrence, from the group consisting of a (C_1-C_6)alkyl, (C_2-C_6)alkenyl, and (C_2-C_6)alkynyl; and

a pharmaceutically acceptable excipient.

[0010b] In another aspect of the present disclosure, there is provided a use of a liquid pharmaceutical composition in the manufacture of a medicament for treating neurodegenerative conditions and/or conditions characterized by reduced levels of dopamine in the brain, wherein the liquid pharmaceutical composition comprises a levodopa amino acid conjugate (LDAA) of the general formula (I):



I

an enantiomer, diastereomer, racemate, ion, zwitterion, pharmaceutically acceptable salt thereof, or any combination thereof, wherein

R is an amino acid side chain;

R_1 and R_2 are each independently selected from the group consisting of H, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, C_3-C_6cycloalkyl, phenyl, -O-C(=O)-R', -C(=O)-OR', -C(=O)-R', -C(=S)-R', -O-C(=O)-NR'R', -O-C(=S)-NR'R', and -O-C(=O)-R'';

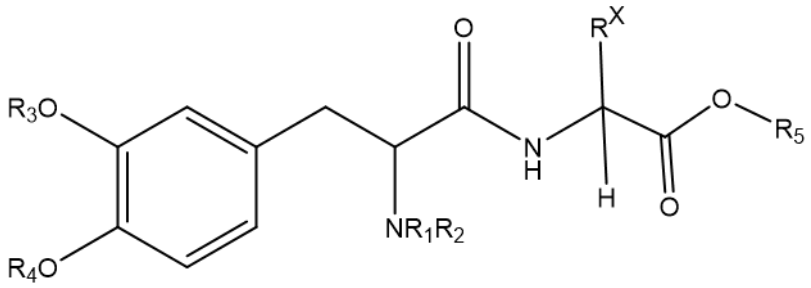
R_3 and R_4 are each independently selected from the group consisting of H, (C_1-C_3)alkyl, C_3-C_6cycloalkyl, phenyl, and-P(=O)(OR')$_2$;

R_5 is selected from the group consisting of H, (C_1-C_3)alkyl, C_3-C_6cycloalkyl and phenyl; R' is independently selected, for each occurrence, from the group consisting of H, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, C_3-C_6cycloalkyl , phenyl, and heteroaryl bonded to the nitrogen through a ring carbon; and

R" is independently selected, for each occurrence, from the group consisting of a (C_1-C_6)alkyl, (C_2-C_6)alkenyl, and (C_2-C_6)alkynyl; and

a pharmaceutically acceptable excipient.

[0010c] In a further aspect of the present disclosure, there is provided a levodopa amino acid conjugate (LDAA) of the general formula (III):



III

an enantiomer, diastereomer, racemate, ion, zwitterion, pharmaceutically acceptable salt thereof, or any combination thereof, wherein

R^X is an amino acid side chain; or an O-phosphorylated amino acid side chain thereof;

R_1 and R_2 are each independently selected from the group consisting of H, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, C_3-C_6cycloalkyl, phenyl, -O-C(=O)-R', -C(=O)-OR', -C(=O)-R', -C(=S)-R', -O-C(=O)-NR'R', -O-C(=S)-NR'R', and -O-C(=O)-R";

R_3 and R_4 are each independently selected from the group consisting of H, (C_1- C_3)alkyl, C_3-C_6cycloalkyl, phenyl, and-P(=O)(OR')$_2$;

R_5 is selected from the group consisting of H, (C_1- C_3)alkyl, C_3-C_6cycloalkyl and phenyl; R' is independently selected, in each occurrence, from the group consisting of H, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, C_3-C_6cycloalkyl , phenyl, and heteroaryl bonded to the nitrogen through a ring carbon; and

R" is independently selected, in each occurrence, from the group consisting of a (C_1-C_6)alkyl, (C_2-C_6)alkenyl, and (C_2-C_6)alkynyl.

[0010d] In another aspect of the present disclosure, there is provided a levodopa amino acid conjugate (LDAA) selected from the group consisting of:

(2S)-2-amino-3-(3-hydroxy-4-phosphonooxyphenyl)propionamide,

2-[[(2S)-2-amino-3-(3-hydroxy-4-phosphonooxyphenyl)propanoyl]amino]ethanesulfonic acid, (2S)-2-amino-6-[[(2S)-2-amino-3-(3-hydroxy-4-phosphonooxyphenyl)propanoyl]amino]hexanoic acid, and

(2S)-2-amino-5-[[(2S)-2-amino-3-(3-hydroxy-4-phosphonooxyphenyl)propanoyl]amino]pentanoic acid.

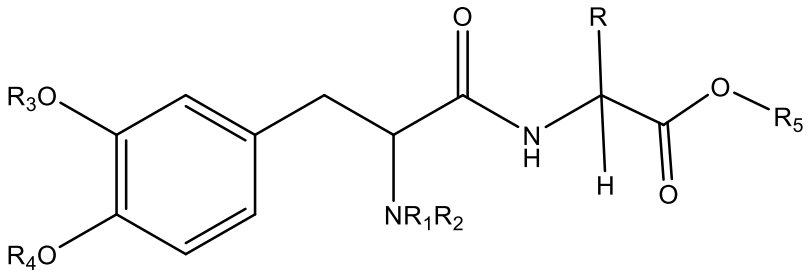
[0010e] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein in the manufacture of a medicament for treating Parkinson's disease in a patient in need thereof, wherein an effective amount of the compound is to be subcutaneously administered to the patient.

[0010f] In another aspect of the present disclosure, there is provided a liquid pharmaceutical composition disclosed herein, or a levodopa amino acid conjugate (LDAA) disclosed herein, for use in therapy.

[0011] Provided herein, *inter alia*, are levodopa amino acids (LDAAs), salts thereof (*e.g.*, pharmaceutically acceptable salts thereof), and compositions comprising the same (*e.g.*, pharmaceutically acceptable compositions, for example, liquid pharmaceutical compositions). Also described herein are methods of preparing LDAAs, pharmaceutically acceptable salts thereof, and compositions comprising the same. Also disclosed are methods of using LDAAs, pharmaceutically acceptable salts thereof, and compositions comprising the same in, for example, the treatment of conditions characterized by neurodegeneration and/or reduced levels of dopamine in the brain, e.g., Parkinson's disease.

[0012] Disclosed herein is a liquid pharmaceutical composition comprising:

a levodopa amino acid conjugate (LDAA) of the general formula (I):



I,

an enantiomer, diastereomer, racemate, ion, zwitterion, pharmaceutically acceptable salt thereof, or any combination thereof, wherein:

R is an amino acid side chain;

R_1 and R_2 are each independently selected from the group consisting of H, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, C_3-C_6cycloalkyl, phenyl, -O-C(=O)-R', -C(=O)-OR', -C(=O)-R', -C(=S)-R', -O-C(=O)-NR'R', -O-C(=S)-NR'R', and -O-C(=O)-R";

R_3 and R_4 are each independently selected from the group consisting of H, (C_1-C_3)alkyl, C_3-C_6cycloalkyl, phenyl, and -P(=O)(OR')$_2$;

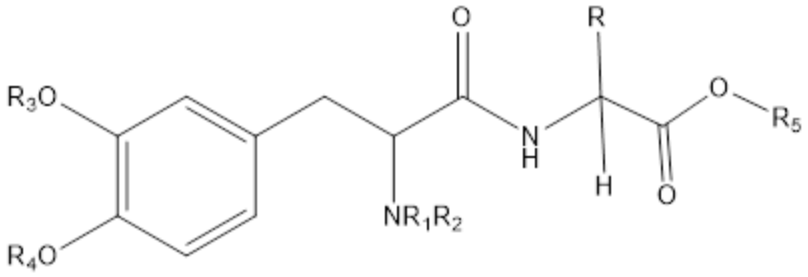
R_5 is selected from the group consisting of H, (C_1-C_3)alkyl, C_3-C_6cycloalkyl and phenyl;

R' is independently selected, in each occurrence, from the group consisting of H, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, C_3-C_6cycloalkyl , phenyl, and heteroaryl bonded to the nitrogen through a ring carbon; and

R" is independently selected, in each occurrence, from the group consisting of a (C_1-C_6)alkyl, (C_2-C_6)alkenyl, and (C_2-C_6)alkynyl; and

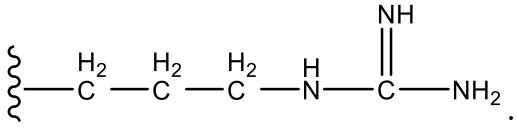
a pharmaceutically acceptable excipient.

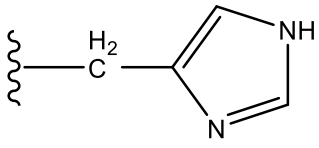
[0013] In some examples, a liquid pharmaceutical composition described herein includes an LDAA of the general formula (I):

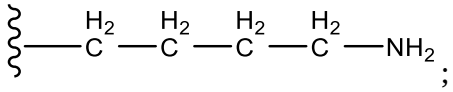


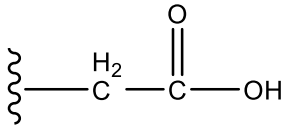
I,

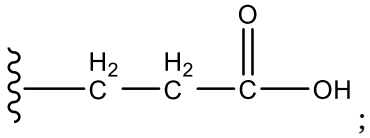
an enantiomer, diastereomer, racemate, ion, zwitterion, pharmaceutically acceptable salt thereof, or any combination thereof, where R is an amino acid side chain selected from the group consisting of arginine, histidine, lysine, aspartic acid, glutamic acid, serine, threonine, asparagine, glutamine, cysteine, selenocysteine, glycine, proline, alanine, valine, isoleucine, leucine, methionine, phenylalanine, tyrosine, tryptophan, and lanthionine side chains. For example, in examples described herein, R can be:

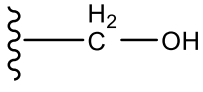

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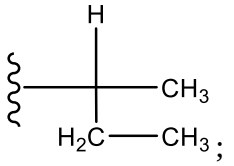

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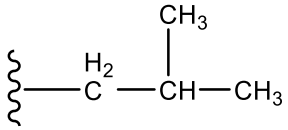

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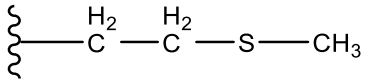

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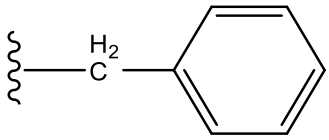
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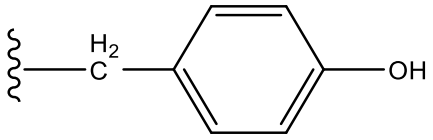
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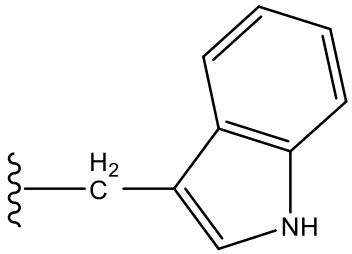
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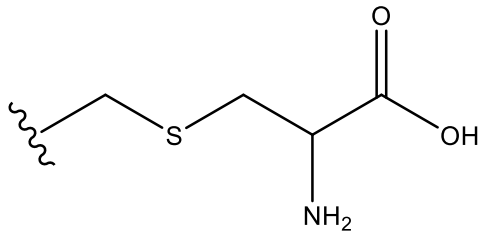
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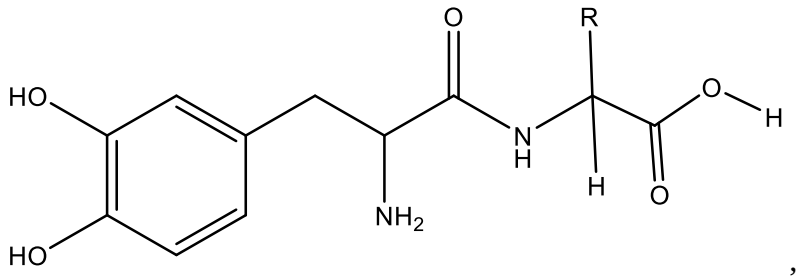
; or



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[0014] In some examples, a liquid pharmaceutical composition described herein includes an LDAA of the general formula (I), where R is an amino acid side chain selected from arginine, tyrosine or lysine. In some examples, R is the amino acid side chain of lanthionine-2.

[0015] Also disclosed herein is a liquid pharmaceutical composition that includes a LDAA of the general formula (I), an enantiomer, diastereomer, racemate, ion, zwitterion, pharmaceutically acceptable salt thereof, or any combination thereof, where each one of R_1, R_2, R_3, R_4 and R_5 are H. For example, in some examples, a liquid pharmaceutical composition described herein includes the compound:



,

an enantiomer, diastereomer, racemate, ion, zwitterion, pharmaceutically acceptable salt thereof, or any combination thereof, where R is an amino acid side chain selected from the group consisting of arginine, histidine, lysine, aspartic acid, glutamic acid, serine, threonine, asparagine, glutamine, cysteine, selenocysteine, glycine, proline, alanine, valine, isoleucine, leucine, methionine, phenylalanine, tyrosine, tryptophan, and lanthionine side chains.

[0016] In some examples, a liquid pharmaceutical composition disclosed herein comprises between about 10 to about 45 % w/v of one, two or more LDAA compounds, or an enantiomer, diastereomer, racemate, ion, zwitterion, pharmaceutically acceptable salt thereof, or any combination thereof.

[0017] In some examples, a liquid pharmaceutical composition disclosed herein has a pH in the range of between about 3 to about 10 at about 25°C.

[0018] In some examples, a liquid pharmaceutical composition disclosed herein can include a free base of the compound of formula I and a counterion.

[0019] In some examples, a liquid pharmaceutical composition disclosed herein can also include a decarboxylase inhibitor. For example, in some examples, the decarboxylase inhibitor is carbidopa. In some examples, a liquid pharmaceutical composition disclosed herein can include between about 0.25 to about 1.5 % w/v of the decarboxylase inhibitor.

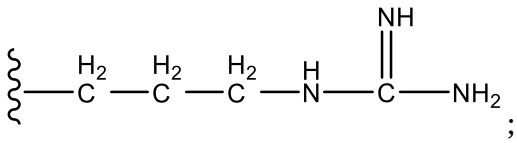
[0020] Any of the aforementioned liquid pharmaceutical compositions described herein can further include an antioxidant or a combination of two or more antioxidants. For example,

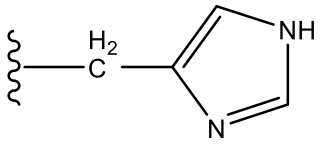
in some examples, a liquid pharmaceutical composition described herein can include an antioxidant selected from the group consisting of ascorbic acid or a salt thereof, a cysteine, a bisulfite or a salt thereof, glutathione, a tyrosinase inhibitor, a Cu^{2+} chelator, and any combination thereof. In some examples, a liquid pharmaceutical composition described herein can include between about 0.05 to about 1.5 % w/v of an antioxidant or a combination of antioxidants.

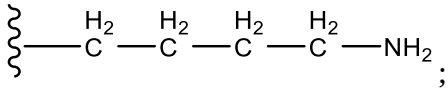
[0021] Any of the aforementioned liquid pharmaceutical composition described herein can further include at least one of: a catechol-O-methyltransferase (COMT) inhibitor, a monoamine oxidase (MAO) inhibitor, a surfactant, a buffer, an acid, a base, a solvent, or any combination thereof. For example, in some examples, a liquid pharmaceutical composition described herein can include a solvent, wherein the solvent may be N-methylpyrrolidone (NMP), tris(hydroxymethyl)aminomethane (tromethamine, TRIS), an ether such as tetrahydrofuran and 1,4-dioxane an amide, such as N,N-dimethylformamide and N-methylpyrrolidone, a nitrile, such as acetonitrile, a halogenated aliphatic hydrocarbon, such as chloroform and dichloromethane, an aromatic hydrocarbon, such as toluene or any combination thereof. It is noted that certain materials, such as tromethamine (TRIS) may be added to the composition and function, e.g., as a base, buffer, solvent, or any combination thereof. In some examples, a liquid pharmaceutical composition described herein can include a surfactant, where the surfactant is Tween-80. In some examples, a liquid pharmaceutical composition described herein can include a solvent and a surfactant, where the solvent is NMP and the surfactant is Tween-80. In some examples, the liquid pharmaceutical composition can include between about 0.1 to about 1.0 % w/v of the surfactant, for example, 0.1 to about 1.0 % w/v of Tween-80. In some examples, the liquid pharmaceutical composition can include between about 5.0 to about 40.0 % w/v of the solvent, for example, between about 5.0 to about 40.0 % w/v of NMP.

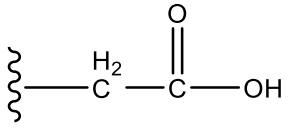
[0022] Also disclosed herein is a method of treating a neurodegenerative condition and/or a condition characterized by reduced levels of dopamine in the brain, wherein the method comprises administering a liquid pharmaceutical composition, wherein the liquid pharmaceutical composition comprises a levodopa amino acid conjugate (LDAA) of the general formula (I):

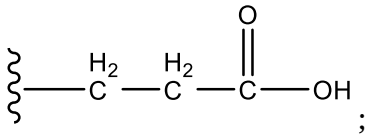
asparagine, glutamine, cysteine, selenocysteine, glycine, proline, alanine, valine, isoleucine, leucine, methionine, phenylalanine, tyrosine, tryptophan, and lanthionine side chains. For example, in examples described herein, R can be:

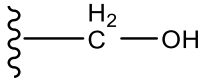

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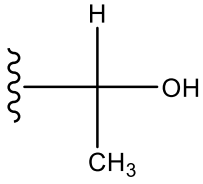

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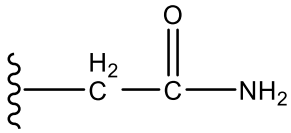

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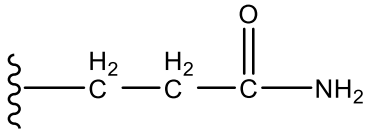

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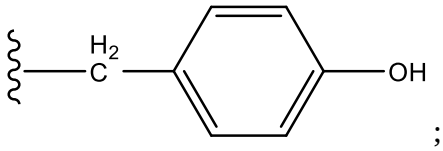

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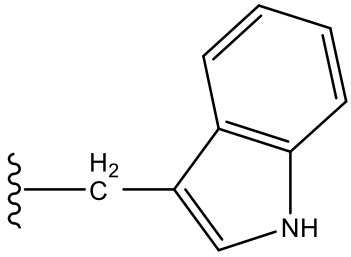

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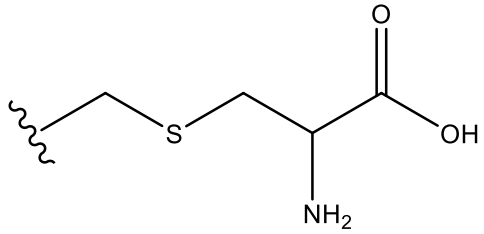

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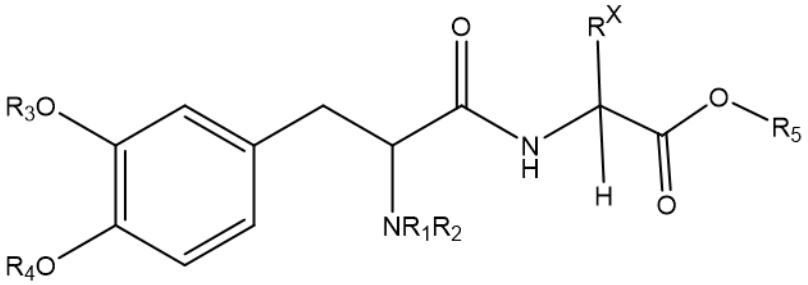
.

[0024] For example, disclosed herein is a method of treating a neurodegenerative condition and/or a condition characterized by reduced levels of dopamine in the brain, wherein the neurodegenerative condition is Parkinson's disease.

[0025] In some examples of the disclosed methods of treating, the liquid pharmaceutical composition is administered concomitantly with an additional active ingredient. For example, in some examples, the additional active ingredient is a decarboxylase inhibitor, a COMT inhibitor, a MAO inhibitor, or any combination thereof.

[0026] In some examples of the methods of treating disclosed herein, the liquid pharmaceutical composition is administered substantially continuously. In some examples, the liquid pharmaceutical composition is administered subcutaneously.

[0027] Also disclosed herein is a levodopa amino acid conjugate (LDAA) of the general formula (III):



III

an enantiomer, diastereomer, racemate, ion, zwitterion, pharmaceutically acceptable salt thereof, or any combination thereof, wherein

R^X is an amino acid side chain; or an O-phosphorylated amino acid side chain thereof.

R_1 and R_2 are each independently selected from the group consisting of H, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, C_3-C_6cycloalkyl, phenyl, -O-C(=O)-R', -C(=O)-OR', -C(=O)-R', -C(=S)-R', -O-C(=O)-NR'R', -O-C(=S)-NR'R', and -O-C(=O)-R";

R_3 and R_4 are each independently selected from the group consisting of H, (C_1-C_3)alkyl, C_3-C_6cycloalkyl, phenyl, and -P(=O)(OR')$_2$;

R_5 is selected from the group consisting of H, (C_1-C_3)alkyl, C_3-C_6cycloalkyl and phenyl;

R' is independently selected, in each occurrence, from the group consisting of H, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, C_3-C_6cycloalkyl , phenyl, and heteroaryl bonded to the nitrogen through a ring carbon; and

R" is independently selected, in each occurrence, from the group consisting of a (C_1-C_6)alkyl, (C_2-C_6)alkenyl, and (C_2-C_6)alkynyl.

[0028] According to some examples, the amino acid side chain in R^x is selected from the group consisting of arginine, histidine, lysine, aspartic acid, glutamic acid, serine, threonine, asparagine, glutamine, cysteine, selenocysteine, glycine, proline, alanine, valine, isoleucine, leucine, methionine, phenylalanine, tyrosine, tryptophan, ornithine, lanthionine and 3,4-dihydroxyphenylalanine side chain.

[0029] According to further examples, the amino acid side chain in R^x is selected from the group consisting of arginine, lysine, serine, glycine, alanine, valine, phenylalanine, tyrosine,

ornithine, and 3,4-dihydroxyphenylalanine. According to some examples, each one of R_1, R_2 and R_5 are H; R_3, and R_4 independently is H or -P(=O)(OR')$_2$; and R' is H.

[0030] According to some examples, the levodopa amino acid conjugate (LDAA) selected from the group consisting of:

(2S)-2-amino-3-(3-hydroxy-4-phosphonooxyphenyl)propionamide,

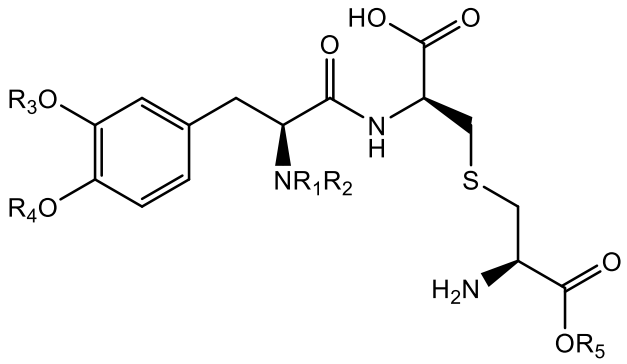
2-[[(2S)-2-amino-3-(3-hydroxy-4-phosphonooxyphenyl)propanoyl]amino]ethanesulfonic acid,

(2S)-2-amino-6-[[(2S)-2-amino-3-(3-hydroxy-4-phosphonooxyphenyl)propanoyl]amino]hexanoic acid, and

(2S)-2-amino-5-[[(2S)-2-amino-3-(3-hydroxy-4-phosphonooxyphenyl)propanoyl]amino]pentanoic acid.

[0031] Examples of the present disclosure are further directed to a method of treating Parkinson's disease in a patient in need thereof, comprising subcutaneously administering to the patient an effective amount of a compound as disclosed herein.

[0032] Also disclosed herein is a compound represented by:



(II-1),

an enantiomer, diastereomer, racemate, ion, zwitterion, pharmaceutically acceptable salt thereof, or any combination thereof, wherein:

R_1 and R_2 are each independently selected from the group consisting of H, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, C_3-C_6cycloalkyl, phenyl, -O-C(=O)-R', -C(=O)-OR', -C(=O)-R', -C(=S)-R', -O-C(=O)-NR'R', -O-C(=S)-NR'R', and -O-C(=O)-R'';

I;

combining the pharmaceutically acceptable salt with at least one solvent thereby forming a solution, gel, cream, emulsion, or suspension; and

adjusting the pH of the solution, gel, cream, emulsion, or suspension, to a physiologically acceptable pH value, thereby providing the liquid pharmaceutical composition, wherein:

R is an amino acid side chain;

R_1 and R_2 are each independently selected from the group consisting of H, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, C_3-C_6cycloalkyl, phenyl, -O-C(=O)-R', -C(=O)-OR', -C(=O)-R', -C(=S)-R', -O-C(=O)-NR'R', -O-C(=S)-NR'R', and -O-C(=O)-R'';

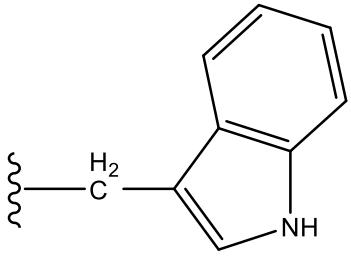
R_3 and R_4 are each independently selected from the group consisting of H, (C_1-C_3)alkyl, C_3-C_6cycloalkyl, phenyl, and -P(=O)(OR')$_2$;

R_5 is selected from the group consisting of H, (C_1-C_3)alkyl, C_3-C_6cycloalkyl and phenyl;

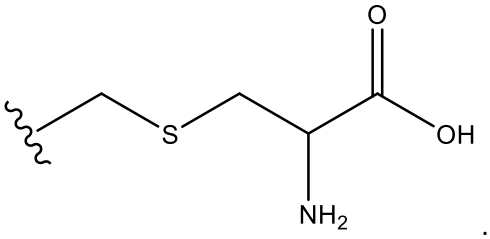
R' is independently selected, in each occurrence, from the group consisting of H, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, C_3-C_6cycloalkyl , phenyl, and heteroaryl bonded to the nitrogen through a ring carbon; and

R'' is independently selected, in each occurrence, from the group consisting of a (C_1-C_6)alkyl, (C_2-C_6)alkenyl, and (C_2-C_6)alkynyl.

[0036] In some examples, a process for preparing a liquid pharmaceutical composition described herein includes providing a pharmaceutically acceptable salt of a LDAA of formula (I), an enantiomer, diastereomer, racemate, ion, zwitterion, pharmaceutically acceptable salt thereof, or any combination thereof, wherein R is an amino acid side chain selected from the group consisting of arginine, histidine, lysine, aspartic acid, glutamic acid, serine, threonine, asparagine, glutamine, cysteine, selenocysteine, glycine, proline, alanine, valine, isoleucine, leucine, methionine, phenylalanine, tyrosine, tryptophan, and lanthionine side chains. For example, in examples described herein, R can be:



; or

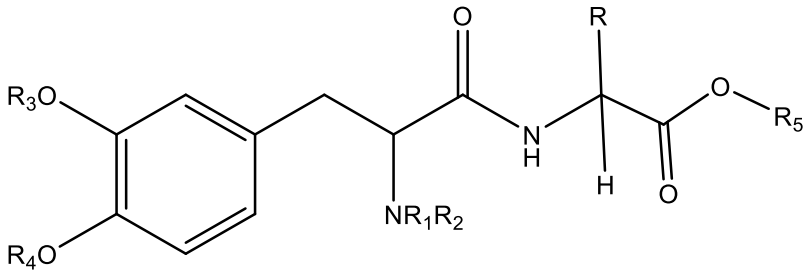


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[0037] In some examples of a process described herein, the LDAA compound of Formula (I) in a pharmaceutically acceptable salt form is mixed with at least one solvent, thereby forming a solution. In some examples, the process includes a step of adjusting the pH that comprises adding a basic solution. For example, in some examples, the process includes a step of adjusting the pH that comprises adding a basic solution, and the basic solution comprises NaOH.

[0038] In some examples of a process described herein, the LDAA compound of Formula (I) is in a pharmaceutically acceptable solid salt form.

[0039] Also disclosed herein is a composition comprising a pharmaceutically acceptable salt of a compound represented by



I,

wherein:

R is an amino acid side chain;

R_1 and R_2 are each independently selected from the group consisting of H, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, C_3-C_6cycloalkyl, phenyl, -O-C(=O)-R', -C(=O)-OR', -C(=O)-R', -C(=S)-R', -O-C(=O)-NR'R', -O-C(=S)-NR'R', and -O-C(=O)-R'';

R_3 and R_4 are each independently selected from the group consisting of H, (C_1-C_3)alkyl, C_3-C_6cycloalkyl, phenyl, and -P(=O)(OR')$_2$;

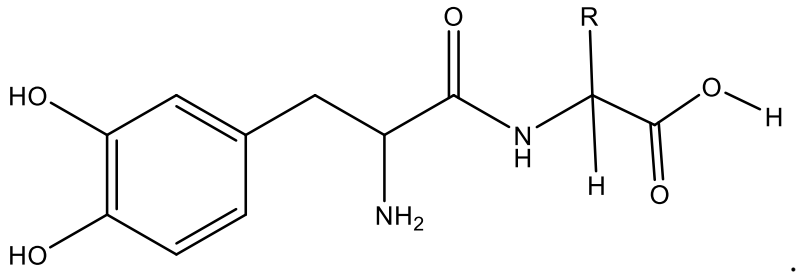
R_5 is selected from the group consisting of H, (C_1-C_3)alkyl, C_3-C_6cycloalkyl and phenyl;

R' is independently selected, in each occurrence, from the group consisting of H, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, C_3-C_6cycloalkyl , phenyl, and heteroaryl bonded to the nitrogen through a ring carbon; and

R'' is independently selected, in each occurrence, from the group consisting of a (C_1-C_6)alkyl, (C_2-C_6)alkenyl, and (C_2-C_6)alkynyl; and

a pharmaceutically acceptable excipient.

[0040] In some examples, a pharmaceutically acceptable salt disclosed herein is a pharmaceutically acceptable salt of the compound:



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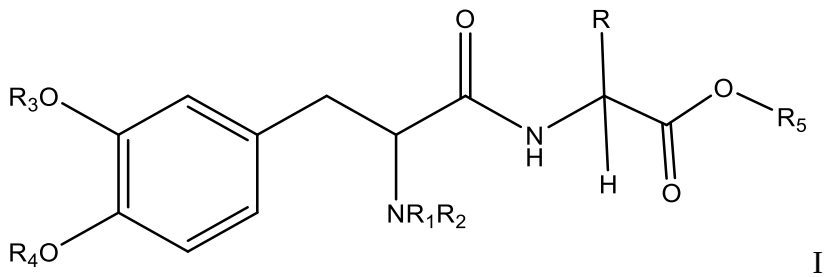
[0041] For example, disclosed herein is a composition that includes a pharmaceutically acceptable salt of a compound of formula (I), wherein the salt is a trifluoroacetic acid (TFA) salt.

[0042] Also disclosed herein are liquid pharmaceutical compositions comprising one or more of the following compounds:

CLAIMS

1. A liquid pharmaceutical composition comprising:

a levodopa amino acid conjugate (LDAA) of the general formula (I):



I

an enantiomer, diastereomer, racemate, ion, zwitterion, pharmaceutically acceptable salt thereof, or any combination thereof, wherein:

R is an amino acid side chain;

R_1 and R_2 are each independently selected from the group consisting of H, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, C_3-C_6cycloalkyl, phenyl, -O-C(=O)-R', -C(=O)-OR', -C(=O)-R', -C(=S)-R', -O-C(=O)-NR'R', -O-C(=S)-NR'R', and -O-C(=O)-R'';

R_3 and R_4 are each independently selected from the group consisting of H, (C_1-C_3)alkyl, C_3-C_6cycloalkyl, phenyl, and-P(=O)(OR')$_2$;

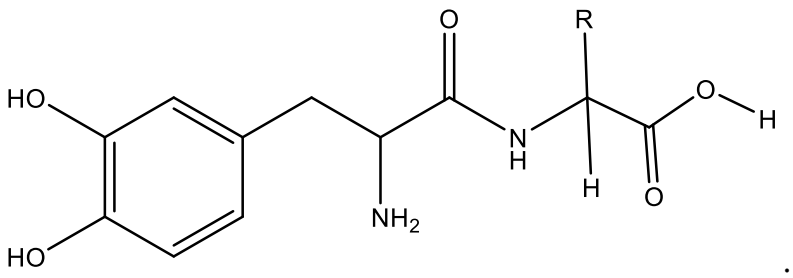
R_5 is selected from the group consisting of H, (C_1- C_3)alkyl, C_3-C_6cycloalkyl and phenyl; R' is independently selected, for each occurrence, from the group consisting of H, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, C_3-C_6cycloalkyl , phenyl, and heteroaryl bonded to the nitrogen through a ring carbon; and

R'' is independently selected, for each occurrence, from the group consisting of a (C_1-C_6)alkyl, (C_2-C_6)alkenyl, and (C_2-C_6)alkynyl; and

a pharmaceutically acceptable excipient.

2. The liquid pharmaceutical composition according to claim 1, wherein R is an amino acid side chain selected from the group consisting of arginine, histidine, lysine, aspartic acid, glutamic acid, serine, threonine, asparagine, glutamine, cysteine, selenocysteine, glycine, proline, alanine, valine, isoleucine, leucine, methionine, phenylalanine, tyrosine, tryptophan, and lanthionine side chains.

3. The liquid pharmaceutical composition according to any one of claims 1-2, wherein the LDAA is represented by:



.

4. The liquid pharmaceutical composition according to any one of claims 1-3, further comprising a decarboxylase inhibitor, wherein, optionally, the decarboxylase inhibitor is carbidopa.

5. The liquid pharmaceutical composition according to any one of claims 1-4, further comprising a base, wherein, optionally, the base is selected from the group consisting of arginine, NaOH, tris(hydroxymethyl)aminomethane (TRIS), and any combination thereof.

6. The liquid pharmaceutical composition according to claim 5, wherein said liquid pharmaceutical composition comprises between about 0.1% to about 30% w/v of the base.

7. The liquid pharmaceutical composition according to any one of claims 4-6, wherein said liquid pharmaceutical composition comprises between about 0.25 to about 1.5 % w/v of the decarboxylase inhibitor.

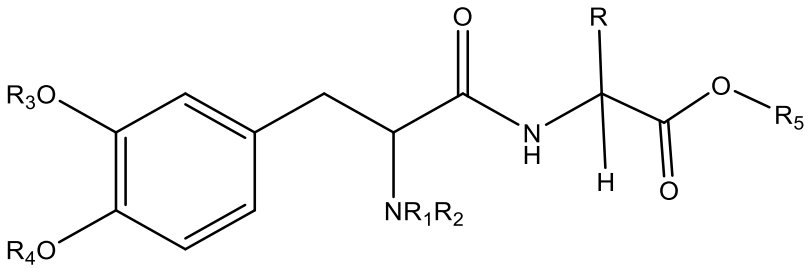
8. The liquid pharmaceutical composition according to any one of claims 1-7, further comprising an antioxidant or a combination of two or more antioxidants.

9. The liquid pharmaceutical composition according to claim 8, wherein the antioxidant is each independently selected from the group consisting of ascorbic acid or a salt thereof, a cysteine, a bisulfite or a salt thereof, glutathione, a tyrosinase inhibitor, a Cu^{2+} chelator, and any combination thereof.

10. The liquid pharmaceutical composition according to claim 8 or 9, wherein said liquid pharmaceutical composition comprises between about 0.05 to about 1.5 % w/v of the antioxidant or the combination of antioxidants.

11. The liquid pharmaceutical composition according to any one of claims 1-10, further comprising at least one of: a catechol-O-methyltransferase (COMT) inhibitor, a monoamine oxidase (MAO) inhibitor, a surfactant, a buffer, an acid, a solvent, and any combination thereof.

12. Use of a liquid pharmaceutical composition in the manufacture of a medicament for treating neurodegenerative conditions and/or conditions characterized by reduced levels of dopamine in the brain, wherein the liquid pharmaceutical composition comprises a levodopa amino acid conjugate (LDAA) of the general formula (I):



I

an enantiomer, diastereomer, racemate, ion, zwitterion, pharmaceutically acceptable salt thereof, or any combination thereof, wherein

R is an amino acid side chain;

R_1 and R_2 are each independently selected from the group consisting of H, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, C_3-C_6cycloalkyl, phenyl, -O-C(=O)-R', -C(=O)-OR', -C(=O)-R', -C(=S)-R', -O-C(=O)-NR'R', -O-C(=S)-NR'R', and -O-C(=O)-R";

R_3 and R_4 are each independently selected from the group consisting of H, (C_1-C_3)alkyl, C_3-C_6cycloalkyl, phenyl, and-P(=O)(OR')$_2$;

R_5 is selected from the group consisting of H, (C_1-C_3)alkyl, C_3-C_6cycloalkyl and phenyl;
R' is independently selected, for each occurrence, from the group consisting of H, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, C_3-C_6cycloalkyl , phenyl, and heteroaryl bonded to the nitrogen through a ring carbon; and

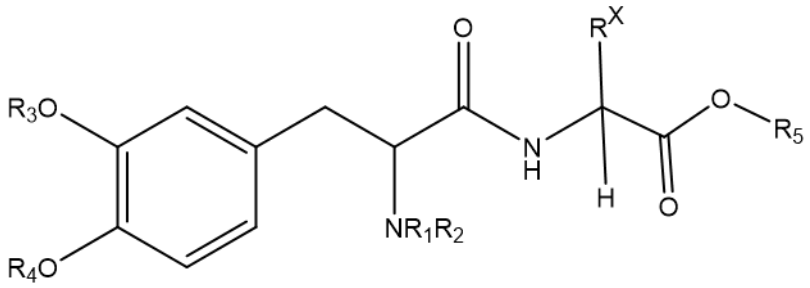
R" is independently selected, for each occurrence, from the group consisting of a (C_1-C_6)alkyl, (C_2-C_6)alkenyl, and (C_2-C_6)alkynyl; and

a pharmaceutically acceptable excipient.

13. The use according to claim 12, wherein the neurodegenerative condition is Parkinson's disease.

14. The use according to claim 12 or 13, wherein the liquid pharmaceutical composition is to be administered subcutaneously.

15. A levodopa amino acid conjugate (LDAA) of the general formula (III):



III

an enantiomer, diastereomer, racemate, ion, zwitterion, pharmaceutically acceptable salt thereof, or any combination thereof, wherein

R^X is an amino acid side chain; or an O-phosphorylated amino acid side chain thereof;

R_1 and R_2 are each independently selected from the group consisting of H, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, C_3-C_6cycloalkyl, phenyl, -O-C(=O)-R', -C(=O)-OR', -C(=O)-R', -C(=S)-R', -O-C(=O)-NR'R', -O-C(=S)-NR'R', and -O-C(=O)-R";

R_3 and R_4 are each independently selected from the group consisting of H, (C_1- C_3)alkyl, C_3-C_6cycloalkyl, phenyl, and-P(=O)(OR')$_2$;

R_5 is selected from the group consisting of H, (C_1- C_3)alkyl, C_3-C_6cycloalkyl and phenyl;

R' is independently selected, in each occurrence, from the group consisting of H, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, C_3-C_6cycloalkyl , phenyl, and heteroaryl bonded to the nitrogen through a ring carbon; and

R" is independently selected, in each occurrence, from the group consisting of a (C_1-C_6)alkyl, (C_2-C_6)alkenyl, and (C_2-C_6)alkynyl.

16. The levodopa amino acid conjugate (LDAA) according to claim 15, wherein the amino acid side chain in R^x is selected from the group consisting of arginine, histidine, lysine, aspartic acid, glutamic acid, serine, threonine, asparagine, glutamine, cysteine, selenocysteine, glycine, proline,

alanine, valine, isoleucine, leucine, methionine, phenylalanine, tyrosine, tryptophan, ornithine, lanthionine and 3,4-dihydroxyphenylalanine side chain.

17. The levodopa amino acid conjugate (LDAA) according to any one of claims 14 to 16, wherein the amino acid side chain in R^x is selected from the group consisting of arginine, lysine, serine, glycine, alanine, valine, phenylalanine, tyrosine, ornithine, and 3,4-dihydroxyphenylalanine.

18. The levodopa amino acid conjugate (LDAA) according to any one of claims 14 to 17, wherein each one of R_1, R_2 and R_5 are H; R_3, and R_4 independently is H or $-P(=O)(OR')_2$; and R' is H.

19. The levodopa amino acid conjugate (LDAA) selected from the group consisting of:
(2S)-2-amino-3-(3-hydroxy-4-phosphonooxyphenyl)propionamide,

2-[[(2S)-2-amino-3-(3-hydroxy-4-phosphonooxyphenyl)propanoyl]amino]ethanesulfonic acid,
(2S)-2-amino-6-[[(2S)-2-amino-3-(3-hydroxy-4-phosphonooxyphenyl)propanoyl]amino]hexanoic acid, and

(2S)-2-amino-5-[[(2S)-2-amino-3-(3-hydroxy-4-phosphonooxyphenyl)propanoyl]amino]pentanoic acid.

20. Use of a compound of claim 19 in the manufacture of a medicament for treating Parkinson's disease in a patient in need thereof, wherein an effective amount of the compound is to be subcutaneously administered to the patient.

21. A liquid pharmaceutical composition of any one of claims 1-11, or a levodopa amino acid conjugate (LDAA) of any one of claims 15-19, for use in therapy.