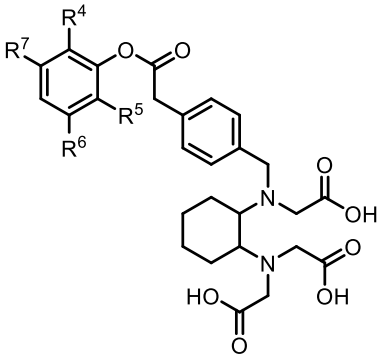
applications for RESCA, the laborious, low-yield synthesis is a potential barrier to widespread development and use of the RESCA-Al^{18}F labeling strategy. An improved process for synthesizing RESCA would be useful for the continued development of the RESCA-Al^{18}F labeling method and its various applications.

BRIEF SUMMARY

[0005] The present application provides methods of preparing RESCA compounds, RESCA compounds and compositions, and methods of use thereof.

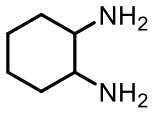
[0005a] In an aspect of the present disclosure, there is provided a method of preparing a compound of Formula (I):



Formula (I)

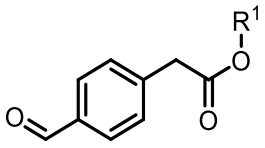
a diastereomer thereof, a salt thereof, a solvate thereof, or a combination of any of the foregoing, wherein the method comprises:

(a) a step (1-1) comprising reacting a compound of Formula (Ia):



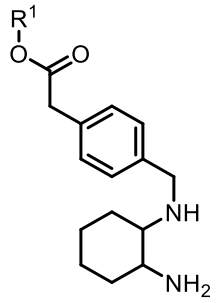
Formula (Ia)

or a diastereomer thereof with a compound of Formula (Ib):



Formula (Ib)

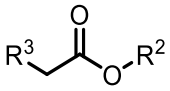
in a solvent and in the presence of a reducing agent to form a compound of Formula (Ic):



Formula (Ic)

or a diastereomer thereof;

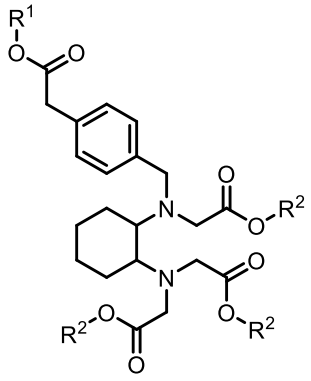
(b) a step (1-2) comprising reacting the compound of Formula (Ic), or a salt thereof, with a compound of Formula (Id):



Formula (Id)

in the presence of a base and in a solvent,

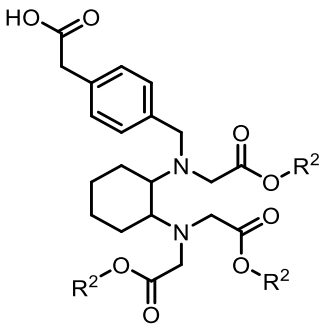
to form a compound of Formula (Ie):



Formula (Ie)

or a diastereomer thereof;

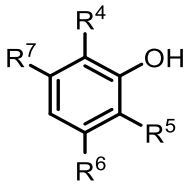
(c) a step (1-3) comprising reacting the compound of Formula (Ie) with a base in a solvent to form a compound of Formula (If):



Formula (If)

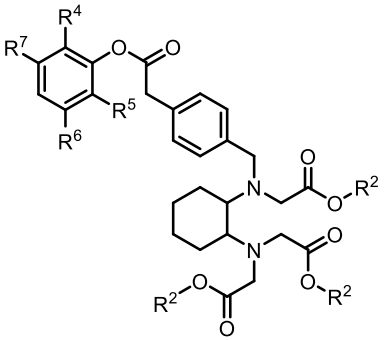
or a diastereomer thereof;

(d) a step (1-4) comprising reacting the compound of Formula (If) with a compound of Formula (1g):



Formula (Ig)

in a solvent and in the presence of a carboxyl activating reagent, to form a compound of Formula (Ih):



Formula (Ih)

or a diastereomer thereof; and

(e) a step (1-5) comprising reacting the compound of Formula (Ih) with an acid to form a compound of Formula (I), a diastereomer thereof, a salt thereof, or a solvate thereof, or a combination of any of the foregoing,

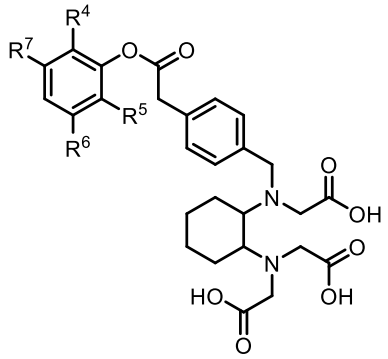
wherein

R^1 and R^2 are each independently C_1-C_6 alkyl;

R^3 is halo; and

$R^{4,}$ R^5, R^6 and R^7 are each independently halo or hydrogen.

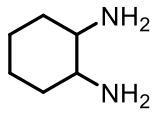
[0005b] In another aspect of the present disclosure, there is provided a method of preparing a compound of Formula (I):



Formula (I)

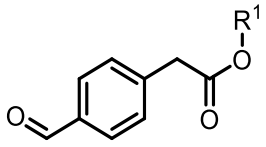
a diastereomer thereof, a salt thereof, or a solvate thereof, or a combination of any of the foregoing, wherein the method comprises:

(a) a step (2-1) comprising reacting a compound of Formula (Ia):



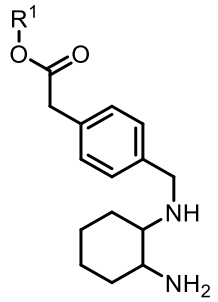
Formula (Ia)

with a compound of Formula (Ib):



Formula (Ib)

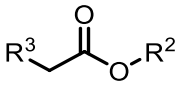
in a solvent and in the presence of a reducing agent to form a compound of Formula (Ic):



Formula (Ic);

(b) a step (2-2) comprising reacting a compound of Formula (Ic) with an acid to produce a salt of Formula (Ic);

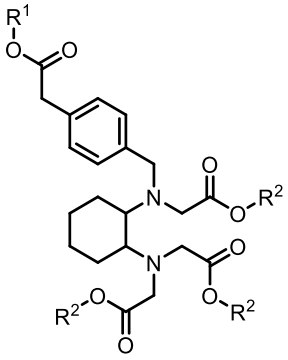
(c) a step (2-3) comprising reacting the salt of Formula (Ic) with a compound of Formula (Id):



Formula (Id)

in the presence of a base and in a solvent,

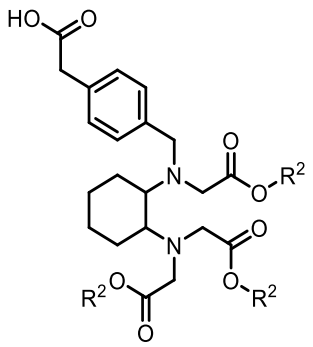
to form a compound of Formula (Ie):



Formula (Ie)

a diastereomer thereof, or a salt thereof;

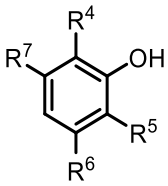
(d) a step (2-4) comprising reacting a compound of Formula (Ie) with a base in a solvent to form a compound of Formula (2f):



Formula (If)

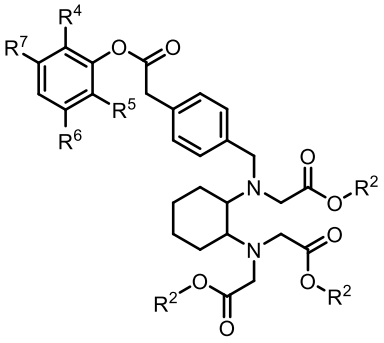
a diastereomer thereof, or a salt thereof; and

(e) a step (2-5) comprising reacting the compound of Formula (If) or salt thereof with a compound of Formula (Ig):



Formula (Ig)

in a solvent and in the presence of a carboxyl activating reagent, to form a compound of Formula (Ih):



Formula (Ih)

a diastereomer thereof, or a salt thereof; and

(f) a step (2-6) comprising reacting the compound of Formula (Ih) with an acid to form a compound of Formula (I), a diastereomer thereof, a salt thereof, a solvate thereof, or a combination of any of the foregoing,

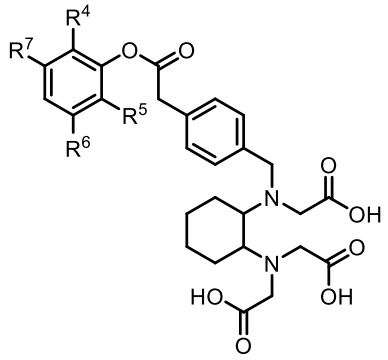
wherein

R^1 and R^2 are each independently C_1-C_6 alkyl;

R^3 is halo; and

R^4, R^5, R^6, and R^7 are each independently halo or hydrogen.

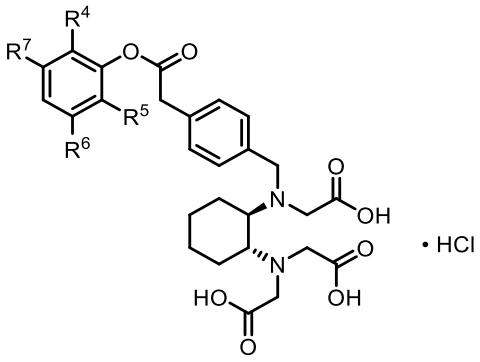
[0005c] In a further aspect of the present disclosure, there is provided a composition comprising one or more diastereomers of compound of Formula (I), salts thereof, or solvates thereof:



Formula (I)

produced by the method disclosed herein.

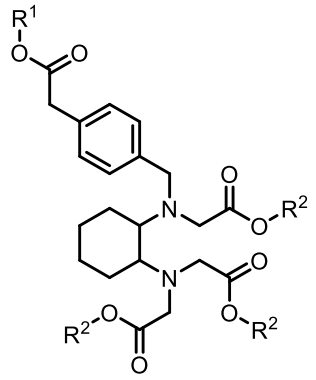
[0005d] In another aspect of the present disclosure, there is provided a salt of Formula (I), or a solvate thereof, wherein the salt of Formula (I) has the structure:



Formula (I-1) HCl

produced by the method disclosed herein.

[0005e] In a further aspect of the present disclosure, there is provided a compound of Formula (Ie):

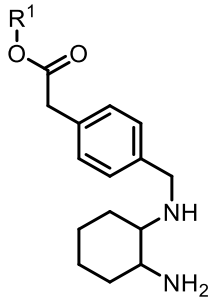


Formula (Ie),

a diastereomer thereof, or a salt thereof,

wherein R^1 and R^2 are each independently C_1-C_6 alkyl.

[0005f] In another aspect of the present disclosure, there is provided a compound of Formula (Ic):



Formula (Ic),

a diastereomer thereof, or a salt thereof,

wherein R^1 is C_1-C_6 alkyl.

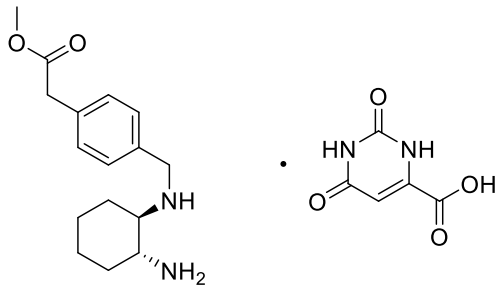
[0005g] In a further aspect of the present disclosure, there is provided a composition comprising a complex comprising the compound prepared using the method disclosed herein and a metal halide.

[0005h] In another aspect of the present disclosure, there is provided a method of preparing a labeled agent comprising a polypeptide and a ^{18}F radionuclide, comprising:

(a) contacting the polypeptide with the compound prepared using the method disclosed herein under a condition that allows conjugation of the complex to the polypeptide to provide a conjugate; and

(b) contacting the conjugate with an aluminum fluoride complex comprising ^{18}F to provide the labeled agent.

[0005i] In a further aspect of the present disclosure, there is provided a crystalline salt of a compound with the structure:



Compound 1c orotate

wherein the salt has at least one of:

(a) an X-ray powder diffraction pattern with characteristic peaks at about 7.5° 2-Theta, about 13.9° 2-Theta, about 16.6° 2-Theta, about 23.4° 2-Theta, and about 25.6° 2-Theta;

(b) an X-ray powder diffraction pattern substantially the same as the "Orotate Type A" pattern in FIG. 1;

(c) a thermo-gravimetric analysis thermogram showing a mass loss of about 3.3% between 20 °C and 150 °C;

(d) a thermo-gravimetric analysis thermogram substantially the same as shown in FIG. 2;

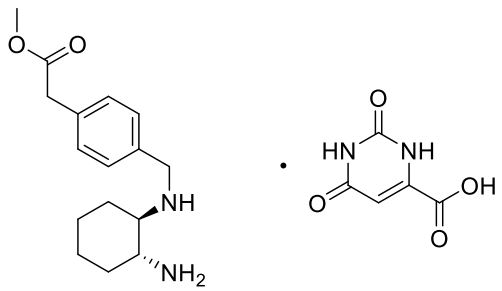
(e) a differential scanning calorimetry thermogram showing an endothermic peak at about 172.8 °C;

(f) a differential scanning calorimetry thermogram substantially the same as shown in FIG. 2;

(g) an ^{1}H nuclear magnetic resonance spectrum with a characteristic peak at about 5.68 ppm; or

(h) an ^{1}H nuclear magnetic resonance spectrum substantially the same as shown in FIG. 3.

[0005j] In another aspect of the present disclosure, there is provided a crystalline salt of a compound with the structure:



Compound 1c orotate

wherein the salt has at least one of:

(a) an X-Ray powder diffraction pattern with characteristic peaks at about 7.2° 2-Theta, about 14.0° 2-Theta, about 15.2° 2-Theta, about 22.7° 2-Theta, and about 25.0° 2-Theta;

(b) an X-Ray powder diffraction pattern substantially the same as the "Orotate Type C" pattern in FIG.1;

(c) a thermo-gravimetric analysis thermogram showing a mass loss of about 2.6% between 20 °C and 150 °C;

(d) a thermo-gravimetric analysis thermogram substantially the same as shown in FIG. 4;

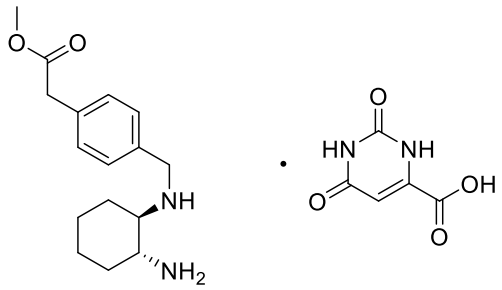
(e) a differential scanning calorimetry thermogram showing an exothermic peak at about 161.7 °C and an endothermic peak at about 182.9 °C;

(f) a differential scanning calorimetry thermogram substantially the same as shown in FIG. 4;

(g) an ^{1}H nuclear magnetic resonance spectrum with a characteristic peak at about 5.69 ppm; and

(h) an ^{1}H nuclear magnetic resonance spectrum substantially the same as shown in FIG. 5.

[0005k] In a further aspect of the present disclosure, there is provided a crystalline salt of a compound with the structure:



Compound 1c orotate

wherein the salt has at least one of:

(a) an X-Ray powder diffraction pattern with characteristic peaks at about .3° 2-Theta, about 7.8° 2-Theta, about 9.7° 2-Theta, about 13.9° 2-Theta, about 16.7° 2-Theta, about 21.4° 2-Theta, about 23.4° 2-Theta;

(b) an X-Ray powder diffraction pattern substantially the same as either "Wet Sample" or "Dry Sample" as shown in FIG.6;

(c) a thermo-gravimetric analysis thermogram showing a mass loss of about 4.8% between 20 °C and 150 °C;

(d) a thermo-gravimetric analysis thermogram substantially the same as shown in FIG. 7;

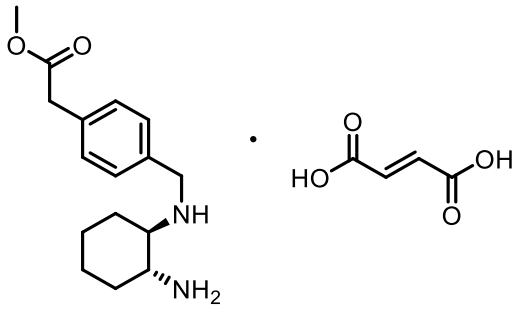
(e) a differential scanning calorimetry thermogram showing an exothermic peak at about 178.1 °C and an endothermic peak at about 185.6 °C;

(f) a differential scanning calorimetry thermogram substantially the same as shown in FIG. 7;

(g) an ^{1}H nuclear magnetic resonance spectrum with a characteristic peak at about 5.68 ppm; and

(h) an ^{1}H nuclear magnetic resonance spectrum substantially the same as shown in FIG. 8.

[0005l] In another aspect of the present disclosure, there is provided a crystallized salt of a compound with the structure:



Compound 1c fumarate

wherein the salt has at least one of:

(a) an X-Ray powder diffraction pattern with characteristic peaks at about 7.9° 2-Theta, about 15.8° 2-Theta, about 18.6° 2-Theta, about 19.3° 2-Theta, about 20.1° 2-Theta, about 21.0° 2-Theta, and about 24.7° 2-Theta;

(b) an X-Ray powder diffraction pattern substantially the same as either “Wet Sample” or “Dry Sample” as shown in FIG.9;

(c) a thermo-gravimetric analysis thermogram showing a mass loss of about 2.4% between 20 °C and 140 °C;

(d) a thermo-gravimetric analysis thermogram substantially the same as shown in FIG. 10;

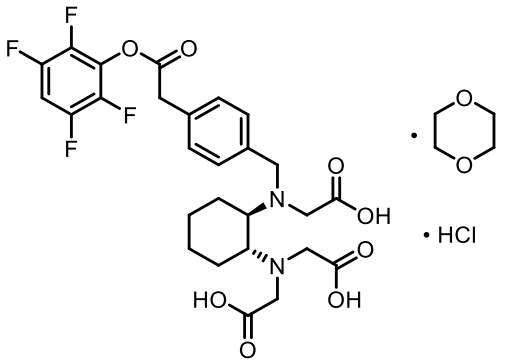
(e) a differential scanning calorimetry thermogram showing an endothermic peak at about 154.7 °C;

(f) a differential scanning calorimetry thermogram substantially the same as shown in FIG. 10;

(g) an ^{1}H nuclear magnetic resonance spectrum with a characteristic peak at about 6.39 ppm; and

(h) an ^{1}H nuclear magnetic resonance spectrum substantially the same as shown in FIG. 11.

[0005m] In a further aspect of the present disclosure, there is provided a crystallized solvate of a salt of a compound with the structure:



Compound 2

wherein the solvate of the salt has at least one of:

(a) an X-Ray powder diffraction pattern with characteristic peaks at about 6.8° 2-Theta, about 17.6° 2-Theta, about 20.3° 2-Theta, about 22.2° 2-Theta, and about 23.3° 2-Theta; and

(b) an X-Ray powder diffraction pattern substantially the same as shown in FIG. 15.

[0005n] In another aspect of the present disclosure, there is provided a restrained complexing agent comprising

(i) a compound prepared using the method disclosed herein; or

(ii) a crystallized salt or solvate disclosed herein.

[0005o] In a further aspect of the present disclosure, there is provided a label moiety comprising a detectable label comprising a metal halide conjugated or chelated to a linker comprising

(i) the compound prepared using the method disclosed herein; or

(ii) a crystallized salt or solvate disclosed herein.

[0005p] In another aspect of the present disclosure, there is provided a label conjugated marker-binder protein comprising a detectable label comprising a metal halide linked to said marker-binder protein by a linker comprising

(i) the compound prepared using the method disclosed herein; or

(ii) a crystallized salt or solvate disclosed herein.

[0005q] In another aspect of the present disclosure, there is provided a method of visualizing a molecule, said method comprising exposing said molecule to a label conjugated marker-binder protein comprising a detectable label comprising a metal halide linked to said marker-binder protein by a linker comprising

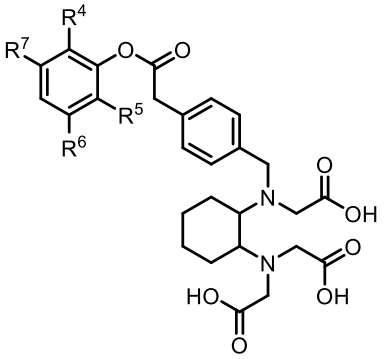
(i) the compound prepared using the method disclosed herein; or

(ii) a crystallized salt or solvate disclosed herein,

wherein said marker-binder protein binds said molecule; and

detecting the label.

[0006] In some examples, provided herein is a method of preparing a compound of Formula (I):

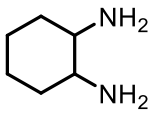


Formula (I)

a diastereomer thereof, a salt thereof, a solvate thereof, or a combination of any of the foregoing,

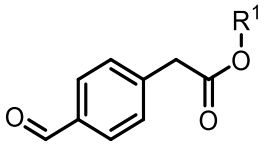
wherein the method comprises:

(a) a step (1-1) comprising reacting a compound of Formula (Ia):



Formula (Ia)

or a diastereomer thereof with a compound of Formula (Ib):



Formula (Ib)

R^1 and R^2 are each independently C_1-C_6 alkyl;

R^3 is halo; and

R^4, R^5, R^6 and R^7 are each independently halo or hydrogen.

[0007] In some examples, the solvent in the step (1-1) comprises an alcohol. In some examples, the solvent is ethanol. In some examples, the reducing agent in the step (1-1) is a hydride. In some examples, the reducing agent is $NaBH(OAc)_3$.

[0008] In some examples, step (1-1) further comprises purifying the compound of Formula (Ic) by column chromatography.

[0009] In some examples, the solvent in the step (1-2) is a polar organic solvent. In some examples, the solvent is CH_3CN. In some examples, the base in the step (1-2) is an organic base. In some examples, the organic base is an amine base. In some examples, the amine base is N,N-diisopropylethylamine (DIPEA).

[0010] In some examples, the step (1-2) further comprises purifying the compound of Formula (1e) by column chromatography.

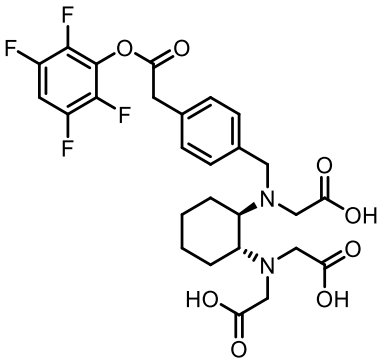
[0011] In some examples, the solvent in the step (1-3) is an aqueous solvent. In some examples, the solvent further comprises tetrahydrofuran (THF). In some examples, the base in the step (1-3) is KOH.

[0012] In some examples, the solvent in the step (1-4) is a halogenated hydrocarbon. In some examples, the solvent is CH_2Cl_2. In some examples, the carboxyl activating reagent is 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI).

[0013] In some examples, the acid in the step (1-5) is trifluoroacetic acid.

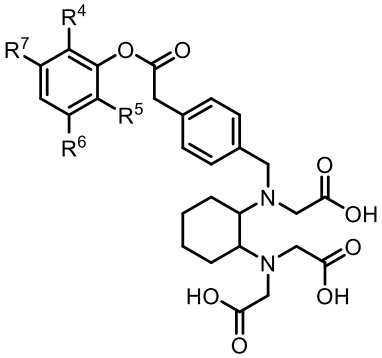
[0014] In some examples, the step (1-5) further comprises purifying the compound of Formula (Ih) by preparative High Performance Liquid Chromatography.

[0015] In some examples of any of the preceding formulae, R^1 is methyl. In some examples, R^2 is tert-butyl. In some examples, R^3 is Br. In some examples, R^4, R^5, R^6 and R^7 are each F. In some examples, the compound of Formula (I) is Compound 1:



Compound 1

[0016] In some examples, provided herein is a method of preparing a compound of Formula (I):

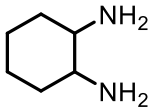


Formula (I)

a diastereomer thereof, a salt thereof, or a solvate thereof, or a combination of any of the foregoing,

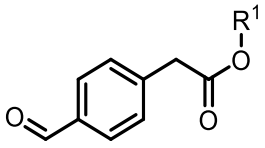
wherein the method comprises:

(a) a step (2-1) comprising reacting a compound of Formula (Ia):



Formula (Ia)

with a compound of Formula (Ib):



Formula (Ib)

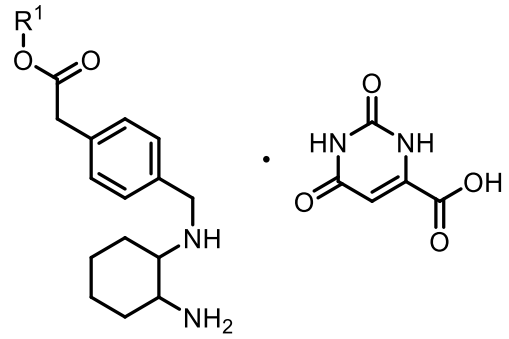
R^1 and R^2 are each independently C_1-C_6 alkyl;

R^3 is halo; and

R^4, R^5, R^6, and R^7 are each independently halo or hydrogen.

[0017] In some examples, the solvent in the step (2-1) comprises an alcohol. In some examples, the alcohol is ethanol. In some examples, the reducing agent in the step (2-1) comprises a hydride. In some examples, the reducing agent is $NaBH(OAc)_3$.

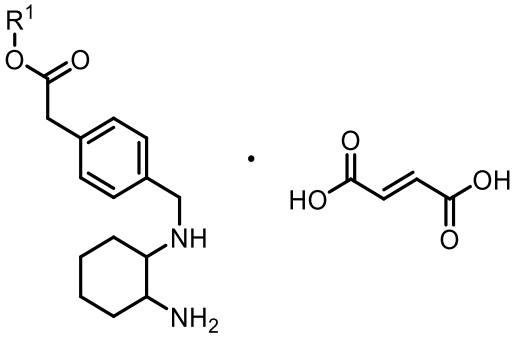
[0018] In some examples, the acid in the step (2-2) is orotic acid. In some examples, the step (2-2) provides a salt of Formula (Ic) having the following structure:



Formula (Ic) orotate

[0019] In some examples, the step (2-2) comprises crystallizing the salt of Formula (Ic), or a diastereomer thereof, as an orotate salt.

[0020] In some examples, the acid in step (2-2) is fumaric acid. In some examples, the step (2-2) provides a salt of Formula (Ic) having the following structure:



Formula (Ic) fumarate

[0021] In some examples, the step (2-2) further comprises crystallizing the salt of Formula (Ic), or a diastereomer thereof, as fumarate salt.

[0022] In some examples, the base in the step (2-3) is K_2CO_3. In some examples, the solvent in the step (2-3) comprises toluene. In some examples, the solvent in the step (2-3) comprises water.

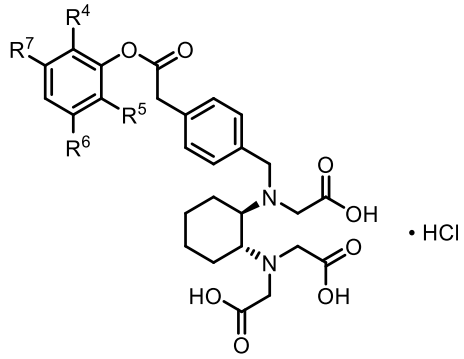
[0023] In some examples, the base in the step (2-4) is KOH. In some examples, the solvent in the step (2-4) comprises THF. In some examples, the solvent in the step (2-4) comprises water.

[0024] In some examples, the step (2-4) provides a salt of Formula (If) as an HCl salt, and wherein the step (2-4) further comprises crystallizing the salt of Formula (If).

[0025] In some examples, the solvent in the step (2-5) is a halogenated hydrocarbon. In some examples, the halogenated hydrocarbon is CH_2Cl_2. In some examples, the carboxyl activating reagent of the step (2-5) is EDCI.

[0026] In some examples, the solvent in the step (2-6) is dioxane. In some examples, the acid in the step (2-6) is HCl.

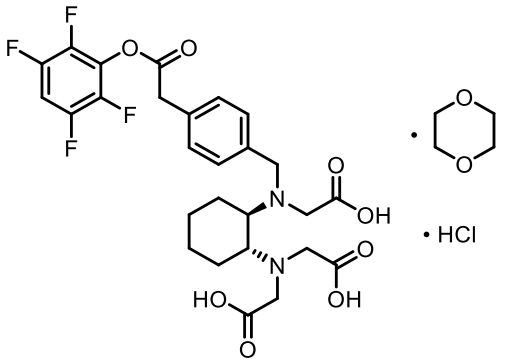
[0027] In some examples, the step (2-6) provides a salt of Formula (I), or a solvate thereof, having the following structure:



Formula (I-1) HCl

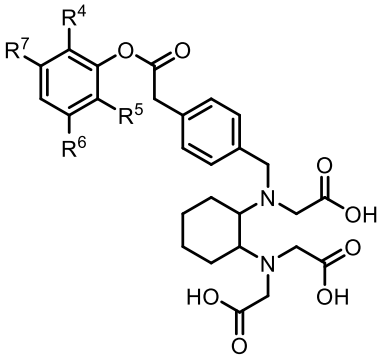
[0028] In some examples, the step (2-6) further comprises crystallizing the salt of Formula (I). In some examples in any of the preceding formulae, R^1 is methyl. In some examples, R^2 is tert-butyl. In some examples, R^3 is Br. In some examples, R^4, R^5, R^6, and R^7 are F.

[0029] In some examples, the salt of the solvate of Formula (I) has the structure:



Compound 2

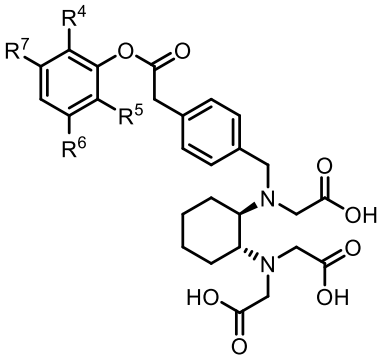
[0030] In some examples, provided herein is a composition comprising one or more diastereomers of compound of Formula (I), salts thereof, or solvates thereof:



Formula (I)

produced by a method as described herein.

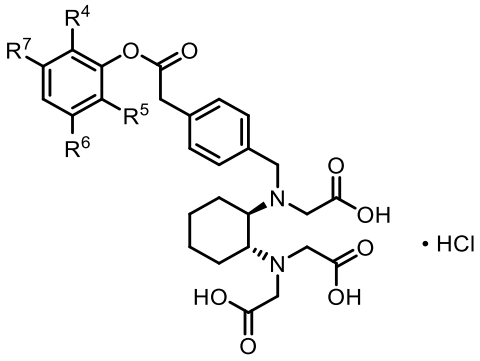
[0031] In some examples, the composition comprises at least about 90 % (weight/weight) of a trans diastereomer of a compound of Formula (I). In some examples, the trans diastereomer has the structure:



Formula (I-1)

[0032] In some examples, R^4, R^5, R^6, and R^7 are F.

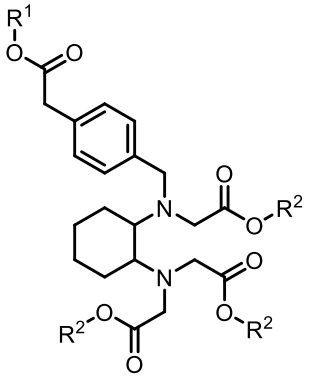
[0033] In some examples, a salt of Formula (I), or a solvate thereof, is provided, wherein the salt of Formula (I) has the structure:



Formula (I-1) HCl

produced by a method as described herein. In some examples, R^4, R^5, R^6, and R^7 are F.

[0034] In some examples, provided herein is a compound of Formula (Ie):

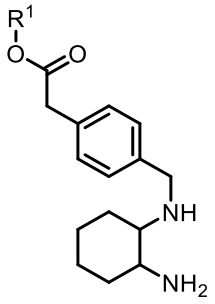


Formula (Ie)

a diastereomer thereof, or a salt thereof,

wherein R^1 and R^2 are each independently C_1-C_6 alkyl.

[0035] In some examples, provided herein is a compound of Formula (Ic):

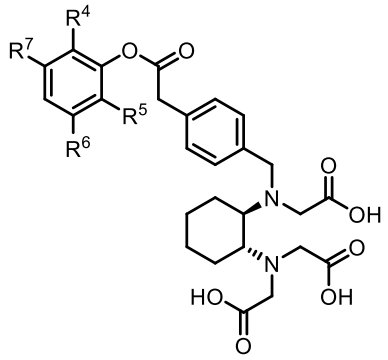


Formula (Ic)

a diastereomer thereof, or a salt thereof,

wherein R^1 is C_1-C_6 alkyl.

[0036] In some examples, provided herein is a composition comprising a complex comprising the compound prepared using a method described herein and a metal halide. In some examples, the metal halide is $\{Al^{18}F\}^{2+}$. In some examples, at least 90% (weight/weight) of the compound in the composition has the following structure:



Formula (I-1)

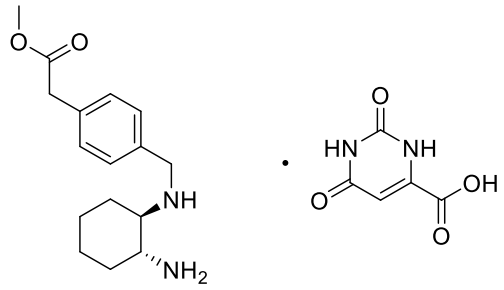
In some examples, R^4, R^5, R^6, and R^7 are F. In some examples, the composition further comprises a polypeptide, wherein the complex is conjugated to the polypeptide. In some examples, the polypeptide is an antibody or antibody fragment. In some examples, the antibody fragment is selected from the group consisting of a VHH, a scFv, a minibody, a Fab, a Fab', and a Fv fragment. In some examples, the polypeptide is a non-antibody scaffold protein. In some examples, the non-antibody scaffold protein is selected from the group consisting of an affibody, an affilin, a knottin, a fibronectin, an anticalin, an atrimer, an avimer, an FN3 scaffold, a fynomer, a Kunitz domain, a pronectin, an OBody, and a DARPin. In some examples, the composition is a pharmaceutical composition suitable for administration to a subject. In some examples, the pharmaceutical composition is suitable for intravenous administration. In some examples, the subject is a human.

[0037] In some examples, provided herein is a method of preparing a labeled agent comprising a polypeptide and a ^{18}F radionuclide, comprising:

(a) contacting the polypeptide with the compound prepared using a method described herein under a condition that allows conjugation of the complex to the polypeptide to provide a conjugate; and

(b) contacting the conjugate with an aluminum fluoride complex comprising ^{18}F to provide the labeled agent.

[0038] In some examples, provided herein is a crystalline salt of a compound with the structure:



Compound 1c orotate

wherein the salt has at least one of:

(a) an X-ray powder diffraction pattern with characteristic peaks at about 7.5° 2-Theta, about 13.9° 2-Theta, about 16.6° 2-Theta, about 23.4° 2-Theta, and about 25.6° 2-Theta;

(b) an X-ray powder diffraction pattern substantially the same as the "Orotate Type A" pattern in FIG. 1;

(c) a thermo-gravimetric analysis thermogram showing a mass loss of about 3.3% between 20 °C and 150 °C;

(d) a thermo-gravimetric analysis thermogram substantially the same as shown in FIG. 2;

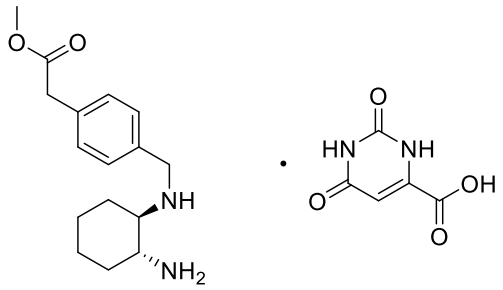
(e) a differential scanning calorimetry thermogram showing an endothermic peak at about 172.8 °C;

(f) a differential scanning calorimetry thermogram substantially the same as shown in FIG. 2;

(g) an ^{1}H nuclear magnetic resonance spectrum with a characteristic peak at about 5.68 ppm; or

(h) an ^{1}H nuclear magnetic resonance spectrum substantially the same as shown in FIG. 3.

[0039] In some examples, provided herein is a crystalline salt of a compound with the structure:



Compound 1c orotate

wherein the salt has at least one of:

(a) an X-Ray powder diffraction pattern with characteristic peaks at about 7.2° 2-Theta, about 14.0° 2-Theta, about 15.2° 2-Theta, about 22.7° 2-Theta, and about 25.0° 2-Theta;

(b) an X-Ray powder diffraction pattern substantially the same as the "Orotate Type C" pattern in FIG.1;

(c) a thermo-gravimetric analysis thermogram showing a mass loss of about 2.6% between 20 °C and 150 °C;

(d) a thermo-gravimetric analysis thermogram substantially the same as shown in FIG. 4;

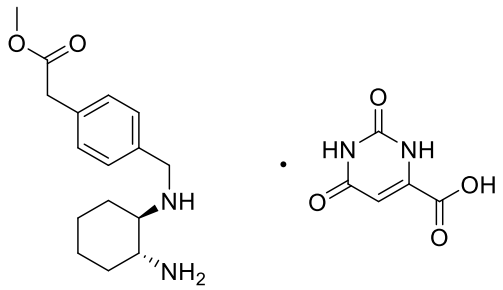
(e) a differential scanning calorimetry thermogram showing an exothermic peak at about 161.7 °C and an endothermic peak at about 182.9 °C;

(f) a differential scanning calorimetry thermogram substantially the same as shown in FIG. 4;

(g) an ^{1}H nuclear magnetic resonance spectrum with a characteristic peak at about 5.69 ppm; and

(h) an ^{1}H nuclear magnetic resonance spectrum substantially the same as shown in FIG. 5.

[0040] In some examples, provided herein is a crystalline salt of a compound with the structure:



Compound 1c orotate

wherein the salt has at least one of:

(a) an X-Ray powder diffraction pattern with characteristic peaks at about .3° 2-Theta, about 7.8° 2-Theta, about 9.7° 2-Theta, about 13.9° 2-Theta, about 16.7° 2-Theta, about 21.4° 2-Theta, about 23.4° 2-Theta;

(b) an X-Ray powder diffraction pattern substantially the same as either "Wet Sample" or "Dry Sample" as shown in FIG.6;

(c) a thermo-gravimetric analysis thermogram showing a mass loss of about 4.8% between 20 °C and 150 °C;

(d) a thermo-gravimetric analysis thermogram substantially the same as shown in FIG. 7;

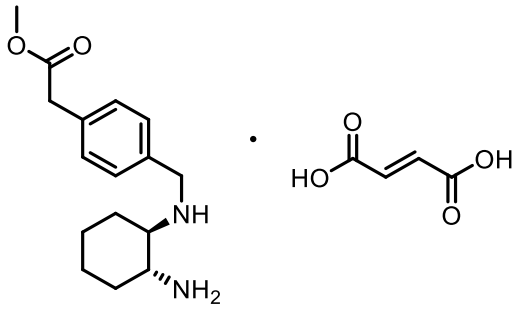
(e) a differential scanning calorimetry thermogram showing an exothermic peak at about 178.1 °C and an endothermic peak at about 185.6 °C;

(f) a differential scanning calorimetry thermogram substantially the same as shown in FIG. 7;

(g) an ^{1}H nuclear magnetic resonance spectrum with a characteristic peak at about 5.68 ppm; and

(h) an ^{1}H nuclear magnetic resonance spectrum substantially the same as shown in FIG. 8.

[0041] In some examples, provided herein is a crystallized salt of a compound with the structure:



Compound 1c fumarate

wherein the salt has at least one of:

(a) an X-Ray powder diffraction pattern with characteristic peaks at about 7.9° 2-Theta, about 15.8° 2-Theta, about 18.6° 2-Theta, about 19.3° 2-Theta, about 20.1° 2-Theta, about 21.0° 2-Theta, and about 24.7° 2-Theta;

(b) an X-Ray powder diffraction pattern substantially the same as either "Wet Sample" or "Dry Sample" as shown in FIG.9;

(c) a thermo-gravimetric analysis thermogram showing a mass loss of about 2.4% between 20 °C and 140 °C;

(d) a thermo-gravimetric analysis thermogram substantially the same as shown in FIG. 10;

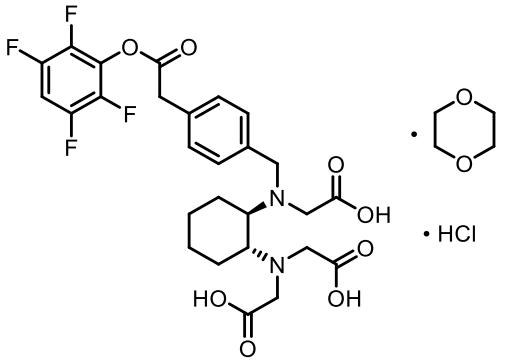
(e) a differential scanning calorimetry thermogram showing an endothermic peak at about 154.7 °C;

(f) a differential scanning calorimetry thermogram substantially the same as shown in FIG. 10;

(g) an ^{1}H nuclear magnetic resonance spectrum with a characteristic peak at about 6.39 ppm; and

(h) an ^{1}H nuclear magnetic resonance spectrum substantially the same as shown in FIG. 11.

[0042] In some examples, provided herein is a crystallized solvate of a salt of a compound with the structure:



Compound 2

wherein the solvate of the salt has at least one of:

(a) an X-Ray powder diffraction pattern with characteristic peaks at about 6.8° 2-Theta, about 17.6° 2-Theta, about 20.3° 2-Theta, about 22.2° 2-Theta, and about 23.3° 2-Theta; and

(b) an X-Ray powder diffraction pattern substantially the same as shown in FIG. 15.

[0043] In some examples, provided herein is a restrained complexing agent comprising

(i) a compound prepared using a method as provided herein; or

(ii) a crystallized salt or solvate as described herein.

[0044] In some examples, provided herein is a label moiety comprising a detectable label comprising a metal halide conjugated or chelated to a linker comprising

(i) the compound prepared using a method as provided herein; or

(ii) a crystallized salt or solvate as described herein.

[0045] In some examples, provided herein is a label conjugated marker-binder protein comprising a detectable label comprising a metal halide linked to said marker-binder protein by a linker comprising

(i) the compound prepared using a method as provided herein; or

(ii) a crystallized salt or solvate as described herein.

[0046] In some examples, provided herein is a method of visualizing a molecule, said method comprising exposing said molecule to a label conjugated marker-binder protein comprising a detectable label comprising a metal halide linked to said marker-binder protein by a linker comprising

(i) the compound prepared using a method as provided herein; or

(ii) a crystallized salt or solvate as described herein,

wherein said marker-binder protein binds said molecule; and

detecting the label.

BRIEF DESCRIPTION OF THE DRAWINGS

[0047] FIG. 1 is a collection of XRPD (X-ray powder diffraction) patterns for samples of a compound of Compound 1c orotate.

[0048] FIG. 2 depicts TGA (thermos-gravimetric analysis) and DSC (differential scanning calorimetry) thermograms for a compound of Compound 1c orotate (Orotate Type A).

[0049] FIG. 3 is an ^{1}H NMR (nuclear magnetic resonance) spectrum of Compound 1c orotate (Orotate Type A).

[0050] FIG. 4 depicts TGA and DSC thermograms for Compound 1c orotate (Orotate Type C).

[0051] FIG. 5 is an ^{1}H NMR spectrum of Compound 1c orotate (Orotate Type C).

[0052] FIG. 6 is a collection of XRPD patterns for samples Compound 1c orotate (re-prepared Orotate Type A).

[0053] FIG. 7 depicts TGA and DSC thermograms for Compound 1c orotate (re-prepared Orotate Type A).