previously as aids in inhibiting radiolysis of radiopharmaceuticals (see, for example, Tofe AJ, et al., *J. Nucl Med*, 17, 820-825, 1976; Knapp FF, et al., *Anticancer Res* 17, 1783-1795, 1997; Liu S, et al., *Bioconj Chem*, 14, 1052-1056, 2003), including F-18 radiopharmceuticals, see, for example, Firnau G, et al., *J Nucl Med*, 25, 1228-1233, 1984). However, the use of ascorbate salts in an aqueous-ethanol solution as a preferred medium for both solubilization and stabilization of an F-18 brain imaging radiopharmaceutical, such as ^{18}F-AV-45, is new.

[0013] The use of a precursor containing a tosylate group for reaction with F-18 fluoride in the production of F-18-containing radiopharmaceuticals has been previously described (see, for example, Zhang W, et al., *Nucl Med Biol* 34, 89-97, 2007). However, an efficient synthetic process for producing larger (*i.e.*, >10gm) quantities of the tosylate precursor (referred to as "AV-105" herein) has not been described previously. Each of the publications cited herein are hereby incorporated by reference in their respective entireties to the extent such references are not inconsistent with the explicit teachings of this specification.

SUMMARY ~~OF THE INVENTION~~

[0013a] In a first aspect, there is provided a radiopharmaceutical composition for positron emission tomography (PET) imaging of neurodegenerative diseases of the brain comprising:

^{18}F-radiolabeled compound, wherein the ^{18}F-radiolabeled compound is ((E)-4-(2-(6-(2-(2-(2-[^{18}F]fluoroethoxy)ethoxy)ethoxy)pyridin-3-yl)vinyl)-*N*-methylbenzenamine (^{18}F-AV-45);

10% (v/v) of ethyl alcohol; and

90% v/v of 0.9% w/v saline solution, wherein said saline solution comprises 0.5% w/v sodium ascorbate.

[0014] Embodiments of the disclosure~~invention~~ are directed to a radiopharmaceutical composition for positron emission tomography (PET) imaging of neurodegenerative diseases of the brain comprising an effective amount of an ^{18}F-radiolabeled compound, about 1.0% to about 20% (v/v) of ethyl alcohol, and at least about 0.1% (w/v) of ascorbic acid or a salt thereof. In various embodiments, the ^{18}F-radiolabeled compound is capable of binding to a pathologic target in the brain of a patient. The pathologic target may include an abnormal concentration of a native or pathologically-altered protein, peptide or oligonucleotide; β-amyloid; α-synuclein; or vesicular monoamine transporter 2 (VMAT2).

[0015] According to some embodiment~~aspects~~ of the disclosure~~invention~~, the ^{18}F-radiolabeled compound is a styrylpyridine derivative. In various embodiment~~aspects~~, the ^{18}F-radiolabeled compound is ((*E*)-4-(2-(6-(2-(2-(2-[^{18}F]fluoroethoxy)ethoxy)ethoxy)pyridin-3-yl)vinyl)-*N*-methylbenzenamine) (^{18}F-AV-45). In some embodiments, the ^{18}F-AV-45 is produced from a tosylate precursor. In other embodiment~~aspects~~, the ^{18}F-radiolabeled compound in the radiopharmaceutical composition is (2*R*,3*R*,11b*R*)-9-(3-[^{18}F]Fluoropropoxy)-3-isopropyl-10-methoxy-11b-methyl-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-*a*]isoquinolin-2-ol ("^{18}F-AV-133"). In still other embodiment~~aspects~~, the ^{18}F-radiolabeled compound is a derivative of dihydrotetrabenazine (DTBZ).

[0016] The radiopharmaceutical composition of some embodiments includes an ethyl alcohol concentration in the range of about 1.0% to about 15.0% (v/v). Other embodiments include a concentration of ascorbic acid or salt thereof in the range of about

0.1% to about 1.0% (w/v). The pH of the radiopharmaceutical composition can range from about 4.5 to about 8.0. In preferred embodiments, the purity of the radiopharmaceutical composition is greater than or equal to about 90% when measured at least about 4 hours post end-of-synthesis (EOS).

[0017] The radiopharmaceutical composition can be used in the diagnosis of neurodegenerative disease such as, for example, dementia, cognitive impairment, Alzheimer's Disease (AD), Parkinson's Disease (PD), Dementia with Lewy Bodies (DLB), Vascular Dementia (VaD) and combinations thereof.

[0017a] In a second aspect, there is provided a radiopharmaceutical composition for positron emission tomography (PET) imaging comprising:

^{18}F-radiolabeled compound, wherein the ^{18}F-radiolabeled compound is (2R,3R,11bR)-9-(3-[^{18}F]fluoropropoxy)-3-isopropyl-10-methoxy-11b-methyl-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinolin-2-01 (^{18}F-AV-133);

10% (v/v) of ethyl alcohol; and

90% v/v of 0.9% w/v saline solution, wherein said saline solution comprises 0.5 w/v sodium ascorbate.

[0018] Other embodiments of the disclosure~~invention~~ are directed to a radiopharmaceutical composition for positron emission tomography (PET) imaging of the brain comprising an effective amount of an ^{18}F-radiolabeled compound, at least about 1.0% (v/v) of ethyl alcohol, and at least about 0.1% (w/v) of an ascorbate salt, wherein the ^{18}F-radiolabeled compound decomposes less than about 10% from the end-of-synthesis to about 12 hours after the end-of-synthesis.

[0019] In another embodiment~~aspect~~ of the disclosure~~invention~~, a method is provided for diagnosing a neurodegenerative disease in a patient comprising the steps of administering a radiopharmaceutical composition capable of binding to a target associated with a neurodegenerative disease to a patient, wherein said radiopharmaceutical composition includes an effective amount of ^{18}F-radiolabeled compound, at least about 1.0% (v/v) of ethyl alcohol, and at least about 0.1% (w/v) sodium ascorbate; imaging at least a portion of the patient's brain including a region wherein the target is expected to be positioned; and detecting the target. The imaging step may be performed using positron emission tomography (PET) imaging, PET with concurrent computed tomography imaging (PET/CT), PET with concurrent magnetic resonance imaging (PET/MRI) or a combination thereof.

[0019a] In a third aspect, there is provided a method of producing the radiopharmaceutical composition as defined above, comprising the steps of:

preparing a mono Boc-protected vinylaniline compound;

converting the vinylaniline compound to a methyl, t-butyl carbamate derivative;

reacting 2-halo 5-iodopyridine with triethyleneglycol;

reacting the methyl, t-butyl carbamate derivative with the resultant compound of the step of reacting 2-halo 5-iodopyridine with triethyleneglycol to produce (*E*)-*tert*-Butyl 4-(2-(6-(2-(2-(2-hydroxyethoxy)ethoxy)ethoxy)pyridin-3 yl)vinyl)phenyl(methyl)carbamate; and

reacting the (*E*)-*tert*-Butyl 4-(2-(6-(2-(2-(2-hydroxyethoxy)ethoxy)ethoxy)pyridin-3-yl)vinyl)phenyl(methyl)carbamate with tosyl chloride to form (*E*)-2-(2-(2-(5-(4-(*tert*-butoxycarbonyl(methyl)amino)styryl)pyridin-2-yloxy)ethoxy)ethoxy)ethyl 4-methylbenzene sulfonate;

reacting (*E*)-2-(2-(2-(5-(4-(*tert*-butoxycarbonyl(methyl)amino)styryl)pyridin-2-yloxy)ethoxy)ethoxy)ethyl 4-methylbenzene sulfonate and an ^{18}F-fluoride ion in dimethylsulfoxide (DMSO) solution or high-boiling point aprotic solvent to produce ((*E*)-4-(2-(6-(2-(2-(2-[^{18}F]fluoroethoxy)ethoxy)ethoxy)pyridin-3-yl)vinyl)-*N*-methylbenzenamine);

isolating the ((*E*)-4-(2-(6-(2-(2-(2-[^{18}F]fluoroethoxy)ethoxy)ethoxy)pyridin-3-yl)vinyl)-*N*-methylbenzenamine);

purifying the ((*E*)-4-(2-(6-(2-(2-(2-[^{18}F]fluoroethoxy)ethoxy)ethoxy)pyridin-3-yl)vinyl)-*N*-methylbenzenamine); and

formulating the ((*E*)-4-(2-(6-(2-(2-(2-[^{18}F]fluoroethoxy)ethoxy)ethoxy)pyridin-3-yl)vinyl)-*N*-methylbenzenamine) in an aqueous-ethyl alcohol solution containing 10% (v/v) of ethyl alcohol; and 90% v/v of 0.9% (w/v) saline solution, wherein said saline solution comprises 0.5% w/v sodium ascorbate.

[0020] In yet another embodiment of the disclosure~~invention~~, a method is provided for producing an ^{18}F-radiolabeled composition capable of binding to β-amyloid including the steps of synthesizing a tosylate precursor; performing nucleophilic ^{18}F fluorination of the tosylate precursor in a dimethylsulfoxide (DMSO) solution to provide an ^{18}F radiopharmaceutical; and formulating the ^{18}F radiopharmaceutical in an aqueous-ethyl alcohol solution containing ascorbic acid or a salt thereof; wherein the ethyl alcohol is present at a minimum concentration of about 1.0% (v/v) and the minimum concentration of the ascorbic acid or salt thereof is about 0.1% (w/v) in the final ^{18}F-radiolabeled pharmaceutical composition.

[0021] In another embodiment, a method of producing the tosylate precursor of ^{18}F-AV-45,(*E*)-2-(2-(2-(5-(4-(*tert*-butoxycarbonyl(methyl)amino)styryl)pyridin-2-yloxy)ethoxy) ethoxy)ethyl 4-methylbenzenesulfonate ("AV-105"), is provided. This method includes the steps of (i) preparing a mono Boc-protected vinylaniline compound; (ii) converting the vinylaniline compound to a methyl, t-butyl carbamate derivative; (iii) reacting 2-halo 5-iodopyridine with triethyleneglycol; (iv) reacting the methyl, t-butyl carbamate derivative of step (ii) with the resultant compound of step (iii) to produce (*E*)-*tert*-Butyl 4-(2-(6-(2-(2-(2-hydroxyethoxy)ethoxy)ethoxy)pyridin-3-yl)vinyl)phenyl(methyl)carbamate; and (v) reacting the (*E*)-*tert*-Butyl 4-(2-(6-(2-(2-(2-hydroxyethoxy)ethoxy)ethoxy)pyridin-3-yl)vinyl)phenyl(methyl)carbamate with tosyl chloride to form AV-105.

[0022] In still another embodiment~~aspect~~ of the disclosure~~invention~~, a method of producing a radiopharmaceutical composition is provided including reacting the AV-105 tosylate precursor with an ^{18}F-fluoride ion in dimethylsulfoxide (DMSO) solution or other high-boiling point aprotic solvent to produce ((*E*)-4-(2-(6-(2-(2-(2-[^{18}F]fluoroethoxy)ethoxy)ethoxy)pyridin-3-yl)vinyl)-*N*-methylbenzenamine) (^{18}F-AV-45); isolating the ^{18}F-AV-45; and purifying the ^{18}F-AV-45. The method of producing the radiopharmaceutical composition may further include the step of formulating the ^{18}F-AV-45 in a solution containing about 1.0% to about 15% (v/v) of ethyl alcohol and about 0.1% to about 1.0% (w/v) of an ascorbate salt. In particular embodiments of the disclosure~~invention~~, the ascorbate salt is sodium ascorbate and the concentration is about 0.5% (w/v).

[0023] The above summary is not intended to describe each illustrated embodiment or every implementation of the present disclosure~~invention~~.

BRIEF DESCRIPTION OF THE FIGURES

[0024] For a better understanding of the disclosure, reference should be made to the following figures, in which:

[0025] **FIG. 1** shows a schematic of the synthesis of tosylate precursor AV-105 and the synthesis of non-radioactive ^{19}F-AV-45 from *p*-toluenesulfonate according to one embodiment of the invention;

[0026] **FIG. 2** shows an alternative synthesis method for tosylate precursor AV-105 according to another embodiment of the invention; and

[0027] **FIG. 3** depicts a radiosynthesis method of one aspect of the invention using a tosylate precursor to produce β-amyloid binding radiopharmaceutical ^{18}F-AV-45.

8. A radiopharmaceutical composition for positron emission tomography (PET) imaging comprising:

^{18}F-radiolabeled compound, wherein the ^{18}F-radiolabeled compound is (2R,3R,11bR)-9-(3-[^{18}F]fluoropropoxy)-3-isopropyl-10-methoxy-11b-methyl-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinolin-2-01 (^{18}F-AV-133);

10% (v/v) of ethyl alcohol; and

90% v/v of 0.9% w/v saline solution, wherein said saline solution comprises 0.5 w/v sodium ascorbate.

~~9. A compound of the formula:~~

