



(43) International Publication Date
21 November 2013 (21.11.2013)

(10) International Publication Number
WO 2013/173630 A1

- (51) **International Patent Classification:**
C07B 59/00 (2006.01) *C07F 9/22* (2006.01)
- (21) **International Application Number:**
PCT/US2013/041427
- (22) **International Filing Date:**
16 May 2013 (16.05.2013)
- (25) **Filing Language:** English
- (26) **Publication Language:** English
- (30) **Priority Data:**
12168377.5 16 May 2012 (16.05.2012) EP
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- (81) **Designated States** (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY,

BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

- (84) **Designated States** (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- *with international search report (Art. 21(3))*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(54) **Title:** FORMULATION OF RADIOPHARMACEUTICALS CONTAINING MULTIPLE ACIDIC GROUPS

(57) **Abstract:** The invention relates to the subject matter referred to in the claims, i.e. surprisingly rapid and simple reformulation of very polar radiopharmaceuticals containing multiple acidic functional groups to solutions suitable for injecting into mammals.



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Formulation of radiopharmaceuticals containing multiple acidic groups

Field of Invention

This invention relates to methods for allowing very polar radiopharmaceuticals to be rapidly converted to solutions ready for injection. This method is suitable for radiopharmaceuticals containing multiple acidic and/or phosphonic acid functional groups.

Background

The invention relates to the subject matter referred to in the claims, i.e. rapid robust formulation of very polar radiopharmaceuticals containing multiple acidic functional groups.

Molecular imaging has the potential to detect disease progression or therapeutic effectiveness earlier than most conventional methods in the fields of oncology, neurology and cardiology. Of the several promising molecular imaging technologies having been developed as optical imaging and MRI, PET is of particular interest for drug development because of its high sensitivity and ability to provide quantitative and kinetic data.

Positron emitting isotopes include carbon, nitrogen, and oxygen. These isotopes can replace their non-radioactive counterparts in target compounds to produce tracers that function biologically and are chemically identical to the original molecules for PET imaging. On the other hand, ^{18}F is the most convenient labelling isotope due to its relatively long half-life (109.6 min) which permits the preparation of diagnostic tracers and subsequent study of biochemical processes. In addition, its high β^+ yield and low β^+ energy (635 keV) are also advantageous.

In the preparation of radiopharmaceuticals the final step of the process is to ensure that the said radiopharmaceutical is suitable for injecting into mammals, e.g. have a suitable pH, osmolality, etc. Typically in the radiosyntheses of radiopharmaceuticals a purification step using high pressure liquid chromatography (HPLC) is used. This HPLC purification step uses toxic or potentially toxic substances, e.g. acetonitrile, methanol, trifluoroacetic acid, formic acid etc., and steps have to be taken to ensure these toxic or potentially toxic substances are removed. The process of taking a HPLC purified solution of the said radiopharmaceutical which contains toxic or potentially toxic substance and converting it into a solution suitable for injecting into mammals is typically referred to as a "reformulation step". This reformulation step is well known for lipophilic compounds as the HPLC purified solution of the said radiopharmaceutical containing the toxic or potentially toxic substances can be diluted with water passed through a silica or polymer based resin functionalized with carbon chains, e.g.

C-18 (octadecyl) solid phase extraction (SPE) cartridge where the said radiopharmaceutical is retained due to the lipophilic character of the said radiopharmaceutical. The toxic or potentially toxic substances are then washed from the SPE cartridge by various washing steps and the desired radiopharmaceutical is eluted from the SPE using a solution which upon dilution is suitable for injecting into mammals, typically ethanol is used and then diluted with saline or phosphate buffered saline (PBS).

For polar compounds ($\log D < 1$) is reformulation step by taken the HPLC purified fraction of the said radiopharmaceutical and concentrating it under reduced pressure or blowing dry under a gas stream at elevated temperatures. This procedure has been successfully used for amino acid imaging agent, D-fluoromethyl tyrosine (DFMT, Tsukada et al., Eur. J. Nuc. Med. Mol. Imag. 2006, 33, 1017-1024), where the final product is concentrated under reduced pressure, which is a time-consuming step, and then redissolved in saline to give the formulated product. Other examples for polar compounds containing multiple carboxylic acid functional groups are glutamate-hetero urea dimers which are imaging agents that target Prostate Specific Membrane Antigen (PSMA). The glutamate-hetero urea N- [N-[(S)-1,3-dicarboxypropyl]carbamoyl]-4-[^{18}F]fluorobenzyl-L-cysteine (DCFBC, Mease et al., Clin Cancer Res. 2008, 14, 3036-3043) where the HPLC purified radiopharmaceutical was concentrated under reduced pressure and then redissolved in saline to give the formulated product. Another glutamate-hetero urea is 2-[3-[1-Carboxy-5-(4-[^{18}F]fluoro-benzoylamino)-pentyl]-ureido]-pentanedioic Acid (Chen et al., J. Med. Chem., 2008, 51, 7933-7943) where the HPLC purified radiopharmaceutical was also purified under reduced pressure. The major drawback with this concentration step is whether all traces of the toxic or potentially toxic additives, i.e. acetonitrile. Trifluoroacetic acid, are really fully removed.

Problem to be solved by the invention and its solution

Despite the aforementioned advances in reformulation methods, there is relatively little known for the reformulation of very polar compounds ($\log D < 0$), especially those very polar radiopharmaceuticals that contain multiple acidic functional groups, for example carboxylic acid or phosphonic acid moieties. For the said radiopharmaceuticals containing multiple acidic functional groups, the reformulation step is typically carried out by concentration either under vacuum or under a stream of nitrogen or helium. This step can be relatively time consuming as one must ensure that all the traces of the toxic or potentially toxic substances are removed. Time consuming steps are to be avoided in the syntheses of radiopharmaceuticals especially those containing positron emitting (PET) radioisotopes as they are not compatible with the half-life of short-lived radioisotopes, e.g. C-11 (20 mins), F-18 (110 mins), Tc-99m (6 h), I-123 (13.2 h), etc.

The reformulations methods for obtaining reformulated radiopharmaceutical solution as

disclosed in the present invention allow for a surprisingly rapid and simple reformulation of very polar radiopharmaceuticals containing multiple acidic functional groups wherein the obtained solution is suitable for injecting into mammals.

5 **Summary**

The invention relates to the subject matter referred to in the claims, i.e. surprisingly rapid and simple reformulation of very polar radiopharmaceuticals containing multiple acidic functional groups to solutions suitable for injecting into mammals.

10 In a first aspect, the invention is directed to a method for reformulation of a radiopharmaceutical, wherein the radiopharmaceutical comprises two or more carboxylic acid groups and/or one or more phosphonic acid. In embodiments of the first aspect, the radiopharmaceutical is a compound of formula (I), (II) or mixture thereof.

In a second aspect, the invention is directed to a reformulated radiopharmaceutical solution.

In a third aspect, the invention is directed to a kit comprising

- 15 - an anionic exchange resin cartridge, and
 - a vial containing an Elution solvent comprising sodium chloride (NaCl)
 characterised in that the kit is useful for conducting the method of the first aspect.

20 **Description**

In a **first aspect**, the invention is directed to a method for reformulation of a radiopharmaceutical, wherein the radiopharmaceutical comprises two or more carboxylic acid groups and/or one or more phosphonic acid, comprising the step of:

- Eluting the radiopharmaceutical from an anionic exchange resin cartridge with an
25 elution solvent comprising sodium chloride (NaCl).

Preferred features:

Preferably, the radiopharmaceutical comprises one (1) to ten (10) carboxylic acid groups and/or one (1) to five (5) phosphonic acid. More preferably, the radiopharmaceutical
30 comprises two (2) to five (5) carboxylic acid groups and/or one (1) or two (2) phosphonic acid groups. Even more preferably, the radiopharmaceutical comprises three (3) or four (4) carboxylic acid groups and/or one (1) or two (2) phosphonic acid groups. Even more preferably, the radiopharmaceutical comprises four (4) carboxylic acid groups and one (1) phosphonic acid.

35

Preferably, the radiopharmaceutical comprises one (1) to ten (10) carboxylic acid groups. More preferably, the radiopharmaceutical comprises one (1) to five (5) carboxylic acid

groups. Even more preferably, the radiopharmaceutical comprises three (3) or four (4) carboxylic acid groups. Even more preferably, the radiopharmaceutical comprises three (3) carboxylic acid groups.

5 Preferably the anionic exchange resin is a silica based or polymer based weak anionic exchange resin, a medium anionic exchange resin or a strong anionic exchange resin or the anionic exchange resin is a silica based or polymer based mixed mode weak anionic exchange resin or strong anionic exchange resin. More preferably the anionic exchange resin is a silica based or polymer based strong anionic exchange resin (SAX – e.g. Sep-Pak Accell
10 Plus QMA, Cleanert SAX, LC-SAX, AccuBOND SAX, Bond Elut SAX etc.) or a mixed mode silica based or polymer based strong anionic exchange resin (MAX – Bond Elut Certify II, Chormabond Drug II, Screen-A, Chromabond HR-XA, Cleanert PAX, Oasis MAX etc.). Even more preferably, the anionic exchange resin is a silica based or polymer based strong anionic resin. Even more preferably the anionic exchange resin is a quaternary alkylated
15 ammonium resin. Even more preferably the anionic exchange resin is a quaternary trimethylated ammonium exchange resin. Even more preferably the anionic exchange resin is a quaternary trimethylammonium exchange resin, wherein the trimethylammonium moiety is connected via a propyl linker to an acrylamide copolymer on diol silica that is commercially available as Sep-Pak Accell Plus QMA Plus Short cartridges.

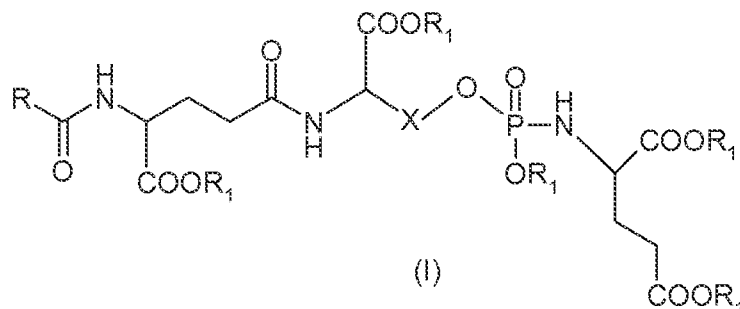
20 Preferably, the elution solvent comprises pharmaceutically acceptable sodium salt at the concentration of 2 M to 0.3 M of the said pharmaceutically acceptable sodium salt. More preferably, the elution solvent comprises pharmaceutically acceptable sodium salt at the concentration of 1 M to 0.3 M of the said pharmaceutically acceptable sodium salt. Even
25 more preferably, the elution solvent comprises pharmaceutically acceptable sodium salt at the concentration of 0.8 M to 0.3 M of the said pharmaceutically acceptable sodium salt. Even more preferably, the Elution solvent comprises pharmaceutically acceptable sodium salt at the concentration of 0.5 M of the said pharmaceutically acceptable sodium salt.

30 As a preferred feature, the invention method for reformulation of a radiopharmaceutical comprises additionally the following steps before eluting:

- Diluting the fraction obtained from the HPLC that contains the purified radiopharmaceutical with an aqueous solution comprising of a base, and
- Trapping the purified radiopharmaceutical on an anionic exchange resin cartridge.

35 In a **first embodiment**, the invention is directed to a method for reformulation of a radiopharmaceutical, comprising the step of:

- Eluting the radiopharmaceutical from an anionic exchange resin cartridge with an elution solvent comprising sodium chloride (NaCl),
wherein the radiopharmaceutical is a compound of formula (I),



- 5 wherein
- R is a radiolabeled pendant group,
- each R₁ is independently from each other hydrogen or a pharmaceutically acceptable salt, and
- X is CH₂ or CH₂-CH₂.

10

In an embodiment of the method, the method for reformulation of a radiopharmaceutical comprises additionally the following steps before eluting:

- Diluting the fraction obtained from the HPLC that contains the purified radiopharmaceutical with an aqueous solution comprising of a base, and
- 15 - Trapping the purified radiopharmaceutical on an anionic exchange resin cartridge,
wherein the radiopharmaceutical is a compound of formula (I).

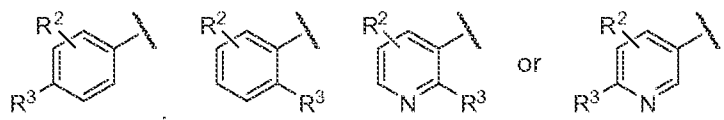
In an embodiment of formula (I), X is CH₂.

- 20 In an embodiment of formula (I), X is CH₂-CH₂.

In an embodiment of formula (I), R is phenyl or pyridyl, each substituted with r one [¹⁸F]-fluoro group and optionally substituted with a second group selected from the group consisting of chloro and cyano.

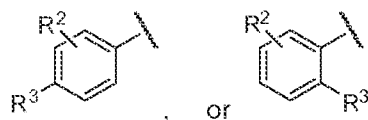
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In an embodiment of formula (I), R is



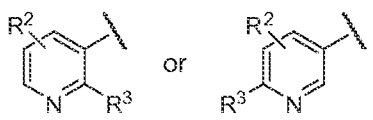
wherein R³ is -¹⁸F; and R² is chloro or cyano.

In an embodiment of formula (I), R is



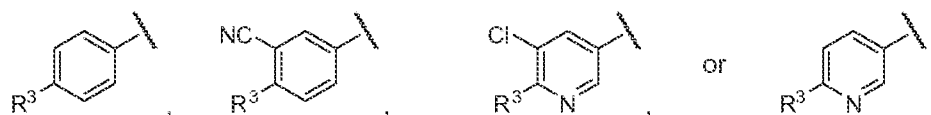
wherein R^3 is ^{-18}F ; and R^2 is chloro or cyano.

5 In an embodiment of formula (I), R is



wherein R^3 is ^{-18}F ; and R^2 is chloro or cyano.

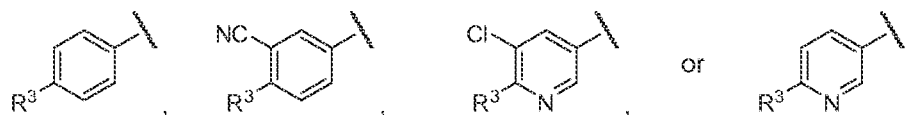
In an embodiment of formula (I), R is



wherein R^3 is ^{-18}F .

10

In an embodiment of formula (I), R is



wherein R^3 is ^{-18}F .

In another embodiment of formula (I), R is

In another embodiment of formula (I), R is

15 In another embodiment of formula (I), R is

In another embodiment of formula (I), R is

In an embodiment of formula (I), R^1 is hydrogen.

In an embodiment of formula (I), R¹ is a pharmaceutically acceptable salt.

In another embodiment, the compound of formula (I) is

SFB-[¹⁸ F]CTT54	N-(4-[¹⁸ F]fluorobenzoyl)-L-gamma-glutamyl-O-[[[(1S)-1,3-dicarboxypropyl]amino](hydroxy)phosphoryl]-L-serine	
[¹⁸ F]CTT1143 [¹⁸ F]F,CNBz-hCTT54;	(N-(3-cyano-4-[¹⁸ F]fluorobenzoyl)-L-γ-glutamyl)-O-[[[(1S)-1,3-dicarboxypropyl]amino](hydroxy)phosphoryl]-L-homoserine	
[¹⁸ F]SFB-hCTT54;	(N-(4-[¹⁸ F]fluorobenzoyl)-L-γ-glutamyl)-O-[[[(1S)-1,3-dicarboxypropyl]amino](hydroxy)phosphoryl]-L-homoserine	
[¹⁸ F]-SFN-hCTT54;	(N-(6-[¹⁸ F]fluoro-pyrid-3-yl)carbonyl-L-γ-glutamyl)-O-[[[(1S)-1,3-dicarboxypropyl]amino](hydroxy)phosphoryl]-L-homoserine	
[¹⁸ F]-SClFN-hCTT-54;	(N-(5-chloro-6-[¹⁸ F]fluoro-pyrid-3-yl)carbonyl-L-γ-glutamyl)-O-[[[(1S)-1,3-dicarboxypropyl]amino](hydroxy)phosphoryl]-L-homoserine	

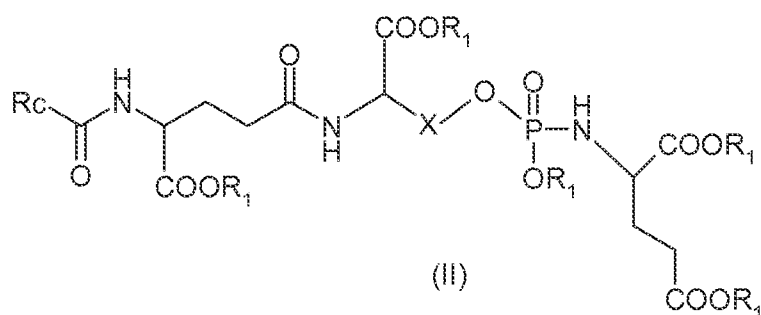
5 or a pharmaceutically acceptable salts thereof.

In a **second embodiment** the invention is directed to a method for reformulation of a radiopharmaceutical, comprising the step of:

- Eluting the radiopharmaceutical from an anionic exchange resin cartridge with an elution solvent comprising sodium chloride (NaCl),

10

wherein the radiopharmaceutical is a compound of formula (II),



wherein

R_c is the cold counter-part of a radiolabeled pendant group,

each R₁ is independently from each other hydrogen or a pharmaceutically acceptable salt, and

X is CH₂ or CH₂-CH₂.

In an embodiment of the method, the method for reformulation of a radiopharmaceutical comprises additionally the following steps before eluting:

- Diluting the fraction obtained from the HPLC that contains the purified radiopharmaceutical with an aqueous solution comprising of a base, and
- Trapping the purified radiopharmaceutical on an anionic exchange resin cartridge,

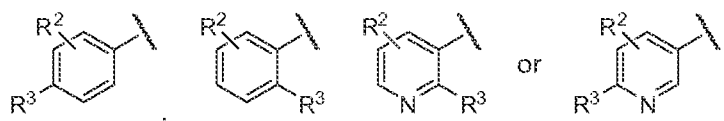
wherein the radiopharmaceutical is a compound of formula (II).

In an embodiment of formula (II), X is CH₂.

In an embodiment of formula (II), X is CH₂-CH₂.

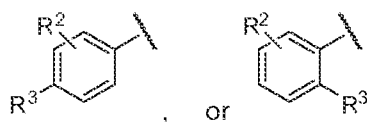
In an embodiment of formula (II), R is phenyl or pyridyl, each substituted with one [F]-fluoro group and optionally substituted with a second group selected from the group consisting of chloro and cyano.

In an embodiment of formula (II), R is



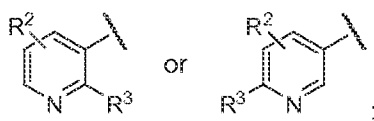
wherein R³ is -F; and R² is chloro or cyano.

In an embodiment of formula (II), R is



wherein R^3 is $-F$; and R^2 is chloro or cyano.

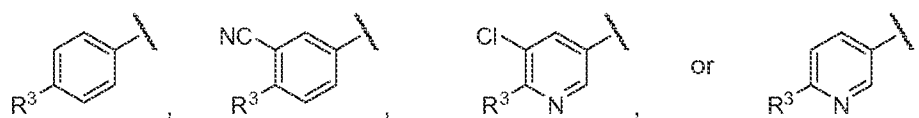
In an embodiment of formula (II), R is



wherein R^3 is $-F$; and R^2 is chloro or cyano.

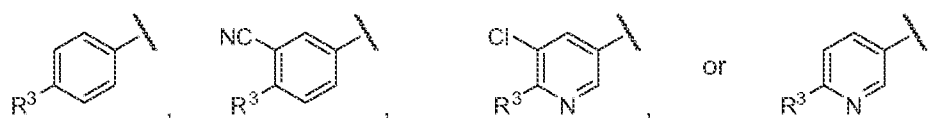
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In an embodiment of formula (II), R is



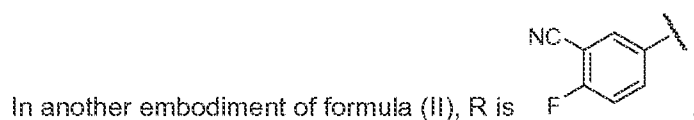
wherein R^3 is $-F$.

In an embodiment of formula (II), R is

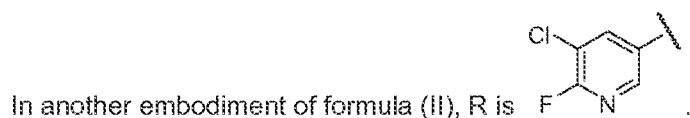


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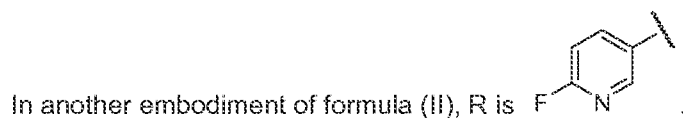
wherein R^3 is $-F$.



In another embodiment of formula (II), R is



In another embodiment of formula (II), R is



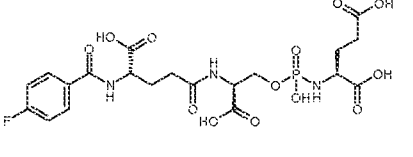
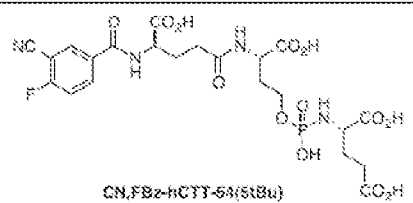
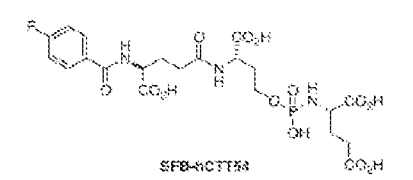
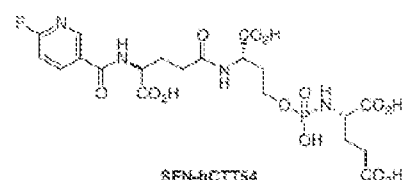
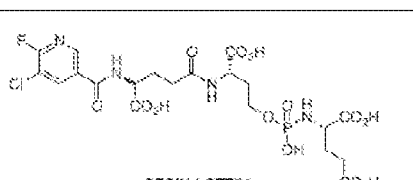
In another embodiment of formula (II), R is

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In an embodiment of formula (II), R^1 is hydrogen.

In an embodiment of formula (II), R^1 is pharmaceutically acceptable salt.

In another embodiment, the compound of formula (II) is

SFB-F-CTT54	N-(4-fluorobenzoyl)-L-gamma-glutamyl-O-[[[(1S)-1,3-dicarboxypropyl]amino](hydroxy)phosphoryl]-L-serine	
CTT1143 = F,CNBz-hCTT54;	(N-(3-cyano-4-fluorobenzoyl)-L-γ-glutamyl)-O-[[[(1S)-1,3-dicarboxypropyl]amino](hydroxy)p hosphoryl]-L-homoserine	
SFB-hCTT54;	(N-(4-fluorobenzoyl)-L-γ-glutamyl)-O-[[[(1S)-1,3-dicarboxypropyl]amino](hydroxy)p hosphoryl]-L-homoserine	
SFN-hCTT54;	(N-(6-fluoro-pyrid-3-yl)carbonyl-L-γ-glutamyl)-O-[[[(1S)-1,3-dicarboxypropyl]amino](hydroxy)p hosphoryl]-L-homoserine	
SCIFN-hCTT-54;	(N-(5-chloro-6-fluoro-pyrid-3-yl)carbonyl-L-γ-glutamyl)-O-[[[(1S)-1,3-dicarboxypropyl]amino](hydroxy)p hosphoryl]-L-homoserine	

or a pharmaceutically acceptable salts thereof.

In a **third embodiment** the invention is directed to a method for reformulation of a radiopharmaceutical, wherein the radiopharmaceutical comprises two or more carboxylic acid groups and/or one or more phosphonic acid, comprising the steps of

- Diluting the fraction obtained from the HPLC that contains the purified radiopharmaceutical with an aqueous solution comprising of a base,
- Trapping the purified radiopharmaceutical on an anionic exchange resin cartridge, and
- Eluting the radiopharmaceutical from an anionic exchange resin cartridge with an elution solvent comprising sodium chloride (NaCl).

Preferably, the elution solvent comprises pharmaceutically acceptable sodium salt at the concentration of 2 M to 0.3 M of the said pharmaceutically acceptable sodium salt. More preferably the elution solvent comprises pharmaceutically acceptable sodium salt at the concentration of 1 M to 0.3 M of the said pharmaceutically acceptable sodium salt. Even more preferably, the elution solvent comprises pharmaceutically acceptable sodium salt at the concentration of 0.8 M to 0.3 M of the said pharmaceutically acceptable sodium salt. Even more preferably, the Elution solvent comprises pharmaceutically acceptable sodium salt at the concentration of 0.5 M of the said pharmaceutically acceptable sodium salt.

Preferred features as disclosed in first aspect are included the first, second and third embodiment thereof.

In a **second aspect**, the invention is directed to a reformulated radiopharmaceutical solution, wherein the radiopharmaceutical comprises two or more carboxylic acid groups and/or one or more phosphonic acid, comprising

- a radiopharmaceutical, wherein the radiopharmaceutical comprises two or more carboxylic acid groups and/or one or more phosphonic acid, and
- an elution solvent comprising sodium chloride (NaCl).

Preferably, the radiopharmaceutical comprising two or more carboxylic acid groups and/or one or more phosphonic acid is a compound formula (I), (II) or mixture thereof.

Preferably, the reformulated radiopharmaceutical solution is obtained by the method as described in first aspect.

In a **first embodiment** the invention is directed to a reformulated radiopharmaceutical solution, wherein the radiopharmaceutical comprises two or more carboxylic acid groups and/or one or more phosphonic acid, comprising

- a reformulated radiopharmaceutical, and
- an elution solvent comprising sodium chloride (NaCl).

Preferably, the radiopharmaceutical comprising two or more carboxylic acid groups and/or one or more phosphonic acid is a compound formula (I), (II) or mixture thereof.

Preferably, the reformulated radiopharmaceutical solution is obtained by the method as described in first aspect.

Preferred features and embodiments as disclosed in first aspect are included here thereof.

In a **third aspect**, the invention is directed to a kit comprising

- an anionic exchange resin cartridge, and
- 5 - a vial containing an Elution solvent comprising sodium chloride (NaCl)
characterised in that the kit is useful for conducting the method of the first
aspect.

10 The preferred features and sub-embodiments disclosed in the first aspect are herein
incorporated in the second and third aspects.

Definitions

The terms used in the present invention are defined below but are not limiting the invention
scope.

15

An anionic exchange resin is a resin containing a cation group, typically amino groups that
are protonated to give ammonium salt or quaternary alkylated amino groups, which attract
and retain anions present in the solution surrounding the said resin.

20

A resin is organic polymer or functionalized silica that is insoluble in most organic solvents,
aqueous solutions and mixtures thereof.

25

A quaternary alkylated amino resin is a resin that it functionalized with one or more amino
groups and these amino groups are substituted independently with three alkyl or alkaryl
groups or mixture thereof to give an ammonium salt ($N^+R^1R^2R^3R^4$) where R^1 is the resin.
 R^2 , R^3 and R^4 is methyl, ethyl, propyl, butyl, benzyl, or ethylphenyl.

30

If chiral centers or other forms of isomeric centers are present in a compound according to
the present invention, all forms of such stereoisomers, including enantiomers and
diastereoisomers, are intended to be covered herein. Compounds containing chiral centers
may be used as racemic mixture or as an enantiomerically enriched mixture or as a
diastereomeric mixture or as a diastereomerically enriched mixture, or these isomeric
mixtures may be separated using well-known techniques, and an individual stereoisomer
maybe used alone. In cases wherein compounds may exist in tautomeric forms, such as
35 keto-enol tautomers, each tautomeric form is contemplated as being included within this
invention whether existing in equilibrium or predominantly in one form.

In the context of the present invention, preferred salts are pharmaceutically acceptable salts of the compounds according to the invention. The invention also comprises salts which for their part are not suitable for pharmaceutical applications, but which can be used, for example, for isolating or purifying the compounds according to the invention.

- 5 Pharmaceutically acceptable salts of the compounds according to the invention include acid addition salts of mineral acids, carboxylic acids and sulphonic acids, for example salts of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, ethanesulphonic acid, toluenesulphonic acid, benzenesulphonic acid, naphthalene disulphonic acid, formic acid, acetic acid, trifluoroacetic acid, propionic acid, lactic acid, 10 tartaric acid, malic acid, citric acid, fumaric acid, maleic acid and benzoic acid.

Pharmaceutically acceptable salts of the compounds according to the invention also include salts of customary bases, such as, by way of example and by way of preference, alkali metal salts (for example sodium salts and potassium salts), alkaline earth metal salts (for example calcium salts and magnesium salts) and ammonium salts, derived from ammonia or organic 15 amines having 1 to 16 carbon atoms, such as, by way of example and by way of preference, ethylamine, diethylamine, triethylamine, ethyldiisopropylamine, monoethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, dimethylaminoethanol, procaine, dibenzylamine, N-methylmorpholine, arginine, lysine, ethylenediamine and N-methylpiperidine.

20

Those skilled in the art will further recognise that acid addition salts of the claimed compounds may be prepared by reaction of the compounds with the appropriate inorganic or organic acid via any of a number of known methods. Alternatively, alkali and alkaline earth metal salts of acidic compounds of the invention are prepared by reacting the compounds of 25 the invention with the appropriate base via a variety of known methods.

The present invention includes all possible salts of the compounds of the present invention as single salts, or as any mixture of said salts, in any ratio.

30

The term "buffering agents" as employed herein include but are not limited to potassium metaphosphate, dipotassium phosphate, sodium acetate, sodium citrate anhydrous and sodium citrate dehydrate.

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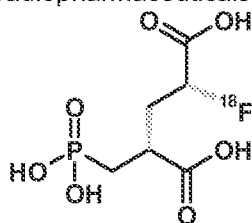
A compound is polar when an electric charge is not symmetrically distributed, so that there is a separation of charge or partial charge and formation of definite positive and negative poles. Polar compounds are defined as having a log D (partition coefficient determined with octanol and water at pH 7.4) in the range of -2 to 0, and very polar compounds are defined as having a log D < -3.

The term "halide" as employed herein by itself or as part of another group is known or obvious to someone skilled in the art, and means fluoro, chloro, bromo, and iodo.

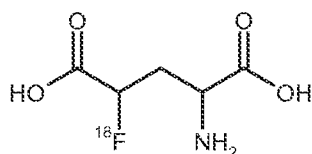
- 5 The term "Radiopharmaceutical" as employed herein refers to a drug that contains radioactive atom(s). Radiopharmaceuticals are administered to patient as diagnostic tracer for the diagnosis and/or treatment of diseases. Radioactive atom(s) are ^{18}F -fluorine, ^{124}I -, ^{124}I -, ^{123}I -, and ^{125}I -, ^{131}I -iodine, ^{68}Ga -Gallium and $^{99\text{m}}\text{Tc}$ -Technetium (list not exhaustive). Present invention is directed to any radiopharmaceuticals falling within the scope of the invention. Preferably the radiopharmaceutical contains fluorine or iodine radioisotope.

For the purpose of the invention, radiopharmaceutical includes also drug comprising the non-radioactive counterpart (cold isotope).

Well known radiopharmaceuticals are



(2S,4S)-2-Fluoro-4-phosphonomethyl-pentanedioic acid and



[F-18]-glutamic acid.

Where the plural form of the word compounds, salts, polymorphs, hydrates, solvates and the like, is used herein, this is taken to mean also a single compound, salt, polymorph, isomer, hydrate, solvate or the like.

Unless otherwise specified, when referring to the compounds of formula the present invention per se as well as to any pharmaceutical composition thereof the present invention includes all of the hydrates, salts, and complexes.

30 General synthesis of F-18 compounds

All solvents and chemicals were obtained from commercial sources and used without further purification. Anhydrous solvents and inert atmosphere (nitrogen or argon) were used if not stated otherwise. The preceding table lists the abbreviations used in this paragraph and in the Intermediates and Examples sections as far as they are not explained within the text body.

The radiofluorination reaction can be carried out, for example in a typical reaction vessel (e.g. Wheaton vial) which is known to someone skilled in the art or in a microreactor. The reaction can be heated by typical methods, e.g. oil bath, heating block or microwave. The radiofluorination reactions are carried out in dimethylformamide with potassium carbonate as base and "kryptofix" as crown-ether. But also other solvents can be used which are well known to experts. These possible conditions include, but are not limited to: dimethylsulfoxide and acetonitrile as solvent and tetraalkyl ammonium and tetraalkyl phosphonium carbonate as base. Water and/or alcohol can be involved in such a reaction as co-solvent. The radiofluorination reactions are conducted for one to 60 minutes. Preferred reaction times are five to 50 minutes. Further preferred reaction times are 10 to 40 min. This and other conditions for such radiofluorination are known to experts (Coenen, Fluorine-18 Labeling Methods: Features and Possibilities of Basic Reactions, (2006), in: Schubiger P.A., Friebe M., Lehmann L., (eds), PET-Chemistry - The Driving Force in Molecular Imaging. Springer, Berlin Heidelberg, pp.15-50). The radiofluorination can be carried out in a "hot-cell" and/or by use of a module (review: Krasikowa, Synthesis Modules and Automation in F-18 labeling (2006), in: Schubiger P.A., Friebe M., Lehmann L., (eds), PET-Chemistry - The Driving Force in Molecular Imaging. Springer, Berlin Heidelberg, pp. 289-316) which allows an automated or semi-automated synthesis.

The compounds produced may require purification. Purification of organic compounds is well known to the person skilled in the art and there may be several ways of purifying the same compound. In some cases, no purification may be necessary. In some cases, the compounds may be purified by preparative HPLC according to the preparative HPLC methods listed below.

Experimental Section

Abbreviations

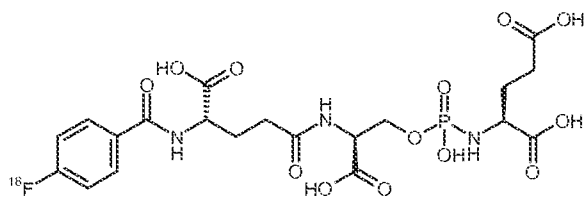
AcCl	Acetyl Chloride

Cs ₂ CO ₃	Cesium carbonate
DMF	<i>N,N</i> -Dimethylformamide
DMF-DMA	Dimethylformamide dimethyl acetal
DMSO	Dimethylsulfoxide
EtOAc	Ethyl Acetate
EtOH	Ethanol
GBq	GigaBequerel
h	Hour
HBF ₄	Tetrafluoroboric acid
HPLC	High Pressure Liquid Chromatography
K ₂ CO ₃	Potassium carbonate
K ₂₂₂	Kryptofix 2.2.2
M	Molar concentration "1 molar" (1 M). 1 mol/L
Min(s)	Minute(s)
MBq	MegaBequerel
MTB	Methyl t-butyl ether
MeCN	Acetonitrile
MeOH	Methanol
MS	Mass Spectrometry
N ₂	Nitrogen
nd	Not determined
NMR	Nuclear Magnetic Resonance
PET	Positron Emission Technology
PMPA	2-(Phosphonomethyl) pentanedioic acid
RT	Room Temperature
SPE	Solid Phase Extraction
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography

1. Radiolabeling and HPLC purification

Example 1

N-(4-[¹⁸F]fluorobenzoyl)-L-gamma-glutamyl-O-[[[(1S)-1,3 dicarboxypropyl]amino](hydroxy) phosphoryl]-L-serine (SFB-CTT)

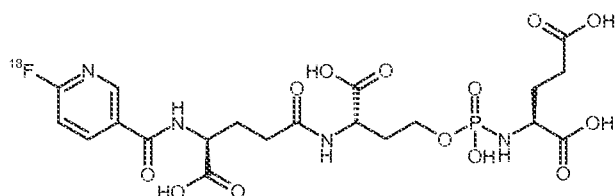


- 5 [¹⁸F] Fluoride was produced by an ¹⁸O (p, n) ¹⁸F nuclear reaction by bombardment of a 98% ¹⁸O-enriched water target with an 11MeV proton beam at the RDS111 cyclotron. The aqueous [¹⁸F]fluoride solution was trapped in a small anion exchange Sep-PakTM Plus QMA cartridge (Waters) (preconditioned with 5 ml 0.5 M K₂CO₃ solution and 10 mL water). The radioactivity was eluted with a solution mixture (1.0 mg K₂CO₃ in 0.5 ml water and 5.27 mg K₂₂₂ in 1.5 ml
- 10 MeCN) from the QMA cartridge into a 5 mL conic Wheaton vial. The solvent was evaporated under a stream of nitrogen at 110°C. Azeotropic drying was repeated three times with 1.0 mL portions of acetonitrile. Ethyl 4-(trimethylammonium triflate)benzoate (5.0 mg, 20 mmol) in anhydrous MeCN (1 mL) was added to the dried K₂₂₂/K[¹⁸F]F and the mixture heated at 100°C for 10 min to produce ethyl 4-[¹⁸F]fluorobenzoate. The ethyl ester was subsequently
- 15 hydrolyzed with 20 µL of tetrapropylammonium hydroxide (40%) in acetonitril (1 mL) at 120°C for 3 min, and then the mixture azeotropically dried using MeCN (1 mL). Subsequently, a solution of N,N,N',N'-tetramethyl-O-(N-succinimidyl) uronium hexafluorophosphate (HSTU) (12 mg, 33 mmol) in MeCN (1 mL) was added and the solution heated at 100°C for 6 min. After cooling, the reaction mixture was diluted with water (2.5 mL) and acetonitrile (1 mL) and
- 20 purified by prep. HPLC (ACE 5µ C18, 250 x 10mm, isocratic 65% MeCN in 35% water + 0.1%TFA, flow: 4ml/min). The SFB product peak was collected and diluted with 40ml water and passed through a preconditioned Sep-PakTM Light C18 cartridge (Waters) (preconditioned with 5ml acetonitrile and with 10ml water). The SPE was washed with water (5 mL) and was eluted with acetonitrile (1.5 ml). The acetonitrile solution was dried under
- 25 gentle N₂-stream at 60°C. To the dried SFB was added a solution of CTT54 (2 mg) in 50 µl water and 100 µl 0.1M Na₂CO₃. The reaction vessel was sealed and heated at 50°C for 10 mins. The reaction mixture was diluted with water (4 ml) and purified by prep. HPLC (Synergi Hydro RP 4µ, 250 x 9.4mm, isocratic 5% MeCN in 95% water + 0.1%TFA, flow: 3ml/min). The product peak was collected and diluted with 15ml 0.02M K₂CO₃ aqueous solution and
- 30 passed through a preconditioned small anion exchange Sep-PakTM Plus QMA cartridge (Waters) (preconditioned by washing the cartridge with 5ml methanol and 10 ml 0.02M K₂CO₃ aqueous solution). The QMA was washed with water (2 ml) and eluted with 0.5M NaCl (500 µl) into PBS buffer (1 ml, pH ~ 8) to give the desired product in a radiochemical yield 3.88±2.70% in a synthesis time of 215±46 min. The radiochemical purity was 94±3.3%.
- 35 Radiochemical purity was analyzed on a ZIC HILIC column (4.6mm x 100mm; 5µ; SeQuant)

and radioactivity detection was performed on a GABI Star from Raytest. The elution solution was 0.1 M ammonium formate (pH 3.2)/acetonitrile (3:7), and the flow rate was 0.5 mL/min. A Corona charged aerosol detector (CAD) from ESA was used to check the separation of the final hot tracer from excess of non-UV-active excess of biological vector CTT54. The residual amount of CTT54 was below detection limit of 0.5 µg/mL.

Example 2

N-[(6-[¹⁸F]fluoropyridin-3-yl)carbonyl]-L-gamma-glutamyl-O-[[[(1S)-1,3-dicarboxypropyl]amino](hydroxy)phosphoryl]-L-homoserine (SFN-hCTT)

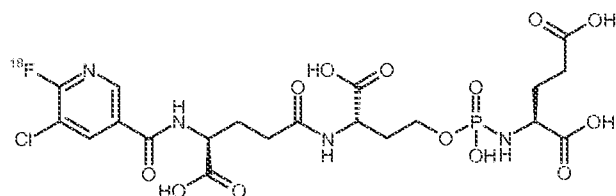


[¹⁸F] Fluoride was produced by an ¹⁸O (p, n) ¹⁸F nuclear reaction by bombardment of a 98% ¹⁸O-enriched water target with an 11MeV proton beam at the RDS111 cyclotron. The aqueous [¹⁸F]fluoride solution was trapped in a small anion exchange Sep-PakTM Plus QMA cartridge (Waters) (preconditioned with 5 ml 0.5 M K₂CO₃ solution and 10 mL water). The radioactivity was eluted with a solution mixture (1.0 mg K₂CO₃ in 0.5 ml water and 5.27 mg K₂₂₂ in 1.5 ml MeCN) from the QMA cartridge into a 5 mL conic Wheaton vial. The solvent was evaporated under a stream of nitrogen at 110°C. Azeotropic drying was repeated three times with 1.0 mL portions of acetonitrile. Ethyl 6-chloronicotinate (15.0 mg, 8.1 mmol) in anhydrous MeCN (1 mL) was added to the dried K₂₂₂/K[¹⁸F]F and the mixture heated at 100°C for 15 min to produce ethyl 6-[¹⁸F]fluoronicotinate. The ethyl ester was subsequently hydrolyzed with 65 µL of tetrapropylammonium hydroxide (40%) in acetonitrile (1 mL) at 35°C for 3 min, and then the mixture azeotropically dried using MeCN (1 mL). Subsequently, a solution of N,N,N',N'-tetramethyl-O-(N-succinimidyl) uronium hexafluorophosphate (HSTU) (40 mg, 110 mmol) in MeCN (1 mL) was added and the solution heated at 90°C for 6 min. After cooling, the reaction mixture was diluted with water (3.0 mL) and acetonitrile (0.5 mL) and purified by prep. HPLC (ACE 5µ C18, 250 x 10mm, isocratic 75% acetonitrile in 25% water + 0.1%TFA, flow: 4ml/min). The N-succinimidyl 4-[¹⁸F]fluoronicotinate ([¹⁸F]SFN) peak was collected and diluted with 30ml water and passed through a preconditioned Sep-PakTM Light C18 cartridge (Waters) (preconditioned with 5ml acetonitrile and with 10ml water). The SPE was washed with water (5 mL) and was eluted with acetonitrile (1.5 ml). The acetonitrile solution was dried under gentle N₂-stream at 60°C. To the dried SFB was added a solution of hCTT54 (2 mg) in 10 µl water and 50 µl 1 M Na₂CO₃ buffer. The reaction vessel was sealed and heated at 50°C

for 10 min. The reaction mixture was diluted with water (4 ml) and purified by prep. HPLC (Zorbax Bonus RP 4 μ , 250 x 9.4mm, flow: 3ml/min) using the following gradient: (the eluent components were A: water + 0.1%TFA; B: acetonitrile + 0.1%TFA): 0 min—95%A/5%B; 20 min—50%A/50%B. The product peak was collected and diluted with 20 ml 0.02M K₂CO₃ aqueous solution and passed through a preconditioned small anion exchange Sep-Pak™ Plus QMA cartridge (Waters) (preconditioned by washing the cartridge with 5ml methanol and 10 ml 0.02M K₂CO₃ aqueous solution). The QMA was washed with water (2 ml) and eluted with 0.5M NaCl (500 μ l) into PBS buffer (1 ml, pH ~ 8) to give the desired product in a radiochemical yield 2.32 $\pm$ 1.54 % in a synthesis time of 201 $\pm$ 74 min. The radiochemical purity was 98 $\pm$ 0.5%. Radiochemical purity was analyzed on a ZIC HILIC column (4.6mm x 100mm; 5 μ ; SeQuant) and radioactivity detection was performed on a GABI Star from Raytest. The elution solution was 0.1 M ammonium formate (pH 3.2)/acetonitrile (3:7), and the flow rate was 0.5 mL/min. A Corona charged aerosol detector (CAD) from ESA was used to check the separation of the final hot tracer from excess of non-UV-active excess of biological vector hCTT54. The residual amount of hCTT54 was below detection limit of 0.5 μ g/mL.

Example 3

N-[(5-chloro-6-[¹⁸F]fluoropyridin-3-yl)carbonyl]-L-gamma-glutamyl-O-[[[(1S)-1,3-dicarboxypropyl]amino](hydroxy)phosphoryl]-L-homoserine (SCIFN-hCTT)



[¹⁸F] Fluoride was produced by an ¹⁸O (p, n) ¹⁸F nuclear reaction by bombardment of a 98% ¹⁸O-enriched water target with an 11MeV proton beam at the RDS111 cyclotron. The aqueous [¹⁸F]fluoride solution was trapped in a small anion exchange Sep-Pak™ Plus QMA cartridge (Waters) (preconditioned with 5 ml 0.5 M K₂CO₃ solution and 10 mL water). The radioactivity was eluted with a solution mixture (1.0 mg K₂CO₃ in 0.5 ml water and 5.27 mg K₂22 in 1.5 ml MeCN) from the QMA cartridge into a 5 mL conic Wheaton vial. The solvent was evaporated under a stream of nitrogen at 110°C. Azeotropic drying was repeated three times with 1.0 mL portions of acetonitrile. Ethyl 5,6-dichloronicotinate (15.0 mg, 6.8 mmol) in anhydrous MeCN (1 mL) was added to the dried K222/K[¹⁸F]F and the mixture heated at 100°C for 15 min to produce ethyl 5-chloro-6-[¹⁸F]fluoronicotinate. The ethyl ester was subsequently hydrolyzed with 65 μ L of tetrapropylammonium hydroxide (40%) in acetonitril (1 mL) at 35°C for 3 min, and then the mixture azeotropically dried using MeCN (1 mL). Subsequently, a solution of N,N,N',N'-tetramethyl-O-(N-succinimidyl) uronium hexafluorophosphate (HSTU) (40 mg, 110

mmol) in MeCN (1 mL) was added and the solution heated at 90°C for 6 min. After cooling, the reaction mixture was diluted with water (3.0 mL) and acetonitrile (0.5 mL) and purified by prep. HPLC (ACE 5 μ C18, 250 x 10mm, isocratic 70% acetonitrile in 30% water + 0.1%TFA, flow: 4ml/min). The N-succinimidyl 5-chloro-6-fluoro-[¹⁸F]fluoronicotinate ([¹⁸F]SCIFN) peak was collected and diluted with 30ml water and passed through a preconditioned Sep-Pak™ Light C18 cartridge (Waters) (preconditioned with 5ml acetonitrile and with 10ml water). The SPE was washed with water (5 mL) and was eluted with acetonitrile (1.0 ml). To the acetonitrile solution S was added a solution of hCTT54 (2 mg) in 10 μ l water and 50 μ l 1M NaHCO₃ buffer. The reaction vessel was left open and heated at 60°C for 10 min. The reaction mixture was diluted with water (4 ml) and purified by prep. HPLC (Zorbax Bonus RP 4 μ , 250 x 9.4mm, flow: 3ml/min) using the following gradient (the eluent components were A: water + 0.1%TFA; B: acetonitrile + 0.1%TFA): 0 min—95%A/5%B; 20 min—50%A/50%B. The product peak was collected and diluted with 20 ml 0.02 M K₂CO₃ aqueous solution and passed through a preconditioned small anion exchange Sep-Pak™ Plus QMA cartridge (Waters) (preconditioned by washing the cartridge with 5ml methanol and 10 ml 0.02 M K₂CO₃ aqueous solution). The QMA was washed with water (2 ml) and eluted with 0.5 M NaCl (500 μ l) into PBS buffer (1 ml, pH ~ 8) to give the desired product in a radiochemical yield 2.02 $\pm$ 0.86 % in a synthesis time of 147 $\pm$ 6 min. The radiochemical purity was 99 $\pm$ 0.5%. Radiochemical purity was analyzed on a ZIC HILIC column (4.6mm x 100mm; 5 μ ; SeQuant) and radioactivity detection was performed on a GABI Star from Raytest. The elution solution was 0.1 M ammonium formate (pH 3.2)/actonitrile (3:7), and the flow rate was 0.5 mL/min. A Corona charged aerosol detector (CAD) from ESA was used to check the separation of the final hot tracer from excess of non-UV-active excess of biological vector hCTT54. The residual amount of hCTT54 was below detection limit of 0.5 μ g/mL.

2. QMA Formulation

Example 1

Reformulation of N-(4-[¹⁸F]fluorobenzoyl)-L-gamma-glutamyl-O-[[[(1S)-1,3 dicarboxypropyl]amino](hydroxy)phosphoryl]-L-serine(SFB-CTT) on C18 plus, ZIC-HILIC and QMA plus cartridges

Table 1: Tested solid-phase extraction cartridges for reformulation after final preparative HPLC in the synthesis of N-(4-[¹⁸F]fluorobenzoyl)-L-gamma-glutamyl-O-[[[(1S)-1,3 dicarboxypropyl]amino](hydroxy)phosphoryl]-L-serine (SFB-CTT)

Cartridge	Loading Solvent [%]: activity sticking on SPE	Washing Solvent [%]: activity sticking on SPE	Eluting Solvent [%]: activity sticking on SPE
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C18 plus¹	water (15 ml) 2% (n =1)	nd	nd
ZIC-HILIC²	Acetonitrile (15 ml) 7% (n =1)	nd	nd
QMA plus³	0.02 M K ₂ CO ₃ (15 ml) 78±16% (n =4)	Water (2 ml) 76±15% (n =4)	0.5 M NaCl (0.5 ml) 3±2% (n =4)

1 SPE from Waters (preconditioned with 5 ml ethanol and 10 ml water); 2 SPE from Sequant (Product P/N: 2942-051– 500 mg solid phase material in 3 ml polypropylene cartridge) (preconditioned with 5 ml ethanol and 10 ml water); 3 SPE from Waters (preconditioned with 5ml methanol and 10 ml 0.02M K₂CO₃ aqueous solution)

5

Example 2

Reformulation of N-[(6-[¹⁸F]fluoropyridin-3-yl)carbonyl]-L-gamma-glutamyl-O-[[[(1S)-1,3-dicarboxypropyl] amino](hydroxy)phosphoryl]-L-homoserine (SFN-hCTT) on QMA plus cartridge

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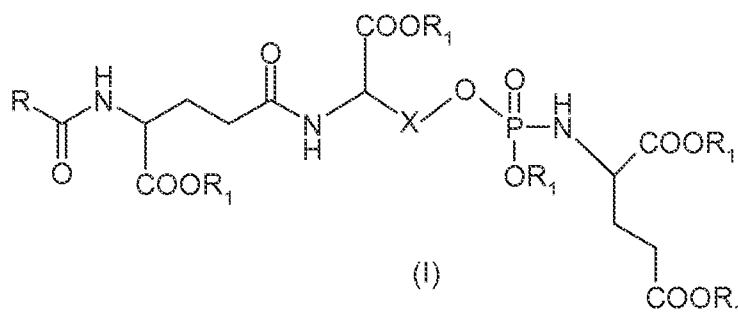
Table 2: Tested solid-phase extraction cartridges for reformulation after final preparative HPLC in the synthesis of N-[(6-[¹⁸F]fluoropyridin-3-yl)carbonyl]-L-gamma-glutamyl-O-[[[(1S)-1,3-dicarboxypropyl] amino](hydroxy)phosphoryl]-L-homoserine (SFN-hCTT)

Cartridge	Loading Solvent [%]: activity sticking on SPE	Washing Solvent [%]: activity sticking on SPE	Eluting Solvent [%]: activity sticking on SPE
QMA plus¹	0.02 M K ₂ CO ₃ (20 ml) 95±3% (n =6)	Water (2 ml) 94±2% (n =6)	0.15 M NaCl (1 ml) 92% (n =1)
QMA plus¹	0.02 M K ₂ CO ₃ (20 ml) 95±3% (n =6)	Water (2 ml) 94±2% (n =6)	1 M HCl (1 ml) 1% (n =1)
QMA plus¹	0.02 M K ₂ CO ₃ (20 ml) 95±3% (n =6)	Water (2 ml) 94±2% (n =6)	0.5 M NaCl (0.5 ml) 1±1% (n =6)

15 1 SPE from Waters (preconditioned with 5ml methanol and 10 ml 0.02M K₂CO₃ aqueous solution)

Claims:

1. A method for reformulation of a radiopharmaceutical, comprising the step of:
 eluting the radiopharmaceutical from an anionic exchange resin cartridge with an elution
 solvent comprising sodium chloride (NaCl),
 wherein the radiopharmaceutical comprises a compound of formula (I),



wherein

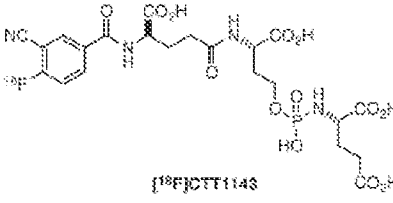
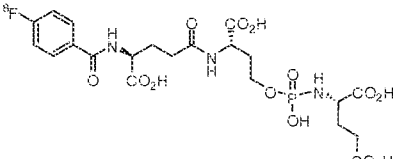
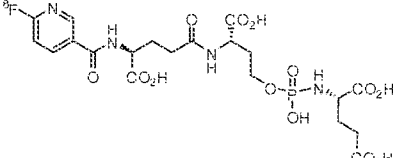
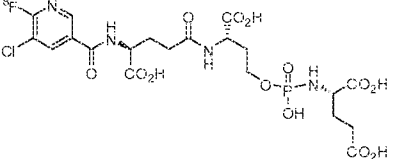
R is a radiolabeled pendant group,

each R₁ is independently from each other hydrogen or a pharmaceutically acceptable salt, and

X is CH₂ or CH₂-CH₂.

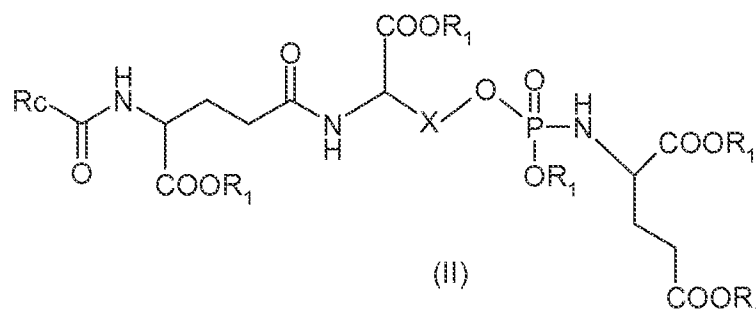
2. The method according to claim 1, wherein the elution solvent comprises a
 pharmaceutically acceptable sodium chloride (NaCl) is at the concentration of 2 M to 0.3
 M.
3. The method according to claim 1 or 2, comprising the steps of before the step of eluting:
 diluting the fraction obtained from the HPLC that contains the purified radiopharmaceutical
 with an aqueous solution comprising of a base, and
 trapping the purified radiopharmaceutical on an anionic exchange resin cartridge.
4. The method according to claim 1, wherein compounds of formula (I) are selected from

SFB-[¹⁸ F]CTT54	N-(4-[¹⁸ F]fluorobenzoyl)-L-gamma-glutamyl-O-[[[(1S)-1,3 dicarboxypropyl]amino](hydroxy) phosphoryl]-L-serine	
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$[^{18}\text{F}]\text{CTT1143}$ $[^{18}\text{F}]\text{F,CNBz-hCTT54};$	$(N-(3\text{-cyano-4-}[^{18}\text{F}]\text{fluorobenzoyl})\text{-L-}\gamma\text{-glutamyl})\text{-O-}[[[(1\text{S})\text{-1,3-dicarboxypropyl}]\text{amino}](\text{hydroxy})\text{p}]\text{hosphoryl}]\text{-L-homoserine}$	
$[^{18}\text{F}]\text{SFB-hCTT54};$	$(N-(4\text{-}[^{18}\text{F}]\text{fluorobenzoyl})\text{-L-}\gamma\text{-glutamyl})\text{-O-}[[[(1\text{S})\text{-1,3-dicarboxypropyl}]\text{amino}](\text{hydroxy})\text{p}]\text{hosphoryl}]\text{-L-homoserine}$	
$[^{18}\text{F}]\text{-SFN-hCTT54};$	$(N-(6\text{-}[^{18}\text{F}]\text{fluoro-pyrid-3-yl})\text{carbonyl-L-}\gamma\text{-glutamyl})\text{-O-}[[[(1\text{S})\text{-1,3-dicarboxypropyl}]\text{amino}](\text{hydroxy})\text{p}]\text{hosphoryl}]\text{-L-homoserine}$	
$[^{18}\text{F}]\text{-SCIFN-hCTT-54};$	$(N-(5\text{-chloro-6-}[^{18}\text{F}]\text{fluoro-pyrid-3-yl})\text{carbonyl-L-}\gamma\text{-glutamyl})\text{-O-}[[[(1\text{S})\text{-1,3-dicarboxypropyl}]\text{amino}](\text{hydroxy})\text{p}]\text{hosphoryl}]\text{-L-homoserine}$	

or a pharmaceutically acceptable salts thereof.

5. A method for reformulation of a radiopharmaceutical, comprising the step of:
 eluting the radiopharmaceutical from an anionic exchange resin cartridge with an elution
 solvent comprising sodium chloride (NaCl),
 wherein the radiopharmaceutical is a compound of formula (II),



wherein

R_c is the cold counter-part of a radiolabeled pendant group,

each R₁ is independently from each other hydrogen or a pharmaceutically acceptable salt, and

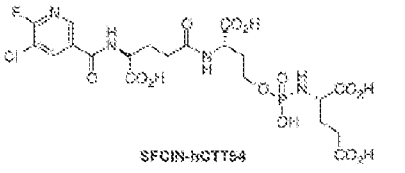
X is CH₂ or CH₂-CH₂.

5 6. The method according to claim 5, wherein the elution solvent comprising a pharmaceutically acceptable sodium chloride (NaCl) is at the concentration of 2 M to 0.3 M.

7. The method according to claim 5 or 6, comprising the steps of before the step of eluting:
diluting the fraction obtained from the HPLC that contains the purified radiopharmaceutical
10 with an aqueous solution comprising of a base, and
trapping the purified radiopharmaceutical on an anionic exchange resin cartridge.

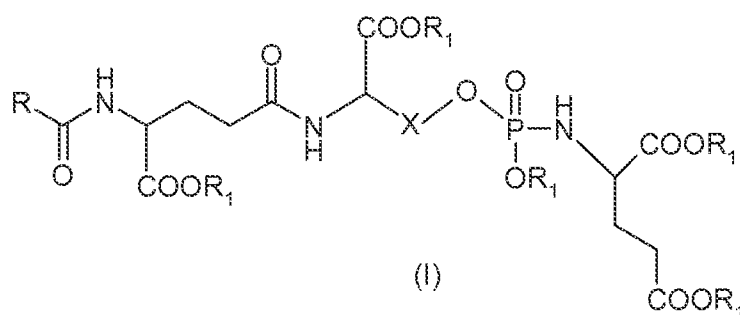
8. The method according to claim 5 wherein compounds of formula (II) are selected from

SFB-F-CTT54	N-(4-fluorobenzoyl)-L-gamma-glutamyl-O-[[[(1S)-1,3-dicarboxypropyl]amino](hydroxy)phosphoryl]-L-serine	
CTT1143 = F,CNBz- hCTT54;	(N-(3-cyano-4-fluorobenzoyl)-L-γ-glutamyl)-O-[[[(1S)-1,3-dicarboxypropyl]amino](hydroxy)p hosphoryl]-L-homoserine	
SFB-hCTT54;	(N-(4-fluorobenzoyl)-L-γ-glutamyl)-O-[[[(1S)-1,3-dicarboxypropyl]amino](hydroxy)p hosphoryl]-L-homoserine	
SFN-hCTT54;	(N-(6-fluoro-pyrid-3-yl)carbonyl-L-γ-glutamyl)-O-[[[(1S)-1,3-dicarboxypropyl]amino](hydroxy)p hosphoryl]-L-homoserine	

SCIFN-hCTT-54;	(N-(5-chloro-6-fluoro-pyrid-3-yl)carbonyl-L-γ-glutamyl)-O-[[[(1S)-1,3-dicarboxypropyl]amino](hydroxy)p hosphoryl]-L-homoserine	 SCIFN-hCTT54
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or a pharmaceutically acceptable salts thereof.

9. A reformulated radiopharmaceutical solution, comprising
a radiopharmaceutical, wherein the radiopharmaceutical comprises a compound of
formula (I),



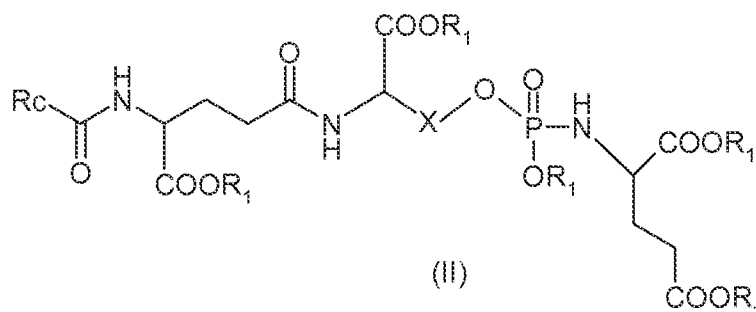
wherein

R is a radiolabeled pendant group,

each R₁ is independently from each other hydrogen or a pharmaceutically acceptable salt,

- 10 X is CH₂ or CH₂-CH₂, or

a compound of formula (II),



wherein

Rc is the cold counter-part of a radiolabeled pendant group,

- 15 each R₁ is independently from each other hydrogen or a pharmaceutically acceptable salt, and

X is CH₂ or CH₂-CH₂, and

an elution solvent comprising sodium chloride (NaCl).

10. A kit comprising
- an anionic exchange resin cartridge, and
 - a vial containing an elution solvent comprising sodium chloride (NaCl),
- characterized in that the kit is useful for conducting the method according to claims 1 to 8.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/041427

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07B59/00 C07F9/22
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07B C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	S. E. LAPI ET AL: "Assessment of an 18F-Labeled Phosphoramidate Peptidomimetic as a New Prostate-Specific Membrane Antigen-Targeted Imaging Agent for Prostate Cancer", THE JOURNAL OF NUCLEAR MEDICINE, vol. 50, no. 12, 1 December 2009 (2009-12-01), pages 2042-2048, XP55034294, ISSN: 0161-5505, DOI: 10.2967/jnumed.109.066589 the whole document -----	1-10



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

25 September 2013

Date of mailing of the international search report

04/10/2013

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