

provide the final purified formulation of ^{18}F -FACBC. Prior to intravenous administration, this formulation is passed through a sterile filter.

The present inventors have found that the quality of the final ^{18}F -FACBC drug product obtained using the above-described known FASTlabTM cassette and process can be somewhat variable. Residual acetonitrile levels have been found to range from about 100 $\mu\text{g}/\text{ml}$ to about 600 $\mu\text{g}/\text{ml}$. While acceptable in terms of permitted daily exposure and in the context of the acceptance criteria for ^{18}F -FACBC drug product, the amount and observed variability is less than ideal. Furthermore, residual aluminium have been found to range from about 7 $\mu\text{g}/\text{ml}$ to nearly 20 $\mu\text{g}/\text{ml}$, which would mean a potential amount of 100 μg in a 5 ml ^{18}F -FACBC injection. Where the ^{18}F -FACBC drug product also comprises citrate buffer, complexes of aluminium and citrate are likely to be present, which is problematic as it is known that such complexes cross the blood-brain barrier (Rengel 2004 Biometals; 17: 669-689).

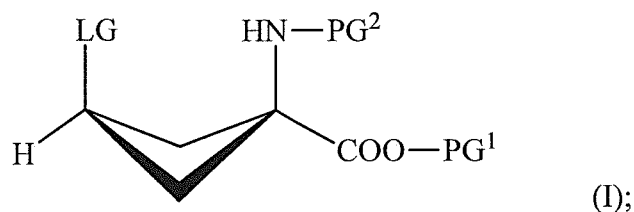
There is therefore scope to for an improved ^{18}F -FACBC drug product formulation.

15 Summary

In an aspect, there is provided a positron emission tomography (PET) tracer composition comprising *anti*-1-amino-3- ^{18}F -fluorocyclobutyl-1-carboxylic acid (^{18}F -FACBC) characterised in that said composition comprises no more than 5.0 $\mu\text{g}/\text{mL}$ dissolved aluminium (Al).

20 In another aspect, there is provided a method to prepare a PET tracer composition as defined above wherein said method comprises:

- (a) reacting in a reaction vessel a source of ^{18}F -fluoride with a precursor compound of Formula I:



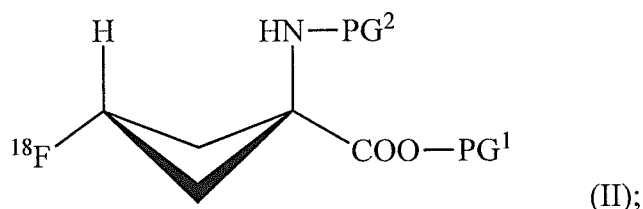
25 wherein:

LG is a leaving group;

PG^1 is a carboxy protecting group; and,

PG² is an amine protecting group;

to obtain a reaction mixture comprising a compound of Formula II:



5 wherein PG¹ and PG² are as defined for Formula I;

(b) carrying out removal of PG¹ and PG² to obtain a reaction mixture comprising ¹⁸F-FACBC; and

(c) purifying said reaction mixture comprising ¹⁸F-FACBC by passing it through a hydrophilic lipophilic balanced (HLB) solid phase, characterised in
10 that said purifying does not comprise passing the reaction mixture comprising ¹⁸F-FACBC through an alumina solid phase.

In another aspect, there is provided a positron emission tomography (PET) tracer composition comprising *anti*-1-amino-3-¹⁸F-fluorocyclobutyl-1-carboxylic acid (¹⁸F-FACBC) wherein the PET tracer is made by a method as defined above characterised in
15 that said composition comprises no more than 5.0 µg/mL dissolved aluminium (Al).

The present disclosure provides a drug product composition comprising ¹⁸F-FACBC that overcomes the problems seen with known such compositions. In particular, the composition as defined above has an improved impurity profile, making it safer and more effective for imaging as compared with the prior art. Low and predictable levels
20 of acetonitrile and/or aluminium in the final drug product mean that the composition as defined above more easily meets worldwide pharmacopeia requirements. In addition to a significant reduction in the concentration of aluminium in the final drug product, removal of the alumina cartridge has the allied advantages that a shorter and simplified process is permitted and that no particles arising from this cartridge are present, which
25 the present inventors have noted can block the sterile filter used prior to injection of the drug product. Furthermore, the advantages of the present invention are achieved with only minor changes to the known

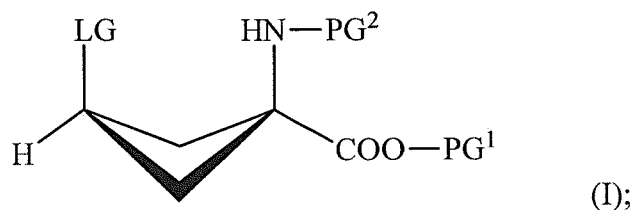
process and without impairing the desirable qualities of known ^{18}F -FACBC compositions.

Detailed Description of the Preferred Embodiments

To more clearly and concisely describe and point out the subject matter of the claimed
5 invention, definitions are provided in the detailed description hereinbelow for specific

Claims

- (1) A positron emission tomography (PET) tracer composition comprising *anti*-1-amino-3-¹⁸F-fluorocyclobutyl-1-carboxylic acid (¹⁸F-FACBC) characterised in that said composition comprises no more than 5.0 µg/mL dissolved aluminium (Al).
- 5 (2) The PET tracer composition as defined in Claim 1 wherein said composition comprises no more than 50 µg/mL acetonitrile (MeCN).
- (3) The PET tracer composition as defined in Claim 1 or Claim 2 wherein said composition comprises no more than 3.0 µg/mL dissolved Al.
- (4) The PET tracer composition as defined in Claim 3 wherein said composition
10 comprises no more than 1.5 µg/mL dissolved Al.
- (5) The PET tracer composition as defined in any one of Claims 1-4 having an end of synthesis (EOS) radiochemical purity (RCP) of at least 95%.
- (6) The PET tracer composition as defined in Claim 5 having an EOS RCP of at least 98%.
- 15 (7) The PET tracer composition as defined in any one of Claims 1-6 comprising 50-100 mM citrate buffer.
- (8) A method to prepare a PET tracer composition as defined in any one of claims 1-7 wherein said method comprises:
- (a) reacting in a reaction vessel a source of ¹⁸F-fluoride with a precursor
20 compound of Formula I:



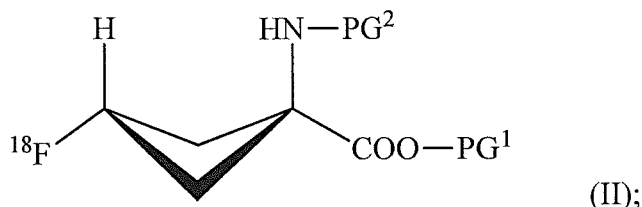
wherein:

LG is a leaving group;

PG¹ is a carboxy protecting group; and,

PG² is an amine protecting group;

to obtain a reaction mixture comprising a compound of Formula II:



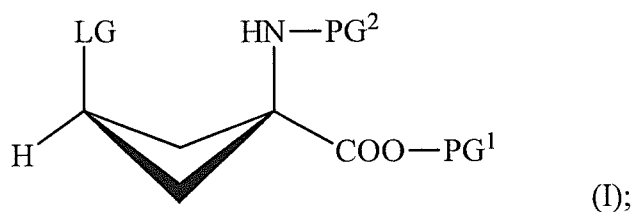
wherein PG¹ and PG² are as defined for Formula I;

(b) carrying out removal of PG¹ and PG² to obtain a reaction mixture comprising ¹⁸F-FACBC; and

10 (c) purifying said reaction mixture comprising ¹⁸F-FACBC by passing it through a hydrophilic lipophilic balanced (HLB) solid phase, characterised in that said purifying does not comprise passing the reaction mixture comprising ¹⁸F-FACBC through an alumina solid phase.

(9) A method according to claim 8 wherein said method comprises:

15 (a) reacting in a reaction vessel a source of ¹⁸F-fluoride with a precursor compound of Formula I:



wherein:

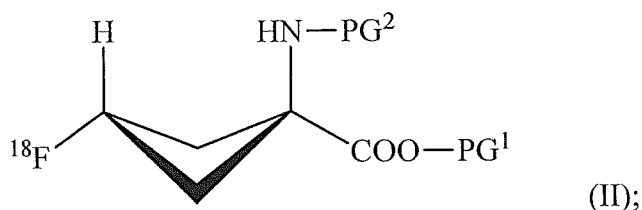
LG is a leaving group;

PG¹ is a carboxy protecting group; and,

20 PG² is an amine protecting group;

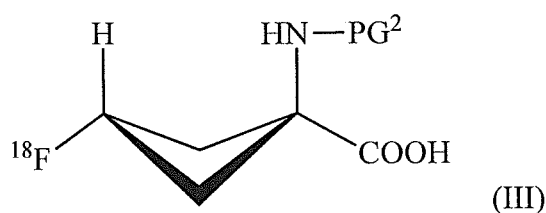
wherein said reacting step is carried out in acetonitrile;

to obtain a reaction mixture comprising a compound of Formula II:



wherein PG¹ and PG² are as defined for Formula I;

- (b) transferring said reaction mixture comprising said compound of Formula II out of said reaction vessel and carrying out removal of PG¹ to obtain a reaction mixture comprising a compound of Formula III:



wherein PG² is as defined for Formula I;

- (c) applying heat to said reaction vessel at the same time as carrying out removal of PG¹;
- (d) transferring said reaction mixture comprising said compound of Formula III back into said reaction vessel and carrying out removal of PG² to obtain a reaction mixture comprising ¹⁸F-FACBC;
- (e) purifying said reaction mixture comprising ¹⁸F-FACBC by passing it through a hydrophilic lipophilic balanced (HLB) solid phase, characterised in that said purifying does not comprise passing the reaction mixture comprising ¹⁸F-FACBC through an alumina solid phase.

- (10) The method as defined in Claim 8 or Claim 9 wherein LG is a linear or branched C₁₋₁₀ haloalkyl sulfonic acid substituent, a linear or branched C₁₋₁₀ alkyl sulfonic acid substituent, a fluorosulfonic acid substituent, or an aromatic sulfonic acid substituent.

- (11) The method as defined in any one of Claims 8-10 wherein PG¹ is a linear or branched C₁₋₁₀ alkyl chain or an aryl substituent.
- (12) The method as defined in any one of Claims 8-11 wherein PG² is a carbamate substituent, an amide substituent, an imide substituent or an amine substituent.
- 5 (13) The method as defined in any one of Claims 8-12 further comprising formulating said purified reaction mixture obtained in steps (c) or (e) with citrate buffer.
- (14) A positron emission tomography (PET) tracer composition comprising *anti*-1-amino-3-¹⁸F-fluorocyclobutyl-1-carboxylic acid (¹⁸F-FACBC) wherein the PET tracer is made by a method according to any one of Claims 8-13 characterised in that said
- 10 composition comprises no more than 5.0 µg/mL dissolved aluminium (Al).
- (15) A positron emission tomography (PET) tracer composition as defined in claim 14 characterised in that said composition comprises no more than 5.0 µg/mL dissolved aluminium (Al) and no more than 50 µg/mL acetonitrile (MeCN).