^{18}F labelling

Recently, several groups have focused on the development of novel ^{18}F-labelled urea-based inhibitors for PCa diagnosis. The ^{18}F-labelled urea-based PSMA inhibitor ^{18}F-DCFPyl demonstrated promising results in the detection of primary and metastatic PCa. Based on the structure of PSMA-617, the ^{18}F-labelled analogue PSMA-1007 was recently developed, which showed comparable tumor-to-organ ratios.

An attractive approach for introducing ^{18}F labels is the use of silicon-fluoride acceptors (SIFA). Silicon-fluoride acceptors are described, for example, in Lindner et al., Bioconjugate Chemistry 25, 738-749 (2014). In order to preserve the silicon-fluoride bond, the use of silicon-fluoride acceptors introduces the necessity of sterically demanding groups around the silicon atom. This in turn renders silicon-fluoride acceptors highly hydrophobic. In terms of binding to the target molecule, in particular to the target molecule which is PSMA, the hydrophobic moiety provided by the silicon-fluoride acceptor may be exploited for the purpose of establishing interactions of the radio-diagnostic or -therapeutic compound with the hydrophobic pocket described in Zhang et al., Journal of the American Chemical Society 132, 12711-12716 (2010). Yet, prior to binding, the higher degree of lipophilicity introduced into the molecule poses a severe problem with respect to the development of radiopharmaceuticals with suitable in vivo biodistribution, i.e. low unspecific binding in non-target tissue.

Despite many attempts, the hydrophobicity problem caused by silicon-fluoride acceptors has only recently been solved by the use of agents having a hydrophilic chelator moiety. Application WO2019/020831 describes a new type of radio-hybrid agent having both a SIFA moiety and a metal chelator. In developing the compounds described therein the inventors have identified improved pharmaceutical formulations for patient delivery. The formulations described herein show improved radio-stability and shelf-life over previously described formulations.

In view of the above, the technical problem underlying the present invention can be seen in providing improved radio-diagnostic formulations which contain a silicon-fluoride acceptor and a metal chelator which are, at the same time, characterized by favourable pharmaco-stability properties.

Summary ~~of the invention~~

In an aspect of the present disclosure, there is provided a pharmaceutical composition comprising a radiohybrid agent containing a silicon-fluoride and a chelating group wherein either the fluorine is ^{18}F or the chelating group contains a chelated radioactive metal, wherein the composition has a pH of 4.0-6.0 and further comprises:

a) 0.1-200 mM citrate buffer; and

b) 1-100 mg/mL ethanol; and

c) 5-10 mg/mL sodium chloride.

In another aspect of the present disclosure, there is provided a pharmaceutical composition as disclosed herein for use in therapy.

In a further aspect of the present disclosure, there is provided a use of a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for use as a cancer diagnostic or imaging agent.

In another aspect of the present disclosure, there is provided a use of a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for the diagnosis, imaging or prevention of neoangiogenesis/angiogenesis.

In a further aspect of the present disclosure, there is provided a use of a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for use as a cancer diagnostic or imaging agent wherein the cancer is prostate, breast, lung, colorectal or renal cell carcinoma.

In another aspect of the present disclosure, there is provided a method of producing a composition as disclosed herein comprising preparing a formulation of a radiohybrid agent containing a silicon-fluoride and a chelating group wherein either the fluorine is ^{18}F or the chelating group contains a chelated radioactive metal, wherein the composition has a pH of 4.0-6.0 and a citrate concentration of at least 10 mM, and diluting the citrate concentration with a solution of sodium chloride.

Detailed Description

As will be become apparent in the following, the present invention established a proof-of-principle using specific conjugates, formulated in specific ways, which bind with high affinity to prostate-specific antigen (PSMA) as target. The composition in which the compounds are prepared and stored affects the chemical and radiochemical stability of the agents. Accordingly, a further technical

Claims

1. A pharmaceutical composition comprising a radiohybrid agent containing a silicon-fluoride and a chelating group wherein either the fluorine is ^{18}F or the chelating group contains a chelated radioactive metal, wherein the composition has a pH of 4.0-6.0 and further comprises:
   a) 0.1-200 mM citrate buffer; and
   b) 1-100 mg/mL ethanol; and
   c) 5-10 mg/mL sodium chloride.

2. The pharmaceutical composition as defined in claim 1 comprising 1-15 mM citrate buffer.

3. The pharmaceutical composition as defined in claim 1 comprising 1-10 mM (±10%) citrate buffer.

4. The pharmaceutical composition as defined in any one of claims 1 to 3 comprising 5-50 mg/mL (±10%) ethanol.

5. The pharmaceutical composition as defined in claim 4 comprising 5-50 mg/mL ethanol.

6. The pharmaceutical composition as defined in any one of claims 1 to 5 that has a pH of 4.5 to 5.5.

7. The pharmaceutical composition as defined in any one of claims 1 to 6, wherein the composition comprises 6-9 mg/mL sodium chloride.

8. The pharmaceutical composition as defined in any one of claims 1 to 7 wherein the citrate buffer is prepared from citric acid and sodium hydroxide, or sodium citrate and hydrochloric acid.

9. The pharmaceutical composition as defined in claim 8, wherein 1-3 mg/mL citric acid and 0.5-1.0 mg/mL sodium hydroxide are used to prepare the citrate buffer.

10. The pharmaceutical composition as defined in claim 8, wherein 1.9 mg/mL citric acid and 0.75 mg/mL sodium hydroxide are used to prepare the citrate buffer.

11. The pharmaceutical composition as defined in any one of claims 1 to 10 wherein the metal is radioactive and the fluoride is ^{19}F.

12. The pharmaceutical composition as defined in any one any one of claims 1 to 11 wherein the chelated metal is selected from the cations of: Sc, Cu, Ga, Y, In, Tb, Ho, Lu, Re, Pb, Bi, Ac, Th or Er.

13. The pharmaceutical composition as defined in any one of claims 1 to 10 wherein the fluoride is ^{18}F and the metal is non-radioactive.

14. The pharmaceutical composition as defined in claim 12 wherein the chelated radioactive metal cation is a positron emitting isotope.

15. The pharmaceutical composition as defined in any one of claims 1-14 that has an end of synthesis (EOS) radioactive concentration (RAC) of 5-200 mCi/mL.

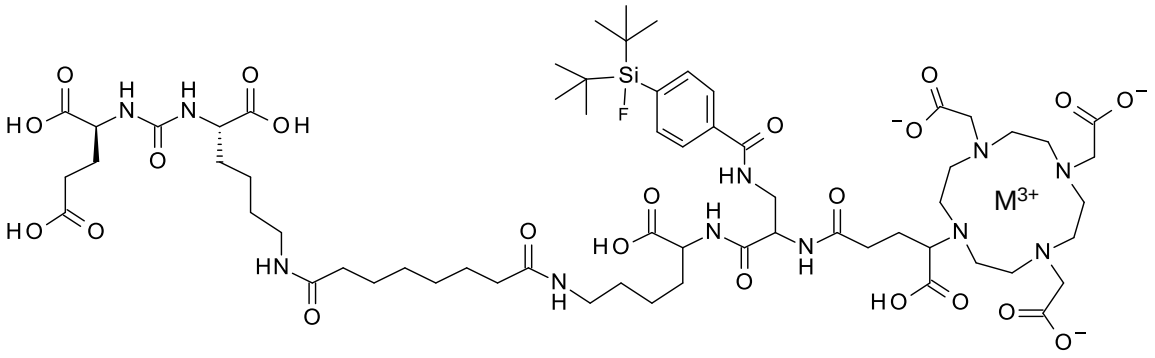
16. The pharmaceutical composition as defined in any one preceding claim comprising 1-10 mM (±10%) citrate buffer, 5-50 mg/mL (±10%) ethanol, 6-9 mg/mL sodium chloride and that has a pH of 4.5 to 5.5.

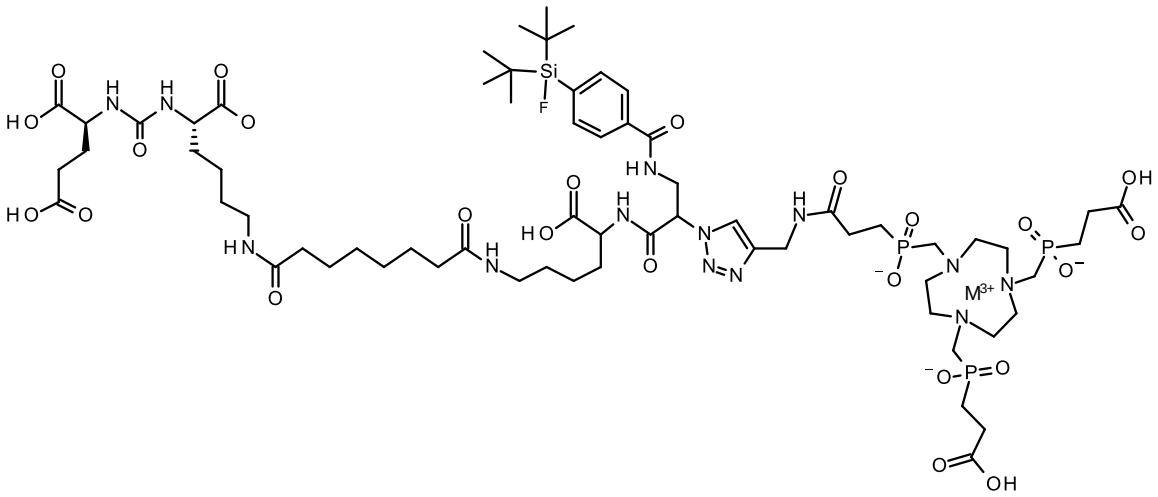
17. The pharmaceutical composition as defined in any one preceding claim comprising 10 mM citrate buffer, 50 mg/mL ethanol, 7.2 mg/mL sodium chloride, and that is pH 5.

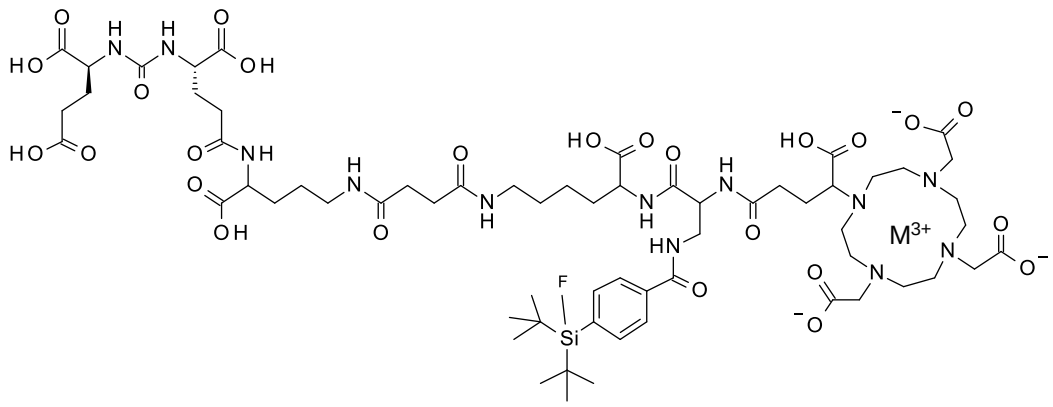
18. The pharmaceutical composition as defined in any one of claims 1 to 17, which is diluted with sodium chloride solution prior to administration.

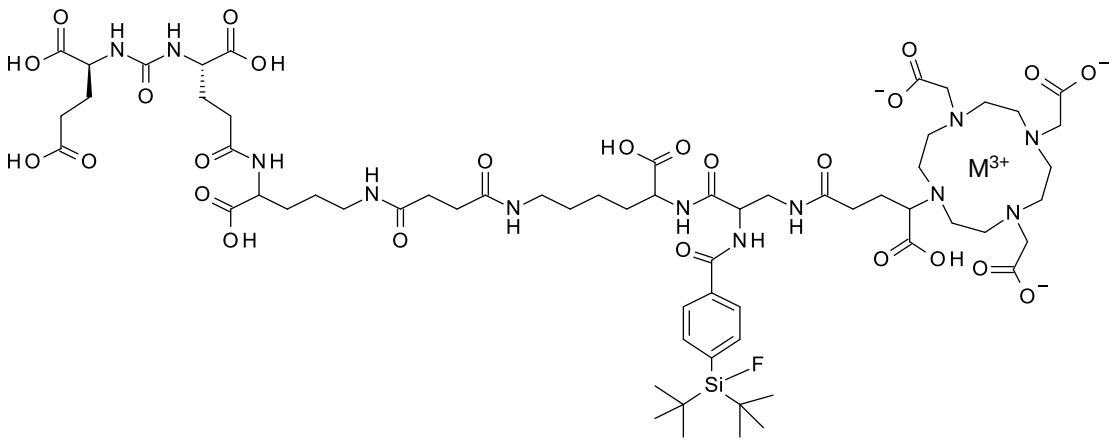
19. The pharmaceutical composition as defined in claim 18 comprising 1.1 mM (±10%) citrate buffer, 5.3 mg/mL (±10%) ethanol, 8.8 mg/mL (±10%) sodium chloride, and which has a pH of 4.5 to 5.5.

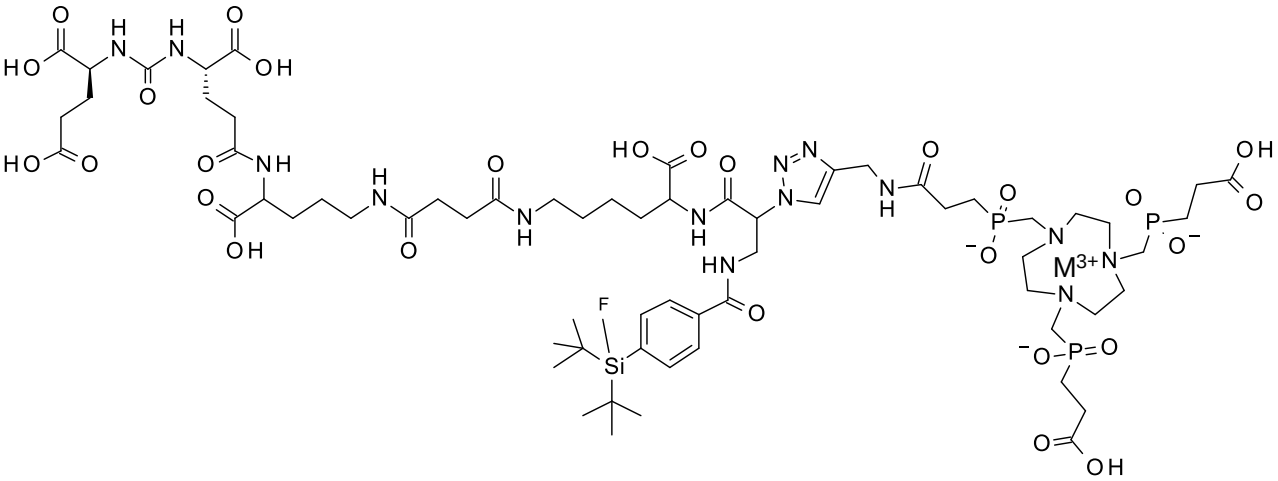
20. The pharmaceutical composition as defined in any one of claims 1 to 19 wherein the radiohybrid agent is selected from:

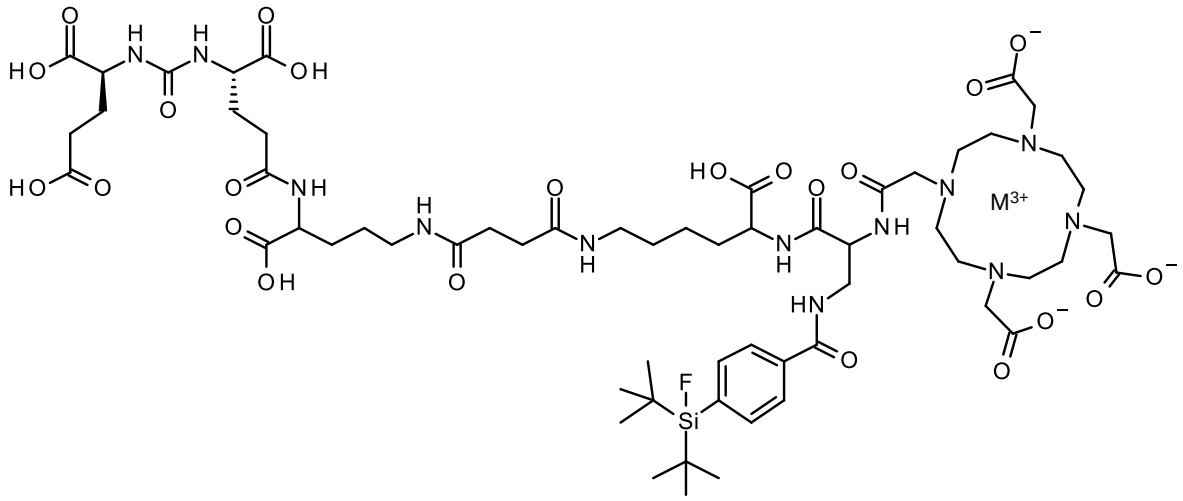


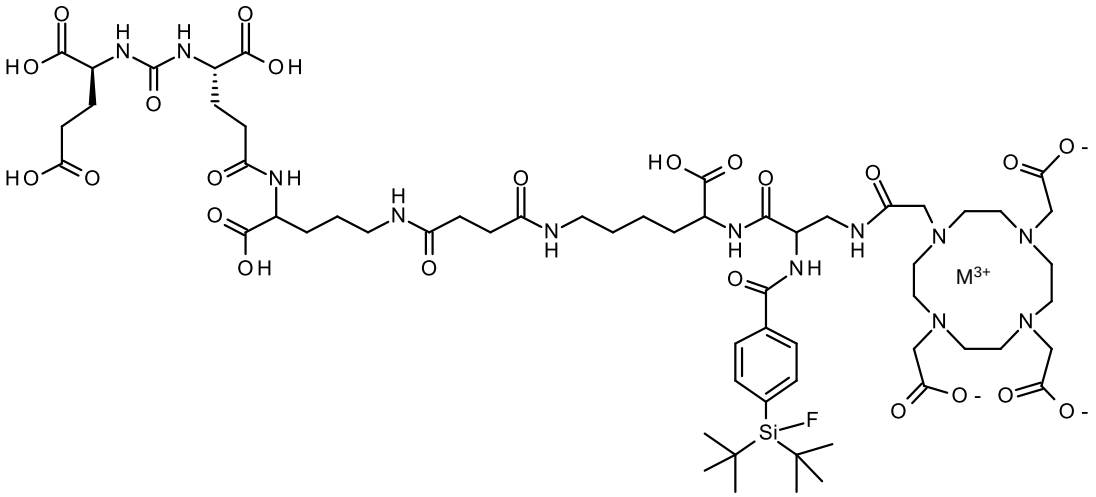






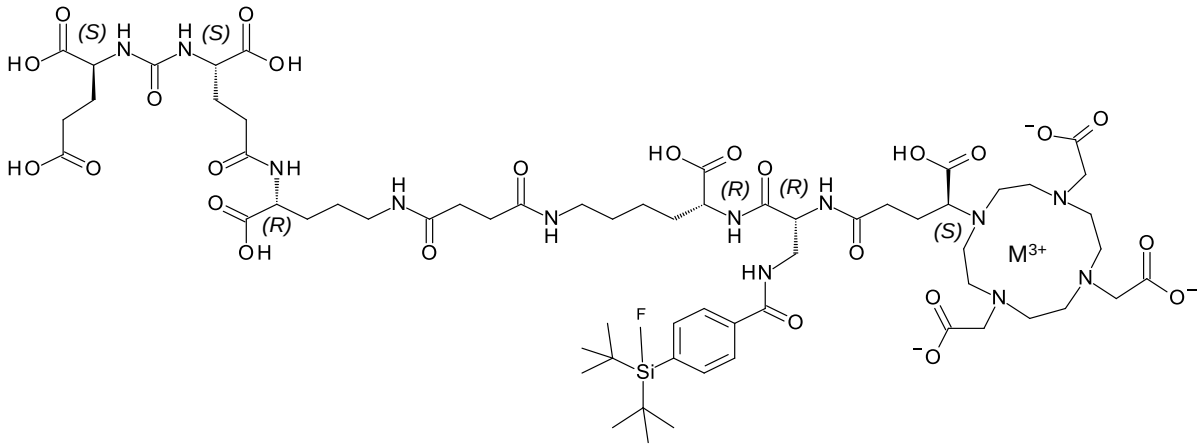






and salts or isomers thereof wherein M^{3+} is a chelated radioactive or non-radioactive metal.

21. The pharmaceutical composition as defined in claim 20 wherein the radiohybrid agent is:



or an isomer thereof.

22. A pharmaceutical composition as defined in any one of claims 1-21, for use in therapy.

~~22.~~23. Use of a~~The~~ pharmaceutical composition as defined in any one of claims 1-21, in the manufacture of a medicament for use as a cancer diagnostic or imaging agent.

~~23. A method of imaging and/or diagnosing cancer comprising administering a composition according to any one of claims 1-21 to a patient in need thereof.~~

24. Use of a~~The~~ pharmaceutical composition as defined in any one of claims 1-21, in the manufacture of a medicament for the diagnosis, imaging or prevention of neoangiogenesis/angiogenesis.

25. Use of a~~The~~ pharmaceutical composition as defined in any one of claims 1-21, in the manufacture of a medicament for use as a cancer diagnostic or imaging agent wherein the cancer is prostate, breast, lung, colorectal or renal cell carcinoma.

26. A method of producing a composition as defined in any one of claims 1-~~25~~ 21 comprising preparing a formulation of a radiohybrid agent containing a silicon-fluoride and a chelating group wherein either the fluorine is ^{18}F or the chelating group contains a chelated radioactive metal, wherein the composition has a pH of 4.0-6.0 and a citrate concentration of at least 10 mM, and diluting the citrate concentration with a solution of sodium chloride.