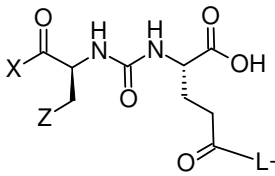
In view of the above, the technical problem underlying the present invention can be seen in providing radio-diagnostics and radio-therapeutics which contain a silicone fluoride acceptor and which are, at the same time, characterized by favourable in-vivo properties.

WO2019/020831 and WO2020/157184 disclose ligand-SIFA-chelator conjugates.

In the present invention a proof-of-principle has been established using specific conjugates which bind with high affinity to prostate-specific membrane antigen (PSMA) as target. Accordingly, a further technical problem underlying the present invention can be seen in providing improved radio-therapeutics and –diagnostics for the medical indication which is cancer, preferably prostate cancer.

SUMMARY

In one aspect, the present disclosure provides a compound of Formula (3a):



(3a);

or a pharmaceutically acceptable salt thereof, wherein;

L represents a linker group comprising a silicon-fluoride acceptor (SIFA) moiety which comprises a covalent bond between a silicon and a fluorine atom;

CM represents a chelator moiety, optionally containing a chelated nonradioactive or radioactive cation;

X is selected from OH and an amino acid group;

Z is selected from -V-NH_2, -V-PO_3H_2, -V-COY, -V-W and a C_{1-6} saturated or unsaturated hydrocarbon group optionally substituted with 1 to 3 fluorine atoms, where Y is an amino acid, W is 5- or 6-membered heterocyclic ring, and V is a bond or a C_{1-3} alkyl group optionally substituted with 1 to 3 fluorine atoms.

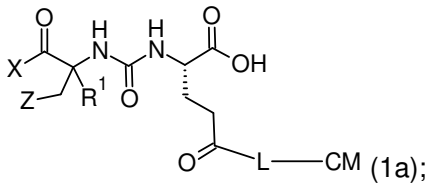
In another aspect, the present disclosure provides a pharmaceutical or diagnostic composition comprising or consisting of one or more compounds according to the disclosure.

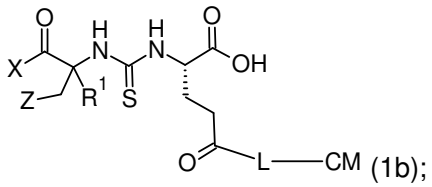
In another aspect, the present disclosure provides a use of a compound or composition according to the disclosure in the manufacture of a medicament for treating cancer.

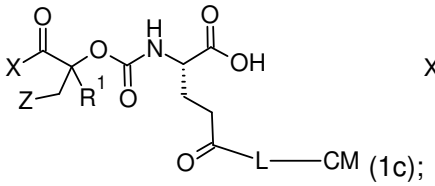
In another aspect, the present disclosure provides a use of a compound or composition according to the disclosure in the manufacture of a cancer diagnostic or imaging agent for use in a method of cancer diagnosis or imaging.

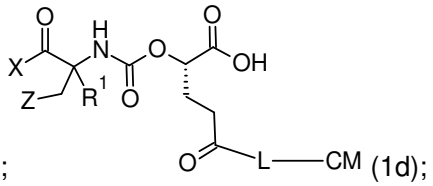
THE INVENTION

The present disclosure relates to compounds of Formula (1a), (1b), (1c) or (1d):


(1a);


(1b);


(1c);


(1d);

or a pharmaceutically acceptable salt thereof, wherein;

L represents a linker group comprising a silicon-fluoride acceptor (SIFA) moiety which comprises a covalent bond between a silicon and a fluorine atom;

CM represents a chelator moiety, optionally containing a chelated nonradioactive or radioactive cation;

R^1 is H or a C_{1-3} alkyl group optionally substituted with 1 to 3 fluorine atoms;

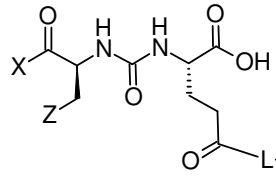
X is selected from OH and an amino acid group;

Z is selected from -V-CO_2H, -V-NH_2, -V-PO_3H_2, -V-COY, -V-W and a C_{1-6} saturated or unsaturated hydrocarbon group optionally substituted with 1 to 3 fluorine atoms, where Y is an amino acid, W is a 5- or 6-membered heterocyclic ring, and V is a bond or a C_{1-3} alkyl group optionally substituted with 1 to 3 fluorine atoms;

and when the compound is a compound of formula (1a) and X is OH, Z is not CH_2CO_2H.

Claims

1. A compound of Formula (3a):



(3a);

or a pharmaceutically acceptable salt thereof, wherein;

L represents a linker group comprising a silicon-fluoride acceptor (SIFA) moiety which comprises a covalent bond between a silicon and a fluorine atom;

CM represents a chelator moiety, optionally containing a chelated nonradioactive or radioactive cation;

X is selected from OH and an amino acid group;

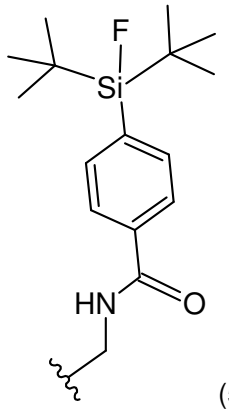
Z is selected from -V-NH_2, -V-PO_3H_2, -V-COY, -V-W and a C_{1-6} saturated or unsaturated hydrocarbon group optionally substituted with 1 to 3 fluorine atoms, where Y is an amino acid, W is 5- or 6-membered heterocyclic ring, and V is a bond or a C_{1-3} alkyl group optionally substituted with 1 to 3 fluorine atoms.

2. The compound according to claim 1, wherein X is -NHCH(C_6H_{13})CO_2H.

3. The compound according to claim 1, wherein X is OH.

4. The compound according to any one of claims 1 to 3, wherein Z is -$CHFCO_2H$, -CH_2CONH_2, -$CH_2PO_3H_2$, *n*-butyl, acetylene, furan, -CH_2-tetrazole, -NHCH(C_6H_{13})CO_2H, CH_2CO_2H or -NHCH($CH_2CH_2SCH_3$)CO_2H.

5. The compound according to any one of claims 1 to 5, wherein the silicon-fluoride acceptor (SIFA) moiety has the structure represented by formula (5b):



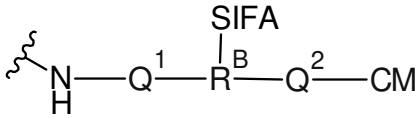
(5b).

6. The compound according to any one of claims 1 to 5, wherein the fluorine atom of the silicon-fluoride acceptor (SIFA) moiety is ^{18}F.

7. The compound according to any one of claims 1 to 6, wherein the chelator moiety is 1,4,7,10-tetracyclododecan-N,N',N'',N'''-tetraacetic acid (DOTA) or α-(2-carboxyethyl)-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTAGA).

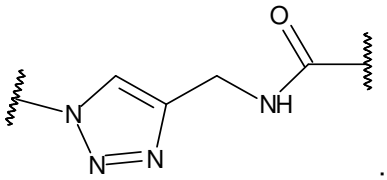
8. The compound according to any one of claims 1 to 7, wherein the chelator moiety contains a chelated cation selected from the cations of ^{68}Ga or ^{177}Lu.

9. The compound according to any one of claims 1 to 8, wherein the group -L-CM is:



;

wherein Q^1 is a divalent linking group with a structure selected from an oligoamide, an oligoether, an oligothioether, an oligoester, an oligothioester, an oligourea, an oligo(ether-amide), an oligo(thioether-amide), an oligo(ester-amide), an oligo(thioester-amide), oligo(urea-amide), an oligo(ether-thioether), an oligo(ether-ester), an oligo(ether-thioester), an oligo ether-urea), an oligo(thioether-ester), an oligo(thioether-thioester), an oligo(thioether-urea), an oligo(ester-thioester), an oligo(ester-urea), and an oligo(thioester-urea), wherein Q^1 is optionally substituted with one or more substituents independently selected from –OH, $-OCH_3$, $-CH_2OH$, $-CO_2H$, $–CO_2CH_3$, $-NH_2$, $-CH_2NH_2$ and $-NHC(NH)NH_2$;
Q^2 is selected from an amide bond, an ether bond, a thioether bond, an ester bond, a thioester bond, a urea bridge, an amine bond and linking groups of the formula:



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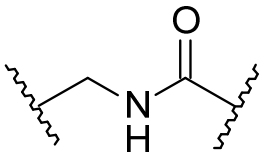
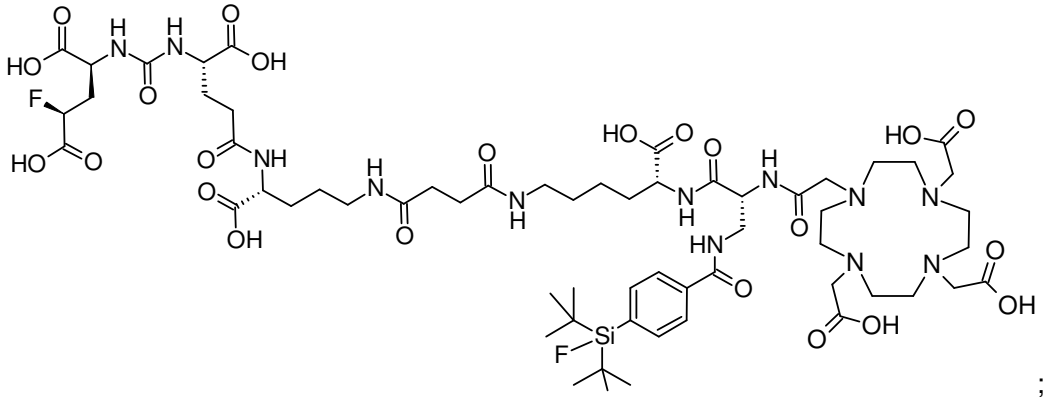


;

R^B is a trivalent coupling group;

and SIFA is the silicon-fluoride acceptor moiety.

10. The compound according to claim 1 which is selected from:



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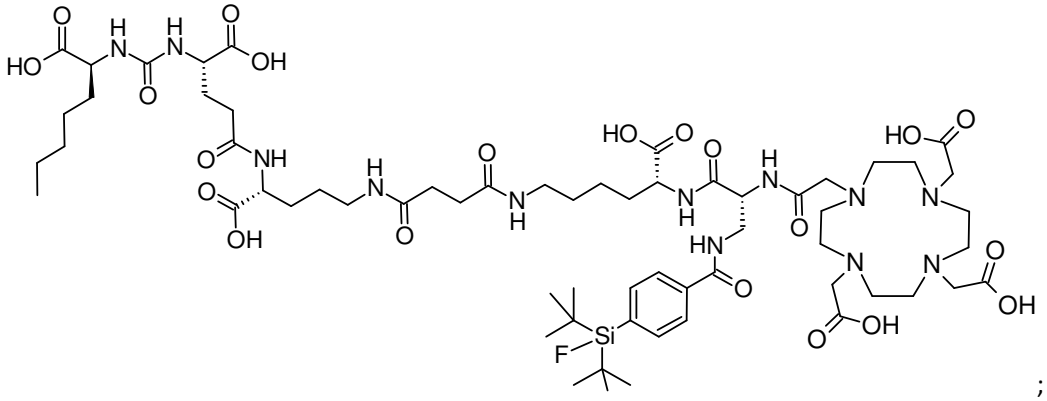

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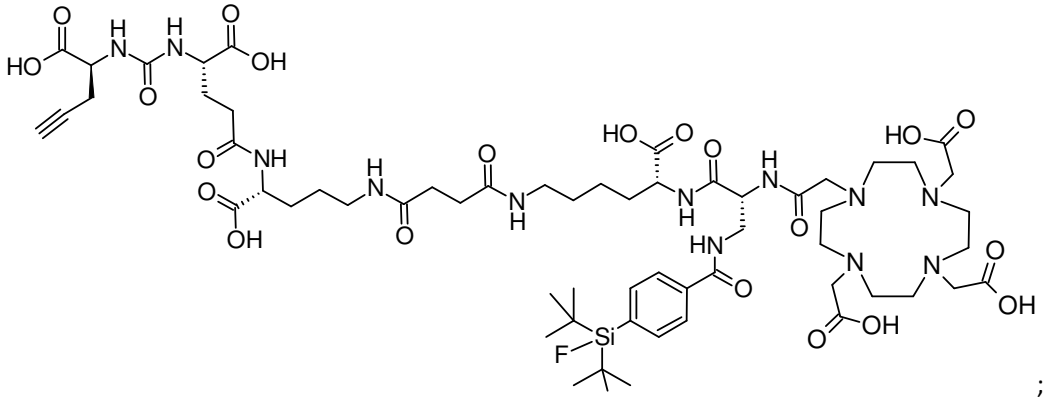

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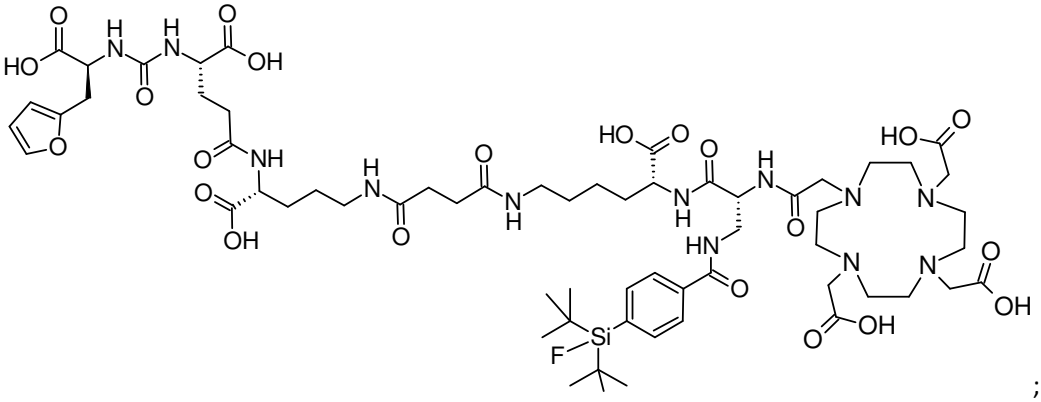

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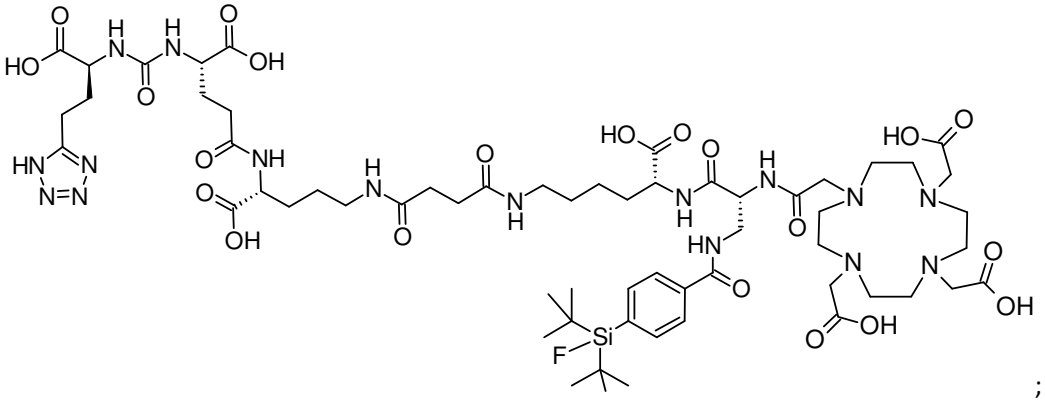

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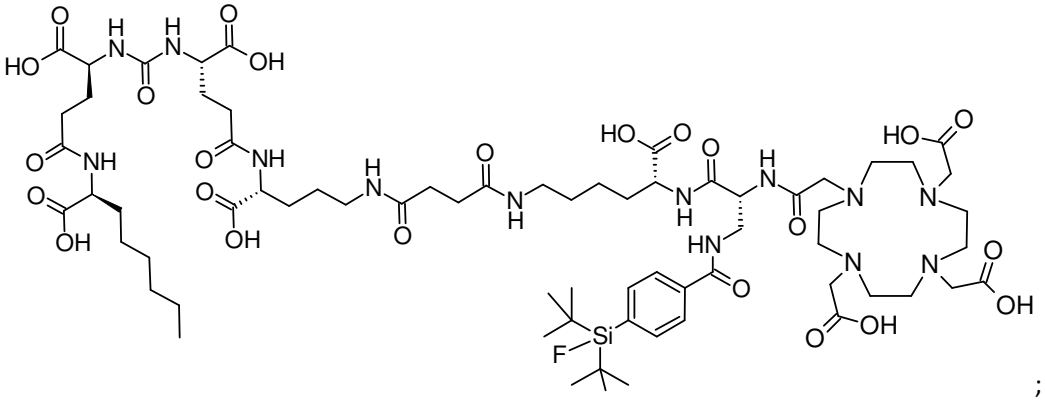

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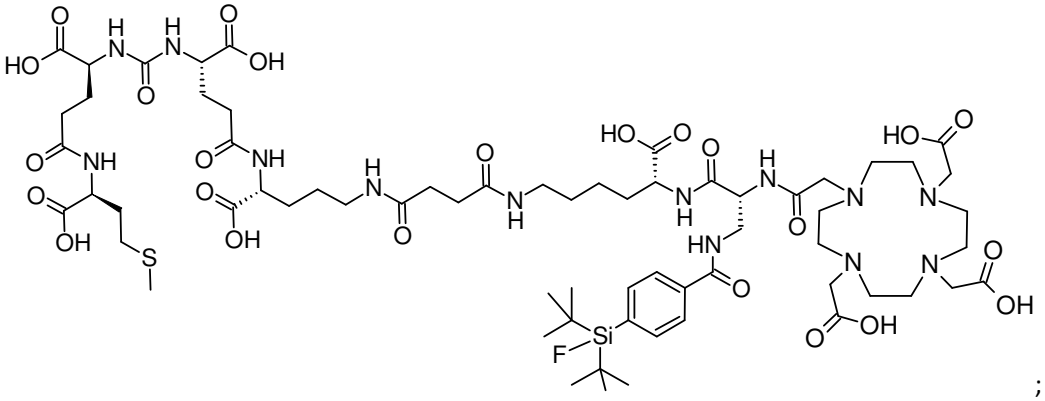

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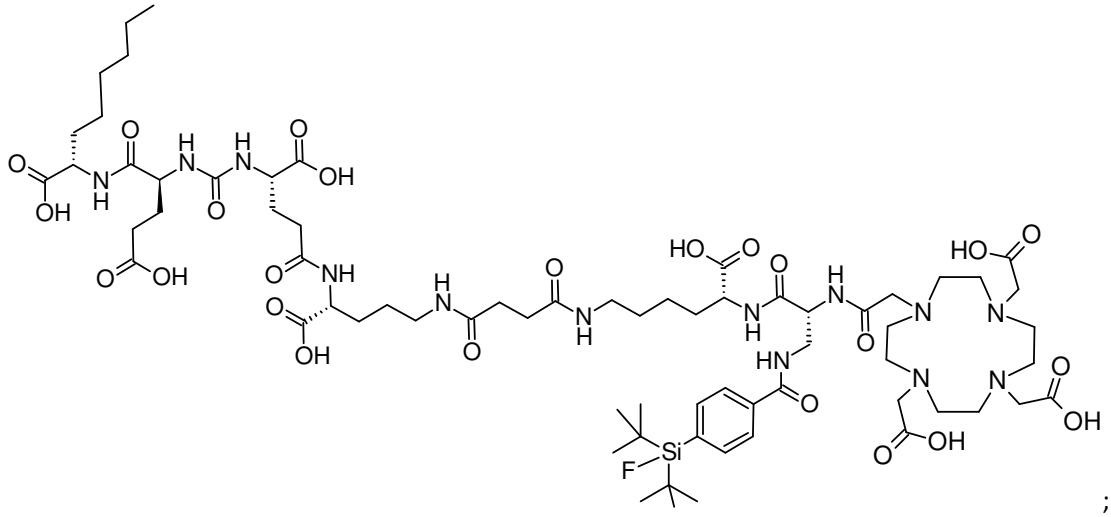

;

or a pharmaceutically acceptable salt thereof, wherein the fluorine atom is optionally ^{18}F and wherein the chelator moiety is optionally coordinated to Lu^{3+}.

11. A pharmaceutical or diagnostic composition comprising or consisting of one or more compounds according to any one of claims 1 to 10.

12. ~~A~~ Use of a compound or composition according to any one of claims 1 to 11 ~~for use as a cancer diagnostic or imaging agent or for use in the treatment of~~in the manufacture of a medicament for treating cancer.

13. Use of a compound or composition according to any one of claims 1 to 11 in the manufacture of a cancer diagnostic or imaging agent for use in a method of cancer diagnosis or imaging.