Both, ^{68}Ga- and ^{177}Lu-RM2 show favorable pharmacokinetics as high tumor accumulation, fast clearance from non-tumor tissue and good retention in the tumor over a large time span in humans leading to a high contrast and good therapy results, respectively.

Nonetheless, certain Bombesin analogs are metabolically unstable in animals which limits the desired accumulation in tumor tissues.

On the other hand, it has to be mentioned that more stable GRPR derivatives show slower washout from the GRPR rich pancreas which has to be considered before the usage for therapy of humans due to a possible pancreatitis.

In other malignant indications, yet further markers and targets are of interest. These include Neuromedin-B receptor (Bombesin-1 receptor, NMBR), Bombesin receptor subtype 3 (BRS-3) and Cholecystokinin-2 receptor (CCK-2R).

In view of the above, the technical problem underlying the present invention can be seen in the provision of improved radiopharmaceuticals and radiodiagnostics, in particular in the field of cancer, improvements including pharmacokinetic properties.

This technical problem has been solved by the subject-matter disclosed below.

SUMMARY

In one aspect, the present disclosure provides a GRPR antagonist of formula (I)

S — Y — Xaa_1 — Xaa_2 — L-Ala — L-Val — Xaa_5 — L-His — T (I)

wherein

S is a moiety capable of generating therapeutically active radiation;

Y is an optional linker;

Xaa_1 is L-Gln, D-Gln, or L-His;

Xaa_2 is α-Me-Trp;

Xaa_5 is Gly, N-Me-Gly, D-Ala, or β-Ala; and

T is Sta-Leu-NH_2, Leu-$\psi(CH_2N)$-Pro-NH_2, Leu-NHEt or NH-CH[CH_2-$CH(CH_3)_2$]$_2$, wherein Sta is (3S,4S)-4-amino-3-hydroxy-6-methylheptanoic acid.

In yet another aspect, the present disclosure provides a GRPR antagonist of formula (II)

S — Y — Xaa_3 — Xaa_4 — L-Ala — L-Val — Xaa_5 — L-His — T (II)

wherein

S is a moiety capable of generating a detectable signal;

Y is an optional linker;

Xaa_3 is L-Gln, D-Gln, or L-His;

Xaa_4 is Bta;

Xaa_5 is Gly, N-Me-Gly, or β-Ala; and

T is Sta-Leu-NH_2, Leu-ψ(CH_2N)-Pro-NH_2, Leu-NHEt or NH-CH[CH_2-$CH(CH_3)_2$]$_2$, wherein Sta is (3S,4S)-4-amino-3-hydroxy-6-methylheptanoic acid.

In another aspect, the present disclosure provides a GRPR antagonist of formula (II)

S — Y — Xaa_3 — Xaa_4 — L-Ala — L-Val — Xaa_5 — L-His — T (II)

wherein

S is a moiety capable of generating a detectable signal;

Y is an optional linker;

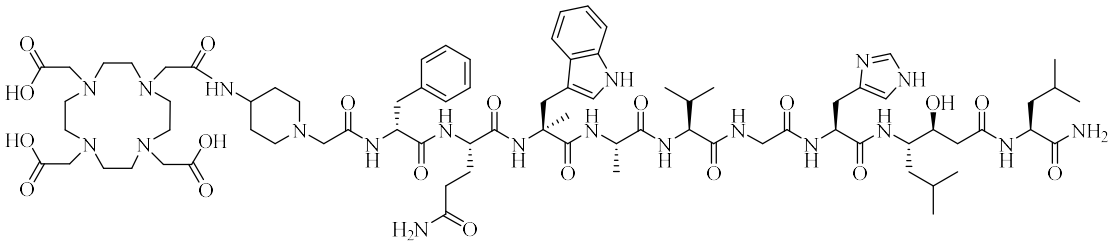
Xaa_3 is Hse;

Xaa_4 is Trp;

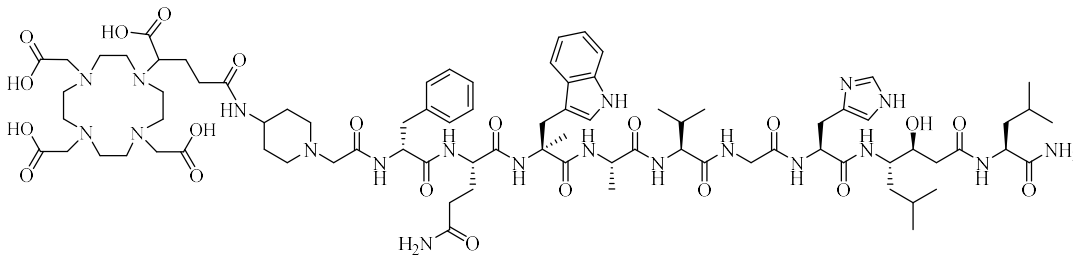
Xaa_5 is Gly, N-Me-Gly, or β-Ala; and

T is Sta-Leu-NH_2, Leu-ψ(CH_2N)-Pro-NH_2, Leu-NHEt or NH-CH[CH_2-$CH(CH_3)_2$]$_2$, wherein Sta is (3S,4S)-4-amino-3-hydroxy-6-methylheptanoic acid.

In another aspect, the present disclosure provides a compound of formula (IIIa) or (IIIb)



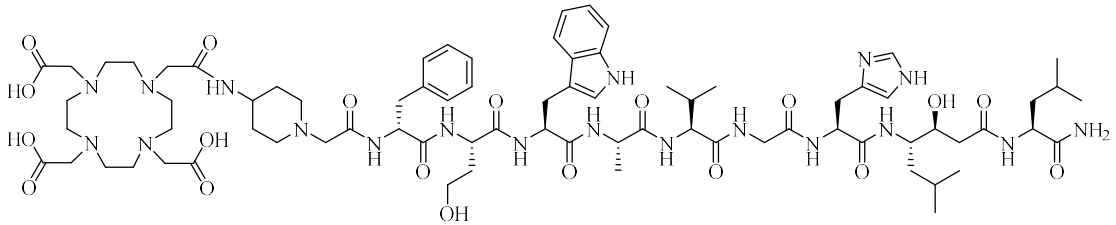
(IIIa)



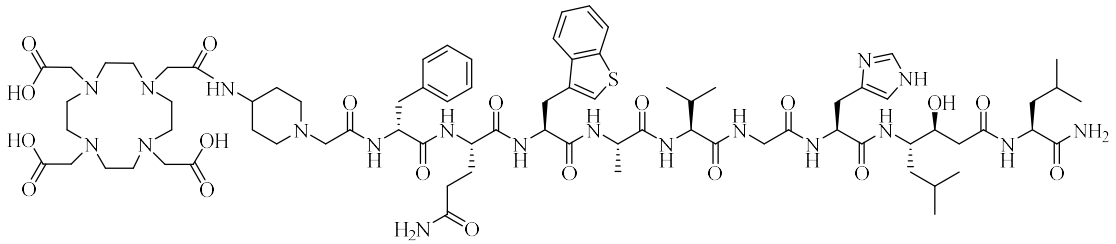
(IIIb)

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In another aspect, the present disclosure provides a compound of formula (IV) or (V)



(IV)



(V)

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In another aspect, the present disclosure provides a GRPR antagonist disclosed herein or a compound disclosed herein for use in medicine.

In another aspect, the present disclosure provides a pharmaceutical composition comprising or consisting of a GRPR antagonist disclosed herein or a compound disclosed herein.

DESCRIPTION

In a first aspect, the present invention relates to a compound binding to an endogenous receptor, said compound comprising (i) an oligopeptide comprising a dipeptide with Trp being the C-terminal amino acid of said dipeptide, wherein said Trp is replaced with an α-amino acid Xaa_2, whereby the stability in serum or plasma

(preferably mammalian serum or plasma) of the peptide bond connecting Xaa_2 to the N-terminally adjacent amino acid is increased as compared to the peptide bond connecting Trp to the N-terminally adjacent amino acid in an otherwise identical compound; and (ii) a moiety capable of generating therapeutically effective radiation, said moiety being covalently bound to said oligopeptide.

Claims

1. A GRPR antagonist of formula (I)

S — Y — Xaa_1 — Xaa_2 — L-Ala — L-Val — Xaa_5 — L-His — T (I)

wherein
S is a moiety capable of generating therapeutically active radiation;
Y is an optional linker;
Xaa_1 is L-Gln, D-Gln, or L-His;
Xaa_2 is α-Me-Trp;
Xaa_5 is Gly, N-Me-Gly, D-Ala, or β-Ala; and
T is Sta-Leu-NH_2, Leu-$\psi(CH_2N)$-Pro-NH_2, Leu-NHEt or NH-CH[CH_2-$CH(CH_3)_2$]$_2$,
wherein Sta is (3S,4S)-4-amino-3-hydroxy-6-methylheptanoic acid.

2. The GRPR antagonist of claim 1, wherein Xaa_1 is L-Gln.

3. The GRPR antagonist of claim 1, wherein Xaa_5 is Gly.

4. A GRPR antagonist of formula (II)

S — Y — Xaa_3 — Xaa_4 — L-Ala — L-Val — Xaa_5 — L-His — T (II)

wherein
S is a moiety capable of generating a detectable signal;
Y is an optional linker;
Xaa_3 is L-Gln, D-Gln, or L-His;
Xaa_4 is Bta;
Xaa_5 is Gly, N-Me-Gly, or β-Ala; and
T is Sta-Leu-NH_2, Leu-$\psi(CH_2N)$-Pro-NH_2, Leu-NHEt or NH-CH[CH_2-$CH(CH_3)_2$]$_2$,
wherein Sta is (3S,4S)-4-amino-3-hydroxy-6-methylheptanoic acid.

5. A GRPR antagonist of formula (II)

S — Y — Xaa_3 — Xaa_4 — L-Ala — L-Val — Xaa_5 — L-His — T (II)

wherein

S is a moiety capable of generating a detectable signal;

Y is an optional linker;

Xaa_3 is Hse;

Xaa_4 is Trp;

Xaa_5 is Gly, N-Me-Gly, or β-Ala; and

T is Sta-Leu-NH_2, Leu-ψ(CH_2N)-Pro-NH_2, Leu-NHEt or NH-CH[CH_2-CH(CH_3)$_2$]$_2$, wherein Sta is (3S,4S)-4-amino-3-hydroxy-6-methylheptanoic acid.

6. The GRPR antagonist of claim 4, wherein Xaa_3 is L-Gln.

7. The GRPR antagonist of claim 4 or 5, wherein Xaa_5 is Gly.

8. The GRPR antagonist of any one of claims 1 to 3, wherein S is selected from a radioactive moiety and a moiety capable of being loaded with a radioactive nuclide.

9. The GRPR antagonist of any one of claims 4 to 7, wherein S is selected from a fluorescent moiety, a radioactive moiety, and a moiety capable of being loaded with a radioactive nuclide.

10. The GRPR antagonist of any of claims 1 to 9, wherein Y
    (a) comprises one, two, three, four, five or six positive and/or negative charge(s);
    (b) comprises or consists of one, two, three, four, five or six amino acids;
    (c) comprises or consists of PEG_n, n being an integer selected from 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10; and/or
    (d) comprises a moiety capable of generating a detectable signal.

11. The GRPR antagonist of claim 10, wherein the amino acid(s) in (b) is(are) D-

amino acid(s).

12. The GRPR antagonist of claim 10, wherein the amino acid(s) in (b) is(are) D-α-amino acid(s).

13. The GRPR antagonist of any one of claims 10 to 12, wherein said linker Y comprises or consists of

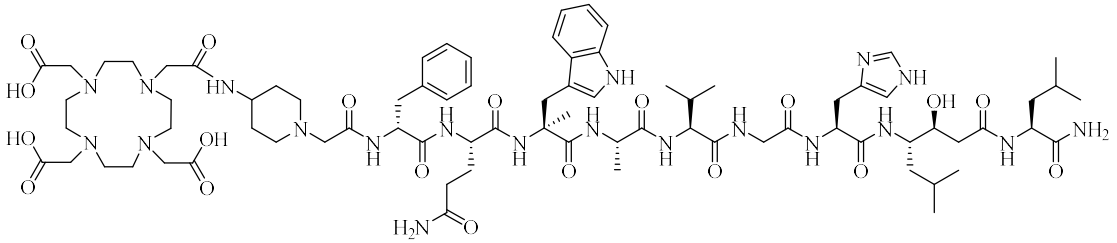
(i) D-Glu-urea-D-Glu;

(ii) one or two 2,3-diaminopropionic acid moieties, optionally substituted with a moiety capable of generating a detectable signal;

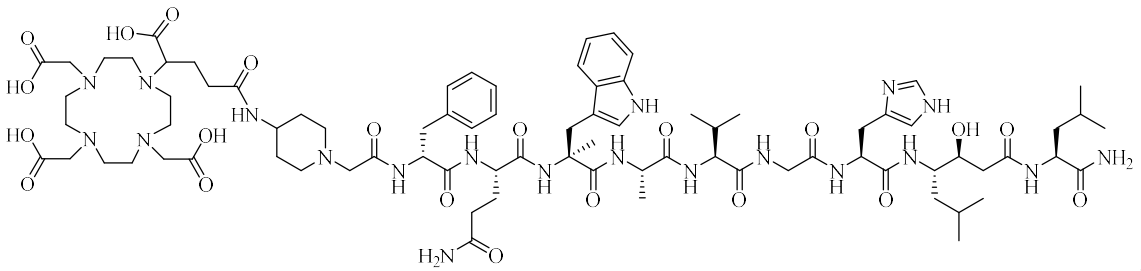
(iii) one, two, three, four, five or six consecutive amino acids comprising or consisting of one or more amino acids selected from D-/L-aspartate, D-/L-ornithine, 4-amino-1-carboxymethyl-piperidine (Pip), D-/L-2,3-diaminopropionic acid, D-/L-serine, D-/L-citrulline moieties, L-cysteic acid (Ala(SO_3H)), amino-valeric acid (Ava), 4-aminobenzoic acid (PABA) and D-Phe; and/or

(iv) p-aminomethylaniline-diglycolic acid (pABza-DIG, AMA-DGA), and/or diglycolate (DIG, DGA).

14. A compound of formula (IIIa) or (IIIb)



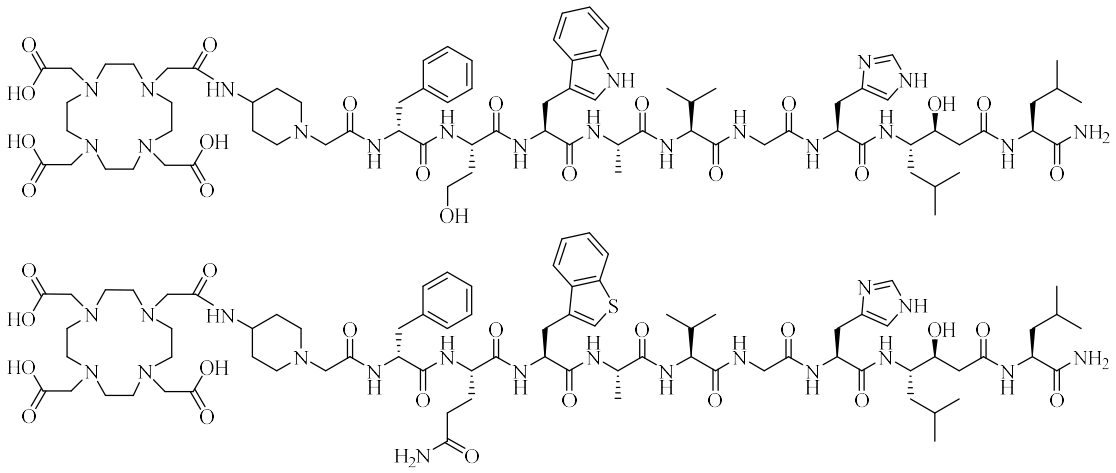
(IIIa)



(IIIb)

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15. A compound of formula (IV) or (V)



(IV)

(V)

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16. The compound of claim 14 or 15 labeled with ^{177}Lu.

17. The compound of claim 14 or 15 labeled with ^{68}Ga.

18. A GRPR antagonist of any one of claims 1 to 13 or a compound of any one of claims 14 to 17 for use in medicine.

19. A pharmaceutical composition comprising or consisting of a GRPR antagonist of any one of claims 1 to 13 or a compound of any one of claims 14 to 17.