

Claims

1. A neurokinin receptor 2 (NK2R) agonist according to formula (I):

5 (A)-(B) (I),

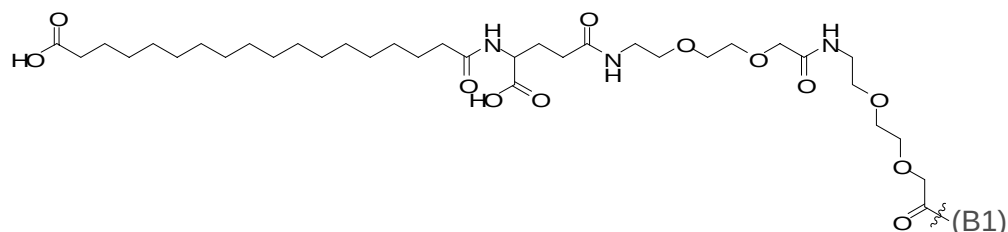
wherein;

(A) is a peptide comprising an amino acid sequence of the general formula $X_1X_2X_3X_4X_5X_6X_7$, wherein

- 10 X_1 is selected from the group consisting of: aspartic acid (D) and glutamic acid (E);
 X_2 is selected from the group consisting of: lysine (K), arginine (R), and histidine (H);
 X_3 is selected from the group consisting of: tyrosine (Y), phenylalanine (F), *meta*-tyrosine (*m*-Y), valine (V), tryptophan (W), methionine (M), leucine (L), isoleucine (I), and alanine (A);
 15 X_4 is selected from the group consisting of: valine (V), threonine (T), serine (S), asparagine (N), glutamine (Q), glycine (G), and alanine (A);
 X_5 is selected from the group consisting of: glycine (G), 2-aminoisobutyric acid (Aib), serine (S), alanine (A), valine (V), leucine (L), beta-alanine (bA) and isoleucine (I);
 20 X_6 is selected from the group consisting of: leucine (L), isoleucine (I), alanine (A) and N-methyl leucine (Me-Leu); and
 X_7 is selected from the group consisting of: norleucine (Nle), methoxinine (Mox), methionine (M), 4-fluorophenylalanine (4fF), and 4-methoxyphenylalanine (4MeOF);

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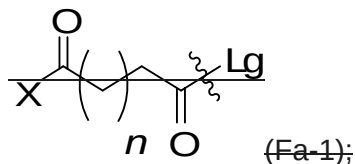
(B) is a conjugated moiety of the general formula (B1#)



30 Fa-Lg (II),

wherein;

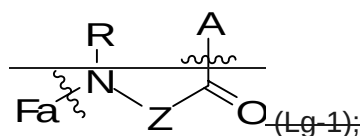
Fa is of formula (Fa-1),



5 wherein n is from 14 to 17, preferably wherein n is 15;

and wherein X is selected from the group consisting of OH , OC_{1-6} , NH_{27} , NHC_{1-6} , and $\text{N}(\text{C}_{1-6})_2$,

Lg is a linking group of formula (Lg-1),



10 wherein Z is a chain comprising from 18 to 23 atoms in the backbone selected from the group consisting of: C, O, and N;

and wherein R is selected from the group consisting of H, and C_{1-6} alkyl; and Lg covalently links (B) to the peptide (A),

and wherein (B) is covalently linked to a terminal amino acid.

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2. The NK2R agonist according to any one of the preceding claim 1s, wherein the peptide (A) is of the general formula $\text{X}_1\text{X}_2\text{X}_3\text{X}_4\text{X}_5\text{X}_6\text{X}_7$, wherein

X_1 is selected from the group consisting of: aspartic acid (D) and glutamic acid (E);

20 X_2 is selected from the group consisting of: lysine (K), and arginine (R);

X_3 is selected from the group consisting of: tyrosine (Y), and phenylalanine (F), and *meta*-tyrosine (*m*-Y),

X_4 is selected from the group consisting of: valine (V), and threonine (T);

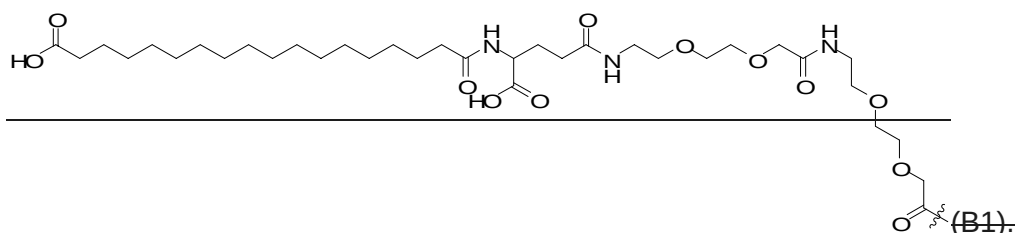
25 X_5 is selected from the group consisting of: glycine (G), 2-aminoisobutyric acid (Aib), beta-alanine (bA) and serine (S);

X_6 is selected from the group consisting of: leucine (L), and N-methyl leucine (Me-Leu); and

X_7 is selected from the group consisting of: norleucine (Nle), methoxinine (Mox), methionine (M), 4-fluorophenylalanine (4fF), and 4-methoxyphenylalanine (4MeOF).

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3. ~~The NK2R agonist according to any one of the preceding claims, wherein X₂ is arginine (R).~~
- 5 4. ~~The NK2R agonist according to any one of the preceding claims, wherein X₃ is tyrosine (Y).~~
- 5 5. ~~The NK2R agonist according to any one of the preceding claims, wherein X₄ is threonine (T).~~
- 10 6. ~~The NK2R agonist according to any one of the preceding claims, wherein X₅ is selected from the group consisting of: 2-aminoisobutyric acid (Aib) and serine (S).~~
- 15 7. ~~The NK2R agonist according to any one of the preceding claims, wherein X₆ is N-methyl-leucine (Me-Leu).~~
8. ~~The NK2R agonist according to any one of the preceding claims, wherein X₇ is methoxinine (Mox).~~
- 20 9. ~~The NK2R agonist according to any one of the preceding claims, wherein n is 15 and wherein X is OH.~~
10. ~~The NK2R agonist according to any one of the preceding claims, wherein Lg of the conjugated moiety does not comprise functional groups that are positively charged at pH = 7.4.~~
- 25 11. ~~The NK2R agonist according to any one of the preceding claims, wherein Lg of the conjugated moiety has a net neutral charge or -1 at pH = 7.4.~~
- 30 12. ~~The NK2R agonist according to any one of the preceding claims, wherein the conjugated moiety is of formula (B1);~~



13.3. The NK2R agonist according to any one of the preceding claims, wherein the conjugated moiety (B) is covalently attached to the N-terminus of (A), optionally via an amide bond.

14.4. The NK2R agonist according to any one of the preceding claims, wherein the conjugated moiety (B) is covalently attached to the N-terminus of (A) via an amide bond with the N-terminal α -NH₂ group.

15.5. The NK2R agonist according to any one of the preceding claims, wherein the peptide (A) is amidated on the C-terminus.

16. The NK2R agonist according to any one of the preceding claims, wherein the peptide (A) comprises from 7 to 15 amino acids, such as from 7 to 14 amino acids, such as from 7 to 13 amino acids, such as from 7 to 12 amino acids, such as from 7 to 11 amino acids, such as from 7 to 10 amino acids, such as from 7 to 9 amino acids, such as from 7 to 8 amino acids, preferably wherein the peptide comprises 7 amino acids.

17. The NK2R agonist according to any one of the preceding claims, wherein the peptide (A) comprises no more than 15 amino acids, such as no more than 14 amino acids, such as no more than 13 amino acids, such as no more than 12 amino acids, such as no more than 11 amino acids, such as no more than 10 amino acids, such as no more than 9 amino acids, such as no more than 8 amino acids, such as no more than 7 amino acids.

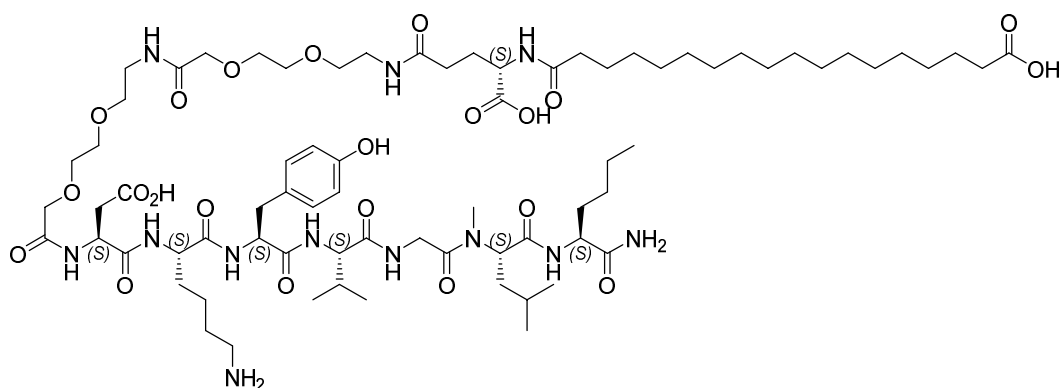
18.6. The NK2R agonist according to any one of the preceding claims, wherein the peptide (A) consists of 7 amino acids of the general formula X₁X₂X₃X₄X₅X₆X₇.

~~19.7.~~_____ The NK2R agonist according to any one of the preceding claims, wherein
 (A) is: Asp;Lys;Phe;Val;Gly;Me-NmLeu;Nle;NH₂ (compound 305), and
 (B) is of formula (B1) covalently attached to the N-terminal aspartate of (A).

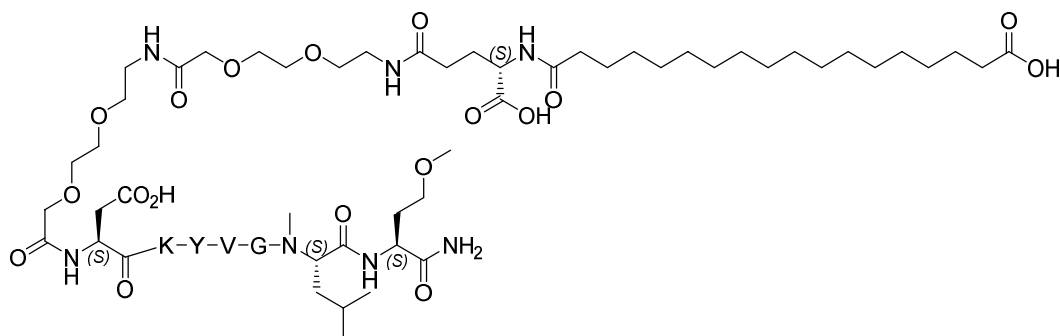
5 ~~20.8.~~_____ The NK2R agonist according to any one of claims 1-**Error! Reference source not found.**, wherein
 (A) is: Asp;Lys;Tyr;Val;Gly;Me-NmLeu;Metex;NH₂ (compound 344), and
 (B) is of formula (B1) covalently attached to the N-terminal aspartate of (A).

10 ~~21.9.~~_____ The NK2R agonist according to any one of claims 1-**Error! Reference source not found.**, wherein the NK2R agonist consists of the sequence of any one of SEQ ID NO: 1 to SEQ ID NO: 57.

15 ~~22.10.~~_____ The NK2R agonist according to any one of claims 1-**Error! Reference source not found.**, wherein the NK2R agonist is:

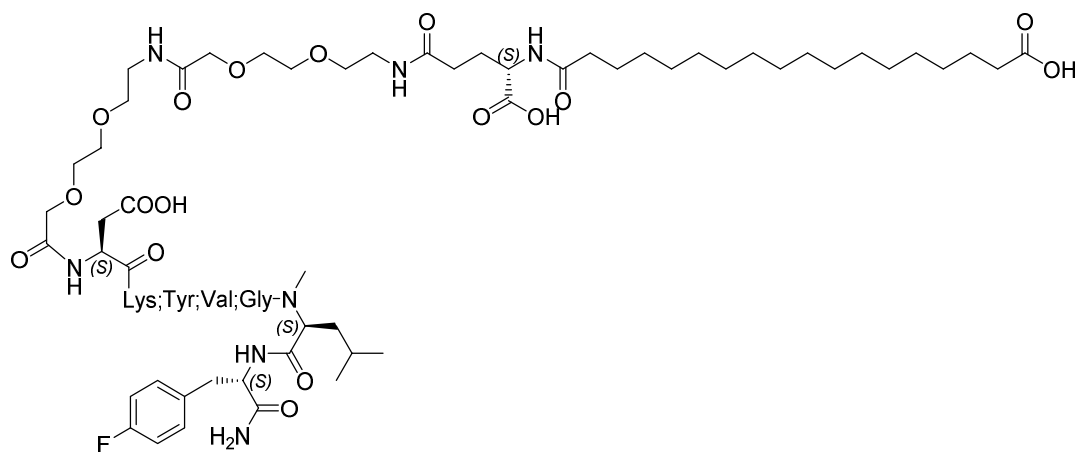


(ID 305);

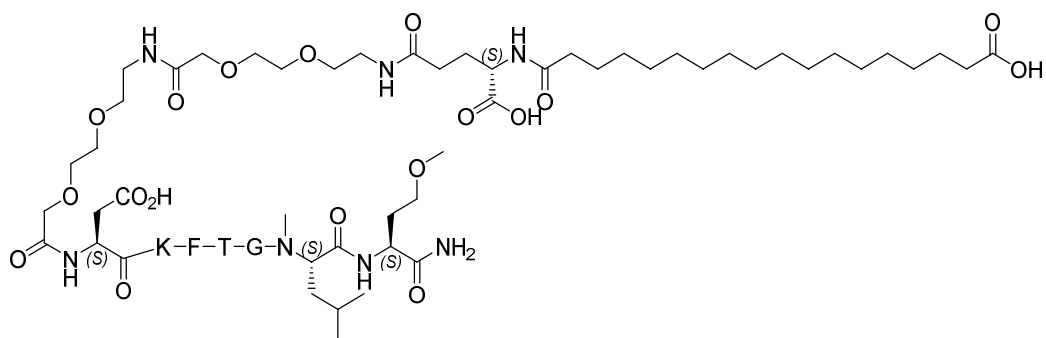


(ID 344); or

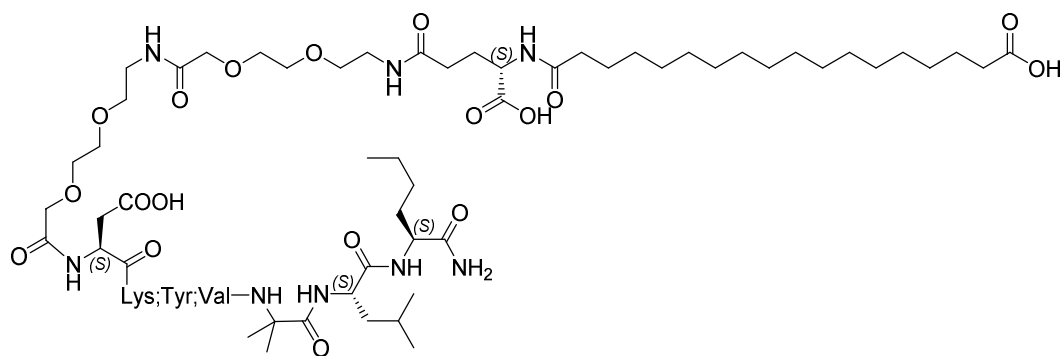
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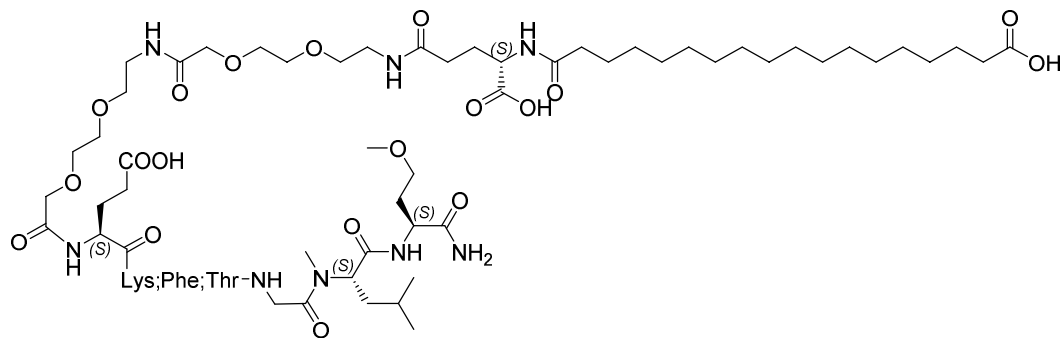
ID 369);



(ID 383);

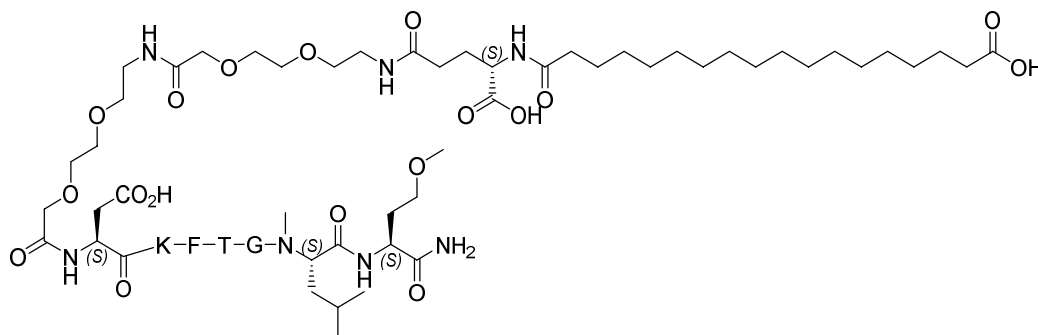


395) or;



398).

11. A NK2R agonist which is



(compound 383).

23. The NK2R agonist according to any one of the preceding claims, wherein the NK2R agonist is a selective neurokinin receptor 2 (NK2R) agonist.

24. The NK2R agonist according to any one of the preceding claims, wherein the NK2R agonist has an EC₅₀ towards human NK2R of 300 nM or less, such as 250 nM or less, such as 200 nM or less, such as 150 nM or less, such as 100 nM or less, such as 90 nM or less, such as 80 nM or less, such as 70 nM or less, such as 60 nM or less, such as 50 nM or less.

25. The NK2R agonist according to any one of the preceding claims, wherein the NK2R agonist has an EC₅₀ towards human NK2R of 50 nM or less, such as 40 nM or less, such as 30 nM or less, such as 20 nM or less, such as 15 nM or less, such as 14 nM or less, such as 13 nM or less, such as 12 nM or less, such as 11 nM or less, such as 10 nM or less.

26. The NK2R agonist according to any one of the preceding claims, wherein the NK2R agonist has an EC₅₀ towards human NK1R of at least 100 nM, such as at least 200 nM, such as at least 300 nM, such as at least 400 nM, such as at least 500 nM.

27. The NK2R agonist according to any one of the preceding claims, wherein the NK2R agonist has an EC₅₀ towards human NK3R of at least 100 nM, such as at least 200 nM, such as at least 300 nM, such as at least 400 nM, such as at least 500 nM.

~~28.12.~~ A pharmaceutical composition comprising the neurokinin receptor 2 (NK2R) agonist as defined in any one of the preceding claims, and one or more pharmaceutically acceptable adjuvants, excipients, carriers, buffers and/or diluents.

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~~29.13.~~ A neurokinin receptor 2 (NK2R) agonist as defined in any one of claims 1 to 2711 for use as a medicament.

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~~30.~~ ~~The~~ A method for treating a disease in a subject comprising administering a neurokinin receptor 2 (NK2R) agonist for use as defined in any one claims 131 to 29 ~~for treatment of~~ in treating a NK2R mediated disorder.

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~~31.~~ The method according to claim 30, wherein the NK2R mediated disorder is selected from the group consisting of: obesity, dysfunctional voiding, diabetes, such as type-II diabetes, and diabetes-related disorders, such as.

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~~32.~~ The method according to any one of claims 30-31, wherein the NK2R mediated disorder is a metabolic disorder.

~~33.~~ The method according to any one of claims 30-32, wherein the metabolic disorder is a diabetes-related disorder.

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~~34.14.~~ The method according to claim 33, wherein the diabetes-related disorder is selected from the group consisting of: impaired insulin tolerance and impaired glucose tolerance.

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~~35.~~ A method for modulating the activity of NK2R, comprising contacting NK2R with a neurokinin receptor 2 (NK2R) agonist as defined in any one claims 1 to 27.

~~36.15.~~ Use of a neurokinin receptor 2 (NK2R) agonist as defined in any one claims 1 to ~~11-27~~ for in the manufacture of a medicament for the treatment of a metabolic disorder, such as a diabetes-related, such as impaired insulin tolerance and impaired glucose tolerance.