

With such a short half-life, PYY₃₋₃₆ should be administered at least once-daily to exert a therapeutic effect, which is inconvenient for an individual in need thereof. Efforts therefore have been made to increase PYY₃₋₃₆'s half-life and/or to increase its NPY2 receptor selectivity. For example, Rubinstein *et al.* describe PYY analogs having a 9-fluorenylmethoxy-carbonyl (Fmoc) or a 2-sulfo-9-fluorenyl-methoxycarbonyl (FMS) radical to increase half-life (*see*, Intl. Patent Application Publication No. WO 2004/089279). Moreover, DeCarr *et al.* describe PYY analogs having amino-terminally linked PEG moieties to increase half-life (*see*, DeCarr *et al.* (2007) *Bioorg. Med. Chem. Lett.* 17:1916-1919; *see also*, Ortiz *et al.* (2007) *J. Pharmacol. Exp. Ther.* 323:692-700). Furthermore, Kofoed *et al.* describe PYY analogs having albumin-binding side chains, at least one modified residue close to PYY's cleavage site (*e.g.* an N-methyl amino acid analog of an amino acid residue of interest), a N-glycine, and/or an arginine mimetic to increase half-life (*see*, Intl. Patent Application Publication No. WO 2011/033068).

[0006] Despite significant increases in understanding PYY₃₋₃₆'s role in metabolism, there remains a need for additional PYY analogs, especially PYY analogs having improved potency and selectivity at the NPY2 receptor.

Summary

[0006a] In one aspect of the present disclosure, there is provided a Peptide Tyrosine-Tyrosine (PYY) analog comprising an amino acid sequence of:

PKPEX₇PX₉X₁₀DASPEEX₁₇X₁₈RYXX₂₂X₂₃LRHYLN₃₀LTRQRY (Formula I),

wherein X₇ is any amino acid with a functional group available for conjugation and the functional group is conjugated to a C₁₆-C₂₂ fatty acid, wherein the C₁₆-C₂₂ fatty acid is conjugated to the amino acid with the functional group available for conjugation via a linker, and wherein the linker can be one or more units selected from the group consisting of [2-(2-amino-ethoxy)-ethoxy]-acetic acid (AEEA), aminohexanoic acid (Ahx), glutamic acid (E), gamma glutamic acid (γE) and combinations thereof,

wherein X₉ is E or G,

wherein X₁₀ is E or K,

wherein X₁₇ is L or W,

wherein X₁₈ is N or Q,

wherein X₂₂ is A or I,

wherein X₂₃ is E, D or S,

wherein X₃₀ is E or W (SEQ ID NO:3), and

wherein a C-terminal amino acid is optionally amidated.

[0006b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising:

at least one Peptide Tyrosine-Tyrosine (PYY) analog disclosed herein or a salt thereof; and

one or more pharmaceutically acceptable carriers, diluents and excipients.

[0006c] In a further aspect of the present disclosure, there is provided a use of a Peptide Tyrosine-Tyrosine (PYY) analog disclosed herein or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating obesity or an obesity related disease or disorder in an individual in need thereof.

[0006d] In another aspect of the present disclosure, there is provided a Peptide Tyrosine-Tyrosine (PYY) analog disclosed herein or a pharmaceutically acceptable salt thereof, for use in therapy.

Description

[0007] As noted above, additional PYY analogs for therapeutic uses are needed. To address this need, the disclosure first describes PYY analogs that include a base amino acid sequence of (with respect to the numbering of native, human PYY₁₋₃₆ (SEQ ID NO:1)):

³PKPEX₇PX₉X₁₀DASPEEX₁₇X₁₈RYYX₂₂X₂₃LRHYLNX₃₀LTRQRY³⁶ (Formula I), where X₇ is any amino acid with a functional group available for conjugation and the functional group is conjugated to a C₁₆-C₂₂ fatty acid, X₉ is E or G, X₁₀ is E or K, X₁₇ is L or W, X₁₈ is N or Q, X₂₂ is A or I, X₂₃ is E, D or S, and X₃₀ is E or W (SEQ ID NO:3), and where a carboxy-terminal (C-terminal) amino acid optionally is amidated.

[0008] In certain instances, the amino acid with the functional group available for conjugation at position X₇ can be C, D, E, K or Q. In particular instances, the amino acid with the functional group available for conjugation at position X₇ is K, and the amino acid sequence can be one of the following:

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³PKPEKPGEDASPEEWQRYYAELRHLYLNWLTRQRY³⁶ (SEQ ID NO:4),
³PKPEKPGEDASPEEWQRYYAELRHLYNELTRQRY³⁶ (SEQ ID NO:5),
³PKPEKPEEDASPEEWQRYYIELRHLYLNWLTRQRY³⁶ (SEQ ID NO:6),
³PKPEKPGKDASPEEWNRYYADLRHLYLNWLTRQRY³⁶ (SEQ ID NO:7), or

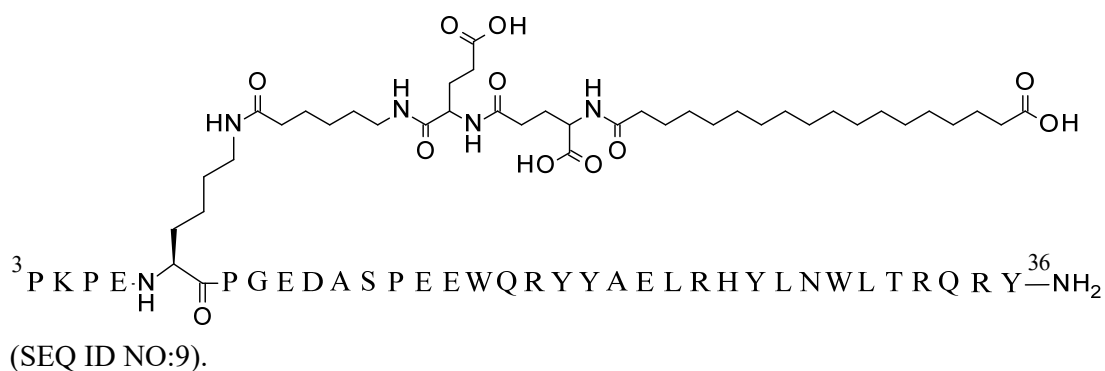
CLAIMS

The invention claimed is:

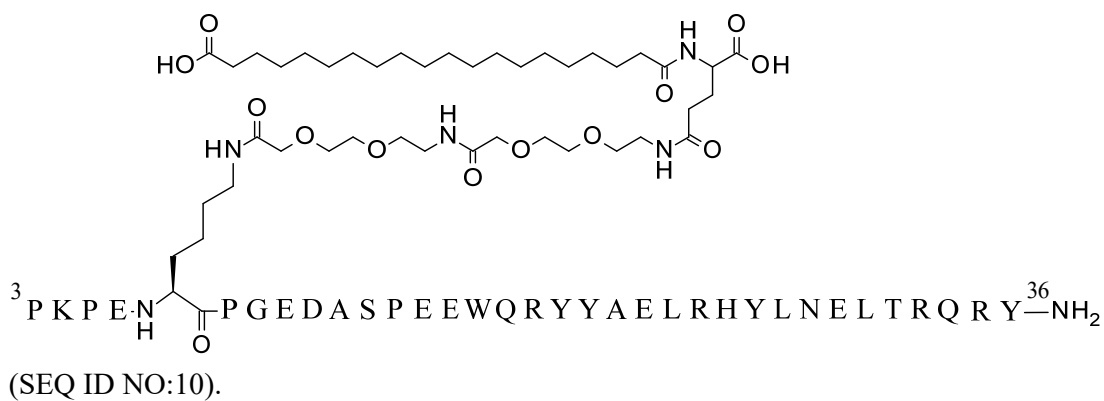
1. A Peptide Tyrosine-Tyrosine (PYY) analog comprising an amino acid sequence of: PKPEX₇PX₉X₁₀DASPEEX₁₇X₁₈RYYX₂₂X₂₃LRHYLN₃₀LTRQRY (Formula I),
wherein X₇ is any amino acid with a functional group available for conjugation and the functional group is conjugated to a C₁₆-C₂₂ fatty acid, wherein the C₁₆-C₂₂ fatty acid is conjugated to the amino acid with the functional group available for conjugation via a linker, and wherein the linker can be one or more units selected from the group consisting of [2-(2-amino-ethoxy)-ethoxy]-acetic acid (AEEA), aminohexanoic acid (Ahx), glutamic acid (E), gamma glutamic acid (γE) and combinations thereof,
wherein X₉ is E or G,
wherein X₁₀ is E or K,
wherein X₁₇ is L or W,
wherein X₁₈ is N or Q,
wherein X₂₂ is A or I,
wherein X₂₃ is E, D or S,
wherein X₃₀ is E or W (SEQ ID NO:3), and
wherein a C-terminal amino acid is optionally amidated.
2. The PYY analog of Claim 1, wherein X₇ is selected from the group consisting of C, D, E, K and Q.
3. The PYY analog of Claim 1, wherein X₇ is K and conjugation to the C₁₆-C₂₂ fatty acid is through an epsilon-amino group of a K side chain.
4. The PYY analog of Claim 1, wherein the amino acid sequence is selected from the group consisting of:
PKPEKPGEDASPEEWQRYYAELRHYLNWLTRQRY (SEQ ID NO:4);
PKPEKPGEDASPEEWQRYYAELRHYLNELTRQRY (SEQ ID NO:5);
PKPEKPEEDASPEEWQRYYIELRHYLNWLTRQRY (SEQ ID NO:6);
PKPEKPGKDASPEEWNRYYADLRHYLNWLTRQRY (SEQ ID NO:7); and

PKPEKPGEDASPEELQRYYYASLRHYLNWLTRQRY (SEQ ID NO:8).

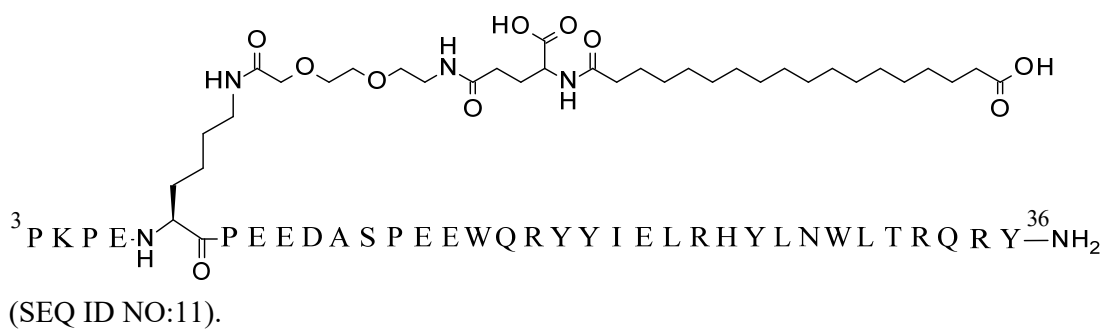
5. The PYY analog of Claim 1, wherein the C₁₆-C₂₂ fatty acid is selected from the group consisting of a hexadecanoic acid, a hexadecanedioic acid, a heptadecanoic acid, a heptadecanedioic acid, a stearic acid, an octadecanedioic acid, a nonadecylic acid, a nonadecanedioic acid, an eicosanoic acid, an eicosanedioic acid, a heneicosanoic acid, a heneicosanedioic acid, a docosanoic acid, a docosanedioic acid, and branched and substituted derivatives thereof.
6. The PYY analog of Claim 5, wherein the C₁₆-C₂₂ fatty acid is a C₁₈-C₂₀ fatty acid.
7. The PYY analog of Claim 6, wherein the C₁₈-C₂₀ fatty acid is a straight-chain fatty acid having a formula of CO-(CH₂)_x-CO₂H, and wherein _x is 16 or 18.
8. The PYY analog of Claim 1, wherein the C₁₆-C₂₂ fatty acid is selected from the group consisting of palmitic acid, stearic acid, arachidic acid and eicosanoic acid.
9. The PYY analog of claim 1, wherein the amino acid sequence is:



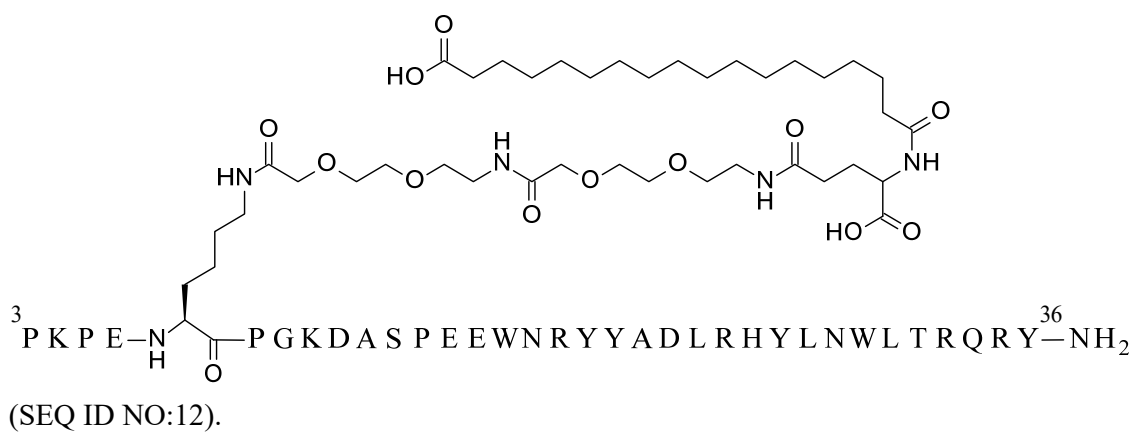
10. The PYY analog of claim 1, wherein the amino acid sequence is:



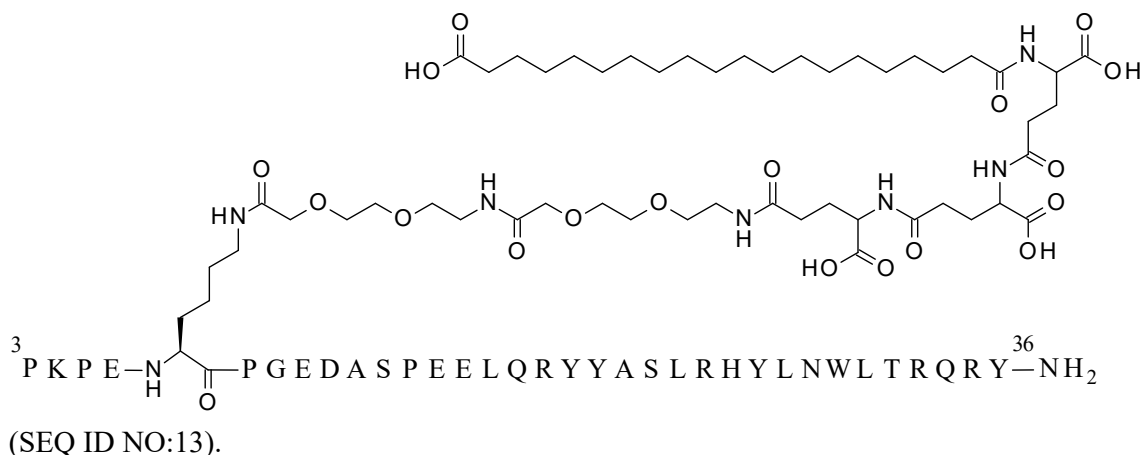
11. The PYY analog of claim 1, wherein the amino acid sequence is:



12. The PYY analog of claim 1, wherein the amino acid sequence is:



13. The PYY analog of claim 1, wherein the amino acid sequence is:



14. The PYY analog of claim 1, wherein the linker and the fatty acid together are selected from the group consisting of (AEEA)2· γ E·C20 diacid, Ahx·E· γ E·C18 diacid, and AEEA· γ E·C18 diacid.

15. A pharmaceutical composition comprising:
at least one Peptide Tyrosine-Tyrosine (PYT) analog of Claim 1 or a salt thereof;
and
one or more pharmaceutically acceptable carriers, diluents and excipients.

16. The pharmaceutical composition of Claim 15 further comprising an additional therapeutic agent.

17. The pharmaceutical composition of Claim 16, wherein the additional therapeutic agent is an incretin selected from the group consisting of glucagon (GCG), a GCG analog, glucagon-like peptide-1 (GLP-1), GLP-1₇₋₃₆-amide, a GLP-1 analog, gastric inhibitory peptide (GIP), a GIP analog, oxyntomodulin (OXM), an OXM analog, a GIP/GLP-1, a GLP-1/GCG, or an incretin analog having triple receptor activity.

18. The pharmaceutical composition of Claim 16, wherein the additional therapeutic agent is a dipeptidyl peptidase-IV (DPP-IV) inhibitor.

19. The PYY analog of claim 18, wherein the (AEEA)₂·γE·C₂₀ diacid is (AEEA)₂-(γE)-CO—(CH₂)₁₈—COOH, wherein the Ahx·E·γE·C₁₈ diacid is (Ahx-E-(γE)-CO—(CH₂)₁₆—COOH, and wherein the AEEA·γE·C₁₈ diacid is (AEEA)-(γE)-CO—(CH₂)₁₆—COOH.

20. Use of a Peptide Tyrosine-Tyrosine (PYY) analog of claim 1 or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating obesity or an obesity related disease or disorder in an individual in need thereof.

21. The use of claim 20, wherein the PYY analog or pharmaceutically acceptable salt thereof is to be subcutaneously (SQ) administered to the individual.

22. The use of claim 20, where the PYY analog or pharmaceutically acceptable salt thereof is to be orally administered to the individual.

23. The use of claim 20, wherein the PYY analog or pharmaceutically acceptable salt thereof is to be administered daily, every other day, three times a week, two times a week, one time a week, or biweekly.

24. The use of claim 20, wherein the PYY analog or pharmaceutically acceptable salt thereof is to be administered SQ one time a week (QW).

25. The use of claim 20, wherein the PYY analog or pharmaceutically acceptable salt thereof is to be administered orally one time a week.

26. The use of claim 20, wherein an additional therapeutic agent is to be administered to the individual.

27. The use of claim 26, wherein the additional therapeutic agent is an incretin selected from the group consisting of glucagon (GCG), a GCG analog, glucagon-like peptide-1 (GLP-1), GLP-17-36-amide, a GLP-1 analog, gastric inhibitory peptide (GIP), a GIP analog, oxyntomodulin (OXM), an OXM analog, a GIP/GLP-1, a GLP-1/GCG, or an incretin analog having triple receptor activity.

28. The use of claim 26, wherein the additional therapeutic agent is a dipeptidyl peptidase-IV (DPP-IV) inhibitor.

29. A Peptide Tyrosine-Tyrosine (PYY) analog of claim 1 or a pharmaceutically acceptable salt thereof, for use in therapy.