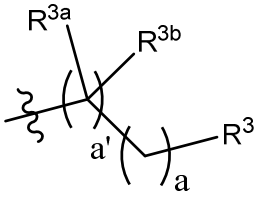
R$^{2'}$ is as defined according to **(AA)** or **(BB)** below:

(AA)

R$^{2'}$ is 

, wherein:

R^{3} is -C(O)OH, -C(O)OR^{31}, -CH(C(O)OH)$_2$ or a carboxylic acid isostere (e.g., amide or tetrazolyl);

a is 0-5;

a' is 0 or 1; and

each of **R^{3a}** and **R^{3b}** is independently H or C$_{1-3}$ alkyl;

~~**(BB)**~~

~~**R$^{2'}$** and **R^{4}** taken together with the atoms connecting them form a ring including from 5-8 ring atoms, wherein from 3-7 are ring carbon atoms each substituted with from 1-2 substituents independently selected from H, halo, hydroxy, oxo, and C$_{1-3}$ alkyl; and from 0-1 is a heteroatom (in addition to the N attached to **R^{1}**) selected from O, -NH, -N(C$_{1-3}$ alkyl), and S (e.g., R^{4} and R^{3}, taken together with the atoms to which each is attached form a ring including 5-8 ring atoms);~~

R^{31} is:

(**i**) C$_{1-6}$ alkyl optionally substituted with from 1-2 independently selected **R^{e}**;

(**ii**) -(C$_{0-3}$ alkylene)-C$_{3-10}$ cycloalkyl, wherein the cycloalkyl is optionally substituted with from 1-4 independently selected **R^{d}**;

(**iii**) -(C$_{0-3}$ alkylene)-heterocyclyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are each independently selected from the group consisting of N(**R^{a}**), O, and S, wherein the heterocyclyl is optionally substituted with from 1-4 independently selected **R^{d}**;

pharmaceutically acceptable salt thereof or compositions containing the same) and one or more pharmaceutically acceptable excipients. In one aspect, the present disclosure refers to a pharmaceutical composition comprising a compound or salt as described herein and one or more pharmaceutically acceptable excipients.

In one example, methods for modulating (e.g., agonizing, partially agonizing, or antagonizing) GLP-1R and/or GIPR activities are featured that include contacting GLP-1R and/or GIPR with a chemical entity described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same). Methods include *in vitro* methods, e.g., contacting a sample that includes one or more cells, each independently comprising one or more of GLP-1R and/or GIPR with the chemical entity. Methods can also include *in vivo* methods; e.g., administering the chemical entity to a subject (e.g., a human) having a disease, disorder, or condition in which modulation of GLP-1R and/or GIPR signaling is beneficial for the treatment of the underlying pathology and/or symptoms and/or progression of the disease, disorder, or condition (e.g., diabetes; e.g., NASH; e.g., obesity). *In vivo* methods include, but are not limited to modulating (e.g., increasing) insulin levels and modulating (e.g., decreasing) glucose levels in a subject (e.g., a human). In some of the foregoing examples, said methods of modulating are achieved without substantially stimulating β-arrestin signaling; e.g., without stimulating the recruitment of β-arrestin to a G-protein coupled receptor (e.g., GLP-1R); e.g., without stimulating the formation of a complex (e.g., a signaling complex) between β-arrestin and a G-protein coupled receptor (e.g., GLP-1R). In some of the foregoing examples, said methods of modulating are achieved without causing aversion or nausea.

In one aspect, the present disclosure refers to an *in vitro* method for modulating GLP-1R and/or GIPR activity, the method comprising contacting GLP-1R and/or GIPR with a compound as described herein. In another ~~aspect~~example, the present disclosure refers to use of a compound as described herein in the manufacture of a medicament for modulating GLP-1R and/or GIPR activity *in vivo*.

In one aspect, the present disclosure refers to use of a compound as described herein in the manufacture of a medicament for ~~modulating~~ treating GLP-1R and/or GIPR induced aversion, nausea and/or vomiting.

In one aspect, the present disclosure refers to use of a compound as described herein in the manufacture of a medicament for ~~modulating (e.g.,~~ increasing~~)~~ insulin levels in a subject in need of such ~~modulating~~increasing.

In one aspect, the present disclosure refers to use of a compound as described herein in the manufacture of a medicament for ~~modulating (e.g.,~~ decreasing~~)~~ glucose levels in a subject in need of such ~~modulating~~decreasing.

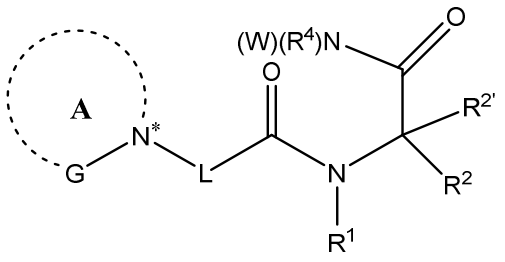
In one aspect, the present disclosure refers to use of a compound as described herein in the manufacture of a medicament for treating a disease, disorder, or condition selected from the group consisting of diabetes, NASH, obesity, fatty liver disease, and steatohepatitis~~, in which modulating GLP-1R and/or GIPR signaling can alter the pathology and/or symptoms and/or progression of the disease, disorder, or condition~~.

In one ~~aspect~~example, the present disclosure refers to use of a compound as described herein in the manufacture of a medicament for treating a disease, disorder, or condition, in which modulating GLP-1R and/or GIPR signaling causes aversion, nausea or vomiting.

In a further example, methods of treatment of a disease, disorder, or condition are featured, in which modulation of GLP-1R and/or GIPR signaling is beneficial for the treatment of the underlying pathology and/or symptoms and/or progression of the disease, disorder, or condition. The methods include administering to a subject in need of such treatment an effective amount of a chemical entity described herein (e.g., a compound described generically or specifically herein, a pharmaceutically acceptable salt thereof, or compositions containing the same).

WHAT IS CLAIMED IS:

1. A compound having formula (IAA), or a pharmaceutically acceptable salt thereof:



(IAA)

wherein:

ring A is:

(**i**) a saturated or unsaturated monocyclic ring that includes from 3-8 ring atoms (inclusive of **G** and the nitrogen atom labelled N*); or

(**ii**) a saturated or unsaturated bicyclic or tricyclic ring that includes from 6-14 ring atoms (inclusive of **G** and the nitrogen atom labelled N*), wherein:

- **G** is C(O), S(O), or SO_2; and
- the dotted, circular line connecting **G** and N* is a divalent group that includes from 1-6 ring atoms; wherein:

(**a**) from 0-2 of the divalent group's ring atoms are ring heteroatoms, which are each independently selected from the group consisting of N, N(**R**^{a}), O, S, and SO_2; and

(**b**) from 1-6 of the divalent group's ring atoms are ring carbon atoms, which are each independently selected from the group consisting of C, CH, CH_2, CR^b, $C(R^b)_2$, and CHR^b;

wherein:

(**1**) when **ring A** is a monocyclic ring, then each of the divalent group's 1-6 ring carbon atoms is independently selected from the group consisting of CH, CH_2, CR^b, $C(R^b)_2$, and CHR^b; and

(**2**) when **ring A** is a bicyclic or tricyclic ring, then (**A**) or (**B**) applies:

(**A**) two or three adjacent ring carbon atoms of the divalent group are each independently selected from the group consisting of C, CH, CH_2, CR^b, $C(R^b)_2$, and CHR^b and are fused to a second ring that is selected from the group consisting of:

(**a**) C_{6-10} aryl optionally substituted with from 1-5 independently selected $\mathbf{R^c}$;

(**b**) heteroaryl including from 5-10 ring atoms, wherein from 1-4 ring atoms are each independently selected from the group consisting of N, N($\mathbf{R^a}$), O, and S, wherein the heteroaryl is optionally substituted with from 1-3 independently selected $\mathbf{R^c}$;

(**c**) C_{3-10} cycloalkyl optionally substituted with from 1-4 independently selected $\mathbf{R^d}$;

(**d**) heterocyclyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are each independently selected from the group consisting of N($\mathbf{R^a}$), O, and S, wherein the heterocyclyl is optionally substituted with from 1-4 independently selected $\mathbf{R^d}$; or

(**B**) one of the divalent group's ring carbon atoms is C and is spiro-fused to a second ring that is selected from the group consisting of:

(**a**) C_{3-10} cycloalkyl optionally substituted with from 1-4 independently selected $\mathbf{R^d}$;

(**b**) heterocyclyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are each independently selected from the group consisting of N($\mathbf{R^a}$), O, and S, wherein the heterocyclyl is optionally substituted with from 1-4 independently selected $\mathbf{R^d}$;

L is:

(**i**) $-(CH_2)_{\mathbf{m}}-\mathbf{X^1}-(CH_2)_{\mathbf{n}}-\mathbf{X^2}-(CH_2)_{\mathbf{p}}-$ (formula VIII), wherein **m** is from 1-6; **n** is from 0-2; and **p** is from 0-8;

(**ii**) $-C(O)-(CH_2)_{\mathbf{n}}-\mathbf{X^3}-(CH_2)_{\mathbf{p}}-$ (formula IX), wherein **n** is from 0-2; and **p** is from 0-8;

(**iii**) $-(CH_2)_{\mathbf{q}}-$, wherein **q** is from 1-10;

(**iv**) -C(O)-; or

(**v**) $-(CH_2)_{\mathbf{m}}-\mathbf{X^1}-(CH_2)_{\mathbf{p}}-$ (formula VIII), wherein **m** is from 1-6; and **p** is from 0-8;

$\mathbf{X^1}$ is -C(O)-; -N(R')C(O)-; -C(O)N(R')-; or -N(R')C(O)NR')-; wherein each occurrence of **R'** is independently selected from the group consisting of: H and C_{1-4} alkyl;

$\mathbf{X^2}$ is:

(**i**) -O-;

(**ii**) -S-;

(**iii**) -$S(O)_t$-, wherein **t** is 1 or 2;

(**iv**) -$C(Q^1)(Q^2)$-, wherein each of $\mathbf{Q^1}$ and $\mathbf{Q^2}$ is independently selected from the group consisting of H and C_{1-4} alkyl; or $\mathbf{Q^1}$ and $\mathbf{Q^2}$, together with the carbon atom to which each is attached forms C_{3-10} cycloalkyl that is optionally substituted with from 1-4 independently selected $\mathbf{R^d}$ and optionally fused to phenyl;

(**v**) C_{6-10} arylene optionally substituted with from 1-5 independently selected $\mathbf{R^c}$;

(**vi**) heteroarylene including from 5-10 ring atoms, wherein from 1-4 ring atoms are each independently selected from the group consisting of N, N($\mathbf{R^a}$), O, and S; and which is optionally substituted with from 1-5 independently selected $\mathbf{R^c}$;

(**vii**) C_{3-10} cycloalkylene optionally substituted with from 1-4 independently selected $\mathbf{R^d}$;

(**viii**) heterocycloalkylene including from 3-10 ring atoms, wherein from 1-3 ring atoms are each independently selected from the group consisting of N($\mathbf{R^a}$), O, and S; and which is optionally substituted with from 1-5 independently selected $\mathbf{R^d}$;

(**ix**) C_2-C_4 alkenylene optionally substituted with from 1-2 $\mathbf{R^e}$; or

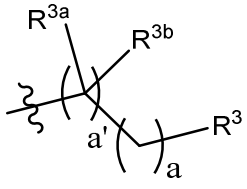
(**x**) C_2-C_4 alkynylene optionally substituted with from 1-2 $\mathbf{R^e}$;

$\mathbf{X^3}$ is: -O-; -S-; or -$S(O)_t$-, wherein **t** is 1 or 2;

each of $\mathbf{R^1}$, $\mathbf{R^2}$, and $\mathbf{R^4}$ is independently selected from the group consisting of H and unsubstituted C_{1-3} alkyl;

$\mathbf{R^{2'}}$ is as defined according to **(AA)** or **(BB)** below:

(AA)

$\mathbf{R^{2'}}$ is 

, wherein:

$\mathbf{R^3}$ is -C(O)OH, -$C(O)OR^{31}$, -$CH(C(O)OH)_2$ or a carboxylic acid isostere (e.g., amide or tetrazolyl);

a is 0-5;

a' is 0 or 1; and

each of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ is independently H or C_{1-3} alkyl;

~~**(BB)**~~

~~$\mathbf{R^{2'}}$ and $\mathbf{R^4}$ taken together with the atoms connecting them form a ring including from 5-8 ring atoms, wherein from 3-7 are ring carbon atoms each substituted with from 1-2 substituents independently selected from H, halo, hydroxy, oxo, and C_{1-3} alkyl; and from 0-1 is a heteroatom (in addition to the N attached to $\mathbf{R^1}$) selected from O, -NH, -N(C_{1-3} alkyl), and S (e.g., R^4 and R^3, taken together with the atoms to which each is attached form a ring including 5-8 ring atoms);~~

$\mathbf{R^{31}}$ is:

(**i**) C_{1-6} alkyl optionally substituted with from 1-2 independently selected $\mathbf{R^e}$;

(**ii**) -(C_{0-3} alkylene)-C_{3-10} cycloalkyl, wherein the cycloalkyl is optionally substituted with from 1-4 independently selected $\mathbf{R^d}$;

(**iii**) -(C_{0-3} alkylene)-heterocyclyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are each independently selected from the group consisting of N($\mathbf{R^a}$), O, and S, wherein the heterocyclyl is optionally substituted with from 1-4 independently selected $\mathbf{R^d}$;

(**iv**) -(C_{0-3} alkylene)-C_{6-10} aryl, wherein the aryl is optionally substituted with from 1-5 independently selected $\mathbf{R^c}$; or

(**v**) -(C_{0-3} alkylene)-heteroaryl including from 5-10 ring atoms, wherein from 1-4 ring atoms are each independently selected from the group consisting of N, N($\mathbf{R^a}$), O, and S, wherein the heteroaryl is optionally substituted with from 1-3 independently selected $\mathbf{R^c}$;

each occurrence of $\mathbf{R^a}$ is independently selected from the group consisting of: H; C_{1-4} alkyl; C_{3-6} cycloalkyl; -C(=O)(C_{1-6} alkyl); -C(=O)O(C_{1-6} alkyl); and -S(O)$_{1-2}$(C_{1-6} alkyl);

each occurrence of $\mathbf{R^b}$ is independently selected from the group consisting of: $\mathbf{R^{31}}$; C_{1-4} haloalkyl; –OH; oxo; -F; -N(R^a)(R''); C_{1-4} alkoxy; C_{1-4} haloalkoxy; -C(=O)(C_{1-4} alkyl); -C(=O)O(C_{1-6} alkyl); -C(=O)OH, -C(=O)N(R''')(R''''), -S(O)$_{1-2}$(C_{1-6} alkyl); and cyano;

each occurrence of **R^{c}** is independently selected from the group consisting of: C_{1-6} alkyl optionally substituted with from 1-2 independently selected **R^{e}**; C_{3-6} cycloalkyl; C_{1-4} haloalkyl; –OH; -halo; $-NO_2$; N_3; $-N(R^a)(R'')$; C_{1-4} alkoxy; C_{1-4} thioalkoxy; C_{1-4} haloalkoxy; $-OC(=O)(C_{1-6}$ alkyl); $-C(=O)(C_{1-6}$ alkyl); $-C(=O)O(C_{1-6}$ alkyl); -C(=O)OH, $-C(=O)N(R''')(R'''')$, $-S(O)_{1-2}(C_{1-6}$ alkyl); and cyano;

each occurrence of **R^{d}** is independently selected from the group consisting of: C_{1-6} alkyl optionally substituted with from 1-2 independently selected **R^{e}**; C_{1-4} haloalkyl; –OH; -F; Cl; $-N(R^a)(R'')$; oxo; C_{1-4} alkoxy; C_{1-4} haloalkoxy; $-OC(=O)(C_{1-6}$ alkyl); $-C(=O)(C_{1-6}$ alkyl); $-C(=O)O(C_{1-6}$ alkyl); -C(=O)OH, $-C(=O)N(R''')(R'''')$, $-S(O)_{1-2}(C_{1-6}$ alkyl); and cyano;

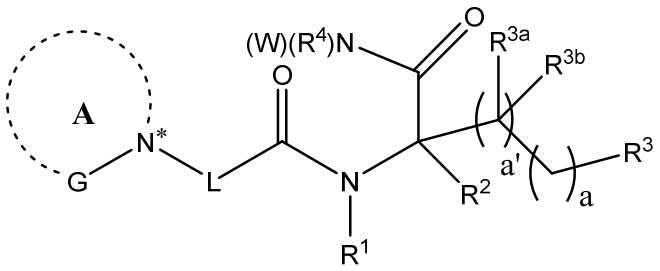
each occurrence of **R^{e}** is independently selected from the group consisting of: –OH; --$N(R^a)(R'')$; C_{1-4} alkoxy; C_{1-4} haloalkoxy; $-OC(=O)(C_{1-6}$ alkyl); $-C(=O)O(C_{1-6}$ alkyl); -C(=O)OH, $-C(=O)N(R''')(R'''')$, $-S(O)_{1-2}(C_{1-6}$ alkyl); and cyano;

each occurrence of **R**", **R**"', and **R**"" is independently selected from the group consisting of: H and C_{1-6} alkyl; and

W is a peptide having the formula W'-R^5, wherein **W'** is a sequence of from 5-60 amino acids, and **R^{5}** is a C-terminal amino acid, amino acid ester, or amino acid amide that is optionally substituted with from 1-2 modifying groups (e.g., 1-2 groups selected from an acyl group and a PEG group); and

provided that one or more of the compound provisions delineated herein apply.

2. The compound of claim 1, wherein the compound has formula (IA), or a pharmaceutically acceptable salt thereof:



(IA)

wherein:

ring A is:

(**i**) a saturated or unsaturated monocyclic ring that includes from 3-8 ring atoms (inclusive of **G** and the nitrogen atom labelled N*); or

(**ii**) a saturated or unsaturated bicyclic or tricyclic ring that includes from 6-14 ring atoms (inclusive of **G** and the nitrogen atom labelled N*), wherein:

- **G** is C(O), S(O), or SO_2; and
- the dotted, circular line connecting **G** and N* is a divalent group that includes from 1-6 ring atoms; wherein:

(**a**) from 0-2 of the divalent group's ring atoms are ring heteroatoms, which are each independently selected from the group consisting of N, N(**R**^{a}), O, S, and SO_2; and

(**b**) from 1-6 of the divalent group's ring atoms are ring carbon atoms, which are each independently selected from the group consisting of C, CH, CH_2, CR^b, $C(R^b)_2$, and CHR^b;

wherein:

(**1**) when **ring A** is a monocyclic ring, then each of the divalent group's 1-6 ring carbon atoms is independently selected from the group consisting of CH, CH_2, CR^b, $C(R^b)_2$, and CHR^b; and

(**2**) when **ring A** is a bicyclic or tricyclic ring, then (**A**) or (**B**) applies:

(**A**) two or three adjacent ring carbon atoms of the divalent group are each independently selected from the group consisting of C, CH, and, CR^b and are fused to a second ring that is selected from the group consisting of:

(**a**) C_{6-10} aryl optionally substituted with from 1-5 independently selected **R**^{c};

(**b**) heteroaryl including from 5-10 ring atoms, wherein from 1-4 ring atoms are each independently selected from the group consisting of N, N(**R**^{a}), O, and S, wherein the heteroaryl is optionally substituted with from 1-3 independently selected **R**^{c};

(**c**) C_{3-10} cycloalkyl optionally substituted with from 1-4 independently selected **R**^{d};

(**d**) heterocyclyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are each independently selected from the group consisting of N(**R**^{a}), O,

and S, wherein the heterocyclyl is optionally substituted with from 1-4 independently selected $\mathbf{R^d}$; or

(**B**) one of the divalent group's ring carbon atoms is C and is spiro-fused to a second ring that is selected from the group consisting of:

(**a**) C_{3-10} cycloalkyl optionally substituted with from 1-4 independently selected $\mathbf{R^d}$;

(**b**) heterocyclyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are each independently selected from the group consisting of N($\mathbf{R^a}$), O, and S, wherein the heterocyclyl is optionally substituted with from 1-4 independently selected $\mathbf{R^d}$;

L is:

(**i**) $-(CH_2)_{\mathbf{m}}-\mathbf{X^1}-(CH_2)_{\mathbf{n}}-\mathbf{X^2}-(CH_2)_{\mathbf{p}}-$ (formula VIII), wherein **m** is from 1-6; **n** is from 0-2; and **p** is from 0-8;

(**ii**) $-C(O)-(CH_2)_{\mathbf{n}}-\mathbf{X^3}-(CH_2)_{\mathbf{p}}-$ (formula IX), wherein **n** is from 0-2; and **p** is from 0-8;

(**iii**) $-(CH_2)_{\mathbf{q}}-$, wherein **q** is from 1-10;

(**iv**) -C(O)-; or

(**v**) $-(CH_2)_{\mathbf{m}}-\mathbf{X^1}-(CH_2)_{\mathbf{p}}-$ (formula VIII), wherein **m** is from 1-6; and **p** is from 0-8;

$\mathbf{X^1}$ is -C(O)-; -N(R')C(O)-; -C(O)N(R')-; or -N(R')C(O)NR')-; wherein each occurrence of **R'** is independently selected from the group consisting of: H and C_{1-4} alkyl;

$\mathbf{X^2}$ is:

(**i**) -O-;

(**ii**) -S-;

(**iii**) $-S(O)_t-$, wherein **t** is 1 or 2;

(**iv**) $-C(Q^1)(Q^2)-$, wherein each of $\mathbf{Q^1}$ and $\mathbf{Q^2}$ is independently selected from the group consisting of H and C_{1-4} alkyl; or $\mathbf{Q^1}$ and $\mathbf{Q^2}$, together with the carbon atom to which each is attached forms C_{3-10} cycloalkyl that is optionally substituted with from 1-4 independently selected $\mathbf{R^d}$ and optionally fused to phenyl;

(**v**) C_{6-10} arylene optionally substituted with from 1-5 independently selected $\mathbf{R^c}$;

(**vi**) heteroarylene including from 5-10 ring atoms, wherein from 1-4 ring atoms are each independently selected from the group consisting of N, N($\mathbf{R^a}$), O, and S; and which is optionally substituted with from 1-5 independently selected $\mathbf{R^c}$;

(**vii**) C_{3-10} cycloalkylene optionally substituted with from 1-4 independently selected $\mathbf{R^d}$;

(**viii**) heterocycloalkylene including from 3-10 ring atoms, wherein from 1-3 ring atoms are each independently selected from the group consisting of N($\mathbf{R^a}$), O, and S; and which is optionally substituted with from 1-5 independently selected $\mathbf{R^d}$;

(**ix**) C_2-C_4 alkenylene optionally substituted with from 1-2 $\mathbf{R^e}$; or

(**x**) C_2-C_4 alkynylene optionally substituted with from 1-2 $\mathbf{R^e}$;

$\mathbf{X^3}$ is: -O-; -S-; or -$S(O)_t$-, wherein **t** is 1 or 2;

each of $\mathbf{R^1}$, $\mathbf{R^2}$, and $\mathbf{R^4}$ is independently selected from the group consisting of H and unsubstituted C_{1-3} alkyl;

$\mathbf{R^3}$ is -C(O)OH, -$C(O)OR^{31}$, -$CH(C(O)OH)_2$ or a carboxylic acid isostere (e.g., amide or tetrazolyl);

a is 0-5;

a' is 0 or 1;

each of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ is independently H or C_{1-3} alkyl;

$\mathbf{R^{31}}$ is:

(**i**) C_{1-6} alkyl optionally substituted with from 1-2 independently selected $\mathbf{R^e}$;

(**ii**) -(C_{0-3} alkylene)-C_{3-10} cycloalkyl, wherein the cycloalkyl is optionally substituted with from 1-4 independently selected $\mathbf{R^d}$;

(**iii**) -(C_{0-3} alkylene)-heterocyclyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are each independently selected from the group consisting of N($\mathbf{R^a}$), O, and S, wherein the heterocyclyl is optionally substituted with from 1-4 independently selected $\mathbf{R^d}$;

(**iv**) -(C_{0-3} alkylene)-C_{6-10} aryl, wherein the aryl is optionally substituted with from 1-5 independently selected $\mathbf{R^c}$; or

(**v**) -(C_{0-3} alkylene)-heteroaryl including from 5-10 ring atoms, wherein from 1-4 ring atoms are each independently selected from the group consisting of N, N(**R^a**), O, and S, wherein the heteroaryl is optionally substituted with from 1-3 independently selected **R^c**;

each occurrence of **R^a** is independently selected from the group consisting of: H; C_{1-4} alkyl; C_{3-6} cycloalkyl; -C(=O)(C_{1-6} alkyl); -C(=O)O(C_{1-6} alkyl); and -S(O)$_{1-2}$(C_{1-6} alkyl);

each occurrence of **R^b** is independently selected from the group consisting of: **R^{31}**; C_{1-4} haloalkyl; –OH; oxo; -F; -N(R^a)(R''); C_{1-4} alkoxy; C_{1-4} haloalkoxy; -C(=O)(C_{1-4} alkyl); -C(=O)O(C_{1-6} alkyl); -C(=O)OH, -C(=O)N(R''')(R''''), -S(O)$_{1-2}$(C_{1-6} alkyl); and cyano;

each occurrence of **R^c** is independently selected from the group consisting of: C_{1-6} alkyl optionally substituted with from 1-2 independently selected **R^e**; C_{3-6} cycloalkyl; C_{1-4} haloalkyl; –OH; -halo; -NO_2; N_3; -N(R^a)(R''); C_{1-4} alkoxy; C_{1-4} thioalkoxy; C_{1-4} haloalkoxy; -OC(=O)(C_{1-6} alkyl); -C(=O)(C_{1-6} alkyl); -C(=O)O(C_{1-6} alkyl); -C(=O)OH, -C(=O)N(R''')(R''''), -S(O)$_{1-2}$(C_{1-6} alkyl); and cyano;

each occurrence of **R^d** is independently selected from the group consisting of: C_{1-6} alkyl optionally substituted with from 1-2 independently selected **R^e**; C_{1-4} haloalkyl; –OH; -F; Cl; -N(R^a)(R''); oxo; C_{1-4} alkoxy; C_{1-4} haloalkoxy; -OC(=O)(C_{1-6} alkyl); -C(=O)(C_{1-6} alkyl); -C(=O)O(C_{1-6} alkyl); -C(=O)OH, -C(=O)N(R''')(R''''), -S(O)$_{1-2}$(C_{1-6} alkyl); and cyano;

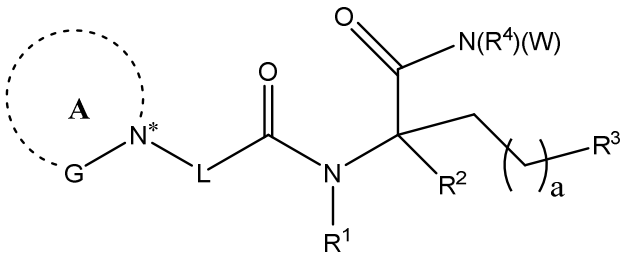
each occurrence of **R^e** is independently selected from the group consisting of: –OH; --N(R^a)(R''); C_{1-4} alkoxy; C_{1-4} haloalkoxy; -OC(=O)(C_{1-6} alkyl); -C(=O)O(C_{1-6} alkyl); -C(=O)OH, -C(=O)N(R''')(R''''), -S(O)$_{1-2}$(C_{1-6} alkyl); and cyano;

each occurrence of **R**'', **R**''', and **R**'''' is independently selected from the group consisting of: H and C_{1-6} alkyl; and

W is a peptide having the formula W'-R^5, wherein **W'** is a sequence of from 5-60 amino acids, and **R^5** is a C-terminal amino acid, amino acid ester, or amino acid amide that is optionally substituted with from 1-2 modifying groups (e.g., 1-2 groups selected from an acyl group and a PEG group); and

provided that one or more of the compound provisions delineated herein apply.

3. The compound of any one of claims 1-2, wherein the compound has formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

ring A is:

(**i**) a saturated or unsaturated monocyclic ring that includes from 3-8 ring atoms (inclusive of **G** and the nitrogen atom labelled N*); or

(**ii**) a saturated or unsaturated bicyclic or tricyclic ring that includes from 6-14 ring atoms (inclusive of **G** and the nitrogen atom labelled N*), wherein:

- **G** is C(O), S(O), or SO_2; and
- the dotted, circular line connecting **G** and N* is a divalent group that includes from 1-6 ring atoms; wherein:

(**a**) from 0-2 of the divalent group's ring atoms are ring heteroatoms, which are each independently selected from the group consisting of N, N(**R**^{a}), O, S, and SO_2; and

(**b**) from 1-6 of the divalent group's ring atoms are ring carbon atoms, which are each independently selected from the group consisting of C, CH, CH_2, CR^b, $C(R^b)_2$, and CHR^b;

wherein:

(**1**) when **ring A** is a monocyclic ring, then each of the divalent group's 1-6 ring carbon atoms is independently selected from the group consisting of CH, CH_2, CR^b, $C(R^b)_2$, and CHR^b; and

(**2**) when **ring A** is a bicyclic or tricyclic ring, then (**A**) or (**B**) applies:

(**A**) two or three adjacent ring carbon atoms of the divalent group are each independently selected from the group consisting of C, CH, and, CR^b and are fused to a second ring that is selected from the group consisting of:

(**a**) $C_{6\text{-}10}$ aryl optionally substituted with from 1-5 independently selected **R**^{c};

(**b**) heteroaryl including from 5-10 ring atoms, wherein from 1-4 ring atoms are each independently selected from the group consisting of N, N(**R**^{a}), O, and S, wherein the heteroaryl is optionally substituted with from 1-3 independently selected **R**^{c};

(**c**) C_{3-10} cycloalkyl optionally substituted with from 1-4 independently selected **R**^{d};

(**d**) heterocyclyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are each independently selected from the group consisting of N(**R**^{a}), O, and S, wherein the heterocyclyl is optionally substituted with from 1-4 independently selected **R**^{d}; or

(**B**) one of the divalent group's ring carbon atoms is C and is spiro-fused to a second ring that is selected from the group consisting of:

(**a**) C_{3-10} cycloalkyl optionally substituted with from 1-4 independently selected **R**^{d};

(**b**) heterocyclyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are each independently selected from the group consisting of N(**R**^{a}), O, and S, wherein the heterocyclyl is optionally substituted with from 1-4 independently selected **R**^{d};

L is:

(**i**) -$(CH_2)_{m}$-**X**^{1}-$(CH_2)_{n}$-**X**^{2}-$(CH_2)_{p}$- (formula VIII), wherein **m** is from 1-6; **n** is from 0-2; and **p** is from 0-8;

(**ii**) -C(O)-$(CH_2)_{n}$-**X**^{3}-$(CH_2)_{p}$- (formula IX), wherein **n** is from 0-2; and **p** is from 0-8;

(**iii**) -$(CH_2)_{q}$-, wherein **q** is from 1-10;

(**iv**) -C(O)-; or

(**v**) -$(CH_2)_{m}$-**X**^{1} -$(CH_2)_{p}$- (formula VIII), wherein **m** is from 1-6; and **p** is from 0-8;

X^{1} is -C(O)-; -N(R')C(O)-; -C(O)N(R')-; or -N(R')C(O)NR')-; wherein each occurrence of **R**' is independently selected from the group consisting of: H and C_{1-4} alkyl;

X^{2} is:

(**i**) -O-;

(**ii**) -S-;

(**iii**) -$S(O)_{t}$-, wherein **t** is 1 or 2;

(**iv**) -$C(Q^{1})(Q^{2})$-, wherein each of **Q**^{1} and **Q**^{2} is independently selected from the group consisting of H and C_{1-4} alkyl; or **Q**^{1} and **Q**^{2}, together with the carbon atom to which each is attached forms C_{3-10} cycloalkyl that is optionally substituted with from 1-4 independently selected **R**^{d} and optionally fused to phenyl;

(**v**) C_{6-10} arylene optionally substituted with from 1-5 independently selected $\mathbf{R^c}$;

(**vi**) heteroarylene including from 5-10 ring atoms, wherein from 1-4 ring atoms are each independently selected from the group consisting of N, N($\mathbf{R^a}$), O, and S; and which is optionally substituted with from 1-5 independently selected $\mathbf{R^c}$;

(**vii**) C_{3-10} cycloalkylene optionally substituted with from 1-4 independently selected $\mathbf{R^d}$;

(**viii**) heterocycloalkylene including from 3-10 ring atoms, wherein from 1-3 ring atoms are each independently selected from the group consisting of N($\mathbf{R^a}$), O, and S; and which is optionally substituted with from 1-5 independently selected $\mathbf{R^d}$;

(**ix**) C_2-C_4 alkenylene optionally substituted with from 1-2 $\mathbf{R^e}$; or

(**x**) C_2-C_4 alkynylene optionally substituted with from 1-2 $\mathbf{R^e}$;

$\mathbf{X^3}$ is: -O-; -S-; or -$S(O)_t$-, wherein **t** is 1 or 2;

each of $\mathbf{R^1}$, $\mathbf{R^2}$, and $\mathbf{R^4}$ is independently selected from the group consisting of H and unsubstituted C_{1-3} alkyl;

$\mathbf{R^3}$ is -C(O)OH, -$C(O)OR^{31}$, or a carboxylic acid isostere; wherein $\mathbf{R^{31}}$ is:

(**i**) C_{1-6} alkyl optionally substituted with from 1-2 independently selected $\mathbf{R^e}$;

(**ii**) -(C_{0-3} alkylene)-C_{3-10} cycloalkyl, wherein the cycloalkyl is optionally substituted with from 1-4 independently selected $\mathbf{R^d}$;

(**iii**) -(C_{0-3} alkylene)-heterocyclyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are each independently selected from the group consisting of N($\mathbf{R^a}$), O, and S, wherein the heterocyclyl is optionally substituted with from 1-4 independently selected $\mathbf{R^d}$;

(**iv**) -(C_{0-3} alkylene)-C_{6-10} aryl, wherein the aryl is optionally substituted with from 1-5 independently selected $\mathbf{R^c}$; or

(**v**) -(C_{0-3} alkylene)-heteroaryl including from 5-10 ring atoms, wherein from 1-4 ring atoms are each independently selected from the group consisting of N, N($\mathbf{R^a}$), O, and S, wherein the heteroaryl is optionally substituted with from 1-3 independently selected $\mathbf{R^c}$;

a is 0-5;

each occurrence of $\mathbf{R^a}$ is independently selected from the group consisting of: H; C_{1-4} alkyl; C_{3-6} cycloalkyl; -C(=O)(C_{1-6} alkyl); -C(=O)O(C_{1-6} alkyl); and -S(O)$_{1-2}$(C_{1-6} alkyl);

each occurrence of $\mathbf{R^b}$ is independently selected from the group consisting of: $\mathbf{R^{31}}$; C_{1-4} haloalkyl; –OH; oxo; -F; -N(R^a)(R''); C_{1-4} alkoxy; C_{1-4} haloalkoxy; -C(=O)(C_{1-4} alkyl); -C(=O)O(C_{1-6} alkyl); -C(=O)OH, -C(=O)N(R''')(R''''), -S(O)$_{1-2}$(C_{1-6} alkyl); and cyano;

each occurrence of $\mathbf{R^c}$ is independently selected from the group consisting of: C_{1-6} alkyl optionally substituted with from 1-2 independently selected $\mathbf{R^e}$; C_{3-6} cycloalkyl; C_{1-4} haloalkyl; –OH; -halo; -NO_2; N_3; -N(R^a)(R''); C_{1-4} alkoxy; C_{1-4} thioalkoxy; C_{1-4} haloalkoxy; -OC(=O)(C_{1-6} alkyl); -C(=O)(C_{1-6} alkyl); -C(=O)O(C_{1-6} alkyl); -C(=O)OH, -C(=O)N(R''')(R''''), -S(O)$_{1-2}$(C_{1-6} alkyl); and cyano;

each occurrence of $\mathbf{R^d}$ is independently selected from the group consisting of: C_{1-6} alkyl optionally substituted with from 1-2 independently selected $\mathbf{R^e}$; C_{1-4} haloalkyl; –OH; -F; Cl; -N(R^a)(R''); oxo; C_{1-4} alkoxy; C_{1-4} haloalkoxy; -OC(=O)(C_{1-6} alkyl); -C(=O)(C_{1-6} alkyl); -C(=O)O(C_{1-6} alkyl); -C(=O)OH, -C(=O)N(R''')(R''''), -S(O)$_{1-2}$(C_{1-6} alkyl); and cyano;

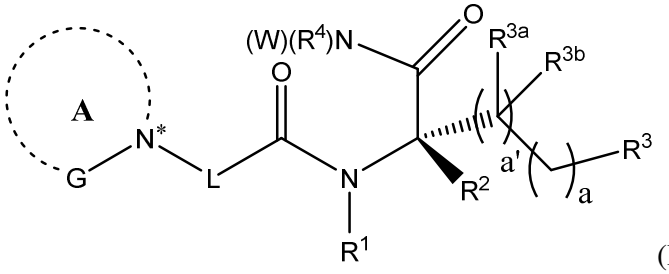
each occurrence of $\mathbf{R^e}$ is independently selected from the group consisting of: –OH; --N(R^a)(R''); C_{1-4} alkoxy; C_{1-4} haloalkoxy; -OC(=O)(C_{1-6} alkyl); -C(=O)O(C_{1-6} alkyl); -C(=O)OH, -C(=O)N(R''')(R''''), -S(O)$_{1-2}$(C_{1-6} alkyl); and cyano;

each occurrence of $\mathbf{R}$'', $\mathbf{R}$''', and $\mathbf{R}$'''' is independently selected from the group consisting of: H and C_{1-6} alkyl; and

W is a peptide having the formula W'-R^5, wherein **W'** is a sequence of from 5-60 amino acids, and $\mathbf{R^5}$ is a C-terminal amino acid, amino acid ester, or amino acid amide that is optionally substituted with from 1-2 modifying groups (e.g., 1-2 groups selected from an acyl group and a PEG group); and

provided that one or more of the compound provisions delineated herein apply.

4. The compound of any one of claims 1-2, wherein the compound has formula (IIA):



(IIA).

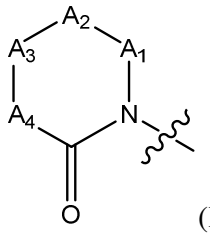
5. The compound of any one of claims 1-4, wherein **G** is C(O).

6. The compound of any one of claims 1-4, wherein **G** is S(O) or SO_2.

7. The compound of any one of claims 1-6, wherein ring A is a saturated or unsaturated monocyclic ring that includes from 3-8 (e.g., 4-8) ring atoms.

8. The compound of any one of claims 1-7, wherein ring A is a saturated monocyclic ring that includes from 3-8 (e.g., 4-8) ring atoms.

9. The compound of any one of claims 1, 2, 4, 5, and 7-8, wherein ring A has the following formula (III):



(III)

wherein:

$\mathbf{A_1}$ is a bond, $\mathbf{A^{1A}}$-$\mathbf{A^{1B}}$, C(O), CH_2, CHR^b, or $C(R^b)_2$;

each of $\mathbf{A^{1A}}$ and $\mathbf{A^{1B}}$ is independently C(O), CH_2, CHR^b, or $C(R^b)_2$;

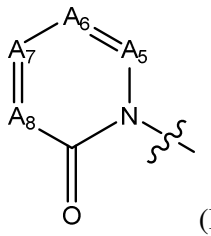
$\mathbf{A_2}$ is C(O), CH_2, CHR^b, or $C(R^b)_2$;

$\mathbf{A_3}$ is C(O), CH_2, CHR^b, or $C(R^b)_2$; O; S; SO_2, or N($\mathbf{R^a}$);

$\mathbf{A_4}$ is C(O), CH_2, CHR^b, or $C(R^b)_2$; O; S; or N($\mathbf{R^a}$); provided that $\mathbf{A_3}$ and $\mathbf{A_4}$ cannot both be O; S; or N($\mathbf{R^a}$); or a combination thereof.

10. The compound of any one of claims 1-6, wherein ring A is an unsaturated monocyclic ring that includes from 3-8 (e.g., 4-8) ring atoms.

11. The compound of claim 10, wherein ring A has formula (IV):



(IV),

wherein:

each of $\mathbf{A_6}$, and $\mathbf{A_7}$ is independently selected from CH and CR^b; and

each of $\mathbf{A_5}$ and $\mathbf{A_8}$ is independently N, CH, or CR^b.

12. The compound of any one of claims 1-6, wherein ring A is a saturated or unsaturated bicyclic or tricyclic ring that includes from 6-14 (e.g., 8-10) ring atoms.

13. The compound of any one of claims 1-6, wherein ring A is a saturated bicyclic or tricyclic ring that includes from 8-10 ring atoms.

14. The compound of any one of the preceding claims, wherein **L** has formula (VIII) : $-(CH_2)_{\mathbf{m}}-\mathbf{X^1}-(CH_2)_{\mathbf{n}}-\mathbf{X^2}-(CH_2)_{\mathbf{p}}-$.

15. The compound of any one of the preceding claims, wherein:

m is from 2-6;

$\mathbf{n + p} \geq 2$; and

$\mathbf{X^2}$ is: -O-; -S-; $-S(O)_t-$, or CH_2.

16. The compound of any one of the preceding claims, wherein:

m is 1;

$\mathbf{n + p} \leq 2$; and

$\mathbf{X^2}$ is: -O-; -S-; $-S(O)_t-$, or $C(\mathbf{Q^1})(\mathbf{Q^2})$.

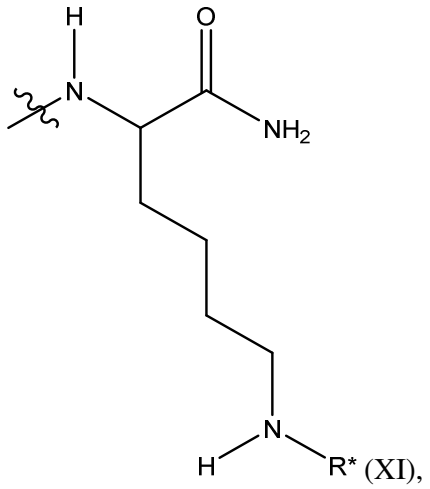
17. The compound of any one of the preceding claims, wherein **L** has formula (IX): -C(O)-$(CH_2)_{\mathbf{n}}$-$\mathbf{X^3}$-$(CH_2)_{\mathbf{p}}$-.

18. The compound of any one of the preceding claims, wherein **W** is a sequence of from 25-45 (e.g., 30-45) amino acids.

19. The compound of any one of the preceding claims, wherein **W** has formula (X): - -GTF-W''-R^5, wherein **W''** is a sequence of 30-40 (e.g., 31-36, 33) amino acids.

20. The compound of any one of the preceding claims, wherein $\mathbf{R^5}$ is a C-terminal amino acid amide that is optionally substituted with from 1-2 modifying groups (e.g., 1-2 groups selected from an acyl group and a PEG group).

21. The compound of any one of the preceding claims, wherein $\mathbf{R^5}$ has formula (XI):

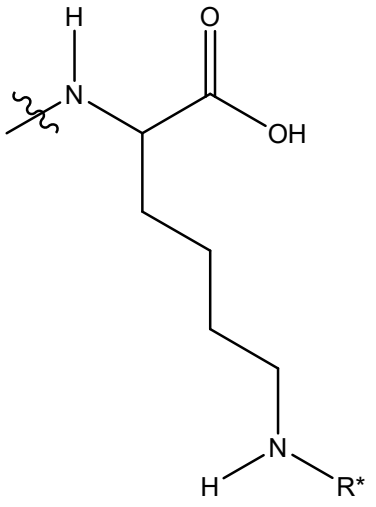


(XI),

wherein R* is H or a modifying group (e.g., an acyl group and a PEG group).

22. The compound of any one of the preceding claims, wherein $\mathbf{R^5}$ is a a C-terminal amino acid that is optionally substituted with from 1-2 modifying groups (e.g., 1-2 groups selected from an acyl group and a PEG group).

23. The compound of any one of the preceding claims, wherein **R**^{5} has formula (XI-OH):



(XI-OH),

wherein R* is H or a modifying group (e.g., an acyl group and a PEG group).

24. The compound of any of the preceding claims, wherein **W** is represented by SEQ ID 6.

25. The compound of claim 1, wherein the compound is selected from the group consisting of those delineated in **FIG. 1**.

26. A pharmaceutical composition comprising a compound or salt as claimed in any one of the preceding claims and one or more pharmaceutically acceptable excipients.

27. An *in vitro* method for modulating GLP-1R and/or GIPR activity, the method comprising contacting GLP-1R and/or GIPR with a compound as claimed in any one of ~~the preceding~~ claims 1-25.

~~28. Use of a compound as claimed in any one of the preceding claims in the manufacture of a medicament for modulating GLP-1R and/or GIPR activity *in vivo*.~~

~~29~~28. Use of a compound as claimed in any one of ~~the preceding~~ claims 1-25 in the manufacture of a medicament for ~~modulating~~ treating GLP-1R and/or GIPR induced aversion, nausea and/or vomiting.

~~30~~29. Use of a compound as claimed in any one of ~~the preceding~~ claims 1-25 in the manufacture of a medicament for ~~modulating (e.g., increasing)~~ insulin levels in a subject in need of such ~~modulating~~increasing.

~~31~~30. Use of a compound as claimed in any one of ~~the preceding~~ claims 1-25 in the manufacture of a medicament for ~~modulating (e.g., decreasing)~~ glucose levels in a subject in need of such ~~modulating~~decreasing.

~~32~~31. Use of a compound as claimed in any one of ~~the preceding~~ claims 1-25 in the manufacture of a medicament for treating a disease, disorder, or condition selected from the group consisting of diabetes, NASH, obesity, fatty liver disease, and steatohepatitis~~, in which modulating GLP-1R and/or GIPR signaling can alter the pathology and/or symptoms and/or progression of the disease, disorder, or condition~~.

~~33. Use of a compound as claimed in any one of the preceding claims in the manufacture of a medicament for treating a disease, disorder, or condition, in which modulating GLP-1R and/or GIPR signaling causes aversion, nausea or vomiting.~~

32. The compound of claim 1, wherein **-N(R^4)W** has formula (XIV-AA):

GT(**Xaa3**)(**Xaa4**)SD(**Xaa7**)S(**Xaa9**)(**Xaa10**)(**Xaa11**)(**Xaa12**)(**Xaa13**)(**Xaa14**)(**Xaa15**)(**Xaa16**)(**Xaa17**)(**Xaa18**)(**Xaa19**)(**Xaa20**)(**Xaa21**)WL(**Xaa24**)(**Xaa25**)(**Xaa26**)GPSSGAPPP(**Xaa36**)-R^5 (**SEQ ID NO: 2A** which is listed as **SEQ ID NO: 35** in sequence listing);

wherein:

Xaa3 is F;

Xaa4 is T or I;

Xaa7 is Y, V, L, or K*;

Xaa9 is I or S;

Xaa10 is Y, Y*, Q, A, or (Aib);

Xaa11 is L, M, or L*;

Xaa12 is D or E;

Xaa13 is K, G, R, or E;

Xaa14 is Q or I;

Xaa15 is A, H, or R;

Xaa16 is A, Q, or V;

Xaa17 is A, (Aib), K*, K, or Q;

Xaa18 is A, D, E, (Aib), or L;

Xaa19 is F, or A;

Xaa20 is V or I;

Xaa21 is N, A, Q, K*, or E;

Xaa24 is I, L or V;

Xaa25 is A, K, or I;

Xaa26 is Q-R, G-R-G-K*, Q, or G; and

Xaa36 is S or absent.

33. The compound of any one of claims 1-25 and 32, wherein **-N(R^4)W** has formula (XIV-A):

GTF(**Xaa4**)SD(**Xaa7**)S(**Xaa9**)(**Xaa10**)(**Xaa11**)(**Xaa12**)(**Xaa13**)QA(**Xaa16**)(**Xaa17**)(**Xaa18**)F-(**Xaa20**)(**Xaa21**)WL(**Xaa24**)(**Xaa25**)GGPSSGAPPPS-R^5 (**SEQ ID NO: 2**);

wherein:

Xaa4 is T or I;

Xaa7 is Y, V, or L;

Xaa9 is I or S (e.g., I);

Xaa10 is Y, Q, or A;

Xaa11 is L, M, or L*;

Xaa12 is D or E;

Xaa13 is K, G, or E;

Xaa16 is A or V;

Xaa17 is (Aib) or K;

Xaa18 is E or L;

Xaa20 is V or I;

Xaa21 is N, A, or E;

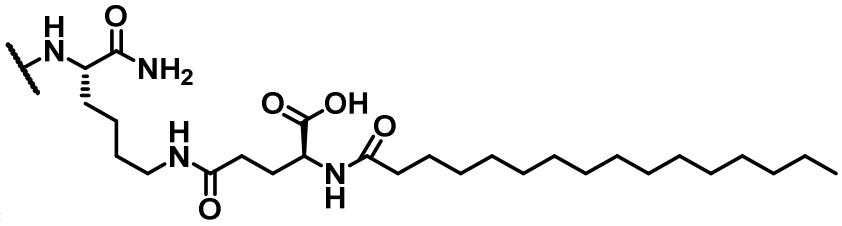
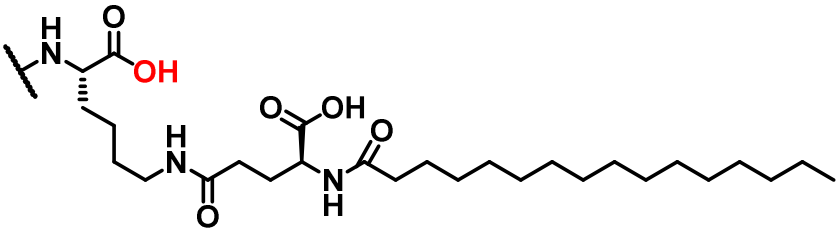
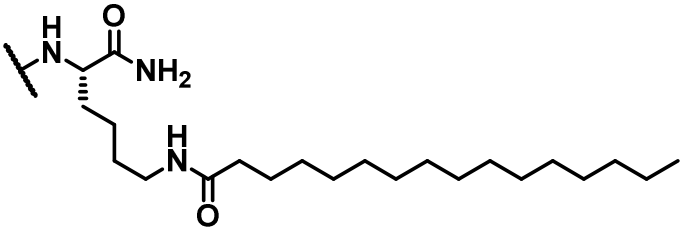
Xaa24 is L or V; and

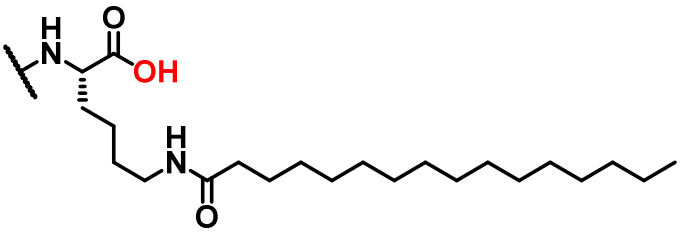
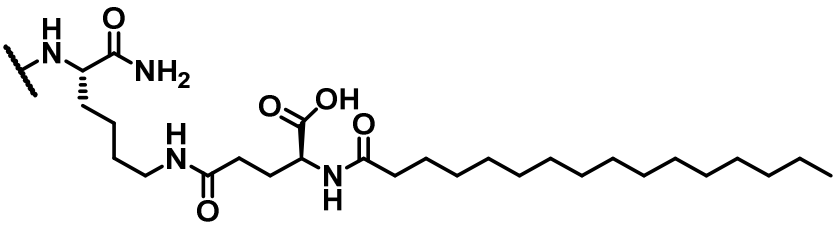
Xaa25 is A or K..

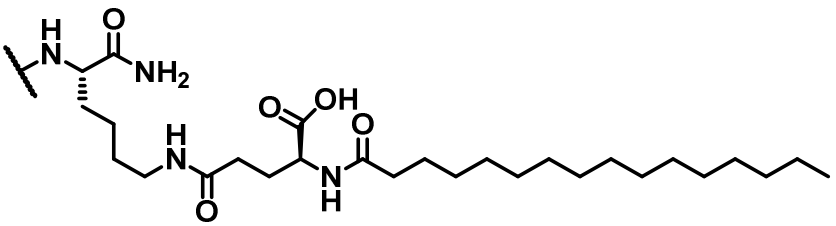
34. The compound of claim 1, wherein **-N(R^4)W** has formula (XIV-B):

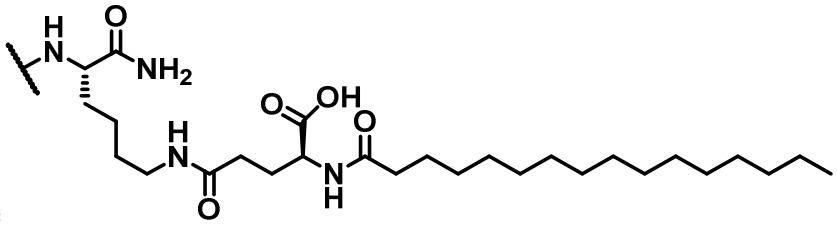
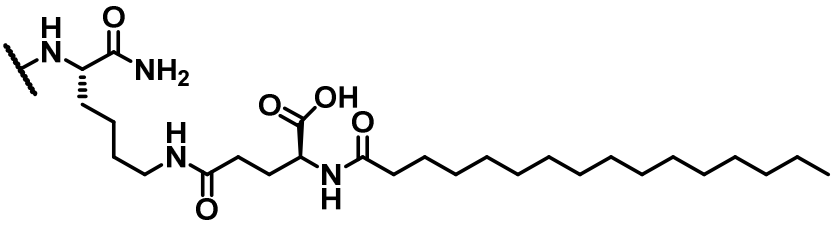
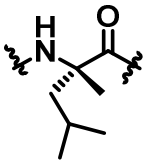
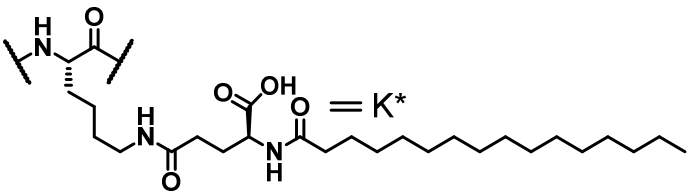
GTFTSDYSIYLDKQAA(Aib)EFVNWLLAGGPSSGAPPPS-R^5 (**SEQ ID NO: 4**).

35. The compound of claim 1, wherein **-N(R^4)W** is selected from the group consisting of:

SEQ ID NO:	Sequence
5	GTFTSDYSIYLDKQAA(Aib)EFVNWLLAGGPSSGAPPPSK——NH_2
6	GTFTSDYSIYLDKQAA(Aib)EFVNWLLAGGPSSGAPPPSK*  K* =
7	GTFTSDYSIYLDKQAA(Aib)EFVNWLLAGGPSSGAPPPSK*  K* =
8	GTFTSDYSIYLDKQAA(Aib)EFVNWLLAGGPSSGAPPPSK*  K* =

9	GTFTSDYSIYLDKQAA(Aib)EFVNWLLAGGPSSGAPPPSK*  K* =
10	GTFTSDVSSYLEGQAAKEFIAWLVKGGPSSGAPPPSK*—NH_2  K* =
12	GTFTSDLSIYLDKQAA(Aib)EFVNWLLAGGPSSGAPPPSK—NH_2
13	GTFTSDYSIYLDEQAA(Aib)EFVNWLLAGGPSSGAPPPSK—NH_2
14	GTFTSDYSIYLDKQAV(Aib)EFVNWLLAGGPSSGAPPPSK—NH_2
15	GTFTSDYSIYLDKQAA(Aib)LFVNWLLAGGPSSGAPPPSK—NH_2
16	GTFTSDYSIYLDKQAA(Aib)EFINWLLAGGPSSGAPPPSK—NH_2
17	GTFTSDYSIYLDKQAA(Aib)EFVEWLLAGGPSSGAPPPSK—NH_2

18	GTFTSDYSIYLDKQAV(Aib)EFINWLLAGGPSSGAPPPSK—NH_2
19	GTFTSDYSIQMDKQAA(Aib)EFVNWLLAGGPSSGAPPPSK*–NH_2  K* =
20	GTFTSDYSIAMDKQAA(Aib)EFVNWLLAGGPSSGAPPPSK*–NH_2

	 K* =
21	GTFTSDYSIYL*DKQAA(Aib)EFVNWLLAGGPSSGAPPPSK*–NH_2  K* =  L* =
22	GTFTSDYSIYLDRQAA(Aib)EFVNWLLAGGPSSGAPPPS–NH_2
28	GTFTSDYSIYLDKQAA(Aib)EFVNWLLAGGPSSGAPPPSK*—NH_2 
30	GTFTSDYSIYLDKQAV(Aib)EFVNWLLAGGPSSGAPPPSK*—NH_2 