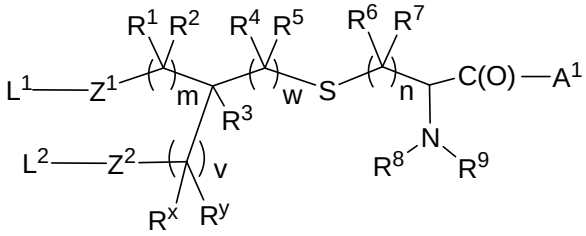
the present invention. It is not to be taken as an admission that any or all of these matters form part of the prior art base or were common general knowledge in the field relevant to the present invention as it existed before the priority date.

SUMMARY

In a first aspect, the present disclosure broadly consists in a peptide conjugate compound of the formula (I):



(I)

wherein

m and w are each independently an integer from 0 to 7 and v is an integer from 0 to 5,

provided that:

the sum of m, v, and w is at least 3; and

the sum of m and w is from 0 to 7;

n is 1 or 2;

Z1 and Z2 are each independently selected from the group consisting of –O–, –NR–, –S–, –S(O)–, –SO_2–, –C(O)O–, –OC(O)–, –C(O)NR–, –NRC(O)–, –C(O)S–, –SC(O)–, –OC(O)O–, –NRC(O)O–, –OC(O)NR–, and –NRC(O)NR–;

R1, R2, Rx, Ry, R4, R5, R6, and R7 at each instance of m, v, w, and n are each independently hydrogen or C1-6aliphatic;

R, R3, and R8 are each independently hydrogen or C1-6aliphatic;

R9 is hydrogen, C1-6aliphatic, an amino protecting group, L3–C(O)–, or A2;

L1 and L2 are each independently selected from is C5-21aliphatic or C4-20heteroaliphatic;

L3 is C1-21aliphatic or C2-20heteroaliphatic;

A1 is an amino acid, a peptide, OH, OP1, NH_2, or NHP2, wherein P1 is a carboxyl protecting group, and wherein P2 is a carboxamide protecting group;

A2 is an amino acid or a peptide;

wherein any aliphatic or heteroaliphatic present in any of R, R1, R2, R3, R4, R5, R6, R7, R8, R9, Rx, Ry, L1, L2, and L3 is optionally substituted;

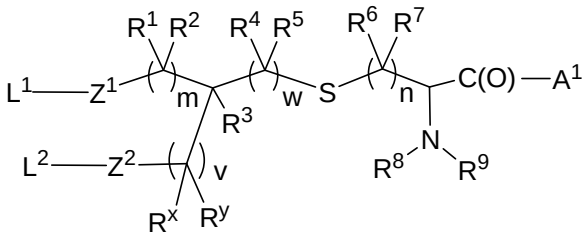
or a pharmaceutically acceptable salt or solvate thereof;

with the proviso that:

wherein Xaa_{22} in each sequence is independently any naturally occurring amino acid except C (for example V, I, or L), and any sequence of 8 or more contiguous amino acid residues from any of the above sequences comprises Xaa_{22}; or

(2) m is an integer from 3 to 7, and at least one of R9 and A1 is an amino acid or a peptide.

The present disclosure also broadly consists in a peptide conjugate compound of the formula (I):



(I)

wherein

m and w are each independently an integer from 0 to 7 and v is an integer from 0 to 5,

provided that:

the sum of m, v, and w is at least 3; and

the sum of m and w is from 0 to 7;

n is 1 or 2;

Z1 and Z2 are each independently selected from the group consisting of –O–, –NR–, –S–, –S(O)–, $–SO_2–$, –C(O)O–, –OC(O)–, –C(O)NR–, –NRC(O)–, –C(O)S–, –SC(O)–, –OC(O)O–, –NRC(O)O–, –OC(O)NR–, and –NRC(O)NR–;

R1, R2, Rx, Ry, R4, R5, R6, and R7 at each instance of m, v, w, and n are each independently hydrogen or C1-6aliphatic;

R, R3, and R8 are each independently hydrogen or C1-6aliphatic;

R9 is hydrogen, C1-6aliphatic, an amino protecting group, L3–C(O)–, or A2;

L1 and L2 are each independently selected from is C5-21aliphatic or C4-20heteroaliphatic;

L3 is C1-21aliphatic or C2-20heteroaliphatic;

A1 is an amino acid, a peptide, OH, OP1, NH_2, or NHP2, wherein P1 is a carboxyl protecting group, and wherein P2 is a carboxamide protecting group;

A2 is an amino acid or a peptide;

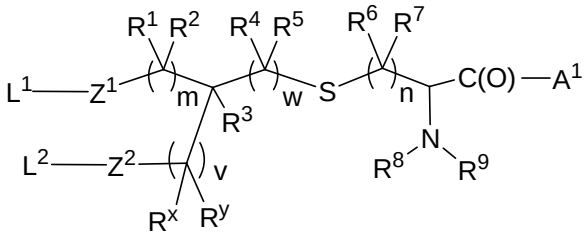
wherein any aliphatic or heteroaliphatic present in any of R, R1, R2, R3, R4, R5, R6, R7, R8, R9, Rx, Ry, L1, L2, and L3 is optionally substituted;

(m) the sequence of SEQ ID NO: 8,

(n) or any combination of two or more of (a) to (m) above,

wherein Xaa_{22} in each sequence is independently any naturally occurring amino acid except C (for example V, I, or L), and any sequence of 8 or more contiguous amino acid residues from any of the above sequences comprises Xaa_{22}.

The present disclosure also broadly consists in a peptide conjugate compound of the formula (I):



(I)

wherein

m and w are each independently an integer from 0 to 7 and v is an integer from 0 to 5,

provided that:

the sum of m, v, and w is at least 3; and

the sum of m and w is from 0 to 7;

n is 1 or 2;

Z1 and Z2 are each independently selected from the group consisting of –O–, –NR–, –S–, –S(O)–, $–SO_2–$, –C(O)O–, –OC(O)–, –C(O)NR–, –NRC(O)–, –C(O)S–, –SC(O)–, –OC(O)O–, –NRC(O)O–, –OC(O)NR–, and –NRC(O)NR–;

R1, R2, Rx, Ry, R4, R5, R6, and R7 at each instance of m, v, w, and n are each independently hydrogen or C1-6aliphatic;

R, R3, and R8 are each independently hydrogen or C1-6aliphatic;

R9 is hydrogen, C1-6aliphatic, an amino protecting group, L3–C(O)–, or A2;

L1 and L2 are each independently selected from is C5-21aliphatic or C4-20heteroaliphatic;

L3 is C1-21aliphatic or C2-20heteroaliphatic;

A1 is an amino acid, a peptide, OH, OP1, NH_2, or NHP2, wherein P1 is a carboxyl protecting group, and wherein P2 is a carboxamide protecting group;

A2 is an amino acid or a peptide;

wherein any aliphatic or heteroaliphatic present in any of R, R1, R2, R3, R4, R5, R6, R7, R8, R9, Rx, Ry, L1, L2, and L3 is optionally substituted;

In various embodiments, Xaa_4 in the sequences referred to herein is absent or is from 1 to 17 hydrophilic amino acids, for example, from 1 to 16, 1 to 15, 1 to 14, 1 to 13, 1 to 12, 1 to 11, 1 to 10, 1 to 9, 1 to 8, 1 to 7, 1 to 6, 1 to 5, 1 to 4, 1 to 3, or 1 to 2 hydrophilic amino acids, or is a hydrophilic amino acid.

In one embodiment, the peptide conjugate comprises two or more epitopes, such as two or more peptide epitopes.

In some embodiments, the peptide conjugate comprises an antigenic peptide.

In specifically contemplated embodiments, the peptide is a synthetic peptide.

In various embodiments, the compound of formula (I) is an isolated compound of formula (I).

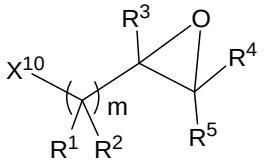
In various embodiments, the compound of formula (I) is a pure, purified or substantially pure compound of formula (I).

In various embodiments, the compound of formula (I) of the disclosure is a compound selected from the group consisting of compounds 910, 911, 912, 913, 930, 931, and 932 of the Examples herein.

The present disclosure also broadly consists in a method of making a peptide conjugate of the formula (IF) or a pharmaceutically acceptable salt or solvate thereof of the present disclosure, the method comprising:

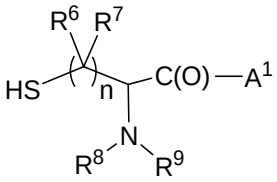
(A) reacting

an epoxide of the formula (XVI):



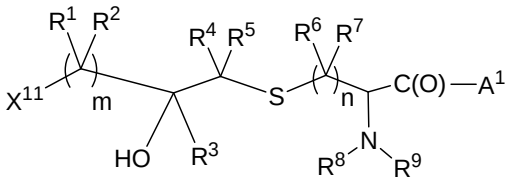
(XVI); and

an amino acid-comprising conjugation partner comprising a thiol of the formula (III):



(III),

under conditions effective to conjugate the epoxide and amino acid-comprising conjugation partner and provide a compound of formula (XV):



(XV)

wherein

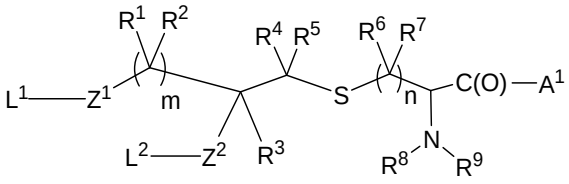
X10 is L1–Z1–, –OH, –SH, –NHR, HNRC(O)O-, P10–O–, P11–S–, P12–NR–, or P12-NRC(O)O-;

X11 is X10 or –OH, –SH, –NHR, or HNRC(O)O- when X10 is P10-O-, P11-S-, P12–NR–, or P12-NRC(O)O- and said conditions are effective to remove P10, P11, or P12;

P10, P11, and P12 are each independently a protecting group;

m, n, L1, Z1, R, R1, R2, R3, R4, R5, R6, R7, R8, R9, and A1 are as defined in the compound of formula (IF) of the disclosure (including provisos (1) and/or (2) of the first aspect); and

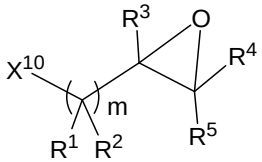
converting the compound of formula (XV) to the peptide-conjugate of the formula (IF) of the disclosure (including provisos (1) and/or (2) of the first aspect) or a pharmaceutically acceptable salt or solvate thereof by one or more additional synthetic steps:



(IF); or

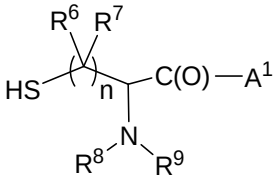
(B) reacting

an epoxide of the formula (XVI):



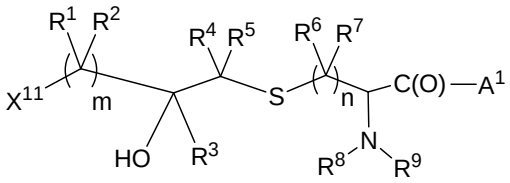
(XVI); and

an amino acid-comprising conjugation partner comprising a thiol of the formula (III):



(III),

under conditions effective to conjugate the epoxide and amino acid-comprising conjugation partner and provide a compound of formula (XV):



(XV)

wherein

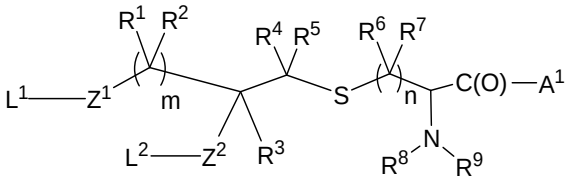
X10 is L1–Z1–, –OH, –SH, –NHR, HNRC(O)O-, P10–O–, P11–S–, P12–NR–, or P12-NRC(O)O-;

X11 is X10 or –OH, –SH, –NHR, or HNRC(O)O- when X10 is P10-O-, P11-S-, P12–NR–, or P12-NRC(O)O- and said conditions are effective to remove P10, P11, or P12;

P10, P11, and P12 are each independently a protecting group;

m, n, L1, Z1, R, R1, R2, R3, R4, R5, R6, R7, R8, R9, and A1 are as defined in the compound of formula (IF) but excluding provisos (1) and (2) of the first aspect; and

converting the compound of formula (XV) to an amino acid- or peptide-conjugate of the formula (IF) but excluding provisos (1) and (2) of of the first aspect or a salt or solvate thereof by one or more additional synthetic steps:



(IF); and

coupling the amino acid of the amino acid conjugate or an amino acid of the peptide conjugate to an amino acid or an amino acid of a peptide to provide the peptide-conjugate of formula (IF) of the present disclosure (including provisos (1) and/or (2) of the first aspect) or pharmaceutically acceptable salt or solvate thereof.

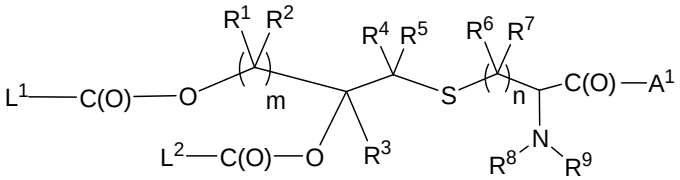
In various embodiments m is from 2 to 5, 2 to 4, or 2 to 3. In exemplary embodiments, m is 2. In other exemplary embodiments, m is from 3 to 5.

In various embodiments, X10 is L1–Z1– or –OH, –SH, –NHR, P10–O–, P11–S–, or P12–NR–; and X11 is X10 or –OH, –SH, or –NHR.

In various embodiments, X10 is L1–Z1–, –OH, or P10–O–; and X11 is X10 or –OH.

In various embodiments, X10 is L1–C(O)O–, OH, or P10–O–; and X11 is L1–C(O)O–, P10–O–, or OH.

In various embodiments, the method comprises converting the compound of formula (XV) to an amino acid- or peptide conjugate of the formula (IF-1) or a pharmaceutically acceptable salt or solvate thereof by one or more additional synthetic steps:



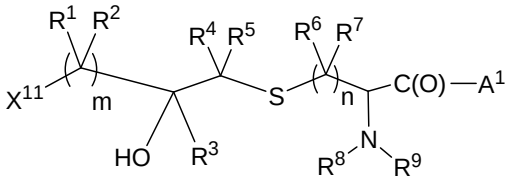
(IF-1).

In various embodiments, the one or more synthetic steps comprises converting the hydroxyl group bound to the carbon to which R3 is attached to L2–Z2–.

In various embodiments, the one or more synthetic steps comprises acylating the compound of formula (XV) so as to replace the hydrogen atom of the hydroxyl group bound to the carbon to which R3 is attached with L2–C(O)–.

In various embodiments, X11 is P10–O– or OH; and the one or more synthetic steps comprise acylating the compound of formula (XV) so as to replace P10 or the hydrogen atom of the hydroxyl group of X11 with L1–C(O)–; and/or acylating the compound of formula (XV) so as to replace the hydrogen atom of the hydroxyl group bound to the carbon to which R3 is attached with L2–C(O)–.

The present disclosure also broadly consists in a compound of the formula (XV):



(XV)

wherein

X11 is L1–Z1–, –OH, –SH, –NHR, HNRC(O)O-, P10–O–, P11–S–, P12–NR–, or P12-NRC(O)O-;

P10, P11, and P12 are each independently a protecting group;

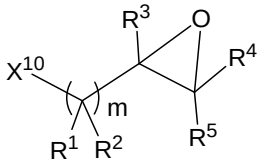
m is an integer from 2 to 6; and

n, L1, Z1, R, R1, R2, R3, R4, R5, R6, R7, R8, R9, and A1 are as defined in the compound of formula (I) of the disclosure (including provisos (1) and/or (2) of the first aspect) or any embodiment thereof; or a salt or solvate thereof.

The present disclosure also broadly consists in a method of making a compound of the formula (XV) or a salt or solvate thereof, the method comprising:

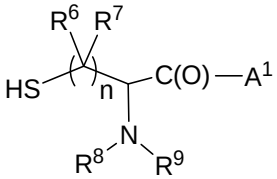
(A) reacting

an epoxide of the formula (XVI):



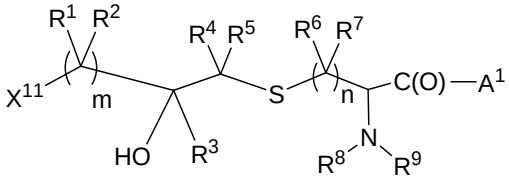
(XVI); and

an amino acid-comprising conjugation partner comprising a thiol of the formula (III):



(III),

under conditions effective to conjugate the epoxide and amino acid-comprising conjugation partner and provide a compound of formula (XV):



(XV)

wherein

X10 is L1–Z1–, –OH, –SH, –NHR, HNRC(O)O-, P10–O–, P11–S–, P12–NR–, or P12-NRC(O)O-;

X11 is X10 or –OH, –SH, –NHR, or HNRC(O)O- when X10 is P10-O-, P11-S-, P12–NR–, or P12-NRC(O)O- and said conditions are effective to remove P10, P11, or P12;

P10, P11, and P12 are each independently a protecting group;

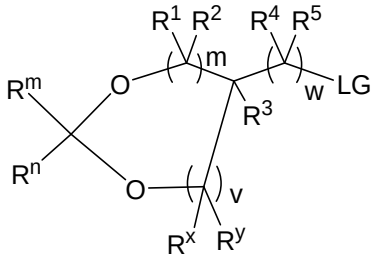
m, n, L1, Z1, R, R1, R2, R3, R4, R5, R6, R7, R8, R9, and A1 are as defined in the compound of formula (IF) of the disclosure (including provisos (1) and/or (2) of the first aspect).

The present disclosure also broadly consists in the use of a compound of the formula (XV) or (XVI) in the synthesis of a peptide-conjugate of the formula (IF) of the present disclosure (including provisos (1) and/or (2) of the first aspect) or a pharmaceutically acceptable salt or solvate thereof.

The present disclosure also broadly consists in a method of making a peptide-conjugate of the formula (I) or a pharmaceutically acceptable salt or solvate thereof of the present disclosure, the method comprising:

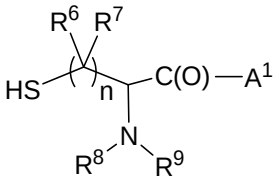
(A) reacting

a compound of the formula (XXI):



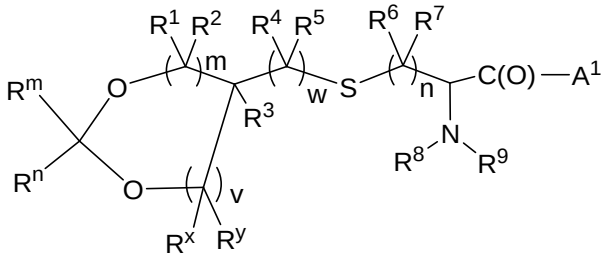
(XXI); and

an amino acid-comprising conjugation partner comprising a thiol of the formula (III):



(III),

under conditions effective to conjugate the compound of formula (XXI) and amino acid-comprising conjugation partner and provide a compound of formula (XX):



(XX)

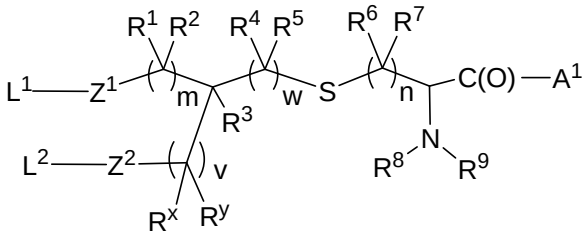
wherein

Rm and Rn are each independently hydrogen, C1-6alkyl, aryl, or heteroaryl;

LG is a leaving group; and

m, w, v, n, Rx, Ry, R1, R2, R3, R4, R5, R6, R7, R8, R9, and A1 are as defined in the compound of formula (I) of the present disclosure (including provisos (1) and/or (2) of the first aspect); and

converting the compound of formula (XX) to a peptide conjugate of the formula (I) of the present disclosure (including provisos (1) and/or (2) of the first aspect) or a pharmaceutically acceptable salt or solvate thereof by one or more additional synthetic steps:



(I); and

coupling the amino acid of the amino acid conjugate or an amino acid of the peptide conjugate to an amino acid or an amino acid of a peptide to provide the peptide-conjugate of formula (I) of the present disclosure (including provisos (1) and/or (2) of the first aspect) or pharmaceutically acceptable salt or solvate thereof..

In various embodiments, Rm and Rn are each independently selected from hydrogen, C1-6alkyl, or aryl.

In certain embodiments, Rm is hydrogen, C1-6alkyl, or aryl; and Rn is C1-6alkyl or aryl.

In various embodiments, the leaving group is a halo (for example chloro, bromo, or iodo) or sulfonate (for example a tosylate or mesylate).

In various embodiments, m and v are such that the compound of formula (XXI) comprises a 5-7-membered cyclic acetal.

In certain embodiment, the cyclic acetal is a 6-membered cyclic acetal.

In various embodiments, the cyclic acetal is a 5-membered cyclic acetal and w is an integer greater than 1.

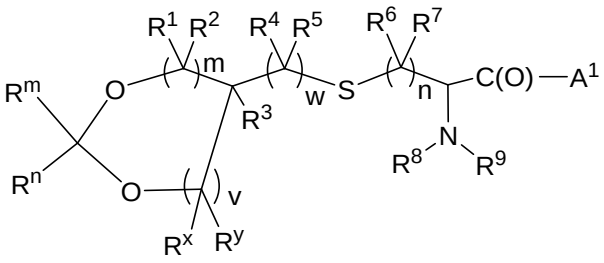
In various embodiments, m is 2 and v is 1.

In various embodiments, R9 is not hydrogen and/or A1 is not OH.

In various embodiments, the amino acid-comprising conjugation partner is a peptide containing conjugation partner comprising 15 or less, 14 or less, 13 or less, 12 or less, 11 or less, 10 or less, 9 or less, 8 or less, 7 or less, 6 or less, 5 or less, 4 or less, or 3 or less amino acid residues.

In various embodiments, the C-terminus of the amino acid comprising conjugation partner is protected with a carboxyl protecting group or a carboxamide protecting group

The present disclosure also broadly consists in a compound of the formula (XX):



(XX)

wherein:

Rm and Rn are each independently hydrogen, C1-6alkyl, aryl, or heteroaryl;

m and w are each independently an integer from 0 to 7 and v is an integer from 0 to 5,

provided that:

the sum of m, v, and w is at least 3; and

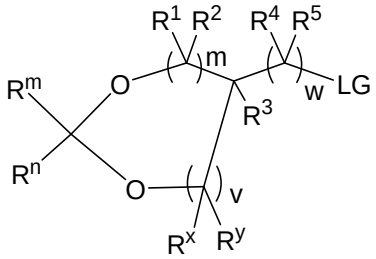
the sum of m and w is from 0 to 7; and

n, Rx, Ry, R1, R2, R3, R4, R5, R6, R7, R8, R9, and A1 are as defined in the compound of formula (I) of the present disclosure (including provisos (1) and/or (2) of the first aspect) or any embodiment thereof; or a salt or solvate thereof.

The present disclosure also broadly consists in a method of making a compound of the formula (XX) or a salt or solvate thereof, the method comprising:

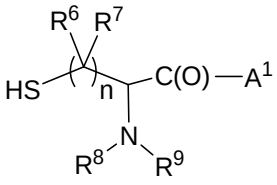
(A) reacting

a compound of the formula (XXI):



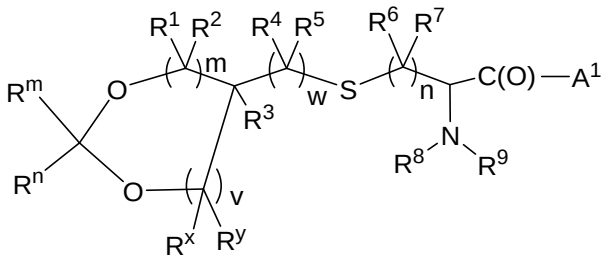
(XXI); and

an amino acid-comprising conjugation partner comprising a thiol of the formula (III):



(III),

under conditions effective to conjugate the compound of formula (XXI) and amino acid-comprising conjugation partner and provide a compound of formula (XX):



(XX)

wherein

Rm and Rn are each independently hydrogen, C1-6alkyl, aryl, or heteroaryl;

LG is a leaving group; and

m, w, v, n, Rx, Ry, R1, R2, R3, R4, R5, R6, R7, R8, R9, and A1 are as defined in the compound of formula (I) of the present disclosure (including provisos (1) and/or (2) of the first aspect).

The present disclosure also broadly consists in the use of a compound of the formula (XX) or (XXI) in the synthesis of a peptide-conjugate of the formula (IA) of the present disclosure (including provisos (1) and/or (2) of the first aspect) or a pharmaceutically acceptable salt or solvate thereof.

The present disclosure also broadly consists in a method of making a peptide conjugate of the formula (I) or a pharmaceutically acceptable salt or solvate thereof of the present disclosure, the method comprising:

(A) reacting

a first lipid-containing conjugation partner comprising a carbon-carbon double bond,

a second lipid-containing conjugation partner comprising a carbon-carbon double bond, and

an amino acid-comprising conjugation partner comprising a thiol

under conditions effective to conjugate the first lipid-containing conjugation partner and the second lipid-containing conjugation partner to the amino acid-comprising conjugation partner and provide the peptide-conjugate of formula (I) or salt or solvate thereof,

wherein in the amino acid- or peptide conjugate the sulfur atom from the thiol of the amino acid-comprising conjugation partner is conjugated to a carbon atom from the carbon-carbon double bond of the first lipid-containing conjugation partner, and a carbon atom from the carbon-carbon double bond of the first lipid-containing conjugation

partner is conjugated to a carbon atom from the carbon-carbon double bond of the second lipid-containing conjugation partner; or

(B) reacting

a first lipid-containing conjugation partner comprising a carbon-carbon double bond,

a second lipid-containing conjugation partner comprising a carbon-carbon double bond, and

an amino acid-comprising conjugation partner comprising a thiol

under conditions effective to conjugate the first lipid-containing conjugation partner and the second lipid-containing conjugation partner to the amino acid-comprising conjugation partner and provide an amino acid- or peptide-conjugate,

wherein in the amino acid- or peptide conjugate the sulfur atom from the thiol of the amino acid-comprising conjugation partner is conjugated to a carbon atom from the carbon-carbon double bond of the first lipid-containing conjugation partner, and a carbon atom from the carbon-carbon double bond of the first lipid-containing conjugation partner is conjugated to a carbon atom from the carbon-carbon double bond of the second lipid-containing conjugation partner; and

coupling the amino acid of the amino acid conjugate or an amino acid of the peptide conjugate to an amino acid or an amino acid of a peptide to provide the peptide-conjugate of formula (I) or salt or solvate thereof.

In one embodiment, the amino acid-comprising conjuation partner is a peptide-containing conjugation partner, and the lipid-containing conjugation partners are coupled to the peptide of the peptide-containing conjugation partner.

In some embodiments, the lipid-containing conjugation partners are conjugated to the or an amino acid of the amino acid-comprising conjugation partner or the peptide of the peptide-containing conjugation partner.

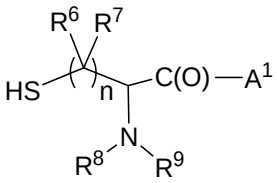
In certain embodiments, the lipid-containing conjugation partners are conjugated to the or an amino acid of the amino acid-comprising conjugation partner.

Accordingly, the present disclosure also broadly consists in a method of making a peptide conjugate of formula (I) or a pharmaceutically acceptable salt or solvate thereof of the present disclosure, the method comprising reacting

a first lipid-containing conjugation partner comprising a carbon-carbon double bond,

a second lipid-containing conjugation partner comprising a carbon-carbon double bond, and

the amino acid-comprising conjugation partner comprises a structure of the formula (III):



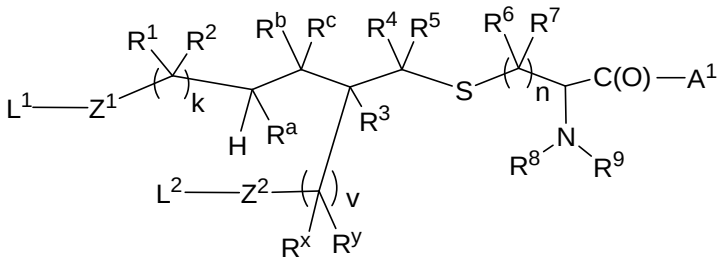
(III);

wherein:

when the method is (A), Ra, Rb, Rc, L1, L2, Z1, Z2, R1, R2, Rx, Ry, R3, R4, R5, R6, R7, R8, R9, A1, k, v, and n are as defined in the compound of formula (IB) of the present disclosure (including provisos (1) and/or (2) of the first aspect); and

when the method is (B), Ra, Rb, Rc, L1, L2, Z1, Z2, R1, R2, Rx, Ry, R3, R4, R5, R6, R7, R8, R9, A1, k, v, and n are as defined in the compound of formula (IB) but excluding provisos (1) and (2) of the first aspect.

In various embodiments, the amino acid- or peptide conjugate is a compound of the formula (IB):



(IB)

wherein:

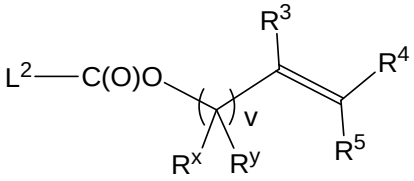
when the method is (A), Ra, Rb, Rc, L1, L2, Z1, Z2, R1, R2, Rx, Ry, R3, R4, R5, R6, R7, R8, R9, A1, k, v, and n are as defined in the compound of formula (IB) of the present disclosure (including provisos (1) and/or (2) of the first aspect); and

when the method is (B), Ra, Rb, Rc, L1, L2, Z1, Z2, R1, R2, Rx, Ry, R3, R4, R5, R6, R7, R8, R9, A1, k, v, and n are as defined in the compound of formula (IB) but excluding provisos (1) and (2) of the first aspect.

In various embodiments, the lipid containing conjugation partners are in stoichiometric excess to the amino acid-comprising conjugation partner.

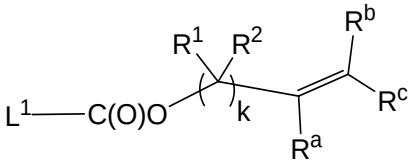
In various embodiments, the mole ratio of the lipid containing conjugation partners (combined) to amino acid-comprising conjugation partner is at least 7:1.

In various embodiments, the first lipid-containing conjugation partner is a compound of the formula (IIA-1):



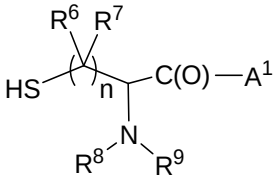
(IIA-1);

the second lipid-containing conjugation partner is a compound of the formula (IIB):



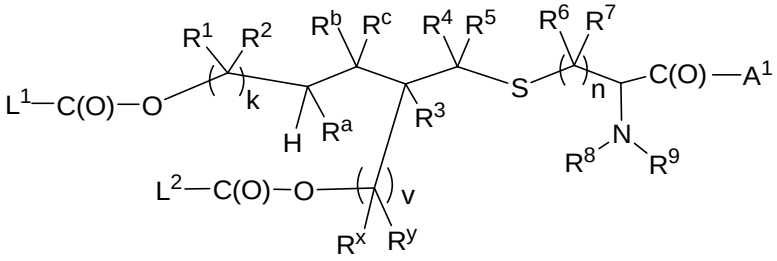
(IIB);

the amino acid-comprising conjugation partner comprises a structure of the formula (III):



(III); and

the conjugate is a compound of the formula (IC):



(IC)

wherein:

when the method is (A), Ra, Rb, Rc, L1, L2, R1, R2, Rx, Ry, R3, R4, R5, R6, R7, R8, R9, A1, k, v, and n are as defined in the compound of formula (IC) of the present disclosure (including provisos (1) and/or (2) of the first aspect); and

when the method is (B), Ra, Rb, Rc, L1, L2, R1, R2, Rx, Ry, R3, R4, R5, R6, R7, R8, R9, A1, k, v, and n are as defined in the compound of formula (IC) but excluding provisos (1) and (2) of the first aspect.

In various embodiments, L1 is C11-21alkyl; k is 0-3, preferably 0; and Ra, Rb, and Rc are each hydrogen.

In one embodiment, the amino acid-comprising conjugation partner consists of a peptide comprising a peptide epitope. In one embodiment, the peptide-containing conjugation partner consists of a peptide. In one embodiment, the peptide-containing conjugation partner consists of a peptide comprising a peptide epitope.

In some embodiments, the amino acid-comprising conjugation partner comprises an epitope bound to the or an amino acid of the conjugation partner. In some embodiments, the peptide-containing conjugation partner comprises an epitope bound to the peptide of the peptide containing conjugation partner. In some embodiments, the epitope is bound to the peptide via linker group.

In some embodiments, the amino acid-comprising conjugation partner comprises a peptide epitope bound to the or an amino acid of the conjugation partner via a linker group. In some embodiments, the peptide-containing conjugation partner comprises a peptide epitope bound to the peptide via a linker group.

In some embodiments, the amino acid-comprising conjugation partner and/or the peptide-containing conjugation partner comprises an antigenic peptide.

In one embodiment, the amino acid-comprising conjugation partner and/or peptide conjugate comprises a synthetic peptide. In some embodiments, the synthetic peptide is a peptide prepared by a method comprising solid phase peptide synthesis (SPPS).

In various embodiments, the method comprises coupling the amino acid of the amino acid conjugate or an amino acid of the peptide conjugate to an amino acid or an amino acid of a peptide to provide a peptide conjugate.

In various embodiments, the method comprises coupling the amino acid of the amino acid conjugate to an amino acid or an amino acid of a peptide to provide a peptide conjugate of the present disclosure.

In various embodiments, the peptide comprises an epitope. In various embodiments, the epitope is a peptide epitope.

In some embodiments, the method further comprises coupling the amino acid of the amino acid conjugate to an amino acid or a peptide to provide a peptide conjugate of the present disclosure.

In some embodiments, coupling a peptide comprises individually coupling one or more amino acids and/or one or more peptides.

In some embodiments, the method further comprises coupling the amino acid of the amino acid conjugate or an amino acid of the peptide conjugate to an amino acid or a peptide so as to provide a peptide conjugate of the disclosure comprising a linker group or one or more amino acids thereof.

In some embodiments, the method further comprises coupling an amino acid of the peptide conjugate comprising a linker group or one or more amino acids thereof to an amino acid or a peptide so as to provide a peptide conjugate of the disclosure comprising a peptide epitope bound to the amino acid to which lipid moieties are conjugated via a linker group.

In some embodiments, the amino acid of the peptide conjugate to which the lipid moeities are conjugated is an N-terminal amino acid residue.

In some embodiments, the method further comprises coupling the amino acid of the amino acid conjugate or an amino acid of the peptide conjugate to an amino acid or a peptide so as to provide a peptide conjugate of the disclosure comprising a peptide epitope.

In some embodiments, the method further comprises coupling an epitope to the amino acid of the amino acid conjugate or an amino acid of the peptide conjugate.

In some embodiments, the method further comprises coupling a peptide epitope to the amino acid of the amino acid conjugate or an amino acid of the peptide conjugate.

In some embodiments, the epitope is coupled or bound via a linker group.

In some embodiments, the method further comprises coupling an epitope to the peptide of the peptide conjugate.

In some embodiments, the method further comprises coupling a peptide epitope to the peptide of the peptide conjugate.

In some embodiments, the epitope is bound to the peptide via a linker group.

In various embodiments, the method is (B) and the amino acid-comprising conjugation partner consists of an amino acid, for example cysteine (including Nα-amino and/or C-terminus protected cysteines).

In various embodiments, the amino acid- or peptide-conjugate compound of formula (I) but excluding provisos (1) and (2) of the first aspect is an amino acid-conjugate.

In some embodiments, one or more protecting groups are removed on cleaving the peptide from the solid phase support. In certain embodiments, all of the protecting groups present in the peptide are removed.

In one embodiment, the SPPS is Fmoc-SPPS.

In some embodiments, the amino acid residue in the peptide of the peptide-containing conjugation partner bearing the thiol to be reacted is an N-terminal amino acid residue and the method comprises acylating the N-terminal amino group prior to cleaving the peptide from the solid phase. In specifically contemplated embodiments, the N-terminal residue is a cysteine residue.

In one embodiment, the method further comprises separating the peptide conjugate from the reaction medium and optionally purifying the peptide conjugate.

The present disclosure also broadly consists in a method of making a peptide conjugate, the method comprising

providing an amino acid- or peptide conjugate of the formula (I) but excluding provisos (1) and (2) of the first aspect or a salt or solvate thereof, and

coupling the amino acid of the amino acid conjugate or an amino acid of the peptide conjugate to an amino acid or an amino acid of a peptide to provide a peptide conjugate of the formula (I) of the disclosure (including provisos (1) and/or (2) of the first aspect) or a salt or solvate thereof.

In various embodiments, the product peptide conjugate is a compound of the formula (I) or a pharmaceutically acceptable salt thereof of the present disclosure.

In various embodiments, the amino acid of the amino acid conjugate is coupled under conditions that reduce epimerisation at the α-carbon of the amino acid. In various embodiments, the conditions are such that less than about 35, 30, 25, 20, 15, 10, 5, 3, 2, or 1% by mol of the amino acid is epimerised. In various embodiments, the conditions that reduce epimerisation comprise the use of PyBOP or BOP as the coupling reagent. In various embodiments, the conditions that reduce epimerisation comprise the use of PyBOP as the coupling reagent. In various embodiments, the conditions comprise the use of PyBOP or BOP; and 2,4,6-trimethylpyridine. In various embodiments, the conditions comprise the use of PyBOP and 2,4,6-trimethylpyridine.

The present disclosure also broadly consists in use of an amino acid- or peptide-conjugate of the formula (I) of the present disclosure (including provisos (1) and/or (2) of the first aspect) or a salt or solvate thereof in the synthesis of an immunogenic peptide-conjugate.

In various embodiments, the immunogenic peptide conjugate is a compound of the formula (I) of the present disclosure or a pharmaceutically acceptable salt thereof.

The present disclosure also broadly consists in a peptide conjugate of the present disclosure produced by a method of the present disclosure.

The present disclosure also broadly consists in a composition comprising a peptide conjugate of formula (I) of the present disclosure or a salt or solvate thereof.

In various embodiments, the composition comprises isolated, pure, purified or substantially purified compound of formula (I) of the present disclosure or a salt or solvate thereof.

In various embodiments, the composition comprises at least about 60, 70, 75, 80, 85, 90, 95, 97, 98, or 99% by weight compound of formula (I) of the present disclosure or a salt or solvate thereof.

In various embodiments, the composition is free of substantially free of amino acid- or peptide containing compounds other than compounds of formula (I) of the present disclosure.

In another aspect, the present disclosure broadly consists in a pharmaceutical composition comprising an effective amount of a peptide conjugate compound of the formula (I) of the present disclosure or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

In various embodiments, the pharmaceutical composition comprises an effective amount of two or more peptide conjugate compounds of the formula (I) of the present disclosure.

In one embodiment, the pharmaceutical composition is an immunogenic composition.

In one embodiment, the pharmaceutical composition does not include an extrinsic adjuvant.

In some embodiments, the pharmaceutical composition is a vaccine.

In one embodiment, the pharmaceutical composition comprises an effective amount of two or more peptide conjugates of the present disclosure, for example the pharmaceutical composition comprises an effective amount of three or more peptide conjugates of the present disclosure.

In one embodiment, the pharmaceutical composition comprises an effective amount of one or more peptide conjugates of the present disclosure together with one or more

peptides described herein, or any combination thereof. For example, the pharmaceutical composition comprises an effective amount of two or more peptide conjugates of the present disclosure and one or more peptides described herein, or an effective amount of one or more peptide conjugates of the present disclosure and two or more peptides described herein.

The present disclosure also broadly consists in a method of vaccinating or eliciting an immune response in a subject comprising administering to the subject an effective amount of one or more peptide conjugate compounds of the formula (I) of the disclosure or a pharmaceutically acceptable salt or solvate thereof, or an effective amount of a pharmaceutical composition of of the present disclosure.

In another aspect, the present disclosure broadly consists in use of one or more peptide conjugate compounds of formula (I) of the present disclosure or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition of the present disclosure in the manufacture of a medicament for vaccinating or eliciting an immune response or for activating TLR2 in a subject.

In another aspect, the present disclosure broadly consists in one or more peptide conjugate compounds of the formula (I) of the present disclosure or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition of the present disclosure for vaccinating or eliciting an immune response or for activating TLR2 in a subject.

The present disclosure also broadly consists in use of one or more peptide conjugate compounds of the formula (I) of the disclosure or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition of the present disclosure for vaccinating or eliciting an immune response in a subject.

The present disclosure also broadly consists in a method of activating TLR2 in a subject, the method comprising administering to the subject an effective amount of one or more peptide conjugate of the disclosure or a pharmaceutically acceptable salt or solvate thereof, or an effective amount of a pharmaceutical composition of the disclosure.

Use of one or more peptide conjugate compounds of the disclosure or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition of the disclosure in the manufacture of a medicament for activating TLR2 in a subject.

One or more peptide conjugate compounds of the disclosure or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition of the disclosure for activating TLR2 in a subject.

In various embodiments, the method, use, one or more compounds, or pharmaceutical composition is for eliciting an immune response in a subject.

In various embodiments, the method, use, one or more compounds, or pharmaceutical composition is for vaccinating a subject.

In some embodiments, the method comprises the administration of one or more peptides described herein and one or more peptide conjugates of the present disclosure or two or more peptide conjugates of the present disclosure, for example one or more peptides in combination with one or more peptide conjugates to the subject.

In some embodiments, one or more peptides described herein and one or more peptide conjugates of the present disclosure or two or more peptide conjugates of the present disclosure, for example one or more peptides in combination with one or more peptide conjugates, are used for vaccinating or eliciting an immune response in the subject or in the manufacture of a medicament for vaccinating or eliciting an immune response in the subject.

In some embodiment, two or more peptide conjugates are used or administered.

In some embodiments the two or more peptide conjugates, or one or more peptides and one or more peptide conjugates are used or administered simultaneously, sequentially, or separately.

In some embodiments, the subject is in need thereof.

Asymmetric centers may exist in the compounds described herein. The asymmetric centers may be designated as (*R*) or (*S*), depending on the configuration of substituents in three dimensional space at the chiral carbon atom. All stereochemical isomeric forms of the compounds, including diastereomeric, enantiomeric, and epimeric forms, as well as d-isomers and l-isomers, and mixtures thereof, including enantiomerically enriched and diastereomerically enriched mixtures of stereochemical isomers, are within the scope of the disclosure.

Individual enantiomers can be prepared synthetically from commercially available enantiopure starting materials or by preparing enantiomeric mixtures and resolving the mixture into individual enantiomers. Resolution methods include conversion of the enantiomeric mixture into a mixture of diastereomers and separation of the diastereomers by, for example, recrystallization or chromatography, and any other appropriate methods known in the art. Starting materials of defined stereochemistry may be commercially available or made and, if necessary, resolved by techniques well known in the art.

The compounds described herein may also exist as conformational or geometric isomers, inlcuding *cis*, *trans*, *syn*, *anti*, entgegen (*E*), and zusammen (*Z*) isomers. All such isomers and any mixtures thereof are within the scope of the disclosure.

Also within the scope of the disclosure are any tautomeric isomers or mixtures thereof of the compounds described. As would be appreciated by those skilled in the art, a wide variety of functional groups and other structures may exhibit tautomerism. Examples include, but are not limited to, keto/enol, imine/enamine, and thioketone/enethiol tautomerism.

The compounds described herein may also exist as isotopologues and isotopomers, wherein one or more atoms in the compounds are replaced with different isotopes. Suitable isotopes include, for example, ^{1}H, ^{2}H (D), ^{3}H (T), ^{12}C, ^{13}C, ^{14}C, ^{16}O, and ^{18}O. Procedures for incorporating such isotopes into the compounds described herein will be apparent to those skilled in the art. Isotopologues and isotopomers of the compounds described herein are also within the scope of the disclosure.

Also within the scope of the disclosure are salts of the compounds described herein, including pharmaceutically acceptable salts. Such salts include, acid addition salts, base addition salts, and quaternary salts of basic nitrogen-containing groups.

Acid addition salts can be prepared by reacting compounds, in free base form, with inorganic or organic acids. Examples of inorganic acids include, but are not limited to, hydrochloric, hydrobromic, nitric, sulfuric, and phosphoric acid. Examples of organic acids include, but are not limited to, acetic, trifluoroacetic, propionic, succinic, glycolic, lactic, malic, tartaric, citric, ascorbic, maleic, fumaric, pyruvic, aspartic, glutamic, stearic, salicylic, methanesulfonic, benzenesulfonic, isethionic, sulfanilic, adipic, butyric, and pivalic.

Base addition salts can be prepared by reacting compounds, in free acid form, with inorganic or organic bases. Examples of inorganic base addition salts include alkali metal salts, alkaline earth metal salts, and other physiologically acceptable metal salts, for example, aluminium, calcium, lithium, magnesium, potassium, sodium, or zinc salts. Examples of organic base addition salts include amine salts, for example, salts of trimethylamine, diethylamine, ethanolamine, diethanolamine, and ethylenediamine.

Quaternary salts of basic nitrogen-containing groups in the compounds may be may be prepared by, for example, reacting the compounds with alkyl halides such as methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides, dialkyl sulfates such as dimethyl, diethyl, dibutyl, and diamyl sulfates, and the like.

The compounds described herein may form or exist as solvates with various solvents. If the solvent is water, the solvate may be referred to as a hydrate, for example, a mono-hydrate, a di- hydrate, or a tri-hydrate. All solvated forms and unsolvated forms of the compounds described herein are within the scope of the disclosure.

The general chemical terms used in the formulae herein have their usual meaning.

The term “aliphatic” is intended to include saturated and unsaturated, nonaromatic, straight chain, branched, acyclic, and cyclic hydrocarbons. Those skilled in the art will appreciate that aliphatic groups include, for example, alkyl, alkenyl, alkynyl, cycloalkyl, and cycloalkenyl groups, and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl and (cycloalkyl)alkenyl groups. In various embodiments, aliphatic groups comprise from 1-12, 1-8, 1-6, or 1-4 carbon atoms. In some embodiments, aliphatic groups comprise 5-21, from 9-21, or from 11-21 carbon atoms, such as from 11, 13, 15, 17, or 19 carbon atoms. In some embodiments, the aliphatic group is saturated.

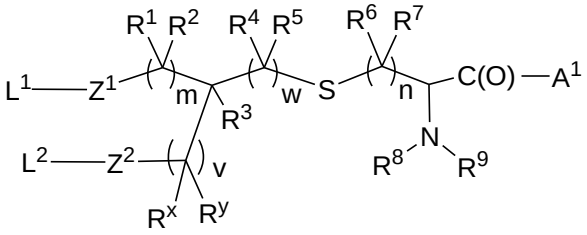
The term "heteroaliphatic" is intended to include aliphatic groups, wherein one or more chain and/or ring carbon atoms are independently replaced with a heteroatom, preferably a heteroatom selected from oxygen, nitrogen and sulfur. In some embodiments, the heteroaliphatic is saturated. Examples of heteroaliphatic groups include linear or branched, heteroalkyl, heteroalkenyl, and heteroalkynyl groups.

The term “alkyl” is intended to include saturated straight chain and branched chain hydrocarbon groups. In some embodiments, alkyl groups have from 1 to 12, 1 to 10, 1 to 8, 1 to 6, or from 1 to 4 carbon atoms. In some embodiments, alkyl groups have from 5-21, from 9-21, or from 11-21 carbon atoms, such as from 11, 13, 15, 17, or 19 carbon atoms. Examples of straight chain alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl, and n-octyl. Examples of branched alkyl groups include, but are not limited to, isopropyl, iso-butyl, sec-butyl, tert-butyl, neopentyl, isopentyl, and 2,2-dimethylpropyl.

The term “alkenyl” is intended to include straight and branched chain alkyl groups having at least one double bond between two carbon atoms. In some embodiments, alkenyl groups have from 2 to 12, from 2 to 10, from 2 to 8, from 2 to 6, or from 2 to 4 carbon atoms. In some embodiments, alkenyl groups have from 5-21, from 9-21, or from 11-21 carbon atoms, such as from 11, 13, 15, 17, or 19 carbon atoms. In some embodiments, alkenyl groups have one, two, or three carbon-carbon double bonds. Examples of alkenyl groups include, but are not limited to, vinyl, allyl, $-CH=CH(CH_3)$, $-CH=C(CH_3)_2$, $-C(CH_3)=CH_2$, and $-C(CH_3)=CH(CH_3)$.

CLAIMS

1. A compound of the formula (I):



(I)

wherein

m and w are each independently an integer from 0 to 7 and v is an integer from 0 to 5,

provided that:

the sum of m, v, and w is at least 3; and

the sum of m and w is from 0 to 7;

n is 1 or 2;

Z1 and Z2 are each independently selected from the group consisting of –O–, –NR–, –S–, –S(O)–, –SO_2–, –C(O)O–, –OC(O)–, –C(O)NR–, –NRC(O)–, –C(O)S–, –SC(O)–, –OC(O)O–, –NRC(O)O–, –OC(O)NR–, and –NRC(O)NR–;

R1, R2, Rx, Ry, R4, R5, R6, and R7 at each instance of m, v, w, and n are each independently hydrogen or C1-6aliphatic;

R, R3, and R8 are each independently hydrogen or C1-6aliphatic;

R9 is hydrogen, C1-6aliphatic, an amino protecting group, L3–C(O)–, or A2;

L1 and L2 are each independently selected from C5-21aliphatic or C4-20heteroaliphatic;

L3 is C1-21aliphatic or C2-20heteroaliphatic;

A1 is an amino acid, a peptide, OH, OP1, NH_2, or NHP2, wherein P1 is a carboxyl protecting group, and wherein P2 is a carboxamide protecting group;

A2 is an amino acid or a peptide;

wherein any aliphatic or heteroaliphatic present in any of R, R1, R2, R3, R4, R5, R6, R7, R8, R9, Rx, Ry, L1, L2, and L3 is optionally substituted;
or a pharmaceutically acceptable salt or solvate thereof;

with the proviso that:

(1) at least one of R9 and A1 is a peptide comprising, consisting essentially of, or consisting of an amino acid sequence selected from the group consisting of:

(a) 8 or more contiguous amino acid residues from the sequence $Xaa_1Xaa_2Xaa_3Xaa_4$LQQLSLLMWITQXaa_{22}FLPVFLAQPPSGQRR [SEQ ID NO:1], wherein Xaa_1 is absent or is S, Xaa_2 is absent or is a hydrophilic amino acid, Xaa_3 is absent or is a hydrophilic amino acid, and Xaa_4 is absent or is one or more hydrophilic amino acids,

(b) 8 or more contiguous amino acid residues from the sequence $Xaa_1Xaa_2Xaa_3$LQQLSLLMWITQXaa_{22}FLPVFLAQPPSGQRR [SEQ ID NO:2], wherein Xaa_1 is absent or is S, Xaa_2 is absent or is a hydrophilic amino acid, and Xaa_3 is absent or is from one to ten hydrophilic amino acids,

(c) 8 or more contiguous amino acid residues from the sequence Xaa_1Xaa_2LQQLSLLMWITQXaa_{22}FLPVFLAQPPSGQRR [SEQ ID NO:3], wherein Xaa_1 is absent or is S, and Xaa_2 is absent or is from one to four hydrophilic amino acids,

(d) 8 or more contiguous amino acid residues from the sequence SKKKKLQQLSLLMWITQXaa_{22}FLPVFLAQPPSGQRR [SEQ ID NO:4],

(e) the sequence of any one of SEQ ID NOs: 1 to 4,

(f) 8 or more contiguous amino acid residues from the sequence LQQLSLLMWITQXaa_{22}FLPVFLAQPPSGQRR [SEQ ID NO:5],

(g) the sequence of SEQ ID NO: 5,

(h) 8 or more contiguous amino acid residues from the sequence SLLMWITQXaa_{22}FLPVF [SEQ ID NO:6],

(i) the sequence of SEQ ID NO: 6,

(j) 8 or more contiguous amino acid residues from the sequence SKKKKSLLMWITQXaa_{22} [SEQ ID NO:7],

(k) the sequence of SEQ ID NO: 7,

(l) 8 or more contiguous amino acid residues from the sequence SLLMWITQXaa_{22} [SEQ ID NO:8],

(m) the sequence of SEQ ID NO: 8,

(n) or any combination of two or more of (a) to (m) above,

wherein Xaa_{22} in each sequence is independently any naturally occurring amino acid except C (for example, V, I, or L), and any sequence of 8 or more contiguous amino acid residues from any of the above sequences comprises Xaa_{22}; or

(2) m is an integer from 3 to 7, and at least one of R9 and A1 is an amino acid or a peptide.

2. The compound of claim 1, wherein at least one of R9 and A1 is a peptide comprising, consisting essentially of, or consisting of one or more amino acid sequences selected from the group as defined in proviso (1) of claim 1.

3. The compound of claim 2, wherein m is 2.

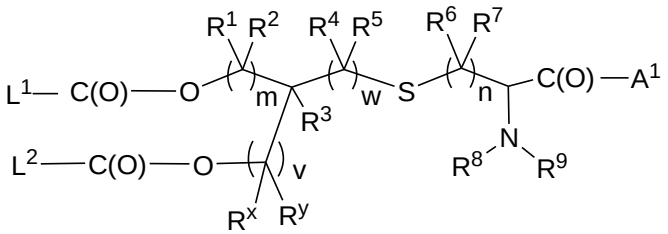
4. The compound of claim 1, wherein m is an integer from 3 to 7 and at least one of R9 and A1 is an amino acid or a peptide as defined in proviso (2) of claim 1.

5. The compound of claim 4, wherein at least one of R9 and A1 is a peptide, wherein the peptide comprises, consists essentially of, or consists of an amino acid sequence selected from the group consisting of 8 or more contiguous amino acids from the amino acid sequence of any one of SEQ ID NOs 8 – 129; or wherein the peptide comprises, consists essentially of, or consists of one or more amino acid sequences selected from the group defined in proviso (1) of claim 1.

6. The compound of any one of the preceding claims, wherein m is from 3 to 5.

7. The compound of any one of the preceding claims, wherein Z1 and Z2 are each independently selected from the group consisting of –C(O)O–, –C(O)NR–, and –C(O)S–.

8. The compound of any one of the preceding claims, wherein the compound is a compound of the formula (IA):



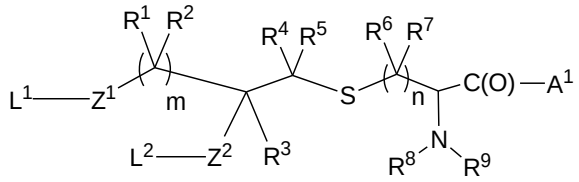
(IA).

9. The compound of any one of the preceding claims, wherein w is 1 or 2; and/or wherein n is 1; and/or wherein v is from 0 to 3.

10. The compound of any one of the preceding claims, wherein L1 and L2 are each independently C5-21alkyl, preferably linear C15alkyl; and/or wherein L3 is methyl or linear C15alkyl, preferably methyl.

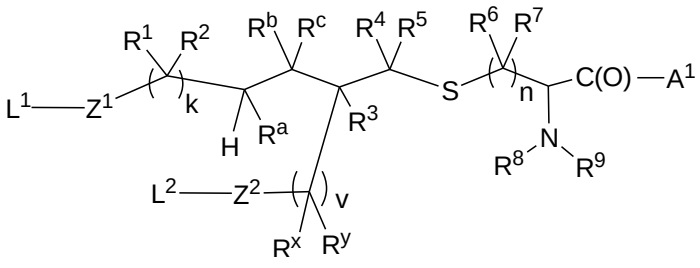
11. The compound of any one of the preceding claims, wherein R1 and R2 at each instance of m are each independently C1-6alkyl or hydrogen, preferably hydrogen; and/or wherein R3 is C1-6alkyl or hydrogen, preferably hydrogen; and/or wherein R4 and R5 at each instance of w are each independently C1-6alkyl or hydrogen, preferably hydrogen; and/or wherein Rx and Ry at each instance of v are each independently C1-6alkyl or hydrogen, preferably hydrogen; and/or wherein R6 and R7 at each instance of n are each independently C1-6alkyl or hydrogen, preferably hydrogen; and/or wherein R8 is independently C1-6alkyl or hydrogen, preferably hydrogen; and/or wherein R9 is C1-6alkyl, hydrogen, an amino protecting group, L3–C(O), or A2, preferably hydrogen, an amino protecting group, L3–C(O), or A2.

12. The compound of any one of the preceding claims, wherein the compound is a compound of the formula (IF):



(IF); or

a compound of the formula (IB):



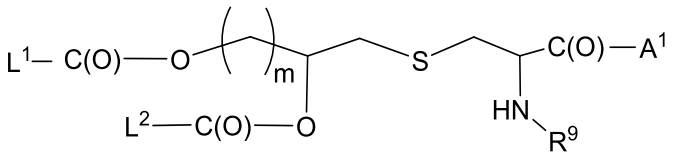
(IB)

wherein

k is an integer from 0 to 4, preferably 0 to 3; and

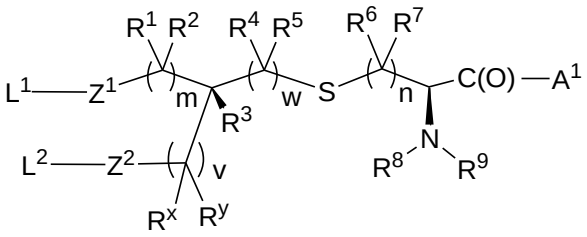
Ra, Rb, and Rc are each independently hydrogen or C1-6aliphatic, preferably hydrogen or C1-6alkyl, preferably hydrogen.

13. The compound of any one of the preceding claims, wherein the compound is a compound of the formula (ID-1):



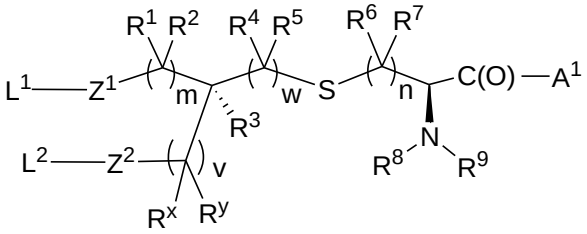
(ID-1).

14. The compound of any one of the preceding claims, wherein the compound has the formula (IE-1):



(IE-1); or

has the formula (IE-2):



(IE-2).

15. The compound of any one of the preceding claims, wherein the amino acid of the peptide conjugate to which the lipid moieties are conjugated is an N-terminal amino acid residue; and/or wherein A1 is serine or a peptide comprising serine as the first N-terminal amino acid residue.

16. A pharmaceutical composition comprising an effective amount of a peptide conjugate compound of any one of claims 1 to 15 or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

17. Use of one or more peptide conjugate compounds of any one of claims 1 to 15 or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition of claim 16 in the manufacture of a medicament for vaccinating or eliciting an immune response or for activating TLR2 in a subject.

18. One or more peptide conjugate compounds of any one of claims 1 to 15 or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition of claim 16 for use in vaccinating or eliciting an immune response or for activating TLR2 in a subject.