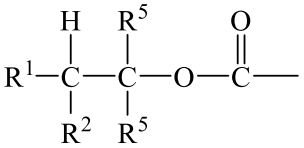
## Claims

1. An extended-release conjugate of a GLP-1 agonist comprising an insoluble matrix with a multiplicity of covalently attached linker-agonist peptide, wherein the extended-release conjugate has the formula M-(L-E)$_a$, wherein:

M is an insoluble matrix comprising a crosslinked polyethylene glycol hydrogel having crosslinkers cleavable by beta elimination;

L is a cleavable linker of formula (3)



(3)

wherein $R^1$ is CN or $R^3SO_2$, wherein $R^3$ is optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, or $(R^9)_2N$, wherein each $R^9$ is independently H or optionally substituted alkyl;

$R^2$ is H;

one of $R^5$ is $(CH_2)_yZ^*$, $(CH_2CH_2O)_xCH_2CH_2Z^*$ or $(CH_2)_yNH\text{-}CO\text{-}(CH_2CH_2O)_xCH_2CH_2Z^*$, wherein x is 1-100, y = 1-6, and the other $R^5$ is H or unsubstituted alkyl, and Z* comprises the residue of a functional group coupled to M, wherein the functional group comprises $N_3$, $NH_2$, NH-$CO_2{}^tBu$, SH, $S^tBu$, maleimide, $CO_2H$, $CO_2{}^tBu$, 1,3-diene, cyclopentadiene, furan, alkyne, cyclooctyne, acrylate, aminooxy, keto or acrylamide;

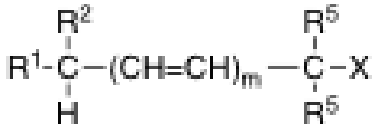
E is an agonist peptide of SEQ ID NO: 2; and

a is an integer representing the number of L-E units required to provide a concentration of 1-1000 mg peptide in one ml of the volume occupied by the matrix.

2. The extended-release conjugate of claim 1 wherein $R^1$ is CN or $CH_3SO_2$; $R^2$ is H; one $R^5$ is $(CH_2)_yZ^*$ wherein y is 5; and the other $R^5$ is H.

3. The extended-release conjugate of claim 1 or 2 wherein the hydrogel is in the form of microspheres.

4. The extended-release conjugate of any one of claims 1-3 wherein said crosslinkers contained in the hydrogel are of formula (1)



(1)

wherein: m is 0 or 1; and

wherein X and one of $R^1$, $R^2$ and $R^5$ is coupled to a polymer contained in the hydrogel, and wherein X comprises the residue of a functional group coupled to a polymer contained in the hydrogel, wherein the functional group comprises $N_3$, $NH_2$, NH-$CO_2{}^tBu$, SH, $S^tBu$, maleimide, $CO_2H$, $CO_2{}^tBu$, 1,3-diene, cyclopentadiene, furan, alkyne, cyclooctyne, acrylate, aminooxy, keto or acrylamide,

with the proviso that at least one of $R^1$ and $R^2$ is CN; $NO_2$;

optionally substituted aryl;

optionally substituted heteroaryl;

optionally substituted alkenyl;

optionally substituted alkynyl;

$COR^3$ or $SOR^3$ or $SO_2R^3$ wherein

$R^3$ is H or optionally substituted alkyl;

aryl or arylalkyl, each optionally substituted;

heteroaryl or heteroarylalkyl, each optionally substituted; or

$OR^9$ or $NR^9{}_2$ wherein each $R^9$ is independently H or optionally substituted alkyl, or both $R^9$ groups taken together with the nitrogen to which they are attached form a heterocyclic ring;

$SR^4$ wherein

$R^4$ is optionally substituted alkyl;

aryl or arylalkyl, each optionally substituted; or

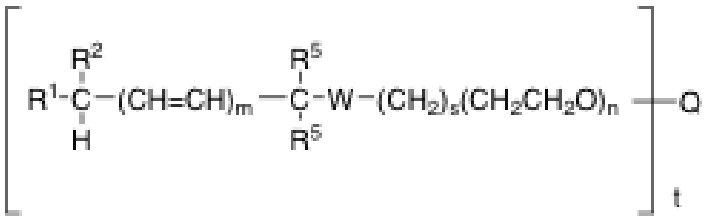
heteroaryl or heteroarylalkyl, each optionally substituted;

wherein $R^1$ and $R^2$ may be joined to form a 3-8 membered ring; and

wherein any remaining $R^1$ and $R^2$ is H or is alkyl, arylalkyl or heteroarylalkyl, each optionally substituted; and

any remaining $R^5$ is independently H or is alkyl, alkenylalkyl, alkynylalkyl, $(OCH_2CH_2)_p$ O-alkyl wherein p=1-1000, aryl, arylalkyl, heteroaryl or heteroarylalkyl, each optionally substituted; or

said crosslinkers when contained in the hydrogel are of formula (2)



(2)

wherein two of $R^1$, $R^2$ and $R^5$ are coupled to a polymer contained in the hydrogel;

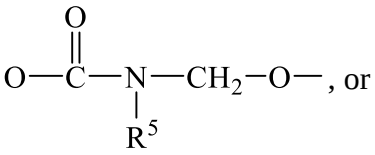
m is 0-1;

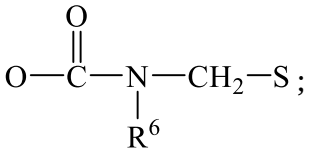
n is 1-1000;

s is 0-2;

t is 2,4, 8, 16 or 32;

Q is a core group having the valency t;

W is O(C=O)O, O(C=O)NH, O(C=O)S, , or



wherein $R^6$ is H, optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, or optionally substituted heteroarylalkyl; and

with the proviso that at least one of $R^1$ and $R^2$ is CN; $NO_2$;

optionally substituted aryl;

optionally substituted heteroaryl;

optionally substituted alkenyl;

optionally substituted alkynyl;

$COR^3$ or $SOR^3$ or $SO_2R^3$ wherein

$R^3$ is H or optionally substituted alkyl;

aryl or arylalkyl, each optionally substituted;

heteroaryl or heteroarylalkyl, each optionally substituted; or

$OR^9$ or $NR^9_2$ wherein each $R^9$ is independently H or optionally substituted alkyl, or both $R^9$ groups taken together with the nitrogen to which they are attached form a heterocyclic ring;

$SR^4$ wherein

$R^4$ is optionally substituted alkyl;

aryl or arylalkyl, each optionally substituted; or

heteroaryl or heteroarylalkyl, each optionally substituted;

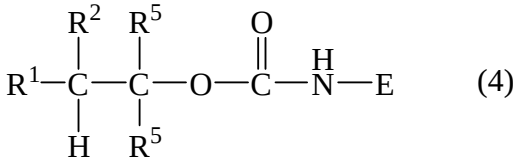
wherein $R^1$ and $R^2$ may be joined to form a 3-8 membered ring; and

wherein any remaining $R^1$ and $R^2$ is H or is alkyl, arylalkyl or heteroarylalkyl, each optionally substituted; and

any remaining $R^5$ is independently H or is alkyl, alkenylalkyl, alkynylalkyl, $(OCH_2CH_2)_p$ O-alkyl wherein p=1-1000, aryl, arylalkyl, heteroaryl or heteroarylalkyl, each optionally substituted.

5. The extended-release conjugate of claim 1 wherein the linker-agonist peptide is covalently coupled to the crosslinkers.

6. A compound of formula (4)



(4)

wherein:

E is of SEQ ID NO: 2;

$R^1$ is CN or $R^3SO_2$, wherein $R^3$ is optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, or $(R^9)_2N$, wherein each $R^9$ is independently H or optionally substituted alkyl;

$R^2$ is H; and

one of $R^5$ is $(CH_2)_yZ$, $(CH_2CH_2O)_xCH_2CH_2Z$ or $(CH_2)_yNH\text{-}CO\text{-}(CH_2CH_2O)_x$ $CH_2CH_2Z$, wherein x is 1-100, y = 1-6, and the other $R^5$ is H or unsubstituted alkyl, and Z is a functional group for coupling to an insoluble matrix, wherein said functional group comprises $N_3$, $NH_2$, $NH\text{-}CO_2{}^tBu$, SH, $S^tBu$, maleimide, $CO_2H$, $CO_2{}^tBu$, 1,3-diene, cyclopentadiene, furan, alkyne, cyclooctyne, acrylate, aminooxy, keto or acrylamide.

7. The compound of claim 6 wherein $R^1$ is CN or $CH_3SO_2$; $R^2$ is H; one $R^5$ is $(CH_2)_yZ$ wherein y is 5; and the other $R^5$ is H.

8. Use of the conjugate of any one of claims 1-5 in the manufacture of a medicament to be administered to a subject for the treatment of a condition benefited by a GLP-1 agonist, wherein the medicament is to be administered at one dosage per one to three months.