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(54) Title: CONJUGATES

(57) Abrégé/Abstract:
The present invention relates to a conjugate comprising a moiety of formula (I) or to conjugates of formula (I') and to pharmaceutical compositions comprising such conjugates.

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CONJUGATES

The present invention relates to a conjugate comprising a moiety of formula (I) or to conjugates of formula (I') and to pharmaceutical compositions comprising such conjugates.

To improve physicochemical or pharmacokinetic properties of a drug *in vivo* such drug can be conjugated to a carrier. Typically, carriers in drug delivery are either used in non-covalent complexation of drug and carrier, or by covalent attachment of a carrier reagent to one of the drug's functional groups.

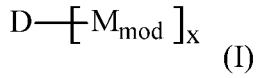
However, the non-covalent approach requires a highly efficient drug-carrier complexation to prevent uncontrolled, burst-type release of the drug due to disintegration of the drug-carrier complex after administration. Restraining the diffusion of an unbound, water-soluble drug molecule requires strong van der Waals contacts, frequently mediated through hydrophobic moieties and charged moieties for electrostatic binding. Many conformationally sensitive drugs, such as proteins or peptides, are rendered dysfunctional during the complexation process and/or during subsequent storage of the non-covalently bound drug.

Alternatively, a drug may be covalently conjugated to a carrier through a stable linkage or a reversible linkage from which the drug is released. If the drug is stably connected to the carrier, such a conjugate needs to exhibit sufficient residual activity to have a pharmaceutical effect, thus the conjugate is constantly in an active form. If the drug is reversibly conjugated to the carrier, such drug may be inactive while bound to the and only exhibits its activity upon release of the reversibly conjugated carrier.

However, in some case it may be advantageous to combine stable attachment of a carrier and reversible attachment of a carrier to one drug.

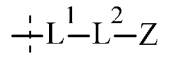
It is therefore an object of the present invention to provide such conjugates.

This object is achieved with a conjugate comprising a moiety of formula (I)



(I)

wherein at least one moiety M_{mod} is substituted with at least one moiety of formula (Ia)



(Ia),

wherein

each moiety M_{mod} is independently a modifying moiety;

D- is a biologically active moiety to which x modifying moieties M_{mod} are stably conjugated;

each -L^1- is independently a linker moiety covalently and reversibly attached to M_{mod};

each -L^2- is independently a chemical bond or is a spacer moiety;

each -Z is independently a polymeric moiety or a substituted fatty acid moiety; and

x is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10.

Within the present invention the terms are used with the meaning as follows:

As used herein, the term “reversible”, “reversibly” or “degradable” with regard to the attachment of a first moiety to a second moiety means that the linkage that connects said first and second moiety is cleavable under physiological conditions, which are aqueous buffer at pH 7.4, 37°C, with a half-life ranging from one hour to three months, preferably from one hour to two months, even more preferably from one hour to one month. Cleavage may be enzymatically or non-enzymatically, preferably non-enzymatically. Accordingly, the term “stable” or “permanent” with regard to the attachment of a first moiety to a second moiety means that the linkage that connects said first and second moiety is cleavable with a half-life of more than three months under physiological conditions.

As used herein, the term “modifying moiety” refers preferably to a substituent or a polymeric moiety.

As used herein, the term “disulfide bridging” refers to the insertion of a moiety between the two sulfur atoms of a disulfide bridge. This is achieved by using a reagent that has said moiety between two thiol-reactive functional groups and reacting each thiol-reactive functional group with one of the sulfur atoms of the disulfide bridge, such that the moiety is inserted between said sulfur atoms after foregone reduction of the disulfide bond. If more than one disulfide bridge is present in a peptide or protein, the disulfide bridge may either be inserted between the sulfur atoms of one disulfide bridge or may be inserted between the sulfur atoms from different disulfide bridges. Such disulfide bridge may be naturally

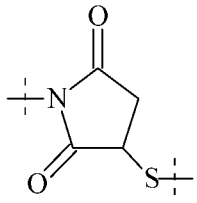
occurring in a peptide or protein or may have been artificially introduced, for example by replacing existing amino acid moieties with or by adding cysteine moieties to a peptide or protein.

As used herein, the term "reagent" means a chemical compound, which comprises at least one functional group for reaction with the functional group of another chemical compound or drug. It is understood that a drug comprising a functional group (such as a primary or secondary amine or hydroxyl functional group) is also a reagent.

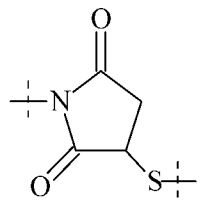
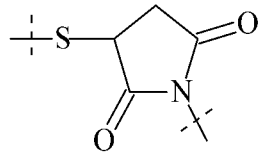
As used herein, the term "moiety" means a part of a molecule, which lacks one or more atom(s) compared to the corresponding reagent. If, for example, a reagent of the formula "H-X-H" reacts with another reagent and becomes part of the reaction product, the corresponding moiety of the reaction product has the structure "H–X–" or "–X–", whereas each "– " indicates attachment to another moiety. Accordingly, a biologically active moiety is released from a reversible linkage as a drug. Another term for "biologically active moiety" is "drug moiety".

The term "drug" as used herein refers to a substance used in the treatment, cure, prevention, or diagnosis of a disease or used to otherwise enhance physical or mental well-being. If a drug is conjugated to another moiety, the part of the resulting product that originated from the drug is referred to as "biologically active moiety".

It is understood that if the sequence or chemical structure of a group of atoms is provided which group of atoms is attached to two moieties or is interrupting a moiety, said sequence or chemical structure can be attached to the two moieties in either orientation, unless explicitly stated otherwise. For example, a moiety "-C(O)N(R^1)-" can be attached to two moieties or interrupting a moiety either as "-C(O)N(R^1)-" or as "-N(R^1)C(O)-". Similarly, a moiety



can be attached to two moieties or can interrupt a moiety either as


or as

.

The term "substituted" as used herein means that one or more -H atom(s) of a molecule or moiety are replaced by a different atom or a group of atoms, which are referred to as "substituent".

As used herein, the term "substituent" refers preferably to a moiety selected from the group consisting of halogen, -CN, -$COOR^{x1}$, -OR^{x1}, -$C(O)R^{x1}$, -$C(O)N(R^{x1}R^{x1a})$, -$S(O)_2N(R^{x1}R^{x1a})$, -$S(O)N(R^{x1}R^{x1a})$, -$S(O)_2R^{x1}$, -$S(O)R^{x1}$, -$N(R^{x1})S(O)_2N(R^{x1a}R^{x1b})$, -$SR^{x1}$, -$N(R^{x1}R^{x1a})$, -$NO_2$, -$OC(O)R^{x1}$, -$N(R^{x1})C(O)R^{x1a}$, -$N(R^{x1})S(O)_2R^{x1a}$, -$N(R^{x1})S(O)R^{x1a}$, -$N(R^{x1})C(O)OR^{x1a}$, -$N(R^{x1})C(O)N(R^{x1a}R^{x1b})$, -$OC(O)N(R^{x1}R^{x1a})$, -$T^0$, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl; wherein -T^0, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally substituted with one or more -R^{x2}, which are the same or different and wherein C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally interrupted by one or more groups selected from the group consisting of -T^0-, -C(O)O-, -O-, -C(O)-, -$C(O)N(R^{x3})$-, -$S(O)_2N(R^{x3})$-, -$S(O)N(R^{x3})$-, -$S(O)_2$-, -S(O)-, -$N(R^{x3})S(O)_2N(R^{x3a})$-, -S-, -$N(R^{x3})$-, -$OC(OR^{x3})(R^{x3a})$-, -$N(R^{x3})C(O)N(R^{x3a})$-, and -$OC(O)N(R^{x3})$-;

-R^{x1}, -R^{x1a}, -R^{x1b} are independently of each other selected from the group consisting of -H, -T^0, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl; wherein -T^0, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally substituted with one or more -R^{x2}, which are the same or different and wherein C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally interrupted by one or more groups selected from the group consisting of -T^0-, -C(O)O-, -O-, -C(O)-, -$C(O)N(R^{x3})$-, -$S(O)_2N(R^{x3})$-, -$S(O)N(R^{x3})$-; -$S(O)_2$-, -S(O)-, -$N(R^{x3})S(O)_2N(R^{x3a})$-, -S-, -$N(R^{x3})$-, -$OC(OR^{x3})(R^{x3a})$-, -$N(R^{x3})C(O)N(R^{x3a})$-, and -$OC(O)N(R^{x3})$-;

each T^0 is independently selected from the group consisting of phenyl, naphthyl, indenyl, indanyl, tetralinyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl, and 8- to 11-membered heterobicyclyl; wherein each T^0 is independently optionally substituted with one or more -R^{x2}, which are the same or different;

each -R^{x2} is independently selected from the group consisting of halogen, -CN, oxo (=O), -$COOR^{x4}$, -OR^{x4}, -$C(O)R^{x4}$, -$C(O)N(R^{x4}R^{x4a})$, -$S(O)_2N(R^{x4}R^{x4a})$, -$S(O)N(R^{x4}R^{x4a})$, -$S(O)_2R^{x4}$, -$S(O)R^{x4}$, -$N(R^{x4})S(O)_2N(R^{x4a}R^{x4b})$, -$SR^{x4}$, -$N(R^{x4}R^{x4a})$, -$NO_2$, -$OC(O)R^{x4}$, -$N(R^{x4})C(O)R^{x4a}$, -$N(R^{x4})S(O)_2R^{x4a}$, -$N(R^{x4})S(O)R^{x4a}$, -$N(R^{x4})C(O)OR^{x4a}$, -$N(R^{x4})C(O)N(R^{x4a}R^{x4b})$, -$OC(O)N(R^{x4}R^{x4a})$, and C_{1-6} alkyl; wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

each -R^{x3}, -R^{x3a}, -R^{x4}, -R^{x4a}, -R^{x4b} is independently selected from the group consisting of -H and C_{1-6} alkyl; wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different.

Preferably, a maximum of 6 -H atoms of an optionally substituted molecule are independently replaced by a substituent, e.g. 5 -H atoms are independently replaced by a substituent, 4 -H atoms are independently replaced by a substituent, 3 -H atoms are independently replaced by a substituent, 2 -H atoms are independently replaced by a substituent, or 1 -H atom is replaced by a substituent.

As used herein, the term “fatty acid” refers to a saturated or unsaturated monocarboxylic acid having an aliphatic tail, which may include from 4 to 28 carbon atoms. The fatty acid may be saturated or unsaturated, linear or branched. The term “fatty acid variant” refers to a modified fatty acid in which certain carbon atoms may be replaced by other atoms or groups of atoms and which may be substituted.

As used herein the term “small molecule biologically active moiety” refers to an organic biologically active moiety having a molecular weight of less than 1000 Da, such as less than 900 Da or less than 800 Da.

As used herein, the term “oligonucleotide” refers to double- or single-stranded RNA and DNA with preferably 2 to 1000 nucleotides and any modifications thereof. Modifications include, but are not limited to, those which provide other chemical groups that incorporate additional charge, polarizability, hydrogen bonding, electrostatic interaction, and fluxionality to the nucleic acid ligand bases or to the nucleic acid ligand as a whole. Such modifications include, but are not limited, to 2’-position sugar modifications, 5-position pyrimidine modifications, 8-position purine modifications, modifications at exocyclic amines,

substitution of 4-thiouridines, substitution of 5-bromo or 5-iodo-uracil; backbone modifications, methylations, unusual base-pairing combinations such as the isobases isocytidine and isoguanidine and the like. Modifications can also include 3' and 5' modifications such as capping and change of stereochemistry. The term also includes aptamers.

The term "peptide nucleic acids" refers to organic polymers having a peptidic backbone, i.e. a backbone in which the monomers are connected to each other through peptide linkages, to which nucleobases, preferably adenine, cytosine, guanine, thymine and uracil, are attached. A preferred backbone comprises N-(2-aminoethyl)-glycine.

The term "peptide" as used herein refers to a chain of at least 2 and up to and including 50 amino acid monomer moieties linked by peptide (amide) linkages. The term "peptide" also includes peptidomimetics, such as D-peptides, peptoids or beta-peptides, and covers such peptidomimetic chains with up to and including 50 monomer moieties.

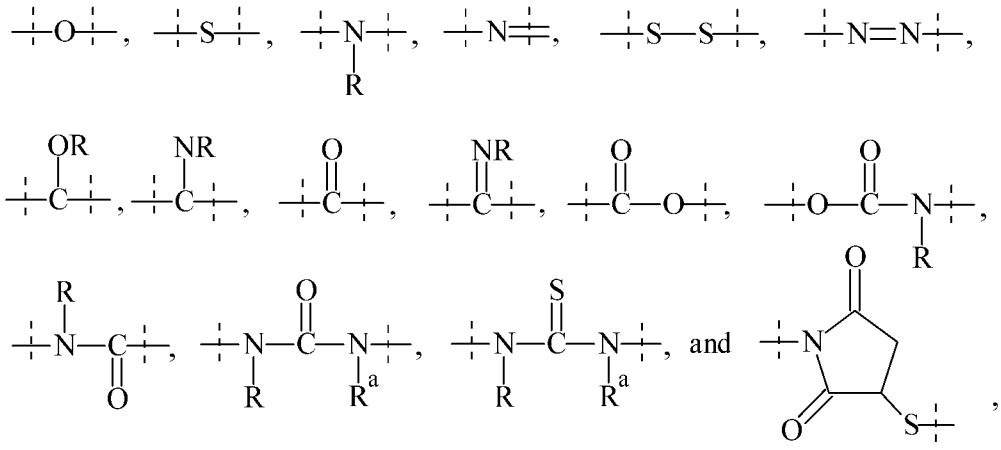
As used herein, the term "protein" refers to a chain of more than 50 amino acid monomer moieties, which may also be referred to as "amino acid residues", linked by peptide linkages, in which preferably no more than 12000 amino acid monomers are linked by peptide linkages, such as no more than 10000 amino acid monomer moieties, no more than 8000 amino acid monomer moieties, no more than 5000 amino acid monomer moieties or no more than 2000 amino acid monomer moieties.

As used herein the term "about" in combination with a numerical value is used to indicate a range ranging from and including the numerical value plus and minus no more than 25% of said numerical value, more preferably no more than 20% of said numerical value and most preferably no more than 10% of said numerical value. For example, the phrase "about 200" is used to mean a range ranging from and including 200 +/- 25%, i.e. ranging from and including 150 to 250; preferably 200 +/- 20%, i.e. ranging from and including 160 to 240; even more preferably ranging from and including 200 +/-10%, i.e. ranging from and including 180 to 220. It is understood that a percentage given as "about 50%" does not mean "50% +/- 25%", i.e. ranging from and including 25 to 75%, but "about 50%" means ranging from and including 37.5 to 62.5%, i.e. plus and minus 25% of the numerical value which is 50.

As used herein, the term "polymer" means a molecule comprising repeating structural units, i.e. the monomers, connected by chemical bonds in a linear, circular, branched, crosslinked or dendrimeric way or a combination thereof, which may be of synthetic or biological origin or a combination of both. It is understood that a polymer may also comprise one or more other chemical group(s) and/or moiety/moieties, such as, for example, one or more functional group(s). Likewise, it is understood that also a peptide or protein is a polymer, even though the side chains of individual amino acid residues may be different. Preferably, a soluble polymer has a molecular weight of at least 0.5 kDa, e.g. a molecular weight of at least 1 kDa, a molecular weight of at least 2 kDa, a molecular weight of at least 3 kDa or a molecular weight of at least 5 kDa. If the polymer is soluble, it preferable has a molecular weight of at most 1000 kDa, such as at most 750 kDa, such as at most 500 kDa, such as at most 300 kDa, such as at most 200 kDa, such as at most 100 kDa. It is understood that for insoluble polymers, such as hydrogels, no meaningful molecular weight ranges can be provided.

As used herein, the term "polymeric" means a reagent or a moiety comprising one or more polymer(s) or polymer moiety/moieties. A polymeric reagent or moiety may optionally also comprise one or more other moiety/moieties, which are preferably selected from the group consisting of:

- C_{1-50} alkyl, C_{2-50} alkenyl, C_{2-50} alkynyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl, 8- to 11-membered heterobicyclyl, phenyl, naphthyl, indenyl, indanyl, and tetralinyl; and
- linkages selected from the group comprising



wherein

dashed lines indicate attachment to the remainder of the moiety or reagent, and

-R and -R^a are independently of each other selected from the group consisting of -H, methyl, ethyl, propyl, butyl, pentyl and hexyl.

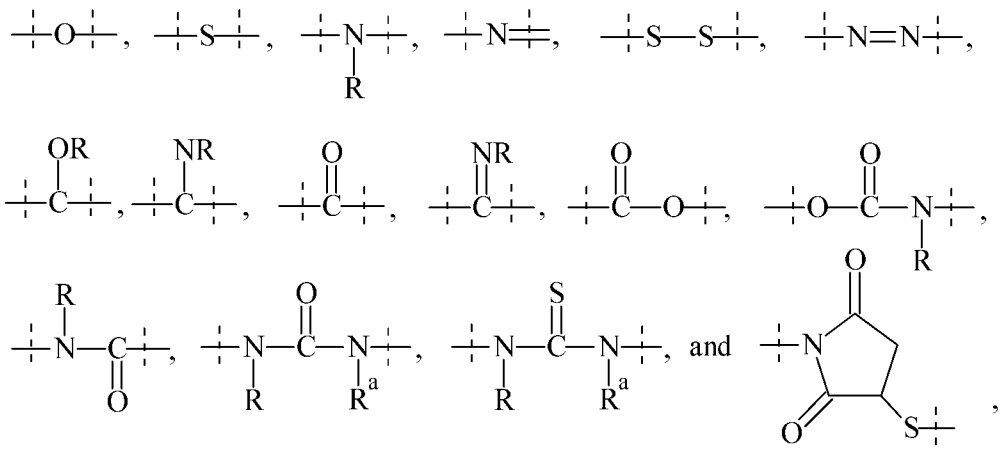
The person skilled in the art understands that the polymerization products obtained from a polymerization reaction do not all have the same molecular weight, but rather exhibit a molecular weight distribution. Consequently, the molecular weight ranges, molecular weights, ranges of numbers of monomers in a polymer and numbers of monomers in a polymer as used herein, refer to the number average molecular weight and number average of monomers, i.e. to the arithmetic mean of the molecular weight of the polymer or polymeric moiety and the arithmetic mean of the number of monomers of the polymer or polymeric moiety.

Accordingly, in a polymeric moiety comprising "x" monomer units any integer given for "x" therefore corresponds to the arithmetic mean number of monomers. Any range of integers given for "x" provides the range of integers in which the arithmetic mean numbers of monomers lies. An integer for "x" given as "about x" means that the arithmetic mean numbers of monomers lies in a range of integers of x +/- 25%, preferably x+/- 20% and more preferably x +/- 10%.

As used herein, the term "number average molecular weight" means the ordinary arithmetic mean of the molecular weights of the individual polymers.

As used herein, the term "PEG-based" in relation to a moiety or reagent means that said moiety or reagent comprises PEG. Preferably, a PEG-based moiety or reagent comprises at least 10% (w/w) PEG, such as at least 20% (w/w) PEG, such as at least 30% (w/w) PEG, such as at least 40% (w/w) PEG, such as at least 50% (w/w), such as at least 60 (w/w) PEG, such as at least 70% (w/w) PEG, such as at least 80% (w/w) PEG, such as at least 90% (w/w) PEG, such as at least 95%. The remaining weight percentage of the PEG-based moiety or reagent are other moieties preferably selected from the following moieties and linkages:

- C_{1-50} alkyl, C_{2-50} alkenyl, C_{2-50} alkynyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl, 8- to 11-membered heterobicyclyl, phenyl, naphthyl, indenyl, indanyl, and tetralinyl; and
- linkages selected from the group comprising



wherein

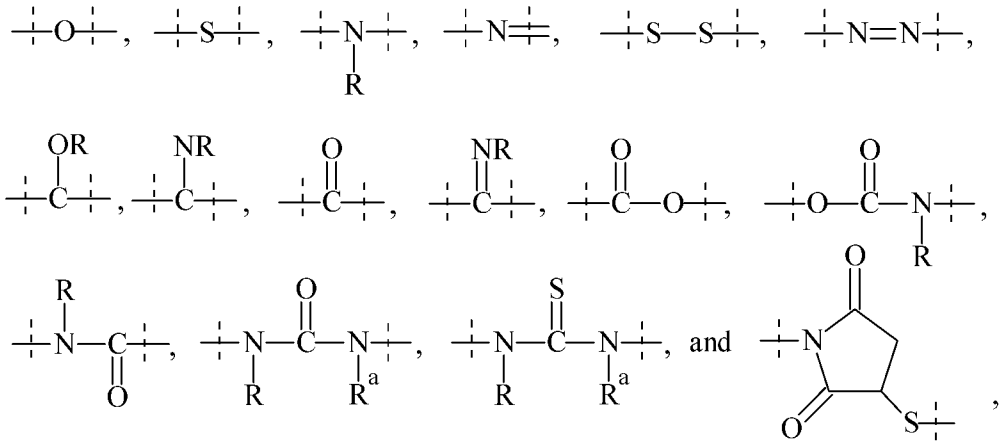
dashed lines indicate attachment to the remainder of the moiety or reagent, and

-R and -R^a are independently of each other selected from the group consisting of -H, methyl, ethyl, propyl, butyl, pentyl and hexyl.

The term "hyaluronic acid-based" is used analogously.

As used herein, the term "PEG-based comprising at least X% PEG" in relation to a moiety or reagent means that said moiety or reagent comprises at least X% (w/w) ethylene glycol units (-CH_2CH_2O-), wherein the ethylene glycol units may be arranged blockwise, alternating or may be randomly distributed within the moiety or reagent and preferably all ethylene glycol units of said moiety or reagent are present in one block; the remaining weight percentage of the PEG-based moiety or reagent are other moieties preferably selected from the following moieties and linkages:

- C_{1-50} alkyl, C_{2-50} alkenyl, C_{2-50} alkynyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl, 8- to 11-membered heterobicyclyl, phenyl, naphthyl, indenyl, indanyl, and tetralinyl; and
- linkages selected from the group comprising



wherein

dashed lines indicate attachment to the remainder of the moiety or reagent, and

-R and -R^a are independently of each other selected from the group consisting of -H, methyl, ethyl, propyl, butyl, pentyl and hexyl.

The term "hyaluronic acid-based comprising at least X% hyaluronic acid" is used accordingly.

The term "interrupted" means that a moiety is inserted between two carbon atoms or – if the insertion is at one of the moiety's ends – between a carbon or heteroatom and a hydrogen atom, preferably between a carbon and a hydrogen atom.

As used herein, the term "C_{1-4} alkyl" alone or in combination means a straight-chain or branched alkyl moiety having 1 to 4 carbon atoms. If present at the end of a molecule, examples of straight-chain or branched C_{1-4} alkyl are methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl. When two moieties of a molecule are linked by the C_{1-4} alkyl, then examples for such C_{1-4} alkyl groups are -CH_2-, -CH_2-CH_2-, -$CH(CH_3)$-, -CH_2-CH_2-CH_2-, -$CH(C_2H_5)$-, -$C(CH_3)_2$-. Each hydrogen of a C_{1-4} alkyl carbon may optionally be replaced by a substituent as defined above. Optionally, a C_{1-4} alkyl may be interrupted by one or more moieties as defined below.

As used herein, the term "C_{1-6} alkyl" alone or in combination means a straight-chain or branched alkyl moiety having 1 to 6 carbon atoms. If present at the end of a molecule, examples of straight-chain and branched C_{1-6} alkyl groups are methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, 2-methylbutyl, 2,2-dimethylpropyl, n-hexyl, 2-methylpentyl, 3-methylpentyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl and 3,3-

dimethylpropyl. When two moieties of a molecule are linked by the C_{1-6} alkyl group, then examples for such C_{1-6} alkyl groups are $-CH_2-$, $-CH_2-CH_2-$, $-CH(CH_3)-$, $-CH_2-CH_2-CH_2-$, $-CH(C_2H_5)-$ and $-C(CH_3)_2-$. Each hydrogen atom of a C_{1-6} carbon may optionally be replaced by a substituent as defined above. Optionally, a C_{1-6} alkyl may be interrupted by one or more moieties as defined below.

Accordingly, "C_{1-10} alkyl", "C_{1-20} alkyl" or "C_{1-50} alkyl" means an alkyl chain having 1 to 10, 1 to 20 or 1 to 50 carbon atoms, respectively, wherein each hydrogen atom of the C_{1-10}, C_{1-20} or C_{1-50} carbon may optionally be replaced by a substituent as defined above. Optionally, a C_{1-10} or C_{1-50} alkyl may be interrupted by one or more moieties as defined below.

As used herein, the term "C_{2-6} alkenyl" alone or in combination means a straight-chain or branched hydrocarbon moiety comprising at least one carbon-carbon double bond having 2 to 6 carbon atoms. If present at the end of a molecule, examples are $-CH=CH_2$, $-CH=CH-CH_3$, $-CH_2-CH=CH_2$, $-CH=CHCH_2-CH_3$ and $-CH=CH-CH=CH_2$. When two moieties of a molecule are linked by the C_{2-6} alkenyl group, then an example for such C_{2-6} alkenyl is $-CH=CH-$. Each hydrogen atom of a C_{2-6} alkenyl moiety may optionally be replaced by a substituent as defined above. Optionally, a C_{2-6} alkenyl may be interrupted by one or more moieties as defined below.

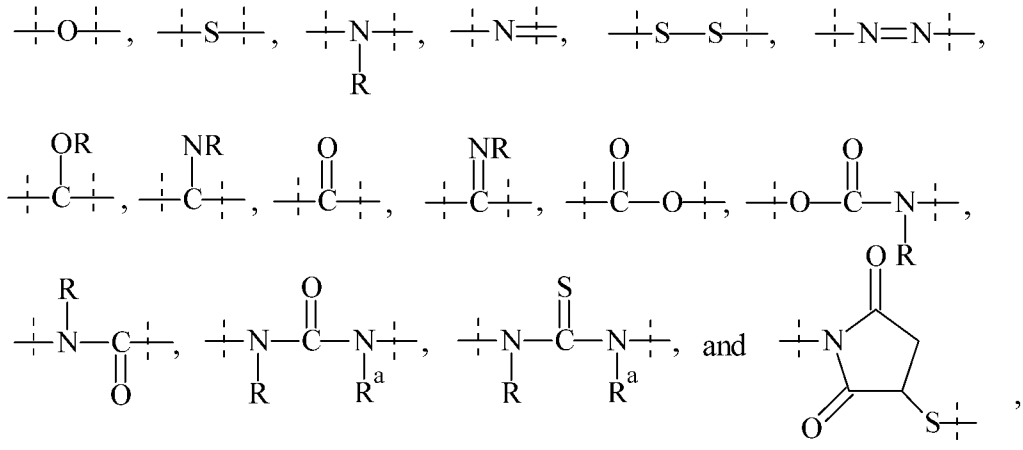
Accordingly, the term "C_{2-10} alkenyl", "C_{2-20} alkenyl" or "C_{2-50} alkenyl" alone or in combination means a straight-chain or branched hydrocarbon moiety comprising at least one carbon-carbon double bond having 2 to 10, 2 to 20 or 2 to 50 carbon atoms. Each hydrogen atom of a C_{2-10} alkenyl, C_{2-20} alkenyl or C_{2-50} alkenyl group may optionally be replaced by a substituent as defined above. Optionally, a C_{2-10} alkenyl, C_{2-20} alkenyl or C_{2-50} alkenyl may be interrupted by one or more moieties as defined below.

As used herein, the term "C_{2-6} alkynyl" alone or in combination means a straight-chain or branched hydrocarbon moiety comprising at least one carbon-carbon triple bond having 2 to 6 carbon atoms. If present at the end of a molecule, examples are $-C\equiv CH$, $-CH_2-C\equiv CH$, $CH_2-CH_2-C\equiv CH$ and $CH_2-C\equiv C-CH_3$. When two moieties of a molecule are linked by the alkynyl group, then an example is $-C\equiv C-$. Each hydrogen atom of a C_{2-6} alkynyl group may optionally be replaced by a substituent as defined above. Optionally, one or more double

bond(s) may occur. Optionally, a C_{2-6} alkynyl may be interrupted by one or more moieties as defined below.

Accordingly, as used herein, the term "C_{2-10} alkynyl", "C_{2-20} alkynyl" and "C_{2-50} alkynyl" alone or in combination means a straight-chain or branched hydrocarbon moiety comprising at least one carbon-carbon triple bond having 2 to 10, 2 to 20 or 2 to 50 carbon atoms, respectively. Each hydrogen atom of a C_{2-10} alkynyl, C_{2-20} alkynyl or C_{2-50} alkynyl group may optionally be replaced by a substituent as defined above. Optionally, one or more double bond(s) may occur. Optionally, a C_{2-10} alkynyl, C_{2-20} alkynyl or C_{2-50} alkynyl may be interrupted by one or more moieties as defined below.

As mentioned above, a C_{1-4} alkyl, C_{1-6} alkyl, C_{1-10} alkyl, C_{1-20} alkyl, C_{1-50} alkyl, C_{2-6} alkenyl, C_{2-10} alkenyl, C_{2-20} alkenyl, C_{2-50} alkenyl, C_{2-6} alkynyl, C_{2-10} alkynyl, C_{2-20} alkenyl or C_{2-50} alkynyl may optionally be interrupted by one or more moieties which are preferably selected from the group consisting of



wherein

dashed lines indicate attachment to the remainder of the moiety or reagent; and

-R and -R^a are independently of each other selected from the group consisting of -H, methyl, ethyl, propyl, butyl, pentyl and hexyl.

As used herein, the term "C_{3-10} cycloalkyl" means a cyclic alkyl chain having 3 to 10 carbon atoms, which may be saturated or unsaturated, e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl, cyclooctyl, cyclononyl or cyclodecyl. Each hydrogen atom of a C_{3-10} cycloalkyl carbon may be replaced by a substituent as defined above. The term "C_{3-10} cycloalkyl" also includes bridged bicycles like norbornane or norbornene.

The term “8- to 30-membered carbopolycyclyl” or “8- to 30-membered carbopolycycle” means a cyclic moiety of two or more rings with 8 to 30 ring atoms, where two neighboring rings share at least one ring atom and that may contain up to the maximum number of double bonds (aromatic or non-aromatic ring which is fully, partially or un-saturated). Preferably a 8- to 30-membered carbopolycyclyl means a cyclic moiety of two, three, four or five rings, more preferably of two, three or four rings.

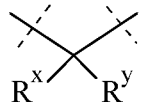
As used herein, the term "3- to 10-membered heterocyclyl" or "3- to 10-membered heterocycle" means a ring with 3, 4, 5, 6, 7, 8, 9 or 10 ring atoms that may contain up to the maximum number of double bonds (aromatic or non-aromatic ring which is fully, partially or un-saturated) wherein at least one ring atom up to 4 ring atoms are replaced by a heteroatom selected from the group consisting of sulfur (including -S(O)-, -$S(O)_2$-), oxygen and nitrogen (including =N(O)-) and wherein the ring is linked to the rest of the molecule via a carbon or nitrogen atom. Examples for 3- to 10-membered heterocycles include but are not limited to aziridine, oxirane, thiirane, azirine, oxirene, thiirene, azetidine, oxetane, thietane, furan, thiophene, pyrrole, pyrroline, imidazole, imidazoline, pyrazole, pyrazoline, oxazole, oxazoline, isoxazole, isoxazoline, thiazole, thiazoline, isothiazole, isothiazoline, thiadiazole, thiadiazoline, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, imidazolidine, pyrazolidine, oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, thiadiazolidine, sulfolane, pyran, dihydropyran, tetrahydropyran, imidazolidine, pyridine, pyridazine, pyrazine, pyrimidine, piperazine, piperidine, morpholine, tetrazole, triazole, triazolidine, tetrazolidine, diazepane, azepine and homopiperazine. Each hydrogen atom of a 3- to 10-membered heterocyclyl or 3- to 10-membered heterocyclic group may be replaced by a substituent as defined below.

As used herein, the term "8- to 11-membered heterobicyclyl" or "8- to 11-membered heterobicycle" means a heterocyclic moiety of two rings with 8 to 11 ring atoms, where at least one ring atom is shared by both rings and that may contain up to the maximum number of double bonds (aromatic or non-aromatic ring which is fully, partially or un-saturated) wherein at least one ring atom up to 6 ring atoms are replaced by a heteroatom selected from the group consisting of sulfur (including -S(O)-, -$S(O)_2$-), oxygen and nitrogen (including =N(O)-) and wherein the ring is linked to the rest of the molecule via a carbon or nitrogen atom. Examples for an 8- to 11-membered heterobicycle are indole, indoline, benzofuran, benzothiophene, benzoxazole, benzisoxazole, benzothiazole, benzisothiazole, benzimidazole, benzimidazoline, quinoline, quinazoline, dihydroquinazoline, quinoline, dihydroquinoline,

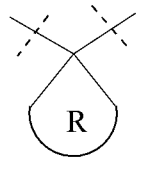
tetrahydroquinoline, decahydroquinoline, isoquinoline, decahydroisoquinoline, tetrahydroisoquinoline, dihydroisoquinoline, benzazepine, purine and pteridine. The term 8- to 11-membered heterobicycle also includes spiro structures of two rings like 1,4-dioxa-8-azaspiro[4.5]decane or bridged heterocycles like 8-aza-bicyclo[3.2.1]octane. Each hydrogen atom of an 8- to 11-membered heterobicyclyl or 8- to 11-membered heterobicycle carbon may be replaced by a substituent as defined below.

Similarly, the term "8- to 30-membered heteropolycyclyl" or "8- to 30-membered heteropolycycle" means a heterocyclic moiety of more than two rings with 8 to 30 ring atoms, preferably of three, four or five rings, where two neighboring rings share at least one ring atom and that may contain up to the maximum number of double bonds (aromatic or non-aromatic ring which is fully, partially or unsaturated), wherein at least one ring atom up to 10 ring atoms are replaced by a heteroatom selected from the group of sulfur (including –S(O)-, -S(O)$_2$-), oxygen and nitrogen (including =N(O)-) and wherein the ring is linked to the rest of a molecule via a carbon or nitrogen atom.

It is understood that the phrase "the pair R^x/R^y is joined together with the atom to which they are attached to form a C_{3-10} cycloalkyl or a 3- to 10-membered heterocyclyl" in relation with a moiety of the structure



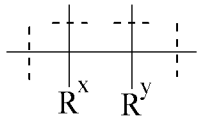
means that R^x and R^y form the following structure:



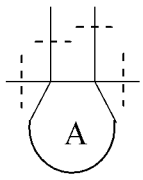
,

wherein R is C_{3-10} cycloalkyl or 3- to 10-membered heterocyclyl.

It is also understood that the phrase "the pair R^x/R^y is joint together with the atoms to which they are attached to form a ring A" in relation with a moiety of the structure



means that R^x and R^y form the following structure:



.

As used herein, "halogen" means fluoro, chloro, bromo or iodo. It is generally preferred that halogen is fluoro or chloro.

As used herein, the term “functional group” means a group of atoms which can react with other groups of atoms. Exemplary functional groups are, for example, carboxylic acid (–(C=O)OH), primary or secondary amine (–NH_2, –NH–), maleimide, thiol (-SH), sulfonic acid (–(O=S=O)OH), carbonate, carbamate (–O(C=O)N<), hydroxyl (–OH), aldehyde (–(C=O)H), ketone (–(C=O)–), hydrazine (>N-N<), isocyanate, isothiocyanate, phosphoric acid (-O(P=O)OHOH), phosphonic acid (-O(P=O)OHH), haloacetyl, alkyl halide, acryloyl, aryl fluoride, hydroxylamine, disulfide, sulfonamides, sulfuric acid, vinyl sulfone, vinyl ketone, diazoalkane, oxirane, and aziridine.

In case the conjugates of the present invention comprise one or more acidic or basic groups, the invention also comprises their corresponding pharmaceutically or toxicologically acceptable salts, in particular their pharmaceutically utilizable salts. Thus, the conjugates of the present invention comprising acidic groups can be used according to the invention, for example, as alkali metal salts, alkaline earth metal salts or as ammonium salts. More precise examples of such salts include sodium salts, potassium salts, calcium salts, magnesium salts or salts with ammonia or organic amines such as, for example, ethylamine, ethanolamine, triethanolamine or amino acids. Conjugates of the present invention comprising one or more basic groups, i.e. groups which can be protonated, can be present and can be used according to the invention in the form of their addition salts with inorganic or organic acids. Examples for suitable acids include hydrogen chloride, hydrogen bromide, phosphoric acid, sulfuric acid, nitric acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acids, oxalic acid, acetic acid, tartaric acid, lactic acid, salicylic acid, benzoic acid, formic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, malic acid, sulfaminic acid, phenylpropionic acid, gluconic acid, ascorbic acid, isonicotinic acid, citric acid, adipic acid, and other acids known to the person skilled in the art. For the person skilled in the art further methods are known for converting

the basic group into a cation like the alkylation of an amine group resulting in a positively-charge ammonium group and an appropriate counterion of the salt. If the conjugates of the present invention simultaneously comprise acidic and basic groups, the invention also includes, in addition to the salt forms mentioned, inner salts or betaines (zwitterions). The respective salts can be obtained by customary methods, which are known to the person skilled in the art like, for example by contacting these prodrugs with an organic or inorganic acid or base in a solvent or dispersant, or by anion exchange or cation exchange with other salts. The present invention also includes all salts of the conjugates of the present invention which, owing to low physiological compatibility, are not directly suitable for use in pharmaceuticals but which can be used, for example, as intermediates for chemical reactions or for the preparation of pharmaceutically acceptable salts.

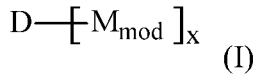
The term "pharmaceutically acceptable" means a substance that does cause harm when administered to a patient and preferably means approved by a regulatory agency, such as the EMA (Europe) and/or the FDA (US) and/or any other national regulatory agency for use in animals, preferably for use in humans.

As used herein, the term "excipient" refers to a diluent, adjuvant, or vehicle with which the therapeutic, such as a drug or prodrug, is administered. Such pharmaceutical excipient can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, including but not limited to peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred excipient when the pharmaceutical composition is administered orally. Saline and aqueous dextrose are preferred excipients when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions are preferably employed as liquid excipients for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, mannitol, trehalose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The pharmaceutical composition, if desired, can also contain minor amounts of wetting or emulsifying agents, pH buffering agents, like, for example, acetate, succinate, tris, carbonate, phosphate, HEPES (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid), MES (2-(*N*-morpholino)ethanesulfonic acid), or can contain detergents, like Tween, poloxamers, poloxamines, CHAPS, Igepal, or amino acids like, for example, glycine, lysine, or histidine. These pharmaceutical compositions can take the form of solutions, suspensions,

emulsions, tablets, pills, capsules, powders, sustained-release formulations and the like. The pharmaceutical composition can be formulated as a suppository, with traditional binders and excipients such as triglycerides. Oral formulation can include standard excipients such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Such compositions will contain a therapeutically effective amount of the drug or biologically active moiety, together with a suitable amount of excipient so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

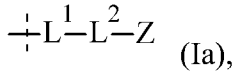
In general, the term "comprise" or "comprising" also encompasses "consist of" or "consisting of".

In certain embodiments the present invention relates to a conjugate comprising a moiety of formula (I)



(I)

wherein at least one moiety M_{mod} is substituted with at least one moiety of formula (Ia)



(Ia),

wherein

each moiety M_{mod} is independently a modifying moiety;

D- is a biologically active moiety to which x modifying moieties M_{mod} are stably conjugated;

each $-L^1-$ is independently a linker moiety covalently and reversibly attached to M_{mod};

each $-L^2-$ is independently a chemical bond or is a spacer moiety;

each -Z is independently a polymeric moiety or a substituted fatty acid moiety; and

x is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10.

In other words, x moieties M_{mod} are covalently conjugated to a moiety D- and at least one moiety M_{mod} is covalently and reversibly conjugated to a moiety of formula (Ia).

In certain embodiments all moieties M_{mod} conjugated to D- are substituted with at least one moiety of formula (Ia). In certain embodiments D- comprises moieties M_{mod} that are substituted with at least one moiety of formula (Ia) and moieties M_{mod} that are not substituted with a moiety of formula (Ia). In both embodiments D- may in addition also be directly

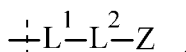
substituted with one or more moieties of formula (Ia), i.e. a moiety of formula (Ia) is conjugated to D- via one of its functional groups.

In certain embodiments the present invention relates to a conjugate of formula (I')



(I')

wherein at least one moiety M_{mod} is substituted with at least one moiety of formula (Ia)



(Ia),

wherein

each moiety M_{mod} is independently a modifying moiety;

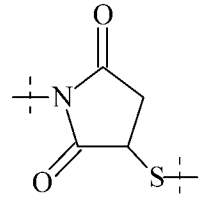
D- is a biologically active moiety to which x modifying moieties M_{mod} are stably conjugated;

each $-L^1-$ is independently a linker moiety covalently and reversibly attached to M_{mod};

each $-L^2-$ is independently a chemical bond or is a spacer moiety;

each -Z is independently a polymeric moiety or a substituted fatty acid moiety; and

x is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10.

Attachment of a moiety M_{mod} to D- is via a stable covalent linkage. In certain embodiments the linkage between D- and a moiety M_{mod} is via an amide. In certain embodiments the linkage between D- and a moiety M_{mod} is via a moiety .

D- of formula (I) or (I') is preferably selected from the group consisting of small molecule biologically active moieties, oligonucleotide moieties, peptide nucleic acid moieties, peptide moieties and protein moieties. More preferably D- of formula (I) is selected from the group consisting of small molecule biologically active moieties, peptide moieties and protein moieties. In certain embodiments D- of formula (I) or (I') is a peptide moiety or a protein moiety.

In one embodiment D- of formula (I) or (I') is a small molecule biologically active moiety.

In another embodiment D- of formula (I) or (I') is a peptide moiety.

In another embodiment D- of formula (I) or (I') is a protein moiety. In one embodiment such protein moiety is a monoclonal or polyclonal antibody or fragment or fusion thereof.

In certain embodiments D- is a protein selected from the group consisting of ACTH, adenosine deaminase, agalsidase, albumin, alfa-1 antitrypsin (AAT), alfa-1 proteinase inhibitor (API), alglucosidase, alteplase, anistreplase, ancrod serine protease, antithrombin III, antitrypsins, aprotinin, asparaginases, biphalin, bone-morphogenic proteins, calcitonin from salmon, collagenase, DNase, endorphins, enfuvirtide, enkephalins, erythropoietins, factor VIIa, factor VIII, factor VIIIa, factor IX, fibrinolysin, fusion proteins, follicle-stimulating hormones, granulocyte colony stimulating factor (G-CSF), galactosidase, glucagon, glucagon-like peptides like GLP-1, glucocerebrosidase, granulocyte macrophage colony stimulating factor (GM-CSF), chorionic gonadotropin (hCG), hemoglobins, hepatitis B vaccines, hirudin, hyaluronidases, idurnonidase, immune globulins, influenza vaccines, an interleukine, IL-1 receptor antagonist (rhIL-1ra), insulins, an interferon, keratinocyte growth factor (KGF), lactase, leuprolide, levothyroxine, luteinizing hormone, lyme vaccine, natriuretic peptide, pancrelipase, papain, parathyroid hormone, PDGF, pepsin, phospholipase-activating protein (PLAP), platelet activating factor alcetylhydrolase (PAF-AH), prolactin, protein C, octreotide, secretin, sermorelin, superoxide dismutase (SOD), somatropins (growth hormone), somatostatin, streptokinase, sucrase, tetanus toxin fragment, tilactase, thrombins, thymosin, thyroid stimulating hormone, thyrothropin, transforming growth factors, tumor necrosis factor (TNF), TNF receptor-IgG Fc, tissue plasminogen activator (tPA), transferrin, TSH, urate oxidase and urokinase.

The conjugates of the present invention comprise 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 moieties M_{mod} and each moiety M_{mod} may be the same or different. In one embodiment the conjugates of the present invention comprise one moiety M_{mod}, i.e. x of formula (I) or (I') is 1. In another embodiment the conjugates of the present invention comprise two moieties M_{mod}, which may be the same or different, i.e. x is 2.

Preferably, M_{mod} is a substituent or a polymeric moiety.

In one embodiment M_{mod} is a substituent. Preferably, such substituent has a molecular weight ranging from 15 Da to 1 kDa.

In another embodiment M_{mod} is a polymeric moiety. Such polymeric moiety may comprise a linear, branched or multi-arm polymer. In one embodiment the polymer is a linear polymer. In another embodiment the polymer is a branched polymer. Such branched polymer preferably has one, two, three, four or five branching points. From each branching point preferably two, three or four polymer arms extend. In another embodiment the polymer is a multi-arm polymer. Such multi-arm polymer preferably has 3, 4, 5, 6, 7 or 8 polymeric arms.

If M_{mod} is a polymeric moiety, such polymeric moiety preferably has a molecular weight ranging from 0.5 kDa to 1000 kDa, such as from 1 kDa to 1000 kDa, more preferably from 2 kDa to 500 kDa, even more preferably from 3 kDa to 200 kDa, most preferably from 5 kDa to 120 kDa or has a molecular weight ranging from 7 to 40 kDa. In one embodiment such polymer has a molecular weight of about 0.5 kDa. In one embodiment such polymer has a molecular weight of about 1 kDa. In one embodiment such polymer has a molecular weight of about 2 kDa. In one embodiment such polymer has a molecular weight of about 3 kDa. In one embodiment such polymer has a molecular weight of about 4 kDa. In one embodiment such polymer has a molecular weight of about 5 kDa. In one embodiment such polymer has a molecular weight of about 7.5 kDa. In another embodiment such polymeric moiety has a molecular weight of about 10 kDa. In another embodiment such polymeric moiety has a molecular weight of about 15 kDa. In another embodiment such polymeric moiety has a molecular weight of about 20 kDa. In another embodiment such polymeric moiety has a molecular weight of about 30 kDa. In another embodiment such polymeric moiety has a molecular weight of about 40 kDa. In another embodiment such polymeric moiety has a molecular weight of about 50 kDa. about In another embodiment such polymeric moiety has a molecular weight of about 70 kDa. In another embodiment such polymeric moiety has a molecular weight of about 80 kDa. In another embodiment such polymeric moiety has a molecular weight of about 90 kDa. In another embodiment such polymeric moiety has a molecular weight of about 100 kDa. In one embodiment such polymer has a molecular weight of 0.5 kDa. In one embodiment such polymer has a molecular weight of 1 kDa. In one embodiment such polymer has a molecular weight of 2 kDa. In one embodiment such polymer has a molecular weight of 3 kDa. In one embodiment such polymer has a molecular weight of 4 kDa. In one embodiment such polymer has a molecular weight of 5 kDa. In one

embodiment such polymer has a molecular weight of 7.5 kDa. In another embodiment such polymeric moiety has a molecular weight of 10 kDa. In another embodiment such polymeric moiety has a molecular weight of 15 kDa. In another embodiment such polymeric moiety has a molecular weight of 20 kDa. In another embodiment such polymeric moiety has a molecular weight of 30 kDa. In another embodiment such polymeric moiety has a molecular weight of 40 kDa. In another embodiment such polymeric moiety has a molecular weight of 50 kDa. about In another embodiment such polymeric moiety has a molecular weight of 70 kDa. In another embodiment such polymeric moiety has a molecular weight of 80 kDa. In another embodiment such polymeric moiety has a molecular weight of 90 kDa. In another embodiment such polymeric moiety has a molecular weight of 100 kDa.

If M_{mod} is a polymeric moiety, such polymeric moiety preferably comprises a polymer selected from the group consisting of 2-methacryloyl-oxyethyl phosphoyl cholins, poly(acrylic acids), poly(acrylates), poly(acrylamides), poly(alkyloxy) polymers, poly(amides), poly(amidoamines), poly(amino acids), poly(anhydrides), poly(aspartamides), poly(butyric acids), poly(glycolic acids), polybutylene terephthalates, poly(caprolactones), poly(carbonates), poly(cyanoacrylates), poly(dimethylacrylamides), poly(esters), poly(ethylenes), poly(ethyleneglycols), poly(ethylene oxides), poly(ethyl phosphates), poly(ethyloxazolines), poly(glycolic acids), poly(hydroxyethyl acrylates), poly(hydroxyethyl-oxazolines), poly(hydroxymethacrylates), poly(hydroxypropylmethacrylamides), poly(hydroxypropyl methacrylates), poly(hydroxypropyloxazolines), poly(iminocarbonates), poly(lactic acids), poly(lactic-co-glycolic acids), poly(methacrylamides), poly(methacrylates), poly(methyloxazolines), poly(organophosphazenes), poly(ortho esters), poly(oxazolines), poly(propylene glycols), poly(siloxanes), poly(urethanes), poly(vinyl alcohols), poly(vinyl amines), poly(vinylmethylethers), poly(vinylpyrrolidones), silicones, celluloses, carbomethyl celluloses, hydroxypropyl methylcelluloses, chitins, chitosans, dextrans, dextrins, gelatins, hyaluronic acids and derivatives, functionalized hyaluronic acids, alginate, mannans, pectins, rhamnogalacturonans, starches, hydroxyalkyl starches, hydroxyethyl starches and other carbohydrate-based polymers, xylans, and copolymers thereof.

In one embodiment M_{mod} is a PEG-based polymer.

In another embodiment M_{mod} is a hyaluronic acid-based polymer.

In another embodiment M_{mod} comprises a peptide or protein moiety.

A moiety M_{mod} may be attached to any functional group present in D-H.

If D- is a peptide or protein moiety attachment of M_{mod} may be at the N-terminus, C-terminus, at an amino acid side chain or at an internal site of such moiety D-. In certain embodiments attachment of such moiety M_{mod} occurs at the N-terminus of such moiety D-. In certain embodiments attachment of such moiety M_{mod} occurs at the C-terminus of such moiety D- In certain embodiments attachment of such moiety M_{mod} occurs at an amino acid side chain of such moiety D- In certain embodiments attachment of such moiety M_{mod} occurs at an internal site of such moiety D-. Such moiety M_{mod} may preferably be a substituent or a polymeric moiety.

If D- is a peptide or protein moiety M_{mod} may in one embodiment be introduced in the form of a disulfide bridging. Preferably, such disulfide bridging is formed between the thiol groups of two cysteine residues. Such disulfide bridging is one example for attachment of a modifying moiety at an internal site. In one embodiment these cysteine residues may be naturally occurring cysteine residues. In another embodiment, one or both of the cysteine residues do not naturally occur but were added to or inserted into the peptide or protein moiety D- or replaced a naturally occurring cysteine of the peptide or protein moiety D-.

Preferred ways of obtaining such disulfide bridging are disclosed in Jones et al. (J. Am. Chem. Soc., 2012, 134 (3), pp 1847-1852), WO2011/018611, WO2011/018612 and WO2011/018613.

If D- and at least one moiety M_{mod} are a peptide or protein moiety, such peptide or protein moiety D- and the at least one peptide or protein moiety M_{mod} may be a translational fusion or may be chemically conjugated to each other. In certain embodiments D- and M_{mod} are not a translational fusion. Preferably, if D- is a peptide or protein moiety D- and any peptide or protein moiety M_{mod} are chemically conjugated.

M_{mod} in the form of a peptide or protein moiety may be a synthetic or natural protein moiety or a portion or variant thereof. Exemplary moieties in the form of a peptide or protein moiety include albumin; antibody domains, such as Fc domains or antigen binding domains of

immunoglobulins; CTP, and CD25; each either in their naturally occurring form or as a variant or fragment thereof.

A peptide or protein moiety M_{mod} fused to a peptide or protein moiety D- may be attached at the N-terminus or the C-terminus or may be inserted at an internal position of D-. It is understood that more than one peptide or protein moiety M_{mod} may be translationally fused or chemically conjugated to and/or inserted into a peptide or protein moiety D-. Said more than one peptide or protein moiety M_{mod} may have the same or a different sequence. For example, a peptide or protein moiety D- may have a first peptide or protein moiety M_{mod} translationally fused or chemically conjugated to the N-terminus of D- and a second peptide or protein moiety M_{mod} translationally fused or chemically conjugated to the C-terminus of D-. In another example, a peptide or protein moiety D- may comprise a first peptide or protein moiety M_{mod} translationally fused or chemically conjugated to the N-terminus of D- and a second peptide or protein moiety M_{mod} translationally inserted into or chemically conjugated to an internal position D-. In another example, a peptide or protein moiety D- may comprise a first peptide or protein moiety M_{mod} translationally fused or chemically conjugated to the C-terminus of D- and a second peptide or protein moiety M_{mod} translationally inserted into or chemically conjugated to an internal position of D-. In an even further example a peptide or protein moiety D- may comprise a first peptide or protein moiety M_{mod} translationally fused or chemically conjugated to the N-terminus of D-, a second peptide or protein moiety M_{mod} translationally fused or chemically conjugated to the C-terminus of D- and a third peptide or protein moiety M_{mod} translationally inserted into or chemically conjugated an internal position of D-.

If D- is a peptide or protein moiety attachment of M_{mod} may be at a proteinogenic or non-proteinogenic amino acid residue of D-. In certain embodiments attachment of M_{mod} occurs to a proteinogenic amino acid. Such proteinogenic amino acid residue is preferably selected from the group consisting of cysteine, methionine, histidine, lysine, tryptophan, serine, threonine, tyrosine, aspartic acid, glutamic acid, glutamine and arginine. In certain embodiments at least one moiety M_{mod} is attached to a cysteine of D-. In certain embodiments at least one moiety M_{mod} is attached to a methionine of D-. In certain embodiments at least one moiety M_{mod} is attached to a histidine of D-. In certain embodiments at least one moiety M_{mod} is attached to a lysine of D-. In certain embodiments at least one moiety M_{mod} is attached to a tryptophan of D-. In certain embodiments at least one moiety M_{mod} is attached to

a serine of D-. In certain embodiments at least one moiety M_{mod} is attached to a threonine of D-. In certain embodiments at least one moiety M_{mod} is attached to a tyrosine of D-. In certain embodiments at least one moiety M_{mod} is attached to an aspartic acid of D-. In certain embodiments at least one moiety M_{mod} is attached to a glutamic acid of D-. In certain embodiments at least one moiety M_{mod} is attached to a glutamine of D-. In certain embodiments at least one moiety M_{mod} is attached to a arginine of D-.

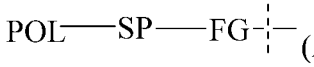
If attachment of M_{mod} occurs at a non-proteinogenic amino acid residue of D- such non-proteinogenic amino acid residue may be any non-proteinogenic amino acid residue having a functional group available for conjugating M_{mod} to D-. In certain embodiments attachment of M_{mod} occurs to a non-proteinogenic amino acid. If the modifying moiety is attached to a non-proteinogenic amino acid residue, it is understood that such non-proteinogenic amino acid residue is artificially introduced into D-. Such non-proteinogenic amino acid residue may be any non-proteinogenic amino acid residue having a functional group available for conjugating M_{mod} to D-. In certain embodiments such non-proteinogenic amino acids comprise a functional group in their side chains selected from the group consisting of carbonyl; carbonyl derivatives, such as carbonyl-like, marked carbonyl and protected carbonyl groups; azide; oxime; and hydroxylamine.

In certain embodiments such non-proteinogenic amino acid is a non-proteinogenic amino acid as described in WO2006/069246A2, which non-proteinogenic amino acids are incorporated by reference herewith. In certain embodiments the non-proteinogenic amino acid has a structure as described in formula (I) in [00265] to [00283], of formula (XXX) in [00284], of formula (XXX-A) in [00285], of formula (XXX-B) in [00286], of formula (XXXI) in [00287], of formula (XXXI-A) in [00288], of formula (XXXI-B) in [00289], of formula (XXXII) in [00290], of formula (XXXII-A) in [00291], of formula (XXXII-B) in [00292], of formula (XXXX) in [00293], of formula (XXXXI) in [00294], of formula (XXXXII) in erroneously labelled paragraph [0100], i.e. the paragraph between [00294] and [00295], of formula (XXXXIII) in [00295] and [00296], of formula (XIV) in [00302] to [00305], of formula (XV) in [00306] and [00307], of formula (XI) in [00310] to [00312], of formula (XII) in [00313], of formula (XII) in [00314] and [00315], of formula (XIV) in [00316], of formula (XVI) in [00317], of formula (XVI) in [00318] and [00319], of formula (XVIII) in [00320] and [00321], or of formula (XXIX) in [00530] of WO2006/069246A2, which non-proteinogenic amino acids are incorporated by reference herewith.

Preferably, attachment of at least one moiety M_{mod} occurs at an amino acid position of D- known to be required for undesired activity. Such undesired activity may be binding to a receptor or subunit of a receptor which is known to cause unwanted physiological effects.

In certain embodiments D- is a peptide moiety and protein moiety and each M_{mod} is a polymer. In certain embodiments one such polymer moiety M_{mod} is attached to D- at an internal site of D-. In certain embodiments two such polymer moieties M_{mod} are attached to D- at an internal site of D-.

In certain embodiments M_{mod} is of formula (A-1)


(A-1),

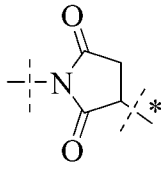
wherein

-FG- is a linkage;

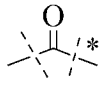
-SP- is a spacer moiety; and

-POL is a polymer.

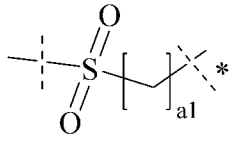
In certain embodiments -FG- of formula (A-1) is


; wherein the dashed line marked with the asterisk indicates attachment to a sulfur of D- and the unmarked dashed line indicates attachment -SP-. Said sulfur may be a sulfur provided by the side chain of a cysteine-, if D- is a peptide or protein moiety.

In certain embodiments -FG- of formula (A-1) is

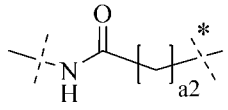

; wherein the dashed line marked with the asterisk indicates attachment to a nitrogen of D- and the unmarked dashed line indicates attachment to -SP-. Said nitrogen may be a nitrogen from the N-terminal amine or a nitrogen of the side chain of a lysine of D-, if D- is a peptide or protein moiety. In certain embodiments said nitrogen is the nitrogen of the N-terminal amine of D--, if D- is a peptide or protein moiety. In certain embodiments said nitrogen is a nitrogen of the side chain of a lysine of D-, if D- is a peptide or protein moiety.

In certain embodiments -FG- of formula (A-1) is



; wherein the dashed line marked with the asterisk indicates attachment to a sulfur of nitrogen of D-; the unmarked dashed line indicates attachment to -SP- and a1 is selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18. 19 and 20. Said sulfur may be a sulfur provided by the side chain of a cysteine and said nitrogen may be a nitrogen from the N-terminal amine or a nitrogen of the side chain of a lysine of D--, if D- is a peptide or protein moiety. In certain embodiments the dashed line marked with the asterisk indicates attachment to a sulfur, which sulfur is provided by the side chain of a cysteine-, if D- is a peptide or protein moiety. In certain embodiments a1 is an integer ranging from 1 to 8. In certain embodiments a1 is an integer ranging from 1 to 6. In certain embodiments a1 is an integer ranging from 1 to 4. In certain embodiments a1 is 1. In certain embodiments a1 is 2. In certain embodiments a1 is 3. In certain embodiments a1 is 4. In certain embodiments a1 is 5. In certain embodiments a1 is 6.

In certain embodiments -FG- of formula (A-1) is



; wherein the dashed line marked with the asterisk indicates attachment to a sulfur of nitrogen of D-; the unmarked dashed line indicates attachment to -SP-; and a2 is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18. 19 and 20. In certain embodiments a2 is an integer ranging from 1 to 8. In certain embodiments a2 is an integer ranging from 1 to 6. In certain embodiments a2 is an integer ranging from 1 to 4. In certain embodiments a2 is 1. In certain embodiments a2 is 2. In certain embodiments a2 is 3. In certain embodiments a2 is 4. In certain embodiments a2 is 5. In certain embodiments a2 is 6. Said sulfur may be a sulfur provided by the side chain of a cysteine and said nitrogen may be a nitrogen from the N-terminal amine or a nitrogen of the side chain of a lysine of D--, if D- is a peptide or protein moiety. In certain embodiments the dashed line marked with the asterisk indicates attachment to a sulfur, which sulfur is provided by the side chain of a cysteine.

In certain embodiments -SP- of formula (A-1) is selected from the group consisting of C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl; wherein C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally substituted with one or more R^9, which are the same or different and wherein C_{1-50}

alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally interrupted by one or more groups selected from the group consisting of -T-, -C(O)O-, -O-, -C(O)-, -C(O)N(R^{10})-, -S(O)$_2$N(R^{10})-, -S(O)N(R^{10})-, -S(O)$_2$-, -S(O)-, -N(R^{10})S(O)$_2$N(R^{10a})-, -S-, -N(R^{10})-, -OC(OR^{10})(R^{10a})-, -N(R^{10})C(O)N(R^{10a})-, and -OC(O)N(R^{10})-;

each T is independently selected from the group consisting of phenyl, naphthyl, indenyl, indanyl, tetralinyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl, 8- to 11-membered heterobicyclyl, 8-to 30-membered carbopolycyclyl, and 8- to 30-membered heteropolycyclyl; wherein each T is independently optionally substituted with one or more R^9, which are the same or different;

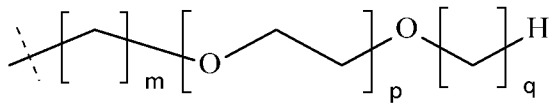
each -R^9 is independently selected from the group consisting of halogen, -CN, oxo (=O), -COOR^{11}, -OR^{11}, -C(O)R^{11}, -C(O)N($R^{11}R^{11a}$), -S(O)$_2$N($R^{11}R^{11a}$), -S(O)N($R^{11}R^{11a}$), -S(O)$_2R^{11}$, -S(O)R^{11}, -N(R^{11})S(O)$_2$N($R^{11a}R^{11b}$), -SR^{11}, -N($R^{11}R^{11a}$), -NO$_2$, -OC(O)R^{11}, -N(R^{11})C(O)R^{11a}, -N(R^{11})S(O)$_2R^{11a}$, -N(R^{11})S(O)R^{11a}, -N(R^{11})C(O)OR^{11a}, -N(R^{11})C(O)N($R^{11a}R^{11b}$), -OC(O)N($R^{11}R^{11a}$), and C_{1-6} alkyl; wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different; and

each -R^{10}, -R^{10a}, -R^{11}, -R^{11a} and -R^{11b} is independently selected from the group consisting of -H, and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different.

In certain embodiments -SP- of formula (A-1) is C_{1-20} alkyl, which C_{1-20} alkyl is optionally substituted with one or more -R^9, and which C_{1-20} alkyl is optionally interrupted by one or more groups selected from the group consisting of -O-, -C(O)N(R^{10})-, -S(O)$_2$-, -S(O)-, -S-, -N(R^{10})-, -OC(OR^{10})(R^{10a})-, -N(R^{10})C(O)N(R^{10a})-, and -OC(O)N(R^{10})-; wherein each -R^9 is selected from the group consisting of C_{1-6} alkyl; and each -R^{10} and -R^{10a} is independently selected from the group consisting of -H and C_{1-6} alkyl.

In certain embodiments -SP- of formula (A-1) is C_{1-10} alkyl, which C_{1-10} alkyl is optionally substituted with one or more -R^9, and which C_{1-10} alkyl is optionally interrupted by one or more groups selected from the group consisting of -O-, -C(O)N(R^{10})-, -S(O)$_2$-, -S(O)-, -S-, -N(R^{10})-, -OC(OR^{10})(R^{10a})-, -N(R^{10})C(O)N(R^{10a})-, and -OC(O)N(R^{10})-; wherein each -R^9 is selected from the group consisting of C_{1-6} alkyl; and each -R^{10} and -R^{10a} is independently selected from the group consisting of -H and C_{1-6} alkyl.

In certain embodiments -POL of formula (A-1) is a PEG-based polymer. In certain embodiments -POL is of formula (A-1i)



(A-1i),

wherein

the dashed line indicates attachment to -SP;

m is 0 or 1;

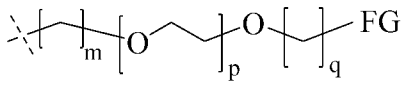
p is an integer ranging from 12 to 22700; and

q is selected from the group consisting of 1, 2, 3, 4, 5, and 6.

In certain embodiments m of formula (A-1i) is 0. In certain embodiments m of formula (A-1i) is 1.

In certain embodiments p of formula (A-1i) is an integer ranging from 23 to 227000, such as from 45 to 11300, or from 69 to 4540, or from 114 to 2700. In certain embodiments p of formula (A-1i) is about 12. In certain embodiments p of formula (A-1i) is about 23. In certain embodiments p of formula (A-1i) is about 46. In certain embodiments p of formula (A-1i) is about 68. In certain embodiments p of formula (A-1i) is about 90. In certain embodiments p of formula (A-1i) is about 112. In certain embodiments p of formula (A-1i) is about 170. In certain embodiments p of formula (A-1a) is about 227. In certain embodiments p of formula (A-1i) is about 340. In certain embodiments p of formula (A-1i) is about 450. In certain embodiments p of formula (A-1i) is about 680. In certain embodiments p of formula (A-1i) is about 900. In certain embodiments p of formula (A-1i) is about 1130. In certain embodiments p of formula (A-1i) is about 1350. In certain embodiments p of formula (A-1i) is about 1590. In certain embodiments p of formula (A-1i) is about 1800. In certain embodiments p of formula (A-1i) is about 2045. In certain embodiments p of formula (A-1i) is about 2275.

In certain embodiments -POL of formula (A-1) is of formula (A-1ii)



(A-1ii),

wherein

the dashed line indicates attachment to -SP-;

FG is a functional group;

m is 0 or 1;

p is an integer ranging from 12 to 22700; and

q is selected from the group consisting of 1, 2, 3, 4, 5, and 6.

If the moiety M_{mod} of formula (A-1) is to be conjugated to further moieties, such as to one or more moieties $-L^1-L^2-Z$, it is advantageous if a moiety -POL ends with a functional group. It is understood the if -POL is of formula (A-1ii), such compound is a reagent and that after conjugation of such one or more moieties, such as one or more moieties $-L^1-L^2-Z$, to the functional group of said reagent, FG is no longer present, but has formed a linkage with a suitable functional group present in the reagent form of the one or more further moieties.

It is also understood that also other attachment sites for moieties to be conjugated to M_{mod}, such as moieties $-L^1-L^2-Z$, may be possible.

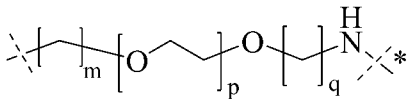
In certain embodiments m of formula (A-1ii) is 0. In certain embodiments m of formula (A-1ii) is 1.

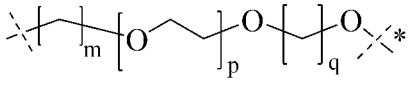
In certain embodiments p of formula (A-1ii) is an integer ranging from 23 to 227000, such as from 45 to 11300, or from 69 to 4540, or from 114 to 2700. In certain embodiments p of formula (A-1ii) is about 12. In certain embodiments p of formula (A-1ii) is about 23. In certain embodiments p of formula (A-1ii) is about 46. In certain embodiments p of formula (A-1ii) is about 68. In certain embodiments p of formula (A-1ii) is about 90. In certain embodiments p of formula (A-1ii) is about 112. In certain embodiments p of formula (A-1ii) is about 170. In certain embodiments p of formula (A-1ii) is about 227. In certain embodiments p of formula (A-1ii) is about 340. In certain embodiments p of formula (A-1ii) is about 450. In certain embodiments p of formula (A-1ii) is about 680. In certain embodiments p of formula (A-1ii) is about 900. In certain embodiments p of formula (A-1ii) is about 1130. In certain embodiments p of formula (A-1ii) is about 1350. In certain embodiments p of formula (A-1ii) is about 1590. In certain embodiments p of formula (A-1ii) is about 1800. In certain embodiments p of formula (A-1ii) is about 2045. In certain embodiments p of formula (A-1ii) is about 2275.

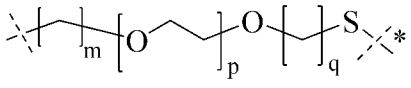
In certain embodiments q of formula (A-1ii) is 1. In certain embodiments q of formula (A-1ii) is 2. In certain embodiments q of formula (A-1ii) is 3. In certain embodiments q of formula

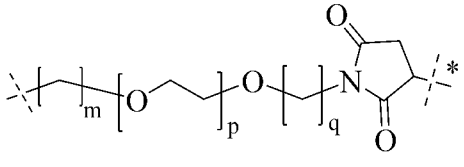
(A-1ii) is 4. In certain embodiments q of formula (A-1ii) is 5. In certain embodiments q of formula (A-1ii) is 6.

If a further moiety, such as a moiety -L^1-L^2-Z, is conjugated to M_{mod} via a moiety -POL of formula (A-1), the moiety -POL may be of formula (A-1iii), (A-1iv), (A-1v) or (A-1vi)


(A-1iii)


(A-1iv)


(A-1v)


(A-1vi),

wherein

the dashed line marked with the asterisk indicates attachment to the further moiety, such as to a moiety -L^1-L^2-Z;

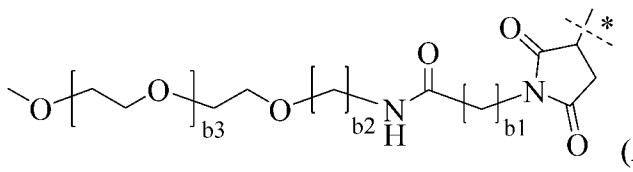
the unmarked dashed line indicates attachment to -SP-; and

m, p and q are used as defined in formula (A-1i).

In certain embodiments a further moiety, such as a moiety -L^1-L^2-Z, is conjugated to M_{mod} via a moiety -POL of formula (A-1), resulting in a moiety of -POL of formula (A-1iii). In certain embodiments a further moiety, such as a moiety -L^1-L^2-Z, is conjugated to M_{mod} via a moiety -POL of formula (A-1), resulting in a moiety of -POL of formula (A-1iv). In certain embodiments a further moiety, such as a moiety -L^1-L^2-Z, is conjugated to M_{mod} via a moiety -POL of formula (A-1), resulting in a moiety of -POL of formula (A-1v). In certain embodiments a further moiety, such as a moiety -L^1-L^2-Z, is conjugated to M_{mod} via a moiety -POL of formula (A-1), resulting in a moiety of -POL of formula (A-1vi).

In certain embodiments -POL of formula (A-1) is a hyaluronic acid-based polymer.

In certain embodiments M_{mod} is of formula (A-1a)



(A-1a),

wherein

the dashed line marked with the asterisk indicates attachment to the sulfur of a side chain of an amino acid residue of D-;

b1 is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18. 19 and 20;

b2 is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18. 19 and 20; and

b3 is an integer ranging from 12 to 22700.

In certain embodiments b1 of formula (A-1a) is an integer ranging from 1 to 8. In certain embodiments b1 of formula (A-1a) is an integer ranging from 1 to 6. In certain embodiments b1 of formula (A-1a) is an integer ranging from 1 to 4. In certain embodiments b1 of formula (A-1a) is 1. In certain embodiments b1 of formula (A-1a) is 2. In certain embodiments b1 of formula (A-1a) is 3. In certain embodiments b1 of formula (A-1a) is 4. In certain embodiments b1 of formula (A-1a) is 5. In certain embodiments b1 of formula (A-1a) is 6.

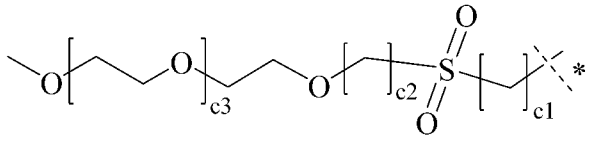
In certain embodiments b2 of formula (A-1a) is an integer ranging from 1 to 8. In certain embodiments b2 of formula (A-1a) is an integer ranging from 1 to 6. In certain embodiments b2 of formula (A-1a) is an integer ranging from 1 to 4. In certain embodiments b2 of formula (A-1a) is 1. In certain embodiments b2 of formula (A-1a) is 2. In certain embodiments b2 of formula (A-1a) is 3. In certain embodiments b2 of formula (A-1a) is 4. In certain embodiments b2 of formula (A-1a) is 5. In certain embodiments b2 of formula (A-1a) is 6.

In certain embodiments b3 of formula (A-1a) is an integer ranging from 23 to 227000, such as from 45 to 11300, or from 69 to 4540, or from 114 to 2700. In certain embodiments b3 of formula (A-1a) is about 12. In certain embodiments b3 of formula (A-1a) is about 23. In certain embodiments b3 of formula (A-1a) is about 46. In certain embodiments b3 of formula (A-1a) is about 68. In certain embodiments b3 of formula (A-1a) is about 90. In certain embodiments b3 of formula (A-1a) is about 112. In certain embodiments b3 of formula (A-1a) is about 170. In certain embodiments b3 of formula (A-1a) is about 227. In certain embodiments b3 of formula (A-1a) is about 340. In certain embodiments b3 of formula (A-

1a) is about 450. In certain embodiments b3 of formula (A-1a) is about 680. In certain embodiments b3 of formula (A-1a) is about 900. In certain embodiments b3 of formula (A-1a) is about 1130. In certain embodiments b3 of formula (A-1a) is about 1350. In certain embodiments b3 of formula (A-1a) is about 1590. In certain embodiments b3 of formula (A-1a) is about 1800. In certain embodiments b3 of formula (A-1a) is about 2045. In certain embodiments b3 of formula (A-1a) is about 2275.

In certain embodiments b1 of formula (A-1a) is 2, b2 of formula (A-1a) is 3 and b3 of formula (A-1a) is about 12. In certain embodiments b1 of formula (A-1a) is 2, b2 of formula (A-1a) is 3 and b3 of formula (A-1a) is about 23. In certain embodiments b1 of formula (A-1a) is 2, b2 of formula (A-1a) is 3 and b3 of formula (A-1a) is about 46. In certain embodiments b1 of formula (A-1a) is 2, b2 of formula (A-1a) is 3 and b3 of formula (A-1a) is about 68. In certain embodiments b1 of formula (A-1a) is 2, b2 of formula (A-1a) is 3 and b3 of formula (A-1a) is about 90. In certain embodiments b1 of formula (A-1a) is 2, b2 of formula (A-1a) is 3 and b3 of formula (A-1a) is about 112. In certain embodiments b1 of formula (A-1a) is 2, b2 of formula (A-1a) is 3 and b3 of formula (A-1a) is about 170. In certain embodiments b1 of formula (A-1a) is 2, b2 of formula (A-1a) is 3 and b3 of formula (A-1a) is about 227. In certain embodiments b1 of formula (A-1a) is 2, b2 of formula (A-1a) is 3 and b3 of formula (A-1a) is about 340. In certain embodiments b1 of formula (A-1a) is 2, b2 of formula (A-1a) is 3 and b3 of formula (A-1a) is about 450.

In certain embodiments M_{mod} is of formula (A-1b)



(A-1b),

wherein

the dashed line marked with the asterisk indicates attachment to the sulfur of a side chain of an amino acid residue of D-;

c1 is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18. 19 and 20;

c2 is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18. 19 and 20; and

c3 is an integer ranging from 12 to 22700.

In certain embodiments c1 of formula (A-1b) is an integer ranging from 1 to 8. In certain embodiments c1 of formula (A-1b) is an integer ranging from 1 to 6. In certain embodiments c1 of formula (A-1b) is an integer ranging from 1 to 4. In certain embodiments c1 of formula (A-1b) is 1. In certain embodiments c1 of formula (A-1b) is 2. In certain embodiments c1 of formula (A-1b) is 3. In certain embodiments c1 of formula (A-1b) is 4. In certain embodiments c1 of formula (A-1b) is 5. In certain embodiments c1 of formula (A-1b) is 6.

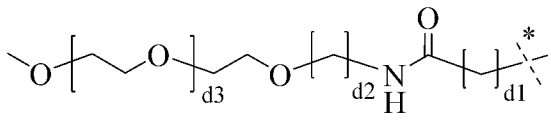
In certain embodiments c2 of formula (A-1b) is an integer ranging from 1 to 8. In certain embodiments c2 of formula (A-1b) is an integer ranging from 1 to 6. In certain embodiments c2 of formula (A-1b) is an integer ranging from 1 to 4. In certain embodiments c2 of formula (A-1b) is 1. In certain embodiments c2 of formula (A-1b) is 2. In certain embodiments c2 of formula (A-1b) is 3. In certain embodiments c2 of formula (A-1b) is 4. In certain embodiments c2 of formula (A-1b) is 5. In certain embodiments c2 of formula (A-1b) is 6.

In certain embodiments c3 of formula (A-1b) is an integer ranging from 23 to 227000, such as from 45 to 11300, or from 69 to 4540, or from 114 to 2700. In certain embodiments c3 of formula (A-1b) is about 12. In certain embodiments c3 of formula (A-1b) is about 23. In certain embodiments c3 of formula (A-1b) is about 46. In certain embodiments c3 of formula (A-1b) is about 68. In certain embodiments c3 of formula (A-1b) is about 90. In certain embodiments c3 of formula (A-1b) is about 112. In certain embodiments c3 of formula (A-1b) is about 170. In certain embodiments c3 of formula (A-1b) is about 227. In certain embodiments c3 of formula (A-1b) is about 340. In certain embodiments c3 of formula (A-1b) is about 450. In certain embodiments c3 of formula (A-1b) is about 680. In certain embodiments c3 of formula (A-1b) is about 900. In certain embodiments c3 of formula (A-1b) is about 1130. In certain embodiments c3 of formula (A-1b) is about 1350. In certain embodiments c3 of formula (A-1b) is about 1590. In certain embodiments c3 of formula (A-1b) is about 1800. In certain embodiments c3 of formula (A-1b) is about 2045. In certain embodiments c3 of formula (A-1b) is about 2275.

In certain embodiments c1 of formula (A-1b) is 2, c2 of formula (A-1b) is 3 and c3 of formula (A-1b) is about 12. In certain embodiments c1 of formula (A-1b) is 2, c2 of formula (A-1b) is 3 and c3 of formula (A-1b) is about 23. In certain embodiments c1 of formula (A-1b) is 2, c2 of formula (A-1b) is 3 and c3 of formula (A-1b) is about 46. In certain embodiments c1 of formula (A-1b) is 2, c2 of formula (A-1b) is 3 and c3 of formula (A-1b) is about 68. In certain

embodiments c1 of formula (A-1b) is 2, c2 of formula (A-1b) is 3 and c3 of formula (A-1b) is about 90. In certain embodiments c1 of formula (A-1b) is 2, c2 of formula (A-1b) is 3 and c3 of formula (A-1b) is about 112. In certain embodiments c1 of formula (A-1b) is 2, c2 of formula (A-1b) is 3 and c3 of formula (A-1b) is about 170. In certain embodiments c1 of formula (A-1b) is 2, c2 of formula (A-1b) is 3 and c3 of formula (A-1b) is about 227. In certain embodiments c1 of formula (A-1b) is 2, c2 of formula (A-1b) is 3 and c3 of formula (A-1b) is about 340. In certain embodiments c1 of formula (A-1b) is 2, c2 of formula (A-1b) is 3 and c3 of formula (A-1b) is about 450.

In certain embodiments M_{mod} is of formula (A-1c)



(A-1c),

wherein

the dashed line marked with the asterisk indicates attachment to the sulfur of a side chain of an amino acid residue of D-;

d1 is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18. 19 and 20;

d2 is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18. 19 and 20; and

d3 is an integer ranging from 12 to 22700.

In certain embodiments d1 of formula (A-1c) is an integer ranging from 1 to 8. In certain embodiments d1 of formula (A-1c) is an integer ranging from 1 to 6. In certain embodiments d1 of formula (A-1c) is an integer ranging from 1 to 4. In certain embodiments d1 of formula (A-1c) is 1. In certain embodiments d1 of formula (A-1c) is 2. In certain embodiments d1 of formula (A-1c) is 3. In certain embodiments d1 of formula (A-1c) is 4. In certain embodiments d1 of formula (A-1c) is 5. In certain embodiments d1 of formula (A-1c) is 6.

In certain embodiments d2 of formula (A-1c) is an integer ranging from 1 to 8. In certain embodiments d2 of formula (A-1c) is an integer ranging from 1 to 6. In certain embodiments d2 of formula (A-1c) is an integer ranging from 1 to 4. In certain embodiments d2 of formula (A-1c) is 1. In certain embodiments d2 of formula (A-1c) is 2. In certain embodiments d2 of

formula (A-1c) is 3. In certain embodiments d2 of formula (A-1c) is 4. In certain embodiments d2 of formula (A-1c) is 5. In certain embodiments d2 of formula (A-1c) is 6.

In certain embodiments d3 of formula (A-1c) is an integer ranging from 23 to 227000, such as from 45 to 11300, or from 69 to 4540, or from 114 to 2700. In certain embodiments d3 of formula (A-1c) is about 12. In certain embodiments d3 of formula (A-1c) is about 23. In certain embodiments d3 of formula (A-1c) is about 46. In certain embodiments d3 of formula (A-1c) is about 68. In certain embodiments d3 of formula (A-1c) is about 90. In certain embodiments d3 of formula (A-1c) is about 112. In certain embodiments d3 of formula (A-1c) is about 170. In certain embodiments d3 of formula (A-1c) is about 227. In certain embodiments d3 of formula (A-1c) is about 340. In certain embodiments d3 of formula (A-1c) is about 450. In certain embodiments d3 of formula (A-1c) is about 680. In certain embodiments d3 of formula (A-1c) is about 900. In certain embodiments d3 of formula (A-1c) is about 1130. In certain embodiments d3 of formula (A-1c) is about 1350. In certain embodiments d3 of formula (A-1c) is about 1590. In certain embodiments d3 of formula (A-1c) is about 1800. In certain embodiments d3 of formula (A-1c) is about 2045. In certain embodiments d3 of formula (A-1c) is about 2275.

In certain embodiments d1 of formula (A-1c) is 2, d2 of formula (A-1c) is 3 and d3 of formula (A-1cd) is about 12. In certain embodiments d1 of formula (A-1c) is 2, d2 of formula (A-1c) is 3 and d3 of formula (A-1c) is about 23. In certain embodiments d1 of formula (A-1c) is 2, d2 of formula (A-1c) is 3 and d3 of formula (A-1c) is about 46. In certain embodiments d1 of formula (A-1c) is 2, d2 of formula (A-1c) is 3 and d3 of formula (A-1c) is about 68. In certain embodiments d1 of formula (A-1c) is 2, d2 of formula (A-1c) is 3 and d3 of formula (A-1c) is about 90. In certain embodiments d1 of formula (A-1c) is 2, d2 of formula (A-1c) is 3 and d3 of formula (A-1c) is about 112. In certain embodiments d1 of formula (A-1c) is 2, d2 of formula (A-1c) is 3 and d3 of formula (A-1c) is about 170. In certain embodiments d1 of formula (A-1c) is 2, d2 of formula (A-1c) is 3 and d3 of formula (A-1c) is about 227. In certain embodiments d1 of formula (A-1c) is 2, d2 of formula (A-1c) is 3 and d3 of formula (A-1c) is about 340. In certain embodiments d1 of formula (A-1c) is 2, d2 of formula (A-1c) is 3 and d3 of formula (A-1c) is about 450.

The conjugates of the present invention comprise at least one polymeric moiety and/or substituted fatty acid moiety -Z covalently and reversibly conjugated to at least one moiety M_{mod}.

In one embodiment the conjugates of the present invention comprise one moiety -Z, which is either a substituted fatty acid or a polymeric moiety. In one embodiment -Z is a substituted fatty acid. In another embodiment -Z is a polymeric moiety.

In another embodiment the conjugates of the present invention comprise two moieties -Z, which may be the same or different. In one embodiment both moieties -Z are a substituted fatty acid, which may be the same or different. In another embodiment both moieties -Z are a polymeric moiety, which may be the same or different. In another embodiment one moiety -Z is a substituted fatty acid and the other moiety -Z is a polymeric moiety.

In another embodiment the conjugates of the present invention comprise three moieties -Z, which may be the same or different. In one embodiment all three moieties -Z are a substituted fatty acid, which may be the same or different. In another embodiment all three moieties -Z are a polymeric moiety, which may be the same or different. In another embodiment one or two moieties -Z are a substituted fatty acid and the remaining moiety/moieties -Z is/are a polymeric moiety.

In another embodiment the conjugates of the present invention comprise four moieties -Z, which may be the same or different. In one embodiment all four moieties -Z are a substituted fatty acid, which may be the same or different. In another embodiment all four moieties -Z are a polymeric moiety, which may be the same or different. In another embodiment one, two or three moieties -Z are a substituted fatty acid and the remaining moiety/moieties -Z is/are a polymeric moiety.

If -Z is a substituted fatty acid moiety it is preferably a substituted fatty acid moiety disclosed in WO 2005/027978 A2 and WO 2014/060512 A1, which are herewith incorporated by reference.

In certain embodiments -Z is a polymer selected from the group consisting of linear, branched and multi-arm polymers. In certain embodiments -Z is a linear polymer. In certain embodiments -Z is a branched polymer. In certain embodiments -Z is a multi-arm polymer.

If -Z is a polymeric moiety, such polymeric moiety has preferably a molecular weight ranging from 1 kDa to 1000 kDa, more preferably from 2 kDa to 500 kDa, even more preferably from 3 kDa to 200 kDa, even more preferably from 5 kDa to 120 kDa, even more preferably from 10 kDa to 100 kDa and most preferably from 15 kDa to 80kDa. In one embodiment -Z is a polymeric moiety having a molecular weight of about 2 kDa. In another embodiment -Z is a polymeric moiety having a molecular weight of about 5 kDa. In another embodiment -Z is a polymeric moiety having a molecular weight of about 10 kDa. In another embodiment -Z is a polymeric moiety having a molecular weight of about 15 kDa. In another embodiment -Z is a polymeric moiety having a molecular weight of about 20 kDa. In another embodiment -Z is a polymeric moiety having a molecular weight of about 30 kDa. In another embodiment -Z is a polymeric moiety having a molecular weight of about 40 kDa. In another embodiment -Z is a polymeric moiety having a molecular weight of about 50 kDa. In another embodiment -Z is a polymeric moiety having a molecular weight of about 60 kDa. In another embodiment -Z is a polymeric moiety having a molecular weight of about 70 kDa. In another embodiment -Z is a polymeric moiety having a molecular weight of about 80 kDa. In another embodiment -Z is a polymeric moiety having a molecular weight of about 90 kDa. In another embodiment -Z is a polymeric moiety having a molecular weight of about 100 kDa. In one embodiment -Z is a polymeric moiety having a molecular weight of 2 kDa. In another embodiment -Z is a polymeric moiety having a molecular weight of 5 kDa. In another embodiment -Z is a polymeric moiety having a molecular weight of 10 kDa. In another embodiment -Z is a polymeric moiety having a molecular weight of 15 kDa. In another embodiment -Z is a polymeric moiety having a molecular weight of 20 kDa. In another embodiment -Z is a polymeric moiety having a molecular weight of 30 kDa. In another embodiment -Z is a polymeric moiety having a molecular weight of 40 kDa. In another embodiment -Z is a polymeric moiety having a molecular weight of 50 kDa. In another embodiment -Z is a polymeric moiety having a molecular weight of 60 kDa. In another embodiment -Z is a polymeric moiety having a molecular weight of 70 kDa. In another embodiment -Z is a polymeric moiety having a molecular weight of 80 kDa. In another embodiment -Z is a polymeric moiety having a molecular weight of 90 kDa. In another embodiment -Z is a polymeric moiety having a molecular weight of 100 kDa.

If -Z is a polymeric moiety, such polymeric moiety preferably comprises a polymer selected from the group consisting of 2-methacryloyl-oxyethyl phosphoyl cholins, poly(acrylic acids),

poly(acrylates), poly(acrylamides), poly(alkyloxy) polymers, poly(amides), poly(amidoamines), poly(amino acids), poly(anhydrides), poly(aspartamides), poly(butyric acids), poly(glycolic acids), polybutylene terephthalates, poly(caprolactones), poly(carbonates), poly(cyanoacrylates), poly(dimethylacrylamides), poly(esters), poly(ethylenes), poly(ethyleneglycols), poly(ethylene oxides), poly(ethyl phosphates), poly(ethyloxazolines), poly(glycolic acids), poly(hydroxyethyl acrylates), poly(hydroxyethyl-oxazolines), poly(hydroxymethacrylates), poly(hydroxypropylmethacrylamides), poly(hydroxypropyl methacrylates), poly(hydroxypropyloxazolines), poly(iminocarbonates), poly(lactic acids), poly(lactic-co-glycolic acids), poly(methacrylamides), poly(methacrylates), poly(methyloxazolines), poly(organophosphazenes), poly(ortho esters), poly(oxazolines), poly(propylene glycols), poly(siloxanes), poly(urethanes), poly(vinyl alcohols), poly(vinyl amines), poly(vinylmethylethers), poly(vinylpyrrolidones), silicones, celluloses, carbomethyl celluloses, hydroxypropyl methylcelluloses, chitins, chitosans, dextrans, dextrins, gelatins, hyaluronic acids and derivatives, functionalized hyaluronic acids, alginate, mannans, pectins, rhamnogalacturonans, starches, hydroxyalkyl starches, hydroxyethyl starches and other carbohydrate-based polymers, xylans, and copolymers thereof.

In one embodiment -Z is a peptide or protein moiety. Such peptide or protein moiety -Z may be chemically conjugated to D- via $-L^1-L^2-$ or may be translationally fused to D- via $-L^1-L^2-$, in which case $-L^1-$ is a peptide or protein moiety and $-L^2-$ is a chemical bond. In one embodiment such peptide or protein moiety -Z is chemically conjugated to D- via $-L^1-L^2-$. In another embodiment such peptide or protein moiety -Z is translationally fused via $-L^1-L^2-$, in which case $-L^1-$ is a peptide or protein moiety and $-L^2-$ is a chemical bond. It is understood that such peptide or protein reversible linker moiety $-L^1-$ may be enzymatically or non-enzymatically degradable. To facilitate enzymatic degradation $-L^1-$ may comprise a protease recognition site.

If -Z is a peptide or protein moiety it is preferably selected from the group consisting of moieties comprising the carboxyl-terminal peptide of the chorionic gonadotropin as described in US 2012/0035101 A1, which are herewith incorporated by reference; albumin moieties; random coil protein moieties and Fc fusion protein moieties.

In one embodiment -Z comprises a random coil peptide or protein moiety.

Preferably such random coil peptide or protein moiety comprises at least 25 amino acid residues and at most 2000 amino acids. Even more preferably such random coil peptide or protein moiety comprises at least 30 amino acid residues and at most 1500 amino acid residues. Even more preferably such random coil peptide or protein moiety comprises at least 50 amino acid residues and at most 500 amino acid residues.

In a preferred embodiment, -Z comprises a random coil protein moiety of which at least 80%, preferably at least 85%, even more preferably at least 90%, even more preferably at least 95%, even more preferably at least 98% and most preferably at least 99% of the total number of amino acids forming said random coil protein moiety are selected from alanine and proline. Even more preferably, at least 10%, but less than 75%, preferably less than 65%, of the total number of amino acid residues of such random coil protein moiety are proline residues. Preferably, such random coil protein moiety is as described in WO 2011/144756 A1 which is hereby incorporated by reference in its entirety. Even more preferably -Z comprises at least one moiety selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:51 and SEQ ID NO:61 as disclosed in WO2011/144756 which are hereby incorporated by reference. A moiety comprising such random coil protein comprising alanine and proline will be referred to as "PA" or "PA moiety".

Accordingly, in one embodiment -Z comprises a PA moiety.

In another embodiment, -Z comprises a random coil protein moiety of which at least 80%, preferably at least 85%, even more preferably at least 90%, even more preferably at least 95%, even more preferably at least 98% and most preferably at least 99% of the total number of amino acids forming said random coil protein moiety are selected from alanine, serine and proline. Even more preferably, at least 4%, but less than 40% of the total number of amino acid residues of such random coil protein moiety are proline residues. Preferably, such random coil protein moiety is as described in WO 2008/155134 A1, which is hereby incorporated by reference in its entirety. Even more preferably -Z comprises at least one moiety selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID

NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:40, SEQ ID NO:42, SEQ ID NO:44, SEQ ID NO:46, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54 and SEQ ID NO:56 as disclosed in WO 2008/155134 A1, which are hereby incorporated by reference. A moiety comprising such random coil protein moiety comprising alanine, serine and proline will be referred to as "PAS" or "PAS moiety".

Accordingly, in one embodiment -Z comprises a PAS moiety.

In another embodiment, -Z comprises a random coil protein moiety of which at least 80%, preferably at least 85%, even more preferably at least 90%, even more preferably at least 95%, even more preferably at least 98% and most preferably at least 99% of the total number of amino acids forming said random coil protein moiety are selected from alanine, glycine, serine, threonine, glutamate and proline. Preferably, such random coil protein moiety is as described in WO 2010/091122 A1, which is hereby incorporated by reference. Even more preferably -Z comprises at least one moiety selected from the group consisting of SEQ ID NO:182, SEQ ID NO:183, SEQ ID NO:184; SEQ ID NO:185, SEQ ID NO:186, SEQ ID NO:187, SEQ ID NO:188, SEQ ID NO:189, SEQ ID NO:190, SEQ ID NO:191, SEQ ID NO:192, SEQ ID NO:193, SEQ ID NO:194, SEQ ID NO:195, SEQ ID NO:196, SEQ ID NO:197, SEQ ID NO:198, SEQ ID NO:199, SEQ ID NO:200, SEQ ID NO:201, SEQ ID NO:202, SEQ ID NO:203, SEQ ID NO:204, SEQ ID NO:205, SEQ ID NO:206, SEQ ID NO:207, SEQ ID NO:208, SEQ ID NO:209, SEQ ID NO:210, SEQ ID NO:211, SEQ ID NO:212, SEQ ID NO:213, SEQ ID NO:214, SEQ ID NO:215, SEQ ID NO:216, SEQ ID NO:217, SEQ ID NO:218, SEQ ID NO:219, SEQ ID NO:220, SEQ ID NO:221, SEQ ID NO:759, SEQ ID NO:760, SEQ ID NO:761, SEQ ID NO:762, SEQ ID NO:763, SEQ ID NO:764, SEQ ID NO:765, SEQ ID NO:766, SEQ ID NO:767, SEQ ID NO:768, SEQ ID NO:769, SEQ ID NO:770, SEQ ID NO:771, SEQ ID NO:772, SEQ ID NO:773, SEQ ID NO:774, SEQ ID NO:775, SEQ ID NO:776, SEQ ID NO:777, SEQ ID NO:778, SEQ ID NO:779, SEQ ID NO:1715, SEQ ID NO:1716, SEQ ID NO:1718, SEQ ID NO:1719, SEQ ID NO:1720, SEQ ID NO:1721 and SEQ ID NO:1722 as disclosed in WO2010/091122A1, which are hereby incorporated by reference. A moiety comprising such random coil protein moiety comprising alanine, glycine, serine, threonine, glutamate and proline will be referred to as "XTEN" or "XTEN moiety" in line with its designation in WO 2010/091122 A1.

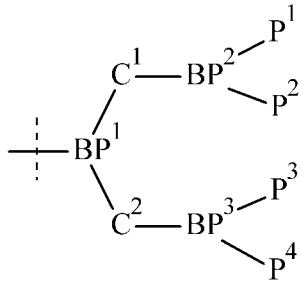
Accordingly, in one embodiment -Z comprises an XTEN moiety.

In another embodiment -Z is a hyaluronic acid-based polymer.

In another embodiment -Z is a PEG-based moiety, such as a linear, branched or multi-arm PEG-based moiety. In one embodiment -Z is a branched PEG-based moiety. Preferably, such branched PEG-based moiety -Z is a branched PEG-based moiety having one, two, three, four, five or six branching points. Preferably, -Z is a branched PEG-based moiety having one, two or three branching points. In one embodiment -Z is a branched PEG-based moiety having one branching point. In another embodiment -Z is a branched PEG-based moiety having two branching points. In another embodiment -Z is a branched PEG-based moiety having three branching points. In another embodiment -Z is a linear PEG-based polymer.

Each branching point is preferably independently selected from the group consisting of -N<, -CH< and >C<.

In certain embodiments -Z comprises a moiety of formula (A)



(A),

wherein

$-BP^1<$, $-BP^2<$, $-BP^3<$ are independently of each other selected from the group consisting of -N< and $-C(R^8)<$;

R^8 is selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl;

$-P^1$, $-P^2$, $-P^3$, $-P^4$ are independently of each other a PEG-based chain comprising at least 40% PEG and having a molecular weight ranging from 3 to 40 kDa;

$-C^1-$, $-C^2-$ are independently of each other selected from the group consisting of C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl; wherein C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally substituted with one or more R^9, which are the same or different and wherein C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally interrupted by one or more groups selected from the group consisting of -T-, -C(O)O-, -O-, -C(O)-,

-C(O)N(R^{10})-, -S(O)$_2$N(R^{10})-, -S(O)N(R^{10})-, -S(O)$_2$-, -S(O)-, -N(R^{10})S(O)$_2$N(R^{10a})-, -S-, -N(R^{10})-, -OC(OR^{10})(R^{10a})-, -N(R^{10})C(O)N(R^{10a})-, and -OC(O)N(R^{10})-;

each T is independently selected from the group consisting of phenyl, naphthyl, indenyl, indanyl, tetralinyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl, 8- to 11-membered heterobicyclyl, 8-to 30-membered carbopolycyclyl, and 8- to 30-membered heteropolycyclyl; wherein each T is independently optionally substituted with one or more R^9, which are the same or different;

each R^9 is independently selected from the group consisting of halogen, -CN, oxo (=O), -COOR^{11}, -OR^{11}, -C(O)R^{11}, -C(O)N($R^{11}R^{11a}$), -S(O)$_2$N($R^{11}R^{11a}$), -S(O)N($R^{11}R^{11a}$), -S(O)$_2R^{11}$, -S(O)R^{11}, -N(R^{11})S(O)$_2$N($R^{11a}R^{11b}$), -SR^{11}, -N($R^{11}R^{11a}$), -NO$_2$, -OC(O)R^{11}, -N(R^{11})C(O)R^{11a}, -N(R^{11})S(O)$_2R^{11a}$, -N(R^{11})S(O)R^{11a}, -N(R^{11})C(O)OR^{11a}, -N(R^{11})C(O)N($R^{11a}R^{11b}$), -OC(O)N($R^{11}R^{11a}$), and C_{1-6} alkyl; wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different; and

each R^{10}, R^{10a}, R^{11}, R^{11a} and R^{11b} is independently selected from the group consisting of -H, and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different.

In certain embodiments -P^1, -P^2, -P^3, -P^4 are independently of each other a PEG-based chain comprising at least 50% PEG and having a molecular weight ranging from 3 to 40 kDa. In certain embodiments -P^1, -P^2, -P^3, -P^4 are independently of each other a PEG-based chain comprising at least 60% PEG and having a molecular weight ranging from 3 to 40 kDa. In certain embodiments -P^1, -P^2, -P^3, -P^4 are independently of each other a PEG-based chain comprising at least 70% PEG and having a molecular weight ranging from 3 to 40 kDa. In certain embodiments -P^1, -P^2, -P^3, -P^4 are independently of each other a PEG-based chain comprising at least 80% PEG and having a molecular weight ranging from 3 to 40 kDa.

In certain embodiments the molecular weight of a moiety P^1, P^2, P^3 and P^4 of formula (A) ranges independently of each other from 5 to 30 kDa, such as from 5 to 25 kDa or from 8 to 20 kDa. In certain embodiments the molecular weight of a moiety P^1, P^2, P^3 or P^4 may be about 5 kDa. In certain embodiments the molecular weight of a moiety P^1, P^2, P^3 or P^4 may be about 7 kDa. In certain embodiments the molecular weight of a moiety P^1, P^2, P^3 or P^4 may be about 10 kDa. In certain embodiments the molecular weight of a moiety P^1, P^2, P^3 or P^4 may be about 12 kDa. In certain embodiments the molecular weight of a moiety P^1, P^2, P^3 or P^4 may be about 15 kDa. In certain embodiments the molecular weight of a moiety P^1, P^2, P^3 or

P^4 may be about 20 kDa. In certain embodiments the molecular weight of a moiety P^1, P^2, P^3 or P^4 may be about 25 kDa. In certain embodiments the molecular weight of a moiety P^1, P^2, P^3 or P^4 may be about 30 kDa. In certain embodiments the molecular weight of a moiety P^1, P^2, P^3 or P^4 may be 7 kDa. In certain embodiments the molecular weight of a moiety P^1, P^2, P^3 or P^4 may be 10 kDa. In certain embodiments the molecular weight of a moiety P^1, P^2, P^3 or P^4 may be 12 kDa. In certain embodiments the molecular weight of a moiety P^1, P^2, P^3 or P^4 may be 15 kDa. In certain embodiments the molecular weight of a moiety P^1, P^2, P^3 or P^4 may be 20 kDa. In certain embodiments the molecular weight of a moiety P^1, P^2, P^3 or P^4 may be 25 kDa. In certain embodiments the molecular weight of a moiety P^1, P^2, P^3 or P^4 may be 30 kDa.

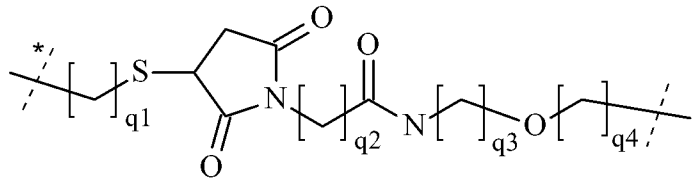
In certain embodiments P^1, P^2, P^3 and P^4 of formula (A) have the same structure.

In certain embodiments BP^1 of formula (A) is –N<.

In certain embodiments BP^2 and BP^2 of formula (A) have the same structure. In certain embodiments BP^2 and BP^2 of formula (A) are both –CH<.

In certain embodiments C^1 and C^2 of formula (A) have the same structure. In certain embodiments C^1 and C^2 of formula (A) are C_{1-50} alkyl interrupted by one or more of the groups selected from the group consisting of -O-, -C(O)N(R^{10})- and 3- to 10 membered heterocyclyl; wherein the 3- to 10 membered heterocyclyl is substituted with at least one oxo (=O).

In certain embodiments C^1 and C^2 of formula (A) are of formula (A-a)



(A-a),

wherein

the dashed line marked with the asterisk indicates attachment to BP^1;

the unmarked dashed line indicates attachment to BP^2 or BP^3, respectively;

q1 is selected from the group consisting of 1, 2, 3, 4, 5, 6, 7 and 8;

q2 is selected from the group consisting of 1, 2, 3, 4, and 5;

q3 is selected from the group consisting of 1, 2, 3, 4, 5, 6, 7 and 8; and
q4 is selected from the group consisting of 1, 2 and 3.

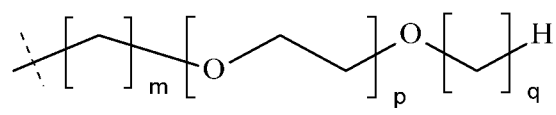
In certain embodiments q1 of formula (A-a) is selected from the group consisting of 4, 5, 6, 7, and 8. In certain embodiments q1 of formula (A-a) is selected from the group consisting of 5, 6 and 7. In certain embodiments q1 of formula (A-a) is 1. In certain embodiments q1 of formula (A-a) is 2. In certain embodiments q1 of formula (A-a) is 3. In certain embodiments q1 of formula (A-a) is 4. In certain embodiments q1 of formula (A-a) is 5. In certain embodiments q1 of formula (A-a) is 6. In certain embodiments q1 of formula (A-a) is 7. In certain embodiments q1 of formula (A-a) is 8.

In certain embodiments q2 of formula (A-a) is selected from the group consisting of 1, 2 and 3. In certain embodiments q2 of formula (A-a) is 1. In certain embodiments q2 of formula (A-a) is 2. In certain embodiments q2 of formula (A-a) is 3. In certain embodiments q2 of formula (A-a) is 4. In certain embodiments q2 of formula (A-a) is 5.

In certain embodiments q3 of formula (A-a) is selected from the group consisting of 2, 3, 4, and 5. In certain embodiments q3 of formula (A-a) is selected from the group consisting of 2, 3 and 4. In certain embodiments q3 of formula (A-a) is 1. In certain embodiments q3 of formula (A-a) is 2. In certain embodiments q3 of formula (A-a) is 3. In certain embodiments q3 of formula (A-a) is 4. In certain embodiments q3 of formula (A-a) is 5. In certain embodiments q3 of formula (A-a) is 6. In certain embodiments q3 of formula (A-a) is 7. In certain embodiments q3 of formula (A-a) is 8.

In certain embodiments q4 of formula (A-a) is 1. In certain embodiments q4 of formula (A-a) is 2. In certain embodiments q4 of formula (A-a) is 3.

In certain embodiments P^1, P^2, P^3 and P^4 of formula (A) are independently of each other of formula (A-b)



(A-b),

wherein
the dashed line indicates attachment to the remainder of -Z;

m is 0 or 1;

p is an integer ranging from 70 to 900; and

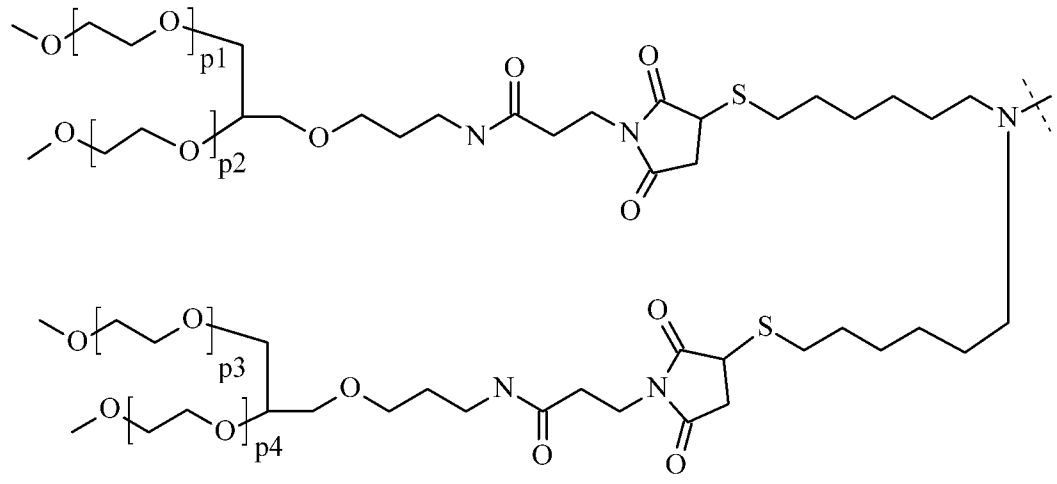
q is selected from the group consisting of 1, 2, 3, 4, 5, and 6.

In certain embodiments m of formula (A-b) is 0. In certain embodiments m of formula (A-b) is 1.

In certain embodiments p of formula (A-b) is an integer ranging from 115 to 680. In certain embodiments p of formula (A-b) is an integer ranging from 115 to 560. In certain embodiments p of formula (A-b) is an integer ranging from 185 to 450. In certain embodiments p of formula (A-b) is about 115. In certain embodiments p of formula (A-b) is about 160. In certain embodiments p of formula (A-b) is about 225. In certain embodiments p of formula (A-b) is about 270. In certain embodiments p of formula (A-b) is about 340. In certain embodiments p of formula (A-b) is about 450. In certain embodiments p of formula (A-b) is about 560.

In certain embodiments q of formula (A-b) is 1. In certain embodiments q of formula (A-b) is 2. In certain embodiments q of formula (A-b) is 3. In certain embodiments q of formula (A-b) is 4. In certain embodiments q of formula (A-b) is 5. In certain embodiments q of formula (A-b) is 6.

In certain embodiments -Z comprises a moiety of formula (A-c):



(A-c),

wherein

p1, p2, p3, p4 are independently of each other an integer ranging from 70 to 900.

In certain embodiments p1 of formula (A-c) is an integer ranging from 115 to 680. In certain embodiments p1 of formula (A-c) is an integer ranging from 115 to 560. In certain embodiments p1 of formula (A-c) is an integer ranging from 185 to 450. In certain embodiments p1 of formula (A-c) is an integer ranging from 220 to 240. In certain embodiments p1 of formula (A-c) is about 115. In certain embodiments p1 of formula (A-c) is about 160. In certain embodiments p1 of formula (A-c) is about 225. In certain embodiments p1 of formula (A-c) is about 270. In certain embodiments p1 of formula (A-c) is about 340. In certain embodiments p1 of formula (A-c) is about 450. In certain embodiments p1 of formula (A-c) is about 560.

In certain embodiments p2 of formula (A-c) is an integer ranging from 115 to 680. In certain embodiments p2 of formula (A-c) is an integer ranging from 115 to 560. In certain embodiments p2 of formula (A-c) is an integer ranging from 185 to 450. In certain embodiments p2 of formula (A-c) is an integer ranging from 220 to 240. In certain embodiments p2 of formula (A-c) is about 115. In certain embodiments p2 of formula (A-c) is about 160. In certain embodiments p2 of formula (A-c) is about 225. In certain embodiments p2 of formula (A-c) is about 270. In certain embodiments p2 of formula (A-c) is about 340. In certain embodiments p2 of formula (A-c) is about 450. In certain embodiments p2 of formula (A-c) is about 560.

In certain embodiments p3 of formula (A-c) is an integer ranging from 115 to 680. In certain embodiments p3 of formula (A-c) is an integer ranging from 115 to 560. In certain embodiments p3 of formula (A-c) is an integer ranging from 185 to 450. In certain embodiments p3 of formula (A-c) is an integer ranging from 220 to 240. In certain embodiments p3 of formula (A-c) is about 115. In certain embodiments p3 of formula (A-c) is about 160. In certain embodiments p3 of formula (A-c) is about 225. In certain embodiments p3 of formula (A-c) is about 270. In certain embodiments p3 of formula (A-c) is about 340. In certain embodiments p3 of formula (A-c) is about 450. In certain embodiments p3 of formula (A-c) is about 560.

In certain embodiments p4 of formula (A-c) is an integer ranging from 115 to 680. In certain embodiments p4 of formula (A-c) is an integer ranging from 115 to 560. In certain embodiments p4 of formula (A-c) is an integer ranging from 185 to 450. In certain embodiments p4 of formula (A-c) is an integer ranging from 220 to 240. In certain

embodiments p4 of formula (A-c) is about 115. In certain embodiments p4 of formula (A-c) is about 160. In certain embodiments p4 of formula (A-c) is about 225. In certain embodiments p4 of formula (A-c) is about 270. In certain embodiments p4 of formula (A-c) is about 340. In certain embodiments p4 of formula (A-c) is about 450. In certain embodiments p4 of formula (A-c) is about 560.

In certain embodiments p1, p2, p3 of formula (A-c) and p4 are identical. In certain embodiments p1, p2, p3 and p4 range from 220 to 240.

In one embodiment -Z is a moiety as disclosed in WO 2012/02047 A1, which is herewith incorporated by reference.

In another embodiment -Z is a moiety as disclosed in WO 2013/024048 A1, which is herewith incorporated by reference.

In certain embodiments -Z is water-insoluble. In certain embodiments -Z is a hydrogel.

In certain embodiments such hydrogel comprises a polymer selected from the group consisting of 2-methacryloyl-oxyethyl phosphoyl cholins, poly(acrylic acids), poly(acrylates), poly(acrylamides), poly(alkyloxy) polymers, poly(amides), poly(amidoamines), poly(amino acids), poly(anhydrides), poly(aspartamides), poly(butyric acids), poly(glycolic acids), polybutylene terephthalates, poly(caprolactones), poly(carbonates), poly(cyanoacrylates), poly(dimethylacrylamides), poly(esters), poly(ethylenes), poly(alkylene glycols), such as poly(ethylene glycols) and poly(propylene glycol), poly(ethylene oxides), poly(ethyl phosphates), poly(ethyloxazolines), poly(glycolic acids), poly(hydroxyethyl acrylates), poly(hydroxyethyl-oxazolines), poly(hydroxymethacrylates), poly(hydroxypropylmethacrylamides), poly(hydroxypropyl methacrylates), poly(hydroxypropyloxazolines), poly(iminocarbonates), poly(lactic acids), poly(lactic-co-glycolic acids), poly(methacrylamides), poly(methacrylates), poly(methyloxazolines), poly(organophosphazenes), poly(ortho esters), poly(oxazolines), poly(propylene glycols), poly(siloxanes), poly(urethanes), poly(vinyl alcohols), poly(vinyl amines), poly(vinylmethylethers), poly(vinylpyrrolidones), silicones, celluloses, carbomethyl celluloses, hydroxypropyl methylcelluloses, chitins, chitosans, dextrans, dextrins, gelatins, hyaluronic acids and derivatives, functionalized hyaluronic acids, mannans, pectins,

rhamnogalacturonans, starches, hydroxyalkyl starches, hydroxyethyl starches and other carbohydrate-based polymers, xylans, and copolymers thereof.

In certain embodiments -Z is a poly(alkylene glycol)-based or hyaluronic acid-based hydrogel.

In certain embodiments -Z is a poly(propylene glycol)-based hydrogel.

In certain embodiments -Z is a PEG-based hydrogel.

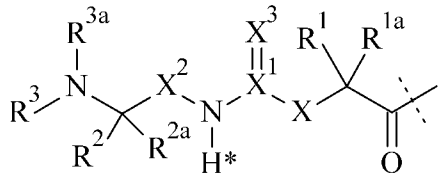
In certain embodiments -Z is a PEG-based hydrogel as disclosed in WO2011/012715A1 or WO2014/056926A1, which are herewith incorporated by reference.

In certain embodiments -Z is a hyaluronic acid-based hydrogel.

In certain embodiments -Z is a hyaluronic acid-based hydrogel as disclosed in WO2018/175788A1, which is herewith incorporated by reference.

A moiety $-L^1-$ is connected to a moiety M_{mod} via a reversible linkage. In other words, the moiety $-L^1-$ ensures that a moiety $-L^{1'}-L^2-Z$ is released from the conjugates of the present invention, wherein $-L^{1'}-$ refers to the moiety that remains of $-L^1-$ after cleavage of the reversible linkage between $-L^1-$ and M_{mod}.

In one embodiment $-L^1-$ has a structure as disclosed in WO 2009/095479 A2. Accordingly, in one embodiment the moiety $-L^1-$ is of formula (II):



(II)

,

wherein the dashed line indicates attachment to a nitrogen of M_{mod} by forming an amide bond;

-X- is $-C(R^4R^{4a})-$; $-N(R^4)-$; $-O-$; $-C(R^4R^{4a})-C(R^5R^{5a})-$; $-C(R^5R^{5a})-C(R^4R^{4a})-$; $-C(R^4R^{4a})-N(R^6)-$; $-N(R^6)-C(R^4R^{4a})-$; $-C(R^4R^{4a})-O-$; $-O-C(R^4R^{4a})-$; or $-C(R^7R^{7a})-$;

X^1 is C; or S(O);

$-X^2-$ is $-C(R^8R^{8a})-$; or $-C(R^8R^{8a})-C(R^9R^{9a})-$;

$=X^3$ is =O; =S; or =N-CN;

$-R^1$, $-R^{1a}$, $-R^2$, $-R^{2a}$, $-R^4$, $-R^{4a}$, $-R^5$, $-R^{5a}$, $-R^6$, $-R^8$, $-R^{8a}$, $-R^9$, $-R^{9a}$ are independently selected from the group consisting of -H; and C_{1-6} alkyl;

$-R^3$, $-R^{3a}$ are independently selected from the group consisting of -H; and C_{1-6} alkyl, provided that in case one of $-R^3$, $-R^{3a}$ or both are other than -H they are connected to N to which they are attached through an SP^3-hybridized carbon atom;

$-R^7$ is $-N(R^{10}R^{10a})$; or $-NR^{10}-(C=O)-R^{11}$;

$-R^{7a}$, $-R^{10}$, $-R^{10a}$, $-R^{11}$ are independently of each other -H; or C_{1-6} alkyl;

optionally, one or more of the pairs $-R^{1a}/-R^{4a}$, $-R^{1a}/-R^{5a}$, $-R^{1a}/-R^{7a}$, $-R^{4a}/-R^{5a}$, $-R^{8a}/-R^{9a}$ form a chemical bond;

optionally, one or more of the pairs $-R^1/-R^{1a}$, $-R^2/-R^{2a}$, $-R^4/-R^{4a}$, $-R^5/-R^{5a}$, $-R^8/-R^{8a}$, $-R^9/-R^{9a}$ are joined together with the atom to which they are attached to form a C_{3-10} cycloalkyl; or 3- to 10-membered heterocyclyl;

optionally, one or more of the pairs $-R^1/-R^4$, $-R^1/-R^5$, $-R^1/-R^6$, $-R^1/-R^{7a}$, $-R^4/-R^5$, $-R^4/-R^6$, $-R^8/-R^9$, $-R^2/-R^3$ are joined together with the atoms to which they are attached to form a ring A;

optionally, R^3/R^{3a} are joined together with the nitrogen atom to which they are attached to form a 3- to 10-membered heterocycle;

A is selected from the group consisting of phenyl; naphthyl; indenyl; indanyl; tetralinyl; C_{3-10} cycloalkyl; 3- to 10-membered heterocyclyl; and 8- to 11-membered heterobicyclyl; and

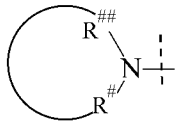
wherein $-L^1-$ is substituted with at least one $-L^2-Z$ and wherein $-L^1-$ is optionally further substituted, provided that the hydrogen marked with the asterisk in formula (II) is not replaced by $-L^2-Z$ or a substituent.

Preferably $-L^1-$ of formula (II) is substituted with one moiety $-L^2-Z$..

In one embodiment $-L^1-$ of formula (II) is not further substituted.

It is understood that if $-R^3/-R^{3a}$ of formula (II) are joined together with the nitrogen atom to which they are attached to form a 3- to 10-membered heterocycle, only such 3- to 10-

membered heterocycles may be formed in which the atoms directly attached to the nitrogen are SP^3-hybridized carbon atoms. In other words, such 3- to 10-membered heterocycle formed by $-R^3/-R^{3a}$ together with the nitrogen atom to which they are attached has the following structure:



,

wherein

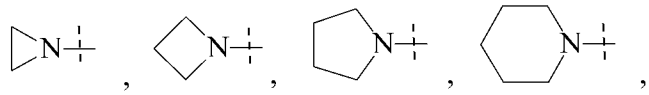
the dashed line indicates attachment to the rest of $-L^1-$;

the ring comprises 3 to 10 atoms comprising at least one nitrogen; and

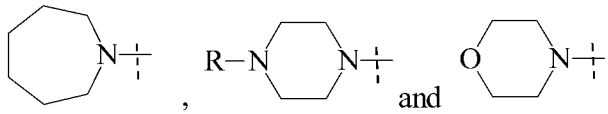
$R^{\#}$ and $R^{\#\#}$ represent an SP^3-hydridized carbon atom.

It is also understood that the 3- to 10-membered heterocycle may be further substituted.

Exemplary embodiments of suitable 3- to 10-membered heterocycles formed by $-R^3/-R^{3a}$ of formula (II) together with the nitrogen atom to which they are attached are the following:



,



and

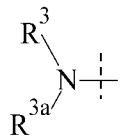
,

wherein

dashed lines indicate attachment to the rest of the molecule; and

-R is selected from the group consisting of -H and C_{1-6} alkyl.

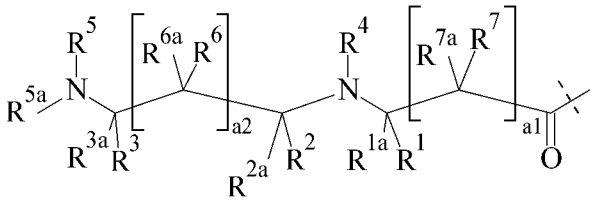
$-L^1-$ of formula (II) may optionally be further substituted. In general, any substituent may be used as far as the cleavage principle is not affected, i.e. the hydrogen marked with the asterisk in formula (II) is not replaced and the nitrogen of the moiety



of formula (II) remains part of a primary, secondary or tertiary amine, i.e. $-R^3$ and $-R^{3a}$ are independently of each other -H or are connected to –N< through an SP^3-hybridized carbon atom.

In one embodiment $-R^1$ or $-R^{1a}$ of formula (II) is substituted with $-L^2$-Z or $-L^2$-Z'. In another embodiment $-R^2$ or $-R^{2a}$ of formula (II) is substituted with $-L^2$-Z or $-L^2$-Z'. In another embodiment $-R^3$ or $-R^{3a}$ of formula (II) is substituted with $-L^2$-Z or $-L^2$-Z'. In another embodiment $-R^4$ of formula (II) is substituted with $-L^2$-Z or $-L^2$-Z'. In another embodiment $-R^5$ or $-R^{5a}$ of formula (II) is substituted with $-L^2$-Z or $-L^2$-Z'. In another embodiment $-R^6$ of formula (II) is substituted with $-L^2$-Z or $-L^2$-Z'. In another embodiment $-R^7$ or $-R^{7a}$ of formula (II) is substituted with $-L^2$-Z or $-L^2$-Z'. In another embodiment $-R^8$ or $-R^{8a}$ of formula (II) is substituted with $-L^2$-Z or $-L^2$-Z'. In another embodiment $-R^9$ or $-R^{9a}$ of formula (II) is substituted with $-L^2$-Z or $-L^2$-Z'.

In another embodiment $-L^1$- has a structure as disclosed in WO2016/020373A1. Accordingly, in another embodiment the moiety $-L^1$- is of formula (III):



(III),

wherein

the dashed line indicates attachment to a primary or secondary amine or hydroxyl of M_{mod} by forming an amide or ester linkage, respectively;

$-R^1$, $-R^{1a}$, $-R^2$, $-R^{2a}$, $-R^3$ and $-R^{3a}$ are independently of each other selected from the group consisting of -H, $-C(R^8R^{8a}R^{8b})$, $-C(=O)R^8$, -C≡N, $-C(=NR^8)R^{8a}$, $-CR^8(=CR^{8a}R^{8b})$, $-C{\equiv}CR^8$ and -T;

$-R^4$, $-R^5$ and $-R^{5a}$ are independently of each other selected from the group consisting of -H, $-C(R^9R^{9a}R^{9b})$ and -T;

a1 and a2 are independently of each other 0 or 1;

each $-R^6$, $-R^{6a}$, $-R^7$, $-R^{7a}$, $-R^8$, $-R^{8a}$, $-R^{8b}$, $-R^9$, $-R^{9a}$, $-R^{9b}$ are independently of each other selected from the group consisting of -H, halogen, -CN, $-COOR^{10}$, $-OR^{10}$, $-C(O)R^{10}$, $-C(O)N(R^{10}R^{10a})$, $-S(O)_2N(R^{10}R^{10a})$, $-S(O)N(R^{10}R^{10a})$, $-S(O)_2R^{10}$, $-S(O)R^{10}$, $-N(R^{10})S(O)_2N(R^{10a}R^{10b})$, $-SR^{10}$, $-N(R^{10}R^{10a})$, $-NO_2$, $-OC(O)R^{10}$,

$-N(R^{10})C(O)R^{10a}$, $-N(R^{10})S(O)_2R^{10a}$, $-N(R^{10})S(O)R^{10a}$, $-N(R^{10})C(O)OR^{10a}$, $-N(R^{10})C(O)N(R^{10a}R^{10b})$, $-OC(O)N(R^{10}R^{10a})$, -T, C_{1-20} alkyl, C_{2-20} alkenyl, and C_{2-20} alkynyl; wherein -T, C_{1-20} alkyl, C_{2-20} alkenyl, and C_{2-20} alkynyl are optionally substituted with one or more $-R^{11}$, which are the same or different and wherein C_{1-20} alkyl, C_{2-20} alkenyl, and C_{2-20} alkynyl are optionally interrupted by one or more groups selected from the group consisting of -T-, -C(O)O-, -O-, -C(O)-, $-C(O)N(R^{12})-$, $-S(O)_2N(R^{12})-$, $-S(O)N(R^{12})-$, $-S(O)_2-$, -S(O)-, $-N(R^{12})S(O)_2N(R^{12a})-$, -S-, $-N(R^{12})-$, $-OC(OR^{12})(R^{12a})-$, $-N(R^{12})C(O)N(R^{12a})-$, and $-OC(O)N(R^{12})-$;

each $-R^{10}$, $-R^{10a}$, $-R^{10b}$ is independently selected from the group consisting of -H, -T, C_{1-20} alkyl, C_{2-20} alkenyl, and C_{2-20} alkynyl; wherein -T, C_{1-20} alkyl, C_{2-20} alkenyl, and C_{2-20} alkynyl are optionally substituted with one or more $-R^{11}$, which are the same or different and wherein C_{1-20} alkyl, C_{2-20} alkenyl, and C_{2-20} alkynyl are optionally interrupted by one or more groups selected from the group consisting of -T-, -C(O)O-, -O-, -C(O)-, $-C(O)N(R^{12})-$, $-S(O)_2N(R^{12})-$, $-S(O)N(R^{12})-$, $-S(O)_2-$, -S(O)-, $-N(R^{12})S(O)_2N(R^{12a})-$, -S-, $-N(R^{12})-$, $-OC(OR^{12})(R^{12a})-$, $-N(R^{12})C(O)N(R^{12a})-$, and $-OC(O)N(R^{12})-$;

each T is independently of each other selected from the group consisting of phenyl, naphthyl, indenyl, indanyl, tetralinyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl, and 8- to 11-membered heterobicyclyl; wherein each T is independently optionally substituted with one or more $-R^{11}$, which are the same or different;

each $-R^{11}$ is independently of each other selected from halogen, -CN, oxo (=O), $-COOR^{13}$, $-OR^{13}$, $-C(O)R^{13}$, $-C(O)N(R^{13}R^{13a})$, $-S(O)_2N(R^{13}R^{13a})$, $-S(O)N(R^{13}R^{13a})$, $-S(O)_2R^{13}$, $-S(O)R^{13}$, $-N(R^{13})S(O)_2N(R^{13a}R^{13b})$, $-SR^{13}$, $-N(R^{13}R^{13a})$, $-NO_2$, $-OC(O)R^{13}$, $-N(R^{13})C(O)R^{13a}$, $-N(R^{13})S(O)_2R^{13a}$, $-N(R^{13})S(O)R^{13a}$, $-N(R^{13})C(O)OR^{13a}$, $-N(R^{13})C(O)N(R^{13a}R^{13b})$, $-OC(O)N(R^{13}R^{13a})$, and C_{1-6} alkyl; wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

each $-R^{12}$, $-R^{12a}$, $-R^{13}$, $-R^{13a}$, $-R^{13b}$ is independently selected from the group consisting of -H, and C_{1-6} alkyl; wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

optionally, one or more of the pairs -R^1/-R^{1a}, -R^2/-R^{2a}, -R^3/-R^{3a}, -R^6/-R^{6a}, -R^7/-R^{7a} are joined together with the atom to which they are attached to form a C_{3-10} cycloalkyl or a 3- to 10-membered heterocyclyl;

optionally, one or more of the pairs -R^1/-R^2, -R^1/-R^3, -R^1/-R^4, -R^1/-R^5, -R^1/-R^6, -R^1/-R^7, -R^2/-R^3, -R^2/-R^4, -R^2/-R^5, -R^2/-R^6, -R^2/-R^7, -R^3/-R^4, -R^3/-R^5, -R^3/-R^6, -R^3/-R^7, -R^4/-R^5, -R^4/-R^6, -R^4/-R^7, -R^5/-R^6, -R^5/-R^7, -R^6/-R^7 are joint together with the atoms to which they are attached to form a ring A;

A is selected from the group consisting of phenyl; naphthyl; indenyl; indanyl; tetralinyl; C_{3-10} cycloalkyl; 3- to 10-membered heterocyclyl; and 8- to 11-membered heterobicyclyl;

wherein -L^1- is substituted with at least one -L^2-Z and wherein -L^1- is optionally further substituted.

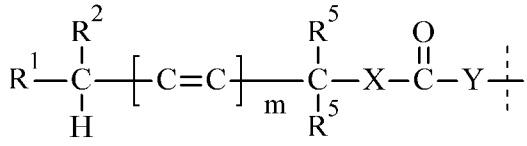
The optional further substituents of -L^1- of formula (III) are preferably as described above.

Preferably -L^1- of formula (III) is substituted with one moiety -L^2-Z.

In one embodiment -L^1- of formula (III) is not further substituted.

In another embodiment -L^1- has a structure as disclosed in EP1536334B1, WO2009/009712A1, WO2008/034122A1, WO2009/143412A2, WO2011/082368A2, and US8618124B2, which are herewith incorporated by reference.

In another embodiment -L^1- has a structure as disclosed in US8946405B2 and US8754190B2, which are herewith incorporated by reference. Accordingly, in another embodiment -L^1- is of formula (IV):



(IV),

wherein

the dashed line indicates attachment to M_{mod} through a functional group of M_{mod} selected from the group consisting of -OH, -SH and -NH_2;

m is 0 or 1;

at least one or both of $-R^1$ and $-R^2$ is/are independently of each other selected from the group consisting of -CN, $-NO_2$, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkenyl, optionally substituted alkynyl, $-C(O)R^3$, $-S(O)R^3$, $-S(O)_2R^3$, and $-SR^4$,

one and only one of $-R^1$ and $-R^2$ is selected from the group consisting of -H, optionally substituted alkyl, optionally substituted arylalkyl, and optionally substituted heteroarylalkyl;

$-R^3$ is selected from the group consisting of -H, optionally substituted alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-OR^9$ and $-N(R^9)_2$;

$-R^4$ is selected from the group consisting of optionally substituted alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, and optionally substituted heteroarylalkyl;

each $-R^5$ is independently selected from the group consisting of -H, optionally substituted alkyl, optionally substituted alkenylalkyl, optionally substituted alkynylalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl;

$-R^9$ is selected from the group consisting of -H and optionally substituted alkyl;

-Y- is absent and –X- is -O- or -S-; or

-Y- is $-N(Q)CH_2-$ and -X- is -O-;

Q is selected from the group consisting of optionally substituted alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl;

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

optionally, both $-R^9$ together with the nitrogen to which they are attached form a heterocyclic ring;

wherein $-L^1-$ is substituted with $-L^2-Z$ and wherein $-L^1-$ is optionally further substituted.

Only in the context of formula (IV) the terms used have the following meaning:

The term “alkyl” as used herein includes linear, branched or cyclic saturated hydrocarbon groups of 1 to 8 carbons, or in some embodiments 1 to 6 or 1 to 4 carbon atoms.

The term “alkoxy” includes alkyl groups bonded to oxygen, including methoxy, ethoxy, isopropoxy, cyclopropoxy, cyclobutoxy, and similar.

The term “alkenyl” includes non-aromatic unsaturated hydrocarbons with carbon-carbon double bonds.

The term “alkynyl” includes non-aromatic unsaturated hydrocarbons with carbon-carbon triple bonds.

The term “aryl” includes aromatic hydrocarbon groups of 6 to 18 carbons, preferably 6 to 10 carbons, including groups such as phenyl, naphthyl, and anthracenyl. The term “heteroaryl” includes aromatic rings comprising 3 to 15 carbons containing at least one N, O or S atom, preferably 3 to 7 carbons containing at least one N, O or S atom, including groups such as pyrrolyl, pyridyl, pyrimidinyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, quinolyl, indolyl, indenyl, and similar.

In some instance, alkenyl, alkynyl, aryl or heteroaryl moieties may be coupled to the remainder of the molecule through an alkylene linkage. Under those circumstances, the substituent will be referred to as alkenylalkyl, alkynylalkyl, arylalkyl or heteroarylalkyl, indicating that an alkylene moiety is between the alkenyl, alkynyl, aryl or heteroaryl moiety and the molecule to which the alkenyl, alkynyl, aryl or heteroaryl is coupled.

The term “halogen” includes bromo, fluoro, chloro and iodo.

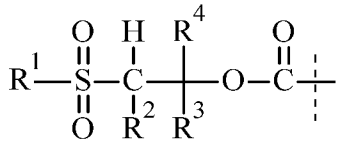
The term “heterocyclic ring” refers to a 4 to 8 membered aromatic or non-aromatic ring comprising 3 to 7 carbon atoms and at least one N, O, or S atom. Examples are piperidinyl, piperazinyl, tetrahydropyranyl, pyrrolidine, and tetrahydrofuranyl, as well as the exemplary groups provided for the term “heteroaryl” above.

When a ring system is optionally substituted, suitable substituents are selected from the group consisting of alkyl, alkenyl, alkynyl, or an additional ring, each optionally further substituted. Optional substituents on any group, including the above, include halo, nitro, cyano, -OR, -SR, -NR_2, -OCOR, -NRCOR, -COOR, -$CONR_2$, -SOR, -SO_2R, -$SONR_2$, -SO_2N

R_2, wherein each R is independently alkyl, alkenyl, alkynyl, aryl or heteroaryl, or two R groups taken together with the atoms to which they are attached form a ring.

Preferably -L^1- of formula (IV) is substituted with one moiety -L^2-Z.

In another embodiment -L^1- has a structure as disclosed in WO2013/036857A1, which is herewith incorporated by reference. Accordingly, in another embodiment -L^1- is of formula (V):



(V),

wherein

the dashed line indicates attachment to M_{mod} through an amine functional group of M_{mod};

-R^1 is selected from the group consisting of optionally substituted C_1-C_6 linear, branched, or cyclic alkyl; optionally substituted aryl; optionally substituted heteroaryl; alkoxy; and -NR^5_2;

-R^2 is selected from the group consisting of -H; optionally substituted C_1-C_6 alkyl; optionally substituted aryl; and optionally substituted heteroaryl;

-R^3 is selected from the group consisting of -H; optionally substituted C_1-C_6 alkyl; optionally substituted aryl; and optionally substituted heteroaryl;

-R^4 is selected from the group consisting of -H; optionally substituted C_1-C_6 alkyl; optionally substituted aryl; and optionally substituted heteroaryl;

each -R^5 is independently of each other selected from the group consisting of -H; optionally substituted C_1-C_6 alkyl; optionally substituted aryl; and optionally substituted heteroaryl; or when taken together two -R^5 can be cycloalkyl or cycloheteroalkyl;

wherein -L^1- is substituted with -L^2-Z and wherein -L^1- is optionally further substituted.

Only in the context of formula (V) the terms used have the following meaning:

"Alkyl", "alkenyl", and "alkynyl" include linear, branched or cyclic hydrocarbon groups of 1-8 carbons or 1-6 carbons or 1-4 carbons wherein alkyl is a saturated hydrocarbon, alkenyl

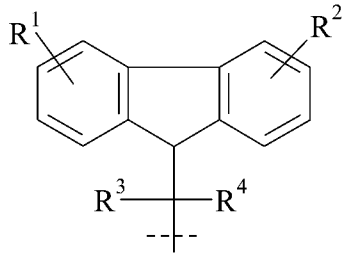
includes one or more carbon-carbon double bonds and alkynyl includes one or more carbon-carbon triple bonds. Unless otherwise specified these contain 1-6 C.

"Aryl" includes aromatic hydrocarbon groups of 6-18 carbons, preferably 6-10 carbons, including groups such as phenyl, naphthyl, and anthracene "Heteroaryl" includes aromatic rings comprising 3-15 carbons containing at least one N, O or S atom, preferably 3-7 carbons containing at least one N, O or S atom, including groups such as pyrrolyl, pyridyl, pyrimidinyl, imidazolyl, oxazolyl, isoxazolyl, thiszolyl, isothiazolyl, quinolyl, indolyl, indenyl, and similar.

The term "substituted" means an alkyl, alkenyl, alkynyl, aryl, or heteroaryl group comprising one or more substituent groups in place of one or more hydrogen atoms. Substituents may generally be selected from halogen including F, Cl, Br, and I; lower alkyl including linear, branched, and cyclic; lower haloalkyl including fluoroalkyl, chloroalkyl, bromoalkyl, and iodoalkyl; OH; lower alkoxy including linear, branched, and cyclic; SH; lower alkylthio including linear, branched and cyclic; amino, alkylamino, dialkylamino, silyl including alkylsilyl, alkoxysilyl, and arylsilyl; nitro; cyano; carbonyl; carboxylic acid, carboxylic ester, carboxylic amide, aminocarbonyl; aminoacyl; carbamate; urea; thiocarbamate; thiourea; ketne; sulfone; sulfonamide; aryl including phenyl, naphthyl, and anthracenyl; heteroaryl including 5-member heteroaryls including as pyrrole, imidazole, furan, thiophene, oxazole, thiazole, isoxazole, isothiazole, thiadiazole, triazole, oxadiazole, and tetrazole, 6-member heteroaryls including pyridine, pyrimidine, pyrazine, and fused heteroaryls including benzofuran, benzothiophene, benzoxazole, benzimidazole, indole, benzothiazole, benzisoxazole, and benzisothiazole.

Preferably -L^1- of formula (V) is substituted with one moiety -L^2-Z.

In another embodiment -L^1- has a structure as disclosed in US7585837B2, which is herewith incorporated by reference. Accordingly, in another embodiment -L^1- is of formula (VI):



(VI),

wherein

the dashed line indicates attachment to M_{mod} through an amine functional group of M_{mod};

R^1 and R^2 are independently selected from the group consisting of hydrogen, alkyl, alkoxy, alkoxyalkyl, aryl, alkaryl, aralkyl, halogen, nitro, $-SO_3H$, $-SO_2NHR^5$, amino, ammonium, carboxyl, PO_3H_2, and OPO_3H_2;

R^3, R^4, and R^5 are independently selected from the group consisting of hydrogen, alkyl, and aryl;

wherein $-L^1-$ is substituted with $-L^2-Z$ o and wherein $-L^1-$ is optionally further substituted.

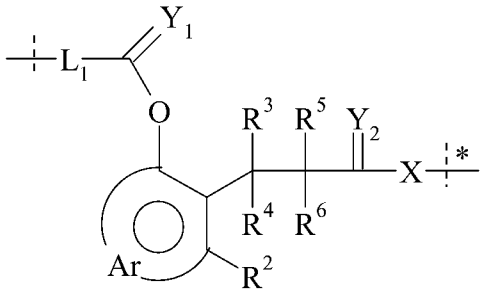
Suitable substituents for formulas (VI) are alkyl (such as C_{1-6} alkyl), alkenyl (such as C_{2-6} alkenyl), alkynyl (such as C_{2-6} alkynyl), aryl (such as phenyl), heteroalkyl, heteroalkenyl, heteroalkynyl, heteroaryl (such as aromatic 4 to 7 membered heterocycle) or halogen moieties.

Only in the context of formula (VI) the terms used have the following meaning:

The terms “alkyl”, “alkoxy”, “alkoxyalkyl”, “aryl”, “alkaryl” and “aralkyl” mean alkyl radicals of 1-8, preferably 1-4 carbon atoms, e.g. methyl, ethyl, propyl, isopropyl and butyl, and aryl radicals of 6-10 carbon atoms, e.g. phenyl and naphthyl. The term “halogen” includes bromo, fluoro, chloro and iodo.

Preferably $-L^1-$ of formula (VI) is substituted with one moiety $-L^2-Z$.

In another embodiment $-L^1-$ has a structure as disclosed in WO2002/089789A1, which is herewith incorporated by reference. Accordingly, in another embodiment $-L^1-$ is of formula (VII):



(VII),

wherein

the dashed line indicates attachment to M_{mod} through an amine functional group of M_{mod};

L_1 is a bifunctional linking group,

Y_1 and Y_2 are independently O, S or NR^7;

R^2, R^3, R^4, R^5, R^6 and R^7 are independently selected from the group consisting of hydrogen, C_{1-6} alkyls, C_{3-12} branched alkyls, C_{3-8} cycloalkyls, C_{1-6} substituted alkyls, C_{3-8} substituted cycloalkyls, aryls, substituted aryls, aralkyls, C_{1-6} heteroalkyls, substituted C_{1-6} heteroalkyls, C_{1-6} alkoxy, phenoxy, and C_{1-6} heteroalkoxy;

Ar is a moiety which when included in formula (VII) forms a multisubstituted aromatic hydrocarbon or a multi-substituted heterocyclic group;

X is a chemical bond or a moiety that is actively transported into a target cell, a hydrophobic moiety, or a combination thereof,

y is 0 or 1;

wherein $-L^1-$ is substituted with $-L^2-Z$ and wherein $-L^1-$ is optionally further substituted.

Only in the context of formula (VII) the terms used have the following meaning:

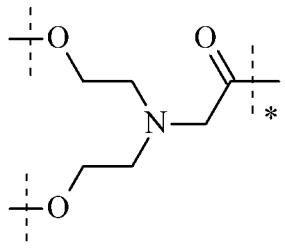
The term “alkyl” shall be understood to include, e.g. straight, branched, substituted C_{1-12} alkyls, including alkoxy, C_{3-8} cycloalkyls or substituted cycloalkyls, etc.

The term “substituted” shall be understood to include adding or replacing one or more atoms contained within a functional group or compounds with one or more different atoms.

Substituted alkyls include carboxyalkyls, aminoalkyls, dialkylaminos, hydroxyalkyls and mercaptoalkyls; substtued cycloalkyls include moieties such as 4-chlorocyclohexyl; aryls include moieties such as napthyl; substituted aryls include moieties such as 3-bromo-phenyl; aralkyls include moieties such as toluyl; heteroalkyls include moieties such as ethylthiophene; substituted heteroalkyls include moieties such as 3-methoxythiophone; alkoxy includes moieities such as methoxy; and phenoxy includes moieties such as 3-nitrophenoxy. Halo- shall be understood to include fluoro, chloro, iodo and bromo.

Preferably $-L^1-$ of formula (VII) is substituted with one moiety $-L^2-Z$.

In another embodiment -L^1- comprises a substructure of formula (VIII)



(VIII),

wherein

the dashed line marked with the asterisk indicates attachment to a nitrogen of M_{mod} by forming an amide bond;

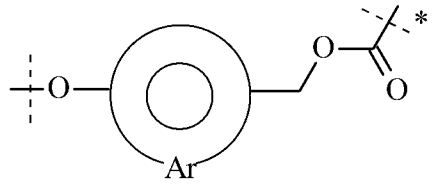
the unmarked dashed lines indicate attachment to the remainder of -L^1-; and

wherein -L^1- is substituted with -L^2-Z and wherein -L^1- is optionally further substituted.

Preferably -L^1- of formula (VIII) is substituted with one moiety -L^2-Z.

In one embodiment -L^1- of formula (VIII) is not further substituted.

In another embodiment -L^1- comprises a substructure of formula (IX)



(IX),

wherein

the dashed line marked with the asterisk indicates attachment to a nitrogen of M_{mod} by forming a carbamate bond;

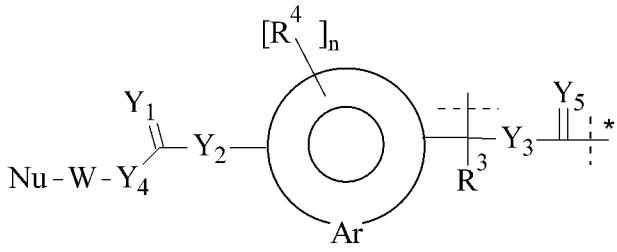
the unmarked dashed lines indicate attachment to the remainder of -L^1-; and

wherein -L^1- is substituted with -L^2-Z and wherein -L^1- is optionally further substituted.

Preferably -L^1- of formula (IX) is substituted with one moiety -L^2-Z.

In one embodiment -L^1- of formula (IX) is not further substituted.

In one embodiment -L^1- of formula (IX) is of formula (IX-a):



(IX-a),

wherein

the dashed line marked with the asterisk indicates attachment to a nitrogen of M_{mod} and the unmarked dashed line indicates attachment to -L^2-Z;

n is 0, 1, 2, 3, or 4;

=Y_1, is selected from the group consisting of =O and =S;

-Y_2- is selected from the group consisting of -O- and -S-;

-Y_3- is selected from the group consisting of -O- and -S-;

-Y_4- is selected from the group consisting of -O-, -NR^5- and -$C(R^6R^{6a})$-;

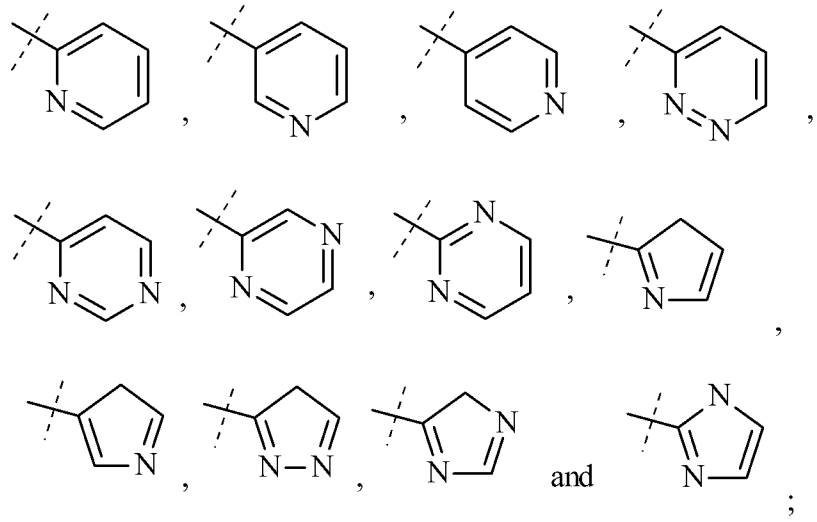
=Y_5 is selected from the group consisting of =O and =S;

-R^3, -R^5, -R^6, -R^{6a} are independently of each other selected from the group consisting of -H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, 2-methylbutyl, 2,2-dimethylpropyl, n-hexyl, 2-methylpentyl, 3-methylpentyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl and 3,3-dimethylpropyl;

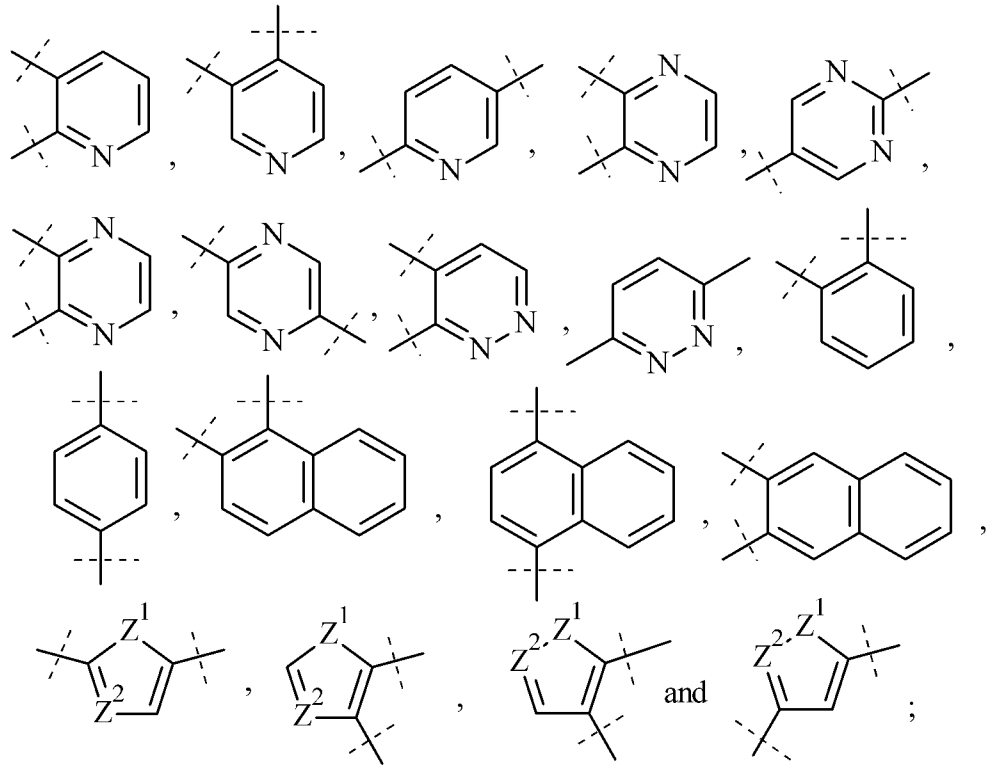
-R^4 is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, 2-methylbutyl, 2,2-dimethylpropyl, n-hexyl, 2-methylpentyl, 3-methylpentyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl and 3,3-dimethylpropyl;

-W- is selected from the group consisting of C_{1-20} alkyl optionally interrupted by one or more groups selected from the group consisting of C_{3-10} cycloalkyl, 8- to 30-membered carbopolycyclyl, 3- to 10-membered heterocyclyl, -C(O)-, -C(O)$N(R^7)$-, -O-, -S- and -$N(R^7)$-;

-Nu is a nucleophile selected from the group consisting of -$N(R^7R^{7a})$, -$N(R^7OH)$, -$N(R^7)$-$N(R^{7a}R^{7b})$, -$S(R^7)$,-COOH,



-Ar- is selected from the group consisting of



wherein

dashed lines indicate attachment to the remainder of -L^1-,

-Z^1- is selected from the group consisting of -O-, -S- and -N(R^7)-, and

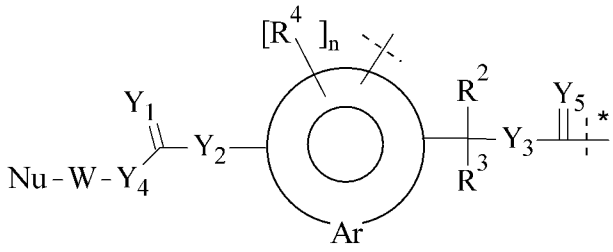
-Z^2- is -N(R^7)-; and

-R^7, -R^{7a}, -R^{7b} are independently of each other selected from the group consisting of -H, C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl;

wherein -L^1- is optionally further substituted.

In one embodiment -L^1- of formula (IX-a) is not further substituted.

In another embodiment -L^1- of formula (IX) is of formula (IX-b):



(IX-b),

wherein

the dashed line marked with the asterisk indicates attachment to a nitrogen of M_{mod} and the unmarked dashed line indicates attachment to -L^2-Z;

n is 0, 1, 2, 3, or 4;

=Y_1, is selected from the group consisting of =O and =S;

-Y_2- is selected from the group consisting of -O- and -S-;

-Y_3- is selected from the group consisting of -O- and -S-;

-Y_4- is selected from the group consisting of -O-, -NR^5- and -$C(R^6R^{6a})$-;

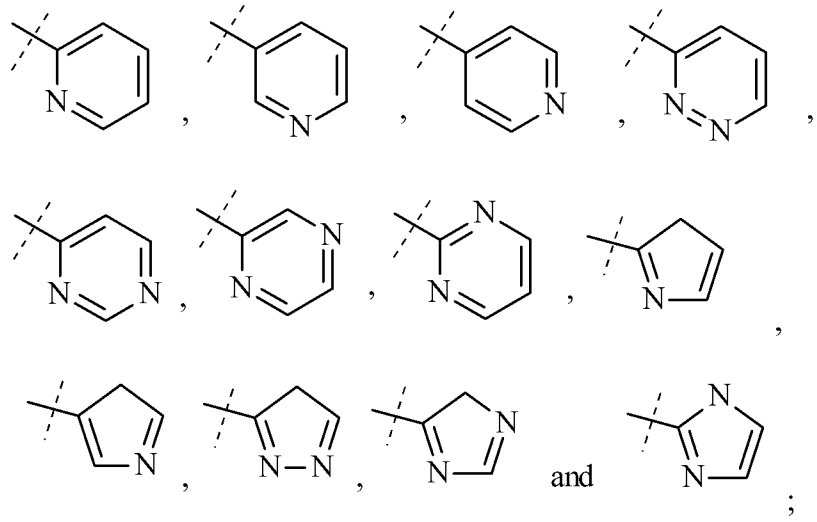
=Y_5 is selected from the group consisting of =O and =S;

-R^2, -R^3, -R^5, -R^6, -R^{6a} are independently of each other selected from the group consisting of -H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, 2-methylbutyl, 2,2-dimethylpropyl, n-hexyl, 2-methylpentyl, 3-methylpentyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl and 3,3-dimethylpropyl;

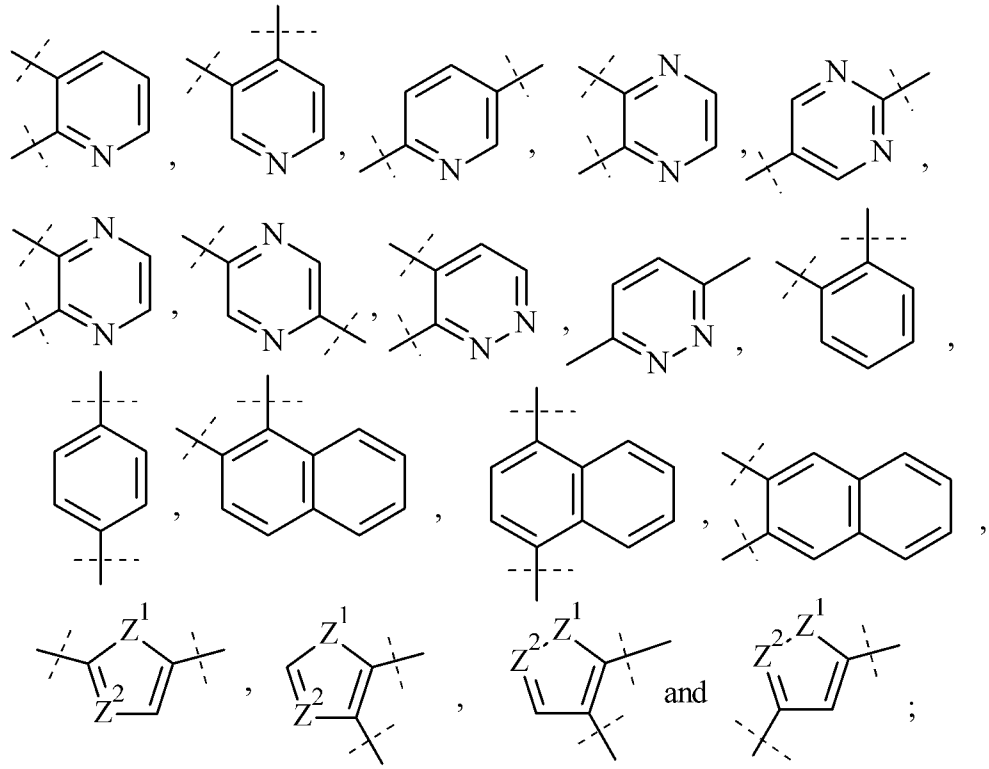
-R^4 is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, 2-methylbutyl, 2,2-dimethylpropyl, n-hexyl, 2-methylpentyl, 3-methylpentyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl and 3,3-dimethylpropyl;

-W- is selected from the group consisting of C_{1-20} alkyl optionally interrupted by one or more groups selected from the group consisting of C_{3-10} cycloalkyl, 8- to 30-membered carbopolycyclyl, 3- to 10-membered heterocyclyl, -C(O)-, -C(O)$N(R^7)$-, -O-, -S- and -$N(R^7)$-;

-Nu is a nucleophile selected from the group consisting of -$N(R^7R^{7a})$, -$N(R^7OH)$, -$N(R^7)$-$N(R^{7a}R^{7b})$, -$S(R^7)$,-COOH,



-Ar- is selected from the group consisting of



wherein

dashed lines indicate attachment to the remainder of -L^1-,

-Z^1- is selected from the group consisting of -O-, -S- and -N(R^7)-, and

-Z^2- is -N(R^7)-; and

-R^7, -R^{7a}, -R^{7b} are independently of each other selected from the group consisting of -H, C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl;

wherein -L^1- is optionally further substituted.

In one embodiment -L^1- of formula (IX-b) is not further substituted.

In certain embodiments $=Y^1$ of formula (IX-a) and (IX-b) is =O.

In certain embodiments $-Y^2-$ of formula (IX-a) and (IX-b) is -O-.

In certain embodiments $-Y^3-$ of formula (IX-a) and (IX-b) is -O-.

In certain embodiments $-Y^4-$ of formula (IX-a) and (IX-b) is $-NR^5-$.

In certain embodiments $=Y^5$ of formula (IX-a) and (IX-b) is =O.

In certain embodiments n of formula (IX-a) and (IX-b) is 0 or 1. In certain embodiments n of formula (IX-a) and (IX-b) is 0. In certain embodiments n of formula (IX-a) and (IX-b) is 1.

In certain embodiments $-R^2$ of formula (IX-b) is selected from the group consisting of -H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl. In certain embodiments $-R^2$ of formula (IX-b) is selected from the group consisting of -H, methyl, ethyl, n-propyl and isopropyl. In certain embodiments $-R^2$ of formula (IX-b) is selected from -H, methyl and ethyl. In certain embodiments $-R^2$ of formula (IX-b) is -H.

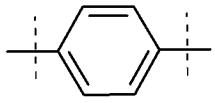
In certain embodiments $-R^3$ of formula (IX-a) and (IX-b) is selected from the group consisting of -H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl. In certain embodiments $-R^3$ of formula (IX-a) and (IX-b) is selected from the group consisting of -H, methyl, ethyl, n-propyl and isopropyl. In certain embodiments $-R^3$ of formula (IX-a) and (IX-b) is selected from -H, methyl and ethyl. In certain embodiments $-R^3$ of formula (IX-a) and (IX-b) is -H.

In a preferred embodiment, each $-R^4$ of formula (IX-a) and (IX-b) is independently selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl. In certain embodiments $-R^4$ of formula (IX-a) and (IX-b) is selected from the group consisting of methyl, ethyl, n-propyl and isopropyl. In certain embodiments $-R^4$ of formula (IX-a) and (IX-b) is selected from methyl and ethyl.

In certain embodiments -R^5 of formula (IX-a) and (IX-b) is selected from the group consisting of -H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl. In certain embodiments -R^5 of formula (IX-a) and (IX-b) is selected from the group consisting of -H, methyl, ethyl, n-propyl and isopropyl. In certain embodiments -R^5 of formula (IX-a) and (IX-b) is selected from methyl and ethyl. In certain embodiments -R^5 of formula (IX-a) and (IX-b) is methyl.

In certain embodiments -R^6 and -R^{6a} of formula (IX-a) and (IX-b) are independently selected from the group consisting of -H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl. In certain embodiments -R^6 and -R^{6a} of formula (IX-a) and (IX-b) are independently selected from the group consisting of -H, methyl, ethyl, n-propyl and isopropyl. In certain embodiments -R^6 and -R^{6a} of formula (IX-a) and (IX-b) are independently selected from -H, methyl and ethyl. In certain embodiments -R^6 and -R^{6a} of formula (IX-a) and (IX-b) are both -H.

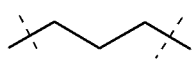
In certain embodiments Ar of formula (IX-a) and (IX-b) is phenyl. In certain embodiments Ar of formula (IX-a) and (IX-b) is



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wherein the dashed lines indicate attachment to the remainder of the moiety of formula (IX-a) and (IX-b).

In certain embodiments W of formula (IX-a) and (IX-b) is C_{1-20} alkyl, optionally interrupted with C_{3-10} cycloalkyl, -C(O)-, -C(O)N(R^7)-, -O-, -S- and -N(R^7)-. In certain embodiments W of formula (IX-a) and (IX-b) is C_{1-10} alkyl, optionally interrupted with C_{3-10} cycloalkyl, -C(O)-, -C(O)N(R^7)-, -O-, -S- and -N(R^7)-. In certain embodiments W of formula (IX-a) and (IX-b) is C_{1-6} alkyl, optionally interrupted with C_{3-10} cycloalkyl, -C(O)-, -C(O)N(R^7)-, -O-, -S- and -N(R^7)-. In certain embodiments W of formula (IX-a) and (IX-b) is



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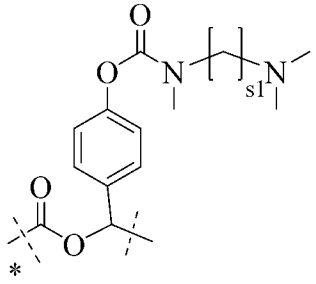
wherein

the dashed lines indicate attachment to the remainder of the moiety of formula (IX-a) or (IX-b), respectively.

In certain embodiments -Nu of formula (IX-a) and (IX-b) is $-N(R^7R^{7a})$.

In certain embodiments $-R^7$, $-R^{7a}$ and $-R^{7b}$ of formula (IX-a) and (IX-b) are independently of each other selected from the group consisting of -H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl. In certain embodiments $-R^7$, $-R^{7a}$ and $-R^{7b}$ of formula (IX-a) and (IX-b) are independently of each other selected from -H, methyl, ethyl, n-propyl and isopropyl. In certain embodiments $-R^7$, $-R^{7a}$ and $-R^{7b}$ of formula (IX-a) and (IX-b) are independently of each other selected from methyl or ethyl. In certain embodiments $-R^7$, $-R^{7a}$ and $-R^{7b}$ of formula (IX-a) and (IX-b) are both methyl.

In certain embodiments $-L^1-$ is of formula (IX-c)



(IX-c),

wherein

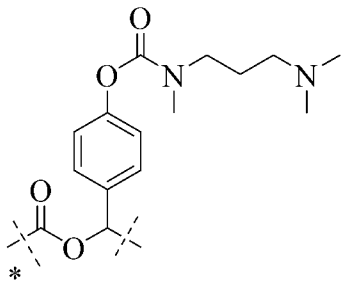
the dashed line marked with the asterisk indicates attachment to a nitrogen of M_{mod};

the unmarked dashed line indicates attachment to $-L^2-Z$; and

s1 is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10.

In certain embodiments s1 of formula (IX-c) is an integer selected from the group consisting of 1, 2, 3, 4 and 5. In certain embodiments s1 of formula (IX-c) is 1. In certain embodiments s1 of formula (IX-c) is 2. In certain embodiments s1 of formula (IX-c) is 3. In certain embodiments s1 of formula (IX-c) is 4. In certain embodiments s1 of formula (IX-c) is 5.

In certain embodiments $-L^1-$ is of formula (IX-d)



(IX-d),

wherein

the dashed line marked with the asterisk indicates attachment to a nitrogen of M_{mod}; and the unmarked dashed line indicates attachment to $-L^2-Z$.

The moiety $-L^1-$ may be connected to M_{mod} through any type of linkage, provided that it is reversible. Preferably, $-L^1-$ is connected to M_{mod} through a linkage selected from the group consisting of amide, ester, carbamate, acetal, aminal, imine, oxime, hydrazone, disulfide and acylguanidine. It is understood that these linkages may not be reversible *per se*, but that neighboring groups present in $-L^1-$ ensure reversibility of said linkage. Even more preferably $-L^1-$ is connected to M_{mod} through a linkage selected from the group consisting of amide, ester, carbamate and acylguanidine.

In one embodiment $-L^1-$ is connected to M_{mod} through an ester linkage.

In another embodiment $-L^1-$ is connected to M_{mod} through a carbamate linkage.

In another embodiment $-L^1-$ is connected to M_{mod} through an acylguanidine.

In a preferred embodiment $-L^1-$ is connected to M_{mod} through an amide linkage.

In one embodiment $-L^2-$ is a chemical bond.

In another embodiment $-L^2-$ is a spacer moiety.

When $-L^2-$ is other than a chemical bond, $-L^2-$ is preferably selected from the group consisting of -T-, -C(O)O-, -O-, -C(O)-, $-C(O)N(R^{y1})-$, $-S(O)_2N(R^{y1})-$, $-S(O)N(R^{y1})-$, $-S(O)_2-$, -S(O)-, $-N(R^{y1})S(O)_2N(R^{y1a})-$, -S-, $-N(R^{y1})-$, $-OC(OR^{y1})(R^{y1a})-$, $-N(R^{y1})C(O)N(R^{y1a})-$, $-OC(O)N(R^{y1})-$, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl; wherein -T-, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50}

alkynyl are optionally substituted with one or more -R^{y2}, which are the same or different and wherein C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally interrupted by one or more groups selected from the group consisting of -T-, -C(O)O-, -O-, -C(O)-, -C(O)N(R^{y3})-, -S(O)$_2$N(R^{y3})-, -S(O)N(R^{y3})-, -S(O)$_2$-, -S(O)-, -N(R^{y3})S(O)$_2$N(R^{y3a})-, -S-, -N(R^{y3})-, -OC(OR^{y3})(R^{y3a})-, -N(R^{y3})C(O)N(R^{y3a})-, and -OC(O)N(R^{y3})-;

-R^{y1} and -R^{y1a} are independently of each other selected from the group consisting of -H, -T, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl; wherein -T, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally substituted with one or more -R^{y2}, which are the same or different, and wherein C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally interrupted by one or more groups selected from the group consisting of -T-, -C(O)O-, -O-, -C(O)-, -C(O)N(R^{y4})-, -S(O)$_2$N(R^{y4})-, -S(O)N(R^{y4})-, -S(O)$_2$-, -S(O)-, -N(R^{y4})S(O)$_2$N(R^{y4a})-, -S-, -N(R^{y4})-, -OC(OR^{y4})(R^{y4a})-, -N(R^{y4})C(O)N(R^{y4a})-, and -OC(O)N(R^{y4})-;

each T is independently selected from the group consisting of phenyl, naphthyl, indenyl, indanyl, tetralinyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl, 8- to 11-membered heterobicyclyl, 8-to 30-membered carbopolycyclyl, and 8- to 30-membered heteropolycyclyl; wherein each T is independently optionally substituted with one or more -R^{y2}, which are the same or different;

each -R^{y2} is independently selected from the group consisting of halogen, -CN, oxo (=O), -COOR^{y5}, -OR^{y5}, -C(O)R^{y5}, -C(O)N($R^{y5}R^{y5a}$), -S(O)$_2$N($R^{y5}R^{y5a}$), -S(O)N($R^{y5}R^{y5a}$), -S(O)$_2R^{y5}$, -S(O)R^{y5}, -N(R^{y5})S(O)$_2$N($R^{y5a}R^{y5b}$), -SR^{y5}, -N($R^{y5}R^{y5a}$), -NO$_2$, -OC(O)R^{y5}, -N(R^{y5})C(O)R^{y5a}, -N(R^{y5})S(O)$_2R^{y5a}$, -N(R^{y5})S(O)R^{y5a}, -N(R^{y5})C(O)OR^{y5a}, -N(R^{y5})C(O)N($R^{y5a}R^{y5b}$), -OC(O)N($R^{y5}R^{y5a}$), and C_{1-6} alkyl; wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different; and

each -R^{y3}, -R^{y3a}, -R^{y4}, -R^{y4a}, -R^{y5}, -R^{y5a} and -R^{y5b} is independently selected from the group consisting of -H, and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different.

When -L^2- is other than a single chemical bond, -L^2- is more preferably selected from -T-, -C(O)O-, -O-, -C(O)-, -C(O)N(R^{y1})-, -S(O)$_2$N(R^{y1})-, -S(O)N(R^{y1})-, -S(O)$_2$-, -S(O)-, -N(R^{y1})S(O)$_2$N(R^{y1a})-, -S-, -N(R^{y1})-, -OC(OR^{y1})(R^{y1a})-, -N(R^{y1})C(O)N(R^{y1a})-,

-OC(O)N(R^{y1})-, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl; wherein -T-, C_{1-20} alkyl, C_{2-20} alkenyl, and C_{2-20} alkynyl are optionally substituted with one or more -R^{y2}, which are the same or different and wherein C_{1-20} alkyl, C_{2-20} alkenyl, and C_{2-20} alkynyl are optionally interrupted by one or more groups selected from the group consisting of -T-, -C(O)O-, -O-, -C(O)-, -C(O)N(R^{y3})-, -S(O)$_2$N(R^{y3})-, -S(O)N(R^{y3})-, -S(O)$_2$-, -S(O)-, -N(R^{y3})S(O)$_2$N(R^{y3a})-, -S-, -N(R^{y3})-, -OC(OR^{y3})(R^{y3a})-, -N(R^{y3})C(O)N(R^{y3a})-, and -OC(O)N(R^{y3})-;

-R^{y1} and -R^{y1a} are independently of each other selected from the group consisting of -H, -T, C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl; wherein -T, C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl are optionally substituted with one or more -R^{y2}, which are the same or different, and wherein C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl are optionally interrupted by one or more groups selected from the group consisting of -T-, -C(O)O-, -O-, -C(O)-, -C(O)N(R^{y4})-, -S(O)$_2$N(R^{y4})-, -S(O)N(R^{y4})-, -S(O)$_2$-, -S(O)-, -N(R^{y4})S(O)$_2$N(R^{y4a})-, -S-, -N(R^{y4})-, -OC(OR^{y4})(R^{y4a})-, -N(R^{y4})C(O)N(R^{y4a})-, and -OC(O)N(R^{y4})-;

each T is independently selected from the group consisting of phenyl, naphthyl, indenyl, indanyl, tetralinyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl, 8- to 11-membered heterobicyclyl, 8-to 30-membered carbopolycyclyl, and 8- to 30-membered heteropolycyclyl; wherein each T is independently optionally substituted with one or more -R^{y2}, which are the same or different;

-R^{y2} is selected from the group consisting of halogen, -CN, oxo (=O), -COOR^{y5}, -OR^{y5}, -C(O)R^{y5}, -C(O)N($R^{y5}R^{y5a}$), -S(O)$_2$N($R^{y5}R^{y5a}$), -S(O)N($R^{y5}R^{y5a}$), -S(O)$_2R^{y5}$, -S(O)R^{y5}, -N(R^{y5})S(O)$_2$N($R^{y5a}R^{y5b}$), -SR^{y5}, -N($R^{y5}R^{y5a}$), -NO$_2$, -OC(O)R^{y5}, -N(R^{y5})C(O)R^{y5a}, -N(R^{y5})S(O)$_2R^{y5a}$, -N(R^{y5})S(O)R^{y5a}, -N(R^{y5})C(O)OR^{y5a}, -N(R^{y5})C(O)N($R^{y5a}R^{y5b}$), -OC(O)N($R^{y5}R^{y5a}$), and C_{1-6} alkyl; wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different; and

each -R^{y3}, -R^{y3a}, -R^{y4}, -R^{y4a}, -R^{y5}, -R^{y5a} and -R^{y5b} is independently of each other selected from the group consisting of -H, and C_{1-6} alkyl; wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different.

When -L^2- is other than a single chemical bond, -L^2- is even more preferably selected from the group consisting of -T-, -C(O)O-, -O-, -C(O)-, -C(O)N(R^{y1})-, -S(O)$_2$N(R^{y1})-,

-S(O)N(R^{y1})-, -S(O)$_2$-, -S(O)-, -N(R^{y1})S(O)$_2$N(R^{y1a})-, -S-, -N(R^{y1})-, -OC(OR^{y1})(R^{y1a})-, -N(R^{y1})C(O)N(R^{y1a})-, -OC(O)N(R^{y1})-, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl; wherein -T-, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally substituted with one or more -R^{y2}, which are the same or different and wherein C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally interrupted by one or more groups selected from the group consisting of -T-, -C(O)O-, -O-, -C(O)-, -C(O)N(R^{y3})-, -S(O)$_2$N(R^{y3})-, -S(O)N(R^{y3})-, -S(O)$_2$-, -S(O)-, -N(R^{y3})S(O)$_2$N(R^{y3a})-, -S-, -N(R^{y3})-, -OC(OR^{y3})(R^{y3a})-, -N(R^{y3})C(O)N(R^{y3a})-, and -OC(O)N(R^{y3})-;

-R^{y1} and -R^{y1a} are independently selected from the group consisting of -H, -T, C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl;

each T is independently selected from the group consisting of phenyl, naphthyl, indenyl, indanyl, tetralinyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl, 8- to 11-membered heterobicyclyl, 8-to 30-membered carbopolycyclyl, and 8- to 30-membered heteropolycyclyl;

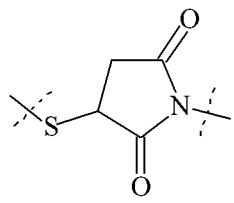
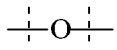
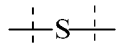
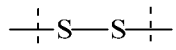
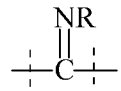
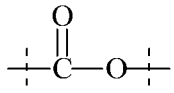
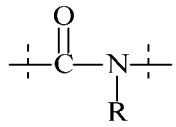
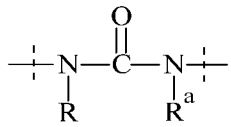
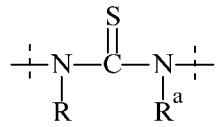
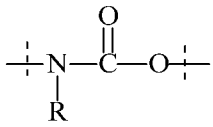
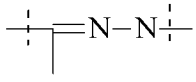
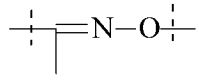
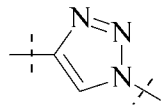
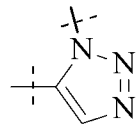
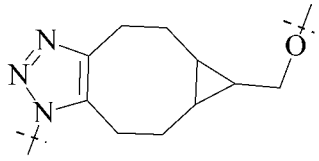
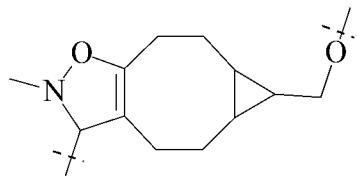
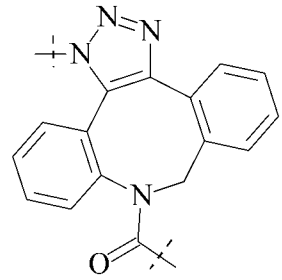
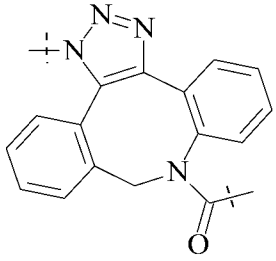
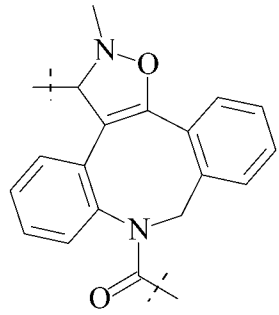
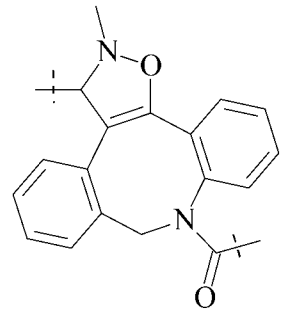
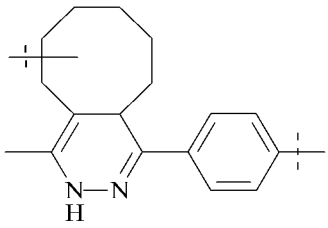
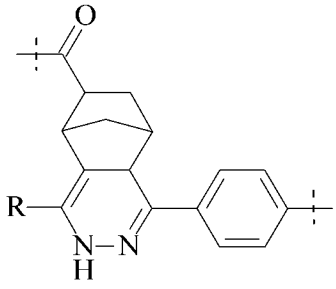
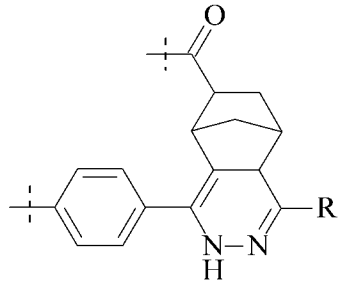
each -R^{y2} is independently selected from the group consisting of halogen, and C_{1-6} alkyl; and

each -R^{y3}, -R^{y3a}, -R^{y4}, -R^{y4a}, -R^{y5}, -R^{y5a} and -R^{y5b} is independently of each other selected from the group consisting of -H, and C_{1-6} alkyl; wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different.

Even more preferably, -L^2- is a C_{1-20} alkyl chain, which is optionally interrupted by one or more groups independently selected from -O-, -T- and -C(O)N(R^{y1})-; and which C_{1-20} alkyl chain is optionally substituted with one or more groups independently selected from -OH, -T and -C(O)N($R^{y6}R^{y6a}$); wherein -R^{y1}, -R^{y6}, -R^{y6a} are independently selected from the group consisting of H and C_{1-4} alkyl and wherein T is selected from the group consisting of phenyl, naphthyl, indenyl, indanyl, tetralinyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl, 8- to 11-membered heterobicyclyl, 8-to 30-membered carbopolycyclyl, and 8- to 30-membered heteropolycyclyl.

Preferably, -L^2- has a molecular weight in the range of from 14 g/mol to 750 g/mol.

Preferably, -L^2- comprises a moiety selected from

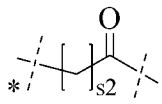
























wherein

dashed lines indicate attachment to -L^1-, the remainder of -L^2- or -Z, respectively; and

-R and -R^a are independently of each other selected from the group consisting of -H, methyl, ethyl, propyl, butyl, pentyl and hexyl.

In certain embodiments -L^2- is of formula (IX-e)



(IX-e),

wherein

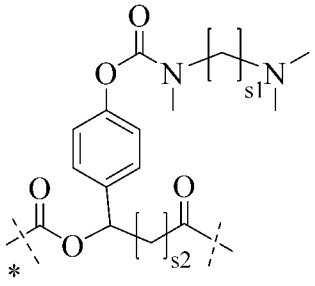
the dashed line marked with the asterisk indicates attachment to -L^1-;

the unmarked dashed line indicates attachment to -Z; and

s2 is an integer selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 and 20.

In certain embodiments s2 of formula (IX-e) is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12. In certain embodiments s2 of formula (IX-e) is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7 and 8. In certain embodiments s2 of formula (IX-e) is 1. In certain embodiments s2 of formula (IX-e) is 2. In certain embodiments s2 of formula (IX-e) is 3. In certain embodiments s2 of formula (IX-e) is 4. In certain embodiments s2 of formula (IX-e) is 5. In certain embodiments s2 of formula (IX-e) is 6. In certain embodiments s2 of formula (IX-e) is 7. In certain embodiments s2 of formula (IX-e) is 8.

In certain embodiments the moiety -L^1-L^2- is of formula (IX-f)



(IX-f),

wherein

the dashed line marked with the asterisk indicates attachment to a nitrogen of M_{mod};

the unmarked dashed line indicates attachment to -Z;

s1 is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10; and

s2 is an integer selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 and 20.

In certain embodiments s1 of formula (IX-f) is an integer selected from the group consisting of 1, 2, 3, 4 and 5. In certain embodiments s1 of formula (IX-f) is 1. In certain embodiments s1 of formula (IX-f) is 2. In certain embodiments s1 of formula (IX-f) is 3. In certain embodiments s1 of formula (IX-f) is 4. In certain embodiments s1 of formula (IX-f) is 5.

In certain embodiments s2 of formula (IX-f) is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12. In certain embodiments s2 of formula (IX-f) is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7 and 8. In certain embodiments s2 of formula (IX-f) is 1. In certain embodiments s2 of formula (IX-f) is 2. In certain embodiments s2 of formula (IX-f) is 3. In certain embodiments s2 of formula (IX-e) is 4. In certain embodiments s2 of formula (IX-f) is 5. In certain embodiments s2 of formula (IX-e) is 6. In certain embodiments s2 of formula (IX-f) is 7. In certain embodiments s2 of formula (IX-f) is 8.

In certain embodiments s1 of formula (IX-f) is 3 and s2 of formula (IX-f) is 3.

Another aspect of the present invention is a pharmaceutical composition comprising at least one conjugate of the present invention and at least one excipient.

Preferably, the pharmaceutical composition comprising at least one conjugate of the present invention has a pH ranging from and including pH 3 to pH 8.

In one embodiment the pharmaceutical composition comprising at least one conjugate of the present invention and at least one excipient is a liquid formulation.

In another embodiment the pharmaceutical composition comprising at least one conjugate of the present invention and at least one excipient is a dry formulation.

Such liquid or dry pharmaceutical composition comprises at least one excipient. Excipients used in parenteral formulations may be categorized as, for example, buffering agents, isotonicity modifiers, preservatives, stabilizers, anti-adsorption agents, oxidation protection agents, viscosifiers/viscosity enhancing agents, or other auxiliary agents. However, in some cases, one excipient may have dual or triple functions. Preferably, the at least one excipient

comprised in the pharmaceutical composition of the present invention is selected from the group consisting of

(i) Buffering agents: physiologically tolerated buffers to maintain pH in a desired range, such as sodium phosphate, bicarbonate, succinate, histidine, citrate and acetate, sulphate, nitrate, chloride, pyruvate; antacids such as $Mg(OH)_2$ or $ZnCO_3$ may be also used;

(ii) Isotonicity modifiers: to minimize pain that can result from cell damage due to osmotic pressure differences at the injection depot; glycerin and sodium chloride are examples; effective concentrations can be determined by osmometry using an assumed osmolality of 285-315 mOsmol/kg for serum;

(iii) Preservatives and/or antimicrobials: multidose parenteral formulations require the addition of preservatives at a sufficient concentration to minimize risk of patients becoming infected upon injection and corresponding regulatory requirements have been established; typical preservatives include m-cresol, phenol, methylparaben, ethylparaben, propylparaben, butylparaben, chlorobutanol, benzyl alcohol, phenylmercuric nitrate, thimerosol, sorbic acid, potassium sorbate, benzoic acid, chlorocresol, and benzalkonium chloride;

(iv) Stabilizers: Stabilisation is achieved by strengthening of the protein-stabilising forces, by destabilisation of the denatured state, or by direct binding of excipients to the protein; stabilizers may be amino acids such as alanine, arginine, aspartic acid, glycine, histidine, lysine, proline, sugars such as glucose, sucrose, trehalose, polyols such as glycerol, mannitol, sorbitol, salts such as potassium phosphate, sodium sulphate, chelating agents such as EDTA, hexaphosphate, ligands such as divalent metal ions (zinc, calcium, etc.), other salts or organic molecules such as phenolic derivatives; in addition, oligomers or polymers such as cyclodextrins, dextran, dendrimers, PEG or PVP or protamine or HSA may be used;

(v) Anti-adsorption agents: Mainly ionic or non-ionic surfactants or other proteins or soluble polymers are used to coat or adsorb competitively to the inner surface of the formulation´s container; e.g., poloxamer (Pluronic F-68), PEG dodecyl ether (Brij 35),

polysorbate 20 and 80, dextran, polyethylene glycol, PEG-polyhistidine, BSA and HSA and gelatins; chosen concentration and type of excipient depends on the effect to be avoided but typically a monolayer of surfactant is formed at the interface just above the CMC value;

(vi) Oxidation protection agents: antioxidants such as ascorbic acid, ectoine, methionine, glutathione, monothioglycerol, morin, polyethylenimine (PEI), propyl gallate, and vitamin E; chelating agents such as citric acid, EDTA, hexaphosphate, and thioglycolic acid may also be used;

(vii) Viscosifiers or viscosity enhancers: retard settling of the particles in the vial and syringe and are used in order to facilitate mixing and resuspension of the particles and to make the suspension easier to inject (i.e., low force on the syringe plunger); suitable viscosifiers or viscosity enhancers are, for example, carbomer viscosifiers like Carbopol 940, Carbopol Ultrez 10, cellulose derivatives like hydroxypropylmethylcellulose (hypromellose, HPMC) or diethylaminoethyl cellulose (DEAE or DEAE-C), colloidal magnesium silicate (Veegum) or sodium silicate, hydroxyapatite gel, tricalcium phosphate gel, xanthans, carrageenans like Satia gum UTC 30, aliphatic poly(hydroxy acids), such as poly(D,L- or L-lactic acid) (PLA) and poly(glycolic acid) (PGA) and their copolymers (PLGA), terpolymers of D,L-lactide, glycolide and caprolactone, poloxamers, hydrophilic poly(oxyethylene) blocks and hydrophobic poly(oxypropylene) blocks to make up a triblock of poly(oxyethylene)-poly(oxypropylene)-poly(oxyethylene) (e.g. Pluronic®), polyetherester copolymer, such as a polyethylene glycol terephthalate/polybutylene terephthalate copolymer, sucrose acetate isobutyrate (SAIB), dextran or derivatives thereof, combinations of dextrans and PEG, polydimethylsiloxane, collagen, chitosan, polyvinyl alcohol (PVA) and derivatives, polyalkylimides, poly (acrylamide-co-diallyldimethyl ammonium (DADMA)), polyvinylpyrrolidone (PVP), glycosaminoglycans (GAGs) such as dermatan sulfate, chondroitin sulfate, keratan sulfate, heparin, heparan sulfate, hyaluronan, ABA triblock or AB block copolymers composed of hydrophobic A-blocks, such as polylactide (PLA) or poly(lactide-co-glycolide) (PLGA), and hydrophilic B-blocks, such as polyethylene glycol (PEG) or polyvinyl pyrrolidone; such block copolymers as well as the abovementioned poloxamers may exhibit reverse

thermal gelation behavior (fluid state at room temperature to facilitate administration and gel state above sol-gel transition temperature at body temperature after injection);

(viii) Spreading or diffusing agent: modifies the permeability of connective tissue through the hydrolysis of components of the extracellular matrix in the intrastitial space such as but not limited to hyaluronic acid, a polysaccharide found in the intercellular space of connective tissue; a spreading agent such as but not limited to hyaluronidase temporarily decreases the viscosity of the extracellular matrix and promotes diffusion of injected drugs; and

(ix) Other auxiliary agents: such as wetting agents, viscosity modifiers, antibiotics, hyaluronidase; acids and bases such as hydrochloric acid and sodium hydroxide are auxiliary agents necessary for pH adjustment during manufacture.

Another aspect of the present invention is the Iconjugate or a pharmaceutically acceptable salt thereof or a pharmaceutical composition comprising at least one conjugate of the present invention for use as a medicament.

Another aspect of the present invention is the conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical composition comprising at least one conjugate of the present invention for use in a method of treatment of a disease.

Another aspect of the present invention is the use of the conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical composition comprising at least one conjugate of the present invention for the manufacture of a medicament for treating a disease.

A further aspect of the present invention is a method of treating, controlling, delaying or preventing in a mammalian patient, preferably a human patient, in need of the treatment of one or more diseases, comprising the step of administering to said patient in need thereof a therapeutically effective amount of the conjugate or a pharmaceutically acceptable salt thereof or a pharmaceutical composition comprising the conjugate of the present invention.

An additional aspect of the present invention is a method of administering the conjugate, a pharmaceutically acceptable salt thereof or the pharmaceutical composition of the present

invention, wherein the method comprises the step of administering the conjugate, a pharmaceutically acceptable salt thereof or the pharmaceutical composition of the present invention via topical, enteral or parenteral administration and by methods of external application, injection or infusion, including intraarticular, periarticular, intradermal, subcutaneous, intramuscular, intravenous, intraosseous, intraperitoneal, intrathecal, intracapsular, intraorbital, intravitreal, intratympanic, intravesical, intracardiac, transtracheal, subcuticular, subcapsular, subarachnoid, intraspinal, intraventricular, intrasternal injection and infusion, direct delivery to the brain via implanted device allowing delivery of the invention or the like to brain tissue or brain fluids (e.g., Ommaya Reservoir), direct intracerebroventricular injection or infusion, injection or infusion into brain or brain associated regions, injection into the subchoroidal space, retro-orbital injection and ocular instillation, preferably via subcutaneous injection.

Materials

10 kDa Mal-PEG-NH_2 (catalog # PHB-943) may be acquired from Creative PEGWorks, Chapell Hill, NC, USA.

General methods

Example 1: Preparation of IL-2 variants

IL-2 variants (muteins) were custom made and sourced from an external supplier where expression of the proteins was performed in *E. coli* followed by standard purification strategies known to the one skilled in the art. The following proteins were prepared

1a - SEQ ID NO: 1: PTSSSTKKTQ LQLEHLLLDL QMILNGINNY KNPKLTCMLT FKFYMPKKAT ELKHLQCLEE ELKPLEEVLN LAQSKNFHLR PRDLISNINV IVLELKGSET TFMCEYADET ATIVEFLNRW ITFSQSIIST LT

1b - SEQ ID NO: 2: PTSSSTKKTQ LQLEHLLLDL QMILNGINNY KNPKLTRMLT CKFYMPKKAT ELKHLQCLEE ELKPLEEVLN LAQSKNFHLR PRDLISNINV IVLELKGSET TFMCEYADET ATIVEFLNRW ITFSQSIIST LT

1c - SEQ ID NO: 3: PTSSSTKKTQ LQLEHLLLDL QMILNGINNY KNPKLTRMLT FKFCMPKKAT ELKHLQCLEE ELKPLEEVLN LAQSKNFHLR PRDLISNINV IVLELKGSET TFMCEYADET ATIVEFLNRW ITFSQSIIST LT

1d - SEQ ID NO: 4: PTSSSTKKTQ LQLEHLLLDL QMILNGINNY KNPKLTRMLT FKFYMPKKAT ELKHLQCLEE CLKPLEEVLN LAQSKNFHLR PRDLISNINV IVLELKGSET TFMCEYADET ATIVEFLNRW ITFSQSIIST LT

Example 2: Preparation of novel conjugate 2

40 kDa mPEG-linker reagent (as described in patent WO 2016079114 example 2) is dissolved in water to yield a 32 g/L solution. 10 kDa Mal-PEG-NH_2 is dissolved in 0.1 M sodium phosphate, 6 mM sodium EDTA, pH 7.4 to a final concentration of 1 mM. Both solutions are mixed in a volumetric ratio of 1 to 1 and incubated for 2 h at ambient temperature. Afterwards, 0.5 volume equivalents (with respect to the volume of the reaction mixture of 40 kDa mPEG-linker reagent and 10 kDa Mal-PEG-NH_2) of an IL-2 mutein **1a** solution at a concentration of 2 mg/mL in 50 mM sodium phosphate, 3 mM sodium EDTA, pH 7.4 is added to the reaction mixture and incubated for 1 h at ambient temperature. 40+10 kDa PEG IL-2 mutein conjugate **2** is isolated from the reaction mixture by cation exchange chromatography and analyzed by size exclusion chromatography.

Abbreviations

E. coli	*Escherichia coli*
EDTA	ethylenediaminetetraacetic acid
IL-2	interleukin-2
Mal	maleimide
PEG	poly(ethylene glycol)

Claims

1. A conjugate comprising a moiety of formula (I)

$$D\text{—}[\text{—}M_{mod}\text{—}]_x \quad (I)$$

wherein at least one moiety M_{mod} is substituted with at least one moiety of formula (Ia)

$$\text{—}L^1\text{—}L^2\text{—}Z \quad (Ia),$$

wherein

each moiety M_{mod} is independently a modifying moiety;

D- is a biologically active moiety to which x modifying moieties M_{mod} are stably conjugated;

each $-L^1-$ is independently a linker moiety covalently and reversibly attached to M_{mod};

each $-L^2-$ is independently a chemical bond or is a spacer moiety;

each -Z is independently a polymeric moiety or a substituted fatty acid moiety; and

x is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10.

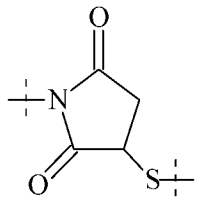
2. The conjugate of claim 1, wherein D- is selected from the group consisting of small molecule biologically active moieties, oligonucleotide moieties, peptide nucleic acid moieties, peptide moieties and protein moieties.

3. The conjugate of claim 1 or 2, wherein M_{mod} is a substituent or a polymeric moiety.

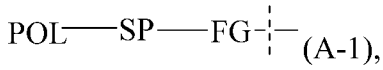
4. The conjugate of any one of claims 1 to 3, wherein attachment of M_{mod} is to a proteinogenic amino acid of D-.

5. The conjugate of any one of claims 1 to 4, wherein attachment of M_{mod} is to a proteinogenic amino acid selected from the group consisting of cysteine, methionine, histidine, lysine, tryptophan, serine, threonine, tyrosine, aspartic acid, glutamic acid, glutamine and arginine of D-.

6. The conjugate of any one of claims 1 to 3, wherein attachment of M_{mod} is to a non-proteinogenic amino acid.

7. The conjugate of any one of claims 1 to 6, wherein the linkage between D- and a moiety M_{mod} is via a moiety  .

8. The conjugate of any one of claims 1 to 8, wherein M_{mod} is of formula (A-1)



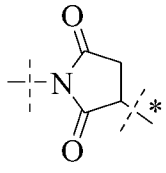
wherein

-FG- is a linkage;

-SP- is a spacer moiety; and

-POL is a polymer.

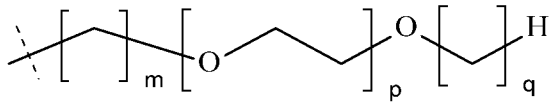
9. The conjugate of claim 8, wherein -FG- of formula (A-1) is



wherein the dashed line marked with the asterisk indicates attachment to a sulfur of D- and the unmarked dashed line indicates attachment -SP-.

10. The conjugate of claim 8 or 9, wherein -SP- is C_{1-10} alkyl, which C_{1-10} alkyl is optionally substituted with one or more $-R^9$, and which C_{1-10} alkyl is optionally interrupted by one or more groups selected from the group consisting of -O-, $-C(O)N(R^{10})-$, $-S(O)_2-$, -S(O)-, -S-, $-N(R^{10})-$, $-OC(OR^{10})(R^{10a})-$, $-N(R^{10})C(O)N(R^{10a})-$, and $-OC(O)N(R^{10})-$; wherein each $-R^9$ is selected from the group consisting of C_{1-6} alkyl; and each $-R^{10}$ and $-R^{10a}$ is independently selected from the group consisting of -H and C_{1-6} alkyl.

11. The conjugate of any one of claims 8 to 10, wherein -POL is of formula (A-1i)



(A-1i),

wherein

the dashed line indicates attachment to -SP;

m is 0 or 1;

p is an integer ranging from 12 to 22700; and

q is selected from the group consisting of 1, 2, 3, 4, 5, and 6.

12. The conjugate of any one of claims 1 to 11, wherein $-L^2-$ is selected from the group consisting of -T-, -C(O)O-, -O-, -C(O)-, $-C(O)N(R^{y1})-$, $-S(O)_2N(R^{y1})-$, $-S(O)N(R^{y1})-$, $-S(O)_2-$, -S(O)-, $-N(R^{y1})S(O)_2N(R^{y1a})-$, -S-, $-N(R^{y1})-$, $-OC(OR^{y1})(R^{y1a})-$, $-N(R^{y1})C(O)N(R^{y1a})-$, $-OC(O)N(R^{y1})-$, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl; wherein -T-, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally substituted with one or more $-R^{y2}$, which are the same or different and wherein C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally interrupted by one or more groups selected from the group consisting of -T-, -C(O)O-, -O-, -C(O)-, $-C(O)N(R^{y3})-$, $-S(O)_2N(R^{y3})-$, $-S(O)N(R^{y3})-$, $-S(O)_2-$, -S(O)-, $-N(R^{y3})S(O)_2N(R^{y3a})-$, -S-, $-N(R^{y3})-$, $-OC(OR^{y3})(R^{y3a})-$, $-N(R^{y3})C(O)N(R^{y3a})-$, and $-OC(O)N(R^{y3})-$;

$-R^{y1}$ and $-R^{y1a}$ are independently of each other selected from the group consisting of -H, -T, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl; wherein -T, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally substituted with one or more $-R^{y2}$, which are the same or different, and wherein C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally interrupted by one or more groups selected from the group consisting of -T-, -C(O)O-, -O-, -C(O)-, $-C(O)N(R^{y4})-$, $-S(O)_2N(R^{y4})-$, $-S(O)N(R^{y4})-$, $-S(O)_2-$, -S(O)-, $-N(R^{y4})S(O)_2N(R^{y4a})-$, -S-, $-N(R^{y4})-$, $-OC(OR^{y4})(R^{y4a})-$, $-N(R^{y4})C(O)N(R^{y4a})-$, and $-OC(O)N(R^{y4})-$;

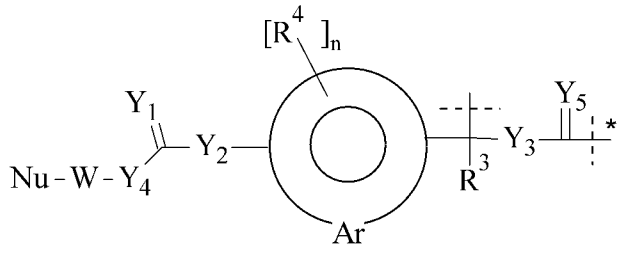
each T is independently selected from the group consisting of phenyl, naphthyl, indenyl, indanyl, tetralinyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl, 8- to 11-membered heterobicyclyl, 8-to 30-membered carbopolycyclyl, and 8- to 30-membered heteropolycyclyl; wherein each T is independently optionally substituted with one or more $-R^{y2}$, which are the same or different;

each $-R^{y2}$ is independently selected from the group consisting of halogen, -CN, oxo (=O), $-COOR^{y5}$, $-OR^{y5}$, $-C(O)R^{y5}$, $-C(O)N(R^{y5}R^{y5a})$, $-S(O)_2N(R^{y5}R^{y5a})$,

-S(O)N($R^{y5}R^{y5a}$), -S(O)$_2R^{y5}$, -S(O)R^{y5}, -N(R^{y5})S(O)$_2$N($R^{y5a}R^{y5b}$), -SR^{y5}, -N($R^{y5}R^{y5a}$), -NO_2, -OC(O)R^{y5}, -N(R^{y5})C(O)R^{y5a}, -N(R^{y5})S(O)$_2R^{y5a}$, -N(R^{y5})S(O)R^{y5a}, -N(R^{y5})C(O)OR^{y5a}, -N(R^{y5})C(O)N($R^{y5a}R^{y5b}$), -OC(O)N($R^{y5}R^{y5a}$), and C_{1-6} alkyl; wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different; and

each -R^{y3}, -R^{y3a}, -R^{y4}, -R^{y4a}, -R^{y5}, -R^{y5a} and -R^{y5b} is independently selected from the group consisting of -H, and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different.

13. The conjugate of any one of claims 1 to 12, wherein -L^1- of formula (IX) is of formula (IX-a):



(IX-a),

wherein

the dashed line marked with the asterisk indicates attachment to a nitrogen of M_{mod} and the unmarked dashed line indicates attachment to -L^2-Z;

n is 0, 1, 2, 3, or 4;

=Y_1 is selected from the group consisting of =O and =S;

-Y_2- is selected from the group consisting of -O- and -S-;

-Y_3-, -Y_5- are independently of each other selected from the group consisting of -O- and -S-;

-Y_4- is selected from the group consisting of -O-, -NR^5- and -C(R^6R^{6a})-;

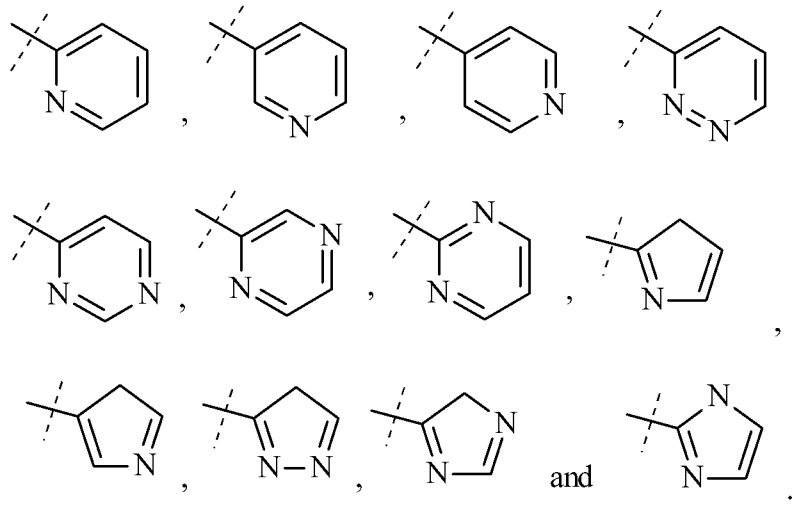
-R^3, -R^5, -R^6, -R^{6a} are independently of each other selected from the group consisting of -H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, 2-methylbutyl, 2,2-dimethylpropyl, n-hexyl, 2-methylpentyl, 3-methylpentyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl and 3,3-dimethylpropyl;

-R^4 is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, 2-methylbutyl, 2,2-dimethylpropyl,

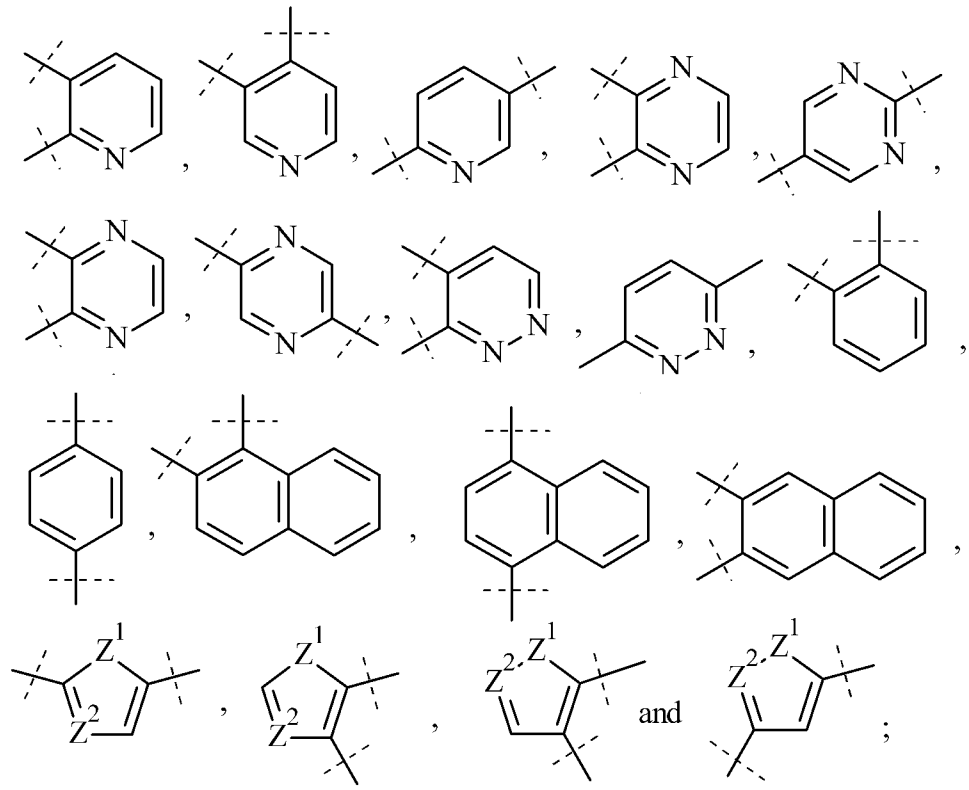
n-hexyl, 2-methylpentyl, 3-methylpentyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl and 3,3-dimethylpropyl;

-W- is selected from the group consisting of C_{1-20} alkyl optionally interrupted by one or more groups selected from the group consisting of C_{3-10} cycloalkyl, 8- to 30-membered carbopolycyclyl, 3- to 10-membered heterocyclyl, -C(O)-, -C(O)N(R^7)-, -O-, -S- and -N(R^7)-;

-Nu is a nucleophile selected from the group consisting of -N(R^7R^{7a}), -N(R^7OH), -N(R^7)-N($R^{7a}R^{7b}$), -S(R^7),-COOH,



-Ar- is selected from the group consisting of



wherein

dashed lines indicate attachment to the remainder of -L^1-,

-Z^1- is selected from the group consisting of -O-, -S- and -N(R^7)-, and

-Z^2- is -N(R^7)-; and

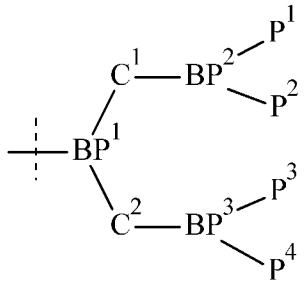
-R^7, -R^{7a}, -R^{7b} are independently of each other selected from the group consisting of -H, C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl;

wherein -L^1- is optionally further substituted.

14. The conjugate of any one of claims 1 to 13, wherein -Z is a polymeric moiety.

15. The conjugate of any one of claims 1 to 14, wherein -Z has a molecular weight ranging from 1 kDa to 1000 kDa.

16. The conjugate of any one of claims 1 to 15, wherein -Z comprises a moiety of formula (A)



(A),

wherein

-BP^1<, -BP^2<, -BP^3< are independently of each other selected from the group consisting of -N< and -C(R^8)<;

R^8 is selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl;

-P^1, -P^2, -P^3, -P^4 are independently of each other a PEG-based chain comprising at least 40% PEG and having a molecular weight ranging from 3 to 40 kDa;

-C^1-, -C^2- are independently of each other selected from the group consisting of C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl; wherein C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally substituted with one or more R^9, which are the same or different and wherein C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally interrupted by one or more groups selected from the group consisting of -T-, -C(O)O-, -O-, -C(O)-, -C(O)N(R^{10})-, -$S(O)_2$N(R^{10})-, -S(O)N(R^{10})-, -$S(O)_2$-,

-S(O)-, -N(R^{10})S(O)$_2$N(R^{10a})-, -S-, -N(R^{10})-, -OC(OR^{10})(R^{10a})-, -N(R^{10})C(O)N(R^{10a})-, and -OC(O)N(R^{10})-;

each T is independently selected from the group consisting of phenyl, naphthyl, indenyl, indanyl, tetralinyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl, 8- to 11-membered heterobicyclyl, 8-to 30-membered carbopolycyclyl, and 8- to 30-membered heteropolycyclyl; wherein each T is independently optionally substituted with one or more R^9, which are the same or different;

each R^9 is independently selected from the group consisting of halogen, -CN, oxo (=O), -COOR^{11}, -OR^{11}, -C(O)R^{11}, -C(O)N($R^{11}R^{11a}$), -S(O)$_2$N($R^{11}R^{11a}$), -S(O)N($R^{11}R^{11a}$), -S(O)$_2R^{11}$, -S(O)R^{11}, -N(R^{11})S(O)$_2$N($R^{11a}R^{11b}$), -SR^{11}, -N($R^{11}R^{11a}$), -NO$_2$, -OC(O)R^{11}, -N(R^{11})C(O)R^{11a}, -N(R^{11})S(O)$_2R^{11a}$, -N(R^{11})S(O)R^{11a}, -N(R^{11})C(O)OR^{11a}, -N(R^{11})C(O)N($R^{11a}R^{11b}$), -OC(O)N($R^{11}R^{11a}$), and C_{1-6} alkyl; wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different; and

each R^{10}, R^{10a}, R^{11}, R^{11a} and R^{11b} is independently selected from the group consisting of -H, and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different.

17. The conjugate of any one of claims 1 to 16, wherein x is 1.

18. A pharmaceutical composition comprising at least one conjugate of any one of claims 1 to 16 and at least one excipient.