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US 20170146519 A1

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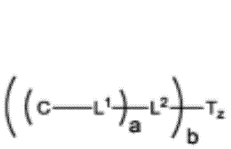
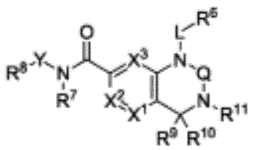
(54) Title of the Invention: **Small molecule modulators of human STING, conjugates and therapeutic applications**
Abstract Title: **Small molecule modulators of human STING and conjugates thereof**

(57) A compound of Formula (I) or a pharmaceutically acceptable salt or prodrug thereof, wherein C is a compound of Formula (II):



(I)



(II)

Wherein L^1 and L^2 are linkers; T is a targetting moeity; a is 1-5; b is 1-10; z is 1-5; X^{1-3} is CR^{1-3}respectively or N; Q is C=O, S=O, SO_2 or CR^4R^5; Y and L are as herein defined; R^{1-11} arer as herein defined. T may comprise an antibody, an antibody fragment, a nucleic acid based molecule, a carbohydrate, an optionally modified peptide or small molecule. T may be configured to target a tumour antigen. Compounds of formula (I) are conjugates of small molecule modulators of the Stimulator of Interferon Genes (STING) protein and may be used to treat diseases such as cancer and microbial infections. Pharmaceutical compositions comprising a compound of Formula (I) are also disclosed. Compounds of Formula (III); $(C\text{-}L^1)\text{-}L^{2a}$ are also disclosed wherein such compounds are suitable for preparing a compound of Formula (I), wherein C and L^1 are as defined above, and L^{2a} is L^2-LG wherein LG is a leaving group, or L^2 as define above, except that the linker comprises a terminal double bond.

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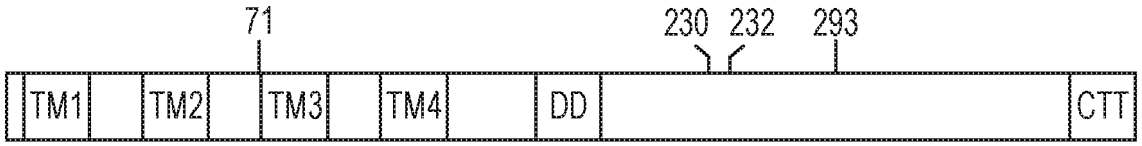
At least one drawing originally filed was informal and the print reproduced here is taken from a later filed formal copy.

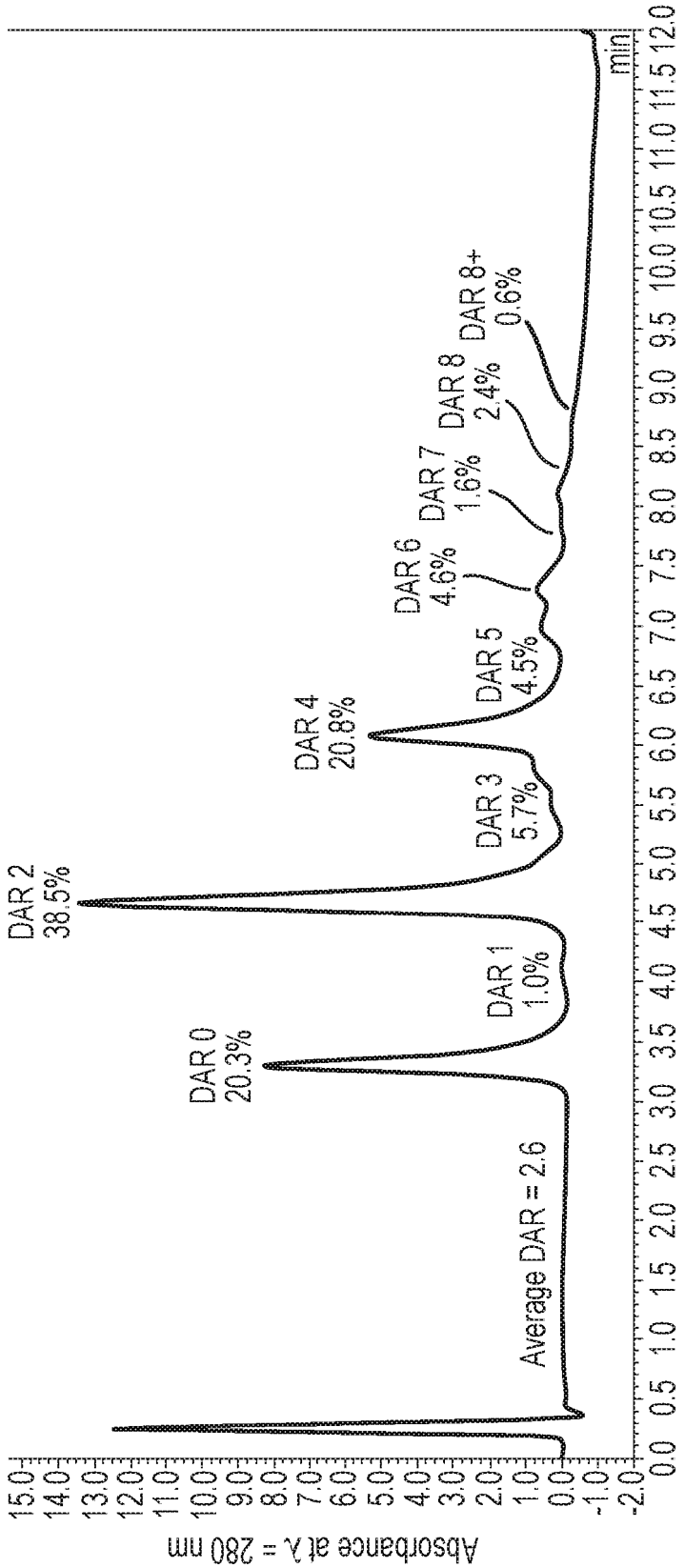
Fig. 1



STING variant				Allele frequency
WT	R	GR	R	57.9%
HAQ	H	AR	Q	20.4%
REF	R	GH	R	13.7%
AQ	R	AR	Q	5.2%
Q	R	GR	Q	1.5%

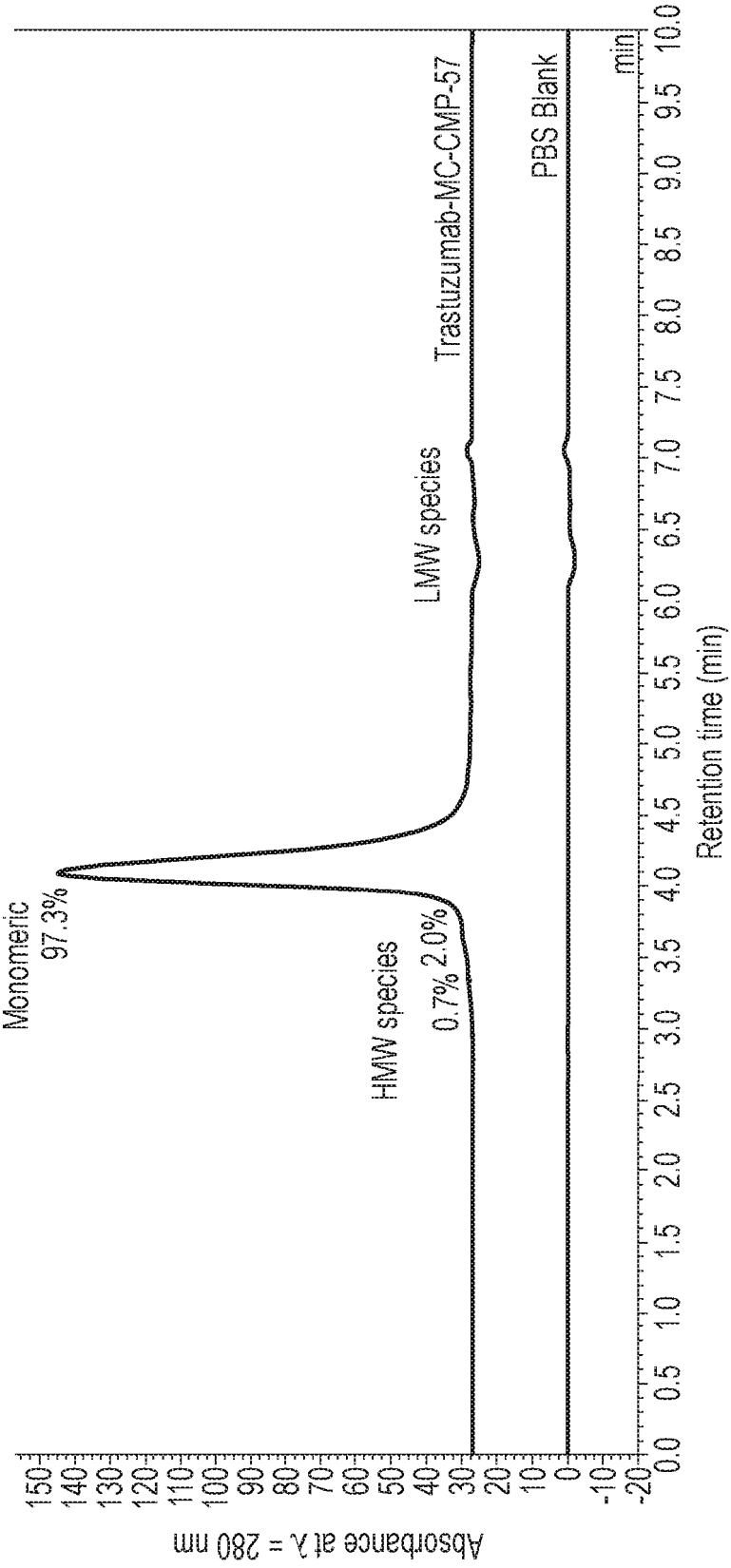
28 10 19

Fig. 2


DAR 2
38.5%
DAR 0
20.3%
DAR 1
1.0%
DAR 4
20.8%
DAR 3
5.7%
DAR 5
4.5%
DAR 6
4.6%
DAR 7
1.6%
DAR 8
2.4%
DAR 8+
0.6%
Average DAR = 2.6
Absorbance at λ = 280 nm
Retention time (min)
min

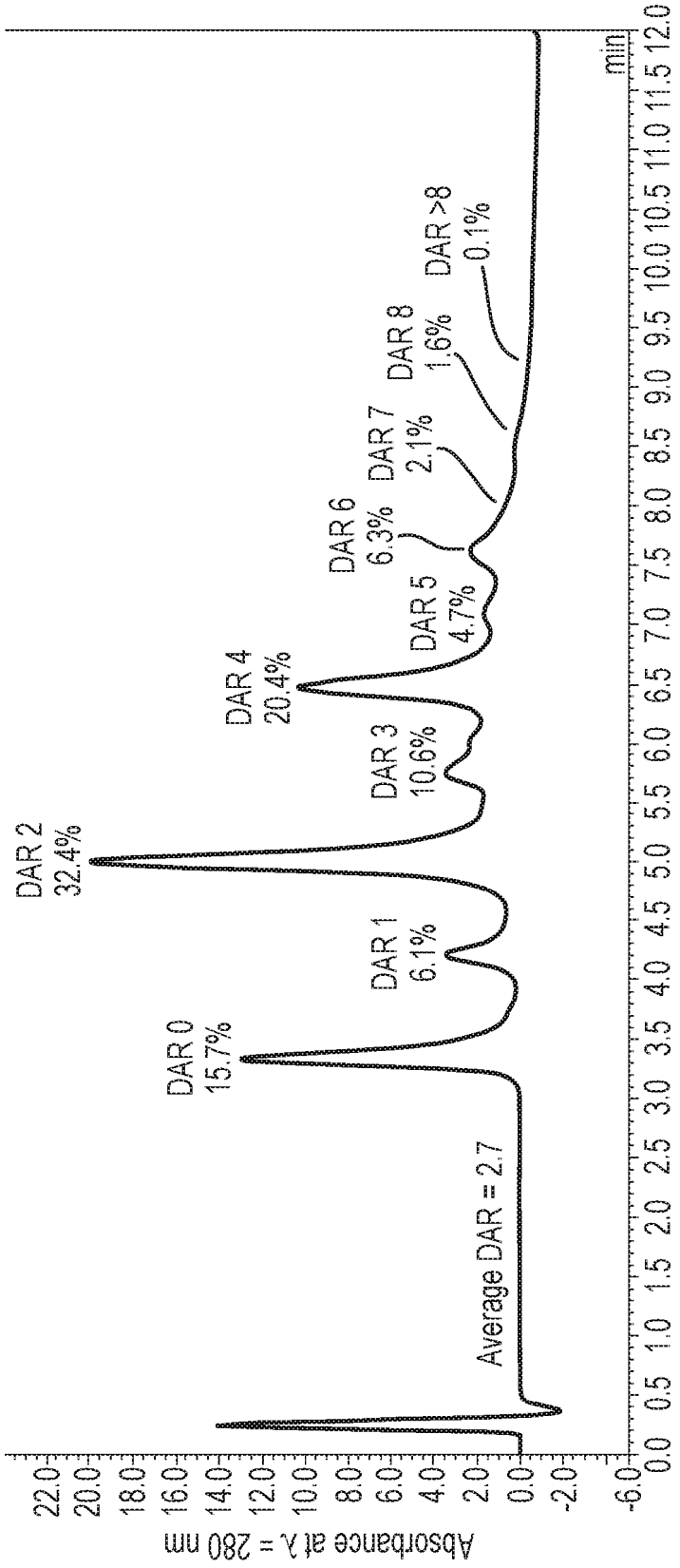
28 10 19

Fig. 3


Monomeric
97.3%
HMW species
0.7%
2.0%
LMW species
Trastuzumab-MC-CMP-57
PBS Blank
min
Retention time (min)
Absorbance at λ = 280 nm

28 10 19

Fig. 4


DAR 0
15.7%
DAR 1
6.1%
DAR 2
32.4%
DAR 3
10.6%
DAR 4
20.4%
DAR 5
4.7%
DAR 6
6.3%
DAR 7
2.1%
DAR 8
1.6%
DAR >8
0.1%
Average DAR = 2.7
Absorbance at λ = 280 nm
Retention time (min)
min

28 10 19

Fig. 5

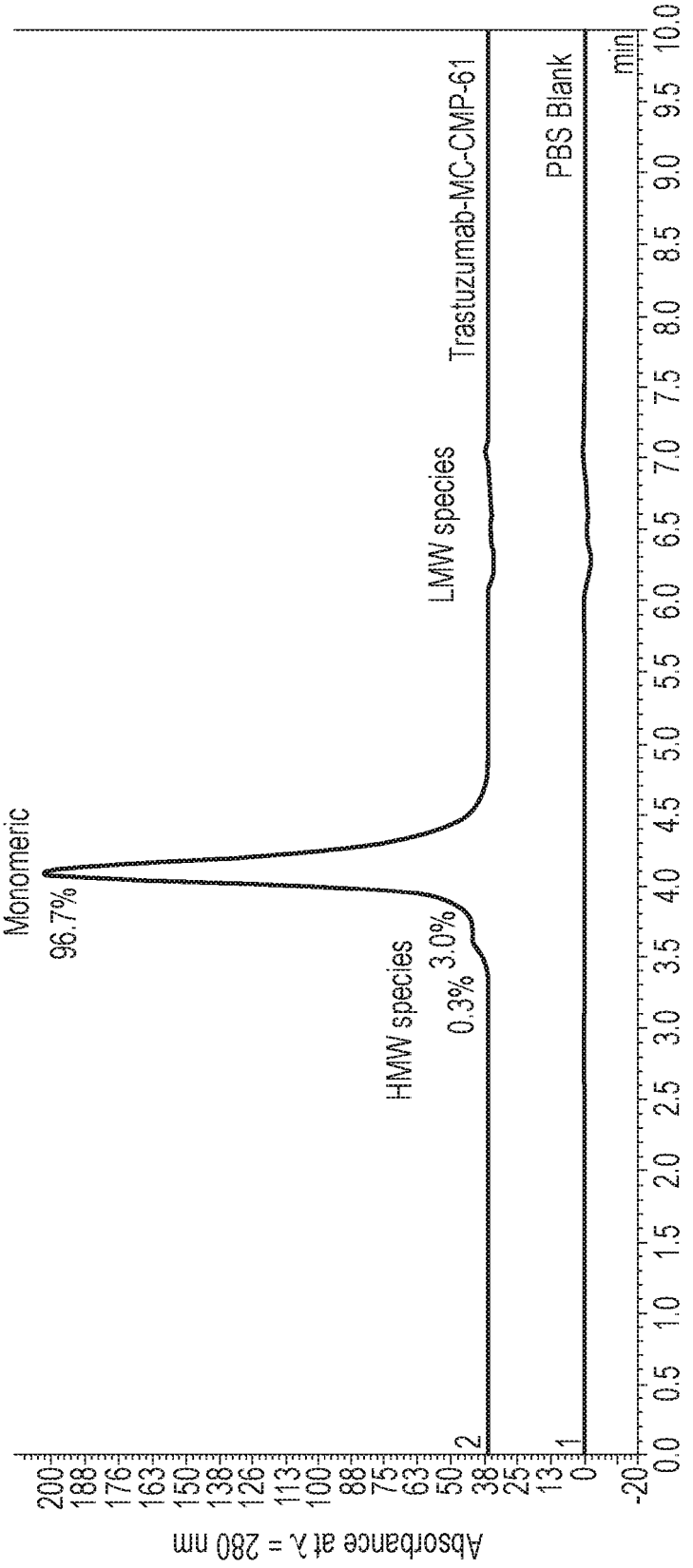
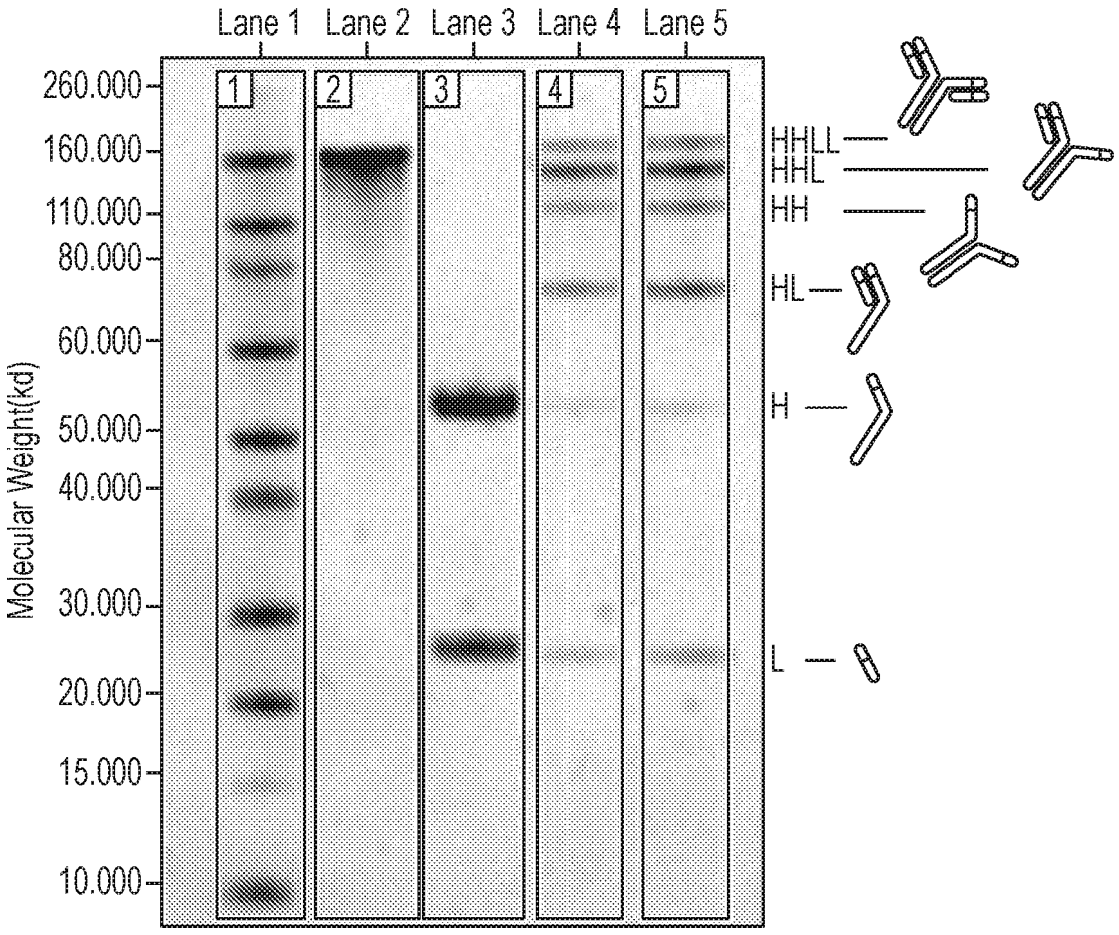

Monomeric
96.7%
HMW species
0.3%
3.0%
LMW species
Trastuzumab-MC-CMP-61
PBS Blank
Absorbance at λ = 280 nm
Retention time (min)
min
200
188
176
163
150
138
126
113
100
88
75
63
50
38
25
13
0
-20
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0
1
2

Fig. 6


Lane 1
Lane 2
Lane 3
Lane 4
Lane 5
1
2
3
4
5
260.000
160.000
110.000
80.000
60.000
50.000
40.000
30.000
20.000
15.000
10.000
Molecular Weight(kd)
HHLL
HHL
HH
HL
H
L

Small Molecule Modulators of Human STING, Conjugates and Therapeutic Applications

The present invention relates to conjugates of small molecule modulators of the Stimulator of Interferon Genes (STING) protein. Accordingly, the small molecule conjugates may be of use in the treatment of diseases, such as cancer and microbial infections, and so on. The invention extends to the pharmaceutical compositions of the compounds *per se* wherein a STING ligand is covalently bonded to a targeting moiety through a linker, methods of making such conjugates and methods of modulating the STING protein using these conjugates.

The human immune system has evolved to recognize and respond to different types of threats and pathogens to maintain a healthy host. The immune system may generally be divided into two arms, referred to as the 'innate immune system' and the 'adaptive immune system'. The innate arm is mainly responsible for a rapid initial inflammatory response to danger signals associated with cellular or tissue damage from bacteria, viruses and other infectious threats via a number of factors such as cytokines, chemokines and complement factors. These factors act upon a number of different cell types including mast cells, macrophages, dendritic cells and natural killer cells to directly attenuate pathogen viability and to stimulate an adaptive immune response. Unlike the innate immune system which does not respond to specific antigens, the adaptive immune system recognises specific antigens not expressed naturally in the host to mount anti-antigen specific responses. Adaptive responses, which occur later and are longer lasting than the more immediate innate responses, are characterized by antibody production together with CD8+ and CD4+ T-cell responses and B-lymphocyte responses that are critical for immunological memory.

The innate immune system senses pathogens or abberant cells by detecting damage-associated molecular patterns (DAMPs) or pathogen-associated molecular patterns (PAMPs) through an array of sentinel proteins called pattern recognition receptors (PRRs) that provide broad and lasting protection to the host against a wide range of threats (reviewed in Broz, P. *et. al.*, *Nat. Rev. Immunol.*, **2013**, *13*, 551-565). PRRs include Toll-like receptors (TLRs; Horscroft, *J. Antimicrob. Ther.*, **2012**, 67(4), 789-801; Diebold et al., *Science*, **2004**, 303, 1529-1531), C-type lectin receptors, retinoic acid inducible gene I (RIG-I like receptors; Pichlmair et. al., *Science*, **2006**,

314, 997-1001) and NOD-like receptors (NLRs) and also double stranded DNA sensors (cGAS/STING) (Takeuchi, O. *et. al.*, **2010**, *140*, 805-820).

PRRs respond to DAMPs and PAMPs by up-regulating Type-I interferons and other pro-inflammatory cytokines. Free cytosolic nucleic acids (DNA and RNA) are known PAMPs/DAMPs. The main sensor for cytosolic DNA is cGAS (cyclic GMP-AMP synthase). Upon recognition of cytosolic dsDNA, cGAS triggers formation of the hybrid cyclic dinucleotide cyclo-(AMP/GMP) (cGAMP) . cGAMP and other cyclic dinucleotides (CDNs) consist of two ribonucleotides that are connected via phosphodiester bonds to make a cyclic structure. CDNs cyclo-di(GMP) (c-diGMP), cyclo-di(AMP) (c-diAMP) and hybrid cyclo-(AMP/GMP) (cGAMP) derivatives all bind strongly to the ER-transmembrane adaptor protein STING (Burdette, D.L. *et. al.*, *Nature*, **2012**, *478*, 515-518; Ichikawa, H. *et. al.*, *Nature*, **2008**, *455*, 674-678; DeFilippis, V.R. *et. al.*, *J. Virol.*, **2010**, *84*, 585-598) with subsequent activation of the interferon pathway via the TANK binding kinase (TBK1) and the transcription factors IRF-3 and NF-$_K$B (Gao et. al., *Cell,* **2013**, 153, 1094-1107; Zhang et. al., *Mol. Cell*, **2013**, 51, 226-235). The canonical 5'-3' phosphodiester linkage is recognised along with various other linkage isomers (notably the 5'-2' linkage, *e.g.* c[G(2',5')pA(3',5')p]) which all bind to STING with various affinities (Shi et. al., *PNAS*, **2015**, 112, 1947-8952). These observations have been corroborated by structural studies (Gao et. al., *Cell,* **2013**, 154, 748-762; Burdette, D.L. *et. al.*, *Nature Immunol.*, **2013**, *14*, 19-26; Cai, X. *et. al.*, *Mol. Cell.*, **2014**, *54*, 289-296) of various linkage isomers of CDNs bound to the human and mouse STING proteins. Studies in STING-deficient mice have confirmed the role of STING in innate responses to cytosolic nucleic-acid ligands, particularly double stranded DNA and bacterial nucleic acids based on a cyclic dinucleotide structure (Ishikawa et. al., *Nature*, **2009**, 461, 788-792). STING has a critical role in the innate response to many bacterial, viral and eukaryotic pathogens (Watson et. al., *Cell*, **2012**, 150, 803-815; de Almeida et. al., *PLoS One*, **2011**, 6, e23135; Holm et. al, *Nat. Immunol*, **2012**, 13, 737-743; Stein et. al., *J. Virol.*, **2012**, 86, 4527-4537; Sharma et. al., *Immunity*, **2011**, 35, 194-207).

The importance of Type I interferons (IFNα and IFNβ) and pro-inflammatory cytokines on various cells of the immune system has been well established. They strongly potentiate T cell activation by enhancing the ability of dendritic cells and macrophages to present antigens to T cells. They upregulate co-stimulatory molecules such as CD80 and CD86, whichrapidly engage their cognate cell-surface receptors and trigger a phosphorylation cascade involving JAK kinases and STAT transcription factors to

activate interferon-stimulated genes (ISGs) that themselves can contribute to adaptive immune cell activation. The IFN system is therefore able to render cells and tissues refractory to replication of viruses (Ireton, R.C. *et. al.*, *Antiviral. Res.*, **2014**, *108*, 156-164) and drive T-cell priming against tumor-associated antigens for the treatment of cancer (Corrales *et. al.*, *Clin. Cancer Res.*, **2015**, *21*, 4774-4779). Indeed, recombinant IFNα has become an important therapy in viral infections and cancer.

The field of immunotherapy holds great promise (Oiseth, S.J.; Aziz, M.S., J. *Cancer Metastasis Treat.*, **2017**, *3*, 250-261). Administration of a small molecule compound which could modulate the innate immune response, including the activation or inhibition of Type I interferon production and other cytokines, could be an important strategy for the treatment or prevention of human diseases including viral infections (Barber *et. al.*, *Nat. Rev. Immunol.*, **2015**, *15*, 87-103), cancer (Zitvogel, L. *et. al.*, *Nat. Rev. Immunol.*, 2015, 15, 405-414), autoimmune disease (Rakoff-Nahoum, S. *et. al.*, *Cell*, **2004**, *23*, 229-241) and as a vaccine adjuvant (Dubensky et. al., Therapeutic Advances in Vaccines, published online Sept. 5, 2013).

One possible mechanism by which traditional vaccine adjuvants such as alum potentiate an immune response is through the release of DAMPs. Alum triggers the release of host cell DNA, which induce T cell responses and the production of IgG1 and IgE. Ideally, adjuvants should be molecularly defined and able to enhance the magnitude and timeframe of a specific immune response to an antigen resulting inenhanced protection against intracellular pathogens and/or reduced tumor burden. Examples of tumor-associated antigens include proto-oncogenes, tumor suppressor genes, overexpressed proteins, antigens expressed by oncogenic viruses, oncofetal antigens, altered glycolipids and glycoproteins.

Activation of the STING protein can create an activated or primed immune system, similar to that generated by an adjuvant. This may produce a protective or prophylactic state that withstands challenge or re-challenge by intracellular pathogens or by tumors by inhibiting their growth.

It can also be appreciated that when a STING activator is administered therapeutically to a system in which tumors/ pathogens are present it can act beneficially in two different, but related, ways. First, by direct shrinkage of tumors/ pathogen eradication through up-regulation of Type-I interferons and cytokines to act directly upon the

tumor/pathogens, as described above. Second, a STING activator will also induce a lasting immune response, such that re-challenge or re-inoculation with a pathogen or tumors will be resisted both through a general activation of the immune system and through a latent antigen-specific response to said pathogen or tumor.

STING is broadly expressed throughout the body in both immune cells and non-immune cells, for example in the spleen, heart, thymus, placenta, lung and peripheral leukocytes, indicating a role in triggering the innate immune system in response to PAMPs/DAMPs (Sun et. al., *PNAS*, **2009**, 106, 8653-8658). Its expression in immune cells leads to rapid amplification of the initial immune signal and maturation of APCs. It is expressed in several transformed cell lines including HEK293 human embryonic kidney cells, A549 adenocarcinomic human alveolar basal epithelial cells, THP-1 monocytic cells and U937 leukemic monocytic lymphoma cells.

STING also has a central role in certain autoimmune disorders initiated by inappropriate recognition of self DNA (Gall et. al., *Immunity*, **2012**, 36, 120-131) and has been proposed to sense membrane-fusing events associated with viral entry, in a manner independent of the sensing of nucleic acids (Holm et. al., *Nat. Immunol.*, **2012**, 13, 737-743).

STING is comprised of an N-terminal transmembrane domain, a central globular domain and a C-terminal tail. The protein forms a symmetrical dimer in the ligand bound state, with the cyclic dinucleotides binding at a dimer interface binding pocket. Binding of CDNs to STING activates a cascade of events whereby the protein recruits and activates TANK-binding kinase (TBK1), which following their phosphorylation activate nuclear transcription factors (NFκB) and interferon regulatory factor 3 (IRF3), respectively. These activated proteins translocate to the nucleus to induce transcription of the genes that encode Type I interferon and cytokines for promoting intercellular immune system defense. Sequence variations are known between human and mouse STING proteins, and between STING proteins within the human population. Five major haplotypes of human STING have been reported to encompass some 99% of the human population (WT, REF, HAQ, AQ and Q) (Yi *et. al.*, *PLoS One*, **2013**, 8, e77846).

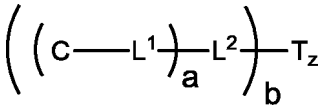
Derivatives of the CDN class are currently being developed as antitumor agents upon intratumoral injection (Corrales et.al., *Cell Rep.*, **2015**, 19, 1018-1030). The xanthene-based small molecule 5,6-dimethyl-xanthenone acetic acid (DMXAA) was initially

identified as an orally bioavailable small molecule exhibiting immune modulatory activities through induction of cytokines and disrupting tumor vascularization in mouse xenograft models (Baguley and Ching, *Int. J. Radiat. Oncol. Biol. Phys.*, **2002**, 54, 1503-1511). This promising efficacy led to its investigation in a Phase II clinical trial against non-small cell lung carcinoma but subsequently failed its endpoints. The mechanism of DMXAA's activity against murine tumors was eventually ascribed to its activity as a murine STING activator. Its failure in human clinical trials was due to the fact that DMXAA was only capable of activating mouse STING and not human STING (Lara et. al., *J. Clin. Oncol.*, **2011**, 29, 2965-2971; Conlon et. al., *J. Immunol.*, **2013**, 190, 5216-5225). This lack of human activity has hampered all further attempts to develop this agent as a tumor therapy. Recently, a related small molecule 10-carboxymethyl-9-acridanone (CMA) (Cavlar et. al., *EMBO J.*, **2013**, 32, 1440-1450) has been found to bind to mouse STING, but also not to human STING. Both DMXAA and CMA have been shown to bind two molecules of each ligand to the STING dimer at a region close to the dimer interface.

Accordingly, there remains a need in the art for improved therapies for treating diseases, such as cancer, which can be refractory to traditional therapeutic approaches. Immunologic strategies show promise for the treatment of cancer, and there is a need to develop improved compositions and methods in this field. In particular, there is a need for compounds that modulate the human STING protein, as well as methods for treating diseases that can benefit from such modulation.

The present invention has arisen from the inventors work in attempting to identify STING protein modulators.

Hence, in a first aspect of the invention, there is provided a compound of formula (**I**):



(**I**)

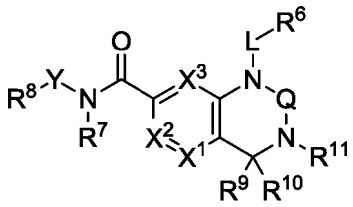
or a pharmaceutically acceptable salt or prodrug thereof, wherein:
L^1 and L^2 are linkers;
T is a targeting moiety;

a is an integer between 1 and 5;

b is an integer between 1 and 10;

z is an integer between 1 and 5; and

C is a compound of formula (**II**);



(**II**)

, wherein

X^1 is CR^1 or N;

X^2 is CR^2 or N;

X^3 is CR^3 or N;

Q is C=O, S=O, SO_2, C=S or CR^4R^5;

L is optionally substituted C_1-C_6 alkyl, C_1-C_3 polyfluoroalkyl, optionally substituted C_3-C_6 cycloalkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, C=O, S=O, SO_2, $-CH_2C(O)-$, $-CH_2CONH-$, or -CONH-;

Y is an optionally substituted C_1-C_6 alkyl, C_1-C_3 polyfluoroalkyl, an optionally substituted C_2-C_6 alkenyl, an optionally substituted C_2-C_6 alkynyl, an optionally substituted C_3-C_6 cycloalkyl, or an optionally substituted mono or bicyclic 3 to 8 membered heterocycle;

R^1, R^2 and R^3 are each independently selected from the group consisting of H, halogen, CN, hydroxyl, COOH, $CONR^1R^2$, NR^1R^2, $NHCOR^1$, optionally substituted C_1-C_6 alkyl, C_1-C_3 polyfluoroalkyl, optionally substituted C_1-C_6 alkylsulfonyl, optionally substituted mono or bicyclic C_3-C_6 cycloalkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted C_1-C_6 alkoxy, optionally substituted C_1-C_6 alkoxycarbonyl group, mono or bicyclic optionally substituted C_5-C_{10} aryl, mono or bicyclic optionally substituted 5 to 10 membered heteroaryl, optionally substituted mono or bicyclic 3 to 8 membered heterocycle, optionally substituted aryloxy, optionally substituted heteroaryloxy, and optionally substituted heterocyclyloxy;

R^4 and R^5 are each independently selected from the group consisting of H, halogen, optionally substituted C_1-C_6 alkyl and optionally substituted C_3-C_6 cycloalkyl; or R^4 and R^5 together with the atom to which they are attached form a spirocyclic ring;

R^6 is a ring optionally substituted with one or more R^{12} groups, wherein the ring is selected from the group consisting of a mono or bicyclic C_5-C_{10} aryl; a mono or bicyclic 5 to 10 membered heteroaryl; a C_3-C_6 cycloalkyl; and a mono or bicyclic 3 to 8 membered heterocycle;

R^7 is H, optionally substituted C_1-C_6 alkyl, optionally substituted sulfonyl, optionally substituted C_1-C_6 alkylsulfonyl, optionally substituted C_3-C_6 cycloalkyl, optionally substituted C_2-C_6 alkenyl or optionally substituted C_2-C_6 alkynyl;

R^8 is a mono or bicyclic optionally substituted C_5-C_{10} aryl, a mono or bicyclic optionally substituted 5 to 10 membered heteroaryl, optionally substituted mono or bicyclic C_3-C_6 cycloalkyl or an optionally substituted mono or bicyclic 3 to 8 membered heterocycle;

R^9 and R^{10} are each independently selected from the group consisting of optionally substituted C_1-C_6 alkyl, H, halogen, CN, CO_2H, $CONR^1R^2$, azido, sulfonyl, C_1-C_3 polyfluoroalkyl, optionally substituted C_1-C_6 thioalkyl, optionally substituted C_1-C_6 alkylsulfonyl, optionally substituted C_3-C_6 cycloalkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted C_1-C_6 alkoxy, optionally substituted C_1-C_6 alkoxycarbonyl, mono or bicyclic optionally substituted C_5-C_{10} aryl, mono or bicyclic optionally substituted 5 to 10 membered heteroaryl, optionally substituted heterocycle, optionally substituted aryloxy, and an optionally substituted heteroaryloxy; or R^9 and R^{10} together with the C atom to which they are attached can combine to form an optionally substituted spirocyclic ring;

R^{11} is selected from the group consisting of optionally substituted C_1-C_6 alkyl, H, hydroxyl, C_1-C_3 polyfluoroalkyl, optionally substituted C_1-C_6 thioalkyl, optionally substituted C_1-C_6 alkylsulfonyl, optionally substituted C_3-C_6 cycloalkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted C_1-C_6 alkoxy, optionally substituted C_1-C_6 alkoxycarbonyl, mono or bicyclic optionally substituted C_5-C_{10} aryl, mono or bicyclic optionally substituted 5 to 10 membered heteroaryl, optionally substituted heterocycle, optionally substituted aryloxy, and an optionally substituted heteroaryloxy;

the or each R^{12} group is independently selected from the group consisting of halogen, OH, SH, $OP(O)(OH)_2$, $NR^{13}R^{14}$, $CONR^{13}R^{14}$, CN, $COOR^{13}$, NO_2, azido, SO_2R^{13}, OSO_2R^{13}, $NR^{13}SO_2R^{14}$, $NR^{13}C(O)R^{14}$, $O(CH_2)_nOC(O)R^{13}$, $NR^{13}(CH_2)_nOC(O)R^{14}$, $OC(O)R^{13}$, $OC(O)OR^{13}$, $OC(O)NR^{13}R^{14}$, $OC(O)O(CH_2)_nCOOR^{14}$, $OC(O)NR^{13}(CH_2)_nCOOR^{14}$, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 alkoxy, optionally substituted aryloxy, optionally substituted heteroaryloxy, an optionally substituted mono or bicyclic C_5-C_{10} aryl, an optionally substituted mono or bicyclic 5 to 10

membered heteroaryl, an optionally substituted C_3-C_6 cycloalkyl and an optionally substituted mono or bicyclic 3 to 8 membered heterocycle;
R^{13} and R^{14} are each independently selected from the group consisting of H, optionally substituted C_1-C_6 alkyl, optionally substituted mono or bicyclic C_3-C_6 cycloalkyl, mono or bicyclic optionally substituted C_5-C_{10} aryl, mono or bicyclic optionally substituted 5 to 10 membered heteroaryl, and optionally substituted mono or bicyclic 3 to 8 membered heterocycle; and
n is an integer between 0 and 6;
or a pharmaceutically acceptable complex, salt, solvate, tautomeric form or polymorphic form thereof.

The inventors have found that the compounds of formula (**I**) are useful in therapy or as a medicament.

Hence, in a second aspect, there is provided a compound of formula (I) or a pharmaceutically acceptable complex, salt, solvate, tautomeric form or polymorphic form thereof, for use in therapy.

The inventors have also found that compounds of formula (I) are useful in modulating the Stimulator of Interferon Genes (STING) protein.

Hence, in a third aspect, there is provided a compound of formula (I) or a pharmaceutically acceptable complex, salt, solvate, tautomeric form or polymorphic form thereof, for use in modulating the Stimulator of Interferon Genes (STING) protein.

It will be appreciated that an 'agonist', an 'effector' or an activator, as it relates to a ligand and STING, comprises a molecule, combination of molecules, or a complex, that stimulates STING. Conversely, an 'antagonist', as it relates to a ligand and STING, comprises a molecule, combination of molecules, or a complex, that inhibits, counteracts, downregulates, and/or desensitizes STING. 'Antagonist' encompasses any reagent that inhibits a constitutive activity of STING. A constitutive activity is one that is manifest in the absence of a ligand/STING interaction. 'Antagonist' also encompasses any reagent that inhibits or prevents a stimulated (or regulated) activity of STING.

Preferably, the compound of formula (I) is for use in activating, or agonising, the STING protein. Accordingly, the compound of formula (**I**) may be an activator of the STING protein.

Advantageously, the compounds of the invention modulate the major human polymorphs of the human STING protein. There are several STING polymorphs reported, but the 5 polymorphs listed below are the major ones which comprise almost 99% of the total human population. Accordingly, the STING protein may be a wild type polymorph (WT/R232), a HAQ polymorph, a REF polymorph (H232), an AQ polymorph or a Q polymorph. As shown in Figure 1, the wild type polymorph has arginines at the 71, 232 and 293 positions and a glycine at the 230 position, the HAQ polymorph has a histidine at the 71 position, an alanine at the 230 position, an arginine at the 232 position and a glutamine at the 293 position, the REF polymorph has arginines at the 71 and 293 positions, a glycine at the 230 position and a histidine at the 232 position, the AQ polymorph has arginines at the 71 and 232 positions, an alanine at the 230 position and a glutamine at the 293 position, and the Q polymorph has arginines at the 71 and 232 positions, a glycine at the 230 position and a glutamine at the 293 position.

By modulating the STING protein, it is possible to treat, ameliorate or prevent cancer, bacterial infection, viral infection, parasitic infection, fungal infection, immune-mediated disorder, central nervous system disease, peripheral nervous system disease, neurodegenerative disease, mood disorder, sleep disorder, cerebrovascular disease, peripheral artery disease or cardiovascular disease.

Accordingly, in a fourth aspect there is provided a compound of formula (I) or a pharmaceutically acceptable complex, salt, solvate, tautomeric form or polymorphic form thereof, for use in treating, ameliorating or preventing a disease selected from cancer, bacterial infection, viral infection, parasitic infection, fungal infection, immune-mediated disorder, central nervous system disease, peripheral nervous system disease, neurodegenerative disease, mood disorder, sleep disorder, cerebrovascular disease, peripheral artery disease or cardiovascular disease.

Preferably, the disease is cancer.

In a fifth aspect, there is provided a method of modulating the Stimulator of Interferon Genes (STING) protein in a subject, the method comprising administering, to a subject in need of such treatment, a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable complex, salt, solvate, tautomeric form or polymorphic form thereof.

Preferably, the method comprises activating the STING protein.

The STING protein may be a wild type polymorph, a HAQ polymorph, a REF polymorph, an AQ polymorph or a Q polymorph.

In a sixth aspect, there is provided a method of treating, ameliorating or preventing a disease selected from cancer, bacterial infection, viral infection, parasitic infection, fungal infection, immune-mediated disorder, central nervous system disease, peripheral nervous system disease, neurodegenerative disease, mood disorder, sleep disorder, cerebrovascular disease, peripheral artery disease or cardiovascular disease, the method comprising administering, to a subject in need of such treatment, a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable complex, salt, solvate, tautomeric form or polymorphic form thereof.

It may be appreciated that the term "preventing" can mean "reducing the likelihood of".

The neurodegenerative disease may be Alzheimer's disease or dementia. The viral disease may be Hepatitis. The parasitic infection may be malaria. The mood disorder may be depression. The sleep disorder may be insomnia.

In one preferred embodiment, the disease is cancer. The cancer may be selected from the group consisting of colorectal cancer, aero-digestive squamous cancer, lung cancer, brain cancer, neuroblastoma, glioblastoma, Hodgkin lymphoma, non-Hodgkin lymphoma, thyroid cancer, adrenal cancer, liver cancer, testicular cancer, urothelial cancer, stomach cancer, kidney cancer, hepatocellular carcinoma, cancer of the pharynx, rectal cancer, gastrointestinal stromal tumors, gastroesophageal cancer, sarcoma, adenosarcoma, pituitary adenoma, Kaposi's sarcoma, neuroendocrine tumors, mesothelioma, leukaemia, acute myeloid leukaemia, small cell lung cancer, non-small cell lung cancer, lymphoma, lymphoid cancer, multiple myeloma, myelodysplasia syndrome, transitional cell carcinoma, malignant mesothelioma,

ovarian cancer, cervical cancer, uterine cancer, breast cancer, melanoma, prostate cancer, bladder cancer, bone cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular malignant melanoma, pancreatic carcinoma or renal cell carcinoma.

In an alternative preferred embodiment, the disease is a viral infection. The viral infection may be a hepatitis C virus (HCV) infection.

The following definitions are used in connection with the compounds of the present invention unless the context indicates otherwise.

Throughout the description and the claims of this specification the word "comprise" and other forms of the word, such as "comprising" and "comprises," means including but not limited to, and is not intended to exclude for example, other additives, components, integers, or steps.

As used in the description and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a composition" includes mixtures of two or more such compositions.

"Optional" or "optionally" means that the subsequently described event, operation or circumstances can or cannot occur, and that the description includes instances where the event, operation or circumstance occurs and instances where it does not.

"STING" refers to Stimulator of Interferon Genes receptor, also known as TMEM173, ERIS, MITA, MPYS, SAVI or NET23. As used herein, the terms "STING" or "STING receptor" are used interchangeably, and include different isoforms and variants of STING.

The terms "cancer" and "cancerous" refer to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth.

The term "tumor antigen" refers to a molecule (typically a protein, carbohydrate or lipid) that is expressed on the surface of a cancer cell, either entirely or as a fragment and is useful for the preferential targeting of a pharmacological agent to the cancer cell.

The term "alkyl", as used herein, unless otherwise specified, refers to a saturated straight or branched hydrocarbon. In certain embodiments, the alkyl group is a primary, secondary, or tertiary hydrocarbon. In certain embodiments, the alkyl group includes one to six carbon atoms, *i.e.* C_1-C_6 alkyl. C_1-C_6 alkyl includes for example methyl, ethyl, n-propyl (1-propyl) and isopropyl (2-propyl, 1-methylethyl), butyl, pentyl, hexyl, *iso*butyl, *sec*-butyl, *tert*-butyl, *iso*pentyl, *neo*pentyl, and *iso*hexyl. An alkyl group can be unsubstituted or substituted with one or more of halogen, OH, SeH, $OP(O)(OH)_2$, SR^1, SO_2R^1, OSO_2R^1, $NHSO_2R^1$, optionally substituted C_1-C_6 alkoxy, NR^1R^2, $NHC(NH)NH_2$, $CONR^1R^2$, CN, COOH, optionally substituted C_5-C_{10} aryl, optionally substituted 5 to 10 membered heteroaryl, C_3-C_6 cycloalkyl and 3 to 8 membered heterocycle. Accordingly, it will be appreciated that an optionally substituted C_1-C_6 alkyl may be an optionally substituted C_1-C_6 haloalkyl, *i.e.* a C_1-C_6 alkyl substituted with at least one halogen, and optionally further substituted with one or more of OH, C_1-C_6 alkoxy, NR^1R^2, $CONR^1R^2$, CN, COOH, an optionally substituted C_5-C_{10} aryl, an optionally substituted 5 to 10 membered heteroaryl, C_3-C_6 cycloalkyl and 3 to 8 membered heterocycle. It will be appreciated that an optionally substituted C_1-C_6 alkyl may be an optionally substituted polyfluoroalkyl. R^1 and R^2 may each independently be selected from the group consisting of H, halogen and optionally substituted C_1-C_6 alkyl.

The term "alkylene", as used herein, unless otherwise specified, refers to a bivalent saturated straight or branched hydrocarbon. In certain embodiments, the alkylene group is a primary, secondary, or tertiary hydrocarbon. In certain embodiments, the alkylene group includes one to six carbon atoms, *i.e.* C_1-C_6 alkylene. C_1-C_6 alkylene includes for example methylene, ethylene, n-propylene and isopropylene, butylene, pentylene, hexylene, *iso*butylene, *sec*-butylene, *tert*-butylene, *iso*pentylene, *neo*pentylene, and *iso*hexylene. An alkylene group can be unsubstituted or substituted with one or more of optionally substituted C_1-C_6 alkyl, halogen, OH, $OP(O)(OH)_2$, OSO_2R^1, $NHSO_2R^1$, C_1-C_6 alkoxy, NR^1R^2, $CONR^1R^2$, CN, COOH, optionally substituted C_5-C_{10} aryl, optionally substituted 5 to 10 membered heteroaryl, C_3-C_6 cycloalkyl and 3 to 8 membered heterocycle. Accordingly, it will be appreciated that an optionally substituted C_1-C_6 alkylene may be an optionally substituted C_1-C_6 haloalkylene, *i.e.* a C_1-C_6 alkylene substituted with at least one halogen, and optionally further substituted with one or more of OH, C_1-C_6 alkoxy, NR^1R^2, $CONR^1R^2$, CN, COOH, an optionally substituted C_5-C_{10} aryl, an optionally substituted 5 to 10 membered heteroaryl, C_3-C_6 cycloalkyl and 3 to 8 membered heterocycle. It will be appreciated that an optionally

substituted C_1-C_6 alkylene may be an optionally substituted polyfluoroalkylene. R^1 and R^2 may each independently be selected from the group consisting of H, halogen and optionally substituted C_1-C_6 alkyl.

The term "alkylyne", as used herein, unless otherwise specified, refers to a bivalent unsaturated straight or branched hydrocarbon. In certain embodiments, the alkylyne group is a primary, secondary, or tertiary hydrocarbon. In certain embodiments, the alkylyne group includes one to six carbon atoms, *i.e.* C_2-C_6 alkylyne. C_2-C_6 alkylyne includes for example ethylyne, propylyne, butylyne, pentylyne or hexylyne. An alkylyne group can be unsubstituted or substituted with one or more of optionally substituted C_1-C_6 alkyl, halogen, OH, $OP(O)(OH)_2$, OSO_2R^1, $NHSO_2R^1$, C_1-C_6 alkoxy, NR^1R^2, $CONR^1R^2$, CN, COOH, optionally substituted C_5-C_{10} aryl, optionally substituted 5 to 10 membered heteroaryl, C_3-C_6 cycloalkyl and 3 to 8 membered heterocycle. Accordingly, it will be appreciated that an optionally substituted C_2-C_6 alkylyne may be an optionally substituted C_2-C_6 haloalkylyne, *i.e.* a C_2-C_6 alkylyne substituted with at least one halogen, and optionally further substituted with one or more of OH, C_1-C_6 alkoxy, NR^1R^2, $CONR^1R^2$, CN, COOH, an optionally substituted C_5-C_{10} aryl, an optionally substituted 5 to 10 membered heteroaryl, C_3-C_6 cycloalkyl and 3 to 8 membered heterocycle. It will be appreciated that an optionally substituted C_2-C_6 alkylyne may be an optionally substituted polyfluoroalkylyne. R^1 and R^2 may each independently be selected from the group consisting of H, halogen and optionally substituted C_1-C_6 alkyl.

The term "halo" includes fluoro (-F), chloro (-Cl), bromo (-Br) and iodo (-I).

The term "polyfluoroalkyl" may denote a C_1-C_3 alkyl group in which two or more hydrogen atoms are replaced by fluorine atoms. The term may include perfluoroalkyl groups, *i.e.* a C_1-C_3 alkyl group in which all the hydrogen atoms are replaced by fluorine atoms. Accordingly, the term C_1-C_3 polyfluoroalkyl includes, but is not limited to, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, 3,3,3-trifluoropropyl, 2,2,3,3,3-pentafluoropropyl, and 2,2,2-trifluoro-1-(trifluoromethyl)ethyl.

"Alkoxy" refers to the group R^{15}-O- where R^{15} is an optionally substituted C_1-C_6 alkyl group, an optionally substituted C_3-C_6 cycloalkyl group, an optionally substituted C_2-C_6 alkenyl or an optionally substituted C_2-C_6 alkynyl. Exemplary C_1-C_6 alkoxy groups include but are not limited to methoxy, ethoxy, n-propoxy (1-propoxy), n-butoxy and

tert-butoxy. An alkoxy group can be unsubstituted or substituted with one or more of halogen, OH, $OP(O)(OH)_2$, OSO_2R^{13}, $N(H)SO_2R^{13}$, alkoxy, NR^1R^2, $CONR^1R^2$, CN, COOH, aryl, heteroaryl, cycloalkyl and heterocycle. R^1 and R^2 may each independently be selected from the group consisting of H, halogen and optionally substituted C_1-C_6 alkyl.

"Thioalkyl" refers to the group R^{15}-S- where R^{15} is an optionally substituted C_1-C_6 alkyl group or an optionally substituted C_3-C_6 cycloalkyl group. A thioalkyl group can be unsubstituted or substituted with one or more of halogen, OH, $OP(O)(OH)_2$, alkoxy, NR^1R^2, $CONR^1R^2$, CN, COOH, aryl, heteroaryl, cycloalkyl and heterocycle. R^1 and R^2 may each independently be selected from the group consisting of H, halogen and optionally substituted C_1-C_6 alkyl.

"Aryl" refers to an aromatic 5 to 10 membered hydrocarbon group. Examples of a C_5-C_{10} aryl group include, but are not limited to, phenyl, α-naphthyl, β-naphthyl, biphenyl, tetrahydronaphthyl and indanyl. An aryl group can be unsubstituted or substituted with one or more of optionally substituted C_1-C_6 alkyl, halogen, OH, $OP(O)(OH)_2$, optionally substituted C_1-C_6 alkoxy, NR^1R^2, $CONR^1R^2$, CN, COOH, NO_2, azido, C_1-C_3 polyfluoroalkyl, aryloxy, heteroaryloxy, 5 to 10 membered heteroaryl, 3 to 8 membered heterocycle, SO_2R^1, $NHCOR^1$, $OC(O)OR^1$, $OC(O)NR^1R^2$ and $OC(O)R^1$. R^1 and R^2 may each independently be selected from the group consisting of H, halogen and optionally substituted C_1-C_6 alkyl.

The term "bicycle" or "bicyclic" as used herein refers to a molecule that features two fused rings, which rings are a cycloalkyl, heterocyclyl, or heteroaryl. In one embodiment, the rings are fused across a bond between two atoms. The bicyclic moiety formed therefrom shares a bond between the rings. In another embodiment, the bicyclic moiety is formed by the fusion of two rings across a sequence of atoms of the rings to form a bridgehead. Similarly, a "bridge" is an unbranched chain of one or more atoms connecting two bridgeheads in a polycyclic compound. In another embodiment, the bicyclic molecule is a "spiro" or "spirocyclic" moiety. The spirocyclic group may be a C_3-C_6 cycloalkyl or a mono or bicyclic 3 to 8 membered heterocycle which is bound through a single carbon atom of the spirocyclic moiety to a single carbon atom of a carbocyclic or heterocyclic moiety. Alternatively, the spirocyclic group may be a C_3-C_{12} cycloalkyl or a mono or bicyclic 3 to 12 membered heterocycle which is bound through a single carbon atom of the spirocyclic moiety to a single

carbon atom of a carbocyclic or heterocyclic moiety. In one embodiment, the spirocyclic group is a cycloalkyl and is bound to another cycloalkyl. In another embodiment, the spirocyclic group is a cycloalkyl and is bound to a heterocyclyl. In a further embodiment, the spirocyclic group is a heterocyclyl and is bound to another heterocyclyl. In still another embodiment, the spirocyclic group is a heterocyclyl and is bound to a cycloalkyl. A spirocyclic group can be unsubstituted or substituted with one or more of optionally substituted C_1-C_6 alkyl, halogen, OH, optionally substituted C_1-C_6 alkoxy, NR^1R^2, $CONR^1R^2$, CN, COOH, NO_2, azido, C_1-C_3 polyfluoroalkyl and $NHCOR^1$. R^1 and R^2 may each independently be selected from the group consisting of H, halogen and optionally substituted C_1-C_6 alkyl.

"Alkoxycarbonyl" refers to the group alkyl-O-C(O)-, where alkyl is am optionally substituted C_1-C_6 alkyl. An alkoxycarbonyl group can be unsubstituted or substituted with one or more of halogen, OH, NR^1R^2, CN, C_1-C_6 alkoxy, COOH, C_5-C_{10} aryl, 5 to 10 membered heteroaryl or C_3-C_6 cycloalkyl. R^1 and R^2 may each independently be selected from the group consisting of H, halogen and optionally substituted C_1-C_6 alkyl.

"Aryloxy" refers to the group Ar-O- where Ar is a mono or bicyclic optionally substituted C_5-C_{10} aryl group, as defined above.

"Cycloalkyl" refers to a non-aromatic, saturated, partially saturated, monocyclic, bicyclic or polycyclic hydrocarbon 3 to 6 membered ring system. Representative examples of a C_3-C_6 cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl. A cycloalkyl group can be unsubstituted or substituted with one or more of optionally substituted C_1-C_6 alkyl, halogen, CN, hydroxyl, COOH, $CONR^1R^2$, NR^1R^2, $NHCOR^1$, C_1-C_6 alkoxy, azido, C_1-C_3 polyfluoroalkyl, aryloxy, heteroaryloxy, 5 to 10 membered heteroaryl, SO_2R^1, mono or bicyclic optionally substituted C_5-C_{10} aryl, mono or bicyclic optionally substituted 5 to 10 membered heteroaryl, optionally substituted mono or bicyclic 3 to 8 membered heterocycle, C_3-C_6 cycloalkyl. R^1 and R^2 may each independently be selected from the group consisting of H, halogen and optionally substituted C_1-C_6 alkyl.

"Heteroaryl" refers to a monocyclic or bicyclic aromatic 5 to 10 membered ring system in which at least one ring atom is a heteroatom. The or each heteroatom may be

independently selected from the group consisting of oxygen, sulfur and nitrogen. Examples of 5 to 10 membered heteroaryl groups include furan, thiophene, indole, azaindole, oxazole, thiazole, isoxazole, isothiazole, imidazole, N-methylimidazole, pyridine, pyrimidine, pyrazine, pyrrole, N-methylpyrrole, pyrazole, N-methylpyrazole, 1,3,4-oxadiazole, 1,2,4-triazole, 1- methyl-1,2,4-triazole, 1H-tetrazole, 1-methyltetrazole, benzoxazole, benzothiazole, benzofuran, benzisoxazole, benzimidazole, N-methylbenzimidazole, azabenzimidazole, indazole, quinazoline, quinoline, and isoquinoline. Bicyclic 5 to 10 membered heteroaryl groups include those where a phenyl, pyridine, pyrimidine, pyrazine or pyridazine ring is fused to a 5 or 6-membered monocyclic heteroaryl ring. A heteroaryl group can be unsubstituted or substituted with one or more of optionally substituted C_1-C_6 alkyl, halogen, OH, CN, NR^1R^2, azido, COOH, C_1-C_6 alkoxycarbonyl, C_1-C_3 polyfluoroalkyl, $CONR^1R^2$, NO_2, $NHCOR^1$ and SO_2R^1. R^1 and R^2 may each independently be selected from the group consisting of H, halogen and optionally substituted C_1-C_6 alkyl.

"Heterocycle" or "heterocyclyl" refers to 3 to 8 membered monocyclic, bicyclic or bridged molecules in which at least one ring atom is a heteroatom. The or each heteroatom may be independently selected from the group consisting of oxygen, sulfur and nitrogen. A heterocycle may be saturated or partially saturated. Exemplary 3 to 8 membered heterocyclyl groups include but are not limited to aziridine, oxirane, oxirene, thiirane, pyrroline, pyrrolidine, dihydrofuran, tetrahydrofuran, dihydrothiophene, tetrahydrothiophene, dithiolane, piperidine, 1,2,3,6-tetrahydropyridine-1-yl, tetrahydropyran, pyran, morpholine, piperazine, thiane, thiine, piperazine, azepane, diazepane, oxazine. A heterocyclyl group can be unsubstituted or substituted with one or more of optionally substituted C_1-C_6 alkyl, halogen, C_1-C_6 alkoxy, OH, NR^1R^2, COOH, C_1-C_6 alkoxycarbonyl, $CONR^1R^2$, NO_2, $NHCOR^1$, mono or bicyclic optionally substituted C_5-C_{10} aryl and SO_2R^1. R^1 and R^2 may each independently be selected from the group consisting of H, halogen and optionally substituted C_1-C_6 alkyl.

"Alkenyl" refers to olefinically unsaturated hydrocarbon groups which can be unbranched or branched. In certain embodiments, the alkenyl group has 2 to 6 carbons, *i.e.* it is a C_2-C_6 alkenyl. C_2-C_6 alkenyl includes for example vinyl, allyl, propenyl, butenyl, pentenyl and hexenyl. An alkenyl group can be unsubstituted or substituted with one or more of C_1-C_6 alkyl, halogen, OH, C_1-C_6 alkoxy, C_1-C_3 polyfluoroalkyl, NR^1R^2, $CONR^1R^2$, SO_2R^1, $NHCOR^1$, CN, COOH, C_5-C_{10} aryl, 5 to 10

membered heteroaryl, C_3-C_6 cycloalkyl, aryloxy, heteroaryloxy, and 3 to 8 membered heterocycle. R^1 and R^2 may each independently be selected from the group consisting of H, halogen and optionally substituted C_1-C_6 alkyl.

"Alkynyl" refers to acetylenically unsaturated hydrocarbon groups which can be unbranched or branched. In certain embodiments, the alkynyl group has 2 to 6 carbons, *i.e.* it is a C_2-C_6 alkynyl. C_2-C_6 alkynyl includes for example propargyl, propynyl, butynyl, pentynyl and hexynyl. An alkynyl group can be unsubstituted or substituted with one or more of C_1-C_6 alkyl, halogen, OH, C_1-C_6 alkoxy, C_1-C_3 polyfluoroalkyl, NR^1R^2, $CONR^1R^2$, SO_2R^1, $NHCOR^1$, CN, COOH, C_5-C_{10} aryl, 5 to 10 membered heteroaryl, C_3-C_6 cycloalkyl, aryloxy, heteroaryloxy, and 3 to 8 membered heterocycle. R^1 and R^2 may each independently be selected from the group consisting of H, halogen and optionally substituted C_1-C_6 alkyl.

"Alkylsulfonyl" refers to the group alkyl-SO_2- where alkyl is an optionally substituted C_1-C_6 alkyl, and is as defined as above.

"Heteroaryloxy" refers to the group heteroaryl-O- where the heteroaryl is a mono or bicyclic optionally substituted 5 to 10 membered heteroaryl, and is as defined above.

"Heterocyclyloxy" refers to the group heterocycle-O- where heterocycle is an optionally substituted mono or bicyclic 3 to 8 membered heterocycle, and is as defined as above.

Preferably, the targeting moiety targets an antigen and/or a receptor expressed on a cell surface.

Preferably, the compound of formula (**I**) is configured to release a compound of formula (**II**), or a cleavage product comprising the compound of formula (**II**). Preferably, the compound of formula (**I**) is configured to release a compound of formula (**II**), or the cleavage product comprising the compound of formula (**II**), when the compound of formula (**I**) is substantially adjacent to the cell expressing the antigen and/or receptor on the surface thereof.

The inventors have found that it is the compound of formula (**II**), or the cleavage product comprising the compound of formula (**II**), which modulates the STING

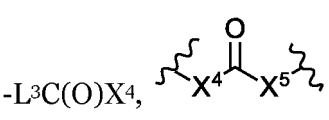
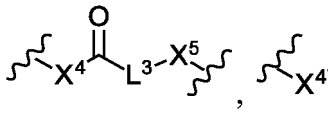
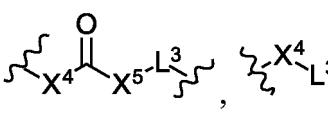
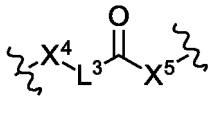
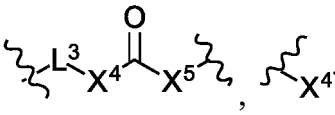
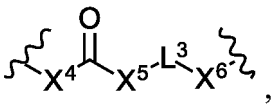
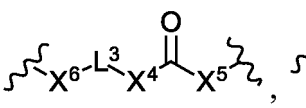
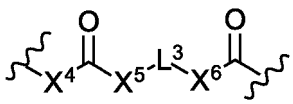
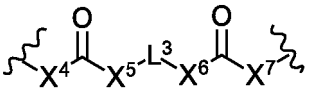
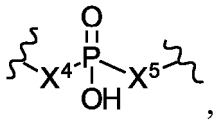
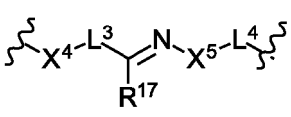
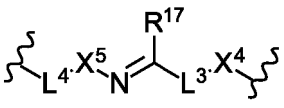
protein. Advantageously, the compound of formula (**I**) may be configured to deliver the compound of formula (**II**), or the cleavage product comprising the compound of formula (**II**), directly to a targeted cell.

The structure $(-L^1-)_a-L^2-$ may be referred to as "the linker".

L^1 may be absent or may be:

-A-W-D-

wherein:

A is absent or is selected from the group consisting of $-L^3-$, $-X^4L^3-$, $-L^3X^4-$, $-C(O)X^4$, $-L^3C(O)X^4$,  ,  ,  ,  ,  ,  ,  ,  ,  , $-X^4L^4-$, $-L^4X^4-$, $-X^4L^3L^4-$, $-L^4L^3X^4-$, $-X^4L^3L^4L^5-$, $-L^5L^4L^3X^4-$, $-L^3L^4-$, $-L^4L^3-$, $-L^3X^4L4-$, $-L^4X^4L^3-$, $-L^3L^4L^6-$, $-L^3X^4L^4X^5L^6-$,  ,  and  ;

W is either absent or is selected from the group consisting of $-L^7NH-$, $-L^3L^7NH-$, $-L^7NHC(O)-$, $-L^3L^7NHC(O)-$, $-L^7L^8NH-$, $-L^3L^7L^8NH-$, $-L^7L^8NHC(O)-$, and $-L^3L^7L^8NHC(O)-$;

D is either absent or has formula $-(D^1)_q-$ or $-(D^1)_qC(O)-$, wherein $(D^1)_q$ is either linear or cyclic;

the or each L^3 and L^6 are each independently an optionally substituted C_1-C_{25} alkylene or an optionally substituted C_2-C_{25} alkylyne;

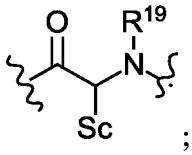
L^4 and L^5 are each independently selected from the group consisting of an optionally substituted mono or bicyclic C_5-C_{10} aryl; an optionally mono or bicyclic 5 to 10 membered heteroaryl; an optionally C_3-C_{12} cycloalkyl; and an optionally mono or bicyclic 3 to 12 membered heterocycle;

L^7 and L^8 are each independently an optionally substituted mono or bicyclic C_5-C_{10} aryl; or an optionally substituted mono or bicyclic 5 to 10 membered heteroaryl, wherein the aryl or heteroaryl is optionally further substituted with at least one $-OR^{18}$ group;

the or each of X^4, X^5, X^6 and X^7 is independently O, S or NR^1;

R^{17} is hydrogen or an optionally substituted $C_{1\text{-}6}$ alkyl;

R^{18} is an optionally substituted C_3-C_6 cycloalkyl, or an optionally substituted mono or bicyclic 3 to 8 membered heterocycle;

each D^1 independently has general formula  ;

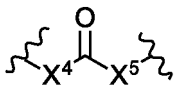
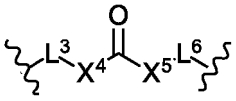
Sc is a side chain of a natural or unnatural amino acid and R^{19} is H, or Sc and R^{19} together with the atoms to which they are attached form a ring; and

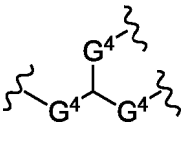
q is an integer between 2 and 20.

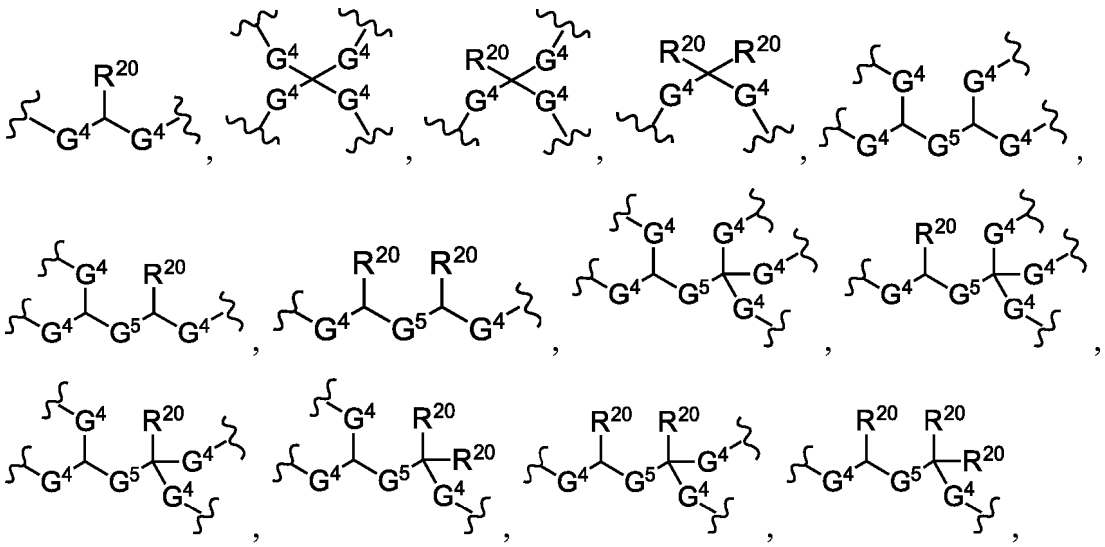
L^2 may be absent or may be:

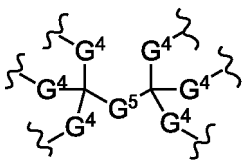
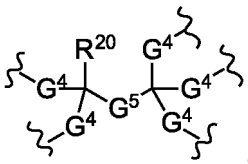
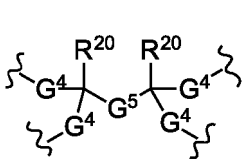
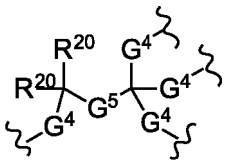
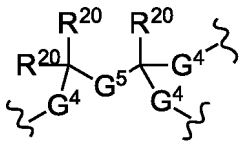
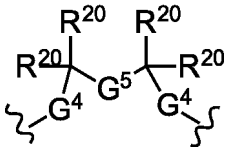
$$\text{-G-(S-)}_z$$

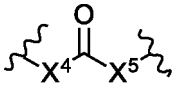
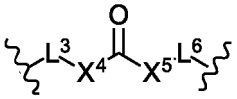
wherein, G is either absent or is $(-G^1)_a\text{-}G^2\text{-}(G^3\text{-})_z$,

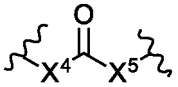
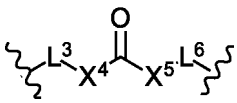
wherein, the or each G^1 is independently either absent or selected from the group consisting of $-L^3$-, $-(X^4L^3)_p$-, $-(L^3X^4)_p$-, $-L^4$-, $-X^4$-, $-X^8$-, $-X^4C(O)$-, $-C(O)X^4$-,  , $-L^3X^4C(O)$-, $-L^3C(O)X^4$,  , $-L^9$-, $-L^9L^3$-, $-L^9L^3C(O)$-, $-C(O)L^3$-, $-C(O)L^9$-, $-C(O)L^3X^4L^6$-, $-C(O)L^3X^4C(O)L^6$-, $-C(O)L^9L^3$-, $-C(O)L^3C(O)$-, $-C(O)L^9C(O)$-, $-C(O)L^9L^3C(O)$-, a poly(ethylene glycol) (PEG) chain of between 1 and 25 units and a cyclodextrin;

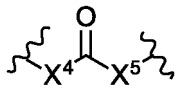
G^2 is either absent or is selected from the group consisting of  ,

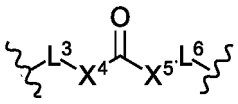







and  wherein a wavy line indicates either the attachment of G^2 to G^1 or, in embodiments where G^1 is absent, to L^1, or the attachment of the G^2 to G^3 or, in embodiments where G^3 is absent, to S, and each G^2, in embodiments where it is present, is attached to at least one G^1 or, in embodiments where G^1 is absent, to at least one group L^1, and each G^2, in embodiments where it is present, is attached to at least one G^3 or, in embodiments where G^3 is absent, to at least one group S;

the or each G^3 is independently either absent or selected from the group consisting of – L^3-, -$(X^4L^3)_p$-, -$(L^3X^4)_p$-, -L^4-, -X^4-, -X^8-, -$X^4C(O)$-, -$C(O)X^4$-,  , -$L^3X^4C(O)$-, -$L^3C(O)X^4$, -$L^3X^4C(O)L^6$-, -$L^3C(O)X^4L^6$-,  , -L^9-, -X^4L^9-, -L^9L^3-, -$L^9L^3C(O)$-, -$C(O)L^3$-, -$C(O)L^9$-, -$C(O)L^3X^4L^6$-, -$C(O)L^3X^4C(O)L^6$-, -$C(O)L^9L^3$-, -$C(O)L^3C(O)$-, -$C(O)L^9C(O)$-, -$C(O)L^9L^3C(O)$-, a poly(ethylene glycol) (PEG) chain of between 1 and 25 units and a cyclodextrin;

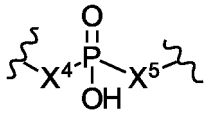
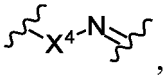
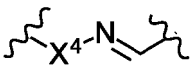
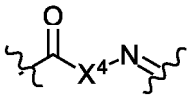
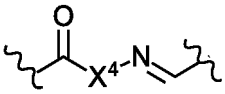
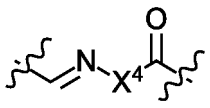
the or each G^4 is independently either absent or selected from the group consisting of –L^3-, -$(X^4L^3)_p$-, -$(L^3X^4)_p$-, -X^4-, -X^8-, -$X^4C(O)$-, -$C(O)X^4$-,  , -$L^3X^4C(O)$-, -$C(O)X^4L^3$-,-$L^3C(O)X^4$-, -$X^4C(O)L^3$-, -$X^4L^3C(O)X^5$-, -$X^4C(O)L^3X^5$-, -$L^3X^4L^6C(O)X^5$-, -$X^4C(O)L^3X^5L^3$-  , -L^9-, -L^9L^3-, -$L^9L^3C(O)$-, -$C(O)L^3$-, -$C(O)L^9$-, -$C(O)L^3X^4L^6$-, -$C(O)L^3X^4C(O)L^6$-, -$C(O)L^9L^3$-, -$C(O)L^3C(O)$-, -$C(O)L^9C(O)$-, -$C(O)L^9L^3C(O)$-, a poly(ethylene glycol) (PEG) chain of between 1 and 25 units and a cyclodextrin;

G^5 is either $-L^3-$, $-(X^4L^3)_p-$, $-(L^3X^4)_p-$, $-X^4-$, $-X^8-$, $-X^4C(O)-$, $-C(O)X^4-$,  ,

$-L^3X^4C(O)-$, $-L^3C(O)X^4$, $-L^3X^4C(O)L^6-$, $-L^3C(O)X^4L^6-$,  , $-L^9-$, $-X^4L^9-$, $-L^9L^3-$, $-L^9L^3C(O)-$, $-C(O)L^3-$, $-C(O)L^9-$, $-C(O)L^3X^4L^6-$, $-C(O)L^3X^4C(O)L^6-$, $-C(O)L^9L^3-$, $-C(O)L^3C(O)-$, $-C(O)L^9C(O)-$,

$-C(O)L^9L^3C(O)-$, a poly(ethylene glycol) (PEG) chain of between 1 and 25 units and a cyclodextrin;

S is either absent or is selected from the group consisting of $-X^4-$, $-X^4-$, $-X^8-$, $-C(X^9)-$, $-X^4C(X^9)-$, $-X^4C(X^9)L^3-$, $-X^4C(X^9)L^3C(O)-$, $-X^8L^3-$, $-X^4X^8L^3-$, $X^8L^3C(O)-$, $-L^3-$, $-L^4-$, $-L^4L^3-$, $-L^4C(O)-$, $-C(O)L^4C(O)-$, $-L^3C(O)L^4C(O)-$, $-L^4L^3L^5-$, $L^4L^3L^5C(O)-$,

 ,  ,  ,  ,  and  ;

L^3 to L^8 and X^4 to X^7 are as defined above,

L^9 is a poly(ethylene glycol) (PEG) chain between 1 and 25 units long;

X^8 is $-S(O)-$ or $-SO_2-$;

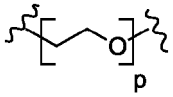
X^9 is O or S;

R^{20} is an optionally substituted C_1-C_6 alkyl, an optionally substituted C_2-C_6 alkenyl, an optionally substituted C_2-C_6 alkynyl, $-L^9H$, $-C(O)L^3H$, $-C(O)L^9H$, $-X^4L^3H$, $-X^4L^9H$, $-X^4C(O)L^3H$, $-X^4C(O)L^9H$, $-C(O)X^4L^3H$ or $-C(O)X^4L^9H$; and

p is an integer between 1 and 25.

a may be 1, 2, 3, 4 or 5. Preferably, a is an integer between 1 and 3.

z may be 1, 2, 3, 4 or 5. Preferably, z is an integer between 1 and 3.

$-L^9-$ may be  .

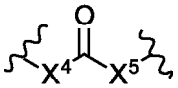
Preferably, at least one of L^1 and L^2 is present.

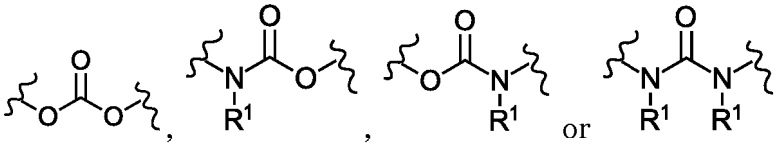
Preferably, 3 or less of A, W, D, G and S are absent, and more preferably 2 or less or 1 or less of A, W, D, G and S are absent. In some embodiments, non of A, W, D, G and S are absent.

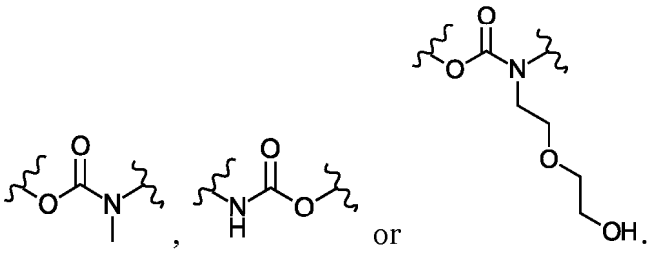
A may be $-L^3-$. L^3 may be an optionally substituted C_1-C_6 alkylene. Preferably, L^3 is an optionally substituted C_1-C_2 alkylene or an optionally substituted C_1 alkylene.

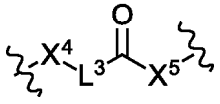
A may be $-L^3X^4-$. L^3 may be an optionally substituted C_1-C_6 alkylene, and is preferably $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$. Accordingly, A may be $-CH_2CH_2O-$, $-CH_2CH_2NH-$, $-CH_2CH_2S-$, $-CH_2CH_2CH_2O-$, $-CH_2CH_2CH_2NH-$ or $-CH_2CH_2CH_2S-$.

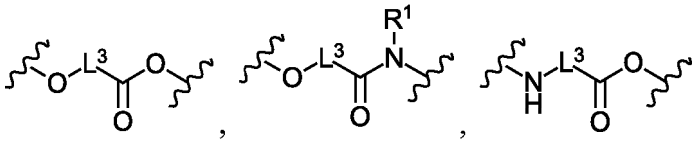
A may be $-C(O)X^4$ or $-L^3C(O)X^4$. X^4 may be O. L^3 may be an optionally substituted C_1-C_6 alkylene, and is preferably a C_1-C_3 alkylene, and most preferably is $-CH_2-$. Accordingly A may be $-C(O)O-$ or $-CH_2C(O)O-$.

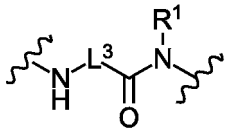
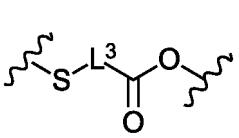
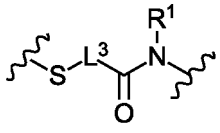
A may be  . X^4 may be $-O-$ or $-NR^1-$. X^5 may be $-O-$ or NR^1-.

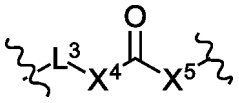
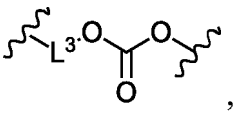
Accordingly, A may be  . R^1 may be an optionally substituted C_1-C_6 alkyl or hydrogen. The optionally substituted C_1-C_6 alkyl may be substituted with an optionally substituted C_1-C_6 alkoxy, which may be substituted with an -OH. Accordingly, R^1 may be methyl or $-CH_2CH_2OCH_2CH_2OH$.

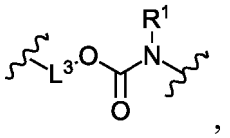
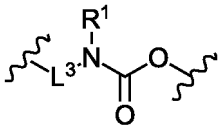
Accordingly, A may be  .

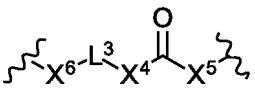
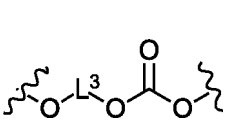
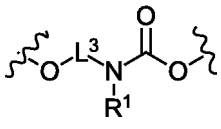
A may be  . X^4 may be $-O-$, $-S-$ or $-NH-$. X^5 may be $-O-$ or $-NR^1-$.

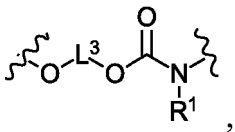
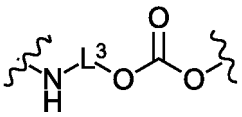
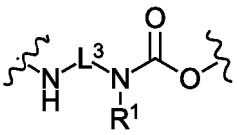
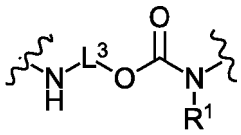
Accordingly, A may be  ,


, 
or 
. L^3 may be an optionally substituted C_1-C_{10} alkylene, and is preferably an optionally substituted C_1-C_6 alkylene.

A may be 
. X^4 may be –O- or –NR^1-. X^5 may be –O- or NR^1-. L3 may be an optionally substituted C_1-C_6 alkylene. Accordingly, A may be 
,


, 
or 
. Preferably, L^3 is an optionally substituted C_1-C_2 alkylene or an optionally substituted C_1 alkylene.

A may be 
. X^6 may be –O-, -S- or –NH-. X^4 may be –O- or –NR^1-. X^5 may be –O- or –NR^1-. A may be 
, 
,


, 
, 
, 
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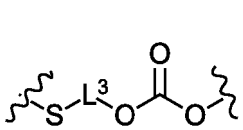
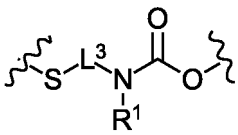
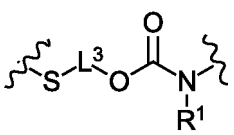
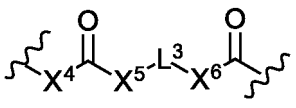
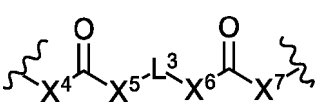
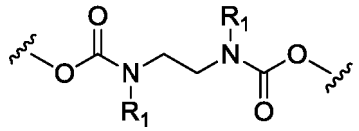
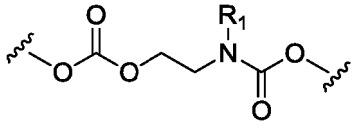
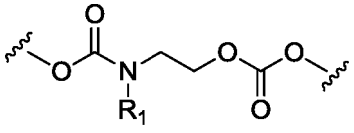
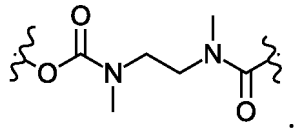
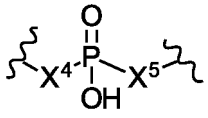
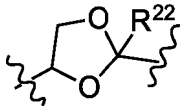
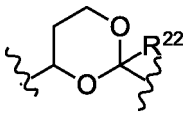
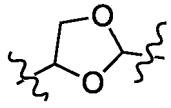
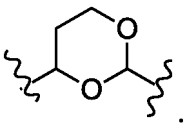
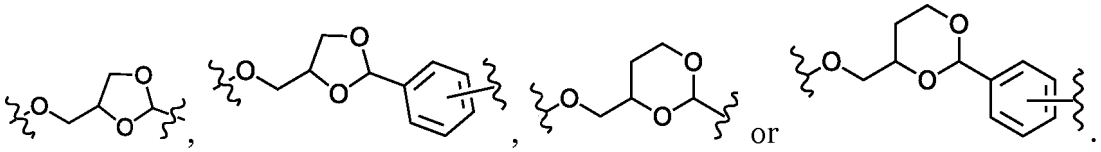

, 
or 
.

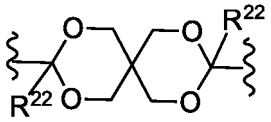
A may be 
or 
. X^4 may be –O-. X^5 may be –O- or NR^1-. L^3 may an optionally substituted C_1-C_6 alkylene, and is preferably –CH_2CH_2-. X^6 may be –O- or NR^1-. X^7 may be –O-. Accordingly, A may be:

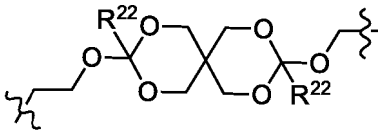
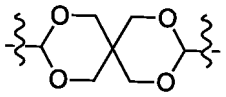
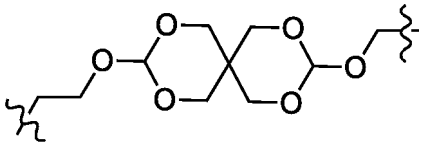




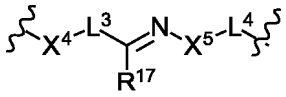
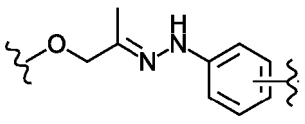
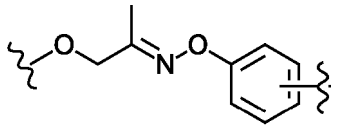
or  .

A may be  . Preferably, X^4 is –O-. Preferably, X^5 is –O-.

A may be -X^4L^3L4- or -$X^4L^3L^4L^5$-. X^4 may be –O-. L^3 may be an optionally substituted C_1-C_6 alkylene, and is preferably a C_1-C_2 alkylene, and more preferably is $–CH_2$-. L^4 may be an optionally substituted 3 to 12 membered heterocycle, preferably L^4 may is an optionally substituted 3 to 8 membered heterocycle, and most preferably L^4 is an optionally substituted 5 or 6 membered heterocycle. L^4 may be  or  , where R^{22} may be a hydrogen, a C_1-C_6 alkyl or a mono or bicyclic C_5-C_{10} aryl. Accordingly, L^4 may be  or  . L^5 may be an optionally substituted mono or bicyclic C_5-C_{10} aryl. Preferably, L^5 is an optionally substituted phenyl, and in some embodiments is an unsubstituted phenyl. Accordingly, A may be 

A may be -$L^3X^4L^4X^5L^6$-. L^3 and L^6 may independently be an optionally substituted C_1-C_6 alkylene, and are preferably independently a C_1-C_2 alkylene. L^3 may be $–CH_2CH_2$-. L^6 may be $–CH_2$-. X^4 may be –O-. X^5 may be –O-. L4 may be an optionally substituted 3 to 12 membered heterocycle. L^4 is preferably an optionally substituted 6 to 12 membered bicyclic heterocycle, and more preferably an optionally substituted 6 to 12 membered spirocyclic heterocycle. Accordingly, L^4 may be  , where R^{22} may be a hydrogen, a C_1-C_6 alkyl or a mono or bicyclic C_5-C_{10} aryl. Accordingly, L^4

may be  and is preferably  . Accordingly, A may be  .

A may be  . X^4 is preferably –O-. L^3 may be an optionally substituted C_1-C_6 alkylene, and preferably is a C_1-C_2 alkylene, and more preferably is –CH_2-. R^{17} may be an optionally substituted C_{1-6} alkyl, and is preferably a C_{1-3} alkyl and more preferably is a methyl. X^5 is preferably –NH- or –O-. L^4 may be an optionally substituted mono or bicyclic C_5-C_{10} aryl. Preferably, L^4 is an optionally substituted phenyl, and in some embodiments is an unsubstituted phenyl. Accordingly, A may be  or  .

As explained above, W is –L^7NH-, –L^3L^7NH-, -L^7NHC(O)-, -L^3L^7NHC(O)-, –L^7L^8NH-, –$L^3L^7L^8$NH-, -L^7L^8NHC(O)-, or -$L^3L^7L^8$NHC(O)-.

L^3 may an optionally substituted C_1-C_6 alkylene or C_1-C_6 alkylyne, preferably C_1-C_3 alkylene or C_1-C_3 alkylyne, and most preferably is –CH_2- or –CH_2CHCH-.

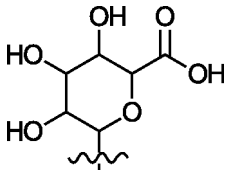
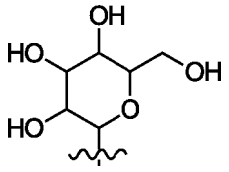
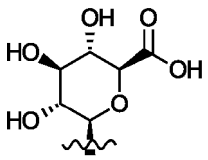
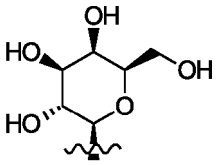
Preferably, L^7 and L^8 are each independently a mono or bicyclic C_5-C_{10} aryl; or a mono or bicyclic 5 to 10 membered heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one -OR^{18} group.

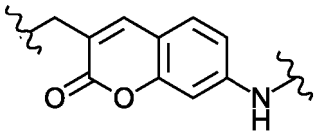
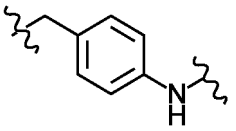
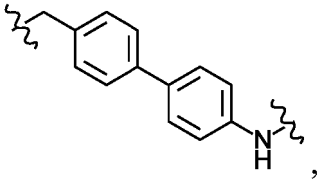
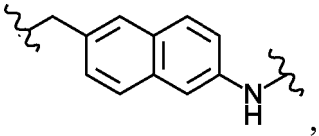
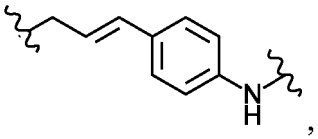
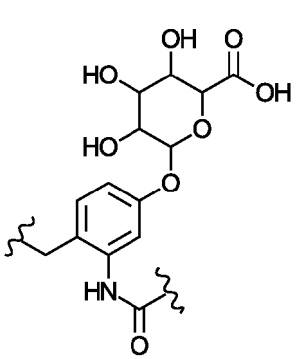
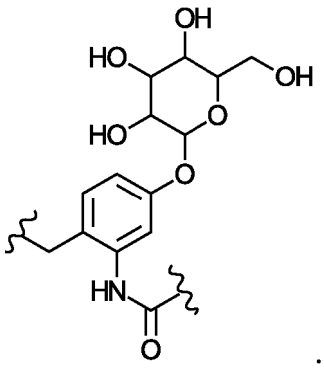
L^7 may be a phenyl, napthalenyl or a 2H-chromen-2-onyl group, wherein each group may be further substituted with one -OR^{18} group.

L^8 is preferably a phenyl.

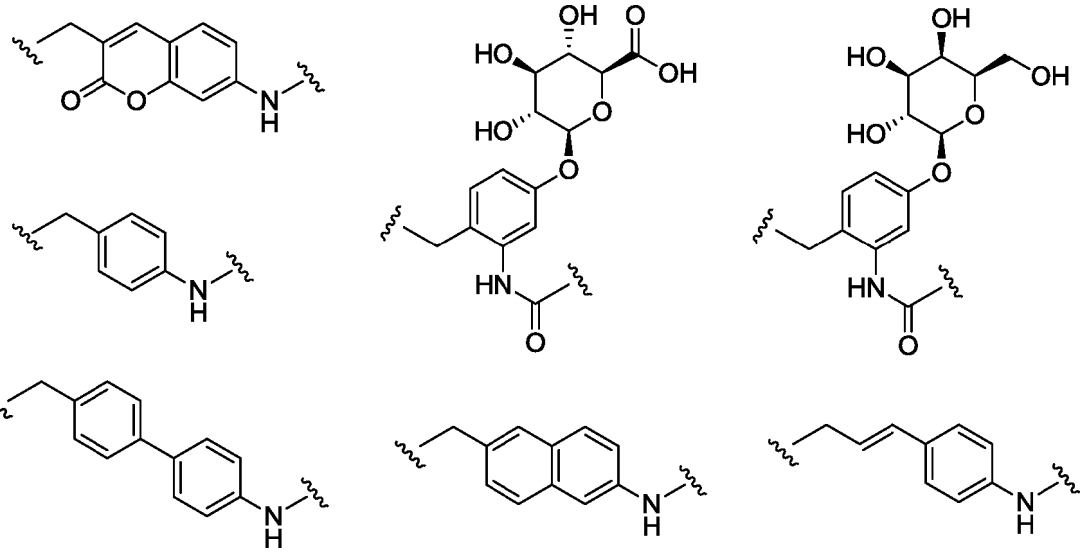
R^{18} is preferably an optionally substituted mono or bicyclic 3 to 8 membered heterocycle. More preferably, R^{18} is an optionally substituted 6 membered heterocycle,

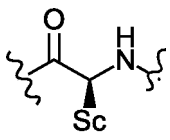
and most preferably an optionally substituted tetrahydropyranyl. Preferably, the heterocycle is substituted with between 1 and 9 substituents, more preferably between 2 and 7 or between 3 and 5 substituents, and most preferably with 4 substituents. The substituents may be selected from C_1-C_6 alkoxy, OH and COOH. Preferably, the C_1-C_6 alkoxy is a C_1-C_4 alkoxy, more preferably a C_1-C_2 alkoxy, and most preferably -CH_2OH. Preferably, the heterocycle is substituted with between 1 and 9 OH groups, more preferably between 2 and 5 OH groups, and most preferably with 3 OH groups. Preferably, the heterocycle is substituted with between 1 and 9 C_1-C_6 alkoxy and/or COOH groups, more preferably between 1 and 5 C_1-C_6 alkoxy and/or COOH groups, and most preferably with one C_1-C_6 alkoxy or COOH group.

R^{18} may be  or  . More preferably, R^{18} is  or  .

Accordingly, W may be  ,  ,  ,  ,  ,  or  .

More preferably W is selected from:



D^1 may have general formula  .

Sc may be H, an optionally substituted C_1-C_6 alkyl, an optionally substituted mono or bicyclic C_5-C_{10} aryl, an optionally mono or bicyclic 5 to 10 membered heteroaryl, an optionally C_3-C_{12} cycloalkyl, or an optionally mono or bicyclic 3 to 12 membered heterocycle. Preferably, Sc is H, an optionally substituted C_1-C_6 alkyl, a mono or bicyclic C_5-C_{10} aryl, a mono or bicyclic 5 to 10 membered heteroaryl, a C_3-C_{12} cycloalkyl, or a mono or bicyclic 3 to 12 membered heterocycle.

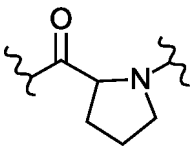
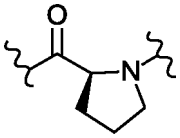
In embodiments where Sc is an optionally substituted C_1-C_6 alkyl, the alkyl may be substituted with at least one of NR^1R^2, $NHC(NH)NH_2$, OH, COOH, $CONR^1R^2$, SeH, SR^1, an optionally substituted C_5-C_{10} aryl, an optionally substituted 5 to 10 membered heteroaryl, an optionally substituted C_3-C_6 cycloalkyl or an optionally substituted 3 to 8 membered heterocycle. When the alkyl is substituted with NR^1R^2 then R^2 may be H. R^1 may also be H. Alternatively, R^1 may be $C(O)NH_2$. Accordingly, the alkyl may be substituted with $NHC(O)NH_2$. When the alkyl is substituted with $CONR^1R^2$ then R^2 may be H. R^1 may also be H. Alternatively, R^1 may be $C(O)NH_2$. When the alkyl is substituted with SR^1, R^1 may be H or a C_1-C_6 alkyl, preferably R^1 is H or methyl. When the alkyl is substituted with an optionally substituted C_5-C_{10} aryl, the optionally substituted C_5-C_{10} aryl is preferably optionally substituted phenyl. The phenyl may

optionally be substituted with an –OH. When the alkyl is substituted with an optionally substituted 5 to 10 membered heteroaryl, the optionally substituted 5 to 10 membered heteroaryl is preferably imidazolyl or 1H-indolyl.

In embodiments where Sc is $NC(O)R^1$, R^1 may be a C_1-C_6 alkyl, and preferably is methyl.

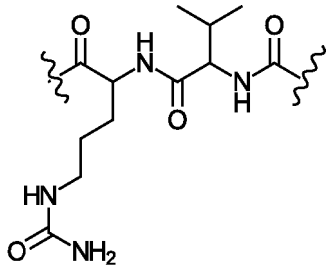
Accordingly, in some embodiments, Sc is H or a C_1-C_6 alkyl optionally substituted with at least one substituent selected from the group consisting of NH_2, $NHC(NH)NH_2$, OH, COOH, $CONR^1H$, SeH, SH, SCH_3, a phenyl optionally substituted with an OH, imidazolyl and 1H-indolyl.

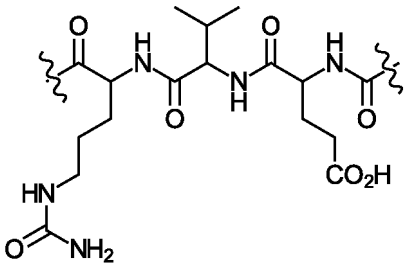
Preferably, Sc is a C_1-C_6 alkyl optionally substituted with $NHC(O)NH_2$ or COOH. More preferably, Sc is methyl, isopropyl, $-CH_2CH_2CH_2NHC(O)NH^2$ or $-CH_2CH_2COOH$.

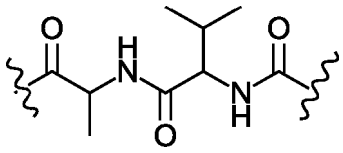
Alternatively, D^1 may be  , or more preferably  .

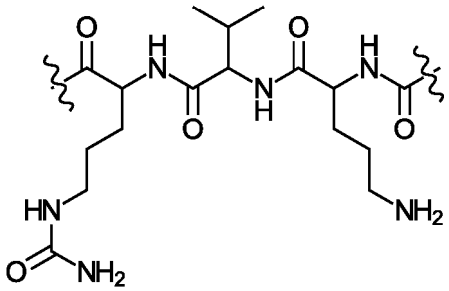
q may be an integer between 1 and 10, more preferably between 2 and 7, and most preferably between 3 and 5.

Accordingly, D may be:

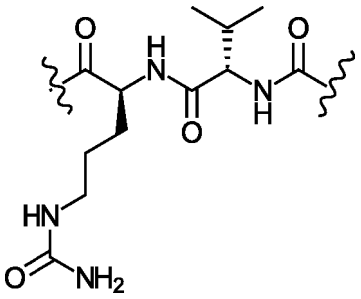
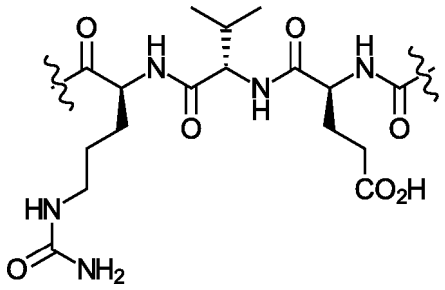
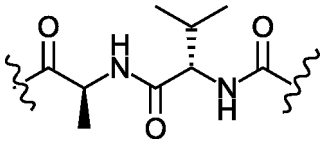
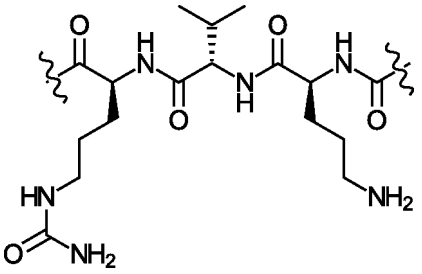




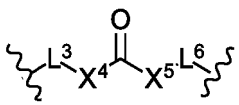
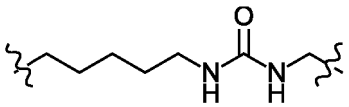
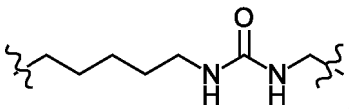




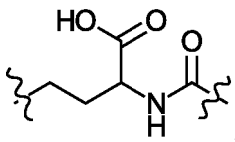
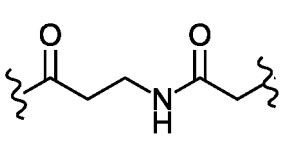
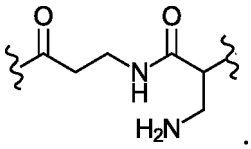
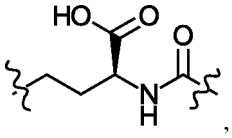
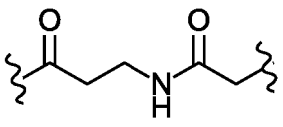
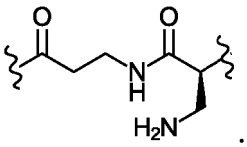
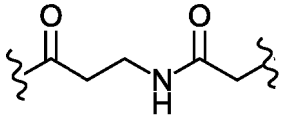
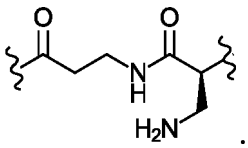
More preferably, D is:

G^1 and G^3 may each independently be $-L^3-$, $-(X^4L^3)_p-$ or $-(L^3X^4-)_p$. p may be 1 or 2. L^3 may be an optionally substituted C_1-C_{15} alkylene, more preferably an optionally substituted C_1-C_{10} alkylene, and most preferably optionally substituted C_1-C_6 alkylene. L^3 may be substituted with one or more optionally substituted C_1-C_6 alkyl. Preferably, the C_1-C_6 alkyl is unsubstituted. Accordingly, G^1 and G^3 may each independently be substituted with one or more methyl groups. G^1 and G^3 may each independently be $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-CH_2C(Me)H-$, CH_2CMe_2-, $-CH_2CMe_2S-$ $-CH_2O-$, $-CH_2CH_2O-$, $-CH_2CH_2OCH_2CH_2O-$ or $-(CH_2)_5NH-$. In embodiments where G^2 and G^3 are absent, G may be $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-CH_2C(Me)H-$, CH_2CMe_2-, $-CH_2CMe_2S-$ or $-(CH_2)_5NH-$. In some embodiments where G^1 and G^3 are present, but G^2 is absent, G may be $-CH_2OCH_2CH_2OCH_2CH_2O-$.

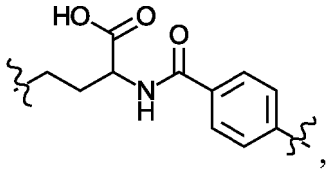
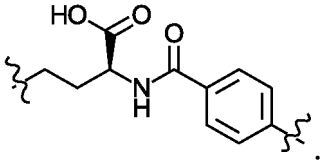
G^1 and G^3 may each independently be  . L^3 and L^6 may independently be an optionally substituted C_1-C_{10} alkylene, and more preferably an optionally substituted C_1-C_6 alkylene. X^4 may be NH. X^5 may be NH. Accordingly, G^1 and/or G^3 may be  . In embodiments where G^2 and G^3 are absent, G may be  .

G^1 and G^3 may each independently be may be $-L^3X^4C(O)-$ or $-C(O)L^3X^4C(O)L^6-$. Preferably, L^3 is an optionally substituted C_1-C_{15} alkylene, more preferably an optionally substituted C_1-C_{10} alkylene, and most preferably an optionally substituted C_1-C_6 alkylene. The alkylene may be substituted with an optionally substituted C_1-C_6 alkyl or –COOH. The alkyl may be substituted with NH_2. Preferably X^4 is –NH-. L^6 is preferably, an optionally substituted C_1-C_{15} alkylene, more preferably an optionally substituted C_1-C_{10} alkylene, and most preferably an optionally substituted C_1-C_6 alkylene. The alkylene may be substituted with an optionally substituted C_1-C_6 alkyl or –COOH. The alkyl may be substituted with NH_2. Alternatively, the alkylene may be unsubstituted. Accordingly, G^1 and G^3 may each independently be–$(CH_2)_5NHC(O)$-,

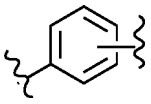


or

. More preferably, G^1 and G^3 may each independently be –$(CH_2)_5NHC(O)$-,

,

or

. In embodiments where G^2 and G^3 are absent, G may be–$(CH_2)_5NHC(O)$-,

or

.

G^1 and G^3 may each independently bean optionally substituted C_3-C_6 cycloalkyl, a mono or bicyclic optionally substituted C_5-C_{10} aryl, a mono or bicyclic optionally substituted 5 to 10 membered heteroaryl or a mono or bicyclic optionally substituted 5 to 10 membered heterocycle.

In some embodiments G may be -$L^3X^4C(O)$-. G^2 may be absent. G^3 may be $-L^4$-.

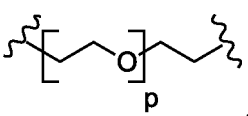
Accordingly, G may be  , and is preferably  .

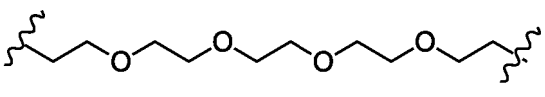
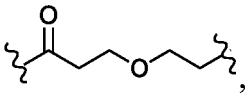
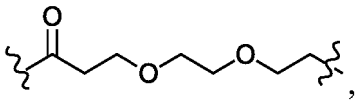
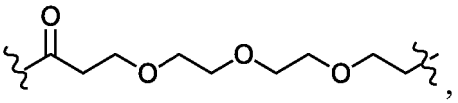
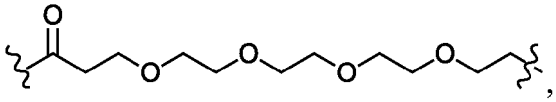
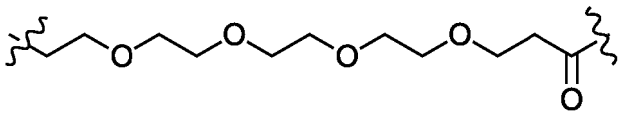
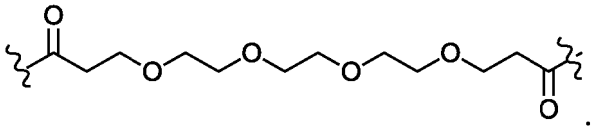
G^1 and G^3 may each independently be–O-, -S-, -NR^1-, -S(O)-, $-SO_2$-, -$C(O)L^3$-,-$C(O)L^3C(O)$-, -$OC(O)$-, -$C(O)O$-, -$OC(O)O$-, -$L^3OC(O)$ -, -$L^3C(O)O$-, -$(OL^3)_p$-, -$(L^3O)_p$-, -$C(O)NR^1$-, -$NR^1C(O)O$- or -$NR^1C(O)NR^1$-. In some embodiments, G^1 and G^3 may each independently be-$C(O)L^3$- or -$C(O)L^3C(O)$- where L^3 is an optionally substituted C_1-C_6 alkylene, and more preferably an optionally substituted C_4-C_5 alkylene. In embodiments where G^2 and G^3 are absent, G may be -$C(O)L^3$- or -$C(O)L^3C(O)$- where L^3 is an optionally substituted C_1-C_6 alkylene, and more preferably an optionally substituted C_4-C_5 alkylene.

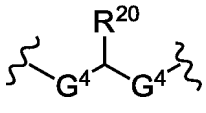
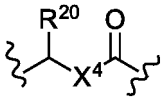
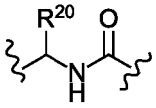
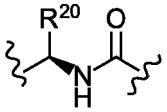
G^1 and/or G^3 may be $-L^4$-. Accordingly, G^1 and/or G^3 may be an optionally substituted mono or bicyclic C_5-C_{10} aryl. G^1 and/or G^3 may be an optionally substituted phenyl. In embodiments where G^2 and G^3 are absent, G may be  .

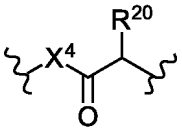
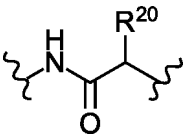
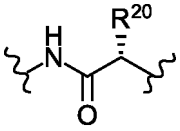
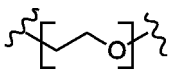
G^1 and/or G^3 may be a poly(ethylene glycol) (PEG) chain of between 1 and 25 units. The PEG chain may be a cyclic PEG chain, branched PEG chain or a linear PEG chain.

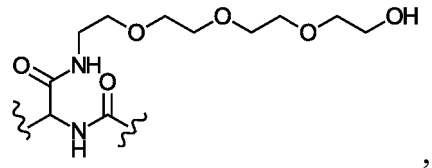
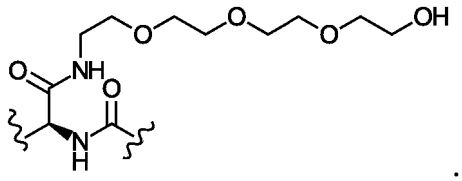
G^1 and/or G^3 may be a cyclodextrin. The cyclodextrin may be α, β or γ cyclodextrin.

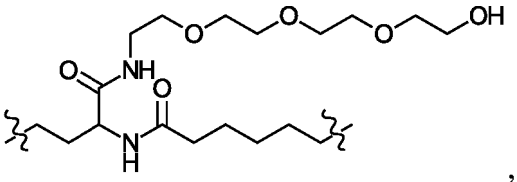
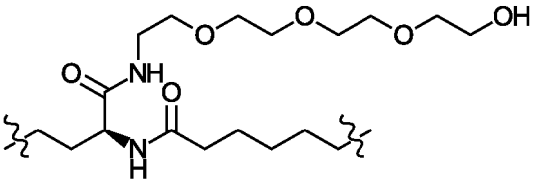
G^1 and/or G^3 may be -$C(O)L^9L^3$-, -$L^9L^3C(O)$-, -$C(O)L^9L^3C(O)$- or -L^9L^3-. L^3 may be an optionally substituted C_1-C_6 alkylene, and is more preferably methylene or ethylene. G^1 and/or G^3 may be  . p may be an integer between 1 and 15, more preferably between 2 and 10 or between 3 and 5. In embodiments where G^2 and G^3 are

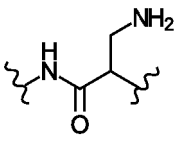
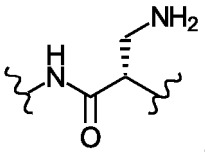
absent, G may be  ,  ,  ,  ,  ,  or  .

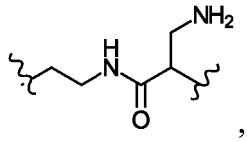
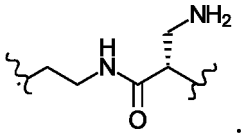
G^2 may be  . Each G^4 may be absent, $-L^3-$ or $-X^4C(O)-$. In one embodiment, one G^4 is absent and one G^4 is $-X^4C(O)-$. X^4 may be –NH-. Accordingly, G^2 may be  , preferably is  , and more preferably is  .

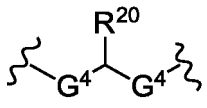
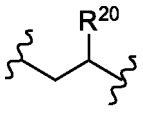
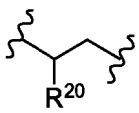
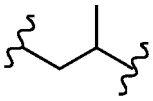
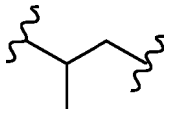
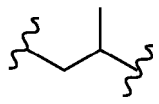
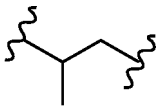
Alternatively, G^2 may be  , preferably is  , and more preferably is  . In one embodiment, R^{20} may be $-L^9H$, $-C(O)L^9H$, $-X^4L^9H$, $-X^4C(O)L^9H$ or $-C(O)X^4L^9H$. Preferably R^{20} is $-C(O)X^4L^9H$. X^4 may be –NH-. L^9- may be  . p may be an integer between 2 and 10, more preferably between 3 and

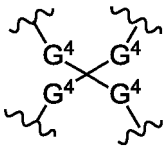
5, and most preferably 4. Accordingly, G^2 may be  , and more preferably is  .

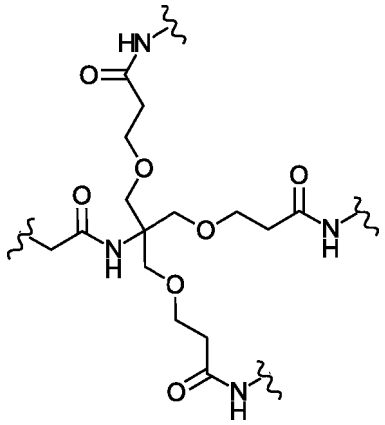
G^1 and G^3 may each independently be an optionally substituted C_1-C_{10} alkylene, more preferably an optionally substituted C_1-C_6 alkylene. G^1 may be ethylene. G^3 may be pentylene. Accordingly, G may be  , and preferably is  .

In an alternative embodiment, R^{20} may be an optionally substituted C_1-C_6 alkyl, an optionally substituted C_2-C_6 alkenyl or an optionally substituted C_2-C_6 alkynyl. More preferably, R^{20} is an optionally substituted C_1-C_3 alkyl, and most preferably is optionally substituted methyl. Preferably, the alkyl, alkenyl or C_2-C_6 alkynyl is substituted with – NR^1R^2. Preferably, R^1 and R^2 are H. Accordingly, G^2 may be  and mpre preferably is  .

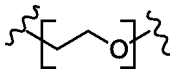
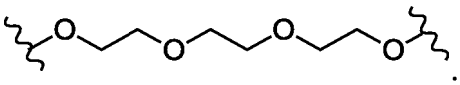
G^1 may be an optionally substituted C_1-C_{10} alkylene, more preferably an optionally substituted C_1-C_6 alkylene. G^1 may be ethylene. G^3 may be absent. Accordingly, G may be  , and preferably is  .

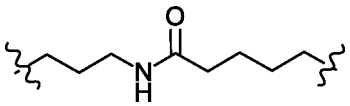
In an alternative embodiment, G^2 may be  and one G^4 is absent and one if $-L^3$-. $-L^3$- may be a an optionally substituted C_1-C_{12} alkylene, more preferably an optionally substituted C_1-C_6 alkylene, and most preferably methylene or ethylene. Accordingly, G^2 may be  or  . R^{20} may be an optionally substituted C_1-C_6 alkyl, and in some embodiments is methyl. Accordingly, G^2 may be  or  . G^1 and G^3 may be absent. Accordingly, in some embodiments, G may be  or  .

In some embodiments, G^2 may be  . Each G^4 may independently be absent, or selected from the group consisting of $-L^3X^4C(O)$-, $-C(O)X^4L^3$-,$-L^3C(O)X^4$, $-X^4C(O)L^3$-, $-X^4L^3C(O)X^5$-, $-X^4C(O)L^3X^5$-, $-L^3X^4L^6C(O)X^5$- and $-X^4C(O)L^3X^5L^3$-. At least one G^4 group may be $-X^4C(O)L^3$-. X^4 may be –NH-. $-L^3$- may be an optionally substituted C_1-C_{12} alkylene, more preferably an optionally substituted C_1-C_6 alkylene, and most preferably methylene or ethylene. At least one G^4 group may be $-L^3X^4L^6C(O)X^5$-. Preferably, at least two or at least three G^4 groups are $-L^3X^4L^6C(O)X^5$-. Each X^4 may be –NH-. Each X^5 may be –NH-. Each $-L^3$- and $-L^6$- may independently be an optionally substituted C_1-C_{12} alkylene, more preferably an optionally substituted C_1-C_6 alkylene, and most preferably methylene or ethylene. Accordingly, G^2 may be:

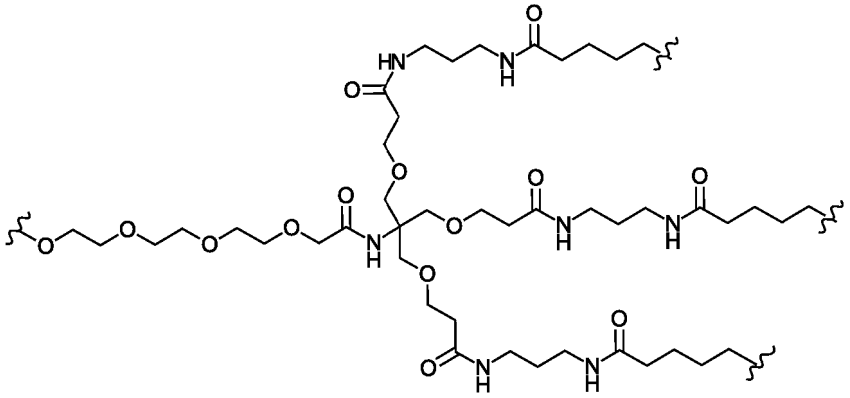


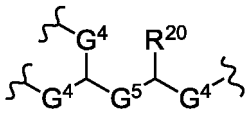
Each G^1 and G^3 may independently be absent, $-L^3$-, -L^9-, -X^4L^9-, -L^9L^3-,-$L^3X^4C(O)$-, -$L^3C(O)X^4$, -$L^3X^4C(O)L^6$- or -$L^3C(O)X^4L^6$-.

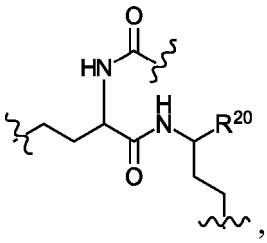
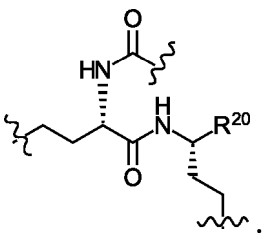
The G group may comprise at least one G^1 group. Accordingly, a may be 1, 2 or 3. Preferably, a is 1. G^1 may be -L^9- or -X^4L^9-. Preferably, G^1 is -X^4L^9-. Preferably, X^4 is –O-. Preferably, $-L^9$- is  and p is an integer between 1 and 10, more preferably between 2 and 5, most preferably p is 3. Accordingly, G^1 may be  .

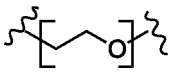
The G group may comprise at least one, at least two or at least three G^3 groups. Accordingly, z may be 1, 2 or 3. Preferably, z is 3. G^3 may be -$L^3X^4C(O)$-, -$L^3C(O)X^4$, -$L^3X^4C(O)L^6$- or -$L^3C(O)X^4L^6$-.. Preferably, G^3 is -$L^3X^4C(O)L^6$-. -L^3- and $-L^6$- may independently be an optionally substituted C_1-C_{12} alkylene, more preferably an optionally substituted C_1-C_6 alkylene, and most preferably a C_2-C_5 alkylene. Preferably, X^4 is –NH-. Accordingly, each G^3 may be  .

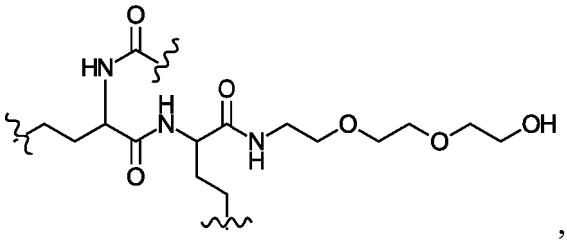
Accordingly, in some embodiments, G may be:



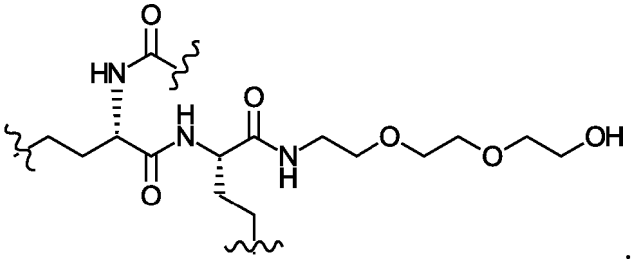
G^2 may be  . Each G^4 may independently be absent, -L^3-, -X^4-, -X^8-, -$X^4C(O)$- or -$C(O)X^4$-. Preferably, at least one, and more preferably at least two G^4 groups are –L^3-. –L^3- may be an optionally substituted C_1-C_{12} alkylene, more preferably an optionally substituted C_1-C_6 alkylene, and most preferably methylene or ethylene. Preferably, at least one G^4 group is -$X^4C(O)$-. Preferably X^4 is –NH-. Preferably, G^5 is -$X^4C(O)$- or -$C(O)X^4$-. Preferably, X^4 is –NH-. Accordingly, G^2 may be

 , and more preferably is  . R^{20} may be -$X^4C(O)L^3H$, -$X^4C(O)L^9H$, -$C(O)X^4L^3H$ or -$C(O)X^4L^9H$. Preferably, X^4 is –NH-.

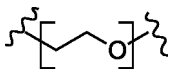
Preferably, R^{20} is -$C(O)X^4L^9H$. Preferably, –L^9- is  and p is an integer between 1 and 10, more preferably between 2 and 5, and most preferably p is 3.



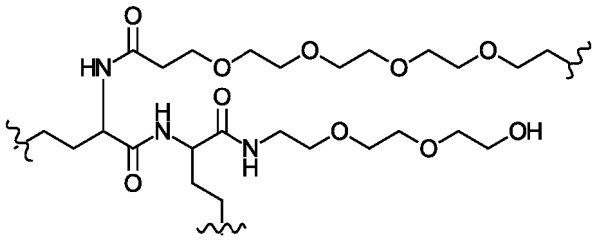
Accordingly, G^2 may be , and more



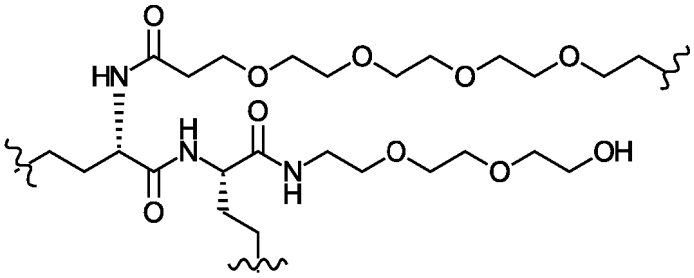
preferably is .



G^1 may be absent. G^3 may be $-L^3-$, $-L^9-$, or $-L^9L^3-$. Preferably, $-L^9-$ is and p is an integer between 1 and 10, more preferably between 2 and 5, and most preferably p is 4. $-L^3-$ may be an optionally substituted C_1-C_{12} alkylene, more preferably an optionally substituted C_1-C_6 alkylene, and most preferably ethylene.



Accordingly, G may be , and is more

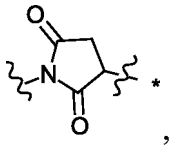
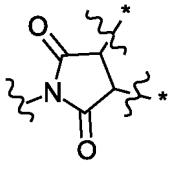
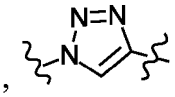
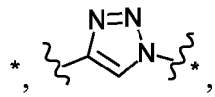
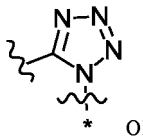
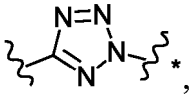


preferably .

S may be $-L^3-$. L^3 may an optionally substituted C_1-C_{10} alkylene, more preferably an optionally substituted C_1-C_6 alkylene. Preferably, the alkylene is unsubstituted.

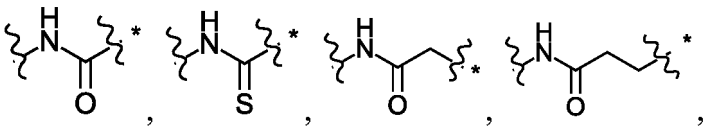
S may be -X^4L^3-. X^4 may be –NH-. L^3 may be a C_1-C_{12} optionally substituted alkylene, more preferably a C_1-C_6 optionally substituted alkylene and most preferably methylene or ethylene. Accordingly, S may be –$NHCH_2$-.

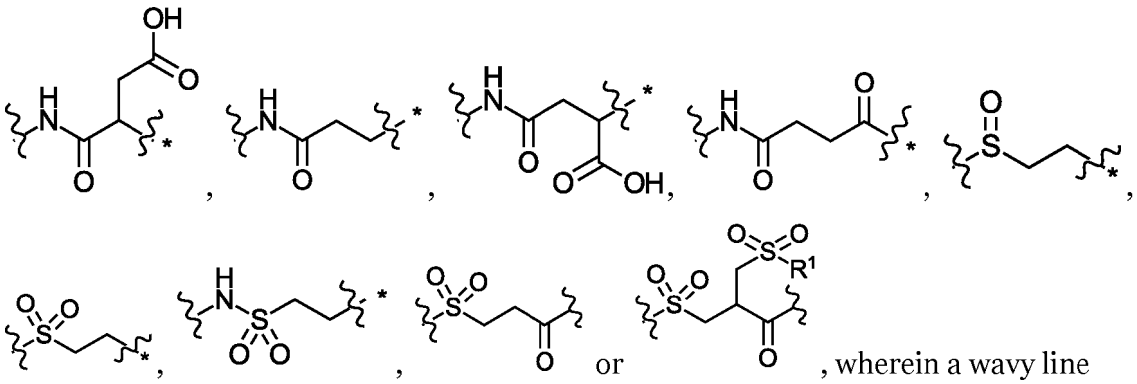
S may be an optionally substituted mono or bicyclic C_5-C_{10} aryl, an optionally mono or bicyclic 5 to 10 membered heteroaryl, an optionally C_3-C_{12} cycloalkyl, or an optionally mono or bicyclic 3 to 12 membered heterocycle. Preferably S is an optionally mono or bicyclic 5 to 10 membered heteroaryl or an optionally mono or bicyclic 3 to 12 membered heterocycle. More preferably, S is an optionally mono or bicyclic 5 membered heteroaryl or an optionally mono or bicyclic 5 membered heterocycle. In some embodiments, G is a succinimidyl group, a triazolyl group or a tetrazolyl group.

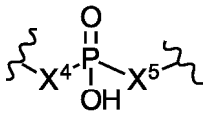
The triazolyl group may be a 1,2,3-trazolyl group. Accordingly, S may be  ,  ,  ,  ,  or  , wherein a wavy line and asterisk indicate the attachment of the group S to the targeting moiety T. It may be appreciated that where two attachments sites are shown then S may be attached to the same targeting moiety at two separate points.

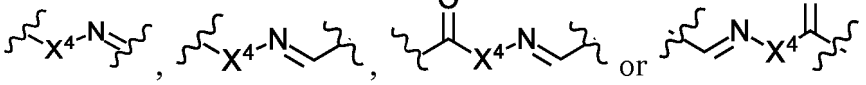
S may be –O-, -NH-, -S- or -C(O)-.

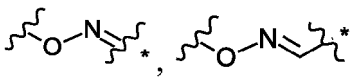
S may be L^3. L^3 may be an optionally substituted C_1-C_{15} alkylene, more preferably an optionally substituted C_1-C_{10} alkylene, and most preferably an optionally substituted C_1-C_6 alkylene. In some embodiments, the alkylene is unsubstituted.

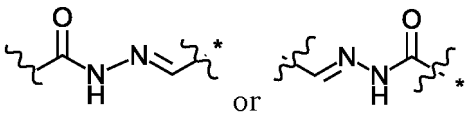
S may be -$X^4C(X^9)L^3$-, -$X^4C(X^9)$-, -$X^4C(X^9)L^3C(O)$-, -X^8L^3-, -$X^4X^8L^3$- or -$X^8L^3C(O)$-. X^4 may be NH. X^9 may be O or S. L^3 may be an optionally substituted C_1-C_6 alkylene, and more preferably an optionally substituted C_1-C_2 alkylene. The alkylene may be substituted with COOH or a C_1-C_6 alkyl which is optionally substituted with COOH or SO_2R^1. Accordingly, S may be  ,

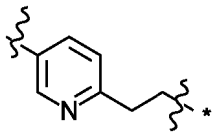

, wherein a wavy line and asterisk indicate the attachment of the group S to the targeting moiety T.

S may be  . Preferably X^4 and X^5 are O.

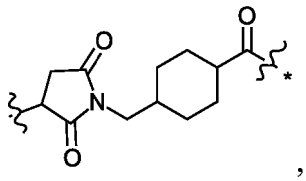
S may be  .

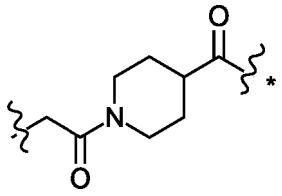
Preferably, X^4 is O or NH. Accordingly, S may be  ,

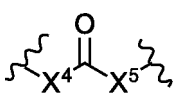
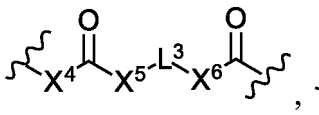
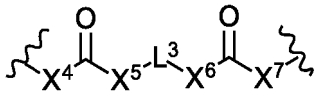
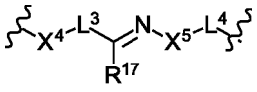

, wherein a wavy line and asterisk indicate the attachment of the group S to the targeting moiety T.

S may be -L^4L^3-. L^3 may be an optionally substituted C_1-C_6 alkylene, and more preferably a C_1-C_2 alkylene. L^4 may be an optionally substituted mono or bicyclic C_5-C_{10} aryl or an optionally mono or bicyclic 5 to 10 membered heteroaryl, and preferably is a phenyl or a 6 membered heteroaryl. Accordingly, S may be  , wherein a wavy line and asterisk indicate the attachment of the group S to the targeting moiety T.

S may be -$L^4L^3L^5C(O)$-. L^3 may be an optionally substituted C_1-C_6 alkylene, more preferably a C_1-C_2 alkylene, and most preferably methylene. L^4 may be an optionally C_3-C_{12} cycloalkyl or an optionally mono or bicyclic 3 to 12 membered heterocycle, more preferably is an optionally substituted C_3-C_6 cycloalkyl or an optionally mono or bicyclic 3 to 6 membered heterocycle, even more preferably is an optionally mono or bicyclic 5

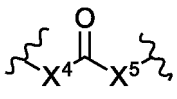
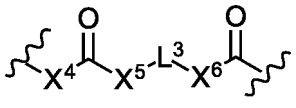
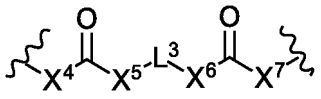
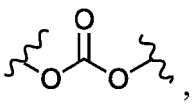
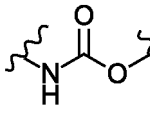
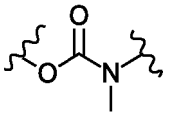
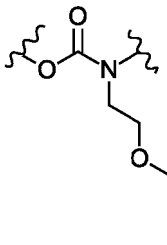
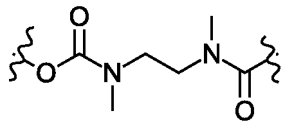
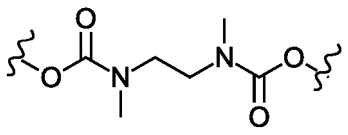
membered heterocycle, and most preferably is a succinimidyl. L^5 may be an optionally C_3-C_{12} cycloalkyl or an optionally mono or bicyclic 3 to 12 membered heterocycle, more preferably is an optionally substituted C_3-C_6 cycloalkyl or an optionally mono or bicyclic 3 to 6 membered heterocycle, and most preferably is a cyclohexyl. Accordingly, S may be  , wherein a wavy line and asterisk indicate the attachment of the group S to the targeting moiety T.

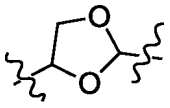
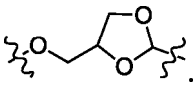
S may be -$L^3C(O)L^4C(O)$-. L^3 may be an optionally substituted C_1-C_6 alkylene, more preferably a C_1-C_2 alkylene, and most preferably methylene. L^4 may be an optionally C_3-C_{12} cycloalkyl or an optionally mono or bicyclic 3 to 12 membered heterocycle, more preferably is an optionally substituted C_3-C_6 cycloalkyl or an optionally mono or bicyclic 3 to 6 membered heterocycle, most preferably is a mono or bicyclic 6 membered heterocycle. Accordingly, S may be  , wherein a wavy line and asterisk indicate the attachment of the group S to the targeting moiety T.

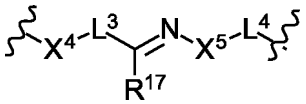
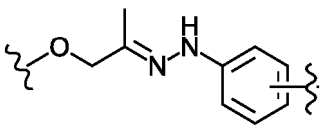
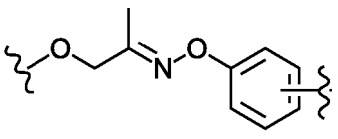
In a preferred embodiment, A may be absent -L^3X^4-, -$C(O)X^4$-, -$L^3C(O)X^4$,  ,  ,  , -$X^4L^3L^4$- or  .

In embodiments where A is -L^3X^4-, L^3 may be an optionally substituted C_1-C_{12} alkylene, and is preferably a C_1-C_6 alkylene, and more preferably is $-CH_2$-, $-CH_2CH_2$- or– $CH_2CH_2CH_2$-. Preferably X^4 is O. Accordingly, A may be $-CH_2O$-, $-CH_2CH_2O$- or – $CH_2CH_2CH_2O$-.

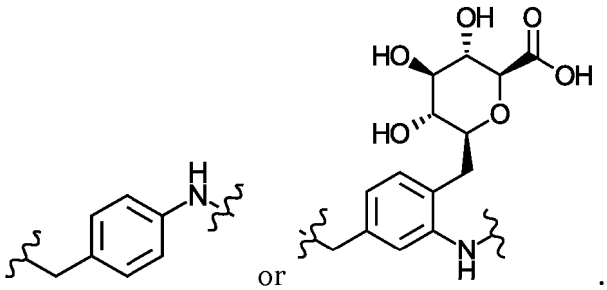
In embodiments where A is -$C(O)X^4$- or -$L^3C(O)X^4$, X^4 may be –O-. L^3 may be an optionally substituted C_1-C_6 alkylene, and is preferably a C_1-C_3 alkylene, and most preferably is $-CH_2$-. Accordingly A may be –C(O)O- or -$CH_2C(O)O$-.

In embodiments where A is  ,  or  , A may be  ,  ,  ,  ,  or  .

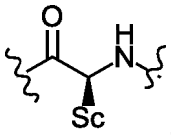
In embodiments where A is -X4L3L4-, X4 is preferably –O-. L3 may be an optionally substituted C_1-C_6 alkylene, and is preferably a C_1-C_2 alkylene, and more preferably is –CH_2-. L4 may be an optionally substituted 3 to 12 membered heterocycle, preferably L4 may is an optionally substituted 3 to 8 membered heterocycle, and most preferably L4 is an optionally substituted 5 or 6 membered heterocycle. L4 may be  . Accordingly, A may be  .

In embodiments where A is  , X4 is preferably –O-. L3 may be an optionally substituted C_1-C_6 alkylene, and preferably is a C_1-C_2 alkylene, and more preferably is –CH_2-. R17 may be an optionally substituted C_{1-6} alkyl, and is preferably a C_{1-3} alkyl and more preferably is a methyl. X5 is preferably –NH- or –O-. L4 may be an optionally substituted mono or bicyclic C_5-C_{10} aryl. Preferably, L4 is an optionally substituted phenyl, and in some embodiments is an unsubstituted phenyl. Accordingly, A may be  or  .

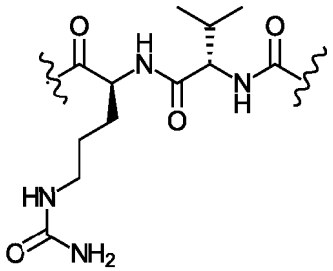
In a preferred embodiment, W is absent or is $-L^3L^7NH-$. More preferably W is

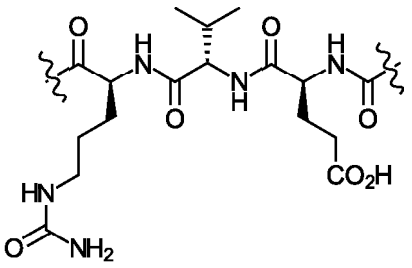


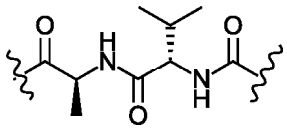
In a preferred embodiment, D is absent or is $-(D^1)_qC(O)-$, where q is an integer between 2 and 10, and more preferably between 3 and 4. Preferably, D^1 may have general formula

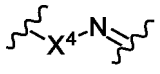


. Preferably, each Sc group is an optionally substituted C_1-C_6 alkyl. Preferably, the alkyl is optionally substituted with $NHC(O)NH_2$ or COOH. Accordingly, D may be







In a preferred embodiment, S is $-L^3-$, $-X^4-$, $-X^4L^3-$, $-C(X^9)-$, $-L^4-$, $-X^4C(X^9)L^3-$,$-X^8L^3-$, $-X^4X^8L^3-$,  or $-L^4L^3-$.

In embodiments where S is $-X^4L^3-$, X^4 may be $-NH-$. L^3 may be a C_1-C_{12} optionally substituted alkylene, more preferably a C_1-C_6 optionally substituted alkylene and most preferably methylene or ethylene.

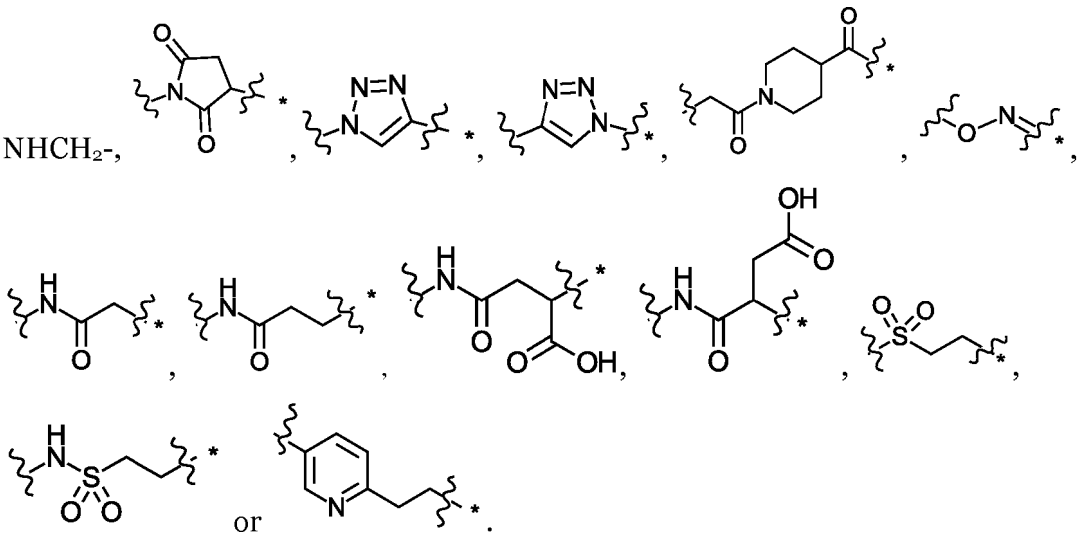
In embodiments where S is $-L^4-$, S may be an optionally mono or bicyclic 5 to 10 membered heteroaryl or an optionally mono or bicyclic 3 to 12 membered heterocycle.

More preferably, S is an optionally mono or bicyclic 5 membered heteroaryl or an optionally mono or bicyclic 5 membered heterocycle.

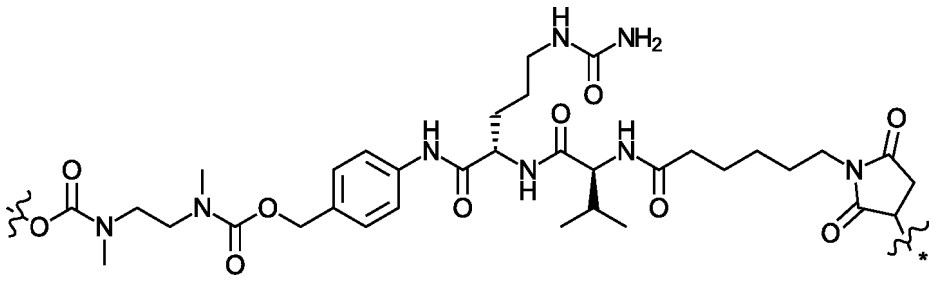
In embodiments where S is -$X^4C(X^9)L^3$-,-X^8L^3- or -$X^4X^8L^3$-, X^4 may be NH. X^9 may be O. C^8 may be –SO_2-. L^3 may be an optionally substituted C_1-C_6 alkylene, and more preferably an optionally substituted C_1-C_2 alkylene. The alkylene may be unsubstituted or substituted with COOH or a C_1-C_6 alkyl which is optionally substituted with COOH.

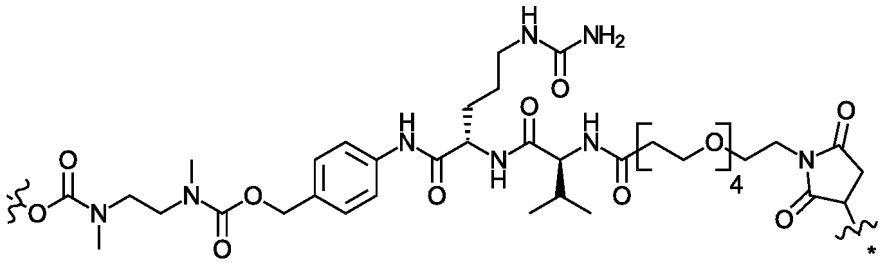
In embodiments where S is -L^4L^3-, L^3 may be an optionally substituted C_1-C_6 alkylene, and more preferably a C_1-C_2 alkylene. L^4 may be an optionally substituted mono or bicyclic C_5-C_{10} aryl or an optionally mono or bicyclic 5 to 10 membered heteroaryl, and preferably is a phenyl or a 6 membered heteroaryl.

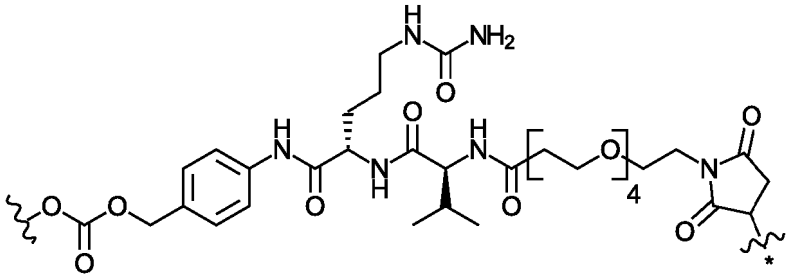
Accordingly, in a preferred embodiment, S may be –$(CH_2)_5$-, –NH-, -S-, -C(O)-, -NHCH$_2$-,

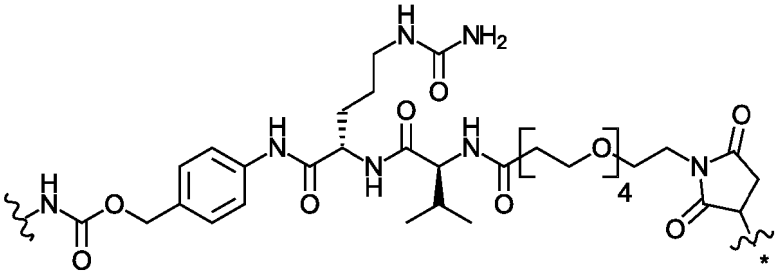


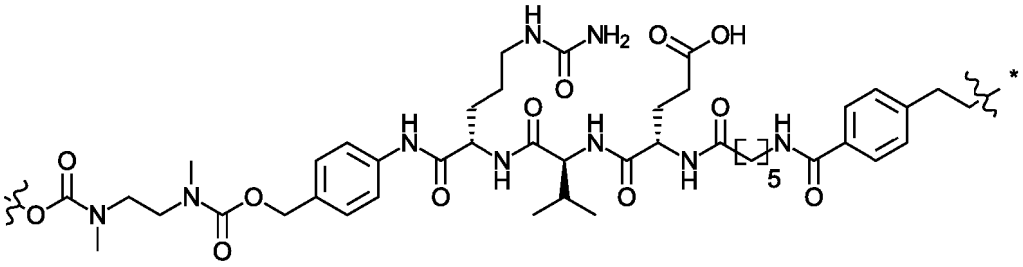
A, W, D, G and S may all be present. In some embodiments, a is 1 and z is 1. Accordingly, the linker may be:

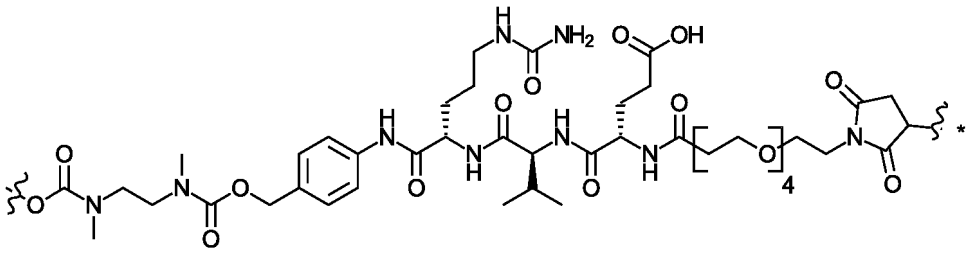


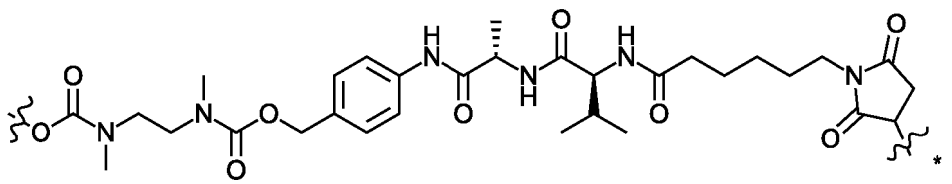


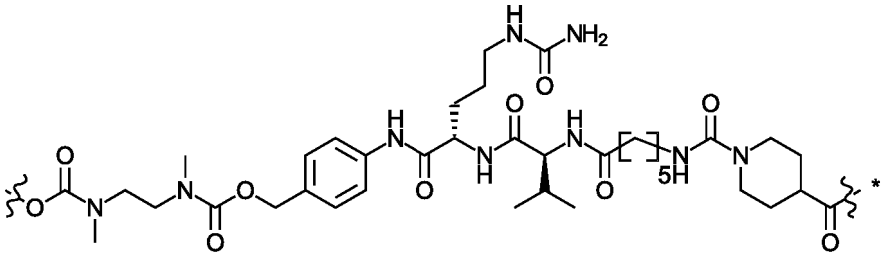


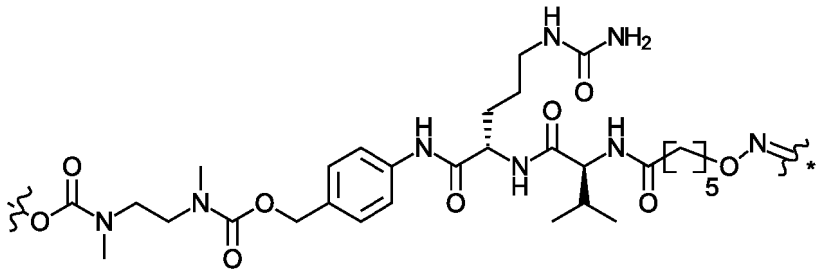


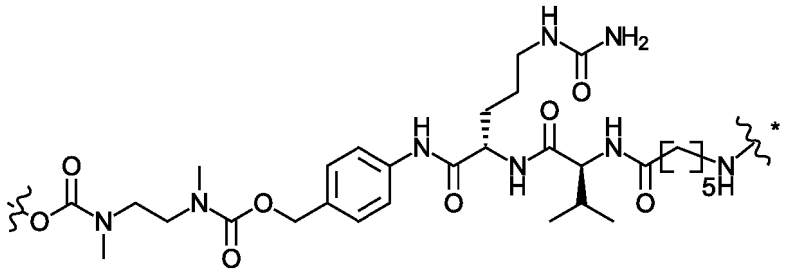


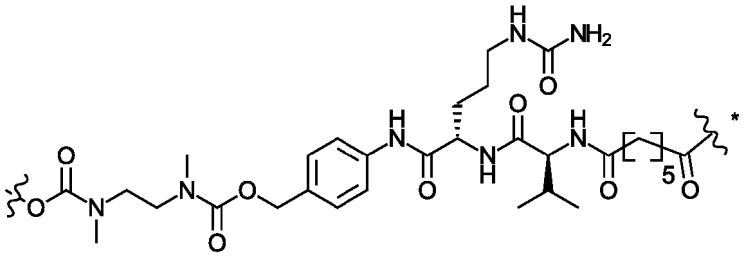


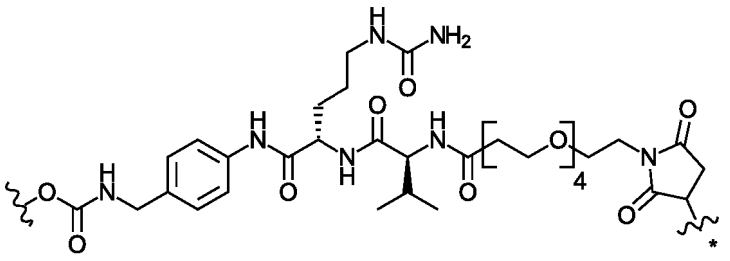


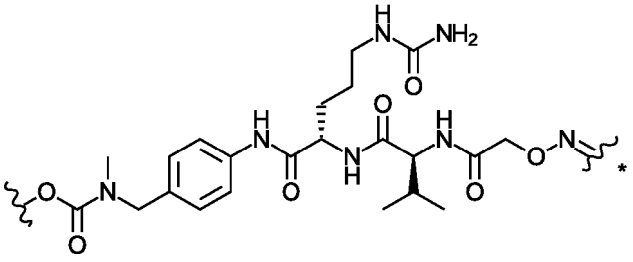


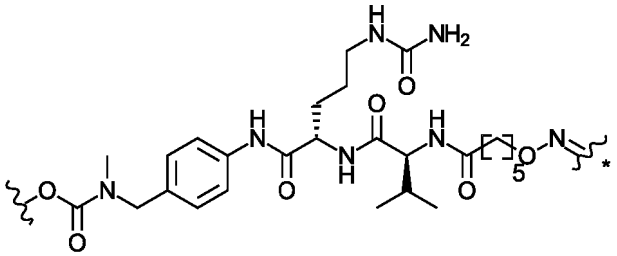


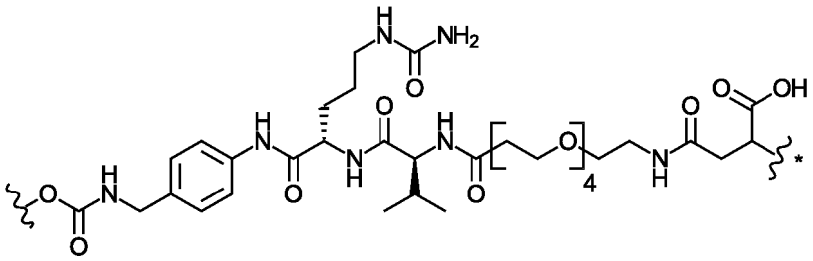


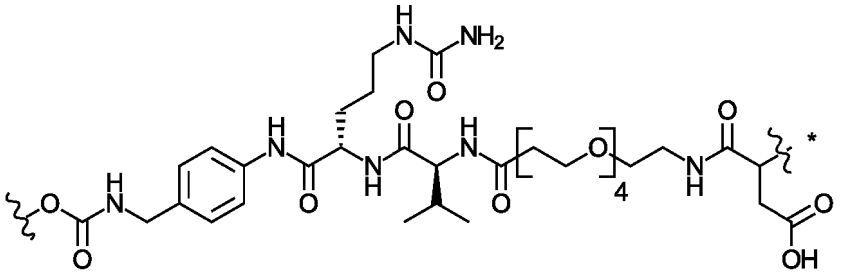


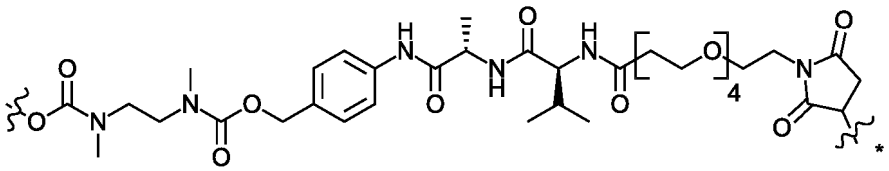


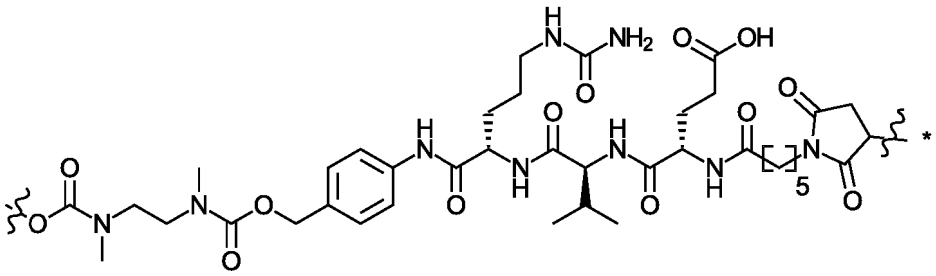












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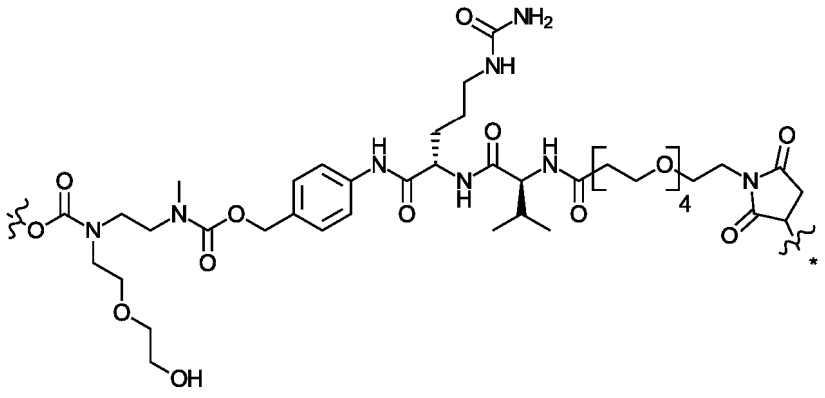

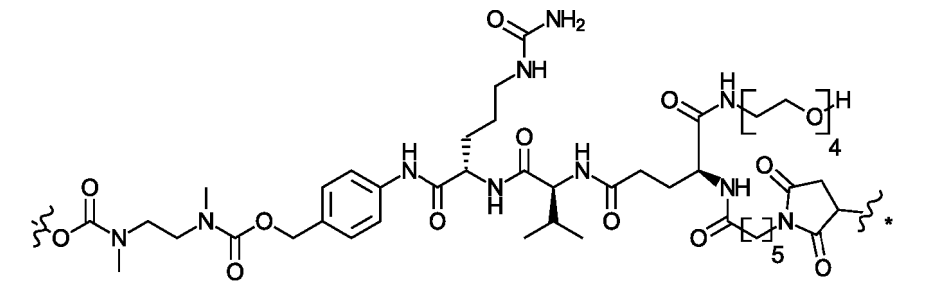

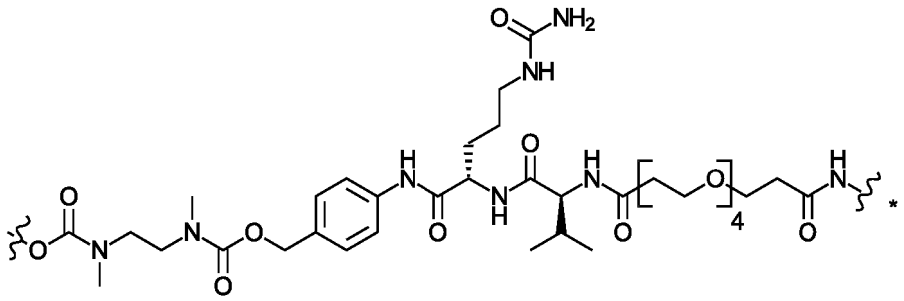

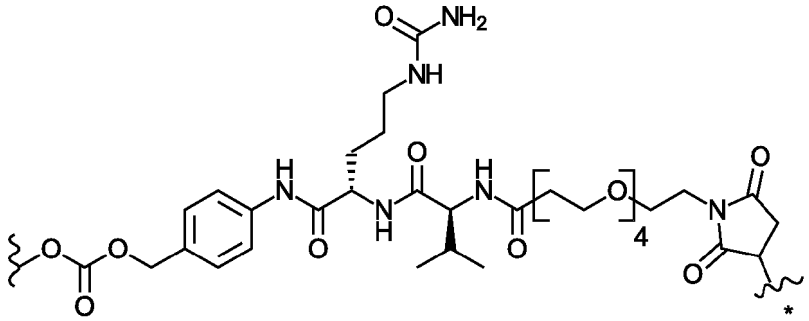

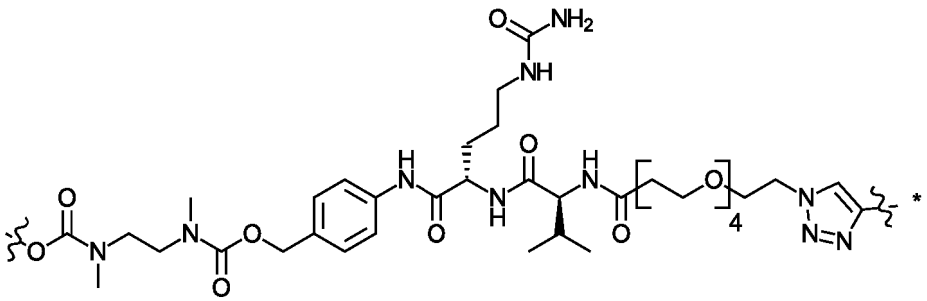

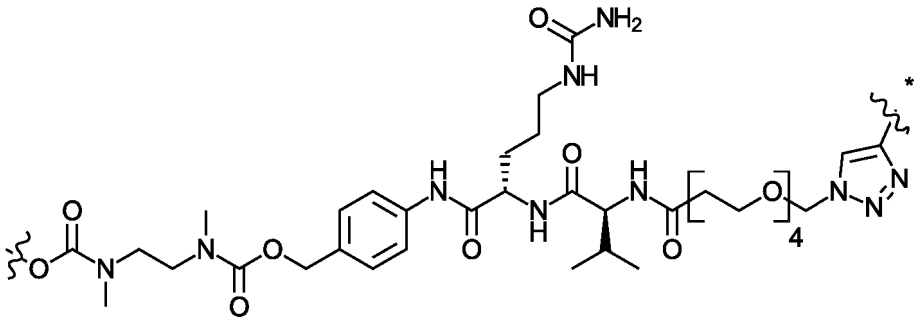

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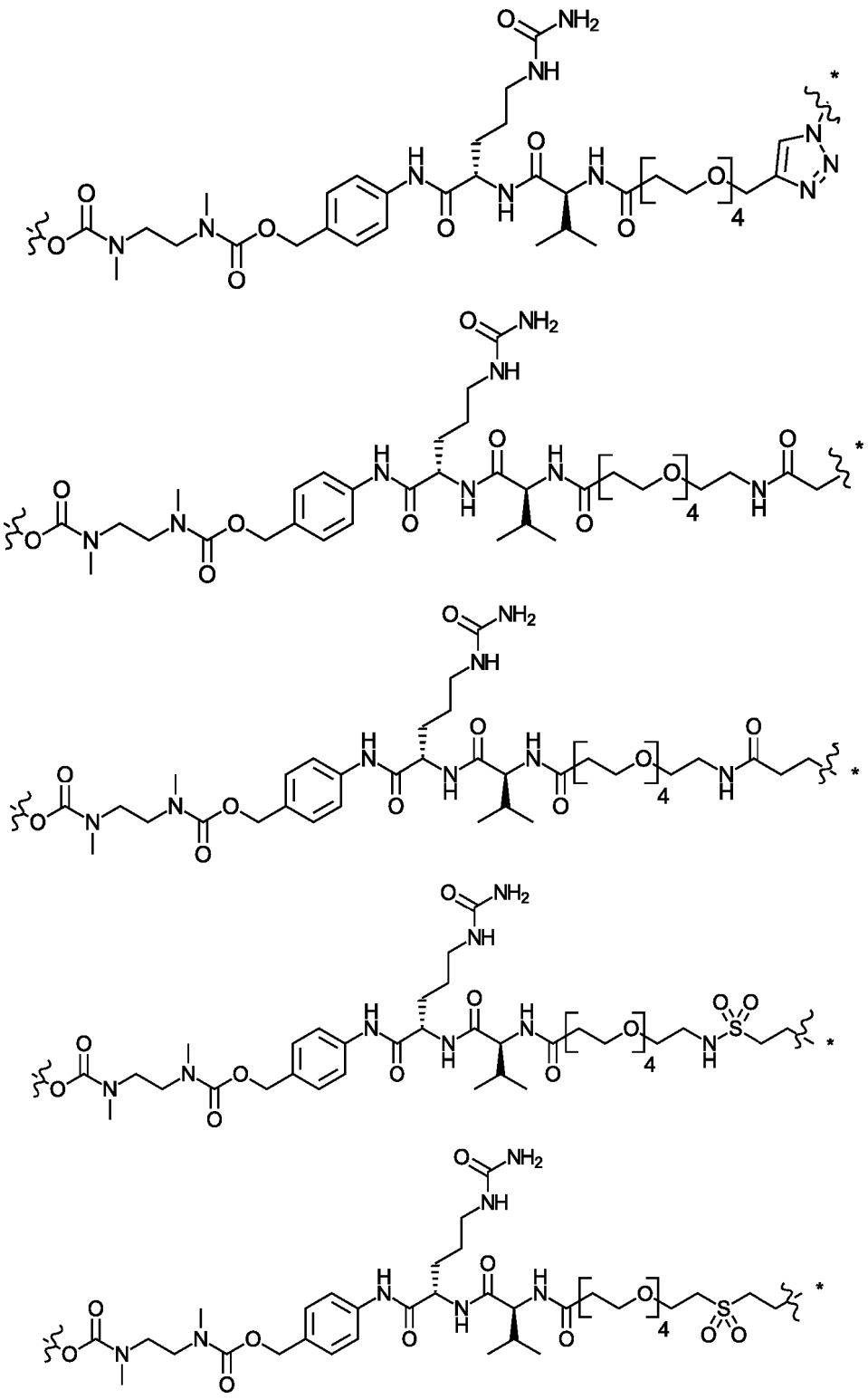
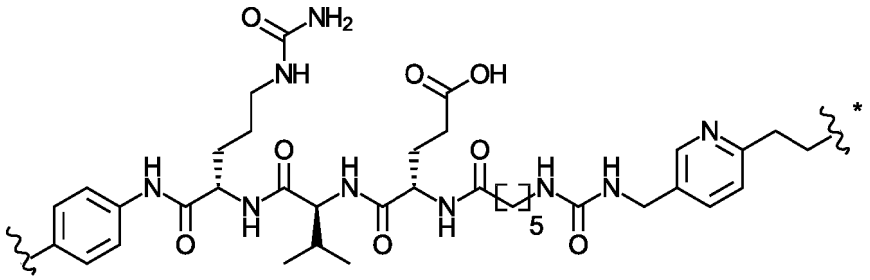
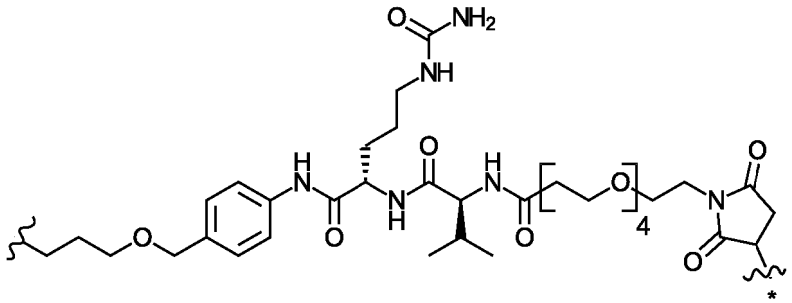
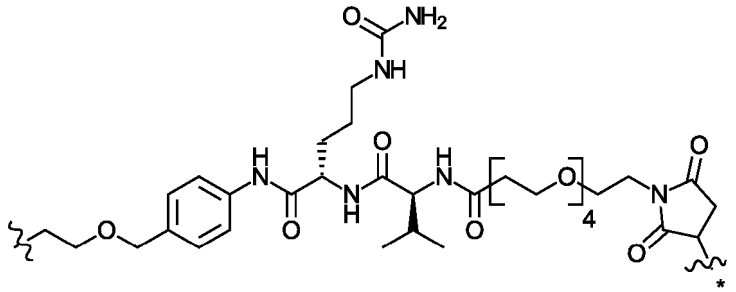
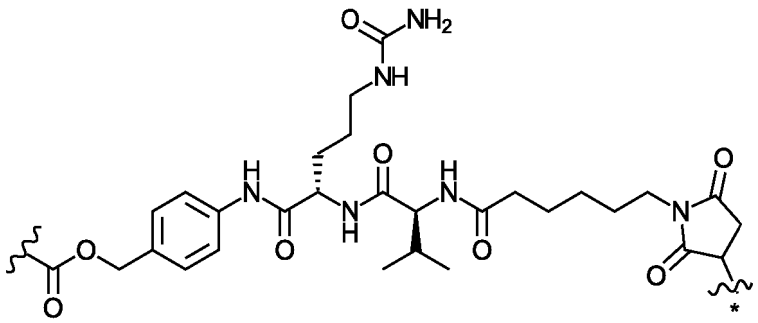
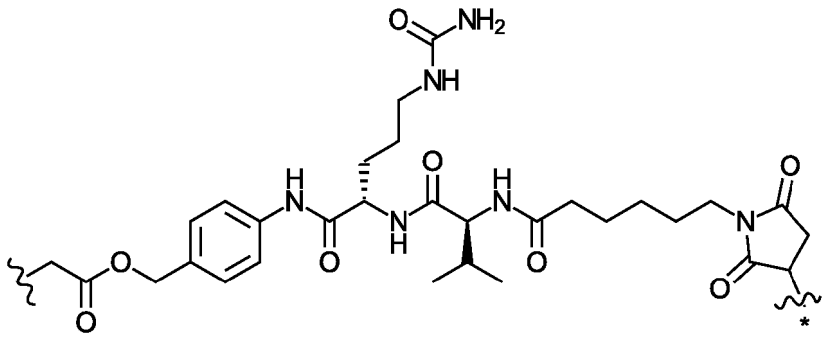




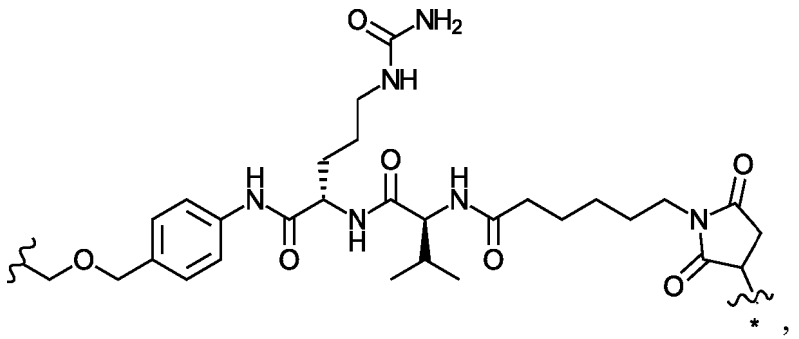






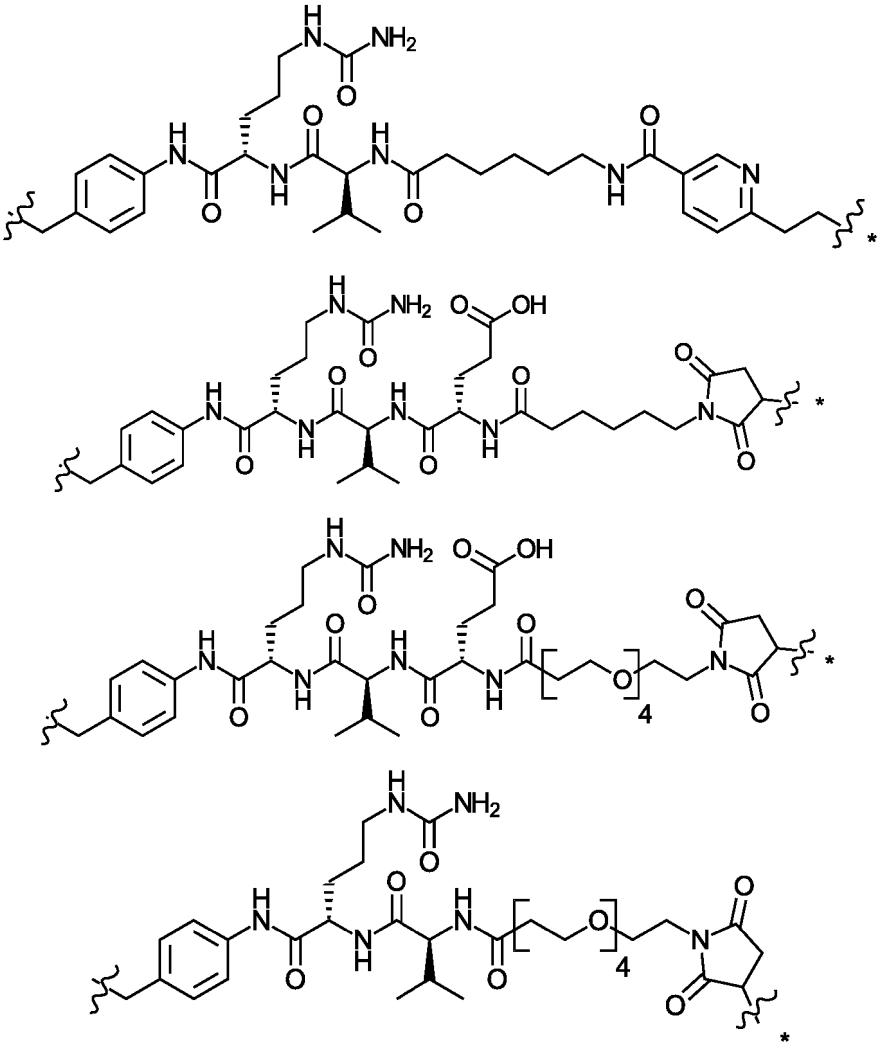


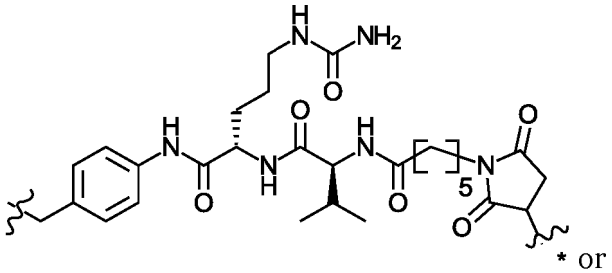
or



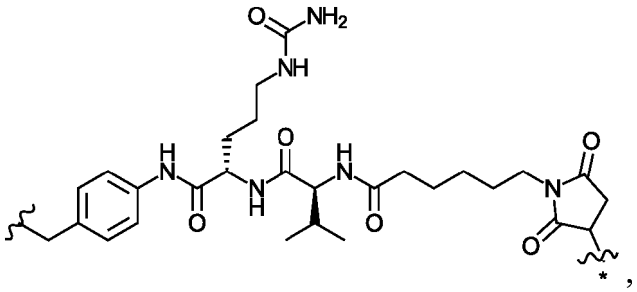
wherein a wavy line and asterisk indicates the attachment of the linker to the targeting moiety T, and a wavy line and no asterix indicates the attachment of the linker to the active compound C.

W, D, G and S may all be present. A may be absent. In some embodiments, a is 1 and z is 1. Accordingly, the linker may be:





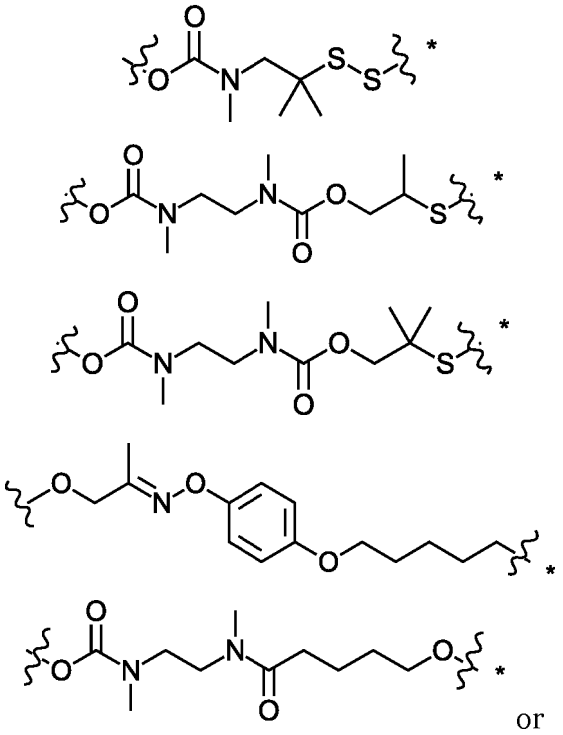
* or



* ,

wherein a wavy line and asterisk indicates the attachment of the linker to the targeting moiety T, and a wavy line and no asterix indicates the attachment of the linker to the active compound C.

A, G and S may all be present. D may be absent. W may be absent. In some embodiments, a is 1 and z is 1. Accordingly, the linker may be:



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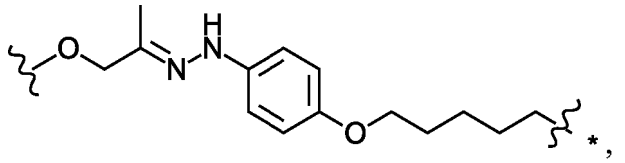
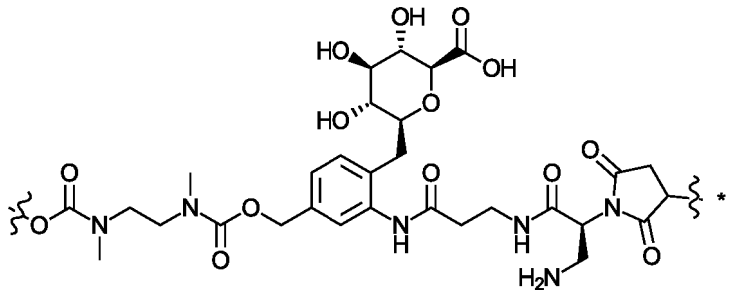
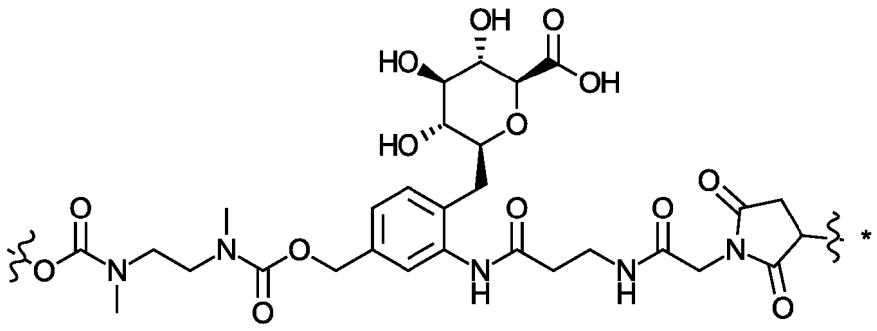
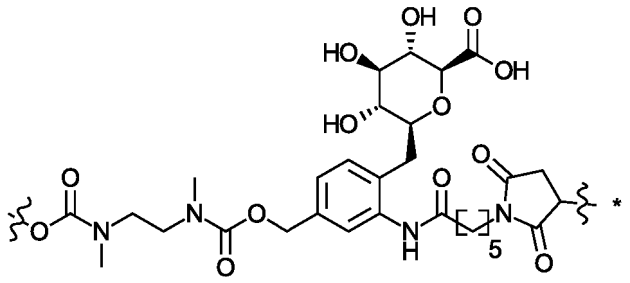


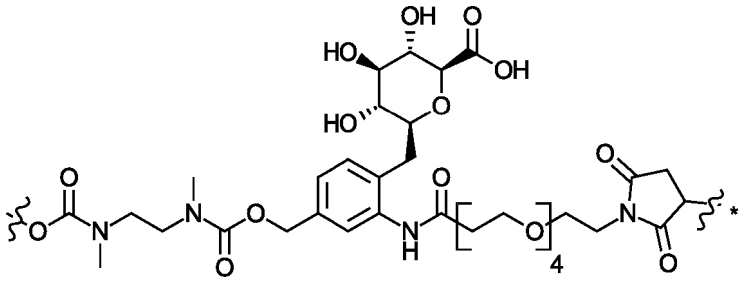
wherein a wavy line and asterisk indicates the attachment of the linker to the targeting moiety T, and a wavy line and no asterix indicates the attachment of the linker to the active compound C.

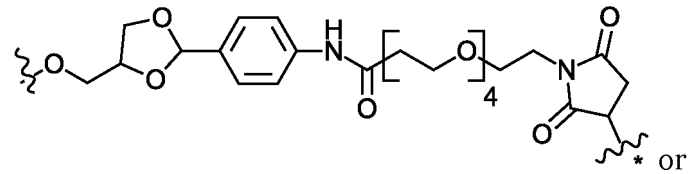
A, W, G and S may all be present. D may be absent. In some embodiments, a is 1 and z is 1. Accordingly, the linker may be:



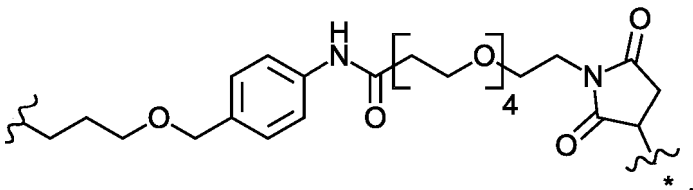








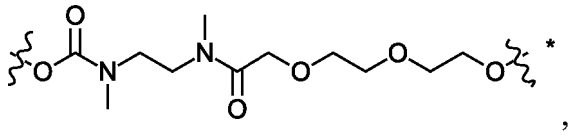
or



,

wherein a wavy line and asterisk indicates the attachment of the linker to the targeting moiety T, and a wavy line and no asterix indicates the attachment of the linker to the active compound C.

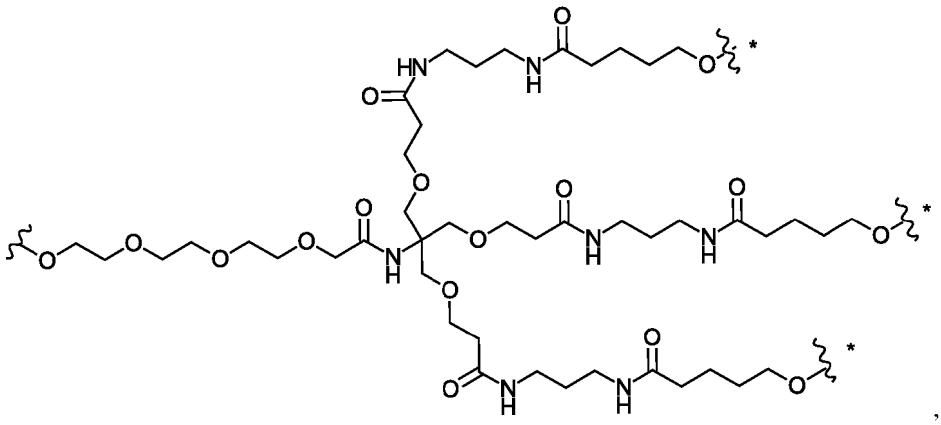
A and G may both be present. D may be absent. W may be absent. S may be absent. In some embodiments, a is 1 and z is 1. Accordingly, the linker may be:



,

wherein a wavy line and asterisk indicates the attachment of the linker to the targeting moiety T, and a wavy line and no asterix indicates the attachment of the linker to the active compound C.

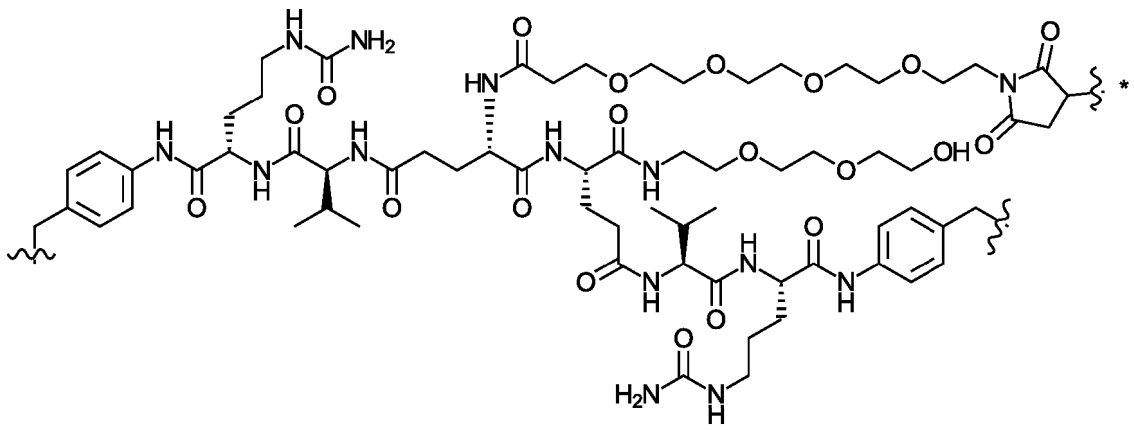
In some embodiments, a is 1 and z is 2 or 3. Accordingly, a may be 1 and z may be 3. In some embodiments, G and S may both be present. A may be absent. D may be absent. W may be absent. Accordingly, the linker may be:



,

wherein a wavy line and asterisk indicates the attachment of the linker to the targeting moiety T, and a wavy line and no asterix indicates the attachment of the linker to the active compound C.

In some embodiments, a is 2 or 3 and z is a. Accordingly, a may be 2 and z may be a. In some embodiments, W, D, G and S may all be present. A may be absent. Accordingly, the linker may be:



wherein a wavy line and asterisk indicates the attachment of the linker to the targeting moiety T, and a wavy line and no asterix indicates the attachment of the linker to the active compound C.

The linker will be known to those skilled in the art as either 'stable' linkers which are resistant to degradation in cells and in the systemic circulation or 'cleavable' or 'conditionally labile' linkers which are designed to degrade under intracellular conditions and/or in the systemic circulation following a defined trigger event, which may be a change in pH or a metabolic process such as ester or amide hydrolysis. Conjugates of the present invention may comprise two or more cleavage elements which may be selected from acid-induced cleavage, peptidase-induced cleavage (for example, a peptide linker cleaved by an intracellular protease, such as a lysosomal protease or an endosomal protease, see Trout *et. al.*, **1982**, *PNAS USA*, 79, 626-629), esterase-induced cleavage, glycosidase-induced cleavage, glucuronidase-induced cleavage, phosphodiesterase-induced cleavage, phosphatase-induced cleavage, lipase-induced cleavage or disulfide bond cleavage. Certain intracellular compartments, such as endosomes and lysosomes, have an acidic pH (pH 4.5), and provide conditions suitable to cleave acid-labile linkers. Specific hydrolysis processes have been described, such as the protease cleavage of a dipeptide e.g. the valine-citrulline dipeptide moiety (Ducry *et. al.*, *Bioconj. Chem.*, **2010**, 21, 5-13) contained in the clinically precedented ADC brentuximab vedotin, a phenylalanine-lysine dipeptide, maleimidocaproyl or a maleimidocaproyl-valine-citrulline linker. The self-immolative group para-aminobenzyloxycarbonyl (PABC) may also form part of the linker structure in which, in

response to a suitable trigger event, will eliminate from the conjugate to release the parent structure (Carl et. al., *J. Med. Chem.*, **1981**, 24, 479 and Chakravarty et. al., *J. Med. Chem.*, **1983**, 26, 638), for example in the maleimidocaproyl-valine-citrulline-PABC linker. Other linkers include those linkers that are cleaved at a specific pH or pH range such as a hydrazone e.g. the hydrazone moiety in gemtuzumab ozogamicin.

A non-cleavable linker may be protease insensitive. Non-cleavable linkers include that contained in the clinically precedented ADC trastuzumab emtansine and will require the conjugate to be degraded intracellularly to release the active drug C. See for example; Wong, Chemistry of Protein Conjugation and Cross-Linking, CRC Press Inc., Boca Raton, **1991**.

The linker may be dendritic in nature, in that more than one small molecule C may be covalently attached through a branched, multifunctional unit to the targeting moiety (US2006/116422, US2005/271615). Dendritic linkers can increase the molar ratio of drug to targeting group which is related to the potency of the conjugate. Thus, where a targeting group contains for example just a single thiol group, a multitude of small molecules may be attached through a dendritic or branched linker.

The linker may be attached to a targeting moiety T in a variety of ways at any suitable available position on the targeting moiety through a reactive group thereon. Examples of suitable reactive groups include a surface lysine, an oxidised carbohydrate and a cysteine residue. Suitable reactive groups will be known by the skilled person. For instance, a variety of antibody-drug conjugate (ADC) linkage technologies are known in the art, including via alkylation, reductive amination, transesterification, amidation and thiol Michael additions. The resulting linkages include hydrazone, disulphide, maleimide, succinimide and peptide-based functional groups. For example thiol groups, or cysteine residues may be bonded to the linker or spacer group via a maleimide group. Alternative conjugation chemistries include lysine-reactive groups, such as succinyl or HOBt esters, pentafluorophenyl esters, β-lactam amides, isocyanates, and isothiocyanates; azide reactive groups, such as alkynes and strained alkynes; cysteine reactive groups, such as maleimides, α-haloacetamides, pyridyl disulfides and vinyl sulfoxides; and ketone reactive groups, such as hydroxylamines, hydrazines and acyl hydrazides.

In some embodiments, the number of drug/linker moieties conjugated per antibody molecule ranges from 1 to 10. The drug antibody ratio (DAR) is typically from 1 to 10, and may be from 2 to 5 or 2 to 3. Accordingly, b may be 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10.

Such conjugates may be designed to specifically target certain cell types or tumour types via the targeting moiety. Accordingly, the targeting moiety may be configured to direct the compound of formula (**I**) to a specific cell or tumour type, and thereby deliver the STING modulator in a cell-specific manner. The conjugate can therefore be used accordingly in a therapeutic setting. The principle of this targeted delivery will be known to those skilled in the art as being closely related to ADC technology, for example as described in Polakis, P., *Pharmacol. Revs.*, **2016**, 68, 3-19 and Beck *et. al.*, *Nat. Revs. Drug Disc.*, **2017**, 16, 315-337. The conjugate may then be taken up inside a cell or tumour through receptor-mediated endocytosis. The target antigen or receptor may be part of a cell or tumour or can be an extracellular matrix protein within the microenvironment of the cell or tumour. Once inside a cell or tumour, one or more specific peptide sequences within the conjugate may be hydrolytically cleaved by one or more cell or tumour proteases. For example, a tumour-associated protease, cathepsin B, C or D, or a plasmin protease to cleave the linker and release the active compound either in the target cells or in the tumour microenvironment of the target cells. The active drug is then free to migrate within the cell or microenvironment and thereby contact and subsequently modulate the STING protein. In some embodiments, the active drug may be cleaved from the targeting moiety outside of cells or tumours and the active drug subsequently acts at the cell surface or penetrates the cell or tumour.

T is a targeting moiety and may comprise an antibody, an antibody fragment, a nucleic acid based molecule, a carbohydrate, a peptide, a modified peptide or a small molecule.

In one embodiment, T may be configured to target a tumour antigen. Accordingly, T may be configured to target the Human Epidermal Growth Factor Receptor (EGFR), a plasminogen activator, a cytotoxic T-lymphocyte associated antigen (CTLA) such as CTLA-4, vascular endothelial growth factor (VEGF), neurotrophic factors such as BDNF, fibroblast growth factor receptor (FGFR), a nerve growth factor, platelet-derived growth factor (PDGF), transforming growth factor (TGF), tissue factor (TF), EpCAM, CEACAM5, CEACAM6, colon-specific antigen p, FLT3, PSA, PSMA, PSCA, STEAP, BCMA, CEA, folate receptor, cathepsin D, estrogen receptor, progesterone receptor, NCA-95, NCA-90, A3, A33, Ep-CAM, the CD33/CD30/CD37/CD52/CD66e,

CD56/CD74/CD79/CD22 receptors, the SLC34A2 gene product, SLC44A4, the mesothelin protein, the integrin $\alpha_V\beta 3$, PD-1, PD-L1, EGP-1, EGP-2, the EphA2 tyrosine kinase, the mucin cell-surface antigens e.g. MUC16, the hLewis Y antigen, carbonic anhydrase IX, 5T4, EFNA4, DLL4, Axl, B7, ALK, Fyn3, HLA, HIF, IGF, CC49, AFP, NaPi2b, brc-abl, caspase-8, guanylyl cyclase C, CD19, CD20, CD21, CD22, CD40, CD79a, CD79b, CD98, CD123, PTK7, CDK4, RANTES, CD44, CD48, CD133, CD70, CD72, CD74, CD166, c-kit, cMet, ErbB2/Her2, ErbB3/Her3, ErbB4/Her4, OX40, p53, α-fetoprotein, R1, PAP, PAX3, PAX5, Ras, Rho, ROR2, nectin-4, E-cadherin, P-cadherin, cadherin-6, LRRC15, BMPR1B, E16, Sema 5b, ETBR, MSG783, Trop2, TRPM4, ENPP3, SLITRK6, LIV-1, CRIPTO, FcRH1, IRTA2, TENB2, FcRH2, NCA, MDP, IL30Rα, ERK, gpNMB, LYPD3, GEDA, CXCR5, HLA-DOB, P2X5, LY64 or LY75.

In a preferred embodiment, T is configured to target Her2. It may be appreciated that HER2 may also be called Erbb2, and is a biomarker for breast cancer, gastric cancer, ovarian cancer and/or lung cancer.

In a preferred embodiment, T is an antibody, or a fragment thereof. Certain antibodies have been applied in the field of immune oncology previously. Exemplary anti-PD1 antibodies include lambrolizumab (MK-3475, Merck), nivolumab (BMS-936558, Bristol-Myers Squibb), AMP-224 (Merck) and pidilizumab (CT-011, Curetech Ltd.). Known anti-PDL1 antibodies include MDX-1105 (Medarex), MEDI4736 (Medimmune), MPDL4280A (Genentech) and BMS-936559 (Bristol-Myers Squibb). Exemplary anti-CTLA4 antibodies include ipilimumab (Yervoy, Bristol-Myers Squibb) and tremelimumab (Pfizer). Exemplary anti-ErbB2/Her2 antibodies include trastuzumab (Roche), pertuzumab (Genentech), margetuximab (Macrogenics) and HT-19 (Mersana Therapeutics). In a preferred embodiment, T is trastuzumab or a fragment or derivative thereof.

As an example, conjugates which comprise an anti-HER2 antibody can be specifically targeted to HER2-positive cancer cells or tumours. Trastuzumab (Herceptin or Herclon) is a humanized monoclonal antibody that binds to the juxtamembrane portion of the extracellular domain of the HER2 receptor (Hudis et. al., *N. Engl. J. Med.*, **2007**, 357, 39-51; Cho et. al., *Nature*, **2003**, 421, 756-760). Trastuzumab gained US FDA approval in September 1998 for the treatment of metastatic breast cancer in

patients whose tumours overexpress HER2 and who received one or more chemotherapy regimens for their metastatic disease.

The invention extends to both whole antibodies, as well as to antigen-binding fragments or regions of the corresponding full-length antibody.

The antibody or antigen-binding fragment thereof may be monovalent, divalent or polyvalent. Monovalent antibodies are dimers (HL) comprising a heavy (H) chain associated by a disulphide bridge with a light chain (L). Divalent antibodies are tetramer (H_2L_3) comprising two dimers associated by at least one disulphide bridge. Polyvalent antibodies may also be produced, for example by linking multiple dimers. The basic structure of an antibody molecule consists of two identical light chains and two identical heavy chains which associate non-covalently and can be linked by disulphide bonds. Each heavy and light chain contains an amino-terminal variable region of about 110 amino acids, and constant sequences in the remainder of the chain. The variable region includes several hypervariable regions, or Complementarity Determining Regions (CDRs), that form the antigen-binding site of the antibody molecule and determine its specificity for the antigen or variant or fragment thereof (e.g. an epitope). On either side of the CDRs of the heavy and light chains is a framework region, a relatively conserved sequence of amino acids that anchors and orients the CDRs. Antibody fragments may include a bi-specific antibody (BsAb) or a chimeric antigen receptor (CAR).

The constant region consists of one of five heavy chain sequences (μ, γ, ζ, α, or ε) and one of two light chain sequences (κ or λ). The heavy chain constant region sequences determine the isotype of the antibody and the effector functions of the molecule.

Preferably, the antibody or antigen-binding fragment thereof is isolated or purified.

In one preferred embodiment, the antibody or antigen-binding fragment thereof comprises a polyclonal antibody, or an antigen-binding fragment thereof. The antibody or antigen-binding fragment thereof may be generated in a rabbit, mouse or rat.

In another preferred embodiment, the antibody or antigen-binding fragment thereof comprises a monoclonal antibody or an antigen-binding fragment thereof. Preferably, the antibody is a human antibody. As used herein, the term “human antibody” can

mean an antibody, such as a monoclonal antibody, which comprises substantially the same heavy and light chain CDR amino acid sequences as found in a particular human antibody exhibiting immunospecificity. An amino acid sequence, which is substantially the same as a heavy or light chain CDR, exhibits a considerable amount of sequence identity when compared to a reference sequence. Such identity is definitively known or recognizable as representing the amino acid sequence of the particular human antibody. Substantially the same heavy and light chain CDR amino acid sequence can have, for example, minor modifications or conservative substitutions of amino acids.

The term "human monoclonal antibody" can include a monoclonal antibody with substantially or entirely human CDR amino acid sequences produced, for example by recombinant methods such as production by a phage library, by lymphocytes or by hybridoma cells.

The term "humanised antibody" can mean an antibody from a non-human species (e.g. mouse or rabbit) whose protein sequences have been modified to increase their similarity to antibodies produced naturally in humans.

The antibody may be a recombinant antibody. The term "recombinant human antibody" can include a human antibody produced using recombinant DNA technology.

The term "antigen-binding region" can mean a region of the antibody having specific binding affinity for its target antigen or a variant or fragment thereof. Preferably, the fragment is an epitope. The binding region may be a hypervariable CDR or a functional portion thereof. The term "functional portion" of a CDR can mean a sequence within the CDR which shows specific affinity for the target antigen. The functional portion of a CDR may comprise a ligand which specifically binds to the target antigen or a fragment thereof.

The term "CDR" can mean a hypervariable region in the heavy and light variable chains. There may be one, two, three or more CDRs in each of the heavy and light chains of the antibody. Normally, there are at least three CDRs on each chain which, when configured together, form the antigen-binding site, i.e. the three-dimensional combining site with which the antigen binds or specifically reacts. It has however been postulated that there may be four CDRs in the heavy chains of some antibodies.

The definition of CDR also includes overlapping or subsets of amino acid residues when compared against each other. The exact residue numbers which encompass a particular CDR or a functional portion thereof will vary depending on the sequence and size of the CDR. Those skilled in the art can routinely determine which residues comprise a particular CDR given the variable region amino acid sequence of the antibody.

The term "functional fragment" of an antibody can mean a portion of the antibody which retains a functional activity. A functional activity can be, for example antigen binding activity or specificity. A functional activity can also be, for example, an effector function provided by an antibody constant region. The term "functional fragment" is also intended to include, for example, fragments produced by protease digestion or reduction of a human monoclonal antibody and by recombinant DNA methods known to those skilled in the art. Human monoclonal antibody functional fragments include, for example individual heavy or light chains and fragments thereof, such as VL, VH and Fd; monovalent fragments, such as Fv, Fab, and Fab'; bivalent fragments such as $F(ab')_2$; single chain Fv (scFv); and Fc fragments.

The term "VL fragment" can mean a fragment of the light chain of a human monoclonal antibody which includes all or part of the light chain variable region, including the CDRs. A VL fragment can further include light chain constant region sequences.

The term "VH fragment" can means a fragment of the heavy chain of a human monoclonal antibody which includes all or part of the heavy chain variable region, including the CDRs.

The term "Fd fragment" can mean the heavy chain variable region coupled to the first heavy chain constant region, i.e. VH and CH-1. The "Fd fragment" does not include the light chain, or the second and third constant regions of the heavy chain.

The term "Fv fragment" can mean a monovalent antigen-binding fragment of a human monoclonal antibody, including all or part of the variable regions of the heavy and light chains, and absent of the constant regions of the heavy and light chains. The variable regions of the heavy and light chains include, for example, the CDRs. For example, an Fv fragment includes all or part of the amino terminal variable region of about 110 amino acids of both the heavy and light chains.

The term “Fab fragment” can mean a monovalent antigen-binding fragment of a human monoclonal antibody that is larger than an Fv fragment. For example, a Fab fragment includes the variable regions, and all or part of the first constant domain of the heavy and light chains. Thus, a Fab fragment additionally includes, for example, amino acid residues from about 110 to about 220 of the heavy and light chains.

The term “Fab' fragment” can mean a monovalent antigen-binding fragment of a human monoclonal antibody that is larger than a Fab fragment. For example, a Fab' fragment includes all of the light chain, all of the variable region of the heavy chain, and all or part of the first and second constant domains of the heavy chain. For example, a Fab' fragment can additionally include some or all of amino acid residues 220 to 330 of the heavy chain.

The term “$F(ab')_2$ fragment” can mean a bivalent antigen-binding fragment of a human monoclonal antibody. An $F(ab')_2$ fragment includes, for example, all or part of the variable regions of two heavy chains-and two light chains, and can further include all or part of the first constant domains of two heavy chains and two light chains.

The term “single chain Fv (scFv)” can mean a fusion of the variable regions of the heavy (VH) and light chains (VL) connected with a short linker peptide.

The term “bispecific antibody (BsAb)” can mean a bispecific antibody comprising two scFv linked to each other by a shorter linked peptide.

One skilled in the art knows that the exact boundaries of a fragment of an antibody are not important, so long as the fragment maintains a functional activity. Using well-known recombinant methods, one skilled in the art can engineer a polynucleotide sequence to express a functional fragment with any endpoints desired for a particular application. A functional fragment of the antibody may comprise or consist of a fragment with substantially the same heavy and light chain variable regions as the human antibody.

The antigen-binding fragment thereof may comprise or consist of any of the fragments selected from a group consisting of VH, VL, Fd, Fv, Fab, Fab', scFv, $F(ab')_2$ and Fc fragment.

The antigen-binding fragment thereof may comprise or consist of any one of the antigen binding region sequences of the VL, any one of the antigen binding region sequences of the VH, or a combination of VL and VH antigen binding regions of a human antibody. The appropriate number and combination of VH and VL antigen binding region sequences may be determined by those skilled in the art depending on the desired affinity and specificity and the intended use of the antigen-binding fragment. Functional fragments or antigen-binding fragments of antibodies may be readily produced and isolated using methods well known to those skilled in the art. Such methods include, for example, proteolytic methods, recombinant methods and chemical synthesis. Proteolytic methods for the isolation of functional fragments comprise using human antibodies as a starting material. Enzymes suitable for proteolysis of human immunoglobulins may include, for example, papain, and pepsin. The appropriate enzyme may be readily chosen by one skilled in the art, depending on, for example, whether monovalent or bivalent fragments are required. For example, papain cleavage results in two monovalent Fab' fragments that bind antigen and an Fc fragment. Pepsin cleavage, for example, results in a bivalent F (ab') fragment. An F $(ab')_2$ fragment of the invention may be further reduced using, for example, DTT or 2-mercaptoethanol to produce two monovalent Fab' fragments.

Functional or antigen-binding fragments of antibodies produced by proteolysis may be purified by affinity and column chromatographic procedures. For example, undigested antibodies and Fc fragments may be removed by binding to protein A. Additionally, functional fragments may be purified by virtue of their charge and size, using, for example, ion exchange and gel filtration chromatography. Such methods are well known to those skilled in the art.

The antibody or antigen-binding fragment thereof may be produced using techniques well known in the art. For example, by recombinant methodology (see US Pat. No. 4,816,567), hydridoma technology (Kohler et. al., *Nature*, **1975**, 256, 495), phage display technologies (for example, see Clackson et. al., *Nature*, **1991**, 352, 624 and Marks et. al., *J. Mol. Biol.*, **1991**, 222, 581), synthetic technologies or combinations of such technologies. Preferably, one initially isolates a polynucleotide encoding desired regions of the antibody heavy and light chains. Such regions may include, for example, all or part of the variable region of the heavy and light chains. Preferably, such regions can particularly include the antigen binding regions of the heavy and light chains, preferably the antigen binding sites, most preferably the CDRs.

The polynucleotide encoding the antibody or antigen-binding fragment thereof according to the invention may be produced using methods known to those skilled in the art. The polynucleotide encoding the antibody or antigen-binding fragment thereof may be directly synthesized by methods of oligonucleotide synthesis known in the art. Alternatively, smaller fragments may be synthesized and joined to form a larger functional fragment using recombinant methods known in the art. Antibodies of use may be commercially obtained from a wide variety of known sources e.g. the American Type Culture Collection (ATCC, Manassas, Va.). A large number of antibodies against a wide variety of disease targets and tumor-associated antigens have been deposited at the ATCC and/or have published variable region sequences and are available for use in the claimed methods and compositions.

Cysteine-engineered antibodies have been designed as Fab antibody fragments (ThioFab) and expressed as full-length IgG monoclonal (thioMab) antibodies (US. Pat. 7,521,541). ThioFab and ThioMab antibodies have been conjugated through linkers at the newly introduced cysteine thiols to prepare site-specific antibody-drug conjugates (US. Pat. 7521541, US2008/0050310, WO2008/052187).

Polytherics have described a method for bridging a pair of sulfhydryl groups contained in antibody proteins derived from reduction of a native disulfide hinge (Badescu *et. al.*, *Bioconjugate Chem.*, **2014**, 25, 1124-1136) to synthesise homogenous drug-loaded ADCs. Similar methods have been described by Concortis (US Patent 0105540, April 26 2015), Thiologics (Schumacher *et. al.*, *Org Biomol. Chem.*, **2014**, 12, 7261-7269) and Igenica (Behrens *et. al.*, *Mol. Pharm.*, **2015**, 12, 3986-3998). Related methods have been described in Frigerio *et. al.*, *Curr. Top. Med. Chem.*, **2018**, 18, 1-32.

Other recent methods that have been used to target homogeneous drug-loaded ADCs include the incorporation of unnatural amino acids such as selenocysteine (Hofer, T. *et. al.*, *Biochem.*, **2009**, 48, 12047-12057) or formyl glycine (Drake, P.M. *et. al.*, *Bioconj. Chem.*, **2014**, 25, 1331-1341) groups into antibodies. Glycoengineering has been used to introduce sialic acid residues at specific sites (Zhou, Q. et. al., *Bioconj. Chem.*, **2014**, 25, 510-520) and transglutaminases used to enzymatically conjugate primary amine-containing linker/payloads to glutamine residues (Dorywalska, M. *et. al.*, *Bioconj. Chem.*, **2015**, 26, 650-659). These, and other, methods are described in Sochaj, A.M. *et. al.*, *Biotech. Adv.*, **2015**, 33, 775-784.

As used herein, the term "immunospecificity" can mean the binding region is capable of immunoreacting with the target antigen, or a variant or fragment thereof, by specifically binding therewith. The antibody or antigen-binding fragment thereof can selectively interact with an antigen with an affinity constant of approximately 10^{-5} to 10^{-13} M^{-1}, preferably 10^{-6} to 10^{-9} M^{-1}, even more preferably, 10^{-10} to 10^{-12} M^{-1}.

The term "immunoreact" can mean the binding region is capable of eliciting an immune response upon binding with the target antigen, or an epitope thereof.

The term "epitope" can mean any region of an antigen with the ability to elicit, and combine with, a binding region of the antibody or antigen-binding fragment thereof.

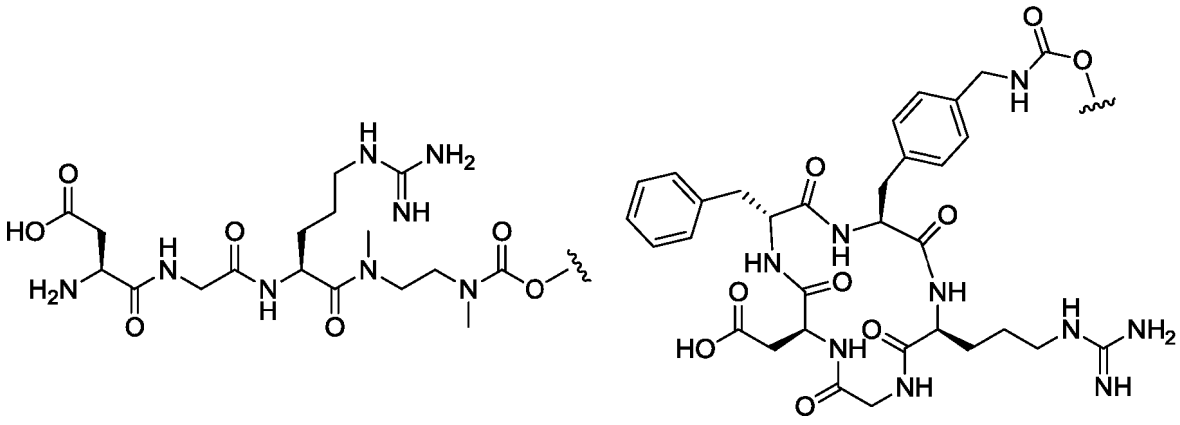
In one embodiment, T comprises a nucleic acid based molecule. The nucleic acid based molecule may be an aptamer. The nucleic acid based molecule may target the CD33/CD34 antigen as described in Zaimy, M.A. et. al., Cancer Gene Ther., **2016**, 23, 315-320 or PSMA tumor antigens such as A9, A10 and A9L described by Lupold, S.E. et. al., *Cancer Res.*, **2002**, 62, 4029-4033; Dassie, J.P. et. al., *Nat. Biotech.*, **2009**, 27, 839-849; Rockey, W.M. et. al., *Nucleic Acid Ther.*, **2011**, 21, 299-314, or any other tumor antigen known to those skilled in the art, for example as described in Orava, E., *Biochem. Biophys. Acta*, **2010**, 1798, 2190-2200.

Aptamers are nucleic acid or peptide molecules that assume a specific, sequence-dependent shape and bind to specific target ligands based on a lock-and-key fit between the aptamer and ligand. Typically, aptamers may comprise either single- or double-stranded DNA molecules (ssDNA or dsDNA) or single-stranded RNA molecules (ssRNA). Peptide aptamers consist of a short variable peptide domain, attached at both ends to a protein scaffold. Aptamers may be used to bind both nucleic acid and non-nucleic acid targets.

Suitable aptamers may be selected from random sequence pools, from which specific aptamers may be identified which bind to the selected antigen with high affinity. Methods for the production and selection of aptamers having desired specificity are well known to those skilled in the art, and include the SELEX (systematic evolution of ligands by exponential enrichment) process. Briefly, large libraries of oligonucleotides are produced, allowing the isolation of large amounts

of functional nucleic acids by an iterative process of *in vitro* selection and subsequent amplification through polymerase chain reaction. Preferred methodologies for producing aptamers include those disclosed in WO 2004/042083.

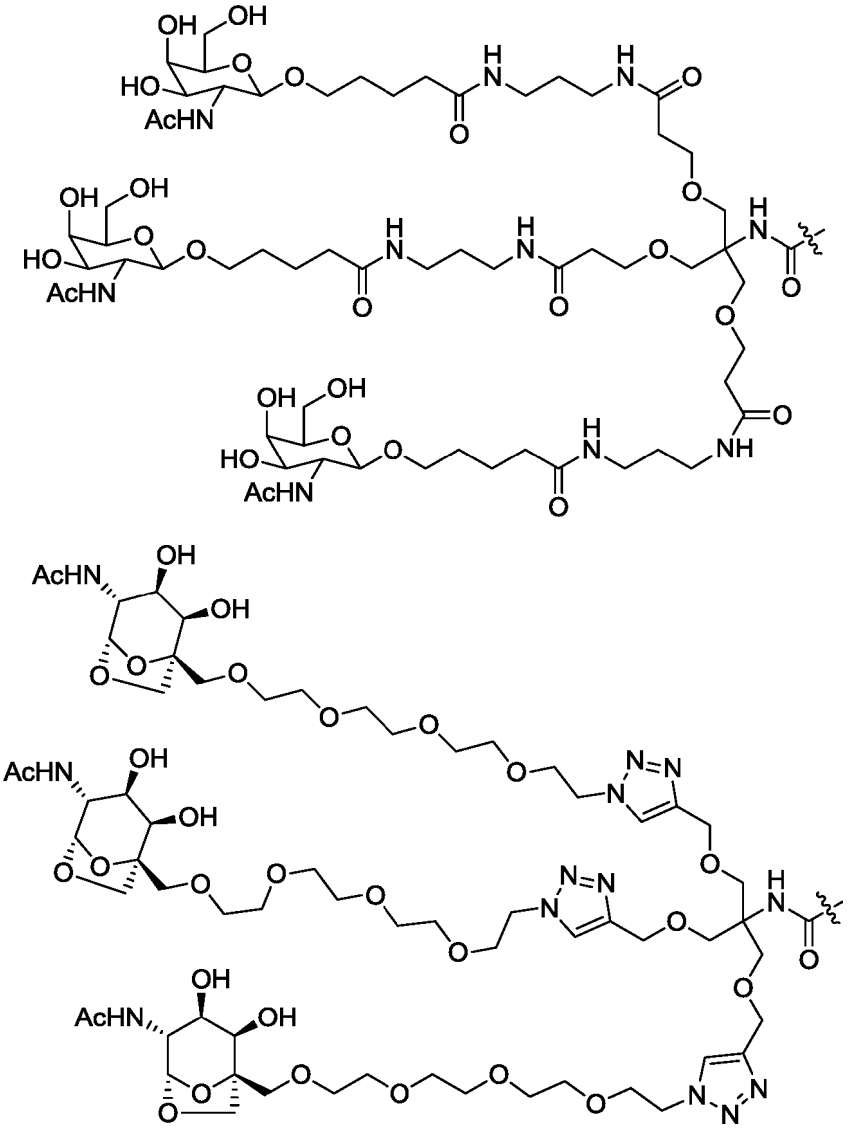
In an alternative embodiment, T comprises a peptide or a modified peptide. The peptide or modified peptide may comprise the RGD sequence motif, as described in Mousavizadeh, A., *Colloids Surfaces B.*, **2017**, 158, 507-517 to include linear RGD peptide sequences or cyclised versions thereof as described in Belvisi, L et. al., *Curr. Top., Med Chem.*, **2016**, 16, 314-329. Exemplary embodiments of an RGD ligand which the targeting moiety may target and bind are as follows:

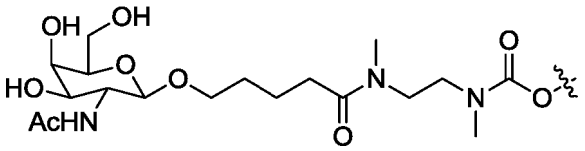


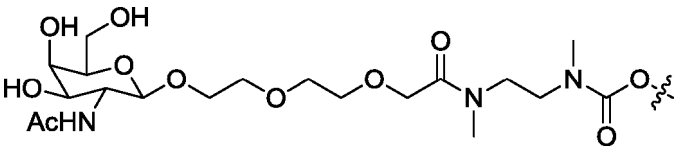
The peptide or modified peptide may comprise transferrin, or modified versions of transferrin, which has been described as showing promise for the targeted delivery of xenobiotics (Kratz *et. al.*, *Cancer Chemother. Pharmacol.*, **1998**, 41, 155-160), including crossing the blood-brain barrier (Fishman *et. al.*, *J. Cell Biol.*, **1987**, 101, 423-427). The peptide or modified peptide may also comprise albumin, or modified versions of albumin, in which the albumin protein may be conjugated to a suitable linker via Cys34 or other suitable residue as described in Larsen *et. al.*, *Mol Cell Ther.*, **2016**, 4, 3.

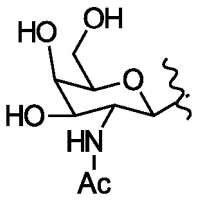
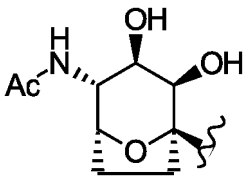
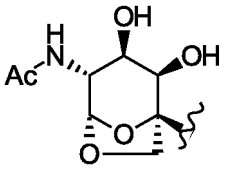
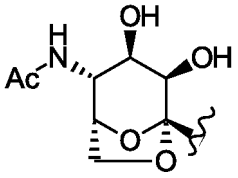
In an alternative embodiment, T comprises a carbohydrate or a modified carbohydrate molecule which can target a tumour-associated carbohydrate antigen receptor on target tumours and cells. For example, glycosphingolipids, gangliosides, sialic acids and mucins are indicative of malignant transformation and an aberrant glycosylation pattern on cancer cells (as reviewed in Feng, D. *et. al.*, *ACS Chem. Biol.* **2016**, *11*, 850-863; Hakomori, S., *Ann. Rev. Immunol.*, **1984**, *2*, 103-126; Dube, D.H. and Bertozzi, C.R., *Nat. Rev. Drug Disc.*, **2005**, *4*, 477-488) and targeting ligands based on

carbohydrate molecules have been designed against them, for example mannose, galactose or cerebrosidase derivatives. In a related method, cell-surface receptors on tissues of interest may also be targeted; a recent example includes derivatives of N-acetyl-galactosamine (GalNAc) which have been developed to target the asialoglycoprotein receptor on hepatocytes (reviewed in D'Souza, A. et. al., *J. Controlled Rel.*, **2015**, *203*, 126-139 and a recent example in Sanhueza, C.A. et. al., *JACS*, **2017**, *139*, 3528-3536). Exemplary embodiments of carbohydrates which may be used as the targeting moiety are as follows:



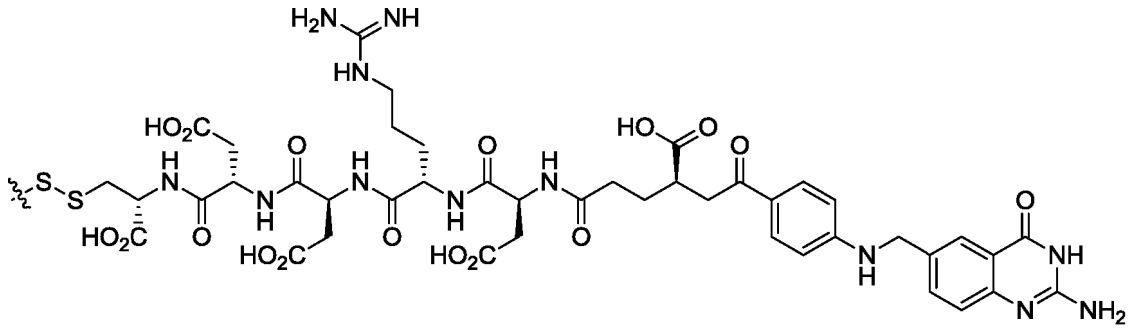




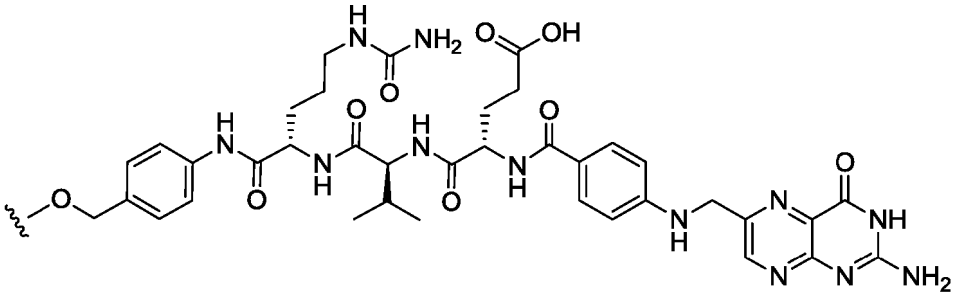
Accordingly, T may be  ,  ,  or  .

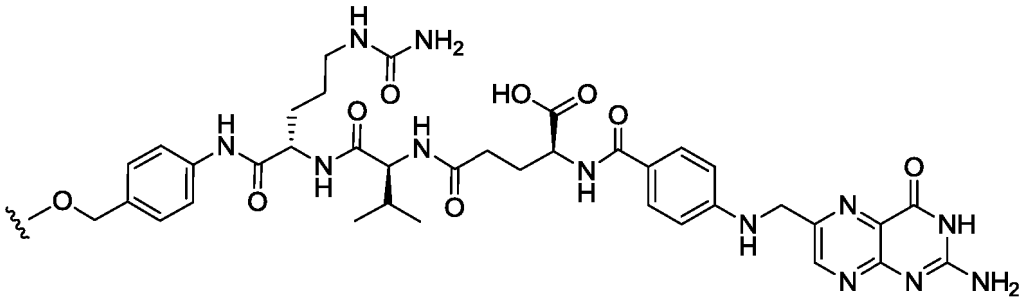
In another embodiment, T comprises a small molecule ligand with affinity for a cell or tumour-surface receptor. For example, folic acid or derivatives thereof may be used to target folate receptors α, β or γ (FRα, FRβ and FRγ). FRα in particular is known to be expressed in multiple endothelial tumour types such as breast, lung and kidney (see Fernandez, M. *et. al.*, **2018**, 4, 790-810 for a recent review) and conjugates of folate derivatives and toxins have been described previously (Vlahov, I. and Leamon, C.P., *Bioconjugate Chem.*, **2012**, 23, 1357-1369).

An exemplary embodiment of a small molecule ligand (a folate derivative) which targets a folate receptor on the target cell surface is shown below conjugated to a linker.

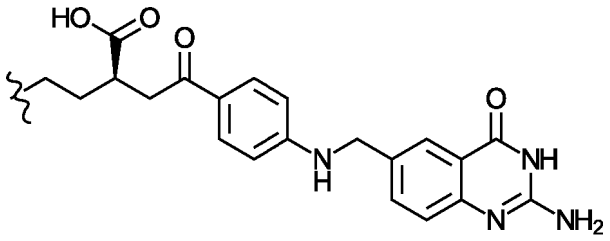


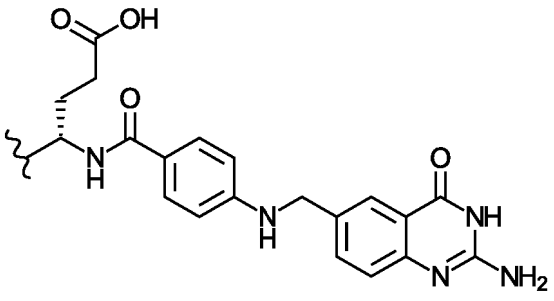
Such conjugate designs may be combined with the linker designs outlined above to provide composite folate receptor-targeting designs, for example;

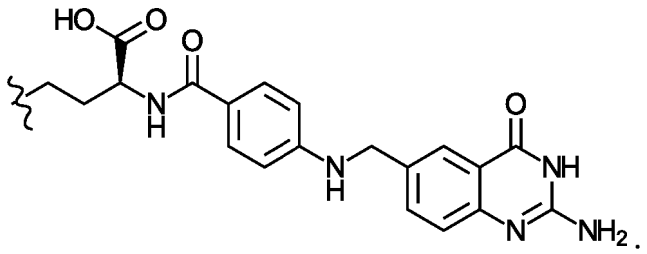




Accordingly, T may be a folate or a derivate thereof. T may be:

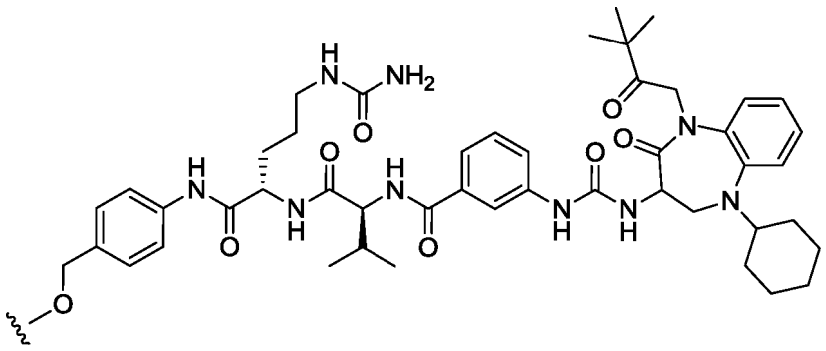


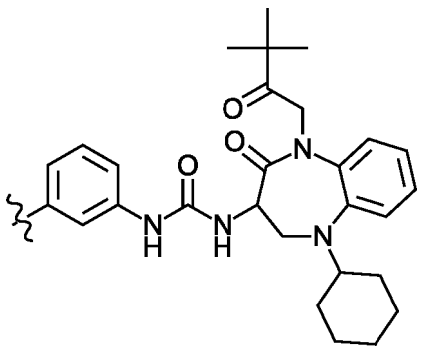

or



Similarly, the cholecystokinin 2 receptor (CCK2R) is a transmembrane receptor primarily found in epithelial cells of the GI tract and the brain. CCK2R is overexpressed in many cancers of the lung, pancreas, liver and GI tract (Reubi, J.C. *et. al.*, *Cancer Res.*, **1997**, 57, 1377-1386). A recent report has described conjugates of a potent CCK2 receptor antagonist, Z-360, linked to a vinblastine derivative (Wayua, C. *et. al.*, *Mol. Pharm.*, **2015**, 12, 2477-2483).

Another exemplary embodiment of a small molecule ligand (a CCK2R antagonist) which targets CCK2R on the target cell surface is shown below conjugated to a linker.



Accordingly, T may be a CCK2R antagonist. T may be  .

Other ligand-targeted small molecules are described in Srinivasarao, M. *et. al.*, *Chem. Revs.*, **2017**, 117, 12133-12164. For, example vintafolide (targeting folate receptors),

glufosfamide (targeting β-D-glucose), vitamin D (targeting vitamin D receptors), cholesterol and lipophilic esters (targeting the liver) have been described.

C is a small molecule modulator of the STING protein of formula (II) as described above. C can therefore be attached to the linker through a C atom, an O atom, an N atom or an S atom at any available position, for example through the R^1-R^{14} groups.

L may be CH_2, C=O or SO_2.

Q may be C=O, SO_2, S=O, CR^4R^5 or C=S.

In one embodiment X^1 is CR^1, X^2 is CR^2 and X^3 is CR^3. R^1, R^2 and R^3 may each independently be selected from the group consisting of H, halogen, and optionally substituted C_1-C_6 alkyl. Preferably, R^1, R^2 and R^3 are each independently selected from the group consisting of H, halogen, and C_1-C_3 alkyl. More preferably, R^1, R^2 and R^3 are each independently selected from the group consisting of H, halogen, and methyl. Most preferably, R^1, R^2 and R^3 are each H.

In an alternative embodiment, one or two of X^1, X^2 and X^3 is N. Accordingly, X^1 may be N, X^2 may be CR^2 and X^3 may be CR^3, X^1 may be CR^1, X^2 may be N and X^3 may be CR^3 or X^1 may be CR^1, X^2 may be CR^2 and X^3 may be N.

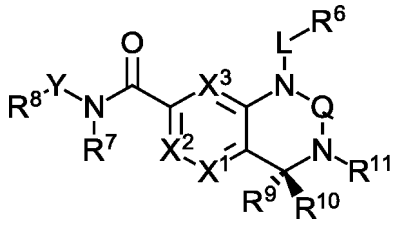
Preferably X^2 is CR^2. Accordingly, X^1 may be CR^1 or N and X^3 may be CR^3 or N. X^1 may be N, X^2 may be CR^2 and X^3 may be CR^3, or X^1 may be CR^1, X^2 may be CR^2 and X^3 may be N, or X^1 may be N, X^2 may be CR^2 and X^3 may be N. Preferably, R^2 is H, halogen or C_1-C_3 alkyl. More preferably, R^2 is H, halogen or methyl. Most preferably, R^2 is each H.

Preferably, R^1 and/or R^3, in embodiments where they are present, are independently H, halogen or C_1-C_3 alkyl. More preferably, R^1 and/or R^3, in embodiments where they are present, are independently H, halogen or methyl. Most preferably, R^1 and/or R^3, in embodiments where they are present, are H.

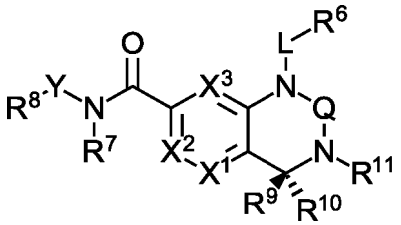
Compounds of formula (**II**) may include one or more stereogenic centres and so may exist as optical isomers, such as enantiomers and diastereomers. All such isomers and mixtures thereof are included within the scope of the present invention.

In embodiments where R^9 is different to R^{10} then the compound of formula (**I**) will include a first stereogenic centre. In may be appreciated that the first stereogenic centre, or stereocentre, is the carbon atom to which R^9 and R^{10} are covalently bonded.

Compounds of formula (**II**) may be represented by a formula (**II**)-ent 1 or (**II**)-ent 2:



(**II**)-ent.1



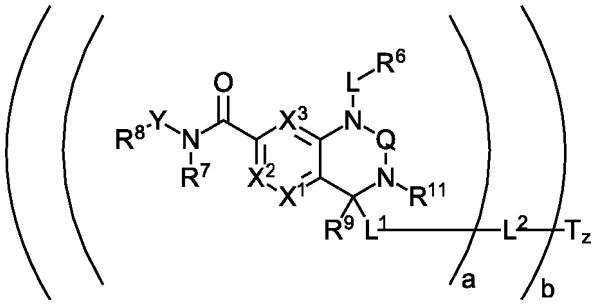
(**II**)-ent.2

Preferably, the first stereogenic centre defines an S enantiomer.

Preferably, at least one of R^9 and R^{10} is an optionally substituted C_1-C_6 alkyl, halogen, H, a C_3-C_6 cycloalkyl or C_1-C_3 polyfluoroalkyl. More preferably, at least one of R^9 and R^{10} is a C_1-C_6 alkyl, H or a C_3-C_6 cycloalkyl, even more preferably a C_1-C_3 alkyl, H or a C_3-C_6 cycloalkyl, and most preferably at least one of R^9 and R^{10} is H, methyl, ethyl, isopropyl or cyclopropyl. In one embodiment, R^9 and R^{10} are both H. However, in a most preferred embodiment, one of R^9 and R^{10} is methyl and the other is H. In one embodiment, both R^9 and R^{10} are an optionally substituted C_1-C_6 alkyl or H. In one embodiment, both R^9 and R^{10} are a C_1-C_6 alkyl, more preferably a C_1-C_3 alkyl, even more preferably methyl, ethyl or isopropyl, and most preferably both R^9 and R^{10} are methyl. However, in a most preferred embodiment, one of R^9 and R^{10} is methyl and the other is H.

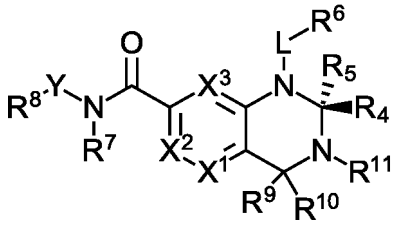
In one embodiment, the compound is a compound of formula (**II**)-ent 1, R^9 is H and R^{10} is an optionally substituted C_1-C_6 alkyl, halogen, a C_3-C_6 cycloalkyl or C_1-C_3 polyfluoroalkyl. Preferably R^{10} is a C_1-C_6 alkyl or a C_3-C_6 cycloalkyl, more preferably R^{10} is a C_1-C_3 alkyl or a C_3-C_6 cycloalkyl, and most preferably R^{10} is methyl, ethyl, isopropyl or cyclopropyl. In a most preferred embodiment, R^{10} is methyl.

Alternatively, R^{10} may be absent, and the linker may be bonded directly to the carbon atom. Accordingly, the compound of formula (**I**) may be a compound of formula (**I-A**):

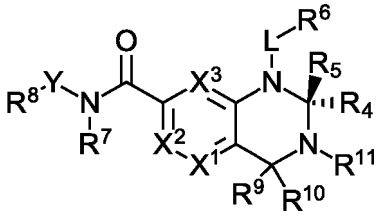


(**I-A**)

As mentioned above, Q may be CR^4R^5. Accordingly, the compound may be a compound of formula (**II**)-ent 3 or (**II**)-ent 4:

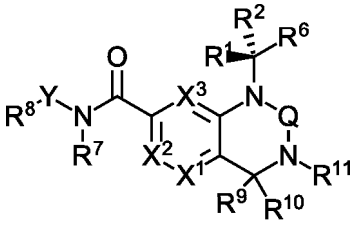


(**II**)-ent 3

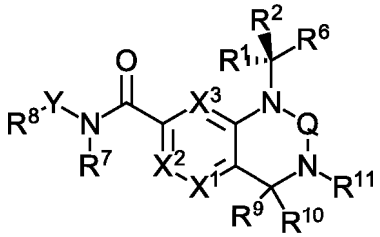


(**II**)-ent 4

Alternatively, or additionally, L is a branched alkyl group. Accordingly, the compound may be a formula (**II**)-ent. 5 or (**II**)-ent. 6:

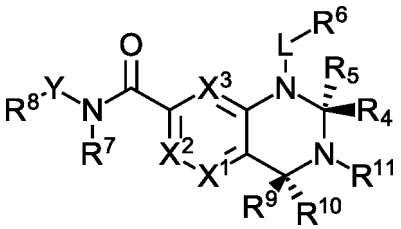


(**II**)-ent 5

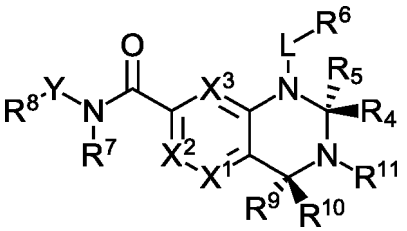


(**II**)-ent 6

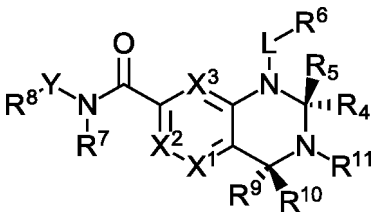
In yet another embodiment, the compound could possess two chiral centres, and could be represented by a compound of formula (**II-I-IV**)-ent 1, formula (**II-I-IV**)-ent 2, formula (**II-I-IV**)-ent 3 or formula (**II-I-IV**)-ent 4:



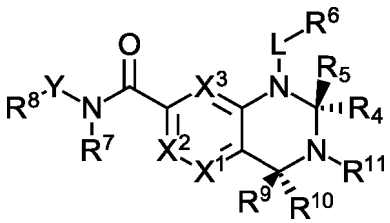
(**II-I-IV**)-ent 1



(**II-I-IV**)-ent 2



(**II-I-IV**)-ent 3



(**II-I-IV**)-ent 4

It will be understood that the above compounds may exist as enantiomers and as diastereoisomeric pairs. These isomers also represent further embodiments of the invention.

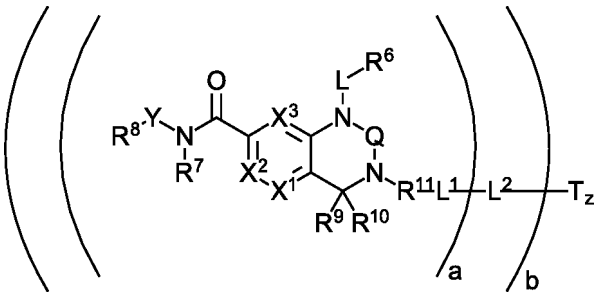
Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC).

Alternatively, the racemate (or a racemic precursor) may be reacted with a suitable optically active compound, for example, an alcohol, or, in the case where the compound of formula (I) contains an acidic or basic moiety, a base or acid such as 1-phenylethylamine or tartaric acid. The resulting diastereomeric mixture may be separated by chromatography and/or fractional crystallization and one or both of the diastereoisomers converted to the corresponding pure enantiomer(s) by means well known to a skilled person.

Chiral compounds of the invention (and chiral precursors thereof) may be obtained in enantiomerically-enriched form using chromatography, typically HPLC, on an asymmetric resin with a mobile phase consisting of a hydrocarbon, typically heptane or hexane, containing from 0 to 50% by volume of isopropanol, typically from 2% to 20%, and from 0 to 5% by volume of an alkylamine, typically 0.1% diethylamine. Concentration of the eluate affords the enriched mixture.

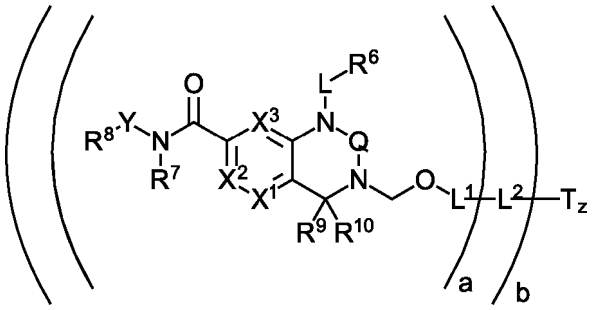
Mixtures of stereoisomers may be separated by conventional techniques known to those skilled in the art; see, for example, "Stereochemistry of Organic Compounds" by E. L. Eliel and S. H. Wilen (Wiley, New York, 1994).

C may be attached to the linker through the R^{11} group. Accordingly, the R^{11} group may be substituted by the linker, and the compound of formula (**I**) may be a compound of formula (**I-B**):



(I-B)

In one embodiment, R^{11} is selected from the group consisting of optionally substituted C_1-C_6 alkyl, H, hydroxyl, C_1-C_3 polyfluoroalkyl, optionally substituted C_3-C_6 cycloalkyl, optionally substituted C_1-C_6 alkoxy and optionally substituted C_2-C_6 alkenyl. In embodiments where R^{11} is optionally substituted C_1-C_6 alkoxy, the linker may be bonded to the oxygen in the alkoxy. Accordingly, the compound of formula (**I**) may be a compound of formula (**I-B-a**):



(I-B-a)

, wherein f is an integer between 1 and 6.

Preferably, R^{11} is selected from the group consisting of C_1-C_6 alkyl, C_2-C_4 alkenyl and H. More preferably, R^{11} is a C_1-C_3 alkyl or H, and most preferably is methyl or H.

Preferably, R^{11} is an optionally substituted C_1-C_6 alkyl, an optionally substituted C_2-C_6 alkenyl, a C_3-C_6 cycloalkyl or C_1-C_3 polyfluoroalkyl. More preferably, R^{11} is a C_1-C_6 alkyl, a C_2-C_6 alkenyl, or a C_3-C_6 cycloalkyl, even more preferably a C_1-C_3 alkyl, a C_2-C_3 alkenyl or a C_3-C_6 cycloalkyl, and most preferably R^{11} is methyl, ethyl, isopropyl or cyclopropyl.

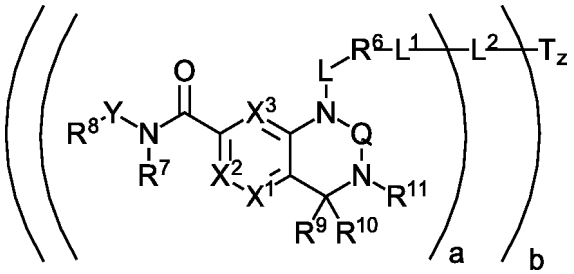
In a most preferred embodiment, R^{11} is methyl.

In a preferred embodiment, Q is C=O, SO_2 or CR^4R^5. More preferably, Q is C=O or CR^4R^5. Preferably, R^4 and R^5 are each independently selected from the group consisting of H, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_6 cycloalkyl or R^4 and R^5 together with the atom to which they are attached form a spirocyclic ring. More preferably, R^4 and R^5 are each independently selected from the group consisting of H and optionally substituted C_1-C_6 alkyl. Accordingly, R^4 and R^5 may both be H. Alternatively, R^4 and R^5 may both be Me or R^4 may be Me and R^5 may be H.

Most preferably, Q is C=O.

L may be C=O or SO_2. However, in a preferred embodiment, L is optionally substituted C_1-C_6 alkyl, -CH_2C(O)- or -CH_2CONH-. Preferably, L is optionally substituted C_1-C_3 alkyl, more preferably -CH_2-, -CH_2CH_2-, –$CH_2CH_2CH_2$-, C(Me)H, CF_2 or C(H)F and most preferably –CH_2-.

Preferably, C is attached to the linker through the R^6 group. Accordingly, the R^6 group may be substituted by the linker. The compound of formula (**I**) may be a compound of formula (**I-C**):



(**I-C**)

Preferably, R^6 is a ring optionally substituted with one or more R^{12} groups, wherein the ring is selected from the group consisting of a mono or bicyclic C_5-C_{10} aryl; mono or bicyclic 5 to 10 membered heteroaryl; and a C_3-C_6 cycloalkyl. More preferably, R^6 is a ring optionally substituted with one or more R^{12} groups, wherein the ring is selected from the group consisting of a mono or bicyclic C_5-C_{10} aryl; and mono or bicyclic 5 to 10 membered heteroaryl. Most preferably, R^6 is a mono or bicyclic C_5-C_{10} aryl optionally substituted with one or more R^{12} groups. The ring may be directly substituted to the linker. Alternatively, the linker may substitute an R^{12} group.

In some embodiments R^6 is unsubstituted or only substituted by the linker.

Alternatively, R^6 may comprise a ring substituted with between 1 and 5 R^{12}. Accordingly, the ring could be substituted with 1, 2, 3, 4 or 5 R^{12} groups. The ring may further be directly substituted with the linker. Alternatively, the linker may substitute an R^{12} group.

An R^{12} group may be a halogen. The halogen may be fluorine, chlorine, bromine or iodine, more preferably fluorine, chlorine or bromine, even more preferably fluorine or chlorine, and most preferably fluorine.

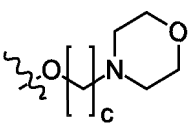
An R^{12} group may be an optionally substituted C_1-C_6 alkyl, and more preferably an optionally substituted C_1-C_3 alkyl. In some embodiments, the alkyl may be unsubstituted. Accordingly, an R^{12} group may be methyl, ethyl, n-propyl (1-propyl) and isopropyl (2-propyl, 1-methylethyl), butyl, pentyl, hexyl, *iso*butyl, *sec*-butyl, *tert*-butyl, *iso*pentyl, *neo*pentyl, *iso*hexyl or *neo*hexyl. Alternatively, the alkyl may be substituted with one or more groups selected from a halogen, OH, NH_2 or CN. Alternatively, a H in the OH or NH_2 group could be omitted and the oxygen or nitrogen could be bonded directly to the linker. Preferably, the halogen is a chlorine or fluorine and most preferably a fluorine. In a preferred embodiment, an R^{12} group is an optionally substituted methyl or ethyl. The optionally substituted alkyl may be a fluorinated methyl or ethyl. In a preferred embodiment, an R^{12} group is a methyl, -CHF_2, –CF_3, –CH_2OH or –$CH(OH)CH_3$. Alternatively, in embodiments comprising an OH group, the H could be omitted and the oxygen could be bonded directly to the linker.

An R^{12} group may be an optionally substituted C_1-C_6 alkoxy. Accordingly, an R^{12} group may be –OR^{15}, where R^{15} is an optionally substituted C_1-C_6 alkyl group, an optionally substituted C_3-C_6 cycloalkyl group, an optionally substituted C_2-C_6 alkenyl or an optionally substituted C_2-C_6 alkynyl. Preferably, R^{15} is an optionally substituted C_1-C_3 alkyl group, an optionally substituted C_2-C_3 alkenyl or an optionally substituted C_2-C_3 alkynyl. In some embodiments, the C_1-C_6 alkoxy may be unsubstituted. Accordingly, an R^{12} group may be methoxy, ethoxy, n-propoxy (1-propoxy), n-butoxy and *tert*-butoxy. In a preferred embodiment, an R^{12} group is methoxy or –OCH_2CHCH_2. Alternatively, the C_1-C_6 alkoxy may be substituted with one or more groups selected from –OH, - -NH_2, CN, $OP(O)(OH)_2$, COOH, a halogen, OSO_2R^{13}, $N(H)SO_2R^{13}$, a C_3-C_6

cycloalkyl and a 3 to 8 membered heterocycle. Alternatively, a H in the OH or NH_2 group or R^{13} in the OSO_2R^{13} or $N(H)SO_2R^{13}$ group could be omitted and the oxygen or nitrogen could be bonded directly to the linker. In embodiments where it is present, R^{13} may be independently selected from the group consisting of H and optionally substituted C_1-C_6 alkyl. Preferably, R^{13} is selected from the group consisting of H and C_1-C_6 alkyl, more preferably H and C_1-C_3 alkyl. In a preferred embodiment R^{13} is Me. The C_3-C_6 cycloalkyl may be cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. The 3 to 8 membered heterocycle may be aziridine, oxirane, oxirene, thiirane, pyrroline, pyrrolidine, dihydrofuran, tetrahydrofuran, dihydrothiophene, tetrahydrothiophene, dithiolane, piperidine, 1,2,3,6-tetrahydropyridine-1-yl, tetrahydropyran, pyran, morpholine, piperazine, thiane, thiine, piperazine, azepane, diazepane or oxazine. Preferably, the 3 to 8 membered heterocycle is morpholine.

In one embodiment, an R^{12} group is an optionally substituted alkoxy, *i.e.* $-OR^{15}$. R^{15} may be an optionally substituted C_1-C_6 alkyl.

In one embodiment, R^{15} is a C_1-C_6 alkyl substituted with a halogen, preferably a chlorine or fluorine and most preferably a fluorine. In a preferred embodiment, the R^{15} group is a halogenated methyl, more preferably a fluorinated methyl and most preferably $-CHF_2$ or $-CF_3$. Accordingly, an R^{12} group may be $-OCHF_2$ or $-OCF_3$.

Alternatively, R^{15} may be a C_1-C_6 alkyl substituted with one or more substituents selected from the group consisting of OH, $OP(O)(OH)_2$, OSO_2R^1, $NHSO_2R^1$, C_1-C_6 alkoxy, NR^1R^2, $CONR^1R^2$, CN, COOH, optionally substituted C_5-C_{10} aryl, optionally substituted 5 to 10 membered heteroaryl, C_3-C_6 cycloalkyl and 3 to 8 membered heterocycle, more preferably R^{15} is a C_1-C_6 alkyl substituted with one or more substituents selected from the group consisting of OH, $OP(O)(OH)_2$, $NHSO_2R^1$, COOH and 3 to 8 membered heterocycle. The optionally substituted C_5-C_{10} aryl or optionally substituted 5 to 10 membered heteroaryl may be substituted with the linker. Alternatively, a H in a group comprising an OH or NH_2 or the R^1 in the OSO_2R^1, $NHSO_2R^1$ or $CONR^1R^2$ group could be omitted and the oxygen or nitrogen could be bonded directly to the linker. Accordingly, an R^{12} group may be 

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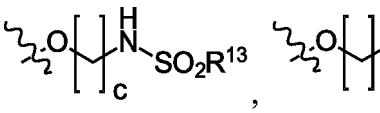

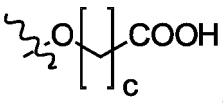
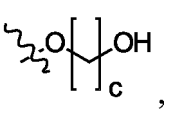
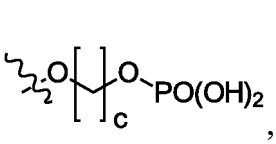
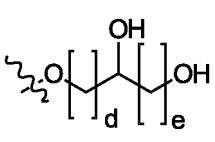
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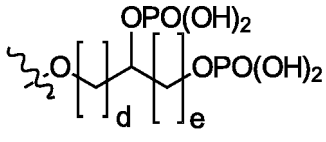
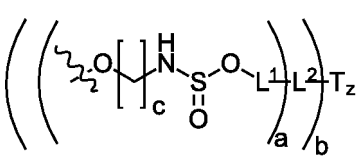
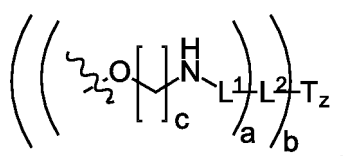
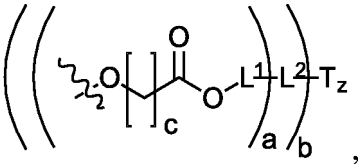
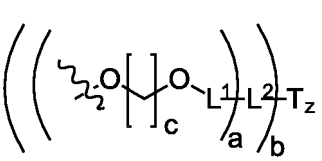
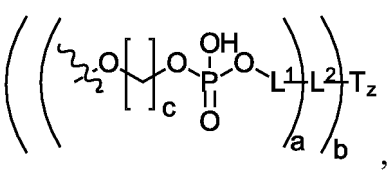
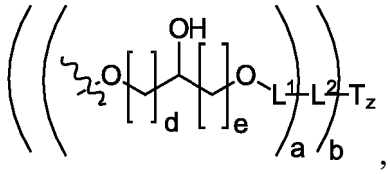
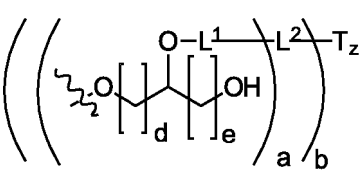
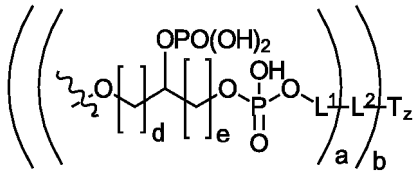

where c is an integer between 1 and 6, and d and e are both integers between 0 and 5 wherein the sum of d and e is an integer between 0 and 5.

Alternatively, the R^{12} group may be connected to the linker like so: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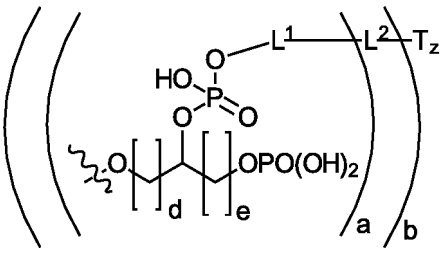
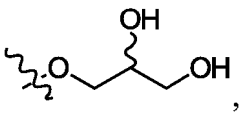
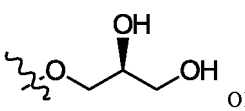

, where c, d and e are as defined above.

Accordingly, c may be 1, 2, 3, 4, 5 or 6, and is preferably 1, 2 or 3. Accordingly, d and e may be 0, 1, 2, 3, 4 or 5. Preferably, d and e are both integers between 0 and 2 wherein the sum of d and e is an integer between 0 and 2. In a preferred embodiment, d is 1 and e is 1. An R^{12} group may be 

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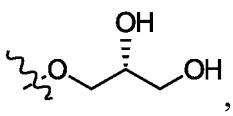
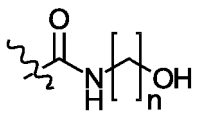

, or a H in a group comprising an OH could be omitted and the oxygen could be bonded directly to the linker.

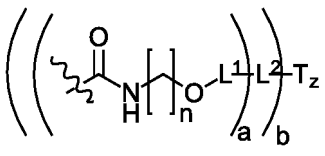
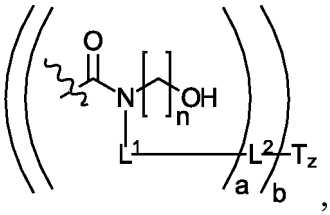
An R^{12} may be –OH or -SH, or the hydrogen may be omitted and the oxygen or sulphur may be bonded directly to the linker.

An R^{12} group may be $NR^{13}R^{14}$, or the R^{13} may omitted and the nitrogen is bonded directly to the linker. R^{14}, and R^{13} in embodiments where it is present, may each be independently selected from the group consisting of H and optionally substituted C_1-C_6 alkyl. Preferably, R^{14}, and R^{13} in embodiments where it is present, are each independently selected from the group consisting of H and optionally substituted C_1-C_3 alkyl. In one embodiment, R^{13} and R^{14} are both H. Accordingly, an R^{12} group may be NH_2 or a hydrogen may be omitted and the nitrogen may be bonded directly to the linker. Alternatively, at least one of R^{13} and R^{14} may be an optionally substituted C_1-C_6 alkyl, preferably an optionally substituted C_1-C_3 alkyl. The or each alkyl may be unsubstituted. Accordingly, the or each alkyl may be methyl, ethyl, n-propyl (1-propyl) and isopropyl (2-propyl, 1-methylethyl), butyl, pentyl, hexyl, *iso*butyl, *sec*-butyl, *tert*-butyl, *iso*pentyl, *neo*pentyl, *iso*hexyl or *neo*hexyl. Accordingly, an R^{12} group may be N(H)Me or $N(Me)_2$ or the hydrogen may be omitted and the nitrogen may be bonded directly to the linker. Alternatively, the or each alkyl may be substituted with a halogen, -OH, CN or NH_2 group. In one embodiment, an R^{12} group may be $–NH(CH_2)_mOH$, wherein m is an integer between 1 and 6, more preferably between 1 and 3, or the hydrogen bonded to either the nitrogen or the oxygen may be omitted and the nitrogen or oxygen may be bonded directly to the linker. In a preferred embodiment, m is 2 or 3.

An R^{12} group may be $CONR^{13}R^{14}$, or the R^{13} may be omitted and the nitrogen may be bonded directly to the linker. R^{14}, and R^{13} in embodiments where it is present, may each be independently selected from the group consisting of H and optionally substituted C_1-C_6 alkyl. Preferably, R^{14}, and R^{13} in embodiments where it is present, are each independently selected from the group consisting of H and optionally substituted C_1-C_3 alkyl. In one embodiment, R^{13} and R^{14} are both H. Accordingly, an R^{12} group may be $CONH_2$ or a hydrogen may be omitted and the nitrogen may be bonded directly to the linker. Alternatively, at least one of R^{13} and R^{14} may be an optionally substituted C_1-C_6 alkyl, preferably optionally substituted C_1-C_3 alkyl. Preferably, the alkyl is substituted with an OH group. Accordingly, in one embodiment, an R^{12} group may be



where n is an integer between 1 and 6. Preferably, n is an integer between 1 and 3, and most preferably n is 2. Alternatively, the R^{12} may be bonded

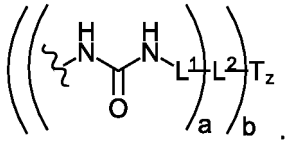
directly to the linker like so  or  , where n is as defined above.

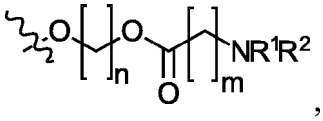
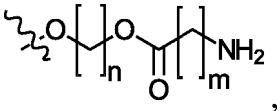
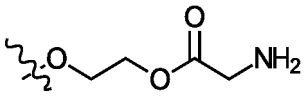
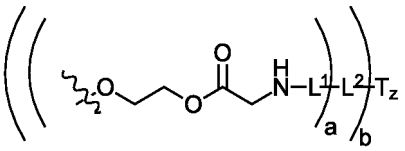
An R^{12} group may be $COOR^{13}$, or the R^{13} may be omitted and the oxygen may be bonded directly to the linker. R^{13} may be independently selected from the group consisting of H and optionally substituted C_1-C_6 alkyl. Preferably, R^{13} is selected from the group consisting of H and C_1-C_6 alkyl, more preferably H and C_1-C_3 alkyl. In a preferred embodiment R^{13} is H or Me.

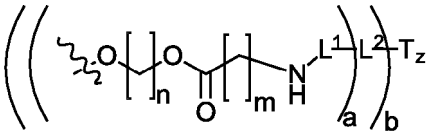
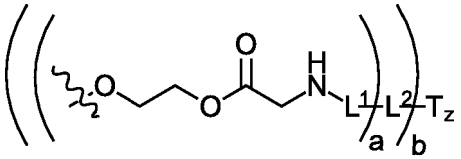
An R^{12} group may be OSO_2R^{13}, or the R^{13} may be omitted and the oxygen may be bonded directly to the linker. R^{13} may be selected from the group consisting of H and optionally substituted C_1-C_6 alkyl. Preferably, R^{13} is selected from the group consisting of H and C_1-C_6 alkyl, more preferably H and C_1-C_3 alkyl. In a preferred embodiment R^{13} is Me.

An R^{12} group may be $NR^{13}SO_2R^{14}$, or the R^{13} or R^{14} may be omitted and the nitrogen or oxygen may be bonded directly to the linker. R^{13} and R^{14}, in embodiments where they are present, may be independently selected from the group consisting of H and optionally substituted C_1-C_6 alkyl. Preferably, R^{13} and R^{14}, in embodiments where they are present, are selected from the group consisting of H and C_1-C_6 alkyl, more preferably H and C_1-C_3 alkyl. In a preferred embodiment, R^{13} is H and R^{14} is Me.

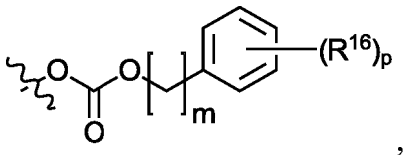
An R^{12} group may be $NR^{13}C(O)R^{14}$, or the R^{13} may be omitted and the nitrogen may be bonded directly to the linker. R^{13} and R^{14}, in embodiments where they are present, may be independently selected from the group consisting of H and optionally substituted C_1-C_6 alkyl. Preferably, R^{13} and R^{14}, in embodiments where they are present, are selected from the group consisting of H and an optionally substituted C_1-C_3 alkyl. The or each alkyl may be substituted with a halogen, -OH, CN or NH_2 group, or a hydrogen may be omitted and the oxygen or nitrogen may be bonded directly to the linker. In one preferred embodiment, R^{13} is H and R^{14} is an optionally substituted methyl. Preferably, R^{14} is Me or $-CH_2NH_2$, or a hydrogen may be omitted and the linker may be bonded directly to the nitrogen. Accordingly, an R^{12} group may be –

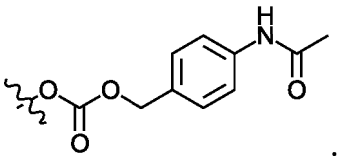
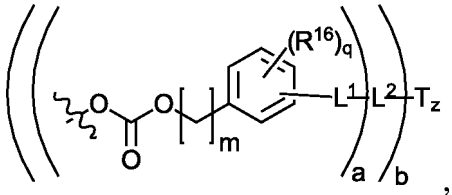
$NHC(O)CH_3$ or $-NHC(O)CH_2NH_2$. Alternatively, the R^{12} group may be directly bonded to the linker, like so  .

An R^{12} group may be $O(CH_2)_nOC(O)R^{13}$. n is preferably an integer between 1 and 6, more preferably between 1 and 3. In a preferred embodiment n is 2. R^{13} may be H or optionally substituted C_1-C_6 alkyl. In one embodiment, R^{13} is an optionally substituted C_1-C_6 alkyl, more preferably an optionally substituted C_1-C_3 alkyl, and most preferably an optionally substituted methyl. The alkyl may be substituted with a halogen, OH, CN, NR^1R^2 or an optionally substituted mono or bicyclic C_5-C_{10} aryl, or a hydrogen or the R^1 group may be omitted and the oxygen or nitrogen may be bonded directly to the linker. Alternatively, the aryl may be substituted with the linker. Preferably, the alkyl is substituted with NR^1R^2 or R^1 is omitted and the nitrogen is bonded directly to the nitrogen. Preferably, R^1 and R^2 are each independently selected from the group consisting of H and C_1-C_6 alkyl, more preferably H and C_1-C_3 alkyl. Most preferably, R^1 and R^2 are both H. Accordingly, an R^{12} group may be  , where m is an integer between 1 and 6, more preferably between 1 and 3, and most preferably is 1. More preferably, more preferably an R^{12} group may be  , and most preferably is  or  .

Alternatively, the R^{12} group may be bonded to the linker like so  , and most preferably like so  .

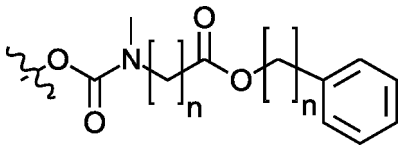
An R^{12} group may be $OC(O)OR^{13}$, or the R^{13} may be omitted and the oxygen may be bonded directly to the linker. In embodiments where it is present, R^{13} may be H or optionally substituted C_1-C_6 alkyl. In one embodiment, R^{13} is an optionally substituted C_1-C_6 alkyl, more preferably an optionally substituted C_1-C_3 alkyl, and most preferably an optionally substituted methyl. The alkyl may be substituted with a halogen, OH, CN, NR^1R^2 or an optionally substituted mono or bicyclic C_5-C_{10} aryl, or a hydrogen or the R^1 group may be omitted and the oxygen or nitrogen may be bonded directly to the linker. Alternatively, the aryl may be substituted with the linker. Preferably, the alkyl is substituted with an optionally substituted mono or bicyclic C_5-C_{10} aryl. The optionally substituted mono or bicyclic C_5-C_{10} aryl is preferably optionally substituted phenyl.

Accordingly, an R^{12} group may be  , wherein m is an integer between 1 and 6, p is an integer between 0 and 5 and the or each R^{16} is independently selected from the group consisting of an optionally substituted C_1-C_6 alkyl, halogen, OH, $OP(O)(OH)_2$, optionally substituted C_1-C_6 alkoxy, NR^1R^2, $CONR^1R^2$, CN, COOH, NO_2, azido, C_1-C_3 polyfluoroalkyl, aryloxy, heteroaryloxy, 5 to 10 membered heteroaryl, 3 to 8 membered heterocycle, SO_2R^1, $NHCOR^1$ and –OC(O)O-(optionally substituted C_1-C_6 alkyl), or a H or R^1 group may be omitted and the linker may be bonded directly to an oxygen, nitrogen, phosphorous or sulphur. In a preferred embodiment, m is 1. In a preferred embodiment, p is 1. In a preferred embodiment R^{16} is $NHCOR^1$. Preferably, R^1 is a C_1-C_6 alkyl, more preferably a C_1-C_3 alkyl and most preferably a methyl. Accordingly, in a preferred embodiment, an R^{12} group may be

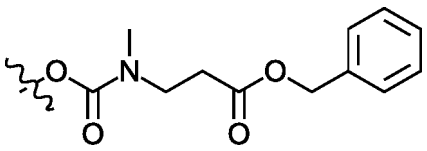
 . Alternatively, an R^{12} group may be bonded to the linker like so  , wherein m is an integer between 1 and 6, q is an integer between 0 and 4 and the or each R^{16} is independently selected from the group consisting of an optionally substituted C_1-C_6 alkyl, halogen, OH, $OP(O)(OH)_2$, optionally substituted C_1-C_6 alkoxy, NR^1R^2, $CONR^1R^2$, CN, COOH, NO_2, azido, C_1-C_3

polyfluoroalkyl, aryloxy, heteroaryloxy, 5 to 10 membered heteroaryl, 3 to 8 membered heterocycle, SO_2R^1, $NHCOR^1$ and –OC(O)O-(optionally substituted C_1-C_6 alkyl).

An R^{12} group may be $OC(O)NR^{13}(CH_2)_nCOOR^{14}$, or the R^{13} or R^{14} group may be omitted and the linker may be bonded directly to the nitrogen or oxygen. In embodiments where it is present, R^{13} may be H or optionally substituted C_1-C_6 alkyl, preferably H or a C_1-C_6 alkyl, more preferably H or a C_1-C_3 alkyl and most preferably methyl. Preferably, n is an integer between 1 and 6. Accordingly, n may be 1, 2, 3, 4, 5 or 6, and is most preferably 1, 2 or 3. In a preferred embodiment, n is 2. In embodiments where it is present, R^{14} may be H or optionally substituted C_1-C_6 alkyl. In one embodiment, R^{14} is an optionally substituted C_1-C_6 alkyl, more preferably an optionally substituted C_1-C_3 alkyl, and most preferably an optionally substituted methyl. The C_1-C_6 alkyl may be substituted with an optionally substituted mono or bicyclic C_5-C_{10} aryl. The aryl may be substituted with the linker. The optionally substituted mono or bicyclic C_5-C_{10} aryl is preferably optionally substituted phenyl. In one embodiment, the mono or bicyclic C_5-C_{10} aryl is unsubstituted. Accordingly, in a preferred embodiment, an R^{12} group may be

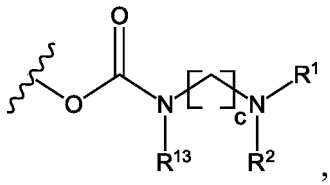
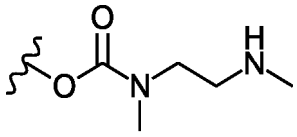
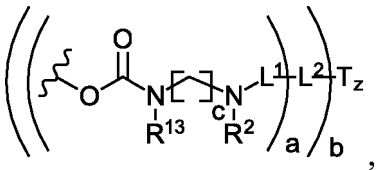
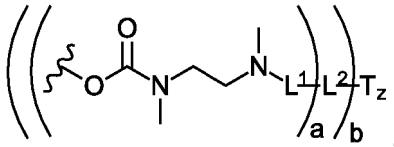


, wherein each n is independently an integer between 0 and 6, preferably between 1 and 6, more preferably between 1 and 3. In a most preferred embodiment, an R^{12} group may be



.

An R^{12} group may be $OC(O)NR^{13}R^{14}$, or the R^{13} group may be omitted and the nitrogen bonded directly to the linker. In embodiments where it is present, R^{13} may be H or optionally substituted C_1-C_6 alkyl, preferably H or a C_1-C_6 alkyl, more preferably H or a C_1-C_3 alkyl and most preferably methyl. R^{14} may be H or an optionally substituted C_1-C_6 alkyl, preferably H or an optionally substituted C_1-C_3 alkyl, more preferably an optionally substituted C_1-C_2 alkyl. The alkyl may be substituted with one or more of halogen, OH, $OP(O)(OH)_2$, C_1-C_6 alkoxy, NR^1R^2, $CONR^1R^2$, CN or COOH, or a hydrogen or R^1 group may be omitted and the linker may be bonded directly to an oxygen or nitrogen. In a preferred embodiment, the alkyl is substituted with NR^1R^2, or the R^1 is omitted and the nitrogen is bonded directly to the linker. R^2, and R^1 in embodiments where it is present, may each independently be selected from the group consisting of H,

halogen and optionally substituted C_1-C_6 alkyl, more H or a C_1-C_6 alkyl, even more preferably H or a C_1-C_3 alkyl, and most preferably H or methyl. In a preferred embodiment, R^1 is H and R^2 is methyl. Accordingly, in a preferred embodiment, an R^{12} group may be  , wherein c is an integer between 1 and 6, preferably between 1 and 3. In a more preferred embodiment, an R^{12} group may be  . Alternatively, the R^{12} group may be bonded to the linker like so  , or more preferably like so  .

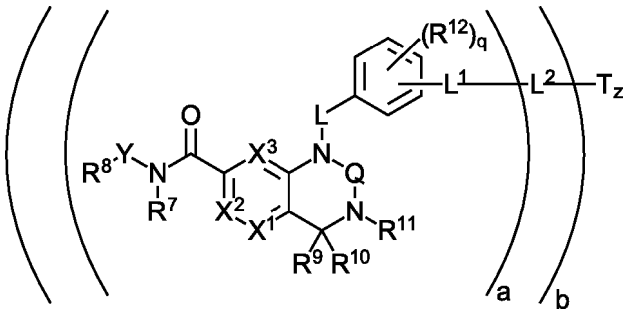
An R^{12} group may be an optionally substituted mono or bicyclic C_5-C_{10} aryl. The optionally substituted mono or bicyclic C_5-C_{10} aryl may be an optionally substituted phenyl. The mono or bicyclic C_5-C_{10} aryl group may be substituted with one or more of an optionally substituted C_1-C_6 alkyl, halogen, OH, optionally substituted C_1-C_6 alkoxy, CN and/or the linker. In one embodiment, the mono or bicyclic C_5-C_{10} aryl is substituted with a C_1-C_6 alkyl, more preferably a C_1-C_3 alkyl and most preferably methyl. In one embodiment, the mono or bicyclic C_5-C_{10} aryl is substituted with a halogen, more preferably a fluorine or chlorine and most preferably a fluorine.

An R^{12} group may be an optionally substituted C_3-C_6 cycloalkyl. The cycloalkyl may be substituted with the linker. In some embodiments, the C_3-C_6 cycloalkyl may be unsubstituted. Accordingly, the C_3-C_6 cycloalkyl may be a cyclopropyl, a cyclobutyl, a cyclopentyl or a cyclohexyl. In a preferred embodiment, an R^{12} group is a cyclopropyl.

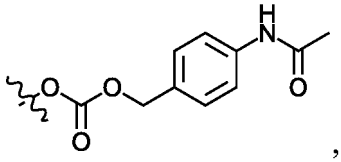
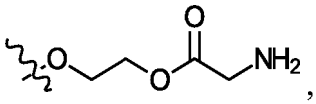
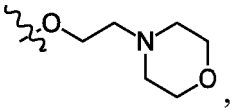
Alternatively, or additionally, an R^{12} group may be CN, OH, $OP(O)(OH)_2$ or azido, or a hydrogen may be omitted and the oxygen may be bonded directly to the linker.

Preferably, R^6 is a mono or bicyclic C_5-C_{10} aryl or a mono or bicyclic 5 to 10 membered heteroaryl, optionally substituted with one or more R^{12} groups, and optionally further substituted with the linker. More preferably, R^6 is a phenyl or a pyridinyl, optionally

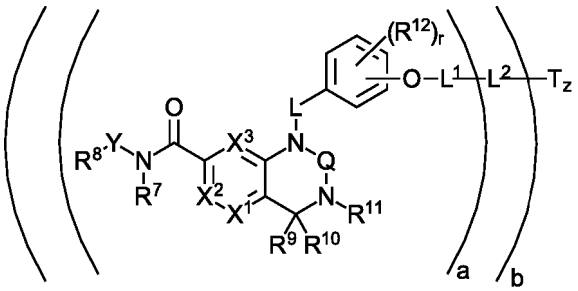
substituted with one or more R^{12} groups, and optionally further substituted with the linker. Preferably, the mono or bicyclic C_5-C_{10} aryl or the mono or bicyclic 5 to 10 membered heteroaryl are substituted with one or more R^{12} groups, and optionally further substituted with the linker. Accordingly, the compound of formula (**I**) may be a compound of formula (**I-C-a**):



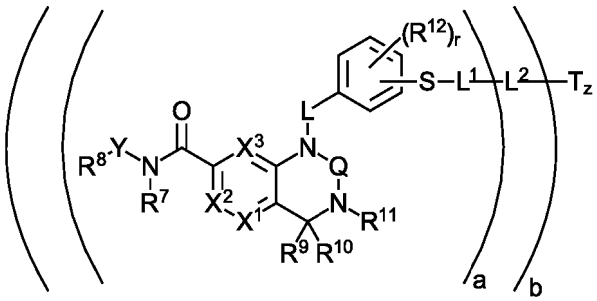
(**I-C-a**)

The one or more R^{12} groups may be as defined above and q may be an integer between 0 and 4. More preferably, the or each R^{12} group is independently selected from halogen, methyl, CF_3, OH, SH, NH_2, CH_2OH, $OPO(OH)_2$, OMe, $OCHF_2$, OCF_3, OCH_2CHCH_2, $O(CH_2)_mOH$, $O(CH_2)_mOPO(OH)_2$,  , $OCH_2C(OH)HCH_2OH$, NH_2, NHMe, $C(O)NH_2$, $CO(CH_2)_mOH$,  , $OCH_2CH_2NS(O)_2Me$ and  , or in groups comprising an OH, SH or NH, the hydrogen may be omitted and the oxygen, sulphur or nitrogen may be bonded directly to the linker, where m is an integer between 1 and 6. More preferably, m is an integer between 1 and 3.

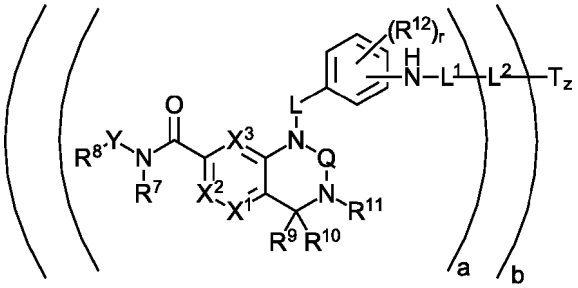
Accordingly, the compound of formula (**I**) may be a compound of formula (**I-C-b**), (**I-C-c**) or (**I-C-d**):



(I-C-b)

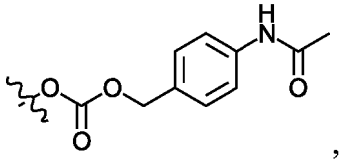


(I-C-c)

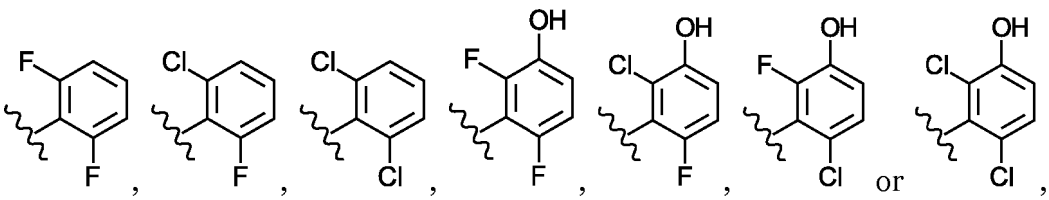


(I-C-d)

, wherein r is an integer between 0 and 4.

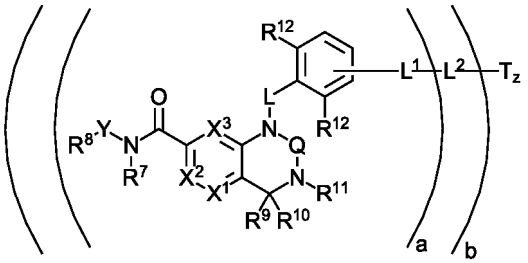
More preferably, the one or more R^{12} groups preferably comprise one or more halogens. The one or more R^{12} groups may comprise one or 2 halogens. Preferably, the one or more halogens comprise one or more chlorines and/or fluorines, most preferably one or more fluorines. The one or more R^{12} groups may further comprise one or more groups selected from methyl, OH, OMe, $C(O)NH_2$, OCH_2CH_2OH, $OCH_2CH_2CH_2OH$, $OCH_2C(OH)HCH_2OH$,  , NH_2 and $OCH_2CH_2NS(O)_2Me$, or in groups comprising an OH or NH, the hydrogen may be omitted and the oxygen or nitrogen may be bonded directly to the linker.

In one embodiment, R^6 may comprise:

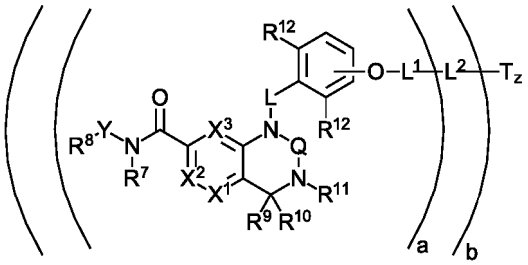


, and may optionally be substituted with the linker. The linker may be directly substituted to the phenyl ring or may replace the H in the OH group.

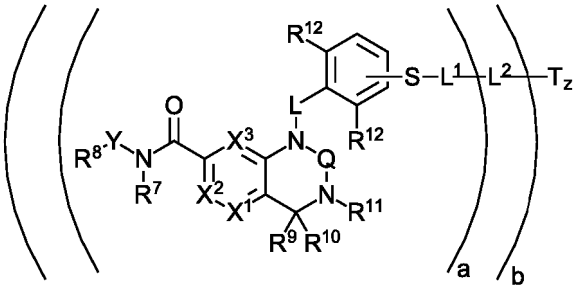
Accordingly, the compound of formula (**I**) may be a compound of one of formula (**I-C-e**) to (**I-C-h**):



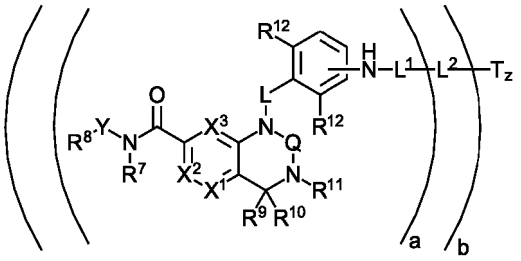
(**I-C-e**)



(**I-C-f**)

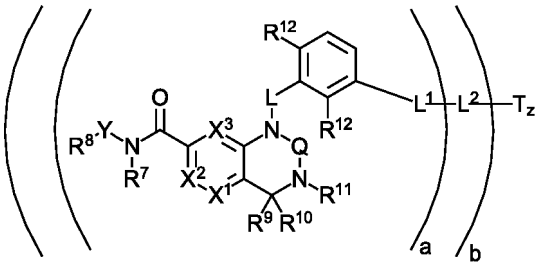


(**I-C-g**)

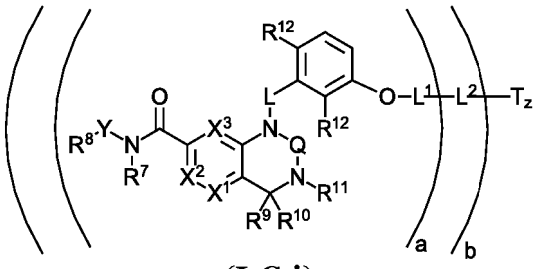


(**I-C-h**)

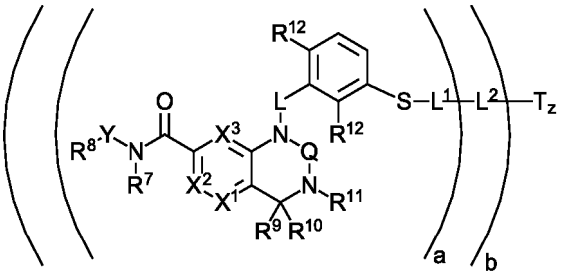
More preferably, the compound of formula (**I**) is a compound of one of formula (**I-C-i**) to (**I-C-l**):



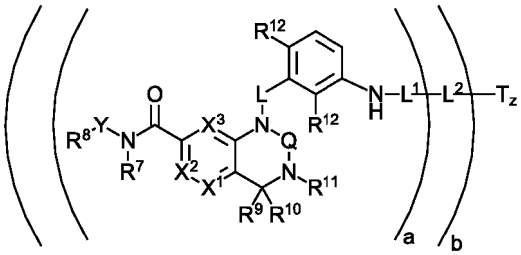
(**I-C-i**)



(**I-C-j**)



(**I-C-k**)



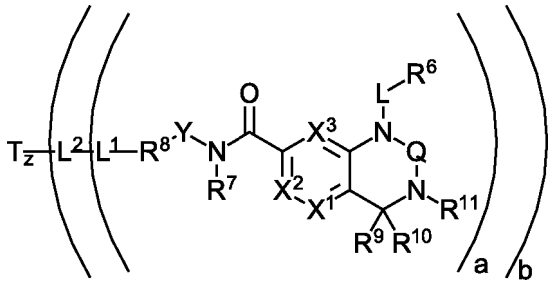
(**I-C-l**)

Preferably, each R^{12} is a halogen, and more preferably is independently Cl or F.

R^7 is preferably H or an optionally substituted C_1-C_6 alkyl, more preferably H or a C_1-C_3 alkyl, and most preferably R^7 is H.

Preferably, Y is an optionally substituted C_1-C_6 alkyl, more preferably a C_1-C_3 alkyl, even more preferably $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH(CH_3)-$, -CH(F)- and $-CF_2-$ and most preferably $-CH_2-$.

C may be attached to the linker through the R^8 group. Accordingly, the R^8 group may be substituted by the linker. The compound of formula (**I**) may be a compound of formula (**I-D**):



(**I-D**)

Preferably, R^8 is a mono or bicyclic optionally substituted C_5-C_{10} aryl, a mono or bicyclic optionally substituted 5 to 10 membered heteroaryl, an optionally substituted C_3-C_6 cycloalkyl or an optionally substituted C_3-C_6 heterocyclyl, wherein the aryl, heteroaryl, cycloalkyl or heterocyclyl may optionally be substituted with the linker.

In some embodiments, R^8 may be an optionally substituted C_3-C_6 cycloalkyl or C_3-C_6 heterocyclyl, which may optionally be substituted with the linker. R^8 may comprise a C_6 cycloalkyl or a 6 membered heterocycle. The C_6 cycloalkyl or 6 membered heterocycle may be substituted with an optionally substituted C_1-C_6 alkyl, a mono or bicyclic optionally substituted C_5-C_{10} aryl and/or the linker. Preferably, the C_6 cycloalkyl or 6 membered heterocycle is substituted with a phenyl or a C_1-C_3 alkyl substituted with a phenyl, more preferably the C_6 cycloalkyl or 6 membered heterocycle is substituted with a phenyl or $-CH_2$-phenyl.

However, in a preferred embodiment, R^8 is a mono or bicyclic optionally substituted C_5-C_{10} aryl or a mono or bicyclic optionally substituted 5 to 10 membered heteroaryl, which may optionally be substituted with the linker. R^8 may be an optionally substituted phenyl, an optionally substituted pyridine, an optionally substituted

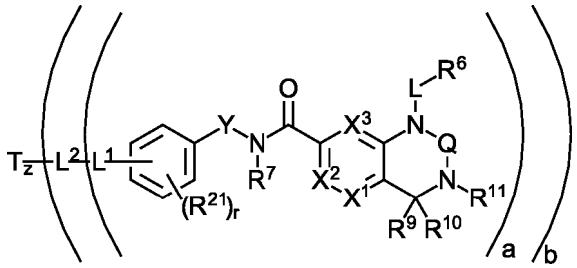
naphthyl, an optionally substituted furanyl, an optionally substituted benzofuranyl, an optionally substituted thiophene, an optionally substituted pyridofuran, an optionally substituted benzoxazole or an optionally substituted benzothiazole. The mono or bicyclic C_5-C_{10} aryl or the mono or bicyclic 5 to 10 membered heteroaryl may be substituted with between 1 and 5 substituents. Accordingly, the mono or bicyclic C_5-C_{10} aryl or the mono or bicyclic 5 to 10 membered heteroaryl may be substituted with 1, 2, 3, 4 or 5 substituents. In one embodiment, the mono or bicyclic C_5-C_{10} aryl or the mono or bicyclic 5 to 10 membered heteroaryl is substituted with 3 substituents. The aryl or heteroaryl may be substituted directly with the linker. Alternatively or additionally, the or each substituent may independently be selected from the list consisting of C_1-C_6 alkyl, halogen, OH, C_1-C_6 alkoxy, $CONR^1R^2$, CN, azido, NO_2, NH_2, OCH_2CH_2OH, $OCH_2C(O)OH$, $OP(O)(OH)_2$ and an optionally substituted mono or bicyclic 3 to 8 membered heterocycle, or in a group comprising an OH or NH or R^1, the H or R^1 may be omitted and the oxygen or nitrogen may be bonded directly to the linker. The optionally substituted mono or bicyclic 3 to 8 membered heterocycle preferably is a 6 membered heterocycle, more preferably is an optionally substituted piperazinyl, and most preferably is N-methylpiperazinyl. Preferably, the mono or bicyclic C_5-C_{10} aryl or the mono or bicyclic 5 to 10 membered heteroaryl may be substituted with at least one C_1-C_6 alkyl, C_1-C_6 alkoxy or halogen, even more preferably at least one C_1-C_3 alkyl, C_1-C_3 alkoxy or halogen, and most preferably at least one methyl, OMe and/or fluorine.

In a preferred embodiment, R^8 is an optionally substituted benzofuranyl. Preferably, R^8 is an unsubstituted benzofuranyl or is only substituted with the linker.

In an alternative preferred embodiment, R^8 is an optionally substituted furanyl. The furanyl may be an unsubstituted furanyl or may only be substituted with the linker. Alternatively, the furanyl may be substituted. Preferably, the furanyl is substituted with at least one of C_1-C_3 alkyl or halogen, and optionally also the linker, more preferably at least one of methyl or fluorine and most preferably with one methyl group.

In an alternative preferred embodiment, R^8 is an optionally substituted phenyl. The phenyl may be unsubstituted or may only be substituted with the linker. Alternatively, the phenyl may be substituted. Preferably, the phenyl is substituted with at least one of C_1-C_3 alkyl, C_1-C_3 alkoxy or halogen, and may optionally be further substituted with the linker, more preferably at least one of methyl, methoxy or fluorine and most preferably with 1, 2 or 3 fluorines.

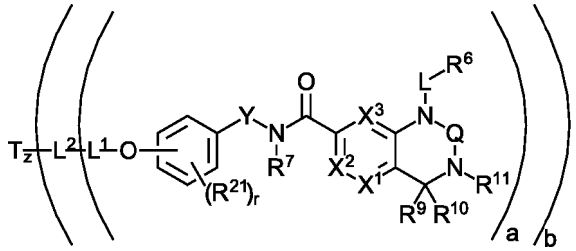
Accordingly, the compound of formula (**I**) may be a compound of formula (**I-D-a**):



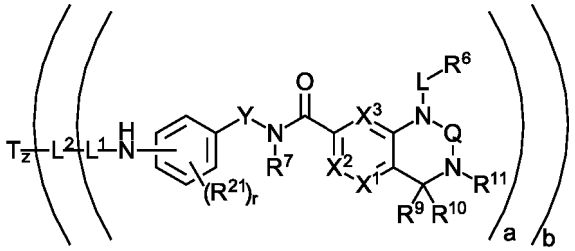
(**I-D-a**)

, wherein R^{21} is a substituent on the R^8 phenyl ring, and may be as defined above, and r is an integer between 0 and 4. In some embodiments, r is an integer between 1 and 3. Preferably, each R^{21} is independently a C_1-C_3 alkyl, a C_1-C_3 alkoxy or a halogen. More preferably, each R^{21} is independently a methyl, methoxy or fluorine and most preferably, each R^{21} is a fluorine.

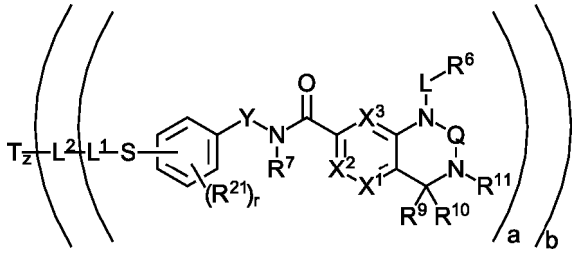
Alternatively, the linker may be bonded to a substituent on the phenyl ring. Accordingly, the compound of formula (**I**) may be a compound of formula (**I-D-b**), (**I-D-c**) or (**I-D-d**):



(**I-D-b**)



(**I-D-c**)



(**I-D-d**)

In a preferred embodiment, X^1 is CR^1; X^2 is CR^2; X^3 is CR^3; Q is CO; L is -CH_2-; Y is -CH_2-; and R^7 is H.

In a further preferred embodiment X^1 is N; X^2 is CR^2; X^3 is CR^3; Q is CO; L is $-CH_2-$; Y is $-CH_2-$; and R^7 is H.

In a further preferred embodiment, X^1 is CR^1; X^2 is CR^2; X^3 is CR^3; Q is CR^4R^5; L is C=O; Y is $-CH_2-$; and R^7 is H.

In a further preferred embodiment, X^1 is CR^1; X^2 is CR^2; X^3 is CR^3; Q is CR^4R^5; L is SO_2; Y is $-CH_2-$; and R^7 is H.

In a further preferred embodiment, X^1 is CR^1. Preferably, X^2 is CR^2. Preferably, X^3 is CR^3. Preferably, Q is C=O or CR^4R^5. Preferably, L is optionally substituted C_1-C_3 alkyl. L is most preferably C_1-C_2 alkyl. Preferably, Y is an optionally substituted C_1-C_6 alkyl, more preferably a C_1-C_3 alkyl, and most preferably a C_1-C_2 alkyl. Preferably, R^1, R^2 and R^3 are each independently selected from the group consisting of H, halogen, CN, optionally substituted C_1-C_6 alkyl, C_1-C_3 polyfluoroalkyl, and optionally substituted mono or bicyclic C_3-C_6 cycloalkyl. Preferably, R^4 and R^5 are each independently selected from the group consisting of H and C_1-C_6 alkyl. Preferably, R^6 is a ring optionally substituted with one or more R^{12} groups, wherein the ring is selected from the group consisting of a mono or bicyclic C_5-C_{10} aryl; a mono or bicyclic 5 to 10 membered heteroaryl; and a C_3-C_6 cycloalkyl. Preferably, R^6 is substituted, either directly or indirectly, with the linker. Preferably, R^7 is H. Preferably, R^8 is a mono or bicyclic optionally substituted C_5-C_{10} aryl, a mono or bicyclic optionally substituted 5 to 10 membered heteroaryl. Preferably, R^9 and R^{10} are each independently selected from the group consisting of optionally substituted C_1-C_6 alkyl, H, halogen, CN, hydroxyl, azido, NR^1R^2, C_1-C_3 polyfluoroalkyl, optionally substituted C_3-C_6 cycloalkyl, optionally substituted C_1-C_6 alkoxy or optionally substituted C_2-C_6 alkenyl. Preferably, R^{11} is selected from the group consisting of optionally substituted C_1-C_6 alkyl, H, hydroxyl, NR^1R^2, C_1-C_3 polyfluoroalkyl, optionally substituted C_3-C_6 cycloalkyl, optionally substituted C_1-C_6 alkoxy or optionally substituted C_2-C_6 alkenyl. Preferably, the first stereogenic centre defines an S enantiomer.

In a more preferred embodiment X^1 is CH. Preferably, X^2 is CH. Preferably, X^3 is CH. Preferably, Q is C=O. Preferably, L is a C_1-C_2 alkyl. More preferably, L is $-CH_2-$. Preferably, Y is a C_1-C_2 alkyl. More preferably, Y is $-CH_2-$. Preferably, R^6 is a ring optionally substituted with one or more R^{12} groups, wherein the ring is selected from the group consisting of a mono or bicyclic C_5-C_{10} aryl; and a mono or bicyclic 5 to 10

membered heteroaryl. Preferably, R^6 is substituted, either directly or indirectly, with the linker. Preferably, R^6 is a phenyl or a pyridinyl optionally substituted with one or more R^{12} groups. Preferably, R^6 is substituted with at least one R^{12} group selected from the group consisting of a halogen, -OH, optionally substituted C_1-C_4 alkoxy, amino, optionally substituted C_1-C_3 alkyl or $C(O)NH_2$, or a hydrogen is omitted and an oxygen or nitrogen in a substituent of the R^6 ring which is bonded directly to the linker. Most preferably, R^6 is substituted with one or two halogens. The or each halogen is preferably independently chlorine or fluorine. Preferably, R^6 is further substituted, either directly or indirectly with the linker. Optionally, the C_5-C_{10} aryl may also be substituted with a hydroxyl or an oxygen bonded directly to the linker. Preferably, R^7 is H. Preferably, R^8 is a mono or bicyclic optionally substituted C_5-C_{10} aryl or a mono or bicyclic optionally substituted 5 to 10 membered heteroaryl. Most preferably, R^8 is an optionally substituted phenyl ring. Preferably, R^8 is substituted with at least one halogen. Preferably, R^8 is substituted with 1, 2 or 3 halogens, more preferably 2 or 3 halogens. Preferably, the or each halogen is fluorine. Preferably, R^9 and R^{10} are each independently selected from the group consisting of optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_4 alkenyl, H, halogen, CN and azido. More preferably, R^9 and R^{10} are each independently selected from the group consisting of C_1-C_3 alkyl and H. More preferably, R^9 and R^{10} are each independently selected from the group consisting of CH_3 and H. Preferably, R^{11} is selected from the group consisting of optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_4 alkenyl and H. More preferably, R^{11} is selected from the group consisting of C_1-C_3 alkyl and H. More preferably, R^{11} is selected from the group consisting of CH_3 and H. Preferably, the first stereogenic centre defines an S enantiomer.

It will be appreciated that the compounds described herein or a pharmaceutically acceptable salt, solvate, tautomeric form or polymorphic form thereof may be used in a medicament which may be used in a monotherapy (i.e. use of the compound alone), for modulating the STING protein and/or treating, ameliorating or preventing a disease.

Alternatively, the compounds or a pharmaceutically acceptable salt, solvate, tautomeric form or polymorphic form thereof may be used as an adjunct to, or in combination with, known therapies for modulating the STING protein and/or treating, ameliorating or preventing a disease.

Accordingly, in one aspect, a second therapeutic agent may be administered with a compound of formula (**I**). The compound of formula (**I**) may be administered before, after, and/or together with the second therapeutic agent. The second therapeutic agent may comprise an antiviral agent, an anti-inflammation agent, conventional chemotherapy, an anti-cancer vaccine and/or hormonal therapy. Alternatively, or additionally, the second therapeutic agent may comprise a B7 costimulatory molecule, interleukins (IL-2, IL-15, IL-7, IL-21), interferons, GM-CSF, a CTLA-4 antagonist (such as Ipilimumab and tremilimumab), an IDO inhibitor or IDO/TDO inhibitor (such as Epacadostat and GDC-0919), a PD-1 inhibitor (such as Nivolumab, Pembrolizumab, Pidilizumab, AMP-514, MDX-1106, REGN2810, PF-6801591, INCSHR1210), a PD-L1 inhibitor (such as Durvalumab/MEDI-4736, MDX-1105, Avelumab and Atezolizumab), an OX-40 ligand, a LAG3 inhibitor (LAG525, BMS-986016, TSR-033), a T-cell immunoglobulin domain (TIM-3) inhibitor, a CD40 ligand, a 4-1BB/CD137 ligand, a CD27 ligand, Bacille Calmette-Guerin (BCG), a TIM-3 inhibitor (MGB453, TSR-022,) ICAM-1, LFA-1, ICOS, GITR, CD7, LIGHT, CD160, CD83, liposomes, alum, Freund's complete or incomplete adjuvant, a TLR agonist (such as Poly I:C, MPL, LPS, bacterial flagellin, imiquimod, resiquimod, loxoribine and a CpG dinucleotide) and/or detoxified endotoxins.

Methods for co-administration with an additional therapeutic agent are well known in the art (Hardman et. al. (eds.), Goodman and Gilman's The Pharmacological Basis of Therapeutics, 10th ed., **2001**, McGraw-Hill New York, NY; Poole and Peterson (eds.), Pharmacotherapeutics for Advanced Practice: A Practical Approach, **2001**, Lippincott, Williams and Wilkins, Philadelphia, PA; Chabner and Longo (eds.), Cancer Chemotherapy and Biotherapy, **2001**, Lippincott, Williams and Wilkins, Philadelphia, PA).

In one aspect, the disease is cancer and a chemotherapeutic agent may be administered with a compound of Formula (**I**). The chemotherapeutic agent may be selected from a group further consisting of a cancer vaccine, a targeted drug, a targeted antibody, an antibody fragment, an antimetabolite, an angiogenesis inhibitor, an antineoplastic, an antifolate, a toxin, an alkylating agent, a DNA strand breaking agent, a DNA minor groove binding agent, a pyrimidine analogue, a ribonucleotide reductase inhibitor, a tubulin interactive agent, an anti-hormonal agent, an immunomodulator, an anti-adrenal agent, a cytokine, radiation therapy, a cell therapy, cell depletion therapy such as B-cell depletion therapy and a hormone therapy. For example, the combination

agent may target MEK, EGFR, BRAF, PI3K, HER2/HER3, IGFR, SHP2, mTOR, CDK, IAP, Bcl-2, Mcl-1, CHK, heat shock protein, HDAC, EZH2, LSD1, EED. Alternatively or additionally, the chemotherapeutic agent may comprise abiraterone, Erlotinib, Linifanib, Sunitinib, Bosutinib, Dasatinib, Pazopanib, Sorafenib, Zactima, Imatinib, Gefitinib, Vandetanib, Lapatinib, Canertinib, Mubritinib, Pelitinib, Afatnib, Neratinib, Cetuximab, Panitumumab, Matuzumab, Nimotuzumab, Zalatumumab, Cabozantinib, Foretinib, Tivantinib, Crizotinib, altretamine, anhydrovinblastine, auristatin, bexarotene, bicalutamide, bleomycin, cachectin, cemadotin, chlorambucil, cyclophosphamide, docetaxol, doxetaxel, carboplatin, cysplatin, cytarabine, dactinomycin, daunorubicin, decitabine, doxorubicin, etoposide, 5-fluorouracil, finasteride, flutamide, hydroxyurea, streptozocin, mitomycin, methotrexate, taxanes, tamoxifen, vinblastine, vincristine and/or vindesine.

The compound of Formula (**I**) may be combined in compositions having a number of different forms depending, in particular, on the manner in which the composition is to be used. Thus, for example, the composition may be in the form of a liquid, aerosol, spray, micellar solution or any other suitable form that may be administered to a person or animal in need of treatment. It will be appreciated that the vehicle of medicaments according to the invention should be one which is well-tolerated by the subject to whom it is given.

Medicaments comprising the compounds described herein may be administered parenterally, or intra-tumorally. Preferably, medicaments comprising the compounds of the invention may be delivered intravenously, subcutaneously, nasally, topically, rectally, intramuscularly, intracerebrally or by inhalation. Most preferably, the compounds of the invention are delivered intravenously, subcutaneously, intramuscularly or intracerebrally.

The compounds of the invention may be administered directly into the blood stream, into muscle, or into an internal organ. Suitable means for parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

Parenteral formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (preferably to a pH of from 3 to 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water (see e.g. Hardman et. al., Goodman and Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, NY, 2011; Avis et. al. (eds.), Pharmaceutical Dosage Forms: Parenteral Medications, Marcel Dekker, NY, 1993).

The preparation of parenteral formulations under sterile conditions, for example, by lyophilisation, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art. In certain embodiments, the pharmaceutical composition comprising the conjugate is a lyophilisate which contains the conjugate, sucrose, histidine, polysorbate, sodium succinate, citrate, water and saline.

The compounds of the invention may also be administered directly to a site of interest by injection of a solution or suspension containing the active drug substance. The site of interest may be a tumour and the compound may be administered via intratumoral injection. Typical injection solutions are comprised of propylene glycol, sterile water, ethanol and sodium chloride. Alternative solvents which may be used instead of propylene glycol include glycerol and polyethylene glycol.

It will be appreciated that the amount of the compound that is required is determined by its biological activity and bioavailability, which in turn depends on the mode of administration, the physiochemical properties of the compound, and whether it is being used as a monotherapy, or in a combined therapy. The frequency of administration will also be influenced by the half-life of the compound within the subject being treated. Optimal dosages to be administered may be determined by those skilled in the art, and will vary with the particular compound in use, the strength of the pharmaceutical composition, the mode of administration, and the advancement of the disease. Additional factors depending on the particular subject being treated will result in a need to adjust dosages, including subject age, weight, gender, diet, and time of administration.

Generally, for administration to a human, compositions comprising the conjugate may be provided by continuous infusion or by doses at intervals of e.g. one day, one week, several times a week, once every other week, once every three weeks, once every four weeks, once every five weeks, once every six weeks, once every seven weeks or once every eight weeks. The total daily dose of the compounds of the invention is typically in the range 0.0001 mg/kg to 10 mg/kg of the patient's body weight. The total daily dose may be administered in single or divided doses and may, at the physician's discretion, fall outside of the typical range given herein. These dosages are based on an average human subject having a weight of about 60kg to 70kg. The physician will readily be able to determine doses for subjects whose weight falls outside this range, such as infants and the elderly.

It will be appreciated by those skilled in the art that for agents that modulate the immune system, both the dose and the frequency of administration may be different to those of more traditional therapies. In particular, for agents that stimulate the immune system, for example through modulation of STING, they may be administered in small doses, and quite infrequently, for example twice weekly, weekly or monthly. Administration may then be repeated.

The compound may be administered before, during or after onset of the disease to be treated.

Known procedures, such as those conventionally employed by the pharmaceutical industry (e.g. *in vivo* experimentation, clinical trials, etc.), may be used to form specific formulations comprising the compounds according to the invention and precise therapeutic regimes (such as daily doses of the compounds and the frequency of administration). The inventors believe that they are the first to describe a pharmaceutical composition for treating a disease, based on the use of the compounds of the invention.

Hence, in a seventh aspect of the invention, there is provided a pharmaceutical composition comprising a compound according to the first aspect, or a pharmaceutically acceptable salt, solvate, tautomeric form or polymorphic form thereof, and a pharmaceutically acceptable vehicle.

The invention also provides, in an eighth aspect, a process for making the composition according to the seventh aspect, the process comprising contacting a therapeutically effective amount of a compound of the first aspect, or a pharmaceutically acceptable salt, solvate, tautomeric form or polymorphic form thereof, and a pharmaceutically acceptable vehicle.

A "subject" may be a vertebrate, mammal, or domestic animal. Hence, compounds, compositions and medicaments according to the invention may be used to treat any mammal, for example livestock (e.g. a horse), pets, or may be used in other veterinary applications. Most preferably, however, the subject is a human being.

A "therapeutically effective amount" of compound is any amount which, when administered to a subject, is the amount of drug that is needed to treat the target disease, or produce the desired effect, i.e. modulate the STING protein.

For example, the therapeutically effective amount of compound used may be from about 0.001 mg to about 1000 mg, and preferably from about 0.01 mg to about 100 mg. It is preferred that the amount of compound is an amount from about 0.05 mg to about 50 mg, and most preferably from about 0.1 mg to about 20 mg.

A "pharmaceutically acceptable vehicle" as referred to herein, is any known compound or combination of known compounds that are known to those skilled in the art to be useful in formulating pharmaceutical compositions.

The pharmaceutical vehicle may be a liquid, and the pharmaceutical composition is in the form of a solution. Liquid vehicles are used in preparing solutions, suspensions, emulsions, syrups, elixirs and pressurized compositions. The compound according to the invention may be dissolved or suspended in a pharmaceutically acceptable liquid vehicle such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fats. The liquid vehicle can contain other suitable pharmaceutical additives such as solubilisers, emulsifiers, buffers, preservatives, sweeteners, flavouring agents, suspending agents, thickening agents, colours, viscosity regulators, stabilizers or osmo-regulators. Suitable examples of liquid vehicles for oral and parenteral administration include water (partially containing additives as above, e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols

and polyhydric alcohols, e.g. glycols) and their derivatives, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration, the vehicle can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid vehicles are useful in sterile liquid form compositions for parenteral administration. The liquid vehicle for pressurized compositions can be a halogenated hydrocarbon or other pharmaceutically acceptable propellant.

Liquid pharmaceutical compositions, which are sterile solutions or suspensions, can be utilized by, for example, intramuscular, intrathecal, epidural, intraperitoneal, intravenous and particularly subcutaneous injection. The compound may be prepared as a sterile solid composition that may be dissolved or suspended at the time of administration using sterile water, saline, or other appropriate sterile injectable medium.

The scope of the invention includes all pharmaceutically acceptable isotopically-labelled compounds of the invention wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number which predominates in nature.

Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen, such as ^{2}H and ^{3}H, carbon, such as ^{11}C, ^{13}C and ^{14}C, chlorine, such as ^{36}Cl, fluorine, such as ^{18}F, iodine, such as ^{123}I and ^{125}I, nitrogen, such as ^{13}N and ^{15}N, oxygen, such as ^{15}O, ^{17}O and ^{18}O, phosphorus, such as ^{32}P, and sulphur, such as ^{35}S.

Certain isotopically-labelled compounds of the invention, for example those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, i.e. ^{3}H, and carbon-14, i.e. ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection. Substitution with isotopes such as deuterium, i.e. ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life or reduced dosage requirements, and hence may be preferred in some circumstances. Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

Isotopically-labelled compounds of formula **I** can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labelled reagent in place of the non-labelled reagent previously employed.

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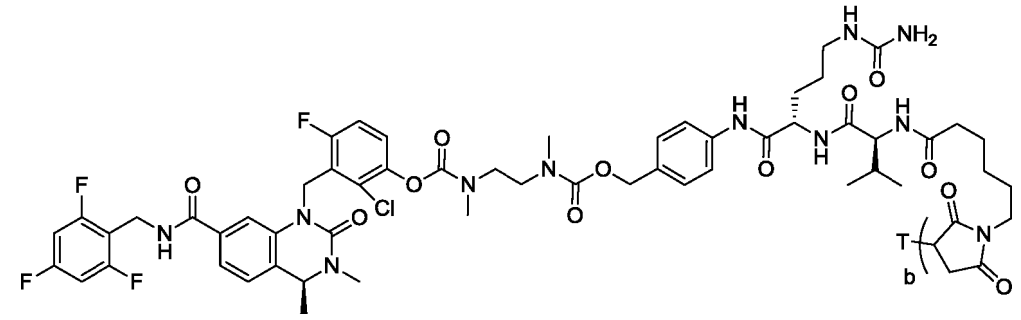
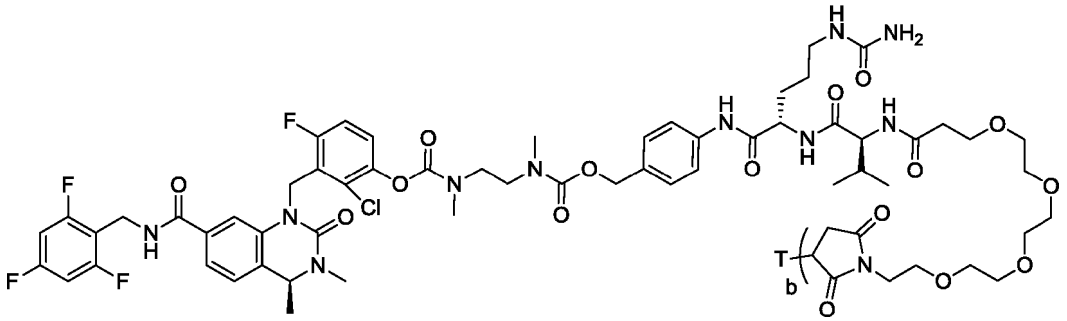
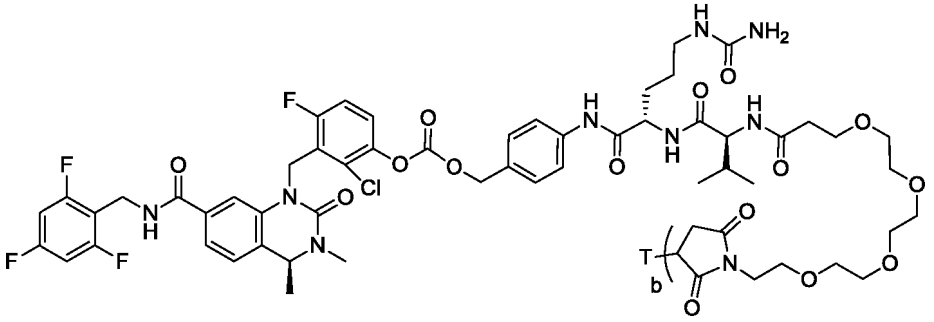
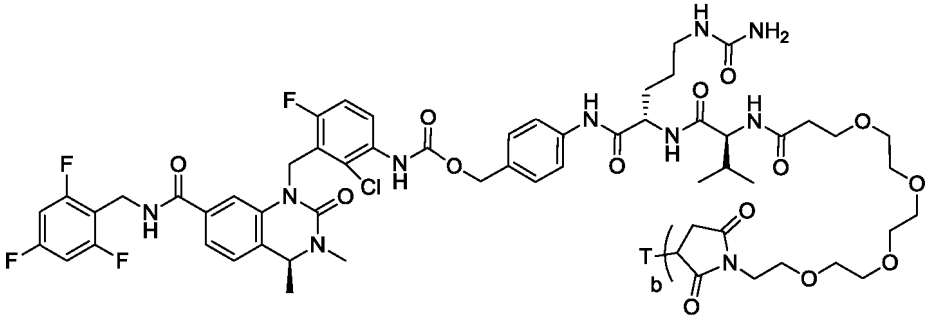
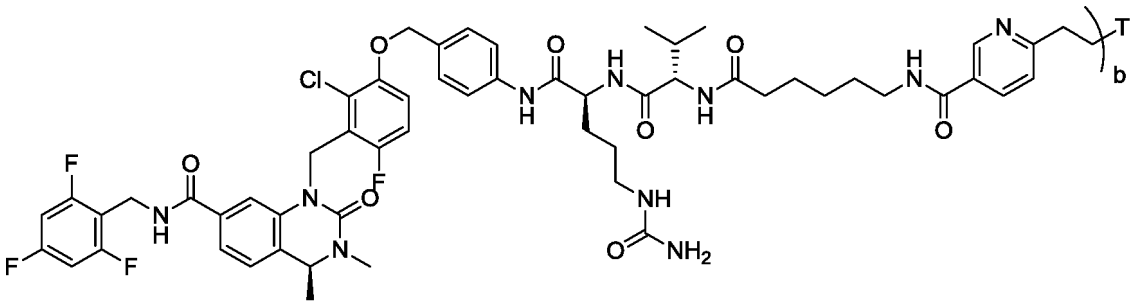
For illustrative purposes, compounds of formula **I** may include but are not limited to:

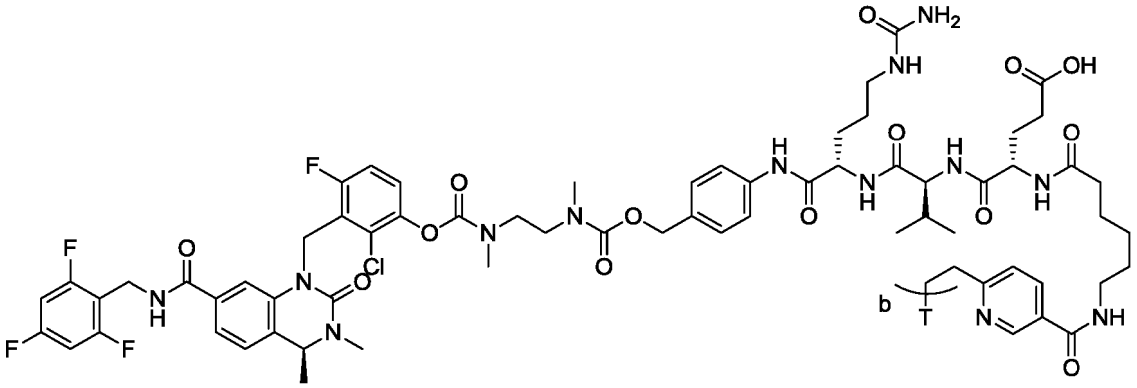


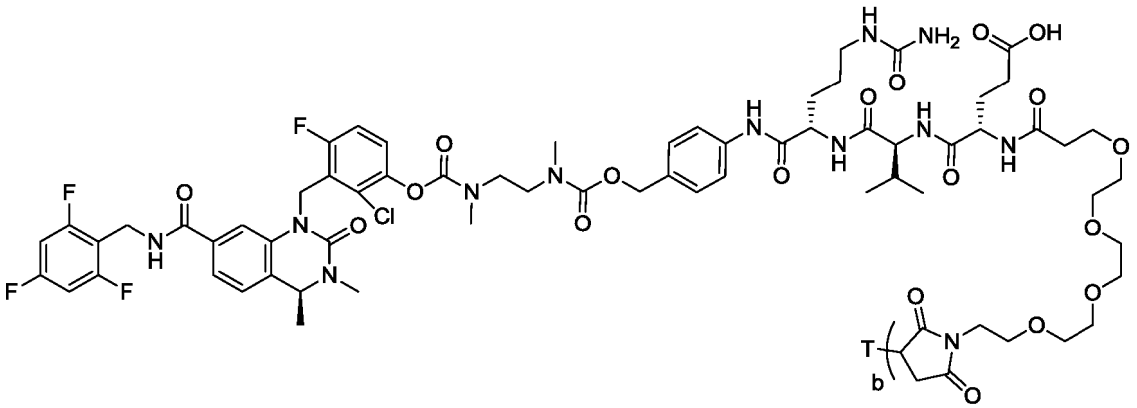


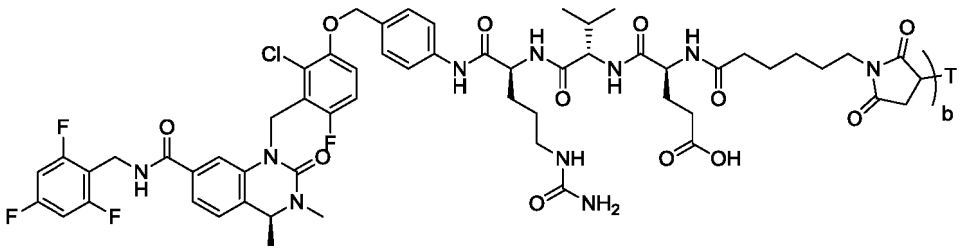


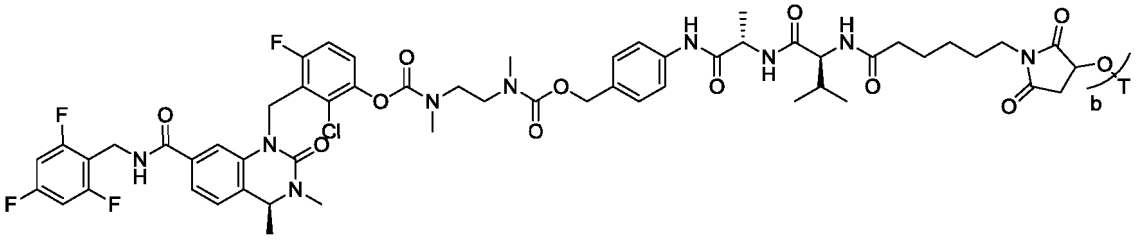












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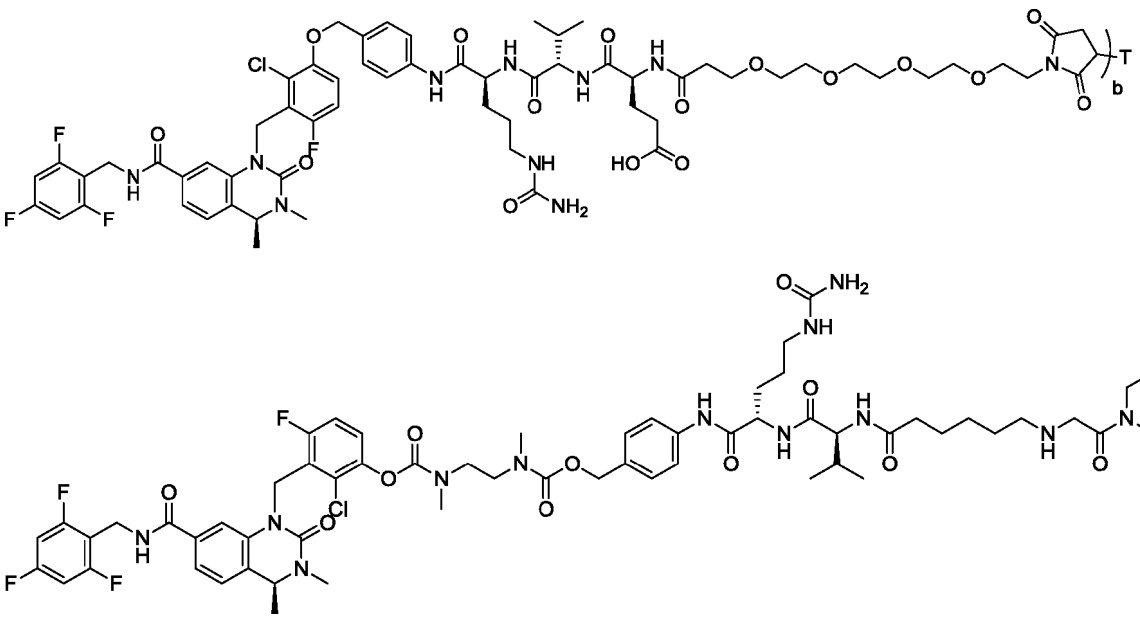

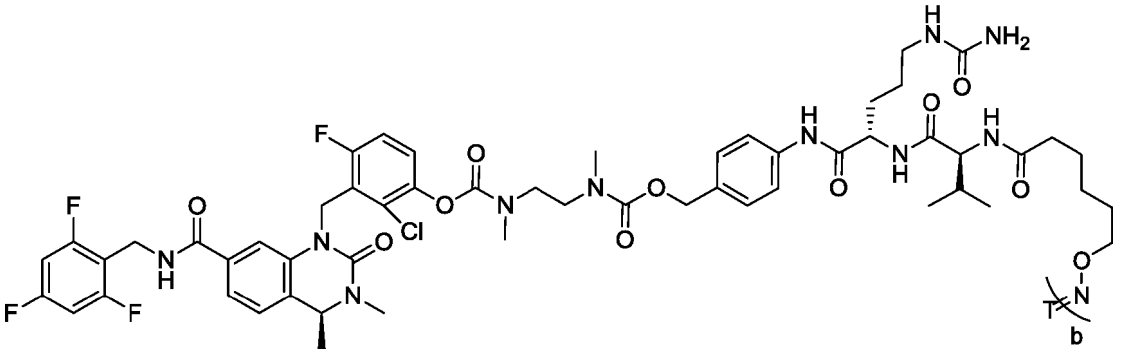

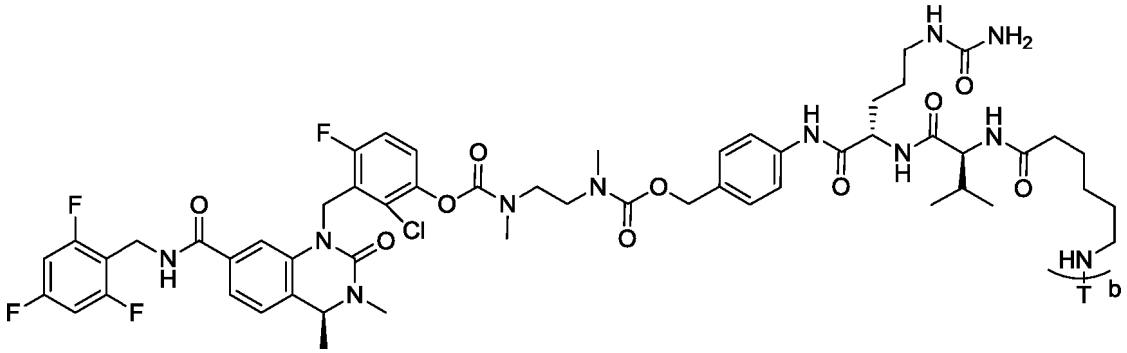

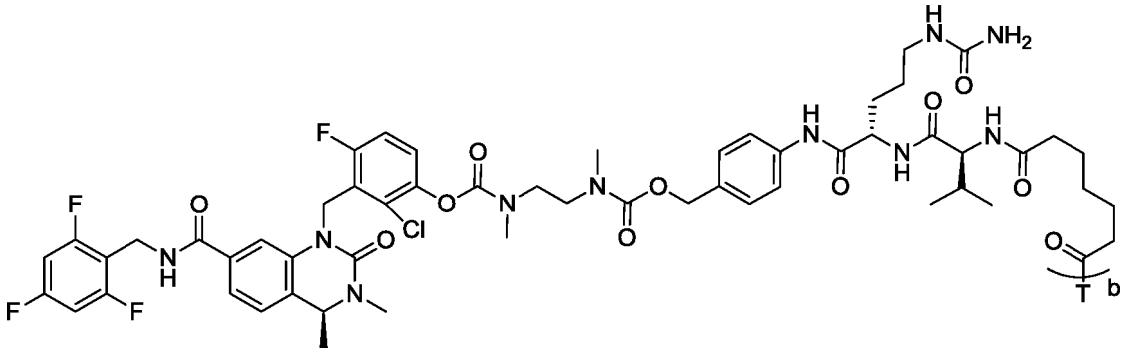

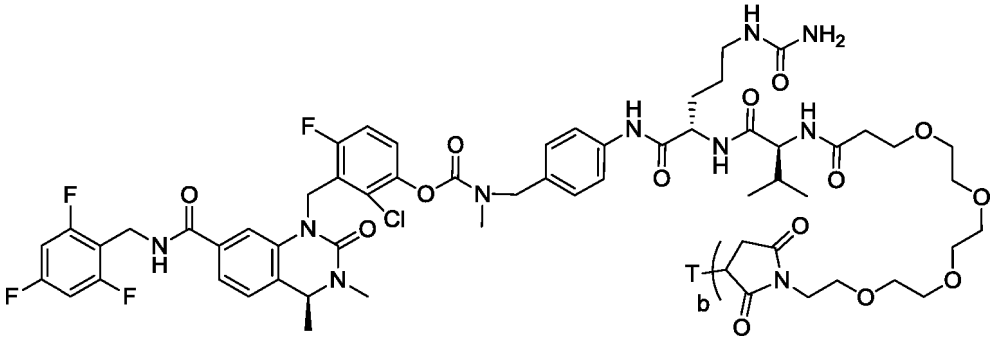

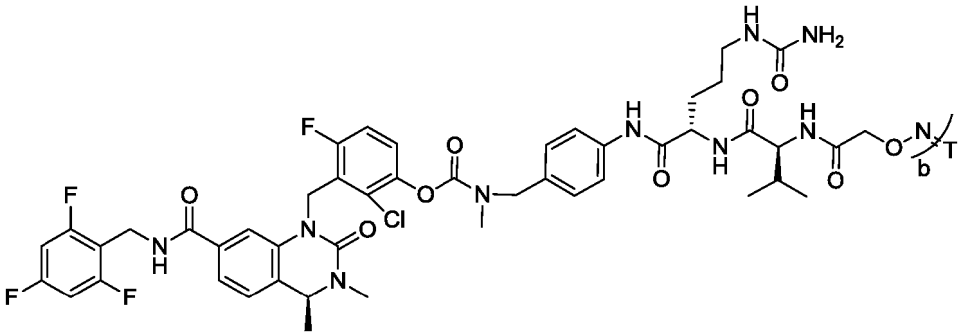

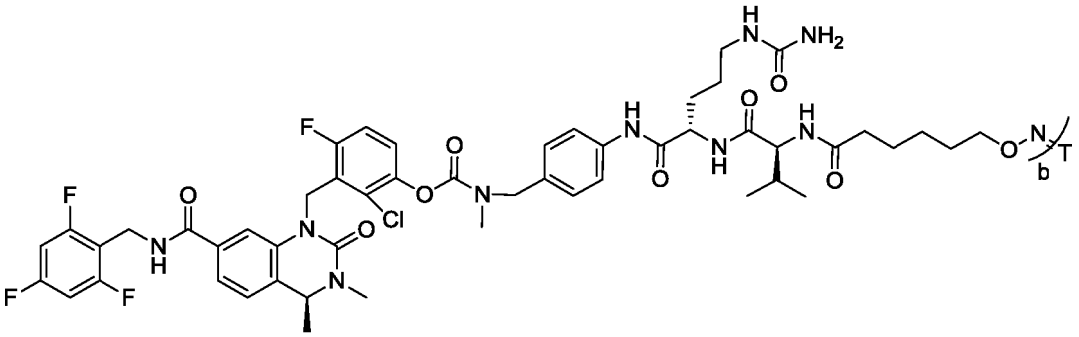

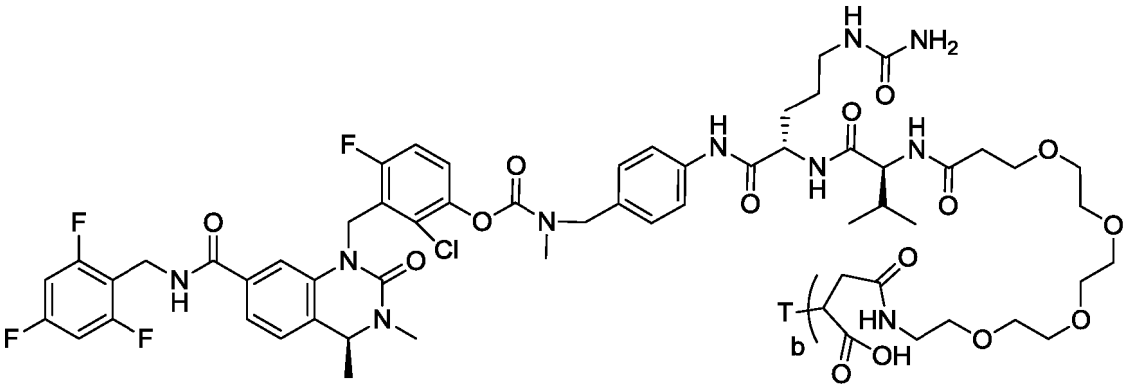

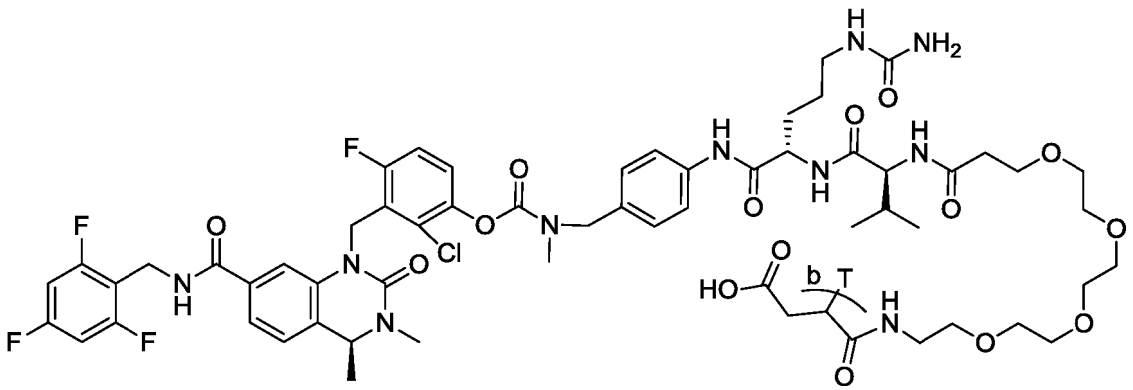

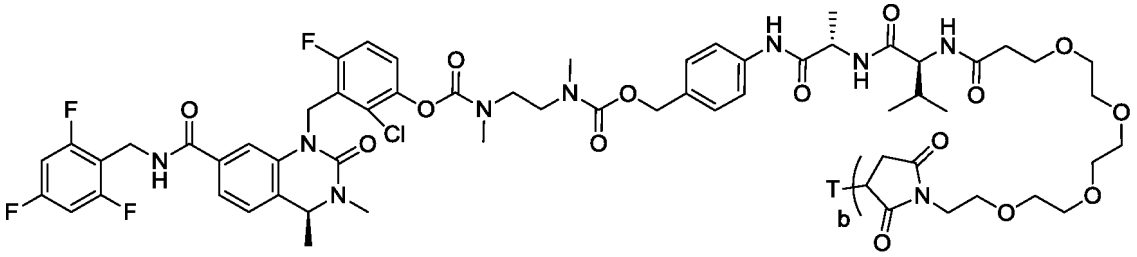

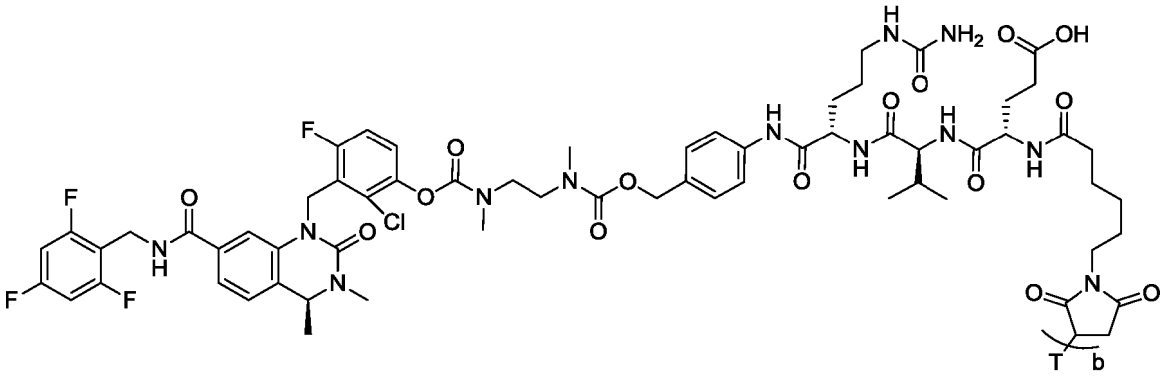

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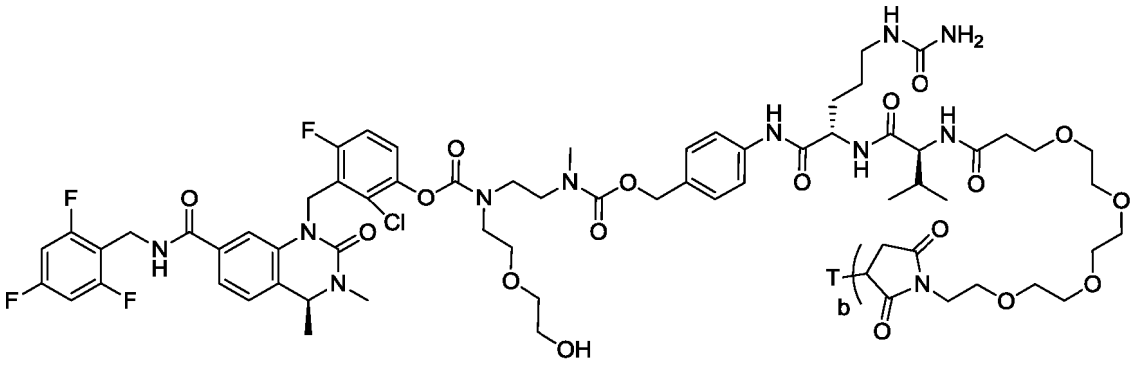

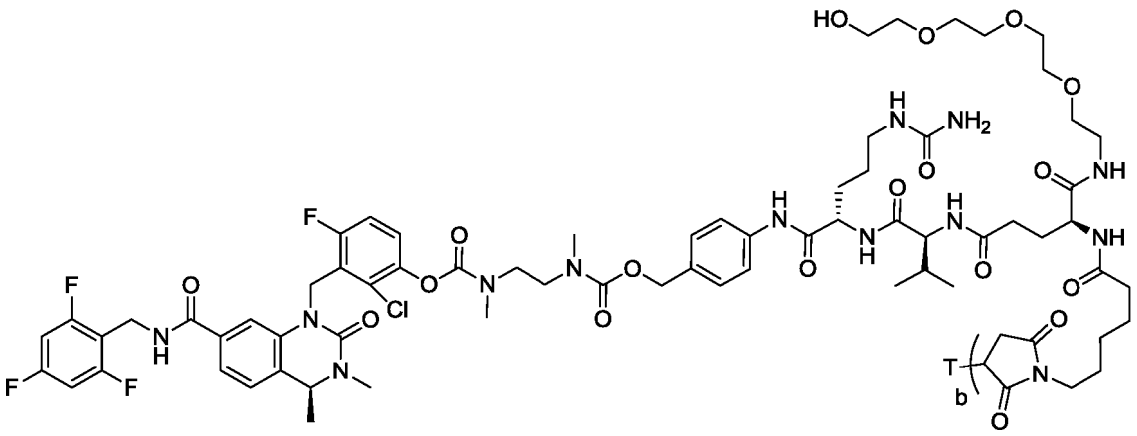

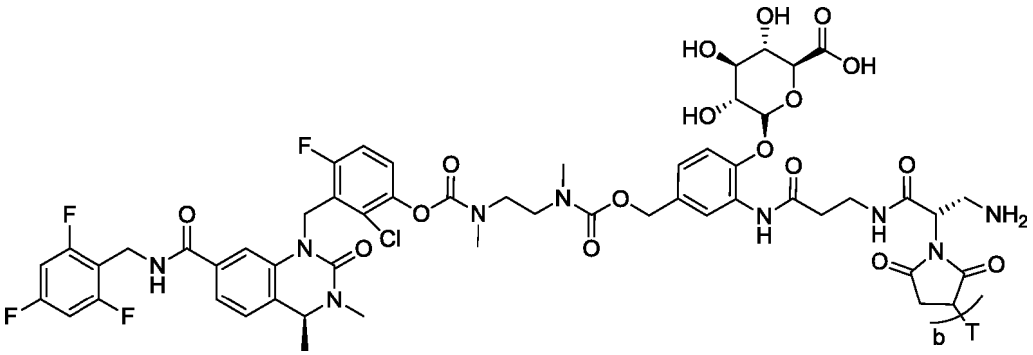

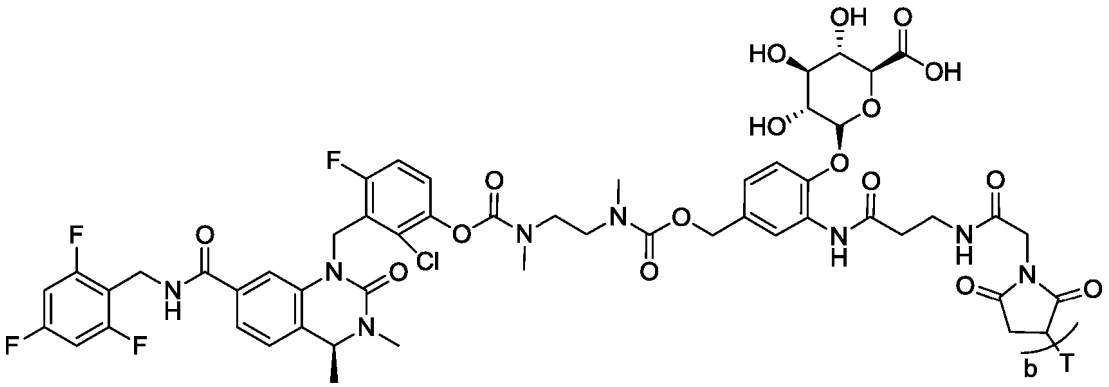

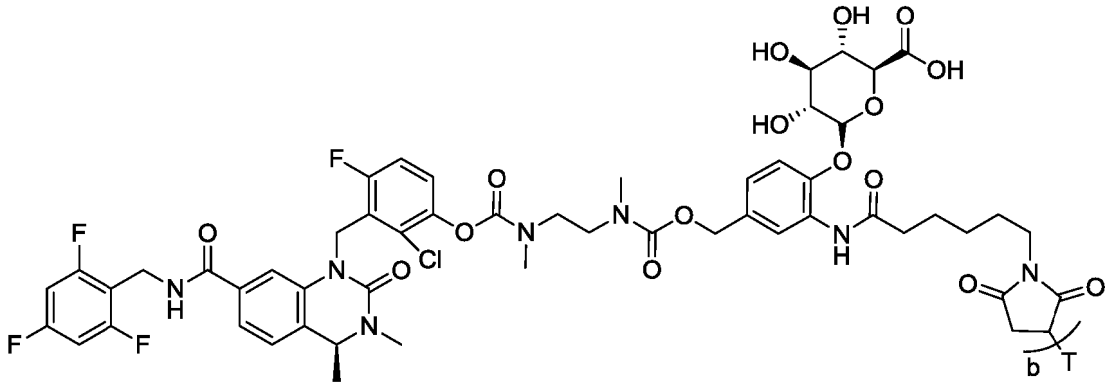

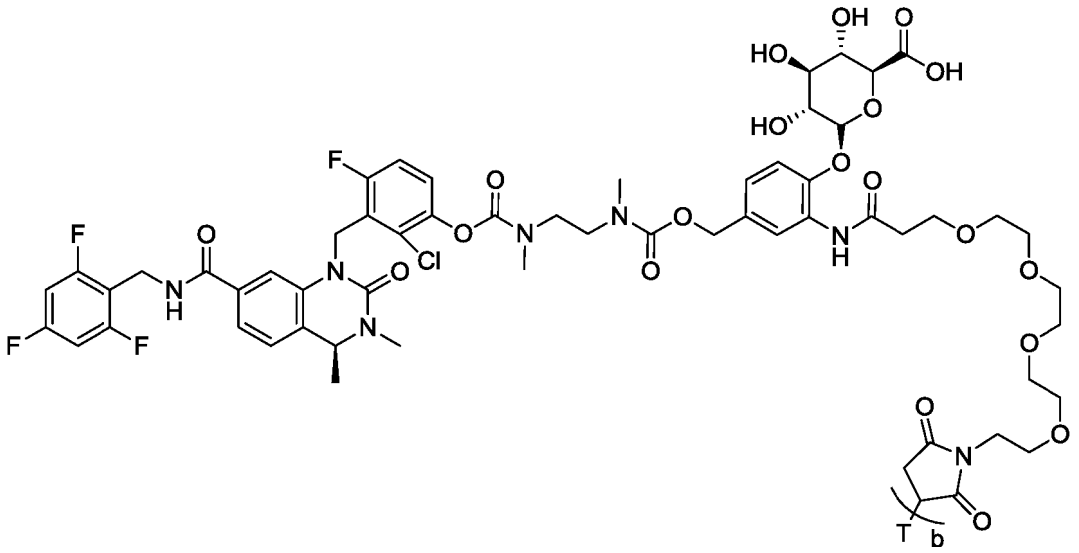

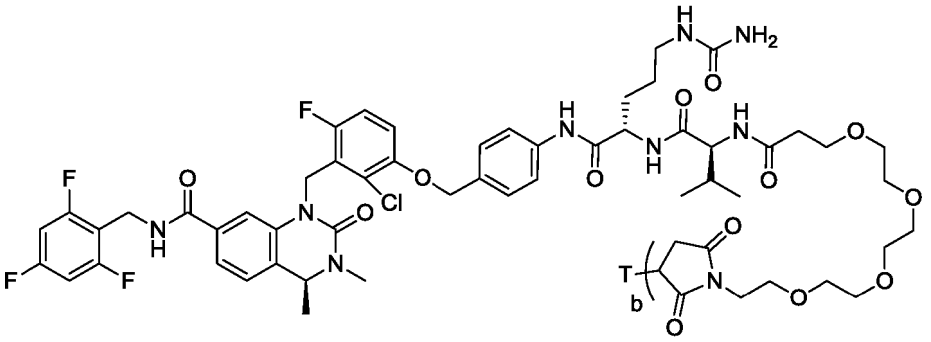

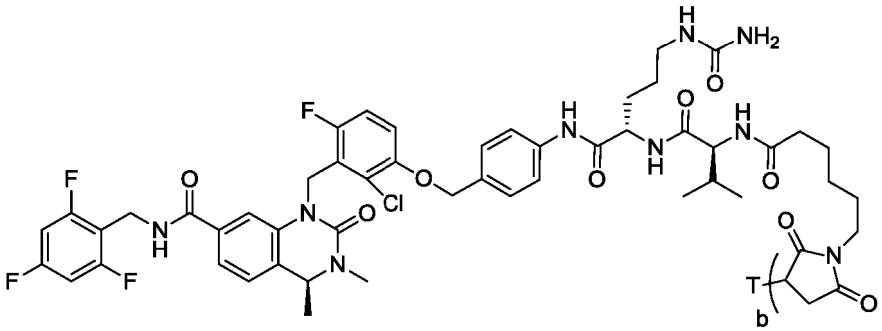

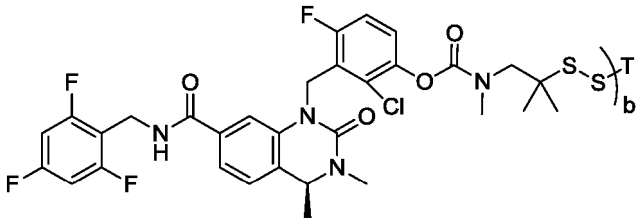

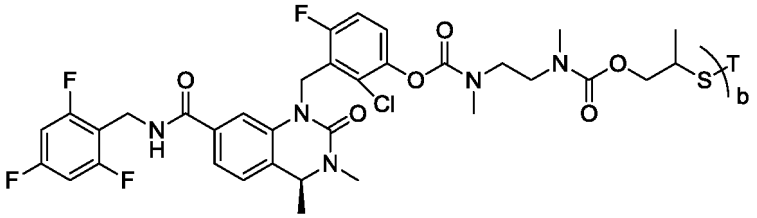

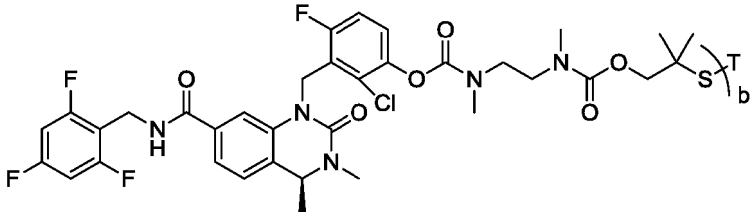

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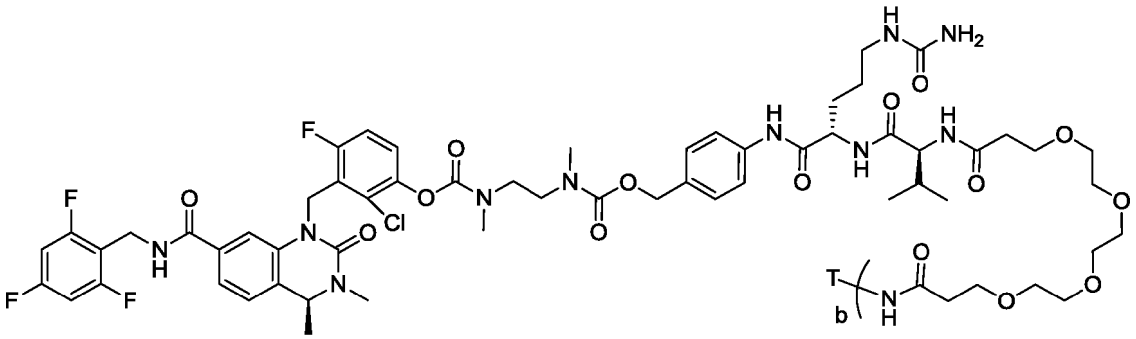

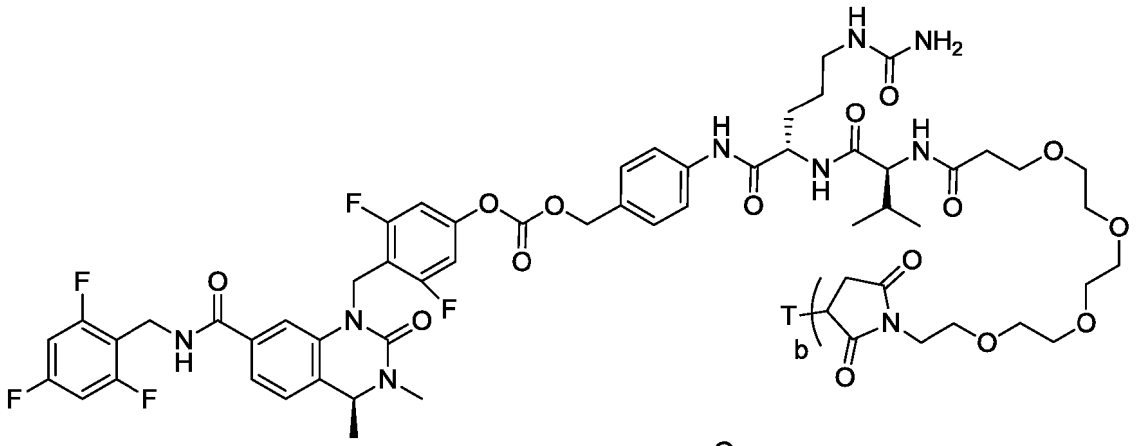

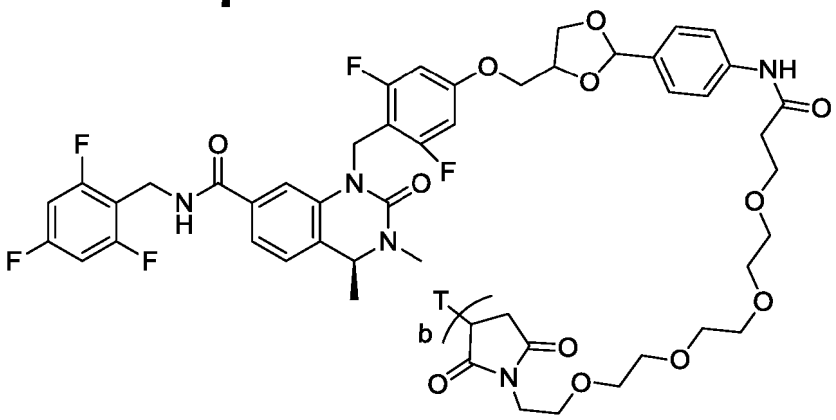

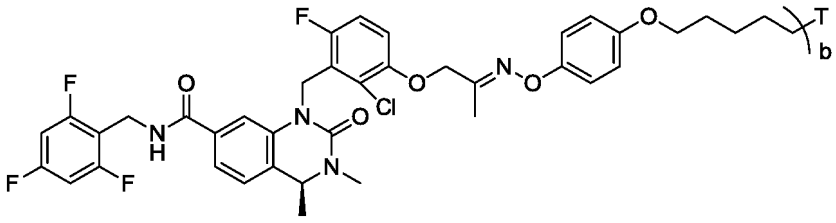

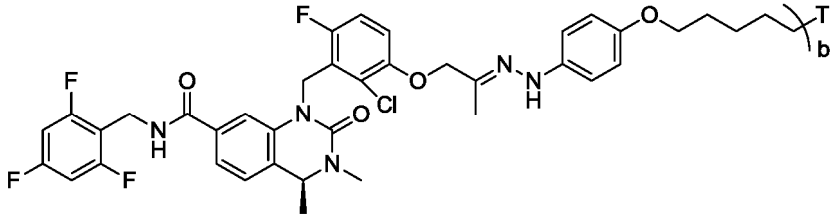

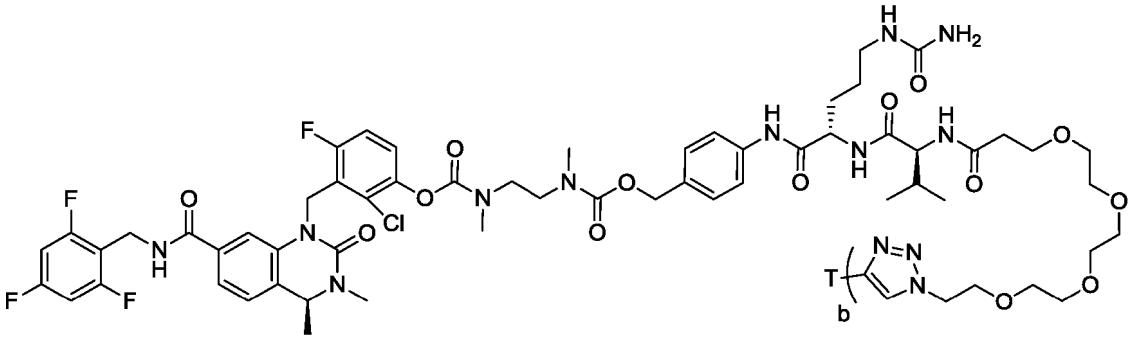

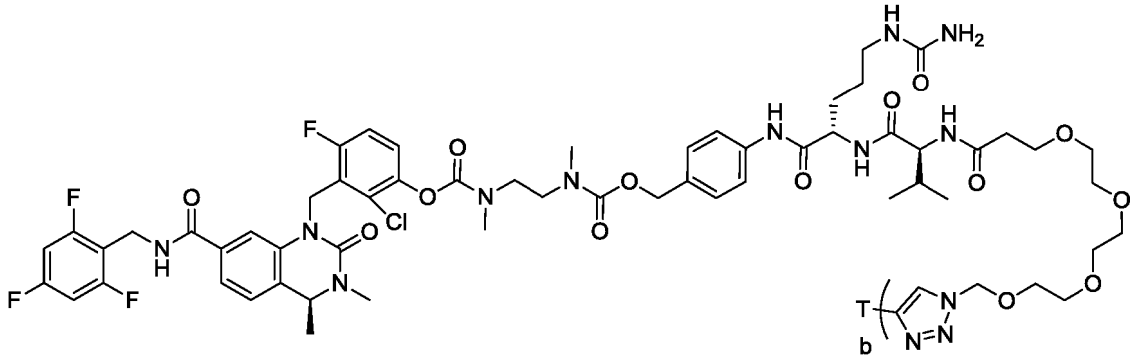

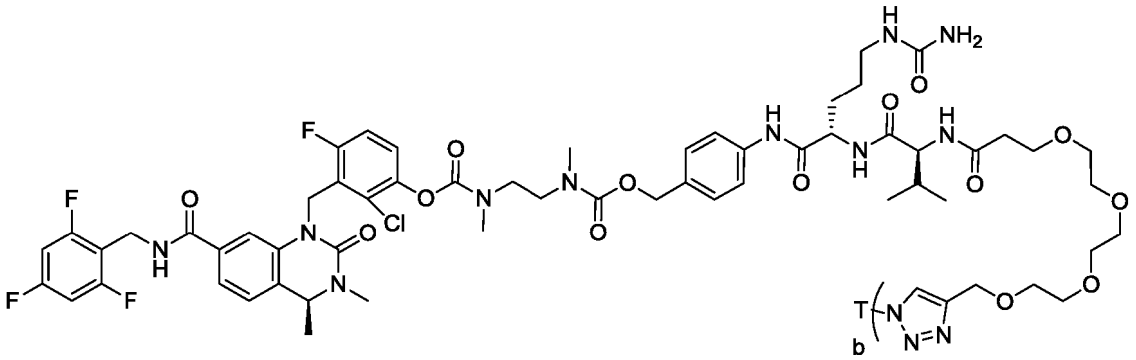

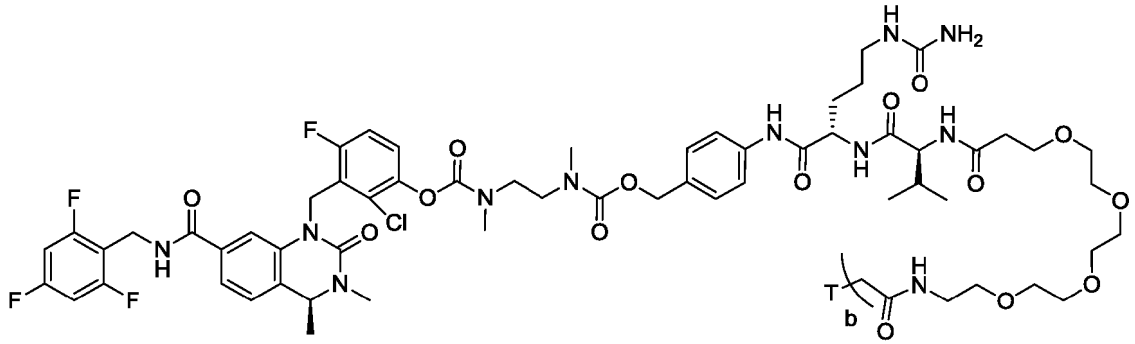

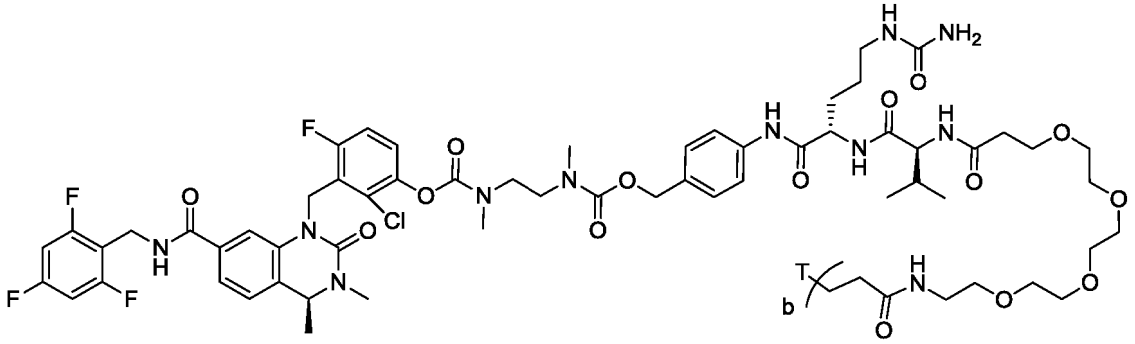

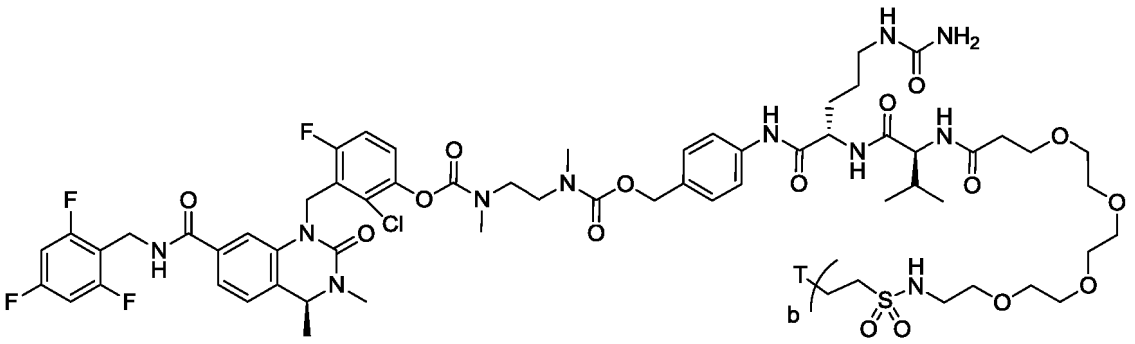

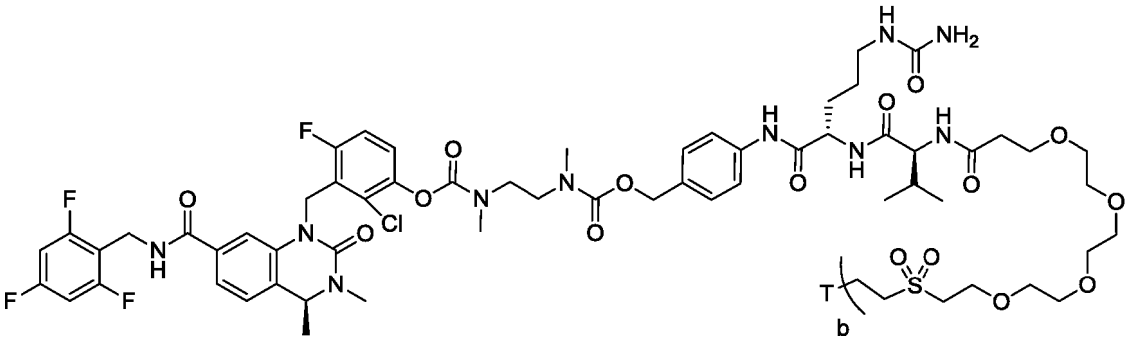

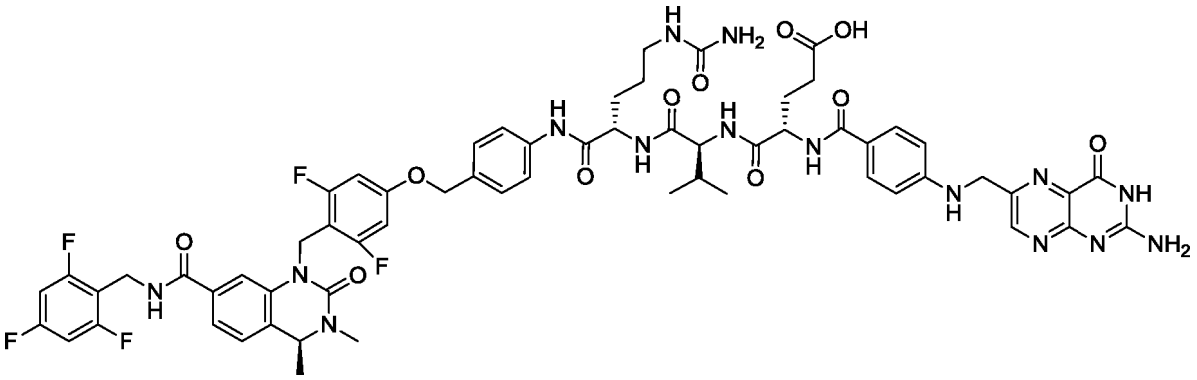

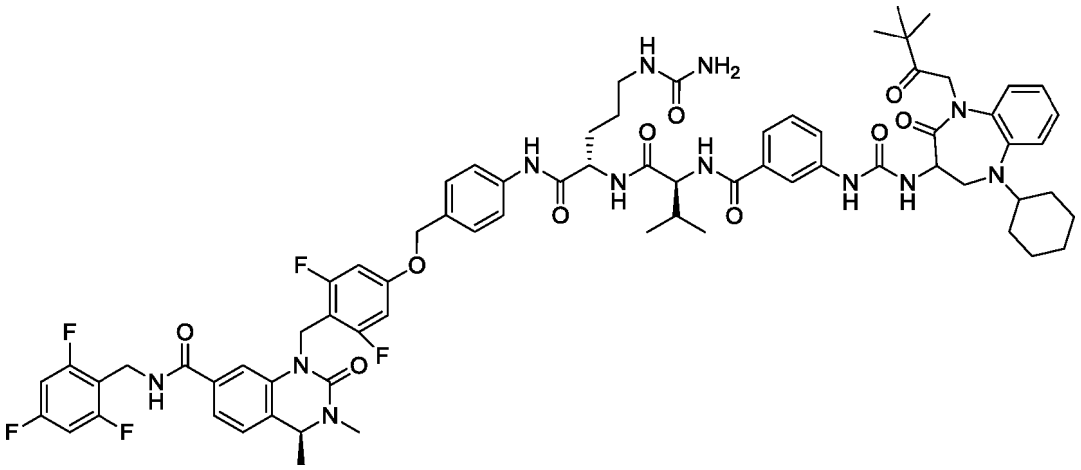

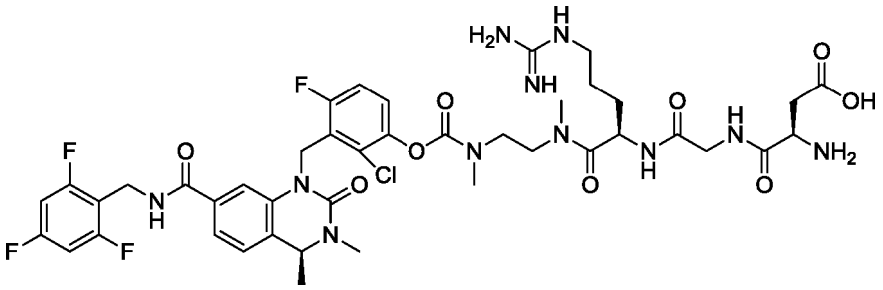

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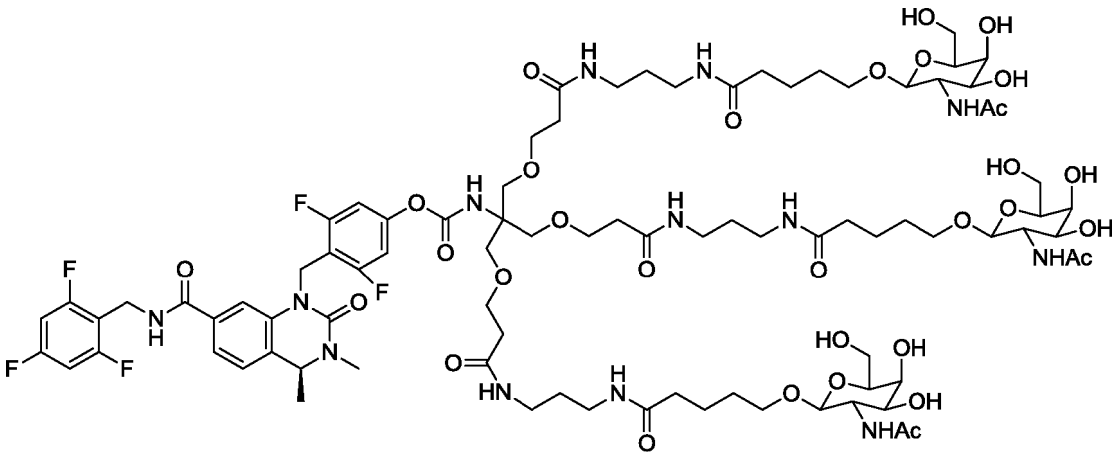
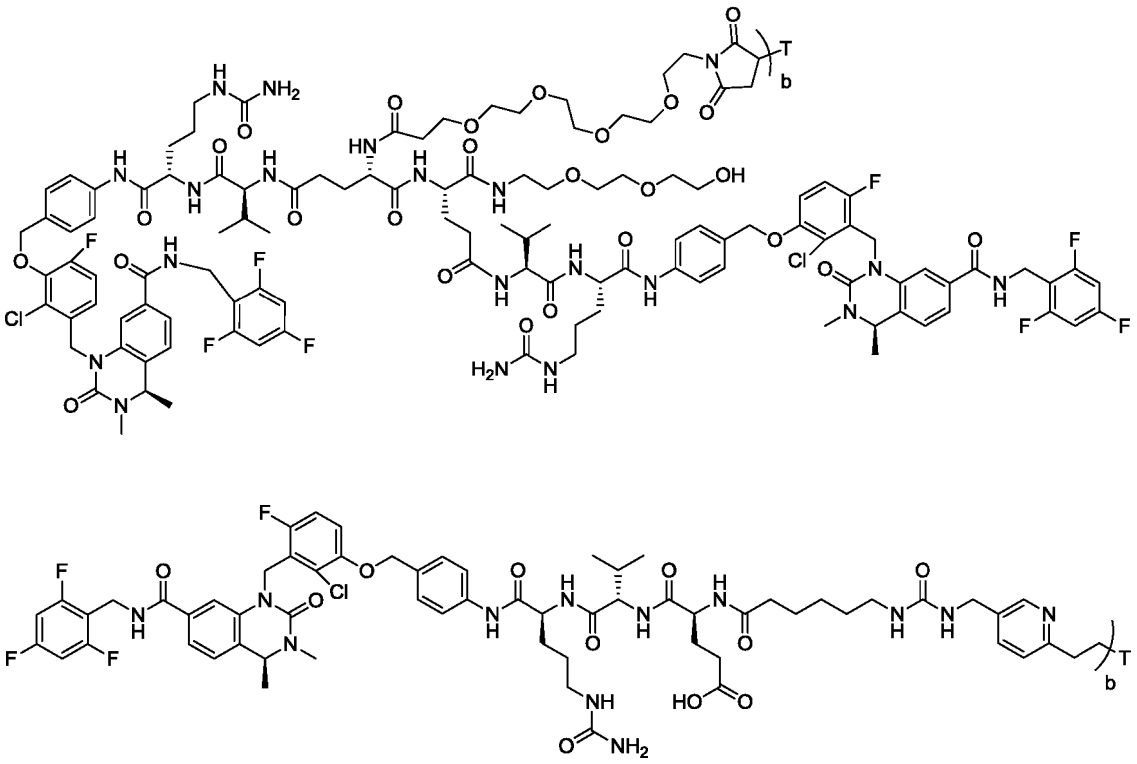
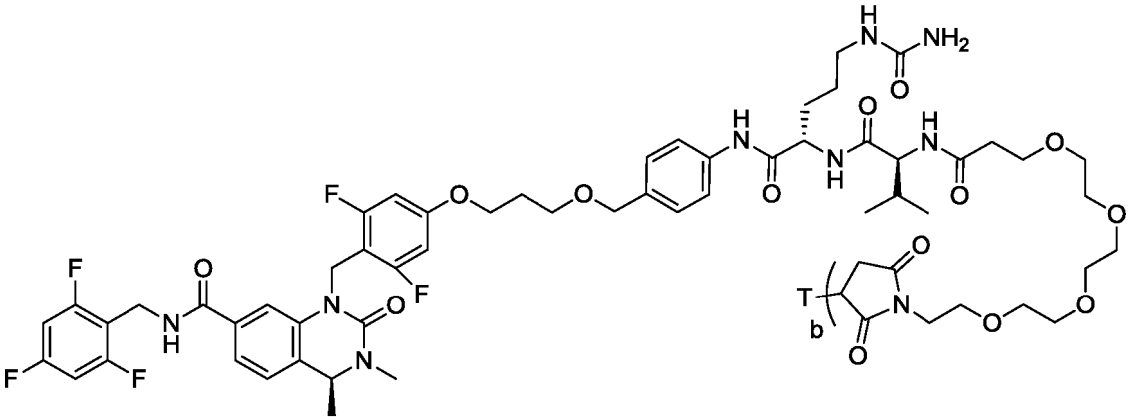
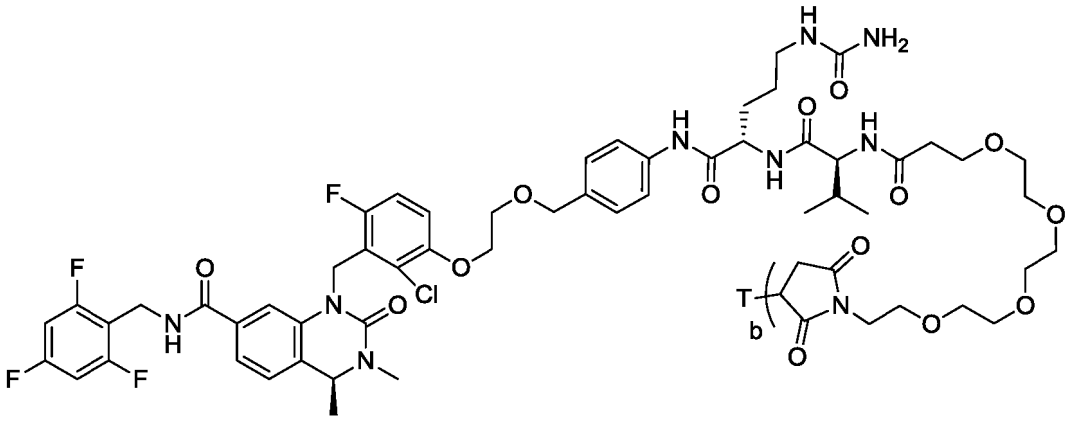
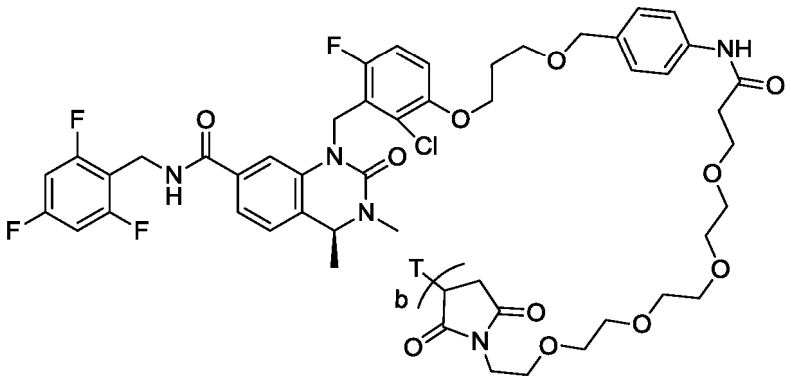
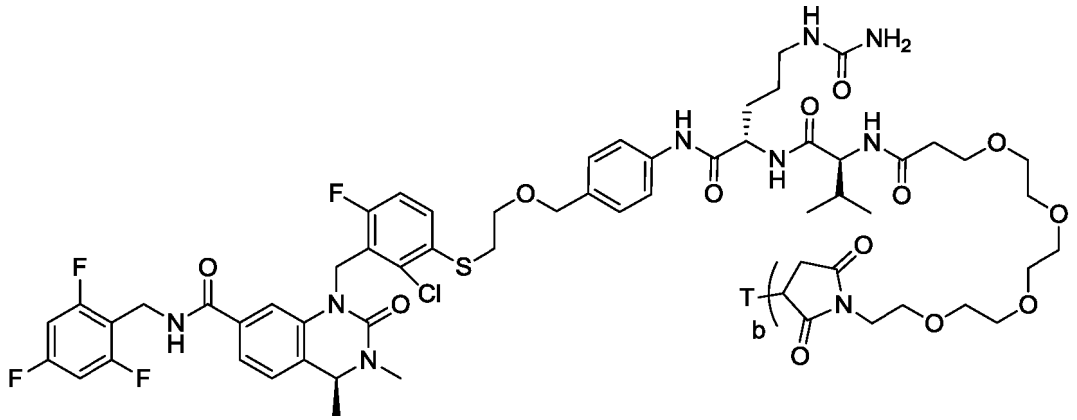


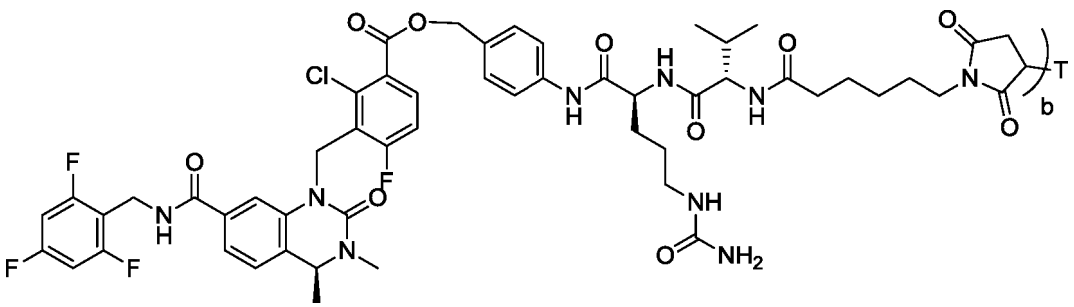


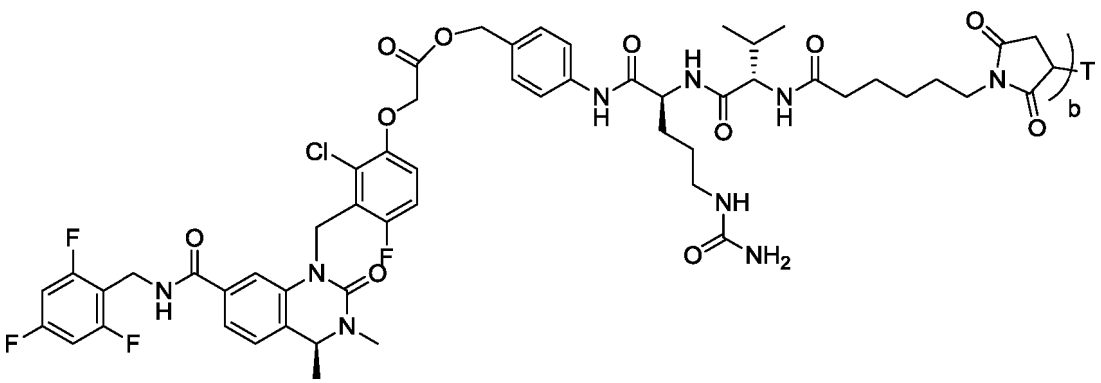


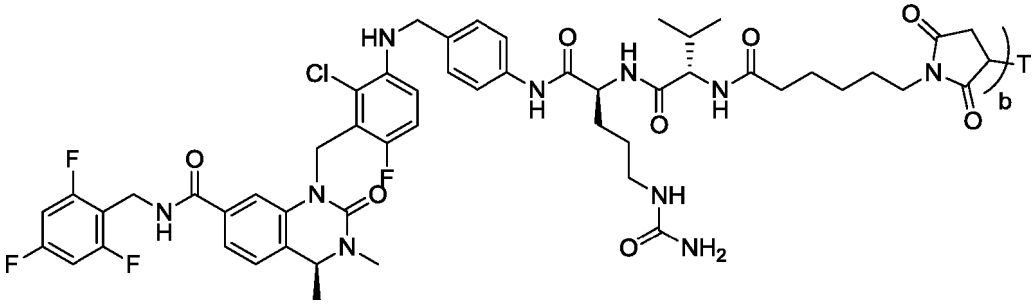


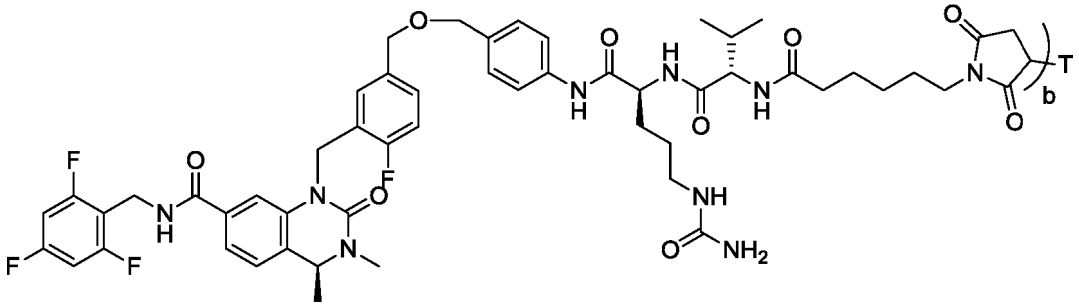


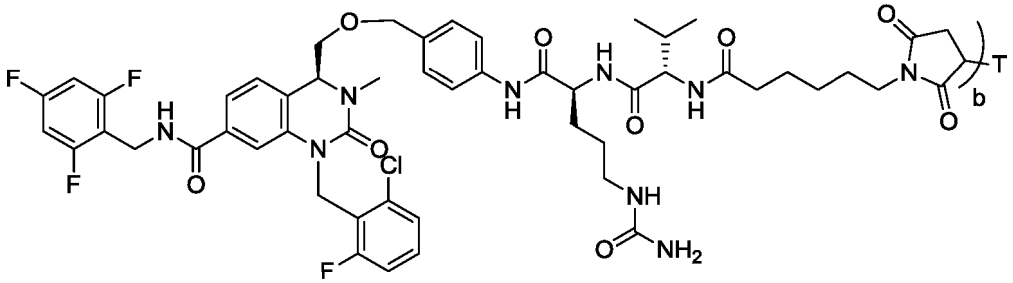


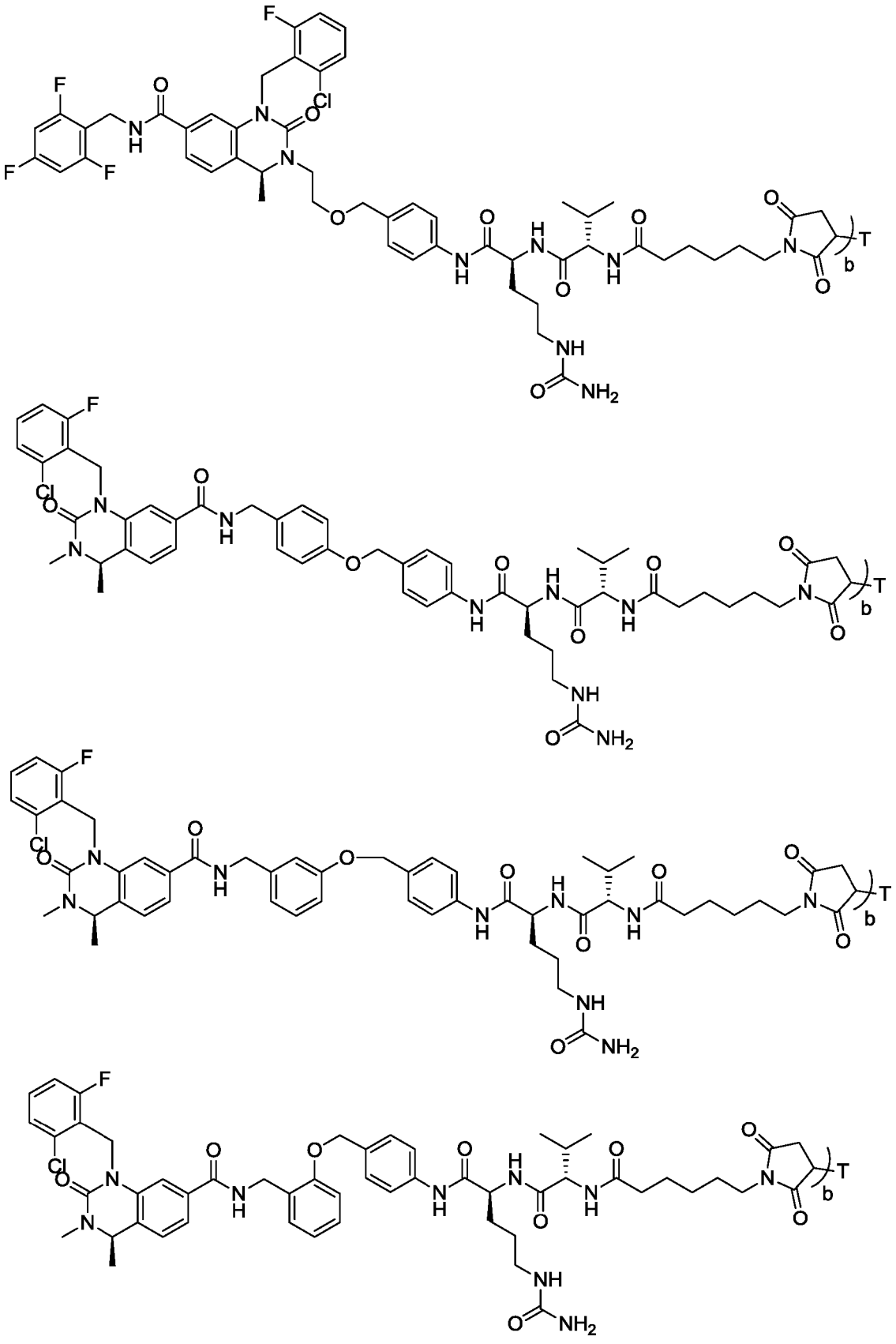






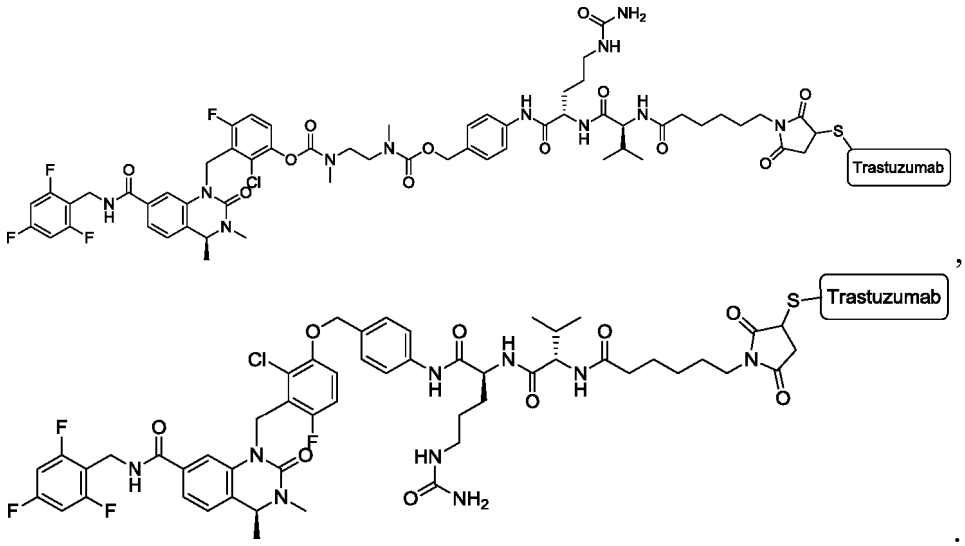






wherein T and b are as defined above.

In a specific embodiment, the compound of formula (**I**) may be:

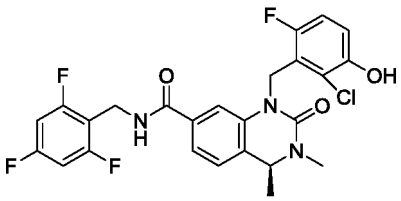


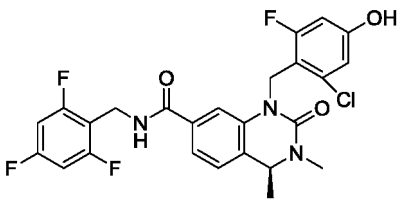
, or

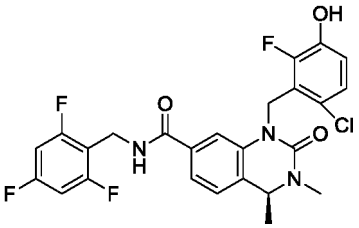
.

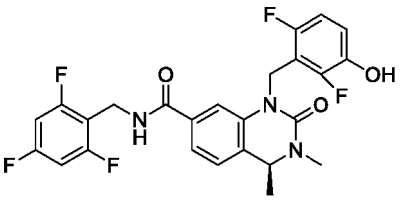
It may be appreciated that the sulphur shown in the above compounds may be a sulphur from a cysteine residue on the trastuzumab.

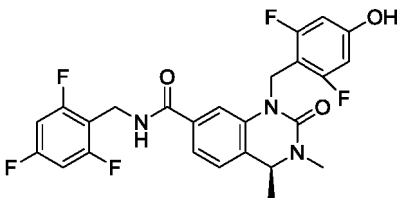
Compounds of formula **II** may include but are not limited to:

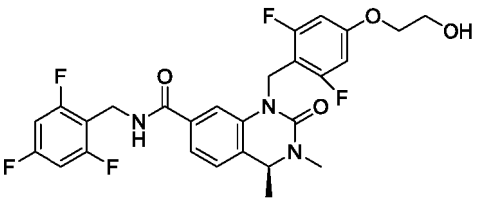


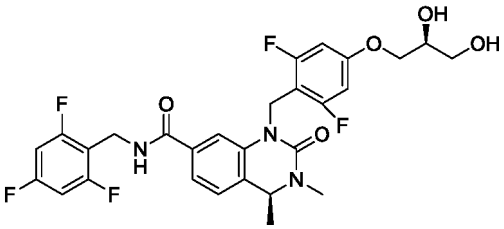


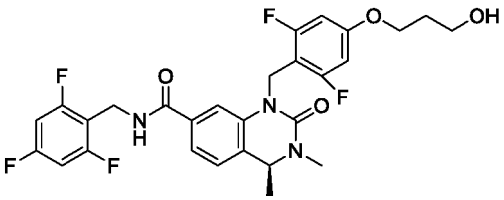


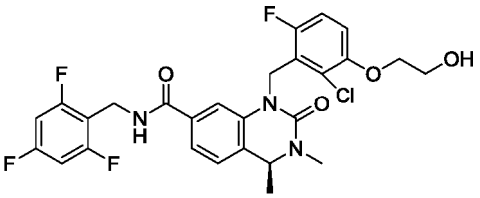


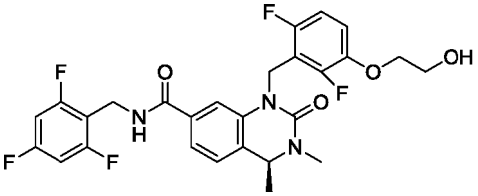


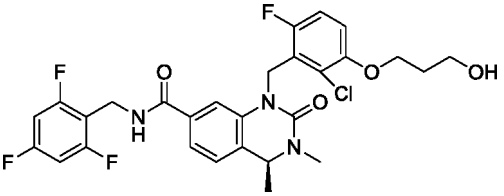


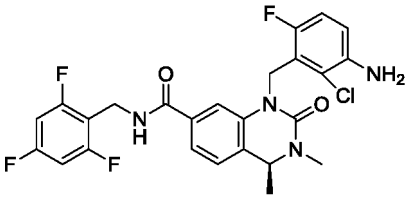


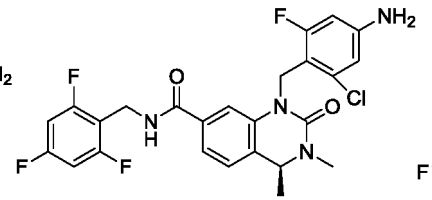


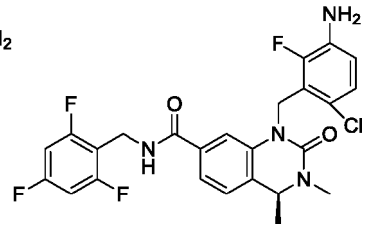


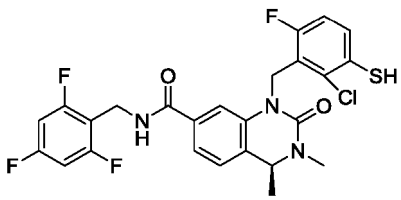


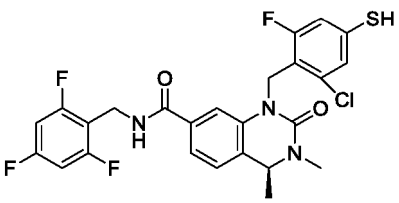


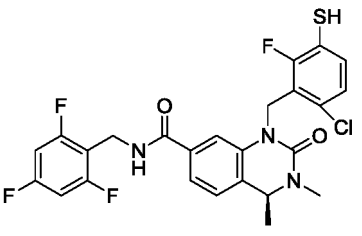


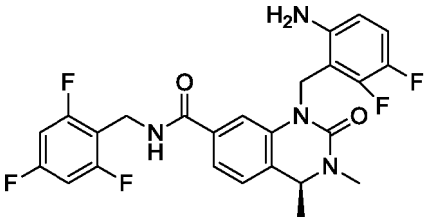


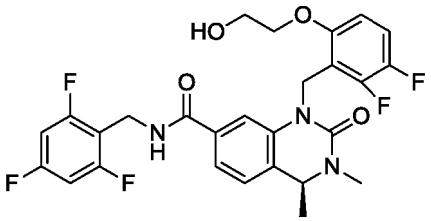


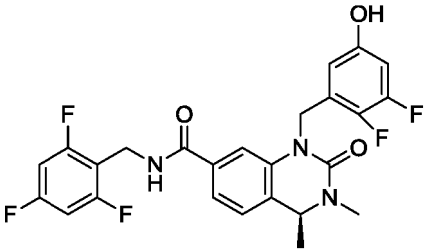


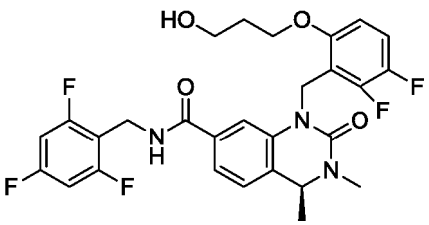


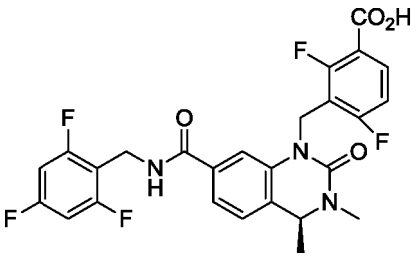


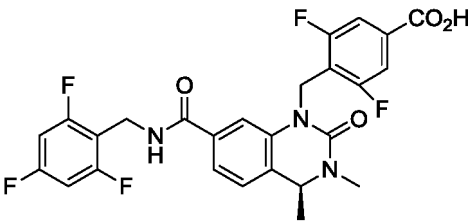


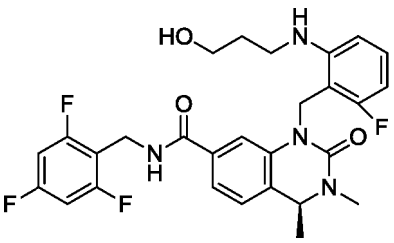


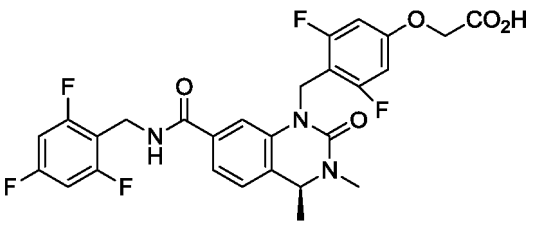


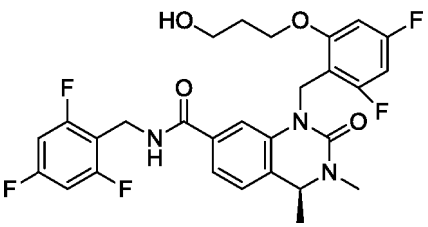


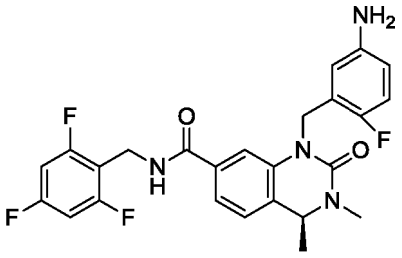


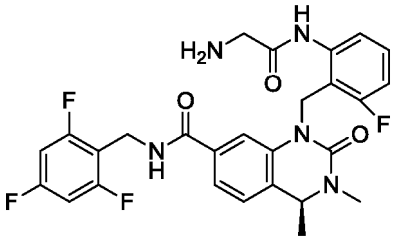


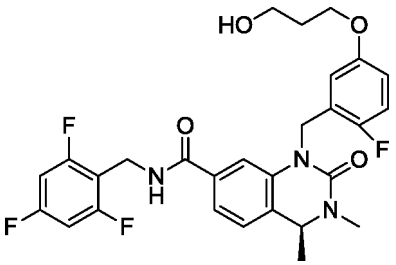


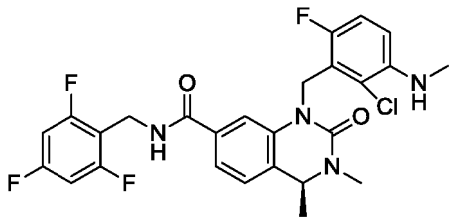


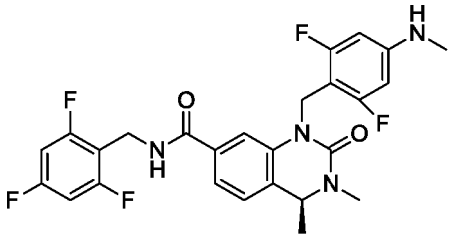


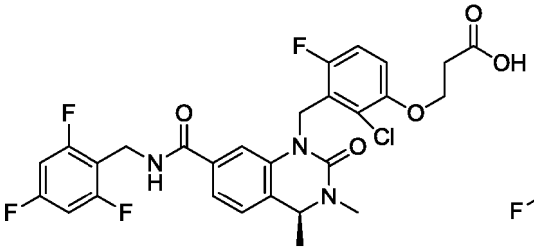


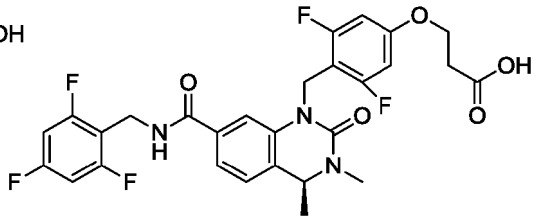


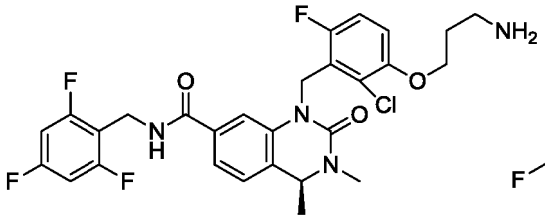


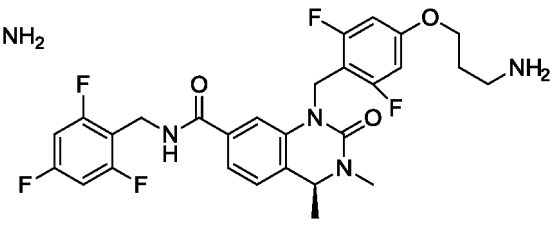


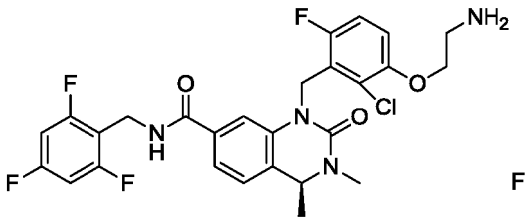


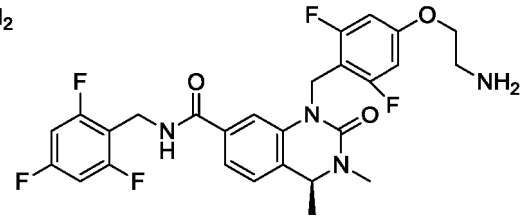


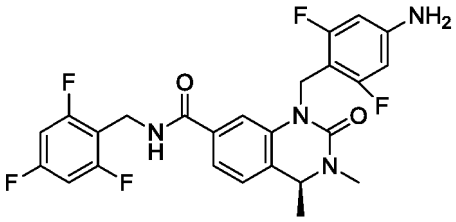


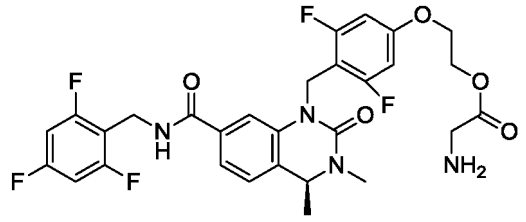


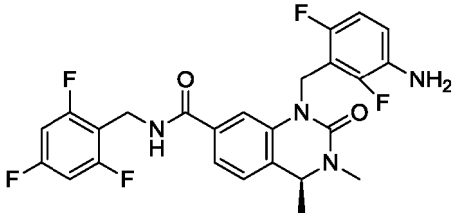


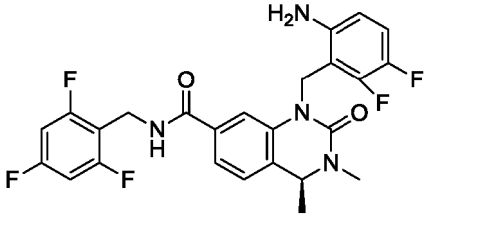


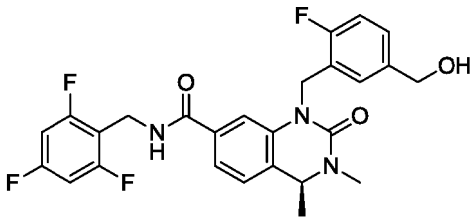


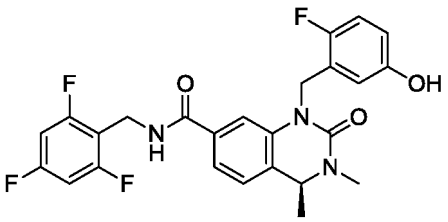


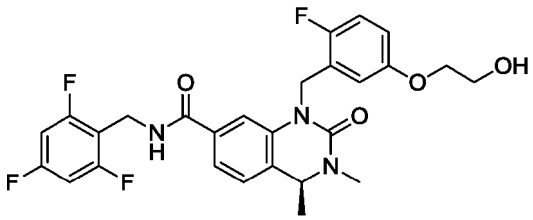


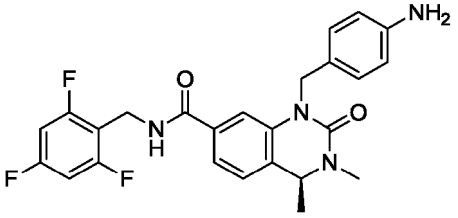


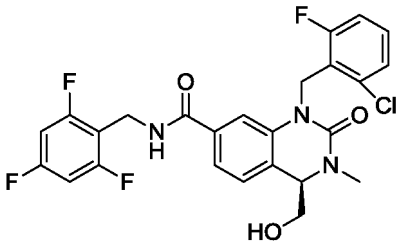


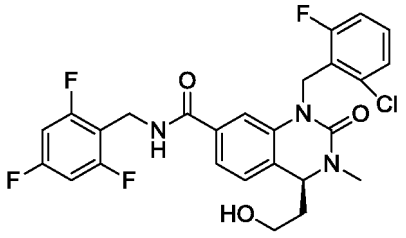


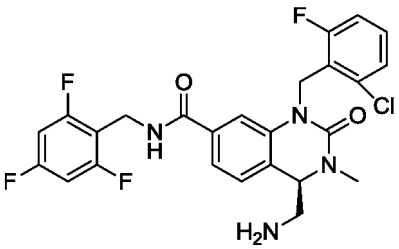


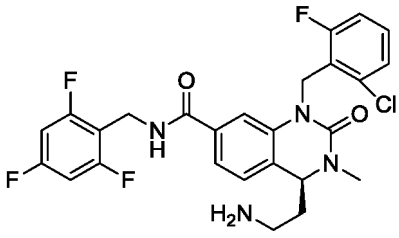


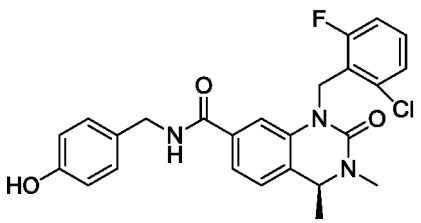
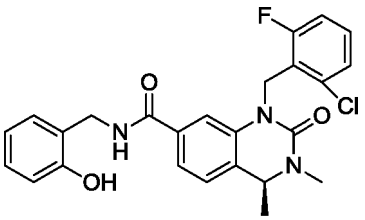
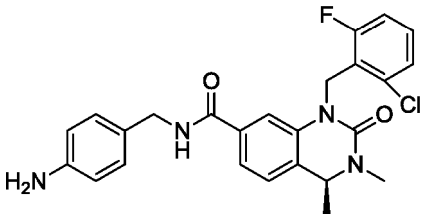
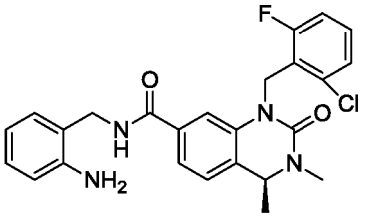
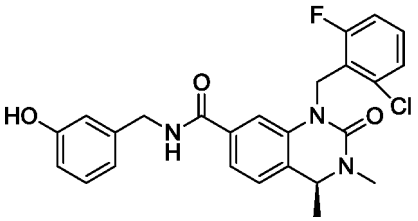
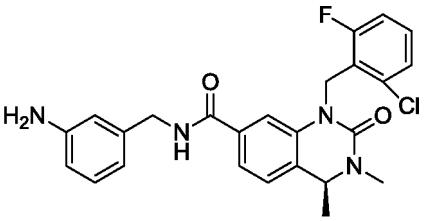
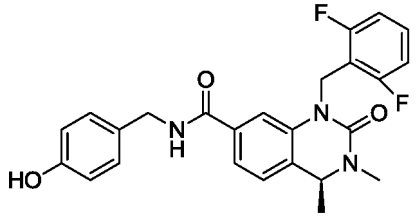
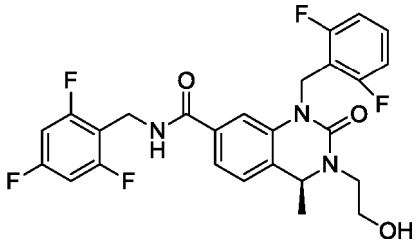
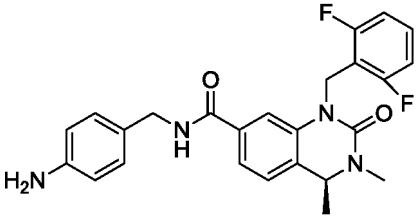
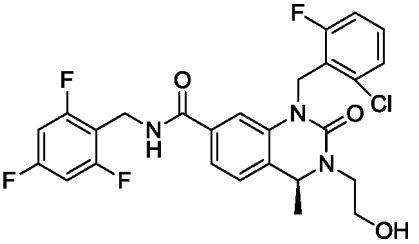
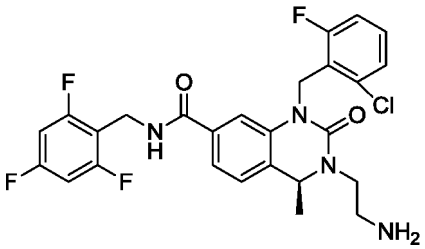
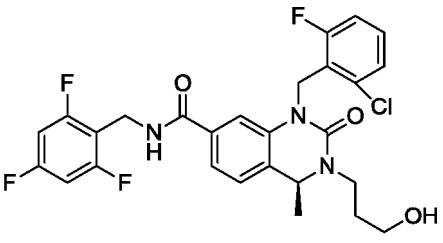


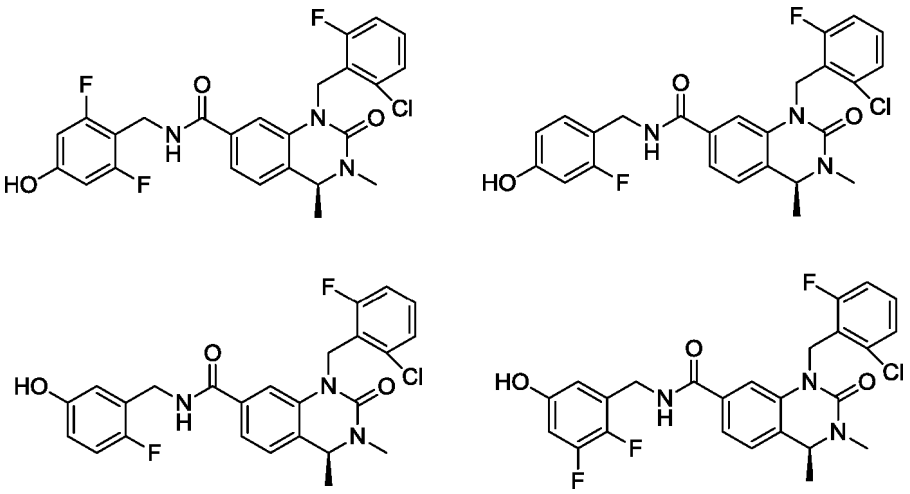






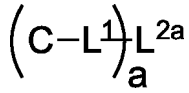




The linker may be directly bonded to the R^6 or R^8 phenyl ring in any of the above compounds. Alternatively, the linker may replace a hydrogen bonded to a nitrogen, oxygen or sulphur in any of the above compounds. Alternatively, the linker may replace R^{10} in any of the above compounds.

In accordance with a further aspect of the invention, there is provided a compound of formula (**III**):



(**III**)

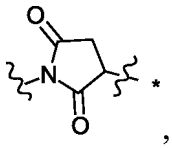
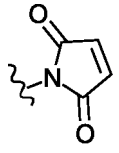
or a pharmaceutically acceptable salt or prodrug thereof, wherein:

L^1, a and C may be as defined in relation to the first aspect; and

L^{2a} is either L^2-Lg_z, where L^2 and z are as defined in relation to the first aspect and Lg is a leaving group, or L^{2a} is a linker which is the same as L^2, as defined in relation to the first aspect, except that the linker comprises a terminal double bond.

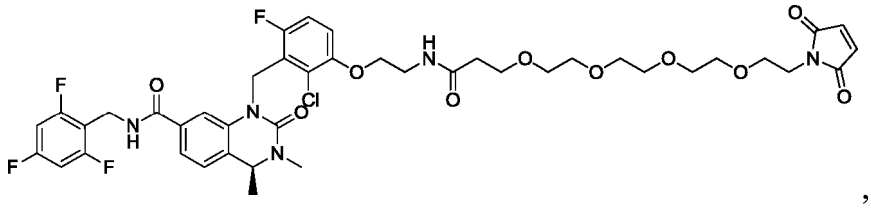
Advantageously, the compound of formula (**III**) may be used to produce a compound of formula (**I**).

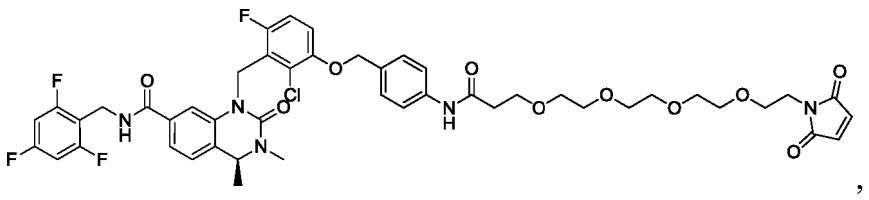
Lg may be a halogen, –OH, -NH_2 or SH.

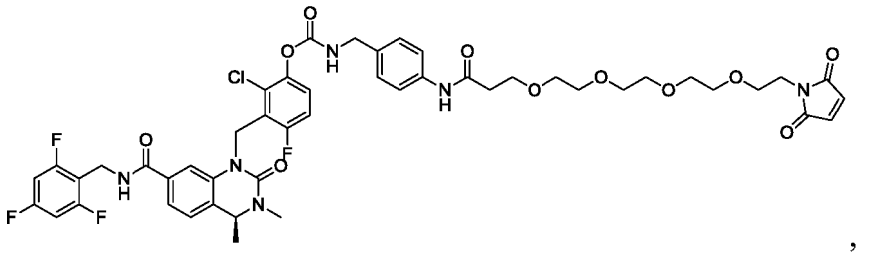
A terminal double bond may be a double bond disposed adjacent to the atom through which the L^{2a} group would otherwise be bonded to T. Preferably, the terminal double bond forms part of a conjugated system. Preferably, the conjugated system further comprises at least one carbonyl group. For instance, where L^2 in the first aspect comprises an S group which is  , L^{2a} in this aspect may comprise an S group which is  .

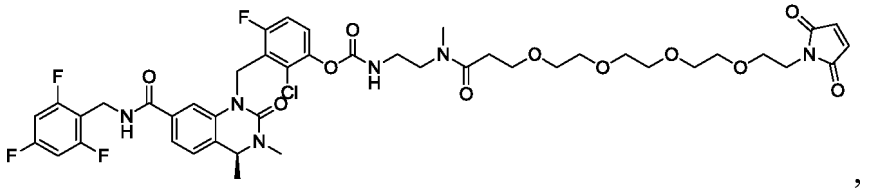
It may be appreciated that in embodiments where the linker is a branched linker then L^{2a} may comprise multiple terminal double bonds, with one terminal double bond on each branch of the linker. Accordingly, L^{2a} may comprise z terminal double bonds, where z is as defined in relation to the first aspect.

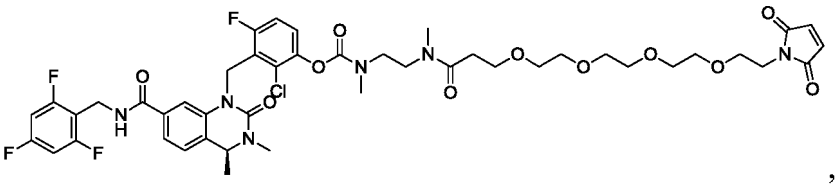
Accordingly, in certain embodiments, the compound of formula (**III**) may be:

 ,

 ,

 ,

 ,



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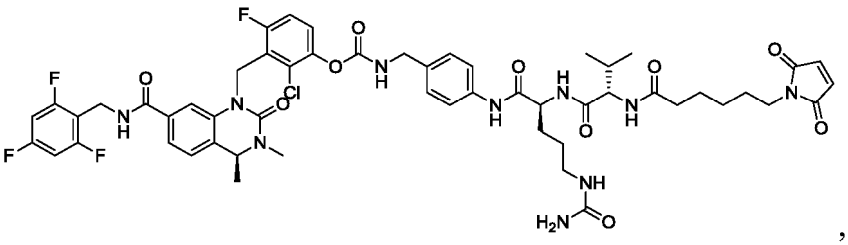

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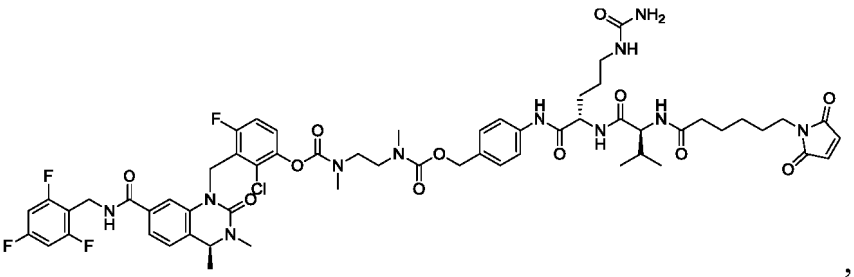

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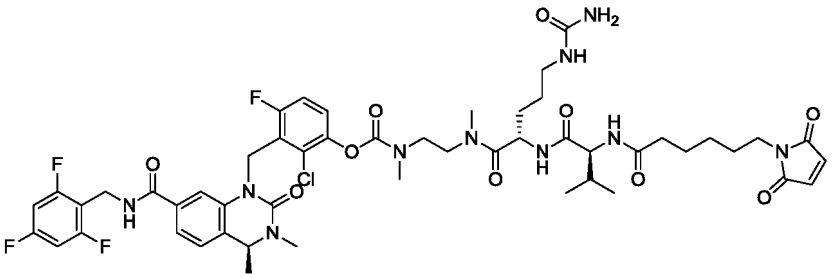

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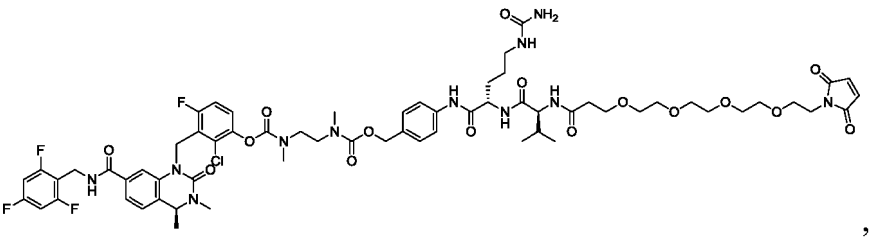

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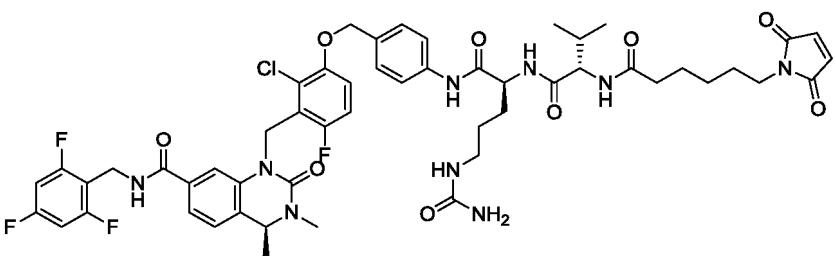

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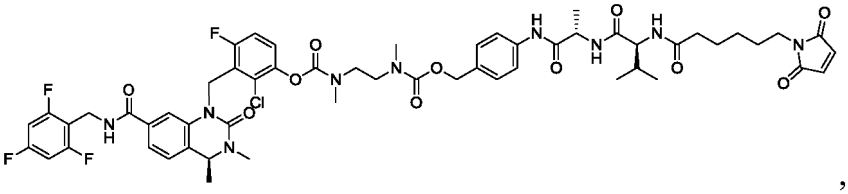

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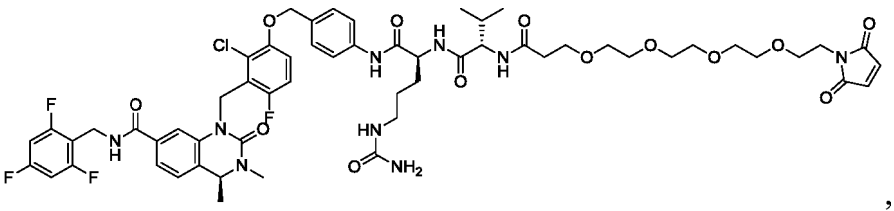

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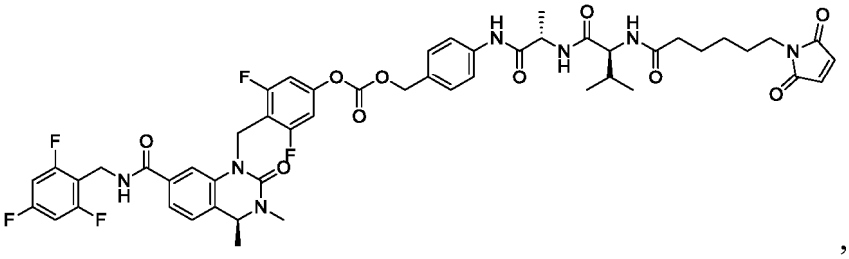

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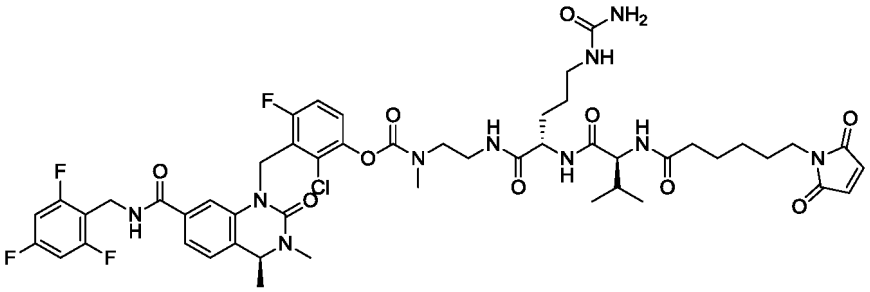

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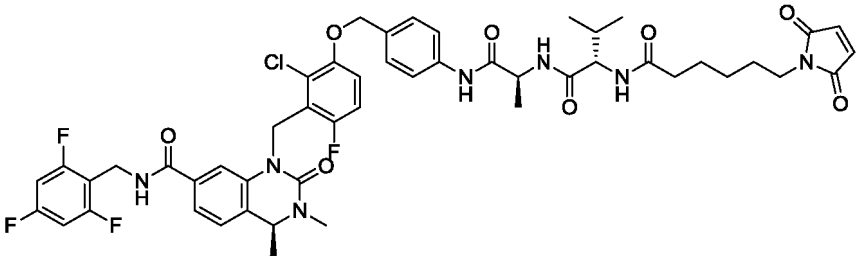

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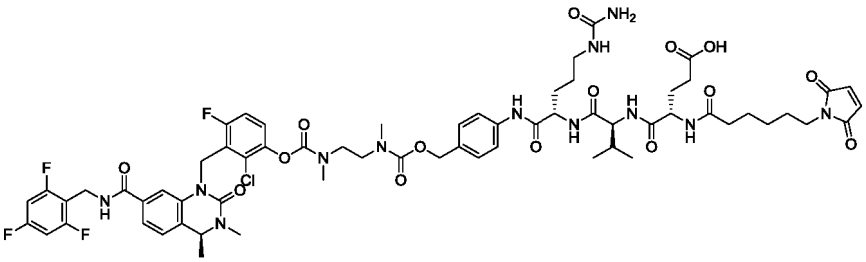

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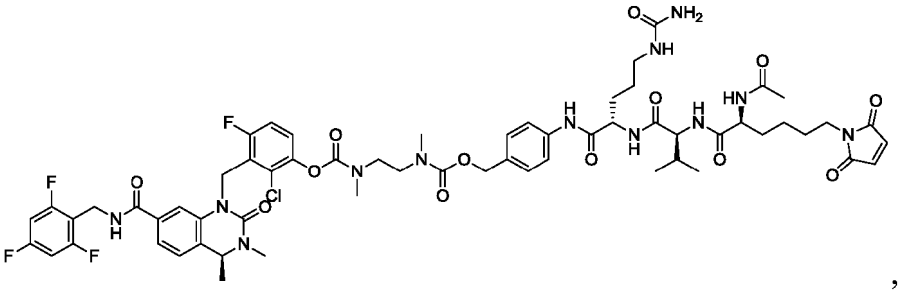

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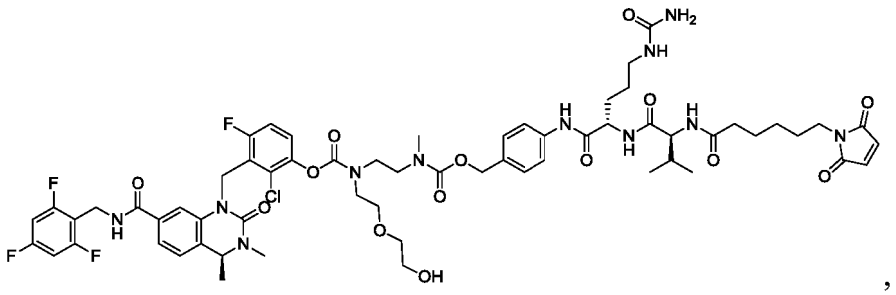

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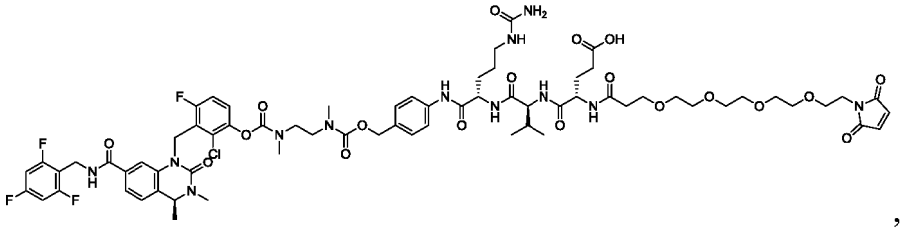

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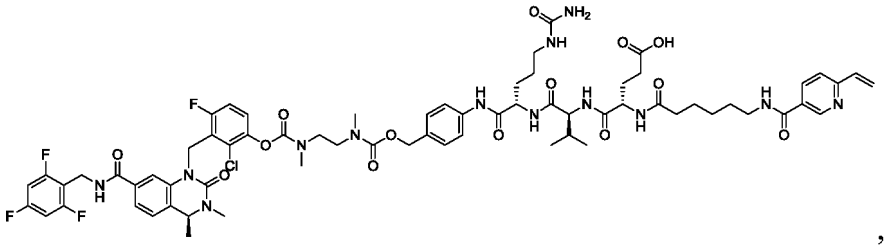

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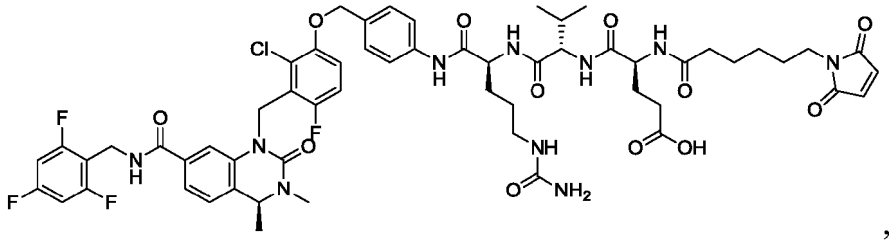

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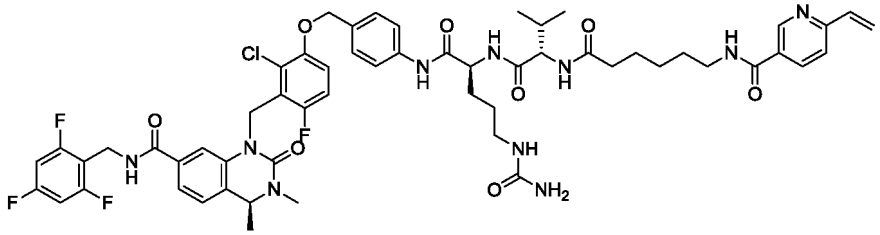

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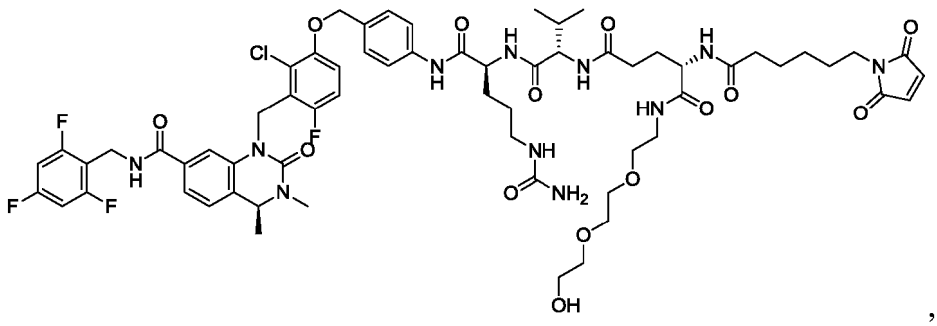

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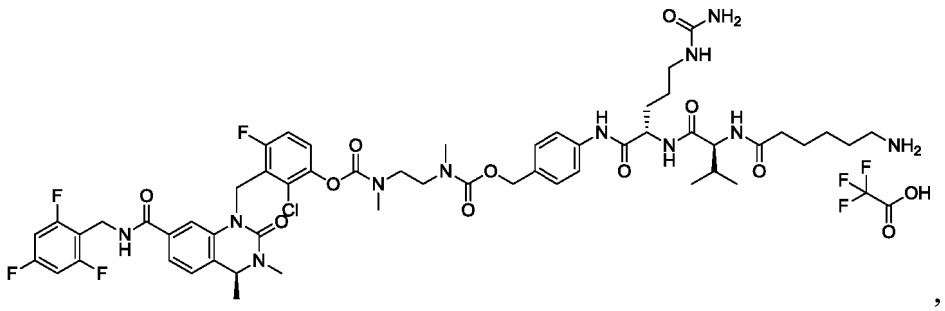

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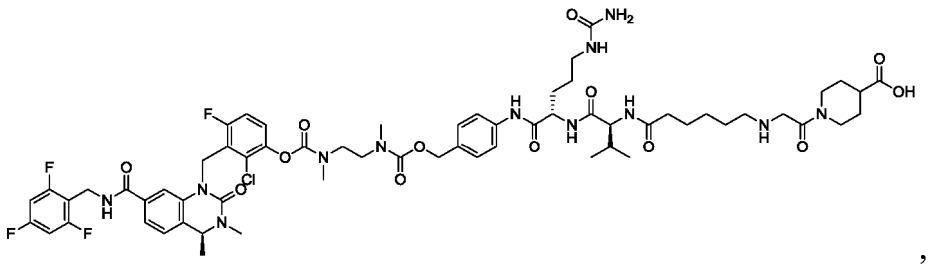

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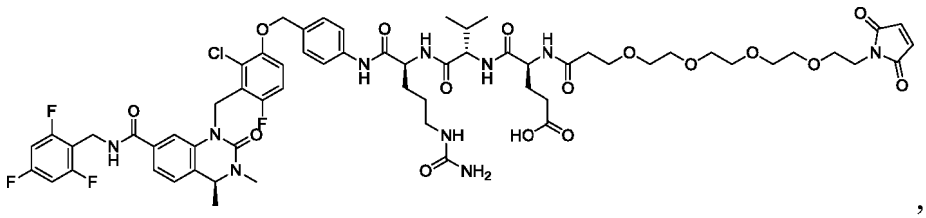

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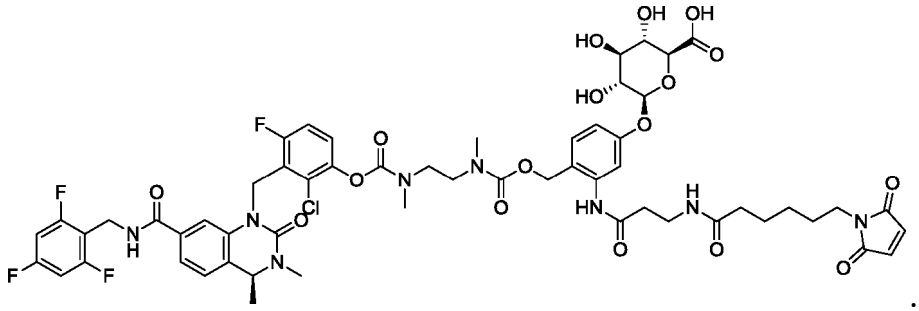

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All features described herein (including any accompanying claims, drawings and abstract), and/or all of the steps of any method or process so disclosed, may be combined with any of the above aspects in any combination, except combinations where at least some of such features and/or steps are mutually exclusive.

For a better understanding of the invention, and to show embodiments of the same may be carried into effect, reference will now be made, by way of example, to the accompanying Figures, in which:-

Figure 1 shows some of the major polymorphisms of human STING;

Figure 2 is a hydrophobic interaction chromatogram (HIC) (λ=280 nm) for example 28;

Figure 3 is a size-exclusion chromatogram (SEC) (λ=280 nm) for example 28;

Figure 4 is a HIC spectrum (λ=280 nm) for example 29;

Figure 5 is a SEC spectrum (λ=280 nm) for example 29; and

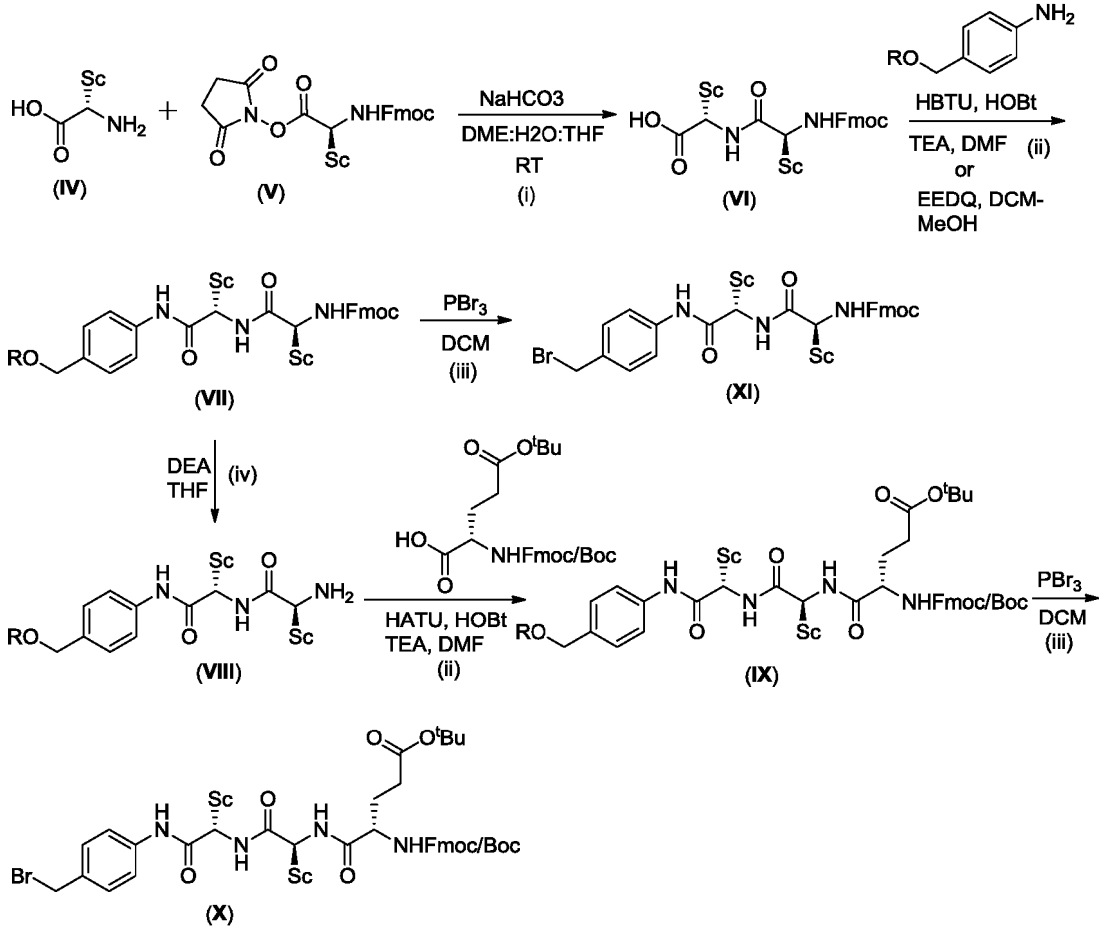
Figure 6 shows SDS-polyacrylamide gel electrophoresis (SDS-PAGE) analysis of examples 28 and 29, where lane 1 shows the results for Novex Sharp Markers; lane 2 shows the results for trastuzumab in reaction buffer; lane 3 shows the results for reduced trastuzumab in reaction buffer; lane 4 shows the results for example 28 in PBS; and lane 5 shows the results for example 29 in PBS.

General Schemes for synthesis of common pre-conjugates and linkers

The following schemes indicate the methods used to synthesise common fragments used to make compounds of the invention.

General Scheme 1a: Synthesis of peptides

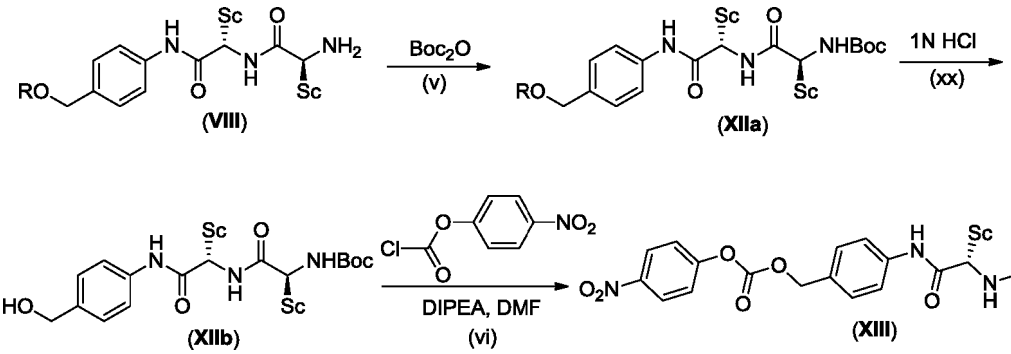
Compounds of formulae (**VIII**), (**X**) and (**XI**) may be synthesized from a compound of formula (**IV**) and (**V**) in the sequence of reactions described below, where Sc is an optionally substituted alkyl or aryl.



Compounds of formula (**VI**) can be synthesized from a compound of formula (**IV**) and (**V**) under basic conditions using for example a bicarbonate or carbonate base to generate an amide bond. Compounds of formulae (**VI**) are then used to make a further amide bond. Typical conditions employ activation of the carboxylic acid function using a suitable organic base and a suitable coupling agent. Preferred coupling agents include HBTU with HOBt or HATU and HOAt or EDCI with HOBt or EEDQ. Preferred organic bases comprise either DIPEA or TEA in a suitable organic solvent such as DCM, DCM-MeOH, DMF, DMA or MeCN. The reaction may be shaken or stirred at room temperature to give a compound of formula (**VII**). The compound of formula (**VII**) may undergo bromination with brominating agents such as PBr_3 or $POBr_3$ to give a compound of formula (**XI**). Alternatively, the Fmoc group of a compound of formula (**VII**) can be deprotected with, for example, diethyl amine in THF to give a compound of formula (**VIII**) which may be further subjected to an amide coupling reaction with another amino acid such as glutamic acid using the typical conditions outlined above to give a tripeptide compound of formula (**IX**). Compounds of formula (**IX**) may then be brominated as above to provide a compound of formula (**X**).

General Scheme 1b: Synthesis of carbonates

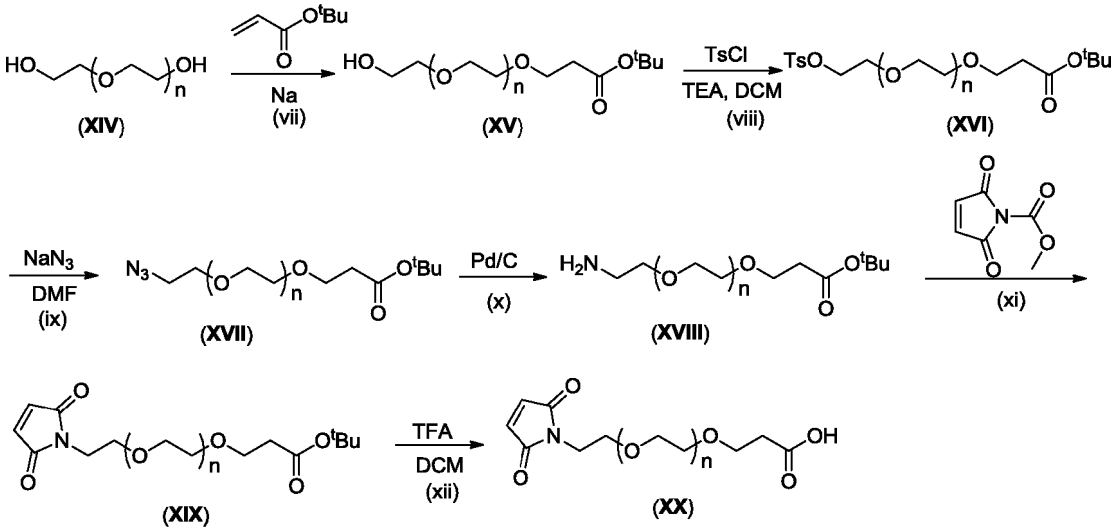
Compounds of formula (**XIII**) may be prepared from a compound of formula (**VIII**) as depicted in the below scheme, where Sc is an optionally substituted alkyl or aryl and R is a silyl protecting group.



The free amino group of (**VIII**) can be protected with a BOC group using BOC anhydride to give a compound of formula (**XIIa**). The silyl protection can be removed in mildly acidic conditions to give a compound of formula (**XIIb**) which may be further transformed into a carbonate (**XIII**) using p-nitro-chloroformate in a suitable organic base such as DIPEA or TEA and suitable solvent, for example, THF or DMF.

General Scheme 2a: Synthesis of linkers

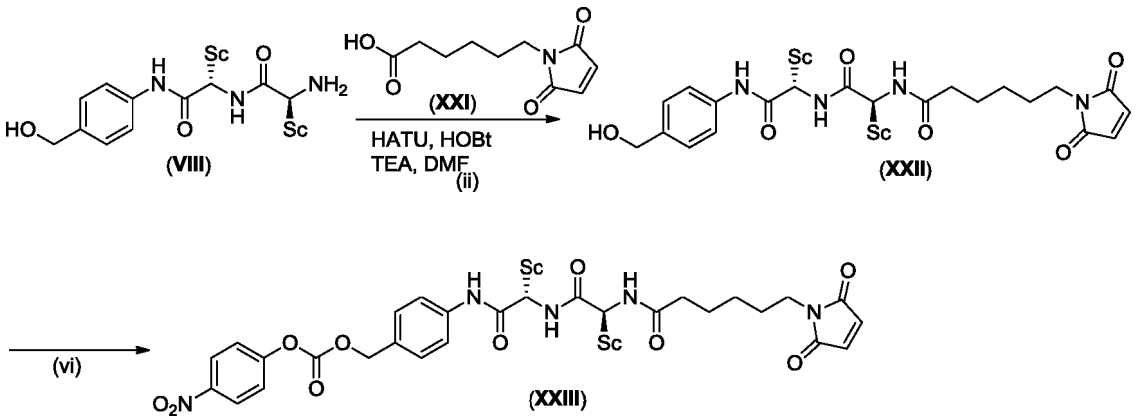
Linkers that connect the targeting moiety and the active payload may be prepared according to methods known to those skilled in the art. For example, in the case of a PEG-containing linker, a compound of formula (**XIV**) may undergo a Michael addition reaction to an unsaturated ester to provide a compound of formula (**XV**). The remaining free alcohol functional group may then be converted into a suitable leaving group, for example a tosylate (**XVI**), and then displaced with an azide reagent such as sodium azide in a polar solvent such as DMF to give the azide (**XVII**). Reduction of the azide using either chemical means or hydrogenolysis, for example using palladised charcoal and hydrogen gas, subsequently allows access to the amines (**XVIII**).



Compounds of formula (**XVIII**) may then be used in an exchange reaction with methyl-2,5-dioxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate to produce a maleimide of formula (**XIX**). Subsequent deprotection, for example using TFA in DCM, may provide a free carboxylic acid (**XX**) ready for coupling to the payload.

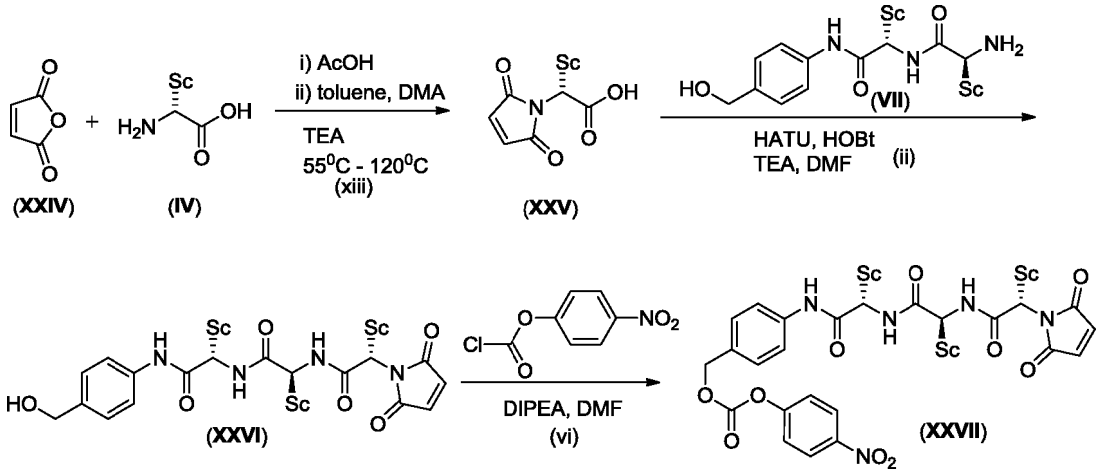
General Scheme 2b: Linker attachment to peptides

Compounds of formula (**VII**) may be attached to maleimide-containing acids such as compounds of formula (**XXI**) using a standard amide-bond forming reaction, for example using HBTU, HATU or EDCI with a suitable base in a suitable polar solvent such as DMF to provide the extended linkers (**XXII**). Reacting compounds of the formula (**XXII**) with p-nitrophenyl-chloroformate in the presence of an organic base such as TEA or DIPEA in a suitable solvent such as DCM gives the carbonate (**XXIII**) ready for attachment to a payload.



General Scheme 2c: Linker attachment to peptides

In an alternative method, compounds of formula (**IV**) may be reacted with maleic anhydride (**XXIV**) in a two-step process starting with acetic acid treatment, followed by heating at temperatures up to 120°C in a polar solvent such as DMA in the presence of a base, for example TEA. The ensuing maleimide-acid (**XXV**) may then be reacted with compounds of formula (**VII**) in a standard HATU, EDCI or HBTU amide forming reaction to give the extended linkers (**XXVI**).

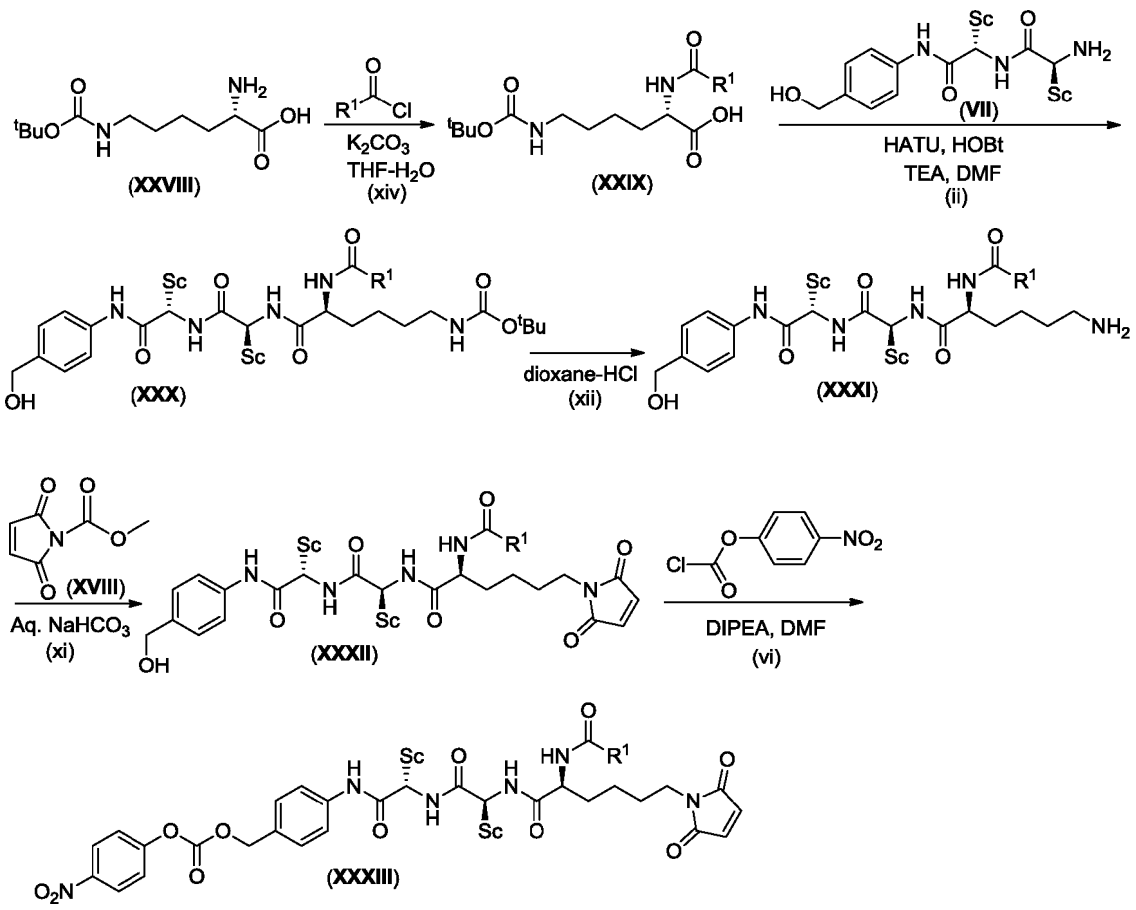


The extended linkers (**XXVI**) may then be reacted with p-nitrophenyl-chloroformate in the presence of an organic base such as TEA or DIPEA in a suitable solvent such as DCM or DMF to give the carbonate (**XXVII**) ready for attachment to a payload.

General Scheme 2d: Linker attachment to peptides

In an analogous manner to the above schemes, BOC-protected lysine (**XXVIII**) may be reacted with an acid chloride or other activated acyl reagent in the presence of an inorganic base such as potassium or caesium carbonate in mixtures of THF and water to give the amides (**XXIX**). These amides may then be subjected to a standard HATU, EDCI or HBTU amide forming reaction with amines (**VII**) to give the extended linkers

of formula (**XXX**). Deprotection may then be carried out using acidic conditions, for example with solutions of HCl in dioxane to reveal the free amine in compounds of formula (**XXXI**). Said amines may then be converted to the maleimides (**XXXII**) using the same reagent (**XVIII**) and procedure described in Scheme 2a.

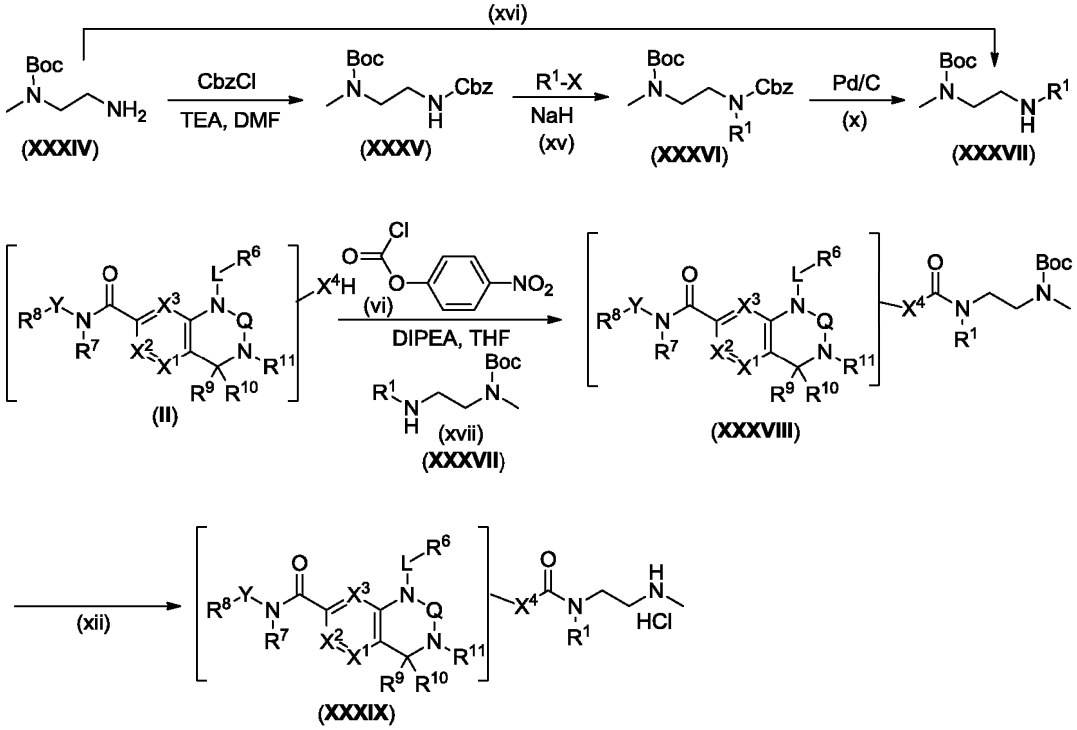


The maleimides (**XXXII**) may then be reacted with p-nitrophenyl-chloroformate in the presence of an organic base such as TEA or DIPEA in a suitable solvent such as DCM or DMF to give the carbonate (**XXXIII**) ready for attachment to a payload.

General Scheme 3: Synthesis of payload carbamates, thiocarbamates and ureas

Compounds of formula (**II**) may be joined with linkers via a carbamate functional group. Thus, mono BOC-protected ethylene diamine compounds of formula (**XXXIV**) may be orthogonally protected with, for example, a Cbz group (**XXXV**) and then further alkylated with a strong base such as NaH and an electrophile Z-X where X is a suitable leaving group, for example an alkyl halide, mesylate or tosylate and Z is an optionally substituted alkyl or aryl group to give the alkylated diamines (**XXXVI**). Removal of the Cbz group under standard conditions, for example hydrogenolysis over

palladised charcoal allows access to the mono alkylated, mono BOC-protected diamines (**XXXVII**).

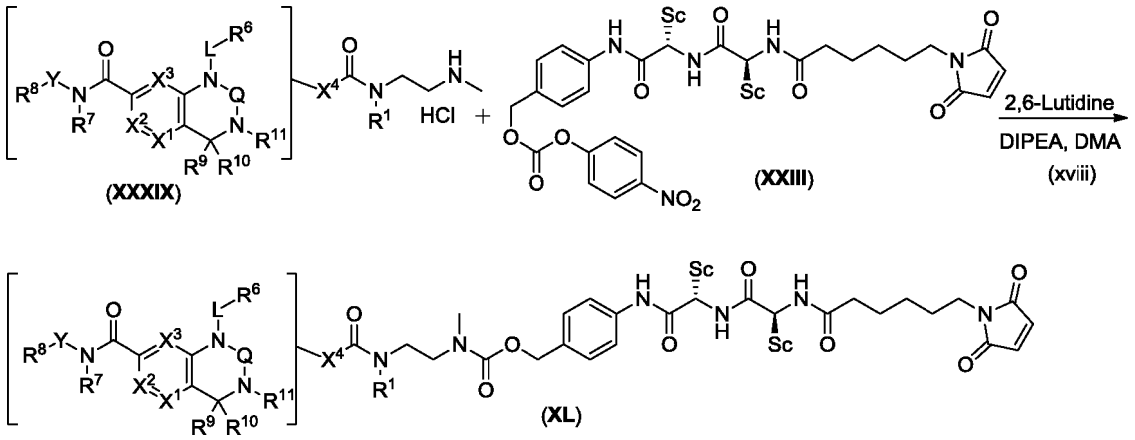


Treatment of compounds of formula (**II**) with p-nitrophenyl-carbamoyl chloride in the presence of an organic base such as DIPEA or TEA in a suitable solvent such as THF, followed by (**XXXVII**) may result in compounds of formula (**XXXVIII**). In the cases where compounds of formula (**II**) feature a hydroxyl group (X=O) a carbamate linkage is created, a thiol group (X=S) creates a thiocarbamate linkage whilst in those cases where X=N, a urea linkage is created. BOC deprotection under acidic conditions provides the free amines (**XXXIX**).

The following schemes indicate the methods used to synthesise linked payloads prior to attachment of the targeting moiety (the 'pre-conjugates').

General Scheme 4: Synthesis of linked payloads

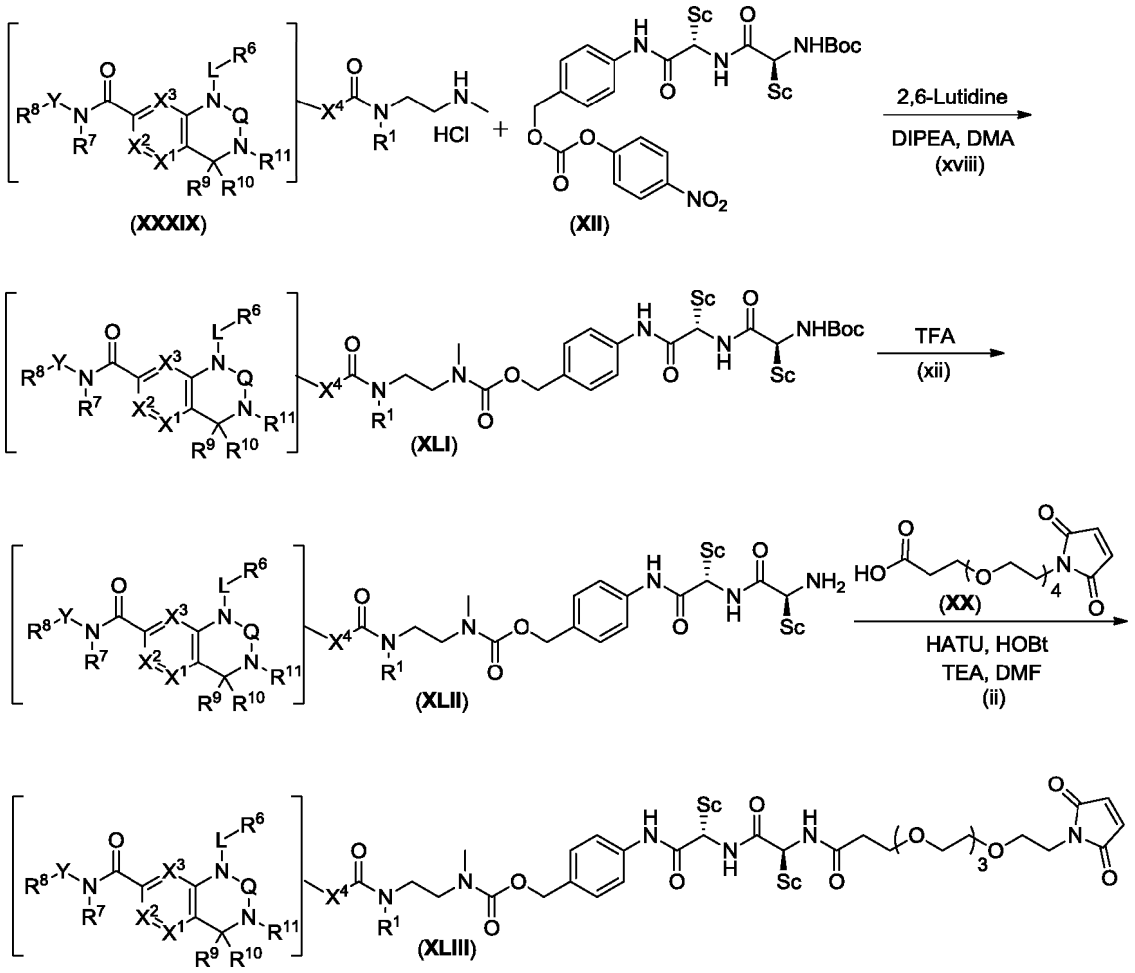
Compounds of formula (**XXXIX**) may be joined to compounds of formula (**XXIII**) with a base such as DIPEA, TEA or 2,6-lutidine in a suitable solvent such as DMF or DMA at room temperature. The free amines in (**XXXIX**) react through the p-nitrophenyl carbonate moiety to create a new carbamate linkage.



The resulting linked payloads (**XL**) may then be used directly to append the targeting moiety.

5 General Scheme 5: Synthesis of linked payloads

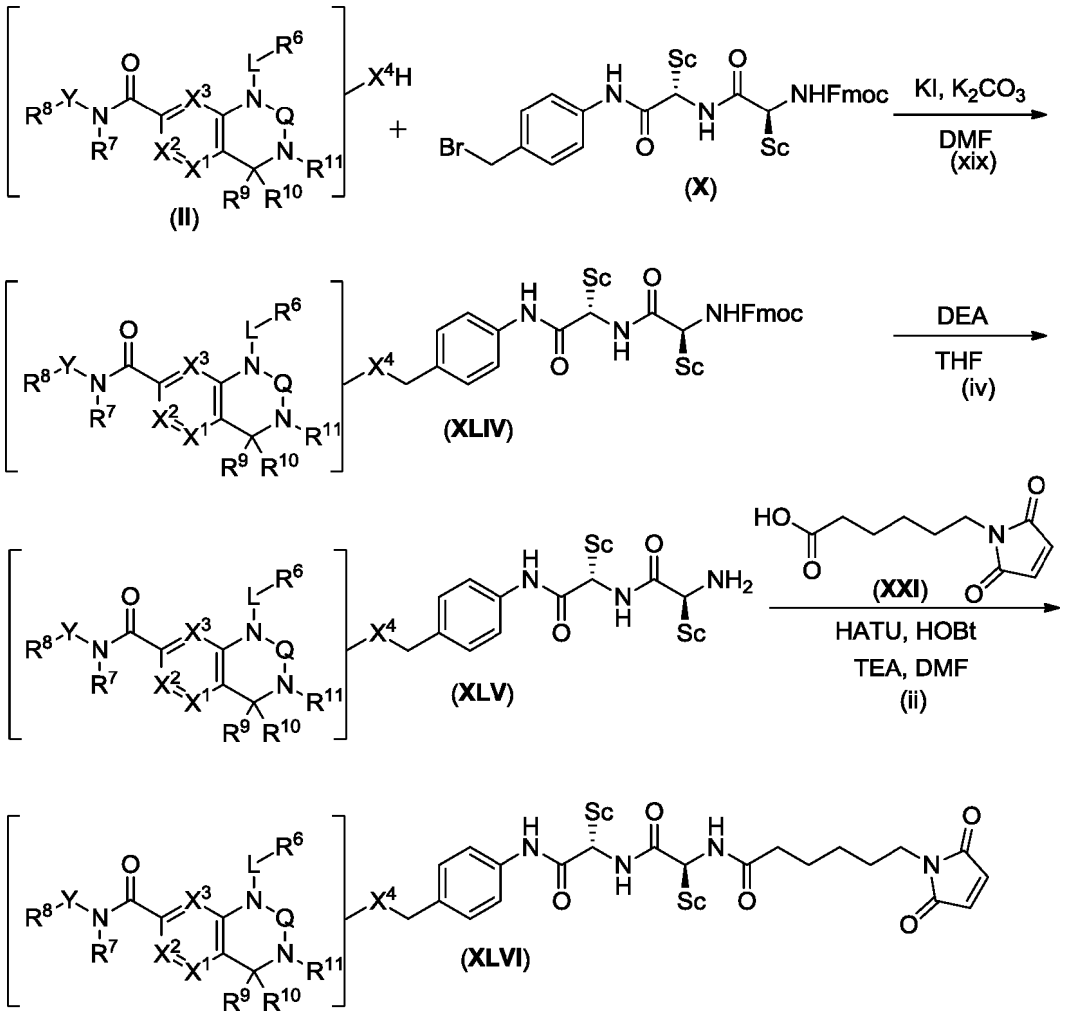
Analogously, compounds of formula (**XXXIX**) may be joined to compounds of formula (**XII**) under the same basic conditions in a polar solvent such as DMF or DMA.



The resulting BOC-protected carbamates (**XLI**) may be subjected to BOC deprotection with an acid reagent, for example TFA, HCl or HF to provide the free amines (**XLII**). Compounds of formula (**II**) may then be reacted with compounds of formula (**XX**) in a standard amide bond forming reaction using, for example, HATU, EDCI or HBTU in mixtures of an organic base and a polar solvent to give the fully linked payloads (**XLIII**) which may then be used directly to append the targeting moiety.

General Scheme 6: Synthesis of linked payloads

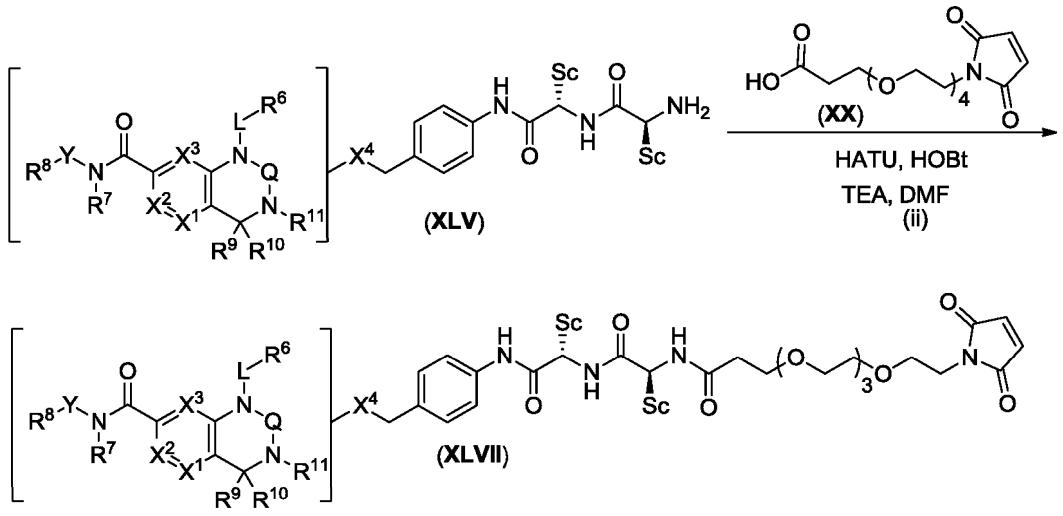
Compounds of formula (**II**) may be linked to compounds of formula (**X**) in which the nucleophilic function of (**II**), typically X=O, S or N, carries out a nucleophilic displacement reaction in the presence of a base such as potassium or sodium carbonate, optionally with an additive such as KI, in a polar solvent, for example DMF. The resulting compounds of formula (**XLIV**) were then subjected to Fmoc deprotection under mildly basic conditions to reveal the free amines (**XLV**).



Said amines may then be reacted with compounds of formula (**XXI**) in a standard amide bond forming reaction using, for example, HATU, EDCI or HBTU in mixtures of an organic base and a polar solvent to give the fully linked payloads (**XLVI**) which may then be used directly to append the targeting moiety.

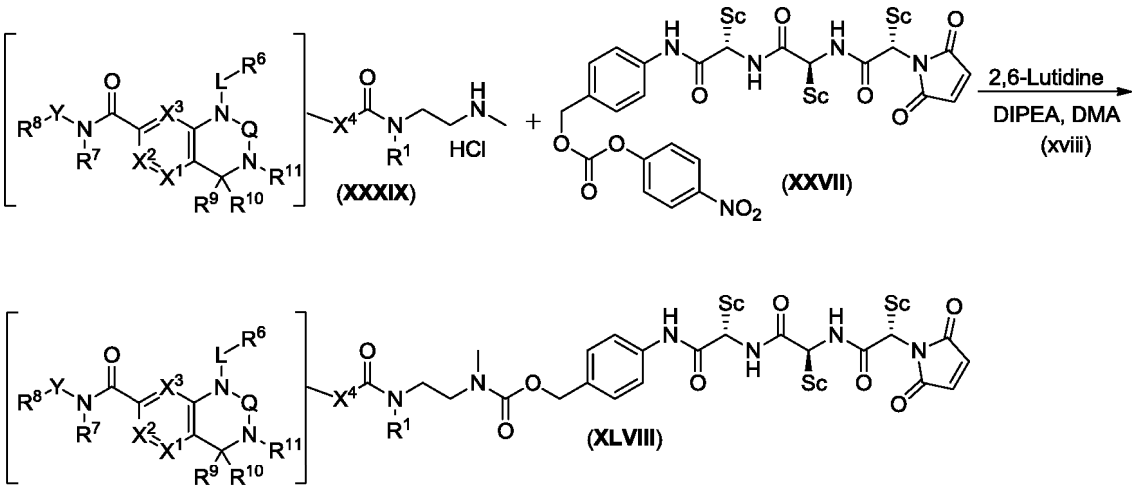
General Scheme 7: Synthesis of linked payloads

Analogously, amines of formula (**XLV**) may be reacted with compounds of formula (**XX**) in a standard amide bond forming reaction using, for example, HATU, EDCI or HBTU in mixtures of an organic base and a polar solvent to give the fully linked payloads (**XLVII**) which may then be used directly to append the targeting moiety.



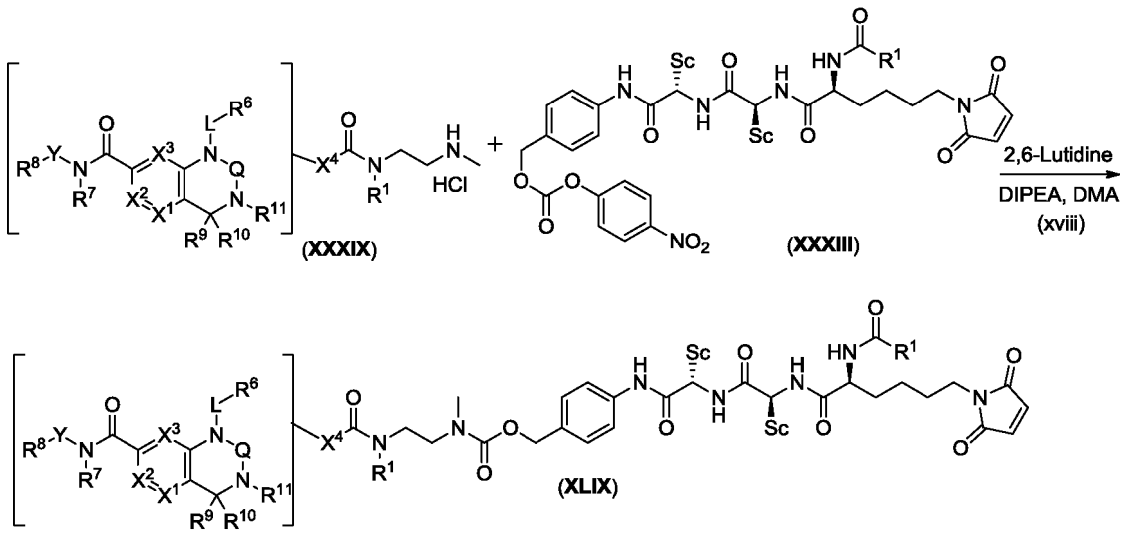
General Scheme 8: Synthesis of linked payloads

Analogously, ethylene diamines of formula (**XXXIX**) may be used in a displacement reaction with compounds of formula (**XXVII**) in the presence of a base and a polar solvent to give the carbamate fully linked payloads (**XLVIII**) which may then be used directly to append the targeting moiety.



General Scheme 9: Synthesis of linked payloads

Analogously, amines of formula (**XXXIX**) may be reacted with compounds of formula (**XXXIII**) in the presence of a base and a polar solvent to give the carbamate fully linked payloads (**XLIX**) which may then be used directly to append the targeting moiety.



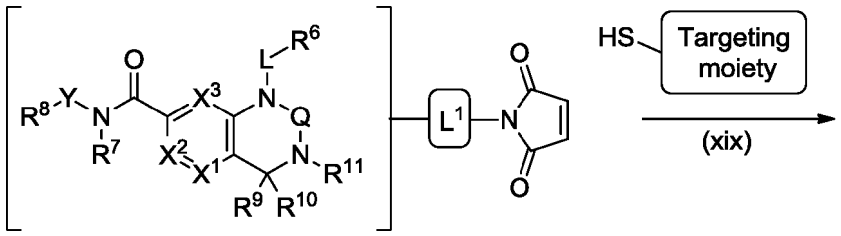
General Schemes for ADC Synthesis

The linked payloads (pre-conjugates) (**XL**), (**XLIII**), (**XLVI**), (**XLVII**), (**XLVIII**), (**XLIX**) depicted in the above schemes may then be used to prepare ADCs according to the scheme below.

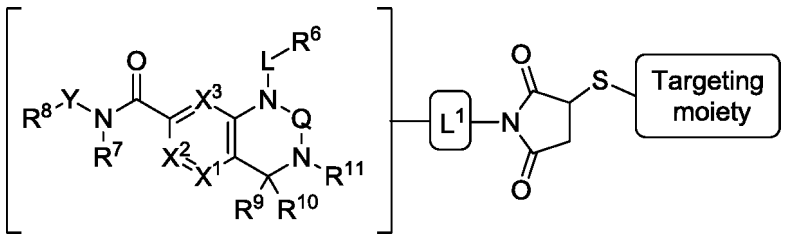
General Scheme 10: Synthesis of ADCs

Linked payloads (**XL**), (**XLIII**), (**XLVI**), (**XLVII**), (**XLVIII**) and (**XLIX**) were attached to a thiol-containing biomolecule using the following general method. The antibody or protein was first treated with between 2 and 3 equivalents of a suitable

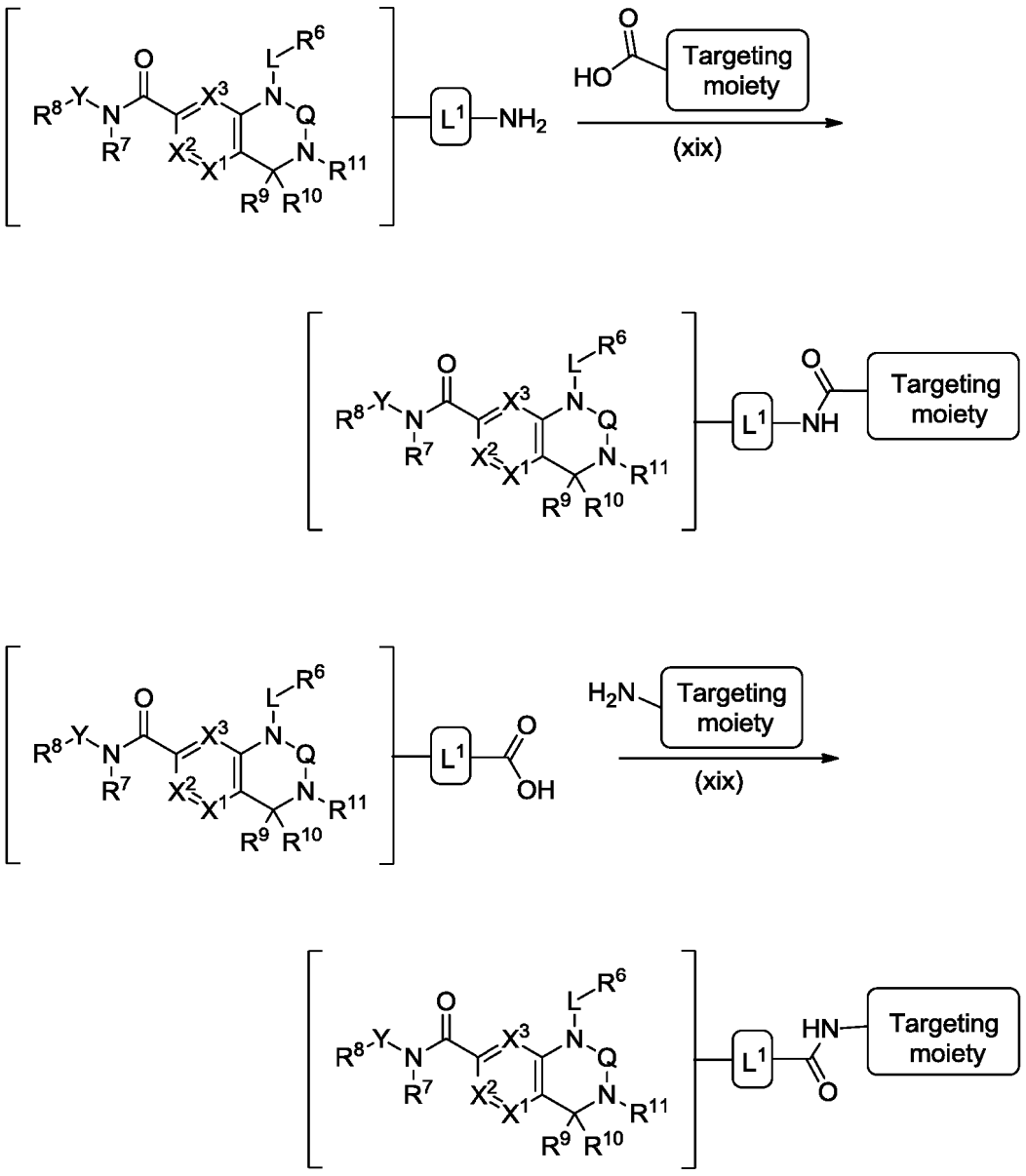
reducing agent such as TCEP (tris(2-carboxyethyl)phosphine), DTT (dithiothreitol) or BME (beta-mercaptoethanol) at between 25 and 50°C for 1 h at a concentration of between 2 and 10 mg/mL in a suitable solvent such as phosphate buffered saline or isopropanol in admixture with either sodium phosphate or ammonium sulfate to produce free thiol-containing antibody. Between 1 and 5 equivalents of linked payloads were then taken up in an aqueous buffer solution, for example phosphate-buffered saline, HEPES or TEN buffer, optionally with an organic co-solvent, for example DMF, DMA, polysorbate, ethylene glycol or propylene glycol and added to the reduced biomolecule solution and the whole stirred at room temperature for between 1 and 24 h. Analysis of the reaction mixture using hydrophobic interaction chromatography (HIC) and/or size exclusion chromatography (SEC) showed the progress of the reaction, with the presence of the conjugate and the drug-antibody ratio (DAR) confirmed by LC-MS and SDS-PAGE analysis. The final solution concentration was determined by a photometric method.



(XL), (XLIII), (XLVI), (XLVII), (XLVIII), (XLIX)



(L)



General Synthetic Procedures

Synthesis of STING modulators

The synthesis of the payloads of formula **II** of the invention have been described previously in PCT/GB2018/051730, IN201711021858, IN201811014462 and GB1709959.9.

General Purification and Analytical Methods

All final compounds prior to conjugation were purified by either Combi-flash or prep-HPLC purification, and analysed for purity and product identity by UPLC or LCMS according to one of the below conditions.

Prep-HPLC

Preparative HPLC was carried out on a Waters auto purification instrument using either a YMC Triart C18 column (250 x 20 mm, 5 µm) or a Phenyl Hexyl column (250 x 21.2 mm, 5 µm) operating at between ambient temperature and 50 °C with a flow rate of 16.0 – 50.0 mL/min.

Mobile phase 1: A = 20mM Ammonium Bicarbonate in water, B = Acetonitrile; Gradient Profile: Mobile phase initial composition of 80% A and 20% B, then to 60% A and 40% B after 3 min., then to 30% A and 70% B after 20 min., then to 5% A and 95% B after 21 min., held at this composition for 1 min. for column washing, then returned to initial composition for 3 min.

Mobile phase 2: A = 10mM Ammonium Acetate in water, B = Acetonitrile; Gradient Profile: Mobile phase initial composition of 90% A and 10% B, then to 70% A and 30% B after 2 min., then to 20% A and 80% B after 20 min., then to 5% A and 95% B after 21 min., held at this composition for 1 min. for column washing, then returned to initial composition for 3 min.

LCMS method

General 5 min method: Zorbax Extend C18 column (50 x 4.6 mm, 5µm) operating at ambient temperature and a flow rate of 1.2 mL/min. Mobile phase: A = 10 mM Ammonium Acetate in water, B = Acetonitrile; Gradient profile: from 90 % A and 10 % B to 70 % A and 30 B in 1.5 min, and then to 10 % A and 90 % B in 3.0 min, held at this composition for 1.0 min, and finally back to initial composition for 2.0 min.

UPLC method

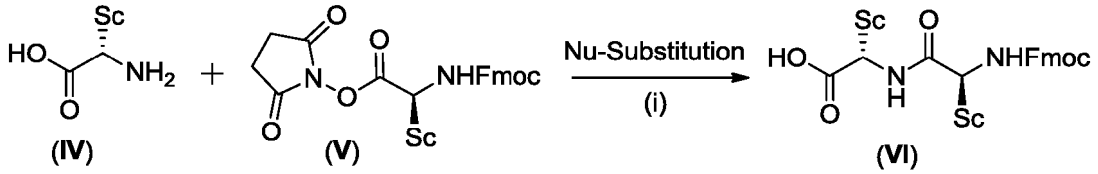
UPLC was carried out on a Waters auto purification instrument using a Zorbax Extend C18 column (50 x 4.6 mm, 5µm) at ambient temperature and a flow rate of 1.5ml/min.

Mobile phase 1: A = 5 mM Ammonium Acetate in water, B = 5 mM Ammonium Acetate in 90:10 Acetonitrile/water; Gradient profile from 95% A and 5% B to 65% A and 35% B

in 2 min., then to 10% A and 90% B in 3.0 min., held at this composition for 4.0 min. and finally back to the initial composition for 5.0 min.

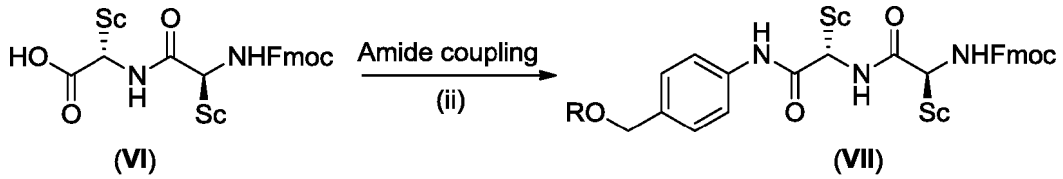
Mobile phase 2: A = 0.05 % formic acid in water, B = Acetonitrile; Gradient profile from 98 % A and 2 % B over 1 min., then 90 % A and 10 % B for 1 min., then 2 % A and 98 % B for 2 min. and then back to the initial composition for 3 min.

General Procedure 1



To a stirred solution of a protected amino acid ester (**V**) (22.9 mmol, 1.0 eq.) in dimethoxyethane (0.45 mL/mmol) was added an amino acid compound of formula (**IV**) (1.04 eq.) followed by an aqueous $NaHCO_3$ solution (1.05 eq. 2.5 mL water/mmol). The resulting reaction mixture was further diluted with THF (5 mL/mmol) and stirred at RT for 35-40 h. After completion of the reaction (monitored by TLC and UPLC-MS), it was acidified to pH 1 by the addition of 2N HCl solution at 0-5 °C. The aqueous mixture was then extracted with a mixture of 10% IPA in EtOAc. The obtained organic layer was washed with water and the water layer was again extracted with a mixture of 10% IPA in EtOAc. The combined organic layers were further washed with brine solution and concentrated under reduced pressure to dryness to afford a white solid material, which was purified by trituration with Et_2O to give a dipeptide compound of formula (**VI**) (85-90% yield) as a white solid.

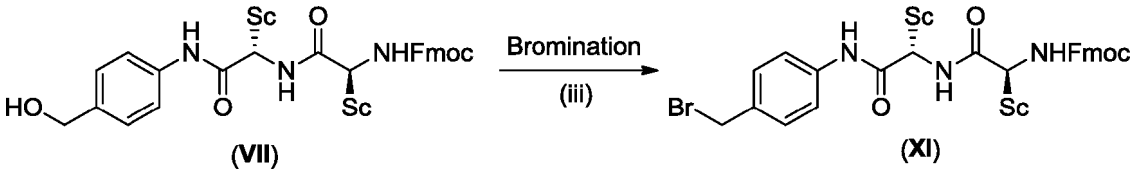
General Procedure 2



To a stirred suspension of a compound of formula (**VI**) (22.0 mmol, 1.0 eq.) in a mixture of suitable solvents such as DCM/MeOH or DMF/THF (2:1, 10 mL/mmol) was added p-aminobenzyl alcohol (3.0 eq.) followed by a coupling reagent such as EEDQ (2.0 eq.), HATU-HOAt, EDCI-HOBt or HBTU-HOBt (1.0 eq) at RT. The preferred organic base DIPEA or TEA (2.0 eq.) was used in all cases except with EEDQ. The reaction mixture was stirred at 35-40 °C for 12-16 h. The progress of the reaction was

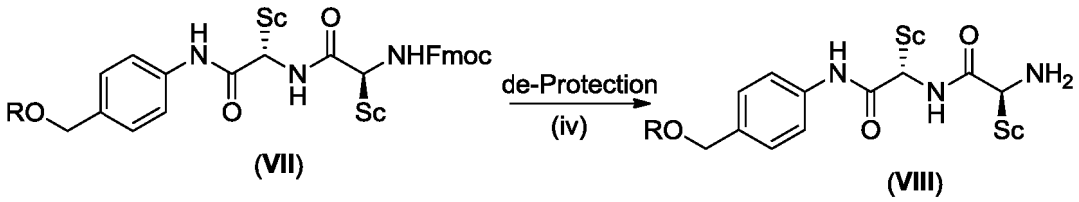
monitored by TLC and UPLC-MS and after complete consumption of starting material the reaction mixture was filtered and washed repeatedly with a mixture of EtOAc/MTBE (5:2, 23 mL/mmol). The resulting solid material was dried in an oven to afford a compound of formula (**VII**) (70-75% yield) as an off white solid. A similar procedure can be followed to synthesize all amides of formula (**VII**).

General Procedure 3



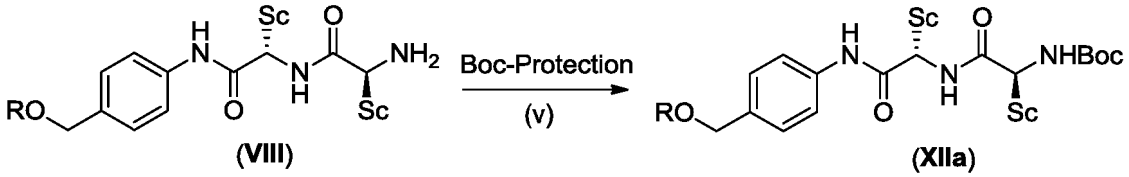
To a stirred suspension of a compound of formula (**VII**) (4.985 mmol, 1.0 eq.) in DCM (12 mL/mmol) was added $POBr_3$ or PBr_3 (2.5 eq.) dropwise under a N_2 atmosphere at 0-5 °C and the whole then allowed to warm slowly to RT. The resulting reaction mixture was stirred at RT for 12-16 h. Progress of the reaction was monitored by UPLC-MS and after completion the reaction mixture was suspended in a cold saturated solution of $NaHCO_3$ and stirred vigorously for 10-20 min. The resulting precipitate was filtered off to afford a solid material which was dried in a rotary evaporator and then purified by trituration with diethyl ether or MTBE to afford a compound of formula (**XI**) (purity 58-65%) as a light yellow solid.

General Procedure 4



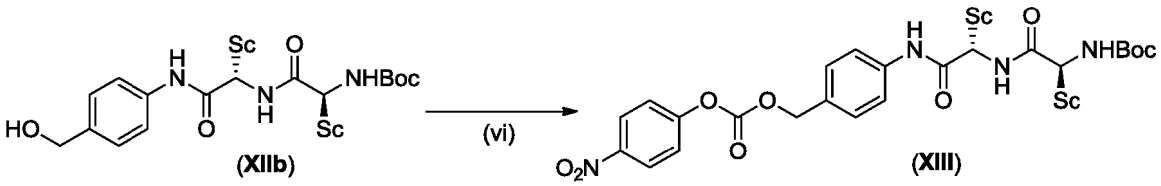
To a stirred solution of a compound of formula (**VII**) (1.33 mmol) in DMF or THF (12 mL/mmol) was added diethylamine, piperidine, dimethylamine, DIPEA or TEA (12 mL/mmol) at RT and the resulting reaction mixture was stirred at RT for 14-16 h. Progress of the reaction was monitored by TLC and UPLC-LC and after completion of the reaction the solvents were evaporated under reduced pressure to give a crude solid which was purified by trituration with diethyl ether to afford a compound of formula (**VIII**) (85-90% yield) as a white solid which was used in the next step without any further purification.

General Procedure 5



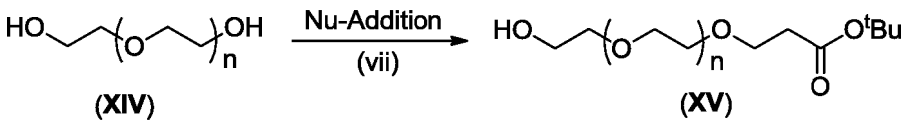
To a stirred solution of compound of formula (**VIII**) (2.23 mmol, 1.0 eq.) in DCM (10 mL/mmol) was added triethylamine (2.5 eq.) at 0-5 °C and the resulting reaction mixture was stirred at the same temperature for 5-10 min. then Boc_2O 1.2 eq.) was added and the temperature was slowly raised to RT and the whole stirred for 10-12 h. Progress of the reaction was monitored by TLC and UPLC-MS and after completion; the reaction mixture was diluted with EtOAc) and washed with a saturated solution of $NaHCO_3$ followed by water and brine (25 mL). The organic layer was dried over anhydrous Na_2SO_4. The dried organic layer was evaporated under reduced pressure to give a compound of formula (**XIIa**) (yield 90-100%) as crude which was taken into the next step without any further purification.

General Procedure 6



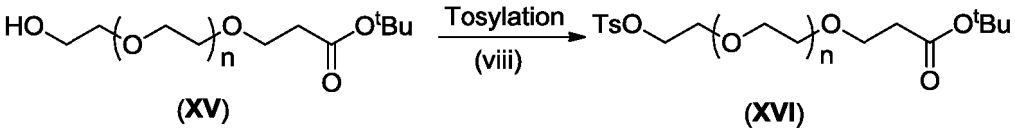
To a stirred solution of a compound of formula (**XIIb**) (1.96 mmol, 1.0 eq.) in DMF (2.5 mL/mmol) was added DIPEA (7.0 eq.) followed by p-nitrophenylchloroformate (4.0 eq.) at RT and the mixture maintained at this temperature for 10-14 h. Progress of the reaction was monitored by TLC and UPLC-MS and after completion the reaction mixture was diluted with EtOAc and washed with water followed by brine and dried over anhydrous Na_2SO_4. The dried organic layer was evaporated under reduced pressure to give a crude product which was purified by trituration using Et_2O to produce a compound of formula (**XIII**) (yield 82-87%) as a white solid.

General Procedure 7



To a stirred solution of a compound of formula (**XIV**) (298.3 mmol, 1.0 eq.) in dry THF, EtOH or DMF (0.5 mL/mmol) was added sodium metal (0.01 eq.) under a N_2 gas atmosphere at -5 to -10 °C and the reaction mixture stirred at this temperature for 1-2 h until complete dissolution of the Na metal. *tert*-Butyl acrylate (0.35 eq.) was then added at RT and the mixture was further stirred for 15-20 h. The progress of the reaction was monitored by UPLC-MS and after completion the reaction mixture was quenched with 1N HCl (pH = 6). The solvent was distilled off and the residue was diluted with brine solution. The organics were extracted with EtOAc and the combined organic layers were dried over anhydrous Na_2SO_4, concentrated under reduced pressure to dryness to give a crude product which was purified by column chromatography on silica gel using a mixture of 2-5% MeOH/DCM as the solvent system to give a compound of formula (**XV**) (20-25% yield) as a brown liquid.

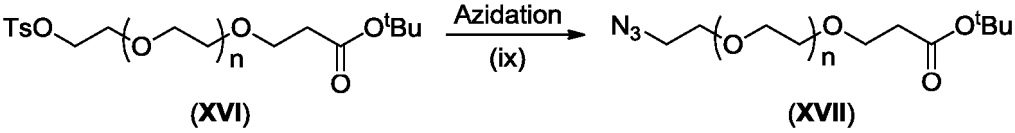
General Procedure 8



(**XV**) (**XVI**)

To a stirred solution of a compound of formula (**XV**) (62.03 mmol, 1.0 eq.) in anhydrous THF, EtOH or DCM (5 mL/mmol) was added TEA or DIPEA (1.5 eq.) under a N_2 atmosphere at RT. The reaction mixture was cooled to 0-5 °C and then tosyl chloride added (1.5 eq.) portion-wise. After the addition was complete, the reaction mixture was stirred at RT for 30-36 h. The reaction was monitored by UPLC-MS and after completion the reaction mixture was quenched with water and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated to obtain a crude compound which was then purified by column chromatography on silica gel using 50% EtOAc in hexane as eluent to afford a compound of formula (**XVI**) (90-95% yield) as a colourless liquid.

General Procedure 9

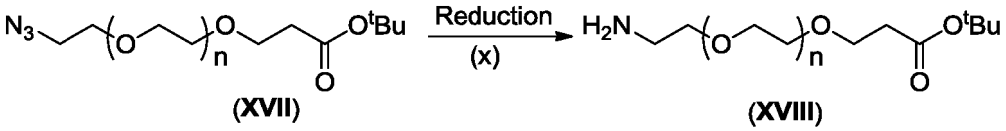


(**XVI**) (**XVII**)

To a stirred solution of a compound of formula (**XVI**) (58.7 mmol, 1.0 eq.) in anhydrous THF or DMF (5.1 mL/mmol) was added NaN_3 (3.5 eq.) under a N_2 atmosphere at RT, then the reaction was stirred at RT overnight. The reaction was

monitored by UPLC-MS and after completion the reaction mixture was quenched with water and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a compound of formula (**XVII**) (100 % yield) as a pale yellow liquid which was pure enough to use in the next step without any further purification.

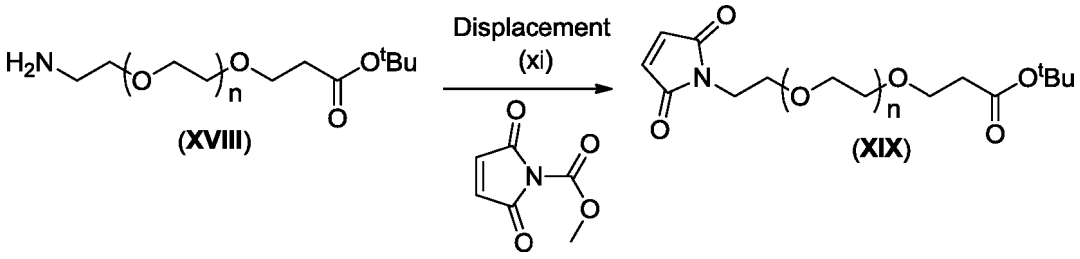
General Procedure 10



(**XVII**) (**XVIII**)

To a stirred solution of a compound of formula (**XVII**) (14.41 mmol, 1.0 eq.) in methanol or EtOAc (3.5 mL/mmol) was added 10% Pd/C (70 mg/mmol, 50 % w/w in water) at RT under a N_2 gas atmosphere. The resulting reaction mixture was stirred under H_2 gas balloon pressure at RT for 3-5 h. After completion of the reaction (monitored by TLC using ninhydrin stain and UPLC-MS) the mixture was filtered through a celite bed under a N_2 atmosphere and washed with excess solvent used in the reaction. The filtrate was evaporated under reduced pressure to afford a compound of formula (**XVIII**) (95-98% yield) as a colourless liquid which was pure enough to use in the next step without any further purification.

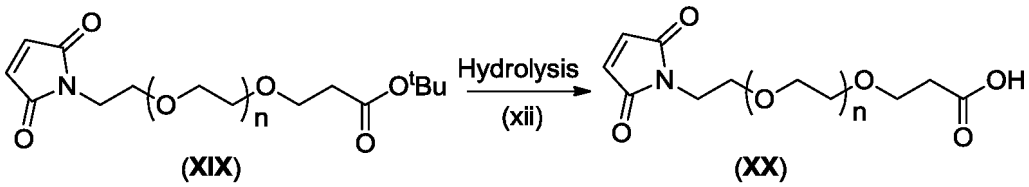
General Procedure 11



(**XVIII**) (**XIX**)

To a stirred solution of a compound of formula (**XVIII**) (15.5 mmol, 1.0 eq.) in a saturated solution of $NaHCO_3$ (3.2 mL/mmol) was added commercially available methyl-2,5-dioxo-2,5-dihydro-1H-pyrrole-1-carboxylate (1.2 eq.) at RT. The resulting reaction mixture was further stirred at RT for 2-3 h. After completion of the reaction (monitored by TLC using I_2 stain and UPLC-MS), it was then extracted with DCM and the combined organics were dried over Na_2SO_4, filtered and evaporated to give a crude product which was purified by column chromatography on silica gel using a mixture of EtOAc and hexane as the mobile phase to give a compound of formula (**XIX**) (25-30% yield) as a colourless liquid.

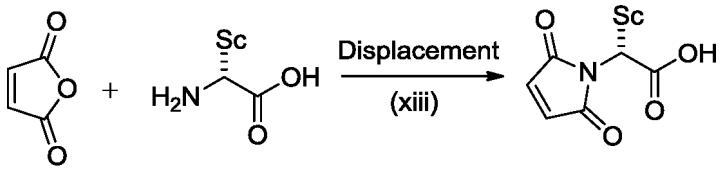
General Procedure 12



(XIX) (XX)

To a stirred solution of a compound of formula (**XIX**) (2.5 mmol, 1.0 eq.) in anhydrous THF or DCM (4 mL/mmol) was added TFA (0.8 mL/mmol) dropwise at 0-5 °C under an inert atmosphere and the reaction then stirred at RT for 3-5 h. The progress of the reaction was monitored by TLC (stained in bromocresol green) and UPLC-MS. After completion of the reaction the solvent was evaporated under reduced pressure to give a residue. Final traces of TFA were removed by co-distillation using acetonitrile and DCM to afford a crude product which was subjected to high vacuum drying to give a compound of formula (**XX**) (90-95% yield) as a colourless liquid.

General Procedure 13

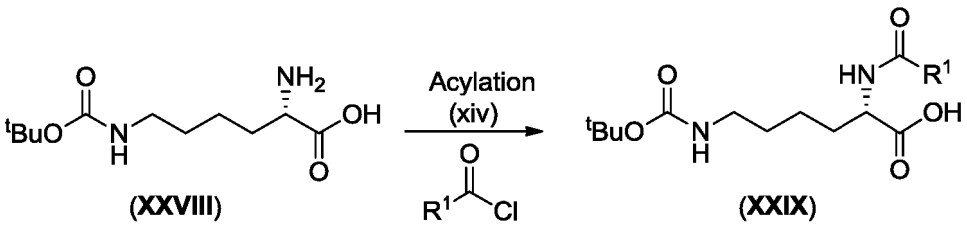


(XXIV) (IV) (XXV)

A solution of a compound of formula (**IV**) (1.39 g, 1.0 eq.) and (**XXIV**) (1.0 eq.) in acetic acid (1 ml/mmol) was stirred at room temperature for 3-5 h. Formation of maleic acid intermediate was confirmed by UPLC-MS. Reaction mixture was then concentrated under reduced pressure to give oil which was precipitated by adding CH2Cl3/hexane (8 ml/mmol 1:1, v/v). This material was then suspended in toluene (9 ml/mmol) followed by the addition of DMA (0.3 ml/mmol) and triethylamine (3.0 eq.). The resulting mixture was stirred at 40–60 °C under N2 until all material was in solution. The flask was then equipped with a condenser and the solution was refluxed at 120-125 °C for 4-5 h over molecular sieves. The completion of the reaction was confirmed by UPLC-MS showing fully formation of the compound of formula (**XXV**). The reaction mixture was filtered on celite pad through a sintered glass funnel and concentrated to near dryness under reduced pressure. The residue was dissolved in ethyl acetate, washed with 10% citric acid in water and brine. The organic layer was dried over anhydrous sodium sulphate, concentrated under reduced pressure and dried

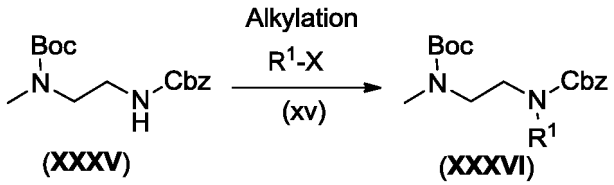
under high vacuum for overnight to give compound of formula (**XXV**) (40-45%) as a pale brown viscous oil which was used in the next step without any further purification.

General Procedure 14



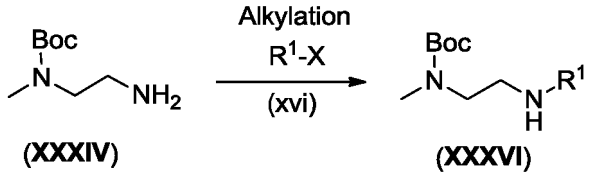
To a stirred solution of a compound of formula (**XXVIII**) (4.065 mmol, 1.0 eq.) in THF (2.5 mL/mmol) was added K_2CO_3 (5.0 eq., aqueous solution of 2.5 mL/mmol) and after a few minutes, an acylating agent Z-COCl (1.2 eq.) was added at 0-5 °C. The resulting reaction mixture was stirred at RT for 2-6 h. Progress of the reaction was monitored by UPLC-MS and after completion the organic solvent was evaporated under reduced pressure to give an aqueous residue which was acidified to pH 2-3 with 2N HCl. The product was extracted with EtOAc, washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give a compound of formula (**XXIX**) (90-95% yield) as a light yellow solid which was used in the next step without any further purification.

General Procedure 15



To a stirred solution of a compound of formula (**XXXV**) (29.221 mmol, 1.0 eq.) and R^1-X (1.5 eq.) in THF or DMF (3 mL/mmol) was added NaH (1.2 eq.) under an inert atmosphere at 0-5 °C. The cooling bath was removed and the temperature allowed to rise to RT. The reaction mixture was then further stirred at RT for 1-2 h. Progress of the reaction was monitored by UPLC-MS or TLC and after completion the reaction mixture was diluted with water and extracted with EtOAc, washed with brine solution, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to afford the crude product which was purified by combi-flash to give a compound of formula (**XXXVI**) (yield 80-87%) as a colourless oil.

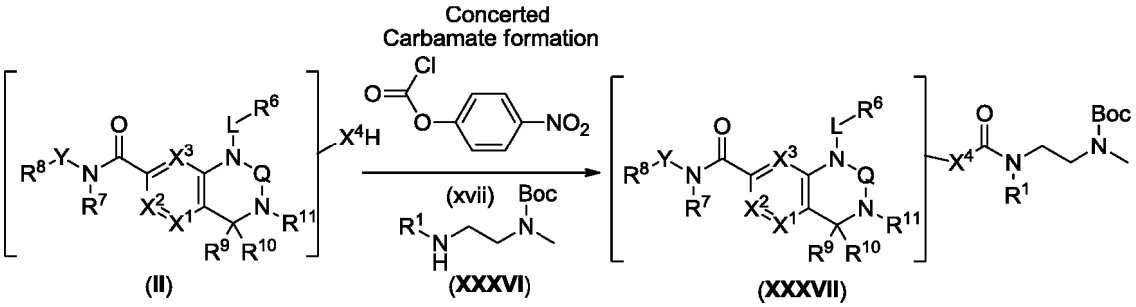
General Procedure 16



(XXXIV) (XXXVI)

To a stirred solution of a compound of formula (**XXXIV**) (29.185 mmol, 1.0 eq.) and R^1-X (1.5 eq.) in THF or DMF (3 mL/mmol) was added NaH (1.1 eq.) under an inert atmosphere at 0-5 °C. The cooling bath was removed and the temperature allowed rising slowly to RT. The reaction mixture was then further stirred at RT until completion of the reaction was confirmed by UPLC-MS or TLC. The reaction mixture was diluted with water and extracted with EtOAc, washed with brine solution, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to afford the crude product which was purified by combi-flash to give a compound of formula (**XXXVI**) (yield 80-85%) as a colourless oil.

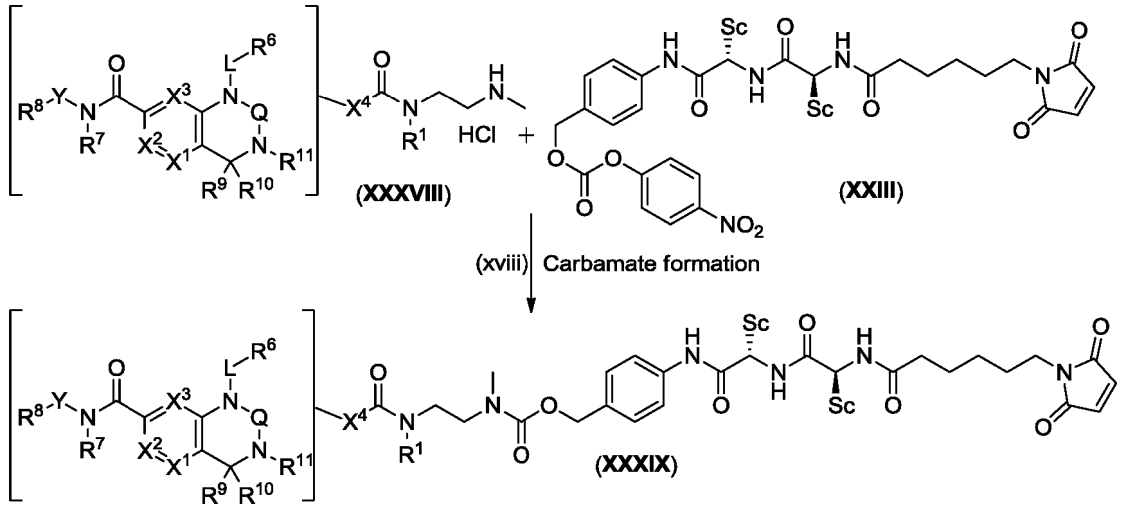
General Procedure 17



To a stirred solution of a compound of formula (**II**) (9.59 mmol, 1.0 eq.) in DMF or THF (5.2 mL/mmol) was added DIPEA (9.6 eq.) followed by p-nitrophenylchloroformate (1.6 eq.) at 0-5 °C under an inert atmosphere. The resulting reaction mixture was stirred at 0-5 °C for 20-30 min. and after complete consumption of a compound of formula (**II**) (monitored by UPLC-MS) a compound of formula (**XXXVI**) (2.5 eq.) was then added at RT. The resulting reaction mixture was stirred at RT for 1 h. Progress of the reaction was monitored by UPLC-MS and after completion the reaction mixture was diluted with water and extracted with EtOAc, the organic layer was separated, washed with 1N HCl followed by 10% $NaHCO_3$ solution and finally with brine. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give a crude mass which was vigorously stirred with Et_2O followed

by n-hexane and dried under vacuum to afford a compound of formula (**XXXVII**) (yield 55-60%) as a white solid.

General Procedure 18



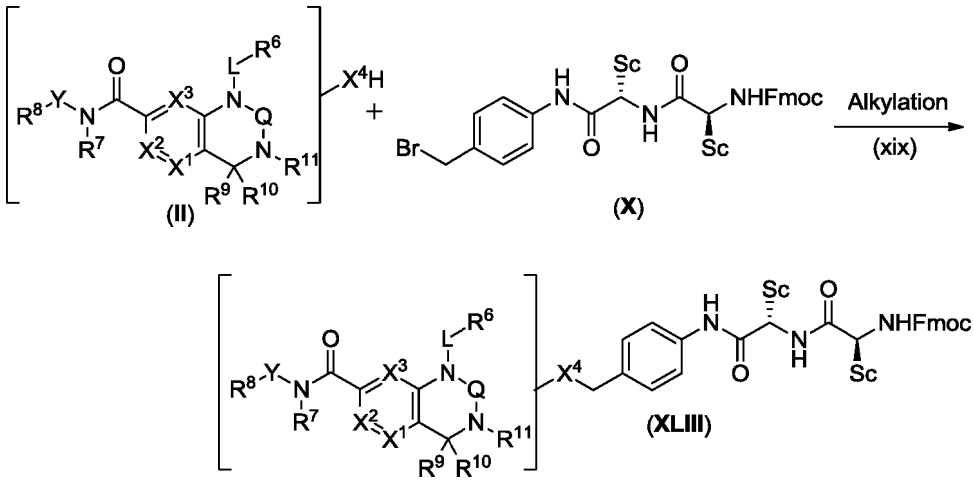
Option a:

To a stirred solution of a compound of formula (**XXIII**) (0.678 mmol, 1.0 eq.) and a compound of formula (**XXXVIII**) (2.0 eq.) in DMA (15 mL/mmol) were added 2,6-lutidine (1.0 eq.) and DIPEA (1.0 eq.) at 0-5 °C. The temperature of the reaction mixture was allowed to rise to RT. Progress of the reaction was monitored by UPLC-MS and after completion the reaction mixture was diluted with Et_2O and left for another 30 min. to 1 h without stirring to give a gummy material. The solvents were decanted and the residue was purified by prep-HPLC to afford a compound of formula (**XXXIX**) (yield 5-10%) as a white solid.

Option b:

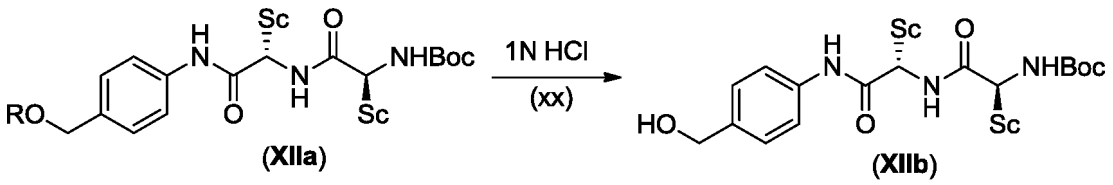
To a stirred solution of compound of formula (**XXIII**) (300 mg, 1.0 eq) in DMF (7 mL/mmol) was added compound of formula (**XXXVIII**) (1.5 eq.) at RT and after 5-10 min of stirring DIPEA (2.0 eq.) was added to this reaction mixture. The reaction was continued for till completion at RT. Progress of the reaction was monitored by UPLC-MS and after completion; the reaction mass was diluted with Et_2O and kept for few minutes without stirring to settle the gummy material then Et_2O was decanted and the crude was purified by prep-HPLC to give compound of formula (**XXXIX**) (yield 5-10%) as a white solid.

General Procedure 19



To a stirred solution of a compound of formula (**II**) (2.111 mmol, 1.0 eq.) in anhydrous DMF (13 mL/mmol) was added NaH (6.0 eq., 60% suspension in mineral oil) followed by KI (0.1 eq.) under a N_2 atmosphere at 0-5 °C. The resulting reaction mixture was further treated with a compound of formula (**X**) (2.0 eq.). The combined reaction mixture was stirred at RT and after completion (monitored by UPLC-MS) of the reaction the reaction mixture was poured into a cold saturated solution of K_2CO_3 and stirred for a further few minutes. The solid was filtered off in a Buchner funnel and washed with excess water to give a crude product which was further purified by slurry wash with water followed by hexane and Et_2O to afford a compound of formula (**XLIII**) (yield 75-80%) as a white solid.

General Procedure 20



To a stirred solution of a compound of formula (**XIIa**) (2.27 mmol, 1.0 eq.) in THF (10 mL/mmol) was added 1N HCl (2 mL/mmol) at RT and the resulting reaction mixture was stirred overnight. Progress of the reaction was monitored by TLC and UPLC-MS and after completion the reaction mixture was diluted with EtOAc and washed with a saturated solution of $NaHCO_3$ followed by water, brine and dried over anhydrous Na_2SO_4. The dried organic layer was evaporated under reduced pressure to give a crude product which was purified by trituration using Et_2O to give a compound of formula (**XIIb**) (yield 82-90%) as a white solid.

General antibody conjugation method

Linked payloads were attached to a thiol-containing antibody using the following general method. The antibody was first treated with between 2 and 3 equivalents of TCEP at between 25 and 50°C for 1 h at a concentration of between 2 and 10 mg/mL in a suitable solvent such as phosphate buffered saline or isopropanol in admixture with either sodium phosphate or ammonium sulfate to produce free thiol-containing antibody. Between 1 and 5 equivalents of a pre-conjugate in which the linker group comprises a maleimide functional group were then added in a suitable co-solvent such as DMF or propylene glycol, and the whole stirred at room temperature for between 1 and 24 h. Analysis of the reaction mixture using hydrophobic interaction chromatography (HIC) and/or size exclusion chromatography (SEC) showed the progress of the reaction, with the presence of the conjugate and the drug-antibody ratio (DAR) confirmed by LC-MS and SDS-PAGE analysis. The final solution concentration was determined by a photometric method.

HIC method

Analytical HIC was carried out using a TOSOH TSKgel Butyl-NPR column (4.6 mm x 3.5 cm, 2.5 µm), connected to a Dionex Ultimate 3000 UPLC system. The mobile phase was buffer A: 1.5 M ammonium sulfate, 50 mM sodium phosphate, pH 7.0. A linear gradient (10-100% B in 10.5 min) was applied using Buffer B (20 % isopropanol, 50 mM sodium phosphate, pH 7.0) at a flow rate of 1.35 mL/min to elute bound species. The column was maintained at 30 °C throughout the analysis. The analysis was carried with UV detection at 280 nm and 248 nm. 10 µg of ADC were injected for analysis. The percentage of each DAR species was calculated by comparing the peak areas of each assigned peak with total peak area. Average DAR was calculated as a weighted average of peak areas.

SEC method

Analytical SEC (size exclusion chromatography) was carried out using an ACQUITY UPLC BEH 200 SEC column (4.6 mm x 15 cm, 200 Å, 1.7 µm) and guard column (4.6 mm x 3 cm), connected to a Dionex Ultimate 3000 UPLC system. The mobile phase was 0.2 M potassium phosphate buffer, pH 6.8, 0.2 M potassium chloride, 15% (v/v) isopropanol. The flow rate was kept constant at 0.35 mL/min. The column was maintained at 30 °C throughout the analysis. The analysis was carried out in a 10 min isocratic elution with UV detection at 280 nm. 10 µg of ADC were injected for analysis.

The percentage of high molecular weight (HMW) species was calculated by comparing the peak area corresponding to HWM species to total peak area corresponding to HWM and monomeric species.

LC-MS analysis

LC-MS analysis was carried out using a Waters XEVO G2S TOF mass spectrometer and a POROSHELL 300SBC3 column (2.1 x 12.5 mm, 5 µm) connected to a Waters Acquity H Class UPLC system. The mobile phase was buffer A (0.1 % formic acid in water). A gradient (2.5 min 10% B, 10-80% B gradient in 3.5 min) was applied using Buffer B (acetonitrile, 0.1 % formic acid) at a flow rate of 0.6 mL/min and column temperature of 60 °C. Maleimide ADCs were analysed after reduction (10 mM DTT, 1 h at 40 °C) and then diluted to 0.02 mg/mL with PBS. 10 µL of diluted ADC solution were injected for analysis.

SDS-PAGE analysis

SDS-PAGE analysis was carried out using NuPAGE® 4-12% Bis-Tris gels (Invitrogen) under non-reducing conditions with MES buffer. Prior to analysis, samples were incubated at 40 °C for 1h in 10% SDS solution. For analysis, 1 µg of ADC sample (based on protein) was loaded onto the gel per lane. Electrophoresis was carried out at 200 V for 35 min. The gels were stained with InstantBlue™ (Expedeon) for protein detection and analysed using ImageQuant™ imaging equipment (GE Healthcare).

Solution concentration method

The concentration of the conjugate (based on protein) was determined by UV absorbance at 280 nm (A280) using a Nanodrop spectrophotometer. The extinction coefficient used was the extinction coefficient of the antibody (for example, for Trastuzumab ε280 = 1.480 mL/(mg.cm)). Measurements were taken in triplicate and the average value was used to determine the conjugate concentration:

$c = Abs / \varepsilon.l$

Where: c = concentration (mg/mL)

Abs = absorbance at 280 nm

ε = extinction coefficient (mL/(mg.cm))

l = length (cm)

Examples

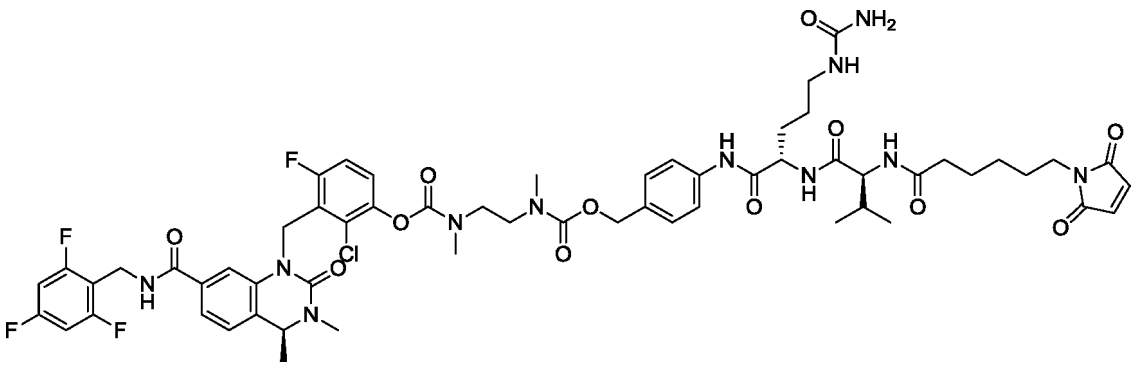
Nuclear magnetic resonance (NMR) spectra were in all cases consistent with the proposed structures. Characteristic chemical shifts (δ) are given in parts-per-million downfield from tetramethylsilane (for ^{1}H-NMR) and up-field from trichloro-fluoro-methane (for ^{19}F NMR) using conventional abbreviations for designation of major peaks: e.g. s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. The following abbreviations have been used for common solvents: CDCl4, deuterochloroform; d_6-DMSO, deuterodimethylsulphoxide; and CD_3OD, deuteromethanol.

Mass spectra, MS (m/z), were recorded using electrospray ionisation (ESI). Where relevant and unless otherwise stated the m/z data provided are for isotopes ^{19}F, ^{35}Cl, ^{79}Br and ^{127}I.

All chemicals, reagents and solvents were purchased from commercial sources and used without further purification. All reactions were performed under an atmosphere of nitrogen unless otherwise noted.

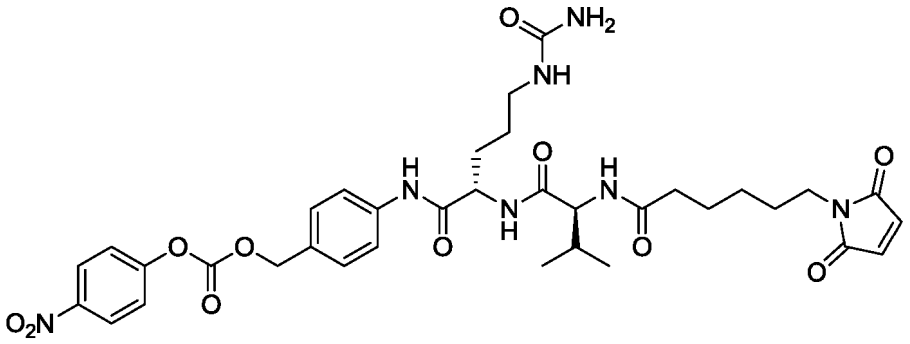
Flash column chromatography was carried out using pre-packed silica gel cartridges in a Combi-Flash platform. Prep-HPLC purification was carried out according to the General purification and analytical methods described above. Thin layer chromatography (TLC) was carried out on Merck silica gel 60 plates (5729). All final compounds were >95% pure as judged by the LCMS or UPLC analysis methods described in the General purification and analytical methods above unless otherwise stated.

Example 7: 2-Chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenyl 4-((S)-2-((S)-2-(6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanamido)-3-methylbutanamido)-5-ureidopentanamido)benzyl ethane-1,2-diylbis(methylcarbamate)

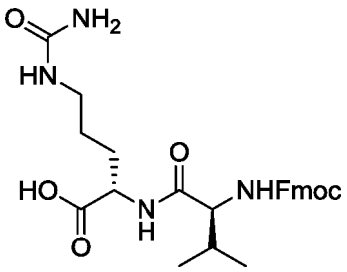


Example 7 was prepared according to the methods described in General Procedures 1,2, 4, 6, 10, 12, 15, 17-18 and the methods described below

Preparation-1: 4-((S)-2-((S)-2-(6-(2,5-Dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanamido)-3-methylbutanamido)-5-ureidopentanamido)benzyl (4-nitrophenyl) carbonate



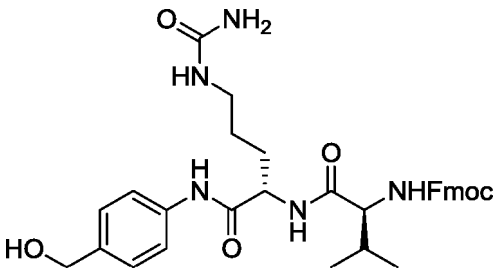
Step 1: (S)-2-((S)-2-((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)-3-methylbutanamido)-5-ureidopentanoic acid



To a stirred solution of (S)-2,5-dioxopyrrolidin-1-yl 2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-methylbutanoate (Fmoc-Val-OSu) (10.0 g, 0.023 mol) in dimethoxyethane (10 mL) was added (S)-2-amino-5-ureidopentanoic acid (citrulline) (4.21 g, 0.024 mol) followed by an aqueous $NaHCO_3$ solution (2.02 g in 60 mL water). The resulting reaction mixture was further diluted with THF (120 mL) and stirred at RT for 40 h. After completion of the reaction (monitored by TLC and UPLC-

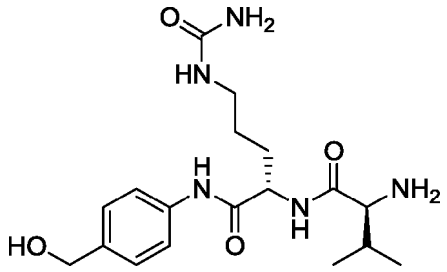
MS), it was acidified to pH 1 by the addition of 2N HCl solution at 0-5 °C . The aqueous mixture was extracted with a mixture of 10% IPA in EtOAc (500 mL). The obtained organic layer was washed with water (100 mL) and the water layer was again extracted with a mixture of 10% IPA in EtOAc (250 mL). The combined organic layers were further washed with brine solution (2 x 100 mL) and concentrated under reduced pressure to dryness to afford a white solid material, which was purified by trituration with diethyl ether to give the title compound (10.0 g, 0.02 mol and yield 87.8%) as a white solid. LCMS m/z: 497 [M+H].

Step 2: (9H-Fluoren-9-yl)methyl ((S)-1-(((S)-1-((4-(hydroxymethyl)phenyl)amino)-1-oxo-5-ureidopentan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate



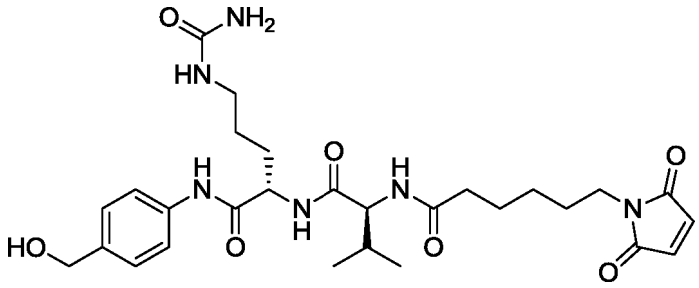
To a stirred suspension of (S)-2-((S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-methylbutanamido)-5-ureidopentanoic acid (Step 1) (11.0 g, 0.022 mol) in a mixture of DCM and MeOH (2:1, 220 mL) was added p-aminobenzyl alcohol (8.18 g, 0.066 mol) followed by EEDQ (10.96 g, 0.044 mol) at RT. The reaction mixture was stirred at 40 °C for 12 h. The progress of the reaction was monitored by TLC and UPLC-MS and after complete consumption of the starting material the reaction mixture was filtered and washed repeatedly with a mixture of EtOAc and MTBE (5:2, 500 mL). The resulting solid material was dried in an oven to afford the title compound (9.5 g, 0.019 mol and yield 71.8%) as an off white solid. LCMS m/z: 602 [M+H].

Step 3: (S)-2-((S)-2-Amino-3-methylbutanamido)-N-(4-(hydroxymethyl)phenyl)-5-ureidopentanamide



To a stirred solution of (9H-fluoren-9-yl)methyl ((S)-1-(((S)-1-((4-(hydroxymethyl)phenyl)amino)-1-oxo-5-ureidopentan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (Preparation 1; Step 2) (0.8 g, 0.001 mol) in THF (16 mL) was added diethylamine (16 mL) at RT and the resulting reaction mixture was stirred at RT for 16 h. Progress of the reaction was monitored by TLC and UPLC-LC and after completion the solvents were evaporated under reduced pressure to give a crude solid which was purified by trituration with diethyl ether to afford the title compound (0.45 g, 0.001 mol and yield 89.3%) as a white solid which was used in the next step without any further purification. LCMS m/z: 380 [M+H].

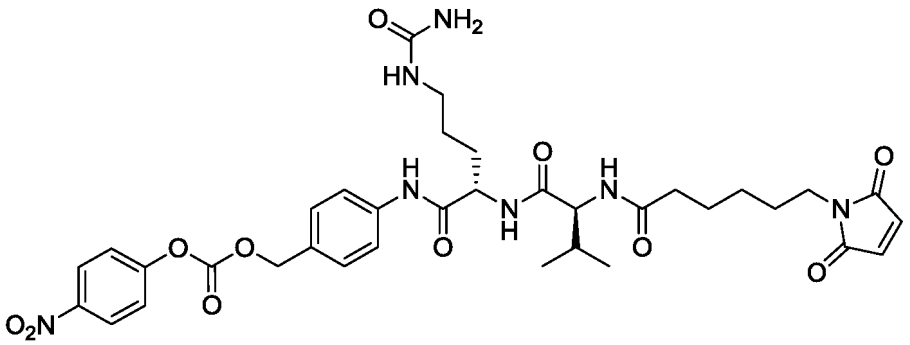
Step 4: 6-(2,5-Dioxo-2,5-dihydro-1H-pyrrol-1-yl)-N-((S)-1-(((S)-1-((4-(hydroxymethyl)phenyl)amino)-1-oxo-5-ureidopentan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)hexanamide



To a stirred solution of commercially available 6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoic acid (0.6 g, 2.843 mmol)) in anhydrous DMF (6 mL) was added DIPEA (1.43 g, 11.37 mmol) and HATU(1.30 g, 0.453 mmol) under a N_2 atmosphere at RT. The resulting reaction mixture was stirred for 5-10 min., before (S)-2-((S)-2-amino-3-methylbutanamido)-N-(4-(hydroxymethyl)phenyl)-5-ureidopentanamide (Preparation 1; Step 3) (0.86 g, 2.274 mmol) was added. The whole reaction mixture was stirred at RT for 15 min. and after completion (monitored by UPLC-MS) of the reaction, the reaction mixture was acidified with 2N HCl at 0-5 ^{o}C. The aqueous mixture was

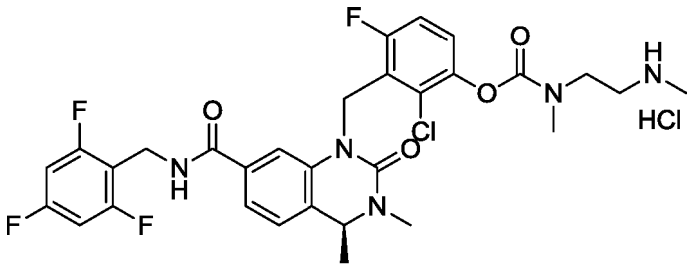
extracted twice with 10% IPA in EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give a crude product which was purified by trituration with diethyl ether to produce the title compound (0.54 g, 1.167 mmol and yield 51.4%) as a light yellow solid. LCMS m/z: 468 [M+H].

Step 5: 4-((S)-2-((S)-2-(6-(2,5-Dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanamido)-3-methylbutanamido)-5-ureidopentanamido)benzyl (4-nitrophenyl) carbonate

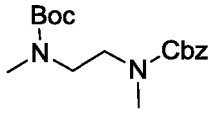


To a stirred solution of 6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-N-((S)-1-(((S)-1-((4-(hydroxymethyl)phenyl)amino)-1-oxo-5-ureidopentan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)hexanamide (Preparation 1; Step 4) (545 mg, 1.167 mmol) in DMF (8 mL) was added DIPEA (835 mg, 6.669 mmol) at 0-5 ^{o}C and stirring continued for 5-10 min. before 4-nitrophenyl-chloroformate (766 mg, 3.811 mmol) was added. The resulting reaction mixture was stirred at RT for 12 h. The progress of the reaction was monitored by UPLC-MS and upon completion, it was diluted with EtOAc (300 mL) and washed with 0.5N HCl (50 mL) followed by water (50 mL) and brine. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to dryness. The crude obtained was triturated with Et_2O to afford the title compound (505 mg, 0.685 mmol and yield 58.7%) as a yellow solid. The solid obtained was used in the next step without any further purification. LCMS m/z: 738 [M+H].

Preparation 2: (S)-2-Chloro-3-((3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenyl methyl(2-(methylamino)ethyl)carbamate hydrochloride

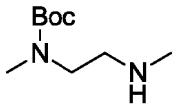


Step 1: Benzyl-*tert*-butyl ethane-1,2-diylbis(methylcarbamate)



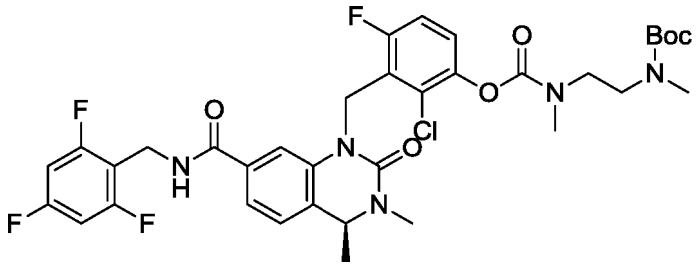
To a stirred solution of tert-butyl (2-(((benzyloxy)carbonyl)amino)ethyl)(methyl)-carbamate (9.0 g, 29.185 mmol) and MeI (2.74 mL, 43.83 mmol) in DMF (90 mL) was added NaH (1.4 g, 35.06 mmol) under an inert atmosphere at 0-5 °C. The cooling bath was removed and the whole allowed warming to RT. The reaction mixture was then further stirred at RT for 1 h. Progress of the reaction was monitored by UPLC-MS or TLC and after completion the reaction mixture was diluted with water and extracted with EtOAc, washed with brine solution, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to afford the crude product which was purified by combi-flash (8.0 g column) using 45% EtOAc in hexane as eluent to afford the title compound (8.2 g, 25.46 mmol and yield 87%) as a colourless oil. LCMS m/z: 323 [M+H].

Step 2: *tert*-Butyl methyl(2-(methylamino)ethyl)carbamate



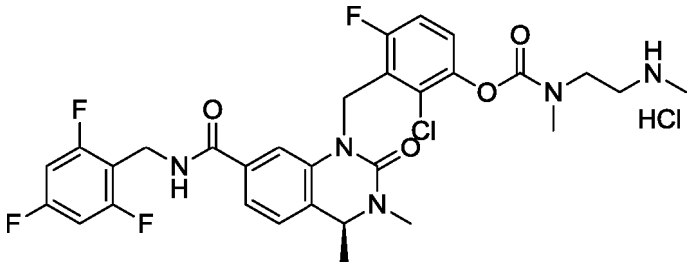
To a stirred solution of benzyl-*tert*-butyl ethane-1,2-diylbis(methylcarbamate) (Preparation 2; Step 1) (8.2 g, 25.46 mmol) in THF (100 mL) was added 10% Pd/C (800 mg, 50% w/w in water), under a N_2 atmosphere and the mixture was then degassed with N_2 using a mild vacuum. The resulting reaction mixture was stirred under H_2 balloon pressure at RT for 4 h. The reaction was monitored by UPLC-MS which showed formation of the desired compound and after completion the reaction mixture was filtered through a short celite bed and washed with excess EtOAc under a N_2 atmosphere. The filtrate was evaporated under reduced pressure to afford the title compound (4.7 g, 24.96 mmol and yield 98%) as colourless oil which was used in the next step without any further purification. LCMS m/z: 189 [M+H].

Step 3: (S)-*tert*-Butyl (2-chloro-3-((3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenyl) ethane-1,2-diylbis(methylcarbamate)



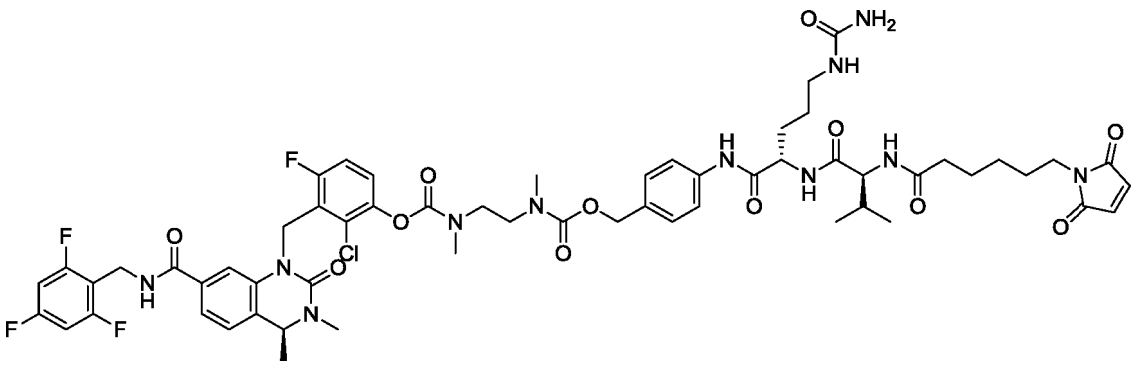
To a stirred solution of (S)-1-(2-chloro-6-fluoro-3-hydroxybenzyl)-3,4-dimethyl-2-oxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4-tetrahydroquinazoline-7-carboxamide (Payload) (5.0 g, 9.59 mmol) in THF (50 mL) was added DIPEA (10.61 mL, 92.13 mmol) followed by p-nitrophenylchloroformate (3.09 g, 15.35 mmol)) at 0-5 °C under an inert atmosphere. The resulting reaction mixture was stirred at 0-5 °C for 30 min. UPLC-MS showed complete conversion of the starting material to intermediate (S)-2-chloro-3-((3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenyl-(4-nitrophenyl) carbonate and into this reaction mixture was added *tert*-butyl-methyl(2-(methylamino)ethyl)carbamate (Preparation 2; Step 2) (4.5 g, 23.99 mmol) at RT. The resulting reaction mixture was stirred at RT for 30 min. Progress of the reaction was monitored by UPLC-MS and after completion the reaction mixture was diluted with water and extracted with EtOAc, the organic layer was separated, washed with 1N HCl followed by 10% $NaHCO_3$ solution and finally with brine. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give a sticky mass which was vigorously stirred with diethyl ether (250 mL) followed by n-hexane (250 mL) and dried under vacuum to afford the title compound (4.2 g, 5.71 mmol and yield 59.5%) as a white solid. LCMS m/z: 736 [M+H], 753 [M+17].

Step 4: (S)-2-Chloro-3-((3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenyl methyl(2-(methylamino)ethyl)carbamate hydrochlorid



To a stirred solution of (S)-*tert*-butyl-(2-chloro-3-((3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenyl) ethane-1,2-diylbis(methylcarbamate) (Preparation 2; Step 3) (1.2 g, 1.63 mmol) in 1,4-dioxane (12 mL) was added 4M HCl solution in 1,4 dioxane (12 mL) and the whole stirred for 2 h at RT. Progress of the reaction was monitored by TLC or LC-MS and after completion the solvents were evaporated by azeotropic distillation with acetonitrile under reduced pressure to afford the title compound (1.0 g, 1.48 mmol and yield 91%) as a pale yellow solid which was used in the next step without any further purification. LCMS m/z: 636 [M+H].

Preparation 3: 2-Chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenyl-4-((S)-2-((S)-2-(6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanamido)-3-methylbutanamido)-5-ureidopentanamido)benzyl-ethane-1,2-diylbis(methylcarbamate) (**Example 7**)



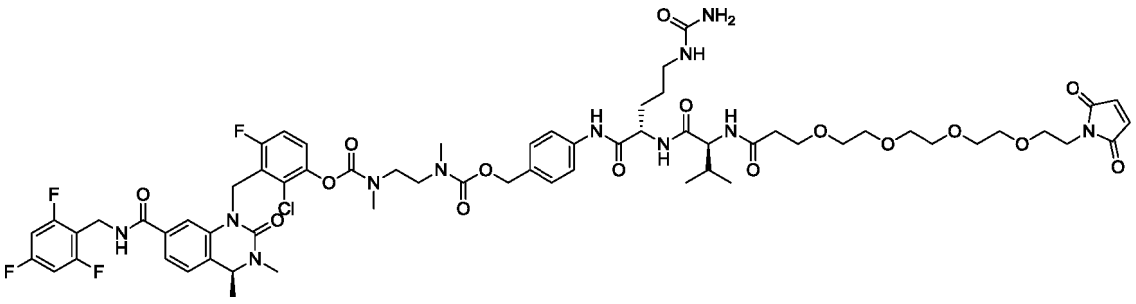
To a stirred solution of 4-((S)-2-((S)-2-(6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanamido)-3-methylbutanamido)-5-ureidopentanamido)benzyl (4-nitrophenyl) carbonate (Preparation 1; Step 5) (500 mg, 0.678 mmol) and (S)-2-chloro-3-((3,4-

dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenyl methyl(2-(methylamino)ethyl)carbamate hydrochloride (Preparation 2; Step 4) (911 mg, 1.355 mmol) in DMA (10 mL) were added 2,6-lutidine (72 mg, 0.677 mmol) and DIPEA (87 mg, 0.677 mmol) at 0-5 °C and after 5-10 min. the temperature was raised to RT and stirring was continued for another 30 min. at RT. Progress of the reaction was monitored by UPLC-MS and after completion the reaction mixture was diluted with diethyl ether and left for another 30 min. without stirring to give a gummy material. The solvents were decanted and the residue was purified by prep- HPLC to afford the title compound (0.042 g, 0.034 mmol and yield 5%) as a white solid. LCMS m/z: 1234.5 [M+H].

Examples 6 and 8:

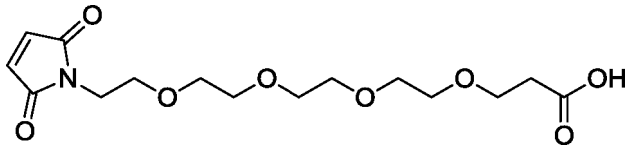
Examples 6 and 8 were prepared according to the above method used to make Example 7 and those methods described in General Procedures 1, 2, 4, 10, 12, 15, 17 using the product of Preparation 2 step 4 and the appropriate product of Preparation 1, step 4. Purification was as stated in the aforementioned methods.

Example 9: 2-Chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenyl-4-((17S,20S)-1-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-17-isopropyl-15,18-dioxo-20-(3-ureidopropyl)-3,6,9,12-tetraoxa-16,19-diazahenicosanamido)benzyl-ethane-1,2-diylbis(methylcarbamate)

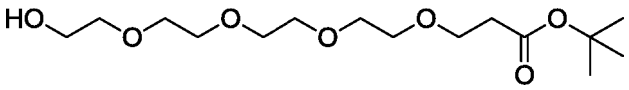


Example 9 was prepared according to the methods described in General Procedures 1, 2, 4, 5-12, 15, 17-18, 20 and the methods described below.

Preparation 4: 1-(2,5-Dioxo-2,5-dihydro-1H-pyrrol-1-yl)-3,6,9,12-tetraoxapentadecan-15-oic acid

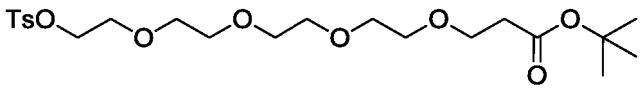


Step 1: tert-Butyl 1-hydroxy-3,6,9,12-tetraoxapentadecan-15-oate



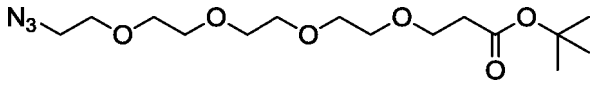
To a stirred solution of 2,2'-((oxybis(ethane-2,1-diyl))bis(oxy))diethanol (56.25 g, 0.298 mol) in dry THF (150 mL) was added sodium metal (68.6 mg, 2.983 mmol) under a N_2 gas atmosphere at -10 °C and the reaction mixture was stirred for 1 h until complete dissolution of the Na metal. *tert*-Butyl acrylate (13.38 g, 0.104 mol) was then added at RT and the mixture further stirred for 20 h. The progress of the reaction was monitored by UPLC-MS and after completion the reaction mixture was quenched with 1N HCl (to pH ~ 6). The solvent was evaporated and the residue was diluted with brine solution (40 mL). The organics were extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to dryness to give a crude product (32.0 g) which was purified by column chromatography on silica gel using a mixture of 2% MeOH inDCM as the solvent system to give the title compound (20.0 g, 0.062 mol, yield 21%) as a brown liquid. LCMS m/z: 323 [M+H].

Step 2: tert-Butyl 1-(tosyloxy)-3,6,9,12-tetraoxapentadecan-15-oate



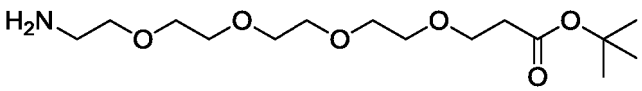
To a stirred solution of *tert*-butyl-1-hydroxy-3,6,9,12-tetraoxapentadecan-15-oate (Preparation 4; Step 1) (20.0 g, 0.062 mol) in anhydrous DCM (300 mL) was added TEA (9.46 g, 0.093 mol) under a N_2 atmosphere at RT. The reaction mixture was cooled to 0 °C and then tosyl chloride (17.75 g, 0.093 mol) added portionwise. After the addition was complete, the reaction mixture was stirred at RT for 36 h. The reaction was monitored by UPLC-MS and after completion the reaction mixture was quenched with water and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated to obtain a crude compound as a pale yellow liquid which was then purified by column chromatography on silica gel using 50% EtOAc in hexane as eluent to afford the title compound (28.0 g, 0.587 mol and yield 94%) as a colourless liquid. LCMS m/z: 477 [M+H].

Step 3: tert-Butyl-1-azido-3,6,9,12-tetraoxapentadecan-15-oate



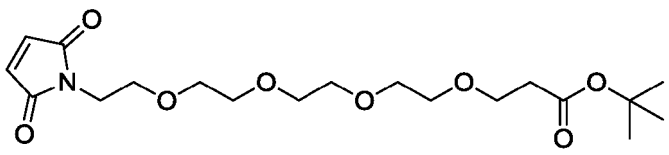
To a stirred solution of *tert*-butyl-1-(tosyloxy)-3,6,9,12-tetraoxapentadecan-15-oate (Preparation 4; Step 2) (28.0 g, 0.059 mol) in anhydrous DMF (300 mL) was added NaN_3 (2.34 g, 0.036 mol) under a N_2 atmosphere at RT, and the whole then stirred at RT overnight. The reaction was monitored by UPLC-MS and after completion the reaction mixture was quenched with water and extracted with EtOAc. The organic layer was dried over anhydrous $Na_2SO_4$and concentrated under reduced pressure to give the title compound (23.0 g, 0.066 mol, crude) as a pale yellow liquid which was pure enough to use in the next step without any further purification. LCMS m/z: 348.11 [M+H].

Step 4: tert-Butyl 1-amino-3,6,9,12-tetraoxapentadecan-15-oate



To a stirred solution of *tert*-butyl-1-azido-3,6,9,12-tetraoxapentadecan-15-oate (Preparation 4; Step 3) (5.0 g, 0.014 mol) in methanol (50 mL) was added 10% Pd/C (1.0 g, 50 % w/w in water) at RT under a N_2 gas atmosphere. The resulting reaction mixture was stirred under H_2 gas balloon pressure at RT for 3 h. After completion of the reaction (monitored by TLC using ninhydrin stain and UPLC-MS) the mixture was filtered through a celite bed under a N_2 atmosphere and washed with excess methanol. The filtrate was evaporated under reduced pressure to afford the title compound (4.5 g, 0.014 mol, yield 97%) as a colourless liquid which was pure enough to use in the next step without any further purification. LCMS m/z: 322 [M+H].

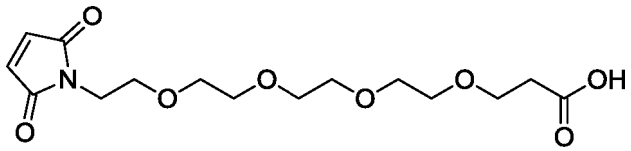
Step 5: tert-Butyl 1-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-3,6,9,12-tetraoxapentadecan-15-oate



To a stirred solution of *tert*-butyl-1-amino-3,6,9,12-tetraoxapentadecan-15-oate (Preparation 4; Step 4) (5.0 g, 0.016 mol) in a saturated solution of $NaHCO_3$ (50 mL) was added methyl 2,5-dioxo-2,5-dihydro-1H-pyrrole-1-carboxylate (2.895 g, 0.019 mol)

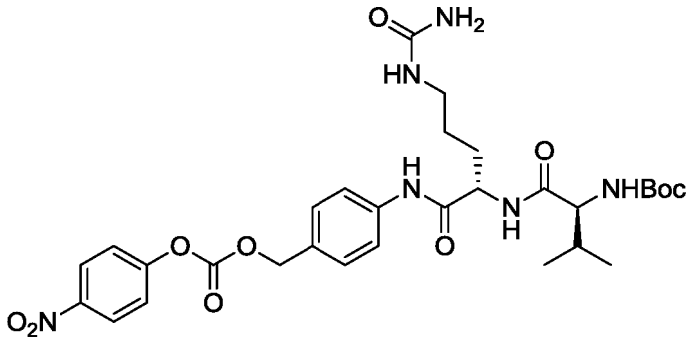
at RT. The resulting reaction mixture was further stirred at RT for 2 h. After completion of the reaction (monitored by TLC using I_2 stain and UPLC-MS), it was then extracted with DCM and the combined organics were dried and evaporated to give a crude product which was purified by column chromatography on silica gel using a mixture of 50% EtOAc in hexane as the mobile phase to give the title compound (1.8 g, 0.004 mol and yield 29%) as a colourless liquid. LCMS m/z: 402 [M+H].

Step 6: 1-(2,5-Dioxo-2,5-dihydro-1H-pyrrol-1-yl)-3,6,9,12-tetraoxapentadecan-15-oic acid

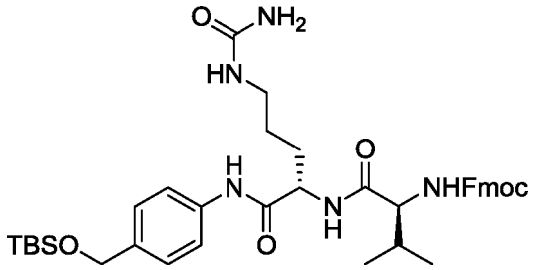


To a stirred solution of *tert*-butyl-1-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-3,6,9,12-tetraoxapentadecan-15-oate (Preparation 4; Step 5) (1.0 g, 0.002 mol) in anhydrous DCM (10 mL) was added TFA (2.0 mL) dropwise at 0 °C under an inert atmosphere and the reaction then stirred at RT for 4 h. The progress of the reaction was monitored by TLC (stain in bromocresol green) and UPLC-MS. After completion of the reaction the solvent was evaporated under reduced pressure to give a residue. Final traces of TFA were removed by co-distillation with acetonitrile and DCM to afford the crude product which was subjected to high vacuum drying to give the title compound (0.8 g, 0.002 mol and yield 93%) as a colourless liquid. LCMS m/z: 346.11 [M+H].

Preparation-5: tert-Butyl-((S)-3-methyl-1-(((S)-1-((4-((((4-nitrophenoxy)carbonyl)oxy)methyl)phenyl)amino)-1-oxo-5-ureidopentan-2-yl)amino)-1-oxobutan-2-yl)carbamate

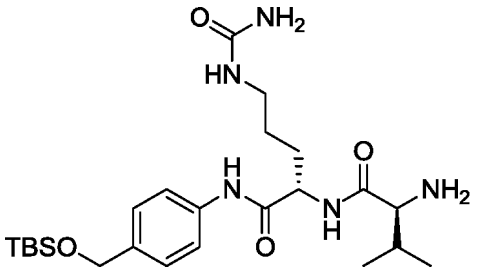


Step 1: (9H-Fluoren-9-yl)methyl-((S)-1-(((S)-1-((4-(((tert-butyldimethylsilyl)oxy)methyl)phenyl)amino)-1-oxo-5-ureidopentan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate



To a stirred suspension of (S)-2-((S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-methylbutanamido)-5-ureidopentanoic acid (Preparation 1; Step 1) (2.0 g, 4.03 mmol) in a mixture of DCM and MeOH (2:1, 50 mL) was added 4-(((tert-butyldimethylsilyl)oxy)methyl)aniline (1.89 g, 8.06 mmol) followed by EEDQ (1.9 g, 8.05 mmol) at RT. The reaction mixture was stirred at 40 °C for 12 h. The progress of the reaction was monitored by TLC and UPLC-MS and after complete consumption of the starting material the reaction mixture was filtered and washed with a mixture of DCM and MeOH (2:1, 20 mL) followed by EtOAc (50 mL). The resulting solid material was dried in an oven to afford the title compound (1.7 g, 2.38 mmol and yield 59%) as a yellowish solid. LCMS m/z: 716.4 [M+H].

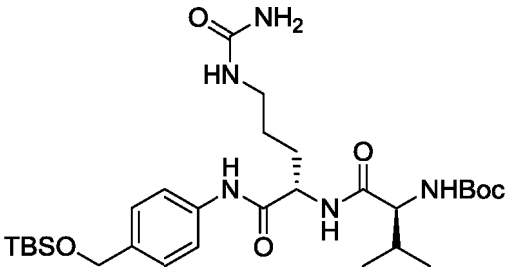
Step 2: (S)-2-((S)-2-Amino-3-methylbutanamido)-N-(4-(((tert-butyldimethylsilyl)oxy)methyl)phenyl)-5-ureidopentanamide



To a stirred solution of (9H-fluoren-9-yl)methyl ((S)-1-(((S)-1-((4-(((tert-butyldimethylsilyl)oxy)methyl)phenyl)amino)-1-oxo-5-ureidopentan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (Preparation 5; Step 1) (1.7 g, 2.38 mmol) in THF (24 mL) was added diethylamine (24 mL) at RT and the resulting reaction mixture was stirred at RT for 4 h. Progress of the reaction was monitored by TLC and UPLC-MS and after completion the solvents were evaporated under reduced pressure to give a gummy

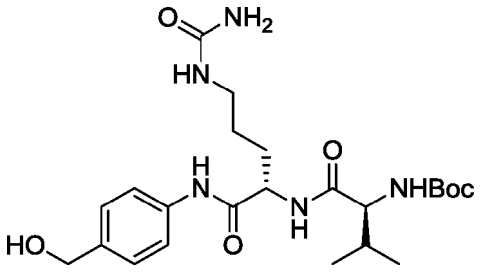
solid which was purified by trituration with diethyl ether to afford the title compound (1.1 g, 2.23 mmol and yield 93.6%) as a white solid. LCMS m/z: 494 [M+H].

Step 3: *tert*-Butyl-((S)-1-(((S)-1-((4-(((tert-butyldimethylsilyl)oxy)methyl)phenyl)amino)-1-oxo-5-ureidopentan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate



To a stirred solution of (S)-2-((S)-2-amino-3-methylbutanamido)-N-(4-(((tert-butyldimethylsilyl)oxy)methyl)phenyl)-5-ureidopentanamide (Preparation 5; Step 2) (1.1 g, 2.23 mmol) in DCM (22 mL) was added triethylamine (0.78 mL, 5.57 mmol) at 0-5 °C and the resulting reaction mixture was stirred at the same temperature for 5-10 min. before Boc_2O (0.61 mL, 2.68 mmol) was added and the temperature was slowly raised to RT and the whole stirred for 12 h. Progress of the reaction was monitored by TLC and UPLC-MS and after completion the reaction mixture was diluted with EtOAc (200 mL) and washed with a saturated solution of $NaHCO_3$ (25 mL) followed by water (25 mL), brine (25 mL) and dried over anhydrous Na_2SO_4. The dried organic layer was evaporated under reduced pressure to give the title compound (1.34 g, 2.27 mmol and yield 101%) as crude which was taken into the next step without any further purification. LCMS m/z: 594.3 [M+H].

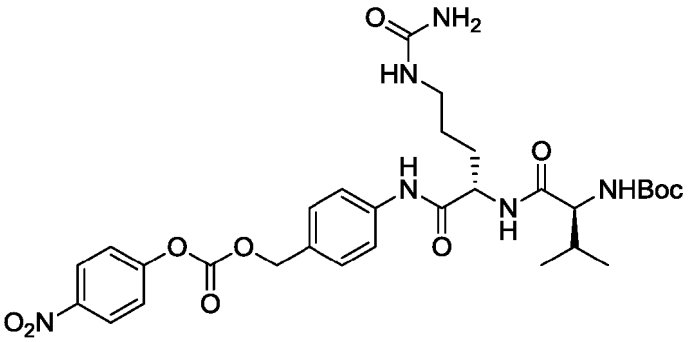
Step 4: *tert*-Butyl-((S)-1-(((S)-1-((4-(hydroxymethyl)phenyl)amino)-1-oxo-5-ureidopentan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate



To a stirred solution of *tert*-butyl-((S)-1-(((S)-1-((4-(((tert-butyldimethylsilyl)oxy) -methyl)phenyl)amino)-1-oxo-5-ureidopentan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (Preparation 5; Step 3) (1.34 g, 2.27 mmol) in THF (22.5 mL) was added

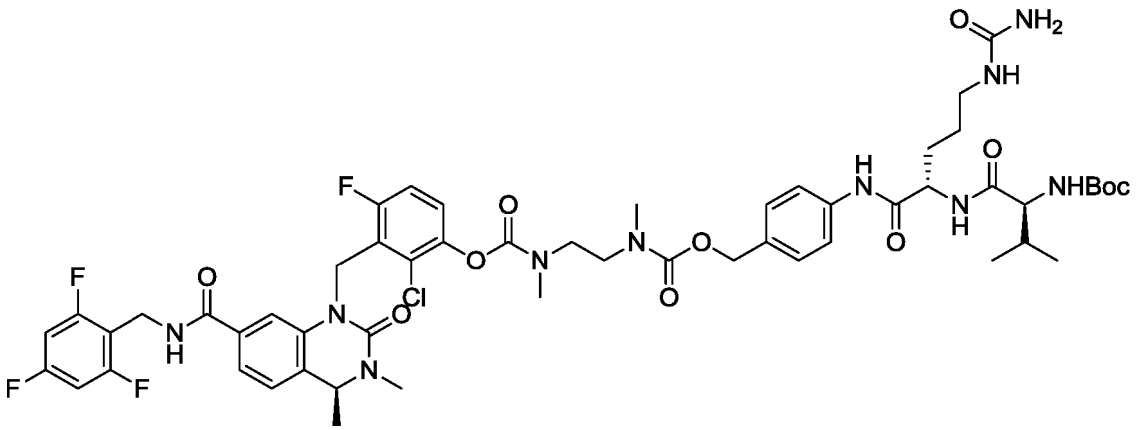
1H HCl (4.5 mL) at RT and the resulting reaction mixture was stirred at the same temperature for 30 min. Progress of the reaction was monitored by TLC and UPLC-MS and after completion the reaction mixture was diluted with EtOAc (400 mL) and washed with a saturated solution of $NaHCO_3$ (20 mL) followed by water (20 mL), brine (25 mL) and dried over anhydrous Na_2SO_4. The dried organic layer was evaporated under reduced pressure to give a crude product which was purified by trituration using diethyl ether (50 mL) to give the title compound (0.94 g, 1.96 mmol and yield 86%) as a white solid. LCMS m/z: 480 [M+H].

Step 5: *tert*-Butyl-((S)-3-methyl-1-(((S)-1-((4-((((4-nitrophenoxy)carbonyl)oxy)methyl)phenyl)amino)-1-oxo-5-ureidopentan-2-yl)amino)-1-oxobutan-2-yl)carbamate



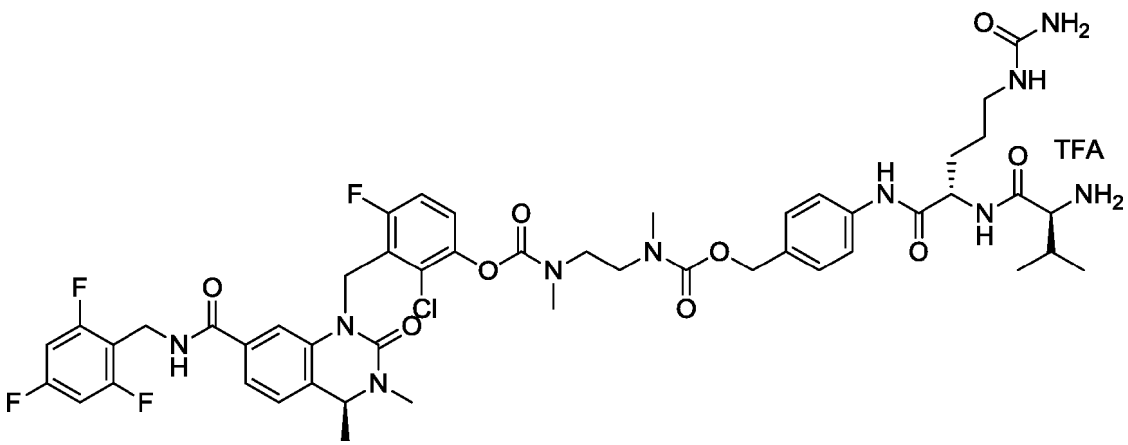
To a stirred solution of *tert*-butyl-((S)-1-(((S)-1-((4-(hydroxymethyl)phenyl)amino)-1-oxo-5-ureidopentan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (Preparation 5; Step 4) (0.94 g, 1.96 mmol) in DMF (5 mL) was added DIPEA (2.4 mL, 13.72 mmol) followed by p-nitrophenylchloroformate (1.57 g, 7.84 mmol) at RT and the mixture maintained at this temperature for 12 h. Progress of the reaction was monitored by TLC and UPLC-MS and after completion the reaction mixture was diluted with EtOAc (500 mL) and washed with water (2 x 50 mL) followed by brine (50 mL) and dried over anhydrous Na_2SO_4. The dried organic layer was evaporated under reduced pressure to give a crude product which was purified by trituration using diethyl ether (50 mL) to give the title compound (1.1 g, 1.71 mmol and yield 87%) as a white solid. LCMS m/z: 645.6 [M+H].

Preparation-6: 4-((S)-2-((S)-2-((*tert*-Butoxycarbonyl)amino)-3-methylbutanamido)-5-ureidopentanamido)benzyl (2-chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenyl) ethane-1,2-diylbis(methylcarbamate)



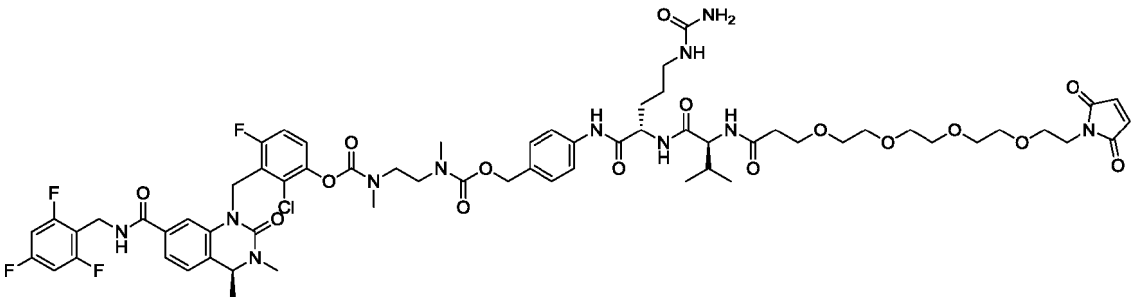
To a stirred solution of *tert*-butyl-((S)-3-methyl-1-(((S)-1-((4-((((4-nitrophenoxy)carbonyl)oxy)methyl)phenyl)amino)-1-oxo-5-ureidopentan-2-yl)amino)-1-oxobutan-2-yl)carbamate (Preparation 5; Step 5) (1.0 g, 1.55 mmol) and (S)-2-chloro-3-((3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenyl methyl(2-(methylamino)ethyl)carbamate hydrochloride (Preparation 2; Step 3) (1.5 g, 2.33 mmol) in a mixture of THF and DMF (1:1, 5 mL) was added DIPEA (0.67 mL, 8.87 mmol) at RT. The reaction mixture was stirred at RT for a further 1 h. Progress of the reaction was monitored by UPLC-MS and after complete consumption of the carbonate starting material (from Preparation 5; Step 5) the reaction mixture was diluted with diethyl ether (100 mL), allowed to settle for 10 min. and then the solvent was decanted. The remaining gummy material was purified by trituration with diethyl ether to afford the title compound (0.84 g, 0.735 mmol and yield 47.5%) as a white solid. LCMS m/z: 1141.5 [M+H].

Preparation-7: 4-((S)-2-((S)-2-Amino-3-methylbutanamido)-5-ureidopentanamido)benzyl (2-chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenyl) ethane-1,2-diylbis(methylcarbamate) trifluoroacetic acid



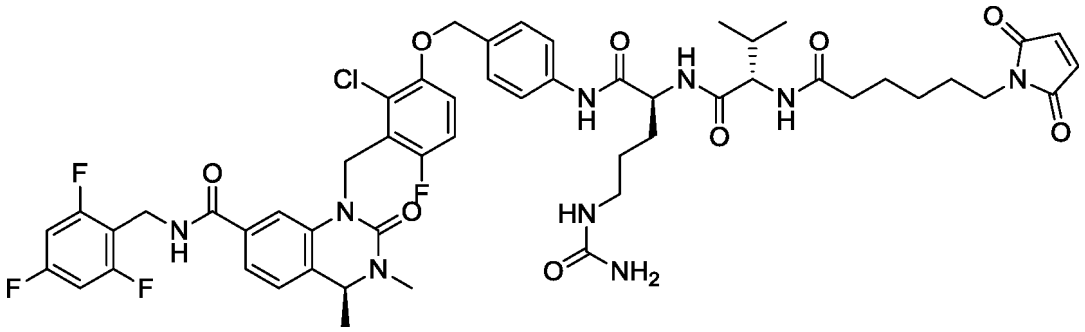
To a stirred solution of 4-((S)-2-((S)-2-((*tert*-butoxycarbonyl)amino)-3-methylbutanamido)-5-ureidopentanamido)benzyl (2-chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenyl) ethane-1,2-diylbis(methylcarbamate) (Preparation 6) (0.8 g, 0.701 mmol) in DCM (16 mL) was added TFA (3.2 mL) at RT and stirring continued at the same temperature for 30 min. The reaction was monitored by TLC and UPLC-MS and after completion the solvents were evaporated under reduced pressure to give the title compound (0.67 g, 0.643 mmol and yield 91.7%) as a colourless gummy liquid which was used in the next step without any further purification. LCMS m/z: 1041 [M+H].

Preparation-8: 2-Chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenyl 4-((17S,20S)-1-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-17-isopropyl-15,18-dioxo-20-(3-ureidopropyl)-3,6,9,12-tetraoxa-16,19-diazahenicosanamido)benzyl ethane-1,2-diylbis(methylcarbamate) **(Example 9)**



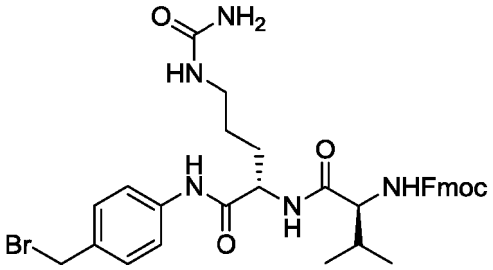
To a stirred suspension of 1-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-3,6,9,12-tetraoxapentadecan-15-oic acid (Preparation 4; Step 6) (220 mg, 0.64 mmol) in DMF (3 mL) was added TEA (0.2 mL, 1.45 mmol), HATU (220 mg, 0.58 mmol) and HOAt (78 mg, 0.58 mmol) at RT and stirring continued for a further 5-10 min. A solution of 4-((S)-2-((S)-2-Amino-3-methylbutanamido)-5-ureidopentanamido)benzyl (2-chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenyl) ethane-1,2-diylbis(methylcarbamate)trifluoroacetic acid (Preparation 7) (670 mg, 0.58 mmol) in DMF (6 mL) was then added in one portion. The resulting reaction mixture was stirred at RT for 30 min. and monitored by UPLC-MS which confirmed completion of the reaction. The reaction mixture was diluted with diethyl ether (100 mL), allowed to settle for 10 min. and then the solvents were decanted. The remaining gummy material was purified by prep-HPLC to afford the title compound (44 mg, 0.0321 mmol and yield 5%) as a white solid. LCMS m/z: 1368.5 [M+H].

Example 10: (S)-1-(2-Chloro-3-((4-((S)-2-((S)-2-(6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanamido)-3-methylbutanamido)-5-ureidopentanamido)benzyl)oxy)-6-fluorobenzyl)-3,4-dimethyl-2-oxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4-tetrahydroquinazoline-7-carboxamide



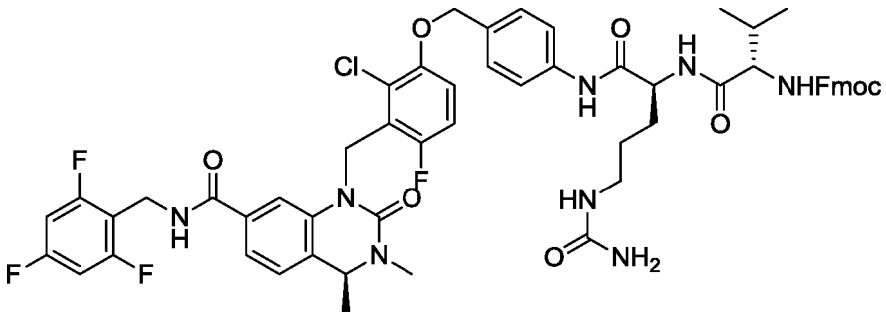
Example 10 was prepared according to the methods described in General Procedures 1-4, 19 and the methods described below.

Preparation 9: (9H-Fluoren-9-yl)methyl ((S)-1-(((S)-1-((4-(bromomethyl)phenyl)amino)-1-oxo-5-ureidopentan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate



To a suspension of (9H-fluoren-9-yl)methyl ((S)-1-(((S)-1-((4-(hydroxymethyl)phenyl)amino)-1-oxo-5-ureidopentan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (Preparation 1; Step 2) (3.0 g, 4.985 mmol) in DCM (60 mL) was added PBr_3 (3.37 g, 12.46 mmol) dropwise under a N_2 atmosphere at 0-5 °C and then allowed to warm slowly to RT. The resulting reaction mixture was stirred at RT for 16 h. Progress of the reaction was monitored by UPLC-MS and after completion the reaction mixture was suspended in cold saturated $NaHCO_3$ solution (500 mL) and stirred vigorously for 20 min. The resulting precipitate was filtered off to afford a light yellow solid which was dried in a rotary evaporator and then purified by trituration with diethylether (100 mL) to afford the title compound (3.7 g, 5.567 mmol and purity 60%) as a light yellow solid. LCMS m/z: 664 [M+H].

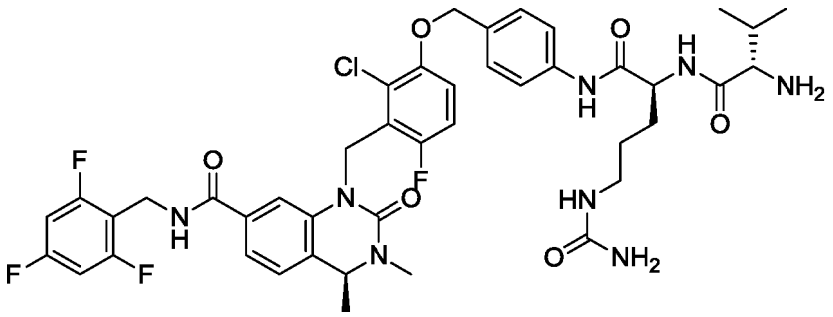
Preparation 10: (9H-Fluoren-9-yl)methyl-((S)-1-(((S)-1-((4-((2-chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenoxy)methyl)phenyl)amino)-1-oxo-5-ureidopentan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate



To a stirred solution of (S)-1-(2-chloro-6-fluoro-3-hydroxybenzyl)-3,4-dimethyl-2-oxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4-tetrahydroquinazoline-7-carboxamide (1.1 g, 2.111 mmol) in anhydrous DMF (28 mL) was added NaH (305 mg, 12.74 mmol, 60% suspension in oil) followed by KI (35 mg. 0.211 mmol) under a N_2 atmosphere at 0-5 °C.

The resulting reaction mixture was further treated with (9H-fluoren-9-yl)methyl ((S)-1-(((S)-1-((4-(bromomethyl)phenyl)amino)-1-oxo-5-ureidopentan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (Preparation 9) (2.81 g, 4.222 mmol). The combined reaction mixture was stirred at RT for 1 h and after completion (monitored by UPLC-MS) of the reaction the reaction mixture was poured into a cold saturated solution of K_2CO_3 (250 mL) and stirred for a further 15 min. The solid was filtered off in a Buchner funnel and washed with excess water to give a crude product which was further purified by washing the resulting slurry with water followed by hexane and diethyl ether to afford the title compound (1.8 g, 1.628 mmol and yield 77%) as a white solid. LCMS m/z: 1105 [M+H].

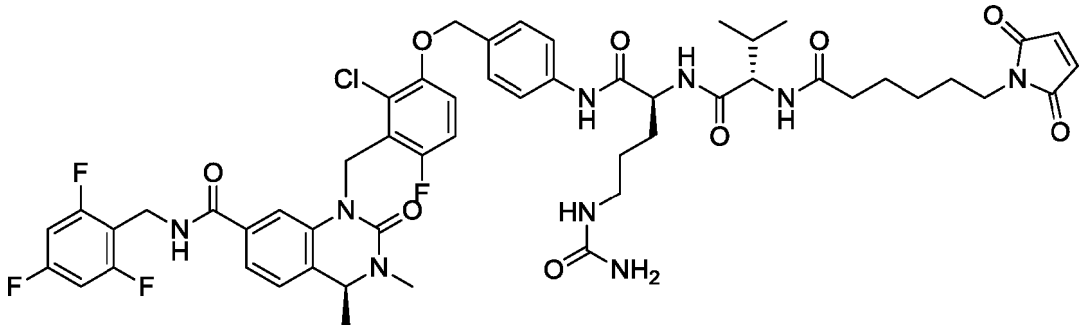
Preparation 11: (S)-1-(3-((4-((S)-2-((S)-2-Amino-3-methylbutanamido)-5-ureidopentanamido)benzyl)oxy)-2-chloro-6-fluorobenzyl)-3,4-dimethyl-2-oxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4-tetrahydroquinazoline-7-carboxamide



To a stirred suspension of (9H-fluoren-9-yl)methyl ((S)-1-(((S)-1-((4-((2-chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenoxy)methyl)phenyl)amino)-1-oxo-5-ureidopentan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (Preparation 10) (800 mg, 0.723 mmol) in anhydrous THF (8 mL) was added diethylamine (16 mL) at RT. The resulting reaction mixture was stirred at RT for 16 h. Progress of the reaction was monitored by UPLC-MS and after completion the solvents were evaporated under reduced pressure to give a crude product which was further subjected to dissolution and evaporation from acetonitrile and DCM 3 times. The obtained solid was purified by trituration with diethyl ether to give the title compound (600 mg, 0.679 mmol and yield 93.7%) as a white solid. LCMS m/z: 883.4 [M+H].

Preparation 12: (S)-1-(2Chloro-3-((4-((S)-2-((S)-2-(6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanamido)-3-methylbutanamido)-5-ureidopentanamido)benzyl)oxy)-6-

fluorobenzyl)-3,4-dimethyl-2-oxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4-tetrahydroquinazoline-7-carboxamide (**Example 10**)

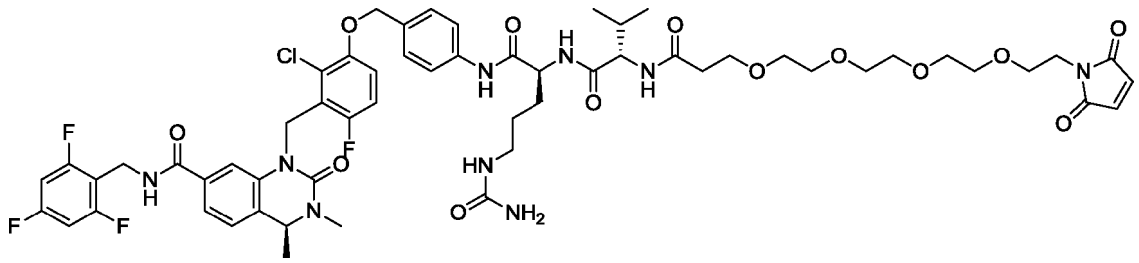


To a stirred solution of commercially available 6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoic acid (105 mg, 0.4986 mmol)) in anhydrous DMF (4 mL) was added TEA (91.68 mg, 0.906 mmol), HATU(172 mg, 0.453 mmol) and HOAt (62 mg, 0.453 mmol) under N_2 at RT. The resulting reaction mixture was cooled to 0-5 °C and then (S)-1-(3-((4-((S)-2-((S)-2-Amino-3-methylbutanamido)-5-ureidopentanamido)benzyl)oxy)-2-chloro-6-fluorobenzyl)-3,4-dimethyl-2-oxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4-tetrahydroquinazoline-7-carboxamide (Preparation 11) (400 mg, 0.453 mmol) was added. The whole reaction mixture was stirred at 0-5 °C for 15 min. and after completion (monitored by UPLC-MS) of the reaction the product was purified by prep-HPLC to afford the title compound (45 mg, 0.0418 mmol and yield 9%) as a white solid. LCMS m/z: 1076.43 [M+H].

Example 11:

Example 11 was prepared according to the above method used to make Example 7 and those methods described in General Procedures 1,2, 4, 6, 10, 12, 15, 17-18 using the product of Preparation 2 step 4 and the appropriate product of Preparation 1 step 5. Purification was as stated in the aforementioned methods.

Example 12: (S)-1-(2-Chloro-3-((4-((17S,20S)-1-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-17-isopropyl-15,18-dioxo-20-(3-ureidopropyl)-3,6,9,12-tetraoxa-16,19-diazahenicosanamido)benzyl)oxy)-6-fluorobenzyl)-3,4-dimethyl-2-oxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4-tetrahydroquinazoline-7-carboxamide

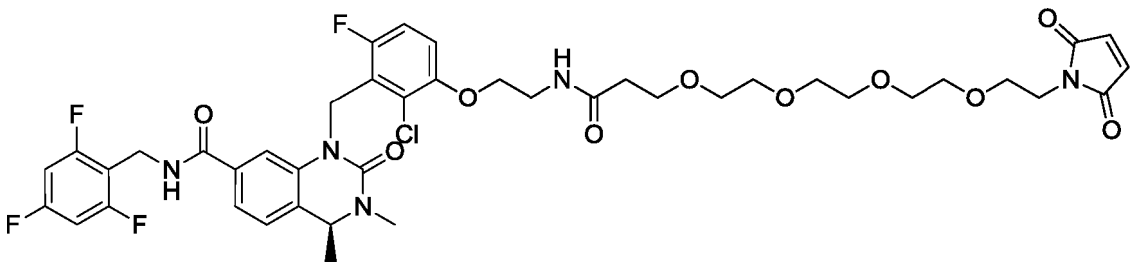


Example 12 was prepared according to the methods described in General Procedures 1-4, 7-12, 19 and the method described below.

Preparation 13:

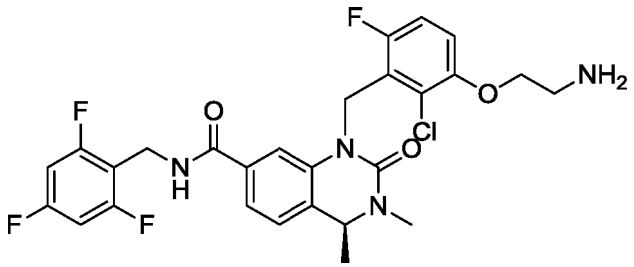
To a stirred solution of 1-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-3,6,9,12-tetraoxapentadecan-15-oic acid (Preparation 4; Step 6) (235 mg, 0.68 mmol) in anhydrous DMF (4 mL) was added TEA (92 mL, 0.906 mmol), HATU (172 mg, 0.453 mmol) and HOAt (62 mg, 0.453 mmol) at RT and stirring was then continued for 5-10 min. The resulting reaction mixture was cooled to 0-5 °C and then (S)-1-(3-((4-((S)-2-((S)-2-amino-3-methylbutanamido)-5-ureidopentanamido)benzyl)oxy)-2-chloro-6-fluorobenzyl)-3,4-dimethyl-2-oxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4-tetrahydroquinazoline-7-carboxamide (Preparation 11) (400 mg, 0.453 mmol) was added. The whole reaction mixture was stirred at 0-5 °C for 15 min. and after completion (monitored by UPLC-MS) of the reaction the product was purified by prep-HPLC to afford the title compound (50 mg, 0.0413 mmol and yield 9%) as a white solid. LCMS m/z: 1210 [M+H].

Example 1: (S)-1-(2-Chloro-3-((1-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-15-oxo-3,6,9,12-tetraoxa-16-azaoctadecan-18-yl)oxy)-6-fluorobenzyl)-3,4-dimethyl-2-oxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4-tetrahydroquinazoline-7-carboxamide

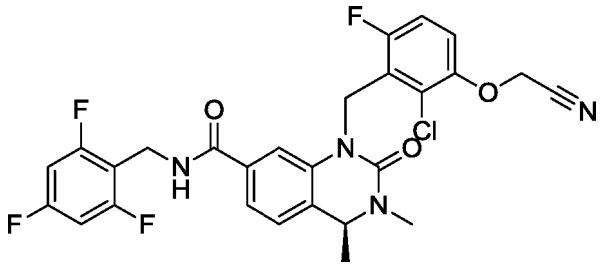


Example 1 was prepared according to the methods described in General Procedures 2, 7-12 and the methods described below.

Preparation 14: (S)-1-(3-(2-Aminoethoxy)-2-chloro-6-fluorobenzyl)-3,4-dimethyl-2-oxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4-tetrahydroquinazoline-7-carboxamide



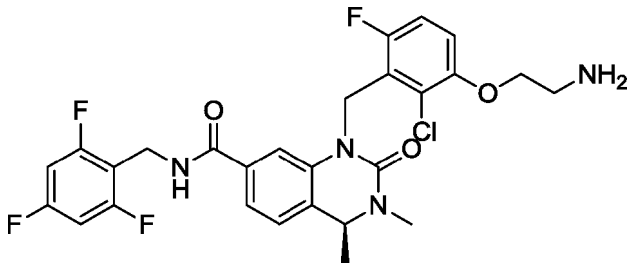
Step 1: (S)-1-(2-Chloro-3-(cyanomethoxy)-6-fluorobenzyl)-3,4-dimethyl-2-oxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4-tetrahydroquinazoline-7-carboxamide



To a stirred solution of (S)-1-(2-chloro-6-fluoro-3-hydroxybenzyl)-3,4-dimethyl-2-oxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4-tetrahydroquinazoline-7-carboxamide (500 mg, 0.959 mmol) in DMF (10 mL) was added K_2CO_3 (662 mg, 2.87 mmol) followed by bromoacetonitrile (80 µL, 1.15 mmol) at RT and the reaction mixture was further stirred at RT for 24 h. Completion of the reaction was confirmed by UPLC-MS and after complete consumption of the strating material the reaction mixture was diluted with water and extracted with MTBE. The organic layer was separated, washed with brine,

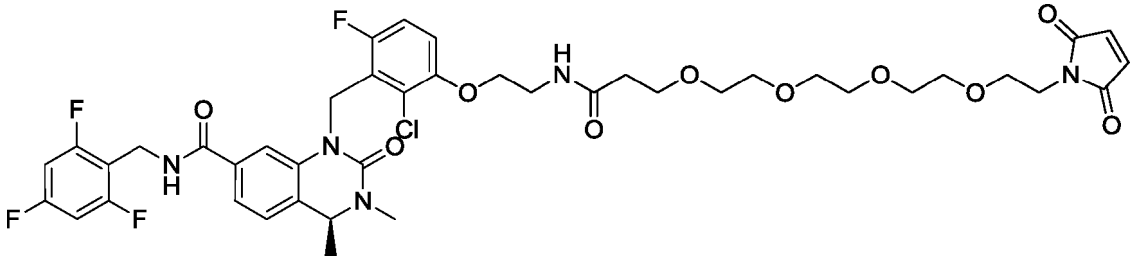
dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to afford the title compound (500 mg, 0.893 mmol and yield 93%) as a crude off white solid which was used in the next step as such. LCMS m/z: 561 [M+H].

Step 2: (S)-1-(3-(2-Aminoethoxy)-2-chloro-6-fluorobenzyl)-3,4-dimethyl-2-oxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4-tetrahydroquinazoline-7-carboxamide



To a stirred solution of (S)-1-(2-chloro-3-(cyanomethoxy)-6-fluorobenzyl)-3,4-dimethyl-2-oxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4-tetrahydroquinazoline-7-carboxamide (Preparation 14; Step 1) (500 mg, 0.893 mmol) in dry THF (100 mL) was added LAH (224 mg, 5.868 mmol) under a N_2 atmosphere and the whole stirred at RT for 1 h. Completion of the reaction was confirmed by UPLC-MS and after complete conversion of the starting material the reaction mixture was quenched with saturated Na_2SO_4 solution and stirred for 15 min. at RT. The solid was filtered off and the filtrate was evaporated *in vacuo* to give a residue which was washed with n-pentane and diethyl ether and then dried *in vacuo* to afford the title compound (500 mg, 0.885 mmol and yield 99% on crude basis) as an off white solid which was used in the next step without any further purification. LCMS m/z: 565 [M+H].

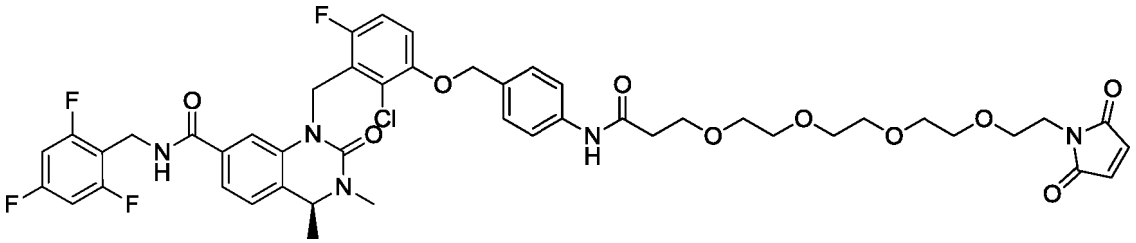
Preparation 15: (S)-1-(2-Chloro-3-((1-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-15-oxo-3,6,9,12-tetraoxa-16-azaoctadecan-18-yl)oxy)-6-fluorobenzyl)-3,4-dimethyl-2-oxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4-tetrahydroquinazoline-7-carboxamide (**Example 1**)



To a stirred solution of 1-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-3,6,9,12-tetraoxapentadecan-15-oic acid (Preparation 4; Step 6) (150 mg, 0.43 mmol) in anhydrous DMF (5 mL) was added TEA (0.24 mL, 1.73 mmol) and HBTU (180 mg, 0.47

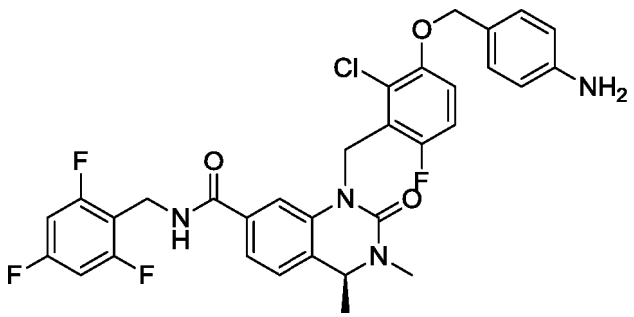
mmol) at 0-5 °C and stirring was then continued for 5-10 min. Then, (S)-1-(3-(2-aminoethoxy)-2-chloro-6-fluorobenzyl)-3,4-dimethyl-2-oxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4-tetrahydroquinazoline-7-carboxamide (Preparation 14; Step 2) (270 mg, 0.47 mmol) was added to the reaction mixture and the whole stirred for 2 h at RT. Progress of the reaction was monitored by TLC and LC-MS and after completion the reaction mixture was diluted with water, extracted with EtOAc and washed with brine. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude product which was purified by prep-HPLC to give the title compound (50 mg, 0.056 mmol and yield 12%) as a white solid. LCMS m/z: 892.45 [M+H].

Example 2: (S)-1-(2-chloro-3-((4-(1-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-3,6,9,12-tetraoxapentadecanamido)benzyl)oxy)-6-fluorobenzyl)-3,4-dimethyl-2-oxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4-tetrahydroquinazoline-7-carboxamide

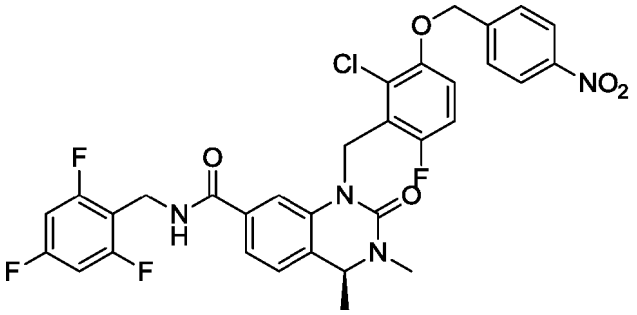


Example 2 was prepared according to the methods described in General Procedures 2-3, 7-12 and the methods described below.

Preparation 16: (S)-1-(3-((4-Aminobenzyl)oxy)-2-chloro-6-fluorobenzyl)-3,4-dimethyl-2-oxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4-tetrahydroquinazoline-7-carboxamide

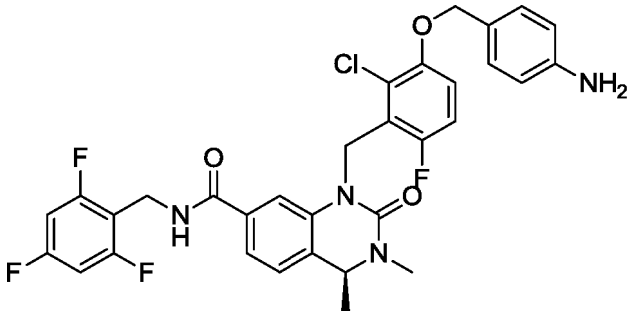


Step 1: (S)-1-(2-Chloro-6-fluoro-3-((4-nitrobenzyl)oxy)benzyl)-3,4-dimethyl-2-oxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4-tetrahydroquinazoline-7-carboxamide



To a stirred solution of (S)-1-(2-chloro-6-fluoro-3-hydroxybenzyl)-3,4-dimethyl-2-oxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4-tetrahydroquinazoline-7-carboxamide (300 mg, 0.575 mmol) in DMF (3.0 mL) was added K_2CO_3 (238 mg. 1.725 mmol) followed by a catalytic amount of KI and then p-nitrobenzylbromide (136.6 mg, 0.632 mmol) at RT. The resulting reaction mixture was stirred at RT for 3 h. The reaction was monitored by TLC and LCMS and after completion the reaction mixture was diluted with EtOAc, washed with cold water and brine. The organic layer was dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to give a crude product was purified by Combi-Flash using a EtOAc-hexane solvent system in a 12 g column to afford the title compound (360 mg, 0.548 mmol and yield 95%) as a light yellow solid. LCMS m/z: 657 [M+H].

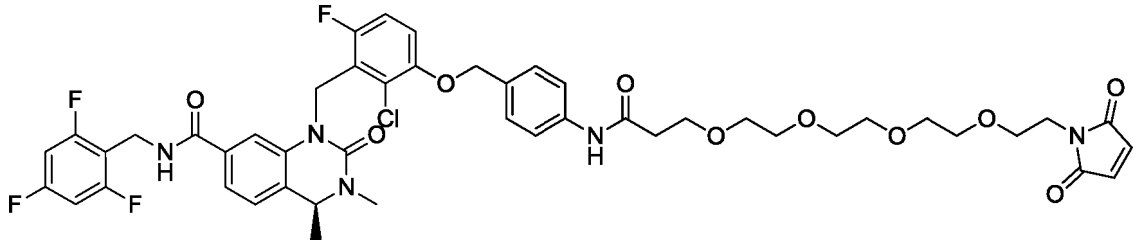
Step 2: (S)-1-(3-((4-Aminobenzyl)oxy)-2-chloro-6-fluorobenzyl)-3,4-dimethyl-2-oxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4-tetrahydroquinazoline-7-carboxamide



To a stirred suspension of (S)-1-(2-chloro-6-fluoro-3-((4-nitrobenzyl)oxy)benzyl)-3,4-dimethyl-2-oxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4-tetrahydroquinazoline-7-carboxamide (Preparation 16: Step 1) (330 mg, 0.502 mmol) in a mixture of ACN (5.0 mL) and water (2.5 mL), was added K_2CO_3 (416.5 mg, 3.014 mmol) and $Na_2S_2O_4$ (699.6 mg, 4.018 mmol) at 0-5 ^oC and the resulting reaction mixture was stirred at RT for 30 min. The reaction was monitored by TLC and LCMS and after completion the reaction mixture was diluted with EtOAc and washed with cold water. The organic layer was

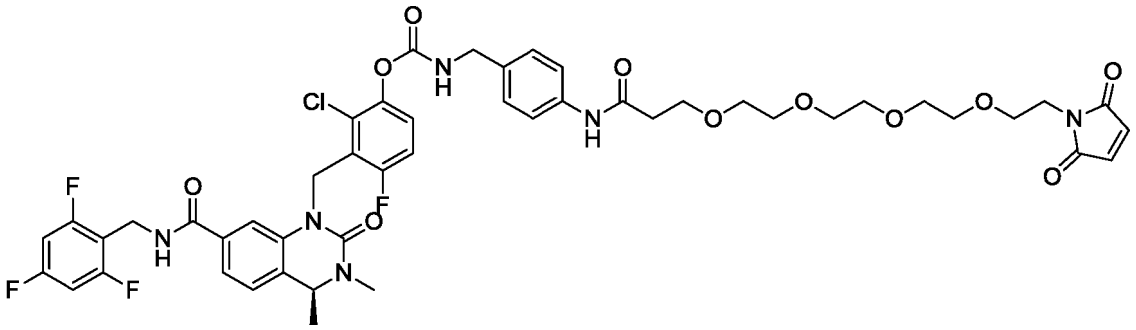
dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the title compound (310 mg, 0.794 mmol and yield 97%, purity 75%) as a crude pale brown solid which was used in the next step without any further purification. LCMS m/z: 627 [M+H].

Preparation 17: (S)-1-(2-Chloro-3-((4-(1-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-3,6,9,12-tetraoxapentadecanamido)benzyl)oxy)-6-fluorobenzyl)-3,4-dimethyl-2-oxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4-tetrahydroquinazoline-7-carboxamide (**Example 2**)



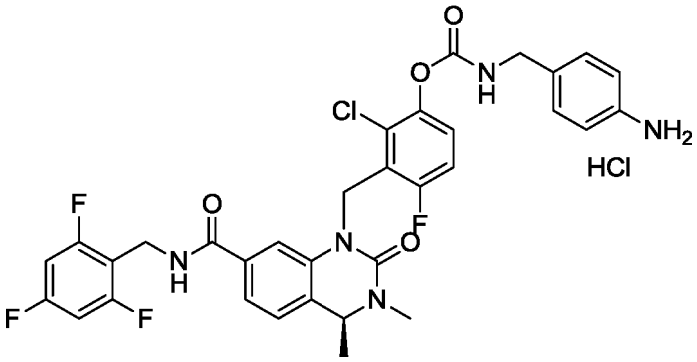
To a stirred solution of 1-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-3,6,9,12-tetraoxapentadecan-15-oic acid (Preparation 4; Step 6) (120 mg, 0.34 mmol) in anhydrous DMF (4 mL) was added TEA (0.193 mL, 1.39 mmol) and HATU (158 mg, 0.41 mmol) at 0-5 °C and stirring was then continued for 5-10 min. Then, (S)-1-(3-((4-aminobenzyl)oxy)-2-chloro-6-fluorobenzyl)-3,4-dimethyl-2-oxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4-tetrahydroquinazoline-7-carboxamide (Preparation 16; Step 2) (330 mg, 0.52 mmol) was added to the reaction mixture and the whole stirred at RT for 3 h. Progress of the reaction was monitored by TLC and LC-MS and after completion the reaction mixture was diluted with water, extracted with EtOAc and washed with brine. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude product which was purified by prep-HPLC to give the title compound (25 mg, 0.0262 mmol and yield 5%) as a white solid. LCMS m/z: 954 [M+H].

Example 3: (S)-2-Chloro-3-((3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenyl 4-(1-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-3,6,9,12-tetraoxapentadecanamido)benzylcarbamate

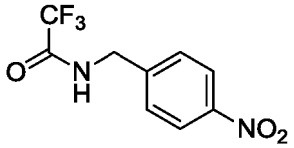


Example 3 was prepared according to the methods described in General Procedures 2, 7-12 and the methods described below.

Preparation 18: (S)-2-Chloro-3-((3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenyl 4-aminobenzylcarbamate hydrochloride



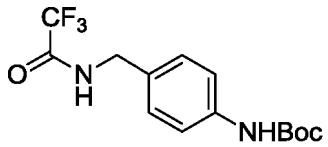
Step 1: 2,2,2-Trifluoro-N-(4-nitrobenzyl)acetamide



To a stirred suspension of (4-nitrophenyl)methanamine hydrochloride (1.0 g, 5.32 mmol) in DCM (10 mL) was added TEA (1.92 mL, 13.78 mmol) followed by TFAA (0.934 ml, 6.62 mmol) dropwise at 0-5 ^{o}C. The resulting reaction mixture was stirred at RT for 3 h. Progress of the reaction was monitored by TLC and LCMS and after completion of the reaction it was diluted with water and basified by adding $NaHCO_3$ solution to pH ~10 and then extracted with EtOAc and washed with brine. The organic

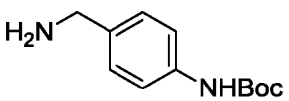
layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give the crude product which was purified by Combi-Flash using EtOAc-hexane solvent system to afford the title compound (1.18 g, 4.758 mmol and yield 89.5%) as yellow solid. LCMS m/z: 247 [M-H].

Step 2: tert-Butyl (4-((2,2,2-trifluoroacetamido)methyl)phenyl)carbamate



To a stirred suspension of 2,2,2-trifluoro-N-(4-nitrobenzyl)acetamide (Preparation 18; Step 1) (1.18 g, 4.758 mmol) in EtOH (20 mL) was added 0.12N HCl (20 mL) slowly followed by Fe powder (1.119 g, 19.02 mmol) portionwise at RT and then the reaction mixture was refluxed for 30 min at 90 ^oC. The reaction was monitored by TLC and LCMS and after completion of the reaction it was diluted with water and basified by adding $NaHCO_3$ to pH ~10 and then extracted with EtOAc (350 mL) followed by a brine wash. The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give the intermediate compound N-(4-aminobenzyl)-2,2,2-trifluoroacetamide (1.0 g, 4.587 mmol and yield 96%) as a crude yellow solid. The obtained intermediate was dissolved in THF (20 mL) and water (20 mL) followed by $NaHCO_3$ (1.925 g, 22.9 mmol) added portionwise. The resulting reaction mixture was cooled to 0-5 ^oC and Boc anhydride (3.15 mL, 13.74 mmol) added, and the whole then stirred for 18 h. The reaction was monitored by TLC and LCMS and after completion of the reaction it was diluted with water and extracted with EtOAc (350 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give a crude product which was purified by Combi-Flash using EtOAc-hexane mixture to afford the title compound (1.36 g, 4.276 mmol and yield 93%) as white solid. LCMS m/z: 317 [M-H].

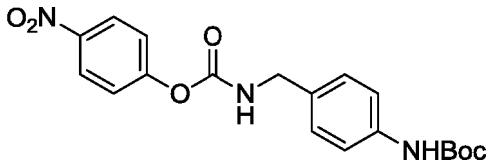
Step 3: tert-Butyl-(4-(aminomethyl)phenyl)carbamate



To a stirred solution of tert-butyl (4-((2,2,2-trifluoroacetamido)methyl)phenyl) - carbamate (Preparation 18; Step 2) (1.36 g, 4.27 mmol) in MeOH (14 mL) was added K_2CO_3 (1.18 g, 8.54 mmol) slowly at RT and the reaction mixture was stirred for 48h at RT. Progress of the reaction was monitored by TLC and LCMS and after completion the

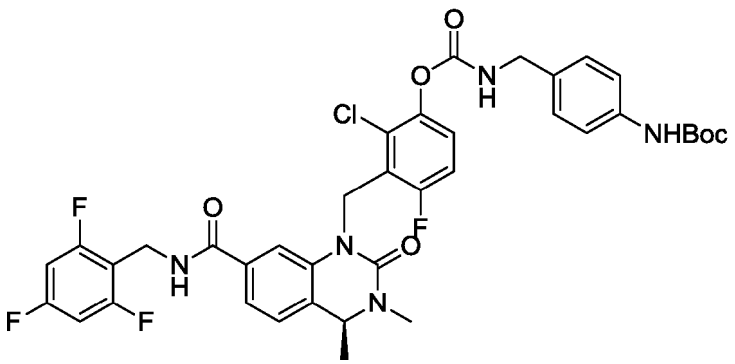
reaction mixture was diluted with water (250mL) and extracted with EtOAc (350 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give the title compound (900 mg, 4.048 mmol and yield 95%) as a yellow solid which was used in the next step without any further purification. LCMS m/z: 223 [M+H].

Step 4: tert-Butyl (4-((3-(4-nitrophenyl)carbamido)methyl)phenyl)carbamate



To a stirred solution of tert-butyl (4-(aminomethyl)phenyl)carbamate (Preparation 18; Step 3) (0.5 g, 2.24 mmol) in DCM (10.0 mL) was added water (10.0 mL) and K_2CO_3 (0.93 g, 6.74 mmol) at 0-5 ^oC. The resulting reaction mixture was further treated with p-nitrochloroformate (0.5 g, 2.47 mmol) at 0-5 ^oC and stirred at RT for 2h. The reaction was monitored by TLC and LCMS and after completion the reaction mixture was diluted with DCM and washed with cold water. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to dryness to give a crude material which was purified by Combi-Flash using an EtOAc-hexane solvent system to afford the title compound (550 mg, 1.421 mmol and yield 63.5%) as a light yellow solid. LCMS m/z: 388 [M+H].

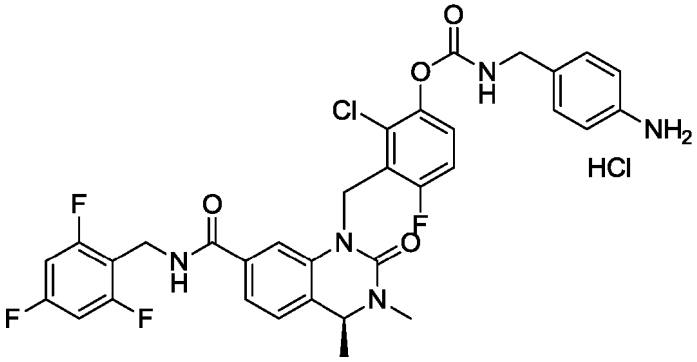
Step 5: (S)-2-Chloro-3-((3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenyl 4-tert-butyl-aminobenzylcarbamate



To a stirred solution of tert-butyl (4-((3-(4-nitrophenyl)carbamido)methyl)phenyl)-carbamate (Preparation 18; Step 4) (0.3 g, 0.57 mmol) in dry DMF (12 mL) was added K_2CO_3 (0.158 g, 1.14 mmol) followed by (S)-1-(2-chloro-6-fluoro-3-hydroxybenzyl)-3,4-

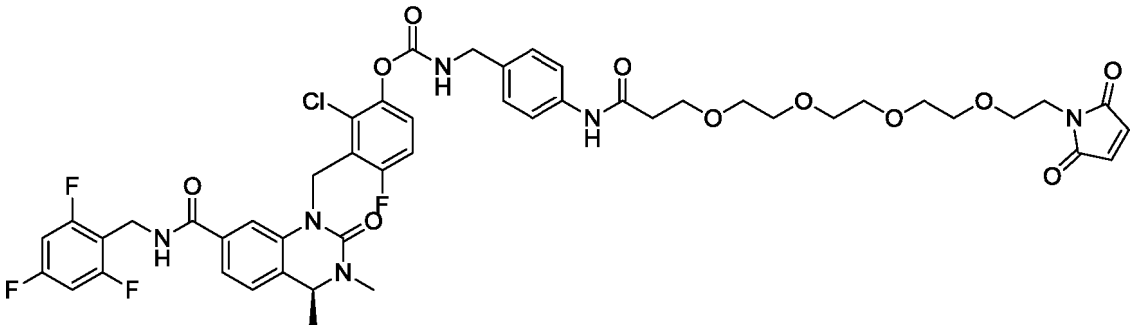
dimethyl-2-oxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4-tetrahydroquinazoline-7-carboxamide (0.24 g, 0.63 mmol) at 0-5 ^{0}C and stirring continued at the same temperature for 30 min. Progress of the reaction was monitored by UPLC-MS and after completion the reaction mixture was diluted with 1N NaOH and extracted with EtOAc followed by a brine wash. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford a crude product which was purified by Combi-flash using 50% EtOAc/hexane as eluent to give the title compound (400 mg, 0.52 mmol and yield 90%) as a yellow viscous oil. LCMS m/z: 770 [M+H].

Step 6: (S)-2-Chloro-3-((3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenyl 4-aminobenzylcarbamate hydrochloride



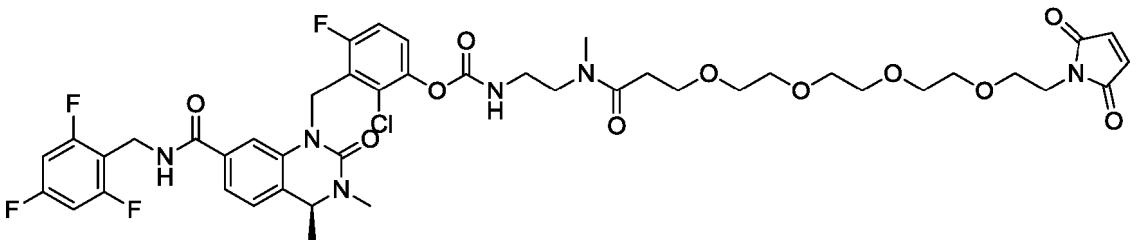
To a stirred solution of (S)-2-chloro-3-((3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenyl 4-tert-butyl-aminobenzylcarbamate (Preparation 18; Step 5) (0.3 g, 0.389 mmol) in 1,4-dioxane (8 mL) was added 4M HCl solution in 1,4 dioxane (8 mL) and the whole stirred for 5 h at RT. Progress of the reaction was monitored by TLC and LCMS and after completion the reaction solvent was evaporated by azeotropic distillation with ACN under reduced pressure to afford the title compound (250 mg, 0.354 mmol and yield 90%) as yellow solid which was used in the next step without any further purification. LCMS m/z: 670 [M+H].

Preparation 19: (S)-2-Chloro-3-((3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenyl 4-(1-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-3,6,9,12-tetraoxapentadecanamido)benzylcarbamate (**Example 3**)



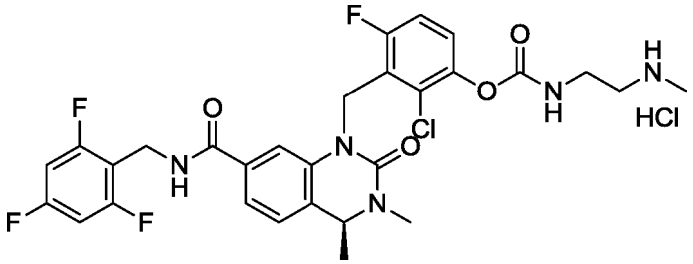
To a stirred solution of (S)-2-chloro-3-((3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenyl 4-aminobenzylcarbamate hydrochloride (213 mg, 0.318 mmol) and 1-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-3,6,9,12-tetraoxapentadecan-15-oic acid (Preparation 4; Step 6) (100 mg, 0.29 mmol) in DMF (4 mL) were added HATU (121 mg, 0.31 mmol) followed by triethylamine (0.161 mL, 1.15 mmol) at 0-5 ^{o}C and the reaction mixture was brought to RT and further stirred for 1 h. Progress of the reaction was monitored by TLC and LCMS and after completion the reaction mixture was diluted with cold water and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude product which was purified by prep-HPLC to give the title compound (30 mg, 0.030 mmol and yield 10%) as a white solid. LCMS m/z: 1014 [M+NH4].

Example 4: (S)-2-Chloro-3-((3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenyl (1-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-16-methyl-15-oxo-3,6,9,12-tetraoxa-16-azaoctadecan-18-yl)carbamate

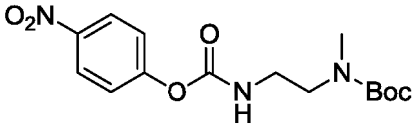


Example 4 was prepared according to the methods described in General Procedures 2, 7-12 and the methods described below.

Preparation 20: (S)-2-Chloro-3-((3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenyl (2-(methylamino)ethyl)carbamate hydrochloride

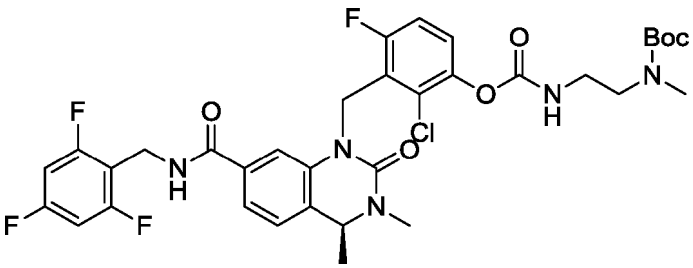


Step 1: tert-Butyl methyl(2-(((4-nitrophenoxy)carbonyl)amino)ethyl)carbamate



To a stirred solution of commercially available tert-butyl (2-aminoethyl)(methyl) carbamate (500 mg, 2.87 mmol) in THF (40 mL) was added p-nitro-phenylchloroformate (630 mg, 3.15 mmol) at 0-5 ^{o}C and the resulting reaction mixture was stirred at the same temperature for 45 min. Completion of the reaction was confirmed by TLC after which the reaction mixture was diluted with water, extracted with EtOAc and washed with brine. The organics were dried over Na_2SO_4 and evaporated *in vacuo* to give the crude product which was purified by column chromatography to afford the title compound (442 mg, 1.303 mmol and yield 45.5%) as a gummy solid. LCMS m/z: 340 [M+H].

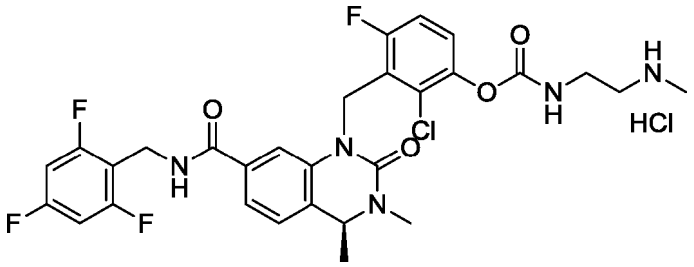
Step 2: (S)-tert-Butyl (2-(((2-chloro-3-((3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenoxy)carbonyl)amino)ethyl)(methyl)carbamate



To a stirred solution of (S)-1-(2-chloro-6-fluoro-3-hydroxybenzyl)-3,4-dimethyl-2-oxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4-tetrahydroquinazoline-7-carboxamide (Payload) (140

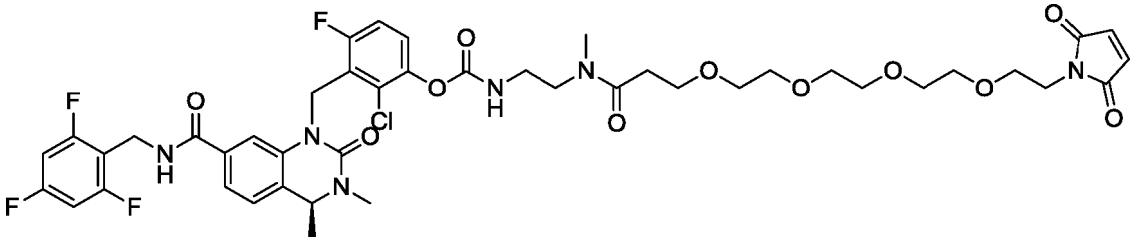
mg, 0.27 mmol) in anhydrous THF (2.7 mL) was added NaH (12 mg, 0.297 mmol, 60% suspension in mineral oil) under a N_2 atmosphere at 0-5 °C. The resulting reaction mixture was further stirred for 30 min. then treated with tert-butyl methyl(2-(((4-nitrophenoxy)carbonyl)amino)ethyl)carbamate (Preparation 20, Step 1) (26 mg, 0.76 mmol). The combined reaction mixture was stirred at 0-5 °C for 4 h and after completion (monitored by UPLC-MS and TLC) the reaction mixture was quenched with NH_4Cl solution, extracted with EtOAc and washed with brine. The organics were dried and evaporated *in vacuo* to give the crude product which was purified by column chromatography to afford the title compound (160 mg, 0.221 mmol and yield 82.5%) as a white solid. LCMS m/z: 722 [M+H].

Step 3: (S)-2-Chloro-3-((3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenyl (2-(methylamino)ethyl)carbamate hydrochloride



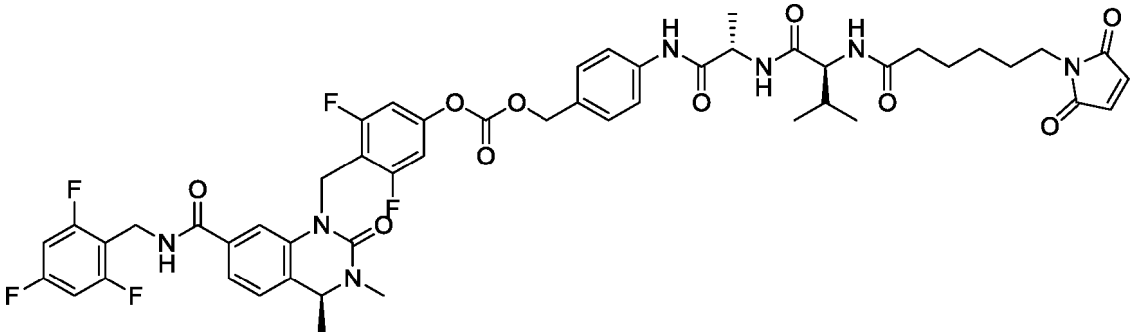
To a stirred solution of (S)-tert-butyl (2-(((2-chloro-3-((3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenoxy)carbonyl)amino)ethyl)(methyl)carbamate (Preparation 20; Step 2) (160 mg, 0.221 mmol) in 1,4-dioxane (2.5 mL) was added 4M HCl solution in 1,4 dioxane (2.5 mL) at 0-5 °C and the whole stirred at RT for 4 h. Progress of the reaction was monitored by TLC or LC-MS and after completion the solvent was evaporated *in vacuo* and the residue was triturated with diethyl ether to afford the title compound (180 mg, 0.273 mmol) as a white solid which was used in the next step without any further purification. LCMS m/z: 622 [M+H].

Preparation 21: (S)-2-Chloro-3-((3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenyl (1-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-16-methyl-15-oxo-3,6,9,12-tetraoxa-16-azaoctadecan-18-yl)carbamate (**Example 4**)



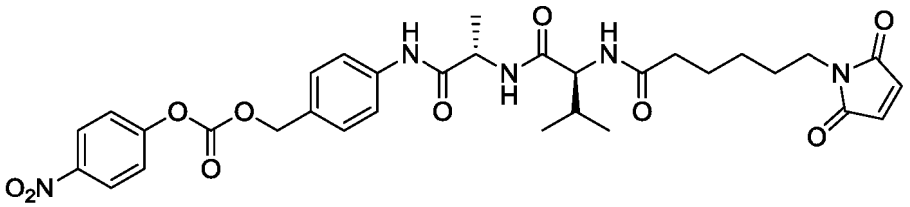
To a stirred solution of (S)-2-chloro-3-((3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenyl (2-(methylamino)ethyl)carbamate hydrochloride (Preparation 20; Step 3) (130 mg, 0.187 mmol) and 1-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-3,6,9,12-tetraoxapentadecan-15-oic acid (Preparation 4; Step 6) (70 mg, 0.206 mmol) in DMF (2.5 mL) were added TEA (0.078 mL, 0.56 mmol) and HATU (78 mg, 0.206 mmol) at 0-5 ^{o}C. The resulting reaction mixture was stirred at RT for 2 h. After completion of the reaction (monitored by TLC and UPLC-MS) the reaction mixture was diluted with water and extracted with EtOAc. The organics were concentrated to give the crude product which was purified by prep-HPLC to afford the title compound (15 mg, 0.016 mmol and yield 8.5%) as a white solid. LCMS m/z: 949.4 [M+H].

Example 13: 4-(((S)-3,4-Dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-3,5-difluorophenyl 4-((S)-2-((S)-2-(6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanamido)-3-methylbutanamido)propanamido)benzyl carbonate

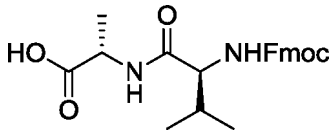


Example 13 was prepared according to the methods described in General Procedures 1-2, 4, 6 and the methods described below.

Preparation 22: 4-((S)-2-((S)-2-(6-(2,5-Dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanamido)-3-methylbutanamido)propanamido)benzyl (4-nitrophenyl) carbonate

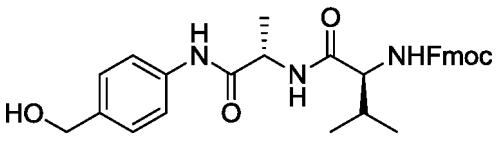


Step 1: (S)-2-((S)-2-((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)-3-methylbutanamido)propanoic acid



To a stirred solution of commercially available (S)-2,5-dioxopyrrolidin-1-yl 2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-methylbutanoate (2.5 g, 5.727 mmol) in DME (15 mL) was added an aqueous solution of sodium bicarbonate (0.5 g, 6.014 mmol in water (15 mL) followed by (S)-alanine (0.54 g, 6.014 mmol) at RT and the resulting reaction mixture was stirred at RT overnight. Progress of the reaction was monitored by TLC and LCMS and after completion the reaction mixture was acidified with 1N HCl, diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the title compound (1.5 g, 3.658 mmol and yield 64%) as a white solid which was used in the next step without further purification. LCMS m/z: 411 [M+H].

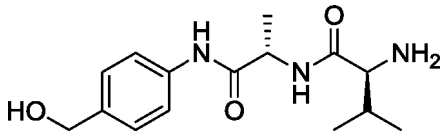
Step 2: (9H-Fluoren-9-yl)methyl ((S)-1-(((S)-1-((4-(hydroxymethyl)phenyl)amino)-1-oxopropan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate



To a stirred solution of (S)-2-((S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-methylbutanamido)propanoic acid (Preparation 22; Step 1) (1.5 g, 3.658 mmol) in a mixture of DCM and MeOH (30 mL, 2:1) was added EEDQ (1.8 g, 7.308 mmol) followed by 4-aminobenzyl alcohol (0.9 g, 7.308 mmol) at RT and the resulting reaction mixture was refluxed at 40 ^{o}C overnight. Progress of the reaction was monitored by TLC and LCMS and after completion the reaction mixture was filtered and washed with a mixture of EtOAc and MTBE (140 mL, 2.5:1). The white residue was collected and

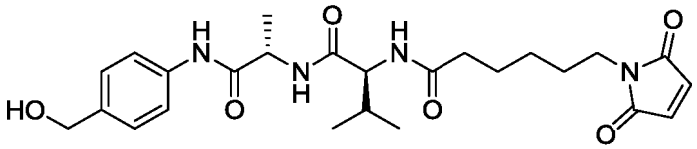
dried under reduced pressure to give the title compound (1.1 g, 2.136 mmol and yield 58.5%) as a white solid. LCMS m/z: 516 [M+H].

Step 3: (S)-2-Amino-N-((S)-1-((4-(hydroxymethyl)phenyl)amino)-1-oxopropan-2-yl)-3-methylbutanamide



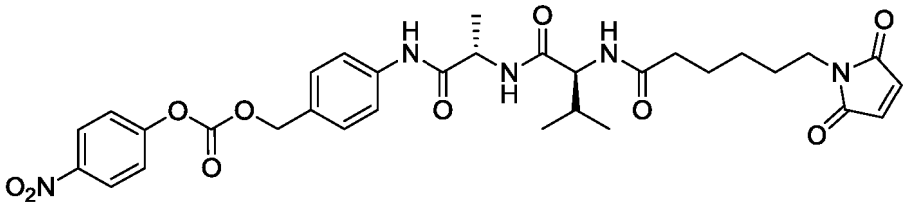
To a stirred solution of (9H-fluoren-9-yl)methyl ((S)-1-(((S)-1-((4-(hydroxymethyl)phenyl)amino)-1-oxopropan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (Preparation 22; Step 2) (1.1 g, 2.136 mmol) in THF (7 mL) was added diethylamine (15 mL) at RT and the resulting reaction mixture was stirred at RT for 1 h. Progress of the reaction was monitored by TLC and LCMS and after completion the solvent was evaporated by azeotropic distillation with acetonitrile under reduced pressure to give a residue which was purified by trituration with diethyl ether to afford the title compound (430 mg, 1.467 mmol and yield 68%) as a white solid. LCMS m/z: 294 [M+H].

Step 4: 6-(2,5-Dioxo-2,5-dihydro-1H-pyrrol-1-yl)-N-((S)-1-(((S)-1-((4-(hydroxymethyl)phenyl)amino)-1-oxopropan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)hexanamid



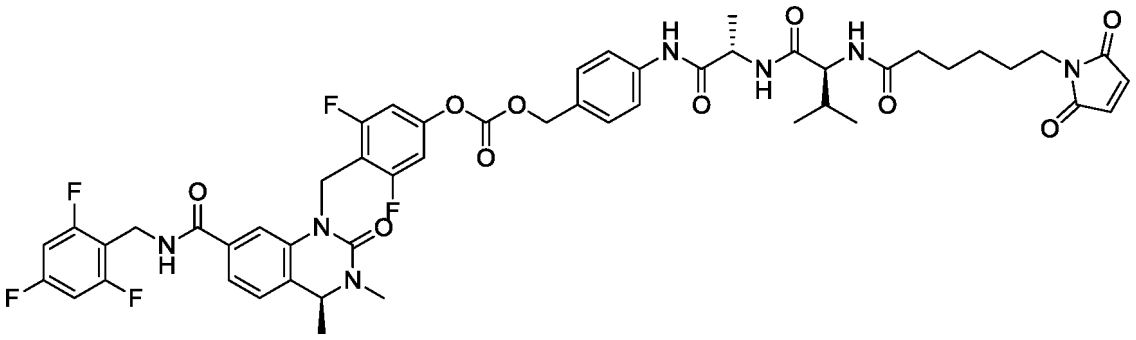
To a stirred solution of commercially available 6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoic acid (340 mg, 1.608 mmol) in DMF (8 mL) was added HATU (550 mg, 1.462 mmol), TEA (0.4 mL, 2.92 mmol) and finally (S)-2-amino-N-((S)-1-((4-(hydroxymethyl)phenyl)amino)-1-oxopropan-2-yl)-3-methylbutanamide (Preparation 22; Step 3) (430 mg, 1.467 mmol) at 0-5 ^{0}C. The resulting reaction mixture was further stirred at the same temperature for 15 min. The reaction was monitored by TLC and LCMS. After completion of the reaction the reaction mixture was diluted with EtOAc and washed with cold water followed by brine. The organic layer was dried over anhydrous Na_2SO_4, filtered and distilled under reduced pressure to afford the title compound (650 mg, 1.337 mmol and yield 91%) as a white solid. LCMS m/z: 487 [M+H].

Step 5: 4-((S)-2-((S)-2-(6-(2,5-Dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanamido)-3-methylbutanamido)propanamido)benzyl-(4-nitrophenyl) carbonate



To a stirred solution of 6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-N-((S)-1-(((S)-1-((4-(hydroxymethyl)phenyl)amino)-1-oxopropan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)hexanamid (Preparation 22; Step 4) (640 mg, 1.315 mmol) in DMF (10 mL) was added p-nitrophenyl chloroformate (660.9 mg, 3.288 mmol) followed by DIPEA (0.9 mL, 5.261 mmol) at 0-5 °C and the whole further stirred for 5 min at the same temperature. The reaction mixture was brought to RT and then stirred overnight. Progress of the reaction was monitored by TLC and LCMS and after completion the reaction mixture was diluted with EtOAc. The resulting organics were washed with cold water followed by brine, dried over anhydrous Na_2SO_4, filtered and distilled under reduced pressure to afford the title compound (580 mg, 0.891 mmol and yield 67.7%) as a white solid which was used in the next step without any further purification. LCMS m/z: 652 [M+H].

Preparation 23: 4-(((S)-3,4-Dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-3,5-difluorophenyl 4-((S)-2-((S)-2-(6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanamido)-3-methylbutanamido)propanamido)benzyl carbonate (**Example 13**)



To a stirred solution of (S)-1-(2,6-difluoro-4-hydroxybenzyl)-3,4-dimethyl-2-oxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4-tetrahydroquinazoline-7-carboxamide (190 mg, 0.376 mmol) and 4-((S)-2-((S)-2-(6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanamido)-3-

methylbutanamido)propanamido)benzyl (4-nitrophenyl) carbonate (Preparation 22; Step 5) (200 mg, 0.31 mg) in dry DMF (3 mL) was added solid K_2CO_3 (87 mg, 0.63 mmol) at RT. The resulting reaction mixture was stirred at RT for 1 h. Completion of the reaction was confirmed by LCMS after which the reaction mixture was purified by prep-HPLC to afford the title compound (55 mg, 0.054 mmol and yield 14%) as a white solid. LCMS m/z: 1018 [M+H].

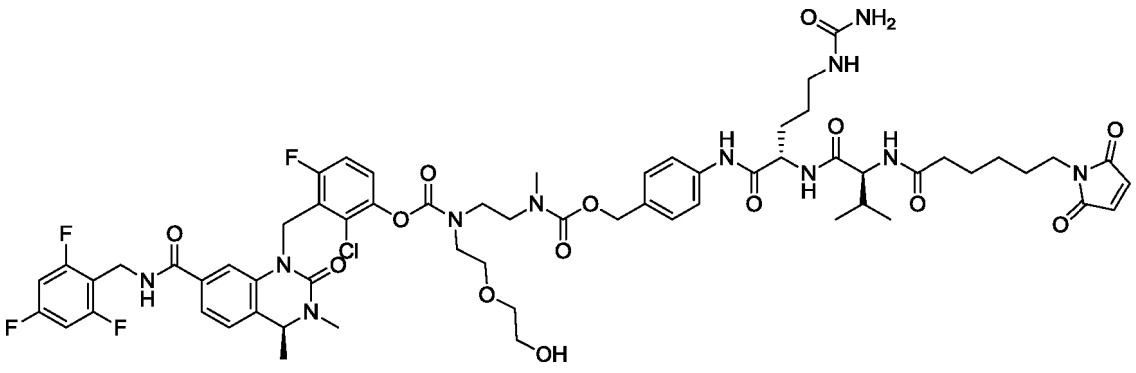
Examples 14 and 16:

Examples 14 and 16 were prepared according to the above method used to make Example 8, 20 and those methods described in General Procedures 1, 2, 4, 6, 10, 12, 15, 17-18 using the product of Preparation 2 step 4 and the appropriate product of Preparation 2 step 4 for example 14 and Preparation 27-29 for Example 16. Purification was as stated in the aforementioned methods.

Example 15:

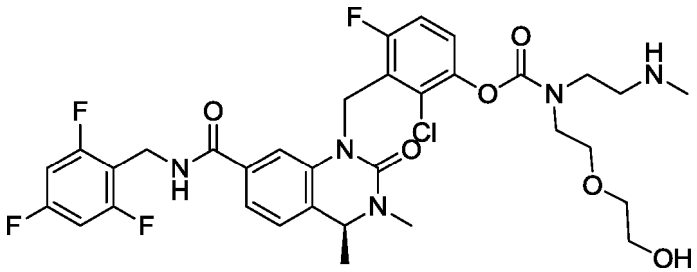
Example 15 was prepared according to the above method used to make Example 10 and those methods described in General Procedures 1-4 and 19 using the appropriate product of Preparation 11 and commercially available compound 6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoic acid . Purification was as stated in the aforementioned methods.

Example 18: 2-Chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenyl (2-((((4-((S)-2-((S)-2-(6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanamido)-3-methylbutanamido)-5-ureidopentanamido)benzyl)oxy)carbonyl)(methyl)amino)ethyl)(2-(2-hydroxyethoxy)ethyl)carbamate

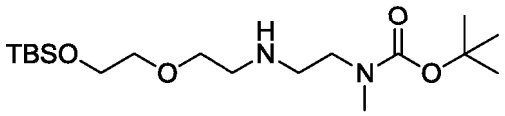


Example 18 was prepared according to the methods described in General Procedures 1-2, 4, 6, 12, 16-18 and the methods described below.

Preparation 24: (S)-2-Chloro-3-((3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenyl (2-(2-hydroxyethoxy)ethyl)(2-(methylamino)ethyl)carbamate

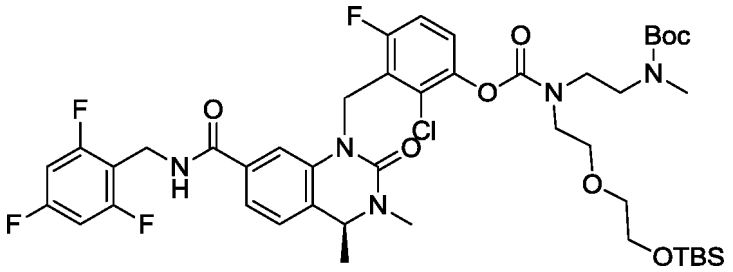


Step 1: tert-Butyl-methyl(2,2,3,3-tetramethyl-4,7-dioxa-10-aza-3-siladodecan-12-yl)carbamate



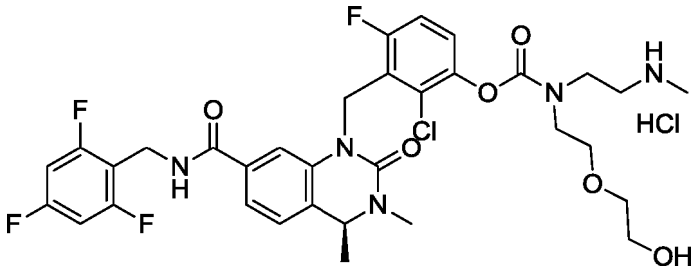
To a stirred solution of tert-butyl (2-aminoethyl)(methyl)carbamate (4.0 g, 22.975 mmol) in DMF (10 mL) was added tert-butyl(2-(2-chloroethoxy)ethoxy)dimethylsilane (8.206 g, 34.482 mmol), K_2CO_3 (7.926 g, 57.438 mmol) and KI (381.4 mg, 2.297 mmol) at RT. The resulting reaction mixture was stirred at 80°C for 12 h. The progress of the reaction was monitored by LCMS which showed the desired mass as a major product along with unreacted starting material. The reaction mass was diluted with EtOAc, washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo to give the crude product which was purified by column chromatography using a mixture of EtOAc and hexane to produce the title compound (6.4 g, 1.702 mmol and yield 74%) as a colourless liquid. LCMS m/z: 377 [M+H].

Step 2: (S)-2-Chloro-3-((3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenyl (2-((tert-butoxycarbonyl)(methyl)amino)ethyl)(2-(2-((tert-butyldimethylsilyl)oxy)ethoxy)ethyl)carbamate



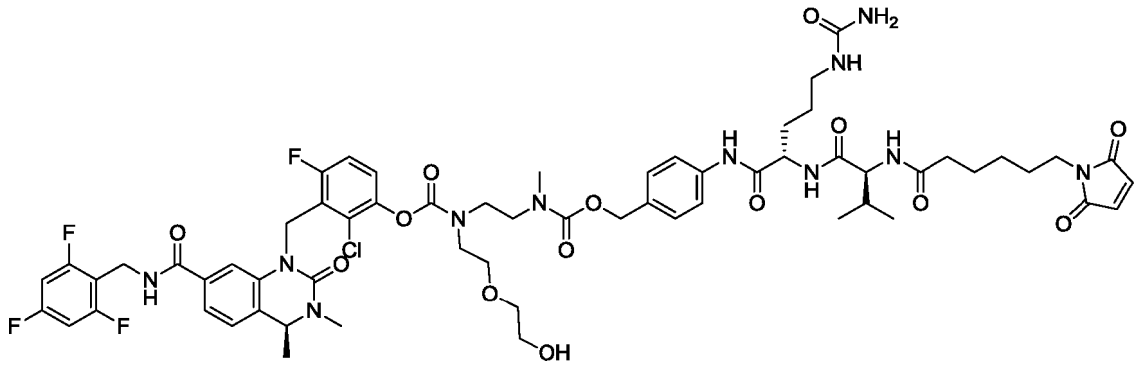
To a stirred solution of (S)-1-(2-chloro-6-fluoro-3-hydroxybenzyl)-3,4-dimethyl-2-oxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4-tetrahydroquinazoline-7-carboxamide (1.0 g, 1.919 mmol) in THF (10 mL) was added DIPEA (619 mg, 4.798 mmol) at 0-5 ^{o}C. p-Nitrophenyl chloroformate (578.69 mg, 2.879 mmol) was then added in one portion. The resulting reaction mixture was stirred at the same temperature for 30 min. to give an intermediate carbonate compound (S)-2-chloro-3-((3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenyl(4-nitrophenyl)carbonate which was confirmed by LCMS. To the reaction mixture was added another portion of DIPEA (619 mg, 4.798 mmol) and THF (10 mL) followed by *tert*-butyl methyl(2,2,3,3-tetramethyl-4,7-dioxa-10-aza-3-siladodecan-12-yl)carbamate (Preparation 24; Step 1) (2.71 g, 7.197 mmol). The resulting mixture was further stirred at 0-5 ^{o}C for 12 h. Progress of the reaction was monitored by TLC and LCMS and after completion the reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the crude material which was purified by column chromatography to give the title compound (700 mg, 0.757 mmol and yield 39.5%) as a white solid. LCMS m/z: 924 [M+H].

Step 3: (S)-2-Chloro-3-((3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenyl (2-(2-hydroxyethoxy)ethyl)(2-(methylamino)ethyl)carbamate hydrochloride



To a stirred solution of (S)-2-chloro-3-((3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenyl (2-((tert-butoxycarbonyl)(methyl)amino)ethyl)(2-(2-((tert-butyldimethylsilyl)oxy)ethoxy)ethyl)carbamate (Preparation 24; Step 2) (700 mg, 0.758 mmol) in 1,4-dioxane (4 mL) was added a 4M HCl solution in 1,4-dioxane (4 mL) at RT and the reaction was continued for 2 h. The progress of the reaction was monitored by UPLC-MS and after completion the solvent was evaporated under reduced pressure to give the crude as a hydrochloride salt which was purified by trituration with Et_2O to yield the title compound (450 mg, 0.603 mmol and yield 79.6%) as a white solid. LCMS m/z: 710 [M+H].

Preparation 25: 2-Chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenyl (2-((((4-((S)-2-((S)-2-(6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanamido)-3-methylbutanamido)-5-ureidopentanamido)benzyl)oxy)carbonyl)(methyl)amino)ethyl)(2-(2-hydroxyethoxy)ethyl)carbamate (**Example 18**)



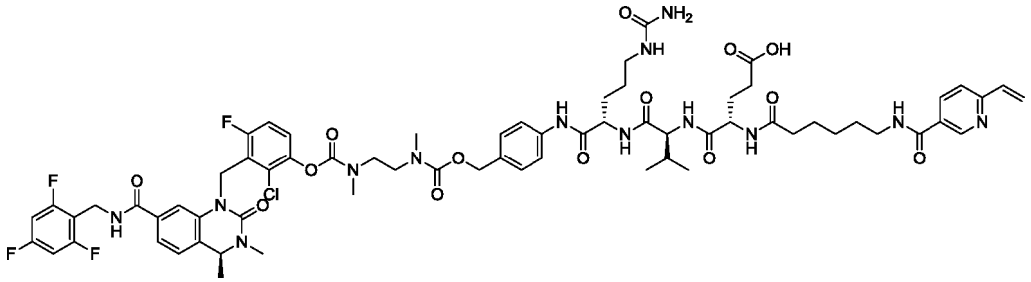
To a stirred solution of 4-((S)-2-((S)-2-(6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanamido)-3-methylbutanamido)-5-ureidopentanamido)benzyl (4-nitrophenyl)

carbonate (Preparation 1; Step 5) (300 mg, 0.407 mmol) in DMF (3 mL) was added (S)-2-chloro-3-((3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenyl(2-(2-hydroxyethoxy)ethyl)(2(methylamino)ethyl)carbamate hydrochloride (Preparation 24; Step 3) (454 mg, 0.610 mmol) at RT and after 5 min of stirring DIPEA (104.9 mg, 0.813 mmol) was added to the mixture. The reaction was allowed to stir for 30 min. at RT. Progress of the reaction was monitored by UPLC-MS and after completion the reaction mass was diluted with Et_2O and set aside for 15 min to allow the gummy material to settle, then the Et_2O was decanted and the crude was purified by prep-HPLC to give the title compound (40 mg, 0.031 mmol and yield 5%) as a white solid. LCMS m/z: 1308 [M+H].

Example 19:

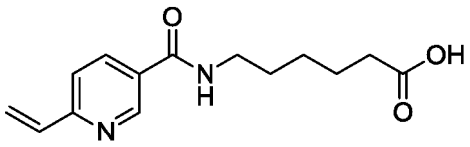
Example 19 was prepared according to the above method used to make Example 20 or 9 and those methods described in General Procedures 1, 2, 4, 6-12, 15, 17-18 using the product of Preparation 29 and the product of Preparation 4. Purification was as stated in the aforementioned methods.

Example 20: (S)-5-(((S)-1-(((S)-1-((4-((((2-(((2-Chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenoxy)carbonyl)(methyl)amino)ethyl)(methyl)carbamoyl)oxy)methyl)phenyl)amino)-1-oxo-5-ureidopentan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)amino)-5-oxo-4-(6-(6-vinylnicotinamido)hexanamido)pentanoic acid

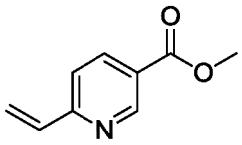


Example 20 was prepared according to the methods described in General Procedures 1-2, 4, 6, 10, 12, 15, 17-18 and the methods described below.

Preparation 26: 6-(6-Vinylnicotinamido)hexanoic acid

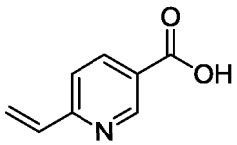


Step 1: Methyl 6-vinylnicotinate



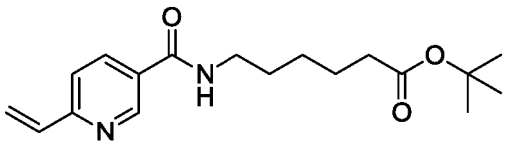
To a stirred solution of commercially available methyl-6-chloronicotinate (1.0 g, 5.828 mmol) in DMF (8 mL) was added tributylvinyltin (2.771 g, 8.742 mmol), Pd[P(O-tolyl)$_3$]$_2$Cl3 (208 mg, 0.291 mmol) and LiCl (494 mg, 11.656 mmol). The resulting reaction mixture was degassed with N_2 and then heated at 100 ^{O}C for 4 h. Completion of the reaction was confirmed by UPLC-MS after which the reaction temperature was lowered to RT and the mixture diluted with EtOAc, then filtered through a small celite pad and the pad washed with EtOAc. The filtrate was diluted with H_2O (100 mL) and extracted with EtOAc. The combined organic layers were collected, dried over Na_2SO_4 and evaporated in vacuo to give a crude product which was purified by Combi-flash column chromatography and finally by trituration with pentane to afford the title compound (700 mg, 4.294 mmol and yield 73.6%) as a gummy solid. UPLC-MS m/z: 164 [M+H].

Step 2: 6-Vinylnicotinic acid



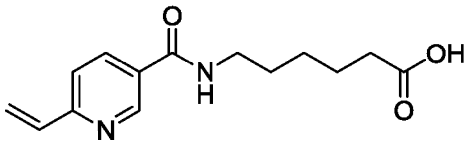
To a stirred solution of methyl-6-vinylnicotinate (Preparation 26; Step 1) (700 mg, 4.294 mmol) in a mixture of THF:MeOH:H_2O (2:2:1, 10 mL) was added LiCl (515 mg, 8.579 mmol) at RT. The resulting reaction mixture was further stirred at RT for 2 h. Progress of the reaction was monitored by TLC and upon completion it was neutralized to ~pH 7 with 1 N HCl solution. The solvents were evaporated in vacuo to give a residue which was extracted with EtOAc, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to afford the title compound (630 mg, 4.228 mmol and yield 98%) as a white solid. LCMS m/z: 150 [M+H].

Step 3: *tert*-Butyl-6-(6-vinylnicotinamido)hexanoate



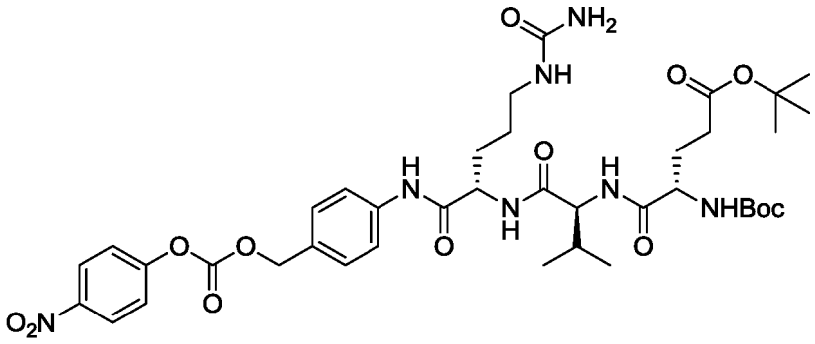
To a stirred solution of 6-vinylnicotinic acid (Preparation 26; Step 2) (495 mg, 3.322 mmol) and commercially available *tert*-butyl-6-aminohexanoate (684 mg, 3.654 mmol) in DMF (10 mL) were added HATU (1.262 g, 3.322 mmol) and TEA (1.0 g, 9.966 mmol) at RT. Progress of the reaction was monitored by UPLC-MS and after 30 min stirring at RT the reaction was complete and was diluted with water (100 mL). The aqueous mixture was extracted with EtOAc and washed with brine. The organic part was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give the crude product which was purified by column chromatography to afford the title compound (600 mg, 1.886 mmol and yield 56.8%) as a colourless liquid. UPLC-MS m/z: 319 [M+H].

Step 4: 6-(6-Vinylnicotinamido)hexanoic acid

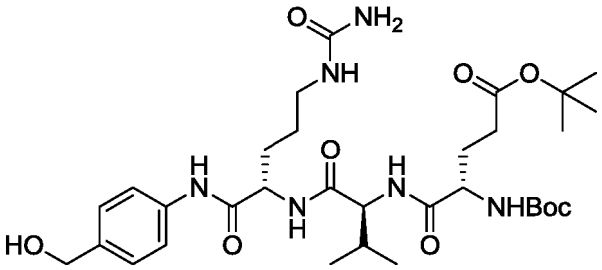


To a stirred solution of *tert*-butyl-6-(6-vinylnicotinamido)hexanoate (Preparation 26; Step 3) (600 mg, 1.886 mmol) in DCM (50 mL) was added TFA (5 mL) at RT. The reaction was continued for 30 min. and checked by UPLC-MS. After completion the excess TFA was evaporated under reduced pressure. The crude obtained was triturated with Et_2O to afford the title compound (420 mg, 1.603 mmol and yield 85%) as an off white semi-solid which was used in the next step without any further purification. UPLC-MS m/z: 263 [M+H].

Preparation 27: (S)-*tert*-Butyl 4-((tert-butoxycarbonyl)amino)-5-(((S)-3-methyl-1-(((S)-1-((4-((((4-nitrophenoxy)carbonyl)oxy)methyl)phenyl)amino)-1-oxo-5-ureidopentan-2-yl)amino)-1-oxobutan-2-yl)amino)-5-oxopentanoate

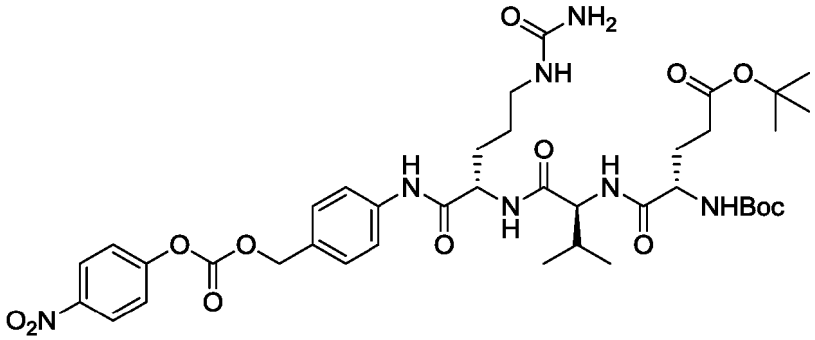


Step 1: (S)-*tert*-Butyl 4-((tert-butoxycarbonyl)amino)-5-(((S)-1-(((S)-1-((4-(hydroxymethyl)phenyl)amino)-1-oxo-5-ureidopentan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)amino)-5-oxopentanoate



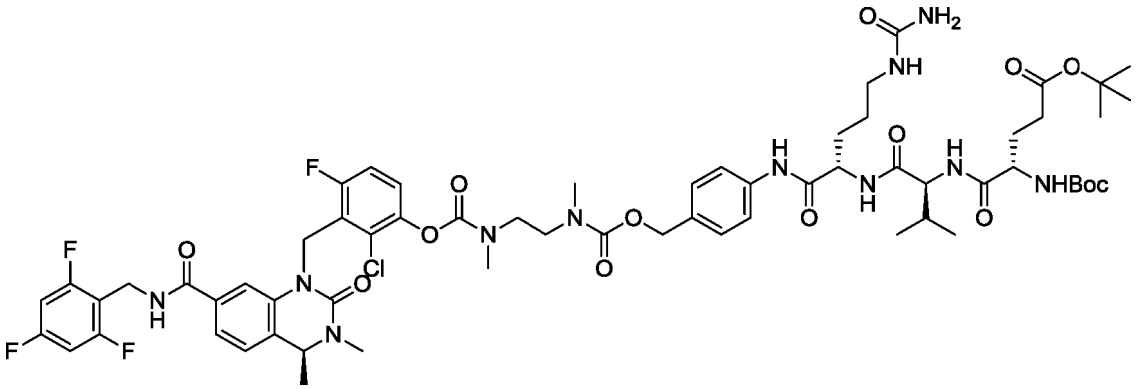
To a stirred solution of commercially available (S)-5-(*tert*-butoxy)-2-((*tert*-butoxycarbonyl)amino)-5-oxopentanoic acid (0.7 g, 2.307 mmol) in DMF (10 mL) was added TEA (0.65 mL, 4.614 mmol), HATU (0.876 g, 2.307 mmol) and HOAt (0.314 g, 2.307 mmol) at 0-5 ^{0}C. Into this reaction mixture was added (S)-2-((S)-2-amino-3-methylbutanamido)-N-(4-(hydroxymethyl)phenyl)-5-ureidopentanamide (Preparation 1; Step 3) (0.875 g, 2.307 mmol) and the resulting reaction mixture was stirred at 0-5 ^{0}C for 20 min. Completion of the reaction was monitored by TLC and LCMS and after completion the reaction mixture was diluted with EtOAc and washed with cold water followed by brine. The collected organic layer was dried over anhydrous Na_2SO_4, filtered and distilled under reduced pressure to afford a viscous oil which solidified when sonicated with a small volume of Et_2O to afford the title compound (1.3 g, 1.955 mmol and yield 84.8%) as a pale yellow solid. LCMS m/z: 665 [M+H].

Step 2: (S)-*tert*-Butyl 4-((tert-butoxycarbonyl)amino)-5-(((S)-3-methyl-1-(((S)-1-((4-((((4-nitrophenoxy)carbonyl)oxy)methyl)phenyl)amino)-1-oxo-5-ureidopentan-2-yl)amino)-1-oxobutan-2-yl)amino)-5-oxopentanoate



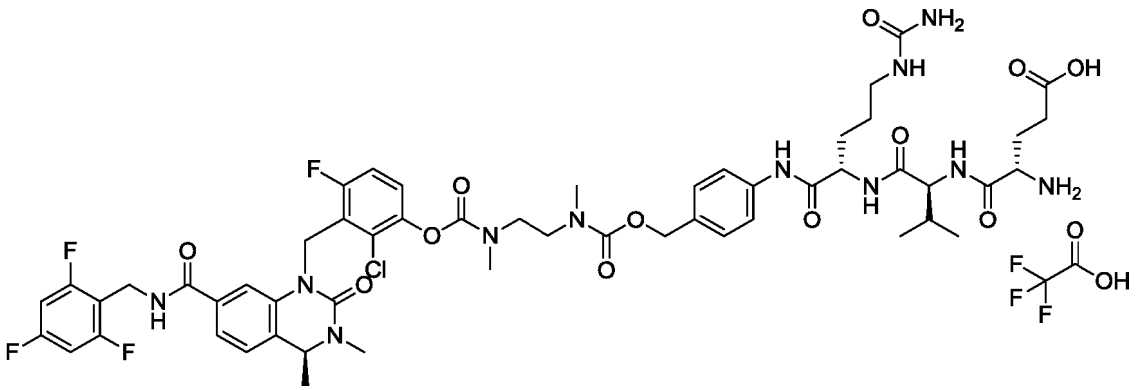
To a stirred solution of (S)-*tert*-butyl-4-((tert-butoxycarbonyl)amino)-5-(((S)-1-(((S)-1-((4-(hydroxymethyl)phenyl)amino)-1-oxo-5-ureidopentan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)amino)-5-oxopentanoate (Preparation 27; Step 1) (528 mg, 0.759 mmol) in DMF (5 mL) was added DIPEA (0.97 mL, 5.566 mmol). The resulting reaction mixture was cooled to 0-5 ^{o}C and 4-nitrophenyl chloroformate added in one portion. The temperature of the reaction was then raised to RT and the whole stirred overnight. After completion of the reaction (monitored by LCMS and TLC), the mixture was diluted with water and extracted with an EtOAc/isopropanol mixture (10% EtOAc in isopropanol). The organic layer was dried over anhydrous Na_2SO_4 and concentrated to give the crude product which was purified by trituration with Et_2O to afford the title compound (400 mg, 0.482 mmol and yield 60.6%) as a pale yellow solid. LCMS m/z: 830 [M+H].

Preparation 28: (S)-*tert*-Butyl 4-((tert-butoxycarbonyl)amino)-5-(((S)-1-(((S)-1-((4-((((2-(((2-chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenoxy)carbonyl)(methyl)amino)ethyl)(methyl)carbamoyl)oxy)methyl)phenyl)amino)-1-oxo-5-ureidopentan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)amino)-5-oxopentanoate



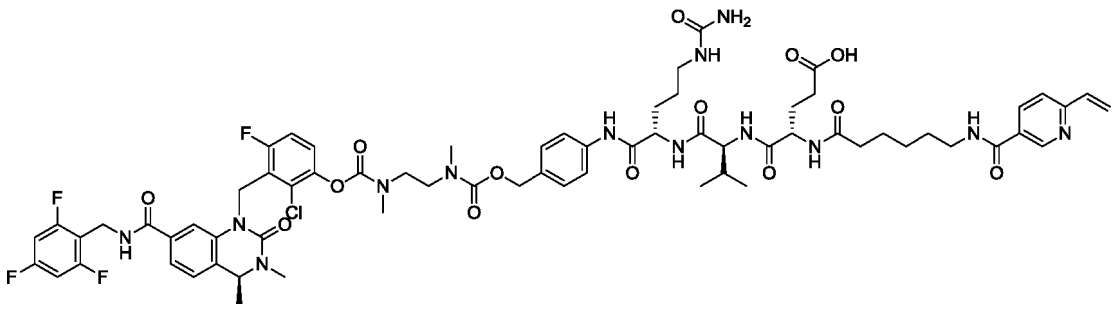
To a stirred solution of (S)-*tert*-butyl 4-((tert-butoxycarbonyl)amino)-5-(((S)-3-methyl-1-(((S)-1-((4-((((4-nitrophenoxy)carbonyl)oxy)methyl)phenyl)amino)-1-oxo-5-ureidopentan-2-yl)amino)-1-oxobutan-2-yl)amino)-5-oxopentanoate (Preparation 27; Step 2) (400 mg, 0.482 mmol) and (S)-2-chloro-3-((3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenyl methyl(2-(methylamino)ethyl)carbamate hydrochloride (Preparation 2; Step 4) (485 mg, 0.723 mmol) in DMF (4 mL) were added DIPEA (124 mg, 0.964 mmol). The reaction was continued at RT until complete as monitored by UPLC-MS. After approx. 30 min, the reaction mixture was diluted with Et_2O and left for a few minutes to allow the resulting gummy liquid to settle, and was then separated out by decanting the Et_2O layer and drying under vacuum to give the title compound (940 mg, 0.7088 mmol) as a gummy oil. LCMS m/z: 1326 [M+H].

Preparation 29: (S)-4-Amino-5-(((S)-1-(((S)-1-((4-((((2-(((2-chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)fluorophenoxy)carbonyl)(methyl)amino)ethyl)(methyl)carbamoyl)oxy)methyl)phenyl)amino)-1-oxo-5-ureidopentan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)amino)-5-oxopentanoic acid compound with 2,2,2-trifluoroacetic acid



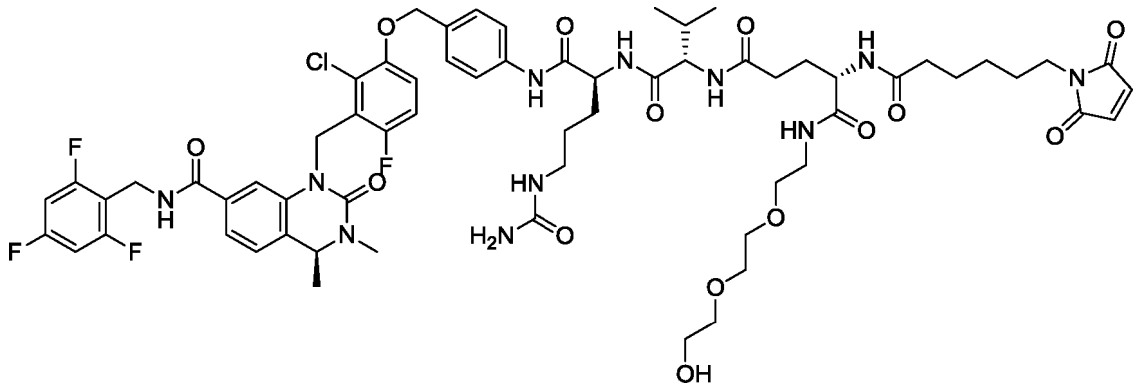
To a stirred solution of (S)-*tert*-butyl 4-((tert-butoxycarbonyl)amino)-5-(((S)-1-(((S)-1-((4-((((2-(((2-chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenoxy)carbonyl)(methyl)amino)-ethyl)(methyl)carbamoyl)oxy)methyl)phenyl)amino)-1-oxo-5-ureidopentan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)amino)-5-oxopentanoate (Preparation 28) (940 mg, 0.709 mmol) in DCM (50 mL) was added TFA (5 mL) at RT and stirring continued for 30 min. Completion of the reaction was confirmed by UPLC-MS and the solvents were then evaporated in vacuo to give a crude mass which was triturated with Et_2O to afford the title compound (800 mg, 0.622 mmol) as a crude off white solid which was used in the next step without any further purification. LCMS m/z: 1170 [M+H].

Preparation 30: (S)-5-(((S)-1-(((S)-1-((4-((((2-(((2-Chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenoxy)carbonyl)(methyl)amino)ethyl)(methyl)carbamoyl)oxy)methyl)phenyl)amino)-1-oxo-5-ureidopentan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)amino)-5-oxo-4-(6-(6-vinylnicotinamido)hexanamido)pentanoic acid (**Example 20**)



To a stirred solution of 6-(6-vinylnicotinamido)-hexanoic acid (Preparation 26, Step 4) (199 mg, 0.758 mmol) in DMF (10 mL) was added HATU (240 mg, 0.632 mmol) and TEA (159 mg, 1.579 mmol) at 0-5 °C. After 5 min. stirring (S)-4-amino-5-(((S)-1-(((S)-1-((4-((((2-(((2-chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4 fluorophenoxy)carbonyl)(methyl)amino)ethyl)(methyl)carbamoyl)oxy)methyl)phenyl)amino)-1-oxo-5-ureidopentan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)amino)-5-oxopentanoic acid (Preparation 29) (800 mg, 0.622 mmol) in DMF was added and the whole was further stirred for another 30 min. The progress of the reaction was monitored by UPLC-MS and after completion the reaction mixture was diluted with Et_2O and left for a few minutes for the resulting gummy liquid to settle which was then separated by decanting the solvents. The crude material was then purified by prep-HPLC to give the title compound (32 mg, 0.023 mmol and yield 3%) as a white solid. LCMS m/z: 1414 [M+H].

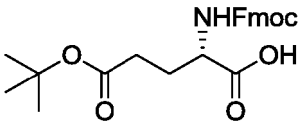
Example 23: (S)-N5-((S)-1-(((S)-1-((4-((2-Chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenoxy)methyl)phenyl)amino)-1-oxo-5-ureidopentan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)-2-(6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanamido)-N1-(2-(2-(2-hydroxyethoxy)ethoxy)ethyl)pentanediamide



Example 23 was prepared according to the methods described in General Procedures 1-4, 19-20 and the method described below.

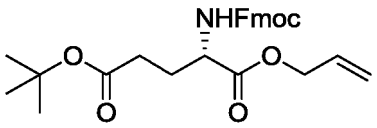
Preparation 31: (S)-4-((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)-5-(allyloxy)-5-oxopentanoic acid

Step 1: (S)-2-((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)-5-(*tert*-butoxy)-5-oxopentanoic acid



To a stirred solution of commercially available (S)-2-amino-5-(*tert*-butoxy)-5-oxopentanoic acid hydrate (4.0 g, 18.07 mmol) in 1,4-dioxane (60 mL) was added an aqueous solution of Na_2CO_3 (3.832 g, 36.158 mmol, 40 mL, 10%) followed by Fmoc-OSu (6.4 g, 18.98 mmol) at 0-5 °C and stirring continued at the same temperature for 5 min. The reaction mixture was allowed to warm slowly to RT and further stirred for 2 h. Completion of the reaction was monitored by TLC and LCMS and after completion the reaction solvents were evaporated under reduced pressure to give a residue which was diluted with water and acidified with 1N HCl to make the pH ~4-5. The resulting mixture was extracted with EtOAc and washed with brine. The organic layer was dried over anhydrous Na_2SO_4, filtered and distilled under reduced pressure to afford the title compound (7.0 g, 18.82 mmol and yield 91%) as an off white solid which was used in the next step without any further purification. LCMS m/z: 426 [M+H].

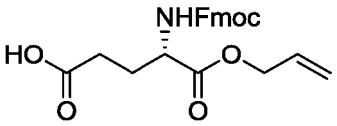
Step 2: (S)-1-Allyl-5-*tert*-butyl 2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino) pentanedioate



To a stirred solution of (S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-5-(*tert*-butoxy)-5-oxopentanoic acid (Preparation 31; Step 1) (1.3 g, 3.05 mmol) in DCM (25 mL) was added allyl alcohol (0.228 mL, 3.36 mmol) followed by DCC (630 mg, 3.36 mmol) and DMAP (18.6 mg, 0.15 mmol). The resulting reaction mixture was stirred at RT for 16 h. Progress of the reaction was monitored by UPLC-MS which confirmed the formation of the desired product. The reaction mixture was diluted with EtOAc and the solid precipitate was filtered off. The filtrate was evaporated in vacuo and purified by

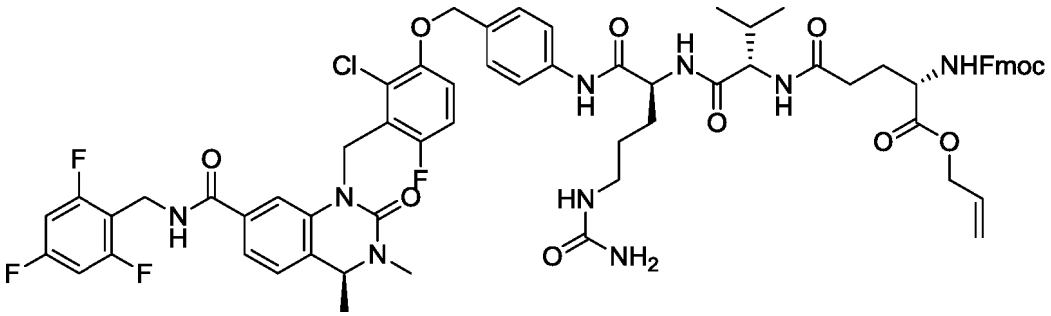
Combi-flash (20 g column) using 45% EtOAc in hexane to afford the title compound (1.1 g, 2.365 mmol and yield 77.5%) as colourless oil. UPLC-MS m/z: 466 [M+H].

Step 3: (S)-4-((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)-5-(allyloxy)-5-oxopentanoic acid



To a stirred solution of (S)-1-allyl-5-*tert*-butyl-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)pentanedioate (Preparation 31; Step 2) (1.1 g, 2.365 mmol) in DCM (10 mL) was added 25% TFA in DCM (12 mL) and the whole stirred at RT for 1 h. UPLC showed formation of the desired compound, whereupon the solvent was evaporated to give a residue which was purified by trituration with n-hexane and Et_2O to afford the title compound (0.9 g, 2.2 mmol and yield 93%) as a faint pinkish solid. UPLC-MS m/z: 410 [M+H].

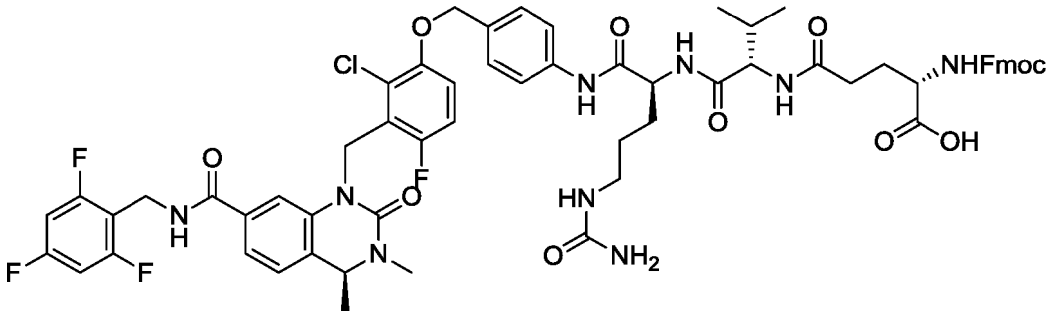
Preparation 32: (S)-Allyl-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-5-(((S)-1-(((S)-1-((4-((2-chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenoxy)methyl)phenyl)amino)-1-oxo-5-ureidopentan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)amino)-5-oxopentanoate



To a stirred solution of (S)-1-(3-((4-((S)-2-((S)-2-amino-3-methylbutanamido)-5-ureidopentanamido)benzyl)oxy)-2-chloro-6-fluorobenzyl)-3,4-dimethyl-2-oxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4-tetrahydroquinazoline-7-carboxamide (Preparation 11) (1.5 g, 1.7 mmol) in DMF (25 mL) was added HATU (645 mg, 1.70 mmol), HOAt (231 mg, 1.70 mmol), TEA (0.490 mL, 1.19 mmol) and (S)-4-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-5-(allyloxy)-5-oxopentanoic acid (Preparation 31; Step 3) (1.048 g, 1.19 mmol) at 0-5 °C and stirring was continued at RT for 2 h. The reaction

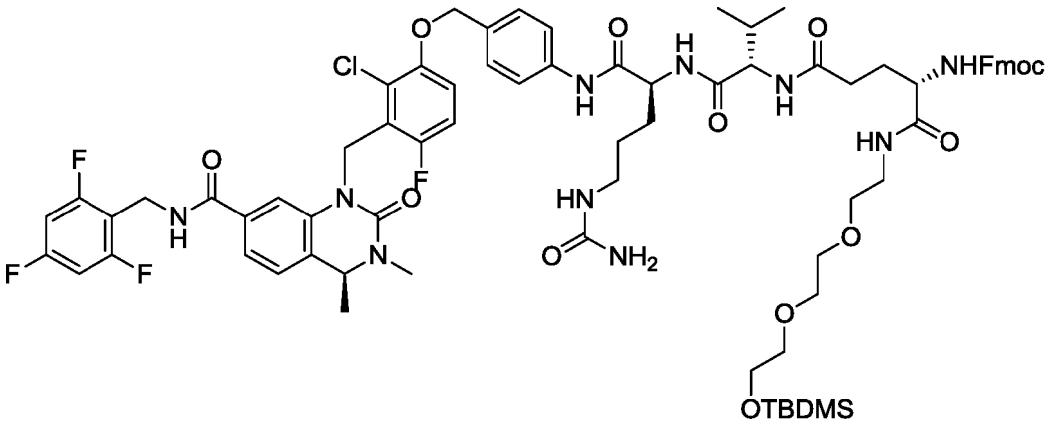
was monitored by UPLC-MS and after completion the reaction mixture was diluted with water to produce a solid material which was filtered and dried in an oven to afford the title compound (800 mg) as a crude white solid. UPLC-MS m/z: 1275 [M+H].

Preparation 33: (S)-2-((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)-5-(((S)-1-(((S)-1-((4-((2-chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenoxy)methyl)phenyl)amino)-1-oxo-5-ureidopentan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)amino)-5-oxopentanoic acid



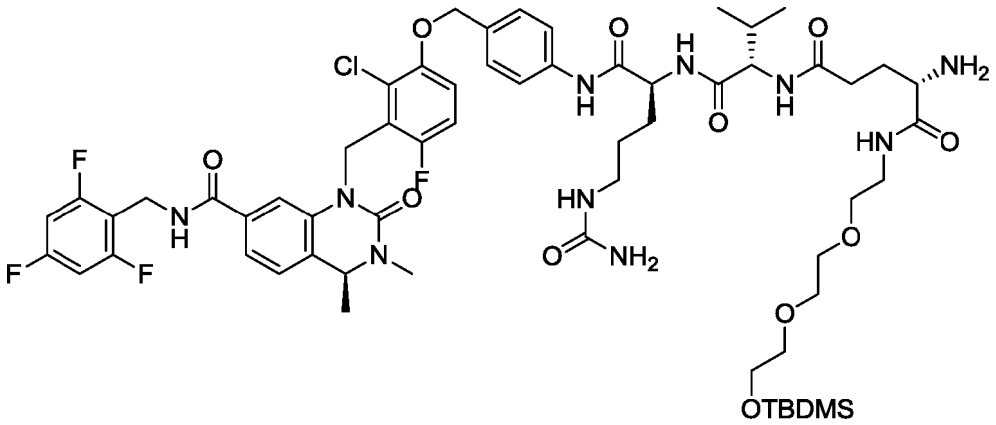
To a stirred solution of (S)-allyl-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-5-(((S)-1-(((S)-1-((4-((2-chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenoxy)methyl)phenyl)amino)-1-oxo-5-ureidopentan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)amino)-5-oxopentanoate (Preparation 32) (1.0 g, 0.78 mmol) in DCM (25 mL) was added piperidine (93 µl, 0.94 mmol), PPh_3 (308 mg, 1.41 mmol) and $Pd(PPh_3)_4$ (317.5 mg, 0.27 mmol) at -15 °C. After the addition was complete, the resulting reaction mixture was allowed to warm to RT and stirred for 5 h. Progress of the reaction was monitored by UPLC-MS and after completion the reaction mixture was diluted with MeCN and water, the layers were separated and the organic layer was dried over anhydrous Na_2SO_4 and evaporated to give a residue which was washed with hexane to remove excess PPh_3 and evaporated to afford the title compound (800 mg) as a white solid. UPLC-MS m/z: 1234 [M+H].

Preparation 34: (9H-Fluoren-9-yl)methyl-((6S,9S,14S)-1-amino-6-((4-((2-chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenoxy)methyl)phenyl)carbamoyl)-9-isopropyl-26,26,27,27-tetramethyl-1,8,11,15-tetraoxo-19,22,25-trioxa-2,7,10,16-tetraaza-26-silaoctacosan-14-yl)carbamate



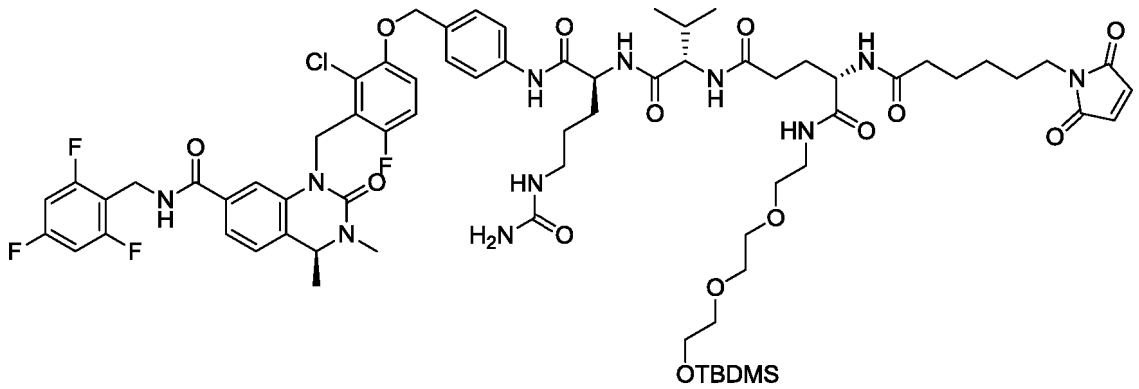
To a stirred solution of (S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-5-(((S)-1-(((S)-1-((4-((2-chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenoxy)methyl)phenyl)amino)-1-oxo-5-ureidopentan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)amino)-5-oxopentanoic acid (Preparation 33) (800 mg, 0.65 mmol) in DMF (15 mL) was added HATU (246.3 mg, 0.65 mmol), HOAt (88 mg, 0.65 mmol) and TEA (182 µL, 1.30 mmol) at 0-5 °C. The whole was stirred for 5 min. then 2,2,3,3-tetramethyl-4,7,10-trioxa-3-siladodecan-12-amine (256 mg, 0.97 mmol) was added in one portion. The resulting reaction mixture was further stirred at RT for 1 h. UPLC-MS showed formation of the desired product and after completion of the reaction the whole was diluted with water and the solid precipitate was filtered off and dried in an oven to afford the title compound (800 mg) as a crude off white solid which was used in the next step without any further purification. UPLC-MS m/z: 1280 [M+H].

Preparation 35: (S)-2-Amino-N5-((S)-1-(((S)-1-((4-((2-chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenoxy)methyl)phenyl)amino)-1-oxo-5-ureidopentan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)-N1-(2,2,3,3-tetramethyl-4,7,10-trioxa-3-siladodecan-12-yl)pentanediamide



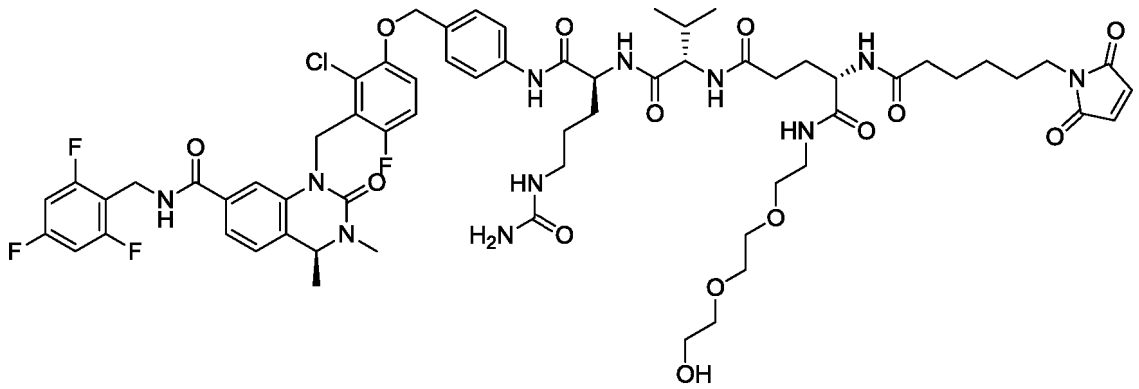
To a stirred solution of (9H-fluoren-9-yl)methyl ((6S,9S,14S)-1-amino-6-((4-((2-chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenoxy)methyl)phenyl)carbamoyl)-9-isopropyl-26,26,27,27-tetramethyl-1,8,11,15-tetraoxo-19,22,25-trioxa-2,7,10,16-tetraaza-26-silaoctacosan-14-yl)carbamate (Preparation 34) (800 mg, 0.54 mmol) in THF (20 mL) was added diethyl amine (50 mL) at RT and the whole was stirred at RT for 2 h. Progress of the reaction was monitored by UPLC-MS and after completion the solvent was evaporated to give a crude product which was triturated with n-hexane and Et_2O to afford the title compound (700 mg) as a grey solid. UPLC-MS m/z: 1275 [M+H].

Preparation 36: (S)-N5-((S)-1-(((S)-1-((4-((2-Chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenoxy)methyl)phenyl)amino)-1-oxo-5-ureidopentan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)-2-(6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanamido)-N1-(2,2,3,3-tetramethyl-4,7,10-trioxa-3-siladodecan-12-yl)pentanediamide



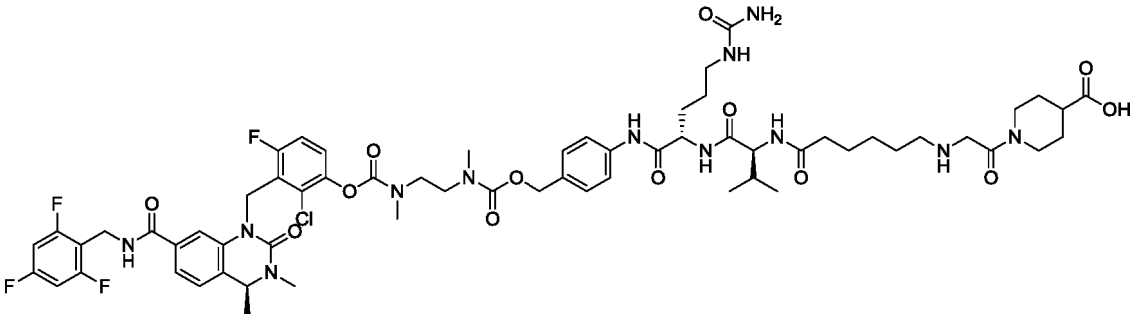
To a stirred solution of commercially available 6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoic acid (59 mg, 0.278 mmol) in DMF (10 mL) was added HATU (106 mg, 0.278 mmol), HOAt (38 mg, 0.278 mmol), TEA (80 µL, 0.557 mmol) and (S)-2-amino-N5-((S)-1-(((S)-1-((4-((2-chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenoxy)methyl)phenyl)amino)-1-oxo-5-ureidopentan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)-N1-(2,2,3,3-tetramethyl-4,7,10-trioxa-3-siladodecan-12-yl)pentanediamide (Preparation 35) (350 mg, 0.278 mmol) at 0-5 °C and then allowed to warm to RT. The whole was stirred at RT for 1 h. UPLC-MS showed formation of the desired product and after completion of the reaction the whole was diluted with water and the solid precipitate was filtered off and dried in an oven to afford the title compound (350 mg) as an off white solid which was used in the next step without any further purification. UPLC-MS m/z: 1451 [M+H].

Preparation 37: (S)-N5-((S)-1-(((S)-1-((4-((2-Chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenoxy)methyl)phenyl)amino)-1-oxo-5-ureidopentan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)-2-(6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanamido)-N1-(2-(2-(2-hydroxyethoxy)ethoxy)ethyl)pentanediamide (**Example 23**)



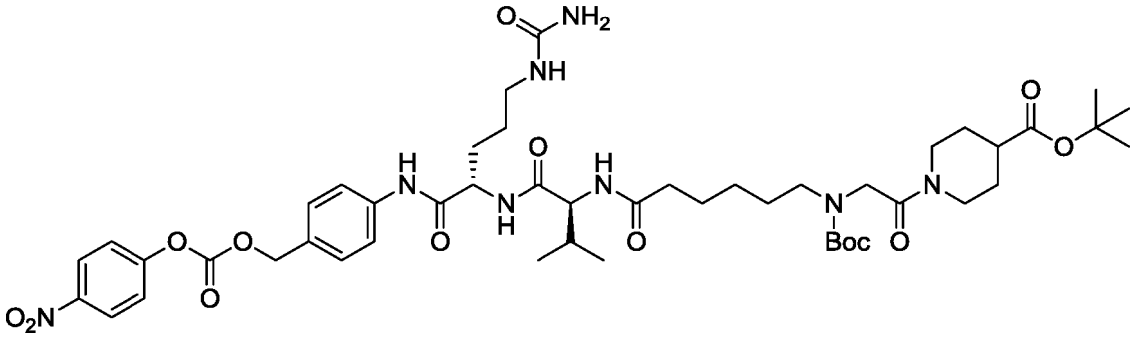
To a stirred solution of (S)-N5-((S)-1-(((S)-1-((4-((2-chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenoxy)methyl)phenyl)amino)-1-oxo-5-ureidopentan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)-2-(6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanamido)-N1-(2,2,3,3-tetramethyl-4,7,10-trioxa-3-siladodecan-12-yl)pentanediamide (Preparation 36) (350 mg, 0.241 mmol) in THF (5 mL) was added 1N HCl in THF (10 mL) at RT and the whole was stirred at RT for 5 min. at which time UPLC-MS showed complete conversion of starting material into the desired product. The reaction mixture was neutralized by dropwise addition of TEA to pH ~7 at 5-10°C. The neutralized reaction mixture was evaporated in vacuo to give a residue which was purified by prep-HPLC to afford the title compound (10 mg, 0.0075 mmol and yield 3%) as a white solid. UPLC-MS m/z: 1336.3 [M+H].

Example 25: 1-((6S,9S)-1-Amino-6-((4-((((2-(((2-chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenoxy)carbonyl)(methyl)amino)ethyl)(methyl)carbamoyl)oxy)methyl)phenyl)carbamoyl)-9-isopropyl-1,8,11-trioxo-2,7,10,17-tetraazanonadecan-19-oyl)piperidine-4-carboxylic acid

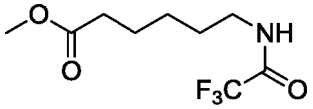


Example 25 was prepared according to the methods described in General Procedures 1-2, 4-6, 10, 12, 15, 17-18, 20 and the method described below.

Preparation 38: *tert*-Butyl-1-((6S,9S)-1-amino-17-(tert-butoxycarbonyl)-9-isopropyl-6-((4-((((4-nitrophenoxy)carbonyl)oxy)methyl)phenyl)carbamoyl)-1,8,11-trioxo-2,7,10,17-tetraazanonadecan-19-oyl)piperidine-4-carboxylate



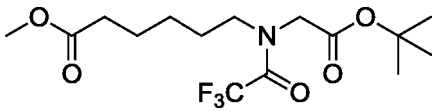
Step 1: Methyl-6-(2,2,2-trifluoroacetamido)hexanoate



To a stirred solution of commercially available methyl-6-aminohexanoate hydrochloride (0.5 g, 2.75 mmol) in DCM (10 mL) was added TFAA (0.42 mL, 3.02 mmol) followed by TEA (0.76 mL, 5.5 mmol) at 0-5 °C and the whole was stirred for 2 h at RT. Progress of the reaction was monitored by TLC and LCMS and after completion the reaction mixture was quenched with 1N HCl and extracted with DCM. The organic

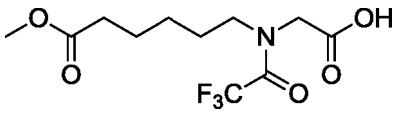
layer was washed with aqueous sodium bicarbonate solution followed by brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the title compound (600 mg, 2.489 mmol and yield 90%) as a crude yellow liquid which was used in the next step without any further purification. LCMS m/z: 242 [M+H].

Step 2: Methyl-6-(N-(2-(*tert*-butoxy)-2-oxoethyl)-2,2,2-trifluoroacetamido)hexanoate



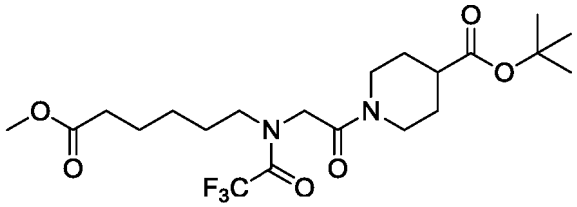
To a stirred solution of methyl-6-(2,2,2-trifluoroacetamido)hexanoate (Preparation 38; Step 1) (0.55 g, 2.28 mmol) in DMF (8 mL) was added NaH (0.065 g, 2.73 mmol) followed by *tert*-butyl-bromoacetate (0.367 mL, 2.50 mmol) at 0-5 °C and the whole was stirred for 2 h at RT. Progress of the reaction was monitored by LCMS and after completion the reaction mixture was quenched with a saturated solution of ammonium chloride and extracted with EtOAc followed by a brine wash. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the title compound (800 mg, 2.253 mmol and yield 90%) as a yellow liquid which was used in the next step without any further purification. LCMS m/z: 356 [M+H].

Step 3: 2-(2,2,2-Trifluoro-N-(6-methoxy-6-oxohexyl)acetamido)acetic acid



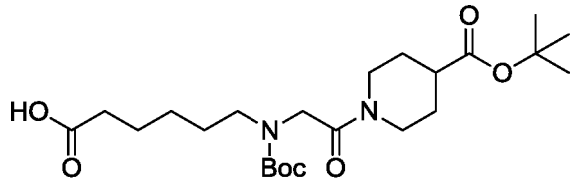
To a stirred solution of methyl-6-(N-(2-(*tert*-butoxy)-2-oxoethyl)-2,2,2-trifluoroacetamido)hexanoate (Preparation 38; Step 2) (0.8 g, 2.25 mmol) in DCM (8 mL) was added TFA (1.6 mL, 20.26 mmol) at 0-5 °C and the whole was stirred at RT overnight. Progress of the reaction was monitored by TLC and LCMS and after completion the solvents were evaporated by azeotropic distillation using DCM as co-solvent to give a residue which was dried under high vacuum to afford the title compound (650 mg, 2.17 mmol and yield 96%) as a pale yellow viscous liquid which was used in the next step without any further purification. LCMS m/z: 300 [M+H].

Step 4: *tert*-Butyl-1-(2-(2,2,2-trifluoro-N-(6-methoxy-6-oxohexyl)acetamido)acetyl) piperidine-4-carboxylate



To a stirred solution of 2-(2,2,2-trifluoro-N-(6-methoxy-6-oxohexyl)acetamido)acetic acid (Preparation 38; Step 3) (0.65 g, 2.17 mmol) in DMF (10 mL) was added TEA (0.77 mL, 4.34 mmol) and HATU (0.825 g, 2.17 mmol) at 0-5 °C and the mixture stirred for 5 min. Commercially available *tert*-butyl-piperidine-4-carboxylate hydrochloride (0.480 g, 2.17 mmol) was then added to the reaction mixture and the whole stirred at RT for 20 min. The reaction was monitored by LCMS and after completion the reaction mixture was diluted with EtOAc and washed with cold water followed by brine. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the title compound (1.0 g, yield 98% as crude) as a yellow viscous liquid which was used in the next step without any further purification. LCMS m/z: 467 [M+H].

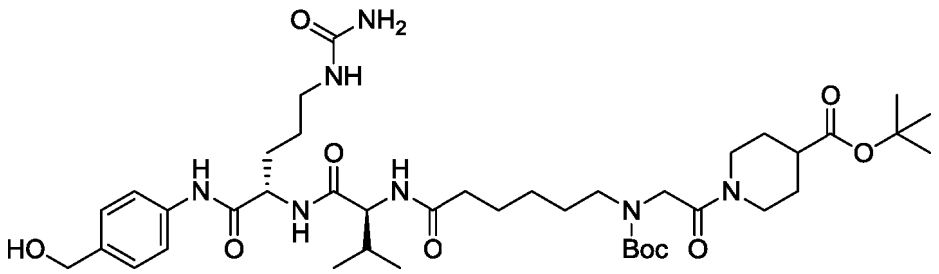
Step 5: 6-((*tert*-Butoxycarbonyl)-(2-(4-(tert-butoxycarbonyl)piperidin-1-yl)-2-oxoethyl)amino)hexanoic acid



To a stirred solution of *tert*-butyl-1-(2-(2,2,2-trifluoro-N-(6-methoxy-6-oxohexyl)acetamido)acetyl)piperidine-4-carboxylate (Preparation 38; Step 4) (0.9 g, 1.92 mmol) in a mixture of THF:MeOH:H_2O (2:1:1, 20 mL) was added LiOH.H_2O (0.32 g, 7.71 mmol) at RT and the whole stirred at RT for 1 h. Progress of the reaction was monitored by LCMS. It was found that both the methyl ester and trifluoroacetyl groups were deprotected simultaneously to give intermediate 6-((2-(4-(*tert*-butoxycarbonyl)piperidin-1-yl)-2-oxoethyl)amino)hexanoic acid. To this reaction mixture was added Boc-anhydride (1.77 mL, 7.71 mmol) and the whole stirred for another 3 h at RT. Progress of the reaction was monitored by LCMS and after completion the solvents were evaporated under reduced pressure to give a residue which was diluted with water and acidified with 1N HCl to pH ~4-5. The resulting

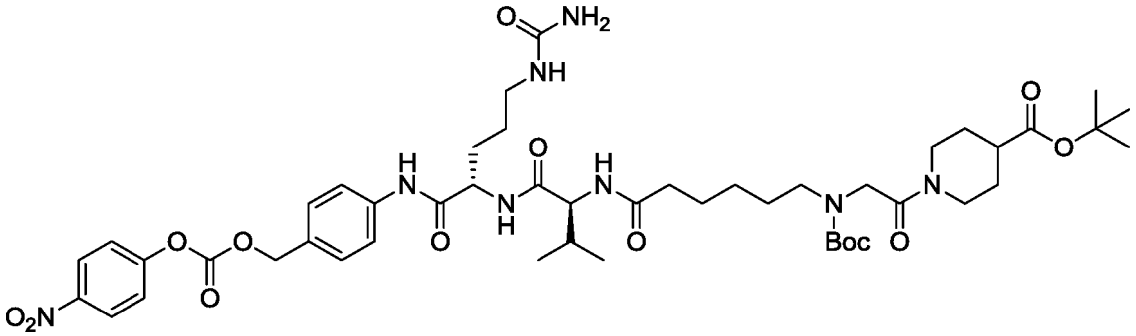
aqueous mixture was extracted with EtOAc and washed with brine. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the title compound (800 mg, yield 91% as crude) as a pale yellow viscous oil which was used in the next step without any further purification. LCMS m/z: 457 [M+H].

Step 6: *tert*-Butyl-1-((6S,9S)-1-amino-17-(tert-butoxycarbonyl)-6-((4-(hydroxymethyl)phenyl)carbamoyl)-9-isopropyl-1,8,11-trioxo-2,7,10,17-tetraazanonadecan-19-oyl)piperidine-4-carboxylate



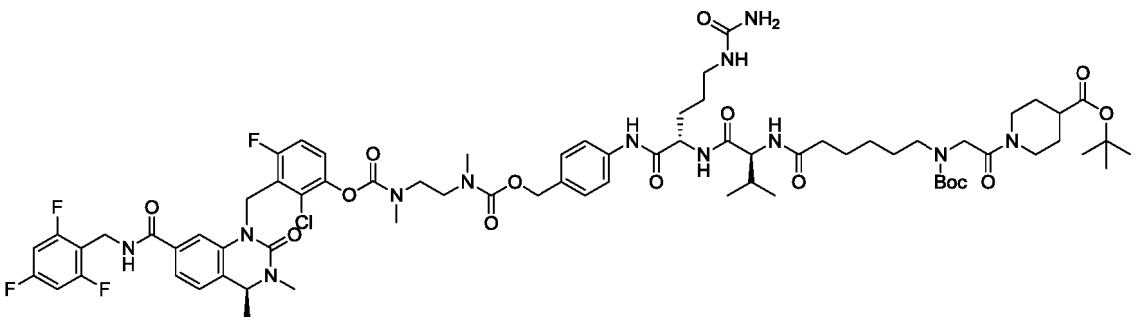
To a stirred solution of 6-((*tert*-butoxycarbonyl)-(2-(4-(tert-butoxycarbonyl)piperidin-1-yl)-2-oxoethyl)amino)hexanoic acid (Preparation 38; Step 5) (0.7 g, 1.53 mmol) in DMF (10 mL) was added TEA (0.54 mL, 3.06 mmol) and HATU (0.58 g, 1.53 mmol) at 0-5 °C and the whole stirred for 5 min. (S)-2-((S)-2-amino-3-methylbutanamido)-N-(4-(hydroxymethyl)phenyl)-5-ureidopentanamide (Preparation 1; Step 3) (0.581 g, 1.53 mmol) was then added in one portion. The resulting reaction mixture was brought to RT and stirred for 20 min. After completion of the reaction it was diluted with EtOAc and washed with cold water followed by brine. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the title compound (600 mg, yield 50% as crude) as a yellow viscous liquid which was used in the next step without any further purification. LCMS m/z: 818 [M+H].

Step 7: *tert*-Butyl-1-((6S,9S)-1-amino-17-(tert-butoxycarbonyl)-9-isopropyl-6-((4-((((4-nitrophenoxy)carbonyl)oxy)methyl)phenyl)carbamoyl)-1,8,11-trioxo-2,7,10,17-tetraazanonadecan-19-oyl)piperidine-4-carboxylate



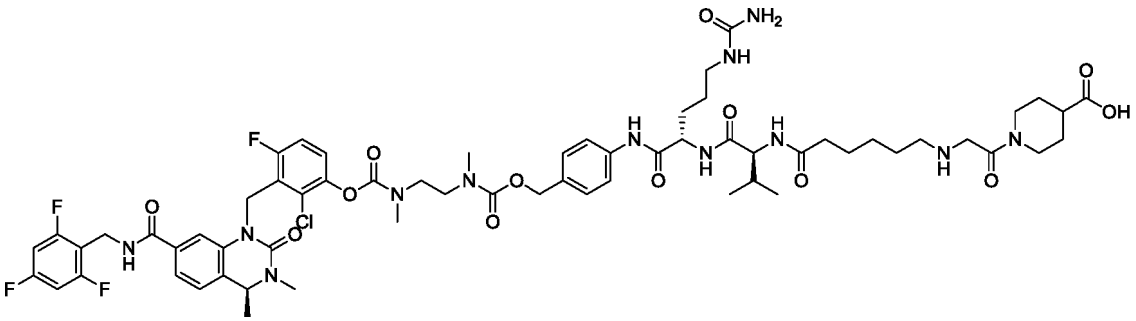
To a stirred solution of *tert*-butyl-1-((6S,9S)-1-amino-17-(tert-butoxycarbonyl)-6-((4-(hydroxymethyl)phenyl)carbamoyl)-9-isopropyl-1,8,11-trioxo-2,7,10,17-tetraazanonadecan-19-oyl)piperidine-4-carboxylate (Preparation 38; Step 6) (0.6 g, 0.73 mmol) in DMF (7 mL) was added DIPEA (0.62 mL, 3.66 mmol) followed by p-nitrophenyl chloroformate (0.44 g, 2.20 mmol) at 0-5 °C and the whole was stirred for 5 min. The reaction mixture was then brought to RT and stirred overnight. Progress of the reaction was monitored by TLC and LCMS and after completion the reaction mixture was poured into cold water and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to afford a crude compound which was redissolved in a mixture of Et_2O and hexane. Evaporation under reduced pressure gave the title compound (400 mg, yield 55%) as a yellow solid. LCMS m/z: 983 [M+H].

Preparation 39: *tert*-Butyl-1-((6S,9S)-1-amino-17-(tert-butoxycarbonyl)-6-((4-((((2-(((2-chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenoxy)carbonyl)(methyl)amino)ethyl)(methyl)carbamoyl)oxy)methyl)phenyl)carbamoyl)-9-isopropyl-1,8,11-trioxo-2,7,10,17-tetraazanonadecan-19-oyl)piperidine-4-carboxylate



To a stirred solution of *tert*-butyl 1-((6S,9S)-1-amino-17-(tert-butoxycarbonyl)-9-isopropyl-6-((4-((((4-nitrophenoxy)carbonyl)oxy)methyl)phenyl)carbamoyl)-1,8,11-trioxo-2,7,10,17-tetraazanonadecan-19-oyl)piperidine-4-carboxylate (Preparation 38; Step 7) (0.3 g, 0.305 mmol) and (S)-2-chloro-3-((3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenyl methyl(2-(methylamino)ethyl)carbamate hydrochloride (Preparation 2; Step 4) (0.29 g, 0.457 mmol) in DMA (5 mL) were added 2,6-lutidine (0.035 mL, 0.305 mmol) and DIPEA (0.052 mL, 0.305 mmol) at 0-5 °C. The resulting reaction mixture was stirred at 0-5 °C for 1 h and checked to ensure the pH of the reaction mixture was ~7-7.5. Progress of the reaction was monitored by LCMS and after completion the reaction mixture was diluted with EtOAc, washed with cold water and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford an oily liquid which was triturated with Et_2O and EtOAc to give the title compound (350 mg, yield 64.7% as crude) as a pale yellow solid. LCMS m/z: 1479.8 [M+H].

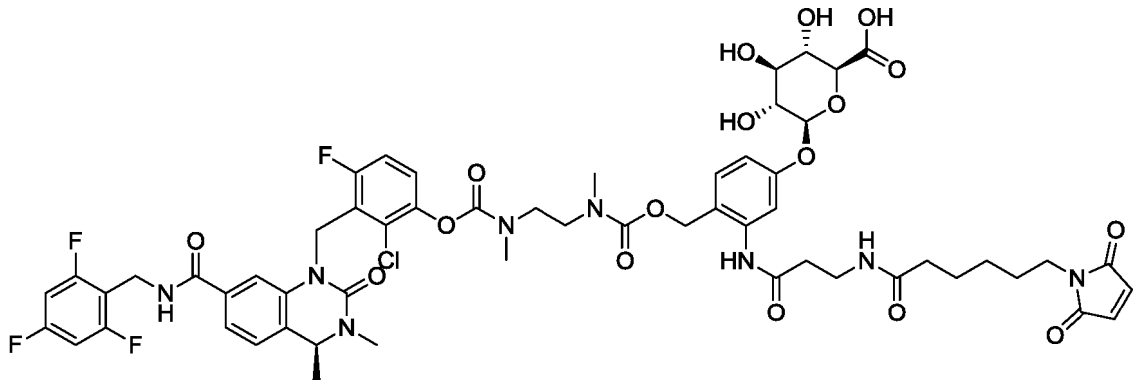
Preparation 40: 1-((6S,9S)-1-Amino-6-((4-((((2-(((2-chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenoxy)carbonyl)(methyl)amino)ethyl)(methyl)carbamoyl)oxy)methyl)phenyl)carbamoyl)-9-isopropyl-1,8,11-trioxo-2,7,10,17-tetraazanonadecan-19-oyl)piperidine-4-carboxylic acid (**Example 25**)



To a stirred solution of *tert*-butyl-1-((6S,9S)-1-amino-17-(tert-butoxycarbonyl)-6-((4-((((2-(((2-chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenoxy)carbonyl)(methyl)amino)ethyl)(methyl)carbamoyl)oxy)methyl)phenyl)carbamoyl)-9-isopropyl-1,8,11-trioxo-2,7,10,17-tetraazanonadecan-19-oyl)piperidine-4-carboxylate (Preparation 39) (0.27 g, 0.18 mmol) in DCM (6 mL) was added TFA (1 mL) at 0-5 °C and stirring continued for 5 min. at the same temperature. The reaction mixture was brought to RT and stirred for 2.5 h. Progress of the reaction was monitored by TLC and LCMS and after completion

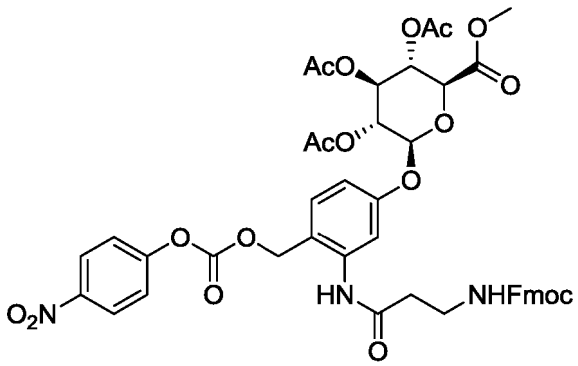
the solvents were evaporated to give a crude product which was triturated with Et_2O to afford a yellow solid. The obtained solid was further purified by prep-HPLC to give the title compound (10 mg, yield 4%) as a white solid. LCMS m/z: 1323.7 [M+H].

Example 27: (2S,3S,4S,5R,6S)-6-(4-((((2-(((2-Chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4 fluorophenoxy)carbonyl) (methyl)amino)ethyl)(methyl)carbamoyl)oxy)methyl)-3-(3-(6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1 yl)hexanamido)propanamido) phenoxy)-3,4,5-trihydroxytetrahydro-2H-pyran-2-carboxylic acid

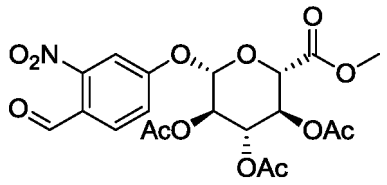


Example 27 was prepared according to the methods described in General Procedures 2, 6, 10, 12, 15, 17-18 and the method described below.

Preparation 41: (2S,3R,4S,5S,6S)-2-(3-(3-((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)propanamido)-4-((((4-nitrophenoxy)carbonyl)oxy)methyl)phenoxy)-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate

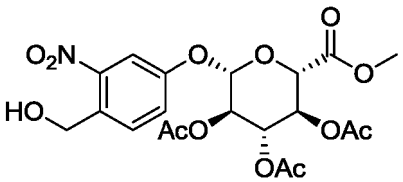


Step 1: (2S,3R,4S,5S,6S)-2-(4-Formyl-3-nitrophenoxy)-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate



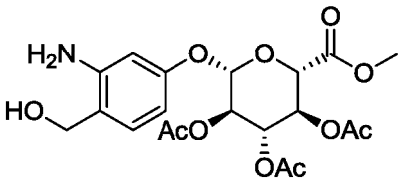
To a stirred solution of commercially available (2R,3R,4S,5S,6S)-2-bromo-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (1.5 g, 3.786 mmol) in anhydrous MeCN (30 mL) was added 4-hydroxy-3-nitrobenzaldehyde (1.075 g, 6.436 mmol) followed by Ag_2O (3.948 g, 17.036 mmol) at RT and the resulting slurry mixture was stirred in the dark under N_2 at RT for 2 h. Completion of the reaction was confirmed by TLC. The solution was filtered through a celite bed to remove solid material and the filtrate was concentrated in vacuo to give a residue which was diluted with EtOAc (500 mL) and washed with a saturated solution of NaHCO3 (2 × 100 mL), water (100 mL) and brine (100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to afford the title compound (1.5 g, 3.103 mmol and yield 82%) as an off white solid.

Step 2: (2S,3S,4S,5R,6S)-Methyl-6-(4-(hydroxymethyl)-3-nitrophenoxy)-3,4,5-trimethoxytetrahydro-2H-pyran-2-carboxyla(2S,3R,4S,5S,6S)-2-(4-(hydroxymethyl)-3-nitrophenoxy)-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate



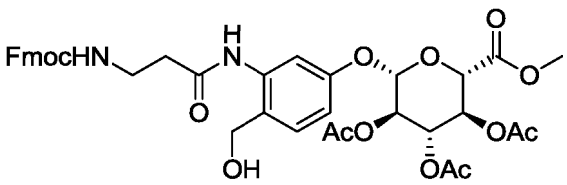
To a stirred solution of (2S,3R,4S,5S,6S)-2-(4-formyl-3-nitrophenoxy)-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (Preparation 41; Step 1) (1.5 g, 3.103 mmol) in a mixture of chloroform and isopropanol (5:1, 25 mL) was added silica gel (630 mg, 100-200 mesh) at RT. The resulting reaction mixture was cooled to 0-5 °C and then NaBH4 (176 mg, 4.658 mmol) was added. The whole was stirred at 0-5 °C for 3 h. Progress of the reaction was monitored by TLC and after completion the reaction mixture was diluted with dichloromethane (250 mL), filtered through a celite bed and the filtrate was washed with water (100 mL), brine (75 mL) and concentrated in vacuo to give the title compound (1.2 g, as crude) as an off white solid which was used in the next step without any further purification.

Step 3: (2S,3R,4S,5S,6S)-2-(3-Amino-4-(hydroxymethyl)phenoxy)-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate



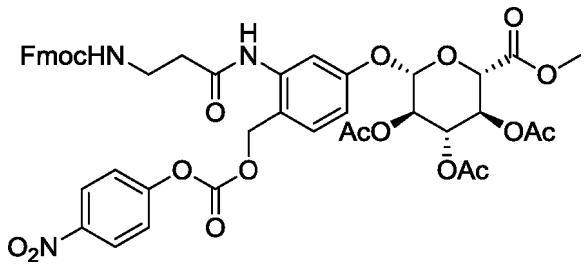
To a stirred suspension of (2S,3R,4S,5S,6S)-2-(4-(hydroxymethyl)-3-nitrophenoxy)-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (Preparation 41; Step 2) (1.2 g, 2.474 mmol) in EtOAc (12 mL) was added 10% Pd/C (300 mg, 50% wet) under a N_2 atmosphere. The resulting reaction mixture was stirred under H_2 balloon pressure at RT for 3 h. After completion (monitored by TLC) the reaction mixture was diluted with EtOAc and filtered through a pad of diatomaceous earth. The filtrate was concentrated in vacuo to give the title compound (1.0 g, as crude) as a light yellow solid which was used in the next step without any further purification. UPLC-MS m/z: 456 [M+H].

Step 4: (2S,3R,4S,5S,6S)-2-(3-(3-((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)propanamido)-4-(hydroxymethyl)phenoxy)-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate



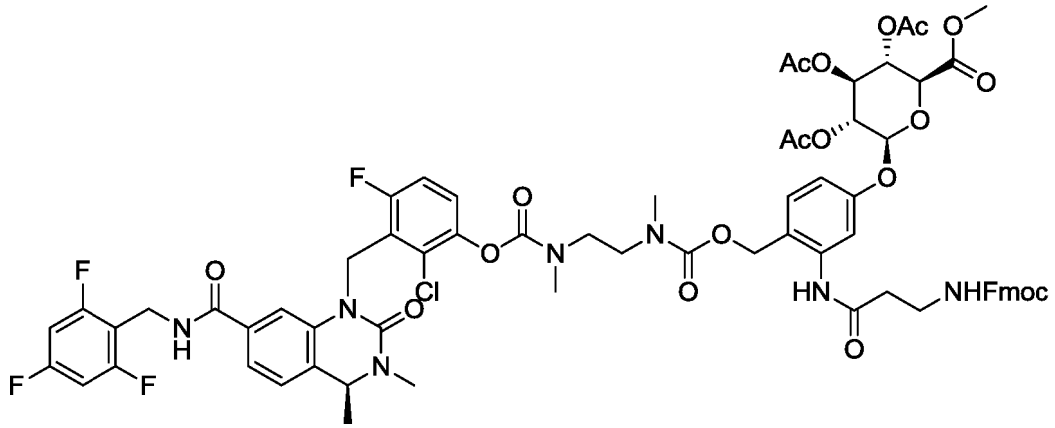
To a stirred solution of (2S,3R,4S,5S,6S)-2-(3-amino-4-(hydroxymethyl)phenoxy)-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (Preparation 41; Step 3) (1.0 g, 2.197 mmol) in dichloromethane (10 mL) was added DIPEA (0.752 mg, 0.0058 mmol) and separately synthesized (9H-fluoren-9-yl)methyl-(3-chloro-3-oxopropyl)carbamate (904 mg, 2.746 mmol) in DCM (5 mL) and the whole was stirred for 30 min. After completion of the reaction (monitored by TLC and UPLC-MS) the reaction mixture was poured into saturated aqueous sodium bicarbonate solution and extracted with EtOAc (2 x 250 mL). The combined extracts were washed with water followed by brine, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to give the crude product which was purified by column chromatography using EtOAc/hexane mixtures as the mobile phase to give the title compound (1.3 g, 1.736 mmol and yield 79%) as a white solid. UPLC-MS m/z: 749 [M+H].

Step 5: (2S,3R,4S,5S,6S)-2-(3-(3-((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)propanamido)-4-((((4-nitrophenoxy)carbonyl)oxy)methyl)phenoxy)-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate



To a stirred solution of (2S,3R,4S,5S,6S)-2-(3-(3-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)propanamido)-4-(hydroxymethyl)phenoxy)-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (Preparation 41; Step 4) (1.2 g, 1.603 mmol) in DCM (15 mL) was added pyridine (0.78 mL) at ice cold temperature. The resulting reaction mixture was treated with 4-nitrophenyl chloroformate (1.29 g, 6.417 mmol) at 0-5 °C and the whole was stirred at RT for 2 h which yielded approximately 50% conversion of the starting material. A further portion of pyridine (0.78 mL) and 4-nitrophenyl chloroformate (1.29 g, 6.417 mmol) were added to the reaction mixture at 0-5 °C and stirred for another 1 h at RT. Progress of the reaction was monitored by UPLC-MS and TLC and after completion the reaction mixture was poured into water and extracted with EtOAc (2 × 250 mL). The combined extracts were washed with 0.5 N HCl (100 mL) and brine (100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue which was purified by column chromatography using 50% EtOAc in hexane as the mobile phase to afford the title compound (850 mg, 0.93 mmol and yield 58%) as an off white solid. UPLC-MS m/z: 914 [M+H].

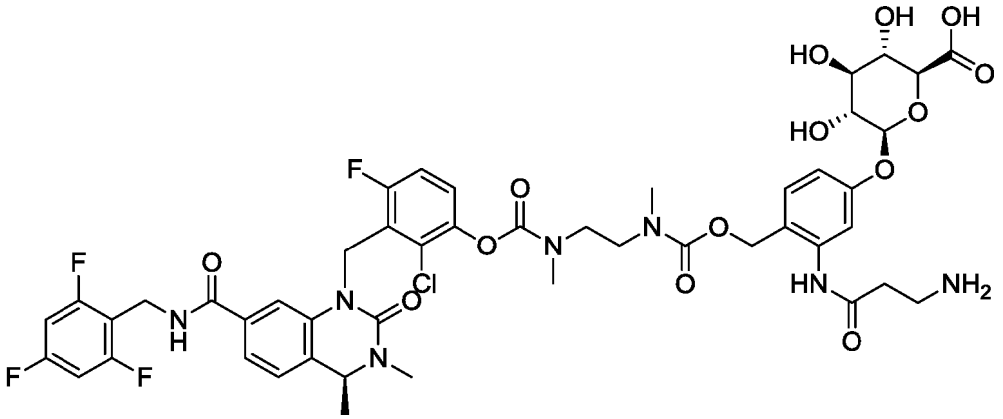
Preparation 42: (2S,3R,4S,5S,6S)-2-(3-(3-((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)propanamido)-4-((((2-(((2-chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenoxy)carbonyl)(methyl)amino)ethyl)(methyl)carbamoyl)oxy)methyl)phenoxy)-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate



To a stirred solution of (2S,3R,4S,5S,6S)-2-(3-(3-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)propanamido)-4-((((4-nitrophenoxy)carbonyl)oxy) methyl)phenoxy)-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (Preparation 41; Step 5) (850 mg, 0.93 mmol) and (S)-2-chloro-3-((3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenyl methyl(2-(methylamino)ethyl)carbamate hydrochloride (Preparation 2; Step 4) (1251 mg, 1.86 mmol) in DMF (10 mL) were added DIPEA (2.47 mL, 18.72 mmol) at RT and the whole was stirred at RT for 15 min. After completion of the reaction (monitored by UPLC-MS) the reaction mixture was poured into water and extracted with EtOAc (2 × 150 mL). The combined extracts were washed with 0.5 N HCl (75 mL) followed by brine (50 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated to give a residue which was purified by column chromatography using 70% EtOAc in hexane as mobile phase to afford the title compound (950 mg, 0.673 mmol and yield 72.5%) as a white solid. UPLC-MS m/z: 1410 [M+H].

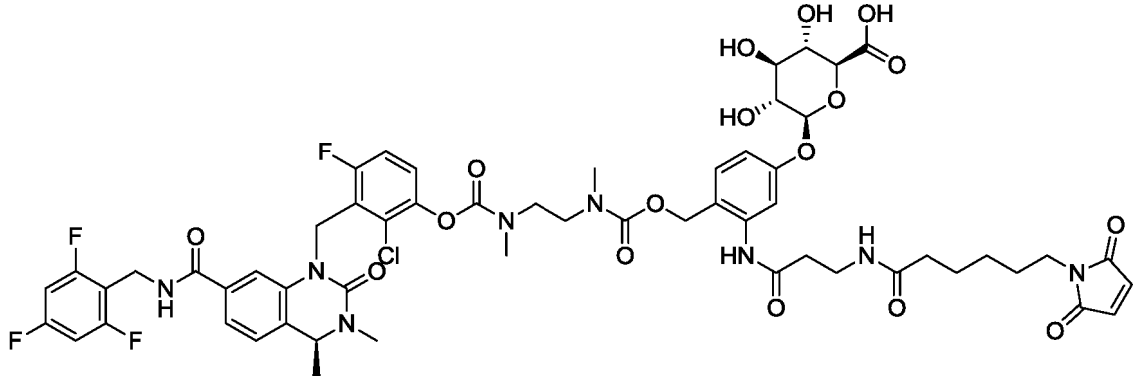
Preparation 43: (2S,3S,4S,5R,6S)-6-(3-(3-aminopropanamido)-4-((((2-(((2-chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenoxy)carbonyl)(methyl)amino)ethyl)(methyl)carbamoyl)

oxy)methyl)phenoxy)-3,4,5-trihydroxytetrahydro-2H-pyran-2-carboxylic acid



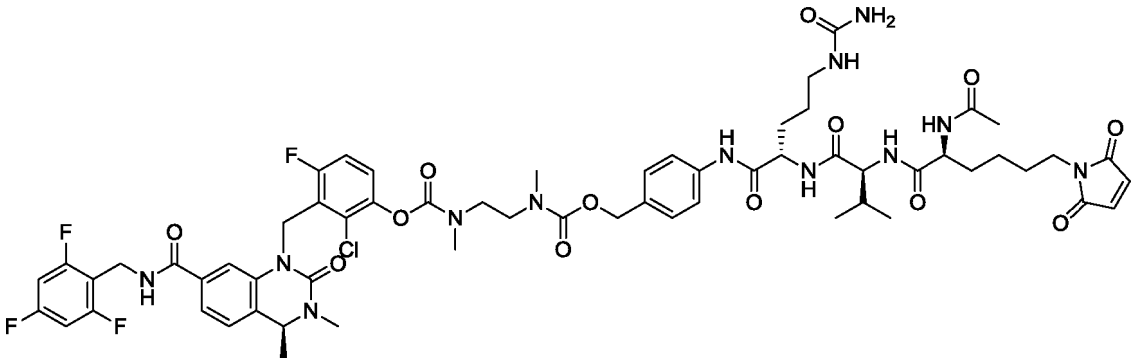
To a stirred solution of (2S,3R,4S,5S,6S)-2-(3-(3-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)propanamido)-4-((((2-(((2-chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenoxy)carbonyl)(methyl)amino)ethyl)(methyl)carbamoyl)oxy)methyl)phenoxy)-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (Preparation 42) (450 mg, 0.319 mmol) in a mixture of solvents MeOH:H_2O:THF (1:1:2, 9 mL) was added LiOH.H_2O (162.3 mg, 3.868 mmol) and the whole was stirred at RT for 1 h. Progress of the reaction was monitored by UPLC-MS and after completion the solvents were evaporated under reduced pressure to give a residue which was diluted with water and acidified with 1 N HCl (pH 5-6) to produce a solid precipitate. The obtained solid was filtered and dried in a vacuum oven to afford the title compound (300 mg, 0.286 mmol and yield 89.8%) as a white solid. UPLC-MS m/z: 1048 [M+H].

Preparation 44: (2S,3S,4S,5R,6S)-6-(4-((((2-(((2-Chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4 fluorophenoxy)carbonyl)(methyl)amino)ethyl)(methyl)carbamoyl)oxy)methyl)-3-(3-(6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1 yl)hexanamido)propanamido) phenoxy)-3,4,5-trihydroxytetrahydro-2H-pyran-2-carboxylic acid (**Example 27**)



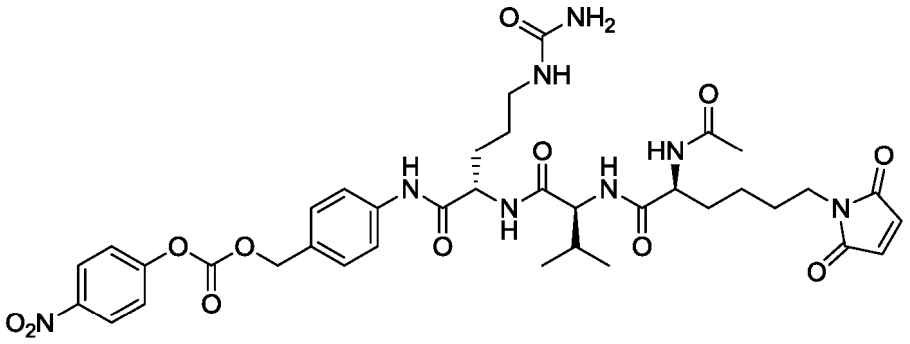
To a stirred solution of (2S,3S,4S,5R,6S)-6-(3-(3-aminopropanamido)-4-((((2-(((2-chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenoxy)carbonyl)(methyl)amino)ethyl)(methyl)carbamoyl)oxy)methyl)phenoxy)-3,4,5-trihydroxytetrahydro-2H-pyran-2-carboxylic acid (Preparation 43) (300 mg, 0.286 mmol) and commercially available 2,5-dioxopyrrolidin-1-yl 6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoate (88 mg, 0.286 mmol) in DMF (3 mL) was added DIPEA (74 mg, 0.574 mmol) at RT and the whole was stirred at RT for 15 min. Progress of the reaction was monitored by UPLC-MS and after completion the reaction mixture was subjected to purification by prep-HPLC to afford the title compound (20 mg, 0.016 mmol and yield 5.6%) as a white solid. UPLC-MS m/z: 1241 [M+H].

Example 17: 4-((S)-2-((S)-2-((S)-2-Acetamido-6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanamido)-3-methylbutanamido)-5-ureidopentanamido)benzyl (2-chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenyl) ethane-1,2-diylbis(methylcarbamate)

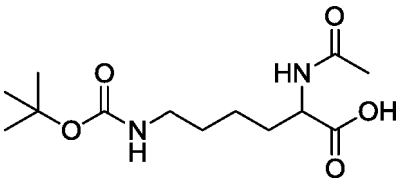


Example 17 was prepared according to the methods described in General Procedures 1-2, 4, 6, 10-12, 14, 15, 17-18 and the method described below.

Preparation 45: 4-((S)-2-((S)-2-((S)-2-Acetamido-6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanamido)-3-methylbutanamido)-5-ureidopentanamido)benzyl (4-nitrophenyl) carbonate

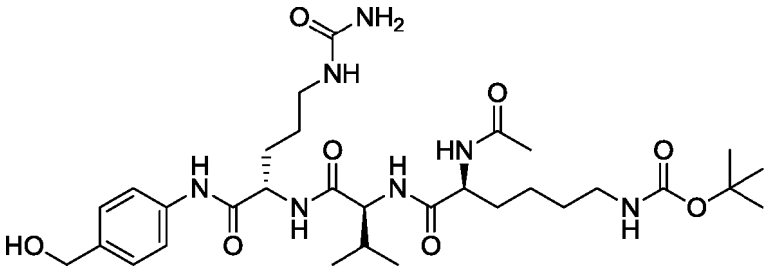


Step 1: 2-Acetamido-6-((*tert*-butoxycarbonyl)amino)hexanoic acid



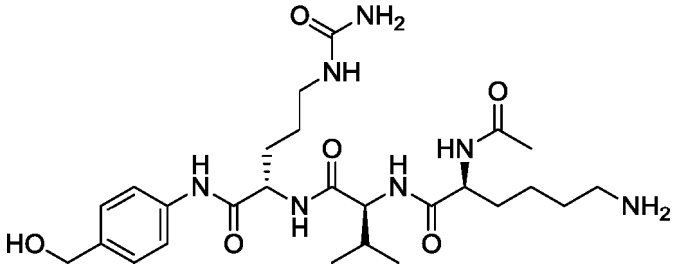
To a stirred suspension of commercially available 2-amino-6-((*tert*-butoxycarbonyl)amino)hexanoic acid (1.0 g, 4.066 mmol) was added a suspension of K_2CO_3 (2.81 g, 20.325 mmol) in water (10 mL) at RT and after 5 min. the reaction mixture was cooled to 0-5 °C and stirred for 4 h. Progress of the reaction was monitored by UPLC-MS and after completion, the solvents were evaporated under reduced pressure to give a residue which was acidified with 2N HCl solution to pH 2-3. The acidic aqueous reaction mass was extracted with EtOAc and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to afford the title compound (1.1 g, 3.82 mmol and yield 93.9%) as a light yellow fluffy solid. UPLC-MS m/z: 289 [M+H].

Step 2: *tert*-Butyl ((S)-5-acetamido-6-(((S)-1-(((S)-1-((4-(hydroxymethyl)phenyl)amino)-1-oxo-5-ureidopentan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)amino)-6-oxohexyl)carbamate



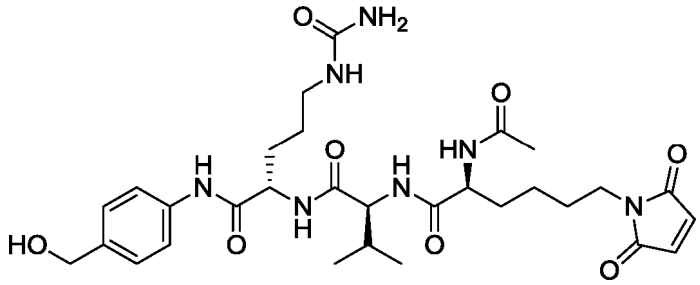
To a stirred solution of (S)-2-((S)-2-amino-3-methylbutanamido)-N-(4-(hydroxymethyl)phenyl)-5-ureidopentanamide (Preparation 1, Step 3) (1.2 g, 3.166 mmol) and 2-acetamido-6-((*tert*-butoxycarbonyl)amino)hexanoic acid (Preparation 45, Step 1) (9.255 g, 3.213 mmol) in anhydrous DMF (18 mL) were added DIPEA (352.18 mg, 3.483 mmol) and HATU (1.203 g, 3.166 mmol) at 0-5 °C. The reaction mixture was allowed to warm slowly to RT and stirred for 30 min. Progress of the reaction was monitored by UPLC-MS and after completion, the whole reaction mixture was poured into EtOAc, a white precipitate was observed which was filtered and washed with Et_2O followed by hexane and dried under vacuum to give the title compound (1.6 g, 2.462 mmol and yield 77.8%) as a white solid. UPLC-MS m/z: 650 [M+H].

Step 3: (S)-2-Acetamido-6-amino-N-((S)-1-(((S)-1-((4-(hydroxymethyl)phenyl)amino)-1-oxo-5-ureidopentan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)hexanamide



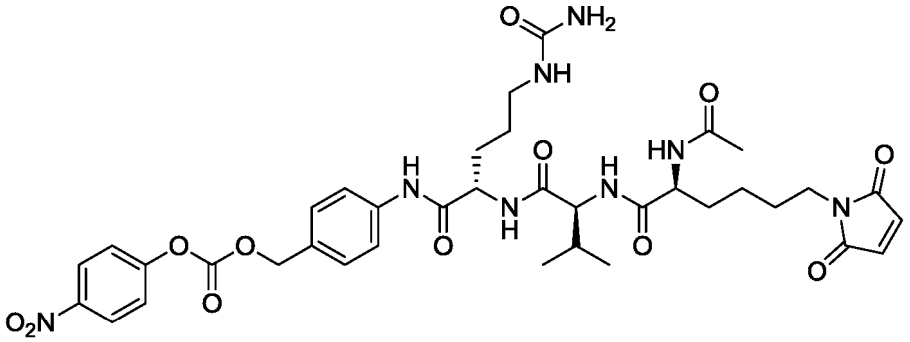
To a stirred solution of *tert*-butyl ((S)-5-acetamido-6-(((S)-1-(((S)-1-((4-(hydroxymethyl)phenyl)amino)-1-oxo-5-ureidopentan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)amino)-6-oxohexyl)carbamate (Preparation 45, Step 2) (1.6 g, 2.465 mmol) in 1, 4-dioxane (8 mL) was added HCl solution (8 mL, 5M solution in 1,4 dioxane) and stirred at RT overnight. Completion of the reaction was monitored by TLC and LCMS and after completion of the reaction the solvents were evaporated by azeotropic distillation with acetonitrile under reduced pressure to afford the title compound (1.3 g as crude) as a yellowish white solid which was used in the next step without further purification. UPLC-MS m/z: 549 [M+H].

Step 4: (S)-2-Acetamido-6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-N-((S)-1-(((S)-1-((4-(hydroxymethyl)phenyl)amino)-1-oxo-5-ureidopentan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)hexanamide



To a stirred solution of (S)-2-acetamido-6-amino-N-((S)-1-(((S)-1-((4-(hydroxymethyl)phenyl)amino)-1-oxo-5-ureidopentan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)hexanamide (Preparation 45, Step 3) (1.2 g, 2.18 mmol) in a saturated solution of $NaHCO_3$ (20 mL) was added commercially available methyl-2,5-dioxo-2,5-dihydro-1H-pyrrole-1-carboxylate (407 mg, 2.622 mmol) and the whole reaction mixture was stirred at RT for 2 h. After completion of the reaction (monitored by UPLC-MS), the product was extracted with 10% IPA/EtOAc solution and the combined organic layers dried and distilled under reduced pressure to give the title compound (0.8 g, crude) as a crude off white solid. UPLC-MS m/z: 630 [M+H].

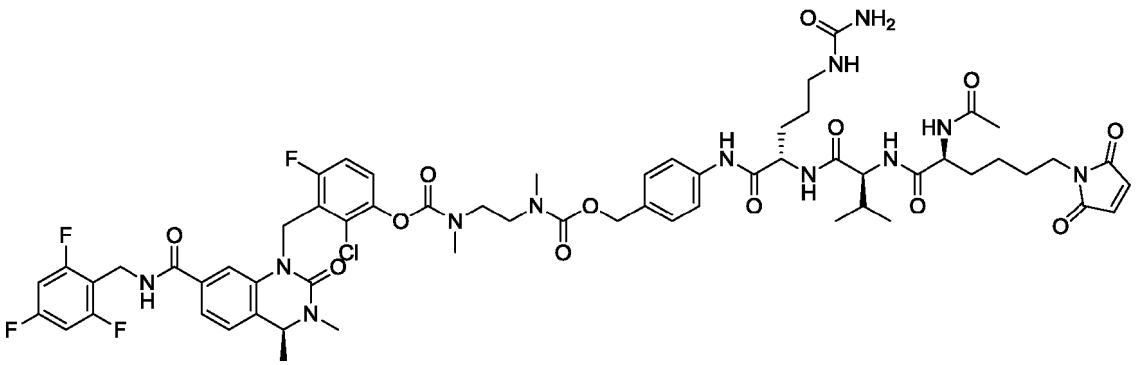
Step 5: 4-((S)-2-((S)-2-((S)-2-Acetamido-6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanamido)-3-methylbutanamido)-5-ureidopentanamido)benzyl (4-nitrophenyl) carbonate



To a stirred solution of (S)-2-acetamido-6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-N-((S)-1-(((S)-1-((4-(hydroxymethyl)phenyl)amino)-1-oxo-5-ureidopentan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)hexanamide (Preparation 45, Step 4) (500 mg, 0.080 mmol) in DMF (10 mL) was added DIPEA (719 mg, 5.564 mmol). After 5 min. stirring, 4-nitrophenyl chloroformate (639 mg, 3.179 mmol) was added at 0-5 °C and the whole stirred at RT overnight. Progress of the reaction was monitored by UPLC-MS which showed incomplete conversion, hence a further portion of 4-nitrophenyl chloroformate

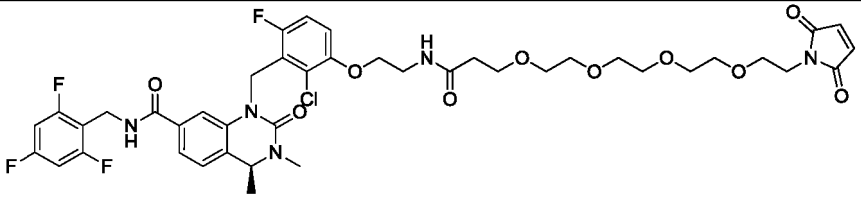
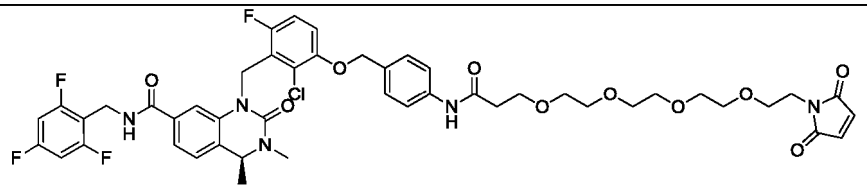
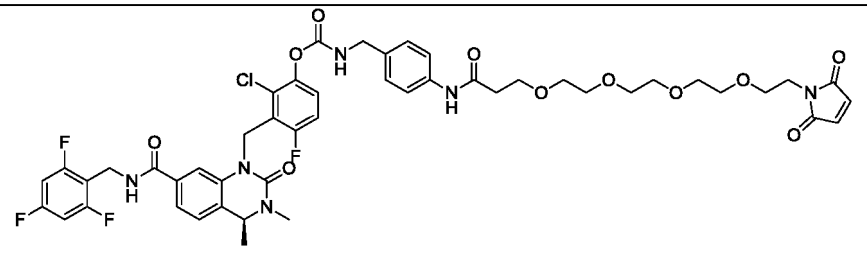
(639 mg, 3.179 mmol) and DIPEA (719 mg, 5.564 mmol) were added into the reaction mixture and stirring continued at RT for 4 h. After completion of the reaction the reaction mixture was diluted with EtOAc, washed with cold water and 1N HCl solution followed by brine. The organics were evaporated to give semi solid material which was purified by trituration with Et_2O and DCM and finally filtered to afford the title compound (300 mg, 0.3778 mmol and yield 47.5%) as a light yellow solid. UPLC-MS m/z: 795 [M+H].

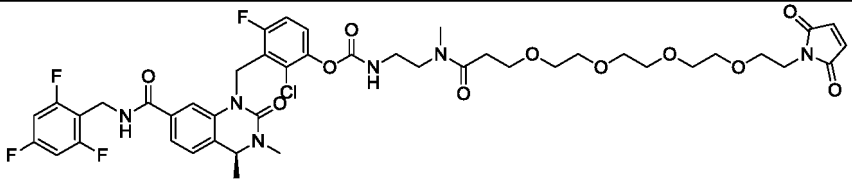
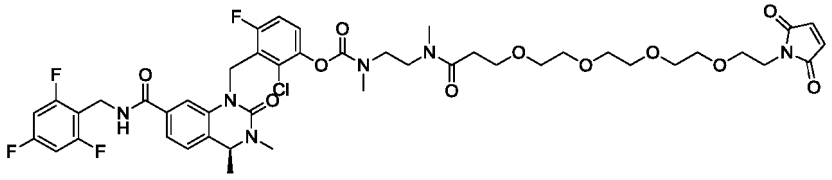
Preparation 46: : 4-((S)-2-((S)-2-((S)-2-Acetamido-6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanamido)-3-methylbutanamido)-5-ureidopentanamido)benzyl (2-chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenyl) ethane-1,2-diylbis(methylcarbamate) (**Example 17**)

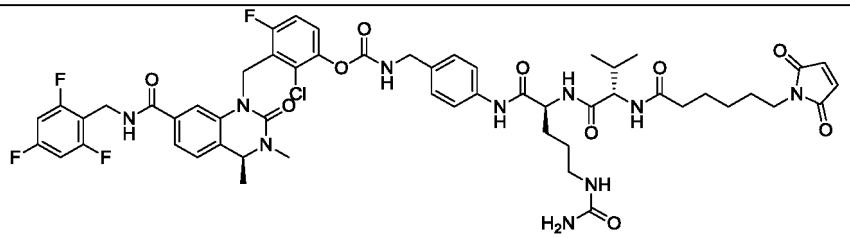
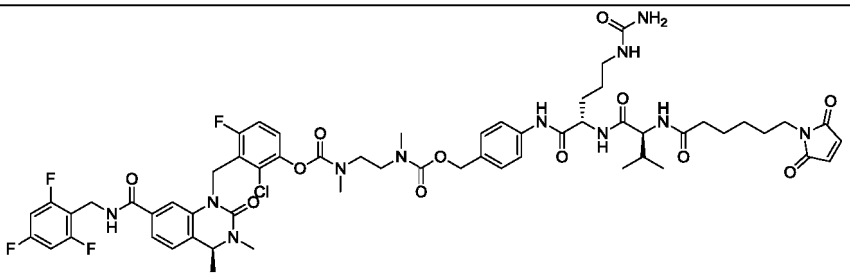


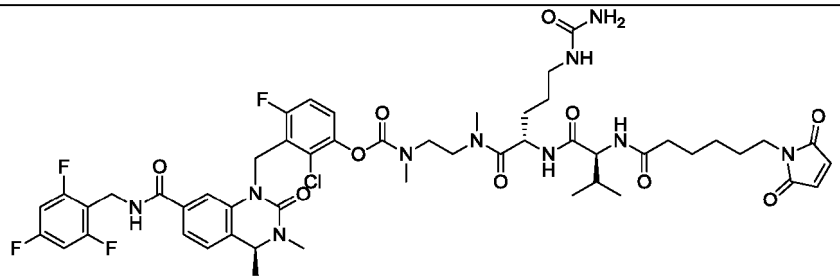
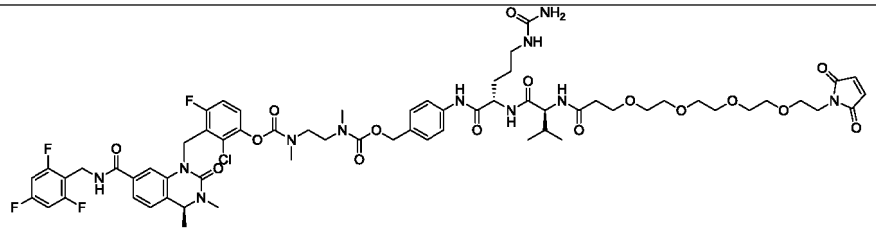
To a stirred solution of 4-((S)-2-((S)-2-((S)-2-acetamido-6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanamido)-3-methylbutanamido)-5-ureidopentanamido)benzyl (4-nitrophenyl) carbonate (Preparation 45, Step 5) (300 mg, 0.3778 mmol) and (S)-2-Chloro-3-((3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenyl methyl(2-(methylamino)ethyl)carbamate hydrochloride (Preparation 2, Step 4) (380.8 mg, 0.567 mmol) in DMA (3 mL) were added 2, 6-lutidine (40.42 mg, 0.378 mmol) and DIPEA (48.83 mg, 0.378 mmol) at 0-5 °C, which caused the reaction mixture to become pale yellow in color and then the reaction mixture was stirred for 30 min. at the same temperature. Completion of the reaction was monitored by UPLC-MS, showing formation of the desired product and after completion the reaction mixture was subjected to purification by prep-HPLC to give the title compound (35 mg, 0.027 mmol and yield 7.2%) as a white solid. UPLC-MS m/z: 1291 [M+H].

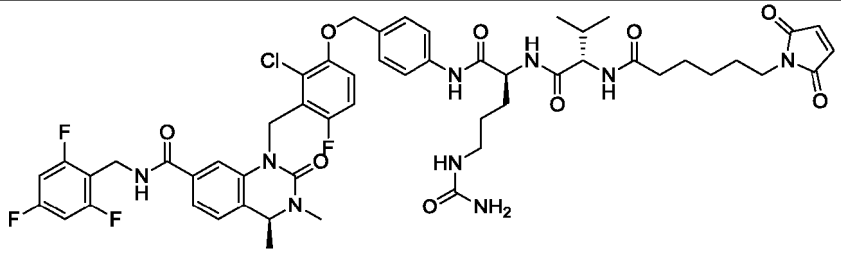
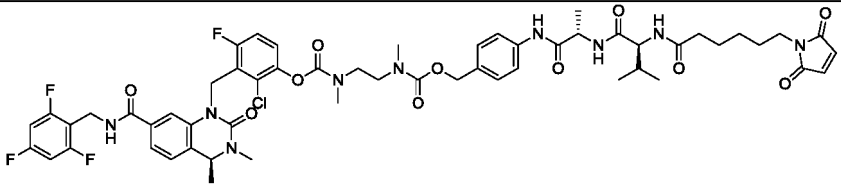
Pre-conjugates

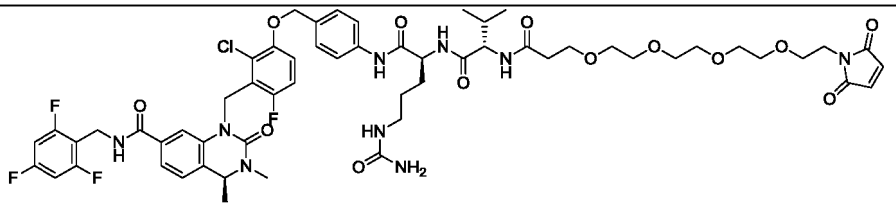
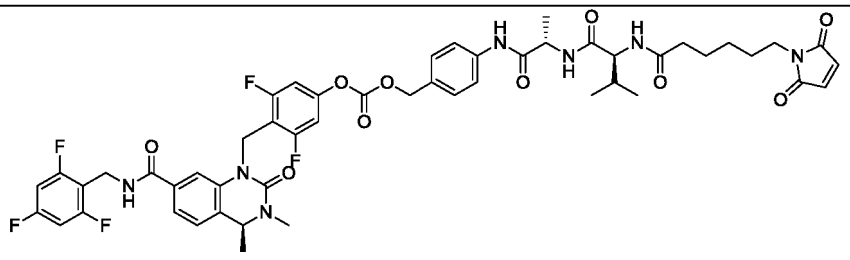
Ex	Structure/IUPAC Name/^{1}H-NMR	LC-MS [M+H]
1		892.44
	(S)-1-(2-chloro-3-((1-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-15-oxo-3,6,9,12-tetraoxa-16-azaoctadecan-18-yl)oxy)-6-fluorobenzyl)-3,4-dimethyl-2-oxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4-tetrahydroquinazoline-7-carboxamide	
	(500 MHz; DMSO-d6): δ 1.24 (s, 3H), 2.34 (s, 2H), 2.94 (s, 3H), 3.59-3.45 (m, 20H), 4.02 (s, 2H), 4.53-4.39 (m, 3H), 4.92 (d, *J* = 7.8 Hz, 1H), 5.54 (d, J = 8.0 Hz, 1H), 7.19-7.04 (m, 7H), 7.44-7.40 (m, 2H), 8.03 (s, 1H), 8.74 (s, 1H)	
2		952.5 (M-H)
	(S)-1-(2-chloro-3-((4-(1-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-3,6,9,12-tetraoxapentadecanamido)benzyl)oxy)-6-fluorobenzyl)-3,4-dimethyl-2-oxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4-tetrahydroquinazoline-7-carboxamide	
	(500 MHz; DMSO-d_6): δ 1.22 (d, *J* = 6.2 Hz, 3), 2.54-2.57 (m, 2H), 2.93 (s, 3H), 3.35-3.55 (m, 16H), 3.69-3.71 (m, 2H), 4.40 (d, *J* = 14.2 Hz, 1H), 4.47-4.53 (m, 2H), 4.92 (d, *J* = 15.75 Hz, 1H), 5.07 (s, 2H), 5.55 (d, *J* = 15.75 Hz, 1H), 7.02 (s, 2H), 7.09-7.20 (m, 5H), 7.36-7.41 (m, 3H), 7.45 (s, 1H), 7.61 (d, *J* = 8.1 Hz, 2H), 8.76 (s, 1H), 10.01 (s, 1H)	
3		997.48
	(S)-2-chloro-3-((3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-	

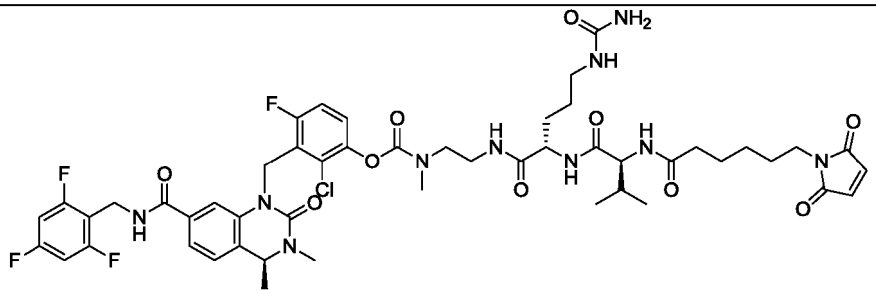
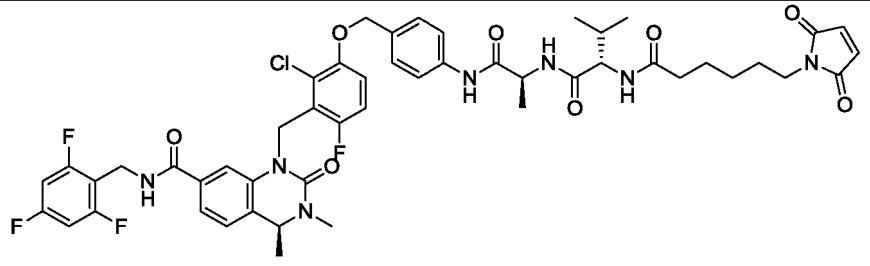
Ex	Structure/IUPAC Name/^{1}H-NMR	LC-MS [M+H]
	fluorophenyl 4-(1-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-3,6,9,12-tetraoxapentadecanamido)benzylcarbamate	
	(500 MHz; DMSO-d_6): δ 1.21 (d, *J* = 6.3 Hz, 3H), 2.53-2.56 (m, 2H), 2.94 (s, 3H), 3.44-3.51 (m, 14H), 3.54-3.57 (m, 2H), 3.68-3.71 (m, 2H), 4.21 (d, *J* = 5.45 Hz, 2H), 4.43-4.53 (m, 3H), 4.94 (d, *J* = 15.7 Hz, 1H), 5.53 (d, *J* = 15.75 Hz, 1H), 7.02 (s, 2H), 7.17-7.29 (m, 7H), 7.42 (d, *J* = 7.7 Hz, 1H), 7.49 (s, 1H), 7.55 (d, *J* = 8.2 Hz, 2H), 8.49 (d, *J* = 5.95 Hz, 1H), 8.76 (d, *J* = 4.75 Hz, 1H), 9.94 (s, 1H)	
4		949.4
	(S)-2-chloro-3-((3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenyl (1-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-16-methyl-15-oxo-3,6,9,12-tetraoxa-16-azaoctadecan-18-yl)carbamate	
	(500 MHz; DMSO-d_6): δ 1.21 (s, 3H), 2.81 (s, 2H), 2.93-2.99 (m, 5H), 3.20-3.23 (m, 3H), 3.35-3.61 (m, 19H), 4.43-4.52 (m, 3H), 4.94 (d, *J* = 15.0 Hz, 1H), 5.51 (d, *J* = 12.50 Hz, 1H), 7.05 (s, 2H), 7.20 (s, 5H), 7.42 (s, 1H), 7.49 (s, 1H), 7.98 (s, 1H), 8.14 (d, *J* = 18.0 Hz, 1H), 8.76 (s, 1H)	
5		961.33 (M-H)
	(S)-2-chloro-3-((3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenyl (1-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-16-methyl-15-oxo-3,6,9,12-tetraoxa-16-azaoctadecan-18-yl)(methyl)carbamate	
	(500 MHz; DMSO-d_6): δ 1.16-1.21 (m, 3H), 2.83-2.93 (m, 8H), 3.01-3.09 (m, 2H), 3.41-3.60 (m, 22H), 4.43-4.52 (m, 3H), 4.96 (d, *J* = 14.8 Hz, 1H), 5.50 (d, *J* = 15.55 Hz, 1H), 7.02 (s, 2H), 7.19-7.22 (m, 5H), 7.42-7.49 (m, 3H), 8.77 (s, 1H),	

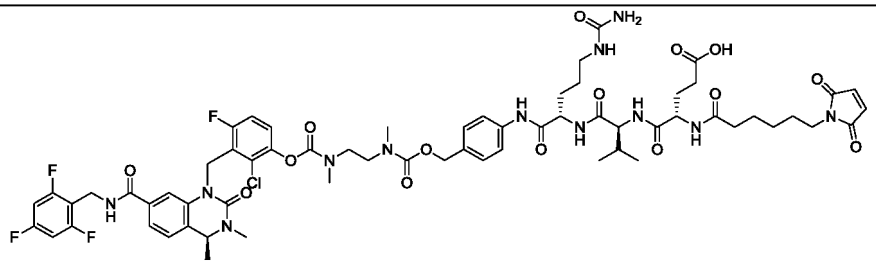
Ex	Structure/IUPAC Name/^{1}H-NMR	LC-MS [M+H]
6		1119.42
	2-chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenyl 4-((S)-2-((S)-2-(6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanamido)-3-methylbutanamido)-5-ureidopentanamido)benzylcarbamate	
	(500 MHz; DMSO-d_6): δ 0.87-0.83 (m, 6H), 1.21 (d, *J* = 6.30 Hz, 6H), 1.52-1.48 (m, 5H), 1.61-1.59 (m, 1H), 1.71 (bs, 1H), 2.00-1.90 (m, 1H), 2.22-2.11 (m, 3H), 2.94 (s, 5H), 4.21-4.18 (m, 3H), 4.54-4.37 (m, 5H), 4.97-4.89 (m, 1H), 5.39 (s, 2H), 5.52 (d, *J* = 15.5 Hz, 1H), 5.99 (bs, 1H), 6.91 (s, 2H), 7.27-7.15 (m, 7H), 7.42 (d, *J* = 10.3 Hz, 1H), 7.49 (s, 1H), 7.65-7.55 (m, 2H), 7.79 (d, *J* = 8.50 Hz, 1H), 8.05 (d, *J* = 7.20 Hz, 1H), 8.45 (bs, 1H), 8.72 (bs, 1H), 9.92 (bs, 1H).	
7		1234.35
	2-chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenyl 4-((S)-2-((S)-2-(6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanamido)-3-methylbutanamido)-5-ureidopentanamido)benzyl ethane-1,2-diylbis(methylcarbamate)	
	(500 MHz; DMSO-d_6): δ 0.84 (d, *J* = 8.35 Hz, 6H), 1.10-1.21 (m, 6H), 1.38-1.70 (m, 9H), 1.98-2.17 (m, 4H), 2.85-3.05 (m, 10H), 3.37-3.51 (m, 5H), 4.20 (s, 1H), 4.40-4.52 (m, 4H), 4.97 (s, 3H), 5.40 (s, 2H), 5.50 (d, *J* = 14.3 Hz, 1H), 5.98 (s, 1H), 7.00 (s, 2H), 7.17-7.29 (m, 6H), 7.43-7.59 (m, 5H), 7.80 (s, 1H), 8.08 (s, 1H), 9.99 (s, 1H)	

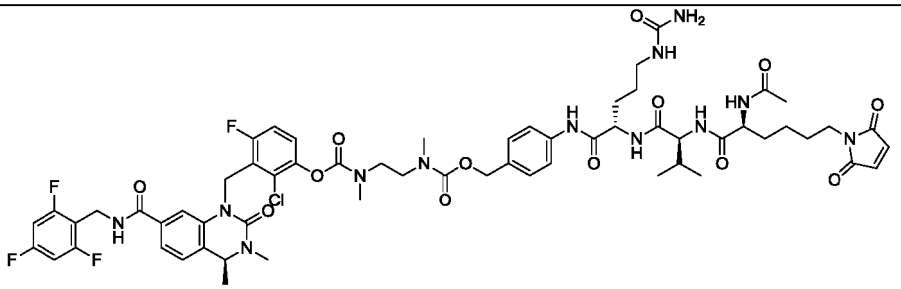
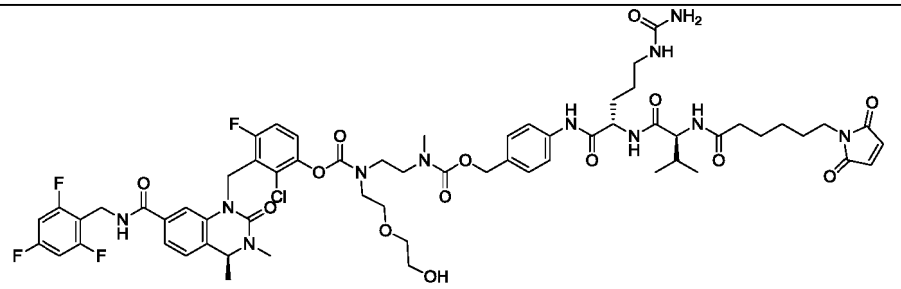
Ex	Structure/IUPAC Name/^{1}H-NMR	LC-MS [M+H]
8		1085.35
	2-chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenyl (2-((S)-2-((S)-2-(6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanamido)-3-methylbutanamido)-N-methyl-5-ureidopentanamido)ethyl)(methyl)carbamate	
	(500 MHz; DMSO-d_6): δ 0.78 (d, *J* = 6.56 Hz, 6H), 1.17-1.23 (m, 3H), 1.36 (bs, 2H), 1.45-1.50 (m, 5H), 1.58 (bs, 1H), 1.92 (bs, 1H), 2.08-2,20 (m, 3H), 2.83-3.13 (m, 12H), 3.36-3.39 (m, 3H), 3.51 (s, 1H), 3.57 (bs, 2H), 4.19 (d, *J* = 7.45 Hz, 1H), 4.42-4.54 (m, 3H), 4.66 (s, 1H), 4.96 (d, *J* = 15.7 Hz, 1H), 5.34 (s, 2H), 5.49 (d, *J* = 15.5 Hz, 1H), 5.87 (s, 1H), 6.99 (s, 2H), 7.16-7.29 (m, 5H), 7.43 (d, *J* = 7.75 Hz, 1H), 7.49 (s, 1H), 7.71 (d, *J* = 8.85 Hz, 1H), 7.98-8.08 (m, 1H), 8.74 (s, 1H)	
9		1368.52
	2-chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenyl 4-((17S,20S)-1-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-17-isopropyl-15,18-dioxo-20-(3-ureidopropyl)-3,6,9,12-tetraoxa-16,19-diazahenicosanamido)benzyl ethane-1,2-diylbis(methylcarbamate)	
	(500 MHz; DMSO-d_6): δ 0.84 (dd, *J'* = 6.6 Hz, *J"* = 16.05 Hz, 6H), 1.20 (d, *J* = 6.1 Hz, 3H), 1.37 (s, 1H), 1.44 (s, 1H), 1.59 (d, *J* = 8.6 Hz, 1H), 1.69 (s, 1H), 1.97 (dd, *J'* = 6.65 Hz, *J"* = 13.35 Hz, 1H), 2.36-2.40 (m, 2H), 2.82-3.05 (m, 12H), 3.46-3.60 (m, 20H), 4.22-4.25 (m, 1H), 4.40-4.53 (m, 4H), 4.95 (d, *J* = 15.05 Hz, 3H), 5.41 (s, 2H), 5.50 (d, *J* = 15.65 Hz, 1H), 5.97 (s, 1H), 7.02 (s, 2H), 7.16-7.21 (m, 6H), 7.29 (d, *J* = 6.2	

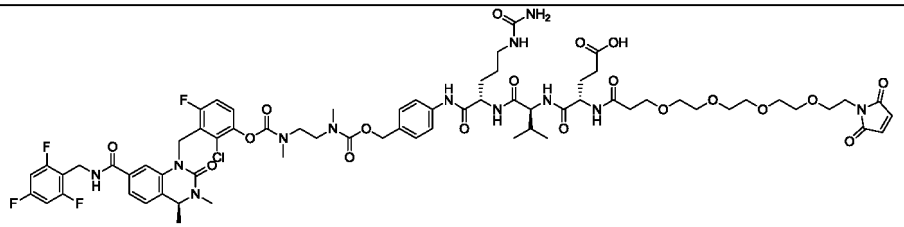
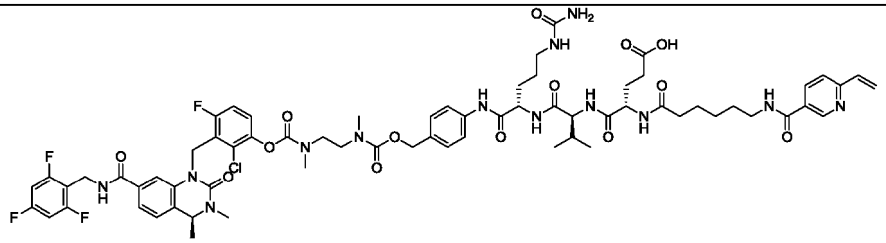
Ex	Structure/IUPAC Name/^{1}H-NMR	LC-MS [M+H]
	Hz, 1H), 7.42 (d, *J* = 7.65 Hz, 1H), 7.49-7.59 (m, 3H), 7.86 (d, *J* = 8.45 Hz, 1H), 8.11 (d, *J* = 7.15 Hz, 1H), 8.15 (s, 1H), 8.75 (d, *J* = 4.7 Hz, 1H), 9.99 (s, 1H)	
10		1076.54
	(S)-1-(2-chloro-3-((4-((S)-2-((S)-2-(6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanamido)-3-methylbutanamido)-5-ureidopentanamido)benzyl)oxy)-6-fluorobenzyl)-3,4-dimethyl-2-oxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4-tetrahydroquinazoline-7-carboxamide	
	(500 MHz; DMSO-d_6): δ 0.84 (dd, *J'* = 6.45 Hz, *J"* = 15.8 Hz, 6H), 1.19-1.23 (m, 5H), 1.38 (bs, 1H), 1.47-1.50 (m, 5H), 1.59 (d, *J* = 9.25 Hz, 1H), 1.70 (s, 1H), 1.97 (dd, *J'* = 6.5 Hz, *J"* = 13.05 Hz, 1H), 2.09-2.20 (m, 2H), 2.93 (s, 4H), 3.02 (t, *J* = 6.25 Hz, 1H), 3.37 (s, 1H), 4.20 (t, *J* = 7.65 Hz, 1H), 4.39-4.47 (m, 4H), 4.92 (d, *J* = 15.75 Hz, 1H), 5.08 (s, 2H), 5.42 (s, 2H), 5.53 (d, *J* = 15.65 Hz, 1H), 5.98 (s, 1H), 7.00 (s, 2H), 7.13-7.20 (m, 5H), 7.36-7.41 (m, 3H), 7.45 (s, 1H), 7.62 (d, *J* = 8.05 Hz, 2H), 7.80 (d, *J* = 8.4 Hz, 1H), 8.08 (d, *J* = 7.15 Hz, 1H), 8.15 (s, 1H), 8.75 (s, 1H), 10.01 (s, 1H)	
11		1148.49
	2-chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenyl 4-((S)-2-((S)-2-(6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanamido)-3-methylbutanamido)propanamido)benzyl ethane-1,2-diylbis(methylcarbamate)	
	(500 MHz; DMSO-d_6): δ 0.85 (bs, 6H), 1.21-1.31 (m, 9H), 1.49 (bs, 4H), 1.97 (s, 1H), 2.15 (bs, 2H), 2.93 (bs, 9H), 3.50 (bs, 5H), 4.19 (s, 1H), 4.45 (bs, 4H), 4.97 (s, 3H), 5.51 (s, 1H), 7.01 (s, 2H), 7.20-7.58 (m, 11H),	

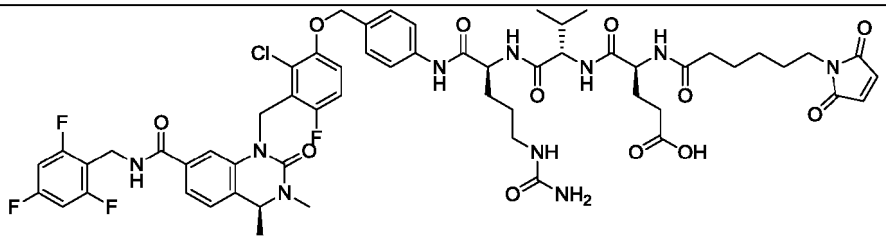
Ex	Structure/IUPAC Name/^{1}H-NMR	LC-MS [M+H]
	7.83 (s, 1H), 8.18 (s, 1H), 8.78 (s, 1H), 9.96 (s, 1H),	
12		1210.56
	(S)-1-(2-chloro-3-((4-((17S,20S)-1-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-17-isopropyl-15,18-dioxo-20-(3-ureidopropyl)-3,6,9,12-tetraoxa-16,19-diazahenicosanamido)benzyl)oxy)-6-fluorobenzyl)-3,4-dimethyl-2-oxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4-tetrahydroquinazoline-7-carboxamide	
	(500 MHz; DMSO-d_6): δ 0.85 (dd, *J'* = 6.65 Hz, *J"* = 16.65 Hz, 6H), 1.22 (d. *J* = 6.45 Hz, 3H), 1.37-1.44 (m, 2H), 1.59-1.70 (m, 2H), 1.98 (dd, *J'* = 6.55 Hz, *J"* = 13.2 Hz, 1H), 2.37-2.41 (m, 1H), 2.44-2.47 (m, 1H), 2.93 (s, 3H), 3.02-3.08 (m, 1H), 3.46-3.52 (m, 14H), 3.55-3.64 (m, 4H), 4.24 (t, *J* = 7.25 Hz, 1H), 4.39-4.47 (m, 2H), 4.49-4.53 (m, 2H), 4.91 (d, *J* = 15.7 Hz, 1H), 5.08 (s, 2H), 5.43 (s, 2H), 5.54 (d, *J* = 15.8 Hz, 1H), 5.99 (s, 1H), 6.35 (s, 1H), 7.02 (s, 2H), 7.07-7.20 (m, 5H), 7.36-7.41 (m, 3H), 7.45 (s, 1H), 7.62 (d, *J* = 8.35 Hz, 2H), 7.88 (d, *J* = 8.6 Hz, 1H), 8.13 (d, *J* = 6.9 Hz, 1H), 8.76 (t, *J* = 4.65 Hz, 1H), 10.02 (s, 1H)	
13		1018.57
	4-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-3,5-difluorophenyl 4-((S)-2-((S)-2-(6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanamido)-3-methylbutanamido)propanamido)benzyl carbonate	
	(400 MHz; DMSO-d6): δ 0.84 (dd, *J'* = 6.60 Hz, *J"* = 17.2 Hz, 7H), 1.15-1.19 (m, 6H), 1.30 (d, *J* = 4.0 Hz, 3H), 1.45-1.50 (m, 4H), 1.92-1.99 (m, 1H), 2.08 (s, 1H), 2.10-2.17 (m, 1H), 2.93 (s, 3H), 4.17 (t, *J* = 7.92 Hz, 1H), 4.36-4.43 (m, 2H), 4.46-4.54 (m, 2H), 4.86 (d, *J* = 16.0 Hz, 1H),	

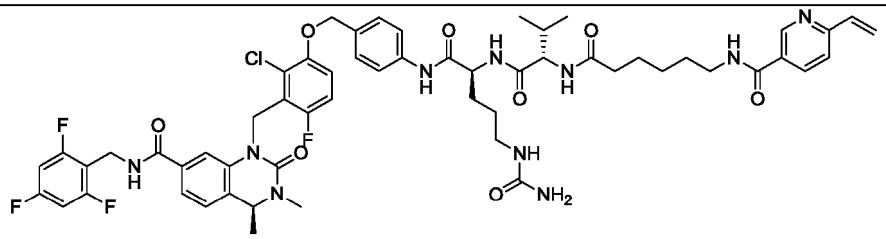
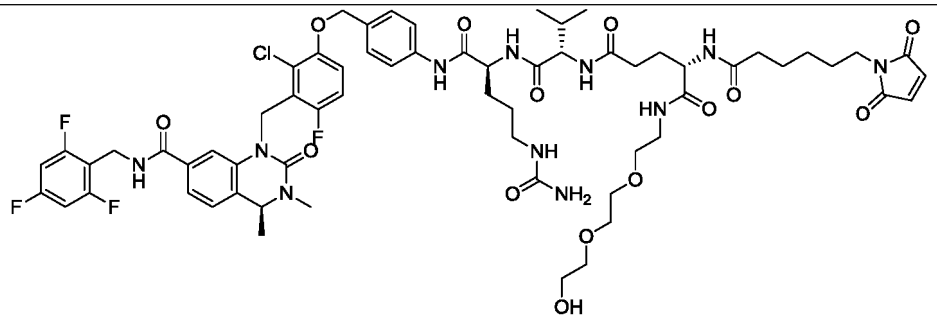
Ex	Structure/IUPAC Name/^{1}H-NMR	LC-MS [M+H]
	5.19 (s, 2H), 5.52 (d, *J* = 16.12 Hz, 1H), 7.00 (s, 2H), 7.14-7.22 (m, 5H), 7.38 (d, *J* = 8.24 Hz, 2H), 7.42 (d, *J* = 7.96 Hz, 1H), 7.47 (s, 1H), 7.62 (d, *J* = 8.48 Hz, 2H), 7.83 (d, *J* = 8.52 Hz, 1H), 8.20 (d, *J* = 6.84 Hz, 1H), 8.80 (t, *J* = 8.84 Hz, 1H), 10.02 (s, 1H)	
14		1071.58
	2-chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenyl (2-((S)-2-((S)-2-(6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanamido)-3-methylbutanamido)-5-ureidopentanamido)ethyl)(methyl)carbamate	
	(500 MHz; DMSO-d6): δ 0.81 (d, *J* = 6.45 Hz, 6H), 1.18-1.22 (m, 5H), 1.34 (bs, 1H), 1.46-1.50 (m, 5H), 1.61 (s, 1H), 1.95 (s, 1H), 2.08-2.17 (m, 2H), 2.92 (d, *J* = 6.4 Hz, 7H), 3.06 (s, 1H), 3.35-3.38 (m, 7H), 4.18 (d, *J* = 20.0 Hz, 2H), 4.43-4.54 (m, 3H), 4.97 (d, *J* = 15.4 Hz, 1H), 5.37 (s, 2H), 5.45-5.48 (m, 1H), 5.91 (s, 1H), 6.55 (s, 1H), 7.00 (s, 2H), 7.17-7.22 (m, 4H), 7.27 (d, *J* = 4.3 Hz, 1H), 7.43 (d, *J* = 7.35 Hz, 1H), 7.49 (s, 1H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.91 (s, 1H), 8.08 (d, *J* = 32.55 Hz, 1H), 8.7 (s, 1H)	
15		990.48
	(S)-1-(2-chloro-3-((4-((S)-2-((S)-2-(6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanamido)-3-methylbutanamido)propanamido)benzyl)oxy)-6-fluorobenzyl)-3,4-dimethyl-2-oxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4-tetrahydroquinazoline-7-carboxamide	

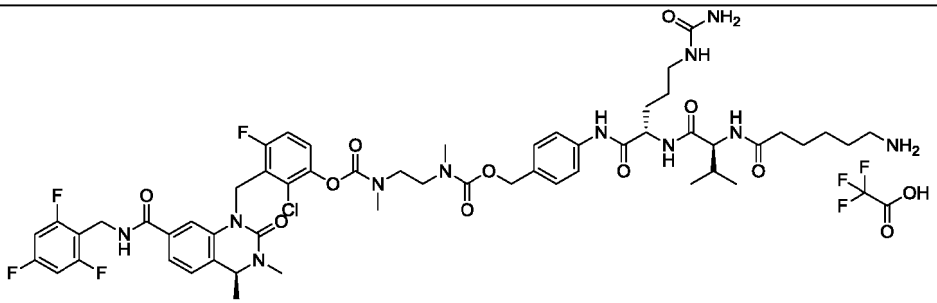
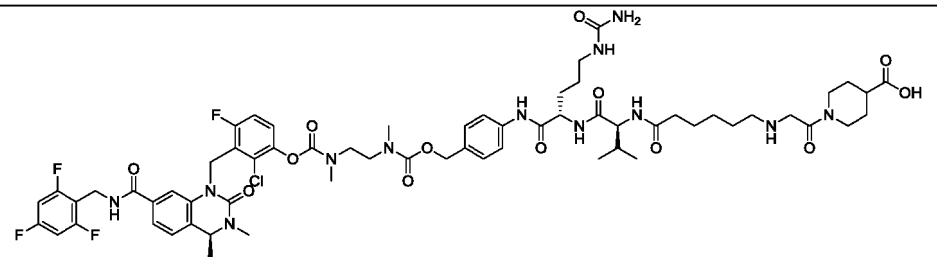
Ex	Structure/IUPAC Name/^{1}H-NMR	LC-MS [M+H]
	(400 MHz; DMSO-d_6): δ 0.81-0.85 (m, 6H), 1.21-1.31 (m, 9H), 1.47 (s, 4H), 1.95-2.16 (m, 4H), 2.93 (s, 3H), 4.17 (s, 1H), 4.38-4.53 (m, 4H), 4.91 (d, *J* = 15.96 Hz, 1H), 5.07 (s, 2H), 5.53 (d, *J* = 15.68 Hz, 1H), 6.98-7.00 (m, 2H), 7.09-7.20 (m, 5H), 7.36-7.45 (m, 4H), 7.61-7.70 (m, 2H), 7.85 (d, *J* = 8.32 Hz, 0.87H), 8.02 (d, *J* = 7.28 Hz, 0.21H), 8.26 (d, *J* = 5.96 Hz, 0.78H), 8.49 (s, 0.52H), 8.78 (s, 1H), 9.88 (s, 0.16H), 10.04 (s, 0.79H)	
16		1363.48
	(S)-5-(((S)-1-(((S)-1-((4-((((2-(((2-chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenoxy)carbonyl)(methyl)amino)ethyl)(methyl)carbamoyl)oxy)methyl)phenyl)amino)-1-oxo-5-ureidopentan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)amino)-4-(6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanamido)-5-oxopentanoic acid	
	(400 MHz; DMSO-d_6): δ 0.82 (dd, *J'* = 6.2 Hz, *J"* = 14.72 Hz, 6H), 1.19-1.21 (m, 5H), 1.38 (bs, 1H), 1.46 (bs, 5H), 1.57-1.70 (m, 3H), 1.86-1.98 (m, 2H), 2.09 (d, *J* = 4.44 Hz, 2H), 2.22 (t, *J* = 7.44 Hz, 2H), 2.81-3.04 (m, 11H), 3.43-3.55 (m, 6H), 4.10-4.52 (m, 6H), 4.93-4.96 (m, 3H), 5.44-5.51 (m, 3H), 5.99 (s, 1H), 7.00 (s, 2H), 7.16-7.28 (m, 7H), 7.42 (d, *J* = 7.24 Hz, 1H), 7.49-7.58 (m, 3H), 7.70 (d, *J* = 7.88 Hz, 1H), 8.02 (d, *J* = 7.36Hz, 1H), 8.20 (d, *J* = 6.68 Hz, 1H), 8.79 (s, 1H), 10.05 (s, 1H), 12.13 (s, 1H)	

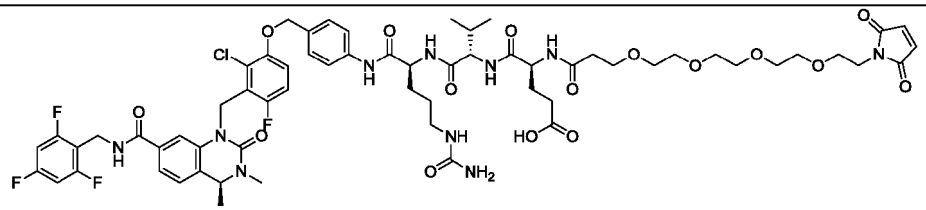
Ex	Structure/IUPAC Name/^{1}H-NMR	LC-MS [M+H]
17		1291.44
	4-((S)-2-((S)-2-((S)-2-acetamido-6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanamido)-3-methylbutanamido)-5-ureidopentanamido)benzyl (2-chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenyl) ethane-1,2-diylbis(methylcarbamate)	
	(400 MHz; DMSO-d_6): δ 0.84 (s, 6H), 1.22 (s, 5H), 1.46 (bs, 5H), 1.61 (bs, 3H), 1.84 (s, 3H), 1.98 (s, 1H), 2.85-3.05 (m, 12H), 3.47-3.50 (m, 5H), 4.21 (d, *J* = 13.48 Hz, 2H), 4.40-4.52 (m, 4 H), 4.97 (s, 3H), 5.42-5.50 (m, 3H), 5.98 (s, 1H), 7.00 (s, 2H), 7.18-7.26 (m, 7H), 7.42-7.58 (m, 4H), 7.71 (s, 1H), 8.03 (s, 1H), 8.09 (s, 1H), 8.77 (s, 1H), 10.04 (s, 1H)	
18		1308.62
	2-chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenyl (2-((((4-((S)-2-((S)-2-(6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanamido)-3-methylbutanamido)-5-ureidopentanamido)benzyl)oxy)carbonyl)(methyl)amino)ethyl)(2-(2-hydroxyethoxy)ethyl)carbamate	
	(500 MHz; DMSO-d_6): δ 0.83 (dd, *J'* = 6.45 Hz, *J"* = 16.4 Hz, 6H), 1.16-1.21 (m, 5H), 1.36-1.49 (m, 7H), 1.58 (d, *J* = 8.7 Hz, 1H), 1.68 (s, 1H), 1.94-1.96 (m, 1H), 2.09-2.19 (m, 2H), 2.83-3.02 (m, 8H), 3.43-3.66 (m, 13H), 4.18-4.21 (m, 1H), 4.37-4.52 (m, 4H), 4.62 (s, 1H), 4.92-4.96 (m,	

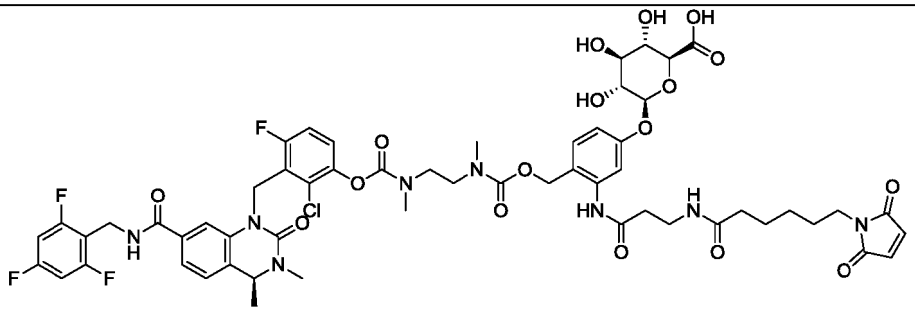
Ex	Structure/IUPAC Name/^{1}H-NMR	LC-MS [M+H]
	3H), 5.43 (s, 2H), 5.48 (d, *J* = 15.55 Hz, 1H), 6.00 (s, 1H), 7.01 (s, 2H), 7.17-7.29 (m, 7H), 7.42 (d, *J* = 7.6 Hz, 1H), 7.50-7.57 (m, 3H), 7.82 (d, *J* = 8.2 Hz, 1H), 8.12 (d, *J* = 7.2 Hz, 1H), 8.79 (s, 1H), 10.02 (d, *J* = 15.15 Hz, 1H)	
19		1497.9
	(S)-17-(((S)-1-(((S)-1-((4-((((2-(((2-chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenoxy)carbonyl)(methyl)amino)ethyl)(methyl) carbamoyl)oxy)methyl)phenyl)amino)-1-oxo-5-ureidopentan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamoyl)-1-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-15-oxo-3,6,9,12-tetraoxa-16-azaicosan-20-oic acid	
	(500 MHz; DMSO-d_6): δ 0.83 (dd, *J'* = 6.15 Hz, *J"* = 18.4 Hz, 6H), 1.21 (s, 3H), 1.38 (bs, 1H), 1.44 (bs, 1H), 1.60 (s, 1H), 1.68 (bs, 2H), 1.87-1.97 (m, 3H), 2.23 (s, 2H), 2.35 (bs, 2H), 2.83-3.04 (m, 11H), 3.46-3.56 (m, 21H), 4.20 (s, 1H), 4.35-4.51 (m, 5H), 4.94-4.96 (m, 3H), 5.45-5.51 (m, 3H), 6.02 (s, 1H), 7.03 (s, 2H), 7.19-7.28 (m, 7H), 7.42 (d, *J* = 6.85 Hz, 1H), 7.50-7.58 (m, 3H), 7.74 (d, *J* = 7.85 Hz, 1H), 8.10 (d, *J* = 7.5 Hz, 1H), 8.20 (d, *J* = 13.8 Hz, 1H), 8.78 (s, 1H), 10.06 (s, 1H)	
20		1414,87
	(S)-5-(((S)-1-(((S)-1-((4-((((2-(((2-chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenoxy)carbonyl)(methyl)amino)ethyl)(methyl) carbamoyl)oxy)methyl)phenyl)amino)-1-oxo-5-ureidopentan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)amino)-5-oxo-4-(6-(6-	

Ex	Structure/IUPAC Name/^{1}H-NMR	LC-MS [M+H]
	vinylnicotinamido)hexanamido)pentanoic acid	
	(400 MHz; DMSO-d_6): δ 0.83 (dd, *J'* = 6.52 Hz, *J"* = 14.4 Hz, 6H), 1.20 (d, *J* = 5.84 Hz, 3H), 1.30 (bs, 2H), 1.53 (t, *J* = 6.8 Hz, 4H), 1.69-1.72 (m, 2H), 1.88 (bs, 1H), 1.97-1.98 (m, 1H), 2.14 (bs, 2H), 2.24 (t, *J* = 7.36 Hz, 2H), 2.83 (d, *J* = 7.68 Hz, 2H), 2.88 (d, *J* = 8.0 Hz, 2H), 2.92 (s, 4H), 2.97 (s, 1H), 3.05 (s, 2H), 3.17 (s, 2H), 3.25 (d, *J* = 6 Hz, 2H), 3.43-3.50 (m, 4H), 4.21 (t, *J* = 7.16 Hz, 1H), 4.31-4.53 (m, 5H), 4.94-4.97 (m, 3H), 5.50 (d, *J* = 15.36 Hz, 2H), 5.57 (d, *J* = 10.88 Hz, 1H), 5.98 (s, 1H), 6.33 (d, *J* = 17.32 Hz, 1H), 6.87 (dd, *J'* = 10.72 Hz, *J"* = 17.52 Hz, 1H), 7.17-7.29 (m, 8H), 7.42 (d, *J* = 7.44 Hz, 1H), 7.50-7.61 (m, 4H), 7.68 (d, *J* = 7.8 Hz, 1H), 8.03 (d, *J* = 7.48 Hz, 1H), 8.14-8.20 (m, 2H), 8.61 (s, 1H), 8.77 (s, 1H), 8.96 (s, 1H), 10.03 (s, 1H)	
21		1205.45
	(S)-5-(((S)-1-(((S)-1-((4-((2-chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenoxy)methyl)phenyl)amino)-1-oxo-5-ureidopentan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)amino)-4-(6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanamido)-5-oxopentanoic acid	
	(400 MHz; DMSO-d_6): δ 0.84 (dd, *J'* = 6.64 Hz, *J"* = 14.28 Hz, 6H), 1.17-1.23 (m, 5H), 1.38-1.48 (m, 6H), 1.60-1.74 (m, 3H), 1.85-1.91 (m, 1H), 1.97-2.00 (m, 1H), 2.08-2.11 (m, 2H), 2.20-2.51 (m, 2H), 2.93 (s, 2H), 3.01-3.04 (m, 2H), 3.38 (bs, 4H), 4.18-4.24 (m, 1H), 4.30-4.34 (m, 1H), 4.37-4.42 (m, 2H), 4.46-4.53 (m, 2H), 4.92 (d, *J* = 15.8 Hz, 1H), 5.08 (s, 2H), 5.46 (s, 2H), 5.54 (d, *J* = 15.88 Hz, 1H), 6.07 (s, 1H), 6.99 (s, 2H), 7.07-7.20 (m, 4H), 7.25 (bs, 1H), 7.36-7.41 (m, 2H), 7.45 (s, 1H), 7.52 (bs, 1H), 7.62 (d, *J* = 8.36 Hz, 2H), 7.70 (d, *J* = 8.76 Hz, 1H), 8.02 (d, *J* = 7.6 Hz, 1H), 8.24 (d, *J* = 6.0 Hz, 1H), 8.75 (t, *J* = 5.12 Hz, 1H), 10.06 (s, 1H)	

Ex	Structure/IUPAC Name/^{1}H-NMR	LC-MS [M+H]
22		1127.62
	(S)-1-(2-chloro-6-fluoro-3-((4-((S)-2-((S)-3-methyl-2-(6-(6-vinylnicotinamido)hexanamido)butanamido)-5-ureidopentanamido)benzyl)oxy)benzyl)-3,4-dimethyl-2-oxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4-tetrahydroquinazoline-7-carboxamide	
	(500 MHz; DMSO-d_6): δ 0.83 (dd, *J'* = 6.50 Hz, *J"* = 15.0 Hz, 6H), 1.21-1.24 (m, 3H), 1.29-1.43 (m, 4H), 1.52-1.60 (m, 4H), 1.69 (s, 1H), 1.96 (t, *J* = 6.7 Hz, 1H), 2.14-2.22 (m, 2H), 2.93-2.96 (m, 3H), 3.01-3.03 (m, 1H), 3.25-3.35 (m, 5H), 4.20 (t, *J* = 7.85 Hz, 1H), 4.39-4.41 (m, 2H), 4.46-4.53 (m, 2H), 4.91 (d, *J* = 15.7 Hz, 1H), 5.07 (s, 2H), 5.43 (s, 2H), 5.52-5.58 (m, 2H), 6.00 (s, 1H), 6.32 (d, *J* = 17.5 Hz, 1H), 6.84-6.89 (m, 1H), 7.09-7.20 (m, 4H), 7.36-7.41 (m, 2H), 7.45 (s, 1H), 7.58-7.63 (m, 3H), 7.83 (d, *J* = 8.45 Hz, 1H), 8.11-8.16 (m, 2H), 8.36 (s, 1H), 8.61 (s, 1H), 8.76 (s, 1H), 8.95 (s, 1H), 10.04 (s, 1H)	
23		1336.3
	(S)-N5-((S)-1-(((S)-1-((4-((2-chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenoxy)methyl)phenyl)amino)-1-oxo-5-ureidopentan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)-2-(6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanamido)-N1-(2-(2-(2-hydroxyethoxy)ethoxy)ethyl)pentanediamide	
	(500 MHz; DMSO-d_6): δ 0.84 (dd, *J'* = 6.10 Hz, *J"* = 16.85 Hz, 6H), 1.19-1.23 (m, 5H), 1.38 (bs, 1H), 1.48 (bs, 5H), 1.61 (bs, 1H), 1.70 (bs, 2H), 1.83 (bs, 1H), 1.97 (d, *J* = 6.05 Hz, 1H), 2.10 (d, *J* = 6.9 Hz, 2H),	

Ex	Structure/IUPAC Name/^{1}H-NMR	LC-MS [M+H]
	2.18 (s, 2H), 2.94 (s, 4H), 2.99-3.06 (m, 1H), 3.17-3.24 (m, 3H), 3.37-3.41 (m, 6H), 3.50 (s, 6H), 4.17-4.21 (m, 2H), 4.40 (d, *J* = 10.4 Hz, 2H), 4.47-4.53 (m, 2H), 4.58 (s, 1H), 4.93 (d, *J* = 15.55 Hz, 1H), 5.08 (s, 2H), 5.42 (s, 2H), 5.53 (d, *J* = 15.7 Hz, 1H), 6.01 (s, 1H), 7.00 (s, 2H), 7.07-7.20 (m, 5H), 7.36-7.41 (m, 3H), 7.45 (s, 1H), 7.62 (d, *J* = 7.8 Hz, 2H), 7.81 (d, *J* = 7.8 Hz, 1H), 7.88-7.92 (m, 2H), 8.14 (d, *J* = 7.15 Hz, 1H), 8.75 (s, 1H)	
24		1154.38
	4-((S)-2-((S)-2-(6-aminohexanamido)-3-methylbutanamido)-5-ureidopentanamido)benzyl (2-chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenyl) ethane-1,2-diylbis(methylcarbamate) 2,2,2-trifluoroacetate	
	(500 MHz; DMSO-d_6): δ 0.85 (dd, *J'* = 6.15 Hz, *J"* = 13.0 Hz, 6H), 1.10-1.11 (m, 1H), 1.21-1.24 (m, 4H), 1.29 (bs, 2H), 1.37 (s, 1H), 1.45 (s, 1H), 1.52-1.53 (m, 4H), 1.60 (s, 1H), 1.70 (s, 1H), 1.98 (d, *J* = 6.35 Hz, 1H), 2.17-2.20 (m, 2H), 2.75 (s, 2H), 2.89-3.05 (m, 10H), 3.44 (s, 2H), 3.51 (s, 3H), 4.21 (bs, 1H), 4.41-4.44 (m, 3H), 4.47 (s, 1H), 4.95 (s, 1H), 4.98 (s, 2H), 5.50 (d, *J* = 15.6 Hz, 1H), 6.01 (s, 1H), 7.17-7.29 (m, 5H), 7.42 (d, *J* = 7.15 Hz, 1H), 7.49 (s, 1H), 7.54-7.58 (m, 2H), 7.66 (s, 2H), 7.80 (d, *J* = 8.2 Hz, 1H), 8.07 (d, *J* = 7.2 Hz, 1H), 9.74 (s, 1H), 9.99 (s, 1H) , 10.08 (s, 1H)	
25		1323.7

Ex	Structure/IUPAC Name/^{1}H-NMR	LC-MS [M+H]
	1-((6S,9S)-1-amino-6-((4-((((2-(((2-chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenoxy)carbonyl)(methyl)amino)ethyl)(methyl)carbamoyl) oxy)methyl)phenyl)carbamoyl)-9-isopropyl-1,8,11-trioxo-2,7,10,17-tetraazanonadecan-19-oyl)piperidine-4-carboxylic acid	
	(500 MHz; DMSO-d_6): δ 0.84 (dd, *J'* = 6.45 Hz, *J"* = 13.65 Hz, 6H), 1.25-1.84 (m, 17H), 1.96-2.00 (m, 1H), 2.13-2.22 (m, 2H), 2.68-2.71 (m, 2H), 2.87-3.05 (m, 10H), 3.44-3.76 (m, 10H), 4.19-4.21 (m, 3H), 4.40-4.53 (m, 5H), 4.94 (s, 1H), 4.97 (s, 2H), 5.44 (s, 2H), 5.50 (d, *J* = 16.1 Hz, 1H), 6.06 (s, 1H), 7.15-7.30 (m, 6H), 7.42 (d, *J* = 7.65 Hz, 1H), 7.50 (s, 1H), 7.53 (d, *J* = 7.1 Hz, 1H), 7.59 (d, *J* = 7.35 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 8.14 (d, *J* = 6.75 Hz, 1H), 8.27 (s, 2H), 8.75 (d, *J* = 4.15 Hz, 1H), 10.05 (s, 1H)	
26		
	(S)-17-(((S)-1-(((S)-1-((4-((2-chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenoxy)methyl)phenyl)amino)-1-oxo-5-ureidopentan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamoyl)-1-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-15-oxo-3,6,9,12-tetraoxa-16-azaicosan-20-oic acid	
	(500 MHz; DMSO-d_6): δ 0.84 (dd, *J'* = 5.4 Hz, *J"* = 15.15 Hz, 6H), 1.22 (d, *J* = 5.6 Hz, 3H), 1.39 (bs, 1H), 1.46 (bs, 1H), 1.67-1.75 (m, 3H), 1.87 (bs, 1H), 2.02-2.19 (m, 4H), 2.35-2.37 (m, 1H), 2.93 (s, 3H), 2.99 (bs, 1H), 3.18 (s, 1H), 3.47-3.57 (m, 18H), 4.21 (s, 1H), 4.34-4.41 (m, 3H), 4.47-4.53 (m, 2H), 4.93 (d, *J* = 15.65 Hz, 1H), 5.08 (s, 2H), 5.52-5.55 (m, 3H), 6.28 (s, 1H), 7.02 (s, 2H), 7.09-7.20 (m, 5H), 7.36-7.45 (m, 4H), 7.62 (d, *J* = 7.55 Hz, 2H), 7.79 (d, *J* = 7.4 Hz, 1H), 8.13 (d, *J* = 6.25 Hz, 1H), 8.36 (s, 1H), 8.75 (s, 1H), 10.07 (s, 1H)	

Ex	Structure/IUPAC Name/^{1}H-NMR	LC-MS [M+H]
27		1241
	(2S,3S,4S,5R,6S)-6-(4-((((2-(((2-chloro-3-(((S)-3,4-dimethyl-2-oxo-7-((2,4,6-trifluorobenzyl)carbamoyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)-4-fluorophenoxy)carbonyl)(methyl)amino)ethyl)(methyl) carbamoyl)oxy)methyl)-3-(3-(6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanamido)propanamido)phenoxy)-3,4,5-trihydroxytetrahydro-2H-pyran-2-carboxylic acid	
	(500 MHz; DMSO-d_6): δ 1.08-1.24 (m, 6H), 1.40-1.48 (m, 4H), 2.01-2.03 (m, 2H), 2.28-2.37 (m, 1H), 2.55-2.59 (m, 1H), 2.83-2.85 (m, 3H), 2.90-2.92 (m, 4H), 2.99 (s, 1H), 3.05 (s, 1H), 3.17-3.21 (m, 1H), 3.22-3.36 (m, 6H), 3.37-3.41 (m, 2H), 3.44 (s, 2H), 3.50 (s, 1H), 3.56 (s, 1H), 4.40-4.52 (m, 3H), 5.58 (d, *J* = 7.4 Hz, 1H), 4.93-4.98 (m, 3H), 5.46-5.50 (dd, *J'* = 6.25 Hz, *J"* = 15.65 Hz, 1H), 6.93-7.08 (m, 3H), 7.12-7.22 (m, 6H), 7.43 (d, *J* = 7.35 Hz, 1H), 7.52 (s, 1H), 8.01 (s, 1H), 8.15 (s, 1H), 8.33 (s, 1H), 8.83 (s, 1H), 9.24-9.28 (m, 1H)	

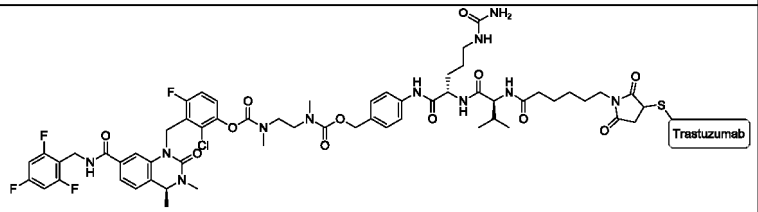
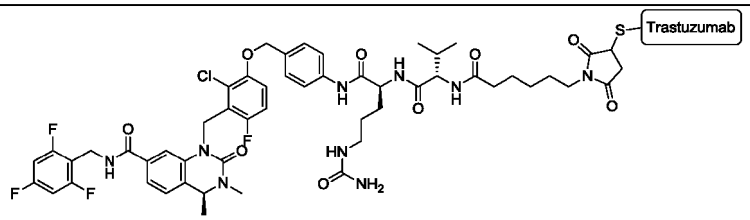
Conjugate examples

Antibody conjugation method

The linked payloads 7 and 10 were separately attached to a thiol-containing antibody using the procedures described in the General Antibody Conjugation Method and the following method. The antibody was first treated with 2.25 equivalents TCEP at 40°C for 1 h at a concentration of 5 mg/mL in phosphate buffered saline to produce free thiol-containing antibody. 3 equivalents of the pre-conjugates were then added in a mixture of DMF and polysorbate 80, and the whole stirred at room temperature for 3 h. Analysis of the reaction mixture using size exclusion chromatography (SEC) showed the progress of the reaction, with the presence of the conjugates 28 and 29 and the drug-antibody ratio (DAR) confirmed by LC-MS, hydrophobic interaction chromatography (HIC) and SDS-PAGE analysis. The final solution concentration was determined by a

photometric method and the endotoxin content of the samples using the Endosafe-PTS platform (Charles River) as described in the general procedures.

ADC molecules

Ex	Structure	Average DAR	% Purity (monomeric)	Endotoxin content by UV analysis (EU/mg)
28		2.6	97.3	0.60
29		2.7	96.7	0.57

Examples 28 and 29 were characterised by HIC to confirm the average DAR of the prepared samples, shown in Figures 2 and 4, respectively. The purity of the conjugates was determined by SEC to determine the purity of monomeric species contained in the sample, shown in Figures 3 and 5, respectively, and SDS-PAGE analysis confirmed conjugation and the presence of monomeric species as shown in Figure 6.

Biological Assays

Stable cell line generation

a) Stable STING expressing cells - Stable HEK293T STING-expressing cell lines were generated using plasmids purchased from Invivogen, CA, USA, that contain STING cDNA cloned into the pUNO-1 vector under hEF1-HTLV promoter and containing the Blasticidin selection cassette. The plasmids hSTING(R232), hSTING(H232), hSTING(HAQ) were directly procured from Invivogen while hSTING (AQ) and hSTING (Q) were derived from hSTING(HAQ) and hSTING (R232) plasmids respectively by using a PCR based

site directed mutagenesis method. These vectors were individually transfected into HEK293T cells using Lipofectamine (Invitrogen) and transfected cells were selected under Blasticidin selection. These transfected cells were further subjected to clonal selection using the limiting dilution method to obtain clonally pure populations of HEK cells transfected with each of the above mentioned human STING variants. Clones were selected in which ligand independent activation of STING was minimal.

b) Stable Luciferase reporter gene expressing cells - Stable HEK293T Luciferase reporter gene expressing cell lines were generated using pCDNA4 plasmids under an IRF-inducible promoter. This promoter is comprised of five tandem interferon-stimulated response elements (ISRE) fused to an ISG54 minimal promoter. This vector was transfected into HEK293T cells using Lipofectamine (Invitrogen) and transfected cells were selected under Zeocin selection. These transfected cells were further subjected to clonal selection using the limiting dilution method to obtain clonally pure populations of HEK cells transfected the Luciferase reporter construct. Clones were selected in which ligand independent induction of luciferase was minimal.

Luciferase Assay

5 x 10^5 clonally selected HEK293T-hSTING-Luciferase cells were seeded in 384-well plates in growth medium and stimulated with novel compounds. After 20hr of stimulation supernatant were removed and secretory reporter gene activity were measured using the Quanti-Luc detection system (Invivogen) on a Spectramax i3X luminometer.

In the tables below, EC_{50} value ranges for exemplary compounds are given. The EC_{50} ranges are indicated as "A" for values less than or equal to 1 μM, "B" for values greater than 1 μM and less than or equal to 10 μM, and "C" for values greater than 10 μM.

All compounds were first tested in a primary screen to obtain a 'fold-induction' over baseline levels of protein activity. Only those compounds that had a fold induction >1 have been included in the table and all are considered 'active'.

Release of Payload in Tumor Homogenate

CT26.hSTING cell line induced tumors were harvested when the average tumor size was around 450mm^3 to 500mm^3 and stored at -80°C for further use. Frozen mouse tumors were homogenized in lysis buffer (10mM 2-morpholino-ethane sulfonic acid, pH6.0; 40µM dithiothreitol) in a ratio of 1:3 w/v (*e.g.* 500mg solid tumor was homogenized in 1500ml lysis buffer) using a tissue homogenizer. A 100µl reaction using 1:1 homogenate and test compound containing 1% DMSO was incubated at 37°C for the desired time. Following incubation, the reaction was quenched by the addition of chilled acetonitrile and the supernatant used to measure the release of payload by LC-MS/MS.

Release of Payload in Human or Mouse Plasma

Test compound was spiked with freshly collected/frozen mouse or human plasma containing 1% DMSO and incubated at 37°C for the desired time. Following incubation, the reaction was quenched by addition of chilled acetonitrile and the supernatant used to measure the release of payload by LC-MS/MS.

Release of Payload in Mouse after IV or IT dosing

1 x 10^6 CT26 tumor cells stably expressing R232.hSTING were injected subcutaneously in 100 µl RPMI on the right side of the flanks of Balb/C mice. Following tumor implantation, when the average tumor size was around 250mm^3 to 300mm^3, mice were randomized into three different groups (two for IV and one for IT dosing). The total number of animals per group was three. Test compound was formulated in 40% PEG400, 20% PG, 10% DMA and 30% saline and dosed via IV or IT routes. Following administration, blood samples and tumors were harvested at 0.25h & 1h post-dosing time points for IV and at 1h only for the IT route of dosing through terminal sacrifice of each animal. After collection of tissue samples, plasma was separated from blood and stored at -80°C along with tumors for further analysis.

To estimate the release of payload in plasma and the tumor microenvironment, both tumor homogenate which was prepared in 1:10 w/v ratio with RIPA buffer (20mM Tris-Cl, 150mM NaCl, 0.5mM EDTA, 1% NP-40 of pH 7.4) and frozen plasma were quenched by addition of chilled acetonitrile and the supernatant subsequently used to measure payload by LC-MS/MS.

Pre-conjugate examples

Ex	Release of payload (nM) in tumor homogenate		Release of payload in mouse plasma		Release of payload in human plasma		Human EC_{50} (nM)	Monkey EC_{50} (nM)
	oh	4h	oh	4h	oh	4h		
1	-	-	-	-	-	-	**B**	-
2	-	-	-	-	-	-	**B**	**B**
3	-	-	-	-	-	-	**A**	**A**
4	-	-	-	-	-	-	**A**	**A**
5	-	-	-	-	-	-	**B**	-
6	270	3830	-	-	-	-	**A**	**A**
7	33	2088	136	2203	48	53	**B**	**B**
8	113	171	-	-	-	-	**A**	**B**
9	257	2146	392	1836	392	370	**A**	**B**
10	128	2457	298	1460	64	70	**B**	**B**
11	598	5976	171	3222	-	-	**B**	**B**
12	987	3365	3	355	-	-	**B**	**C**
13	3842	7272	5674	8790	4131	9568	-	-
14	72	164	37	104	4	50	-	-
15	892	5100	48	661	-	-	**A**	**B**
16	240	4723	-	74	-	-	**B**	**C**
17	798	6093	38	1721	19	54	**A**	**B**
18	54	1776	103	2513	41	87	**A**	**B**
19	24	3921	79	695	32	94	**A**	**B**
20	62	6451	15	7534	12	124	**A**	**B**
21	262	2134	61	105	24	24	**A**	**B**
22	135	3017	132	5238	15	48	**B**	**C**
23	309	2088	188	1093	152	155	**A**	**B**

Ex	Release of payload (nM) in tumor homogenate		Release of payload in mouse plasma		Release of payload in human plasma		Human EC_{50} (nM)	Monkey EC_{50} (nM)
	0h	4h	0h	4h	0h	4h		
24	567	5590	757	5496	516	777	**A**	**A**
25	103	4264	27	6447	20	149	**B**	**C**
26	284	4985	29	456	12	12	**B**	**C**
27	81	6639	86	188	54	89	**B**	**C**

Pre-conjugate examples

Ex	Release of payload (nM) in mouse after IV dosing					Release of payload (nM) in mouse after IT dosing	
	Plasma (ng/mL)		Tumor (ng/g)		T/P ratio	Plasma (ng/mL)	Tumor (ng/g)
	0.25h	1h	0.25h	1h	1h	1h	1h
7	60	31	99	211	6.8	152	3009
9	150	85	110	179	2.1	258	2783
10	33	12	172	272	22.7	3	785
11	143	80	0	58	0.7	129	7727
12	26	24	55	208	8.7	19	1682
14	4	4	0	0	-	2	169
15	170	48	150	0	-	28	4425
16	20	18	0	114	6.3	31	2136
17	157	117	114	235	2.0	168	4174
18	400	99	198	31	0.3	173	5257
19	158	68	0	40	0.6	72	2536
21	24	14	78	235	16.8	5	879
22	76	0	126	0	-	0	1806
24	815	529	268	388	0.7	385	5681
26	13	4	0	189	52	12	3224

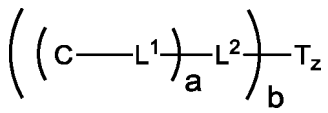
Ex	Release of payload (nM) in mouse after IV dosing					Release of payload (nM) in mouse after IT dosing	
	Plasma (ng/mL)		Tumor (ng/g)		T/P ratio	Plasma (ng/mL)	Tumor (ng/g)
	0.25h	1h	0.25h	1h	1h	1h	1h
27	0	4	0	513	128	4	5650

Conclusion

The inventors have synthesised a large number of compounds which fall within the general formula (**I**). They have shown that these compounds activate the STING protein, and so could be used to treat a number of diseases, including cancer.

Claims

1. A compound of formula (**I**):



(**I**)

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

L^1 and L^2 are linkers;

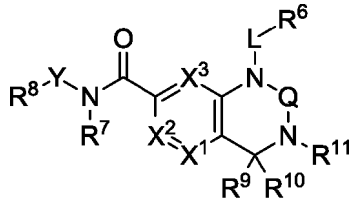
T is a targeting moiety;

a is an integer between 1 and 5;

b is an integer between 1 and 10;

z is an integer between 1 and 5; and

C is a compound of formula (**II**);



(**II**)

, wherein

X^1 is CR^1 or N;

X^2 is CR^2 or N;

X^3 is CR^3 or N;

Q is C=O, S=O, SO_2, C=S or CR^4R^5;

L is optionally substituted C_1-C_6 alkyl, C_1-C_3 polyfluoroalkyl, optionally substituted C_3-C_6 cycloalkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, C=O, S=O, SO_2, $-CH_2C(O)-$, $-CH_2CONH-$, or -CONH-;

Y is an optionally substituted C_1-C_6 alkyl, C_1-C_3 polyfluoroalkyl, an optionally substituted C_2-C_6 alkenyl, an optionally substituted C_2-C_6 alkynyl, an optionally substituted C_3-C_6 cycloalkyl, or an optionally substituted mono or bicyclic 3 to 8 membered heterocycle;

R^1, R^2 and R^3 are each independently selected from the group consisting of H, halogen, CN, hydroxyl, COOH, $CONR^1R^2$, NR^1R^2, $NHCOR^1$, optionally substituted C_1-C_6 alkyl, C_1-

C_3 polyfluoroalkyl, optionally substituted C_1-C_6 alkylsulfonyl, optionally substituted mono or bicyclic C_3-C_6 cycloalkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted C_1-C_6 alkoxy, optionally substituted C_1-C_6 alkoxycarbonyl group, mono or bicyclic optionally substituted C_5-C_{10} aryl, mono or bicyclic optionally substituted 5 to 10 membered heteroaryl, optionally substituted mono or bicyclic 3 to 8 membered heterocycle, optionally substituted aryloxy, optionally substituted heteroaryloxy, and optionally substituted heterocyclyloxy;

R^4 and R^5 are each independently selected from the group consisting of H, halogen, optionally substituted C_1-C_6 alkyl and optionally substituted C_3-C_6 cycloalkyl; or R^4 and R^5 together with the atom to which they are attached form a spirocyclic ring;

R^6 is a ring optionally substituted with one or more R^{12} groups, wherein the ring is selected from the group consisting of a mono or bicyclic C_5-C_{10} aryl; a mono or bicyclic 5 to 10 membered heteroaryl; a C_3-C_6 cycloalkyl; and a mono or bicyclic 3 to 8 membered heterocycle;

R^7 is H, optionally substituted C_1-C_6 alkyl, optionally substituted sulfonyl, optionally substituted C_1-C_6 alkylsulfonyl, optionally substituted C_3-C_6 cycloalkyl, optionally substituted C_2-C_6 alkenyl or optionally substituted C_2-C_6 alkynyl;

R^8 is a mono or bicyclic optionally substituted C_5-C_{10} aryl, a mono or bicyclic optionally substituted 5 to 10 membered heteroaryl, optionally substituted mono or bicyclic C_3-C_6 cycloalkyl or an optionally substituted mono or bicyclic 3 to 8 membered heterocycle;

R^9 and R^{10} are each independently selected from the group consisting of optionally substituted C_1-C_6 alkyl, H, halogen, CN, CO_2H, $CONR^1R^2$, azido, sulfonyl, C_1-C_3 polyfluoroalkyl, optionally substituted C_1-C_6 thioalkyl, optionally substituted C_1-C_6 alkylsulfonyl, optionally substituted C_3-C_6 cycloalkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted C_1-C_6 alkoxy, optionally substituted C_1-C_6 alkoxycarbonyl, mono or bicyclic optionally substituted C_5-C_{10} aryl, mono or bicyclic optionally substituted 5 to 10 membered heteroaryl, optionally substituted heterocycle, optionally substituted aryloxy, and an optionally substituted heteroaryloxy; or R^9 and R^{10} together with the C atom to which they are attached can combine to form an optionally substituted spirocyclic ring;

R^{11} is selected from the group consisting of optionally substituted C_1-C_6 alkyl, H, hydroxyl, C_1-C_3 polyfluoroalkyl, optionally substituted C_1-C_6 thioalkyl, optionally substituted C_1-C_6 alkylsulfonyl, optionally substituted C_3-C_6 cycloalkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted C_1-C_6 alkoxy, optionally substituted C_1-C_6 alkoxycarbonyl, mono or bicyclic optionally substituted C_5-C_{10} aryl, mono or bicyclic optionally substituted 5 to 10 membered

heteroaryl, optionally substituted heterocycle, optionally substituted aryloxy, and an optionally substituted heteroaryloxy;

the or each R^{12} group is independently selected from the group consisting of halogen, OH, SH, $OP(O)(OH)_2$, $NR^{13}R^{14}$, $CONR^{13}R^{14}$, CN, $COOR^{13}$, NO_2, azido, SO_2R^{13}, OSO_2R^{13}, $NR^{13}SO_2R^{14}$, $NR^{13}C(O)R^{14}$, $O(CH_2)_nOC(O)R^{13}$, $NR^{13}(CH_2)_nOC(O)R^{14}$, $OC(O)R^{13}$, $OC(O)OR^{13}$, $OC(O)NR^{13}R^{14}$, $OC(O)O(CH_2)_nCOOR^{14}$, $OC(O)NR^{13}(CH_2)_nCOOR^{14}$, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 alkoxy, optionally substituted aryloxy, optionally substituted heteroaryloxy, an optionally substituted mono or bicyclic C_5-C_{10} aryl, an optionally substituted mono or bicyclic 5 to 10 membered heteroaryl, an optionally substituted C_3-C_6 cycloalkyl and an optionally substituted mono or bicyclic 3 to 8 membered heterocycle;

R^{13} and R^{14} are each independently selected from the group consisting of H, optionally substituted C_1-C_6 alkyl, optionally substituted mono or bicyclic C_3-C_6 cycloalkyl, mono or bicyclic optionally substituted C_5-C_{10} aryl, mono or bicyclic optionally substituted 5 to 10 membered heteroaryl, and optionally substituted mono or bicyclic 3 to 8 membered heterocycle; and

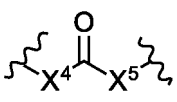
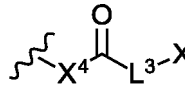
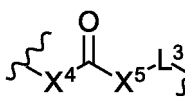
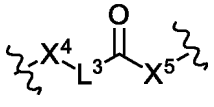
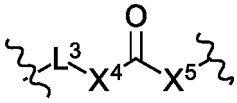
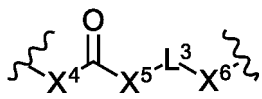
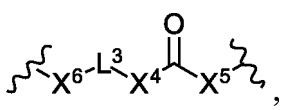
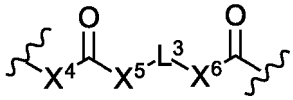
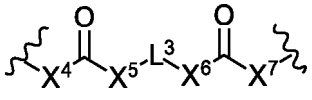
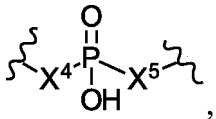
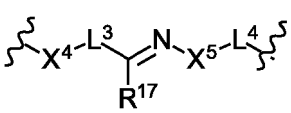
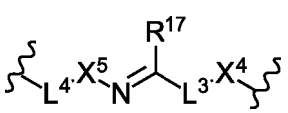
n is an integer between 0 and 6;

or a pharmaceutically acceptable complex, salt, solvate, tautomeric form or polymorphic form thereof.

2. A compound according to claim 1, wherein L^1 is absent or is:

-A-W-D-

wherein:

A is absent or is selected from the group consisting of $-L^3-$, $-X^4L^3-$, $-L^3X^4-$, $-C(O)X^4$, $-L^3C(O)X^4$,  ,  ,  ,  ,  ,  ,  ,  ,  , $-X^4L^4-$, $-L^4X^4-$, $-X^4L^3L^4-$, $-L^4L^3X^4-$, $-X^4L^3L^4L^5-$, $-L^5L^4L^3X^4-$, $-L^3L^4-$, $-L^4L^3-$, $-L^3X^4L4-$, $-L^4X^4L^3-$, $-L^3L^4L^6-$, $-L^3X^4L^4X^5L^6-$,  ,  and  ;

W is either absent or is selected from the group consisting of –L^7NH-, –L^3L^7NH-, -L^7NHC(O)-, -L^3L^7NHC(O)-, –L^7L^8NH-, –$L^3L^7L^8$NH-, -L^7L^8NHC(O)-, and -$L^3L^7L^8$NHC(O)-;

D is either absent or has formula –$(D^1)_q$- or –$(D^1)_q$C(O)-, wherein $(D^1)_q$ is either linear or cyclic;

the or each L^3 and L^6 are each independently an optionally substituted C_1-C_{25} alkylene or an optionally substituted C_2-C_{25} alkylyne;

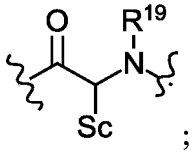
L^4 and L^5 are each independently selected from the group consisting of an optionally substituted mono or bicyclic C_5-C_{10} aryl; an optionally mono or bicyclic 5 to 10 membered heteroaryl; an optionally C_3-C_{12} cycloalkyl; and an optionally mono or bicyclic 3 to 12 membered heterocycle;

L^7 and L^8 are each independently an optionally substituted mono or bicyclic C_5-C_{10} aryl; or an optionally substituted mono or bicyclic 5 to 10 membered heteroaryl, wherein the aryl or heteroaryl is optionally further substituted with at least one -OR^{18} group;

the or each of X^4, X^5, X^6 and X^7 is independently O, S or NR^1;

R^{17} is hydrogen or an optionally substituted C_{1-6} alkyl;

R^{18} is an optionally substituted C_3-C_6 cycloalkyl, or an optionally substituted mono or bicyclic 3 to 8 membered heterocycle;

each D^1 independently has general formula 

;

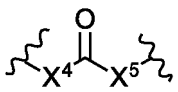
Sc is a side chain of a natural or unnatural amino acid and R^{19} is H, or Sc and R^{19} together with the atoms to which they are attached form a ring; and

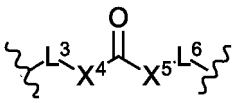
q is an integer between 2 and 20.

3. A compound according to either claim 1 or claim 2, wherein L^2 is absent or is:

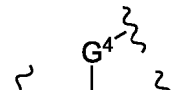
-G-(S-)$_z$

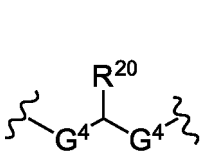
wherein, G is either absent or is $(–G^1)_a$-G^2-$(G^3-)_z$,

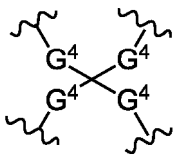
wherein, the or each G^1 is independently either absent or selected from the group consisting of –L^3-, -$(X^4L^3)_p$-, -$(L^3X^4)_p$-, -L^4-, -X^4-, -X^8-, -X^4C(O)-, -C(O)X^4-, 

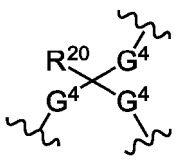
, -L^3X^4C(O)-, -L^3C(O)X^4, 

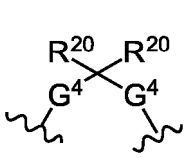
, -L^9-, -L^9L^3-, -L^9L^3C(O)-, -C(O)L^3-, -C(O)L^9-, -C(O)$L^3X^4L^6$-, -C(O)L^3X^4C(O)L^6-,

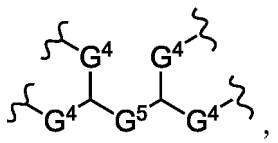


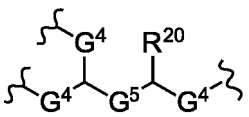


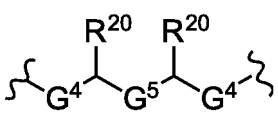


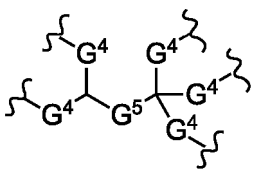


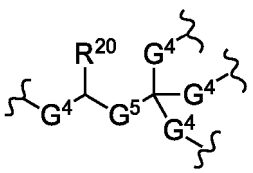


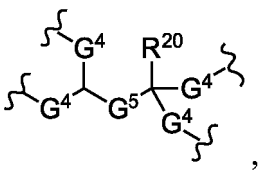


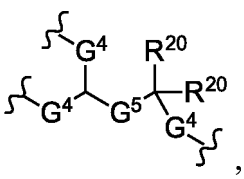


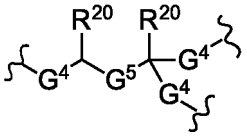


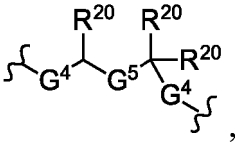


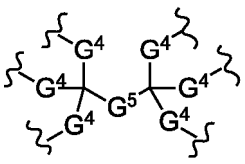


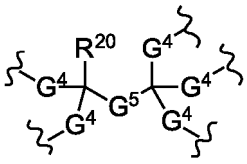


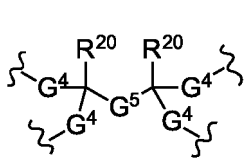


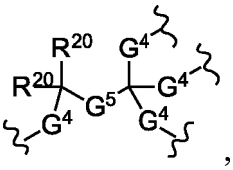


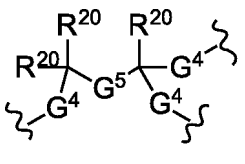


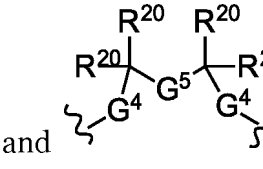


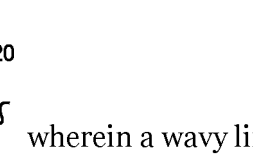


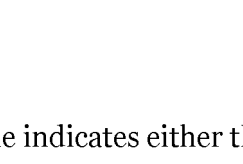


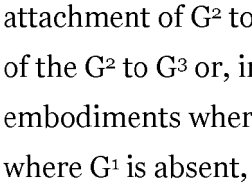


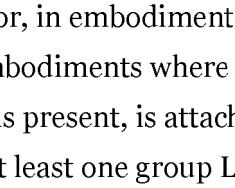


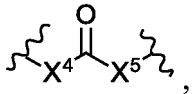


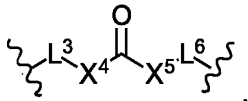












$-C(O)L^9L^3-$, $-C(O)L^3C(O)-$, $-C(O)L^9C(O)-$, $-C(O)L^9L^3C(O)-$, a poly(ethylene glycol) (PEG) chain of between 1 and 25 units and a cyclodextrin;

G^2 is either absent or is selected from the group consisting of ,

, , , , ,

, , , ,

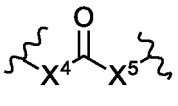
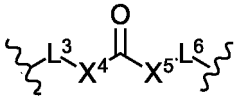
, , , ,

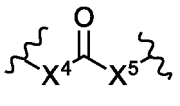
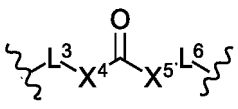
, , , ,

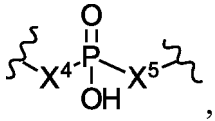
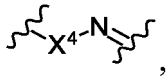
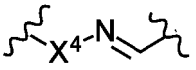
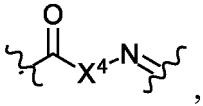
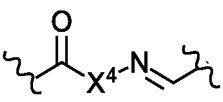
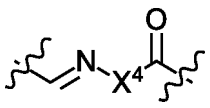
 and wherein a wavy line indicates either the attachment of G^2 to G^1 or, in embodiments where G^1 is absent, to L^1, or the attachment of the G^2 to G^3 or, in embodiments where G^3 is absent, to S, and each G^2, in embodiments where it is present, is attached to at least one G^1 or, in embodiments where G^1 is absent, to at least one group L^1, and each G^2, in embodiments where it is present, is attached to at least one G^3 or, in embodiments where G^3 is absent, to at least one group S;

the or each G^3 is independently either absent or selected from the group consisting of $-L^3-$, $-(X^4L^3)_p-$, $-(L^3X^4)_p-$, $-L^4-$, $-X^4-$, $-X^8-$, $-X^4C(O)-$, $-C(O)X^4-$, , $-L^3X^4C(O)-$, $-L^3C(O)X^4$, $-L^3X^4C(O)L^6-$, $-L^3C(O)X^4L^6-$, , $-L^9-$, $-X^4L^9-$, $-L^9L^3-$, $-L^9L^3C(O)-$, $-C(O)L^3-$, $-C(O)L^9-$, $-C(O)L^3X^4L^6-$, $-C(O)L^3X^4C(O)L^6-$, $-C(O)L^9L^3-$, -

$C(O)L^3C(O)$-, -$C(O)L^9C(O)$-, -$C(O)L^9L^3C(O)$-, a poly(ethylene glycol) (PEG) chain of between 1 and 25 units and a cyclodextrin;

the or each G^4 is independently either absent or selected from the group consisting of –L^3-, -$(X^4L^3)_p$-, -$(L^3X^4)_p$-, -X^4-, -X^8-, -$X^4C(O)$-, -$C(O)X^4$-,  , -$L^3X^4C(O)$-, -$C(O)X^4L^3$-,-$L^3C(O)X^4$-, -$X^4C(O)L^3$-, -$X^4L^3C(O)X^5$-, -$X^4C(O)L^3X^5$-, -$L^3X^4L^6C(O)X^5$-, -$X^4C(O)L^3X^5L^3$-  , -L^9-, -L^9L^3-, -$L^9L^3C(O)$-, -$C(O)L^3$-, -$C(O)L^9$-, -$C(O)L^3X^4L^6$-, -$C(O)L^3X^4C(O)L^6$-, -$C(O)L^9L^3$-, -$C(O)L^3C(O)$-, -$C(O)L^9C(O)$-, -$C(O)L^9L^3C(O)$-, a poly(ethylene glycol) (PEG) chain of between 1 and 25 units and a cyclodextrin;

G^5 is either –L^3-, -$(X^4L^3)_p$-, -$(L^3X^4)_p$-, -X^4-, -X^8-, -$X^4C(O)$-, -$C(O)X^4$-,  , -$L^3X^4C(O)$-, -$L^3C(O)X^4$, -$L^3X^4C(O)L^6$-, -$L^3C(O)X^4L^6$-,  , -L^9-, -X^4L^9-, -L^9L^3-, -$L^9L^3C(O)$-, -$C(O)L^3$-, -$C(O)L^9$-, -$C(O)L^3X^4L^6$-, -$C(O)L^3X^4C(O)L^6$-, -$C(O)L^9L^3$-, -$C(O)L^3C(O)$-, -$C(O)L^9C(O)$-, -$C(O)L^9L^3C(O)$-, a poly(ethylene glycol) (PEG) chain of between 1 and 25 units and a cyclodextrin;

S is either absent or is selected from the group consisting of –X^4-, -X^8-, -$C(X^9)$-, -$X^4C(X^9)$-, -$X^4C(X^9)L^3$-, -$X^4C(X^9)L^3C(O)$-, -X^8L^3-, -$X^4X^8L^3$-, $X^8L^3C(O)$-, -L^3-, –L^4-, -L^4L^3-, -$L^4C(O)$-, -$C(O)L^4C(O)$-, -$L^3C(O)L^4C(O)$-, -$L^4L^3L^5$-, $L^4L^3L^5C(O)$-,  ,  ,  ,  ,  and  ;

L^3 to L^8 and X^4 to X^7 are as defined above,

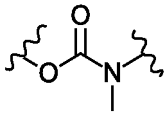
L^9 is a poly(ethylene glycol) (PEG) chain between 1 and 25 units long;

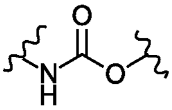
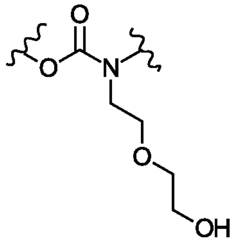
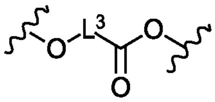
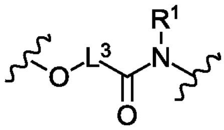
X^8 is –S(O)- or –SO_2-;

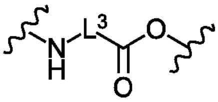
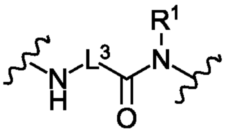
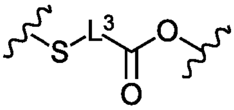
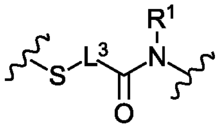
X^9 is O or S;

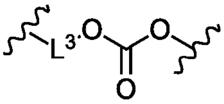
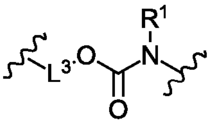
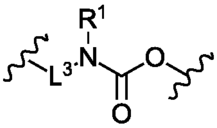
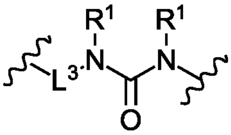
R^{20} is an optionally substituted C_1-C_6 alkyl, an optionally substituted C_2-C_6 alkenyl, an optionally substituted C_2-C_6 alkynyl, -L^9H, -$C(O)L^3H$, -$C(O)L^9H$, -X^4L^3H, -X^4L^9H, -$X^4C(O)L^3H$, -$X^4C(O)L^9H$, -$C(O)X^4L^3H$ or -$C(O)X^4L^9H$; and

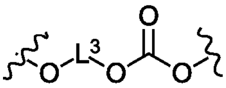
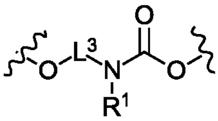
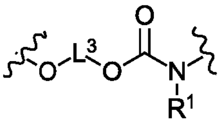
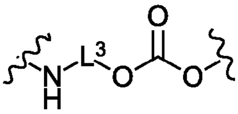
p is an integer between 1 and 25.

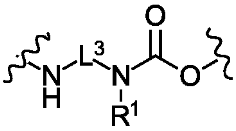
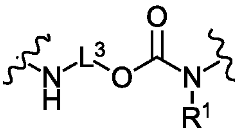
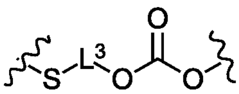
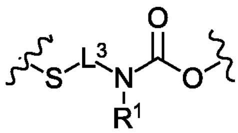
4. A compound according to any preceding claim, wherein A is an optionally substituted C_1-C_6 alkylene, $-CH_2CH_2O-$, $-CH_2CH_2NH-$, $-CH_2CH_2S-$, $-CH_2CH_2CH_2O-$, $-CH_2CH_2CH_2NH-$, $-CH_2CH_2CH_2S-$, $-C(O)O-$, $-CH_2C(O)O-$,  ,

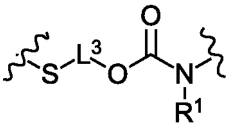
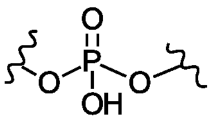
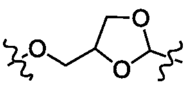
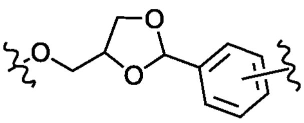
 ,  ,  ,  ,

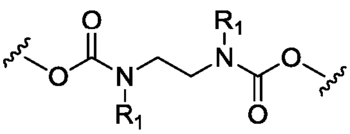
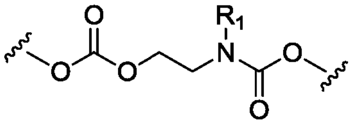
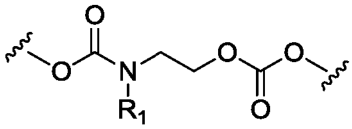
 ,  ,  ,  ,

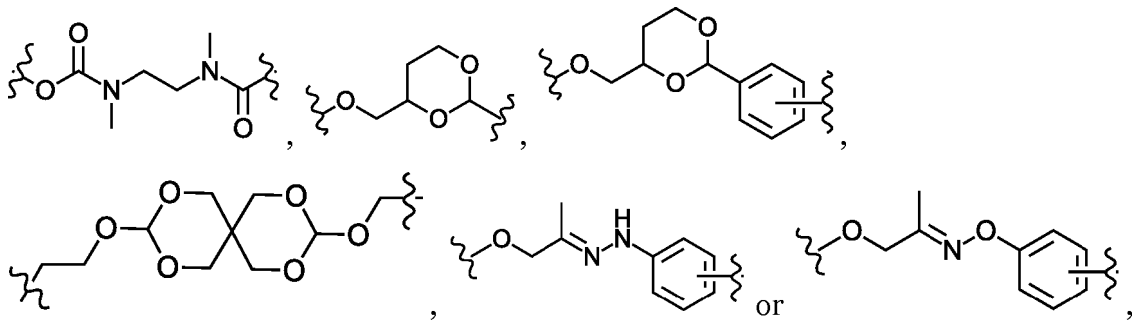
 ,  ,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,  or

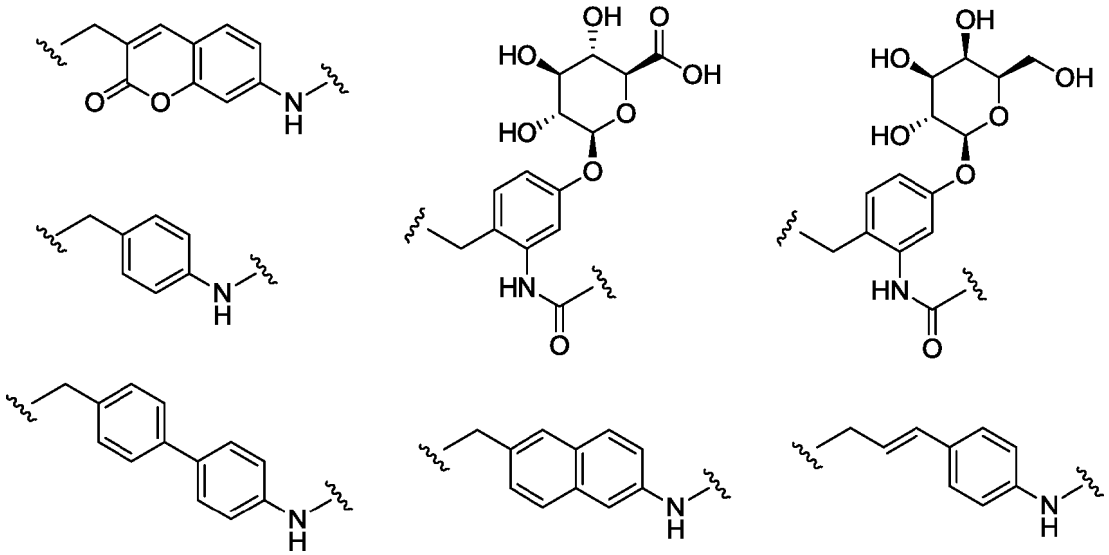
 ,  ,  ,  ,

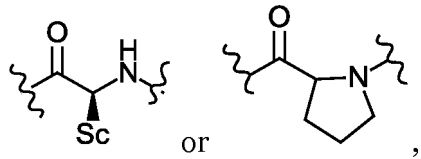


wherein L^3 is an optionally substituted C_1-C_6 alkylene.

5. A compound according to any preceding claim, wherein W is selected from:

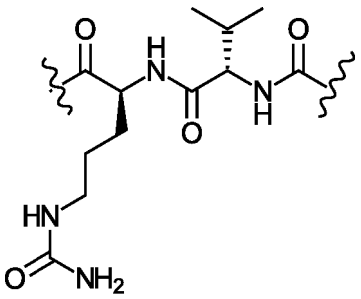
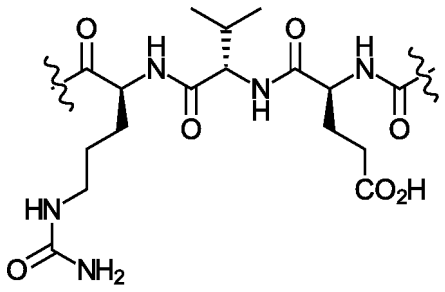
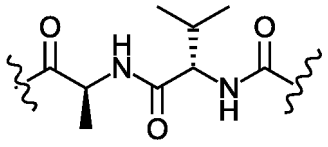
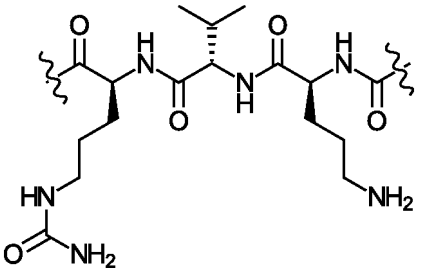


6. A compound according to any preceding claim, wherein D^1 has general formula

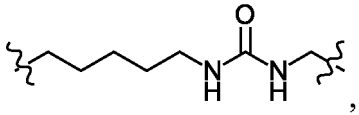


and Sc is H, an optionally substituted C_1-C_6 alkyl, an optionally substituted mono or bicyclic C_5-C_{10} aryl, an optionally mono or bicyclic 5 to 10 membered heteroaryl, an optionally C_3-C_{12} cycloalkyl, or an optionally mono or bicyclic 3 to 12 membered heterocycle.

7. A compound according to claim 6, wherein D is selected from:

8. A compound according to any preceding claim, wherein G is $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-CH_2C(Me)H-$, CH_2CMe_2-, $-CH_2CMe_2S-$ $-CH_2O-$, $-CH_2CH_2O-$, $-CH_2CH_2OCH_2CH_2O-$, $-(CH_2)_5NH-$, $-CH_2OCH_2CH_2OCH_2CH_2O-$, $-(CH_2)_5NHC(O)-$, $-C(O)L^3-$ or $-C(O)L^3C(O)-$,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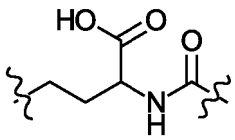
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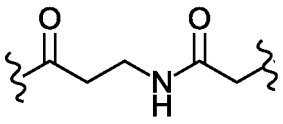
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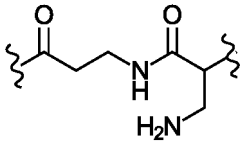
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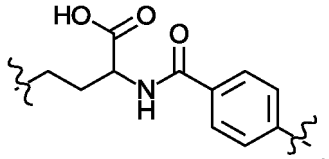
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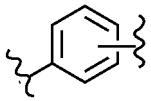
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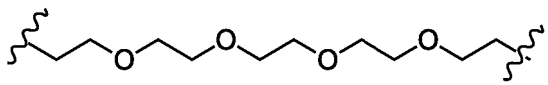
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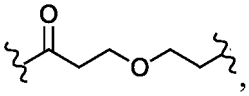
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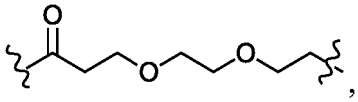
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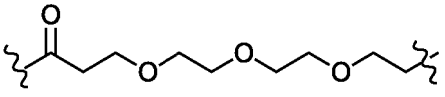
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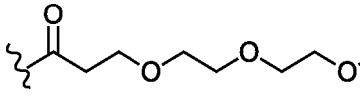
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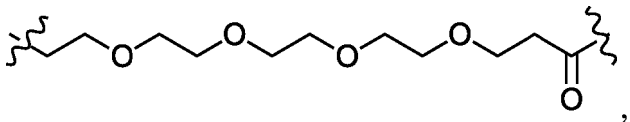
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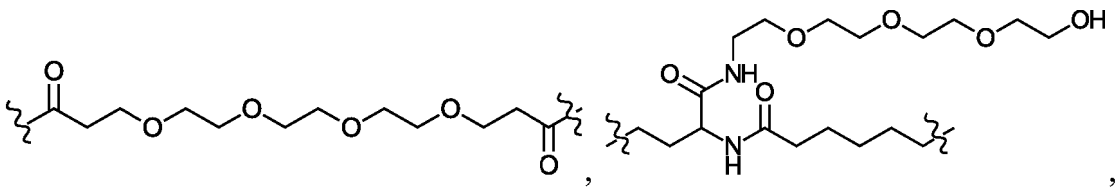
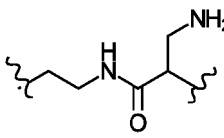
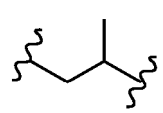
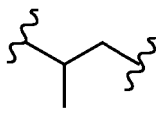
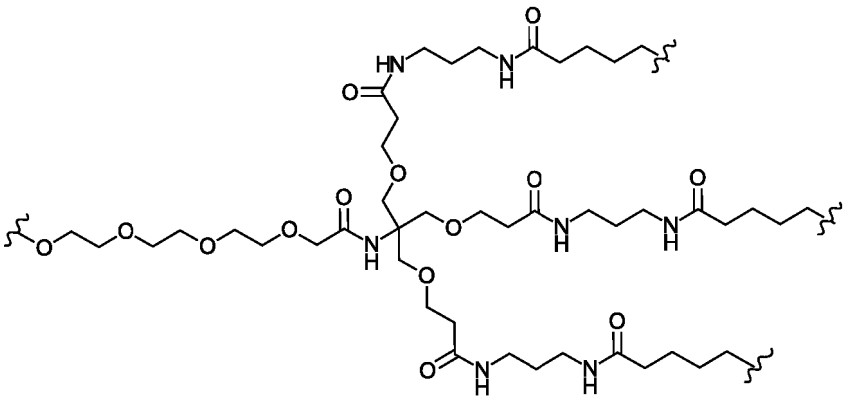

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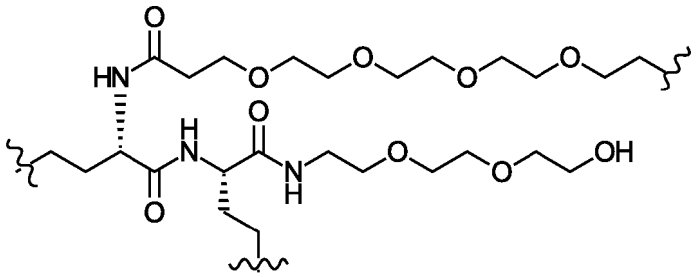
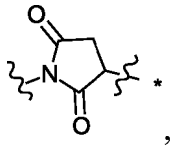
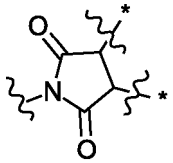
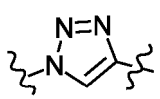
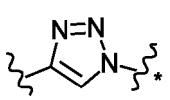
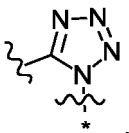
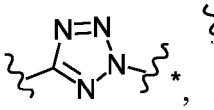
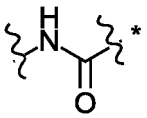
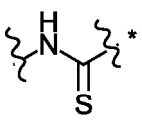
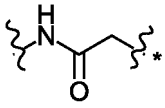
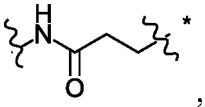
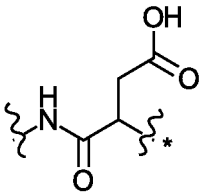
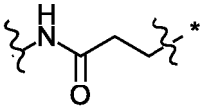
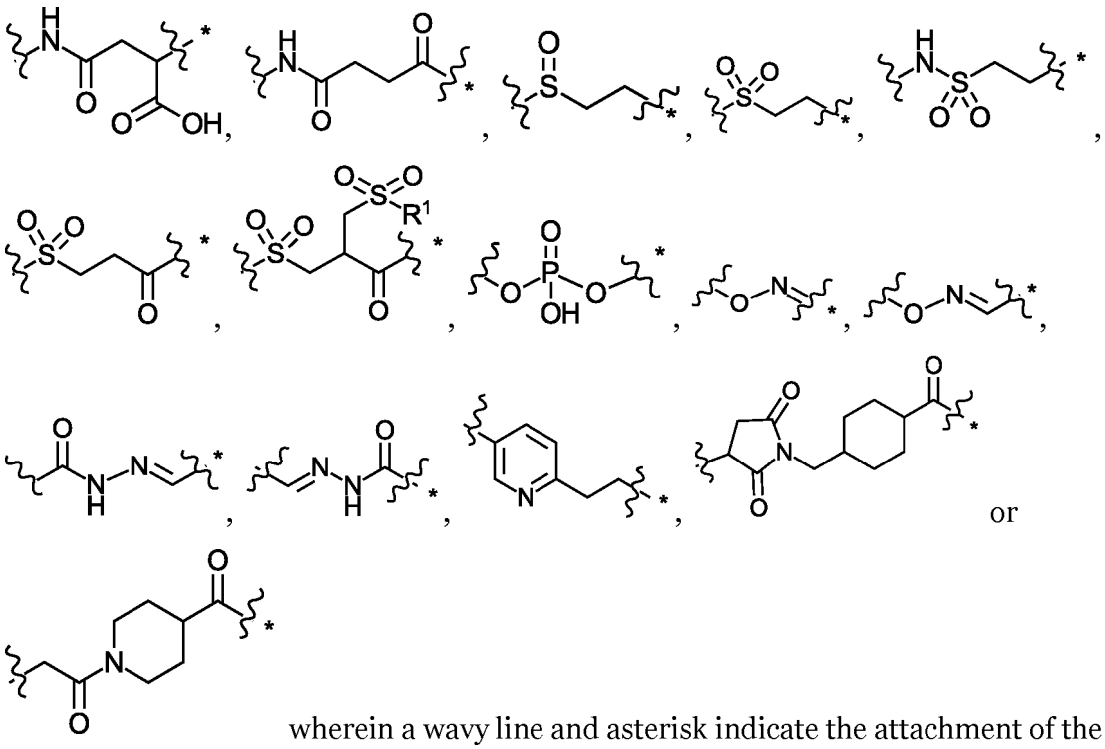


where L^3 is an optionally substituted C_1-C_6 alkylene.

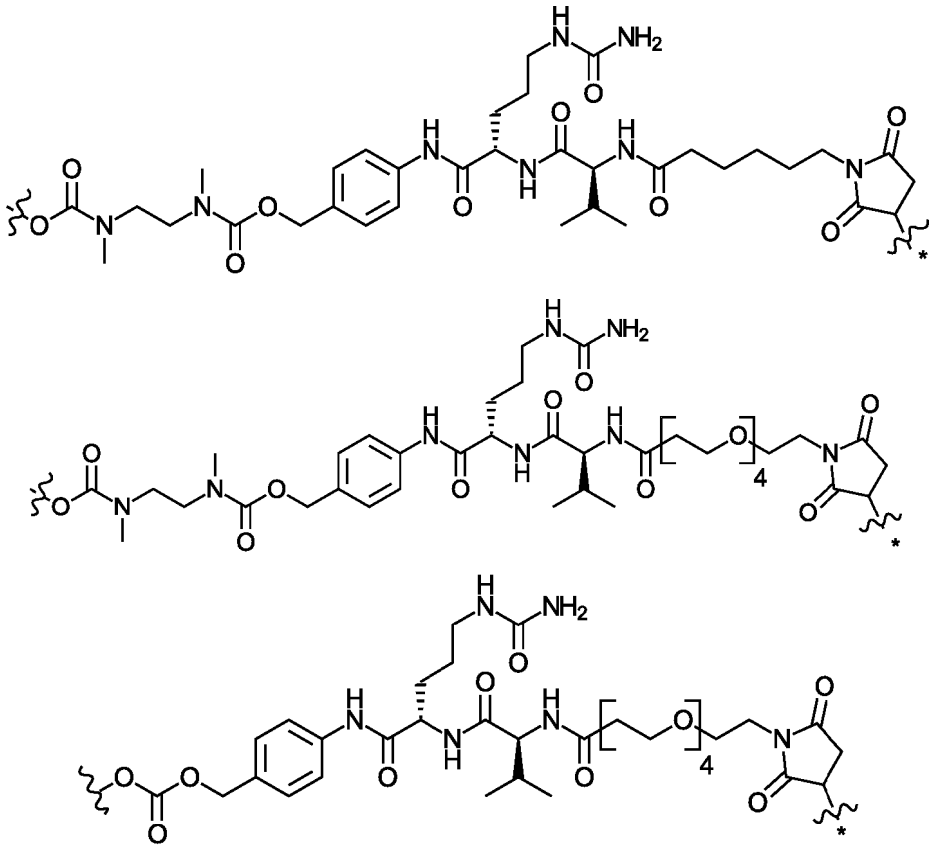
9. A compound according to any preceding claim, wherein S is an optionally substituted C_1-C_{10} alkylene, $-NHCH_2$-, –O-, -NH-, -S- or -C(O)-,

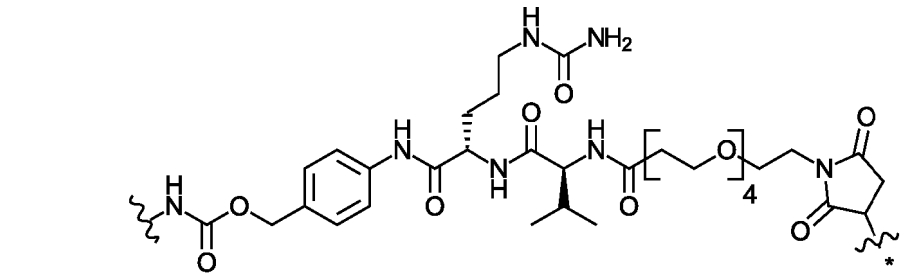













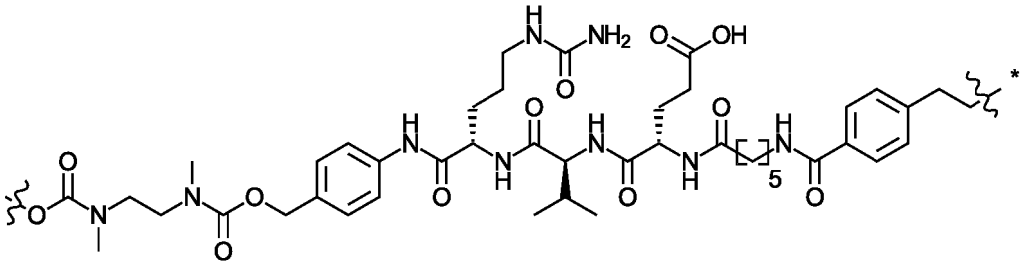


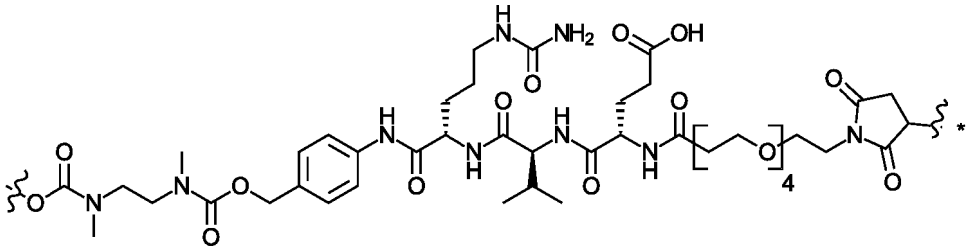
wherein a wavy line and asterisk indicate the attachment of the group S to the targeting moiety T.

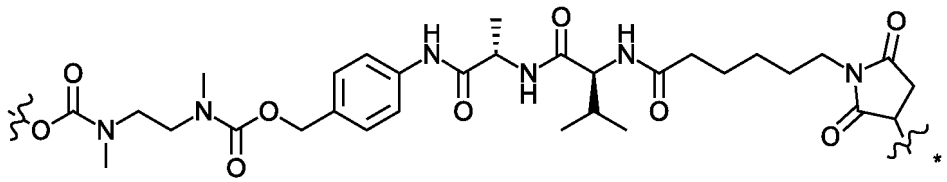
10. A compound according to claim 1, wherein -L^1-L^2- is selected from











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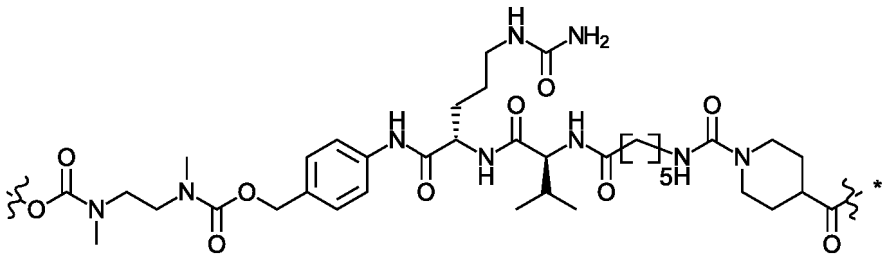

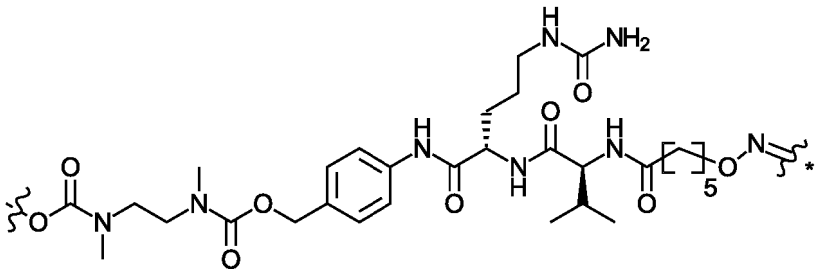

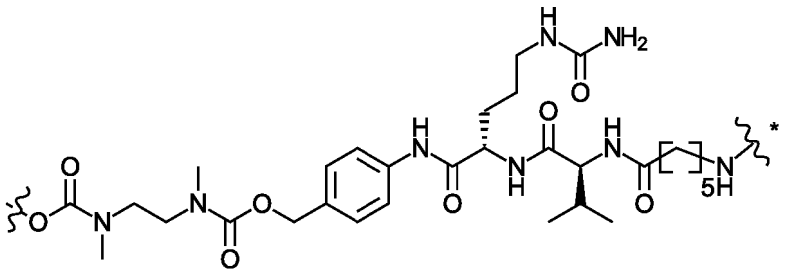

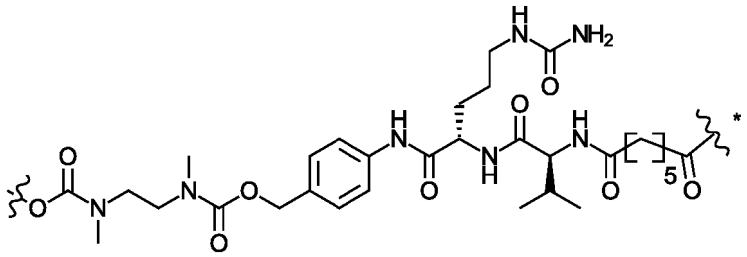

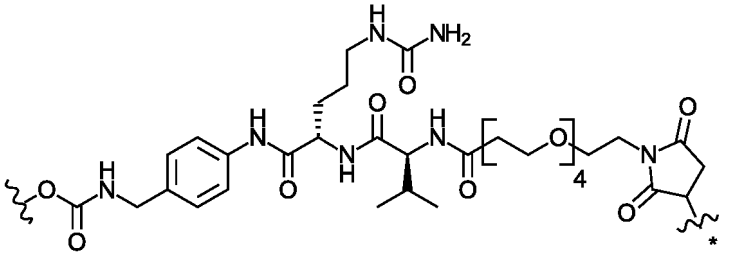

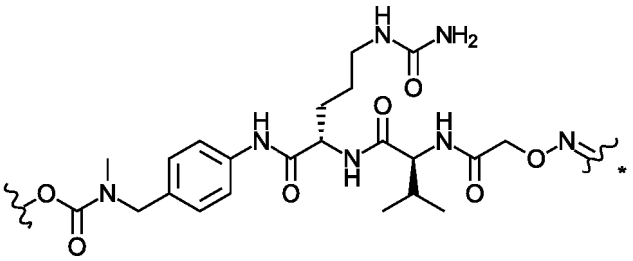

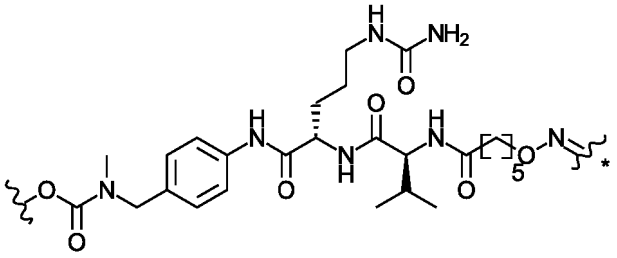

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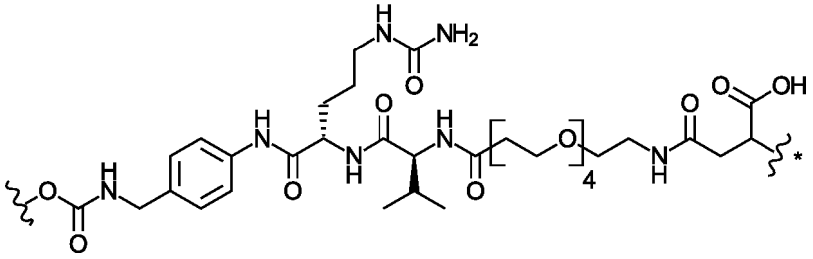

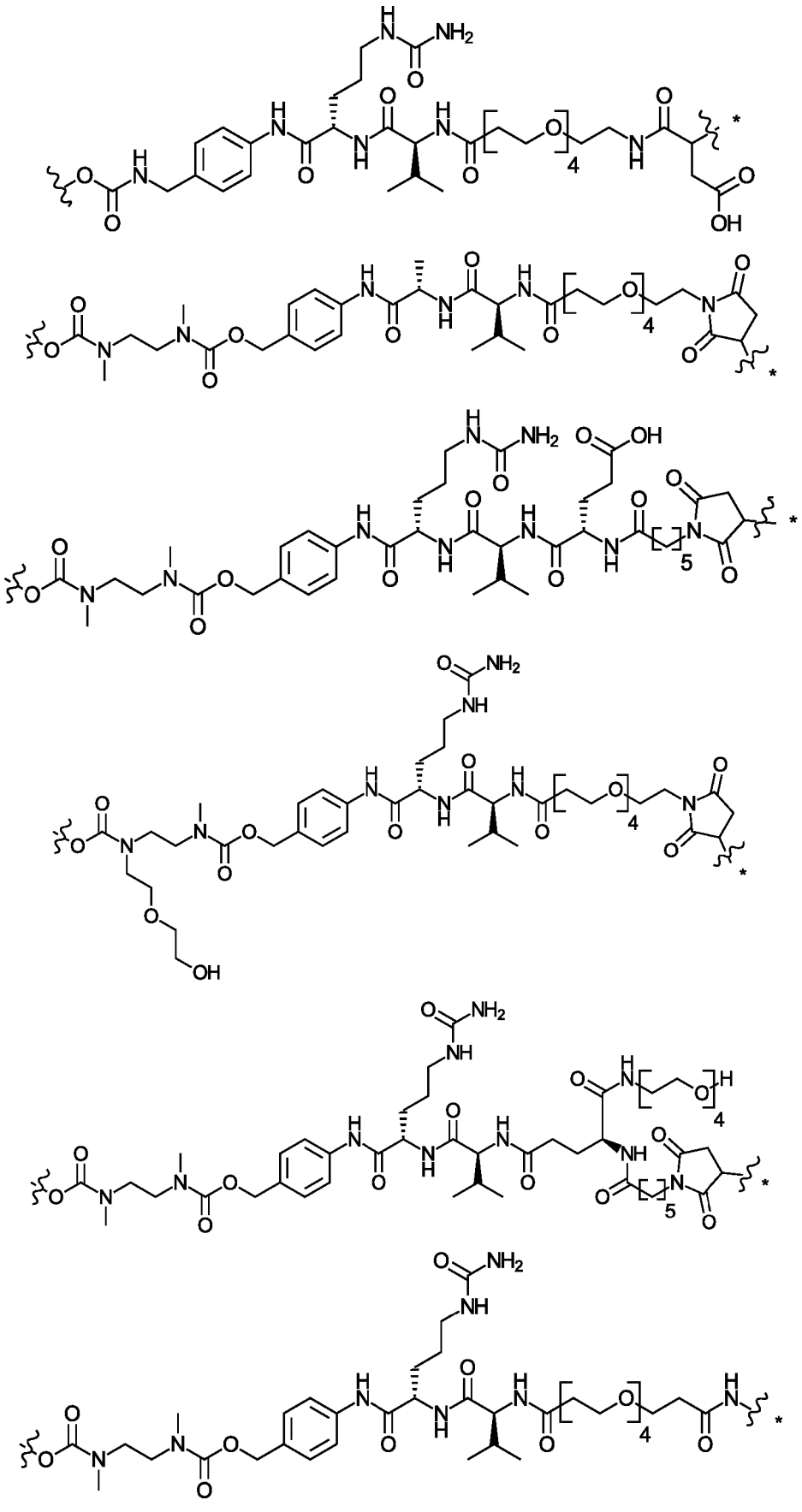

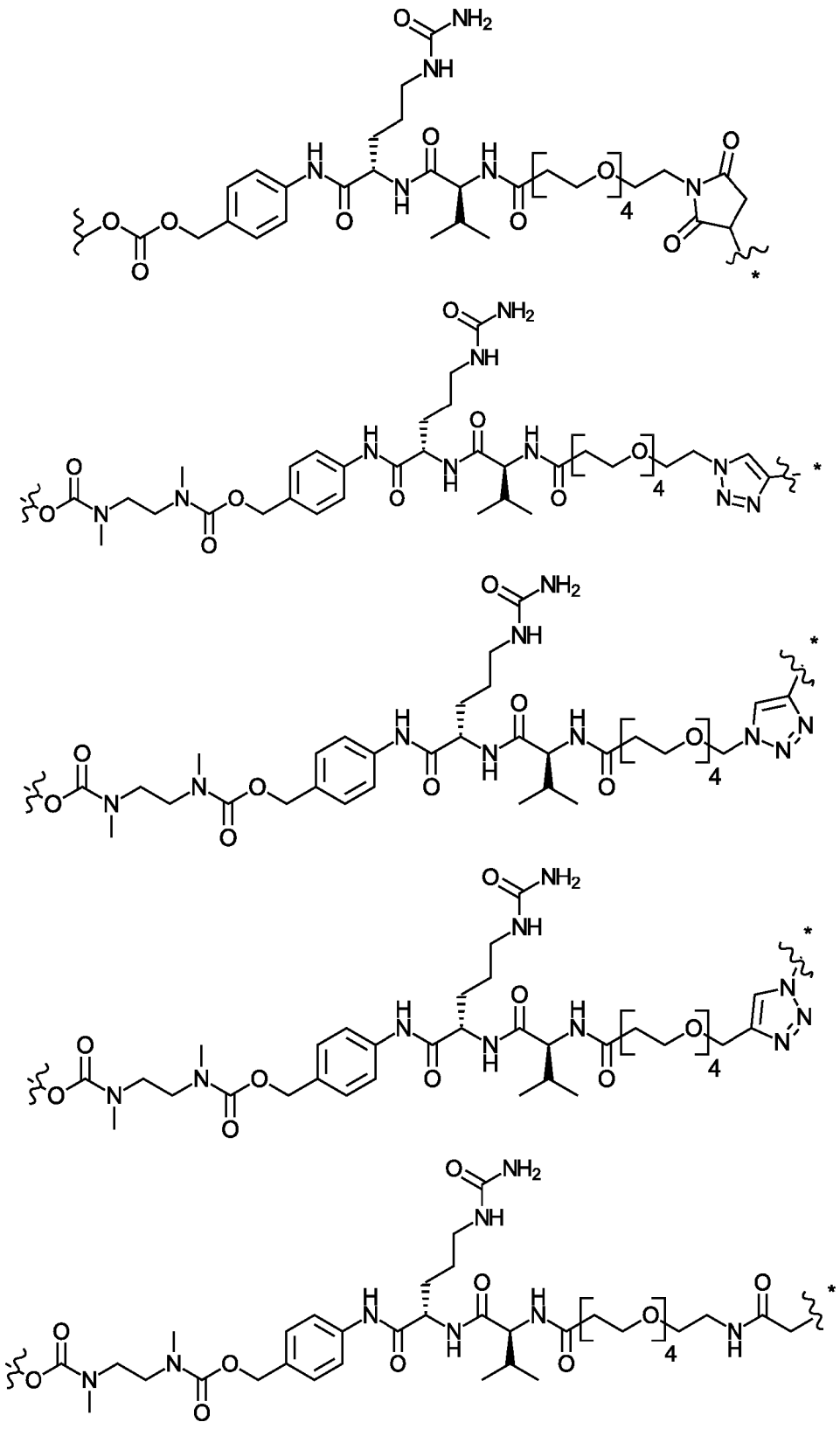

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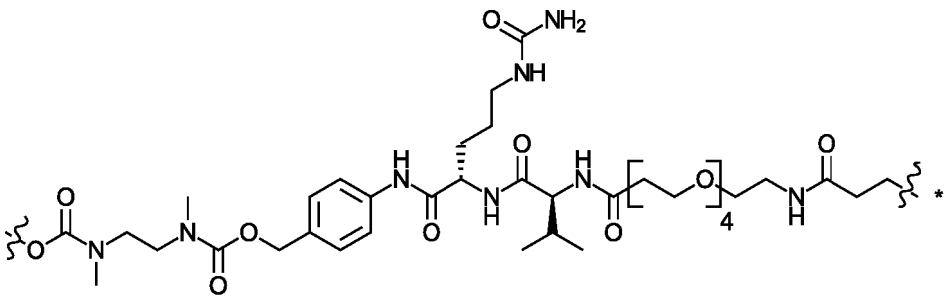

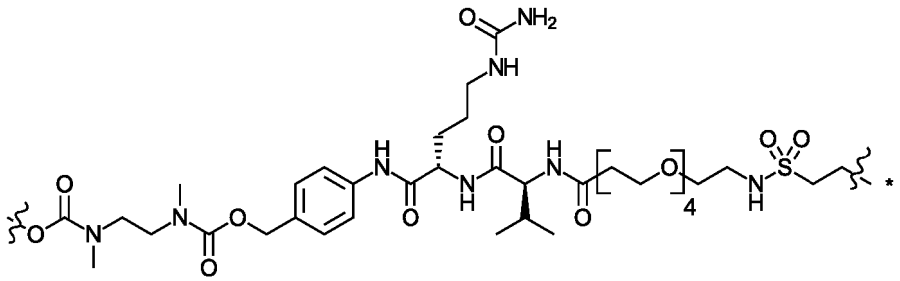

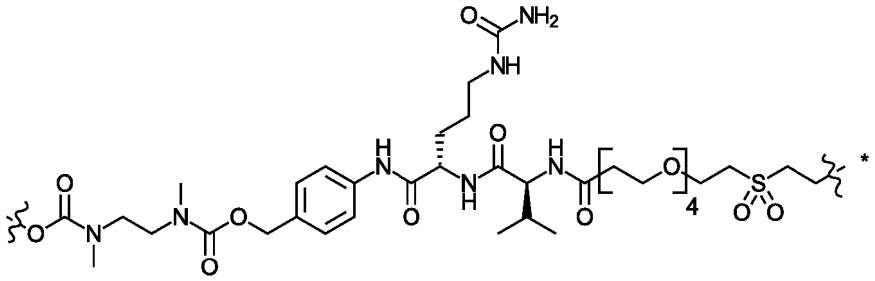

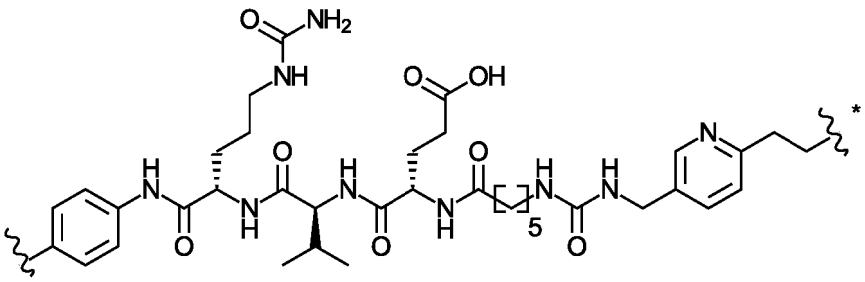

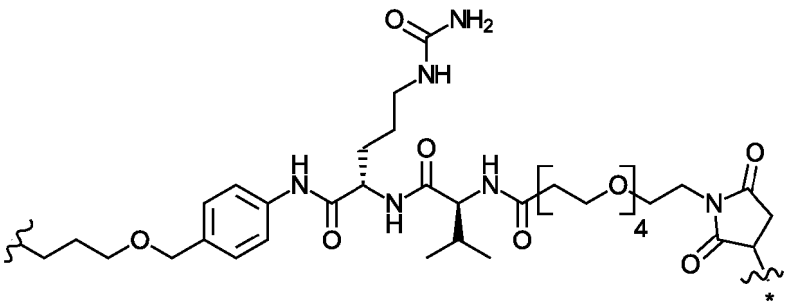

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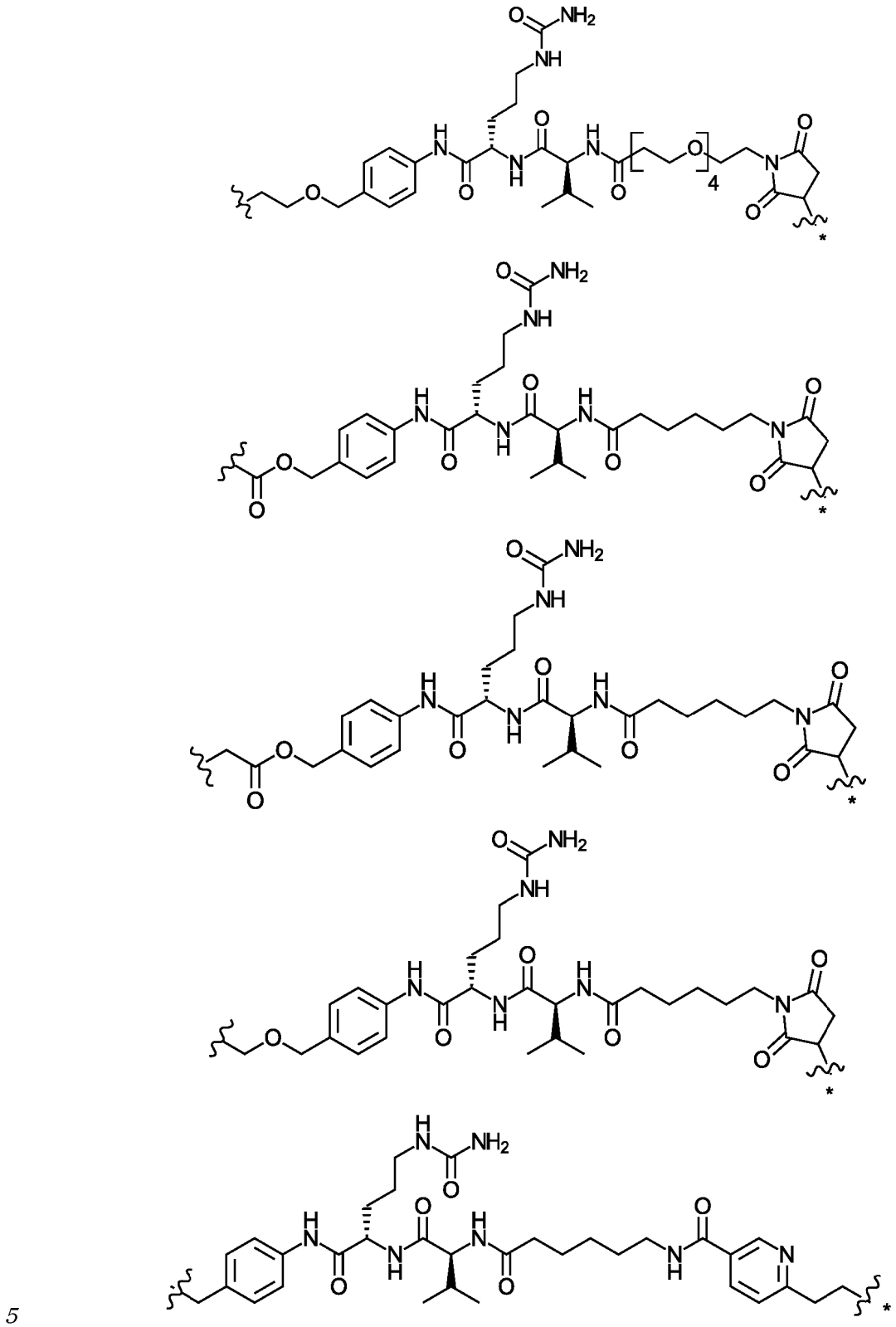

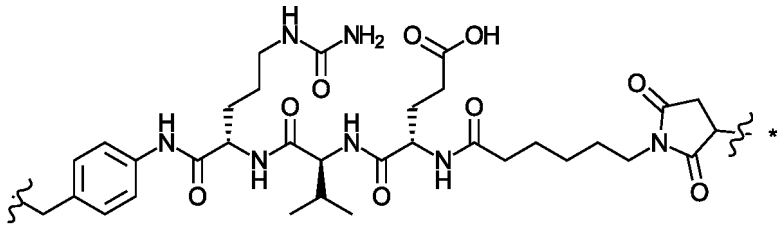

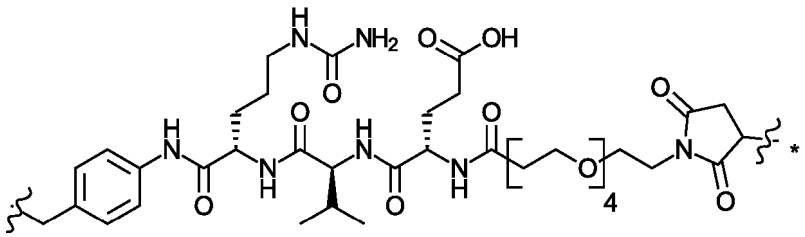

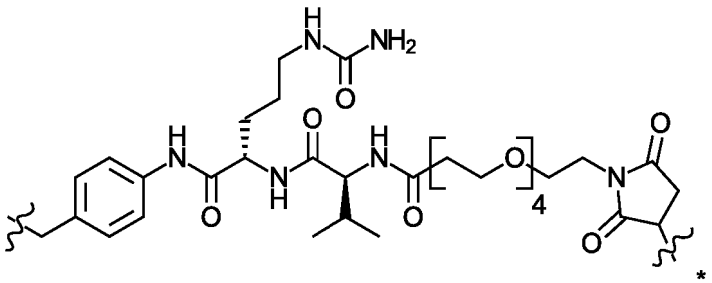

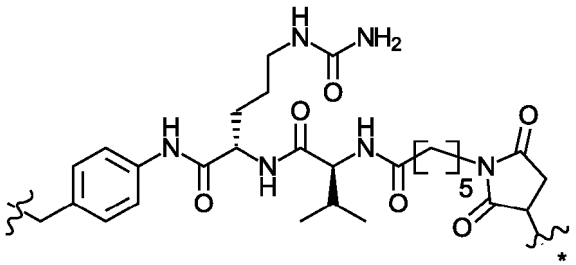

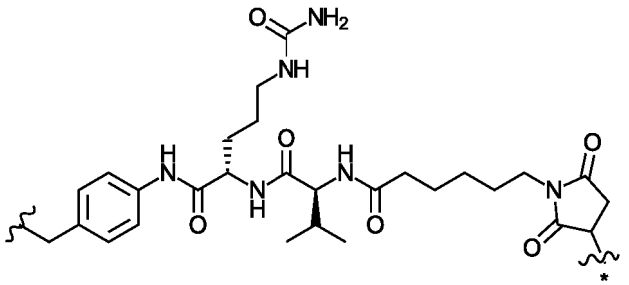

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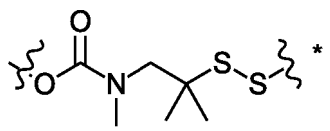

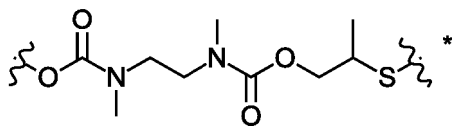

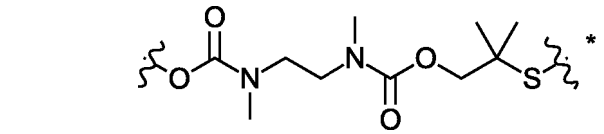

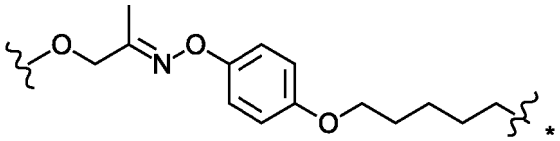

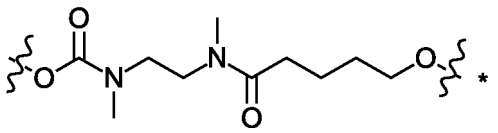

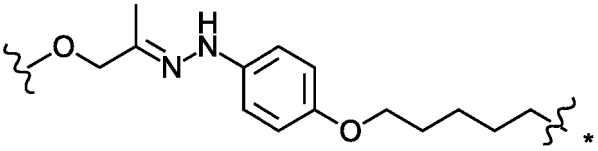

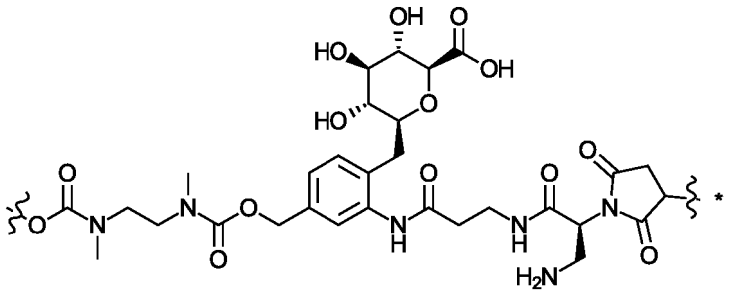

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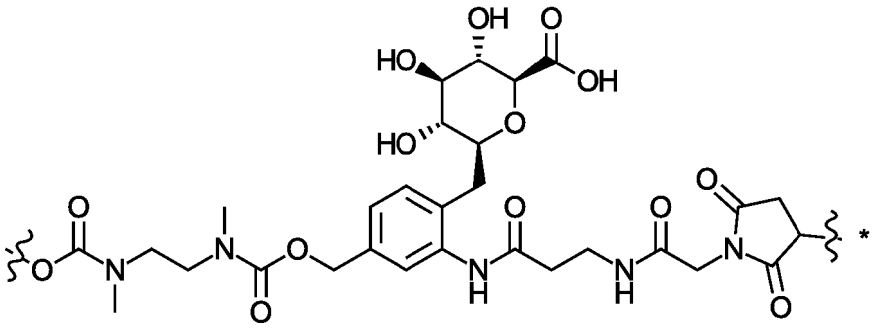
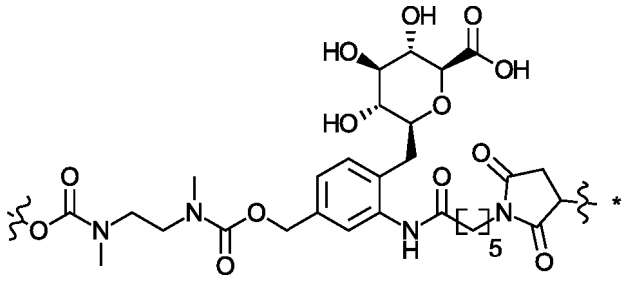
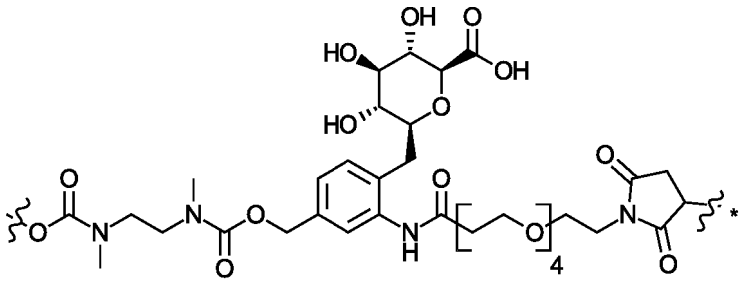
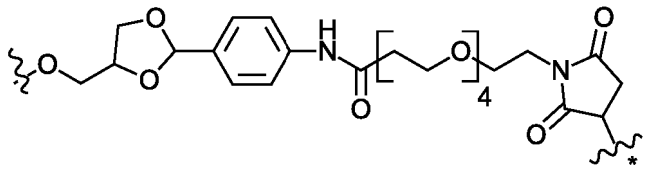
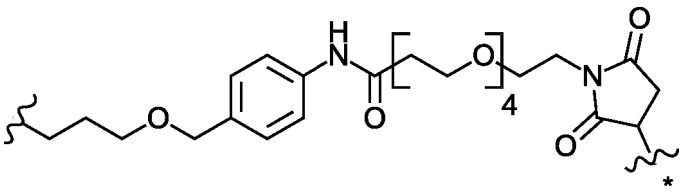
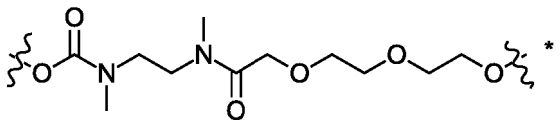


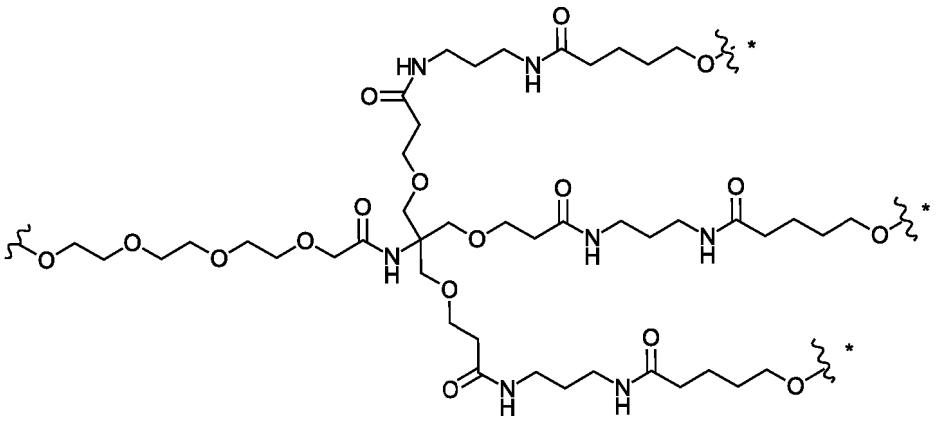




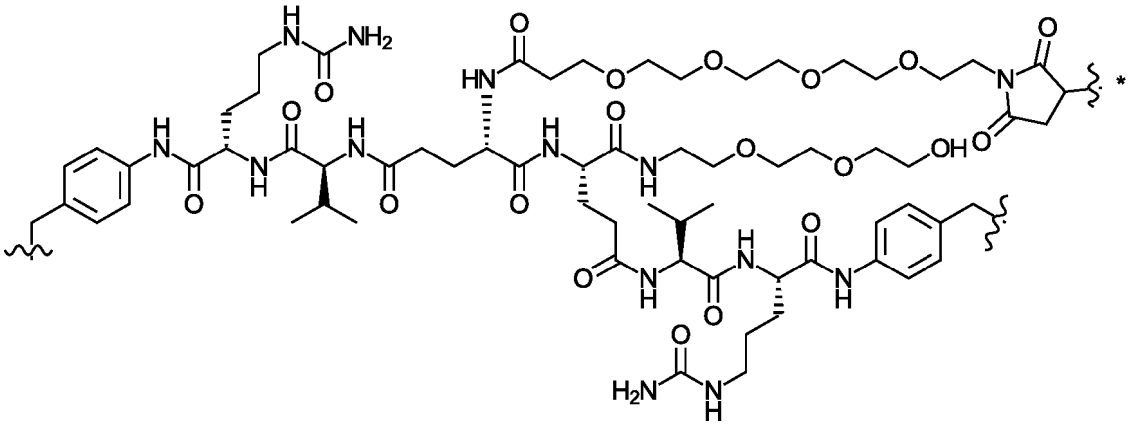








or



wherein a wavy line and asterisk indicates the attachment of the linker to the targeting

moiety T, and a wavy line and no asterix indicates the attachment of the linker to the active compound C.

11. A compound accord to any preceding claim, wherein T comprises an antibody, an antibody fragment, a nucleic acid based molecule, a carbohydrate, a peptide, a modified peptide or a small molecule.

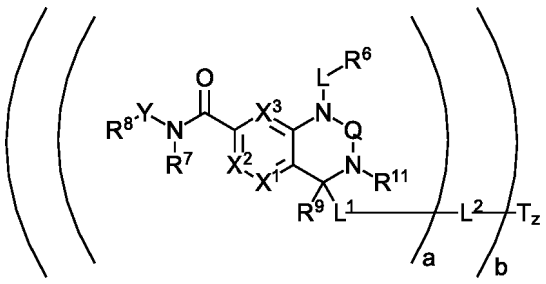
12. A compound according to claim 11, wherein T is an antibody, or a fragment thereof.

13. A compound according to claim 12, wherein T is trastuzumab or a fragment or derivative thereof.

14. A compound according to any preceding claim, wherein T is configured to target a tumour antigen.

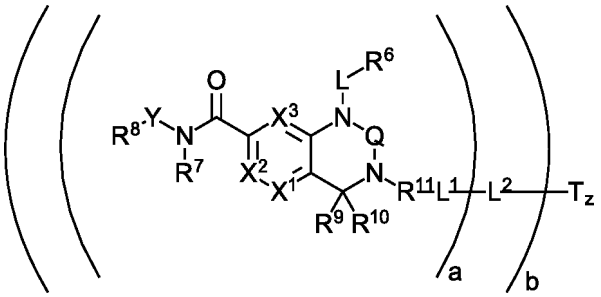
15. A compound according to any preceding claim, wherein C is attached to the linker through a C atom, an O atom, an N atom or an S atom.

16. A compound according to any preceding claim, wherein the compound is a compound of formula (**I-A**):



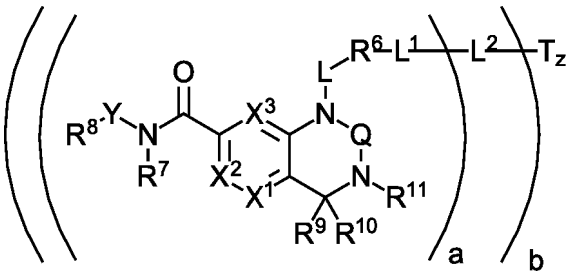
(I-A)

17. A compound according to any one of claims 1 to 15, wherein the compound is a compound of formula (**I-B**):



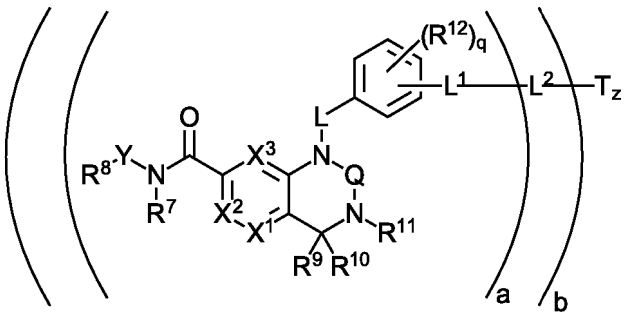
(**I-B**)

18. A compound according to any one of claims 1 to 15, wherein the compound is a compound of formula (**I-C**):

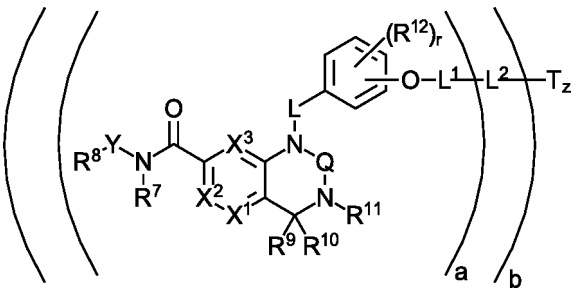


(**I-C**)

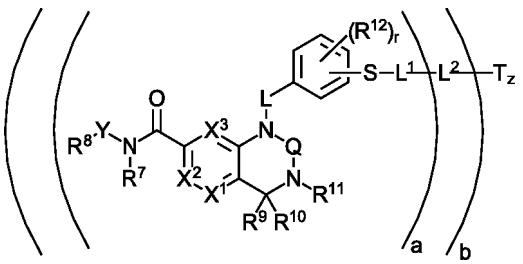
19. A compound according to claim 18, wherein the compound is a compound of one of formula (**I-C-a**) to (**I-C-d**):

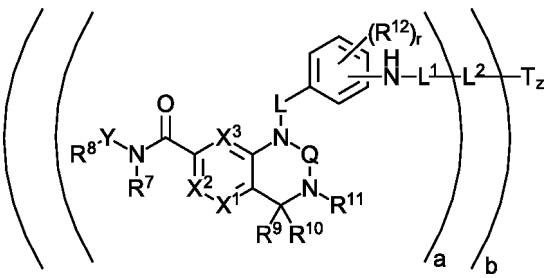


(**I-C-a**)



(**I-C-b**)

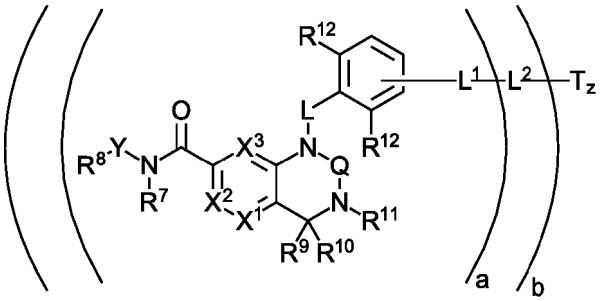




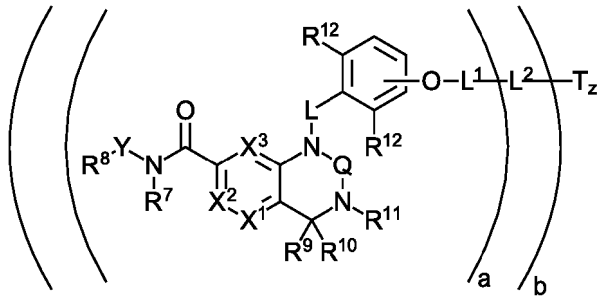
(I-C-c) **(I-C-d)**

, wherein r is an integer between 0 and 4.

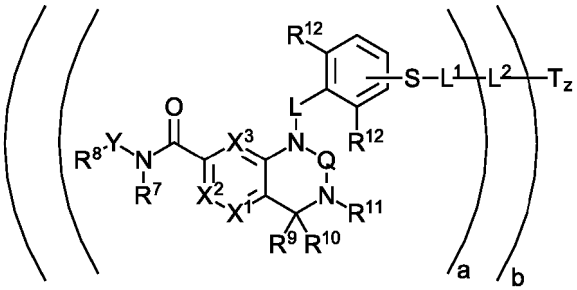
20. A compound according to claim 19, wherein the compound is a compound of one of formula (**I-C-e**) to (**I-C-h**):



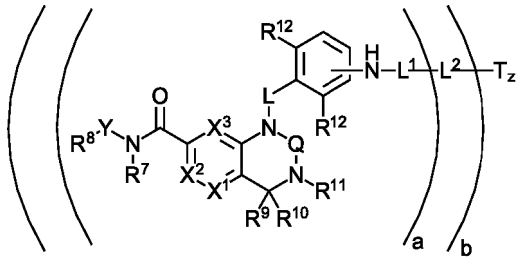
(I-C-e)



(I-C-f)

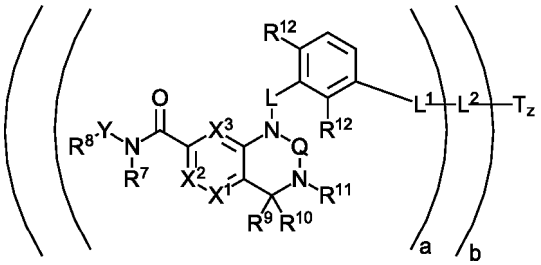


(I-C-g)

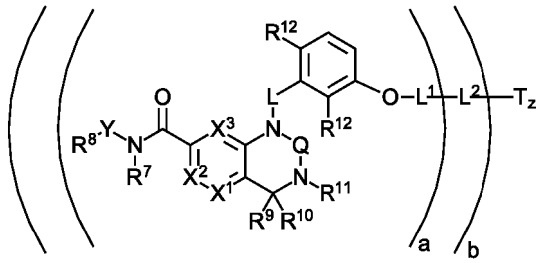


(I-C-h)

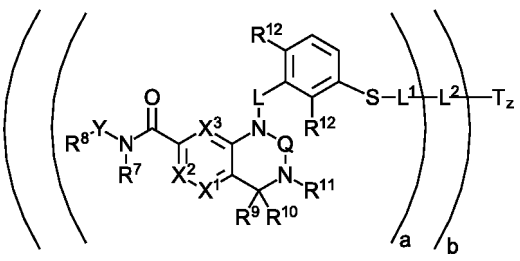
21. A compound according to claim 20, wherein the compound is a compound of one of formula (**I-C-i**) to (**I-C-l**):

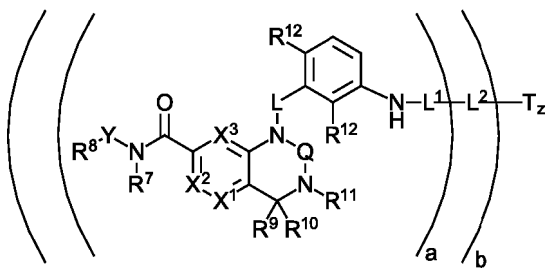


(I-C-i)



(I-C-j)

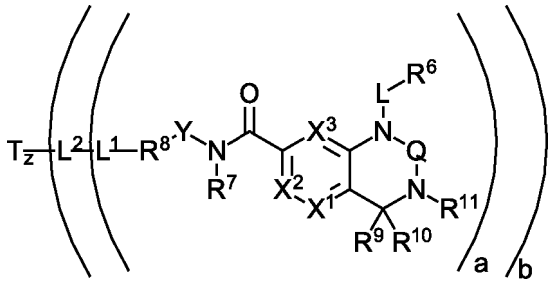




(I-C-k) **(I-C-l)**

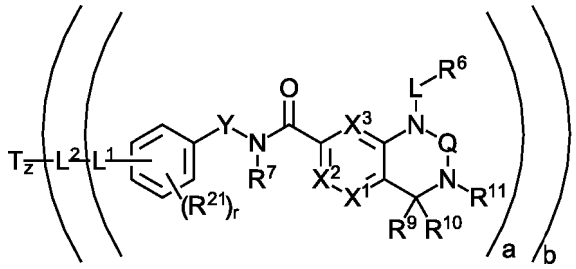
22. A compound according to either claim 20 or claim 21, wherein each R^{12} is a halogen.

23. A compound according to any one of claims 1 to 15, wherein the compound is a compound of formula (**I-D**):

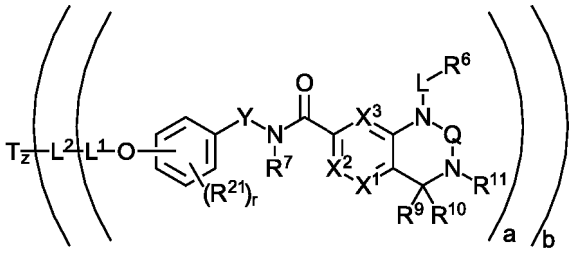


(I-D)

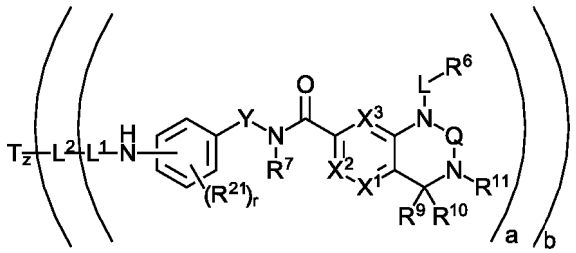
24. A compound according to claim 23, wherein the compound is a compound of one of formula (**I-D-a**) to (**I-D-d**):



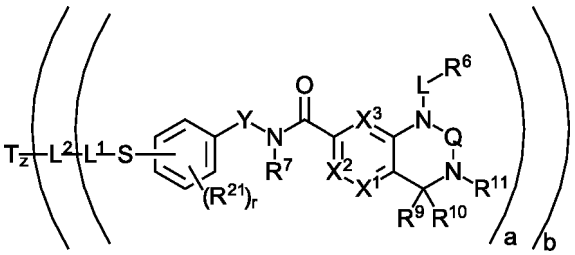
(I-D-a)



(I-D-b)



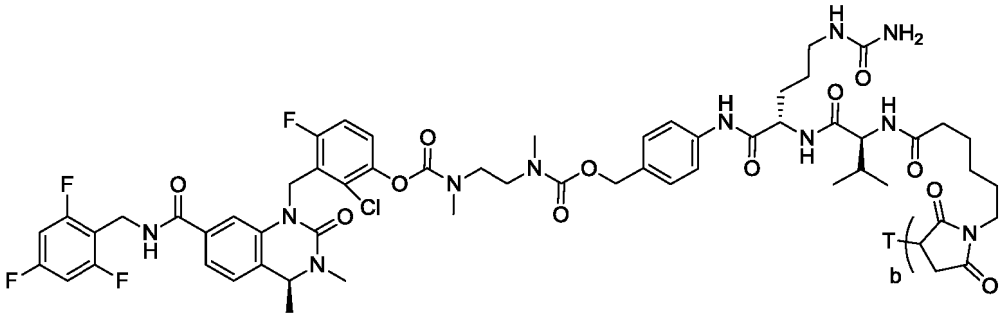
(I-D-c)

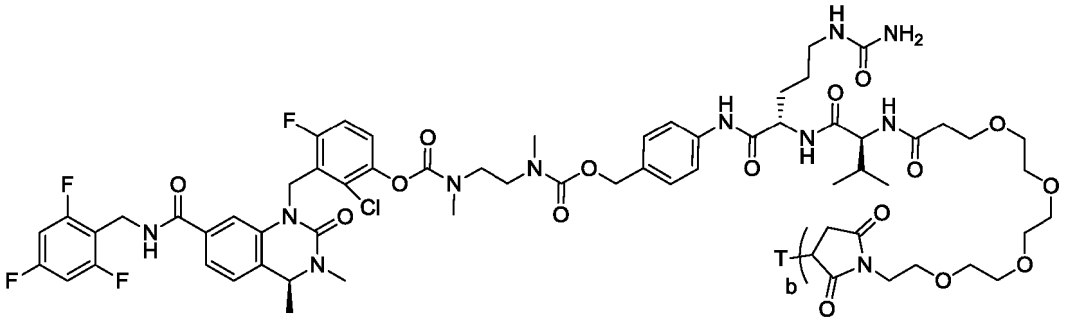


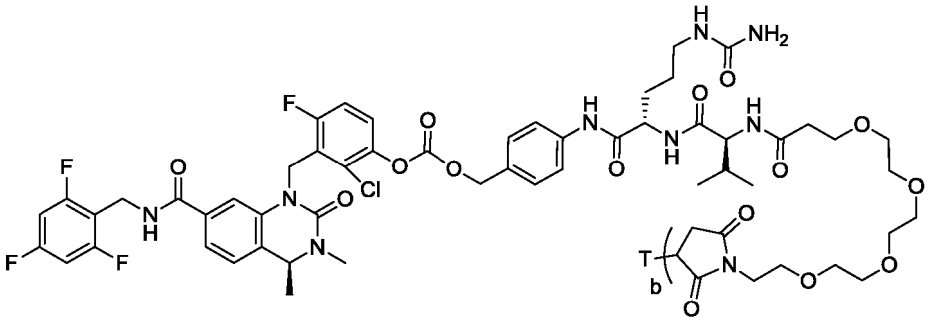
(I-D-d)

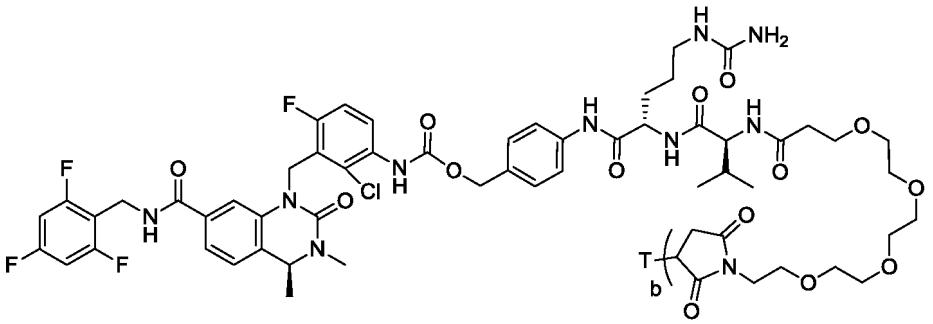
, wherein R^{21} is a substituent on the phenyl ring and r is an integer between 0 and 4.

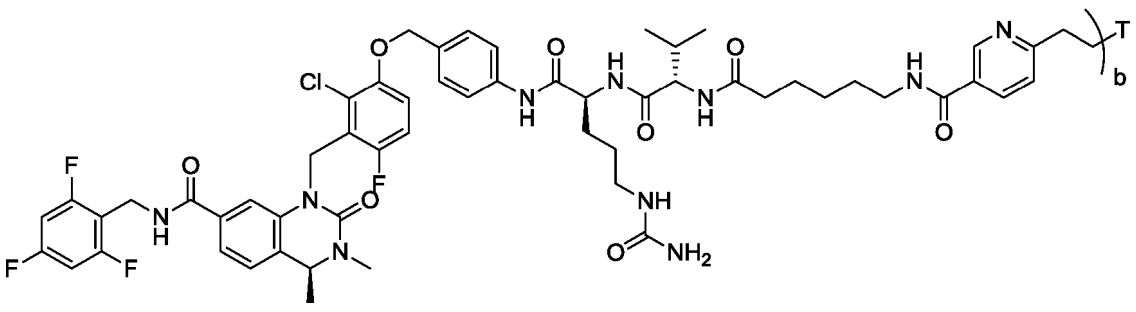
25. A compound according to claim 1, wherein the compound is selected from:

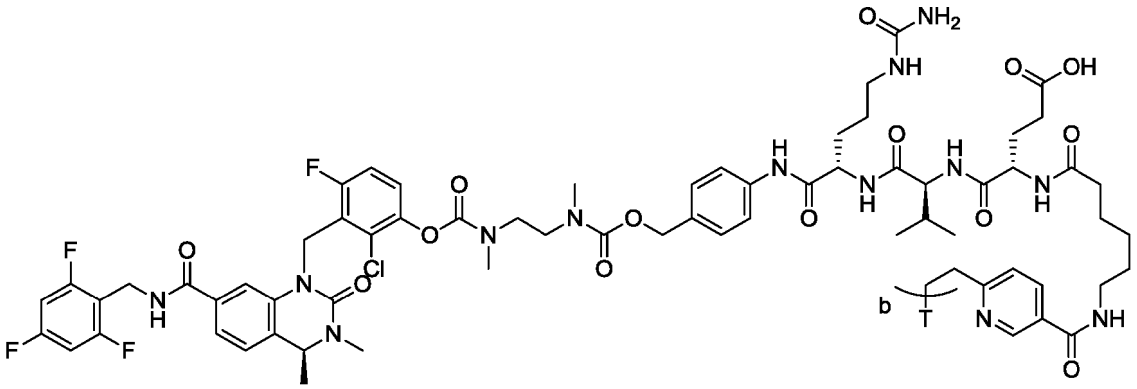


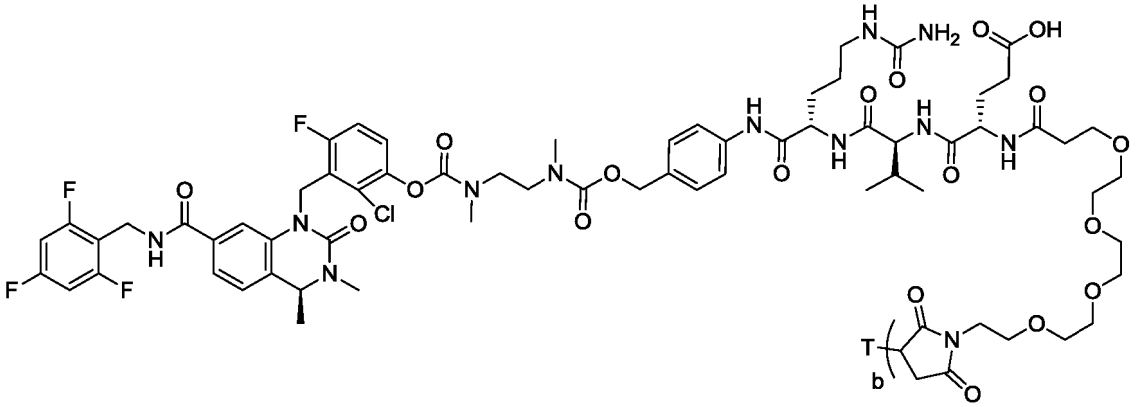


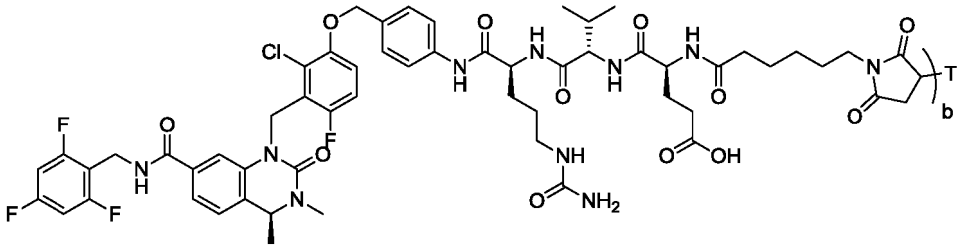


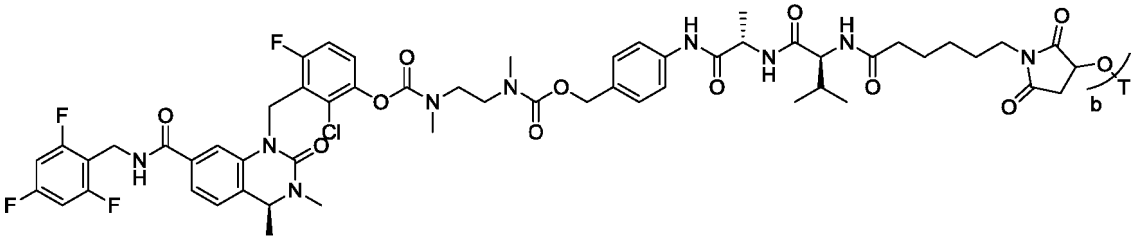


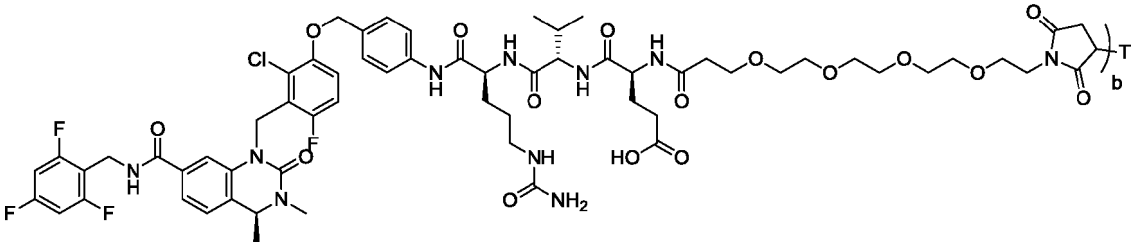












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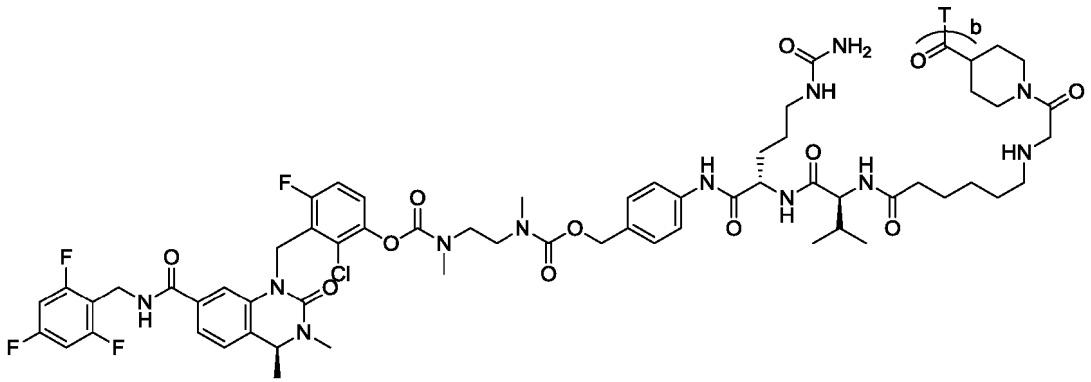

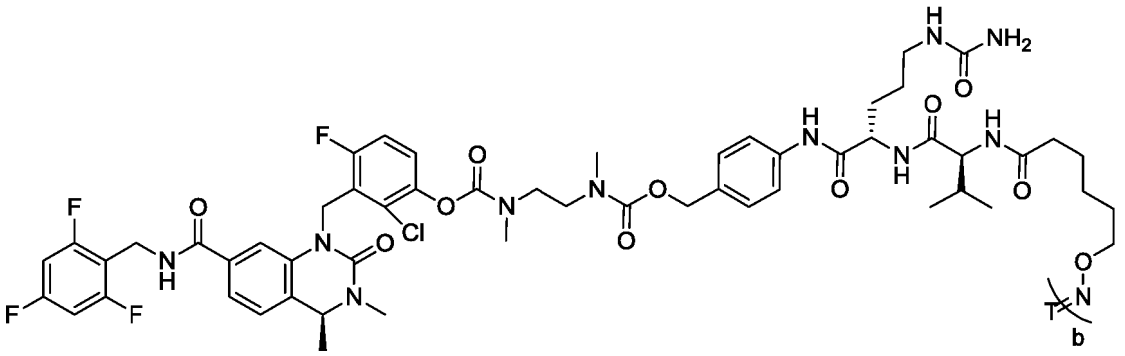

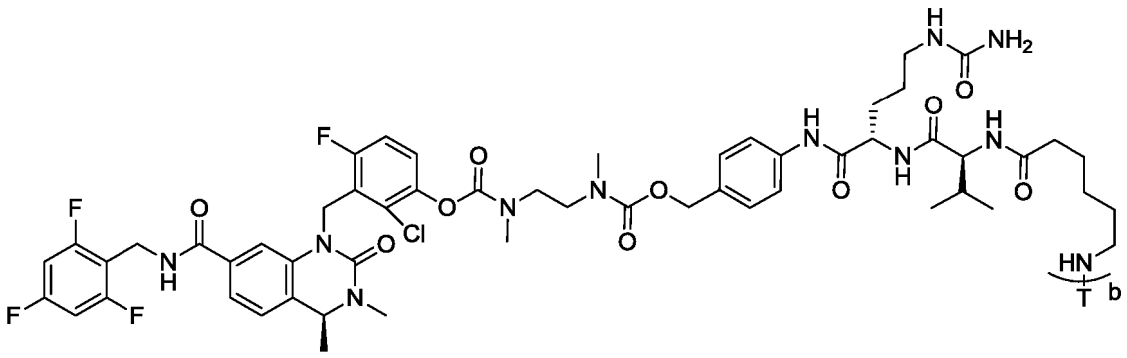

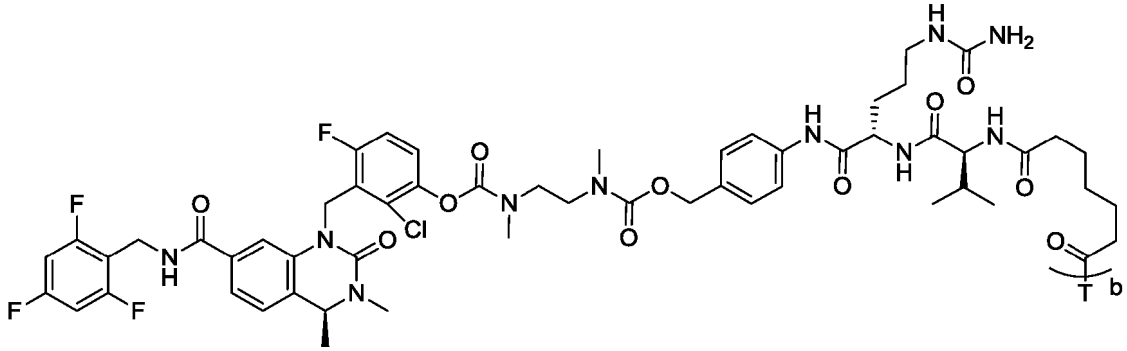

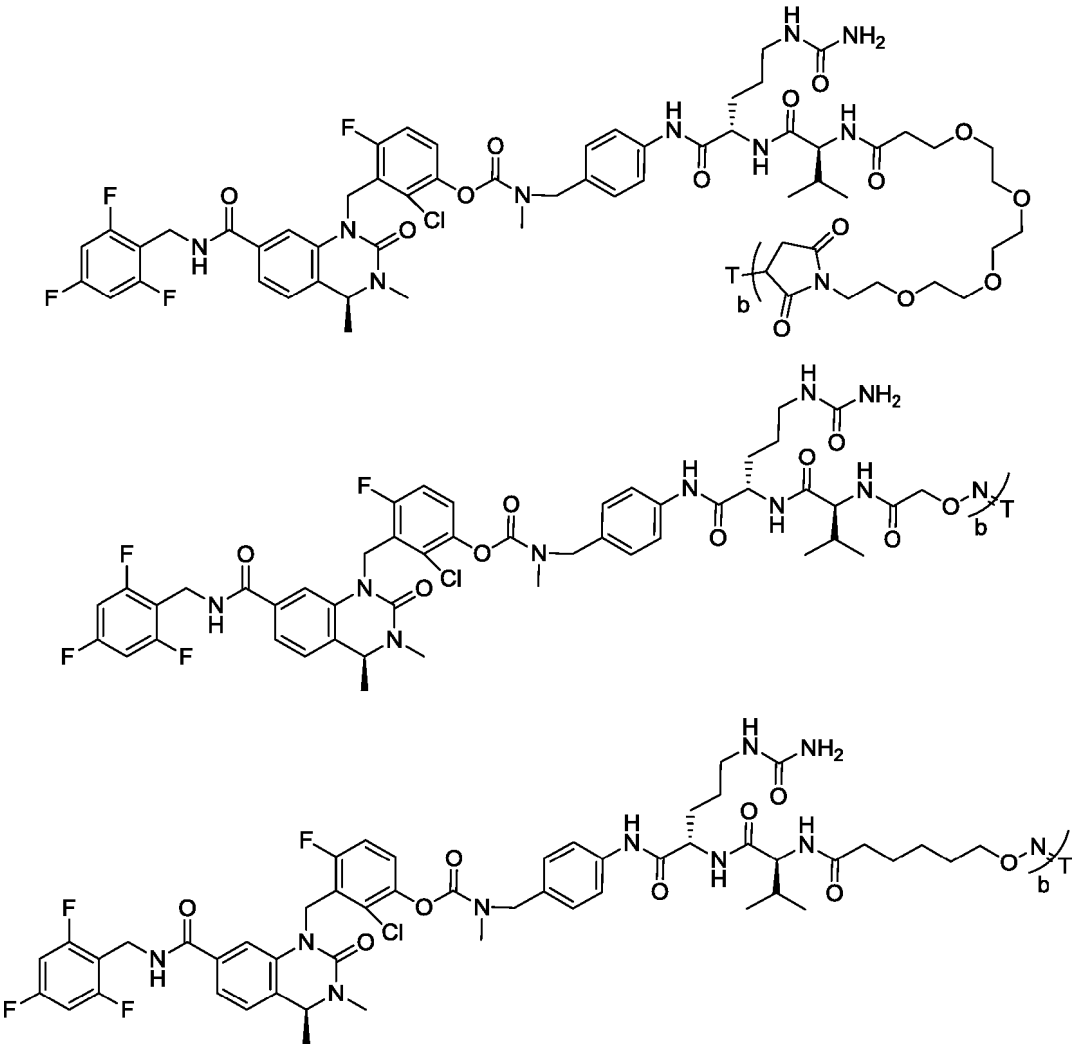

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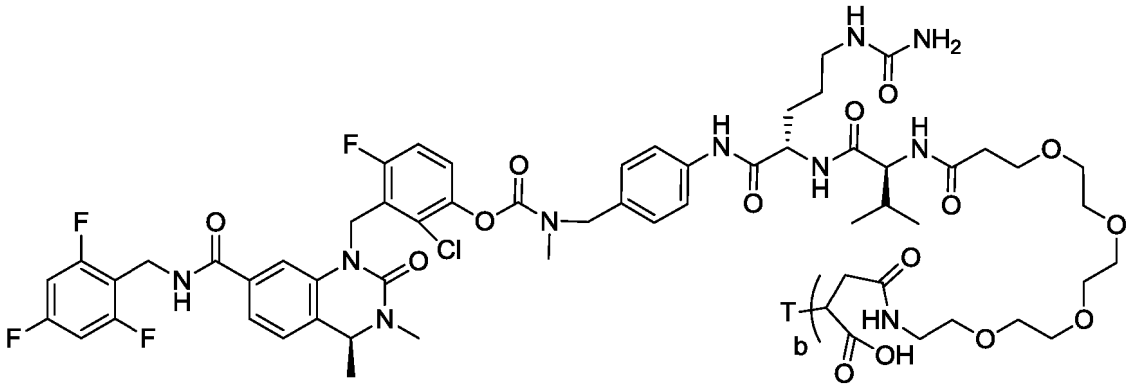

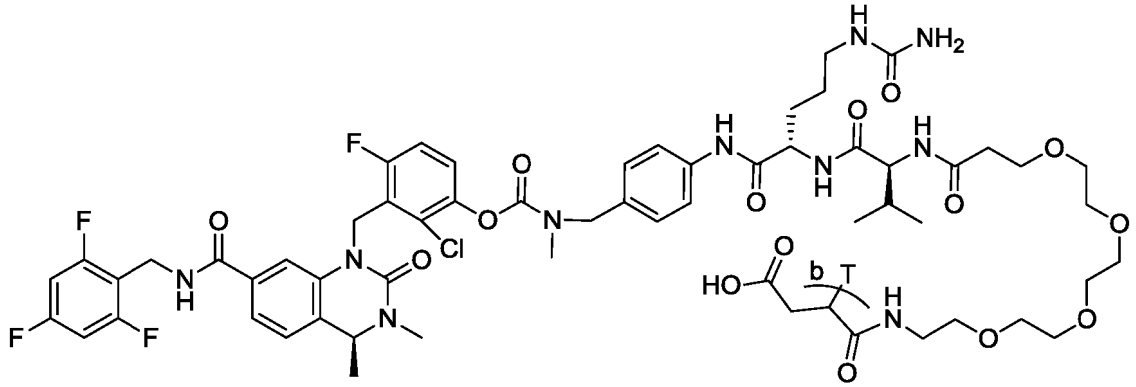

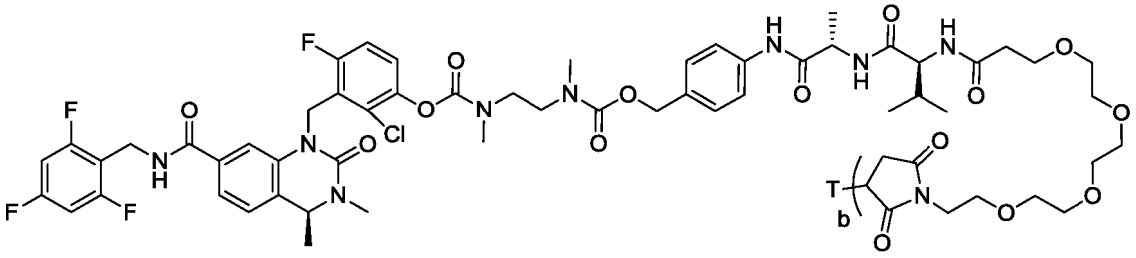

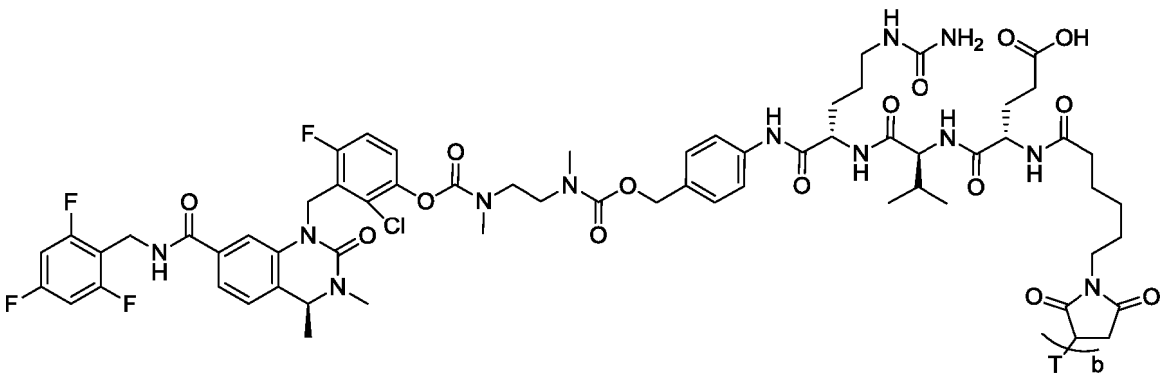

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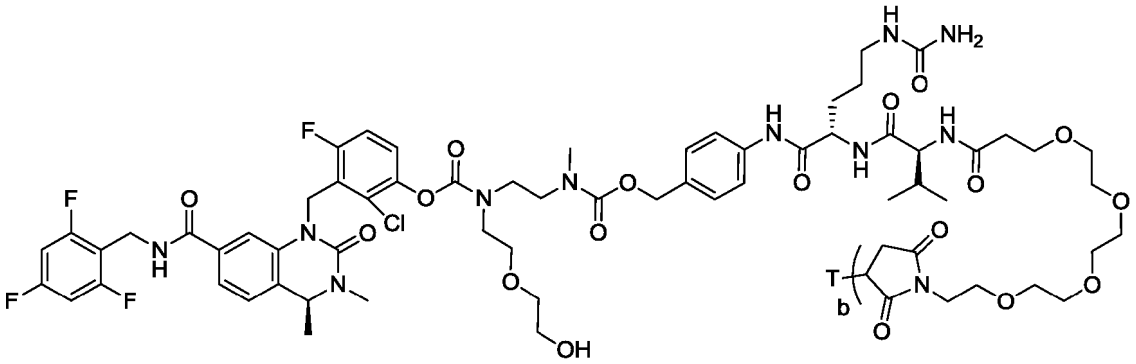

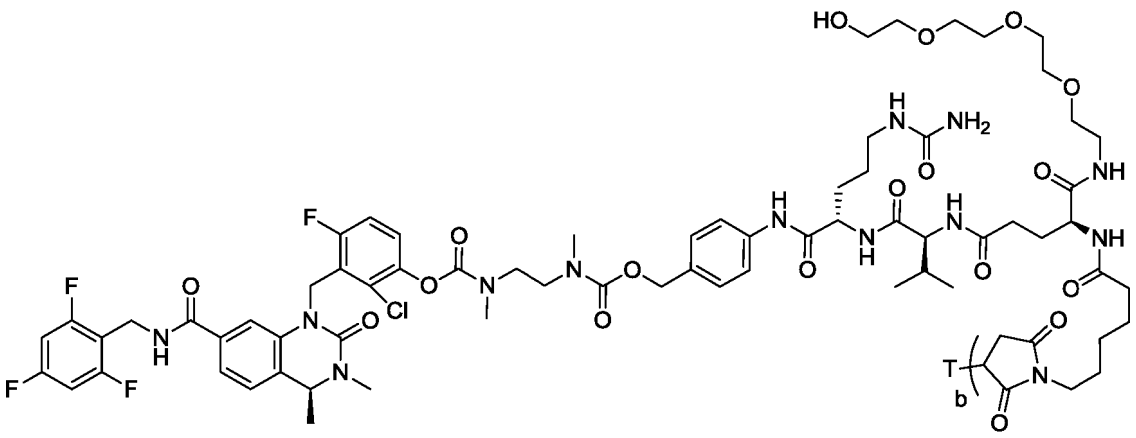

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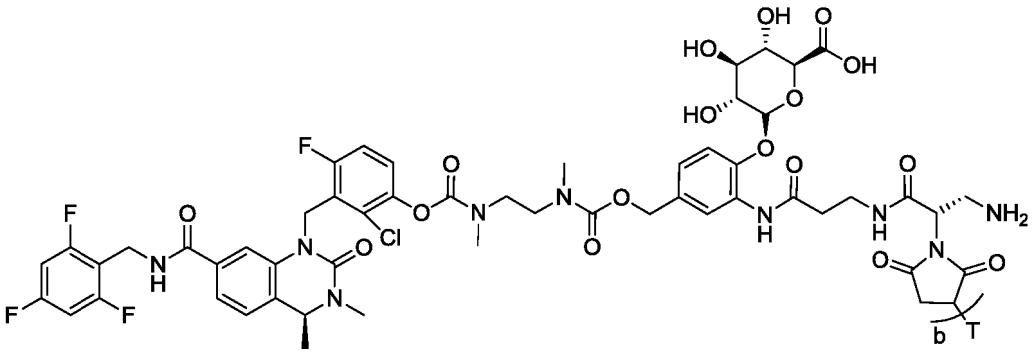

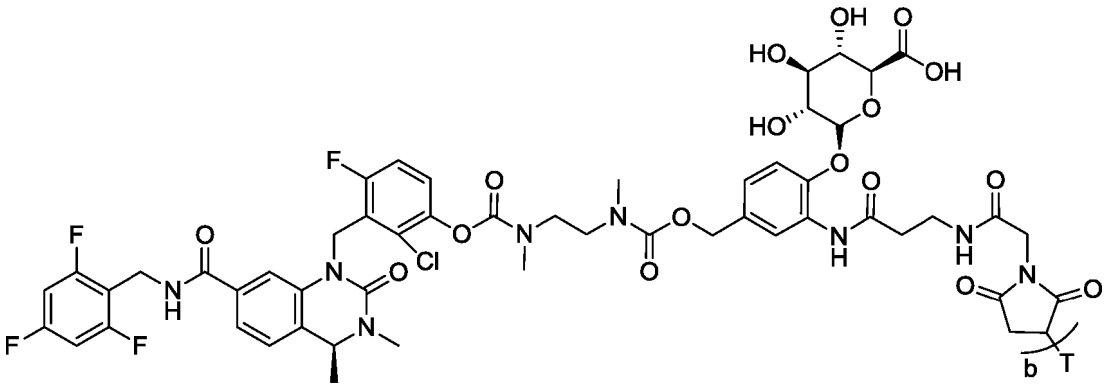

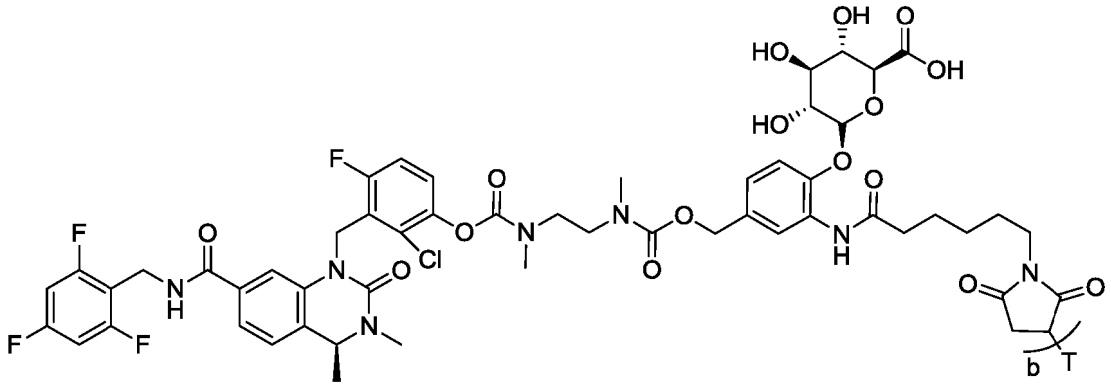

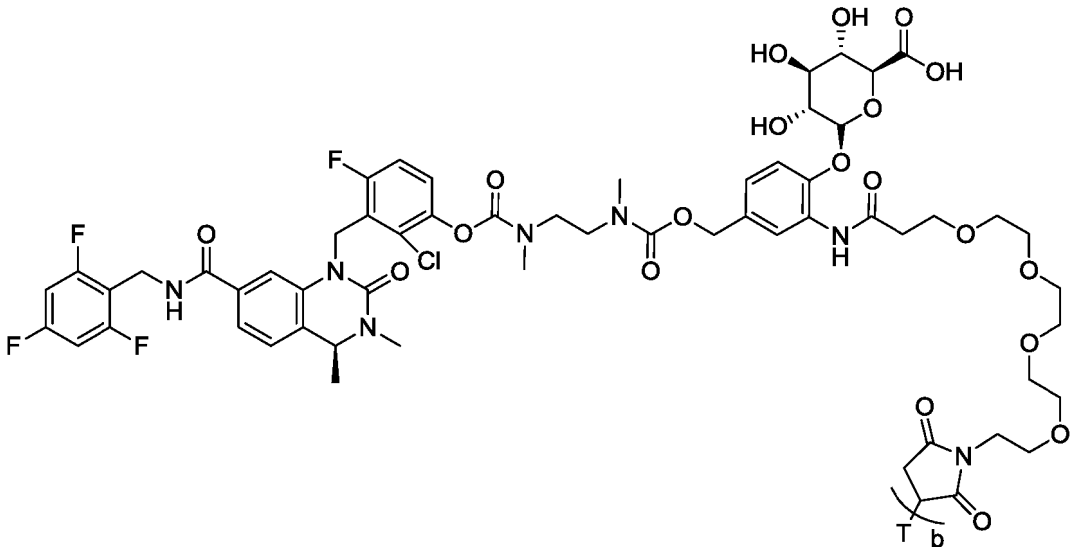

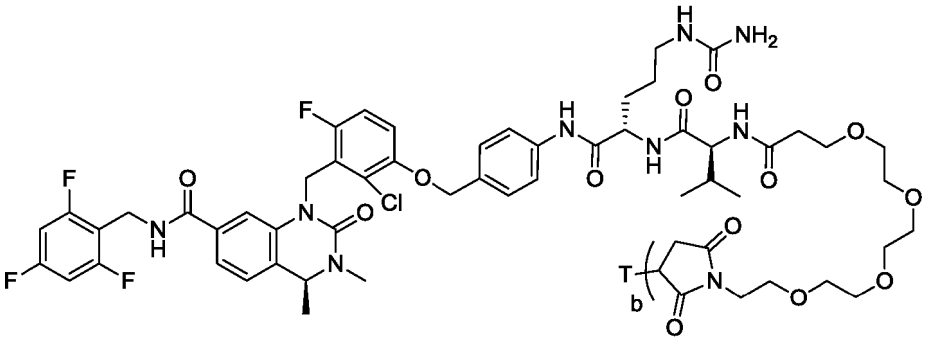

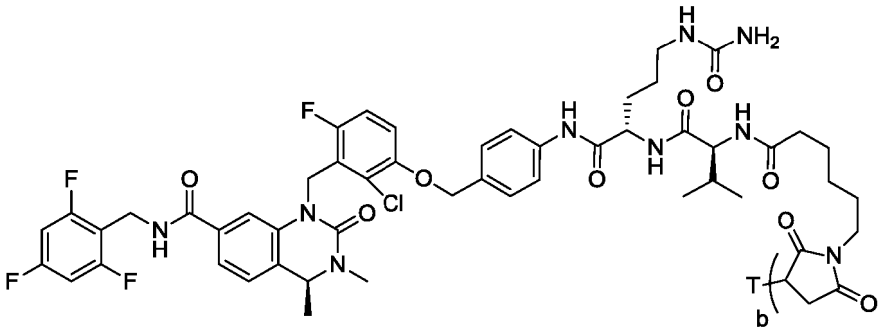

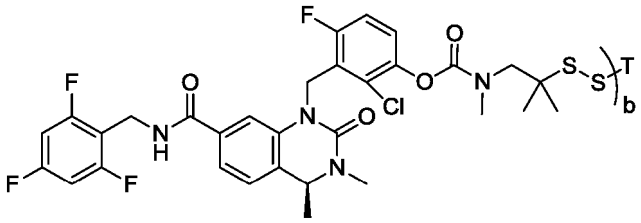

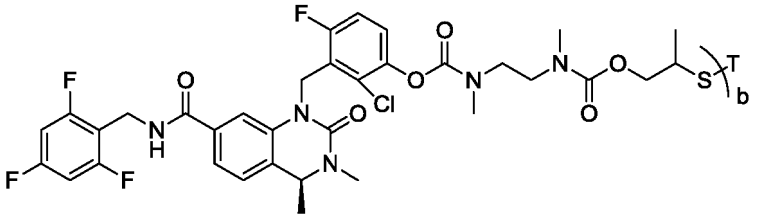

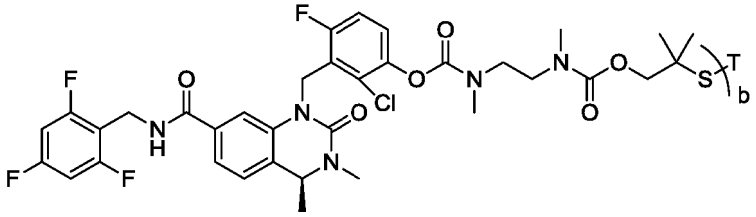

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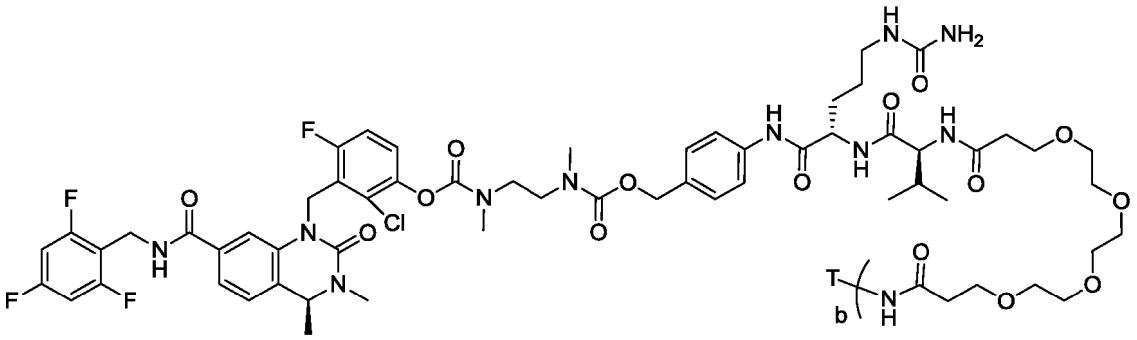

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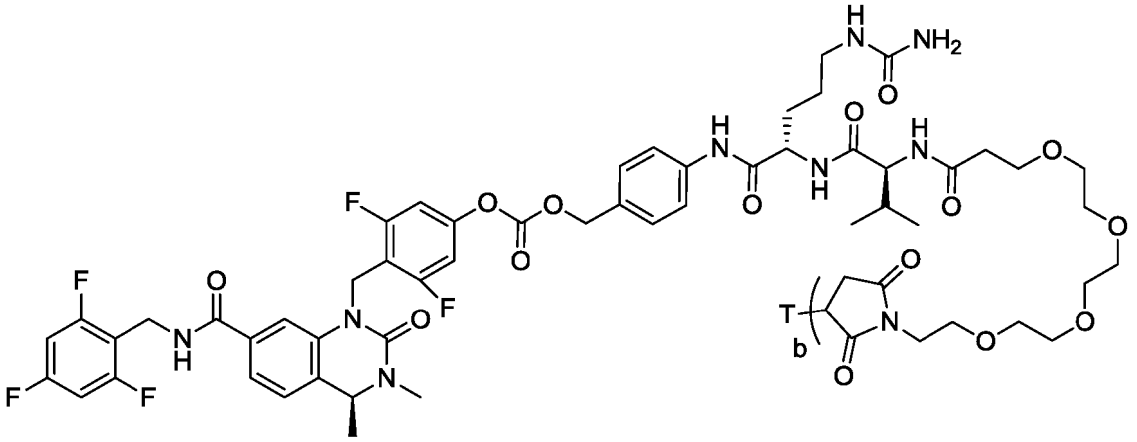

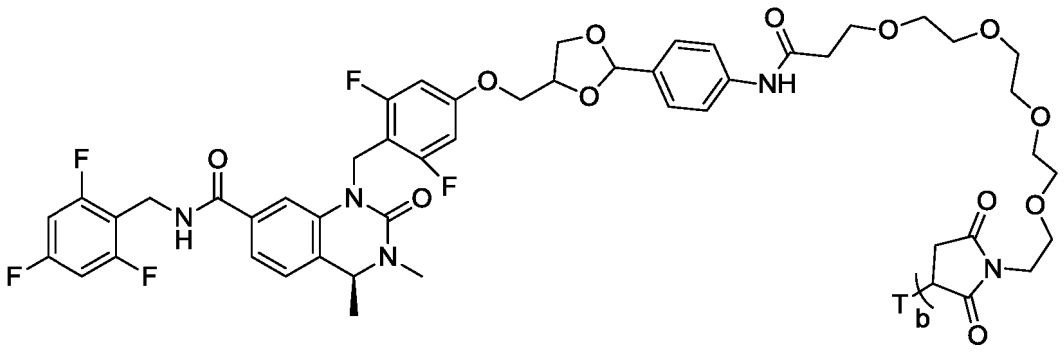

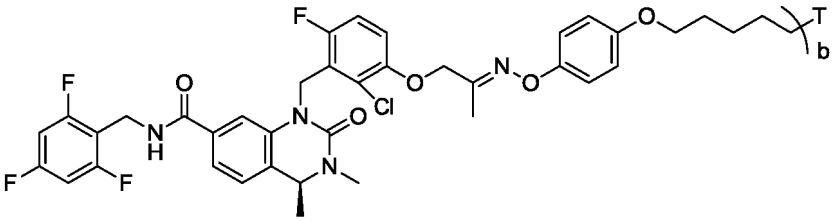

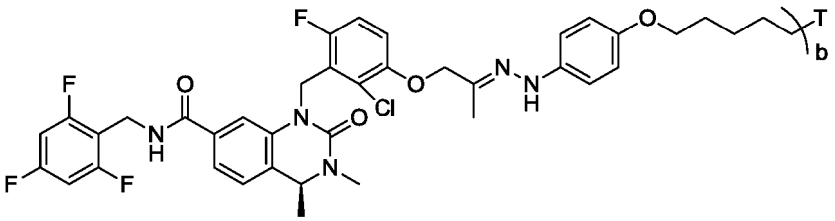

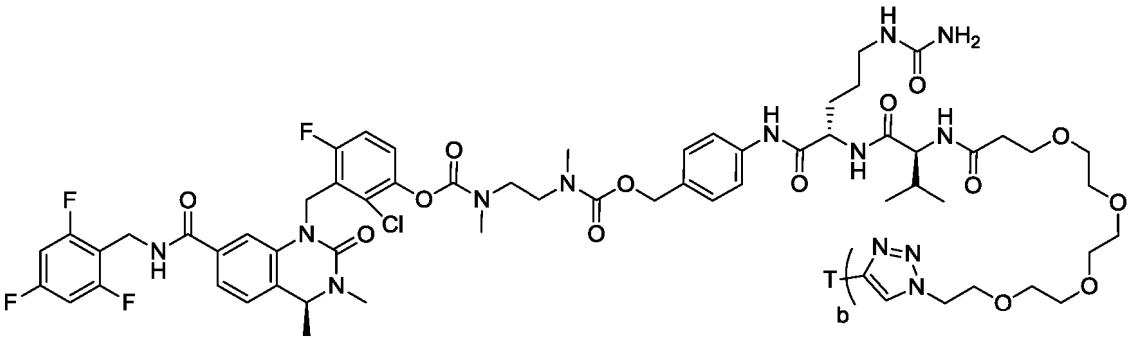

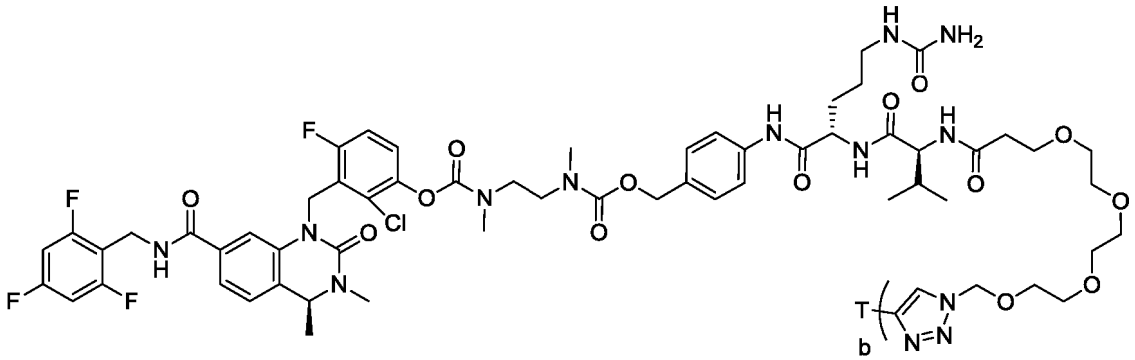

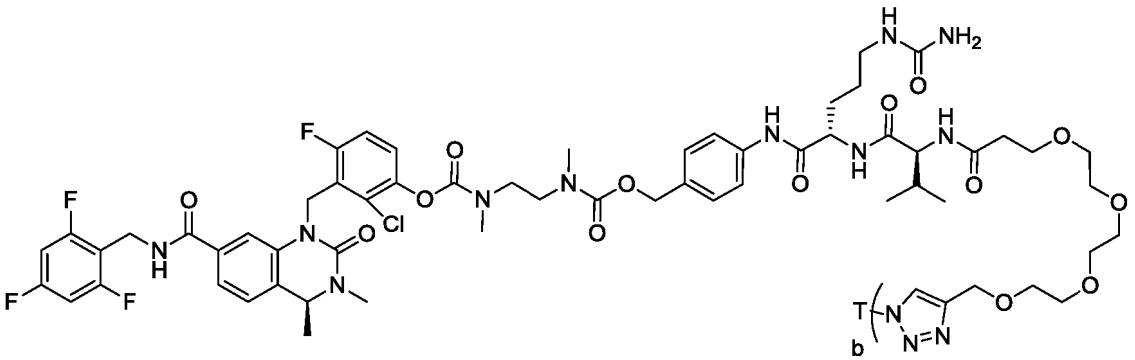

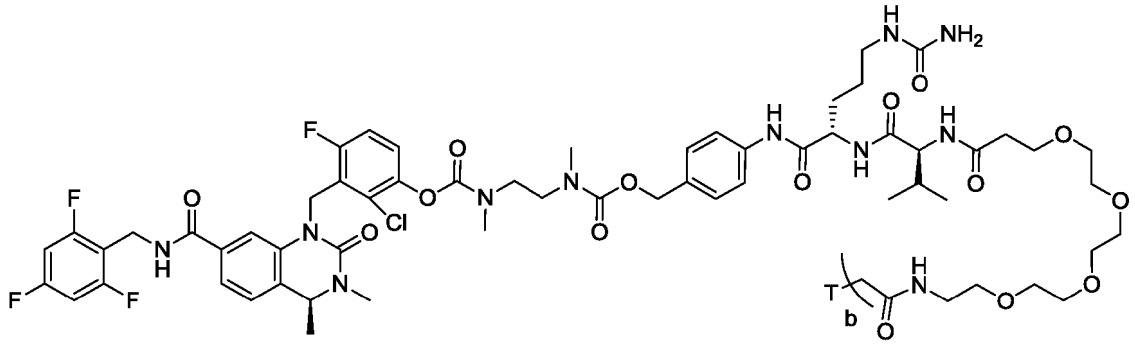

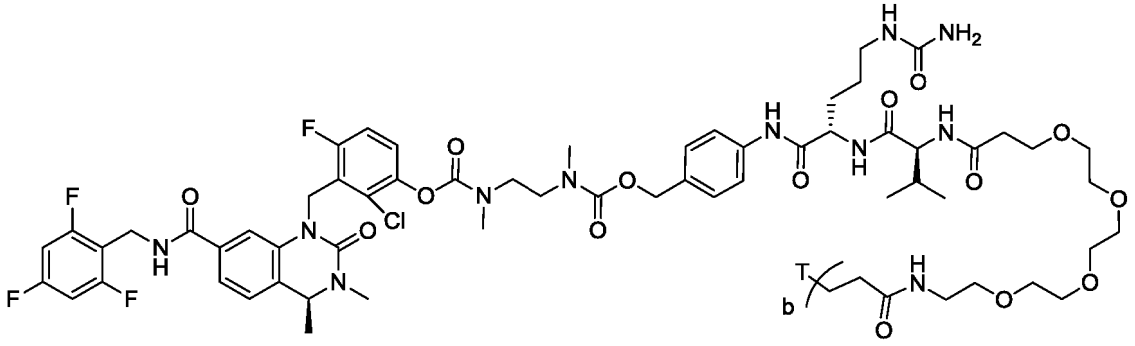

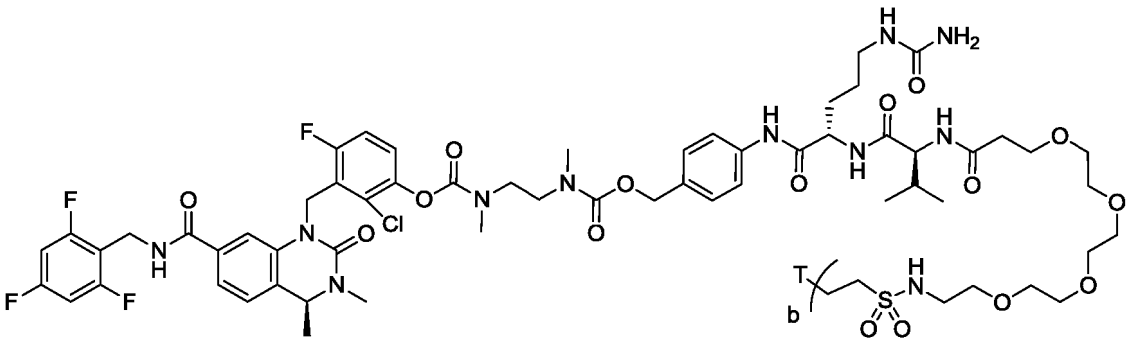

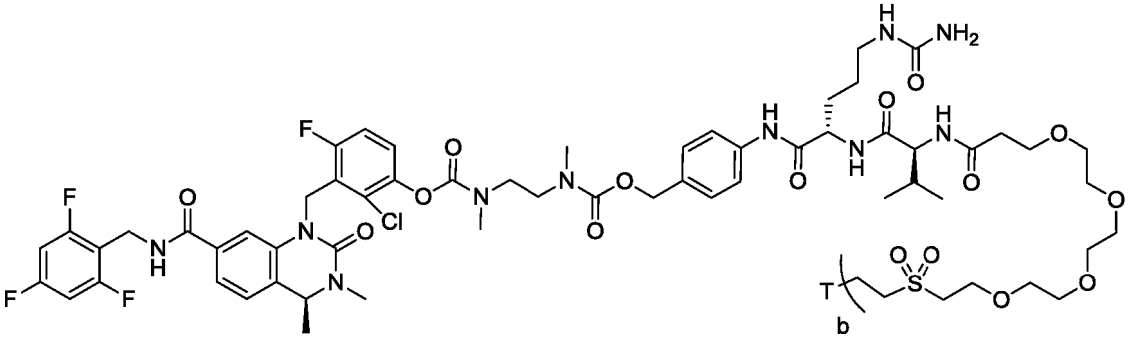

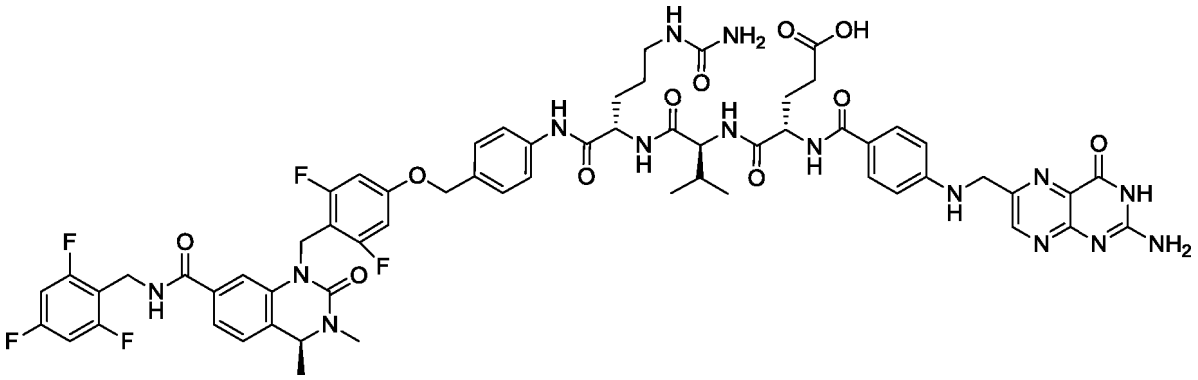

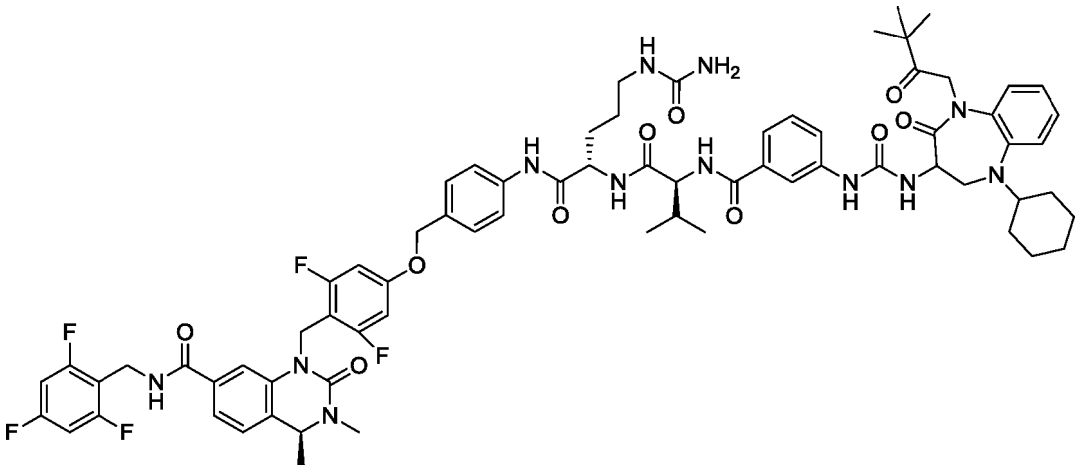

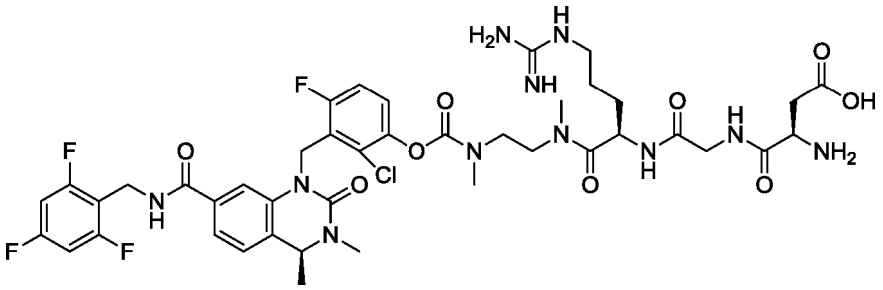

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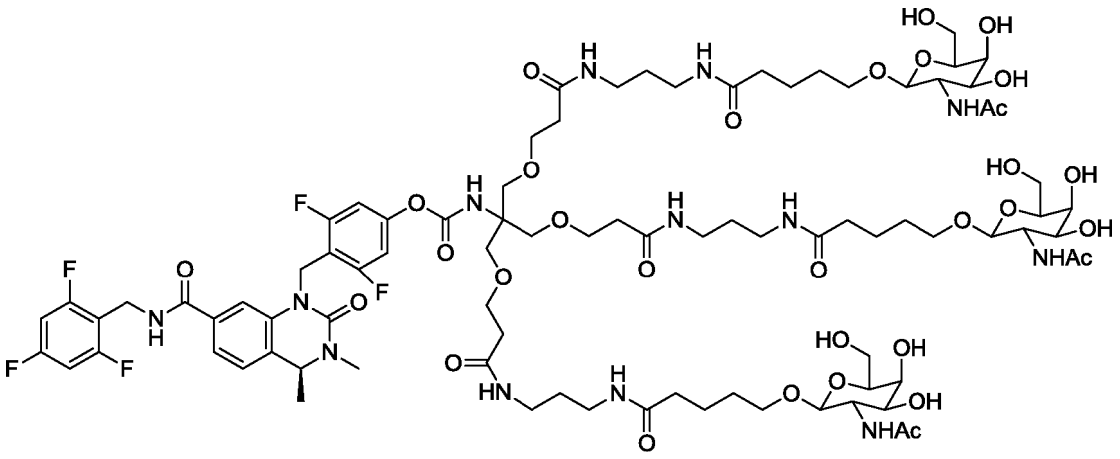

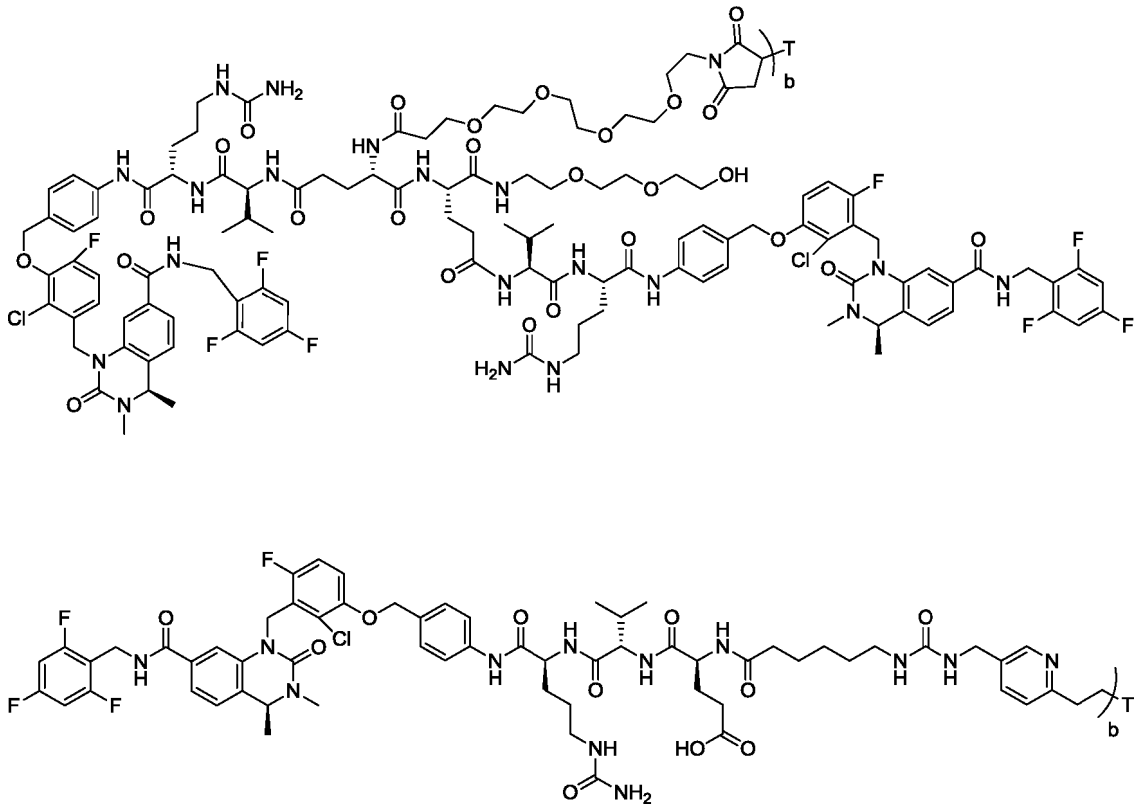

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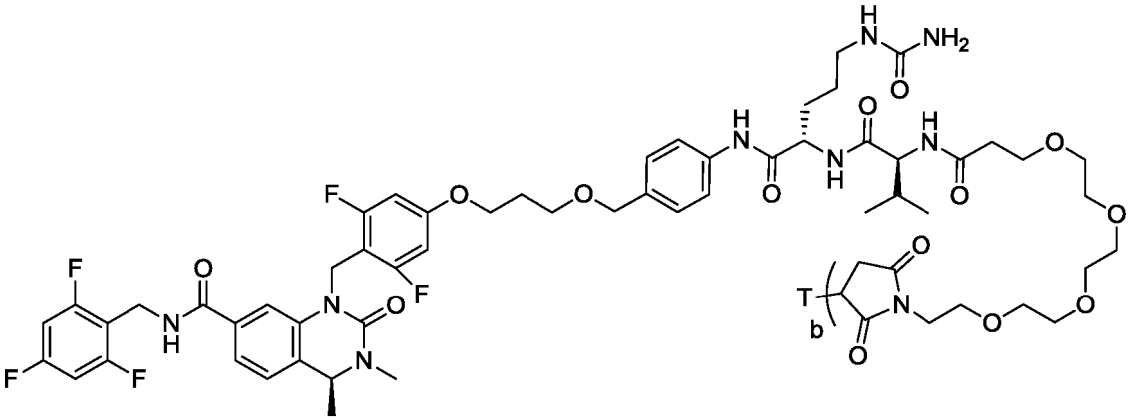
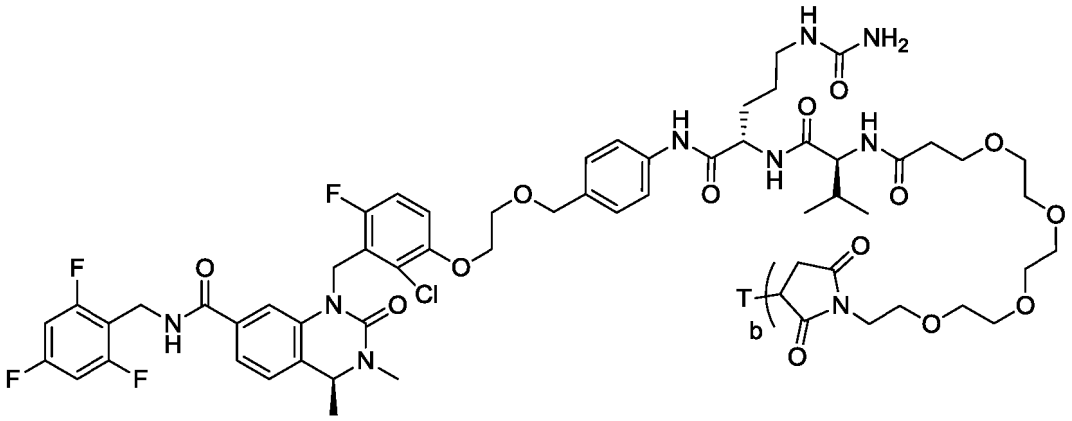
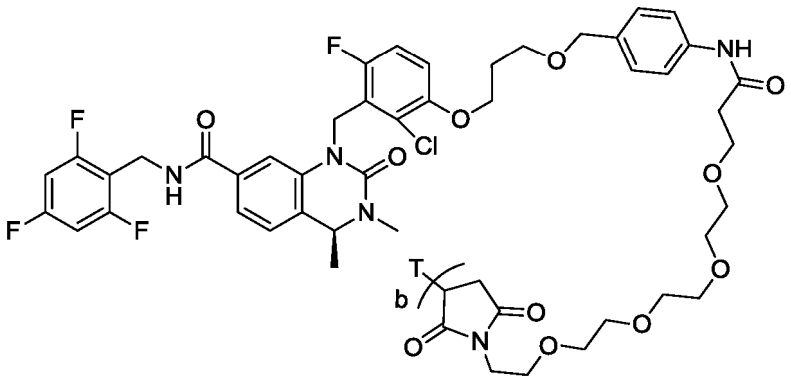
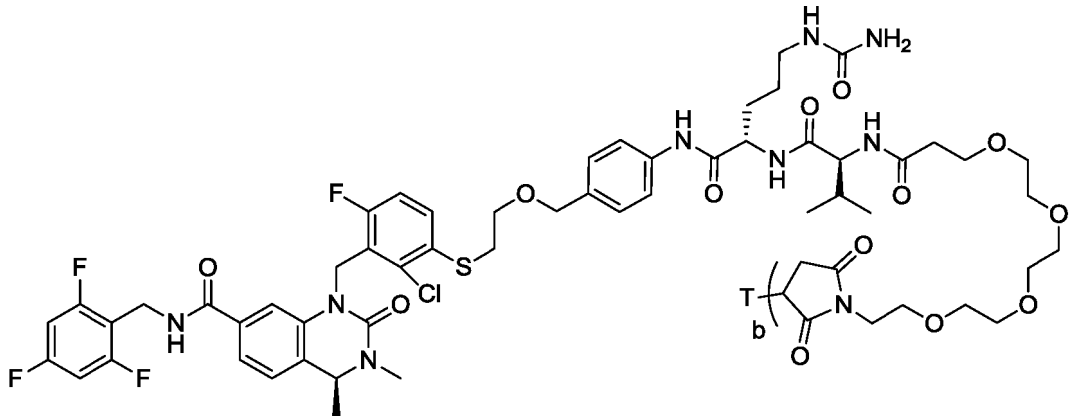
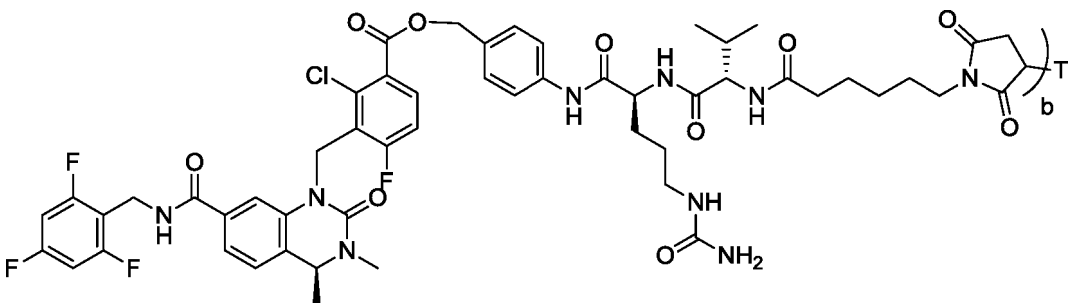
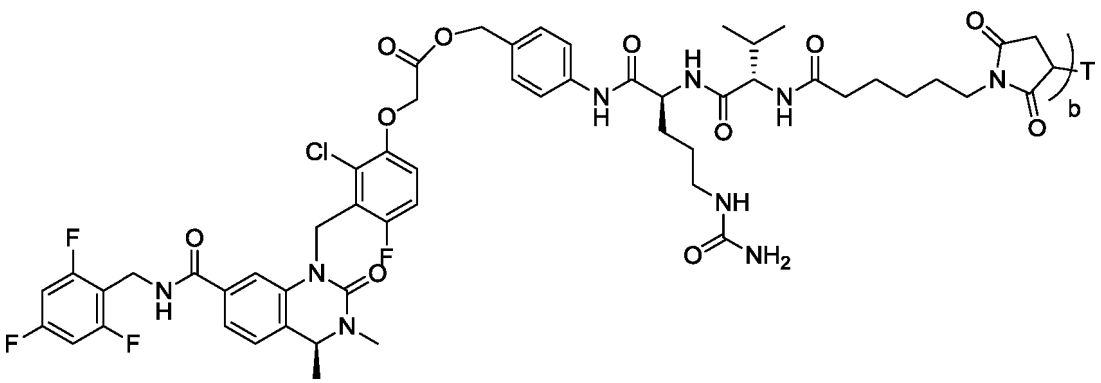


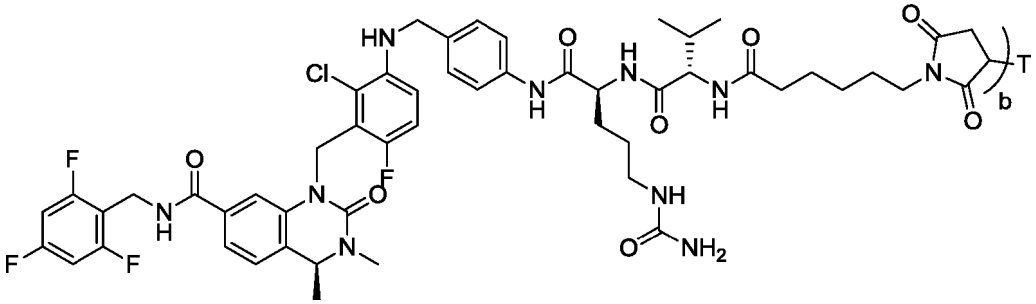


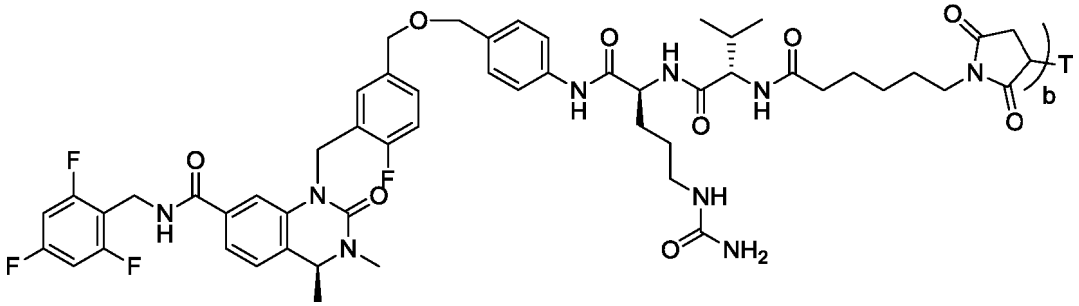


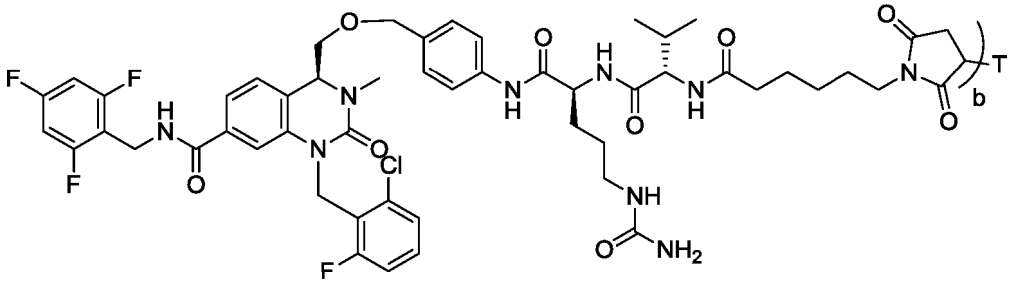


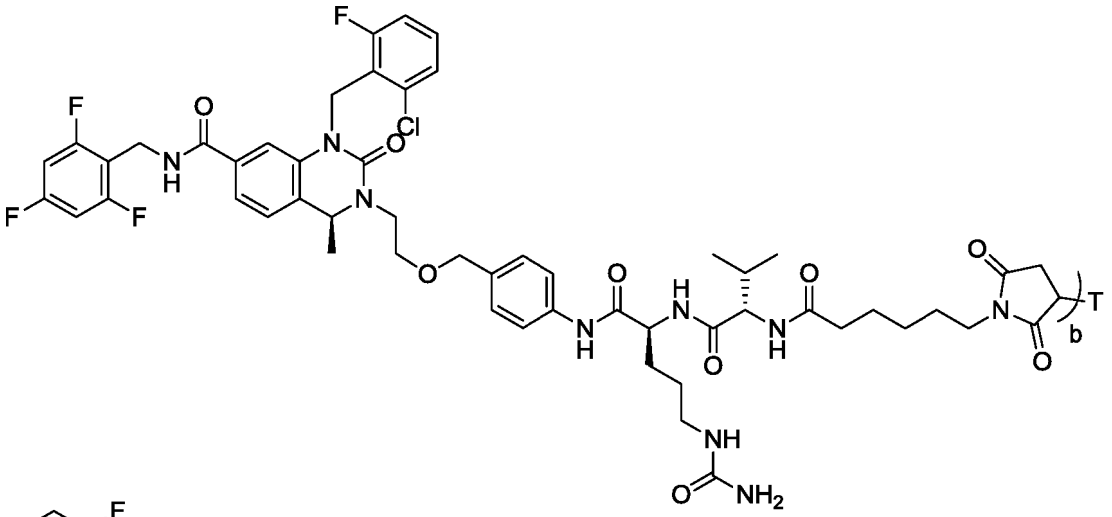


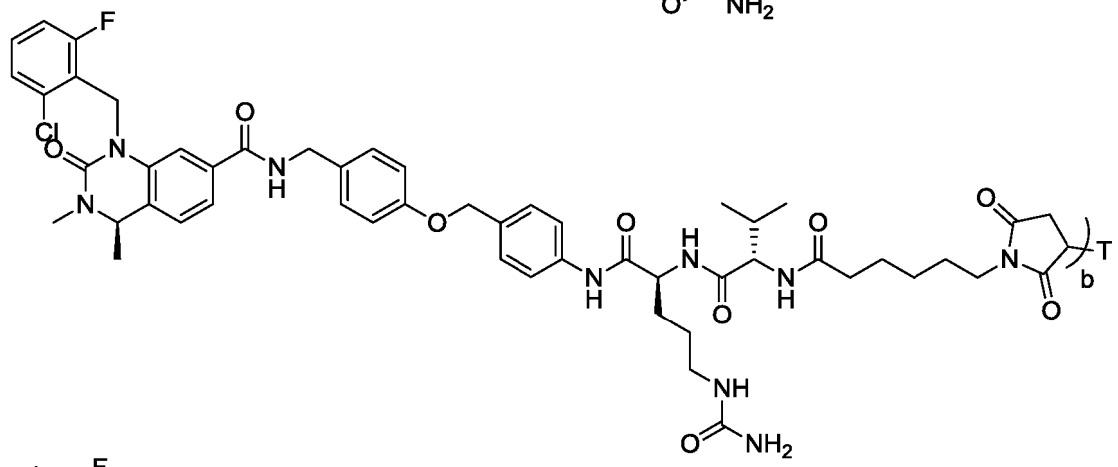


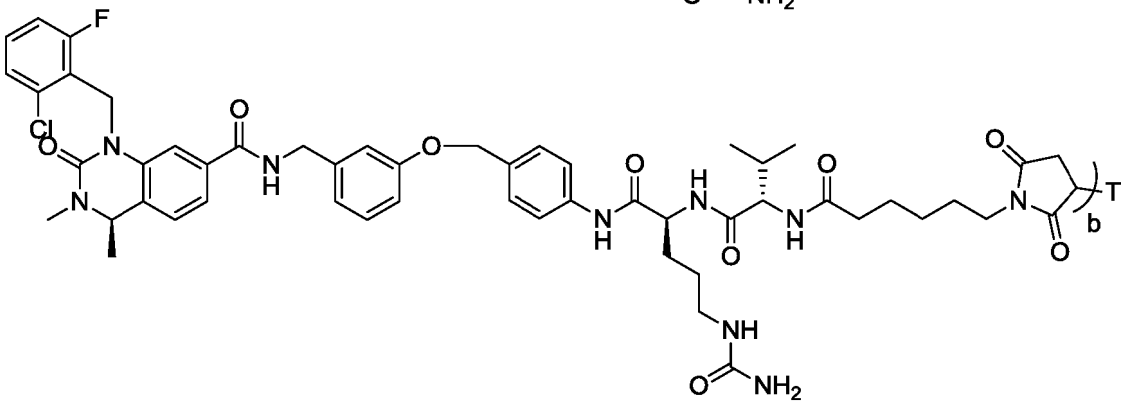


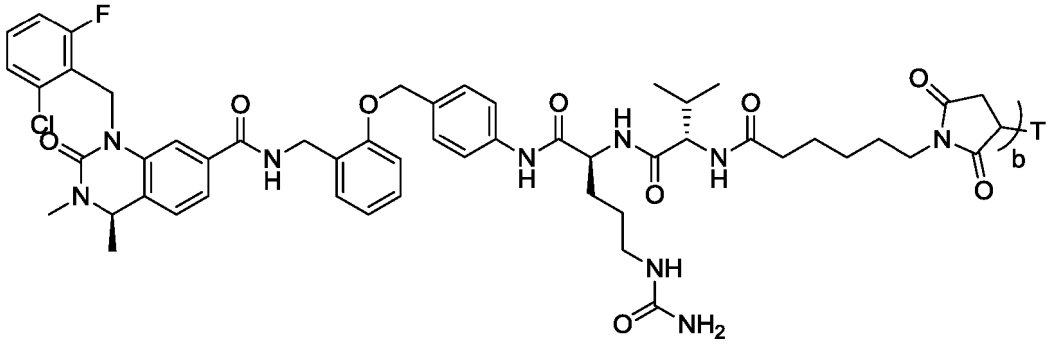




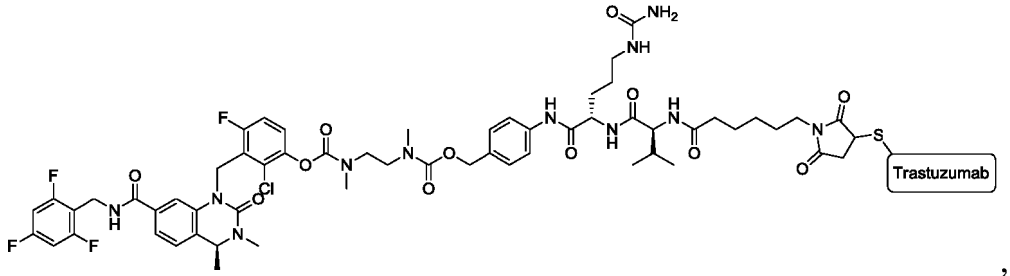








26. A compound according to claim 1, wherein the the compound of formula (**I**) is:



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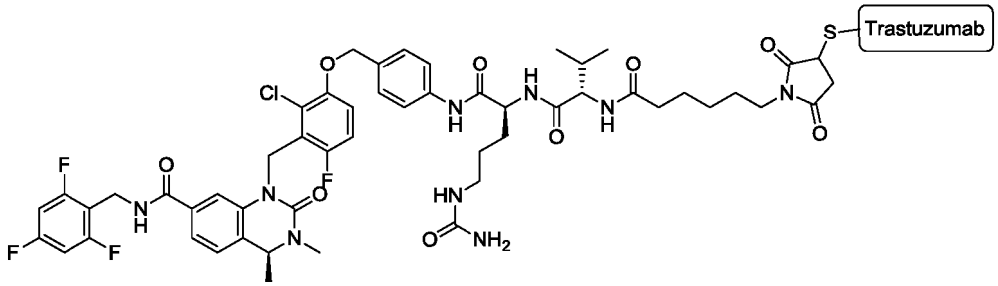

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27. A pharmaceutical composition comprising a compound according to any one of claims 1 to 26, or a pharmaceutically acceptable salt, solvate, tautomeric form or polymorphic form thereof, and a pharmaceutically acceptable vehicle.

28. A compound of formula (I) or a pharmaceutically acceptable complex, salt, solvate, tautomeric form or polymorphic form thereof, as defined in any one of claims 1 to 26, or a pharmaceutical composition, as defined by claim 27, for use in therapy.

29. A compound of formula (I) or a pharmaceutically acceptable complex, salt, solvate, tautomeric form or polymorphic form thereof, as defined in any one of claims 1 to 26, or a pharmaceutical composition, as defined by claim 27, for use in modulating the Stimulator of Interferon Genes (STING) protein.

30. A compound or composition for use according to claim 29, wherein the compound or composition is for use in activating the STING protein.

31. A compound of formula (I) or a pharmaceutically acceptable complex, salt, solvate, tautomeric form or polymorphic form thereof, as defined in any one of claims 1 to 26, or a pharmaceutical composition, as defined by claim 27, for use in treating, ameliorating or preventing a disease selected from cancer, bacterial infection, viral infection, parasitic infection, fungal infection, immune-mediated disorder, central

nervous system disease, peripheral nervous system disease, neurodegenerative disease, mood disorder, sleep disorder, cerebrovascular disease, peripheral artery disease or cardiovascular disease.

32. A compound or composition for use according to claim 31, wherein the disease is cancer.

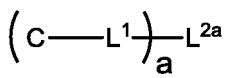
33. A compound or composition for use according to claim 32, wherein the cancer is selected from the group consisting of colorectal cancer, aero-digestive squamous cancer, lung cancer, brain cancer, neuroblastoma, glioblastoma, Hodgkin lymphoma, non-Hodgkin lymphoma, thyroid cancer, adrenal cancer, liver cancer, testicular cancer, urothelial cancer, stomach cancer, kidney cancer, hepatocellular carcinoma, cancer of the pharynx, rectal cancer, gastrointestinal stromal tumors, gastroesophageal cancer, sarcoma, adenosarcoma, pituitary adenoma, Kaposi's sarcoma, neuroendocrine tumors, mesothelioma, leukaemia, acute myeloid leukaemia, small cell lung cancer, non-small cell lung cancer, lymphoma, lymphoid cancer, multiple myeloma, myelodysplasia syndrome, transitional cell carcinoma, malignant mesothelioma, ovarian cancer, cervical cancer, uterine cancer, breast cancer, melanoma, prostate cancer, bladder cancer, bone cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular malignant melanoma, pancreatic carcinoma or renal cell carcinoma.

34. A compound or composition for use according to any one of claims 31 to 33, wherein the compound or composition is for use with a second therapeutic agent, optionally wherein the second therapeutic agent comprises an antiviral agent, an antiinflammation agent, conventional chemotherapy, an anti-cancer vaccine and/or hormonal therapy.

35. A compound or composition for use according to claim 34, wherein the second therapeutic agent comprises a B7 costimulatory molecule, interleukin-2, interferon-g, GM-CSF, a CTLA-4 antagonist (such as Ipilimumab and tremilimumab), an IDO inhibitor or IDO/TDO inhibitor (such as Epacadostat and GDC-0919), a PD-1 inhibitor (such as Nivolumab, Pembrolizumab, Pidilizumab, AMP-224, and MDX-1106), a PD-L1 inhibitor (such as Durvalumab, Avelumab and Atezolizumab), an OX-40 ligand, a LAG3 inhibitor, a CD40 ligand, a 41BB/CD137 ligand, a CD27 ligand, Bacille Calmette-Guerin (BCG), liposomes, alum, Freund's complete or incomplete adjuvant, a TLR

agonist (such as Poly I:C, MPL, LPS, bacterial flagellin, imiquimod, resiquimod, loxoribine and a CpG dinucleotide) and/or detoxified endotoxins.

36. A compound of formula (**III**):



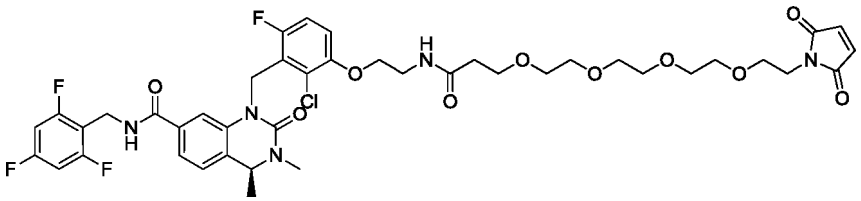
(**III**)

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

L^1, a and C are as defined in any one of claims 1 to 24; and

L^{2a} is either L^2-Lg_z, where L^2 and z are as defined in any one of claims 1 to 24 and Lg is a leaving group, or L^{2a} is a linker which is the same as L^2, as defined in any one of claims 1 to 24, except that the linker comprises a terminal double bond.

37. A compound according to claim 36, where the compound of formula (**III**) is:



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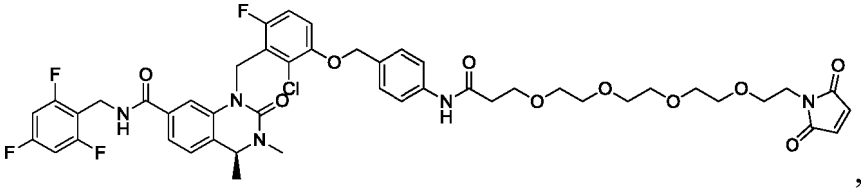

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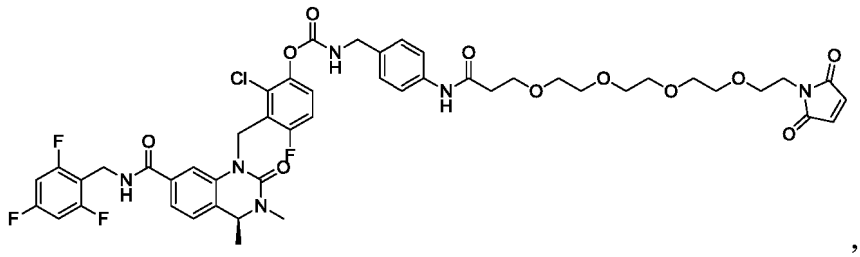

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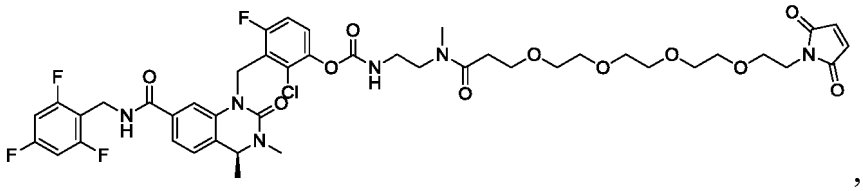

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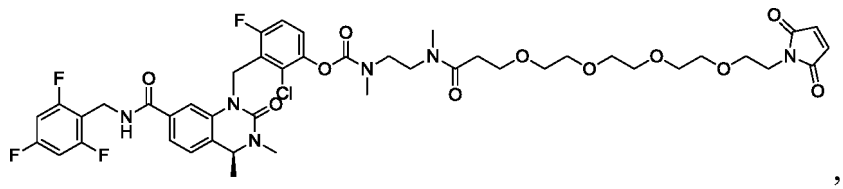

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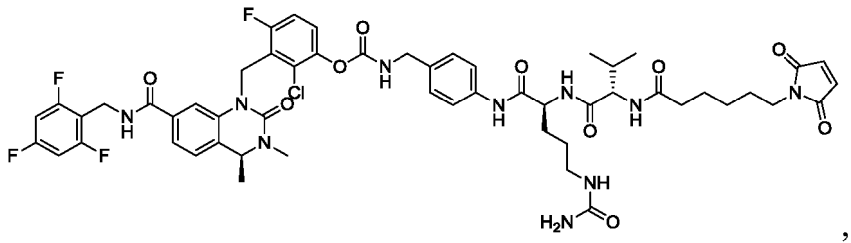

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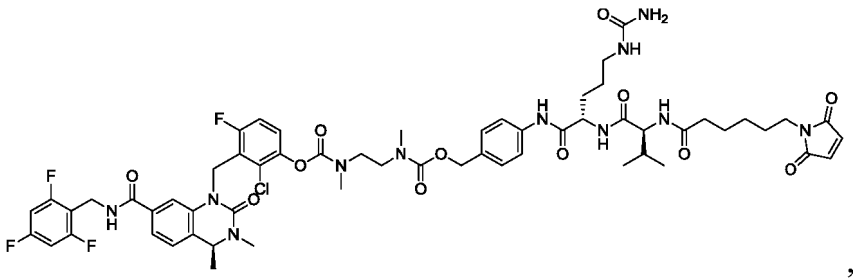

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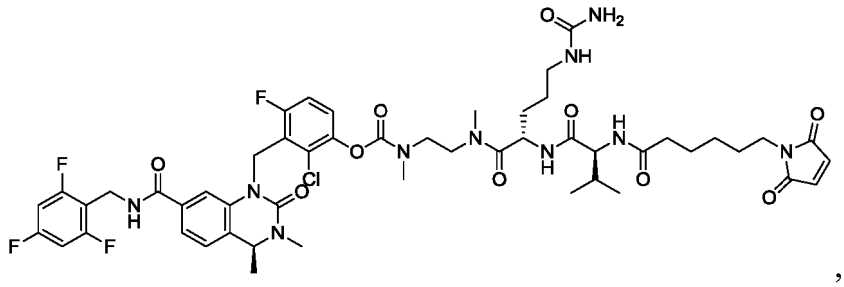

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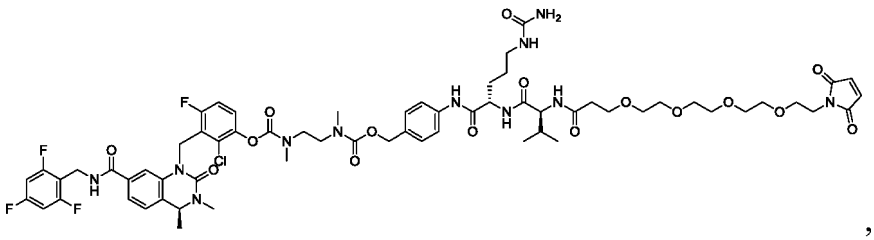

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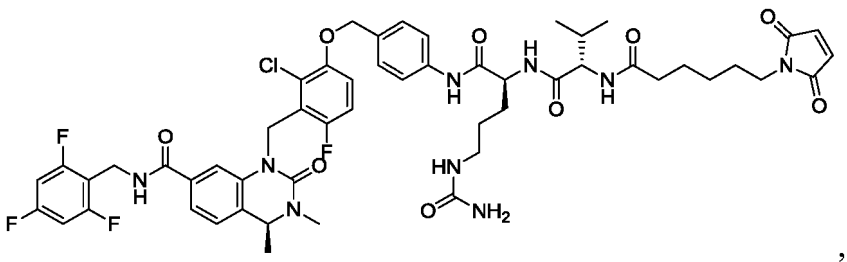

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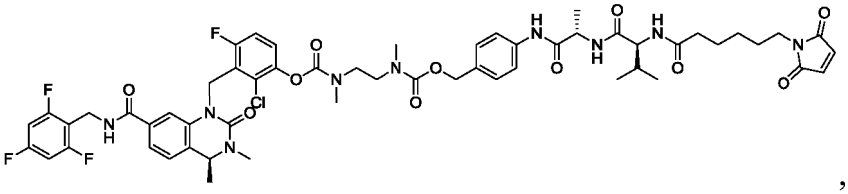

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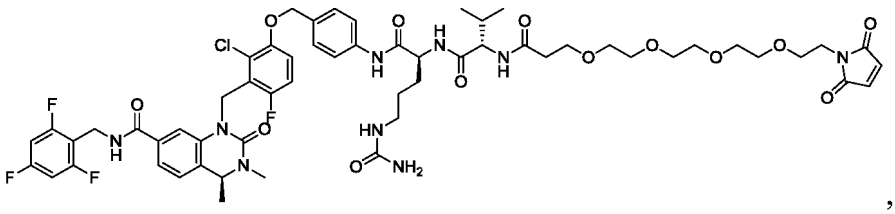

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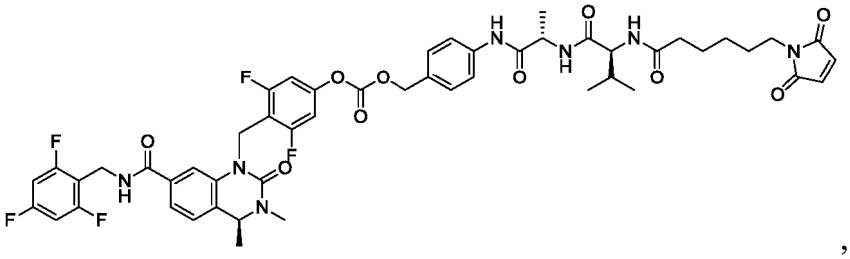

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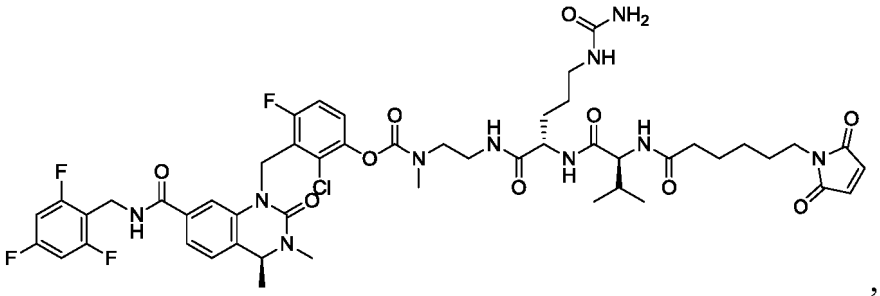

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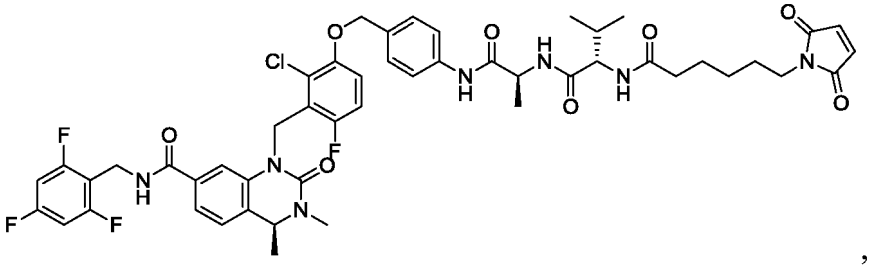

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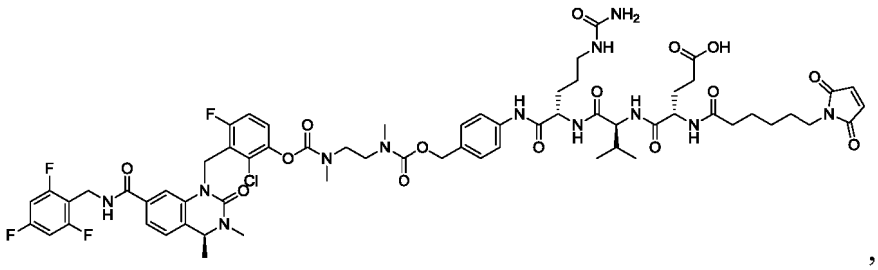

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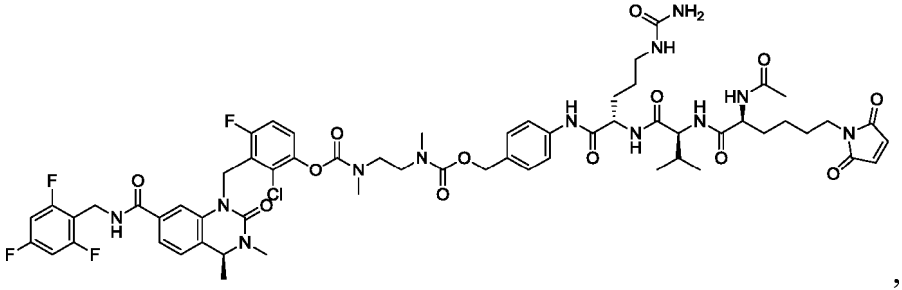

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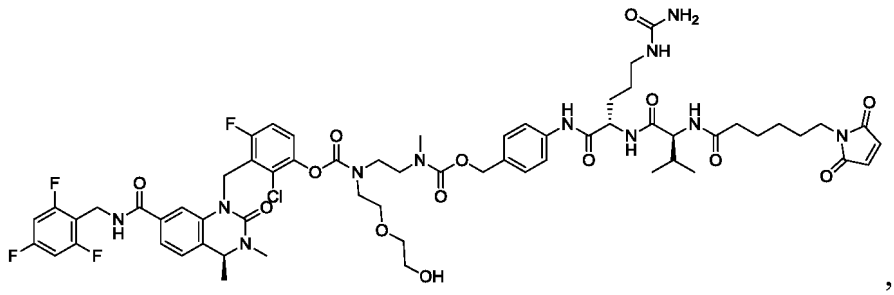

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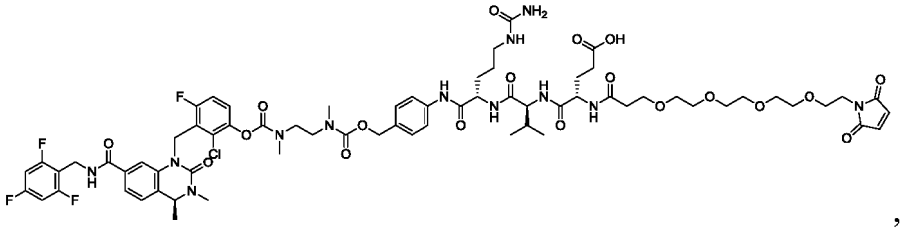

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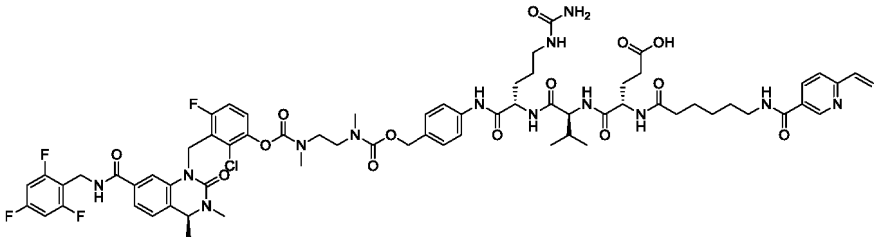

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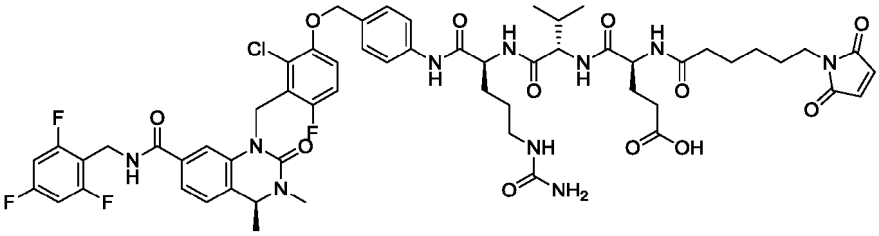

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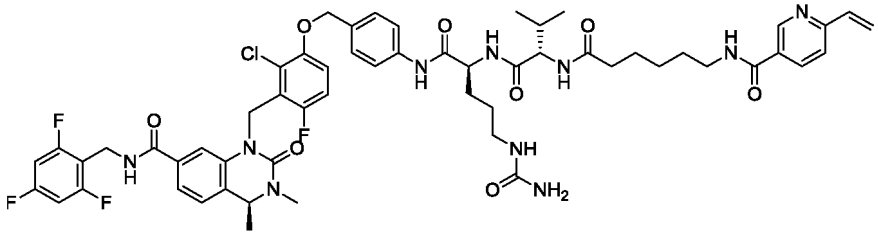

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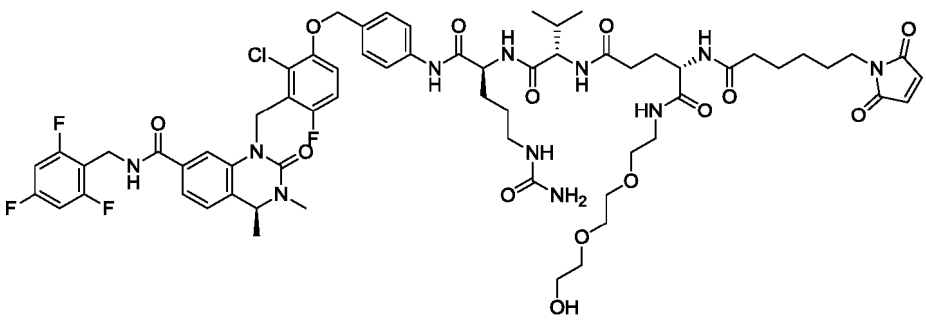

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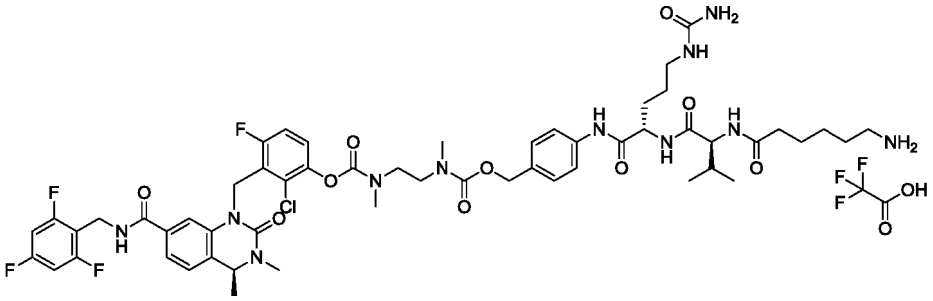

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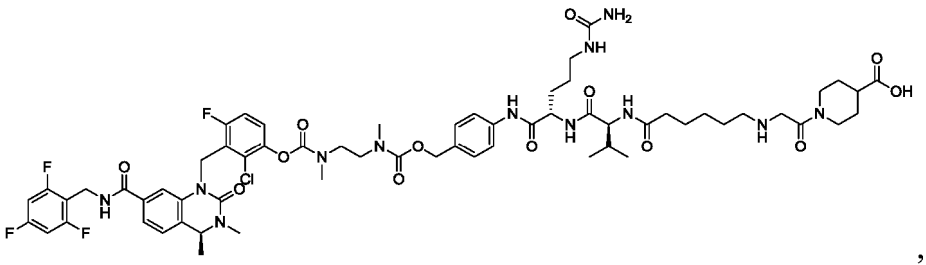

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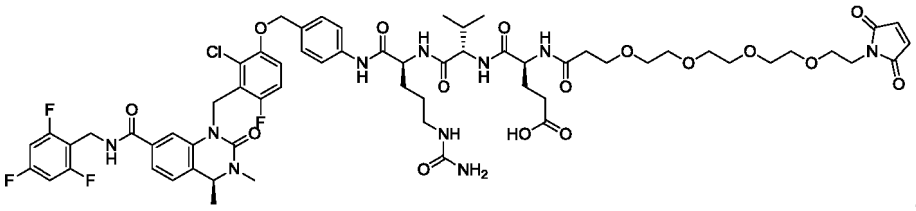

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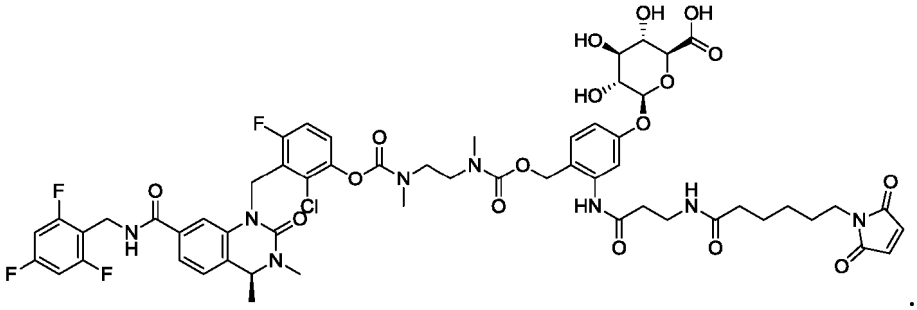

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Intellectual Property Office

Application No: GB1820991.6 **Examiner:** Mr Aaron Butt

Claims searched: 1-36 **Date of search:** 19 June 2019

Patents Act 1977: Search Report under Section 17

Documents considered to be relevant:

Category	Relevant to claims	Identity of document and passage or figure of particular relevance
A,E	-	WO 2018/234808 A1 (CRADEV PHARMA LTD) See whole document, esp. Formula (I).
A,E	-	GB 2563642 A (CURADEV PHARMA LTD) See whole document, esp. Formula (I).
A	-	US 2017/146519 A1 (DEFILIPPOS ET AL) See whole document, esp. Claims.

Categories:

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.

Field of Search:

Search of GB, EP, WO & US patent documents classified in the following areas of the UKC^{X} :

Worldwide search of patent documents classified in the following areas of the IPC

A61K; A61P; C07D; C07K

The following online and other databases have been used in the preparation of this search report

EPODOC, WPI, CAS Online, MARPAT

International Classification:

Subclass	Subgroup	Valid From
A61K	0047/65	01/01/2017
A61K	0047/68	01/01/2017
A61P	0035/00	01/01/2006
C07D	0239/80	01/01/2006
C07K	0005/06	01/01/2006
C07K	0005/08	01/01/2006