(12) STANDARD PATENT (11) Application No. **AU 2020291014 B2**
(19) AUSTRALIAN PATENT OFFICE

(54) Title
Aminobenzazepine compounds, immunoconjugates, and uses thereof

(51) International Patent Classification(s)
C07D 223/16 (2006.01) ***C07D 401/14*** (2006.01)
A61K 31/55 (2006.01) ***C07D 403/12*** (2006.01)
A61P 35/00 (2006.01) ***C07H 15/00*** (2006.01)
C07D 401/12 (2006.01)

(21) Application No: **2020291014** (22) Date of Filing: **2020.06.12**

(87) WIPO No: **WO20/252294**

(30) Priority Data

(31) Number	(32) Date	(33) Country
62/861,139	**2019.06.13**	**US**
62/963,884	**2020.01.21**	**US**

(43) Publication Date: **2020.12.17**
(44) Accepted Journal Date: **2025.06.05**

(71) Applicant(s)
Bolt Biotherapeutics, Inc.

(72) Inventor(s)
ACKERMAN, Shelley Erin;ALONSO, Michael N.;KUDIRKA, Romas;LEE, Arthur;SAFINA, Brian;ZHOU, Matthew

(74) Agent / Attorney
Spruson & Ferguson, GPO Box 3898, Sydney, NSW, 2001, AU

(56) Related Art
WO 2019/118884 A1
WO 2020/056008 A1
WO 2018/170179 A1
WO 2018/140831 A2

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 December 2020 (17.12.2020)

WIPO | PCT

(10) International Publication Number
WO 2020/252294 A1

(51) International Patent Classification:
A61P 35/00 (2006.01) *C07D 403/12* (2006.01)
C07D 223/16 (2006.01) *C07H 15/00* (2006.01)
C07D 401/12 (2006.01) *A61K 31/55* (2006.01)
C07D 401/14 (2006.01)

(21) International Application Number:
PCT/US2020/037477

(22) International Filing Date:
12 June 2020 (12.06.2020)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/861,139 13 June 2019 (13.06.2019) US
62/963,884 21 January 2020 (21.01.2020) US

(71) Applicant: **BOLT BIOTHERAPEUTICS, INC.** [US/US]; 640 Galveston Drive, Redwood City, California 94063 (US).

(72) Inventors: **ACKERMAN, Shelley Erin**; 640 Galveston Drive, Redwood City, California 94063 (US). **ALONSO, Michael N.**; 640 Galveston Drive, Redwood City, California 94063 (US). **KUDIRKA, Romas**; 640 Galveston Drive, Redwood City, California 94063 (US). **LEE, Arthur**; 640 Galveston Drive, Redwood City, California 94063 (US). **SAFINA, Brian**; 640 Galveston Drive, Redwood City, California 94063 (US). **ZHOU, Matthew**; 640 Galveston Drive, Redwood City, California 94063 (US).

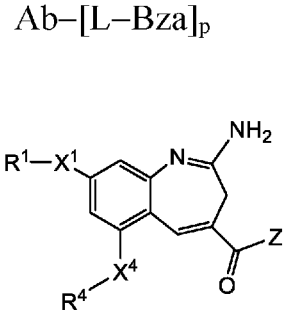
(74) Agent: **ANDRUS, Alex** et al.; Viksnins Harris Padys Malen LLP, 7851 Metro Parkway, Suite 325, Bloomington, Minnesota 55425 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*
— *with sequence listing part of description (Rule 5.2(a))*

(54) Title: AMINOBENZAZEPINE COMPOUNDS, IMMUNOCONJUGATES, AND USES THEREOF



I

II

(57) Abstract: The application relates to immunoconjugates of Formula (I) comprising an antibody linked by conjugation to one or more aminobenzazepine derivatives. The application also provides aminobenzazepine derivative intermediate compositions of Formula (II) comprising a reactive functional group. Such intermediate compositions are suitable substrates for formation of the immunoconjugates through a linker or linking moiety. The application further provides the above- mentioned immunoconjugates for use in methods of treating cancer.

WO 2020/252294 A1

AMINOBENZAZEPINE COMPOUNDS, IMMUNOCONJUGATES, AND USES THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

This non-provisional application claims the benefit of priority to U.S. Provisional Application No. 62/963,884, filed 21 January 2020, and U.S. Provisional Application No. 62/861,139, filed 13 June 2019, each of which are incorporated by reference in their entirety.

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on June 2, 2020, is named 17019_002WO1_SL.txt and is 299,523 bytes in size

FIELD OF THE INVENTION

The invention relates generally to an immunoconjugate comprising an antibody conjugated to one or more aminobenzazepine molecules.

BACKGROUND OF THE INVENTION

New compositions and methods for the delivery of antibodies and immune adjuvants are needed in order to reach inaccessible tumors and/or to expand treatment options for cancer patients and other subjects. The invention provides such compositions and methods.

Any reference to any prior art in this specification is not, and should not be taken as an acknowledgement or any form of suggestion that the prior art forms part of the common general knowledge.

SUMMARY OF THE INVENTION

In a first aspect of the invention, there is provided an immunoconjugate comprising an antibody covalently attached to one or more aminobenzazepine moieties by a linker, and having Formula I:

$$Ab–[L–Bza]_p \qquad I$$

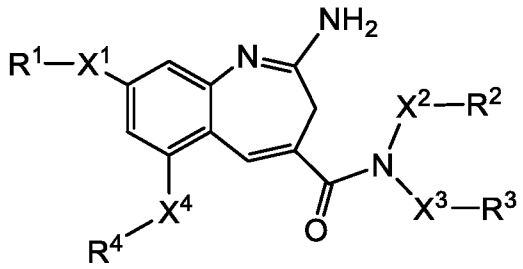
or a pharmaceutically acceptable salt thereof,

wherein:

Ab is the antibody;

p is an integer from 1 to 8;

Bza is the aminobenzazepine moiety having the formula:



R^1 is C_1-C_{20} heteroaryl, and X^1 is a bond;

R^2 is C_1-C_{12} alkyl, and X^2 is a bond;

R^3 is C_1-C_{12} alkyl, and X^3 is O;

R^4 is H, and X^4 is a bond;

wherein R^1 or R^3 is attached to a linker L;

L is the linker selected from the group consisting of:

–C(=O)–(PEG)–;

–C(=O)–(PEG)–C(=O)–;

–C(=O)–(PEG)–O–;

–C(=O)–(PEG)–C(=O)N(R^5)–(C_1-C_{12} alkyldiyl)–;

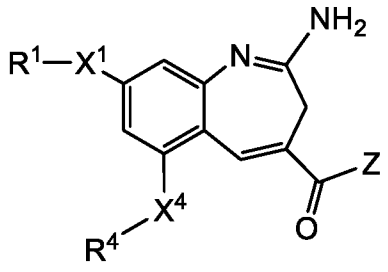
–C(=O)–(PEG)–C(=O)N(R^5)–(C_1-C_{12} alkyldiyl)–N(R^5)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–; and

–C(=O)–(PEG)–N(R^5)–;

wherein R^5 is selected from the group consisting of H, C_6-C_{20} aryl, C_6-C_{20} aryldiyl, C_1-C_{12} alkyl, and C_1-C_{12} alkyldiyl, or two R^5 groups together form a 5- or 6-membered heterocyclyl ring; and

PEG has the formula: $–(CH_2CH_2O)_n–(CH_2)_m–$; m is an integer from 1 to 5, and n is an integer from 5 to 20.

In a second aspect of the invention, there is provided an aminobenzazepine-linker compound of Formula II:



II

wherein

Z is $N(X^2–R^2)(X^3–R^3)$;

R^1 is C_1-C_{20} heteroaryl, and X^1 is a bond;

R^2 is C_1-C_{12} alkyl, and X^2 is a bond;

R^3 is C_1-C_{12} alkyl, and X^3 is O;

R^4 is H, and X^4 is a bond;

wherein R^1 or R^3 is attached to a linker L;

L is a linker selected from the group consisting of:

Q–C(=O)–(PEG)–;

Q–C(=O)–(PEG)–C(=O)–;

Q–C(=O)–(PEG)–O–;

Q–C(=O)–(PEG)–C(=O)N(R^5)–(C_1-C_{12} alkyldiyl)–;

Q–C(=O)–(PEG)–C(=O)N(R^5)–(C_1-C_{12} alkyldiyl)–N(R^5)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–; and

Q–C(=O)–(PEG)–N(R^5)–;

wherein R^5 is selected from the group consisting of H, C_6-C_{20} aryl, C_6-C_{20} aryldiyl, C_1-C_{12} alkyl, and C_1-C_{12} alkyldiyl, or two R^5 groups together form a 5- or 6-membered heterocyclyl ring;

PEG has the formula: $–(CH_2CH_2O)_n–(CH_2)_m–$; m is an integer from 1 to 5, and n is an integer from 5 to 20; and

Q is selected from the group consisting of N-hydroxysuccinimidyl, N-hydroxysulfosuccinimidyl, and phenoxy substituted with one or more groups independently selected from F, Cl, NO_2, and SO_3^-.

In a third aspect of the invention, there is provided a pharmaceutical composition comprising a therapeutically effective amount of an immunoconjugate according to the first aspect and one or more pharmaceutically acceptable diluent, vehicle, carrier or excipient.

In a fourth aspect of the invention, there is provided a method for treating cancer comprising administering a therapeutically effective amount of the immunoconjugate of the first aspect or the pharmaceutical composition of the third aspect to a patient in need thereof, wherein the cancer is selected from bladder cancer, urinary tract cancer, urothelial carcinoma, lung cancer, non-small cell lung cancer, Merkel cell carcinoma, colon cancer, colorectal cancer, gastric cancer, and breast cancer.

In a fifth aspect of the invention, there is provided the use of an immunoconjugate of the first aspect or the pharmaceutical composition of the third aspect in the manufacture of a medicament for treating cancer, wherein the cancer is selected from bladder cancer, urinary tract cancer, urothelial carcinoma, lung cancer, non-small cell lung cancer, Merkel cell carcinoma, colon cancer, colorectal cancer, gastric cancer, and breast cancer.

In a sixth aspect of the invention, there is provided an immunoconjugate as defined in the first aspect for use in treating cancer, wherein the cancer is selected from bladder cancer, urinary tract cancer, urothelial carcinoma, lung cancer, non-small cell lung cancer, Merkel cell carcinoma, colon cancer, colorectal cancer, gastric cancer, and breast cancer.

In a seventh aspect of the invention, there is provided a method of preparing an immunoconjugate of Formula I of the first aspect wherein an aminobenzazepine-linker compound of the second aspect is conjugated with the antibody.

The term "comprise" and variants of the term such as "comprises" or "comprising" are used herein to denote the inclusion of a stated integer or stated integers but not to exclude any other integer or any other integers, unless in the context or usage an exclusive interpretation of the term is required.

The invention is generally directed to immunoconjugates comprising an antibody linked by conjugation to one or more aminobenzazepine derivatives. The invention is further directed to aminobenzazepine derivative intermediate compositions comprising a reactive functional group. Such intermediate compositions are suitable substrates for formation of immunoconjugates wherein an antibody may be covalently bound to one or more aminobenzazepine derivatives, through a linker or linking moiety. The invention is further directed to use of such an immunoconjugates in the treatment of an illness, in particular cancer.

An aspect of the invention is an immunoconjugate comprising an antibody covalently attached to a linker which is covalently attached to one or more aminobenzazepine moieties.

Another aspect of the invention is an aminobenzazepine-linker compound.

[Text continues on page 2]

Another aspect of the invention is a method for treating cancer comprising administering a therapeutically effective amount of an immunoconjugate comprising an antibody linked by conjugation to one or more aminobenzazepine moieties.

Another aspect of the invention is a use of an immunoconjugate comprising an antibody linked by conjugation to one or more aminobenzazepine moieties for treating cancer.

Another aspect of the invention is a method of preparing an immunoconjugate by conjugation of one or more aminobenzazepine moieties with an antibody.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A-D show heavy chain and light chain CDRs of PD-L1 Type A binding agents 1-42.

Figures 2A-D show first (HFW1), second (HFW2), third (HFW3), and fourth (HFW4) heavy chain framework region polypeptides of PD-L1 Type A binding agents 1-42.

Figures 3A-D show first (LFW1), second (LFW2), third (LFW3), and fourth (LFW4) light chain framework region polypeptides of PD-L1 Type A binding agents 1-42.

Figures 4 A-D show heavy chain variable region (VH) of PD-L1 Type A binding agents 1-42.

Figures 4 E-G show light chain variable region (VL) of PD-L1 Type A binding agents 1-42.

Figures 5A-B show heavy chain and light chain CDRs of PD-L1 Type B binding agents 1-21.

Figures 6A-B show first (HFW1), second (HFW2), third (HFW3), and fourth (HFW4) heavy chain framework region polypeptides of PD-L1 Type B binding agents 1-21.

Figures 7A-B show first (LFW1), second (LFW2), third (LFW3), and fourth (LFW4) light chain framework region polypeptides of PD-L1 Type B binding agents 1-21.

Figures 8A-B show heavy chain variable region (VH) of PD-L1 Type B binding agents 1-21.

Figures 8C-D show light chain variable region (VL) of PD-L1 Type B binding agents 1-21.

DETAILED DESCRIPTION OF THE INVENTION

Reference will now be made in detail to certain embodiments of the invention, examples of which are illustrated in the accompanying structures and formulas. While the invention will be described in conjunction with the enumerated embodiments, it will be understood that they are not intended to limit the invention to those embodiments. On the contrary, the invention is

intended to cover all alternatives, modifications, and equivalents, which may be included within the scope of the invention as defined by the claims.

One skilled in the art will recognize many methods and materials similar or equivalent to those described herein, which could be used in the practice of the present invention. The invention is in no way limited to the methods and materials described.

DEFINITIONS

The term "immunoconjugate" refers to an antibody construct that is covalently bonded to an adjuvant moiety via a linker. the term "adjuvant" refers to a substance capable of eliciting an immune response in a subject exposed to the adjuvant. The phrase "adjuvant moiety" refers to an adjuvant that is covalently bonded to an antibody construct, e.g., through a linker, as described herein. The adjuvant moiety can elicit the immune response while bonded to the antibody construct or after cleavage (e.g., enzymatic cleavage) from the antibody construct following administration of an immunoconjugate to the subject.

"Adjuvant" refers to a substance capable of eliciting an immune response in a subject exposed to the adjuvant. The phrase "adjuvant moiety" refers to an adjuvant that is covalently bonded to an antibody construct, e.g., through a linker, as described herein. The adjuvant moiety can elicit the immune response while bonded to the antibody construct or after cleavage (e.g., enzymatic cleavage) from the antibody construct following administration of an immunoconjugate to the subject.

The terms "Toll-like receptor" and "TLR" refer to any member of a family of highly-conserved mammalian proteins which recognizes pathogen-associated molecular patterns and acts as key signaling elements in innate immunity. TLR polypeptides share a characteristic structure that includes an extracellular domain that has leucine-rich repeats, a transmembrane domain, and an intracellular domain that is involved in TLR signaling.

The terms "Toll-like receptor 7" and "TLR7" refer to nucleic acids or polypeptides sharing at least about 70%, about 80%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, or more sequence identity to a publicly-available TLR7 sequence, e.g., GenBank accession number AAZ99026 for human TLR7 polypeptide, or GenBank accession number AAK62676 for murine TLR7 polypeptide.

The terms "Toll-like receptor 8" and "TLR8" refer to nucleic acids or polypeptides sharing at least about 70%, about 80%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, or more sequence identity to a publicly-available TLR7 sequence, e.g., GenBank accession number AAZ95441 for human TLR8 polypeptide, or GenBank accession number AAK62677 for murine TLR8 polypeptide.

A "TLR agonist" is a substance that binds, directly or indirectly, to a TLR (e.g., TLR7 and/or TLR8) to induce TLR signaling. Any detectable difference in TLR signaling can indicate that an agonist stimulates or activates a TLR. Signaling differences can be manifested, for example, as changes in the expression of target genes, in the phosphorylation of signal transduction components, in the intracellular localization of downstream elements such as nuclear factor-κB (NF-κB), in the association of certain components (such as IL-1 receptor associated kinase (IRAK)) with other proteins or intracellular structures, or in the biochemical activity of components such as kinases (such as mitogen-activated protein kinase (MAPK)).

"Antibody" refers to a polypeptide comprising an antigen binding region (including the complementarity-determining regions (CDRs)) from an immunoglobulin gene or fragments thereof. The term "antibody" specifically encompasses monoclonal antibodies (including full length monoclonal antibodies), polyclonal antibodies, multispecific antibodies (e.g., bispecific antibodies), and antibody fragments that exhibit the desired biological activity. An exemplary immunoglobulin (antibody) structural unit comprises a tetramer. Each tetramer is composed of two identical pairs of polypeptide chains, each pair having one "light" (about 25 kDa) and one "heavy" chain (about 50-70 kDa) connected by disulfide bonds. Each chain is composed of structural domains, which are referred to as immunoglobulin domains. These domains are classified into different categories by size and function, e.g., variable domains or regions on the light and heavy chains (V_L and V_H, respectively) and constant domains or regions on the light and heavy chains (C_L and C_H, respectively). The N-terminus of each chain defines a variable region of about 100 to 110 or more amino acids, referred to as the paratope, primarily responsible for antigen recognition, i.e., the antigen binding domain. Light chains are classified as either kappa or lambda. Heavy chains are classified as gamma, mu, alpha, delta, or epsilon, which in turn define the immunoglobulin classes, IgG, IgM, IgA, IgD and IgE, respectively. IgG antibodies are large molecules of about 150 kDa composed of four peptide chains. IgG antibodies contain two identical class γ heavy chains of about 50 kDa and two identical light chains of about 25 kDa, thus a tetrameric quaternary structure. The two heavy chains are linked to each other and to a light chain each by disulfide bonds. The resulting tetramer has two identical halves, which together form the Y-like shape. Each end of the fork contains an identical antigen binding domain. There are four IgG subclasses (IgG1, IgG2, IgG3, and IgG4) in humans, named in order of their abundance in serum (i.e., IgG1 is the most abundant). Typically, the antigen binding domain of an antibody will be most critical in specificity and affinity of binding to cancer cells.

"Antibody construct" refers to an antibody or a fusion protein comprising (i) an antigen binding domain and (ii) an Fc domain.

In some embodiments, the binding agent is an antigen-binding antibody "fragment," which is a construct that comprises at least an antigen-binding region of an antibody, alone or with other components that together constitute the antigen-binding construct. Many different types of antibody "fragments" are known in the art, including, for instance, (i) a Fab fragment, which is a monovalent fragment consisting of the V_L, V_H, C_L, and CH_1 domains, (ii) a $F(ab')_2$ fragment, which is a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region, (iii) a Fv fragment consisting of the V_L and V_H domains of a single arm of an antibody, (iv) a Fab' fragment, which results from breaking the disulfide bridge of an $F(ab')_2$ fragment using mild reducing conditions, (v) a disulfide-stabilized Fv fragment (dsFv), and (vi) a single chain Fv (scFv), which is a monovalent molecule consisting of the two domains of the Fv fragment (i.e., V_L and V_H) joined by a synthetic linker which enables the two domains to be synthesized as a single polypeptide chain.

The antibody or antibody fragments can be part of a larger construct, for example, a conjugate or fusion construct of the antibody fragment to additional regions. For instance, in some embodiments, the antibody fragment can be fused to an Fc region as described herein. In other embodiments, the antibody fragment (e.g., a Fab or scFv) can be part of a chimeric antigen receptor or chimeric T-cell receptor, for instance, by fusing to a transmembrane domain (optionally with an intervening linker or "stalk" (e.g., hinge region)) and optional intercellular signaling domain. For instance, the antibody fragment can be fused to the gamma and/or delta chains of a t-cell receptor, so as to provide a T-cell receptor like construct that binds PD-L1. In yet another embodiment, the antibody fragment is part of a bispecific T-cell engager (BiTEs) comprising a CD1 or CD3 binding domain and linker.

"Epitope" means any antigenic determinant or epitopic determinant of an antigen to which an antigen binding domain binds (i.e., at the paratope of the antigen binding domain). Antigenic determinants usually consist of chemically active surface groupings of molecules, such as amino acids or sugar side chains, and usually have specific three dimensional structural characteristics, as well as specific charge characteristics.

The terms "Fc receptor" or "FcR" refer to a receptor that binds to the Fc region of an antibody. There are three main classes of Fc receptors: (1) FcγR which bind to IgG, (2) FcαR which binds to IgA, and (3) FcεR which binds to IgE. The FcγR family includes several members, such as FcγI (CD64), FcγRIIA (CD32A), FcγRIIB (CD32B), FcγRIIIA (CD16A), and FcγRIIIB (CD16B). The Fcγ receptors differ in their affinity for IgG and also have different affinities for the IgG subclasses (e.g., IgG1, IgG2, IgG3, and IgG4).

Nucleic acid or amino acid sequence "identity," as referenced herein, can be determined by comparing a nucleic acid or amino acid sequence of interest to a reference nucleic acid or

amino acid sequence. The percent identity is the number of nucleotides or amino acid residues that are the same (i.e., that are identical) as between the optimally aligned sequence of interest and the reference sequence divided by the length of the longest sequence (i.e., the length of either the sequence of interest or the reference sequence, whichever is longer). Alignment of sequences and calculation of percent identity can be performed using available software programs. Examples of such programs include CLUSTAL-W, T-Coffee, and ALIGN (for alignment of nucleic acid and amino acid sequences), BLAST programs (e.g., BLAST 2.1, BL2SEQ, BLASTp, BLASTn, and the like) and FASTA programs (e.g., FASTA3x, FASTM, and SSEARCH) (for sequence alignment and sequence similarity searches). Sequence alignment algorithms also are disclosed in, for example, Altschul et al., *J. Molecular Biol.*, 215(3): 403-410 (1990), Beigert et al., *Proc. Natl. Acad. Sci. USA*, *106*(10): 3770-3775 (2009), Durbin et al., eds., *Biological Sequence Analysis: Probalistic Models of Proteins and Nucleic Acids*, Cambridge University Press, Cambridge, UK (2009), Soding, *Bioinformatics*, 21(7): 951-960 (2005), Altschul et al., *Nucleic Acids Res.*, 25(17): 3389-3402 (1997), and Gusfield, *Algorithms on Strings, Trees and Sequences*, Cambridge University Press, Cambridge UK (1997)). Percent (%) identity of sequences can be also calculated, for example, as 100 x [(identical positions)/min(TG_A, TG_B)], where TG_A and TG_B are the sum of the number of residues and internal gap positions in peptide sequences A and B in the alignment that minimizes TG_A and TG_B. See, e.g., Russell et al., *J. Mol Biol.*, 244: 332-350 (1994).

The binding agent comprises Ig heavy and light chain variable region polypeptides that together form the antigen binding site. Each of the heavy and light chain variable regions are polypeptides comprising three complementarity determining regions (CDR1, CDR2, and CDR3) connected by framework regions. The binding agent can be any of a variety of types of binding agents known in the art that comprise Ig heavy and light chains. For instance, the binding agent can be an antibody, an antigen-binding antibody "fragment," or a T-cell receptor.

"Biosimilar" refers to an approved antibody construct that has active properties similar to, for example, a PD-L1-targeting antibody construct previously approved such as atezolizumab (TECENTRIQ™, Genentech, Inc.), durvalumab (IMFINZI™, AstraZeneca), and avelumab (BAVENCIO™, EMD Serono, Pfizer); a HER2-targeting antibody construct previously approved such as trastuzumab (HERCEPTIN™, Genentech, Inc.), and pertuzumab (PERJETA™, Genentech, Inc.); or a CEA-targeting antibody such as labetuzumab (CEA-CIDE™, MN-14, hMN14, Immunomedics) CAS Reg. No. 219649-07-7).

"Biobetter" refers to an approved antibody construct that is an improvement of a previously approved antibody construct, such as atezolizumab, durvalumab, avelumab, trastuzumab, pertuzumab, and labetuzumab. The biobetter can have one or more modifications

(e.g., an altered glycan profile, or a unique epitope) over the previously approved antibody construct.

"Amino acid" refers to any monomeric unit that can be incorporated into a peptide, polypeptide, or protein. Amino acids include naturally-occurring α-amino acids and their stereoisomers, as well as unnatural (non-naturally occurring) amino acids and their stereoisomers. "Stereoisomers" of a given amino acid refer to isomers having the same molecular formula and intramolecular bonds but different three-dimensional arrangements of bonds and atoms (e.g., an L-amino acid and the corresponding D-amino acid). The amino acids can be glycosylated (e.g., *N*-linked glycans, *O*-linked glycans, phosphoglycans, *C*-linked glycans, or glypication) or deglycosylated. Amino acids may be referred to herein by either the commonly known three letter symbols or by the one-letter symbols recommended by the IUPAC-IUB Biochemical Nomenclature Commission.

Naturally-occurring amino acids are those encoded by the genetic code, as well as those amino acids that are later modified, e.g., hydroxyproline, γ-carboxyglutamate, and *O*-phosphoserine. Naturally-occurring α-amino acids include, without limitation, D and L stereoisomers where they exist of alanine (Ala), cysteine (Cys), aspartic acid (Asp), glutamic acid (Glu), phenylalanine (Phe), glycine (Gly), histidine (His), isoleucine (Ile), arginine (Arg), lysine (Lys), leucine (Leu), methionine (Met), asparagine (Asn), proline (Pro), glutamine (Gln), serine (Ser), threonine (Thr), valine (Val), tryptophan (Trp), tyrosine (Tyr), and combinations thereof. Stereoisomers of naturally-occurring α-amino acids include, without limitation, D-alanine (D-Ala), D-cysteine (D-Cys), D-aspartic acid (D-Asp), D-glutamic acid (D-Glu), D-phenylalanine (D-Phe), D-histidine (D-His), D-isoleucine (D-Ile), D-arginine (D-Arg), D-lysine (D-Lys), D-leucine (D-Leu), D-methionine (D-Met), D-asparagine (D-Asn), D-proline (D-Pro), D-glutamine (D-Gln), D-serine (D-Ser), D-threonine (D-Thr), D-valine (D-Val), D-tryptophan (D-Trp), D-tyrosine (D-Tyr), and combinations thereof.

Naturally-occurring amino acids include those formed in proteins by post-translational modification, such as citrulline (Cit).

Unnatural (non-naturally occurring) amino acids include, without limitation, amino acid analogs, amino acid mimetics, synthetic amino acids, *N*-substituted glycines, and *N*-methyl amino acids in either the L- or D-configuration that function in a manner similar to the naturally-occurring amino acids. For example, "amino acid analogs" can be unnatural amino acids that have the same basic chemical structure as naturally-occurring amino acids (i.e., a carbon that is bonded to a hydrogen, a carboxyl group, an amino group) but have modified side-chain groups or modified peptide backbones, e.g., homoserine, norleucine, methionine sulfoxide, and methionine methyl sulfonium. "Amino acid mimetics" refer to chemical compounds that have a

structure that is different from the general chemical structure of an amino acid, but that functions in a manner similar to a naturally-occurring amino acid.

"Linker" refers to a functional group that covalently bonds two or more moieties in a compound or material. For example, the linking moiety can serve to covalently bond an adjuvant moiety to an antibody construct in an immunoconjugate.

"Linking moiety" refers to a functional group that covalently bonds two or more moieties in a compound or material. For example, the linking moiety can serve to covalently bond an adjuvant moiety to an antibody in an immunoconjugate. Useful bonds for connecting linking moieties to proteins and other materials include, but are not limited to, amides, amines, esters, carbamates, ureas, thioethers, thiocarbamates, thiocarbonates, and thioureas.

"Divalent" refers to a chemical moiety that contains two points of attachment for linking two functional groups; polyvalent linking moieties can have additional points of attachment for linking further functional groups. Divalent radicals may be denoted with the suffix "diyl". For example, divalent linking moieties include divalent polymer moieties such as divalent poly(ethylene glycol), divalent cycloalkyl, divalent heterocycloalkyl, divalent aryl, and divalent heteroaryl group. A "divalent cycloalkyl, heterocycloalkyl, aryl, or heteroaryl group" refers to a cycloalkyl, heterocycloalkyl, aryl, or heteroaryl group having two points of attachment for covalently linking two moieties in a molecule or material. Cycloalkyl, heterocycloalkyl, aryl, or heteroaryl groups can be substituted or unsubstituted. Cycloalkyl, heterocycloalkyl, aryl, or heteroaryl groups can be substituted with one or more groups selected from halo, hydroxy, amino, alkylamino, amido, acyl, nitro, cyano, and alkoxy.

A wavy line () or an asterisk (*) represents a point of attachment of the specified chemical moiety. If the specified chemical moiety has two wavy lines () present, it will be understood that a divalent chemical moiety can be used bilaterally, i.e., as read from left to right or from right to left. In some embodiments, a specified moiety having two wavy lines () present is considered to be used as read from left to right.

"Alkyl" refers to a straight or branched, saturated, aliphatic radical having the number of carbon atoms indicated. Alkyl can include any number of carbons. For example, C_1-C_4 alkyl includes, but is not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, and *tert*-butyl. Alkyl can also refer to alkyl groups having up to 30 carbons atoms, such as, but not limited to heptyl, octyl, nonyl, decyl, etc. Alkyl groups can be substituted or unsubstituted. "Substituted alkyl" groups can be substituted with one or more groups selected from halo, hydroxy, amino, oxo (=O), alkylamino, amido, acyl, nitro, cyano, and alkoxy.

The term "alkyldiyl" refers to a divalent alkyl radical.

"Cycloalkyl" refers to a saturated or partially unsaturated, monocyclic, fused bicyclic, or bridged polycyclic ring assembly containing from 3 to 12 ring atoms, or the number of atoms indicated. Saturated monocyclic carbocyclic rings include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cyclooctyl. Saturated bicyclic and polycyclic carbocyclic rings include, for example, norbornane, [2.2.2] bicyclooctane, decahydronaphthalene and adamantane. Carbocyclic groups can also be partially unsaturated, having one or more double or triple bonds in the ring. Representative carbocyclic groups that are partially unsaturated include, but are not limited to, cyclobutene, cyclopentene, cyclohexene, cyclohexadiene (1,3- and 1,4-isomers), cycloheptene, cycloheptadiene, cyclooctene, cyclooctadiene (1,3-, 1,4- and 1,5-isomers), norbornene, and norbornadiene.

The term "cycloalkyldiyl" refers to a divalent cycloalkyl radical.

"Aryl" refers to an aromatic ring system having any suitable number of ring atoms and any suitable number of rings. Aryl groups can be monocyclic, fused to form bicyclic or tricyclic groups, or linked by a bond to form a biaryl group. Representative aryl groups include phenyl, naphthyl and biphenyl. Other aryl groups include benzyl, having a methylene linking group. Some aryl groups have from 6 to 12 ring members, such as phenyl, naphthyl or biphenyl. Other aryl groups have from 6 to 10 ring members, such as phenyl or naphthyl.

"Heterocycloalkyl" and "heteroaryl" refer to a "cycloalkyl" or "aryl" group as described herein, wherein one or more carbon atoms are optionally and independently replaced with heteroatom selected from N, O, and S. "Heteroaryl," by itself or as part of another substituent, refers to a monocyclic or fused bicyclic or tricyclic aromatic ring assembly containing 5 to 16 ring atoms, where from 1 to 5 of the ring atoms are a heteroatom such as N, O or S. Additional heteroatoms can also be useful, including, but not limited to, B, Al, Si and P. The heteroatoms can be oxidized to form moieties such as, but not limited to, -S(O)- and -$S(O)_2$-. Any suitable number of heteroatoms can be included in the heteroaryl groups, such as 1, 2, 3, 4, or 5, or 1 to 2, 1 to 3, 1 to 4, 1 to 5, 2 to 3, 2 to 4, 2 to 5, 3 to 4, or 3 to 5. The heteroaryl group can include groups such as pyrrole, pyridine, imidazole, pyrazole, triazole, tetrazole, pyrazine, pyrimidine, pyridazine, triazine (1,2,3-, 1,2,4- and 1,3,5-isomers), thiophene, furan, thiazole, isothiazole, oxazole, and isoxazole. The heteroaryl groups can also be fused to aromatic ring systems, such as a phenyl ring, to form members including, but not limited to, benzopyrroles such as indole and isoindole, benzopyridines such as quinoline and isoquinoline, benzopyrazine (quinoxaline), benzopyrimidine (quinazoline), benzopyridazines such as phthalazine and cinnoline, benzothiophene, and benzofuran. Other heteroaryl groups include heteroaryl rings linked by a bond, such as bipyridine. Heteroaryl groups can be substituted or unsubstituted. "Substituted

heteroaryl" groups can be substituted with one or more groups selected from halo, hydroxy, amino, oxo (=O), alkylamino, amido, acyl, nitro, cyano, and alkoxy.

The term "heterocycloalkyldiyl" refers to a divalent heterocycloalkyl radical.

Heteroaryl groups can be linked via any position on the ring. For example, pyrrole includes 1-, 2- and 3-pyrrole, pyridine includes 2-, 3- and 4-pyridine, imidazole includes 1-, 2-, 4- and 5-imidazole, pyrazole includes 1-, 3-, 4- and 5-pyrazole, triazole includes 1-, 4- and 5-triazole, tetrazole includes 1- and 5-tetrazole, pyrimidine includes 2-, 4-, 5- and 6- pyrimidine, pyridazine includes 3- and 4-pyridazine, 1,2,3-triazine includes 4- and 5-triazine, 1,2,4-triazine includes 3-, 5- and 6-triazine, 1,3,5-triazine includes 2-triazine, thiophene includes 2- and 3-thiophene, furan includes 2- and 3-furan, thiazole includes 2-, 4- and 5-thiazole, isothiazole includes 3-, 4- and 5-isothiazole, oxazole includes 2-, 4- and 5-oxazole, isoxazole includes 3-, 4- and 5-isoxazole, indole includes 1-, 2- and 3-indole, isoindole includes 1- and 2-isoindole, quinoline includes 2-, 3- and 4-quinoline, isoquinoline includes 1-, 3- and 4-isoquinoline, quinazoline includes 2- and 4-quinoazoline, cinnoline includes 3- and 4-cinnoline, benzothiophene includes 2- and 3-benzothiophene, and benzofuran includes 2- and 3-benzofuran.

The term "heteroaryldiyl" refers to a divalent heteroaryl radical.

"Heterocycloalkyl," by itself or as part of another substituent, refers to a saturated ring system having from 3 to 12 ring members and from 1 to 4 heteroatoms of N, O and S. Additional heteroatoms can also be useful, including, but not limited to, B, Al, Si and P. The heteroatoms can be oxidized to form moieties such as, but not limited to, -S(O)- and -$S(O)_2$-. Heterocycloalkyl groups can include any number of ring atoms, such as, 3 to 6, 4 to 6, 5 to 6, 3 to 8, 4 to 8, 5 to 8, 6 to 8, 3 to 9, 3 to 10, 3 to 11, or 3 to 12 ring members. Any suitable number of heteroatoms can be included in the heterocycloalkyl groups, such as 1, 2, 3, or 4, or 1 to 2, 1 to 3, 1 to 4, 2 to 3, 2 to 4, or 3 to 4. The heterocycloalkyl group can include groups such as aziridine, azetidine, pyrrolidine, piperidine, azepane, azocane, quinuclidine, pyrazolidine, imidazolidine, piperazine (1,2-, 1,3- and 1,4-isomers), oxirane, oxetane, tetrahydrofuran, oxane (tetrahydropyran), oxepane, thiirane, thietane, thiolane (tetrahydrothiophene), thiane (tetrahydrothiopyran), oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, dioxolane, dithiolane, morpholine, thiomorpholine, dioxane, or dithiane. The heterocycloalkyl groups can also be fused to aromatic or non-aromatic ring systems to form members including, but not limited to, indoline. Heterocycloalkyl groups can be unsubstituted or substituted.

Heterocycloalkyl groups can be linked via any position on the ring. For example, aziridine can be 1- or 2-aziridine, azetidine can be 1- or 2- azetidine, pyrrolidine can be 1-, 2- or 3-pyrrolidine, piperidine can be 1-, 2-, 3- or 4-piperidine, pyrazolidine can be 1-, 2-, 3-, or 4-

pyrazolidine, imidazolidine can be 1-, 2-, 3- or 4-imidazolidine, piperazine can be 1-, 2-, 3- or 4-piperazine, tetrahydrofuran can be 1- or 2-tetrahydrofuran, oxazolidine can be 2-, 3-, 4- or 5-oxazolidine, isoxazolidine can be 2-, 3-, 4- or 5-isoxazolidine, thiazolidine can be 2-, 3-, 4- or 5-thiazolidine, isothiazolidine can be 2-, 3-, 4- or 5- isothiazolidine, and morpholine can be 2-, 3- or 4-morpholine.

The term "heterocycloalkyldiyl" refers to a divalent heterocycloalkyl radical.

The terms "halo" and "halogen," by themselves or as part of another substituent, refer to a fluorine, chlorine, bromine, or iodine atom.

The term "carbonyl," by itself or as part of another substituent, refers to C(=O) or –C(=O)–, i.e., a carbon atom double-bonded to oxygen and bound to two other groups in the moiety having the carbonyl.

As used herein, the phrase "quaternary ammonium salt" refers to a tertiary amine that has been quaternized with an alkyl substituent (e.g., a C_1-C_4 alkyl such as methyl, ethyl, propyl, or butyl).

The terms "treat," "treatment," and "treating" refer to any indicia of success in the treatment or amelioration of an injury, pathology, condition (e.g., cancer), or symptom (e.g., cognitive impairment), including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the symptom, injury, pathology, or condition more tolerable to the patient; reduction in the rate of symptom progression; decreasing the frequency or duration of the symptom or condition; or, in some situations, preventing the onset of the symptom. The treatment or amelioration of symptoms can be based on any objective or subjective parameter, including, for example, the result of a physical examination.

The terms "cancer," "neoplasm," and "tumor" are used herein to refer to cells which exhibit autonomous, unregulated growth, such that the cells exhibit an aberrant growth phenotype characterized by a significant loss of control over cell proliferation. Cells of interest for detection, analysis, and/or treatment in the context of the invention include cancer cells (e.g., cancer cells from an individual with cancer), malignant cancer cells, pre-metastatic cancer cells, metastatic cancer cells, and non-metastatic cancer cells. Cancers of virtually every tissue are known. The phrase "cancer burden" refers to the quantum of cancer cells or cancer volume in a subject. Reducing cancer burden accordingly refers to reducing the number of cancer cells or the cancer cell volume in a subject. The term "cancer cell" as used herein refers to any cell that is a cancer cell (e.g., from any of the cancers for which an individual can be treated, e.g., isolated from an individual having cancer) or is derived from a cancer cell, e.g., clone of a cancer cell. For example, a cancer cell can be from an established cancer cell line, can be a primary cell isolated from an individual with cancer, can be a progeny cell from a primary cell

isolated from an individual with cancer, and the like. In some embodiments, the term can also refer to a portion of a cancer cell, such as a sub-cellular portion, a cell membrane portion, or a cell lysate of a cancer cell. Many types of cancers are known to those of skill in the art, including solid tumors such as carcinomas, sarcomas, glioblastomas, melanomas, lymphomas, and myelomas, and circulating cancers such as leukemias.

As used herein, the term "cancer" includes any form of cancer, including but not limited to, solid tumor cancers (e.g., skin, lung, prostate, breast, gastric, bladder, colon, ovarian, pancreas, kidney, liver, glioblastoma, medulloblastoma, leiomyosarcoma, head & neck squamous cell carcinomas, melanomas, and neuroendocrine) and liquid cancers (e.g., hematological cancers); carcinomas; soft tissue tumors; sarcomas; teratomas; melanomas; leukemias; lymphomas; and brain cancers, including minimal residual disease, and including both primary and metastatic tumors.

"PD-L1 expression" refers to a cell that has a PD-L1 receptor on the cell's surface. As used herein "PD-L1 overexpression" refers to a cell that has more PD-L1 receptors as compared to corresponding non-cancer cell.

"HER2" refers to the protein human epidermal growth factor receptor 2.

"HER2 expression" refers to a cell that has a HER2 receptor on the cell's surface. For example, a cell may have from about 20,000 to about 50,000 HER2 receptors on the cell's surface. As used herein "HER2 overexpression" refers to a cell that has more than about 50,000 HER2 receptors. For example, a cell 2, 5, 10, 100, 1,000, 10,000, 100,000, or 1,000,000 times the number of HER2 receptors as compared to corresponding non-cancer cell (e.g., about 1 or 2 million HER2 receptors). It is estimated that HER2 is overexpressed in about 25% to about 30% of breast cancers.

The "pathology" of cancer includes all phenomena that compromise the well-being of the patient. This includes, without limitation, abnormal or uncontrollable cell growth, metastasis, interference with the normal functioning of neighboring cells, release of cytokines or other secretory products at abnormal levels, suppression or aggravation of inflammatory or immunological response, neoplasia, premalignancy, malignancy, and invasion of surrounding or distant tissues or organs, such as lymph nodes.

As used herein, the phrases "cancer recurrence" and "tumor recurrence," and grammatical variants thereof, refer to further growth of neoplastic or cancerous cells after diagnosis of cancer. Particularly, recurrence may occur when further cancerous cell growth occurs in the cancerous tissue. "Tumor spread," similarly, occurs when the cells of a tumor disseminate into local or distant tissues and organs, therefore, tumor spread encompasses tumor metastasis. "Tumor invasion" occurs when the tumor growth spread out locally to compromise

the function of involved tissues by compression, destruction, or prevention of normal organ function.

As used herein, the term "metastasis" refers to the growth of a cancerous tumor in an organ or body part, which is not directly connected to the organ of the original cancerous tumor. Metastasis will be understood to include micrometastasis, which is the presence of an undetectable amount of cancerous cells in an organ or body part that is not directly connected to the organ of the original cancerous tumor. Metastasis can also be defined as several steps of a process, such as the departure of cancer cells from an original tumor site, and migration and/or invasion of cancer cells to other parts of the body.

The phrases "effective amount" and "therapeutically effective amount" refer to a dose or amount of a substance such as an immunoconjugate that produces therapeutic effects for which it is administered. The exact dose will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (see, e.g., Lieberman, *Pharmaceutical Dosage Forms* (vols. 1-3, 1992); Lloyd, *The Art, Science and Technology of Pharmaceutical Compounding* (1999); Pickar, *Dosage Calculations* (1999); *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 11th Edition (McGraw-Hill, 2006); and *Remington: The Science and Practice of Pharmacy*, 22nd Edition, (Pharmaceutical Press, London, 2012)). In the case of cancer, the therapeutically effective amount of the immunoconjugate may reduce the number of cancer cells; reduce the tumor size; inhibit (i.e., slow to some extent and preferably stop) cancer cell infiltration into peripheral organs; inhibit (i.e., slow to some extent and preferably stop) tumor metastasis; inhibit, to some extent, tumor growth; and/or relieve to some extent one or more of the symptoms associated with the cancer. To the extent the immunoconjugate may prevent growth and/or kill existing cancer cells, it may be cytostatic and/or cytotoxic. For cancer therapy, efficacy can, for example, be measured by assessing the time to disease progression (TTP) and/or determining the response rate (RR)

"Recipient," "individual," "subject," "host," and "patient" are used interchangeably and refer to any mammalian subject for whom diagnosis, treatment, or therapy is desired (e.g., humans). "Mammal" for purposes of treatment refers to any animal classified as a mammal, including humans, domestic and farm animals, and zoo, sports, or pet animals, such as dogs, horses, cats, cows, sheep, goats, pigs, camels, etc. In certain embodiments, the mammal is human.

The phrase "synergistic adjuvant" or "synergistic combination" in the context of this invention includes the combination of two immune modulators such as a receptor agonist, cytokine, and adjuvant polypeptide, that in combination elicit a synergistic effect on immunity relative to either administered alone. Particularly, the immunoconjugates disclosed herein

comprise synergistic combinations of the claimed adjuvant and antibody construct. These synergistic combinations upon administration elicit a greater effect on immunity, e.g., relative to when the antibody construct or adjuvant is administered in the absence of the other moiety. Further, a decreased amount of the immunoconjugate may be administered (as measured by the total number of antibody constructs or the total number of adjuvants administered as part of the immunoconjugate) compared to when either the antibody construct or adjuvant is administered alone.

As used herein, the term "administering" refers to parenteral, intravenous, intraperitoneal, intramuscular, intratumoral, intralesional, intranasal, or subcutaneous administration, oral administration, administration as a suppository, topical contact, intrathecal administration, or the implantation of a slow-release device, e.g., a mini-osmotic pump, to the subject.

The terms "about" and "around," as used herein to modify a numerical value, indicate a close range surrounding the numerical value. Thus, if "X" is the value, "about X" or "around X" indicates a value of from 0.9X to 1.1X, e.g., from 0.95X to 1.05X or from 0.99X to 1.01X. A reference to "about X" or "around X" specifically indicates at least the values X, 0.95X, 0.96X, 0.97X, 0.98X, 0.99X, 1.01X, 1.02X, 1.03X, 1.04X, and 1.05X. Accordingly, "about X" and "around X" are intended to teach and provide written description support for a claim limitation of, e.g., "0.98X."

ANTIBODIES

The immunoconjugate of the invention comprises an antibody. Included in the scope of the embodiments of the invention are functional variants of the antibody constructs or antigen binding domain described herein. The term "functional variant" as used herein refers to an antibody construct having an antigen binding domain with substantial or significant sequence identity or similarity to a parent antibody construct or antigen binding domain, which functional variant retains the biological activity of the antibody construct or antigen binding domain of which it is a variant. Functional variants encompass, for example, those variants of the antibody constructs or antigen binding domain described herein (the parent antibody construct or antigen binding domain) that retain the ability to recognize target cells expressing PD-L1, HER2 or CEA to a similar extent, the same extent, or to a higher extent, as the parent antibody construct or antigen binding domain.

In reference to the antibody construct or antigen binding domain, the functional variant can, for instance, be at least about 30%, about 50%, about 75%, about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about

98%, about 99% or more identical in amino acid sequence to the antibody construct or antigen binding domain.

A functional variant can, for example, comprise the amino acid sequence of the parent antibody construct or antigen binding domain with at least one conservative amino acid substitution. Alternatively, or additionally, the functional variants can comprise the amino acid sequence of the parent antibody construct or antigen binding domain with at least one non-conservative amino acid substitution. In this case, it is preferable for the non-conservative amino acid substitution to not interfere with or inhibit the biological activity of the functional variant. The non-conservative amino acid substitution may enhance the biological activity of the functional variant, such that the biological activity of the functional variant is increased as compared to the parent antibody construct or antigen binding domain.

The antibodies comprising the immunoconjugates of the invention include Fc engineered variants. In some embodiments, the mutations in the Fc region that result in modulated binding to one or more Fc receptors can include one or more of the following mutations: SD (S239D), SDIE (S239D/I332E), SE (S267E), SELF (S267E/L328F), SDIE (S239D/I332E), SDIEAL (S239D/I332E/A330L), GA (G236A), ALIE (A330L/I332E), GASDALIE (G236A/S239D/A330L/I332E), V9 (G237D/P238D/P271G/A330R), and V11 (G237D/P238D/H268D/P271G/A330R), and/or one or more mutations at the following amino acids: E345R, E233, G237, P238, H268, P271, L328 and A330. Additional Fc region modifications for modulating Fc receptor binding are described in, for example, U.S. Patent Application Publication 2016/0145350 and U.S. Patents 7,416,726 and 5,624,821, which are hereby incorporated by reference in their entireties herein.

The antibodies comprising the immunoconjugates of the invention include glycan variants, such as afucosylation. In some embodiments, the Fc region of the binding agents are modified to have an altered glycosylation pattern of the Fc region compared to the native non-modified Fc region.

Amino acid substitutions of the inventive antibody constructs or antigen binding domains are preferably conservative amino acid substitutions. Conservative amino acid substitutions are known in the art, and include amino acid substitutions in which one amino acid having certain physical and/or chemical properties is exchanged for another amino acid that has the same or similar chemical or physical properties. For instance, the conservative amino acid substitution can be an acidic/negatively charged polar amino acid substituted for another acidic/negatively charged polar amino acid (e.g., Asp or Glu), an amino acid with a nonpolar side chain substituted for another amino acid with a nonpolar side chain (e.g., Ala, Gly, Val, Ile, Leu, Met, Phe, Pro, Trp, Cys, Val, etc.), a basic/positively charged polar amino acid substituted for another

basic/positively charged polar amino acid (e.g., Lys, His, Arg, etc.), an uncharged amino acid with a polar side chain substituted for another uncharged amino acid with a polar side chain (e.g., Asn, Gln, Ser, Thr, Tyr, etc.), an amino acid with a beta-branched side-chain substituted for another amino acid with a beta-branched side-chain (e.g., Ile, Thr, and Val), an amino acid with an aromatic side-chain substituted for another amino acid with an aromatic side chain (e.g., His, Phe, Trp, and Tyr), etc.

The antibody construct or antigen binding domain can consist essentially of the specified amino acid sequence or sequences described herein, such that other components, e.g., other amino acids, do not materially change the biological activity of the antibody construct or antigen binding domain functional variant.

Methods for generating antibodies are described in, for example, Köhler and Milstein, *Eur. J. Immunol.*, 5: 511-519 (1976); Harlow and Lane (eds.), *Antibodies: A Laboratory Manual*, CSH Press (1988); and Janeway et al. (eds.), *Immunobiology, 9th Ed.*, Garland Publishing, New York, NY (2017). In certain embodiments, a human or chimeric antibody or antibody fragment can be generated using a transgenic animal (e.g., a mouse) wherein one or more endogenous immunoglobulin genes are replaced with one or more human immunoglobulin genes. Examples of transgenic mice wherein endogenous antibody genes are effectively replaced with human antibody genes include, but are not limited to, the Medarex HUMAB-MOUSE™, the Kirin TC MOUSE™, and the Kyowa Kirin KM-MOUSE™ (see, e.g., Lonberg, *Nat. Biotechnol.*, 23(9): 1117-25 (2005), and Lonberg, *Handb. Exp. Pharmacol.*, 181: 69-97 (2008)). A humanized antibody can be generated using any suitable method known in the art (see, e.g., An, Z. (ed.), *Therapeutic Monoclonal Antibodies: From Bench to Clinic*, John Wiley & Sons, Inc., Hoboken, New Jersey (2009)), including, e.g., grafting of non-human CDRs onto a human antibody scaffold (see, e.g., Kashmiri et al., *Methods*, 36(1): 25-34 (2005); and Hou et al., *J. Biochem.*, 144(1): 115-120 (2008) and use of phage display (see, e.g., Fellouse, et al., *Journal of Molecular Biology*, 373(4): 924-940 (2007) and Glanville, et al., PNAS, 106(48): 20216-20221 (2009)).

In an exemplary embodiment, the immunoconjugates of the invention comprise an antibody construct that comprises an antigen binding domain that specifically recognizes and binds PD-L1.

Programmed Death-Ligand 1 (PD-L1, cluster of differentiation 274, CD274, B7-homolog 1, or B7-H1) belongs to the B7 protein superfamily, and is a ligand of programmed cell death protein 1 (PD-1, PDCD1, cluster of differentiation 279, or CD279). PD-L1 can also interact with B7.1 (CD80) and such interaction is believed to inhibit T cell priming. The PD-L1/PD-1 axis plays a large role in suppressing the adaptive immune response. More

specifically, it is believed that engagement of PD-L1 with its receptor, PD-1, delivers a signal that inhibits activation and proliferation of T-cells. Agents that bind to PD-L1 and prevent the ligand from binding to the PD-1 receptor prevent this immunosuppression, and can, therefore, enhance an immune response when desired, such as for the treatment of cancers, or infections. PD-L1/PD-1 pathway also contributes to preventing autoimmunity and therefore agonistic agents against PD-L1 or agents that deliver immune inhibitory payloads may help treatment of autoimmune disorders.

Several antibodies targeting PD-L1 have been developed for the treatment of cancer, including atezolizumab (TECENTRIQ™), durvalumab (IMFINZI™), and avelumab (BAVENCIO™). Nevertheless, there continues to be a need for new PD-L1-binding agents, including agents that bind PD-L1 with high affinity and effectively prevent PD-L1/PD-1 signaling and agents that can deliver therapeutic payloads to PD-L1 expressing cells. In addition, there is a need for new PD-L1-binding agents to treat autoimmune disorders and infections.

A method is provided of delivering an aminobenzazepine derivative payload to a cell expressing PD-L1 comprising administering to the cell, or mammal comprising the cell, an immunoconjugate comprising an anti-PD-L1 antibody covalently attached to a linker which is covalently attached to one or more aminobenzazepine moieties.

Also provided is a method for enhancing or reducing or inhibiting an immune response in a mammal, and a method for treating a disease, disorder, or condition in a mammal that is responsive to PD-L1 inhibition, which methods comprise administering a PD-L1 immunoconjugate thereof, to the mammal.

The invention provides a PD-L1 binding agent comprising an immunoglobulin heavy chain variable region polypeptide and an immunoglobulin light chain variable region polypeptide.

The PD-L1 binding agent specifically binds PD-L1. The binding specificity of the agent allows for targeting PD-L1 expressing cells, for instance, to deliver therapeutic payloads to such cells.

In some embodiments, the PD-L1 binding agent (Type A or Type B) binds to human PD-L1, for example, a protein comprising SEQ ID NO: 307. However, binding agents that bind to any PD-L1 homolog or paralog also are encompassed. In some embodiments, the PD-L1 protein comprises at least about 70%, about 75%, about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or more sequence identity to SEQ ID NO: 307. In some embodiments, the binding agent binds human PD-L1 and cynomolgus PD-L1; or human, cynomolgus and mouse PD-L1.

MRIFAVFIFMTYWHLLNAFTVTVPKDLYVVEYGSNMTIECKFPVEKQLDLAALI
VYWEMEDKNIIQFVHGEEDLKVQHSSYRQRARLLKDQLSLGNAALQITDVKLQD
AGVYRCMISYGGADYKRITVKVNAPYNKINQRILVVDPVTSEHELTCQAEGYPK
AEVIWTSSDHQVLSGKTTTTNSKREEKLFNVTSTLRINTTTNEIFYCTFRRLDP
EENHTAELVIPELPLAHPPNERTHLVILGAILLCLGVALTFIFRLRKGRMMDVK
KCGIQDTNSKKQSDTHLEET SEQ ID NO: 307

In some embodiments, the PD-L1 binding agent binds PD-L1 without substantially inhibiting or preventing PD-L1 from binding to its receptor, PD-1. However, in other embodiments, the PD-L1 binding agent can completely or partially block (inhibit or prevent) binding of PD-L1 to its receptor, PD-1, such that the antibody can be used to inhibit PD-L1/PD-1 signaling (e.g., for therapeutic purposes).

The antibody or antigen-binding antibody fragment can be monospecific for PD-L1, or can be bispecific or multi-specific. For instance, in bivalent or multivalent antibodies or antibody fragments, the binding domains can be different targeting different epitopes of the same antigen or targeting different antigens. Methods of constructing multivalent binding constructs are known in the art. Bispecific and multispecific antibodies are known in the art. Furthermore, a diabody, triabody, or tetrabody can be provided, which is a dimer, trimer, or tetramer of polypeptide chains each comprising a V_H connected to a V_L by a peptide linker that is too short to allow pairing between the V_H and V_L on the same polypeptide chain, thereby driving the pairing between the complementary domains on different V_H -V_L polypeptide chains to generate a multimeric molecule having two, three, or four functional antigen binding sites. Also, bis-scFv fragments, which are small scFv fragments with two different variable domains can be generated to produce bispecific bis-scFv fragments capable of binding two different epitopes. Fab dimers (Fab2) and Fab trimers (Fab3) can be produced using genetic engineering methods to create multispecific constructs based on Fab fragments.

The PD-L1-binding agent also can be an antibody conjugate. In this respect, the PD-L1-binding agent can be a conjugate of (1) an antibody, an alternative scaffold, or fragments thereof, and (2) a protein or non-protein moiety. For example, the PD-L1 binding agent can be conjugated to a peptide, a fluorescent molecule, chemotherapeutic or other cytotoxic payload, immune-activating or immune-suppressive agent.

The PD-L1-binding agent can be, or can be obtained from, a human antibody, a non-human antibody, a humanized antibody, or a chimeric antibody, or corresponding antibody fragments. A “chimeric” antibody is an antibody or fragment thereof typically comprising human constant regions and non-human variable regions. A “humanized” antibody is a monoclonal antibody typically comprising a human antibody scaffold but with non-human origin amino acids or sequences in at least one CDR (e.g., 1, 2, 3, 4, 5, or all six CDRs).

PD-L1-binding agents – Type A

Provided herein are PD-L1 binding agents comprising an immunoglobulin heavy chain variable region polypeptide and an immunoglobulin light chain variable region polypeptide. In some embodiments, the PD-L1 binding agents (Type A) comprise an immunoglobulin heavy chain variable region of any one of SEQ ID NOs: 223-264, or at least the CDRs thereof; and an immunoglobulin light chain variable region of any one of SEQ ID NOs: 265-306 or at least the CDRs thereof. In other embodiments, the PD-L1 binding agents (Type A) comprise an immunoglobulin heavy chain variable region polypeptide with an amino acid sequence that is at least 90% identical to any one of SEQ ID NOs: 223-264, and an immunoglobulin light chain variable region polypeptide with an amino acid sequence that is at least 90% identical to any one of SEQ ID NOs: 265-306. In yet other embodiments, the PD-L1 binding agent (Type A), the immunoglobulin heavy chain variable region polypeptide comprises a complementarity determining region 1 (HCDR1) comprising any one of SEQ ID NOs: 1-23, a complementarity determining region 2 (HCDR2) comprising any one of SEQ ID NOs: 24-57, and a complementarity determining region 3 (HCDR3) comprising any one of SEQ ID NOs: 58-95; and/or the immunoglobulin light chain variable region polypeptide comprises a complementarity determining region 1 (LCDR1) comprising any one of SEQ ID NOs: 96-128, a complementarity determining region 2 (LCDR2) comprising any one of SEQ ID NOs: 129-151, and a complementarity determining region 3 (LCDR3) comprising any one of SEQ ID NOs: 152-155. Also provided are nucleic acids encoding the PD-L1 binding agents, or the individual heavy and light chains thereof; vectors and cells comprising the nucleic acids; and compositions comprising the binding agents or nucleic acids.

Furthermore, in some embodiments, the PD-L1 binding agents (Type A) provided herein cause cellular internalization of PD-L1 or the PD-L1/PD-L1 binding agent complex upon binding to PD-L1 on the cell surface. Without wishing to be bound by any particular theory or mechanism of action, it is believed that the PD-L1 binding agents according to this embodiment cause PD-L1 internalization upon binding, and remain bound to PD-L1 during internalization resulting in internalization of the binding agent along with PD-L1. Cellular internalization of PD-L1 and bound PD-L1 binding agent can be determined by any suitable method, such as assaying for persistence on the cell surface and/or detection of internalized antibodies. In some embodiments, the PD-L1 binding agent internalizes strongly enough that at least about 25% (e.g., at least about 35%, at least about 50%, at least about 75%, or at least about 90%) of the PD-L1 binding agent that binds PD-L1 on the cell surface is internalized (e.g., using a surface persistence assay, about 75% or less, about 65% or less, about 50% or less, about 25% or less or

about 10% or less of PD-L1 binding agent molecules bound to PD-L1 on the cell surface at the beginning of the assay remain bound at the end of the assay).

In an embodiment, the PD-L1 binding agent (Type A) comprises an immunoglobulin heavy chain variable region of any one of SEQ ID NOs: 223-264, a sequence that is at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% identical to SEQ ID NOs: 223-264, or at least the CDRs thereof; and/or an immunoglobulin light chain variable region of any one of SEQ ID NOs: 265-306, a sequence that is at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% identical to SEQ ID NOs: 265-306, or at least the CDRs thereof.

By way of further illustration, the PD-L1 binding agent (Type A) can comprise:

(1) an immunoglobulin heavy chain variable region of SEQ ID NO: 223, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 265, or at least the CDRs thereof;

(2) an immunoglobulin heavy chain variable region of SEQ ID NO: 224, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 266, or at least the CDRs thereof;

(3) an immunoglobulin heavy chain variable region of SEQ ID NO: 225, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 267, or at least the CDRs thereof;

(4) an immunoglobulin heavy chain variable region of SEQ ID NO: 226, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 268, or at least the CDRs thereof;

(5) an immunoglobulin heavy chain variable region of SEQ ID NO: 227, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 269, or at least the CDRs thereof;

(6) an immunoglobulin heavy chain variable region of SEQ ID NO: 228, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 270, or at least the CDRs thereof;

(7) an immunoglobulin heavy chain variable region of SEQ ID NO: 229, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 271, or at least the CDRs thereof;

(8) an immunoglobulin heavy chain variable region of SEQ ID NO: 230, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 272, or at least the CDRs thereof;

(9) an immunoglobulin heavy chain variable region of SEQ ID NO: 231, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 273, or at least the CDRs thereof;

(10) an immunoglobulin heavy chain variable region of SEQ ID NO: 232, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 274, or at least the CDRs thereof;

(11) an immunoglobulin heavy chain variable region of SEQ ID NO: 233, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 275, or at least the CDRs thereof;

(12) an immunoglobulin heavy chain variable region of SEQ ID NO: 234, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 276, or at least the CDRs thereof;

(13) an immunoglobulin heavy chain variable region of SEQ ID NO: 235, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 277, or at least the CDRs thereof;

(14) an immunoglobulin heavy chain variable region of SEQ ID NO: 236, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 278, or at least the CDRs thereof;

(15) an immunoglobulin heavy chain variable region of SEQ ID NO: 237, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 279, or at least the CDRs thereof;

(16) an immunoglobulin heavy chain variable region of SEQ ID NO: 238, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 280, or at least the CDRs thereof;

(17) an immunoglobulin heavy chain variable region of SEQ ID NO: 239, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 281, or at least the CDRs thereof;

(18) an immunoglobulin heavy chain variable region of SEQ ID NO: 240, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 282, or at least the CDRs thereof;

(19) an immunoglobulin heavy chain variable region of SEQ ID NO: 241, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 283, or at least the CDRs thereof;

(20) an immunoglobulin heavy chain variable region of SEQ ID NO: 242, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 284, or at least the CDRs thereof;

(21) an immunoglobulin heavy chain variable region of SEQ ID NO: 243, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 285, or at least the CDRs thereof;

(22) an immunoglobulin heavy chain variable region of SEQ ID NO: 244, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 286, or at least the CDRs thereof;

(23) an immunoglobulin heavy chain variable region of SEQ ID NO: 245, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 287, or at least the CDRs thereof;

(24) an immunoglobulin heavy chain variable region of SEQ ID NO: 246, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 288, or at least the CDRs thereof;

(25) an immunoglobulin heavy chain variable region of SEQ ID NO: 247, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 289, or at least the CDRs thereof;

(26) an immunoglobulin heavy chain variable region of SEQ ID NO: 248, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 290, or at least the CDRs thereof;

(27) an immunoglobulin heavy chain variable region of SEQ ID NO: 249, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 291, or at least the CDRs thereof;

(28) an immunoglobulin heavy chain variable region of SEQ ID NO: 250, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 292, or at least the CDRs thereof;

(29) an immunoglobulin heavy chain variable region of SEQ ID NO: 251, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 293, or at least the CDRs thereof;

(30) an immunoglobulin heavy chain variable region of SEQ ID NO: 252, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 294, or at least the CDRs thereof;

(31) an immunoglobulin heavy chain variable region of SEQ ID NO: 253, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 295, or at least the CDRs thereof;

(32) an immunoglobulin heavy chain variable region of SEQ ID NO: 254, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 296, or at least the CDRs thereof;

(33) an immunoglobulin heavy chain variable region of SEQ ID NO: 255, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 297, or at least the CDRs thereof;

(34) an immunoglobulin heavy chain variable region of SEQ ID NO: 256, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 298, or at least the CDRs thereof;

(35) an immunoglobulin heavy chain variable region of SEQ ID NO: 257, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 299, or at least the CDRs thereof;

(36) an immunoglobulin heavy chain variable region of SEQ ID NO: 258, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 300, or at least the CDRs thereof;

(37) an immunoglobulin heavy chain variable region of SEQ ID NO: 259, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 301, or at least the CDRs thereof;

(38) an immunoglobulin heavy chain variable region of SEQ ID NO: 260, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 302, or at least the CDRs thereof;

(39) an immunoglobulin heavy chain variable region of SEQ ID NO: 261, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 303, or at least the CDRs thereof;

(40) an immunoglobulin heavy chain variable region of SEQ ID NO: 262, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 304, or at least the CDRs thereof;

(41) an immunoglobulin heavy chain variable region of SEQ ID NO: 263, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 305, or at least the CDRs thereof;

(42) an immunoglobulin heavy chain variable region of SEQ ID NO: 164, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 306, or at least the CDRs thereof; and/or

(43) an immunoglobulin heavy chain variable region of Figures 4A-D and/or an immunoglobulin light chain variable region of Figures 4E-G, or at least the CDRs thereof.

The CDRs of a given heavy or light chain Ig sequence can be determined in accordance with any of the various known Ig numbering schemes (e.g., Kabat, Chothia, Martin (Enhanced Chothia), IGMT, AbM). In certain embodiments, the PD-L1 binding agent (Type A) comprises one or more of the following CDRs:

a HCDR1 comprising or consisting of any one of SEQ ID NOs: 1-23 or a sequence that is at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% identical to SEQ ID NOs: 1-23;

a HCDR2 comprising or consisting of any one of SEQ ID NOs: 24-57 or a sequence that is at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% identical to SEQ ID NOs: 24-57; and

a HCDR3 comprising or consisting of any one of SEQ ID NOs: 58-95 or a sequence that is at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% identical to SEQ ID NOs: 58-95; and/or the immunoglobulin light chain polypeptide comprises

a LCDR1 comprising or consisting of any one of SEQ ID NOs: 96-128 or a sequence that is at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% identical to SEQ ID NOs: 96-128;

a LCDR2 comprising or consisting of any one of SEQ ID NOs: 129-151 or a sequence that is at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% identical to SEQ ID NOs: 129-151; and

a LCDR3 comprising or consisting of any one of SEQ ID NOs: 152-155 or a sequence that is at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least

about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% identical to SEQ ID NOs: 152-155.

In particular embodiments, the binding agent (Type A) comprises an immunoglobulin heavy chain polypeptide and an immunoglobulin light chain polypeptide, wherein:

(1) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 1, a HCDR2 comprising or consisting of SEQ ID NO: 24, and a HCDR3 comprising or consisting of SEQ ID NO: 58; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 96, a LCDR2 comprising or consisting of SEQ ID NO: 129, and a LCDR3 comprising or consisting of SEQ ID NO: 152;

(2) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 2, a HCDR2 comprising or consisting of SEQ ID NO: 25, and a HCDR3 comprising or consisting of SEQ ID NO: 59; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 97, a LCDR2 comprising or consisting of SEQ ID NO: 129, and a LCDR3 comprising or consisting of SEQ ID NO: 153;

(3) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 3, a HCDR2 comprising or consisting of SEQ ID NO: 26, and a HCDR3 comprising or consisting of SEQ ID NO: 60; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 98, a LCDR2 comprising or consisting of SEQ ID NO: 129, and a LCDR3 comprising or consisting of SEQ ID NO: 154;

(4) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 4, a HCDR2 comprising or consisting of SEQ ID NO: 27, and a HCDR3 comprising or consisting of SEQ ID NO: 61; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 99, a LCDR2 comprising or consisting of SEQ ID NO: 130, and a LCDR3 comprising or consisting of SEQ ID NO: 155;

(5) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 5, a HCDR2 comprising or consisting of SEQ ID NO: 28, and a HCDR3 comprising or consisting of SEQ ID NO: 62; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 100, a LCDR2 comprising or consisting of SEQ ID NO: 129, and a LCDR3 comprising or consisting of SEQ ID NO: 153;

(6) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 6, a HCDR2 comprising or consisting of SEQ ID NO: 29, and a HCDR3 comprising or consisting of SEQ ID NO: 63; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 101, a LCDR2 comprising or consisting of SEQ ID NO: 131, and a LCDR3 comprising or consisting of SEQ ID NO: 156;

(7) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 7, a HCDR2 comprising or consisting of SEQ ID NO: 30, and a HCDR3 comprising or consisting of SEQ ID NO: 64; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 102, a LCDR2 comprising or consisting of SEQ ID NO: 132, and a LCDR3 comprising or consisting of SEQ ID NO: 157;

(8) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 2, a HCDR2 comprising or consisting of SEQ ID NO: 31, and a HCDR3 comprising or consisting of SEQ ID NO: 65; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 103, a LCDR2 comprising or consisting of SEQ ID NO: 133, and a LCDR3 comprising or consisting of SEQ ID NO: 155;

(9) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 8, a HCDR2 comprising or consisting of SEQ ID NO: 32, and a HCDR3 comprising or consisting of SEQ ID NO: 66; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 104, a LCDR2 comprising or consisting of SEQ ID NO: 134, and a LCDR3 comprising or consisting of SEQ ID NO: 158;

(10) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 9, a HCDR2 comprising or consisting of SEQ ID NO: 33, and a HCDR3 comprising or consisting of SEQ ID NO: 67; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 97, a LCDR2 comprising or consisting of SEQ ID NO: 135, and a LCDR3 comprising or consisting of SEQ ID NO: 159;

(11) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 7, a HCDR2 comprising or consisting of SEQ ID NO: 34, and a HCDR3 comprising or consisting of SEQ ID NO: 64; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 102, a LCDR2

comprising or consisting of SEQ ID NO: 132, and a LCDR3 comprising or consisting of SEQ ID NO: 160;

(12) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 10, a HCDR2 comprising or consisting of SEQ ID NO: 35, and a HCDR3 comprising or consisting of SEQ ID NO: 68; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 105, a LCDR2 comprising or consisting of SEQ ID NO: 136, and a LCDR3 comprising or consisting of SEQ ID NO: 161;

(13) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 2, a HCDR2 comprising or consisting of SEQ ID NO: 25, and a HCDR3 comprising or consisting of SEQ ID NO: 69; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 106, a LCDR2 comprising or consisting of SEQ ID NO: 129, and a LCDR3 comprising or consisting of SEQ ID NO: 162;

(14) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 11, a HCDR2 comprising or consisting of SEQ ID NO: 36, and a HCDR3 comprising or consisting of SEQ ID NO: 70; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 107, a LCDR2 comprising or consisting of SEQ ID NO: 129, and a LCDR3 comprising or consisting of SEQ ID NO: 163;

(15) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 12, a HCDR2 comprising or consisting of SEQ ID NO: 37, and a HCDR3 comprising or consisting of SEQ ID NO: 71; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 108, a LCDR2 comprising or consisting of SEQ ID NO: 137, and a LCDR3 comprising or consisting of SEQ ID NO: 164;

(16) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 1, a HCDR2 comprising or consisting of SEQ ID NO: 38, and a HCDR3 comprising or consisting of SEQ ID NO: 72; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 109, a LCDR2 comprising or consisting of SEQ ID NO: 138, and a LCDR3 comprising or consisting of SEQ ID NO: 165;

(17) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 13, a HCDR2 comprising or consisting of SEQ ID NO: 39, and a HCDR3 comprising or consisting of SEQ ID NO: 73; and/or the immunoglobulin light chain

polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 98, a LCDR2 comprising or consisting of SEQ ID NO: 129, and a LCDR3 comprising or consisting of SEQ ID NO: 155;

(18) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 2, a HCDR2 comprising or consisting of SEQ ID NO: 40, and a HCDR3 comprising or consisting of SEQ ID NO: 74; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 110, a LCDR2 comprising or consisting of SEQ ID NO: 137, and a LCDR3 comprising or consisting of SEQ ID NO: 166;

(19) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 14, a HCDR2 comprising or consisting of SEQ ID NO: 41, and a HCDR3 comprising or consisting of SEQ ID NO: 75; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 111, a LCDR2 comprising or consisting of SEQ ID NO: 129, and a LCDR3 comprising or consisting of SEQ ID NO: 165;

(20) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 15, a HCDR2 comprising or consisting of SEQ ID NO: 42, and a HCDR3 comprising or consisting of SEQ ID NO: 74; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 97, a LCDR2 comprising or consisting of SEQ ID NO: 139, and a LCDR3 comprising or consisting of SEQ ID NO: 152;

(21) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 14, a HCDR2 comprising or consisting of SEQ ID NO: 43, and a HCDR3 comprising or consisting of SEQ ID NO: 76; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 112, a LCDR2 comprising or consisting of SEQ ID NO: 137, and a LCDR3 comprising or consisting of SEQ ID NO: 155;

(22) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 16, a HCDR2 comprising or consisting of SEQ ID NO: 44, and a HCDR3 comprising or consisting of SEQ ID NO: 77; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 113, a LCDR2 comprising or consisting of SEQ ID NO: 140, and a LCDR3 comprising or consisting of SEQ ID NO: 165;

(23) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 9, a HCDR2 comprising or consisting of SEQ ID NO: 45, and a

HCDR3 comprising or consisting of SEQ ID NO: 78; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 114, a LCDR2 comprising or consisting of SEQ ID NO: 141, and a LCDR3 comprising or consisting of SEQ ID NO: 165;

(24) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 17, a HCDR2 comprising or consisting of SEQ ID NO: 46, and a HCDR3 comprising or consisting of SEQ ID NO: 79; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 98, a LCDR2 comprising or consisting of SEQ ID NO: 129, and a LCDR3 comprising or consisting of SEQ ID NO: 155;

(25) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 9, a HCDR2 comprising or consisting of SEQ ID NO: 25, and a HCDR3 comprising or consisting of SEQ ID NO: 80; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 115, a LCDR2 comprising or consisting of SEQ ID NO: 142, and a LCDR3 comprising or consisting of SEQ ID NO: 165;

(26) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 17, a HCDR2 comprising or consisting of SEQ ID NO: 41, and a HCDR3 comprising or consisting of SEQ ID NO: 81; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 116, a LCDR2 comprising or consisting of SEQ ID NO: 143, and a LCDR3 comprising or consisting of SEQ ID NO: 167;

(27) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 7, a HCDR2 comprising or consisting of SEQ ID NO: 47, and a HCDR3 comprising or consisting of SEQ ID NO: 82; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 117, a LCDR2 comprising or consisting of SEQ ID NO: 144, and a LCDR3 comprising or consisting of SEQ ID NO: 155;

(28) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 2, a HCDR2 comprising or consisting of SEQ ID NO: 41, and a HCDR3 comprising or consisting of SEQ ID NO: 83; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 118, a LCDR2 comprising or consisting of SEQ ID NO: 131, and a LCDR3 comprising or consisting of SEQ ID NO: 168;

(29) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 18, a HCDR2 comprising or consisting of SEQ ID NO: 48, and a HCDR3 comprising or consisting of SEQ ID NO: 84; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 119, a LCDR2 comprising or consisting of SEQ ID NO: 145, and a LCDR3 comprising or consisting of SEQ ID NO: 165;

(30) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 19, a HCDR2 comprising or consisting of SEQ ID NO: 49, and a HCDR3 comprising or consisting of SEQ ID NO: 85; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 120, a LCDR2 comprising or consisting of SEQ ID NO: 146, and a LCDR3 comprising or consisting of SEQ ID NO: 155;

(31) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 2, a HCDR2 comprising or consisting of SEQ ID NO: 50, and a HCDR3 comprising or consisting of SEQ ID NO: 86; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 121, a LCDR2 comprising or consisting of SEQ ID NO: 147, and a LCDR3 comprising or consisting of SEQ ID NO: 169;

(32) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 2, a HCDR2 comprising or consisting of SEQ ID NO: 51, and a HCDR3 comprising or consisting of SEQ ID NO: 87; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 122, a LCDR2 comprising or consisting of SEQ ID NO: 137, and a LCDR3 comprising or consisting of SEQ ID NO: 155;

(33) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 20, a HCDR2 comprising or consisting of SEQ ID NO: 44, and a HCDR3 comprising or consisting of SEQ ID NO: 88; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 123, a LCDR2 comprising or consisting of SEQ ID NO: 148, and a LCDR3 comprising or consisting of SEQ ID NO: 170;

(34) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 3, a HCDR2 comprising or consisting of SEQ ID NO: 52, and a HCDR3 comprising or consisting of SEQ ID NO: 60; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 98, a LCDR2

comprising or consisting of SEQ ID NO: 129, and a LCDR3 comprising or consisting of SEQ ID NO: 171;

(35) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 2, a HCDR2 comprising or consisting of SEQ ID NO: 53, and a HCDR3 comprising or consisting of SEQ ID NO: 89; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 97, a LCDR2 comprising or consisting of SEQ ID NO: 147, and a LCDR3 comprising or consisting of SEQ ID NO: 172;

(36) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 21, a HCDR2 comprising or consisting of SEQ ID NO: 38, and a HCDR3 comprising or consisting of SEQ ID NO: 90; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 109, a LCDR2 comprising or consisting of SEQ ID NO: 150, and a LCDR3 comprising or consisting of SEQ ID NO: 165;

(37) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 22, a HCDR2 comprising or consisting of SEQ ID NO: 41, and a HCDR3 comprising or consisting of SEQ ID NO: 91; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 124, a LCDR2 comprising or consisting of SEQ ID NO: 151, and a LCDR3 comprising or consisting of SEQ ID NO: 173;

(38) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 2, a HCDR2 comprising or consisting of SEQ ID NO: 54, and a HCDR3 comprising or consisting of SEQ ID NO: 92; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 126, a LCDR2 comprising or consisting of SEQ ID NO: 129, and a LCDR3 comprising or consisting of SEQ ID NO: 165;

(39) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 2, a HCDR2 comprising or consisting of SEQ ID NO: 55, and a HCDR3 comprising or consisting of SEQ ID NO: 93; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 97, a LCDR2 comprising or consisting of SEQ ID NO: 149, and a LCDR3 comprising or consisting of SEQ ID NO: 174;

(40) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 23, a HCDR2 comprising or consisting of SEQ ID NO: 56, and a HCDR3 comprising or consisting of SEQ ID NO: 94; and/or the immunoglobulin light chain

polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 125, a LCDR2 comprising or consisting of SEQ ID NO: 142, and a LCDR3 comprising or consisting of SEQ ID NO: 175;

(41) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 14, a HCDR2 comprising or consisting of SEQ ID NO: 43, and a HCDR3 comprising or consisting of SEQ ID NO: 76; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 127, a LCDR2 comprising or consisting of SEQ ID NO: 137, and a LCDR3 comprising or consisting of SEQ ID NO: 176;

(42) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 3, a HCDR2 comprising or consisting of SEQ ID NO: 57, and a HCDR3 comprising or consisting of SEQ ID NO: 95; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 128, a LCDR2 comprising or consisting of SEQ ID NO: 137, and a LCDR3 comprising or consisting of SEQ ID NO: 155; and/or

(43) the immunoglobulin heavy chain polypeptide and light chain polypeptide comprises any combination of the CDRs listed in Figures 1A-D of PD-L1 Type A binding agents 1-42

In particular embodiments, the binding agent comprises an immunoglobulin heavy chain polypeptide and an immunoglobulin light chain polypeptide, wherein the immunoglobulin heavy chain polypeptide comprises a first framework region, a second framework region, a third framework region, and/or a fourth framework region; and/or the immunoglobulin light chain polypeptide comprises a first framework region, a second framework region, a third framework region, and/or a fourth framework region; and/or the immunoglobulin heavy chain polypeptide and light chain polypeptide comprises any combination of the framework regions listed in Figures 2A-D and Figures 3A-D, respectively.

PD-L1-binding agents – Type B

Provided herein are PD-L1 binding agents (Type B) comprising an immunoglobulin heavy chain variable region polypeptide and an immunoglobulin light chain variable region polypeptide. In some embodiments, the PD-L1 binding agents (Type B) comprise an immunoglobulin heavy chain variable region of any one of SEQ ID NOs: 430-450, or at least the CDRs thereof; and an immunoglobulin light chain variable region of any one of SEQ ID NOs: 451-471, or at least the CDRs thereof. In other embodiments, the PD-L1 binding agents comprise an immunoglobulin heavy chain variable region polypeptide with an amino acid sequence that is at least 90% identical to any one of SEQ ID NOs: 430-450, and an

immunoglobulin light chain variable region polypeptide with an amino acid sequence that is at least 90% identical to any one of SEQ ID NOs: 451-471. In yet other embodiments, the PD-L1 binding agent, the immunoglobulin heavy chain variable region polypeptide comprises a complementarity determining region 1 (HCDR1) comprising any one of SEQ ID NOs: 308-321, a complementarity determining region 2 (HCDR2) comprising any one of SEQ ID NOs: 322-338, and a complementarity determining region 3 (HCDR3) comprising any one of SEQ ID NOs: 339-359; and/or the immunoglobulin light chain variable region polypeptide comprises a complementarity determining region 1 (LCDR1) comprising any one of SEQ ID NOs: 360-374, a complementarity determining region 2 (LCDR2) comprising any one of SEQ ID NOs: 131 and 375-386, and a complementarity determining region 3 (LCDR3) comprising any one of SEQ ID NOs: 387-398. Also provided are nucleic acids encoding the PD-L1 binding agents, or the individual heavy and light chains thereof; vectors and cells comprising the nucleic acids; and compositions comprising the binding agents or nucleic acids.

In an embodiment, the PD-L1 binding agent (Type B) comprises an immunoglobulin heavy chain variable region of any one of SEQ ID NOs: 430-450, a sequence that is at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% identical to SEQ ID NOs: 430-450, or at least the CDRs thereof; and/or an immunoglobulin light chain variable region of any one of SEQ ID NOs: 451-471, a sequence that is at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% identical to SEQ ID NOs: 451-471, or at least the CDRs thereof.

By way of further illustration, the PD-L1 binding agent (Type B) can comprise:

(1) an immunoglobulin heavy chain variable region of SEQ ID NO: 429, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 450, or at least the CDRs thereof;

(2) an immunoglobulin heavy chain variable region of SEQ ID NO: 430, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 451, or at least the CDRs thereof;

(3) an immunoglobulin heavy chain variable region of SEQ ID NO: 431, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 452, or at least the CDRs thereof;

(4) an immunoglobulin heavy chain variable region of SEQ ID NO: 432, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 453, or at least the CDRs thereof;

(5) an immunoglobulin heavy chain variable region of SEQ ID NO: 433, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 454, or at least the CDRs thereof;

(6) an immunoglobulin heavy chain variable region of SEQ ID NO: 434, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 455, or at least the CDRs thereof;

(7) an immunoglobulin heavy chain variable region of SEQ ID NO: 435, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 456, or at least the CDRs thereof;

(8) an immunoglobulin heavy chain variable region of SEQ ID NO: 436, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 457, or at least the CDRs thereof;

(9) an immunoglobulin heavy chain variable region of SEQ ID NO: 437, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 458, or at least the CDRs thereof;

(10) an immunoglobulin heavy chain variable region of SEQ ID NO: 438, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 459, or at least the CDRs thereof;

(11) an immunoglobulin heavy chain variable region of SEQ ID NO: 439, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 460, or at least the CDRs thereof;

(12) an immunoglobulin heavy chain variable region of SEQ ID NO: 440, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 461, or at least the CDRs thereof;

(13) an immunoglobulin heavy chain variable region of SEQ ID NO: 441, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 462, or at least the CDRs thereof;

(14) an immunoglobulin heavy chain variable region of SEQ ID NO: 442, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 463, or at least the CDRs thereof;

(15) an immunoglobulin heavy chain variable region of SEQ ID NO: 443, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 464, or at least the CDRs thereof;

(16) an immunoglobulin heavy chain variable region of SEQ ID NO: 444, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 465, or at least the CDRs thereof;

(17) an immunoglobulin heavy chain variable region of SEQ ID NO: 445, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 466, or at least the CDRs thereof;

(18) an immunoglobulin heavy chain variable region of SEQ ID NO: 446, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 467, or at least the CDRs thereof;

(19) an immunoglobulin heavy chain variable region of SEQ ID NO: 447, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 468, or at least the CDRs thereof;

(20) an immunoglobulin heavy chain variable region of SEQ ID NO: 448, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 469, or at least the CDRs thereof; and/or

(21) an immunoglobulin heavy chain variable region of SEQ ID NO: 449, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 470, or at least the CDRs thereof; and/or

(22) an immunoglobulin heavy chain variable region of Figures 8A-B and/or an immunoglobulin light chain variable region of Figures 8C-D, or at least the CDRs thereof.

The CDRs of a given heavy or light chain Ig sequence can be determined in accordance with any of the various known Ig numbering schemes (e.g., Kabat, Chothia, Martin (Enhanced Chothia), IGMT, AbM). In certain embodiments, the PD-L1 binding agent comprises one or more of the following CDRs:

a HCDR1 comprising or consisting of any one of SEQ ID NOs: 308-321 or a sequence that is at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% identical to SEQ ID NOs: 308-321;

a HCDR2 comprising or consisting of any one of SEQ ID NOs: 322-338 or a sequence that is at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% identical to SEQ ID NOs: 322-338; and

a HCDR3 comprising or consisting of any one of SEQ ID NOs: 339-359 or a sequence that is at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at

least about 99% identical to SEQ ID NOs: 339-359; and/or the immunoglobulin light chain polypeptide comprises

a LCDR1 comprising or consisting of any one of SEQ ID NOs: 360-374 or a sequence that is at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% identical to SEQ ID NOs: 360-374;

a LCDR2 comprising or consisting of any one of SEQ ID NOs: 375-386 or a sequence that is at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% identical to SEQ ID NOs: 375-386; and

a LCDR3 comprising or consisting of any one of SEQ ID NOs: 387-398 or a sequence that is at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% identical to SEQ ID NOs: 387-398.

In particular embodiments, the binding agent comprises an immunoglobulin heavy chain polypeptide and an immunoglobulin light chain polypeptide, wherein:

(1) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 308, a HCDR2 comprising or consisting of SEQ ID NO: 322, and a HCDR3 comprising or consisting of SEQ ID NO: 339; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 360, a LCDR2 comprising or consisting of SEQ ID NO: 375, and a LCDR3 comprising or consisting of SEQ ID NO: 387;

(2) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 309, a HCDR2 comprising or consisting of SEQ ID NO: 323, and a HCDR3 comprising or consisting of SEQ ID NO: 340; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 361, a LCDR2 comprising or consisting of SEQ ID NO: 376, and a LCDR3 comprising or consisting of SEQ ID NO: 388;

(3) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 310, a HCDR2 comprising or consisting of SEQ ID NO: 324, and a HCDR3 comprising or consisting of SEQ ID NO: 341; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 360, a LCDR2 comprising or consisting of SEQ ID NO: 375, and a LCDR3 comprising or consisting of SEQ ID NO: 387;

(4) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 311, a HCDR2 comprising or consisting of SEQ ID NO: 325, and a HCDR3 comprising or consisting of SEQ ID NO: 342; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 362, a LCDR2 comprising or consisting of SEQ ID NO: 377, and a LCDR3 comprising or consisting of SEQ ID NO: 389;

(5) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 312, a HCDR2 comprising or consisting of SEQ ID NO: 326, and a HCDR3 comprising or consisting of SEQ ID NO: 343; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 360, a LCDR2 comprising or consisting of SEQ ID NO: 378, and a LCDR3 comprising or consisting of SEQ ID NO: 387;

(6) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 313, a HCDR2 comprising or consisting of SEQ ID NO: 327, and a HCDR3 comprising or consisting of SEQ ID NO: 344; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 363, a LCDR2 comprising or consisting of SEQ ID NO: 379, and a LCDR3 comprising or consisting of SEQ ID NO: 390;

(7) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 314, a HCDR2 comprising or consisting of SEQ ID NO: 327, and a HCDR3 comprising or consisting of SEQ ID NO: 345; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 364, a LCDR2 comprising or consisting of SEQ ID NO: 380, and a LCDR3 comprising or consisting of SEQ ID NO: 391;

(8) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 312, a HCDR2 comprising or consisting of SEQ ID NO: 328, and a HCDR3 comprising or consisting of SEQ ID NO: 346; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 365, a LCDR2 comprising or consisting of SEQ ID NO: 375, and a LCDR3 comprising or consisting of SEQ ID NO: 387;

(9) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 314, a HCDR2 comprising or consisting of SEQ ID NO: 329, and a HCDR3 comprising or consisting of SEQ ID NO: 347; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 366, a LCDR2

comprising or consisting of SEQ ID NO: 375, and a LCDR3 comprising or consisting of SEQ ID NO: 389;

(10) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 309, a HCDR2 comprising or consisting of SEQ ID NO: 330, and a HCDR3 comprising or consisting of SEQ ID NO: 348; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 360, a LCDR2 comprising or consisting of SEQ ID NO: 381, and a LCDR3 comprising or consisting of SEQ ID NO: 392;

(11) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 309, a HCDR2 comprising or consisting of SEQ ID NO: 327, and a HCDR3 comprising or consisting of SEQ ID NO: 349; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 367, a LCDR2 comprising or consisting of SEQ ID NO: 382, and a LCDR3 comprising or consisting of SEQ ID NO: 389;

(12) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 309, a HCDR2 comprising or consisting of SEQ ID NO: 322, and a HCDR3 comprising or consisting of SEQ ID NO: 350; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 360, a LCDR2 comprising or consisting of SEQ ID NO: 383, and a LCDR3 comprising or consisting of SEQ ID NO: 387;

(13) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 315, a HCDR2 comprising or consisting of SEQ ID NO: 323, and a HCDR3 comprising or consisting of SEQ ID NO: 351; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 368, a LCDR2 comprising or consisting of SEQ ID NO: 375, and a LCDR3 comprising or consisting of SEQ ID NO: 393;

(14) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO:316, a HCDR2 comprising or consisting of SEQ ID NO: 331, and a HCDR3 comprising or consisting of SEQ ID NO: 352; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 365, a LCDR2 comprising or consisting of SEQ ID NO: 375, and a LCDR3 comprising or consisting of SEQ ID NO: 389;

(15) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 317, a HCDR2 comprising or consisting of SEQ ID NO: 332, and a HCDR3 comprising or consisting of SEQ ID NO: 353; and/or the immunoglobulin light chain

polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 369, a LCDR2 comprising or consisting of SEQ ID NO: 384, and a LCDR3 comprising or consisting of SEQ ID NO: 394;

(16) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 318, a HCDR2 comprising or consisting of SEQ ID NO: 333, and a HCDR3 comprising or consisting of SEQ ID NO: 354; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 370, a LCDR2 comprising or consisting of SEQ ID NO: 379, and a LCDR3 comprising or consisting of SEQ ID NO: 395;

(17) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO:310, a HCDR2 comprising or consisting of SEQ ID NO: 334, and a HCDR3 comprising or consisting of SEQ ID NO: 355; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 371, a LCDR2 comprising or consisting of SEQ ID NO: 375, and a LCDR3 comprising or consisting of SEQ ID NO: 387;

(18) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO:310, a HCDR2 comprising or consisting of SEQ ID NO: 335, and a HCDR3 comprising or consisting of SEQ ID NO: 356; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 360, a LCDR2 comprising or consisting of SEQ ID NO: 385, and a LCDR3 comprising or consisting of SEQ ID NO: 396;

(19) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 319, a HCDR2 comprising or consisting of SEQ ID NO: 336, and a HCDR3 comprising or consisting of SEQ ID NO: 357; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 372, a LCDR2 comprising or consisting of SEQ ID NO: 386, and a LCDR3 comprising or consisting of SEQ ID NO: 397;

(20) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 320, a HCDR2 comprising or consisting of SEQ ID NO: 337, and a HCDR3 comprising or consisting of SEQ ID NO: 358; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 373, a LCDR2 comprising or consisting of SEQ ID NO: 379, and a LCDR3 comprising or consisting of SEQ ID NO: 398;

(21) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 321, a HCDR2 comprising or consisting of SEQ ID NO: 338, and a

HCDR3 comprising or consisting of SEQ ID NO: 359; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 374, a LCDR2 comprising or consisting of SEQ ID NO: 379, and a LCDR3 comprising or consisting of SEQ ID NO: 389; and/or

(22) the immunoglobulin heavy chain polypeptide and light chain polypeptide comprises any combination of the CDRs listed in Figures 5A-B (Type B).

In particular embodiments, the binding agent comprises an immunoglobulin heavy chain polypeptide and an immunoglobulin light chain polypeptide, wherein the immunoglobulin heavy chain polypeptide comprises a first framework region, a second framework region, a third framework region, and/or a fourth framework region; and/or the immunoglobulin light chain polypeptide comprises a first framework region, a second framework region, a third framework region, and/or a fourth framework region; and/or the immunoglobulin heavy chain polypeptide and light chain polypeptide comprises any combination of the framework regions listed in Figures 6A-B and/or Figures 7A-B (Type B), respectively.

In an exemplary embodiment, the immunoconjugates of the invention comprise an antibody construct that comprises an antigen binding domain that specifically recognizes and binds HER2.

In certain embodiments, immunoconjugates of the invention comprise anti-HER2 antibodies. In one embodiment of the invention, an anti-HER2 antibody of an immunoconjugate of the invention comprises a humanized anti-HER2 antibody, e.g., huMAb4D5-1, huMAb4D5-2, huMAb4D5-3, huMAb4D5-4, huMAb4D5-5, huMAb4D5-6, huMAb4D5-7 and huMAb4D5-8, as described in Table 3 of US 5821337, which is specifically incorporated by reference herein. Those antibodies contain human framework regions with the complementarity-determining regions of a murine antibody (4D5) that binds to HER2. The humanized antibody huMAb4D5-8 is also referred to as trastuzumab, commercially available under the tradename HERCEPTIN™ (Genentech, Inc.).

Trastuzumab (CAS 180288-69-1, HERCEPTIN®, huMAb4D5-8, rhuMAb HER2, Genentech) is a recombinant DNA-derived, IgG1 kappa, monoclonal antibody that is a humanized version of a murine anti-HER2 antibody (4D5) that selectively binds with high affinity in a cell-based assay (Kd = 5 nM) to the extracellular domain of HER2 (US 5677171; US 5821337; US 6054297; US 6165464; US 6339142; US 6407213; US 6639055; US 6719971; US 6800738; US 7074404; Coussens et al (1985) Science 230:1132-9; Slamon et al (1989) Science 244:707-12; Slamon et al (2001) New Engl. J. Med. 344:783-792).

In an embodiment of the invention, the antibody construct or antigen binding domain comprises the CDR regions of trastuzumab. In an embodiment of the invention, the anti-HER2

antibody further comprises the framework regions of the trastuzumab. In an embodiment of the invention, the anti-HER2 antibody further comprises one or both variable regions of trastuzumab.

In another embodiment of the invention, an anti-HER2 antibody of an immunoconjugate of the invention comprises a humanized anti-HER2 antibody, e.g., humanized 2C4, as described in US 7862817. An exemplary humanized 2C4 antibody is pertuzumab (CAS Reg. No. 380610-27-5), PERJETA™ (Genentech, Inc.). Pertuzumab is a HER dimerization inhibitor (HDI) and functions to inhibit the ability of HER2 to form active heterodimers or homodimers with other HER receptors (such as EGFR/HER1, HER2, HER3 and HER4). See, for example, Harari and Yarden, Oncogene 19:6102-14 (2000); Yarden and Sliwkowski. Nat Rev Mol Cell Biol 2:127-37 (2001); Sliwkowski Nat Struct Biol 10:158-9 (2003); Cho et al. Nature 421:756-60 (2003); and Malik et al. Pro Am Soc Cancer Res 44:176-7 (2003). PERJETA™ is approved for the treatment of breast cancer.

In an embodiment of the invention, the antibody construct or antigen binding domain comprises the CDR regions of pertuzumab. In an embodiment of the invention, the anti-HER2 antibody further comprises the framework regions of the pertuzumab. In an embodiment of the invention, the anti-HER2 antibody further comprises one or both variable regions of pertuzumab.

In an exemplary embodiment, the immunoconjugates of the invention comprise an antibody construct that comprises an antigen binding domain that specifically recognizes and binds Caprin-1 (Ellis JA, Luzio JP (1995) *J Biol Chem.* 270(35):20717–23; Wang B, et al (2005) *J Immunol.* 175 (7):4274–82; Solomon S, et al (2007) *Mol Cell Biol.* 27(6):2324–42). Caprin-1 is also known as GPIAP1, GPIP137, GRIP137, M11S1, RNG105, p137GPI, and cell cycle associated protein 1.

Cytoplasmic activation/proliferation-associated protein-1 (caprin-1) is an RNA-binding protein that participates in the regulation of cell cycle control-associated genes. Caprin-1 selectively binds to c-Myc and cyclin D2 mRNAs, which accelerates cell progression through the G_1 phase into the S phase, enhances cell viability and promotes cell growth, indicating that it may serve an important role in tumorigenesis (Wang B, et al (2005) *J Immunol.* 175:4274–4282). Caprin-1 acts alone or in combination with other RNA-binding proteins, such as RasGAP SH3-domain-binding protein 1 and fragile X mental retardation protein. In the tumorigenesis process, caprin-1 primarily functions by activating cell proliferation and upregulating the expression of immune checkpoint proteins. Through the formation of stress granules, caprin-1 is also involved in the process by which tumor cells adapt to adverse conditions, which contributes to radiation and chemotherapy resistance. Given its role in various clinical malignancies,

caprin-1 holds the potential to be used as a biomarker and a target for the development of novel therapeutics (Yang, Z-S, et al (2019) *Oncology Letters* 18:15-21).

Antibodies that target caprin-1 for treatment and detection have been described (WO 2011/096519; WO 2013/125654; WO 2013/125636; WO 2013/125640; WO 2013/125630; WO 2013/018889; WO 2013/018891; WO 2013/018883; WO 2013/018892; WO 2014/014082; WO 2014/014086; WO 2015/020212; WO 2018/079740).

In an exemplary embodiment, the immunoconjugates of the invention comprise an antibody construct that comprises an antigen binding domain that specifically recognizes and binds CEA.

Elevated expression of carcinoembryonic antigen (CEA, CD66e, CEACAM5) has been implicated in various biological aspects of neoplasia, especially tumor cell adhesion, metastasis, the blocking of cellular immune mechanisms, and having antiapoptosis functions. CEA is also used as a blood marker for many carcinomas. Labetuzumab (CEA-CIDE™, Immunomedics, CAS Reg. No. 219649-07-7), also known as MN-14 and hMN14, is a humanized IgG1 monoclonal antibody and has been studied for the treatment of colorectal cancer (Blumenthal, R. et al (2005) Cancer Immunology Immunotherapy 54(4):315-327). Labetuzumab conjugated to a camptothecin analog (labetuzumab govitecan, IMMU-130) targets carcinoembryonic antigen-related cell adhesion mol. 5 (CEACAM5) and is being studied in patients with relapsed or refractory metastatic colorectal cancer (Sharkey, R. et al, (2018), Molecular Cancer Therapeutics 17(1):196-203; Cardillo, T. et al (2018) Molecular Cancer Therapeutics 17(1):150-160).

In an embodiment of the invention, the CEA-targeting antibody construct or antigen binding domain comprises the Variable light chain (VL kappa) of hMN-14/labetuzumab SEQ ID NO. 472 (US 6676924).

DIQLTQSPSSLSASVGDRVTITCKASQDVGTSVAWYQQKPGKAPKLLIYWTSTRHTGVPSRFSGSGSGTD
FTFTISSLQPEDIATYYCQQYSLYRSFGQGTKVEIK SEQ ID NO. 472

In an embodiment of the invention, the CEA-targeting antibody construct or antigen binding domain comprises the light chain CDR (complementarity determining region) or light chain framework (LFR) sequences of hMN-14/labetuzumab SEQ ID NO. 473-479 (US 6676924).

Region	Sequence Fragment	Residues	Length	SEQ ID NO.
LFR1	DIQLTQSPSSLSASVGDRVTITC	1 - 23	23	473
CDR-L1	KASQDVGTSVA	24 - 34	11	474
LFR2	WYQQKPGKAPKLLIY	35 - 49	15	475
CDR-L2	WTSTRHT	50 - 56	7	476
LFR3	GVPSRFSGSGSGTDFTFTISSLQPEDIATYYC	57 - 88	32	477
CDR-L3	QQYSLYRS	89 - 96	8	478
LFR4	FGQGTKVEIK	97 - 106	10	479

In an embodiment of the invention, the CEA-targeting antibody construct or antigen binding domain comprises the Variable heavy chain (VH) of hMN-14/labetuzumab SEQ ID NO. 480 (US 6676924).

EVQLVESGGGVVQPGRSLRLSCSSSGFDFTTYWMSWVRQAPGKGLEWVAEIHPDSSTINYAPSLKDRFTI
SRDNSKNTLFLQMDSLRPEDTGVYFCASLYFGFPWFAYWGQGTPVTVSS SEQ ID NO. 480

In an embodiment of the invention, the CEA-targeting antibody construct or antigen binding domain comprises the heavy chain CDR (complementarity determining region) or heavy chain framework (HFR) sequences of hMN-14/labetuzumab SEQ ID NO. 481-487 (US 6676924).

Region	Sequence Fragment	Residues	Length	SEQ ID NO.
HFR1	EVQLVESGGGVVQPGRSLRLSCSSSGFDFT	1 - 30	30	481
CDR-H1	TYWMS	31 - 35	5	482
HFR2	WVRQAPGKGLEWVA	36 - 49	14	483
CDR-H2	EIHPDSSTINYAPSLKD	50 - 66	17	484
HFR3	RFTISRDNSKNTLFLQMDSLRPEDTGVYFCAS	67 - 98	32	485
CDR-H3	LYFGFPWFAY	99 - 108	10	486
HFR4	WGQGTPVTVSS	109 - 119	11	487

In an embodiment of the invention, the CEA-targeting antibody construct or antigen binding domain comprises the Variable light chain (VL kappa) of hPR1A3 SEQ ID NO. 488 (US 8642742).

DIQMTQSPSSLSASVGDRVTITCKASAAVGTYVAWYQQKPGKAPKLLIYSASYRKRGVPSRFSGSGSGTD
FTLTISSLQPEDFATYYCHQYYTYPLFTFGQGTKLEIK SEQ ID NO. 488

In an embodiment of the invention, the CEA-targeting antibody construct or antigen binding domain comprises the light chain CDR (complementarity determining region) or light chain framework (LFR) sequences of hPR1A3 SEQ ID NO. 489-495 (US 8642742).

Region	Sequence Fragment	Residues	Length	SEQ ID NO.
LFR1	DIQMTQSPSSLSASVGDRVTITC	1 - 23	23	489
CDR-L1	KASAAVGTYVA	24 - 34	11	490
LFR2	WYQQKPGKAPKLLIY	35 - 49	15	491
CDR-L2	SASYRKR	50 - 56	7	492
LFR3	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC	57 - 88	32	493
CDR-L3	HQYYTYPLFT	89 - 98	10	494
LFR4	FGQGTKLEIK	99 - 108	10	495

In an embodiment of the invention, the CEA-targeting antibody construct or antigen binding domain comprises the heavy chain CDR (complementarity determining region) or heavy chain framework (HFR) sequences of hPR1A3 SEQ ID NO. 496-502 (US 8642742).

Region	Sequence Fragment	Residues	Length	SEQ ID NO.
HFR1	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	1 - 30	30	496

CDR-H1	EFGMN	31 - 35	5	497
HFR2	WVRQAPGQGLEWMG	36 - 49	14	498
CDR-H2	WINTRTGEATYVEEFKG	50 - 66	17	499
HFR3	RVTFTTDTSTSTAYMELRSLRSDDTAVYYCAR	67 - 98	32	500
CDR-H3	WDFAYYVEAMDY	99 - 110	12	501
HFR4	WGQGTTVTVSS	111 - 121	11	502

In an embodiment of the invention, the CEA-targeting antibody construct or antigen binding domain comprises the Variable light chain (VL kappa) of hMFE-23 SEQ ID NO. 503 (US 723288).

ENVLTQSPSSMSASVGDRVNIACSASSSVSYMHWFQQKPGKSPKLWIYSTSNLASGVPSRFSGSGSGTDY SLTISSMQPEDAATYYCQQRSSYPLTFGGGTKLEIK SEQ ID NO. 503

In an embodiment of the invention, the CEA-targeting antibody construct or antigen binding domain comprises the light chain CDR (complementarity determining region) or light chain framework (LFR) sequences of hMFE-23 SEQ ID NO. 504-510 (US 723288).

Region	Sequence Fragment	Residues	Length	SEQ ID NO.
LFR1	ENVLTQSPSSMSASVGDRVNIAC	1 - 23	23	504
CDR-L1	SASSSVSYMH	24 - 33	10	505
LFR2	WFQQKPGKSPKLWIY	34 - 48	15	506
CDR-L2	STSNLAS	49 - 55	7	507
LFR3	GVPSRFSGSGSGTDYSLTISSMQPEDAATYYC	56 - 87	32	508
CDR-L3	QQRSSYPLT	88 - 96	9	509
LFR4	FGGGTKLEIK	97 - 106	10	510

In an embodiment of the invention, the CEA-targeting antibody construct or antigen binding domain comprises the Variable heavy chain (VH) of hMFE-23 SEQ ID NO. 511 (US 723288).

QVKLEQSGAEVVKPGASVKLSCKASGFNIKDSYMHWLRQGPGQRLEWIGWIDPENGDTEYAPKFQGKATF TTDTSANTAYLGLSSLRPEDTAVYYCNEGTPTGPYYFDYWGQGTLVTVSS SEQ ID NO. 511

In an embodiment of the invention, the CEA-targeting antibody construct or antigen binding domain comprises the heavy chain CDR (complementarity determining region) or heavy chain framework (HFR) sequences of hMFE-23 SEQ ID NO. 512-518 (US 723288).

Region	Sequence Fragment	Residues	Length	SEQ ID NO.
HFR1	QVKLEQSGAEVVKPGASVKLSCKASGFNIK	1 - 30	30	512
CDR-H1	DSYMH	31 - 35	5	513
HFR2	WLRQGPGQRLEWIG	36 - 49	14	514
CDR-H2	WIDPENGDTEYAPKFQG	50 - 66	17	515
HFR3	KATFTTDTSANTAYLGLSSLRPEDTAVYYCNE	67 - 98	32	516
CDR-H3	GTPTGPYYFDY	99 - 109	11	517
HFR4	WGQGTLVTVSS	110 - 120	11	518

In an embodiment of the invention, the CEA-targeting antibody construct or antigen binding domain comprises the Variable light chain (VL kappa) of SM3E SEQ ID NO. 519 (US 723288).

ENVLTQSPSSMSVSVGDRVTIACSASSSVPYMHWLQQKPGKSPKLLIYLTSNLASGVPSRFSGSGSGTDY
SLTISSVQPEDAATYYCQQRSSYPLTFGGGTKLEIK SEQ ID NO. 519

In an embodiment of the invention, the CEA-targeting antibody construct or antigen binding domain comprises the light chain CDR (complementarity determining region) or light chain framework (LFR) sequences of SM3E SEQ ID NO. 520-526 (US 723288).

Region	Sequence Fragment	Residues	Length	SEQ ID NO.
LFR1	ENVLTQSPSSMSVSVGDRVTIAC	1 - 23	23	520
CDR-L1	SASSSVPYMH	24 - 33	10	521
LFR2	WLQQKPGKSPKLLIY	34 - 48	15	522
CDR-L2	LTSNLAS	49 - 55	7	523
LFR3	GVPSRFSGSGSGTDYSLTISSVQPEDAATYYC	56 - 87	32	524
CDR-L3	QQRSSYPLT	88 - 96	9	525
LFR4	FGGGTKLEIK	97 - 106	10	526

In an embodiment of the invention, the CEA-targeting antibody construct or antigen binding domain comprises the Variable heavy chain (VH) of SM3E SEQ ID NO. 527 (US 723288).

QVKLEQSGAEVVKPGASVKLSCKASGFNIKDSYMHWLRQGPGQRLEWIGWIDPENGDTEYAPKFQGKATF
TTDTSANTAYLGLSSLRPEDTAVYYCNEGTPTGPYYFDYWGQGTLVTVSS SEQ ID NO. 527

In an embodiment of the invention, the CEA-targeting antibody construct or antigen binding domain comprises the heavy chain CDR (complementarity determining region) or heavy chain framework (HFR) sequences of SM3E SEQ ID NO. 528-534 (US 723288).

Region	Sequence Fragment	Residues	Length	SEQ ID NO.
HFR1	QVKLEQSGAEVVKPGASVKLSCKASGFNIK	1 - 30	30	528
CDR-H1	DSYMH	31 - 35	5	529
HFR2	WLRQGPGQRLEWIG	36 - 49	14	530
CDR-H2	WIDPENGDTEYAPKFQG	50 - 66	17	531
HFR3	KATFTTDTSANTAYLGLSSLRPEDTAVYYCNE	67 - 98	32	532
CDR-H3	GTPTGPYYFDY	99 - 109	11	533
HFR4	WGQGTLVTVSS	110 - 120	11	534

In an embodiment of the invention, the CEA-targeting antibody construct or antigen binding domain comprises the light chain CDR (complementarity determining region) or light chain framework (LFR) sequences of NP-4/arcitumomab SEQ ID NO. 535-541.

Region	Sequence Fragment	Residues	Length	SEQ ID NO.
LFR1	QTVLSQSPAILSASPGEKVTMTC	1 - 23	23	535
CDR-L1	RASSSVTYIH	24 - 33	10	536
LFR2	WYQQKPGSSPKSWIY	34 - 48	15	537
CDR-L2	ATSNLAS	49 - 55	7	538
LFR3	GVPARFSGSGSGTSYSLTISRVEAEDAATYYC	56 - 87	32	539

CDR-L3	QHWSSKPPT	88 - 96	9	540
LFR4	FGGGTKLEIK	97 - 106	10	541

In an embodiment of the invention, the CEA-targeting antibody construct or antigen binding domain comprises the Variable heavy chain (VH) of NP-4/arcitumomab SEQ ID NO. 542.

EVKLVESGGGLVQPGGSLRLSCATSGFTFTDYYMNWVRQPPGKALEWLGFIGNKANGYTTEYSASVKGRF
TISRDKSQSILYLQMNTLRAEDSATYYCTRDRGLRFYFDYWGQGTTLTVSS SEQ ID NO. 542.

In an embodiment of the invention, the CEA-targeting antibody construct or antigen binding domain comprises the heavy chain CDR (complementarity determining region) or heavy chain framework (HFR) sequences of NP-4 SEQ ID NO. 543-549.

Region	Sequence Fragment	Residues	Length	SEQ ID NO.
HFR1	EVKLVESGGGLVQPGGSLRLSCATSGFTFT	1 - 30	30	543
CDR-H1	DYYMN	31 - 35	5	544
HFR2	WVRQPPGKALEWLG	36 - 49	14	545
CDR-H2	FIGNKANGYTTEYSASVKG	50 - 68	19	546
HFR3	RFTISRDKSQSILYLQMNTLRAEDSATYYCTR	69 - 100	32	547
CDR-H3	DRGLRFYFDY	101 - 110	10	548
HFR4	WGQGTTLTVSS	111 - 121	11	549

In an embodiment of the invention, the CEA-targeting antibody construct or antigen binding domain comprises the Variable light chain (VL kappa) of M5A/hT84.66 SEQ ID NO. 550 (US 7776330).

DIQLTQSPSSLSASVGDRVTITCRAGESVDIFGVGFLHWYQQKPGKAPKLLIYRASNLESGVPSRFSGSG
SRTDFTLTISSLQPEDFATYYCQQTNEDPYTFGQGTKVEIK SEQ ID NO. 550

In an embodiment of the invention, the CEA-targeting antibody construct or antigen binding domain comprises the light chain CDR (complementarity determining region) or light chain framework (LFR) sequences of M5A/hT84.66 SEQ ID NO. 551-557 (US 7776330).

Region	Sequence Fragment	Residues	Length	SEQ ID NO.
LFR1	DIQLTQSPSSLSASVGDRVTITC	1 - 23	23	551
CDR-L1	RAGESVDIFGVGFLH	24 - 38	15	552
LFR2	WYQQKPGKAPKLLIY	39 - 53	15	553
CDR-L2	RASNLES	54 - 60	7	554
LFR3	GVPSRFSGSGSRTDFTLTISSLQPEDFATYYC	61 - 92	32	555
CDR-L3	QQTNEDPYT	93 - 101	9	556
LFR4	FGQGTKVEIK	102 - 111	10	557

In an embodiment of the invention, the CEA-targeting antibody construct or antigen binding domain comprises the Variable heavy chain (VH) of M5A/hT84.66 SEQ ID NO. 558 (US 7776330).

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYMHWVRQAPGKGLEWVARIDPANGNSKYADSVKGRFTI
SADTSKNTAYLQMNSLRAEDTAVYYCAPFGYYVSDYAMAYWGQGTLVTVSS SEQ ID NO. 558

In an embodiment of the invention, the CEA-targeting antibody construct or antigen binding domain comprises the heavy chain CDR (complementarity determining region) or heavy chain framework (HFR) sequences of M5A/hT84.66 SEQ ID NO. 559-565 (US 7776330).

Region	Sequence Fragment	Residues	Length	SEQ ID NO.
HFR1	EVQLVESGGGLVQPGGSLRLSCAASGFNIK	1 - 30	30	559
CDR-H1	DTYMH	31 - 35	5	560
HFR2	WVRQAPGKGLEWVA	36 - 49	14	561
CDR-H2	RIDPANGNSKYADSVKG	50 - 66	17	562
HFR3	RFTISADTSKNTAYLQMNSLRAEDTAVYYCAP	67 - 98	32	563
CDR-H3	FGYYVSDYAMAY	99 - 110	12	564
HFR4	WGQGTLVTVSS	111 - 121	11	565

In an embodiment of the invention, the CEA-targeting antibody construct or antigen binding domain comprises the Variable light chain (VL kappa) of hAb2-3 SEQ ID NO. 566 (US 9617345).

DIQMTQSPASLSASVGDRVTITCRASENIFSYLAWYQQKPGKSPKLLVYNTRTLAEGVPSRFSGSGSGTD
FSLTISSLQPEDFATYYCQHHYGTPFTFGSGTKLEIK SEQ ID NO. 566

In an embodiment of the invention, the CEA-targeting antibody construct or antigen binding domain comprises the light chain CDR (complementarity determining region) or light chain framework (LFR) sequences of hAb2-3 SEQ ID NO. 567-573 (US 9617345).

Region	Sequence Fragment	Residues	Length	SEQ ID NO.
LFR1	DIQMTQSPASLSASVGDRVTITC	1 - 23	23	567
CDR-L1	RASENIFSYLA	24 - 34	11	568
LFR2	WYQQKPGKSPKLLVY	35 - 49	15	569
CDR-L2	NTRTLAE	50 - 56	7	570
LFR3	GVPSRFSGSGSGTDFSLTISSLQPEDFATYYC	57 - 88	32	571
CDR-L3	QHHYGTPFT	89 - 97	9	572
LFR4	FGSGTKLEIK	98 - 107	10	573

In an embodiment of the invention, the CEA-targeting antibody construct or antigen binding domain comprises the Variable heavy chain (VH) of SEQ ID NO. 574 (US 9617345).

EVQLQESGPGLVKPGGSLSLSCAASGFVFSSYDMSWVRQTPERGLEWVAYISSGGGITYAPSTVKGRFTV
SRDNAKNTLYLQMNSLTSEDTAVYYCAAHYFGSSGPFAYWGQGTLVTVSS SEQ ID NO. 574

In an embodiment of the invention, the CEA-targeting antibody construct or antigen binding domain comprises the heavy chain CDR (complementarity determining region) or heavy chain framework (HFR) sequences of hAb2-3 SEQ ID NO. 575-581.

Region	Sequence Fragment	Residues	Length	SEQ ID NO.
HFR1	EVQLQESGPGLVKPGGSLSLSCAASGFVFS	1 - 30	30	575
CDR-H1	SYDMS	31 - 35	5	576
HFR2	WVRQTPERGLEWVA	36 - 49	14	577

CDR-H2	YISSGGGITYAPSTVKG	50 - 66	17	578
HFR3	RFTVSRDNAKNTLYLQMNSLTSEDTAVYYCAA	67 - 98	32	579
CDR-H3	HYFGSSGPFAY	99 - 109	11	580
HFR4	WGQGTLVTVSS	110 - 120	11	581

In an embodiment of the invention, the CEA-targeting antibody construct or antigen binding domain comprises the Variable light chain (VL kappa) of A240VL-B9VH/AMG-211 SEQ ID NO. 582 (US 9982063).

QAVLTQPASLSASPGASASLTCTLRRGINVGAYSIYWYQQKPGSPPQYLLRYKSDSDKQQGSGVSSRFSA
SKDASANAGILLISGLQSEDEADYYCMIWHSGASAVFGGGTKLTVL SEQ ID NO. 582

In an embodiment of the invention, the CEA-targeting antibody construct or antigen binding domain comprises the light chain CDR (complementarity determining region) or light chain framework (LFR) sequences of A240VL-B9VH/AMG-211 SEQ ID NO. 583-589 (US 9982063).

Region	Sequence Fragment	Residues	Length	SEQ ID NO.
LFR1	QAVLTQPASLSASPGASASLTC	1 - 22	22	583
CDR-L1	TLRRGINVGAYSIY	23 - 36	14	584
LFR2	WYQQKPGSPPQYLLR	37 - 51	15	585
CDR-L2	YKSDSDKQQGS	52 - 62	11	586
LFR3	GVSSRFSASKDASANAGILLISGLQSEDEADYYC	63 - 96	34	587
CDR-L3	MIWHSGASAV	97 - 106	10	588
LFR4	FGGGTKLTVL	107 - 116	10	589

In an embodiment of the invention, the CEA-targeting antibody construct or antigen binding domain comprises the Variable heavy chain (VH) of B9VH SEQ ID NO. 590 (US 9982063).

EVQLVESGGGLVQPGRSLRLSCAASGFTVSSYWMHWVRQAPGKGLEWVGFIRNKANGGTTEYAASVKGRF
TISRDDSKNTLYLQMNSLRAEDTAVYYCARDRGLRFYFDYWGQGTTVTVSS SEQ ID NO. 590

In an embodiment of the invention, the CEA-targeting antibody construct or antigen binding domain comprises the heavy chain CDR (complementarity determining region) or heavy chain framework (HFR) sequences of SEQ ID NO. 591-598 (US 9982063). The embodiment includes two variants of CDR-H2, SEQ ID NO.:594 and SEQ ID NO.:595.

Region	Sequence Fragment	Residues	Length	SEQ ID NO.
HFR1	EVQLVESGGGLVQPGRSLRLSCAASGFTVS	1 - 30	30	591
CDR-H1	SYWMH	31 - 35	5	592
HFR2	WVRQAPGKGLEWVG	36 - 49	14	593
CDR-H2	FIRNKANGGTTEYAASVKG	50 - 68	19	594
CDR-H2	FIRNKANSGTTEYAASVKG	50 - 68	19	595
HFR3	RFTISRDDSKNTLYLQMNSLRAEDTAVYYCAR	69 - 100	32	596
CDR-H3	DRGLRFYFDY	101 - 110	10	597
HFR4	WGQGTTVTVSS	111 - 121	11	598

In an embodiment of the invention, the CEA-targeting antibody construct or antigen binding domain comprises the Variable heavy chain (VH) of E12VH SEQ ID NO. 599 (US 9982063).

EVQLVESGGGLVQPGRSLRLSCAASGFTVSSYWMHWVRQAPGKGLEWVGFILNKANGGTTEYAASVKGRF
TISRDDSKNTLYLQMNSLRAEDTAVYYCARDRGLRFYFDYWGQGTTVTVSS SEQ ID NO. 599

In an embodiment of the invention, the CEA-targeting antibody construct or antigen binding domain comprises the heavy chain CDR (complementarity determining region) or heavy chain framework (HFR) sequences of SEQ ID NO. 600-606 (US 9982063).

Region	Sequence Fragment	Residues	Length	SEQ ID NO.
HFR1	EVQLVESGGGLVQPGRSLRLSCAASGFTVS	1 - 30	30	600
CDR-H1	SYWMH	31 - 35	5	601
HFR2	WVRQAPGKGLEWVG	36 - 49	14	602
CDR-H2	FILNKANGGTTEYAASVKG	50 - 68	19	603
HFR3	RFTISRDDSKNTLYLQMNSLRAEDTAVYYCAR	69 - 100	32	604
CDR-H3	DRGLRFYFDY	101 - 110	10	605
HFR4	WGQGTTVTVSS	111 - 121	11	606

In some embodiments, the antibody construct further comprises an Fc domain. In certain embodiments, the antibody construct is an antibody. In certain embodiments, the antibody construct is a fusion protein. The antigen binding domain can be a single-chain variable region fragment (scFv). A single-chain variable region fragment (scFv), which is a truncated Fab fragment including the variable (V) domain of an antibody heavy chain linked to a V domain of a light antibody chain via a synthetic peptide, can be generated using routine recombinant DNA technology techniques. Similarly, disulfide-stabilized variable region fragments (dsFv) can be prepared by recombinant DNA technology. The antibody construct or antigen binding domain may comprise one or more variable regions (e.g., two variable regions) of an antigen binding domain of an anti-PD-L1 antibody, an anti-HER2 antibody, or an anti-CEA antibody, each variable region comprising a CDR1, a CDR2, and a CDR3.

In some embodiments, the antibodies in the immunoconjugates contain a modified Fc region, wherein the modification modulates the binding of the Fc region to one or more Fc receptors.

In some embodiments, the Fc region is modified by inclusion of a transforming growth factor beta 1 (TGFβ1) receptor, or a fragment thereof, that is capable of binding TGFβ1. For example, the receptor can be TGFβ receptor II (TGFβRII). In some embodiments, theTGFβ receptor is a human TGFβ receptor. In some embodiments, the IgG has a C-terminal fusion to a TGFβRII extracellular domain (ECD) as described in US 9676863, incorporated herein. An "Fc linker" may be used to attach the IgG to the TGFβRII extracellular domain, for example, a G_4S_4G Fc linker (SEQ ID NO: 608). The Fc linker may be a short, flexible peptide that allows

for the proper three-dimensional folding of the molecule while maintaining the binding-specificity to the targets. In some embodiments, the N-terminus of the TGFβ receptor is fused to the Fc of the antibody construct (with or without an Fc linker). In some embodiments, the C-terminus of the antibody construct heavy chain is fused to the TGFβ receptor (with or without an Fc linker). In some embodiments, the C-terminal lysine residue of the antibody construct heavy chain is mutated to alanine.

In some embodiments, the antibodies in the immunoconjugates are glycosylated.

In some embodiments, the antibodies in the immunoconjugates is a cysteine-engineered antibody which provides for site-specific conjugation of an adjuvant, label, or drug moiety to the antibody through cysteine substitutions at sites where the engineered cysteines are available for conjugation but do not perturb immunoglobulin folding and assembly or alter antigen binding and effector functions (Junutula, et al., 2008b Nature Biotech., 26(8):925-932; Dornan et al. (2009) Blood 114(13):2721-2729; US 7521541; US 7723485; US 2012/0121615; WO 2009/052249). A "cysteine engineered antibody" or "cysteine engineered antibody variant" is an antibody in which one or more residues of an antibody are substituted with cysteine residues. Cysteine-engineered antibodies can be conjugated to the aminobenzazepine adjuvant moiety as an aminobenzazepine-linker compound with uniform stoichiometry (e.g., up to 2 aminobenzazepine moieties per antibody in an antibody that has a single engineered cysteine site).

In some embodiments, cysteine-engineered antibodies used to prepare the immunoconjugates of Table 3 have a cysteine residue introduced at the 149-lysine site of the light chain (LC K149C). In other embodiments, the cysteine-engineered antibodies have a cysteine residue introduced at the 118-alanine site (EU numbering) of the heavy chain (HC A118C). This site is alternatively numbered 121 by Sequential numbering or 114 by Kabat numbering. In other embodiments, the cysteine-engineered antibodies have a cysteine residue introduced in the light chain at G64C or R142C according to Kabat numbering, or in the heavy chain at D101C, V184C or T205C according to Kabat numbering.

AMINOBENZAZEPINE ADJUVANT COMPOUNDS

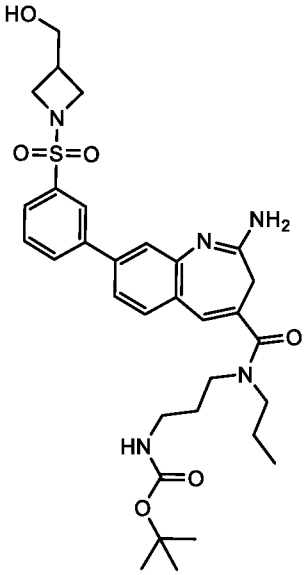
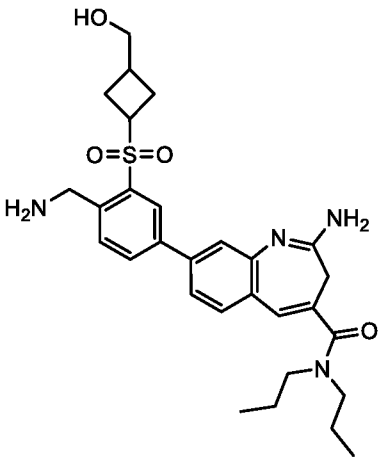
The immunoconjugate of the invention comprises an aminobenzazepine adjuvant moiety. The adjuvant moiety described herein is a compound that elicits an immune response (i.e., an immunostimulatory agent). Generally, the adjuvant moiety described herein is a TLR agonist. TLRs are type-I transmembrane proteins that are responsible for the initiation of innate immune responses in vertebrates. TLRs recognize a variety of pathogen-associated molecular patterns from bacteria, viruses, and fungi and act as a first line of defense against invading pathogens.

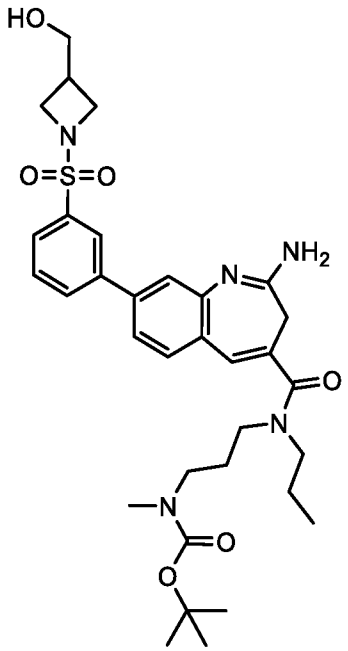
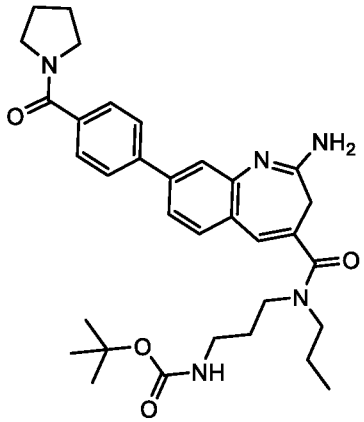
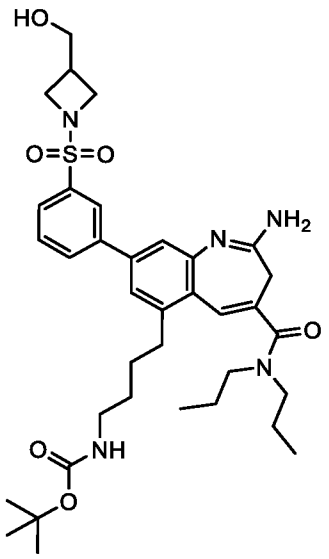
TLRs elicit overlapping yet distinct biological responses due to differences in cellular expression and in the signaling pathways that they initiate. Once engaged (e.g., by a natural stimulus or a synthetic TLR agonist), TLRs initiate a signal transduction cascade leading to activation of nuclear factor-κB (NF-κB) via the adapter protein myeloid differentiation primary response gene 88 (MyD88) and recruitment of the IL-1 receptor associated kinase (IRAK). Phosphorylation of IRAK then leads to recruitment of TNF-receptor associated factor 6 (TRAF6), which results in the phosphorylation of the NF-κB inhibitor I-κB. As a result, NF-κB enters the cell nucleus and initiates transcription of genes whose promoters contain NF-κB binding sites, such as cytokines. Additional modes of regulation for TLR signaling include TIR-domain containing adapter-inducing interferon-β (TRIF)-dependent induction of TNF-receptor associated factor 6 (TRAF6) and activation of MyD88 independent pathways via TRIF and TRAF3, leading to the phosphorylation of interferon response factor three (IRF3). Similarly, the MyD88 dependent pathway also activates several IRF family members, including IRF5 and IRF7 whereas the TRIF dependent pathway also activates the NF-κB pathway.

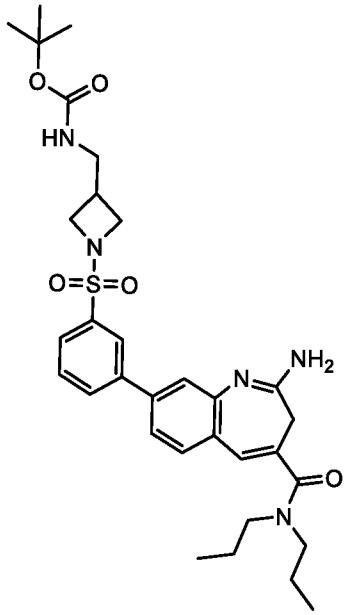
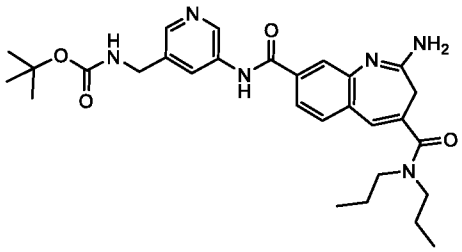
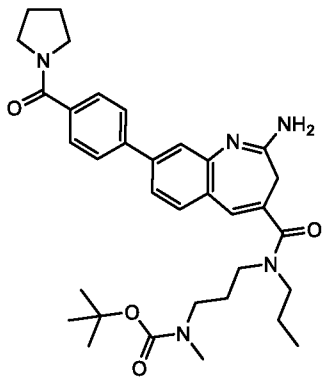
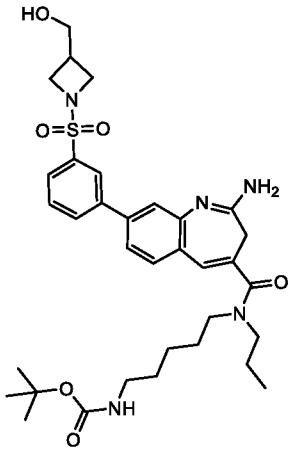
Typically, the adjuvant moiety described herein is a TLR7 and/or TLR8 agonist. TLR7 and TLR8 are both expressed in cells of myeloid lineage (e.g. monocytes and dendritic cells). In humans, TLR7 is also expressed in plasmacytoid dendritic cells (pDCs) and B cells. TLR8 is expressed mostly in cells of myeloid origin, i.e., monocytes, granulocytes, and myeloid dendritic cells. TLR7 and TLR8 are capable of detecting the presence of "foreign" single-stranded RNA within a cell, as a means to respond to viral invasion. Treatment of TLR8-expressing cells, with TLR8 agonists can result in production of high levels of IL-12, IFN-γ, IL-1, TNF-α, IL-6, and other inflammatory cytokines. Similarly, stimulation of TLR7-expressing cells, such as pDCs, with TLR7 agonists can result in production of high levels of IFN-α and other inflammatory cytokines. TLR7/TLR8 engagement and resulting cytokine production can activate dendritic cells and other antigen-presenting cells, driving diverse innate and acquired immune response mechanisms leading to tumor destruction.

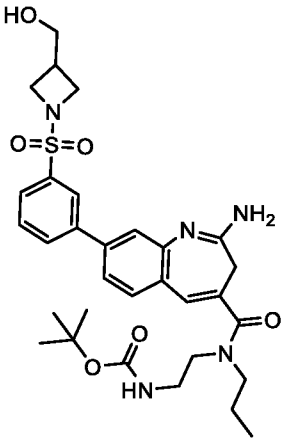
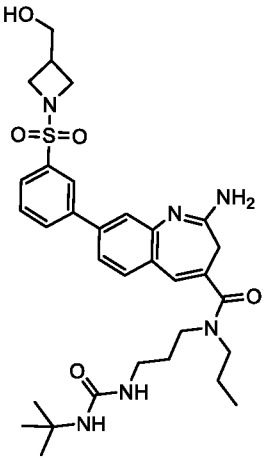
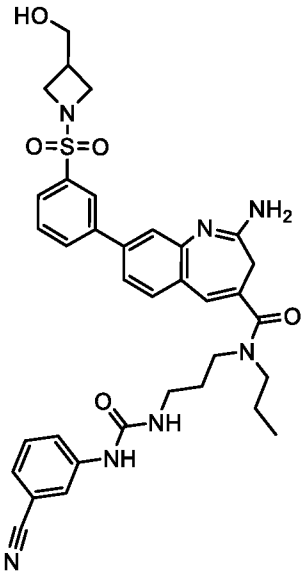
Exemplary aminobenzazepine compounds (Bz) of the invention are shown in Tables 1a, 1b, and 1c. Each compound was synthesized and purified by the methods in the Examples provided herein, characterized by mass spectrometry, and shown to have the mass indicated. Activity against HEK293 NFKB reporter cells expressing human TLR7 or human TLR8 was measured according to Example 68. The aminobenzazepine compounds of Tables 1a,1b, and 1c demonstrate the surprising and unexpected property of TLR8 agonist selectivity which may predict useful therapeutic activity to treat cancer and other disorders.

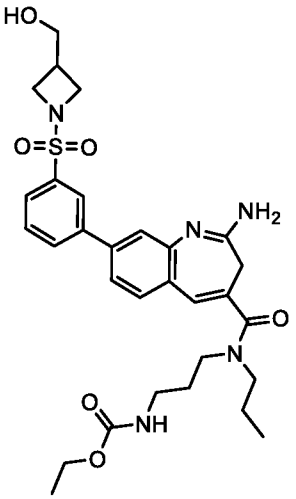
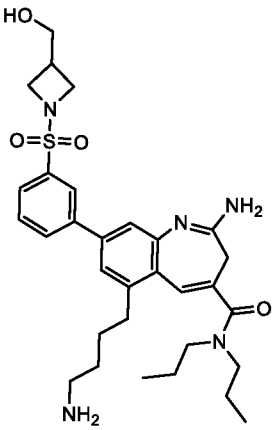
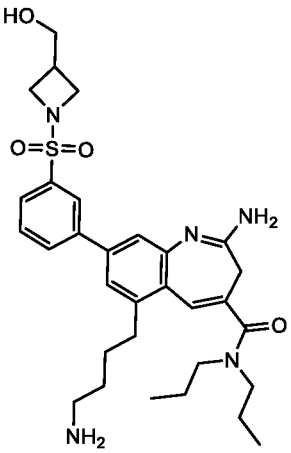
Table 1a: Aminobenzazepine compounds (Bz)

Bz No.	Structure	MW	HEK293 hTLR7 EC50 (nM)	HEK293 hTLR8 EC50 (nM)
Bz-1		625.8	571	106
Bz-2		538.7	>9000	9760

Bz-3		639.8	545.2	4306
Bz-4		573.7	1484	1681
Bz-5		681.9	155.2	255.5

Bz-6		609.8	>9000	264.7
Bz-7		534.7	>9000	4.283
Bz-8		587.8	3367	>9000
Bz-9		653.8	8647	629.1

Bz-10		611.8	>9000	>9000
Bz-11		624.8	7843	1387
Bz-12		669.8	2487	2375

Bz-13		597.7	1371	134
Bz-14		581.8	>9000	1700
Bz-15		509.7	>9000	103

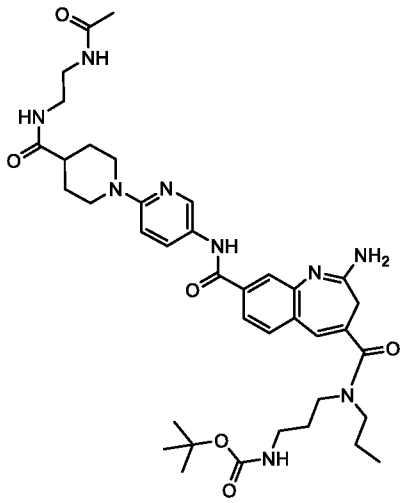
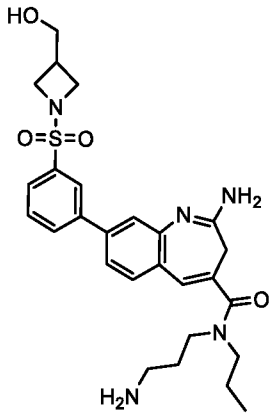
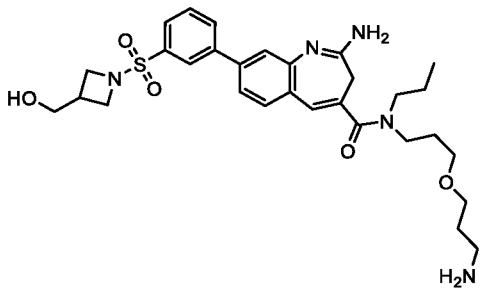
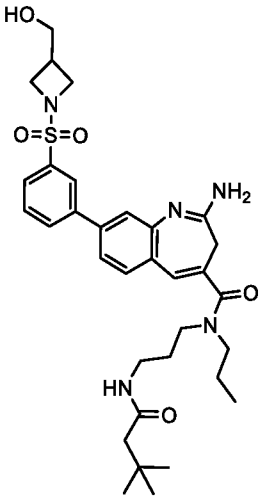
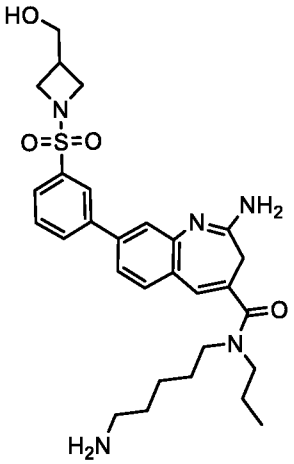
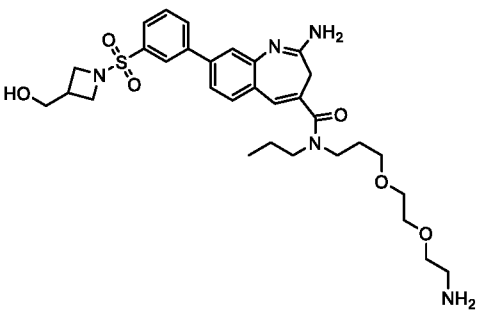
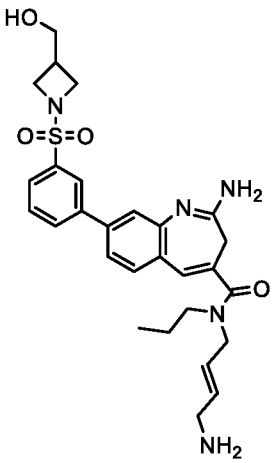
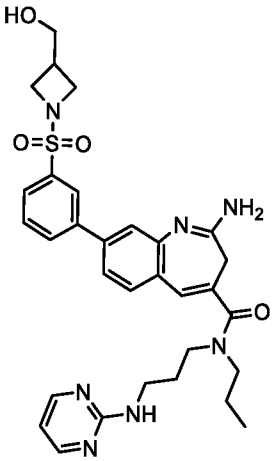
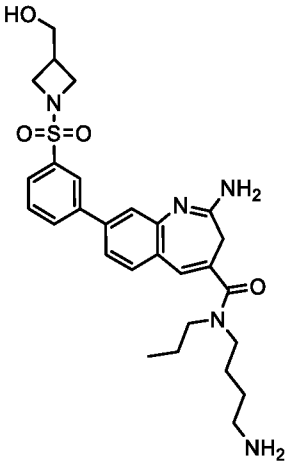
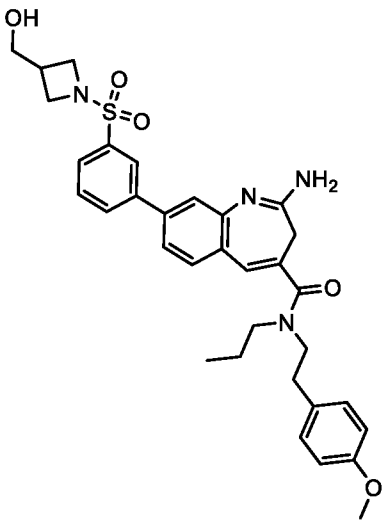
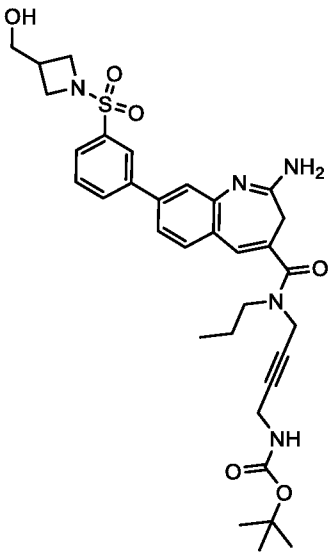
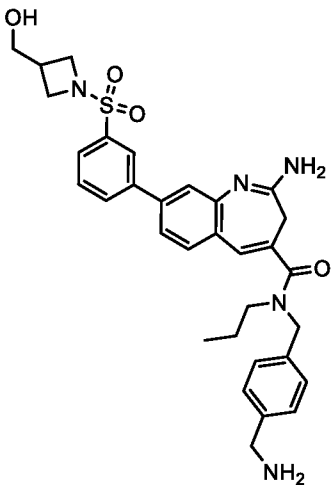
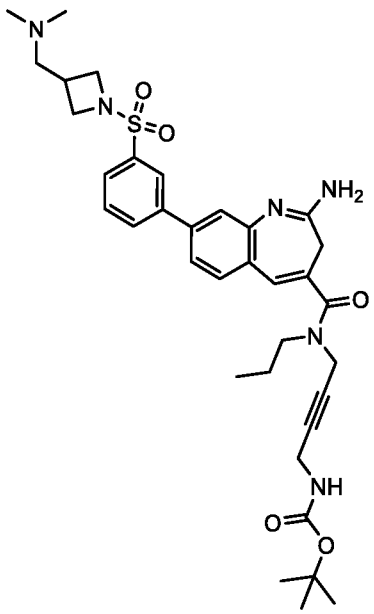
Bz-16		731.9	>9000	1047

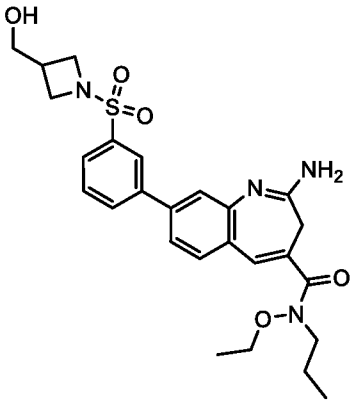
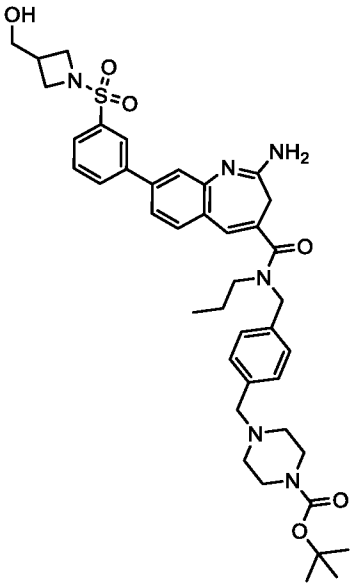
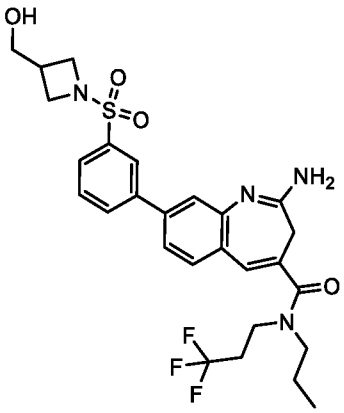
Table 1b: Aminobenzazepine compounds (Bz)

Bz No.	Structure	MW	HEK293 hTLR7 EC50 (nM)	HEK293 hTLR8 EC50 (nM)
Bz-17		525.7	>9000	>9000
Bz-18		583.7	1994	3403

Bz-19		623.8	1067	3168
Bz-20		553.7	>9000	>9000
Bz-21		613.8	>9000	>9000
Bz-22		537.7	>9000	>9000

Bz-23		603.7	2427	1162
Bz-24		539.7	>9000	>9000
Bz-25		602.8	>9000	1403

Bz-26		635.8	>9000	318
Bz-27		587.7	>9000	138
Bz-28		662.9	4253.9	42.8

Bz-29		512.6	>9000	32
Bz-30		757.0	>9000	1022.3
Bz-31		564.6	>9000	341

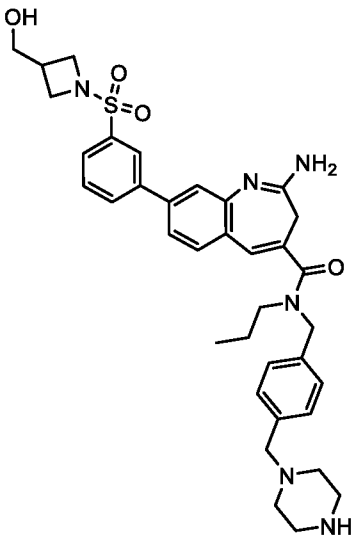
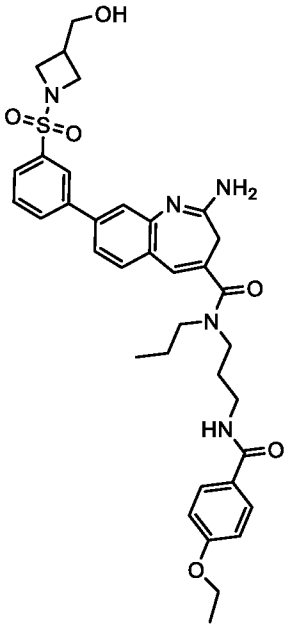
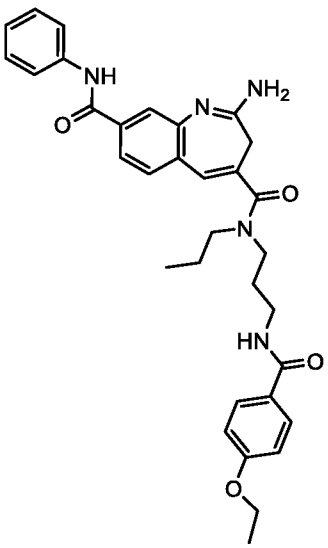
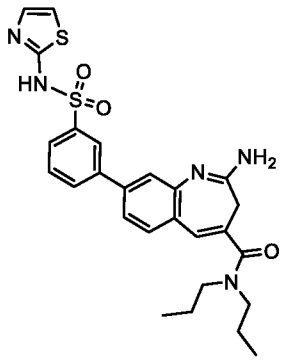
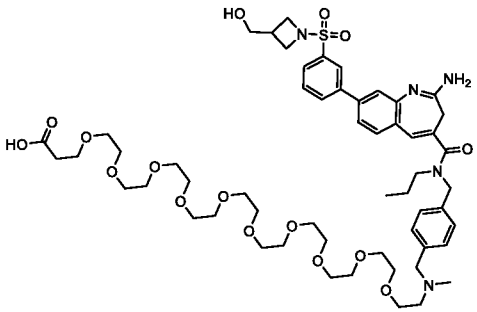
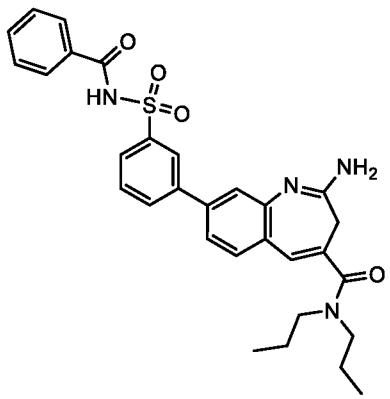
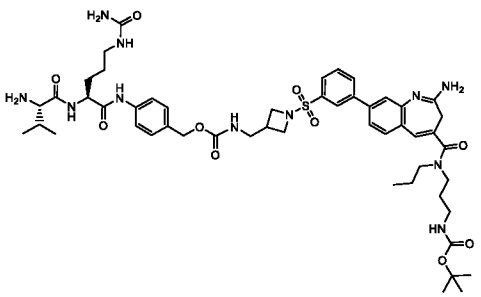
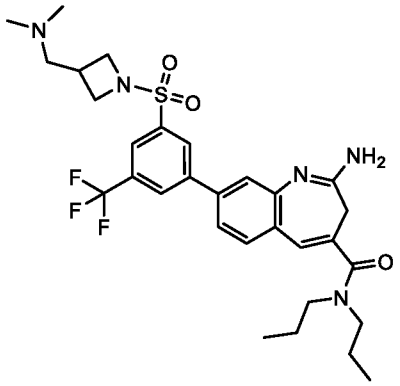
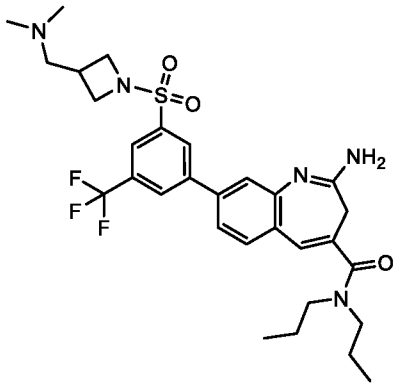
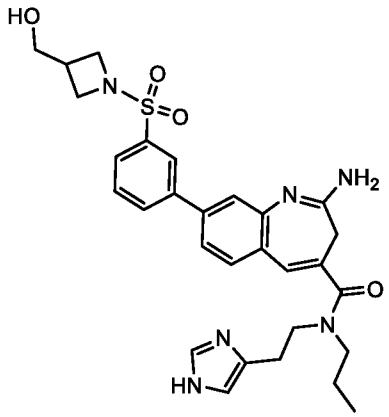
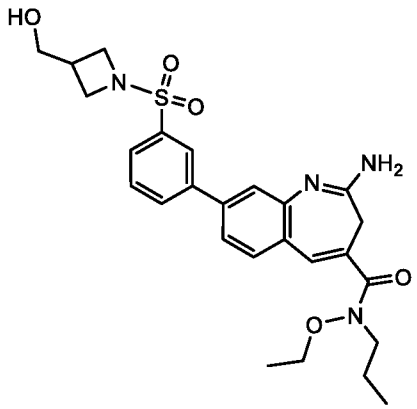
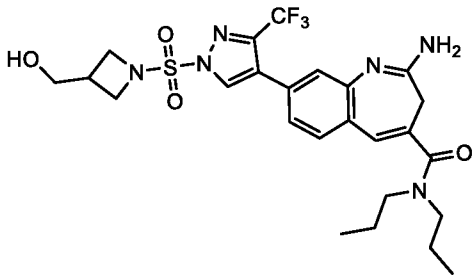
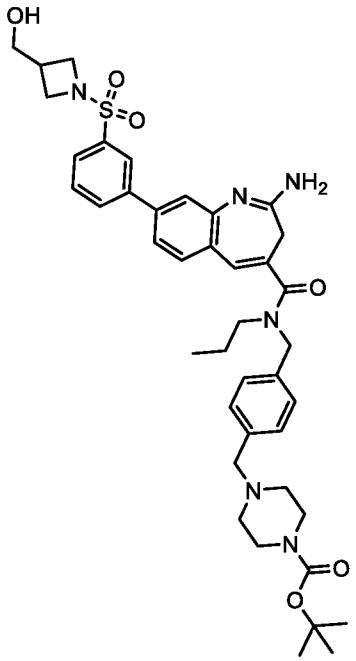
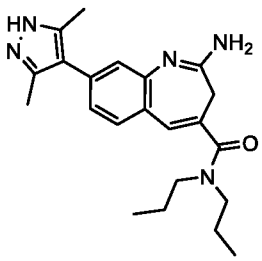
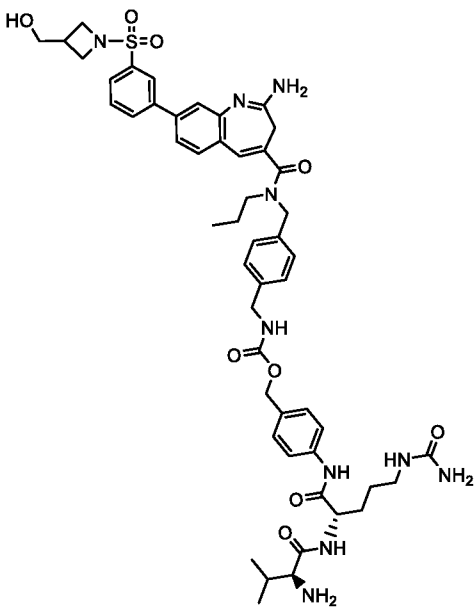
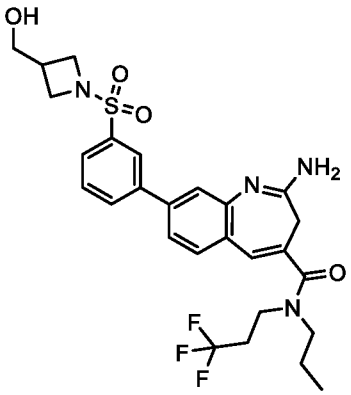
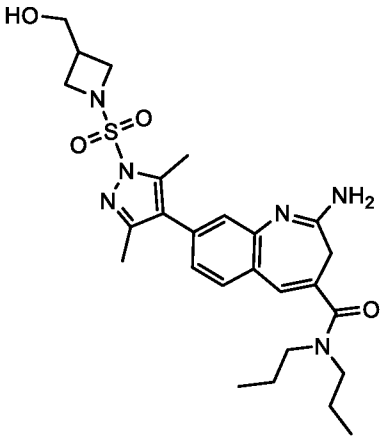
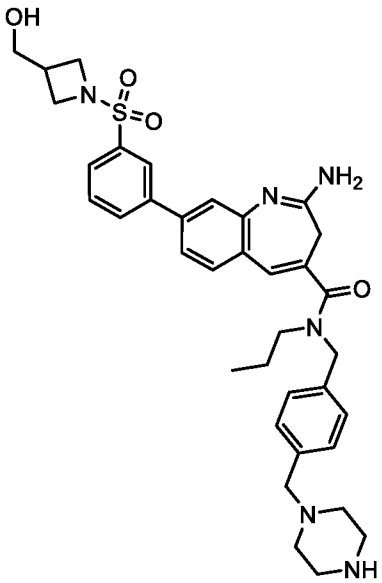
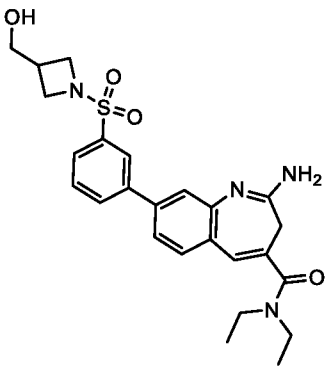
Bz-32		656.8	>9000	>9000
Bz-33		673.8	1428	1919
Bz-34		567.7	>9000	1040

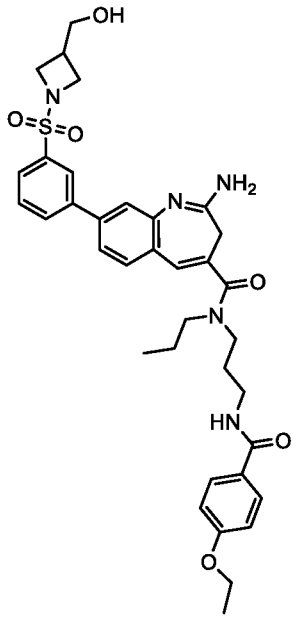
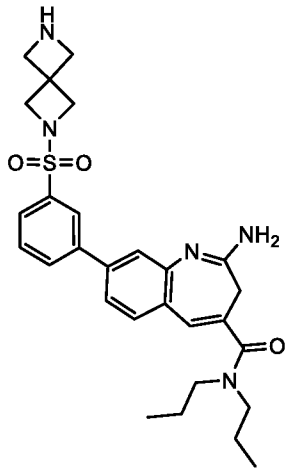
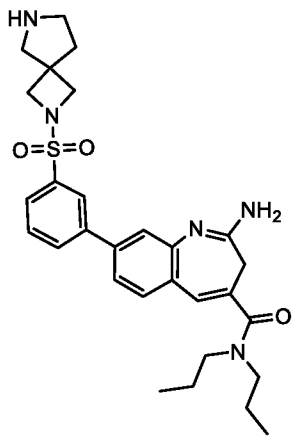
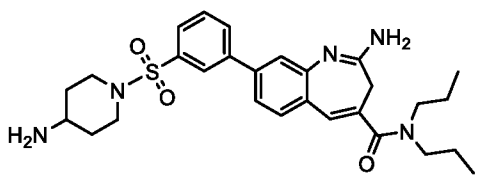
Table 1c: Aminobenzazepine compounds (Bz)

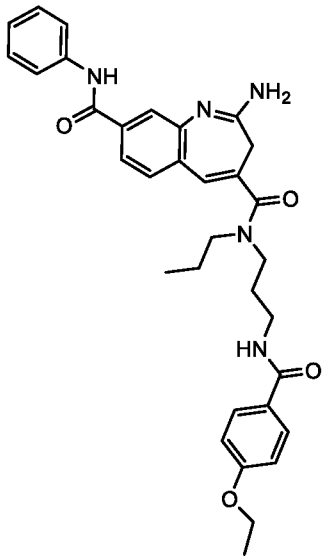
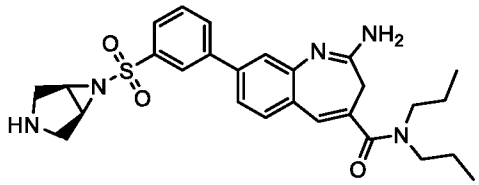
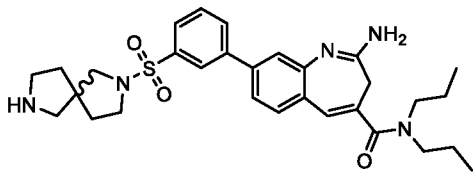
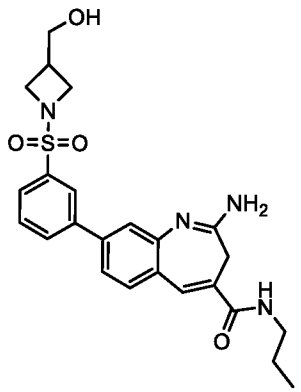
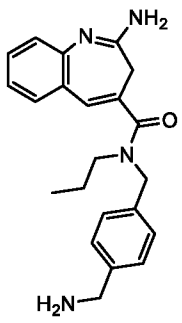
Bz No.	Structure	MW	HEK293 hTLR7 EC50 (nM)	HEK293 hTLR8 EC50 (nM)
Bz-35		523.7	9000	9000
Bz-36		1114.4	ND	ND
Bz-37		544.7	9000	9000
Bz-38		1030.2	ND	ND

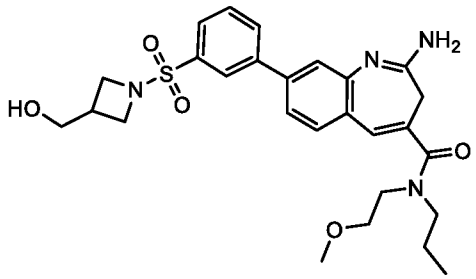
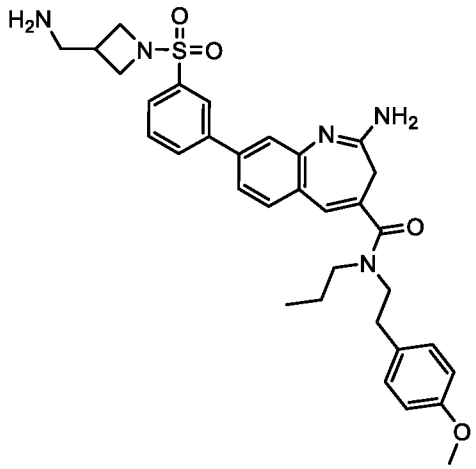
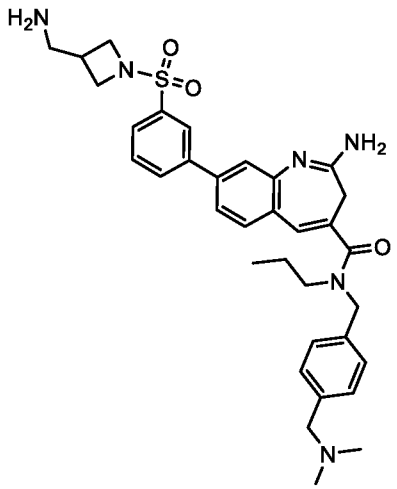
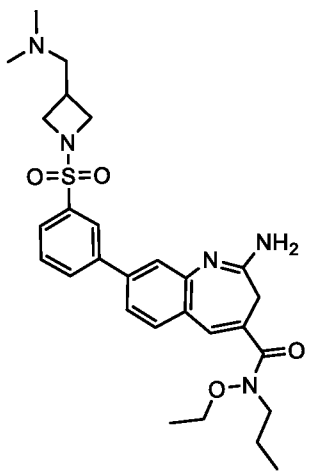
Bz-39		605.7	42	728
Bz-40		509.8	332	9000
Bz-41		562.7	9000	9000
Bz-42		512.6	9000	49

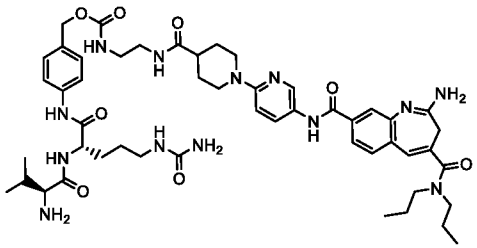
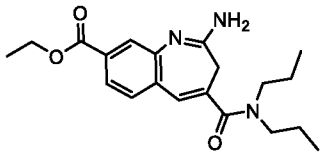
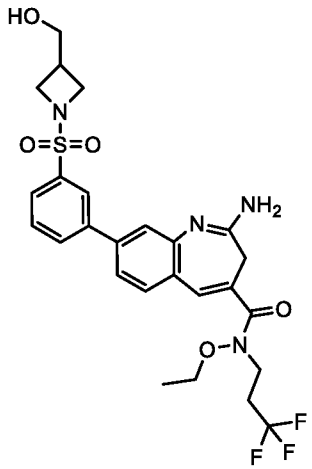
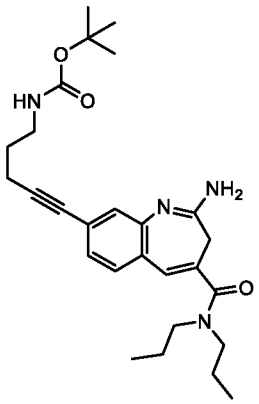
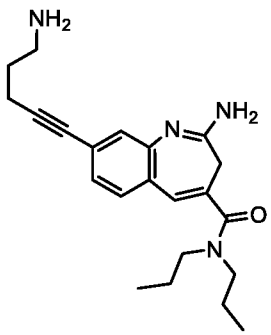
Bz-43		568.6	9000	7005
Bz-44		757.0	9000	1022
Bz-45		379.5	9000	345
Bz-46		993.2	ND	ND

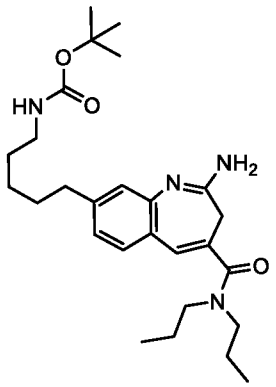
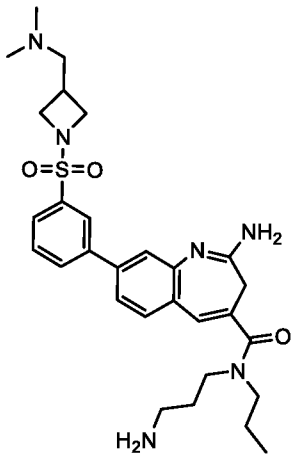
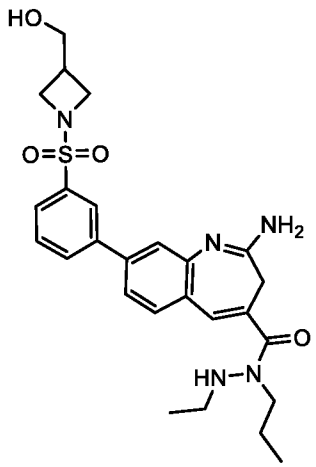
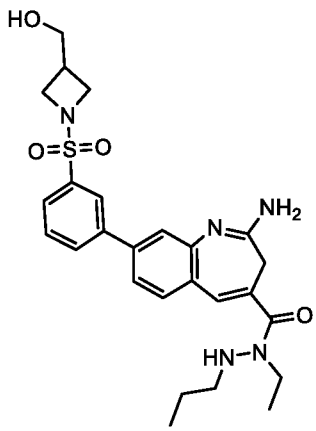
Bz-47		564.6	9000	341
Bz-48		528.7	ND	499
Bz-49		656.8	9000	9000
Bz-50		482.6	ND	9000

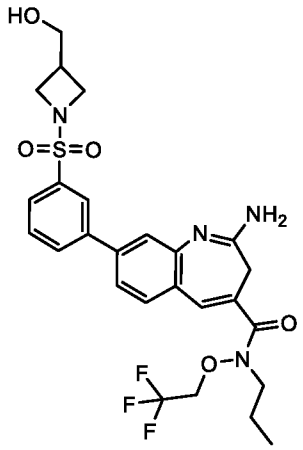
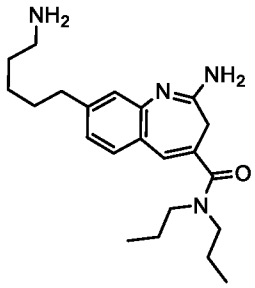
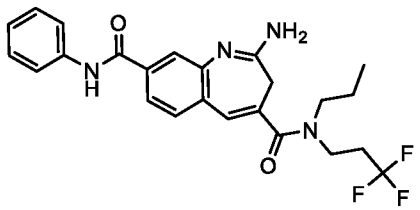
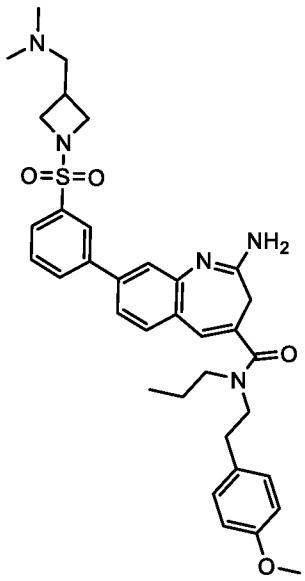
Bz-51		673.8	1428	1919
Bz-52		521.7	ND	1320
Bz-53		535.7	ND	249
Bz-54		523.7	ND	198

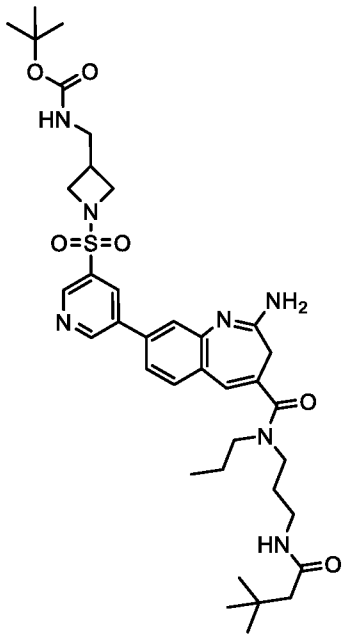
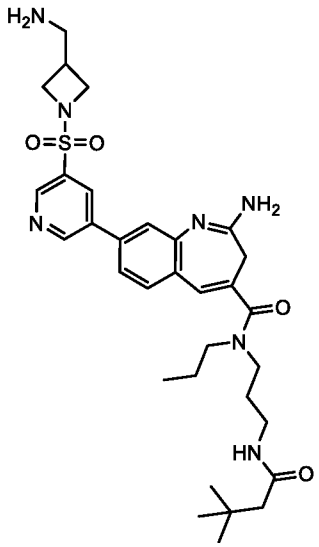
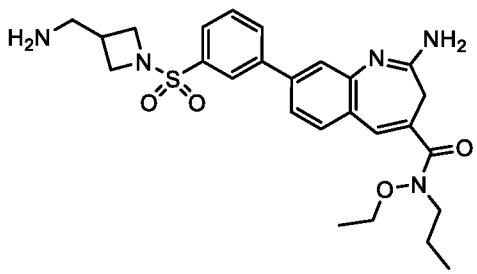
Bz-55		567.7	9000	1040
Bz-56		507.7	ND	111
Bz-57		549.7	ND	741
Bz-58		468.6	9000	9000
Bz-59		362.5	9000	870

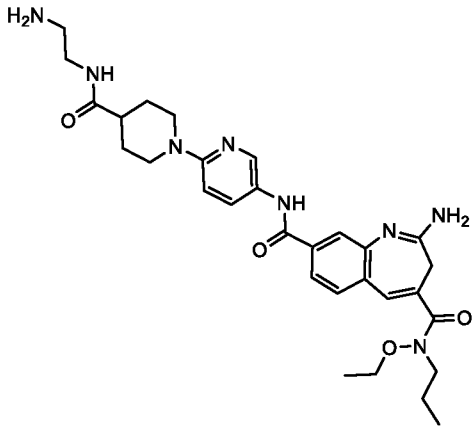
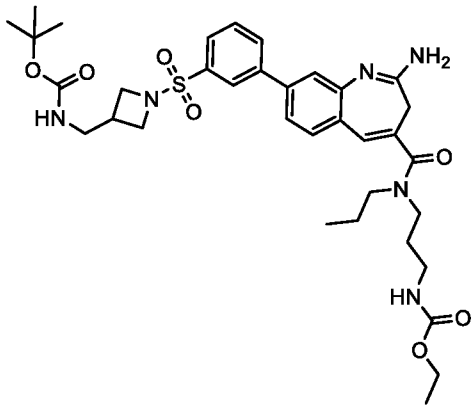
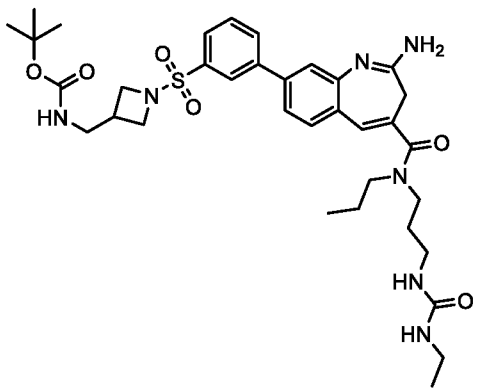
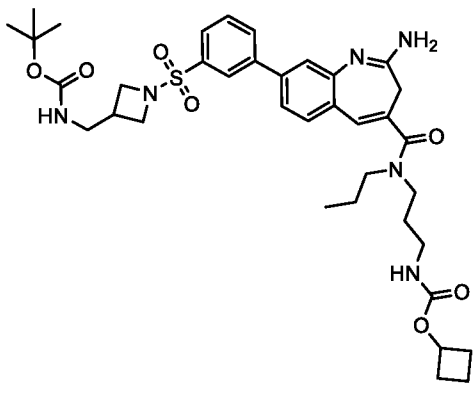
Bz-60		562.7	9000	288
Bz-61		601.8	9000	5846
Bz-62		614.8	9000	9000
Bz-63		539.7	1270	8

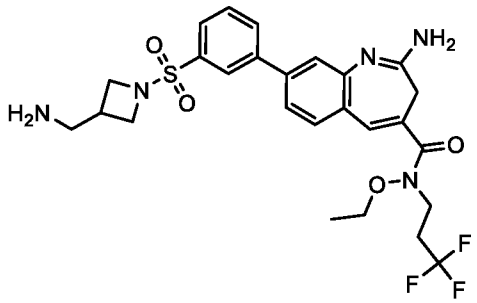
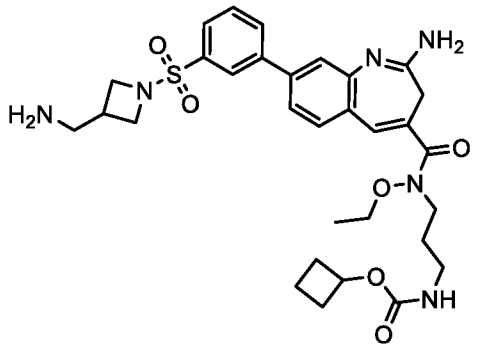
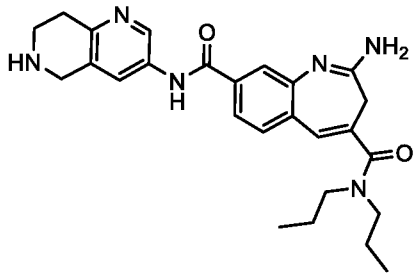
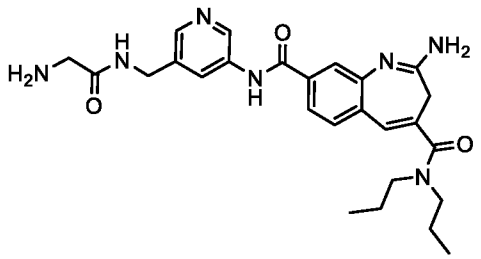
Bz-64		980.2	ND	ND
Bz-65		357.5	3929	5902
Bz-66		566.6	4614	26
Bz-67		466.6	3926	2053
Bz-68		366.5	4595	3070

Bz-69		470.7	3205	6670
Bz-70		552.7	ND	ND
Bz-71		511.6	9000	2752
Bz-72		511.6	ND	4253

Bz-73		566.6	4478	120
Bz-74		370.5	9000	2555
Bz-75		458.5	9000	246
Bz-76		629.8	969	786

Bz-77		723.9	ND	ND
Bz-78		623.8	ND	ND
Bz-79		511.6	ND	ND

Bz-80		576.7	ND	ND
Bz-81		696.9	ND	ND
Bz-82		695.9	ND	ND
Bz-83		722.9	ND	ND

Bz-84		565.6	ND	ND
Bz-85		624.8	ND	ND
Bz-86		460.6	ND	ND
Bz-87		491.6	ND	ND

AMINOBENZAZEPINE-LINKER COMPOUNDS

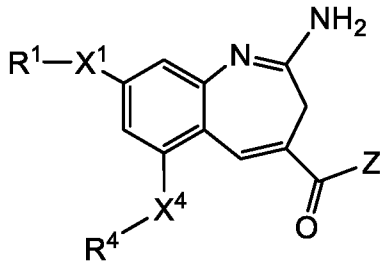
The immunoconjugates of the invention are prepared by conjugation of an antibody with an aminobenzazepine-linker compound. The aminobenzazepine-linker compounds comprise an aminobenzazepine moiety covalently attached to a linker unit. The linker units comprise functional groups and subunits which affect stability, permeability, solubility, and other pharmacokinetic, safety, and efficacy properties of the immunoconjugates. The linker unit includes a reactive functional group which reacts, i.e. conjugates, with a reactive functional group of the antibody. For example, a nucleophilic group such as a lysine side chain amino of the antibody reacts with an electrophilic reactive functional group of the aminobenzazepine-linker compound to form the immunoconjugate. Also, for example, a cysteine thiol of the

antibody reacts with a maleimide or bromoacetamide group of the aminobenzazepine-linker compound to form the immunoconjugate.

Electrophilic reactive functional group suitable for the aminobenzazepine-linker compounds include, but are not limited to, N-hydroxysuccinimidyl (NHS) esters and N-hydroxysulfosuccinimidyl (sulfo-NHS) esters (amine reactive); carbodiimides (amine and carboxyl reactive); hydroxymethyl phosphines (amine reactive); maleimides (thiol reactive); halogenated acetamides such as *N*-iodoacetamides (thiol reactive); aryl azides (primary amine reactive); fluorinated aryl azides (reactive via carbon-hydrogen (C-H) insertion); pentafluorophenyl (PFP) esters (amine reactive); tetrafluorophenyl (TFP) esters (amine reactive); imidoesters (amine reactive); isocyanates (hydroxyl reactive); vinyl sulfones (thiol, amine, and hydroxyl reactive); pyridyl disulfides (thiol reactive); and benzophenone derivatives (reactive via C-H bond insertion). Further reagents include, but are not limited, to those described in Hermanson, *Bioconjugate Techniques* 2nd Edition, Academic Press, 2008.

The invention provides solutions to the limitations and challenges to the design, preparation and use of immunoconjugates. Some linkers may be labile in the blood stream, thereby releasing unacceptable amounts of the adjuvant/drug prior to internalization in a target cell (Khot, A. et al (2015) *Bioanalysis* 7(13):1633–1648). Other linkers may provide stability in the bloodstream, but intracellular release effectiveness may be negatively impacted. Linkers that provide for desired intracellular release typically have poor stability in the bloodstream. Alternatively stated, bloodstream stability and intracellular release are typically inversely related. In addition, in standard conjugation processes, the amount of adjuvant/drug moiety loaded on the antibody, i.e. drug loading, the amount of aggregate that is formed in the conjugation reaction, and the yield of final purified conjugate that can be obtained are interrelated. For example, aggregate formation is generally positively correlated to the number of equivalents of adjuvant/drug moiety and derivatives thereof conjugated to the antibody. Under high drug loading, formed aggregates must be removed for therapeutic applications. As a result, drug loading-mediated aggregate formation decreases immunoconjugate yield and can render process scale-up difficult.

Exemplary embodiments include an aminobenzazepine-linker compound of Formula **II**:



II

wherein

Z is selected from H, $-O(C_1\text{-}C_8$ alkyl), and $N(X^2R^2)(X^3R^3)$;

R^1, R^2, R^3, and R^4 are independently selected from the group consisting of H, $C_1\text{-}C_{12}$ alkyl, $C_2\text{-}C_6$ alkenyl, $C_2\text{-}C_6$ alkynyl, $C_3\text{-}C_{12}$ carbocyclyl, $C_6\text{-}C_{20}$ aryl, $C_2\text{-}C_9$ heterocyclyl, and $C_1\text{-}C_{20}$ heteroaryl, where alkyl, alkenyl, alkynyl, carbocyclyl, aryl, heterocyclyl, and heteroaryl are independently and optionally substituted with one or more groups selected from:

$-(C_1\text{-}C_{12}$ alkyldiyl$)-N(R^5)-*$;

$-(C_1\text{-}C_{12}$ alkyldiyl$)-N(R^5)_2$;

$-(C_3\text{-}C_{12}$ carbocyclyl$)$;

$-(C_3\text{-}C_{12}$ carbocyclyl$)-*$;

$-(C_3\text{-}C_{12}$ carbocyclyl$)-(C_1\text{-}C_{12}$ alkyldiyl$)-NR^5-*$;

$-(C_3\text{-}C_{12}$ carbocyclyl$)-(C_1\text{-}C_{12}$ alkyldiyl$)-N(R^5)_2$;

$-(C_3\text{-}C_{12}$ carbocyclyl$)-NR^5-C(=NR^5)NR^5-*$;

$-(C_6\text{-}C_{20}$ aryl$)$;

$-(C_6\text{-}C_{20}$ aryl$)-*$;

$-(C_6\text{-}C_{20}$ aryldiyl$)-N(R^5)-*$;

$-(C_6\text{-}C_{20}$ aryldiyl$)-(C_1\text{-}C_{12}$ alkyldiyl$)-N(R^5)-*$;

$-(C_6\text{-}C_{20}$ aryldiyl$)-(C_1\text{-}C_{12}$ alkyldiyl$)-N(R^5)_2$;

$-(C_6\text{-}C_{20}$ aryldiyl$)-(C_1\text{-}C_{12}$ alkyldiyl$)-NR^5-C(=NR^{5a})N(R^5)-*$;

$-(C_2\text{-}C_{20}$ heterocyclyl$)$;

$-(C_2\text{-}C_{20}$ heterocyclyl$)-*$;

$-(C_2\text{-}C_9$ heterocyclyl$)-(C_1\text{-}C_{12}$ alkyldiyl$)-NR^5-*$;

$-(C_2\text{-}C_9$ heterocyclyl$)-(C_1\text{-}C_{12}$ alkyldiyl$)-N(R^5)_2$;

$-(C_2\text{-}C_9$ heterocyclyl$)-NR^5-C(=NR^{5a})NR^5-*$;

$-(C_1\text{-}C_{20}$ heteroaryl$)$;

$-(C_1\text{-}C_{20}$ heteroaryl$)-*$;

$-(C_1\text{-}C_{20}$ heteroaryl$)-(C_1\text{-}C_{12}$ alkyldiyl$)-N(R^5)-*$;

$-(C_1\text{-}C_{20}$ heteroaryl$)-(C_1\text{-}C_{12}$ alkyldiyl$)-N(R^5)_2$;

$-(C_1\text{-}C_{20}$ heteroaryl$)-NR^5-C(=NR^{5a})N(R^5)-*$;

$-C(=O)-*$;

$-C(=O)-(C_2\text{-}C_{20}$ heterocyclyldiyl$)-*$;

$-C(=O)N(R^5)_2$;

$-C(=O)N(R^5)-*$;

$-C(=O)N(R^5)-(C_1\text{-}C_{12}$ alkyldiyl$)-N(R^5)C(=O)R^5$;

–C(=O)N(R^5)–(C_1-C_{12} alkyldiyl)–N(R^5)C(=O)N(R^5)$_2$;

–C(=O)NR^5–(C_1-C_{12} alkyldiyl)–N(R^5)CO_2R^5;

–C(=O)NR^5–(C_1-C_{12} alkyldiyl)–N(R^5)C(=NR^{5a})N(R^5)$_2$;

–C(=O)NR^5–(C_1-C_{12} alkyldiyl)–NR^5C(=NR^{5a})R^5;

–C(=O)NR^5–(C_1-C_8 alkyldiyl)–NR^5(C_2-C_5 heteroaryl);

–C(=O)NR^5–(C_1-C_{20} heteroaryldiyl)–N(R^5)–*;

–C(=O)NR^5–(C_1-C_{20} heteroaryldiyl)–*;

–C(=O)NR^5–(C_1-C_{20} heteroaryldiyl)–(C_1-C_{12} alkyldiyl)–N(R^5)$_2$;

–C(=O)NR^5–(C_1-C_{20} heteroaryldiyl)–(C_2-C_{20} heterocyclyldiyl)–C(=O)NR^5–(C_1-C_{12} alkyldiyl)–NR^5–*;

–N(R^5)$_2$;

–N(R^5)–*;

–N(R^5)C(=O)R^5;

–N(R^5)C(=O)–*;

–N(R^5)C(=O)N(R^5)$_2$;

–N(R^5)C(=O)N(R^5)–*;

–N(R^5)CO_2R^5;

–NR^5C(=NR^{5a})N(R^5)$_2$;

–NR^5C(=NR^{5a})N(R^5)–*;

–NR^5C(=NR^{5a})R^5;

–N(R^5)–(C_2-C_5 heteroaryl);

–O–(C_1-C_{12} alkyl);

–O–(C_1-C_{12} alkyldiyl)–N(R^5)$_2$;

–O–(C_1-C_{12} alkyldiyl)–N(R^5)–*;

–S(=O)$_2$–(C_2-C_{20} heterocyclyldiyl)–*;

–S(=O)$_2$–(C_2-C_{20} heterocyclyldiyl)–(C_1-C_{12} alkyldiyl)–N(R^5)$_2$;

–S(=O)$_2$–(C_2-C_{20} heterocyclyldiyl)–(C_1-C_{12} alkyldiyl)–NR^5–*; and

–S(=O)$_2$–(C_2-C_{20} heterocyclyldiyl)–(C_1-C_{12} alkyldiyl)–OH;

or R^2 and R^3 together form a 5- or 6-membered heterocyclyl ring;

X^1, X^2, X^3, and X^4 are independently selected from the group consisting of a bond, C(=O), C(=O)N(R^5), O, N(R^5), S, S(O)$_2$, and S(O)$_2$N(R^5);

R^5 is selected from the group consisting of H, C_6-C_{20} aryl, C_6-C_{20} aryldiyl, C_1-C_{12} alkyl, and C_1-C_{12} alkyldiyl, or two R^5 groups together form a 5- or 6-membered heterocyclyl ring;

R^{5a} is selected from the group consisting of C_6-C_{20} aryl and C_1-C_{20} heteroaryl;

where the asterisk * indicates the attachment site of L, and where one of R^1, R^2, R^3 and R^4 is attached to L;

L is the linker selected from the group consisting of:

Q–C(=O)–(PEG)–;

Q–C(=O)–(PEG)–C(=O)–;

Q–C(=O)–(PEG)–O–;

Q–C(=O)–(PEG)–C(=O)–(PEP)–;

Q–C(=O)–(PEG)–C(=O)N(R^5)–(C_1-C_{12} alkyldiyl)–;

Q–C(=O)–(PEG)–C(=O)N(R^5)–(C_1-C_{12} alkyldiyl)–N(R^5)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–;

Q–C(=O)–(PEG)–C(=O)N(R^5)–(C_1-C_{12} alkyldiyl)–(MCgluc)–;

Q–C(=O)–(PEG)–C(=O)–(MCgluc)–;

Q–C(=O)–(PEG)–C(=O)–(PEP)–N(R^5)–(C_1-C_{12} alkyldiyl)–;

Q–C(=O)–(PEG)–C(=O)–(PEP)–N(R^5)–(C_1-C_{12} alkyldiyl)–N(R^5)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–;

Q–C(=O)–(PEG)–N(R^5)–;

Q–C(=O)–(PEG)–N(R^5)–(PEG)–C(=O)–(PEP)–;

Q–C(=O)–(PEG)–N^+(R^5)$_2$–(PEG)–C(=O)–(PEP)–;

Q–C(=O)–(PEG)–C(=O)–N(R^5)CH(AA_1)C(=O)–(PEG)–C(=O)–(PEP)–;

Q–C(=O)–(PEG)–C(=O)–N(R^5)CH(AA_1)C(=O)–N(R^5)–(C_1-C_{12} alkyldiyl)–;

Q–C(=O)–(PEG)–SS–(C_1-C_{12} alkyldiyl)–OC(=O)–;

Q–C(=O)–(PEG)–SS–(C_1-C_{12} alkyldiyl)–C(=O)–;

Q–C(=O)–(C_1-C_{12} alkyldiyl)–C(=O)–(PEP)–;

Q–C(=O)–(C_1-C_{12} alkyldiyl)–C(=O)–(PEP)–N(R^5)–(C_1-C_{12} alkyldiyl)–;

Q–C(=O)–(C_1-C_{12} alkyldiyl)–C(=O)–(PEP)–N(R^5)–(C_1-C_{12} alkyldiyl)–N(R^5)–C(=O);

Q–C(=O)–(C_1-C_{12} alkyldiyl)–C(=O)–(PEP)–N(R^5)–(C_1-C_{12} alkyldiyl)–N(R^5)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–;

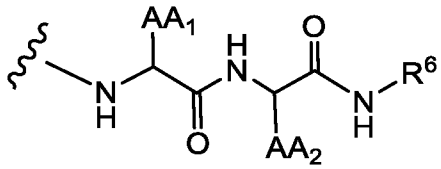
Q–C(=O)–$CH_2CH_2OCH_2CH_2$–(C_1-C_{20} heteroaryldiyl)–CH_2O–(PEG)–C(=O)–(MCgluc)–;

Q–C(=O)–$CH_2CH_2OCH_2CH_2$–(C_1-C_{20} heteroaryldiyl)–CH_2O–(PEG)–C(=O)–(MCgluc)–N(R^5)–(C_1-C_{12} alkyldiyl)–N(R^5)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–; and

Q–$(CH_2)_m$–C(=O)–(PEP)–N(R^5)–(C_1-C_{12} alkyldiyl)–N(R^5)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–;

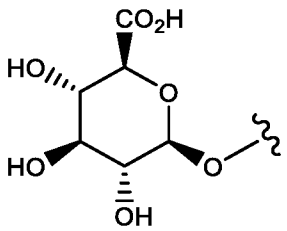
where PEG has the formula:–$(CH_2CH_2O)_n$–$(CH_2)_m$–; m is an integer from 1 to 5, and n is an integer from 2 to 50;

PEP has the formula:



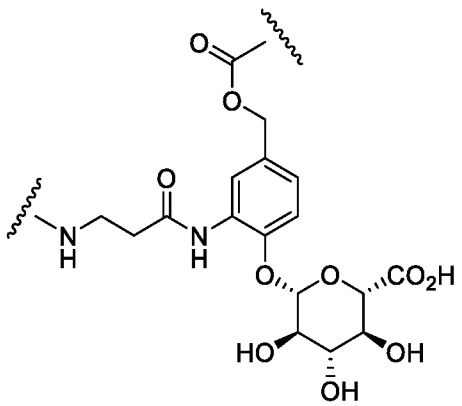
where AA_1 and AA_2 are independently selected from an amino acid side chain, or AA_1 or AA_2 and an adjacent nitrogen atom form a 5-membered ring proline amino acid, and the wavy line indicates a point of attachment and;

R^6 is selected from the group consisting of C_6-C_{20} aryldiyl and C_1-C_{20} heteroaryldiyl, substituted with –CH_2O–C(=O)– and optionally with:

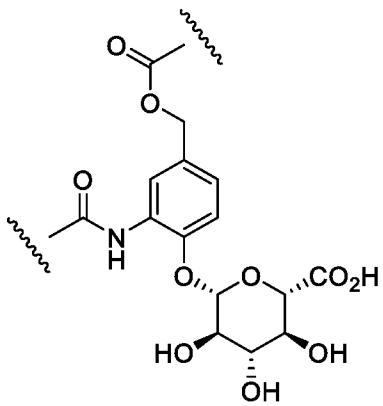


; and

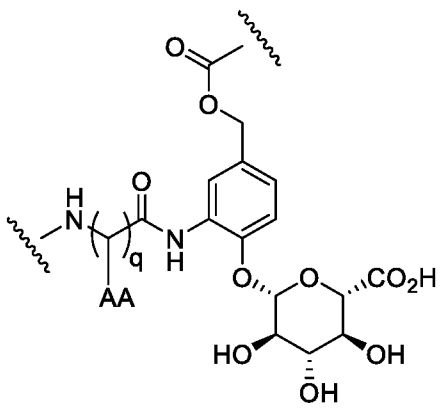
MCgluc is selected from the groups:



;



; and

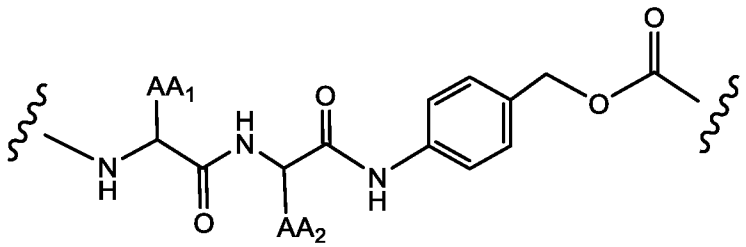


where q is 1 to 8, and AA is an amino acid side chain; and

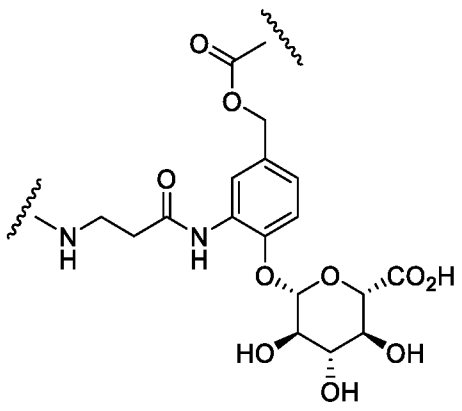
Q is selected from the group consisting of N-hydroxysuccinimidyl, N-hydroxysulfosuccinimidyl, maleimide, and phenoxy substituted with one or more groups independently selected from F, Cl, NO_2, and SO_3^-;

where alkyl, alkyldiyl, alkenyl, alkenyldiyl, alkynyl, alkynyldiyl, aryl, aryldiyl carbocyclyl, carbocyclyldiyl, heterocyclyl, heterocyclyldiyl, heteroaryl, and heteroaryldiyl are optionally substituted with one or more groups independently selected from F, Cl, Br, I, –CN, –CH_3, –CH_2CH_3, –$CH{=}CH_2$, –C≡CH, –C≡CCH_3, –$CH_2CH_2CH_3$, –$CH(CH_3)_2$, –$CH_2CH(CH_3)_2$, –CH_2OH, –CH_2OCH_3, –CH_2CH_2OH, –$C(CH_3)_2OH$, –$CH(OH)CH(CH_3)_2$, –$C(CH_3)_2CH_2OH$, –$CH_2CH_2SO_2CH_3$, –$CH_2OP(O)(OH)_2$, –CH_2F, –CHF_2, –CF_3, –CH_2CF_3, –CH_2CHF_2, –$CH(CH_3)CN$, –$C(CH_3)_2CN$, –CH_2CN, –CH_2NH_2, –$CH_2NHSO_2CH_3$, –CH_2NHCH_3, –$CH_2N(CH_3)_2$, –CO_2H, –$COCH_3$, –CO_2CH_3, –$CO_2C(CH_3)_3$, –$COCH(OH)CH_3$, –$CONH_2$, –$CONHCH_3$, –$CON(CH_3)_2$, –$C(CH_3)_2CONH_2$, –NH_2, –$NHCH_3$, –$N(CH_3)_2$, –$NHCOCH_3$, –$N(CH_3)COCH_3$, –$NHS(O)_2CH_3$, –$N(CH_3)C(CH_3)_2CONH_2$, –$N(CH_3)CH_2CH_2S(O)_2CH_3$, –NHC(=NH)H, –$NHC(=NH)CH_3$, –$NHC(=NH)NH_2$, –$NHC(=O)NH_2$, –$NO_2$, =O, –OH, –$OCH_3$, –$OCH_2CH_3$, –$OCH_2CH_2OCH_3$, –$OCH_2CH_2OH$, –$OCH_2CH_2N(CH_3)_2$, –$O(CH_2CH_2O)_n$–$(CH_2)_mCO_2H$, –$O(CH_2CH_2O)_nH$, –$OP(O)(OH)_2$, –$S(O)_2N(CH_3)_2$, –$SCH_3$, –$S(O)_2CH_3$, and –$S(O)_3H$.

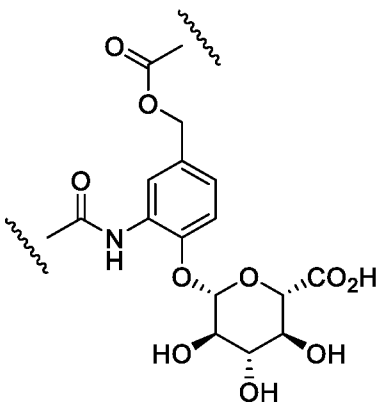
An exemplary embodiment of the aminobenzazepine-linker compound of Formula **II** includes wherein PEP is selected from the groups:



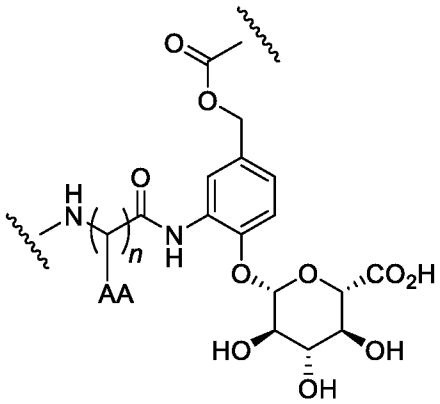
;



;



; and



where n is 1 or more, and AA is an amino acid side chain.

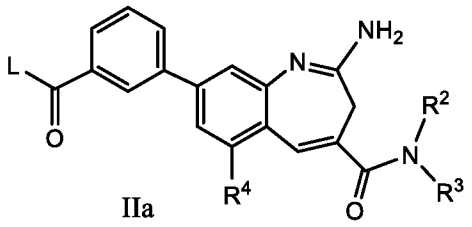
An exemplary embodiment of the aminobenzazepine-linker compound of Formula **II** includes wherein AA_1 and AA_2 are independently selected from a side chain of a naturally-occurring amino acid.

An exemplary embodiment of the aminobenzazepine-linker compound of Formula **II** includes wherein AA_1 and AA_2 are independently selected from H, $-CH_3$, $-CH(CH_3)_2$, $-CH_2(C_6H_5)$, $-CH_2CH_2CH_2CH_2NH_2$, $-CH_2CH_2CH_2NHC(NH)NH_2$, $-CH_2CH(CH_3)_2$, $-CH_2SO_3H$, and $-CH_2CH_2CH_2NHC(O)NH_2$.

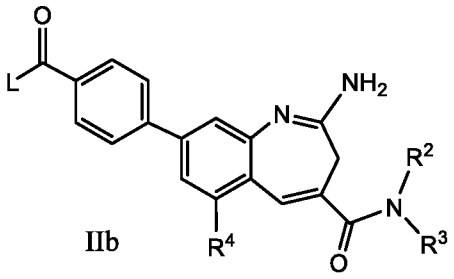
An exemplary embodiment of the aminobenzazepine-linker compound of Formula **II** includes wherein AA_1 is $-CH(CH_3)_2$, and AA_2 is $-CH_2CH_2CH_2NHC(O)NH_2$.

An exemplary embodiment of the aminobenzazepine-linker compound of Formula **II** includes wherein AA_1 and AA_2 are independently selected from GlcNAc aspartic acid, $-CH_2SO_3H$, and $-CH_2OPO_3H$.

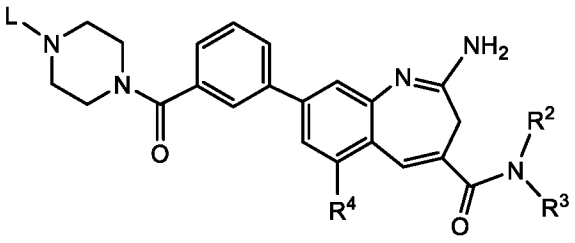
An exemplary embodiment of the aminobenzazepine-linker compound of Formula **II** is selected from Formulas IIa-d:



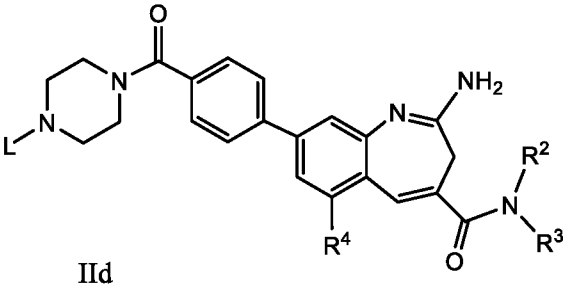
IIa



IIb

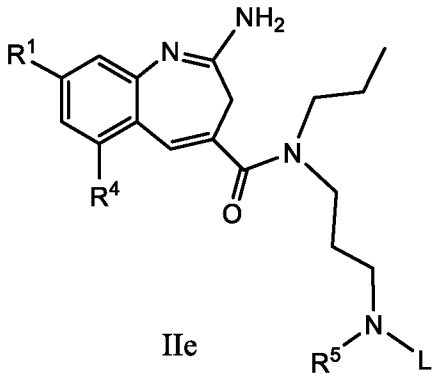


IIc

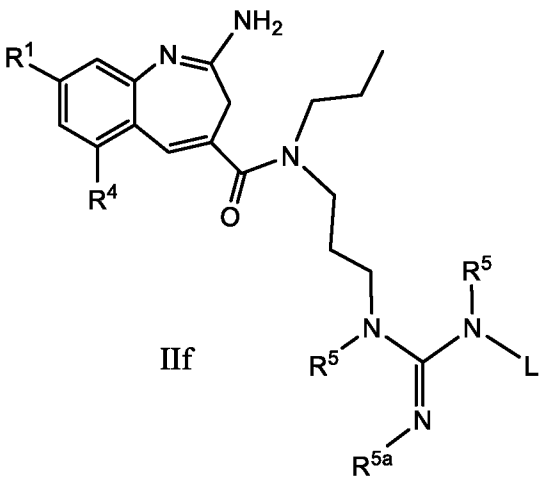


IId

An exemplary embodiment of the aminobenzazepine-linker compound of Formula **II** is selected from Formulas IIe and IIf:



IIe

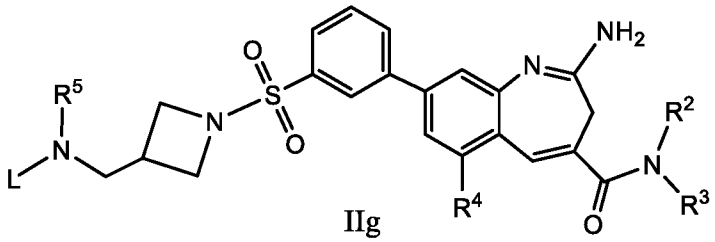


IIf

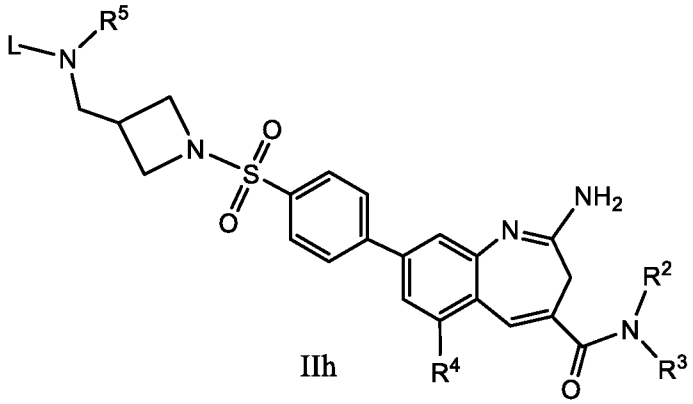
where R^{5a} of formula IIf is phenyl, optionally substituted with one or more groups selected from F, Cl, Br, I, –CN, and $–NO_2$.

An exemplary embodiment of the aminobenzazepine-linker compound of Formula **II** includes wherein L is Q–C(=O)–(PEG)– or Q–C(=O)–(PEG)–C(=O)– .

An exemplary embodiment of the aminobenzazepine-linker compound of Formula **II** is selected from Formulas IIg and IIh:



IIg



IIh

An exemplary embodiment of the aminobenzazepine-linker compound of Formula **II** includes wherein L is –C(=O)–(PEG)–C(=O)–(PEP)–.

An exemplary embodiment of the aminobenzazepine-linker compound of Formula **II** includes wherein R^2 and R^3 are each C_1-C_8 alkyl.

An exemplary embodiment of the aminobenzazepine-linker compound of Formula **II** includes wherein R^2 and R^3 are each $–CH_2CH_2CH_3$.

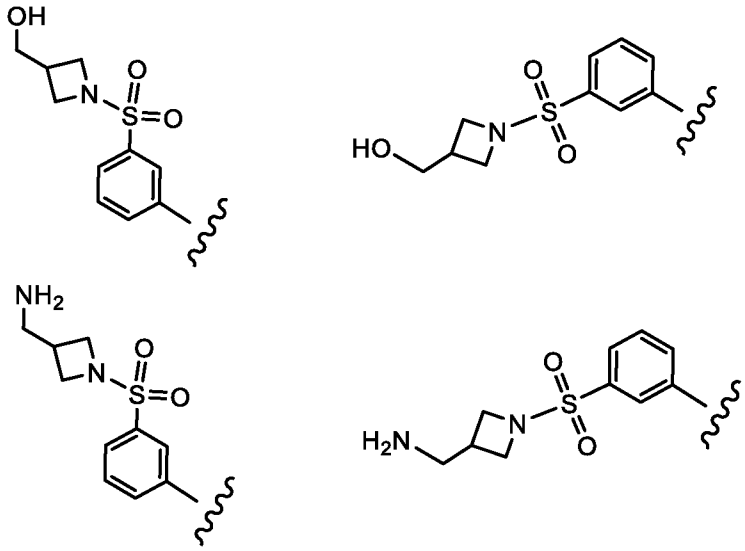
An exemplary embodiment of the aminobenzazepine-linker compound of Formula **II** includes wherein X^2 and X^3 are each a bond, and R^2 or R^3 is –O–(C_1-C_{12} alkyl).

An exemplary embodiment of the aminobenzazepine-linker compound of Formula **II** includes wherein X^2 and X^3 are each a bond, and R^2 or R^3 is $–OCH_2CH_3$.

An exemplary embodiment of the aminobenzazepine-linker compound of Formula **II** includes wherein one of R^1 and R^4 is selected from –(C_6-C_{20} aryldiyl)–$S(=O)_2$–(C_2-C_{20} heterocyclyldiyl)–(C_1-C_{12} alkyldiyl)–$N(R^5)_2$ and –(C_6-C_{20} aryldiyl)–$S(=O)_2$–(C_2-C_{20} heterocyclyldiyl)–(C_1-C_{12} alkyldiyl)–OH.

An exemplary embodiment of the aminobenzazepine-linker compound of Formula **II** includes wherein C_6-C_{20} aryldiyl is phenyldiyl and C_2-C_{20} heterocyclyldiyl is azetidindiyl.

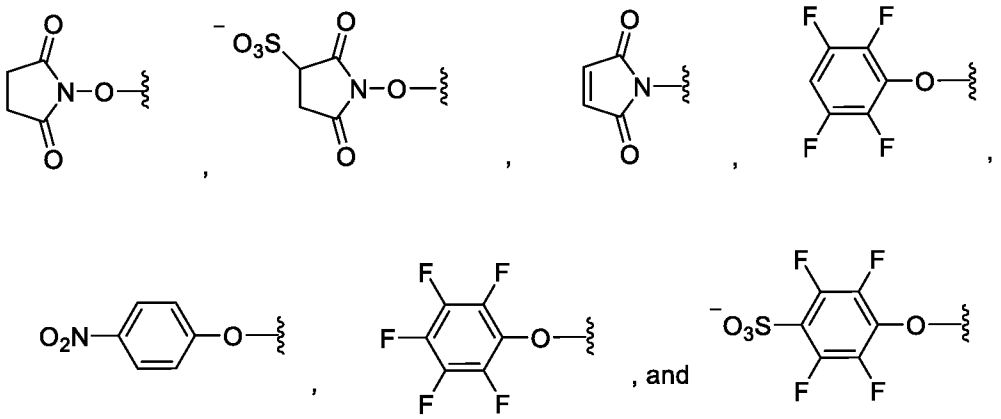
An exemplary embodiment of the aminobenzazepine-linker compound of Formula **II** is selected from the formulas:



An exemplary embodiment of the aminobenzazepine-linker compound of Formula **II** includes wherein one of R^1 and R^4 is $-C(=O)NR^5-(C_1\text{-}C_{20}$ heteroaryldiyl$)-(C_2\text{-}C_{20}$ heterocyclyldiyl$)-C(=O)NR^5-(C_1\text{-}C_{12}$ alkyldiyl$)-NR^5-L$.

An exemplary embodiment of the aminobenzazepine-linker compound of Formula **II** includes wherein $C_1\text{-}C_{20}$ heteroaryldiyl is pyridindiyl and $C_2\text{-}C_{20}$ heterocyclyldiyl is piperidiyl.

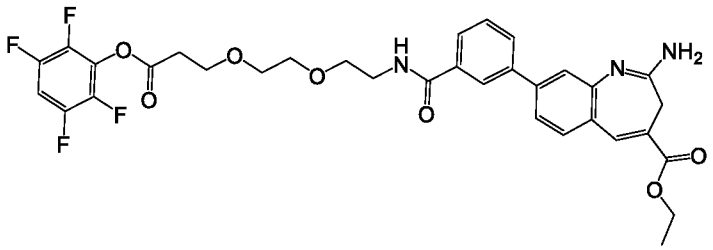
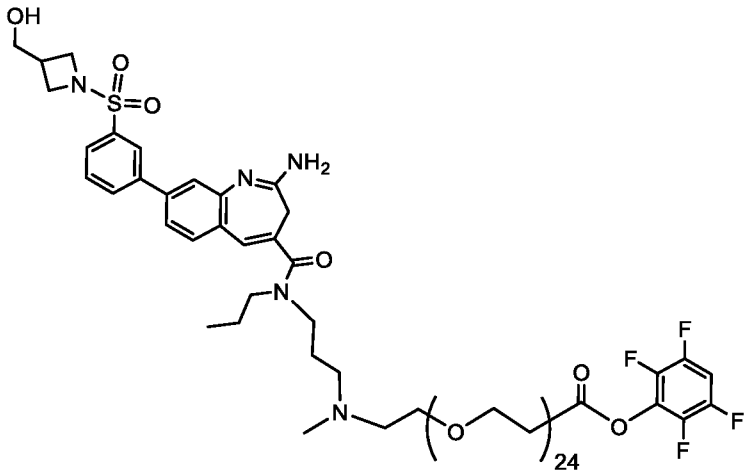
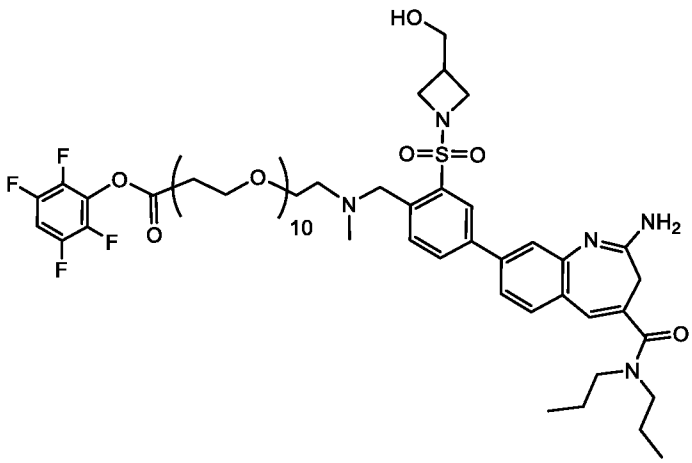
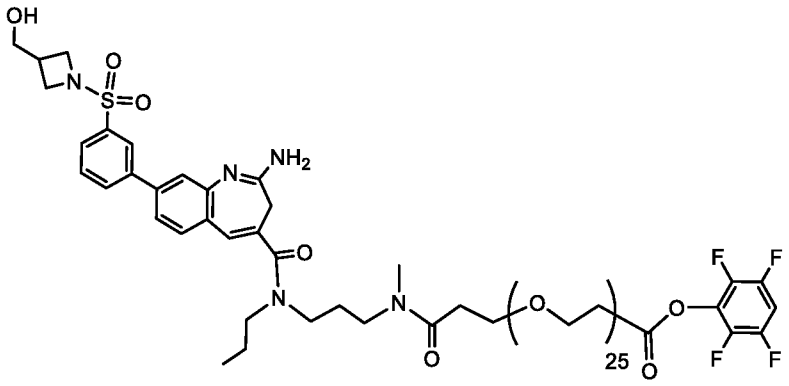
An exemplary embodiment of the aminobenzazepine-linker compound of Formula **II** includes wherein Q is selected from:

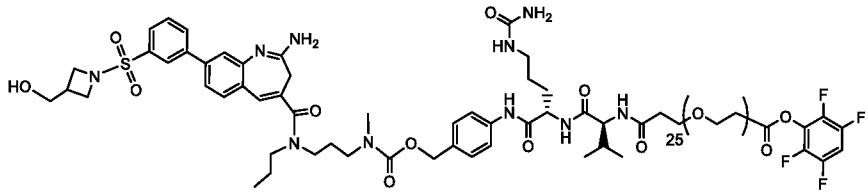
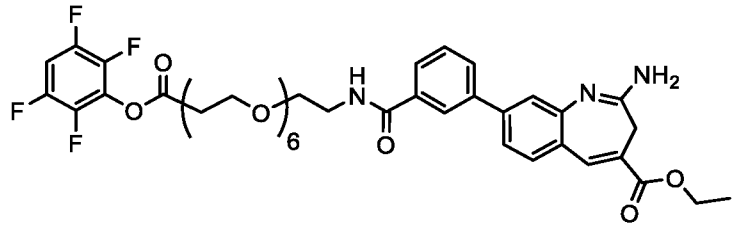
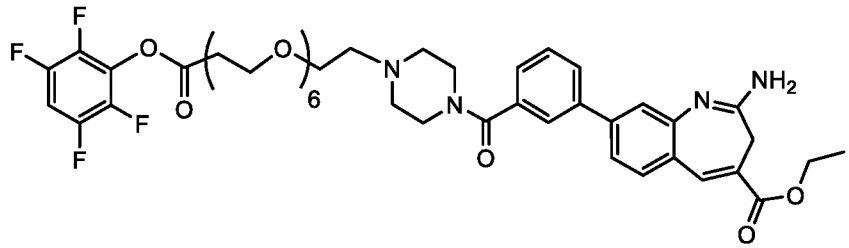
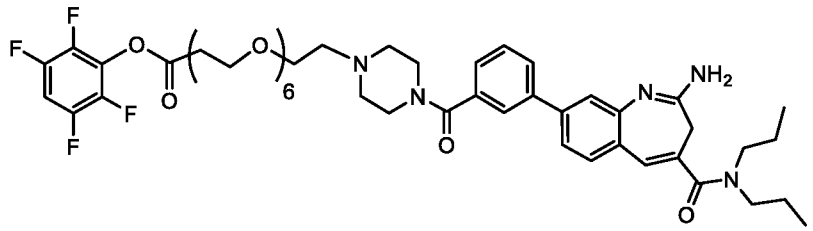
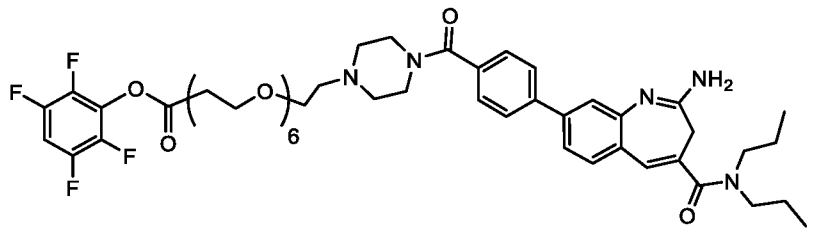
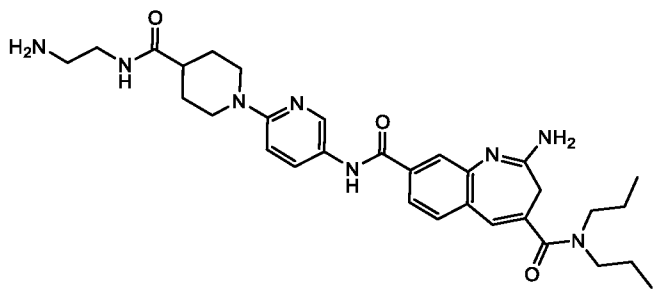


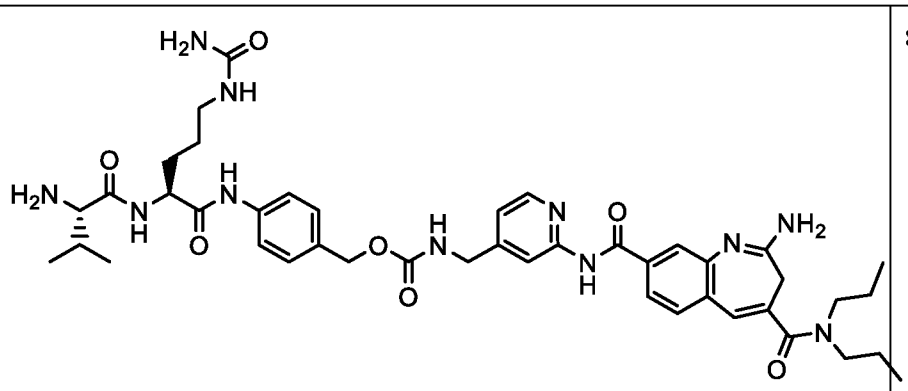
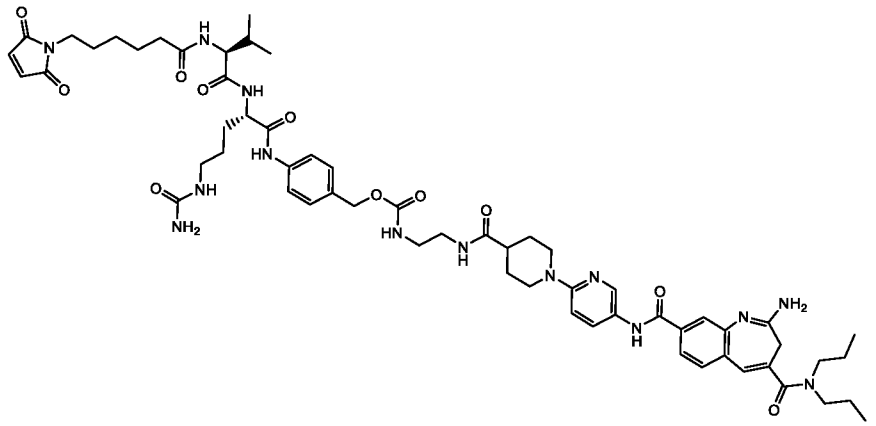
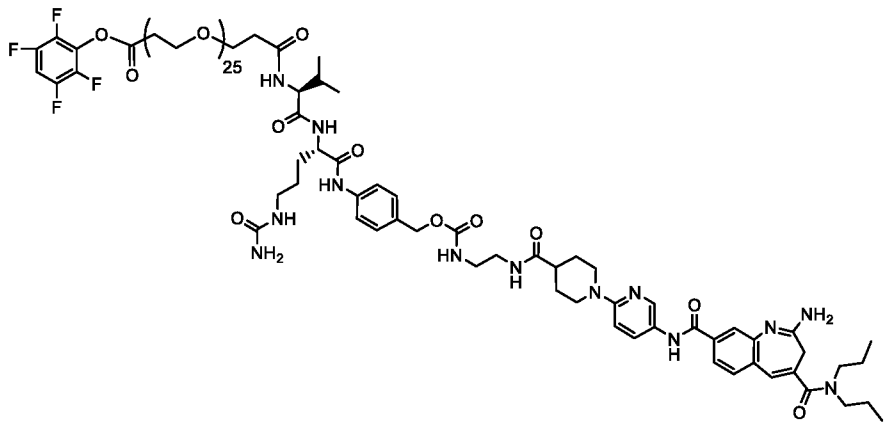
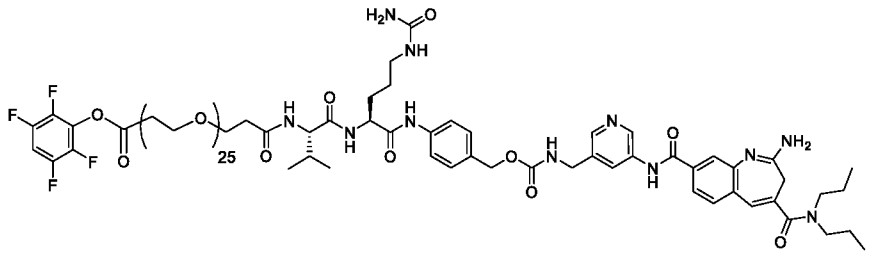
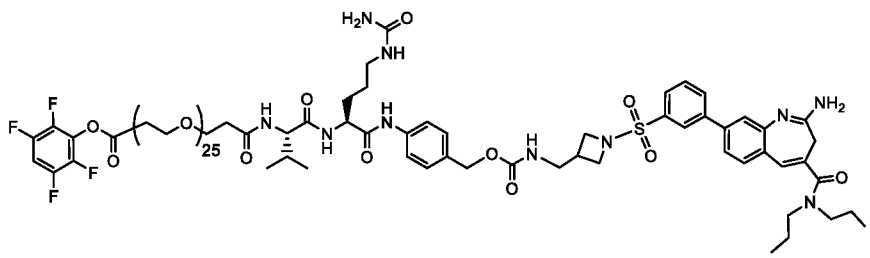
The invention includes all reasonable combinations, and permutations of the features, of the Formula II embodiments.

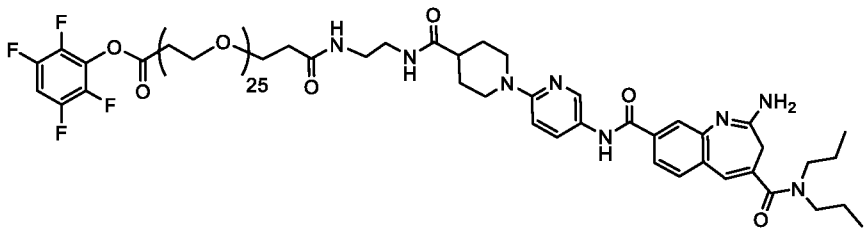
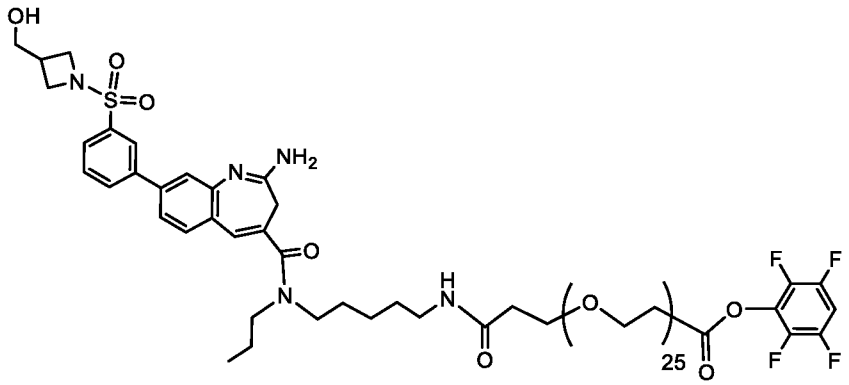
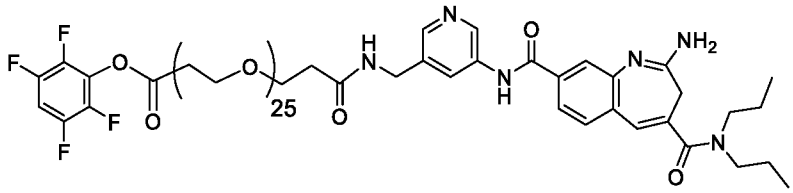
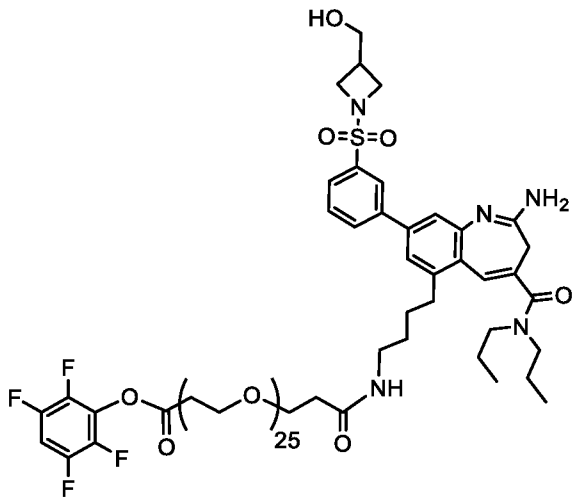
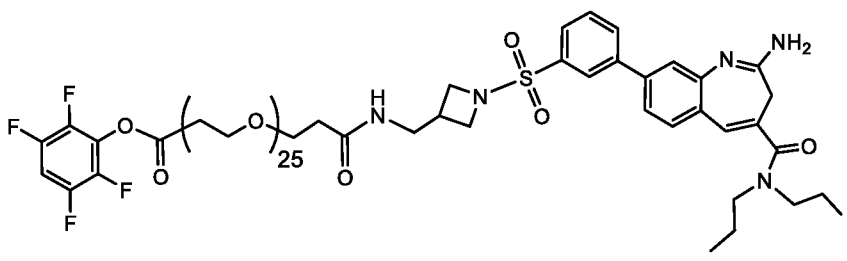
An exemplary embodiment of the aminobenzazepine-linker compound of Formula **II** is selected from the Table 2a, 2b, and 2c compounds. Each compound was synthesized and purified by the methods in the Examples provided herein, characterized by mass spectrometry, and shown to have the mass indicated. The aminobenzazepine-linker compounds of Tables 2a, 2b, and 2c demonstrate the surprising and unexpected property of TLR8 agonist selectivity which may predict useful therapeutic activity to treat cancer and other disorders.

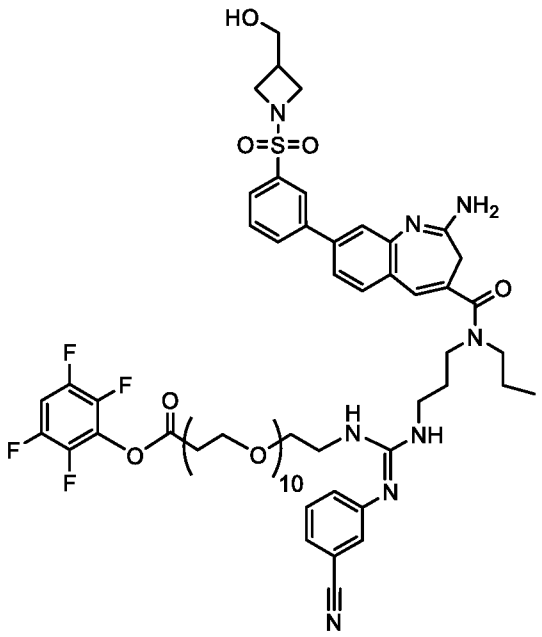
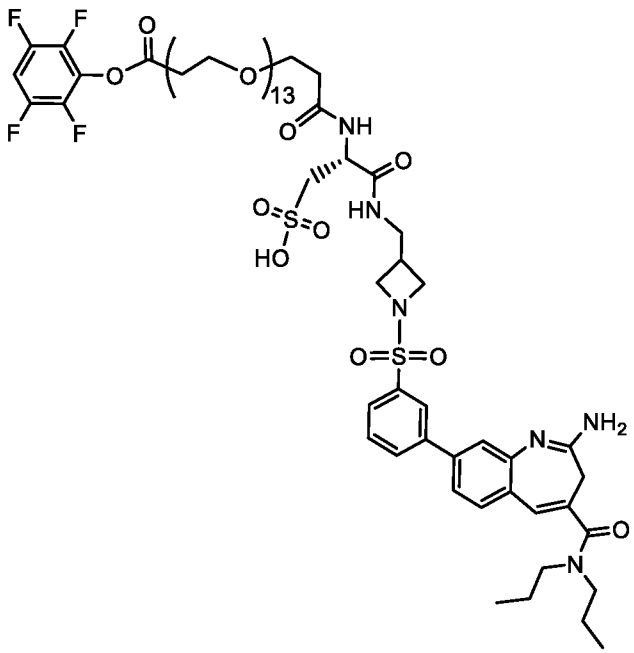
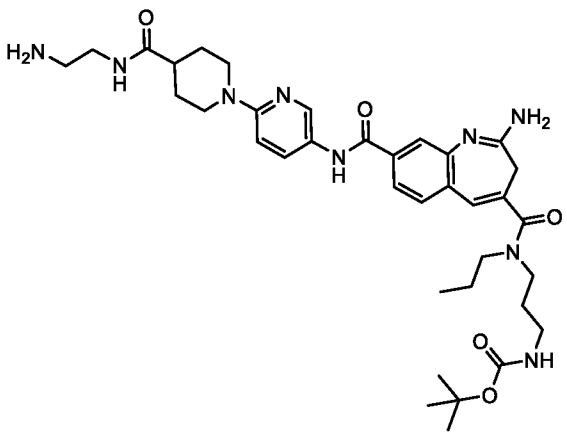
Table 2a: Aminobenzazepine-linker Formula II compounds (BzL) and intermediates

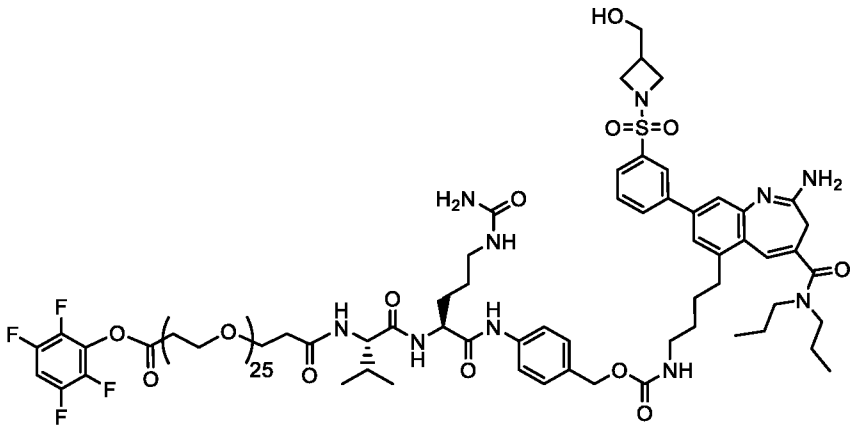
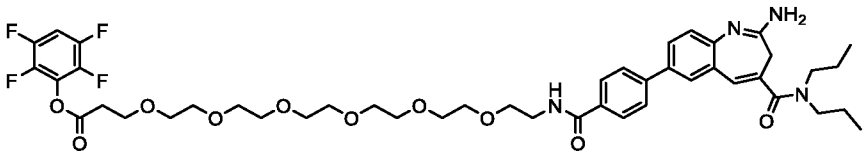
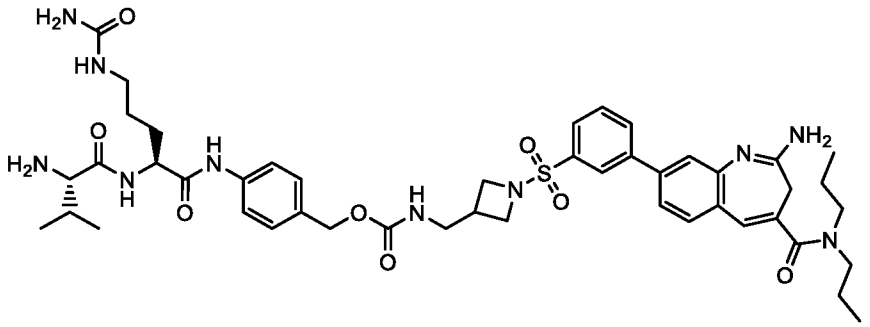
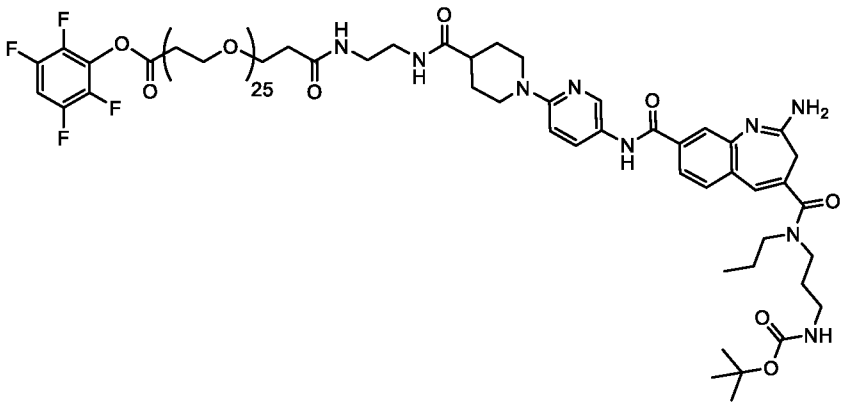
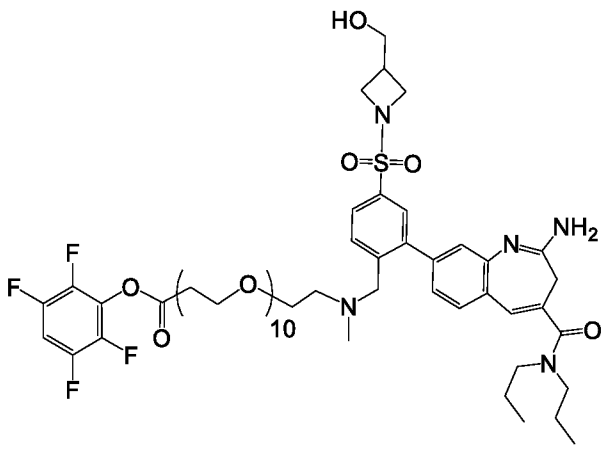
BzL No.	Structure	MW
BzL-1		657.6
BzL-2		1817.1
BzL-3		1214.4
BzL-4		1889.1

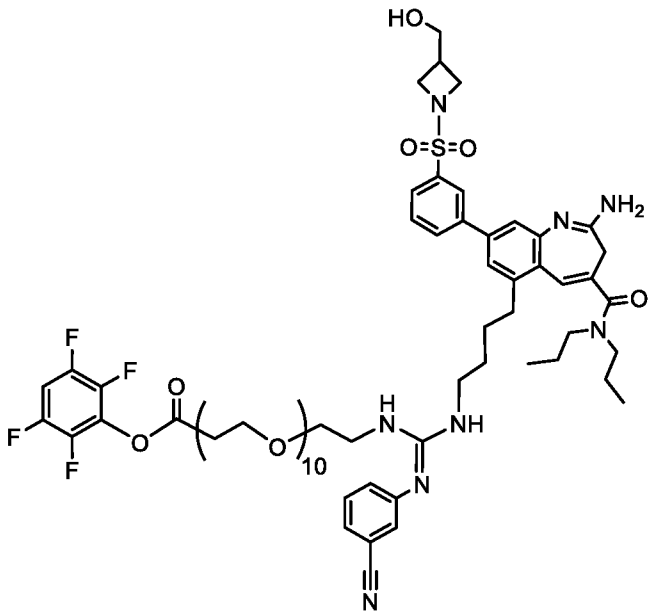
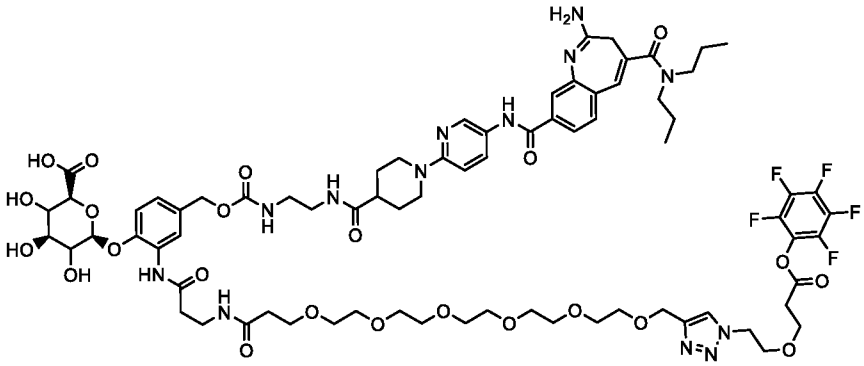
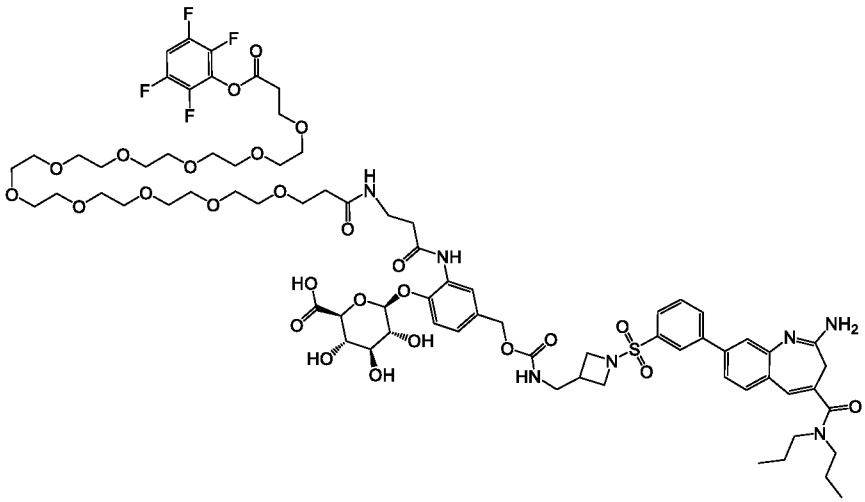
BzL-5		2294.6
BzL-6		833.82
BzL-7		902.9
BzL-8		958.1
BzL-9		958.1
BzL-10		574.7

BzL-11		840.0
BzL-12		1173.4
BzL-13		2329.6
BzL-14		2189.4
BzL-15		2264.6

BzL-16		1924.2
BzL-17		1903.2
BzL-18		1784
BzL-19		1931.2
BzL-20		1859.1

BzL-21		1329.5
BzL-22		1481.6
BzL-23		689.9

BzL-24		2336.7
BzL-25		888.95
BzL-26		915.1
BzL-27		2039.3
BzL-28		1214.4

BzL-29		1385.6
BzL-30		1642.6
BzL-31		1610.7

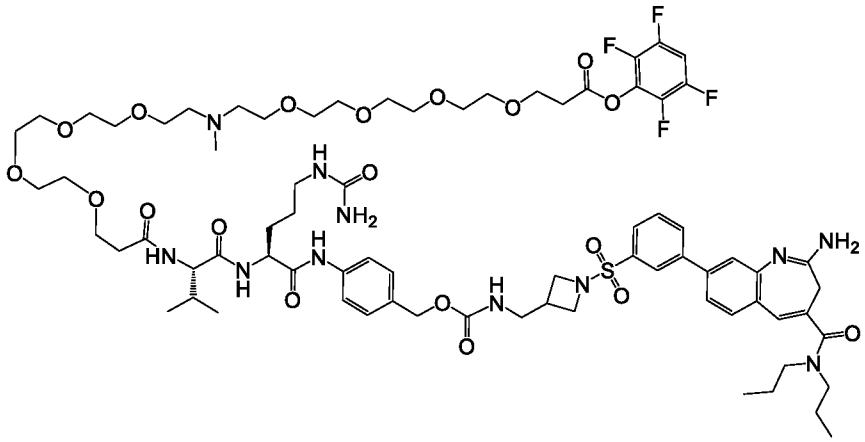
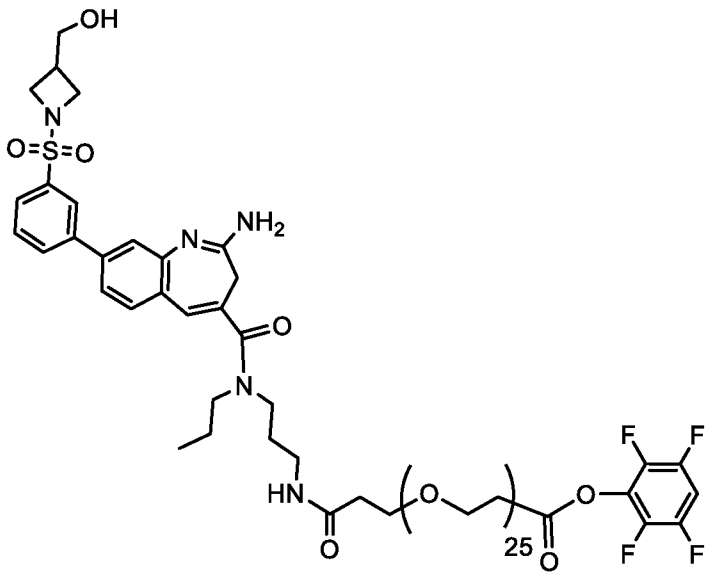
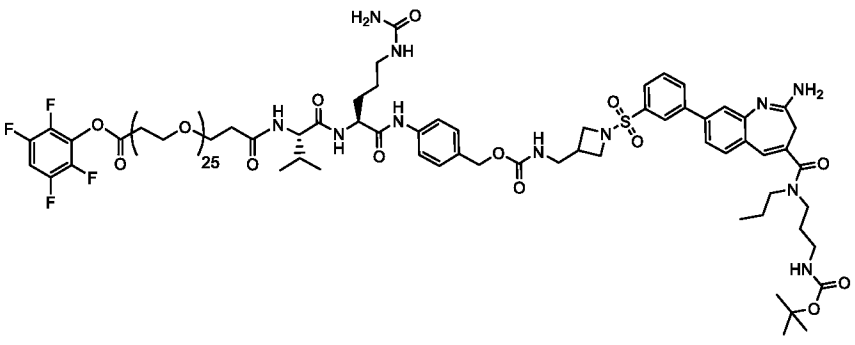
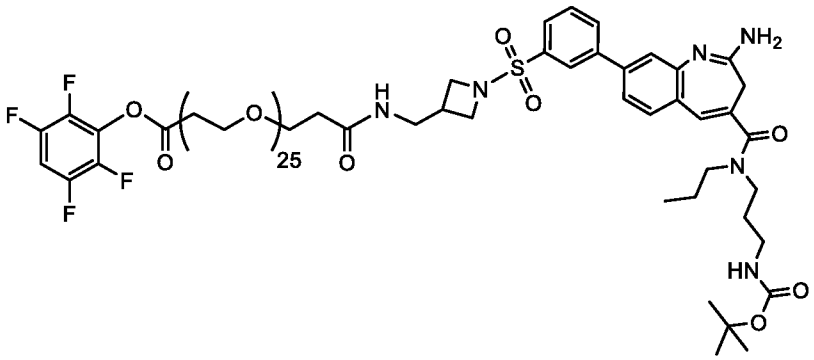
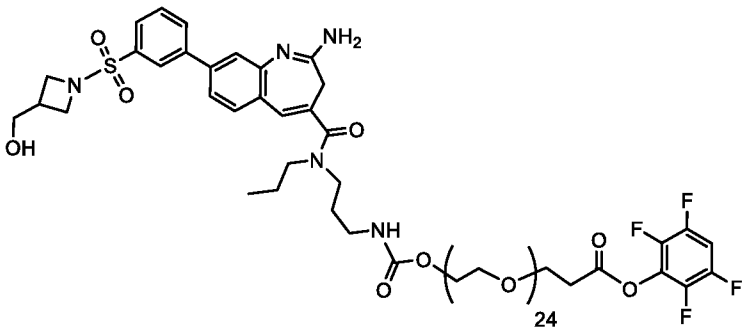
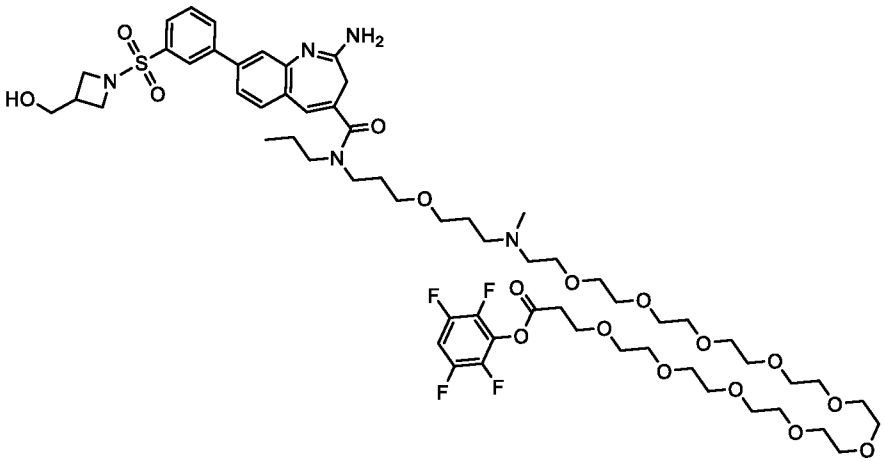
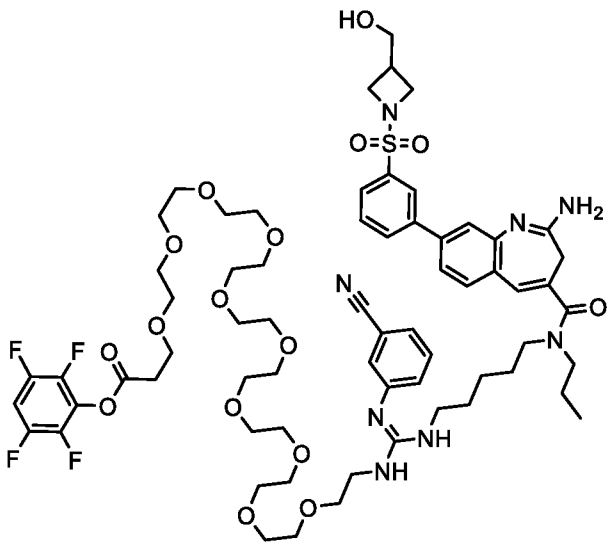
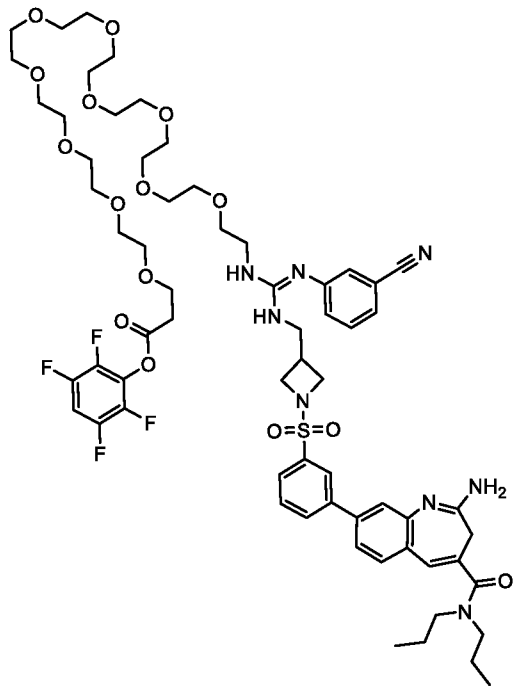
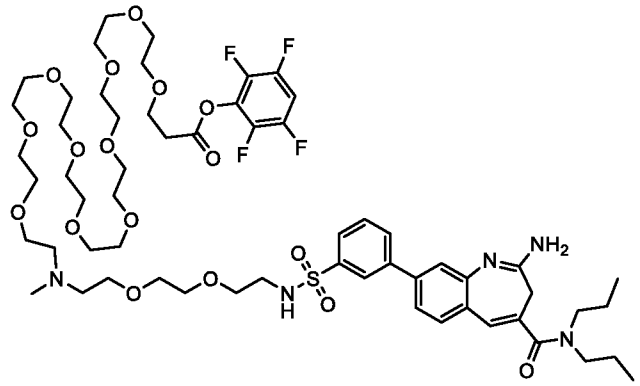
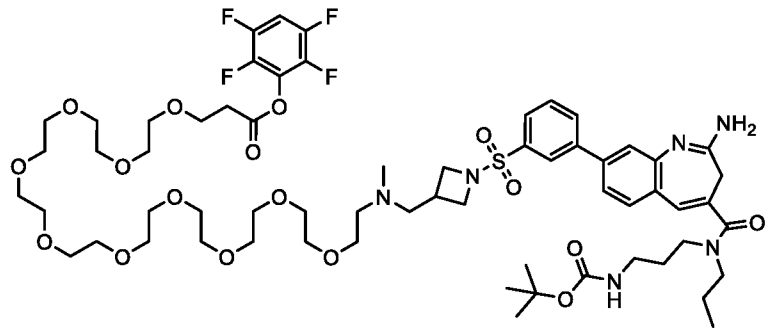
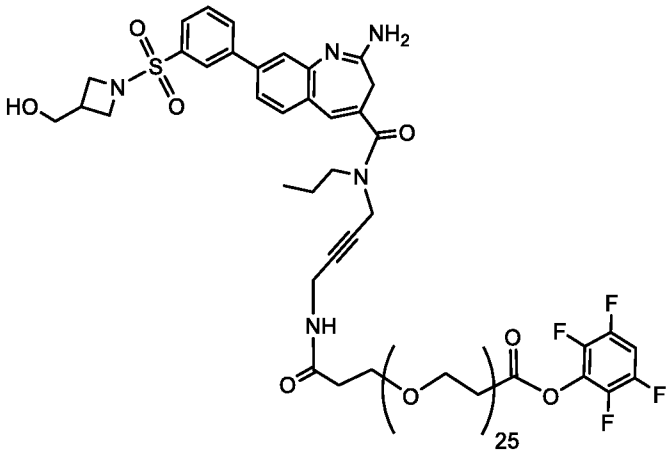
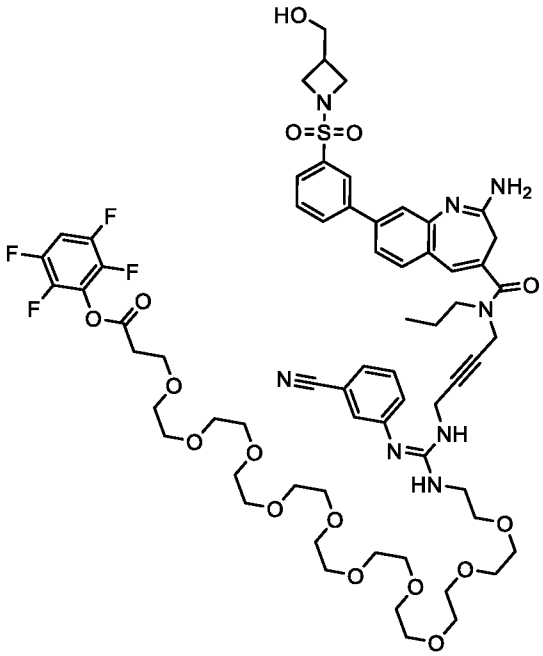
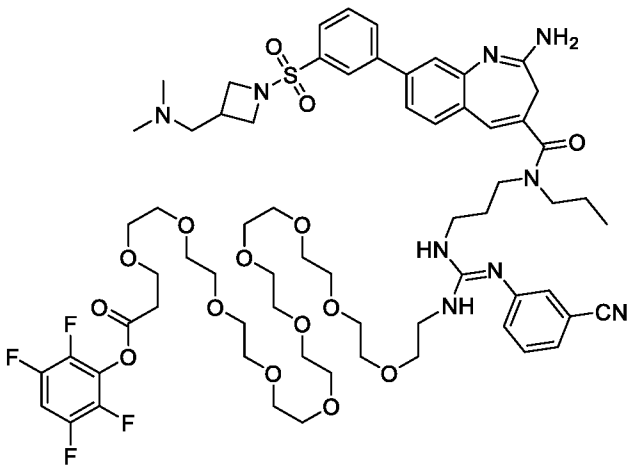
BzL-32		1572.8

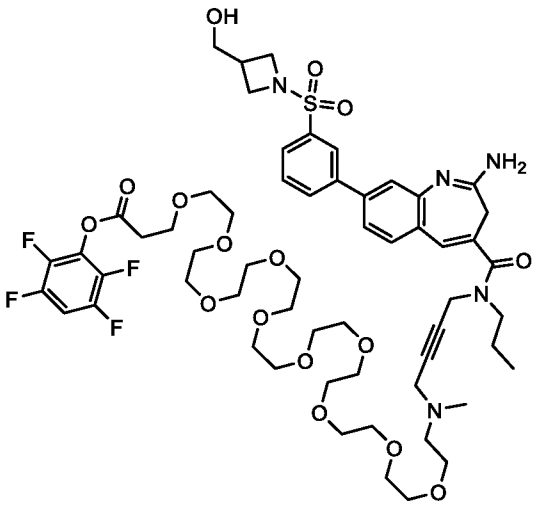
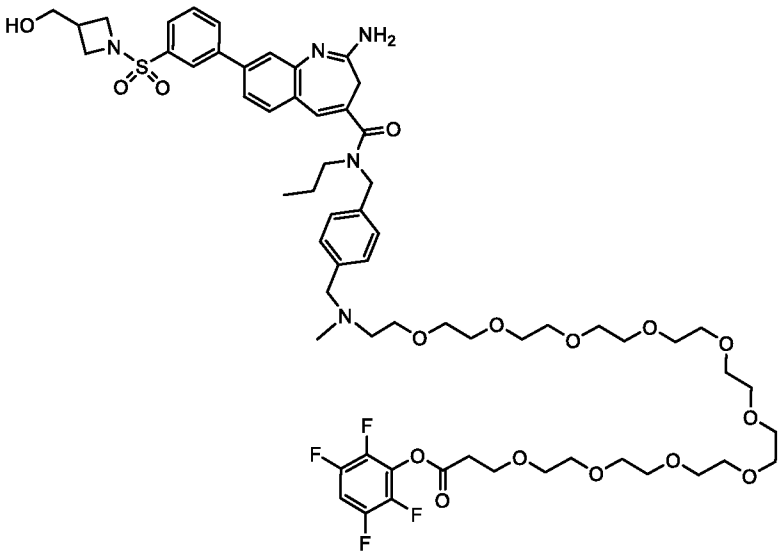
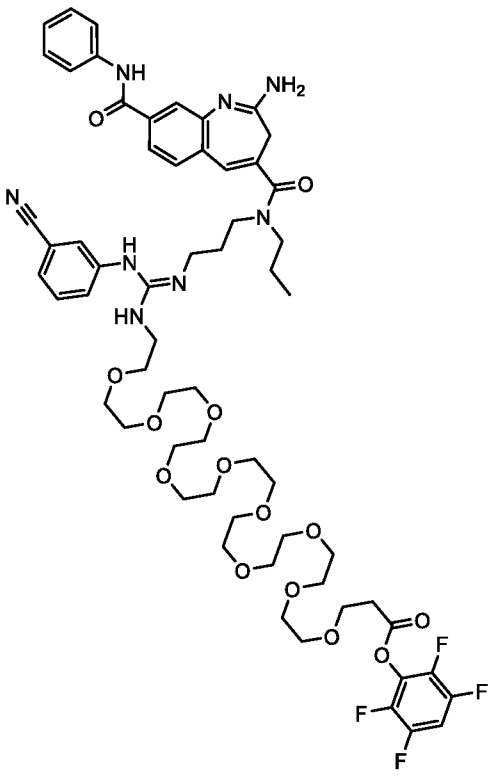
Table 2b: Aminobenzazepine-linker Formula II compounds (BzL) and intermediates

BzL No.	Structure	MW
BzL-33		1875.1
BzL-34		2379.7

BzL-35		1974.2
BzL-36		1847.1
BzL-37		1258.4
BzL-38		1357.5

BzL-39		1313.5
BzL-40		1246.4
BzL-41		1299.5

BzL-42		1885.1
BzL-43		1339.5
BzL-44		1356.5

BzL-45		1210.3
BzL-46		1262.4
BzL-47		1223.3

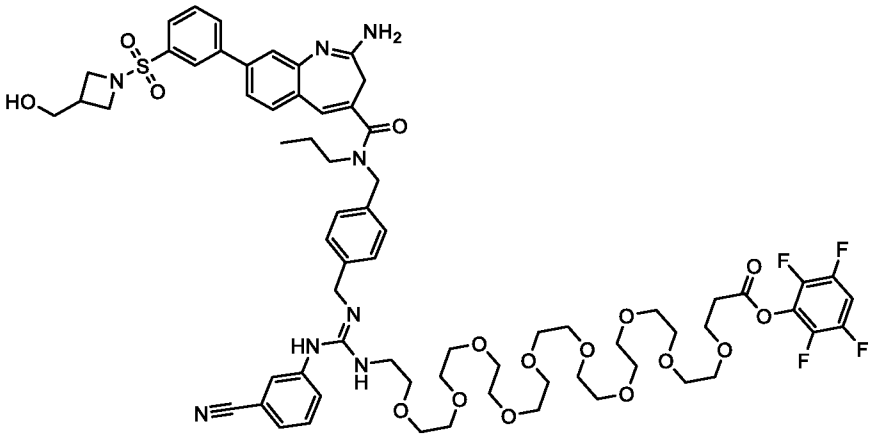
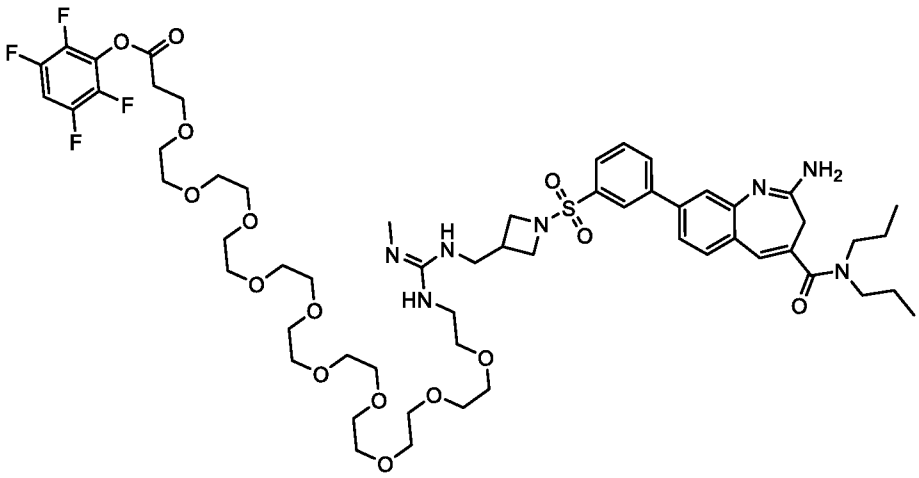
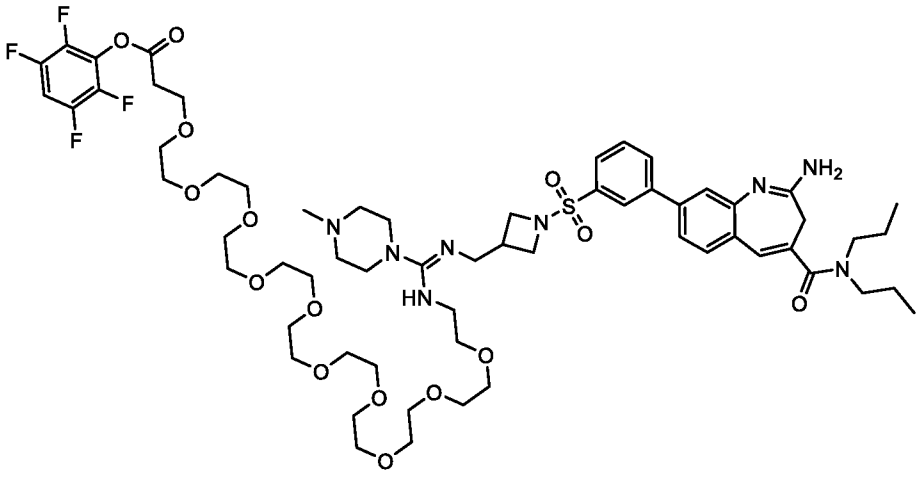
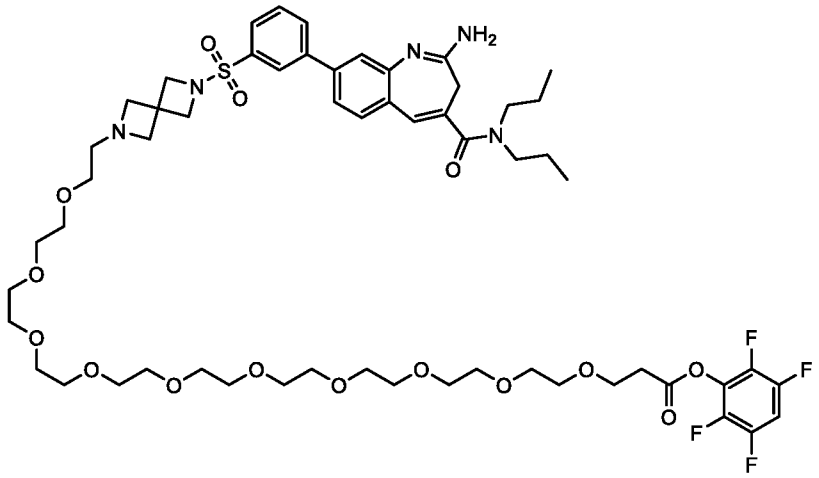
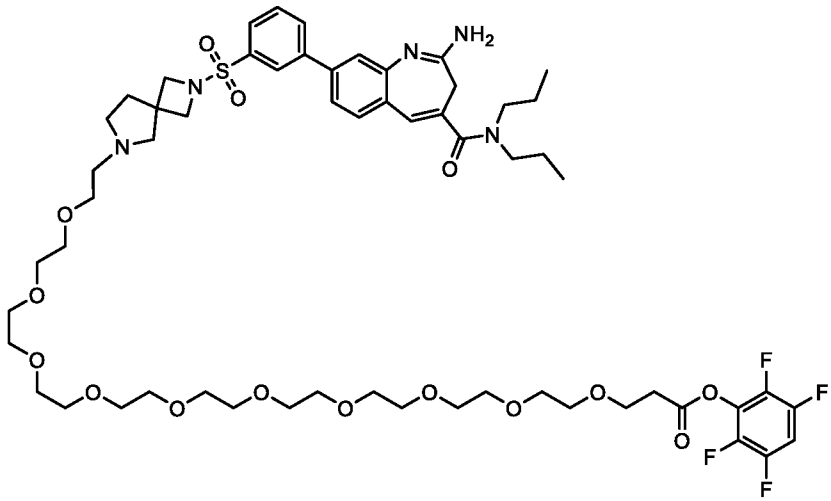
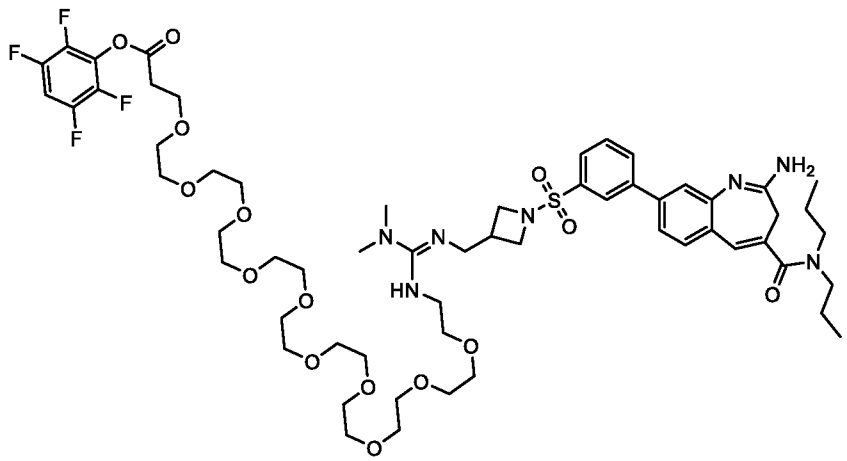
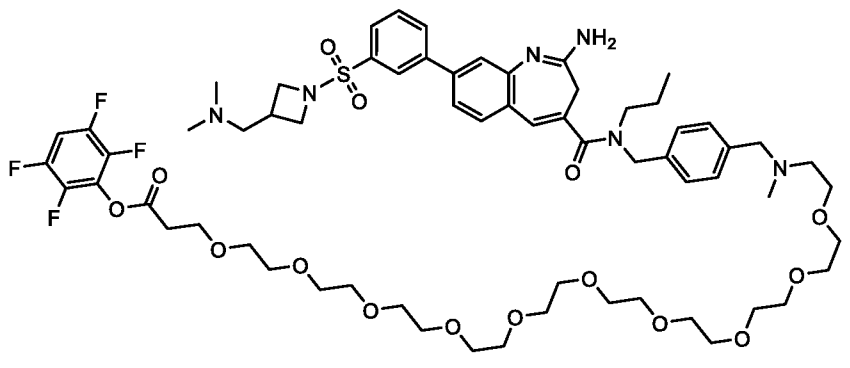
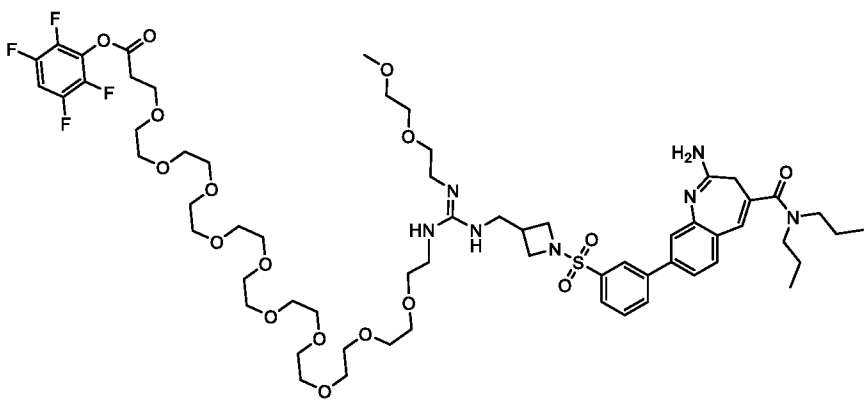
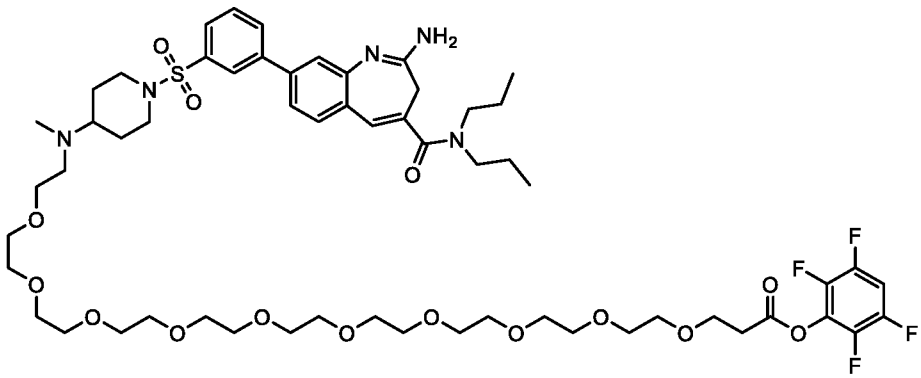
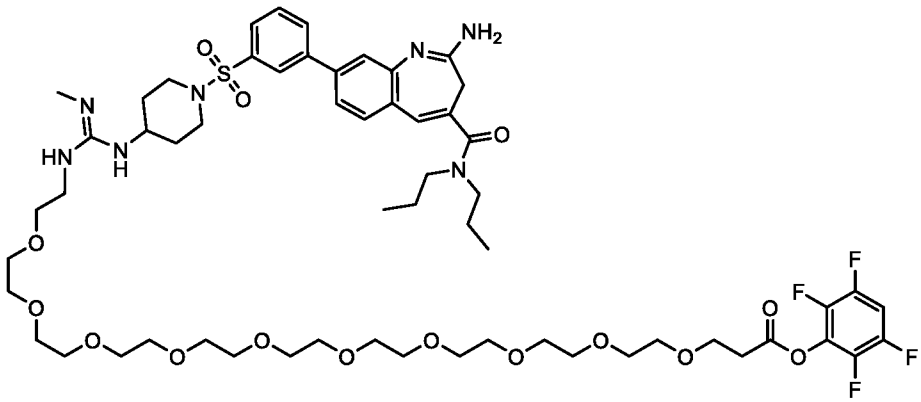
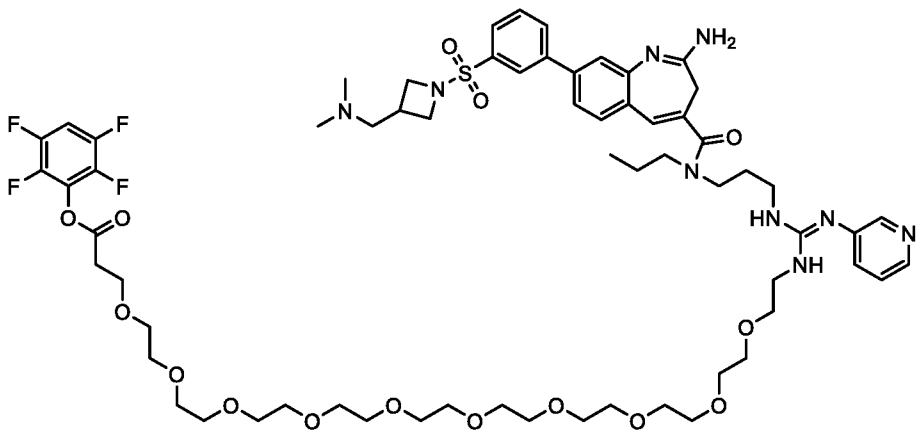
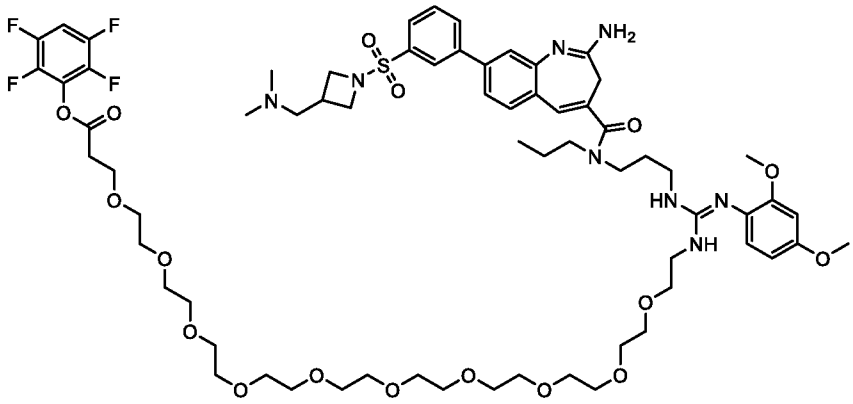
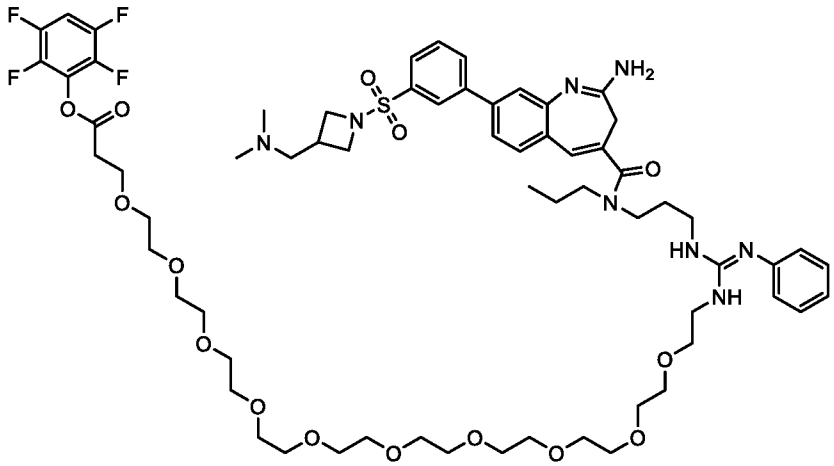
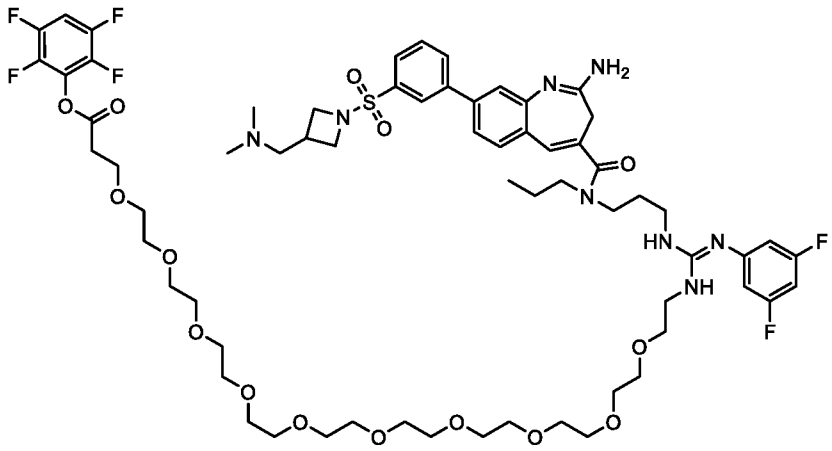
BzL-48		1391.5

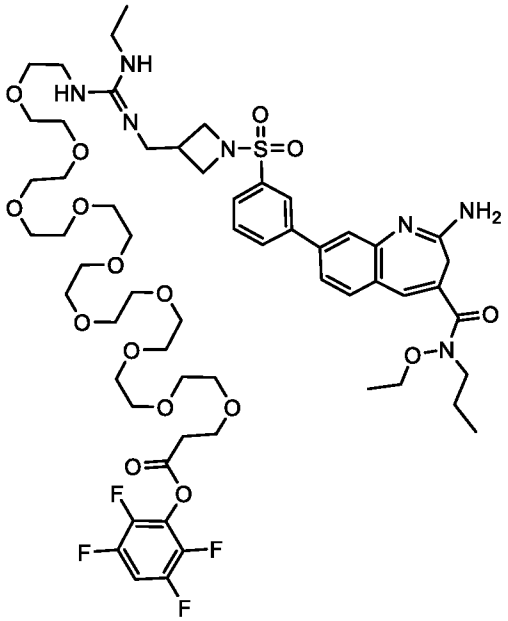
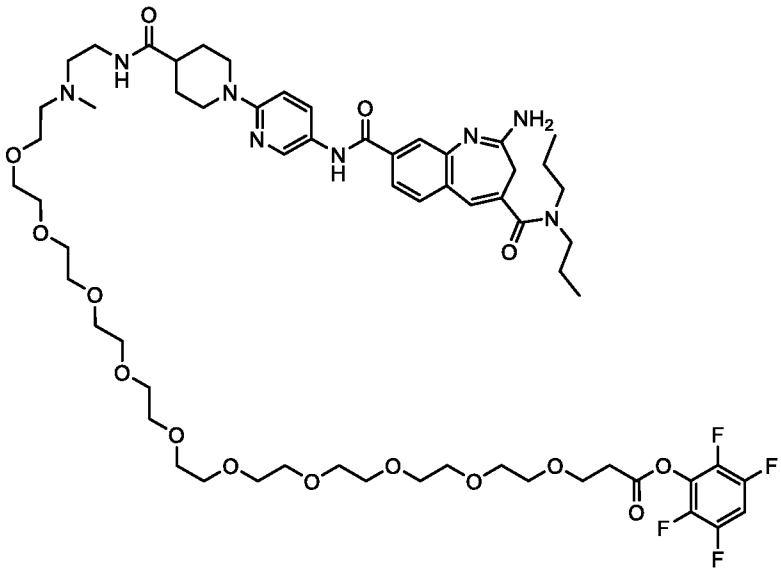
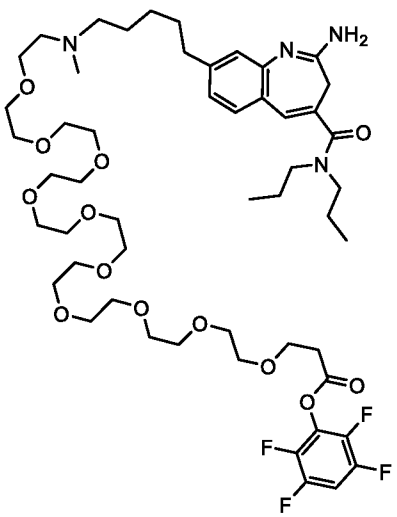
Table 2c: Aminobenzazepine-linker Formula II compounds (BzL) and intermediates

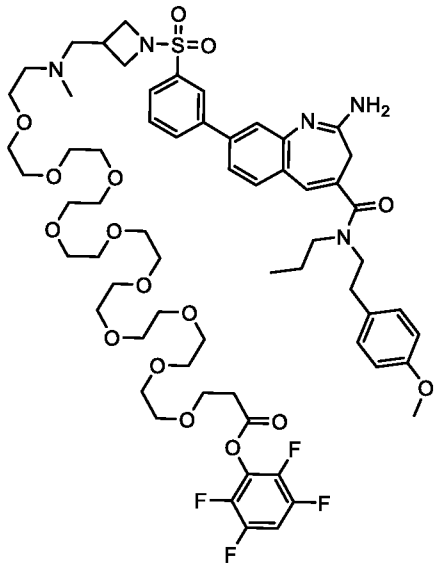
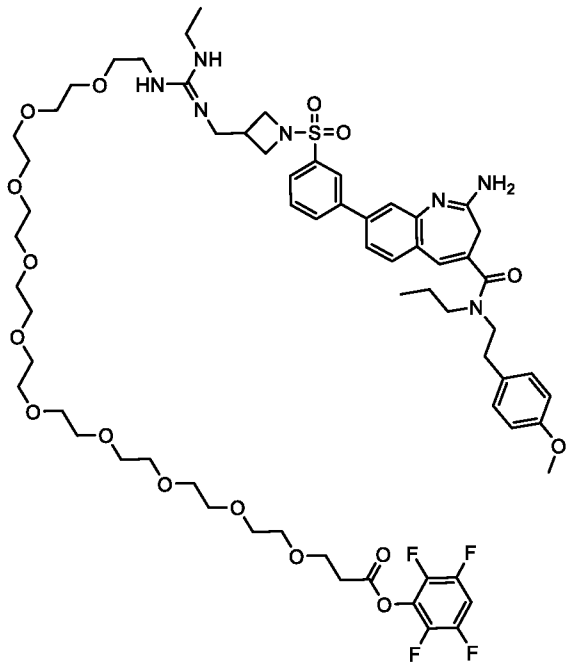
BzL No.	Structure	MW
BzL-49		1226.4
BzL-50		1295.5

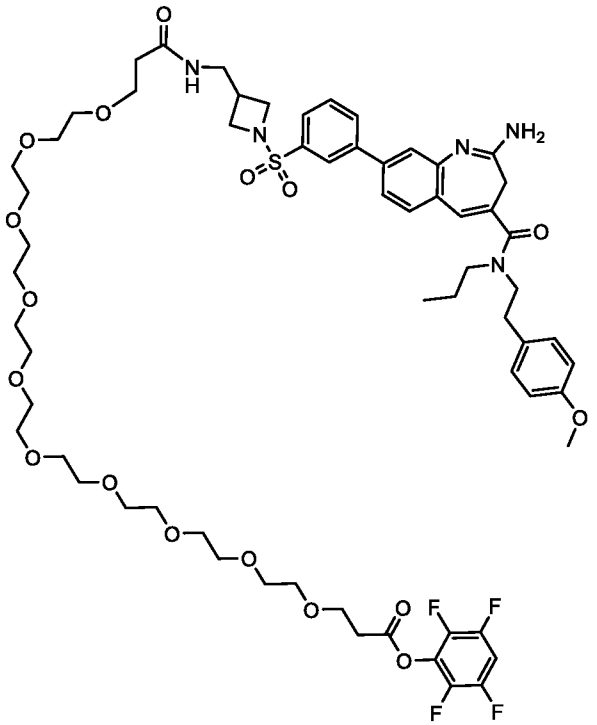
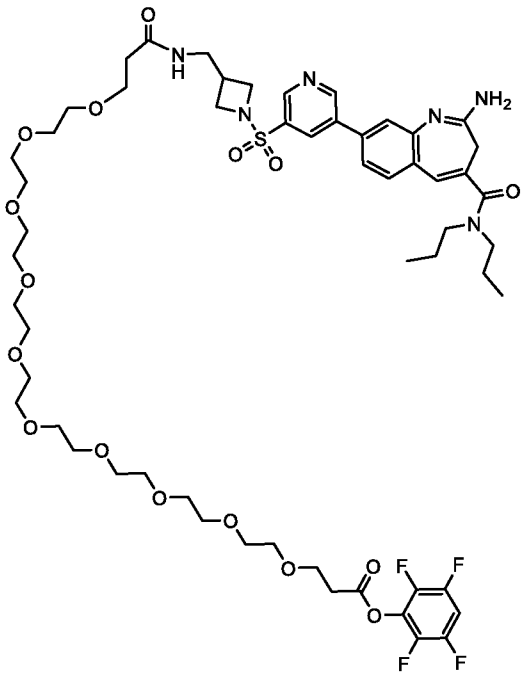
BzL-51		1182.3
BzL-52		1196.4
BzL-53		1240.4
BzL-54		1289.5

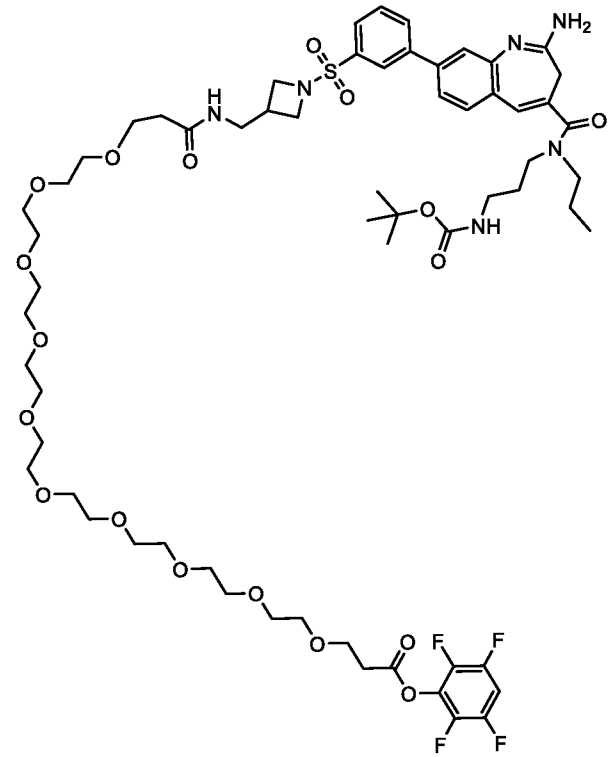
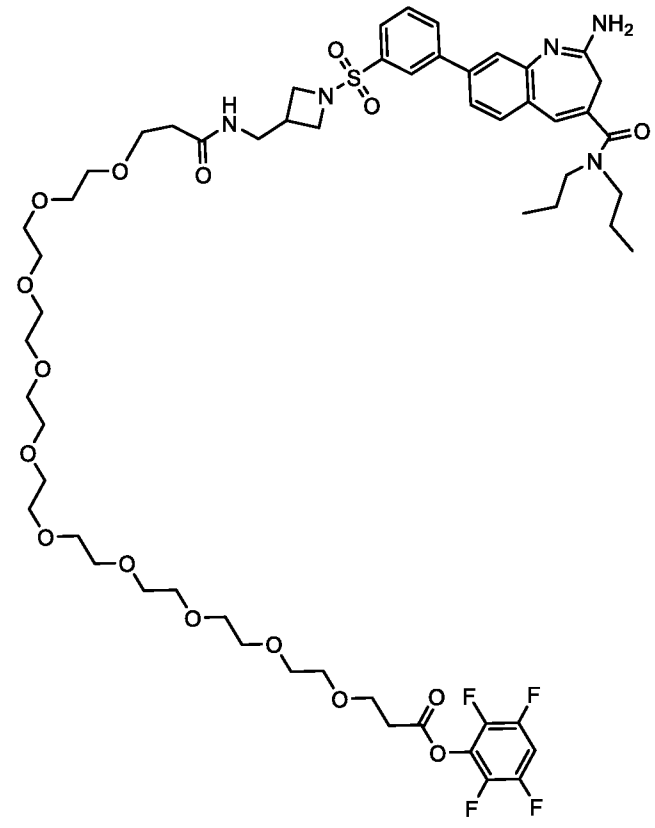
BzL-55		1314.5
BzL-56		1198.4
BzL-57		1240.4
BzL-58		1332.5

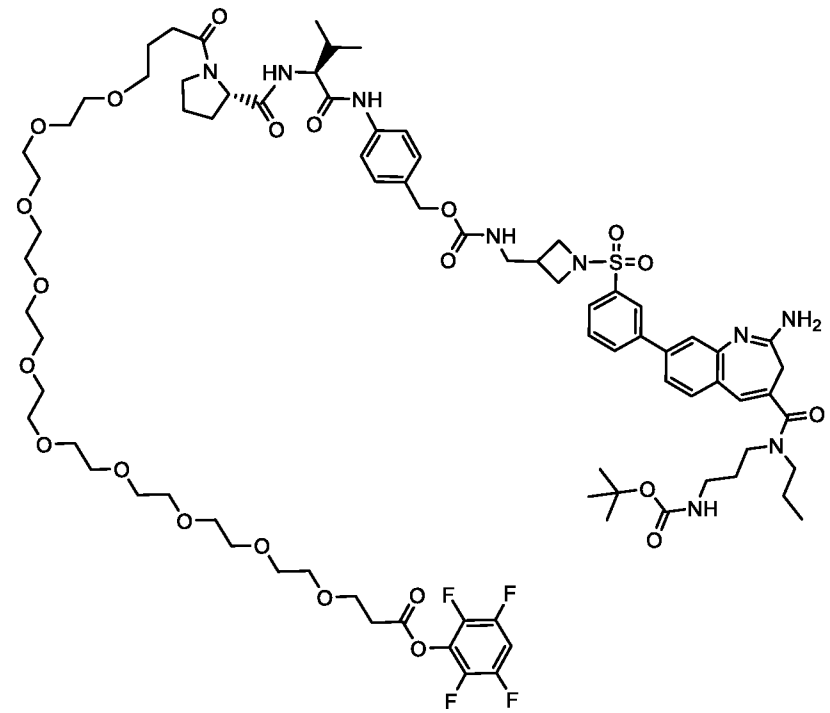
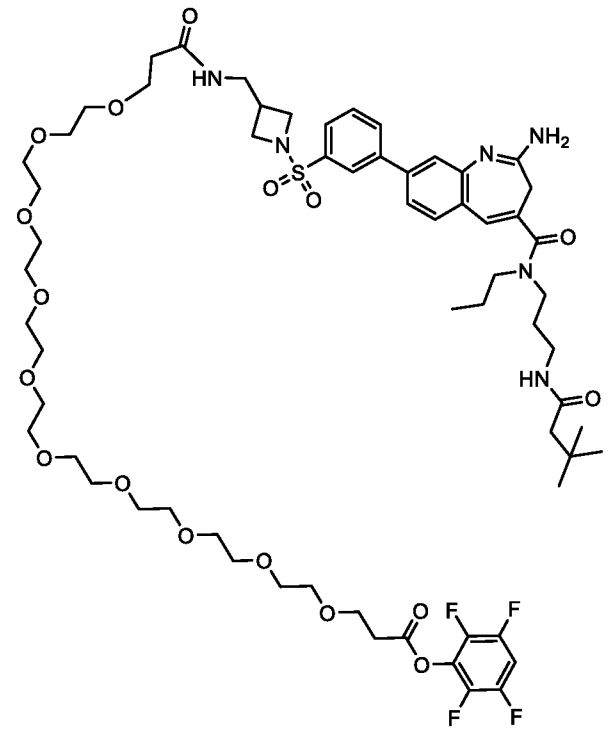
BzL-59		1391.6
BzL-60		1331.5
BzL-61		1367.5

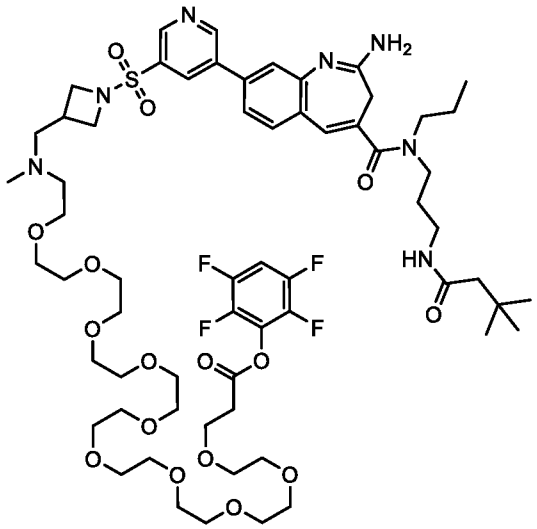
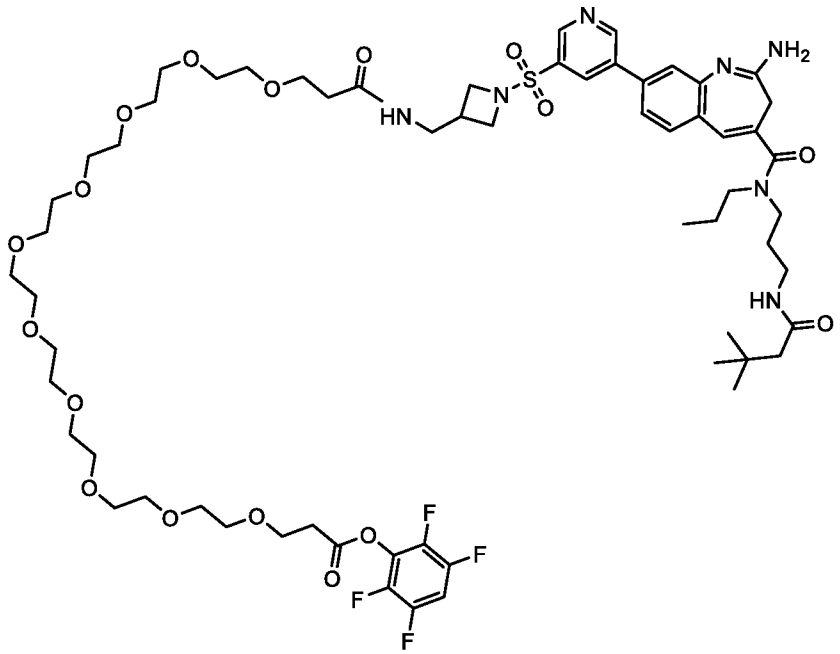
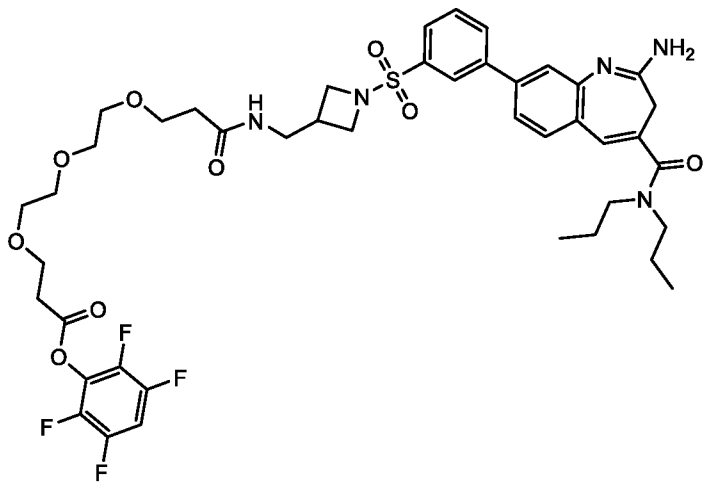
BzL-62		1242.4
BzL-63		1249.4
BzL-64		1045.2

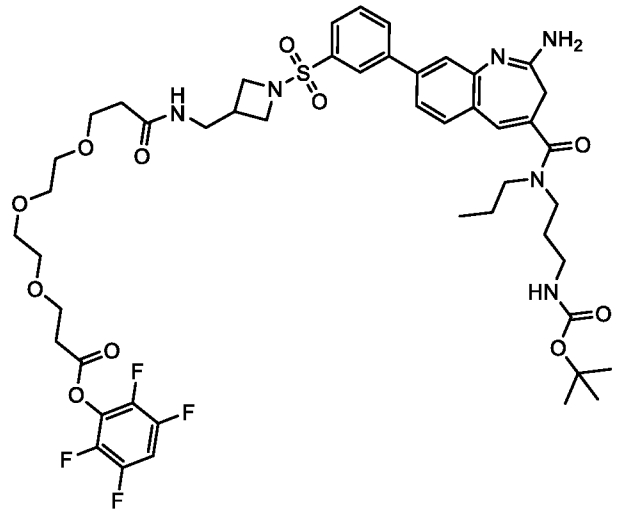
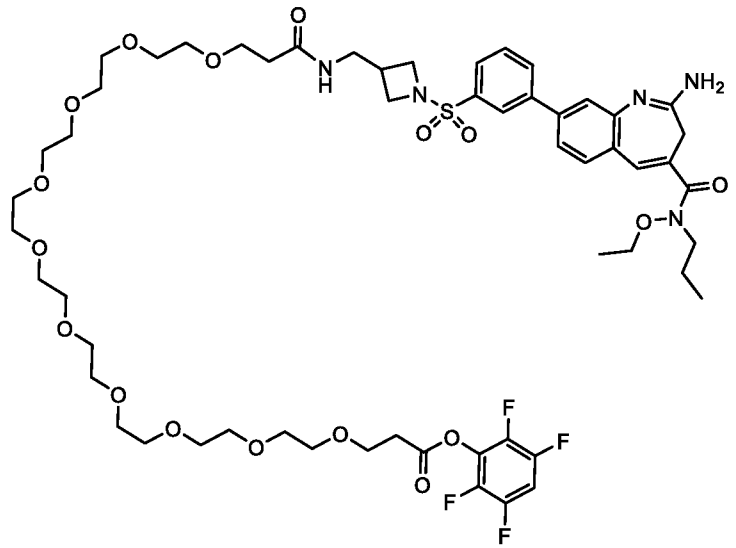
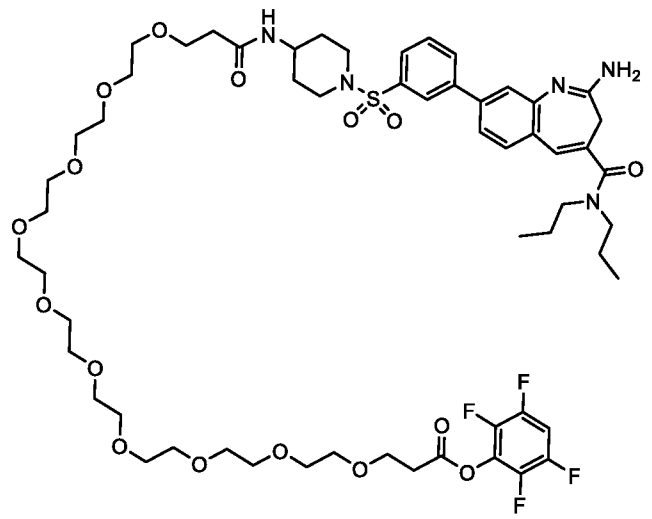
BzL-65		1276.4
BzL-66		1332.5

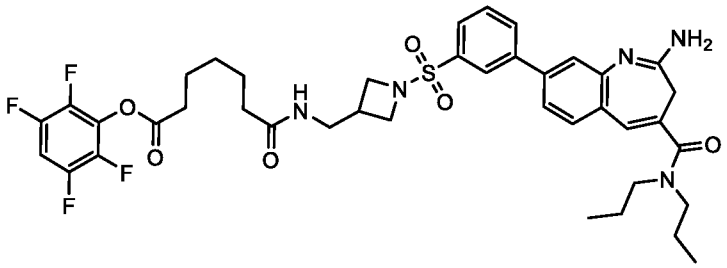
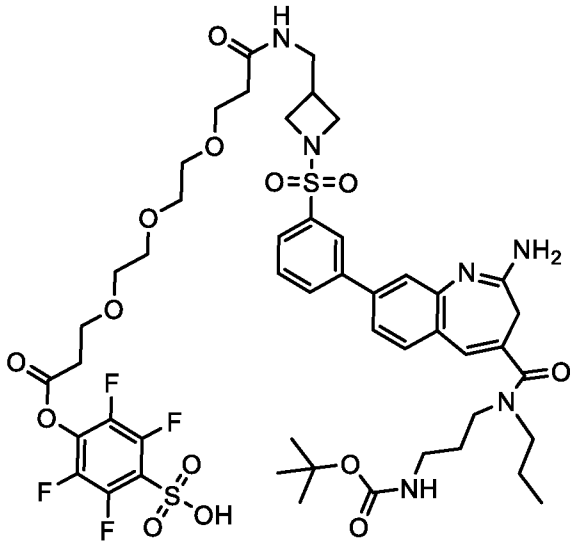
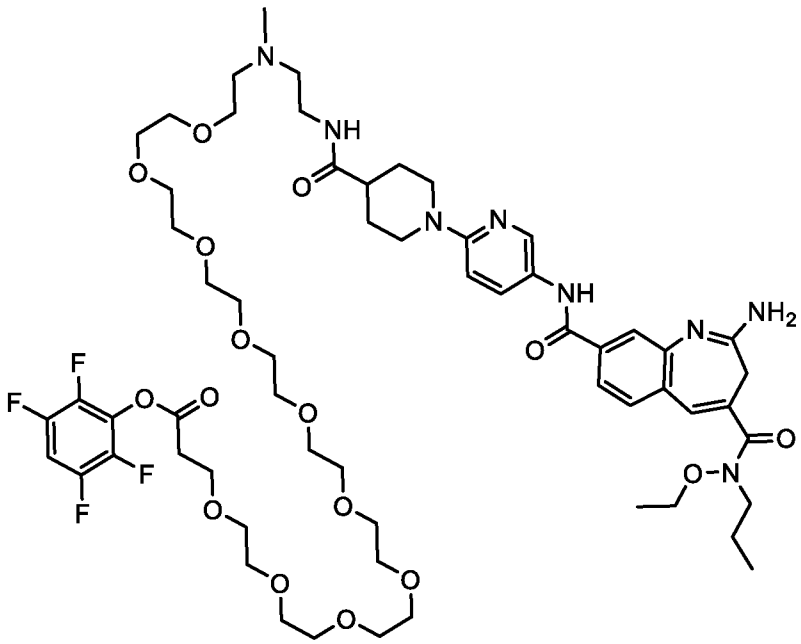
BzL-67		1290.4
BzL-68		1199.3

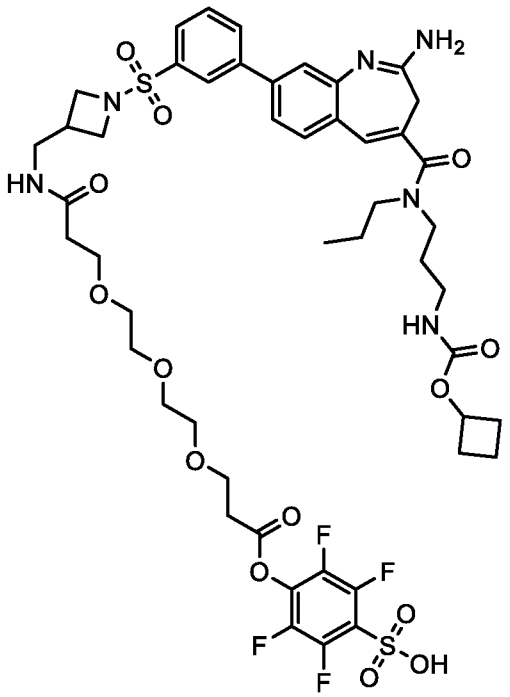
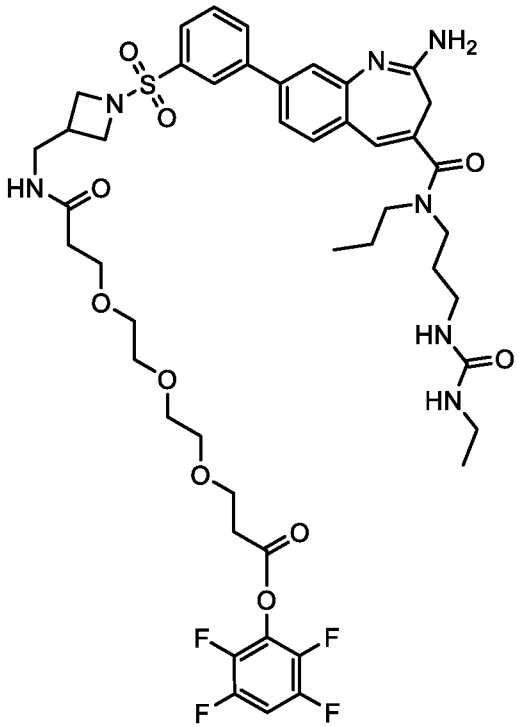
BzL-69		1313.5
BzL-70		1198.3

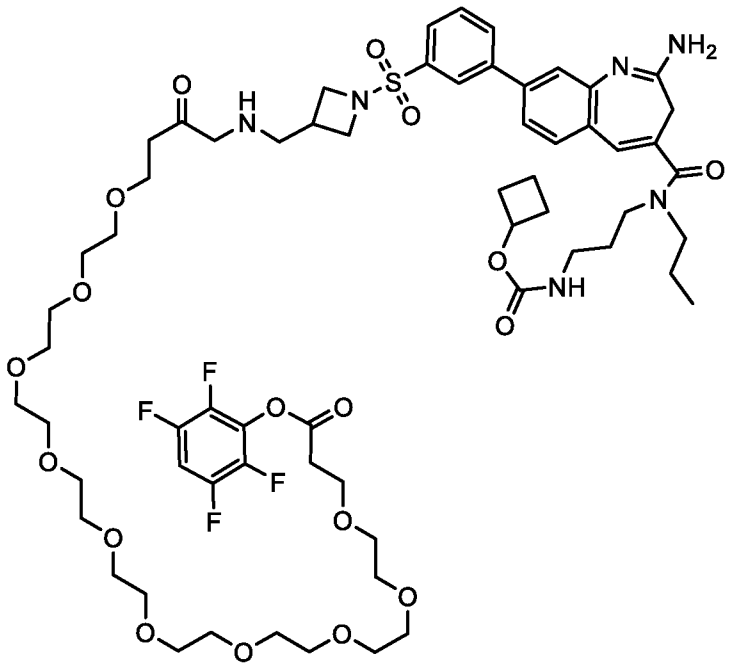
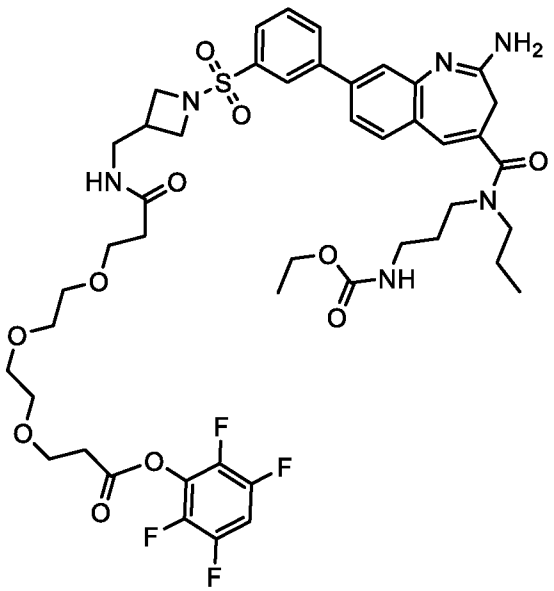
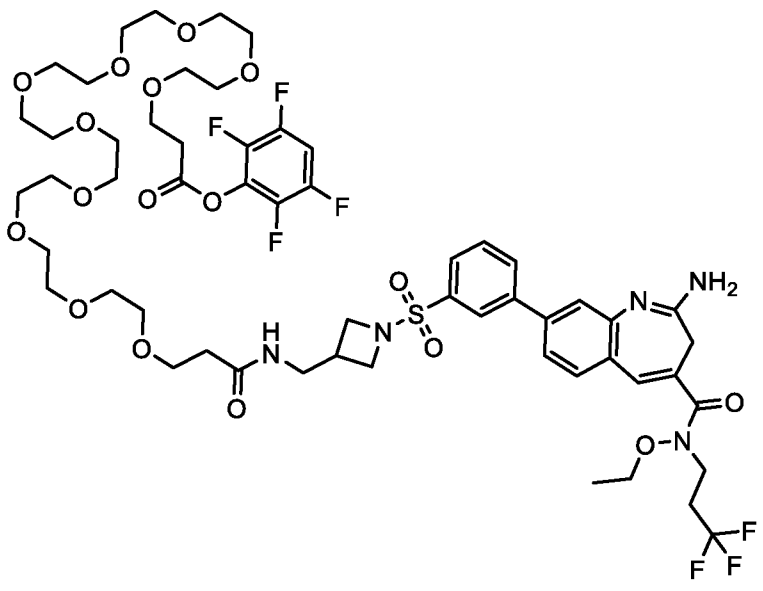
BzL-71		1658.9
BzL-72		1311.5

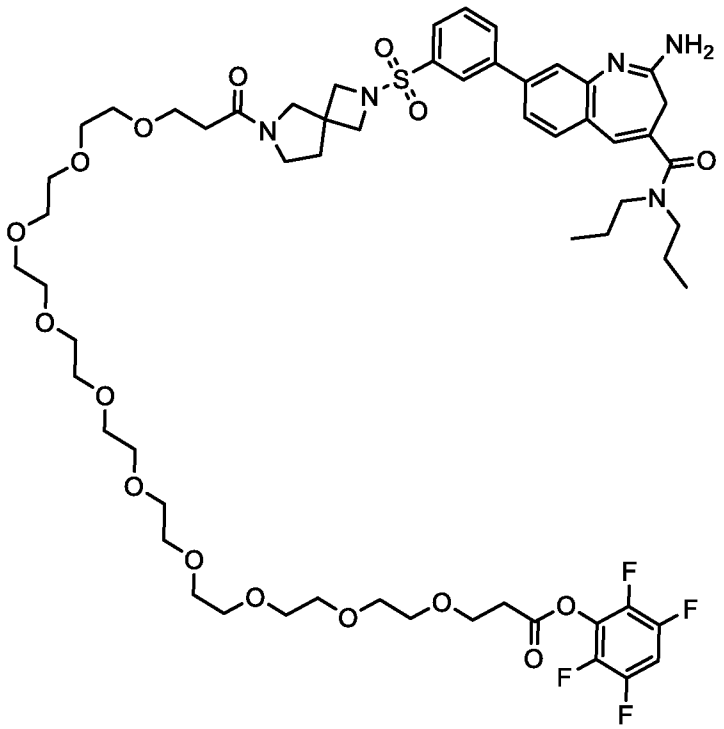
BzL-73		1298.5
BzL-74		1312.5
BzL-75		890.0

BzL-76		1005.1
BzL-77		1200.3
BzL-78		1212.4

BzL-79		799.9
BzL-80		1085.1
BzL-81		1251.4

BzL-82		1083.1
BzL-83		976.1

BzL-84		1325.5
BzL-85		977.0
BzL-86		1254.3

BzL-87		1224.4

IMMUNOCONJUGATES

Exemplary embodiments of immunoconjugates comprise an antibody covalently attached to a divalent linker which is covalently attached to one or more aminobenzazepine moieties, and having Formula **I**:

$$Ab–[L–Bza]_p \qquad \textbf{I}$$

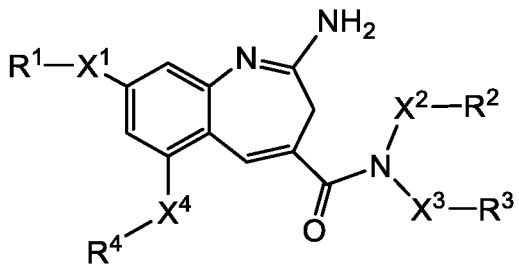
or a pharmaceutically acceptable salt thereof,

wherein:

Ab is the antibody;

p is an integer from 1 to 8;

Bza is the aminobenzazepine moiety having the formula:



R^1, R^2, R^3, and R^4 are independently selected from the group consisting of H, C_1-C_{12} alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{12} carbocyclyl, C_6-C_{20} aryl, C_2-C_9 heterocyclyl, and

C_1-C_{20} heteroaryl, where alkyl, alkenyl, alkynyl, carbocyclyl, aryl, heterocyclyl, and heteroaryl are independently and optionally substituted with one or more groups selected from:

–(C_1-C_{12} alkyldiyl)–N(R^5)–*;

–(C_1-C_{12} alkyldiyl)–N(R^5)$_2$;

–(C_3-C_{12} carbocyclyl);

–(C_3-C_{12} carbocyclyl)–*;

–(C_3-C_{12} carbocyclyl)–(C_1-C_{12} alkyldiyl)–NR^5–*;

–(C_3-C_{12} carbocyclyl)–(C_1-C_{12} alkyldiyl)–N(R^5)$_2$;

–(C_3-C_{12} carbocyclyl)–NR^5–C(=NR^5)NR^5–*;

–(C_6-C_{20} aryl);

–(C_6-C_{20} aryl)–*;

–(C_6-C_{20} aryldiyl)–N(R^5)–*;

–(C_6-C_{20} aryldiyl)–(C_1-C_{12} alkyldiyl)–N(R^5)–*;

–(C_6-C_{20} aryldiyl)–(C_1-C_{12} alkyldiyl)–N(R^5)$_2$;

–(C_6-C_{20} aryldiyl)–(C_1-C_{12} alkyldiyl)–NR^5–C(=NR^{5a})N(R^5)–*;

–(C_2-C_{20} heterocyclyl);

–(C_2-C_{20} heterocyclyl)–*;

–(C_2-C_9 heterocyclyl)–(C_1-C_{12} alkyldiyl)–NR^5–*;

–(C_2-C_9 heterocyclyl)–(C_1-C_{12} alkyldiyl)–N(R^5)$_2$;

–(C_2-C_9 heterocyclyl)–NR^5–C(=NR^{5a})NR^5–*;

–(C_1-C_{20} heteroaryl);

–(C_1-C_{20} heteroaryl)–*;

–(C_1-C_{20} heteroaryl)–(C_1-C_{12} alkyldiyl)–N(R^5)–*;

–(C_1-C_{20} heteroaryl)–(C_1-C_{12} alkyldiyl)–N(R^5)$_2$;

–(C_1-C_{20} heteroaryl)–NR^5–C(=NR^{5a})N(R^5)–*;

–C(=O)–*;

–C(=O)–(C_2-C_{20} heterocyclyldiyl)–*;

–C(=O)N(R^5)$_2$;

–C(=O)N(R^5)–*;

–C(=O)N(R^5)–(C_1-C_{12} alkyldiyl)–N(R^5)C(=O)R^5;

–C(=O)N(R^5)–(C_1-C_{12} alkyldiyl)–N(R^5)C(=O)N(R^5)$_2$;

–C(=O)NR^5–(C_1-C_{12} alkyldiyl)–N(R^5)CO_2R^5;

–C(=O)NR^5–(C_1-C_{12} alkyldiyl)–N(R^5)C(=NR^{5a})N(R^5)$_2$;

–C(=O)NR^5–(C$_1$-C$_{12}$ alkyldiyl)–NR^{5}C(=NR^{5a})R^5;

–C(=O)NR^5–(C$_1$-C$_8$ alkyldiyl)–NR^5(C$_2$-C$_5$ heteroaryl);

–C(=O)NR^5–(C$_1$-C$_{20}$ heteroaryldiyl)–N(R^5)–*;

–C(=O)NR^5–(C$_1$-C$_{20}$ heteroaryldiyl)–*;

–C(=O)NR^5–(C$_1$-C$_{20}$ heteroaryldiyl)–(C$_1$-C$_{12}$ alkyldiyl)–N(R^5)$_2$;

–C(=O)NR^5–(C$_1$-C$_{20}$ heteroaryldiyl)–(C$_2$-C$_{20}$ heterocyclyldiyl)–C(=O)NR^5–(C$_1$-C$_{12}$ alkyldiyl)–NR^5–*;

–N(R^5)$_2$;

–N(R^5)–*;

–N(R^5)C(=O)R^5;

–N(R^5)C(=O)–*;

–N(R^5)C(=O)N(R^5)$_2$;

–N(R^5)C(=O)N(R^5)–*;

–N(R^5)CO$_2$R^5;

–NR^{5}C(=NR^{5a})N(R^5)$_2$;

–NR^{5}C(=NR^{5a})N(R^5)–*;

–NR^{5}C(=NR^{5a})R^5;

–N(R^5)–(C$_2$-C$_5$ heteroaryl);

–O–(C$_1$-C$_{12}$ alkyl);

–O–(C$_1$-C$_{12}$ alkyldiyl)–N(R^5)$_2$;

–O–(C$_1$-C$_{12}$ alkyldiyl)–N(R^5)–*;

–S(=O)$_2$–(C$_2$-C$_{20}$ heterocyclyldiyl)–*;

–S(=O)$_2$–(C$_2$-C$_{20}$ heterocyclyldiyl)–(C$_1$-C$_{12}$ alkyldiyl)–N(R^5)$_2$;

–S(=O)$_2$–(C$_2$-C$_{20}$ heterocyclyldiyl)–(C$_1$-C$_{12}$ alkyldiyl)–NR^5–*; and

–S(=O)$_2$–(C$_2$-C$_{20}$ heterocyclyldiyl)–(C$_1$-C$_{12}$ alkyldiyl)–OH;

or R^2 and R^3 together form a 5- or 6-membered heterocyclyl ring;

X^1, X^2, X^3, and X^4 are independently selected from the group consisting of a bond, C(=O), C(=O)N(R^5), O, N(R^5), S, S(O)$_2$, and S(O)$_2$N(R^5);

R^5 is selected from the group consisting of H, C$_6$-C$_{20}$ aryl, C$_6$-C$_{20}$ aryldiyl, C$_1$-C$_{12}$ alkyl, and C$_1$-C$_{12}$ alkyldiyl, or two R^5 groups together form a 5- or 6-membered heterocyclyl ring;

R^{5a} is selected from the group consisting of C$_6$-C$_{20}$ aryl and C$_1$-C$_{20}$ heteroaryl;

where the asterisk * indicates the attachment site of L, and where one of R^1, R^2, R^3 and R^4 is attached to L;

L is the linker selected from the group consisting of:

–C(=O)–(PEG)–;

–C(=O)–(PEG)–C(=O)–;

–C(=O)–(PEG)–O–;

–C(=O)–(PEG)–C(=O)–(PEP)–;

–C(=O)–(PEG)–C(=O)N(R^5)–(C_1-C_{12} alkyldiyl)–;

–C(=O)–(PEG)–C(=O)N(R^5)–(C_1-C_{12} alkyldiyl)–N(R^5)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–;

–C(=O)–(PEG)–C(=O)N(R^5)–(C_1-C_{12} alkyldiyl)–(MCgluc)–;

–C(=O)–(PEG)–C(=O)–(MCgluc)–;

–C(=O)–(PEG)–C(=O)–(PEP)–N(R^5)–(C_1-C_{12} alkyldiyl)–;

–C(=O)–(PEG)–C(=O)–(PEP)–N(R^5)–(C_1-C_{12} alkyldiyl)–N(R^5)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–;

–C(=O)–(PEG)–N(R^5)–;

–C(=O)–(PEG)–N(R^5)–(PEG)–C(=O)–(PEP)–;

–C(=O)–(PEG)–N^+(R^5)$_2$–(PEG)–C(=O)–(PEP)–;

–C(=O)–(PEG)–C(=O)–N(R^5)CH(AA_1)C(=O)–(PEG)–C(=O)–(PEP)–;

–C(=O)–(PEG)–C(=O)–N(R^5)CH(AA_1)C(=O)–N(R^5)–(C_1-C_{12} alkyldiyl)–;

–C(=O)–(PEG)–SS–(C_1-C_{12} alkyldiyl)–OC(=O)–;

–C(=O)–(PEG)–SS–(C_1-C_{12} alkyldiyl)–C(=O)–;

–C(=O)–(C_1-C_{12} alkyldiyl)–C(=O)–(PEP)–;

–C(=O)–(C_1-C_{12} alkyldiyl)–C(=O)–(PEP)–N(R^5)–(C_1-C_{12} alkyldiyl)–;

–C(=O)–(C_1-C_{12} alkyldiyl)–C(=O)–(PEP)–N(R^5)–(C_1-C_{12} alkyldiyl)–N(R^5)–C(=O);

–C(=O)–(C_1-C_{12} alkyldiyl)–C(=O)–(PEP)–N(R^5)–(C_1-C_{12} alkyldiyl)–N(R^5)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–;

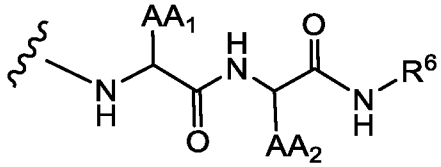
–C(=O)–$CH_2CH_2OCH_2CH_2$–(C_1-C_{20} heteroaryldiyl)–CH_2O–(PEG)–C(=O)–(MCgluc)–;

–C(=O)–$CH_2CH_2OCH_2CH_2$–(C_1-C_{20} heteroaryldiyl)–CH_2O–(PEG)–C(=O)–(MCgluc)–N(R^5)–(C_1-C_{12} alkyldiyl)–N(R^5)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–; and

–(succinimidyl)–$(CH_2)_m$–C(=O)–(PEP)–N(R^5)–(C_1-C_{12} alkyldiyl)–N(R^5)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–;

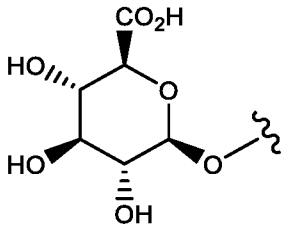
PEG has the formula: $–(CH_2CH_2O)_n–(CH_2)_m–$; m is an integer from 1 to 5, and n is an integer from 2 to 50;

PEP has the formula:



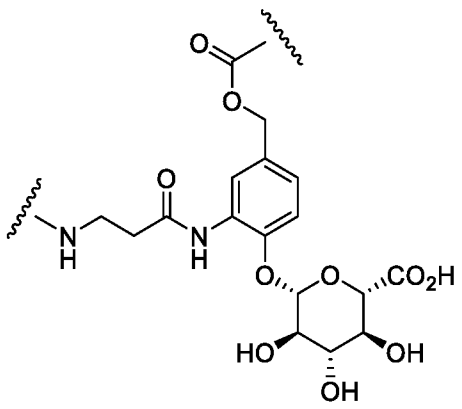
where AA_1 and AA_2 are independently selected from an amino acid side chain, or AA_1 or AA_2 and an adjacent nitrogen atom form a 5-membered ring proline amino acid, and the wavy line indicates a point of attachment;

R^6 is selected from the group consisting of C_6-C_{20} aryldiyl and C_1-C_{20} heteroaryldiyl, substituted with $-CH_2O-C(=O)-$ and optionally with:

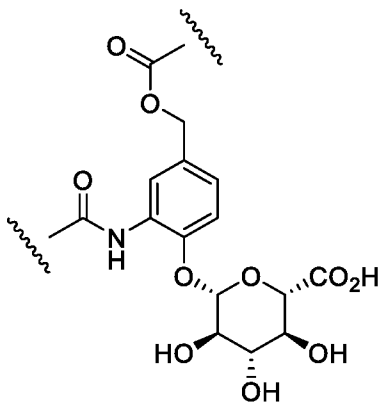


; and

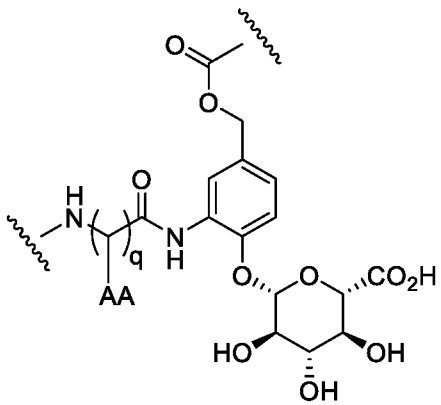
MCgluc is selected from the groups:



;



; and



where q is 1 to 8, and AA is an amino acid side chain; and

alkyl, alkyldiyl, alkenyl, alkenyldiyl, alkynyl, alkynyldiyl, aryl, aryldiyl, carbocyclyl, carbocyclyldiyl, heterocyclyl, heterocyclyldiyl, heteroaryl, and heteroaryldiyl are independently and optionally substituted with one or more groups independently selected from F, Cl, Br, I, –

CN, $-CH_3$, $-CH_2CH_3$, $-CH=CH_2$, $-C\equiv CH$, $-C\equiv CCH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2CH_2OH$, $-C(CH_3)_2OH$, $-CH(OH)CH(CH_3)_2$, $-C(CH_3)_2CH_2OH$, $-CH_2CH_2SO_2CH_3$, $-CH_2OP(O)(OH)_2$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH(CH_3)CN$, $-C(CH_3)_2CN$, $-CH_2CN$, $-CH_2NH_2$, $-CH_2NHSO_2CH_3$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CO_2H$, $-COCH_3$, $-CO_2CH_3$, $-CO_2C(CH_3)_3$, $-COCH(OH)CH_3$, $-CONH_2$, $-CONHCH_3$, $-CON(CH_3)_2$, $-C(CH_3)_2CONH_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHCOCH_3$, $-N(CH_3)COCH_3$, $-NHS(O)_2CH_3$, $-N(CH_3)C(CH_3)_2CONH_2$, $-N(CH_3)CH_2CH_2S(O)_2CH_3$, $-NHC(=NH)H$, $-NHC(=NH)CH_3$, $-NHC(=NH)NH_2$, $-NHC(=O)NH_2$, $-NO_2$, =O, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2OCH_3$, $-OCH_2CH_2OH$, $-OCH_2CH_2N(CH_3)_2$, $-O(CH_2CH_2O)_n-(CH_2)_mCO_2H$, $-O(CH_2CH_2O)_nH$, $-OP(O)(OH)_2$, $-S(O)_2N(CH_3)_2$, $-SCH_3$, $-S(O)_2CH_3$, and $-S(O)_3H$.

An exemplary embodiment of the immunoconjugate of Formula **I** includes wherein the antibody is an antibody construct that has an antigen binding domain that binds PD-L1

An exemplary embodiment of the immunoconjugate of Formula **I** includes wherein the antibody is selected from the group consisting of atezolizumab, durvalumab, and avelumab, or a biosimilar or a biobetter thereof.

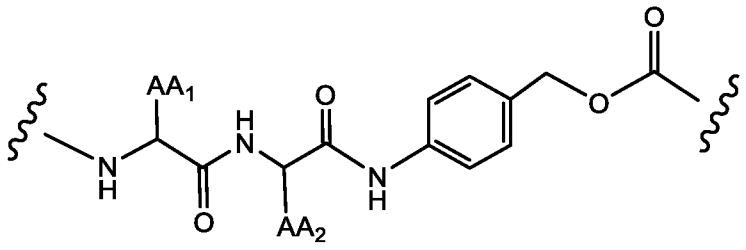
An exemplary embodiment of the immunoconjugate of Formula **I** includes wherein the antibody is an antibody construct that has an antigen binding domain that binds HER2.

An exemplary embodiment of the immunoconjugate of Formula **I** includes wherein the antibody is selected from the group consisting of trastuzumab and pertuzumab, or a biosimilar or a biobetter thereof.

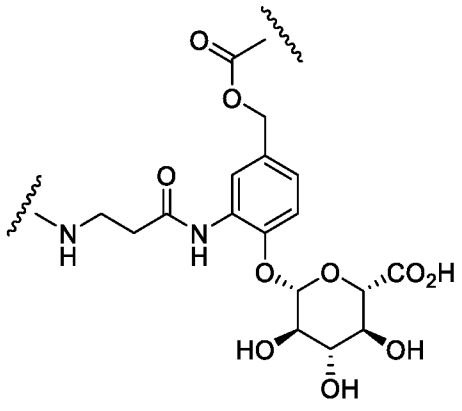
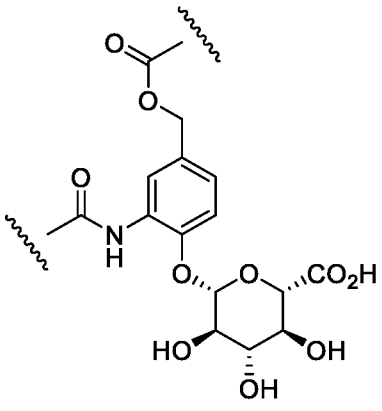
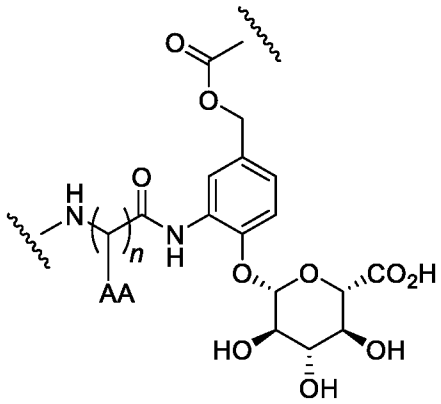
An exemplary embodiment of the immunoconjugate of Formula **I** includes wherein the antibody is an antibody construct that has an antigen binding domain that binds CEA.

An exemplary embodiment of the immunoconjugate of Formula **I** includes wherein the antibody is labetuzumab, or a biosimilar or a biobetter thereof.

An exemplary embodiment of the immunoconjugate of Formula **I** includes wherein PEP is selected from the groups:



;


;

; and


where n is 1 or more, and AA is an amino acid side chain.

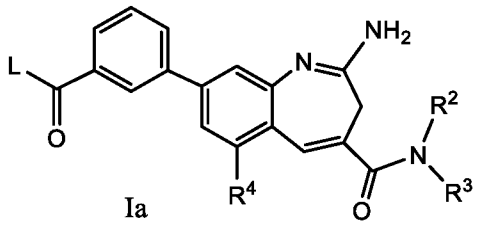
An exemplary embodiment of the immunoconjugate of Formula **I** includes wherein AA_1 and AA_2 are independently selected from a side chain of a naturally-occurring amino acid.

An exemplary embodiment of the immunoconjugate of Formula **I** includes wherein AA_1 and AA_2 are independently selected from H, $-CH_3$, $-CH(CH_3)_2$, $-CH_2(C_6H_5)$, $-CH_2CH_2CH_2CH_2NH_2$, $-CH_2CH_2CH_2NHC(NH)NH_2$, $-CH_2CH(CH_3)_2$, $-CH_2SO_3H$, and $-CH_2CH_2CH_2NHC(O)NH_2$.

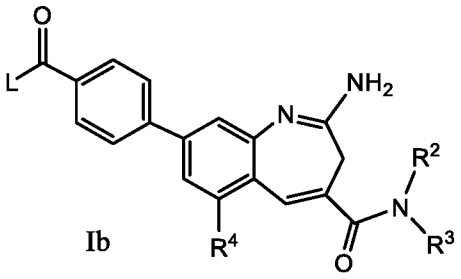
An exemplary embodiment of the immunoconjugate of Formula **I** includes wherein AA_1 is $-CH(CH_3)_2$, and AA_2 is $-CH_2CH_2CH_2NHC(O)NH_2$.

An exemplary embodiment of the immunoconjugate of Formula **I** includes wherein AA_1 and AA_2 are independently selected from GlcNAc aspartic acid, $-CH_2SO_3H$, and $-CH_2OPO_3H$.

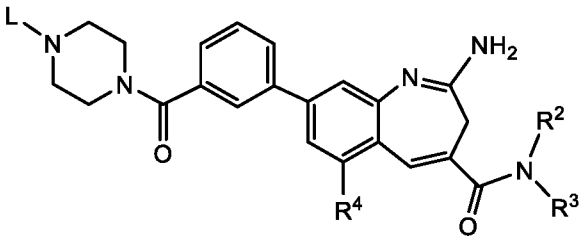
An exemplary embodiment of the immunoconjugate of Formula **I** includes wherein Bza is selected from Formulas Ia-d:



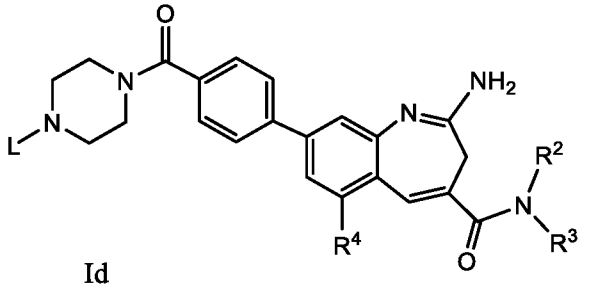
Ia



Ib

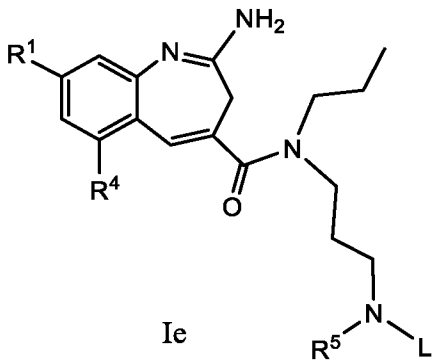


Ic

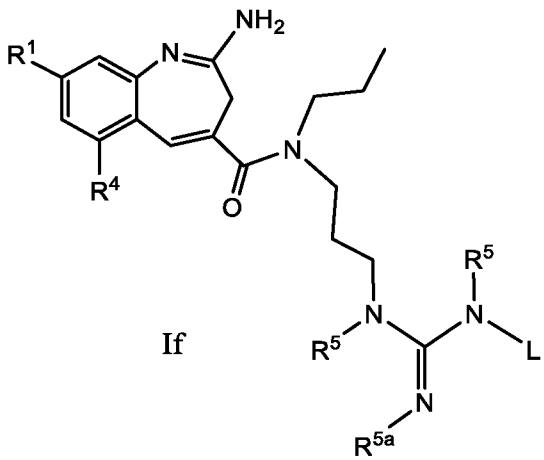


Id

An exemplary embodiment of the immunoconjugate of Formula **I** includes wherein Bza is selected from Formulas Ie and If:



Ie

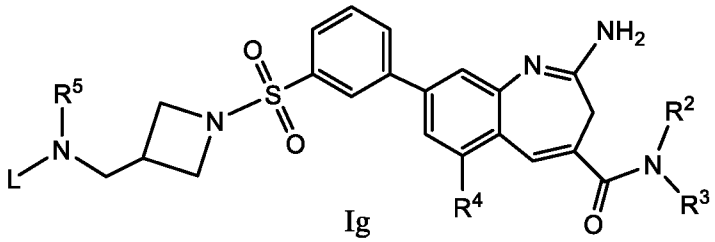


If

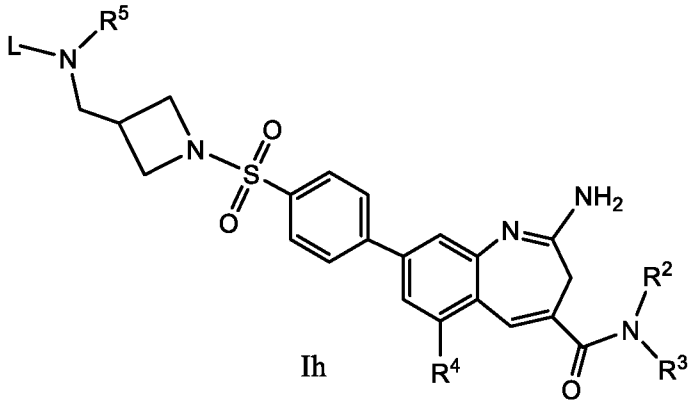
where R^{5a} of Formula If is phenyl, optionally substituted with one or more groups selected from F, Cl, Br, I, –CN, and $–NO_2$.

An exemplary embodiment of the immunoconjugate of Formula **I** includes wherein L is –C(=O)–(PEG)– or –C(=O)–(PEG)–C(=O)–.

An exemplary embodiment of the immunoconjugate of Formula **I** includes wherein Bza is selected from Formulas Ig and Ih:



Ig



Ih

An exemplary embodiment of the immunoconjugate of Formula **I** includes wherein L is –C(=O)–(PEG)–C(=O)–(PEP)–.

An exemplary embodiment of the immunoconjugate of Formula **I** includes wherein R^2 and R^3 are each C_1-C_8 alkyl.

An exemplary embodiment of the immunoconjugate of Formula **I** includes wherein R^2 and R^3 are each $–CH_2CH_2CH_3$.

An exemplary embodiment of the immunoconjugate of Formula **I** includes wherein X^2 and X^3 are each a bond, and R^2 or R^3 is –O–(C_1-C_{12} alkyl).

An exemplary embodiment of the immunoconjugate of Formula **I** includes wherein X^2 and X^3 are each a bond, and R^2 or R^3 is $–OCH_2CH_3$.

An exemplary embodiment of the immunoconjugate of Formula **I** includes wherein one of R^1 and R^4 is selected from:

–(C_1-C_{12} alkyldiyl)–$N(R^5)$–*;

–(C_1-C_{12} alkyldiyl)–$N(R^5)C(=NR^5)N(R^5)$–*;

–(C_6-C_{20} aryldiyl)–$S(=O)_2$–(C_2-C_{20} heterocyclyldiyl)–*;

–(C_6-C_{20} aryldiyl)–$S(=O)_2$–(C_2-C_{20} heterocyclyldiyl)–(C_1-C_{12} alkyldiyl)–$N(R^5)$–*;

–(C_6-C_{20} aryldiyl)–C(=O)–*;

–(C_6-C_{20} aryldiyl)–(C_1-C_{12} alkyldiyl)–$N(R^5)$–*;

–(C_6-C_{20} aryldiyl)–C(=O)–(C_2-C_{20} heterocyclyldiyl)–*;

–$C(=O)NR^5$–(C_1-C_{20} heteroaryldiyl)–*; and

–C(=O)NR^5–(C_1-C_{20} heteroaryldiyl)–(C_2-C_{20} heterocyclyldiyl)–C(=O)NR^5–(C_1-C_{12} alkyldiyl)–NR^5–*.

An exemplary embodiment of the immunoconjugate of Formula **I** includes wherein one of R^2 and R^3 is selected from:

–(C_1-C_{12} alkyldiyl)–N(R^5)–*;

–(C_1-C_{12} alkyldiyl)–O–(C_1-C_{12} alkyldiyl)–N(R^5)–*;

–(C_1-C_{12} alkyldiyl)–N(R^5)C(=NR^5)–N(R^5)–*;

–(C_1-C_{12} alkyldiyl)–(C_6-C_{20} aryldiyl)–(C_1-C_{12} alkyldiyl)–N(R^5)–*;

–(C_1-C_{12} alkyldiyl)–(C_6-C_{20} aryldiyl)–(C_1-C_{12} alkyldiyl)–N(R^5)–C(=NR^5)N(R^5)–*;

–(C_2-C_6 alkynyldiyl)–N(R^5)–*; and

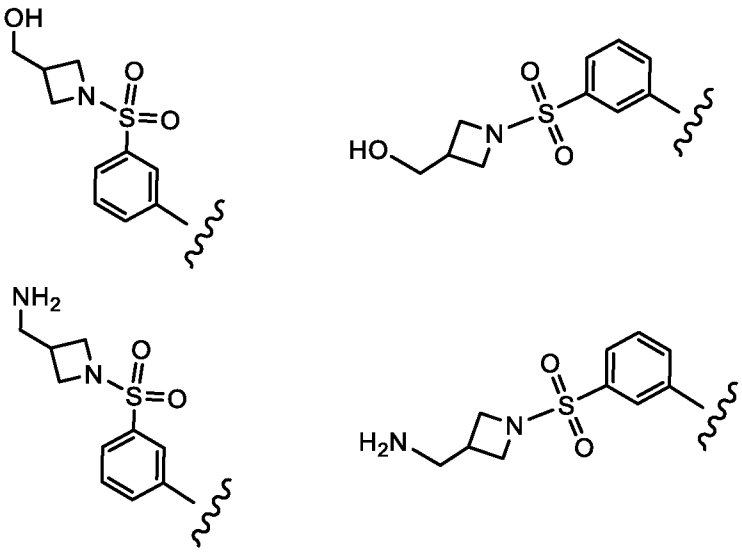
–(C_2-C_6 alkynyldiyl)–N(R^5)C(=NR^5)N(R^5)–*;

X^2 and X^3 are a bond, and where the asterisk * indicates the attachment site of L.

An exemplary embodiment of the immunoconjugate of Formula **I** includes wherein one of R^1 and R^4 is selected from –(C_6-C_{20} aryldiyl)–S(=O)$_2$–(C_2-C_{20} heterocyclyldiyl)–(C_1-C_{12} alkyldiyl)–N(R^5)$_2$ and –(C_6-C_{20} aryldiyl)–S(=O)$_2$–(C_2-C_{20} heterocyclyldiyl)–(C_1-C_{12} alkyldiyl)–OH.

An exemplary embodiment of the immunoconjugate of Formula **I** includes wherein C_6-C_{20} aryldiyl is phenyldiyl and C_2-C_{20} heterocyclyldiyl is azetidindiyl.

An exemplary embodiment of the immunoconjugate of Formula **I** includes wherein one of R^1 and R^4 is selected from the formulas:

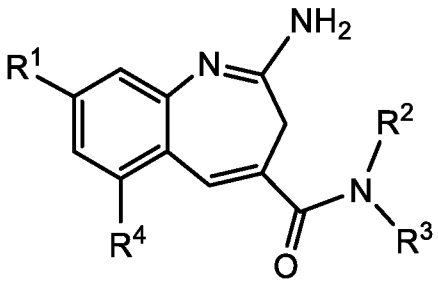


An exemplary embodiment of the immunoconjugate of Formula **I** includes wherein one of R^1 and R^4 is –C(=O)NR^5–(C_1-C_{20} heteroaryldiyl)–(C_2-C_{20} heterocyclyldiyl)–C(=O)NR^5–(C_1-C_{12} alkyldiyl)–NR^5–L.

An exemplary embodiment of the immunoconjugate of Formula **I** includes wherein C_1-C_{20} heteroaryldiyl is pyridindiyl and C_2-C_{20} heterocyclyldiyl is piperidiyl.

In an exemplary embodiment, p is 1, 2, 3, or 4.

Exemplary embodiments of immunoconjugates comprise an antibody covalently attached to a linker which is covalently attached to one or more aminobenzazepine moieties, and having Formula **III**:

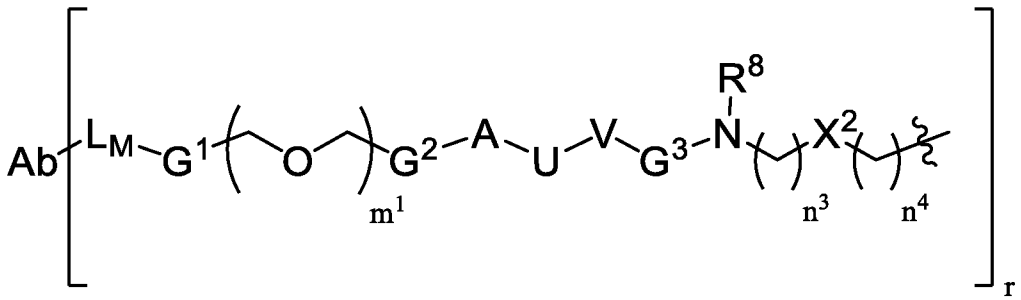


III,

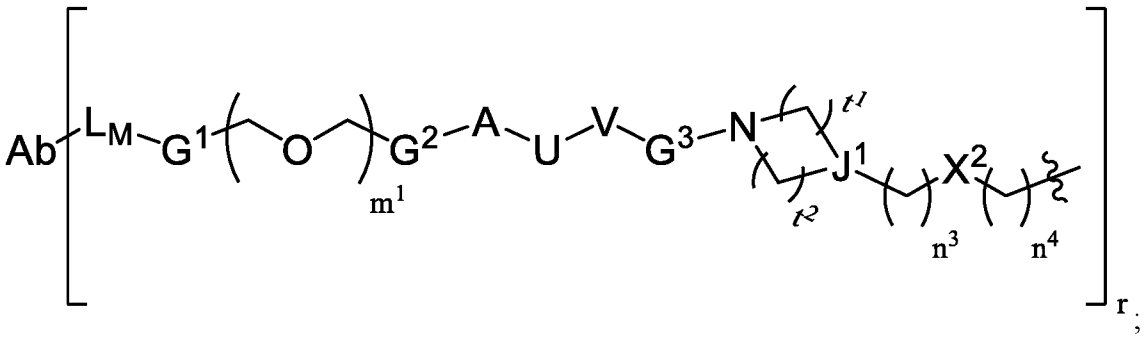
a pharmaceutically acceptable salt thereof, or a quaternary ammonium salt thereof,

wherein

R^1, R^2, R^3, and R^4 are independently Y or Z, wherein one of R^1, R^2, R^3, and R^4 is Y, having the formula:

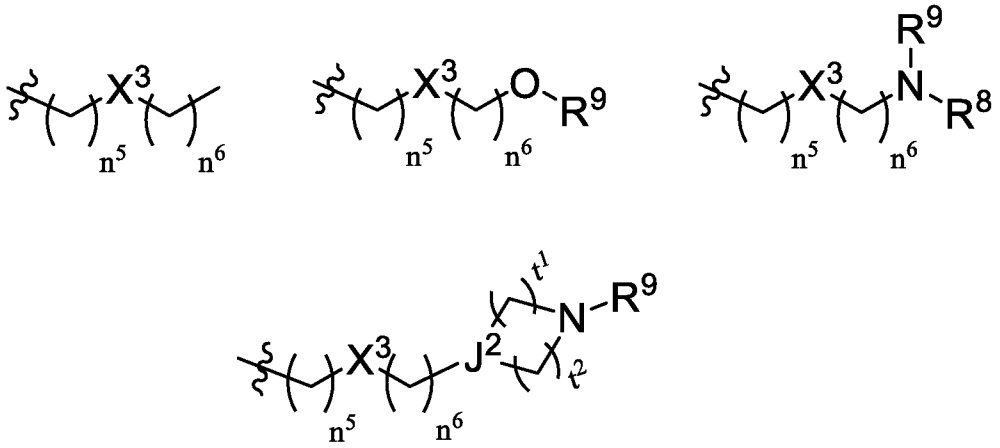


or



;

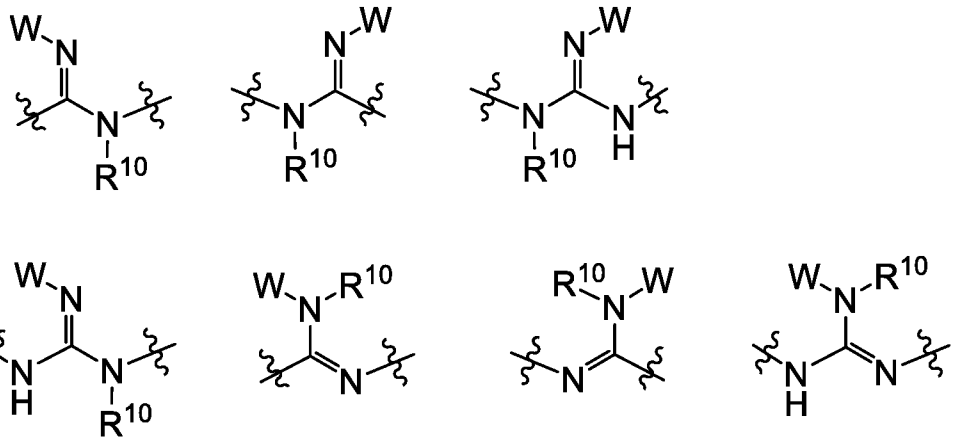
each Z independently is hydrogen or selected from the formulas:



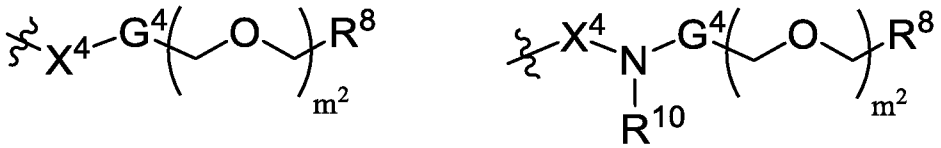
;

U is optionally present and is CH_2, C(=O), $CH_2C(=O)$, or $C(=O)CH_2$,

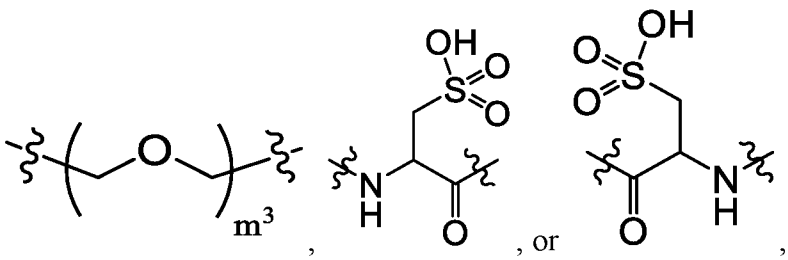
A is optionally present and is NR^{10} or selected from the formulas:



R^{10} and W independently are hydrogen, Ar^1, or of formula:



V is optionally present and is of formula:



, , or ,

J^1 and J^2 independently are CH or N,

m^1, m^2, and m^3 independently are an integer from 0 to 25, except that at least one of m^1, m^2, and m^3 is a non-zero integer,

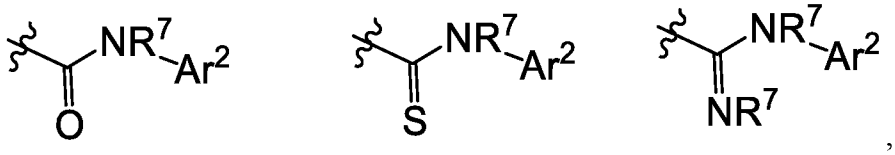
n^1, n^2, n^3, n^4, n^5, and n^6 independently are an integer from 0 to 10,

t^1 and t^2 independently are an integer from 1 to 3,

G^1, G^2, G^3, and G^4 independently are CH_2, C(=O), $CH_2C(=O)$, $C(=O)CH_2$, or a bond,

X^1, X^2, X^3, and X^4 are each optionally present and independently are O, NR^7, CHR^7, SO_2, S, or one or two cycloalkyldiyl, heterocycloalkyldiyl, aryldiyl, or heteroaryldiyl groups, and when more than one cycloalkyldiyl, heterocycloalkyldiyl, aryldiyl, or heteroaryldiyl group is present, the more than one cycloalkyldiyl, heterocycloalkyldiyl, aryldiyl, or heteroaryldiyl groups are linked or fused, wherein linked cycloalkyldiyl, heterocycloalkyldiyl, aryldiyl, or heteroaryldiyl groups are linked through a bond or –CO–,

R^9 is hydrogen, C_1-C_4 alkyl, or selected from the formulas:



,

R^8 is independently hydrogen or C_1-C_4 alkyl,

Ar^1 and Ar^2 independently are an aryl or heteroaryl group, optionally substituted with one or more halogens (e.g., fluorine, chlorine, bromine, or iodine), nitriles, hydroxyls, C_1-C_4 alkyl groups, or a combination thereof,

L_M is a linking moiety that comprises a functional group selected from an amide, amine, ester, carbamate, urea, thioether, thiocarbamate, thiocarbonate, and thiourea,

r is an integer from 1 to 10,

Ab is an antibody, and

each wavy line ( ) represents a point of attachment.

An exemplary embodiment of the immunoconjugate of Formula **III** includes wherein subscript r is 1.

An exemplary embodiment of the immunoconjugate of Formula **I** or **III** includes wherein the antibody is an antibody construct that has an antigen binding domain that binds PD-L1.

An exemplary embodiment of the immunoconjugate of Formula **I** or **III** includes wherein the antibody is selected from the group consisting of atezolizumab, durvalumab, and avelumab, or a biosimilar or a biobetter thereof.

An exemplary embodiment of the immunoconjugate of Formula **I** or **III** includes wherein the antibody is an antibody construct that has an antigen binding domain that binds HER2.

An exemplary embodiment of the immunoconjugate of Formula **I** or **III** includes wherein the antibody is selected from the group consisting of trastuzumab and pertuzumab, or a biosimilar or a biobetter thereof.

An exemplary embodiment of the immunoconjugate of Formula **I** or **III** includes wherein the antibody is an antibody construct that has an antigen binding domain that binds CEA.

An exemplary embodiment of the immunoconjugate of Formula **I** or **III** includes wherein the antibody is selected from the group consisting of labetuzumab (also known as MN-14, hMN14, or CEA-CIDE™), PR1A3, MFE-23, SM3E, or a biosimilar or a biobetter thereof.

The invention includes all reasonable combinations, and permutations of the features, of the Formula I and III embodiments.

In certain embodiments, the immunoconjugate compounds of the invention include those with immunostimulatory activity. The antibody-drug conjugates of the invention selectively deliver an effective dose of an aminobenzazepine drug to tumor tissue, whereby greater selectivity (*i.e.,* a lower efficacious dose) may be achieved while increasing the therapeutic index ("therapeutic window") relative to unconjugated aminobenzazepine.

Drug loading is represented by p, the number of aminobenzazepine moieties per antibody in an immunoconjugate of Formula I or III. Drug (aminobenzazepine) loading may range from 1 to about 8 drug moieties (D) per antibody. Immunoconjugates of Formula I and III include mixtures or collections of antibodies conjugated with a range of drug moieties, from 1 to about 8. In some embodiments, the number of drug moieties that can be conjugated to an antibody is limited by the number of reactive or available amino acid side chain residues such as lysine and cysteine. In some embodiments, free cysteine residues are introduced into the antibody amino acid sequence by the methods described herein. In such aspects, p may be 1, 2, 3, 4, 5, 6, 7, or 8, and ranges thereof, such as from 1 to 8 or from 2 to 5. In any such aspect, p and n are equal (i.e., p = n = 1, 2, 3, 4, 5, 6, 7, or 8, or some range there between). Exemplary antibody-drug conjugates of Formula I include, but are not limited to, antibodies that have 1, 2, 3, or 4 engineered cysteine amino acids (Lyon, R. et al. (2012) *Methods in Enzym*. 502:123-138). In some embodiments, one or more free cysteine residues are already present in an antibody forming intrachain disulfide bonds, without the use of engineering, in which case the existing free cysteine residues may be used to conjugate the antibody to a drug. In some embodiments, an antibody is exposed to reducing conditions prior to conjugation of the antibody in order to generate one or more free cysteine residues.

For some immunoconjugates, p may be limited by the number of attachment sites on the antibody. For example, where the attachment is a cysteine thiol, as in certain exemplary embodiments described herein, an antibody may have only one or a limited number of cysteine thiol groups, or may have only one or a limited number of sufficiently reactive thiol groups, to which the drug may be attached. In other embodiments, one or more lysine amino groups in the

antibody may be available and reactive for conjugation with an aminobenzazepine-linker compound of Formula II. In certain embodiments, higher drug loading, *e.g.* p >5, may cause aggregation, insolubility, toxicity, or loss of cellular permeability of certain antibody-drug conjugates. In certain embodiments, the average drug loading for an immunoconjugate ranges from 1 to about 8; from about 2 to about 6; or from about 3 to about 5. In certain embodiments, an antibody is subjected to denaturing conditions to reveal reactive nucleophilic groups such as lysine or cysteine.

The loading (drug/antibody ratio) of an immunoconjugate may be controlled in different ways, and for example, by: (i) limiting the molar excess of the aminobenzazepine-linker intermediate compound relative to antibody, (ii) limiting the conjugation reaction time or temperature, and (iii) partial or limiting reductive denaturing conditions for optimized antibody reactivity.

It is to be understood that where more than one nucleophilic group of the antibody reacts with a drug, then the resulting product is a mixture of antibody-drug conjugate compounds with a distribution of one or more drug moieties attached to an antibody. The average number of drugs per antibody may be calculated from the mixture by a dual ELISA antibody assay, which is specific for antibody and specific for the drug. Individual immunoconjugate molecules may be identified in the mixture by mass spectroscopy and separated by HPLC, *e.g.* hydrophobic interaction chromatography (*see, e.g.*, McDonagh et al. (2006) Prot. Engr. Design & Selection 19(7):299-307; Hamblett et al. (2004) Clin. Cancer Res. 10:7063-7070; Hamblett, K.J., et al. "Effect of drug loading on the pharmacology, pharmacokinetics, and toxicity of an anti-CD30 antibody-drug conjugate," Abstract No. 624, American Association for Cancer Research, 2004 Annual Meeting, March 27-31, 2004, Proceedings of the AACR, Volume 45, March 2004; Alley, S.C., et al. "Controlling the location of drug attachment in antibody-drug conjugates," Abstract No. 627, American Association for Cancer Research, 2004 Annual Meeting, March 27-31, 2004, Proceedings of the AACR, Volume 45, March 2004). In certain embodiments, a homogeneous immunoconjugate with a single loading value may be isolated from the conjugation mixture by electrophoresis or chromatography.

An exemplary embodiment of the immunoconjugate of Formula **I** is selected from the Tables 3a, 3b, 3c Immunoconjugates.

Table 3a: Immunoconjugates (IC)

Immunoconjugate No.	BzL linker-adjuvant Table 2a	Ab Antigen	DAR	Myeloid TNFα Secretion EC50 nM
IC-1	BzL-2	Trastuzumab HER2	2.33	>1000
IC-2	BzL-3	Trastuzumab HER2	2.06	14.8
IC-3	BzL-4	Trastuzumab HER2	2.05	>1000
IC-4	BzL-5	Trastuzumab HER2	1.82	>1000
IC-5	BzL-7	Trastuzumab HER2	1.6	nd
IC-6	BzL-8	Trastuzumab HER2	0.5	nd
IC-7	BzL-9	Trastuzumab HER2	1.6	nd
IC-8	BzL-15	Trastuzumab HER2	1.9	233.7
IC-9	BzL-15	Avelumab PD-L1	2.16	161.03
IC-10	BzL-16	Trastuzumab HER2	2.49	>1000
IC-11	BzL-17	Trastuzumab HER2	1.84	>1000
IC-12	BzL-18	Trastuzumab HER2	2.49	>1000
IC-13	BzL-19	Trastuzumab HER2	2.05	>1000
IC-14	BzL-20	Trastuzumab HER2	1.91	>1000
IC-15	BzL-21	Avelumab PD-L1	2.85	199.5

IC-16	BzL-21	Trastuzumab HER2	1.74	>1000
IC-17	BzL-22	Trastuzumab HER2	2.65	>1000
IC-18	BzL-25	Trastuzumab HER2	nd	nd
IC-19	BzL-27	Trastuzumab HER2	1.61	>1000
IC-20	BzL-31	Trastuzumab HER2	2.57	788
IC-21	BzL-28	Trastuzumab HER2	2.39	>1000

Table 3b: Immunoconjugates (IC)

Immunoconjugate No.	BzL linker-adjuvant Table 2b	Ab Antigen	DAR	Myeloid TNFα Secretion EC50 nM
IC-22	BzL-33	Trastuzumab HER2	2.37	>1000
IC-23	BzL-35	Trastuzumab HER2	2.65	464
IC-24	BzL-36	Trastuzumab HER2	2.60	>1000
IC-25	Bzl-37	Trastuzumab HER2	2.28	>1000
IC-26	Bzl-38	Trastuzumab HER2	2.0	62
IC-27	BzL-34	Trastuzumab HER2	2.06	97
IC-28	BzL-39	Trastuzumab HER2	2.32	>1000
IC-29	BzL-40	Trastuzumab HER2	2.95	>1000

IC-30	BzL-41	Trastuzumab HER2	2.83	459
IC-31	BzL-42	Trastuzumab HER2	2.05	17.2
IC-32	BzL-43	Trastuzumab HER2	2.05	133
IC-33	BzL-44	Trastuzumab HER2	2.0	71
IC-34	BzL-45	Trastuzumab HER2	2.26	78
IC-35	BzL-46	Trastuzumab HER2	1.54	68

Table 3c: Immunoconjugates (IC)

Immunoconjugate No.	BzL linker-adjuvant Tables 2a-c	Ab Antigen	DAR
IC-36	BzL-40	PDL1.24-G1f	2.39
IC-37	BzL-39	PDL1.24-G1f	1.6
IC-38	Bzl-49	Trastuzumab HER2	2.24
IC-39	BzL-35	Rituximab CD20	2.40
IC-40	BzL-50	Trastuzumab HER2	2.48
IC-41	BzL-51	Trastuzumab HER2	2.57
IC-42	BzL-52	Trastuzumab HER2	2.62
IC-43	BzL-53	Trastuzumab HER2	2.18
IC-44	BzL-55	Trastuzumab HER2	2.18

IC-45	BzL-56	Trastuzumab HER2	1.96
IC-46	BzL-35	anti-mPD-L1	2.27
IC-47	BzL-35	rat IgG2b isotype control	2.4
IC-48	Bzl-49	PDL1.85-G1f	2.21
IC-49	Bzl-49	PDL1.85-G1f	2.21
IC-50	BzL-54	Trastuzumab HER2	2.13 2.36
IC-51	Bzl-49	CEA.5G1fhL2	2.35
IC-52	BzL-57	Trastuzumab HER2	2.58
IC-53	BzL-60	Trastuzumab HER2	2.11
IC-54	BzL-62	Trastuzumab HER2	2.46
IC-55	BzL-58	Trastuzumab HER2	2.35
IC-56	BzL-65	Trastuzumab HER2	1.80
IC-57	BzL-35	CEA.5G1fhL2	2.21
IC-58	BzL-35	Tras-G1f-N297A	2.34
IC-59	BzL-66	Trastuzumab HER2	2.38
IC-60	BzL-67	Trastuzumab HER2	2.15 1.93
IC-61	BzL-68	Trastuzumab HER2	2.36
IC-62	BzL-69	Trastuzumab HER2	2.15 2.99
IC-63	BzL-69	Rituximab CD20	2.60
IC-64	BzL-69	Tras-G1f-N297A	2.41

IC-65	BzL-70	Trastuzumab HER2	2.39
IC-66	BzL-72	Trastuzumab HER2	2.39
IC-67	BzL-41	CEA.9-G1fhL2	2.26
IC-68	BzL-35	CEA.9-G1fhL2	2.37
IC-69	BzL-69	CEA.9-G1fhL2	2.41
IC-70	BzL-63	Trastuzumab HER2	2.24
IC-71	BzL-64	Trastuzumab HER2	2.34
IC-72	BzL-35	PDL1.24-G1f	2.66
IC-73	BzL-35	PDL1.85-G1f	2.84
IC-74	BzL-73	Trastuzumab HER2	2.17
IC-75	BzL-74	Trastuzumab HER2	2.74
IC-76	BzL-77	Trastuzumab HER2	2.43
IC-77	BzL-76	Trastuzumab HER2	1.19
IC-78	BzL-78	Trastuzumab HER2	2.10
IC-79	BzL-75	Trastuzumab HER2	1.45
IC-80	BzL-69	CEACAM5	1.84 2.74
IC-81	BzL-77	CEA.9-G1fhL2	2.39 2.45
IC-82	BzL-72	CEA.9-G1fhL2	2.70
IC-83	BzL-74	CEA.9-G1fhL2	2.41
IC-84	BzL-80	CEA.9-G1fhL2	1.81
IC-85	BzL-69	PDL1.85-G1f	2.69

IC-86	BzL-80	Trastuzumab HER2	2.92
IC-87	BzL-82	Trastuzumab HER2	2.56
IC-88	BzL-77	PDL1.85-G1f	2.55
IC-89	BzL-74	PDL1.85-G1f	2.68
IC-90	BzL-81	Trastuzumab HER2	1.91
IC-91	BzL-85	Trastuzumab HER2	2.18
IC-92	BzL-69	Trastuzumab HER2	3.07

COMPOSITIONS OF IMMUNOCONJUGATES

The invention provides a composition, e.g., a pharmaceutically or pharmacologically acceptable composition or formulation, comprising a plurality of immunoconjugates as described herein and optionally a carrier therefor, e.g., a pharmaceutically or pharmacologically acceptable carrier. The immunoconjugates can be the same or different in the composition, i.e., the composition can comprise immunoconjugates that have the same number of adjuvants linked to the same positions on the antibody construct and/or immunoconjugates that have the same number of adjuvants linked to different positions on the antibody construct, that have different numbers of adjuvants linked to the same positions on the antibody construct, or that have different numbers of adjuvants linked to different positions on the antibody construct.

In an exemplary embodiment, a composition comprising the immunoconjugate compounds comprises a mixture of the immunoconjugate compounds, wherein the average drug loading per antibody in the mixture of immunoconjugate compounds is about 2 to about 5.

A composition of immunoconjugates of the invention can have an average adjuvant to antibody construct ratio of about 0.4 to about 10. A skilled artisan will recognize that the number of aminobenzazepine adjuvants conjugated to the antibody construct may vary from immunoconjugate to immunoconjugate in a composition comprising multiple immunoconjugates of the invention, and, thus, the adjuvant to antibody construct (e.g., antibody) ratio can be measured as an average, which may be referred to as the drug to antibody ratio (DAR). The adjuvant to antibody construct (e.g., antibody) ratio can be assessed by any suitable means, many of which are known in the art.

The average number of adjuvant moieties per antibody (DAR) in preparations of immunoconjugates from conjugation reactions may be characterized by conventional means such as mass spectrometry, ELISA assay, and HPLC. The quantitative distribution of immunoconjugates in a composition in terms of p may also be determined. In some instances, separation, purification, and characterization of homogeneous immunoconjugates where p is a certain value from immunoconjugates with other drug loadings may be achieved by means such as reverse phase HPLC or electrophoresis.

PHARMACEUTICAL COMPOSITIONS AND METHODS OF ADMINISTRATION

In other embodiments, another aspect of the invention relates to pharmaceutical compositions or dosage forms including therapeutically effective amount of an immunoconjugate of the invention and one or more pharmaceutically acceptable diluent, vehicle, carrier or excipient.

The pharmaceutical compositions can be any form that allows for administration to a patient. For example, the pharmaceutical composition can be in the form of a solid or liquid. Typical routes of administration include, without limitation, parenteral, ocular and intra-tumoral. Parenteral administration includes subcutaneous injections, intravenous, intramuscular or intrasternal injection or infusion techniques. In one embodiment, the compositions are administered parenterally. In a specific embodiment, the compositions are administered intravenously.

In some embodiments, the pharmaceutical composition further comprises one or more pharmaceutically or pharmacologically acceptable excipients. For example, the immunoconjugates of the invention can be formulated for parenteral administration, such as IV administration or administration into a body cavity or lumen of an organ. Alternatively, the immunoconjugates can be injected intra-tumorally. Compositions for injection will commonly comprise a solution of the immunoconjugate dissolved in a pharmaceutically acceptable carrier. Among the acceptable vehicles and solvents that can be employed are water and an isotonic solution of one or more salts such as sodium chloride, e.g., Ringer's solution. In addition, sterile fixed oils can conventionally be employed as a solvent or suspending medium. For this purpose, any bland fixed oil can be employed, including synthetic monoglycerides or diglycerides. In addition, fatty acids such as oleic acid can likewise be used in the preparation of injectables. These compositions desirably are sterile and generally free of undesirable matter. These compositions can be sterilized by conventional, well known sterilization techniques. The compositions can contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions such as pH adjusting and buffering agents, toxicity

adjusting agents, e.g., sodium acetate, sodium chloride, potassium chloride, calcium chloride, sodium lactate and the like.

The composition can contain any suitable concentration of the immunoconjugate. The concentration of the immunoconjugate in the composition can vary widely, and will be selected primarily based on fluid volumes, viscosities, body weight, and the like, in accordance with the particular mode of administration selected and the patient's needs. In certain embodiments, the concentration of an immunoconjugate in a solution formulation for injection will range from about 0.1% (w/w) to about 10% (w/w).

METHOD OF TREATING CANCER WITH IMMUNOCONJUGATES

The invention provides a method for treating cancer. The method includes administering a therapeutically effective amount of an immunoconjugate as described herein (e.g., as a pharmaceutical composition as described herein) to a subject in need thereof, e.g., a subject that has cancer and is in need of treatment for the cancer. The method includes administering a therapeutically effective amount of an immunoconjugate (IC) selected from Table 3.

It is contemplated that the immunoconjugate of the present invention may be used to treat various hyperproliferative diseases or disorders, e.g. characterized by the overexpression of a tumor antigen. Exemplary hyperproliferative disorders include benign or malignant solid tumors and hematological disorders such as leukemia and lymphoid malignancies.

In another aspect, an immunoconjugate for use as a medicament is provided. In certain embodiments, the invention provides an immunoconjugate for use in a method of treating an individual comprising administering to the individual an effective amount of the immunoconjugate. In one such embodiment, the method further comprises administering to the individual an effective amount of at least one additional therapeutic agent, *e.g.*, as described herein.

In a further aspect, the invention provides for the use of an immunoconjugate in the manufacture or preparation of a medicament. In one embodiment, the medicament is for treatment of cancer, the method comprising administering to an individual having cancer an effective amount of the medicament. In one such embodiment, the method further comprises administering to the individual an effective amount of at least one additional therapeutic agent, *e.g.*, as described herein.

Carcinomas are malignancies that originate in the epithelial tissues. Epithelial cells cover the external surface of the body, line the internal cavities, and form the lining of glandular tissues. Examples of carcinomas include, but are not limited to, adenocarcinoma (cancer that begins in glandular (secretory) cells such as cancers of the breast, pancreas, lung, prostate,

stomach, gastroesophageal junction, and colon) adrenocortical carcinoma; hepatocellular carcinoma; renal cell carcinoma; ovarian carcinoma; carcinoma in situ; ductal carcinoma; carcinoma of the breast; basal cell carcinoma; squamous cell carcinoma; transitional cell carcinoma; colon carcinoma; nasopharyngeal carcinoma; multilocular cystic renal cell carcinoma; oat cell carcinoma; large cell lung carcinoma; small cell lung carcinoma; non-small cell lung carcinoma; and the like. Carcinomas may be found in prostrate, pancreas, colon, brain (usually as secondary metastases), lung, breast, and skin. In some embodiments, methods for treating non-small cell lung carcinoma include administering an immunoconjugate containing an antibody construct that is capable of binding PD-L1 (e.g., atezolizumab, durvalumab, avelumab, biosimilars thereof, or biobetters thereof). In some embodiments, methods for treating breast cancer include administering an immunoconjugate containing an antibody construct that is capable of binding PD-L1 (e.g., atezolizumab, durvalumab, avelumab, biosimilars thereof, or biobetters thereof). In some embodiments, methods for treating triple-negative breast cancer include administering an immunoconjugate containing an antibody construct that is capable of binding PD-L1 (e.g., atezolizumab, durvalumab, avelumab, biosimilars thereof, or biobetters thereof).

Soft tissue tumors are a highly diverse group of rare tumors that are derived from connective tissue. Examples of soft tissue tumors include, but are not limited to, alveolar soft part sarcoma; angiomatoid fibrous histiocytoma; chondromyoxid fibroma; skeletal chondrosarcoma; extraskeletal myxoid chondrosarcoma; clear cell sarcoma; desmoplastic small round-cell tumor; dermatofibrosarcoma protuberans; endometrial stromal tumor; Ewing's sarcoma; fibromatosis (Desmoid); fibrosarcoma, infantile; gastrointestinal stromal tumor; bone giant cell tumor; tenosynovial giant cell tumor; inflammatory myofibroblastic tumor; uterine leiomyoma; leiomyosarcoma; lipoblastoma; typical lipoma; spindle cell or pleomorphic lipoma; atypical lipoma; chondroid lipoma; well-differentiated liposarcoma; myxoid/round cell liposarcoma; pleomorphic liposarcoma; myxoid malignant fibrous histiocytoma; high-grade malignant fibrous histiocytoma; myxofibrosarcoma; malignant peripheral nerve sheath tumor; mesothelioma; neuroblastoma; osteochondroma; osteosarcoma; primitive neuroectodermal tumor; alveolar rhabdomyosarcoma; embryonal rhabdomyosarcoma; benign or malignant schwannoma; synovial sarcoma; Evan's tumor; nodular fasciitis; desmoid-type fibromatosis; solitary fibrous tumor; dermatofibrosarcoma protuberans (DFSP); angiosarcoma; epithelioid hemangioendothelioma; tenosynovial giant cell tumor (TGCT); pigmented villonodular synovitis (PVNS); fibrous dysplasia; myxofibrosarcoma; fibrosarcoma; synovial sarcoma; malignant peripheral nerve sheath tumor; neurofibroma; pleomorphic adenoma of soft tissue;

and neoplasias derived from fibroblasts, myofibroblasts, histiocytes, vascular cells/endothelial cells, and nerve sheath cells.

A sarcoma is a rare type of cancer that arises in cells of mesenchymal origin, e.g., in bone or in the soft tissues of the body, including cartilage, fat, muscle, blood vessels, fibrous tissue, or other connective or supportive tissue. Different types of sarcoma are based on where the cancer forms. For example, osteosarcoma forms in bone, liposarcoma forms in fat, and rhabdomyosarcoma forms in muscle. Examples of sarcomas include, but are not limited to, askin's tumor; sarcoma botryoides; chondrosarcoma; ewing's sarcoma; malignant hemangioendothelioma; malignant schwannoma; osteosarcoma; and soft tissue sarcomas (e.g., alveolar soft part sarcoma; angiosarcoma; cystosarcoma phyllodesdermatofibrosarcoma protuberans (DFSP); desmoid tumor; desmoplastic small round cell tumor; epithelioid sarcoma; extraskeletal chondrosarcoma; extraskeletal osteosarcoma; fibrosarcoma; gastrointestinal stromal tumor (GIST); hemangiopericytoma; hemangiosarcoma (more commonly referred to as "angiosarcoma"); kaposi's sarcoma; leiomyosarcoma; liposarcoma; lymphangiosarcoma; malignant peripheral nerve sheath tumor (MPNST); neurofibrosarcoma; synovial sarcoma; and undifferentiated pleomorphic sarcoma).

A teratoma is a type of germ cell tumor that may contain several different types of tissue (e.g., can include tissues derived from any and/or all of the three germ layers: endoderm, mesoderm, and ectoderm), including, for example, hair, muscle, and bone. Teratomas occur most often in the ovaries in women, the testicles in men, and the tailbone in children.

Melanoma is a form of cancer that begins in melanocytes (cells that make the pigment melanin). Melanoma may begin in a mole (skin melanoma), but can also begin in other pigmented tissues, such as in the eye or in the intestines.

Merkel cell carcinoma is a rare type of skin cancer that usually appears as a flesh-colored or bluish-red nodule on the face, head or neck. Merkel cell carcinoma is also called neuroendocrine carcinoma of the skin. In some embodiments, methods for treating Merkel cell carcinoma include administering an immunoconjugate containing an antibody construct that is capable of binding PD-L1 (e.g., atezolizumab, durvalumab, avelumab, biosimilars thereof, or biobetters thereof). In some embodiments, the Merkel cell carcinoma has metastasized when administration occurs.

Leukemias are cancers that start in blood-forming tissue, such as the bone marrow, and cause large numbers of abnormal blood cells to be produced and enter the bloodstream. For example, leukemias can originate in bone marrow-derived cells that normally mature in the bloodstream. Leukemias are named for how quickly the disease develops and progresses (e.g., acute versus chronic) and for the type of white blood cell that is affected (e.g., myeloid versus

lymphoid). Myeloid leukemias are also called myelogenous or myeloblastic leukemias. Lymphoid leukemias are also called lymphoblastic or lymphocytic leukemia. Lymphoid leukemia cells may collect in the lymph nodes, which can become swollen. Examples of leukemias include, but are not limited to, Acute myeloid leukemia (AML), Acute lymphoblastic leukemia (ALL), Chronic myeloid leukemia (CML), and Chronic lymphocytic leukemia (CLL).

Lymphomas are cancers that begin in cells of the immune system. For example, lymphomas can originate in bone marrow-derived cells that normally mature in the lymphatic system. There are two basic categories of lymphomas. One category of lymphoma is Hodgkin lymphoma (HL), which is marked by the presence of a type of cell called the Reed-Sternberg cell. There are currently 6 recognized types of HL. Examples of Hodgkin lymphomas include nodular sclerosis classical Hodgkin lymphoma (CHL), mixed cellularity CHL, lymphocyte-depletion CHL, lymphocyte-rich CHL, and nodular lymphocyte predominant HL.

The other category of lymphoma is non-Hodgkin lymphomas (NHL), which includes a large, diverse group of cancers of immune system cells. Non-Hodgkin lymphomas can be further divided into cancers that have an indolent (slow-growing) course and those that have an aggressive (fast-growing) course. There are currently 61 recognized types of NHL. Examples of non-Hodgkin lymphomas include, but are not limited to, AIDS-related Lymphomas, anaplastic large-cell lymphoma, angioimmunoblastic lymphoma, blastic NK-cell lymphoma, Burkitt's lymphoma, Burkitt-like lymphoma (small non-cleaved cell lymphoma), chronic lymphocytic leukemia/small lymphocytic lymphoma, cutaneous T-Cell lymphoma, diffuse large B-Cell lymphoma, enteropathy-type T-Cell lymphoma, follicular lymphoma, hepatosplenic gamma-delta T-Cell lymphomas, T-Cell leukemias, lymphoblastic lymphoma, mantle cell lymphoma, marginal zone lymphoma, nasal T-Cell lymphoma, pediatric lymphoma, peripheral T-Cell lymphomas, primary central nervous system lymphoma, transformed lymphomas, treatment-related T-Cell lymphomas, and Waldenstrom's macroglobulinemia.

Brain cancers include any cancer of the brain tissues. Examples of brain cancers include, but are not limited to, gliomas (e.g., glioblastomas, astrocytomas, oligodendrogliomas, ependymomas, and the like), meningiomas, pituitary adenomas, and vestibular schwannomas, primitive neuroectodermal tumors (medulloblastomas).

Immunoconjugates of the invention can be used either alone or in combination with other agents in a therapy. For instance, an immunoconjugate may be co-administered with at least one additional therapeutic agent, such as a chemotherapeutic agent. Such combination therapies encompass combined administration (where two or more therapeutic agents are included in the same or separate formulations), and separate administration, in which case, administration of the immunoconjugate can occur prior to, simultaneously, and/or following, administration of the

additional therapeutic agent and/or adjuvant. Immunoconjugates can also be used in combination with radiation therapy.

The immunoconjugates of the invention (and any additional therapeutic agent) can be administered by any suitable means, including parenteral, intrapulmonary, and intranasal, and, if desired for local treatment, intralesional administration. Parenteral infusions include intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration. Dosing can be by any suitable route, *e.g.* by injections, such as intravenous or subcutaneous injections, depending in part on whether the administration is brief or chronic. Various dosing schedules including but not limited to single or multiple administrations over various time-points, bolus administration, and pulse infusion are contemplated herein.

Atezolizumab, durvalumab, avelumab, biosimilars thereof, and biobetters thereof are known to be useful in the treatment of cancer, particularly breast cancer, especially triple negative (test negative for estrogen receptors, progesterone receptors, and excess HER2 protein) breast cancer, bladder cancer, and Merkel cell carcinoma. The immunoconjugate described herein can be used to treat the same types of cancers as atezolizumab, durvalumab, avelumab, biosimilars thereof, and biobetters thereof, particularly breast cancer, especially triple negative (test negative for estrogen receptors, progesterone receptors, and excess HER2 protein) breast cancer, bladder cancer, and Merkel cell carcinoma.

The immunoconjugate is administered to a subject in need thereof in any therapeutically effective amount using any suitable dosing regimen, such as the dosing regimens utilized for atezolizumab, durvalumab, avelumab, biosimilars thereof, and biobetters thereof. For example, the methods can include administering the immunoconjugate to provide a dose of from about 100 ng/kg to about 50 mg/kg to the subject. The immunoconjugate dose can range from about 5 mg/kg to about 50 mg/kg, from about 10 μg/kg to about 5 mg/kg, or from about 100 μg/kg to about 1 mg/kg. The immunoconjugate dose can be about 100, 200, 300, 400, or 500 μg/kg. The immunoconjugate dose can be about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 mg/kg. The immunoconjugate dose can also be outside of these ranges, depending on the particular conjugate as well as the type and severity of the cancer being treated. Frequency of administration can range from a single dose to multiple doses per week, or more frequently. In some embodiments, the immunoconjugate is administered from about once per month to about five times per week. In some embodiments, the immunoconjugate is administered once per week.

In another aspect, the invention provides a method for preventing cancer. The method comprises administering a therapeutically effective amount of an immunoconjugate (e.g., as a composition as described above) to a subject. In certain embodiments, the subject is susceptible to a certain cancer to be prevented. For example, the methods can include administering the

immunoconjugate to provide a dose of from about 100 ng/kg to about 50 mg/kg to the subject. The immunoconjugate dose can range from about 5 mg/kg to about 50 mg/kg, from about 10 μg/kg to about 5 mg/kg, or from about 100 μg/kg to about 1 mg/kg. The immunoconjugate dose can be about 100, 200, 300, 400, or 500 μg/kg. The immunoconjugate dose can be about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 mg/kg. The immunoconjugate dose can also be outside of these ranges, depending on the particular conjugate as well as the type and severity of the cancer being treated. Frequency of administration can range from a single dose to multiple doses per week, or more frequently. In some embodiments, the immunoconjugate is administered from about once per month to about five times per week. In some embodiments, the immunoconjugate is administered once per week.

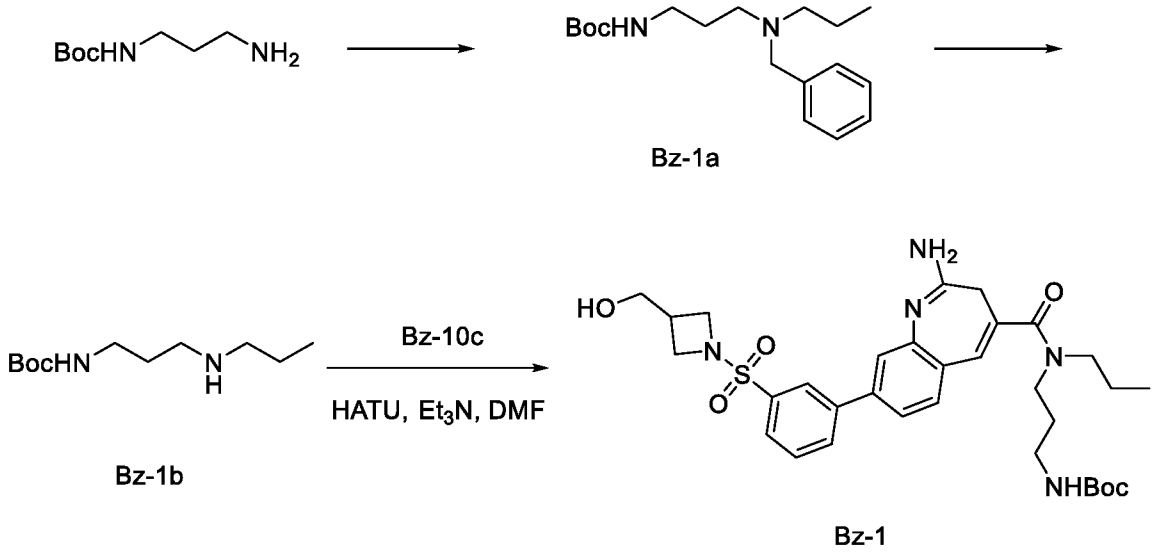
Some embodiments of the invention provide methods for treating cancer as described above, wherein the cancer is breast cancer. Breast cancer can originate from different areas in the breast, and a number of different types of breast cancer have been characterized. For example, the immunoconjugates of the invention can be used for treating ductal carcinoma *in situ;* invasive ductal carcinoma (*e.g.,* tubular carcinoma; medullary carcinoma; mucinous carcinoma; papillary carcinoma; or cribriform carcinoma of the breast); lobular carcinoma *in situ*; invasive lobular carcinoma; inflammatory breast cancer; and other forms of breast cancer such as triple negative (test negative for estrogen receptors, progesterone receptors, and excess HER2 protein) breast cancer. In some embodiments, methods for treating breast cancer include administering an immunoconjugate containing an antibody construct that is capable of binding HER2 (e.g. trastuzumab, pertuzumab, biosimilars, or biobetters thereof) and PD-L1 (e.g., atezolizumab, durvalumab, avelumab, biosimilars, or biobetters thereof). In some embodiments, methods for treating colon cancer lung cancer, renal cancer, pancreatic cancer, gastric cancer, and esophageal cancer include administering an immunoconjugate containing an antibody construct that is capable of binding CEA, or tumors over-expressing CEA (e.g. labetuzumab, biosimilars, or biobetters thereof).

In some embodiments, the cancer is susceptible to a pro-inflammatory response induced by TLR7 and/or TLR8.

EXAMPLES

Preparation of aminobenzazepine compounds (Bz) and intermediates

Example 1 Synthesis of Bz-1



Synthesis of *tert*-butyl (3-(benzyl(propyl)amino)propyl)carbamate Bz-1a.

tert-Butyl N-(3-aminopropyl)carbamate (10 g, 57.39 mmol, 10.02 mL, 1 eq) and benzaldehyde (6.09 g, 57.39 mmol, 5.80 mL, 1 eq) in DCE (100 mL) was stirred at 70 °C for 24 hours. MeOH (100 mL) and $NaBH_3CN$ (16.23 g, 258.26 mmol, 4.5 eq) was added to the mixture in portions at 0°C. The mixture was stirred at 0°C for 2 hours, then propanal (16.67 g, 286.96 mmol, 20.89 mL, 5 eq) was added at 0 °C and stirred for 2 hours. LCMS showed the reaction was completed. The mixture was added a few drops water and concentrated in reduced pressure at 40°C. The residue was poured into ice water (200 mL) and stirred for 5 min. The aqueous phase was extracted with ethyl acetate (200 mL x 3). The combined organic phase was washed with brine (300 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (Petroleum ether/Ethyl acetate=10/1, 3/1) to afford tert-butyl N-[3-[benzyl(propyl)amino]propyl]carbamate, Bz-1a (16 g, 52.21 mmol, 90.98% yield) as light yellow oil. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.39-7.29 (m, 5H), 3.60-3.52 (m, 2H), 3.20-3.08 (m, 2H), 2.56-2.45 (m, 2H), 2.39 (s, 2H), 1.73-1.61 (m, 2H), 1.58-1.48 (m, 2H), 1.42 (s, 1H), 1.45 (s, 9H), 0.89 (t, J = 7.2 Hz, 3H).

Synthesis of tert-butyl N-[3-(propylamino)propyl]carbamate, Bz-1b.

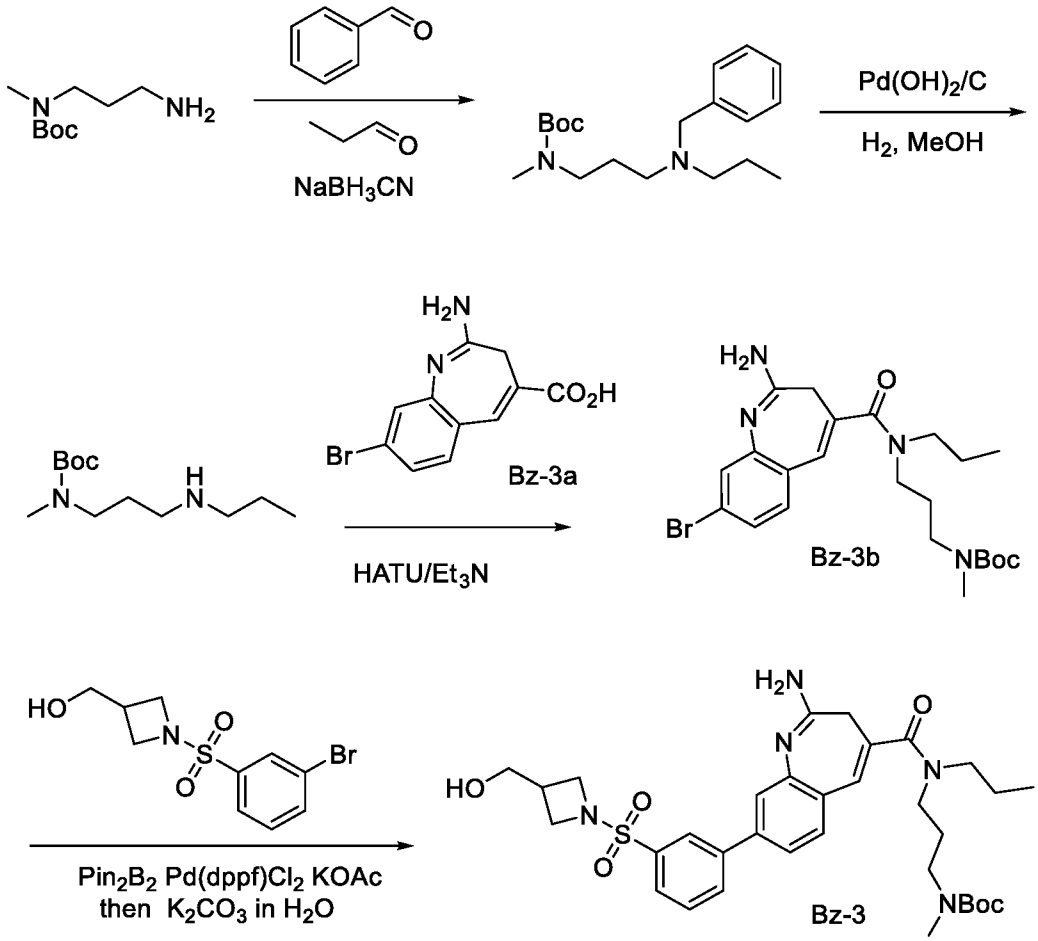
To a solution of tert-butyl N-[3-[benzyl(propyl)amino]propyl]carbamate, Bz-1a (10 g, 32.63 mmol, 1 eq) in MeOH (150 mL) was added $Pd(OH)_2/C$ (10%, 3 g) under N_2. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (50 psi) at 50 °C for 12 hours. TLC (Petroleum ether/Ethyl acetate=3:1) showed the starting material was consumed completely. The reaction mixture was filtered and the filtrate was concentrated to give tert-butyl N-[3-(propylamino)propyl]carbamate, Bz-1b (5 g, 23.11 mmol, 70.83% yield) as colorless oil which was used into the next step without further

purification. ^{1}H NMR (MeOD, 400 MHz) δ 3.13-3.05 (m, 2H), 2.60 (t, *J* = 7.2 Hz, 2H), 2.56-2.50 (m, 2H), 1.66 (m, 2H), 1.58-1.48 (m, 2H), 1.44 (s, 9H), 0.94 (t, *J* = 7.2 Hz, 3H).

Synthesis of tert-butyl N-[3-[[2-amino-8-[3-[3-(hydroxymethyl)azetidin-1-yl] sulfonylphenyl]-3H-1-benzazepine-4-carbonyl]-propyl-amino]propyl]carbamate , Bz-1.

To a mixture of tert-butyl N-[3-(propylamino)propyl]carbamate, Bz-1b (202.42 mg, 935.73 μmol (micromole), 2 eq) and 2-amino-8-[3-[3-(hydroxymethyl)azetidin-1-yl]sulfonylphenyl]-3H-1-benzazepine-4- carboxylic acid, Bz-10c from Example 6 (0.2 g, 467.87 μmol, 1 eq) in DMF (2 mL) was added HATU (213.48 mg, 561.44 μmol, 1.2 eq) and Et_3N (94.69 mg, 935.73 μmol, 130.24 μL (microliter), 2 eq) in one portion at 15°C. The mixture was stirred at 15°C for 30 min. LCMS and HPLC showed the reaction was completed. The mixture was filtered and purified by prep-HPLC (column: Waters Xbridge 150x25 mm, 5micron particle size; mobile phase: [water (10mM NH_4HCO_3)-ACN]; B%: 30%-50%, 20min) to afford tert-butyl N-[3-[[2-amino-8-[3-[3-(hydroxymethyl)azetidin-1-yl]sulfonylphenyl] -3H-1-benzazepine-4-carbonyl]-propyl-amino]propyl]carbamate, Bz-1 (0.087 g, 139.03 μmol, 29.72% yield) as light yellow solid. ^{1}H NMR (MeOD, 400 MHz) δ 8.07 (s, 1H), 8.03 (d, *J* = 8.0 Hz, 1H), 7.86-7.81 (m, 1H), 7.79-7.73 (m, 1H), 7.50-7.45 (m, 2H), 7.39 (m, 1H), 6.92 (s, 1H), 3.86 (t, *J* = 8.0 Hz, 2H), 3.61-3.58 (m, 2H), 3.52-3.48 (m, 2H), 3.45-3.41 (m, 4H), 3.10 (s, 4H), 2.62-2.52 (m, 1H), 1.86-1.79 (m, 2H), 1.71-1.65 (m, 2H), 1.42-1.50 (m, 9H), 0.87-0.95 (m, 3H). LC/MS [M+H] 626.30 (calculated); LC/MS [M+H] 626.40 (observed).

Example 2 Synthesis of Bz-3



Synthesis of tert-butyl (3-(benzyl(propyl)amino)propyl)(methyl)carbamate

To a mixture of benzaldehyde (310.02 mg, 2.92 mmol, 295.26 μL, 1 *eq*) in DCE (10 mL) was added tert-butyl N-(3-aminopropyl)-N-methyl-carbamate (0.55 g, 2.92 mmol, 1 *eq*) at 25°C under N_2. The mixture was stirred at 60°C for 12 hours, then cooled to 0°C, MeOH (10 mL) was added to the mixture, $NaBH_3CN$ (550.48 mg, 8.76 mmol, 3 *eq*) was added to the mixture stirred for 1 hr. Propanal (339.18 mg, 5.84 mmol, 425.04 μL, 2 *eq*) was added to the mixture and stirred at 0°C for 1 hr. LCMS showed the reaction was completed. The mixture was concentrated in vacuum. The residue was purified by prep-HPLC column: Luna C18 100x30 5u;mobile phase: [water(0.1%TFA)-ACN];B%: 10%-40%,10min to give tert-butyl N-[3-[benzyl(propyl)amino]propyl]-N-methyl -carbamate (0.4 g, 1.25 mmol, 42.75% yield) as colorless oil. ^1H NMR (MeOD, 400 MHz) δ 7.18-7.37 (m, 5H), 3.57 (s, 2H), 3.20 (t, J = 7.2 Hz, 2H), 2.78 (s, 3H), 2.35-2.52 (m, 4H), 1.70 (quin, J = 7.2 Hz, 2H), 1.47-1.57 (m, 2H), 1.42 (s, 9H), 0.88 (t, J = 7.2 Hz, 3H)

Synthesis of tert-butyl methyl(3-(propylamino)propyl)carbamate

To a solution of tert-butyl N-[3-[benzyl(propyl)amino]propyl]-N-methyl-carbamate (0.4 g, 1.25 mmol, 1 *eq*) in MeOH (20 mL) was added $Pd(OH)_2/C$ (0.2 g, 5% purity) under N_2. The

suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (50 psi) at 50°C for 12 hours. LCMS showed the reactant was consumed, desired mass was detected. The mixture was filtered and concentrated in vacuum. Afforded tert-butyl N-methyl-N-[3-(propylamino)propyl]carbamate (0.25 g, 1.09 mmol, 86.95% yield) as colorless oil. ^{1}H NMR (MeOD, 400 MHz) δ 3.26-3.31 (m, 2H), 2.85 (s, 3H), 2.56 (q, *J* = 8.0 Hz, 4H), 1.74 (quin, *J* = 7.2 Hz, 2H), 1.48-1.59 (m, 2H), 1.46 (s, 9H), 0.94 (t, *J* = 7.2 Hz, 3H)

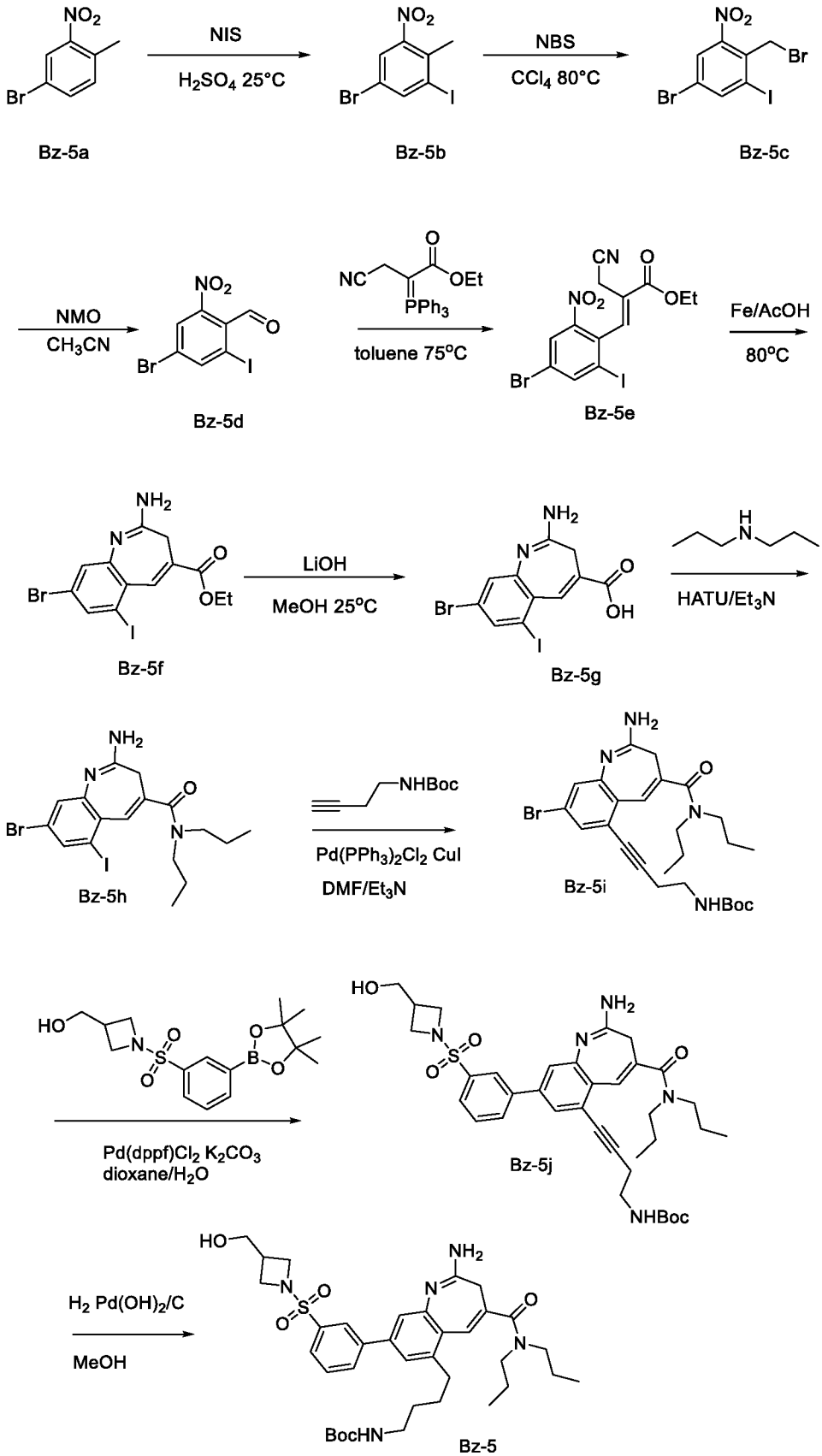
Synthesis of tert-butyl (3-(2-amino-8-bromo-N-propyl-3H-benzo[b] azepine-4-carboxamido)propyl)(methyl)carbamate, Bz-3b

To a mixture of 2-amino-8-bromo-3H-1-benzazepine-4-carboxylic acid, Bz-3a (80 mg, 284.59 µmol, 1 *eq*) and tert-butyl N-methyl-N-[3-(propylamino)propyl]carbamate (78.67 mg, 341.51 µmol, 1.2 *eq*) in DMF (1 mL) was added HATU (162.32 mg, 426.89 µmol, 1.5 *eq*) Et_3N (57.60 mg, 569.18 µmol, 79.22 µL, 2 *eq*) at 25°C under N_2. The mixture was stirred at 25°C for 1 hr. LCMS showed major as desired. The mixture was poured into water (20 mL). The aqueous phase was extracted with ethyl acetate (20 mLx3). The combined organic phase was washed with brine (20 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-TLC (Petroleum ether/Ethyl acetate=0/1) to give Bz-3b (60 mg, 121.60 µmol, 42.73% yield) as yellow oil.

Synthesis of tert-butyl (3-(2-amino-8-(3-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-N-propyl-3H-benzo[b]azepine-4-carboxamido)propyl)(methyl)carbamate, Bz-3

To a mixture of [1-(3-bromophenyl)sulfonylazetidin-3-yl]methanol (155.12 mg, 506.65 µmol, 1 *eq*) Pin_2B_2 (154.39 mg, 607.98 µmol, 1.2 *eq*) potassium acetate, KOAc (124.31 mg, 1.27 mmol, 2.5 *eq*) in dioxane (30 mL) was added $Pd(dppf)Cl_2.CH_2Cl_2$ (41.38 mg, 50.67 µmol, 0.1 *eq*) at 25°C under N_2. The mixture was stirred at 90 °C for 2 hours. tert-butyl N-[3-[(2-amino-8-bromo-3H-1-benzazepine -4-carbonyl)-propyl-amino]propyl]-N-methyl -carbamate, Bz-3b (0.25 g, 506.65 µmol, 1 *eq*) K_2CO_3 (140.04 mg, 1.01 mmol, 2 *eq*) in H_2O (2 mL) were added to the mixture, stirred at 90°C for 2 hrs (hours) under nitrogen gas, N_2. LCMS showed the reaction was completed. The mixture was filtered and concentrated in vacuum. The residue was purified by prep-TLC (EtOAc/MeOH=7:1) to give Bz-3 (112 mg, 175.05 µmol, 34.55% yield) as a light yellow solid. ^{1}H NMR (MeOD, 400 MHz) δ 8.07 (s, 1H), 8.03 (d, *J* = 7.6 Hz, 1H), 7.85 (br d, *J* = 7.6 Hz, 1H), 7.73-7.79 (m, 1H), 7.41-7.54 (m, 3H), 6.95 (s, 1H), 3.86 (t, *J* = 8.2 Hz, 2H), 3.60 (dd, *J* = 8.0, 6.0 Hz, 2H), 3.39-3.52 (m, 6H), 3.17-3.29 (m, 2H), 2.82-2.90 (m, 4H), 2.53-2.67 (m, 1H), 1.89-1.92 (m, 2H), 1.66-1.72 (m, 2H), 1.42-1.46 (m, 9H), 0.80-1.05 (m, 3H). LC/MS [M+H] 640.32 (calculated); LC/MS [M+H] 640.30 (observed).

Example 3 Synthesis of Bz-5



Synthesis of 5-bromo-1-iodo-2-methyl-3-nitrobenzene, Bz-5b

To a mixture of 4-bromo-1-methyl-2-nitro-benzene, Bz-5a (20 g, 92.58 mmol, 20.00 mL, 1 *eq*) in H_2SO_4 (20 mL) was added NIS (37.49 g, 166.64 mmol, 1.8 *eq*)at 0°C under N_2. The

mixture was stirred at 0°C for 1 hour. TLC showed the reactant was consumed and two points formed. The mixture was poured into ice-water (200 mL) slowly. The aqueous phase was extracted with ethyl acetate (150 mLx2). The combined organic phase was washed with brine (150 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, Petroleum ether/Ethyl acetate=100/1, 20/1) to afford Bz-5b (14 g, 40.94 mmol, 44.23% yield) as white solid. ^{1}H NMR (CDCl3, 400 MHz) δ 8.20 (d, J = 2.0 Hz, 1H), 7.87 (d, J = 2.0 Hz, 1H), 2.55 (s, 3H).

Synthesis of 5-bromo-2-(bromomethyl)-1-iodo-3-nitrobenzene, Bz-5c

To a mixture of 5-bromo-1-iodo-2-methyl-3-nitro-benzene, Bz-5b (13 g, 38.02 mmol, 1 *eq*) in CCl_4 (100 mL) was added NBS (10.15 g, 57.03 mmol, 1.5 *eq*) BPO (920.94 mg, 3.80 mmol, 0.1 *eq*) at 25°C under N_2. The mixture was stirred at 90°C for 12 hours. TLC showed one new point formed, HPLC and LCMS showed about 50% as desired and about 50% the reactant remained. The mixture was concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, Petroleum ether/Ethyl acetate=50/1, 10/1) to afford Bz-5c (7 g, 16.63 mmol, 43.75% yield) as white solid. ^{1}H NMR (CDCl3-d_6, 400 MHz) δ 8.29 (d, J = 2.0 Hz, 1H), 8.02 (d, J = 2.0 Hz, 1H), 4.82 (s, 3H).

Synthesis of 4-bromo-2-iodo-6-nitrobenzaldehyde, Bz-5d

To a mixture of 5-bromo-2-(bromomethyl)-1-iodo-3-nitro-benzene, Bz-5c (7 g, 16.63 mmol, 1 *eq*) in CH_3CN (10 mL) was added NMO (3.90 g, 33.27 mmol, 3.51 mL, 2 *eq*) at 25°C under N_2. The mixture was stirred at 25°C for 2 hours. TLC showed the reaction was completed. The mixture was concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, Petroleum ether/Ethyl acetate=20/1, 4/1) to afford Bz-5d (5 g, 14.05 mmol, 84.46% yield) as white solid. ^{1}H NMR (CDCl3, 400 MHz) δ 10.00 (s, 1H), 8.37 (d, J = 1.6 Hz, 1H), 8.15 (d, J = 1.6 Hz, 1H)

Synthesis of (E)-ethyl 3-(4-bromo-2-iodo-6-nitrophenyl) -2-(cyanomethyl)acrylate, Bz-5e

To a mixture of 4-bromo-2-iodo-6-nitro-benzaldehyde, Bz-5d (3.5 g, 9.83 mmol, 1 *eq*) in toluene (30 mL) was added ethyl 3-cyano-2-(triphenyl-phosphanylidene)propanoate (5.71 g, 14.75 mmol, 1.5 *eq*) at 25°C under N_2. The mixture was stirred at 85°C for 12 hours. TLC showed major as desired. The mixture was concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, Petroleum ether/Ethyl acetate=10/1, 1/1) to afford Bz-5e (2 g, 4.30 mmol, 43.73% yield) as

yellow oil. ^{1}H NMR (CDCl3, 400 MHz) δ 8.62 (d, *J* = 1.8 Hz, 1H), 8.42 (d, *J* = 1.8 Hz, 1H), 7.74 (s, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 3.33 (s, 2H), 1.31 (t, *J* = 7.2 Hz, 3H)

Synthesis of ethyl 2-amino-8-bromo-6-iodo-3H-benzo[b] azepine-4-carboxylate, Bz-5f

To a mixture of ethyl (E)-3-(4-bromo-2-iodo-6-nitro-phenyl)-2- (cyanomethyl)prop-2-enoate, Bz-5e (2 g, 4.30 mmol, 1 *eq*) in acetic acid, AcOH (20 mL) was added Fe (1.20 g, 21.50 mmol, 5 *eq*) at 25°C under N_2. The mixture was stirred at 80°C for 5 hours. LCMS showed major as desired and the reactant was consumed. The reaction was filtered and the filtrate was concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, Petroleum ether/Ethyl acetate=1/1, 0/1) to afford Bz-5f (1.8 g, 4.14 mmol, 96.20% yield) as off-white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.71 (s, 1H), 7.69 (d, *J* = 2.0 Hz, 1H), 7.22 (br d, *J* = 2.0 Hz, 1H), 4.26 (q, *J* = 7.0 Hz, 3H), 2.83 (s, 2H), 1.30 (t, *J* = 7.2 Hz, 3H).

Synthesis of 2-amino-8-bromo-6-iodo-3H-benzo[b]azepine-4-carboxylic acid, Bz-5g

To a mixture of ethyl 2-amino-8-bromo-6-iodo-3H-1-benzazepine-4-carboxylate, Bz-5f (1.8 g, 4.14 mmol, 1 *eq*) in EtOH (40 mL) was added LiOH.H_2O (1.04 g, 24.82 mmol, 6 *eq*) in H_2O (10 mL) at 25°C under N_2. The mixture was stirred at 35°C for 2 hours. LCMS showed the reaction was completed. The mixture was concentrated to remove the EtOH, then adjusted PH to 5 by aq HCl (4M), filtered to get desired solid to afford Bz-5g (1.2 g, 2.95 mmol, 71.26% yield) as white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.77 (s, 1H), 7.69 (s, 1H), 7.29 (s, 1H), 2.92 (s, 2H)

Synthesis of 2-amino-8-bromo-6-iodo-*N*,*N*-dipropyl-3H -benzo[b]azepine-4-carboxamide, Bz-5h

To a mixture of N-propylpropan-1-amine (186.47 mg, 1.84 mmol, 254.04 µL, 1.5 *eq*) and 2-amino-8-bromo-6-iodo-3H-1-benzazepine-4-carboxylic acid, Bz-5g (0.5 g, 1.23 mmol, 1 *eq*) in DMF (10 mL) was added HATU (700.67 mg, 1.84 mmol, 1.5 *eq*) Et_3N (186.47 mg, 1.84 mmol, 256.49 µL, 1.5 *eq*) at 25°C. The mixture was stirred at 25°C for 30 min. LCMS showed the reaction was completed. The mixture was poured into water (50 mL), separated out from the mixture, and filtered to obtain Bz-5h (0.55 g, 1.12 mmol, 91.33% yield) as yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.74 (d, *J* = 2.0 Hz, 1H), 7.33 (d, *J* = 2.0 Hz, 1H), 6.81 (s, 1H), 3.43-3.47 (m, 4H), 1.66-1.72 (m, 4H), 0.93 (s, 6H)

Synthesis of tert-butyl (4-(2-amino-8-bromo-4-(dipropylcarbamoyl)-3H-benzo[b]azepin-6-yl)but-3-yn-1-yl)carbamate, Bz-5i

To a mixture of 2-amino-8-bromo-6-iodo-N,N-dipropyl-3H-1-benzazepine -4-carboxamide, Bz-5h (200 mg, 408.02 µmol, 1 *eq*) and tert-butyl N-but-3-ynylcarbamate (72.50 mg, 428.42 µmol, 1.05 *eq*) in DMF (5 mL) Et_3N (1 mL) was added $Pd(PPh_3)_2Cl_2$ (14.32 mg,

20.40 μmol, 0.05 *eq*) Et_3N (0.5 mL) CuI (15.54 mg, 81.60 μmol, 0.2 *eq*) at 25°C under N_2. The mixture was stirred at 80°C for 1 hours. LCMS showed major as desired. The mixture was poured into water (20 mL). The aqueous phase was extracted with ethyl acetate (20 mLx3). The combined organic phase was washed with brine (20 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-TLC(Petroleum ether/Ethyl acetate=0/1) to give Bz-5i (0.2 g, 376.31 μmol, 92.23% yield) as a yellow solid. ^1H NMR (CDCl3, 400 MHz) δ 7.40 (s, 1H), 7.35 (s, 1H), 7.13 (s, 1H), 3.46-3.52 (m, 4H), 3.35-3.40 (m, 2H), 2.65 (s, 2H), 1.58-1.78 (m, 4H), 1.46 (s, 9H), 0.93 (t, *J* = 7.2 Hz, 6H)

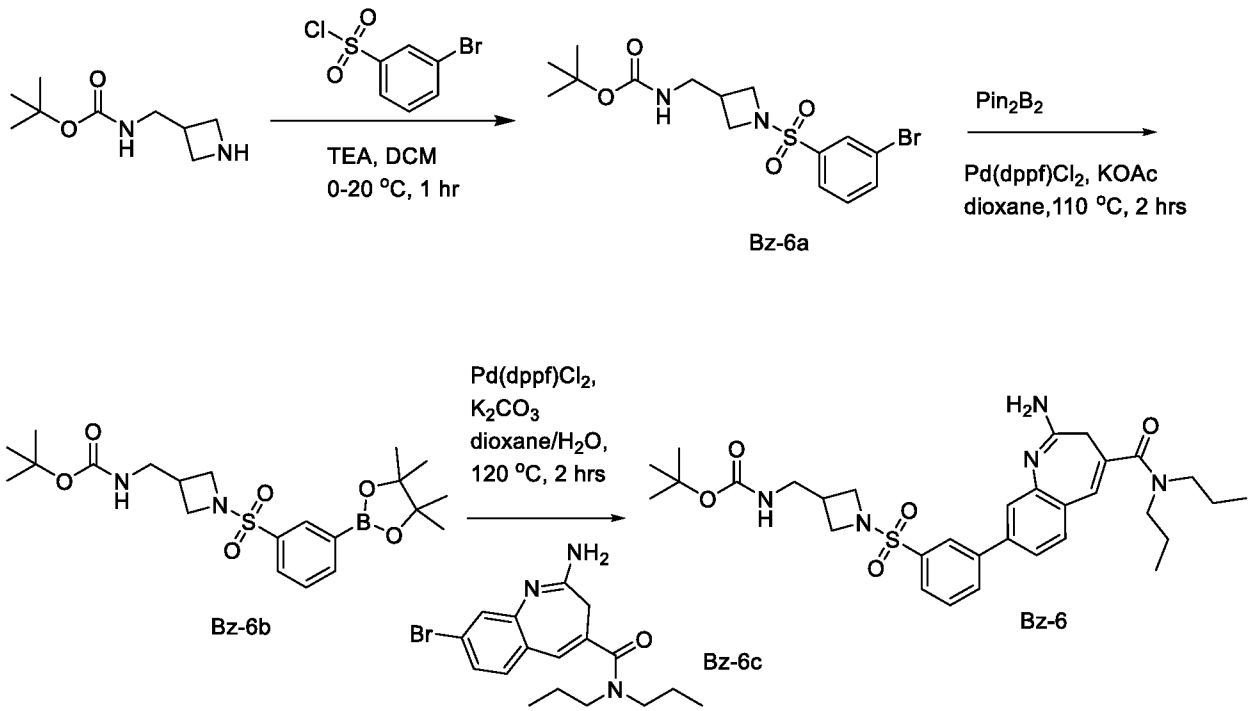
Synthesis of tert-butyl (4-(2-amino-4-(dipropylcarbamoyl)-8-(3- ((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-3H-benzo[b]azepin-6-yl)but-3-yn-1-yl)carbamate, Bz-5j

To a mixture of tert-butyl N-[4-[2-amino-8-bromo-4-(dipropylcarbamoyl)- 3H-1-benzazepin-6-yl]but-3-ynyl]carbamate, Bz-5i (0.18 g, 338.67 μmol, 1 *eq*) and [1-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]sulfonylazetidin-3-yl]methanol (179.45 mg, 508.01 μmol, 1.5 *eq*) in dioxane (10 mL) H_2O (1 mL) was added $Pd(dppf)Cl_2$ (12.39 mg, 16.93 μmol, 0.05 *eq*) K_2CO_3 (93.61 mg, 677.35 μmol, 2 *eq*) at 25°C under N_2. The mixture was stirred at 90°C for 2 hours. LCMS showed desired mass was detected. The mixture was concentrated in vacuum to give Bz-5j (0.2 g, crude) as a yellow solid.

Synthesis of tert-butyl (4-(2-amino-4-(dipropylcarbamoyl)-8-(3-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-3H-benzo[b]azepin-6-yl)butyl)carbamate, Bz-5

To a solution of tert-butyl N-[4-[2-amino-4-(dipropylcarbamoyl)-8-[3-[3-(hydroxymethyl)azetidin-1-yl]sulfonylphenyl]-3H-1-benzazepin-6-yl]but-3-ynyl]carbamate, Bz-5j (140 mg, 206.53 μmol, 1 *eq*) in MeOH (20 mL) was added $Pd(OH)_2/C$ (0.1 g, 5% purity) under N_2. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (50 psi) at 25 °C for 2 hours. LCMS showed the reaction was completed. The mixture was filtered and concentrated in vacuum. The residue was purified by prep-HPLC column: Xtimate C18 150x25mm, 5micron particle size;mobile phase: [water(0.04%NH_3H_2O+10mM NH_4HCO_3)-ACN];B%: 50%-60%, 10.5min. Afforded Bz-5 (45 mg, 65.99 μmol, 31.95% yield) as a white solid. ^1H NMR (MeOD, 400 MHz) δ 8.00-8.08 (m, 2H), 7.83 (d, *J* = 7.6 Hz, 1H), 7.71-7.79 (m, 1H), 7.33 (s, 1H), 7.28 (s, 1H), 6.99 (s, 1H), 3.86 (t, *J* = 8.0 Hz, 2H), 3.57-3.66 (m, 2H), 3.38-3.51 (m, 6H), 3.06 (t, *J* = 6.4 Hz, 2H), 2.84 (t, *J* = 7.6 Hz, 2H), 2.52-2.63 (m, 1H), 1.50-1.77 (m, 8H), 1.41 (s, 9H), 0.94 (s, 6H). LC/MS [M+H] 682.36 (calculated); LC/MS [M+H] 682.40 (observed).

Example 4 Synthesis of Bz-6



Synthesis of *tert*-butyl ((1-((3-bromophenyl)sulfonyl)azetidin-3-yl)methyl)carbamate, Bz-6a

To a mixture of tert-butyl N-(azetidin-3-ylmethyl)carbamate (1.6 g, 8.59 mmol, 1.2 *eq*) in DCM (5 mL) was added TEA (1.45 g, 14.32 mmol, 1.99 mL, 2 *eq*) and 3-bromobenzenesulfonyl chloride (1.83 g, 7.16 mmol, 1.03 mL, 1 *eq*) at 0°C. The mixture was stirred at 20°C for 1 hr. The mixture was diluted with water (50 mL) and extracted with DCM (25 ml x 3). The organic layer was washed with brine (25 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether gradient @ 35 mL/min). Compound tert-butyl N-[[1-(3-bromophenyl)sulfonylazetidin-3-yl]methyl]carbamate, Bz-6a (2.5 g, 6.17 mmol, 86.16% yield) was obtained as white solid. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.99 (t, J = 4.0 Hz, 1H), 7.74-7.81 (m, 2H), 7.47 (t, J = 8.0 Hz, 1H), 4.61 (s, 1H), 3.86 (t, J = 8.0 Hz, 2H), 3.50-3.58 (m, 2H), 3.19 (t, J = 4.0 2H), 2.58-2.70 (m, 1H), 1.42 (s, 9H).

Preparation of tert-butyl N-[[1-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan- 2-yl)phenyl]sulfonylazetidin-3-yl]methyl]carbamate, Bz-6b

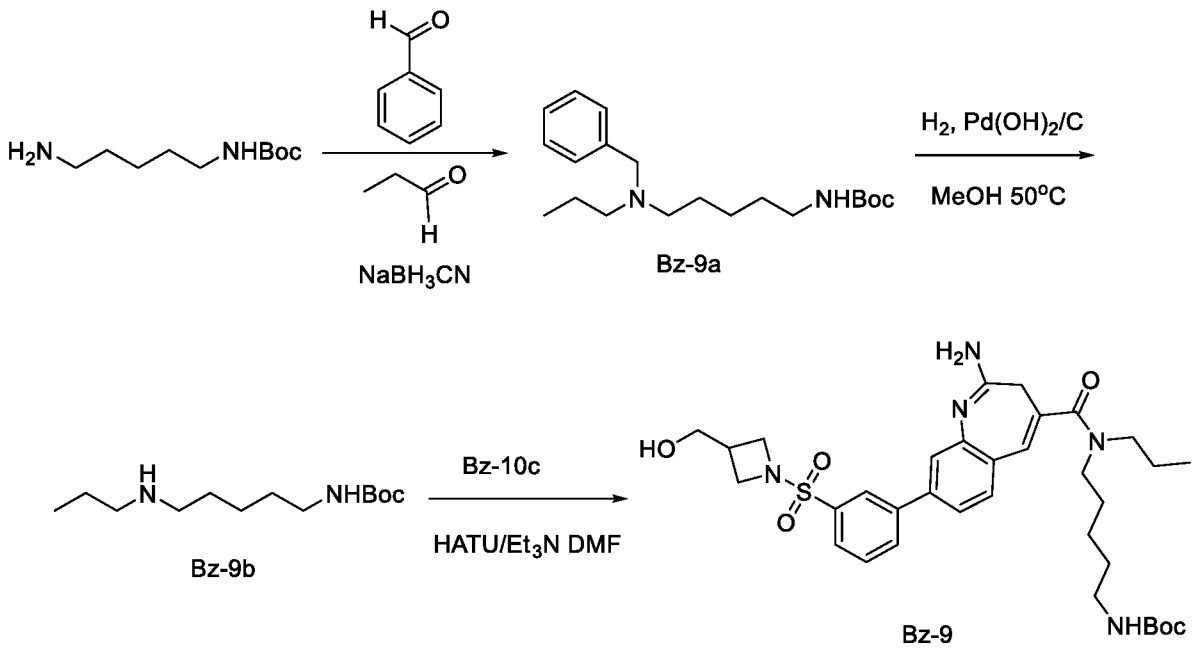
To a mixture of tert-butyl-N-[[1-(3-bromophenyl)sulfonylazetidin-3-yl]methyl] carbamate, Bz-6a (1 g, 2.47 mmol, 1 *eq*) in dioxane (10 mL) was added Pin_2B_2 (939.80 mg, 3.70 mmol, 1.5 *eq*) and KOAc (484.29 mg, 4.93 mmol, 2 *eq*), $Pd(dppf)Cl_2$ (90.27 mg, 123.36 μmol, 0.05 *eq*) at 15°C under N_2. The mixture was stirred at 110°C for 2 hrs. The product tert-butyl

N-[[1-[3-(4,4,5,5-tetramethy l-1,3,2-dioxaborolan-2-yl)phenyl] sulfonylazetidin-3-yl]methyl]carbamate, Bz-6b was not isolated and used into next step.

Synthesis of tert-butyl ((1-((3-(2-amino-4-(dipropylcarbamoyl)-3H-benzo[b]azepin-8-yl)phenyl)sulfonyl)azetidin-3-yl)methyl)carbamate, Bz-6

To a mixture of tert-butyl N-[[1-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl]sulfonylazetidin-3-yl]methyl]carbamate, Bz-6b (1.12 g, 2.48 mmol, 1 *eq*) and 2-amino-8-bromo-N,N-dipropyl-3H-1-benzazepine-4-carboxamide, Bz-6c (901.90 mg, 2.48 mmol, 1 *eq*) in dioxane (3 mL) was added K_2CO_3 (684.35 mg, 4.95 mmol, 2 *eq*) and $Pd(dppf)Cl_2$ (90.58 mg, 123.79 µmol, 0.05 *eq*) at 15°C under N_2. The mixture was stirred at 120 °C for 2 hrs. The mixture was filtered and concentrated. The residue was purified by flash silica gel chromatography (ISCO®; 2 g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether gradient @ 60 mL/min) to give Bz-6 (600 mg, 983.97 µmol, 39.74% yield, 100% purity) as yellow solid. ^{1}H NMR (MeOD-d_4, 400 MHz) δ 7.99-8.10 (m, 2H), 7.74-7.86 (m, 2H), 7.36-7.52 (m, 3H), 6.89 (s, 1H), 3.83 (t, *J* = 8.0 Hz, 2H), 3.54 (t, *J* = 8.0 Hz, 2H), 3.34-3.48 (m, 6H), 3.02 (d, *J* = 8.0 Hz, 2H), 2.48-2.64 (m, 1H), 1.59-1.76 (m, 4H), 1.37 (s, 9H), 0.96-0.89 (m, 6H). LC/MS [M+H] 610.31 (calculated); LC/MS [M+H] 610.40 (observed).

Example 5 Synthesis of Bz-9



Synthesis of tert-butyl (5-(benzyl(propyl)amino)pentyl)carbamate Bz-9a

To a mixture of tert-butyl N-(5-aminopentyl)carbamate (1 g, 4.94 mmol, 1.03 mL, 1 *eq*) and benzaldehyde (524.59 mg, 4.94 mmol, 499.61 µL, 1 *eq*) in DCE (10 mL) and stirred at 60 °C for 12 h. Then the mixture was cooled to 0 °C and MeOH (10 mL) was added to the mixture. $NaBH_3CN$ (931.94 mg, 14.83 mmol, 3 *eq*) was added to the mixture and stirred for 1 h at 0°C.

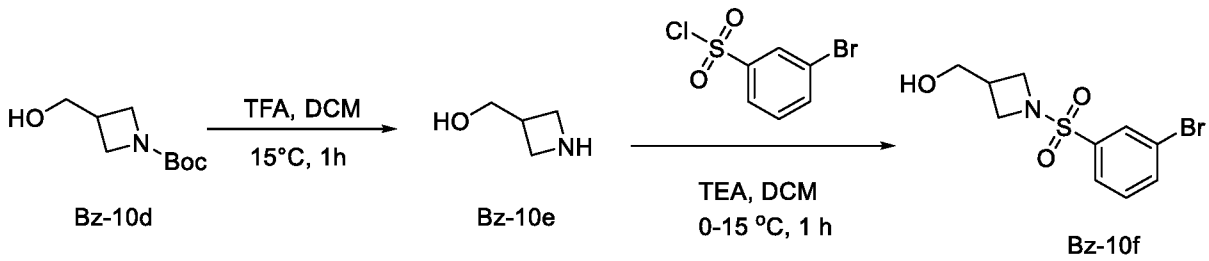
Propanal (574.20 mg, 9.89 mmol, 719.55 μL, 2 *eq*) was added to the mixture and stirred for 1 h. LCMS showed the reaction was finished. The mixture was concentrated. The residue was further purification by prep-HPLC(column: Luna C18 100x30, 5micron particle size;mobile phase: [water(0.1%TFA)-ACN];B%: 25%-40%,10min) to give tert-butyl-N-[5-[benzyl(propyl)amino] pentyl]carbamate Bz-9a (0.5 g, 1.49 mmol, 30.24% yield) as a yellow oil. ^{1}H NMR (400MHz, METHANOL-d_4) δ = 7.33-7.28 (m, 3H), 7.27-7.19 (m, 1H), 3.58 (s, 2H), 3.00 (t, *J* =7.2 Hz, 2H), 2.47-2.37 (m, 4H), 1.58-1.46 (m, 6H), 1.47 (s, 9H) 1.37-1.20 (m, 3H), 0.87 (t, *J* =7.6 Hz, 3H)

Synthesis of tert-butyl (5-(propylamino)pentyl)carbamate Bz-9b

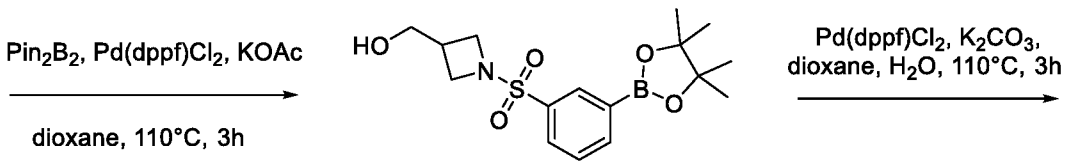
To a solution of tert-butyl N-[5-[benzyl(propyl)amino]pentyl]carbamate Bz-9a (0.5 g, 1.49 mmol, 1 *eq*) in MeOH (20 mL) was added Pd(OH)2/C (0.2 g, 5% purity) at 25 °C under N_2. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (50psi) at 50°C for 12 hours. LCMS showed the reaction was finished. The mixture was filtered and concentrated. To give the product tert-butyl N-[5-(propylamino)pentyl]carbamate Bz-9b (0.3 g, crude) as colorless oil. ^{1}H NMR (400MHz, METHANOL-d_4) δ = 3.03 (t, *J* = 6.8 Hz, 2H), 2.55 (d, *J* = 7.6, 13.6 Hz, 4H), 1.59-1.44 (m, 6H), 1.47 (s. 9H)1.43-1.20 (m, 2H), 0.97-0.88 (m, 3H).

To a mixture of tert-butyl N-[5-(propylamino)pentyl]carbamate Bz-9b (57.17 mg, 233.93 μmol, 1 *eq*) and 2-amino-8-[3-[3-(hydroxymethyl)azetidin-1-yl]sulfonylphenyl]-3H-1-benzazepine-4- carboxylic acid Bz-10c (0.1 g, 233.93 μmol, 1 *eq*) in DMF (4 mL) was added HATU (133.42 mg, 350.90 μmol, 1.5 *eq*) and Et_3N (71.02 mg, 701.80 μmol, 97.68 μL, 3 *eq*) in one portion at 25 °C. The mixture was stirred at 25 °C for 0.5 h. LCMS showed the reaction was finished. The mixture was diluted with water and extracted with EA (30 mlx3). The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was further purification by pre-HPLC(column: Xtimate C18 150x25mm,5micron particle size;mobile phase: [water(0.1%TFA)-ACN];B%: 32%-62%, 10.5min) to give tert-butyl N-[5-[[2-amino-8-[3-[3-(hydroxymethyl) azetidin-1-yl] sulfonylphenyl]-3H-1-benzazepine-4-carbonyl]-propyl-amino]pentyl]carbamate Bz-9 (0.128 g, 179.48 μmol, 76.72% yield, 91.68% purity) as yellow solid. ^{1}H NMR (400MHz, METHANOL-d_4) δ = 8.10 (s, 1H), 8.07 (d, *J* = 7.6 Hz, 1H), 7.89 (d, *J* = 7.8 Hz, 1H), 7.83-7.78 (m, 1H), 7.77-7.65 (m, 3H), 7.09 (s, 1H), 3.86 (t, *J* = 8.2 Hz, 2H), 3.61 (*J* = 5.6, 8.0 Hz, 2H), 3.56-3.35 (m, 8H), 3.31 (s, 2H), 3.10-2.99 (m, 2H), 2.64-2.53 (m, 1H), 1.80-1.59 (m, 4H), 1.57-1.47 (m, 2H), 1.40 (s, 9H), 1.03-0.86 (m, 3H). LC/MS [M+H] 654.33 (calculated); LC/MS [M+H] 654.50 (observed).

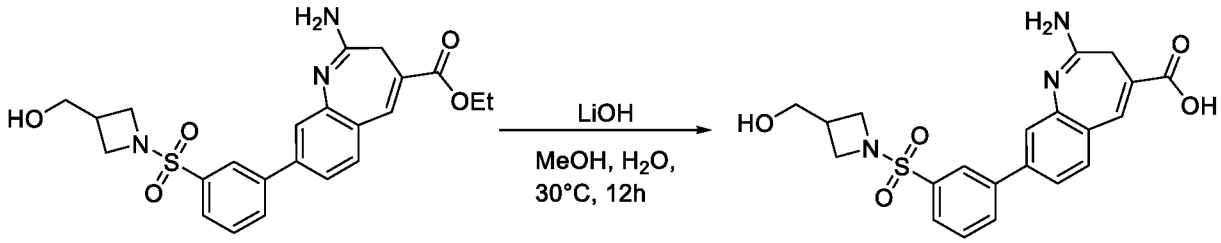
Example 6 Synthesis of Bz-10



Bz-10d Bz-10e Bz-10f



Bz-10g



Bz-10h Bz-10c

Preparation of Bz-10c: To a mixture of tert-butyl 3-(hydroxymethyl)azetidine-1-carboxylate Bz-10d (15 g, 80.11 mmol) in DCM (100 mL) was added TFA (63.94 g, 560.79 mmol, 41.52 mL, 7 *eq*) at 15°C. The mixture was stirred at 15°C for 1 h. The mixture was concentrated to give azetidin-3-ylmethanol Bz-10e (36 g, crude, TFA) as yellow oil. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 4.50-4.56 (m, 2H), 3.94-4.10 (m, 2H), 3.80-3.93 (m, 2H), 3.15-3.30 (m, 1H).

Preparation of [1-(3-bromophenyl)sulfonylazetidin-3-yl]methanol, Bz-10f: To a mixture of azetidin-3-ylmethanol (33.06 g, 164.37 mmol, 2 *eq*, TFA) and 3-bromobenzenesulfonyl chloride (21 g, 82.19 mmol, 11.86 mL, 1 *eq*) in DCM (200 mL) was added TEA (33.27 g, 328.75 mmol, 45.76 mL, 4 *eq*) at 0°C. The mixture was stirred at 15°C for 1 h. The residue was poured into saturated sodium bicarbonate in aqueous solution (200 mL) and stirred 10 min. The aqueous phase was extracted with DCM (100 mL x 3). The combined organic phase was washed with brine (100 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 1 g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether gradient at 50 mL/min). Compound [1-(3-bromophenyl)sulfonylazetidin-3-yl] methanol Bz-10f (21 g, 68.59 mmol, 83.45% yield) was obtained as white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.89-8.11 (m, 1H),

7.78 (dd, J = 8.0, 2.0 Hz, 2H), 7.39-7.54 (m, 1H), 3.78-3.97 (m, 2H), 3.49-3.74 (m, 4H), 2.41-2.77 (m, 1H).

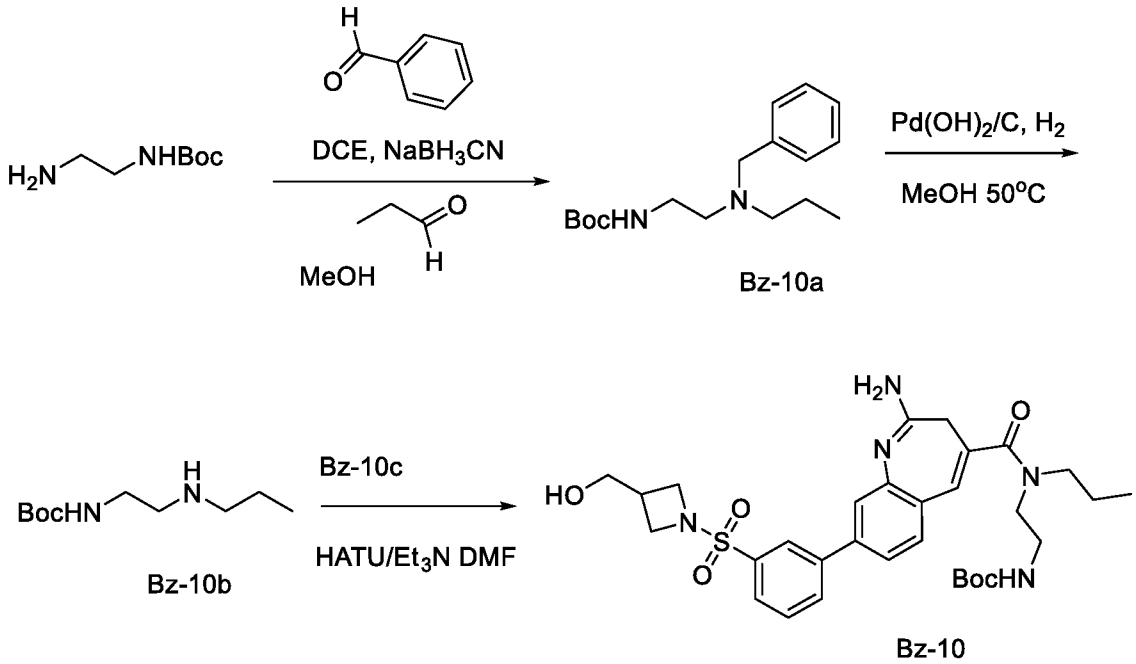
Preparation of [1-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl] sulfonylazetidin-3-yl]methanol, Bz-10g: To a mixture of [1-(3-bromophenyl)sulfonylazetidin-3-yl]methanol (8 g, 26.13 mmol, 1 *eq*) in dioxane (10 mL) was added Pin_2B_2 (9.95 g, 39.19 mmol, 1.5 *eq*), KOAc (5.13 g, 52.26 mmol, 2 *eq*) and $Pd(dppf)Cl_2$ (1.91 g, 2.61 mmol, 0.1 *eq*) at 15°C. The mixture was stirred at 110°C for 3 h. LC-MS showed reactant 1 was consumed completely and one main peak with desired mass was detected. The mixture was filtered, washed by using ethyl acetate. Then the filtrate was concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, Petroleum ether/Ethyl acetate=1/1, 0/1) to give 12g crude product. The crude product was triturated with heptane/methyl tertiary butyl ether=5/1(50mL), filtered, the filter cake was dried in vacuum. Compound [1-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl] sulfonylazetidin-3-yl]methanol (8.2 g, 23.21 mmol, 88.84% yield) was obtained as pink solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.28 (s, 1H), 8.06 (d, J = 8.0 Hz, 1H), 7.89-7.95 (m, 1H), 7.58 (t, J = 8.0 Hz, 1H), 3.87 (t, J = 8.0 Hz, 2H), 3.62-3.68 (m, 4H), 2.55-2.65 (m, 1H), 1.37 (s, 12H).

Preparation of ethyl 2-amino-8-[3-[3-(hydroxymethyl)azetidin-1-yl] sulfonylphenyl]-3H-1-benzazepine-4-carboxylate, Bz-10h: To a mixture of [1-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl] sulfonylazetidin-3-yl]methanol, Bz-10g (4.11 g, 11.64 mmol, 1.2 *eq*) and ethyl 2-amino- 8-bromo-3H-1-benzazepine-4-carboxylate (3 g, 9.70 mmol, 1 *eq*) in dioxane (40 mL) and H_2O (3 mL) was added K_2CO_3 (2.68 g, 19.41 mmol, 2 *eq*) and $Pd(dppf)Cl_2$ (355.02 mg, 485.19 μmol, 0.05 *eq*) at 15°C under N_2. The mixture was stirred at 110°C for 3 h. LC-MS showed reactant 1 was consumed completely and one main peak with desired mass was detected. The mixture was concentrated. The crude product was triturated with EtOAc/H2O=1:1 (200 mL) at 0°C for 10 min and filtered, the filter cake was dried in vacuum. Compound ethyl 2-amino-8-[3-[3- (hydroxymethyl)azetidin-1-yl]sulfonylphenyl]-3H-1-benzazepine-4-carboxylate, Bz-10h (4 g, crude) was obtained as a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.06-8.15 (m, 1H), 7.96 (s, 1H), 7.71-7.85 (m, 3H), 7.57 (d, J = 8.0 Hz, 1H), 7.29-7.38 (m, 2H), 6.94 (s, 2H), 4.17-4.30 (m, 2H), 3.77 (t, J = 8.0 Hz, 2H), 3.49 (t, J = 8.0 Hz, 2H), 3.2 (d, J = 8.0 Hz, 2H), 2.93 (s, 2H), 2.43-2.49 (m, 1H), 1.31 (t, J = 8.0 Hz, 3H).

2-Amino-8-[3-[3- (hydroxymethyl)azetidin-1-yl]sulfonylphenyl]-3H-1-benzazepine-4-carboxylic acid, Bz-10c

To a solution of ethyl 2-amino-8-[3-[3-(hydroxymethyl)azetidin-1-yl]sulfonylphenyl]-3H-1-benzazepine-4-carboxylate, Bz-10h (4 g, 8.78 mmol, 1 *eq*) in MeOH (50 mL) and H_2O (10 mL) was added $LiOH.H_2O$ (1.84 g, 43.91 mmol, 5 *eq*). The mixture was stirred at 30°C for 12

h. LC-MS showed reactant 1 was consumed completely and one main peak with desired mass was detected. The reaction mixture was concentrated under reduced pressure to remove MeOH. The mixture was filtered. The filtrate was adjusted pH to around 6 by progressively adding a solution of HCl (1 M) and then filtered to give crude product. The crude product was triturated with CH_3CN (100 mL) at 0°C for 10 min. The product was dried in vacuum. Compound 2-amino-8-[3-[3- (hydroxymethyl)azetidin-1-yl]sulfonylphenyl]-3H-1-benzazepine-4-carboxylic acid, Bz-10c (2.51 g, 5.72 mmol, 65.11% yield, 97.375% purity) was obtained as a gray solid. ^1H NMR (DMSO-d_6, 400 MHz) δ 8.11-8.16 (m, 1H), 8.02 (s, 1H), 7.92 (s, 1H), 7.78-7.88 (m, 4H), 7.75 (s, 1H), 3.76 (t, J = 8.0 Hz, 2H), 3.45-3.54 (m, 4H), 3.20 (d, J = 4.0 Hz, 2H), 2.45-2.49 (m, 1H). LC/MS [M+H] 428.13 (calculated); LC/MS [M+H] 428.20 (observed).



Synthesis of tert-butyl N-[2-[benzyl(propyl)amino]ethyl] carbamate Bz-10a

To a mixture of benzaldehyde (2 g, 18.85 mmol, 1.90 mL, 1 eq) and tert-butyl N-(2-aminoethyl)carbamate (3.32 g, 20.73 mmol, 3.26 mL, 1.1 eq) in DCE (30 mL) was added $NaBH_3CN$ (2.37 g, 37.69 mmol, 2 eq) at 0°C. The mixture was stirred at 0°C for 30 min, propanal (5.47 g, 94.23 mmol, 6.86 mL, 5 eq) was added to the mixture and stirred for 1 hour at 25°C. The mixture was poured into ice water (50 mL) and the aqueous phase was extracted with ethyl acetate (50 mL x 3). The combined organic phase was washed with brine (50 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, Petroleum ether/Ethyl acetate=5/1, 1/1) to afford tert-butyl N-[2-[benzyl(propyl)amino]ethyl] carbamate Bz-10a (3 g, 10.26 mmol, 54.44% yield) as a colorless oil.

Synthesis of tert-butyl N-[2-(propylamino)ethyl]carbamate Bz-10b

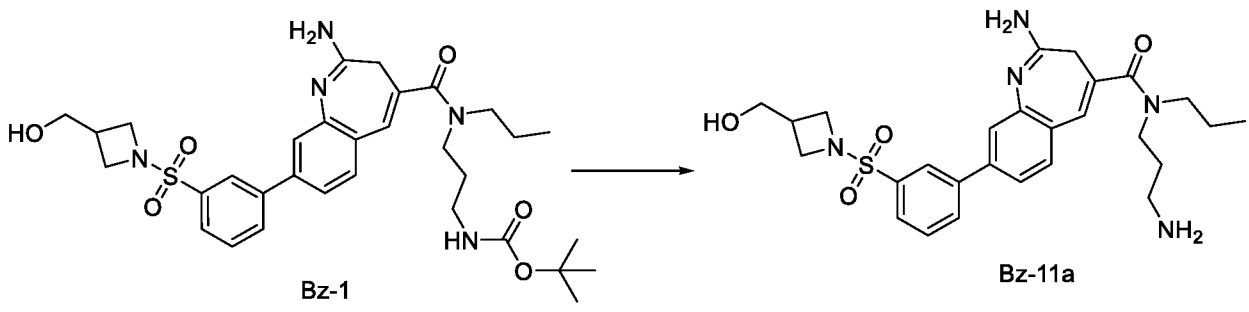
To a solution of tert-butyl N-[2-[benzyl(propyl)amino]ethyl]carbamate (2 g, 6.84 mmol, 1 eq) in MeOH (50 mL) was added $Pd(OH)_2/C$ (10%, 1 g) under N_2. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (50 psi) at 50°C for 12 hours. TLC (Petroleum ether/Ethyl acetate=3:1) showed the starting material was consumed completely. The reaction mixture was filtered and the filtrate was concentrated to give the crude product tert-butyl N-[2-(propylamino)ethyl]carbamate (1.3 g, 6.43 mmol, 93.96% yield) as colorless oil which was used into the next step without further purification. ^{1}H NMR (MeOD, 400MHz) δ 3.18 (t, *J* = 6.0 Hz, 2H), 2.68 (t, *J* = 6.0 Hz, 2H), 2.56 (t, *J* = 8.0 Hz, 2H), 1.58-1.48 (m, 2H), 1.44 (s, 9H), 0.94 (t, *J* = 8.0 Hz, 3H).

Synthesis of tert-butyl (2-(2-amino-8-(3-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-N-propyl-3H-benzo[b]azepine-4-carboxamido)ethyl)carbamate, Bz-10

To a mixture of 2-amino-8-[3-[3-(hydroxymethyl)azetidin-1-yl]sulfonylphenyl]-3H-1-benzazepine-4-carboxylic acid, Bz-10c (0.15 g, 350.90 µmol, 1 *eq*) and tert-butyl-N-[2-(propylamino)ethyl]carbamate (141.97 mg, 701.80 µmol, 2 *eq*) in DMF (4 mL) was added HATU (160.11 mg, 421.08 µmol, 1.2 *eq*), Et_3N (106.52 mg, 1.05 mmol, 146.52 µL, 3 *eq*) in one portion at 25°C. The mixture was stirred at 25°C for 12 h. LCMS showed the reaction was finished. The mixture was filtered and purified by prep-HPLC (column: Waters Xbridge 150x25 5u; mobile phase: [water (10mM NH_4HCO_3) - ACN]; B%: 25%-45%, 20min) to give tert-butyl N-[2-[[2-amino-8-[3-[3-(hydroxymethyl)azetidin-1-yl]sulfonylphenyl]-3H-1-benzazepine-4-carbonyl]-propyl-amino]ethyl]carbamate (0.036 g, 55.05 µmol, 15.69% yield, 93.54% purity) as yellow solid. ^{1}H NMR (MeOD, 400MHz) δ 8.07 (s, 1H), 8.03 (d, *J* = 7.6 Hz, 1H), 7.86-7.81 (d, *J* = 8.0 Hz, 1H), 7.78-7.73 (m, 1H), 7.47 (s, 2H), 7.41-7.36 (m, 1H), 6.95 (s, 1H), 3.86 (t, *J* = 8.4 Hz, 2H), 3.62-3.53 (m, 4H), 3.49-3.44 (m, 2H), 3.41 (d, *J* = 6.4 Hz, 2H), 3.32-3.29 (m, 3H), 2.63-2.51 (m, 1H), 1.68 (d, *J* = 7.2 Hz, 2H), 1.43 (s, 9H), 0.98-0.83 (m, 3H). LC/MS [M+H] 612.29 (calculated); LC/MS [M+H] 612.40 (observed).

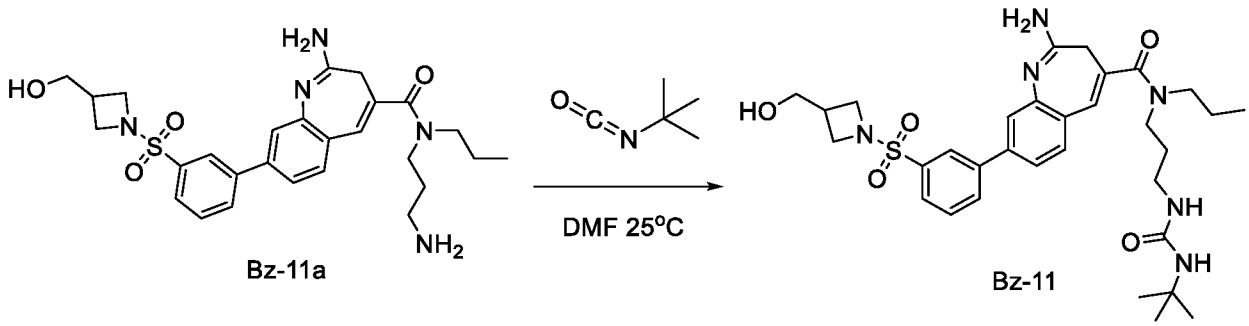
Example 7 Synthesis of Bz-11

Synthesis of 2-amino-N-(3-aminopropyl)-8-[3-[3-(hydroxymethyl)azetidin-1-yl] sulfonylphenyl]-N-propyl-3H-1-benzazepine-4-carboxamide, Bz-11a.



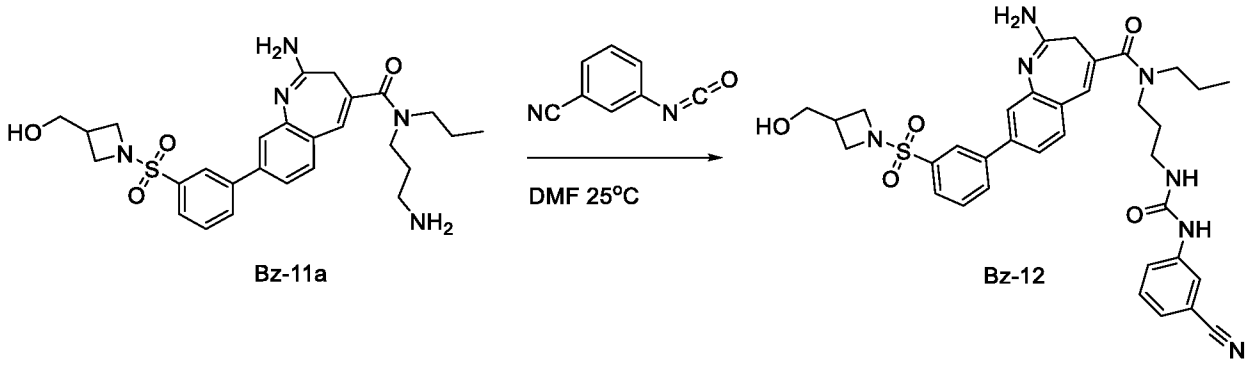
To a mixture of tert-butyl N-[3-[[2-amino-8-[3-[3-(hydroxymethyl)azetidin-1-yl] sulfonylphenyl]-3H-1-benzazepine-4-carbonyl]-propyl-amino]propyl]carbamate, Bz-1 (0.5 g, 799.01 μmol, 1 eq) in DCM (20 mL) was added TFA (1.82 g, 15.98 mmol, 1.18 mL, 20 eq) in one portion at 15°C. The mixture was stirred at 15°C for 3 hours. LCMS showed the reactant was consumed. The mixture was concentrated in vacuum, the residue was poured into ice water (30 mL) and adjusted pH=11 with Na_2CO_3.aq. The aqueous phase was extracted with DCM/i-PrOH=3/1 (20 mL x 3). The combined organic phase was washed with brine (10 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The crude product 2-amino-N-(3-aminopropyl)-8-[3-[3-(hydroxymethyl)azetidin-1-yl] sulfonylphenyl]-N-propyl-3H-1-benzazepine-4-carboxamide, Bz-11a (0.4 g, crude) as yellow oil which was used into the next step without further purification.

Synthesis of 2-amino-N-[3-(tert-butylcarbamoylamino)propyl]-8-[3-[3-(hydroxymethyl)azetidin-1-yl]sulfonylphenyl]-N-propyl-3H-1-benzazepine-4-carboxamide, Bz-11



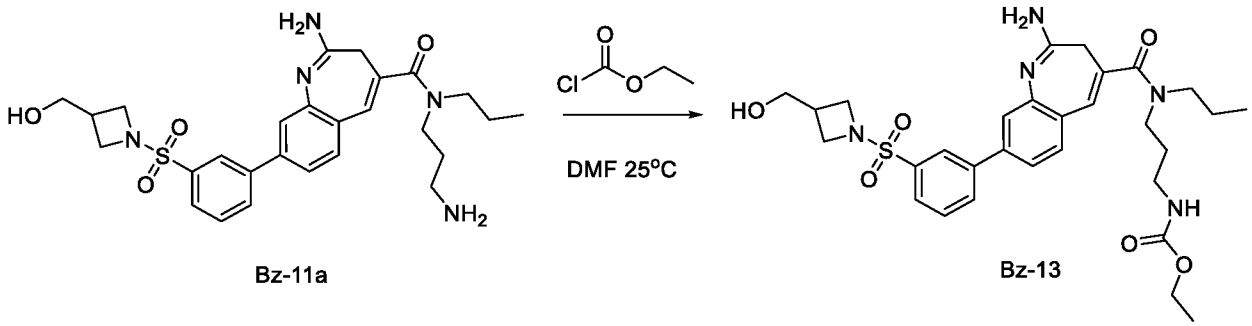
To a solution of 2-amino-N-(3-aminopropyl)-8-[3-[3-(hydroxymethyl)azetidin-1-yl] sulfonylphenyl]-N-propyl-3H-1-benzazepine-4-carboxamide, Bz-11a (0.1 g, 190.24 μmol, 1 eq) in DMF (2 mL) was added 2-isocyanato-2-methyl-propane (18.86 mg, 190.24 μmol, 22.45 μL, 1 eq) in one portion at 15°C. The mixture was stirred at 15°C for 12 hours. LCMS showed the reaction was completed. The mixture was filtered and purified by prep-HPLC (column: Nano-micro Kromasil® (Nouryon) C18 100x30mm, 5 micron particle size; mobile phase: [water (0.1%TFA)-ACN]; B%: 25%-45%, 10min) to give crude product, then purified by prep-HPLC (column: Welch Xtimate C18 150x25mm, 5micron particle size; mobile phase: [water (10mM NH_4HCO_3)-ACN]; B%: 25%-65%,10.5min) to give Bz-11 (0.007 g, 11.20 μmol, 5.89% yield) as light yellow solid. ^{1}H NMR (MeOD, 400 MHz) δ 8.09 (s, 1H), 8.05 (d, J = 8.0 Hz, 1H), 7.87-7.85 (m, 1H), 7.80-7.76 (m, 1H), 7.51-7.49 (m, 2H), 7.43-7.41 (m, 1H), 6.94 (s, 1H), 3.88 (t, J = 8.0 Hz, 2H), 3.63-3.60 (m, 2H), 3.54-3.50 (m, 2H), 3.44-3.43 (m, 4H), 3.15-2.91 (m, 4H), 2.67-2.58 (m, 1H), 1.84-1.79 (m, 2H), 1.73-1.66 (m, 2H), 1.40-1.14 (m, 9H), 1.00-0.90 (m, 3H).

Example 8 Synthesis of Bz-12



To a solution of 2-amino-N-(3-aminopropyl)-8-[3-[3-(hydroxymethyl)azetidin-1-yl] sulfonylphenyl]-N-propyl-3H-1-benzazepine-4-carboxamide, Bz-11a (0.1 g, 190.24 μmol, 1 eq) in DMF (0.3 mL) was added 3-isocyanatobenzonitrile (27.42 mg, 190.24 μmol, 1 eq) in one portion at 15°C. The mixture was stirred at 15°C for 12 hours. LCMS showed the reaction was completed. The mixture was filtered and purified by prep-HPLC (column: Nano-micro Kromasil C18 100x30mm 5um;mobile phase: [water(0.1%TFA)-ACN];B%: 25%-45%,10min) to give 2-amino-N-[3-[(3-cyanophenyl)carbamoylamino]propyl]-8-[3-[3-(hydroxymethyl)azetidin-1-yl]sulfonylphenyl]-N-propyl-3H-1-benzazepine-4-carboxamide, Bz-12 (10 mg, 14.93 μmol, 7.85% yield) as yellow solid. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.21-7.88 (m, 4H), 7.86-7.80 (m, 1H), 7.68 (s, 3H), 7.59-7.24 (m, 3H), 7.15 (s, 1H), 3.89 (t, J = 8.0 Hz, 2H), 3.64 (m, 4H), 3.51 (s, 2H), 3.46 (d, J = 6.0 Hz, 2H), 3.40 (s, 2H), 3.30-3.19 (m, 2H), 2.63-2.60 (m, 1H), 1.96-1.92 (m, 2H), 1.77-1.71 (m, 2H), 1.07-0.86 (m, 3H).

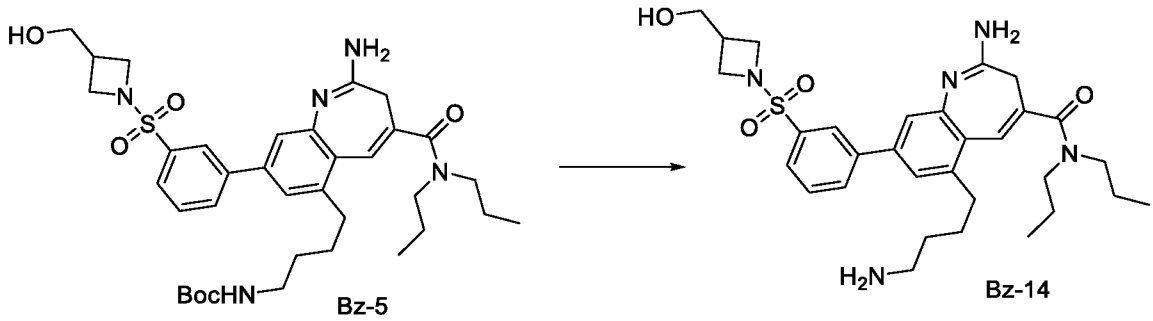
Example 9 Synthesis of Bz-13



To a mixture of 2-amino-N-(3-aminopropyl)-8-[3-[3-(hydroxymethyl)azetidin-1-yl] sulfonylphenyl]-N-propyl-3H-1-benzazepine-4-carboxamide, Bz-11a (0.1 g, 190.24 μmol, 1 eq) in DMF (2 mL) was added ethyl carbonochloridate (ethylchloroformate) (61.94 mg, 570.72 μmol, 54.33 μL, 3 eq) in one portion at 15 °C. The mixture was stirred at 15°C for 1 hour. LCMS and HPLC showed the desired was detected. The mixture was filtered and purified by prep-HPLC (column: Waters Xbridge BEH C18 100x25mm, 5um;mobile phase:

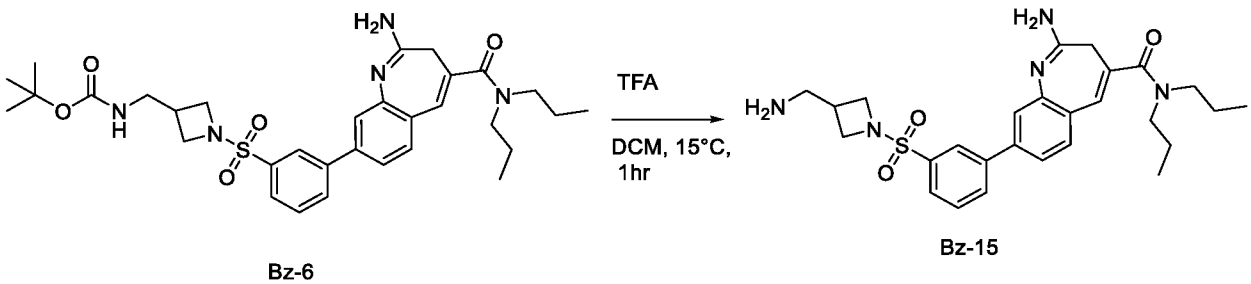
[water(0.1%TFA)-ACN];B%: 25%-45%,20min) to give ethyl N-[3-[[2-amino-8-[3-[3-(hydroxymethyl)azetidin-1-yl] sulfonylphenyl]-3H-1-benzazepine-4-carbonyl]-propyl-amino]propyl]carbamate, Bz-13 (0.018 g, 30.11 μmol, 15.83% yield) as light yellow solid. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.11 (s, 1H), 8.08 (d, J = 8.0 Hz, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.81-7.75 (m, 1H), 7.74-7.68 (m, 2H), 7.12 (s, 1H), 4.07 (brs, 2H), 3.87 (t, J = 8.0 Hz, 2H), 3.61 (m, 2H), 3.55 (m, 2H), 3.48 (m, 2H), 3.42 (d, J = 6.4 Hz, 2H), 3.37 (s, 2H), 3.14 (m, 2H), 2.67-2.51 (m, 1H), 1.93-1.80 (m, 2H), 1.77-1.64 (m, 2H), 1.33-1.06 (m, 3H), 0.95 (s, 3H).

Example 10 Synthesis of Bz-14



2-Amino-6-(4-aminobutyl)-8-(3-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-*N*,*N*-dipropyl-3*H*-benzo[*b*]azepine-4-carboxamide, Bz-14 was synthesized from Bz-5 according to the procedure described for Bz-11a. LC/MS [M+H] 582.31(calculated); LC/MS [M+H] 582.57 (observed).

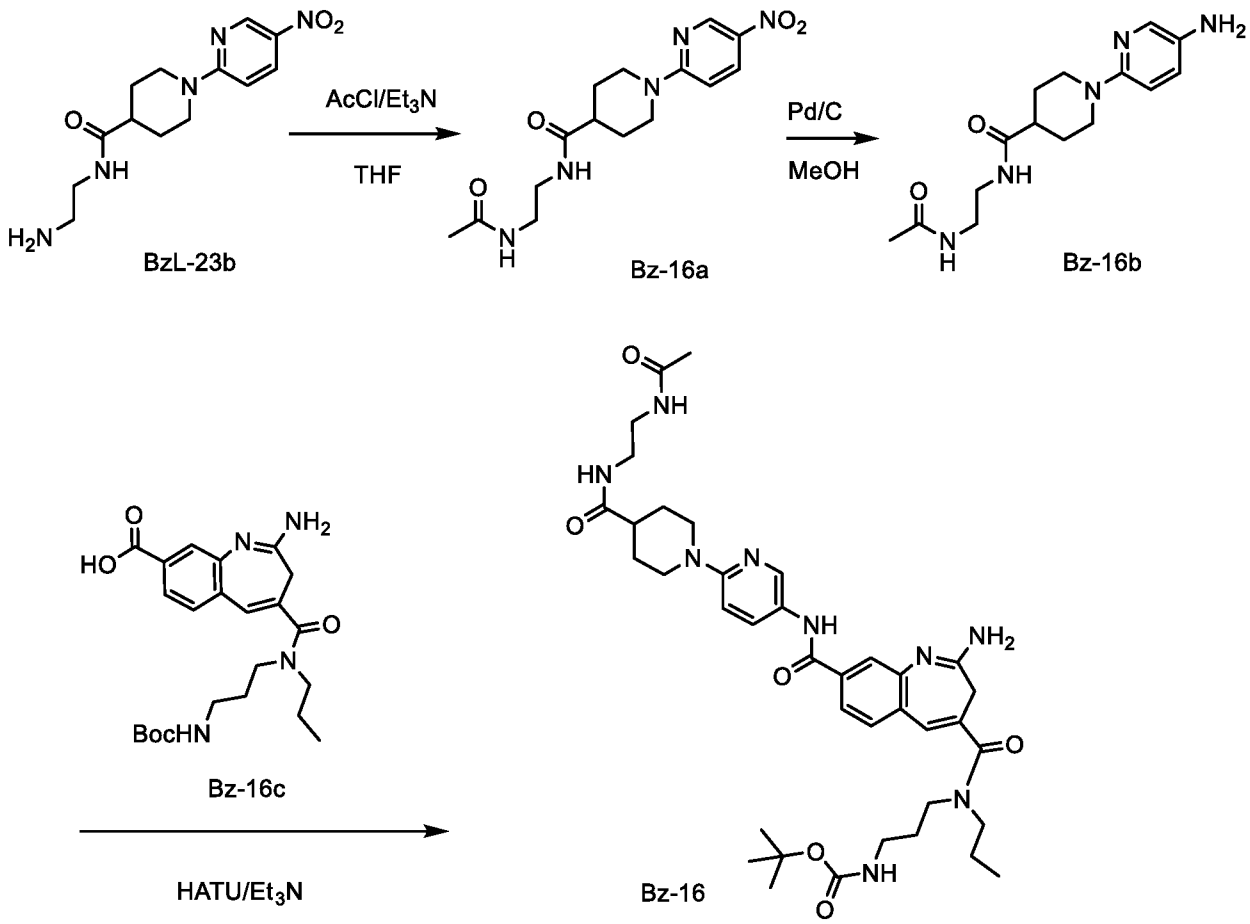
Example 11 Synthesis of Bz-15



To a solution of tert-butyl N- [[1-[3- [2-amino-4- (dipropylcarbamoyl) -3H- 1-benzazepin- 8-yl]phenyl]sulfonylazetidin-3-yl]methyl]carbamate, Bz-6 (0.15 g, 245.99 μmol, 1 eq) in DCM (20 mL) was added TFA (56.10 mg, 491.98 μmol, 36.43 μL, 2 eq) at 25°C and stirred for 1 hour. The mixture was concentrated in reduced pressure at 40°C. The residue was purified by prep-HPLC (column: Nano-micro Kromasil C18 100 x 30mm 5um; mobile phase: [water (0.1%TFA)-ACN]; B%: 25%-50%, 10min) to give 2-amino-8-[3-[3-(aminomethyl)azetidin-1-yl]sulfonylphenyl]-N,N-dipropyl-3H-1-benzazepine-4-carboxamide,

Bz-15 (0.0546 g, 105.69 μmol, 42.97% yield, 98.66% purity) as a yellow solid. ^{1}H NMR (MeOD-d_4, 400 MHz) δ 8.16-8.07 (m, 2H), 7.92 (d, J = 8.0 Hz, 1H), 7.83 (t, J = 7.6 Hz, 1H), 7.79-7.72 (m, 2H), 7.68 (d, J = 8.4 Hz, 1H), 7.09 (s, 1H), 3.96 (t, J = 8.4 Hz, 2H), 3.67-3.63 (m, 2H), 3.50-3.42 (m, 4H), 3.37 (s, 2H), 3.05 (d, J = 7.4 Hz, 2H), 2.78-2.65 (m, 1H), 1.75-1.66 (m, 4H), 1.08-0.82 (m, 6H). LC/MS [M+H] 510.25 (calculated); LC/MS [M+H] 510.10 (observed).

Example 12 Synthesis of Bz-16



Synthesis of N-(2-acetamidoethyl)-1-(5-nitropyridin-2-yl) piperidine-4-carboxamide, Bz-16a.

To a mixture of acetyl chloride (142.82 mg, 1.82 mmol, 129.83 μL, 3 *eq*) and N-(2-aminoethyl)-1-(5-nitro-2-pyridyl)piperidine-4-carboxamide, BzL-23b (0.2 g, 606.46 μmol, 1 *eq*, HCl) in THF (10 mL) was added Et_3N (245.47 mg, 2.43 mmol, 337.65 μL, 4 *eq*) at 25°C under N_2. The mixture was stirred at 25°C for 1 hour. LCMS showed the reaction was completed. The mixture was pour into water (20 mL). The mixture was filtered to give Bz-16a (0.2 g, 596.38 μmol, 98.34% yield) as a yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.95 (d, J = 2.4 Hz, 1H), 8.19 (dd, J = 9.6, 2.4 Hz, 1H), 7.78-7.98 (m, 2H), 6.95 (d, J = 9.6 Hz, 1H), 4.50 (d, J = 9.6 Hz, 2H), 2.93-3.15 (m, 7H), 1.73-1.80 (m, 5H), 1.43-1.62 (m, 2H), 1.07-1.28 (m, 3H).

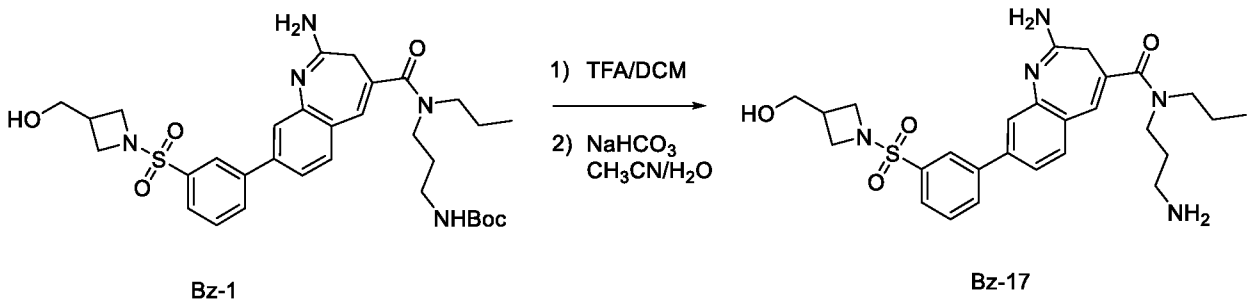
Synthesis of N-(2-acetamidoethyl)-1-(5-aminopyridin-2-yl) piperidine-4-carboxamide, Bz-16b.

To a solution of N-(2-acetamidoethyl)-1-(5-nitro-2-pyridyl)piperidine-4-carboxamide, Bz-16a (0.2, 596.38 μmol, 1 *eq*) in MeOH (20 mL) was added Pd/C (0.2 g, 5% purity) under N_2. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (15psi) at 25°C for 4 hours. LCMS showed the reaction was completed. The mixture was filtered and concentrated to give Bz-16b (0.18 g, 589.44 μmol, 98.84% yield) as yellow solid.

Synthesis of tert-butyl (3-(8-((6-(4-((2-acetamidoethyl)carbamoyl)piperidin-1-yl)pyridin-3-yl)carbamoyl)-2-amino-N-propyl-3H-benzo[b]azepine-4-carboxamido)propyl)carbamate, Bz-16.

To a mixture of 2-amino-4-[3-(tert-butoxycarbonylamino) propyl-propyl-carbamoyl]-3H-1-benzazepine-8-carboxylic acid, Bz-16c (0.22 g, 494.91 μmol, 1 *eq*) HATU (225.82 mg, 593.90 μmol, 1.2 *eq*) in DMF (5 mL) was added Et_3N (150.24 mg, 1.48 mmol, 206.66 μL, 3 *eq*) at 25°C. The mixture was stirred at 25 °C for 5 min, then N-(2-acetamidoethyl)-1-(5-amino-2-pyridyl)piperidine-4-carboxamide, Bz-16b (151.13 mg, 494.91 μmol, 1 *eq*) was added to the mixture, stirred for 30 min. The mixture was poured into water (50mL). The aqueous phase was extracted with ethyl acetate (50 mL). The combined organic phase was washed with brine (50 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC column: Welch Xtimate C18 150x25mm, 5um;mobile phase: [water(10mM NH4HCO3)-ACN];B%: 30%-50%,10.5min to afford Bz-16 (96 mg, 131.17 μmol, 26.50% yield) as an off-white solid. ^{1}H NMR (MeOD, 400 MHz) δ 8.39 (d, J = 2.6 Hz, 1H), 7.90 (dd, J = 9.2, 2.6 Hz, 1H), 7.69 (d, J = 1.2 Hz, 1H), 7.54-7.60 (m, 1H), 7.46 (br d, J = 8.0 Hz, 1H), 6.85-6.95 (m, 2H), 4.30 (d, J = 13.6 Hz, 2H), 3.39-3.53 (m, 4H), 3.28 (s, 2H), 3.08-3.12 (m, 2H), 2.83-2.93 (m, 2H), 2.37-2.47 (m, 1H), 1.94 (s, 3H), 1.60-1.90 (m, 8H), 1.24-1.50 (m, 9H). LC/MS [M+H] 732.42 (calculated); LC/MS [M+H] 732.40 (observed).

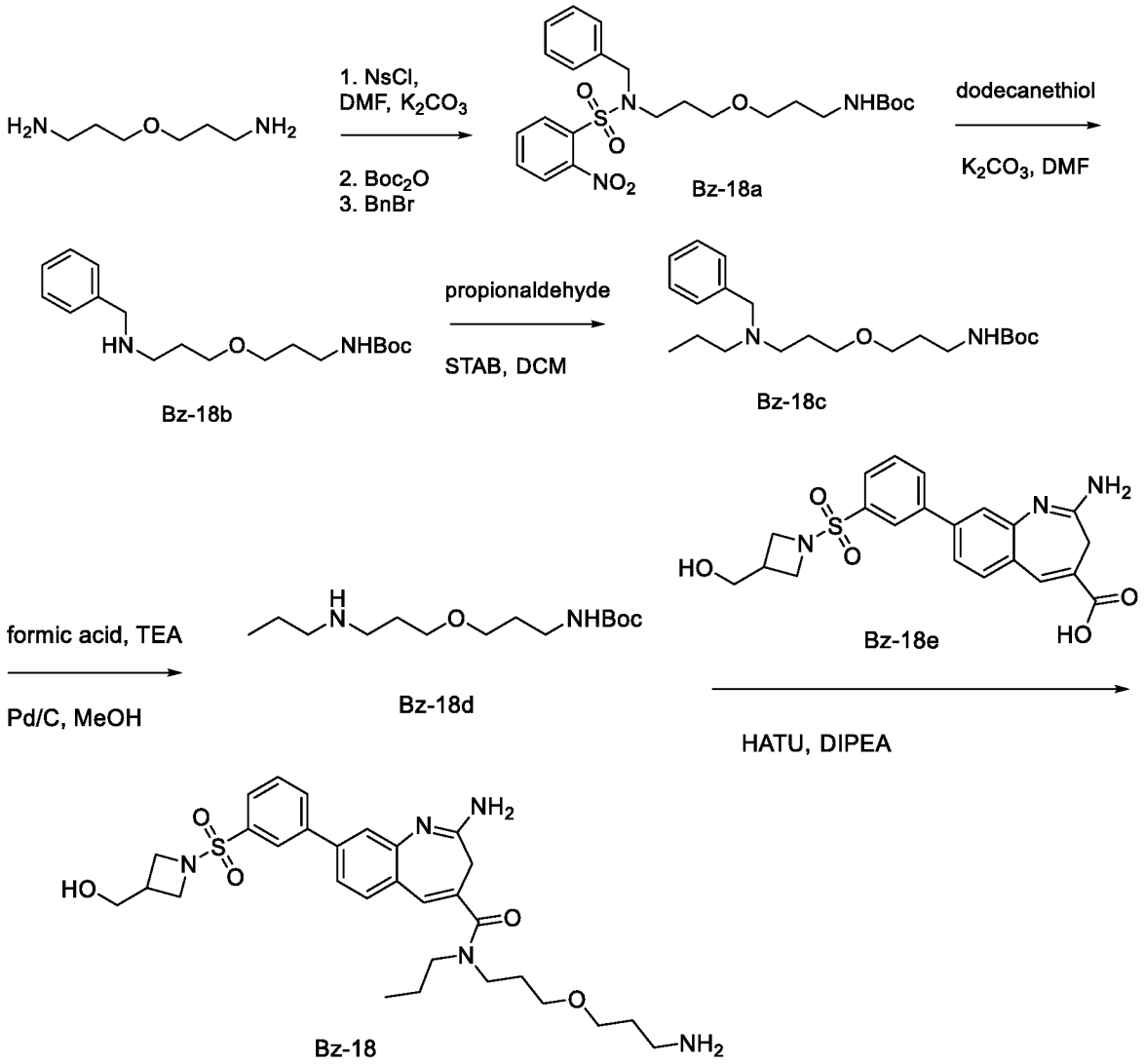
Example 13 Synthesis of Bz-17



Bz-1 Bz-17

To a solution of tert-butyl N-[3-[[2-amino-8-[3-[3-(hydroxymethyl)azetidin-1-yl] sulfonylphenyl]-3H-1-benzazepine-4-carbonyl]-propyl-amino]propyl]carbamate, Bz-1 (1.5 g, 2.40 mmol, 1 *eq*) in DCM (20 mL) was added TFA (6.16 g, 54.03 mmol, 4 mL, 22.54 *eq*) at 25 °C under N_2 and then stirred at this temperature for 1 h. The reaction mixture was concentrated under reduced pressure. The residue was diluted with CH_3CN (30 mL) and H_2O (10 mL) and adjusted pH = 8-9 with aq. $NaHCO_3$ at 0 °C. The mixture was stirred for 30 min at 25 °C and then concentrated under reduced pressure to remove CH_3CN. The aqueous phase was extracted with DCM/i-PrOH = 3/1 (20 mL x 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (TFA condition; column: luna® (Phenomenex) C18 250*80mm*10 μm (micron); mobile phase: [water(0.1%TFA)-ACN];B%: 10%-40%,20min) to afford 2-amino-N-(3-aminopropyl)-8-[3-[3-(hydroxymethyl)azetidin-1-yl]sulfonylphenyl]-N-propyl-3H-1-benzazepine-4-carboxamide, Bz-17 (1.00 g, 1.57 mmol, 65.48% yield, TFA salt) as a white solid. ^{1}H NMR (MeOD-d_4, 400 MHz) δ8.14-8.05 (m, 2H), 7.91 (d, *J* = 7.6 Hz, 1H), 7.86-7.81 (m, 1H), 7.80-7.72 (m, 2H), 7.71-7.67 (m, 1H), 7.15 (s, 1H), 3.87 (t, *J* = 8.0 Hz, 2H), 3.65-3.57 (m, 4H), 3.55-3.52 (m, 2H), 3.45-3.36 (m, 4H), 3.04-3.01 (m, 2H), 2.63-2.53 (m, 1H), 2.04 (quin, *J* = 7.2 Hz, 2H), 1.77-1.70 (m, 2H), 0.94 (br t, *J* = 6.8 Hz, 3H). LC/MS [M+H] 526.2 (calculated); LC/MS [M+H] 526.2 (observed).

Example 14 Synthesis of Bz-18



Preparation of *tert*-butyl (3-(3-((N-benzyl-2-nitrophenyl)sulfonamido)propoxy)propyl)carbamate, Bz-18a.

3,3'-Oxybis(propan-1-amine) (0.5 g, 3.8 mmol, 1 eq.) and potassium carbonate (1.3 g, 9.5 mmol, 2.5 eq.) were taken up in 10 ml DMF. 2-Nitrophenyl sulfonyl chloride (0.84 g, 3.8 mmol, 1 eq.) was added and the reaction monitored by LCMS. Di-*tert*-butyl dicarbonate (0.87 ml, 3.8 mmol, 1 eq.) was subsequently added. After approximately one additional hour, benzyl bromide (0.45 ml, 3.8 mmol, 1 eq.) was added and the reaction heated to 75 °C. Upon completion, the reaction was filtered, concentrated, and purified by flash chromatography to give Bz-18a (0.47 g, 0.93 mmol, 25%). LC/MS [M+H] 508.21 (calculated); LC/MS [M+H] 508.43 (observed).

Preparation of *tert*-butyl (3-(3-(benzylamino)propoxy)propyl)carbamate, Bz-18b

Bz-18a (0.47 g, 0.93 mmol, 1 eq.) was dissolved in DMF. Potassium carbonate (0.19 g, 1.4 mmol, 1.5 eq.) was added, followed by dodecanethiol (0.33 ml, 1.4 mmol, 1.5 eq.). The reaction was stirred at 60 °C overnight, and then purified by column chromatography to give Bz-

18b (0.18 g, 0.57 mmol, 61%). LC/MS [M+H] 323.23 (calculated); LC/MS [M+H] 323.38 (observed).

Preparation of *tert*-butyl (3-(3-(benzyl(propyl)amino)propoxy)propyl)carbamate, Bz-18c

Bz-18b (0.183 g, 0.57 mmol, 1 eq.) was dissolved in DCM. Propionaldehyde (0.1 ml, 1.4 mmol, 2.5 eq.) and sodium triacetoxyborohydride (0.3 g, 1.4 mmol, 2.5 eq.) were added. The reaction was stirred at room temperature, then concentrated and purified by HPLC to give Bz-18c (0.058 g, 0.159 mmol, 31%). LC/MS [M+H] 365.28 (calculated); LC/MS [M+H] 365.44 (observed).

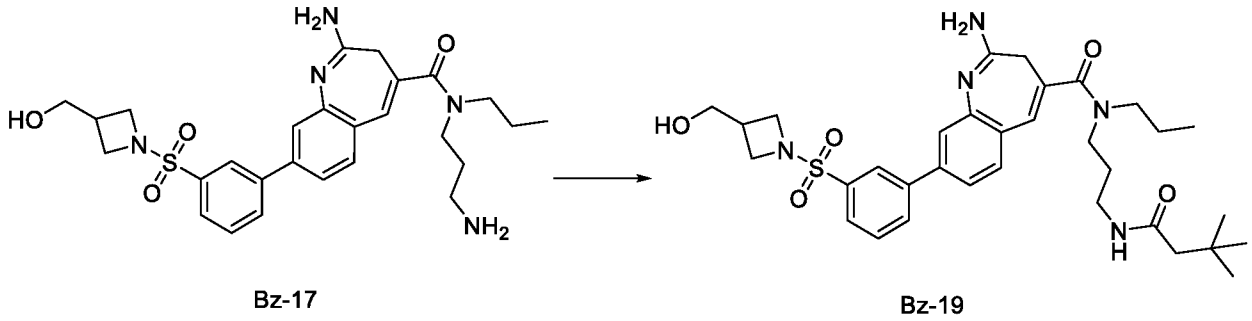
Preparation of *tert*-butyl (3-(3-(propylamino)propoxy)propyl)carbamate, Bz-18d

Bz-18c (0.058 g, 0.159 mmol, 1 eq.) was dissolved in 4 ml methanol. To the solution were added triethylamine (0.067 ml, 0.48 mmol, 3 eq.), followed by formic acid (0.015 ml, 0.40 mmol, 2.5 eq.) and then Pd/C (5 mg, 10 wt%). The mixture was heated to 60 °C. Upon consumption of starting material, the reaction mixture was filtered and concentrated to give Bz-18d (0.007 g, 0.0092 mmol, 26%). LC/MS [M+H] 275.23 (calculated); LC/MS [M+H] 275.27 (observed).

Preparation of Bz-18

2-Amino-8-(3-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-3H-benzo[b]azepine-4-carboxylic acid, Bz-18e (0.025 g, 0.075 mmol, 1 eq.), Bz-18d (0.02 g, 0.075 mmol, 1 eq.), and diisopropylethylamine (0.065 ml, 0.38 mmol, 5 eq.) were dissolved in DMF. HATU (0.043 g, 0.113 mmol, 1.5 eq.) was added and the mixture stirred at room temperature. When complete, the reaction mixture was concentrated and purified by RP-HPLC. The isolated product was concentrated, dissolved in minimal TFA, and allowed to stand at room temperature for 15 minutes. The solution was then concentrated, purified by RP-HPLC, and lyophilized to give 2-amino-N-(3-(3-aminopropoxy)propyl)-8-(3-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-N-propyl-3H-benzo[b]azepine-4-carboxamide, Bz-18 as a white powder (1.2 mg, 0.002 mmol, 3%). LC/MS [M+H] 584.29 (calculated); LC/MS [M+H] 584.50 (observed).

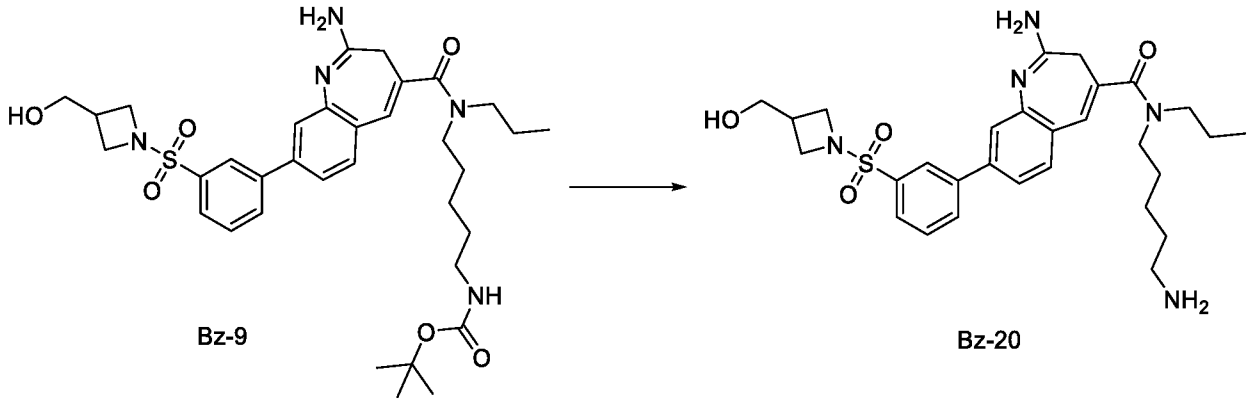
Example 15 Synthesis of Bz-19



Bz-17 Bz-19

A vial was charged with Bz-17 (0.0275 mmol), diisopropylethylamine (15 µL, 0.0825 mmol), *tert*-butylacetyl chloride (0.0275 mmol), 250 µL DCM, and 250 µL DMF. The reaction was maintained for three hours and purified by normal phase chromatography using a 0-10% MeOH:DCM gradient affording 6.6 mg of 2-amino-N-(3-(3,3-dimethylbutanamido)propyl)-8-(3-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-N-propyl-3H-benzo[b]azepine-4-carboxamide, Bz-19 in 39% yield. LC/MS [M+H] 624.3 (calculated); LC/MS [M+H] 624.3 (observed).

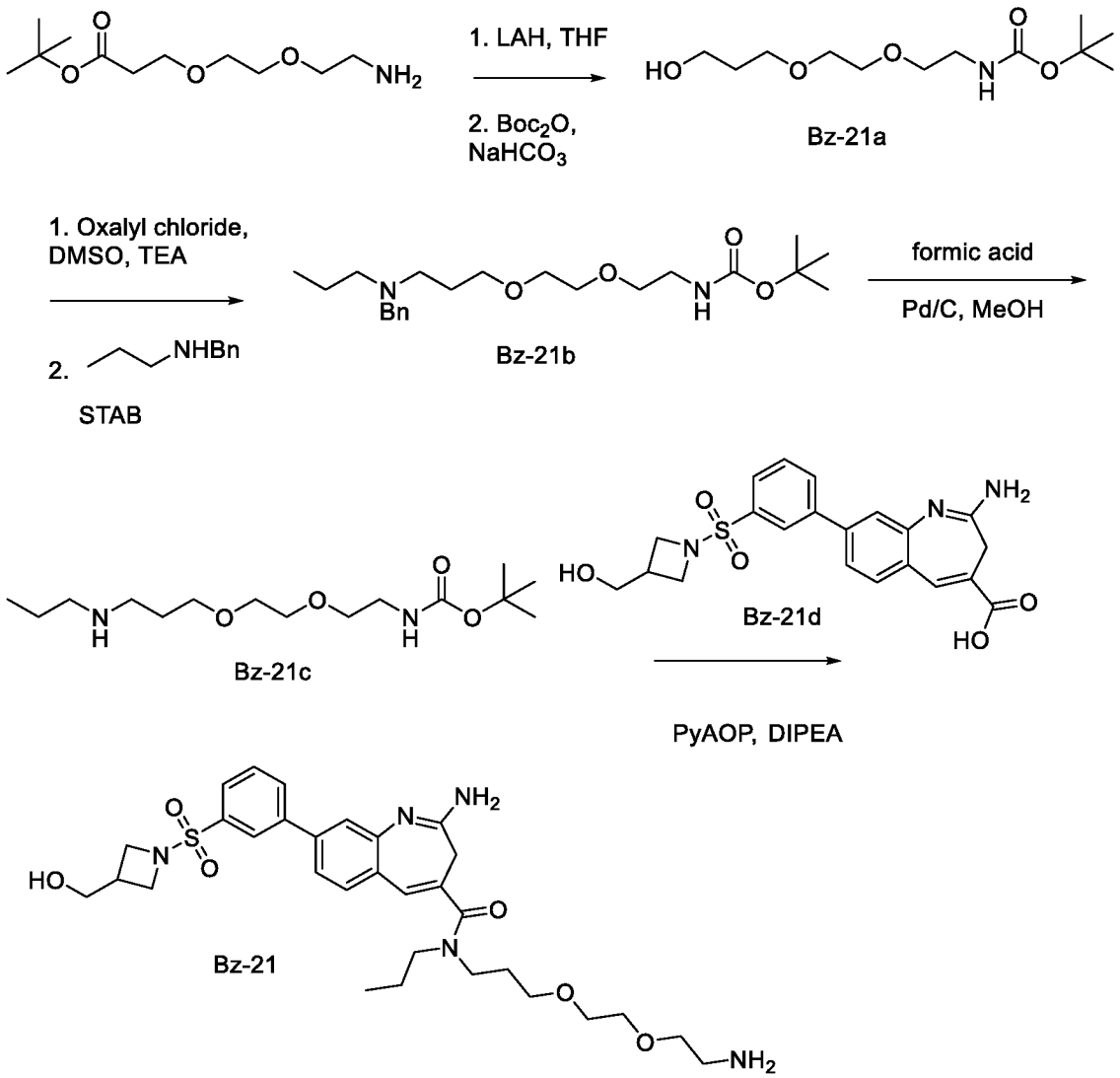
Example 16 Synthesis of Bz-20



Bz-9 Bz-20

A vial was charged with Bz-9 (28 mg, 0.043 mmol), 300 µL DCM and 100 µL trifluoroacetic acid. The reaction was maintained for 1h, upon which it was concentrated under reduced pressure. The resultant oil was azeotroped thrice with 1 mL toluene, after which was added 1 mL methanol and K_2CO_3 (38 mg, 0.28 mmol). After stirring for 16 h, the reaction was filtered and concentrated under reduced pressure and then purified by reverse phase preparative HPLC utilizing a 25-75% gradient of acetonitrile:water containing 0.1% trifluoroacetic acid. The purified fractions were combined and lyophilized to afford 5.8 mg of 2-amino-N-(5-aminopentyl)-8-(3-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-N-propyl-3H-benzo[b]azepine-4-carboxamide, Bz-20 in 24% yield. LC/MS [M+H] 554.28 (calculated); LC/MS [M+H] 554.47 (observed).

Example 17 Synthesis of Bz-21



Preparation of *tert*-butyl (2-(2-(3-hydroxypropoxy)ethoxy)ethyl)carbamate, Bz-21a

tert-butyl 3-(2-(2-aminoethoxy)ethoxy)propanoate (0.5 g, 2.1 mmol, 1 eq.) was dissolved in THF. Lithium aluminum hydride (0.244 g, 6.4 mmol, 3 eq.) was added, and the reaction heated to 60 °C. Upon complete ester reduction, the reaction was cooled on ice and saturated aqueous sodium bicarbonate was added. The mixture was stirred for 10 minutes, and then Di-*tert*-butyl dicarbonate (0.49 ml, 2.1 mmol, 1 eq.) added. The reaction was stirred at room temperature, and then concentrated to remove THF before HPLC purification to give Bz-21a (0.205 g, 0.78 mmol, 36%). LC/MS [M+H] 264.18 (calculated); LC/MS [M+H] 264.27 (observed).

Preparation of *tert*-butyl (2-(2-(3-(benzyl(propyl)amino)propoxy)ethoxy)ethyl)carbamate, Bz-21b

Oxalyl chloride (0.205 ml, 2.4 mmol, 3 eq.) was dissolved in 0.5 ml DCM at -78 °C. DMSO (0.34 ml, 4.8 mmol, 6 eq.) was added dropwise. The reaction was stirred at -78 °C for 15 minutes, then Bz-21a (0.21 g, 0.80 mmol, 1 eq.) added dropwise as a solution in 0.5 ml DCM.

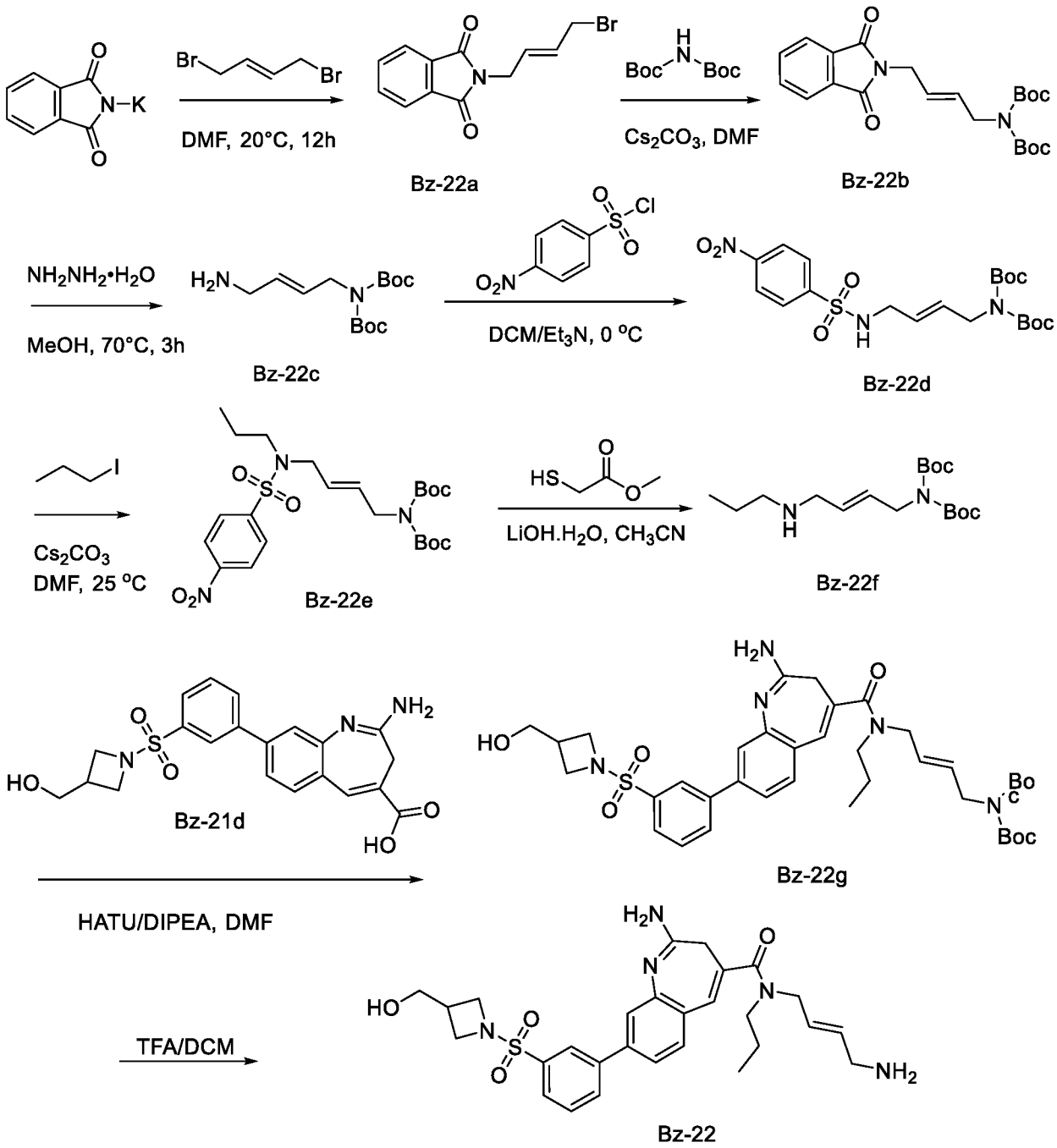
The reaction was stirred 30 minutes at -78 °C, and then triethylamine (1 ml, 7.2 mmol, 9 eq.) was added dropwise. The reaction was stirred 30 more minutes at -78 °C, then removed from cooling and allowed to warm to ambient temperature over 30 minutes. N-Benzylpropan-1-amine (0.119 g, 0.80 mmol, 1 eq.) and sodium triacetoxyborohydride, STAB (0.845 g, 4.0 mmol, 5 eq.) were suspended in 2 ml DCM. The crude aldehyde solution was added to the stirring amine solution. After 30 minutes, the reaction was added to a separatory funnel and washed with saturated $NaHCO_3$, water, and then brine. The organic fraction was dried over sodium sulfate, filtered, concentrated, and then purified by RP-HPLC to give Bz-21b (0.228 g, 0.58 mmol, 73%). LC/MS [M+H] 395.29 (calculated); LC/MS [M+H] 395.44 (observed).

Preparation of *tert*-butyl (2-(2-(3-(propylamino)propoxy)ethoxy)ethyl)carbamate, Bz-21c

Bz-21b (0.228 g, 0.58 mmol, 1 eq.) was dissolved in methanol. Formic acid (0.033 mol, 0.87 mmol, 1.5 eq.) was added, followed by 10 wt% Pd/C (0.02 g). The reaction was stirred at 60 °C and then filtered, concentrated, and purified by HPLC to give Bz-21c as a TFA salt (0.193 g, 0.46 mmol, 80%). LC/MS [M+H] 305.24 (calculated); LC/MS [M+H] 305.38 (observed).

Preparation of Bz-21: 2-Amino-8-(3-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-3*H*-benzo[b]azepine-4-carboxylic acid, Bz-21d (0.042 g, 0.099 mmol, 1 eq.), Bz-21c (0.03 g, 0.099 mmol, 1 eq.), and diisopropylethylamine (0.1 ml, 0.57 mmol, 5.8 eq.) were dissolved in DMF. 7-Aza-benzotriazol-1-yloxy-tripyrrolidino-phosphonium hexafluorophosphate, PyAOP, CAS Reg. No. 156311-83-0 (0.077 g, 0.15 mmol, 1.5 eq.) was added and the mixture stirred at room temperature. When complete, the reaction mixture was concentrated and purified by HPLC. The isolated product was concentrated, dissolved in minimal TFA, and allowed to stand at room temperature for 15 minutes. The solution was then concentrated and purified by HPLC to give an oil that was triturated with diethyl ether to give 2-amino-*N*-(3-(2-(2-aminoethoxy)ethoxy)propyl)-8-(3-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-*N*-propyl-3*H*-benzo[b]azepine-4-carboxamide, Bz-21 as a white solid (0.037 g, 0.060 mmol, 61%). LC/MS [M+H] 614.30 (calculated); LC/MS [M+H] 614.58 (observed).

Example 18 Synthesis of Bz-22



Preparation of (E)-2-(4-bromobut-2-en-1-yl)isoindoline-1,3-dione, Bz-22a

To a solution of (1,3-dioxoisoindolin-2-yl)potassium (7.5 g, 40.5 mmol, 1 *eq*) in DMF (100 mL) was added (E)-1,4-dibromobut-2-ene (17.3 g, 80.9 mmol, 2 *eq*). The mixture was stirred at 20°C for 12 h and then diluted with water (200 mL) and extracted with EtOAc (80 mL x 3). The organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash silica gel chromatography (ISCO®;12 g SepaFlash® Silica Flash Column, Eluent of 0~60% Ethyl acetate/Petroleum ether gradient at 60 mL/min) to give Bz-22a (8.6 g, 30.7 mmol, 75.82% yield) as white solid. ^1H NMR ($CDCl_3$, 400

MHz) δ7.90-7.83 (m, 2H), 7.78-7.70 (m, 2H), 6.01-5.90 (m, 1H), 5.89-5.79 (m, 1H), 4.32 (d, *J* = 5.6 Hz, 2H), 3.92 (d, *J* = 7.2 Hz, 2H).

Preparation of tert-butyl N-tert-butoxycarbonyl-N-[(E)-4-(1,3-dioxoisoindolin-2-yl)but-2-enyl]carbamate, Bz-22b

To a solution of Bz-22a (11 g, 39.3mmol, 1 *eq*) in DMF (200 mL) was added Cs_2CO_3 (19.2g, 58.9 mmol, 1.5 *eq*) and tert-butyl N-tert-butoxycarbonylcarbamate (11.1g, 51.1mmol, 1.3 *eq*). The mixture was stirred at 20°C for 12 h and then diluted with water (400 mL) and extracted with EtOAc (100 mL x 3). The organic layer was washed with brine (80 mL x 3), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash silica gel chromatography (ISCO®; 5 g SepaFlash® Silica Flash Column, Eluent of 0~70% Ethyl acetate/Petroleum ether gradient @ 65 mL/min) to give Bz-22b (16 g, 38.4 mmol, 97.83% yield) as white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ7.90-7.83 (m, 4H), 5.63-5.53 (m, 2H), 4.20-4.12 (m, 2H), 4.05-3.99 (m, 2H), 1.36 (s, 18H)

Preparation of tert-butyl N-[(E)-4-aminobut-2-enyl]-N-tert-butoxycarbonyl-carbamate, Bz-22c

To a solution of Bz-22b (18 g, 43.2 mmol, 1 *eq*) in MeOH (200 mL) was added hydrazine;hydrate (10.2g, 173mmol, 9.90 mL 85% purity, 4 *eq*) at 20°C and then stirred at 70°C for 3 h. The mixture was filtered and the filtrate was concentrated. The crude product was triturated with CH_3CN at 20°C for 20 min and filtered, the filtrate was concentrated to give Bz-22c (10 g, 34.9 mmol, 80.80% yield) as light yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ5.78-5.69 (m, 1H), 5.64-5.54 (m, 1H), 4.17-4.09 (m, 2H), 3.31-3.23 (m, 2H), 1.49 (s, 18H)

Preparation of tert-butyl N-tert-butoxycarbonyl-N-[(E)-4-[(4-nitrophenyl)sulfonylamino]but-2-enyl]carbamate, Bz-22d

To a solution of Bz-22c (1 g, 3.49 mmol, 1 *eq*) in DCM (10 mL) was added TEA (706.72 mg, 6.98 mmol, 972.10 uL (microliters), 2 *eq*) and 4-nitrobenzenesulfonyl chloride (851.29 mg, 3.84 mmol, 1.1 *eq*) at 0°C under N_2. The mixture was stirred at 25 °C for 1 h and then quenched by addition of H_2O (20 mL) at 0°C, and then extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue which was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 1/0 to 1/1) to give Bz-22d (1.2 g, 2.54 mmol, 72.74% yield) as a light yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ8.41-8.35 (m, 2H), 8.05 (d, *J* = 9.2 Hz, 2H), 5.71-5.61 (m, 1H), 5.57-5.47 (m, 1H), 4.61 (t, *J* = 5.6 Hz, 1H), 4.10 (d, *J* = 5.6 Hz, 2H), 3.67 (t, *J* = 6.0 Hz, 2H), 1.49 (s, 18H).

Preparation of tert-butyl N-tert-butoxycarbonyl-N-[(E)-4-[(4-nitrophenyl)sulfonyl-propyl-amino]but-2-enyl]carbamate, Bz-22e

To a solution of Bz-22d (1 g, 2.12 mmol, 1 *eq*) in DMF (10 mL) was added Cs_2CO_3 (1.38 g, 4.24 mmol, 2 *eq*) and 1-iodopropane (360.52 mg, 2.12 mmol, 207.19 uL, 1 *eq*) at 25°C and then stirred at this temperature for 12 h. The reaction mixture was quenched by addition of H_2O (50 mL) at 0°C, and then extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (10 mL x 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 1/0 to 3/1) to give Bz-22e (0.89 g, 1.73 mmol, 81.71% yield) as a light yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ8.36 (d, *J* = 8.8 Hz, 2H), 7.99 (d, *J* = 8.8 Hz, 2H), 5.74-5.60 (m, 1H), 5.51-5.37 (m, 1H), 4.11 (d, *J* = 7.2 Hz, 2H), 3.86 (d, *J* = 6.4 Hz, 2H), 3.16-3.07 (m, 2H), 1.55-1.46 (m, 20H), 0.86 (t, *J* = 7.6 Hz, 3H)

Preparation of tert-butyl N-tert-butoxycarbonyl-N-[(E)-4-(propylamino)but-2-enyl] carbamate, Bz-22f

To a solution of Bz-22e (0.79 g, 1.54 mmol, 1 *eq*) in CH_3CN (10 mL) was added $LiOH.H_2O$ (387.25 mg, 9.23 mmol, 6 *eq*) and methyl 2-sulfanylacetate (490 mg, 4.61 mmol, 419 uL, 3 *eq*) at 0°C. The resulting mixture was stirred at 25°C for 12 h and then filtered and concentrated under reduced pressure. The residue was diluted with H_2O (20 mL) at 0°C, and then adjusted pH = 2-3 with 1 M HCl and extracted with MTBE (10 mL x 3). The pH of water phase was adjusted to ~10 with aq. K_2CO_3 and extracted with (10 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give Bz-22f (0.35 g, 1.07 mmol, 69.28% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ5.79-5.58 (m, 2H), 4.15 (d, *J* = 5.2 Hz, 2H), 3.23 (d, *J* = 5.6 Hz, 2H), 2.56 (t, *J* = 6.8 Hz, 2H), 1.56-1.42 (m, 20H), 0.92 (t, *J* = 7.6 Hz, 3H).

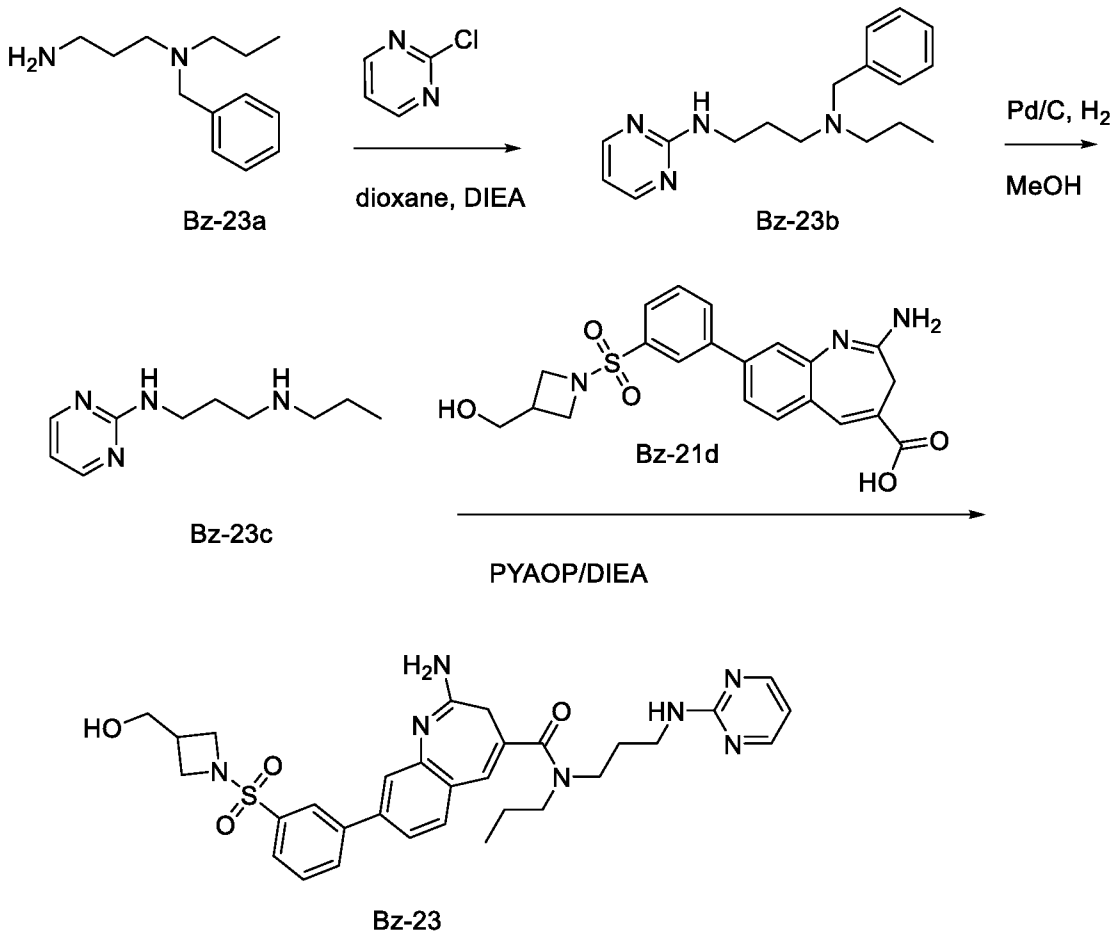
Preparation of tert-butyl N-[(E)-4-[[2-amino-8-[3-[3-(hydroxymethyl)azetidin-1-yl]sulfonylphenyl]-3H-1-benzazepine-4-carbonyl]-propyl-amino]but-2-enyl]-N-tert-butoxycarbonyl-carbamate, Bz-22g

To a mixture of 2-amino-8-(3-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-3*H*-benzo[b]azepine-4-carboxylic acid, Bz-21d (0.45 g, 1.05 mmol, 1 *eq*) in DMF (5 mL) was added HATU (440 mg, 1.16 mmol, 1.1 *eq*) and DIPEA (408 mg, 3.16 mmol, 550 uL, 3 *eq*) at 25 °C. After 10 min, Bz-22f (345.75 mg, 1.05 mmol, 1 *eq*) was added to the mixture at 25°C and then stirred at this temperature for 1 h. The reaction mixture was poured into ice water (30 mL) at 0°C, and extracted with DCM/i-PrOH = 3/1 (20 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give Bz-22g (0.41 g, crude) as a brown solid.

Preparation of Bz-22: To a solution of tert-butyl N-[(E)-4-[[2-amino-8-[3-[3-(hydroxymethyl)azetidin-1-yl] sulfonylphenyl]-3H-1-benzazepine-4-carbonyl]-propyl-

amino]but-2-enyl]-N-tert-butoxycarbonyl-carbamate (13 mg, 17.6 umol (micromoles), 1 *eq*) in DCM (1 mL) was added TFA (154 mg, 1.35 mmol, 0.1 mL, 76.7 *eq*) at 25 °C and then stirred at this temperature for 1 h. The reaction mixture was concentrated under reduced pressure. The residue was dissolved with CH_3CN (10 mL) and H_2O (1 mL) and adjusted pH = 9 with aq. LiOH at 0 °C. The mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (TFA condition; column: Welch Xtimate C18 100*25mm*3um;mobile phase: [water(0.1%TFA)-ACN];B%: 5%-35%,12min) to give 2-amino-N-[(E)-4-aminobut-2-enyl]-8-[3-[3- (hydroxymethyl)azetidin-1-yl]sulfonylphenyl]-N-propyl-3H-1-benzazepine-4-carboxamide, Bz-22 (7 mg, 10.74 umol, 60.97% yield, TFA) as a white solid. ^{1}H NMR (MeOD-d_4, 400 MHz) δ8.15-8.04 (m, 2H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.86-7.72 (m, 3H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.13 (s, 1H), 6.07-5.94 (m, 1H), 5.89-5.77 (m, 1H), 4.21 (br s, 2H), 3.87 (t, *J* = 8.4 Hz, 2H), 3.67-3.56 (m, 4H), 3.48 (br s, 2H), 3.45-3.37 (m, 4H), 2.68-2.50 (m, 1H), 1.77-1.61 (m, 2H), 0.95-0.93 (m, 3H). LC/MS [M+H] 538.2 (calculated); LC/MS [M+H] 538.3 (observed).

Example 19 Synthesis of Bz-23



Preparation of N'-benzyl-N'-propyl-N-pyrimidin-2-yl-propane-1,3-diamine, Bz-23b

A mixture of N'-benzyl-N'-propyl-propane-1,3-diamine, Bz-23a (0.2 g, 823.77 umol, 1 *eq*, HCl), DIEA (426 mg, 3.30 mmol, 574 uL, 4 *eq*) in dioxane (4 mL) was stirred at 25°C for 10

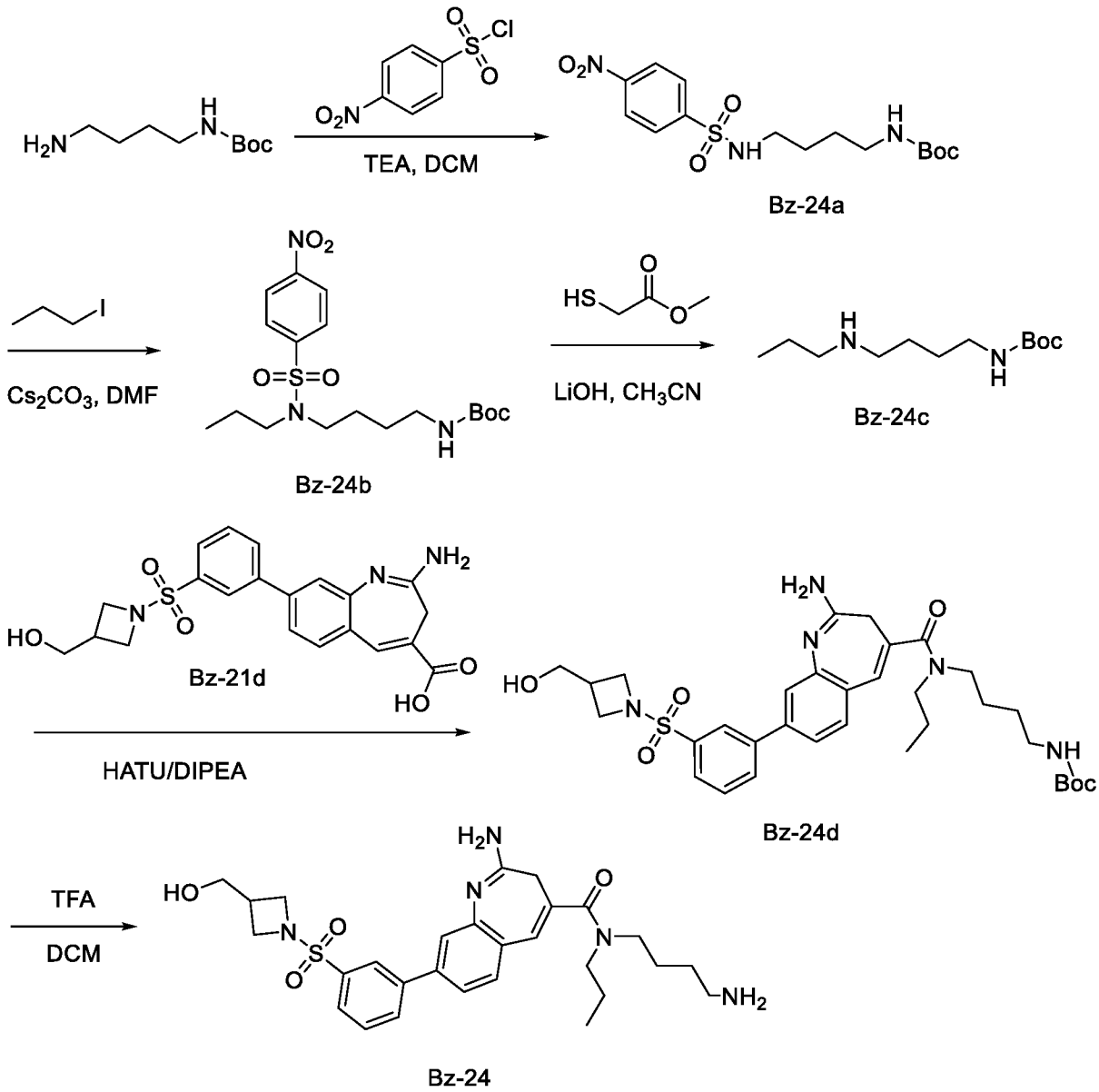
min, and then 2-chloropyrimidine (188.70 mg, 1.65 mmol, 2 *eq*) was added, then mixture was stirred at 25 °C for 16 h. The reaction was quenched with H_2O (15 mL) and extracted with ethyl acetate (15 mL x 3). The combined organic phase was washed with brine (10 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-TLC (SiO_2, DCM:MeOH = 7:1) to give Bz-23b (130 mg, 457 umol, 55.49% yield) as yellow oil. ^1H NMR ($CDCl_3$, 400 MHz) δ8.26 (d, *J* = 4.8 Hz, 2H), 7.38-7.32 (m, 2H), 7.30 (t, *J* = 7.2 Hz, 2H), 7.26-7.20 (m, 1H), 6.49 (t, *J* = 5.2 Hz, 1H), 5.74 (br s, 1H), 3.58 (s, 2H), 3.47-3.39 (m, 2H), 2.54 (t, *J* = 6.8 Hz, 2H), 2.44-2.38 (m, 2H), 1.77 (quin, *J* = 6.4 Hz, 2H), 1.57-1.50 (m, 2H), 0.88 (t, *J* = 7.2 Hz, 3H)

Preparation of N-propyl-N'-pyrimidin-2-yl-propane-1,3-diamine, Bz-23c

To a solution of Bz-23b (130 mg, 457 umol, 1 *eq*) in MeOH (10 mL) was added Pd/C (0.1 g, 10% purity) under N_2 atmosphere. The suspension was degassed and purged thrice with hydrogen gas, H_2, the mixture was stirred at 25°C for 16 h and then filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (SiO_2, DCM:MeOH = 5:1) to give Bz-23c (80 mg, 412 umol, 90.09% yield) as a brown oil.

Preparation of Bz-23: To a solution of 2-amino-8-[3-[3-(hydroxymethyl)azetidin-1-yl]sulfonylphenyl] -3H-1-benzazepine-4-carboxylic acid, Bz-21d (264 mg, 618 umol, 1 *eq*) in DMF (2 mL) was added DIEA (240 mg, 1.85 mmol, 323 uL, 3 *eq*), 7-Aza-benzotriazol-1-yloxy-tripyrrolidino-phosphonium hexafluorophosphate, PYAOP (483 mg, 927 umol, 1.5 *eq*) and Bz-23c (120 mg, 618 umol, 1 *eq*). The mixture was stirred at 25°C for 1 h, and then filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC WelchXtimateC18100 x 25mm x 3um;mobilephase:[water(0.1%TFA)-ACN];B%:15%-35%,12min) to give 2-amino-8-[3-[3-(hydroxymethyl)azetidin-1-yl]sulfonylphenyl]-N-propyl-N-[3-(pyrimidin-2-ylamino)propyl]-3H-1-benzazepine-4-carboxamide, Bz-23 (16 mg, 26.5 umol, 4.29% yield) as a white solid. ^1H NMR (MeOD-d_4, 400 MHz) δ8.38 (br s, 1H), 8.15 (s, 1H), 8.11 (s, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.85-7.79 (m, 1H), 7.75 (br s, 1H), 7.71 (br s, 1H), 7.53 (s, 1H), 7.11 (br s, 1H), 6.74 (br s, 1H), 3.87 (t, *J* = 8.0 Hz, 2H), 3.62 (dd, *J* = 6.0, 8.0 Hz, 4H), 3.54-3.49 (m, 2H), 3.42 (d, *J* = 6.8 Hz, 2H), 3.35 (br s, 2H), 2.64-2.51 (m, 1H), 2.08-1.95 (m, 2H), 1.77-1.66 (m, 2H), 0.99-0.94 (m, 3H). LC/MS [M+H] 604.3 (calculated); LC/MS [M+H] 604.3 (observed).

Example 20 Synthesis of Bz-24



Preparation of tert-butyl N-[4-[(4-nitrophenyl)sulfonylamino]butyl]carbamate, Bz-24a

To a solution of tert-butyl N-(4-aminobutyl)carbamate (0.5 g, 2.66 mmol, 1 *eq*) and Et_3N(537 mg, 5.31 mmol, 739 uL, 2 *eq*) in DCM (5 mL) was added 4-nitrobenzenesulfonyl chloride (647 mg, 2.92 mmol, 1.1 *eq*) at 0°C. After addition, the resulting mixture was stirred at 25 °C for 1 h and then quenched by addition of H_2O (20 mL) at 0°C, and then extracted with DCM(10 mL x 3). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was triturated with PE/MTBE = 10/1 (20 mL) and stirred for 30 min, filtered and the filter cake was dried under reduced pressure to give Bz-24a (0.99 g, 2.65 mmol, 99.82% yield) as a white solid. ^1H NMR ($CDCl_3$, 400 MHz) δ8.37 (d, *J* = 8.8 Hz, 2H), 8.07 (d, *J* = 8.4 Hz, 2H), 5.28 (br s, 1H), 4.59 (br s, 1H), 3.12-3.03 (m, 4H), 1.58-1.48 (m, 4H), 1.44 (s, 9H)

Preparation of tert-butyl N-[4-[(4-nitrophenyl)sulfonyl-propyl-amino]butyl]carbamate, Bz-24b

To a solution of Bz-24a (0.99 g, 2.65 mmol, 1 *eq*) in DMF (7 mL) was added Cs_2CO_3 (1.73 g, 5.30 mmol, 2 *eq*) and 1-iodopropane (451 mg, 2.65 mmol, 259 uL, 1 *eq*) at 0°C. The mixture was stirred at 25°C for 12 h and then poured into ice water (30 mL) at 0°C, and then extracted with EtOAc(20 mL x 3). The combined organic layers were washed with brine (10 mL x 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was triturated with PE/MTBE = 10/1 (20 mL) and stirred at 25°C for 30 min, filtered and the filter cake was dried under reduced pressure to give Bz-24b (0.97 g, 2.33 mmol, 88.06% yield) as a light yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ8.39 (d, *J* = 8.8 Hz, 2H), 8.07 (d, *J* = 8.8 Hz, 2H), 6.79 (br t, *J* = 6.0 Hz, 1H), 3.13-3.05 (m, 4H), 2.88 (q, *J* = 6.4 Hz, 2H), 1.54-1.40 (m, 4H), 1.39-1.27 (m, 11H), 0.81 (t, *J* = 7.2 Hz, 3H).

Preparation of tert-butyl N-[4-(propylamino)butyl]carbamate, Bz-24c

To a solution of Bz-24b (0.97 g, 2.33 mmol, 1 *eq*) in CH_3CN (10 mL) was added $LiOH.H_2O$ (587.74 mg, 14.01 mmol, 6 *eq*) and methyl 2-sulfanylacetate (744 mg, 7.00 mmol, 635 uL, 3 *eq*) at 0°C. The resulting mixture was stirred at 25°C for 12 h and then filtered and concentrated under reduced pressure. The residue was diluted with H_2O (20 mL) at 0°C, and then adjusted pH = 2-3 with 1 M HCl and extracted with MTBE(10 mL x 3). The pH of water phase was adjusted to ~ 10 with aq. K_2CO_3 and extracted with EtOAc(10 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give Bz-24c (445 mg, 1.93 mmol, 82.75% yield) as a brown oil. ^{1}H NMR (DMSO-d_6, 400 MHz) δ6.81 (br s, 1H), 2.89 (q, *J* = 6.4 Hz, 2H), 2.47-2.39 (m, 4H), 1.44-1.31 (m, 15H), 0.85 (t, *J* = 7.6 Hz, 3H).

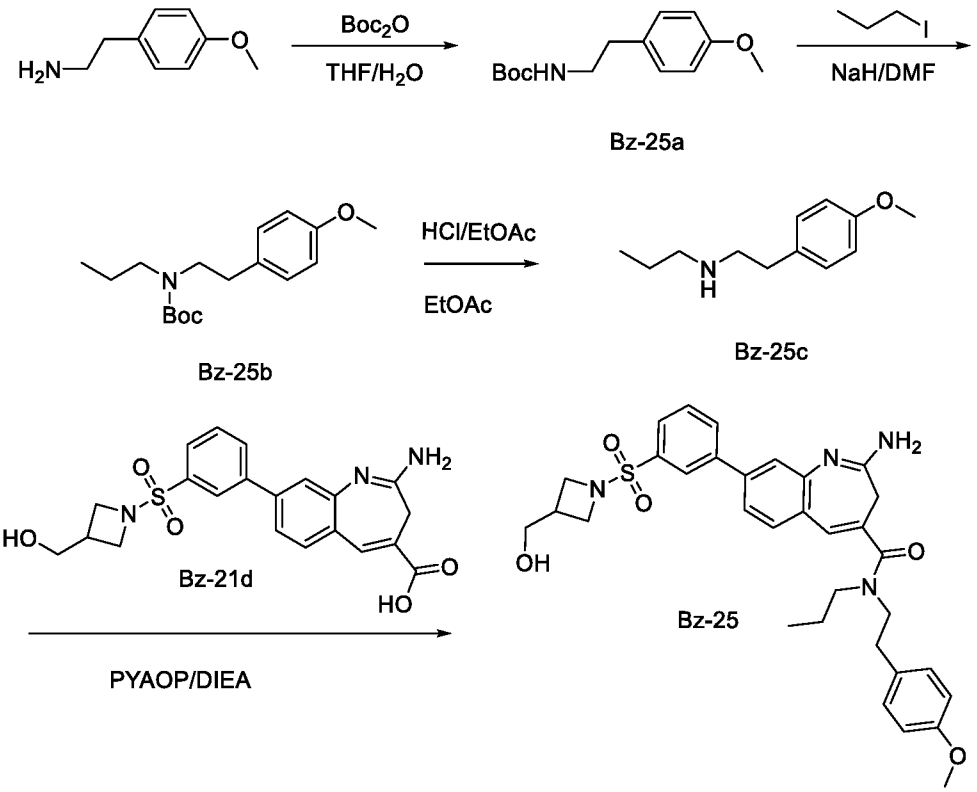
Preparation of tert-butyl N-[4-[[2-amino-8-[3-[3-(hydroxymethyl)azetidin-1-yl]sulfonylphenyl]-3H-1-benzazepine-4-carbonyl]-propyl-amino]butyl]carbamate, Bz-24d

To a solution of 2-amino-8-[3-[3-(hydroxymethyl)azetidin-1-yl]sulfonylphenyl] -3H-1-benzazepine-4-carboxylic acid, Bz-21d (100 mg, 234 umol, 1 *eq*) and DIPEA (90.7 mg, 702 umol, 122.24 uL, 3 *eq*) in DMF (1 mL) was added HATU (97.8 mg, 257 umol, 1.1 *eq*) at 25°C. After 10 min, Bz-24c (64.66 mg, 280.72 umol, 1.2 *eq*) was added at **25** °C and then stirred at this temperature for 1 h. The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (TFA condition; column: Welch Xtimate C18 100*25mm*3um;mobile phase: [water(0.1%TFA)-ACN];B%: 30%-45%,12min). Bz-24d (8 mg, 12.50 umol, 5.35% yield) was obtained as a yellow solid. ^{1}H NMR (MeOD-d_4, 400 MHz) δ8.14-8.04 (m, 2H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.85-7.81 (m, 1H), 7.81-7.76 (m, 1H), 7.73-7.68 (m, 2H), 7.11 (s, 1H), 3.87 (t, *J* = 7.6 Hz, 2H), 3.61 (dd, *J* = 6.0Hz, 7.6 Hz, 2H), 3.58-3.45 (m,

4H), 3.44-3.35 (m, 4H), 3.12-3.04 (m, 2H), 2.65-2.52 (m, 1H), 1.78-1.63 (m, 4H), 1.55-1.40 (m, 11H), 0.95-0.93 (m, 3H). LC/MS [M+H] 640.3 (calculated); LC/MS [M+H] 640.3 (observed).

Preparation of Bz-24: To a solution of Bz-24d (0.1 g, 156 umol, 1 *eq*) in DCM (2 mL) was added TFA (308 mg, 2.70 mmol, 0.2 mL, 17.28 *eq*) at 25°C and then stirred at this temperature for 1 h. The reaction mixture was concentrated under reduced pressure. The residue was dissolved with CH_3CN (10 mL) and H_2O (1 mL) and adjusted pH = 9 with aq. LiOH at 0°C. The mixture was stirred for 1 h at 25°C and then filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (TFA condition; column: Welch Xtimate C18 100*25mm*3um;mobile phase: [water(0.1%TFA)-ACN];B%: 5%-30%,12min) to give 2-amino-N-(4-aminobutyl)-8-[3-[3-(hydroxymethyl)azetidin-1-yl]sulfonylphenyl]-N-propyl-3H-1-benzazepine-4-carboxamide, Bz-24 (34 mg, 52.01 umol, 33.28% yield, TFA) as a white solid. ^{1}H NMR (MeOD-d_4, 400 MHz) δ8.13-8.05 (m, 2H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.85-7.78 (m, 1H), 7.77-7.72 (m, 2H), 7.71-7.65 (m, 1H), 7.10 (s, 1H), 3.86 (t, *J* = 8.4 Hz, 2H), 3.61 (dd, *J* = 5.6 Hz, 7.6 Hz, 2H), 3.58-3.46 (m, 4H), 3.44-3.36 (m, 4H), 3.05-2.94 (m, 2H), 2.64-2.52 (m, 1H), 1.84-1.62 (m, 6H), 1.03-0.85 (m, 3H). LC/MS [M+H] 540.3 (calculated); LC/MS [M+H] 540.3 (observed).

Example 21 Synthesis of Bz-25



Preparation of tert-butyl N-[2-(4-methoxyphenyl)ethyl] carbamate, Bz-25a

To a mixture of 2-(4-methoxyphenyl) ethanamine (1 g, 6.61 mmol, 970.87 uL, 1 *eq*) in THF and H_2O (10 mL) was added Boc_2O (2.17 g, 9.92 mmol, 2.28 mL, 1.5 *eq*) and then stirred

at 25 °C for 30 min under N_2 atmosphere. The mixture was diluted with water and extracted with EtOAc (50 ml x 3). The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography (column height:250 mm, diameter:100 mm, 100-200 mesh silica gel, Petroleum ether/Ethylacetate=5/1-1/1) to give Bz-25a (1.60 g, 6.37 mmol, 96.26% yield) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ7.12 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 4.53(br s, 1H), 3.80 (s, 3H), 3.37-3.33 (m, 2H), 2.74 (br t, *J* = 6.4 Hz, 2H), 1.44 (s, 9H)

Preparation of tert-butyl 4-methoxyphenethyl(propyl)carbamate, Bz-25b

To a mixture of Bz-25a (0.8 g, 3.18 mmol, 1 *eq*) and 1-iodopropane (1.08 g, 6.37 mmol, 621 uL, 2 *eq*) in DMF (8 mL) was added NaH (191 mg, 4.77 mmol, 60% purity, 1.5 *eq*) at 0°C, and then stirred at 25°C for 2 hr. The mixture was poured into water (20 mL). The aqueous phase was extracted with ethyl acetate (15 mL x 3). The combined organic phase was washed with brine (10 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel chromatography (column height:250 mm, diameter: 100 mm, 100-200 mesh silica gel, Petroleum ether/Ethyl acetate=5/1,1/1) to afford Bz-25b (365 mg, 1.24 mmol, 39.08% yield) as white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ7.11 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 3.79 (s, 3H), 3.36-3.30 (m, 2H), 3.15-3.09 (m, 2H), 2.79-2.71 (m, 2H), 1.57-1.50 (m, 2H), 1.46 (s, 9H), 0.87 (t, *J* = 7.6 Hz, 3H).

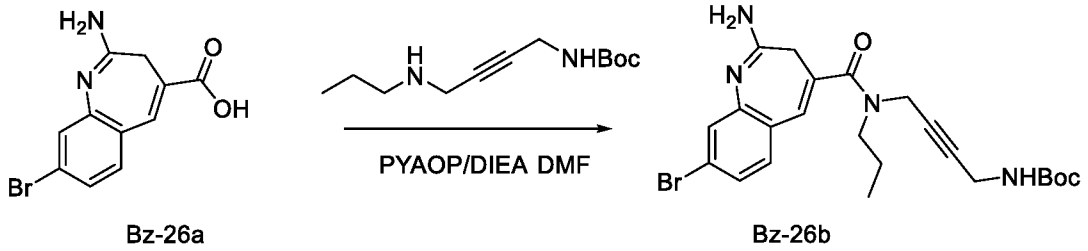
Preparation of N-[2-(4-methoxyphenyl)ethyl]propan-1-amine, Bz-25c

To a solution of Bz-25b (365 mg, 1.24 mmol, 1 *eq*) in EtOAc (5 mL) was added HCl/EtOAc (5 mL). The mixture was stirred at 25°C for 3 h and then concentrated in vacuum to give Bz-25c.

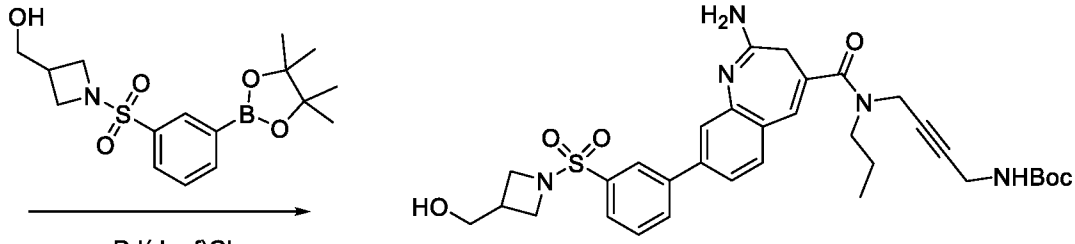
Preparation of Bz-25: To a solution of 2-amino-8-[3-[3-(hydroxymethyl)azetidin-1-yl]sulfonylphenyl] -3H-1-benzazepine-4-carboxylic acid, Bz-21d (186 mg, 435 umol, 1 *eq*) in DMF (1.00 mL) was added PYAOP (340 mg, 653 umol, 1.5 *eq*) and DIEA (393 mg, 3.05 mmol, 531 uL, 7 *eq*), and then Bz-25c (100 mg, 435 umol, 1 *eq*, HCl) was added. The mixture was stirred at 25 °C for 3 h, and then filtered and concentrated. The residue was purified by pre-HPLC (column:Nano-micro Kromasil® C18 100*30mm 8um;mobile phase:[water(0.1%TFA)-ACN];B%:25%-55%,10min]) to give 2-amino-8-[3-[3-(hydroxymethyl)azetidin-1-yl]sulfonylphenyl]-N-[2-(4-methoxyphenyl)ethyl]-N-propyl-3H-1-benzazepine-4-carboxamide, Bz-25 (14 mg, 23.23 umol, 5.34% yield) as a light yellow solid. ^{1}H NMR (MeOD-d_4, 400 MHz) δ8.13-8.03 (m, 2H), 7.93-7.87 (m, 1H), 7.84-7.80 (m, 1H), 7.79-7.74 (m, 1H), 7.69 (br s, 1H), 7.60 (br d, *J* = 8.0 Hz, 1H), 7.08 -6.51 (m, 5H), 3.86 (t, *J* = 8.4 Hz, 2H), 3.75 (s, 4H), 3.61 (dd, *J* = 5.8, 8.1 Hz, 2H), 3.56-3.45 (m, 1H), 3.54-3.49 (m, 1H), 3.42 (d, *J* = 6.2 Hz, 2H), 2.93-2.87 (m,

2H), 2.65-2.47 (m, 1H), 1.75-1.68 (m, 2H), 1.03-0.94 (m, 3H). LC/MS [M+H] 603.3 (calculated); LC/MS [M+H] 603.3 (observed).

Example 22 Synthesis of Bz-26.



Bz-26a Bz-26b



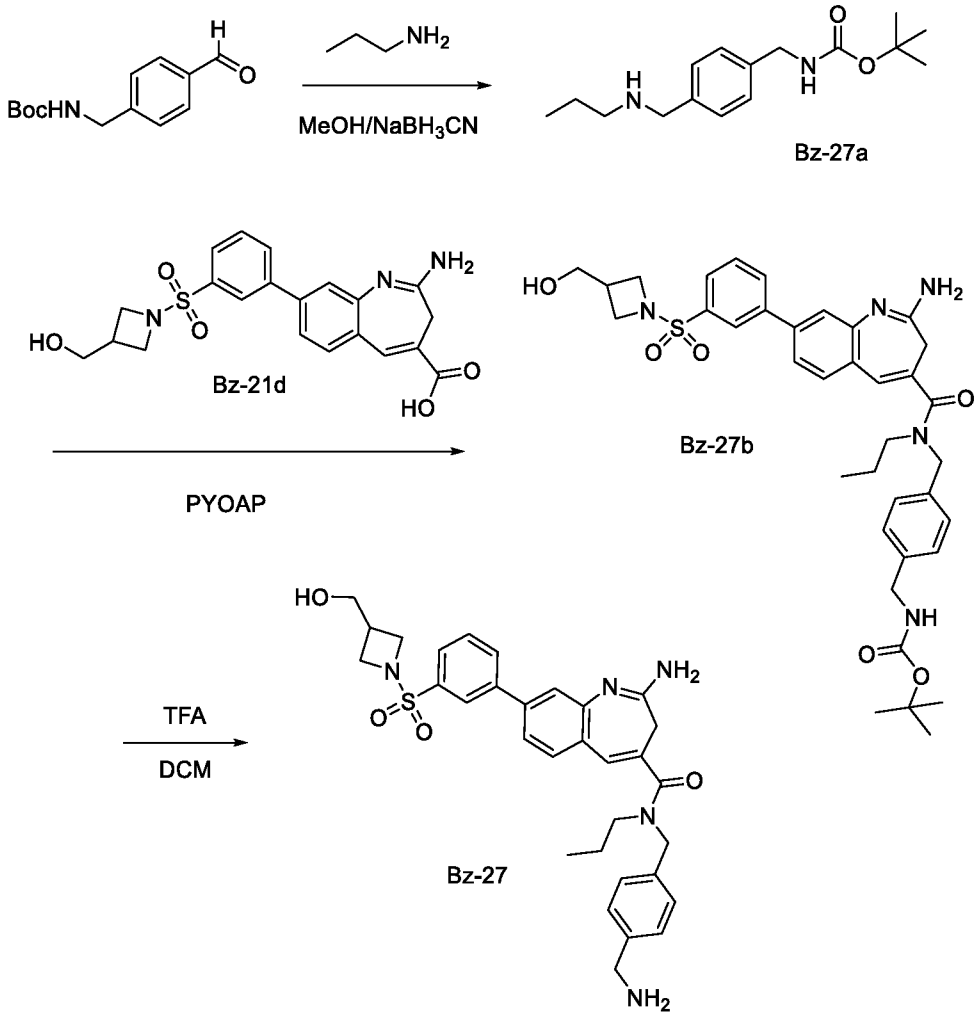
Bz-26

Preparation of Bz-26b: To a mixture of 2-amino-8-bromo-3H-1-benzazepine-4-carboxylic acid, Bz-26a (0.5 g, 1.78 mmol, 1.0 *eq*), PYAOP (1.02 g, 1.96 mmol, 1.1 *eq*) and DIEA (920 mg, 7.11 mmol, 1.24 mL, 4.0 *eq*) in DMF (8 mL) was added tert-butyl N-[4-(propylamino)but-2-ynyl]carbamate (400 mg, 1.78 mmol, 1.0 *eq*) at 25°C and then stirred for 0.5 hours at this temperature. The mixture was poured into water (40 mL). The aqueous phase was extracted with ethyl acetate (30 mL x 3). The combined organic phase was washed with brine (30 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, Petroleum ether/Ethyl acetate=1/1, 0/1) to give tert-butyl N-[4-[(2-amino-8-bromo-3H-1-benzazepine -4-carbonyl)-propyl-amino]but-2-ynyl]carbamate, Bz-26b (0.5 g, 1.02 mmol, 57.4% yield) as light yellow solid. ^{1}H NMR ($CDCl_3$, 400MHz) δ7.52 (s, 1H), 7.39 (s, 2H), 7.07 (br s, 1H), 4.37 (s, 2H), 4.06 (d, J = 5.2 Hz, 2H), 3.65 (s, 2H), 2.91 (s, 2H), 1.88-1.74 (m, 2H), 1.57 (s, 9H), 1.06 (t, J = 7.2 Hz, 3H).

Preparation of Bz-26: To a mixture of [1-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl] sulfonylazetidin-3-yl]methanol (1.73 g, 4.90 mmol, 1.2 *eq*), Bz-26b (2.0 g, 4.09 mmol, 1.0 *eq*) and $Pd(dppf)Cl_2$ (150 mg, 204 umol, 0.05 *eq*) in dioxane (40 mL) was added K_2CO_3 (1.13 g, 8.17 mmol, 2 *eq*) in H_2O (5 mL) at 25°C under N_2 and then stirred at 100°C for 1 hour. The mixture was filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, Petroleum ether/Ethyl acetate=1/1, 0/1) to afford tert-butyl N-[4-[[2-amino-8-[3-[3-

(hydroxymethyl)azetidin-1-yl]sulfonylphenyl]-3H-1-benzazepine-4-carbonyl]-propyl-amino]but-2-ynyl]carbamate, Bz-26 (2.0 g, 3.15 mmol, 76.9% yield) as light yellow solid. ^{1}H NMR (MeOD, 400MHz) δ8 .07 (s, 1H), 8.04 (br d, *J* = 7.6 Hz, 1H), 7.88-7.82 (m, 1H), 7.79-7.73 (m, 1H), 7.53-7.46 (m, 2H), 7.43-7.37 (m, 1H), 7.12 (s, 1H), 4.29 (s, 2H), 3.93-3.82 (m, 4H), 3.62-3.50 (m, 4H), 3.42 (d, *J* = 6.4 Hz, 2H), 3.31 (s, 2H), 2.64-2.52 (m, 1H), 1.76-1.70 (m, 2H), 1.43 (s, 9H), 0.99-0.91 (m, 3H). LC/MS [M+H] 636.3 (calculated); LC/MS [M+H] 636.3 (observed). LCMS (ESI): mass calcd. for $C_{33}H_{41}N_5O_6S$ 635.28, m/z found 636.3[M+H]$^+$

Example 23 Synthesis of Bz-27:



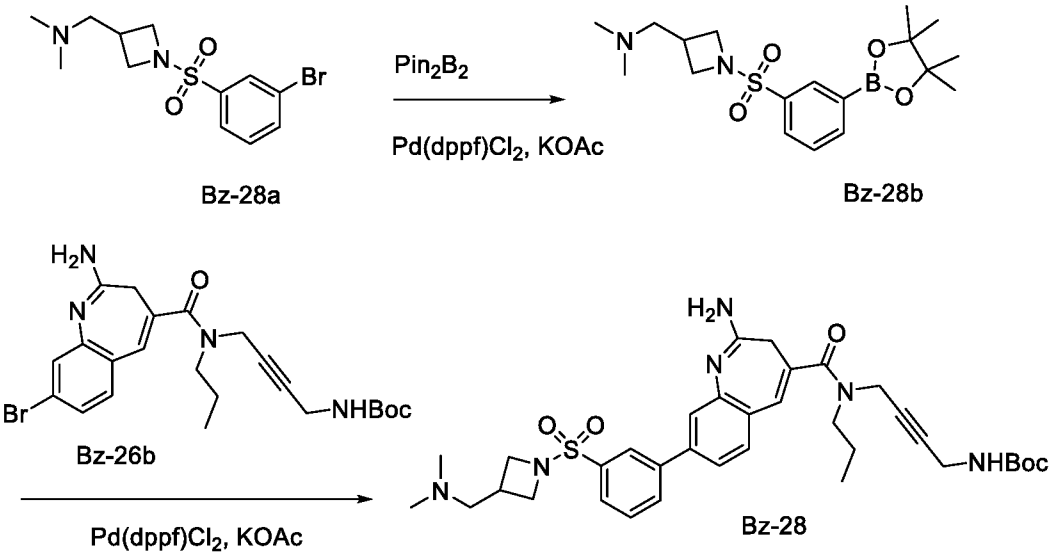
Preparation of Bz-27a: To a solution of tert-butyl N-[(4-formylphenyl)methyl] carbamate (400 mg, 1.70 mmol, 1 *eq*), propan-1-amine (1.00 g, 17.0 mmol, 1.40 mL, 10 *eq*) and AcOH (10 mg, 170 umol, 9.72 uL, 0.1 *eq*) in MeOH (1 mL) was added $NaBH_3CN$ (213 mg, 3.40 mmol, 2 *eq*), the mixture was stirred at 25°C for 3h. The reaction mixture was poured into water (10 mL), and then extracted with EtOAc (5 mL x 3). The combined organic layers were washed with brine (5 mL x 1), dried over, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, EtOAC:MeOH=5:1) to give tert-butyl-N-[[4-(propylaminomethyl)phenyl]methyl]carbamate, Bz-27a (200 mg, 718 umol, 42.26% yield)

as colorless oil. ^{1}H NMR (MeOD-d_4, 400 MHz) δ7.43 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 4.24 (s, 2H), 4.17 (s, 2H), 3.00-2.96 (m, 2H), 1.77-1.67 (m, 2H), 1.44 (s, 9H), 1.01 (t, *J* = 7.6 Hz, 3H).

Preparation of Bz-27b: To a solution of 2-amino-8-[3-[3-(hydroxymethyl)azetidin-1-yl]sulfonylphenyl] -3H-1-benzazepine-4-carboxylic acid, Bz-21d (122 mg, 287 umol, 1 *eq*) in DMF (0.80 mL) was added PYAOP (224 mg, 431.05 umol, 1.5 *eq*) and DIEA (111 mg, 862.10 umol, 150.16 uL, 3 *eq*). And then the tert-butyl N-[[4-(propylaminomethyl)phenyl]methyl]carbamate (80 mg, 287 umol, 1 *eq*) was added. The mixture was stirred at 25°C for 3h, which was filtered and concentrated. The residue was purified by prep-HPLC (column: Welch Xtimate C18100*25mm*3um; mobilephase:[water(0.1%TFA)-ACN];B%:30%-50%,12min]). Compound tert-butylN-[[4-[[[2-amino-8-[3-[3-(hydroxymethyl)azetidin-1-yl]sulfonylphenyl] -3H-1- benzazepine-4-carbonyl]-propyl-amino]methyl]phenyl]methyl]carbamate (27 mg, 39.3 umol, 13.66% yield) was obtained as a light yellow solid. ^{1}H NMR (MeOD-d_4, 400 MHz) δ8.08 (t, *J* = 9.6Hz, 2H), 7.92-7.90 (m, 1H),7.82 (t, *J* = 8.4 Hz, 1H), 7.81-7.79 (m, 1H), 7.69-7.64 (m, 4H), 7.57(s, 1H), 7.30-7.29 (m, 4H), 7.13 (s, 1H), 4.23 (s, 2H), 3.87 (t, *J* = 8.4Hz, 2H), 3.61 (t, *J* = 6.0Hz, 2H), 3.42-3.41 (m, 2H), 3.31 (t, *J* = 1.6Hz, 2H), 2.60-2.55 (m, 1H), 1.71-1.70 (m, 2H), 1.44 (s, 9H), 0.99-0.90(m, 3H). LC/MS [M+H] 688.3 (calculated); LC/MS [M+H] 688.3 (observed).

Preparation of Bz-27: To a solution of Bz-27b (50 mg, 72.7 umol,1 *eq*) in DCM (1 mL) was added TFA (165 mg, 1.45 mmol, 108 uL, 20 *eq*), and then stirred at 25°C for 2 h. The mixture was filtered and concentrated. The residue was purified by prep-HPLC(column: Nano-micro Kromasil C18 100*30mm8um;mobilephase:[water(0.1%TFA)-CAN];B%:5%-30%,10min]) to give 2-amino-N-[[4-(aminomethyl)phenyl]methyl]-8-[3-[3-(hydroxymethyl)azetidin-1-yl]sulfonylphenyl]-N-propyl-3H-1-benzazepine-4-carboxamide, Bz-27 (4 mg, 6.81 umol, 9.36% yield) as a white solid. ^{1}H NMR (MeOH-d_4, 400 MHz) δ8.13-8.03 (m, 2H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.85-7.78 (m, 1H), 7.75-7.70 (m, 2H), 7.59-7.33 (m, 5H), 7.15 (s, 1H), 4.13 (s, 2H), 3.86 (t, *J* = 8.4 Hz, 2H), 3.61 (dd, *J* = 6.1, 7.8 Hz, 2H), 3.48 (br d, *J* = 7.6 Hz, 2H), 3.42 (d, *J* = 6.2 Hz, 4H), 3.32 (br s, 1H), 3.31-3.31 (m, 1H), 3.31-3.30 (m, 2H), 2.63-2.52 (m, 1H), 1.76-1.61 (m, 2H), 0.91 (br s, 3H). LC/MS [M+H] 588.3 (calculated); LC/MS [M+H] 588.3 (observed).

Example 24 Synthesis of Bz-28

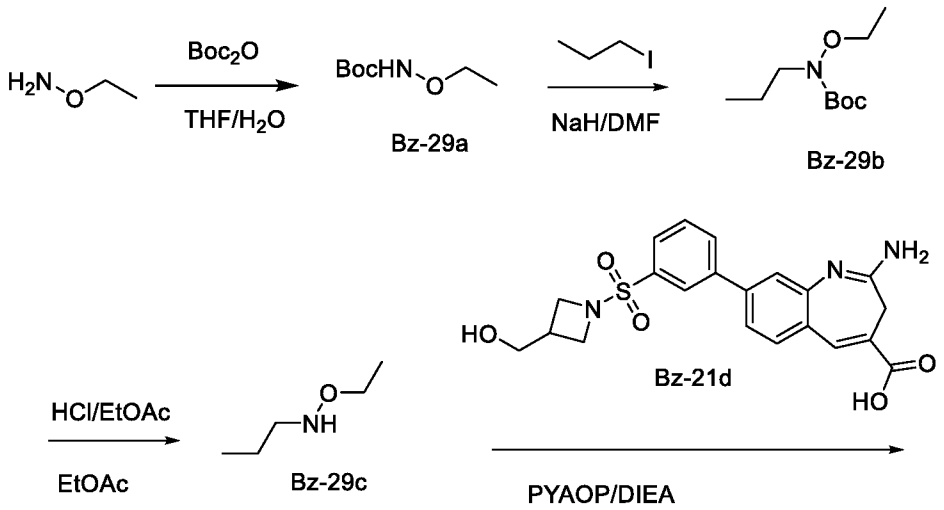


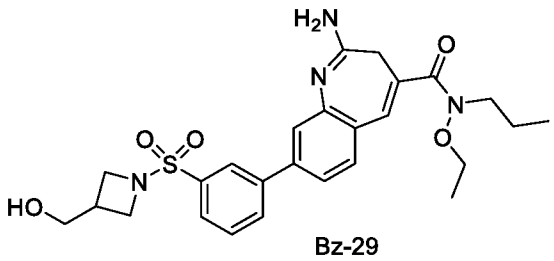
Preparation of Bz-28b: A mixture of 1-[1-(3-bromophenyl)sulfonylazetidin-3-yl]-N,N-dimethyl-methanamine, Bz-28a (0.3 g, 900.24 umol, 1 *eq*), Pin_2B_2 (342.91 mg, 1.35 mmol, 1.5 *eq*), $Pd(dppf)Cl_2$ (32.94 mg, 45.01 umol, 0.05 *eq*) and KOAc (176.70 mg, 1.80 mmol, 2 *eq*) in dioxane (6 mL) was degassed and purged with N_2 for 3 times, and then stirred at 90°C for 2 h under N_2 atmosphere. The reaction mixture was cooled to 25°C, and added with de-Pd silica gel (1 g) and then stirred at 25°C for 30 min. The mixture was filtered and washed with EtOAc (10 mL x 5) and concentrated under reduced pressure to give N,N-dimethyl-1-[1-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]sulfonylazetidin-3-yl]methanamine, Bz-28b (0.6 g, crude) as a yellow oil.

Preparation of Bz-28: A mixture of Bz-28b (699 mg, 920 umol, 1.5 *eq*), tert-butyl N-[4-[(2-amino-8-bromo-3H-1-benzazepine-4-carbonyl)-propyl-amino]but-2-ynyl]carbamate, Bz-26b (300 mg, 613 umol, 1 *eq*), $Pd(dppf)Cl_2$ (22.4 mg, 30.6 umol, 0.05 *eq*) and K_2CO_3 (169 mg, 1.23 mmol, 2 *eq*) in dioxane (20 mL) and H_2O (2 mL) was degassed and purged with N_2 for 3 times, and then stirred at 90°C for 2 h under N_2 atmosphere. The reaction mixture was quenched by addition of H_2O (60 mL) at 0°C, and then extracted with EtOAc(30 mL x 3). The combined organic layers were washed with brine (10 mL x 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, Petroleum ether:Ethyl acetate = 1:0 to 0:1) and then (SiO_2, EtOAc: MeOH = 1:0 to 1:1) to give tert-butyl N-[4-[[2-amino-8-[3-[3-[(dimethylamino)methyl]azetidin-1-yl]sulfonylphenyl]-3H-1-benzazepine-4-carbonyl]-propyl-amino]but-2-ynyl]carbamate, Bz-28 (230 mg crude product, 347 umol, 56.61% yield) as a brown solid. ^1H NMR (MeOD-d_4, 400 MHz) δ8.16-8.06 (m, 2H), 7.97-7.90 (m, 1H), 7.89-7.65 (m, 4H), 7.34 (br s, 1H), 4.34 (s, 2H), 4.01 (t, J = 8.4 Hz, 2H), 3.87 (s, 2H), 3.69 (dd, J = 5.6, 8.4 Hz, 2H), 3.56 (br s, 2H), 3.39 (s,

2H), 3.33 (s, 2H), 3.03-2.89 (m, 1H), 2.82 (s, 6H), 1.81-1.67 (m, 2H), 1.43 (s, 9H), 0.97 (br t, *J* = 6.8 Hz, 3H). LC/MS [M+H] 663.3 (calculated); LC/MS [M+H] 663.3 (observed).

Example 25 Synthesis of Bz-29





Preparation of Bz-29a: To a mixture of O-ethylhydroxylamine (3 g, 30.8 mmol, 1 *eq*, HCl) and Na_2CO_3 (32.6 g, 307.55 mmol, 10 *eq*) in DCM (30 mL) and Water (30 mL) was added tert-butoxycarbonyl tert-butyl carbonate (8.05 g, 36.9 mmol, 8.48 mL, 1.2 *eq*) at 25°C and then stirred for 3hr. The mixture was separated, and the organic layer was dried over Na_2SO_4, concentrated to residue. The crude was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1:0-5:1) to give tert-butyl N-ethoxycarbamate, Bz-29a (4 g, 24.81 mmol, 80.68% yield) as colorless oil. ^{1}H NMR (400MHz, CHLOROFORM-d) δ3.87 (q, *J* = 7.2 Hz, 2H), 1.45 (s, 9H), 1.20 (t, *J* = 7.2 Hz, 3H).

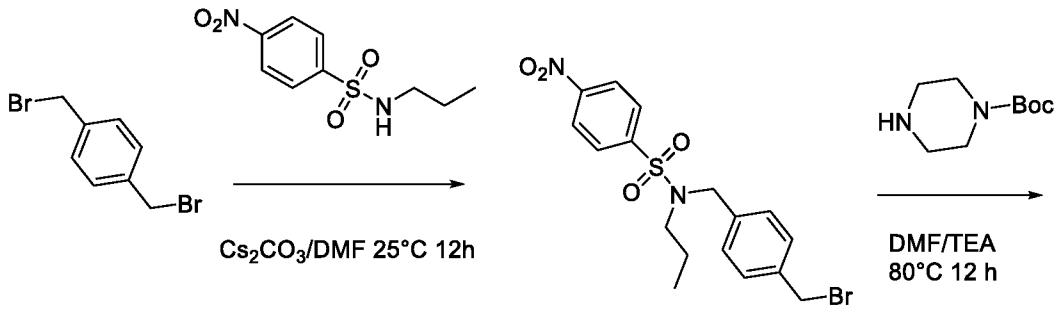
Preparation of Bz-29b: To a mixture of Bz-29a (1 g, 6.20 mmol, 1 *eq*) in DMF (10 mL) was added NaH (298 mg, 7.44 mmol, 60% purity, 1.2 *eq*) at 0°C, and then stirred at 0 °C for 0.5 hr, 1-iodopropane (1.16 g, 6.82 mmol, 666.67 uL, 1.1 *eq*) was added to the mixture at 0 °C and it was stirred at 25 °C for 10 hr. The mixture was quenched with saturated solution of NH_4Cl (10mL), and then extracted with EtOAc (3* 10 mL). The organic layer was dried over Na_2SO_4, concentrated to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1:0-5:1) to give tert-butyl N-ethoxy-N-propyl-carbamate, Bz-29b (0.84 g, 4.13 mmol, 66.61% yield) as colorless oil. ^{1}H NMR (400MHz, CHLOROFORM-d)

δ3.89 (q, *J* = 7.2 Hz, 2H), 3.47-3.25 (m, 2H), 1.69-1.59 (m, 2H), 1.49 (s, 9H), 1.23 (t, *J* = 7.2 Hz, 3H), 0.91 (t, *J* = 7.2 Hz, 3H).

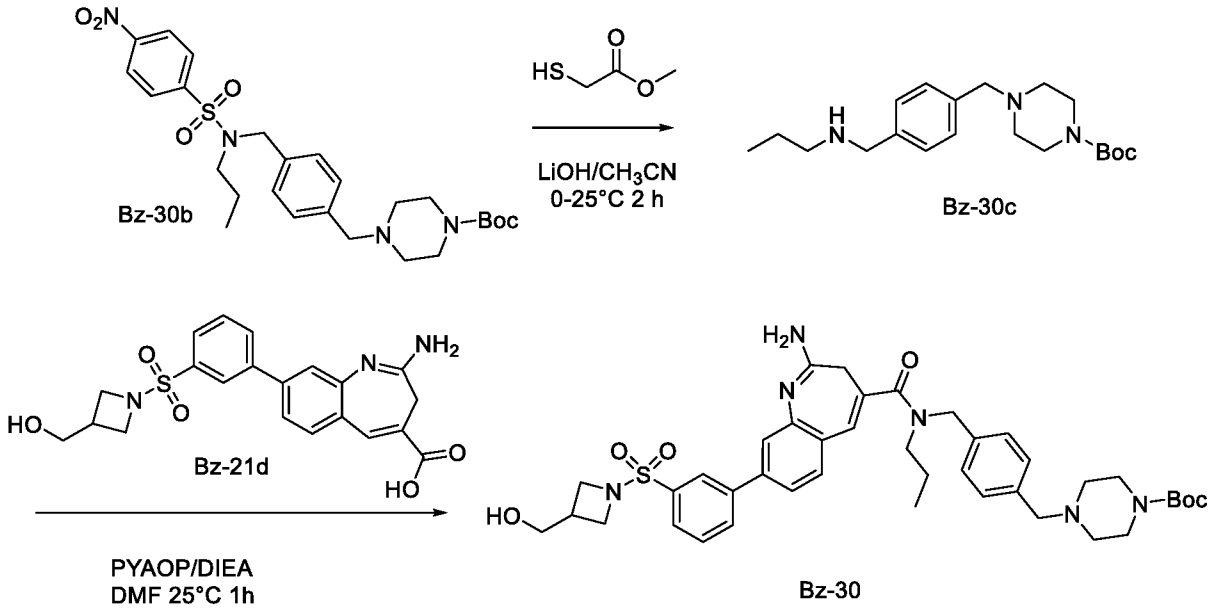
Preparation of Bz-29c: To a mixture of Bz-29b (0.84 g, 4.13 mmol, 1 eq) in EtOAc (10 mL) was added HCl/EtOAc (4 M, 5 mL, 4.84 eq). The mixture was stirred at 25°C for 2 hr. The mixture was concentrated to give N-ethoxypropan-1-amine, Bz-29c (0.4 g, 2.86 mmol, 69.33% yield, HCl) as white solid. ^{1}H NMR (400MHz, METHANOL-d_4) δ4.16 (dq, *J* = 2.0, 7.2 Hz, 2H), 3.29-3.23 (m, 2H), 1.76 (sxt, *J* = 7.6 Hz, 2H), 1.32 (t, *J* = 7.2 Hz, 3H), 1.05 (t, *J* = 7.2 Hz, 3H).

Preparation of Bz-29: To a mixture of 2-amino-8-[3-[3-(hydroxymethyl)azetidin-1-yl]sulfonylphenyl]-3H-1- benzazepine-4-carboxylic acid (200 mg, 468 umol, 1 *eq*) in DMF (2 mL) was added PYAOP (293 mg, 561 umol, 1.2 *eq*) and DIEA (181 mg, 1.40 mmol, 245 uL, 3 *eq*), after 3 min, N-ethoxypropan-1-amine (71.86 mg, 514.65 umol, 1.1 *eq*, HCl) was added. The mixture was stirred at 25°C for 1 hr, and then concentrated to get a residue. The residue was purified by Prep-HPLC (column: Phenomenex Gemini-NX C18 75*30mm*3um;mobile phase: [water(10mM NH4HCO3)-ACN];B%:30%-60%, 10.5min) to give 2-amino-N-ethoxy-8-[3-[3-(hydroxyl methyl)azetidin-1-yl]sulfonylphenyl]-N-propyl-3H-1- benzazepine-4-carboxamide, Bz-29 (3.5 mg, 6.36 umol, 1.36% yield, 93.17% purity) as white solid. ^{1}H NMR (400MHz, METHANOL-d_4) δ8.10-8.02 (m, 2H), 7.89-7.73 (m, 2H), 7.53-7.48 (m, 2H), 7.46-7.40 (m, 1H), 7.31 (s, 1H), 3.95 (q, *J* = 7.2 Hz, 2H), 3.86 (t, *J* = 8.4 Hz, 2H), 3.74 (t, *J* = 7.2 Hz, 2H), 3.60 (dd, *J* = 6.4, 8.2 Hz, 2H), 3.41 (d, *J* = 6.4 Hz, 2H), 3.34-3.31 (m, 2H), 2.67-2.43 (m, 1H), 1.77 (sxt, *J* = 7.2 Hz, 2H), 1.18 (t, *J* = 7.2 Hz, 3H), 0.99 (t, *J* = 7.6 Hz, 3H). LC/MS [M+H] 513.2 (calculated); LC/MS [M+H] 513.4 (observed).

Example 26 Synthesis of Bz-30



Bz-30a



Preparation of Bz-30a: To a mixture of 1,4-bis(bromomethyl)benzene (6.48 g, 24.6 mmol, 2.0 *eq*) and 4-nitro-N- propyl-benzenesulfonamide (3.0 g, 12.3 mmol, 1.0 *eq*) in DMF (40 mL) was added Cs_2CO_3 (4.80 g, 14.7 mmol, 1.2 *eq*) in one portion at 25°C and then stirred for 12 h. The reaction was diluted with water (100 mL) and extracted with EtOAc (50 mL x 3). The organic layer was washed with brine, dried over Na_2SO_4 filtered and concentrated. The residue was purified by silica gel chromatography (Petroleum ether/Ethyl acetate=1/0, 3/1) to afford N-[[4-(bromomethyl)phenyl]methyl]-4-nitro -N-propyl-benzenesulfonamide, Bz-30a (1.5 g, 3.51 mmol, 28.6% yield) as white solid. ^{1}H NMR ($CDCl_3$, 400MHz) δ8.35 (d, *J* = 8.8 Hz, 2H), 7.98 (d, *J* = 8.8 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 4.48 (s, 2H), 4.40 (s, 2H), 3.19-3.11 (m, 2H), 1.42 (m, 2H), 0.76 (t, *J* = 7.6 Hz, 3H).

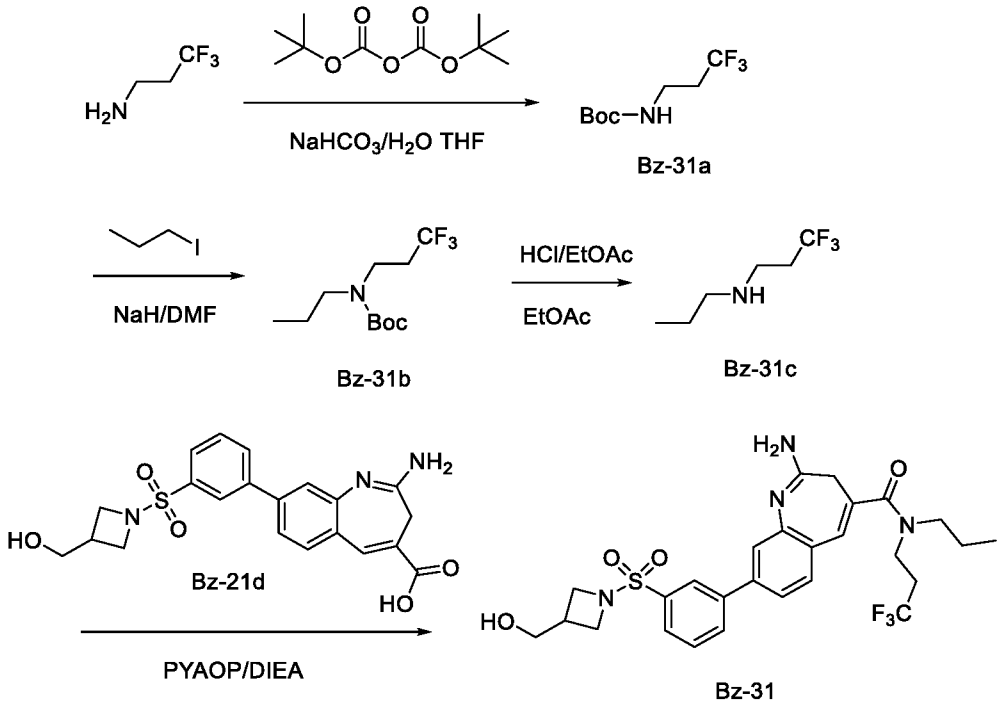
Preparation of Bz-30b: To a mixture of Bz-30a (1.3 g, 3.04 mmol, 1.0 *eq*) and tert-butyl piperazine-1-carboxylate (2.27 g, 12.2 mmol, 4.0 *eq*) in DMF (15 mL) was added Et_3N (1.23 g, 12.2 mmol, 1.69 mL, 4.0 *eq*) at 25 °C and then stirred at 80 °C for 12 h. The mixture was diluted with water (50 mL) and extracted with EtOAc (50 mL x 3). The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography (Petroleum ether/Ethyl acetate=1/0, 3/1) to afford tert-butyl 4-[[4-[[(4-nitrophenyl)sulfonyl-propyl-amino] methyl]phenyl]methyl]piperazine-1-carboxylate, Bz-30b (1.7 g, crude) as yellow solid. ^{1}H NMR (DMSO, 400MHz) δ8.39 (d, *J* = 8.8 Hz, 2H), 8.11 (d, *J* = 8.8 Hz, 2H), 7.21 (s, 4H),4.36 (s, 2H), 3.45 (s, 2H), 3.31-2.27 (m, 4H), 3.12-3.05 (m, 2H), 2.28-2.26 (m, 4H), 1.38 (s, 9H), 1.33-1.25 (m, 2H), 0.65 (t, *J* = 7.6 Hz, 3H).

Preparation of Bz-30c: To a solution of Bz-30b (1.0 g, 1.88 mmol, 1.0 *eq*) in CH_3CN (6 mL) was added $LiOH•H_2O$ (473 mg, 11.3 mmol, 6.0 *eq*) in one portion at 0 °C. Then methyl 2-sulfanylacetate (598 mg, 5.63 mmol, 511 uL, 3.0 *eq*) was added and it was stirred at 25 °C for 2

h. The mixture was filtered and concentrated. The residue was diluted with MTBE (5 ml) and then adjusted the pH of the mixture to about 2 with aq. HCl (1M), extracted with MTBE (20 mL) (discarded). The aqueous phase was adjusted pH = 9 with aq.$NaHCO_3$ and then extracted with EtOAc (30 mL x 3). The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated to obtain tert-butyl 4-[[4-(propylaminomethyl)phenyl] methyl]piperazine-1-carboxylate, Bz-30c (0.5 g, crude) as yellow oil. ^{1}H NMR (MeOD, 400MHz) δ7.32-7.30 (m, 4H), 3.73 (s, 2H), 3.53 (s, 2H), 3.43-3.40 (m, 4H), 2.57-2.50 (m, 2H), 2.41-2.48 (m, 4H), 1.58-1.51 (m, 2H), 1.45 (s, 9H), 0.92 (t, *J* = 7.6 Hz, 3H).

Preparation of Bz-30: To a mixture of 2-amino-8-[3-[3-(hydroxymethyl)azetidin-1-yl]sulfonylphenyl]-3H-1- benzazepine-4-carboxylic acid, Bz-21d (400 mg, 936 umol, 1.0 *eq*) in DMF (8 mL) was added PYAOP (585 mg, 1.12 mmol, 1.2 *eq*), DIEA (363 mg, 2.81 mmol, 489 uL, 3.0 *eq*) and Bz-30c (358 mg, 1.03 mmol, 1.1 *eq*) in one portion at 25°C and then stirred for 1 h. The mixture was filtered and concentrated. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 100 * 30mm * 5um; mobile phase: [water (0.1%TFA) - ACN]; B%: 15%-45%, 10min) to give tert-butyl 4-[[4-[[[2-amino-8-[3-[3-(hydroxymethyl)azetidin-1-yl]sulfonylphenyl]-3H-1-benzazepine-4-carbonyl]-propyl-amino]methyl]phenyl]methyl]piperazine-1-carboxylate, Bz-30 (0.35 g, 462 umol, 49.4% yield) as white solid. ^{1}H NMR (MeOD, 400MHz) δ 8.14-8.05 (m, 2H), 7.92 (d, *J* = 7.6 Hz, 1H), 7.82 (t, *J* = 7.6 Hz, 1H), 7.78-7.69 (m, 2H), 7.63-7.42 (m, 5H), 7.17 (s, 1H), 4.37 (s, 2H), 3.86 (t, *J* = 8.0 Hz, 2H), 3.61 (dd, *J* = 6.0, 8.0 Hz, 2H), 3.53-3.49 (m, 2H), 3.43-3.41 (m, 6H), 3.31-3.29 (m, 8H), 2.63-2.54 (m, 1H), 1.76-1.65 (m, 2H), 1.47 (s, 9H), 0.95-0.89 (m, 3H). LC/MS [M+H] 757.4 (calculated); LC/MS [M+H] 757.4 (observed).

Example 27 Synthesis of Bz-31



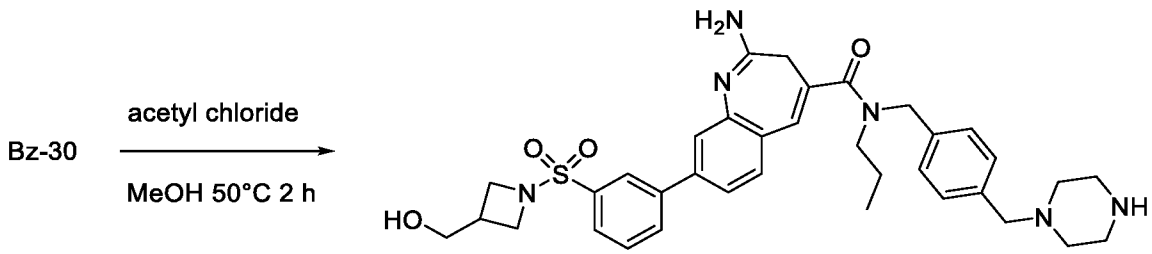
Preparation of Bz-31a: To a mixture of 3,3,3-trifluoropropan-1-amine (0.5 g, 3.34 mmol, 1 *eq*, HCl) and $NaHCO_3$ (842.64 mg, 10.03 mmol, 390.11 uL, 3 *eq*) in THF (3 mL) and H_2O (3 mL) was added tert-butoxycarbonyl tert-butyl carbonate (730 mg, 3.34 mmol, 768 uL, 1 *eq*), and then stirred at 25°C for 1 h under N_2 atmosphere. The mixture was poured into H_2O (15 mL), extracted with ethyl acetate (15 mL x 3). The combined organic phase was washed with brine (15 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The crude product was purified by silica gel chromatography eluted with (Petroleum ether:Ethyl acetate = 5:0 to 1:1) to give tert-butyl N-(3,3,3-trifluoropropyl)carbamate, Bz-31a (500 mg, 2.35 mmol, 70.14% yield) as a colorless oil. ^1H NMR ($CDCl_3$, 400 MHz) δ4.75 (br s, 1H), 3.40 (q, J = 6.4 Hz, 2H), 2.40-2.27 (m, 2H), 1.45 (s, 9H).

Preparation of Bz-31b: To a solution of Bz-31a (400 mg, 1.88 mmol, 1 *eq*) in DMF (5 mL) was added NaH (113 mg, 2.81 mmol, 60% purity, 1.5 *eq*) at 0°C. After 30 min, 1-iodopropane (637.88 mg, 3.75 mmol, 366 uL, 2 *eq*) was added to the mixture and then stirred at 20°C for 2 h. The reaction mixture was quenched at 0°C by the addition of saturated NH_4Cl (10 mL), then extracted with EtOAc (10 mL x 3). The organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The reaction mixture was purified by silica gel column chromatography (Petroleum ether:Ethyl acetate = 5:1 to 1:1). Compound tert-butyl N-propyl-N-(3,3,3-trifluoropropyl)carbamate, Bz-31b (400 mg, 1.57 mmol, 83.52% yield) was obtained as a colorless oil. ^1H NMR ($CDCl_3$, 400 MHz) δ3.41 (t, J = 7.2 Hz, 2H), 3.19-3.12 (m, 1H), 2.40-2.32 (m, 2H), 1.58-1.50 (m, 2H), 1.47 (s, 9H), 0.89 (t, J = 7.6 Hz, 3H).

Preparation of Bz-31c: To a solution of tert-butyl N-propyl-N-(3,3,3-trifluoropropyl)carbamate (400 mg, 1.57 mmol, 1 *eq*) in EtOAc (3 mL) was added HCl/EtOAc (4 M, 5.88 mL, 15 *eq*) and then stirred at 20°C for 2 h. The mixture was filtered and concentrated in vacuum to give 3,3,3-trifluoro-N-propyl-propan-1-amine, Bz-31c (240 mg, crude, HCl) as a white solid. ^{1}H NMR (MeOD-d_4, 400 MHz) δ3.34-3.31 (m, 2H), 3.06-3.00 (m,

Preparation of Bz-31: a solution of 2-amino-8-[3-[3-(hydroxymethyl)azetidin-1-yl]sulfonylphenyl] -3H-1-benzazepine-4-carboxylic acid, Bz-21d (100 mg, 233 umol, 1 *eq*), DIEA (90.7 mg, 702 umol, 122 uL, 3 *eq*) and PYAOP (183 mg, 351 umol, 1.5 *eq*) in DMF (1 mL) was added Bz-31c (44.8 mg, 234 umol, 1 *eq*, HCl), and then stirred at 20 °C for 1 h. The mixture was filtered and concentrated in vacuum. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100*30mm*10um;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 30%-60%,8min) to afford 2-amino-8-[3-[3-(hydroxymethyl)azetidin-1-yl]sulfonylphenyl]-N-propyl-N-(3,3,3-trifluoropropyl)-3H-1-benzazepine-4-carboxamide, Bz-31 (7 mg, 12.40 umol, 5.30% yield) as a white solid. ^{1}H NMR (MeOD-d_4,400MHz) δ8.07 (s, 1H), 8.04 (br d, J = 7.6 Hz, 1H), 7.86-7.81 (m, 1H), 7.80-7.73 (m, 1H), 7.49-7.44 (m, 2H), 7.42-7.37 (m, 1H), 6.94 (s, 1H), 3.86 (t, J = 8.4 Hz, 2H), 3.73 (br s, 2H), 3.60 (dd, J = 6.0, 8.0 Hz, 2H), 3.52-3.45 (m, 2H), 3.42 (d, J = 6.4 Hz, 2H), 3.33-3.32 (m, 2H), 2.68-2.53 (m, 3H), 1.74-1.64 (m, 2H), 0.91 (br s, 3H). LC/MS [M+H] 565.2 (calculated); LC/MS [M+H] 565.3 (observed).

Example 28 Synthesis of Bz-32

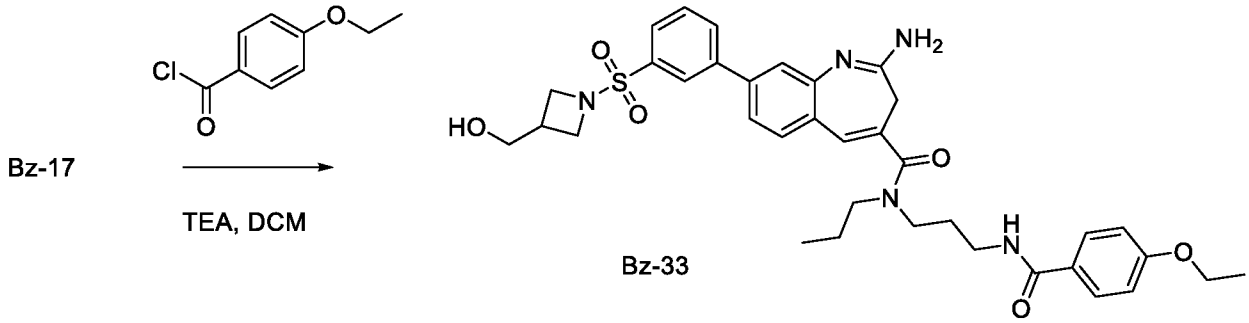


Bz-32

Preparation of Bz-32: To a solution of tert-butyl 4-[[4-[[[2-amino-8-[3-[3-(hydroxymethyl)azetidin-1-yl] sulfonylphenyl]-3H-1-benzazepine-4-carbonyl]-propyl-amino]methyl]phenyl]methyl]piperazine-1-carboxylate, Bz-30 (0.16 g, 211 umol, 1.0 *eq*) in MeOH (10 mL) was added acetyl chloride (49.8 mg, 634 umol, 45.3 uL, 3.0 *eq*) at 25°C and it was stirred at 50°C for 2 h. The mixture was concentrated in vacuum, and the residue was purification by prep-HPLC (column: Waters Xbridge BEH C18 100*25mm*5um;mobile phase: [water(10mM NH4HCO3)-ACN];B%: 25%-55%,10min) to give 2-amino-8-[3-[3-(hydroxymethyl)azetidin-1-yl]sulfonylphenyl]- N-[[4-(piperazin-1-ylmethyl)phenyl]methyl]-N-propyl-3H-1-benzazepine-4-carboxamide, Bz-32 (36 mg, 54.8 umol, 25.9% yield) as white

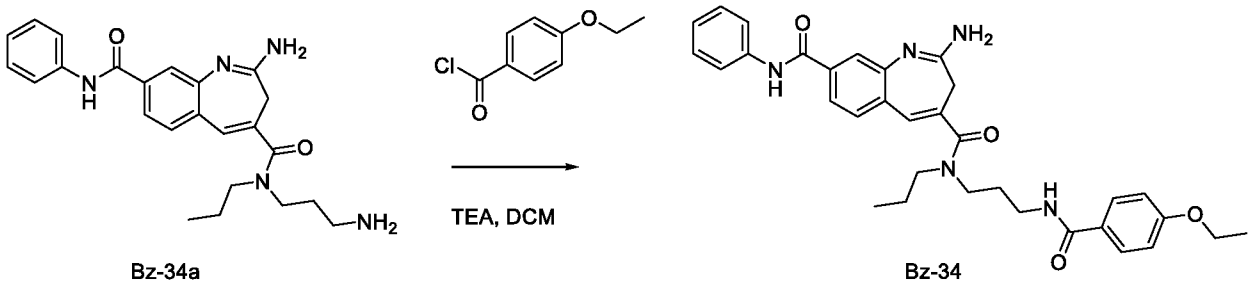
solid. ^{1}H NMR (MeOD, 400MHz) δ8.06 (s, 1H), 8.02 (d, J = 7.6 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.79-7.72 (m, 1H), 7.46 (s, 2H), 7.40-7.22 (m, 5H), 6.93 (s, 1H), 4.74 (s, 2H), 3.85 (t, J = 8.4 Hz, 2H), 3.62-3.56 (m, 2H), 3.52 (s, 2H), 3.45-3.34 (m, 4H), 2.85 (t, J = 4.4 Hz, 4H), 2.66-2.52 (m, 2H), 2.48-2.44 (m, 4H), 1.72-1.60 (m, 2H), 0.90-0.88 (m, 3H). LC/MS [M+H] 657.3 (calculated); LC/MS [M+H] 657.5 (observed).

Example 29 Synthesis of Bz-33



2-Amino-*N*-(3-aminopropyl)-8-(3-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-*N*-propyl-3*H*-benzo[*b*]azepine-4-carboxamide, Bz-17 (0.01 g, 0.019 mmol, 1 eq.) was dissolved in DCM. Triethylamine (4 µl, 0.029 mmol, 1.5 eq.) was added, followed by 4-ethoxybenzoyl chloride (0.004 g, 0.019 mmol, 1 eq.). The reaction was stirred at room temperature, then concentrated and purified by HPLC to give 2-amino-*N*-(3-(4-ethoxybenzamido)propyl)-8-(3-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-*N*-propyl-3*H*-benzo[*b*]azepine-4-carboxamide, Bz-33 (0.0028 g, 0.0042 mmol, 22%). LC/MS [M+H] 674.30 (calculated); LC/MS [M+H] 674.74 (observed).

Example 30 Synthesis of Bz-34



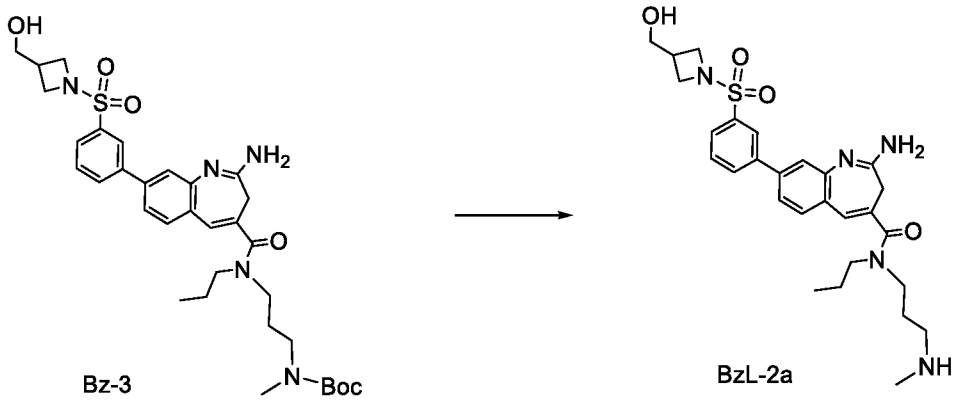
2-Amino-N^4-(3-aminopropyl)-N^8-phenyl-N^4-propyl-3*H*-benzo[*b*]azepine-4,8-dicarboxamide, Bz-34a (0.01 g, 0.024 mmol, 1 eq.) was dissolved in DCM. Triethylamine (5 µl, 0.036 mmol, 1.5 eq.) was added, followed by 4-ethoxybenzoyl chloride (0.004 g, 0.024 mmol, 1 eq.). The reaction was stirred at room temperature, then concentrated and purified by HPLC to give 2-amino-N^4-(3-(4-ethoxybenzamido)propyl)-N^8-phenyl-N^4-propyl-3*H*-benzo[*b*]azepine-4,8-dicarboxamide, Bz-34 (0.005 g, 0.009 mmol, 38%). LC/MS [M+H] 568.29 (calculated); LC/MS [M+H] 568.50 (observed).

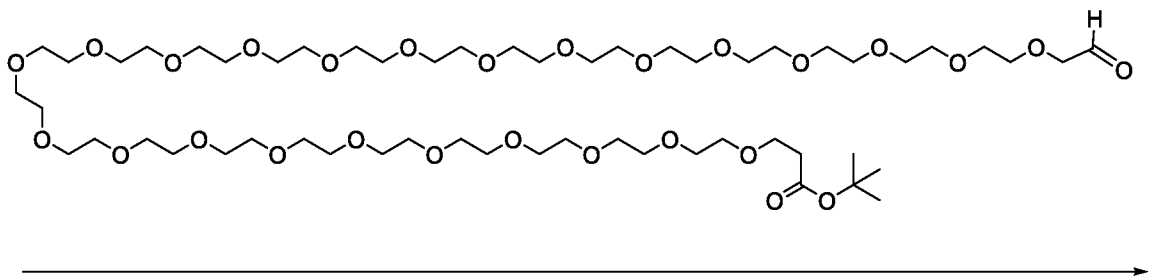
Preparation of Aminobenzazepine-linker Formula II compounds (BzL) and intermediates

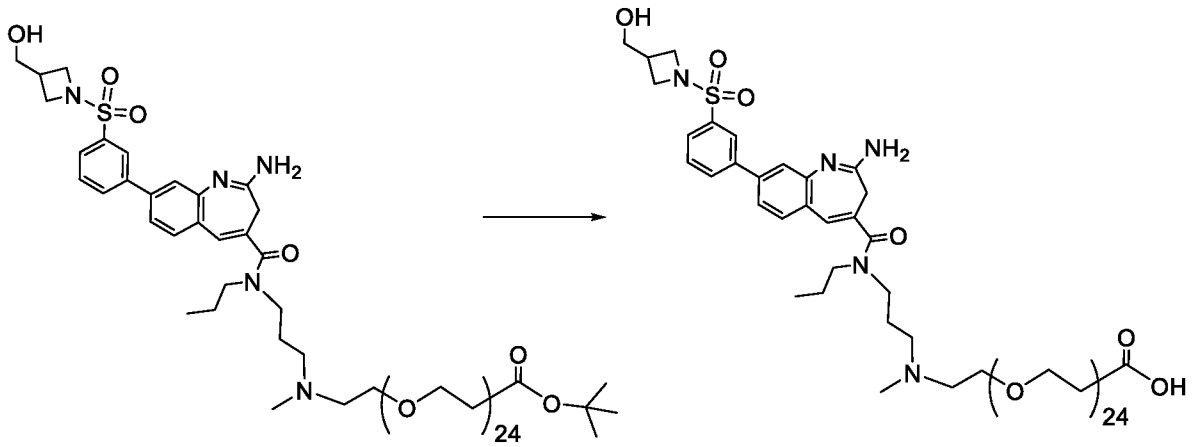
Example 31 Synthesis of BzL-1

Following the procedures described herein, ethyl 2-amino-8-(3-((2-(2-(3-oxo-3-(2,3,5,6-tetrafluorophenoxy)propoxy)ethoxy)ethyl)carbamoyl)phenyl)-3H-benzo[b]azepine-4-carboxylate, BzL-1 was prepared and characterized.

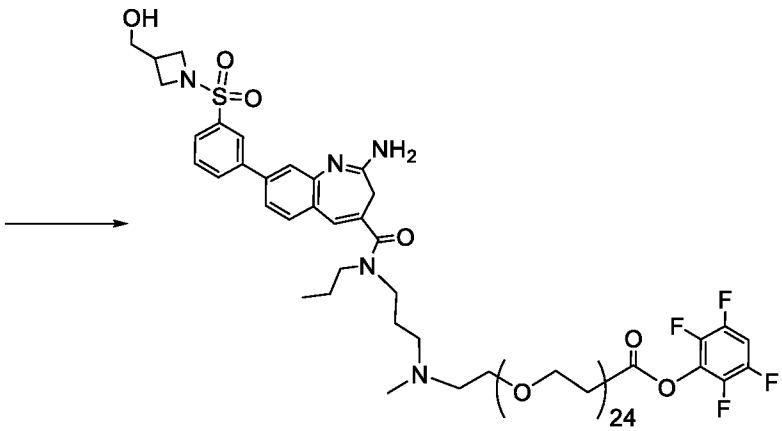
Example 32 Synthesis of BzL-2







BzL-2b BzL-2c



BzL-2

Synthesis of 2-amino-8-(3-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-*N*-(3-(methylamino)propyl)-*N*-propyl-3*H*-benzo[*b*]azepine-4-carboxamide, BzL-2a

BzL-2a was synthesized from Bz-3 according to the procedure described for Bz-11a. LC/MS [M+H] 540.26 (calculated); LC/MS [M+H] 540.53 (observed).

Synthesis of *tert*-butyl 80-(2-amino-8-(3-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-3*H*-benzo[*b*]azepine-4-carbonyl)-76-methyl-4,7,10,13,16,19,22,25,28,31,34,37,40,43,46,49,52,55,58,61,64,67,70,73-tetracosaoxa-76,80-diazatrioctacontanoate, BzL-2b.

A vial was charged with BzL-2a (15.1 mg, 0.028 mmol), tert-butyl 1-oxo-3,6,9,12,15,18,21,24,27,30,33,36,39,42,45,48,51,54,57,60,63,66,69,72-tetracosaoxapentaheptacontan-75-oate (0.042 mmol), sodium triacetoxyborohydride (30 mg, 0.14 mmol) in 100 µL DMF. The reaction was stirred for 5 h, upon which 100 µL of 10% sodium carbonate was added and stirred for 1h. The mixture was filtered and purified by reverse phase preparative HPLC utilizing a 25-75% gradient of acetonitrile:water containing 0.1%

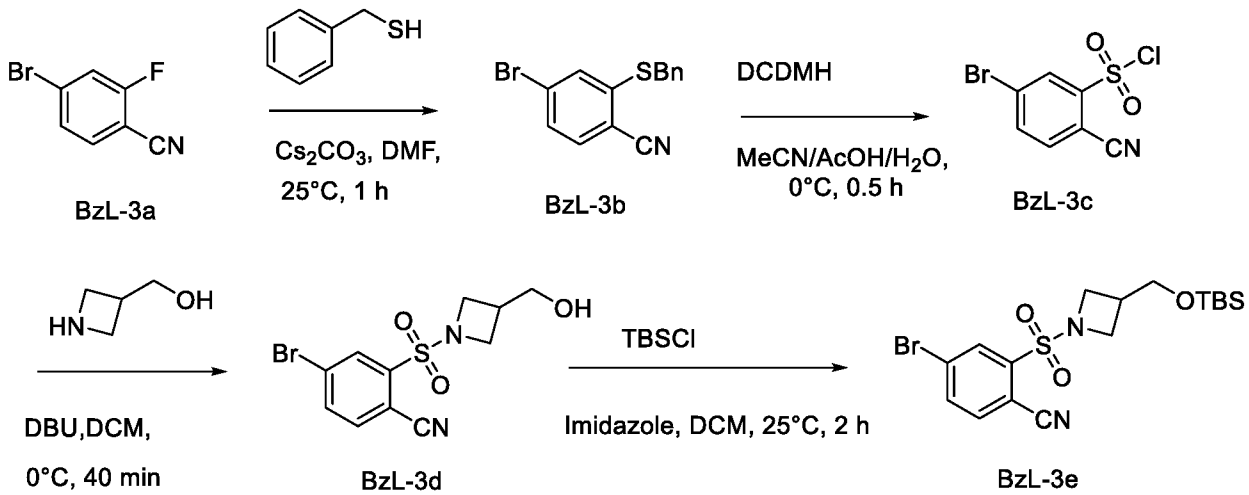
trifluoroacetic acid. The purified fractions were combined and lyophilized to afford 40.7 mg of BzL-2b in 84% yield. LC/MS [M+H] 1724.98 (calculated); LC/MS [M+H] 1726.52 (observed).

Synthesis of 80-(2-amino-8-(3-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-3*H*-benzo[*b*]azepine-4-carbonyl)-76-methyl-4,7,10,13,16,19,22,25,28,31,34,37,40,43,46,49,52,55,58,61,64,67,70,73-tetracosaoxa-76,80-diazatrioctacontanoic acid, BzL-2c.

A vial was charged with BzL-2b (18 mg, 0.010 mmol), 300 µL DCM, and 100 µL trifluoroacetic acid. The reaction was maintained for 45min, concentrated under vacuum, and azeotroped thrice with 1 mL toluene. The reaction was taken forward without any further purification.

2,3,5,6-Tetrafluorophenyl 80-(2-amino-8-(3-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-3*H*-benzo[*b*]azepine-4-carbonyl)-76-methyl-4,7,10,13,16,19,22,25,28,31,34,37,40,43,46,49,52,55,58,61,64,67,70,73-tetracosaoxa-76,80-diazatrioctacontanoate, BzL-2 was synthesized according to the procedure described for BzL-22. LC/MS [M+H] 1816.91 (calculated); LC/MS [M+H] 1818.51 (observed).

Example 33 Synthesis of BzL-3



Synthesis of 2-benzylsulfanyl-4-bromo-benzonitrile, BzL-3b

To a mixture of phenylmethanethiol (3.10 g, 25.00 mmol, 2.93 mL, 1 eq) and 4-bromo-2-fluoro-benzonitrile, BzL-3a (5 g, 25.00 mmol, 1 eq) in DMF (10 mL) was added Cs_2CO_3 (12.22 g, 37.50 mmol, 1.5 eq) at 25°C. The mixture was stirred at 25 °C for 1 hour. TLC and LCMS showed the reaction was completed. The mixture was poured into ice water (100 mL), stirred for 5 min and filtered to give BzL-3b (4 g, 13.15 mmol, 52.60% yield) as a white solid which was used into next step without further purification. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.50 (d, J = 2.0 Hz, 1H), 7.47-7.43 (m, 1H), 7.41-7.38 (m, 1H), 7.35-7.28 (m, 5H), 4.23 (s, 2H).

Synthesis of 5-bromo-2-cyano-benzenesulfonyl chloride, BzL-3c

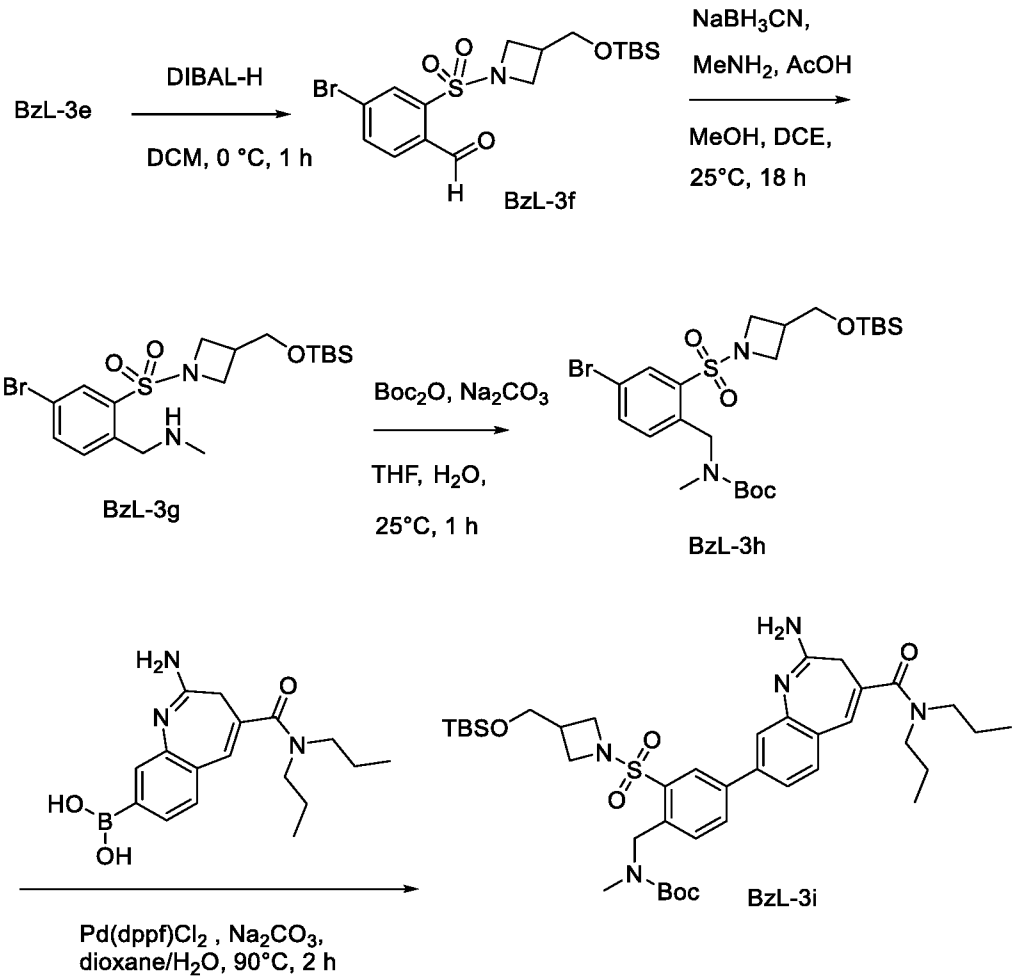
To a mixture of 2-benzylsulfanyl-4-bromo-benzonitrile (1 g, 3.29 mmol, 1 eq) in CH_3CN (20 mL), AcOH (0.7 mL) and H_2O (0.5 mL) was added 1,3-dichloro-5,5- imethyl-imidazolidine-2,4-dione (1.30 g, 6.57 mmol, 2 eq) in portions at 0°C. The mixture was stirred at 0°C for 30 min. TLC and LCMS showed the reaction was completed. The mixture was poured into ice water (50 mL) and stirred for 2 min. The aqueous phase was extracted with DCM (20 mL x 2). The combined organic phase was washed with brine (30 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (Petroleum ether/Ethyl acetate=20/1, 10/1) to afford BzL-3c (0.8 g, 2.85 mmol, 86.75% yield) as a white solid. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.34 (d, J = 2.0 Hz, 1H), 7.99 (dd, J = 8.4, 2.0 Hz, 1H), 7.83 (d, J = 8.4 Hz, 1H).

Synthesis of 4-bromo-2-[3-(hydroxymethyl)azetidin-1-yl]sulfonyl-benzonitrile, BzL-3d

To a mixture of azetidin-3-ylmethanol (1.54 g, 12.48 mmol, 1 eq, HCl) in DCM (100 mL) was added DBU (3.80 g, 24.95 mmol, 3.76 mL, 2 eq) dropwise at 0 °C and stirred for 10 min. The mixture was added 5-bromo-2-cyano-benzenesulfonyl chloride, BzL-3c (3.5 g, 12.48 mmol, 1 eq) and stirred at 0°C for 30 min. TLC showed the reaction was completed. The mixture was poured into ice water (100 mL) and stirred for 2 min. The aqueous phase was extracted with DCM (50 mL x 3). The combined organic phase was washed with brine (20 mL), dried with anhydrous Na_2SO_4, filtered and concentrated to obtain BzL-3d (3.5 g, crude) as colorless oil which was used into the next step without further purification.

Synthesis of 4-bromo-2-[3-[[tert-butyl(dimethyl)silyl]oxymethyl]azetidin-1-yl]sulfonyl-benzonitrile, BzL-3e

To a mixture of 4-bromo-2-[3-(hydroxymethyl)azetidin-1-yl]sulfonyl-benzonitrile, BzL-3d (3.5 g, 10.57 mmol, 1 eq) and tert-butyldimethylsilyl chloride, TBSCl (1.91 g, 12.68 mmol, 1.55 mL, 1.2 eq) in DCM (30 mL) was added imidazole (1.08 g, 15.85 mmol, 1.5 eq) in one portion at 25°C. The mixture was stirred at 25°C for 2 hours. LCMS showed the reaction was completed. The mixture was poured into ice water (200 mL) and stirred for 2 min. The aqueous phase was extracted with DCM (100 mL x 3).The combined organic phase was washed with brine (50 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (Petroleum ether/Ethyl acetate=20/1, 10/1) to afford BzL-3e (3.8 g, 8.53 mmol, 80.72% yield) as colorless oil. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.20 (d, J = 2.0 Hz, 1H), 7.82 (dd, J = 8.4, 2.0 Hz, 1H), 7.72 (d, J = 8.4 Hz, 1H), 4.10-4.06 (m, 2H), 3.96-3.93 (m, 2H), 3.68 (d, J = 5.2 Hz, 2H), 2.82-2.76 (m, 1H), 0.86 (s, 9H), 0.00 (s, 6H).



Synthesis of 4-bromo-2-[3-[[tert-butyl(dimethyl)silyl]oxymethyl]azetidin-1-yl]sulfonyl-benzaldehyde, BzL-3f

To a solution of 4-bromo-2-[3-[[tert-butyl(dimethyl)silyl]oxymethyl]azetidin-1-yl] sulfonyl-benzonitrile, BzL-3e (3.8 g, 8.53 mmol, 1 eq) in DCM (100 mL) was added diisobutylaluminum hydride, DIBAL-H (1 M, 9.38 mL, 1.1 eq) dropwise at 0 °C under N_2. The mixture was stirred at 0°C for 1 hour. LCMS showed the reaction was completed. The mixture was added saturated aqueous NH_4Cl (3 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, Petroleum ether/Ethyl acetate=20/1, 5/1) to give BzL-3f (3.5 g, 7.80 mmol, 91.49% yield) as a light yellow oil. ^1H NMR ($CDCl_3$, 400 MHz) δ 10.69 (s, 1H), 8.16 (d, J = 1.6 Hz, 1H), 7.97 (d, J = 8.4 Hz, 1H), 7.86 (dd, J = 1.6, 8.4 Hz, 1H), 3.95-3.88 (m, 2H), 3.81-3.76 (m, 2H), 3.65-3.64 (m, 2H), 2.85-2.71 (m, 1H), 0.85 (s, 8H), 0.03 (s, 6H).

Synthesis of 1-[4-bromo-2-[3-[[tert-butyl(dimethyl)silyl]oxymethyl] azetidin-1-yl]sulfonyl-phenyl]-N-methyl-methanamine, BzL-3g

To a solution of methanamine (4.16 g, 40.14 mmol, 5 *eq*) (30 % in MeOH) and 4-bromo-2-[3-[[tert-butyl(dimethyl)silyl]oxymethyl]azetidin-1-yl]sulfonyl-benzaldehde, BzL-3f

(3.6 g, 8.03 mmol, 1 *eq*) in MeOH (15 mL) and DCE (15 mL) was added AcOH(482.08 mg, 8.03 mmol, 459.12 µL, 1 *eq*) and $NaBH_3CN$ (1.26 g, 20.07 mmol, 2.5 *eq*). The mixture was stirred at 25°C for 18 hrs. The mixture was added a few drops of water and concentrated. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1:1) to obtain BzL-3g (2 g, 4.31 mmol, 53.75% yield) as colorless oil. ^1H NMR (DMSO-d_6, 400 MHz) δ 8.09-8.06 (m, 1H), 8.01-7.99 (m, 1H), 7.71 (d, J = 8.4 Hz, 1H), 4.27 (s, 2H), 3.85-3.80 (m, 2H), 3.62-3.58 (m, 2H), 3.55 (d, J = 5.2 Hz, 2H), 2.69-2.75 (m, 1H), 2.56 (s, 3H), 0.82 (s, 9H), 0.00 (s, 6H)

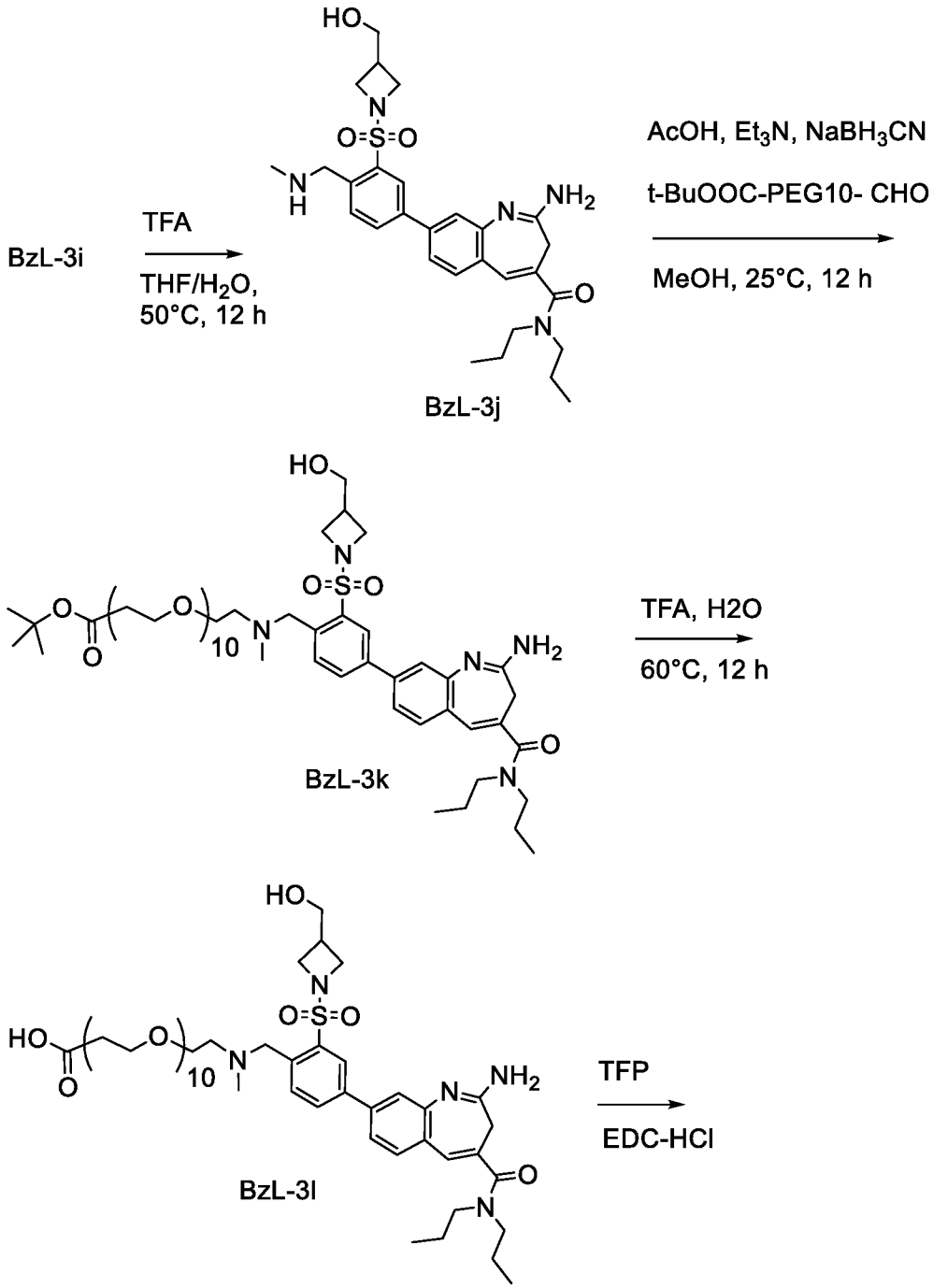
Synthesis of tert-butyl N-[[4-bromo-2-[3-[[tert-butyl(dimethyl)silyl] oxymethyl]azetidin-1-yl]sulfonyl-phenyl]methyl]-N-methyl-carbamate, BzL-3h

To a mixture of 1-[4-bromo-2-[3-[[tert-butyl(dimethyl)silyl]oxymethyl]azetidin-1-yl]sulfonyl-phenyl]-N-methyl-methanamine, BzL-3g (2 g, 4.31 mmol, 1 *eq*) in THF (15 mL) and H_2O (3 mL) was added Na_2CO_3 (914.68 mg, 8.63 mmol, 2 *eq*) and Boc_2O (1.41 g, 6.47 mmol, 1.49 mL, 1.5 *eq*) in one portion at 25 °C. The mixture was stirred at 25 °C for 1 hr. The mixture was poured into ice water (10 mL) and stirred for 1 min. The aqueous phase was extracted with ethyl acetate (10 mL x 3). The combined organic phase was washed with brine (20 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 2 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient at 45 mL/min) to give BzL-3h (1.4 g, 2.48 mmol, 57.57% yield) was obtained as colorless oil. ^1H NMR (DMSO-d_6, 400 MHz) δ 8.00-7.99 (m, 2H), 7.23 (d, J = 8.4 Hz, 1H), 4.66 (s, 2H), 3.85-3.79 (m, 2H), 3.61-3.57 (m, 4H), 2.85 (s, 3H), 2.51-2.49 (m, 1H), 1.47-1.31 (m, 9H), 0.81 (s, 9H), -0.01 (s, 6H)

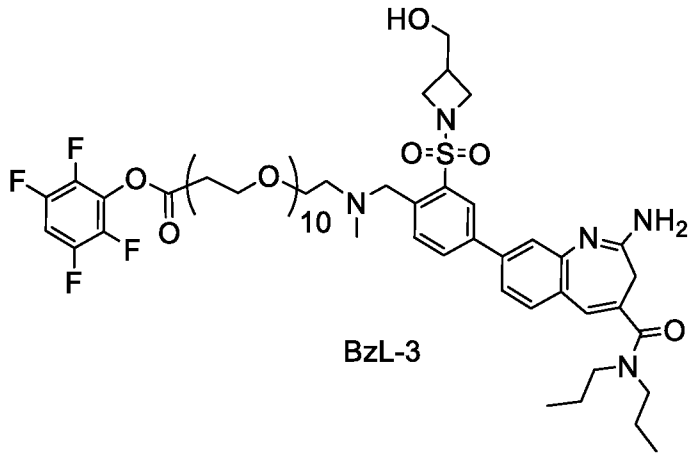
Synthesis of tert-butyl N-[[4-[2-amino-4-(dipropylcarbamoyl)-3H-1- benzazepin-8-yl]-2-[3-[[tert-butyl(dimethyl)silyl]oxymethyl]azetidin-1-yl]sulfonyl-phenyl]methyl]-N-methyl-carbamate, BzL-3i

To a mixture of [2-amino-4-(dipropylcarbamoyl)-3H-1-benzazepin-8-yl]boronic acid (360 mg, 1.09 mmol, 1 *eq*) and tert-butyl N-[[4-bromo-2-[3-[[tert-butyl(dimethyl)silyl] oxymethyl]azetidin-1- yl]sulfonyl-phenyl]methyl]-N-methyl-carbamate, BzL-3h (616.35 mg, 1.09 mmol, 1 *eq*) in dioxane (3 mL) and H_2O (0.5 mL) was added $Pd(dppf)Cl_2$ (80.02 mg, 109.36 µmol, 0.1 *eq*) and Na_2CO_3 (231.81 mg, 2.19 mmol, 2 *eq*) in one portion at 25 °C under N_2. The mixture was stirred at 90 °C for 2 hrs. The mixture was filtered and concentrated. The residue was poured into H_2O (20 mL) and extracted with ethyl acetate (20 mL x 2). The combined organic phase was washed with brine (20 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 1 g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether

gradient at 75 mL/min) to obtain BzL-3i (360 mg, 468.69 µmol, 42.86% yield) was obtained as yellow solid.



5



BzL-3

Synthesis of 2-amino-8-[3-[3-(hydroxymethyl)azetidin-1-yl]sulfonyl-4-(methylamineomethyl)phenyl]-N,N-dipropyl-3H-1-benzazepine-4-carboxamide, BzL-3j

A mixture of tert-butyl N-[[4-[2-amino-4-(dipropylcarbamoyl)-3H-1-benzazepin-8-yl] -2-[3-[[tert-butyl(dimethyl)silyl]oxymethyl]azetidin-1-yl]sulfonyl-phenyl]methyl]-N-methyl-carbamate, BzL-3i (170 mg, 221.33 μmol, 1 *eq*) in THF (5 mL) and H_2O (1 mL) was added TFA (504.72 mg, 4.43 mmol, 327.74 μL, 20 *eq*) the mixture was stirred at 50°C for 12 hrs. LC-MS showed reactant 1 was consumed completely and one main peak with desired mass was detected. The reaction mixture was filtered, and the filtrate was concentrated under reduced. The residue was purified by prep-HPLC (column: Nano-micro Kromasil C18 100 x 30mm 5um;mobile phase: [water(0.1%TFA)-ACN];B%: 20%-45%,10min) to give BzL-3j (95 mg crude) product as a yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.49 (s, 1H), 9.88 (s, 1H), 9.50 (s, 1H), 8.87 (s, 2H), 8.24-8.22 (m, 1H), 8.17-8.16 (m, 1H), 7.92-7.90 (m, 1H), 7.74-7.71 (m, 1H), 7.67-7.70 (m, 2H), 7.06 (s, 1H), 4.79 (s, 1H), 4.46 (s, 2H), 3.85 (t, J = 8.0 Hz, 2H), 3.61 (t, J = 4.0 Hz, 2H), 3.35 (s, 4H), 2.67 (s, 3H), 2.64-2.55 (m, 2H), 1.74-1.39 (m, 4H), 0.86-0.80 (m, 6H). LC/MS [M+H] 554.28 (calculated); LC/MS [M+H] 554.40 (observed).

Synthesis of tert-butyl 3-[2-[2-[2-[2-[2-[2-[2-[2-[2-[2-[[4-[2-amino- 4-(dipropylcarbamoyl)-3H-1-benzazepin-8-yl]-2-[3-(hydroxymethyl)azetidin-1-yl]sulfonyl-phenyl]methyl-methyl-amino]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]propanoate, BzL-3k

To a mixture of 2-amino-8-[3-[3-(hydroxymethyl)azetidin-1-yl]sulfonyl-4-(methylaminomethyl)phenyl]-N,N-dipropyl-3H-1-benzazepine-4-carboxamide, BzL-3j (0.05 g, 90.30 μmol, 1 *eq*) and tert-butyl 3-[2-[2-[2-[2-[2-[2-[2-[2-[2-(2-oxoethoxy)ethoxy] ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]propanoate, t-BuOOC-PEG10-CHO (52.80 mg, 90.30 μmol, 1 *eq*) in MeOH (2 mL) was added Et_3N (27.41 mg, 270.90 μmol, 37.71 μL, 3 *eq*) and AcOH (5.42 mg, 90.30 μmol, 5.16 μL, 1 *eq*) and $NaBH_3CN$ (14.19 mg,

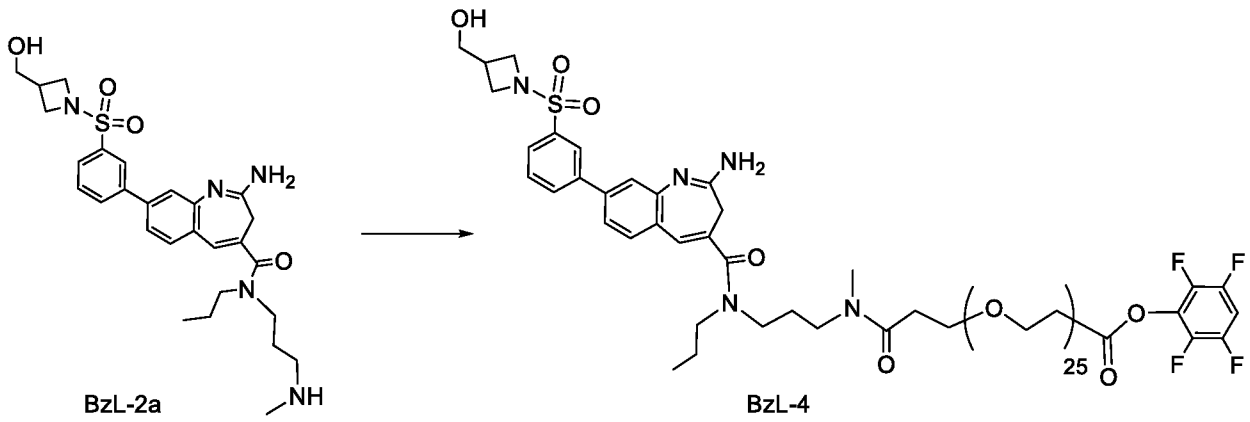
225.75 μmol, 2.5 *eq*) at 25 °C. The mixture was stirred for 12 hrs. The mixture was concentrated in vacuum to afford BzL-3k (100 mg crude) as yellow oil.

Synthesis of 3-[2-[2-[2-[2-[2-[2-[2-[2-[2-[[4-[2-amino-4-(dipropylcarbamoyl)- 3H-1-benzazepin-8-yl]-2-[3-(hydroxymethyl)azetidin-1-yl]sulfonyl-phenyl]methyl-methyl-amino]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]propanoic acid, BzL-3l

To a solution of BzL-3k (100 mg, 89.09 μmol, 1 *eq*) in H_2O (1 mL) was added TFA (203.18 mg, 1.78 mmol, 131.93 μL, 20 *eq*). The mixture was stirred at 60 °C for 12 hrs. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Luna C18 100 x 30 5u; liquid phase: [A-TFA/H_2O=0.075% v/v; B-ACN], B%: 20%-45%,10min]) to obtain BzL-3l (20 mg, 18.38 μmol, 20.63% yield, 97.989% purity) as colorless oil. ^{1}H NMR (MeOD, 400 MHz) δ 8.39-8.38 (m, 1H), 8.23-8.20 (m, 1H), 7.98-7.96 (m, 1H), 7.83-7.81 (m, 2H), 7.73-7.71 (m, 1H), 7.11 (s, 1H), 4.02-4.00 (m, 2H), 3.94-3.88 (m, 2H), 3.79-3.74 (m, 2H), 3.74-3.40 (m, 45H), 3.40-3.35 (m, 2H), 2.98-2.94 (m, 3H), 2.79-2.71 (m, 2H), 2.56-2.51 (m, 2H), 1.80-1.66 (m, 5H), 0.95 (s, 6H). LC/MS [M+2H/2] 533.78 (calculated); LC/MS [M+2H/2] 534.20 (observed).

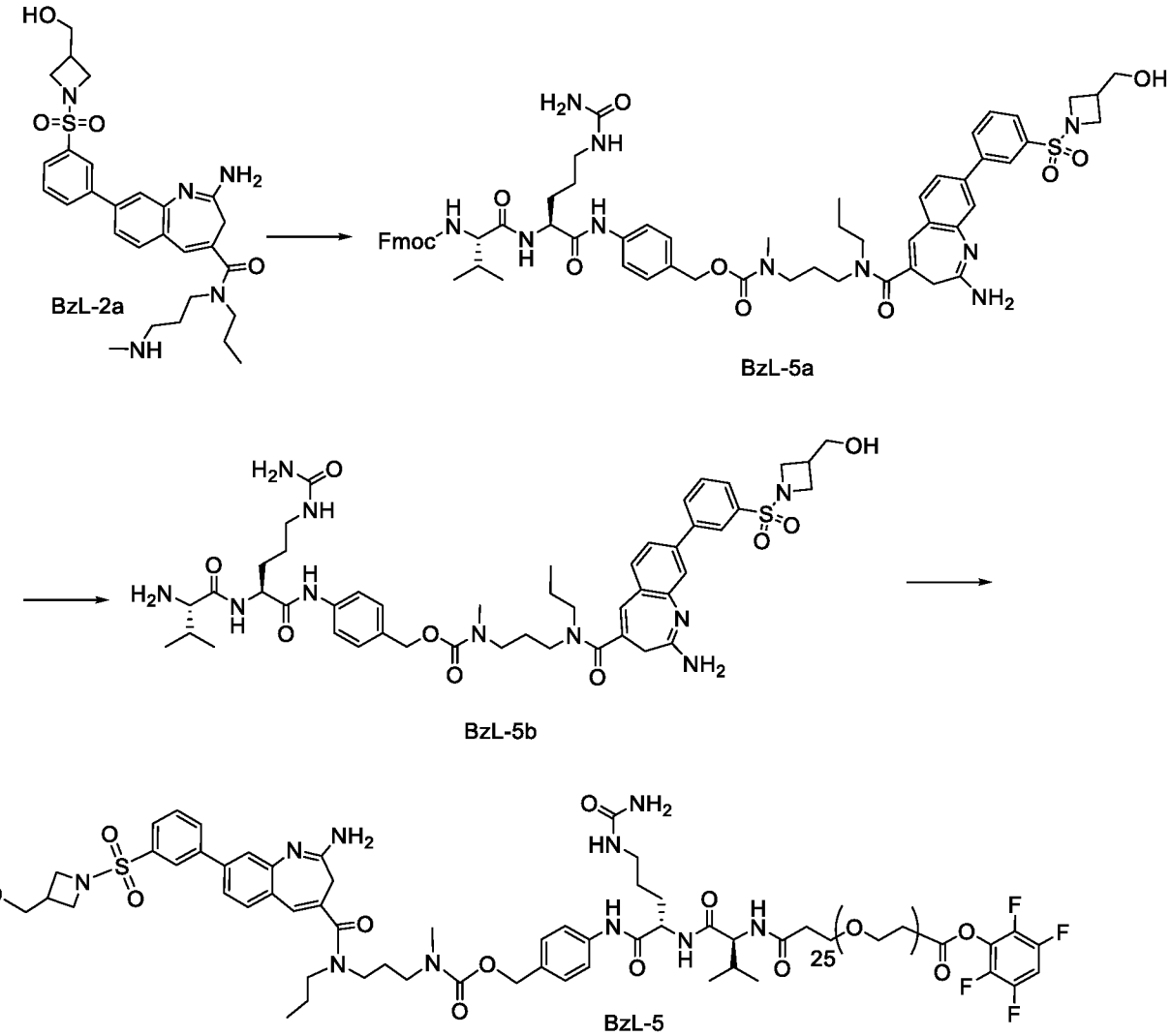
2,3,5,6-Tetrafluorophenyl 1-(4-(2-amino-4-(dipropylcarbamoyl)-3*H*-benzo[*b*]azepin-8-yl)-2-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-2-methyl-5,8,11,14,17,20,23,26,29,32-decaoxa-2-azapentatriacontan-35-oate, BzL-3 was synthesized according to the procedure described for BzL-22. LC/MS [M+H] 1214.56 (calculated); LC/MS [M+H] 1214.97 (observed).

Example 34 Synthesis of BzL-4



2,3,5,6-Tetrafluorophenyl 84-(2-amino-8-(3-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-3*H*-benzo[*b*]azepine-4-carbonyl)-80-methyl-79-oxo-4,7,10,13,16,19,22,25,28,31,34,37,40,43,46,49,52,55,58,61,64,67,70,73,76-pentacosaoxa-80,84-diazaheptaoctacontanoate, BzL-4 was synthesized according to the procedure described for BzL-15. LC/MS [M+H] 1888.93 (calculated); LC/MS [M+H] 1889.53 (observed).

Example 35 Synthesis of BzL-5



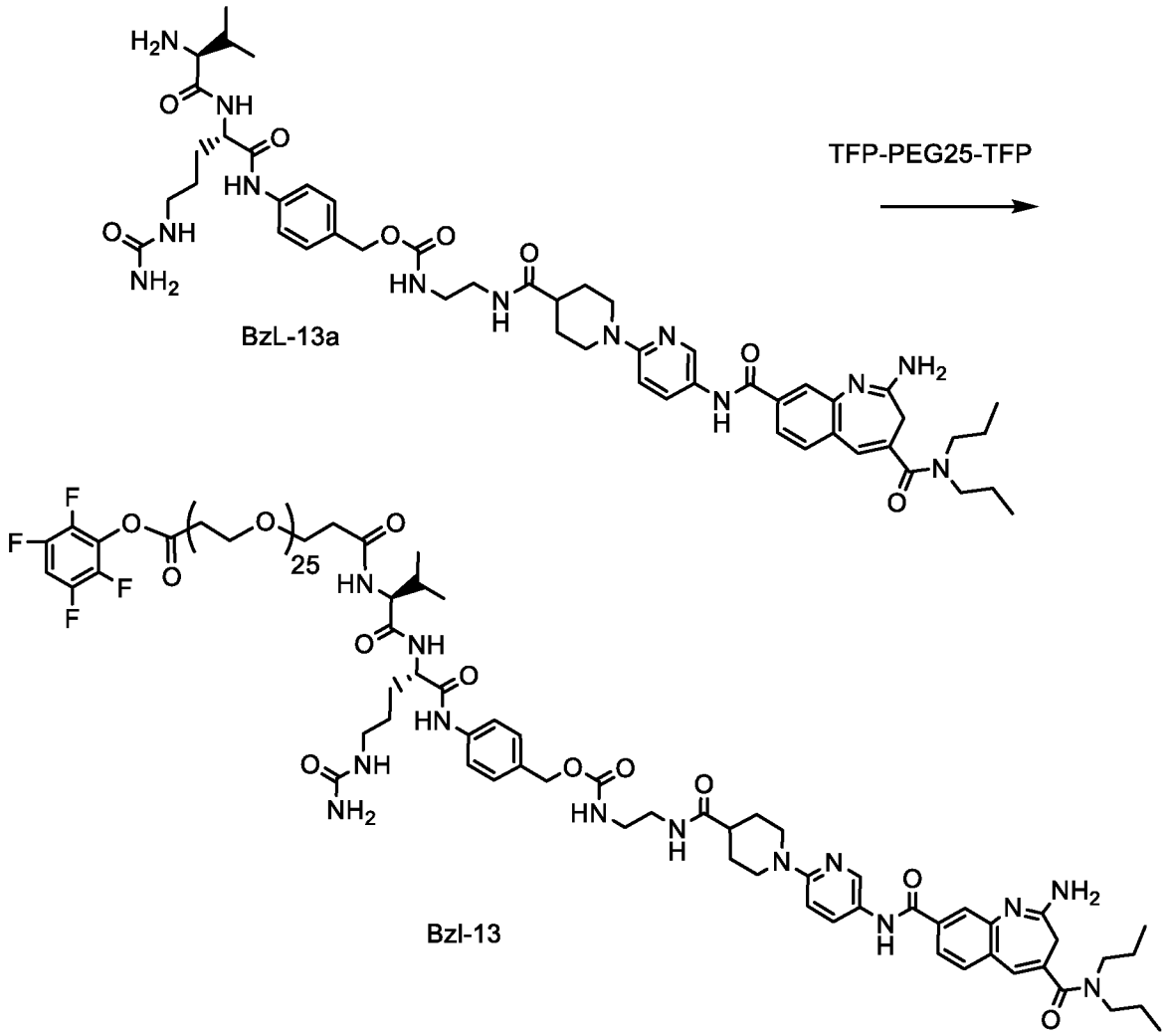
4-((*S*)-2-((*S*)-2-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)-3-methylbutanamido)-5-ureidopentanamido)benzyl (3-(2-amino-8-(3-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-*N*-propyl-3*H*-benzo[*b*]azepine-4-carboxamido)propyl)(methyl)carbamate, BzL-5a was synthesized according to the procedure described for BzL-26a.

4-((*S*)-2-((*S*)-2-Amino-3-methylbutanamido)-5-ureidopentanamido)benzyl (3-(2-amino-8-(3-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-*N*-propyl-3*H*-benzo[*b*]azepine-4-carboxamido)propyl)(methyl)carbamate, BzL-5b was synthesized according to the procedure described for BzL-26. LC/MS [M+H] 945.47 (calculated); LC/MS [M+H] 945.82 (observed).

2,3,5,6-Tetrafluorophenyl (6*S*,9*S*)-1-amino-6-((4-((((3-(2-amino-8-(3-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-*N*-propyl-3*H*-benzo[*b*]azepine-4-carboxamido)propyl)(methyl)carbamoyl)oxy)methyl)phenyl)carbamoyl)-9-isopropyl-1,8,11-trioxo-14,17,20,23,26,29,32,35,38,41,44,47,50,53,56,59,62,65,68,71,74,77,80,83,86-pentacosaoxa-2,7,10-triazanonaoctacontan-89-oate, BzL-5 was synthesized according to the

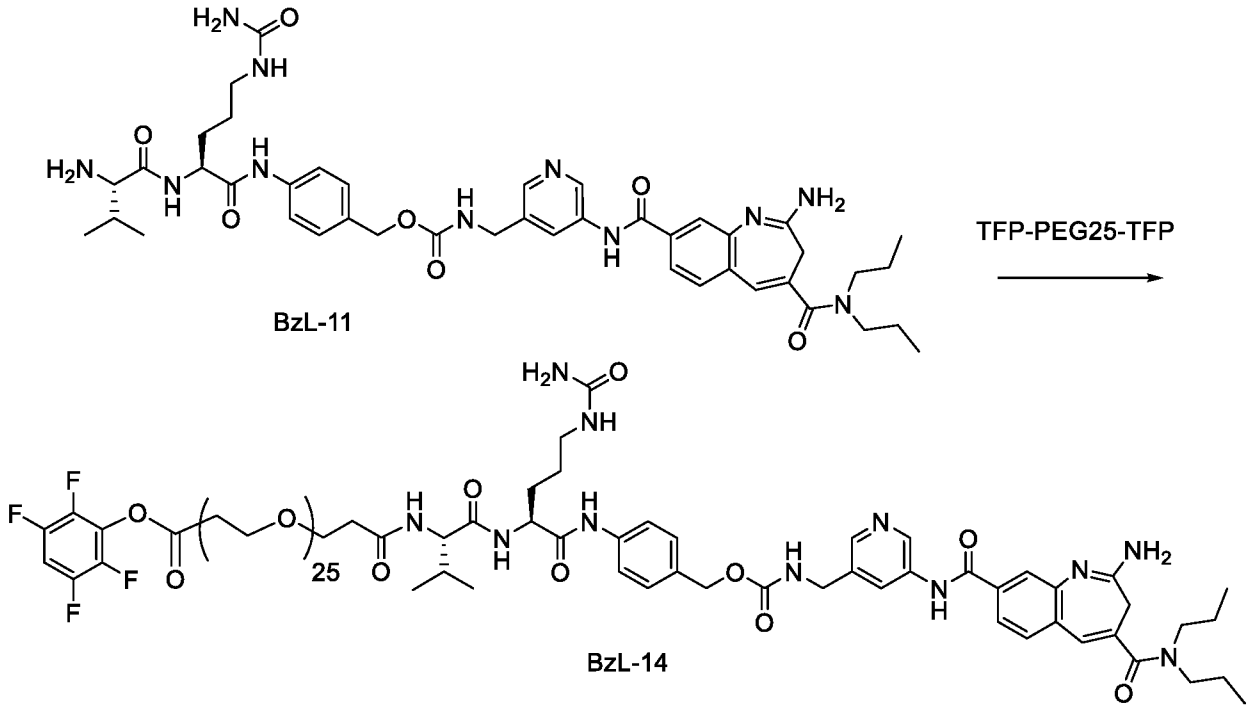
procedure described for BzL-15. LC/MS [M+2H/2] 1147.57 (calculated); LC/MS [M+H] 1148.37 (observed).

Example 36 Synthesis of BzL-13



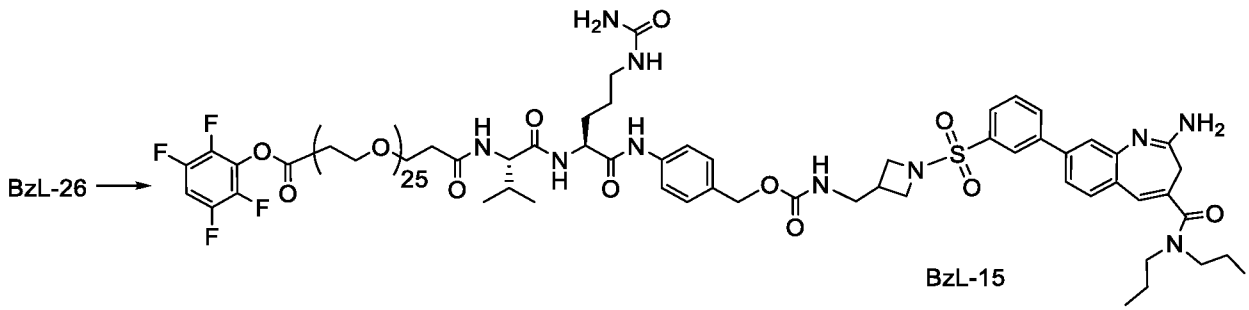
2,3,5,6-Tetrafluorophenyl (6*S*,9*S*)-1-amino-6-((4-((((2-(1-(5-(2-amino-4-(dipropylcarbamoyl)-3*H*-benzo[*b*]azepine-8-carboxamido)pyridin-2-yl)piperidine-4-carboxamido)ethyl)carbamoyl)oxy)methyl)phenyl)carbamoyl)-9-isopropyl-1,8,11-trioxo-14,17,20,23,26,29,32,35,38,41,44,47,50,53,56,59,62,65,68,71,74,77,80,83,86-pentacosaoxa-2,7,10-triazanonaoctacontan-89-oate, BzL-13 was synthesized from BzL-13a and TFP-PEG25-TFP according to the procedure described for BzL-15. LC/MS [M+2H/2] 1165.10 (calculated); LC/MS [M+H] 1165.91 (observed).

Example 37 Synthesis of BzL-14



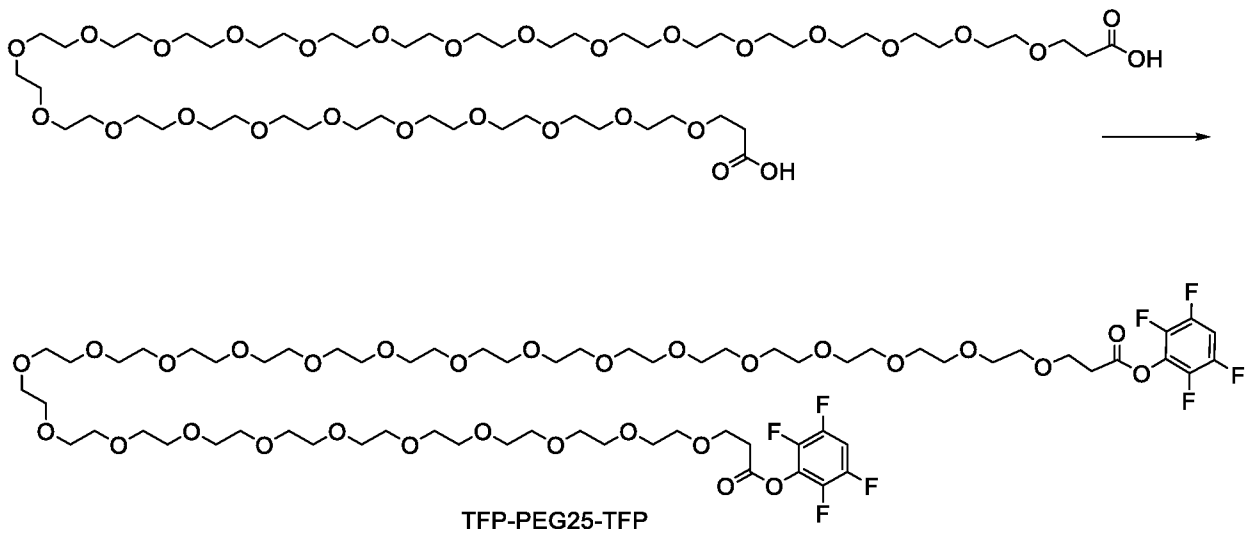
2,3,5,6-Tetrafluorophenyl (6*S*,9*S*)-1-amino-6-((4-(((((6-(2-amino-4-(dipropylcarbamoyl)-3*H*-benzo[*b*]azepine-8-carboxamido)pyridin-3-yl)methyl)carbamoyl)oxy)methyl)phenyl)carbamoyl)-9-isopropyl-1,8,11-trioxo-14,17,20,23,26,29,32,35,38,41,44,47,50,53,56,59,62,65,68,71,74,77,80,83,86-pentacosaoxa-2,7,10-triazanonaoctacontan-89-oate, BzL-14 was synthesized from BzL-11 and TFP-PEG25-TFP according to the procedure described for BzL-15. LC/MS [M+2H/2] 1095.06 (calculated); LC/MS [M+H] 1095.87 (observed).

Example 38 Synthesis of BzL-15



Synthesis of 2,3,5,6-tetrafluorophenyl (6*S*,9*S*)-1-amino-6-((4-(((((1-((3-(2-amino-4-(dipropylcarbamoyl)-3*H*-benzo[*b*]azepin-8-yl)phenyl)sulfonyl)azetidin-3-yl)methyl)carbamoyl)oxy)methyl)phenyl)carbamoyl)-9-isopropyl-1,8,11-trioxo-14,17,20,23,26,29,32,35,38,41,44,47,50,53,56,59,62,65,68,71,74,77,80,83,86-pentacosaoxa-2,7,10-triazanonaoctacontan-89-oate, BzL-15)

Synthesis of bis(2,3,5,6-tetrafluorophenyl) 4,7,10,13,16,19,22,25,28,31,34,37,40,43,46,49,52,55,58,61,64,67,70,73,76-pentacosaoxanonaheptacontanedioate, TFP-PEG25-TFP

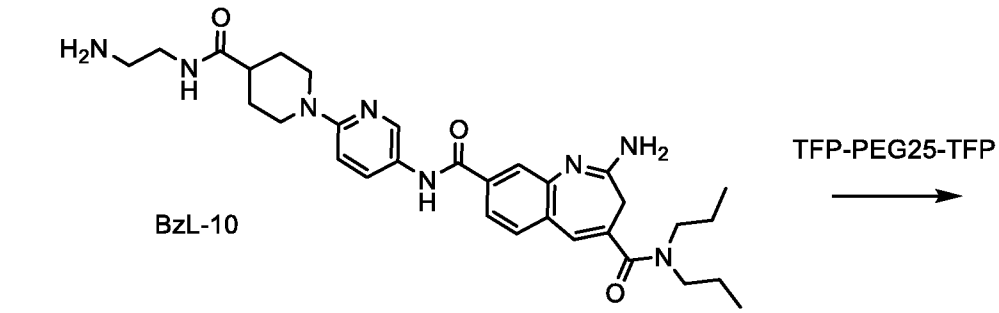


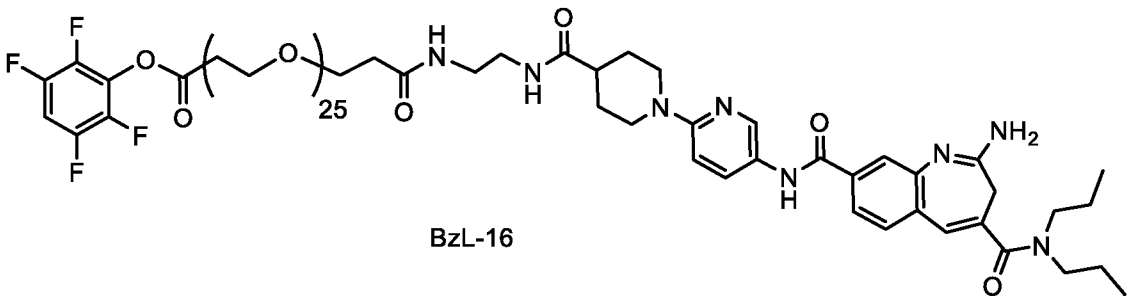
TFP-PEG25-TFP

A vial was charged with 4,7,10,13,16,19,22,25,28,31,34,37,40,43,46,49,52,55,58,61,64,67,70,73,76-pentacosaoxanonaheptacontanedioic acid (269 mg, 0.221 mmol), 2,3,5,6-tetrafluorophenol (110 mg, 0.662 mmol), collidine (176 µL, 1.33 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (127 mg, 0.221 mmol) and 3 mL DMF. The reaction was stirred for 16 h, then purified by reverse phase preparative HPLC utilizing a 25-75% gradient of acetonitrile:water containing 0.1% trifluoroacetic acid. The purified fractions were combined and lyophilized to afford 266 mg of TFP-PEG25-TFP in 79% yield. LC/MS [M+H] 1515.68 (calculated); LC/MS [M+H] 1516.00 (observed).

A vial was charged with BzL-26 (11.9 mg, 0.013 mmol), TFP-PEG25-TFP (19.7 mg, 0.013 mmol), collidine (5.6 µL, 0.042 mmol) in 300 µL DMF. The reaction was maintained for 5h and then purified by reverse phase preparative HPLC utilizing a 25-75% gradient of acetonitrile:water containing 0.1% trifluoroacetic acid. The purified fractions were combined and lyophilized to afford 7.7 mg of BzL-15 in 26% yield. LC/MS [M+2H/2] 1132.56 (calculated); LC/MS [M+2H/2] 1133.30 (observed).

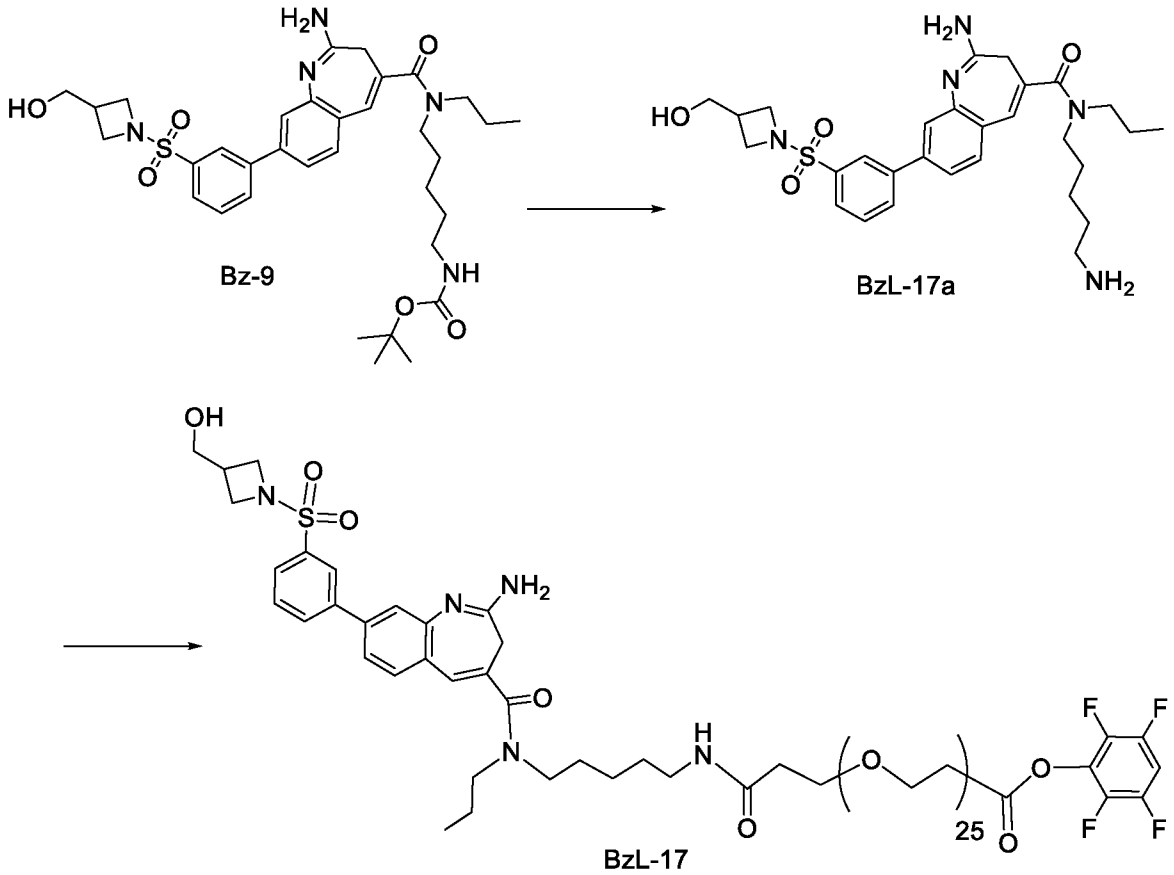
Example 39 Synthesis of BzL-16





Synthesis of 2,3,5,6-tetrafluorophenyl 1-(1-(5-(2-amino-4-(dipropylcarbamoyl)-3*H*-benzo[*b*]azepine-8-carboxamido)pyridin-2-yl)piperidin-4-yl)-1,6-dioxo-9,12,15,18,21,24,27,30,33,36,39,42,45,48,51,54,57,60,63,66,69,72,75,78,81-pentacosaoxa-2,5-diazatetraoctacontan-84-oate, BzL-16 was synthesized from BzL-10 and TFP-PEG25-TFP according to the procedure described for Bz-31. LC/MS [M+H] 1924.01 (calculated); LC/MS [M+H] 1925.23 (observed).

Example 40 Synthesis of BzL-17

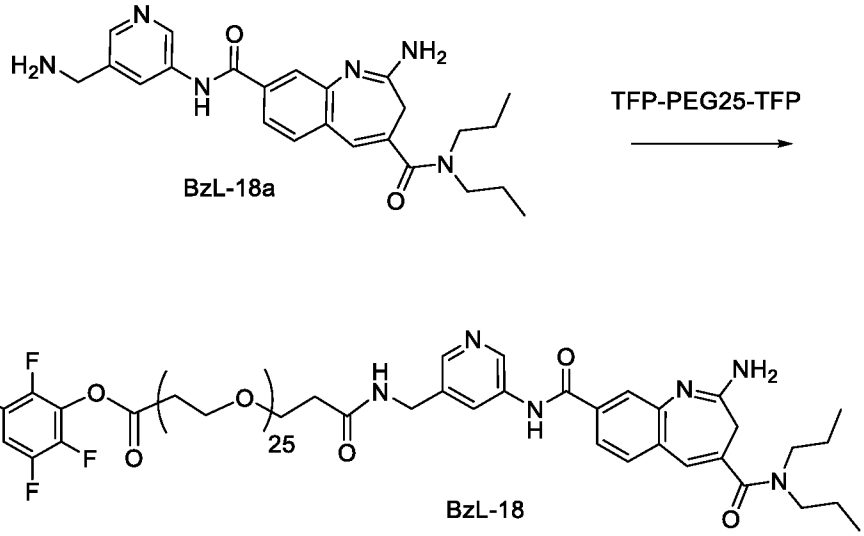


Synthesis of 2-amino-*N*-(5-aminopentyl)-8-(3-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-*N*-propyl-3*H*-benzo[*b*]azepine-4-carboxamide, BzL-17a. A vial was charged with Bz-9 (28 mg, 0.043 mmol), 300 µL DCM and 100 µL trifluoroacetic acid. The reaction was maintained for 1h, upon which it was concentrated under reduced pressure. The resultant oil was azeotroped thrice with 1 mL toluene, after which was added 1 mL methanol and K_2CO_3 (38 mg, 0.28 mmol). After stirring for 16 h, the reaction was filtered and concentrated under reduced pressure and then purified by reverse phase preparative HPLC utilizing a 25-75% gradient of acetonitrile:water containing 0.1% trifluoracetic acid. The purified fractions were combined and lyophilized to afford 5.8 mg of BzL-17a in 24% yield. LC/MS [M+H] 554.28 (calculated); LC/MS [M+H] 554.47 (observed).

Synthesis of 2,3,5,6-tetrafluorophenyl 86-(2-amino-8-(3-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-3*H*-benzo[*b*]azepine-4-carbonyl)-79-oxo-4,7,10,13,16,19,22,25,28,31,34,37,40,43,46,49,52,55,58,61,64,67,70,73,76-pentacosaoxa-80,86-diazanonaoctacontanoate, BzL-17. A vial was charged with BzL-17a (5.8 mg, 0.011 mmol), TFP-PEG25-TFP (23.8 mg, 0.016 mmol), collidine (5.6 µL, 0.042 mmol) in 300 µL DMF. The reaction was maintained for 5h and then purified by reverse phase preparative HPLC utilizing a 25-75% gradient of acetonitrile:water (ACN:H2O) containing 0.1% trifluoroacetic acid (TFA).

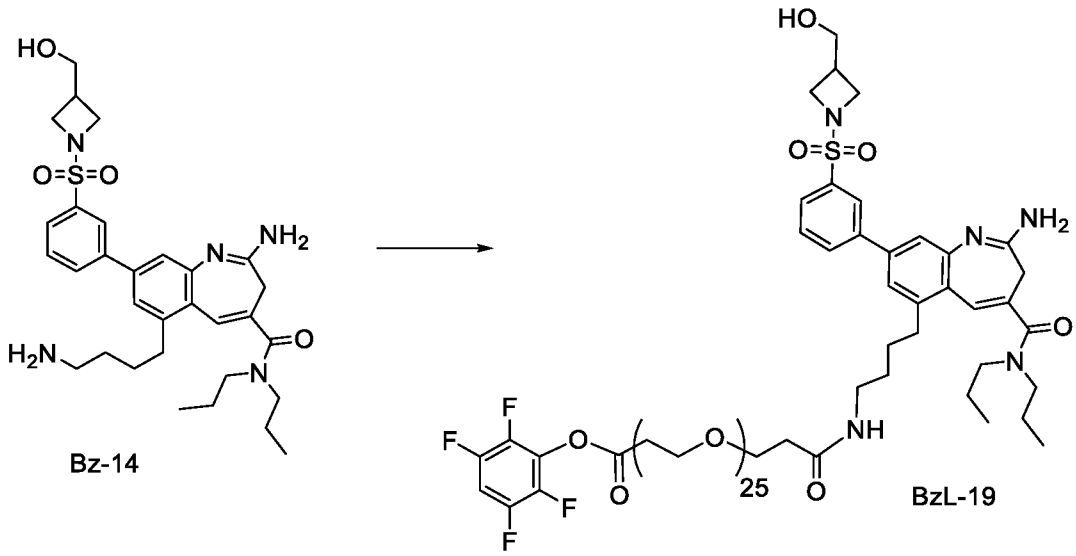
The purified fractions were combined and lyophilized to afford 5.0 mg of BzL-17 in 25% yield. LC/MS [M+H] 1902.95 (calculated); LC/MS [M+H] 1903.37 (observed).

Example 41 Synthesis of BzL-18



2,3,5,6-Tetrafluorophenyl 1-(6-(2-amino-4-(dipropylcarbamoyl)-3*H*-benzo[*b*]azepine-8-carboxamido)pyridin-3-yl)-3-oxo-6,9,12,15,18,21,24,27,30,33,36,39,42,45,48,51,54,57,60,63,66,69,72,75,78-pentacosaoxa-2-azahenoctacontan-81-oate, BzL-18 was synthesized from BzL-18a and TFP-PEG25-TFP according to the procedure described for BzL-15. LC/MS [M+H] 1783.92 (calculated); LC/MS [M+H] 1784.19 (observed).

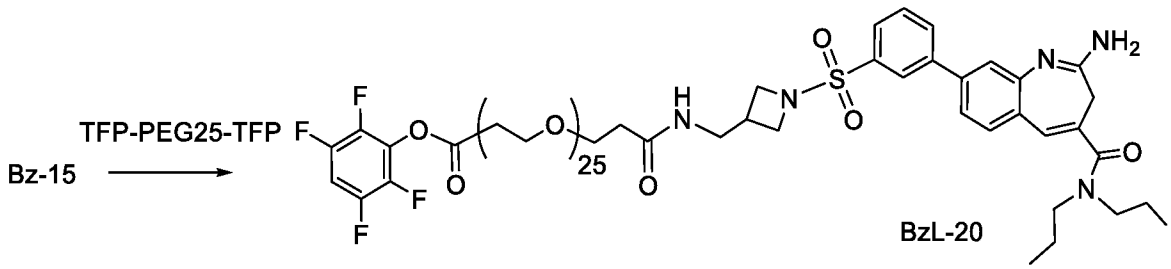
Example 42 Synthesis of BzL-19



2,3,5,6-Tetrafluorophenyl 84-(2-amino-4-(dipropylcarbamoyl)-8-(3-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-3*H*-benzo[*b*]azepin-6-yl)-79-oxo-4,7,10,13,16,19,22,25,28,31,34,37,40,43,46,49,52,55,58,61,64,67,70,73,76-pentacosaoxa-80-

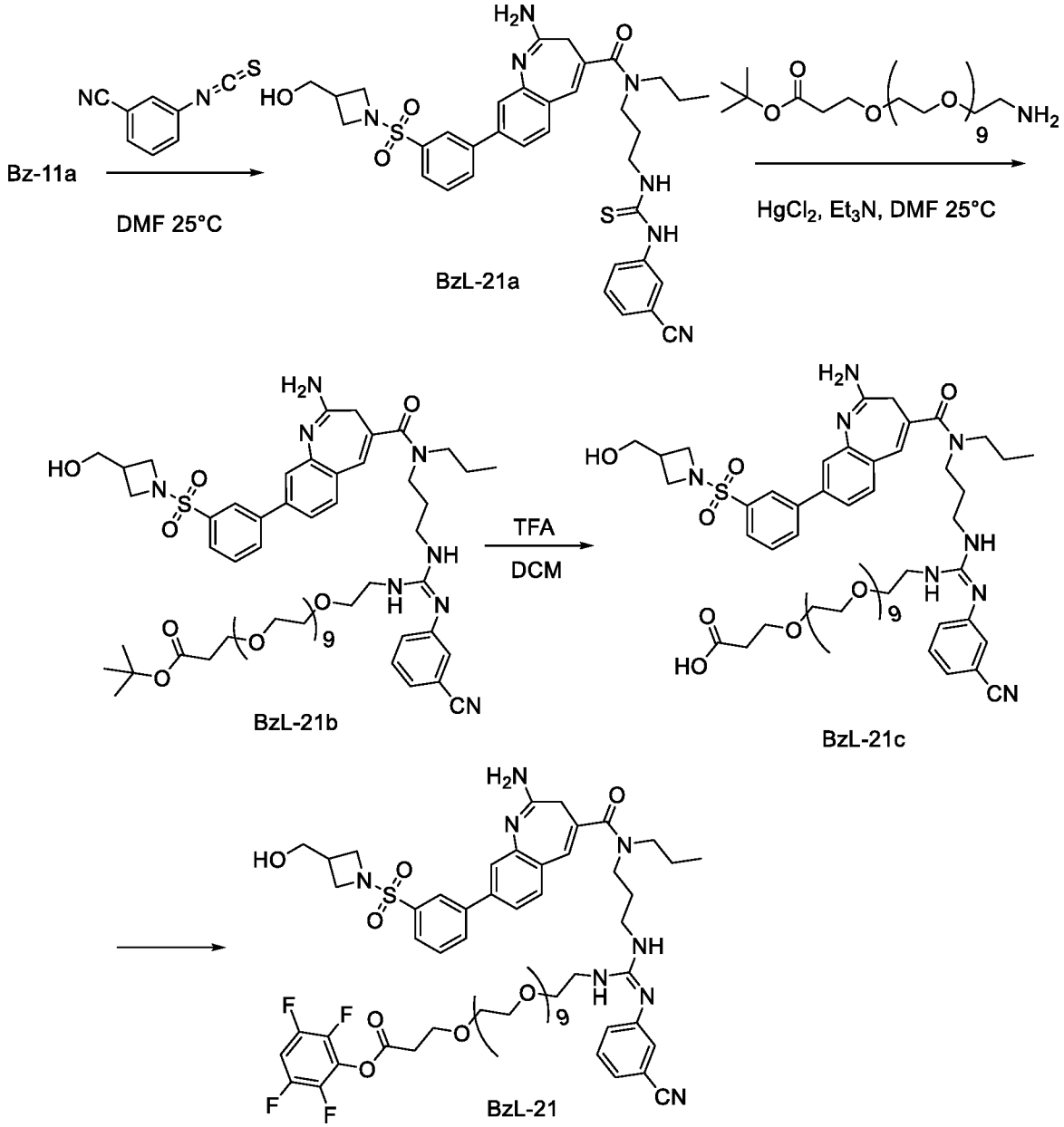
azatetraoctacontanoate, BzL-19 was synthesized from Bz-14 and TFP-PEG25-TFP according to the procedure described for BzL-15. LC/MS [M+H] 1930.98 (calculated); LC/MS [M+H] 1931.24 (observed).

Example 43 Synthesis of BzL-20



2,3,5,6-Tetrafluorophenyl 1-(1-((3-(2-amino-4-(dipropylcarbamoyl)-3*H*-benzo[*b*]azepin-8-yl)phenyl)sulfonyl)azetidin-3-yl)-3-oxo-6,9,12,15,18,21,24,27,30,33,36,39,42,45,48,51,54,57,60,63,66,69,72,75,78-pentacosaoxa-2-azahenoctacontan-81-oate, BzL-20 was synthesized from reaction of TFP-PEG25-TFP and Bz-15 according to the procedure described for BzL-15. LC/MS [M+H] 1858.92 (calculated); LC/MS [M+H] 1859.59 (observed).

Example 44 Synthesis of BzL-21



Synthesis of 2-amino-N-[3-[(3-cyanophenyl)carbamothioylamino]propyl]-8-[3-[3-(hydroxymethyl)azetidin-1-yl]sulfonylphenyl]-N-propyl-3H-1-benzazepine-4-carboxamide, BzL-21a

To a mixture of 2-amino-N-(3-aminopropyl)-8-[3-[3-(hydroxymethyl)azetidin-1-yl] sulfonylphenyl]-N-propyl-3H-1-benzazepine-4-carboxamide, Bz-11a (0.1 g, 190.24 μmol, 1 eq) in DMF (2 mL) was added 3-isothiocyanatobenzonitrile (30.48 mg, 190.24 μmol, 1 eq) in one portion at 15°C. The mixture was stirred at 15°C for 3 hours. LCMS showed the desired was detected. The mixture was filtered and purified by prep-HPLC (column: Nano-micro Kromasil C18 100x30mm, 5um;mobile phase: [water (0.1%TFA)-ACN]; B%: 20%-60%, 10min) to give 2-amino-N-[3-[(3-cyanophenyl)carbamothioylamino]propyl]-8-[3-[3- (hydroxymethyl)azetidin-

1-yl]sulfonylphenyl]-N-propyl-3H-1-benzazepine-4-carboxamide, BzL-21a (0.06 g, 87.48 μmol, 45.99% yield) was obtained as light yellow solid.

Synthesis of tert-butyl 3-[2-[2-[2-[2-[2-[2-[2-[2-[2-[(Z)-[[3-[[2-amino-8-[3-[3-(hydroxymethyl)azetidin-1-yl]sulfonylphenyl]-3H-1-benzazepine-4-carbonyl]-propyl-amino]propylamino]-(3-cyanoanilino)methylene]amino]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]propanoate, BzL-21b

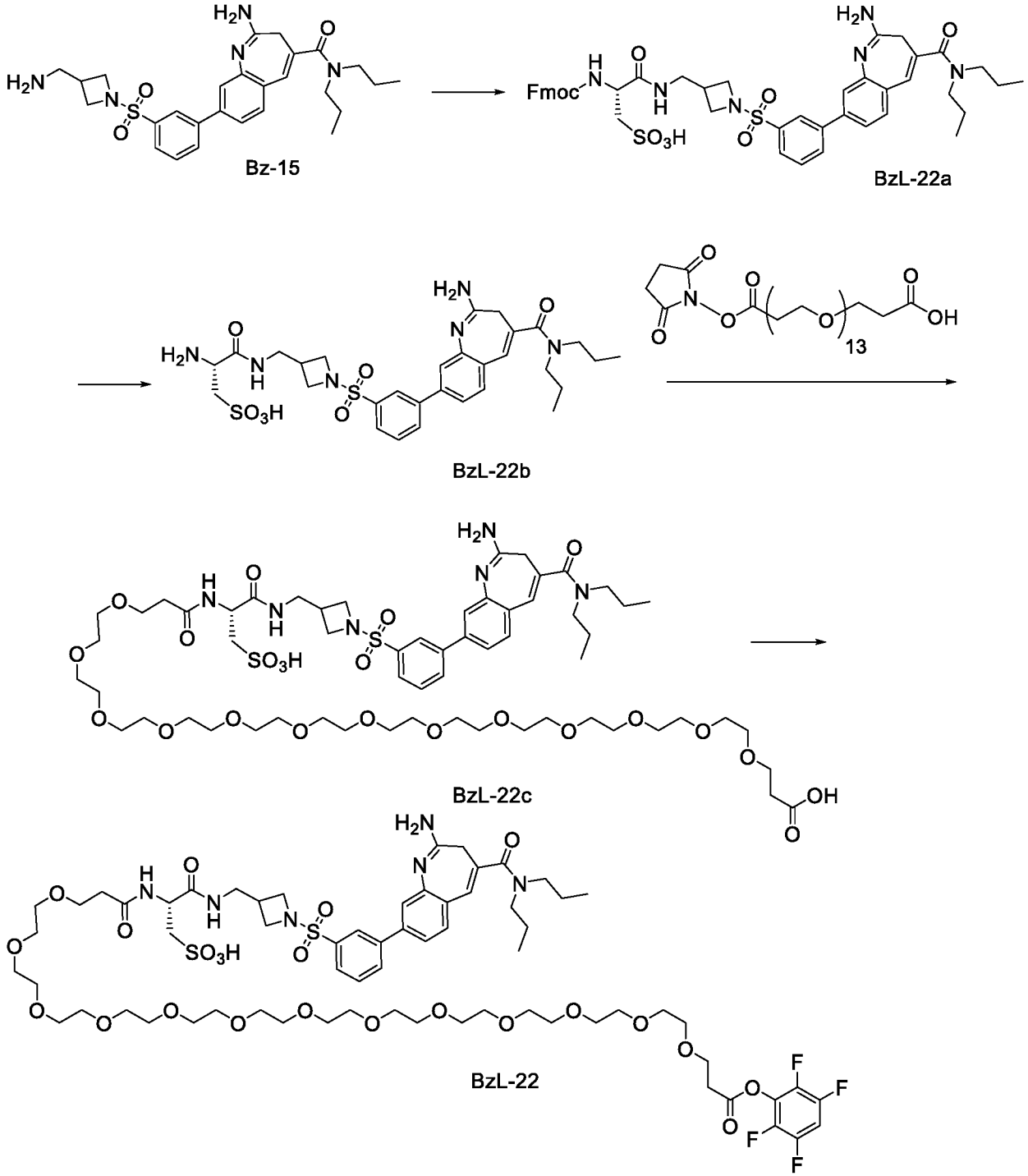
To a mixture of BzL-21a (0.06 g, 87.48 μmol, 1 eq) and tert-butyl 3-[2-[2-[2-[2-[2-[2-[2-[2-[2-(2-aminoethoxy)ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]propanoate (61.49 mg, 104.98 μmol, 1.2 eq) in DMF (2 mL) was added Et_3N (17.70 mg, 174.96 μmol, 24.35 μL, 2 eq) and $HgCl_2$ (28.50 mg, 104.98 μmol, 5.24 μL, 1.2 eq). The mixture was stirred at 15 °C for 18 hours. LCMS showed the reactant was consumed. The mixture was filtered and poured into water (10 mL). The aqueous phase was extracted with ethyl acetate (10 mL x 3). The combined organic phase was concentrated to give BzL-21b (0.1 g, crude) as light yellow oil which was used into the next step without further purification.

Synthesis of 3-[2-[2-[2-[2-[2-[2-[2-[2-[2-[(Z)-[[3-[[2-amino-8-[3-[3-(hydroxymethyl)azetidin-1-yl]sulfonylphenyl]-3H-1-benzazepine-4-carbonyl]-propyl-amino]propylamino]-(3-cyanoanilino)methylene]amino]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]propanoic acid, BzL-21c

To a mixture of BzL-21b (86.04 mg, 69.52 μmol, 1 eq) in H_2O (10 mL) was added TFA (396.36 mg, 3.48 mmol, 257.38 μL, 50 eq) in one portion at 15 °C. The mixture was stirred at 85 °C for 10 min. LCMS showed the reactant was consumed. The mixture was concentrated. The residue was purified by prep-HPLC (column: Nano-micro Kromasil C18 100x30mm, 5um; mobile phase: [water (0.1%TFA)-ACN]; B%: 10%-40%,10min) to give BzL-21c (18 mg, 13.71 μmol, 19.72% yield, 90% purity) was obtained as a white solid. ^1H NMR (MeOD, 400 MHz) δ 8.12-8.08 (m, 2H), 7.92 (d, J = 8.0 Hz, 1H), 7.84-7.81 (m, 4H), 7.64 (s, 3H), 7.12 (s, 1H), 3.87 (t, J = 8.4 Hz, 2H), 3.72-3.70 (m, 9H), 3.63-3.58 (m, 38H), 3.43 -3.41 (m, 6H), 2.62-2.57 (m, 1H), 2.52 (t, J = 6.0 Hz, 2H), 2.04 (s, 2H), 1.75-1.70 (m, 3H), 0.96-0.92 (m, 3H).

2,3,5,6-Tetrafluorophenyl (*Z*)-40-(2-amino-8-(3-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-3*H*-benzo[*b*]azepine-4-carbonyl)-35-((3-cyanophenyl)imino)-4,7,10,13,16,19,22,25,28,31-decaoxa-34,36,40-triazatritetracontanoate, BzL-21 was synthesized according to the procedure described for BzL-22. LC/MS [M+H] 1329.57 (calculated); LC/MS [M+H] 1329.77 (observed).

Example 45 Synthesis of BzL-22



Synthesis of (*R*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-(((1-((3-(2-amino-4-(dipropylcarbamoyl)-3*H*-benzo[*b*]azepin-8-yl)phenyl)sulfonyl)azetidin-3-yl)methyl)amino)-3-oxopropane-1-sulfonic acid, BzL-22a.

A vial was charged with Bz-15 (14.7 mg, 0.024 mmol), Fmoc-L-Cysteic Acid (11.2mg, 0.024 mmol), collidine (12 µL, 0.090 mmol), HATU (12 mg, 0.032 mmol) and 500 µL DMF. The reaction was stirred until Bz-15 was consumed by LCMS. The crude mixture was purified by reverse phase preparative HPLC utilizing a 25-75% gradient of acetonitrile:water containing

0.1% trifluoroacetic acid. The purified fractions were combined and lyophilized to afford 8.6 mg of BzL-22a in 41% yield. LC/MS [M+H] 883.32 (calculated); LC/MS [M+H] 883.49 (observed).

Synthesis of (*R*)-2-amino-3-(((1-((3-(2-amino-4-(dipropylcarbamoyl)-3*H*-benzo[*b*]azepin-8-yl)phenyl)sulfonyl)azetidin-3-yl)methyl)amino)-3-oxopropane-1-sulfonic acid, BzL-22b.

A vial was charged with BzL-22a (8.6 mg, 0.01 mmol), diethylamine (10 µL, 0.10 mmol), 100 µL acetonitrile and 50 µL DMF. The reaction was stirred for 3 h, then concentrated under reduced pressure. The crude reaction was azeotroped thrice with 2 mL toluene and take on to the subsequent step.

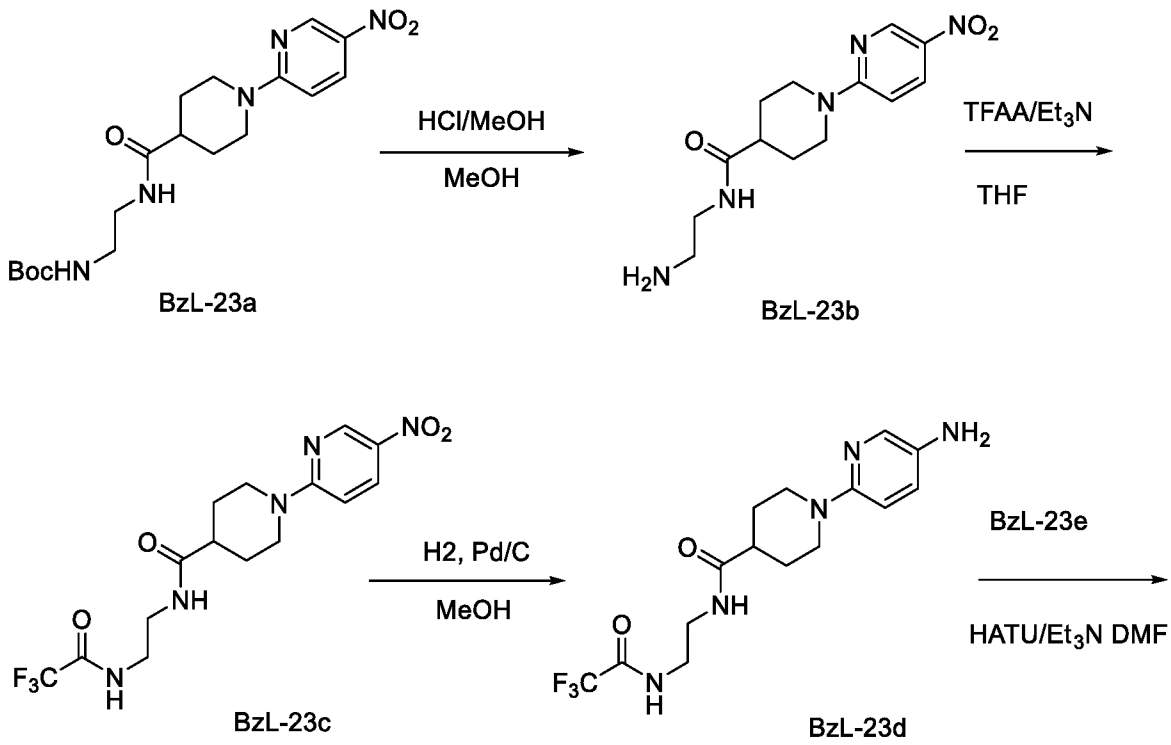
Synthesis of (*R*)-1-(1-((3-(2-amino-4-(dipropylcarbamoyl)-3*H*-benzo[*b*]azepin-8-yl)phenyl)sulfonyl)azetidin-3-yl)-3,6-dioxo-4-(sulfomethyl)-9,12,15,18,21,24,27,30,33,36,39,42,45-tridecaoxa-2,5-diazaoctatetracontan-48-oic acid, BzL-22c

A vial was charged with crude BzL-22b (0.01 mmol), 43-((2,5-dioxopyrrolidin-1-yl)oxy)-43-oxo-4,7,10,13,16,19,22,25,28,31,34,37,40-tridecaoxatritetracontanoic acid (7.7 mg, 0.01 mmol), diisopropylethylamine (5.3 µL, 0.03 mmol), 1-hydroxy-7-azabenzotriazole, HOAt, CAS Reg. No. 39968-33-7 (4 mg, 0.03 mmol) and 140 µL DMF. The reaction was stirred for 8 h, then purified by reverse phase preparative HPLC utilizing a 25-75% gradient of acetonitrile:water containing 0.1% trifluoroacetic acid. The purified fractions were combined and lyophilized to afford 8.4 mg of BzL-22c in 64% yield. LC/MS [M+H] 1333.60 (calculated); LC/MS [M+H] 1333.69 (observed).

Synthesis of (*R*)-2-(((1-((3-(2-amino-4-(dipropylcarbamoyl)-3*H*-benzo[*b*]azepin-8-yl)phenyl)sulfonyl)azetidin-3-yl)methyl)carbamoyl)-4,46-dioxo-46-(2,3,5,6-tetrafluorophenoxy)-7,10,13,16,19,22,25,28,31,34,37,40,43-tridecaoxa-3-azahexatetracontane-1-sulfonic acid, BzL-22.

A vial was charged with BzL-22c (7.2 mg, 0.005 mmol), 2,3,5,6-tetrafluorophenol (1.8 mg, 0.011 mmol), collidine (2.2 µL, 0.016 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (1 mg, 0.005 mmol) and 100 µL DMF. The reaction was stirred for 16 h, then purified by reverse phase preparative HPLC utilizing a 25-75% gradient of acetonitrile:water containing 0.1% trifluoroacetic acid. The purified fractions were combined and lyophilized to afford 5.3 mg of BzL-22 in 66% yield. LC/MS [M+H] 1481.60 (calculated); LC/MS [M+H] 1481.82 (observed).

Example 46 Synthesis of BzL-23



Synthesis of N-(2-aminoethyl)-1-(5-nitropyridin-2-yl)piperidine-4-carboxamide, BzL-23b

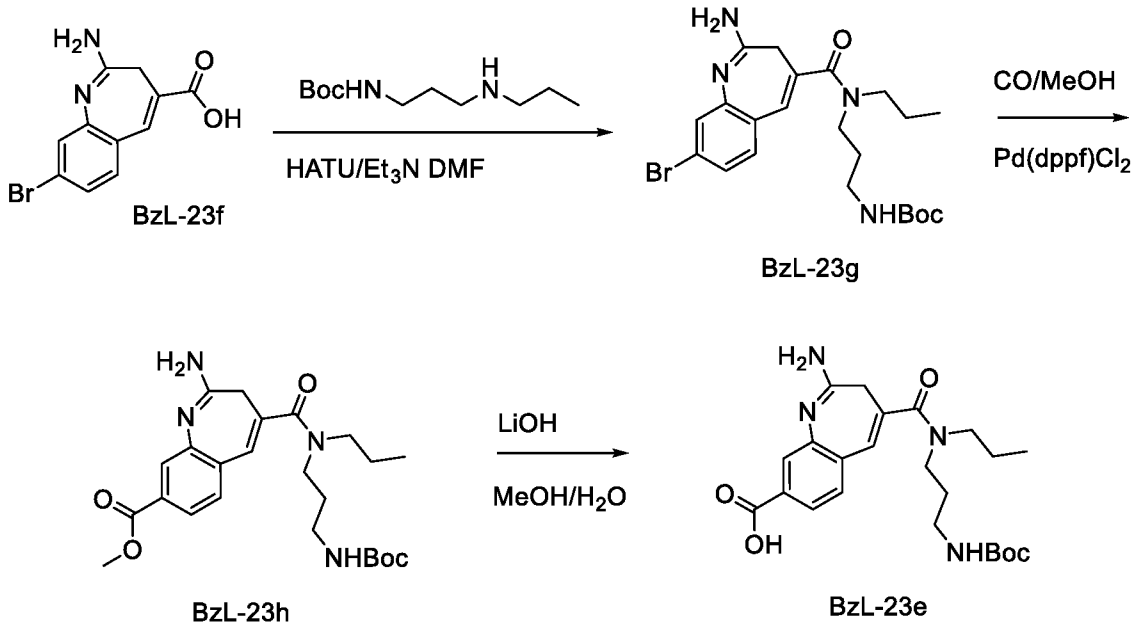
To a mixture of tert-butyl N-[2-[[1-(5-nitro-2-pyridyl)piperidine-4-carbonyl] amino]ethyl]carbamate, BzL-23a (0.5 g, 1.27 mmol, 1 *eq*) in EtOAc (10 mL) was added HCl/EtOAc (4 M, 3.18 mL, 10 *eq*) at 25°C. The mixture was stirred at 25°C for 2 hours. LCMS showed the reaction was completed. The reaction was concentrated in vacuum to give BzL-23b (0.4 g, 1.21 mmol, 95.44% yield, HCl) as a yellow solid.

Synthesis of 1-(5-nitropyridin-2-yl)-N-(2-(2,2,2-trifluoroacetamido) ethyl)piperidine-4-carboxamide, BzL-23c

To a mixture of N-(2-aminoethyl)-1-(5-nitro-2-pyridyl)piperidine-4-carboxamide, BzL-23b (0.4 g, 1.21 mmol, 1 *eq*, HCl) in THF (10 mL) was added Et_3N (368.21 mg, 3.64 mmol, 506.47 μL, 3 *eq*) and (2,2,2-trifluoroacetyl) 2,2,2-trifluoroacetate (382.13 mg, 1.82 mmol, 253.06 μL, 1.5 *eq*) at 25 °C. The mixture was stirred at 25 °C for 1 hours. LCMS showed major as desired. The mixture was poured into water (50 mL). The aqueous phase was extracted with ethyl acetate (30 mLx3). The combined organic phase was washed with brine (30 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was used to next step directly, containing BzL-23c (0.4 g, 1.03 mmol, 84.71% yield) as a yellow solid. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.37-9.45 (m, 1H), 8.95 (d, J = 2.8 Hz, 1H), 8.19 (dd, J = 9.6, 2.8 Hz, 1H), 8.03 (br t, J = 5.2 Hz, 1H), 6.96 (d, J = 9.6 Hz, 1H), 4.47-4.53 (m, 2H), 2.99-3.25 (m, 6H), 2.38-2.47 (m, 3H), 1.73-1.80 (m, 2H), 1.41-1.58 (m, 2H)

Synthesis of 1-(5-aminopyridin-2-yl)-N-(2-(2,2,2-trifluoroacetamido) ethyl)piperidine-4-carboxamide, BzL-23d

To a solution of 1-(5-nitro-2-pyridyl)-N-[2-[(2,2,2-trifluoroacetyl)amino]ethyl] piperidine-4-carboxamide, BzL-23c (0.4 g, 1.03 mmol, 1 *eq*) in MeOH (30 mL) was added Pd/C (0.5 g, 5% purity) under N_2. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (50 psi) at 25°C for 2 hours. TLC showed the reaction was completed. The mixture was filtered and concentrated in vacuum to give BzL-23d (0.3 g, 834.85 µmol, 81.26% yield) as a gray solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.39-9.46 (m, 1H), 7.97 (t, J = 5.2 Hz, 1H), 7.59 (d, J = 2.8 Hz, 1H), 6.90 (dd, J = 8.8, 2.8 Hz, 1H), 6.64 (d, J = 8.8 Hz, 1H), 3.99 (d, J = 12.8 Hz, 2H), 3.15-3.26 (m, 6H), 2.54-2.63 (m, 2H), 2.16-2.26 (m, 1H), 1.65-1.71 (m, 2H), 1.48-1.60 (m, 2H)



Synthesis of *tert*-butyl (3-(2-amino-8-bromo-*N*-propyl-3*H*-benzo[*b*]azepine-4-carboxamido)propyl)carbamate, BzL-23g

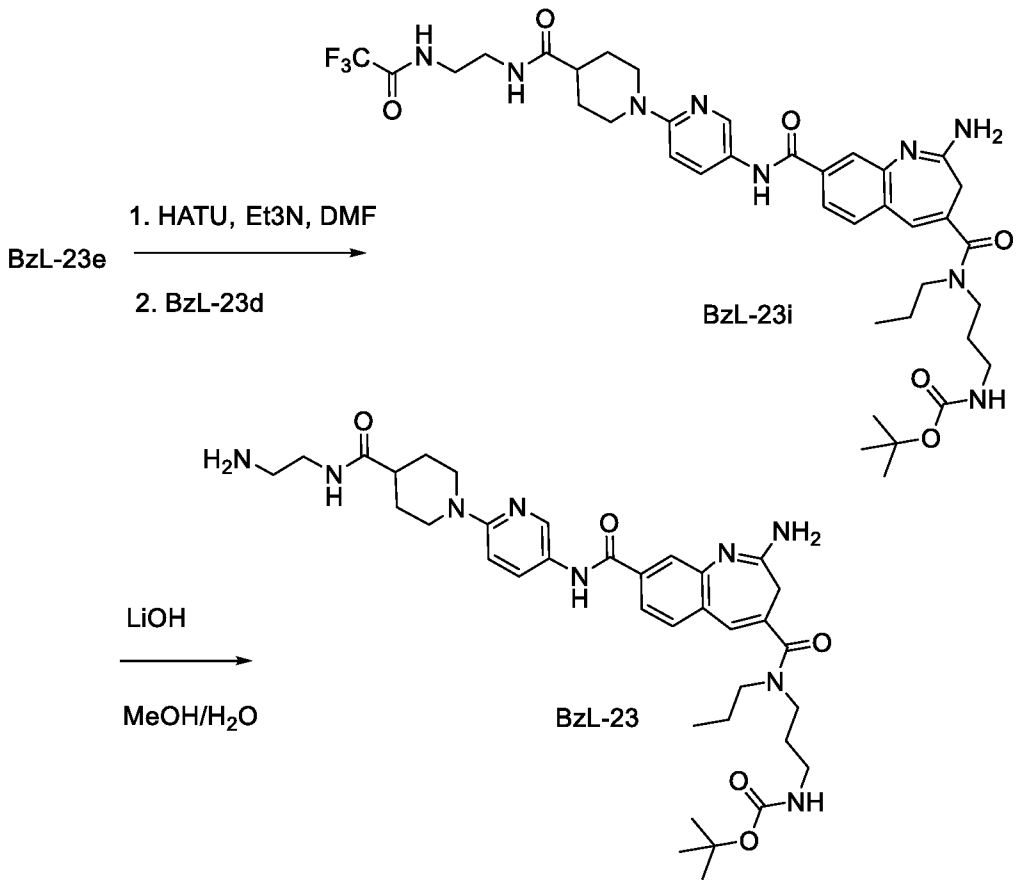
To a mixture of 2-amino-8-bromo-3H-1-benzazepine-4-carboxylic acid, BzL-23f (4.09 g, 14.56 mmol, 1 *eq*) and tert-butyl N-[3-(propylamino)propyl]carbamate (3.78 g, 17.47 mmol, 1.2 *eq*) in DMF (10 mL) was added HATU (6.64 g, 17.47 mmol, 1.2 *eq*) and Et_3N (2.95 g, 29.12 mmol, 4.05 mL, 2 *eq*) in one portion at 25 C. The mixture was stirred at 25 °C for 1 h. LCMS showed the reaction was finished. The mixture was diluted with water and extracted with EtOAc (50 mL x 3). The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, Petroleum ether/Ethyl acetate=1/0, 0/1) to afford BzL-23g (6 g, 12.52 mmol, 85.95% yield) as a yellow oil.

Synthesis of methyl 2-amino-4-[3-(tert-butoxycarbonylamino)propyl-propyl – carbamoyl]-3H-1-benzazepine-8-carboxylate, BzL-23h

To a solution of tert-butyl N-[3-[(2-amino-8-bromo-3H-1-benzazepine-4-carbonyl)–propyl -amino]propyl] carbamate, BzL-23g (5 g, 10.43 mmol, 1 *eq*) in MeOH (50 mL) was added Et_3N (3.17 g, 31.29 mmol, 4.35 mL, 3 *eq*) and $Pd(dppf)Cl_2$ (763.13 mg, 1.04 mmol, 0.1 *eq*) under N_2. The suspension was degassed under vacuum and purged with CO (10.43 mmol, 1 *eq*) several times. The mixture was stirred under CO (50psi) at 80°C for 12 hours. LCMS showed the reaction was finished. The mixture was filtered and concentrated to give BzL-23h (7 g, crude) as yellow oil.

Synthesis of 2-amino-4-((3-((tert-butoxycarbonyl)amino)propyl)(propyl)carbamoyl)-3H-benzo[b]azepine-8-carboxylic acid, BzL-23e

To a mixture of methyl 2-amino-4-[3-(tert-butoxycarbonylamino)propyl-propyl-carbamoyl] -3H-1-benzazepine-8-carboxylate, BzL-23h (6 g, 13.08 mmol, 1 *eq*) in MeOH (80 mL) was added LiOH (1.25 g, 52.34 mmol, 4 *eq*) in one portion at 30°C. The mixture was stirred at 30°C for 12 h. LCMS showed the reaction was finished. The mixture was adjusted pH 6 with aq HCl (1 M) at 25 °C. The mixture was concentrated. The mixture was further purification by pre-HPLC(column: Phenomenex luna C18 250x50mm, 10 um (micron);mobile phase: [water(0.1%TFA)-ACN];B%: 10%-40%,20min) to give BzL-23e (1.4 g, 3.09 mmol, 23.64% yield, 98.23% purity) as yellow oil. ^1H NMR (MeOD, 400MHz) δ 8.06 (d, J =1.2 Hz, 1H), 8.02 (dd, J =1.6, 8.0 Hz, 1H), 7.68 (s, 1H), 7.14 (s, 1H), 3.58-3.44 (m, 4H), 3.37 (s, 2H), 3.10 (m, 2H), 1.85 (m, 2H), 1.71 (m, 2H), 1.51-1.33 (m, 9H), 0.92-0.98 (m, 3H). LC/MS [M+H] 445.25 (calculated); LC/MS [M+H] 445.10 (observed).



Synthesis of tert-butyl (3-(2-amino-N-propyl-8-((6-(4-((2-(2,2,2-trifluoroacetamido)ethyl)carbamoyl)piperidin-1-yl)pyridin-3-yl)carbamoyl)-3H-benzo[b]azepine-4-carboxamido)propyl)carbamate, BzL-23i

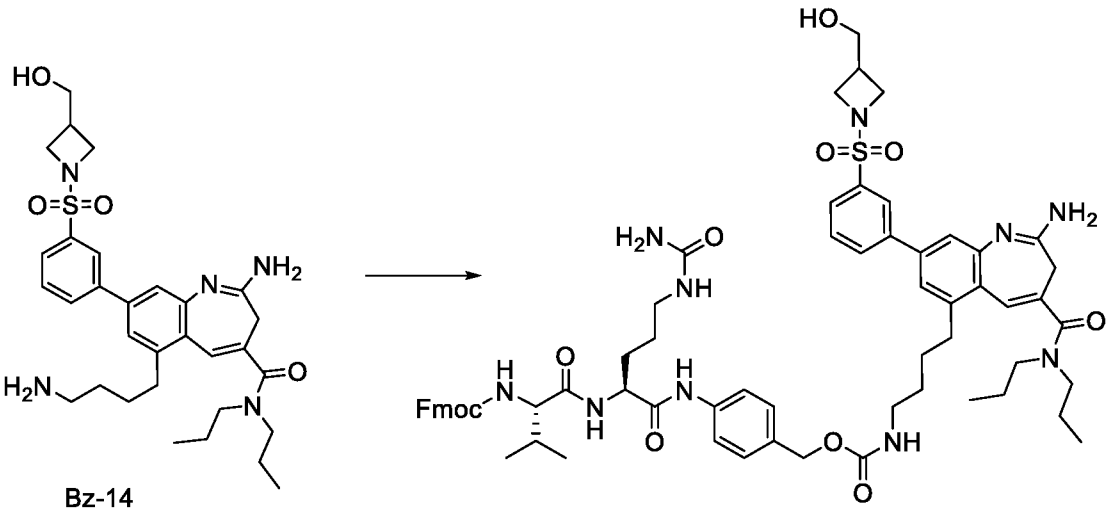
To a mixture of 2-amino-4-[3-(tert-butoxycarbonylamino)propyl-propyl-carbamoyl] -3H-1-benzazepine-8-carboxylic acid, BzL-23e (200 mg, 449.92 µmol, 1 eq) HATU (205.29 mg, 539.90 µmol, 1.2 *eq*) in DMF (3 mL) was added Et_3N (136.58 mg, 1.35 mmol, 187.87 µL, 3 eq) at 25°C. The mixture was stirred at 25°C for 5 min, then 1-(5-amino-2-pyridyl)-N-[2-[(2,2,2-trifluoroacetyl)amino]ethyl]piperidine-4-carboxamide, BzL-23d (161.68 mg, 449.92 µmol, 1 *eq*) was added to the mixture, stirred for 30 min. LCMS showed major as desired. The mixture was poured into water (50mL). The aqueous phase was extracted with ethyl acetate (50 mL). The combined organic phase was washed with brine (50 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum to give BzL-23i (0.3 g, 381.75 µmol, 84.85% yield) as yellow oil.

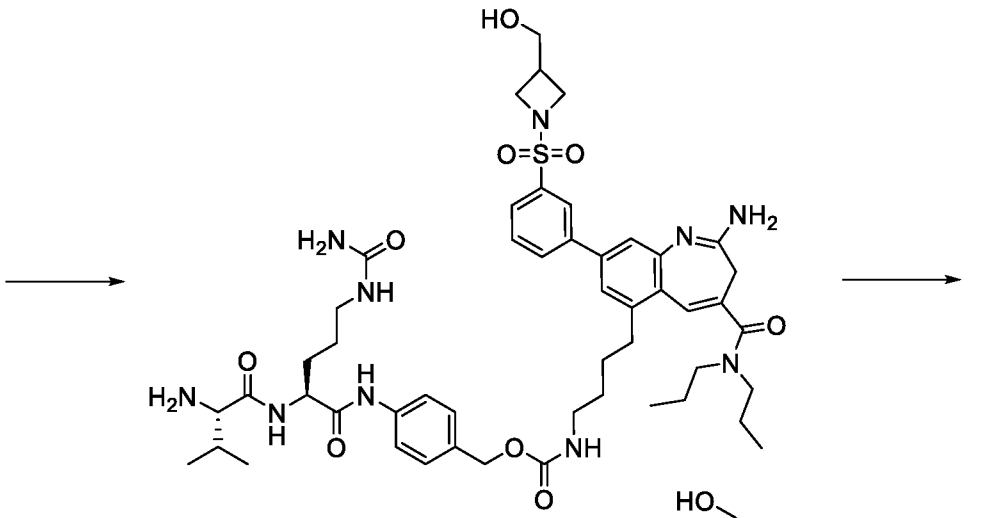
Synthesis of tert-butyl (3-(2-amino-8-((6-(4-((2-aminoethyl)carbamoyl)piperidin-1-yl)pyridin-3-yl)carbamoyl)-N-propyl-3H-benzo[b]azepine-4-carboxamido)propyl)carbamate, BzL-23

To a mixture of tert-butyl N-[3-[[2-amino-8-[[6-[4-[2-[(2,2,2-trifluoroacetyl) amino]ethylcarbamoyl]-1-piperidyl]-3-pyridyl]carbamoyl]-3H-1-benzazepine-4-carbonyl]-propyl-amino]propyl]carbamate, BzL-23i (0.25 g, 318.13 µmol, 1 *eq*) in MeOH (10 mL) was added $LiOH.H_2O$ (40.05 mg, 954.38 µmol, 3 *eq*) in H_2O (1 mL) at 25°C. The mixture was

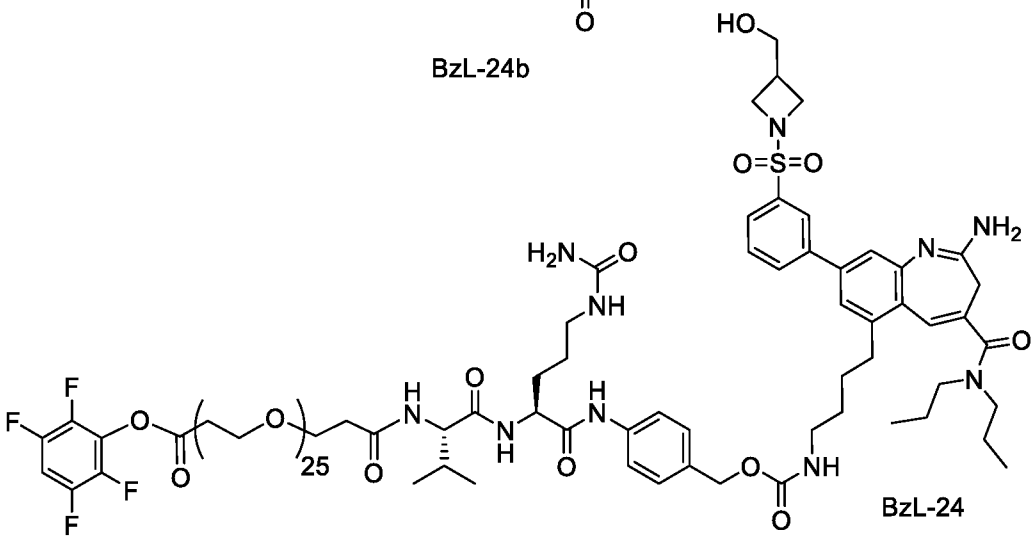
stirred at 40°C for 12 hours. LCMS showed major as desired. The mixture was concentrated in vacuum. The residue was purified by prep-HPLC column: Nano-micro Kromasil C18 100x30mm 5um;mobile phase: [water(0.1%TFA)-ACN];B%: 15%-45%,10min to give BzL-23 (45 mg, 65.23 μmol, 20.51% yield) as a white solid. ^{1}H NMR (MeOD, 400 MHz) δ 8.73 (d, J = 2.4 Hz, 1H), 8.24 (dd, J = 9.8, 2.4 Hz, 1H), 7.75 (br s, 1H), 7.45 (d, J = 9.8 Hz, 1H), 7.15 (br s, 1H), 4.24 (br d, J = 13.6 Hz, 2H), 3.35-3.62 (m, 9H), 3.05-3.12 (m, 4H), 2.59-2.72 (m, 1H), 1.99-2.09 (m, 2H), 1.65-1.94 (m, 6H), 1.45 (s, 9H), 0.90-0.98 (m, 3H). LC/MS [M+H] 690.41 (calculated); LC/MS [M+H] 690.40 (observed).

Example 47 Synthesis of BzL-24





BzL-24b



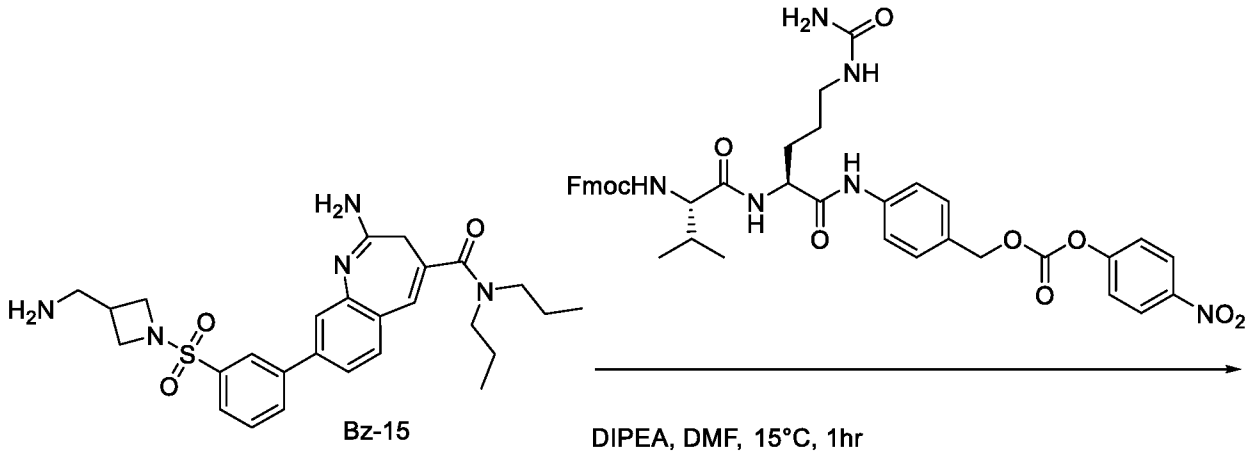
BzL-24

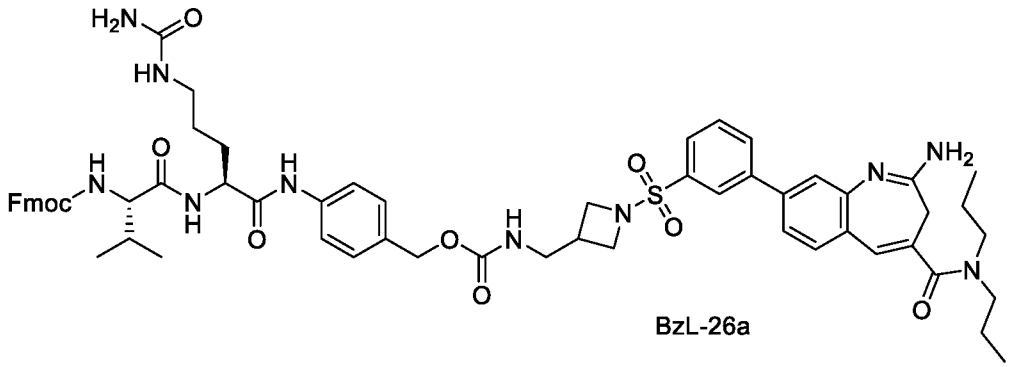
4-((*S*)-2-((*S*)-2-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)-3-methylbutanamido)-5-ureidopentanamido)benzyl (4-(2-amino-4-(dipropylcarbamoyl)-8-(3-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-3*H*-benzo[*b*]azepin-6-yl)butyl)carbamate, BzL-24a was synthesized from Bz-14 according to the procedure described for BzL-26a. LC/MS [M+H] 1209.58 (calculated); LC/MS [M+H] 1209.85 (observed).

4-((*S*)-2-((*S*)-2-Amino-3-methylbutanamido)-5-ureidopentanamido)benzyl (4-(2-amino-4-(dipropylcarbamoyl)-8-(3-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-3*H*-benzo[*b*]azepin-6-yl)butyl)carbamate, BzL-24b was synthesized according to the procedure described for BzL-26. LC/MS [M+H] 987.51 (calculated); LC/MS [M+H] 987.75 (observed).

2,3,5,6-Tetrafluorophenyl (6*S*,9*S*)-1-amino-6-((4-((((4-(2-amino-4-(dipropylcarbamoyl)-8-(3-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-3*H*-benzo[*b*]azepin-6-yl)butyl)carbamoyl)oxy)methyl)phenyl)carbamoyl)-9-isopropyl-1,8,11-trioxo-14,17,20,23,26,29,32,35,38,41,44,47,50,53,56,59,62,65,68,71,74,77,80,83,86-pentacosaoxa-2,7,10-triazanonaoctacontan-89-oate, BzL-24 was synthesized according to the procedure described for BzL-15. LC/MS [M+2H/2] 1168.59 (calculated); LC/MS [M+2H/2] 1169.36 (observed).

Example 48 Synthesis of BzL-26



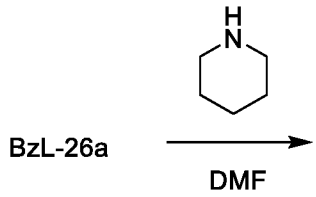


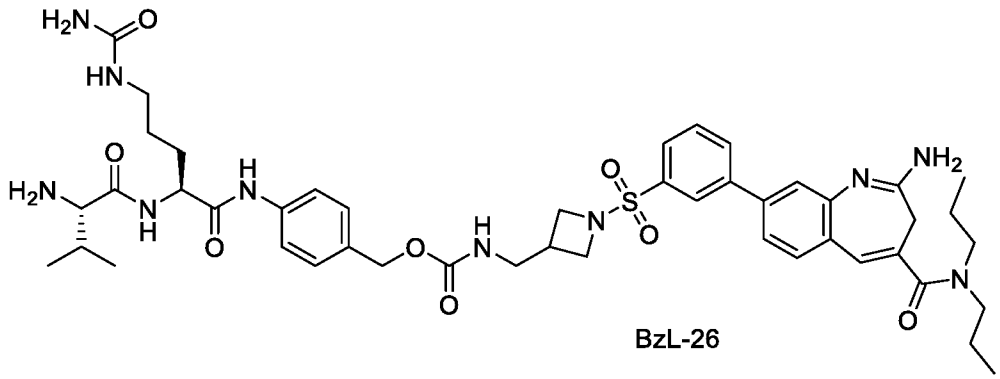
Synthesis of (9H-fluoren-9-yl)methyl ((S)-1-(((S)-1-((4-(((((1-((3-(2-amino-4-(dipropylcarbamoyl)-3H-benzo[b]azepin-8-yl)phenyl)sulfonyl)azetidin-3-yl)methyl)carbamoyl)oxy)methyl)phenyl)amino)-1-oxo-5-ureidopentan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate, BzL-26a

To a solution of [4-[[(2S)-2-[[(2S)-2-(9H-fluoren-9-ylmethoxycarbonylamino) -3-methyl-butanoyl]amino]-5-ureido-pentanoyl]amino]phenyl]methyl (4-nitrophenyl) carbonate (200 mg, 260.83 μmol, 1 *eq*) in DMF(1 mL) was added a solution of 2-amino-8-[3-[3-(aminomethyl)azetidin-1-yl]sulfonylphenyl]-N,N-dipropyl-3H-1-benzazepine-4-carboxamide, Bz-15 (325.35 mg, 521.65 μmol, 2 *eq*, TFA) and DIPEA (67.42 mg, 521.65 μmol, 90.86 μL, 2 *eq*) in DMF(1 mL) at 15 °C under N_2. The mixture was stirred at 15°C for 1 hr. The mixture was filtered. The residue was purified by prep-HPLC (column: Nano-micro Kromasil C18 100 x 30mm 5um; liquid phase: [A-TFA/H2O=0.1% v/v; B-ACN] B%: 30%-60%, 12 min]) to give [4-[[(2S)-2- [[(2S)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-3-methyl-butanoyl]amino]-5-ureido-pentanoyl]amino]phenyl]methylN-[[1-[3-[2-amino-4-(dipropylcarbamoyl)-3H-1-benzazepin-8-yl]phenyl]sulfonylazetidin-3-yl]methyl]carbamate, BzL-26a (73 mg, 63.07 μmol, 24.18% yield, 98.259% purity) as white solid. ^{1}H NMR (MeOD-d_4, 400 MHz) δ 8.05-8.09 (m,

1H), 7.92-7.98 (m, 1H), 7.84-7.90 (m, 1H), 7.58-7.83 (m, 8H), 7.46-7.57 (m, 2H), 7.33-7.42 (m, 2H), 7.25-7.33 (m, 2H), 7.11-7.23 (m, 2H), 7.04-7.09 (m, 1H), 4.87-4.94 (m, 2H), 4.46-4.56 (m, 1H), 4.31-4.45 (m, 2H), 4.16-4.26 (m, 1H), 3.95 (br d, J = 7.0 Hz, 1H), 3.85 (br t, J = 8.0 Hz, 2H), 3.52-3.63 (m, 2H), 3.46 (br d, J = 2.0 Hz, 4H), 3.35 (s, 3H), 3.15-3.23 (m, 1H), 3.01-3.13 (m, 3H), 2.58-2.71 (m, 1H), 2.00-2.16 (m, 1H), 1.84-1.96 (m, 1H), 1.64-1.77 (m, 4H), 1.49-1.62 (m, 2H), 0.75-1.09 (m, 12H) LC/MS [M+H] 1137.52 (calculated); LC/MS [M+H] 1137.10 (observed).

Synthesis of 4-((S)-2-((S)-2-amino-3-methylbutanamido)-5-ureidopentanamido)benzyl ((1-((3-(2-amino-4-(dipropylcarbamoyl)-3H-benzo[b]azepin-8-yl)phenyl)sulfonyl)azetidin-3-yl)methyl)carbamate, BzL-26

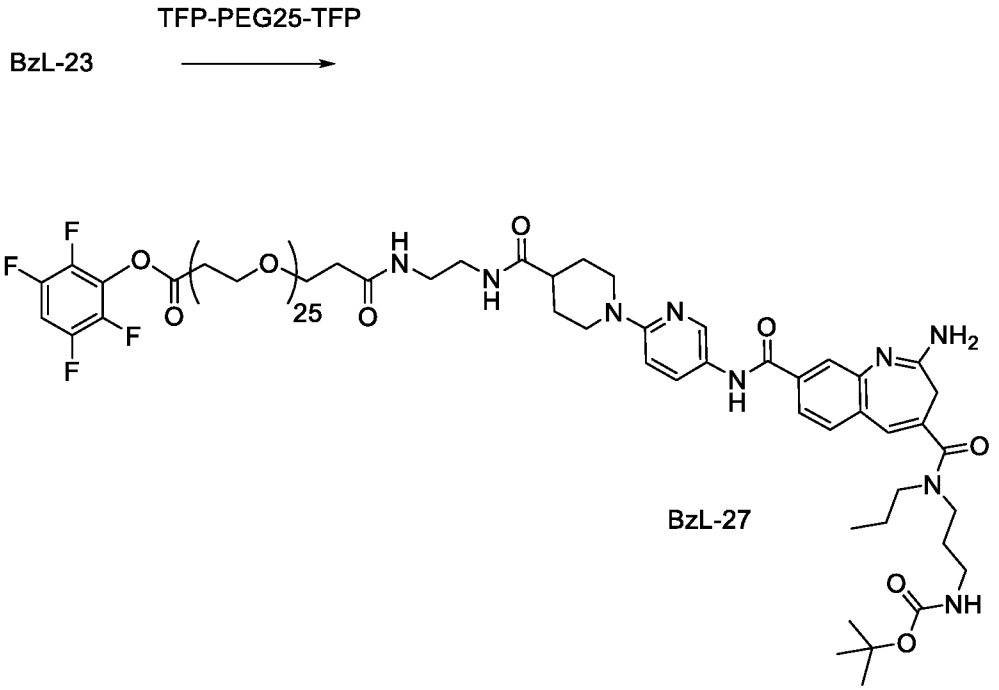




To a solution of [4- [[(2S)-2- [[(2S)-2- (9H-fluoren- 9-ylmethoxycarbonylamino)-3 -methyl- butanoyl]amino]-5-ureido-pentanoyl]amino]phenyl]methylN-[[1-[3-[2-amino-4-(dipropylcarbamoyl)-3H-1-benzazepin-8-yl]phenyl]sulfonylazetidin-3-yl]methyl]carbamate, BzL-26a (0.12 g, 105.51 µmol, 1 *eq*) in DMF (2 mL) was added piperidine (44.92 mg, 527.54 µmol, 52.10 µL, 5 *eq*) at 25 °C and stirred for 1 hour. The reaction mixture was filtered and the filter was concentrated. The residue was purified by prep-HPLC (column: Welch Xtimate C18 100 x 25mm x 3um; mobile phase: [water (10mM NH4HCO3)-ACN]; B%: 25%-65%, 12 min). Compound [4-[[(2S)-2-[[(2S)-2-amino-3-methyl-butanoyl]amino]-5-ureido-pentanoyl]amino]phenyl]methylN-[[1-[3-[2-amino-4-(dipropylcarbamoyl)-3H-1-benzazepin-8-yl]phenyl]sulfonylazetidin-3-yl]methyl]carbamate, BzL-26 (0.037 g, 38.51 µmol, 36.50% yield, 95.25% purity) was obtained as a yellow solid. ^{1}H NMR (MeOD, 400 MHz) δ 8.06 (s, 1H), 7.98 (d, J = 7.4 Hz, 1H), 7.82 (d, J = 7.4 Hz, 1H), 7.74 (t, J = 7.4 Hz, 1H), 7.54 (d, J = 8.4 Hz, 2H), 7.50-7.43 (m, 2H), 7.38 (d, J = 8.0 Hz, 1H), 7.23 (d, J = 8.8 Hz, 2H), 6.90 (s, 1H), 4.95-4.90 (m,

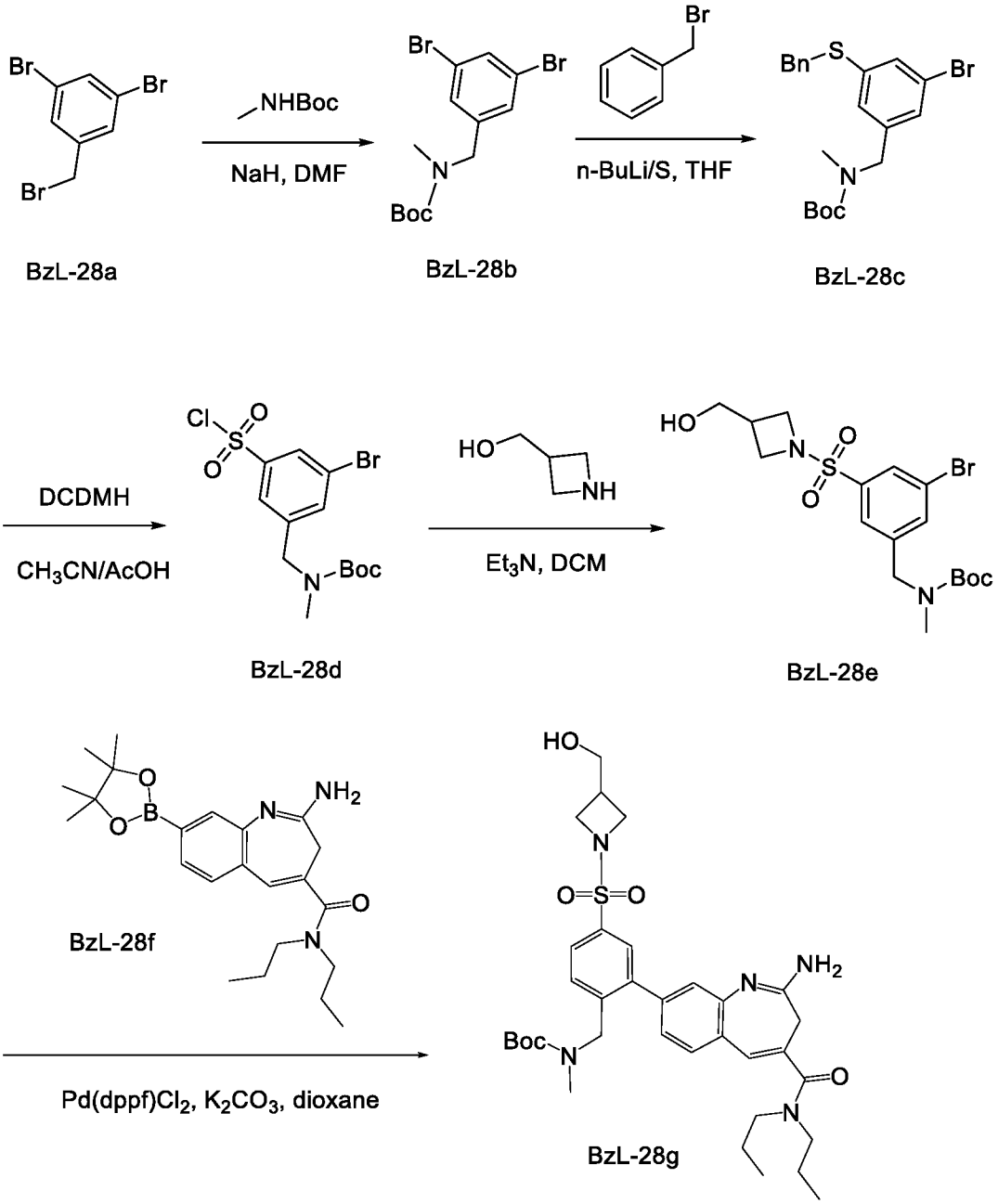
2H), 4.62-4.54 (m, 2H), 3.84 (t, J = 8.2 Hz, 2H), 3.56 (t, J = 4.2 Hz, 2H), 3.44 (t, J = 4.0 Hz, 4H), 3.23 (d, J = 5.2 Hz, 2H), 3.14-3.03 (m, 2H), 2.68-2.62 (m, 1H), 2.04-1.99 (m, 2H), 1.92-1.84 (m, 2H), 1.79-1.47 (m, 8H), 1.08-0.75 (m, 12H). LC/MS [M+H] 915.46 (calculated); LC/MS [M+H] 915.10 (observed).

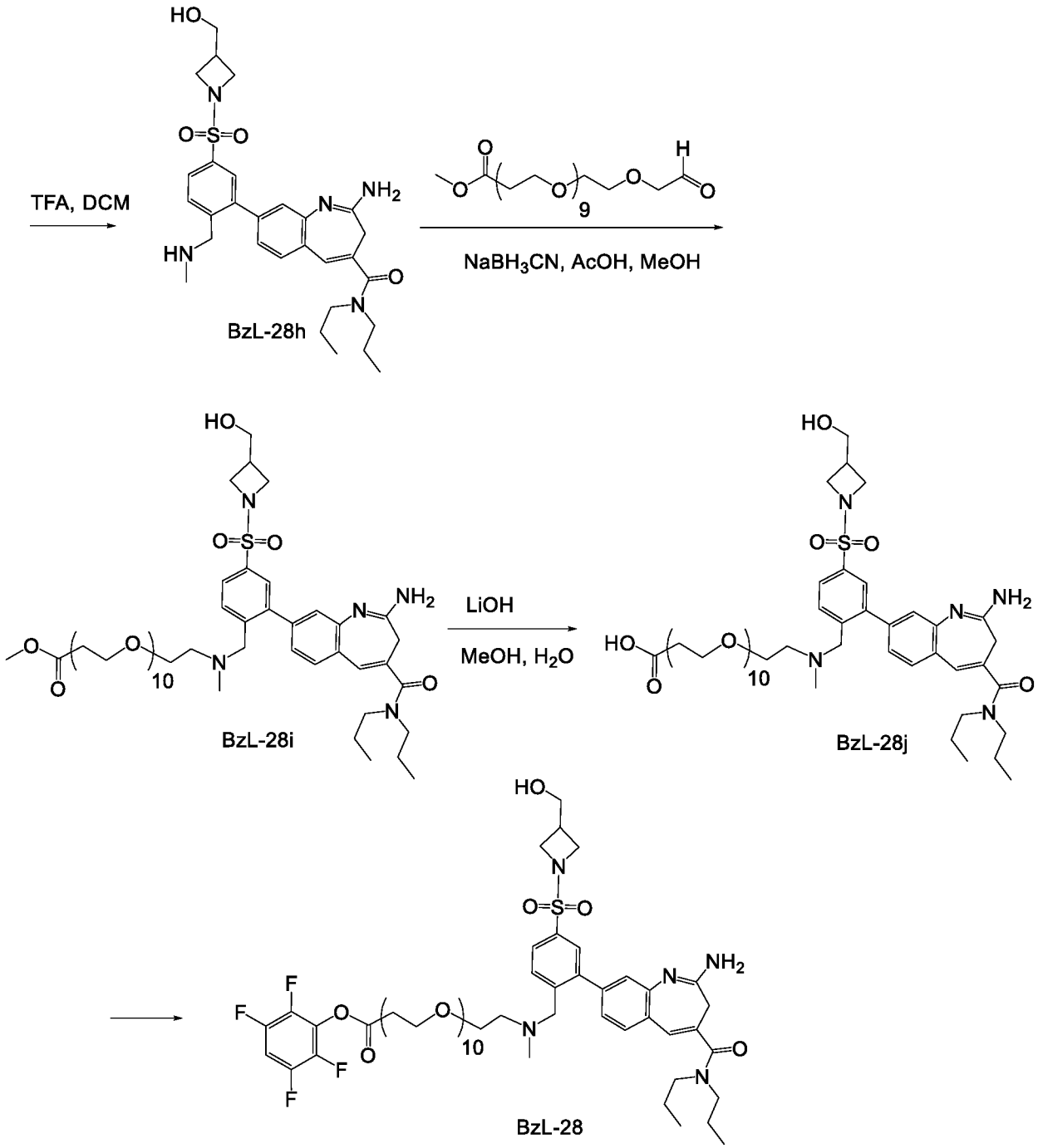
Example 49 Synthesis of BzL-27



2,3,5,6-Tetrafluorophenyl 1-(1-(5-(2-amino-4-((3-((*tert*-butoxycarbonyl)amino)propyl)(propyl)carbamoyl)-3*H*-benzo[*b*]azepine-8-carboxamido)pyridin-2-yl)piperidin-4-yl)-1,6-dioxo-9,12,15,18,21,24,27,30,33,36,39,42,45,48,51,54,57,60,63,66,69,72,75,78,81-pentacosaoxa-2,5-diazatetraoctacontan-84-oate, BzL-27 was synthesized from BzL-23 and TFP-PEG25-TFP according to the procedure described for Bz-31. LC/MS [M+H] 2039.07 (calculated); LC/MS [M+H] 2039.40 (observed).

Example 50 Synthesis of BzL-28.





Synthesis of tert-butyl 3,5-dibromobenzyl(methyl)carbamate, BzL-28b

To a solution of tert-butyl N-methylcarbamate (2.5 g, 19.06 mmol, 1 *eq*) in DMF (80 mL) was added NaH (914.82 mg, 22.87 mmol, 60% purity, 1.2 *eq*) slowly at 0 °C. After addition, the mixture was stirred at 15 °C for 30 min, and then 1,3-dibromo-5-(bromomethyl)benzene, BzL-28a (8.77 g, 26.68 mmol, 1.4 *eq*) was added at 0 °C. The resulting mixture was stirred at 15 °C for 2 h. TLC indicated the reactant was consumed completely. The reaction mixture was quenched by addition of aq. NH_4Cl (250 mL) at 0 °C, and then extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (30 mL x 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether:Ethyl acetate = 1:0 to

5:1) to give BzL-28b (6.6 g, 17.41 mmol, 91.35% yield) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.59-7.56 (m, 1H), 7.31 (s, 2H), 4.36 (s, 2H), 2.87 (s, 3H), 1.49 (s, 9H).

Synthesis of tert-butyl 3-(benzylthio)-5-bromobenzyl(methyl)carbamate, BzL-28c

To a solution of tert-butyl 3,5-dibromobenzyl(methyl)carbamate, BzL-28b (3.6 g, 9.50 mmol, 1 *eq*) in THF (70 mL) was added dropwise n-BuLi (2.5 M, 3.80 mL, 1 *eq*) at -78 °C under N_2. After addition, the mixture was stirred at -78 °C for 15 min, and then sulfur, S (304.55 mg, 9.50 mmol, 1 *eq*) was added at -78 °C. After addition, the mixture was stirred at -78 °C for 45 min, and then bromomethylbenzene (1.62 g, 9.50 mmol, 1.13 mL, 1 *eq*) was added at -78 °C. The resulting mixture was warmed to 15 °C and stirred at 15 °C for 30 min. TLC indicated BzL-28b was consumed completely. The reaction mixture was quenched by addition of aq. NH_4Cl (70 mL) at 0 °C, and then extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether:Ethyl acetate = 1:0 to 5:1) to give BzL-28c (0.97 g, 2.30 mmol, 24.18% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35-7.26 (m, 5H), 7.26-7.21 (m, 1H), 7.17 (s, 1H), 7.04 (s, 1H), 4.34 (s, 2H), 4.12 (s, 2H), 2.79 (s, 3H), 1.48 (s, 9H).

Synthesis of tert-butyl 3-bromo-5-(chlorosulfonyl)benzyl(methyl)carbamate, BzL-28d

To a solution of tert-butyl 3-(benzylthio)-5-bromobenzyl(methyl)carbamate, BzL-28c (1.22 g, 2.89 mmol, 1 *eq*) in CH_3CN (25 mL) and H_2O (1 mL) and acetic acid, AcOH (520.35 mg, 8.67 mmol, 495.57 µL, 3 *eq*) was added 1,3-dichloro-5,5-dimethyl-imidazolidine-2,4-dione, DCDMH (1.14 g, 5.78 mmol, 2 *eq*) at 0 °C. The mixture was stirred at 0 °C for 1h. TLC indicated BzL-28c was consumed completely. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was diluted with H_2O (20 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether:Ethyl acetate = 1:0 to 5:1) to give BzL-28d (0.51 g, 1.28 mmol, 44.29% yield) as a light yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.08 (s, 1H), 7.83 (s, 1H), 7.74 (s, 1H), 4.50 (s, 2H), 2.91 (s, 3H), 1.49 (s, 9H).

Synthesis of tert-butyl 3-bromo-5-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)benzyl(methyl)carbamate, BzL-28e

To a solution of tert-butyl 3-bromo-5-(chlorosulfonyl)benzyl(methyl)carbamate, BzL-28d (0.74 g, 1.86 mmol, 1 *eq*) and azetidin-3-ylmethanol (746.66 mg, 3.71 mmol, 2 *eq*, TFA) in DCM (15 mL) was added TEA (751.25 mg, 7.42 mmol, 1.03 mL, 4 *eq*) at 0 °C. The mixture was stirred at 15°C for 1 h. TLC indicated Reactant 1 was consumed completely. The reaction mixture was quenched by addition of H_2O (15 mL) at 0 °C, and then extracted with EtOAc (15

mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue purified by column chromatography (SiO_2, Petroleum ether:Ethyl acetate = 10:1 to 0:1) to give BzL-28e (640 mg, 1.42 mmol, 76.74% yield) as a light yellow oil. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.90 (s, 1H), 7.69-7.53 (m, 2H), 4.48 (s, 2H), 3.89 (t, *J* = 8.0 Hz, 2H), 3.64 (d, *J* = 6.0 Hz, 3H), 3.42 (s, 1H), 2.95 (s, 3H), 2.65 (s, 1H), 1.49 (s, 9H).

Synthesis of tert-butyl 3-(2-amino-4-(dipropylcarbamoyl)-3H-benzo[b]azepin-8-yl)-5-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)benzyl(methyl)carbamate, BzL-28g

A mixture of tert-butyl 3-bromo-5-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)benzyl(methyl)carbamate, BzL-28e (590 mg, 1.31 mmol, 1 *eq*), 2-amino-N,N-dipropyl-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3H-benzo[b]azepine-4-carboxamide, BzL-28f (702.11 mg, 1.71 mmol, 1.3 *eq*), $Pd(dppf)Cl_2$ (48.0 mg, 65.7 µmol, 0.05 *eq*), K_2CO_3 (362.9 mg, 2.63 mmol, 2 *eq*) in dioxane (10 mL) and H_2O (1 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 90 °C for 3 h under N_2 atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (TFA condition: column: Nano-micro Kromasil C18 100x30mm, 5um;mobile phase: [water(0.1%TFA)-ACN];B%: 40%-60%,10min) to give BzL-28g (180 mg, 275.30 µmol, 20.97% yield) as a yellow solid.

Synthesis of 2-amino-8-(3-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)-5-((methylamino)methyl)phenyl)-N,N-dipropyl-3H-benzo[b]azepine-4-carboxamide, BzL-28h

To a solution of tert-butyl 3-(2-amino-4-(dipropylcarbamoyl)-3H-benzo[b]azepin-8-yl)-5-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)benzyl(methyl)carbamate, BzL-28g (180 mg, 275.30 µmol, 1 *eq*) in DCM (2 mL) was added TFA (627.80 mg, 5.51 mmol, 407.66 µL, 20 *eq*) at 15 °C. The mixture was stirred at 15 °C for 1 h. LC-MS showed Reactant 1 was consumed. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was added with THF (5 mL) and aq. $NaHCO_3$ (5 mL) to pH 8-9 at 0 °C, and then stirred at 15 °C for 30 min. The reaction mixture was concentrated under reduced pressure to give a residue and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give BzL-28h (110 mg, 198.66 µmol, 72.16% yield) as a yellow oil. LC/MS [M+H] 554.28 (calculated); LC/MS [M+H] 554.30 (observed).

Synthesis of methyl 1-(3-(2-amino-4-(dipropylcarbamoyl)-3H-benzo[b]azepin-8-yl)-5-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-2-methyl-5,8,11,14,17,20,23,26,29,32-decaoxa-2-azapentatriacontan-35-oate, BzL-28i

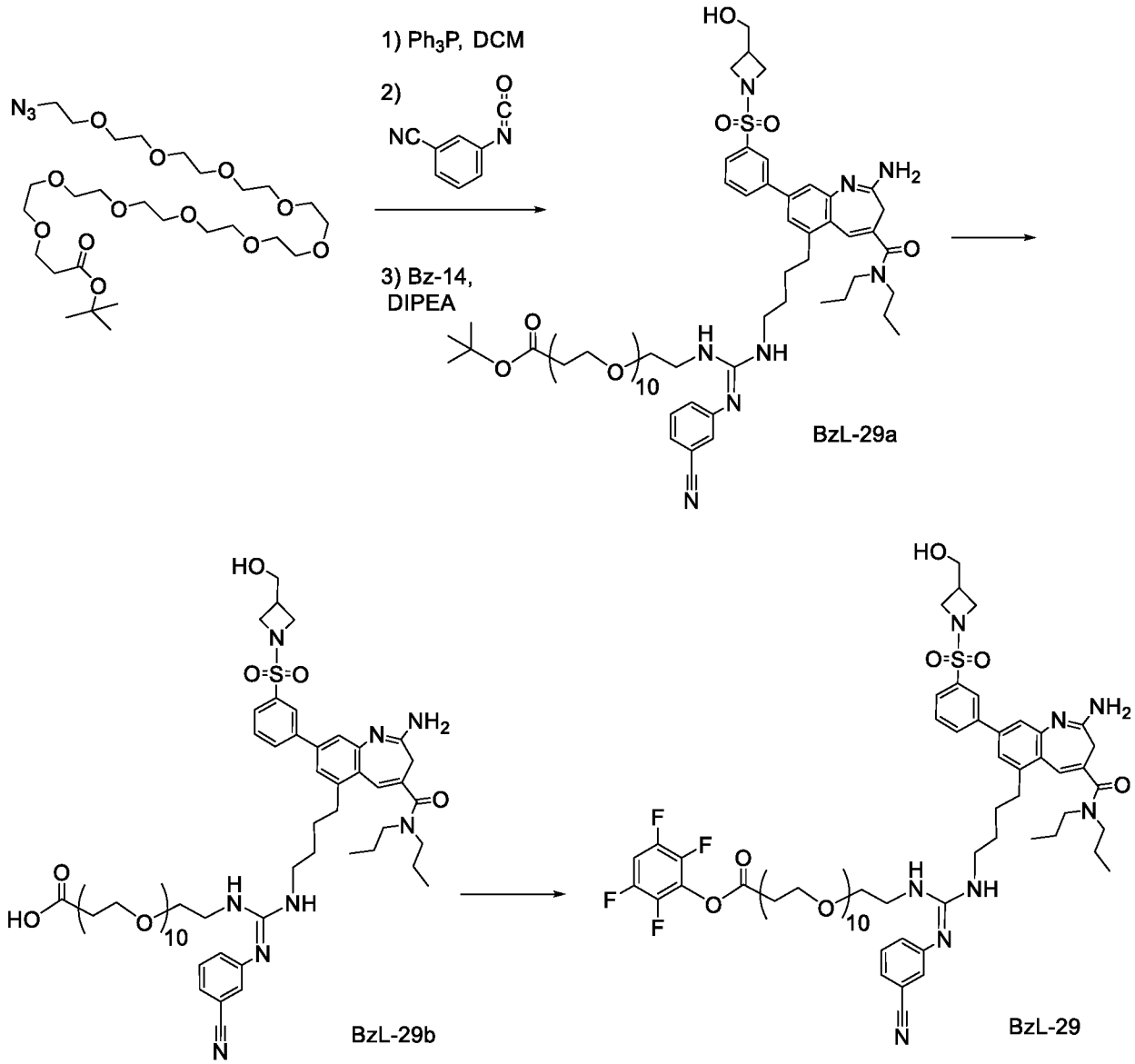
To a solution of 2-amino-8-(3-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)-5-((methylamino)methyl)phenyl)-N,N-dipropyl-3H-benzo[b]azepine-4-carboxamide, BzL-28h (110 mg, 198.66 μmol, 1 *eq*) and methyl 1-oxo-3,6,9,12,15,18,21,24,27,30-decaoxatritriacontan-33-oate (140.13 mg, 258.26 μmol, 1.3 *eq*) in MeOH (2 mL) was added AcOH (11.93 mg, 198.66 μmol, 11.36 μL, 1 *eq*) at 15 °C. After addition, the mixture was stirred at 15 °C for 15 min, and then $NaBH_3CN$ (24.97 mg, 397.32 μmol, 2 *eq*) was added at 15 °C. The resulting mixture was stirred at 15 °C for 12 h. The reaction mixture was used for next step directly, containing BzL-28i (0.22 g, crude) (in MeOH) as a light yellow liquid. LC/MS [M+2H/2] 540.79 (calculated); LC/MS [M+H] 541.1 (observed).

Synthesis of 1-(3-(2-amino-4-(dipropylcarbamoyl)-3H-benzo[b]azepin-8-yl)-5-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-2-methyl-5,8,11,14,17,20,23,26,29,32-decaoxa-2-azapentatriacontan-35-oic acid, BzL-28j

To a solution of methyl 1-(3-(2-amino-4-(dipropylcarbamoyl)-3H-benzo[b]azepin-8-yl)-5-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-2-methyl-5,8,11,14,17,20,23,26,29,32-decaoxa-2-azapentatriacontan-35-oate, BzL-28i (0.22 g, 203.64 μmol, 1 *eq*) in MeOH (2 mL) and H_2O (1 mL) was added $LiOH.H_2O$ (68.36 mg, 1.63 mmol, 8 *eq*) at 15 °C. The mixture was stirred at 15 °C for 5 h. LC-MS showed BzL-28i was consumed. The reaction mixture was adjusted to pH 6-7 with 1 N HCl at 0 °C, and then concentrated under reduced pressure. The residue was purified by prep-HPLC (TFA condition: column: Welch Xtimate C18 100x25mm, 3um;mobile phase: [water(0.1%TFA)-ACN];B%: 20%-40%,12min) twice to give BzL-28j (104 mg, 94.31 μmol, 46.31% yield, HCl) as a light yellow oil. ^1H NMR (MeOD-d_4, 400 MHz) δ 8.33 (s, 1H), 8.24 (s, 1H), 8.12 (s, 1H), 7.90-7.84 (m, 2H), 7.74 (d, J = 8.8 Hz, 1H), 7.12 (s, 1H), 3.96-3.88 (m, 4H), 3.76-3.67 (m, 8H), 3.66-3.52 (m, 33H), 3.51-3.37 (m, 9H), 3.02 (s, 3H), 2.71-2.59 (m, 1H), 2.53 (t, J = 6.0 Hz, 2H), 1.77-1.63 (m, 4H), 0.95 (br s, 6H). LC/MS [M+H] 1066.56 (calculated); LC/MS [M+H] 1066.10 (observed).

2,3,5,6-Tetrafluorophenyl 1-(3-(2-amino-4-(dipropylcarbamoyl)-3*H*-benzo[*b*]azepin-8-yl)-5-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-2-methyl-5,8,11,14,17,20,23,26,29,32-decaoxa-2-azapentatriacontan-35-oate, BzL-28 was synthesized by reaction with 2,3,5,6-tetrafluorophenol according to the procedure described for BzL-22. LC/MS [M+H] 1214.56 (calculated); LC/MS [M+H] 1214.83 (observed).

Example 51 Synthesis of BzL-29.



Synthesis of *tert*-butyl (*Z*)-40-(2-amino-4-(dipropylcarbamoyl)-8-(3-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-3*H*-benzo[*b*]azepin-6-yl)-35-((3-cyanophenyl)imino)-4,7,10,13,16,19,22,25,28,31-decaoxa-34,36-diazatetracontanoate, BzL-29a

A 4 mL vial was charged with *tert*-butyl 1-azido-3,6,9,12,15,18,21,24,27,30-decaoxatritriacontan-33-oate (0.011 mmol, 6.9 mg), triphenylphosphine (0.011 mmol, 3 mg) and 200 µL of anhydrous dichloromethane. The reaction was maintained at 30 °C for 90 min, at which point 3-cyanophenyl isocyanate (0.011 mmol, 1.6 mg) was added. After 45 min a solution containing Bz-14 (0.011 mmol) and diisopropylethylamine, Hunigs base (0.034 mmol) in 200 µL DMF was added. This reaction was maintained for 2 h then concentrated under reduced pressure. The crude reaction was purified using reverse phase preparative HPLC utilizing a 25-75% gradient of acetonitrile:water containing 0.1% trifluoroacetic acid. The

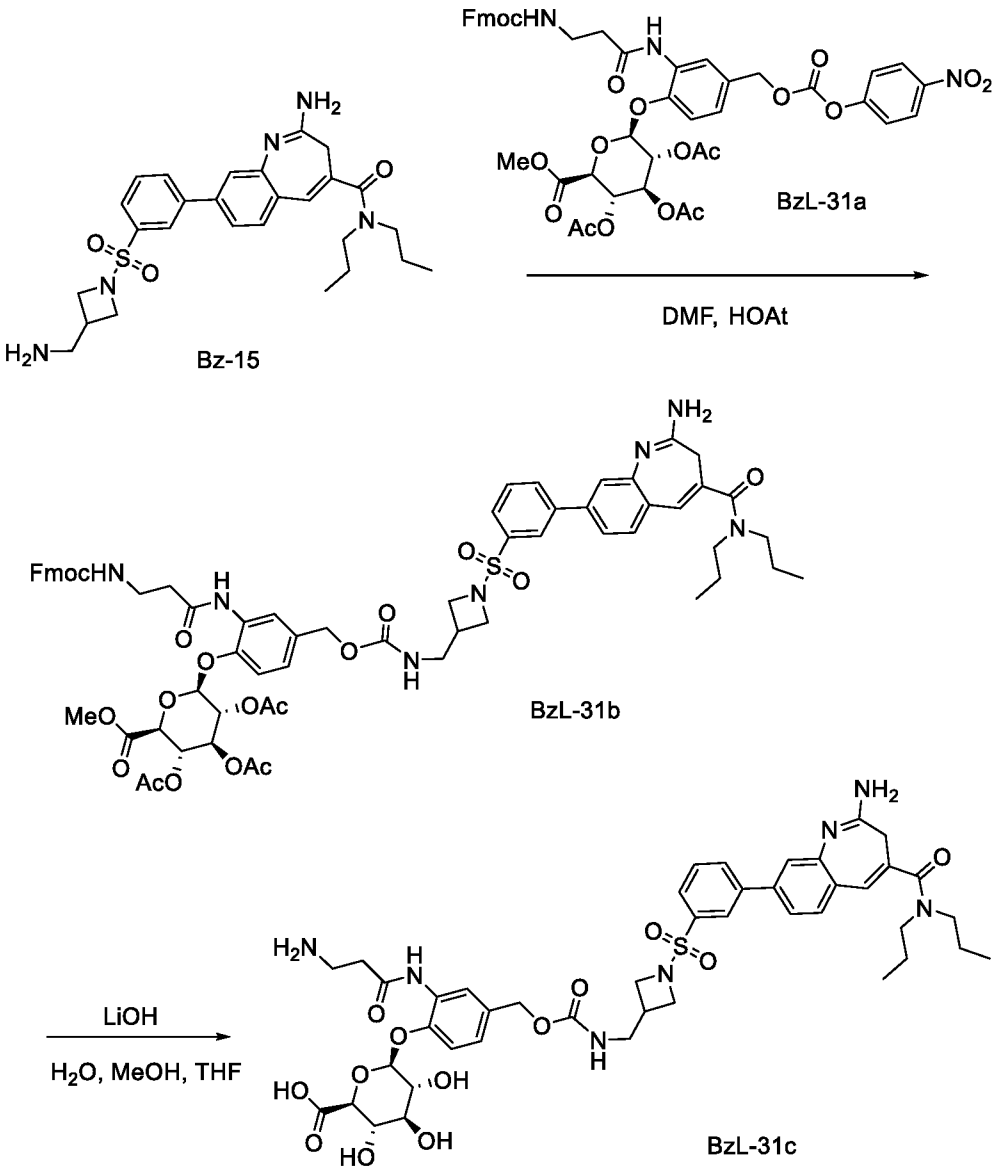
purified fractions were combined and lyophilized to afford 4.1 mg of BzL-29a in 63% yield. LC/MS [M+H] 1293.71 (calculated); LC/MS [M+H] 1294.04 (observed).

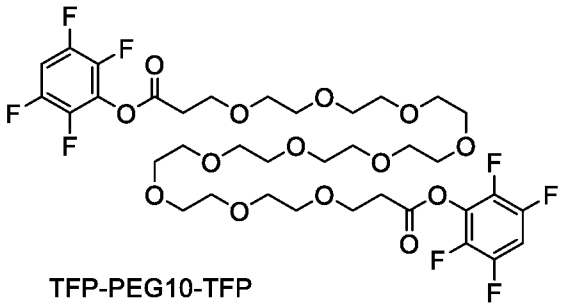
Synthesis of (*Z*)-40-(2-amino-4-(dipropylcarbamoyl)-8-(3-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-3*H*-benzo[*b*]azepin-6-yl)-35-((3-cyanophenyl)imino)-4,7,10,13,16,19,22,25,28,31-decaoxa-34,36-diazatetracontanoic acid, BzL-29b

A vial was charged with BzL-29a (4.1 mg, 0.003 mmol), 500 µL DCM, and 100 µL trifluoroacetic acid. The reaction was maintained for 1 h, concentrated under reduced pressure, and azeotroped thrice with 1 mL toluene. The crude product BzL-29b was taken onto the subsequent step.

2,3,5,6-Tetrafluorophenyl (*Z*)-40-(2-amino-4-(dipropylcarbamoyl)-8-(3-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-3*H*-benzo[*b*]azepin-6-yl)-35-((3-cyanophenyl)imino)-4,7,10,13,16,19,22,25,28,31-decaoxa-34,36-diazatetracontanoate, BzL-29 was synthesized by reaction of BzL-29b with 2,3,5,6-tetrafluorophenol according to the procedure described for Bz-22. LC/MS [M+H] 1385.64 (calculated); LC/MS [M+H] 1385.84 (observed).

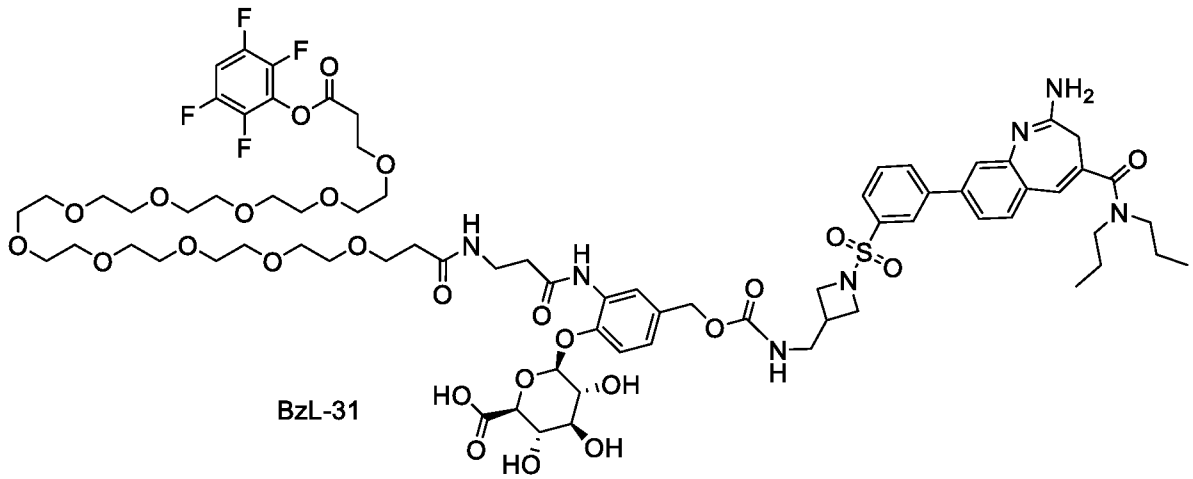
Example 52 Synthesis of BzL-31





DIPEA

DMF, 70 °C



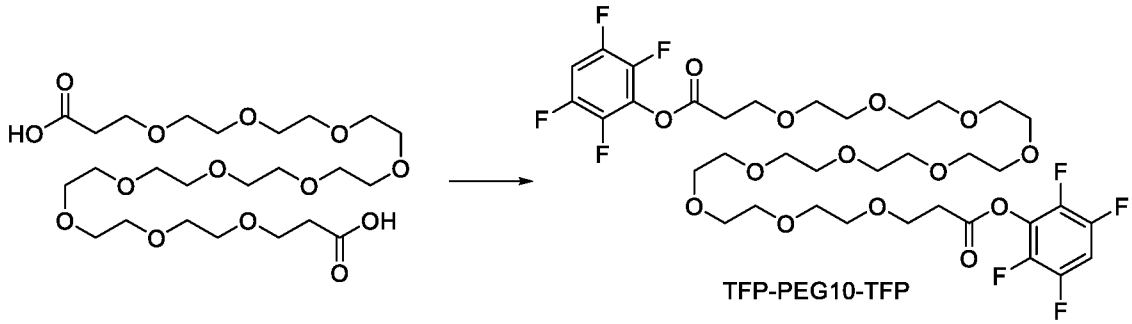
Synthesis of *rac*-(2*R*,3*S*,4*R*,5*R*,6*R*)-2-(2-(3-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)propanamido)-4-(((((1-((3-(2-amino-4-(dipropylcarbamoyl)-3*H*-benzo[*b*]azepin-8-yl)phenyl)sulfonyl)azetidin-3-yl)methyl)carbamoyl)oxy)methyl)phenoxy)-6-(methoxycarbonyl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate, BzL-31b

To a solution of Bz-15 (50 mg, 0.098 mmol, 1 eq) and rac-(2R,3S,4R,5R,6R)-2-(2-(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, BzL-31a (90 mg, 0.098 mmol, 1 eq) in DMF (0.2 ml) was added HOAt (13.3 mg, 0.098 mmol, 1 eq). The reaction was stirred at ambient temperature and monitored by LCMS. The reaction mixture was diluted with 1:1 water:acetonitrile and purified by HPLC to give BzL-31b (67 mg, 0.052 mmol, 53%). LC/MS [M+H] 1284.48 (calculated); LC/MS [M+H] 1284.81 (observed).

Synthesis of *rac*-(2*R*,3*R*,4*R*,5*S*,6*R*)-6-(4-(((((1-((3-(2-amino-4-(dipropylcarbamoyl)-3*H*-benzo[*b*]azepin-8-yl)phenyl)sulfonyl)azetidin-3-yl)methyl)carbamoyl)oxy)methyl)-2-(3-aminopropanamido)phenoxy)-3,4,5-trihydroxytetrahydro-2*H*-pyran-2-carboxylic acid, BzL-31c

BzL-31b (67 mg, 0.052 mmol, 1 eq) was dissolved in a 20 mM solution of LiOH in 5:2:1 THF:MeOH:H_2O (2.6 ml). The reaction was stirred for 1 hour at ambient temperature, then

concentrated and purified by HPLC to give BzL-31c as a white solid (25 mg, 0.027 mmol, 52%). LC/MS [M+H] 922.37 (calculated); LC/MS [M+H] 922.56 (observed).

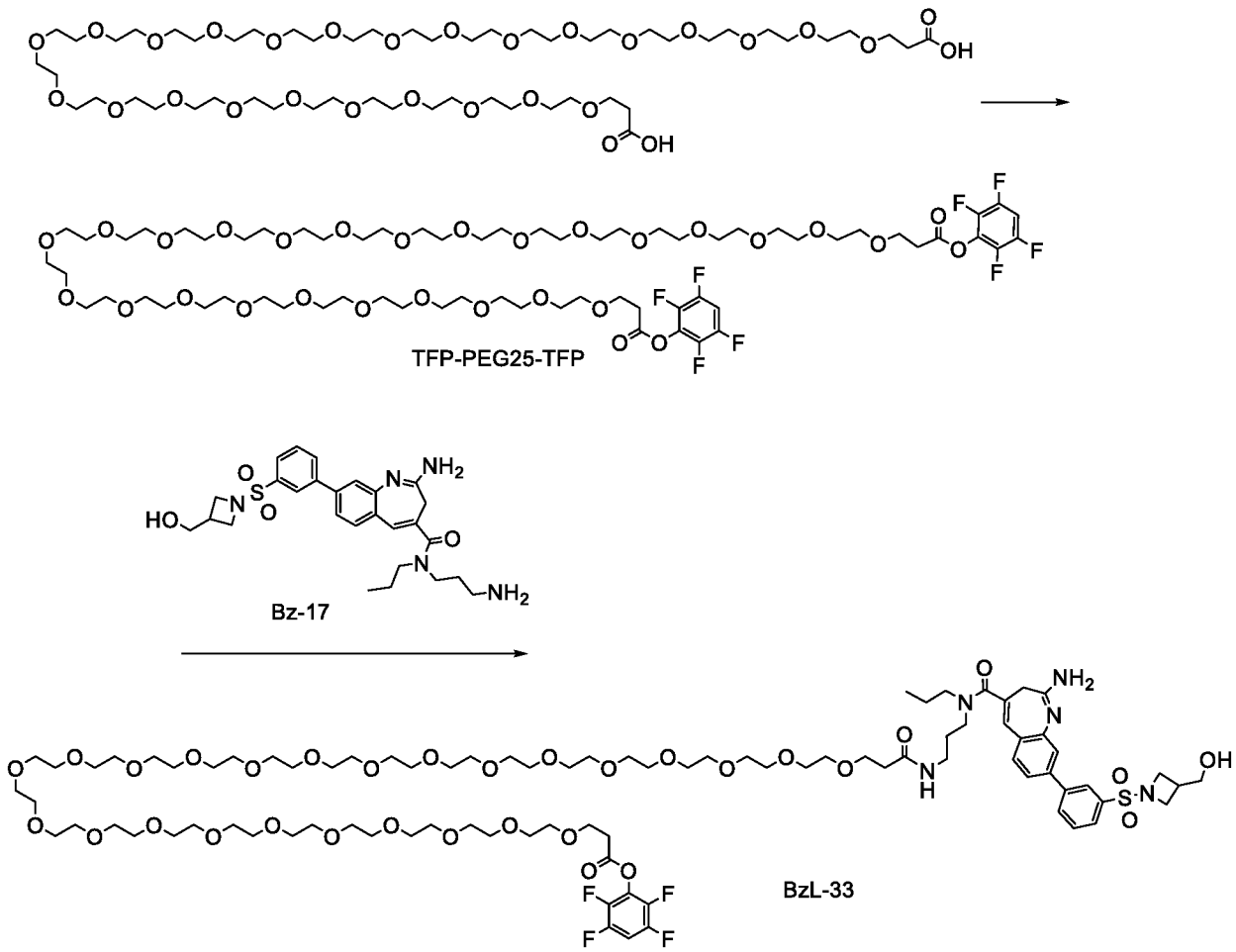


Bis(2,3,5,6-tetrafluorophenyl) 4,7,10,13,16,19,22,25,28,31-decaoxatetratriacontanedioate, TFP-PEG10-TFP was synthesized from 4,7,10,13,16,19,22,25,28,31-decaoxatetratriacontanedioic acid according to the procedure described for TFP-PEG25-TFP. LC/MS [M+H] 855.28 (calculated); LC/MS [M+H] 855.53 (observed).

Synthesis of *rac*-(2*R*,3*R*,4*R*,5*S*,6*R*)-6-(4-(((((1-((3-(2-amino-4-(dipropylcarbamoyl)-3*H*-benzo[*b*]azepin-8-yl)phenyl)sulfonyl)azetidin-3-yl)methyl)carbamoyl)oxy)methyl)-2-(1,34-dioxo-1-(2,3,5,6-tetrafluorophenoxy)-4,7,10,13,16,19,22,25,28,31-decaoxa-35-azaoctatriacontan-38-amido)phenoxy)-3,4,5-trihydroxytetrahydro-2*H*-pyran-2-carboxylic acid, BzL-31

BzL-31c (25 mg, 0.027 mmol, 1 eq) and TFP-PEG10-TFP bis(2,3,5,6-tetrafluorophenyl) 4,7,10,13,16,19,22,25,28,31-decaoxatetratriacontanedioate (35 mg, 0.040 mmol, 1.5 eq) were dissolved in DMF (5 ml). The reaction was neutralized to approximately pH 7 with DIPEA and heated to 70 °C. After 1 hour, another portion of bis(2,3,5,6-tetrafluorophenyl) 4,7,10,13,16,19,22,25,28,31-decaoxatetratriacontanedioate (35 mg, 0.040 mmol, 1.5 eq) was added to the reaction mixture. Upon consumption of BzL-31c, the reaction was concentrated to a yellow film, then triturated with 6 x 3 ml diethyl ether to give a yellow solid that was purified by HPLC to give BzL-31 (14.3 mg, 0.0089 mmol, 33%). LC/MS [M+H] 1610.64 (calculated); LC/MS [M+H] 1610.99 (observed).

Example 53 Synthesis of BzL-33

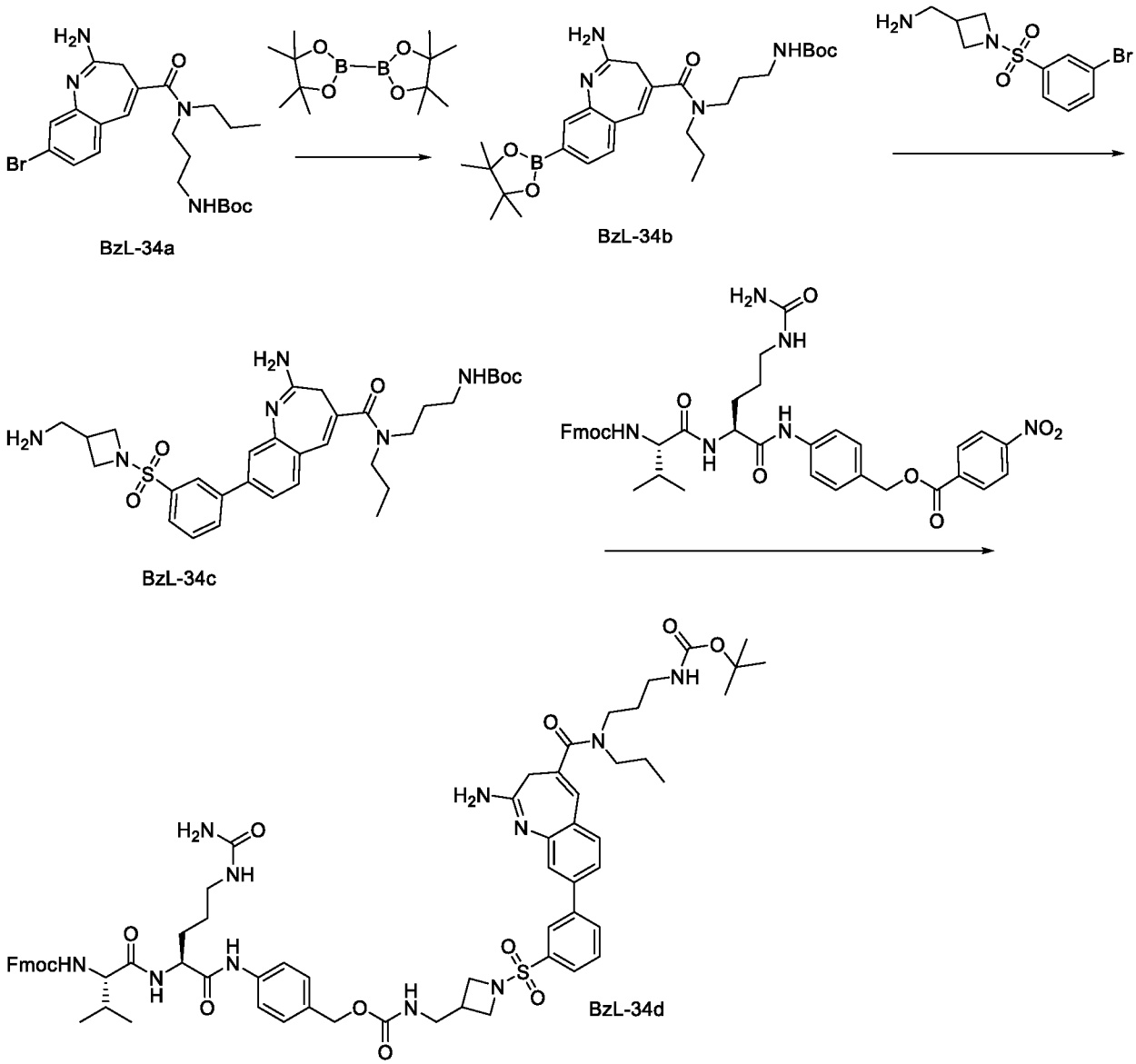


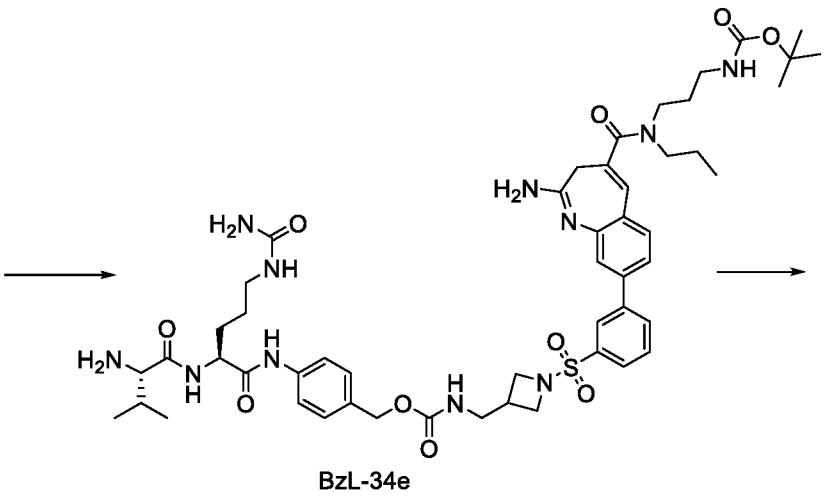
A vial was charged with 4,7,10,13,16,19,22,25,28,31,34,37,40,43,46,49,52,55,58,61,64,67,70,73,76-pentacosaoxanonaheptacontanedioic acid (269 mg, 0.221 mmol), 2,3,5,6-tetrafluorophenol (110 mg, 0.662 mmol), collidine (176 µL, 1.33 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (127 mg, 0.221 mmol) and 3 mL DMF. The reaction was stirred for 16 h, then purified by reverse phase preparative HPLC utilizing a 25-75% gradient of acetonitrile:water containing 0.1% trifluoroacetic acid. The purified fractions were combined and lyophilized to afford 266 mg of bis(2,3,5,6-tetrafluorophenyl) 4,7,10,13,16,19,22,25,28,31,34,37,40,43,46,49,52,55,58,61,64,67,70,73,76-pentacosaoxanonaheptacontanedioate, TFP-PEG25-TFP in 79% yield. LC/MS [M+H] 1515.68 (calculated); LC/MS [M+H] 1516.00 (observed).

A vial was charged with 2-amino-N-(3-aminopropyl)-8-[3-[3-(hydroxymethyl)azetidin-1-yl]sulfonylphenyl]-N-propyl-3H-1-benzazepine-4-carboxamide, Bz-17 (0.0275 mmol), TFP-PEG25-TFP (0.0275 mmol), collidine (0.0825 mmol) in 300 µL DMF. The reaction was maintained for 5h and then purified by reverse phase preparative HPLC utilizing a 25-75% gradient of acetonitrile:water containing 0.1% trifluoroacetic acid. The purified fractions were

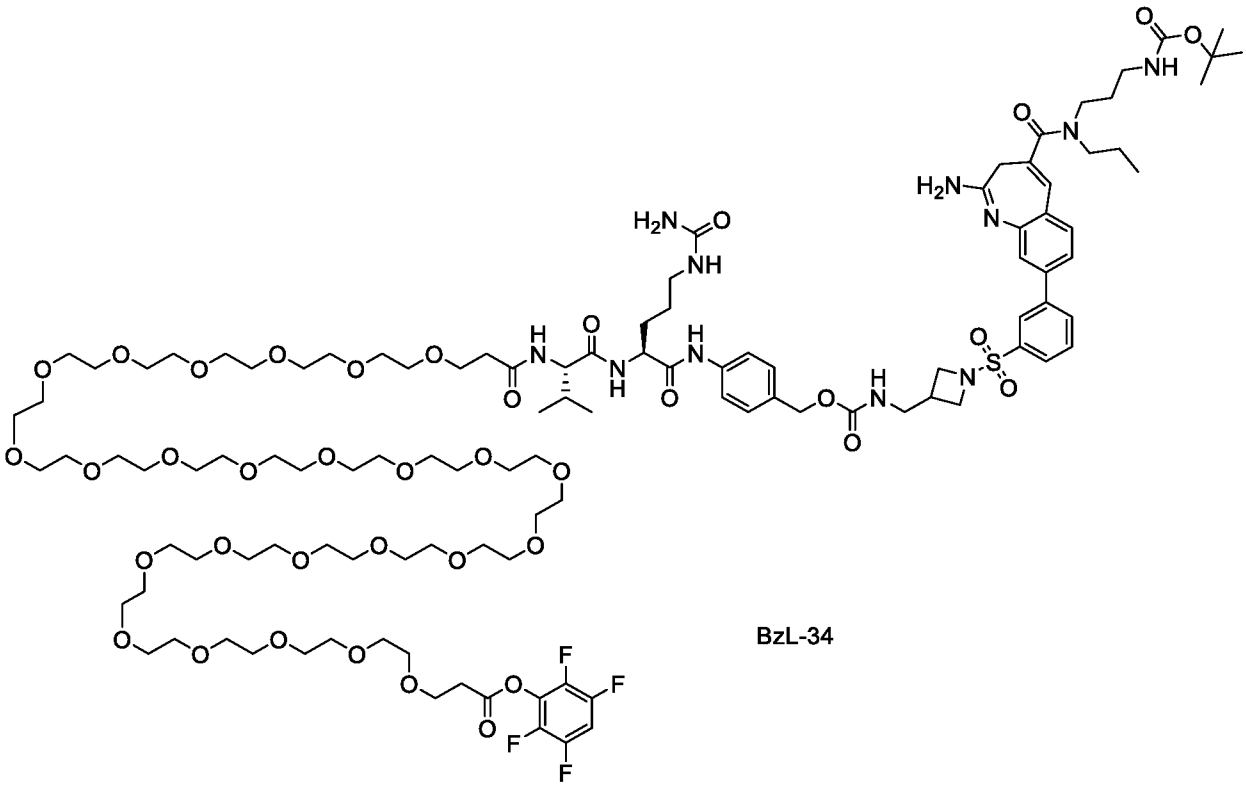
combined and lyophilized to afford 8.2 mg of 2,3,5,6-tetrafluorophenyl 84-(2-amino-8-(3-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-3H-benzo[b]azepine-4-carbonyl)-79-oxo-4,7,10,13,16,19,22,25,28,31,34,37,40,43,46,49,52,55,58,61,64,67,70,73,76-pentacosaoxa-80,84-diazaheptaoctacontanoate, BzL-33 in 25% yield. LC/MS [M+H] 1874.9 (calculated); LC/MS [M+H] 1874.9 (observed).

Example 54 Synthesis of BzL-34





BzL-34e



BzL-34

Preparation of BzL-34b: To a mixture of tert-butyl N-[3-[(2-amino-8-bromo-3H-1-benzazepine-4-carbonyl)–propyl -amino]propyl]carbamate, BzL-34a (0.80 g, 1.67 mmol, 1.0 *eq*) in dioxane (10 mL) was added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane), Pin_2B_2 (509 mg, 2.00 mmol, 1.2 *eq*), KOAc (246 mg, 2.50 mmol, 1.5 *eq*) and $Pd(dppf)Cl_2$ (122 mg, 167 umol, 0.1 *eq*) in one portion at 15°C under N_2 and then stirred at 90°C for 12 h. The mixture was filtered and concentrated to give tert-butyl N-[3-[[2-amino-8-(4,4,5,5-tetramethyl- 1,3,2-dioxaborolan-2-yl)-3H-1-benzazepine-4-carbonyl]-propyl-amino]propyl]carbamate, BzL-34b(0.90 g, crude) as black solid.

Preparation of BzL-34c: To a mixture of [1-(3-bromophenyl)sulfonylazetidin-3-yl]methanamine (0.40 g, 1.17 mmol, 1 *eq*, HCl) and BzL-34b (493 mg, 937 umol, 0.8 *eq*) in dioxane (4 mL) was added a solution of K_2CO_3 (728 mg, 5.27 mmol, 4.5 *eq*) in H_2O (0.4 mL)

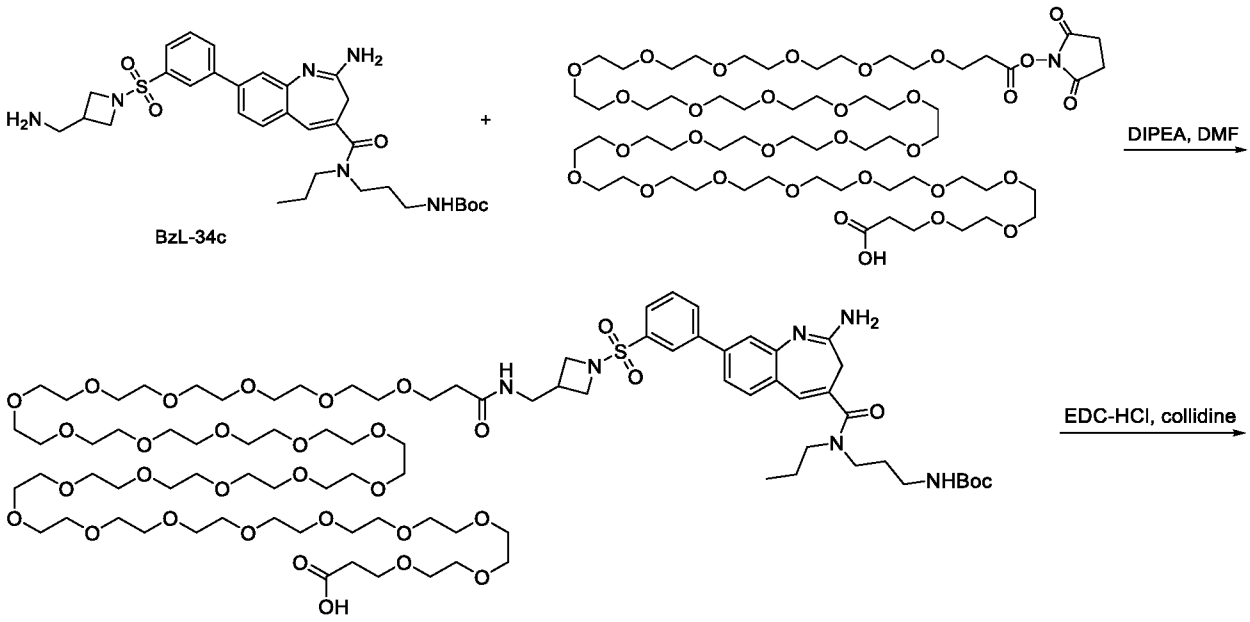
and $Pd(dppf)Cl_2$ (85.7 mg, 117 umol, 0.1 *eq*) at 15°C under N_2 and then stirred at 90 °C for 2 h. The mixture was filtered and concentrated. The residue was purified by prep-HPLC(column: Welch Xtimate C18 100*25mm*3um; mobile phase: [water(0.1% TFA)-ACN]; B%: 20%-45%, 10.5 min) to give tert-butyl N-[3-[[2-amino-8-[3-[3-(aminomethyl)azetidin-1-yl] sulfonylphenyl]-3H-1-benzazepine-4-carbonyl]-propyl-amino]propyl]carbamate, BzL-34c (0.223 g, 357 umol, 30.5% yield) as white solid. ^{1}H NMR (MeOD, 400MHz) δ8.14-8.07 (m, 2H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.86-7.81 (m, 1H), 7.79-7.70 (m, 3H), 7.12 (s, 1H), 3.96 (t, *J* = 8.4 Hz, 2H), 3.65 (dd, *J* = 5.2, 8.4 Hz, 2H), 3.58-3.42 (m, 4H), 3.37 (s, 2H), 3.06 (d, *J* = 7.2 Hz, 4H), 1.90-1.78 (m, 2H), 1.74-1.64 (m, 2H), 1.44 (s, 9H), 0.96-0.90 (m, 3H). LC/MS [M+H] 625.3 (calculated); LC/MS [M+H] 625.0 (observed).

Preparation of BzL-34d: To a mixture of BzL-34c (0.18 g, 288 umol, 1.0 *eq*) and [4-[[(2S)-2-[[(2S)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-3-methyl-butanoyl]amino]-5-ureido-pentanoyl]amino]phenyl]methyl (4-nitrophenyl) carbonate (176.7 mg, 230 umol, 0.8 *eq*) in DMF (2 mL) was added DIEA (74.5 mg, 576 umol, 100 uL, 2.0 *eq*) in one portion at 15 °C. The mixture was stirred at the same temperature for 0.5 h. Then it was filtered and purified by prep-HPLC (column: Welch Xtimate C18 150*25mm*5um; mobile phase: [water (10mM NH_4HCO_3)-ACN]; B%: 55%-75%, 10.5 min) to give [4-[[(2S)-2-[[(2S)-2-(9H-fluoren-9 -ylmethoxycarbonylamino)-3-methyl-butanoyl]amino]-5-ureido-pentanoyl]amino]phenyl] methyl N-[[1-[3-[2-amino-4-[3-(tert-butoxycarbonylamino)propyl-propyl-carbamoyl]-3H-1-benzazepin-8-yl]phenyl]sulfonylazetidin-3-yl]methyl]carbamate, BzL-34d (0.024 g, 19.16 umol, 6.65% yield) as yellow solid. ^{1}H NMR (MeOH,400MHz) δ8.04 (s, 1H), 7.95 (d, *J* = 6.4 Hz, 1H), 7.81-7.79 (m, 3H), 7.73 (d, *J* = 7.6 Hz, 1H), 7.65 (t, *J* = 6.8 Hz, 2H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.48-7.43 (m, 2H), 7.41-7.33 (m, 3H), 7.32-7.27 (m, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 6.91 (s, 1H), 4.59 (s, 2H), 4.52 (s, 1H), 4.42-4.32 (m, 2H), 4.24-4.17 (m, 1H), 3.95 (d, *J* = 7.2 Hz, 1H), 3.86-3.77 (m, 2H), 3.58-3.47 (m, 4H), 3.46-3.39 (m, 2H), 3.19-3.02 (m, 6H), 2.62 (d, *J* = 7.6 Hz, 1H), 2.13-2.01 (m, 1H), 1.97-1.80 (m, 3H), 1.66 (s, 3H), 1.57 (s, 2H), 1.49-1.28 (m, 8H), 1.00-0.95 (m, 10H). LC/MS [M+H] 1252.6 (calculated); LC/MS [M+H] 1252.2 (observed).

Preparation of BzL-34e: A vial was charged with Bz-34d (20 mg, 0.016 mmol), diethylamine (0.08 mmol) and 150 μL DMF. The reaction was maintained for 6 h, then concentrated under reduced pressure to give 4-((S)-2-((S)-2-amino-3-methylbutanamido)-5-ureidopentanamido)benzyl ((1-((3-(2-amino-4-((3-((tert-butoxycarbonyl)amino)propyl)(propyl)carbamoyl)-3H-benzo[b]azepin-8-yl)phenyl)sulfonyl)azetidin-3-yl)methyl)carbamate, BzL-34e which was used in the subsequent step without further purification.

Preparation of BzL-34: Using the procedures described for BzL-33, 2,3,5,6-tetrafluorophenyl (6S,9S)-1-amino-6-((4-(((((1-((3-(2-amino-4-((3-((tert-butoxycarbonyl)amino)propyl)(propyl)carbamoyl)-3H-benzo[b]azepin-8-yl)phenyl)sulfonyl)azetidin-3-yl)methyl)carbamoyl)oxy)methyl)phenyl)carbamoyl)-9-isopropyl-1,8,11-trioxo-14,17,20,23,26,29,32,35,38,41,44,47,50,53,56,59,62,65,68,71,74,77,80,83,86-pentacosaoxa-2,7,10-triazanonaoctacontan-89-oate, BzL-34 was obtained. LC/MS [M+H] 2379.2 (calculated); LC/MS [M+2H/2] 1190.1 (observed).

Example 55 Synthesis of BzL-35

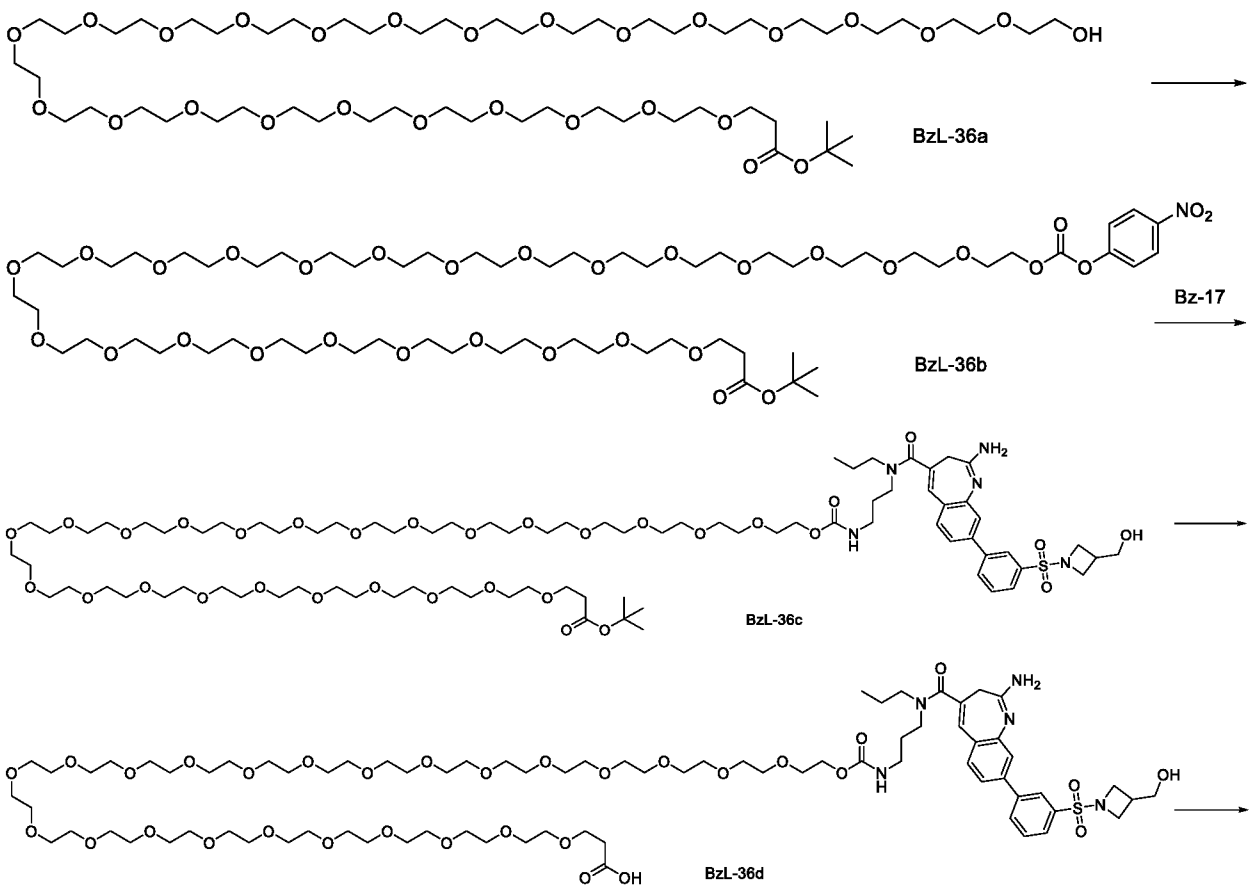


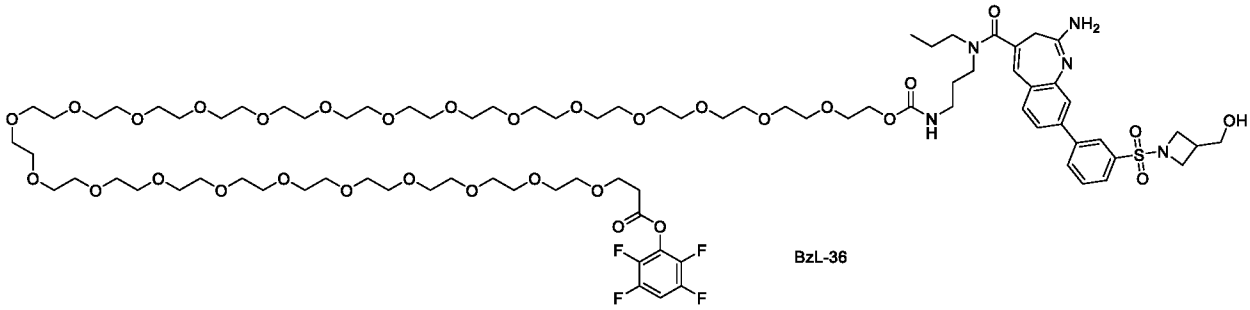
Preparation of BzL-35a: *tert*-Butyl (3-(2-amino-8-(3-((3-(aminomethyl)azetidin-1-yl)sulfonyl)phenyl)-*N*-propyl-3*H*-benzo[*b*]azepine-4-carboxamido)propyl)carbamate, BzL-34c (0.04 g, 0.064 mmol, 1 eq.) and 79-((2,5-dioxopyrrolidin-1-yl)oxy)-79-oxo-4,7,10,13,16,19,22,25,28,31,34,37,40,43,46,49,52,55,58,61,64,67,70,73,76-pentacosaoxanonaheptacontanoic acid (0.084 mg, 0.064 mmol, 1 eq.) were dissolved in DMF with diisopropylethylamine (0.033 ml, 0.192 mmol, 3 eq.). The reaction was monitored by

LCMS and purified by HPLC to give 1-(1-((3-(2-amino-4-((3-((*tert*-butoxycarbonyl)amino)propyl)(propyl)carbamoyl)-3*H*-benzo[*b*]azepin-8-yl)phenyl)sulfonyl)azetidin-3-yl)-3-oxo-6,9,12,15,18,21,24,27,30,33,36,39,42,45,48,51,54,57,60,63,66,69,72,75,78-pentacosaoxa-2-azahenoctacontan-81-oic acid, BzL-35a (0.056, 0.031 mmol, 48%). LC/MS [M+H] 1825.99 (calculated); LC/MS [M+H] 1826.24 (observed).

Preparation of BzL-35: BzL-35a (0.060 g, 0.033 mmol, 1 eq.) and 2,3,5,6-tetrafluorophenol, TFP (0.011 g, 0.065 mmol, 2 eq.) were dissolved in 1 ml DMF. Collidine, 2,4,6-trimethylpyridine (0.022 ml, 0.16 mmol, 5 eq.) was added, followed by *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride, EDC-HCl, CAS Reg. No. 25952-53-8 (0.019 g, 0.098 mmol, 3 eq.). The reaction was stirred at room temperature and monitored by LCMS, then concentrated and purified by HPLC to give 2,3,5,6-tetrafluorophenyl 1-(1-((3-(2-amino-4-((3-((*tert*-butoxycarbonyl)amino)propyl)(propyl)carbamoyl)-3*H*-benzo[*b*]azepin-8-yl)phenyl)sulfonyl)azetidin-3-yl)-3-oxo-6,9,12,15,18,21,24,27,30,33,36,39,42,45,48,51,54,57,60,63,66,69,72,75,78-pentacosaoxa-2-azahenoctacontan-81-oate, BzL-35 (0.027 g, 0.014 mmol, 42%). LC/MS [M+H] 1973.98 (calculated); LC/MS [M+H] 1974.62 (observed).

Example 56 Synthesis of BzL-36:





BzL-36

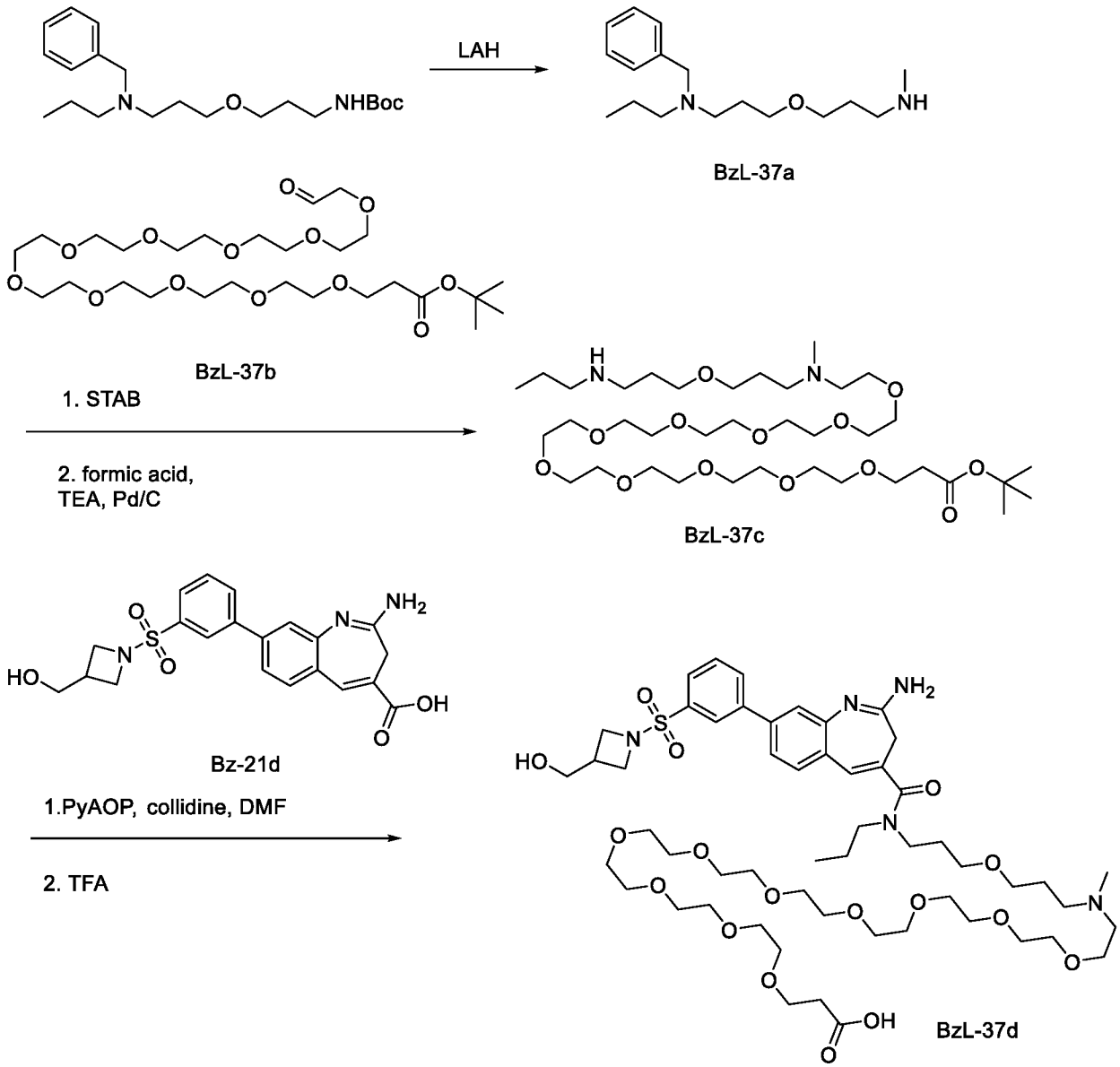
Preparation of BzL-36b: A vial was charged with *tert*-butyl 1-hydroxy-3,6,9,12,15,18,21,24,27,30,33,36,39,42,45,48,51,54,57,60,63,66,69,72-tetracosaoxapentaheptacontan-75-oate, BzL-36a (148 mg, 0.123 mmol), diisopropylethylamine (0.369 mmol) and 0.6 mL anhydrous DMF. The vial was cooled to 0 °C, then 4-nitrophenylchloroformate (0.123 mmol) was added portion-wise. The reaction was warmed to room temperature and maintained for 3 h, then purified by reverse phase preparative HPLC utilizing a 25-75% gradient of acetonitrile:water containing 0.1% trifluoroacetic acid. The purified fractions were combined and lyophilized to afford 42.5 mg of tert-butyl 1-(4-nitrophenoxy)-1-oxo-2,5,8,11,14,17,20,23,26,29,32,35,38,41,44,47,50,53,56,59,62,65,68,71,74-pentacosaoxaheptaheptacontan-77-oate, BzL-36b. LC/MS [M+H] 1368.7 (calculated); LC/MS [M+H] 1368.7 (observed).

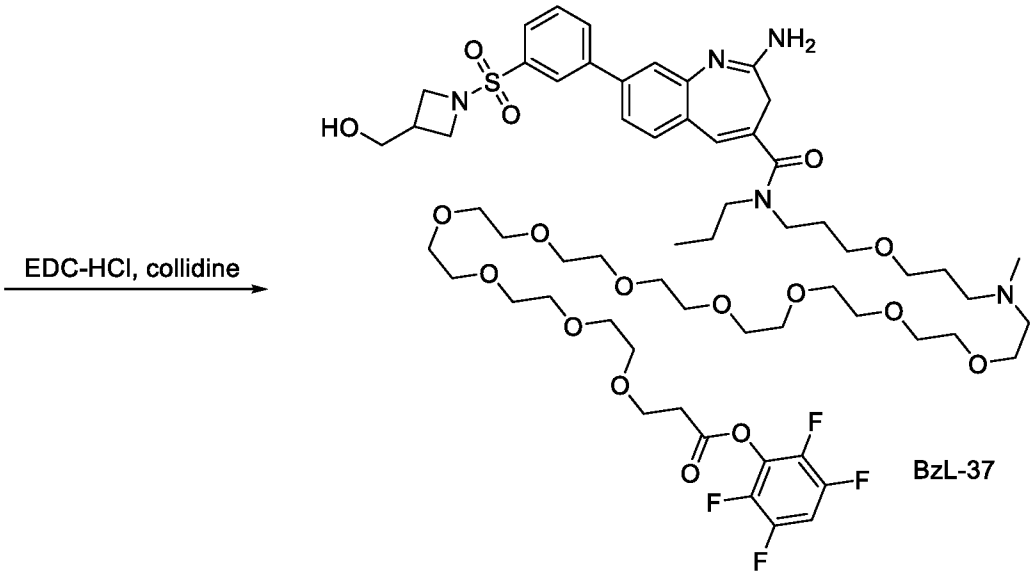
Preparation of BzL-36c: A vial was charged with Bz-17 (0.0275 mmol), BzL-36b (0.0275 mmol), HOAT (0.02 mmol), diisopropylethylamine (0.0825 mmol), 250 µL DCM, and 250 µL DMF. The reaction was maintained until all starting material was consumed by LCMS. The crude reaction was purified by reverse phase preparative HPLC utilizing a 25-75% gradient of acetonitrile:water containing 0.1% trifluoroacetic acid. The purified fractions were combined and lyophilized to afford 22.5 mg of tert-butyl 82-(2-amino-8-(3-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-3H-benzo[b]azepine-4-carbonyl)-77-oxo-4,7,10,13,16,19,22,25,28,31,34,37,40,43,46,49,52,55,58,61,64,67,70,73,76-pentacosaoxa-78,82-diazapentaoctacontanoate, BzL-36c. LC/MS [M+H] 1754.9 (calculated); LC/MS [M+H] 1754.9 (observed).

Preparation of BzL-36d: A vial was charged with BzL-36c (0.0128 mmol), 1 mL DCM, and 0.2 mL trifluoroacetic acid. The reaction was maintained for 3 h, then concentrated under reduced pressure. The resultant residue was azeotroped thrice with toluene to give 82-(2-amino-8-(3-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-3H-benzo[b]azepine-4-carbonyl)-77-oxo-4,7,10,13,16,19,22,25,28,31,34,37,40,43,46,49,52,55,58,61,64,67,70,73,76-pentacosaoxa-78,82-diazapentaoctacontanoic acid, BzL-36d which was used immediately in the subsequent step.

Preparation of BzL-36: A vial was charged with BzL-36d (8.9 mg, 0.005 mmol), 2,3,5,6-tetrafluorophenol (1.8 mg, 0.011 mmol), collidine (2.2 µL, 0.016 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (1 mg, 0.005 mmol) and 100 µL DMF. The reaction was stirred for 6 h, then purified by reverse phase preparative HPLC utilizing a 25-75% gradient of acetonitrile:water containing 0.1% trifluoroacetic acid. The purified fractions were combined and lyophilized to afford 6.3 mg of 2,3,5,6-tetrafluorophenyl 82-(2-amino-8-(3-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-3H-benzo[b]azepine-4-carbonyl)-77-oxo-4,7,10,13,16,19,22,25,28,31,34,37,40,43,46,49,52,55,58,61,64,67,70,73,76-pentacosaoxa-78,82-diazapentaoctacontanoate, BzL-36. LC/MS [M+H] 1846.9 (calculated); LC/MS [M+H] 1846.9 (observed).

Example 57 Synthesis of BzL-37





Preparation of BzL-37a: *tert*-Butyl (3-(3-(benzyl(propyl)amino)propoxy)propyl)carbamate (0.032 g, 0.088 mmol, 1 eq.) was dissolved in THF. Lithium aluminum hydride (0.01 g, 0.26 mmol, 3 eq.) was added and the reaction heated to 60 °C. The reaction was concentrated and purified by HPLC to give *N*-benzyl-3-(3-(methylamino)propoxy)-*N*-propylpropan-1-amine, BzL-37a (0.01 g, 0.036 mmol, 41%). LC/MS [M+H] 279.24 (calculated); LC/MS [M+H] 279.33 (observed).

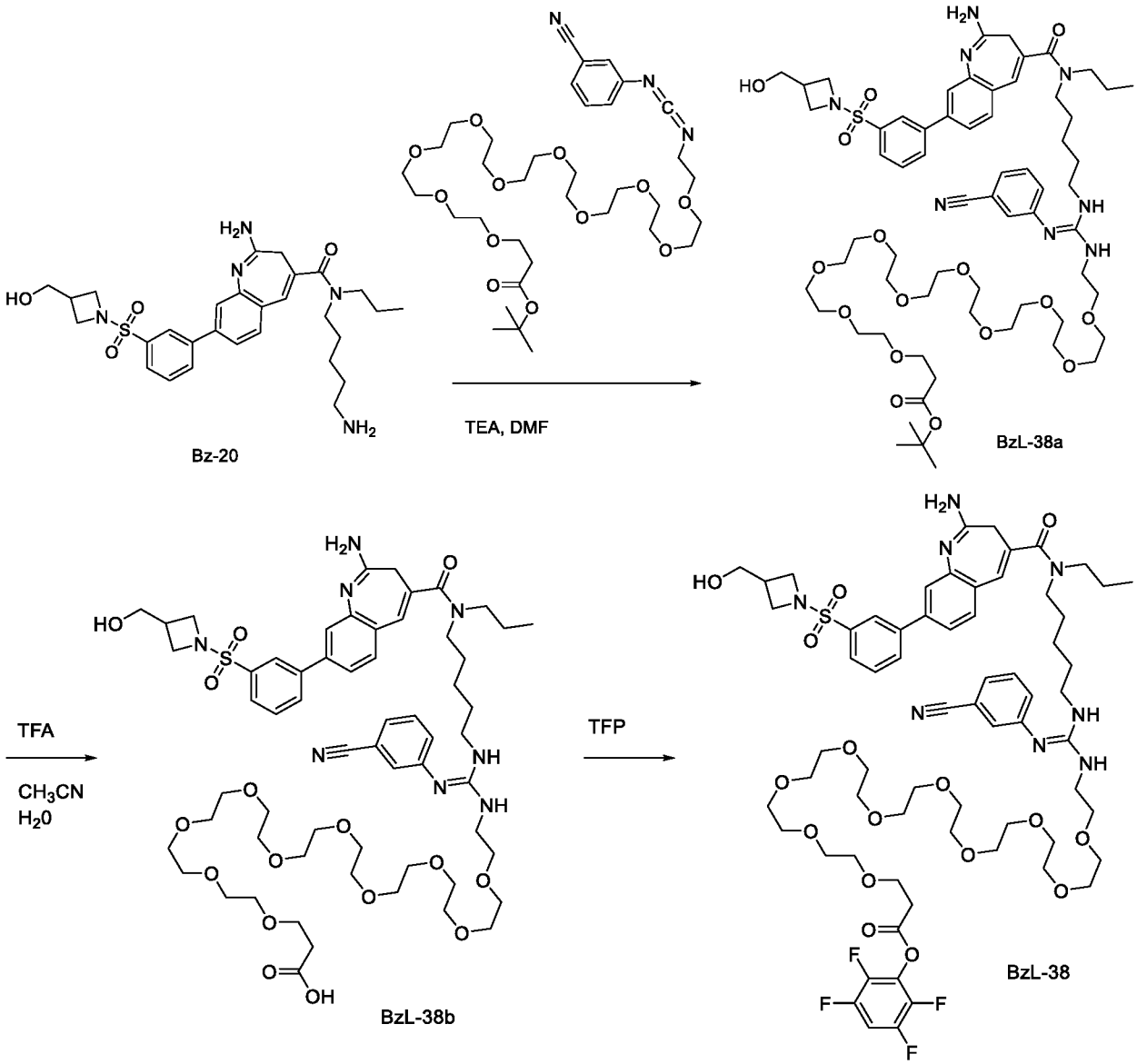
Preparation of BzL-37c: BzL-37a (0.01 g, 0.036 mmol, 1 eq.) and *tert*-butyl 1-oxo-3,6,9,12,15,18,21,24,27,30-decaoxatritriacontan-33-oate, BzL-37b (0.02 g, 0.036 mmol, 1 eq.) were dissolved in DCM. Sodium triacetoxyborohydride, STAB (0.022 g, 0.11 mmol, 3 eq.) was added and the reaction stirred at room temperature. The solution was concentrated and purified by HPLC. The purified product was taken up in methanol with triethylamine. Formic acid was added, followed by 10 wt% Pd/C, and the reaction heated to 60 °C. Upon consumption of starting material, the reaction mixture was filtered and concentrated to give *tert*-butyl 34-methyl-4,7,10,13,16,19,22,25,28,31,38-undecaoxa-34,42-diazapentatetracontanoate, BzL-37c (0.007 g, 0.0092 mmol, 26%). LC/MS [M+H] 757.74 (calculated); LC/MS [M+H] 757.85 (observed).

Preparation of BzL-37d: 2-Amino-8-(3-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-3*H*-benzo[b]azepine-4-carboxylic acid, Bz-21d (0.0040 g, 0.0092 mmol, 1 eq.), BzL-37c (0.007 g, 0.0092 mmol, 1 eq.), and collidine (0.004 ml, 0.028 mmol, 3 eq.) were dissolved in DMF. PyAOP (0.0072 g, 0.014 mmol, 1.5 eq.) was added and the mixture stirred at room temperature. When complete, the reaction mixture was concentrated and purified by RP-HPLC. The isolated product was concentrated, dissolved in minimal TFA, and allowed to stand at room temperature for 15 minutes. The solution was then concentrated and purified by RP-HPLC to give 42-(2-amino-8-(3-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-3*H*-benzo[b]azepine-4-carbonyl)-34-methyl-4,7,10,13,16,19,22,25,28,31,38-undecaoxa-34,42-

diazapentatetracontanoic acid, BzL-37d (0.004 g, 0.0036 mmol, 39%). LC/MS [M+H] 1110.59 (calculated); LC/MS [M+H] 1110.93 (observed).

Preparation of BzL-37: BzL-37d (0.004 g, 0.0036 mmol, 1 eq.) and TFP (0.0033 g, 0.018 mmol, 5 eq.) were dissolved in 1 ml DMF. Collidine (0.005 ml, 0.036 mmol, 10 eq.) was added, followed by EDC-HCl (0.0035 g, 0.018 mmol, 5 eq.). The reaction was stirred at room temperature and monitored by LCMS, then concentrated and purified by HPLC to give 2,3,5,6-tetrafluorophenyl 42-(2-amino-8-(3-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-3*H*-benzo[b]azepine-4-carbonyl)-34-methyl-4,7,10,13,16,19,22,25,28,31,38-undecaoxa-34,42-diazapentatetracontanoate, BzL-37 (0.0016 g, 0.0013 mmol, 35%). LC/MS [M+H] 1258.58 (calculated); LC/MS [M+H] 1258.96 (observed).

Example 58 Synthesis of BzL-38

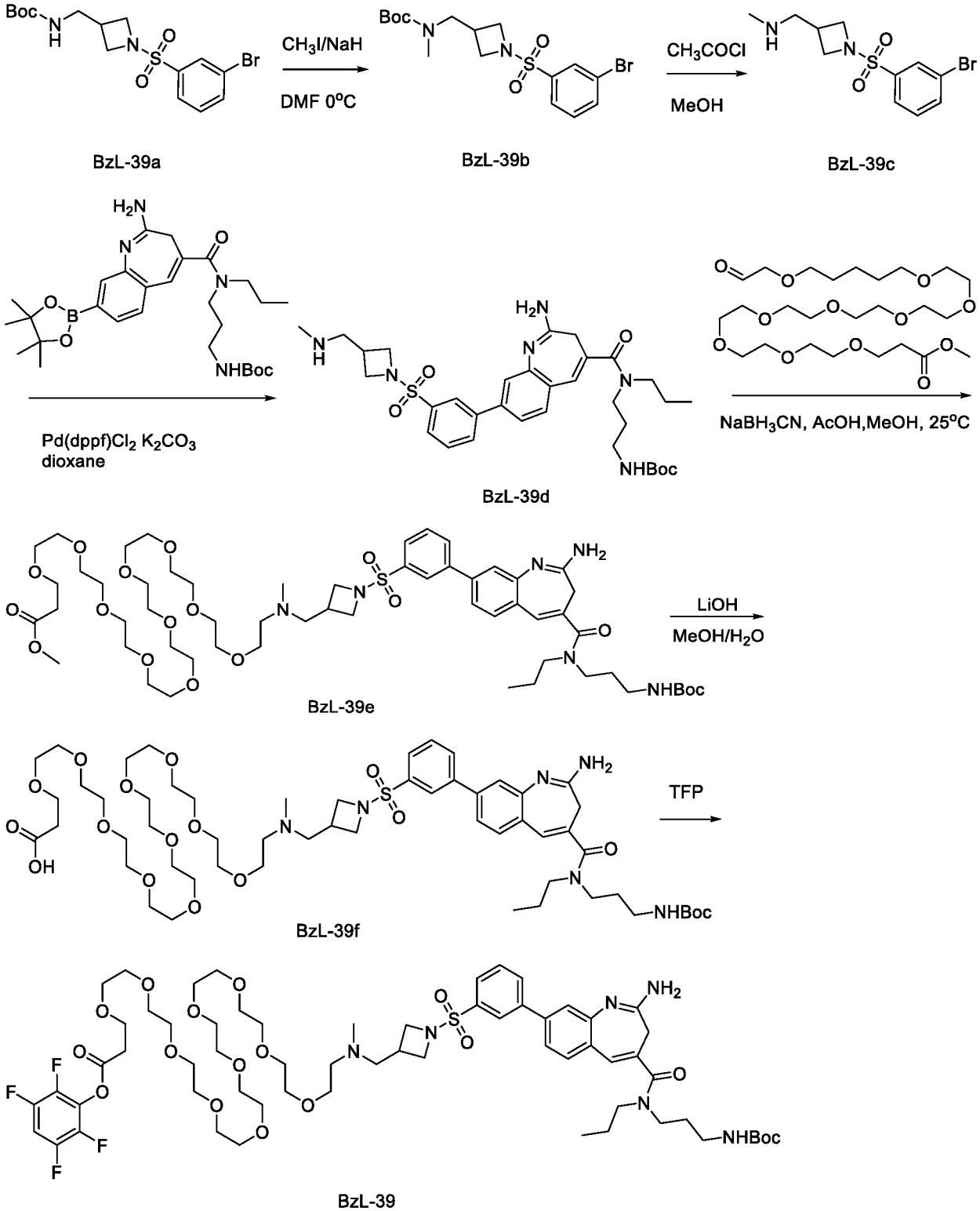


Preparation of BzL-38a: This was prepared using the same methods as described in the synthesis of BzL-42. LC/MS [M+H] 1265.7 (calculated); LC/MS [M+H] 1265.7 (observed).

Preparation of BzL-38b: This was prepared using the same method as described in the synthesis of BzL-42. LC/MS [M+H] 1209.6 (calculated); LC/MS [M+H] 1209.6 (observed).

Preparation of BzL-38: This was prepared using the same method as described in the synthesis of BzL-42. LC/MS [M+H] 1357.6 (calculated); LC/MS [M+H] 1357.6 (observed).

Example 59 Synthesis of BzL-39



Preparation of BzL-39b: To a solution of tert-butyl N-[[1-(3-bromophenyl)sulfonylazetidin-3-yl]methyl]carbamate, BzL-39a (1.0 g, 2.47 mmol, 1.0 *eq*) in DMF (10 mL) was added sodium hydride, NaH (148 mg, 3.70 mmol, 60% purity, 1.5 *eq*) in portions and it was stirred at 0 °C for 0.5 h. Then methyl iodide, CH_3I (1.05 g, 7.40 mmol, 461 uL, 3.0 *eq*) was added and then stirred at 25°C for 1 h. The reaction was quenched with water and extracted with EtOAc (30 mL x 3). The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated to give tert-butyl N-[[1-(3-bromophenyl) sulfonylazetidin-3-yl]methyl]-N-methyl-carbamate, BzL-39b (1.3 g, crude) as yellow oil. ^1H NMR ($CDCl_3$, 400MHz) δ7.99 (t, J = 2.0 Hz, 1H), 7.80-7.75 (m, 2H), 7.47 (t, J = 8.0 Hz, 1H), 3.85 (t, J = 7.6 Hz, 2H), 3.57 (t, J = 7.2 Hz, 2H), 3.29 (d, J = 7.2 Hz, 2H), 2.75 (s, 3H), 2.74-2.70 (m, 1H), 1.43 (s, 9H), 1.26 (t, J = 7.2 Hz, 3H).

Preparation of BzL-39c: To a solution of BzL-39b (1.3 g, 3.10 mmol, 1.0 *eq*) in MeOH (20 mL) was added acetyl chloride (1.22 g, 15.5 mmol, 1.11 mL, 5.0 *eq*) at 25°C and it was stirred at 50°C for 1 h. Then the mixture was concentrated to give 1-[1-(3-bromophenyl)sulfonylazetidin-3-yl]-N- methyl-methanamine, BzL-39c (1 g, crude) as white solid. ^1H NMR (MeOD, 400MHz) δ 8.00-7.98 (m, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.64-7.59 (m, 1H), 3.94 (t, J = 8.4 Hz, 2H), 3.64 (dd, J = 5.6, 8.4 Hz, 2H), 3.14 (d, J = 7.6 Hz, 2H), 2.84-2.77 (m, 1H), 2.66 (s, 3H).

Preparation of BzL-39d: To a mixture of tert-butyl N-[3-[[2-amino-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) -3H-1-benzazepine-4-carbonyl]-propyl-amino]propyl]carbamate (0.44 g, 835 umol, 1.0 eq) and Bzl-39c (357 mg, 1.00 mmol, 1.2 eq, HCl) in dioxane (4 mL) and H_2O (0.5 mL) was added $Pd(dppf)Cl_2$ (30.6 mg, 41.79 umol, 0.05 eq) and K_2CO_3 (231.0 mg, 1.67 mmol, 2.0 eq) at 15°C under N_2. The mixture was stirred at 90°C for 3 hours. The reaction was cooled to 15°C and then filtered. The filtrate was poured into ice water (30 mL) and stirred for 5 min. The aqueous phase was extracted with ethyl acetate (20 mL x 3) and combined organic phase was washed with brine (20 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether to EtOAc/MeOH=3/1 gradient @ 60 mL/min) to afford tert-butyl N-[3-[[2-amino-8-[3-[3-(methylaminomethyl)azetidin-1-yl]sulfonylphenyl]-3H-1-benzazepine-4-carbonyl]-propyl-amino]propyl]carbamate, BzL-39d (0.32 g, 500.92 umol, 59.94% yield) as yellow solid.

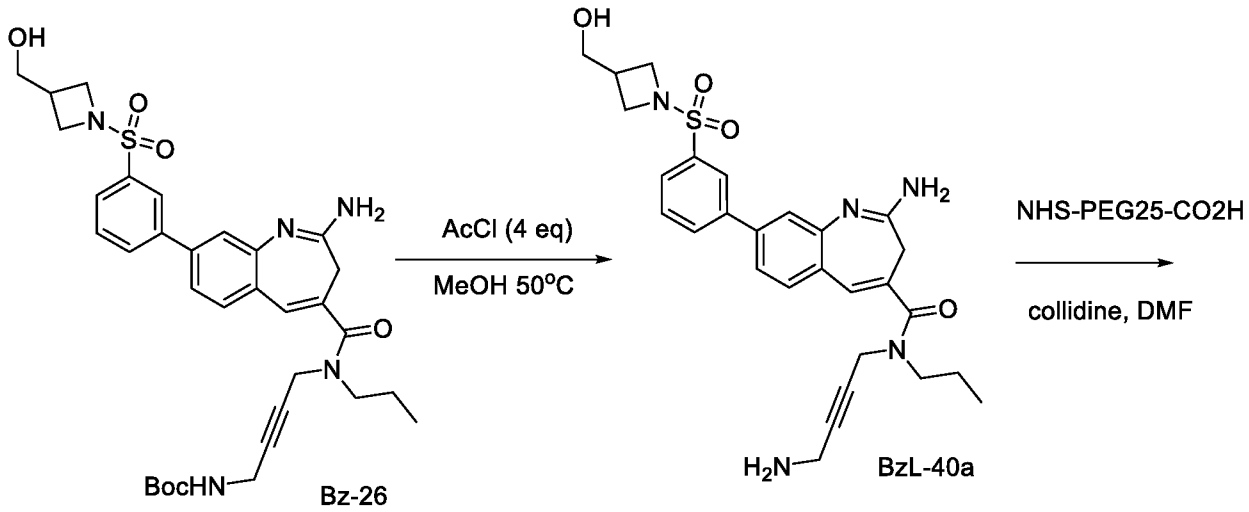
Preparation of BzL-39e: To a mixture of BzL-39d (0.2 g, 313 umol, 1.0 eq) and methyl 3-[2-[2-[2-[2-[2-[2-[2-[2-[2-(2-oxoethoxy)ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]propanoate (170 mg, 313 umol, 1.0 eq) in

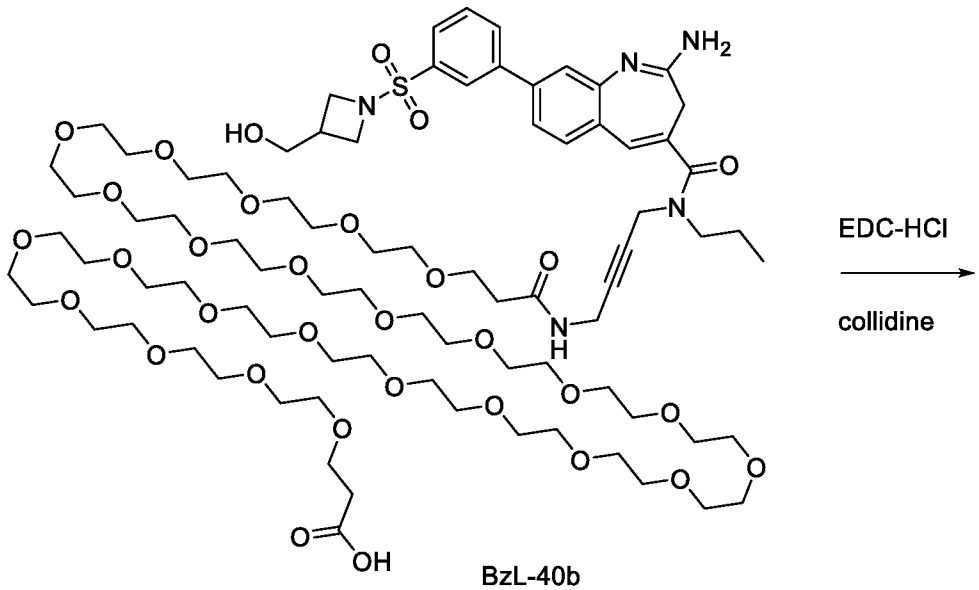
MeOH (20 mL) was added acetic acid, AcOH (94.0 mg, 1.57 mmol, 5.0 eq) at 25 °C. The mixture was stirred at this temperature for 10 min, then sodium cyanoborohydride, $NaBH_3CN$ (39.3 mg, 626. umol, 2.0 eq) was added and the mixture was stirred at 25 °C for 18 hours. The reaction mixture was concentrated to give the crude product methyl 3-[2-[2-[2-[2-[2-[2-[2-[2-[2-[2-[[1-[3- [2-amino-4-[3-(tert-butoxycarbonylamino)propyl-propyl-carbamoyl]-3H-1-benzazepin-8-yl]phenyl]sulfonylazetidin-3-yl]methyl-methyl-amino]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]propanoate, BzL-39e (0.36 g, crude).

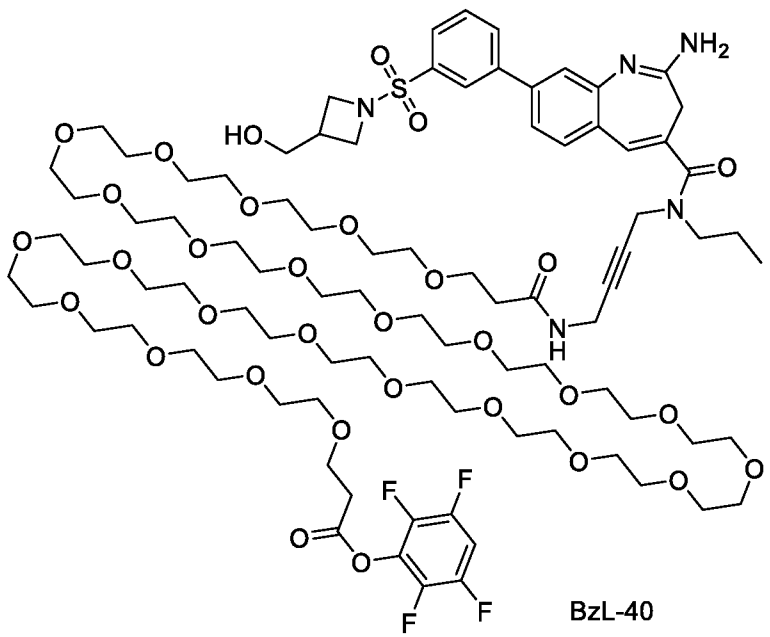
Preparation of BzL-39f: To a mixture of BzL-39e (0.36 g, 308 umol, 1.0 eq) in MeOH (20 mL) was added a solution of lithium hydroxide hydrate, $LiOH•H_2O$ (130 mg, 3.09 mmol, 10.0 eq) in H_2O (2 mL) at 25°C and then stirred at 25°C for 18 hours. The reaction mixture was quenched with aq HCl (4 M) until pH = 7 and concentrated at 40 °C. The residue was purified by prep-HPLC (column: Welch Xtimate C18 100*25mm*3um; mobile phase: [water (0.1% TFA) - ACN]; B%: 20%-40%, 12min) to give 3-[2-[2-[2-[2-[2-[2-[2-[2-[2-[2-[[1-[3-[2-amino-4-[3-(tert- butoxycarbonylamino)propyl-propyl-carbamoyl]-3H-1-benzazepin-8-yl]phenyl]sulfonylazetidin-3-yl]methyl-methyl-amino]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]propanoic acid, BzL-39f (56 mg, 48.64 umol, 16% yield) as light yellow oil. ^{1}H NMR (MeOD, 400MHz) δ8.19-8.03 (m, 2H), 7.97-7.88 (m, 1H), 7.88-7.82 (m, 1H), 7.82-7.76 (m, 2H), 7.73-7.71 (m, 1H), 7.13 (s, 1H), 4.02 (t, J = 8.0 Hz, 2H), 3.79 (t, J = 4.8 Hz, 2H), 3.75-3.68 (m, 4H), 3.64-3.45 (m, 42H), 3.38 (s, 2H), 3.17-2.94 (m, 4H), 2.86 (s, 3H), 2.53 (t, J = 6.4 Hz, 2H), 1.89-1.80 (m, 2H), 1.75-1.63 (m, 2H), 1.47-1.42 (m, 9H), 1.02-0.86 (m, 3H). LC/MS [M+H] 1151.61 (calculated); LC/MS [M+2H/2] 576.5 (observed).

Preparation of BzL-39. BzL-39f (0.056 g, 0.049 mmol, 1 eq.) and TFP (0.040 g, 0.24 mmol, 5 eq.) were dissolved in 2 ml DMF. Collidine (0.064 ml, 0.49 mmol, 10 eq.) was added, followed by EDC-HCl (0.047 g, 0.24 mmol, 5 eq.). The reaction was stirred at room temperature and monitored by LCMS, then concentrated and purified by HPLC to give 2,3,5,6-tetrafluorophenyl 1-(1-((3-(2-amino-4-((3-((*tert*-butoxycarbonyl)amino)propyl)(propyl)carbamoyl)-3*H*-benzo[*b*]azepin-8-yl)phenyl)sulfonyl)azetidin-3-yl)-2-methyl-5,8,11,14,17,20,23,26,29,32-decaoxa-2-azapentatriacontan-35-oate, BzL-39 (0.027 g, 0.021 mmol, 42%). LC/MS [M+H] 1299.61 (calculated); LC/MS [M+H] 1300.00 (observed).

Example 60 Synthesis of BzL-40





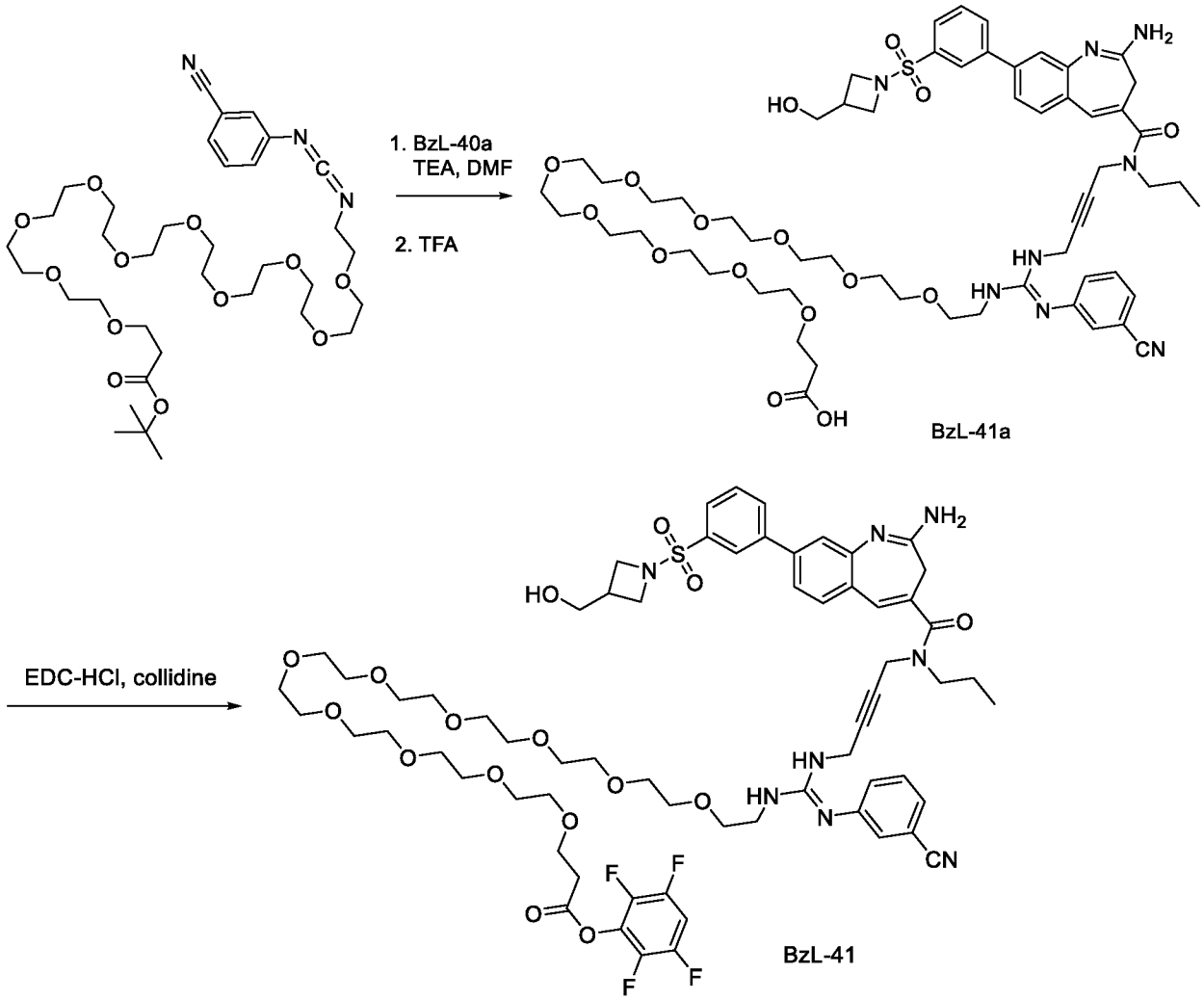


Preparation of BzL-40a: To a mixture of tert-butyl N-[4-[[2-amino-8-[3-[3-(hydroxymethyl)azetidin-1-yl] sulfonylphenyl]-3H-1-benzazepine-4-carbonyl]-propyl-amino]but-2-ynyl]carbamate, Bz-26 (800 mg, 1.26 mmol, 1.0 *eq*) in MeOH (20 mL) was added acetyl chloride (395 mg, 5.03 mmol, 360 uL, 4.0 *eq*) at 25 °C under N_2 and then stirred at 50°C for 1 hour. The mixture was quenched with solid $NaHCO_3$ until pH to ~8, then filtered and concentrated in vacuum. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 200*40mm*10um; mobile phase: [water(10mM NH_4HCO_3)-ACN]; B%: 10%-40%, 10 min) to afford 2-amino-N-(4-aminobut-2-ynyl)-8-[3-[3-(hydroxymethyl)azetidin-1-yl]sulfonylphenyl]-N-propyl-3H-1-benzazepine-4-carboxamide, BzL-40a (220 mg, 411 umol, 32.6% yield) as white solid. ^{1}H NMR (MeOD, 400MHz) δ8.12-8.01 (m, 2H), 7.90-7.82 (m, 1H), 7.80-7.72 (m, 1H), 7.56-7.47 (m, 2H), 7.44-7.38 (m, 1H), 7.15 (s, 1H), 4.32 (s, 2H), 3.86 (t, J = 8.0 Hz, 2H), 3.69-3.47 (m, 6H), 3.41 (d, J = 6.4 Hz, 2H), 2.64-2.51 (m, 1H), 1.84-1.63 (m, 2H), 0.99-0.91 (m, 3H). LC/MS [M+H] 536.2 (calculated); LC/MS [M+H] 536.3 (observed).

Preparation of BzL-40b: BzL-40a (0.045 g, 0.084 mmol, 1 eq.) and 79-((2,5-dioxopyrrolidin-1-yl)oxy)-79-oxo-4,7,10,13,16,19,22,25,28,31,34,37,40,43,46,49,52,55,58,61,64,67,70,73,76-pentacosaoxanonaheptacontanoic acid, NHS-PEG25-CO_2H (0.11 g, 0.084 mmol, 1 eq.) were dissolved in DMF, followed by collidine (0.054 ml, 0.42 mmol, 5 eq.). The reaction was purified by HPLC to give 85-(2-amino-8-(3-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-3*H*-benzo[*b*]azepine-4-carbonyl)-79-oxo-4,7,10,13,16,19,22,25,28,31,34,37,40,43,46,49,52,55,58,61,64,67,70,73,76-pentacosaoxa-80,85-diazaoctaoctacont-82-ynoic acid, BzL-40b (0.1 g, 0.0058 mmol, 69%). LC/MS [M+H] 1736.90 (calculated); LC/MS [M+H] 1737.32 (observed).

Preparation of BzL-40: BzL-40b (0.1 g, 0.0058 mmol, 1 eq.) and TFP (0.014 g, 0.086 mmol, 1.5 eq.) were dissolved in DMF. Collidine (0.038 ml, 0.29 mmol, 5 eq.) was added, followed by EDC-HCl (0.022 g, 0.115 mmol, 2 eq.). The reaction was stirred at room temperature and monitored by LCMS, then concentrated and purified by HPLC to give 2,3,5,6-tetrafluorophenyl 85-(2-amino-8-(3-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-3*H*-benzo[*b*]azepine-4-carbonyl)-79-oxo-4,7,10,13,16,19,22,25,28,31,34,37,40,43,46,49,52,55,58,61,64,67,70,73,76-pentacosaoxa-80,85-diazaoctaoctacont-82-ynoate, BzL-40 (0.014 g, 0.0076 mmol, 13%). LC/MS [M+H] 1884.90 (calculated); LC/MS [M+H] 1885.44 (observed).

Example 61 Synthesis of BzL-41

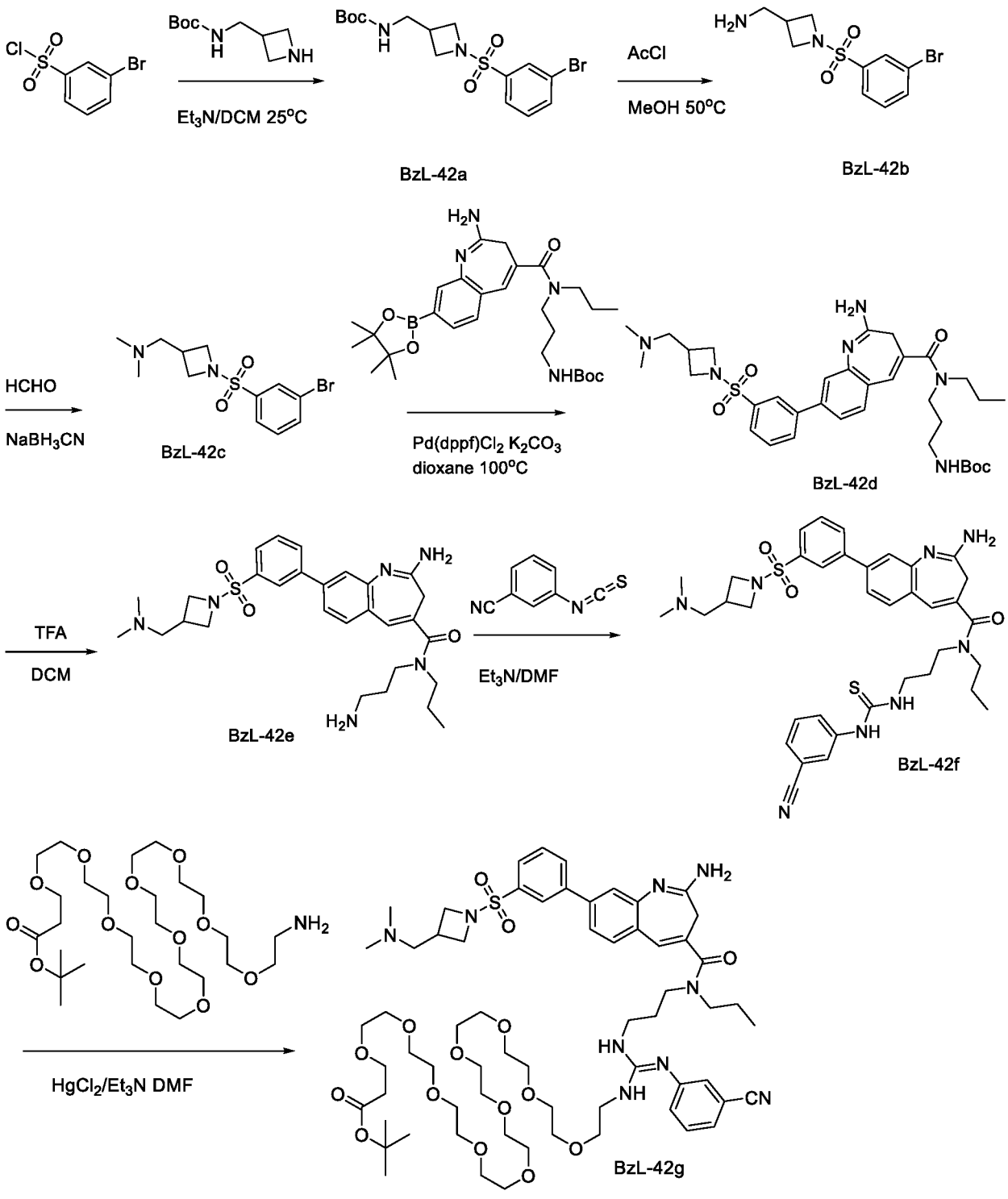


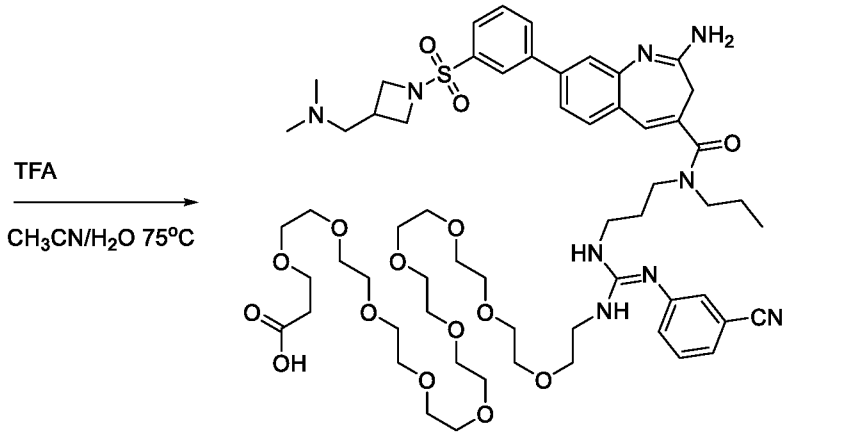
Preparation of BzL-41a: 2-Amino-*N*-(4-aminobut-2-yn-1-yl)-8-(3-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-*N*-propyl-3H-benzo[*b*]azepine-4-carboxamide, BzL-40a (0.05 g, 0.093 mmol, 1 eq.) and *tert*-butyl 1-((3-cyanophenyl)imino)-5,8,11,14,17,20,23,26,29,32-decaoxa-2-azapentatriacont-1-en-35-oate (0.066 g, 0.093 mmol, 1 eq.) were dissolved in DMF. Triethylamine (0.05 ml, 0.36 mmol, 3.8 eq.) was added, and the reaction was stirred at ambient temperature. Upon consumption of amine starting material, the reaction was concentrated and purified by HPLC. The isolated t-butyl ester product was taken up in minimal TFA for 10 minutes, then concentrated to give 41-(2-amino-8-(3-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-3*H*-benzo[*b*]azepine-4-carbonyl)-35-((3-cyanophenyl)imino)-4,7,10,13,16,19,22,25,28,31-decaoxa-34,36,41-triazatetratetracont-38-ynoic acid, BzL-41a (0.05 g, 0.042 mmol, 45%). LC/MS [M+H] 1191.56 (calculated); LC/MS [M+H] 1192.00 (observed).

Preparation of BzL-41: BzL-41a (0.05 g, 0.042 mmol, 1 eq.) and TFP (0.01 g, 0.063 mmol, 1.5 eq.) were dissolved in DMF. Collidine (0.028 ml, 0.21 mmol, 5 eq.) was added, followed by EDC-HCl (0.016 g, 0.084 mmol, 2 eq.). The reaction was stirred at room

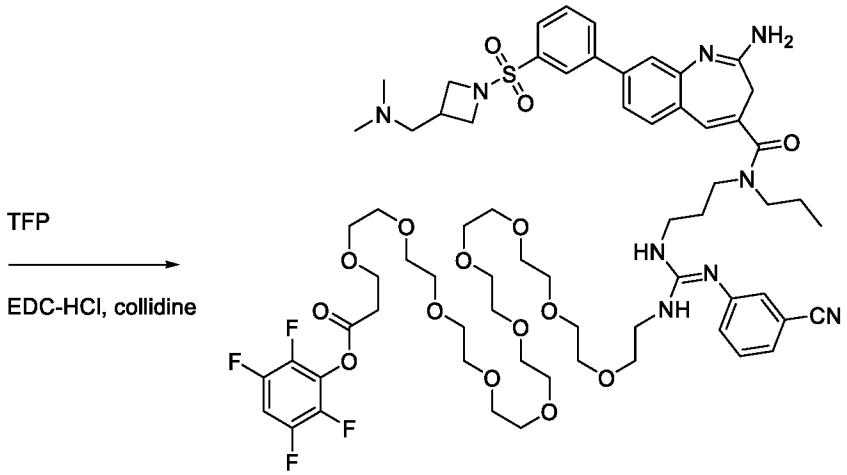
temperature and monitored by LCMS, then concentrated and purified by HPLC to give 2,3,5,6-tetrafluorophenyl 41-(2-amino-8-(3-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-3I-benzo[I]azepine-4-carbonyl)-35-((3-cyanophenyl)imino)-4,7,10,13,16,19,22,25,28,31-decaoxa-34,36,41-triazatetratetracont-38-ynoate, BzL-41 (0.019 g, 0.014 mmol, 35%). LC/MS [M+H] 1339.56 (calculated); LC/MS [M+H] 1340.04 (observed).

Example 62 Synthesis of BzL-42





BzL-42h



BzL-42

Preparation of BzL-42a: To a mixture of 3-bromobenzenesulfonyl chloride (8.23 g, 32.2 mmol, 4.65 mL, 1.0 *eq*) and tert-butyl N-(azetidin-3-ylmethyl)carbamate (6.0 g, 32.2 mmol, 1.0 *eq*) in DCM (100 mL) was added Et_3N (6.52 g, 64.4 mmol, 8.97 mL, 2.0 *eq*) at 0 °C and then stirred at this temperature for 1 h. The reaction was diluted with water and extracted with EtOAc (50 mL x 3). The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated to afford tert-butyl N-[[1-(3-bromophenyl)ulfonylazetidin-3-yl] methyl]carbamate, BzL-42a (12 g, crude) as white solid. ^1H NMR ($CDCl_3$, 400MHz) δ7.99 (t, *J* = 1.6 Hz, 1H), 7.78 (m, 2H), 7.47 (t, *J* = 8.0 Hz, 1H), 4.63 (s, 1H), 3.85 (t, *J* = 8.0 Hz, 2H), 3.54 (dd, *J* = 5.6, 8.0 Hz, 2H), 3.21-3.16 (m, 2H), 2.67-2.62 (m, 1H), 1.42 (s, 9H). LC/MS [M+Na] 427.0 (calculated); LC/MS [M+Na] 427.0 (observed).

Preparation of BzL-42b: To a mixture of BzL-42a (2 g, 4.93 mmol, 1.0 eq) in MeOH (30 mL) was added acetyl chloride (1.94 g, 24.67 mmol, 1.76 mL, 5.0 eq) at 25 °C and then stirred at this temperature for 2 h. The mixture was concentrated to give [1-(3-bromophenyl)sulfonylazetidin-3-yl]methanamine, BzL-42b (1.5 g, crude) as white solid. ^1H NMR (MeOD, 400MHz) δ7.99 (t, *J* = 1.6 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.84 (d, *J* = 7.2 Hz,

1H), 7.62 (t, *J* = 8.0 Hz, 1H), 3.93 (t, *J* = 8.4 Hz, 2H), 3.61 (m, 2H), 3.06-3.03 (m, 2H), 2.78-2.66 (m, 1H).

Preparation of BzL-42c: To a mixture of BzL-42b (4.0 g, 13.1 mmol, 1.0 *eq*) in MeOH (40 mL) was added Et_3N (1.99 g, 19.7 mmol, 2.74 mL, 1.5 *eq*), formaldehyde (4.25 g, 52.4 mmol, 3.90 mL, 37% purity, 4.0 *eq*) and $NaBH_3CN$ (1.65 g, 26.2 mmol, 2.0 *eq*) at 25 °C and it was stirred at 25 °C for 2h. The mixture was diluted with water and extracted with EtOAc (30 mL x 3). The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, EtOAc(1.5% $NH_3 \cdot H_2O$) : MeOH = 1/0, 1/1) to afford 1-[1-(3-bromophenyl) sulfonylazetidin-3-yl]-N,N-dimethyl-methanamine, BzL-42c (1.6 g, 4.80 mmol, 36.6% yield) as yellow oil. ^1H NMR (MeOD, 400MHz) δ8.01 (t, *J* = 1.6 Hz, 1H), 7.96-7.91 (m, 1H), 7.86 (d, *J* = 8.0Hz, 1H), 7.66-7.60 (m, 1H), 3.98-3.90 (m, 2H), 3.47 (dd, *J* = 6.0, 8.4 Hz, 2H), 2.74-2.60 (m, 1H), 2.28 (d, *J* = 7.6Hz, 2H), 2.15 (s, 6H). LC/MS [M+H] 333.0 (calculated); LC/MS [M+H] 333.0 (observed).

Preparation of BzL-42d: To a mixture of BzL-42c (299 mg, 898 umol, 1.1 *eq*) and tert-butyl N-[3-[[2-amino-8-(4,4,5,5-tetramethyl-1,3,2- dioxaborolan-2-yl)-3H-1-benzazepine-4-carbonyl]-propyl-amino]propyl]carbamate (0.43 g, 817 umol, 1.0 *eq*) in dioxane (10 mL), H_2O (1 mL) was added K_2CO_3 (395 mg, 2.86 mmol, 3.5 *eq*), $Pd(dppf)Cl_2$ (29.9 mg, 40.8 umol, 0.05 *eq*) at 25°C under N_2 and then stirred at 100°C for 2 h. The mixture was filtered, diluted with water and extracted with EtOAc (30 mL x 3). The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, Petroleum ether/Ethyl acetate=1/0, 0/1) to afford tert-butylN-[3-[[2-amino-8-[3-[3-[(dimethylamino)methyl]azetidin-1-yl]sulfonylphenyl] -3H-1-benzazepine-4-carbonyl]-propyl-amino]propyl]carbamate, BzL-42d (0.3 g, 459 umol, 56.3% yield) as yellow solid.

Preparation of BzL-42e: To a mixture of BzL-42d (0.25 g, 383 umol, 1.0 *eq*) in DCM (2 mL) was added TFA (1.31 g, 11.5 mmol, 851 uL, 30.0 *eq*) in one portion at 25 °C and then stirred for 1 h. The mixture was concentrated to afford 2-amino-N-(3-aminopropyl)-8-[3-[3-[(dimethylamino)methyl]azetidin-1-yl]sulfonylphenyl]–N -propyl-3H-1-benzazepine-4-carboxamide, BzL-42e (0.2 g, crude) as a yellow oil.

Preparation of BzL-42f: To a mixture of BzL-42e (0.2 g, 362 umol, 1.0 *eq*) in DMF (0.5 mL) was added Et_3N (256 mg, 2.53 mmol, 353 uL, 7.0 *eq*) and 3-isothiocyanatobenzonitrile (52.2 mg, 326 umol, 0.9 *eq*) at 25 °C and then stirred at this temperature for 1 h. The mixture was filtered and the filtrate was purified by prep-HPLC(column: Welch Xtimate C18 100*25mm*3um;mobile phase: [water(0.1%TFA)-ACN];B%: 10%-40%,12min) to give 2-

amino-N-[3-[(3-cyanophenyl) carbamothioylamino]propyl]-8-[3-[3-[(dimethylamino)methyl]azetidin-1-yl]sulfonylphenyl]-N-propyl-3H-1-benzazepine-4-carboxamide, BzL-42f (0.18 g, 252 umol, 69.8% yield) as yellow solid. ^{1}H NMR (MeOD, 400MHz) δ8.12-8.06 (m, 2H), 7.92-7.02(m, 10H), 4.01 (t, *J* = 8.4 Hz, 2H), 3.76-3.40 (m, 8H), 3.40-3.36 (m, 2H), 3.34-3.32 (m, 2H), 3.03-2.91 (m, 1H), 2.82 (s, 6H), 2.04 (s, 2H), 1.77-1.67 (m, 2H), 0.97 (s, 3H).

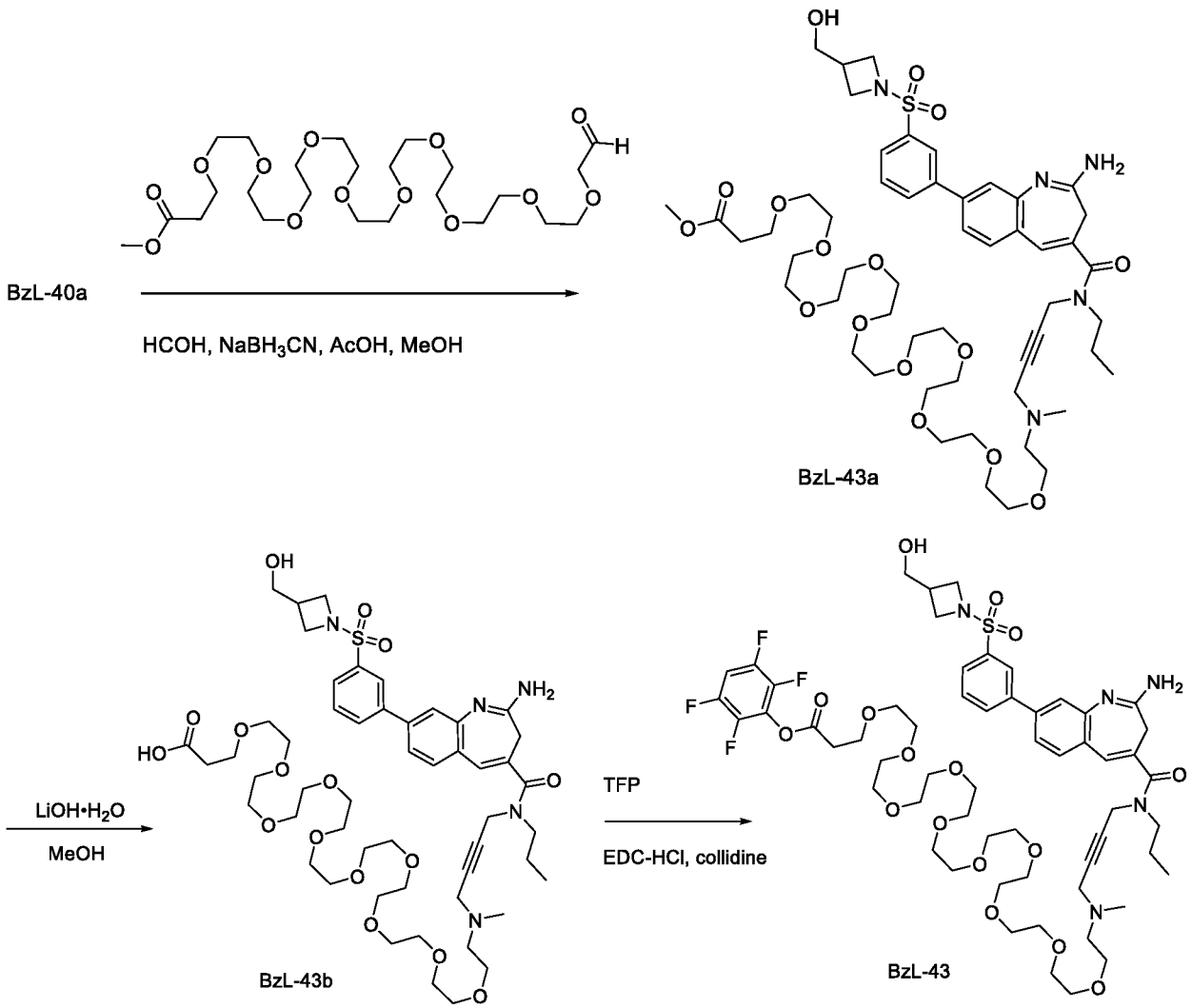
Preparation of BzL-42g: To a mixture of BzL-42f (0.14 g, 196 umol, 1.0 *eq*) and tert-butyl3-[2-[2-[2-[2-[2-[2-[2-[2-[2- (2-aminoethoxy) ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]propanoate (138 mg, 236 umol, 1.2 *eq*) in DMF (0.5 mL) was added Et_3N (40.0 mg, 393 umol, 2.0 *eq*) and $HgCl_2$ (64.0 mg, 236 umol, 1.2 *eq*) at 25 °C and then stirred for 18 h at this temperature. The mixture was filtered and the filtrate was purified by prep-HPLC(column: Nano-micro Kromasil C18 100*30mm 8um;mobile phase: [water (0.1%TFA)-ACN];B%: 15%-45%,10min) to give tert-butyl3-[2-[2-[2-[2-[2-[2-[2-[2-[2-[2-[2-[[(Z)-N-[3-[[2-amino-8-[3- [3-[(dimethylamino)methyl]azetidin-1-yl]sulfonylphenyl]-3H-1-benzazepine-4-carbonyl]-propyl-amino]propyl]-N'-(3-cyanophenyl)carbamimidoyl]amino]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]propanoate, BzL-42g (0.14 g, 111 umol, 56.4% yield) as yellow oil.

Preparation of BzL-42h: To a solution of BzL-42g (0.12 g, 94.9 umol, 1.0 *eq*) in H_2O (2 mL) and CH_3CN (0.5 mL) was added TFA (325mg, 2.85 mmol, 211 uL, 30.0 *eq*) at 25 °C and then stirred at 80°C for 1 h. The mixture was concentrated in vacuum to give a residue, the residue was purified by prep-HPLC(column: Xtimate C18 100*30mm*3um;mobile phase: [water(0.1%TFA)-ACN];B%: 5%-35%,10min) to give 3-[2-[2-[2-[2-[2-[2-[2-[2-[2-[2- [[(Z)-N-[3-[[2-amino-8-[3-[3-[(dimethylamino)methyl]azetidin-1-yl]sulfonylphenyl]-3H-1-benzazepine-4-carbonyl]-propyl-amino]propyl]-N'-(3-cyanophenyl)carbamimidoyl]amino]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]propanoic acid, BzL-42h (32 mg, 26.5 umol, 27.9% yield) as yellow oil. ^{1}H NMR (MeOD, 400MHz) δ8.16-8.09 (m, 2H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.87-7.81 (m, 1H), 7.81-7.74 (m, 3H), 7.66-7.62 (m, 4H), 7.12 (s, 1H), 4.01 (t, *J* = 8.4 Hz, 2H), 3.80-3.66 (m, 10H), 3.66-3.45 (m, 40H), 3.40 (s, 3H), 2.82 (s, 6H), 2.53 (t, *J* = 6.4 Hz, 2H), 2.07-2.01 (m, 1H), 1.77-1.67 (m, 2H), 0.98-0.90 (m, 3H). LC/MS [M+H] 1208.6 (calculated); LC/MS [M+H] 1208.6 (observed).

Preparation of BzL-42: BzL-42h (0.032 g, 0.026 mmol, 1 eq.) and TFP (0.009 g, 0.05 mmol, 2 eq.) were dissolved in DMF. Collidine (0.017 ml, 0.13 mmol, 5 eq.) was added, followed by EDC-HCl (0.015 g, 0.079 mmol, 3 eq.). The reaction was stirred at room

temperature and monitored by LCMS, then concentrated and purified by HPLC to give 2,3,5,6-tetrafluorophenyl 40-(2-amino-8-(3-((3-((dimethylamino)methyl)azetidin-1-yl)sulfonyl)phenyl)-3*H*-benzo[*b*]azepine-4-carbonyl)-35-((3-cyanophenyl)imino)-4,7,10,13,16,19,22,25,28,31-decaoxa-34,36,40-triazatritetracontanoate (0.018 g, 0.013 mmol, 49%). LC/MS [M+H] 1356.62 (calculated); LC/MS [M+H] 1357.10 (observed).

Example 63 Synthesis of BzL-43



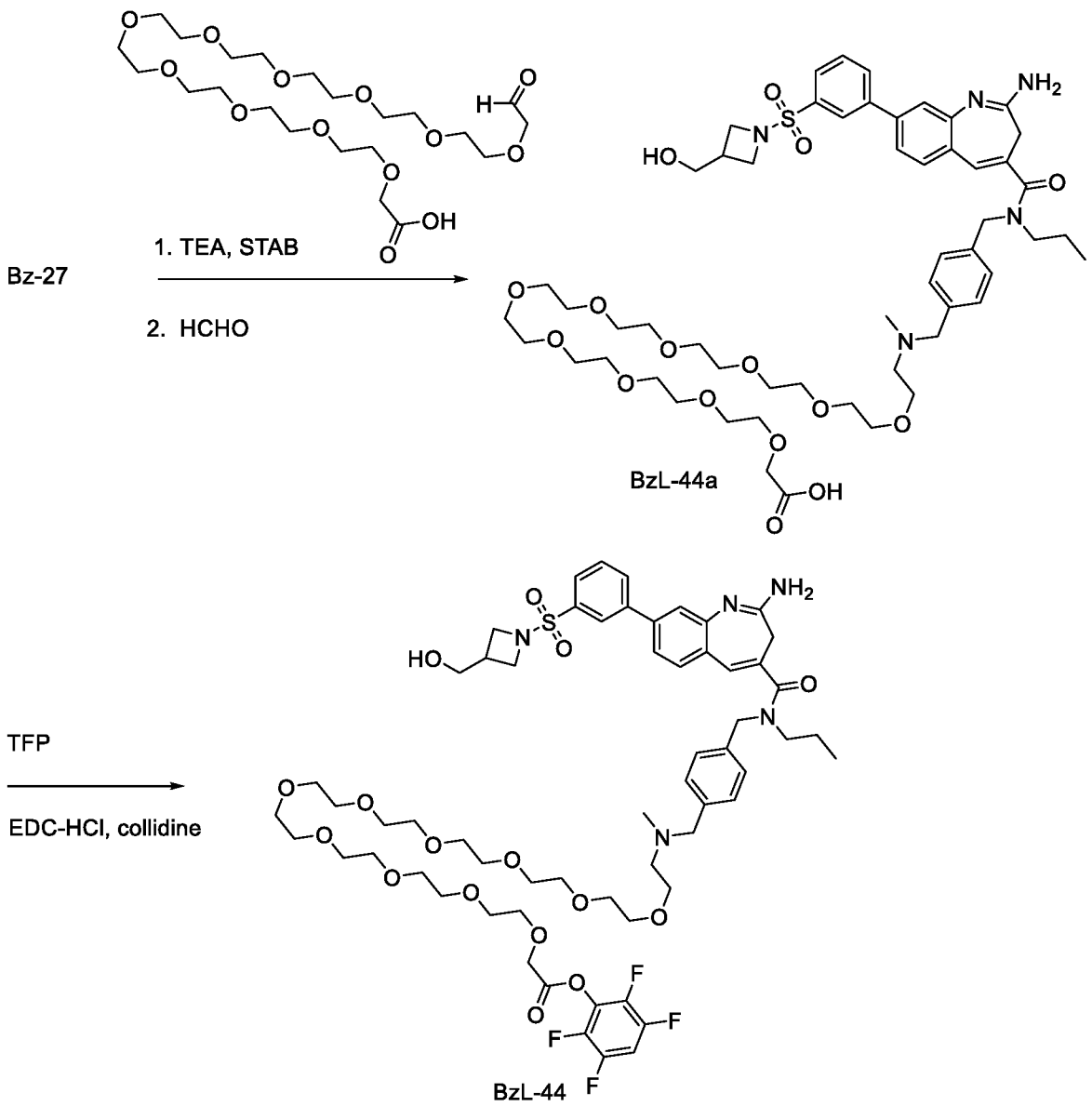
Preparation of BzL-43a: To a mixture of 2-amino-N-(4-aminobut-2-ynyl)-8-[3-[3-(hydroxymethyl)azetidin-1-yl] sulfonylphenyl]-N-propyl-3H-1-benzazepine-4-carboxamide, BzL-40a (0.1 g, 187 umol, 1.0 eq) and methyl 3-[2-[2-[2-[2-[2-[2-[2-[2-(2-oxoethoxy)ethoxy]ethoxy]ethoxy]ethoxy] ethoxy]ethoxy]ethoxy]propanoate (101.3 mg, 187 umol, 1.0 eq) in MeOH (10 mL) was added AcOH (11.2 mg, 187 umol, 11 uL, 1.0 eq) and $NaBH_3CN$ (35.2 mg, 560 umol, 3.0 eq) in one portion at 25°C and then stirred for 2 hours. Then formaldehyde (29.5 mg, 373 umol, 27 uL, 2.0 eq) was added and it was stirred for 1 hour at the same temperature. The mixture was added a few drops water and concentrated. The residue was purified by prep-HPLC (column: Xtimate C18 100*30mm*3um; mobile phase:

[water(0.1%TFA)-ACN];B%: 10%-35%,10min) to give methyl 3-[2-[2-[2-[2-[2-[2-[2-[2-[2-[2-[4-[[2-amino-8-[3-[3-(hydroxymethyl)azetidin-1-yl]sulfonylphenyl]-3H-1-benzazepine-4-carbonyl]-propyl-amino]but-2-ynyl-methyl-amino]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]propanoate, BzL-43a (0.05 g, 46.46 umol, 24.88% yield) as colorless oil.

Preparation of BzL-43b: To a solution of BzL-43a (50 mg, 46.5 umol, 1.0 eq) in MeOH (3.0 mL) and H_2O (0.3 mL) was added $LiOH•H_2O$ (19.5 mg, 465 umol, 10.0 eq) in one portion at 25 °C and it was stirred at the same temperature for 16 hours. The mixture was cooled to 0 °C, adjusted pH = 7 with aq HCl(1M) and concentrated in reduced pressure at 40 °C. The residue was purified by prep-HPLC (column: Nano-micro Kromasil C18 100*30mm 8um; mobile phase: [water (0.1% TFA)-ACN]; B%: 10%-40%, 10min) to afford 3-[2-[2-[2-[2-[2-[2-[2-[2-[2-[2-[4-[[2 -amino-8-[3-[3-(hydroxymethyl)azetidin-1-yl]sulfonylphenyl]-3H-1-benzazepine-4-carbonyl]-propyl-amino]but-2-ynyl-methyl-amino]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]propanoic acid, BzL-43b (30 mg, 28.24 umol, 60.79% yield) as light yellow oil. ^{1}H NMR (MeOD, 400 MHz) δ8.15-8.07 (m, 2H), 7.93 (d, J = 8.0 Hz, 1H), 7.86-7.76 (m, 3H), 7.74-7.69 (m, 1H), 7.24 (s, 1H), 4.29 (s, 2H), 3.91-3.84 (m, 4H), 3.74-3.55 (m, 43H), 3.52-3.38 (m, 7H), 3.34-3.32 (m, 2H), 3.02 (s, 3H), 2.64-2.56 (m, 1H), 2.53 (t, J = 6.4 Hz, 2H), 1.85-1.72 (m, 2H), 0.98 (t, J = 7.2 Hz, 3H). LC/MS [M+H] 1062.5 (calculated); LC/MS [M+H] 1062.6 (observed).

Preparation of BzL-43: Bz-43b (0.03 g, 0.028 mmol, 1 eq.) and TFP (0.009 g, 0.06 mmol, 2 eq.) were dissolved in DMF. Collidine (0.019 ml, 0.14 mmol, 5 eq.) was added, followed by EDC-HCl (0.016 g, 0.085 mmol, 3 eq.). The reaction was stirred at room temperature and monitored by LCMS, then concentrated and purified by HPLC to give 2,3,5,6-tetrafluorophenyl 38-(2-amino-8-(3-((3-((dimethylamino)methyl)azetidin-1-yl)sulfonyl)phenyl)-3*H*-benzo[*b*]azepine-4-carbonyl)-33-methyl-3,6,9,12,15,18,21,24,27,30-decaoxa-33,38-diazahentetracont-35-ynoate, BzL-43 (0.016 g, 0.013 mmol, 46%). LC/MS [M+H] 1210.53 (calculated); LC/MS [M+H] 1210.95 (observed).

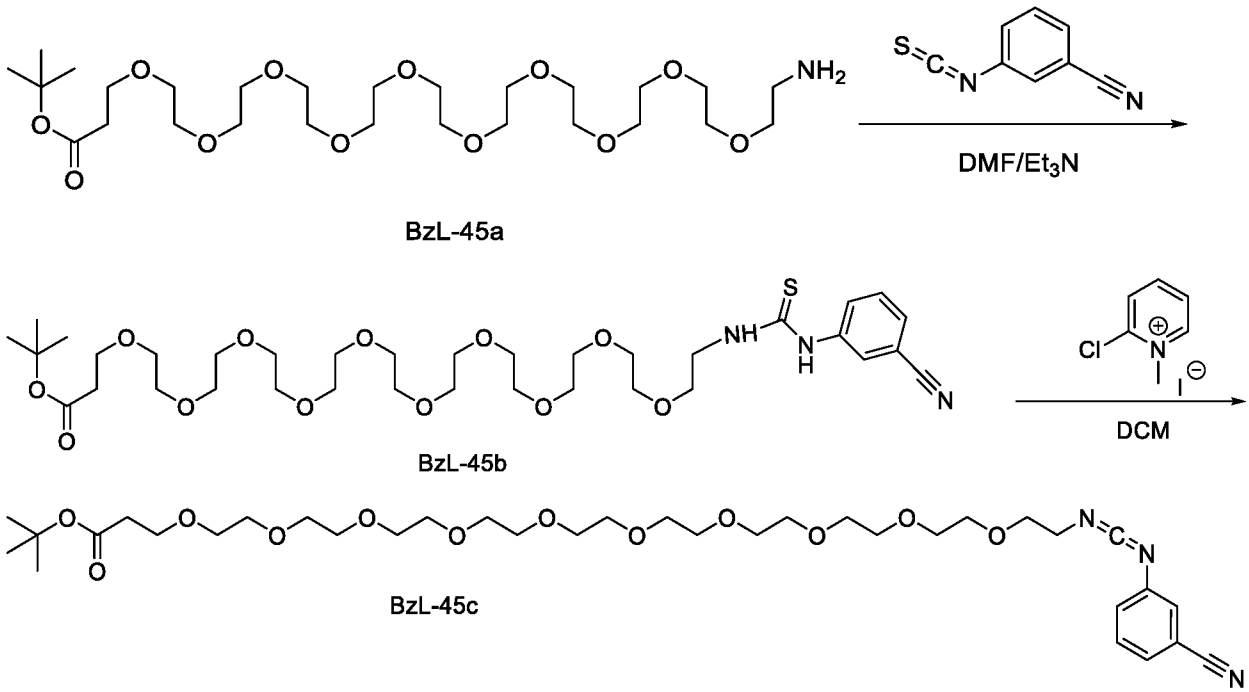
Example 64 Synthesis of BzL-44



Preparation of BzL44a: 2-Amino-N-(4-(aminomethyl)benzyl)-8-(3-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-*N*-propyl-3*H*-benzo[*b*]azepine-4-carboxamide, Bz-27 (0.119 g, 0.203 mmol, 1 eq.) and 32-oxo-3,6,9,12,15,18,21,24,27,30-decaoxadotriacontanoic acid (0.107 g, 0.203 mmol, 1 eq.) were dissolved in 1:1 ACN:DCM. Triethylamine (0.17 ml, 1.2 mmol, 6 eq.) was added, followed by sodium triacetoxyborohydride (0.13 g, 0.61 mmol, 3 eq.). The reaction was stirred at room temperature for 40 minutes, and then formaldehyde was added (0.02 ml, 0.27 mmol, 1.3 eq., 37 wt. % in H_2O). After 10 minutes, the reaction was concentrated and purified by HPLC to give 1-(4-((2-amino-8-(3-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-*N*-propyl-3*H*-benzo[*b*]azepine-4-carboxamido)methyl)phenyl)-2-methyl-5,8,11,14,17,20,23,26,29,32-decaoxa-2-azatetratriacontan-34-oic acid, BzL44a (0.067 g, 0.060 mmol, 30%). LC/MS [M+H] 1114.56 (calculated); LC/MS [M+H] 1114.89 (observed).

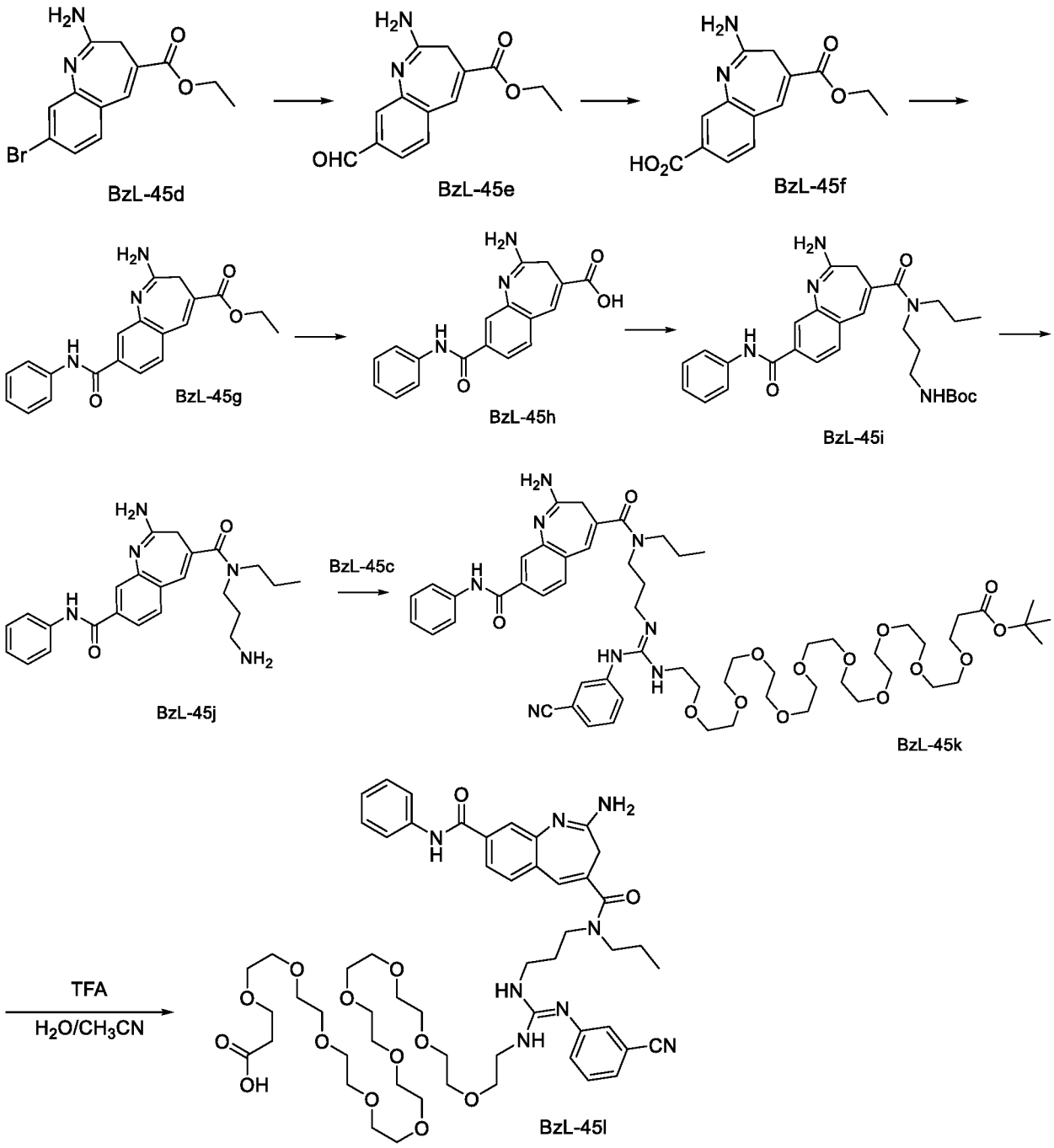
Preparation of BzL-44: BzL-44a (0.067 g, 0.06 mmol, 1 eq.) and TFP (0.020 g, 0.12 mmol, 2 eq.) were dissolved in DMF. Collidine (0.040 ml, 0.30 mmol, 5 eq.) was added, followed by EDC-HCl (0.035 g, 0.18 mmol, 3 eq.). The reaction was stirred at room temperature and monitored by LCMS, then concentrated and purified by HPLC to give 2,3,5,6-tetrafluorophenyl 1-(4-((2-amino-8-(3-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-*N*-propyl-3*H*-benzo[*b*]azepine-4-carboxamido)methyl)phenyl)-2-methyl-5,8,11,14,17,20,23,26,29,32-decaoxa-2-azatetratriacontan-34-oate, BzL-44 (0.026 g, 0.021 mmol, 34%). LC/MS [M+H] 1262.56 (calculated); LC/MS [M+H] 1262.86 (observed).

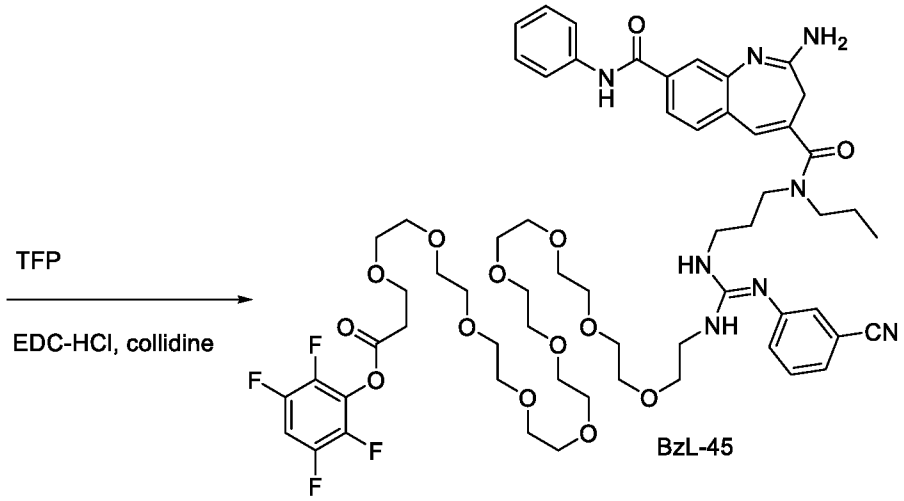
Example 65 Synthesis of BzL-45



Preparation of BzL-45b: To a mixture of tert-butyl 3-[2-[2-[2-[2-[2-[2-[2-[2-(2-aminoethoxy)ethoxy]ethoxy] ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]propanoate, BzL-45a (2.7 g, 4.61 mmol, 1.0 *eq*) in THF (20 mL) was added Et_3N (700 mg, 6.91 mmol, 960 uL, 1.5 *eq*) and 3-isothiocyanatobenzonitrile (1.48 g, 9.22 mmol, 2.0 *eq*) at 25°C and it was stirred for 1 hour at this temperature. Then the mixture was diluted with water (30 mL) and extracted with EtOAc (50 mL x 3). The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography (MeOH/Ethyl acetate=0/1, 1/10) to afford tert-butyl 3-[2-[2-[2-[2-[2-[2-[2-[2- [2-[(3-cyanophenyl)carbamothioylamino]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy] ethoxy]ethoxy]propanoate, BzL-45b (0.5 g, 670 umol, 14.54% yield) as yellow oil. ^1H NMR ($CDCl_3$, 400MHz) δ7.99 (s, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.44-7.39 (m, 2H), 3.76-3.58 (m, 42H), 2.55-2.46 (m, 2H), 1.45 (s, 9H).

Preparation of BzL-45c: To a mixture of BzL-45b (0.4 g, 536 umol, 1.0 *eq*) and Et_3N (163 mg, 1.61 mmol, 223 uL, 3.0 *eq*) in DCM (10 mL) and DMF (0.4 mL) was added 2-chloro-1-methylpyridin-1-ium iodide (164 mg, 643 umol, 1.2 *eq*) at 25 °C under N_2. The mixture was stirred at 25°C for 1 hour and then concentrated under reduce pressure. The residue was purified by silica gel chromatography (CH_3CN/Ethyl acetate = 0/1 to 1/1) to afford tert-butyl 3-[2-[2-[2-[2-[2-[2-[2-[2-[2-[2-[2-[(3-cyanophenyl)iminomethyleneamino]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]propanoate, BzL-45c (0.29 g, 407 umol, 75.9% yield) as yellow oil. ^1H NMR ($CDCl_3$, 400MHz) δ7.43-7.33 (m, 4H), 3.70-3.62 (m, 42H), 2.51 (t, *J* = 6.4 Hz, 2H), 1.45 (s, 9H).





Preparation of BzL-45e: To a solution of ethyl 2-amino-8-bromo-3H-1-benzazepine-4-carboxylate, BzL-45d (10 g, 32.4 mmol, 1.0 *eq*) in DMF (100 mL) was added Et_3SiH (72.8 g, 626.09 mmol, 100 mL, 19.36 *eq*), Et_3N (6.5 g, 64.69 mmol, 9.00 mL, 2.0 *eq*) and $Pd(dppf)Cl_2$ (1.18 g, 1.62 mmol, 0.05 *eq*) under N_2. The suspension was degassed under vacuum and purged with CO several times and it was stirred under CO (50 psi) at 80°C for 12 h. The mixture was diluted with water (300 mL) and extracted with EtOAc (80 mL x 3). The organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated, and the residue was purified by flash silica gel chromatography (ISCO®; 15 g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether gradient @ 65 mL/min) to give ethyl 2-amino-8-formyl-3H-1- benzazepine-4-carboxylate, BzL-45e (3 g, 11.6 mmol, 35.9% yield) as yellow solid. ^1H NMR (DMSO-d_6, 400 MHz) δ10.00 (s, 1H) 7.79 (s, 1H) 7.61 (d, J = 8.4 Hz, 1H) 7.55 (d, J = 1.2 Hz, 1H) 7.40 (dd, J = 8.0, 1.2 Hz, 1H) 7.07 (s, 2 H) 4.25 (q, J = 6.8 Hz, 2H) 2.91 (s, 2H) 1.31 (t, J = 6.8 Hz, 3H).

Preparation of BzL-45f: To a solution of BzL-45e (2.6 g, 10.1 mmol, 1.0 *eq*) in CH_3CN (15 mL) was added NaH_2PO_4 (362 mg, 3.02 mmol, 0.3 *eq*), H_2O_2 (5.71 g, 50.33 mmol, 4.84 mL, 30% purity, 5.0 *eq*) and $NaClO_2$ (1.46 g, 16.1 mmol, 1.6 *eq*) at 0°C and it was stirred at 25°C for 5 h. The reaction mixture was quenched with Na_2SO_3 (aq) and diluted with H_2O (30 mL) and EtOAc (30 ml), the pH of the mixture was adjusted to 4 with aq HCl (1 M), then filtered to give desired solid The solid was dried under vacuum to give 2-amino-4-ethoxycarbonyl-3H-1-benzazepine-8-carboxylic acid, BzL-45f (2.1 g, 7.66 mmol, 76.1% yield) as white solid. ^1H NMR (DMSO-d_6, 400 MHz) δ7.87 (s, 1H), 7.81 (s, 1H), 7.72-7.67 (m, 2H), 4.27 (q, J = 7.2 Hz, 2H), 3.28 (s, 2 H), 1.31 (t, J = 7.2 Hz, 3H).

Preparation of BzL-45g: To a mixture of BzL-45f (1.0 g, 3.65 mmol, 1.0 eq) in DMF (20 mL) was added PYAOP (2.28 g, 4.38 mmol, 1.2 eq) and DIEA (2.36 g, 18.2 mmol, 3.18 mL, 5.0 eq) at 25°C and it was stirred for 10 min, then aniline (373 mg, 4.01 mmol, 366 uL, 1.1 eq) was added and stirred for 1 hour at 25°C. The mixture was poured into ice water (50 mL)

and stirred for 2 min. The aqueous phase was extracted with ethyl acetate (20 mL x 3). The combined organic phase was washed with brine (20 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum and the residue was purified by silica gel chromatography (EtOAc / MeOH = 1:0 ~ 2:1) to afford ethyl 2-amino-8-(phenylcarbamoyl)-3H-1-benzazepine-4-carboxylate, BzL-45g (0.5 g, 1.43 mmol, 39.25% yield) as yellow solid. ^{1}H NMR (MeOD, 400 MHz) δ 7.89 (s, 1H), 7.76-7.65 (m, 3H), 7.62-7.56 (m, 1H), 7.37 (t, J = 8.0 Hz, 2H), 7.16 (t, J = 8.0 Hz, 1H), 4.35 (q, J = 7.2 Hz, 2H), 3.32 (s, 2H), 1.38 (t, J = 7.2 Hz, 3H).

Preparation of BzL-45h: To a mixture of BzL-45g (0.36 g, 1.03 mmol, 1.0 eq) in EtOH (10 mL) was added a solution of $LiOH•H_2O$ (216 mg, 5.15 mmol, 5.0 eq) in H_2O (1 mL) at 25 °C and it was stirred for 16 hours at this temperature. The mixture was quenched with HCl (4M) until pH to 5 and concentrated under reduced pressure at 40°C to remove EtOH. Water (10 mL) was added and then filtered to give 2-amino-8-(phenylcarbamoyl)-3H-1-benzazepine-4-carboxylic acid, BzL-45h (0.2 g, 622 umol, 60.41% yield) as yellow solid which was used in the next step without further purification. ^{1}H NMR (DMSO-d_6, 400 MHz) δ7.84-7.74 (m, 3H), 7.66 (s, 1H), 7.56-7.47 (m, 2H), 7.34 (t, J = 8.0 Hz, 2H), 7.09 (t, J = 7.2 Hz, 2H), 2.92 (s, 2H).

Preparation of BzL-45i: To a solution of BzL-45h (0.2 g, 622 umol, 1.0 eq) in DMF (5 mL) was added HATU (284 mg, 746 umol, 1.2 eq) and DIEA (241 mg, 1.87 mmol, 325 uL, 3.0 eq) at 25 °C and it was stirred for 10 min at this temperature, then tert-butyl N-[3-(propylamino)propyl]carbamate, Bz-1b (161 mg, 746 umol, 1.2 eq) was added to the mixture and stirred at 25 °C for 3 hours. The reaction was poured into ice water (30 mL) and stirred for 10 min. The aqueous phase was extracted with EtOAc (10 mL x 3), and the combined organic phase was washed with H_2O (10 mL x 2) and brine (10 mL), dried by Na_2SO_4 and concentrated to give tert-butyl N-[3-[[2-amino-8-(phenylcarbamoyl)-3H-1- benzazepine-4-carbonyl]-propyl-amino]propyl]carbamate, BzL-45i (0.3 g, 577 umol, 92.76% yield) as yellow oil.

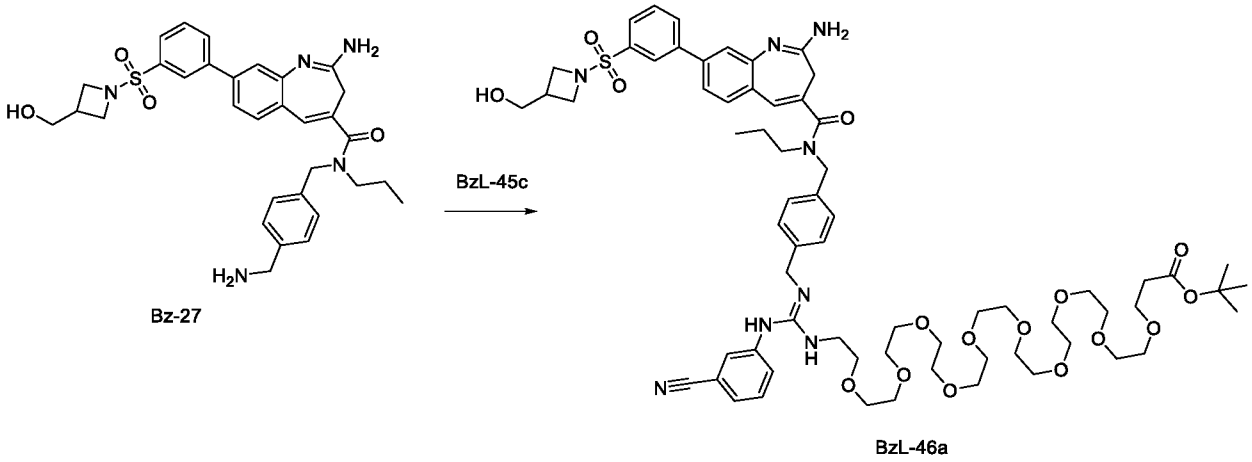
Preparation of BzL-45j: To a solution of BzL-45i (0.4 g, 769 umol, 1.0 eq) in MeOH (10 mL) was added HCl/MeOH (4 M, 9.62 mL, 50 eq) at 25°C. The mixture was stirred at 25°C for 1 hour, and then concentrated under reduced pressure at 40°C. The residue was purified by prep-HPLC (column: Nano-micro Kromasil C18 100*30mm 8um; mobile phase: [water (0.1%TFA) - ACN]; B%: 5% - 30%, 10min) to afford 2-amino-N4 -(3-aminopropyl)-N8-phenyl-N4-propyl-3H-1-benzazepine-4,8-dicarboxamide, BzL-45j (0.23 g, 431 umol, 56.0% yield, TFA salt) as yellow solid. ^{1}H NMR (MeOD, 400 MHz) δ8.01-7.94 (m, 2H), 7.76-7.70 (m, 3H), 7.41 (t, J = 8.0 Hz, 2H), 7.21 (t, J = 7.6 Hz, 2H), 3.63 (t, J = 7.2 Hz, 2H), 3.58-3.49 (m, 2H), 3.41 (s, 2H), 3.10-2.95 (m, 2H), 2.12-1.99 (m, 2H), 1.82-1.68 (m, 2H), 0.95 (t, J = 7.2 Hz, 3H). LC/MS [M+H] 420.2 (calculated); LC/MS [M+H] 420.2 (observed).

Preparation of BzL-45k: To a mixture of Bz-45j (0.06 g, 112 umol, 1.0 eq, TFA salt) in DMF (1 mL) was added Et_3N (28 mg, 281 umol, 2.5 eq) and BzL-45c (88 mg, 123 umol, 1.1 eq) at 25 °C. The mixture was stirred at 25°C for 1 hour and then filtered and purified by prep-HPLC (column: Nano-micro Kromasil C18 100*30mm 8um; mobile phase: [water (0.1%TFA) - ACN]; B%: 20% - 50%, 10min) to afford tert-butyl 3-[2-[2-[2-[2-[2-[2-[2-[2-[2-[2-[[(Z)-N'-[3-[[2-amino-8-(phenylcarbamoyl)-3H-1-benzazepine-4-carbonyl]-propyl-amino]propyl]-N-(3-cyanophenyl)carbamimidoyl]amino]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]propanoate, BzL-45k (0.08 g, 70.7 umol, 62.9% yield) as colorless oil.

Preparation of BzL-45l: To a solution of BzL-45k (0.07 g, 61 umol, 1.0 eq) in H_2O (5 mL) and CH_3CN (1 mL) was added TFA (211 mg, 1.86 mmol, 30 eq) at 25°C. The mixture was stirred at 80 °C for 2 hours and then concentrated under reduced pressure. The residue was freeze-dried to give 3-[2-[2-[2-[2-[2-[2-[2-[2-[2-[2-[[(Z)-N'-[3-[[2-amino-8- (phenylcarbamoyl)-3H-1-benzazepine -4-carbonyl]-propyl-amino]propyl]-N-(3-cyanophenyl)carbamimidoyl]amino]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]propanoic acid, BzL-45l (51 mg, 42.9 umol, 69.3% yield, TFA salt) as light yellow oil. ^{1}H NMR (MeOD, 400 MHz) δ8.01-7.94 (m, 2H), 7.79-7.75 (m, 1H), 7.72 (d, J = 8.0 Hz, 2H), 7.66-7.64 (m, 4H), 7.39 (t, J = 7.6 Hz, 2H), 7.19 (t, J = 7.6 Hz, 1H), 7.13 (s, 1H), 3.76-3.52 (m, 46H), 3.42-3.40 (m, 4H), 2.53 (t, J = 6.4 Hz, 2H), 2.04 (m, 2H), 1.79-1.65 (m, 2H), 0.93 (t, J = 7.2 Hz, 3H). LC/MS [M+H] 1075.6 (calculated); LC/MS [M+H] 1075.6 (observed).

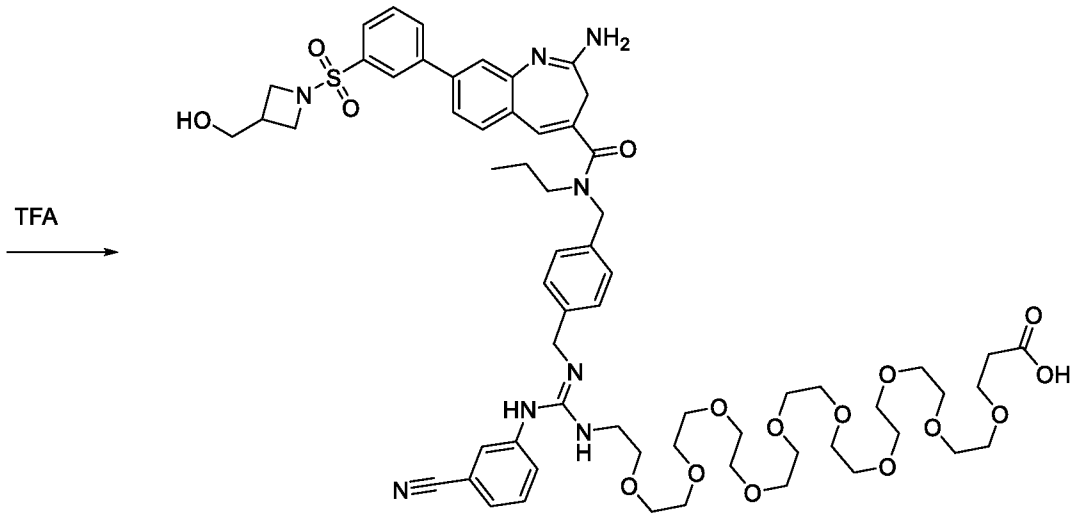
Preparation of BzL-45: BzL-45l (0.051 g, 0.047 mmol, 1 eq.) and TFP (0.016 g, 0.095 mmol, 2 eq.) were dissolved in DMF. Collidine (0.031 ml, 0.24 mmol, 5 eq.) was added, followed by EDC-HCl (0.027 g, 0.14 mmol, 3 eq.). The reaction was stirred at room temperature and monitored by LCMS, then concentrated and purified by HPLC to give 2,3,5,6-tetrafluorophenyl 40-(2-amino-8-(phenylcarbamoyl)-3*H*-benzo[*b*]azepine-4-carbonyl)-35-((3-cyanophenyl)imino)-4,7,10,13,16,19,22,25,28,31-decaoxa-34,36,40-triazatritetracontanoate, BzL-45 (0.043 g, 0.035 mmol, 74%). LC/MS [M+H] 1223.56 (calculated); LC/MS [M+H] 1223.87 (observed).

Example 66 Synthesis of BzL-46

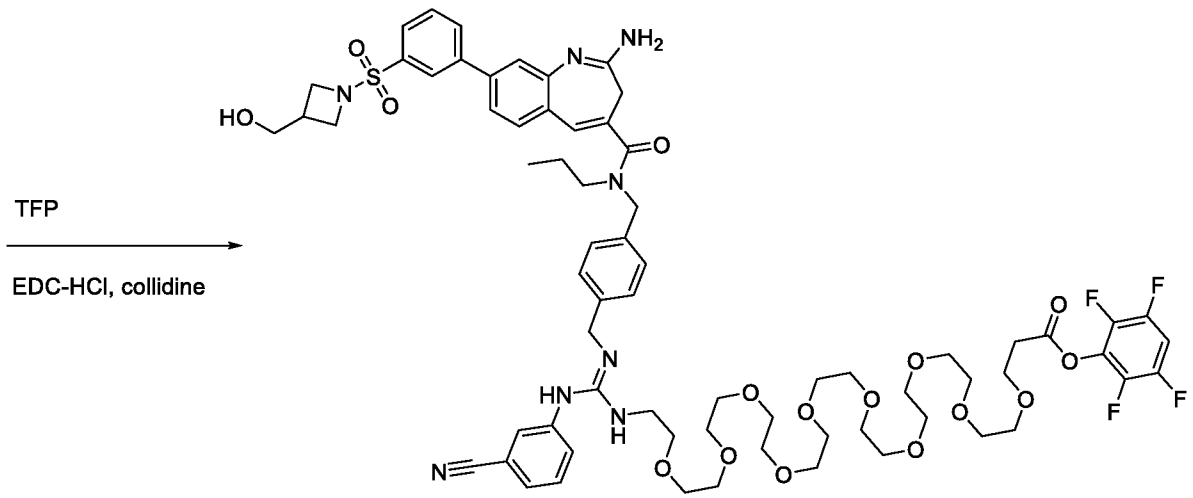


Bz-27

BzL-46a



BzL-46b



BzL-46

Preparation of BzL-46a: Reaction of Bz-27 and BzL-45c gave tert-butyl (Z)-1-(4-((2-amino-8-(3-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-N-propyl-3H-benzo[b]azepine-4-carboxamido)methyl)phenyl)-3-((3-cyanophenyl)amino)-7,10,13,16,19,22,25,28,31,34-

decaoxa-2,4-diazaheptatriacont-2-en-37-oate, BzL-46a by the procedures described for BzL-42. LC/MS [M+H] 1299.7 (calculated); LC/MS [M+H] 1299.7 (observed).

Preparation of BzL-46b: Reaction of BzL-46a with trifluoroacetic acid, TFA by the procedures described in the synthesis of BzL-42 gave (Z)-1-(4-((2-amino-8-(3-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-N-propyl-3H-benzo[b]azepine-4-carboxamido)methyl)phenyl)-3-((3-cyanophenyl)amino)-7,10,13,16,19,22,25,28,31,34-decaoxa-2,4-diazaheptatriacont-2-en-37-oic acid, BzL-46b. LC/MS [M+H] 1243.6 (calculated); LC/MS [M+H] 1243.6 (observed).

Preparation of BzL-46: Reaction of BzL-46b with 2,3,5,6-tetrafluorophenol, TFP and EDC-HCl, as described in the procedures for the synthesis of BzL-42 gave 2,3,5,6-tetrafluorophenyl (Z)-1-(4-((2-amino-8-(3-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-N-propyl-3H-benzo[b]azepine-4-carboxamido)methyl)phenyl)-3-((3-cyanophenyl)amino)-7,10,13,16,19,22,25,28,31,34-decaoxa-2,4-diazaheptatriacont-2-en-37-oate, BzL-46. LC/MS [M+H] 1391.6 (calculated); LC/MS [M+H] 1391.6 (observed).

Example 67 Preparation of Immunoconjugates (IC)

In an exemplary procedure, an antibody is buffer exchanged into a conjugation buffer containing 100 mM boric acid, 50 mM sodium chloride, 1 mM ethylenediaminetetraacetic acid at pH 8.3, using G-25 SEPHADEX™ desalting columns (Sigma-Aldrich, St. Louis, MO). The eluates are then each adjusted to 6 mg/ml using the buffer and then sterile filtered. The antibody at 6 mg/ml is pre-warmed to 30 °C and rapidly mixed with 2-20 (e.g., 7-10) molar equivalents of aminobenzazepine-linker compound of Formula II. The reaction is allowed to proceed for 16 hours at 30 °C and Immunoconjugate A is separated from reactants by running over two successive G-25 desalting columns equilibrated in phosphate buffered saline (PBS) at pH 7.2 to provide the Immunoconjugate (IC) of Tables 3a and 3b. Adjuvant-antibody ratio (DAR) is determined by liquid chromatography mass spectrometry analysis using a C4 reverse phase column on an ACQUITY™ UPLC H-class (Waters Corporation, Milford, Massachusetts) connected to a XEVO™ G2-XS TOF mass spectrometer (Waters Corporation).

For conjugation, the antibody may dissolved in a physiological buffer system known in the art that will not adversely impact the stability or antigen-binding specificity of the antibody. Phosphate buffered saline may be used. The aminobenzazepine-linker intermediate compound is dissolved in a solvent system comprising at least one polar aprotic solvent as described elsewhere herein. In some such aspects, aminobenzazepine-linker intermediate is dissolved to a concentration of about 5 mM, 10 mM, about 20 mM, about 30 mM, about 40 mM or about 50 mM, and ranges thereof such as from about 50 mM to about 50mM or from about 10 mM to

about 30 mM in pH 8 Tris buffer (e.g., 50 mM Tris). In some aspects, the aminobenzazepine-linker intermediate is dissolved in DMSO or acetonitrile, or in DMSO. In the conjugation reaction, an equivalent excess of aminobenzazepine-linker intermediate solution is diluted and combined with chilled antibody solution (e.g. from about 1 °C to about 10 °C). The aminobenzazepine-linker intermediate solution may suitably be diluted with at least one polar aprotic solvent and at least one polar protic solvent, examples of which include water, methanol, ethanol, n-propanol, and acetic acid. In some particular aspects the aminobenzazepine-linker intermediate is dissolved in DMSO and diluted with acetonitrile and water prior to admixture with the antibody solution. The molar equivalents of aminobenzazepine-linker intermediate to antibody may be about 1.5:1, about 3:1, about 5:1, about 10:1 about 15:1 or about 20:1, and ranges thereof, such as from about 1.5:1 to about 20:1 from about 1.5:1 to about 15:1, from about 1.5:1 to about 10:1,from about 3:1 to about 15:1, from about 3:1 to about 10:1, from about 5:1 to about 15:1 or from about 5:1 to about 10:1. The reaction may suitably be monitored for completion by methods known in the art, such as LC-MS, and the reaction is typically complete in from about 1 hour to about 24 hours. After the reaction is complete, a reagent may be added to the reaction mixture to quench the reaction and/or cap unreacted antibody thiol groups. An example of a suitable capping reagent is ethylmaleimide.

Following conjugation according to Example 5, the immunoconjugates may be purified and separated from unconjugated reactants and/or conjugate aggregates by purification methods known in the art such as, for example and not limited to, size exclusion chromatography, hydrophobic interaction chromatography, ion exchange chromatography, chromatofocusing, ultrafiltration, centrifugal ultrafiltration, and combinations thereof. For instance, purification may be preceded by diluting the immunoconjugate, such in 20 mM sodium succinate, pH 5. The diluted solution is applied to a cation exchange column followed by washing with, e.g., at least 10 column volumes of 20 mM sodium succinate, pH 5. The conjugate may be suitably eluted with a buffer such as PBS.

Example 68 HEK Reporter Assay

HEK293 reporter cells expressing human TLR7 or human TLR8 were purchased from Invivogen and vendor protocols were followed for cellular propagation and experimentation. Briefly, cells were grown to 80-85% confluence at 5% CO_2in DMEM supplemented with 10% FBS, Zeocin, and Blasticidin. Cells were then seeded in 96-well flat plates at $4x10^4$cells/well with substrate containing HEK detection medium and immunostimulatory molecules. Activity was measured using a plate reader at 620-655 nm wavelength.

Example 69 Assessment of Immunoconjugate Activity *In Vitro*

This example shows that Immunoconjugates of the invention are effective at eliciting myeloid activation, and therefore are useful for the treatment of cancer.

Isolation of Human Antigen Presenting Cells: Human myeloid antigen presenting cells (APCs) were negatively selected from human peripheral blood obtained from healthy blood donors (Stanford Blood Center, Palo Alto, California) by density gradient centrifugation using a ROSETTESEP™ Human Monocyte Enrichment Cocktail (Stem Cell Technologies, Vancouver, Canada) containing monoclonal antibodies against CD14, CD16, CD40, CD86, CD123, and HLA-DR. Immature APCs were subsequently purified to >90% purity via negative selection using an EASYSEP™ Human Monocyte Enrichment Kit (Stem Cell Technologies) without CD16 depletion containing monoclonal antibodies against CD14, CD16, CD40, CD86, CD123, and HLA-DR.

Myeloid APC Activation Assay: 2 x 10^5 APCs were incubated in 96-well plates (Corning, Corning, NY) containing iscove's modified dulbecco's medium, IMDM (Lonza) supplemented with 10% FBS, 100 U/mL penicillin, 100 µg/mL (micrograms per milliliter) streptomycin, 2 mM L-glutamine, sodium pyruvate, non-essential amino acids, and where indicated, various concentrations of unconjugated (naked) PD-L1 or HER2 antibodies and Immunoconjugate P of the invention (as prepared according to the example above). Trastuzumab and avelumab were used as the antibody constructs. Cell-free supernatants were analyzed after 18 hours by ELISA for TNFα secretion.

Activation of myeloid cell types can be measured using various screen assays in which different myeloid populations are utilized. These may include the following: monocytes isolated from healthy donor blood, M-CSF differentiated Macrophages, GM-CSF differentiated Macrophages, GM-CSF+IL-4 monocyte-derived Dendritic Cells, classical Dendritic Cells isolated from healthy donor blood, and myeloid cells polarized to an immunosuppressive state (also referred to as myeloid derived suppressor cells or MDSCs). Examples of MDSC polarized cells include monocytes differentiated toward immunosuppressive state such as M2a MΦ (IL4/IL13), M2c MΦ (IL10/TGFb), GM-CSF/IL6 MDSCs and tumor-educated monocytes (TEM). TEM differentiation can be performed using tumor-conditioned media (e.g. 786.O, MDA-MB-231, HCC1954). Primary tumor-associated myeloid cells may also include primary cells present in dissociated tumor cell suspensions (Discovery Life Sciences).

Assessment of activation of the described populations of myeloid cells may be performed as a mono-culture or as a co-culture with cells expressing the antigen of interest which the ISAC may bind to via the CDR region of the antibody. Following incubation for 18-48 hours, activation may be assessed by upregulation of cell surface co-stimulatory molecules using flow cytometry or by measurement of secreted proinflammatory cytokines. For cytokine

measurement, cell-free supernatant is harvested and analyzed by cytokine bead array (e.g. LegendPlex from Biolegend) using flow cytometry.

All references, including publications, patent applications, and patents, cited herein are hereby incorporated by reference to the same extent as if each reference were individually and specifically indicated to be incorporated by reference and were set forth in its entirety herein.

CLAIMS:

1. An immunoconjugate comprising an antibody covalently attached to one or more aminobenzazepine moieties by a linker, and having Formula I:

$$Ab–[L–Bza]_p \qquad I$$

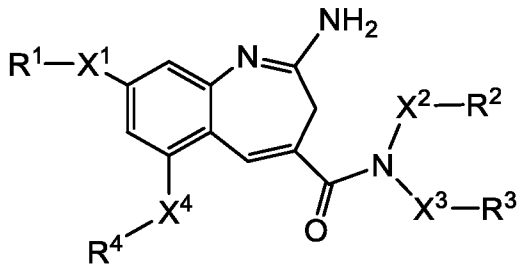
or a pharmaceutically acceptable salt thereof,

wherein:

Ab is the antibody;

p is an integer from 1 to 8;

Bza is the aminobenzazepine moiety having the formula:



R^1 is C_1-C_{20} heteroaryl, and X^1 is a bond;

R^2 is C_1-C_{12} alkyl, and X^2 is a bond;

R^3 is C_1-C_{12} alkyl, and X^3 is O;

R^4 is H, and X^4 is a bond;

wherein R^1 or R^3 is attached to a linker L;

L is the linker selected from the group consisting of:

–C(=O)–(PEG)–;

–C(=O)–(PEG)–C(=O)–;

–C(=O)–(PEG)–O–;

–C(=O)–(PEG)–C(=O)N(R^5)–(C_1-C_{12} alkyldiyl)–;

–C(=O)–(PEG)–C(=O)N(R^5)–(C_1-C_{12} alkyldiyl)–N(R^5)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–; and

–C(=O)–(PEG)–N(R^5)–;

wherein R^5 is selected from the group consisting of H, C_6-C_{20} aryl, C_6-C_{20} aryldiyl, C_1-C_{12} alkyl, and C_1-C_{12} alkyldiyl, or two R^5 groups together form a 5- or 6-membered heterocyclyl ring; and

PEG has the formula: $-(CH_2CH_2O)_n-(CH_2)_m-$; m is an integer from 1 to 5, and n is an integer from 5 to 20.

2. The immunoconjugate of claim 1 wherein R^1 is pyrimidinyl.

3. The immunoconjugate of claim 2 wherein R^1 is pyrimidinyl substituted with $-(C_1\text{-}C_{12}$ alkyldiyl$)-N(R^5)-*$, where the asterisk * indicates the attachment site of L.

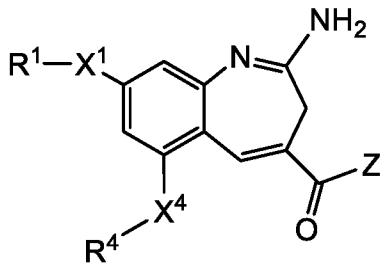
4. The immunoconjugate of claim 3 wherein $-(C_1\text{-}C_{12}$ alkyldiyl$)-N(R^5)-$ * is $-CH_2-NH-*$.

5. The immunoconjugate of claim 4 wherein $-CH_2-NH-*$ is linked at the asterisk to L, wherein L is $-C(=O)-(PEG)-C(=O)-$.

6. The immunoconjugate of claim 1 wherein PEG has the formula: $-(CH_2CH_2O)_n-(CH_2)_m-$; where m is 2 and n is 10.

7. The immunoconjugate of claim 1 wherein X^2-R^2 is $-CH_2CH_2CH_3$, and X^3-R^3 is $-OCH_2CH_3$.

8. An aminobenzazepine-linker compound of Formula II:



II

wherein

Z is $N(X^2-R^2)(X^3-R^3)$;

R^1 is $C_1\text{-}C_{20}$ heteroaryl, and X^1 is a bond;

R^2 is $C_1\text{-}C_{12}$ alkyl, and X^2 is a bond;

R^3 is $C_1\text{-}C_{12}$ alkyl, and X^3 is O;

R^4 is H, and X^4 is a bond;

wherein R^1 or R^3 is attached to a linker L;

L is a linker selected from the group consisting of:

$Q-C(=O)-(PEG)-$;

$Q-C(=O)-(PEG)-C(=O)-$;

$Q-C(=O)-(PEG)-O-$;

Q–C(=O)–(PEG)–C(=O)N(R^5)–(C_1-C_{12} alkyldiyl)–;

Q–C(=O)–(PEG)–C(=O)N(R^5)–(C_1-C_{12} alkyldiyl)–N(R^5)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–; and

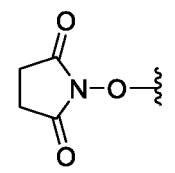
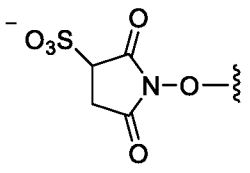
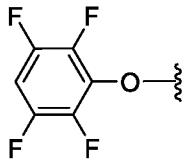
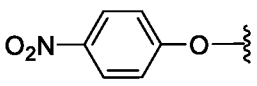
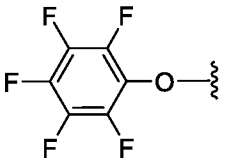
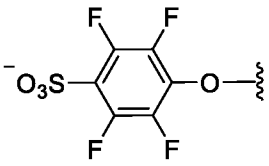
Q–C(=O)–(PEG)–N(R^5)–;

wherein R^5 is selected from the group consisting of H, C_6-C_{20} aryl, C_6-C_{20} aryldiyl, C_1-C_{12} alkyl, and C_1-C_{12} alkyldiyl, or two R^5 groups together form a 5- or 6-membered heterocyclyl ring;

PEG has the formula: $–(CH_2CH_2O)_n–(CH_2)_m–$; m is an integer from 1 to 5, and n is an integer from 5 to 20; and

Q is selected from the group consisting of N-hydroxysuccinimidyl, N-hydroxysulfosuccinimidyl, and phenoxy substituted with one or more groups independently selected from F, Cl, NO_2, and SO_3^-.

9. The aminobenzazepine-linker compound of claim 8 wherein Q is selected from:


,

,

,

,

, and

.

10. A pharmaceutical composition comprising a therapeutically effective amount of an immunoconjugate according to any one of claims 1 to 7 and one or more pharmaceutically acceptable diluent, vehicle, carrier or excipient.

11. A method for treating cancer comprising administering a therapeutically effective amount of the immunoconjugate of any one of claims 1 to 7 or the pharmaceutical composition of claim 10, to a patient in need thereof, wherein the cancer is selected from bladder cancer, urinary tract cancer, urothelial carcinoma, lung cancer, non-small cell lung cancer, Merkel cell carcinoma, colon cancer, colorectal cancer, gastric cancer, and breast cancer.

12. Use of an immunoconjugate of any one of claims 1-7 or the pharmaceutical composition of claim 10 in the manufacture of a medicament for treating cancer, wherein the cancer is selected from bladder cancer, urinary tract cancer, urothelial carcinoma, lung cancer, non-small cell lung cancer, Merkel cell carcinoma, colon cancer, colorectal cancer, gastric cancer, and breast cancer.

13. The method of claim 11, or the use of claim 12 wherein the cancer is susceptible to a pro-inflammatory response induced by TLR7 and/or TLR8 agonism.

14. An immunoconjugate as defined in any one of claims 1-7 for use in treating cancer, wherein the cancer is selected from bladder cancer, urinary tract cancer, urothelial carcinoma, lung cancer, non-small cell lung cancer, Merkel cell carcinoma, colon cancer, colorectal cancer, gastric cancer, and breast cancer.

15. A method of preparing an immunoconjugate of Formula I of claim 1 wherein an aminobenzazepine-linker compound of claim 8 is conjugated with the antibody.

Binding agent	SEQ ID	HCDR1	SEQ ID	HCDR2	SEQ ID	HCDR3	SEQ ID	LCDR1	SEQ ID	LCDR2	SEQ ID	LCDR3
1	1	SYAIS	24	VINPSAGSTDYAQKFQG	58	DLYPYVVVVAAGSYGMDV	96	RASQGIDSYLA	129	AASSLQS	152	QQSYSTPIT
2	2	SYYMH	25	WMMPNSDIAGYAQKFQG	59	PSIVGAYDAFDI	97	RASQSISSWLA	129	AASSLQS	153	QQSYTTPIT
3	3	RHLLH	26	WISPQHGVRNYAQKFQG	60	ESVEGYFDL	98	RASQSISSYLN	129	AASSLQS	154	QQIFSTPLT
4	4	SHHMH	27	WVSPSHGLTGYAQKFQG	61	DNWNVHDAFDI	99	RASQGISSYLA	130	GASNLQS	155	QQSYSTPLT
5	5	RFMH	28	WMSLNSGLTGYAQKFQG	62	GTYNDAFDI	100	RASQTISNYLN	129	AASSLQS	153	QQSYTTPIT
6	6	SYYIH	29	WMKPSSGTTGYAQKFQG	63	EQWLVNDAFDI	101	RASQSVDRNYVT	131	GASTRAT	156	QQSYTTPYT
7	7	NYYIH	30	WMNPNGDVAGYAQKFQG	64	DSSGWMRNDAFDI	102	RASQGISQYLA	132	GASNLHS	157	QQTFTTPLT
8	2	SYYMH	31	GIDPNSGGTNYAQKFQG	65	SMFPTIFGDNAFDI	103	QASQDIGNYLN	133	AASSLES	155	QQSYSTPLT
9	8	HYYMH	32	WMNPDSGSTGYAQKFQG	66	ALFPYPFVYYYMDV	104	RASQGIRNDLG	134	SASNLQS	158	QQANSFPFT
10	9	GYYMH	33	WMSLNSGLTGYAQKFQG	67	DRGWFDP	97	RASQSISSWLA	135	AASTLES	159	QQSYTTPYS

Fig. 1A

11	7	NYYIH	34	WMNPNGDV AGYADSFQG	64	DSSGWMRNDAFDI	102	RASQGISQYLA	132	GASNLHS	160	QQTFITPLT
12	10	NYMYH	35	WISTYHGST NYAQKFQG	68	DARGYSGYDL	105	RASQIIGNYLA	136	HASILET	161	QQSYSTPT
13	2	SYYMH	25	WMNPNSDIA GYAQKFQG	69	EGRHGEYLY	106	RASQIISSYLN	129	AASSLQS	162	QQGFSTPFT
14	11	TYYVH	36	WMNPNTVY TGSAQKFQG	70	EGWGSSGYFDY	107	QASQDISNYLN	129	AASSLQS	163	QQSFTNPVT
15	12	SYALS	37	RIIPAVGSVT YAQKFQG	71	HLFPTVFDDYYGM DV	108	RASQGISNYLA	137	AASTLQS	164	QQSYSAPYT
16	1	SYAIS	38	GIIPIFGTAN YAQKFQG	72	GGYSYGSFQH	109	RASQGISNNLN	138	AATTLQS	165	QQSYSTPYT
17	13	RHYVH	39	WMSPSSGIT GYAQKFQG	73	VRWSSDAFDI	98	RASQSISSYLN	129	AASSLQS	155	QQSYSTPLT
18	2	SYYMH	40	WMTPSTGN AGYAQKFQ G	74	EEWLGHFQH	110	RASQGISNGLS	137	AASTLQS	166	QQSHSTPLT
19	14	SHYMH	41	WMNPNSGN TGYAQKFQ G	75	ERFLGGMDV	111	RASQSITGWLA	129	AASSLQS	165	QQSYSTPYT
20	15	DYYMH	42	WMHPNSGH TGYAQKFQ G	74	EEWLGHFQH	97	RASQSISSWLA	139	DATHLET	152	QQSYSTPIT
21	14	SHYMH	43	WMNPNSGH TGNAQKFQ G	76	GNWVDAFDI	112	RASQGIRNDLA	137	AASTLQS	155	QQSYSTPLT
22	16	GYTLH	44	WIDPNSGVT SSAQKFQG	77	ESEVMMAYFQH	113	QASQDISSYLN	140	AASSLQT	165	QQSYSTPYT
23	9	GYYMH	45	WISPNSGVT DFTQKFQG	78	ESWSGEFDY	114	RASQSITTYLN	141	AASSLQG	165	QQSYSTPYT

Fig. 1B

24	17	NHYMH	46	WMNPNSGH TGYAQRFQG	79	EAVAGPMDV	SEQ ID	LCDR1	SEQ ID	LCDR2	SEQ ID	LCDR3
25	9	GYYMH	25	WMNPNSDIA GYAQKFQG	80	DAWELLAFDI	98	RASQSISSYLN	129	AASSLQS	155	QQSYSTPLT
26	17	NHYMH	41	WMNPNSGN TGYAQKFQ G	81	DRWDGDYYSA	115	RASQSVSTWLA	142	AASNLES	165	QQSYSTPYT
27	7	NYYIH	47	WMSPNGGN TGYAQKFQ G	82	ESWELTGFDY	116	RASQSISNWLA	143	DVSHLES	167	QQSYSTPFT
28	2	SYYMH	41	WMNPNSGN TGYAQKFQ G	83	ERFAGGMDA	117	QASQGISNYLA	144	DASSLQS	155	QQSYSTPLT
29	18	NSYMH	48	WMDPSSGY TGSAHKFQG	84	DSGGAFDI	118	RASQSLSSSSLA	131	GASTRAT	168	QQYGSSPFT
30	19	TYYMH	49	WMNPHSAD TGYAEKFQG	85	EVFEGGMDV	119	RASEHIANWLA	145	GVSSLES	165	QQSYSTPYT
31	2	SYYMH	50	WLTPSTGHA GYAQKFQG	86	EGYGGNYGN	120	RASQSVGSWVA	146	PASTLQS	155	QQSYSTPLT
32	2	SYYMH	51	WMNPNSGH TGYAQKFQ G	87	EDFYGDFDY	121	RASQSISPWLA	147	DASNLET	169	QQTYSTPIT
33	20	RHFIH	44	WIDPNSGVT SSAQKFQG	88	ELSRWGFDY	122	RASQGISRYLA	137	AASTLQS	155	QQSYSTPLT
34	3	RHLLH	52	WISPQHGVR NYAHKFQG	60	ESVEGYFDL	123	RASQTVSSNYLA	148	GASTRAS	170	QQYYTTPLT

Fig. 1C

35	2	SYYMH	53	MINPSGGSTS YAQKFQG	89	DIFPTMIAGGGFDL	98	RASQSISSYLN	129	AASSLQS	171	QQSFSTPLT
36	21	TFGIS	38	GIIPIFGTANY AQKFQG	90	GGYSYGSFDY	97	RASQSISSWLA	147	DASNLET	172	QQSYSTPPT
37	22	SYGIN	41	WMNPNSGNT GYAQKFQG	91	GSFPLVFTIFGVGD V	109	RASQGISNNLN	150	ATSTLQS	165	QQSYSTPYT
38	2	SYYMH	54	WISPRSGVTS YAQKFQG	92	DLDYVRAFDI	124	RSSQGIRNDLS	151	LASNSHS	173	LQHNSYPLT
39	2	SYYMH	55	WMDPNSGNT GYAQKFQG	93	ESWGGYFDL	126	RASQSISRWLA	129	AASSLQS	165	QQSYSTPYT
40	23	NHYVH	56	WMNPTGGIT GYAQKFQG	94	DRTTYAFDI	97	RASQSISSWLA	149	DSSSLQT	174	QQSYSTPVT
41	14	SHYMH	43	WMNPNSGHT GNAQKFQG	76	GNWVDAFDI	125	RDSHSITTWLA	142	AASNLES	175	QHFYNTQYT
42	3	RHLLH	57	WVSPIHGLTG YAPRFQG	95	VHGSGSDGMDV	127	RASQVIRNDLA	137	AASTLQS	176	QQSLQYPSHF

Fig. 1D

Binding Agent	SEQ ID	HFW1	SEQ ID	HFW2	SEQ ID	HFW3	SEQ ID	HFW4
1	177	QVQLVQSGAEVKKPGASVK VSCKASGGTFS	192	WVRQAPGQG LEWMG	196	RVTMTRDTSTSTVYMELSSLR SEDTAVYYCAR	202	WGQGTLVT VSS
2	178	QVQLVQSGAEVKKPGASVK VSCKASGYTFT	192	WVRQAPGQG LEWMG	197	RVTMTRDTSTSTVYMELSSLR SEDTAVYYCAI	202	WGQGTLVT VSS
3	178	QVQLVQSGAEVKKPGASVK VSCKASGYTFT	192	WVRQAPGQG LEWMG	196	RVTMTRDTSTSTVYMELSSLR SEDTAVYYCAR	202	WGQGTLVT VSS
4	178	QVQLVQSGAEVKKPGASVK VSCKASGYTFT	192	WVRQAPGQG LEWMG	196	RVTMTRDTSTSTVYMELSSLR SEDTAVYYCAR	202	WGQGTLVT VSS
5	179	QVQLVQSGAEVKKPGASVK VSCKASGYTFN	192	WVRQAPGQG LEWMG	198	RVTMTRDTSTSTVYMELSSLR SEDTAVYYCTR	202	WGQGTLVT VSS
6	178	QVQLVQSGAEVKKPGASVK VSCKASGYTFT	192	WVRQAPGQG LEWMG	196	RVTMTRDTSTSTVYMELSSLR SEDTAVYYCAR	202	WGQGTLVT VSS
7	178	QVQLVQSGAEVKKPGASVK VSCKASGYTFT	193	WVRQAPGQG LEWLG	197	RVTMTRDTSTSTVYMELSSLR SEDTAVYYCAI	202	WGQGTLVT VSS
8	180	QVQLVQSGAEVKKPGASVK VSCKASGNTFT	192	WVRQAPGQG LEWMG	196	RVTMTRDTSTSTVYMELSSLR SEDTAVYYCAR	202	WGQGTLVT VSS
9	181	QVQLVQSGAEVKKPGASVK VSCKASGHSFT	192	WVRQAPGQG LEWMG	196	RVTMTRDTSTSTVYMELSSLR SEDTAVYYCAR	202	WGQGTLVT VSS
10	178	QVQLVQSGAEVKKPGASVK VSCKASGYTFT	194	WVRQAPGQG LEWIG	196	RVTMTRDTSTSTVYMELSSLR SEDTAVYYCAR	202	WGQGTLVT VSS

Fig. 2A

11	178	QVQLVQSGAEVKKPGASVK VSCKASGYTFT	193	WVRQAPGQG LEWLG	197	RVTMTRDTSTSTVYMELSSLR SEDTAVYYCAI	202	WGQGTLVT VSS
12	177	QVQLVQSGAEVKKPGASVK VSCKASGGTFS	192	WVRQAPGQG LEWMG	196	RVTMTRDTSTSTVYMELSSLR SEDTAVYYCAR	202	WGQGTLVT VSS
13	182	QVQLVQSGAEVKKPGASVK VSCKASGYPFT	192	WVRQAPGQG LEWMG	196	RVTMTRDTSTSTVYMELSSLR SEDTAVYYCAR	202	WGQGTLVT VSS
14	183	QVQLVQSGAEVKKPGASVK VSCKASGYRFT	192	WVRQAPGQG LEWMG	196	RVTMTRDTSTSTVYMELSSLR SEDTAVYYCAR	202	WGQGTLVT VSS
15	184	QVQLVQSGAEVKKPGSSVK VSCKASGGTFS	192	WVRQAPGQG LEWMG	199	RVTITADESTSTAYMELSSLRS EDTAVYYCAR	202	WGQGTLVT VSS
16	184	QVQLVQSGAEVKKPGSSVK VSCKASGGTFS	192	WVRQAPGQG LEWMG	199	RVTITADESTSTAYMELSSLRS EDTAVYYCAR	202	WGQGTLVT VSS
17	185	QVQLVQSGAEVKKPGASVK VSCKASGDTFT	192	WVRQAPGQG LEWMG	196	RVTMTRDTSTSTVYMELSSLR SEDTAVYYCAR	202	WGQGTLVT VSS
18	178	QVQLVQSGAEVKKPGASVK VSCKASGYTFT	195	WVRQAPGQG LEWVG	196	RVTMTRDTSTSTVYMELSSLR SEDTAVYYCAR	202	WGQGTLVT VSS
19	178	QVQLVQSGAEVKKPGASVK VSCKASGYTFT	192	WVRQAPGQG LEWMG	196	RVTMTRDTSTSTVYMELSSLR SEDTAVYYCAR	203	WGQGTTVT VSS
20	178	QVQLVQSGAEVKKPGASVK VSCKASGYTFT	192	WVRQAPGQG LEWMG	200	RVTMTRDTSTSTVNMELSSLR SEDTAVYYCAR	202	WGQGTLVT VSS
21	178	QVQLVQSGAEVKKPGASVK VSCKASGYTFT	192	WVRQAPGQG LEWMG	196	RVTMTRDTSTSTVYMELSSLR SEDTAVYYCAR	204	WGQGTMVT VSS
22	178	QVQLVQSGAEVKKPGASVK VSCKASGYTFT	192	WVRQAPGQG LEWMG	196	RVTMTRDTSTSTVYMELSSLR SEDTAVYYCAR	202	WGQGTLVT VSS

Fig. 2B

23	178	QVQLVQSGAEVKKPGASVK VSCKASGYTFT	192	WVRQAPGQG LEWMG	196	RVTMTRDTSTSTVYMELSSLR SEDTAVYYCAR	202	WGQGTLVT VSS
24	185	QVQLVQSGAEVKKPGASVK VSCKASGDTFT	192	WVRQAPGQG LEWMG	196	RVTMTRDTSTSTVYMELSSLR SEDTAVYYCAR	203	WGQGTTVT VSS
25	178	QVQLVQSGAEVKKPGASVK VSCKASGYTFT	192	WVRQAPGQG LEWMG	196	RVTMTRDTSTSTVYMELSSLR SEDTAVYYCAR	202	WGQGTLVT VSS
26	186	QVQLAQSGAEVKKPGASVK VSCKASGYTFT	192	WVRQAPGQG LEWMG	196	RVTMTRDTSTSTVYMELSSLR SEDTAVYYCAR	202	WGQGTLVT VSS
27	178	QVQLVQSGAEVKKPGASVK VSCKASGYTFT	192	WVRQAPGQG LEWMG	196	RVTMTRDTSTSTVYMELSSLR SEDTAVYYCAR	202	WGQGTLVT VSS
28	178	QVQLVQSGAEVKKPGASVK VSCKASGYTFT	192	WVRQAPGQG LEWMG	196	RVTMTRDTSTSTVYMELSSLR SEDTAVYYCAR	203	WGQGTTVT VSS
29	187	QVQLVQSGAEVKKPGASVK VSCKASGYTFS	192	WVRQAPGQG LEWMG	201	RVTMTRDTSTSTVYMELSSLR SEDTAVYYCAE	204	WGQGTMVT VSS
30	188	QVQLVQSGAEVKKPGASVK VSCKASGYPFS	192	WVRQAPGQG LEWMG	196	RVTMTRDTSTSTVYMELSSLR SEDTAVYYCAR	203	WGQGTTVT VSS
31	178	QVQLVQSGAEVKKPGASVK VSCKASGYTFT	192	WVRQAPGQG LEWMG	196	RVTMTRDTSTSTVYMELSSLR SEDTAVYYCAR	202	WGQGTLVT VSS
32	178	QVQLVQSGAEVKKPGASVK VSCKASGYTFT	192	WVRQAPGQG LEWMG	196	RVTMTRDTSTSTVYMELSSLR SEDTAVYYCAR	202	WGQGTLVT VSS
33	178	QVQLVQSGAEVKKPGASVK VSCKASGYTFT	192	WVRQAPGQG LEWMG	196	RVTMTRDTSTSTVYMELSSLR SEDTAVYYCAR	205	WGPGTMVT VSS
34	178	QVQLVQSGAEVKKPGASVK VSCKASGYTFT	192	WVRQAPGQG LEWMG	196	RVTMTRDTSTSTVYMELSSLR SEDTAVYYCAR	206	WGRGTLVT VSS

Fig. 2C

35	188	QVQLVQSGAEVKKPGASVK VSCKASGYPFS	192	WVRQAPGQG LEWMG	196	RVTMTRDTSTSTVYMELSSLR SEDTAVYYCAR	206	WGRGTLVT VSS
36	184	QVQLVQSGAEVKKPGSSVK VSCKASGGTFS	192	WVRQAPGQG LEWMG	199	RVTITADESTSTAYMELSSLRS EDTAVYYCAR	202	WGQGTLVT VSS
37	178	QVQLVQSGAEVKKPGASVK VSCKASGYTFT	192	WVRQAPGQG LEWMG	196	RVTMTRDTSTSTVYMELSSLR SEDTAVYYCAR	204	WGQGTMVT VSS
38	178	QVQLVQSGAEVKKPGASVK VSCKASGYTFT	192	WVRQAPGQG LEWMG	196	RVTMTRDTSTSTVYMELSSLR SEDTAVYYCAR	203	WGQGTTVT VSS
39	189	QVQLVQSGAEVKKPGASVK VSCKASGYSFT	192	WVRQAPGQG LEWMG	196	RVTMTRDTSTSTVYMELSSLR SEDTAVYYCAR	206	WGRGTLVT VSS
40	190	QVQLVQSGAEVKKPGASVK VSCKASGYTFI	192	WVRQAPGQG LEWMG	196	RVTMTRDTSTSTVYMELSSLR SEDTAVYYCAR	204	WGQGTMVT VSS
41	178	QVQLVQSGAEVKKPGASVK VSCKASGYTFT	192	WVRQAPGQG LEWMG	196	RVTMTRDTSTSTVYMELSSLR SEDTAVYYCAR	204	WGQGTMVT VSS
42	191	QVQLVQSGAEVKKPGSSVK VSCKASGYTFT	192	WVRQAPGQG LEWMG	199	RVTITADESTSTAYMELSSLRS EDTAVYYCAR	203	WGQGTTVT VSS

Fig. 2D

Binding agent	SEQ ID	LFW1	SEQ ID	LFW2	SEQ ID	LFW3	SEQ ID	LFW4
1	207	DIQMTQSPSSLSASVGDRVTITC	210	WYQQKPGKAPKLLIY	213	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC	217	FGGGTKVEIK
2	207	DIQMTQSPSSLSASVGDRVTITC	210	WYQQKPGKAPKLLIY	213	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC	217	FGGGTKVEIK
3	207	DIQMTQSPSSLSASVGDRVTITC	210	WYQQKPGKAPKLLIY	213	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC	217	FGGGTKVEIK
4	207	DIQMTQSPSSLSASVGDRVTITC	210	WYQQKPGKAPKLLIY	213	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC	217	FGGGTKVEIK
5	207	DIQMTQSPSSLSASVGDRVTITC	210	WYQQKPGKAPKLLIY	213	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC	217	FGGGTKVEIK
6	208	EIVMTQSPATLSVSPGERATLSC	211	WYQQKPGQAPRLLIY	214	GIPARFSGSGSGTEFTLTISSLQSEDFAVYYC	218	FGQGTKVEIK
7	207	DIQMTQSPSSLSASVGDRVTITC	210	WYQQKPGKAPKLLIY	213	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC	217	FGGGTKVEIK
8	207	DIQMTQSPSSLSASVGDRVTITC	210	WYQQKPGKAPKLLIY	213	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC	217	FGGGTKVEIK
9	207	DIQMTQSPSSLSASVGDRVTITC	210	WYQQKPGKAPKLLIY	213	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC	217	FGGGTKVEIK
10	207	DIQMTQSPSSLSASVGDRVTITC	210	WYQQKPGKAPKLLIY	213	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC	217	FGGGTKVEIK

Fig. 3A

11	207	DIQMTQSPSSLSASVGDRVTIT C	210	WYQQKPGKAPKLLI Y	213	GVPSRFSGSGSGTDFTLTISSLQPEDFATYY C	217	FGGGTKVEI K
12	207	DIQMTQSPSSLSASVGDRVTIT C	210	WYQQKPGKAPKLLI Y	213	GVPSRFSGSGSGTDFTLTISSLQPEDFATYY C	217	FGGGTKVEI K
13	207	DIQMTQSPSSLSASVGDRVTIT C	210	WYQQKPGKAPKLLI Y	213	GVPSRFSGSGSGTDFTLTISSLQPEDFATYY C	217	FGGGTKVEI K
14	207	DIQMTQSPSSLSASVGDRVTIT C	210	WYQQKPGKAPKLLI Y	213	GVPSRFSGSGSGTDFTLTISSLQPEDFATYY C	217	FGGGTKVEI K
15	207	DIQMTQSPSSLSASVGDRVTIT C	210	WYQQKPGKAPKLLI Y	213	GVPSRFSGSGSGTDFTLTISSLQPEDFATYY C	217	FGGGTKVEI K
16	207	DIQMTQSPSSLSASVGDRVTIT C	210	WYQQKPGKAPKLLI Y	213	GVPSRFSGSGSGTDFTLTISSLQPEDFATYY C	217	FGGGTKVEI K
17	207	DIQMTQSPSSLSASVGDRVTIT C	210	WYQQKPGKAPKLLI Y	213	GVPSRFSGSGSGTDFTLTISSLQPEDFATYY C	217	FGGGTKVEI K
18	207	DIQMTQSPSSLSASVGDRVTIT C	210	WYQQKPGKAPKLLI Y	213	GVPSRFSGSGSGTDFTLTISSLQPEDFATYY C	217	FGGGTKVEI K
19	207	DIQMTQSPSSLSASVGDRVTIT C	210	WYQQKPGKAPKLLI Y	213	GVPSRFSGSGSGTDFTLTISSLQPEDFATYY C	218	FGQGTKVEI K
20	207	DIQMTQSPSSLSASVGDRVTIT C	210	WYQQKPGKAPKLLI Y	213	GVPSRFSGSGSGTDFTLTISSLQPEDFATYY C	219	FGQGTRLEIK
21	207	DIQMTQSPSSLSASVGDRVTIT C	210	WYQQKPGKAPKLLI Y	213	GVPSRFSGSGSGTDFTLTISSLQPEDFATYY C	217	FGGGTKVEI K
22	207	DIQMTQSPSSLSASVGDRVTIT C	210	WYQQKPGKAPKLLI Y	213	GVPSRFSGSGSGTDFTLTISSLQPEDFATYY C	221	FGQGTKLEIK

Fig. 3B

23	207	DIQMTQSPSSLSASVGDRVTITC	210	WYQQKPGKAPKLLIY	213	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC	218	FGQGTKVEIK
24	207	DIQMTQSPSSLSASVGDRVTITC	210	WYQQKPGKAPKLLIY	213	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC	220	FGGGTKLEIK
25	207	DIQMTQSPSSLSASVGDRVTITC	210	WYQQKPGKAPKLLIY	213	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC	221	FGQGTKLEIK
26	207	DIQMTQSPSSLSASVGDRVTITC	210	WYQQKPGKAPKLLIY	213	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC	222	FGPGTKVDIK
27	207	DIQMTQSPSSLSASVGDRVTITC	210	WYQQKPGKAPKLLIY	213	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC	217	FGGGTKVEIK
28	208	EIVMTQSPATLSVSPGERATLSC	211	WYQQKPGQAPRLLIY	214	GIPARFSGSGSGTEFTLTISSLQSEDFAVYYC	222	FGPGTKVDIK
29	207	DIQMTQSPSSLSASVGDRVTITC	210	WYQQKPGKAPKLLIY	213	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC	221	FGQGTKLEIK
30	207	DIQMTQSPSSLSASVGDRVTITC	210	WYQQKPGKAPKLLIY	213	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC	217	FGGGTKVEIK
31	207	DIQMTQSPSSLSASVGDRVTITC	210	WYQQKPGKAPKLLIY	213	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC	219	FGQGTRLEIK
32	207	DIQMTQSPSSLSASVGDRVTITC	210	WYQQKPGKAPKLLIY	213	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC	218	FGQGTKVEIK
33	208	EIVMTQSPATLSVSPGERATLSC	211	WYQQKPGQAPRLLIY	214	GIPARFSGSGSGTEFTLTISSLQSEDFAVYYC	217	FGGGTKVEIK
34	207	DIQMTQSPSSLSASVGDRVTITC	210	WYQQKPGKAPKLLIY	213	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC	219	FGQGTRLEIK

Fig. 3C

35	207	DIQMTQSPSSLSASVGDRVTIT C	210	WYQQKPGKAPKLLI Y	213	GVPSRFSGSGSGTDFTLTISSLQPEDFATYY C	218	FGQGTKVEI K
36	207	DIQMTQSPSSLSASVGDRVTIT C	210	WYQQKPGKAPKLLI Y	213	GVPSRFSGSGSGTDFTLTISSLQPEDFATYY C	218	FGQGTKVEI K
37	207	DIQMTQSPSSLSASVGDRVTIT C	210	WYQQKPGKAPKLLI Y	213	GVPSRFSGSGSGTDFTLTISSLQPEDFATYY C	217	FGGGTKVEI K
38	207	DIQMTQSPSSLSASVGDRVTIT C	210	WYQQKPGKAPKLLI Y	213	GVPSRFSGSGSGTDFTLTISSLQPEDFATYY C	221	FGQGTKLEIK
39	207	DIQMTQSPSSLSASVGDRVTIT C	210	WYQQKPGKAPKLLI Y	213	GVPSRFSGSGSGTDFTLTISSLQPEDFATYY C	218	FGQGTKVEI K
40	209	DIQITHSPSSLSASVGYRLTITC	212	WYHQKPWNAPKLMI Y	215	GVPSRFSGSGSGTYFTLTISSLQPEDFATYY C	218	FGQGTKVEI K
41	207	DIQMTQSPSSLSASVGDRVTIT C	210	WYQQKPGKAPKLLI Y	213	GVPSRFSGSGSGTDFTLTISSLQPEDFATYY C	218	FGQGTKVEI K
42	207	DIQMTQSPSSLSASVGDRVTIT C	210	WYQQKPGKAPKLLI Y	216	GVPSRFSGSGSGTDFTLTISSLQPEDFAPYY C	222	FGPGTKVDI K

Fig. 3D

Binding agent	SEQ ID	VH
1	223	QVQLVQSGAEVKKPGASVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGVINPSAGSTDYAQKFQGRVTMTRDTSTSTV YMELSSLRSEDTAVYYCARDLYPYVVVVAAGSYGMDVWGQGTLVTVSS
2	224	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEWMGWMNPNSDIAGYAQKFQGRVTMTRDTSTS TVYMELSSLRSEDTAVYYCAIPSIVGAYDAFDIWGQGTLVTVSS
3	225	QVQLVQSGAEVKKPGASVKVSCKASGYTFTRHLLHWVRQAPGQGLEWMGWISPQHGVRNYAQKFQGRVTMTRDTSTST VYMELSSLRSEDTAVYYCARESVEGYFDLWGQGTLVTVSS
4	226	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSHHMHWVRQAPGQGLEWMGWVSPSHGLTGYAQKFQGRVTMTRDTSTST VYMELSSLRSEDTAVYYCARDNWNVHDAFDIWGQGTLVTVSS
5	227	QVQLVQSGAEVKKPGASVKVSCKASGYTFNRFMHWVRQAPGQGLEWMGWMSLNSGLTGYAQKFQGRVTMTRDTSTST VYMELSSLRSEDTAVYYCTRGTYNDAFDIWGQGTLVTVSS
6	228	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYIHWVRQAPGQGLEWMGWMKPSSGTTGYAQKFQGRVTMTRDTSTST VYMELSSLRSEDTAVYYCAREQWLVNDAFDIWGQGTLVTVSS
7	229	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYIHWVRQAPGQGLEWMGWMKPSSGTTGYAQKFQGRVTMTRDTSTST VYMELSSLRSEDTAVYYCAREQWLVNDAFDIWGQGTLVTVSS
8	230	QVQLVQSGAEVKKPGASVKVSCKASGNTFTSYYMHWVRQAPGQGLEWMGGIDPNSGGTNYAQKFQGRVTMTRDTSTST VYMELSSLRSEDTAVYYCARSMFPTIFGDNAFDIWGQGTLVTVSS
9	231	QVQLVQSGAEVKKPGASVKVSCKASGHSFTHYYMHWVRQAPGQGLEWMGWMNPDSGSTGYAQKFQGRVTMTRDTSTS TVYMELSSLRSEDTAVYYCARALFPYPFYYYYMDVWGQGTLVTVSS
10	232	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWIGWMSLNSGLTGYAQKFQGRVTMTRDTSTST VYMELSSLRSEDTAVYYCARDRGWFDPWGQGTLVTVSS
11	233	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYYIHWVRQAPGQGLEWLGWMNPNGDVAGYADSFQGRVTMTRDTSTST VYMELSSLRSEDTAVYYCAIDSSGWMRNDAFDIWGQGTLVTVSS

Fig. 4A

12	234	QVQLVQSGAEVKKPGASVKVSCKASGGTFSNYMYHWVRQAPGQGLEWMGWISTYHGSTNYAQKFQGRVTMTRDTSTST VYMELSSLRSEDTAVYYCARDARGYSGYDLWGQGTLVTVSS
13	235	QVQLVQSGAEVKKPGASVKVSCKASGYPFTSYYMHWVRQAPGQGLEWMGWMNPNSDIAGYAQKFQGRVTMTRDTSTS TVYMELSSLRSEDTAVYYCAREGRHGEYLYWGQGTLVTVSS
14	236	QVQLVQSGAEVKKPGASVKVSCKASGYRFTTYYVHWVRQAPGQGLEWMGWMNPNTVYTGSAQKFQGRVTMTRDTSTS TVYMELSSLRSEDTAVYYCAREGWGSSGYFDYWGQGTLVTVSS
15	237	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYALSWVRQAPGQGLEWMGRIIPAVGSVTYAQKFQGRVTITADESTSTAY MELSSLRSEDTAVYYCARHLFPTVFDDYYGMDVWGQGTLVTVSS
16	238	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADESTSTAYM ELSSLRSEDTAVYYCARGGYSYGSFQHWGQGTLVTVSS
17	239	QVQLVQSGAEVKKPGASVKVSCKASGDTFTRHYVHWVRQAPGQGLEWMGWMSPSSGITGYAQKFQGRVTMTRDTSTST VYMELSSLRSEDTAVYYCARVRWSSDAFDIWGQGTLVTVSS
18	240	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEWVGWMTPSTGNAGYAQKFQGRVTMTRDTSTS TVYMELSSLRSEDTAVYYCAREEWLGHFQHWGQGTLVTVSS
19	241	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSHYMHWVRQAPGQGLEWMGWMNPNSGNTGYAQKFQGRVTMTRDTSTS TVYMELSSLRSEDTAVYYCARERFLGGMDVWGQGTTVTVSS
20	242	QVQLVQSGAEVKKPGASVKVSCKASGYTFTDYYMHWVRQAPGQGLEWMGWMHPNSGHTGYAQKFQGRVTMTRDTSTS TVNMELSSLRSEDTAVYYCAREEWLGHFQHWGQGTLVTVSS
21	243	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSHYMHWVRQAPGQGLEWMGWMNPNSGHTGNAQKFQGRVTMTRDTSTS TVYMELSSLRSEDTAVYYCARGNWVDAFDIWGQGTMVTVSS
22	244	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYTLHWVRQAPGQGLEWMGWIDPNSGVTSSAQKFQGRVTMTRDTSTSTV YMELSSLRSEDTAVYYCARESEVMMAYFQHWGQGTLVTVSS
23	245	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWISPNSGVTDFTQKFQGRVTMTRDTSTST VYMELSSLRSEDTAVYYCARESWSGEFDYWGQGTLVTVSS

Fig. 4B

24	246	QVQLVQSGAEVKKPGASVKVSCKASGDTFTNHYMHWVRQAPGQGLEWMGWMNPNSGHTGYAQRFQGRVTMTRDTSTS TVYMELSSLRSEDTAVYYCAREAVAGPMDVWGQGTTVTVSS
25	247	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWMNPNSDIAGYAQKFQGRVTMTRDTSTS TVYMELSSLRSEDTAVYYCARDAWELLAFDIWGQGTLVTVSS
26	248	QVQLAQSGAEVKKPGASVKVSCKASGYTFTNHYMHWVRQAPGQGLEWMGWMNPNSGNTGYAQKFQGRVTMTRDTSTS TVYMELSSLRSEDTAVYYCARDRWDGDYYSAWGQGTLVTVSS
27	249	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYYIHWVRQAPGQGLEWMGWMSPNGGNTGYAQKFQGRVTMTRDTSTST VYMELSSLRSEDTAVYYCARESWELTGFDYWGQGTLVTVSS
28	250	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEWMGWMNPNSGNTGYAQKFQGRVTMTRDTSTS TVYMELSSLRSEDTAVYYCARERFAGGMDAWGQGTTVTVSS
29	251	QVQLVQSGAEVKKPGASVKVSCKASGYTFSNSYMHWVRQAPGQGLEWMGWMDPSSGYTGSAHKFQGRVTMTRDTSTST VYMELSSLRSEDTAVYYCAEDSGGAFDIWGQGTMVTVSS
30	252	QVQLVQSGAEVKKPGASVKVSCKASGYPFSTYYMHWVRQAPGQGLEWMGWMNPHSADTGYAEKFQGRVTMTRDTSTS TVYMELSSLRSEDTAVYYCAREVFEGGMDVWGQGTTVTVSS
31	253	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEWMGWLTPSTGHAGYAQKFQGRVTMTRDTSTST VYMELSSLRSEDTAVYYCAREGYGGNYGNWGQGTLVTVSS
32	254	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEWMGWMNPNSGHTGYAQKFQGRVTMTRDTSTS TVYMELSSLRSEDTAVYYCAREDFYGDFDYWGQGTLVTVSS
33	255	QVQLVQSGAEVKKPGASVKVSCKASGYTFTRHFIHWVRQAPGQGLEWMGWIDPNSGVTSSAQKFQGRVTMTRDTSTSTV YMELSSLRSEDTAVYYCARELSRWGFDYWGPGTMVTVSS
34	256	QVQLVQSGAEVKKPGASVKVSCKASGYTFTRHLLHWVRQAPGQGLEWMGWISPQHGVRNYAHKFQGRVTMTRDTSTST VYMELSSLRSEDTAVYYCARESVEGYFDLWGRGTLVTVSS
35	257	QVQLVQSGAEVKKPGASVKVSCKASGYPFSSYYMHWVRQAPGQGLEWMGMINPSGGSTSYAQKFQGRVTMTRDTSTST VYMELSSLRSEDTAVYYCARDIFPTMIAGGGFDLWGRGTLVTVSS

Fig. 4C

36	258	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSTFGISWVRQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADESTSTAYM ELSSLRSEDTAVYYCARGGYSYGSFDYWGQGTLVTVSS
37	259	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGINWVRQAPGQGLEWMGWMNPNSGNTGYAQKFQGRVTMTRDTSTST VYMELSSLRSEDTAVYYCARGSFPLVFTIFGVGDVWGQGTMVTVSS
38	260	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEWMGWISPRSGVTSYAQKFQGRVTMTRDTSTST VYMELSSLRSEDTAVYYCARDLDYVRAFDIWGQGTTVTVSS
39	261	QVQLVQSGAEVKKPGASVKVSCKASGYSFTSYYMHWVRQAPGQGLEWMGWMDPNSGNTGYAQKFQGRVTMTRDTSTS TVYMELSSLRSEDTAVYYCARESWGGYFDLWGRGTLVTVSS
40	262	QVQLVQSGAEVKKPGASVKVSCKASGYTFINHYVHWVRQAPGQGLEWMGWMNPTGGITGYAQKFQGRVTMTRDTSTST VYMELSSLRSEDTAVYYCARDRTTYAFDIWGQGTMVTVSS
41	263	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSHYMHWVRQAPGQGLEWMGWMNPNSGHTGNAQKFQGRVTMTRDTSTS TVYMELSSLRSEDTAVYYCARGNWVDAFDIWGQGTMVTVSS
42	264	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTRHLLHWVRQAPGQGLEWMGWVSPIHGLTGYAPRFQGRVTITADESTSTAY MELSSLRSEDTAVYYCARVHGSGSDGMDVWGQGTTVTVSS

Fig. 4D

Binding agent	SEQ ID	VL
1	265	DIQMTQSPSSLSASVGDRVTITCRASQGIDSYLAWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPI TFGGGTKVEIK
2	266	DIQMTQSPSSLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYTTPI TFGGGTKVEIK
3	267	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQIFSTPLT FGGGTKVEIK
4	268	DIQMTQSPSSLSASVGDRVTITCRASQGISSYLAWYQQKPGKAPKLLIYGASNLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPL TFGGGTKVEIK
5	269	DIQMTQSPSSLSASVGDRVTITCRASQTISNYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYTTPI TFGGGTKVEIK
6	270	EIVMTQSPATLSVSPGERATLSCRASQSVDRNYVTWYQQKPGQAPRLLIYGASTRATGIPARFSGSGSGTEFTLTISSLQSEDFAVYYCQQSYTT PYTFGQGTKVEIK
7	271	DIQMTQSPSSLSASVGDRVTITCRASQGISQYLAWYQQKPGKAPKLLIYGASNLHSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQTFTTP LTFGGGTKVEIK
8	272	DIQMTQSPSSLSASVGDRVTITCQASQDIGNYLNWYQQKPGKAPKLLIYAASSLESGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTP LTFGGGTKVEIK
9	273	DIQMTQSPSSLSASVGDRVTITCRASQGIRNDLGWYQQKPGKAPKLLIYSASNLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQANSFP FTFGGGTKVEIK
10	274	DIQMTQSPSSLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYAASTLESGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYTTPY SFGGGTKVEIK
11	275	DIQMTQSPSSLSASVGDRVTITCRASQGISQYLAWYQQKPGKAPKLLIYGASNLHSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQTFITPL TFGGGTKVEIK
12	276	DIQMTQSPSSLSASVGDRVTITCRASQIIGNYLAWYQQKPGKAPKLLIYHASILETGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPTF GGGTKVEIK
13	277	DIQMTQSPSSLSASVGDRVTITCRASQIISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQGFSTPFT FGGGTKVEIK
14	278	DIQMTQSPSSLSASVGDRVTITCQASQDISNYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSFTNP VTFGGGTKVEIK
15	279	DIQMTQSPSSLSASVGDRVTITCRASQGISNYLAWYQQKPGKAPKLLIYAASTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSAP YTFGGGTKVEIK
16	280	DIQMTQSPSSLSASVGDRVTITCRASQGISNNLNWYQQKPGKAPKLLIYAATTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTP YTFGGGTKVEIK

Fig. 4E

17	281	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPL TFGGGTKVEIK
18	282	DIQMTQSPSSLSASVGDRVTITCRASQGISNGLSWYQQKPGKAPKLLIYAASTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSHSTPL TFGGGTKVEIK
19	283	DIQMTQSPSSLSASVGDRVTITCRASQSITGWLAWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTP YTFGQGTKVEIK
20	284	DIQMTQSPSSLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYDATHLETGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPI TFGQGTRLEIK
21	285	DIQMTQSPSSLSASVGDRVTITCRASQGIRNDLAWYQQKPGKAPKLLIYAASTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTP LTFGGGTKVEIK
22	286	DIQMTQSPSSLSASVGDRVTITCQASQDISSYLNWYQQKPGKAPKLLIYAASSLQTGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPY TFGQGTKLEIK
23	287	DIQMTQSPSSLSASVGDRVTITCRASQSITTYLNWYQQKPGKAPKLLIYAASSLQGGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPY TFGQGTKVEIK
24	288	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPL TFGGGTKLEIK
25	289	DIQMTQSPSSLSASVGDRVTITCRASQSVSTWLAWYQQKPGKAPKLLIYAASNLESGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTP YTFGQGTKLEIK
26	290	DIQMTQSPSSLSASVGDRVTITCRASQSISNWLAWYQQKPGKAPKLLIYDVSHLESGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPF TFGPGTKVDIK
27	291	DIQMTQSPSSLSASVGDRVTITCQASQGISNYLAWYQQKPGKAPKLLIYDASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPL TFGGGTKVEIK
28	292	EIVMTQSPATLSVSPGERATLSCRASQSLSSSSLAWYQQKPGQAPRLLIYGASTRATGIPARFSGSGSGTEFTLTISSLQSEDFAVYYCQQYGSSP FTFGPGTKVDIK
29	293	DIQMTQSPSSLSASVGDRVTITCRASEHIANWLAWYQQKPGKAPKLLIYGVSSLESGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTP YTFGQGTKLEIK
30	294	DIQMTQSPSSLSASVGDRVTITCRASQSVGSWVAWYQQKPGKAPKLLIYPASTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTP LTFGGGTKVEIK
31	295	DIQMTQSPSSLSASVGDRVTITCRASQSISPWLAWYQQKPGKAPKLLIYDASNLETGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQTYSTPI TFGQGTRLEIK
32	296	DIQMTQSPSSLSASVGDRVTITCRASQGISRYLAWYQQKPGKAPKLLIYAASTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPL TFGQGTKVEIK
33	297	EIVMTQSPATLSVSPGERATLSCRASQTVSSNYLAWYQQKPGQAPRLLIYGASTRASGIPARFSGSGSGTEFTLTISSLQSEDFAVYYCQQYYTT PLTFGGGTKVEIK
34	298	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSFSTPLT FGQGTRLEIK

Fig. 4F

35	299	DIQMTQSPSSLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYDASNLETGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPP TFGQGTKVEIK
36	300	DIQMTQSPSSLSASVGDRVTITCRASQGISNNLNWYQQKPGKAPKLLIYATSTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPY TFGQGTKVEIK
37	301	DIQMTQSPSSLSASVGDRVTITCRSSQGIRNDLSWYQQKPGKAPKLLIYLASNSHSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCLQHNSYPL TFGGGTKVEIK
38	302	DIQMTQSPSSLSASVGDRVTITCRASQSISRWLAWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPY TFGQGTKLEIK
39	303	DIQMTQSPSSLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYDSSSLQTGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPV TFGQGTKVEIK
40	304	DIQITHSPSSLSASVGYRLTITCRDSHSITTWLAWYHQKPWNAPKLMIYAASNLESGVPSRFSGSGSGTYFTLTISSLQPEDFATYYCQHFYNTQ YTFGQGTKVEIK
41	305	DIQMTQSPSSLSASVGDRVTITCRASQVIRNDLAWYQQKPGKAPKLLIYAASTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSLQYP SHFFGQGTKVEIK
42	306	DIQMTQSPSSLSASVGDRVTITCRASQSISRYLNWYQQKPGKAPKLLIYAASTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFAPYYCQQSYSTPL TFGPGTKVDIK

Fig. 4G

Binding agent	SEQ ID	HCDR1	SEQ ID	HCDR2	SEQ ID	HCDR3	SEQ ID	LCDR1	SEQ ID	LCDR2	SEQ ID	LCDR3
1	308	SDYMH	322	WMSPYNGIT GYAQKFQG	339	DRFSGSYDY	360	RASQSISSWLA	375	AASSLQS	387	QQSYSTPYT
2	309	GYYMH	323	WMSPSSGITG YAQKFQG	340	DRGWFDP	361	RASQSVGTWLA	376	AASTLEN	388	QQSFSTPYT
3	310	SYYMH	324	WMTTNSGIT GYAQKFQG	341	EGYSSGLDY	360	RASQSISSWLA	375	AASSLQS	387	QQSYSTPYT
4	311	GYYIH	325	GIIPIFGTASY AQKFQG	342	DGRFWSGYPDY	362	RASQGISNYLA	377	RASNLES	389	QQSYSTPLT
5	312	THYMH	326	WMNPNSGH AGSAQKFQG	343	ESIAVAGYDY	360	RASQSISSWLA	378	AASTLQR	387	QQSYSTPYT
6	313	SHDIN	327	WMNPNSGNT GYAQKFQG	344	DRWYMGSADY	363	RASQSISTWLA	379	AASTLQS	390	QQSYSTPFT
7	310	SYYMH	327	WMNPNSGNT GYAQKFQG	345	DDWGGDWFDP	364	QASQDISNHLN	380	GASNLQR	391	QQSYSTPIT
8	312	THYMH	328	WMNPNSGNT GYSQKFQG	346	ERLSVAGFDY	365	RASQGISSWLA	375	AASSLQS	387	QQSYSTPYT
9	314	DHYLH	329	WMNPNIGNT GYAQKFQG	347	EPLQLGGFDY	366	RASESISSWLA	375	AASSLQS	389	QQSYSTPLT
10	309	GYYMH	330	WMNPNGGTT GYAQNFQG	348	EGFGPNAFDI	360	RASQSISSWLA	381	AASNLQS	392	QQYYSTPYT
11	309	GYYMH	327	WMNPNSGNT GYAQKFQG	349	DSWYGDWFDP	367	RASQSVGSWLA	382	GASSLQS	389	QQSYSTPLT
12	309	GYYMH	322	WMSPYNGIT GYAQKFQG	350	EVIEVGMDV	360	RASQSISSWLA	383	AASHLQS	387	QQSYSTPYT
13	315	NYYMH	323	WMSPSSGITG YAQKFQG	351	EAWFGELST	368	RASQNISNFLN	375	AASSLQS	393	QQSYSLPYT
14	316	AYYVH	331	WMNPNRGIT DSAQKFQG	352	EAYVAAFDI	365	RASQGISSWLA	375	AASSLQS	389	QQSYSTPLT
15	317	RHYVH	332	WMNPNSGSA GYAQKFQG	353	ERGYNAFDY	369	RASQSLSSSYLA	131	GASTRAT	394	HQYFTTPLT
16	318	NYIH	333	WIHPRSGAT GYAPKFQG	354	DSVFGLDY	370	RASQSISSYLN	379	AASTLQS	395	QQSYSMPYT
17	310	SYYMH	334	WISPRSGVTS YAQKFQG	355	DLDYVRAFDI	371	RASQSISRWLA	375	AASSLQS	387	QQSYSTPYT

Fig. 5A

18	310	SYYMH	335	WMDPNSGNT GYAQKFQG	356	ESWGGYFDL	360	RASQSISSWLA	385	DSSSLQT	396	QQSYSTPVT
19	319	NHYVH	336	WMNPTGGIT GYAQKFQG	357	DRTTYAFDI	372	RDSHSITTWLA	386	AASNLES	397	QHFYNTQYT
20	320	SHYMH	337	WMNPNSGHT GNAQKFQG	358	GNWVDAFDI	373	RASQVIRNDLA	379	AASTLQS	398	QQSLQYPSHF
21	321	RHLLH	338	WVSPIHGLTG YAPRFQG	359	VHGSGSDGMDV	374	RASQSISRYLN	379	AASTLQS	389	QQSYSTPLT

Fig. 5B

Binding agent	SEQ ID	HFW1	SEQ ID	HFW2	SEQ ID	HFW3	SEQ ID	HFW4
1	399	QVQLVQSGAEVKKPGASVKV SCKASGYTFS	407	WVRQAPGQGLEW MG	409	RVTMTRDTSTSTVYMELSSLRSED TAVYYCAR	411	WGQGTLVTV SS
2	400	QVQLVQSGAEVKKPGASVKV SCKASGYTFT	407	WVRQAPGQGLEW MG	409	RVTMTRDTSTSTVYMELSSLRSED TAVYYCAR	411	WGQGTLVTV SS
3	399	QVQLVQSGAEVKKPGASVKV SCKASGYTFS	407	WVRQAPGQGLEW MG	409	RVTMTRDTSTSTVYMELSSLRSED TAVYYCAR	411	WGQGTLVTV SS
4	401	QVQLVQSGAEVKKPGSSVKV SCKASGYTFT	407	WVRQAPGQGLEW MG	410	RVTITADESTSTAYMELSSLRSEDT AVYYCAR	411	WGQGTLVTV SS
5	399	QVQLVQSGAEVKKPGASVKV SCKASGYTFS	407	WVRQAPGQGLEW MG	409	RVTMTRDTSTSTVYMELSSLRSED TAVYYCAR	411	WGQGTLVTV SS
6	400	QVQLVQSGAEVKKPGASVKV SCKASGYTFT	407	WVRQAPGQGLEW MG	409	RVTMTRDTSTSTVYMELSSLRSED TAVYYCAR	411	WGQGTLVTV SS
7	400	QVQLVQSGAEVKKPGASVKV SCKASGYTFT	407	WVRQAPGQGLEW MG	409	RVTMTRDTSTSTVYMELSSLRSED TAVYYCAR	411	WGQGTLVTV SS
8	399	QVQLVQSGAEVKKPGASVKV SCKASGYTFS	407	WVRQAPGQGLEW MG	409	RVTMTRDTSTSTVYMELSSLRSED TAVYYCAR	411	WGQGTLVTV SS
9	402	QVQLVQSGAEVKEPGASVKV SCKASGYTFT	407	WVRQAPGQGLEW MG	409	RVTMTRDTSTSTVYMELSSLRSED TAVYYCAR	411	WGQGTLVTV SS
10	400	QVQLVQSGAEVKKPGASVKV SCKASGYTFT	407	WVRQAPGQGLEW MG	409	RVTMTRDTSTSTVYMELSSLRSED TAVYYCAR	412	WGQGTTVTV SS
11	400	QVQLVQSGAEVKKPGASVKV SCKASGYTFT	407	WVRQAPGQGLEW MG	409	RVTMTRDTSTSTVYMELSSLRSED TAVYYCAR	411	WGQGTLVTV SS
12	400	QVQLVQSGAEVKKPGASVKV SCKASGYTFT	408	WMRQAPGQGLEW IG	409	RVTMTRDTSTSTVYMELSSLRSED TAVYYCAR	412	WGQGTTVTV SS
13	400	QVQLVQSGAEVKKPGASVKV SCKASGYTFT	407	WVRQAPGQGLEW MG	409	RVTMTRDTSTSTVYMELSSLRSED TAVYYCAR	411	WGQGTLVTV SS
14	403	QVQLVQSGAEVKKPGASVKV SCKASGYNFS	407	WVRQAPGQGLEW MG	409	RVTMTRDTSTSTVYMELSSLRSED TAVYYCAR	412	WGQGTTVTV SS
15	400	QVQLVQSGAEVKKPGASVKV SCKASGYTFT	407	WVRQAPGQGLEW MG	409	RVTMTRDTSTSTVYMELSSLRSED TAVYYCAR	411	WGQGTLVTV SS
16	607	QVQLVQSGAEVKKPGASVKV SCKASGYTLP	407	WVRQAPGQGLEW MG	409	RVTMTRDTSTSTVYMELSSLRSED TAVYYCAR	411	WGQGTLVTV SS
17	400	QVQLVQSGAEVKKPGASVKV SCKASGYTFT	407	WVRQAPGQGLEW MG	409	RVTMTRDTSTSTVYMELSSLRSED TAVYYCAR	412	WGQGTTVTV SS

Fig. 6A

18	405	QVQLVQSGAEVKKPGASVKV SCKASGYSFT	407	WVRQAPGQGLEW MG	409	RVTMTRDTSTSTVYMELSSLRSED TAVYYCAR	413	WGRGTLVTV SS
19	406	QVQLVQSGAEVKKPGASVKV SCKASGYTFI	407	WVRQAPGQGLEW MG	409	RVTMTRDTSTSTVYMELSSLRSED TAVYYCAR	414	WGQGTMVTV SS
20	400	QVQLVQSGAEVKKPGASVKV SCKASGYTFT	407	WVRQAPGQGLEW MG	409	RVTMTRDTSTSTVYMELSSLRSED TAVYYCAR	414	WGQGTMVTV SS
21	401	QVQLVQSGAEVKKPGSSVKV SCKASGYTFT	407	WVRQAPGQGLEW MG	410	RVTITADESTSTAYMELSSLRSEDT AVYYCAR	412	WGQGTTVTV SS

Fig. 6B

Binding agent	SEQ ID	LFW1	SEQ ID	LFW2	SEQ ID	LFW3	SEQ ID	LFW4
1	415	DIQMTQSPSSLSASVGDR VTITC	418	WYQQKPGKAPKLLIY	421	GVPSRFSGSGSGTDFTLTISSLQPE DFATYYC	425	FGGGTKVEIK
2	415	DIQMTQSPSSLSASVGDR VTITC	418	WYQQKPGKAPKLLIY	421	GVPSRFSGSGSGTDFTLTISSLQPE DFATYYC	425	FGGGTKVEIK
3	415	DIQMTQSPSSLSASVGDR VTITC	418	WYQQKPGKAPKLLIY	421	GVPSRFSGSGSGTDFTLTISSLQPE DFATYYC	425	FGGGTKVEIK
4	415	DIQMTQSPSSLSASVGDR VTITC	418	WYQQKPGKAPKLLIY	421	GVPSRFSGSGSGTDFTLTISSLQPE DFATYYC	425	FGGGTKVEIK
5	415	DIQMTQSPSSLSASVGDR VTITC	418	WYQQKPGKAPKLLIY	421	GVPSRFSGSGSGTDFTLTISSLQPE DFATYYC	426	FGQGTKLEIK
6	415	DIQMTQSPSSLSASVGDR VTITC	418	WYQQKPGKAPKLLIY	421	GVPSRFSGSGSGTDFTLTISSLQPE DFATYYC	427	FGQGTKVEIK
7	415	DIQMTQSPSSLSASVGDR VTITC	418	WYQQKPGKAPKLLIY	421	GVPSRFSGSGSGTDFTLTISSLQPE DFATYYC	428	FGQGTRLEIK
8	415	DIQMTQSPSSLSASVGDR VTITC	418	WYQQKPGKAPKLLIY	421	GVPSRFSGSGSGTDFTLTISSLQPE DFATYYC	427	FGQGTKVEIK
9	415	DIQMTQSPSSLSASVGDR VTITC	418	WYQQKPGKAPKLLIY	421	GVPSRFSGSGSGTDFTLTISSLQPE DFATYYC	426	FGQGTKLEIK
10	415	DIQMTQSPSSLSASVGDR VTITC	418	WYQQKPGKAPKLLIY	421	GVPSRFSGSGSGTDFTLTISSLQPE DFATYYC	427	FGQGTKVEIK
11	415	DIQMTQSPSSLSASVGDR VTITC	418	WYQQKPGKAPKLLIY	421	GVPSRFSGSGSGTDFTLTISSLQPE DFATYYC	425	FGGGTKVEIK
12	415	DIQMTQSPSSLSASVGDR VTITC	418	WYQQKPGKAPKLLIY	421	GVPSRFSGSGSGTDFTLTISSLQPE DFATYYC	428	FGQGTRLEIK

Fig. 7A

13	415	DIQMTQSPSSLSASVGDR VTITC	418	WYQQKPGKAPKLLIY	421	GVPSRFSGSGSGTDFTLTISSLQPE DFATYYC	427	FGQGTKVEIK	
14	415	DIQMTQSPSSLSASVGDR VTITC	418	WYQQKPGKAPKLLIY	421	GVPSRFSGSGSGTDFTLTISSLQPE DFATYYC	425	FGGGTKVEIK	
15	416	EIVMTQSPATLSVSPGER ATLSC	419	WYQQKPGQAPRLLIY	422	GIPARFSGSGSGTEFTLTISSLQSED FAVYYC	428	FGQGTRLEIK	
16	415	DIQMTQSPSSLSASVGDR VTITC	418	WYQQKPGKAPKLLIY	421	GVPSRFSGSGSGTDFTLTISSLQPE DFATYYC	426	FGQGTKLEIK	
17	415	DIQMTQSPSSLSASVGDR VTITC	418	WYQQKPGKAPKLLIY	421	GVPSRFSGSGSGTDFTLTISSLQPE DFATYYC	426	FGQGTKLEIK	
18	415	DIQMTQSPSSLSASVGDR VTITC	418	WYQQKPGKAPKLLIY	421	GVPSRFSGSGSGTDFTLTISSLQPE DFATYYC	427	FGQGTKVEIK	
19	417	DIQITHSPSSLSASVGYRL TITC	420	WYHQKPWNAPKLMIY	423	GVPSRFSGSGSGTYFTLTISSLQPE DFATYYC	427	FGQGTKVEIK	
20	415	DIQMTQSPSSLSASVGDR VTITC	418	WYQQKPGKAPKLLIY	421	GVPSRFSGSGSGTDFTLTISSLQPE DFATYYC	427	FGQGTKVEIK	
21	415	DIQMTQSPSSLSASVGDR VTITC	418	WYQQKPGKAPKLLIY	424	GVPSRFSGSGSGTDFTLTISSLQPE DFAPYYC	429	FGPGTKVDIK	

Fig. 7B

Binding agent	SEQ ID	VH
1	430	QVQLVQSGAEVKKPGASVKVSCKASGYTFSSDYMHWVRQAPGQGLEWMGWMSPYNGITGYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARDRFSGSYDYWGQGTLVTVSS
2	431	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWMSPSSGITGYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARDRGWFDPWGQGTLVTVSS
3	432	QVQLVQSGAEVKKPGASVKVSCKASGYTFSSYYMHWVRQAPGQGLEWMGWMTTNSGITGYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAREGYSSGLDYWGQGTLVTVSS
4	433	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTGYYIHWVRQAPGQGLEWMGGIIPIFGTASYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDGRFWSGYPDYWGQGTLVTVSS
5	434	QVQLVQSGAEVKKPGASVKVSCKASGYTFSTHYMHWVRQAPGQGLEWMGWMNPNSGHAGSAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARESIAVAGYDYWGQGTLVTVSS
6	435	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSHDINWVRQAPGQGLEWMGWMNPNSGNTGYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARDRWYMGSADYWGQGTLVTVSS
7	436	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEWMGWMNPNSGNTGYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARDDWGGDWFDPWGQGTLVTVSS
8	437	QVQLVQSGAEVKKPGASVKVSCKASGYTFSTHYMHWVRQAPGQGLEWMGWMNPNSGNTGYSQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARERLSVAGFDYWGQGTLVTVSS
9	438	QVQLVQSGAEVKEPGASVKVSCKASGYTFTDHYLHWVRQAPGQGLEWMGWMNPNIGNTGYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAREPLQLGGFDYWGQGTLVTVSS
10	439	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWMNPNGGTTGYAQNFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAREGFGPNAFDIWGQGTTVTVSS
11	440	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWMNPNSGNTGYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARDSWYGDWFDPWGQGTLVTVSS

Fig. 8A

12	441	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWMRQAPGQGLEWIGWMSPYNGITGYAQKFQGRVTMTRDTSTSTVYMELSSLRS EDTAVYYCAREVIEVGMDVWGQGTTVTVSS
13	442	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYYMHWVRQAPGQGLEWMGWMSPSSGITGYAQKFQGRVTMTRDTSTSTVYMELSSLRS EDTAVYYCAREAWFGELSTWGQGTLVTVSS
14	443	QVQLVQSGAEVKKPGASVKVSCKASGYNFSAYYVHWVRQAPGQGLEWMGWMNPNRGITDSAQKFQGRVTMTRDTSTSTVYMELSSLRS EDTAVYYCAREAYVAAFDIWGQGTTVTVSS
15	444	QVQLVQSGAEVKKPGASVKVSCKASGYTFTRHYVHWVRQAPGQGLEWMGWMNPNSGSAGYAQKFQGRVTMTRDTSTSTVYMELSSLR SEDTAVYYCARERGYNAFDYWGQGTLVTVSS
16	445	QVQLVQSGAEVKKPGASVKVSCKASGYTLPNYIHWVRQAPGQGLEWMGWIHPRSGATGYAPKFQGRVTMTRDTSTSTVYMELSSLRSED TAVYYCARDSVFGLDYWGQGTLVTVSS
17	446	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEWMGWISPRSGVTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSE DTAVYYCARDLDYVRAFDIWGQGTTVTVSS
18	447	QVQLVQSGAEVKKPGASVKVSCKASGYSFTSYYMHWVRQAPGQGLEWMGWMDPNSGNTGYAQKFQGRVTMTRDTSTSTVYMELSSLR SEDTAVYYCARESWGGYFDLWGRGTLVTVSS
19	448	QVQLVQSGAEVKKPGASVKVSCKASGYTFINHYVHWVRQAPGQGLEWMGWMNPTGGITGYAQKFQGRVTMTRDTSTSTVYMELSSLRS EDTAVYYCARDRTTYAFDIWGQGTMVTVSS
20	449	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSHYMHWVRQAPGQGLEWMGWMNPNSGHTGNAQKFQGRVTMTRDTSTSTVYMELSSLR SEDTAVYYCARGNWVDAFDIWGQGTMVTVSS
21	450	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTRHLLHWVRQAPGQGLEWMGWVSPIHGLTGYAPRFQGRVTITADESTSTAYMELSSLRSED TAVYYCARVHGSGSDGMDVWGQGTTVTVSS

Fig. 8B

Binding agent	SEQ ID	VL
1	451	DIQMTQSPSSLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPYTF GGGTKVEIK
2	452	DIQMTQSPSSLSASVGDRVTITCRASQSVGTWLAWYQQKPGKAPKLLIYAASTLENGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSFSTPYT FGGGTKVEIK
3	453	DIQMTQSPSSLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPYTF GGGTKVEIK
4	454	DIQMTQSPSSLSASVGDRVTITCRASQGISNYLAWYQQKPGKAPKLLIYRASNLESGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTF GGGTKVEIK
5	455	DIQMTQSPSSLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYAASTLQRGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPYTF GQGTKLEIK
6	456	DIQMTQSPSSLSASVGDRVTITCRASQSISTWLAWYQQKPGKAPKLLIYAASTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPFTF GQGTKVEIK
7	457	DIQMTQSPSSLSASVGDRVTITCQASQDISNHLNWYQQKPGKAPKLLIYGASNLQRGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPITF GQGTRLEIK
8	458	DIQMTQSPSSLSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPYTF GQGTKVEIK
9	459	DIQMTQSPSSLSASVGDRVTITCRASESISSWLAWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFG QGTKLEIK
10	460	DIQMTQSPSSLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYAASNLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYYSTPYTF GQGTKVEIK
11	461	DIQMTQSPSSLSASVGDRVTITCRASQSVGSWLAWYQQKPGKAPKLLIYGASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTF GGGTKVEIK
12	462	DIQMTQSPSSLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYAASHLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPYTF GQGTRLEIK

Fig. 8C

13	463	DIQMTQSPSSLSASVGDRVTITCRASQNISNFLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSLPYTF GQGTKVEIK
14	464	DIQMTQSPSSLSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTF GGGTKVEIK
15	465	EIVMTQSPATLSVSPGERATLSCRASQSLSSSYLAWYQQKPGQAPRLLIYGASTRATGIPARFSGSGSGTEFTLTISSLQSEDFAVYYCHQYFTTPLT FGQGTRLEIK
16	466	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSMPYTF GQGTKLEIK
17	467	DIQMTQSPSSLSASVGDRVTITCRASQSISRWLAWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPYTF GQGTKLEIK
18	468	DIQMTQSPSSLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYDSSSLQTGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPVTF GQGTKVEIK
19	469	DIQITHSPSSLSASVGYRLTITCRDSHSITTWLAWYHQKPWNAPKLMIYAASNLES GVPSRFSGSGSGTYFTLTISSLQPEDFATYYCQHFYNTQYTFGQGTKVEIK
20	470	DIQMTQSPSSLSASVGDRVTITCRASQVIRNDLAWYQQKPGKAPKLLIYAASTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSLQYPSHF FGQGTKVEIK
21	471	DIQMTQSPSSLSASVGDRVTITCRASQSISRYLNWYQQKPGKAPKLLIYAASTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFAPYYCQQSYSTPLTF GPGTKVDIK

Fig. 8D

SEQUENCE LISTING

<110> BOLT BIOTHERAPEUTICS, INC.

<120> AMINOBENZAZEPINE COMPOUNDS, IMMUNOCONJUGATES, AND USES THEREOF

<130> 17019.002WO1

<140>
<141>

<150> 62/963,884
<151> 2020-01-21

<150> 62/861,139
<151> 2019-06-13

<160> 608

<170> PatentIn version 3.5

<210> 1
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 1
Ser Tyr Ala Ile Ser
1 5

<210> 2
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 2
Ser Tyr Tyr Met His
1 5

<210> 3
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 3
Arg His Leu Leu His
1 5

<210> 4
<211> 5

<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 4
Ser His His Met His
1   5

<210> 5
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 5
Arg Phe Met His
1

<210> 6
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 6
Ser Tyr Tyr Ile His
1   5

<210> 7
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 7
Asn Tyr Tyr Ile His
1   5

<210> 8
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 8

His Tyr Tyr Met His
1   5

<210> 9
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 9
Gly Tyr Tyr Met His
1   5

<210> 10
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 10
Asn Tyr Met Tyr His
1   5

<210> 11
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 11
Thr Tyr Tyr Val His
1   5

<210> 12
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 12
Ser Tyr Ala Leu Ser
1   5

<210> 13
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 13
Arg His Tyr Val His
1   5

<210> 14
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 14
Ser His Tyr Met His
1   5

<210> 15
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 15
Asp Tyr Tyr Met His
1   5

<210> 16
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 16
Gly Tyr Thr Leu His
1   5

<210> 17
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 17
Asn His Tyr Met His
1   5

<210> 18
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 18
Asn Ser Tyr Met His
1   5

<210> 19
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 19
Thr Tyr Tyr Met His
1   5

<210> 20
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 20
Arg His Phe Ile His
1   5

<210> 21
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 21
Thr Phe Gly Ile Ser
1   5

<210> 22
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic

peptide"

<400> 22
Ser Tyr Gly Ile Asn
1 5

<210> 23
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 23
Asn His Tyr Val His
1 5

<210> 24
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 24
Val Ile Asn Pro Ser Ala Gly Ser Thr Asp Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 25
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 25
Trp Met Asn Pro Asn Ser Asp Ile Ala Gly Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 26
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 26
Trp Ile Ser Pro Gln His Gly Val Arg Asn Tyr Ala Gln Lys Phe Gln
1   5   10   15

Gly

<210> 27
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 27
Trp Val Ser Pro Ser His Gly Leu Thr Gly Tyr Ala Gln Lys Phe Gln
1   5   10   15

Gly

<210> 28
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 28
Trp Met Ser Leu Asn Ser Gly Leu Thr Gly Tyr Ala Gln Lys Phe Gln
1   5   10   15

Gly

<210> 29
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 29
Trp Met Lys Pro Ser Ser Gly Thr Thr Gly Tyr Ala Gln Lys Phe Gln
1   5   10   15

Gly

<210> 30
<211> 17

<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 30
Trp Met Asn Pro Asn Gly Asp Val Ala Gly Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 31
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 31
Gly Ile Asp Pro Asn Ser Gly Gly Thr Asn Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 32
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 32
Trp Met Asn Pro Asp Ser Gly Ser Thr Gly Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 33
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 33
Trp Met Ser Leu Asn Ser Gly Leu Thr Gly Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 34
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 34
Trp Met Asn Pro Asn Gly Asp Val Ala Gly Tyr Ala Asp Ser Phe Gln
1 5 10 15

Gly

<210> 35
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 35
Trp Ile Ser Thr Tyr His Gly Ser Thr Asn Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 36
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 36
Trp Met Asn Pro Asn Thr Val Tyr Thr Gly Ser Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 37
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 37
Arg Ile Ile Pro Ala Val Gly Ser Val Thr Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 38
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 38
Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 39
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 39
Trp Met Ser Pro Ser Ser Gly Ile Thr Gly Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 40
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 40
Trp Met Thr Pro Ser Thr Gly Asn Ala Gly Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 41
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 41
Trp Met Asn Pro Asn Ser Gly Asn Thr Gly Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 42
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 42
Trp Met His Pro Asn Ser Gly His Thr Gly Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 43
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 43
Trp Met Asn Pro Asn Ser Gly His Thr Gly Asn Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 44
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 44
Trp Ile Asp Pro Asn Ser Gly Val Thr Ser Ser Ala Gln Lys Phe Gln

1 5 10 15

Gly

<210> 45
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 45
Trp Ile Ser Pro Asn Ser Gly Val Thr Asp Phe Thr Gln Lys Phe Gln
1 5 10 15

Gly

<210> 46
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 46
Trp Met Asn Pro Asn Ser Gly His Thr Gly Tyr Ala Gln Arg Phe Gln
1 5 10 15

Gly

<210> 47
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 47
Trp Met Ser Pro Asn Gly Gly Asn Thr Gly Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 48
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 48
Trp Met Asp Pro Ser Ser Gly Tyr Thr Gly Ser Ala His Lys Phe Gln
1   5   10   15

Gly

<210> 49
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 49
Trp Met Asn Pro His Ser Ala Asp Thr Gly Tyr Ala Glu Lys Phe Gln
1   5   10   15

Gly

<210> 50
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 50
Trp Leu Thr Pro Ser Thr Gly His Ala Gly Tyr Ala Gln Lys Phe Gln
1   5   10   15

Gly

<210> 51
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 51
Trp Met Asn Pro Asn Ser Gly His Thr Gly Tyr Ala Gln Lys Phe Gln
1   5   10   15

Gly

<210> 52
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 52
Trp Ile Ser Pro Gln His Gly Val Arg Asn Tyr Ala His Lys Phe Gln
1 5 10 15

Gly

<210> 53
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 53
Met Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 54
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 54
Trp Ile Ser Pro Arg Ser Gly Val Thr Ser Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 55
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 55
Trp Met Asp Pro Asn Ser Gly Asn Thr Gly Tyr Ala Gln Lys Phe Gln
1   5   10   15

Gly

<210> 56
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 56
Trp Met Asn Pro Thr Gly Gly Ile Thr Gly Tyr Ala Gln Lys Phe Gln
1   5   10   15

Gly

<210> 57
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 57
Trp Val Ser Pro Ile His Gly Leu Thr Gly Tyr Ala Pro Arg Phe Gln
1   5   10   15

Gly

<210> 58
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 58
Asp Leu Tyr Pro Tyr Val Val Val Val Ala Ala Gly Ser Tyr Gly Met
1   5   10   15

Asp Val

<210> 59
<211> 12
<212> PRT

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 59
Pro Ser Ile Val Gly Ala Tyr Asp Ala Phe Asp Ile
1   5   10

<210> 60
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 60
Glu Ser Val Glu Gly Tyr Phe Asp Leu
1   5

<210> 61
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 61
Asp Asn Trp Asn Val His Asp Ala Phe Asp Ile
1   5   10

<210> 62
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 62
Gly Thr Tyr Asn Asp Ala Phe Asp Ile
1   5

<210> 63
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 63
Glu Gln Trp Leu Val Asn Asp Ala Phe Asp Ile

1 5 10

<210> 64
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 64
Asp Ser Ser Gly Trp Met Arg Asn Asp Ala Phe Asp Ile
1 5 10

<210> 65
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 65
Ser Met Phe Pro Thr Ile Phe Gly Asp Asn Ala Phe Asp Ile
1 5 10

<210> 66
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 66
Ala Leu Phe Pro Tyr Pro Phe Tyr Tyr Tyr Tyr Met Asp Val
1 5 10

<210> 67
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 67
Asp Arg Gly Trp Phe Asp Pro
1 5

<210> 68
<211> 10
<212> PRT
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 68
Asp Ala Arg Gly Tyr Ser Gly Tyr Asp Leu
1 5 10

<210> 69
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 69
Glu Gly Arg His Gly Glu Tyr Leu Tyr
1 5

<210> 70
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 70
Glu Gly Trp Gly Ser Ser Gly Tyr Phe Asp Tyr
1 5 10

<210> 71
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 71
His Leu Phe Pro Thr Val Phe Asp Asp Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> 72
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 72
Gly Gly Tyr Ser Tyr Gly Ser Phe Gln His
1 5 10

<210> 73
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 73
Val Arg Trp Ser Ser Asp Ala Phe Asp Ile
1 5 10

<210> 74
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 74
Glu Glu Trp Leu Gly His Phe Gln His
1 5

<210> 75
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 75
Glu Arg Phe Leu Gly Gly Met Asp Val
1 5

<210> 76
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 76
Gly Asn Trp Val Asp Ala Phe Asp Ile
1 5

<210> 77
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 77
Glu Ser Glu Val Met Met Ala Tyr Phe Gln His
1   5   10

<210> 78
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 78
Glu Ser Trp Ser Gly Glu Phe Asp Tyr
1   5

<210> 79
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 79
Glu Ala Val Ala Gly Pro Met Asp Val
1   5

<210> 80
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 80
Asp Ala Trp Glu Leu Leu Ala Phe Asp Ile
1   5   10

<210> 81
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 81
Asp Arg Trp Asp Gly Asp Tyr Tyr Ser Ala
1   5   10

<210> 82
<211> 10
<212> PRT

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 82
Glu Ser Trp Glu Leu Thr Gly Phe Asp Tyr
1   5   10

<210> 83
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 83
Glu Arg Phe Ala Gly Gly Met Asp Ala
1   5

<210> 84
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 84
Asp Ser Gly Gly Ala Phe Asp Ile
1   5

<210> 85
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 85
Glu Val Phe Glu Gly Gly Met Asp Val
1   5

<210> 86
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 86
Glu Gly Tyr Gly Gly Asn Tyr Gly Asn

1 5

<210> 87
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 87
Glu Asp Phe Tyr Gly Asp Phe Asp Tyr
1 5

<210> 88
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 88
Glu Leu Ser Arg Trp Gly Phe Asp Tyr
1 5

<210> 89
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 89
Asp Ile Phe Pro Thr Met Ile Ala Gly Gly Gly Phe Asp Leu
1 5 10

<210> 90
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 90
Gly Gly Tyr Ser Tyr Gly Ser Phe Asp Tyr
1 5 10

<210> 91
<211> 15
<212> PRT
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 91
Gly Ser Phe Pro Leu Val Phe Thr Ile Phe Gly Val Gly Asp Val
1   5   10   15

<210> 92
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 92
Asp Leu Asp Tyr Val Arg Ala Phe Asp Ile
1   5   10

<210> 93
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 93
Glu Ser Trp Gly Gly Tyr Phe Asp Leu
1   5

<210> 94
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 94
Asp Arg Thr Thr Tyr Ala Phe Asp Ile
1   5

<210> 95
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 95
Val His Gly Ser Gly Ser Asp Gly Met Asp Val
1   5   10

<210> 96
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 96
Arg Ala Ser Gln Gly Ile Asp Ser Tyr Leu Ala
1 5 10

<210> 97
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 97
Arg Ala Ser Gln Ser Ile Ser Ser Trp Leu Ala
1 5 10

<210> 98
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 98
Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu Asn
1 5 10

<210> 99
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 99
Arg Ala Ser Gln Gly Ile Ser Ser Tyr Leu Ala
1 5 10

<210> 100
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 100
Arg Ala Ser Gln Thr Ile Ser Asn Tyr Leu Asn
1   5   10

<210> 101
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 101
Arg Ala Ser Gln Ser Val Asp Arg Asn Tyr Val Thr
1   5   10

<210> 102
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 102
Arg Ala Ser Gln Gly Ile Ser Gln Tyr Leu Ala
1   5   10

<210> 103
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 103
Gln Ala Ser Gln Asp Ile Gly Asn Tyr Leu Asn
1   5   10

<210> 104
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 104
Arg Ala Ser Gln Gly Ile Arg Asn Asp Leu Gly
1   5   10

<210> 105
<211> 11
<212> PRT

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 105
Arg Ala Ser Gln Ile Ile Gly Asn Tyr Leu Ala
1 5 10

<210> 106
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 106
Arg Ala Ser Gln Ile Ile Ser Ser Tyr Leu Asn
1 5 10

<210> 107
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 107
Gln Ala Ser Gln Asp Ile Ser Asn Tyr Leu Asn
1 5 10

<210> 108
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 108
Arg Ala Ser Gln Gly Ile Ser Asn Tyr Leu Ala
1 5 10

<210> 109
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 109
Arg Ala Ser Gln Gly Ile Ser Asn Asn Leu Asn

1 5 10

<210> 110
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 110
Arg Ala Ser Gln Gly Ile Ser Asn Gly Leu Ser
1 5 10

<210> 111
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 111
Arg Ala Ser Gln Ser Ile Thr Gly Trp Leu Ala
1 5 10

<210> 112
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 112
Arg Ala Ser Gln Gly Ile Arg Asn Asp Leu Ala
1 5 10

<210> 113
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 113
Gln Ala Ser Gln Asp Ile Ser Ser Tyr Leu Asn
1 5 10

<210> 114
<211> 11
<212> PRT
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 114
Arg Ala Ser Gln Ser Ile Thr Thr Tyr Leu Asn
1 5 10

<210> 115
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 115
Arg Ala Ser Gln Ser Val Ser Thr Trp Leu Ala
1 5 10

<210> 116
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 116
Arg Ala Ser Gln Ser Ile Ser Asn Trp Leu Ala
1 5 10

<210> 117
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 117
Gln Ala Ser Gln Gly Ile Ser Asn Tyr Leu Ala
1 5 10

<210> 118
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 118
Arg Ala Ser Gln Ser Leu Ser Ser Ser Ser Leu Ala
1 5 10

<210> 119
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 119
Arg Ala Ser Glu His Ile Ala Asn Trp Leu Ala
1 5 10

<210> 120
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 120
Arg Ala Ser Gln Ser Val Gly Ser Trp Val Ala
1 5 10

<210> 121
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 121
Arg Ala Ser Gln Ser Ile Ser Pro Trp Leu Ala
1 5 10

<210> 122
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 122
Arg Ala Ser Gln Gly Ile Ser Arg Tyr Leu Ala
1 5 10

<210> 123
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 123
Arg Ala Ser Gln Thr Val Ser Ser Asn Tyr Leu Ala
1   5   10

<210> 124
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 124
Arg Ser Ser Gln Gly Ile Arg Asn Asp Leu Ser
1   5   10

<210> 125
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 125
Arg Asp Ser His Ser Ile Thr Thr Trp Leu Ala
1   5   10

<210> 126
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 126
Arg Ala Ser Gln Ser Ile Ser Arg Trp Leu Ala
1   5   10

<210> 127
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 127
Arg Ala Ser Gln Val Ile Arg Asn Asp Leu Ala
1   5   10

<210> 128

<400> 128

000

<210> 129
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 129
Ala Ala Ser Ser Leu Gln Ser
1 5

<210> 130
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 130
Gly Ala Ser Asn Leu Gln Ser
1 5

<210> 131
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 131
Gly Ala Ser Thr Arg Ala Thr
1 5

<210> 132
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 132
Gly Ala Ser Asn Leu His Ser
1 5

<210> 133
<211> 7
<212> PRT
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 133
Ala Ala Ser Ser Leu Glu Ser
1   5

<210> 134
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 134
Ser Ala Ser Asn Leu Gln Ser
1   5

<210> 135
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 135
Ala Ala Ser Thr Leu Glu Ser
1   5

<210> 136
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 136
His Ala Ser Ile Leu Glu Thr
1   5

<210> 137
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 137
Ala Ala Ser Thr Leu Gln Ser
1   5

<210> 138
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 138
Ala Ala Thr Thr Leu Gln Ser
1 5

<210> 139
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 139
Asp Ala Thr His Leu Glu Thr
1 5

<210> 140
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 140
Ala Ala Ser Ser Leu Gln Thr
1 5

<210> 141
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 141
Ala Ala Ser Ser Leu Gln Gly
1 5

<210> 142
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 142
Ala Ala Ser Asn Leu Glu Ser
1   5

<210> 143
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 143
Asp Val Ser His Leu Glu Ser
1   5

<210> 144
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 144
Asp Ala Ser Ser Leu Gln Ser
1   5

<210> 145
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 145
Gly Val Ser Ser Leu Glu Ser
1   5

<210> 146
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 146
Pro Ala Ser Thr Leu Gln Ser
1   5

<210> 147
<211> 7
<212> PRT

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 147
Asp Ala Ser Asn Leu Glu Thr
1   5

<210> 148
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 148
Gly Ala Ser Thr Arg Ala Ser
1   5

<210> 149
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 149
Asp Ser Ser Ser Leu Gln Thr
1   5

<210> 150
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 150
Ala Thr Ser Thr Leu Gln Ser
1   5

<210> 151
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 151
Leu Ala Ser Asn Ser His Ser

1 5

<210> 152
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 152
Gln Gln Ser Tyr Ser Thr Pro Ile Thr
1 5

<210> 153
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 153
Gln Gln Ser Tyr Thr Thr Pro Ile Thr
1 5

<210> 154
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 154
Gln Gln Ile Phe Ser Thr Pro Leu Thr
1 5

<210> 155
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 155
Gln Gln Ser Tyr Ser Thr Pro Leu Thr
1 5

<210> 156
<211> 9
<212> PRT
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 156
Gln Gln Ser Tyr Thr Thr Pro Tyr Thr
1   5

<210> 157
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 157
Gln Gln Thr Phe Thr Thr Pro Leu Thr
1   5

<210> 158
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 158
Gln Gln Ala Asn Ser Phe Pro Phe Thr
1   5

<210> 159
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 159
Gln Gln Ser Tyr Thr Thr Pro Tyr Ser
1   5

<210> 160
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 160
Gln Gln Thr Phe Ile Thr Pro Leu Thr
1   5

<210> 161
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 161
Gln Gln Ser Tyr Ser Thr Pro Thr
1 5

<210> 162
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 162
Gln Gln Gly Phe Ser Thr Pro Phe Thr
1 5

<210> 163
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 163
Gln Gln Ser Phe Thr Asn Pro Val Thr
1 5

<210> 164
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 164
Gln Gln Ser Tyr Ser Ala Pro Tyr Thr
1 5

<210> 165
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 165
Gln Gln Ser Tyr Ser Thr Pro Tyr Thr
1   5

<210> 166
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 166
Gln Gln Ser His Ser Thr Pro Leu Thr
1   5

<210> 167
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 167
Gln Gln Ser Tyr Ser Thr Pro Phe Thr
1   5

<210> 168
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 168
Gln Gln Tyr Gly Ser Ser Pro Phe Thr
1   5

<210> 169
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 169
Gln Gln Thr Tyr Ser Thr Pro Ile Thr
1   5

<210> 170
<211> 9
<212> PRT

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 170
Gln Gln Tyr Tyr Thr Thr Pro Leu Thr
1   5

<210> 171
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 171
Gln Gln Ser Phe Ser Thr Pro Leu Thr
1   5

<210> 172
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 172
Gln Gln Ser Tyr Ser Thr Pro Pro Thr
1   5

<210> 173
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 173
Leu Gln His Asn Ser Tyr Pro Leu Thr
1   5

<210> 174
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 174
Gln Gln Ser Tyr Ser Thr Pro Val Thr

1 5

<210> 175
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 175
Gln His Phe Tyr Asn Thr Gln Tyr Thr
1 5

<210> 176
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 176
Gln Gln Ser Leu Gln Tyr Pro Ser His Phe
1 5 10

<210> 177
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 177
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser
20 25 30

<210> 178
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 178
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr
20 25 30

<210> 179
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 179
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Asn
20 25 30

<210> 180
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 180
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Asn Thr Phe Thr
20 25 30

<210> 181
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 181
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly His Ser Phe Thr
20 25 30

<210> 182
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 182
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Pro Phe Thr
            20   25   30

<210> 183
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 183
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Arg Phe Thr
            20   25   30

<210> 184
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 184
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser
            20   25   30

<210> 185
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 185
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Asp Thr Phe Thr
            20   25   30

<210> 186
<211> 30
<212> PRT

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 186
Gln Val Gln Leu Ala Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr
            20   25   30

<210> 187
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 187
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ser
            20   25   30

<210> 188
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 188
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Pro Phe Ser
            20   25   30

<210> 189
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 189
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr
            20   25   30

<210> 190
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 190
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ile
            20   25   30

<210> 191
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 191
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr
            20   25   30

<210> 192
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 192
Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met Gly
1   5   10

<210> 193
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 193
Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Leu Gly

1 5 10

<210> 194
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 194
Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile Gly
1 5 10

<210> 195
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 195
Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Val Gly
1 5 10

<210> 196
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 196
Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr Met Glu
1 5 10 15

Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
20 25 30

<210> 197
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 197
Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr Met Glu
1 5 10 15

Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala Ile
20 25 30

<210> 198
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 198
Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr Met Glu
1 5 10 15

Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Thr Arg
20 25 30

<210> 199
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 199
Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr Met Glu
1 5 10 15

Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
20 25 30

<210> 200
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 200
Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Asn Met Glu
1 5 10 15

Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
20 25 30

<210> 201
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 201
Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr Met Glu
1   5   10   15

Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala Glu
            20   25   30

<210> 202
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 202
Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
1   5   10

<210> 203
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 203
Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
1   5   10

<210> 204
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 204
Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
1   5   10

<210> 205
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 205
Trp Gly Pro Gly Thr Met Val Thr Val Ser Ser
1   5   10

<210> 206
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 206
Trp Gly Arg Gly Thr Leu Val Thr Val Ser Ser
1 5 10

<210> 207
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 207
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys
20

<210> 208
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 208
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys
20

<210> 209
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 209
Asp Ile Gln Ile Thr His Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Tyr Arg Leu Thr Ile Thr Cys

20

<210> 210
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 210
Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
1 5 10 15

<210> 211
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 211
Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr
1 5 10 15

<210> 212
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 212
Trp Tyr His Gln Lys Pro Trp Asn Ala Pro Lys Leu Met Ile Tyr
1 5 10 15

<210> 213
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 213
Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
1 5 10 15

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
20 25 30

<210> 214
<211> 32

<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 214
Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr
1 5 10 15

Leu Thr Ile Ser Ser Leu Gln Ser Glu Asp Phe Ala Val Tyr Tyr Cys
20 25 30

<210> 215
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 215
Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Tyr Phe Thr
1 5 10 15

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
20 25 30

<210> 216
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 216
Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
1 5 10 15

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Pro Tyr Tyr Cys
20 25 30

<210> 217
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 217
Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
1 5 10

<210> 218
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 218
Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
1 5 10

<210> 219
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 219
Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
1 5 10

<210> 220
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 220
Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
1 5 10

<210> 221
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 221
Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
1 5 10

<210> 222
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic

peptide"

<400> 222
Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
1 5 10

<210> 223
<211> 127
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 223
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
20 25 30

Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Val Ile Asn Pro Ser Ala Gly Ser Thr Asp Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Leu Tyr Pro Tyr Val Val Val Val Ala Ala Gly Ser Tyr
100 105 110

Gly Met Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 224
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 224
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35   40   45

Gly Trp Met Asn Pro Asn Ser Asp Ile Ala Gly Tyr Ala Gln Lys Phe
    50   55   60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65   70   75   80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Ile Pro Ser Ile Val Gly Ala Tyr Asp Ala Phe Asp Ile Trp Gly
            100   105   110

Gln Gly Thr Leu Val Thr Val Ser Ser
        115   120

<210> 225
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 225
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg His
            20   25   30

Leu Leu His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35   40   45

Gly Trp Ile Ser Pro Gln His Gly Val Arg Asn Tyr Ala Gln Lys Phe
    50   55   60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65   70   75   80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg Glu Ser Val Glu Gly Tyr Phe Asp Leu Trp Gly Gln Gly Thr
            100   105   110

Leu Val Thr Val Ser Ser
        115

<210> 226
<211> 120

<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 226
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser His
20 25 30

His Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Val Ser Pro Ser His Gly Leu Thr Gly Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Asn Trp Asn Val His Asp Ala Phe Asp Ile Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 227
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 227
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Asn Arg Phe
20 25 30

Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met Gly
35 40 45

Trp Met Ser Leu Asn Ser Gly Leu Thr Gly Tyr Ala Gln Lys Phe Gln
50 55 60

Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr Met

65 70 75 80

Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Thr
85 90 95

Arg Gly Thr Tyr Asn Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 228
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 228
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Met Lys Pro Ser Ser Gly Thr Thr Gly Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gln Trp Leu Val Asn Asp Ala Phe Asp Ile Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 229
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 229

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15


Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30


Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45


Gly Trp Met Lys Pro Ser Ser Gly Thr Thr Gly Tyr Ala Gln Lys Phe
    50                  55                  60


Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80


Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Glu Gln Trp Leu Val Asn Asp Ala Phe Asp Ile Trp Gly Gln
            100                 105                 110


Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> 230
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 230
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15


Ser Val Lys Val Ser Cys Lys Ala Ser Gly Asn Thr Phe Thr Ser Tyr
            20                  25                  30


Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45


Gly Gly Ile Asp Pro Asn Ser Gly Gly Thr Asn Tyr Ala Gln Lys Phe
    50                  55                  60


Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80


Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Ser Met Phe Pro Thr Ile Phe Gly Asp Asn Ala Phe Asp Ile
            100                 105                 110
```

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115   120

<210> 231
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 231
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly His Ser Phe Thr His Tyr
            20   25   30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35   40   45

Gly Trp Met Asn Pro Asp Ser Gly Ser Thr Gly Tyr Ala Gln Lys Phe
    50   55   60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65   70   75   80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg Ala Leu Phe Pro Tyr Pro Phe Tyr Tyr Tyr Tyr Met Asp Val
            100   105   110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115   120

<210> 232
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 232
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr
            20   25   30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile

```
        35                  40                  45

Gly Trp Met Ser Leu Asn Ser Gly Leu Thr Gly Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Arg Gly Trp Phe Asp Pro Trp Gly Gln Gly Thr Leu Val
            100                 105                 110

Thr Val Ser Ser
        115


<210> 233
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 233
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
            20                  25                  30

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Leu
        35                  40                  45

Gly Trp Met Asn Pro Asn Gly Asp Val Ala Gly Tyr Ala Asp Ser Phe
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Ile Asp Ser Ser Gly Trp Met Arg Asn Asp Ala Phe Asp Ile Trp
            100                 105                 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> 234
<211> 119
<212> PRT
```

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 234
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Asn Tyr
20 25 30

Met Tyr His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Ser Thr Tyr His Gly Ser Thr Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Ala Arg Gly Tyr Ser Gly Tyr Asp Leu Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 235
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 235
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Pro Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Met Asn Pro Asn Ser Asp Ile Ala Gly Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Arg His Gly Glu Tyr Leu Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

<210> 236
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 236
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Arg Phe Thr Thr Tyr
20 25 30

Tyr Val His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Met Asn Pro Asn Thr Val Tyr Thr Gly Ser Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Trp Gly Ser Ser Gly Tyr Phe Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 237
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 237
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser

1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
20 25 30

Ala Leu Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Arg Ile Ile Pro Ala Val Gly Ser Val Thr Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg His Leu Phe Pro Thr Val Phe Asp Asp Tyr Tyr Gly Met Asp
100 105 110

Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 238
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 238
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
20 25 30

Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Gly Tyr Ser Tyr Gly Ser Phe Gln His Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
        115

<210> 239
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 239
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Asp Thr Phe Thr Arg His
            20   25   30

Tyr Val His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35   40   45

Gly Trp Met Ser Pro Ser Ser Gly Ile Thr Gly Tyr Ala Gln Lys Phe
    50   55   60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65   70   75   80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg Val Arg Trp Ser Ser Asp Ala Phe Asp Ile Trp Gly Gln Gly
            100   105   110

Thr Leu Val Thr Val Ser Ser
        115

<210> 240
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 240
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20   25   30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Val
        35   40   45

```
Gly Trp Met Thr Pro Ser Thr Gly Asn Ala Gly Tyr Ala Gln Lys Phe
    50                  55                  60


Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80


Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Glu Glu Trp Leu Gly His Phe Gln His Trp Gly Gln Gly Thr
            100                 105                 110


Leu Val Thr Val Ser Ser
        115


<210> 241
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 241
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15


Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser His
            20                  25                  30


Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45


Gly Trp Met Asn Pro Asn Ser Gly Asn Thr Gly Tyr Ala Gln Lys Phe
    50                  55                  60


Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80


Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Glu Arg Phe Leu Gly Gly Met Asp Val Trp Gly Gln Gly Thr
            100                 105                 110


Thr Val Thr Val Ser Ser
        115


<210> 242
<211> 118
<212> PRT
<213> Artificial Sequence
```

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 242
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
            20   25   30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35   40   45

Gly Trp Met His Pro Asn Ser Gly His Thr Gly Tyr Ala Gln Lys Phe
    50   55   60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Asn
65   70   75   80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg Glu Glu Trp Leu Gly His Phe Gln His Trp Gly Gln Gly Thr
            100   105   110

Leu Val Thr Val Ser Ser
        115

<210> 243
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 243
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser His
            20   25   30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35   40   45

Gly Trp Met Asn Pro Asn Ser Gly His Thr Gly Asn Ala Gln Lys Phe
    50   55   60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65   70   75   80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Asn Trp Val Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr
100 105 110

Met Val Thr Val Ser Ser
115

<210> 244
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 244
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr
20 25 30

Thr Leu His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asp Pro Asn Ser Gly Val Thr Ser Ser Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Ser Glu Val Met Met Ala Tyr Phe Gln His Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 245
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 245
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

```
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr
            20                  25                  30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Trp Ile Ser Pro Asn Ser Gly Val Thr Asp Phe Thr Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Ser Trp Ser Gly Glu Phe Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110

Leu Val Thr Val Ser Ser
        115
```

<210> 246
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 246

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Asp Thr Phe Thr Asn His
            20                  25                  30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Trp Met Asn Pro Asn Ser Gly His Thr Gly Tyr Ala Gln Arg Phe
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Ala Val Ala Gly Pro Met Asp Val Trp Gly Gln Gly Thr
            100                 105                 110
```

Thr Val Thr Val Ser Ser
        115

<210> 247
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 247
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr
            20   25   30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35   40   45

Gly Trp Met Asn Pro Asn Ser Asp Ile Ala Gly Tyr Ala Gln Lys Phe
    50   55   60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65   70   75   80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg Asp Ala Trp Glu Leu Leu Ala Phe Asp Ile Trp Gly Gln Gly
            100   105   110

Thr Leu Val Thr Val Ser Ser
        115

<210> 248
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 248
Gln Val Gln Leu Ala Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn His
            20   25   30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35   40   45

```
Gly Trp Met Asn Pro Asn Ser Gly Asn Thr Gly Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Arg Trp Asp Gly Asp Tyr Tyr Ser Ala Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser
        115


<210> 249
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 249
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
            20                  25                  30

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Trp Met Ser Pro Asn Gly Gly Asn Thr Gly Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Ser Trp Glu Leu Thr Gly Phe Asp Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser
        115


<210> 250
<211> 118
<212> PRT
<213> Artificial Sequence
```

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 250
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20   25   30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35   40   45

Gly Trp Met Asn Pro Asn Ser Gly Asn Thr Gly Tyr Ala Gln Lys Phe
    50   55   60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65   70   75   80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg Glu Arg Phe Ala Gly Gly Met Asp Ala Trp Gly Gln Gly Thr
            100   105   110

Thr Val Thr Val Ser Ser
        115

<210> 251
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 251
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ser Asn Ser
            20   25   30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35   40   45

Gly Trp Met Asp Pro Ser Ser Gly Tyr Thr Gly Ser Ala His Lys Phe
    50   55   60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65   70   75   80

```
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Glu Asp Ser Gly Gly Ala Phe Asp Ile Trp Gly Gln Gly Thr Met
            100                 105                 110


Val Thr Val Ser Ser
        115


<210> 252
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 252
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15


Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Pro Phe Ser Thr Tyr
            20                  25                  30


Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45


Gly Trp Met Asn Pro His Ser Ala Asp Thr Gly Tyr Ala Glu Lys Phe
    50                  55                  60


Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80


Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Glu Val Phe Glu Gly Gly Met Asp Val Trp Gly Gln Gly Thr
            100                 105                 110


Thr Val Thr Val Ser Ser
        115


<210> 253
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 253
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15
```

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20   25   30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35   40   45

Gly Trp Leu Thr Pro Ser Thr Gly His Ala Gly Tyr Ala Gln Lys Phe
    50   55   60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65   70   75   80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg Glu Gly Tyr Gly Gly Asn Tyr Gly Asn Trp Gly Gln Gly Thr
            100   105   110

Leu Val Thr Val Ser Ser
        115

<210> 254
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 254
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20   25   30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35   40   45

Gly Trp Met Asn Pro Asn Ser Gly His Thr Gly Tyr Ala Gln Lys Phe
    50   55   60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65   70   75   80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg Glu Asp Phe Tyr Gly Asp Phe Asp Tyr Trp Gly Gln Gly Thr
            100   105   110

Leu Val Thr Val Ser Ser

115

<210> 255
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 255
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg His
20 25 30

Phe Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asp Pro Asn Ser Gly Val Thr Ser Ser Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Leu Ser Arg Trp Gly Phe Asp Tyr Trp Gly Pro Gly Thr
100 105 110

Met Val Thr Val Ser Ser
115

<210> 256
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 256
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg His
20 25 30

Leu Leu His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Ser Pro Gln His Gly Val Arg Asn Tyr Ala His Lys Phe
    50   55   60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65   70   75   80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg Glu Ser Val Glu Gly Tyr Phe Asp Leu Trp Gly Arg Gly Thr
            100   105   110

Leu Val Thr Val Ser Ser
        115

<210> 257
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 257
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Pro Phe Ser Ser Tyr
            20   25   30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35   40   45

Gly Met Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
    50   55   60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65   70   75   80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg Asp Ile Phe Pro Thr Met Ile Ala Gly Gly Gly Phe Asp Leu
            100   105   110

Trp Gly Arg Gly Thr Leu Val Thr Val Ser Ser
        115   120

<210> 258
<211> 119
<212> PRT
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 258
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Thr Phe
            20   25   30

Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35   40   45

Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
    50   55   60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65   70   75   80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg Gly Gly Tyr Ser Tyr Gly Ser Phe Asp Tyr Trp Gly Gln Gly
            100   105   110

Thr Leu Val Thr Val Ser Ser
        115

<210> 259
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 259
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20   25   30

Gly Ile Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35   40   45

Gly Trp Met Asn Pro Asn Ser Gly Asn Thr Gly Tyr Ala Gln Lys Phe
    50   55   60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65   70   75   80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys

85 90 95

Ala Arg Gly Ser Phe Pro Leu Val Phe Thr Ile Phe Gly Val Gly Asp
100 105 110

Val Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
115 120

<210> 260
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 260
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Ser Pro Arg Ser Gly Val Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Leu Asp Tyr Val Arg Ala Phe Asp Ile Trp Gly Gln Gly
100 105 110

Thr Thr Val Thr Val Ser Ser
115

<210> 261
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 261
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

```
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Ser Tyr
            20                  25                  30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Trp Met Asp Pro Asn Ser Gly Asn Thr Gly Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Ser Trp Gly Gly Tyr Phe Asp Leu Trp Gly Arg Gly Thr
            100                 105                 110

Leu Val Thr Val Ser Ser
        115
```

<210> 262
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 262

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ile Asn His
            20                  25                  30

Tyr Val His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Trp Met Asn Pro Thr Gly Gly Ile Thr Gly Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Arg Thr Thr Tyr Ala Phe Asp Ile Trp Gly Gln Gly Thr
            100                 105                 110

Met Val Thr Val Ser Ser
        115
```

<210> 263
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 263
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser His
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Met Asn Pro Asn Ser Gly His Thr Gly Asn Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Asn Trp Val Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr
100 105 110

Met Val Thr Val Ser Ser
115

<210> 264
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 264
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg His
20 25 30

Leu Leu His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Val Ser Pro Ile His Gly Leu Thr Gly Tyr Ala Pro Arg Phe

50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Val His Gly Ser Gly Ser Asp Gly Met Asp Val Trp Gly Gln
100 105 110

Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 265
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 265
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Asp Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Ile
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 266
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 266

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Trp
            20                  25                  30


Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45


Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Thr Thr Pro Ile
                85                  90                  95


Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> 267
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 267
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
            20                  25                  30


Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45


Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ile Phe Ser Thr Pro Leu
                85                  90                  95


Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> 268
<211> 107
```

<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 268
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Gly Ala Ser Asn Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 269
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 269
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Thr Ile Ser Asn Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Thr Thr Pro Ile

```
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> 270
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 270
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1               5                   10                  15


Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Asp Arg Asn
            20                  25                  30


Tyr Val Thr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        35                  40                  45


Ile Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser
    50                  55                  60


Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln
65                  70                  75                  80


Ser Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Ser Tyr Thr Thr Pro
                85                  90                  95


Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> 271
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 271
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Gln Tyr
            20                  25                  30


Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45
```

Tyr Gly Ala Ser Asn Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Thr Phe Thr Thr Pro Leu
                85   90   95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100   105

<210> 272
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 272
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Asp Ile Gly Asn Tyr
            20   25   30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45

Tyr Ala Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Leu
                85   90   95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100   105

<210> 273
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 273
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
            20   25   30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45

Tyr Ser Ala Ser Asn Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Phe
                85   90   95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100   105

<210> 274
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 274
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Trp
            20   25   30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45

Tyr Ala Ala Ser Thr Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Thr Thr Pro Tyr
                85   90   95

Ser Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100   105

<210> 275
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 275
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Gln Tyr
            20   25   30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45

Tyr Gly Ala Ser Asn Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Thr Phe Ile Thr Pro Leu
                85   90   95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100   105

<210> 276
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 276
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ile Ile Gly Asn Tyr
            20   25   30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45

Tyr His Ala Ser Ile Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Thr
                85   90   95

Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 277
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 277
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ile Ile Ser Ser Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly Phe Ser Thr Pro Phe
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 278
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 278
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Asp Ile Ser Asn Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Phe Thr Asn Pro Val
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 279
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 279
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Ala Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 280
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 280
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Asn
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45

Tyr Ala Ala Thr Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Tyr
                85   90   95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100   105

<210> 281
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 281
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
            20   25   30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Leu
                85   90   95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100   105

<210> 282
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic

polypeptide"

<400> 282
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Gly
20 25 30

Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser His Ser Thr Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 283
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 283
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Thr Gly Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 284
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 284
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Thr His Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Ile
85 90 95

Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105

<210> 285
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 285
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 286
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 286
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Asp Ile Ser Ser Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 287
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 287
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Thr Thr Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile

```
        35                  40                  45

Tyr Ala Ala Ser Ser Leu Gln Gly Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Tyr
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 288
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 288

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
            20                  25                  30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Leu
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100                 105
```

<210> 289
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 289

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Val Ser Thr Trp
            20   25   30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45

Tyr Ala Ala Ser Asn Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Tyr
                85   90   95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100   105

<210> 290
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 290
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Asn Trp
            20   25   30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45

Tyr Asp Val Ser His Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Phe
                85   90   95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
            100   105

<210> 291
<211> 107

<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 291
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Gly Ile Ser Asn Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 292
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 292
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Leu Ser Ser Ser
20 25 30

Ser Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln
65 70 75 80

Ser Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Pro

```
                85                  90                  95

Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
            100                 105


<210> 293
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 293
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Glu His Ile Ala Asn Trp
            20                  25                  30


Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45


Tyr Gly Val Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Tyr
                85                  90                  95


Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105


<210> 294
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 294
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Val Gly Ser Trp
            20                  25                  30


Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45
```

Tyr Pro Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Leu
                85   90   95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100   105

<210> 295
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 295
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Pro Trp
            20   25   30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45

Tyr Asp Ala Ser Asn Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Thr Tyr Ser Thr Pro Ile
                85   90   95

Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
            100   105

<210> 296
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 296
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Arg Tyr
            20   25   30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45

Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Leu
                85   90   95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100   105

<210> 297
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 297
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1   5   10   15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Thr Val Ser Ser Asn
            20   25   30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        35   40   45

Ile Tyr Gly Ala Ser Thr Arg Ala Ser Gly Ile Pro Ala Arg Phe Ser
    50   55   60

Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln
65   70   75   80

Ser Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Tyr Thr Thr Pro
                85   90   95

Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100   105

<210> 298
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 298
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
            20   25   30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Phe Ser Thr Pro Leu
                85   90   95

Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
            100   105

<210> 299
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 299
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Trp
            20   25   30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45

Tyr Asp Ala Ser Asn Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Pro
                85   90   95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 300
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 300
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Asn
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Thr Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 301
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 301
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ser Ser Gln Gly Ile Arg Asn Asp
20 25 30

Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Leu Ala Ser Asn Ser His Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Ser Tyr Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 302
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 302
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Arg Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 303
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 303
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45

Tyr Asp Ser Ser Ser Leu Gln Thr Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Val
                85   90   95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100   105

<210> 304
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 304
Asp Ile Gln Ile Thr His Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Tyr Arg Leu Thr Ile Thr Cys Arg Asp Ser His Ser Ile Thr Thr Trp
            20   25   30

Leu Ala Trp Tyr His Gln Lys Pro Trp Asn Ala Pro Lys Leu Met Ile
        35   40   45

Tyr Ala Ala Ser Asn Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Tyr Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln His Phe Tyr Asn Thr Gln Tyr
                85   90   95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100   105

<210> 305
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic

polypeptide"

<400> 305
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Val Ile Arg Asn Asp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Leu Gln Tyr Pro Ser
85 90 95

His Phe Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 306
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 306
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Arg Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Pro Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Leu
85 90 95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
100 105

<210> 307
<211> 290
<212> PRT
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
PD-L1 sequence"

<400> 307
Met Arg Ile Phe Ala Val Phe Ile Phe Met Thr Tyr Trp His Leu Leu
1 5 10 15

Asn Ala Phe Thr Val Thr Val Pro Lys Asp Leu Tyr Val Val Glu Tyr
20 25 30

Gly Ser Asn Met Thr Ile Glu Cys Lys Phe Pro Val Glu Lys Gln Leu
35 40 45

Asp Leu Ala Ala Leu Ile Val Tyr Trp Glu Met Glu Asp Lys Asn Ile
50 55 60

Ile Gln Phe Val His Gly Glu Glu Asp Leu Lys Val Gln His Ser Ser
65 70 75 80

Tyr Arg Gln Arg Ala Arg Leu Leu Lys Asp Gln Leu Ser Leu Gly Asn
85 90 95

Ala Ala Leu Gln Ile Thr Asp Val Lys Leu Gln Asp Ala Gly Val Tyr
100 105 110

Arg Cys Met Ile Ser Tyr Gly Gly Ala Asp Tyr Lys Arg Ile Thr Val
115 120 125

Lys Val Asn Ala Pro Tyr Asn Lys Ile Asn Gln Arg Ile Leu Val Val
130 135 140

Asp Pro Val Thr Ser Glu His Glu Leu Thr Cys Gln Ala Glu Gly Tyr
145 150 155 160

Pro Lys Ala Glu Val Ile Trp Thr Ser Ser Asp His Gln Val Leu Ser
165 170 175

Gly Lys Thr Thr Thr Thr Asn Ser Lys Arg Glu Glu Lys Leu Phe Asn
180 185 190

Val Thr Ser Thr Leu Arg Ile Asn Thr Thr Thr Asn Glu Ile Phe Tyr
195 200 205

Cys Thr Phe Arg Arg Leu Asp Pro Glu Glu Asn His Thr Ala Glu Leu
210 215 220

Val Ile Pro Glu Leu Pro Leu Ala His Pro Pro Asn Glu Arg Thr His

225 230 235 240

Leu Val Ile Leu Gly Ala Ile Leu Leu Cys Leu Gly Val Ala Leu Thr
245 250 255

Phe Ile Phe Arg Leu Arg Lys Gly Arg Met Met Asp Val Lys Lys Cys
260 265 270

Gly Ile Gln Asp Thr Asn Ser Lys Lys Gln Ser Asp Thr His Leu Glu
275 280 285

Glu Thr
290

<210> 308
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 308
Ser Asp Tyr Met His
1 5

<210> 309
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 309
Gly Tyr Tyr Met His
1 5

<210> 310
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 310
Ser Tyr Tyr Met His
1 5

<210> 311
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 311
Gly Tyr Tyr Ile His
1   5

<210> 312
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 312
Thr His Tyr Met His
1   5

<210> 313
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 313
Ser His Asp Ile Asn
1   5

<210> 314
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 314
Asp His Tyr Leu His
1   5

<210> 315
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 315
Asn Tyr Tyr Met His
1   5

<210> 316
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 316
Ala Tyr Tyr Val His
1 5

<210> 317
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 317
Arg His Tyr Val His
1 5

<210> 318
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 318
Asn Tyr Ile His
1

<210> 319
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 319
Asn His Tyr Val His
1 5

<210> 320
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic

peptide"

<400> 320
Ser His Tyr Met His
1 5

<210> 321
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 321
Arg His Leu Leu His
1 5

<210> 322
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 322
Trp Met Ser Pro Tyr Asn Gly Ile Thr Gly Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 323
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 323
Trp Met Ser Pro Ser Ser Gly Ile Thr Gly Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 324
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 324
Trp Met Thr Thr Asn Ser Gly Ile Thr Gly Tyr Ala Gln Lys Phe Gln
1   5   10   15

Gly

<210> 325
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 325
Gly Ile Ile Pro Ile Phe Gly Thr Ala Ser Tyr Ala Gln Lys Phe Gln
1   5   10   15

Gly

<210> 326
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 326
Trp Met Asn Pro Asn Ser Gly His Ala Gly Ser Ala Gln Lys Phe Gln
1   5   10   15

Gly

<210> 327
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 327
Trp Met Asn Pro Asn Ser Gly Asn Thr Gly Tyr Ala Gln Lys Phe Gln
1   5   10   15

Gly

<210> 328
<211> 17

<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 328
Trp Met Asn Pro Asn Ser Gly Asn Thr Gly Tyr Ser Gln Lys Phe Gln
1 5 10 15

Gly

<210> 329
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 329
Trp Met Asn Pro Asn Ile Gly Asn Thr Gly Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 330
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 330
Trp Met Asn Pro Asn Gly Gly Thr Thr Gly Tyr Ala Gln Asn Phe Gln
1 5 10 15

Gly

<210> 331
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 331
Trp Met Asn Pro Asn Arg Gly Ile Thr Asp Ser Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 332
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 332
Trp Met Asn Pro Asn Ser Gly Ser Ala Gly Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 333
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 333
Trp Ile His Pro Arg Ser Gly Ala Thr Gly Tyr Ala Pro Lys Phe Gln
1 5 10 15

Gly

<210> 334
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 334
Trp Ile Ser Pro Arg Ser Gly Val Thr Ser Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 335
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 335
Trp Met Asp Pro Asn Ser Gly Asn Thr Gly Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 336
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 336
Trp Met Asn Pro Thr Gly Gly Ile Thr Gly Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 337
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 337
Trp Met Asn Pro Asn Ser Gly His Thr Gly Asn Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 338
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 338
Trp Val Ser Pro Ile His Gly Leu Thr Gly Tyr Ala Pro Arg Phe Gln
1 5 10 15

Gly

<210> 339
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 339
Asp Arg Phe Ser Gly Ser Tyr Asp Tyr
1 5

<210> 340
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 340
Asp Arg Gly Trp Phe Asp Pro
1 5

<210> 341
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 341
Glu Gly Tyr Ser Ser Gly Leu Asp Tyr
1 5

<210> 342
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 342
Asp Gly Arg Phe Trp Ser Gly Tyr Pro Asp Tyr
1 5 10

<210> 343
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 343
Glu Ser Ile Ala Val Ala Gly Tyr Asp Tyr
1   5   10

<210> 344
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 344
Asp Arg Trp Tyr Met Gly Ser Ala Asp Tyr
1   5   10

<210> 345
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 345
Asp Asp Trp Gly Gly Asp Trp Phe Asp Pro
1   5   10

<210> 346
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 346
Glu Arg Leu Ser Val Ala Gly Phe Asp Tyr
1   5   10

<210> 347
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 347
Glu Pro Leu Gln Leu Gly Gly Phe Asp Tyr
1   5   10

<210> 348
<211> 10
<212> PRT

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 348
Glu Gly Phe Gly Pro Asn Ala Phe Asp Ile
1 5 10

<210> 349
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 349
Asp Ser Trp Tyr Gly Asp Trp Phe Asp Pro
1 5 10

<210> 350
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 350
Glu Val Ile Glu Val Gly Met Asp Val
1 5

<210> 351
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 351
Glu Ala Trp Phe Gly Glu Leu Ser Thr
1 5

<210> 352
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 352
Glu Ala Tyr Val Ala Ala Phe Asp Ile

1 5

<210> 353
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 353
Glu Arg Gly Tyr Asn Ala Phe Asp Tyr
1 5

<210> 354
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 354
Asp Ser Val Phe Gly Leu Asp Tyr
1 5

<210> 355
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 355
Asp Leu Asp Tyr Val Arg Ala Phe Asp Ile
1 5 10

<210> 356
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 356
Glu Ser Trp Gly Gly Tyr Phe Asp Leu
1 5

<210> 357
<211> 9
<212> PRT
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 357
Asp Arg Thr Thr Tyr Ala Phe Asp Ile
1   5

<210> 358
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 358
Gly Asn Trp Val Asp Ala Phe Asp Ile
1   5

<210> 359
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 359
Val His Gly Ser Gly Ser Asp Gly Met Asp Val
1   5   10

<210> 360
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 360
Arg Ala Ser Gln Ser Ile Ser Ser Trp Leu Ala
1   5   10

<210> 361
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 361
Arg Ala Ser Gln Ser Val Gly Thr Trp Leu Ala
1   5   10

<210> 362
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 362
Arg Ala Ser Gln Gly Ile Ser Asn Tyr Leu Ala
1 5 10

<210> 363
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 363
Arg Ala Ser Gln Ser Ile Ser Thr Trp Leu Ala
1 5 10

<210> 364
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 364
Gln Ala Ser Gln Asp Ile Ser Asn His Leu Asn
1 5 10

<210> 365
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 365
Arg Ala Ser Gln Gly Ile Ser Ser Trp Leu Ala
1 5 10

<210> 366
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 366
Arg Ala Ser Glu Ser Ile Ser Ser Trp Leu Ala
1   5   10

<210> 367
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 367
Arg Ala Ser Gln Ser Val Gly Ser Trp Leu Ala
1   5   10

<210> 368
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 368
Arg Ala Ser Gln Asn Ile Ser Asn Phe Leu Asn
1   5   10

<210> 369
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 369
Arg Ala Ser Gln Ser Leu Ser Ser Ser Tyr Leu Ala
1   5   10

<210> 370
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 370
Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu Asn
1   5   10

<210> 371
<211> 11
<212> PRT

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 371
Arg Ala Ser Gln Ser Ile Ser Arg Trp Leu Ala
1 5 10

<210> 372
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 372
Arg Asp Ser His Ser Ile Thr Thr Trp Leu Ala
1 5 10

<210> 373
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 373
Arg Ala Ser Gln Val Ile Arg Asn Asp Leu Ala
1 5 10

<210> 374
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 374
Arg Ala Ser Gln Ser Ile Ser Arg Tyr Leu Asn
1 5 10

<210> 375
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 375
Ala Ala Ser Ser Leu Gln Ser

1 5

<210> 376
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 376
Ala Ala Ser Thr Leu Glu Asn
1 5

<210> 377
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 377
Arg Ala Ser Asn Leu Glu Ser
1 5

<210> 378
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 378
Ala Ala Ser Thr Leu Gln Arg
1 5

<210> 379
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 379
Ala Ala Ser Thr Leu Gln Ser
1 5

<210> 380
<211> 7
<212> PRT
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 380
Gly Ala Ser Asn Leu Gln Arg
1   5

<210> 381
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 381
Ala Ala Ser Asn Leu Gln Ser
1   5

<210> 382
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 382
Gly Ala Ser Ser Leu Gln Ser
1   5

<210> 383
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 383
Ala Ala Ser His Leu Gln Ser
1   5

<210> 384

<400> 384
000

<210> 385
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 385
Asp Ser Ser Ser Leu Gln Thr
1   5

<210> 386
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 386
Ala Ala Ser Asn Leu Glu Ser
1   5

<210> 387
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 387
Gln Gln Ser Tyr Ser Thr Pro Tyr Thr
1   5

<210> 388
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 388
Gln Gln Ser Phe Ser Thr Pro Tyr Thr
1   5

<210> 389
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 389
Gln Gln Ser Tyr Ser Thr Pro Leu Thr
1   5

<210> 390
<211> 9
<212> PRT

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 390
Gln Gln Ser Tyr Ser Thr Pro Phe Thr
1 5

<210> 391
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 391
Gln Gln Ser Tyr Ser Thr Pro Ile Thr
1 5

<210> 392
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 392
Gln Gln Tyr Tyr Ser Thr Pro Tyr Thr
1 5

<210> 393
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 393
Gln Gln Ser Tyr Ser Leu Pro Tyr Thr
1 5

<210> 394
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 394
His Gln Tyr Phe Thr Thr Pro Leu Thr

1 5

<210> 395
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 395
Gln Gln Ser Tyr Ser Met Pro Tyr Thr
1 5

<210> 396
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 396
Gln Gln Ser Tyr Ser Thr Pro Val Thr
1 5

<210> 397
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 397
Gln His Phe Tyr Asn Thr Gln Tyr Thr
1 5

<210> 398
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 398
Gln Gln Ser Leu Gln Tyr Pro Ser His Phe
1 5 10

<210> 399
<211> 30
<212> PRT
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 399
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ser
            20   25   30

<210> 400
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 400
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr
            20   25   30

<210> 401
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 401
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr
            20   25   30

<210> 402
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 402
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Glu Pro Gly Ala
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr
            20   25   30

<210> 403
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 403
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Asn Phe Ser
            20   25   30

<210> 404

<400> 404
000

<210> 405
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 405
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr
            20   25   30

<210> 406
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 406
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ile
            20   25   30

<210> 407
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 407
Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met Gly
1   5   10

<210> 408
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 408
Trp Met Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile Gly
1   5   10

<210> 409
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 409
Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr Met Glu
1   5   10   15

Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
            20   25   30

<210> 410
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 410
Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr Met Glu
1   5   10   15

Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
            20   25   30

<210> 411
<211> 11
<212> PRT
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 411
Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
1 5 10

<210> 412
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 412
Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
1 5 10

<210> 413
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 413
Trp Gly Arg Gly Thr Leu Val Thr Val Ser Ser
1 5 10

<210> 414
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 414
Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
1 5 10

<210> 415
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 415
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys
            20

<210> 416
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 416
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1   5   10   15

Glu Arg Ala Thr Leu Ser Cys
            20

<210> 417
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 417
Asp Ile Gln Ile Thr His Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Tyr Arg Leu Thr Ile Thr Cys
            20

<210> 418
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 418
Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
1   5   10   15

<210> 419
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 419
Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr

1 5 10 15

<210> 420
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 420
Trp Tyr His Gln Lys Pro Trp Asn Ala Pro Lys Leu Met Ile Tyr
1 5 10 15

<210> 421
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 421
Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
1 5 10 15

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
20 25 30

<210> 422
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 422
Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr
1 5 10 15

Leu Thr Ile Ser Ser Leu Gln Ser Glu Asp Phe Ala Val Tyr Tyr Cys
20 25 30

<210> 423
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 423
Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Tyr Phe Thr
1 5 10 15

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
            20   25   30

<210> 424
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 424
Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
1   5   10   15

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Pro Tyr Tyr Cys
            20   25   30

<210> 425
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 425
Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
1   5   10

<210> 426
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 426
Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
1   5   10

<210> 427
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 427
Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
1   5   10

<210> 428
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 428
Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
1 5 10

<210> 429
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 429
Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
1 5 10

<210> 430
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 430
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ser Ser Asp
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Met Ser Pro Tyr Asn Gly Ile Thr Gly Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Arg Phe Ser Gly Ser Tyr Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
        115

<210> 431
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 431
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr
            20   25   30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35   40   45

Gly Trp Met Ser Pro Ser Ser Gly Ile Thr Gly Tyr Ala Gln Lys Phe
    50   55   60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65   70   75   80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg Asp Arg Gly Trp Phe Asp Pro Trp Gly Gln Gly Thr Leu Val
            100   105   110

Thr Val Ser Ser
        115

<210> 432
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 432
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ser Ser Tyr
            20   25   30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35   40   45

Gly Trp Met Thr Thr Asn Ser Gly Ile Thr Gly Tyr Ala Gln Lys Phe
    50   55   60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65   70   75   80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg Glu Gly Tyr Ser Ser Gly Leu Asp Tyr Trp Gly Gln Gly Thr
            100   105   110

Leu Val Thr Val Ser Ser
        115

<210> 433
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 433
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr
            20   25   30

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35   40   45

Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Ser Tyr Ala Gln Lys Phe
    50   55   60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65   70   75   80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg Asp Gly Arg Phe Trp Ser Gly Tyr Pro Asp Tyr Trp Gly Gln
            100   105   110

Gly Thr Leu Val Thr Val Ser Ser
        115   120

<210> 434
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 434
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ser Thr His
            20   25   30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35   40   45

Gly Trp Met Asn Pro Asn Ser Gly His Ala Gly Ser Ala Gln Lys Phe
    50   55   60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65   70   75   80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg Glu Ser Ile Ala Val Ala Gly Tyr Asp Tyr Trp Gly Gln Gly
            100   105   110

Thr Leu Val Thr Val Ser Ser
        115

<210> 435
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 435
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser His
            20   25   30

Asp Ile Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35   40   45

Gly Trp Met Asn Pro Asn Ser Gly Asn Thr Gly Tyr Ala Gln Lys Phe
    50   55   60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65   70   75   80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg Asp Arg Trp Tyr Met Gly Ser Ala Asp Tyr Trp Gly Gln Gly
            100   105   110

Thr Leu Val Thr Val Ser Ser
        115

<210> 436
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 436
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20   25   30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35   40   45

Gly Trp Met Asn Pro Asn Ser Gly Asn Thr Gly Tyr Ala Gln Lys Phe
    50   55   60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65   70   75   80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg Asp Asp Trp Gly Gly Asp Trp Phe Asp Pro Trp Gly Gln Gly
            100   105   110

Thr Leu Val Thr Val Ser Ser
        115

<210> 437
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 437
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

```
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ser Thr His
            20                  25                  30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Trp Met Asn Pro Asn Ser Gly Asn Thr Gly Tyr Ser Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Arg Leu Ser Val Ala Gly Phe Asp Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser
        115
```

<210> 438
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 438

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Glu Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp His
            20                  25                  30

Tyr Leu His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Trp Met Asn Pro Asn Ile Gly Asn Thr Gly Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Pro Leu Gln Leu Gly Gly Phe Asp Tyr Trp Gly Gln Gly
            100                 105                 110
```

Thr Leu Val Thr Val Ser Ser
        115

<210> 439
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 439
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr
            20   25   30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35   40   45

Gly Trp Met Asn Pro Asn Gly Gly Thr Thr Gly Tyr Ala Gln Asn Phe
    50   55   60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65   70   75   80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg Glu Gly Phe Gly Pro Asn Ala Phe Asp Ile Trp Gly Gln Gly
            100   105   110

Thr Thr Val Thr Val Ser Ser
        115

<210> 440
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 440
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr
            20   25   30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35   40   45

```
Gly Trp Met Asn Pro Asn Ser Gly Asn Thr Gly Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Ser Trp Tyr Gly Asp Trp Phe Asp Pro Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser
        115
```

<210> 441
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 441

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr
            20                  25                  30

Tyr Met His Trp Met Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45

Gly Trp Met Ser Pro Tyr Asn Gly Ile Thr Gly Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Val Ile Glu Val Gly Met Asp Val Trp Gly Gln Gly Thr
            100                 105                 110

Thr Val Thr Val Ser Ser
        115
```

<210> 442
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 442
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
            20   25   30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35   40   45

Gly Trp Met Ser Pro Ser Ser Gly Ile Thr Gly Tyr Ala Gln Lys Phe
    50   55   60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65   70   75   80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg Glu Ala Trp Phe Gly Glu Leu Ser Thr Trp Gly Gln Gly Thr
            100   105   110

Leu Val Thr Val Ser Ser
        115

<210> 443
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 443
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Asn Phe Ser Ala Tyr
            20   25   30

Tyr Val His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35   40   45

Gly Trp Met Asn Pro Asn Arg Gly Ile Thr Asp Ser Ala Gln Lys Phe
    50   55   60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65   70   75   80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg Glu Ala Tyr Val Ala Ala Phe Asp Ile Trp Gly Gln Gly Thr
            100   105   110

Thr Val Thr Val Ser Ser
        115

<210> 444
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 444
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg His
            20   25   30

Tyr Val His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35   40   45

Gly Trp Met Asn Pro Asn Ser Gly Ser Ala Gly Tyr Ala Gln Lys Phe
    50   55   60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65   70   75   80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg Glu Arg Gly Tyr Asn Ala Phe Asp Tyr Trp Gly Gln Gly Thr
            100   105   110

Leu Val Thr Val Ser Ser
        115

<210> 445
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 445
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Leu Pro Asn Tyr
            20   25   30

Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met Gly
        35   40   45

Trp Ile His Pro Arg Ser Gly Ala Thr Gly Tyr Ala Pro Lys Phe Gln
    50   55   60

Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr Met
65   70   75   80

Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala
                85   90   95

Arg Asp Ser Val Phe Gly Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val
            100   105   110

Thr Val Ser Ser
        115

<210> 446
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 446
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20   25   30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35   40   45

Gly Trp Ile Ser Pro Arg Ser Gly Val Thr Ser Tyr Ala Gln Lys Phe
    50   55   60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65   70   75   80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg Asp Leu Asp Tyr Val Arg Ala Phe Asp Ile Trp Gly Gln Gly
            100   105   110

Thr Thr Val Thr Val Ser Ser

115

<210> 447
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 447
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Met Asp Pro Asn Ser Gly Asn Thr Gly Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Ser Trp Gly Gly Tyr Phe Asp Leu Trp Gly Arg Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

<210> 448
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 448
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ile Asn His
20 25 30

Tyr Val His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

```
Gly Trp Met Asn Pro Thr Gly Gly Ile Thr Gly Tyr Ala Gln Lys Phe
    50                  55                  60


Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80


Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Asp Arg Thr Thr Tyr Ala Phe Asp Ile Trp Gly Gln Gly Thr
            100                 105                 110


Met Val Thr Val Ser Ser
        115


<210> 449
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 449
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15


Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser His
            20                  25                  30


Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45


Gly Trp Met Asn Pro Asn Ser Gly His Thr Gly Asn Ala Gln Lys Phe
    50                  55                  60


Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80


Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Gly Asn Trp Val Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr
            100                 105                 110


Met Val Thr Val Ser Ser
        115


<210> 450
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
```

<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 450
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg His
20 25 30

Leu Leu His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Val Ser Pro Ile His Gly Leu Thr Gly Tyr Ala Pro Arg Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Val His Gly Ser Gly Ser Asp Gly Met Asp Val Trp Gly Gln
100 105 110

Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 451
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 451
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Tyr

```
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> 452
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 452
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Val Gly Thr Trp
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Ala Ala Ser Thr Leu Glu Asn Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Phe Ser Thr Pro Tyr
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> 453
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 453
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Trp
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45
```

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Tyr
                85   90   95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100   105

<210> 454
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 454
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Tyr
            20   25   30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45

Tyr Arg Ala Ser Asn Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Leu
                85   90   95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100   105

<210> 455
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 455
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Trp
            20   25   30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45

Tyr Ala Ala Ser Thr Leu Gln Arg Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Tyr
                85   90   95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100   105

<210> 456
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 456
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Thr Trp
            20   25   30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45

Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Phe
                85   90   95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100   105

<210> 457
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 457
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Asp Ile Ser Asn His
            20   25   30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45

Tyr Gly Ala Ser Asn Leu Gln Arg Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Ile
                85   90   95

Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
            100   105

<210> 458
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 458
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
            20   25   30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Tyr
                85   90   95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 459
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 459
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Glu Ser Ile Ser Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 460
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 460
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Asn Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Ser Thr Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 461
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 461
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Val Gly Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Gly Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 462
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 462
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45

Tyr Ala Ala Ser His Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Tyr
                85   90   95

Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
            100   105

<210> 463
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 463
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asn Ile Ser Asn Phe
            20   25   30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Leu Pro Tyr
                85   90   95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100   105

<210> 464
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic

polypeptide"

<400> 464
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 465
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 465
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Leu Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln
65 70 75 80

Ser Glu Asp Phe Ala Val Tyr Tyr Cys His Gln Tyr Phe Thr Thr Pro
85 90 95

Leu Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105

<210> 466
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 466
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Met Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 467
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 467
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Arg Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 468
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 468
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ser Ser Ser Leu Gln Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Val
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 469
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 469
Asp Ile Gln Ile Thr His Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Tyr Arg Leu Thr Ile Thr Cys Arg Asp Ser His Ser Ile Thr Thr Trp
20 25 30

Leu Ala Trp Tyr His Gln Lys Pro Trp Asn Ala Pro Lys Leu Met Ile

```
        35                  40                  45

Tyr Ala Ala Ser Asn Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Tyr Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln His Phe Tyr Asn Thr Gln Tyr
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> 470
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 470
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Val Ile Arg Asn Asp
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Leu Gln Tyr Pro Ser
                85                  90                  95

His Phe Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> 471
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 471
```

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Arg Tyr
            20   25   30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45

Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Phe Ala Pro Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Leu
                85   90   95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
            100   105

<210> 472
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 472
Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Gly Thr Ser
            20   25   30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45

Tyr Trp Thr Ser Thr Arg His Thr Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Leu Tyr Arg Ser
                85   90   95

Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100   105

<210> 473
<211> 23

<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 473
Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys
20

<210> 474
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 474
Lys Ala Ser Gln Asp Val Gly Thr Ser Val Ala
1 5 10

<210> 475
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 475
Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
1 5 10 15

<210> 476
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 476
Trp Thr Ser Thr Arg His Thr
1 5

<210> 477
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 477
Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
1   5   10   15

Phe Thr Ile Ser Ser Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr Cys
            20   25   30

<210> 478
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 478
Gln Gln Tyr Ser Leu Tyr Arg Ser
1   5

<210> 479
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 479
Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
1   5   10

<210> 480
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 480
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1   5   10   15

Ser Leu Arg Leu Ser Cys Ser Ser Ser Gly Phe Asp Phe Thr Thr Tyr
            20   25   30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ala Glu Ile His Pro Asp Ser Ser Thr Ile Asn Tyr Ala Pro Ser Leu
    50   55   60

Lys Asp Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe
65 70 75 80

Leu Gln Met Asp Ser Leu Arg Pro Glu Asp Thr Gly Val Tyr Phe Cys
85 90 95

Ala Ser Leu Tyr Phe Gly Phe Pro Trp Phe Ala Tyr Trp Gly Gln Gly
100 105 110

Thr Pro Val Thr Val Ser Ser
115

<210> 481
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 481
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ser Ser Ser Gly Phe Asp Phe Thr
20 25 30

<210> 482
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 482
Thr Tyr Trp Met Ser
1 5

<210> 483
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 483
Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala
1 5 10

<210> 484
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 484
Glu Ile His Pro Asp Ser Ser Thr Ile Asn Tyr Ala Pro Ser Leu Lys
1   5   10   15

Asp

<210> 485
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 485
Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe Leu Gln
1   5   10   15

Met Asp Ser Leu Arg Pro Glu Asp Thr Gly Val Tyr Phe Cys Ala Ser
            20   25   30

<210> 486
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 486
Leu Tyr Phe Gly Phe Pro Trp Phe Ala Tyr
1   5   10

<210> 487
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 487
Trp Gly Gln Gly Thr Pro Val Thr Val Ser Ser
1   5   10

<210> 488
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 488
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Ala Ala Val Gly Thr Tyr
            20   25   30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45

Tyr Ser Ala Ser Tyr Arg Lys Arg Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Phe Ala Thr Tyr Tyr Cys His Gln Tyr Tyr Thr Tyr Pro Leu
                85   90   95

Phe Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100   105

<210> 489
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 489
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Thr Ile Thr Cys
            20

<210> 490
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 490
Lys Ala Ser Ala Ala Val Gly Thr Tyr Val Ala
1   5   10

<210> 491

<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 491
Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
1 5 10 15

<210> 492
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 492
Ser Ala Ser Tyr Arg Lys Arg
1 5

<210> 493
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 493
Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
1 5 10 15

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
20 25 30

<210> 494
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 494
His Gln Tyr Tyr Thr Tyr Pro Leu Phe Thr
1 5 10

<210> 495
<211> 10
<212> PRT
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 495
Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
1   5   10

<210> 496
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 496
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr
            20   25   30

<210> 497
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 497
Glu Phe Gly Met Asn
1   5

<210> 498
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 498
Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met Gly
1   5   10

<210> 499
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 499

Trp Ile Asn Thr Lys Thr Gly Glu Ala Thr Tyr Val Glu Glu Phe Lys
1   5   10   15

Gly

<210> 500
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 500
Arg Val Thr Phe Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr Met Glu
1   5   10   15

Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys Ala Arg
            20   25   30

<210> 501
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 501
Trp Asp Phe Ala Tyr Tyr Val Glu Ala Met Asp Tyr
1   5   10

<210> 502
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 502
Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
1   5   10

<210> 503
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 503
Glu Asn Val Leu Thr Gln Ser Pro Ser Ser Met Ser Ala Ser Val Gly

1 5 10 15

Asp Arg Val Asn Ile Ala Cys Ser Ala Ser Ser Ser Val Ser Tyr Met
20 25 30

His Trp Phe Gln Gln Lys Pro Gly Lys Ser Pro Lys Leu Trp Ile Tyr
35 40 45

Ser Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Ser Met Gln Pro Glu
65 70 75 80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Arg Ser Ser Tyr Pro Leu Thr
85 90 95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 504
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 504
Glu Asn Val Leu Thr Gln Ser Pro Ser Ser Met Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Asn Ile Ala Cys
20

<210> 505
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 505
Ser Ala Ser Ser Ser Val Ser Tyr Met His
1 5 10

<210> 506
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic

peptide"

<400> 506
Trp Phe Gln Gln Lys Pro Gly Lys Ser Pro Lys Leu Trp Ile Tyr
1   5   10   15

<210> 507
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 507
Ser Thr Ser Asn Leu Ala Ser
1   5

<210> 508
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 508
Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser
1   5   10   15

Leu Thr Ile Ser Ser Met Gln Pro Glu Asp Ala Ala Thr Tyr Tyr Cys
            20   25   30

<210> 509
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 509
Gln Gln Arg Ser Ser Tyr Pro Leu Thr
1   5

<210> 510
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 510
Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
1   5   10

<210> 511
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 511
Gln Val Lys Leu Glu Gln Ser Gly Ala Glu Val Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Phe Asn Ile Lys Asp Ser
20 25 30

Tyr Met His Trp Leu Arg Gln Gly Pro Gly Gln Arg Leu Glu Trp Ile
35 40 45

Gly Trp Ile Asp Pro Glu Asn Gly Asp Thr Glu Tyr Ala Pro Lys Phe
50 55 60

Gln Gly Lys Ala Thr Phe Thr Thr Asp Thr Ser Ala Asn Thr Ala Tyr
65 70 75 80

Leu Gly Leu Ser Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Asn Glu Gly Thr Pro Thr Gly Pro Tyr Tyr Phe Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 512
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 512
Gln Val Lys Leu Glu Gln Ser Gly Ala Glu Val Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Phe Asn Ile Lys
20 25 30

<210> 513
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 513
Asp Ser Tyr Met His
1   5

<210> 514
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 514
Trp Leu Arg Gln Gly Pro Gly Gln Arg Leu Glu Trp Ile Gly
1   5   10

<210> 515
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 515
Trp Ile Asp Pro Glu Asn Gly Asp Thr Glu Tyr Ala Pro Lys Phe Gln
1   5   10   15

Gly

<210> 516
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 516
Lys Ala Thr Phe Thr Thr Asp Thr Ser Ala Asn Thr Ala Tyr Leu Gly
1   5   10   15

Leu Ser Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn Glu
            20   25   30

<210> 517
<211> 11
<212> PRT
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 517
Gly Thr Pro Thr Gly Pro Tyr Tyr Phe Asp Tyr
1   5   10

<210> 518
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 518
Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
1   5   10

<210> 519
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 519
Glu Asn Val Leu Thr Gln Ser Pro Ser Ser Met Ser Val Ser Val Gly
1   5   10   15

Asp Arg Val Thr Ile Ala Cys Ser Ala Ser Ser Ser Val Pro Tyr Met
            20   25   30

His Trp Leu Gln Gln Lys Pro Gly Lys Ser Pro Lys Leu Leu Ile Tyr
        35   40   45

Leu Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
    50   55   60

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Ser Val Gln Pro Glu
65   70   75   80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Arg Ser Ser Tyr Pro Leu Thr
                85   90   95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100   105

<210> 520
<211> 23
<212> PRT
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 520
Glu Asn Val Leu Thr Gln Ser Pro Ser Ser Met Ser Val Ser Val Gly
1   5   10   15

Asp Arg Val Thr Ile Ala Cys
            20

<210> 521
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 521
Ser Ala Ser Ser Ser Val Pro Tyr Met His
1   5   10

<210> 522
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 522
Trp Leu Gln Gln Lys Pro Gly Lys Ser Pro Lys Leu Leu Ile Tyr
1   5   10   15

<210> 523
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 523
Leu Thr Ser Asn Leu Ala Ser
1   5

<210> 524
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 524

```
Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser
1               5                   10                  15


Leu Thr Ile Ser Ser Val Gln Pro Glu Asp Ala Ala Thr Tyr Tyr Cys
            20                  25                  30


<210> 525
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 525
Gln Gln Arg Ser Ser Tyr Pro Leu Thr
1               5


<210> 526
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 526
Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
1               5                   10


<210> 527
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 527
Gln Val Lys Leu Glu Gln Ser Gly Ala Glu Val Val Lys Pro Gly Ala
1               5                   10                  15


Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Phe Asn Ile Lys Asp Ser
            20                  25                  30


Tyr Met His Trp Leu Arg Gln Gly Pro Gly Gln Arg Leu Glu Trp Ile
        35                  40                  45


Gly Trp Ile Asp Pro Glu Asn Gly Asp Thr Glu Tyr Ala Pro Lys Phe
    50                  55                  60


Gln Gly Lys Ala Thr Phe Thr Thr Asp Thr Ser Ala Asn Thr Ala Tyr
65                  70                  75                  80
```

Leu Gly Leu Ser Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Asn Glu Gly Thr Pro Thr Gly Pro Tyr Tyr Phe Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 528
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 528
Gln Val Lys Leu Glu Gln Ser Gly Ala Glu Val Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Phe Asn Ile Lys
20 25 30

<210> 529
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 529
Asp Ser Tyr Met His
1 5

<210> 530
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 530
Trp Leu Arg Gln Gly Pro Gly Gln Arg Leu Glu Trp Ile Gly
1 5 10

<210> 531
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic

peptide"

<400> 531
Trp Ile Asp Pro Glu Asn Gly Asp Thr Glu Tyr Ala Pro Lys Phe Gln
1   5   10   15

Gly

<210> 532
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 532
Lys Ala Thr Phe Thr Thr Asp Thr Ser Ala Asn Thr Ala Tyr Leu Gly
1   5   10   15

Leu Ser Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn Glu
            20   25   30

<210> 533
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 533
Gly Thr Pro Thr Gly Pro Tyr Tyr Phe Asp Tyr
1   5   10

<210> 534
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 534
Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
1   5   10

<210> 535
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 535
Gln Thr Val Leu Ser Gln Ser Pro Ala Ile Leu Ser Ala Ser Pro Gly
1   5   10   15

Glu Lys Val Thr Met Thr Cys
            20

<210> 536
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 536
Arg Ala Ser Ser Ser Val Thr Tyr Ile His
1   5   10

<210> 537
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 537
Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro Lys Ser Trp Ile Tyr
1   5   10   15

<210> 538
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 538
Ala Thr Ser Asn Leu Ala Ser
1   5

<210> 539
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 539
Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Ser Tyr Ser
1   5   10   15

Leu Thr Ile Ser Arg Val Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys
            20   25   30

<210> 540
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 540
Gln His Trp Ser Ser Lys Pro Pro Thr
1   5

<210> 541
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 541
Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
1   5   10

<210> 542
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 542
Glu Val Lys Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Thr Ser Gly Phe Thr Phe Thr Asp Tyr
            20   25   30

Tyr Met Asn Trp Val Arg Gln Pro Pro Gly Lys Ala Leu Glu Trp Leu
        35   40   45

Gly Phe Ile Gly Asn Lys Ala Asn Gly Tyr Thr Thr Glu Tyr Ser Ala
    50   55   60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Lys Ser Gln Ser Ile
65   70   75   80

Leu Tyr Leu Gln Met Asn Thr Leu Arg Ala Glu Asp Ser Ala Thr Tyr
                85   90   95

Tyr Cys Thr Arg Asp Arg Gly Leu Arg Phe Tyr Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Thr Leu Thr Val Ser Ser
115 120

<210> 543
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 543
Glu Val Lys Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Thr Ser Gly Phe Thr Phe Thr
20 25 30

<210> 544
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 544
Asp Tyr Tyr Met Asn
1 5

<210> 545
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 545
Trp Val Arg Gln Pro Pro Gly Lys Ala Leu Glu Trp Leu Gly
1 5 10

<210> 546
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 546

Phe Ile Gly Asn Lys Ala Asn Gly Tyr Thr Thr Glu Tyr Ser Ala Ser
1   5   10   15

Val Lys Gly

<210> 547
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 547
Arg Phe Thr Ile Ser Arg Asp Lys Ser Gln Ser Ile Leu Tyr Leu Gln
1   5   10   15

Met Asn Thr Leu Arg Ala Glu Asp Ser Ala Thr Tyr Tyr Cys Thr Arg
            20   25   30

<210> 548
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 548
Asp Arg Gly Leu Arg Phe Tyr Phe Asp Tyr
1   5   10

<210> 549
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 549
Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser
1   5   10

<210> 550
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 550
Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly

1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Gly Glu Ser Val Asp Ile Phe
20 25 30

Gly Val Gly Phe Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
35 40 45

Lys Leu Leu Ile Tyr Arg Ala Ser Asn Leu Glu Ser Gly Val Pro Ser
50 55 60

Arg Phe Ser Gly Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Ser
65 70 75 80

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Thr Asn
85 90 95

Glu Asp Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 551
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 551
Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys
20

<210> 552
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 552
Arg Ala Gly Glu Ser Val Asp Ile Phe Gly Val Gly Phe Leu His
1 5 10 15

<210> 553
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic

peptide"

<400> 553
Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
1   5   10   15

<210> 554
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 554
Arg Ala Ser Asn Leu Glu Ser
1   5

<210> 555
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 555
Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Arg Thr Asp Phe Thr
1   5   10   15

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
            20   25   30

<210> 556
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 556
Gln Gln Thr Asn Glu Asp Pro Tyr Thr
1   5

<210> 557
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 557
Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
1   5   10

<210> 558
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 558
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Asp Thr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Arg Ile Asp Pro Ala Asn Gly Asn Ser Lys Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Pro Phe Gly Tyr Tyr Val Ser Asp Tyr Ala Met Ala Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 559
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 559
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys
20 25 30

<210> 560
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 560
Asp Thr Tyr Met His
1   5

<210> 561
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 561
Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala
1   5   10

<210> 562
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 562
Arg Ile Asp Pro Ala Asn Gly Asn Ser Lys Tyr Ala Asp Ser Val Lys
1   5   10   15

Gly

<210> 563
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 563
Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr Leu Gln
1   5   10   15

Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Pro
            20   25   30

<210> 564
<211> 12
<212> PRT
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 564
Phe Gly Tyr Tyr Val Ser Asp Tyr Ala Met Ala Tyr
1   5   10

<210> 565
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 565
Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
1   5   10

<210> 566
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 566
Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Glu Asn Ile Phe Ser Tyr
            20   25   30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ser Pro Lys Leu Leu Val
        35   40   45

Tyr Asn Thr Arg Thr Leu Ala Glu Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Ser Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln His His Tyr Gly Thr Pro Phe
                85   90   95

Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
            100   105

<210> 567
<211> 23
<212> PRT
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 567
Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Thr Ile Thr Cys
            20

<210> 568
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 568
Arg Ala Ser Glu Asn Ile Phe Ser Tyr Leu Ala
1   5   10

<210> 569
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 569
Trp Tyr Gln Gln Lys Pro Gly Lys Ser Pro Lys Leu Leu Val Tyr
1   5   10   15

<210> 570
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 570
Asn Thr Arg Thr Leu Ala Glu
1   5

<210> 571
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 571

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Ser
1   5   10   15

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
            20   25   30

<210> 572
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 572
Gln His His Tyr Gly Thr Pro Phe Thr
1   5

<210> 573
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 573
Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
1   5   10

<210> 574
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 574
Glu Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Gly Gly
1   5   10   15

Ser Leu Ser Leu Ser Cys Ala Ala Ser Gly Phe Val Phe Ser Ser Tyr
            20   25   30

Asp Met Ser Trp Val Arg Gln Thr Pro Glu Arg Gly Leu Glu Trp Val
        35   40   45

Ala Tyr Ile Ser Ser Gly Gly Gly Ile Thr Tyr Ala Pro Ser Thr Val
    50   55   60

Lys Gly Arg Phe Thr Val Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65   70   75   80

Leu Gln Met Asn Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Ala His Tyr Phe Gly Ser Ser Gly Pro Phe Ala Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 575
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 575
Glu Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Ser Leu Ser Cys Ala Ala Ser Gly Phe Val Phe Ser
20 25 30

<210> 576
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 576
Ser Tyr Asp Met Ser
1 5

<210> 577
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 577
Trp Val Arg Gln Thr Pro Glu Arg Gly Leu Glu Trp Val Ala
1 5 10

<210> 578
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic

peptide"

<400> 578
Tyr Ile Ser Ser Gly Gly Gly Ile Thr Tyr Ala Pro Ser Thr Val Lys
1   5   10   15

Gly

<210> 579
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 579
Arg Phe Thr Val Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr Leu Gln
1   5   10   15

Met Asn Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala Ala
            20   25   30

<210> 580
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 580
His Tyr Phe Gly Ser Ser Gly Pro Phe Ala Tyr
1   5   10

<210> 581
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 581
Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
1   5   10

<210> 582
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 582
Gln Ala Val Leu Thr Gln Pro Ala Ser Leu Ser Ala Ser Pro Gly Ala
1   5   10   15

Ser Ala Ser Leu Thr Cys Thr Leu Arg Arg Gly Ile Asn Val Gly Ala
            20   25   30

Tyr Ser Ile Tyr Trp Tyr Gln Gln Lys Pro Gly Ser Pro Pro Gln Tyr
        35   40   45

Leu Leu Arg Tyr Lys Ser Asp Ser Asp Lys Gln Gln Gly Ser Gly Val
    50   55   60

Ser Ser Arg Phe Ser Ala Ser Lys Asp Ala Ser Ala Asn Ala Gly Ile
65   70   75   80

Leu Leu Ile Ser Gly Leu Gln Ser Glu Asp Glu Ala Asp Tyr Tyr Cys
                85   90   95

Met Ile Trp His Ser Gly Ala Ser Ala Val Phe Gly Gly Gly Thr Lys
            100   105   110

Leu Thr Val Leu
        115

<210> 583
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 583
Gln Ala Val Leu Thr Gln Pro Ala Ser Leu Ser Ala Ser Pro Gly Ala
1   5   10   15

Ser Ala Ser Leu Thr Cys
            20

<210> 584
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 584
Thr Leu Arg Arg Gly Ile Asn Val Gly Ala Tyr Ser Ile Tyr
1   5   10

<210> 585

<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 585
Trp Tyr Gln Gln Lys Pro Gly Ser Pro Pro Gln Tyr Leu Leu Arg
1 5 10 15

<210> 586
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 586
Tyr Lys Ser Asp Ser Asp Lys Gln Gln Gly Ser
1 5 10

<210> 587
<211> 34
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 587
Gly Val Ser Ser Arg Phe Ser Ala Ser Lys Asp Ala Ser Ala Asn Ala
1 5 10 15

Gly Ile Leu Leu Ile Ser Gly Leu Gln Ser Glu Asp Glu Ala Asp Tyr
20 25 30

Tyr Cys

<210> 588
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 588
Met Ile Trp His Ser Gly Ala Ser Ala Val
1 5 10

<210> 589
<211> 10

<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 589
Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
1 5 10

<210> 590
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 590
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Ser Ser Tyr
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Gly Phe Ile Arg Asn Lys Ala Asn Gly Gly Thr Thr Glu Tyr Ala Ala
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Ala Arg Asp Arg Gly Leu Arg Phe Tyr Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 591
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 591
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Ser
            20   25   30

<210> 592
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 592
Ser Tyr Trp Met His
1   5

<210> 593
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 593
Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Gly
1   5   10

<210> 594
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 594
Phe Ile Arg Asn Lys Ala Asn Gly Gly Thr Thr Glu Tyr Ala Ala Ser
1   5   10   15

Val Lys Gly

<210> 595
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 595
Phe Ile Arg Asn Lys Ala Asn Ser Gly Thr Thr Glu Tyr Ala Ala Ser
1   5   10   15

Val Lys Gly

<210> 596
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 596
Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Leu Tyr Leu Gln
1 5 10 15

Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
20 25 30

<210> 597
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 597
Asp Arg Gly Leu Arg Phe Tyr Phe Asp Tyr
1 5 10

<210> 598
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 598
Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
1 5 10

<210> 599
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 599
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Ser Ser Tyr
            20   25   30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Gly Phe Ile Leu Asn Lys Ala Asn Gly Gly Thr Thr Glu Tyr Ala Ala
    50   55   60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65   70   75   80

Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr
                85   90   95

Tyr Cys Ala Arg Asp Arg Gly Leu Arg Phe Tyr Phe Asp Tyr Trp Gly
            100   105   110

Gln Gly Thr Thr Val Thr Val Ser Ser
        115   120

<210> 600
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 600
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Ser
            20   25   30

<210> 601
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 601
Ser Tyr Trp Met His
1   5

<210> 602
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 602
Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Gly
1 5 10

<210> 603
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 603
Phe Ile Leu Asn Lys Ala Asn Gly Gly Thr Thr Glu Tyr Ala Ala Ser
1 5 10 15

Val Lys Gly

<210> 604
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 604
Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Leu Tyr Leu Gln
1 5 10 15

Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
20 25 30

<210> 605
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 605
Asp Arg Gly Leu Arg Phe Tyr Phe Asp Tyr
1 5 10

<210> 606
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic

peptide"

<400> 606
Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
1   5   10

<210> 607
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 607
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Leu Pro
            20   25   30

<210> 608
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 608
Gly Gly Gly Gly Ser Ser Ser Ser Gly
1   5