Innovation, Sciences et Développement économique Canada
Office de la Propriété Intellectuelle du Canada

Innovation, Science and Economic Development Canada
Canadian Intellectual Property Office

CA 3027045 A1 2017/12/14

(21) 3 027 045

(12) DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION

(13) A1

(86) Date de dépôt PCT/PCT Filing Date: 2017/06/07
(87) Date publication PCT/PCT Publication Date: 2017/12/14
(85) Entrée phase nationale/National Entry: 2018/12/07
(86) N° demande PCT/PCT Application No.: US 2017/036445
(87) N° publication PCT/PCT Publication No.: 2017/214335
(30) Priorités/Priorities: 2016/06/08 (US62/347,476);
2016/07/25 (US62/366,511)

(51) Cl.Int./Int.Cl. *C07K 16/28* (2006.01),
A61K 31/00 (2006.01), *A61K 39/00* (2006.01)

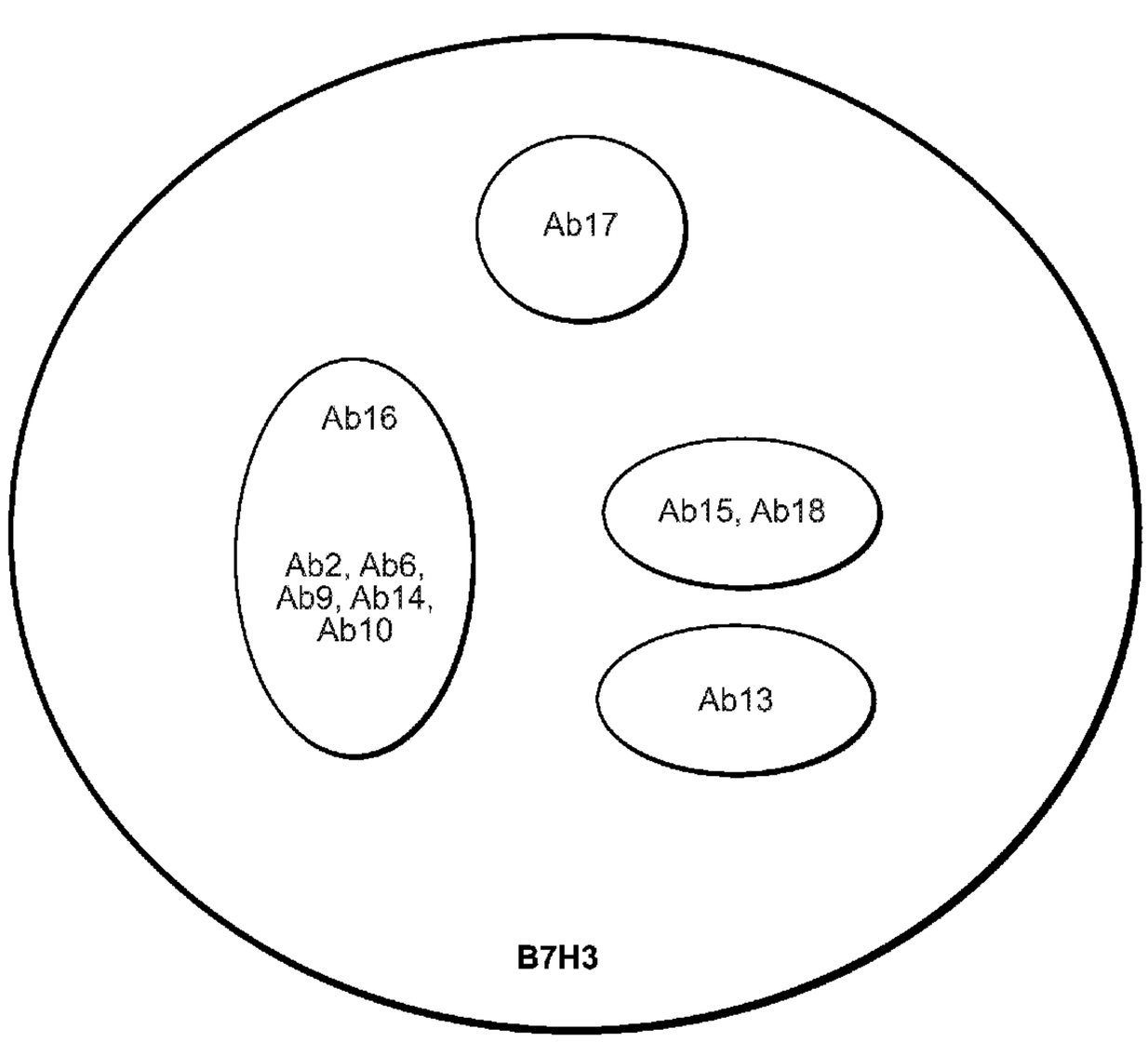
(71) Demandeur/Applicant:
ABBVIE INC., US

(72) Inventeurs/Inventors:
BENATUIL, LORENZO, US;
BRUNCKO, MILAN, US;
CHAO, DEBRA, US;
IZERADJENE, KAMEL, US;
JUDD, ANDREW S., US;
PHILLIPS, ANDREW C., US;
SOUERS, ANDREW J., US;
THAKUR, ARCHANA, US

(74) Agent: TORYS LLP

(54) Titre : ANTICORPS ANTI-B7-H3 ET CONJUGUES ANTICORPS-MEDICAMENTS
(54) Title: ANTI-B7-H3 ANTIBODIES AND ANTIBODY DRUG CONJUGATES

Figure 1



(57) Abrégé/Abstract:
The invention relates to B7 homology 3 protein (B7-H3) antibodies and antibody drug conjugates (ADCs), including compositions and methods of using said antibodies and ADCs.

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 December 2017 (14.12.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/214335 A4

(51) International Patent Classification:
C07K 16/28 (2006.01) *A61K 39/00* (2006.01)
A61K 31/00 (2006.01)

(21) International Application Number:
PCT/US2017/036445

(22) International Filing Date:
07 June 2017 (07.06.2017)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/347,476 08 June 2016 (08.06.2016) US
62/366,511 25 July 2016 (25.07.2016) US

(71) Applicant: **ABBVIE INC.** [US/US]; 1 North Waukegan Road, North Chicago, IL 60064 (US).

(72) Inventors: **BENATUIL, Lorenzo**; 33 Mohawk Drive, Northborough, MA 101532 (US). **BRUNCKO, Milan**; 31231 Prairie Ridge Road, Green Oaks, IL 60048 (US). **CHAO, Debra**; 4846 Balthazar Terrace, Fremont, CA 94555 (US). **IZERADJENE, Kamel**; 1443 Clavey Lane, Gurnee, IL 60031 (US). **JUDD, Andrew, S.**; 138 Mainsail Drive, Grayslake, IL 60030 (US). **PHILLIPS, Andrew, C.**; 519 Garfield Avenue, Libertyville, IL 60048 (US). **SOUERS, Andrew, J.**; 156 Blueberry Road, Libertyville, IL 60048 (US). **THAKUR, Archana**; 8378 Moller Ranch Drive, Pleasanton, CA 94588 (US).

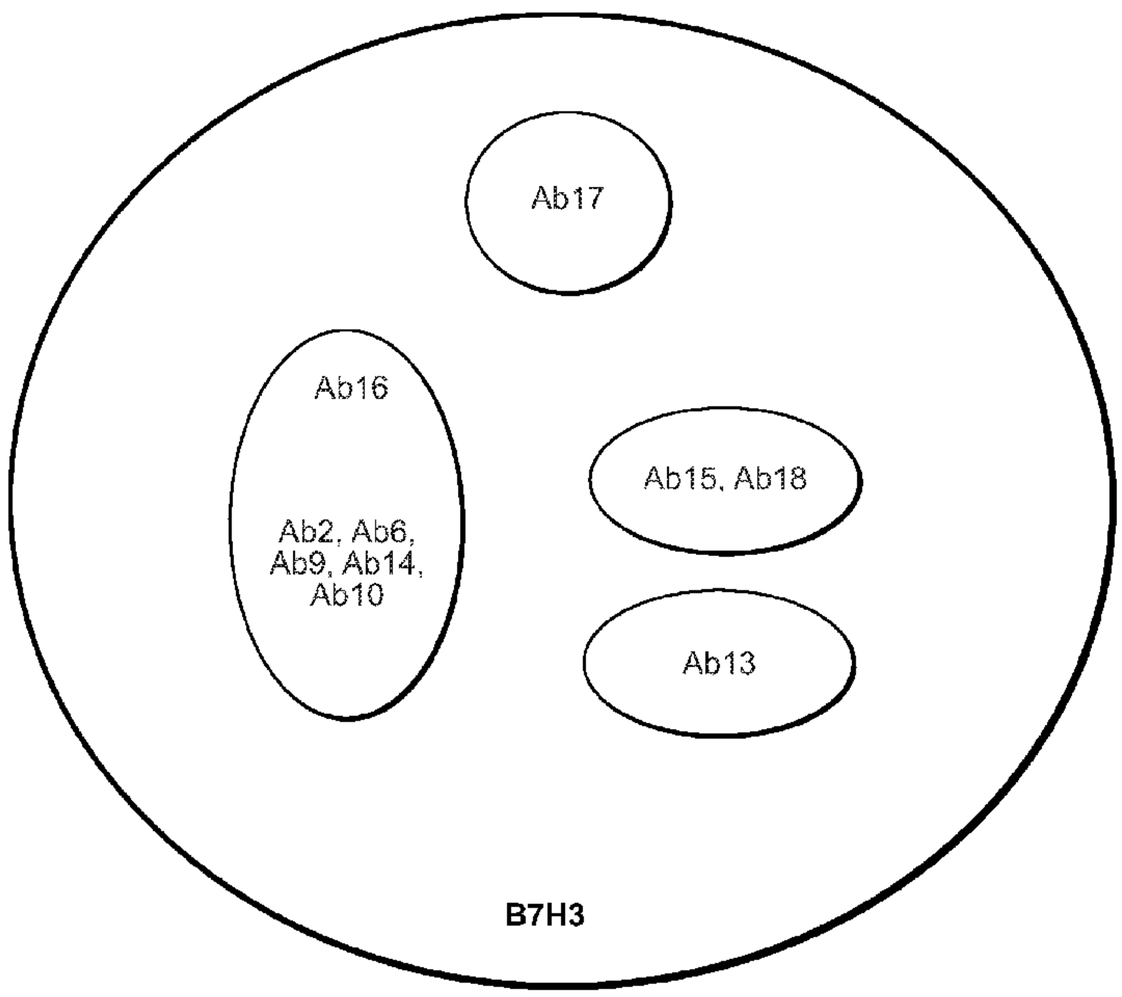
(74) Agent: **COWLES, Cristin, H.** et al.; Womble Bond Dickinson (US) LLP, P.O. Box 7037, Atlanta, Georgia 30357 (US).

(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, 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, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, 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,

(54) Title: ANTI-B7-H3 ANTIBODIES AND ANTIBODY DRUG CONJUGATES

Figure 1



(57) Abstract: The invention relates to B7 homology 3 protein (B7-H3) antibodies and antibody drug conjugates (ADCs), including compositions and methods of using said antibodies and ADCs.

[Continued on next page]

WO 2017/214335 A4

WO 2017/214335 A4

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).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

— *with international search report (Art. 21(3))*

— *with amended claims (Art. 19(1))*

— *with sequence listing part of description (Rule 5.2(a))*

Date of publication of the amended claims:

08 March 2018 (08.03.2018)

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME	1	DE	3
CONTENANT LES PAGES	1	À	432

NOTE : Pour les tomes additionels, veuillez contacter le Bureau canadien des brevets

JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME	1	OF	3
CONTAINING PAGES	1	TO	432

NOTE: For additional volumes, please contact the Canadian Patent Office

NOM DU FICHIER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

ANTI-B7-H3 ANTIBODIES AND ANTIBODY DRUG CONJUGATES

RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application No. 62/347,476, filed on June 8, 2016, and to U.S. Provisional Application No. 62/366,511, filed on July 25, 2016. The entire contents of the foregoing applications are expressly incorporated herein by reference.

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 7, 2017, is named 117813-12620_ST25.txt and is 159,744 bytes in size.

BACKGROUND OF THE INVENTION

The B7 homology 3 protein (B7-H3) (also known as CD276 and B7RP-2, and referred to herein as "B7-H3") is a type I transmembrane glycoprotein of the immunoglobulin superfamily. Human B7-H3 contains a putative signal peptide, V-like and C-like Ig domains, a transmembrane region and a cytoplasmic domain. Exon duplication in humans results in the expression of two B7-H3 isoforms having either a single IgV-IgC-like domain (2IgB7-H3 isoform) or a IgV-IgC-IgV-IgC-like domain (4IgB7-H3 isoform) containing several conserved cysteine residues. The predominant B7-H3 isoform in human tissues and cell lines is the 4IgB7-H3 isoform (Steinberger *et al.*, J. Immunol. 172(4): 2352-9 (2004)).

B7-H3 has been reported as having both co-stimulatory and co-inhibitory signaling functions (see, *e.g.*, Chapoval *et al.*, Nat. Immunol. 2: 269-74 (2001); Suh *et al.*, Nat. Immunol. 4: 899-906 (2003); Prasad *et al.*, J. Immunol. 173: 2500-6 (2004); and Wang *et al.*, Eur. J. Immunol. 35: 428-38 (2005)). For example, *in vitro* studies have shown B7-H3's co-stimulatory function since B7-H3 was able to increase proliferation of cytotoxic T-lymphocytes (CTLs) and upregulate interferon gamma (IFN-γ) production in the presence of anti-CD3 antibody to mimic the T cell receptor signal (Chapoval *et al.*, 2001). Moreover, *in vivo* studies using cardiac allografts in B7-H3 -/- mice showed decreased production of key cytokine, chemokine and chemokine receptor mRNA transcripts (*e.g.*, IL-2, IFN-γ, monocyte chemoattractant protein (MCP-1) and IFN-inducible protein (IP)-10) as compared to wild-type control (Wang *et al.*, 2005). In contrast, B7-H3 co-inhibitory function has been observed, for example, in mice where B7-H3 protein inhibited T-cell activation and effector cytokine production (Suh *et al.*, 2003). Although no ligands have been identified for human B7-H3, murine B7-H3 has been found to bind to the triggering receptor expressed on myeloid cells (TREM-) like transcript 2 (TLT-2), a modulator of adaptive an innate immunity cellular responses. Binding of murine B7-H3 to TLT-2 on $CD8^+$ T-cells enhances T-cell effector functions such as proliferation,

cytotoxicity and cytokine production (Hashiguchi *et al.*, Proc. Nat'l. Acad. Sci. U.S.A. 105(30): 10495-500 (2008)).

B7-H3 is not constitutively expressed in many immune cells (*e.g.*, natural killer (NK) cells, T-cells, and antigen-presenting cells (APCs)), however, its expression can be induced. Further, the expression of B7-H3 is not restricted to immune cells. B7-H3 transcripts are expressed in a variety of human tissues including colon, heart, liver, placenta, prostate, small intestine, testis, and uterus, as well as osteoblasts, fibroblasts, epithelial cells, and other cells of non-lymphoid lineage, potentially indicating immunological and non-immunological functions (Nygren *et al. Front Biosci.* 3:989-93 (2011)). However, protein expression in normal tissue is typically maintained at a low level and thus, may be subject to post-transcriptional regulation.

B7-H3 is also expressed in a variety of human cancers, including prostate cancer, clear cell renal cell carcinoma, glioma, melanoma, lung cancer, non-small cell lung cancer (NSCLC), small cell lung cancer, pancreatic cancer, gastric cancer, acute myeloid leukemia (AML), non-Hodgkin's lymphoma (NHL), ovarian cancer, colorectal cancer, colon cancer, renal cancer, hepatocellular carcinoma, kidney cancer, head and neck cancer, hypopharyngeal squamous cell carcinoma, glioblastoma, neuroblastoma, breast cancer, endometrial cancer, and urothelial cell carcinoma. Although the role of B7-H3 in cancer cells is unclear, its expression may orchestrate signaling events that may protect cancer cells from innate and adaptive immune responses. For example, B7-H3 is overexpressed in high-grade prostatic intraepithelial neoplasia and adenocarcinomas of the prostate, and high expression levels of B7-H3 in these cancerous cells is associated with an increased risk of cancer progression after surgery (Roth *et al. Cancer Res.* 67(16): 7893-900 (2007)). Further, tumor B7-H3 expression in NSCLC inversely correlated with the number of tumor-infiltrating lymphocytes and significantly correlated with lymph node metastasis (Sun *et al.* Lung Cancer 53(2): 143-51 (2006)). The level of circulating soluble B7-H3 in NSCLC patients has also been associated with higher tumor stage, tumor size, lymph node metastasis, and distant metastasis (Yamato *et al.*, Br. J. Cancer 101(10):1709-16 (2009)).

B7-H3 may also play an important role in T-cell-mediated antitumor responses in a context dependent manner. For example, gastric cancer tumor cell expression of B7-H3 positively correlated with survival time, infiltration depth, and tissue type (Wu *et al.*, World J. Gastroenterol. 12(3): 457-9 (2006)). Further, high expression of B7-H3 in pancreatic tumor cells was associated with patient survival after surgical resection and significantly correlated with the number of tumor-infiltrating $CD8^+$ T-cells (Loos *et al.*, BMC Cancer 9:463 (2009).

Antibody drug conjugates (ADC) represent a relatively new class of therapeutics comprising an antibody conjugated to a cytotoxic drug via a chemical linker. The therapeutic concept of ADCs is to combine binding capabilities of an antibody with a drug, where the antibody is used to deliver the drug to a tumor cell by means of binding to a target surface antigen, including target surface antigens that are overexpressed in the tumor cells.

There remains a need in the art for anti-B7-H3 antibodies and anti-B7-H3 ADCs that can be used for therapeutic purposes in the treatment of cancer.

SUMMARY OF THE INVENTION

In certain aspects, the present invention provides for antibodies and antibody drug conjugates (ADCs) that specifically bind to human B7-H3. In certain aspects, the present invention provides novel ADCs that can selectively deliver Bcl-xL inhibitors to target cancer cells, *e.g.*, B7-H3 expressing cells.

In one aspect, the present invention provides an antoi-B7-H3 antibody, or antigen binding portion thereof, that binds to human B7-H3 (hB7-H3), wherein the antibody, or antigen binding portion thereof, comprises a heavy chain variable region comprising a CDR3 having the amino acid sequence of SEQ ID NO: 12 and a light chain variable region comprising a CDR3 having the amino acid sequence of SEQ ID NO: 15.

In one embodiment, the anti-B7-H3 antibody, or antigen binding portion thereof, comprises a heavy chain variable region comprising a CDR2 having the amino acid sequence of SEQ ID NO: 140 and a light chain variable region comprising a CDR2 having the amino acid sequence of SEQ ID NO: 7.

In one embodiment, the anti-B7-H3 antibody, or antigen binding portion thereof, comprises a heavy chain variable region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 10 and a light chain variable region comprising a CDR1 having the amino acid sequence of either SEQ ID NO: 136 or 138.

In one aspect, the present invention provides an anti- B7-H3 antibody, or antigen binding portion thereof, that binds to human B7-H3 (hB7-H3), wherein the antibody, or antigen binding portion thereof, comprises a heavy chain variable region comprising a CDR3 having the amino acid sequence of SEQ ID NO: 35 and a light chain variable region comprising a CDR3 having the amino acid sequence of SEQ ID NO: 39.

In one embodiment, the anti-B7-H3 antibody, or antigen binding portion thereof, comprises a heavy chain variable region comprising a CDR2 having the amino acid sequence of SEQ ID NO: 34, and a light chain variable region comprising a CDR2 having the amino acid sequence of SEQ ID NO: 38.

In one embodiment, the anti-B7-H3 antibody, or antigen binding portion thereof, comprises a heavy chain variable region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 33 and a light chain variable region comprising a CDR1 having the amino acid sequence of either SEQ ID NO: 37.

In one embodiment, the anti-B7-H3 antibody, or antigen binding portion thereof, is an IgG isotype.

In one embodiment, the anti-B7-H3 antibody, or antigen binding portion thereof, is an IgG1 or an IgG4 isotype.

In one embodiment, the anti-B7-H3 antibody, or antigen binding portion thereof, has a K_D of 1.5×10^{-8} or less as determined by surface plasmon resonance.

In one aspect, the present invention provides an anti-B7-H3 antibody, or antigen-binding portion thereof, that binds to hB7-H3, said antibody, or antigen-binding portion thereof, comprising either (i) a heavy chain variable region comprising a CDR set of SEQ ID NOs: 10, 11, and 12, and a light chain variable region comprising a CDR set of SEQ ID NOs: 14, 7, and 15, or (ii) a heavy chain variable region comprising a CDR set of SEQ ID NOs: 33, 34, and 35, and a light chain variable region comprising a CDR set of SEQ ID NOs: 37, 38, and 39.

In one aspect, the present invention provides an anti-B7-H3 antibodythat binds to human B7-H3 (hB7-H3), wherein the antibody comprises a heavy chain variable region comprising a CDR3 having the amino acid sequence of SEQ ID NO: 12 and a light chain variable region comprising a CDR3 having the amino acid sequence of SEQ ID NO: 15.

In one embodiment, the anti-B7-H3 antibody comprises a heavy chain variable region comprising a CDR2 having the amino acid sequence of SEQ ID NO: 140 and a light chain variable region comprising a CDR2 having the amino acid sequence of SEQ ID NO: 7.

In one embodiment, the anti-B7-H3 antibody comprises a heavy chain variable region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 10 and a light chain variable region comprising a CDR1 having the amino acid sequence of either SEQ ID NO: 136 or 138.

In one aspect, the present invention provides an anti- B7-H3 antibody that binds to human B7-H3 (hB7-H3), wherein the antibody, or antigen binding portion thereof, comprises a heavy chain variable region comprising a CDR3 having the amino acid sequence of SEQ ID NO: 35 and a light chain variable region comprising a CDR3 having the amino acid sequence of SEQ ID NO: 39.

In one embodiment, the anti-B7-H3 antibody comprises a heavy chain variable region comprising a CDR2 having the amino acid sequence of SEQ ID NO: 34, and a light chain variable region comprising a CDR2 having the amino acid sequence of SEQ ID NO: 38.

In one embodiment, the anti-B7-H3 antibody comprises a heavy chain variable region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 33 and a light chain variable region comprising a CDR1 having the amino acid sequence of either SEQ ID NO: 37.

In one embodiment, the anti-B7-H3 antibody is an IgG isotype.

In one embodiment, the anti-B7-H3 antibody is an IgG1 or an IgG4 isotype.

In one embodiment, the anti-B7-H3 antibody has a K_D of 1.5×10^{-8} or less as determined by surface plasmon resonance.

In one aspect, the present invention provides an anti-B7-H3 antibody that binds to hB7-H3, said antibody comprising either (i) a heavy chain variable region comprising a CDR set of SEQ ID NOs: 10, 11, and 12, and a light chain variable region comprising a CDR set of SEQ ID NOs: 14, 7,

and 15, or (ii) a heavy chain variable region comprising a CDR set of SEQ ID NOs: 33, 34, and 35, and a light chain variable region comprising a CDR set of SEQ ID NOs: 37, 38, and 39.

In one embodiment, the anti-B7-H3 antibody, or antigen binding portion thereof, is humanized.

In one embodiment, the anti-B7-H3 antibody, or antigen binding portion thereof, further comprises a human acceptor framework. In one embodiment, the human acceptor framework comprises an amino acid sequence selected from the group consisting of SEQ ID Nos: 155,156, 164, 165, 166, and 167. In one embodiment, the human acceptor framework comprises at least one framework region amino acid substitution. In one embodiment, the amino acid sequence of the framework is at least 65% identical to the sequence of said human acceptor framework and comprises at least 70 amino acid residues identical to said human acceptor framework.

In one embodiment, the human acceptor framework comprises at least one framework region amino acid substitution at a key residue, said key residue selected from the group consisting of a residue adjacent to a CDR; a glycosylation site residue; a rare residue; a residue capable of interacting with human B7-H3; a residue capable of interacting with a CDR; a canonical residue; a contact residue between heavy chain variable region and light chain variable region; a residue within a Vernier zone; and a residue in a region that overlaps between a Chothia-defined variable heavy chain CDR1 and a Kabat-defined first heavy chain framework. In one embodiment, the key residue is selected from the group consisting of 48H, 67H, 69H, 71H, 73H, 94H, and 2L. In one embodiment, the key residue substitution is in the variable heavy chain region and is selected from the group consisting of M48I, V67A, I69L, A71V, K73R, and R94G. In one embodiment, the key residue substitution is in the variable light chain region and is I2V.

In one aspect, the present invention provides an anti-B7-H3 antibody, or antigen-binding portion thereof, that binds to hB7-H3 comprising a heavy chain variable region comprising a CDR set of SEQ ID NOs: 25, 26, and 27, and a light chain variable region comprising a CDR set of SEQ ID NOs: 29, 30, and 31. In one embodiment, the anti-B7-H3 antibody, or antigen binding portion thereof, is humanized. In one embodiment, the anti-B7-H3 antibody, or antigen binding portion thereof, further comprises a human acceptor framework.

In one embodiment, the human acceptor framework comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 155 to 158. In one embodiment, the human acceptor framework comprises at least one framework region amino acid substitution. In one embodiment, the amino acid sequence of the framework is at least 65% identical to the sequence of said human acceptor framework and comprises at least 70 amino acid residues identical to said human acceptor framework. In one embodiment, the amino acid sequence of the framework is at least 85% identical, 90% identical, 95% identical, 96% identical, 97% identical, 98% identical, or 99% identical to the sequence of the human acceptor framework and comprises at least 70, at

least 75, at least 80, or at least 85 amino acid residues identical to the human acceptor framework.

In one embodiment, the human acceptor framework comprises at least one framework region amino acid substitution at a key residue, said key residue selected from the group consisting of: a residue adjacent to a CDR; a glycosylation site residue; a rare residue; a residue capable of interacting with human B7-H3; a residue capable of interacting with a CDR; a canonical residue; a contact residue between heavy chain variable region and light chain variable region; a residue within a Vernier zone; and a residue in a region that overlaps between a Chothia-defined variable heavy chain CDR1 and a Kabat-defined first heavy chain framework. In one embodiment, the key residue is selected from the group consisting of 69H, 46L, 47L, 64L, and 71L. In one embodiment, the key residue substitution is in the variable heavy chain region and is L69I. In one embodiment, the key residue substitution is in the variable light chain region and is selected from the group consisting of L46P, L47W, G64V, and F71H.

In one aspect, the present invention provides an anti-hB7-H3 antibody, or antigen-binding portion thereof, comprising a heavy chain CDR1 comprising an amino acid sequence as set forth in SEQ ID NO: 10, a heavy chain CDR2 comprising an amino acid sequence as set forth in SEQ ID NO: 140, a heavy chain CDR3 comprising an amino acid sequence as set forth in SEQ ID NO: 12, a light chain CDR1 comprising an amino acid sequence as set forth in SEQ ID NO: 136 or 138, a light chain CDR2 comprising an amino acid sequence as set forth in SEQ ID NO: 7, and a light chain CDR3 comprising an amino acid sequence as set forth in SEQ ID NO: 15.

In another aspect, the present invention provides an anti-hB7-H3 antibody, or antigen-binding portion thereof, comprising a heavy chain CDR1 comprising an amino acid sequence as set forth in SEQ ID NO: 33, a heavy chain CDR2 comprising an amino acid sequence as set forth in SEQ ID NO: 34, a heavy chain CDR3 comprising an amino acid sequence as set forth in SEQ ID NO: 35, a light chain CDR1 comprising an amino acid sequence as set forth in SEQ ID NO: 37, a light chain CDR2 comprising an amino acid sequence as set forth in SEQ ID NO: 38, and a light chain CDR3 comprising an amino acid sequence as set forth in SEQ ID NO: 39.

In one embodiment, the anti-hB7-H3 antibody, or antigen-binding portion thereof, comprises a heavy chain variable domain comprising an amino acid sequence set forth in SEQ ID NO: 139 and a light chain variable domain comprising an amino acid sequence set forth in SEQ ID NO: 135.

In one embodiment, the anti-hB7-H3 antibody, or antigen-binding portion thereof, comprises a heavy chain comprising an amino acid sequence having at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 139, and/or a light chain comprising an amino acid sequence having at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 135.

In one embodiment, the anti-hB7-H3 antibody, or antigen-binding portion thereof, comprises a heavy chain variable domain comprising an amino acid sequence set forth in SEQ ID NO: 139 and a light chain variable domain comprising an amino acid sequence set forth in SEQ ID NO: 137.

In one embodiment, the anti-hB7-H3 antibody, or antigen-binding portion thereof, comprises a heavy chain comprising an amino acid sequence having at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 139, and/or a light chain comprising an amino acid sequence having at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 137.

In one embodiment, the anti-hB7-H3 antibody, or antigen-binding portion thereof, comprises a heavy chain variable domain comprising an amino acid sequence set forth in SEQ ID NO: 147 and a light chain variable domain comprising an amino acid sequence set forth in SEQ ID NO: 144.

In one embodiment, the anti-hB7-H3 antibody, or antigen-binding portion thereof, comprises a heavy chain comprising an amino acid sequence having at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 147, and/or a light chain comprising an amino acid sequence having at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 144.

In one aspect, the present invention provides an anti-hB7-H3 antibody comprising a heavy chain CDR1 comprising an amino acid sequence as set forth in SEQ ID NO: 10, a heavy chain CDR2 comprising an amino acid sequence as set forth in SEQ ID NO: 140, a heavy chain CDR3 comprising an amino acid sequence as set forth in SEQ ID NO: 12, a light chain CDR1 comprising an amino acid sequence as set forth in SEQ ID NO: 136 or 138, a light chain CDR2 comprising an amino acid sequence as set forth in SEQ ID NO: 7, and a light chain CDR3 comprising an amino acid sequence as set forth in SEQ ID NO: 15.

In another aspect, the present invention provides an anti-hB7-H3 antibody comprising a heavy chain CDR1 comprising an amino acid sequence as set forth in SEQ ID NO: 33, a heavy chain CDR2 comprising an amino acid sequence as set forth in SEQ ID NO: 34, a heavy chain CDR3 comprising an amino acid sequence as set forth in SEQ ID NO: 35, a light chain CDR1 comprising an amino acid sequence as set forth in SEQ ID NO: 37, a light chain CDR2 comprising an amino acid sequence as set forth in SEQ ID NO: 38, and a light chain CDR3 comprising an amino acid sequence as set forth in SEQ ID NO: 39.

In one embodiment, the anti-hB7-H3 antibody comprises a heavy chain variable domain comprising an amino acid sequence set forth in SEQ ID NO: 139 and a light chain variable domain comprising an amino acid sequence set forth in SEQ ID NO: 135.

In one embodiment, the anti-hB7-H3 antibody comprises a heavy chain comprising an amino acid sequence having at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 139, and/or a light chain comprising an amino acid sequence having at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 135.

In one embodiment, the anti-hB7-H3 antibody comprises a heavy chain variable domain comprising an amino acid sequence set forth in SEQ ID NO: 139 and a light chain variable domain comprising an amino acid sequence set forth in SEQ ID NO: 137.

In one embodiment, the anti-hB7-H3 antibody comprises a heavy chain comprising an amino acid sequence having at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 139, and/or a light chain comprising an amino acid sequence having at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 137.

In one embodiment, the anti-hB7-H3 antibody comprises a heavy chain variable domain comprising an amino acid sequence set forth in SEQ ID NO: 147 and a light chain variable domain comprising an amino acid sequence set forth in SEQ ID NO: 144.

In one embodiment, the anti-hB7-H3 antibody comprises a heavy chain comprising an amino acid sequence having at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 147, and/or a light chain comprising an amino acid sequence having at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 144.

In one embodiment, the anti-hB7-H3 antibody, or antigen-binding portion thereof, comprises a heavy chain CDR set corresponding to antibody huAb13v1, and a light chain CDR set corresponding to antibody huAb13v1. In one embodiment, the anti-hB7-H3 antibody, or antigen-binding portion thereof, comprises a heavy chain variable region corresponding to antibody huAb13v1, and a light chain variable region corresponding to antibody huAb13v1.

In one embodiment, the anti-hB7-H3 antibody, or antigen-binding portion thereof, comprises a heavy chain CDR set corresponding to antibody huAb3v2.5, and a light chain CDR set corresponding to antibody huAb3v2.5. In one embodiment, the anti-hB7-H3 antibody, or antigen-binding portion thereof, comprises a heavy chain variable region corresponding to antibody huAb3v2.5, and a light chain variable region corresponding to antibody huAb3v2.5.

In one embodiment, the antibody, or antigen binding portion thereof, binds cynomolgus B7-H3.

In one embodiment, the antibody, or antigen binding portion thereof, has a dissociation constant (K_D) to hB7-H3 selected from the group consisting of: at most about 10^{-7} M; at most about 10^{-8} M; at most about 10^{-9} M; at most about 10^{-10} M; at most about 10^{-11} M; at most about 10^{-12} M; and at most 10^{-13} M.

In one embodiment, the antibody, or antigen binding portion thereof, comprises a heavy chain immunoglobulin constant domain of a human IgM constant domain, a human IgG1 constant domain, a human IgG2 constant domain, a human IgG3 constant domain, a human IgG4 constant domain, a human IgA constant domain, or a human IgE constant domain.

In one embodiment, the antibody is an IgG having four polypeptide chains which are two heavy chains and two light chains.

In one embodiment, the antibody, or antigen-binding portion thereof, comprises the heavy chain immunoglobulin constant region domain is a human IgG1 constant domain. In one embodiment, the human IgG1 constant domain comprises an amino acid sequence of SEQ ID NO: 159 or SEQ ID NO: 160.

In one aspect, the present invention provides an isolated antibody, or antigen binding portion thereof, that binds to human B7-H3 (hB7-H3), wherein the antibody, or antigen binding portion thereof, comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 168 and a light chain comprising the amino acid sequence of SEQ ID NO: 169.

In one aspect, the present invention provides an isolated antibody, or antigen binding portion thereof, that binds to human B7-H3 (hB7-H3), wherein the antibody, or antigen binding portion thereof, comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 170 and a light chain comprising the amino acid sequence of SEQ ID NO: 171.

In one aspect, the present invention provides an isolated antibody, or antigen binding portion thereof, that binds to human B7-H3 (hB7-H3), wherein the antibody, or antigen binding portion thereof, comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 172 and a light chain comprising the amino acid sequence of SEQ ID NO: 173.

In one embodiment, the antibody, or antigen binding portion thereof, further comprises a light chain immunoglobulin constant domain comprising a human Ig kappa constant domain or a human Ig lambda constant domain.

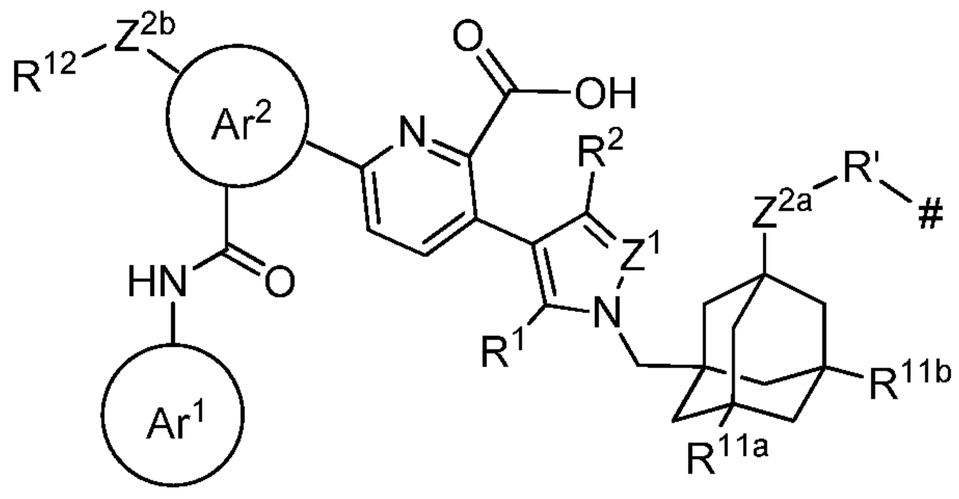
In one embodiment, the anti-hB7-H3 antibody, or antigen-binding portion thereof, competes with the antibody, or antigen binding portion thereof, of any one of the anti-hB7-H3 antibodies, or antigen-binding portions thereof, disclosed herein.

In one aspect, the present invention provides a pharmaceutical composition comprising the anti-hB7-H3 antibody, or antigen binding portion thereof, as disclosed herein, and a pharmaceutically acceptable carrier.

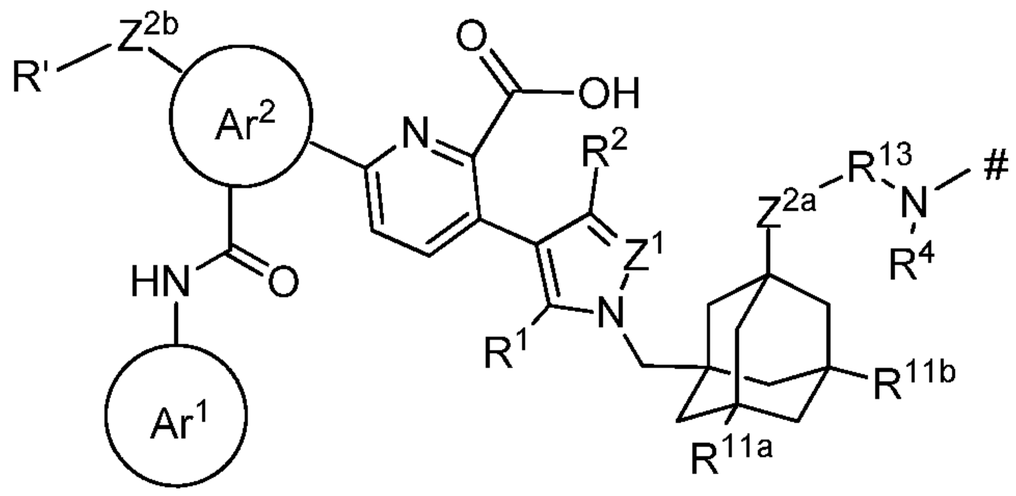
In another aspect, the present invention provides an anti-hB7-H3 Antibody Drug Conjugate (ADC) comprising an anti-hB7-H3 antibody disclosed herein conjugated to a drug via a linker. In one embodiment, the drug is an auristatin or a pyrrolobenzodiazepine (PBD). In one embodiment, the drug is a Bcl-xL inhibitor.

In one aspect, the present invention provides an anti-hB7-H3 antibody drug conjugate (ADC) comprising a drug linked to an anti-human B7-H3 (hB7-H3) antibody by way of a linker, wherein the drug is a Bcl-xL inhibitor according to structural formula (IIa), (IIb), (IIc), or (IId):

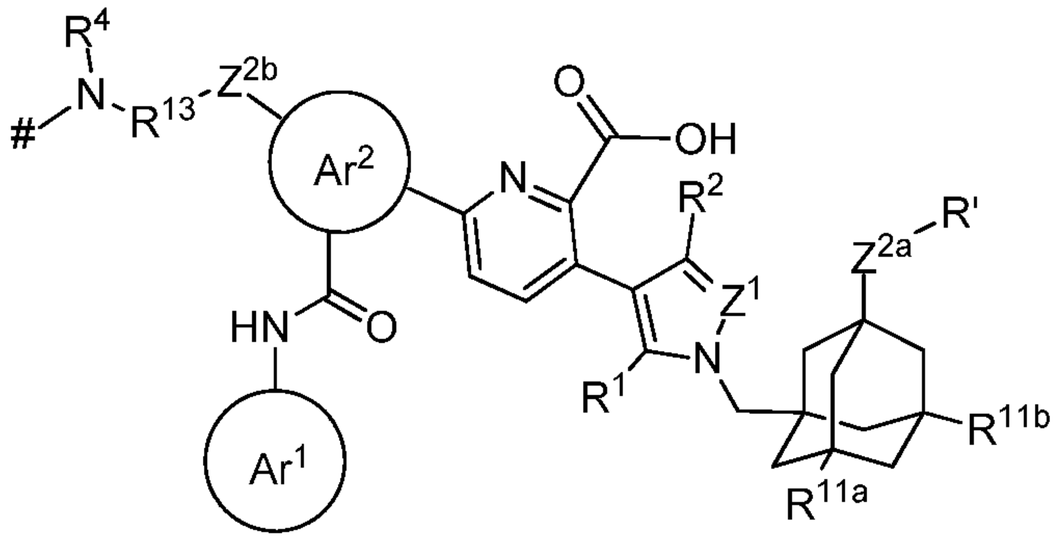
(IIa)



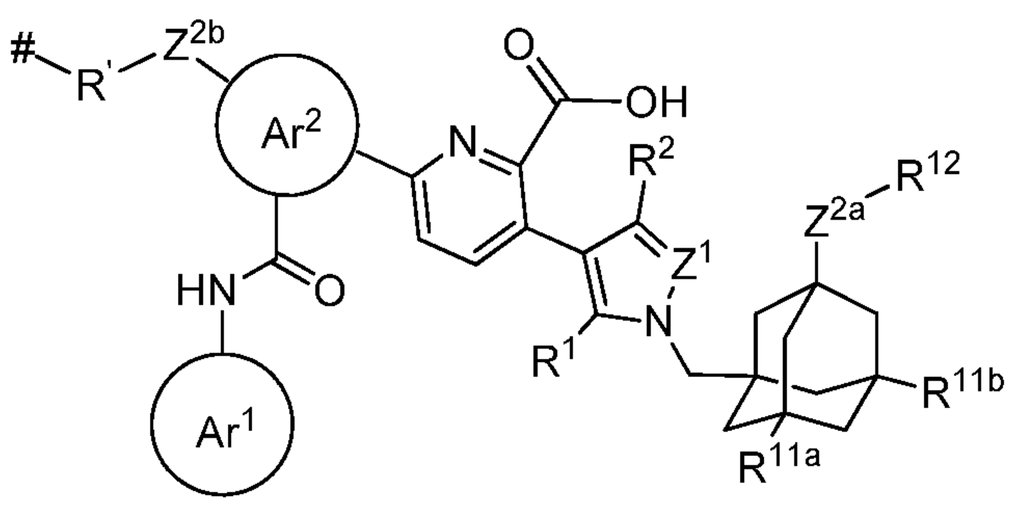
(IIb)



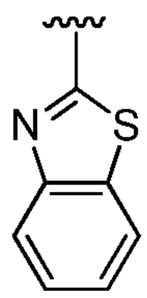
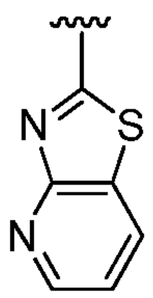
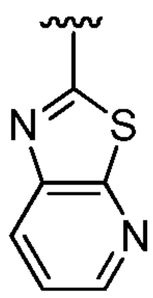
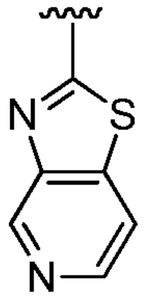
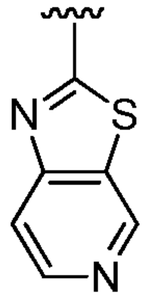
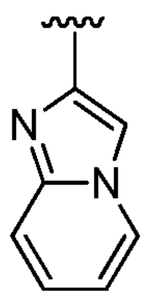
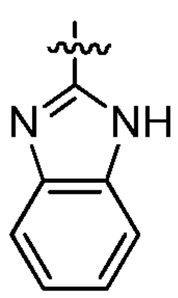
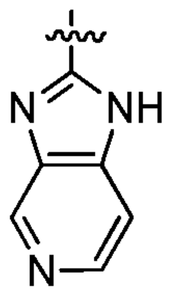
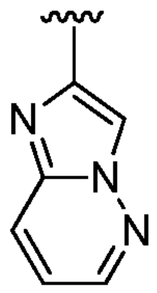
(IIc)

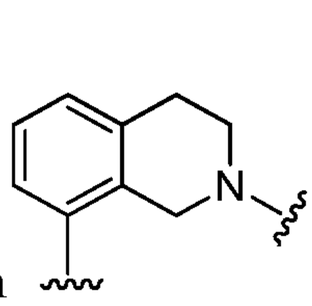
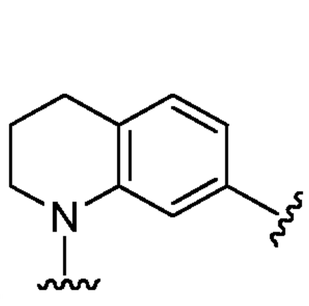
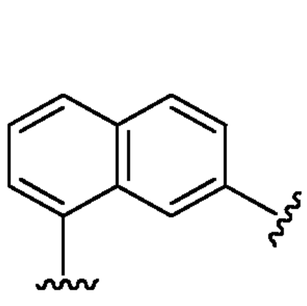
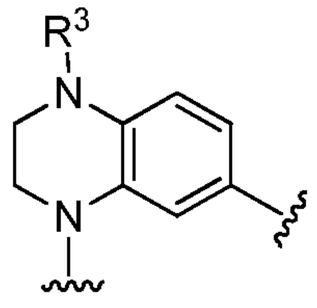
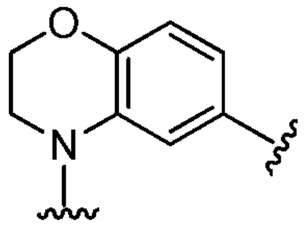
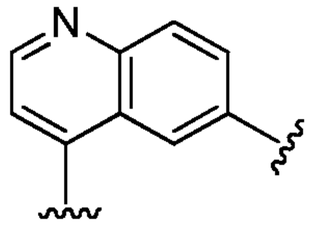
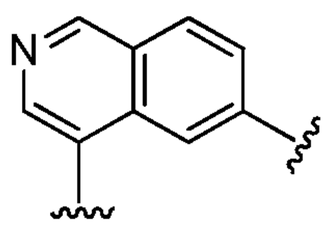
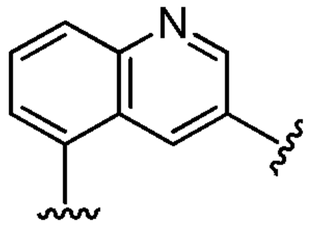
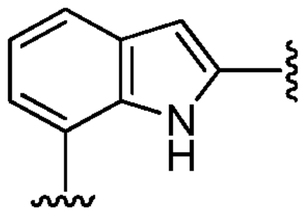
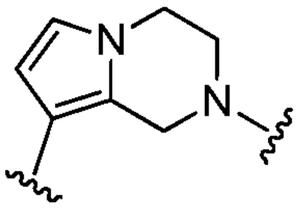
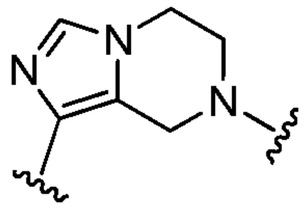
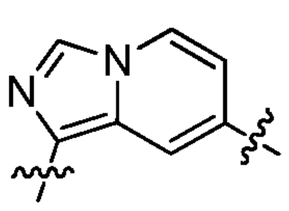


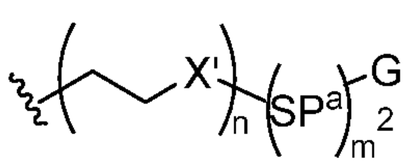
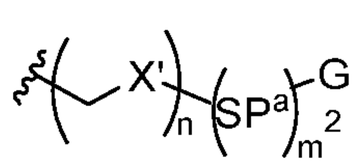
(IId)



wherein:

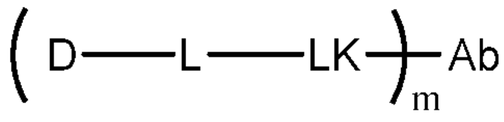
Ar^1 is selected from  ,  ,  ,  ,  ,  ,  ,  , and  and is optionally substituted with one or more substituents independently selected from halo, hydroxy, nitro, lower alkyl, lower heteroalkyl, C_{1-4}alkoxy, amino, cyano and halomethyl;

Ar^2 is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  or an N-oxide thereof, and is optionally substituted with one or more substituents independently selected from halo, hydroxy, nitro, lower alkyl, lower heteroalkyl, C_{1-4}alkoxy, amino, cyano and halomethyl, wherein the R^{12}-Z^{2b}-, R'-Z^{2b}-, #-N(R^4)-R^{13}-Z^{2b}-, or #-R'-Z^{2b}- substituents are attached to Ar^2 at any Ar^2 atom capable of being substituted; Z^1 is selected from N, CH, C-halo, C-CH_3 and C-CN; Z^{2a} and Z^{2b} are each , independently from one another, selected from a bond, NR^6, $CR^{6a}R^{6b}$, O, S, S(O), $S(O)_2$, -NR^6C(O)-,-NR^{6a}C(O)NR^{6b}-, and –NR^6C(O)O-;

R' is  or  , wherein #, where attached to R', is attached to R' at any R' atom capable of being substituted; X' is selected at each occurrence from -N(R^{10})- , -N(R^{10})C(O)-, -N(R^{10})$S(O)_2$-, -$S(O)_2$N(R^{10})-, and -O-; n is selected from 0-3; R^{10} is independently selected at each occurrence from hydrogen, lower alkyl, heterocycle, aminoalkyl, G-alkyl, and -$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$-NH_2; G at each occurrence is independently selected from a polyol, a polyethylene glycol with between 4 and 30 repeating units, a salt and a moiety that is charged at physiological pH; SP^a is independently selected at each occurrence from oxygen, -$S(O)_2$N(H)-, -N(H)$S(O)_2$-, -N(H)C(O)-, -C(O)N(H) -, -N(H)- , arylene, heterocyclene, and optionally substituted methylene; wherein methylene is optionally substituted with one or more of -NH$(CH_2)_2$G, NH_2, C_{1-}

$_{8}$alkyl, and carbonyl; m^2 is selected from 0-12; R^1 is selected from hydrogen, methyl, halo, halomethyl, ethyl, and cyano; R^2 is selected from hydrogen, methyl, halo, halomethyl and cyano; R^3 is selected from hydrogen, methyl, ethyl, halomethyl and haloethyl; R^4 is selected from hydrogen, lower alkyl and lower heteroalkyl or is taken together with an atom of R^{13} to form a cycloalkyl or heterocyclyl ring having between 3 and 7 ring atoms; R^6, R^{6a} and R^{6b} are each, independent from one another, selected from hydrogen, optionally substituted lower alkyl, optionally substituted lower heteroalkyl, optionally substituted cycloalkyl and optionally substituted heterocyclyl, or are taken together with an atom from R^4 and an atom from R^{13} to form a cycloalkyl or heterocyclyl ring having between 3 and 7 ring atoms; R^{11a} and R^{11b} are each, independently of one another, selected from hydrogen, halo, methyl, ethyl, halomethyl, hydroxyl, methoxy, CN, and SCH_3; R^{12} is optionally R' or is selected from hydrogen, halo, cyano, optionally substituted alkyl, optionally substituted heteroalkyl, optionally substituted heterocyclyl, and optionally substituted cycloalkyl; R^{13} is selected from optionally substituted C_{1-8} alkylene, optionally substituted heteroalkylene, optionally substituted heterocyclene, and optionally substituted cycloalkylene; and # represents a point of attachment to a linker; and wherein the anti-hB7-H3 antibody binds to B7-H3 (SEQ ID NO: 149) with a dissociation constant (K_d) of about 1 x 10^{-6} M or less. In a further embodiment, the antibody comprises a heavy chain variable domain comprising the amino acid sequence set forth in SEQ ID NO: 147 and a light chain variable domain comprising the amino acid sequence set forth in SEQ ID NO: 144; binds to B7-H3 (SEQ ID NO: 149) with a dissociation constant (K_d) of about 1 x 10^{-6} M or less, as determined by surface plasmon resonance; and/or inhibits tumor growth in an *in vivo* human small-cell lung carcinoma (SCLC) xenograft assay with a tumor growth inhibition % (TGI%) of at least about 50% relative to a human IgG antibody which is not specific for B7-H3, wherein the human IgG antibody is administered in the SCLC xenograft assay at the same dose and frequency as the anti-hB7-H3 antibody.

In one embodiment, the ADC is a compound according to structural formula (I):

(I) 

wherein D is the Bcl-xL inhibitor drug of formula (IIa), (IIb), (IIc) or (IId); L is the linker; Ab is the anti-hB7-H3 antibody; LK represents a covalent linkage linking the linker (L) to the anti-hB7-H3 antibody (Ab); and m is an integer ranging from 1 to 20.

In one embodiment, G at each occurrence is a salt or a moiety that is charged at physiological pH.

In one embodiment, G at each occurrence is a salt of a carboxylate, a sulfonate, a phosphonate, or ammonium.

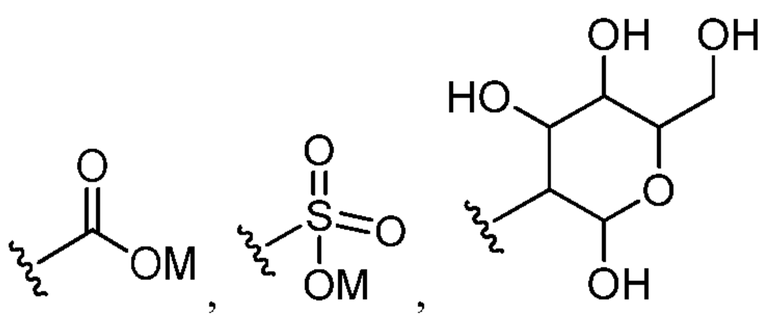
In one embodiment, G at each occurrence is a moiety that is charged at physiological pH selected from the group consisting of carboxylate, a sulfonate, a phosphonate, and an amine.

In one embodiment, G at each occurrence is a moiety containing a polyethylene glycol with between 4 and 30 repeating units, or a polyol.

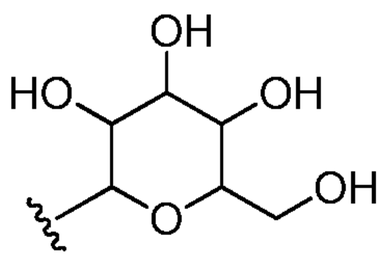
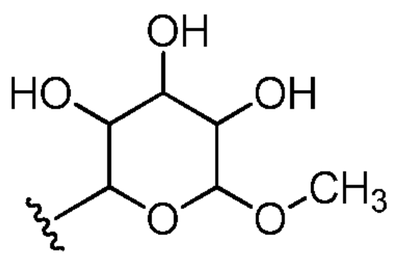
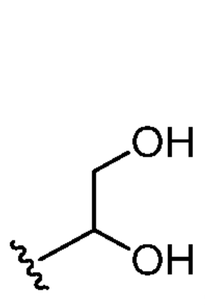
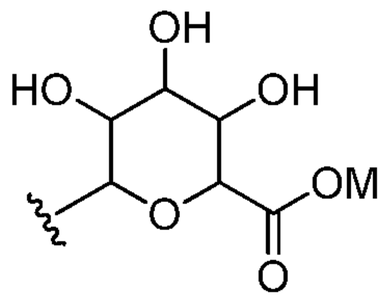
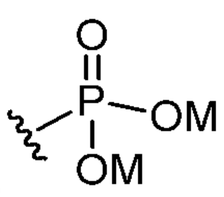
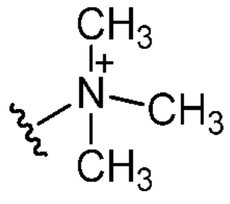
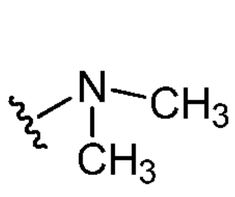
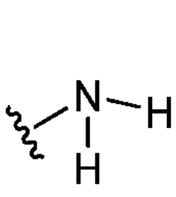
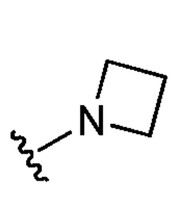
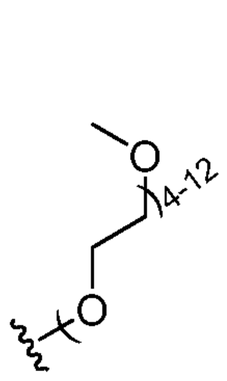
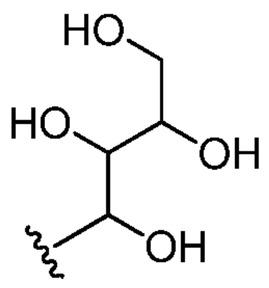
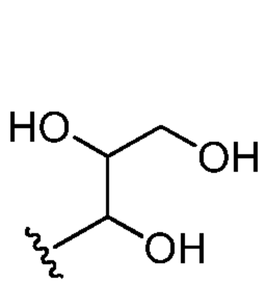
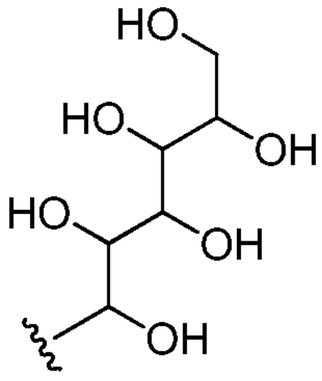
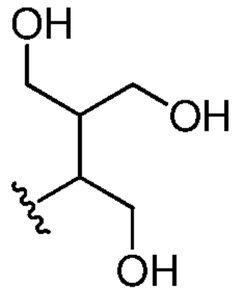
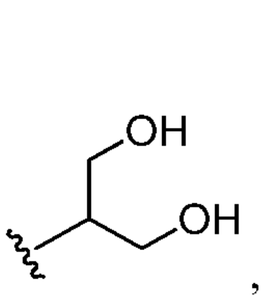
In one embodiment, the polyol is a sugar.

In one embodiment, the ADC is of the formula (IIa) or formula (IId), and R' includes at least one substitutable nitrogen suitable for attachment to a linker.

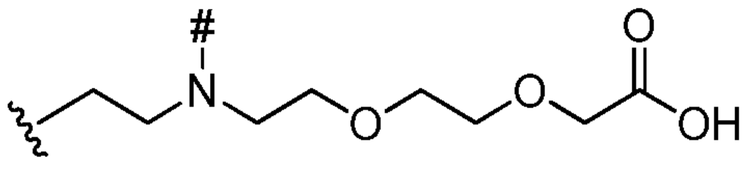
In one embodiment, G is selected at each occurrence from:

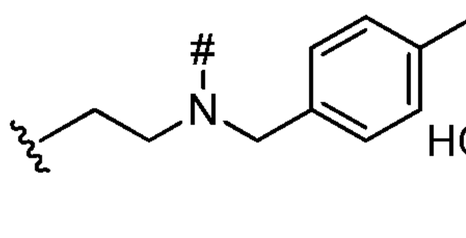
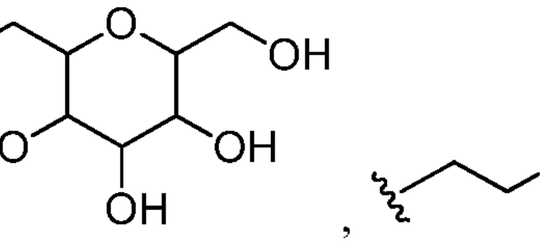

,

,

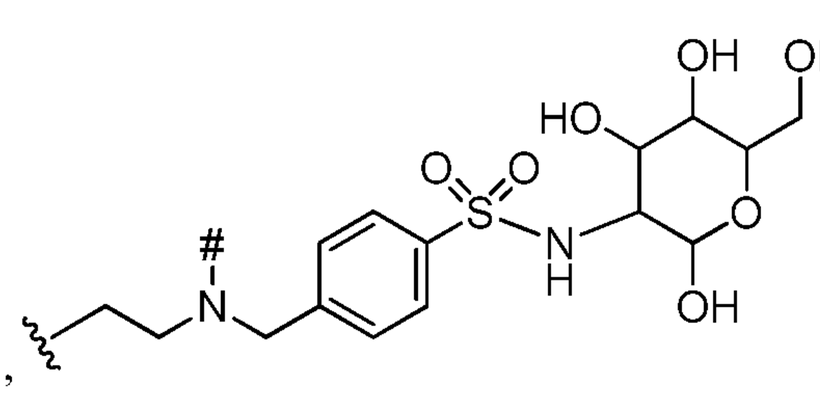
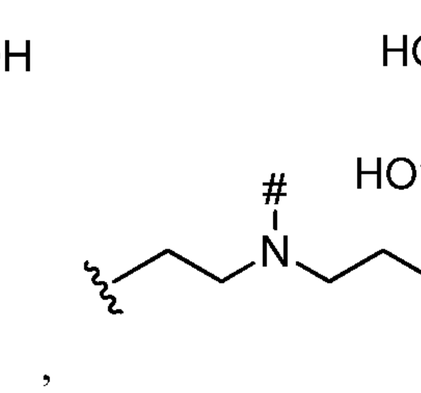
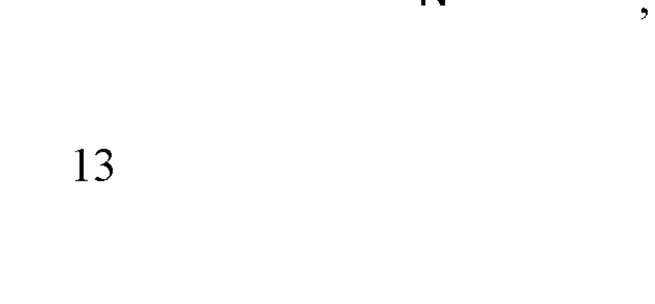
,

,

,

,

,

,

,

,

,

,

,

,

,

,

, and

,

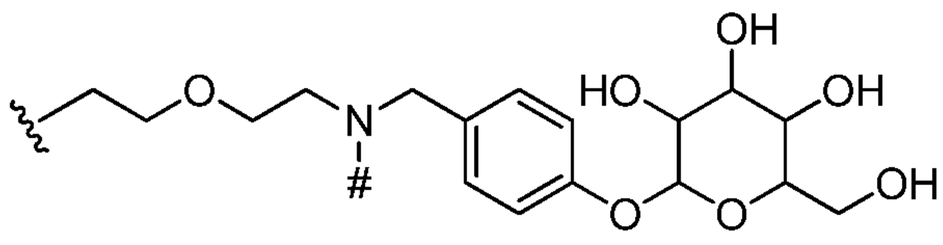
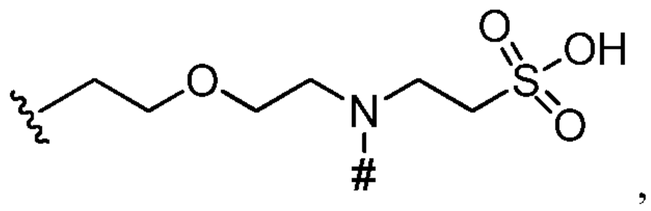
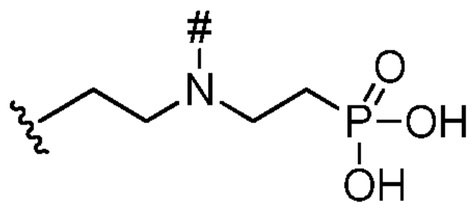
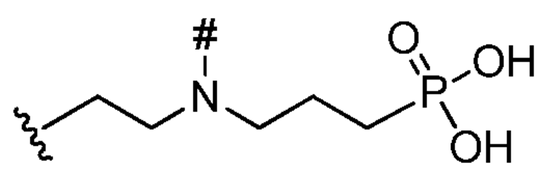
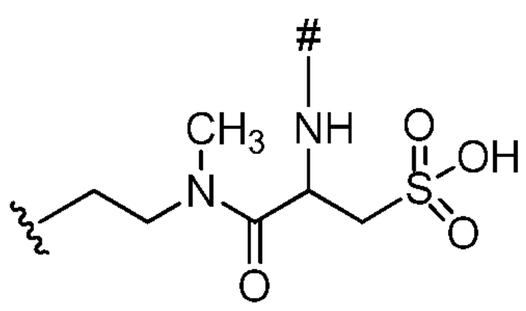
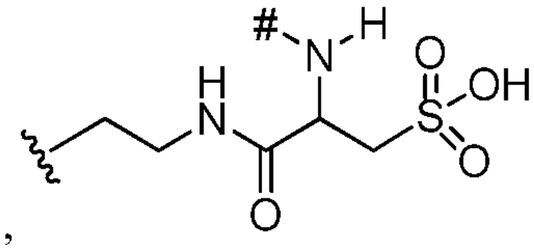
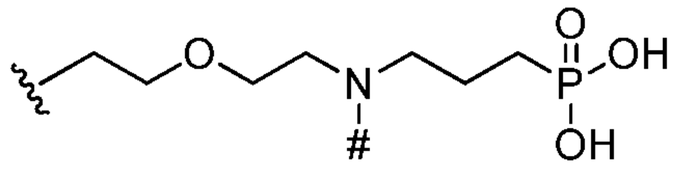
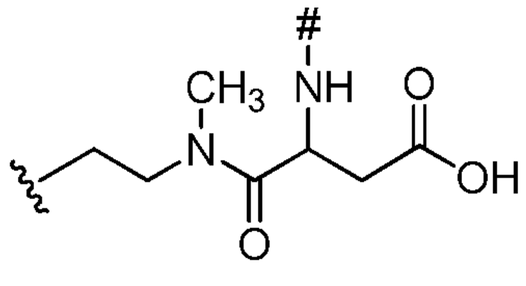
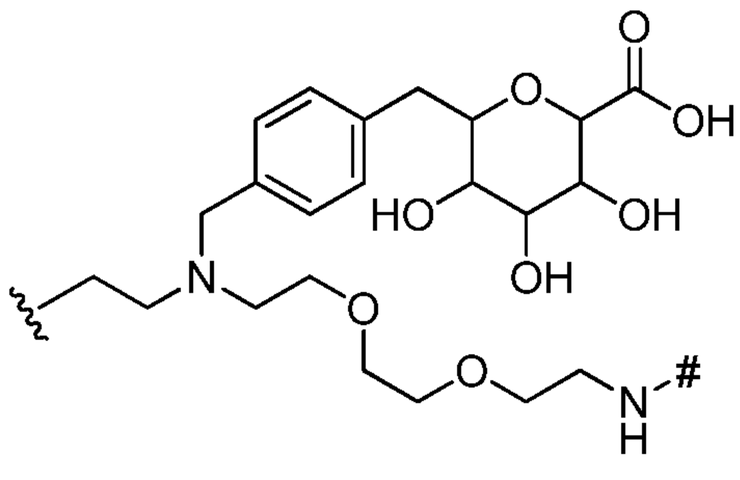
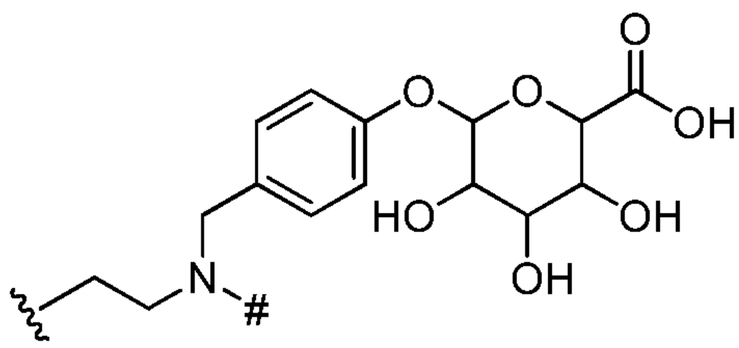
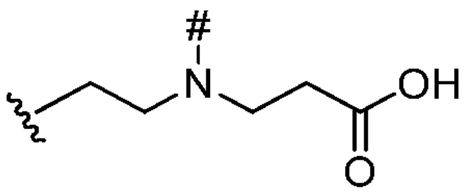
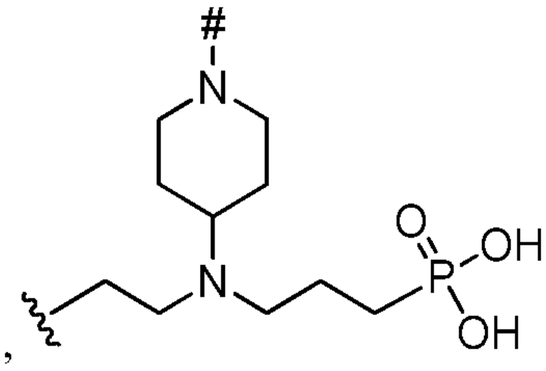
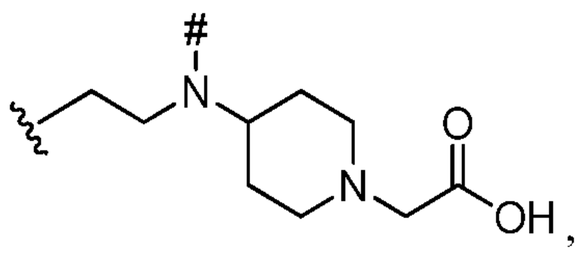
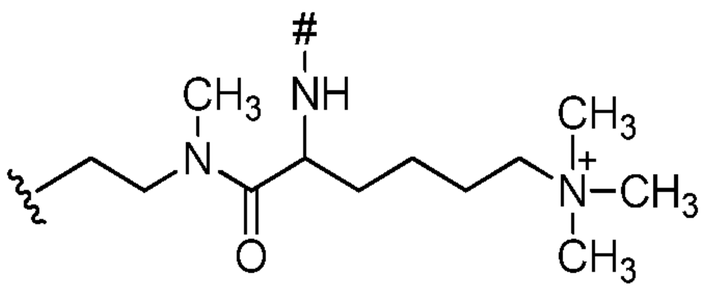
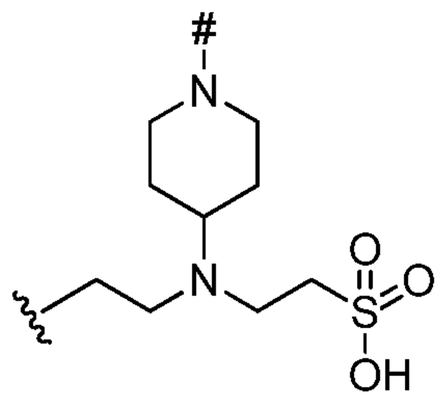
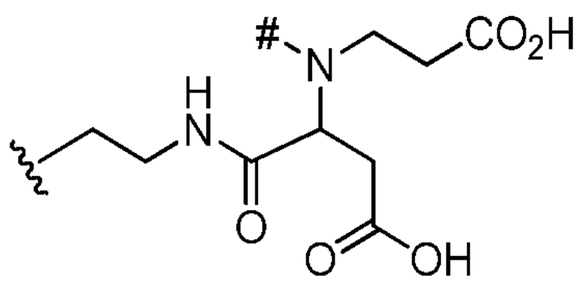
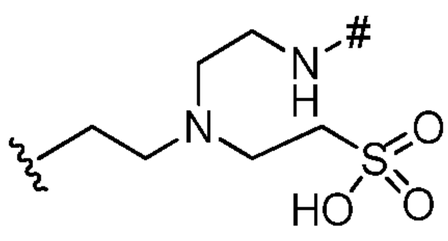
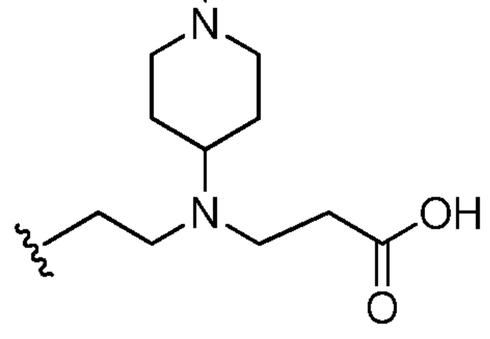
wherein M is hydrogen or a positively charged counterion.

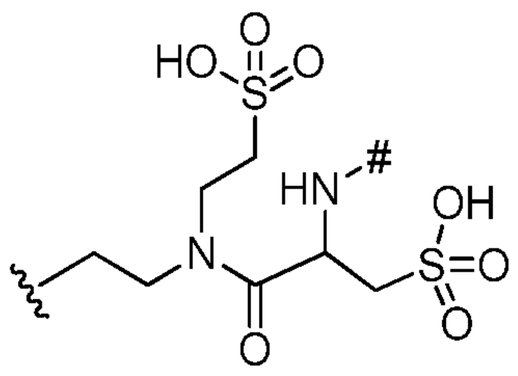
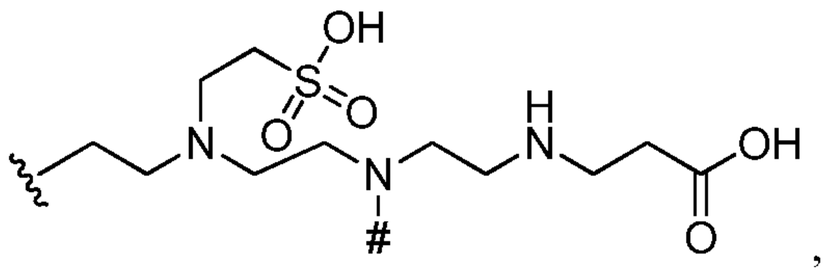
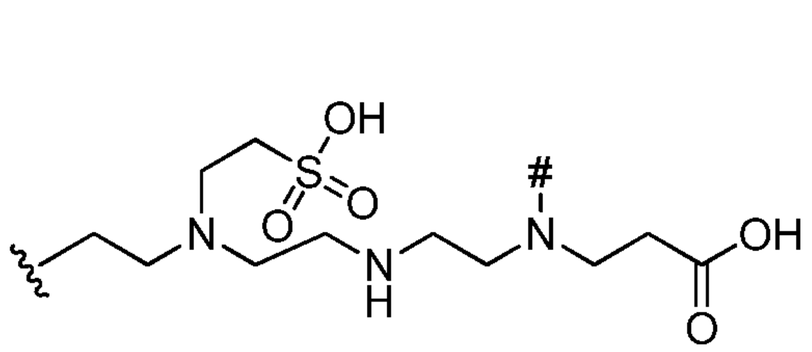
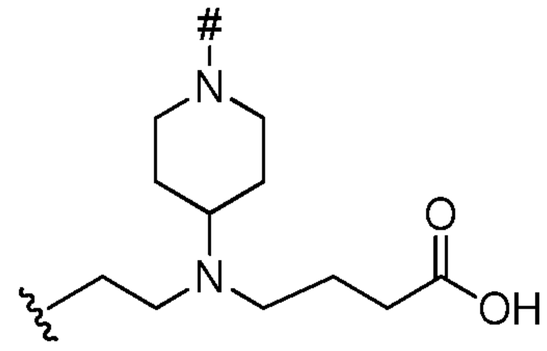
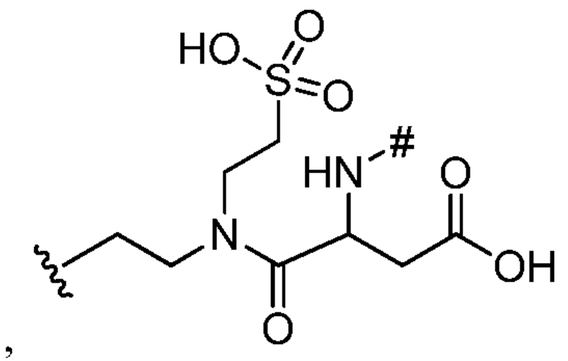
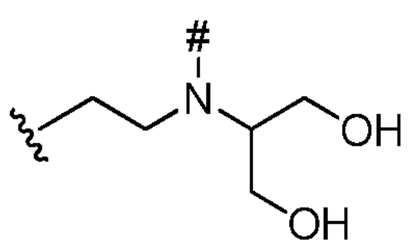
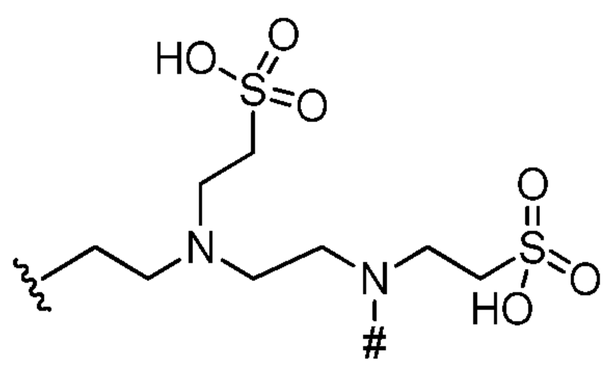
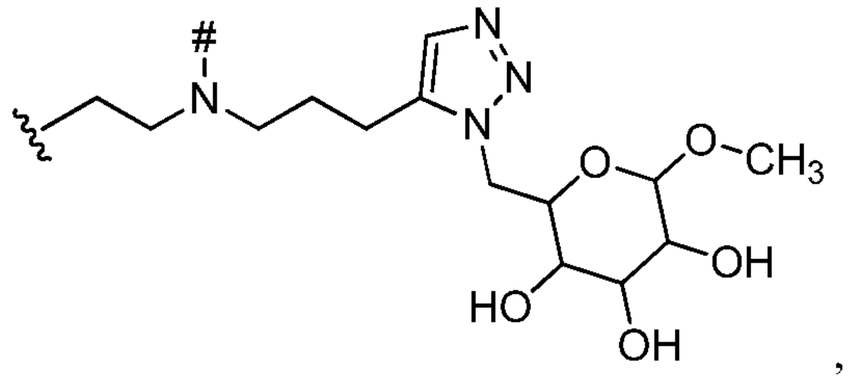
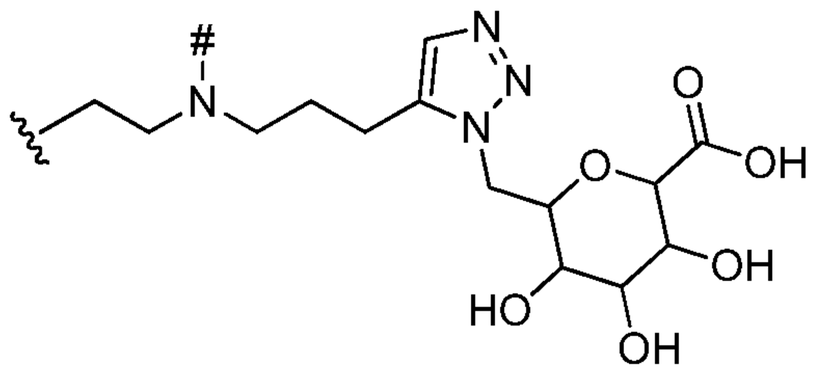
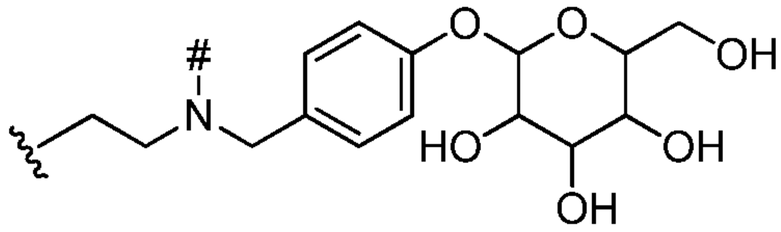
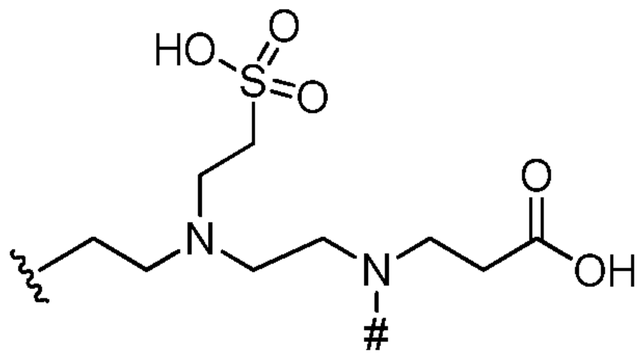
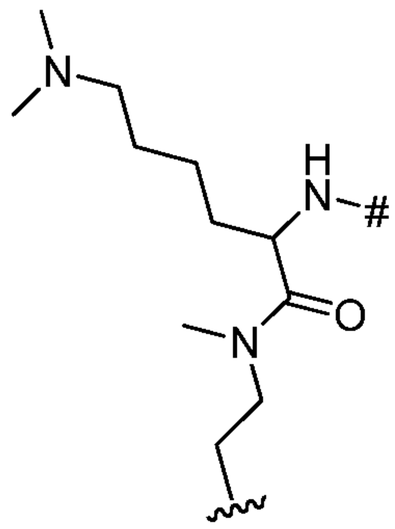
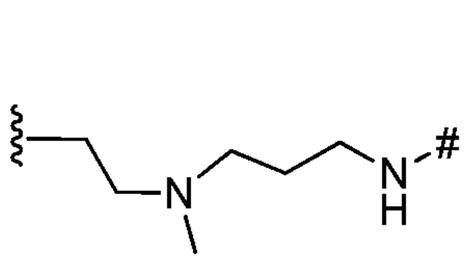
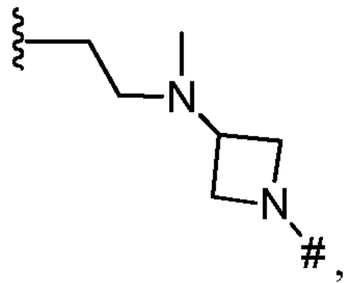
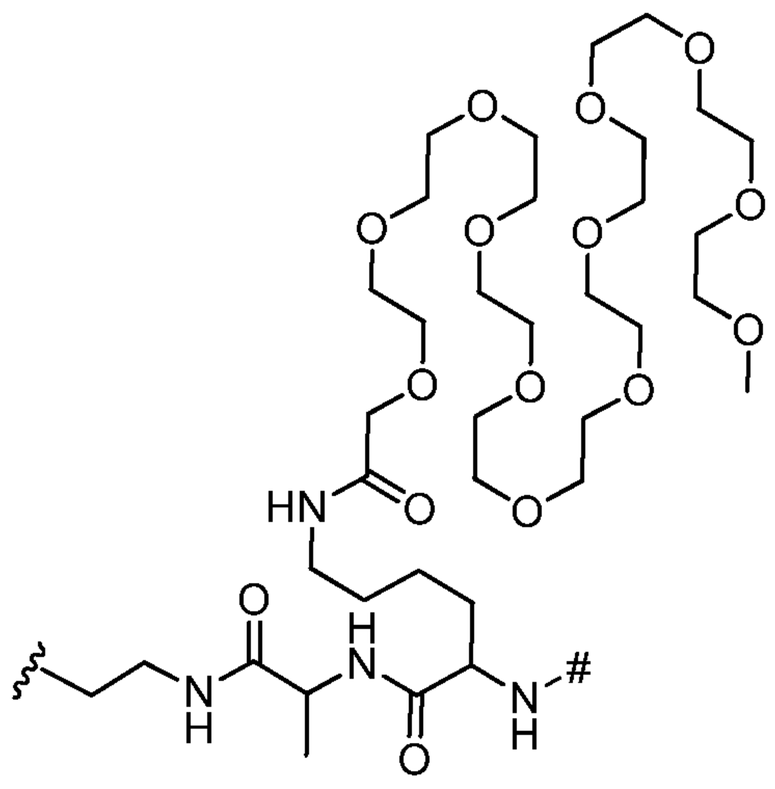
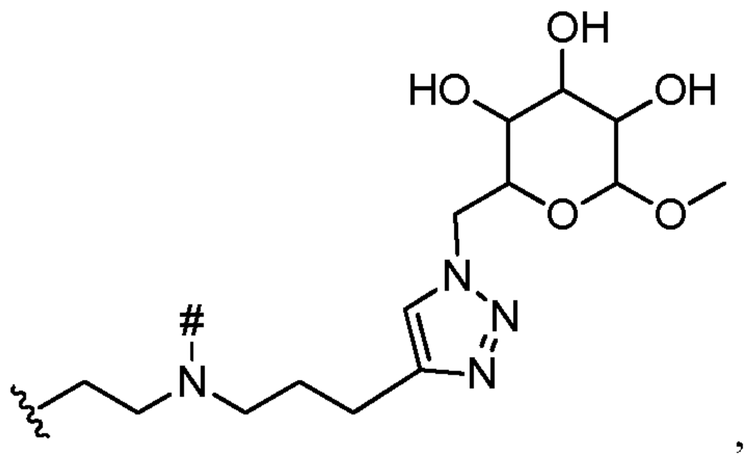
In one embodiment, R' is selected from

,

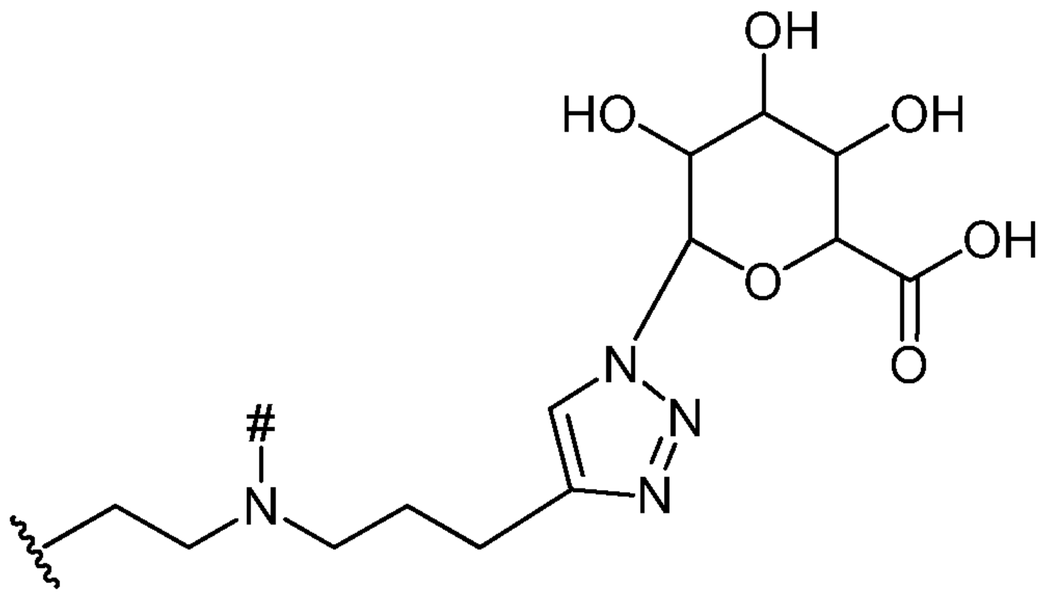
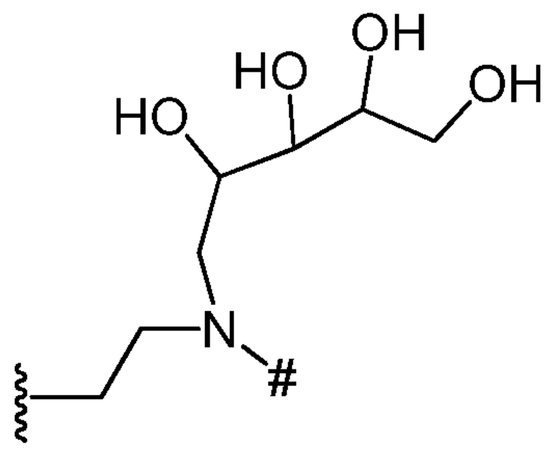
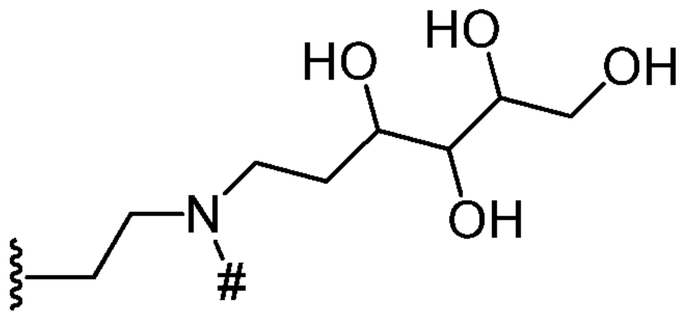
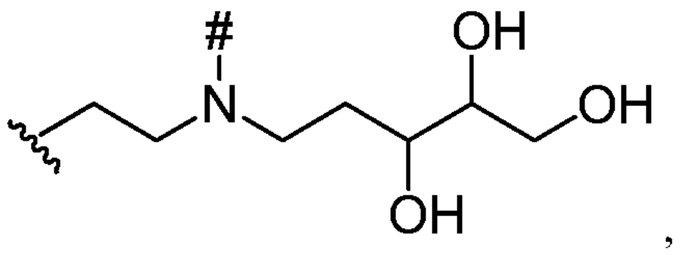
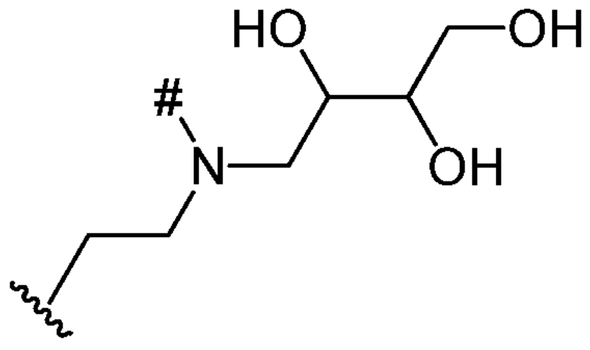
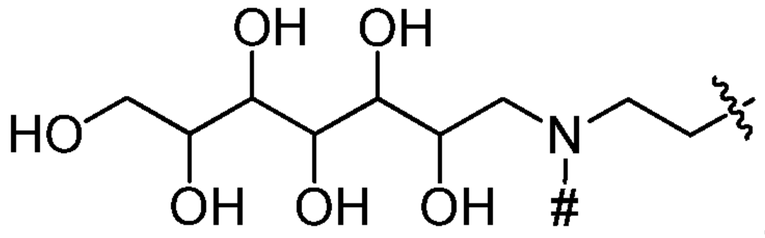
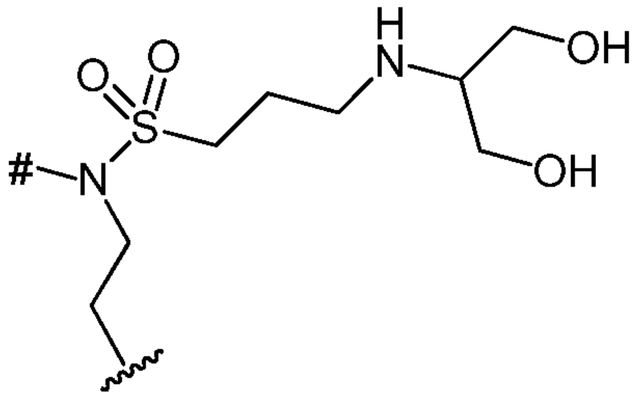
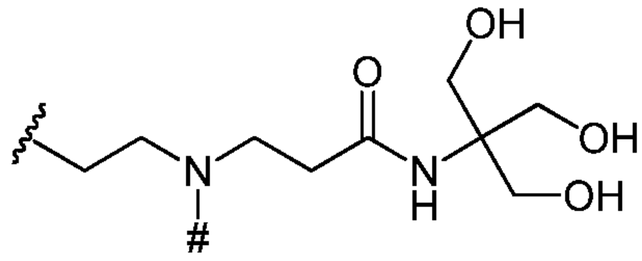
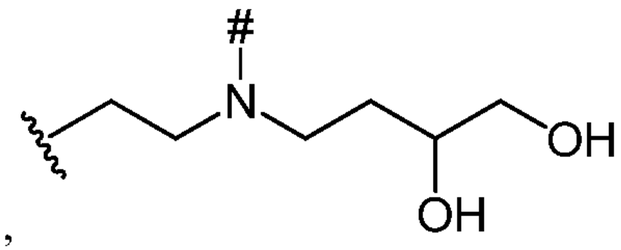
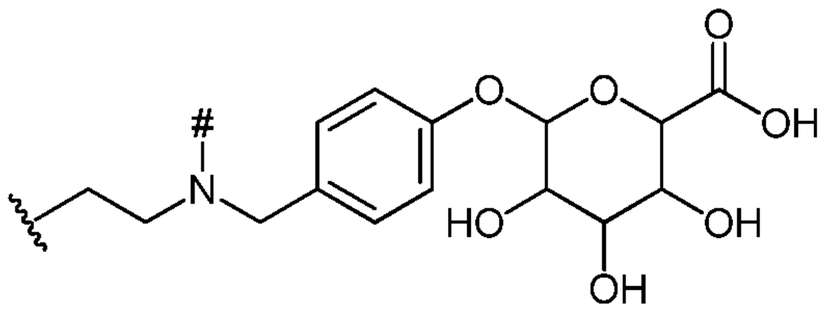
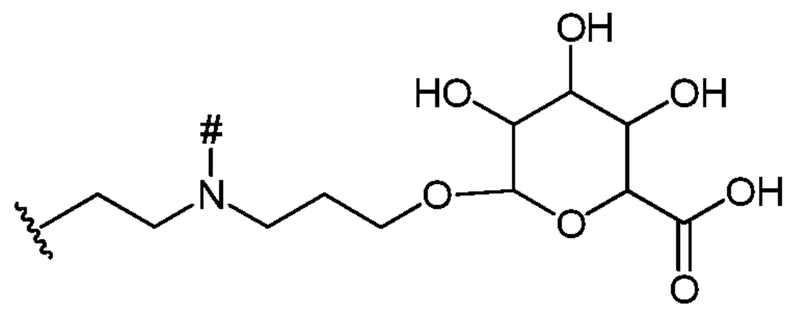
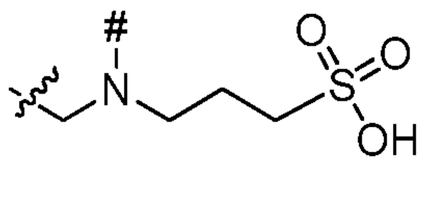

,

,

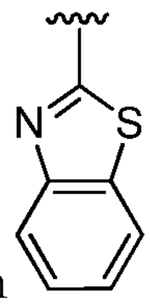
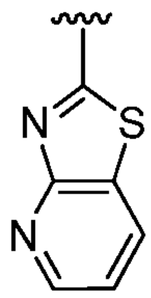
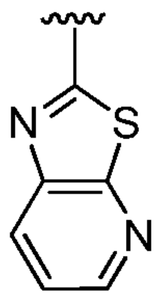
,

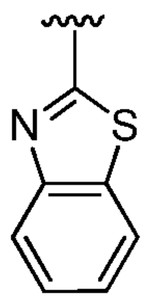

,

,

,

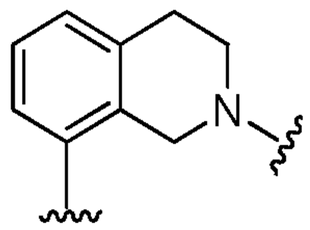

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

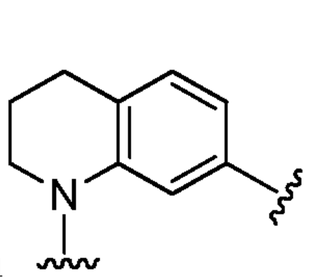
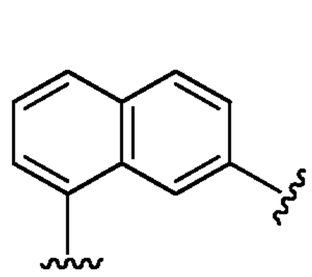
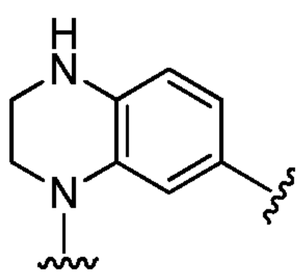
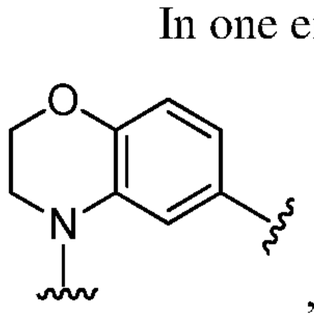
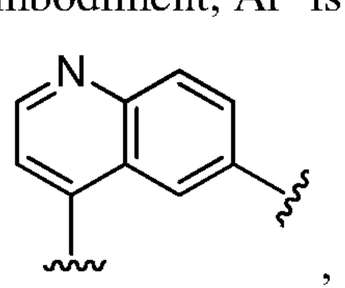
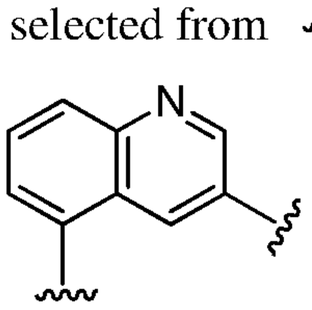
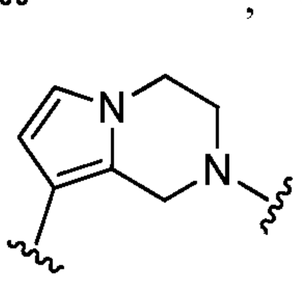
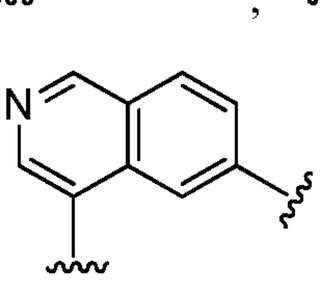
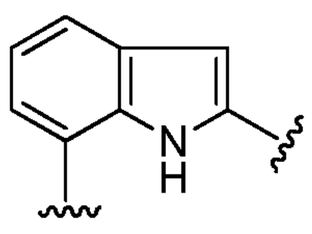
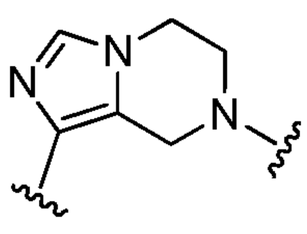

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

, and

, wherein # represents either a hydrogen atom in the Bcl-xL inhibitor drug of the ADCs of formula (IIb) or (IIc) or the point of attachment in the Bcl-xL inhibitor drug of the ADCs of formula (IIa) or (IId) to a linker L.

In one embodiment, Ar^1 is selected from  ,  , and  and is optionally substituted with one or more substituents independently selected from halo, cyano, methyl, and halomethyl.

In one embodiment, Ar^1 is  .

In one embodiment, Ar^2 is  , optionally substituted with one or more substituents.

In one embodiment, Ar^2 is selected from  ,  ,  ,  ,  ,  ,  ,  ,  and  ; and is optionally substituted with one or more substituents.

In one embodiment, Ar^2 is substituted with one or more solubilizing groups.

In one embodiment, each solubilizing group is, independently of the others, selected from a moiety containing a polyol, a polyethylene glycol with between 4 and 30 repeating units, a salt, or a moiety that is charged at physiological pH.

In one embodiment, Ar^2 is substituted with one or more solubilizing groups.

In one embodiment, each solubilizing group is, independently of the others, selected from a moiety containing a polyol, a polyethylene glycol with between 4 and 30 repeating units, a salt, or a moiety that is charged at physiological pH.

In one embodiment, Z^1 is N.

In one embodiment, Z^{2a} is O.

In one embodiment, R^1 is methyl or chloro.

In one embodiment, R^2 is hydrogen or methyl.

In one embodiment, R^2 is hydrogen.

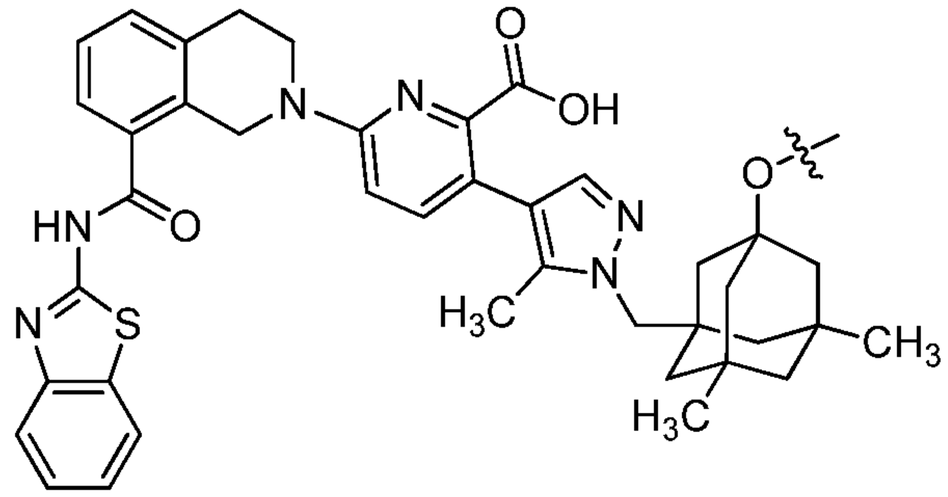
In one embodiment, Z^{2b} is O.

In one embodiment, Z^{2b} is NH or CH_2.

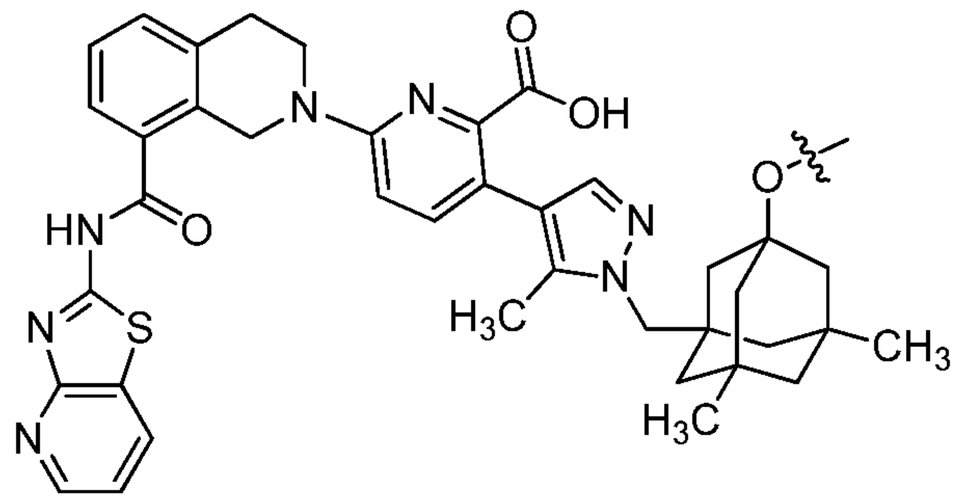
In one embodiment, the ADC is a compound according to structural formula (IIa).

In one embodiment, the ADC is a compound according to structural formula (IIa) which includes a core selected from structures (C.1)-(C.21):

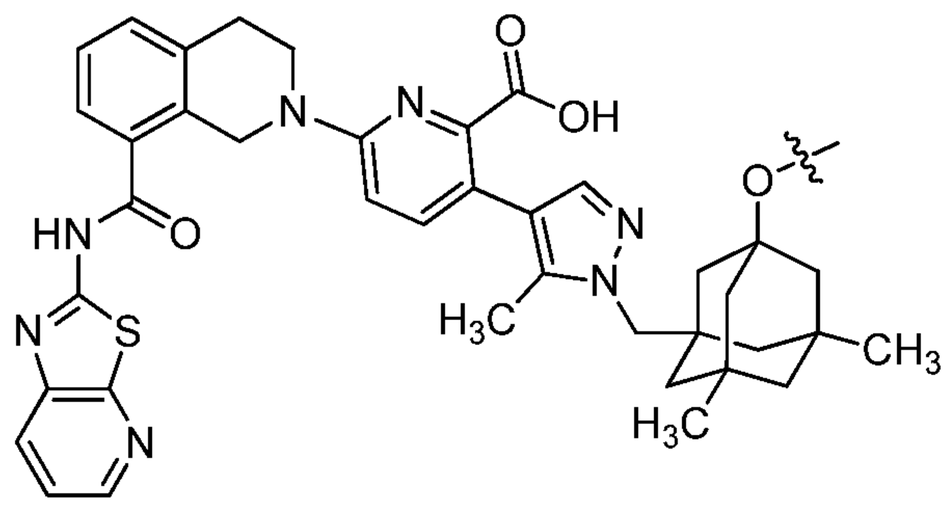
(C.1)



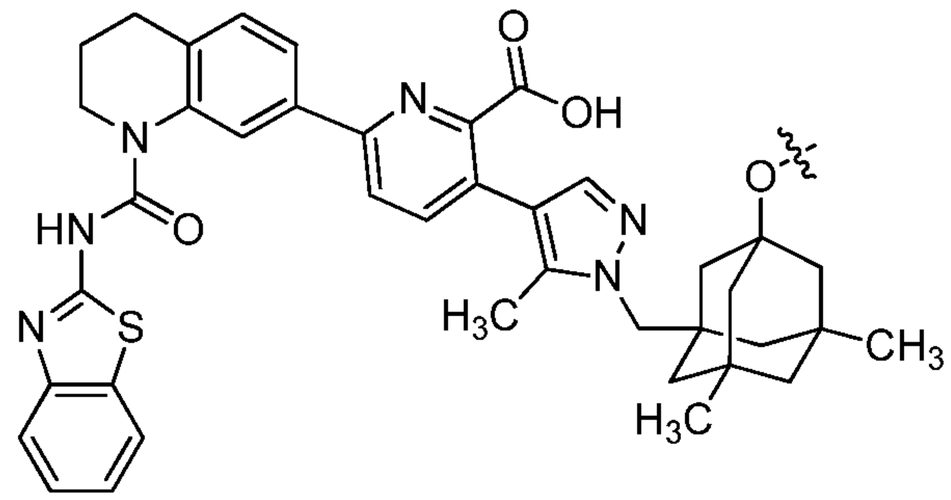
(C.2)



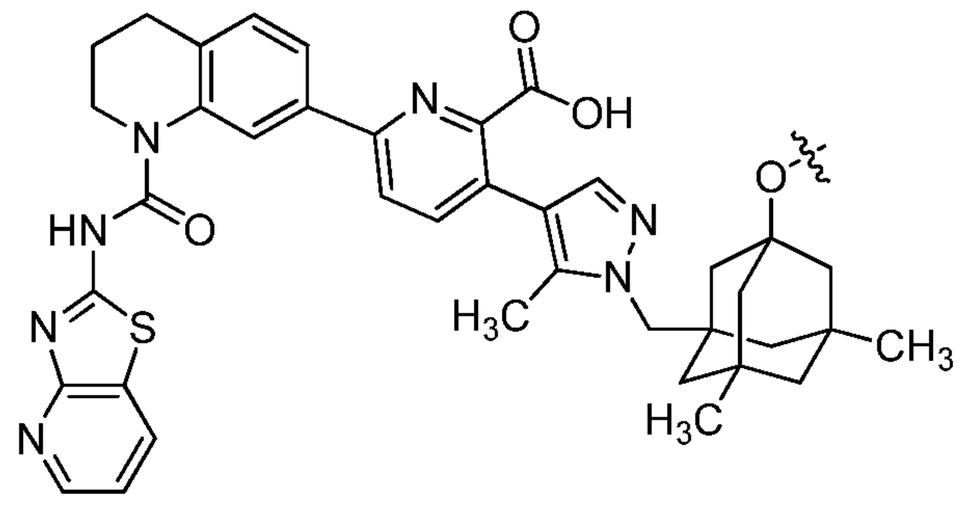
(C.3)



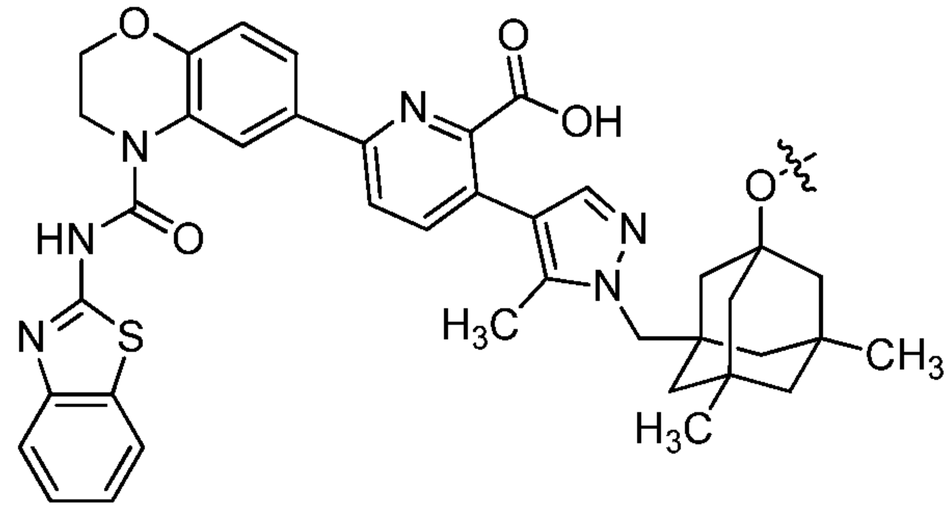
(C.4)



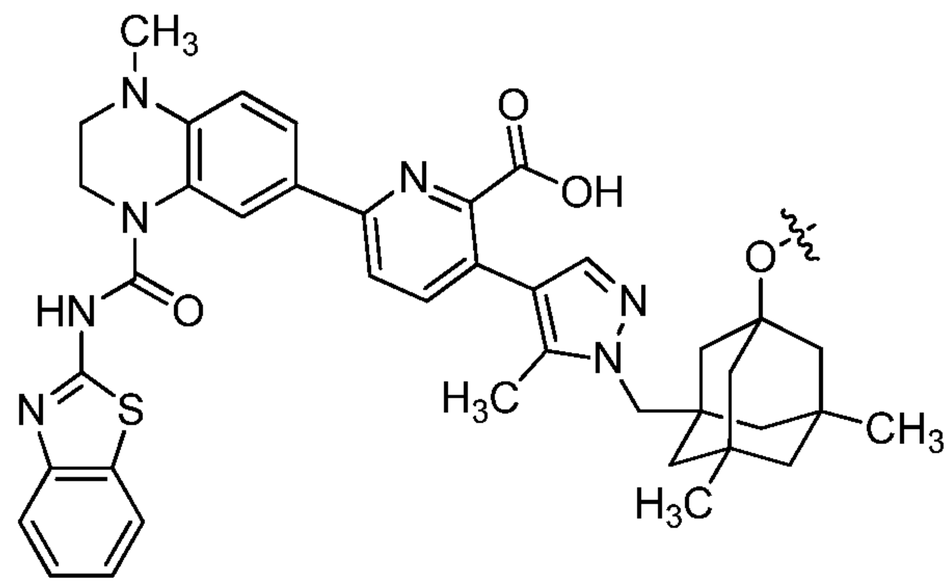
(C.5)

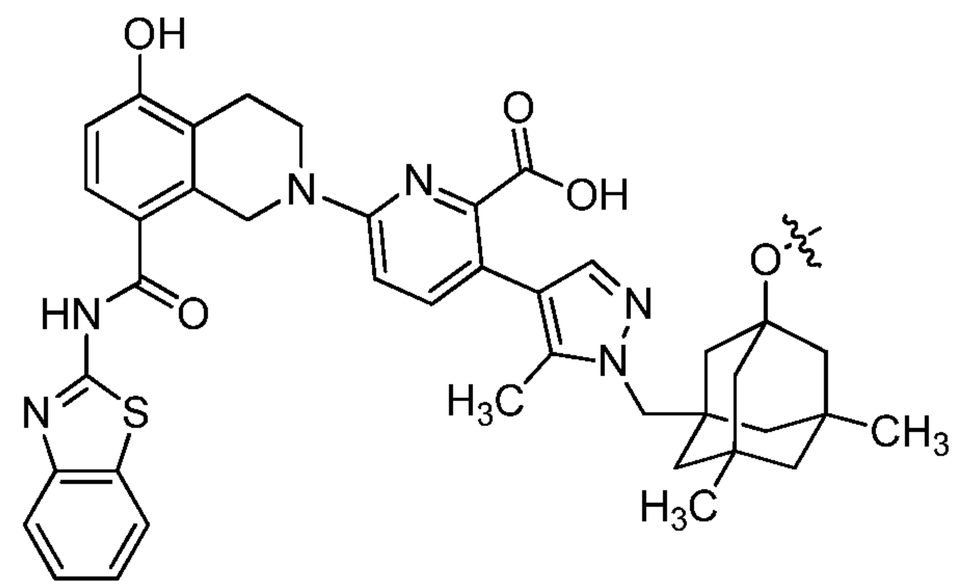


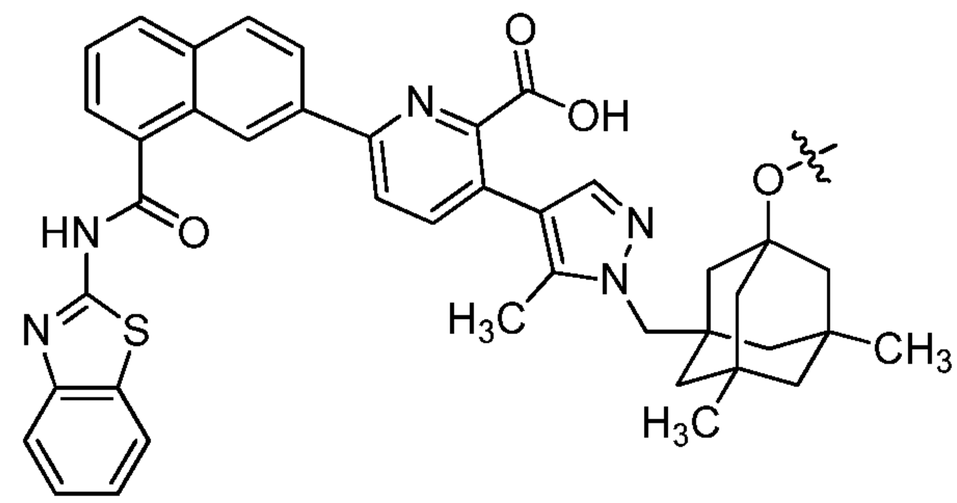
(C.6)

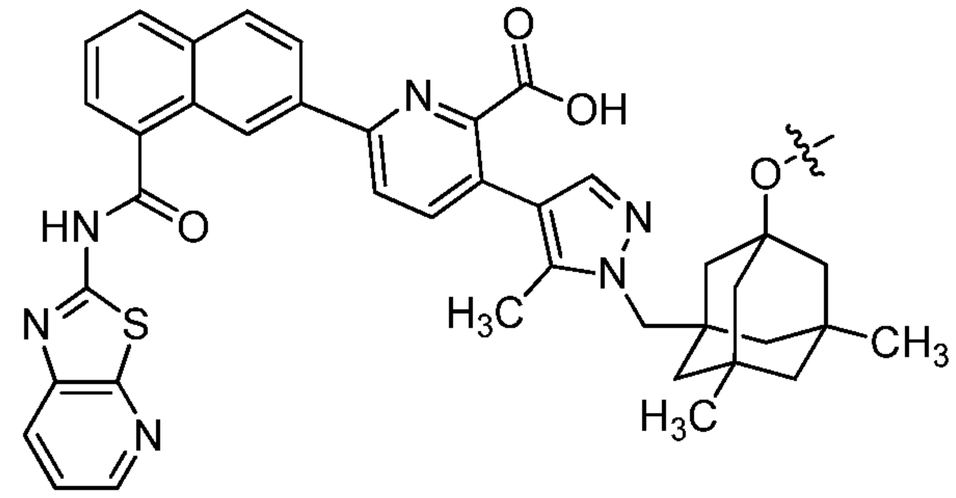


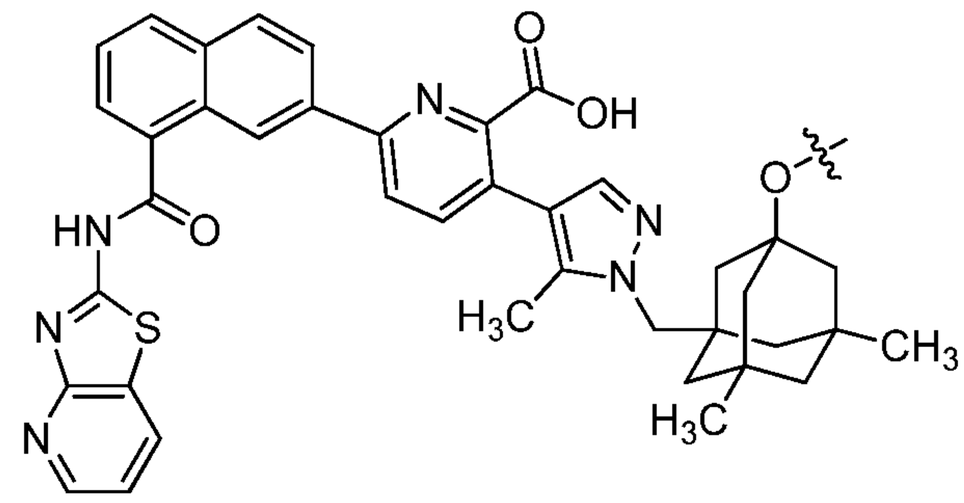
(C.7)

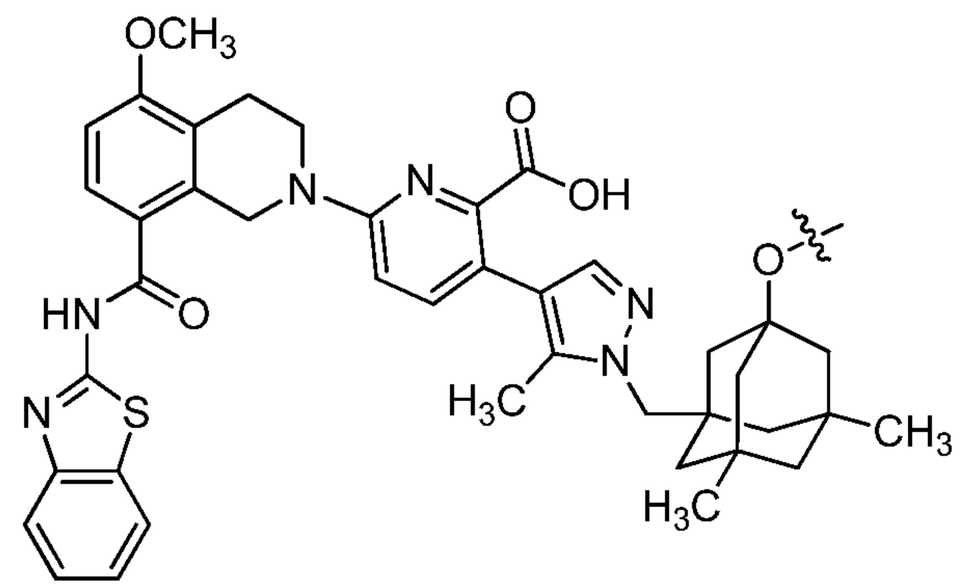


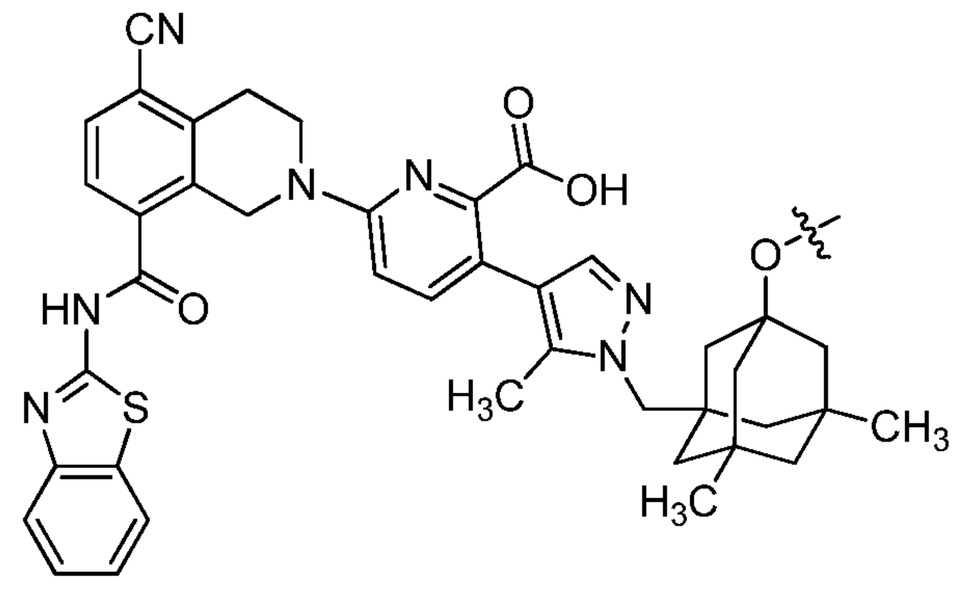
(C.8) 

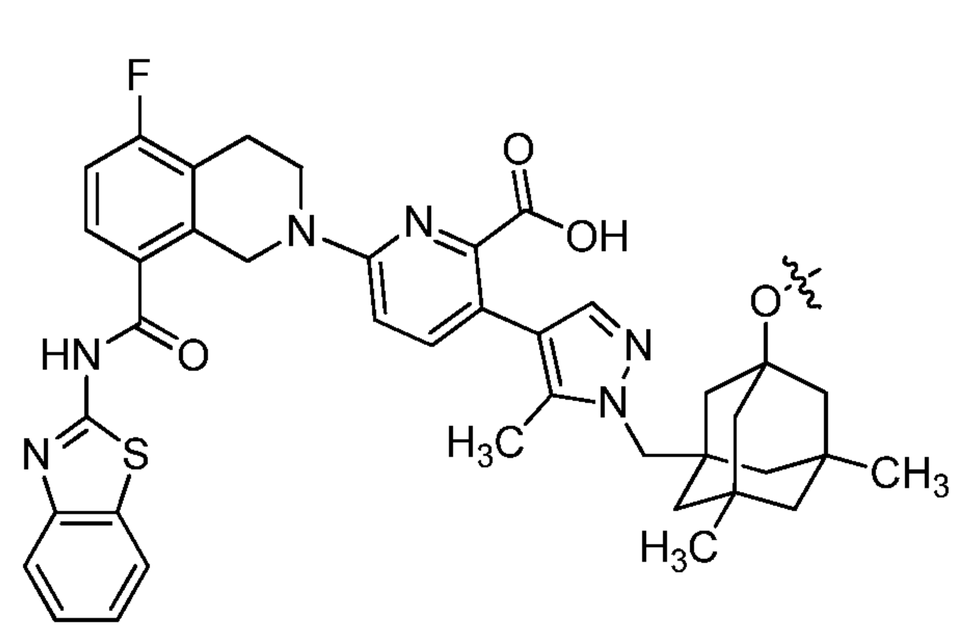
(C.9) 

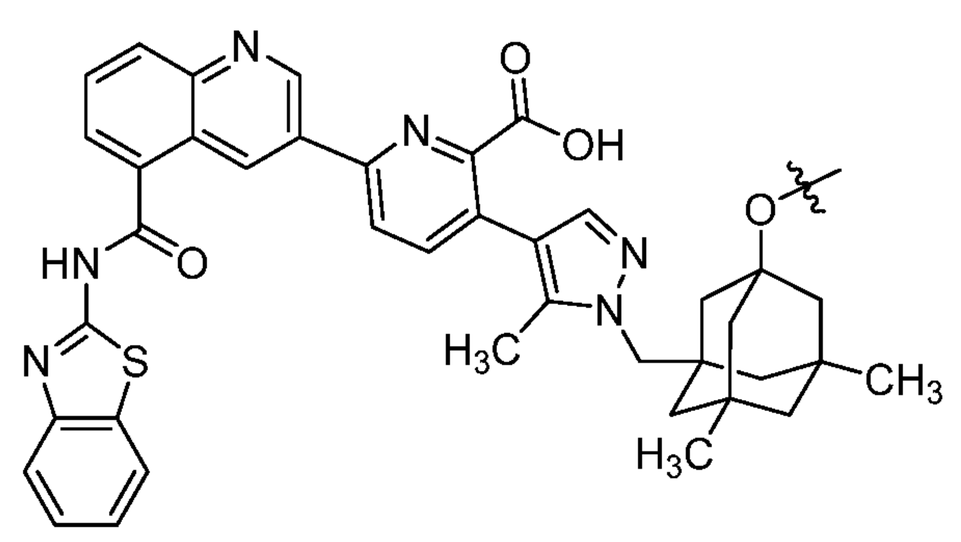
(C.10) 

(C.11) 

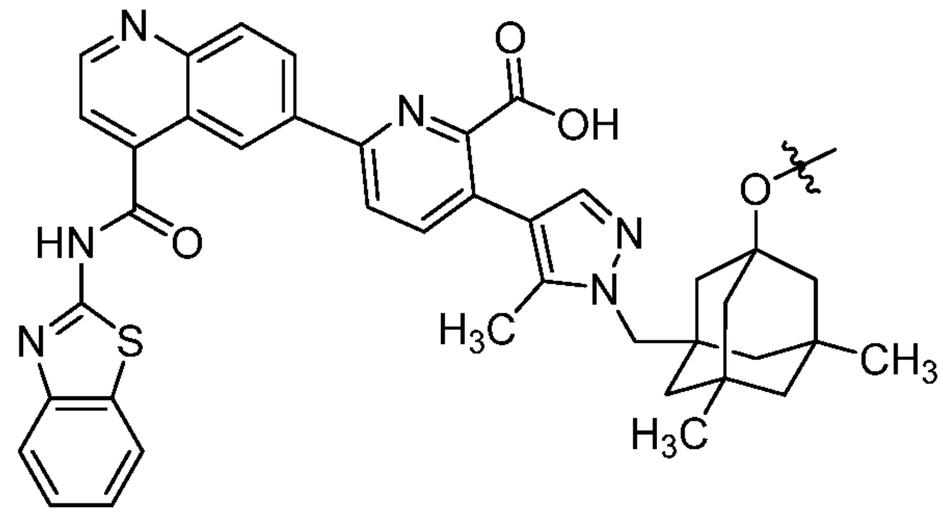
(C.12) 

(C.13) 

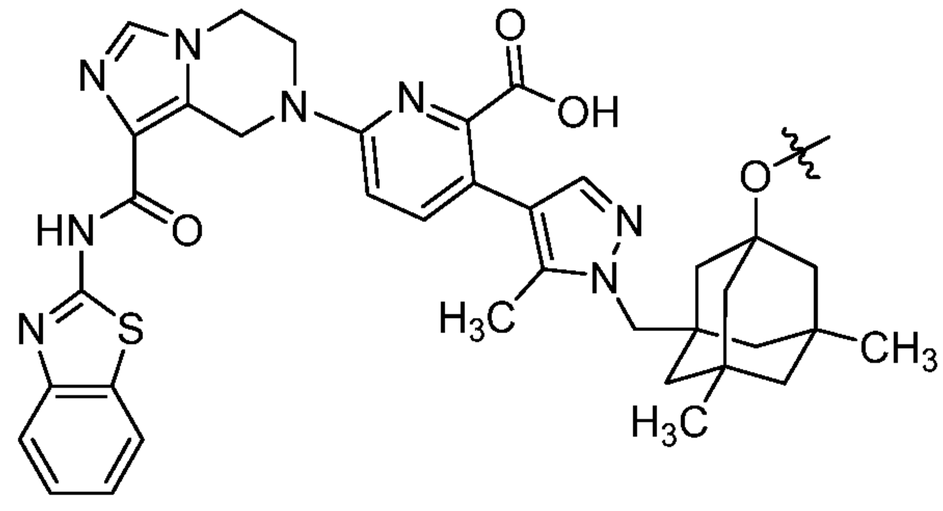
(C.14) 

(C.15) 

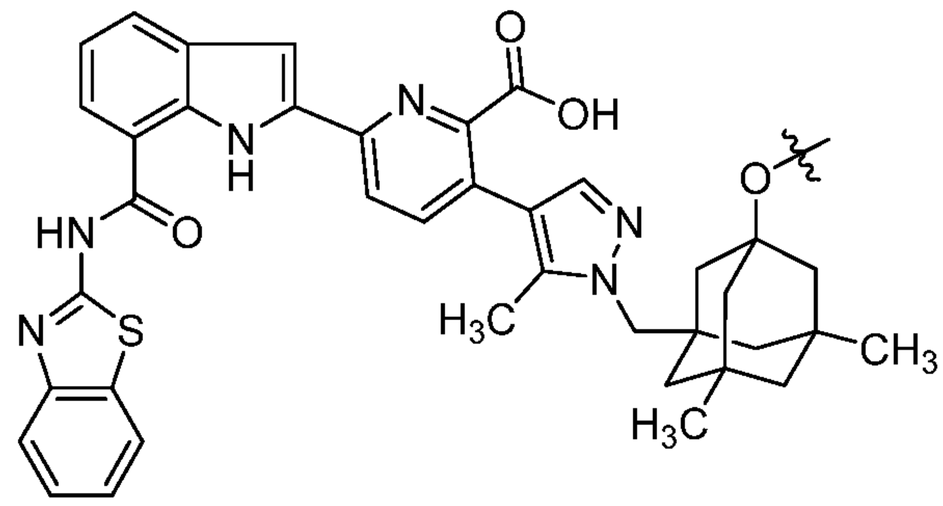
(C.16)



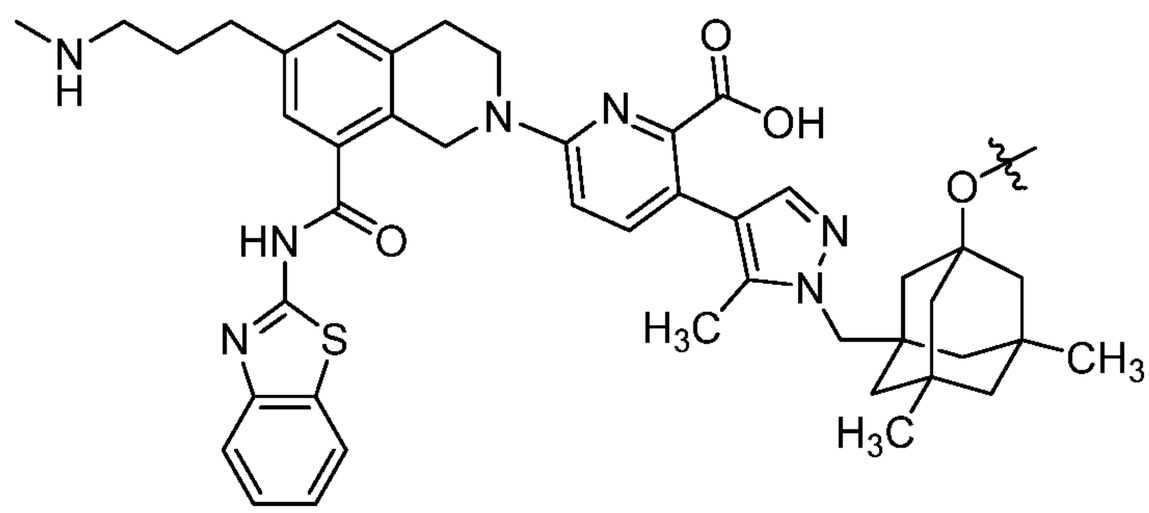
(C.17)



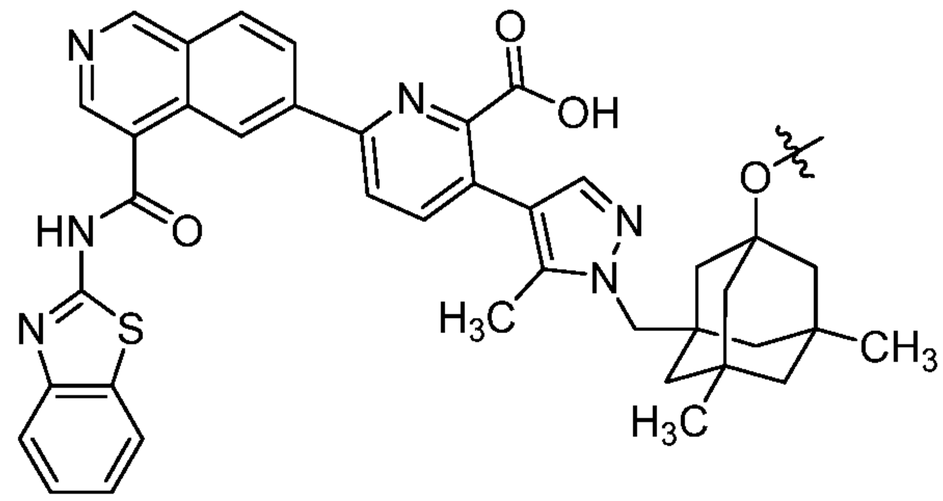
(C.18)



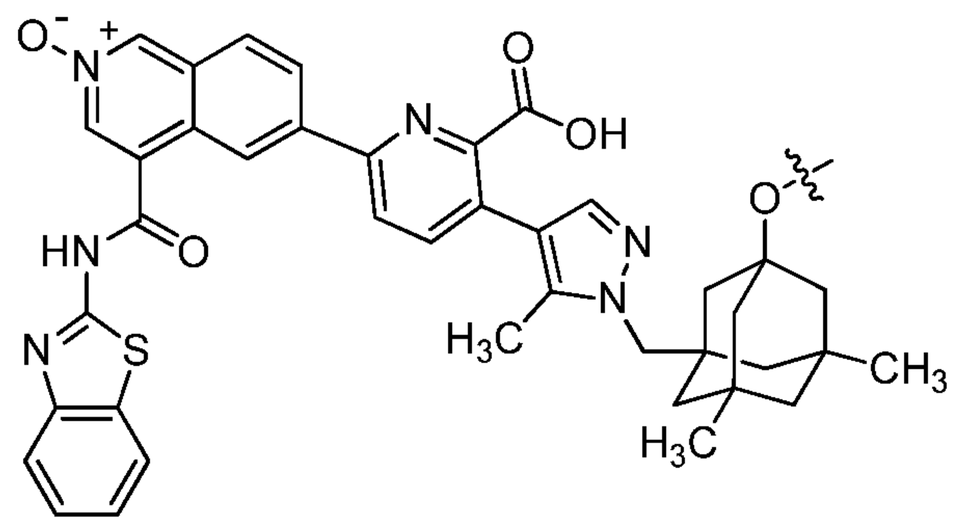
(C.19)



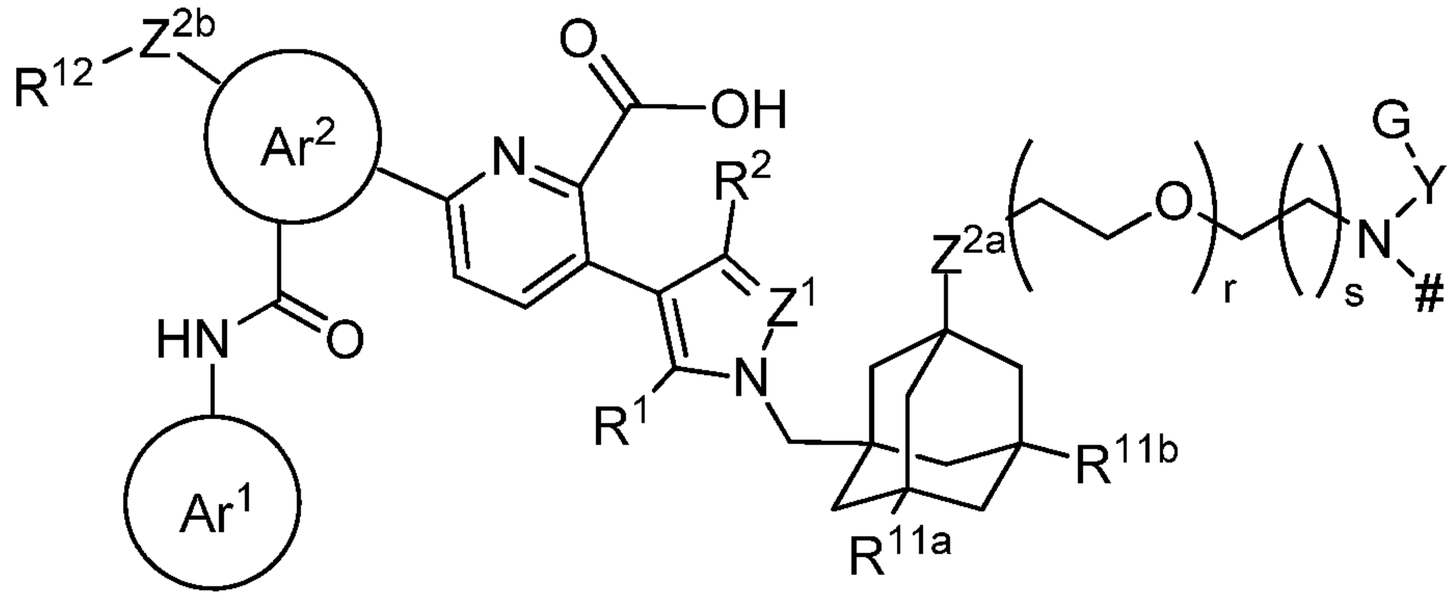
(C.20)



(C.21)



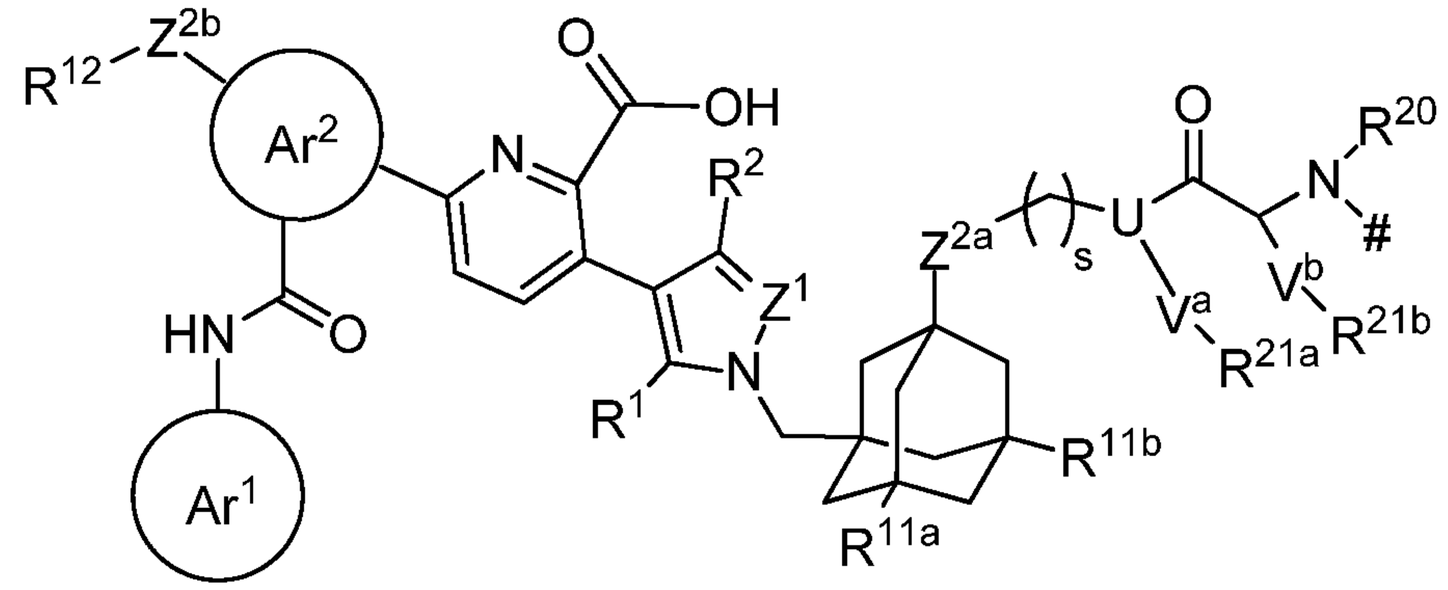
In one embodiment, the ADC is a compound according to structural formula (IIa.1):



(IIa.1)

wherein Y is optionally substituted C_1-C_8 alkylene; r is 0 or 1; and s is 1, 2 or 3.

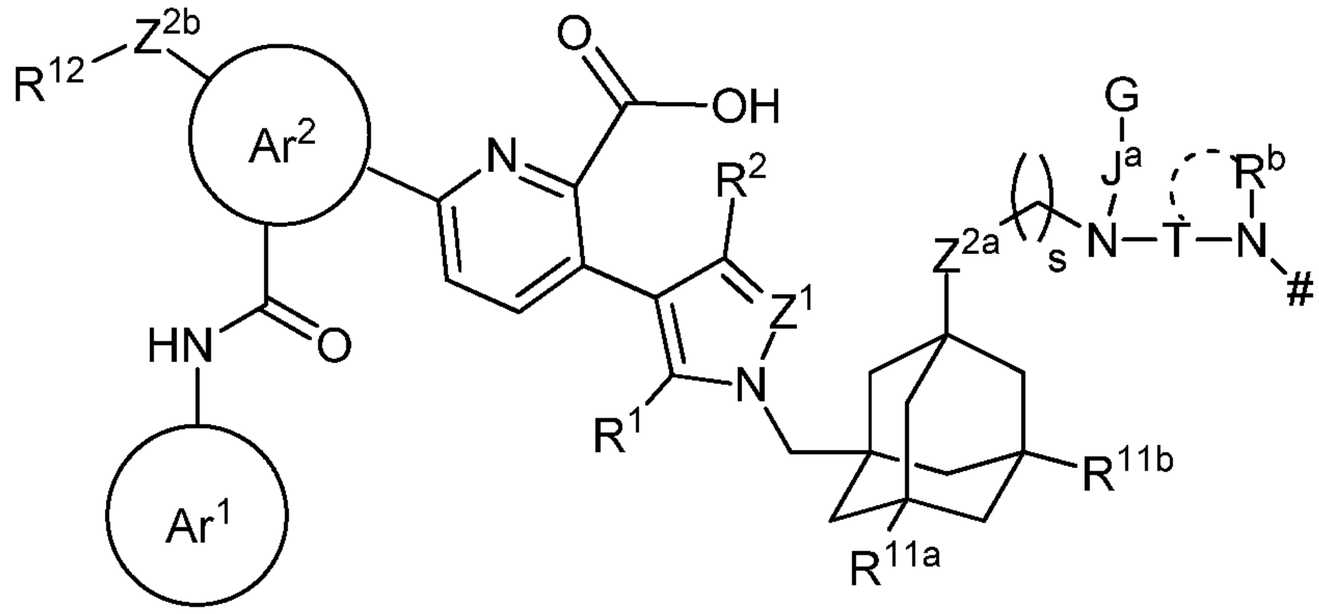
In one embodiment, the ADC is a compound according to structural formula (IIa.2):



(IIa.2)

wherein U is selected from N, O and CH, with the proviso that when U is O, then V^a and R^{21a} are absent; R^{20} is selected from H and C_1-C_4 alkyl; R^{21a} and R^{21b} are each, independently from one another, absent or selected from H, C_1-C_4 alkyl and G, where G is selected from a polyol, PEG4-30, a salt and a moiety that is charged at physiological pH; V^a and V^b are each, independently from one another, absent or selected from a bond, and an optionally substituted alkylene; R^{20} is selected from H and C_1-C_4 alkyl; and s is 1, 2 or 3.

In one embodiment, the ADC is a compound according to structural formula (IIa.3):

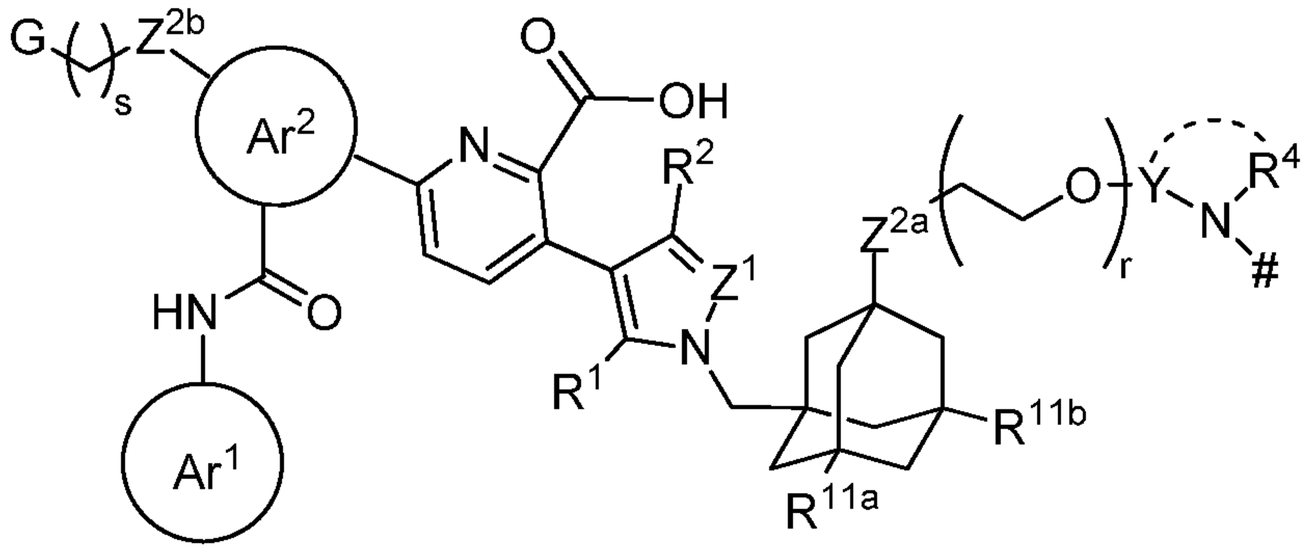


(IIa.3)

wherein R^b is selected from H, C_1-C_4 alkyl and J^b-G or is optionally taken together with an atom of T to form a ring having between 3 and 7 atoms; J^a and J^b are each, independently from one another, selected from optionally substituted C_1-C_8 alkylene and optionally substituted phenylene; T is selected from optionally substituted C_1-C_8 alkylene, $CH_2CH_2OCH_2CH_2OCH_2CH_2$, $CH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2$ and a polyethylene glycol containing from 4 to 10 ethylene glycol units; G is selected from a polyol, PEG4-30, a salt and a moiety that is charged at physiological pH; and s is 1, 2 or 3.

In one embodiment, the ADC is a compound according to structural formula (IIb).

In one embodiment, the ADC is a compound according to structural formula (IIb.1):

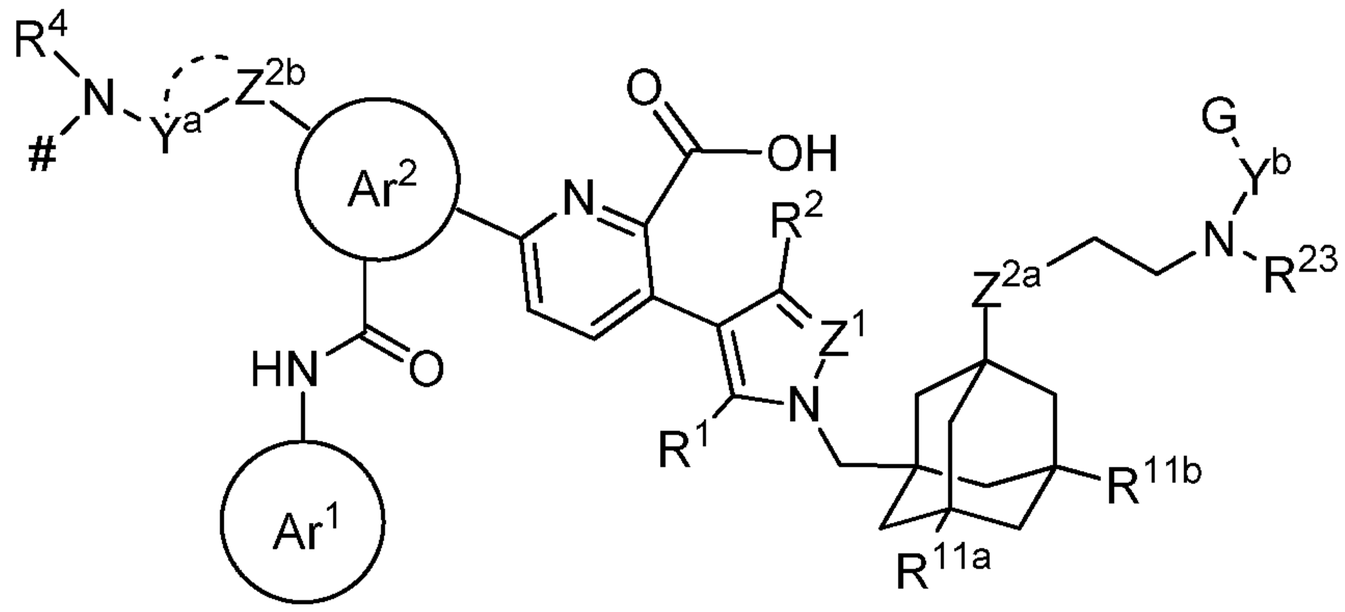


(IIb.1)

wherein Y is optionally substituted C_1-C_8 alkylene; G is selected from a polyol, PEG4-30, a salt and a moiety that is charged at physiological pH; r is 0 or 1; and s is 1, 2 or 3.

In one embodiment, the ADC is a compound according to structural formula (IIc).

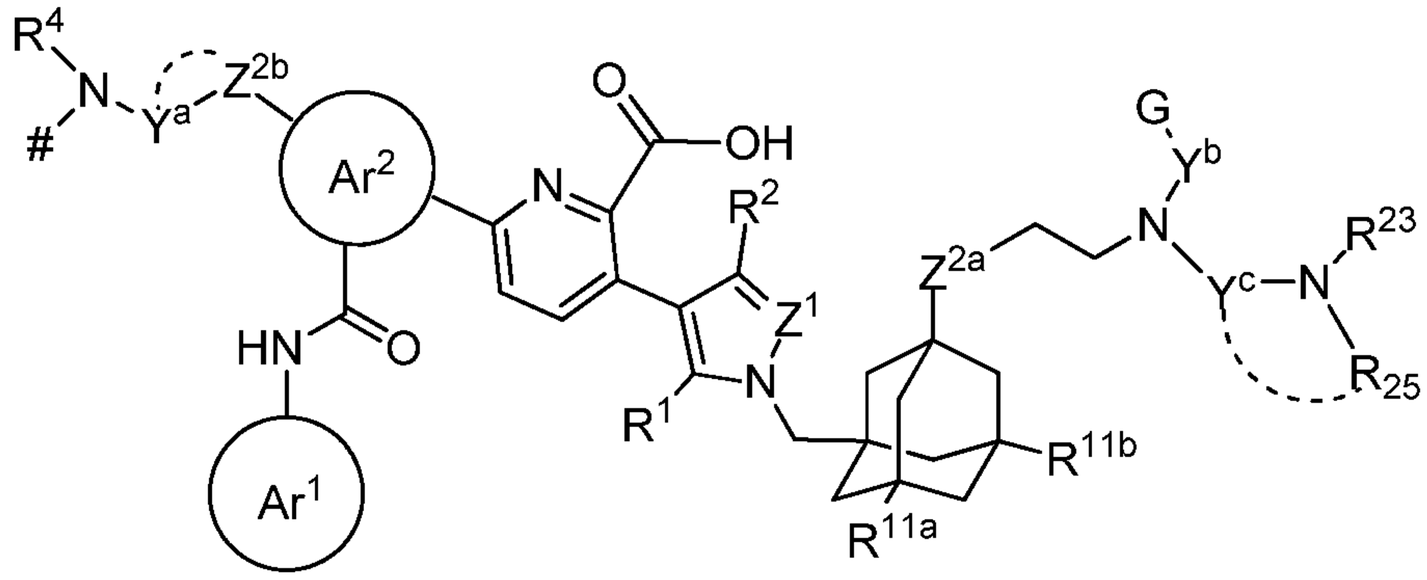
In one embodiment, the ADC is a compound according to structural formula (IIc.1):



(IIc.1)

wherein Y^a is optionally substituted C_1-C_8 alkylene; Y^b is optionally substituted C_1-C_8 alkylene; R^{23} is selected from H and C_1-C_4 alkyl; and G is selected from a polyol, PEG4-30, a salt and a moiety that is charged at physiological pH.

In one embodiment, the ADC is a compound according to structural formula (IIc.2):



(IIc.2)

wherein Y^a is optionally substituted C_1-C_8 alkylene; Y^b is optionally substituted C_1-C_8 alkylene;Y^c is optionally substituted C_1-C_8 alkylene; R^{23} is selected from H and C_1-C_4 alkyl; R^{25} is Y^b-G or is taken together with an atom of Y^c to form a ring having 4-6 ring atoms; and G is selected from a polyol, PEG4-30, a salt and a moiety that is charged at physiological pH.

In one embodiment, the Bcl-xL inhibitor is selected from the group consisting of the following compounds modified in that the hydrogen corresponding to the # position of structural formula (IIa), (IIb), (IIc), or (IId) is not present forming a monoradical:

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-[1-({3-[2-({2-[2-(carboxymethoxy)ethoxy]ethyl}amino)ethoxy]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}methyl)-5-methyl-1H-pyrazol-4-yl]pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3,5-dimethyl-7-{2-[(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

2-{[(2-{[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl]amino}ethyl)sulfonyl]amino}-2-deoxy-D-glucopyranose;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3,5-dimethyl-7-{2-[(4-{[(3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl]methyl}benzyl)amino]ethoxy}tricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3,5-dimethyl-7-{2-[(3-sulfopropyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3-{2-[(2,3-dihydroxypropyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

2-({[4-({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl]amino}methyl)phenyl]sulfonyl}amino)-2-deoxy-beta-D-glucopyranose;

8-(1,3-benzothiazol-2-ylcarbamoyl)-2-{6-carboxy-5-[1-({3-[2-({2-[1-(beta-D-glucopyranuronosyl)-1H-1,2,3-triazol-4-yl]ethyl}amino)ethoxy]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}methyl)-5-methyl-1H-pyrazol-4-yl]pyridin-2-yl}-1,2,3,4-tetrahydroisoquinoline;

3-[1-({3-[2-(2-{[4-(beta-D-allopyranosyloxy)benzyl]amino}ethoxy)ethoxy]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}methyl)-5-methyl-1H-pyrazol-4-yl]-6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-(1-{[3,5-dimethyl-7-(2-{2-[(2-sulfoethyl)amino]ethoxy}ethoxy)tricyclo[3.3.1.1^{3,7}]dec-1-yl]methyl}-5-methyl-1H-pyrazol-4-yl)pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3,5-dimethyl-7-{2-[(2-phosphonoethyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3,5-dimethyl-7-{2-[methyl(3-sulfo-L-alanyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3,5-dimethyl-7-{2-[(3-phosphonopropyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3,5-dimethyl-7-{2-[(3-sulfo-L-alanyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-(1-{[3,5-dimethyl-7-(2-{2-[(3-phosphonopropyl)amino]ethoxy}ethoxy)tricyclo[3.3.1.1^{3,7}]dec-1-yl]methyl}-5-methyl-1H-pyrazol-4-yl)pyridine-2-carboxylic acid;

3-{1-[(3-{2-[L-alpha-aspartyl(methyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}-6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]pyridine-2-carboxylic acid;

6-{4-[({2-[2-(2-aminoethoxy)ethoxy]ethyl}[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl]amino)methyl]benzyl}-2,6-anhydro-L-gulonic acid;

4-({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl]amino}methyl)phenyl hexopyranosiduronic acid;

6-[1-(1,3-benzothiazol-2-ylcarbamoyl)-1,2,3,4-tetrahydroquinolin-7-yl]-3-{1-[(3,5-dimethyl-7-{2-[(2-phosphonoethyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[1-(1,3-benzothiazol-2-ylcarbamoyl)-1,2,3,4-tetrahydroquinolin-7-yl]-3-{1-[(3,5-dimethyl-7-{2-[methyl(3-sulfo-L-alanyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

3-{1-[(3,5-dimethyl-7-{2-[(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}-6-[8-([1,3]thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]pyridine-2-carboxylic acid;

3-{1-[(3,5-dimethyl-7-{2-[(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}-6-[8-([1,3]thiazolo[4,5-b]pyridin-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]pyridine-2-carboxylic acid;

6-[1-(1,3-benzothiazol-2-ylcarbamoyl)-1,2,3,4-tetrahydroquinolin-7-yl]-3-{1-[(3,5-dimethyl-7-{2-[(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3-{2-[(2-carboxyethyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3,5-dimethyl-7-{2-[(3-phosphonopropyl)(piperidin-4-yl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

3-{1-[(3-{2-[D-alpha-aspartyl(methyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}-6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-(1-{[3-(2-{[1-(carboxymethyl)piperidin-4-yl]amino}ethoxy)-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl]methyl}-5-methyl-1H-pyrazol-4-yl)pyridine-2-carboxylic acid;

N-[(5S)-5-amino-6-{[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](methyl)amino}-6-oxohexyl]-N,N-dimethylmethanaminium;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3,5-dimethyl-7-{2-[piperidin-4-yl(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-5-(3-phosphonopropoxy)-3,4-dihydroisoquinolin-2(1H)-yl]-3-[1-({3,5-dimethyl-7-[2-(methylamino)ethoxy]tricyclo[3.3.1.1^{3,7}]dec-1-yl}methyl)-5-methyl-1H-pyrazol-4-yl]pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-(1-{[3-(2-{[N-(2-carboxyethyl)-L-alpha-aspartyl]amino}ethoxy)-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl]methyl}-5-methyl-1H-pyrazol-4-yl)pyridine-2-carboxylic acid;

3-{1-[(3-{2-[(2-aminoethyl)(2-sulfoethyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}-6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]pyridine-2-carboxylic acid;

6-[5-(2-aminoethoxy)-8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-[1-({3,5-dimethyl-7-[2-(methylamino)ethoxy]tricyclo[3.3.1.1^{3,7}]dec-1-yl}methyl)-5-methyl-1H-pyrazol-4-yl]pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)naphthalen-2-yl]-3-{1-[(3,5-dimethyl-7-{2-[(3-sulfopropyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3-{2-[(2-carboxyethyl)(piperidin-4-yl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3,5-dimethyl-7-{2-[(3-sulfo-L-alanyl)(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3-{2-[{2-[(2-carboxyethyl)amino]ethyl}(2-sulfoethyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

3-{1-[(3,5-dimethyl-7-{2-[(3-phosphonopropyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}-6-[8-([1,3]thiazolo[4,5-b]pyridin-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]pyridine-2-carboxylic acid;

3-{1-[(3,5-dimethyl-7-{2-[(3-phosphonopropyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}-6-[8-([1,3]thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-5-(carboxymethoxy)-3,4-dihydroisoquinolin-2(1H)-yl]-3-[1-({3,5-dimethyl-7-[2-(methylamino)ethoxy]tricyclo[3.3.1.1^{3,7}]dec-1-yl}methyl)-5-methyl-1H-pyrazol-4-yl]pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3-{2-[(3-carboxypropyl)(piperidin-4-yl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)naphthalen-2-yl]-3-{1-[(3,5-dimethyl-7-{2-[(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

3-{1-[(3-{2-[L-alpha-aspartyl(2-sulfoethyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}-6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3-{2-[(1,3-dihydroxypropan-2-yl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[5-(2-aminoethoxy)-8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3,5-dimethyl-7-{2-[methyl(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-5-{2-[(2-sulfoethyl)amino]ethoxy}-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3,5-dimethyl-7-{2-[methyl(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3,5-dimethyl-7-{2-[(2-sulfoethyl){2-[(2-sulfoethyl)amino]ethyl}amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-5-{2-[(2-carboxyethyl)amino]ethoxy}-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3,5-dimethyl-7-{2-[methyl(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

3-{1-[(3,5-dimethyl-7-{2-[(3-phosphonopropyl)(piperidin-4-yl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}-6-[8-([1,3]thiazolo[4,5-b]pyridin-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]pyridine-2-carboxylic acid;

6-[4-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydro-2H-1,4-benzoxazin-6-yl]-3-{1-[(3,5-dimethyl-7-{2-[(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-5-(3-sulfopropoxy)-3,4-dihydroisoquinolin-2(1H)-yl]-3-[1-({3,5-dimethyl-7-[2-(methylamino)ethoxy]tricyclo[3.3.1.1^{3,7}]dec-1-yl}methyl)-5-methyl-1H-pyrazol-4-yl]pyridine-2-carboxylic acid;

3-{1-[(3,5-dimethyl-7-{2-[(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}-6-[1-([1,3]thiazolo[4,5-b]pyridin-2-ylcarbamoyl)-1,2,3,4-tetrahydroquinolin-7-yl]pyridine-2-carboxylic acid;

3-{1-[(3,5-dimethyl-7-{2-[(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}-6-[8-([1,3]thiazolo[4,5-b]pyridin-2-ylcarbamoyl)naphthalen-2-yl]pyridine-2-carboxylic acid;

(1ξ)-1-({2-[5-(1-{[3-(2-aminoethoxy)-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl]methyl}-5-methyl-1*H*-pyrazol-4-yl)-6-carboxypyridin-2-yl]-8-(1,3-benzothiazol-2-ylcarbamoyl)-1,2,3,4-tetrahydroisoquinolin-5-yl}methyl)-1,5-anhydro-D-glucitol;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3-{2-[(3-carboxypropyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)naphthalen-2-yl]-3-{1-[(3,5-dimethyl-7-{2-[(3-phosphonopropyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-(1-{[3-(2-{[4-(beta-D-glucopyranosyloxy)benzyl]amino}ethoxy)-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl]methyl}-5-methyl-1H-pyrazol-4-yl)pyridine-2-carboxylic acid;

3-(1-{[3-(2-{[4-(beta-D-allopyranosyloxy)benzyl]amino}ethoxy)-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl]methyl}-5-methyl-1H-pyrazol-4-yl)-6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]pyridine-2-carboxylic acid;

3-{1-[(3-{2-[azetidin-3-yl(2-sulfoethyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}-6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]pyridine-2-carboxylic acid;

3-{1-[(3-{2-[(3-aminopropyl)(2-sulfoethyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}-6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]pyridine-2-carboxylic acid;

6-[1-(1,3-benzothiazol-2-ylcarbamoyl)-1,2,3,4-tetrahydroquinolin-7-yl]-3-{1-[(3-{2-[(2-carboxyethyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3-{2-[(N^6,N^6-dimethyl-L-lysyl)(methyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.$1^{3,7}$]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

3-{1-[(3-{2-[(3-aminopropyl)(methyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.$1^{3,7}$]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}-6-[1-(1,3-benzothiazol-2-ylcarbamoyl)-1,2,3,4-tetrahydroquinolin-7-yl]pyridine-2-carboxylic acid;

3-{1-[(3-{2-[azetidin-3-yl(methyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.$1^{3,7}$]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}-6-[1-(1,3-benzothiazol-2-ylcarbamoyl)-1,2,3,4-tetrahydroquinolin-7-yl]pyridine-2-carboxylic acid;

N^6-(37-oxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxaheptatriacontan-37-yl)-L-lysyl-N-[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.$1^{3,7}$]dec-1-yl}oxy)ethyl]-L-alaninamide;

methyl 6-[4-(3-{[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.$1^{3,7}$]dec-1-yl}oxy)ethyl]amino}propyl)-1H-1,2,3-triazol-1-yl]-6-deoxy-beta-L-glucopyranoside;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)naphthalen-2-yl]-3-{1-[(3-{2-[(2-carboxyethyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.$1^{3,7}$]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[5-(1,3-benzothiazol-2-ylcarbamoyl)quinolin-3-yl]-3-{1-[(3,5-dimethyl-7-{2-[(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.$1^{3,7}$]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[4-(1,3-benzothiazol-2-ylcarbamoyl)quinolin-6-yl]-3-{1-[(3,5-dimethyl-7-{2-[(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.$1^{3,7}$]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[5-(1,3-benzothiazol-2-ylcarbamoyl)quinolin-3-yl]-3-{1-[(3-{2-[(2-carboxyethyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.$1^{3,7}$]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[1-(1,3-benzothiazol-2-ylcarbamoyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl]-3-{1-[(3,5-dimethyl-7-{2-[(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.$1^{3,7}$]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

8-(1,3-benzothiazol-2-ylcarbamoyl)-2-{6-carboxy-5-[1-({3-[2-({3-[1-(beta-D-glucopyranuronosyl)-1H-1,2,3-triazol-4-yl]propyl}amino)ethoxy]-5,7-dimethyltricyclo[3.3.1.$1^{3,7}$]dec-1-yl}methyl)-5-methyl-1H-pyrazol-4-yl]pyridin-2-yl}-1,2,3,4-tetrahydroisoquinoline;

6-[7-(1,3-benzothiazol-2-ylcarbamoyl)-1H-indol-2-yl]-3-{1-[(3,5-dimethyl-7-{2-[(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-6-[3-(methylamino)propyl]-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3,5-dimethyl-7-{2-[(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

5-{[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl]amino}-5-deoxy-D-arabinitol;

1-{[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl]amino}-1,2-dideoxy-D-arabino-hexitol;

6-[4-(1,3-benzothiazol-2-ylcarbamoyl)isoquinolin-6-yl]-3-{1-[(3,5-dimethyl-7-{2-[(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-(1-{[3-(2-hydroxy-2-(hydroxymethyl)propyl]amino}ethoxy)-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl]methyl}-5-methyl-1H-pyrazol-4-yl)pyridine-2-carboxylic acid;

1-{[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl]amino}-1,2-dideoxy-D-erythro-pentitol;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-(1-{[3,5-dimethyl-7-(2-{[(2S,3S)-2,3,4-trihydroxybutyl]amino}ethoxy)tricyclo[3.3.1.1^{3,7}]dec-1-yl]methyl}-5-methyl-1H-pyrazol-4-yl)pyridine-2-carboxylic acid;

6-[8 -(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-(1-{[3-(2-{[(2S,3S,4R,5R,6R)-2,3,4,5,6,7-hexahydroxyheptyl]amino}ethoxy)-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl]methyl}-5-methyl-1H-pyrazol-4-yl)pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3-{2-[({3-[(1,3-dihydroxypropan-2-yl)amino]propyl}sulfonyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3-{2-[(3-{[1,3-dihydroxy-2-(hydroxymethyl)propan-2-yl]amino}-3-oxopropyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]-3-(1-{[3-(2-{[(3*S*)-3,4-dihydroxybutyl]amino}ethoxy)-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl]methyl}-5-methyl-1*H*-pyrazol-4-yl)pyridine-2-carboxylic acid;

4-({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl]amino}methyl)phenyl beta-D-glucopyranosiduronic acid;

3-{[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)naphthalen-2-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl]amino}propyl beta-D-glucopyranosiduronic acid;

6-[4-(1,3-benzothiazol-2-ylcarbamoyl)-2-oxidoisoquinolin-6-yl]-3-[1-({3,5-dimethyl-7-[2-(methylamino)ethoxy]tricyclo[3.3.1.1^{3,7}]dec-1-yl}methyl)-5-methyl-1H-pyrazol-4-yl]pyridine-2-carboxylic acid;

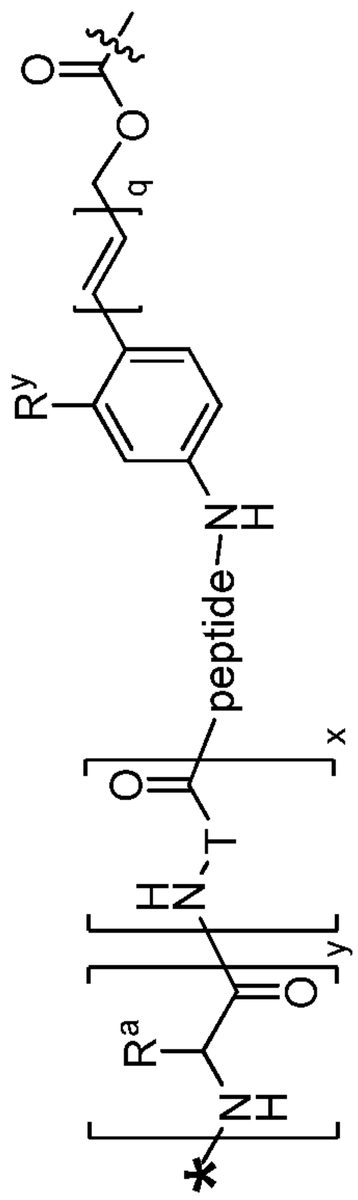
6-{8-[(1,3-benzothiazol-2-yl)carbamoyl]-3,4-dihydroisoquinolin-2(1H)-yl}-3-{1-[(3,5-dimethyl-7-{2-[(2-sulfoethyl)amino]acetamido}tricyclo[3.3.1.1^{3,7}]decan-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]-3-(1-{[3,5-dimethyl-7-({2-[(2-sulfoethyl)amino]ethyl}sulfanyl)tricyclo[3.3.1.1^{3,7}]dec-1-yl]methyl}-5-methyl-1*H*-pyrazol-4-yl)pyridine-2-carboxylic acid; and

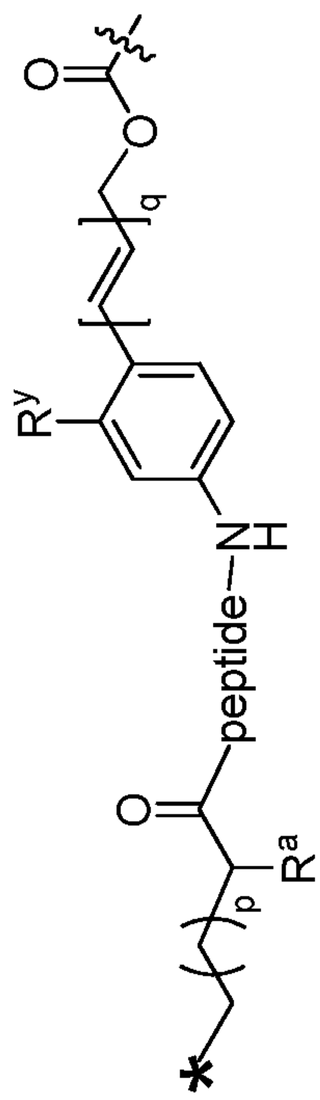
6-{8-[(1,3-benzothiazol-2-yl)carbamoyl]-3,4-dihydroisoquinolin-2(1*H*)-yl}-3-{1-[(3,5-dimethyl-7-{3-[(2-sulfoethyl)amino]propyl}tricyclo[3.3.1.1^{3,7}]decan-1-yl)methyl]-5-methyl-1*H*-pyrazol-4-yl}pyridine-2-carboxylic acid.

In one embodiment, the linker is cleavable by a lysosomal enzyme. In one embodiment, the lysosomal enzyme is Cathepsin B.

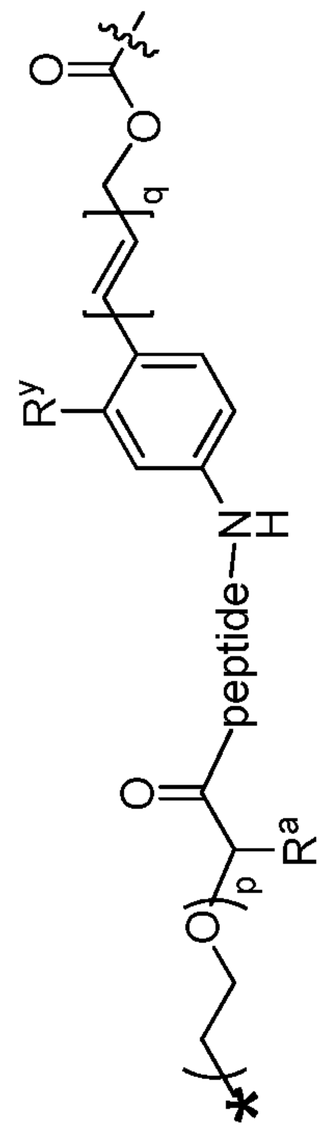
In one embodiment, the linker comprises a segment according to structural formula (IVa), (IVb), (IVc), or (IVd):



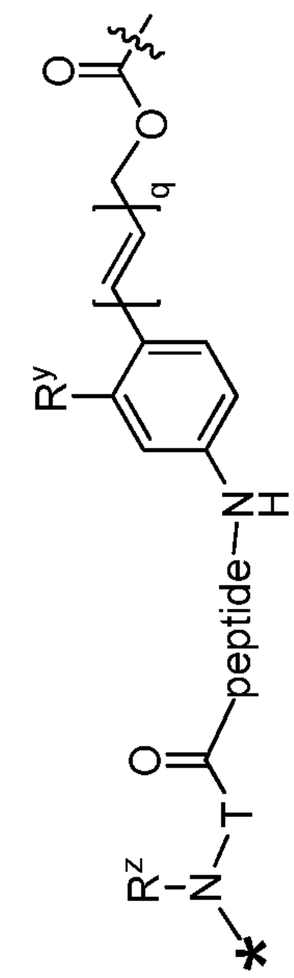
(IVa)



(IVb)



(IVc)



(IVd)

wherein peptide represents a peptide (illustrated N→C, wherein peptide includes the amino and carboxy "termini") a cleavable by a lysosomal enzyme; T represents a polymer comprising one or more ethylene glycol units or an alkylene chain, or combinations thereof;

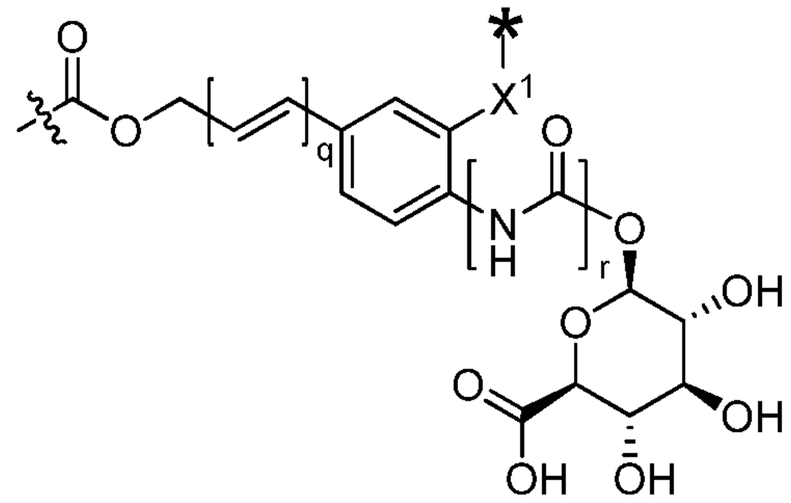
R^a is selected from hydrogen, C_{1-6} alkyl, SO_3H and CH_2SO_3H; R^y is hydrogen or C_{1-4} alkyl-$(O)_r$-(C_{1-4} alkylene)$_s$-G^1 or C_{1-4} alkyl-(N)-[(C_{1-4} alkylene)-G^1]$_2$; R^z is C_{1-4} alkyl-$(O)_r$-(C_{1-4} alkylene)$_s$-G^2; G^1 is SO_3H, CO_2H, PEG 4-32, or sugar moiety; G^2 is SO_3H, CO_2H, or PEG 4-32 moiety; r is 0 or 1; s is 0 or 1; p is an integer ranging from 0 to 5; q is 0 or 1; x is 0 or 1; y is 0 or 1; ≈ represents the point of attachment of the linker to the Bcl-xL inhibitor; and * represents the point of attachment to the remainder of the linker.

In one embodiment, the peptide is selected from the group consisting of Val-Cit; Cit-Val; Ala-Ala; Ala-Cit; Cit-Ala; Asn-Cit; Cit-Asn; Cit-Cit; Val-Glu; Glu-Val; Ser-Cit; Cit-Ser; Lys-Cit; Cit-Lys; Asp-Cit; Cit-Asp; Ala-Val; Val-Ala; Phe-Lys; Lys-Phe; Val-Lys; Lys-Val; Ala-Lys; Lys-Ala; Phe-Cit; Cit-Phe; Leu-Cit; Cit-Leu; Ile-Cit; Cit-Ile; Phe-Arg; Arg-Phe; Cit-Trp; and Trp-Cit.

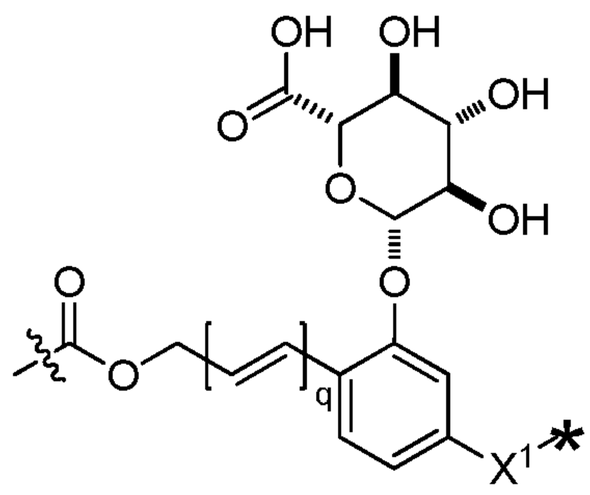
In one embodiment, the lysosomal enzyme is β-glucuronidase or β-galactosidase.

In one embodiment, the linker comprises a segment according to structural formula (Va), (Vb), (Vc), (Vd), or (Ve):

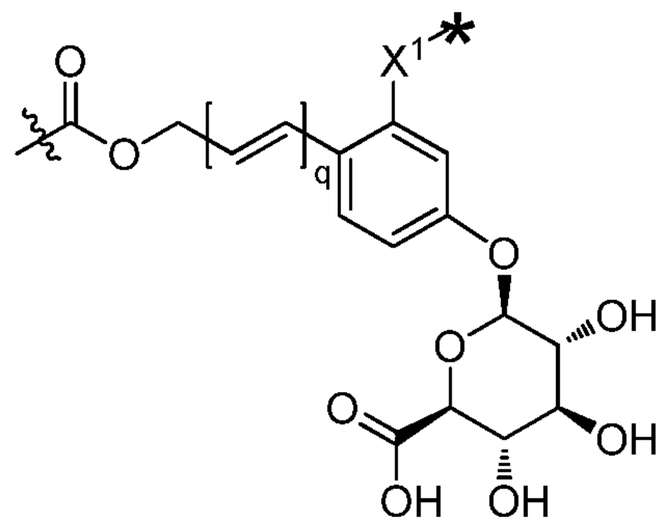
(Va)



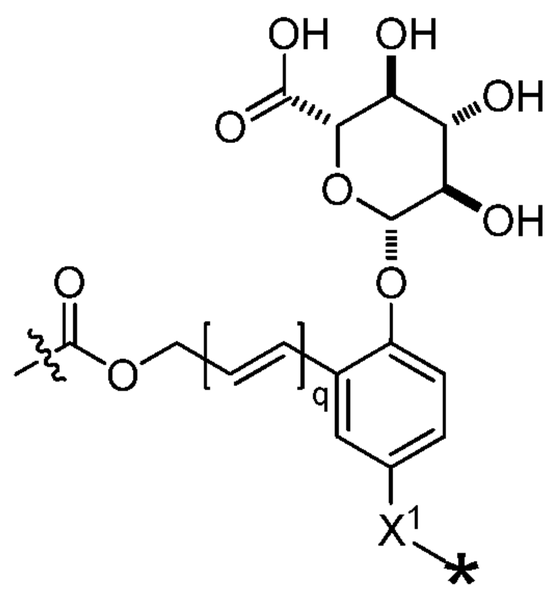
(Vb)



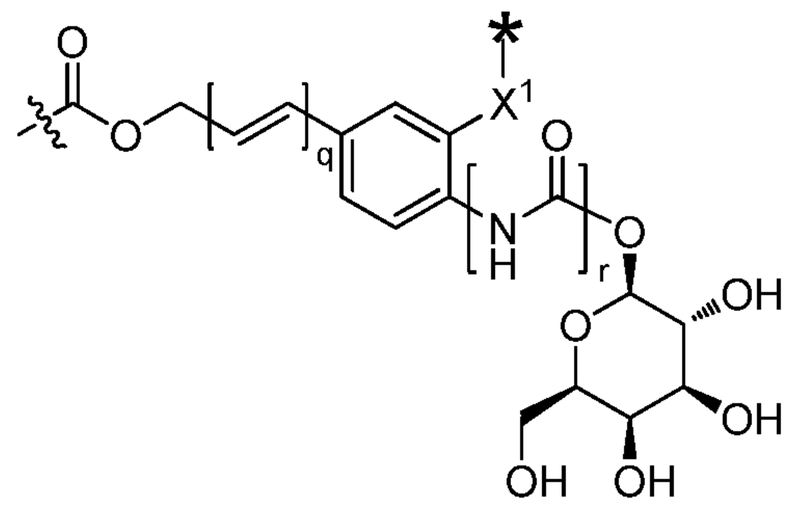
(Vc)



(Vd)

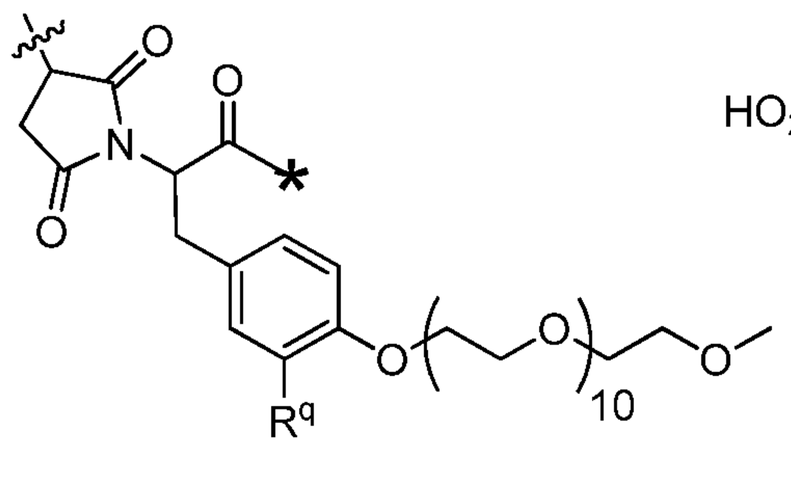


(Ve)

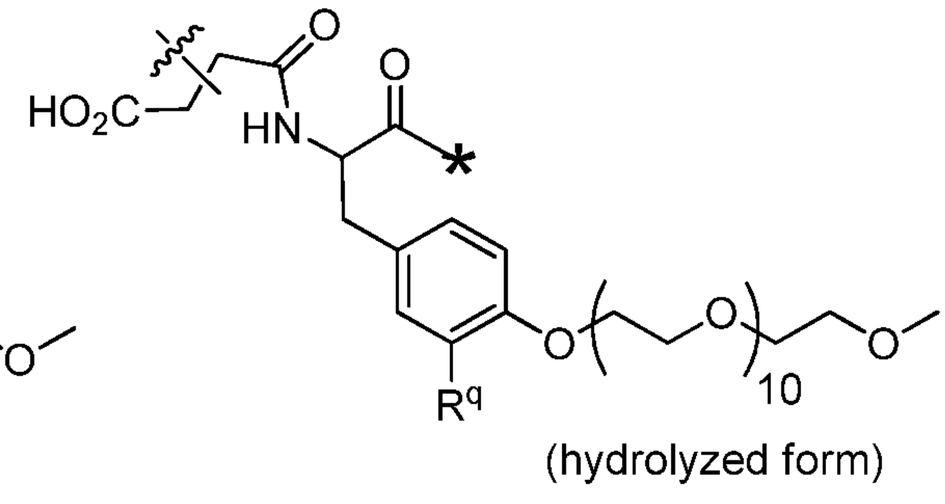


wherein q is 0 or 1; r is 0 or 1; X^1 is CH_2, O or NH; ≈ represents the point of attachment of the linker to the drug; and * represents the point of attachment to the remainder of the linker.

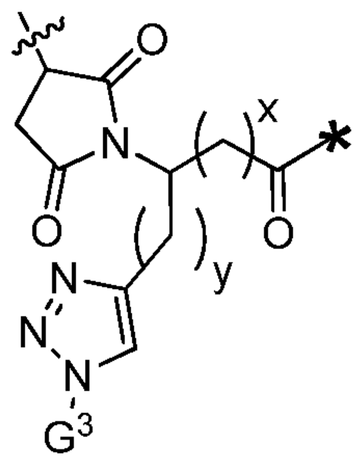
In one embodiment, the linker comprises a segment according to structural formula (VIIIa), (VIIIb), or (VIIIc):



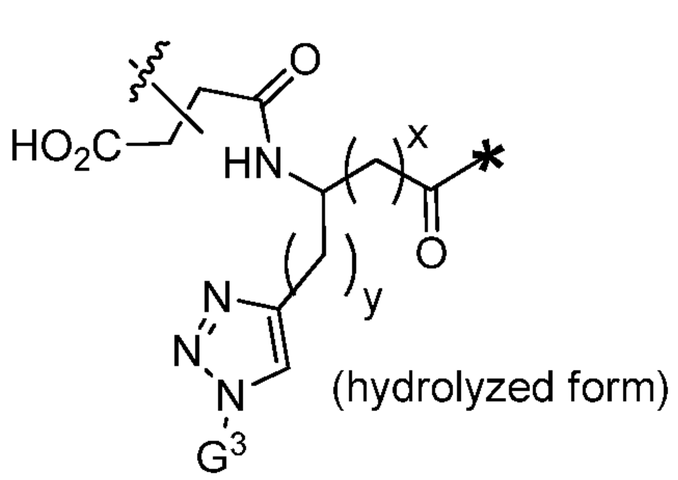
(VIIIa)



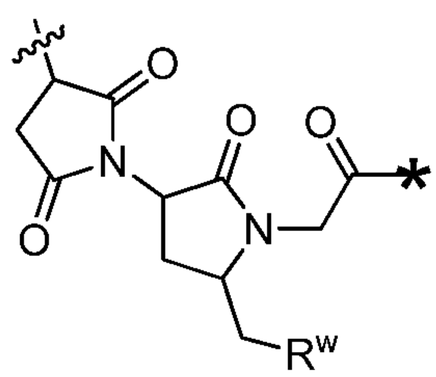
(hydrolyzed form)



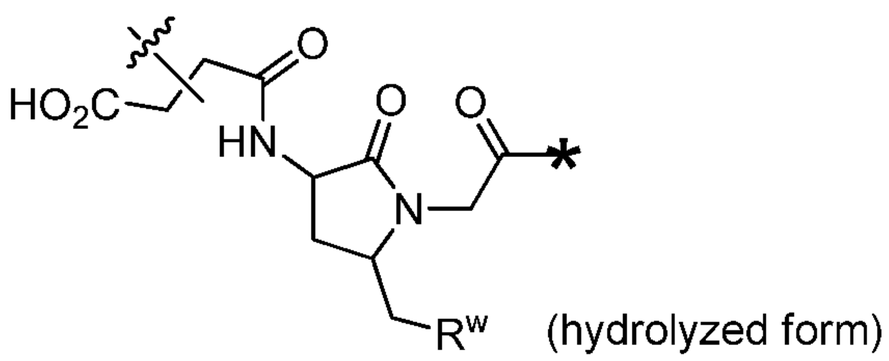
(VIIIb)



(hydrolyzed form)



(VIIIc)



(hydrolyzed form)

or a hydrolyzed derivative thereof, wherein: R^q is H or –O-$(CH_2CH_2O)_{11}$-CH_3; x is 0 or 1; y is 0 or 1; G^3 is –$CH_2CH_2CH_2SO_3H$ or –CH_2CH_2O-$(CH_2CH_2O)_{11}$-CH_3; R^w is –O-$CH_2CH_2SO_3H$ or –NH(CO)-CH_2CH_2O-$(CH_2CH_2O)_{12}$-CH_3; * represents the point of attachment to the remainder of the linker; and ~ represents the point of attachment of the linker to the antibody.

In one embodiment, the linker comprises a polyethylene glycol segment having from 1 to 6 ethylene glycol units.

In one embodiment, m is 2, 3 or 4.

In one embodiment, linker L is selected from IVa or IVb.

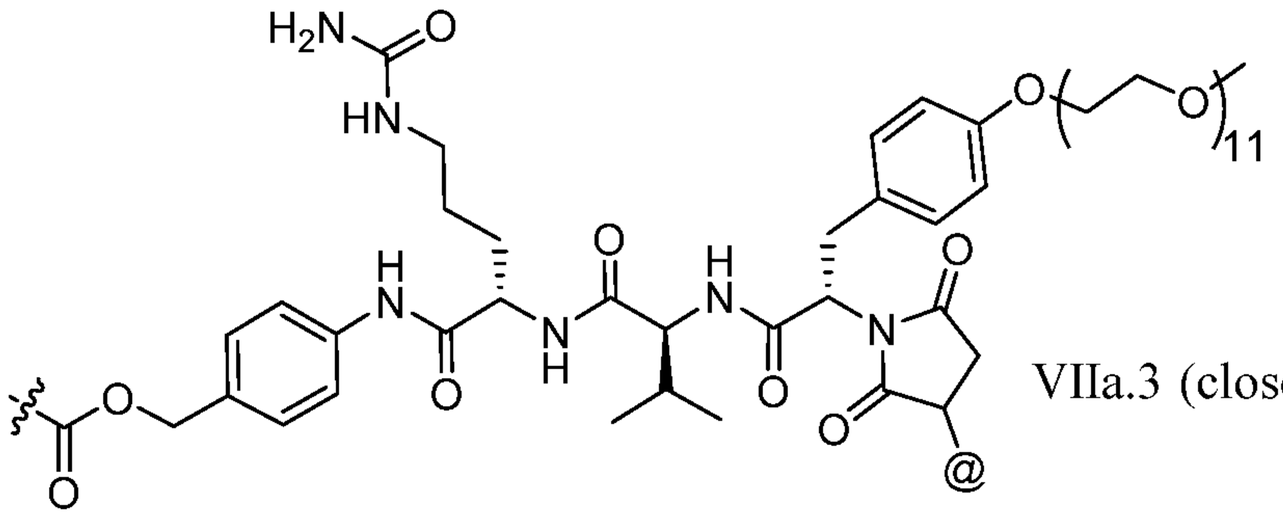
In one embodiment, linker L is selected from the group consisting of IVa.1-IVa.8, IVb.1-IVb.19, IVc.1-IVc.7, IVd.1-IVd.4, Va.1-Va.12, Vb.1-Vb.10, Vc.1-Vc.11, Vd.1-Vd.6, Ve.1-Ve.2, VIa.1, VIc.1-V1c.2, VId.1-VId.4, VIIa.1-VIIa.4, VIIb.1-VIIb.8, VIIc.1-VIIc.6 in either the closed or open form.

In one embodiment, the linker L is selected from the group consisting of IVb.2, IVc.5, IVc.6, IVc.7, IVd.4, Vb.9, VIIa.1, VIIa.3, VIIc.1, VIIc.4, and VIIc.5, wherein the maleimide of each linker

has reacted with the antibody Ab, forming a covalent attachment as either a succinimide (closed form) or succinamide (open form).

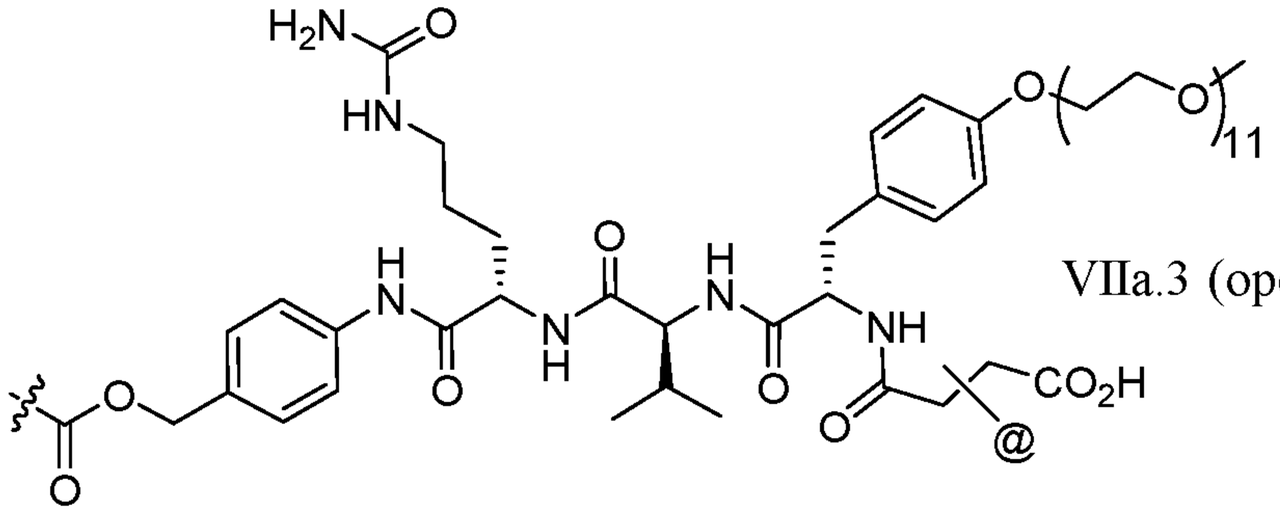
In one embodiment, the linker L is selected from the group consisting of IVb.2, IVc.5, IVc.6, IVd.4, VIIa.1, VIIa.3, VIIc.1, VIIc.4, VIIc.5, wherein the maleimide of each linker has reacted with the antibody Ab, forming a covalent attachment as either a succinimide (closed form) or succinamide (open form).

In one embodiment, the linker L is selected from the group consisting of IVb.2, VIIa.3, IVc.6, and VIIc.1, wherein ~~~ is the attachment point to drug D and @ is the attachment point to the LK, wherein when the linker is in the open form as shown below, @ can be either at the α-position or β-position of the carboxylic acid next to it:



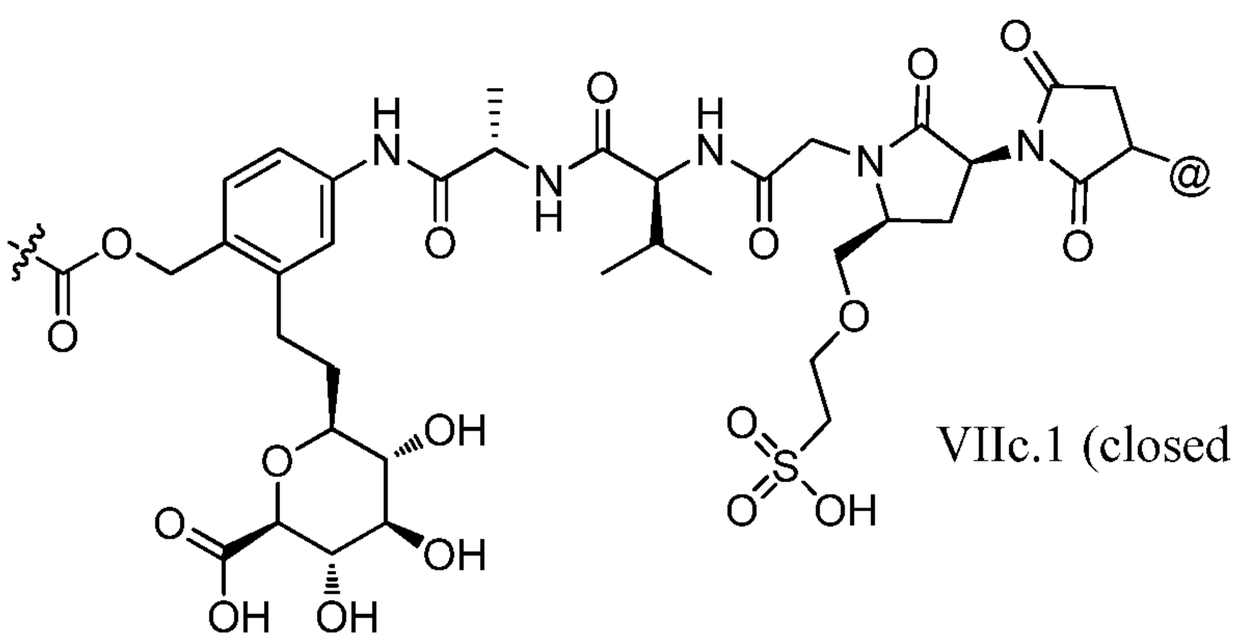
VIIa.3 (closed form)

,



VIIa.3 (open form)

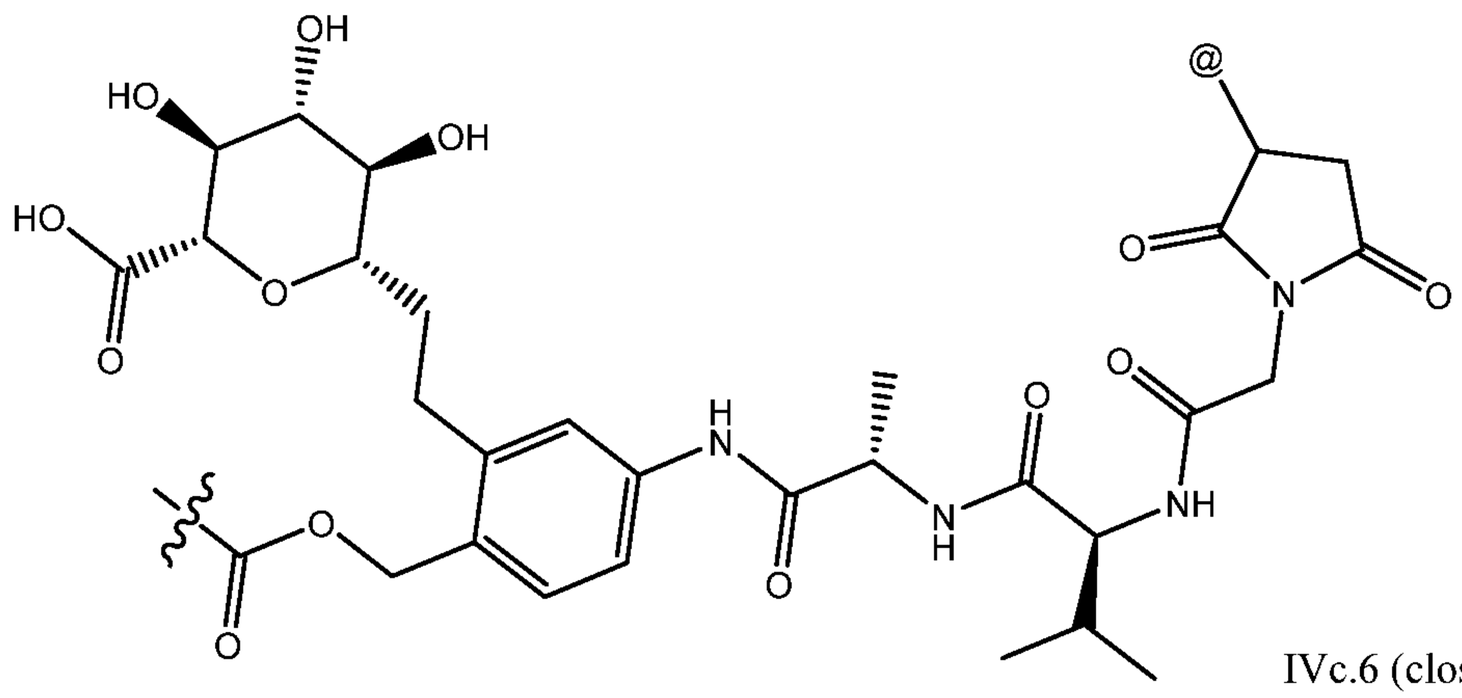
,



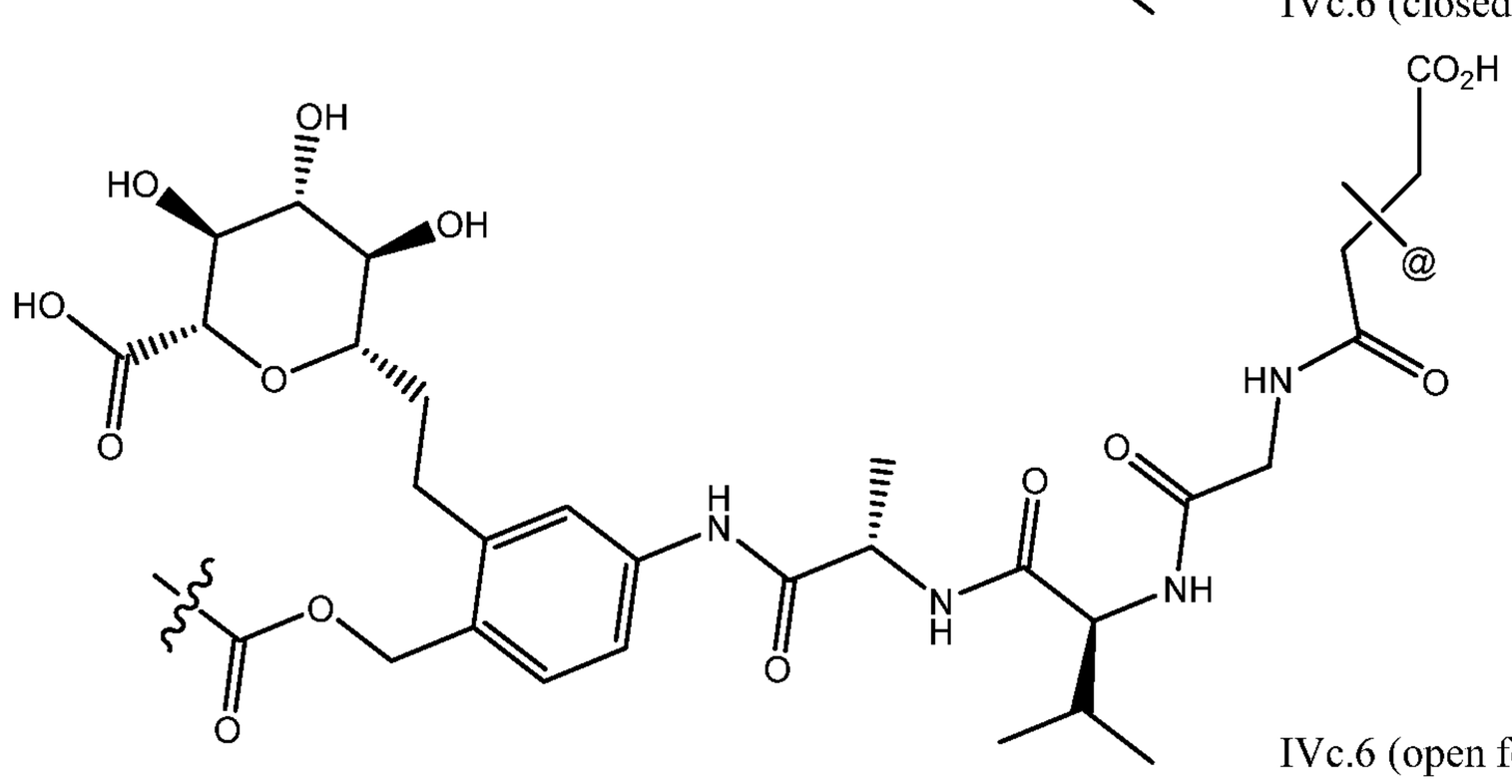
VIIc.1 (closed form)

,

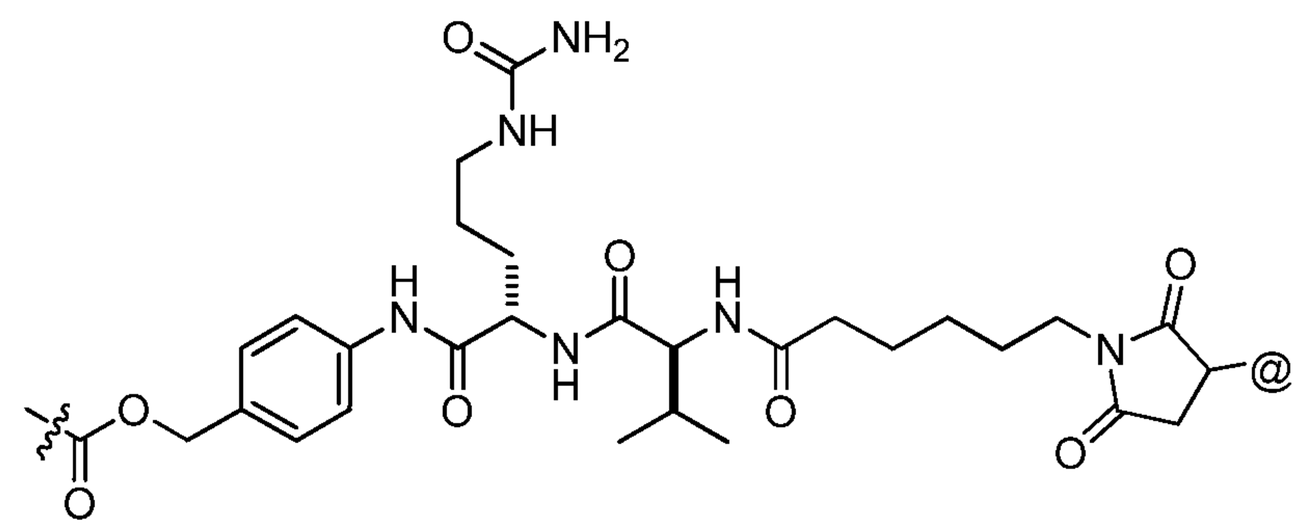
VIIc.1 (open form),



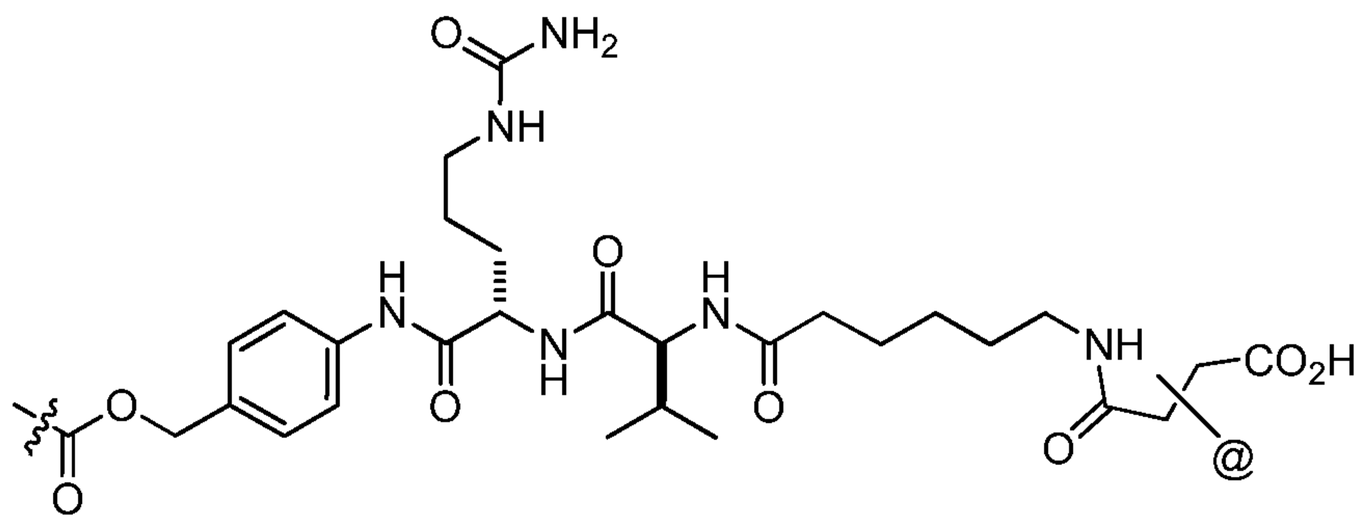
IVc.6 (closed form),



IVc.6 (open form),



IVb.2 (closed form), and



IVb.2 (open form)

In one embodiment, LK is a linkage formed with an amino group on the anti-hB7H3 antibody Ab.

In one embodiment, LK is an amide or a thiourea.

In one embodiment, LK is a linkage formed with a sulfhydryl group on the anti-hB7-H3 antibody Ab.

In one embodiment, LK is a thioether.

In one embodiment, LK is selected from the group consisting of amide, thiourea and thioether; and m is an integer ranging from 1 to 8.

In one embodiment, D is a Bcl-xL inhibitor as described herein; L is selected from the group consisting of linkers IVa.1-IVa.8, IVb.1-IVb.19, IVc.1-IVc.7, IVd.1-IVd.4, Va.1-Va.12, Vb.1-Vb.10, Vc.1-Vc.11, Vd.1-Vd.6, Ve.1-Ve.2, VIa.1, VIc.1-V1c.2, VId.1-VId.4, VIIa.1-VIIa.4, VIIb.1-VIIb.8, and VIIc.1-VIIc.6, wherein each linker has reacted with the antibody, Ab, forming a covalent attachment; LK is thioether; and m is an integer ranging from 1 to 8.

In one embodiment, D is the Bcl-xL inhibitor selected from the group consisting of the following compounds modified in that the hydrogen corresponding to the # position of structural formula (IIa), (IIb), (IIc), or (IId) is not present, forming a monoradical:

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3,5-dimethyl-7-{2-[(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3-{2-[(2-carboxyethyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)naphthalen-2-yl]-3-{1-[(3,5-dimethyl-7-{2-[(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

1-{[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl]amino}-1,2-dideoxy-D-arabino-hexitol;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-(1-{[3-(2-{[3-hydroxy-2-(hydroxymethyl)propyl]amino}ethoxy)-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl]methyl}-5-methyl-1H-pyrazol-4-yl)pyridine-2-carboxylic acid; and

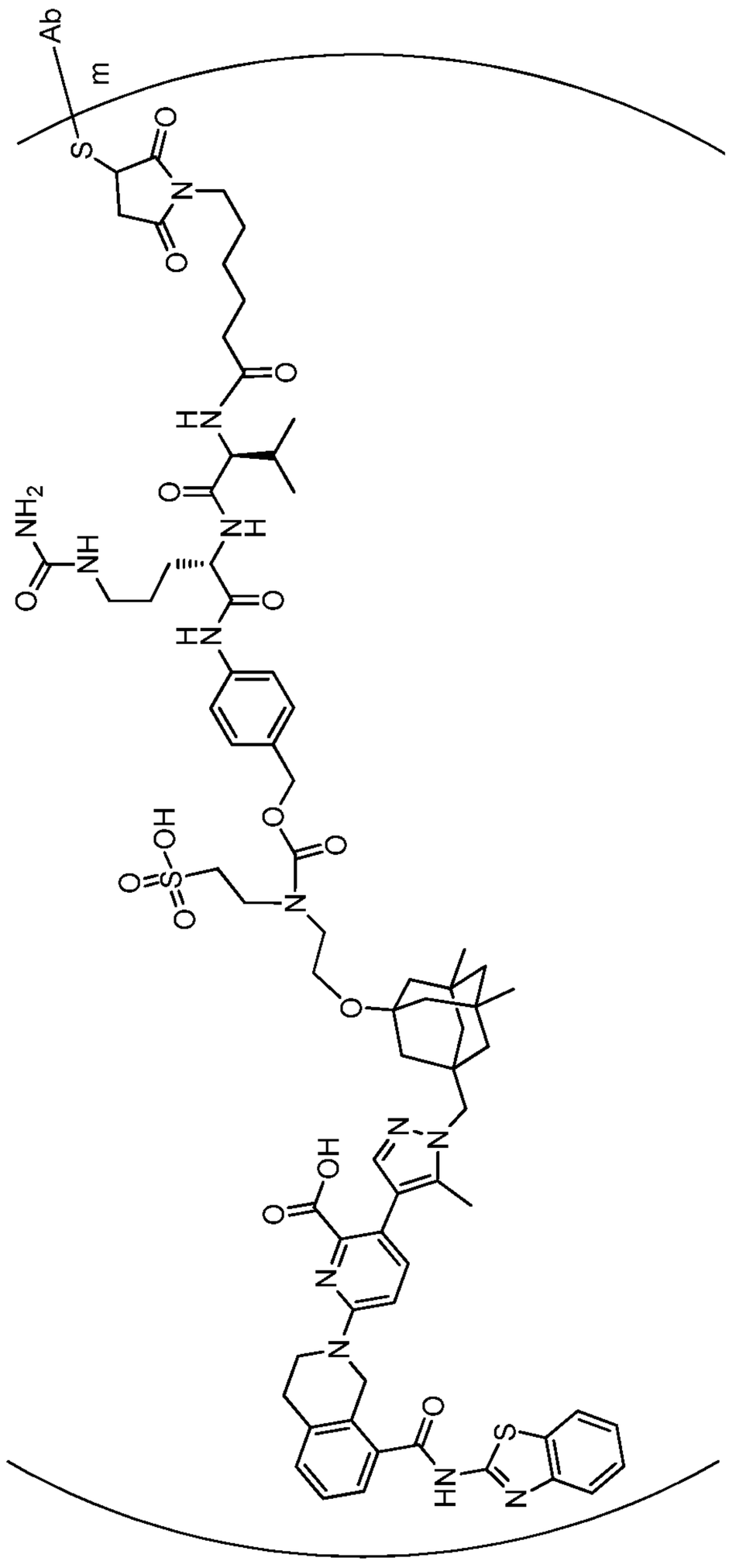
6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]-3-(1-{[3-(2-{[(3*S*)-3,4-dihydroxybutyl]amino}ethoxy)-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl]methyl}-5-methyl-1*H*-pyrazol-4-yl)pyridine-2-carboxylic acid;

L is selected from the group consisting of linkers IVb.2, IVc.5, IVc.6, IVc.7, IVd.4, Vb.9, Vc.11, VIIa.1, VIIa.3, VIIc.1, VIIc.4, and VIIc.5 in either closed or open forms;

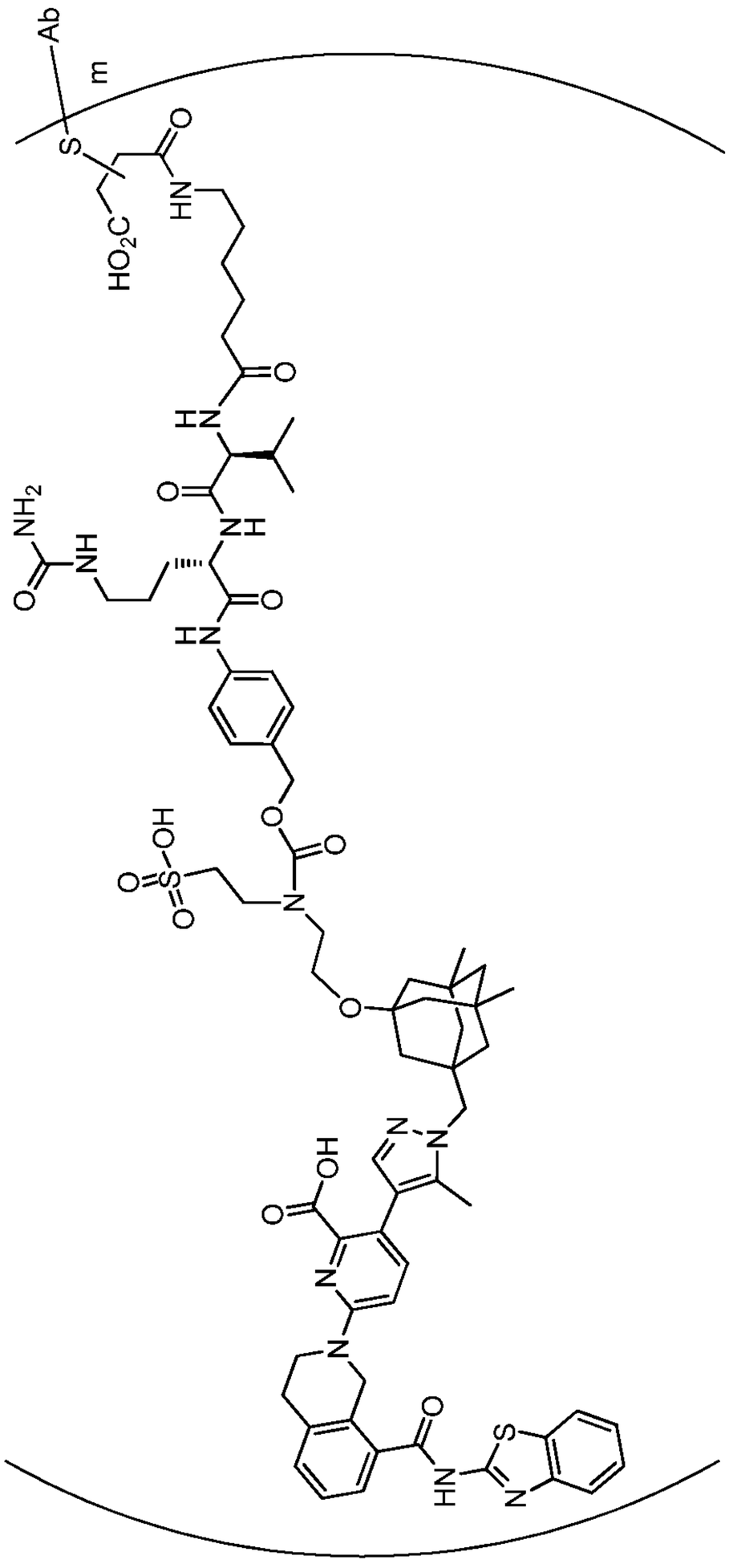
LK is thioether; and

m is an integer ranging from 2 to 4.

In one embodiment, the ADC is selected from the group consisting of formulae i-vi:

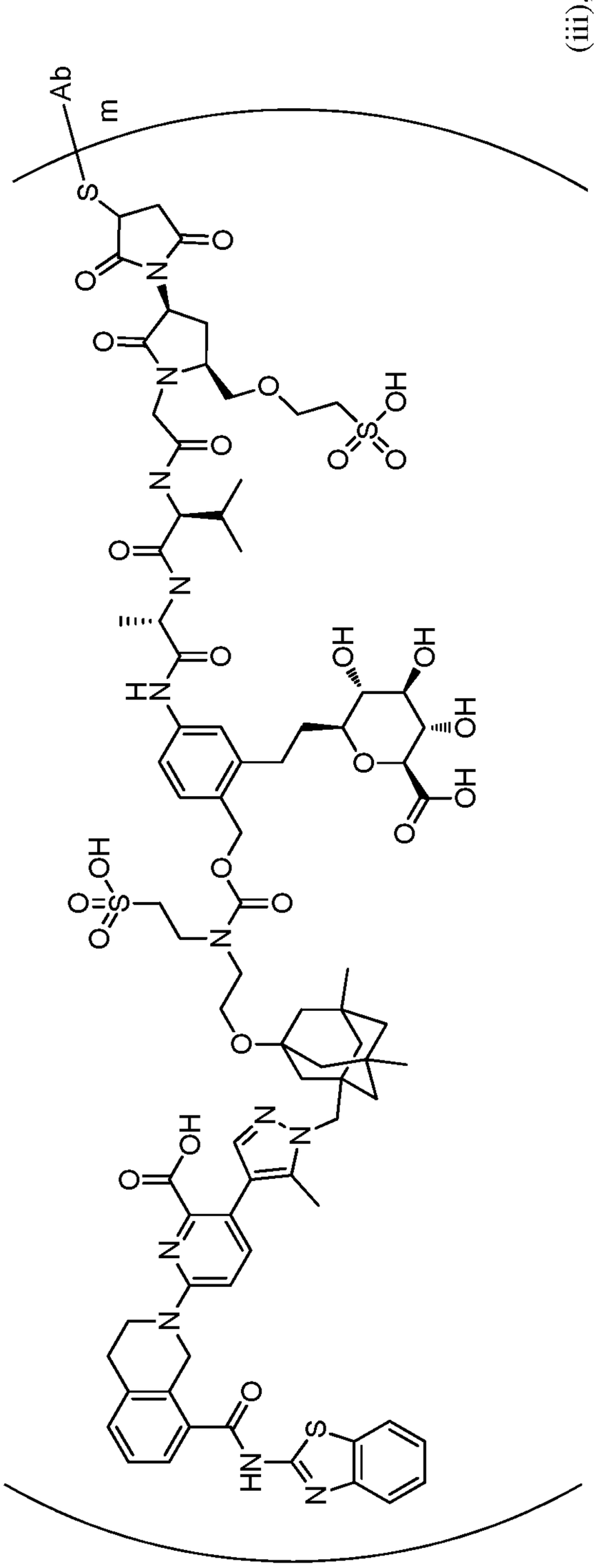


(i),

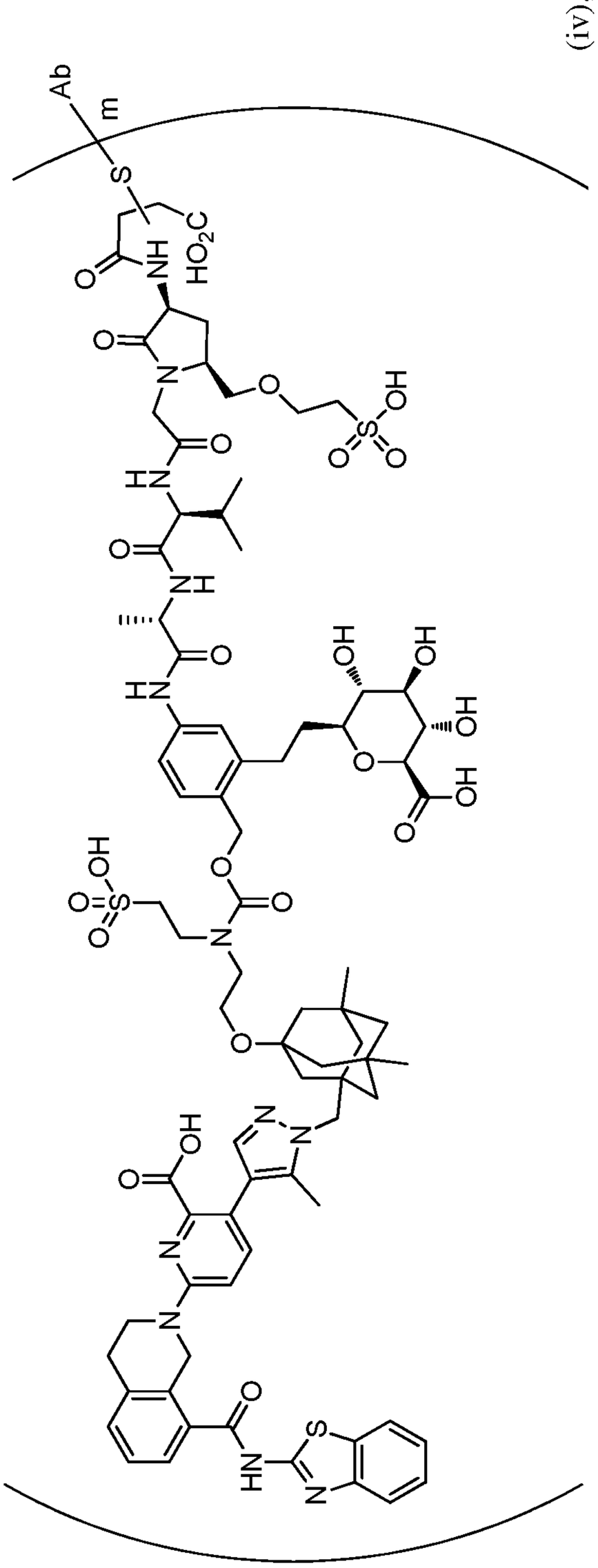


(ii),

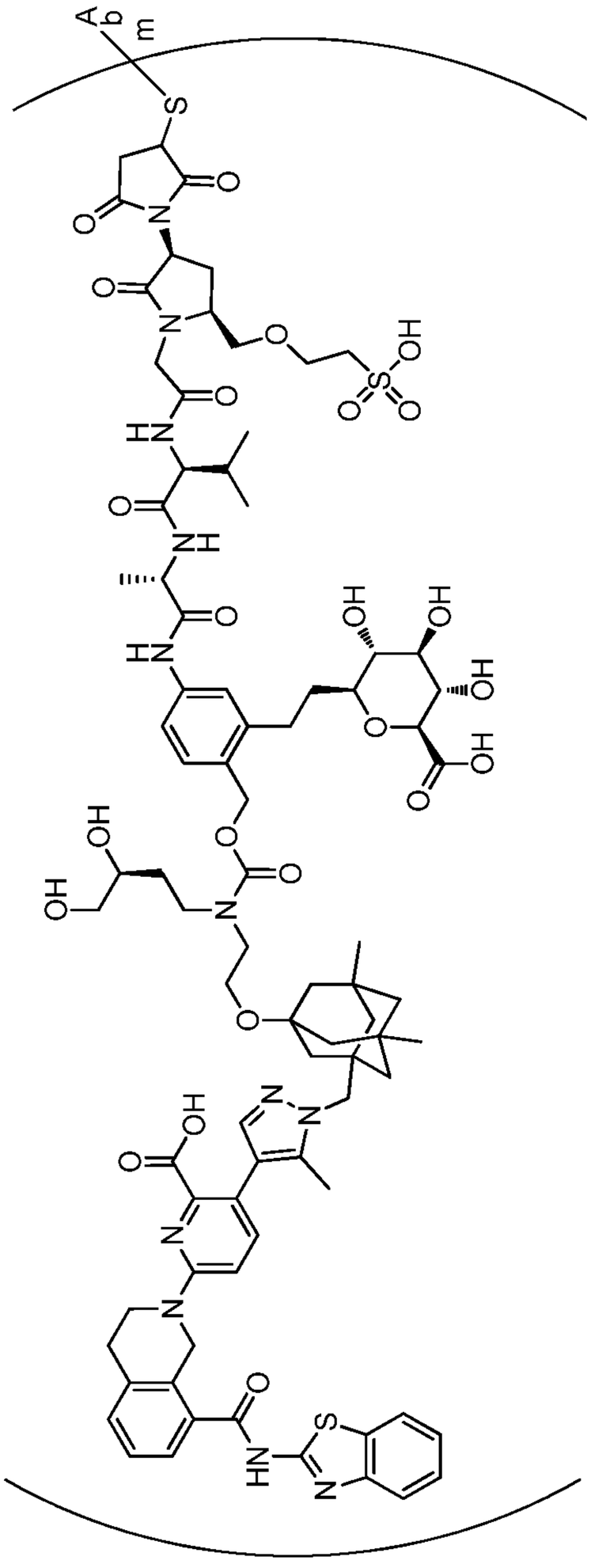
(iii)



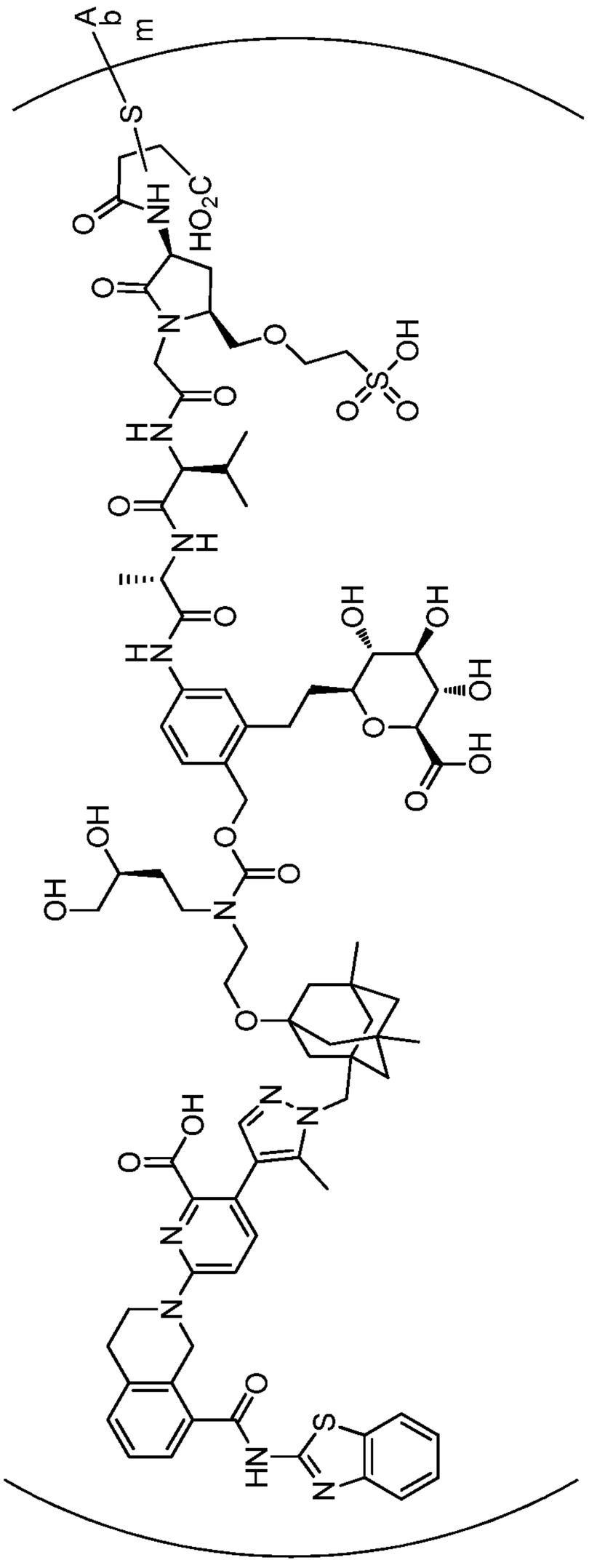
(iv)



(v), and



(vi),



wherein m is an integer from 1 to 6. In one embodiment, Ab is an anti-hB7-H3 antibody, wherein the anti-hB7-H3 antibody comprises a heavy chain CDR3 domain comprising the amino acid sequence set forth in SEQ ID NO: 35, a heavy chain CDR2 domain comprising the amino acid sequence set forth in SEQ ID NO: 34, and a heavy chain CDR1 domain comprising the amino acid sequence set forth in SEQ ID NO: 33; and a light chain CDR3 domain comprising the amino acid sequence set forth in SEQ ID NO: 39, a light chain CDR2 domain comprising the amino acid sequence set forth in SEQ ID NO: 38, and a light chain CDR1 domain comprising the amino acid sequence set forth in SEQ ID NO: 37. In one embodiment, the Ab is an anti-hB7-H3 antibody, wherein the anti-hB7H3 antibody comprises a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 147, and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 144. In one embodiment, Ab is an anti-hB7-H3 antibody, wherein the anti-hB7-H3 antibody comprises a heavy chain constant region comprising the amino acid sequence set forth in SEQ ID NO: 160 and/or a light chain constant region comprising the amino acid sequence set forth in SEQ ID NO: 161. In one embodiment, Ab is an anti-hB7-H3 antibody, wherein the anti-hB7-H3 antibody comprises a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 168, and a light chain comprising the amino acid sequence set forth in SEQ ID NO: 169. In one embodiment, Ab is an anti-hB7-H3 antibody, wherein the anti-hB7-H3 antibody comprises a heavy chain CDR3 domain comprising the amino acid sequence set forth in SEQ ID NO: 12, a heavy chain CDR2 domain comprising the amino acid sequence set forth in SEQ ID NO: 140, and a heavy chain CDR1 domain comprising the amino acid sequence set forth in SEQ ID NO: 10; and a light chain CDR3 domain comprising the amino acid sequence set forth in SEQ ID NO: 15, a light chain CDR2 domain comprising the amino acid sequence set forth in SEQ ID NO: 7, and a light chain CDR1 domain comprising the amino acid sequence set forth in SEQ ID NO: 136. In one embodiment, the Ab is an anti-hB7-H3 antibody, wherein the anti-hB7H3 antibody comprises a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 139, and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 135. In one embodiment, Ab is an anti-hB7-H3 antibody, wherein the anti-hB7-H3 antibody comprises a heavy chain constant region comprising the amino acid sequence set forth in SEQ ID NO: 160 and/or a light chain constant region comprising the amino acid sequence set forth in SEQ ID NO: 161. In one embodiment, Ab is an anti-hB7-H3 antibody, wherein the anti-hB7-H3 antibody comprises a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 170, and a light chain comprising the amino acid sequence set forth in SEQ ID NO: 171.

In one embodiment, m is an integer from 2 to 6. In one embodiment, m is 2.

In one embodiment, the ADC comprises an anti-hB7-H3 antibody comprising a heavy chain CDR3 domain comprising the amino acid sequence set forth in SEQ ID NO: 12, a heavy chain CDR2 domain comprising the amino acid sequence set forth in SEQ ID NO: 140, and a heavy chain CDR1

domain comprising the amino acid sequence set forth in SEQ ID NO: 10; a light chain CDR3 domain comprising the amino acid sequence set forth in SEQ ID NO: 15, a light chain CDR2 domain comprising the amino acid sequence set forth in SEQ ID NO: 7, and a light chain CDR1 domain comprising the amino acid sequence set forth in SEQ ID NO: 136 or 138.

In one embodiment, the ADC comprises an antibody comprising a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 139, and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 135.

In one embodiment, the ADC comprises an the antibody comprising a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 139, and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 137.

In one embodiment, the ADC comprises an antibody comprising a light chain CDR3 domain comprising the amino acid sequence set forth in SEQ ID NO: 39, a light chain CDR2 domain comprising the amino acid sequence set forth in SEQ ID NO: 38, and a light chain CDR1 domain comprising the amino acid sequence set forth in SEQ ID NO: 37; and a heavy chain CDR3 domain comprising the amino acid sequence set forth in SEQ ID NO: 35, a heavy chain CDR2 domain comprising the amino acid sequence set forth in SEQ ID NO: 34, and a heavy chain CDR1 domain comprising the amino acid sequence set forth in SEQ ID NO: 33.

In one embodiment, the ADC comprises an antibody comprising a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 147, and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 144.

In one embodiment, the ADC is selected from the group consisting of huAb3v2.5-CZ, huAb3v2.5-TX, huAb3v2.5-TV, huAb3v2.5-YY, huAb3v2.5-AAA, huAb3v2.5-AAD, huAb3v2.6-CZ, huAb3v2.6-TX, huAb3v2.6-TV, huAb3v2.6-YY, huAb3v2.6-AAD, huAb13v1-CZ, huAb13v1-TX, huAb13v1-TV, huAb13v1-YY, huAb13v1-AAA, huAb13v1-AAD, wherein CZ, TX, TV, YY, AAA, and AAD are synthons disclosed in Table B, and wherein the conjugated synthons are either in open or closed form.

In one aspect, the present invention provides a pharmaceutical composition comprising an effective amount of an ADC described herein, and a pharmaceutically acceptable carrier.

In another aspect, the present invention provides a pharmaceutical composition comprising an ADC mixture comprising a plurality of ADCs described herein, and a pharmaceutically acceptable carrier.

In one embodiment, the ADC mixture has an average drug to antibody ratio (DAR) of 1.5 to 4.

In one embodiment, the ADC mixture comprises ADCs each having a DAR of 1.5 to 8.

In one aspect, the present invention provides a method for treating cancer, comprising administering a therapeutically effective amount of an ADC described herein to a subject in need thereof.

In one embodiment, the cancer is selected from the group consisting of small cell lung cancer, non small cell lung cancer, breast cancer, ovarian cancer, a glioblastoma, prostate cancer, pancreatic cancer, colon cancer, gastric cancer, melanoma, hepatocellular carcinoma, head and neck cancer, kidney cancer, leukemia, e.g., acute myeloid leukemia (AML), and lymphoma, e.g., non-Hodgkin's lymphoma (NHL).

In one embodiment, the cancer is a squamous cell carcinoma. In one embodiment, the squamous cell carcinoma is squamous lung cancer or squamous head and neck cancer.

In one embodiment, the cancer is triple negative breast cancer.

In one embodiment, the cancer is non-small cell lung cancer.

In one embodiment, the cancer is characterized as having an activating EGFR mutation. In one embodiment, the activating EGFR mutation is selected from the group consisting of an exon 19 deletion mutation, a single-point substitution mutation L858R in exon 21, a T790M point mutation, and combinations thereof.

In one aspect, the present invention provides a method for inhibiting or decreasing solid tumor growth in a subject having a solid tumor, said method comprising administering an effective amount of an ADC described herein to the subject having the solid tumor, such that the solid tumor growth is inhibited or decreased.

In one embodiment, the solid tumor is a non-small cell lung carcinoma.

In one embodiment, the ADC is administered in combination with an additional agent or an additional therapy.

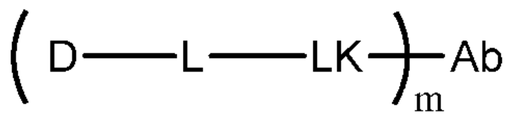
In one embodiment, the additional agent is selected from the group consisting of an anti-PD1 antibody (e.g. pembrolizumab), an anti-PD-L1 antibody (*e.g.*, atezolizumab), an anti-CTLA-4 antibody (e.g. ipilimumab), a MEK inhibitor (e.g. trametinib), an ERK inhibitor, a BRAF inhibitor (e.g. dabrafenib), osimertinib, erlotinib, gefitinib, sorafenib, a CDK9 inhibitor (e.g. dinaciclib), a MCL-1 inhibitor, temozolomide, a Bcl-2 inhibitor (*e.g.* venetoclax), a Bcl-xL inhibitor, ibrutinib, a mTOR inhibitor (e.g. everolimus), a PI3K inhibitor (e.g. buparlisib), duvelisib, idelalisib, an AKT inhibitor, a HER2 inhibitor (e.g. lapatinib), a taxane (e.g. docetaxel, paclitaxel, nab-paclitaxel), an ADC comprising an auristatin, an ADC comprising a PBD (e.g. rovalpituzumab tesirine), an ADC comprising a maytansinoid (e.g. TDM1), a TRAIL agonist, a proteasome inhibitor (e.g. bortezomib), and a nicotinamide phosphoribosyltransferase (NAMPT) inhibitor.

In one embodiment, the anti-B7-H3 ADCs of the invention are administered in combination with venetoclax to a human subject for the treatment of small cell lung cancer (SCLC).

In one embodiment, the additional therapy is radiation.

In one embodiment, the additional agent is a chemotherapeutic agent.

In one aspect, the present invention provides a process for the preparation of an ADC according to structural formula (I):

(I) 

wherein:

D is the Bcl-xL inhibitor drug of formula (IIa), (IIb), (IIc), or (IId) as disclosed herein;

L is the linker as disclosed herein;

Ab is an hB7-H3 antibody, wherein the hB7-H3 antibody comprises the heavy and light chain CDRs of huAb3v2.5, huAb3v2.6, or huAb13v1;

LK represents a covalent linkage linking linker L to antibody Ab; and

m is an integer ranging from 1 to 20;

the process comprising:

treating an antibody in an aqueous solution with an effective amount of a disulfide reducing agent at 30-40 °C for at least 15 minutes, and then cooling the antibody solution to 20-27 °C;

adding to the reduced antibody solution a solution of water/dimethyl sulfoxide comprising a synthon selected from the group of 2.1 to 2.176 (Table B);

adjusting the pH of the solution to a pH of 7.5 to 8.5;

allowing the reaction to run for 48 to 80 hours to form the ADC;

wherein the mass is shifted by 18 ± 2 amu for each hydrolysis of a succinimide to a succinamide as measured by electron spray mass spectrometry; and

wherein the ADC is optionally purified by hydrophobic interaction chromatography.

In one embodiment, m is 2.

In another aspect, the present invention provides an ADC prepared by the process as described above.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graphical representation of the epitope grouping of murine anti-B7-H3 hybridoma antibodies as determined by pair-wise binding assays.

Figure 2 depicts an antibody reduction, modification with a maleimide derivative to give a thiosuccinimide intermediate, and subsequent hydrolysis of thiosuccinimide moiety

Figure 3 depicts the structure of an antibody-maleimidocaproyl-vc-PABA-MMAE ADC.

Figure 4 depicts the structure of a PBD dimer (SGD-1882) conjugated to an antibody (Ab) via a maleimidocaproyl-valine-alanine linker (collectively referred to as SGD-1910).

Figure 5 depicts the MS characterization of light chain and heavy chain of huAb13v1 1) prior to conjugation, 2) after conjugation to a maleimide derivative to give a thiosuccinimide intermediate and 3) post pH 8-mediated hydrolysis of the thiosuccinimide ring.

DETAILED DESCRIPTION OF THE INVENTION

Various aspects of the invention relate to anti-B7-H3 antibodies and antibody fragments, anti-B7-H3 ADCs, and pharmaceutical compositions thereof, as well as nucleic acids, recombinant expression vectors and host cells for making such antibodies and fragments. Methods of using the antibodies, fragments, and ADCs described herein to detect human B7-H3, to inhibit human B7-H3 activity (*in vitro* or *in vivo*), and to treat cancers are also encompassed by the invention. In certain embodiments, the invention provides anti-B7-H3 ADCs, including ADCs comprising Bcl-xL inhibitors, synthons useful for synthesizing the ADCs, compositions comprising the ADCs, methods of making the ADCs, and various methods of using the ADCs.

As will be appreciated by skilled artisans, the ADCs disclosed herein are "modular" in nature. Throughout the instant disclosure, various specific embodiments of the various "modules" comprising the ADCs, as well as the synthons useful for synthesizing the ADCs, are described. As specific non-limiting examples, specific embodiments of antibodies, linkers, and Bcl-xL inhibitors that may comprise the ADCs and synthons are described. It is intended that all of the specific embodiments described may be combined with each other as though each specific combination were explicitly described individually.

It will also be appreciated by skilled artisans that the various ADCs and/or ADC synthons described herein may be in the form of salts, and in certain embodiments, particularly pharmaceutically acceptable salts. The compounds of the present disclosure that possess a sufficiently acidic, a sufficiently basic, or both functional groups, can react with any of a number of inorganic bases, and inorganic and organic acids, to form a salt. Alternatively, compounds that are inherently charged, such as those with a quaternary nitrogen, can form a salt with an appropriate counterion, e.g., a halide such as a bromide, chloride, or fluoride.

Acids commonly employed to form acid addition salts are inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids such as p-toluenesulfonic acid, methanesulfonic acid, oxalic acid, p-bromophenyl-sulfonic acid, carbonic acid, succinic acid, citric acid, etc. Base addition salts include those derived from inorganic bases, such as ammonium and alkali or alkaline earth metal hydroxides, carbonates, bicarbonates, and the like.

In the disclosure below, if both structural diagrams and nomenclature are included and if the nomenclature conflicts with the structural diagram, the structural diagram controls.

An outline of the Detailed Description of the Invention is provided below:

I. Definitions

II. Anti-B7-H3 Antibodies

II.A. Anti-B7-H3 Chimeric Antibodies

II.B. Humanized Anti-B7-H3 Antibodies

III. Anti-B7-H3 Antibody Drug Conjugates (ADCs)

III.A. Anti-B7-H3 / Bcl-xL Inhibitor ADCs

III.A.1. Bcl-xL Inhibitors

III.A.2 Bcl-xL Linkers

Cleavable Linkers

Non-Cleavable Linkers

Groups Used to Attach Linkers to Anti-B7-H3 Antibodies

Linker Selection Considerations

III.A.3. Bcl-xL ADC Synthons

III.A.4 Methods of Synthesis of Bcl-xL ADCs

III.A.5. General Methods for Synthesizing Bcl-xL Inhibitors

III.A.6. General Methods for Synthesizing Synthons

III.A.7. General Methods for Synthesizing Anti-B7-H3 ADCs

III.B. Anti-B7-H3 ADCs: Other Exemplary Drugs for Conjugation

III.C. Anti-B7-H3 ADCs: Other Exemplary Linkers

IV. Purification of Anti-B7-H3 ADCs

V. Uses of Anti-B7-H3 Antibodies and Anti-B7-H3 ADCs

VI. Pharmaceutical Compositions

I. Definitions

In order that the invention may be more readily understood, certain terms are first defined. In addition, it should be noted that whenever a value or range of values of a parameter are recited, it is intended that values and ranges intermediate to the recited values are also intended to be part of this invention.

The term "anti-B7-H3 antibody" refers to an antibody that specifically binds to B7-H3. An antibody "which binds" an antigen of interest, *i.e.,* B7-H3, is one capable of binding that antigen with sufficient affinity such that the antibody is useful in targeting a cell expressing the antigen. In a preferred embodiment, the antibody specifically binds to human B7-H3 (hB7-H3). Examples of anti-B7-H3 antibodies are disclosed in the examples below. Unless otherwise indicated, the term "anti-B7-H3 antibody" is meant to refer to an antibody which binds to wild type B7-H3 (e.g., a 4IgB7-H3 isoform of B7-H3) or any variant of B7-H3. The amino acid sequence of wild type human B7-H3 is provided below as SEQ ID NO: 149, where the signal peptide (amino acid residues 1-28) is underlined.

MLRRRGSPGMGVHVGAALGALWFCLTGALEVQVPEDPVVALVGTDATLCCSFSPEPGFSLAQLNLIWQ
LTDTKQLVHSFAEGQDQGSAYANRTALFPDLLAQGNASLRLQRVRVADEGSFTCFVSIRDFGSAAVSL
QVAAPYSKPSMTLEPNKDLRPGDTVTITCSSYQGYPEAEVFWQDGQGVPLTGNVTTSQMANEQGLFDV
HSILRVVLGANGTYSCLVRNPVLQQDAHSSVTITPQRSPTGAVEVQVPEDPVVALVGTDATLRCSFSP
EPGFSLAQLNLIWQLTDTKQLVHSFTEGRDQGSAYANRTALFPDLLAQGNASLRLQRVRVADEGSFTC
FVSIRDFGSAAVSLQVAAPYSKPSMTLEPNKDLRPGDTVTITCSSYRGYPEAEVFWQDGQGVPLTGNV
TTSQMANEQGLFDVHSVLRVVLGANGTYSCLVRNPVLQQDAHGSVTITGQPMTFPPEALWVTVGLSVC
LIALLVALAFVCWRKIKQSCEEENAGAEDQDGEGEGSKTALQPLKHSDSKEDDGQEIA (SEQ ID
NO: 149)

Thus, in one embodiment of the invention, the antibody or ADC binds human B7-H3 as defined in SEQ ID NO: 149. The extracellular domain (ECD) of human B7-H3 is provided in SEQ ID NO: 152 (inclusive of a His tag). As such, in one embodiment of the invention, the antibody of ADC binds the ECD of human B7-H3 as described in the ECD of SEQ ID NO: 152.

The terms "specific binding" or "specifically binding", as used herein, in reference to the interaction of an antibody or an ADC with a second chemical species, mean that the interaction is dependent upon the presence of a particular structure (*e.g.*, an antigenic determinant or epitope) on the chemical species; for example, an antibody recognizes and binds to a specific protein structure rather than to proteins generally. If an antibody or ADC is specific for epitope "A", the presence of a molecule containing epitope A (or free, unlabeled A), in a reaction containing labeled "A" and the antibody, will reduce the amount of labeled A bound to the antibody or ADC. By way of example, an antibody "binds specifically" to a target if the antibody, when labeled, can be competed away from its target by the corresponding non-labeled antibody. In one embodiment, an antibody specifically binds to a target, *e.g.,* B7-H3, if the antibody has a K_D for the target of at least about 10^{-4} M, 10^{-5} M, 10^{-6} M, 10-7 M, 10^{-8} M, 10^{-9} M, 10^{-10} M, 10^{-11} M, 10^{-12} M, or less (less meaning a number that is less than 10^{-12}, *e.g.* 10^{-13}). In one embodiment, the term "specific binding to B7-H3" or "specifically binds to B7-H3," as used herein, refers to an antibody or an ADC that binds to B7-H3 and has a dissociation constant (K_D) of 1.0 x 10^{-7} M or less, as determined by surface plasmon resonance. It shall be understood, however, that the antibody or ADC may be capable of specifically binding to two or more antigens which are related in sequence. For example, in one embodiment, an antibody can specifically bind to both human and a non-human (e.g., mouse or non-human primate) orthologs of B7-H3.

The term "antibody" refers to an immunoglobulin molecule that specifically binds to an antigen and comprises a heavy (H) chain(s) and a light (L chain(s). Each heavy chain is comprised of a heavy chain variable region (abbreviated herein as HCVR or VH) and a heavy chain constant region. The heavy chain constant region is comprised of three domains, CH1, CH2 and CH3. Each light chain is comprised of a light chain variable region (abbreviated herein as LCVR or VL) and a light chain constant region. The light chain constant region is comprised of one domain, CL. The VH and VL regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each VH and VL is composed of three CDRs and four FRs, arranged from amino-

terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. An antibody can be of any type (e.g., IgG, IgE, IgM, IgD, IgA and IgY) and class (e.g., IgG1, IgG2, IgG 3, IgG4, IgA1 and IgA2) or subclass.

While the term "antibody" is not intended to include antigen binding portions of an antibody (defined below), it is intended, in certain embodiments, to include a small number of amino acid deletions from the carboxy end of the heavy chain(s). In one embodiment, an antibody comprises a heavy chain having 1-5 amino acid deletions the carboxy end of the heavy chain. In one embodiment, an antibody is a monoclonal antibody which is an IgG, having four polypeptide chains, two heavy (H) chains, and two light (L chains) that can bind to hB7-H3. In one embodiment, an antibody is a monoclonal IgG antibody comprising a lambda or a kappa light chain.

The term "antigen binding portion" or "antigen binding fragment" of an antibody (or simply "antibody portion" or "antibody fragment"), as used herein, refers to one or more fragments of an antibody that retain the ability to specifically bind to an antigen (*e.g.*, hB7-H3). It has been shown that the antigen binding function of an antibody can be performed by fragments of a full-length antibody. Such antibody embodiments may also be bispecific, dual specific, or multi-specific formats; specifically binding to two or more different antigens. Examples of binding fragments encompassed within the term "antigen binding portion" of an antibody include (i) a Fab fragment, a monovalent fragment consisting of the VL, VH, CL and CH1 domains; (ii) a $F(ab')_2$ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the VH and CH1 domains; (iv) a Fv fragment consisting of the VL and VH domains of a single arm of an antibody, (v) a dAb fragment (Ward *et al.*, (1989) *Nature* 341:544-546, Winter et al., PCT publication WO 90/05144 A1 herein incorporated by reference), which comprises a single variable domain; and (vi) an isolated complementarity determining region (CDR). Furthermore, although the two domains of the Fv fragment, VL and VH, are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the VL and VH regions pair to form monovalent molecules (known as single chain Fv (scFv); see *e.g.*, Bird *et al.* (1988) *Science* 242:423-426; and Huston *et al.* (1988) *Proc. Natl. Acad. Sci. USA* 85:5879-5883). Such single chain antibodies are also intended to be encompassed within the term "antigen binding portion" of an antibody. In certain embodiments of the invention, scFv molecules may be incorporated into a fusion protein. Other forms of single chain antibodies, such as diabodies are also encompassed. Diabodies are bivalent, bispecific antibodies in which VH and VL domains are expressed on a single polypeptide chain, but using a linker that is too short to allow for pairing between the two domains on the same chain, thereby forcing the domains to pair with complementary domains of another chain and creating two antigen binding sites (see *e.g.*, Holliger, P., *et al.* (1993) *Proc. Natl. Acad. Sci. USA* 90:6444-6448; Poljak, R.J., *et al.* (1994)

Structure 2:1121-1123). Such antibody binding portions are known in the art (Kontermann and Dubel eds., Antibody Engineering (2001) Springer-Verlag. New York. 790 pp. (ISBN 3-540-41354-5).

An IgG is a class of antibody comprising two heavy chains and two light chains arranged in a Y-shape. An IgG constant domain refers to a heavy or light chain constant domain. Exemplary human IgG heavy chain and light chain constant domain amino acid sequences are known in the art and represented below in Table A.

Table A: Sequences of human IgG heavy chain constant domains and light chain constant domains

Protein	Sequence Identifier	Sequence
Ig gamma-1 constant region	SEQ ID NO:159	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAPELLGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKG QPREPQVYTLPPSREEMTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFF LYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK
Ig gamma-1 constant region mutant	SEQ ID NO:160	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKG QPREPQVYTLPPSREEMTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFF LYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK
Ig Kappa constant region	SEQ ID NO:161	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNF YPREAKVQWKVDNALQSGNSQESVTEQDSKDS TYSLSSTLTLSKADYEKHKVYACEVTHQGLSS PVTKSFNRGEC
Ig Lambda constant region	SEQ ID NO:162	QPKAAPSVTLFPPSSEELQANKATLVCLISDF YPGAVTVAWKADSSPVKAGVETTTPSKQSNNK YAASSYLSLTPEQWKSHRSYSCQVTHEGSTVE KTVAPTECS

An "isolated antibody", as used herein, is intended to refer to an antibody that is substantially free of other antibodies having different antigenic specificities (*e.g.*, an isolated antibody that specifically binds B7-H3 is substantially free of antibodies that specifically bind antigens other than B7-H3). An isolated antibody that specifically binds B7-H3 may, however, have cross-reactivity to other antigens, such as B7-H3 molecules from other species. Moreover, an isolated antibody may be substantially free of other cellular material and/or chemicals.

The term "humanized antibody" refers to antibodies which comprise heavy and light chain variable region sequences from a nonhuman species (*e.g.*, a mouse) but in which at least a portion of the VH and/or VL sequence has been altered to be more "human-like", i.e., more similar to human germline variable sequences. In particular, the term "humanized antibody" is an antibody or a variant, derivative, analog or fragment thereof which immunospecifically binds to an antigen of interest and which comprises a framework (FR) region having substantially the amino acid sequence of a human antibody and a complementary determining region (CDR) having substantially the amino acid sequence of a non-human antibody. As used herein, the term "substantially" in the context of a CDR refers to a CDR having an amino acid sequence at least 80%, preferably at least 85%, at least 90%, at least 95%, at least 98% or at least 99% identical to the amino acid sequence of a non-human antibody CDR. A humanized antibody comprises substantially all of at least one, and typically two, variable domains (Fab, Fab', $F(ab')_2$, FabC, Fv) in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin (i.e., donor antibody) and all or substantially all of the framework regions are those of a human immunoglobulin consensus sequence. Preferably, a humanized antibody also comprises at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. In some embodiments, a humanized antibody contains both the light chain as well as at least the variable domain of a heavy chain. The antibody also may include the CH1, hinge, CH2, CH3, and CH4 regions of the heavy chain. In some embodiments, a humanized antibody only contains a humanized light chain. In other embodiments, a humanized antibody only contains a humanized heavy chain. In specific embodiments, a humanized antibody only contains a humanized variable domain of a light chain and/or humanized heavy chain.

The humanized antibody can be selected from any class of immunoglobulins, including IgM, IgG, IgD, IgA and IgE, and any isotype, including without limitation IgG1, IgG2, IgG3 and IgG4. The humanized antibody may comprise sequences from more than one class or isotype, and particular constant domains may be selected to optimize desired effector functions using techniques well-known in the art.

The terms "Kabat numbering," "Kabat definitions," and "Kabat labeling" are used interchangeably herein. These terms, which are recognized in the art, refer to a system of numbering amino acid residues which are more variable (*i.e.,* hypervariable) than other amino acid residues in the heavy and light chain variable regions of an antibody, or an antigen binding portion thereof (Kabat *et al.* (1971) *Ann. NY Acad, Sci.* 190:382-391 and, Kabat, E.A., *et al.* (1991) *Sequences of Proteins of Immunological Interest, Fifth Edition*, U.S. Department of Health and Human Services, NIH Publication No. 91-3242). For the heavy chain variable region, the hypervariable region ranges from amino acid positions 31 to 35 for CDR1, amino acid positions 50 to 65 for CDR2, and amino acid positions 95 to 102 for CDR3. For the light chain variable region, the hypervariable region ranges from amino acid positions 24 to 34 for CDR1, amino acid positions 50 to 56 for CDR2, and amino acid positions 89 to 97 for CDR3.

As used herein, the term "CDR" refers to the complementarity determining region within antibody variable sequences. There are three CDRs in each of the variable regions of the heavy chain (HC) and the light chain (LC), which are designated CDR1, CDR2 and CDR3 (or specifically HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3), for each of the variable regions. The term "CDR set" as used herein refers to a group of three CDRs that occur in a single variable region capable of binding the antigen. The exact boundaries of these CDRs have been defined differently according to different systems. The system described by Kabat (Kabat et al., Sequences of Proteins of Immunological Interest (National Institutes of Health, Bethesda, Md. (1987) and (1991)) not only provides an unambiguous residue numbering system applicable to any variable region of an antibody, but also provides precise residue boundaries defining the three CDRs. These CDRs may be referred to as Kabat CDRs. Chothia and coworkers (Chothia &Lesk, J. Mol. Biol. 196:901-917 (1987) and Chothia et al., Nature 342:877-883 (1989)) found that certain sub- portions within Kabat CDRs adopt nearly identical peptide backbone conformations, despite having great diversity at the level of amino acid sequence. These sub-portions were designated as L1, L2 and L3 or H1, H2 and H3 where the "L" and the "H" designates the light chain and the heavy chains regions, respectively. These regions may be referred to as Chothia CDRs, which have boundaries that overlap with Kabat CDRs. Other boundaries defining CDRs overlapping with the Kabat CDRs have been described by Padlan (FASEB J. 9:133-139 (1995)) and MacCallum (J. Mol. Biol. 262(5):732-45 (1996)). Still other CDR boundary definitions may not strictly follow one of the above systems, but will nonetheless overlap with the Kabat CDRs, although they may be shortened or lengthened in light of prediction or experimental findings that particular residues or groups of residues or even entire CDRs do not significantly impact antigen binding. The methods used herein may utilize CDRs defined according to any of these systems, although preferred embodiments use Kabat or Chothia defined CDRs.

As used herein, the term "framework" or "framework sequence" refers to the remaining sequences of a variable region minus the CDRs. Because the exact definition of a CDR sequence can be determined by different systems, the meaning of a framework sequence is subject to correspondingly different interpretations. The six CDRs (CDR-L1, CDR-L2, and CDR-L3 of light chain and CDR-H1, CDR-H2, and CDR-H3 of heavy chain) also divide the framework regions on the light chain and the heavy chain into four sub-regions (FR1, FR2, FR3 and FR4) on each chain, in which CDR1 is positioned between FR1 and FR2, CDR2 between FR2 and FR3, and CDR3 between FR3 and FR4. Without specifying the particular sub-regions as FR1, FR2, FR3 or FR4, a framework region, as referred by others, represents the combined FR's within the variable region of a single, naturally occurring immunoglobulin chain. As used herein, a FR represents one of the four sub-regions, and FRs represents two or more of the four sub- regions constituting a framework region.

The framework and CDR regions of a humanized antibody need not correspond precisely to the parental sequences, *e.g.*, the donor antibody CDR or the consensus framework may be mutagenized by substitution, insertion and/or deletion of at least one amino acid residue so that the

CDR or framework residue at that site does not correspond to either the donor antibody or the consensus framework. In a preferred embodiment, such mutations, however, will not be extensive. Usually, at least 80%, preferably at least 85%, more preferably at least 90%, and most preferably at least 95% of the humanized antibody residues will correspond to those of the parental FR and CDR sequences. As used herein, the term "consensus framework" refers to the framework region in the consensus immunoglobulin sequence. As used herein, the term "consensus immunoglobulin sequence" refers to the sequence formed from the most frequently occurring amino acids (or nucleotides) in a family of related immunoglobulin sequences (See *e.g.*, Winnaker, From Genes to Clones (Verlagsgesellschaft, Weinheim, Germany 1987). In a family of immunoglobulins, each position in the consensus sequence is occupied by the amino acid occurring most frequently at that position in the family. If two amino acids occur equally frequently, either can be included in the consensus sequence.

The term "human acceptor framework", as used herein, is meant to refer to a framework of an antibody or antibody fragment thereof comprising the amino acid sequence of a VH or VL framework derived from a human antibody or antibody fragment thereof or a human consensus sequence framework into which CDR's from a non-human species may be incorporated.

"Percent (%) amino acid sequence identity" with respect to a peptide or polypeptide sequence is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the specific peptide or polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared. In one embodiment, the invention includes an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to an amino acid sequence set forth in any one of SEQ ID NOs: 1 to 148.

The term "multivalent antibody" is used herein to denote an antibody comprising two or more antigen binding sites. In certain embodiments, the multivalent antibody may be engineered to have the three or more antigen binding sites, and is generally not a naturally occurring antibody.

The term "multispecific antibody" refers to an antibody capable of binding two or more unrelated antigens. In one embodiment, the multispecific antibody is a bispecific antibody that is capable of binding to two unrelated antigens, *e.g.,* a bispecific antibody, or antigen-binding portion thereof, that binds B7-H3 and CD3.

The term "dual variable domain" or "DVD," as used interchangeably herein, are antigen binding proteins that comprise two or more antigen binding sites and are tetravalent or multivalent binding proteins. Such DVDs may be monospecific, *i.e.*, capable of binding one antigen or multispecific, *i.e.* capable of binding two or more antigens. DVD binding proteins comprising two heavy chain DVD polypeptides and two light chain DVD polypeptides are referred to a DVD Ig. Each half of a DVD Ig comprises a heavy chain DVD polypeptide, and a light chain DVD polypeptide, and two antigen binding sites. Each binding site comprises a heavy chain variable domain and a light chain variable domain with a total of 6 CDRs involved in antigen binding per antigen binding site. In one embodiment, the CDRs described herein are used in an anti-B7-H3 DVD.

The term "chimeric antigen receptor" or "CAR" refers to a recombinant protein comprising at least (1) an antigen-binding region, *e.g.,* a variable heavy or light chain of an antibody, (2) a transmembrane domain to anchor the CAR into a T cell, and (3) one or more intracellular signaling domains.

The term "activity" includes activities such as the binding specificity/affinity of an antibody or ADC for an antigen, for example, an anti-hB7-H3 antibody that binds to an hB7-H3 antigen and/or the neutralizing potency of an antibody, for example, an anti-hB7-H3 antibody whose binding to hB7-H3 inhibits the biological activity of hB7-H3, *e.g.*, inhibition of proliferation of B7-H3 expressing cell lines, *e.g.,* human H146 lung carcinoma cells, human H1650 lung carcinoma cells, or human EBC1 lung carcinoma cells.

The term "non small-cell lung carcinoma (NSCLC) xenograft assay," as used herein, refers to an *in vivo* assay used to determine whether an anti-B7-H3 antibody or ADC, can inhibit tumor growth (*e.g.,* further growth) and/or decrease tumor growth resulting from the transplantation of NSCLC cells into an immunodeficient mouse. An NSCLC xenograft assay includes transplantation of NSCLC cells into an immunodeficient mouse such that a tumor grows to a desired size, *e.g.,* 200-250 mm^3, whereupon the antibody or ADC is administered to the mouse to determine whether the antibody or ADC can inhibit and/or decrease tumor growth. In certain embodiments, the activity of the antibody or ADC is determined according to the percent tumor growth inhibition (%TGI) relative to a control antibody, *e.g.,* a human IgG antibody (or collection thereof) which does not specifically bind tumor cells, *e.g.,* is directed to an antigen not associated with cancer or is obtained from a source which is noncancerous (*e.g.,* normal human serum). In such embodiments, the antibody (or ADC) and the control antibody are administered to the mouse at the same dose, with the same frequency, and via the same route. In one embodiment, the mouse used in the NSCLC xenograft assay is a severe combined immunodeficiency (SCID) mouse and/or an athymic CD-1 nude mouse. Examples of NSCLC cells that may be used in the NSCLC xenograft assay include, but are not limited to, H1299 cells (NCI-H1299 [H-1299] (ATCC® CRL-5803)), H1975 cells (NCI-H1975 cells [H1975] (ATCC® CRL-5908™)), and EBC-1 cells.

The term "small-cell lung carcinoma (SCLC) xenograft assay," as used herein, refers to an *in vivo* assay used to determine whether an anti-B7-H3 antibody or ADC, can inhibit tumor growth (*e.g.,* further growth) and/or decrease tumor growth resulting from the transplantation of SCLC cells into an immunodeficient mouse. An SCLC xenograft assay includes transplantation of SCLC cells into an immunodeficient mouse such that a tumor grows to a desired size, *e.g.,* 200-250 mm^3, whereupon the antibody or ADC is administered to the mouse to determine whether the antibody or ADC can inhibit and/or decrease tumor growth. In certain embodiments, the activity of the antibody or ADC is determined according to the percent tumor growth inhibition (%TGI) relative to a control antibody, *e.g.,* a human IgG antibody (or collection thereof) which does not specifically bind tumor cells, *e.g.,* is directed to an antigen not associated with cancer or is obtained from a source which is noncancerous (*e.g.,* normal human serum). In such embodiments, the antibody (or ADC) and the control antibody are administered to the mouse at the same dose, with the same frequency, and via the same route. In one embodiment, the mouse used in the NSCLC xenograft assay is a severe combined immunodeficiency (SCID) mouse and/or an athymic CD-1 nude mouse. Examples of SCLC cells that may be used in the SCLC xenograft assay include, but are not limited to, H146 cells (NCI-H146 cells [H146] (ATCC® HTB-173™)), and H847 cells (NCI-H847 [H847] (ATCC® CRL-5846™)). The term "epitope" refers to a region of an antigen that is bound by an antibody or ADC. In certain embodiments, epitope determinants include chemically active surface groupings of molecules such as amino acids, sugar side chains, phosphoryl, or sulfonyl, and, in certain embodiments, may have specific three dimensional structural characteristics, and/or specific charge characteristics. In certain embodiments, an antibody is said to specifically bind an antigen when it preferentially recognizes its target antigen in a complex mixture of proteins and/or macromolecules.

The term "surface plasmon resonance", as used herein, refers to an optical phenomenon that allows for the analysis of real-time biospecific interactions by detection of alterations in protein concentrations within a biosensor matrix, for example using the BIAcore system (Pharmacia Biosensor AB, Uppsala, Sweden and Piscataway, NJ). For further descriptions, see Jönsson, U., *et al.* (1993) *Ann. Biol. Clin.* 51:19-26; Jönsson, U., *et al.* (1991) *Biotechniques* 11:620-627; Johnsson, B., *et al.* (1995) *J. Mol. Recognit.* 8:125-131; and Johnnson, B., *et al.* (1991) *Anal. Biochem.* 198:268-277. In one embodiment, surface plasmon resonance is determined according to the methods described in Example 2.

The term " k_{on}" or " k_a", as used herein, is intended to refer to the on rate constant for association of an antibody to the antigen to form the antibody/antigen complex.

The term "k_{off}" or " k_d", as used herein, is intended to refer to the off rate constant for dissociation of an antibody from the antibody/antigen complex.

The term "K_D", as used herein, is intended to refer to the equilibrium dissociation constant of a particular antibody-antigen interaction (*e.g.,* huAb13 antibody and B7-H3). K_D is calculated by k_a / k_d.

The term "competitive binding", as used herein, refers to a situation in which a first antibody competes with a second antibody, for a binding site on a third molecule, *e.g.,* an antigen. In one embodiment, competitive binding between two antibodies is determined using FACS analysis.

The term "competitive binding assay" is an assay used to determine whether two or more antibodies bind to the same epitope. In one embodiment, a competitive binding assay is a competition fluorescent activated cell sorting (FACS) assay which is used to determine whether two or more antibodies bind to the same epitope by determining whether the fluorescent signal of a labeled antibody is reduced due to the introduction of a non-labeled antibody, where competition for the same epitope will lower the level of fluorescence.

The term "labeled antibody" as used herein, refers to an antibody, or an antigen binding portion thereof, with a label incorporated that provides for the identification of the binding protein, *e.g.,* an antibody. Preferably, the label is a detectable marker, *e.g.*, incorporation of a radiolabeled amino acid or attachment to a polypeptide of biotinyl moieties that can be detected by marked avidin (*e.g.*, streptavidin containing a fluorescent marker or enzymatic activity that can be detected by optical or colorimetric methods). Examples of labels for polypeptides include, but are not limited to, the following: radioisotopes or radionuclides (*e.g.*, ^{3}H, ^{14}C, ^{35}S, ^{90}Y, ^{99}Tc, ^{111}In, ^{125}I, ^{131}I, ^{177}Lu, ^{166}Ho, or ^{153}Sm); fluorescent labels (*e.g.*, FITC, rhodamine, lanthanide phosphors), enzymatic labels (*e.g.*, horseradish peroxidase, luciferase, alkaline phosphatase); chemiluminescent markers; biotinyl groups; predetermined polypeptide epitopes recognized by a secondary reporter (*e.g.*, leucine zipper pair sequences, binding sites for secondary antibodies, metal binding domains, epitope tags); and magnetic agents, such as gadolinium chelates.

The term "antibody-drug-conjugate" or "ADC" refers to a binding protein, such as an antibody or antigen binding fragment thereof, chemically linked to one or more chemical drug(s) (also referred to herein as agent(s), warhead(s), and payload(s)) that may optionally be therapeutic or cytotoxic agents. In a preferred embodiment, an ADC includes an antibody, a drug, (*e.g.* a cytotoxic drug), and a linker that enables attachment or conjugation of the drug to the antibody. An ADC typically has anywhere from 1 to 8 drugs conjugated to the antibody, including drug loaded species of 2, 4, 6, or 8. Non-limiting examples of drugs that may be included in the ADCs are mitotic inhibitors, antitumor antibiotics, immunomodulating agents, vectors for gene therapy, alkylating agents, antiangiogenic agents, antimetabolites, boron-containing agents, chemoprotective agents, hormones, antihormone agents, corticosteroids, photoactive therapeutic agents, oligonucleotides, radionuclide agents, topoisomerase inhibitors, kinase inhibitors (e.g., TEC-family kinase inhibitors and serine/threonine kinase inhibitors), and radiosensitizers. In one embodiment, the drug is a Bcl-xL inhibitor.

The terms "anti-B7-H3 antibody drug conjugate" or "anti-B7-H3 ADC", used interchangeably herein, refer to an ADC comprising an antibody that specifically binds to B7-H3, whereby the antibody is conjugated to one or more chemical agent(s). In one embodiment, the anti-

B7-H3 ADC comprises antibody huAb13v1, huAb3v2.5, or huAb3v2.6 conjugated to an auristatin, *e.g.*, MMAE or MMAF. In one embodiment, the anti-B7-H3 ADC comprises antibody huAb13v1, huAb3v2.5, or huAb3v2.6 conjugated to a Bcl-xL inhibitor. In a preferred embodiment, the anti-B7-H3 ADC binds to human B7-H3 (hB7-H3).

The term "Bcl-xL inhibitor", as used herein, refers to a compound which antagonizes Bcl-xL activity in a cell. In one embodiment, a Bcl-xL inhibitor promotes apoptosis of a cell by inhibiting Bcl-xL activity.

The term "auristatin", as used herein, refers to a family of antimitotic agents. Auristatin derivatives are also included within the definition of the term "auristatin". Examples of auristatins include, but are not limited to, auristatin E (AE), monomethylauristatin E (MMAE), monomethylauristatin F (MMAF), and synthetic analogs of dolastatin. In one embodiment, an anti-B7-H3 antibody described herein is conjugated to an auristatin to form an anti-B7-H3 ADC.

As used herein, the term "Ab-vcMMAE" is used to refer to an ADC comprising an antibody conjugated to monomethylauristatin E (MMAE) via a maleimidocaproyl valine citrulline p-aminobenzyloxycarbamyl (PABA) linker.

As used herein , the term "mcMMAF" is used to refer to a linker/drug combination of maleimidocaproyl-monomethylauristatin F (MMAF).

The term "drug-to-antibody ratio" or "DAR" refers to the number of drugs, *e.g.*, Bcl-xL inhibitor, attached to the antibody of the ADC. The DAR of an ADC can range from 1 to 8, although higher loads, *e.g.*, 20, are also possible depending on the number of linkage site on an antibody. The term DAR may be used in reference to the number of drugs loaded onto an individual antibody, or, alternatively, may be used in reference to the average or mean DAR of a group of ADCs.

The term "undesired ADC species", as used herein, refers to any drug loaded species which is to be separated from an ADC species having a different drug load. In one embodiment, the term undesired ADC species may refer to drug loaded species of 6 or more, *i.e.*, ADCs with a DAR of 6 or more, including DAR6, DAR7, DAR8, and DAR greater than 8 (*i.e.,* drug loaded species of 6, 7, 8, or greater than 8). In a separate embodiment, the term undesired ADC species may refer to drug loaded species of 8 or more, *i.e.,* ADCs with a DAR of 8 or more, including DAR8, and DAR greater than 8 (*i.e.,* drug loaded species of 8, or greater than 8).

The term "ADC mixture", as used herein, refers to a composition containing a heterogeneous DAR distribution of ADCs. In one embodiment, an ADC mixture contains ADCs having a distribution of DARs of 1 to 8, *e.g.,* 1.5, 2, 4, 6, and 8 (*i.e.,* drug loaded species of 2, 4, 6, and 8). Notably, degradation products may result such that DARs of 1, 3, 5, and 7 may also be included in the mixture. Further, ADCs within the mixture may also have DARs greater than 8. The ADC mixture results from interchain disulfide reduction followed by conjugation. In one embodiment, the ADC mixture comprises both ADCs with a DAR of 4 or less (*i.e.,* a drug loaded species of 4 or less) and ADCs with a DAR of 6 or more (*i.e.,* a drug loaded species of 6 or more).

The term a "xenograft assay", as used herein, refers to a human tumor xenograft assay, wherein human tumor cells are transplanted, either under the skin or into the organ type in which the tumor originated, into immunocompromised mice that do not reject human cells.

The term "cancer" is meant to refer to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth. Examples of cancer include, but are not limited to, carcinoma, lymphoma, blastoma, sarcoma, and leukemia or lymphoid malignancies. More particular examples of such cancers include glioblastoma, acute myeloid leukemia (AML), non-Hodgkin's lymphoma (NHL), non-small cell lung cancer, lung cancer, colon cancer, colorectal cancer, head and neck cancer, breast cancer (e.g., triple negative breast cancer), pancreatic cancer, squamous cell tumors, squamous cell carcinoma (e.g., squamous cell lung cancer or squamous cell head and neck cancer), anal cancer, skin cancer, and vulvar cancer. In one embodiment, the antibodies or ADCs of the invention are administered to a patient having a tumor(s) that overexpresses B7-H3. In one embodiment, the antibodies or ADCs of the invention are administered to a patient having a solid tumor which is likely to over-express B7-H3. In one embodiment, the antibodies or ADCs of the invention are administered to a patient having squamous cell non-small cell lung cancer (NSCLC). In one embodiment, the antibodies or ADCs of the invention are administered to a patient having solid tumors, including advanced solid tumors. In one embodiment, the antibodies or ADCs of the invention are administered to a patient having prostate cancer. In one embodiment, the antibodies or ADCs of the invention are administered to a patient having non-small cell lung cancer. In one embodiment, the antibodies or ADCs of the invention are administered to a patient having a glioblastoma. In one embodiment, the antibodies or ADCs of the invention are administered to a patient having colon cancer. In one embodiment, the antibodies or ADCs of the invention are administered to a patient having head and neck cancer. In one embodiment, the antibodies or ADCs of the invention are administered to a patient having kidney cancer. In one embodiment, the antibodies or ADCs of the invention are administered to a patient having clear cell renal cell carcinoma. In one embodiment, the antibodies or ADCs of the invention are administered to a patient having glioma. In one embodiment, the antibodies or ADCs of the invention are administered to a patient having melanoma. In one embodiment, the antibodies or ADCs of the invention are administered to a patient having pancreatic cancer. In one embodiment, the antibodies or ADCs of the invention are administered to a patient having gastric cancer. In one embodiment, the antibodies or ADCs of the invention are administered to a patient having ovarian cancer. In one embodiment, the antibodies or ADCs of the invention are administered to a patient having colorectal cancer. In one embodiment, the antibodies or ADCs of the invention are administered to a patient having renal cancer. In one embodiment, the antibodies or ADCs of the invention are administered to a patient having small cell lung cancer. In one embodiment, the antibodies or ADCs of the invention are administered to a patient having hepatocellular carcinoma. In one embodiment, the antibodies or ADCs of the invention are administered to a patient having hypopharyngeal squamous cell carcinoma.

In one embodiment, the antibodies or ADCs of the invention are administered to a patient having neuroblastoma. In one embodiment, the antibodies or ADCs of the invention are administered to a patient having breast cancer. In one embodiment, the antibodies or ADCs of the invention are administered to a patient having endometrial cancer. In one embodiment, the antibodies or ADCs of the invention are administered to a patient having urothelial cell carcinoma. In one embodiment, the antibodies or ADCs of the invention are administered to a patient having acute myeloid leukemia (AML). In one embodiment, the antibodies or ADCs of the invention are administered to a patient having non-Hodgkin's lymphoma (NHL).

The term "B7-H3 expressing tumor," as used herein, refers to a tumor which expresses B7-H3 protein. In one embodiment, B7-H3 expression in a tumor is determined using immunohistochemical staining of tumor cell membranes, where any immunohistochemical staining above background level in a tumor sample indicates that the tumor is a B7-H3 expressing tumor. Methods for detecting expression of B7-H3 in a tumor are known in the art, and include immunohistochemical assays. In contrast, a "B7-H3 negative tumor" is defined as a tumor having an absence of B7-H3 membrane staining above background in a tumor sample as determined by immunohistochemical techniques.

The terms "overexpress," "overexpression," or "overexpressed" interchangeably refer to a gene that is transcribed or translated at a detectably greater level, usually in a cancer cell, in comparison to a normal cell. Overexpression therefore refers to both overexpression of protein and RNA (due to increased transcription, post transcriptional processing, translation, post translational processing, altered stability, and altered protein degradation), as well as local overexpression due to altered protein traffic patterns (increased nuclear localization), and augmented functional activity, *e.g.*, as in an increased enzyme hydrolysis of substrate. Thus, overexpression refers to either protein or RNA levels. Overexpression can also be by 50%, 60%, 70%, 80%, 90% or more in comparison to a normal cell or comparison cell. In certain embodiments, the anti-B7-H3 antibodies or ADCs of the invention are used to treat solid tumors likely to overexpress B7-H3.

The term "gene amplification", as used herein, refers to a cellular process characterized by the production of multiple copies of any particular piece of DNA. For example, a tumor cell may amplify, or copy, chromosomal segments as a result of cell signals and sometimes environmental events. The process of gene amplification leads to the production of additional copies of the gene. In one embodiment, the gene is B7-H3, *i.e.,* "B7-H3 amplification." In one embodiment, the compositions and methods disclosed herein are used to treat a subject having B7-H3 amplified cancer.

The term "administering" as used herein is meant to refer to the delivery of a substance (*e.g.*, an anti-B7-H3 antibody or ADC) to achieve a therapeutic objective (*e.g.*, the treatment of a B7-H3-associated disorder). Modes of administration may be parenteral, enteral and topical. Parenteral administration is usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal,

transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion.

The term "combination therapy" or "combination" in the context of a therapeutic method (e.g., a treatment method), as used herein, refers to the administration of two or more therapeutic substances, *e.g.*, an anti-B7-H3 antibody or ADC and an additional therapeutic agent. The additional therapeutic agent may be administered concomitant with, prior to, or following the administration of the anti-B7-H3 antibody or ADC.

As used herein, the term "effective amount" or "therapeutically effective amount" refers to the amount of a drug, *e.g.,* an antibody or ADC, which is sufficient to reduce or ameliorate the severity and/or duration of a disorder, *e.g.,* cancer, or one or more symptoms thereof, prevent the advancement of a disorder, cause regression of a disorder, prevent the recurrence, development, onset or progression of one or more symptoms associated with a disorder, detect a disorder, or enhance or improve the prophylactic or therapeutic effect(s) of another therapy (*e.g.*, prophylactic or therapeutic agent). The effective amount of an antibody or ADC may, for example, inhibit tumor growth (*e.g.,* inhibit an increase in tumor volume), decrease tumor growth (*e.g.,* decrease tumor volume), reduce the number of cancer cells, and/or relieve to some extent one or more of the symptoms associated with the cancer. The effective amount may, for example, improve disease free survival (DFS), improve overall survival (OS), or decrease likelihood of recurrence.

Various chemical substituents are defined below. In some instances, the number of carbon atoms in a substituent (*e.g.*, alkyl, alkanyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, heteroaryl, and aryl) is indicated by the prefix "C_x-C_y" or "C_{x-y}" wherein x is the minimum and y is the maximum number of carbon atoms. Thus, for example, "C_1-C_6 alkyl" refers to an alkyl containing from 1 to 6 carbon atoms. Illustrating further, "C_3-C_8 cycloalkyl" means a saturated hydrocarbyl ring containing from 3 to 8 carbon ring atoms. If a substituent is described as being "substituted," a hydrogen atom on a carbon or nitrogen is replaced with a non-hydrogen group. For example, a substituted alkyl substituent is an alkyl substituent in which at least one hydrogen atom on the alkyl is replaced with a non-hydrogen group. To illustrate, monofluoroalkyl is alkyl substituted with a fluoro radical, and difluoroalkyl is alkyl substituted with two fluoro radicals. It should be recognized that if there is more than one substitution on a substituent, each substitution may be identical or different (unless otherwise stated). If a substituent is described as being "optionally substituted", the substituent may be either (1) not substituted or (2) substituted. Possible substituents include, but are not limited to, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, aryl, cycloalkyl, heterocyclyl, heteroaryl, halogen, C_1-C_6 haloalkyl, oxo, -CN, NO_2, $-OR^{xa}$, $-OC(O)R^{xz}$, $-OC(O)N(R^{xa})_2$, $-SR^{xa}$, $-S(O)_2R^{xa}$, $-S(O)_2N(R^{xa})_2$, $-C(O)R^{xa}$, $-C(O)OR^{xa}$, $-C(O)N(R^{xa})_2$, $-C(O)N(R^{xa})S(O)_2R^{xz}$, $-N(R^{xa})_2$, $-N(R^{xa})C(O)R^{xz}$, $-N(R^{xa})S(O)_2R^{xz}$, $-N(R^{xa})C(O)O(R^{xz})$, $-N(R^{xa})C(O)N(R^{xa})_2$, $-N(R^{xa})S(O)_2N(R^{xa})_2$, -($C_1$-$C_6$ alkylenyl)-CN, -(C_1-C_6 alkylenyl)-OR^{xa}, -(C_1-C_6 alkylenyl)-$OC(O)R^{xz}$, -(C_1-C_6 alkylenyl)-$OC(O)N(R^{xa})_2$, -(C_1-C_6 alkylenyl)-SR^{xa}, -(C_1-C_6 alkylenyl)-$S(O)_2R^{xa}$, -(C_1-C_6 alkylenyl)-$S(O)_2N(R^{xa})_2$, -(C_1-C_6 alkylenyl)-$C(O)R^{xa}$, -(C_1-C_6

alkylenyl)-C(O)OR^{xa}, -(C_1-C_6 alkylenyl)-C(O)N(R^{xa})$_2$, -(C_1-C_6 alkylenyl)-C(O)N(R^{xa})S(O)$_2$R^{xz}, -(C_1-C_6 alkylenyl)-N(R^{xa})$_2$, -(C_1-C_6 alkylenyl)-N(R^{xa})C(O)R^{xz}, -(C_1-C_6 alkylenyl)-N(R^{xa})S(O)$_2$R^{xz}, -(C_1-C_6 alkylenyl)-N(R^{xa})C(O)O(R^{xz}), -(C_1-C_6 alkylenyl)-N(R^{xa})C(O)N(R^{xa})$_2$, or -(C_1-C_6 alkylenyl)-N(R^{xa})S(O)$_2$N(R^{xa})$_2$; wherein R^{xa}, at each occurrence, is independently hydrogen, aryl, cycloalkyl, heterocyclyl, heteroaryl, C_1-C_6 alkyl, or C_1-C_6 haloalkyl; and R^{xz}, at each occurrence, is independently aryl, cycloalkyl, heterocyclyl, heteroaryl, C_1-C_6 alkyl or C_1-C_6 haloalkyl.

Various ADCs, synthons and Bcl-xL inhibitors comprising the ADCs and/or synthons are described in some embodiments herein by reference to structural formulae including substituents. It is to be understood that the various groups comprising substituents may be combined as valence and stability permit. Combinations of substituents and variables envisioned by this disclosure are only those that result in the formation of stable compounds. As used herein, the term "stable" refers to compounds that possess stability sufficient to allow manufacture and that maintain the integrity of the compound for a sufficient period of time to be useful for the purpose detailed herein.

As used herein, the following terms are intended to have the following meanings:

The term "alkoxy" refers to a group of the formula –OR^{xa}, where R^{xa} is an alkyl group. Representative alkoxy groups include methoxy, ethoxy, propoxy, tert-butoxy and the like.

The term "alkoxyalkyl" refers to an alkyl group substituted with an alkoxy group and may be represented by the general formula –R^{b}OR^{xa} where R^{b} is an alkylene group and R^{xa} is an alkyl group.

The term "alkyl" by itself or as part of another substituent refers to a saturated or unsaturated branched, straight-chain or cyclic monovalent hydrocarbon radical that is derived by the removal of one hydrogen atom from a single carbon atom of a parent alkane, alkene or alkyne. Typical alkyl groups include, but are not limited to, methyl; ethyls such as ethanyl, ethenyl, ethynyl; propyls such as propan-1-yl, propan-2-yl, cyclopropan-1-yl, prop-1-en-1-yl, prop-1-en-2-yl, prop-2-en-1-yl, cycloprop-1-en-1-yl; cycloprop-2-en-1-yl, prop-1-yn-1-yl , prop-2-yn-1-yl, *etc.*; butyls such as butan-1-yl, butan-2-yl, 2-methyl-propan-1-yl, 2-methyl-propan-2-yl, cyclobutan-1-yl, but-1-en-1-yl, but-1-en-2-yl, 2-methyl-prop-1-en-1-yl, but-2-en-1-yl , but-2-en-2-yl, buta-1,3-dien-1-yl, buta-1,3-dien-2-yl, cyclobut-1-en-1-yl, cyclobut-1-en-3-yl, cyclobuta-1,3-dien-1-yl, but-1-yn-1-yl, but-1-yn-3-yl, but-3-yn-1-yl, *etc.*; and the like. Where specific levels of saturation are intended, the nomenclature "alkanyl," "alkenyl" and/or "alkynyl" are used, as defined below. The term "lower alkyl" refers to alkyl groups with 1 to 6 carbons.

The term "alkanyl" by itself or as part of another substituent refers to a saturated branched, straight-chain or cyclic alkyl derived by the removal of one hydrogen atom from a single carbon atom of a parent alkane. Typical alkanyl groups include, but are not limited to, methyl; ethanyl; propanyls such as propan-1-yl, propan-2-yl (isopropyl), cyclopropan-1-yl, *etc.*; butanyls such as butan-1-yl, butan-2-yl (*sec*-butyl), 2-methyl-propan-1-yl (isobutyl), 2-methyl-propan-2-yl (*t*-butyl), cyclobutan-1-yl, *etc.*; and the like.

The term "alkenyl" by itself or as part of another substituent refers to an unsaturated branched, straight-chain or cyclic alkyl having at least one carbon-carbon double bond derived by the removal of one hydrogen atom from a single carbon atom of a parent alkene. Typical alkenyl groups include, but are not limited to, ethenyl; propenyls such as prop-1-en-1-yl , prop-1-en-2-yl, prop-2-en-1-yl, prop-2-en-2-yl, cycloprop-1-en-1-yl; cycloprop-2-en-1-yl ; butenyls such as but-1-en-1-yl, but-1-en-2-yl, 2-methyl-prop-1-en-1-yl, but-2-en-1-yl, but-2-en-2-yl, buta-1,3-dien-1-yl, buta-1,3-dien-2-yl, cyclobut-1-en-1-yl, cyclobut-1-en-3-yl, cyclobuta-1,3-dien-1-yl, etc.; and the like.

The term "alkynyl" by itself or as part of another substituent refers to an unsaturated branched, straight-chain or cyclic alkyl having at least one carbon-carbon triple bond derived by the removal of one hydrogen atom from a single carbon atom of a parent alkyne. Typical alkynyl groups include, but are not limited to, ethynyl; propynyls such as prop-1-yn-1-yl , prop-2-yn-1-yl, etc.; butynyls such as but-1-yn-1-yl, but-1-yn-3-yl, but-3-yn-1-yl , etc.; and the like.

The term "alkylamine" refers to a group of the formula -NHR^{xa} and "dialkylamine" refers to a group of the formula –$NR^{xa}R^{xa}$, where each R^{xa} is, independently of the others, an alkyl group.

The term "alkylene" refers to an alkane, alkene or alkyne group having two terminal monovalent radical centers derived by the removal of one hydrogen atom from each of the two terminal carbon atoms. Typical alkylene groups include, but are not limited to, methylene; and saturated or unsaturated ethylene; propylene; butylene; and the like. The term "lower alkylene" refers to alkylene groups with 1 to 6 carbons.

The term "heteroalkylene" refers to a divalent alkylene having one or more -CH_2- groups replaced with a thio, oxy, or -NR^{x3}- where R^{x3} is selected from hydrogen, lower alkyl and lower heteroalkyl. The heteroalkylene can be linear, branched, cyclic, bicyclic, or a combination thereof and can include up to 10 carbon atoms and up to 4 heteroatoms. The term "lower heteroalkylene" refers to alkylene groups with 1 to 4 carbon atoms and 1 to 3 heteroatoms.

The term "aryl" means an aromatic carbocyclyl containing from 6 to 14 carbon ring atoms. An aryl may be monocyclic or polycyclic (*i.e.*, may contain more than one ring). In the case of polycyclic aromatic rings, only one ring the polycyclic system is required to be aromatic while the remaining ring(s) may be saturated, partially saturated or unsaturated. Examples of aryls include phenyl, naphthalenyl, indenyl, indanyl, and tetrahydronaphthyl.

The term "arylene" refers to an aryl group having two monovalent radical centers derived by the removal of one hydrogen atom from each of the two ring carbons. An exemplary arylene group is a phenylene.

An alkyl group may be substituted by a "carbonyl" which means that two hydrogen atoms from a single alkanylene carbon atom are removed and replaced with a double bond to an oxygen atom.

The prefix "halo" indicates that the substituent which includes the prefix is substituted with one or more independently selected halogen radicals. For example, haloalkyl means an alkyl substituent in which at least one hydrogen radical is replaced with a halogen radical. Typical halogen radicals include chloro, fluoro, bromo and iodo. Examples of haloalkyls include chloromethyl, 1-bromoethyl, fluoromethyl, difluoromethyl, trifluoromethyl, and 1,1,1-trifluoroethyl. It should be recognized that if a substituent is substituted by more than one halogen radical, those halogen radicals may be identical or different (unless otherwise stated).

The term "haloalkoxy" refers to a group of the formula $-OR^c$, where R^c is a haloalkyl.

The terms "heteroalkyl," "heteroalkanyl," "heteroalkenyl," "heteroalkynyl," and "heteroalkylene" refer to alkyl, alkanyl, alkenyl, alkynyl, and alkylene groups, respectively, in which one or more of the carbon atoms, *e.g.*, 1, 2 or 3 carbon atoms, are each independently replaced with the same or different heteroatoms or heteroatomic groups. Typical heteroatoms and/or heteroatomic groups which can replace the carbon atoms include, but are not limited to, -O-, -S-, -S-O-, $-NR^c-$, -PH, -S(O)-, $-S(O)_2-$, $-S(O)NR^c-$, $-S(O)_2NR^c-$, and the like, including combinations thereof, where each R^c is independently hydrogen or C_1-C_6 alkyl. The term "lower heteroalkyl" refers to between 1 and 4 carbon atoms and between 1 and 3 heteroatoms.

The terms "cycloalkyl" and "heterocyclyl" refer to cyclic versions of "alkyl" and "heteroalkyl" groups, respectively. For heterocyclyl groups, a heteroatom can occupy the position that is attached to the remainder of the molecule. A cycloalkyl or heterocyclyl ring may be a single-ring (monocyclic) or have two or more rings (bicyclic or polycyclic).

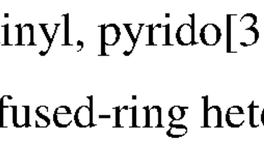
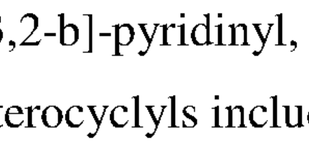
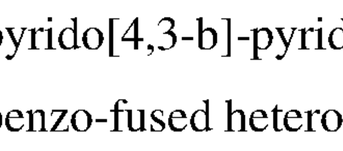
Monocyclic cycloalkyl and heterocyclyl groups will typically contains from 3 to 7 ring atoms, more typically from 3 to 6 ring atoms, and even more typically 5 to 6 ring atoms. Examples of cycloalkyl groups include, but are not limited to, cyclopropyl; cyclobutyls such as cyclobutanyl and cyclobutenyl; cyclopentyls such as cyclopentanyl and cyclopentenyl; cyclohexyls such as cyclohexanyl and cyclohexenyl; and the like. Examples of monocyclic heterocyclyls include, but are not limited to, oxetane, furanyl, dihydrofuranyl, tetrahydrofuranyl, tetrahydropyranyl, thiophenyl (thiofuranyl), dihydrothiophenyl, tetrahydrothiophenyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, triazolyl, tetrazolyl, oxazolyl, oxazolidinyl, isoxazolidinyl, isoxazolyl, thiazolyl, isothiazolyl, thiazolinyl, isothiazolinyl, thiazolidinyl, isothiazolidinyl, thiodiazolyl, oxadiazolyl (including 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl (furazanyl), or 1,3,4-oxadiazolyl), oxatriazolyl (including 1,2,3,4-oxatriazolyl or 1,2,3,5-oxatriazolyl), dioxazolyl (including 1,2,3-dioxazolyl, 1,2,4-dioxazolyl, 1,3,2-dioxazolyl, or 1,3,4-dioxazolyl), 1,4-dioxanyl, dioxothiomorpholinyl, oxathiazolyl, oxathiolyl, oxathiolanyl, pyranyl, dihydropyranyl, thiopyranyl, tetrahydrothiopyranyl, pyridinyl (azinyl), piperidinyl, diazinyl (including pyridazinyl (1,2-diazinyl), pyrimidinyl (1,3-diazinyl), or pyrazinyl (1,4-diazinyl)), piperazinyl, triazinyl (including 1,3,5-triazinyl, 1,2,4-triazinyl, and 1,2,3-triazinyl)), oxazinyl (including 1,2-oxazinyl, 1,3-oxazinyl, or 1,4-oxazinyl)), oxathiazinyl (including 1,2,3-

oxathiazinyl, 1,2,4-oxathiazinyl, 1,2,5-oxathiazinyl, or 1,2,6-oxathiazinyl)), oxadiazinyl (including 1,2,3-oxadiazinyl, 1,2,4-oxadiazinyl, 1,4,2-oxadiazinyl, or 1,3,5-oxadiazinyl)), morpholinyl, azepinyl, oxepinyl, thiepinyl, diazepinyl, pyridonyl (including pyrid-2(1H)-onyl and pyrid-4(1H)-onyl), furan-2(5H)-onyl, pyrimidonyl (including pyramid-2(1H)-onyl and pyramid-4(3H)-onyl), oxazol-2(3H)-onyl, 1H-imidazol-2(3H)-onyl, pyridazin-3(2H)-onyl, and pyrazin-2(1H)-onyl.

Polycyclic cycloalkyl and heterocyclyl groups contain more than one ring, and bicyclic cycloalkyl and heterocyclyl groups contain two rings. The rings may be in a bridged, fused or spiro orientation. Polycyclic cycloalkyl and heterocyclyl groups may include combinations of bridged, fused and/or spiro rings. In a spirocyclic cycloalkyl or heterocyclyl, one atom is common to two different rings. An example of a spirocycloalkyl is spiro[4.5]decane and an example of a spiroheterocyclyls is a spiropyrazoline.

In a bridged cycloalkyl or heterocyclyl, the rings share at least two common non-adjacent atoms. Examples of bridged cycloalkyls include, but are not limited to, adamantyl and norbornanyl rings. Examples of bridged heterocyclyls include, but are not limited to, 2-oxatricyclo[3.3.1.$1^{3,7}$]decanyl.

In a fused-ring cycloalkyl or heterocyclyl, two or more rings are fused together, such that two rings share one common bond. Examples of fused-ring cycloalkyls include decalin, naphthylene, tetralin, and anthracene. Examples of fused-ring heterocyclyls containing two or three rings include imidazopyrazinyl (including imidazo[1,2-a]pyrazinyl), imidazopyridinyl (including imidazo[1,2-a]pyridinyl), imidazopyridazinyl (including imidazo[1,2-b]pyridazinyl), thiazolopyridinyl (including thiazolo[5,4-c]pyridinyl, thiazolo[5,4-b]pyridinyl, thiazolo[4,5-b]pyridinyl, and thiazolo[4,5-c]pyridinyl), indolizinyl, pyranopyrrolyl, 4H-quinolizinyl, purinyl, naphthyridinyl, pyridopyridinyl (including pyrido[3,4-b]-pyridinyl, pyrido[3,2-b]-pyridinyl, or pyrido[4,3-b]-pyridinyl), and pteridinyl. Other examples of fused-ring heterocyclyls include benzo-fused heterocyclyls, such as dihydrochromenyl, tetrahydroisoquinolinyl, indolyl, isoindolyl (isobenzazolyl, pseudoisoindolyl), indoleninyl (pseudoindolyl), isoindazolyl (benzpyrazolyl), benzazinyl (including quinolinyl (1-benzazinyl) or isoquinolinyl (2-benzazinyl)), phthalazinyl, quinoxalinyl, quinazolinyl, benzodiazinyl (including cinnolinyl (1,2-benzodiazinyl) or quinazolinyl (1,3-benzodiazinyl)), benzopyranyl (including chromanyl or isochromanyl), benzoxazinyl (including 1,3,2-benzoxazinyl, 1,4,2-benzoxazinyl, 2,3,1-benzoxazinyl, or 3,1,4-benzoxazinyl), benzo[d]thiazolyl, and benzisoxazinyl (including 1,2-benzisoxazinyl or 1,4-benzisoxazinyl).

The term "cycloalkylene" refers to a cycloalkyl group having two monovalent radical centers derived by the removal of one hydrogen atom from each of two ring carbons. Exemplary cycloalkylene groups include:  ,  , and  .

The term "heteroaryl" refers to an aromatic heterocyclyl containing from 5 to 14 ring atoms. A heteroaryl may be a single ring or 2 or 3 fused rings. Examples of heteroaryls include 6-membered rings such as pyridyl, pyrazyl, pyrimidinyl, pyridazinyl, and 1,3,5-, 1,2,4- or 1,2,3-triazinyl; 5-membered ring substituents such as triazolyl, pyrrolyl, imidazyl, furanyl, thiophenyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, 1,2,3-, 1,2,4-, 1,2,5-, or 1,3,4-oxadiazolyl and isothiazolyl; 6/5-membered fused ring substituents such as imidazopyrazinyl (including imidazo[1,2-a]pyrazinyl)imidazopyridinyl (including imidazo[1,2-a]pyridinyl), imidazopyridazinyl (including imidazo[1,2-b]pyridazinyl), thiazolopyridinyl (including thiazolo[5,4-c]pyridinyl, thiazolo[5,4-b]pyridinyl, thiazolo[4,5-b]pyridinyl, and thiazolo[4,5-c]pyridinyl), benzo[d]thiazolyl, benzothiofuranyl, benzisoxazolyl, benzoxazolyl, purinyl, and anthranilyl; and 6/6-membered fused rings such as benzopyranyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, and benzoxazinyl. Heteroaryls may also be heterocycles having aromatic (4N+2 pi electron) resonance contributors such as pyridonyl (including pyrid-2(1H)-onyl and pyrid-4(1H)-onyl), pyrimidonyl (including pyramid-2(1H)-onyl and pyramid-4(3H)-onyl), pyridazin-3(2H)-onyl and pyrazin-2(1H)-onyl.

The term "sulfonate" as used herein means a salt or ester of a sulfonic acid.

The term "methyl sulfonate" as used herein means a methyl ester of a sulfonic acid group.

The term "carboxylate" as used herein means a salt or ester of a carboxylic acid.

The term "polyol", as used herein, means a group containing more than two hydroxyl groups independently or as a portion of a monomer unit. Polyols include, but are not limited to, reduced C_2-C_6 carbohydrates, ethylene glycol, and glycerin.

The term "sugar" when used in context of "G^1" includes O-glycoside, *N*-glycoside, *S*-glycoside and *C*-glycoside (*C*-glycoslyl) carbohydrate derivatives of the monosaccharide and disaccharide classes and may originate from naturally-occurring sources or may be synthetic in origin. For example "sugar" when used in context of "G^1"includes derivatives such as but not limited to those derived from glucuronic acid, galacturonic acid, galactose, and glucose among others. Suitable sugar substitutions include but are not limited to hydroxyl, amine, carboxylic acid, sulfonic acid, phosphonic acid, esters, and ethers.

The term "NHS ester" means the N-hydroxysuccinimide ester derivative of a carboxylic acid.

The term "amine" includes primary, secondary and tertiary aliphatic amines, including cyclic versions.

The term salt when used in context of "or salt thereof" include salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. In general, these salts typically may be prepared by conventional means by reacting, for example, the appropriate acid or base with a compound of the invention

Where a salt is intended to be administered to a patient (as opposed to, for example, being in use in an *in vitro* context), the salt preferably is pharmaceutically acceptable and/or physiologically compatible. The term "pharmaceutically acceptable" is used adjectivally in this patent application to

mean that the modified noun is appropriate for use as a pharmaceutical product or as a part of a pharmaceutical product. The term "pharmaceutically acceptable salt" includes salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. In general, these salts typically may be prepared by conventional means by reacting, for example, the appropriate acid or base with a compound of the invention.

Various aspects of the invention are described in further detail in the following subsections.

II. Anti-B7-H3 Antibodies

One aspect of the invention provides anti-B7-H3 antibodies, or antigen binding portions thereof. In one embodiment, the present invention provides chimeric anti-B7-H3 antibodies, or antigen binding portions thereof. In yet another embodiment, the present invention provides humanized anti-B7-H3 antibodies, or antigen binding portions thereof. In another aspect, the invention features antibody drug conjugates (ADCs) comprising an anti-B7-H3 antibody described herein and at least one drug(s), such as, but not limited to, a Bcl-xL inhibitor or an auristatin. The antibodies or ADCs of the invention have characteristics including, but not limited to, binding to wild-type human B7-H3 *in vitro*, binding to wild-type human B7-H3 on tumor cells expressing B7-H3, and decreasing or inhibiting xenograft tumor growth in a mouse model.

One aspect of the invention features an anti-human B7-H3 (anti-hB7-H3) Antibody Drug Conjugate (ADC) comprising an anti-hB7-H3 antibody conjugated to a drug via a linker, wherein the drug is a Bcl-xL inhibitor. Exemplary anti-B7-H3 antibodies (and sequences thereof) that can be used in the ADCs are described herein.

The anti-B7-H3 antibodies described herein provide the ADCs of the invention with the ability to bind to B7-H3 such that the cytotoxic Bcl-xL drug attached to the antibody may be delivered to the B7-H3-expressing cell, particularly a B7-H3 expressing cancer cell.

While the term "antibody" is used throughout, it should be noted that antibody fragments (*i.e.*, antigen-binding portions of an anti-B7-H3antibody) are also included in the invention and may be included in the embodiments (methods and compositions) described throughout. For example, an anti-B7-H3antibody fragment may be conjugated to the Bcl-xL inhibitors described herein. Thus, it is within the scope of the invention that in certain embodiments, antibody fragments of the anti-B7-H3antibodies described herein are conjugated to Bcl-xL inhibitors (including those described below in Section III.A) via linkers (including those described below in Section III.A). In certain embodiments, the anti-B7-H3 antibody binding portion is a Fab, a Fab', a F(ab')2, a Fv, a disulfide linked Fv, an scFv, a single domain antibody, or a diabody.

II.A. Anti-B7-H3 Chimeric Antibodies

A chimeric antibody is a molecule in which different portions of the antibody are derived from different animal species, such as antibodies having a variable region derived from a murine monoclonal antibody and a human immunoglobulin constant region. Methods for producing chimeric

antibodies are known in the art. See *e.g.*, Morrison, *Science* 229:1202 (1985); Oi *et al.*, *BioTechniques* 4:214 (1986); Gillies *et al.*, (1989) *J. Immunol. Methods* 125:191-202; U.S. Pat. Nos. 5,807,715; 4,816,567; and 4,816,397, which are incorporated herein by reference in their entireties. In addition, techniques developed for the production of "chimeric antibodies" (Morrison *et al.*, 1984, *Proc. Natl. Acad. Sci.* 81:851-855; Neuberger *et al.*, 1984, *Nature* 312:604-608; Takeda *et al.*, 1985, *Nature* 314:452-454, each of which are incorporated herein by reference in their entireties) by splicing genes from a mouse antibody molecule of appropriate antigen specificity together with genes from a human antibody molecule of appropriate biological activity can be used.

As described in Example 3, eighteen anti-B7-H3 murine antibodies were identified having high specific binding activity against human and cynomolgus B7-H3. Chimeric antibodies, in the context of a human immunoglobulin constant region, were generated from these eighteen antibodies.

Thus, in one aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable region including an amino acid sequence set forth in SEQ ID NOs: 1, 9, 16, 24, 32, 40, 48, 56, 64, 72, 80, 87, 95, 101, or 108; and/or a light chain variable region including an amino acid sequence set forth in SEQ ID NOs: 5, 13, 20, 28, 36, 44, 52, 60, 68, 76, 84, 91, 98, 105, or 112.

In another aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable region including an amino acid sequence as set forth in SEQ ID NO: 1, and a light chain variable region including an amino acid sequence set forth in SEQ ID NO: 5.

In another aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable domain region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 2; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 3; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 4; and a light chain variable region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 6; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 7; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 8.

In another aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable region including an amino acid sequence as set forth in SEQ ID NO: 9, and a light chain variable region including an amino acid sequence set forth in SEQ ID NO: 13.

In another aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable domain region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 10; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 11; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 12; and a light chain variable region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 14 (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 7;

and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 15.

In another aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable region including an amino acid sequence as set forth in SEQ ID NO: 16, and a light chain variable region including an amino acid sequence set forth in SEQ ID NO: 20.

In another aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable domain region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 17; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 18; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 19; and a light chain variable region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 21; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 22; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 23.

In another aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable region including an amino acid sequence as set forth in SEQ ID NO: 24, and a light chain variable region including an amino acid sequence set forth in SEQ ID NO: 28.

In another aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable domain region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 25; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 26; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 27; and a light chain variable region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 29; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 30; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 31.

In another aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable region including an amino acid sequence as set forth in SEQ ID NO: 32, and a light chain variable region including an amino acid sequence set forth in SEQ ID NO: 36.

In another aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable domain region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 33; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 34; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 35; and a light chain variable region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 37; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 38; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 182.

In another aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable region including an amino acid sequence as set

forth in SEQ ID NO: 40, and a light chain variable region including an amino acid sequence set forth in SEQ ID NO: 44.

In another aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable domain region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 41; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 42; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 43; and a light chain variable region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 45; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 46; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 47.

In another aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable region including an amino acid sequence as set forth in SEQ ID NO: 48, and a light chain variable region including an amino acid sequence set forth in SEQ ID NO: 52.

In another aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable domain region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 49; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 50; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 51; and a light chain variable region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 53; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 54; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 55.

In another aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable region including an amino acid sequence as set forth in SEQ ID NO: 56, and a light chain variable region including an amino acid sequence set forth in SEQ ID NO: 60.

In another aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable domain region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 57; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 58; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 59; and a light chain variable region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 61; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 62; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 63.

In another aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable region including an amino acid sequence as set forth in SEQ ID NO: 64, and a light chain variable region including an amino acid sequence set forth in SEQ ID NO: 68.

In another aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable domain region including (a) a CDR1 having an

amino acid sequence as set forth in SEQ ID NO: 65; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 66; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 67; and a light chain variable region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 69; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 70; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 71.

In another aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable region including an amino acid sequence as set forth in SEQ ID NO: 72, and a light chain variable region including an amino acid sequence set forth in SEQ ID NO: 76.

In another aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable domain region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 73; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 74; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 75; and a light chain variable region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 77; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 78; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 79.

In another aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable region including an amino acid sequence as set forth in SEQ ID NO: 80, and a light chain variable region including an amino acid sequence set forth in SEQ ID NO: 84.

In another aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable domain region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 81; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 82; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 83; and a light chain variable region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 85; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 7; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 86.

In another aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable region including an amino acid sequence as set forth in SEQ ID NO: 87, and a light chain variable region including an amino acid sequence set forth in SEQ ID NO: 91.

In another aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable domain region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 88; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 89; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 90; and a light chain variable region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 92; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 93;

and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 94.

In another aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable region including an amino acid sequence as set forth in SEQ ID NO: 95, and a light chain variable region including an amino acid sequence set forth in SEQ ID NO: 98.

In another aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable domain region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 49; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 96; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 97; and a light chain variable region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 99; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 93; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 100.

In another aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable region including an amino acid sequence as set forth in SEQ ID NO: 101, and a light chain variable region including an amino acid sequence set forth in SEQ ID NO: 105.

In another aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable domain region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 102; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 103; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 104; and a light chain variable region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 106; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 46; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 107.

In another aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable region including an amino acid sequence as set forth in SEQ ID NO: 108, and a light chain variable region including an amino acid sequence set forth in SEQ ID NO: 112.

In another aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable domain region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 109; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 110; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 111; and a light chain variable region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 113; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 114; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 115.

II.B. Humanized Anti-B7-H3 Antibodies

The chimeric antibodies disclosed herein may be used in the production of humanized anti-B7-H3 antibodies. For example, following the generation and characterization of chimeric anti-B7-H3 antibodies chAb1-chAb18, antibodies chAb3, chAb13, and chAb18 were selected for humanization. Specifically, six different humanized antibodies were created based on chAb3 (referred to herein as huAb3v1, huAb3v2, huAb3v3, huAb3v4, huAb3v5, and huAb3v6 (see Examples 12 and 13), nine different humanized antibodies were created based on chAb13 (referred to herein as huAb13v1, huAb13v2, huAb13v3, huAb13v4, huAb13v5, huAb13v6, huAb13v7, huAb13v8, huAb13v9), and ten different humanized antibodies were created based on chAb18 (referred to herein as huAb18v1, huAb18v2, huAb18v3, huAb18v4, huAb18v5, huAb18v6, huAb18v7, huAb18v8, huAb18v9, and huAb18v10 (see Examples 9 and 10)). Tables 8, 12, 16, 18, and 19 provide the amino acid sequences of CDR, VH and VL regions of humanized chAb3, chAb13, and chAb18, respectively.

Generally, humanized antibodies are antibody molecules from non-human species antibody that binds the desired antigen having one or more complementarity determining regions (CDRs) from the non-human species and framework regions from a human immunoglobulin molecule. Known human Ig sequences are disclosed, *e.g.*, www.ncbi.nlm.nih.gov/entrez- /query.fcgi; www.atcc.org/phage/hdb.html; www.sciquest.com/; www.abcam.com/; www.antibodyresource.com/onlinecomp.html; www.public.iastate.edu/.about.pedro/research_tools.html; www.mgen.uni-heidelberg.de/SD/IT/IT.html; www.whfreeman.com/immunology/CH- 05/kuby05.htm; www.library.thinkquest.org/12429/Immune/Antibody.html; www.hhmi.org/grants/lectures/1996/vlab/; www.path.cam.ac.uk/.about.mrc7/m- ikeimages.html; www.antibodyresource.com/; mcb.harvard.edu/BioLinks/Immuno-logy.html.www.immunologylink.com/; pathbox.wustl.edu/.about.hcenter/index.- html; www.biotech.ufl.edu/.about.hcl/; www.pebio.com/pa/340913/340913.html- ; www.nal.usda.gov/awic/pubs/antibody/; www.m.ehime-u.acjp/.about.yasuhito- /Elisa.html; www.biodesign.com/table.asp; www.icnet.uk/axp/facs/davies/lin- ks.html; www.biotech.ufl.edu/.about.fccl/protocol.html; www.isac-net.org/sites_geo.html; aximtl.imt.uni-marburg.de/.about.rek/AEP- Start.html; baserv.uci.kun.nl/.about.jraats/linksl.html; www.recab.uni-hd.de/immuno.bme.nwu.edu/; www.mrc-cpe.cam.ac.uk/imt-doc/pu- blic/INTRO.html; www.ibt.unam.mx/vir/V_mice.html; imgt.cnusc.fr:8104/; www.biochem.ucl.ac.uk/.about.martin/abs/index.html; antibody.bath.ac.uk/; abgen.cvm.tamu.edu/lab/wwwabgen.html; www.unizh.ch/.about.honegger/AHOsem-inar/Slide01.html; www.cryst.bbk.ac.uk/.about.ubcg07s/; www.nimr.mrc.ac.uk/CC/ccaewg/ccaewg.htm; www.path.cam.ac.uk/.about.mrc7/h-umanisation/TAHHP.html; www.ibt.unam.mx/vir/structure/stat_aim.html;

www.biosci.missouri.edu/smithgp/index.html; www.cryst.bioc.cam.ac.uk/.abo- ut.fmolina/Web-pages/Pept/spottech.html; www.jerini.de/fr roducts.htm; www.patents.ibm.com/ibm.html.Kabat et al., Sequences of Proteins of Immunological Interest, U.S. Dept. Health (1983), each entirely incorporated herein by reference. Such imported sequences can be used to reduce immunogenicity or reduce, enhance or modify binding, affinity, on-rate, off-rate, avidity, specificity, half-life, or any other suitable characteristic, as known in the art.

Framework residues in the human framework regions may be substituted with the corresponding residue from the CDR donor antibody to alter, preferably improve, antigen binding. These framework substitutions are identified by methods well known in the art, *e.g.*, by modeling of the interactions of the CDR and framework residues to identify framework residues important for antigen binding and sequence comparison to identify unusual framework residues at particular positions. (See, *e.g.*, Queen *et al.*, U.S. Pat. No. 5,585,089; Riechmann *et al.*, Nature 332:323 (1988), which are incorporated herein by reference in their entireties.) Three-dimensional immunoglobulin models are commonly available and are familiar to those skilled in the art. Computer programs are available which illustrate and display probable three-dimensional conformational structures of selected candidate immunoglobulin sequences. Inspection of these displays permits analysis of the likely role of the residues in the functioning of the candidate immunoglobulin sequence, *i.e.*, the analysis of residues that influence the ability of the candidate immunoglobulin to bind its antigen. In this way, FR residues can be selected and combined from the consensus and import sequences so that the desired antibody characteristic, such as increased affinity for the target antigen(s), is achieved. In general, the CDR residues are directly and most substantially involved in influencing antigen binding. Antibodies can be humanized using a variety of techniques known in the art, such as but not limited to those described in Jones *et al.*, Nature 321:522 (1986); Verhoeyen *et al.*, Science 239:1534 (1988)), Sims *et al.*, J. Immunol. 151: 2296 (1993); Chothia and Lesk, J. Mol. Biol. 196:901 (1987), Carter *et al.*, Proc. Natl. Acad. Sci. U.S.A. 89:4285 (1992); Presta *et al.*, J. Immunol. 151:2623 (1993), Padlan, Molecular Immunology 28(4/5):489-498 (1991); Studnicka *et al.*, Protein Engineering 7(6):805-814 (1994); Roguska. *et al.* , PNAS 91:969-973 (1994); PCT publication WO 91/09967, PCT/: US98/16280, US96/18978, US91/09630, US91/05939, US94/01234, GB89/01334, GB91/01134, GB92/01755; WO90/14443, WO90/14424, WO90/14430, EP 229246, EP 592,106; EP 519,596, EP 239,400, U.S. Pat. Nos. 5,565,332, 5,723,323, 5,976,862, 5,824,514, 5,817,483, 5814476, 5763192, 5723323, 5,766886, 5,714,352, 6,204,023, 6,180,370, 5,693,762, 5,530,101, 5,585,089, 5,225,539; 4,816,567, each entirely incorporated herein by reference, included references cited therein.

Humanized anti-B7-H3 antibodies derived from chAb3

Six humanized antibodies based on chAb3 were created. The sequences of each are as follows:

A) huAb3v1 (VH amino acid sequence set forth in SEQ ID NO: 125 and VH CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 10, 11, and 12, respectively; and VL amino acid sequence set forth in SEQ ID NO: 128 and VL CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 14, 7, and 15, respectively);

B) huAb3v2 (VH amino acid sequence set forth in SEQ ID NO: 127 and VH CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 10, 11, and 12, respectively; and VL amino acid sequence set forth in SEQ ID NO: 128 and VL CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 14, 7, and 15, respectively);

C) huAb3v3 (VH amino acid sequence set forth in SEQ ID NO: 126 and VH CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 10, 11, and 12, respectively; and VL amino acid sequence set forth in SEQ ID NO: 129 and VL CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 14, 7, and 15, respectively);

D) huAb3v4 (VH amino acid sequence set forth in SEQ ID NO: 125 and VH CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 10, 11, and 12, respectively; and VL amino acid sequence set forth in SEQ ID NO: 130 and VL CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 14, 7, and 15, respectively);

E) huAb3v5 (VH amino acid sequence set forth in SEQ ID NO: 127 and VH CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 10, 11, and 12, respectively; and VL amino acid sequence set forth in SEQ ID NO: 130 and VL CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 14, 7, and 15, respectively); and

F) huAb3v6 (VH amino acid sequence set forth in SEQ ID NO: 126 and VH CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 10, 11, and 12, respectively; and VL amino acid sequence set forth in SEQ ID NO: 130 and VL CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 14, 7, and 15, respectively).

Of the six humanized versions of chAb3, huAb3v2 was selected for further modified in order to remove potential deamidation or isomerization sites in the light chain CDR1 or in the heavy chain CDR2. Nine variants of the humanized antibody huAb3v2 were generated, and are referred to herein as huAb3v2.1, huAb3v2.2, huAb3v2.3, huAb3v2.4, huAb3v2.5, huAb3v2.6, huAb3v2.7, huAb3v2.8, and huAb3v2.9 (CDR and variable domain sequences are provided in Table 16). The nine variants of the huAb3v2 antibody include the following:

A) huAb3v2.1 (VH amino acid sequence set forth in SEQ ID NO: 131 and VH CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 10, 132, and 12, respectively; and VL amino acid sequence set forth in SEQ ID NO: 133 and VL CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 134, 7, and 15, respectively);

B) huAb3v2.2 (VH amino acid sequence set forth in SEQ ID NO: 131 and VH CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 10, 132, and 12, respectively; and VL amino acid sequence set forth in SEQ ID NO: 135 and VL CDR1, CDR2, and CDR3 amino acid

sequences set forth in SEQ ID NOs: 136, 7, and 15, respectively);

C) huAb3v2.3 (VH amino acid sequence set forth in SEQ ID NO: 131 and VH CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 10, 132, and 12, respectively; and VL amino acid sequence set forth in SEQ ID NO: 137 and VL CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 138, 7, and 15, respectively);

D) huAb3v2.4 (VH amino acid sequence set forth in SEQ ID NO: 139 and VH CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 10, 140, and 12, respectively; and VL amino acid sequence set forth in SEQ ID NO: 133 and VL CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 134, 7, and 15, respectively);

E) huAb3v2.5 (VH amino acid sequence set forth in SEQ ID NO: 139 and VH CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 10, 140, and 12, respectively; and VL amino acid sequence set forth in SEQ ID NO: 135 and VL CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 136, 7, and 15, respectively);

F) huAb3v2.6 (VH amino acid sequence set forth in SEQ ID NO: 139 and VH CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 10, 140, and 12, respectively; and VL amino acid sequence set forth in SEQ ID NO: 137 and VL CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 138, 7, and 15, respectively);

G) huAb3v2.7 (VH amino acid sequence set forth in SEQ ID NO: 141 and VH CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 10, 142, and 12, respectively; and VL amino acid sequence set forth in SEQ ID NO: 133 and VL CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 134, 7, and 15, respectively);

H) huAb3v2.8 (VH amino acid sequence set forth in SEQ ID NO: 141 and VH CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 10, 142, and 12, respectively; and VL amino acid sequence set forth in SEQ ID NO: 135 and VL CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 136, 7, and 15, respectively); and

I) huAb3v2.9 (VH amino acid sequence set forth in SEQ ID NO: 141 and VH CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 10, 142, and 12, respectively; and VL amino acid sequence set forth in SEQ ID NO: 137 and VL CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 138, 7, and 15, respectively).

Thus, in one aspect, the present invention provides antibodies comprising variable and/or CDR sequences from a humanized antibody derived from chAb3. In one embodiment, the invention features anti-B7-H3 antibodies which are derived from Ab3 have improved characteristics, *e.g.*, improved binding affinity to isolated B7-H3 protein and improved binding to B7-H3 expressing cells, as described in the Examples below. Collectively these novel antibodies are referred to herein as "Ab3 variant antibodies." Generally, the Ab3 variant antibodies retain the same epitope specificity as Ab3. In various embodiments, anti-B7-H3 antibodies, or antigen binding fragments thereof, of the invention are capable of modulating a biological function of B7-H3.

In one aspect, the present invention provides a humanized antibody, or antigen binding portion thereof, having a heavy chain variable region including an amino acid sequence set forth in SEQ ID NOs: 125, 126, 127, 131, 139, or 141; and/or a light chain variable region including an amino acid sequence set forth in SEQ ID NOs: 128, 129, 130, 133, 135, or 137.

In another aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen binding portion thereof, of the invention comprises a heavy chain variable region comprising a CDR1 domain comprising an amino acid sequence as set forth in SEQ ID NO: 10; a CDR2 domain comprising an amino acid sequence as set forth in SEQ ID NO: 11, 132, 140, or 142; and a CDR3 domain comprising an amino acid sequence as set forth in SEQ ID NO: 12; and a light chain variable region comprising a CDR1 domain comprising an amino acid sequence as set forth in SEQ ID NO: 14, 134, 136, or 138; a CDR2 domain comprising an amino acid sequence as set forth in SEQ ID NO: 7; and a CDR3 domain comprising an amino acid sequence as set forth in SEQ ID NO: 15.

In one aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable region including an amino acid sequence as set forth in SEQ ID NO: 125, and a light chain variable region including an amino acid sequence set forth in SEQ ID NO: 128.

In one aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable region including an amino acid sequence as set forth in SEQ ID NO: 127, and a light chain variable region including an amino acid sequence set forth in SEQ ID NO: 128.

In one aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable region including an amino acid sequence as set forth in SEQ ID NO: 126, and a light chain variable region including an amino acid sequence set forth in SEQ ID NO: 129.

In one aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable region including an amino acid sequence as set forth in SEQ ID NO: 125, and a light chain variable region including an amino acid sequence set forth in SEQ ID NO: 130.

In one aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable region including an amino acid sequence as set forth in SEQ ID NO: 127, and a light chain variable region including an amino acid sequence set forth in SEQ ID NO: 130.

In one aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable region including an amino acid sequence as set forth in SEQ ID NO: 126, and a light chain variable region including an amino acid sequence set forth in SEQ ID NO: 130.

In another aspect, the present invention is directed to a humanized anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable domain region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 10; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 11; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 12; and a light chain variable region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 14; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 7; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 15.

In one aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable region including an amino acid sequence as set forth in SEQ ID NO: 131, and a light chain variable region including an amino acid sequence set forth in SEQ ID NO: 133.

In another aspect, the present invention is directed to a humanized anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable domain region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 10; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 132; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 12; and a light chain variable region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 134; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 7; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 15.

In one aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable region including an amino acid sequence as set forth in SEQ ID NO: 131, and a light chain variable region including an amino acid sequence set forth in SEQ ID NO: 135.

In another aspect, the present invention is directed to a humanized anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable domain region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 10; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 132; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 12; and a light chain variable region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 136; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 7; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 15.

In one aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable region including an amino acid sequence as set forth in SEQ ID NO: 131, and a light chain variable region including an amino acid sequence set forth in SEQ ID NO: 137.

In another aspect, the present invention is directed to a humanized anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable domain region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 10; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 132; and (c) a CDR3 having an amino acid sequence as set forth

in SEQ ID NO: 12; and a light chain variable region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 138; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 7; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 15.

In one aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable region including an amino acid sequence as set forth in SEQ ID NO: 139, and a light chain variable region including an amino acid sequence set forth in SEQ ID NO: 133.

In another aspect, the present invention is directed to a humanized anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable domain region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 10; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 140; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 12; and a light chain variable region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 134; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 7; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 15.

In one aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable region including an amino acid sequence as set forth in SEQ ID NO: 139, and a light chain variable region including an amino acid sequence set forth in SEQ ID NO: 135.

In another aspect, the present invention is directed to a humanized anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable domain region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 10; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 140; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 12; and a light chain variable region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 136; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 7; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 15.

In another aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain comprising the amino acid sequence of SEQ ID NO: 170 and a light chain comprising the amino acid sequence of SEQ ID NO: 171.

In one aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable region including an amino acid sequence as set forth in SEQ ID NO: 139, and a light chain variable region including an amino acid sequence set forth in SEQ ID NO: 137.

In another aspect, the present invention is directed to a humanized anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable domain region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 10; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 140; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 12; and a light chain variable region including (a) a CDR1 having an amino acid

sequence as set forth in SEQ ID NO: 138; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 7; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 15.

In another aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain comprising the amino acid sequence of SEQ ID NO: 172 and a light chain comprising the amino acid sequence of SEQ ID NO: 173. In one aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable region including an amino acid sequence as set forth in SEQ ID NO: 141, and a light chain variable region including an amino acid sequence set forth in SEQ ID NO: 133.

In another aspect, the present invention is directed to a humanized anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable domain region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 10; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 142; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 12; and a light chain variable region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 134; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 7; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 15.

In one aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable region including an amino acid sequence as set forth in SEQ ID NO: 141, and a light chain variable region including an amino acid sequence set forth in SEQ ID NO: 135.

In another aspect, the present invention is directed to a humanized anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable domain region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 10; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 142; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 12; and a light chain variable region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 136; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 7; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 15.

In one aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable region including an amino acid sequence as set forth in SEQ ID NO: 141, and a light chain variable region including an amino acid sequence set forth in SEQ ID NO: 137.

In another aspect, the present invention is directed to a humanized anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable domain region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 10; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 142; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 12; and a light chain variable region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 138; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 7; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 15.

Humanized anti-B7-H3 antibodies derived from chAb13

The nine different humanized antibodies created based on chAb13 include the following:

A) huAb13v1 (VH amino acid sequence set forth in SEQ ID NO: 147 and VH CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 33, 34, and 35, respectively; and VL amino acid sequence set forth in SEQ ID NO: 144 and VL CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 37, 38, and 39, respectively);

B) huAb13v2 (VH amino acid sequence set forth in SEQ ID NO: 146 and VH CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 33, 34, and 35, respectively; and VL amino acid sequence set forth in SEQ ID NO: 143 and VL CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 37, 38, and 39, respectively);

C) huAb13v3 (VH amino acid sequence set forth in SEQ ID NO: 146 and VH CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 33, 34, and 35, respectively; and VL amino acid sequence set forth in SEQ ID NO: 144 and VL CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 37, 38, and 39, respectively);

D) huAb13v4 (VH amino acid sequence set forth in SEQ ID NO: 146 and VH CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 33, 34, and 35, respectively; and VL amino acid sequence set forth in SEQ ID NO: 145 and VL CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 37, 38, and 39, respectively);

E) huAb13v5 (VH amino acid sequence set forth in SEQ ID NO: 147 and VH CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 33, 34, and 35, respectively; and VL amino acid sequence set forth in SEQ ID NO: 143 and VL CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 37, 38, and 39, respectively);

F) huAb13v6 (VH amino acid sequence set forth in SEQ ID NO: 147 and VH CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 33, 34, and 35, respectively; and VL amino acid sequence set forth in SEQ ID NO: 145 and VL CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 37, 38, and 39, respectively);

G) huAb13v7 (VH amino acid sequence set forth in SEQ ID NO: 148 and VH CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 33, 34, and 35, respectively; and VL amino acid sequence set forth in SEQ ID NO: 143 and VL CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 37, 38, and 39, respectively);

H) huAb13v8 (VH amino acid sequence set forth in SEQ ID NO: 148 and VH CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 33, 34, and 35, respectively; and VL amino acid sequence set forth in SEQ ID NO: 144 and VL CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 37, 38, and 39, respectively);

I) huAb13v9 (VH amino acid sequence set forth in SEQ ID NO: 148 and VH CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 33, 34, and 35, respectively; and VL amino acid sequence set forth in SEQ ID NO: 145 and VL CDR1, CDR2, and CDR3 amino acid

sequences set forth in SEQ ID NOs: 37, 38, and 39, respectively).

Thus, in one aspect the present invention provides antibodies comprising variable and/or CDR sequences from a humanized antibody derived from chAb13. In one embodiment, the invention features anti-B7-H3 antibodies which are derived from chAb13 have improved characteristics, *e.g.*, improved binding affinity to isolated B7-H3 protein and improved binding to B7-H3 expressing cells, as described in the Examples below. Collectively these novel antibodies are referred to herein as "Ab13 variant antibodies." Generally, the Ab13 variant antibodies retain the same epitope specificity as Ab13. In various embodiments, anti-B7-H3 antibodies, or antigen binding fragments thereof, of the invention are capable of modulating a biological function of B7-H3.

In one aspect, the present invention provides a humanized antibody, or antigen binding portion thereof, having a heavy chain variable region including an amino acid sequence set forth in SEQ ID NOs: 146, 147, or 148; and/or a light chain variable region including an amino acid sequence set forth in SEQ ID NOs: 143, 144, or 145.

In another aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen binding portion thereof, of the invention comprises a heavy chain variable region comprising a CDR1 domain comprising an amino acid sequence as set forth in SEQ ID NO: 33; a CDR2 domain comprising an amino acid sequence as set forth in SEQ ID NO: 34; and a CDR3 domain comprising an amino acid sequence as set forth in SEQ ID NO: 35; and a light chain variable region comprising a CDR1 domain comprising an amino acid sequence as set forth in SEQ ID NO: 37; a CDR2 domain comprising an amino acid sequence as set forth in SEQ ID NO: 38; and a CDR3 domain comprising an amino acid sequence as set forth in SEQ ID NO: 39.

In one aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable region including an amino acid sequence as set forth in SEQ ID NO: 147, and a light chain variable region including an amino acid sequence set forth in SEQ ID NO: 144. In one embodiment, the invention provides an anti-B7H3 antibody comprising the CDR sequences set forth in the variable regions of huAb13v1 (SEQ ID NOs. 144 and 147).

In one aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen binding portion thereof, having a heavy chain comprising the amino acid sequence of SEQ ID NO: 168 and a light chain comprising the amino acid sequence of SEQ ID NO: 169.

In one aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable region including an amino acid sequence as set forth in SEQ ID NO: 146, and a light chain variable region including an amino acid sequence set forth in SEQ ID NO: 143.

In one aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable region including an amino acid sequence as set forth in SEQ ID NO: 146, and a light chain variable region including an amino acid sequence set forth in SEQ ID NO: 144.

In one aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable region including an amino acid sequence as set forth in SEQ ID NO: 146, and a light chain variable region including an amino acid sequence set forth in SEQ ID NO: 145.

In one aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable region including an amino acid sequence as set forth in SEQ ID NO: 147, and a light chain variable region including an amino acid sequence set forth in SEQ ID NO: 143.

In one aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable region including an amino acid sequence as set forth in SEQ ID NO: 147, and a light chain variable region including an amino acid sequence set forth in SEQ ID NO: 145.

In one aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable region including an amino acid sequence as set forth in SEQ ID NO: 148, and a light chain variable region including an amino acid sequence set forth in SEQ ID NO: 143.

In one aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable region including an amino acid sequence as set forth in SEQ ID NO: 148, and a light chain variable region including an amino acid sequence set forth in SEQ ID NO: 144.

In one aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable region including an amino acid sequence as set forth in SEQ ID NO: 148, and a light chain variable region including an amino acid sequence set forth in SEQ ID NO: 145.

Humanized anti-B7-H3 antibodies derived from chAb18

The ten different humanized antibodies created based on chAb18 include the following:

A) huAb18v1 (VH amino acid sequence set forth in SEQ ID NO: 116 and VH CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 25, 26, and 27, respectively; and VL amino acid sequence set forth in SEQ ID NO: 120 and VL CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 29, 30, and 31, respectively);

B) huAb18v2 (VH amino acid sequence set forth in SEQ ID NO: 118 and VH CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 25, 119, and 27, respectively; and VL amino acid sequence set forth in SEQ ID NO: 120 and VL CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 29, 30, and 31, respectively);

C) huAb18v3 (VH amino acid sequence set forth in SEQ ID NO: 117 and VH CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 25, 26, and 27, respectively; and VL

amino acid sequence set forth in SEQ ID NO: 121 and VL CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 29, 30, and 31, respectively);

D) huAb18v4 (VH amino acid sequence set forth in SEQ ID NO: 118 and VH CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 25, 119, and 27, respectively; and VL amino acid sequence set forth in SEQ ID NO: 121 and VL CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 29, 30, and 31, respectively);

E) huAb18v5 (VH amino acid sequence set forth in SEQ ID NO: 116 and VH CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 25, 26, and 27, respectively; and VL amino acid sequence set forth in SEQ ID NO: 123 and VL CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 29, 30, and 31, respectively);

F) huAb18v6 (VH amino acid sequence set forth in SEQ ID NO: 118 and VH CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 25, 119, and 27, respectively; and VL amino acid sequence set forth in SEQ ID NO: 123 and VL CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 29, 30, and 31, respectively);

G) huAb18v7 (VH amino acid sequence set forth in SEQ ID NO: 118 and VH CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 25, 119, and 27, respectively; and VL amino acid sequence set forth in SEQ ID NO: 124 and VL CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 29, 30, and 31, respectively);

H) huAb18v8 (VH amino acid sequence set forth in SEQ ID NO: 117 and VH CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 25, 26, and 27, respectively; and VL amino acid sequence set forth in SEQ ID NO: 122 and VL CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 29, 30, and 31, respectively);

I) huAb18v9 (VH amino acid sequence set forth in SEQ ID NO: 117 and VH CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 25, 26, and 27, respectively; and VL amino acid sequence set forth in SEQ ID NO: 124 and VL CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 29, 30, and 31, respectively); and

J) huAb18v10 (VH amino acid sequence set forth in SEQ ID NO: 118 and VH CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 25, 119, and 27, respectively; and VL amino acid sequence set forth in SEQ ID NO: 122 and VL CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 29, 30, and 31, respectively).

Thus, in one aspect the present invention provides antibodies comprising variable and/or CDR sequences from a humanized antibody derived from chAb18. In one embodiment, the invention features anti-B7-H3 antibodies which are derived from Ab18 have improved characteristics, *e.g.*, improved binding affinity to isolated B7-H3 protein and improved binding to B7-H3 expressing cells, as described in the Examples below. Collectively these novel antibodies are referred to herein as "Ab18 variant antibodies." Generally, the Ab18 variant antibodies retain the same epitope specificity

as Ab18. In various embodiments, anti-B7-H3 antibodies, or antigen binding fragments thereof, of the invention are capable of modulating a biological function of B7-H3.

In one aspect, the present invention provides a humanized antibody, or antigen binding portion thereof, having a heavy chain variable region including an amino acid sequence set forth in SEQ ID NOs: 116, 117, or 118; and/or a light chain variable region including an amino acid sequence set forth in SEQ ID NOs: 120, 121, 122, 123 or 124.

In another aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen binding portion thereof, of the invention comprises a heavy chain variable region comprising a CDR1 domain comprising an amino acid sequence as set forth in SEQ ID NO: 25; a CDR2 domain comprising an amino acid sequence as set forth in SEQ ID NO: 26 or 119; and a CDR3 domain comprising an amino acid sequence as set forth in SEQ ID NO: 27; and a light chain variable region comprising a CDR1 domain comprising an amino acid sequence as set forth in SEQ ID NO: 29; a CDR2 domain comprising an amino acid sequence as set forth in SEQ ID NO: 30; and a CDR3 domain comprising an amino acid sequence as set forth in SEQ ID NO: 31.

In one aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable region including an amino acid sequence as set forth in SEQ ID NO: 116, and a light chain variable region including an amino acid sequence set forth in SEQ ID NO: 120.

In another aspect, the present invention is directed to a humanized anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable domain region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 25; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 26; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 27; and a light chain variable region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 29; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 30; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 31.

In one aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable region including an amino acid sequence as set forth in SEQ ID NO: 118, and a light chain variable region including an amino acid sequence set forth in SEQ ID NO: 120.

In another aspect, the present invention is directed to a humanized anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable domain region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 25; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 119; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 27; and a light chain variable region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 29; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 30; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 31.

In one aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable region including an amino acid sequence as set forth in SEQ ID NO: 117, and a light chain variable region including an amino acid sequence set forth in SEQ ID NO: 121.

In one aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable region including an amino acid sequence as set forth in SEQ ID NO: 118, and a light chain variable region including an amino acid sequence set forth in SEQ ID NO: 121.

In one aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable region including an amino acid sequence as set forth in SEQ ID NO: 116, and a light chain variable region including an amino acid sequence set forth in SEQ ID NO: 123.

In one aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable region including an amino acid sequence as set forth in SEQ ID NO: 118, and a light chain variable region including an amino acid sequence set forth in SEQ ID NO: 123.

In one aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable region including an amino acid sequence as set forth in SEQ ID NO: 118, and a light chain variable region including an amino acid sequence set forth in SEQ ID NO: 124.

In one aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable region including an amino acid sequence as set forth in SEQ ID NO: 117, and a light chain variable region including an amino acid sequence set forth in SEQ ID NO: 122.

In one aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable region including an amino acid sequence as set forth in SEQ ID NO: 117, and a light chain variable region including an amino acid sequence set forth in SEQ ID NO: 124.

In one aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen-binding portion thereof, having a heavy chain variable region including an amino acid sequence as set forth in SEQ ID NO: 118, and a light chain variable region including an amino acid sequence set forth in SEQ ID NO: 122.

In one aspect, the present invention provides a humanized antibody, or antigen binding portion thereof, having a heavy chain variable region including an amino acid sequence set forth in SEQ ID NOs: 116, 117, 118, 146, 147, 148, 125, 126, 127, 131, 139, or 141; and/or a light chain variable region including an amino acid sequence set forth in SEQ ID NOs: 120, 121, 122, 123, 124, 143, 144, 145, 128, 129, 130, 133, 135, or 137.

In another aspect, the present invention is directed to an anti-B7-H3 antibody, or antigen binding portion thereof, of the invention comprises a heavy chain variable region comprising a CDR1 domain comprising an amino acid sequence as set forth in SEQ ID NO: 10, 25, or 33; a CDR2 domain comprising an amino acid sequence as set forth in SEQ ID NO: 11, 26, 34, 119, 132, 140, or 142; and a CDR3 domain comprising an amino acid sequence as set forth in SEQ ID NO: 12, 27, or 35; and a light chain variable region comprising a CDR1 domain comprising an amino acid sequence as set forth in SEQ ID NO: 14, 29, 37, 134, 136, or 138; a CDR2 domain comprising an amino acid sequence as set forth in SEQ ID NO: 7, 30, or 38; and a CDR3 domain comprising an amino acid sequence as set forth in SEQ ID NO: 15, 31 or 39.

In another aspect, the invention provides an anti-B7-H3 antibody, or antigen binding fragment thereof, that specifically competes with an anti-B7-H3 antibody, or fragment thereof, as described herein, wherein said competition can be detected in a competitive binding assay using said antibody, the human B7-H3 polypeptide, and the anti-B7-H3 antibody or fragment thereof.

In particular embodiments, the competing antibody, or antigen binding portion thereof, is an antibody, or antigen binding portion thereof, that competes with huAb3v2.5, huAb3v2.6, or huAb13v1.

In one embodiment, the anti-B7-H3 antibodies, or antigen binding portions thereof, of the invention bind to the extracellular domain of human B7-H3 (SEQ ID NO: 152) with a dissociation constant (K_D) of about 1 x 10^{-6} M or less, as determined by surface plasmon resonance. Alternatively, the antibodies, or antigen binding portions thereof, bind to human B7-H3 with a K_D of between about 1 x 10^{-6} M and about 1 x 10^{-11} M, as determined by surface plasmon resonance. In a further alternative, antibodies, or antigen binding portions thereof, bind to human B7-H3 with a K_D of between about 1 x 10^{-6} M and about 1 x 10^{-7} M, as determined by surface plasmon resonance. Alternatively, antibodies, or antigen binding portions thereof, of the invention binds to human B7-H3 with a K_D of between about 1 x 10^{-6} M and about 5 x 10^{-11} M, about 1 x 10^{-6} M and about 5 x 10^{-10} M; a K_D of between about 1 x 10^{-6} M and about 1 x 10^{-9} M; a K_D of between about 1 x 10^{-6} M and about 5 x 10^{-9} M; a K_D of between about 1 x 10^{-6} M and about 1 x 10^{-8} M; a K_D of between about 1 x 10^{-6} M and about 5 x 10^{-8} M; a K_D of between about 1 x 10^{-7} M and about 3.4 x 10^{-11} M; a K_D of between about 5.9 x 10^{-7} M; and about 2.2 x 10^{-7} M, as determined by surface plasmon resonance.

In one embodiment, the antibodies, or antigen binding portions thereof, of the invention bind to human B7-H3 (SEQ ID NO: 149) with a K_D of about 1 x 10^{-6} M or less, as determined by surface plasmon resonance. Alternatively, the antibodies, or antigen binding portions thereof, of the invention bind to human B7-H3 (SEQ ID NO: 149) with a K_D of between about 8.2 x 10^{-9} M and about 6.3 x 10^{-10} M; a K_D of between about 8.2 x 10^{-9} M and about 2.0 x 10^{-9} M; a K_D of between about 2.3 x 10^{-9} M and about 1.5 x 10^{-10} M, as determined by surface plasmon resonance.

The foregoing establish a novel family of B7-H3 binding proteins, isolated in accordance with this invention, and including antigen binding polypeptides that comprise the CDR sequences listed in the Sequence Table provided herein.

Anti-B7-H3 antibodies provided herein may comprise a heavy chain variable region comprising CDR1, CDR2 and CDR3 sequences and a light chain variable region comprising CDR1, CDR2 and CDR3 sequences, wherein one or more of these CDR sequences comprise specified amino acid sequences based on the antibodies described herein (e.g., huAb13v1 or huAb3v2.5), or conservative modifications thereof, and wherein the antibodies retain the desired functional properties of the anti-B7-H3antibodies described herein. Accordingly, the anti-B7-H3 antibody, or antigen binding portion thereof, may comprise a heavy chain variable region comprising CDR1, CDR2, and CDR3 sequences and a light chain variable region comprising CDR1, CDR2, and CDR3 sequences, wherein: (a) the heavy chain variable region CDR3 sequence comprises SEQ ID NO: 12 or 35, and conservative modifications thereof, e.g., 1, 2, 3, 4, 5, 1-2, 1-3, 1-4 or 1-5 conservative amino acid substitutions; (b) the light chain variable region CDR3 sequence comprises SEQ ID NO: 15 or 39, and conservative modifications thereof, e.g., 1, 2, 3, 4, 5, 1-2, 1-3, 1-4 or 1-5 conservative amino acid substitutions; (c) the antibody specifically binds to B7-H3, and (d) the antibody exhibits 1, 2, 3, 4, 5, 6, or all of the following functional properties described herein, *e.g.,* binding to soluble human B7-H3. In a one embodiment, the heavy chain variable region CDR2 sequence comprises SEQ ID NO: 140 or 34, and conservative modifications thereof, e.g., 1, 2, 3, 4, 5, 1-2, 1-3, 1-4 or 1-5 conservative amino acid substitutions; and the light chain variable region CDR2 sequence comprises SEQ ID NO: 7 or 38, and conservative modifications thereof, e.g., 1, 2, 3, 4, 5, 1-2, 1-3, 1-4 or 1-5 conservative amino acid substitutions. In another preferred embodiment, the heavy chain variable region CDR1 sequence comprises SEQ ID NO: 10 or 33, and conservative modifications thereof, e.g., 1, 2, 3, 4, 5, 1-2, 1-3, 1-4 or 1-5 conservative amino acid substitutions; and the light chain variable region CDR1 sequence comprises SEQ ID NO: 136, 138, or 37, and conservative modifications thereof, e.g., 1, 2, 3, 4, 5, 1-2, 1-3, 1-4 or 1-5 conservative amino acid substitutions.

Conservative amino acid substitutions may also be made in portions of the antibodies other than, or in addition to, the CDRs. For example, conservative amino acid modifications may be made in a framework region or in the Fc region. A variable region or a heavy or light chain may comprise 1, 2, 3, 4, 5, 1-2, 1-3, 1-4, 1-5, 1-10, 1-15, 1-20, 1-25, or 1-50 conservative amino acid substitutions relative to the anti-B7-H3 antibody sequences provided herein. In certain embodiments, the anti-B7-H3antibody comprises a combination of conservative and non-conservative amino acid modification.

To generate and to select CDRs having preferred B7-H3 binding and/or neutralizing activity with respect to hB7-H3, standard methods known in the art for generating antibodies, or antigen binding portions thereof, and assessing the B7-H3 binding and/or neutralizing characteristics of those

antibodies, or antigen binding portions thereof, may be used, including but not limited to those specifically described herein.

In certain embodiments, the antibody comprises a heavy chain constant region, such as an IgG1, IgG2, IgG3, IgG4, IgA, IgE, IgM, or IgD constant region. In certain embodiments, the anti-B7-H3 antibody, or antigen binding portion thereof, comprises a heavy chain immunoglobulin constant domain selected from the group consisting of a human IgG constant domain, a human IgM constant domain, a human IgE constant domain, and a human IgA constant domain. In further embodiments, the antibody, or antigen binding portion thereof, has an IgG1 heavy chain constant region, an IgG2 heavy chain constant region, an IgG3 constant region, or an IgG4 heavy chain constant region. Preferably, the heavy chain constant region is an IgG1 heavy chain constant region or an IgG4 heavy chain constant region. Furthermore, the antibody can comprise a light chain constant region, either a kappa light chain constant region or a lambda light chain constant region. Preferably, the antibody comprises a kappa light chain constant region. Alternatively, the antibody portion can be, for example, a Fab fragment or a single chain Fv fragment.

In certain embodiments, the anti-B7-H3 antibody binding portion is a Fab, a Fab', a F(ab')2, a Fv, a disulfide linked Fv, an scFv, a single domain antibody, or a diabody.

In certain embodiments, the anti-B7-H3 antibody, or antigen binding portion thereof, is a multispecific antibody, *e.g.* a bispecific antibody.

Replacements of amino acid residues in the Fc portion to alter antibody effector function have been described (Winter, *et al.* US Patent Nos. 5,648,260 and 5,624,821, incorporated by reference herein). The Fc portion of an antibody mediates several important effector functions *e.g.* cytokine induction, ADCC, phagocytosis, complement dependent cytotoxicity (CDC) and half-life/ clearance rate of antibody and antigen-antibody complexes. In some cases these effector functions are desirable for therapeutic antibody but in other cases might be unnecessary or even deleterious, depending on the therapeutic objectives. Certain human IgG isotypes, particularly IgG1 and IgG3, mediate ADCC and CDC via binding to FcγRs and complement C1q, respectively. Neonatal Fc receptors (FcRn) are the critical components determining the circulating half-life of antibodies. In still another embodiment at least one amino acid residue is replaced in the constant region of the antibody, for example the Fc region of the antibody, such that effector functions of the antibody are altered.

One embodiment of the invention includes a recombinant chimeric antigen receptor (CAR) comprising the binding regions of the antibodies described herein, *e.g.,* the heavy and/or light chain CDRs of huAb13v1. A recombinant CAR, as described herein, may be used to redirect T cell specificity to an antigen in a human leukocyte antigen (HLA)-independent fashion. Thus, CARs of the invention may be used in immunotherapy to help engineer a human subject's own immune cells to recognize and attack the subject's tumor (see, *e.g.*, U.S. Pat. Nos. 6,410,319; 8,389,282; 8,822,647; 8,906,682; 8,911,993; 8,916,381; 8,975,071; and U.S. Patent Appln. Publ. No. US20140322275, each

of which is incorporated by reference herein with respect to CAR technology). This type of immunotherapy is called adoptive cell transfer (ACT), and may be used to treat cancer in a subject in need thereof.

An anti-B7-H3 CAR of the invention preferably contains a extracellular antigen-binding domain specific for B7-H3, a transmembrane domain which is used to anchor the CAR into a T cell, and one or more intracellular signaling domains. In one embodiment of the invention, the CAR includes a transmembrane domain that comprises a transmembrane domain of a protein selected from the group consisting of the alpha, beta or zeta chain of the T-cell receptor, CD28, CD3 epsilon, CD45, CD4, CD5, CD8, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137 and CD154. In one embodiment of the invention, the CAR comprises a costimulatory domain, *e.g.*, a costimulatory domain comprising a functional signaling domain of a protein selected from the group consisting of OX40, CD2, CD27, CD28, CD5, ICAM-1, LFA-1 (CD11a/CD18), ICOS (CD278), and 4-1BB (CD137). In certain embodiments of the invention, the CAR comprises an scFv comprising the CDR or variable regions described herein *e.g.,* CDRs or variable regions from the huAb13v1 antibody, a transmembrane domain, a co-stimulatory domain (*e.g.,* a functional signaling domain from CD28 or 4-1BB), and a signaling domain comprising a functional signaling domain from CD3 (*e.g.,* CD3-zeta).

In certain embodiments, the invention incudes a T cell comprising a CAR (also referred to as a CAR T cell) comprising antigen binding regions, *e.g.* CDRs, of the antibodies described herein or an scFv described herein.

In certain embodiments of the invention, the CAR comprises a heavy chain variable region comprising a CDR1 domain comprising an amino acid sequence as set forth in SEQ ID NO: 10, 25, or 33; a CDR2 domain comprising an amino acid sequence as set forth in SEQ ID NO: 11, 26, 34, 119, 132, 140, or 142; and a CDR3 domain comprising an amino acid sequence as set forth in SEQ ID NO: 12, 27, or 35; and a light chain variable region comprising a CDR1 domain comprising an amino acid sequence as set forth in SEQ ID NO: 14, 29, 37, 134, 136, or 138; a CDR2 domain comprising an amino acid sequence as set forth in SEQ ID NO: 7, 30, or 38; and a CDR3 domain comprising an amino acid sequence as set forth in SEQ ID NO: 15, 31 or 39.

In certain embodiments of the invention, the CAR comprises a heavy chain variable domain region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 10; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 11; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 12; and a light chain variable region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 14; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 7; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 15.

In certain embodiments of the invention, the CAR comprises a heavy chain variable domain region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 10; (b) a

CDR2 having an amino acid sequence as set forth in SEQ ID NO: 132; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 12; and a light chain variable region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 134; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 7; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 15.

In certain embodiments of the invention, the CAR comprises a heavy chain variable domain region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 10; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 132; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 12; and a light chain variable region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 136; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 7; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 15.

In certain embodiments of the invention, the CAR comprises a heavy chain variable domain region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 10; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 132; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 12; and a light chain variable region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 138; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 7; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 15.

In certain embodiments of the invention, the CAR comprises a heavy chain variable domain region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 10; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 140; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 12; and a light chain variable region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 134; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 7; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 15.

In certain embodiments of the invention, the CAR comprises a heavy chain variable domain region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 10; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 140; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 12; and a light chain variable region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 136; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 7; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 15.

In certain embodiments of the invention, the CAR comprises a heavy chain variable domain region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 10; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 140; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 12; and a light chain variable region including (a) a

CDR1 having an amino acid sequence as set forth in SEQ ID NO: 138; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 7; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 15.

In certain embodiments of the invention, the CAR comprises a heavy chain variable domain region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 10; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 142; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 12; and a light chain variable region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 134; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 7; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 15.

In certain embodiments of the invention, the CAR comprises a heavy chain variable domain region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 10; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 142; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 12; and a light chain variable region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 136; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 7; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 15.

In certain embodiments of the invention, the CAR comprises a heavy chain variable domain region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 10; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 142; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 12; and a light chain variable region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 138; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 7; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 15.

In certain embodiments of the invention, the CAR comprises a heavy chain variable region comprising a CDR1 domain comprising an amino acid sequence as set forth in SEQ ID NO: 33; a CDR2 domain comprising an amino acid sequence as set forth in SEQ ID NO: 34; and a CDR3 domain comprising an amino acid sequence as set forth in SEQ ID NO: 35; and a light chain variable region comprising a CDR1 domain comprising an amino acid sequence as set forth in SEQ ID NO: 37; a CDR2 domain comprising an amino acid sequence as set forth in SEQ ID NO: 38; and a CDR3 domain comprising an amino acid sequence as set forth in SEQ ID NO: 39.

In certain embodiments of the invention, the CAR comprises a heavy chain variable region comprising a CDR1 domain comprising an amino acid sequence as set forth in SEQ ID NO: 25; a CDR2 domain comprising an amino acid sequence as set forth in SEQ ID NO: 26 or 119; and a CDR3 domain comprising an amino acid sequence as set forth in SEQ ID NO: 27; and a light chain variable region comprising a CDR1 domain comprising an amino acid sequence as set forth in SEQ ID NO: 29; a CDR2 domain comprising an amino acid sequence as set forth in SEQ ID NO: 30; and a CDR3

domain comprising an amino acid sequence as set forth in SEQ ID NO: 31.

In certain embodiments of the invention, the CAR comprises a heavy chain variable domain region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 25; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 26; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 27; and a light chain variable region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 29; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 30; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 31.

In certain embodiments of the invention, the CAR comprises a heavy chain variable domain region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 25; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 119; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 27; and a light chain variable region including (a) a CDR1 having an amino acid sequence as set forth in SEQ ID NO: 29; (b) a CDR2 having an amino acid sequence as set forth in SEQ ID NO: 30; and (c) a CDR3 having an amino acid sequence as set forth in SEQ ID NO: 31.

One embodiment of the invention includes a labeled anti-B7-H3 antibody, or antibody portion thereof, where the antibody is derivatized or linked to one or more functional molecule(s) (*e.g.*, another peptide or protein). For example, a labeled antibody can be derived by functionally linking an antibody or antibody portion of the invention (by chemical coupling, genetic fusion, noncovalent association or otherwise) to one or more other molecular entities, such as another antibody (*e.g.*, a bispecific antibody or a diabody), a detectable agent, a pharmaceutical agent, a protein or peptide that can mediate the association of the antibody or antibody portion with another molecule (such as a streptavidin core region or a polyhistidine tag), and/or a cytotoxic or therapeutic agent selected from the group consisting of a mitotic inhibitor, an antitumor antibiotic, an immunomodulating agent, a vector for gene therapy, an alkylating agent, an antiangiogenic agent, an antimetabolite, a boron-containing agent, a chemoprotective agent, a hormone, an antihormone agent, a corticosteroid, a photoactive therapeutic agent, an oligonucleotide, a radionuclide agent, a topoisomerase inhibitor, a kinase inhibitor, a radiosensitizer, and a combination thereof.

Useful detectable agents with which an antibody or antibody portion thereof, may be derivatized include fluorescent compounds. Exemplary fluorescent detectable agents include fluorescein, fluorescein isothiocyanate, rhodamine, 5-dimethylamine-1-napthalenesulfonyl chloride, phycoerythrin and the like. An antibody may also be derivatized with detectable enzymes, such as alkaline phosphatase, horseradish peroxidase, glucose oxidase and the like. When an antibody is derivatized with a detectable enzyme, it is detected by adding additional reagents that the enzyme uses to produce a detectable reaction product. For example, when the detectable agent horseradish peroxidase is present the addition of hydrogen peroxide and diaminobenzidine leads to a colored

reaction product, which is detectable. An antibody may also be derivatized with biotin, and detected through indirect measurement of avidin or streptavidin binding.

In one embodiment, the antibody of the invention is conjugated to an imaging agent. Examples of imaging agents that may be used in the compositions and methods described herein include, but are not limited to, a radiolabel (*e.g.,* indium), an enzyme, a fluorescent label, a luminescent label, a bioluminescent label, a magnetic label, and biotin.

In one embodiment, the antibodies or ADCs are linked to a radiolabel, such as, but not limited to, indium (^{111}In). ^{111}Indium may be used to label the antibodies and ADCs described herein for use in identifying B7-H3 positive tumors. In a certain embodiment, anti-B7-H3 antibodies (or ADCs) described herein are labeled with ^{111}I via a bifunctional chelator which is a bifunctional cyclohexyl diethylenetriaminepentaacetic acid (DTPA) chelate (see US Patent Nos. 5,124,471; 5,434,287; and 5,286,850, each of which is incorporated herein by reference).

Another embodiment of the invention provides a glycosylated binding protein wherein the anti-B7-H3 antibody or antigen binding portion thereof comprises one or more carbohydrate residues. Nascent *in vivo* protein production may undergo further processing, known as post-translational modification. In particular, sugar (glycosyl) residues may be added enzymatically, a process known as glycosylation. The resulting proteins bearing covalently linked oligosaccharide side chains are known as glycosylated proteins or glycoproteins. Antibodies are glycoproteins with one or more carbohydrate residues in the Fc domain, as well as the variable domain. Carbohydrate residues in the Fc domain have important effect on the effector function of the Fc domain, with minimal effect on antigen binding or half-life of the antibody (R. Jefferis, *Biotechnol. Prog.* 21 (2005), pp. 11–16). In contrast, glycosylation of the variable domain may have an effect on the antigen binding activity of the antibody. Glycosylation in the variable domain may have a negative effect on antibody binding affinity, likely due to steric hindrance (Co, M.S., *et al.*, *Mol. Immunol.* (1993) 30:1361- 1367), or result in increased affinity for the antigen (Wallick, S.C., *et al.*, *Exp. Med.* (1988) 168:1099-1109; Wright, A., *et al.*, *EMBO J.* (1991) 10:2717-2723).

One aspect of the invention is directed to generating glycosylation site mutants in which the O- or N-linked glycosylation site of the binding protein has been mutated. One skilled in the art can generate such mutants using standard well-known technologies. Glycosylation site mutants that retain the biological activity, but have increased or decreased binding activity, are another object of the invention.

In still another embodiment, the glycosylation of the anti-B7-H3 antibody or antigen binding portion of the invention is modified. For example, an aglycoslated antibody can be made (*i.e.*, the antibody lacks glycosylation). Glycosylation can be altered to, for example, increase the affinity of the antibody for antigen. Such carbohydrate modifications can be accomplished by, for example, altering one or more sites of glycosylation within the antibody sequence. For example, one or more amino acid substitutions can be made that result in elimination of one or more variable region

glycosylation sites to thereby eliminate glycosylation at that site. Such aglycosylation may increase the affinity of the antibody for antigen. Such an approach is described in further detail in PCT Publication WO2003016466A2, and U.S. Pat. Nos. 5,714,350 and 6,350,861, each of which is incorporated herein by reference in its entirety.

Additionally or alternatively, a modified anti-B7-H3 antibody of the invention can be made that has an altered type of glycosylation, such as a hypofucosylated antibody having reduced amounts of fucosyl residues or an antibody having increased bisecting GlcNAc structures. Such altered glycosylation patterns have been demonstrated to increase the ADCC ability of antibodies. Such carbohydrate modifications can be accomplished by, for example, expressing the antibody in a host cell with altered glycosylation machinery. Cells with altered glycosylation machinery have been described in the art and can be used as host cells in which to express recombinant antibodies of the invention to thereby produce an antibody with altered glycosylation. See, for example, Shields, R. L. *et al.* (2002) *J. Biol. Chem.* 277:26733-26740; Umana *et al.* (1999) *Nat. Biotech.* 17:176-1, as well as, European Patent No: EP 1,176,195; PCT Publications WO 03/035835; WO 99/54342 80, each of which is incorporated herein by reference in its entirety.

Protein glycosylation depends on the amino acid sequence of the protein of interest, as well as the host cell in which the protein is expressed. Different organisms may produce different glycosylation enzymes (*e.g.*, glycosyltransferases and glycosidases), and have different substrates (nucleotide sugars) available. Due to such factors, protein glycosylation pattern, and composition of glycosyl residues, may differ depending on the host system in which the particular protein is expressed. Glycosyl residues useful in the invention may include, but are not limited to, glucose, galactose, mannose, fucose, n-acetylglucosamine and sialic acid. Preferably the glycosylated binding protein comprises glycosyl residues such that the glycosylation pattern is human.

Differing protein glycosylation may result in differing protein characteristics. For instance, the efficacy of a therapeutic protein produced in a microorganism host, such as yeast, and glycosylated utilizing the yeast endogenous pathway may be reduced compared to that of the same protein expressed in a mammalian cell, such as a CHO cell line. Such glycoproteins may also be immunogenic in humans and show reduced half-life *in vivo* after administration. Specific receptors in humans and other animals may recognize specific glycosyl residues and promote the rapid clearance of the protein from the bloodstream. Other adverse effects may include changes in protein folding, solubility, susceptibility to proteases, trafficking, transport, compartmentalization, secretion, recognition by other proteins or factors, antigenicity, or allergenicity. Accordingly, a practitioner may prefer a therapeutic protein with a specific composition and pattern of glycosylation, for example glycosylation composition and pattern identical, or at least similar, to that produced in human cells or in the species-specific cells of the intended subject animal.

Expressing glycosylated proteins different from that of a host cell may be achieved by genetically modifying the host cell to express heterologous glycosylation enzymes. Using

recombinant techniques, a practitioner may generate antibodies or antigen binding portions thereof exhibiting human protein glycosylation. For example, yeast strains have been genetically modified to express non-naturally occurring glycosylation enzymes such that glycosylated proteins (glycoproteins) produced in these yeast strains exhibit protein glycosylation identical to that of animal cells, especially human cells (U.S. patent Publication Nos. 20040018590 and 20020137134 and PCT publication WO2005100584 A2).

Antibodies may be produced by any of a number of techniques. For example, expression from host cells, wherein expression vector(s) encoding the heavy and light chains is (are) transfected into a host cell by standard techniques. The various forms of the term "transfection" are intended to encompass a wide variety of techniques commonly used for the introduction of exogenous DNA into a prokaryotic or eukaryotic host cell, *e.g.*, electroporation, calcium-phosphate precipitation, DEAE-dextran transfection and the like. Although it is possible to express antibodies in either prokaryotic or eukaryotic host cells, expression of antibodies in eukaryotic cells is preferable, and most preferable in mammalian host cells, because such eukaryotic cells (and in particular mammalian cells) are more likely than prokaryotic cells to assemble and secrete a properly folded and immunologically active antibody.

Preferred mammalian host cells for expressing the recombinant antibodies of the invention include Chinese Hamster Ovary (CHO cells) (including dhfr- CHO cells, described in Urlaub and Chasin, (1980) *Proc. Natl. Acad. Sci. USA* 77:4216-4220, used with a DHFR selectable marker, *e.g.*, as described in R.J. Kaufman and P.A. Sharp (1982) *Mol. Biol.* 159:601-621), NS0 myeloma cells, COS cells and SP2 cells. When recombinant expression vectors encoding antibody genes are introduced into mammalian host cells, the antibodies are produced by culturing the host cells for a period of time sufficient to allow for expression of the antibody in the host cells or, more preferably, secretion of the antibody into the culture medium in which the host cells are grown. Antibodies can be recovered from the culture medium using standard protein purification methods.

Host cells can also be used to produce functional antibody fragments, such as Fab fragments or scFv molecules. It will be understood that variations on the above procedure are within the scope of the invention. For example, it may be desirable to transfect a host cell with DNA encoding functional fragments of either the light chain and/or the heavy chain of an antibody of this invention. Recombinant DNA technology may also be used to remove some, or all, of the DNA encoding either or both of the light and heavy chains that is not necessary for binding to the antigens of interest. The molecules expressed from such truncated DNA molecules are also encompassed by the antibodies of the invention. In addition, bifunctional antibodies may be produced in which one heavy and one light chain are an antibody of the invention and the other heavy and light chain are specific for an antigen other than the antigens of interest by crosslinking an antibody of the invention to a second antibody by standard chemical crosslinking methods.

In a preferred system for recombinant expression of an antibody, or antigen binding portion thereof, a recombinant expression vector encoding both the antibody heavy chain and the antibody light chain is introduced into dhfr- CHO cells by calcium phosphate-mediated transfection. Within the recombinant expression vector, the antibody heavy and light chain genes are each operatively linked to CMV enhancer/AdMLP promoter regulatory elements to drive high levels of transcription of the genes. The recombinant expression vector also carries a DHFR gene, which allows for selection of CHO cells that have been transfected with the vector using methotrexate selection/amplification. The selected transformant host cells are cultured to allow for expression of the antibody heavy and light chains and intact antibody is recovered from the culture medium. Standard molecular biology techniques are used to prepare the recombinant expression vector, transfect the host cells, select for transformants, culture the host cells and recover the antibody from the culture medium. Still further the invention provides a method of synthesizing a recombinant antibody of the invention by culturing a host cell in a suitable culture medium until a recombinant antibody is synthesized. Recombinant antibodies of the invention may be produced using nucleic acid molecules corresponding to the amino acid sequences disclosed herein The method can further comprise isolating the recombinant antibody from the culture medium.

The N- and C-termini of antibody polypeptide chains of the present invention may differ from the expected sequence due to commonly observed post-translational modifications. For example, C-terminal lysine residues are often missing from antibody heavy chains. Dick et al. (2008) Biotechnol. Bioeng. 100:1132. N-terminal glutamine residues, and to a lesser extent glutamate residues, are frequently converted to pyroglutamate residues on both light and heavy chains of therapeutic antibodies. Dick et al. (2007) Biotechnol. Bioeng. 97:544; Liu et al. (2011) JBC 28611211; Liu et al. (2011) J. Biol. Chem. 286:11211.

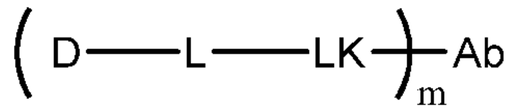
III. Anti-B7-H3 Antibody Drug Conjugates (ADCs)

Anti-B7-H3 antibodies described herein may be conjugated to a drug moiety to form an anti-B7-H3 Antibody Drug Conjugate (ADC). Antibody-drug conjugates (ADCs) may increase the therapeutic efficacy of antibodies in treating disease, *e.g.*, cancer, due to the ability of the ADC to selectively deliver one or more drug moiety(s) to target tissues, such as a tumor-associated antigen, *e.g.*, B7-H3 expressing tumors. Thus, in certain embodiments, the invention provides anti-B7-H3 ADCs for therapeutic use, *e.g.*, treatment of cancer.

Anti-B7-H3 ADCs of the invention comprise an anti-B7-H3 antibody, *i.e.*, an antibody that specifically binds to B7-H3, linked to one or more drug moieties. The specificity of the ADC is defined by the specificity of the antibody, *i.e.*, anti-B7-H3. In one embodiment, an anti-B7-H3 antibody is linked to one or more cytotoxic drug(s) which is delivered internally to a transformed cancer cell expressing B7-H3.

Examples of drugs that may be used in the anti-B7-H3 ADC of the invention are provided below, as are linkers that may be used to conjugate the antibody and the one or more drug(s). The terms "drug," "agent," and "drug moiety" are used interchangeably herein. The terms "linked" and "conjugated" are also used interchangeably herein and indicate that the antibody and moiety are covalently linked.

In some embodiments, the ADC has the following formula (formula I):

(I) 

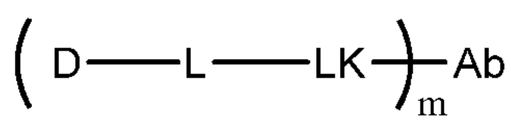
wherein Ab is the antibody, *e.g.*, anti-B7-H3 antibody huAb13v1, huAb3v2.5, or huAb3v2.6, and (L) is a linker, (D) is a drug, and LK represents a covalent linkage linking linker L to antibody Ab; and m is an integer ranging from 1 to 20. D is a drug moiety having, for example, cytostatic, cytotoxic, or otherwise therapeutic activity against a target cell, *e.g.*, a cell expressing B7-H3. In some embodiments, m ranges from 1 to 8, 1 to 7, 1 to 6, 2 to 6, 1 to 5, 1 to 4, 1 to 3, 1 to 2, 1.5 to 8, 1.5 to 7, 1.5 to 6, 1.5 to 5, 1.5 to 4, 2 to 6, 1 to 5, 1 to 4, 1 to 3, 1 to 2,or 2 to 4. The DAR of an ADC is equivalent to the "m" referred to in Formula I. In one embodiment, the ADC has a formula of Ab-$(LK\text{-}L\text{-}D)_m$, wherein Ab is an anti-B7-H3 antibody, *e.g.*huAb13v1, huAb3v2.5, or huAb3v2.6, L is a linker, D is a drug, *e.g.,* a Bcl-xL inhibitor or an auristatin such as MMAF or MMAE, and m is 2 to 4 (equivalent to a DAR of 2-4). Additional details regarding drugs (D of Formula I) and linkers (L of Formula I) that may be used in the ADCs of the invention, as well as alternative ADC structures, are described below.

III. A. Anti-B7-H3 ADCs: Bcl-xL Inhibitors, Linkers, Synthons, and Methods of Making Same

Dysregulated apoptotic pathways have also been implicated in the pathology of cancer. The implication that down-regulated apoptosis (and more particularly the Bcl-2 family of proteins) is involved in the onset of cancerous malignancy has revealed a novel way of targeting this still elusive disease. Research has shown, for example, the anti-apoptotic proteins, Bcl 2 and Bcl-xL, are over-expressed in many cancer cell types. See, Zhang, 2002, Nature Reviews/Drug Discovery 1:101; Kirkin et al., 2004, Biochimica Biophysica Acta 1644:229-249; and Amundson et al., 2000, Cancer Research 60:6101-6110. The effect of this deregulation is the survival of altered cells which would otherwise have undergone apoptosis in normal conditions. The repetition of these defects associated with unregulated proliferation is thought to be the starting point of cancerous evolution.

Aspects of the disclosure concern anti-hB7-H3 ADCs comprising an anti-hB7-H3 antibody conjugated to a drug via a linker, wherein the drug is a Bcl-xL inhibitor. In specific embodiments, the ADCs are compounds according to structural formula (I) below, or a pharmaceutically acceptable salt thereof, wherein Ab represents the anti-hB7-H3 antibody, D represents a Bcl-xL inhibitor drug (i.e., a

compound of formula (IIa), (IIb), (IIc), or (IId) as shown below), L represents a linker, LK represents a covalent linkage linking the linker (L) to the anti-hB7-H3 antibody (Ab) and m represents the number of D-L-LK units linked to the antibody, which is an integer ranging from 1 to 20. In certain embodiments, m is 2, 3 or 4. In some embodiments, m ranges from 1 to 8, 1 to 7, 1 to 6, 2 to 6, 1 to 5, 1 to 4, 2 to 4, 1 to 3, 1 to 2, or is 1.

(I) 

Specific embodiments of various Bcl-xL inhibitors per se, and various Bcl-xL inhibitors (D), linkers (L) and anti-B7-H3 antibodies (Ab) that can comprise the ADCs described herein, as well as the number of Bcl-xL inhibitors linked to the ADCs, are described in more detail below.

Examples of Bcl-xL inhibitors that may be used in the anti-B7-H3 ADC of the invention are provided below, as are linkers that may be used to conjugate the antibody and the one or more Bcl-xL inhibitor(s). The terms "linked" and "conjugated" are also used interchangeably herein and indicate that the antibody and moiety are covalently linked.

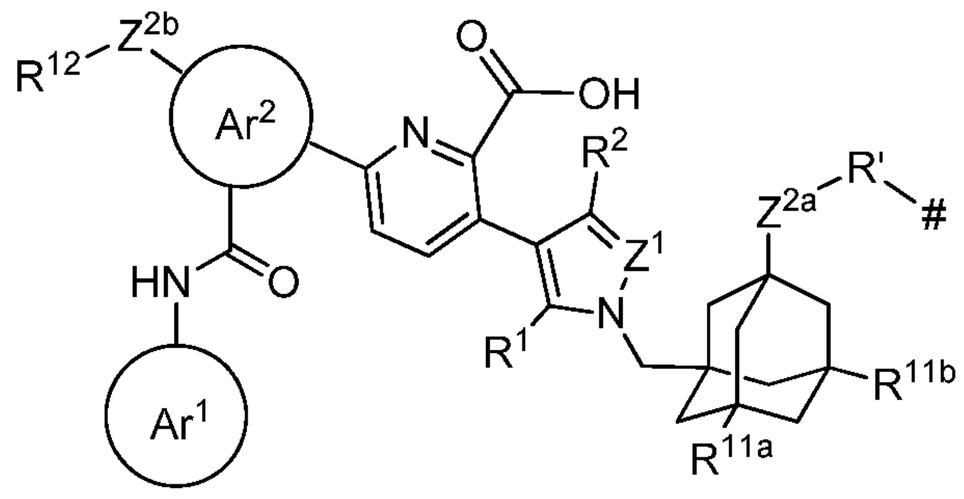
III.A.1. Bcl-xL Inhibitors

One aspect of the instant disclosure concerns Bcl-xL inhibitors that have low cell permeability. The compounds are generally heterocyclic in nature and include one or more solubilizing groups that impart the compounds with high water solubility and low cell permeability. The solubilizing groups are generally groups that are capable of hydrogen bonding, forming dipole-dipole interactions, and/or that include a polyethylene glycol polymer containing from 1 to 30 units, one or more polyols, one or more salts, or one or more groups that are charged at physiological pH.

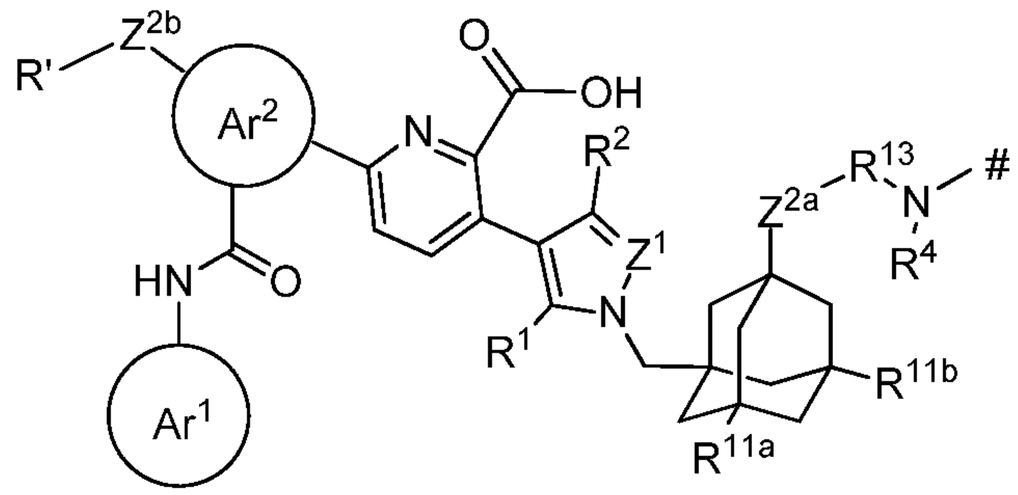
The Bcl-xL inhibitors may be used as compounds or salts *per se* in the various methods described herein, or may be included as a component part of an ADC.

Specific embodiments of Bcl-xL inhibitors that may be used in unconjugated form, or that may be included as part of an ADC include compounds according to structural formulae (IIa), (IIb), (IIc), or (IId). In the present invention, when the Bcl-xL inhibitors are included as part of an ADC, # shown in structural formula (IIa), (IIb), (IIc), or (IId) below represents a point of attachment to a linker, which indicates that they are represented in a monoradical form.

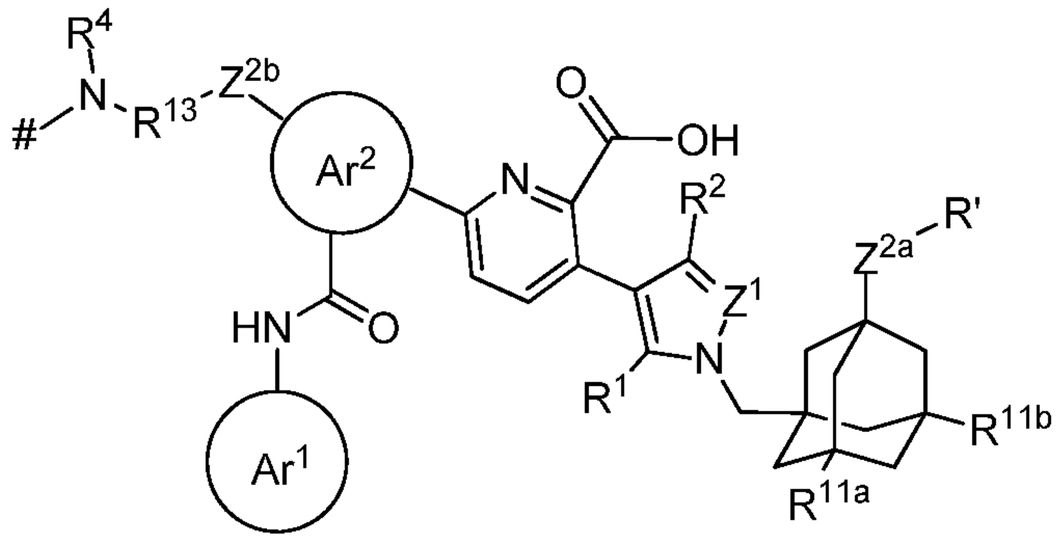
(IIa)



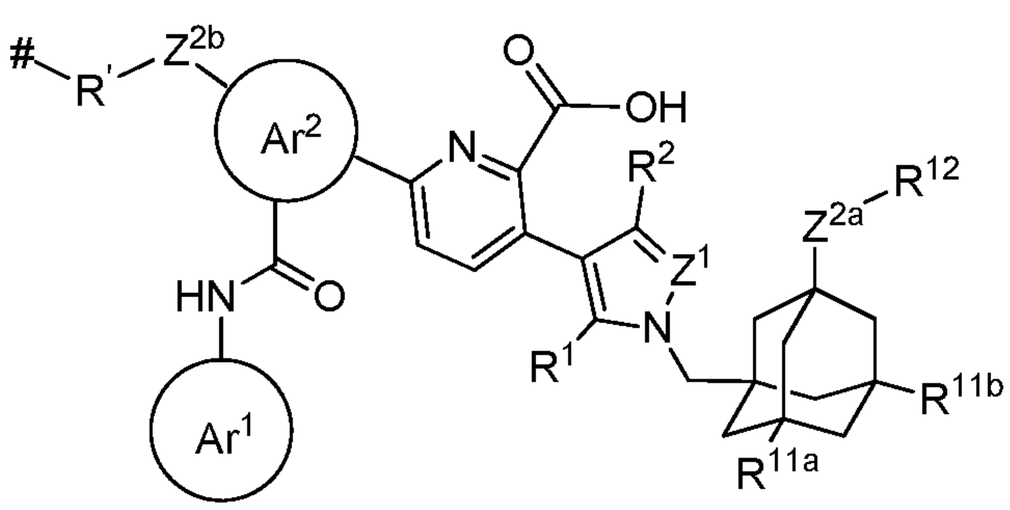
(IIb)



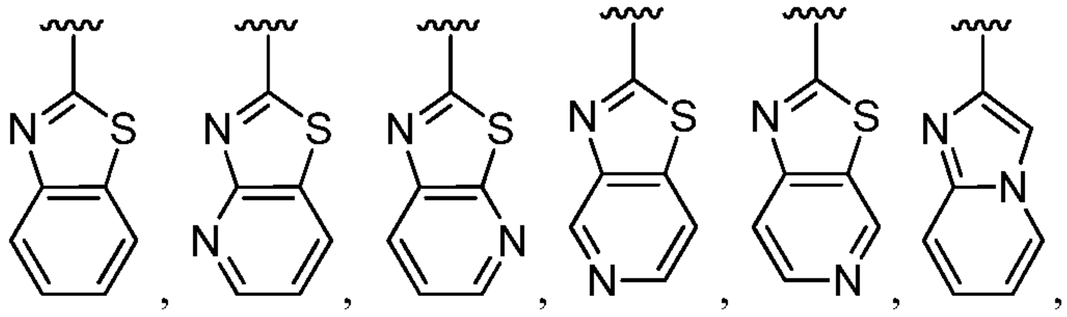
(IIc)

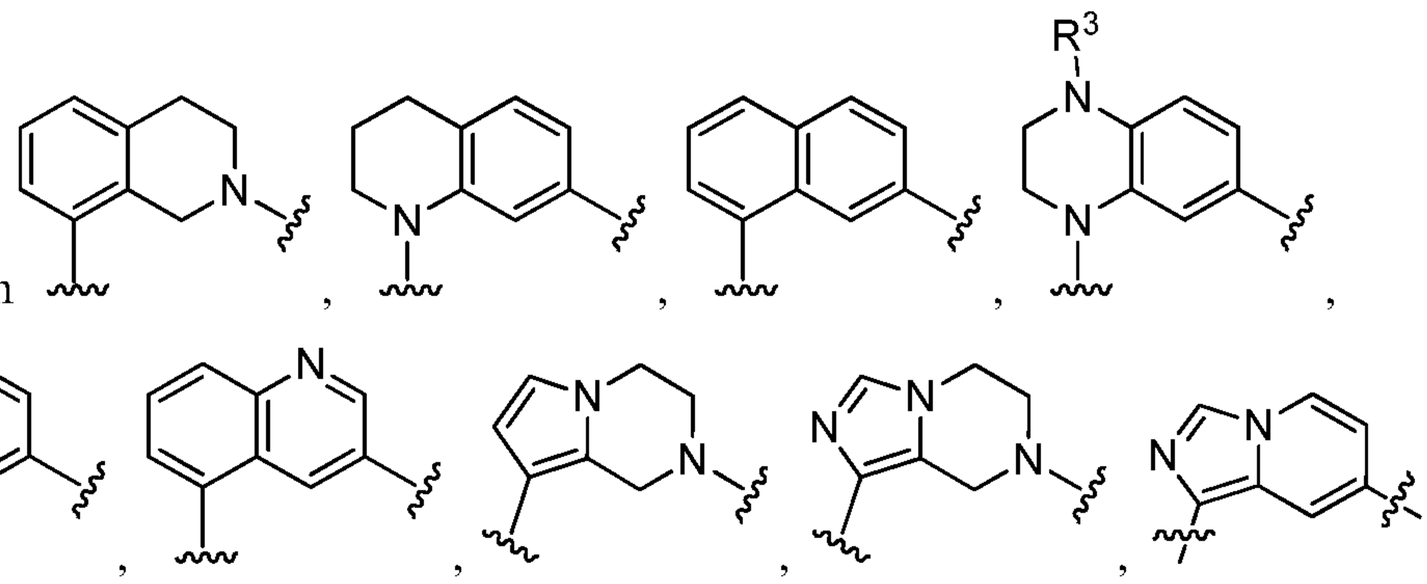


(IId)



or a pharmaceutically acceptable salt thereof, wherein:

Ar^1 is selected from  , and is optionally substituted with one or more substituents independently selected from halo, hydroxy, nitro, lower alkyl, lower heteroalkyl, C_{1-4}alkoxy, amino, cyano and halomethyl;

Ar^2 is selected from  , and is optionally substituted with one or more substituents independently selected from halo, hydroxy, nitro, lower alkyl, lower heteroalkyl, C_{1-4}alkoxy, amino, cyano and halomethyl, wherein the R^{12}-Z^{2b}-, R'-Z^{2b}-, #-N(R^4)-R^{13}-Z^{2b}-, or #-R'-Z^{2b}- substituents are attached to Ar^2 at any Ar^2 atom capable of being substituted;

Z^1 is selected from N, CH, C-halo, C-CH_3 and C-CN;

Z^{2a} and $Z^{2b}$are each, independently from one another, selected from a bond, NR^6, $CR^{6a}R^{6b}$, O, S, S(O), $S(O)_2$, -NR^6C(O)-,-NR^{6a}C(O)NR^{6b}-, and –NR^6C(O)O-;

R' is a alkylene, heteroalkylene, cycloalkylene, heterocyclene, aryl or heteroaryl independently substituted at one or more carbon or heteroatoms with a solubilizing moiety containing a group selected from a polyol, a polyethylene glycol containing from 4 to 30 ethylene glycol units, a salt, and a group that is charged at physiological pH and combinations thereof, wherein #, where attached to R', is attached to R' at any R' atom capable of being substituted;

R^1 is selected from hydrogen, methyl, halo, halomethyl, ethyl, and cyano;

R^2 is selected from hydrogen, methyl, halo, halomethyl and cyano;

R^3 is selected from hydrogen, methyl, ethyl, halomethyl and haloethyl;

R^4 is selected from hydrogen, lower alkyl and lower heteroalkyl or is taken together with an atom of R^{13} to form a cycloalkyl or heterocyclyl ring having between 3 and 7 ring atoms;

R^6, R^{6a} and R^{6b} are each, independent from one another, selected from hydrogen, optionally substituted lower alkyl, optionally substituted lower heteroalkyl, optionally substituted cycloalkyl and

optionally substituted heterocyclyl, or are taken together with an atom from R^4 and an atom from R^{13} to form a cycloalkyl or heterocyclyl ring having between 3 and 7 ring atoms;

R^{11a} and R^{11b} are each, independently of one another, selected from hydrogen, halo, methyl, ethyl, halomethyl, hydroxyl, methoxy, CN, and SCH_3;

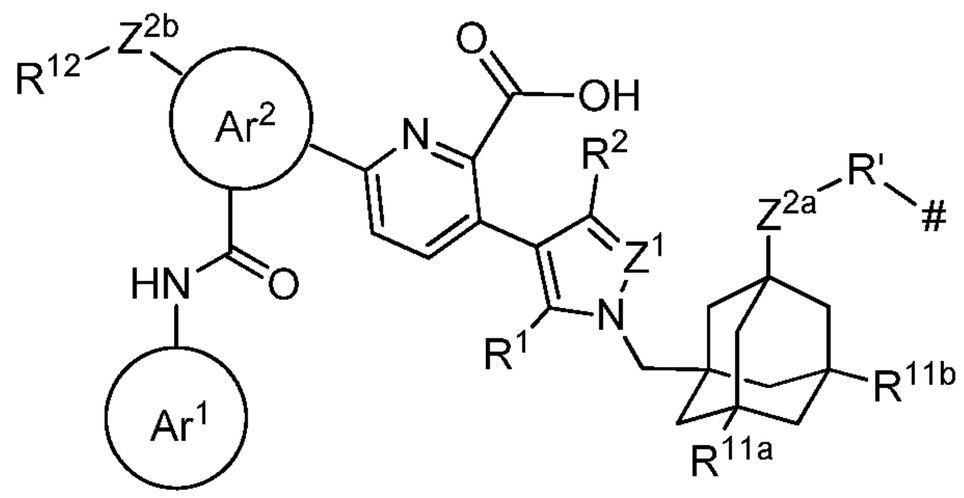
R^{12} is optionally R' or is selected from hydrogen, halo, cyano, optionally substituted alkyl, optionally substituted heteroalkyl, optionally substituted heterocyclyl, and optionally substituted cycloalkyl;

R^{13} is selected from optionally substituted C_{1-8} alkylene, optionally substituted heteroalkylene, optionally substituted heterocyclene, and optionally substituted cycloalkylene; and

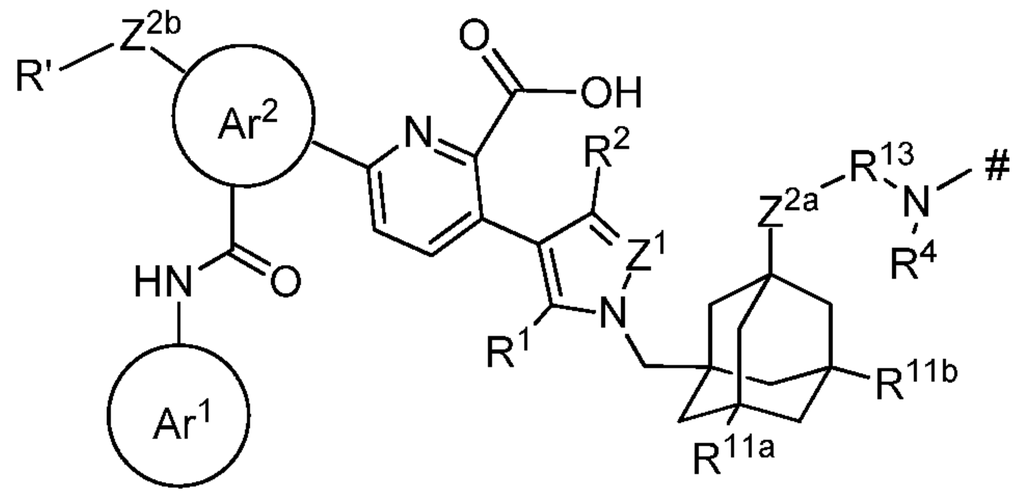
represents the point of attachment to a linker L.

One embodiment of Bcl-xL inhibitors that may be used in unconjugated form, or that may be included as part of an ADC include compounds according to structural formulae (IIa), (IIb), (IIc), or (IId):

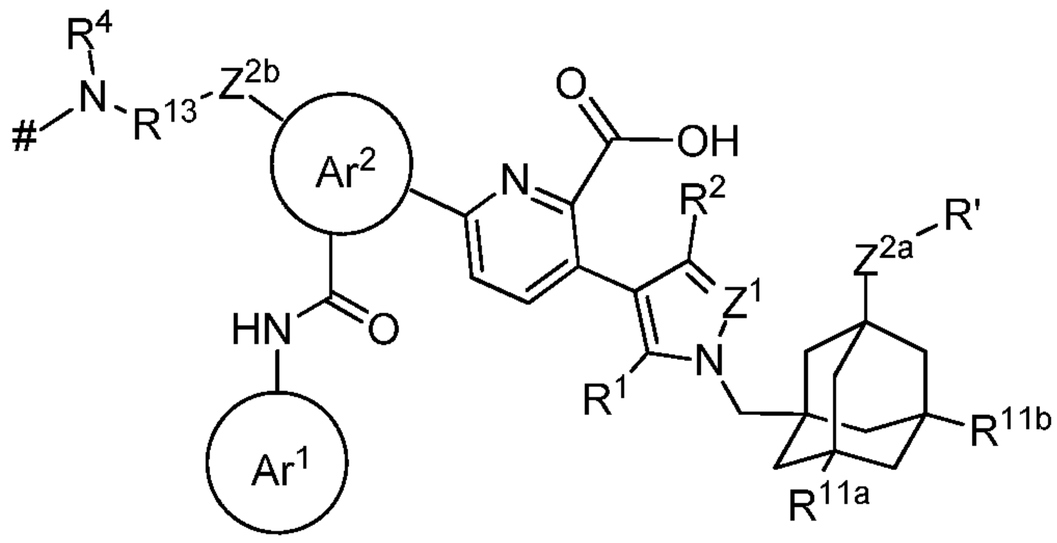
(IIa)



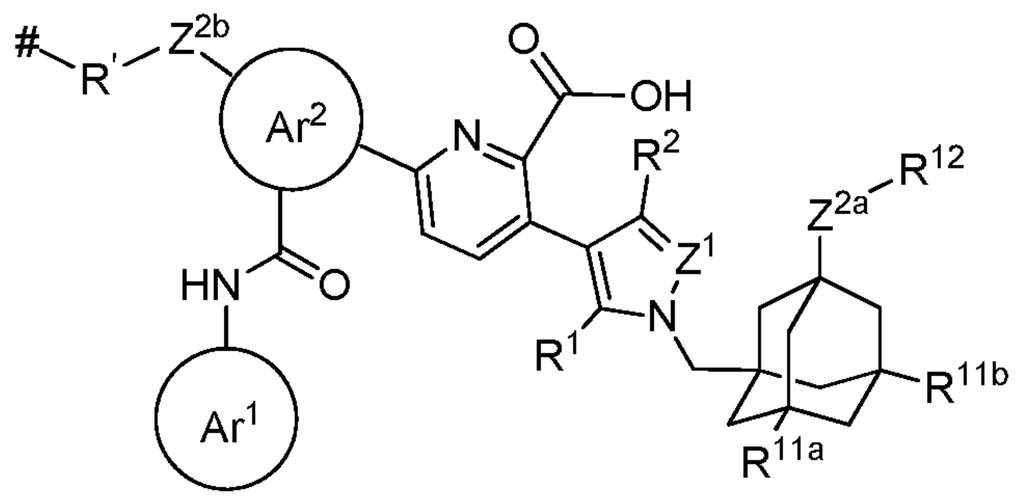
(IIb)



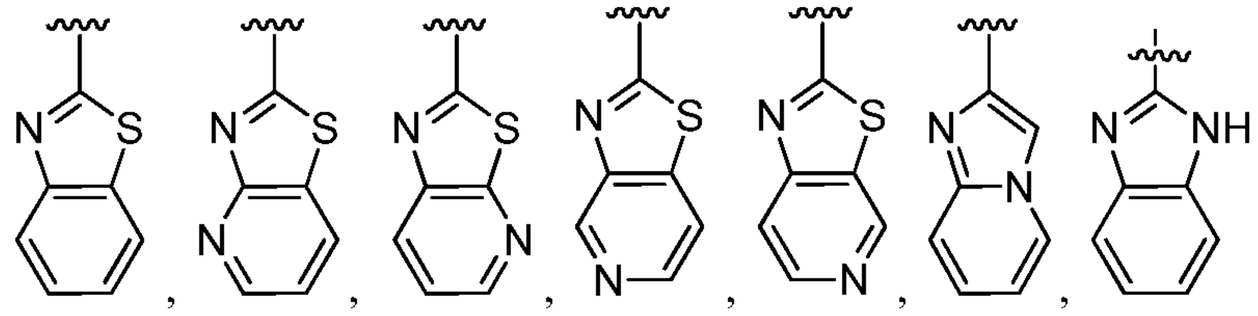
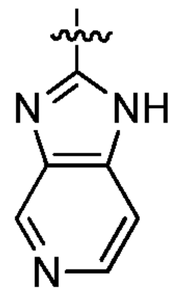
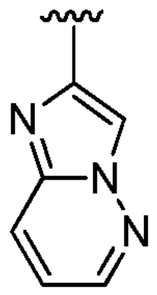
(IIc)

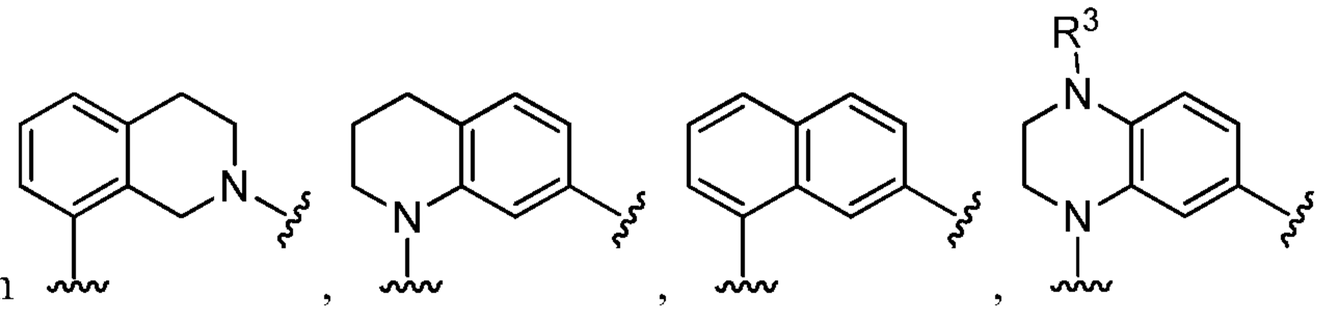
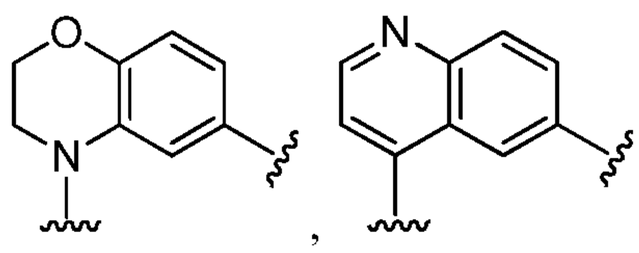
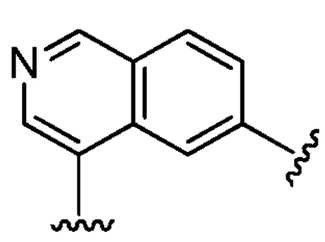
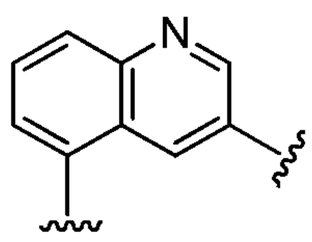
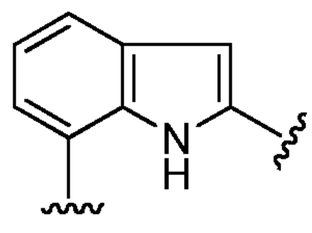
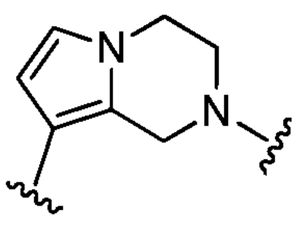
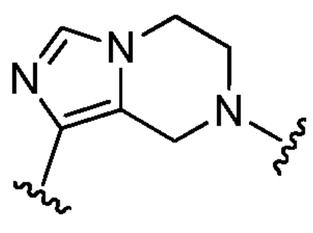
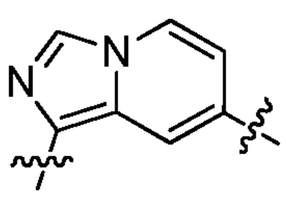


(IId)



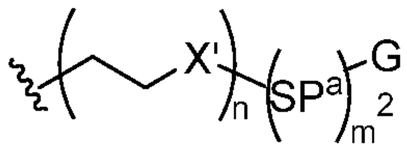
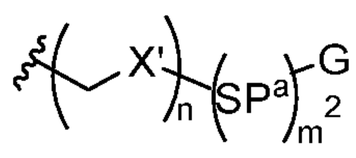
or a pharmaceutically acceptable salt thereof, wherein:

Ar^1 is selected from  ,  and  , and is optionally substituted with one or more substituents independently selected from halo, hydroxy, nitro, lower alkyl, lower heteroalkyl, C_{1-4}alkoxy, amino, cyano and halomethyl;

Ar^2 is selected from  ,  , ,  ,  ,  ,  ,  , and  or an N-oxide thereof, and is optionally substituted with one or more substituents independently selected from halo, hydroxy, nitro, lower alkyl, lower heteroalkyl, C_{1-4}alkoxy, amino, cyano and halomethyl, wherein the R^{12}-Z^{2b}-, R'-Z^{2b}-, #-N(R^4)-R^{13}-Z^{2b}-, or #-R'-Z^{2b}- substituents are attached to Ar^2 at any Ar^2 atom capable of being substituted;

Z^1 is selected from N, CH, C-halo, C-CH_3 and C-CN;

Z^{2a} and $Z^{2b}$are each, independently from one another, selected from a bond, NR^6, $CR^{6a}R^{6b}$, O, S, S(O), $S(O)_2$, -NR^6C(O)-,-NR^{6a}C(O)NR^{6b}-, and –NR^6C(O)O-;

R' is  or  , wherein #, where attached to R', is attached to R' at any R' atom capable of being substituted;

X' is selected at each occurrence from $-N(R^{10})-$, $-N(R^{10})C(O)-$, $-N(R^{10})S(O)_2-$, $-S(O)_2N(R^{10})-$, and -O-;

n is selected from 0-3;

R^{10} is independently selected at each occurrence from hydrogen, lower alkyl, heterocycle, aminoalkyl, G-alkyl, and $-(CH_2)_2-O-(CH_2)_2-O-(CH_2)_2-NH_2$;

G at each occurrence is independently selected from a polyol, a polyethylene glycol with between 4 and 30 repeating units, a salt and a moiety that is charged at physiological pH;

SP^a is independently selected at each occurrence from oxygen, $-S(O)_2N(H)-$, $-N(H)S(O)_2-$, $-N(H)C(O)-$, $-C(O)N(H)-$, $-N(H)-$, arylene, heterocyclene, and optionally substituted methylene; wherein methylene is optionally substituted with one or more of $-NH(CH_2)_2G$, NH_2, C_{1-8}alkyl, and carbonyl;

m^2 is selected from 0-12;

R^1 is selected from hydrogen, methyl, halo, halomethyl, ethyl, and cyano;

R^2 is selected from hydrogen, methyl, halo, halomethyl and cyano;

R^3 is selected from hydrogen, methyl, ethyl, halomethyl and haloethyl;

R^4 is selected from hydrogen, lower alkyl and lower heteroalkyl or is taken together with an atom of R^{13} to form a cycloalkyl or heterocyclyl ring having between 3 and 7 ring atoms;

R^6, R^{6a} and R^{6b} are each, independent from one another, selected from hydrogen, optionally substituted lower alkyl, optionally substituted lower heteroalkyl, optionally substituted cycloalkyl and optionally substituted heterocyclyl, or are taken together with an atom from R^4 and an atom from R^{13} to form a cycloalkyl or heterocyclyl ring having between 3 and 7 ring atoms;

R^{11a} and R^{11b} are each, independently of one another, selected from hydrogen, halo, methyl, ethyl, halomethyl, hydroxyl, methoxy, CN, and SCH_3;

R^{12} is optionally R' or is selected from hydrogen, halo, cyano, optionally substituted alkyl, optionally substituted heteroalkyl, optionally substituted heterocyclyl, and optionally substituted cycloalkyl;

R^{13} is selected from optionally substituted C_{1-8} alkylene, optionally substituted heteroalkylene, optionally substituted heterocyclene, and optionally substituted cycloalkylene; and

represents the point of attachment to a linker L.

When a Bcl-xL inhibitor of structural formulae (IIa)-(IId) is not a component of an ADC, # in formulae (IIa)-(IId) represents the point of attachment to a hydrogen atom. When the Bcl-xL inhibitor is a component of an ADC, # in formulae (IIa)-(IId) represents the point of attachment to the linker.

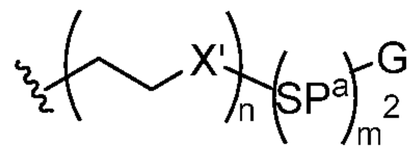
When a Bcl-xL inhibitor is a component of an ADC, the ADC may comprise one or more Bcl-xL inhibitors, which may be the same or different, but are typically the same.

In certain embodiments, R' is a C_2-C_8 heteroalkylene substituted with one or more moieties containing a salt and/or a group that is charged at physiological pH. The salt may be selected, for example, from the salt of a carboxylate, a sulfonate, a phosphonate, and an ammonium ion. For example, the salt may be the sodium or potassium salt of a carboxylate, sulfonate or phosphonate or the chloride salt of an ammonium ion. The group that is charged at physiological pH may be any group that is charged at a physiological pH, including, by way of example and not limitation, a zwitterionic group. In certain embodiments a group that is a salt is a dipolar moiety such as, but not limited to, N-oxides of amines including certain heterocyclyls such as, but not limited to, pyridine and quinoline. In specific embodiments the group that is charged at physiological pH is selected independently at each occurrence, from carboxylate, sulfonate, phosphonate, and amine.

In certain embodiments, R' is a C_2-C_8 heteroalkylene substituted with one or more moieties containing polyethylene glycol or a polyol such as a diol or a sugar moiety.

In certain embodiments, R' may be substituted with groups in addition to a solubilizing moiety. For example, R' may be substituted with one or more of the same or different alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, or halo groups.

In certain embodiments, R' is represented by the formula:



or a pharmaceutically acceptable salt thereof, wherein:

X‘ is selected at each occurrence from -N(R^{10})- and -O-;

n is selected from 1-3;

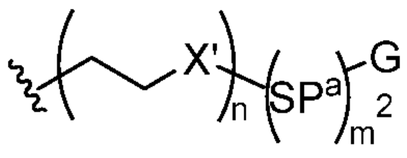
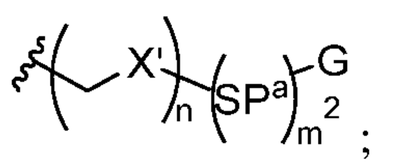
R^{10} is individually selected at each occurrence from hydrogen, alkyl, heterocycle, aminoalkyl, G-alkyl, heterocycle, and -$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$-NH_2;

G at each occurrence is independently selected from a polyol, a polyethylene glycol with between 4 and 30 repeating unit (referred to herein as PEG4-30), a salt and a moiety that is charged at physiological pH;

SP^a is independently selected at each occurrence from oxygen, sulfonamide, arylene, heterocyclene, and optionally substituted methylene; wherein methylene is optionally substituted with one or more of –NH$(CH_2)_2$G, amine and carbonyl; and

m^2 is selected from 0-6,

wherein there is at least one substitutable nitrogen in R' that is attached to a linker or a hydrogen atom at a substitutable nitrogen atom of R'.

In certain embodiments, R' is  or  ;

X' is selected at each occurrence from -N(R^{10})- , -N(R^{10})C(O)-, -N(R^{10})S(O)$_2$-, -S(O)$_2$N(R^{10})-, and -O-;

n is selected from 0-3;

R^{10} is independently selected at each occurrence from hydrogen, alkyl, heterocycle, aminoalkyl, G-alkyl, heterocycle, and -$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$-NH_2;

G at each occurrence is independently selected from a polyol, a polyethylene glycol with between 4 and 30 repeating units, a salt and a moiety that is charged at physiological pH;

SP^a is independently selected at each occurrence from oxygen-S(O)$_2$N(H)-, -N(H)S(O)$_2$-, -N(H)C(O)-, -C(O)N(H) -, -N(H)- , arylene, heterocyclene, and optionally substituted methylene; wherein methylene is optionally substituted with one or more of –NH$(CH_2)_2$G, amine, alkyl, and carbonyl;

m^2 is selected from 0-12, and

#, where attached to R', is attached to R' at any R' atom capable of being substituted.

In certain embodiments, G at each occurrence is a salt or a moiety that is charged at physiological pH.

In certain embodiments, G at each occurrence is a salt of a carboxylate, a sulfonate, a phosphonate, or ammonium.

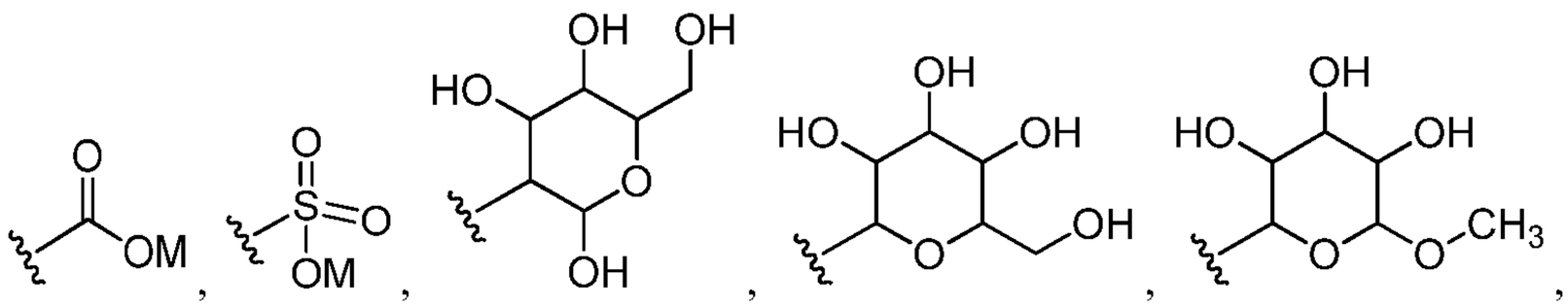
In certain embodiments, G at each occurrence is a moiety that is charged at physiological pH selected from the group consisting of carboxylate, a sulfonate, a phosphonate, and an amine.

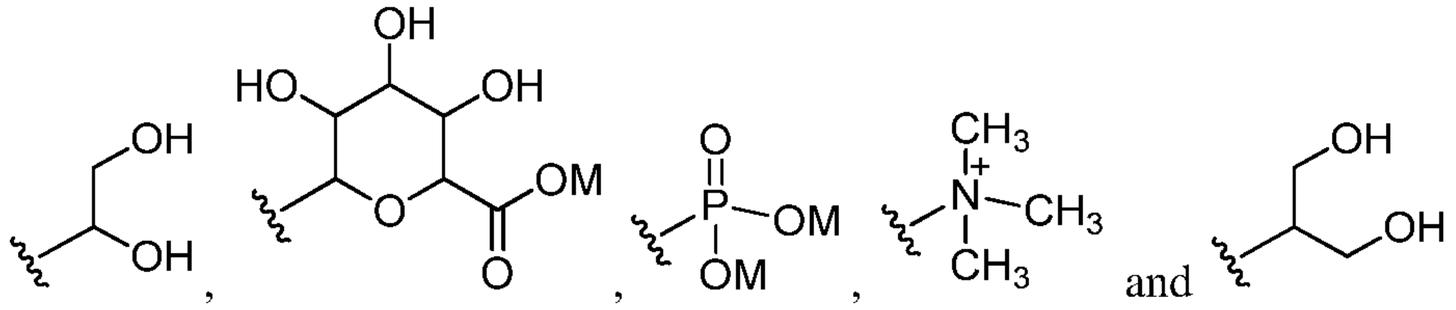
In certain embodiments, G at each occurrence is a moiety containing a polyethylene glycol with between 4 and 30 repeating units, or a polyol.

In certain embodiments, the polyol is a sugar.

In certain embodiments, R' of formula (IIa) or (IId) includes at least one substitutable nitrogen suitable for attachment to a linker.

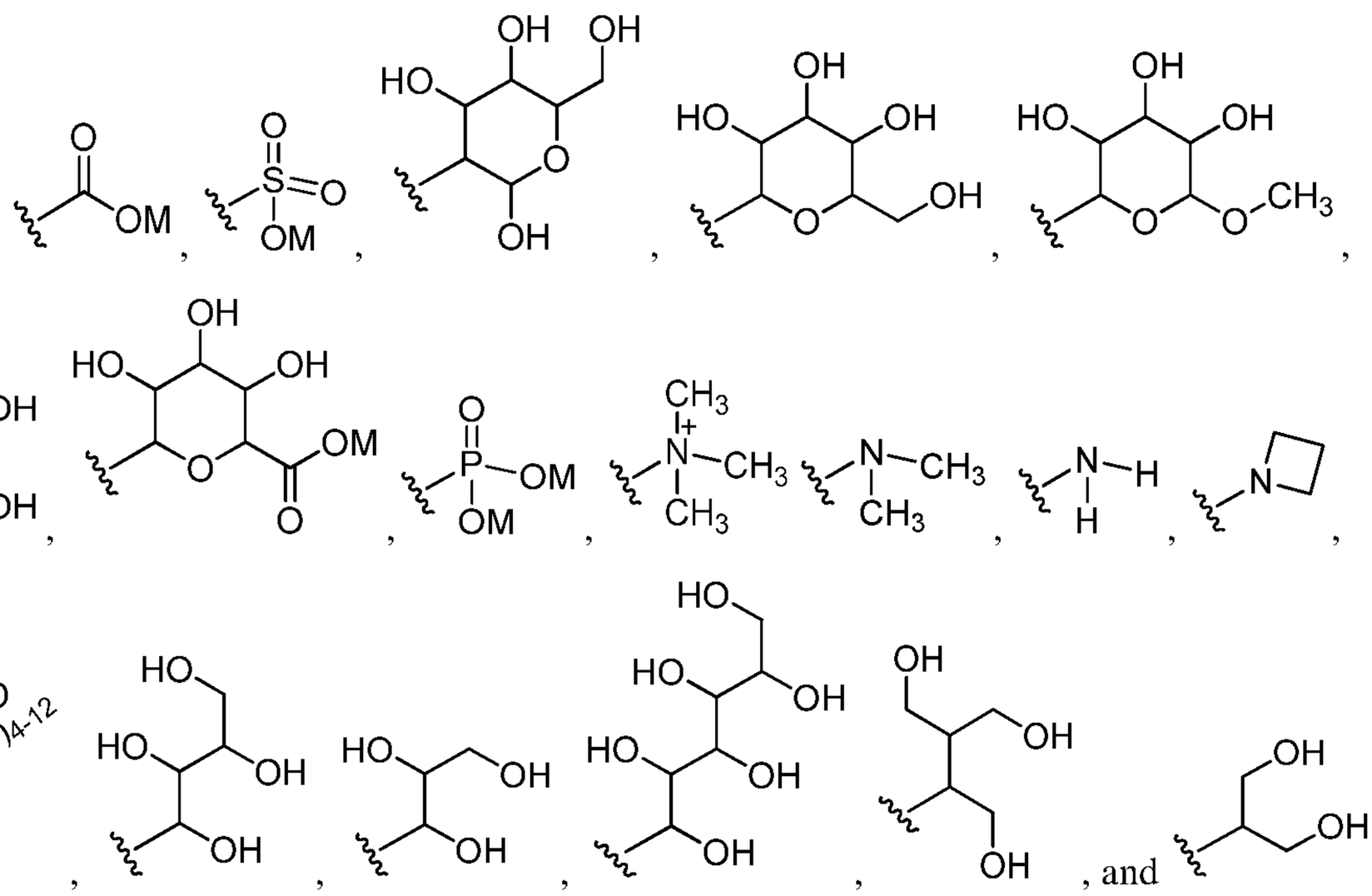
In certain embodiments, G is selected independently at each occurrence from:





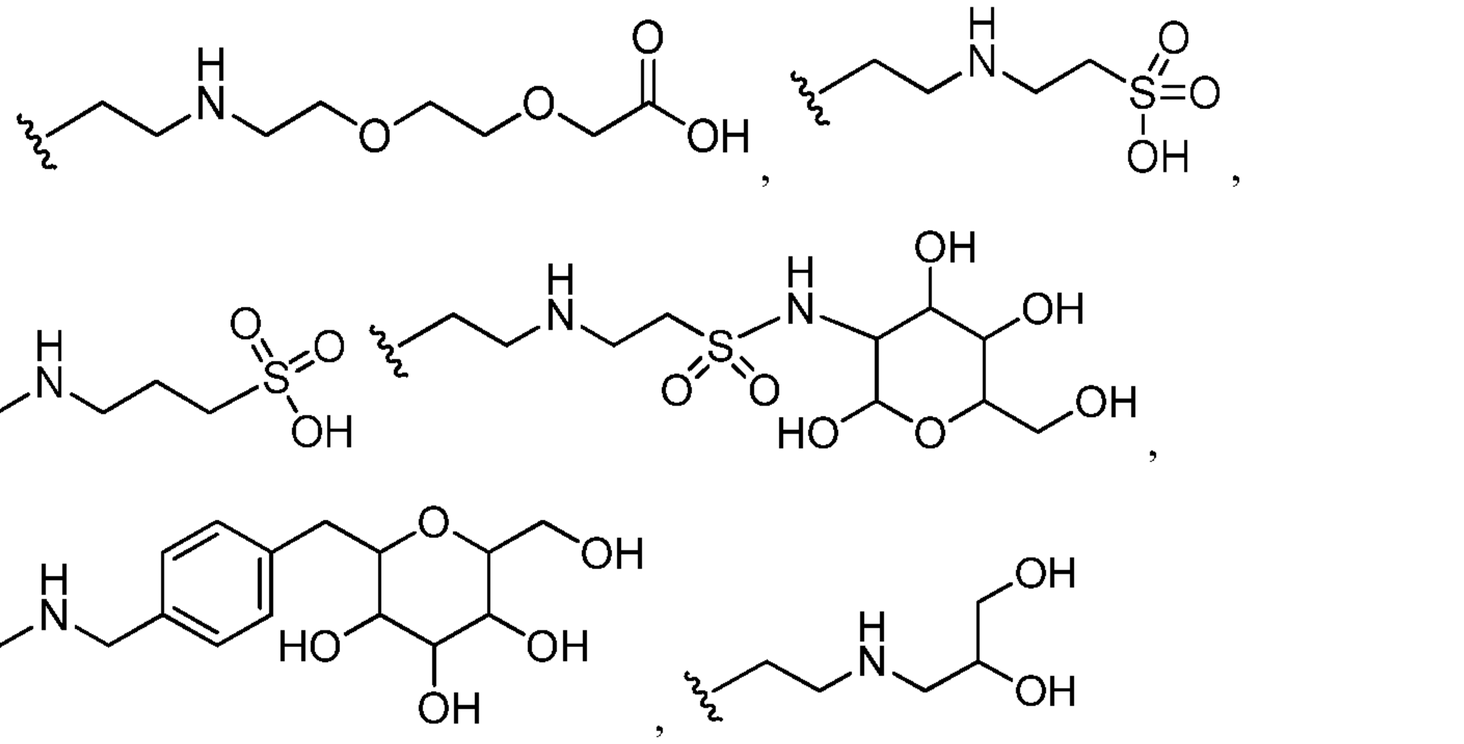
and wherein M is hydrogen or a positively charged counterion. In certain embodiments, M is Na^+, K^+ or Li^+. In certain embodiments, M is hydrogen. In particular embodiments, G is SO_3H.

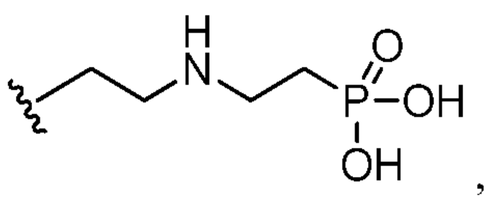
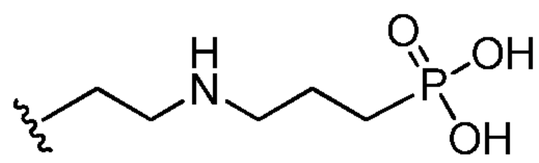
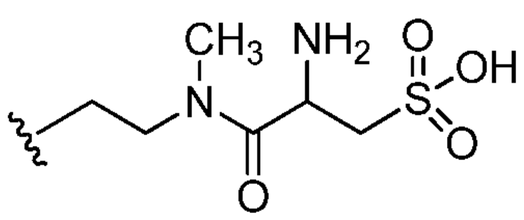
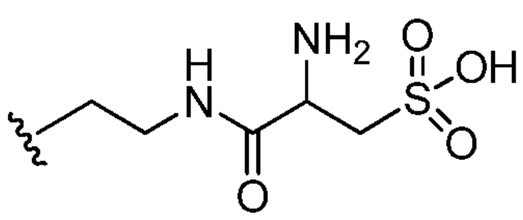
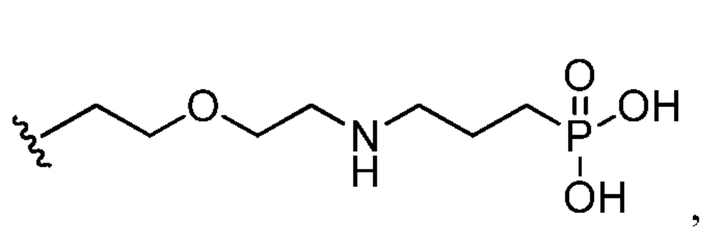
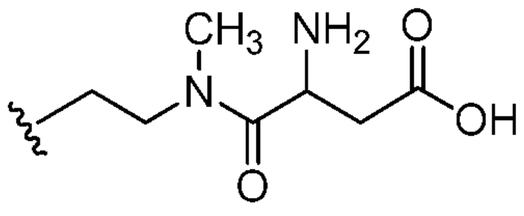
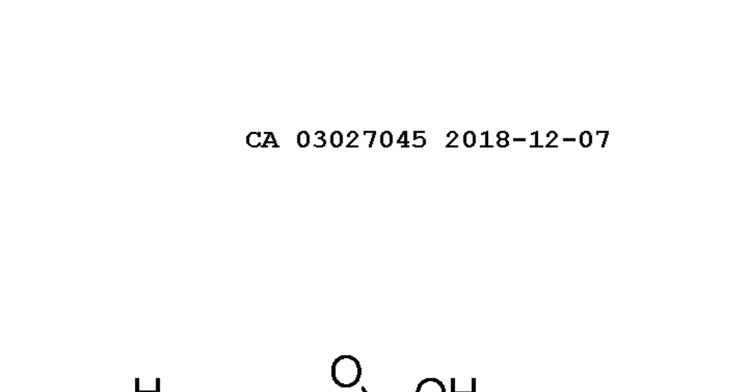
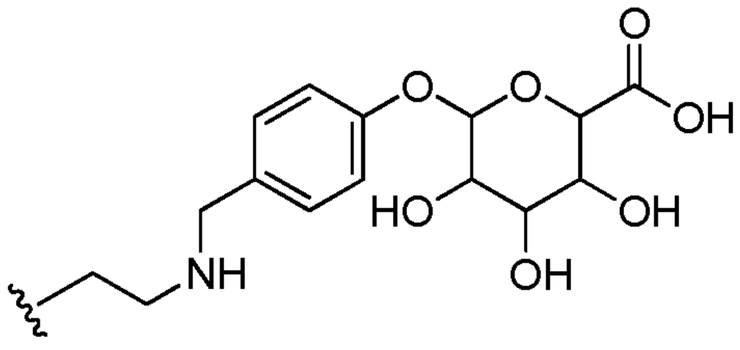
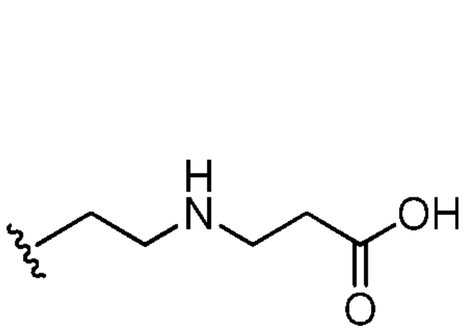
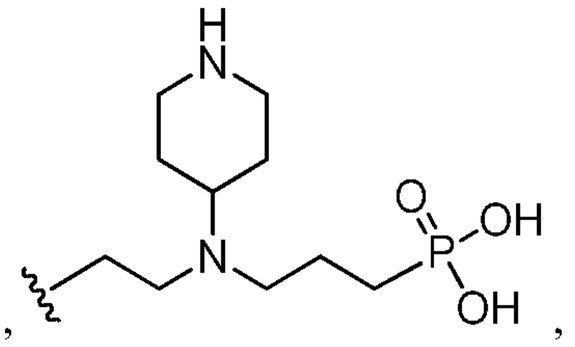
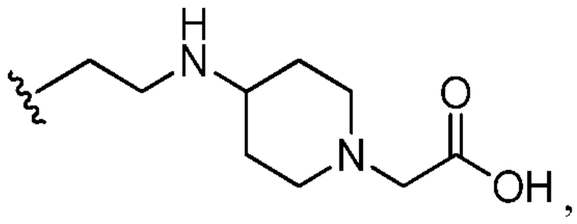
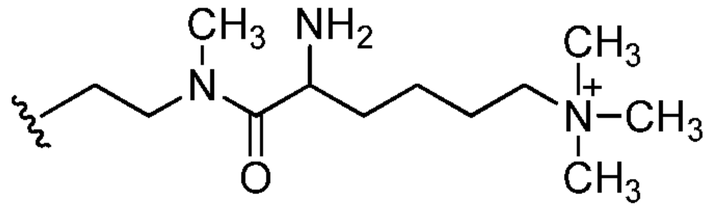
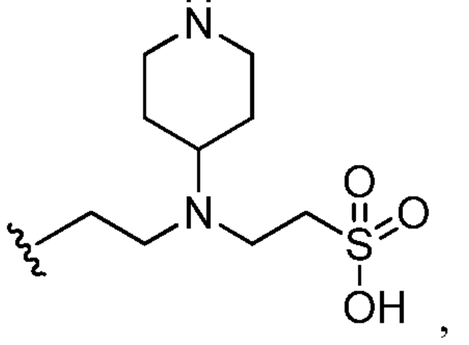
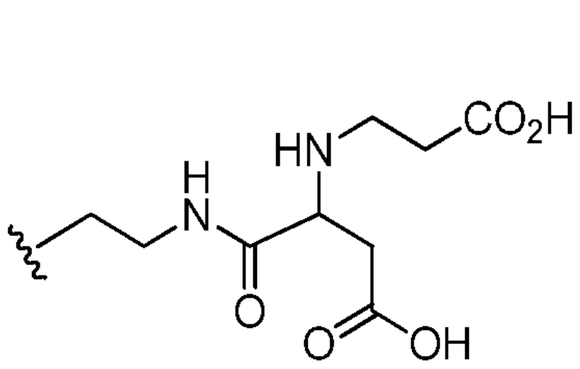
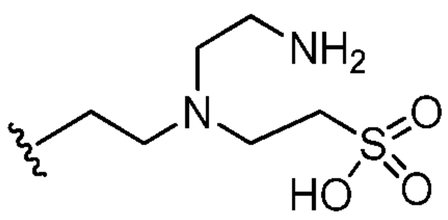
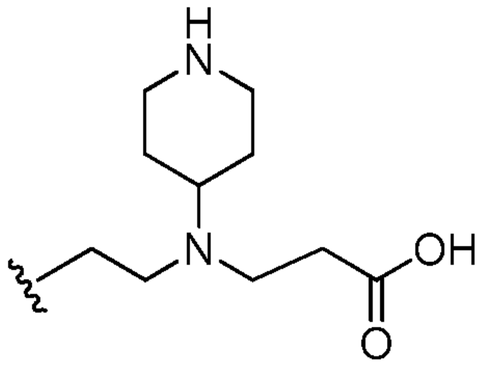
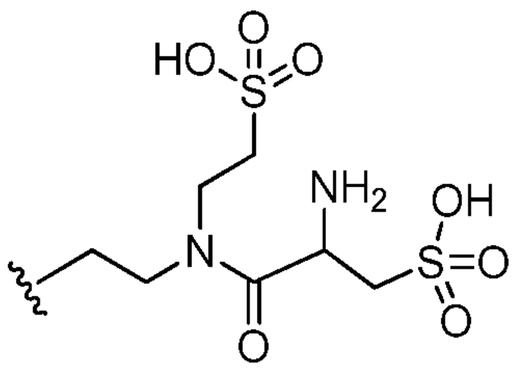
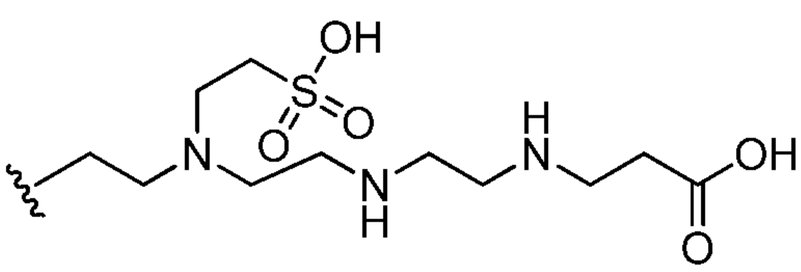
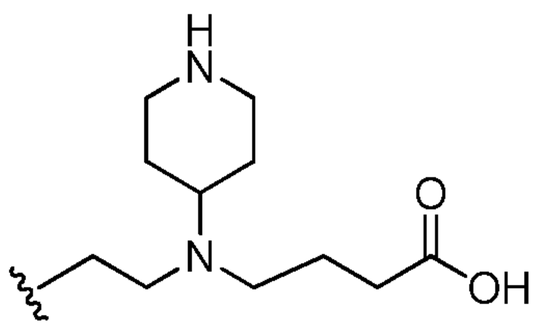
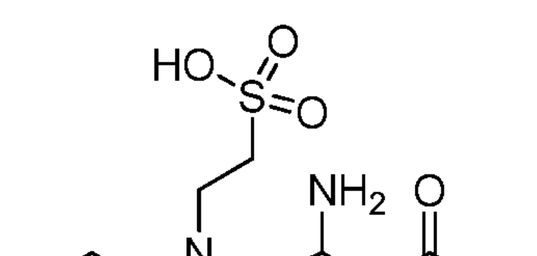
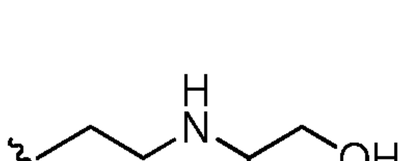
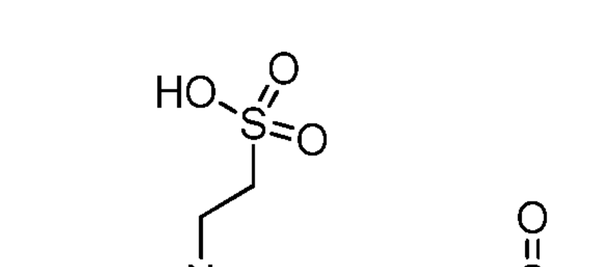
In certain embodiments, G is selected independently at each occurrence from:

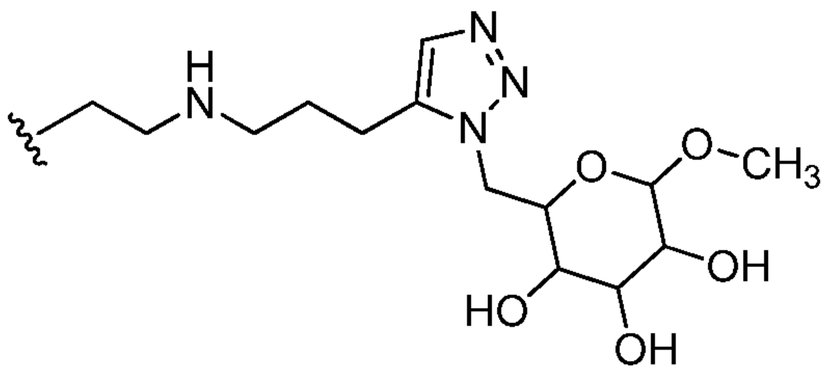
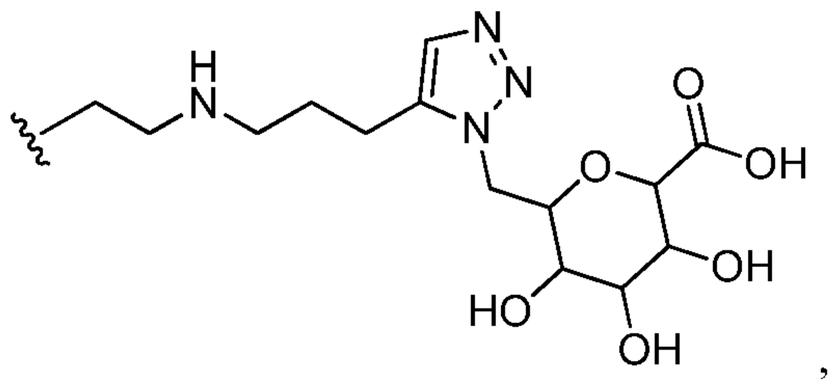
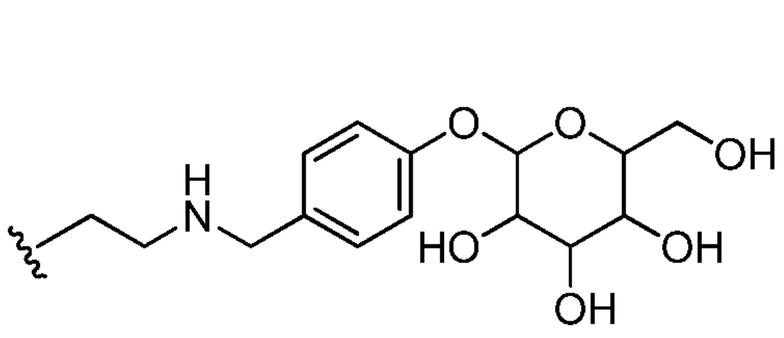
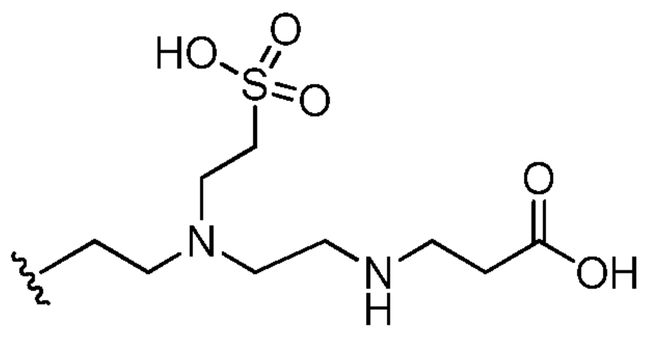


wherein M is hydrogen or a positively charged counterion. In certain embodiments, M is hydrogen. In particular embodiments, G is SO_3H.

In certain embodiments, R' is selected from:

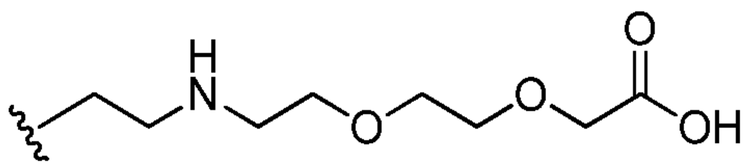
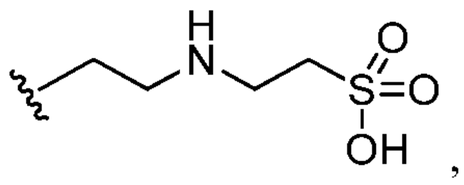
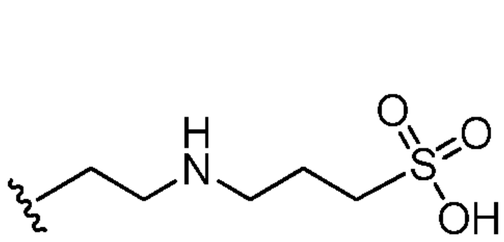
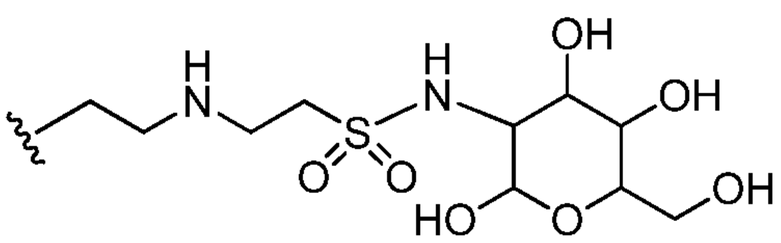
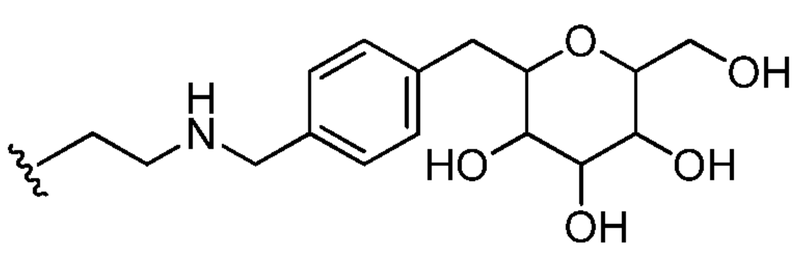
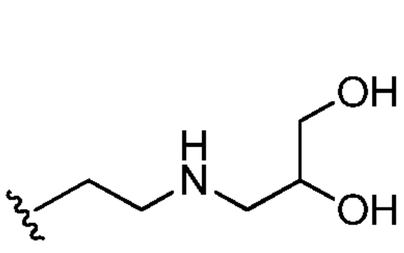
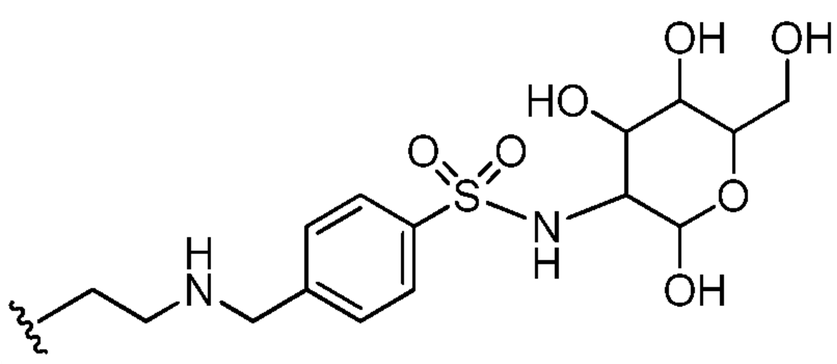
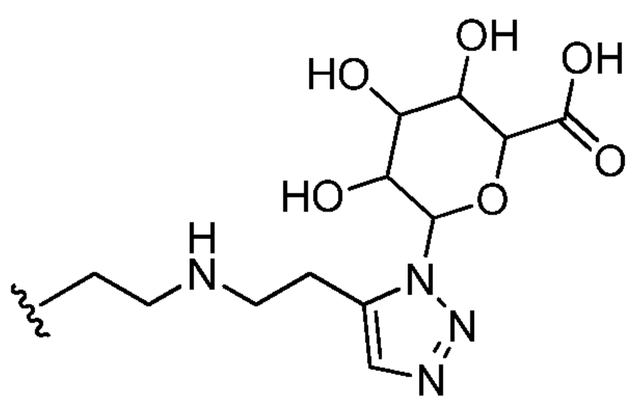
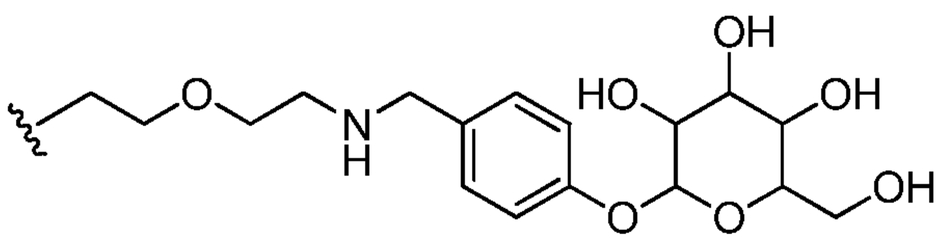
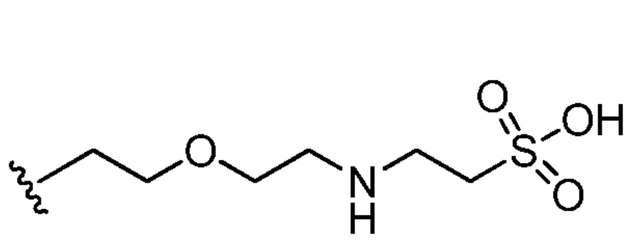
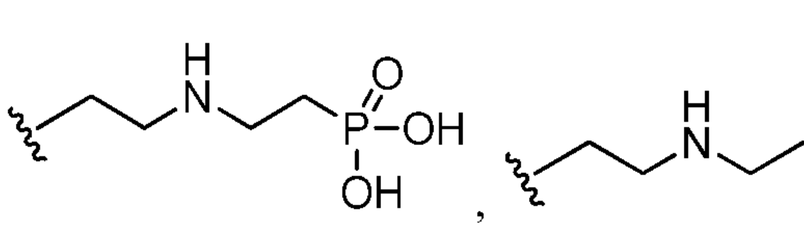
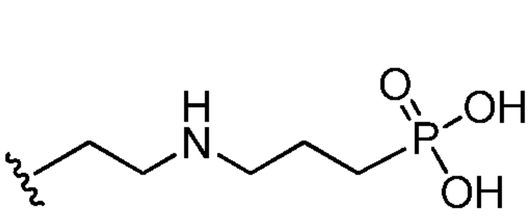
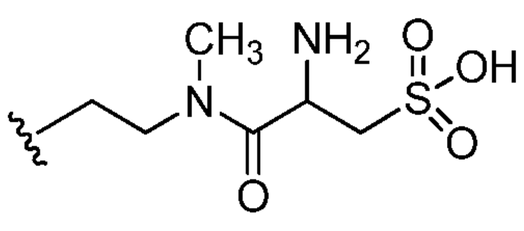
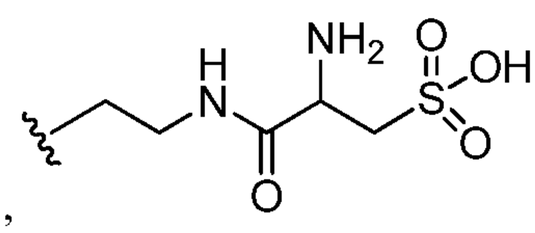
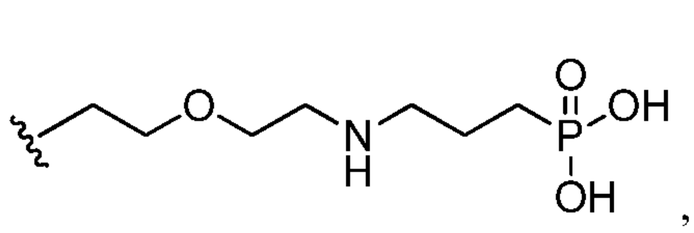


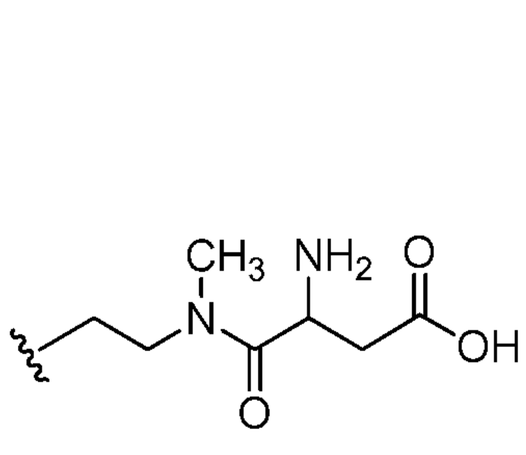
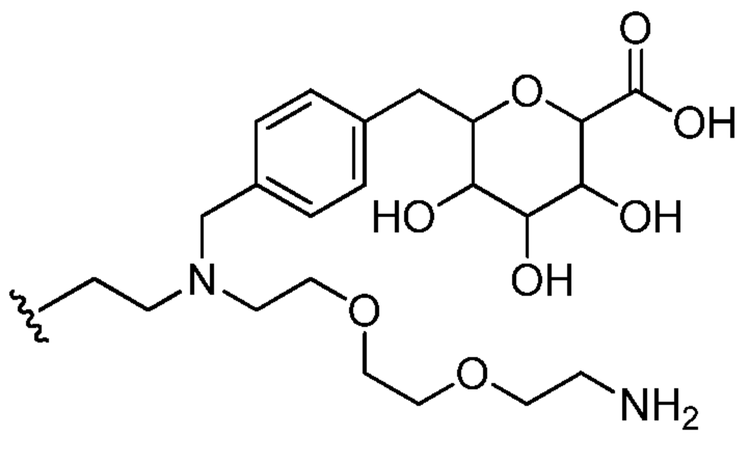
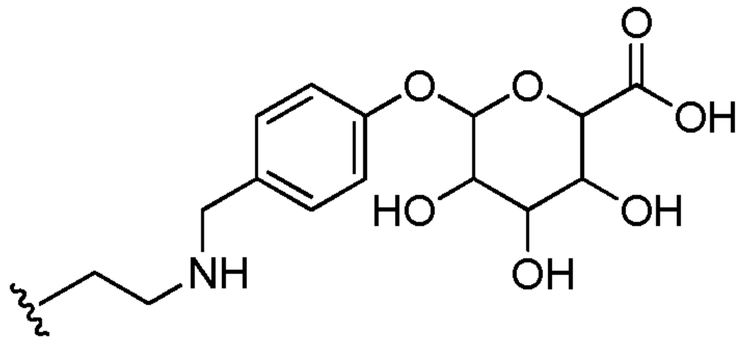
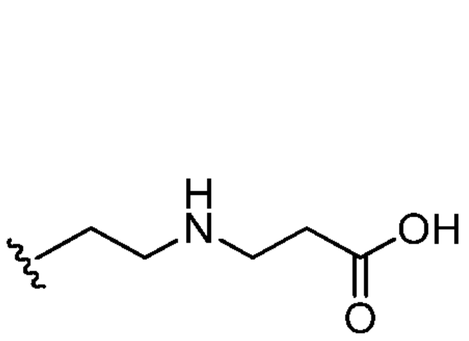
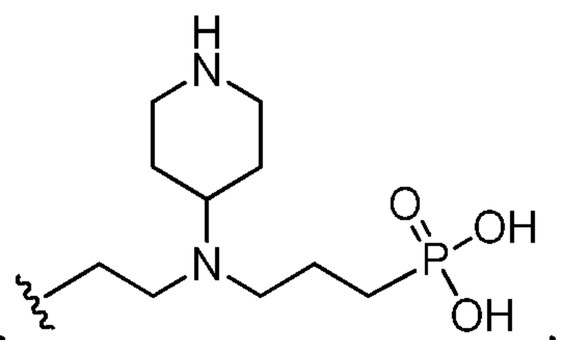
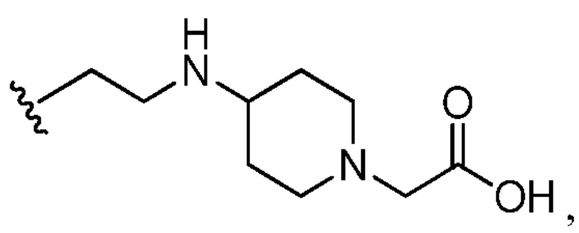
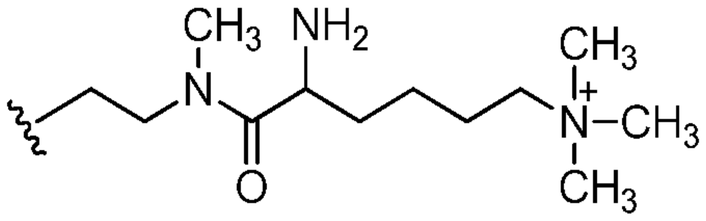
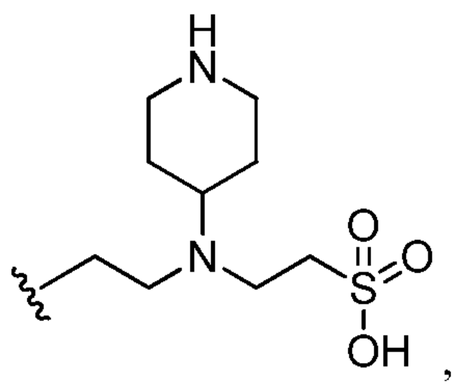
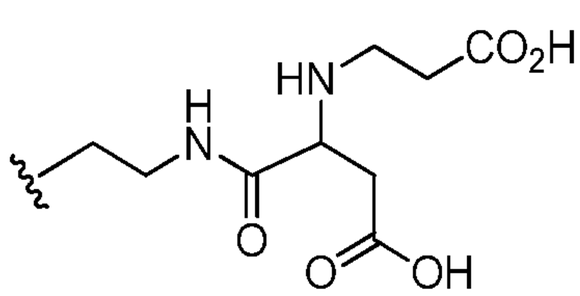
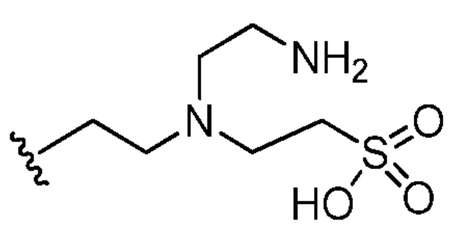
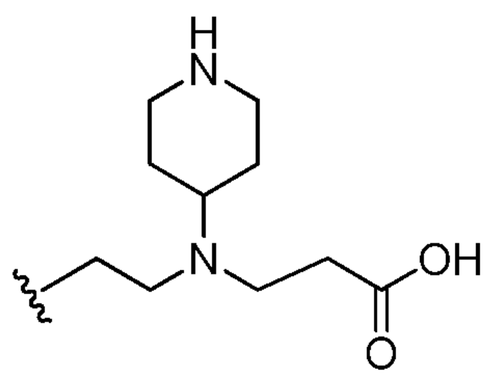
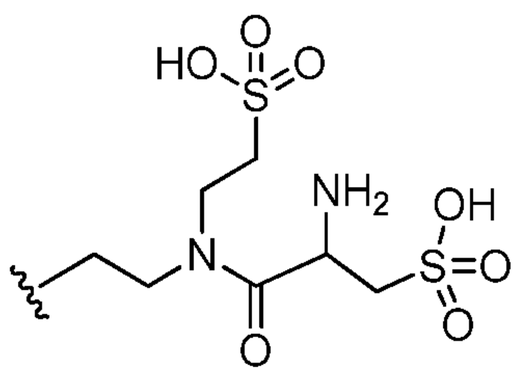
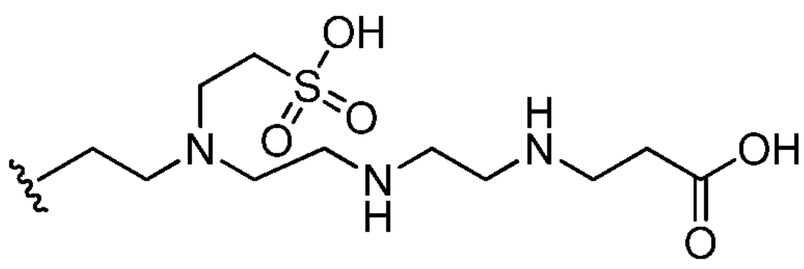
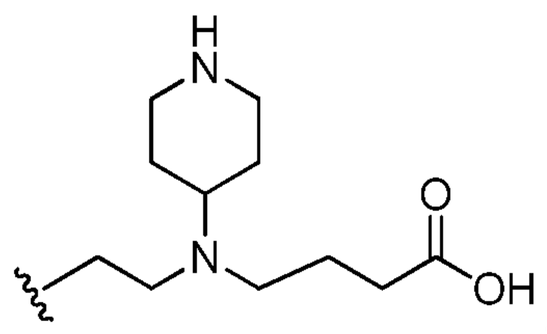
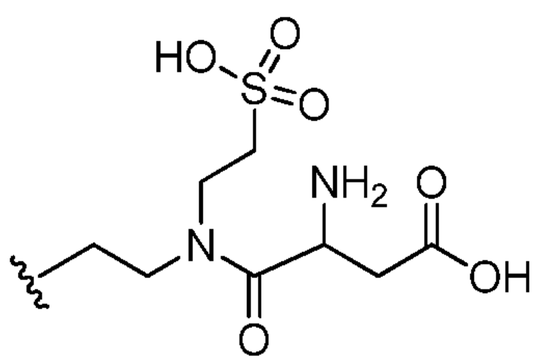
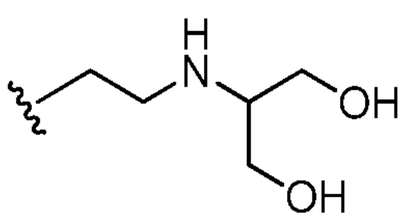
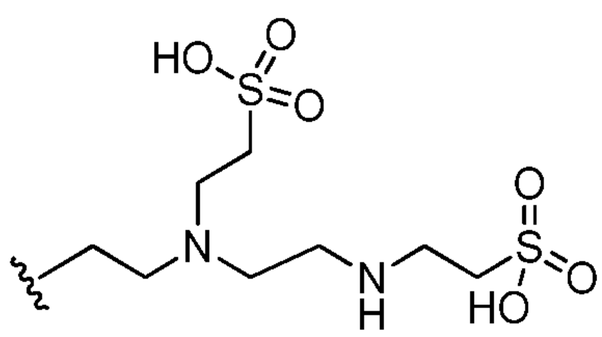
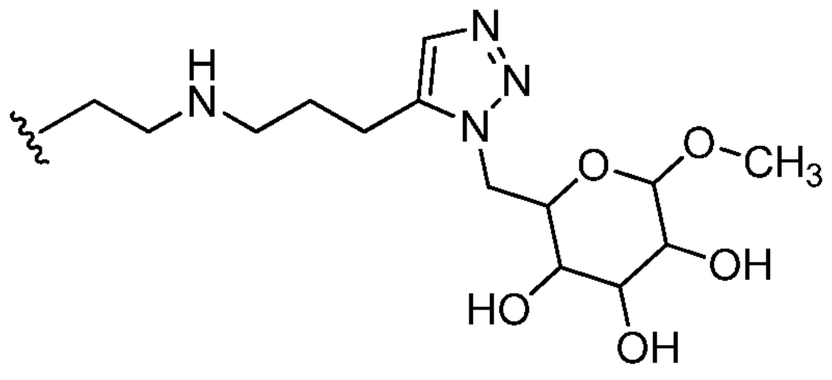
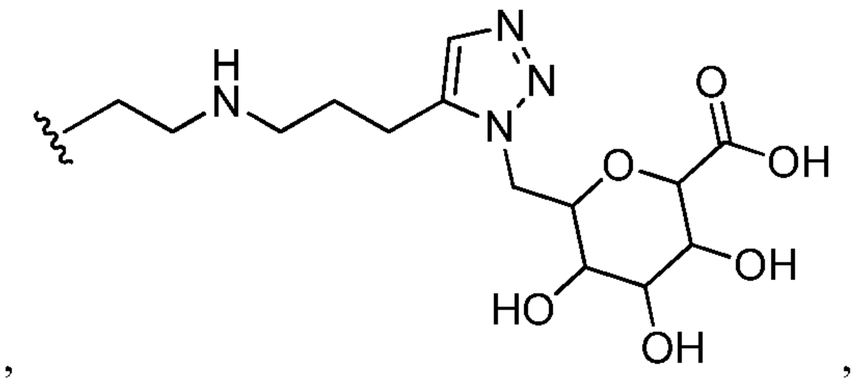

,

,

,

,

,

,

,

,

,

,
5

,

,

,

,

,

,

,

,

,

,

,

,

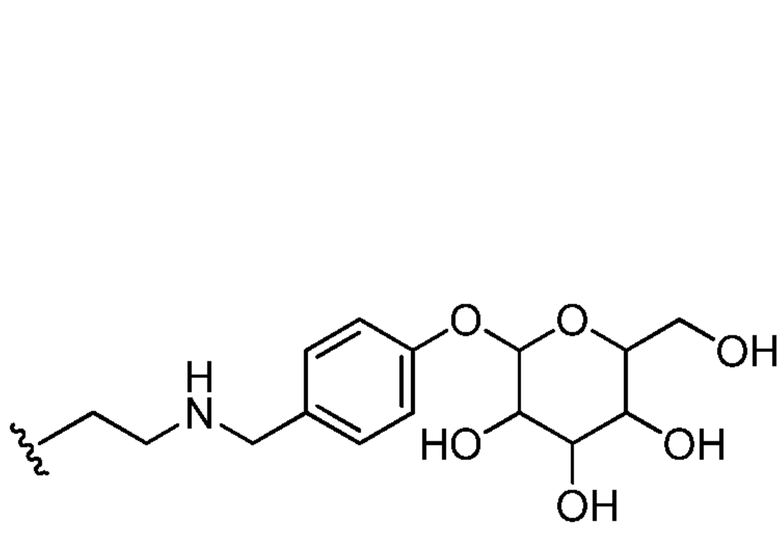
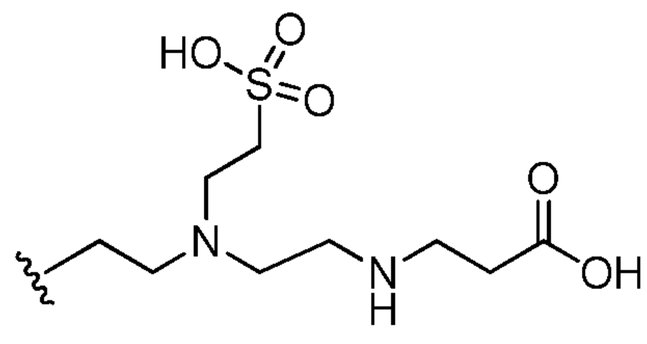
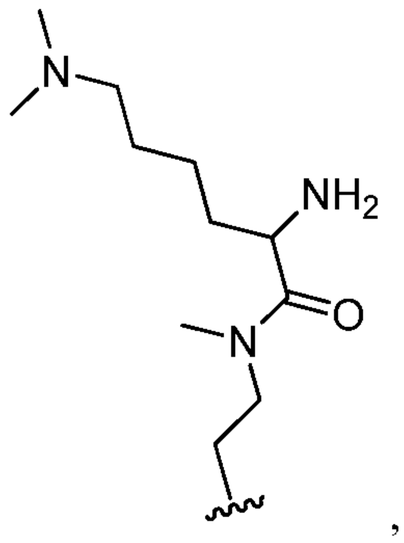
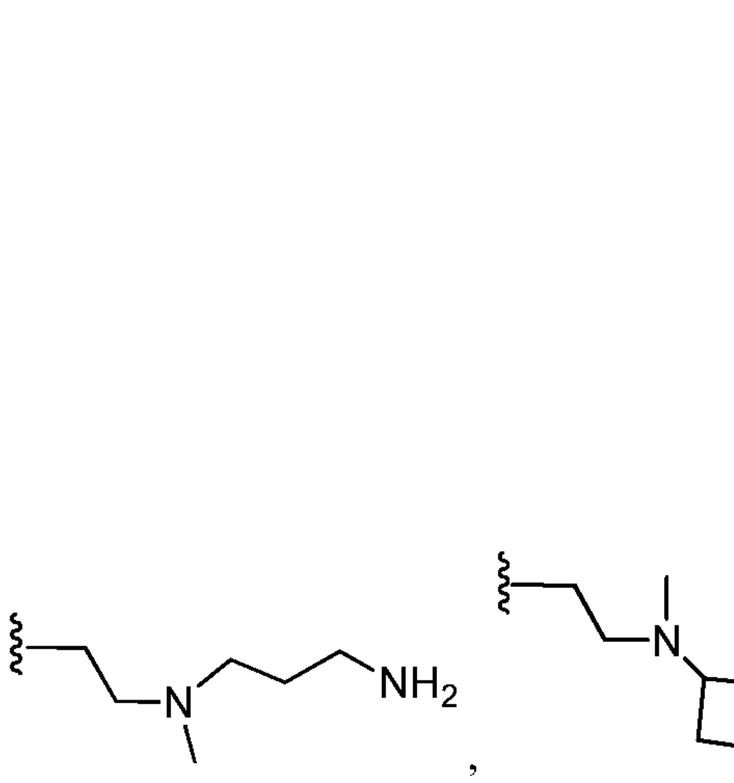

,

,

, and

, or a salt thereof.

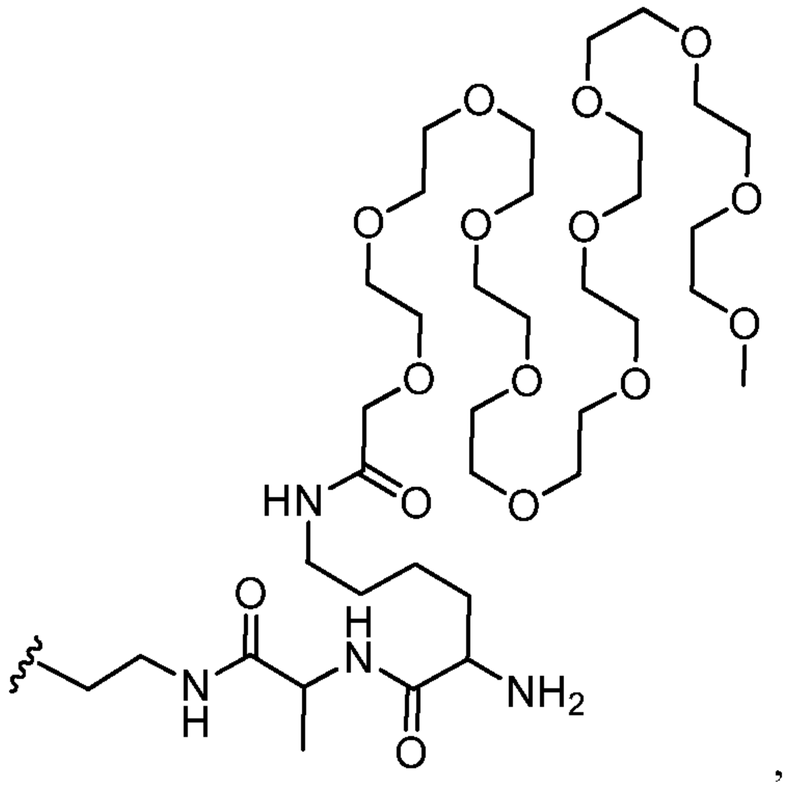
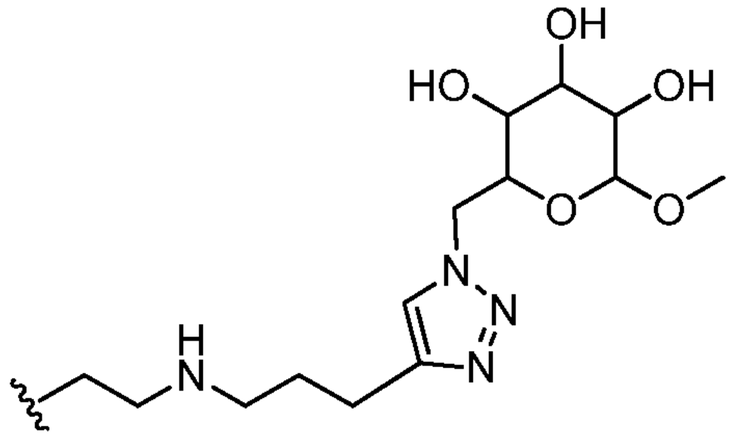
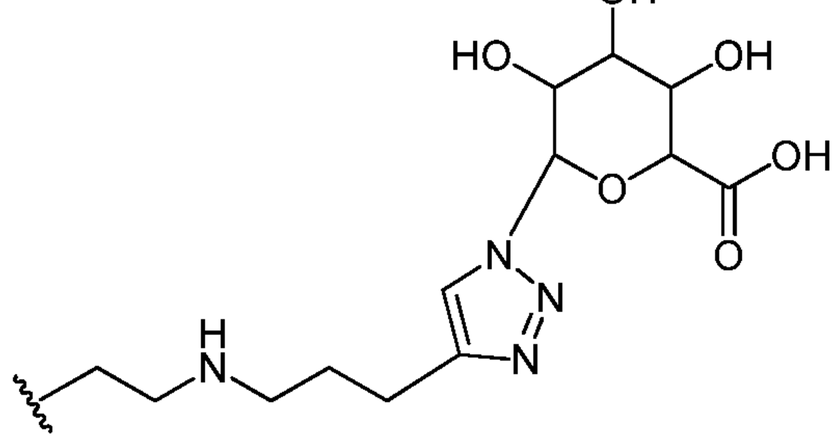
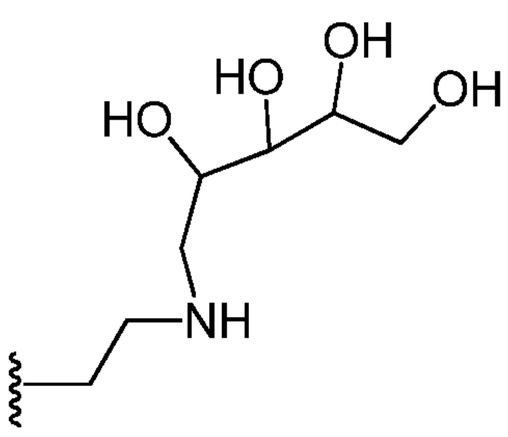
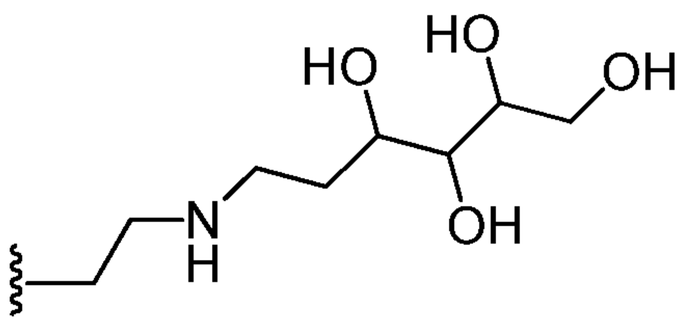
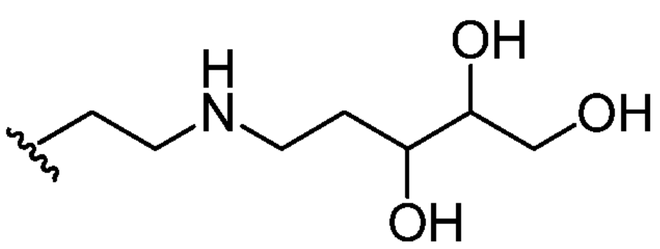
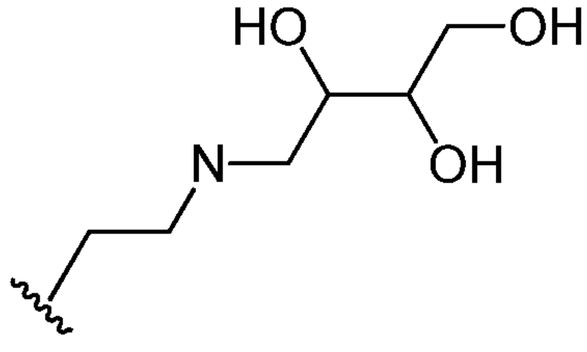
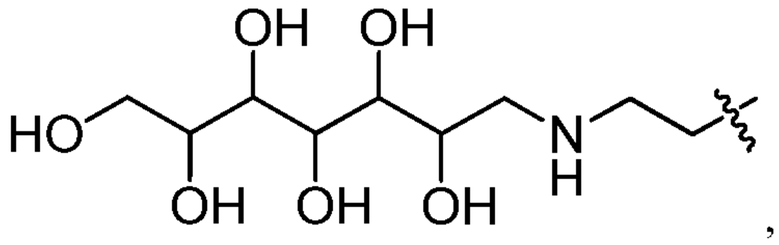
When Bcl-xL inhibitors of this embodiment are included in an ADC, the linker of the ADC is linked to the nitrogen atom of an available primary or secondary amine group.

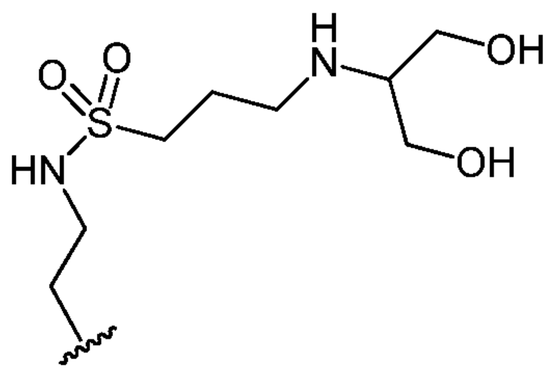
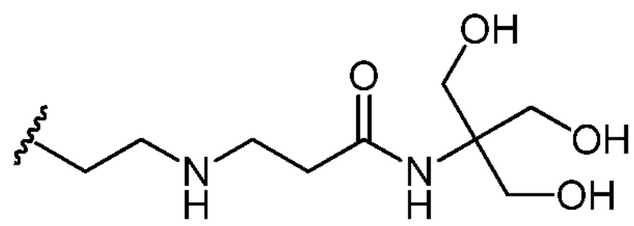
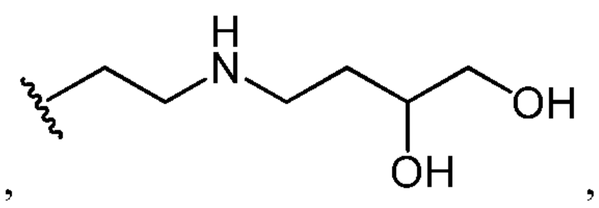
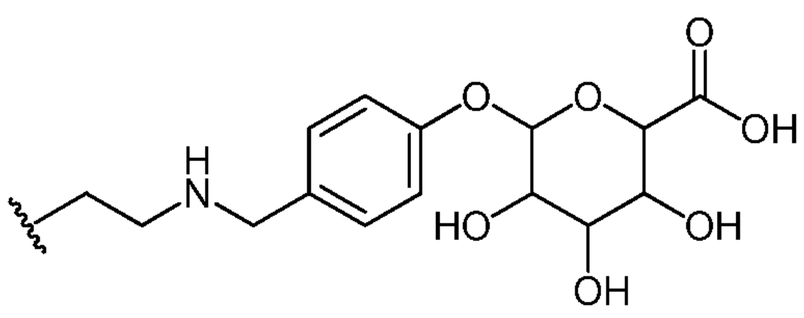
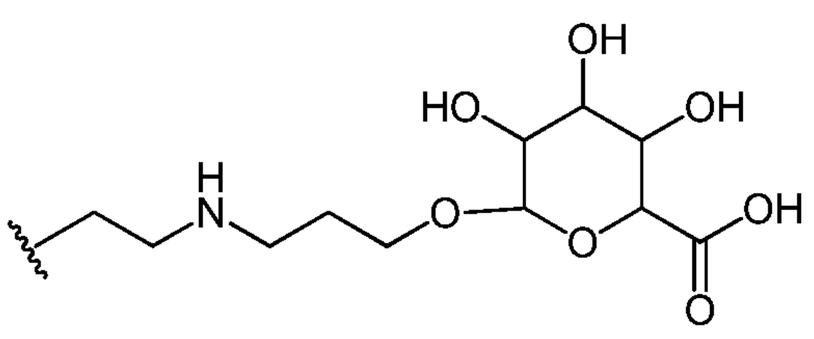
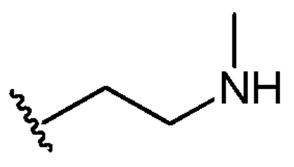
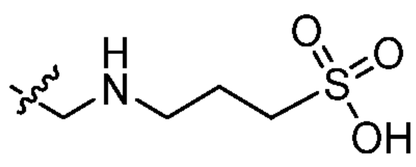
In certain embodiments, R' is selected from:


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

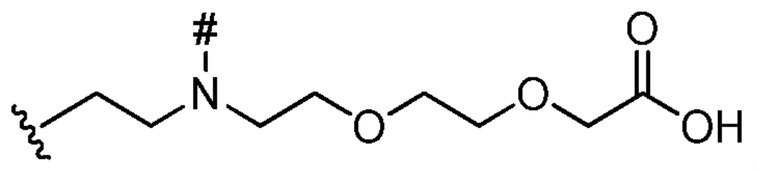

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

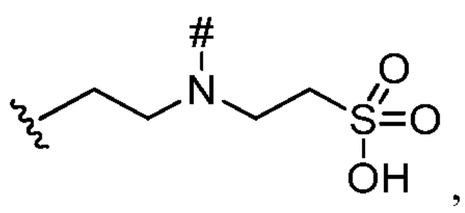
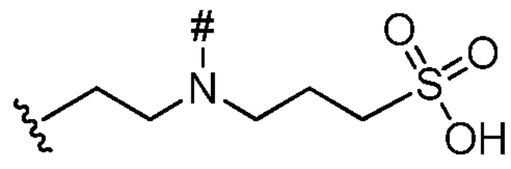
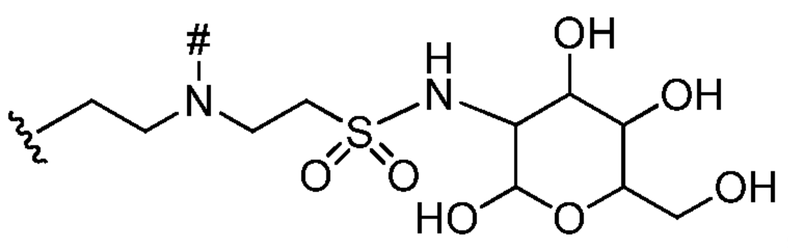
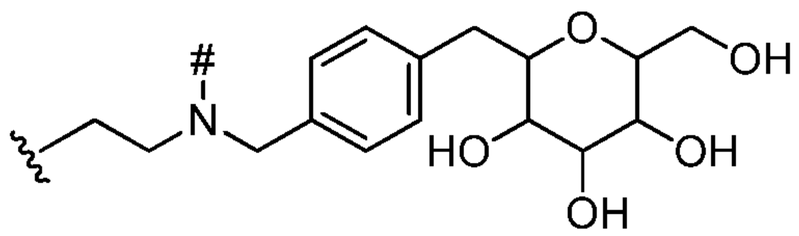
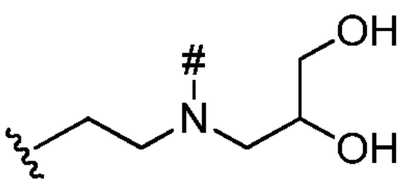
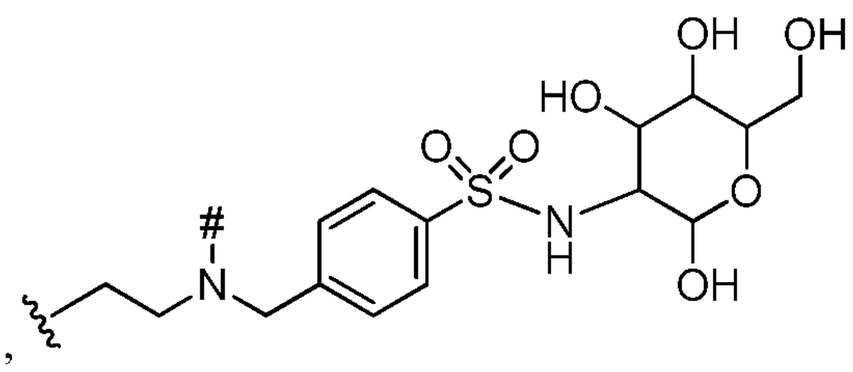
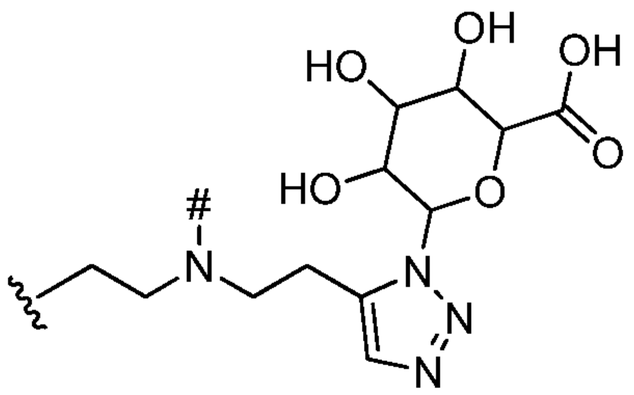
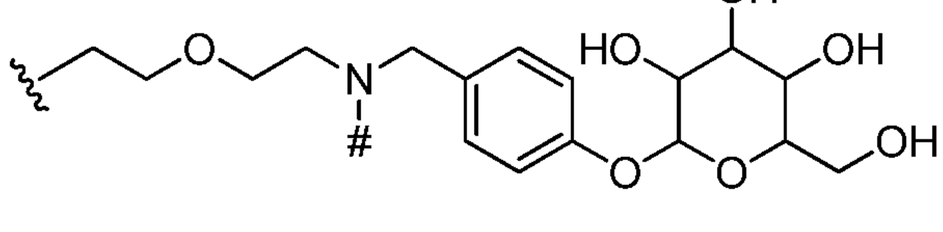
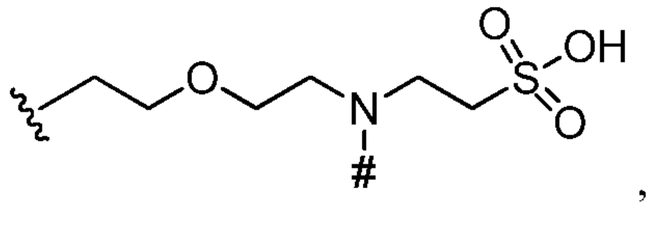
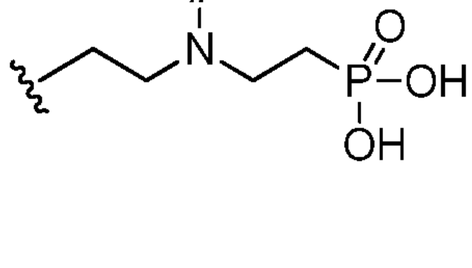
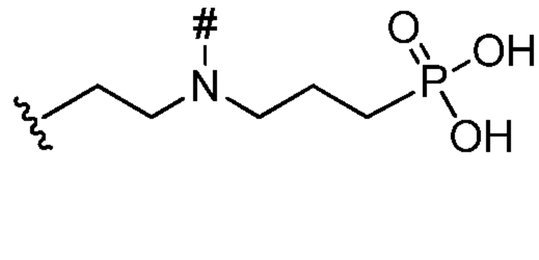





, or a salt thereof. When Bcl-xL inhibitors of this embodiment are included in an ADC, the linker of the ADC is linked to the nitrogen atom of an available primary or secondary amine group.

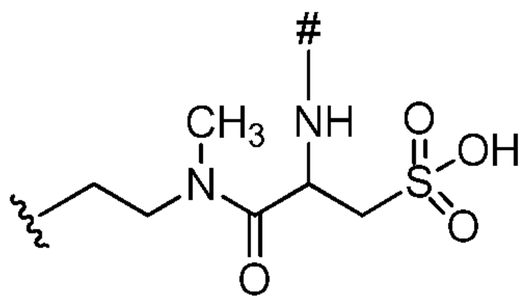
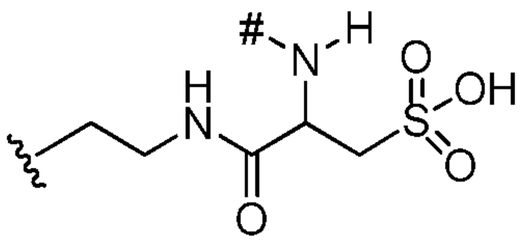
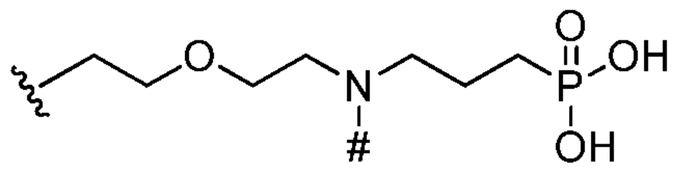
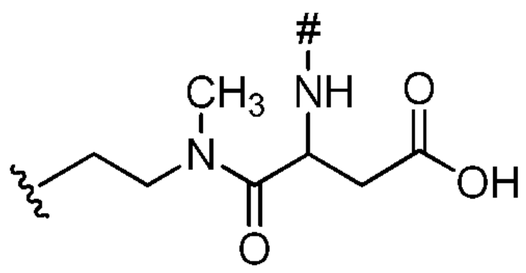
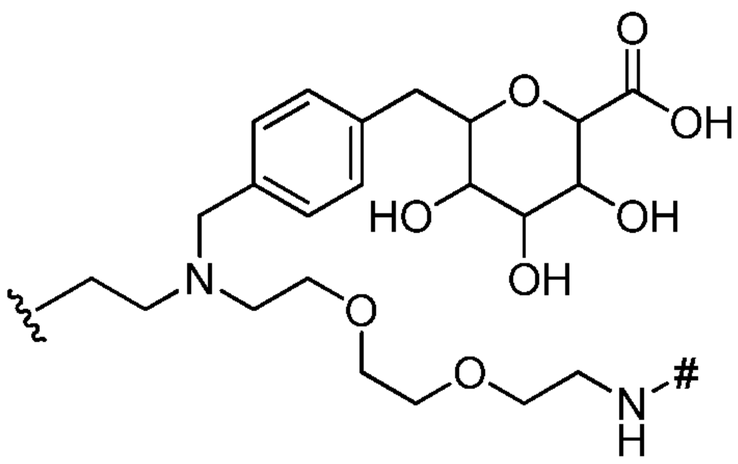
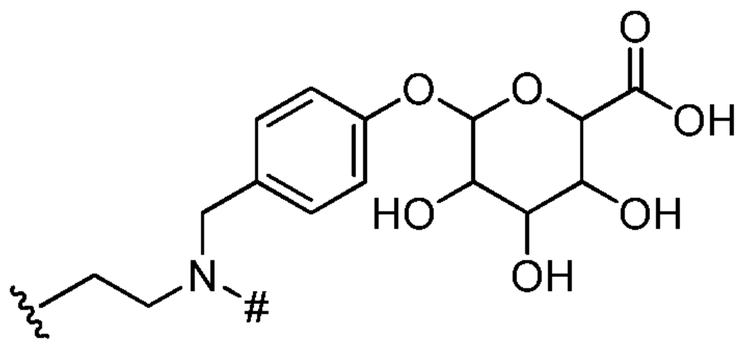
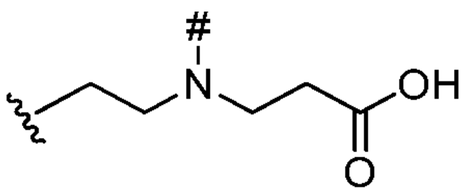
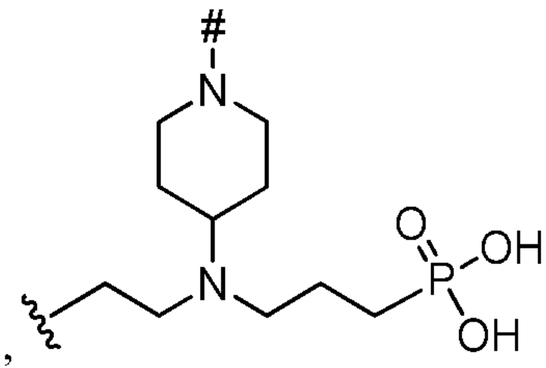
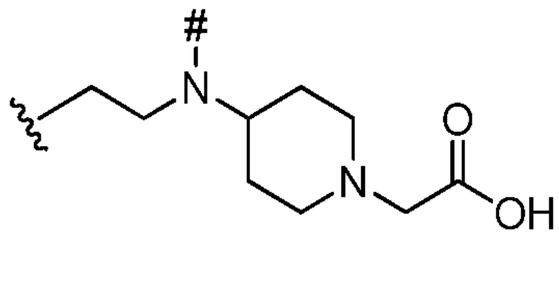
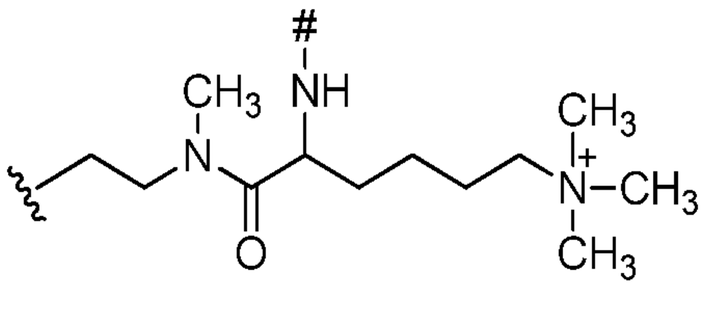
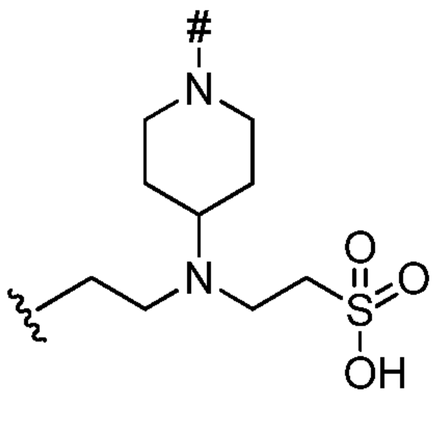
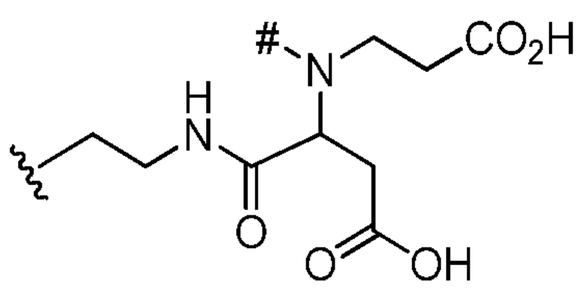
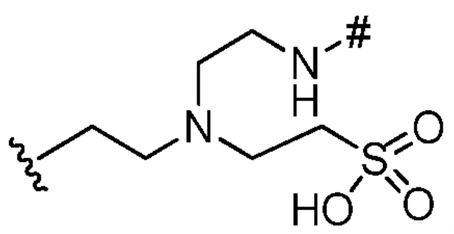
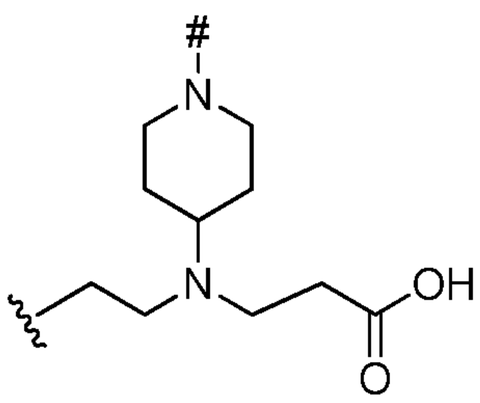
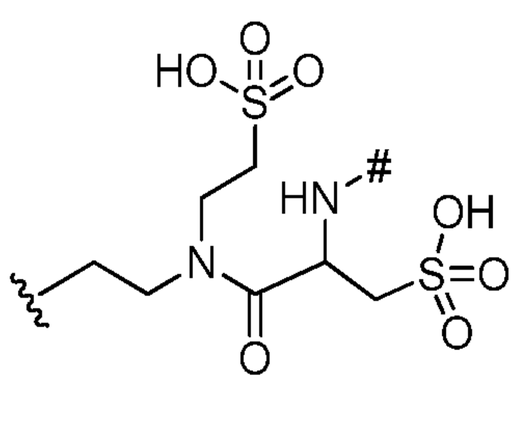
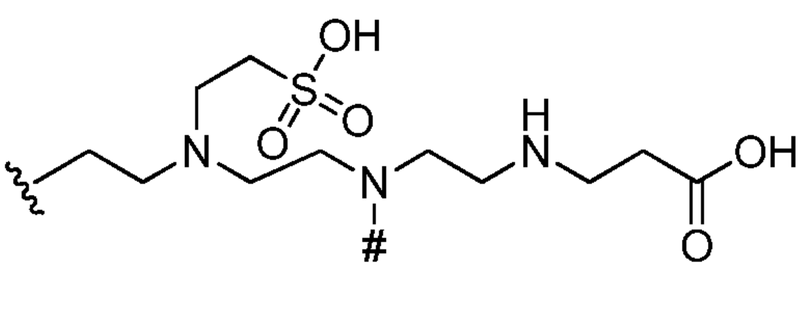
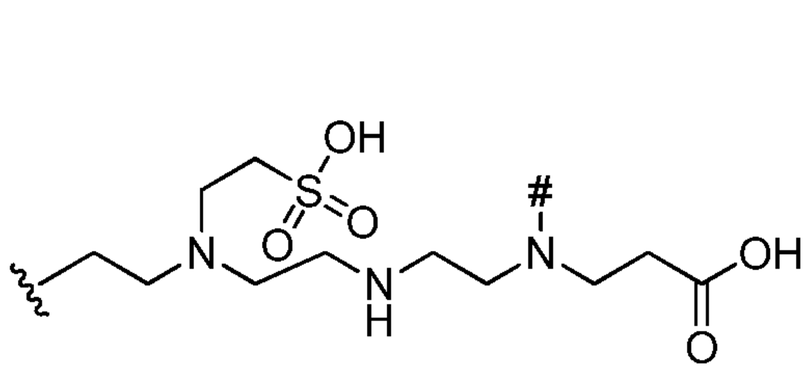
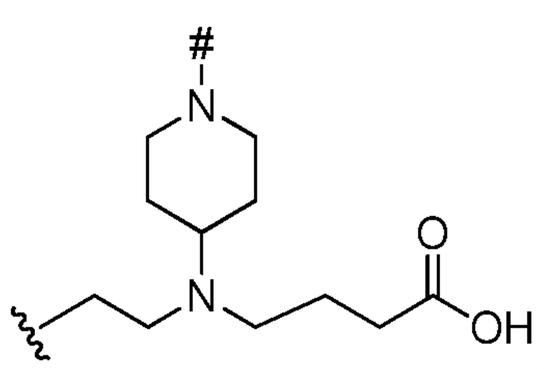
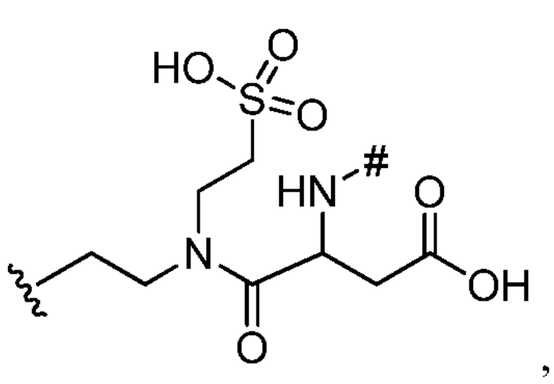
In certain embodiments, R' is selected from  ,

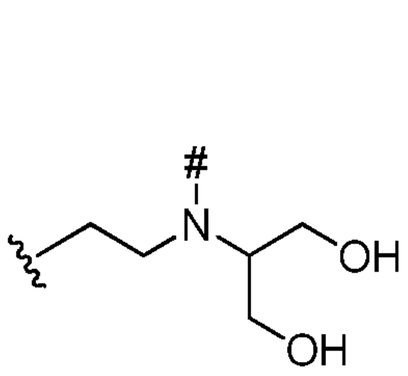
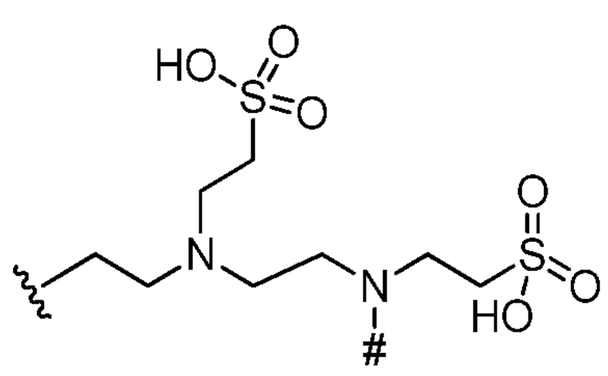
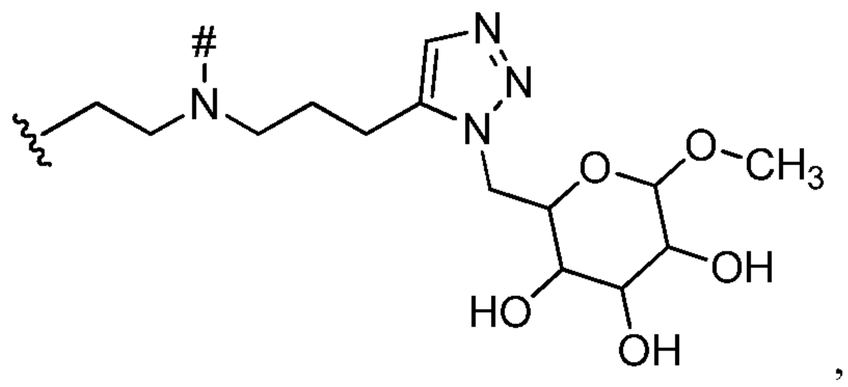
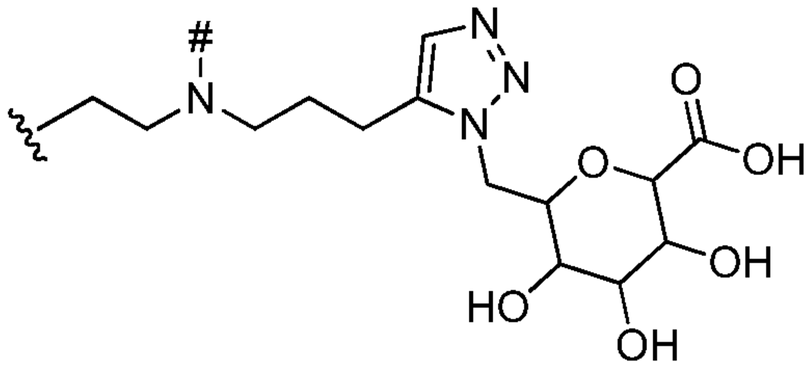
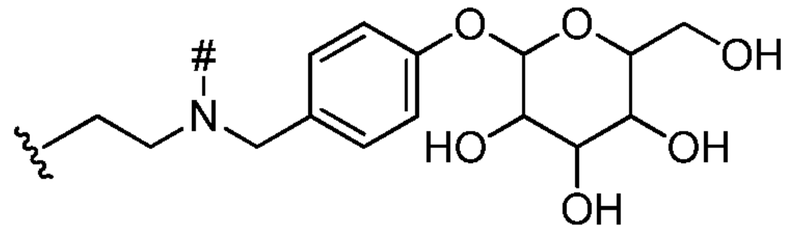
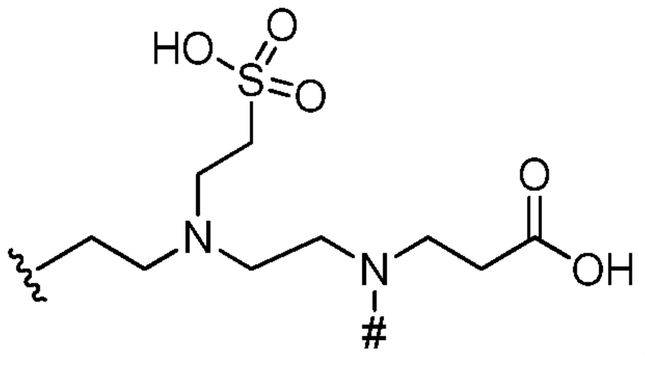
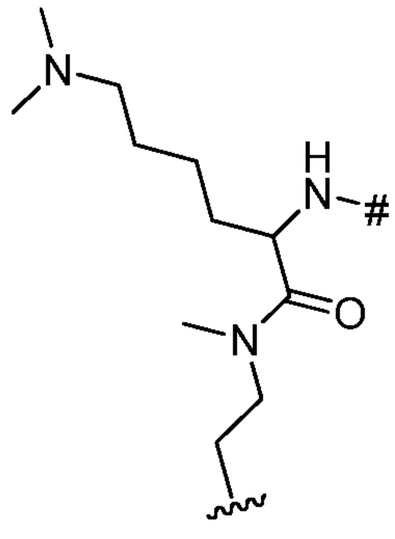
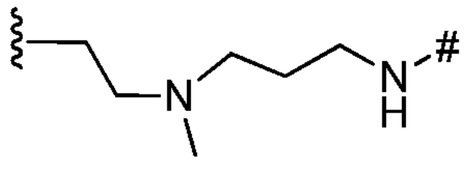
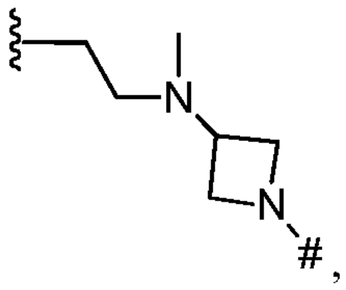
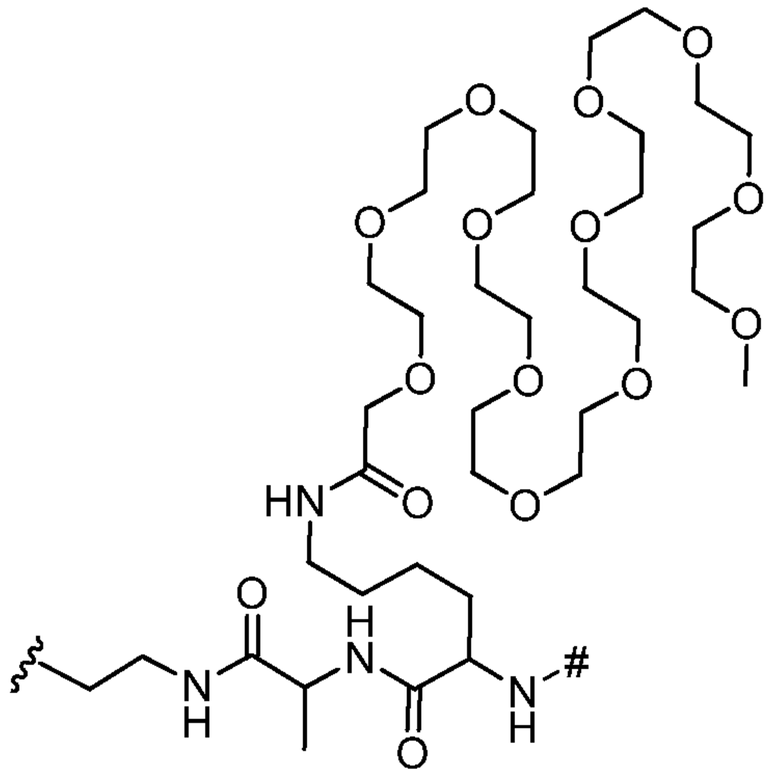
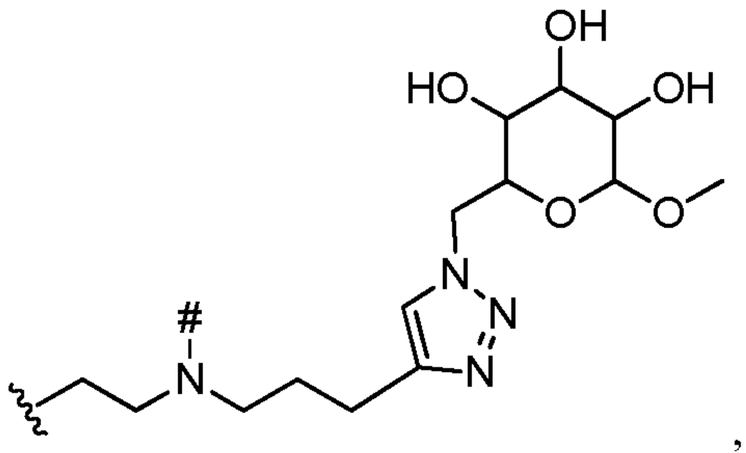
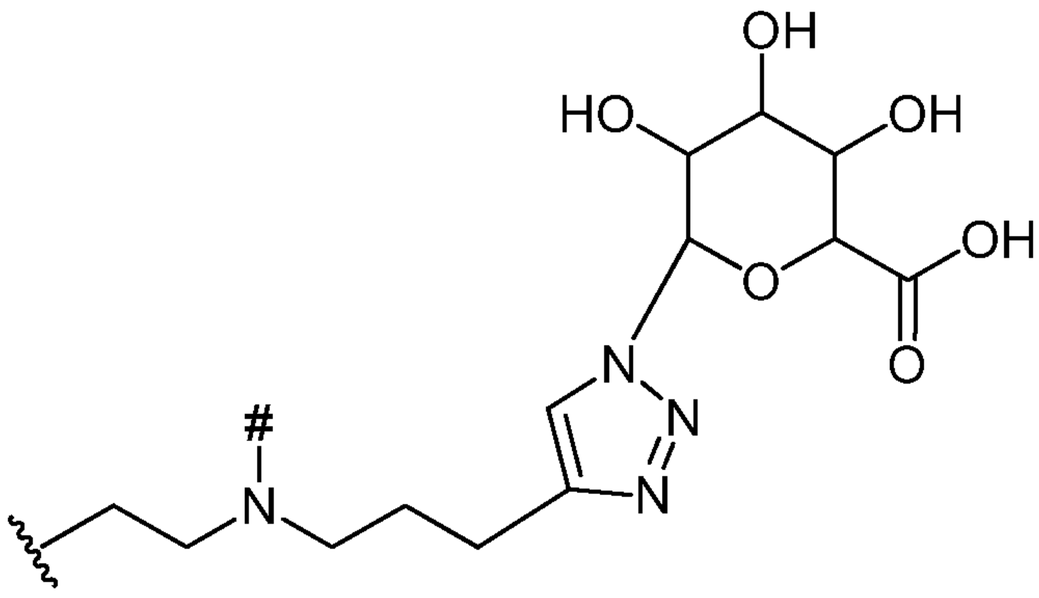
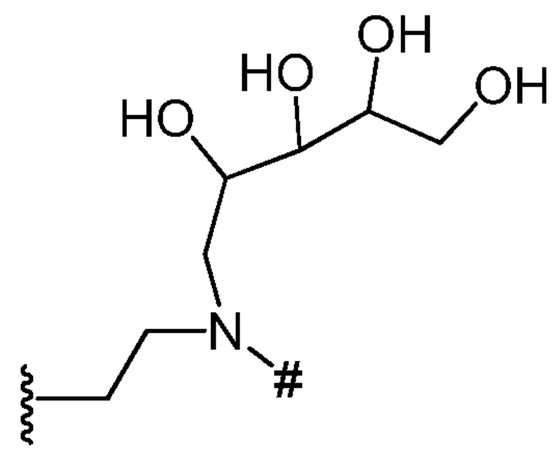












, or a salt thereof.

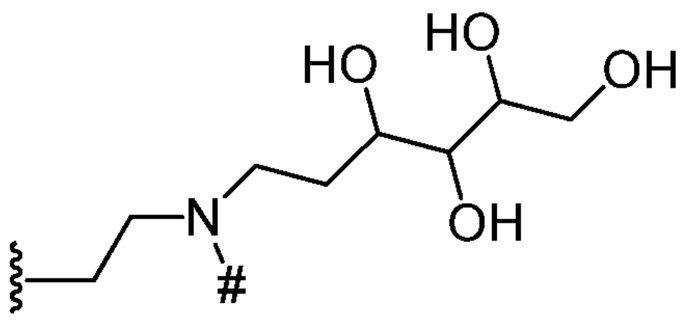
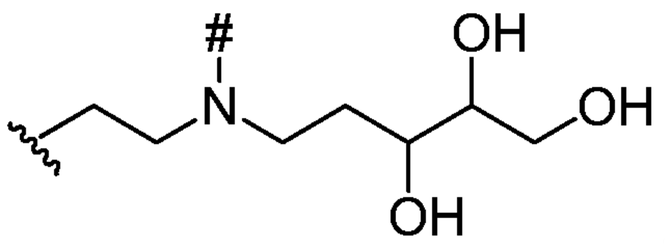
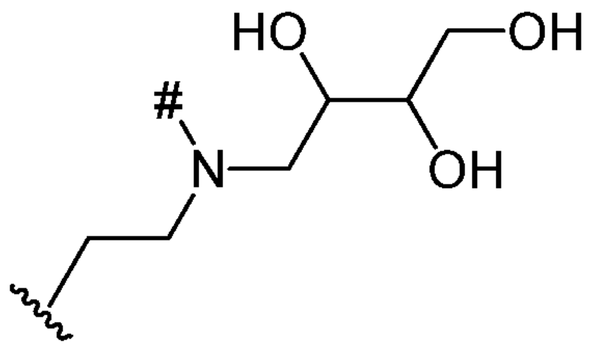
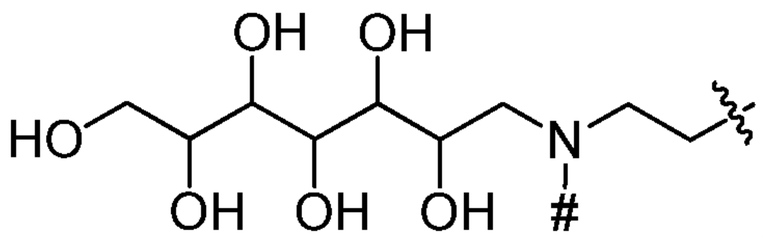
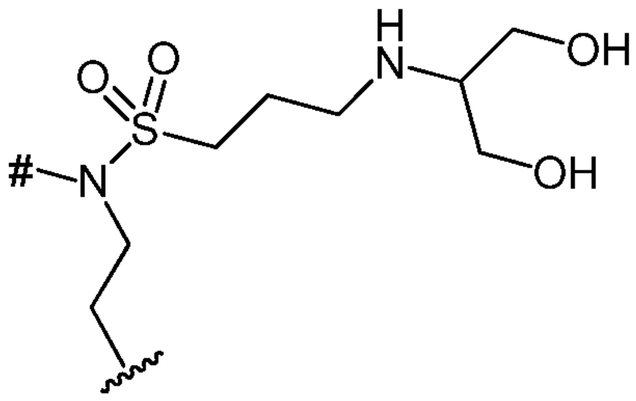
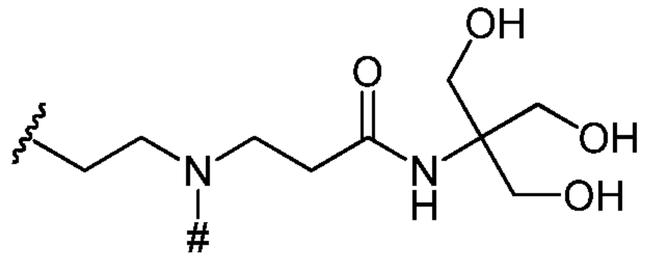
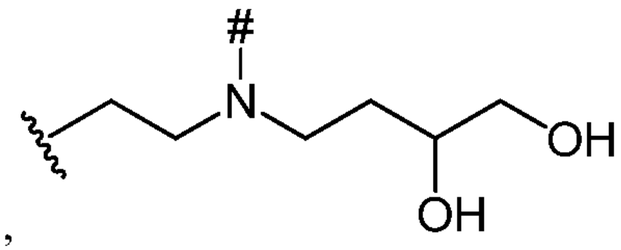
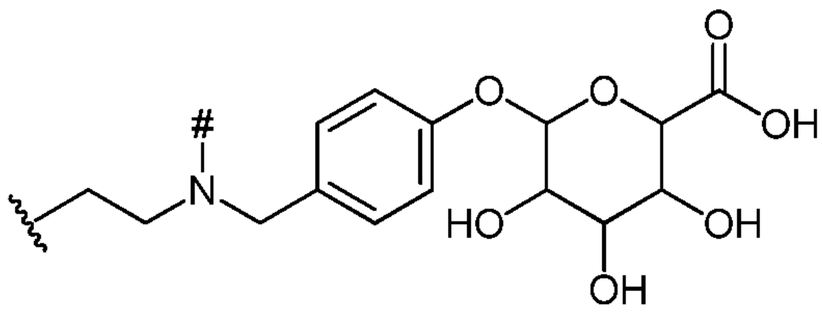
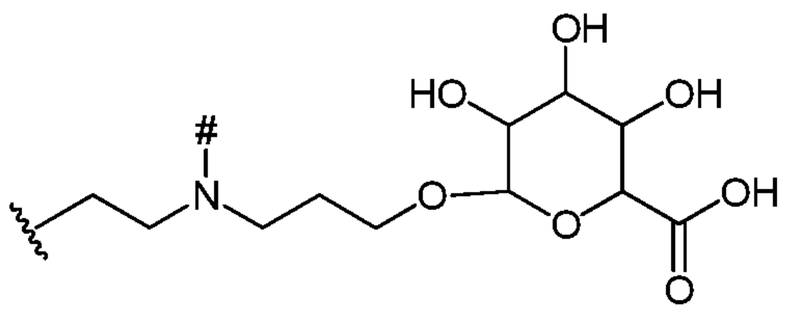
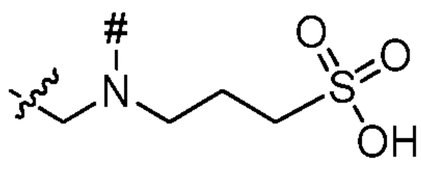
In certain embodiments, R' is selected from

,

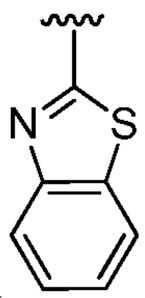
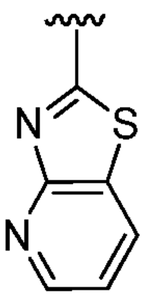
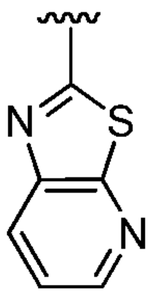
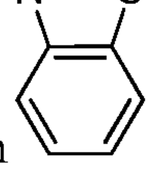
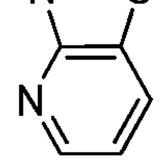

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

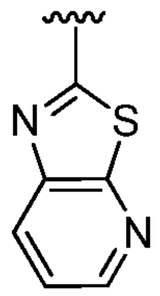
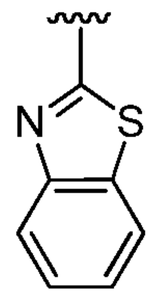

,

,

,

,

,

,

,

,

,

,

,

,

,

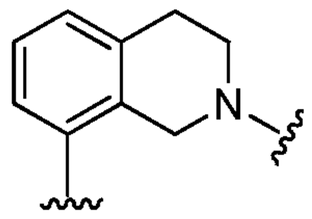
5

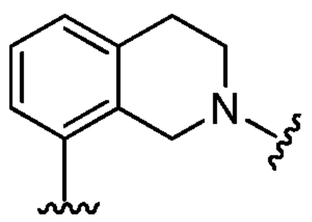
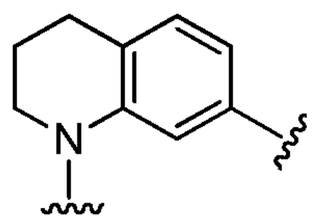
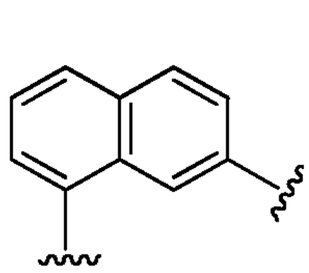
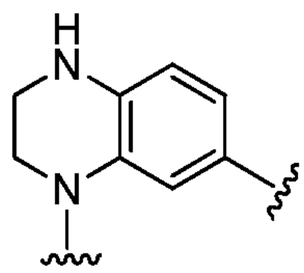
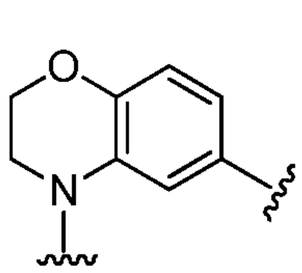
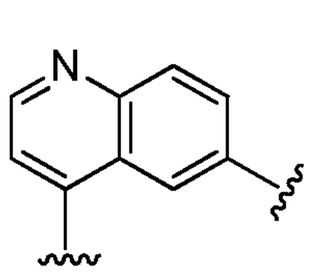
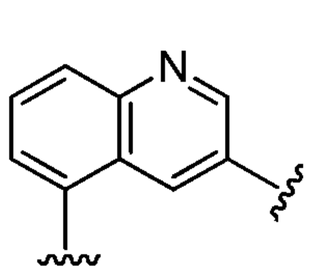
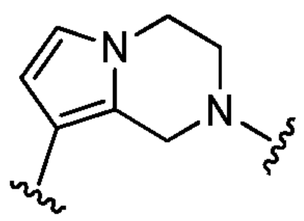
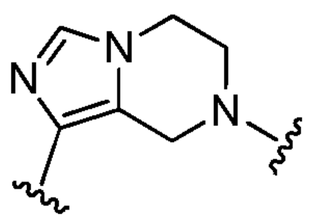
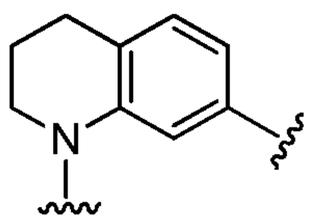
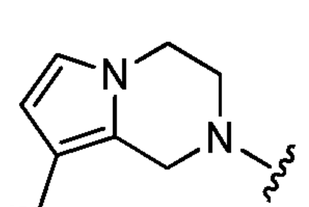
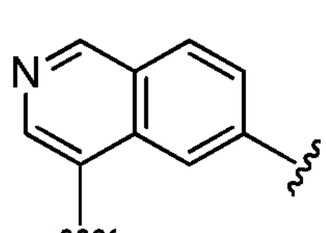
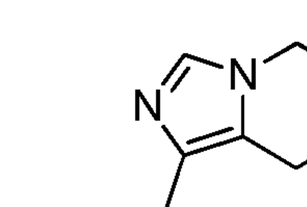
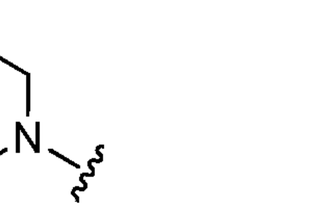
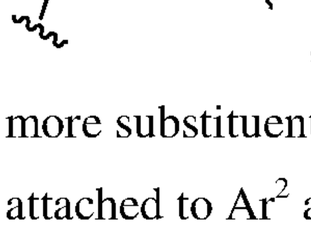
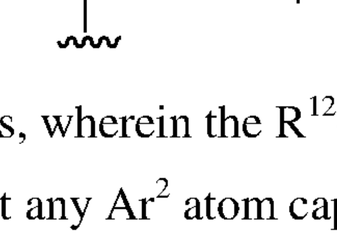
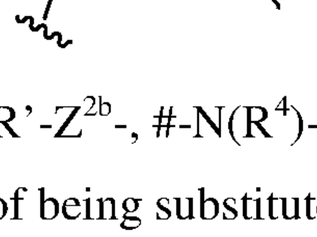











, wherein # represents either a hydrogen atom in the Bcl-xL inhibitor drug of the ADCs of formula (IIb) or (IIc) or the point of attachment in the Bcl-xL inhibitor drug of the ADCs of formula (IIa) or (IId) to a linker L.

In certain embodiments, Ar^1 of formulae (IIa)-(IId) is selected from  ,  , and  . In certain embodiments, Ar^1 of formulae (IIa)-(IId) is selected from  ,  , and


and is optionally substituted with one or more substituents independently selected from halo, cyano, methyl, and halomethyl. In particular embodiments, Ar^1 is  .

In certain embodiments, Ar^2 is  optionally substituted with one or more substituents, wherein the R^{12}-Z^{2b}-, R'-Z^{2b}-, #-N(R^4)-R^{13}-Z^{2b}-, or #-R'-Z^{2b}- substituents are attached to Ar^2 at any Ar^2 atom capable of being substituted.

In certain embodiments, Ar^2 is selected from:  ,  ,  ,  ,  ,  ,  ,  , and  and is optionally substituted with one or more substituents, wherein the R^{12}-Z^{2b}-, R'-Z^{2b}-, #-N(R^4)-R^{13}-Z^{2b}-, or #-R'-Z^{2b}- substituents are attached to Ar^2 at any Ar^2 atom capable of being substituted. In certain embodiments, Ar^2 is selected from:  ,  ,  ,  ,  , ,  ,  , and  ; and is optionally substituted with one or more substituents, wherein the R^{12}-Z^{2b}-, R'-Z^{2b}-, #-N(R^4)-R^{13}-Z^{2b}-, or #-R'-Z^{2b}- substituents are attached to Ar^2 at any Ar^2 atom capable of being substituted. In certain embodiments, Ar^2 is substituted with one or more solubilizing group. In certain embodiments, the each solubilizing group

is, independently of the others, selected from a moiety containing a polyol, a polyethylene glycol with between 4 and 30 repeating units, a salt, or a moiety that is charged at physiological pH.

In certain embodiments, Z^1 of formulae (IIa)-(IId) is N.

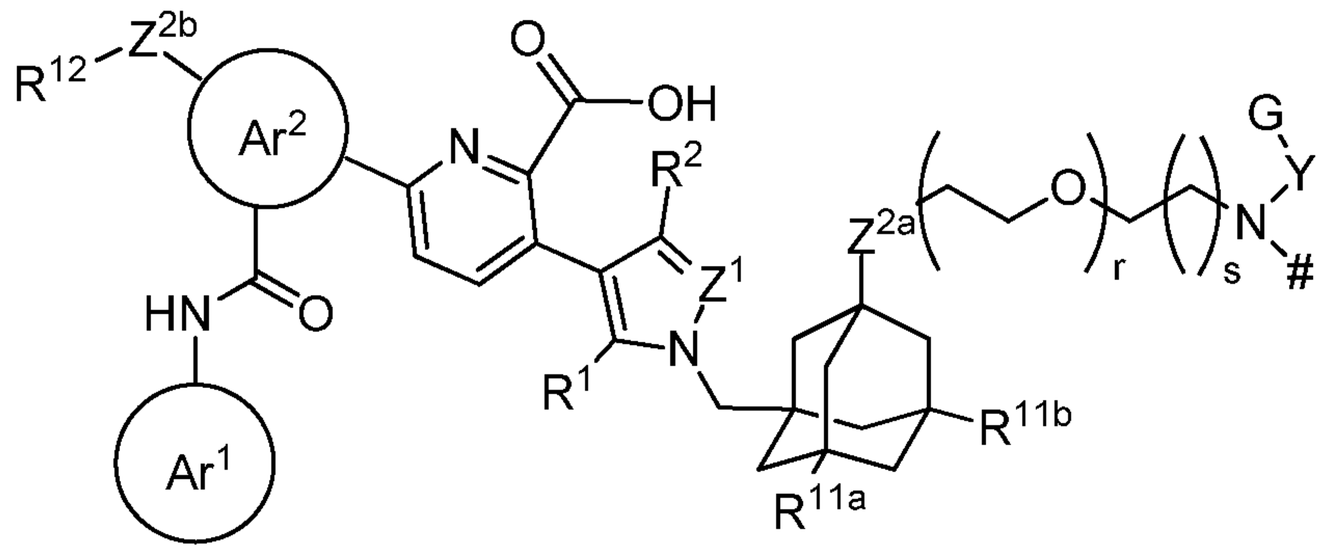
In certain embodiments, Z^{2a} of formulae (IIa)-(IId) is O. In certain embodiments, Z^{2a} of formulae (IIa)-(IId) is $CR^{6a}R^{6b}$. In certain embodiments, Z^{2a} of formulae (IIa)-(IId) is S. In certain embodiments, Z^{2a} of formulae (IIa)-(IId) is $-NR^6C(O)-$. In particular embodiments, R^6 is hydrogen.

In certain embodiments, Z^{2b} of formulae (IIa)-(IId) is O. In certain embodiments, Z^{2b} of formulae (IIa)-(IId) is NH or CH_2.

In certain embodiments, R^1 of formulae (IIa)-(IId) is selected from methyl and chloro.

In certain embodiments, R^2 of formulae (IIa)-(IId) is selected from hydrogen and methyl. In particular embodiments, R^2 is hydrogen.

In certain embodiments the Bcl-xL inhibitor is a compound of formula (IIa). In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIa), the compound has the structural formula (IIa.1),



(IIa.1)

or salts thereof, wherein:

Ar^1, Ar^2, Z^1, Z^{2a}, Z^{2b}, R^1, R^2, R^{11a}, R^{11b}, $R^{12,}$ G and # are defined as above;

Y is optionally substituted C_1-C_8 alkylene;

r is 0 or 1; and

s is 1, 2 or 3.

In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIa.1), r is 0 and s is 1.

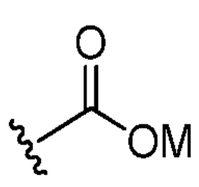
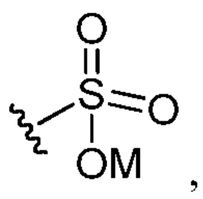
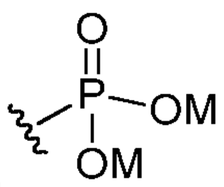
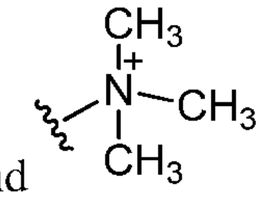
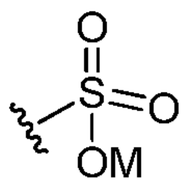
In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIa.1), r is 0 and s is 2.

In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIa.1), r is 1 and s is 2.

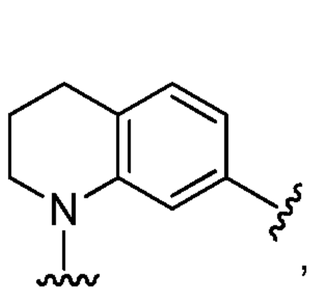
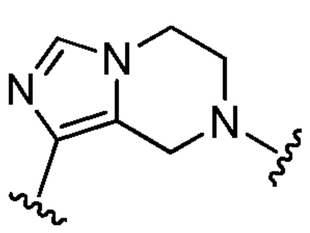
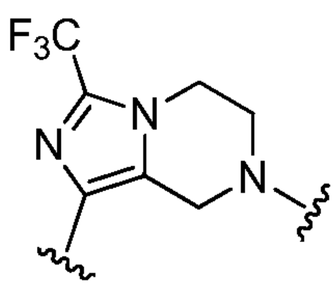
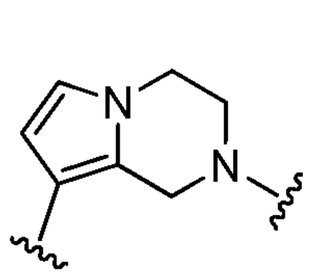
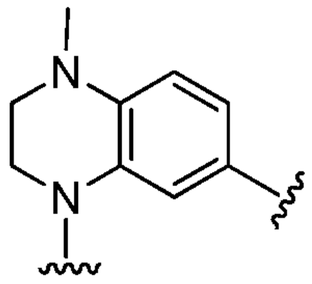
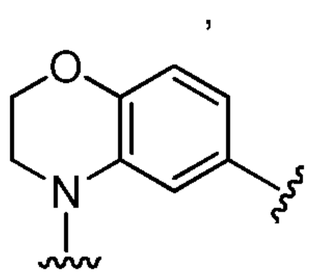
In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIa.1), Z^{2a} is selected from O, NH, CH_2 and S. In particular embodiments, Z^{2a} is O. In certain embodiments, Z^{2a} of formula (IIa.1) is $-CR^{6a}R^{6b}-$. In certain embodiments, Z^{2a} of formula (IIa.1) is CH_2. In certain

embodiments, Z^{2a} of formula (IIa.1) is S . In certain embodiments, Z^{2a} of formula (IIa.1) is $-NR^6C(O)-$.

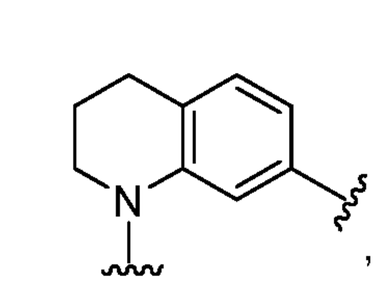
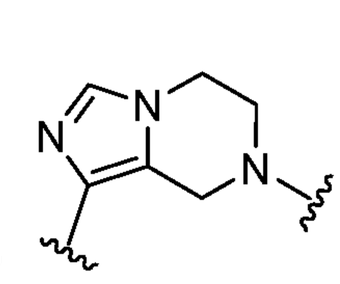
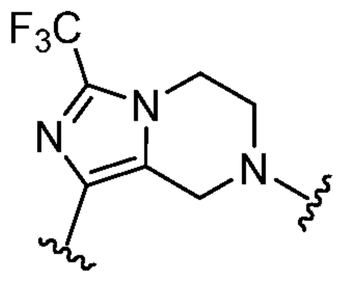
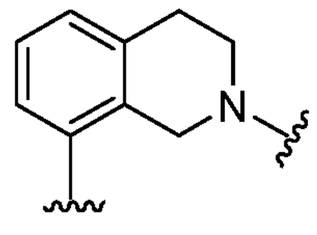
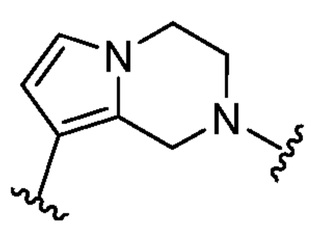
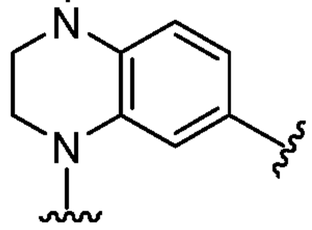
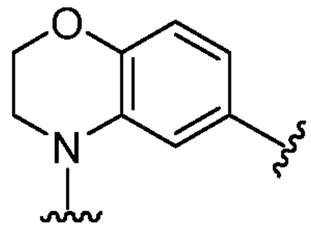
In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIa.1), Y is selected from ethylene, propylene and butylene. In particular embodiments, Y is selected from ethylene and propylene.

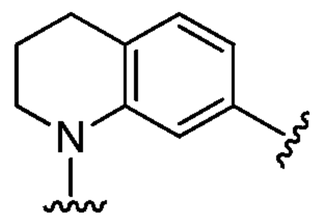
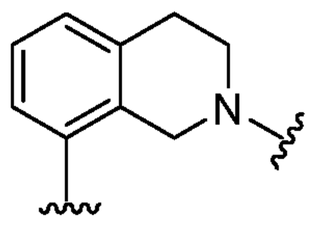
In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIa.1), G is selected from  ,  ,  , and  wherein M is hydrogen or a positively charged counterion. In particular embodiments, G is  . In particular embodiments, G is SO_3H.

In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIa.1), Ar^2 is selected from

 ,  ,  ,  ,  , and  , wherein the R^{12}-Z^{2b}- substituent is attached to Ar^2 at any Ar^2 atom capable of being substituted.

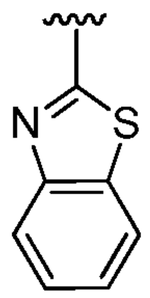
In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIa.1), Ar^2 is selected from

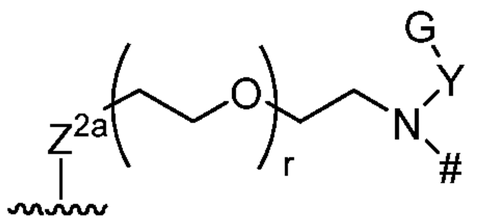
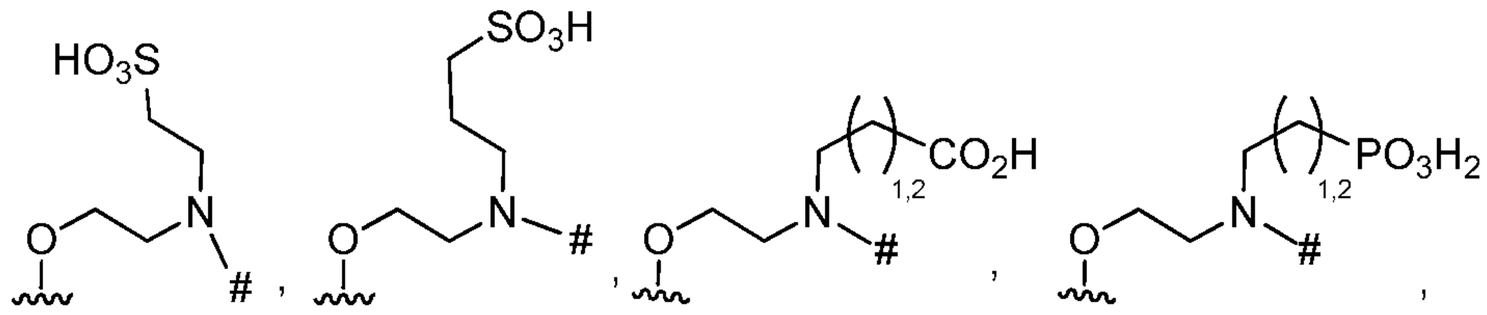
 ,  ,  ,  ,  ,  , and  , wherein the R^{12}-Z^{2b}- substituent is attached to Ar^2 at any Ar^2 atom capable of being substituted.

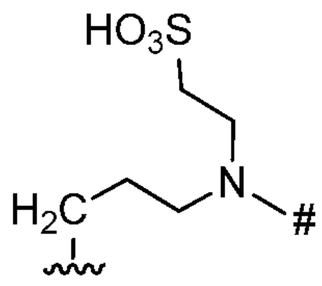
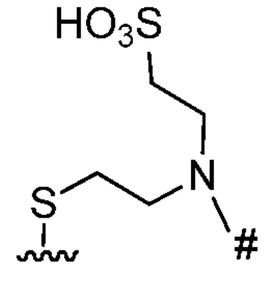
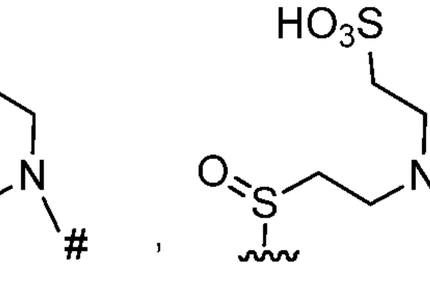
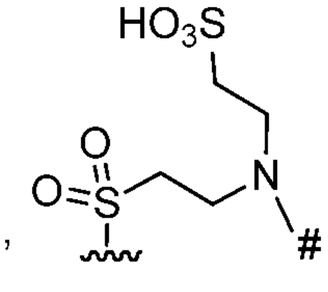
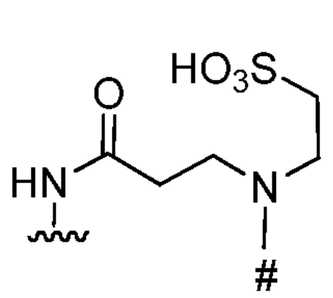
In particular embodiments in which the Bcl-xL inhibitor is a compound of formula (IIa.1), Ar^2 is  . In particular embodiments in which the Bcl-xL inhibitor is a compound of formula (IIa.1), Ar^2 is  .

In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIa.1), Z^{2b}-R^{12} is selected from H, F, CN, OCH_3, OH, NH_2, $OCH_2CH_2OCH_3$, $N(CH_3)C(=O)CH_3$, $CH_2N(CH_3)C(=O)CH_3SCH_3$, $C(=O)N(CH_3)_2$ and $OCH_2CH_2N(CH_3)(C(=O)CH_3)$. In particular embodiments, Z^{2b}-R^{12} is selected from H, F and CN. In particular embodiments, Z^{2b}-R^{12} is H.

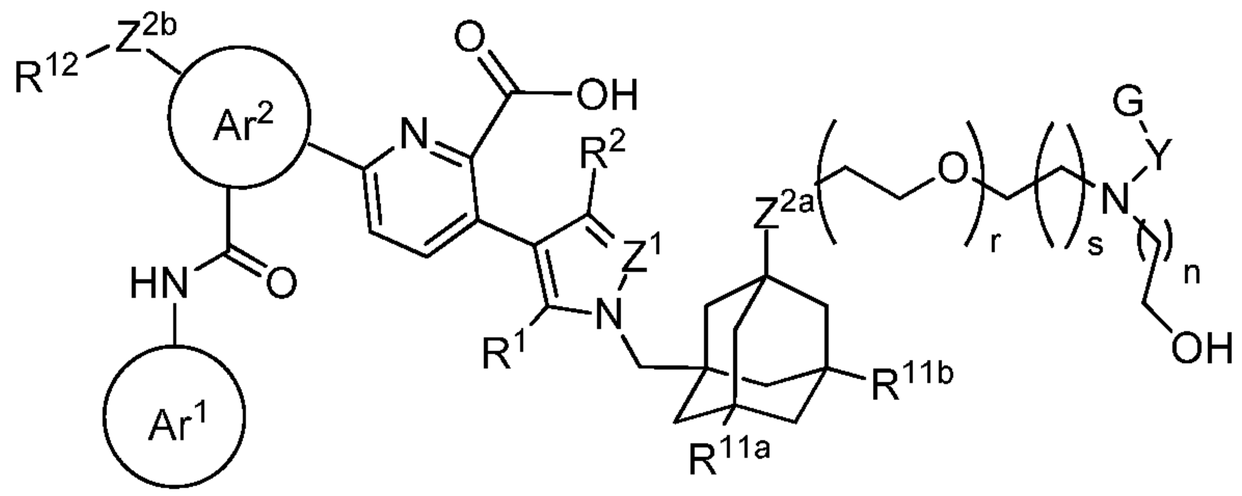
In embodiments where Z^{2b}-R^{12} is substituted with hydroxyl (OH), the oxygen can serve as the point of attachment to a linking group (*See* Section 4.4.1.1).

In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIa.1), Ar^1 is  .

In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIa.1), the group  bonded to the adamantane ring is selected from: 

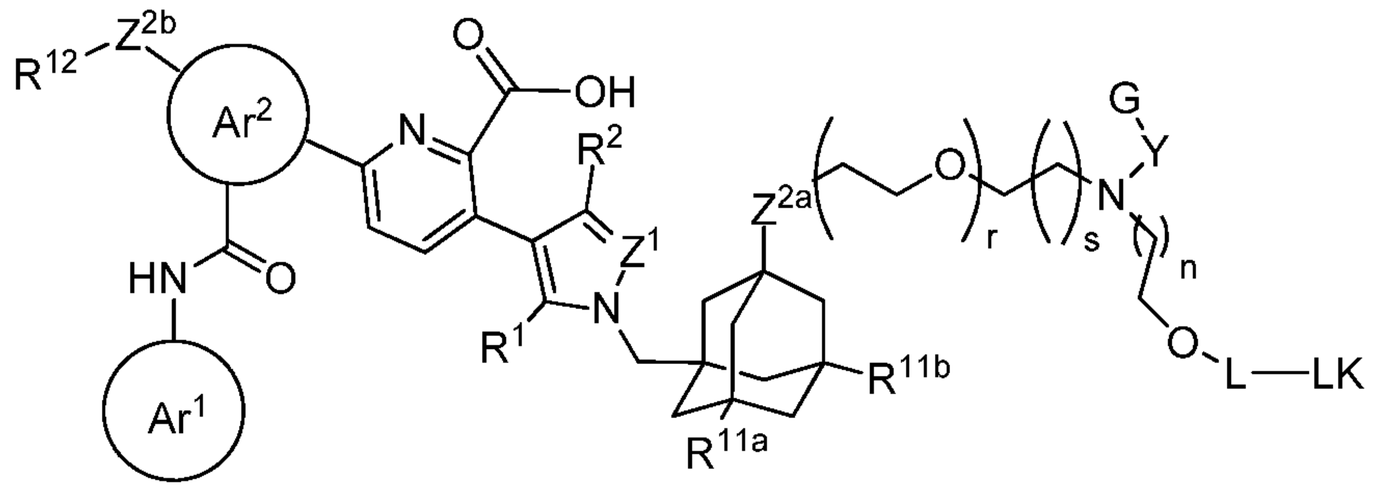
 ,  ,  ,  , and  .

In certain embodiments, a compound of formula (IIa.1) may be converted into the compound of formula IIa.1.1, wherein n is selected from 1-3:



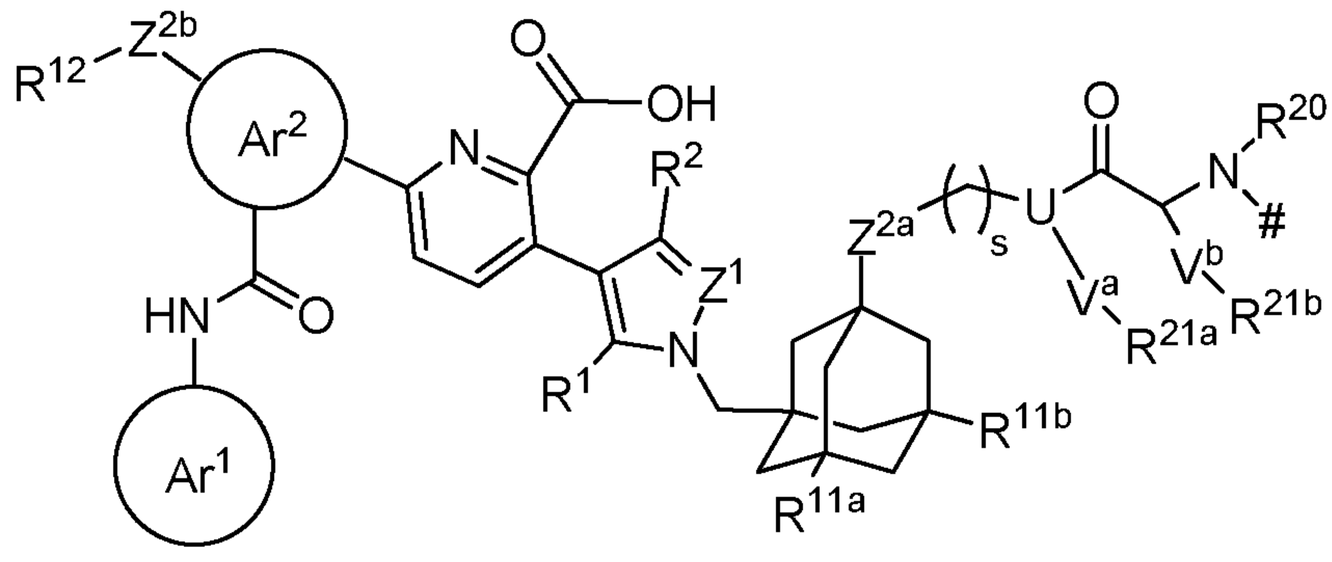
IIa.1.1

In certain embodiments, the compound of formula IIa.1.1 can be converted into a compound of formula IIa.1.2, wherein L represents a linker and LK represents a linkage formed between a reactive functional group on linker L and a complementary functional group on antibody.



IIa.1.2

In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIa), the compound has the structural formula (IIa.2),



(IIa.2)

or salts thereof, wherein:

Ar^1, Ar^2, Z^1, Z^{2a}, Z^{2b}, R^1, R^2, R^{11a}, R^{11b}, R^{12} and # are defined as above;

U is selected from N, O and CH, with the proviso that when U is O, then V^a and R^{21a} are absent;

R^{20} is selected from H and C_1-C_4 alkyl;

R^{21a} and R^{21b} are each, independently from one another, absent or selected from H, C_1-C_4 alkyl and G, where G is selected from a polyol, PEG4-30, a salt and a moiety that is charged at physiological pH;

V^a and V^b are each, independently from one another, absent or selected from a bond, and an optionally substituted alkylene;

R^{20} is selected from H and C_1-C_4 alkyl; and

s is 1, 2 or 3.

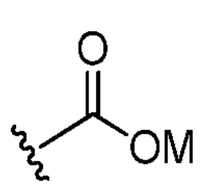
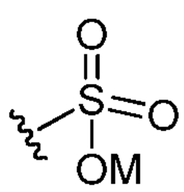
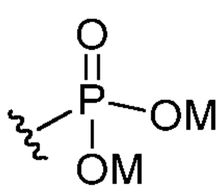
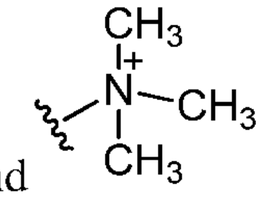
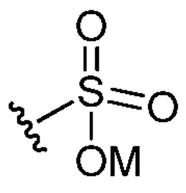
In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIa.2), s is 2.

In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIa.2), Z^{2a} is selected from O, NH, CH_2 and S. In particular embodiments, Z^{2a} is O. In certain embodiments, Z^{2a} of formula (IIa.2) is $CR^{6a}R^{6b}$. In certain embodiments, Z^{2a} of formula (IIa.2) is CH_2. In certain embodiments, Z^{2a} of formula (IIa.2) is S. In certain embodiments, Z^{2a} of formula (IIa.2) is $-NR^6C(O)-$.

In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIa.2), U is selected from N and O. In particular embodiments, U is O.

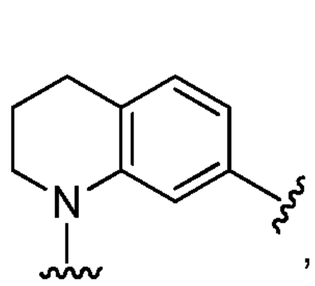
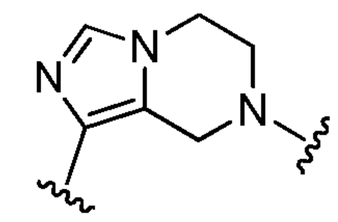
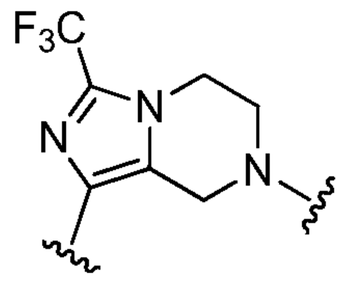
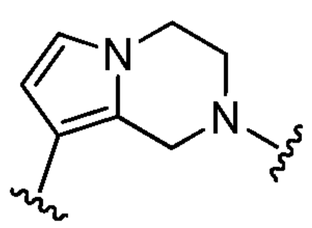
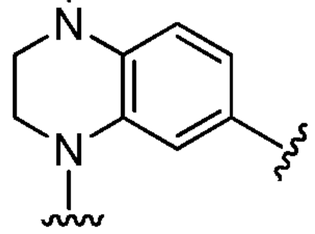
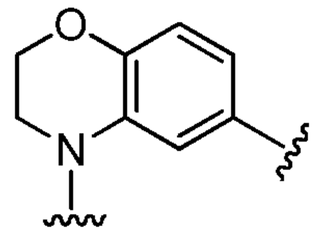
In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIa.2), V^a is a bond, R^{21a} is a C_1-C_4 alkyl group, V^b is selected from methylene and ethylene and R^{21b} is G. In particular embodiments, V^a is a bond, R^{21a} is a methyl group and V^b is selected from methylene and ethylene and R^{21b} is G.

In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIa.2), V^a is selected from methylene and ethylene, R^{21a} is G, V^b is selected from methylene and ethylene and R^{21b} is G. In particular embodiments, V^a is ethylene, R^{21a} is G, V^b is selected from methylene and ethylene and R^{21b} is G.

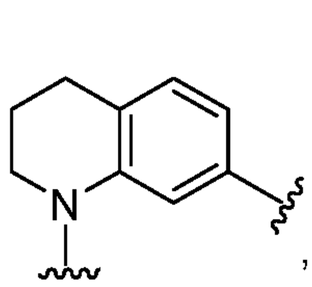
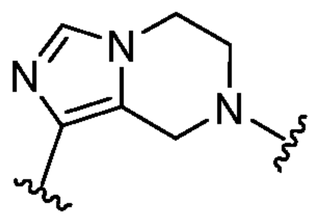
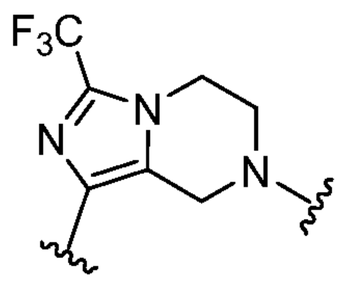
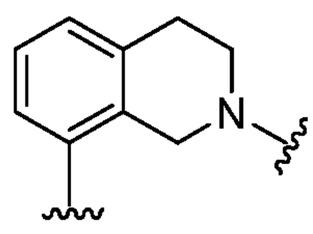
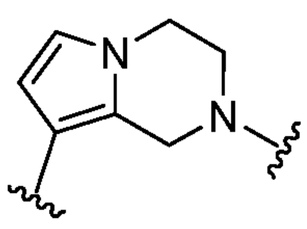
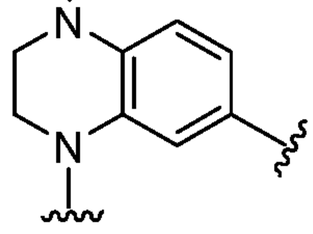
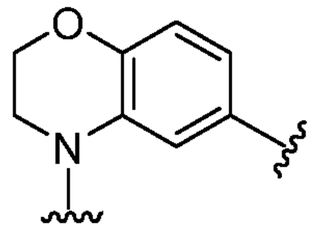
In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIa.2), G is selected from  ,  ,  , and  wherein M is hydrogen or a positively charged counterion. In particular embodiments, G is  . In particular embodiments, G is SO_3H.

In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIa.2), R^{20} is selected from hydrogen and a methyl group.

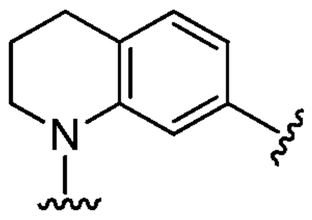
In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIa.2), Ar^2 is selected from

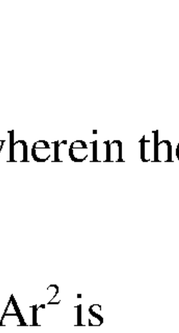

,

,

,

,

,
and

, wherein the R^{12}-Z^{2b}- substituent is attached to Ar^2 at any Ar^2 atom capable of being substituted.

In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIa.2), Ar^2 is selected from

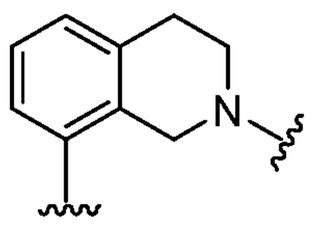

,

,

,

,

,

,
and

, wherein the R^{12}-Z^{2b}- substituent is attached to Ar^2 at any Ar^2 atom capable of being substituted.

In particular embodiments in which the Bcl-xL inhibitor is a compound of formula (IIa.2), Ar^2 is

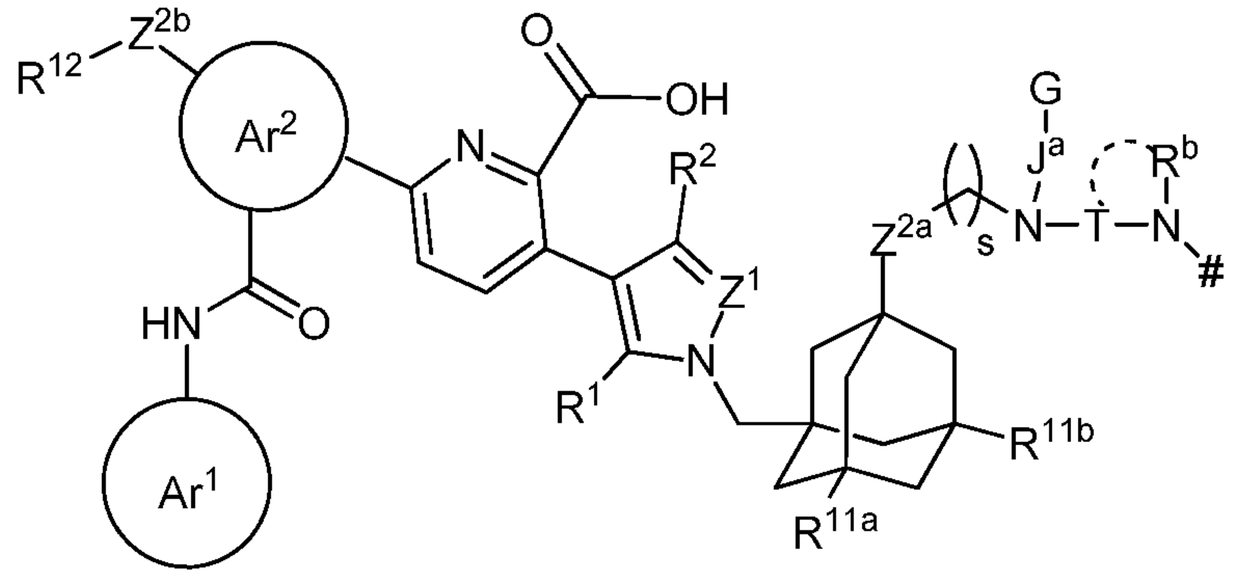

, wherein the R^{12}-Z^{2b}- substituent is attached to Ar^2 at any Ar^2 atom capable of being substituted.

In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIa.2), Z^{2b}-R^{12} is selected from H, F, CN, OCH_3, OH, NH_2, $OCH_2CH_2OCH_3$, $N(CH_3)C(=O)CH_3$, $CH_2N(CH_3)C(=O)CH_3SCH_3$, $C(=O)N(CH_3)_2$ and $OCH_2CH_2N(CH_3)(C(=O)CH_3)$. In particular embodiments, Z^{2b}-R^{12} is selected from H, F and CN. In particular embodiments, Z^{2b}-R^{12} is H. In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIa.2), Ar^1 is

.

In particular embodiments in which the Bcl-xL inhibitor is a compound of formula (IIa.2), Ar^2 is


, wherein the R^{12}-Z^{2b}- substituent is attached to Ar^2 at any Ar^2 atom capable of being substituted.

In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIa), the compound has the structural formula (IIa.3),



(IIa.3)

or salts thereof, wherein:

Ar^1, Ar^2, Z^1, Z^{2a}, Z^{2b}, R^1, R^2, R^{11a}, R^{11b}, R^{12} and # are defined as above;

R^b is selected from H, C_1-C_4 alkyl and J^b-G or is optionally taken together with an atom of T to form a ring having between 3 and 7 atoms;

J^a and J^b are each, independently from one another, selected from optionally substituted C_1-C_8 alkylene and optionally substituted phenylene;

T is selected from optionally substituted C_1-C_8 alkylene, $CH_2CH_2OCH_2CH_2OCH_2CH_2$, $CH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2$ and a polyethylene glycol containing from 4 to 10 ethylene glycol units;

G is selected from a polyol, PEG4-30, a salt and a moiety that is charged at physiological pH; and

s is 1, 2 or 3.

In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIa.3), s is 1. In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIa.3), s is 2.

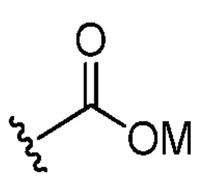
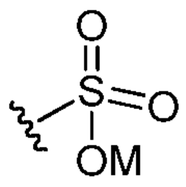
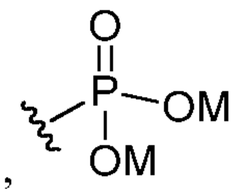
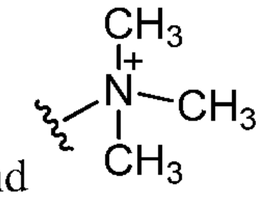
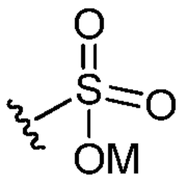
In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIa.3), Z^{2a} is selected from O, CH_2 and S. In particular embodiments, Z^{2a} is O. In certain embodiments, Z^{2a} of formula (IIa.3) is $CR^{6a}R^{6b}$. In certain embodiments, Z^{2a} of formula (IIa.3) is CH_2. In certain embodiments, Z^{2a} of formula (IIa.3) is S. In certain embodiments, Z^{2a} of formula (IIa.3) is $-NR^6C(O)-$.

In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIa.3), J^a is selected from methylene and ethylene and R^b is J^b-G, wherein J^b is methylene or ethylene. In some

such embodiments, T is ethylene. In other such embodiments, T is $CH_2CH_2OCH_2CH_2OCH_2CH_2$. In other such embodiments, T is a polyethylene glycol containing from 4 to 10 ethylene glycol units.

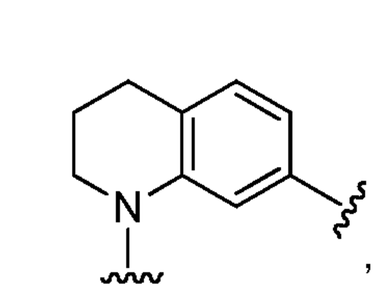
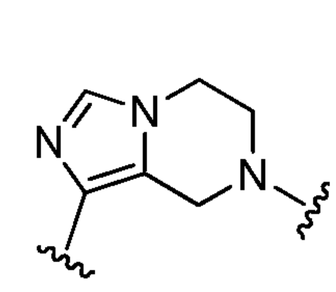
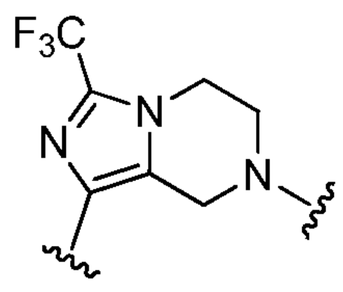
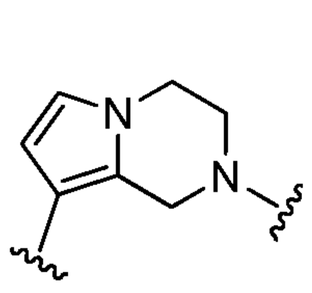
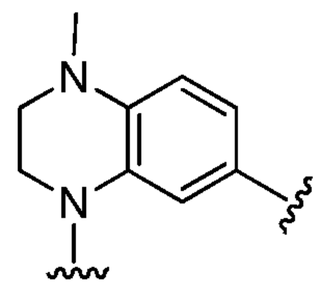
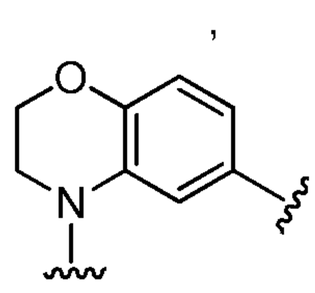
In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIa.3), J^a is selected from methylene and ethylene and R^b is taken together with an atom of T to form a ring having 4-6 ring atoms.

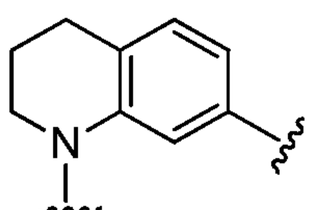
In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIa.3), J^a is selected from methylene and ethylene and R^b is H or alkyl. In some such embodiments, T is ethylene. In other such embodiments, T is $CH_2CH_2OCH_2CH_2OCH_2CH_2$.

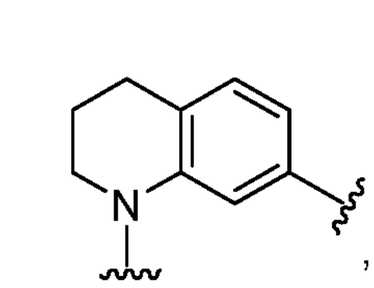
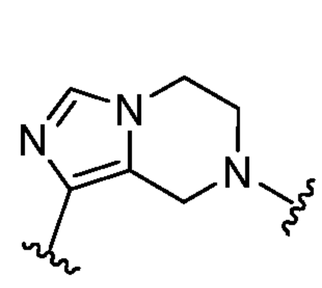
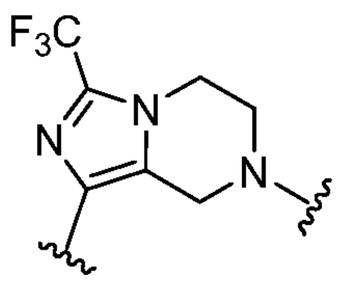
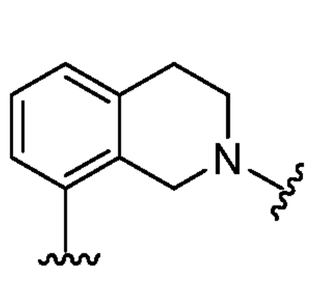
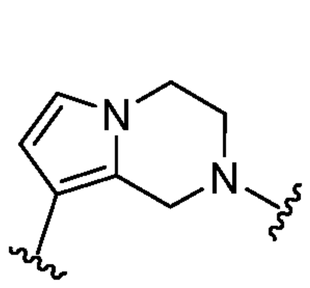
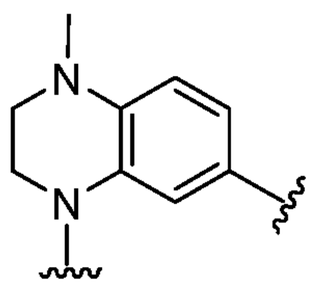
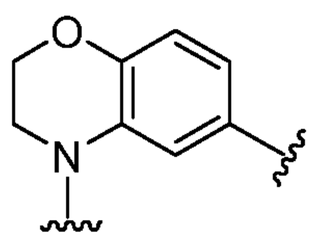
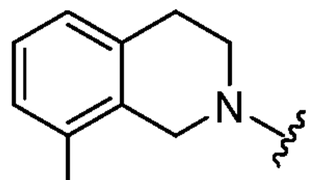
In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIa.3), G is selected from  ,  ,  , and  wherein M is hydrogen or a positively charged counterion. In particular embodiments, G is  . In particular embodiments, G is SO_3H.

In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIa.3), R^{20} is selected from hydrogen and a methyl group.

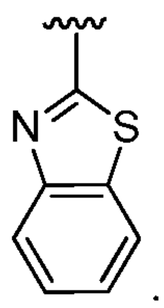
In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIa.3), Ar^2 is selected from

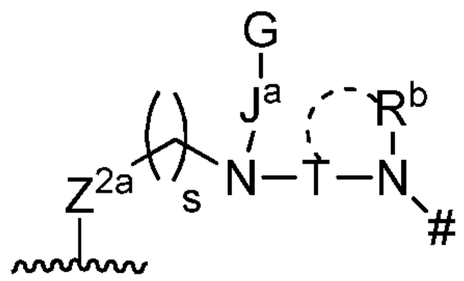
     and  , wherein the R^{12}-Z^{2b}- substituent is attached to Ar^2 at any Ar^2 atom capable of being substituted.

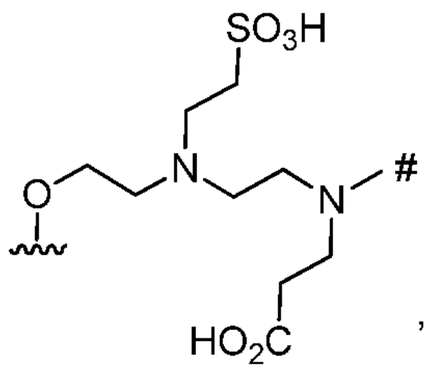
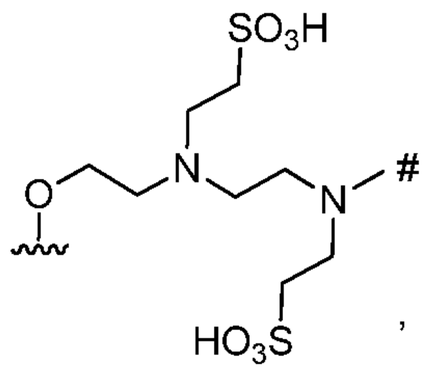
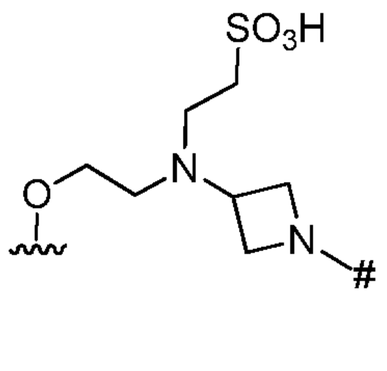
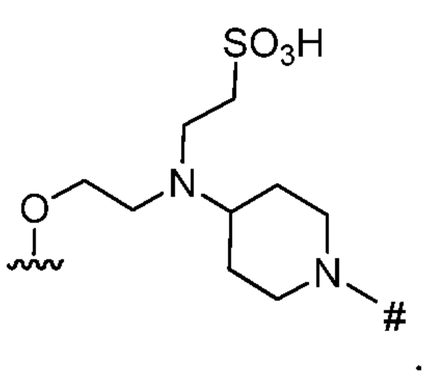
In particular embodiments in which the Bcl-xL inhibitor is a compound of formula (IIa.3), Ar^2 is  , wherein the R^{12}-Z^{2b}- substituent is attached to Ar^2 at any Ar^2 atom capable of being substituted. In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIa.3), Ar^2 is selected from

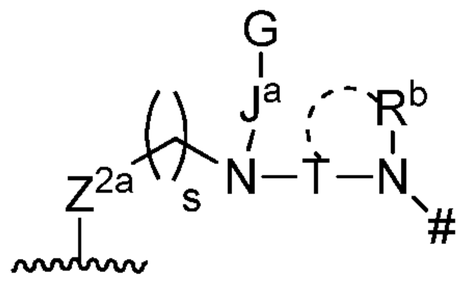






and

, wherein the R^{12}-Z^{2b}- substituent is attached to Ar^2 at any Ar^2 atom capable of being substituted. In particular embodiments in which the Bcl-xL inhibitor is a compound of formula (IIa.3), Ar^2 is  , wherein the R^{12}-Z^{2b}- substituent is attached to Ar^2 at any Ar^2 atom capable of being substituted.

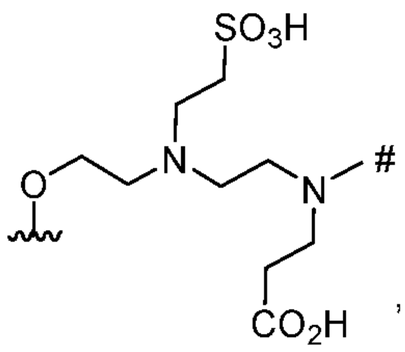
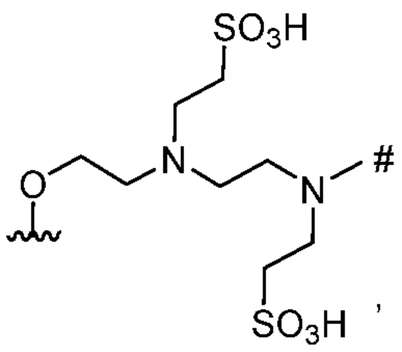
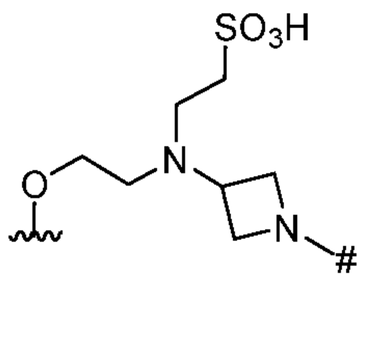
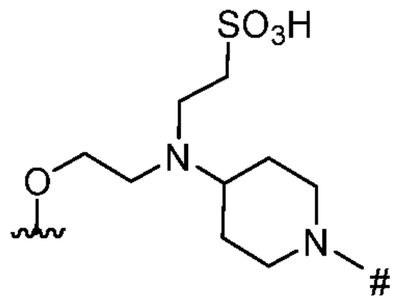
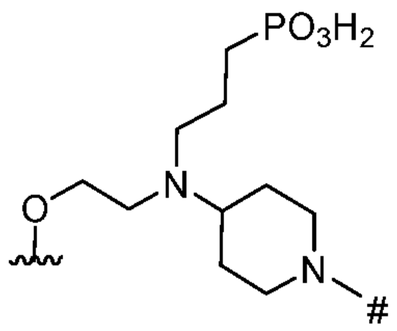
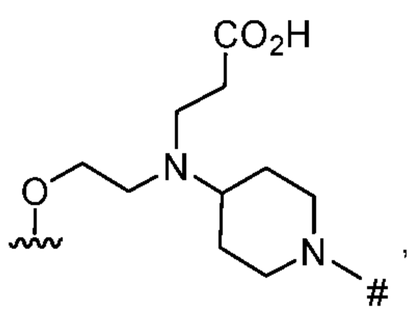
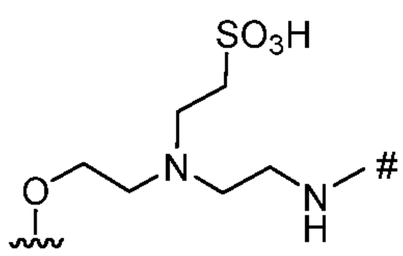
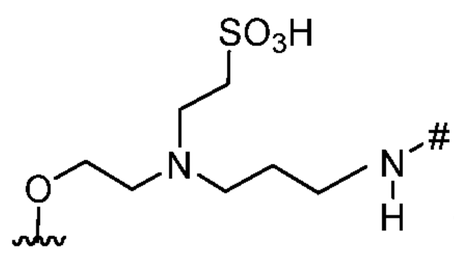
In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIa.3), Z^{2b}-R^{12} is selected from H, F, CN, OCH_3, OH, NH_2, $OCH_2CH_2OCH_3$, $N(CH_3)C(=O)CH_3$, $CH_2N(CH_3)C(=O)CH_3SCH_3$, $C(=O)N(CH_3)_2$ and $OCH_2CH_2N(CH_3)(C(=O)CH_3)$. In particular embodiments, Z^{2b}-R^{12} is selected from H, F and CN. In particular embodiments, Z^{2b}-R^{12} is H.

In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIa.3), Ar^1 is  .

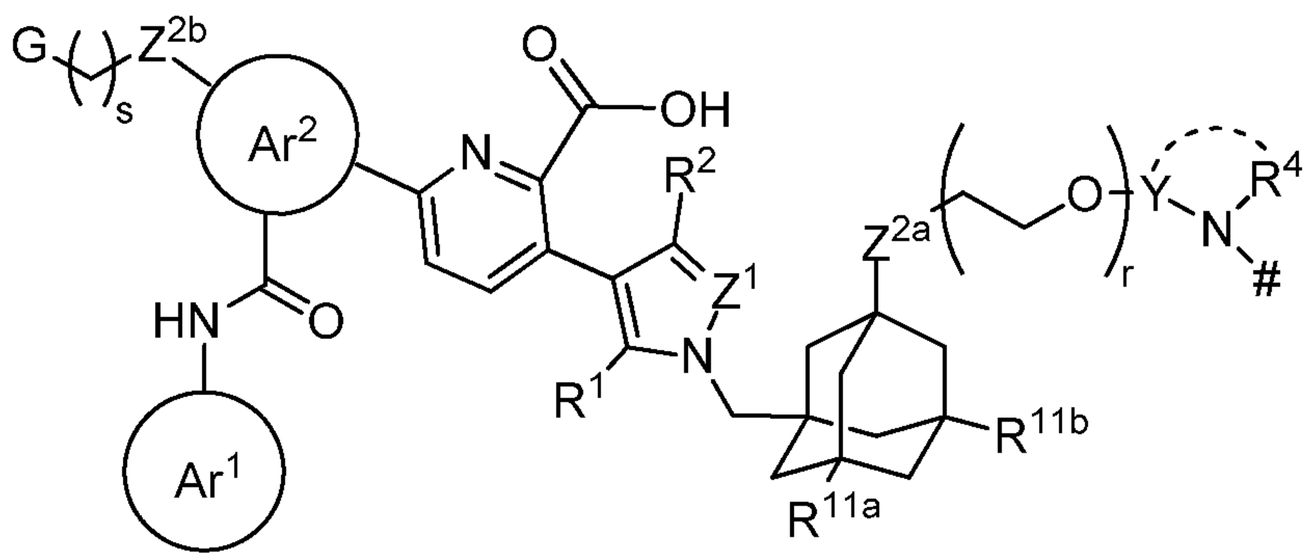
In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIa.3), the group  is selected from:




and

.

In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIa.3), the group  is selected from:


,

,

,

,

,

,

and

.

In certain embodiments the Bcl-xL inhibitor is a compound of formula (IIb). In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIb), the compound has the structural formula (IIb.1),



(IIb.1)

or salts thereof, wherein:

Ar^1, Ar^2, Z^1, Z^{2a}, Z^{2b}, R^1, R^2, R^4, R^{11a}, R^{11b} and # are defined as above;

Y is optionally substituted C_1-C_8 alkylene;

G is selected from a polyol, PEG4-30, a salt and a moiety that is charged at physiological pH;

r is 0 or 1; and

s is 1, 2 or 3.

In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIb.1), s is 1. In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIb.1), s is 2. In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIb.1), s is 3.

In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIb.1), Z^{2a} is selected from O, CH_2, NH and S. In particular embodiments, Z^{2a} is O. In certain embodiments, Z^{2a} of formula (IIb.1) is $CR^{6a}R^{6b}$. In certain embodiments, Z^{2a} of formula (IIb.1) is CH_2. In certain embodiments, Z^{2a} of formula (IIb.1) is S. In certain embodiments, Z^{2a} of formula (IIb.1) is –$NR^6C(O)$-.

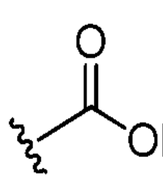
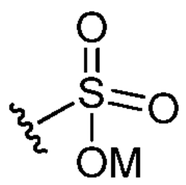
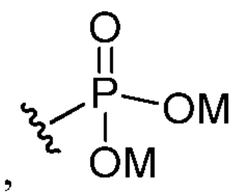
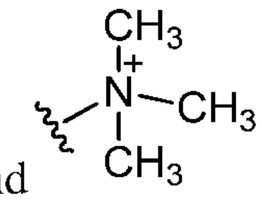
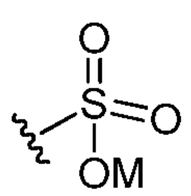
In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIb.1), Z^{2b} is selected from O, CH_2, NH, NCH_3 and S. In particular embodiments, Z^{2b} is O. In particular embodiments, Z^{2b} is NH. In particular embodiments, Z^{2b} is NCH_3.

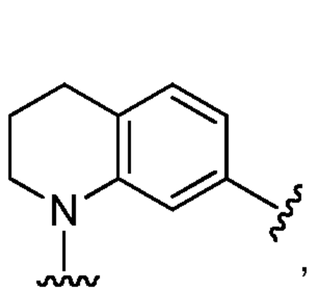
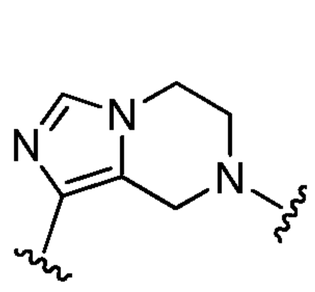
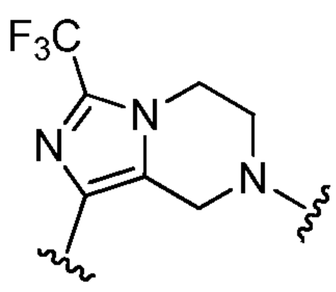
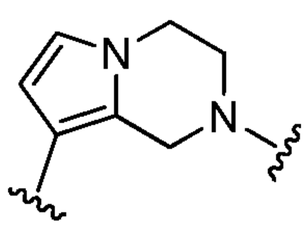
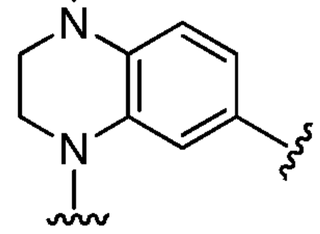
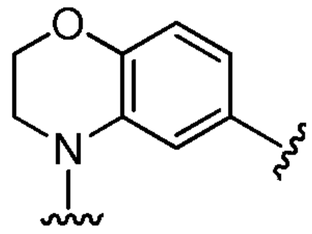
In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIb.1), Y is ethylene and r is 0.

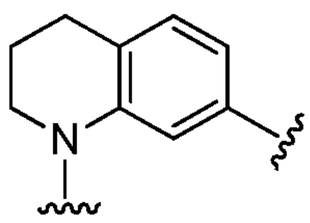
In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIb.1), Y is ethylene and r is 1.

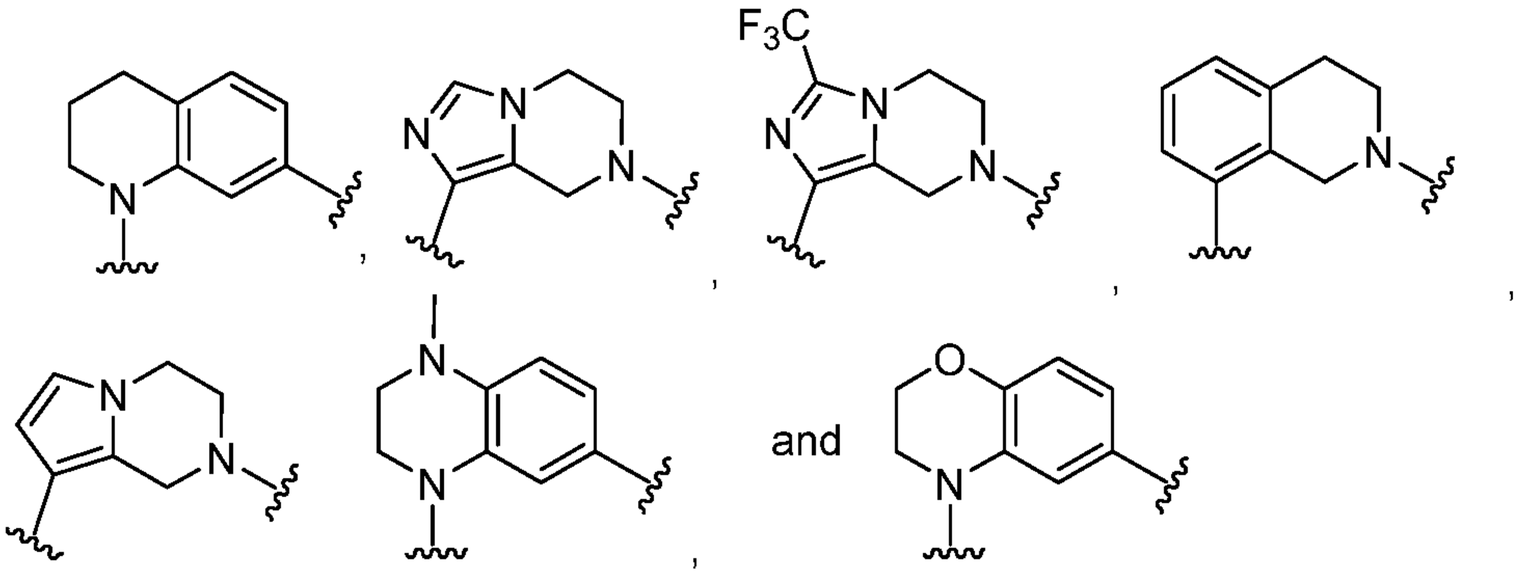
In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIb.1), R^4 is H or methyl. In particular embodiments, R^4 is methyl. In other embodiments, R^4 is H.

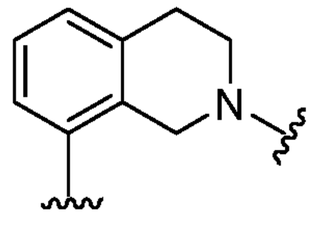
In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIb.1), R^4 is taken together with an atom of Y to form a ring having 4-6 ring atoms. In particular embodiments, the ring is a cyclobutane ring. In other embodiments, the ring is a piperazine ring. In other embodiments, the ring is a morpholine ring.

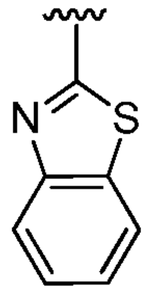
In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIb.1), G is selected from  ,  ,  , and  wherein M is hydrogen or a positively charged counterion. In particular embodiments, G is  . In other embodiments, G is SO_3H. In particular embodiments, G is NH_2. In other embodiments, G is PO_3H_2. In particular embodiments, G is NH_2. In particular embodiments, G is C(O)OH. In particular embodiments, G is polyol.

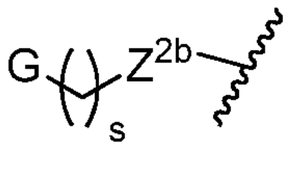
In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIb.1), Ar^2 is selected from  ,  ,  ,  ,  , and  , wherein the G-$(CH_2)_s$-Z^{2b}- substituent is attached to Ar^2 at any Ar^2 atom capable of being substituted.

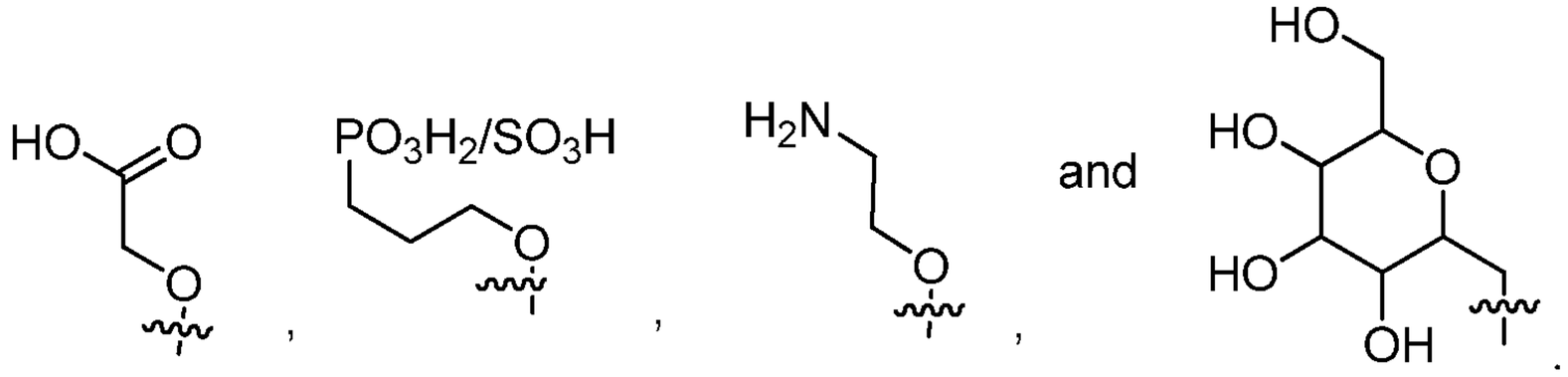
In particular embodiments in which the Bcl-xL inhibitor is a compound of formula (IIb.1), Ar^2 is  , wherein the G-$(CH_2)_s$-Z^{2b}- substituent is attached to Ar^2 at any Ar^2 atom capable of being substituted. In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIb.1), Ar^2 is selected from

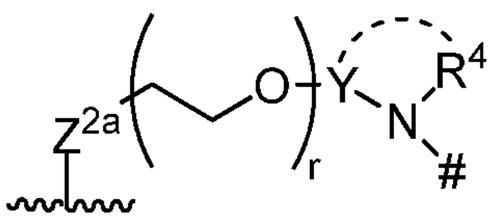


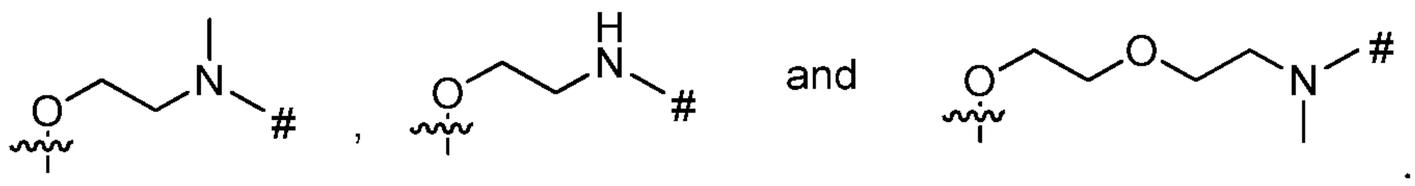
, wherein the G-$(CH_2)_s$-Z^{2b}- substituent is attached to Ar^2 at any Ar^2 atom capable of being substituted. In particular embodiments in which the Bcl-xL inhibitor is a compound of formula (IIb.1), Ar^2 is  , wherein the G-$(CH_2)_s$-Z^{2b}- substituent is attached to Ar^2 at any Ar^2 atom capable of being substituted.

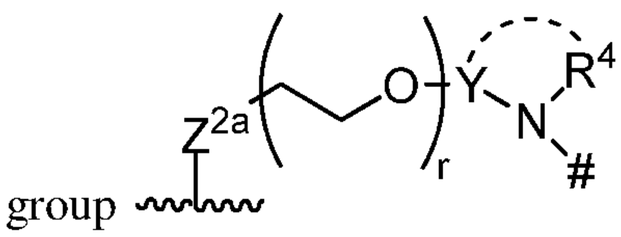
In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIb.1), Ar^1 is  .

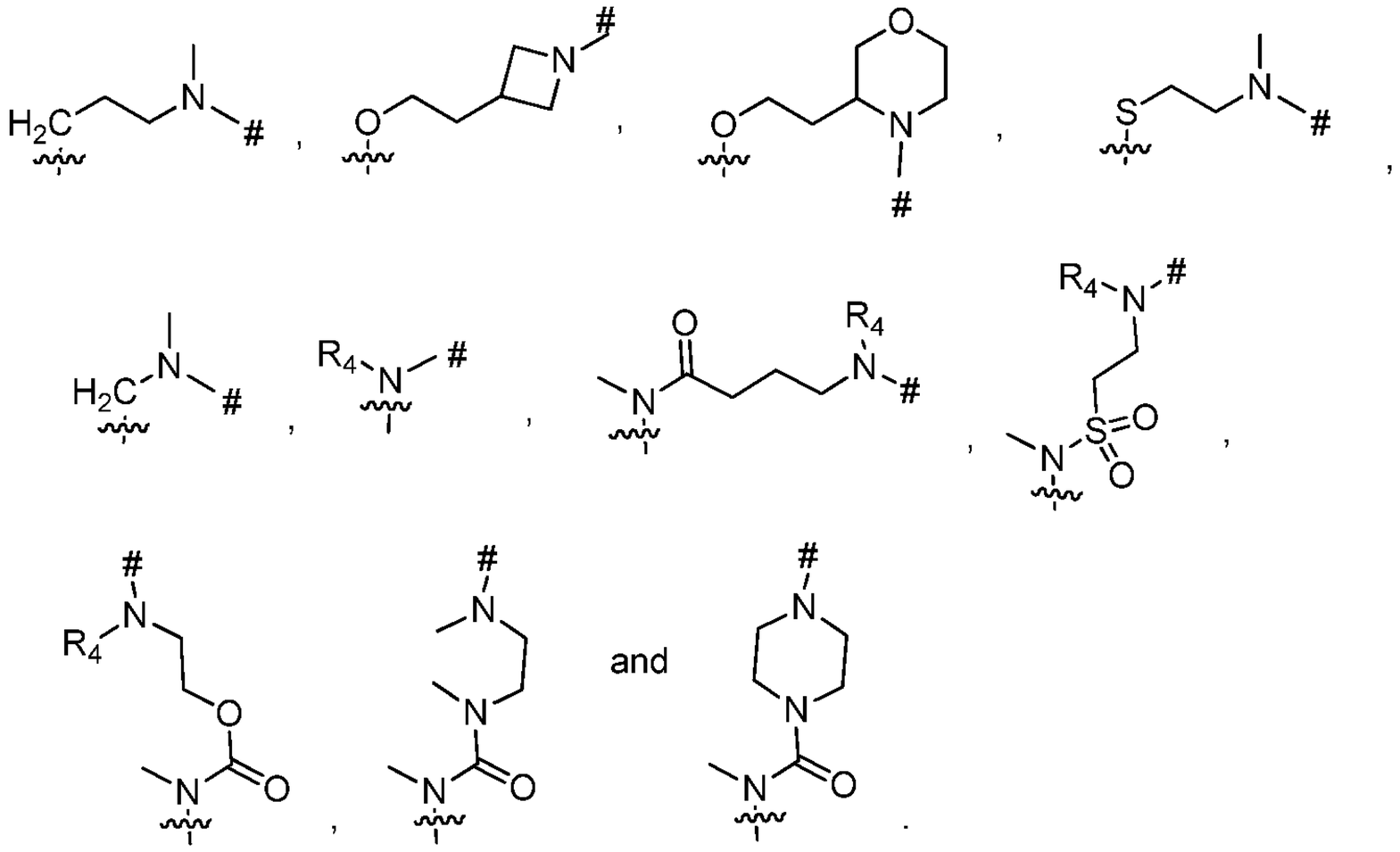
In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIb.1), the group  is selected from:



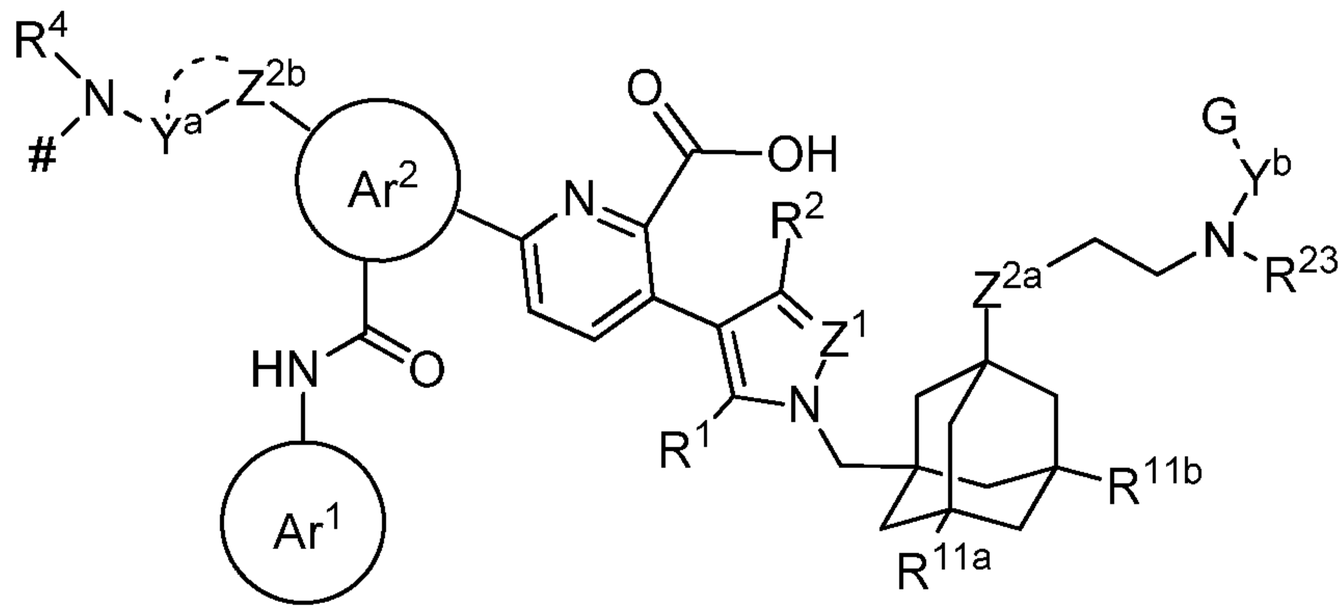
In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIb.1), the group  is selected from:



In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIb.1), the group  is selected from:



In certain embodiments the Bcl-xL inhibitor is a compound of formula (IIc). In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIc), the compound has the structural formula (IIc.1)



(IIc.1)

or salts thereof, wherein:

Ar^1, Ar^2, Z^1, Z^{2a}, Z^{2b}, R^1, R^2, R^4, $R^{11a,}$ R^{11b} and # are defined as above;

Y^a is optionally substituted C_1-C_8 alkylene;

Y^b is optionally substituted C_1-C_8 alkylene;

R^{23} is selected from H and C_1-C_4 alkyl; and

G is selected from a polyol, PEG4-30, a salt and a moiety that is charged at physiological pH;

In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIc.1), Z^{2a} is selected from O, CH_2, NH and S. In particular embodiments, Z^{2a} is O. In certain embodiments, Z^{2a} of formula (IIc.1) is $CR^{6a}R^{6b}$. In certain embodiments, Z^{2a} of formula (IIc.1) is S. In certain embodiments, Z^{2a} of formula (IIc.1) is $-NR^6C(O)-$.

In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIc.1), Z^{2b} is selected from O, CH_2, NH, NCH_3 and S. In particular embodiments, Z^{2b} is O. In particular embodiments, Z^{2b} is NH. In particular embodiments, Z^{2b} is NCH_3.

In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIc.1), Z^{2b} is a bond. In some such embodiments Y^a is methylene or ethylene.

In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIc.1), Z^{2b} is O. In some such embodiments Y^a is methylene, ethylene, or propylene.

In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIc.1), Z^{2b} is NR^6, where R^6 is defined as above. In some such embodiments, R^6 is taken together with an atom from Y^a to form a cycloalkyl or heterocyclyl ring having between 3 and 7 ring atoms. In some such embodiments, the ring has 5 atoms.

In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIc.1), Y^a is ethylene.

In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIc.1), Y^a is methylene.

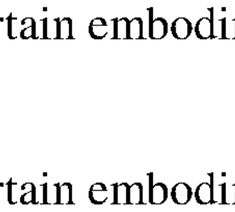
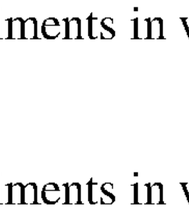
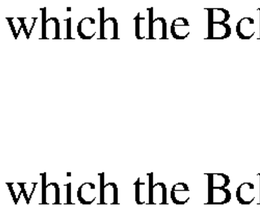
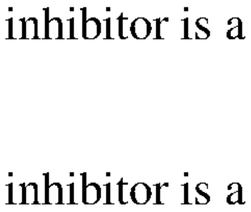
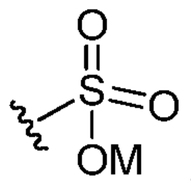
In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIc.1), Y^a is propylene.

In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIc.1), R^4 is H or methyl. In particular embodiments, R^4 is H.

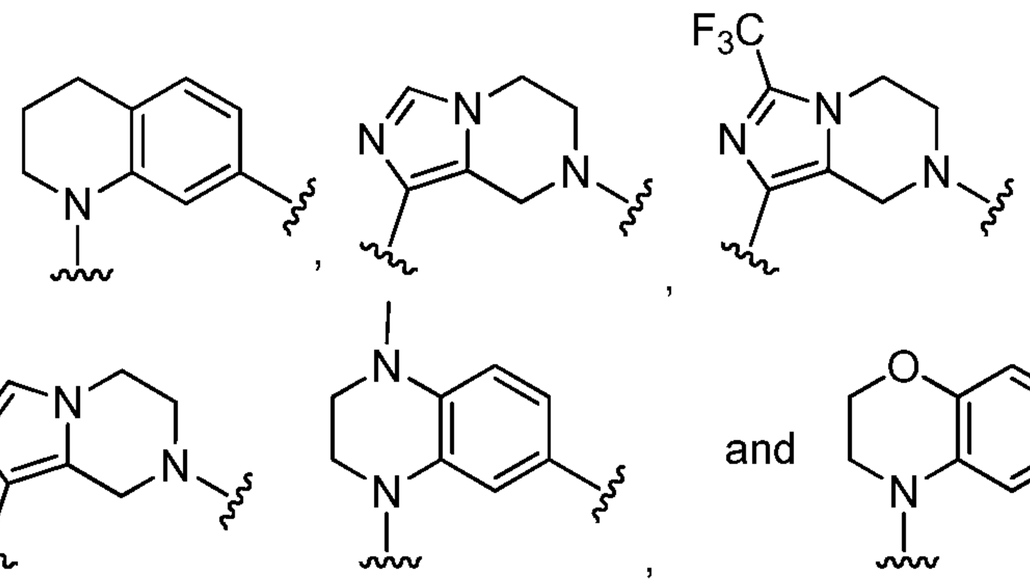
In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIc.1), Y^b is ethylene or propylene. In particular embodiments, Y^b is ethylene.

In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIc.1), R^{23} is methyl.

In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIc.1), R^{23} is H.

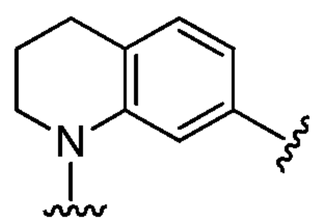
In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIc.1), G is selected from  ,  ,  , and  wherein M is hydrogen or a positively charged counterion. In particular embodiments, G is  . In particular embodiments, G is SO_3H.

In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIc.1), Ar^2 is selected from

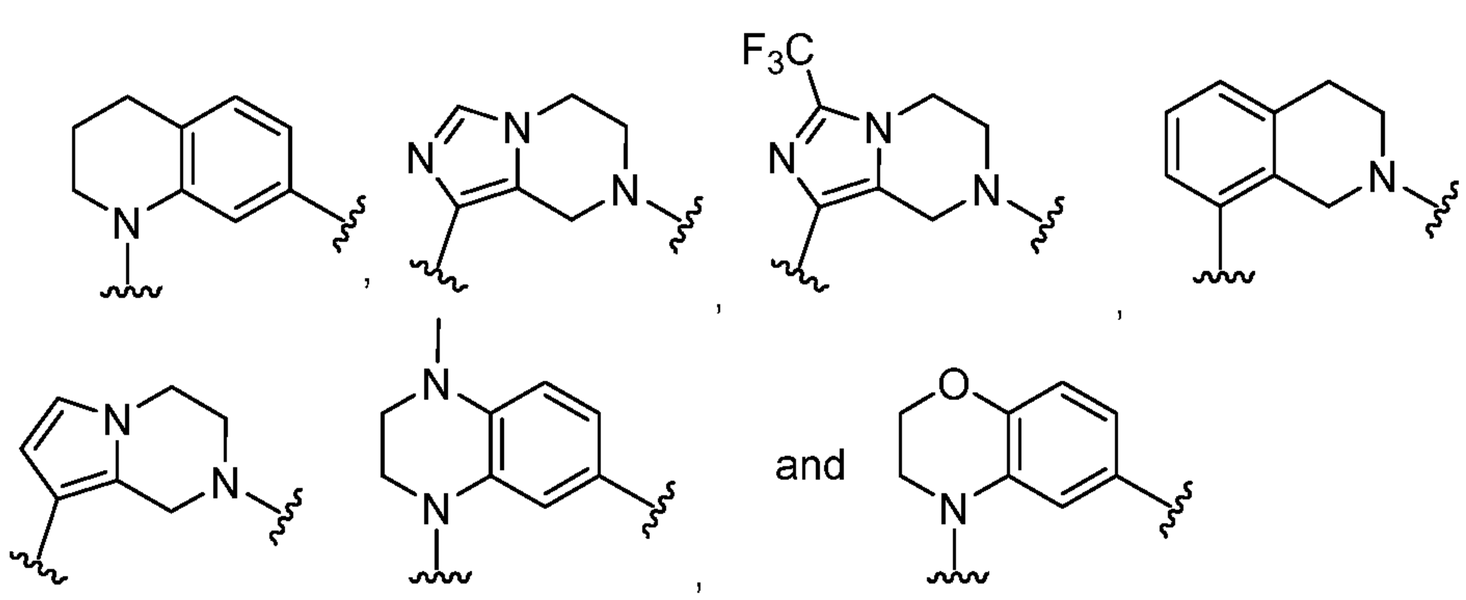


, wherein the #-$N(R^4)$-Y^a-Z^{2b}- substituent is attached to Ar^2 at any Ar^2 atom capable of being substituted.

In particular embodiments in which the Bcl-xL inhibitor is a compound of formula (IIc.1), Ar^2 is



, wherein the #-$N(R^4)$-Y^a-Z^{2b}- substituent is attached to Ar^2 at any Ar^2 atom capable of being substituted. In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIc.1), Ar^2 is selected from

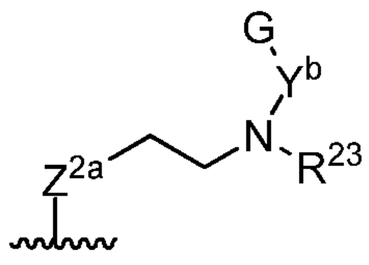


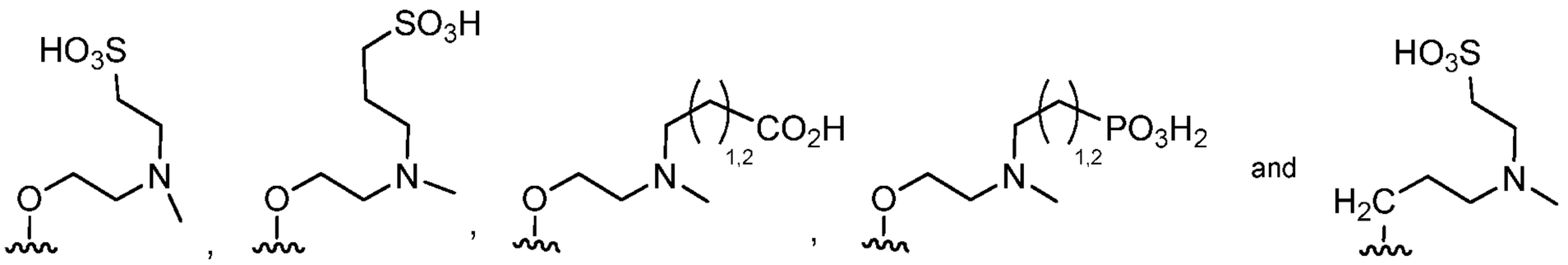
, wherein the #-$N(R^4)$-Y^a-Z^{2b}- substituent is attached to Ar^2 at any Ar^2 atom capable of being substituted. In particular embodiments in which the Bcl-xL inhibitor is a compound of formula (IIc.1), Ar^2 is

, wherein the #-$N(R^4)$-Y^a-Z^{2b}- substituent is attached to Ar^2 at any Ar^2 atom capable of being substituted.

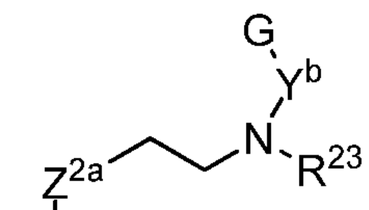
In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIc.1), Ar^1 is

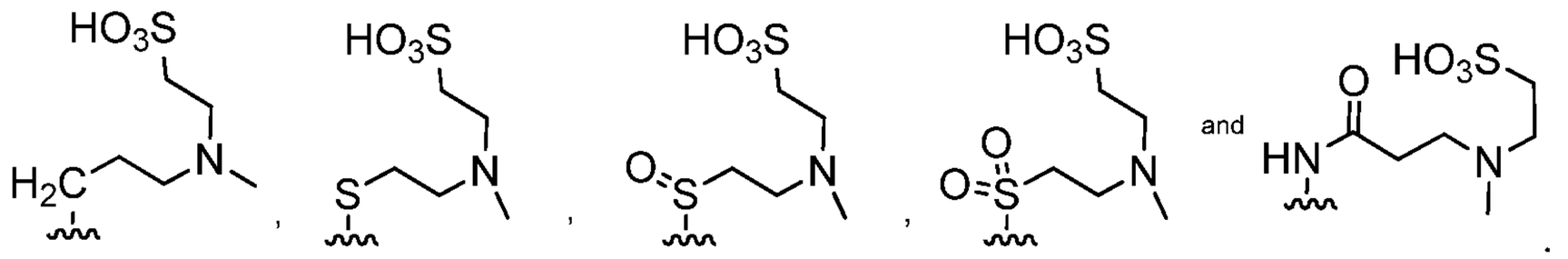
.

In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIc.1), the group  is selected from:



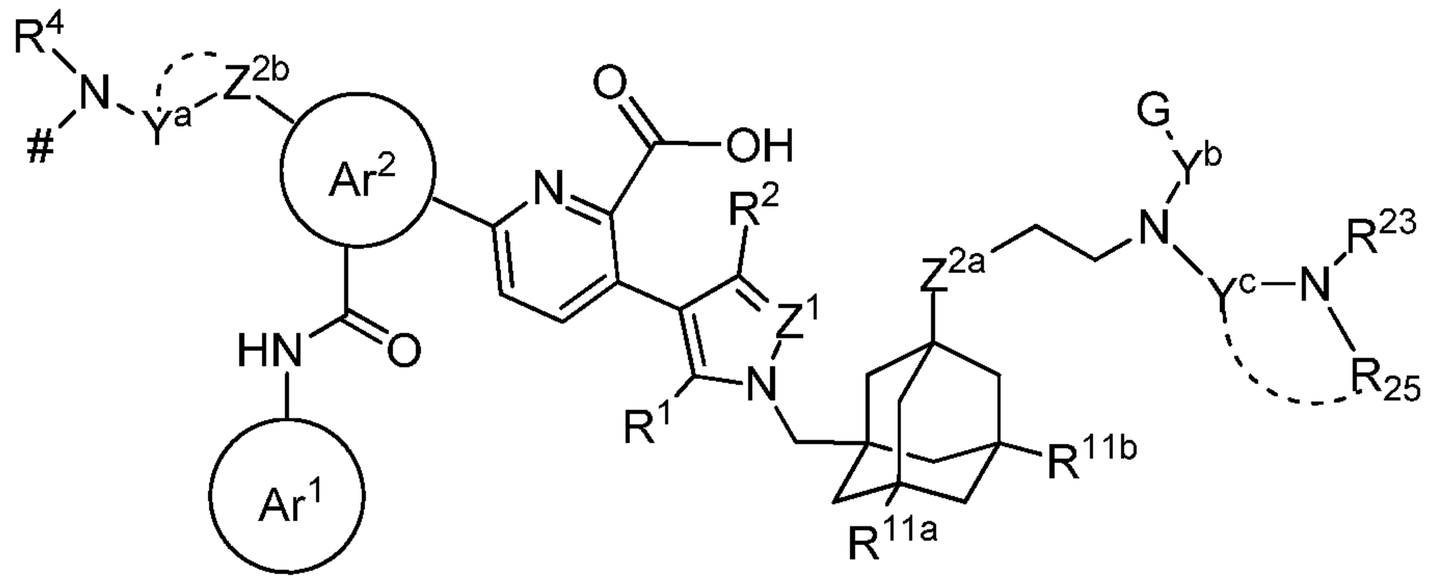
.

In other embodiments in which the Bcl-xL inhibitor is a compound of formula (IIc.1), the group  is selected from:



.

In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIc), the compound has the structural formula (IIc.2),



(IIc.2)

or salts thereof, wherein:

Ar^1, Ar^2, Z^1, Z^{2a}, Z^{2b}, R^1, R^2, R^4, $R^{11a,}$ R^{11b} and # are defined as above;

Y^a is optionally substituted C_1-C_8 alkylene;

Y^b is optionally substituted C_1-C_8 alkylene;

Y^c is optionally substituted C_1-C_8 alkylene;

R^{23} is selected from H and C_1-C_4 alkyl;

R^{25} is Y^b-G or is taken together with an atom of Y^c to form a ring having 4-6 ring atoms; and

G is selected from a polyol, PEG4-30, a salt and a moiety that is charged at physiological pH.

In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIc.2), Z^{2a} is selected from O, CH_2, NH and S. In particular embodiments, Z^{2a} is O. In certain embodiments, Z^{2a} of formula (IIc.2) is $CR^{6a}R^{6b}$. In certain embodiments, Z^{2a} of formula (IIc.2) is S . In certain embodiments, Z^{2a} of formula (IIc.2) is $-NR^6C(O)-$.In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIc.2), Z^{2b} is selected from O, CH_2, NH, NCH_3 and S. In particular embodiments, Z^{2b} is O. In particular embodiments, Z^{2b} is NH. In particular embodiments, Z^{2b} is NCH_3.

In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIc.2), Z^{2b} is a bond. In some such embodiments Y^a is methylene or ethylene.

In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIc.2), Z^{2b} is NR^6, where R^6 is defined as above. In some such embodiments, R^6 is taken together with an atom from Y^a to form a cycloalkyl or heterocyclyl ring having between 3 and 7 ring atoms. In some such embodiments, the ring has 5 atoms.

In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIc.2), Y^a is ethylene.

In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIc.2), Y^a is methylene.

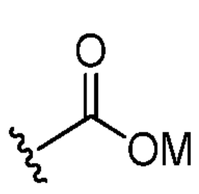
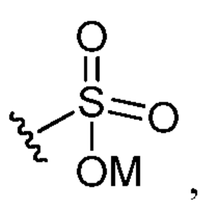
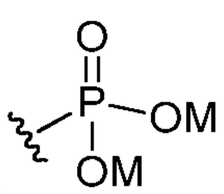
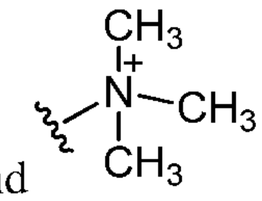
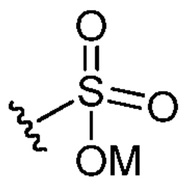
In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIc.2), R^4 is H or methyl.

In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIc.2), Y^b is ethylene or propylene. In particular embodiments, Y^b is ethylene.

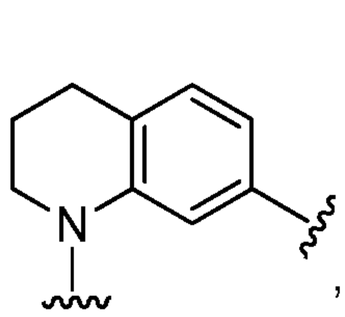
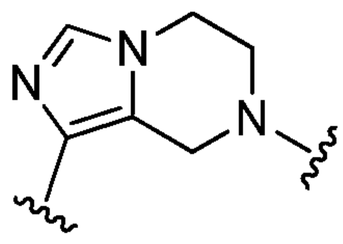
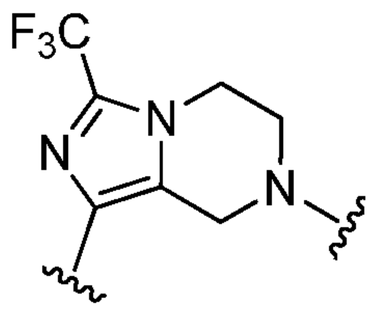
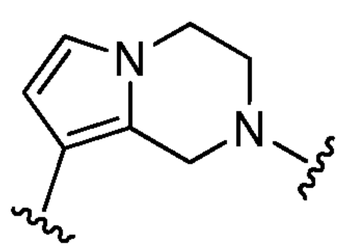
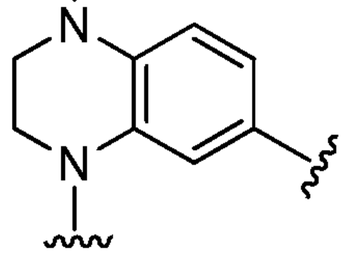
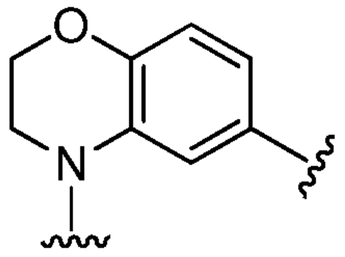
In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIc.2), Y^c is ethylene or propylene. In particular embodiments, Y^b is ethylene.

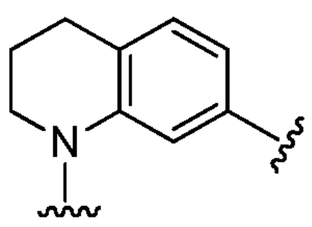
In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIc.2), R^{25} is taken together with an atom of Y^c to form a ring having 4 or 5 ring atoms.

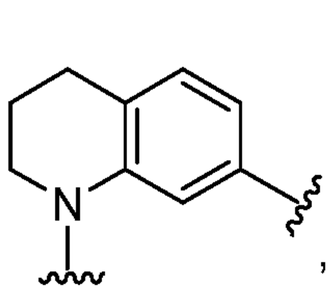
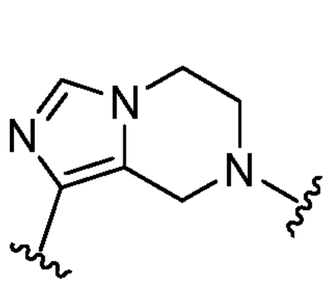
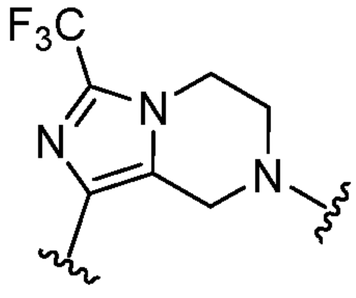
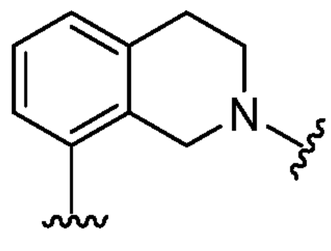
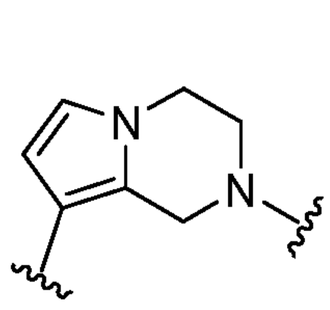
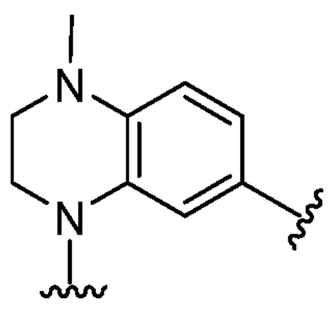
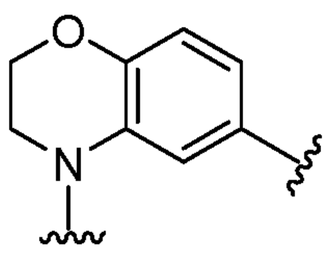
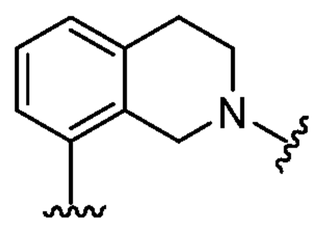
In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIc.2), R^{23} is methyl.

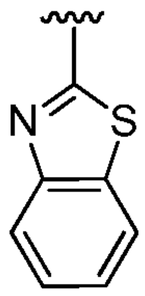
In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIc.2), G is selected from  ,  ,  , and  wherein M is hydrogen or a positively charged counterion. In particular embodiments, G is  . In particular embodiments, G is SO_3H.

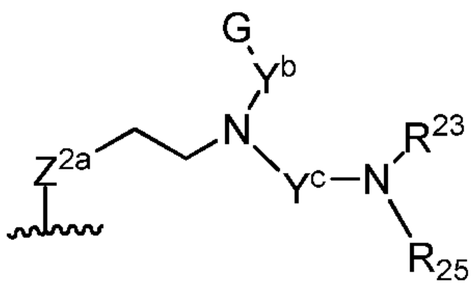
In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIc.2), Ar^2 is selected from

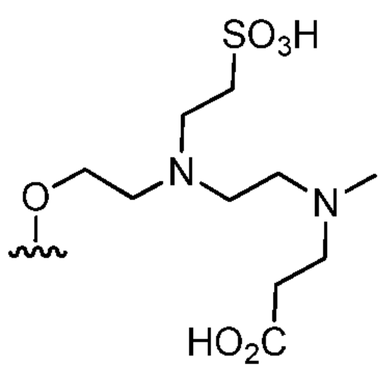
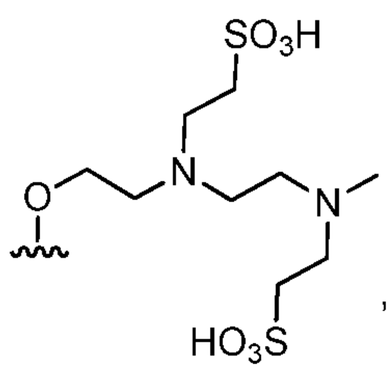
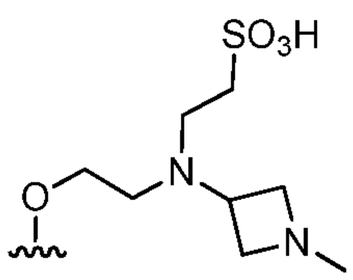
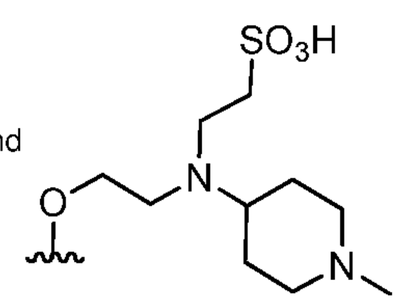

,

,

,

,

,
and

, wherein the #-$N(R^4)$-Y^a-Z^{2b}- substituent is attached to Ar^2 at any Ar^2 atom capable of being substituted.

In particular embodiments in which the Bcl-xL inhibitor is a compound of formula (IIc.2), Ar^2 is  , wherein the #-$N(R^4)$-Y^a-Z^{2b}- substituent is attached to Ar^2 at any Ar^2 atom capable of being substituted. In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIc.2), Ar^2 is selected from

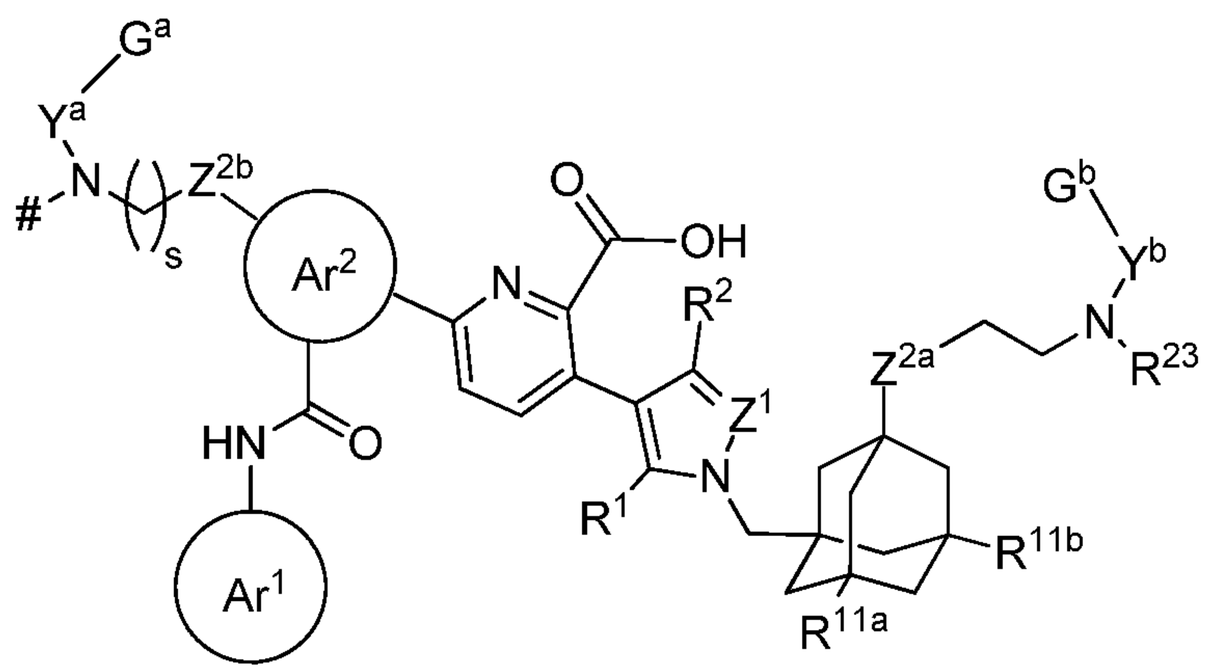

,

,

,

,

,

,
and

, wherein the #-$N(R^4)$-Y^a-Z^{2b}- substituent is attached to Ar^2 at any Ar^2 atom capable of being substituted. In particular embodiments in which the Bcl-xL inhibitor is a compound of formula (IIc.2), Ar^2 is  , wherein the #-$N(R^4)$-Y^a-Z^{2b}- substituent is attached to Ar^2 at any Ar^2 atom capable of being substituted.

In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIc.2), Ar^1 is  .

In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IIc.2), the group  is selected from:

 ,  ,  and  .

In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IId), the compound has the structural formula (IId.1),



(IId.1)

or salts thereof, wherein:

Ar^1, Ar^2, Z^1, Z^{2a}, Z^{2b}, R^1, R^2, $R^{11a,}$ R^{11b} and # are defined as above;

Y^a is optionally substituted alkylene;

Y^b is optionally substituted alkylene;

R^{23} is selected from H and C_1-C_4 alkyl;

G^a is selected from a polyol, PEG4-30, a salt and a moiety that is charged at physiological pH;

G^b is selected from a polyol, PEG4-30, a salt and a moiety that is charged at physiological pH;

In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IId.1), s is 1.

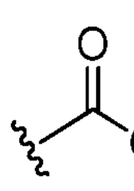
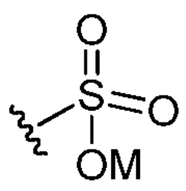
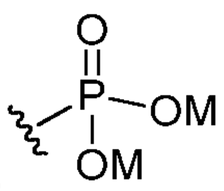
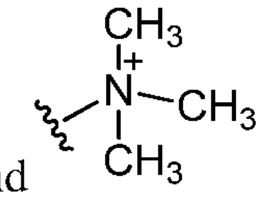
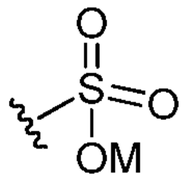
In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IId.1), s is 2.

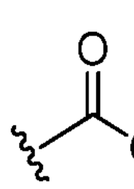
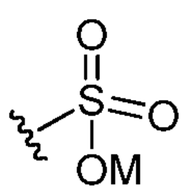
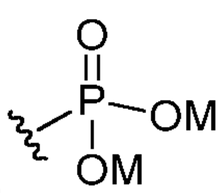
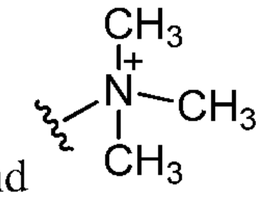
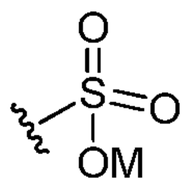
In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IId.1), Z^{2a} is selected from O, NH, CH_2 and S. In particular embodiments, Z^{2a} is O. In certain embodiments, Z^{2a} of formula (IId.1) is $CR^{6a}R^{6b}$. In certain embodiments, Z^{2a} of formula (IId.1) is S. In certain embodiments, Z^{2a} of formula (IId.1) is $-NR^{6}C(O)-$.

In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IId.1), Z^{2b} is selected from O, NH, CH_2 and S. In particular embodiments, Z^{2b} is O.

In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IId.1), Y^a is selected from ethylene, propylene and butylene. In particular embodiments, Y is ethylene.

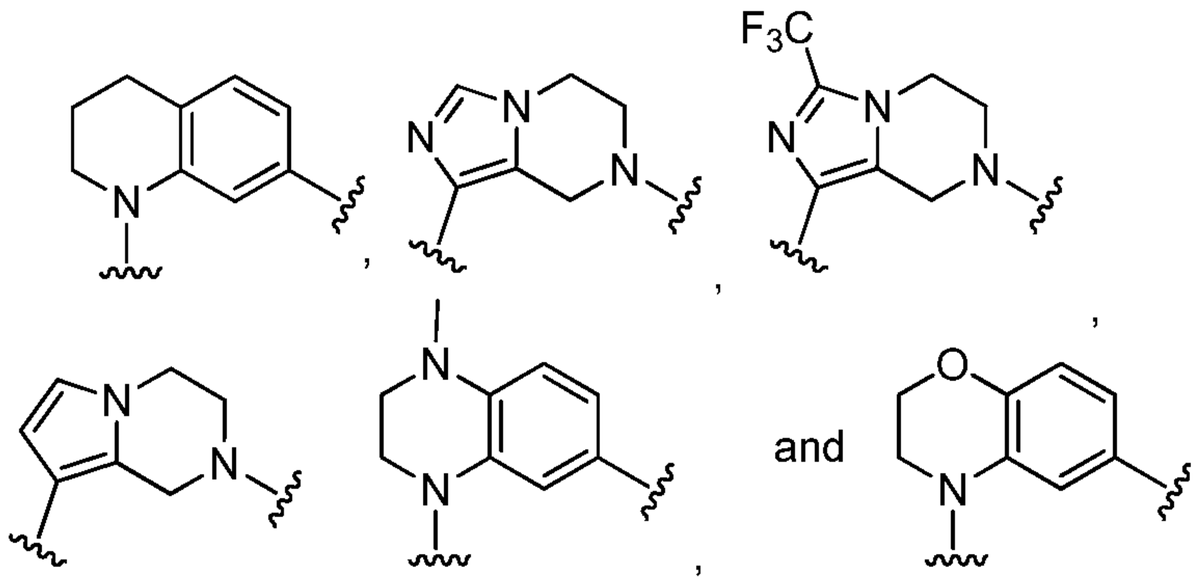
In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IId.1), Y^a is selected from ethylene, propylene and butylene. In particular embodiments, Y is ethylene.

In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IId.1), G^a is selected from  ,  ,  , and  wherein M is hydrogen or a positively charged counterion. In particular embodiments, G^a is  . In particular embodiments, G^a is SO_3H. In particular embodiments, G^a is CO_2H.

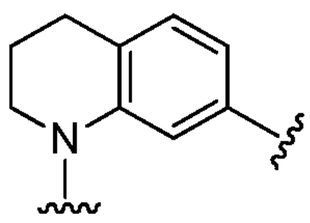
In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IId.1), G^b is selected from  ,  ,  , and  wherein M is hydrogen or a positively charged counterion. In particular embodiments, G^b is  . In particular embodiments, G^b is SO_3H. In particular embodiments, G^b is CO_2H.

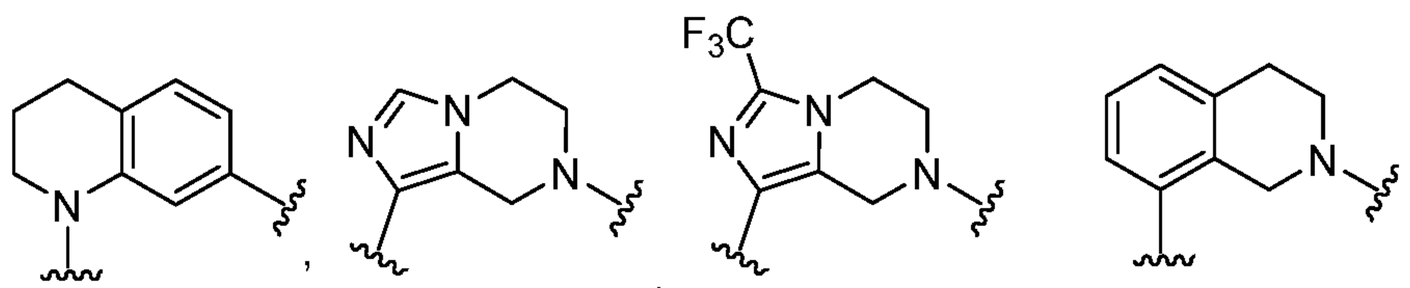
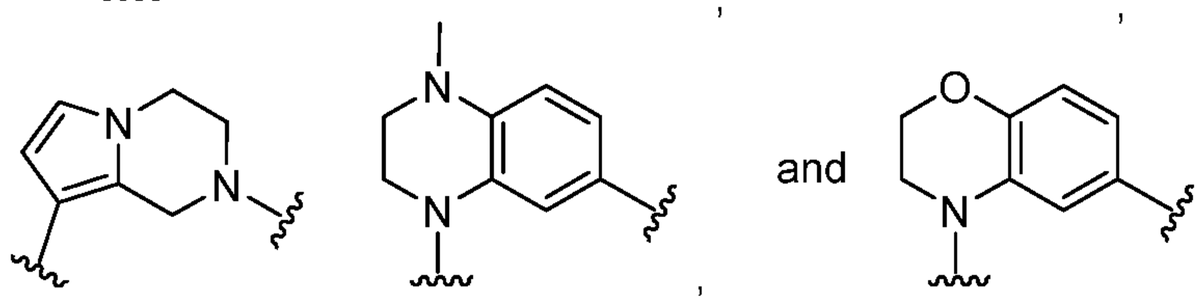
In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IId.1), R^{23} is methyl.

In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IId.1), Ar^2 is selected from

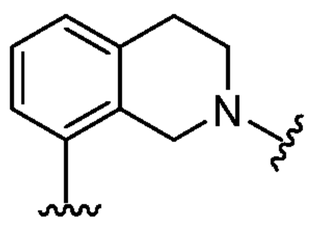


, wherein the G^a-Y^a-N(#)-$(CH_2)_s$-Z^{2b}- substituent is attached to Ar^2 at any Ar^2 atom capable of being substituted.

In particular embodiments in which the Bcl-xL inhibitor is a compound of formula (IId.1), Ar^2 is  , wherein the G^a-Y^a-N(#)-$(CH_2)_s$-Z^{2b}- substituent is attached to Ar^2 at any Ar^2 atom capable of being substituted. In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IId.1), Ar^2 is selected from

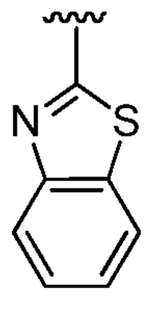



, wherein the G^a-Y^a-N(#)-$(CH_2)_s$-Z^{2b}- substituent is attached to Ar^2 at any Ar^2 atom capable of being substituted. In particular embodiments in which the Bcl-xL inhibitor is a compound of formula (IId.1), Ar^2 is



, wherein the G^a-Y^a-N(#)-$(CH_2)_s$-Z^{2b}- substituent is attached to Ar^2 at any Ar^2 atom capable of being substituted.

In certain embodiments in which the Bcl-xL inhibitor is a compound of formula (IId.1), Ar^1 is

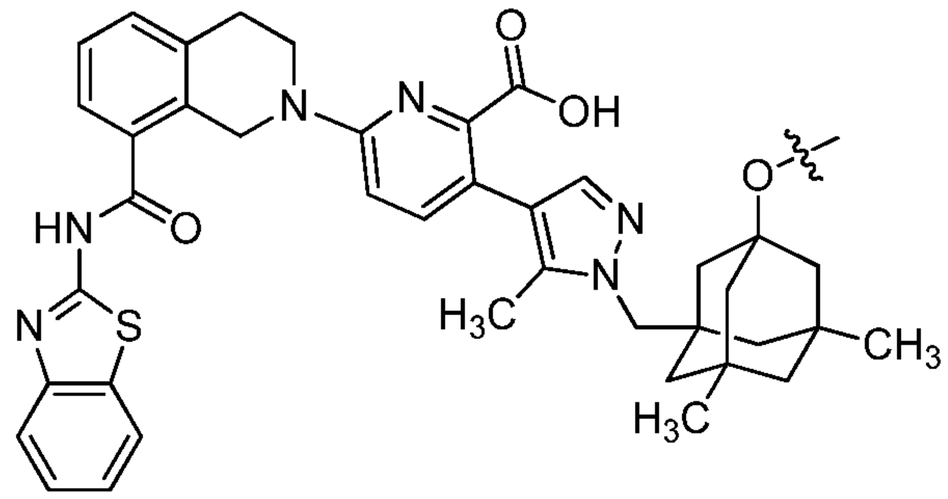


.

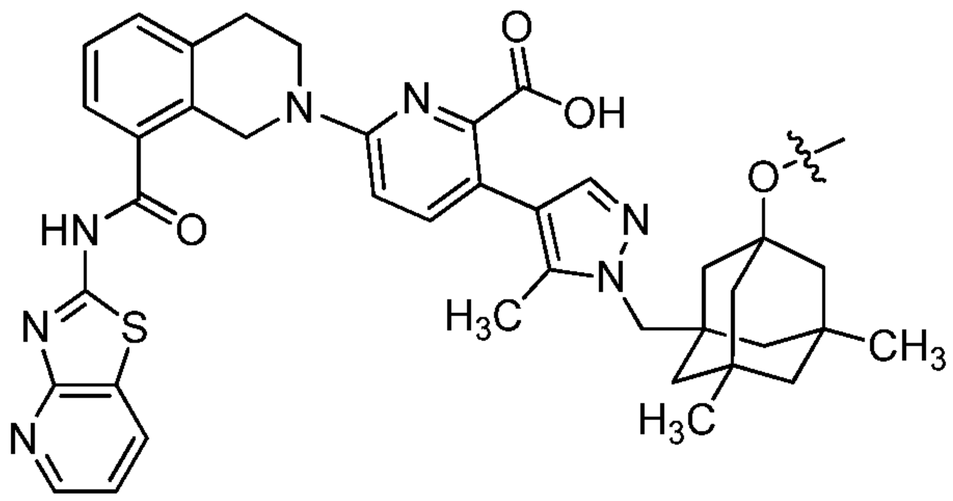
In certain embodiments, R^{11a} and R^{11b} of formulae (IIa)-(IId) are the same. In a particular embodiment, R^{11a} and R^{11b} are each methyl.

In certain embodiments, the compounds of formulae (IIa)-(IId) include one of the following cores (C.1)-(C.21):

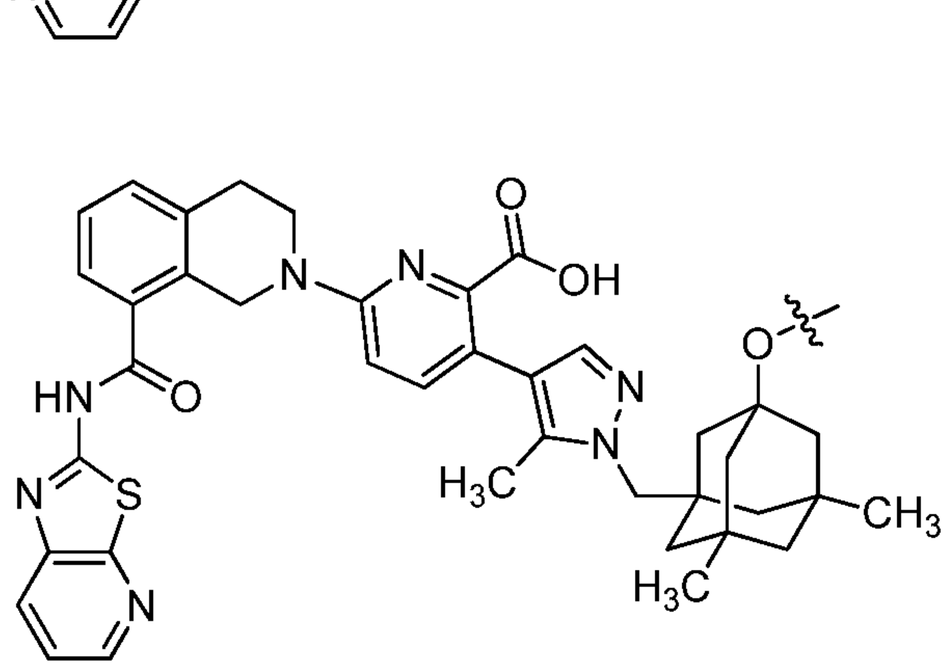
(C.1)



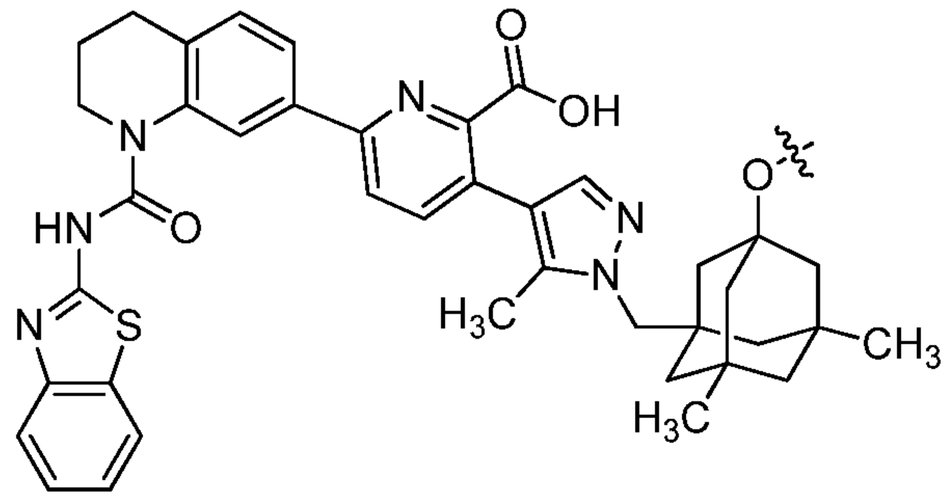
(C.2)



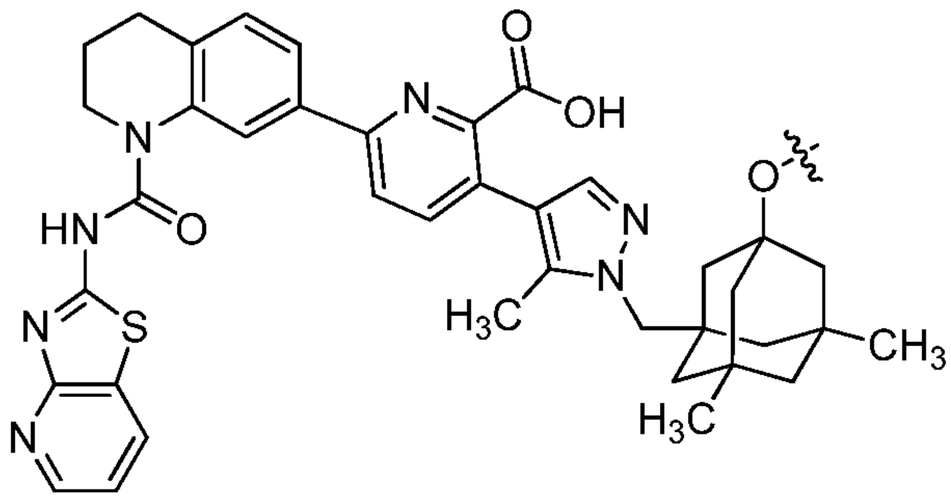
(C.3)



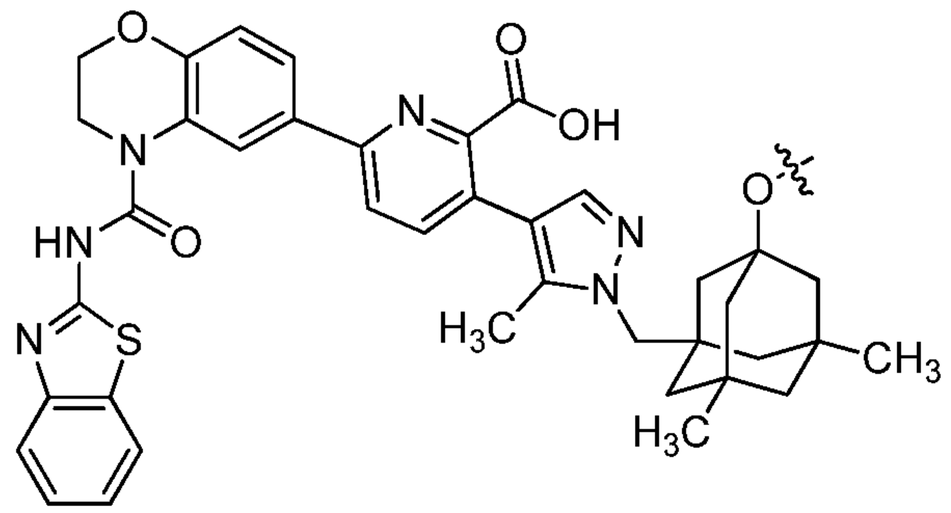
(C.4)



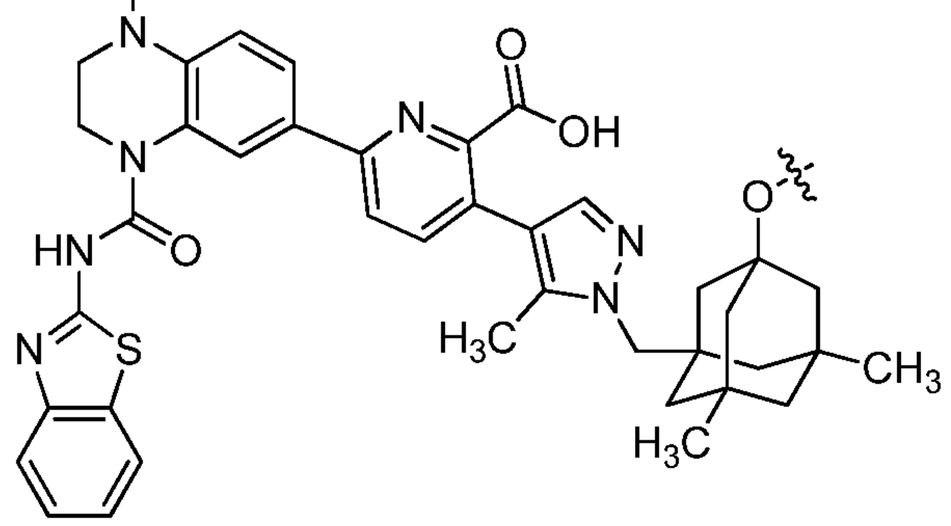
(C.5)



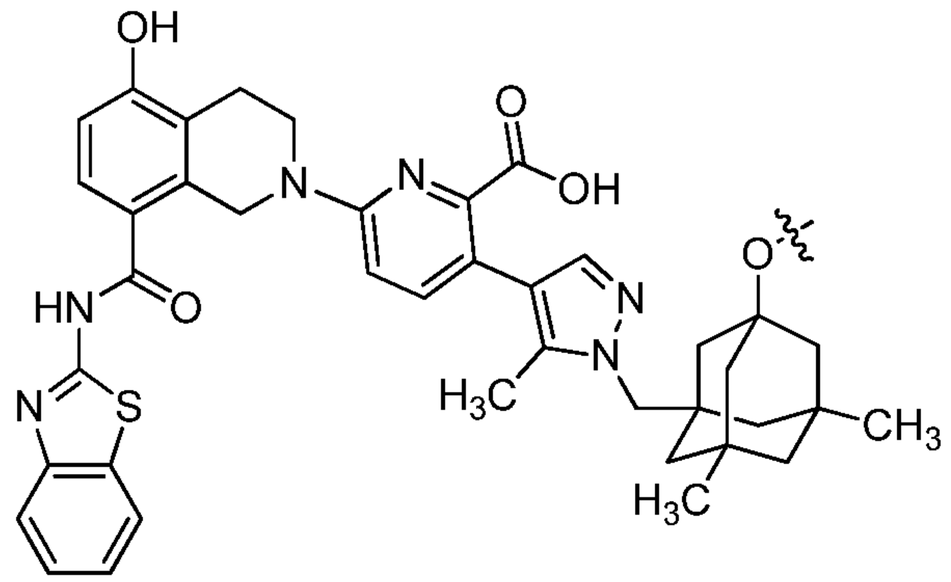
(C.6)



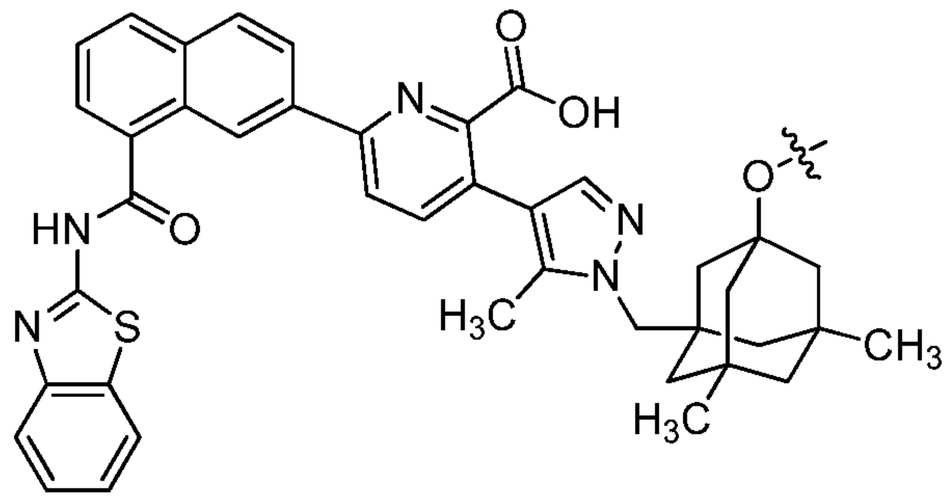
(C.7)



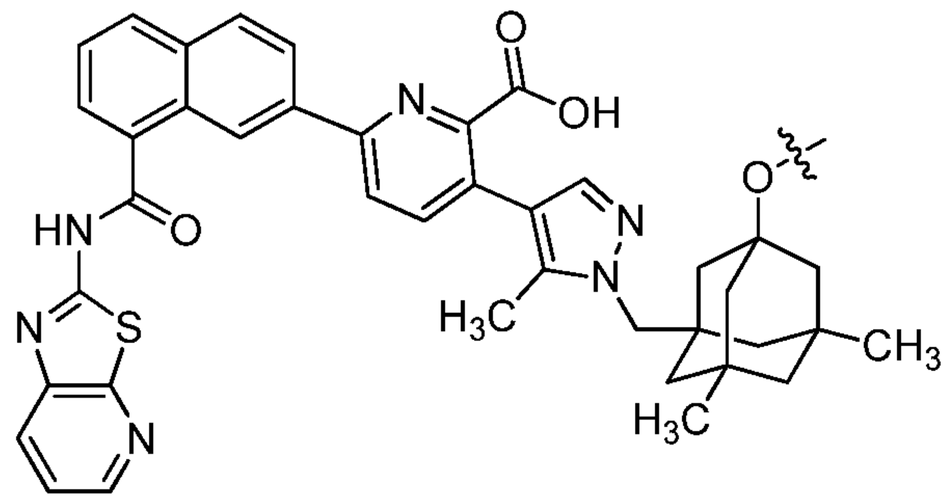
(C.8)



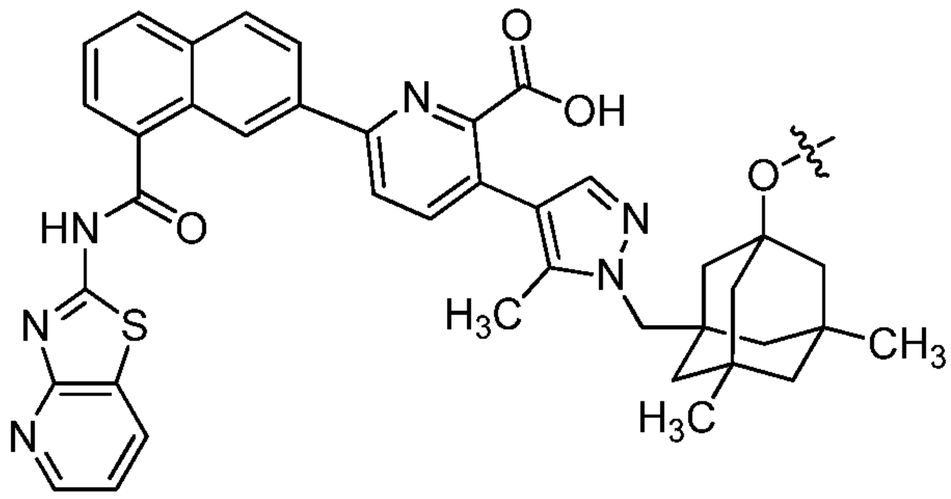
(C.9)



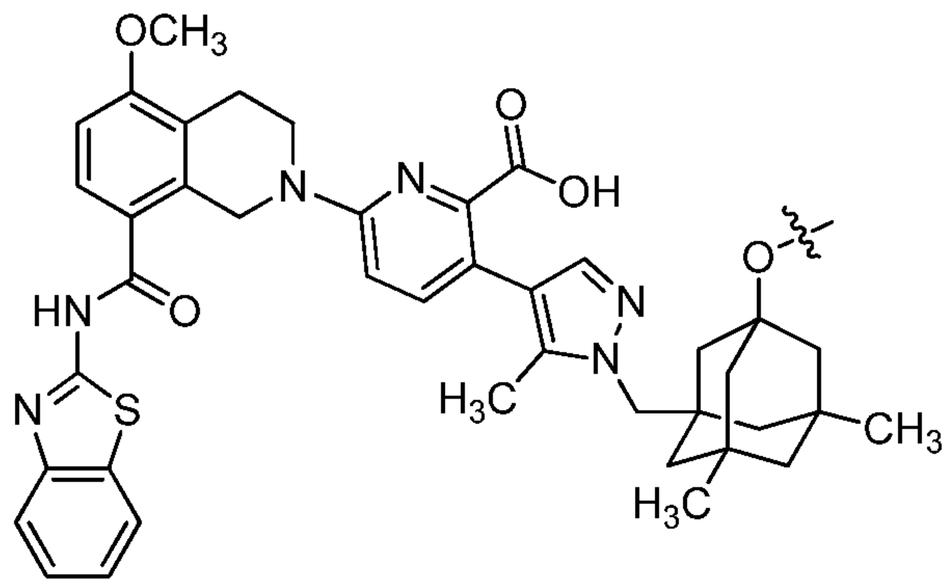
(C.10)



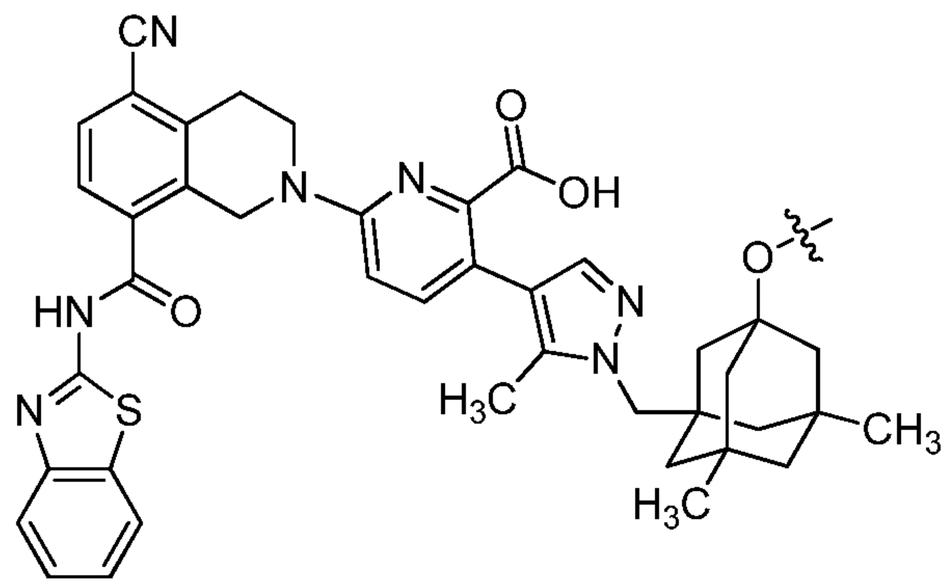
(C.11)



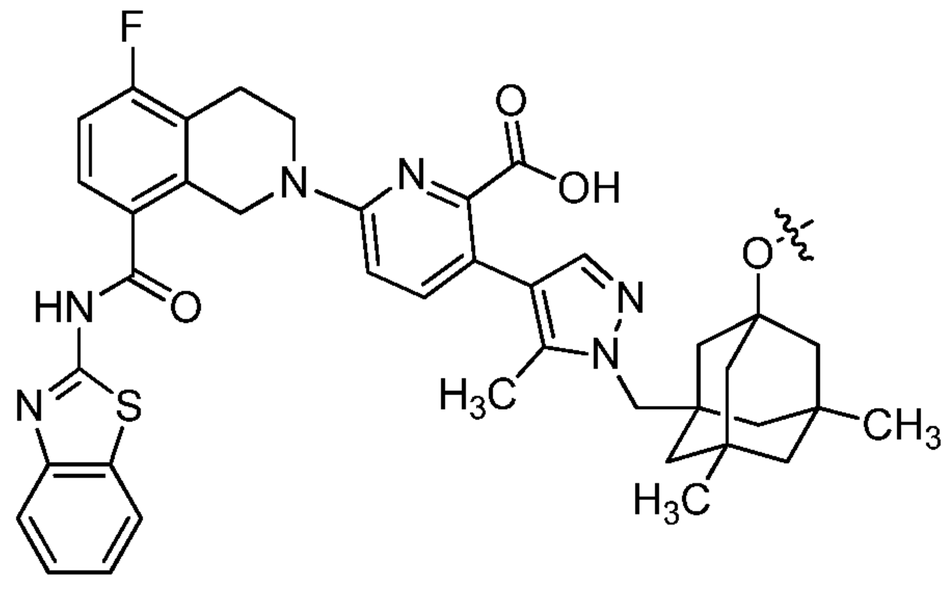
(C.12)



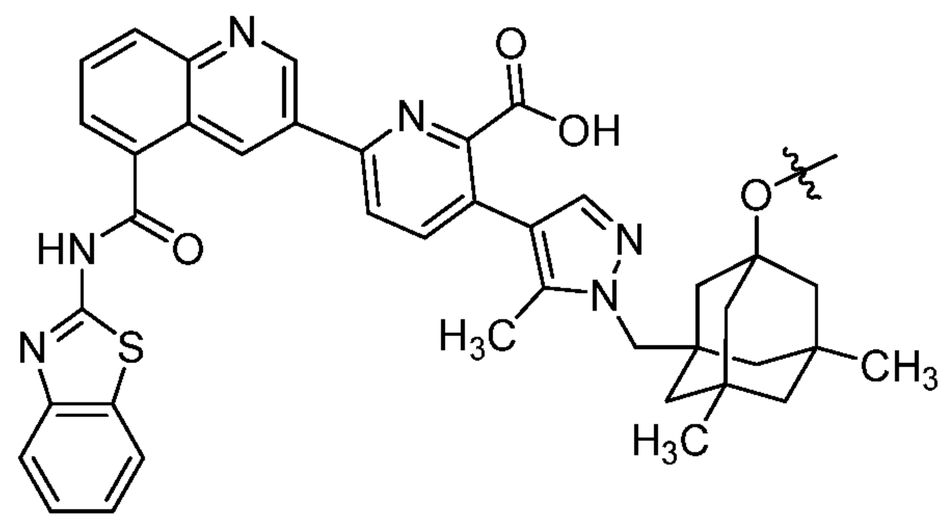
(C.13)



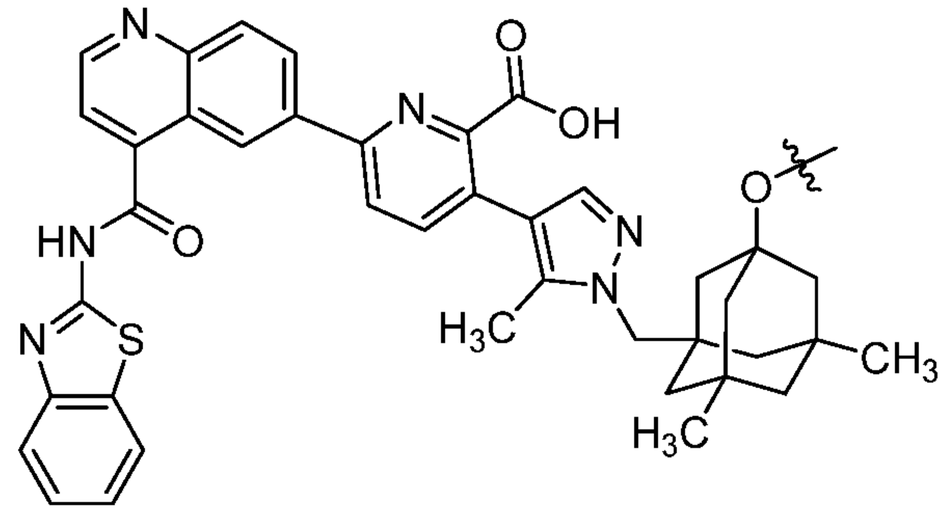
(C.14)



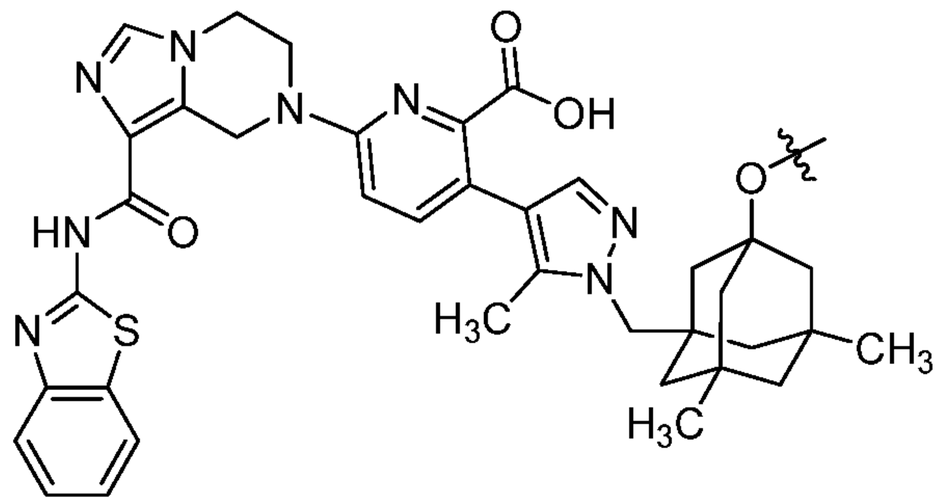
(C.15)



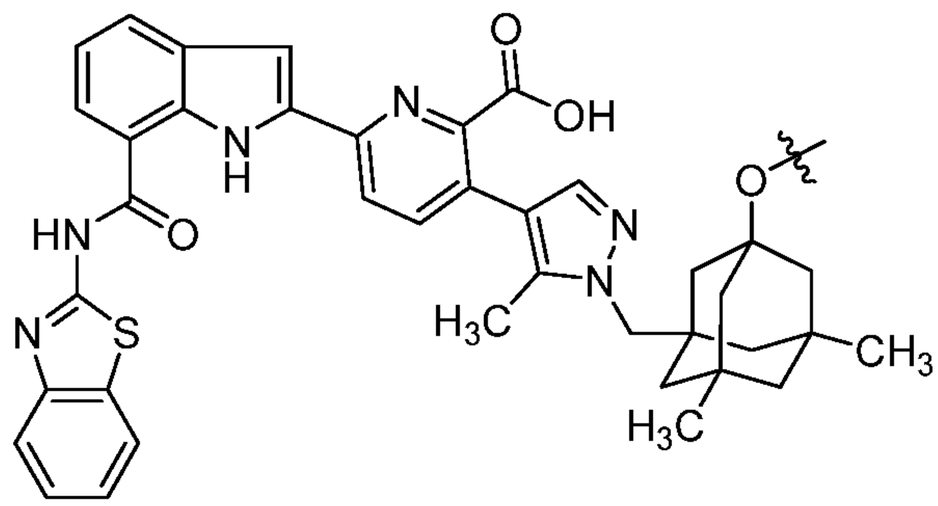
(C.16)



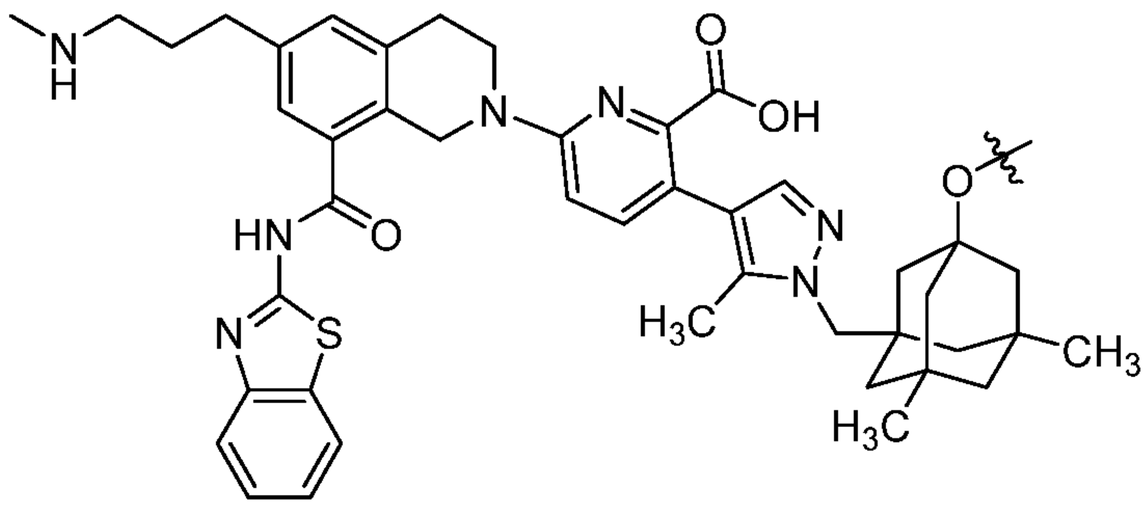
(C.17)



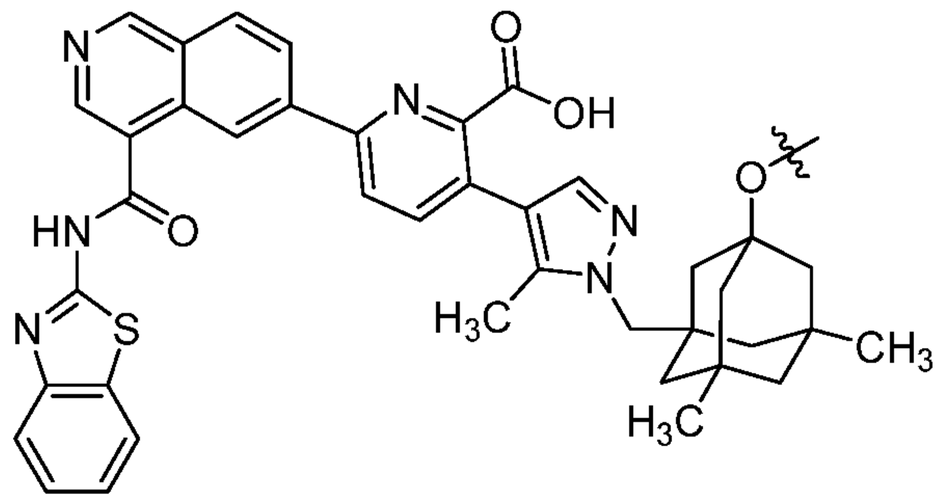
(C.18)

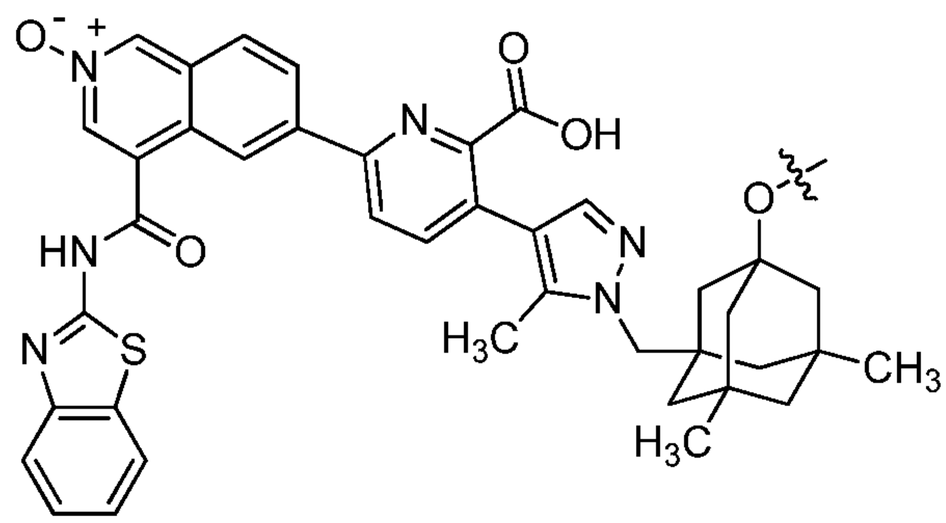


(C.19)



(C.20)



(C.21) 

Exemplary Bcl-xL inhibitors according to structural formulae (IIa)-(IId) that may be used in the methods described herein in unconjugated form and/or included in the ADCs described herein include the following compounds, and/or salts thereof:

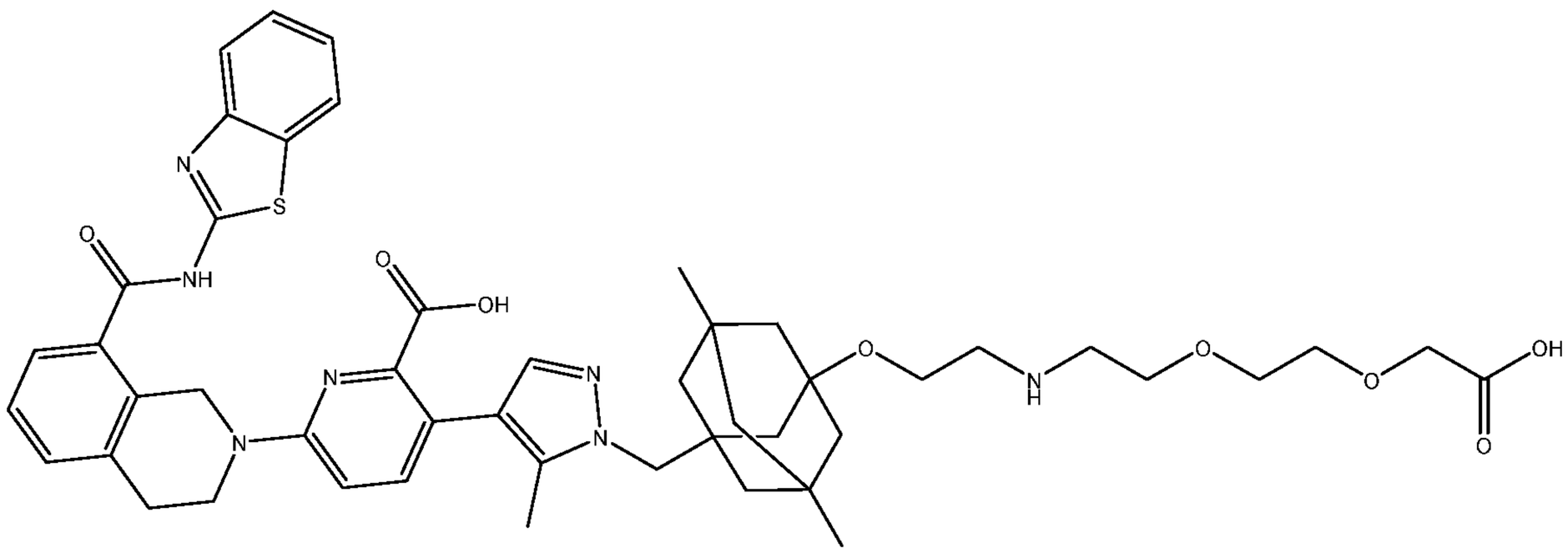
App Ex. No.	Bcl-xL Inhibitor Cmpd No
1.1	W2.01
1.2	W2.02
1.3	W2.03
1.5	W2.05
1.6	W2.06
1.7	W2.07
1.8	W2.08
1.9	W2.09
1.10	W2.10
1.11	W2.11
1.12	W2.12
1.13	W2.13
1.14	W2.14
1.15	W2.15
1.16	W2.16
1.17	W2.17
1.18	W2.18
1.19	W2.19
1.20	W2.20
1.21	W2.21
1.22	W2.22
1.23	W2.23
1.24	W2.24
1.25	W2.25
1.26	W2.26
1.27	W2.27
1.28	W2.28
1.29	W2.29
1.30	W2.30

App Ex. No.	Bcl-xL Inhibitor Cmpd No
1.31	W2.31
1.32	W2.32
1.33	W2.33
1.34	W2.34
1.35	W2.35
1.36	W2.36
1.37	W2.37
1.38	W2.38
1.39	W2.39
1.40	W2.40
1.41	W2.41
1.42	W2.42
1.43	W2.43
1.44	W2.44
1.45	W2.45
1.46	W2.46
1.47	W2.47
1.48	W2.48
1.49	W2.49
1.50	W2.50
1.51	W2.51
1.52	W2.52
1.53	W2.53
1.54	W2.54
1.55	W2.55
1.56	W2.56
1.57	W2.57
1.58	W2.58
1.59	W2.59
1.60	W2.60
1.61	W2.61
1.62	W2.62
1.63	W2.63
1.64	W2.64
1.65	W2.65
1.66	W2.66
1.67	W2.67
1.68	W2.68
1.69	W2.69
1.70	W2.70
1.71	W2.71
1.72	W2.72

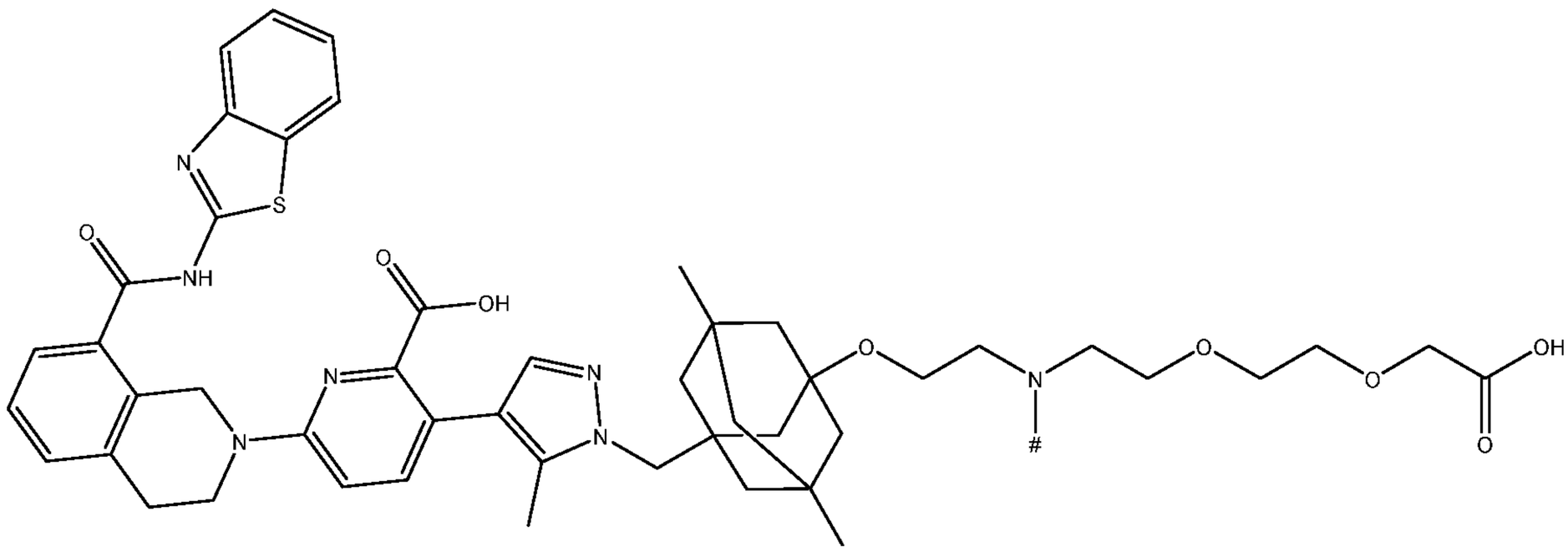
App Ex. No.	Bcl-xL Inhibitor Cmpd No
1.73	W2.73
1.74	W2.74
1.75	W2.75
1.76	W2.76
1.77	W2.77
1.78	W2.78
1.79	W2.79
1.80	W2.80
1.81	W2.81
1.82	W2.82
1.83	W2.83
1.84	W2.84
1.85	W2.85
1.86	W2.86
1.87	W2.87
1.88	W2.88
1.89	W2.89
1.90	W2.90
1.91	W2.91

Notably, when the Bcl-xL inhibitor of the present application is in conjugated form, the hydrogen corresponding to the # position of structural formulae (IIa)-(IId) is not present, forming a monoradical. For example, compound W2.01 (Example 1.1) is 6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-[1-({3-[2-({2-[2-(carboxymethoxy)ethoxy]ethyl}amino)ethoxy]-5,7-dimethyltricyclo[3.3.1.13,7]dec-1-yl}methyl)-5-methyl-1H-pyrazol-4-yl]pyridine-2-carboxylic acid.

When it is in unconjugated form, it has the following structure:



When the same compound is included in the ADCs as shown in structural formula (IIa) or (IIb), the hydrogen corresponding to the # position is not present, forming a monoradical.



In certain embodiments, the Bcl-xL inhibitors according to structural formulae (IIa)-(IId) are selected from the group consisting of W2.01, W2.02, W2.03, W2.04, W2.05, W2.06, W2.07, W2.08, W2.09, W2.10, W2.11, W2.12, W2.13, W2.14, W2.15, W2.16, W2.17, W2.18, W2.19, W2.20, W2.21, W2.22, W2.23, W2.24, W2.25, W2.26, W2.27, W2.28, W2.29, W2.30, W2.31, W2.32, W2.33, W2.34, W2.35, W2.36, W2.37, W2.38, W2.39, W2.40, W2.41, W2.42, W2.43, W2.44, W2.45, W2.46, W2.47, W2.48, W2.49, W2.50, W2.51, W2.52, W2.53, W2.54, W2.55, W2.56, W2.57, W2.58, W2.59, W2.60, W2.61, W2.62, W2.63, W2.64, W2.65, W2.66, W2.67, W2.68, W2.69, W2.70, W2.71, W2.72, W2.73, W2.74, W2.75, W2.76, W2.77, W2.78, W2.79, W2.80, W2.81, W2.82, W2.83, W2.84, W2.85, W2.86, W2.87, W2.88, W2.89, W2.90, and W2.91, or pharmaceutically acceptable salts thereof.

In certain embodiments, the ADC, or a pharmaceutically acceptable salt thereof, comprises a drug linked to an antibody by way of a linker, wherein the drug is a Bcl-xL inhibitor selected from the group consisting of W2.01, W2.02, W2.03, W2.04, W2.05, W2.06, W2.07, W2.08, W2.09, W2.10, W2.11, W2.12, W2.13, W2.14, W2.15, W2.16, W2.17, W2.18, W2.19, W2.20, W2.21, W2.22, W2.23, W2.24, W2.25, W2.26, W2.27, W2.28, W2.29, W2.30, W2.31, W2.32, W2.33, W2.34, W2.35, W2.36, W2.37, W2.38, W2.39, W2.40, W2.41, W2.42, W2.43, W2.44, W2.45, W2.46, W2.47, W2.48, W2.49, W2.50, W2.51, W2.52, W2.53, W2.54, W2.55, W2.56, W2.57, W2.58, W2.59, W2.60, W2.61, W2.62, W2.63, W2.64, W2.65, W2.66, W2.67, W2.68, W2.69, W2.70, W2.71, W2.72, W2.73, W2.74, W2.75, W2.76, W2.77, W2.78, W2.79, W2.80, W2.81, W2.82, W2.83, W2.84, W2.85, W2.86, W2.87, W2.88, W2.89, W2.90, and W2.91.

In certain embodiments, the ADC, or a pharmaceutically acceptable salt thereof, the Bcl-xL inhibitor is selected from the group consisting of the following compounds modified in that the hydrogen corresponding to the # position of structural formula (IIa), (IIb),(IIc), or (IId) is not present forming a monoradical:

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-[1-({3-[2-({2-[2-(carboxymethoxy)ethoxy]ethyl}amino)ethoxy]-5,7-dimethyltricyclo[3.3.1.$1^{3,7}$]dec-1-yl}methyl)-5-methyl-1H-pyrazol-4-yl]pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3,5-dimethyl-7-{2-[(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

2-{[(2-{[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl]amino}ethyl)sulfonyl]amino}-2-deoxy-D-glucopyranose;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]-3-{1-[(3,5-dimethyl-7-{2-[(4-{[(3*R*,4*R*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl]methyl}benzyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1*H*-pyrazol-4-yl}pyridine-2-carboxylic acid

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3,5-dimethyl-7-{2-[(3-sulfopropyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3-{2-[(2,3-dihydroxypropyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

2-({[4-({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl]amino}methyl)phenyl]sulfonyl}amino)-2-deoxy-beta-D-glucopyranose;

8-(1,3-benzothiazol-2-ylcarbamoyl)-2-{6-carboxy-5-[1-({3-[2-({2-[1-(beta-D-glucopyranuronosyl)-1H-1,2,3-triazol-4-yl]ethyl}amino)ethoxy]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}methyl)-5-methyl-1H-pyrazol-4-yl]pyridin-2-yl}-1,2,3,4-tetrahydroisoquinoline;

3-[1-({3-[2-(2-{[4-(beta-D-allopyranosyloxy)benzyl]amino}ethoxy)ethoxy]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}methyl)-5-methyl-1H-pyrazol-4-yl]-6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-(1-{[3,5-dimethyl-7-(2-{2-[(2-sulfoethyl)amino]ethoxy}ethoxy)tricyclo[3.3.1.1^{3,7}]dec-1-yl]methyl}-5-methyl-1H-pyrazol-4-yl)pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3,5-dimethyl-7-{2-[(2-phosphonoethyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3,5-dimethyl-7-{2-[methyl(3-sulfo-L-alanyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3,5-dimethyl-7-{2-[(3-phosphonopropyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3,5-dimethyl-7-{2-[(3-sulfo-L-alanyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-(1-{[3,5-dimethyl-7-(2-{2-[(3-phosphonopropyl)amino]ethoxy}ethoxy)tricyclo[3.3.1.1^{3,7}]dec-1-yl]methyl}-5-methyl-1H-pyrazol-4-yl)pyridine-2-carboxylic acid;

3-{1-[(3-{2-[L-alpha-aspartyl(methyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}-6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]pyridine-2-carboxylic acid;

6-{4-[({2-[2-(2-aminoethoxy)ethoxy]ethyl}[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl]amino)methyl]benzyl}-2,6-anhydro-L-gulonic acid;

4-({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl]amino}methyl)phenyl hexopyranosiduronic acid;

6-[1-(1,3-benzothiazol-2-ylcarbamoyl)-1,2,3,4-tetrahydroquinolin-7-yl]-3-{1-[(3,5-dimethyl-7-{2-[(2-phosphonoethyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[1-(1,3-benzothiazol-2-ylcarbamoyl)-1,2,3,4-tetrahydroquinolin-7-yl]-3-{1-[(3,5-dimethyl-7-{2-[methyl(3-sulfo-L-alanyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

3-{1-[(3,5-dimethyl-7-{2-[(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}-6-[8-([1,3]thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]pyridine-2-carboxylic acid;

3-{1-[(3,5-dimethyl-7-{2-[(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}-6-[8-([1,3]thiazolo[4,5-b]pyridin-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]pyridine-2-carboxylic acid;

6-[1-(1,3-benzothiazol-2-ylcarbamoyl)-1,2,3,4-tetrahydroquinolin-7-yl]-3-{1-[(3,5-dimethyl-7-{2-[(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3-{2-[(2-carboxyethyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3,5-dimethyl-7-{2-[(3-phosphonopropyl)(piperidin-4-yl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

3-{1-[(3-{2-[D-alpha-aspartyl(methyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}-6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-(1-{[3-(2-{[1-(carboxymethyl)piperidin-4-yl]amino}ethoxy)-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl]methyl}-5-methyl-1H-pyrazol-4-yl)pyridine-2-carboxylic acid;

N-[(5S)-5-amino-6-{[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](methyl)amino}-6-oxohexyl]-N,N-dimethylmethanaminium;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3,5-dimethyl-7-{2-[piperidin-4-yl(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-5-(3-phosphonopropoxy)-3,4-dihydroisoquinolin-2(1H)-yl]-3-[1-({3,5-dimethyl-7-[2-(methylamino)ethoxy]tricyclo[3.3.1.1^{3,7}]dec-1-yl}methyl)-5-methyl-1H-pyrazol-4-yl]pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-(1-{[3-(2-{[N-(2-carboxyethyl)-L-alpha-aspartyl]amino}ethoxy)-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl]methyl}-5-methyl-1H-pyrazol-4-yl)pyridine-2-carboxylic acid;

3-{1-[(3-{2-[(2-aminoethyl)(2-sulfoethyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}-6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]pyridine-2-carboxylic acid;

6-[5-(2-aminoethoxy)-8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-[1-({3,5-dimethyl-7-[2-(methylamino)ethoxy]tricyclo[3.3.1.1^{3,7}]dec-1-yl}methyl)-5-methyl-1H-pyrazol-4-yl]pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)naphthalen-2-yl]-3-{1-[(3,5-dimethyl-7-{2-[(3-sulfopropyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3-{2-[(2-carboxyethyl)(piperidin-4-yl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3,5-dimethyl-7-{2-[(3-sulfo-L-alanyl)(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3-{2-[{2-[(2-carboxyethyl)amino]ethyl}(2-sulfoethyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

3-{1-[(3,5-dimethyl-7-{2-[(3-phosphonopropyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}-6-[8-([1,3]thiazolo[4,5-b]pyridin-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]pyridine-2-carboxylic acid;

3-{1-[(3,5-dimethyl-7-{2-[(3-phosphonopropyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}-6-[8-([1,3]thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-5-(carboxymethoxy)-3,4-dihydroisoquinolin-2(1H)-yl]-3-[1-({3,5-dimethyl-7-[2-(methylamino)ethoxy]tricyclo[3.3.1.1^{3,7}]dec-1-yl}methyl)-5-methyl-1H-pyrazol-4-yl]pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3-{2-[(3-carboxypropyl)(piperidin-4-yl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)naphthalen-2-yl]-3-{1-[(3,5-dimethyl-7-{2-[(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

3-{1-[(3-{2-[L-alpha-aspartyl(2-sulfoethyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}-6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3-{2-[(1,3-dihydroxypropan-2-yl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[5-(2-aminoethoxy)-8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3,5-dimethyl-7-{2-[methyl(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-5-{2-[(2-sulfoethyl)amino]ethoxy}-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3,5-dimethyl-7-{2-[methyl(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3,5-dimethyl-7-{2-[(2-sulfoethyl){2-[(2-sulfoethyl)amino]ethyl}amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-5-{2-[(2-carboxyethyl)amino]ethoxy}-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3,5-dimethyl-7-{2-[methyl(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

3-{1-[(3,5-dimethyl-7-{2-[(3-phosphonopropyl)(piperidin-4-yl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}-6-[8-

([1,3]thiazolo[4,5-b]pyridin-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]pyridine-2-carboxylic acid;

6-[4-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydro-2H-1,4-benzoxazin-6-yl]-3-{1-[(3,5-dimethyl-7-{2-[(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-5-(3-sulfopropoxy)-3,4-dihydroisoquinolin-2(1H)-yl]-3-[1-({3,5-dimethyl-7-[2-(methylamino)ethoxy]tricyclo[3.3.1.1^{3,7}]dec-1-yl}methyl)-5-methyl-1H-pyrazol-4-yl]pyridine-2-carboxylic acid;

3-{1-[(3,5-dimethyl-7-{2-[(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}-6-[1-([1,3]thiazolo[4,5-b]pyridin-2-ylcarbamoyl)-1,2,3,4-tetrahydroquinolin-7-yl]pyridine-2-carboxylic acid;

3-{1-[(3,5-dimethyl-7-{2-[(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}-6-[8-([1,3]thiazolo[4,5-b]pyridin-2-ylcarbamoyl)naphthalen-2-yl]pyridine-2-carboxylic acid;

(1ξ)-1-({2-[5-(1-{[3-(2-aminoethoxy)-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl]methyl}-5-methyl-1*H*-pyrazol-4-yl)-6-carboxypyridin-2-yl]-8-(1,3-benzothiazol-2-ylcarbamoyl)-1,2,3,4-tetrahydroisoquinolin-5-yl}methyl)-1,5-anhydro-D-glucitol;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3-{2-[(3-carboxypropyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)naphthalen-2-yl]-3-{1-[(3,5-dimethyl-7-{2-[(3-phosphonopropyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-(1-{[3-(2-{[4-(beta-D-glucopyranosyloxy)benzyl]amino}ethoxy)-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl]methyl}-5-methyl-1H-pyrazol-4-yl)pyridine-2-carboxylic acid;

3-(1-{[3-(2-{[4-(beta-D-allopyranosyloxy)benzyl]amino}ethoxy)-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl]methyl}-5-methyl-1H-pyrazol-4-yl)-6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]pyridine-2-carboxylic acid;

3-{1-[(3-{2-[azetidin-3-yl(2-sulfoethyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}-6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]pyridine-2-carboxylic acid;

3-{1-[(3-{2-[(3-aminopropyl)(2-sulfoethyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}-6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]pyridine-2-carboxylic acid;

6-[1-(1,3-benzothiazol-2-ylcarbamoyl)-1,2,3,4-tetrahydroquinolin-7-yl]-3-{1-[(3-{2-[(2-carboxyethyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3-{2-[(N^6,N^6-dimethyl-L-lysyl)(methyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

3-{1-[(3-{2-[(3-aminopropyl)(methyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}-6-[1-(1,3-benzothiazol-2-ylcarbamoyl)-1,2,3,4-tetrahydroquinolin-7-yl]pyridine-2-carboxylic acid;

3-{1-[(3-{2-[azetidin-3-yl(methyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}-6-[1-(1,3-benzothiazol-2-ylcarbamoyl)-1,2,3,4-tetrahydroquinolin-7-yl]pyridine-2-carboxylic acid;

N^6-(37-oxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxaheptatriacontan-37-yl)-L-lysyl-N-[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl]-L-alaninamide;

methyl 6-[4-(3-{[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl]amino}propyl)-1H-1,2,3-triazol-1-yl]-6-deoxy-beta-L-glucopyranoside;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)naphthalen-2-yl]-3-{1-[(3-{2-[(2-carboxyethyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[5-(1,3-benzothiazol-2-ylcarbamoyl)quinolin-3-yl]-3-{1-[(3,5-dimethyl-7-{2-[(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[4-(1,3-benzothiazol-2-ylcarbamoyl)quinolin-6-yl]-3-{1-[(3,5-dimethyl-7-{2-[(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[5-(1,3-benzothiazol-2-ylcarbamoyl)quinolin-3-yl]-3-{1-[(3-{2-[(2-carboxyethyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[1-(1,3-benzothiazol-2-ylcarbamoyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl]-3-{1-[(3,5-dimethyl-7-{2-[(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

8-(1,3-benzothiazol-2-ylcarbamoyl)-2-{6-carboxy-5-[1-({3-[2-({3-[1-(beta-D-glucopyranuronosyl)-1H-1,2,3-triazol-4-yl]propyl}amino)ethoxy]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}methyl)-5-methyl-1H-pyrazol-4-yl]pyridin-2-yl}-1,2,3,4-tetrahydroisoquinoline;

6-[7-(1,3-benzothiazol-2-ylcarbamoyl)-1H-indol-2-yl]-3-{1-[(3,5-dimethyl-7-{2-[(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-6-[3-(methylamino)propyl]-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3,5-dimethyl-7-{2-[(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

5-{[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl]amino}-5-deoxy-D-arabinitol;

1-{[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl]amino}-1,2-dideoxy-D-arabino-hexitol;

6-[4-(1,3-benzothiazol-2-ylcarbamoyl)isoquinolin-6-yl]-3-{1-[(3,5-dimethyl-7-{2-[(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-(1-{[3-(2-{[3-hydroxy-2-(hydroxymethyl)propyl]amino}ethoxy)-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl]methyl}-5-methyl-1H-pyrazol-4-yl)pyridine-2-carboxylic acid;

1-{[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl]amino}-1,2-dideoxy-D-erythro-pentitol;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-(1-{[3,5-dimethyl-7-(2-{[(2S,3S)-2,3,4-trihydroxybutyl]amino}ethoxy)tricyclo[3.3.1.1^{3,7}]dec-1-yl]methyl}-5-methyl-1H-pyrazol-4-yl)pyridine-2-carboxylic acid;

6-[8 -(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-(1-{[3-(2-{[(2S,3S,4R,5R,6R)-2,3,4,5,6,7-hexahydroxyheptyl]amino}ethoxy)-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl]methyl}-5-methyl-1H-pyrazol-4-yl)pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3-{2-[({3-[(1,3-dihydroxypropan-2-yl)amino]propyl}sulfonyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3-{2-[(3-{[1,3-dihydroxy-2-(hydroxymethyl)propan-2-yl]amino}-3-oxopropyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]-3-(1-{[3-(2-{[(3*S*)-3,4-dihydroxybutyl]amino}ethoxy)-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl]methyl}-5-methyl-1*H*-pyrazol-4-yl)pyridine-2-carboxylic acid;

4-({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl]amino}methyl)phenyl beta-D-glucopyranosiduronic acid;

3-{[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)naphthalen-2-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl]amino}propyl beta-D-glucopyranosiduronic acid;

6-[4-(1,3-benzothiazol-2-ylcarbamoyl)-2-oxidoisoquinolin-6-yl]-3-[1-({3,5-dimethyl-7-[2-(methylamino)ethoxy]tricyclo[3.3.1.1^{3,7}]dec-1-yl}methyl)-5-methyl-1H-pyrazol-4-yl]pyridine-2-carboxylic acid;

6-{8-[(1,3-benzothiazol-2-yl)carbamoyl]-3,4-dihydroisoquinolin-2(1H)-yl}-3-{1-[(3,5-dimethyl-7-{2-[(2-sulfoethyl)amino]acetamido}tricyclo[3.3.1.1^{3,7}]decan-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]-3-(1-{[3,5-dimethyl-7-({2-[(2-sulfoethyl)amino]ethyl}sulfanyl)tricyclo[3.3.1.1^{3,7}]dec-1-yl]methyl}-5-methyl-1*H*-pyrazol-4-yl)pyridine-2-carboxylic acid; and

6-{8-[(1,3-benzothiazol-2-yl)carbamoyl]-3,4-dihydroisoquinolin-2(1*H*)-yl}-3-{1-[(3,5-dimethyl-7-{3-[(2-sulfoethyl)amino]propyl}tricyclo[3.3.1.1^{3,7}]decan-1-yl)methyl]-5-methyl-1*H*-pyrazol-4-yl}pyridine-2-carboxylic acid;

and a pharmaceutically acceptable salt thereof.

The Bcl-xL inhibitors bind to and inhibit anti-apoptotic Bcl-xL proteins, inducing apoptosis. The ability of specific Bcl-xL inhibitors according to structural formulae (IIa)-(IId) to bind to and inhibit Bcl-xL activity may be confirmed in standard binding and activity assays, including, for example, the TR-FRET Bcl-xL binding assays described in Tao *et al.*, 2014, ACS Med. Chem. Lett., 5:1088-1093. A specific TR-FRET Bcl-xL binding assay that can be used to confirm Bcl-xL binding is provided in Example 4, below. Typically, Bcl-xL inhibitors useful as inhibitors *per se* and in the ADCs described herein will exhibit a K_i in the binding assay of Example 5 of less than about 1 nM, but may exhibit a significantly lower K_i, for example a K_i of less than about 1, 0.1, or even 0.01 nM.

Bcl-xL inhibitory activity may also be confirmed in standard cell-based cytotoxicity assays, such as the FL5.12 cellular and Molt-4 cytotoxicity assays described in Tao *et al.*, 2014, ACS Med. Chem. Lett., 5:1088-1093. A specific Molt-4 cellular cytotoxicity assay that may be used to confirm Bcl-xL inhibitory activity of specific Bcl-xL inhibitors that are able to permeate cell membranes is provided in Examples 5 and 6, below. Typically, such cell-permeable Bcl-xL inhibitors will exhibit an EC_{50} of less than about 500 nM in the Molt-4 cytotoxicity assay of Examples 5 and 6, but may

exhibit a significantly lower EC_{50}, for example an EC_{50} of less than about 250, 100, 50, 20, 10 or even 5 nM.

Owing to the presence of solubilizing groups, many of the Bcl-xL inhibitors described herein are expected to exhibit low or very low cell permeability, and therefore will not yield significant activity in certain cellular assays due to the inability of the compound to traverse the cell membrane, including the Molt-4 cellular toxicity assay of Examples 5 and 6. Bcl-xL inhibitory activity of compounds that do not freely traverse cell membranes may be confirmed in cellular assays with permeabilized cells. The process of mitochondrial outer-membrane permeabilization (MOMP) is controlled by the Bcl-2 family proteins. Specifically, MOMP is promoted by the pro-apoptotic Bcl-2 family proteins Bax and Bak which, upon activation oligomerize on the outer mitochondrial membrane and form pores, leading to release of cytochrome c (cyt c). The release of cyt c triggers formulation of the apoptosome which, in turn, results in caspase activation and other events that commit the cell to undergo programmed cell death (*see*, Goldstein *et al.*, 2005, *Cell Death and Differentiation* 12:453-462). The oligomerization action of Bax and Bak is antagonized by the anti-apoptotic Bcl-2 family members, including Bcl-2 and Bcl-xL. Bcl-xL inhibitors, in cells that depend upon Bcl-xL for survival, can cause activation of Bax and/or Bak, MOMP, release of cyt c and downstream events leading to apoptosis. The process of cyt c release can be measured via western blot of both mitochondrial and cytosolic fractions of cells and used as a proxy measurement of apoptosis in cells.

As a means of detecting Bcl-xL inhibitory activity and consequent release of cyt c for Bcl-xL inhibitors with low cell permeability, the cells can be treated with an agent that causes selective pore formation in the plasma, but not mitochondrial, membrane. Specifically, the cholesterol/phospholipid ratio is much higher in the plasma membrane than the mitochondrial membrane. As a result, short incubation with low concentrations of the cholesterol-directed detergent digitonin selectively permeabilizes the plasma membrane without significantly affecting the mitochondrial membrane. This agent forms insoluble complexes with cholesterol leading to the segregation of cholesterol from its normal phospholipid binding sites. This action, in turn, leads to the formation of holes about 40-50 Å wide in the lipid bilayer. Once the plasma membrane is permeabilized, cytosolic components able to pass over digitonin-formed holes can be washed out, including the cytochrome C that was released from mitochondria to cytosol in the apoptotic cells (Campos, 2006, *Cytometry A* 69(6):515-523).

Typically, Bcl-xL inhibitors will yield an EC_{50} of less than about 10 nM in the Molt-4 cell permeabilized cyt c assay of Examples 5 and 6, although the compounds may exhibit significantly lower EC_{50}s, for example, less than about 5, 1, or even 0.5 nM. As demonstrated in Example 6, Bcl-xL inhibitors having low or very low cell permeability that do not exhibit activity in the standard Molt-4 cellular toxicity assay with non-permeablized cells exhibit potent functional activity, as measured by release of cyt c, in cellular cytotoxicity assays with permeabilized cells. In addition to cytochrome c release, mitochondria undergoing apoptosis frequently lose their transmembrane

mitochondrial membrane potential (Bouchier-Hayes *et al.,* 2008, *Methods* 44(3): 222-228). JC-1 is a cationic carbocyanine dye that accumulates in mitochondria and fluoresces red when mitochondria are healthy and is lost when the mitochondrial membrane is compromised (percentage depolarization; Smiley *et al.,* 1991, *Proc. Natl. Acad. Sci. USA*, 88: 3671-3675; Reers *et al.,* 1991: *Biochemistry*, 30: 4480-4486). This loss in signal can be detected in permeabilized cells using a fluorimeter (excitation 545 nm and emission of 590 nm) and is therefore fully quantitative, enhancing both reproducibility and throughput. Typically, Bcl-xL inhibitors will yield an EC_{50} of less than about 10 nM in the Molt-4 cell permeabilized JC-1 assay of Examples 5 and 6, although the compounds may exhibit significantly lower EC_{50}s, for example, less than about 5, 1, 0.5 or even 0.05 nM. As demonstrated in Example 6, Bcl-xL inhibitors having low or very low cell permeability that do not exhibit activity in the standard Molt-4 cellular toxicity assay with non-permeablized cells exhibit potent functional activity, as measured by their loss of transmembrane mitochondrial membrane potential in the JC-1 assay, in cellular cytotoxicity assays with permeabilized cells. Low permeability Bcl-xL inhibitors also exhibit potent activity when administered to cells in the form of ADCs (*see, e.g.,* Example 8).

Although many of the Bcl-xL inhibitors of structural formulae (IIa)-(IId) selectively or specifically inhibit Bcl-xL over other anti-apoptotic Bcl-2 family proteins, selective and/or specific inhibition of Bcl-xL is not necessary. The Bcl-xL inhibitors and ADCs comprising the compounds may also, in addition to inhibiting Bcl-xL, inhibit one or more other anti-apoptotic Bcl-2 family proteins, such as, for example, Bcl-2. In some embodiments, the Bcl-xL inhibitors and/or ADCs are selective and/or specific for Bcl-xL. By specific or selective is meant that the particular Bcl-xL inhibitor and/or ADC binds or inhibits Bcl-xL to a greater extent than Bcl-2 under equivalent assay conditions. In specific embodiments, the Bcl-xL inhibitors and/or ADCs exhibit in the range of about 10-fold, 100-fold, or even greater specificity or selectivity for Bcl-xL than Bcl-2 in binding assays.

III.A.2. Bcl-xL Linkers

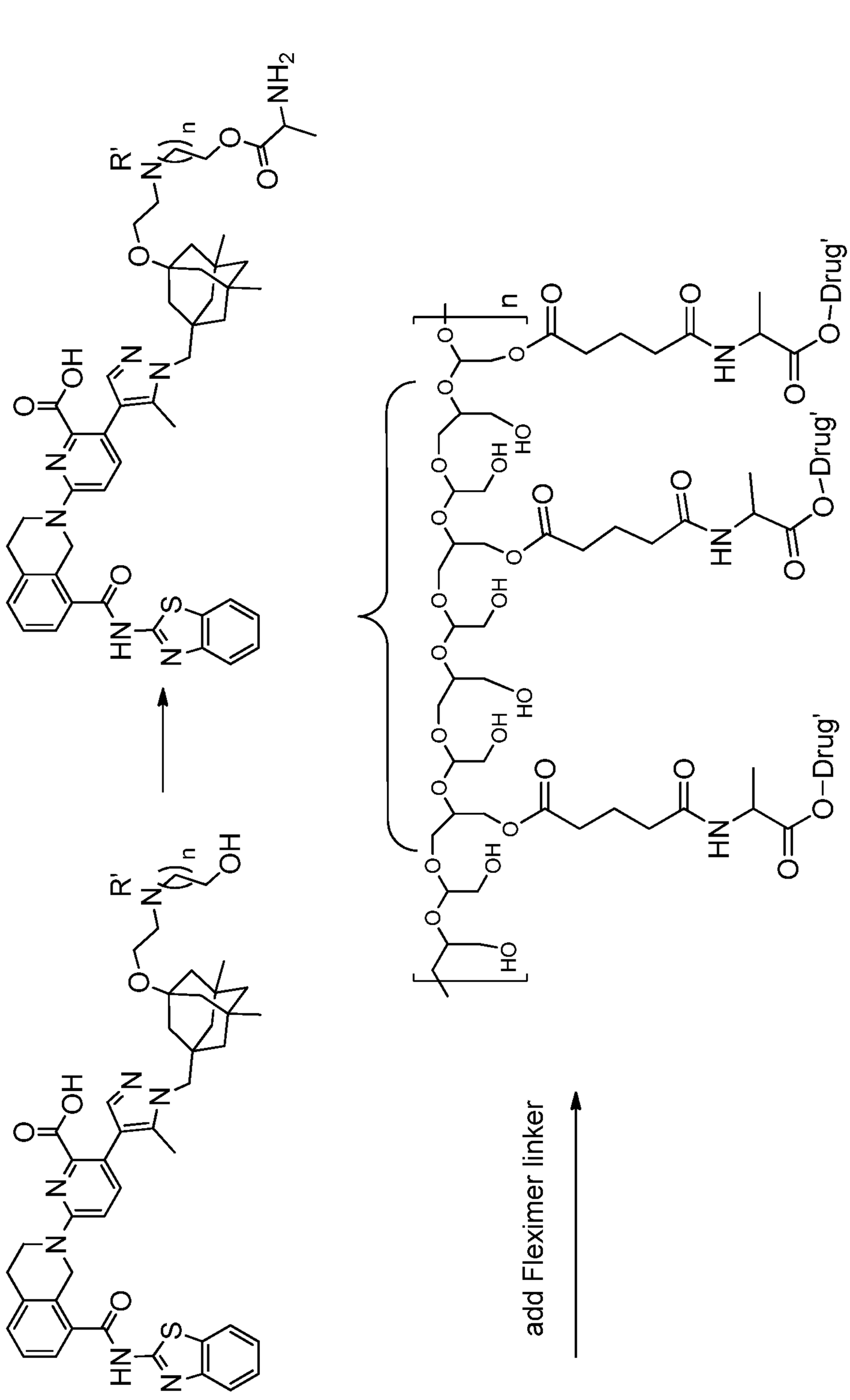
In the ADCs described herein, the Bcl-xL inhibitors are linked to the antibody by way of linkers. The linker linking a Bcl-xL inhibitor to the antibody of an ADC may be short, long, hydrophobic, hydrophilic, flexible or rigid, or may be composed of segments that each independently has one or more of the above-mentioned properties such that the linker may include segments having different properties. The linkers may be polyvalent such that they covalently link more than one Bcl-xL inhibitor to a single site on the antibody, or monovalent such that covalently they link a single Bcl-xL inhibitor to a single site on the antibody.

As will be appreciated by skilled artisans, the linkers link the Bcl-xL inhibitors to the antibody by forming a covalent linkage to the Bcl-xL inhibitor at one location and a covalent linkage to antibody at another. The covalent linkages are formed by reaction between functional groups on the linker and functional groups on the inhibitors and antibody. As used herein, the expression "linker" is intended to include (i) unconjugated forms of the linker that include a functional group capable of covalently linking the linker to a Bcl-xL inhibitor and a functional group capable of

covalently linking the linker to an antibody; (ii) partially conjugated forms of the linker that include a functional group capable of covalently linking the linker to an antibody and that is covalently linked to a Bcl-xL inhibitor, or *vice versa*; and (iii) fully conjugated forms of the linker that is covalently linked to both a Bcl-xL inhibitor and an antibody. In some specific embodiments of intermediate synthons and ADCs described herein, moieties comprising the functional groups on the linker and covalent linkages formed between the linker and antibody are specifically illustrated as R^x and LK, respectively.

The linkers are preferably, but need not be, chemically stable to conditions outside the cell, and may be designed to cleave, immolate and/or otherwise specifically degrade inside the cell. Alternatively, linkers that are not designed to specifically cleave or degrade inside the cell may be used. A wide variety of linkers useful for linking drugs to antibodies in the context of ADCs are known in the art. Any of these linkers, as well as other linkers, may be used to link the Bcl-xL inhibitors to the antibody of the ADCs described herein.

Exemplary polyvalent linkers that may be used to link many Bcl-xL inhibitors to an antibody are described, for example, in U.S. Patent No 8,399,512; U.S. Published Application No. 2010/0152725; U.S. Patent No. 8,524,214; U.S. Patent No. 8,349,308; U.S. Published Application No. 2013/189218; U.S. Published Application No. 2014/017265; WO 2014/093379; WO 2014/093394; WO 2014/093640, the contents of which are incorporated herein by reference in their entireties. For example, the Fleximer® linker technology developed by Mersana *et al.* has the potential to enable high-DAR ADCs with good physicochemical properties. As shown below, the Fleximer® linker technology is based on incorporating drug molecules into a solubilizing poly-acetal backbone via a sequence of ester bonds. The methodology renders highly-loaded ADCs (DAR up to 20) whilst maintaining good physicochemical properties. This methodology could be utilized with Bcl-xL inhibitors as shown in the Scheme below.


add Fleximer linker

To utilize the Fleximer® linker technology depicted in the scheme above, an aliphatic alcohol can be present or introduced into the Bcl-xL inhibitor. The alcohol moiety is then conjugated to an alanine moiety, which is then synthetically incorporated into the Fleximer® linker. Liposomal processing of the ADC *in vitro* releases the parent alcohol –containing drug.

Additional examples of dendritic type linkers can be found in US 2006/116422; US 2005/271615; de Groot *et al.*, (2003) *Angew. Chem. Int. Ed.* 42:4490-4494; Amir *et al.*, (2003) *Angew. Chem. Int. Ed.* 42:4494-4499; Shamis *et al.*, (2004) J. Am. Chem. Soc. 126:1726-1731 ; Sun *et al.*, (2002) *Bioorganic & Medicinal Chemistry Letters* 12:2213-2215; Sun *et al.*, (2003) *Bioorganic & Medicinal Chemistry* 11:1761-1768; King *et al.*, (2002) Tetrahedron Letters 43:1987-1990.

Exemplary monovalent linkers that may be used are described, for example, in Nolting, 2013, Antibody-Drug Conjugates, Methods in Molecular Biology 1045:71-100; Kitson *et al.*, 2013, *CROs/CMOs - Chemica Oggi – Chemistry Today* 31(4): 30-36; Ducry *et al.*, 2010, *Bioconjugate Chem.* 21:5-13; Zhao *et al.*, 2011, J. Med. Chem. 54:3606-3623; U.S. Patent No. 7,223,837; U.S. Patent No. 8,568,728; U.S. Patent No. 8,535,678; and WO2004010957, the content of each of which is incorporated herein by reference in their entireties.

By way of example and not limitation, some cleavable and noncleavable linkers that may be included in the ADCs described herein are described below.

Cleavable Linkers

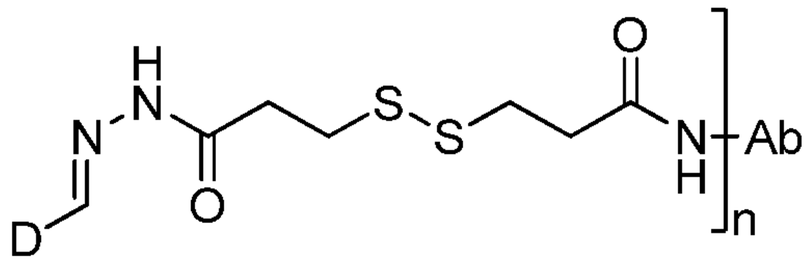
In certain embodiments, the linker selected is cleavable *in vitro* and *in vivo*. Cleavable linkers may include chemically or enzymatically unstable or degradable linkages. Cleavable linkers generally rely on processes inside the cell to liberate the drug, such as reduction in the cytoplasm, exposure to acidic conditions in the lysosome, or cleavage by specific proteases or other enzymes within the cell. Cleavable linkers generally incorporate one or more chemical bonds that are either chemically or enzymatically cleavable while the remainder of the linker is noncleavable.

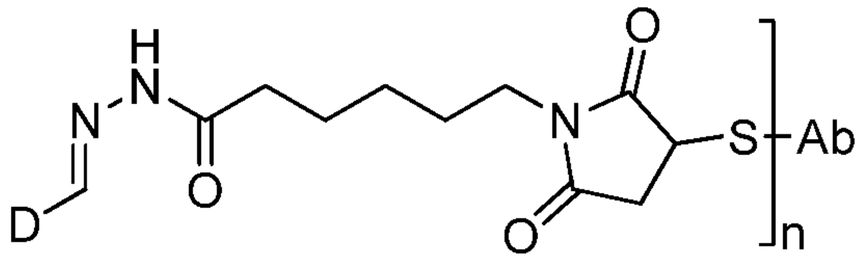
In certain embodiments, a linker comprises a chemically labile group such as hydrazone and/or disulfide groups. Linkers comprising chemically labile groups exploit differential properties between the plasma and some cytoplasmic compartments. The intracellular conditions to facilitate drug release for hydrazone containing linkers are the acidic environment of endosomes and lysosomes, while the disulfide containing linkers are reduced in the cytosol, which contains high thiol concentrations, *e.g.*, glutathione. In certain embodiments, the plasma stability of a linker comprising a chemically labile group may be increased by introducing steric hindrance using substituents near the chemically labile group.

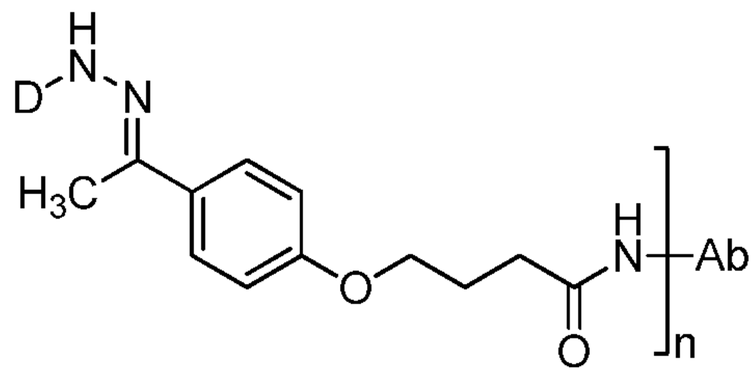
Acid-labile groups, such as hydrazone, remain intact during systemic circulation in the blood's neutral pH environment (pH 7.3-7.5) and undergo hydrolysis and release the drug once the ADC is internalized into mildly acidic endosomal (pH 5.0-6.5) and lysosomal (pH 4.5-5.0) compartments of the cell. This pH dependent release mechanism has been associated with nonspecific

release of the drug. To increase the stability of the hydrazone group of the linker, the linker may be varied by chemical modification, *e.g.*, substitution, allowing tuning to achieve more efficient release in the lysosome with a minimized loss in circulation.

Hydrazone-containing linkers may contain additional cleavage sites, such as additional acid-labile cleavage sites and/or enzymatically labile cleavage sites. ADCs including exemplary hydrazone-containing linkers include the following structures:

(Ig) 

(Ih) 

(Ii) 

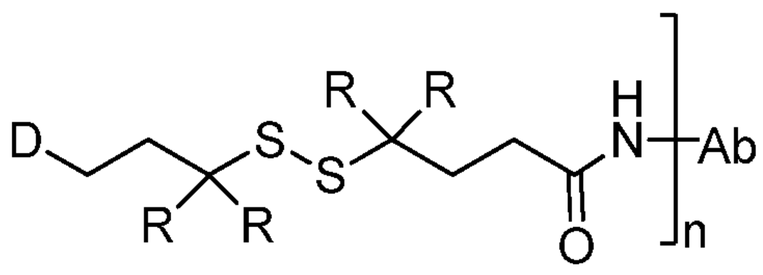
wherein D and Ab represent the drug and Ab, respectively, and n represents the number of drug-linkers linked to the antibody. In certain linkers such as linker (Ig), the linker comprises two cleavable groups – a disulfide and a hydrazone moiety. For such linkers, effective release of the unmodified free drug requires acidic pH or disulfide reduction and acidic pH. Linkers such as (Ih) and (Ii) have been shown to be effective with a single hydrazone cleavage site.

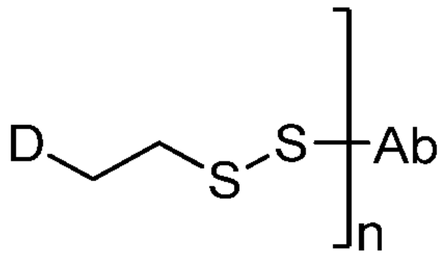
Other acid-labile groups that may be included in linkers include *cis*-aconityl-containing linkers. *cis*-Aconityl chemistry uses a carboxylic acid juxtaposed to an amide bond to accelerate amide hydrolysis under acidic conditions.

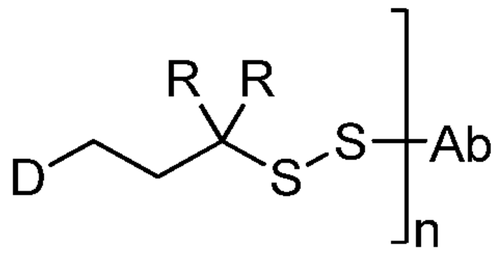
Cleavable linkers may also include a disulfide group. Disulfides are thermodynamically stable at physiological pH and are designed to release the drug upon internalization inside cells, wherein the cytosol provides a significantly more reducing environment compared to the extracellular environment. Scission of disulfide bonds generally requires the presence of a cytoplasmic thiol

cofactor, such as (reduced) glutathione (GSH), such that disulfide-containing linkers are reasonable stable in circulation, selectively releasing the drug in the cytosol. The intracellular enzyme protein disulfide isomerase, or similar enzymes capable of cleaving disulfide bonds, may also contribute to the preferential cleavage of disulfide bonds inside cells. GSH is reported to be present in cells in the concentration range of 0.5-10 mM compared with a significantly lower concentration of GSH or cysteine, the most abundant low-molecular weight thiol, in circulation at approximately 5 μM. Tumor cells, where irregular blood flow leads to a hypoxic state, result in enhanced activity of reductive enzymes and therefore even higher glutathione concentrations. In certain embodiments, the *in vivo* stability of a disulfide-containing linker may be enhanced by chemical modification of the linker, *e.g.*, use of steric hindrance adjacent to the disulfide bond.

ADCs including exemplary disulfide-containing linkers include the following structures:

(Ij) 

(Ik) 

(Il) 

wherein D and Ab represent the drug and antibody, respectively, n represents the number of drug-linkers linked to the antibody and R is independently selected at each occurrence from hydrogen or alkyl, for example. In certain embodiments, increasing steric hindrance adjacent to the disulfide bond increases the stability of the linker. Structures such as (Ij) and (Il) show increased *in vivo* stability when one or more R groups is selected from a lower alkyl such as methyl.

Another type of linker that may be used is a linker that is specifically cleaved by an enzyme. Such linkers are typically peptide-based or include peptidic regions that act as substrates for enzymes. Peptide based linkers tend to be more stable in plasma and extracellular milieu than chemically labile linkers. Peptide bonds generally have good serum stability, as lysosomal proteolytic enzymes have

very low activity in blood due to endogenous inhibitors and the unfavorably high pH value of blood compared to lysosomes. Release of a drug from an antibody occurs specifically due to the action of lysosomal proteases, *e.g.*, cathepsin and plasmin. These proteases may be present at elevated levels in certain tumor tissues. In certain embodiments, the linker is cleavable by a lysosomal enzyme. In certain embodiments, the linker is cleavable by a lysosomal enzyme, and the lysosomal enzyme is Cathepsin B. . In certain embodiments, the linker is cleavable by a lysosomal enzyme, and the lysosomal enzyme is β-glucuronidase or β-galactosidase. In certain embodiments, the linker is cleavable by a lysosomal enzyme, and the lysosomal enzyme is β-glucuronidase. In certain embodiments, the linker is cleavable by a lysosomal enzyme, and the lysosomal enzyme is β-galactosidase.

Those skilled in the art recognize the importance of cleavable linkers that are stable to plasma, yet are readily cleaved by a lysosomal enzyme. Disclosed herein, in certain embodiments, are linkers, cleavable by the lysosomal enzymes β-glucuronidase or β-galactosidase, that show improved plasma stability and reduced non-specific release of small molecule drug.

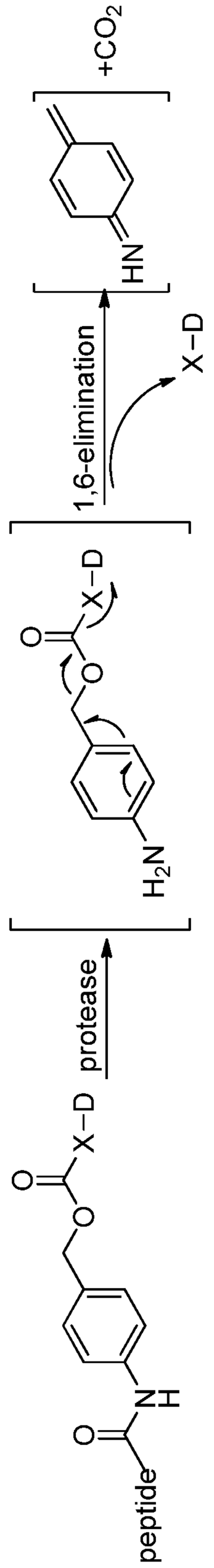
In exemplary embodiments, the cleavable peptide is selected from tetrapeptides such as Gly-Phe-Leu-Gly, Ala-Leu-Ala-Leu or dipeptides such as Val-Cit, Val-Ala, and Phe-Lys. In certain embodiments, dipeptides are preferred over longer polypeptides due to hydrophobicity of the longer peptides.

A variety of dipeptide-based cleavable linkers useful for linking drugs such as doxorubicin, mitomycin, camptothecin, tallysomycin and auristatin/auristatin family members to antibodies have been described (*see*, Dubowchik *et al.*, 1998, *J. Org. Chem.* 67:1866-1872; Dubowchik *et al.*, 1998, *Bioorg. Med. Chem. Lett.* 8:3341-3346; Walker *et al.*, 2002, *Bioorg. Med. Chem. Lett.* 12:217-219; Walker *et al.*, 2004, *Bioorg. Med. Chem. Lett.*14:4323-4327; and Francisco *et al.*, 2003, *Blood* 102:1458-1465, the contents of each of which are incorporated herein by reference). All of these dipeptide linkers, or modified versions of these dipeptide linkers, may be used in the ADCs described herein. Other dipeptide linkers that may be used include those found in ADCs such as Seattle Genetics' Brentuximab Vendotin SGN-35 (Adcetris™), Seattle Genetics SGN-75 (anti-CD-70, MC-monomethyl auristatin F(MMAF), Celldex Therapeutics glembatumumab (CDX-011) (anti-NMB, Val-Cit- monomethyl auristatin E(MMAE), and Cytogen PSMA-ADC (PSMA-ADC-1301) (anti-PSMA, Val-Cit-MMAE).

Enzymatically cleavable linkers may include a self-immolative spacer to spatially separate the drug from the site of enzymatic cleavage. The direct attachment of a drug to a peptide linker can result in proteolytic release of an amino acid adduct of the drug, thereby impairing its activity. The use of a self-immolative spacer allows for the elimination of the fully active, chemically unmodified drug upon amide bond hydrolysis.

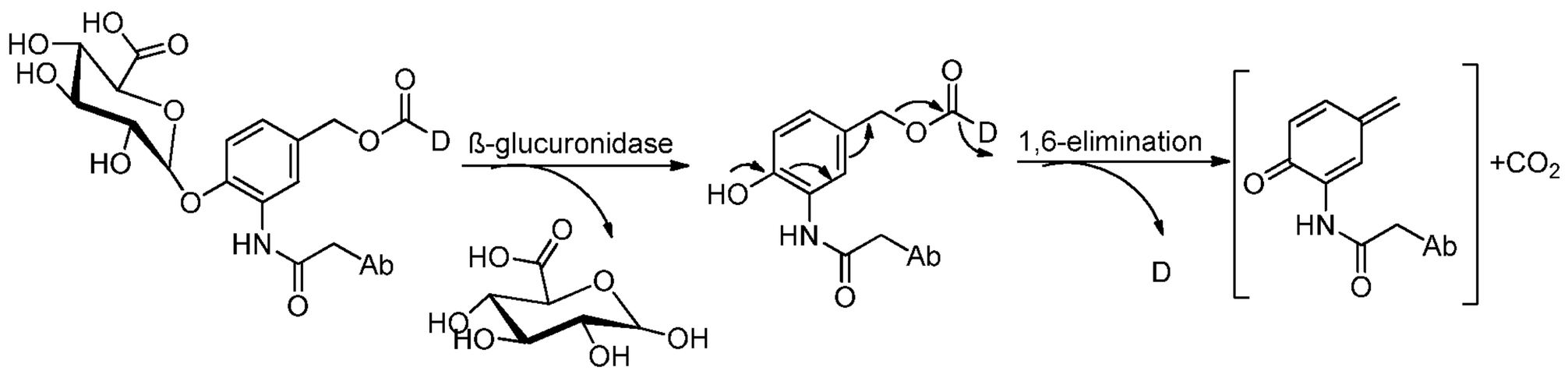
One self-immolative spacer is the bifunctional *para*-aminobenzyl alcohol group, which is linked to the peptide through the amino group, forming an amide bond, while amine containing drugs

may be attached through carbamate functionalities to the benzylic hydroxyl group of the linker (to give a *p*-amidobenzylcarbamate, PABC). The resulting prodrugs are activated upon protease-mediated cleavage, leading to a 1,6-elimination reaction releasing the unmodified drug, carbon dioxide, and remnants of the linker group. The following scheme depicts the fragmentation of *p*-amidobenzyl carbamate and release of the drug:

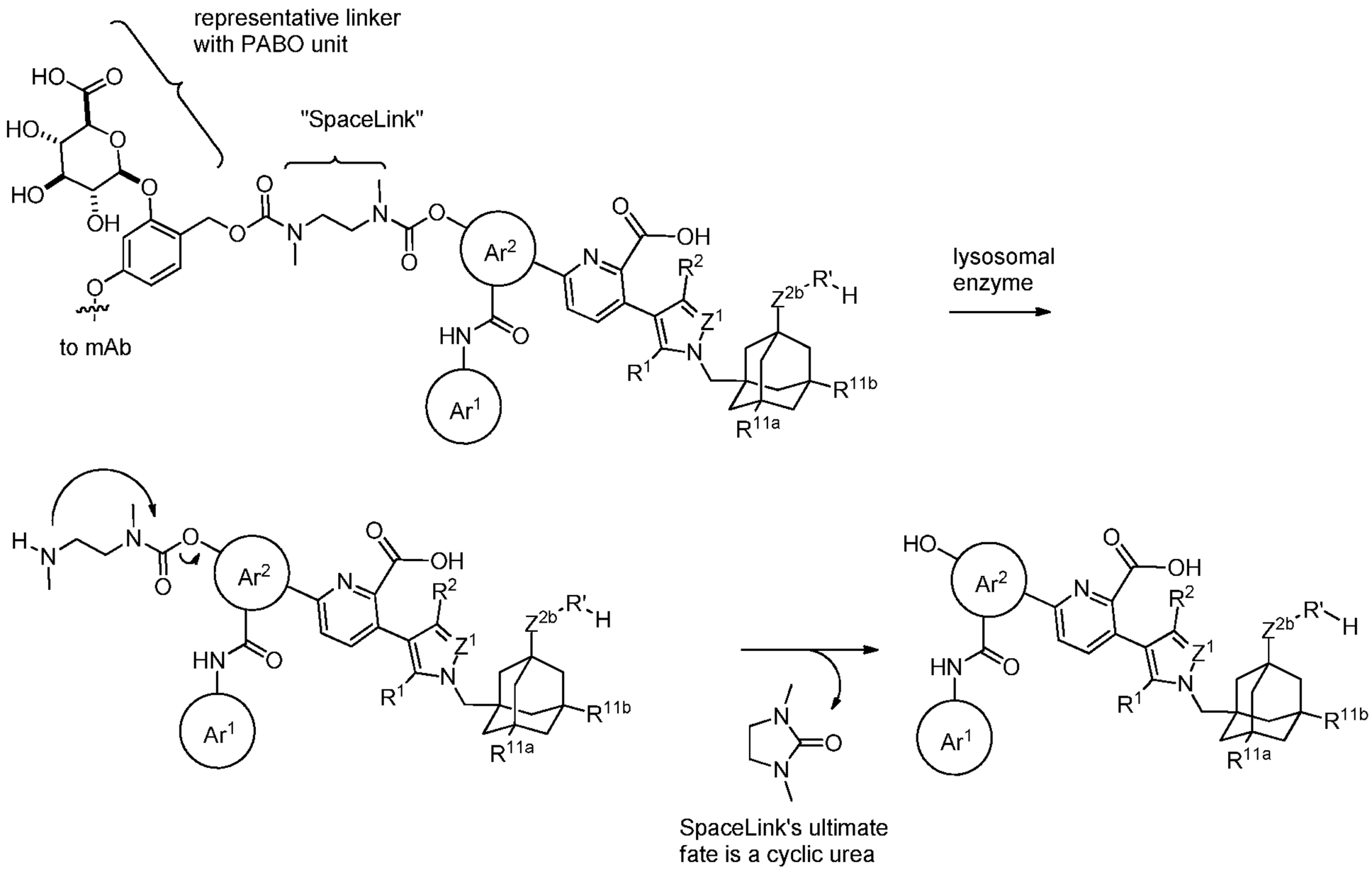

+CO2
HN
1,6-elimination
X–D
O
O
X–D
X–D
protease
H2N
O
NH
peptide

wherein X-D represents the unmodified drug. Heterocyclic variants of this self-immolative group have also been described. *See* U.S. Patent No. 7,989,434.

In certain embodiments, the enzymatically cleavable linker is a ß-glucuronic acid-based linker. Facile release of the drug may be realized through cleavage of the ß-glucuronide glycosidic bond by the lysosomal enzyme ß-glucuronidase. This enzyme is present abundantly within lysosomes and is overexpressed in some tumor types, while the enzyme activity outside cells is low. ß-Glucuronic acid-based linkers may be used to circumvent the tendency of an ADC to undergo aggregation due to the hydrophilic nature of ß-glucuronides. In certain embodiments, ß-glucuronic acid-based linkers are preferred as linkers for ADCs linked to hydrophobic drugs. The following scheme depicts the release of the drug from and ADC containing a ß-glucuronic acid-based linker:



A variety of cleavable ß-glucuronic acid-based linkers useful for linking drugs such as auristatins, camptothecin and doxorubicin analogues, CBI minor-groove binders, and psymberin to antibodies have been described (*see*, Jeffrey *et al.*, 2006, *Bioconjug. Chem.* 17:831-840; Jeffrey *et al.*, *Bioorg. Med. Chem. Lett.* 17:2278-2280; and Jiang *et al.*, 2005, *J. Am. Chem. Soc.* 127:11254-11255, the contents of each of which are incorporated herein by reference). All of these ß-glucuronic acid-based linkers may be used in the ADCs described herein. In certain embodiments, the enzymatically cleavable linker is a ß-galactoside-based linker. ß-Galactoside is present abundantly within lysosomes, while the enzyme activity outside cells is low. Additionally, Bc1-xL inhibitors containing a phenol group can be covalently bonded to a linker through the phenolic oxygen. One such linker, described in U.S. Published App. No. 2009/0318668, relies on a methodology in which a diamino-ethane "SpaceLink" is used in conjunction with traditional "PABO"-based self-immolative groups to deliver phenols. The cleavage of the linker is depicted schematically below using a Bcl-xL inhibitor of the disclosure.

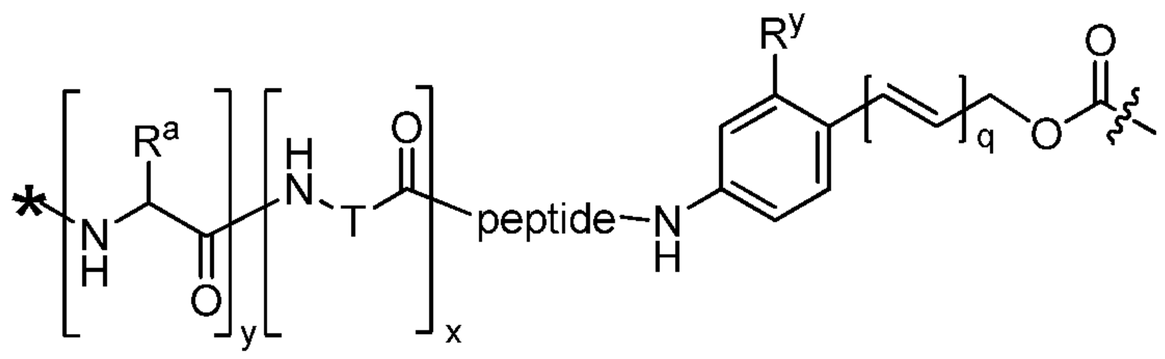


Cleavable linkers may include noncleavable portions or segments, and/or cleavable segments or portions may be included in an otherwise non-cleavable linker to render it cleavable. By way of example only, polyethylene glycol (PEG) and related polymers may include cleavable groups in the polymer backbone. For example, a polyethylene glycol or polymer linker may include one or more cleavable groups such as a disulfide, a hydrazone or a dipeptide.

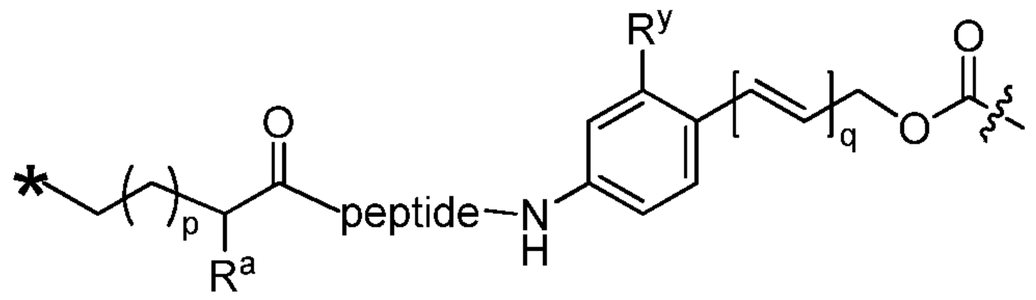
Other degradable linkages that may be included in linkers include ester linkages formed by the reaction of PEG carboxylic acids or activated PEG carboxylic acids with alcohol groups on a biologically active agent, wherein such ester groups generally hydrolyze under physiological conditions to release the biologically active agent. Hydrolytically degradable linkages include, but are not limited to, carbonate linkages; imine linkages resulting from reaction of an amine and an aldehyde; phosphate ester linkages formed by reacting an alcohol with a phosphate group; acetal linkages that are the reaction product of an aldehyde and an alcohol; orthoester linkages that are the reaction product of a formate and an alcohol; and oligonucleotide linkages formed by a phosphoramidite group, including but not limited to, at the end of a polymer, and a 5' hydroxyl group of an oligonucleotide.

In certain embodiments, the linker comprises an enzymatically cleavable peptide moiety, for example, a linker comprising structural formula (IVa), (IVb), (IVc) or (IVd):

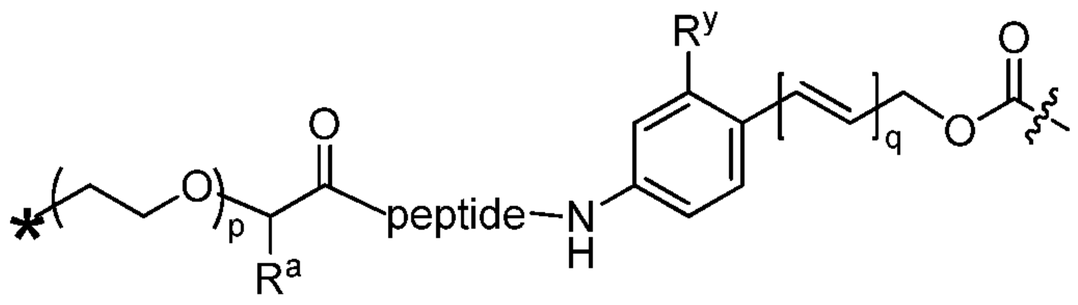
(IVa)



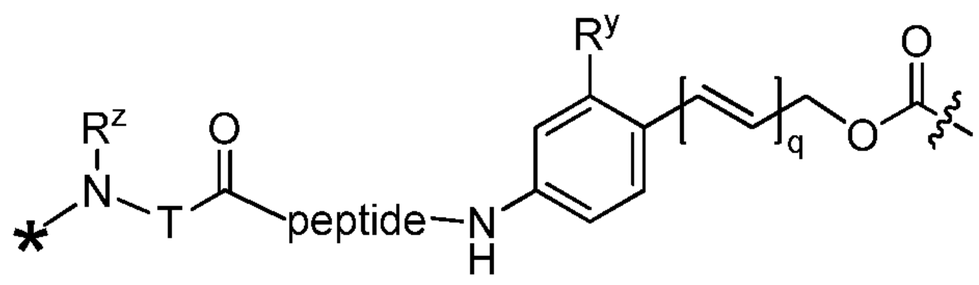
(IVb)



(IVc)



(IVd)



or a pharmaceutically acceptable salt thereof, wherein:

peptide represents a peptide (illustrated N→C, wherein peptide includes the amino and carboxy "termini") cleavable by a lysosomal enzyme;

T represents a polymer comprising one or more ethylene glycol units or an alkylene chain, or combinations thereof;

R^a is selected from hydrogen, C_{1-6} alkyl, SO_3H and CH_2SO_3H;

R^y is hydrogen or C_{1-4} alkyl-$(O)_r$-(C_{1-4} alkylene)$_s$-G^1 or C_{1-4} alkyl-(N)-[(C_{1-4} alkylene)-G^1]$_2$;

R^z is C_{1-4} alkyl-$(O)_r$-(C_{1-4} alkylene)$_s$-G^2;

G^1 is SO_3H, CO_2H, PEG 4-32, or sugar moiety;

G^2 is SO_3H, CO_2H, or PEG 4-32 moiety;

r is 0 or 1;

s is 0 or 1;

p is an integer ranging from 0 to 5;

q is 0 or 1;

x is 0 or 1;

y is 0 or 1;

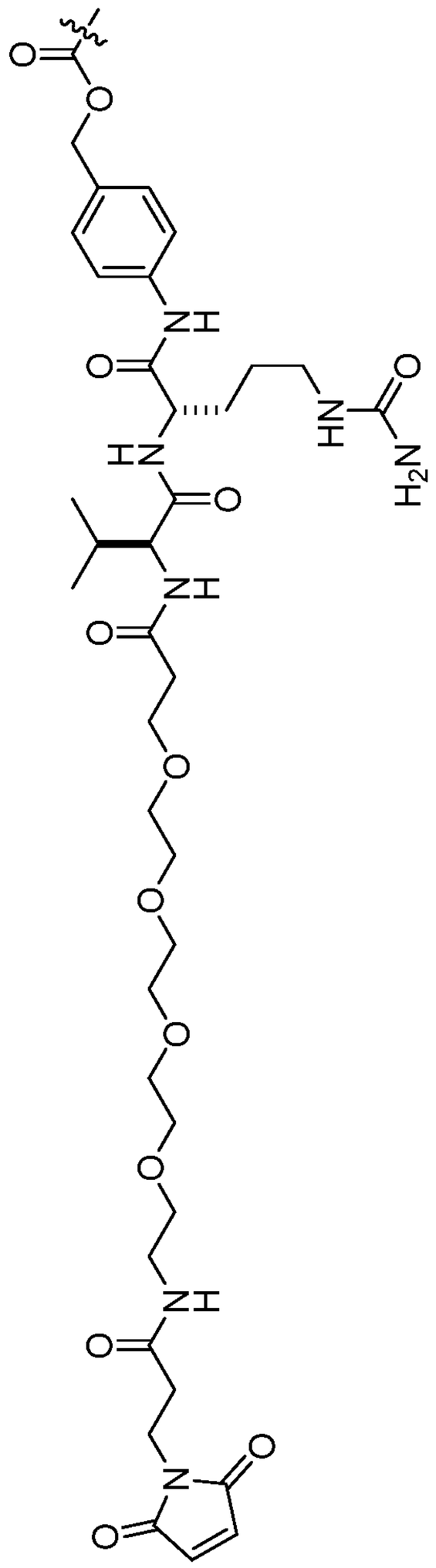
$\sim$ represents the point of attachment of the linker to the Bcl-xL inhibitor; and

* represents the point of attachment to the remainder of the linker.

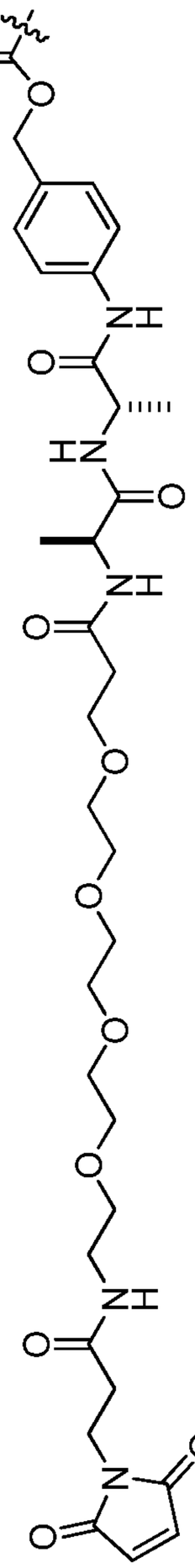
In certain embodiments, the linker comprises an enzymatically cleavable peptide moiety, for example, a linker comprising structural formula (IVa), (IVb), (IVc), or (IVd), or a pharmaceutically acceptable salt thereof.

In certain embodiments, the peptide is selected from a tripeptide or a dipeptide. In particular embodiments, the dipeptide is selected from: Val-Cit; Cit-Val; Ala-Ala; Ala-Cit; Cit-Ala; Asn-Cit; Cit-Asn; Cit-Cit; Val-Glu; Glu-Val; Ser-Cit; Cit-Ser; Lys-Cit; Cit-Lys; Asp-Cit; Cit-Asp; Ala-Val; Val-Ala; Phe-Lys; Lys-Phe; Val-Lys; Lys-Val; Ala-Lys; Lys-Ala; Phe-Cit; Cit-Phe; Leu-Cit; Cit-Leu; Ile-Cit; Cit-Ile; Phe-Arg; Arg-Phe; Cit-Trp; and Trp-Cit; or a pharmaceutically acceptable salt thereof.

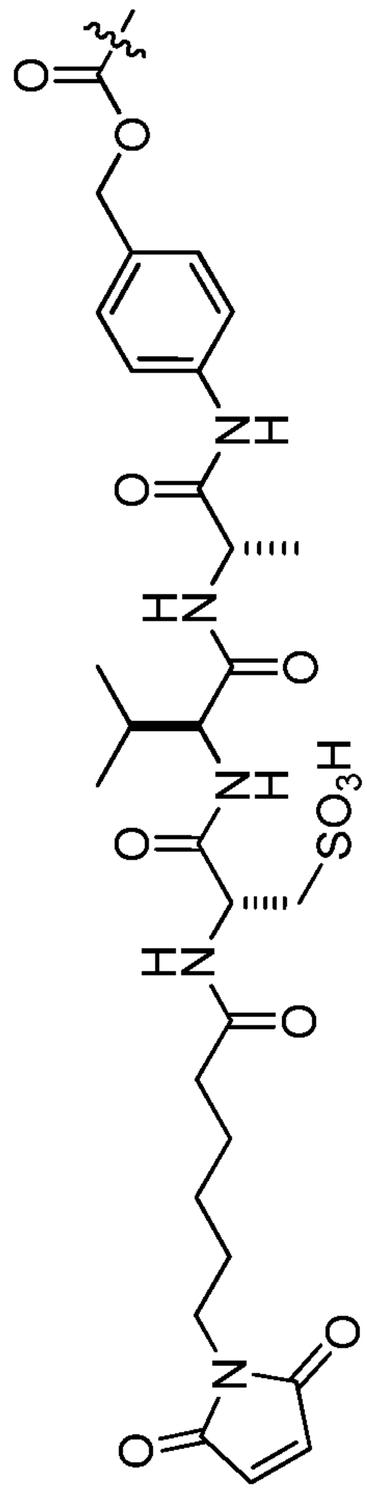
Exemplary embodiments of linkers according to structural formula (IVa) that may be included in the ADCs described herein include the linkers illustrated below (as illustrated, the linkers include a group suitable for covalently linking the linker to an antibody):



(IVa.1)



(IVa.2)

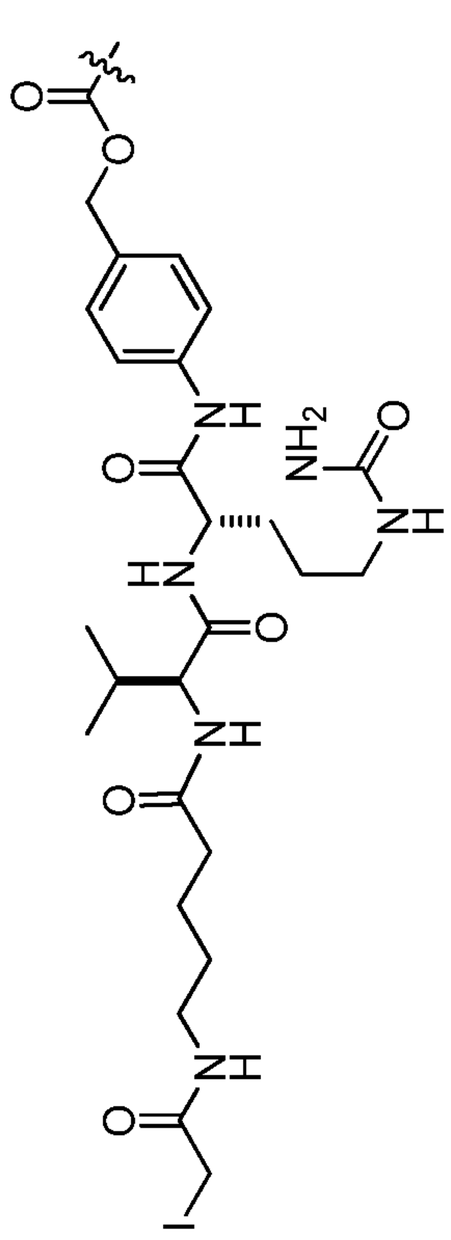


(IVa.3)

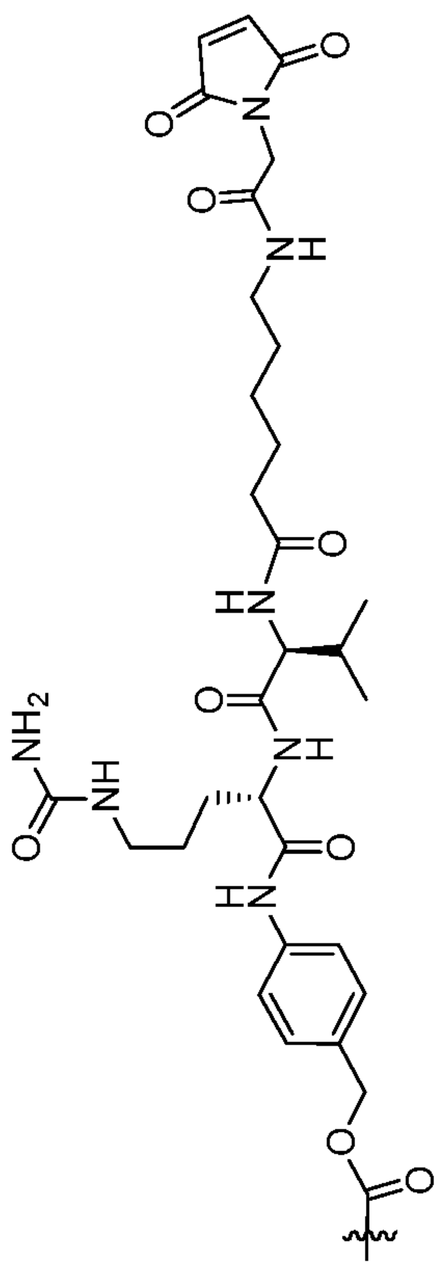
(IVa.4)

(IVa.5)

(IVa.6)



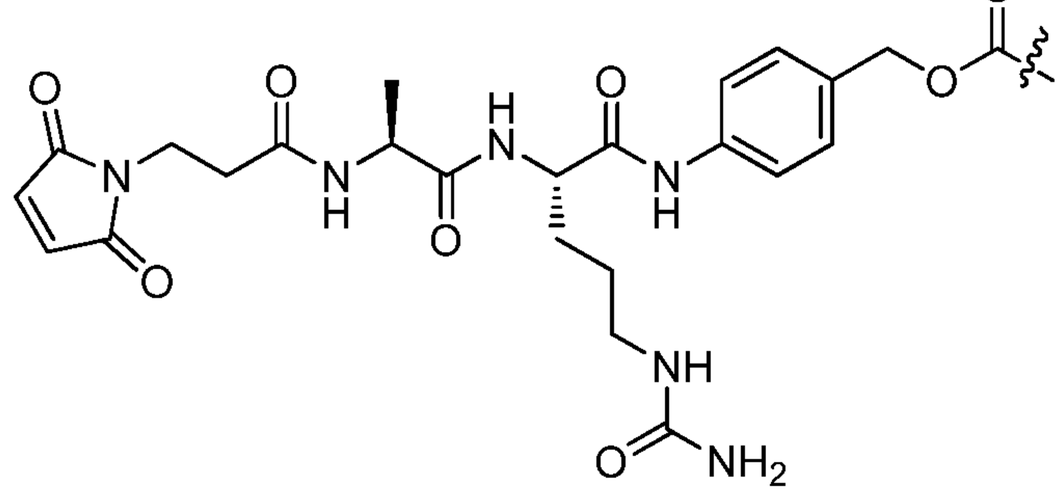
(IVa.7)



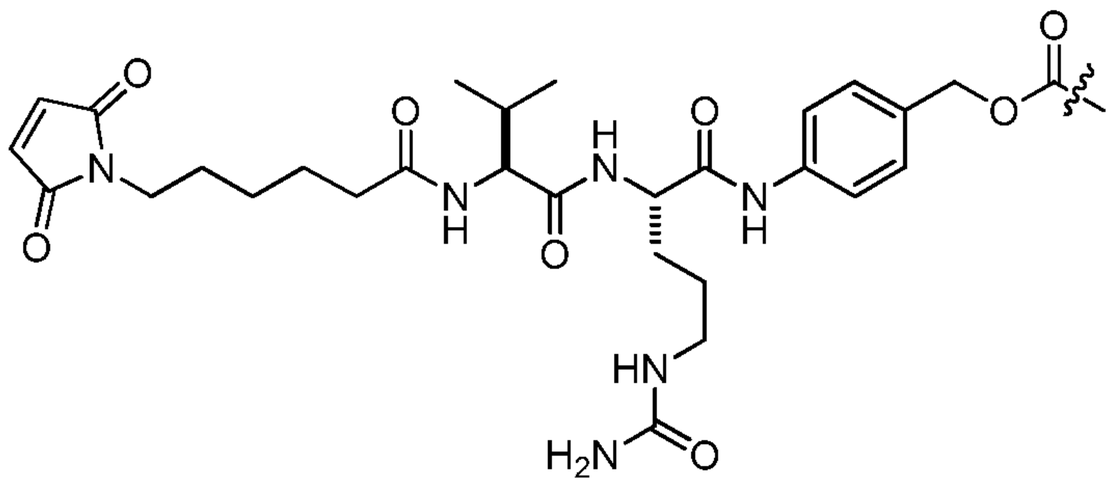
(IVa.8)

Exemplary embodiments of linkers according to structural formula (IVb), (IVc), or (IVd) that may be included in the ADCs described herein include the linkers illustrated below (as illustrated, the linkers include a group suitable for covalently linking the linker to an antibody):

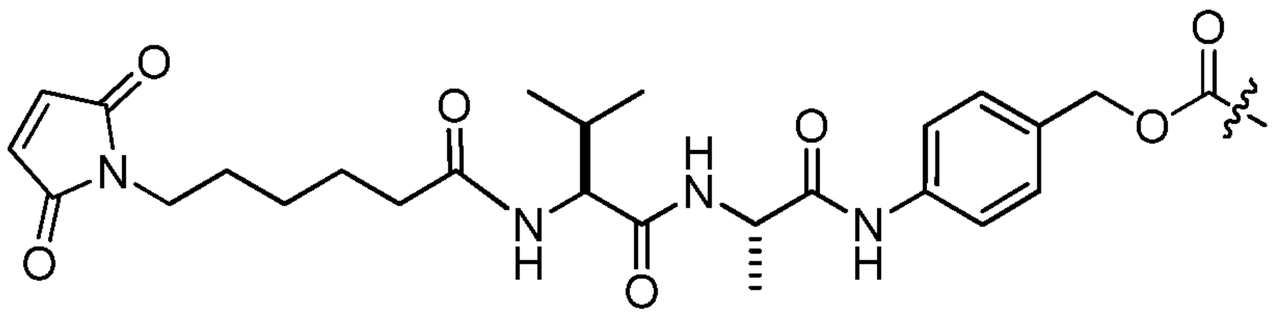
(IVb.1)



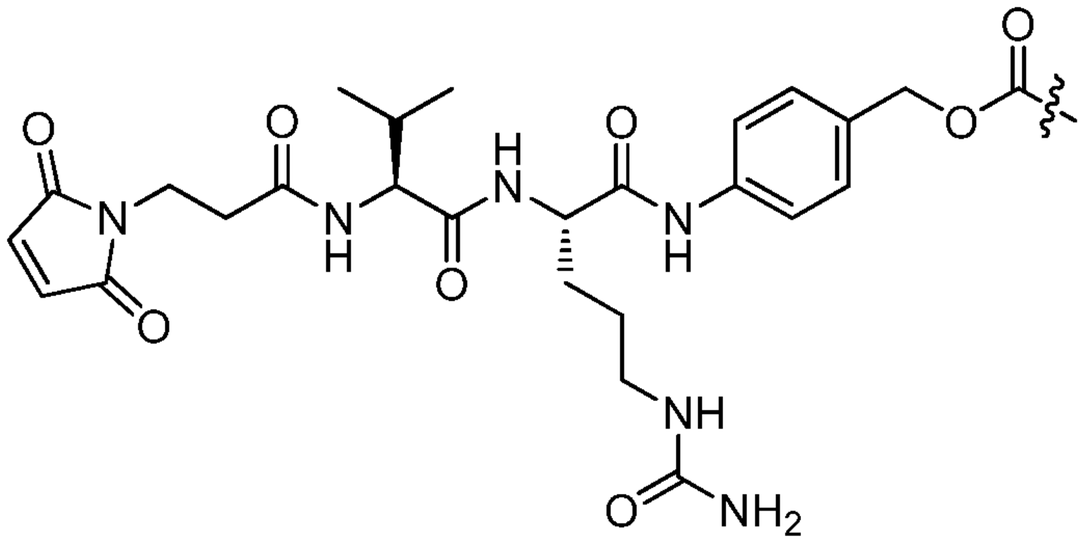
(IVb.2)



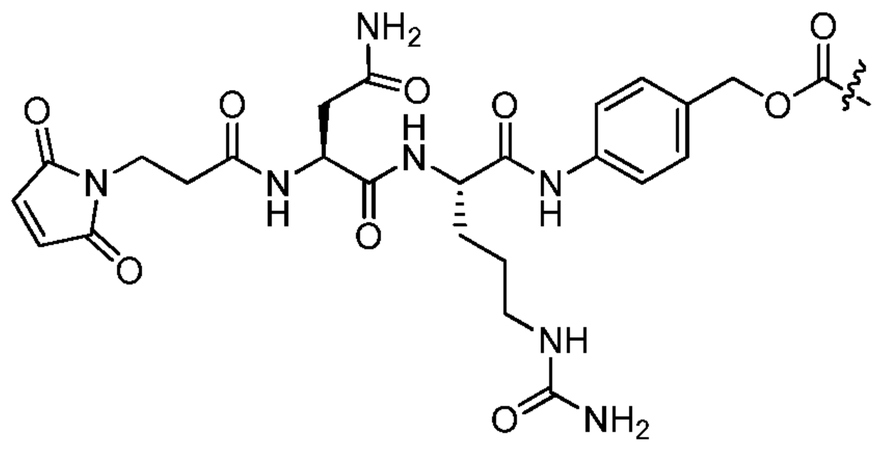
(IVb.3)



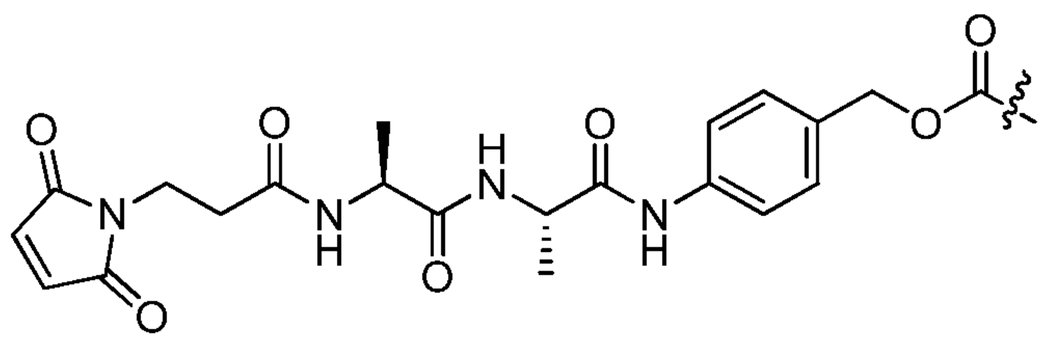
(IVb.4)



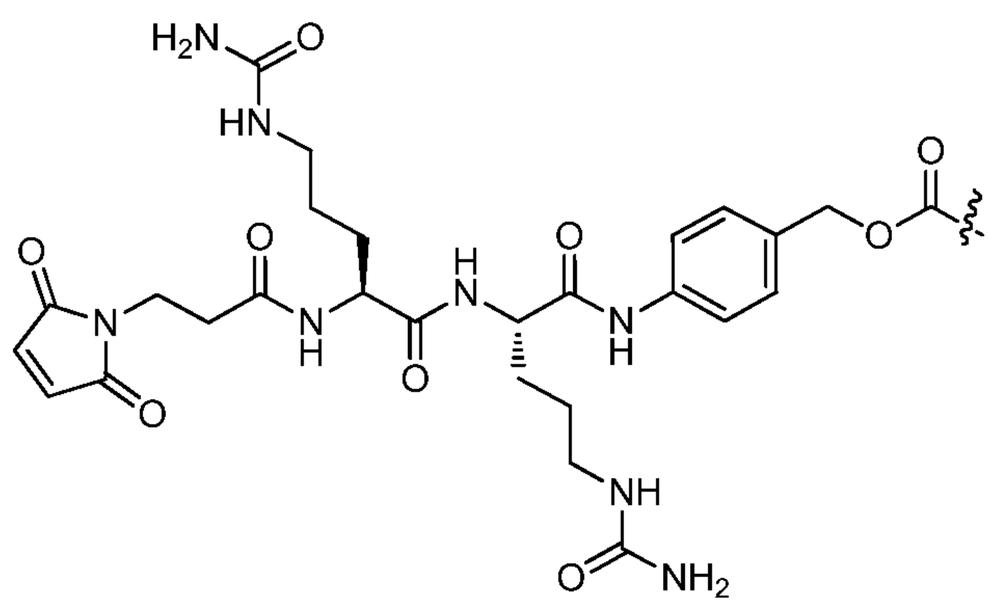
(IVb.5)



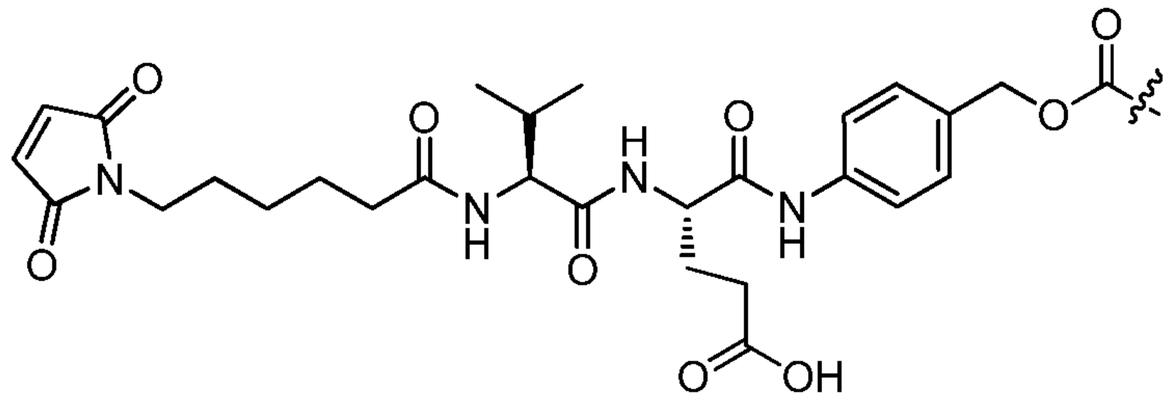
(IVb.6)



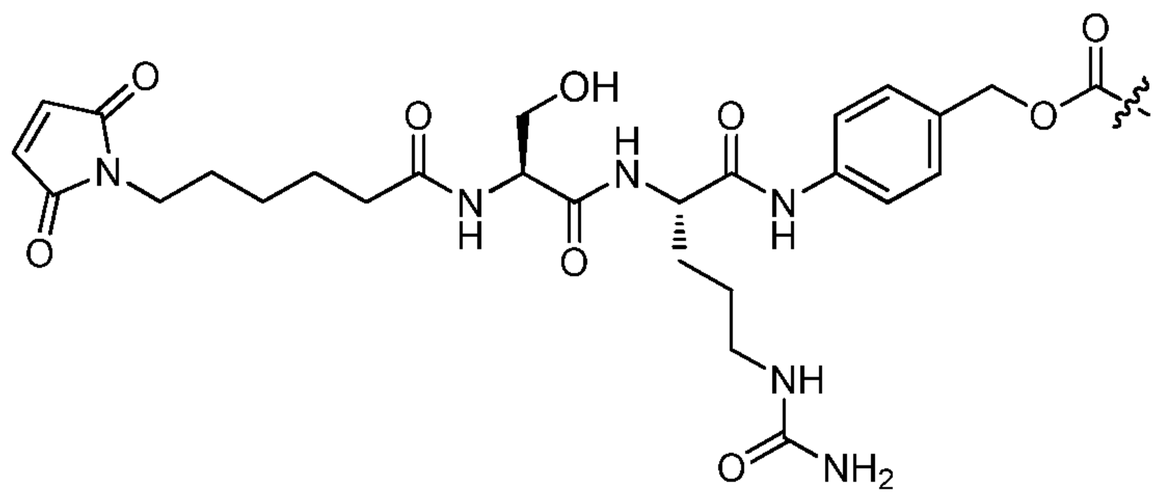
(IVb.7)



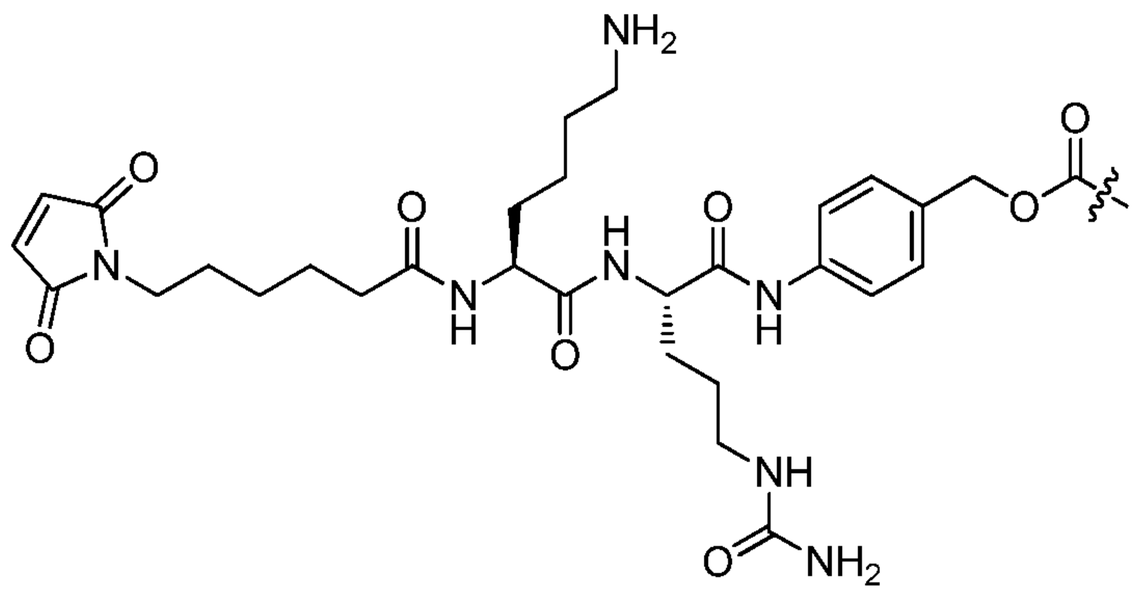
(IVb.8)



(IVb.9)

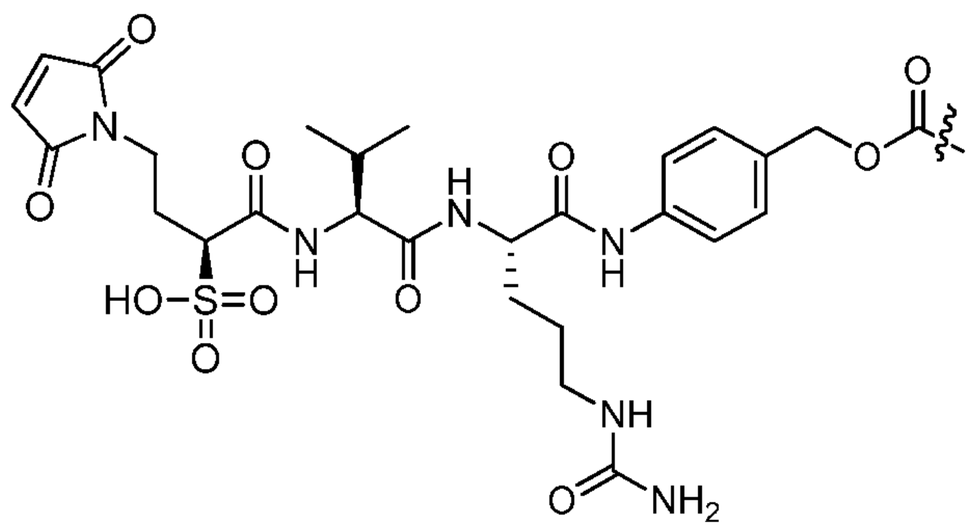


(IVb.10)

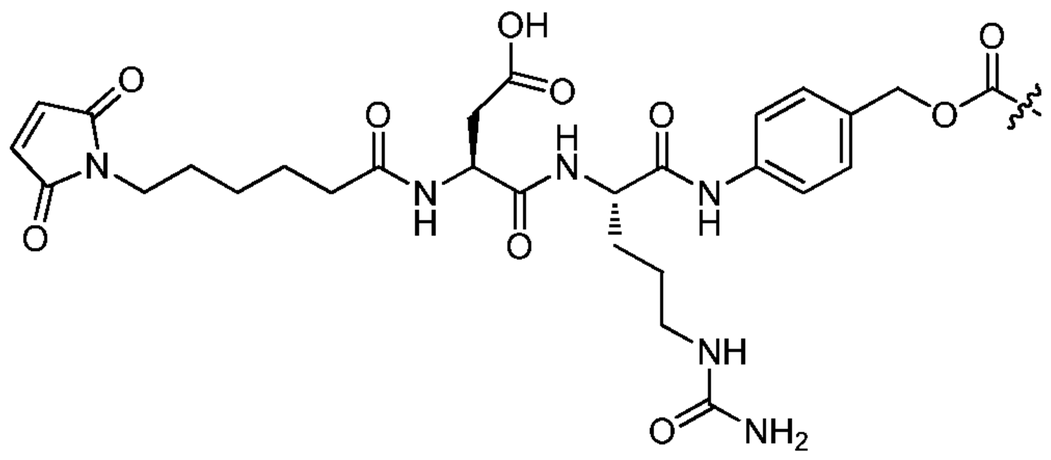


(IVb.11)

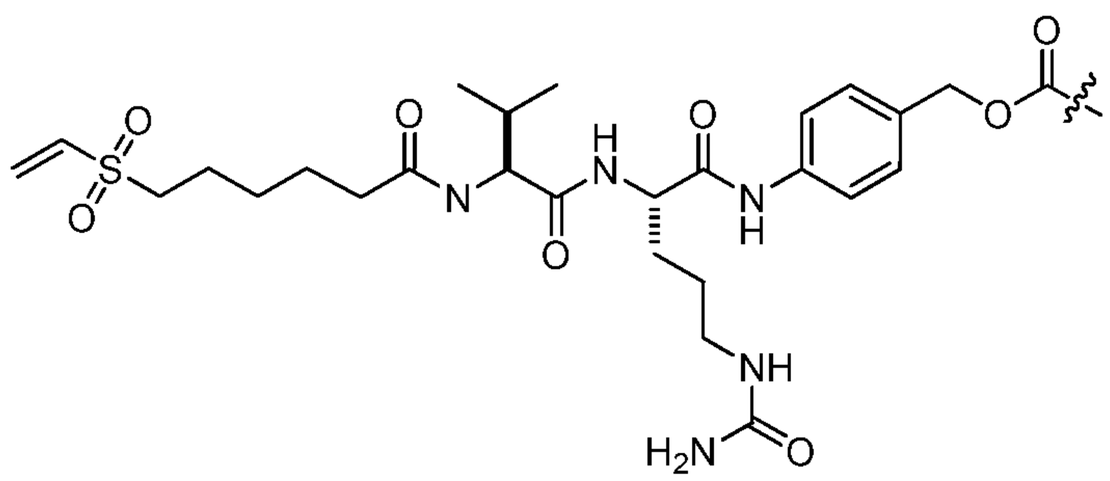
(IVb.12)



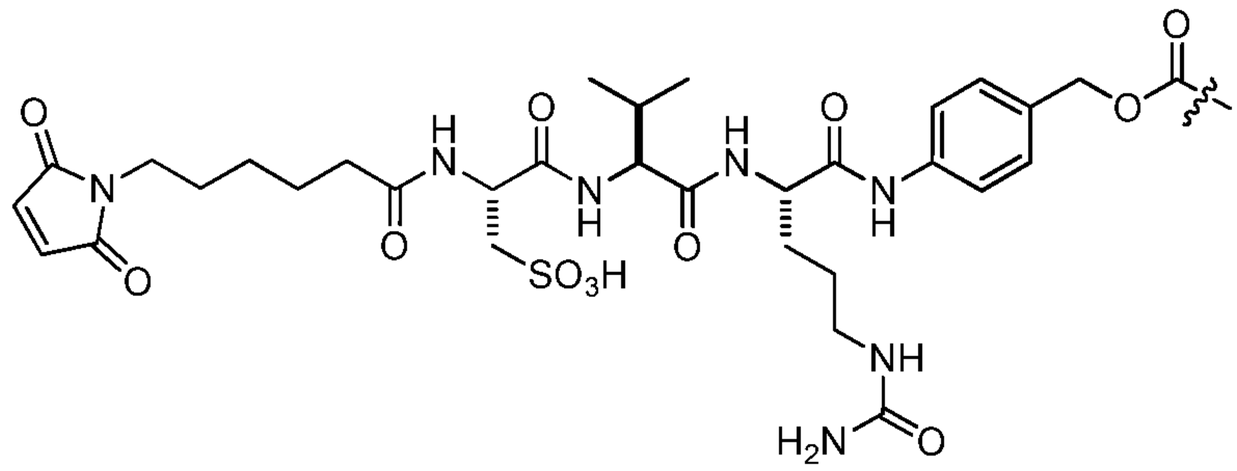
(IVb.13)



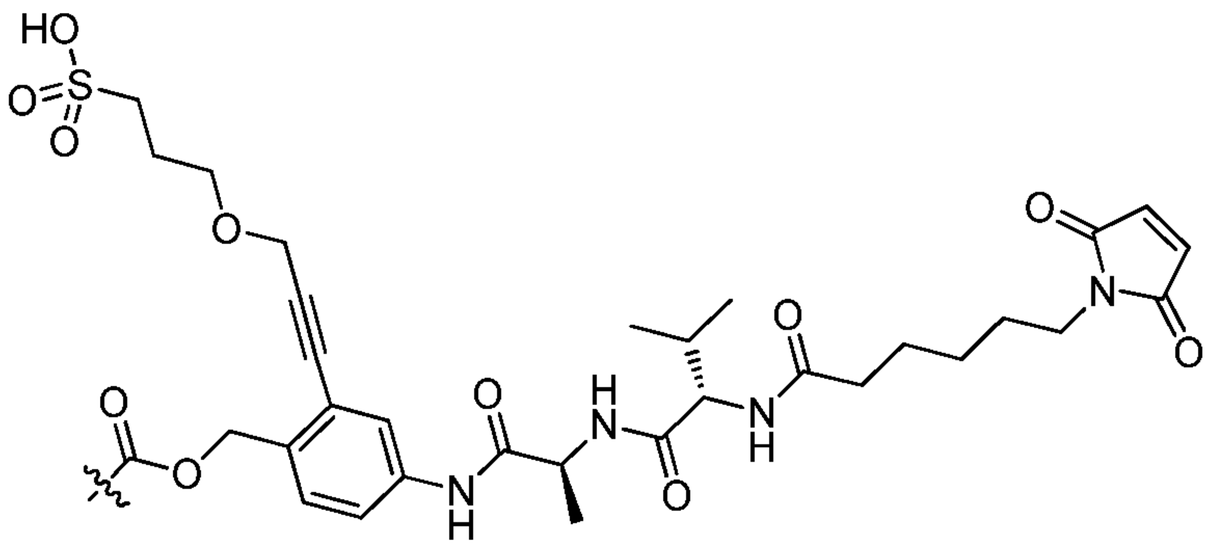
(IVb.14)



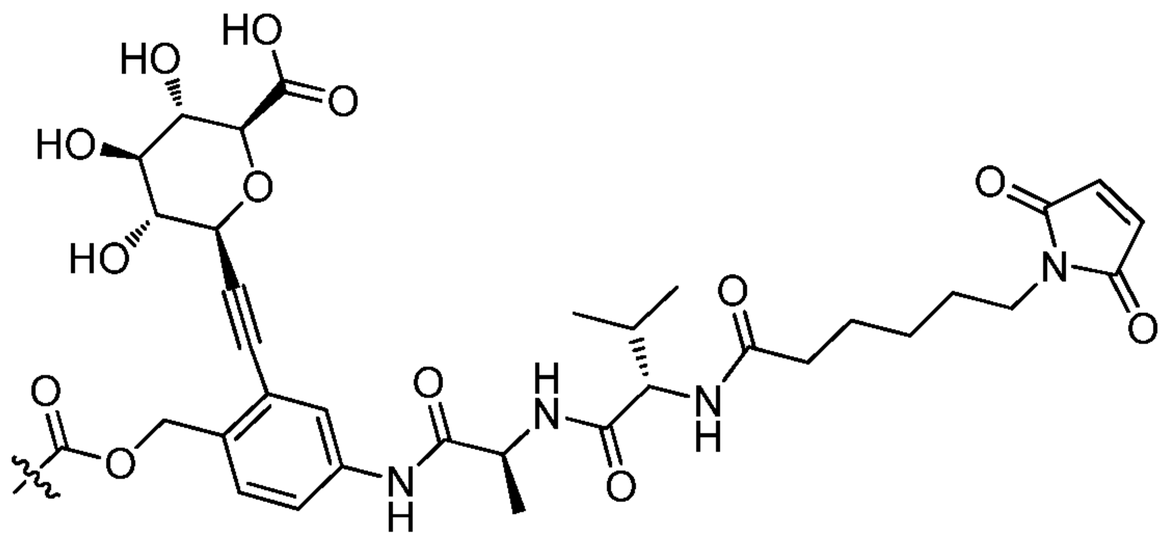
(IVb.15)



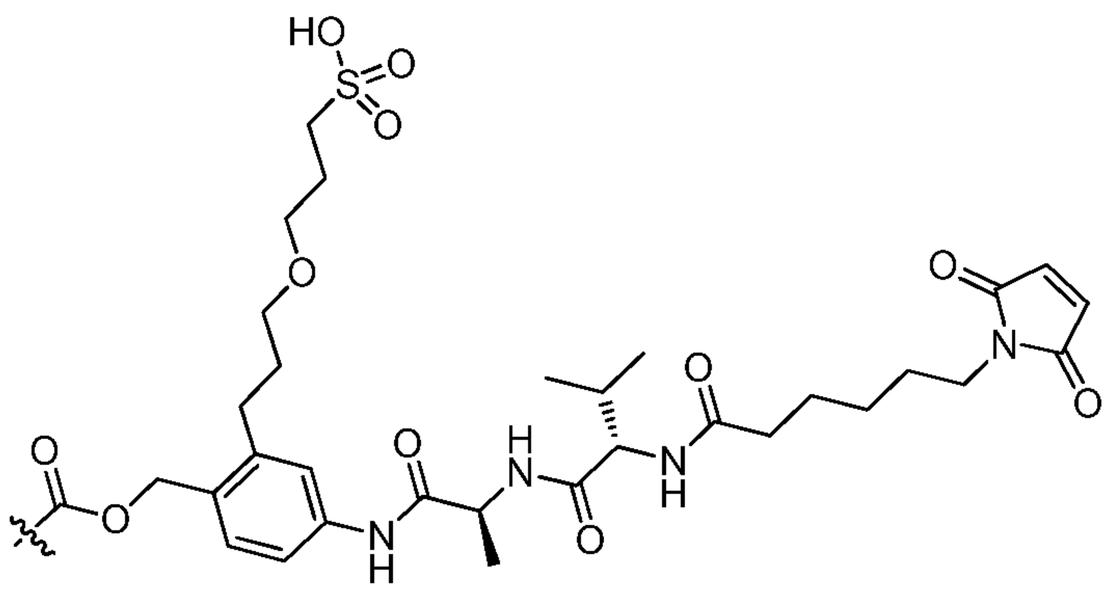
(IVb.16)



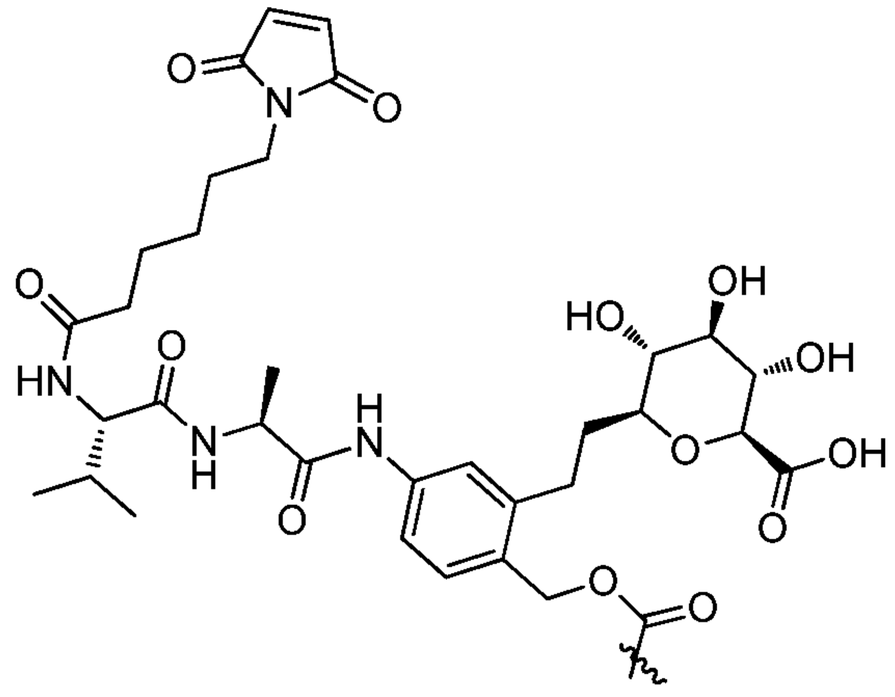
(IVb.17)



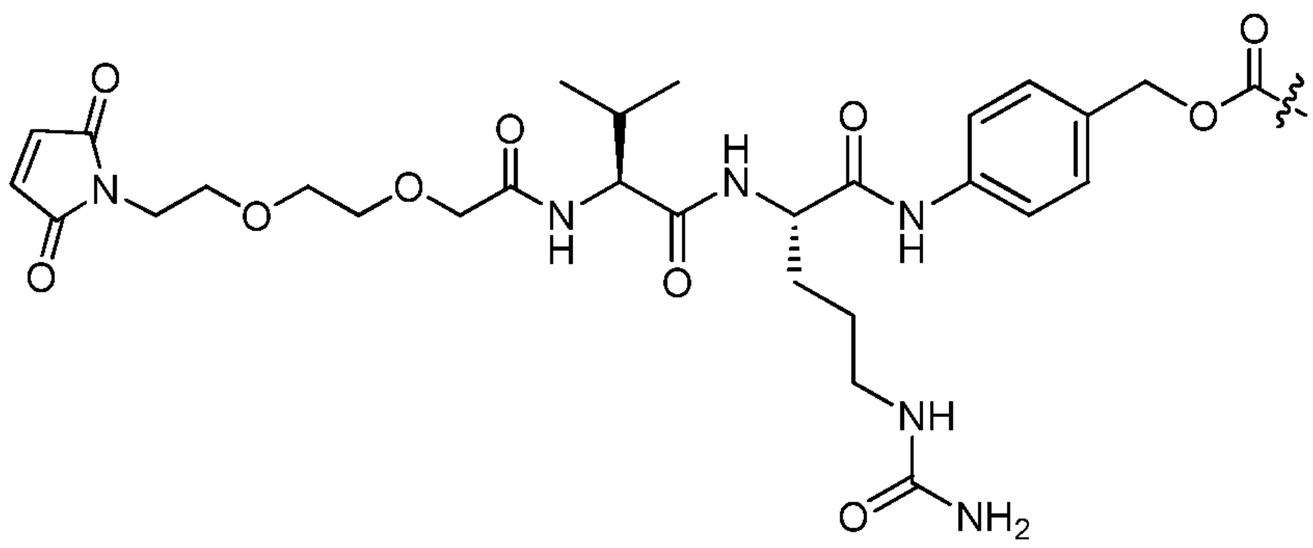
(IVb.18)



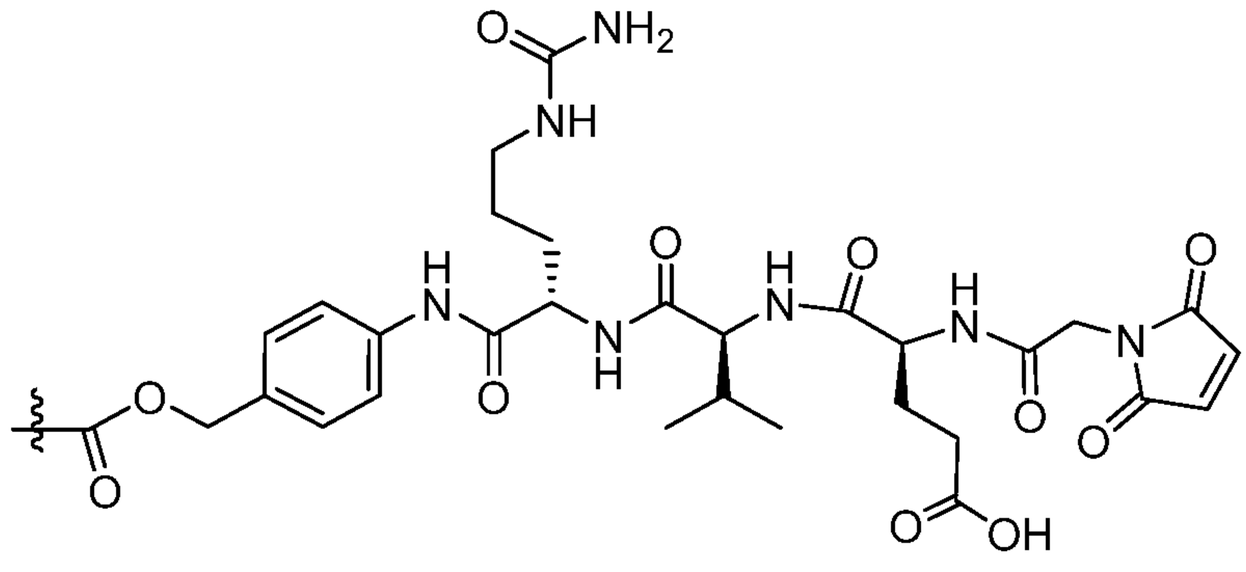
(IVb.19)



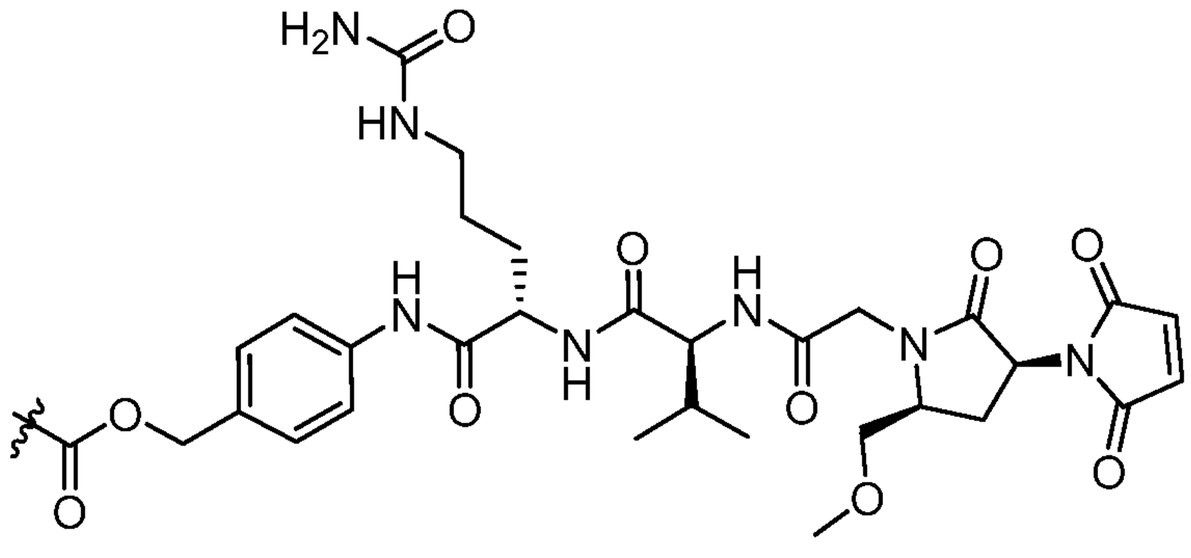
(IVc.1)



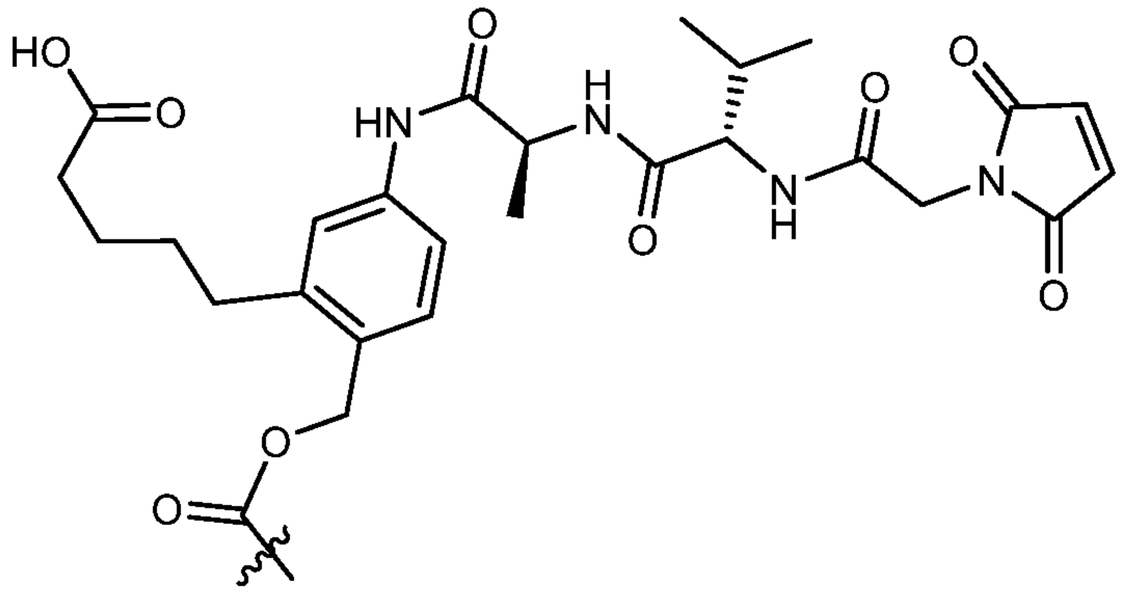
(IVc.2)



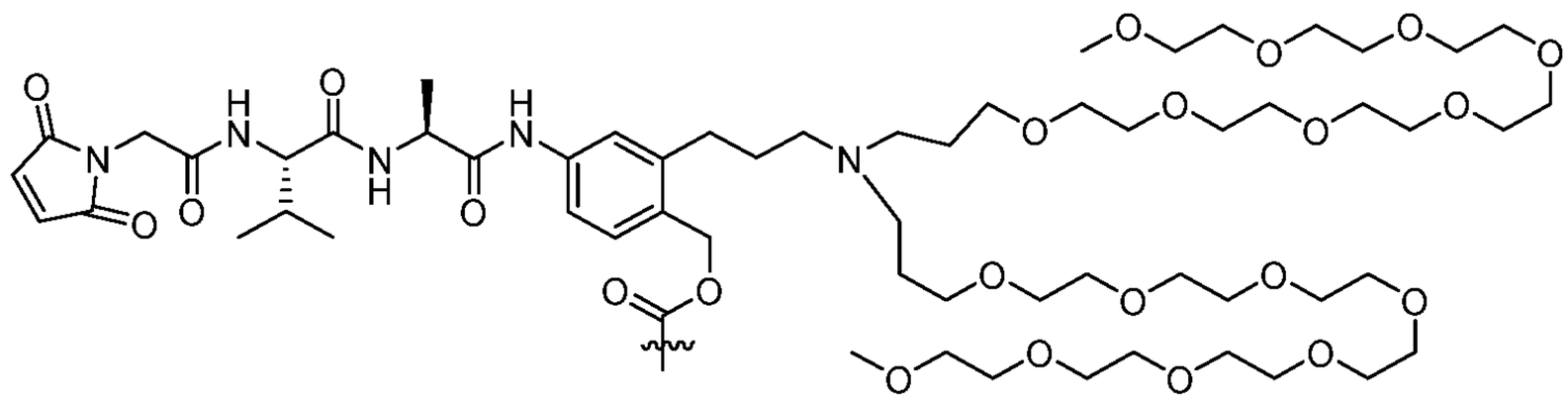
(IVc.3)



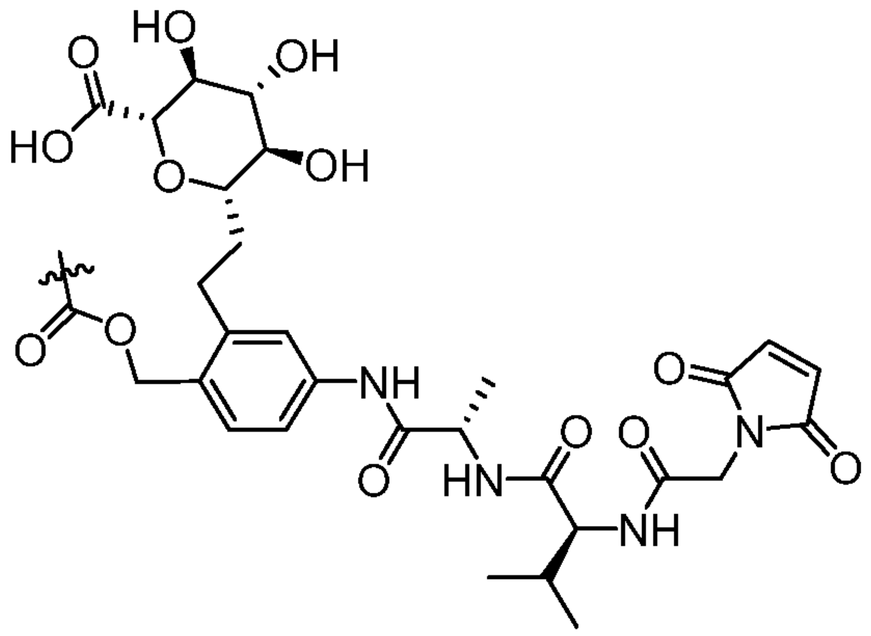
(IVc.4)



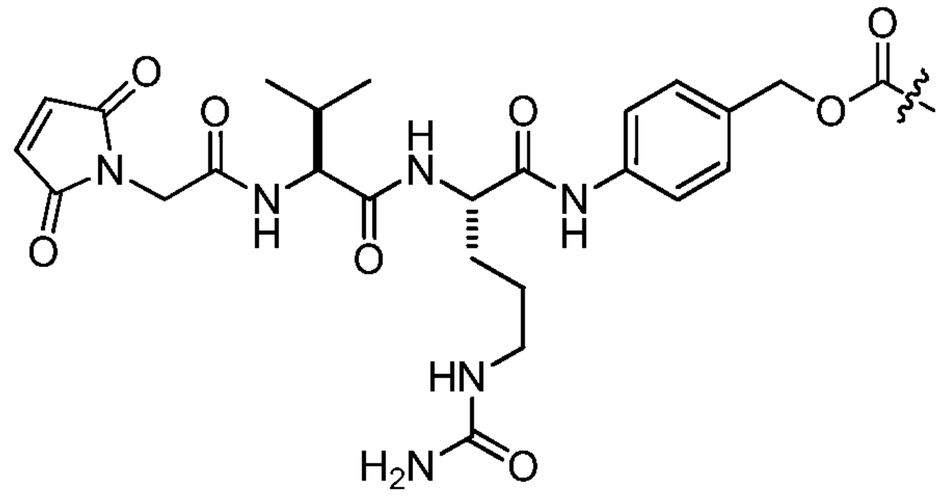
(IVc.5)



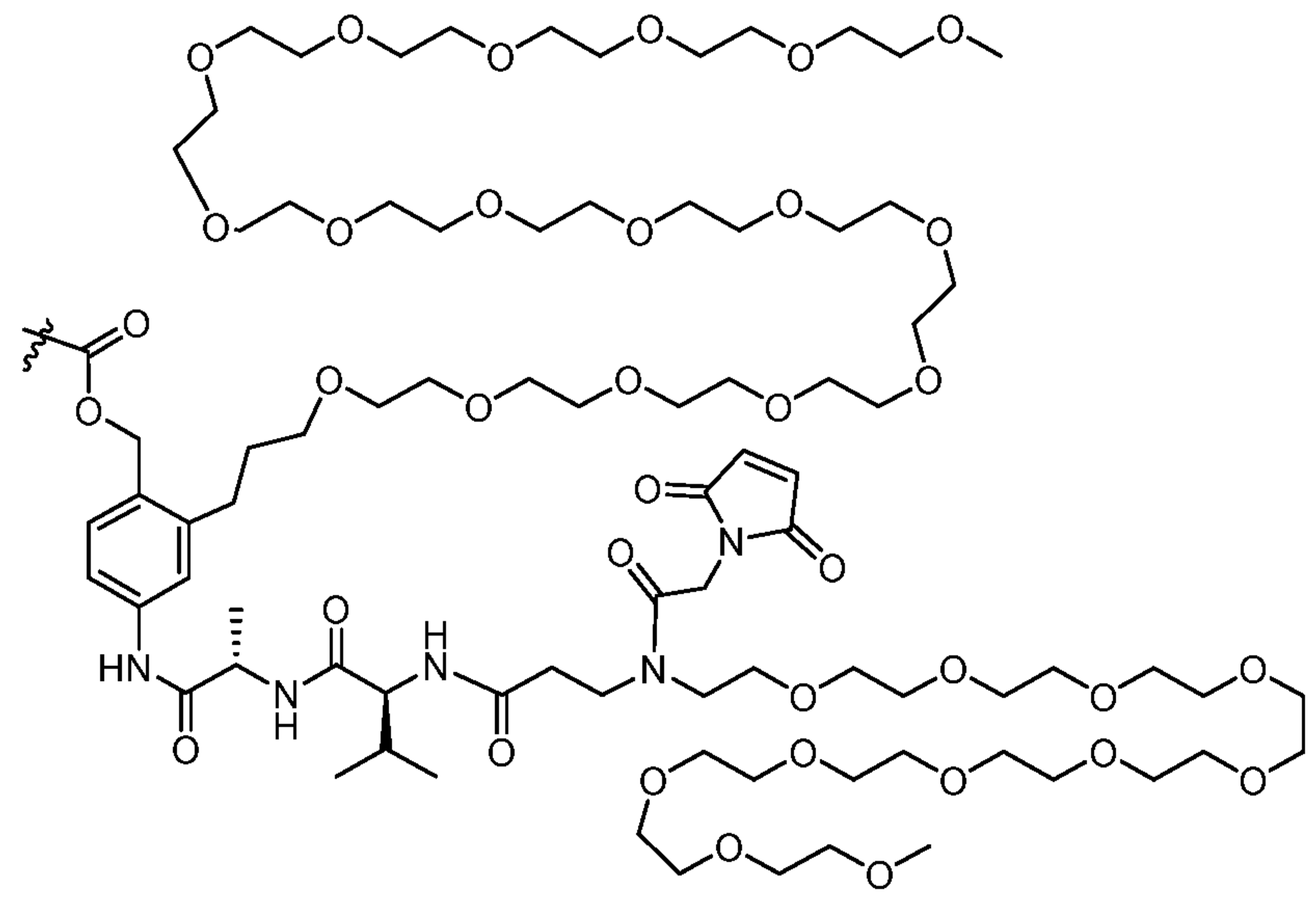
(IVc.6)



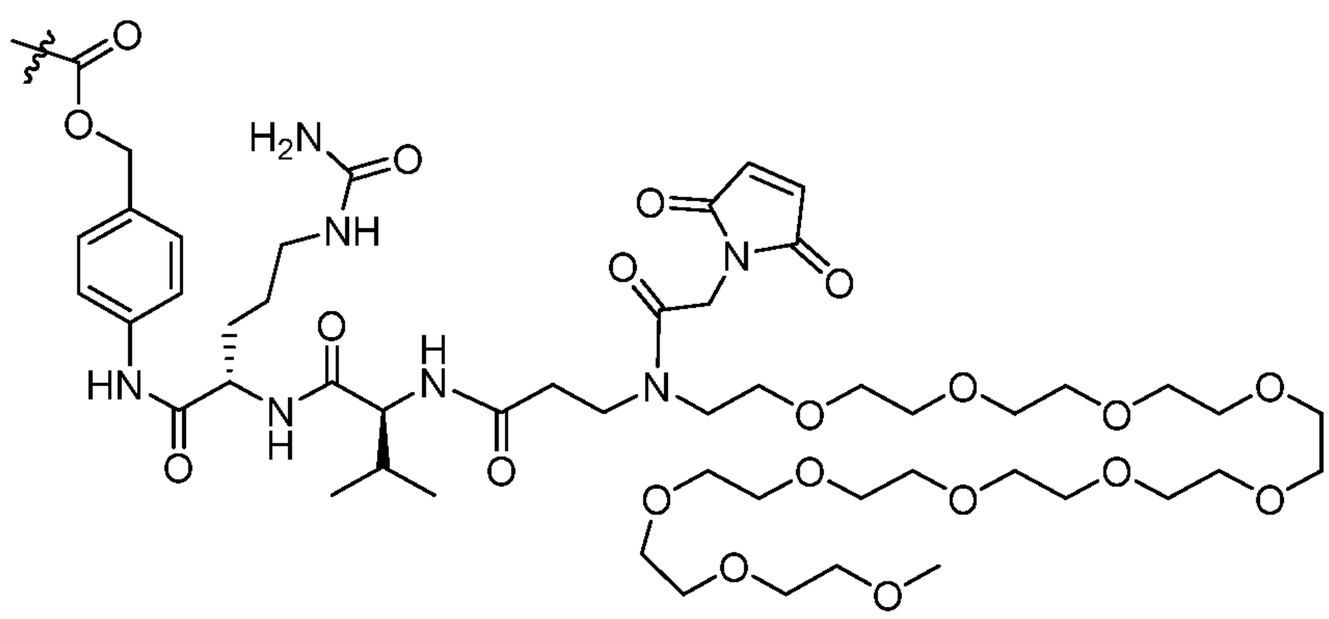
(IVc.7)



(IVd.1)

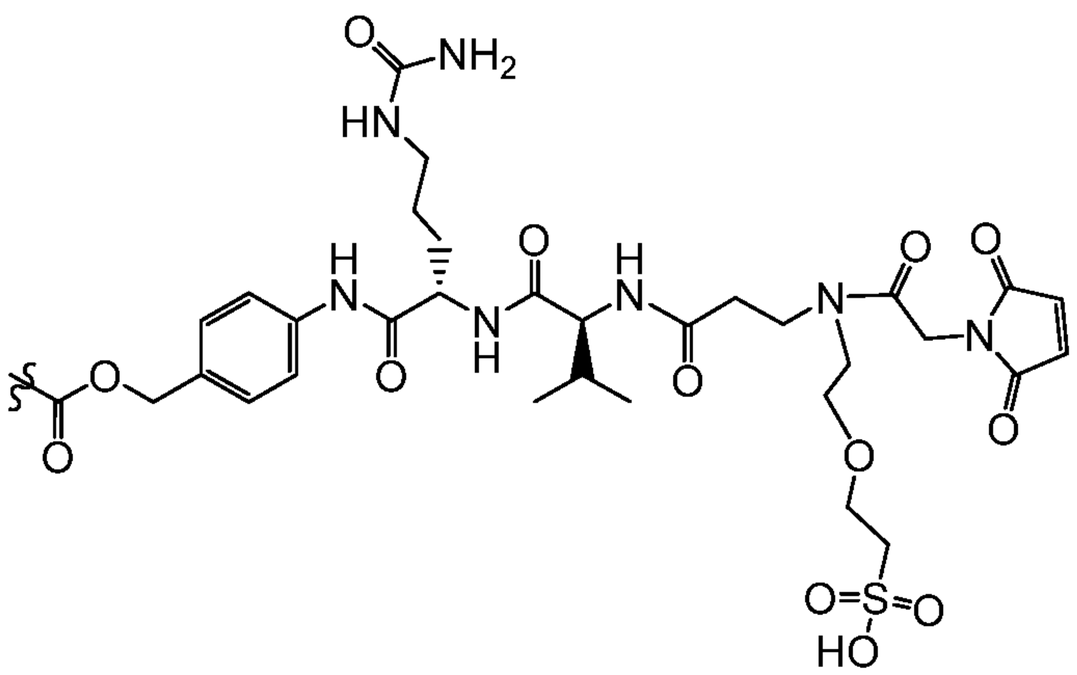


(IVd.2)



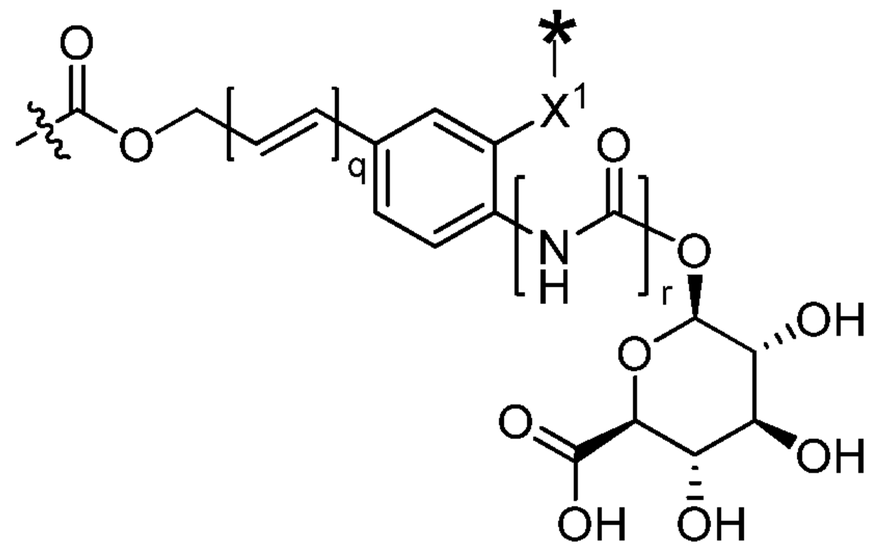
(IVd.3)

(IVd.4)

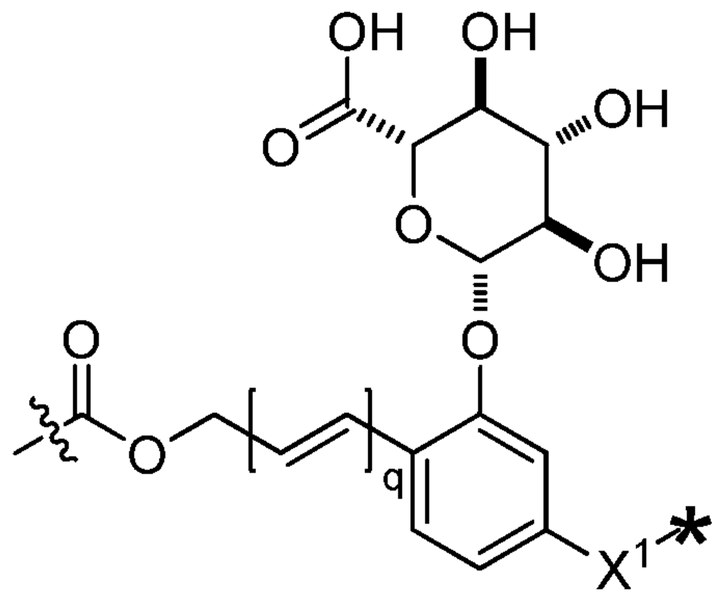


In certain embodiments, the linker comprises an enzymatically cleavable sugar moiety, for example, a linker comprising structural formula (Va), (Vb), (Vc), (Vd), or (Ve):

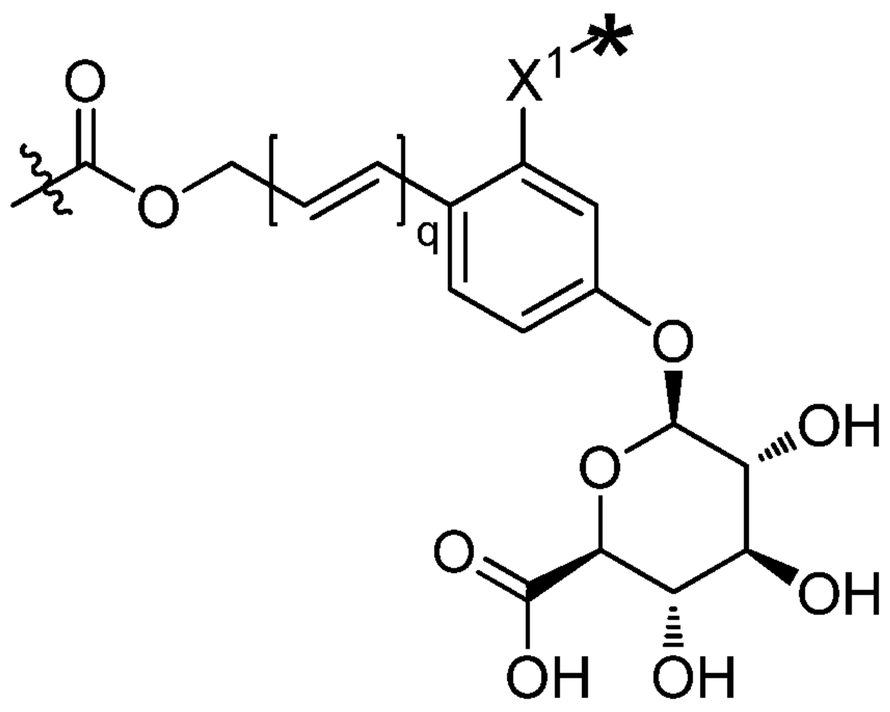
(Va)



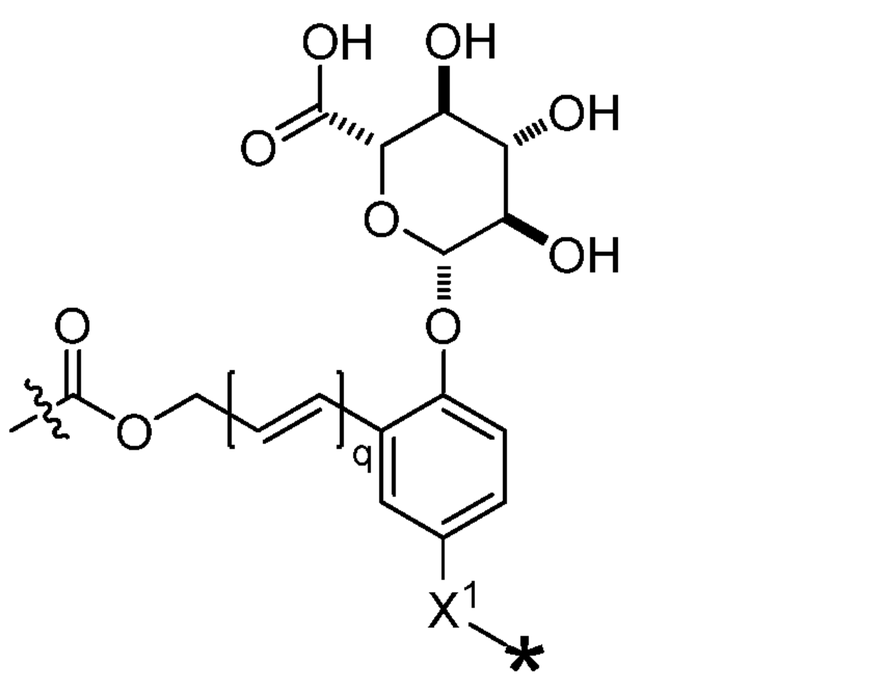
(Vb)



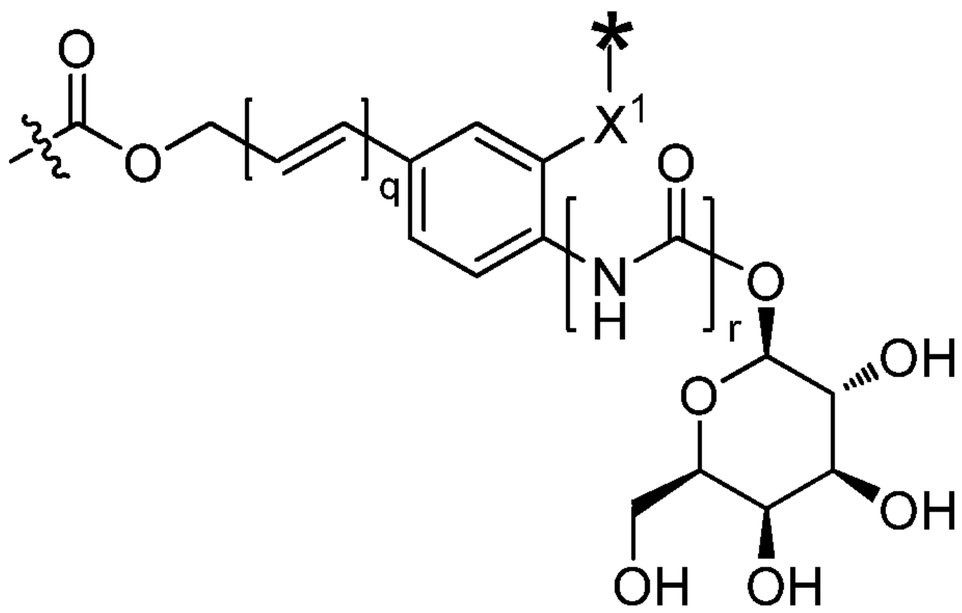
(Vc)



(Vd)



(Ve)

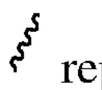


or a pharmaceutically acceptable salt thereof, wherein:

q is 0 or 1;

r is 0 or 1;

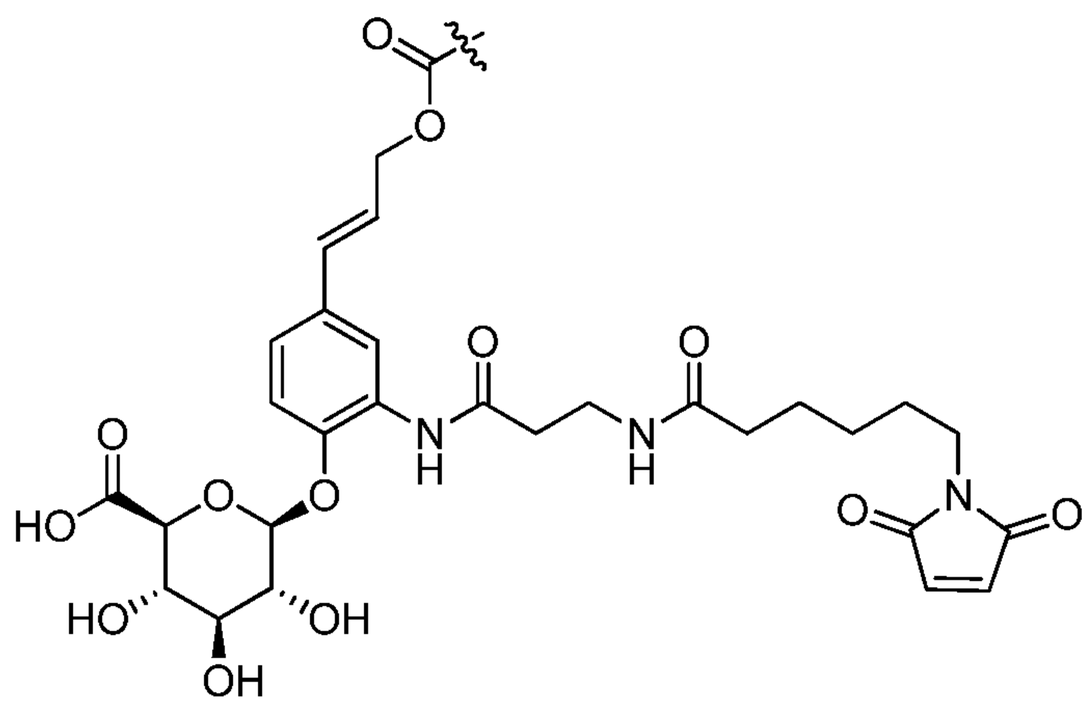
X^1 is CH_2, O or NH;


represents the point of attachment of the linker to the drug; and

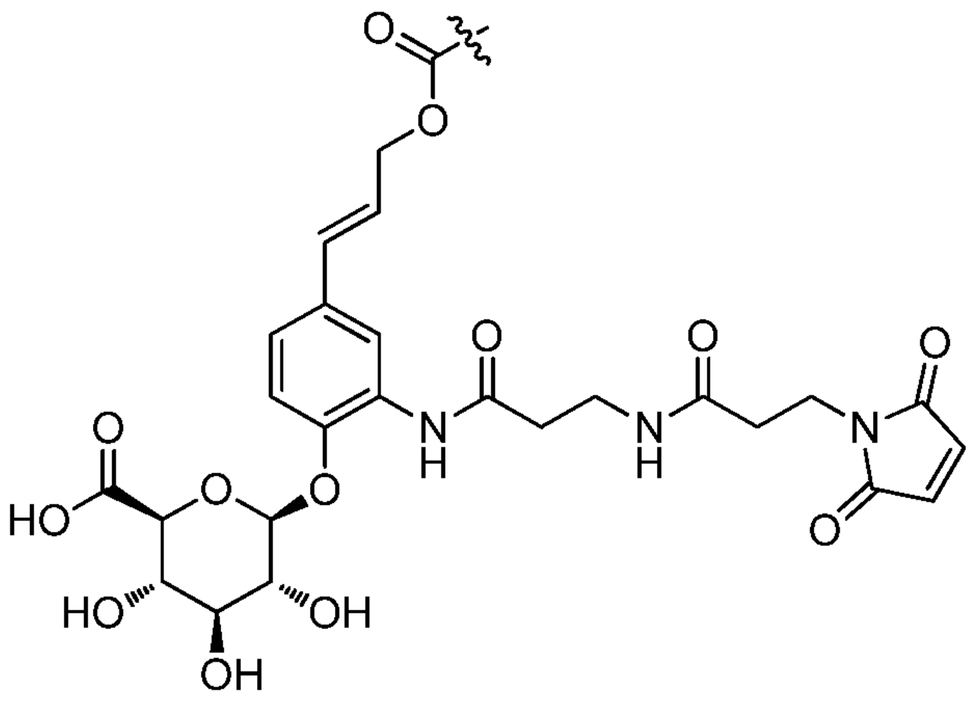
* represents the point of attachment to the remainder of the linker.

Exemplary embodiments of linkers according to structural formula (Va) that may be included in the ADCs described herein include the linkers illustrated below (as illustrated, the linkers include a group suitable for covalently linking the linker to an antibody):

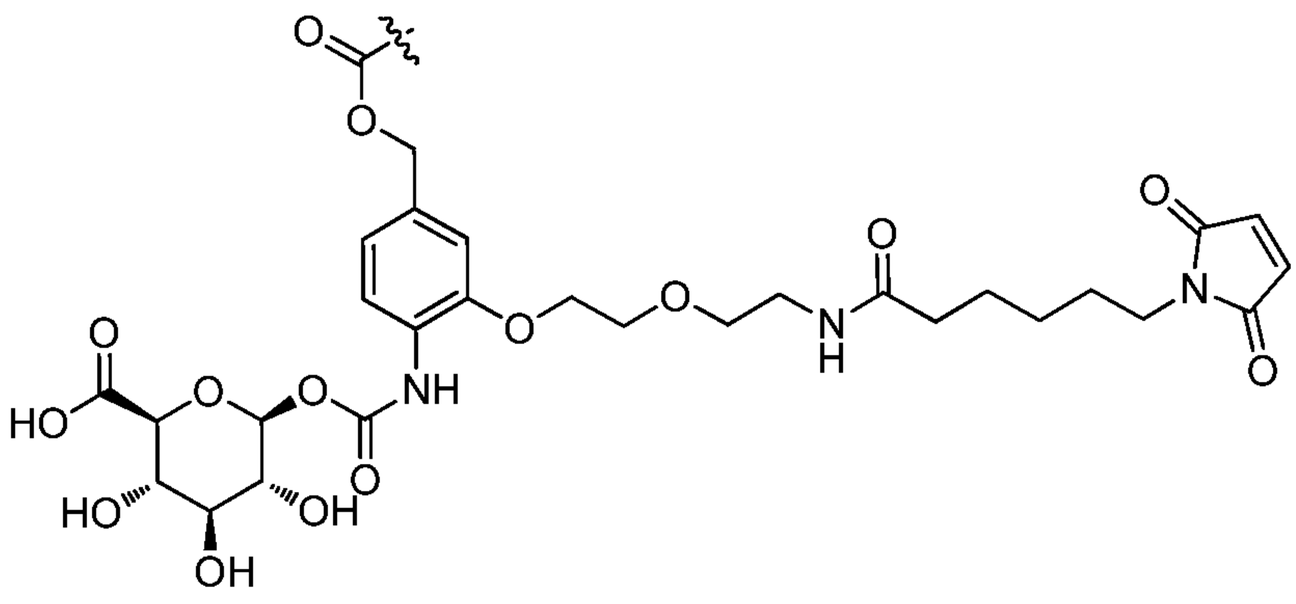
(Va.1)

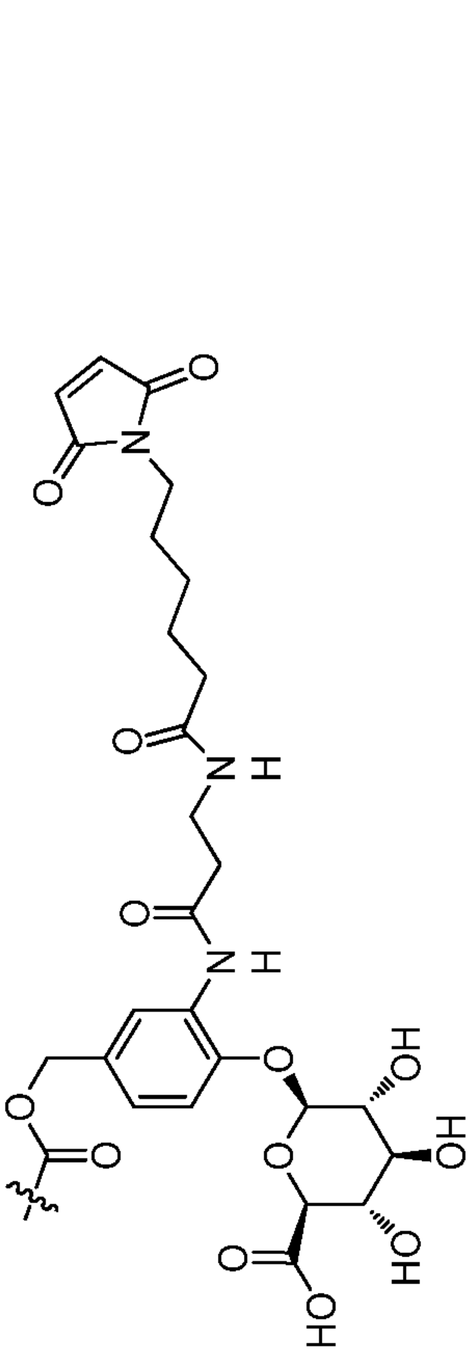


(Va.2)

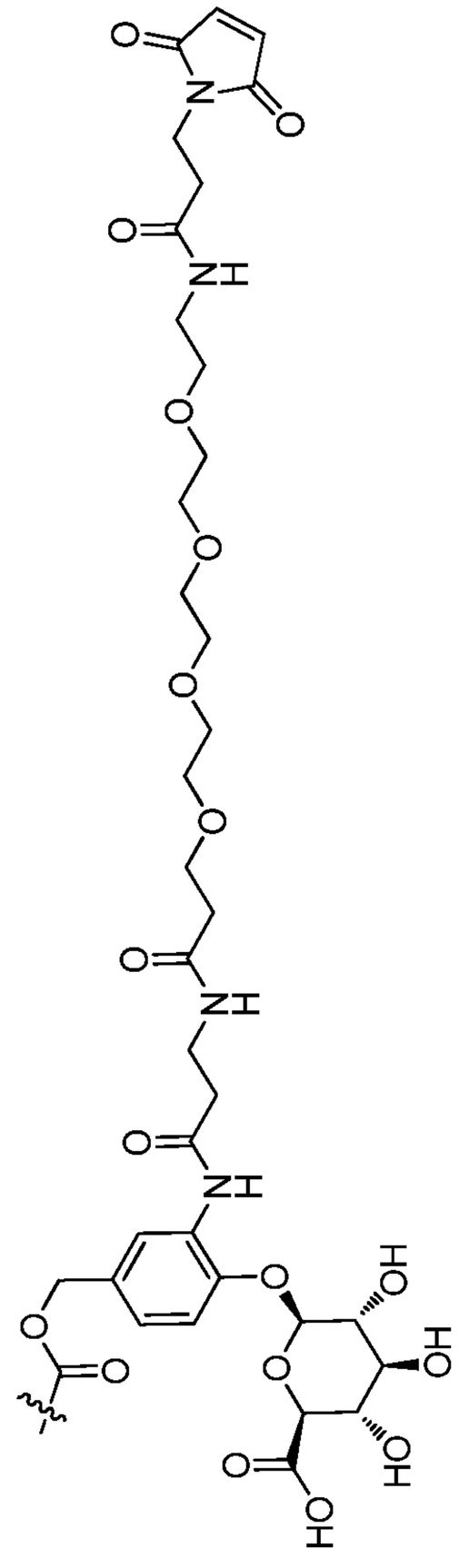


(Va.3)

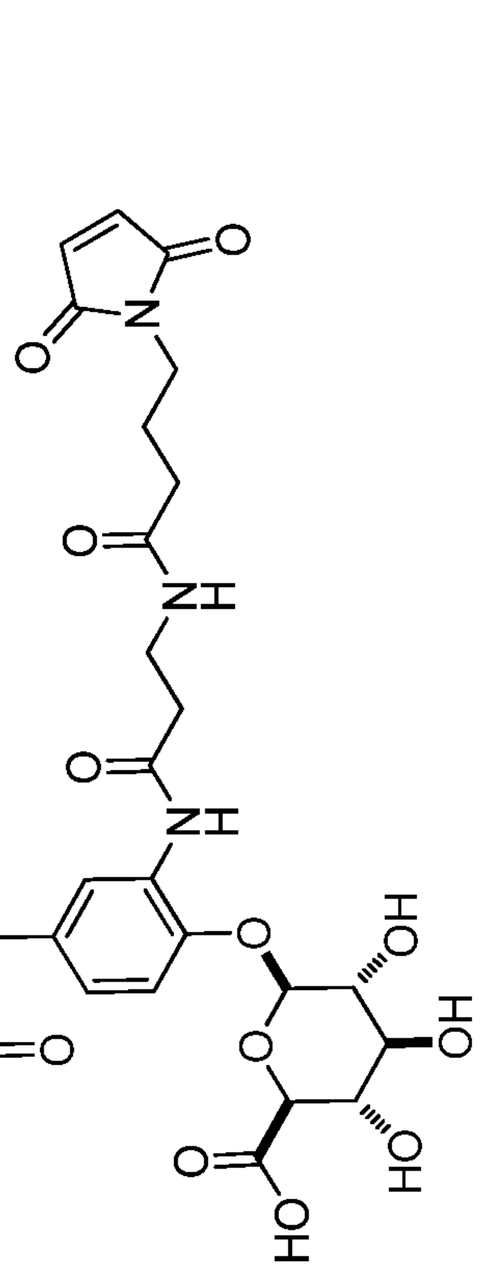




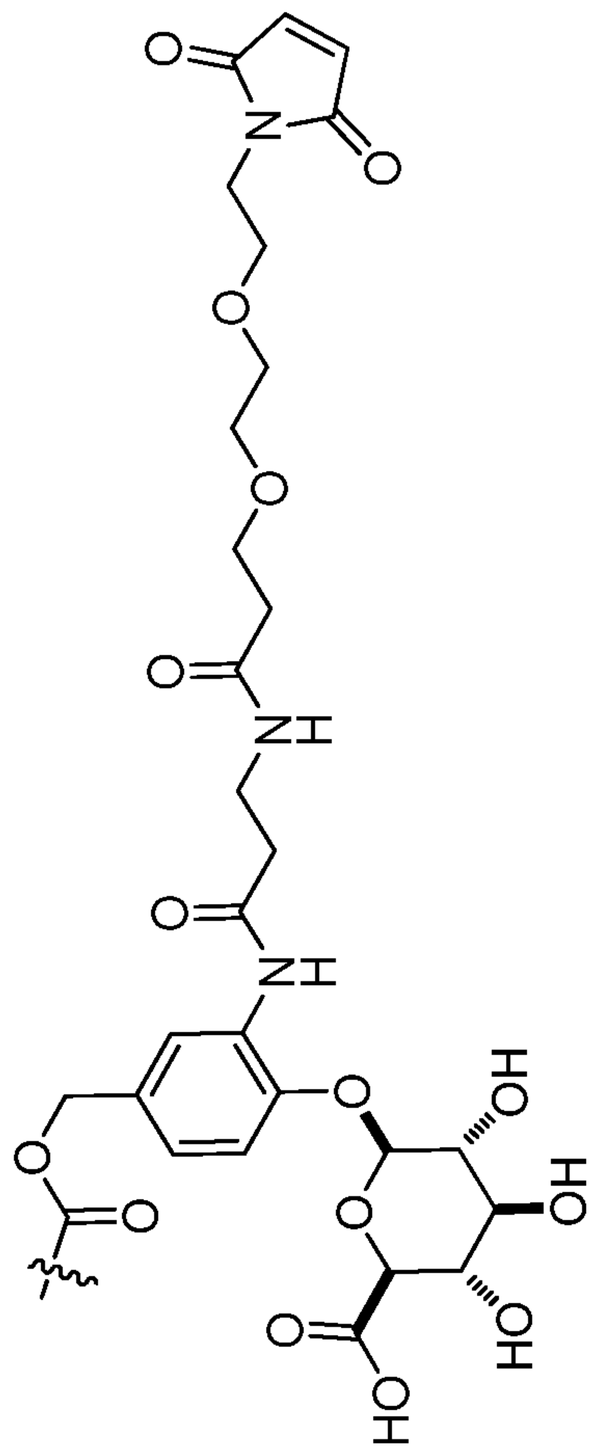
(Va.4)



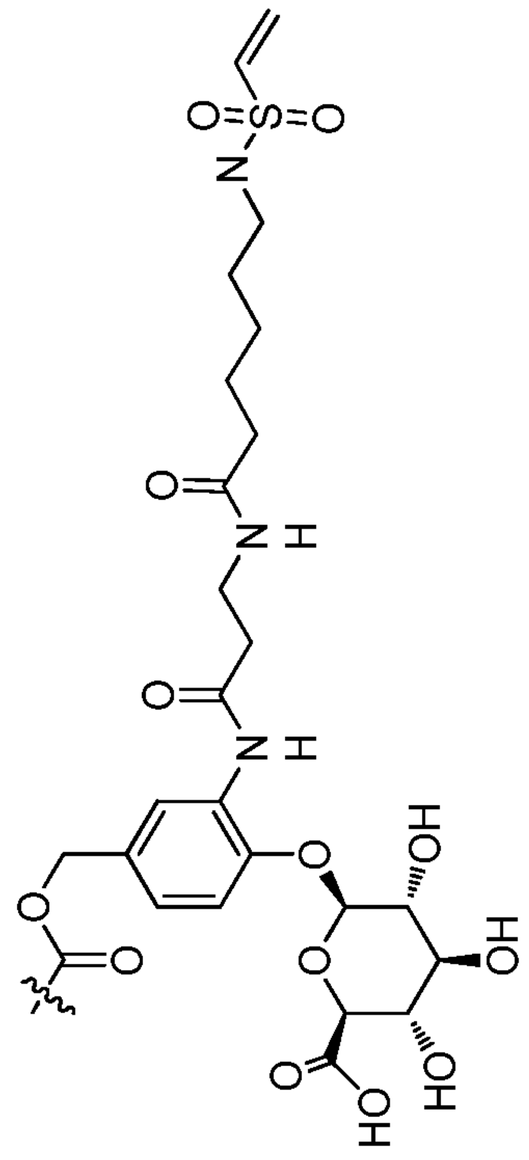
(Va.5)



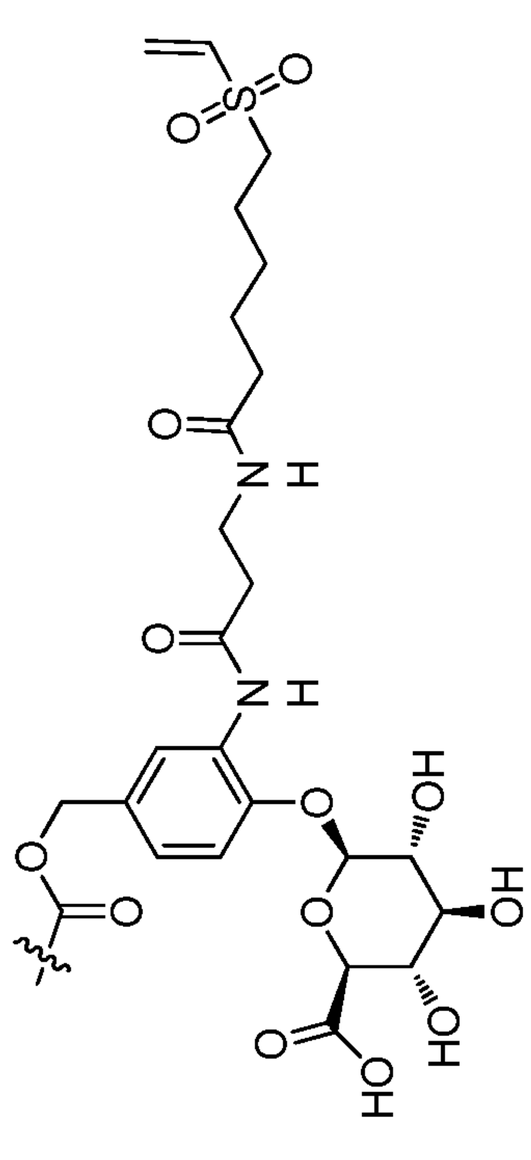
(Va.6)



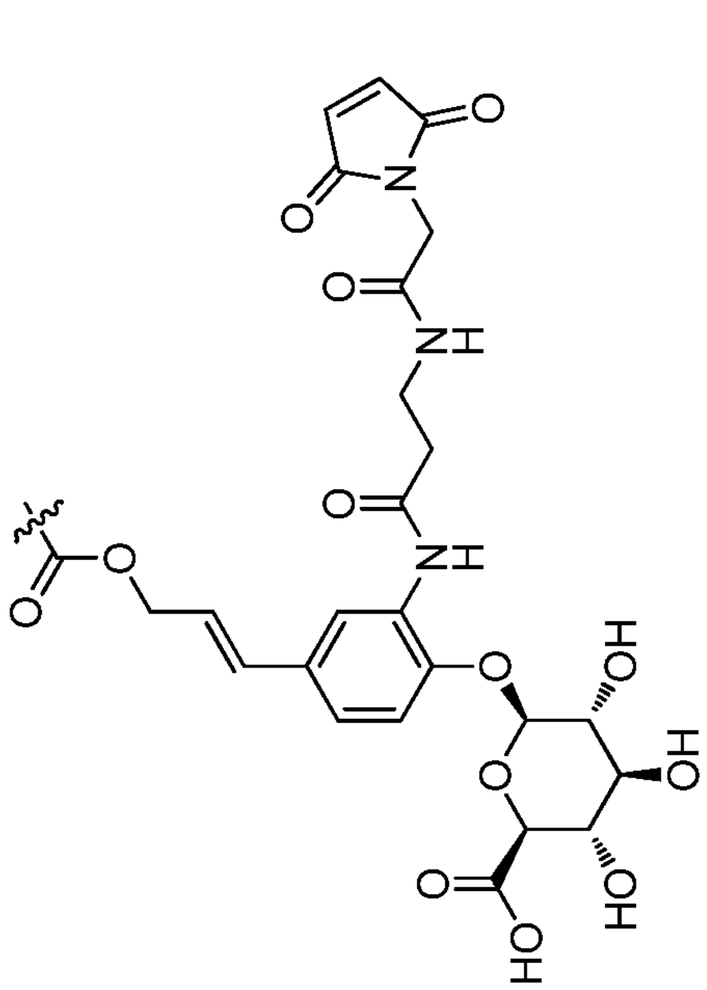
(Va.7)



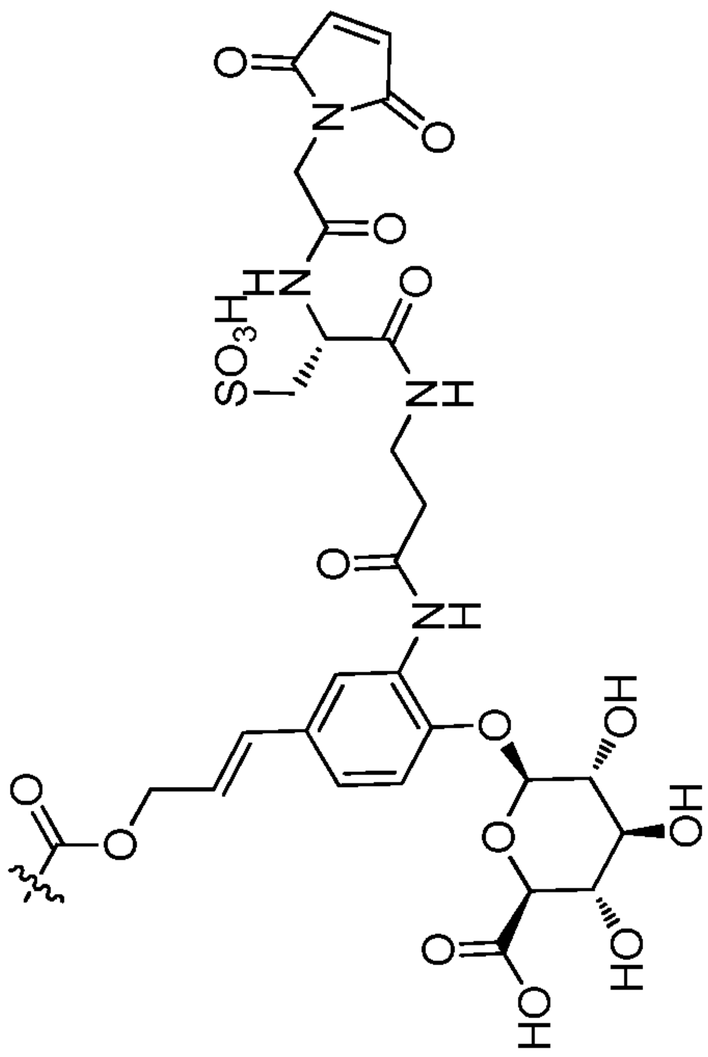
(Va.8)



(Va.9)

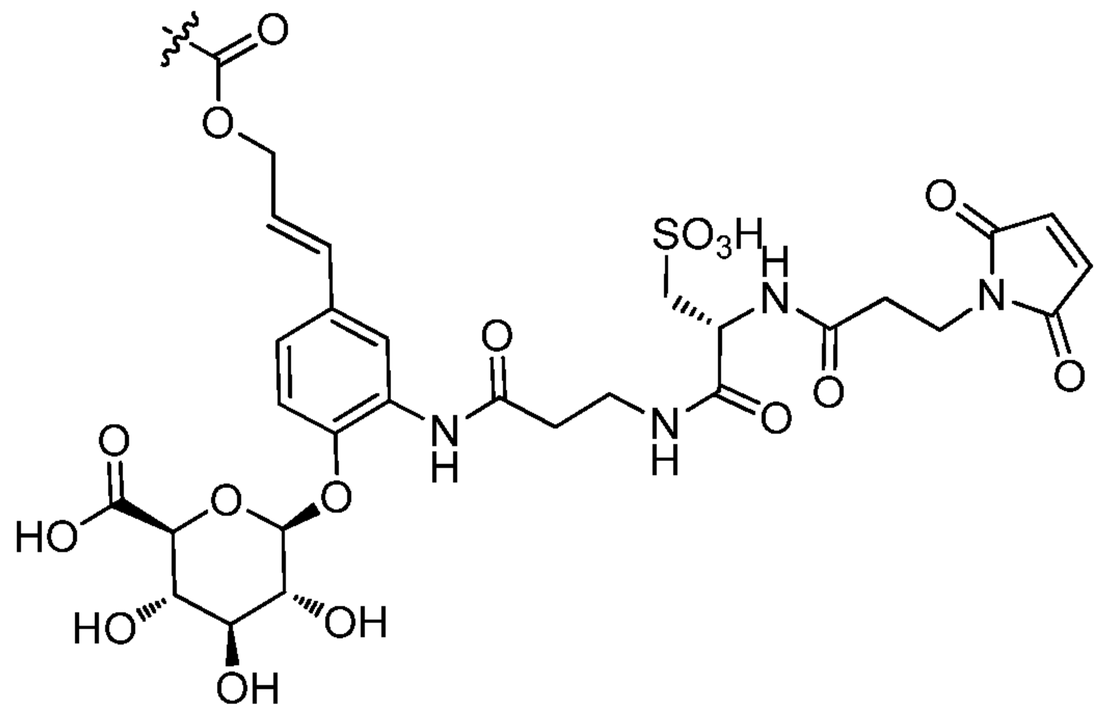


(Va.10)



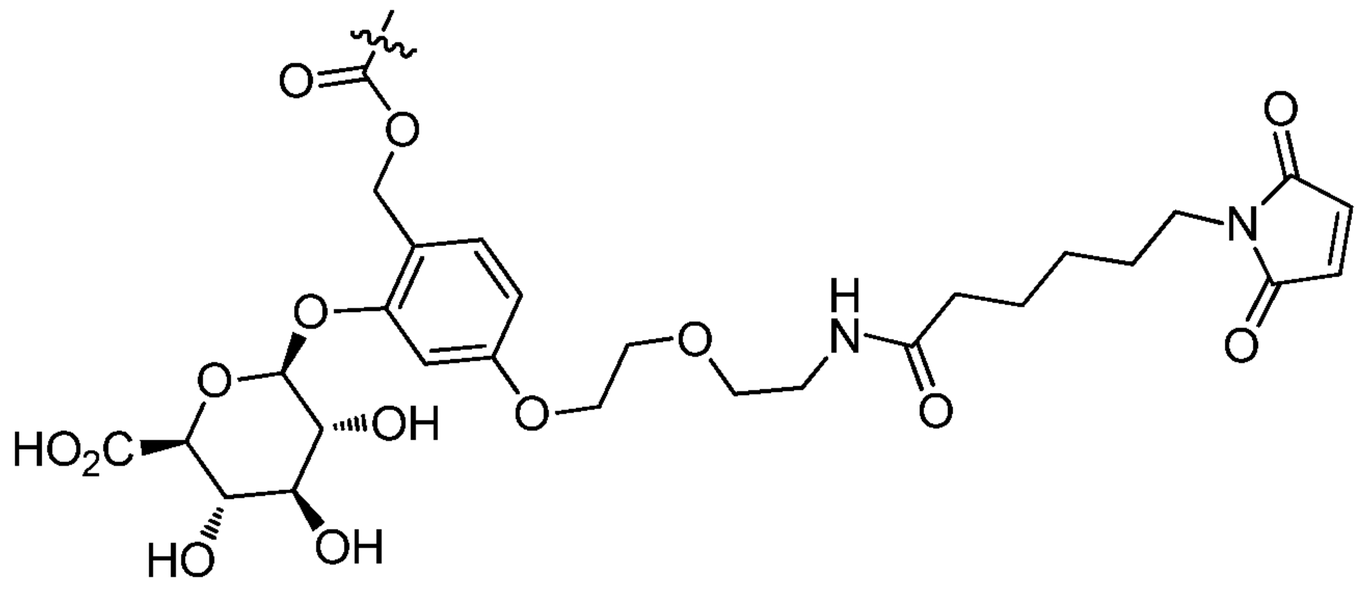
(Va.11)

(Va.12)

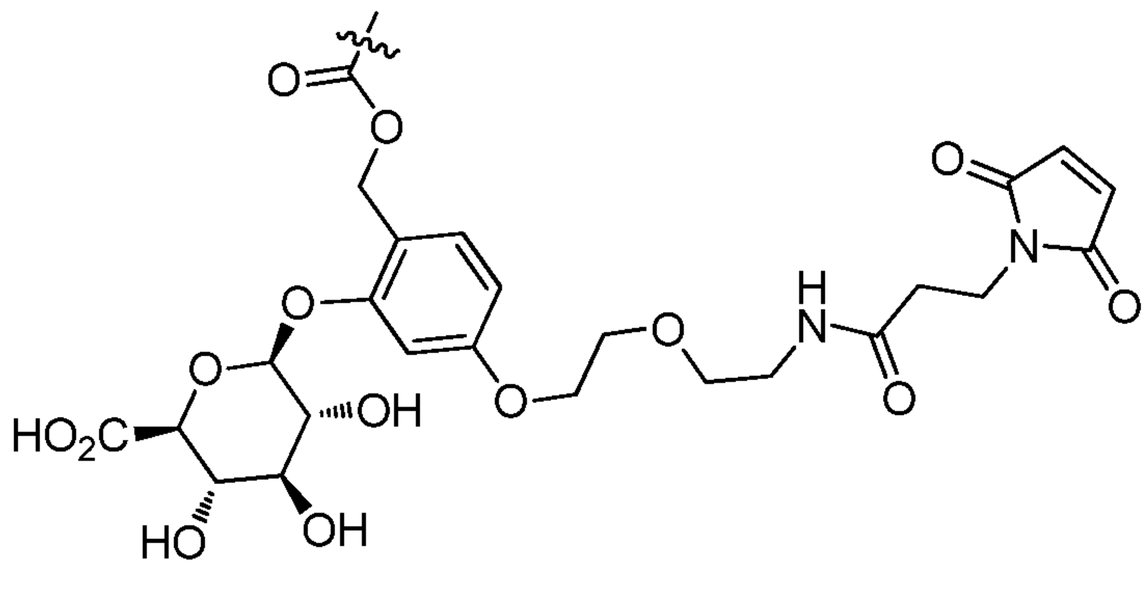


Exemplary embodiments of linkers according to structural formula (Vb) that may be included in the ADCs described herein include the linkers illustrated below (as illustrated, the linkers include a group suitable for covalently linking the linker to an antibody):

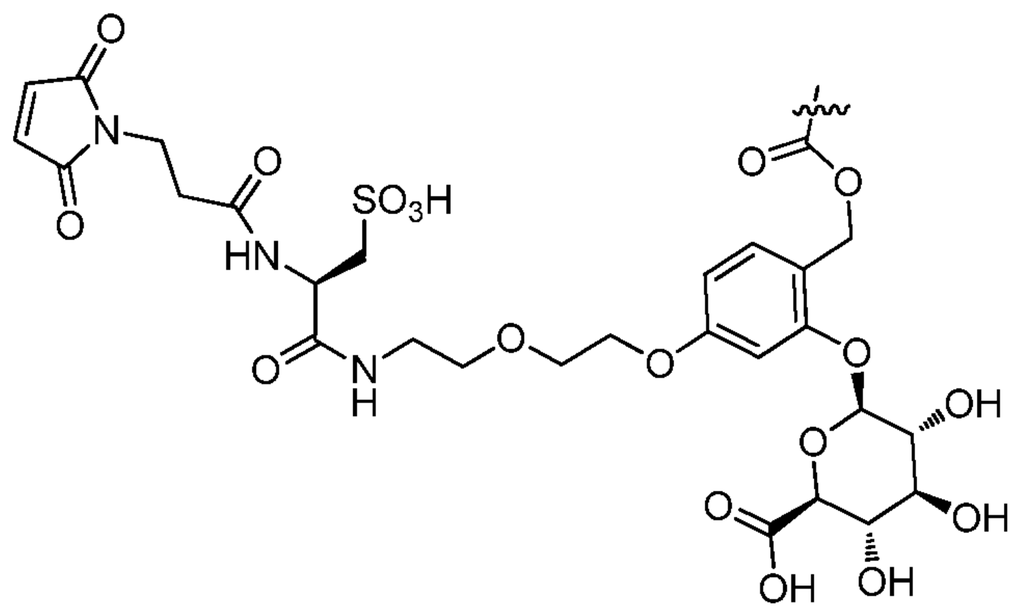
(Vb.1)



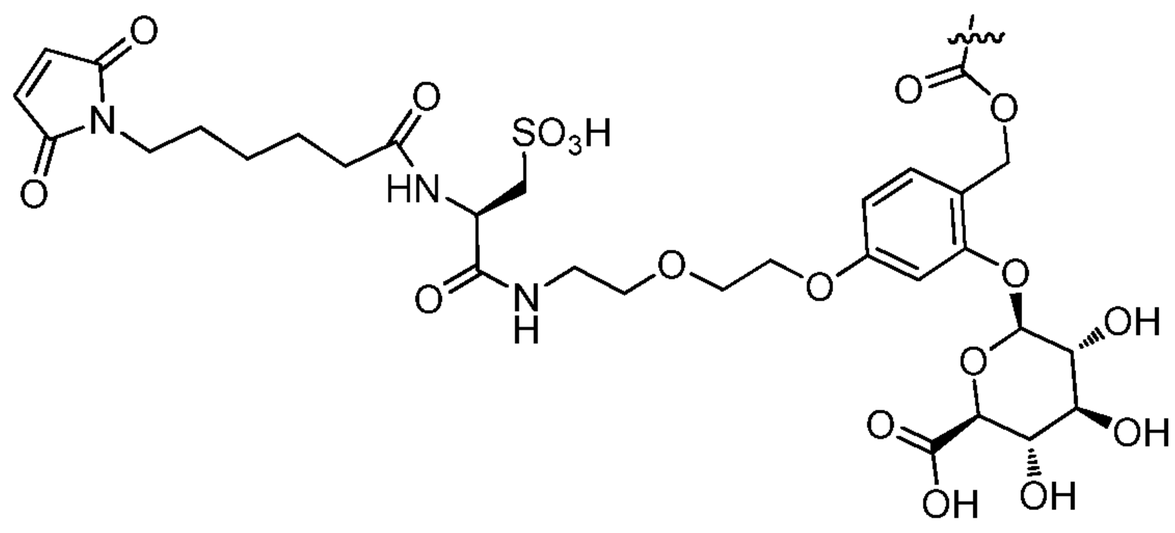
(Vb.2)



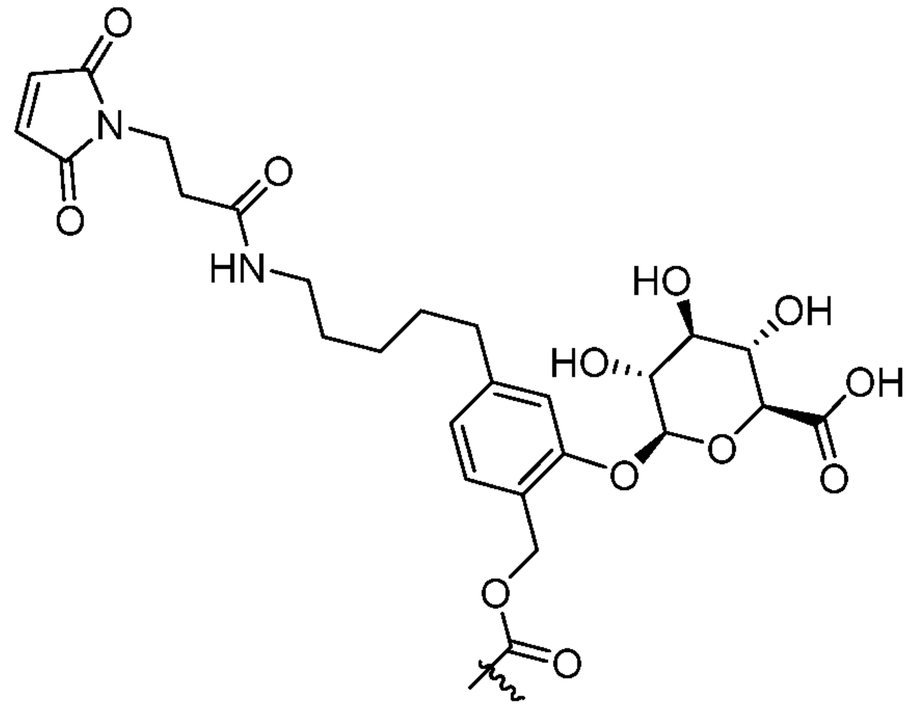
(Vb.3)



(Vb.4)

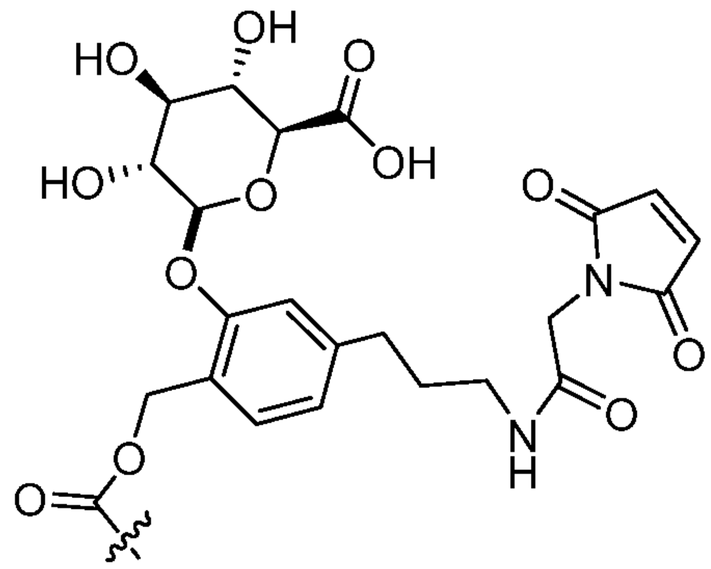


(Vb.5)

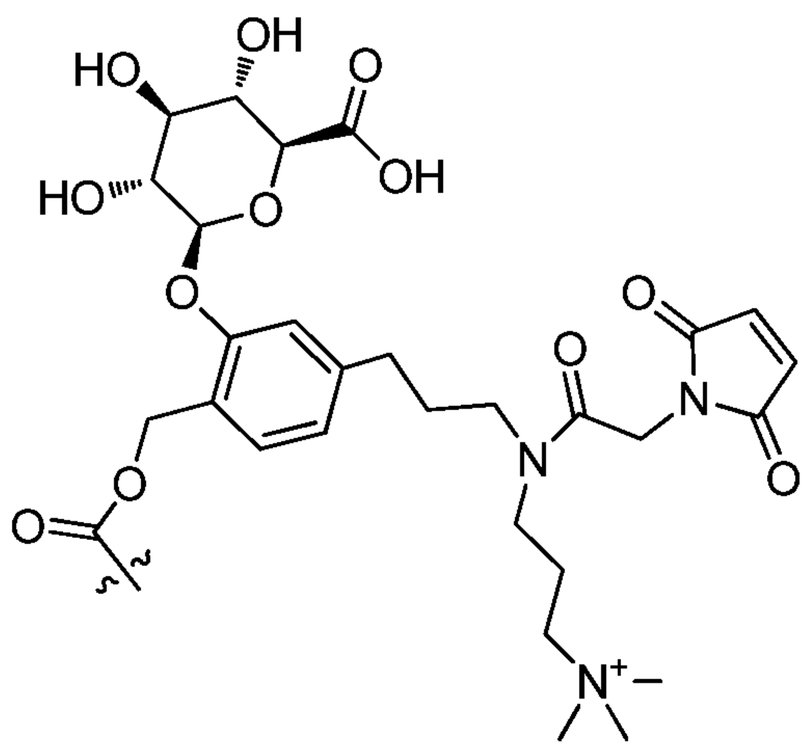


(Vb.6)

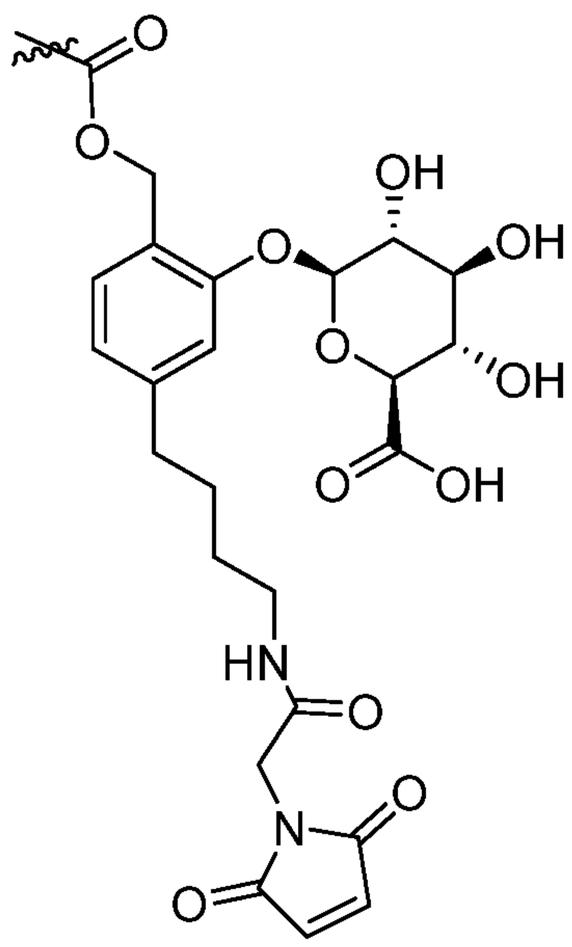
(Vb.7)



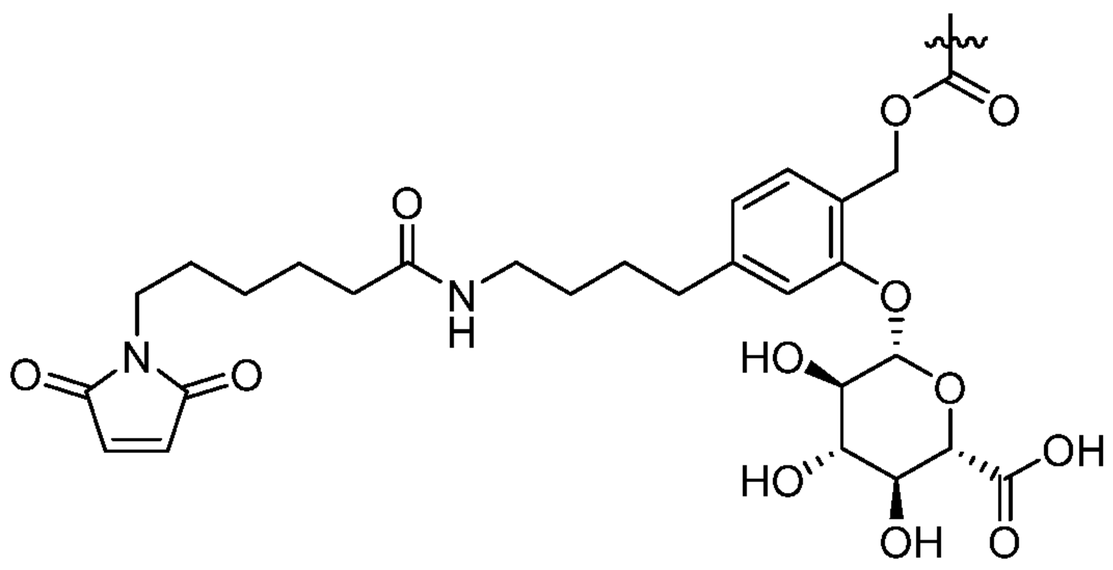
(Vb.8)



(Vb.9)

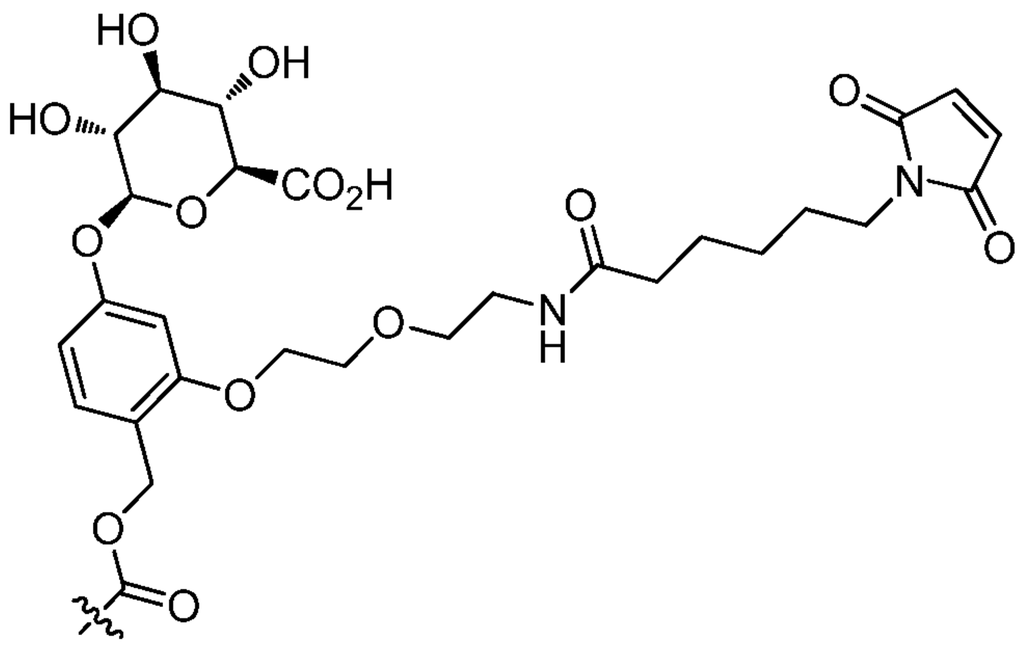


(Vb.10)

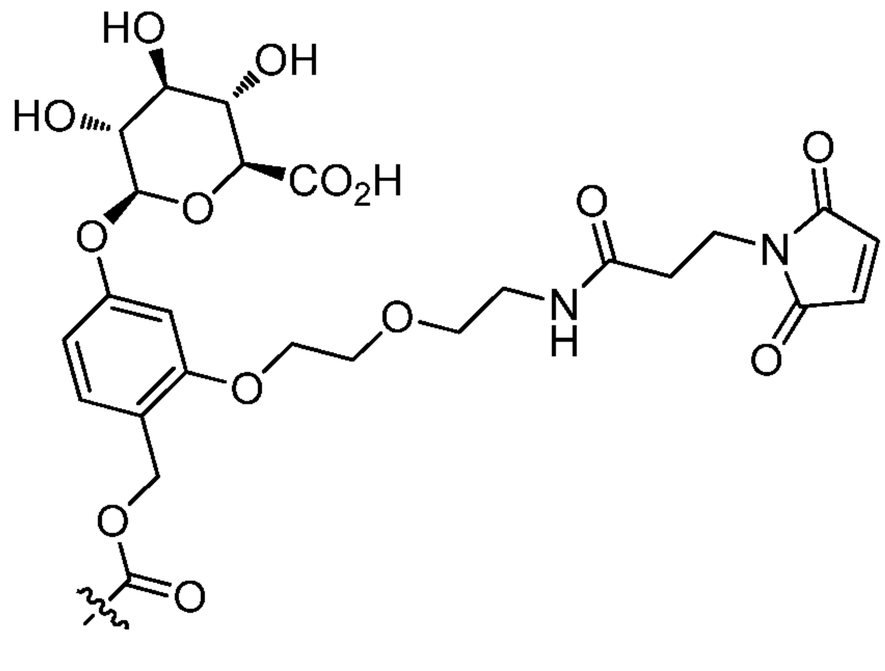


Exemplary embodiments of linkers according to structural formula (Vc) that may be included in the ADCs described herein include the linkers illustrated below (as illustrated, the linkers include a group suitable for covalently linking the linker to an antibody):

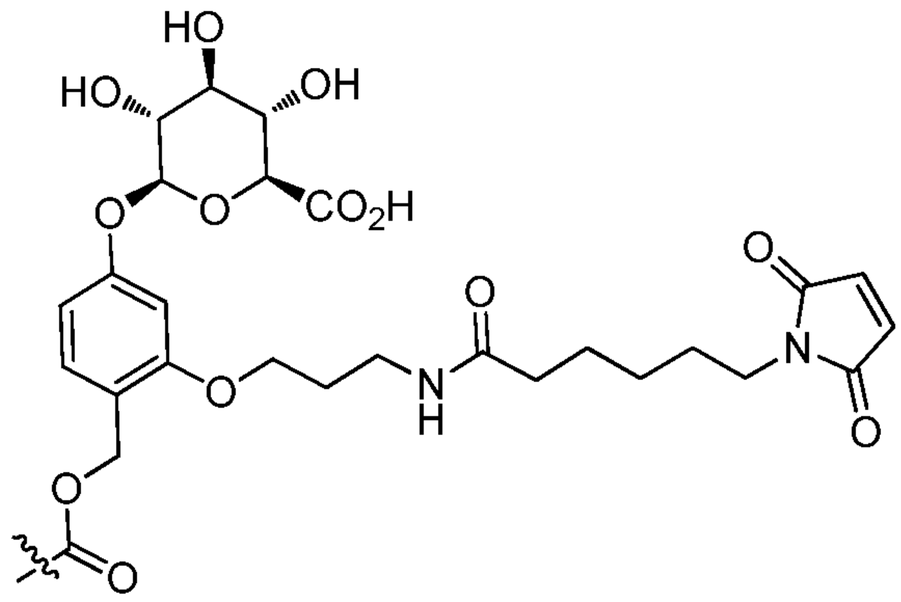
(Vc.1)



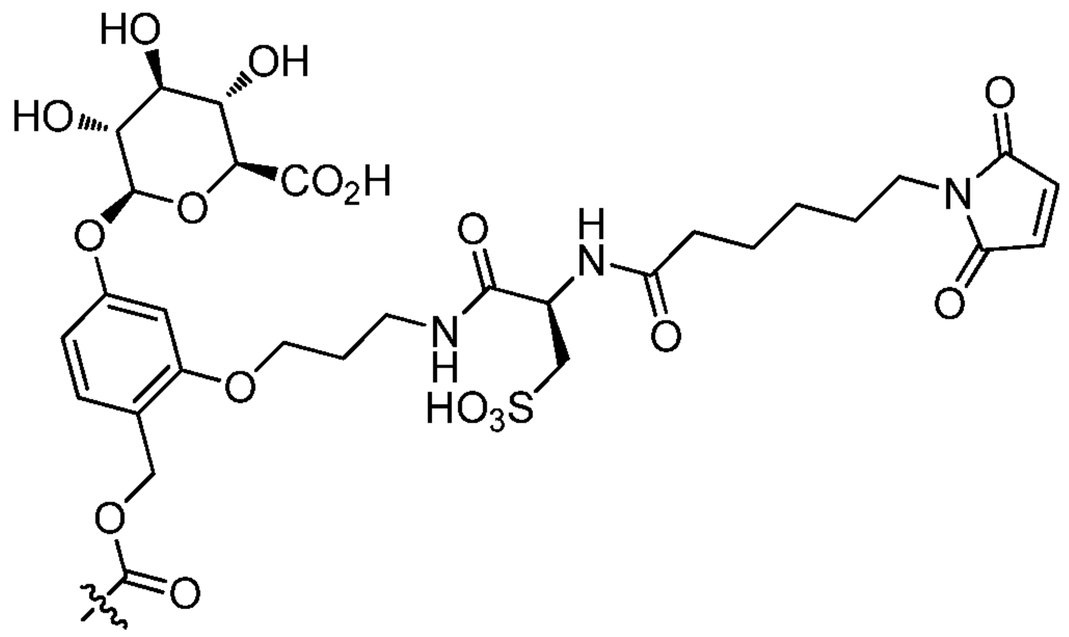
(Vc.2)



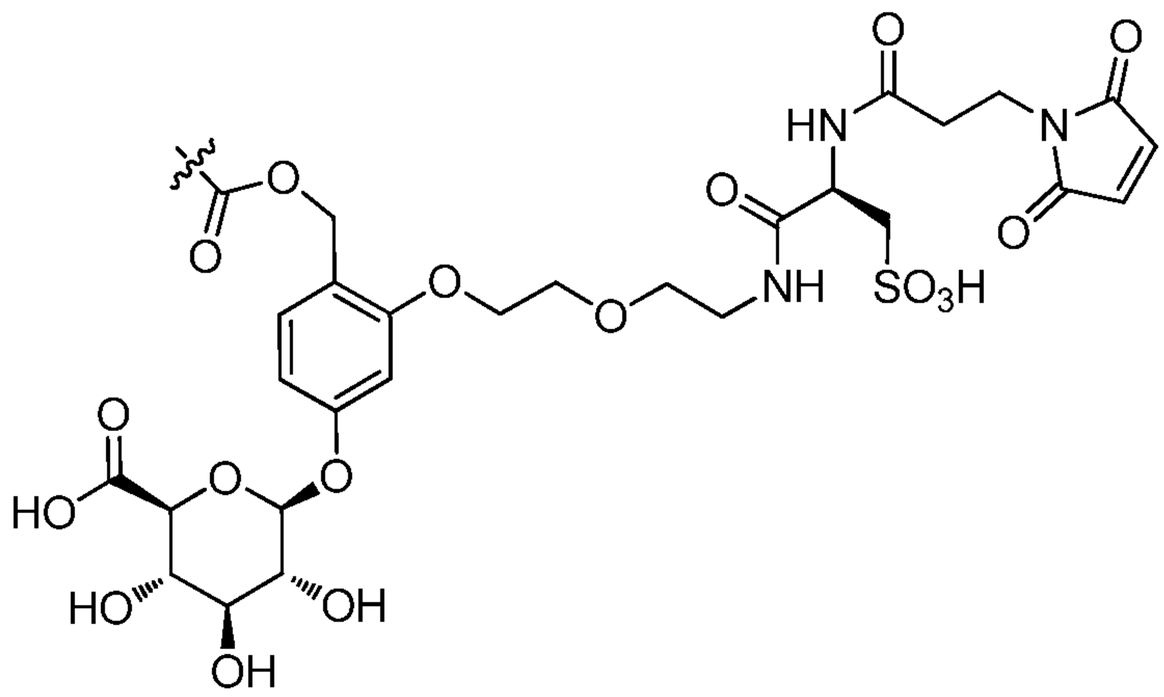
(Vc.3)



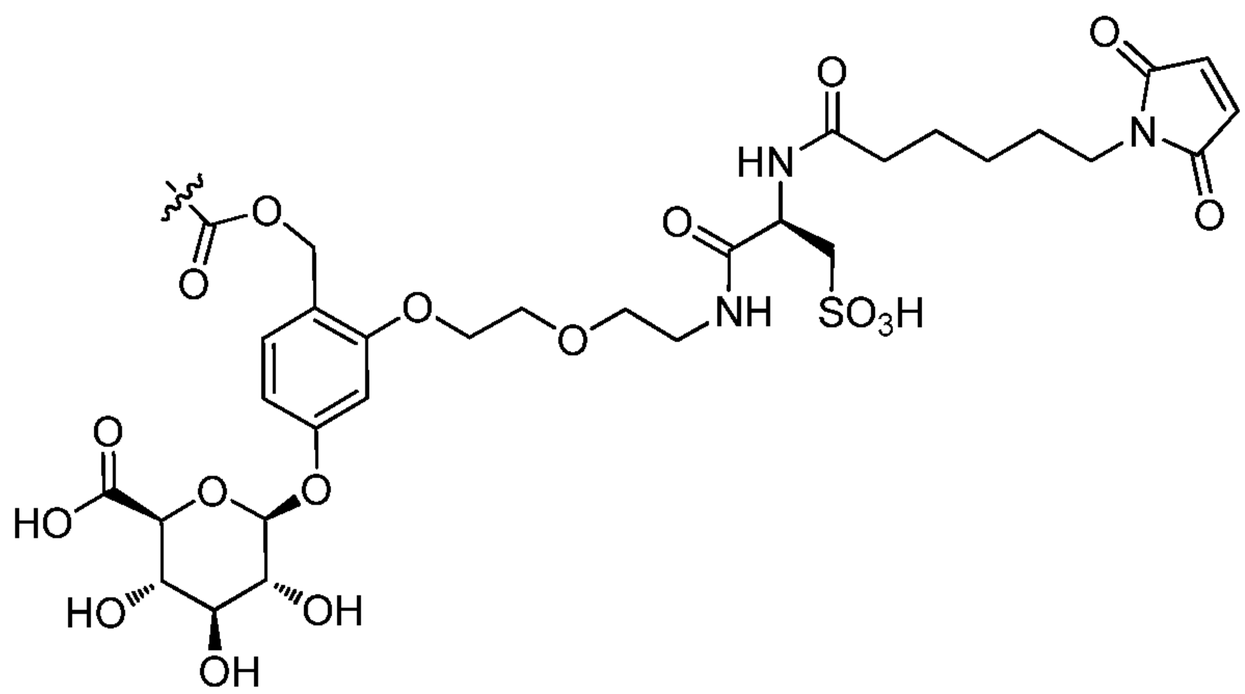
(Vc.4)



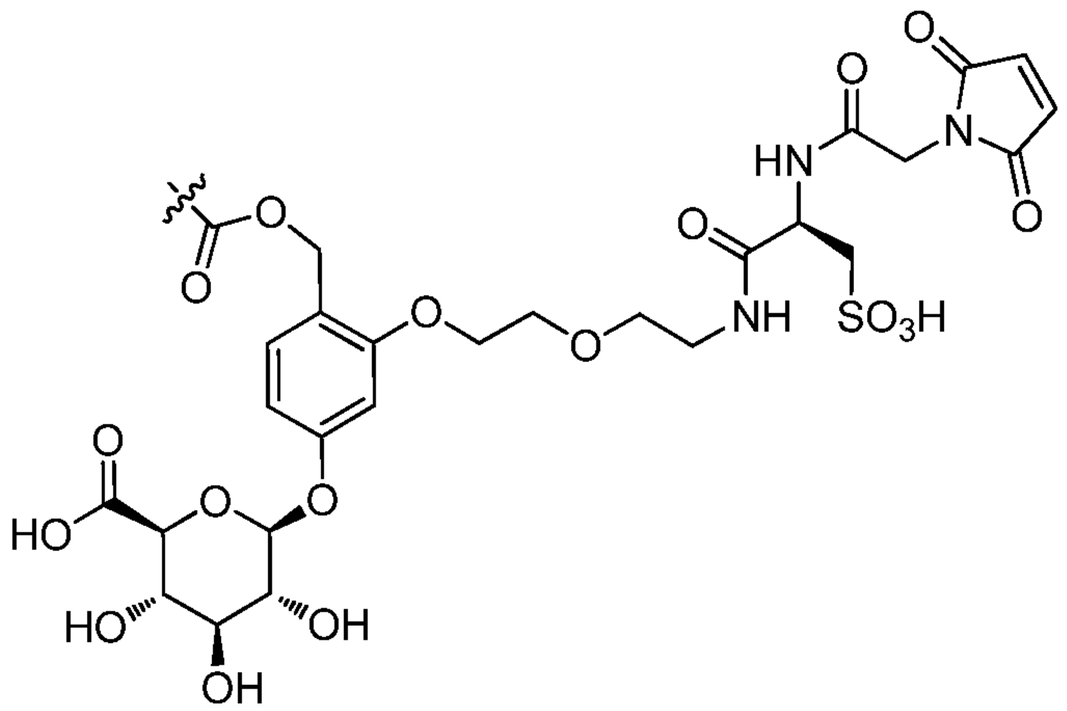
(Vc.5)



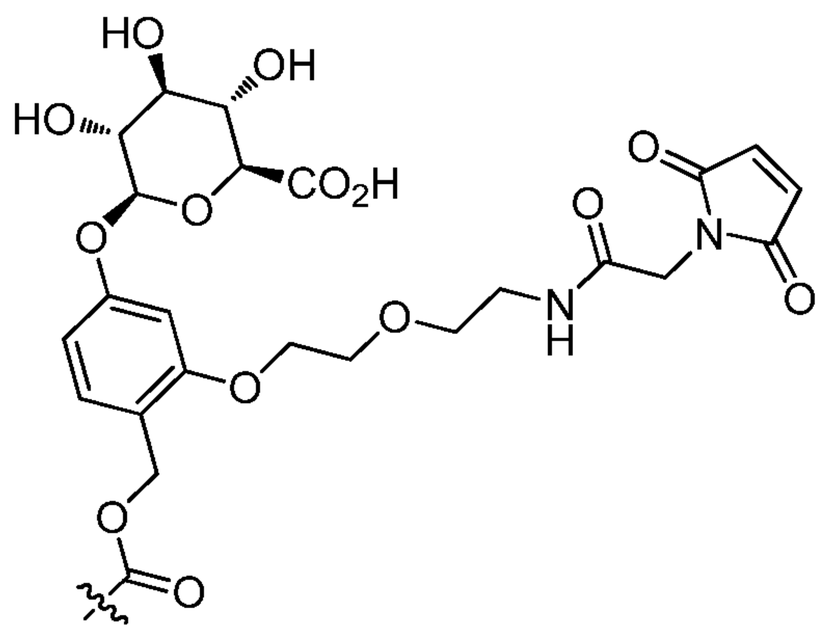
(Vc.6)



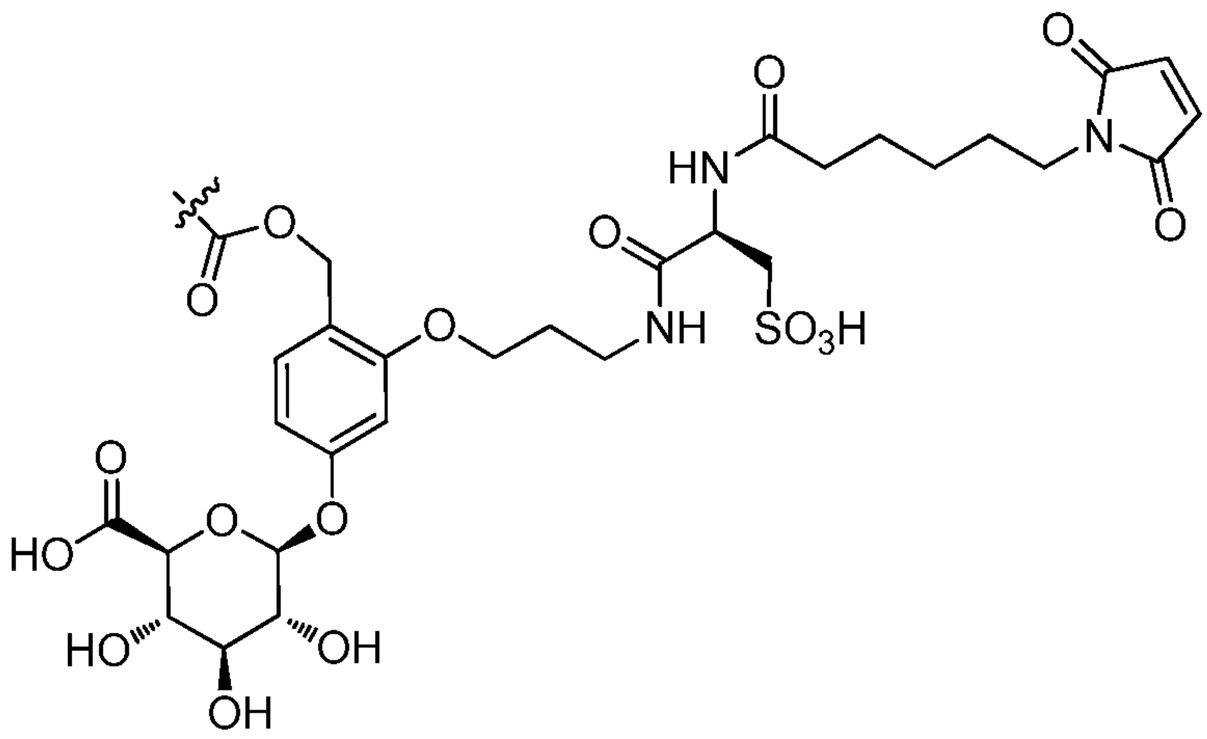
(Vc.7)



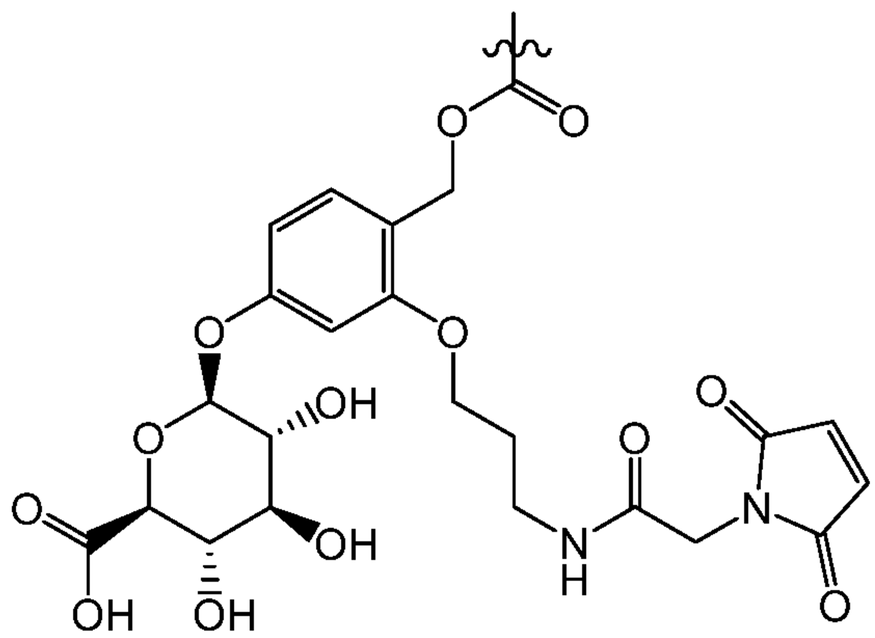
(Vc.8)



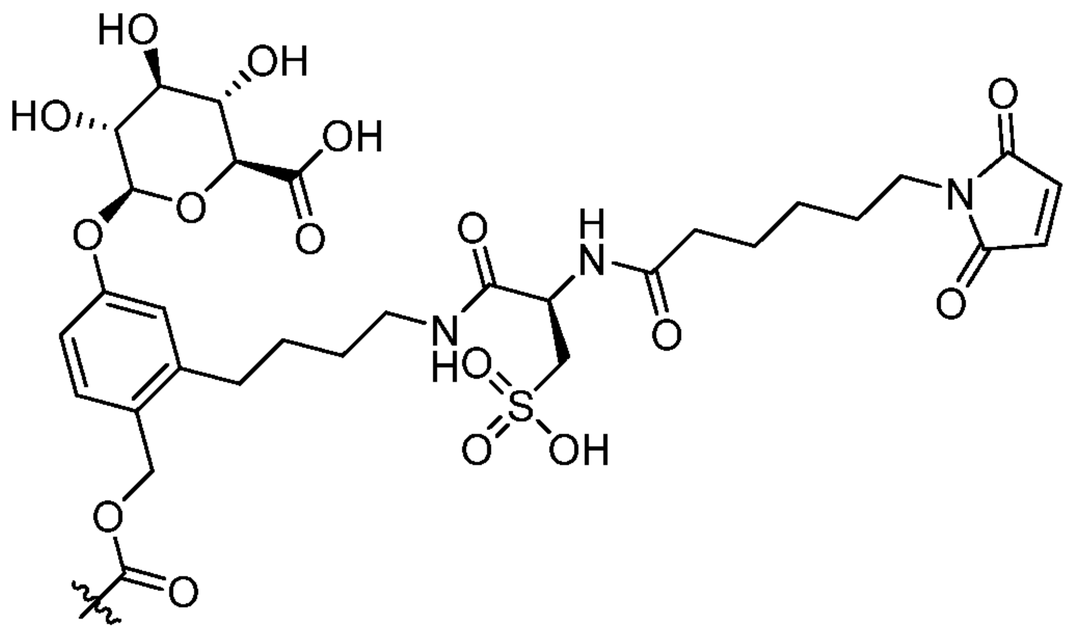
(Vc.9)



(Vc.10)

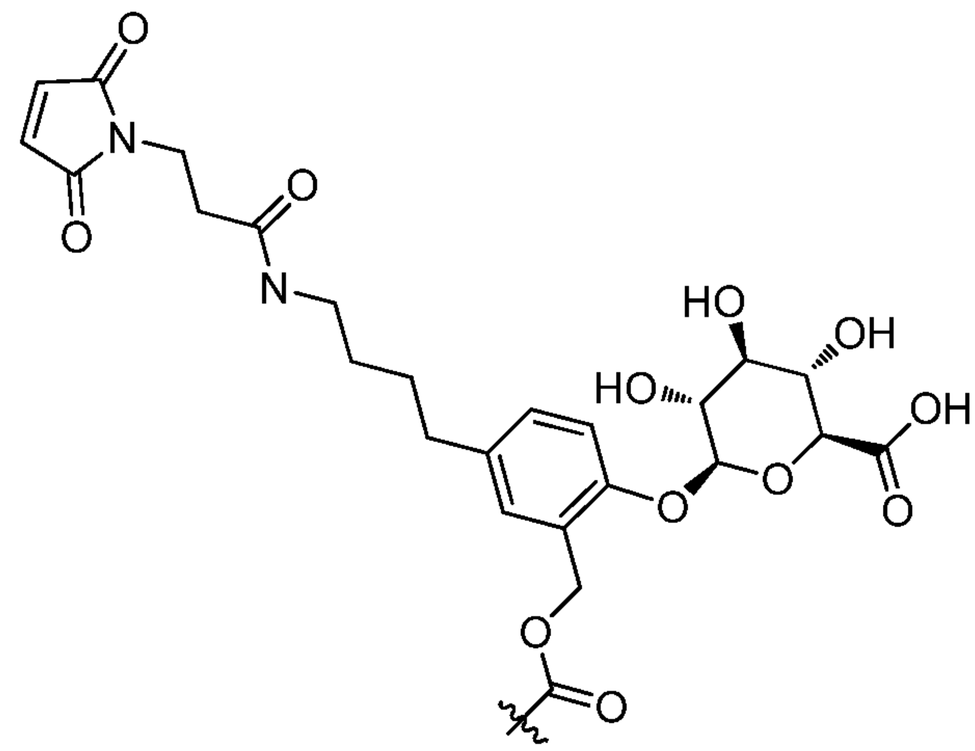


(Vc.11)

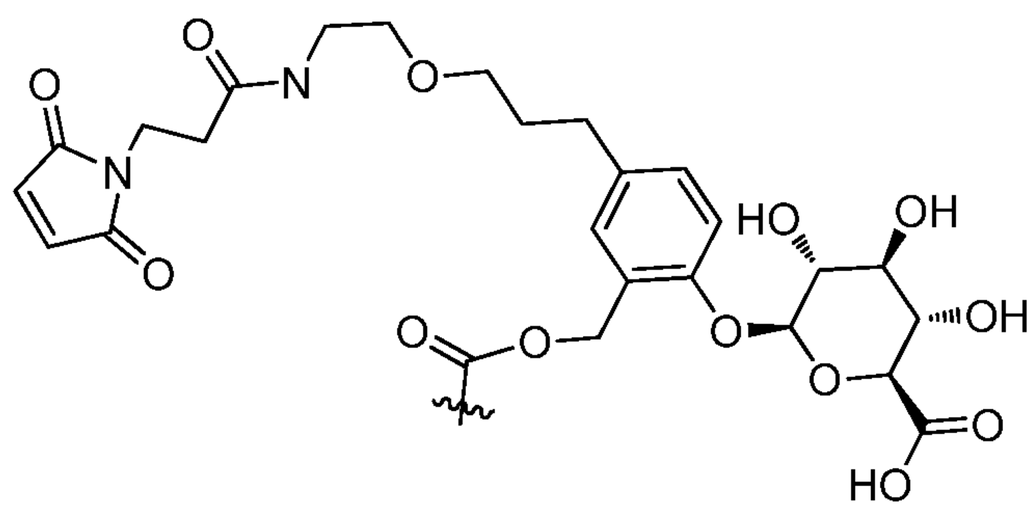


Exemplary embodiments of linkers according to structural formula (Vd) that may be included in the ADCs described herein include the linkers illustrated below (as illustrated, the linkers include a group suitable for covalently linking the linker to an antibody):

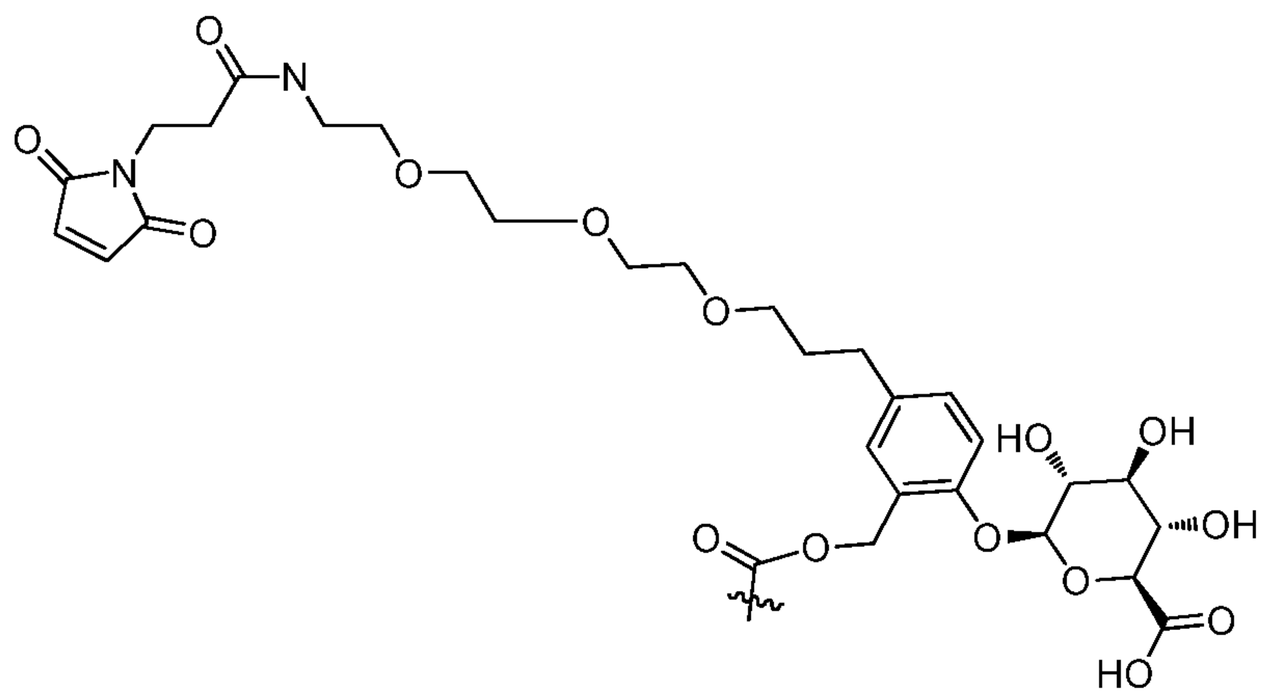
(Vd.1)



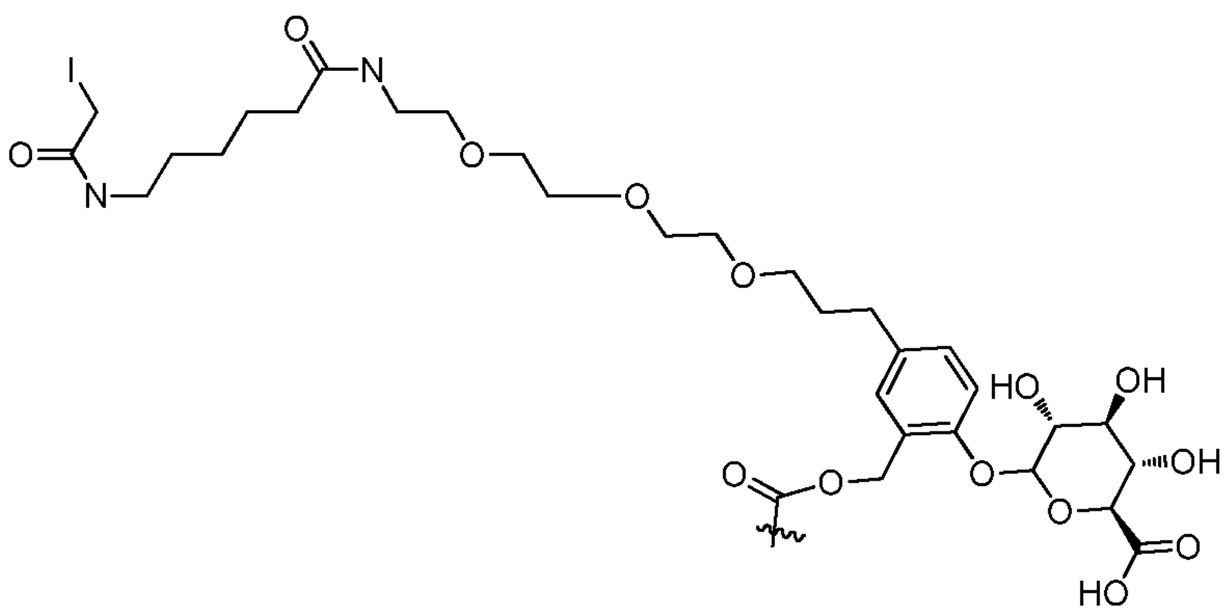
(Vd.2)



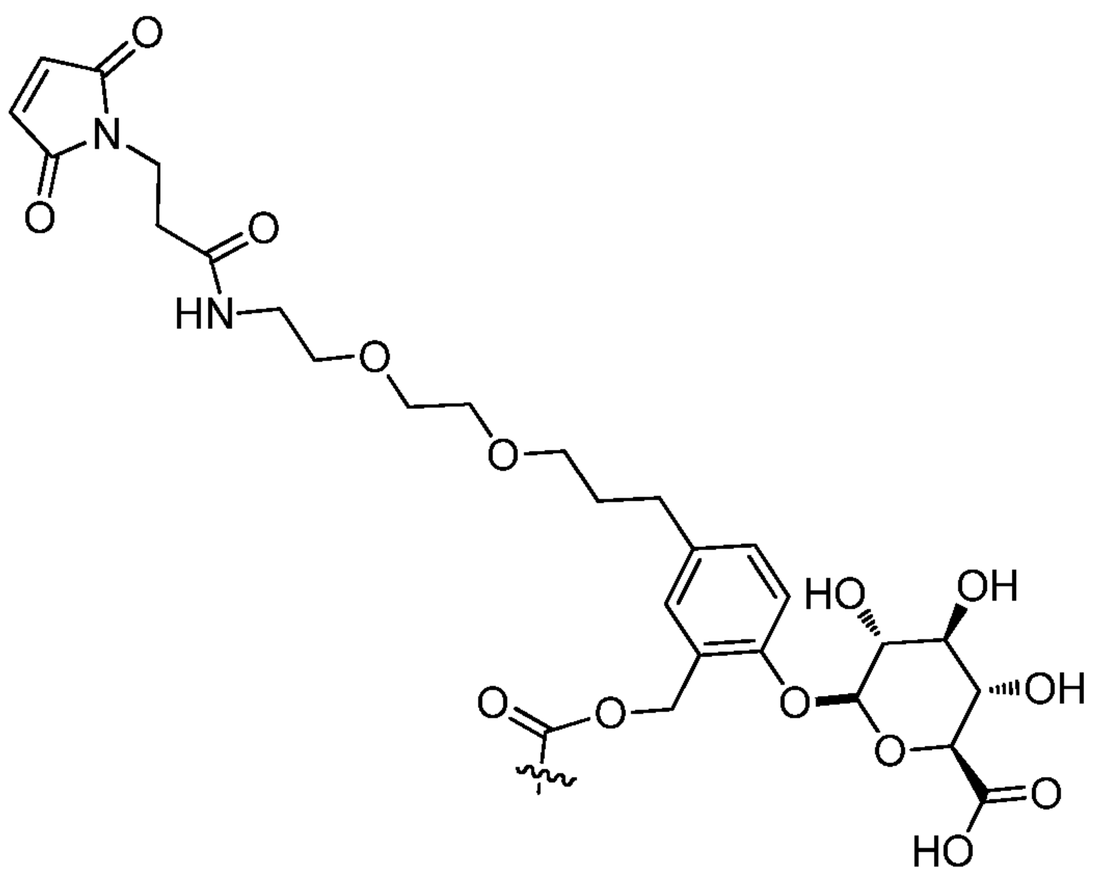
(Vd.3)



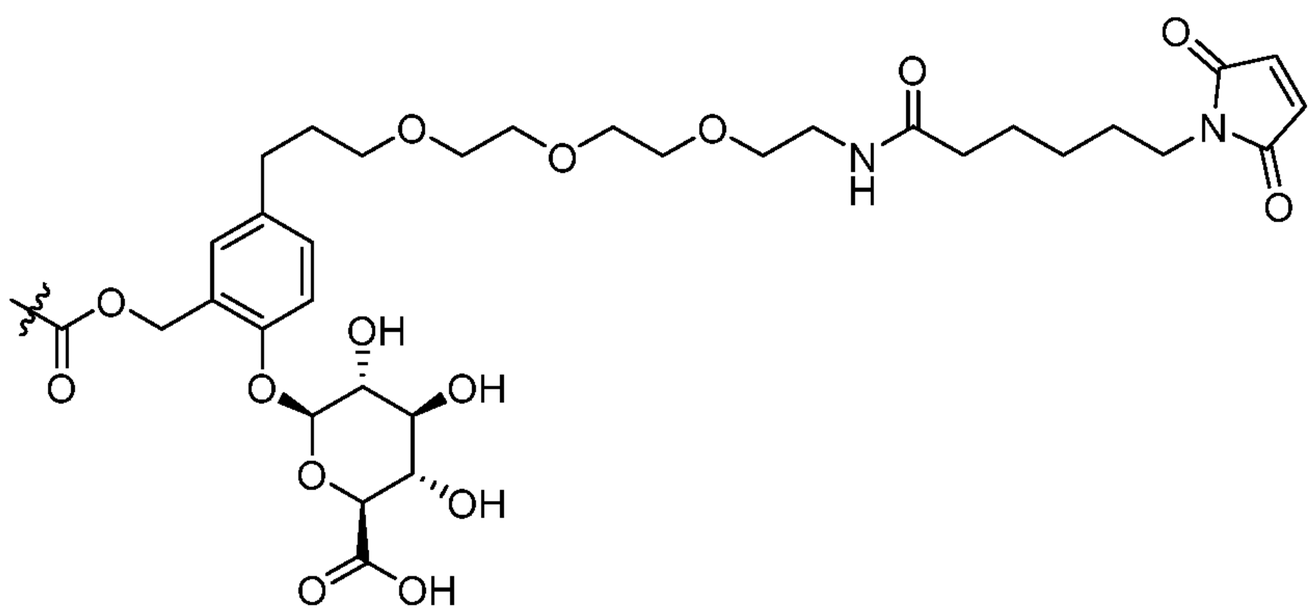
(Vd.4)



(Vd.5)

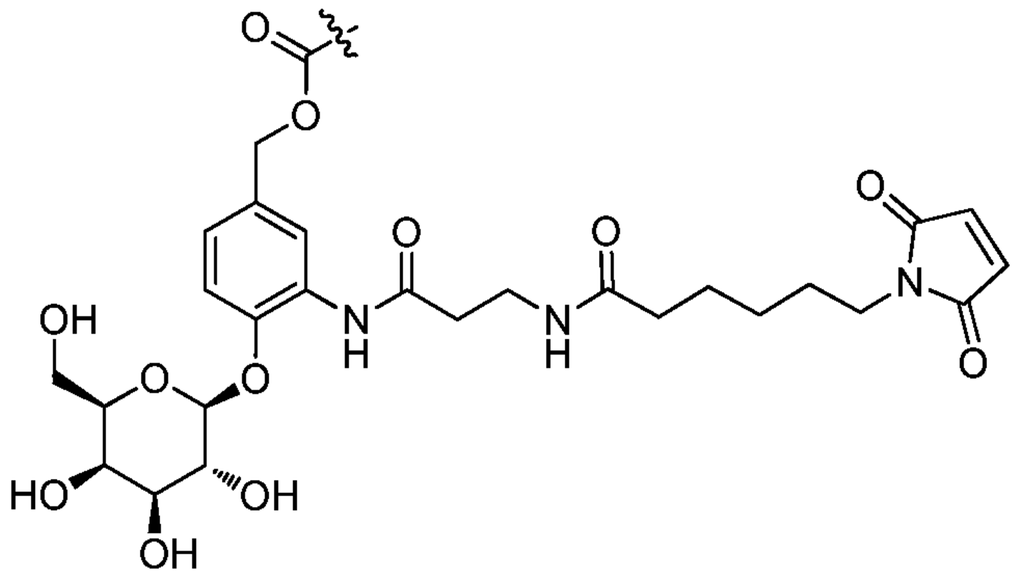


(Vd.6)

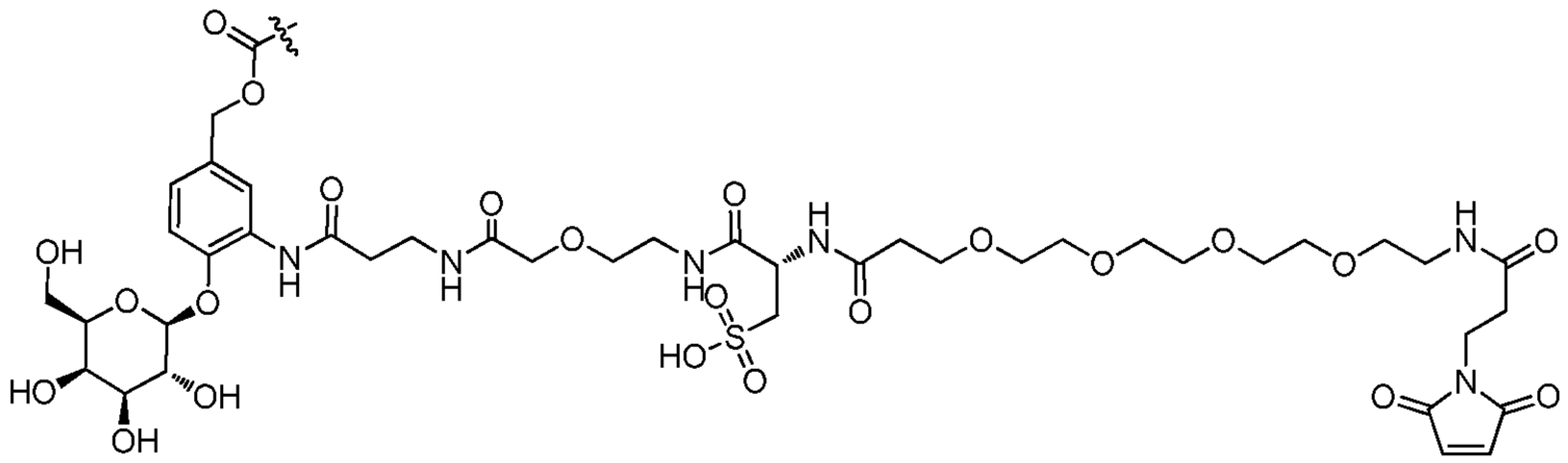


Exemplary embodiments of linkers according to structural formula (Ve) that may be included in the ADCs described herein include the linkers illustrated below (as illustrated, the linkers include a group suitable for covalently linking the linker to an antibody):

(Ve.1)



(Ve.2)



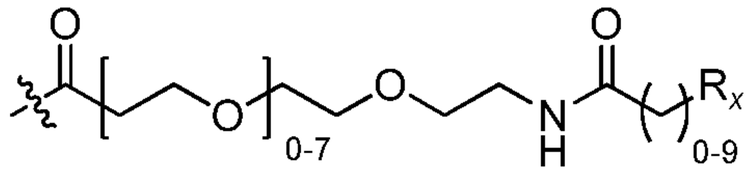
Non-Cleavable Linkers

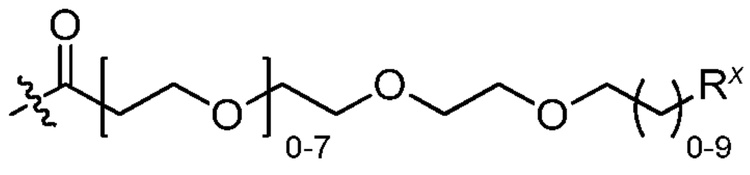
Although cleavable linkers may provide certain advantages, the linkers comprising the ADC described herein need not be cleavable. For noncleavable linkers, the drug release does not depend on the differential properties between the plasma and some cytoplasmic compartments. The release of the drug is postulated to occur after internalization of the ADC via antigen-mediated endocytosis and delivery to lysosomal compartment, where the antibody is degraded to the level of amino acids through intracellular proteolytic degradation. This process releases a drug derivative, which is formed by the drug, the linker, and the amino acid residue to which the linker was covalently attached. The amino-acid drug metabolites from conjugates with noncleavable linkers are more hydrophilic and generally less membrane permeable, which leads to less bystander effects and less nonspecific toxicities compared to conjugates with a cleavable linker. In general, ADCs with noncleavable linkers have greater stability in circulation than ADCs with cleavable linkers. Non-cleavable linkers may be alkylene chains, or maybe polymeric in natures, such as, for example, based upon polyalkylene glycol polymers, amide polymers, or may include segments of alkylene chains, polyalkylene glycols and/or amide polymers. In certain embodiments, the linker comprises a polyethylene glycol segment having from 1 to 6 ethylene glycol units.

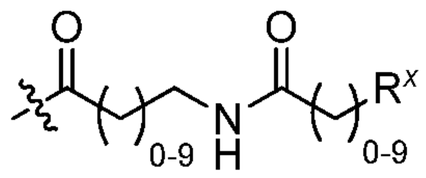
A variety of non-cleavable linkers used to link drugs to antibodies have been described. (*See*, Jeffrey *et al.*, 2006, *Bioconjug. Chem.* 17;831-840; Jeffrey *et al.*, 2007, *Bioorg. Med. Chem. Lett.*

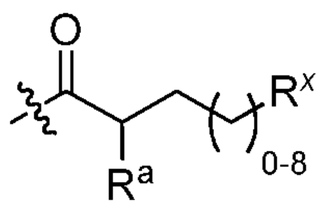
17:2278-2280; and Jiang *et al.*, 2005, *J. Am . Chem. Soc.* 127:11254-11255, the contents of which are incorporated herein by reference). All of these linkers may be included in the ADCs described herein.

In certain embodiments, the linker is non-cleavable *in vivo*, for example a linker according to structural formula (VIa), (VIb), (VIc) or (VId) (as illustrated, the linkers include a group suitable for covalently linking the linker to an antibody:

(VIa) 

(VIb) 

(VIc) 

(VId) 

or a pharmaceutically acceptable salt thereof, , wherein:

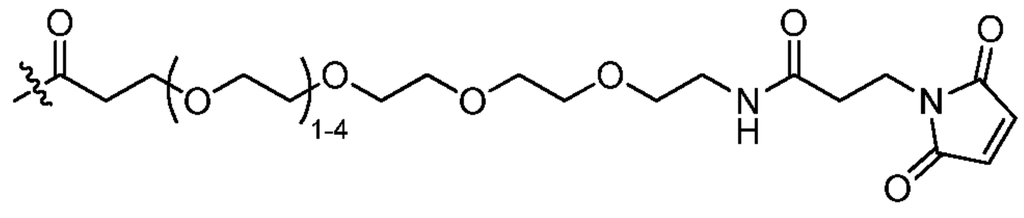
R^a is selected from hydrogen, alkyl, sulfonate and methyl sulfonate;

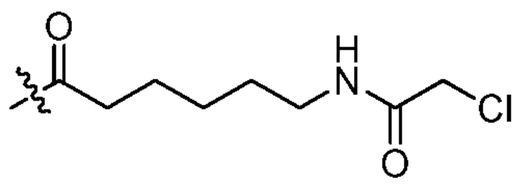
R^x is a moiety including a functional group capable of covalently linking the linker to an antibody; and

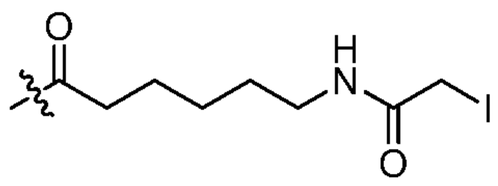
represents the point of attachment of the linker to the Bcl-xL inhibitor.

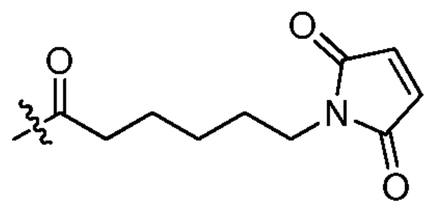
Exemplary embodiments of linkers according to structural formula (VIa)-(VId) that may be included in the ADCs described herein include the linkers illustrated below (as illustrated, the linkers

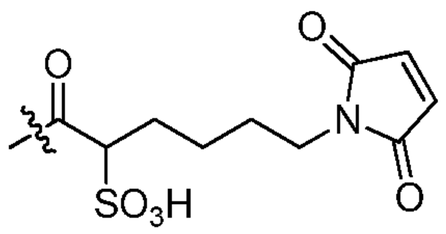
include a group suitable for covalently linking the linker to an antibody, and "~" represents the point of attachment to a Bcl-xL inhibitor):

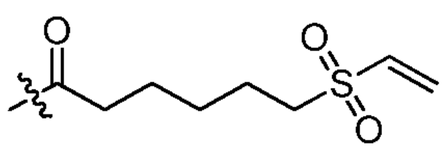
(VIa.1) 

(VIc.1) 

(VIc.2) 

(VId.1) 

(VId.2) 

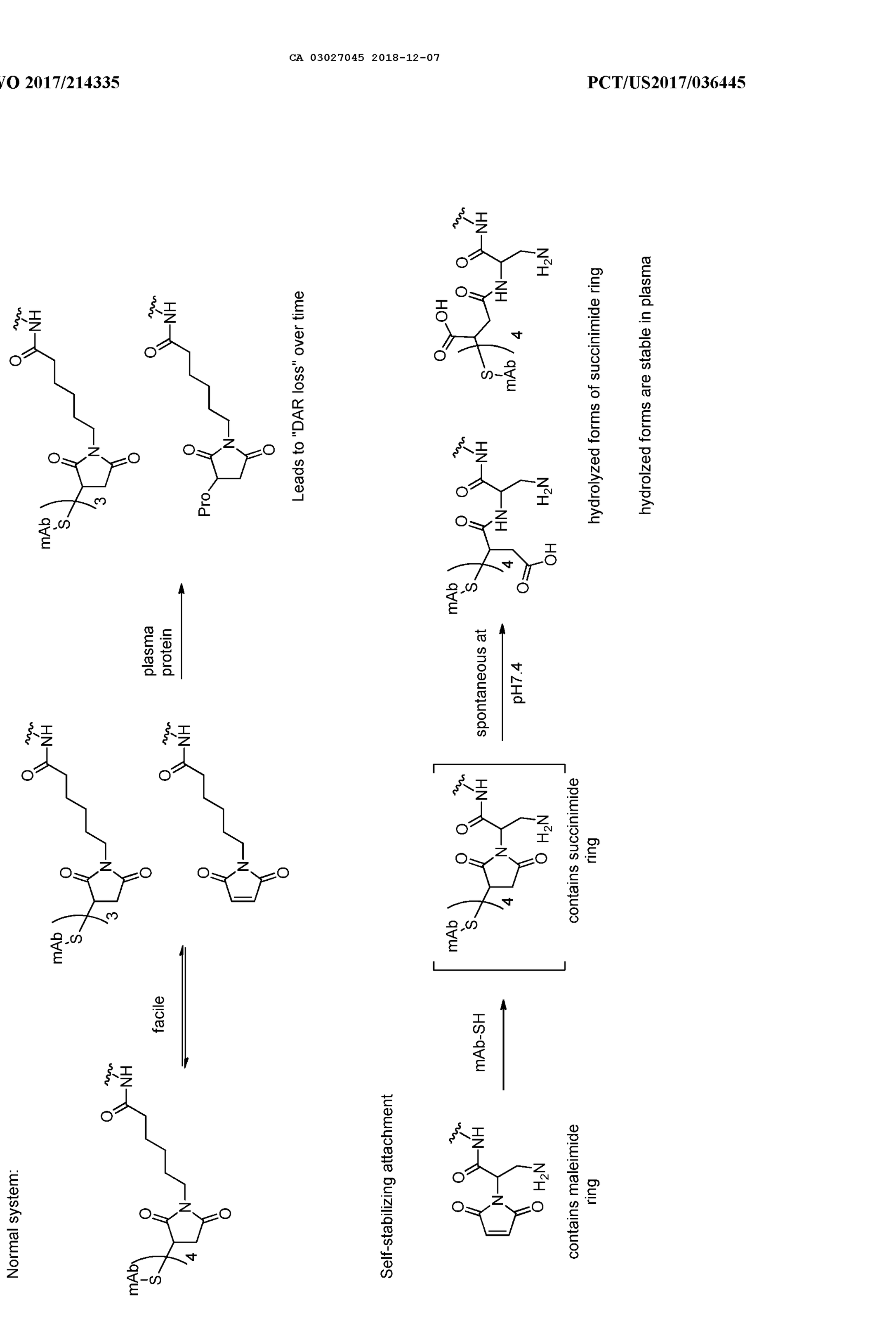
(VId.3) 

(VId.4)

Groups Used to Attach Linkers to Anti-B7-H3 Antibodies

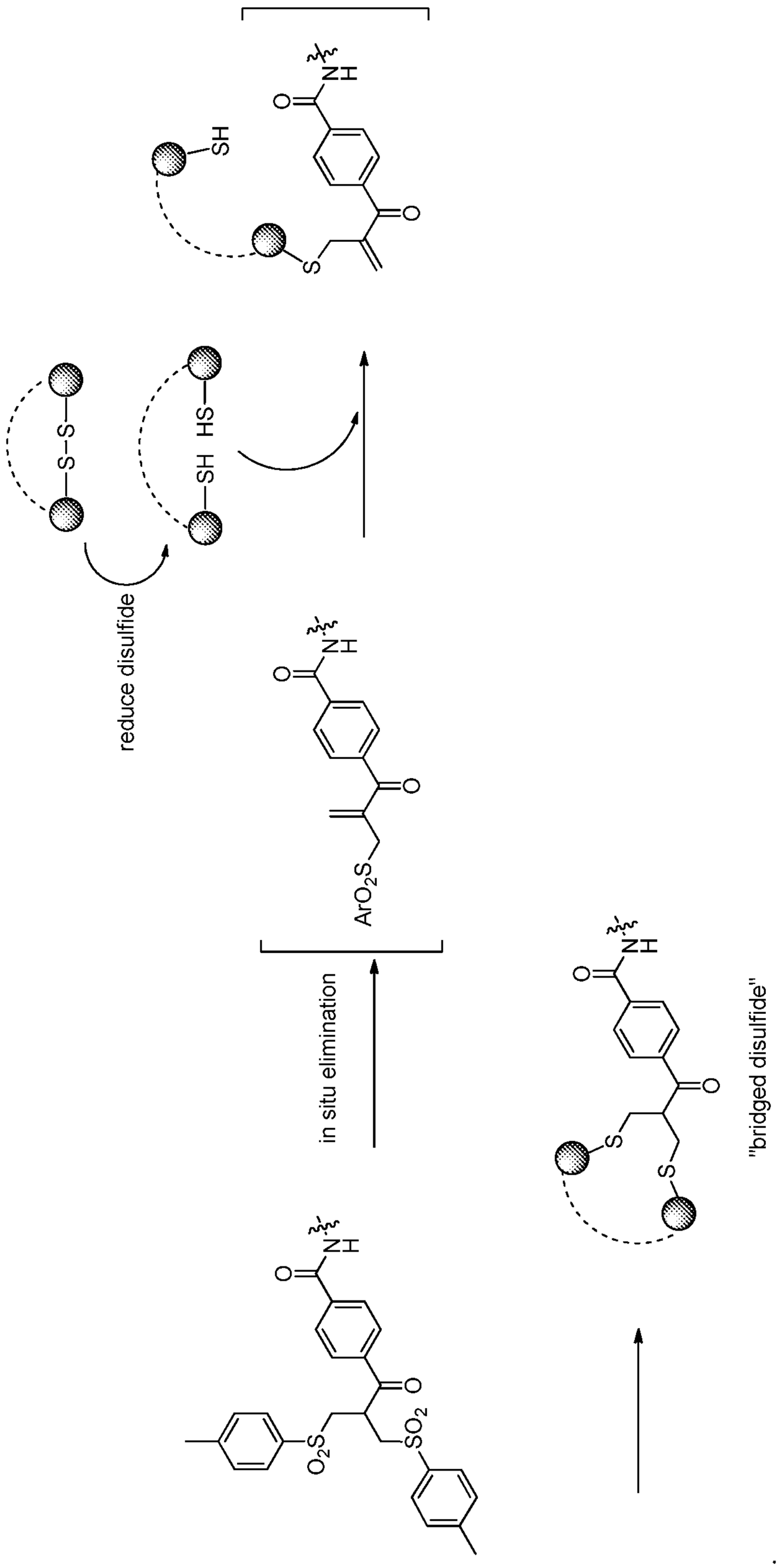
Attachment groups can be electrophilic in nature and include: maleimide groups, activated disulfides, active esters such as NHS esters and HOBt esters, haloformates, acid halides, alkyl and benzyl halides such as haloacetamides. As discussed below, there are also emerging technologies related to "self-stabilizing" maleimides and "bridging disulfides" that can be used in accordance with the disclosure.

Loss of the drug-linker from the ADC has been observed as a result of a maleimide exchange process with albumin, cysteine or glutathione (Alley *et al.*, 2008, *Bioconjugate Chem.* 19: 759-769). This is particularly prevalent from highly solvent-accessible sites of conjugation while sites that are partially accessible and have a positively charged environment promote maleimide ring hydrolysis (Junutula *et al.*, 2008, *Nat. Biotechnol.* 26: 925-932). A recognized solution is to hydrolyze the succinimide formed from conjugation as this is resistant to deconjugation from the antibody, thereby making the ADC stable in serum. It has been reported previously that the succinimide ring will undergo hydrolysis under alkaline conditions (Kalia *et al.*, 2007, *Bioorg. Med. Chem. Lett. 17*: 6286-6289). One example of a "self-stabilizing" maleimide group that hydrolyzes spontaneously under antibody conjugation conditions to give an ADC species with improved stability is depicted in the schematic below. *See* U.S. Published Application No. 2013/0309256, International Application Publication No. WO 2013/173337, Tumey *et al.*, 2014, Bioconjugate Chem. 25: 1871-1880, and Lyon *et al.*, 2014, *Nat. Biotechnol.* 32: 1059-1062. Thus, the maleimide attachment group is reacted with a sulfhydryl of an antibody to give an intermediate succinimide ring. The hydrolyzed form of the attachment group is resistant to deconjugation in the presence of plasma proteins.

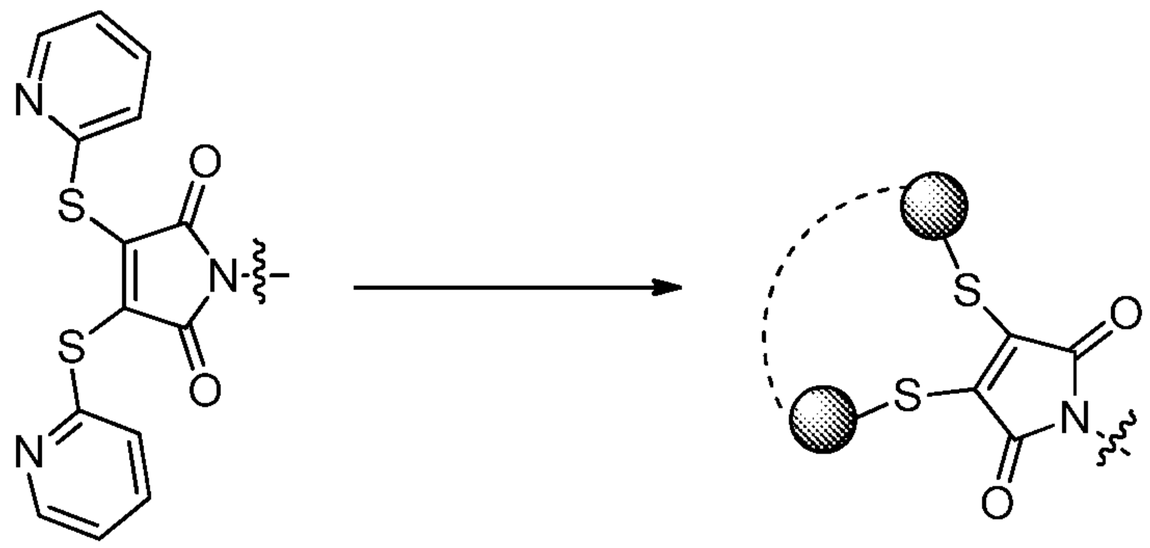

Normal system:
Self-stabilizing attachment
Leads to "DAR loss" over time
plasma protein
spontaneous at pH7.4
hydrolyzed forms of succinimide ring
hydrolzed forms are stable in plasma
facile
mAb-SH
contains maleimide ring
contains succinimide ring
mAb
Pro
NH
HN
OH
H_2N

As shown above, the maleimide ring of a linker may react with an antibody Ab, forming a covalent attachment as either a succinimide (closed form) or succinamide (open form).

Polytherics has disclosed a method for bridging a pair of sulfhydryl groups derived from reduction of a native hinge disulfide bond. *See*, Badescu *et al.*, 2014, *Bioconjugate Chem.* 25:1124-1136. The reaction is depicted in the schematic below. An advantage of this methodology is the ability to synthesize homogenous DAR4 ADCs by full reduction of IgGs (to give 4 pairs of sulfhydryls) followed by reaction with 4 equivalents of the alkylating agent. ADCs containing "bridged disulfides" are also claimed to have increased stability.

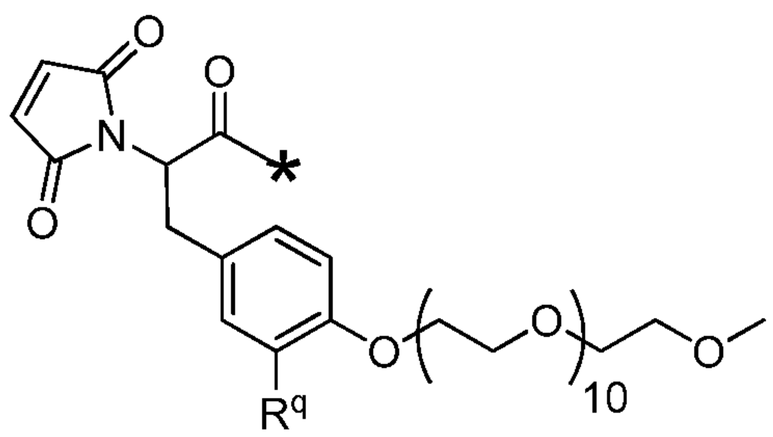

NH
O
SH
O
S
reduce disulfide
S—S
SH HS
NH
O
O
in situ elimination
ArO_2S
NH
O
S
S
"bridged disulfide"
O
O_2S
SO_2
O

Similarly, as depicted below, a maleimide derivative that is capable of bridging a pair of sulfhydryl groups has been developed. *See* U.S. Published Application No. 2013/0224228.

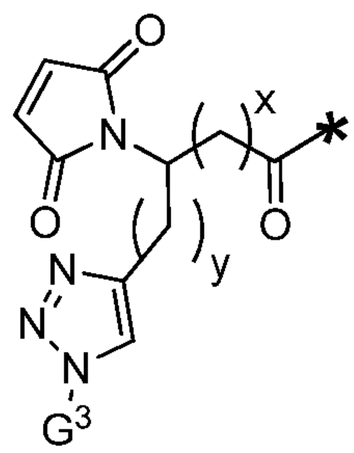


In certain embodiments the attachment moiety comprises the structural formulae (VIIa), (VIIb), or (VIIc):

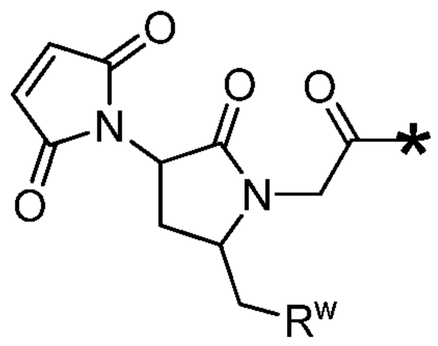
(VIIa)



(VIIb)



(VIIc)



or a pharmaceutically acceptable salt thereof, wherein:

R^q is H or $–O-(CH_2CH_2O)_{11}-CH_3$;

x is 0 or 1;

y is 0 or 1;

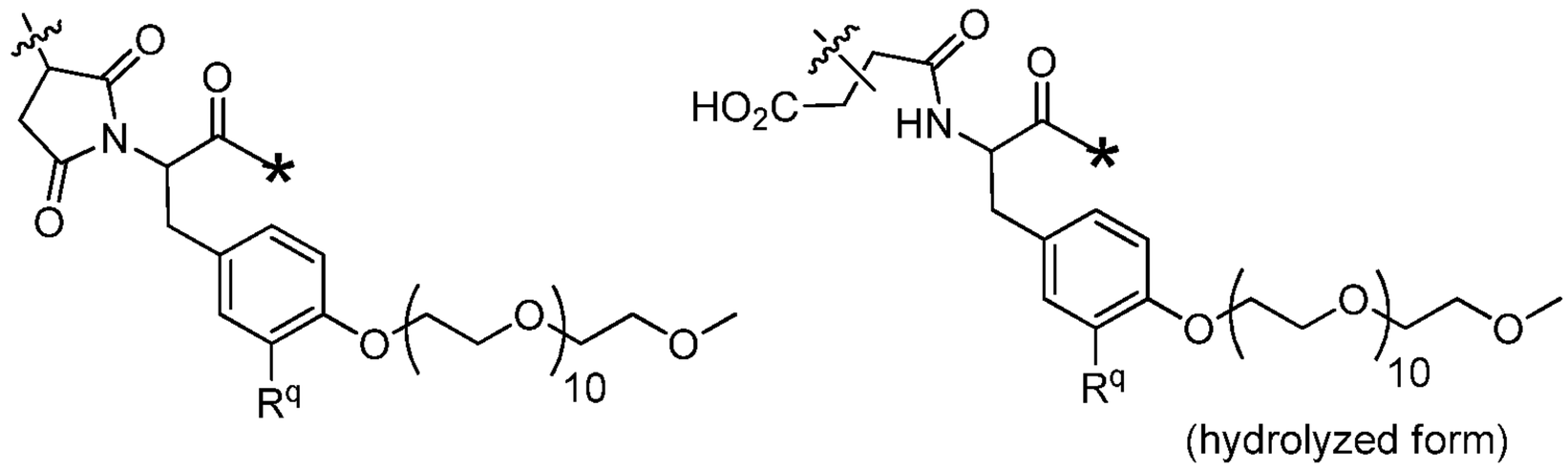
G^3 is $–CH_2CH_2CH_2SO_3H$ or $–CH_2CH_2O-(CH_2CH_2O)_{11}-CH_3$;

R^w is $–O-CH_2CH_2SO_3H$ or $–NH(CO)-CH_2CH_2O-(CH_2CH_2O)_{12}-CH_3$; and

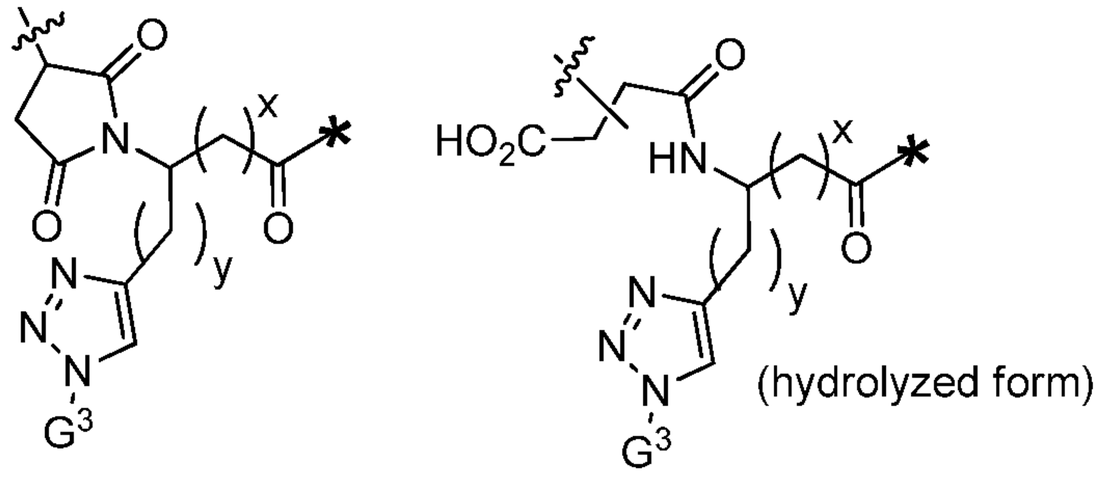
* represents the point of attachment to the remainder of the linker.

In certain embodiments, the linker comprises a segment according to structural formulae (VIIIa), (VIIIb), or (VIIIc):

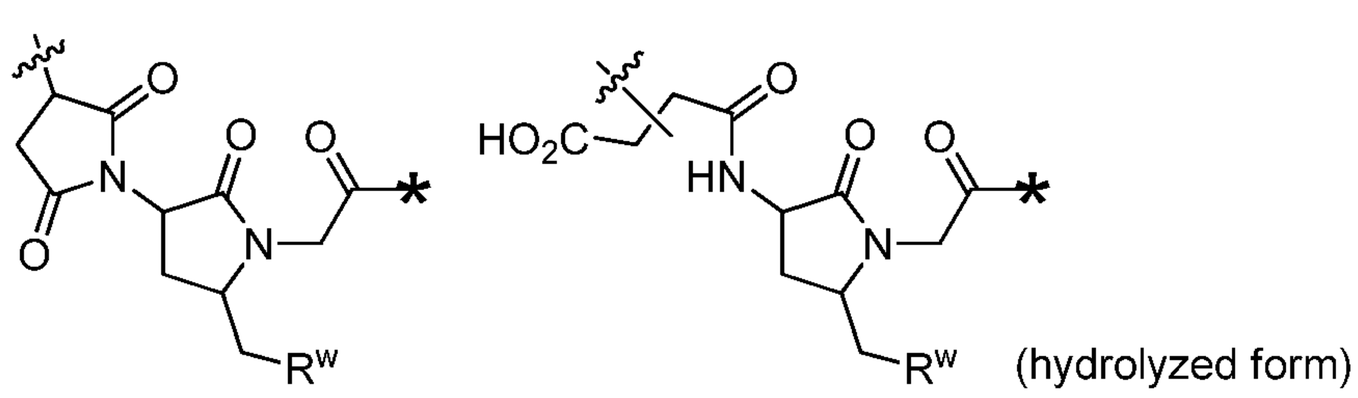
(VIIIa)



(VIIIb)



(VIIIc)



or a hydrolyzed derivative or a pharmaceutically acceptable salt thereof, wherein:

R^q is H or $–O-(CH_2CH_2O)_{11}-CH_3$;

x is 0 or 1;

y is 0 or 1;

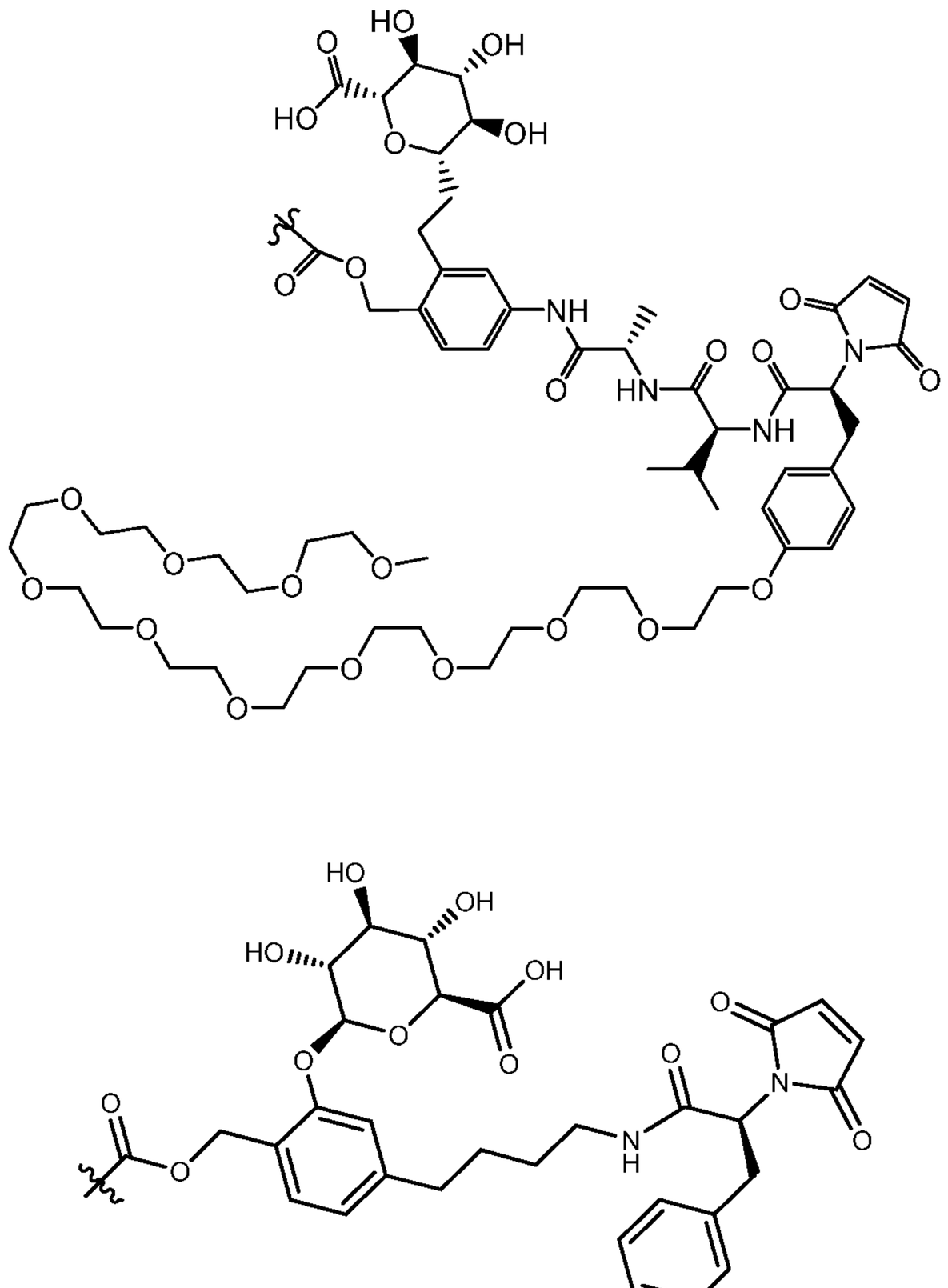
G^3 is $–CH_2CH_2CH_2SO_3H$ or $–CH_2CH_2O-(CH_2CH_2O)_{11}-CH_3$;

R^w is $–O-CH_2CH_2SO_3H$ or $–NH(CO)-CH_2CH_2O-(CH_2CH_2O)_{12}-CH_3$;

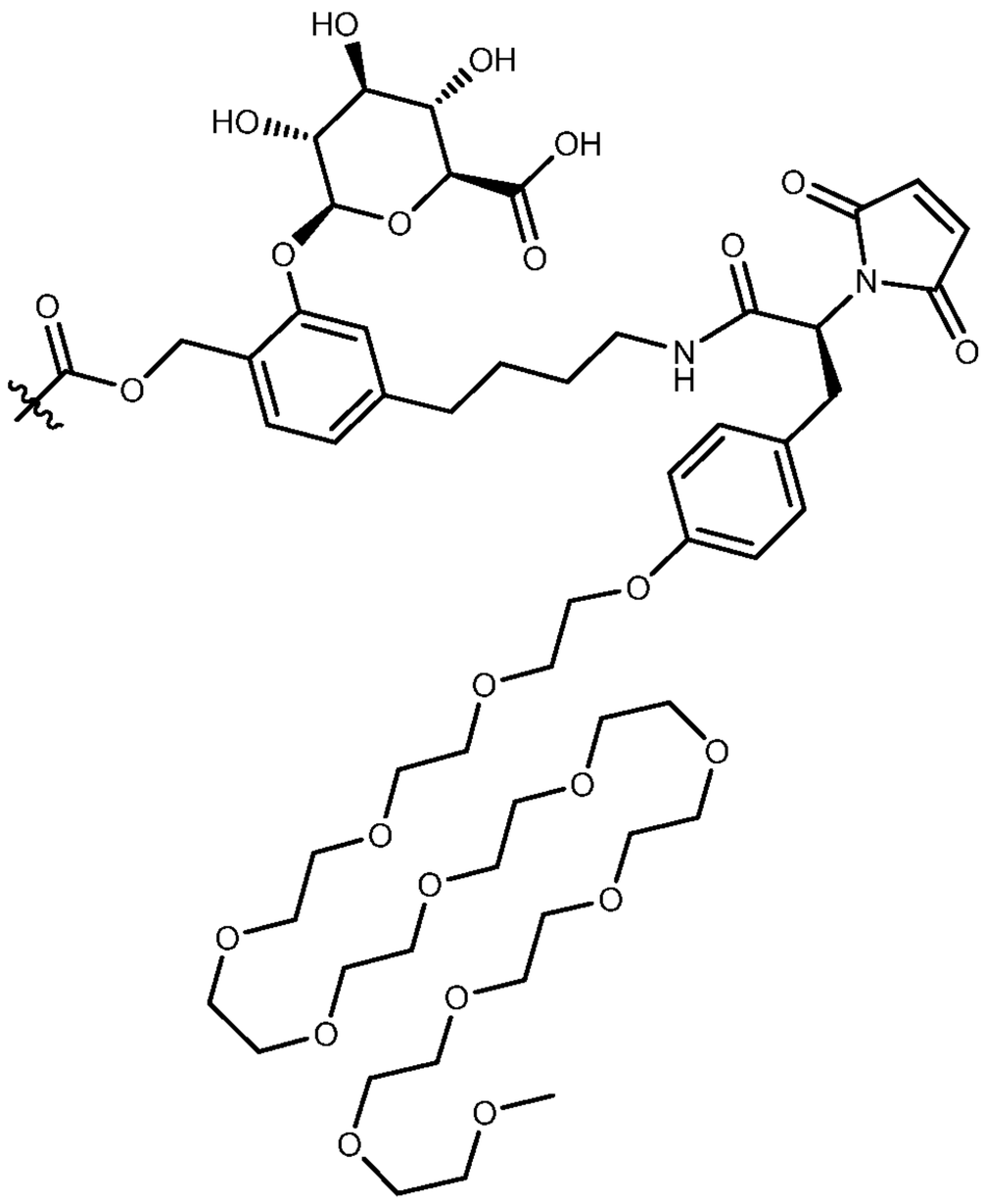
* represents the point of attachment to the remainder of the linker; and

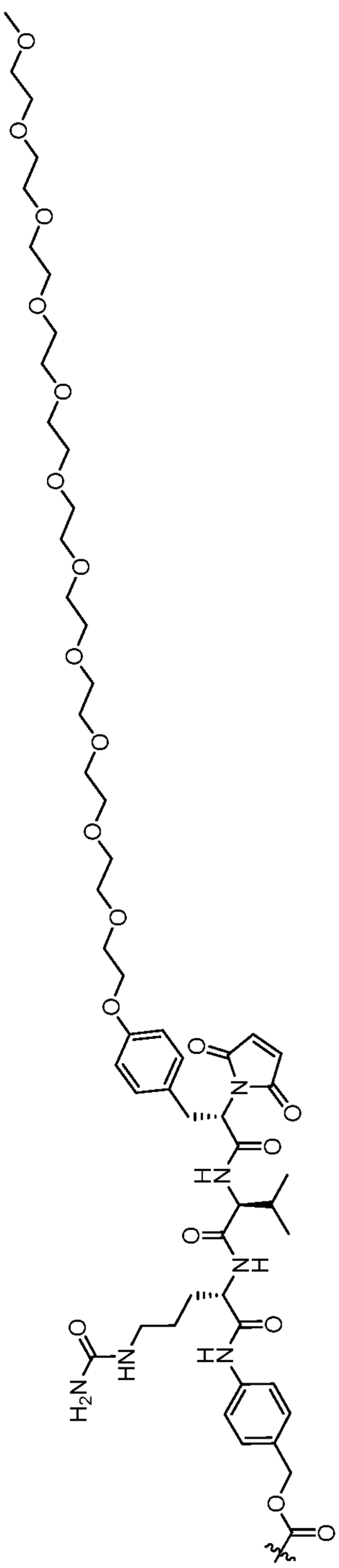
~~~ represents the point of attachment of the linker to the antibody.

Exemplary embodiments of linkers according to structural formula (VIIa) and (VIIb) that may be included in the ADCs described herein include the linkers illustrated below (as illustrated, the linkers include a group suitable for covalently linking the linker to an antibody):
~~~

(VIIa.1)

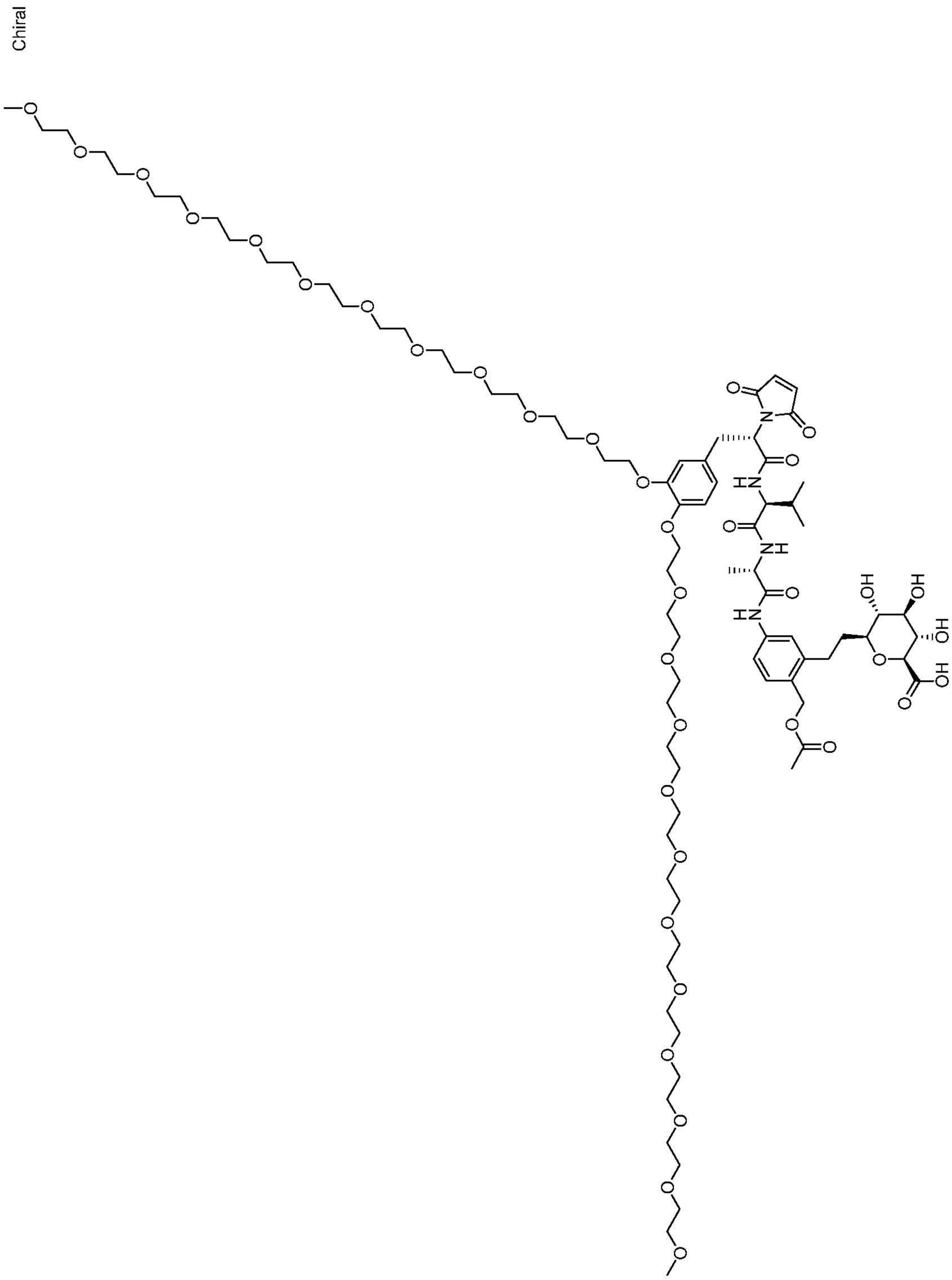


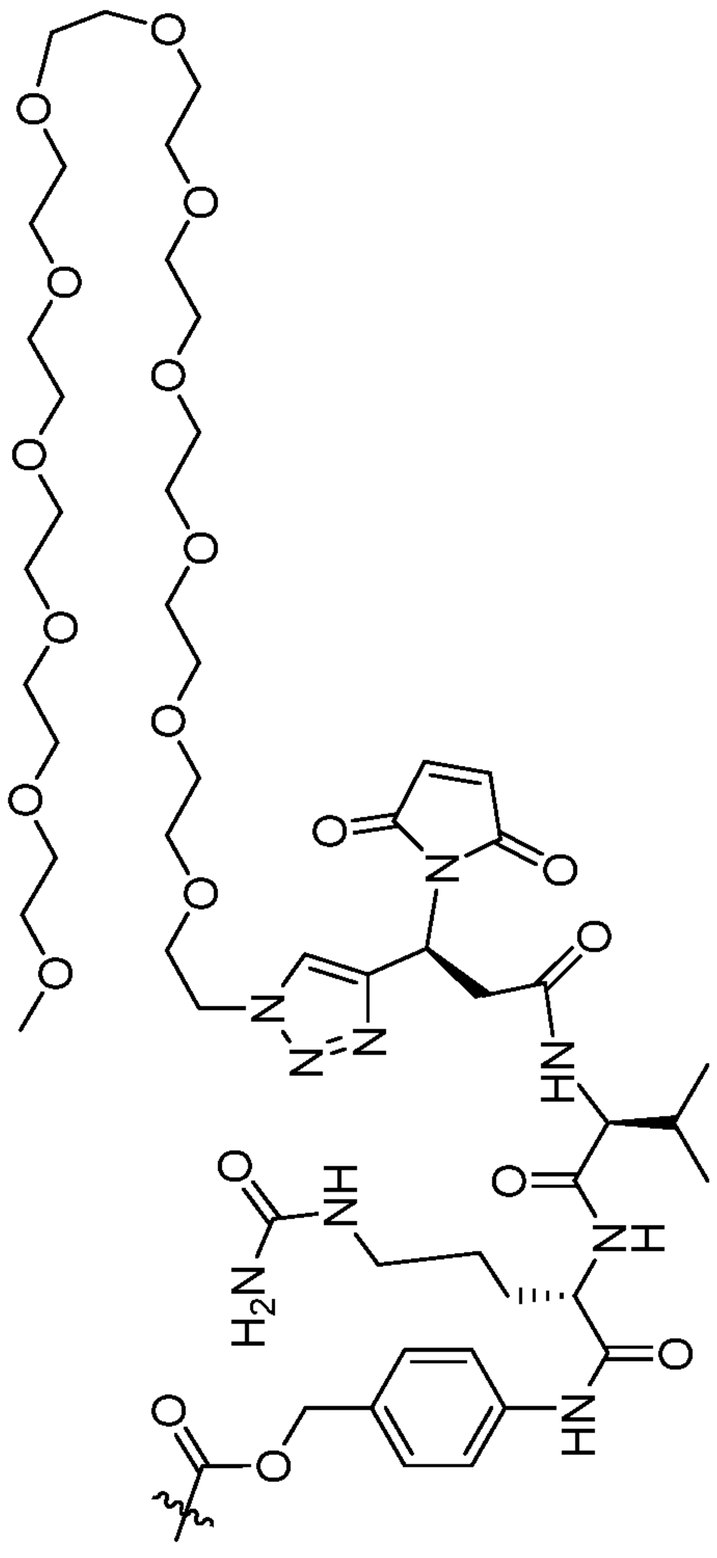
(VIIa.2)



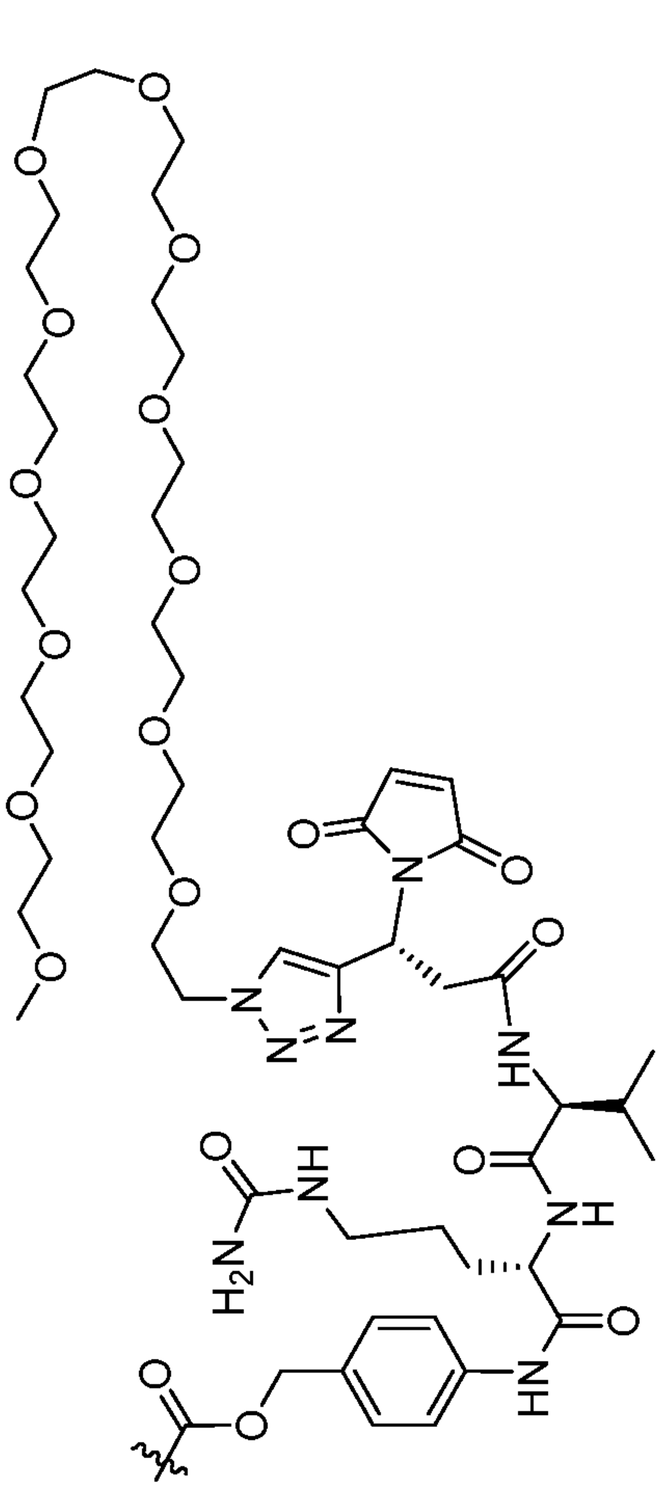


(VIIa.3)

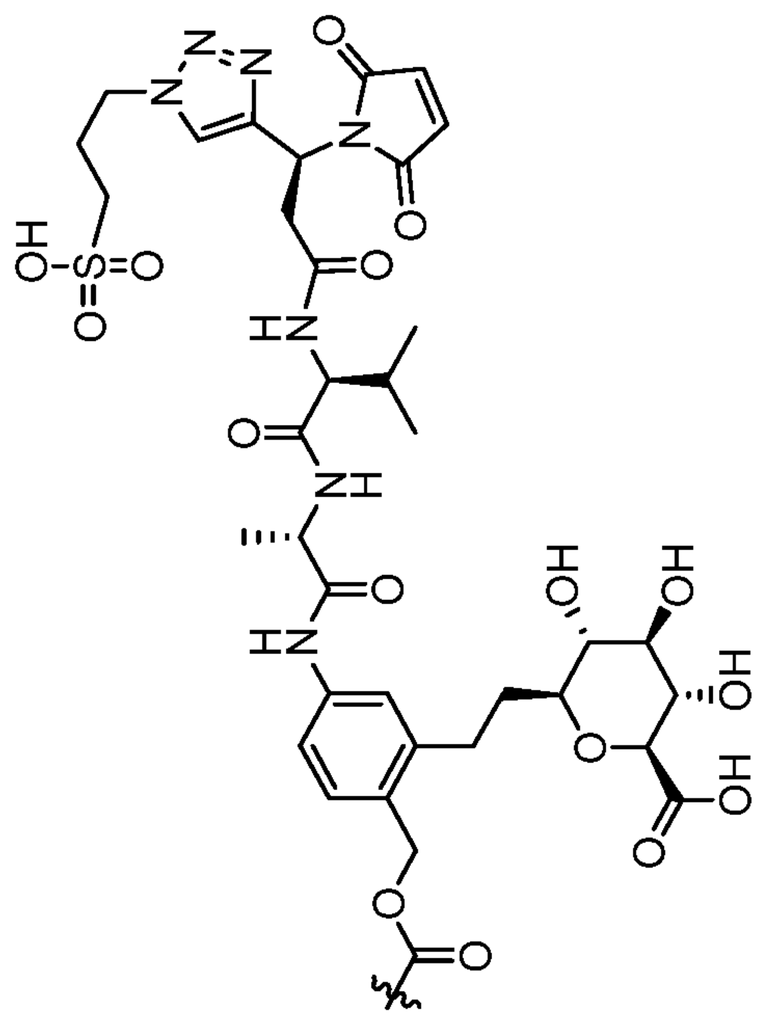

Chiral
O
O
O



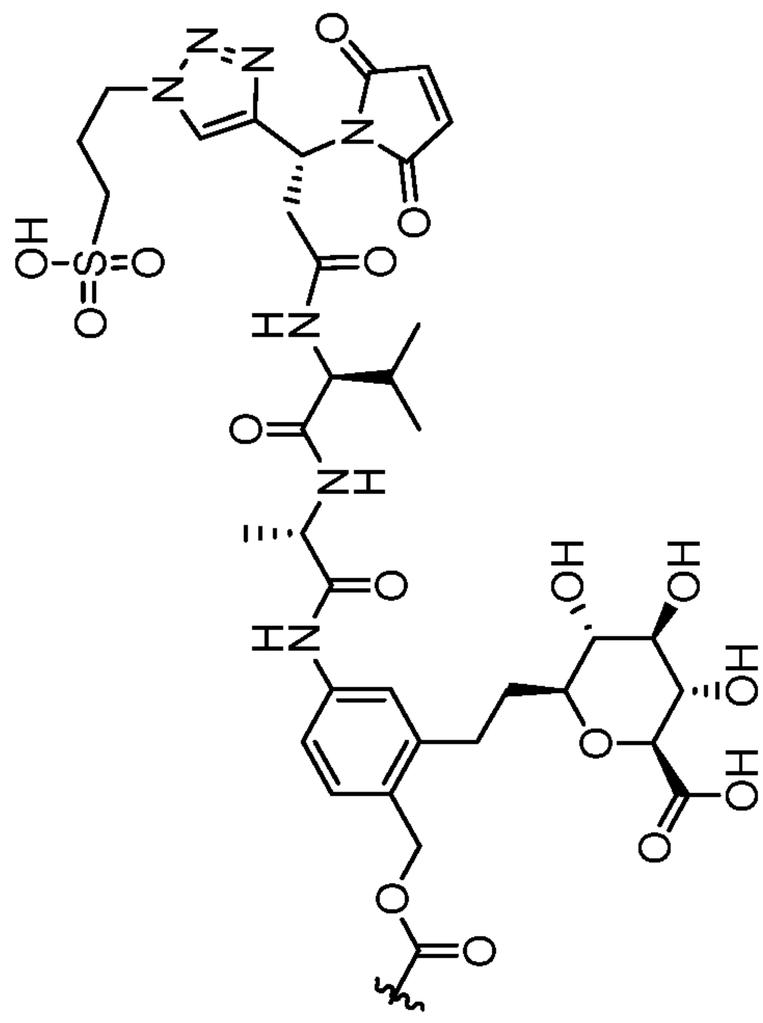
(VIIb.1)



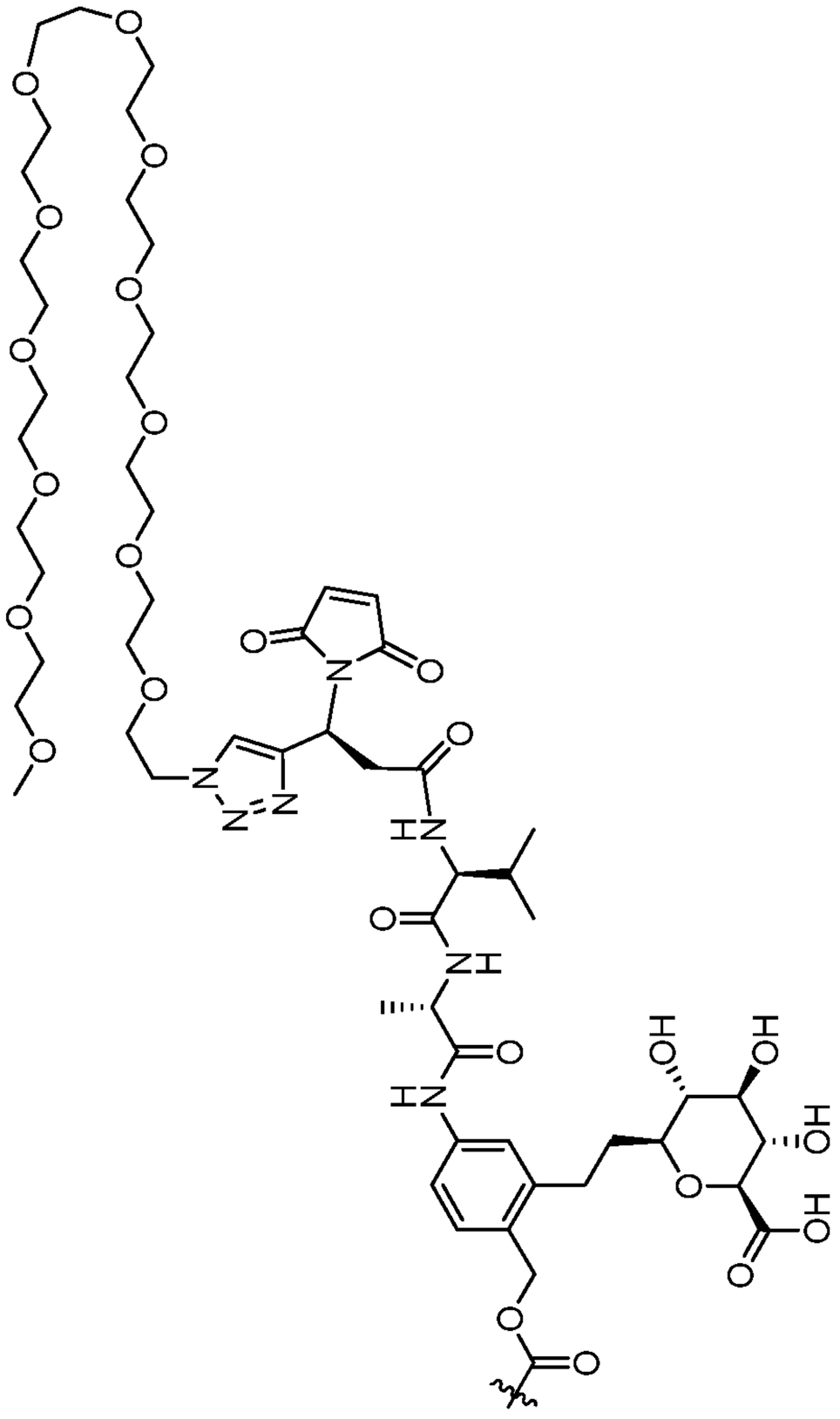
(VIIb.2)



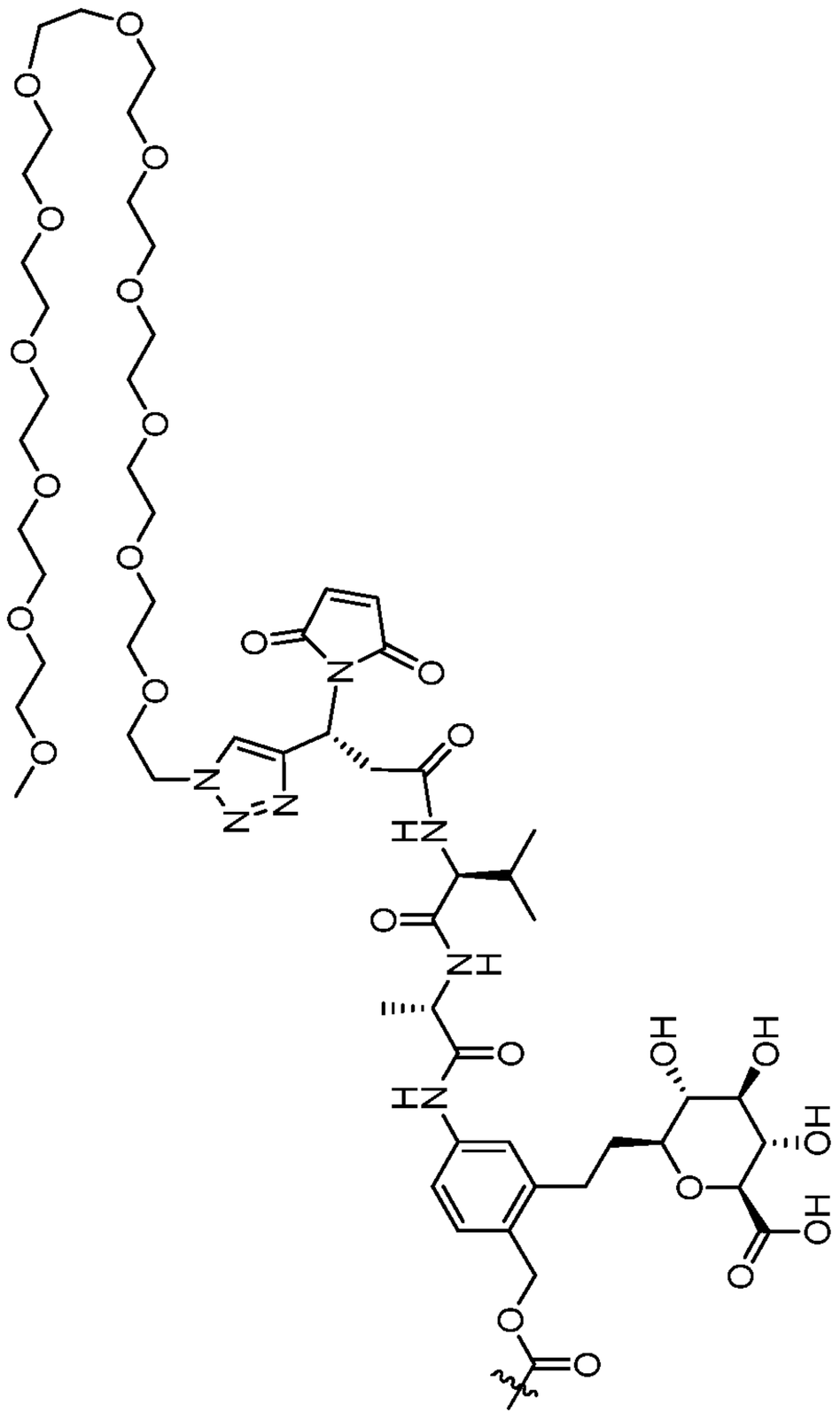
(VIIb.3)



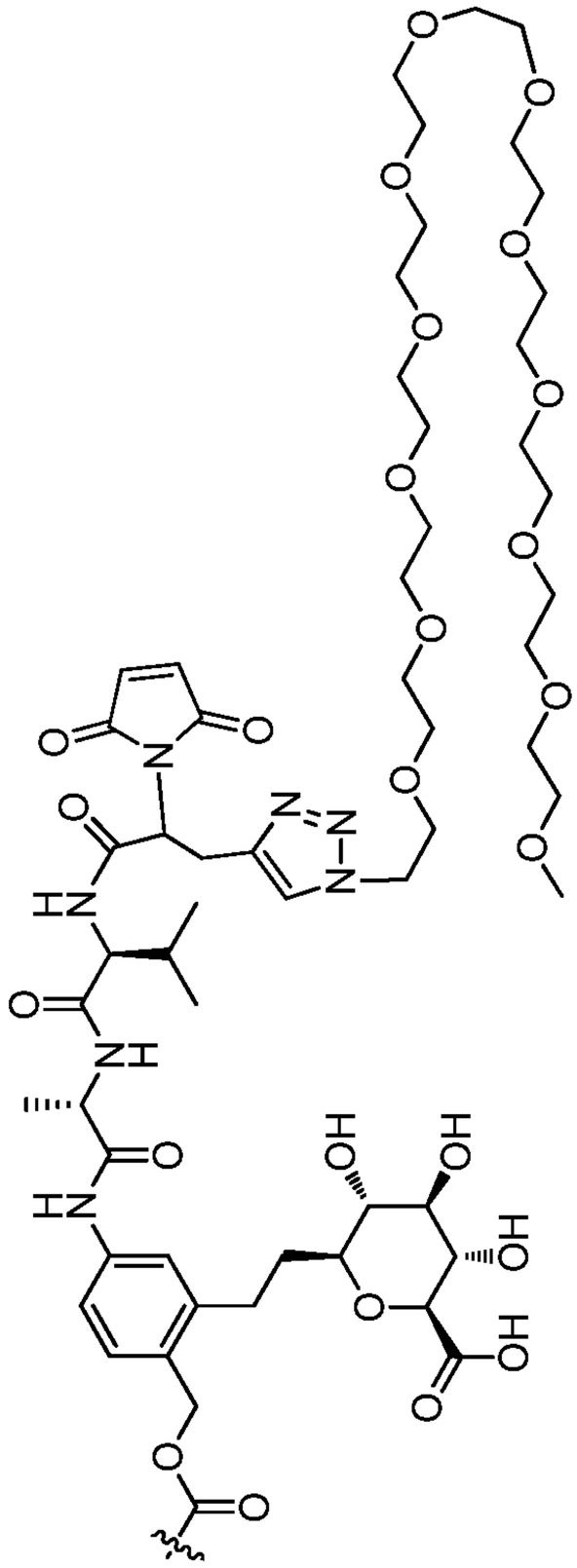
(VIIb.4)



(VIIb.6)



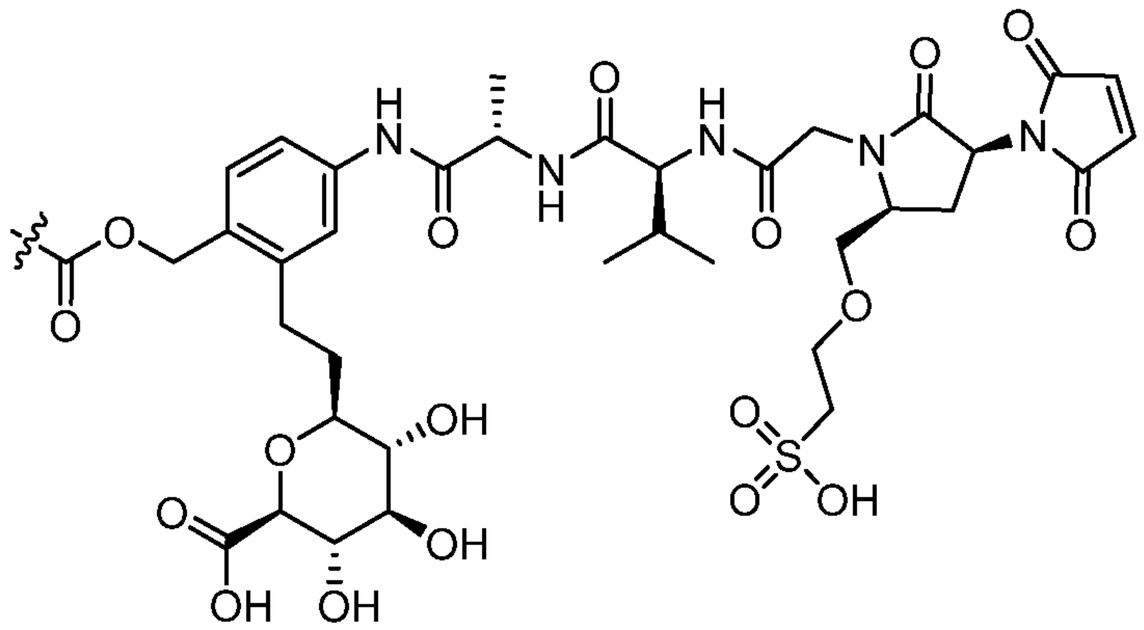
(VIIb.7)



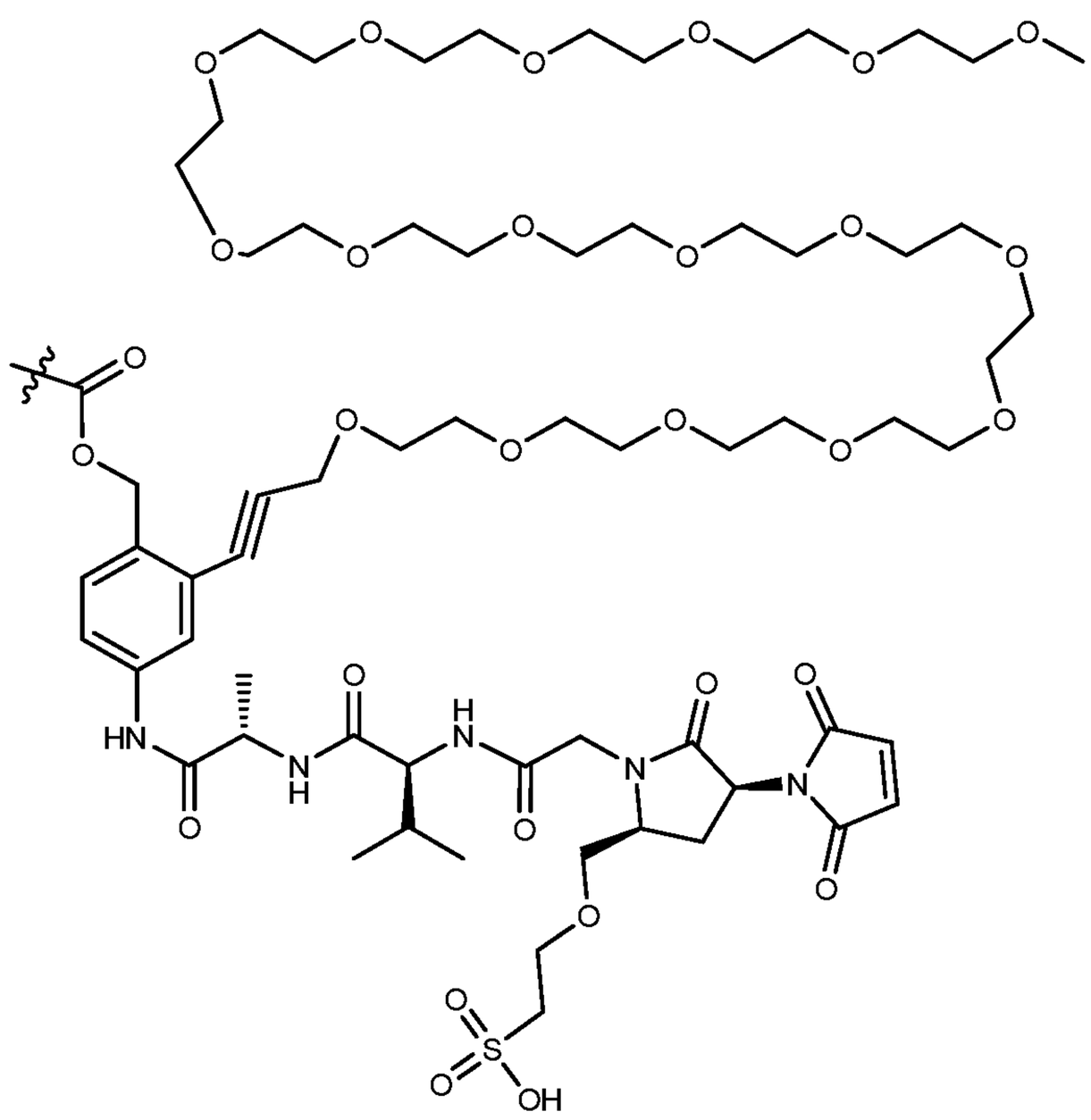
(VIIb.8)

Exemplary embodiments of linkers according to structural formula (VIIc) that may be included in the ADCs described herein include the linkers illustrated below (as illustrated, the linkers include a group suitable for covalently linking the linker to an antibody):

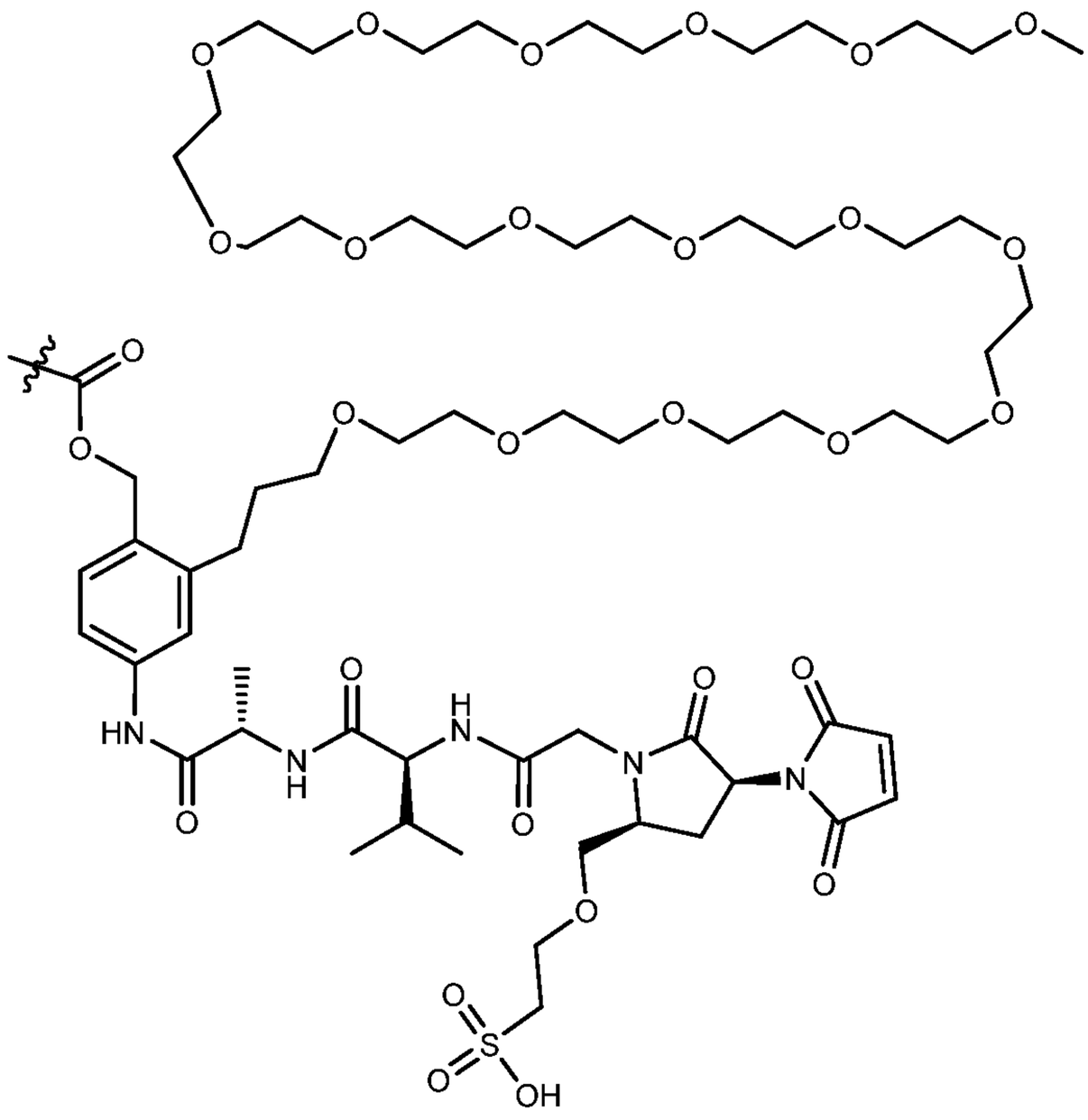
(VIIc.1)



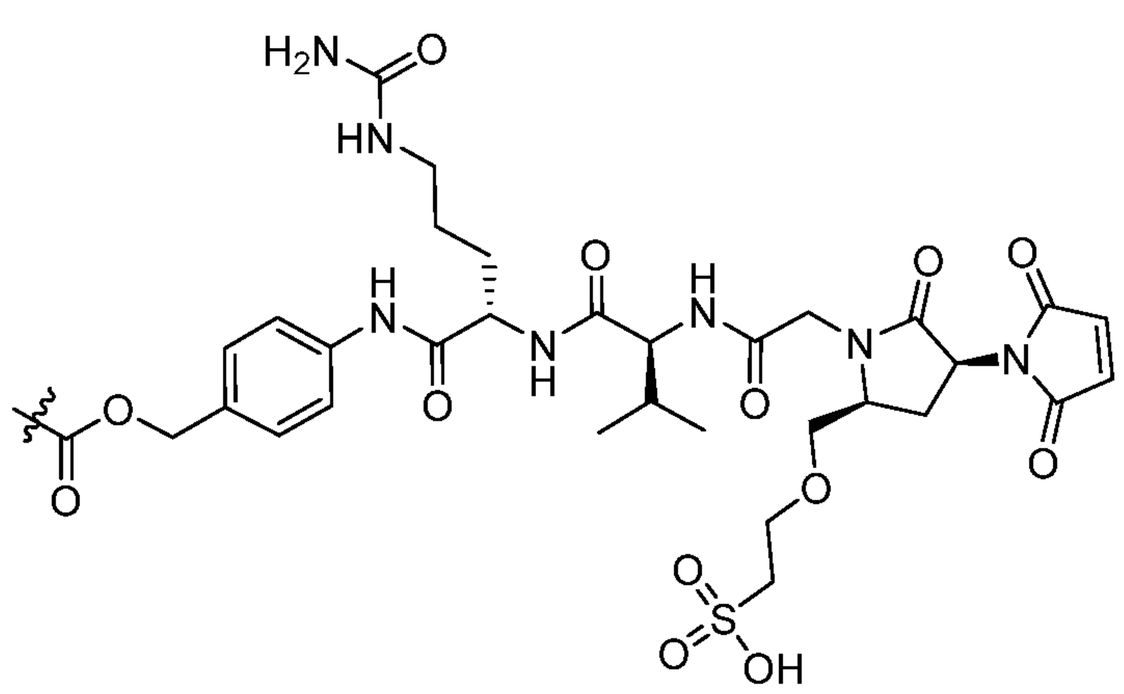
(VIIc.2)



(VIIc.3)

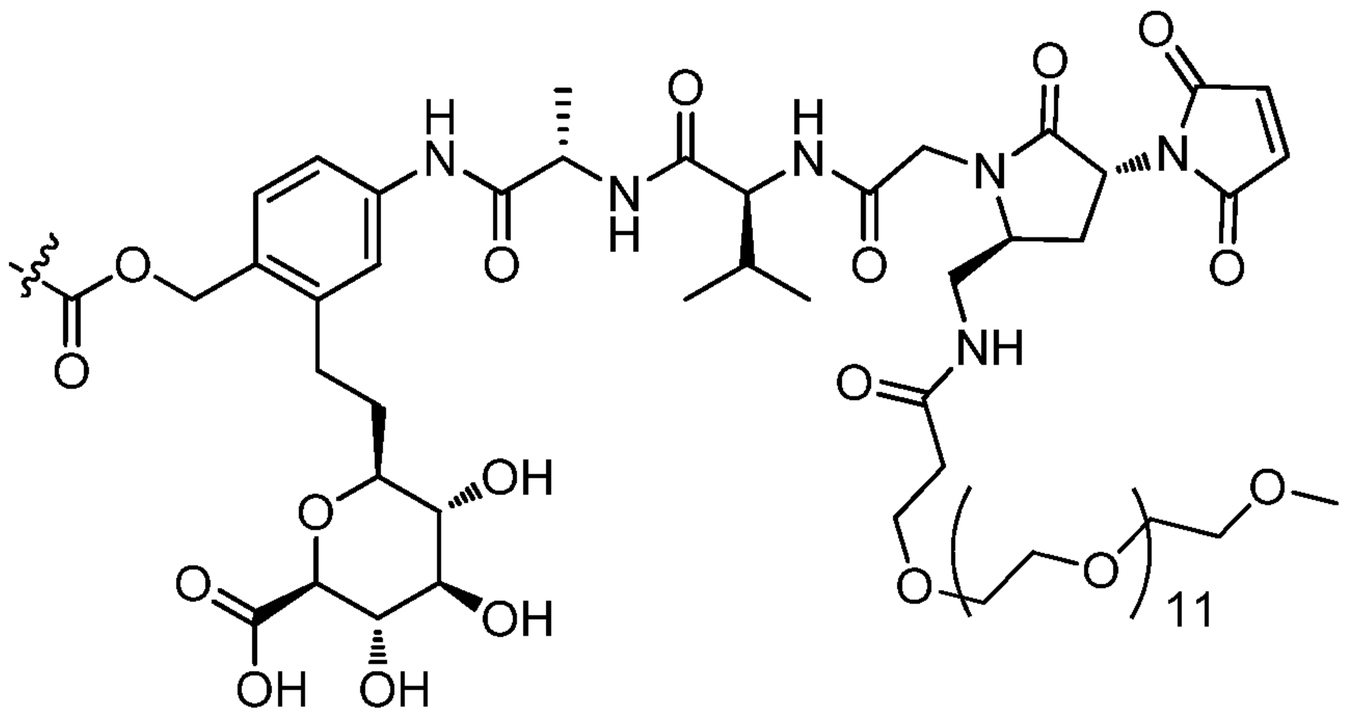


(VIIc.4)



(VIIc.5)

(VIIc.6)

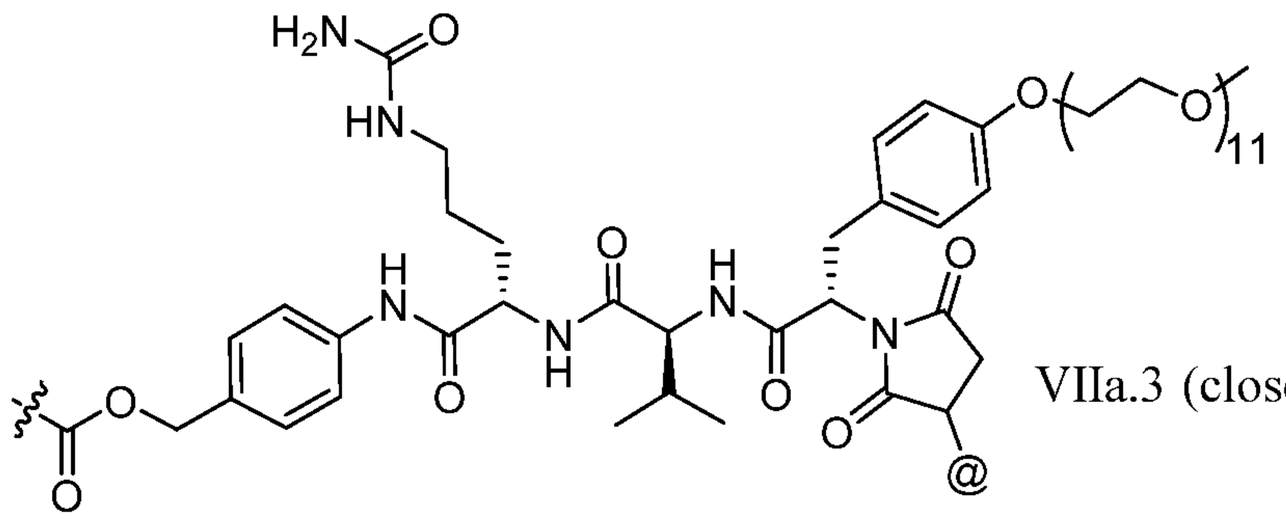


In certain embodiments, L is selected from the group consisting of IVa.1-IVa.8, IVb.1-IVb.19, IVc.1-IVc.7, IVd.1-IVd.4, Va.1-Va.12, Vb.1-Vb.10, Vc.1-Vc.11, Vd.1-Vd.6, Ve.1-Ve.2, VIa.1, VIc.1-V1c.2, VId.1-VId.4, VIIa.1-VIIa.4, VIIb.1-VIIb.8, VIIc.1-VIIc.6 in either the closed or open form, and a pharmaceutically acceptable salt thereof.

In certain embodiments, L is selected from the group consisting of IVb.2, IVc.5, IVc.6, IVc.7, IVd.4, Vb.9, VIIa.1, VIIa.3, VIIc.1, VIIc.4, and VIIc.5, wherein the maleimide of each linker has reacted with the antibody Ab, forming a covalent attachment as either a succinimide (closed form) or succinamide (open form),and a pharmaceutically acceptable salt thereof.

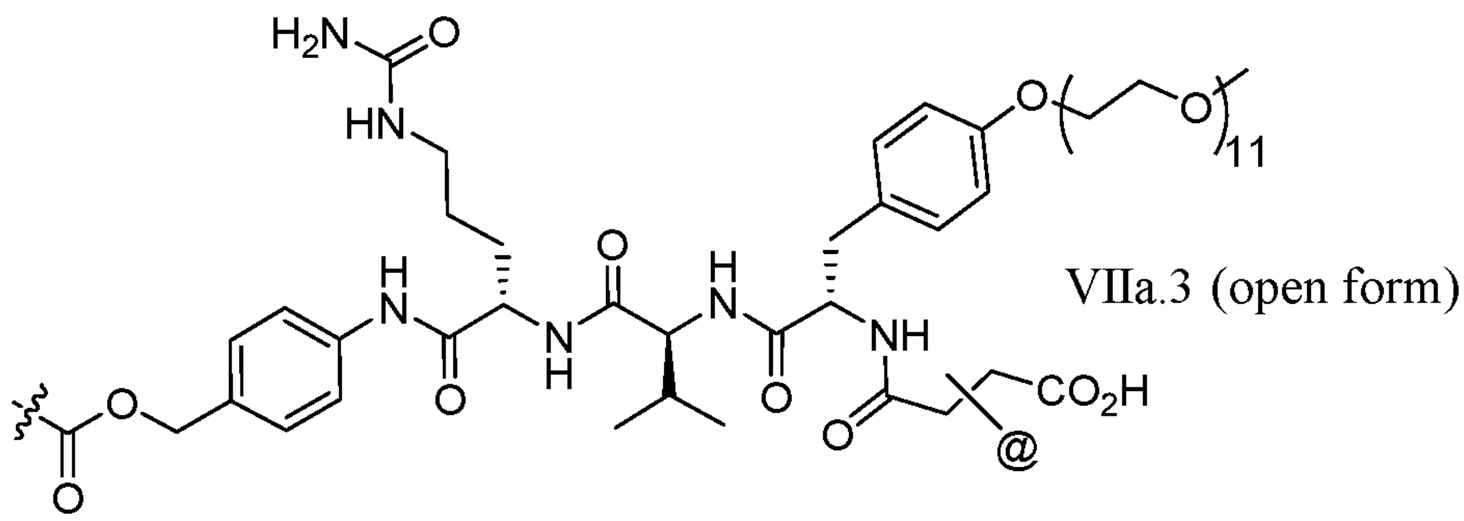
In certain embodiments, L is selected from the group consisting of IVb.2, IVc.5, IVc.6, IVd.4, VIIa.1, VIIa.3, VIIc.1, VIIc.4, VIIc.5, wherein the maleimide of each linker has reacted with the antibody Ab, forming a covalent attachment as either a succinimide (closed form) or succinamide(open form), and a pharmaceutically acceptable salt thereof.

In certain embodiments, L is selected from the group consisting of IVb.2, VIIa.3, IVc.6, and VIIc.1, wherein is the attachment point to drug D and @ is the attachment point to the LK, wherein when the linker is in the open form as shown below, @ can be either at the α-position or β-position of the carboxylic acid next to it:



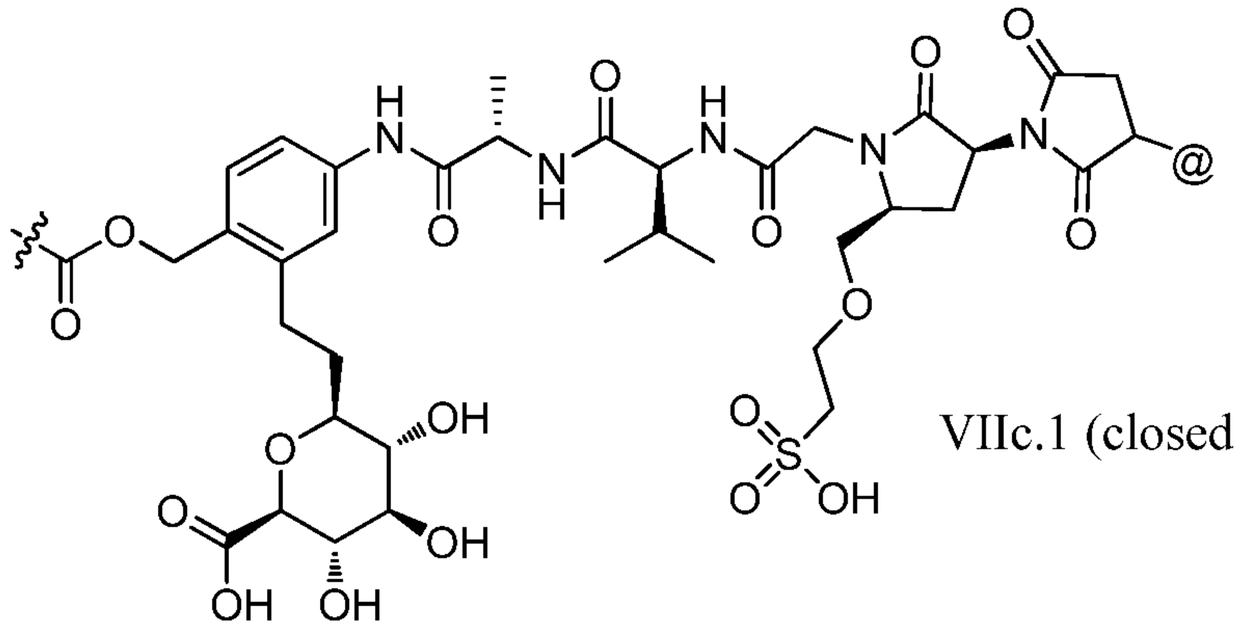
VIIa.3 (closed form)

,



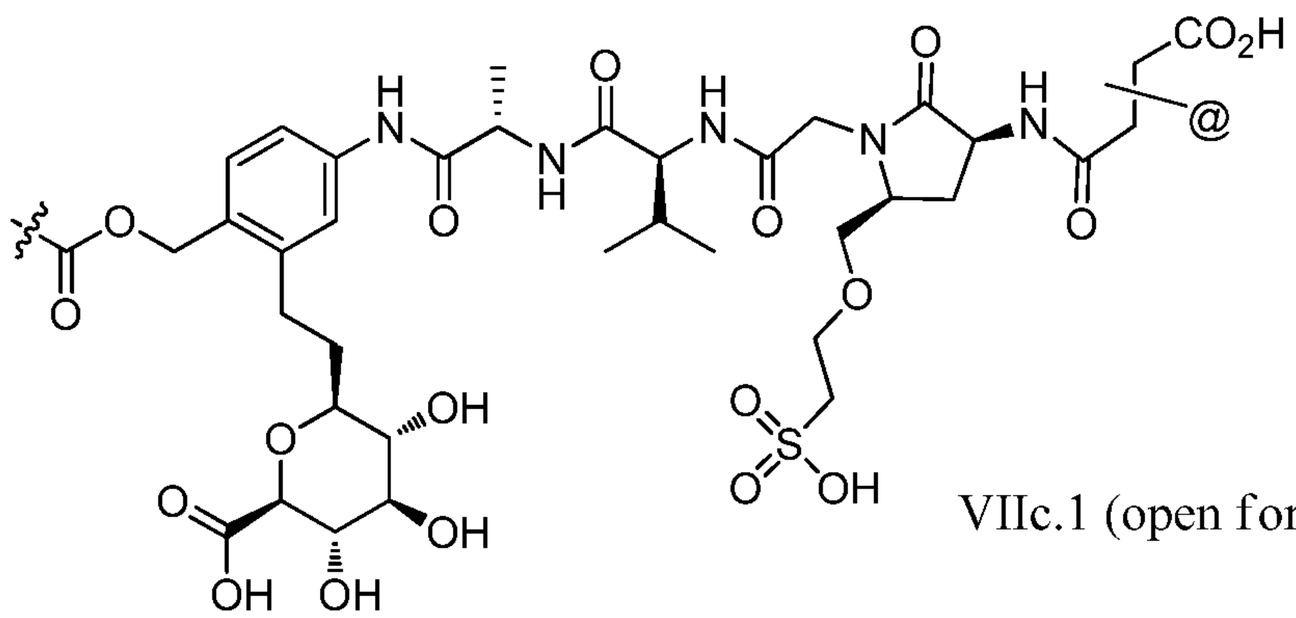
VIIa.3 (open form)

,



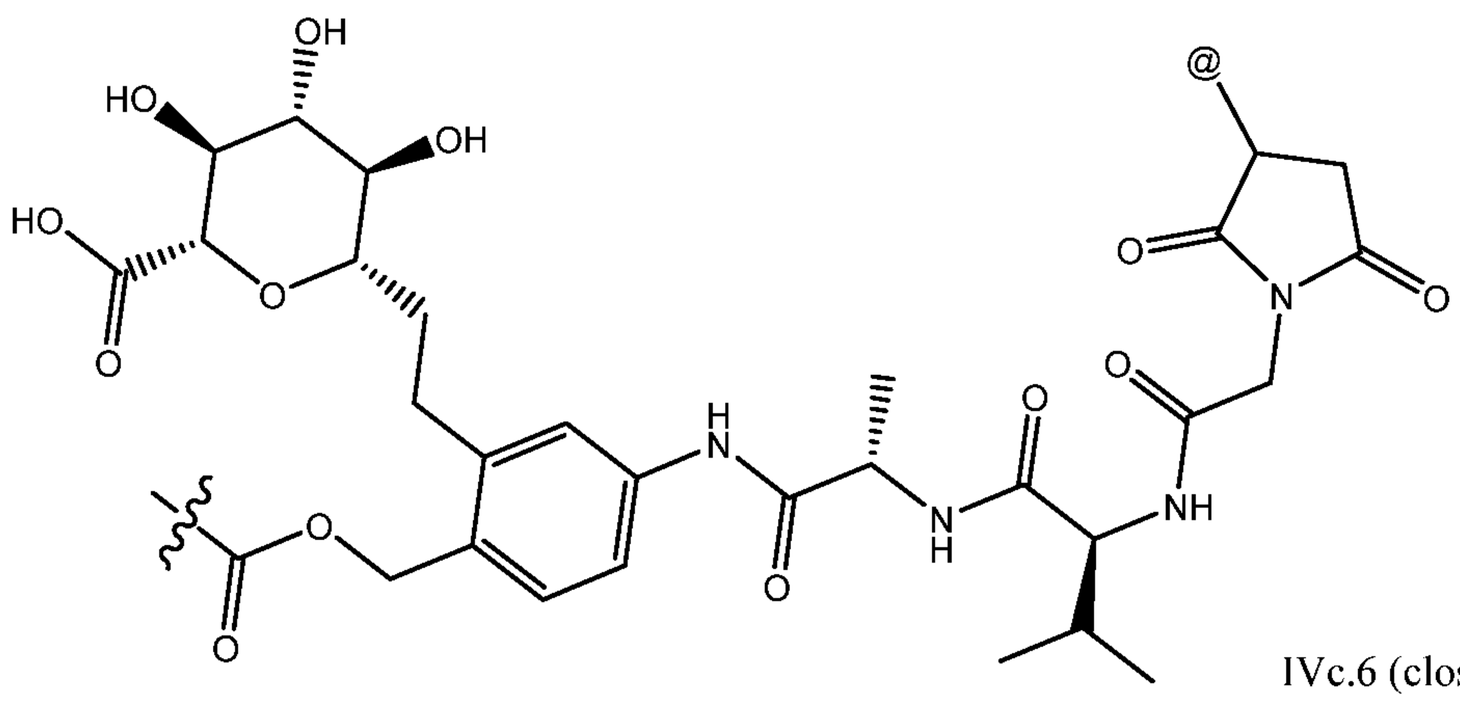
VIIc.1 (closed form)

,



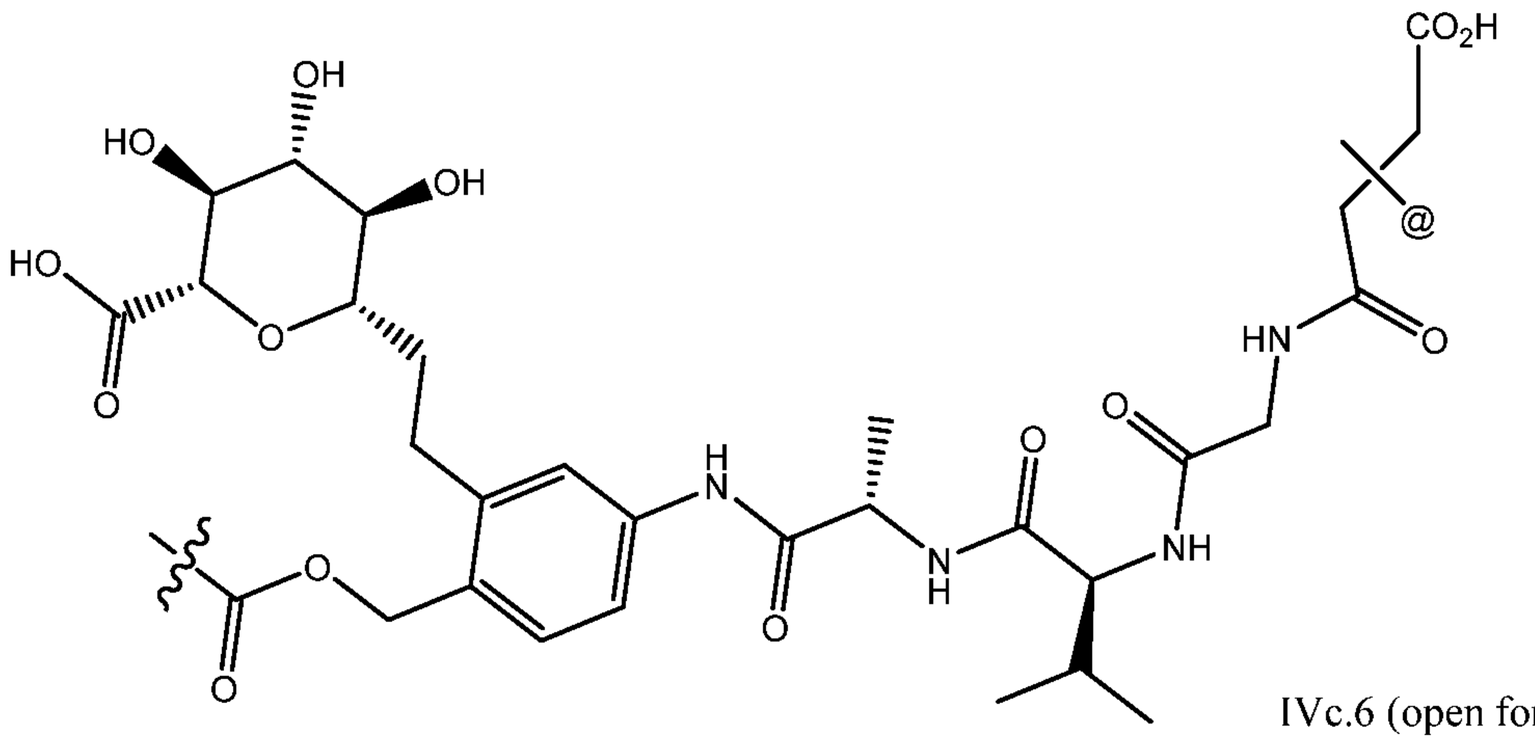
VIIc.1 (open form)

,

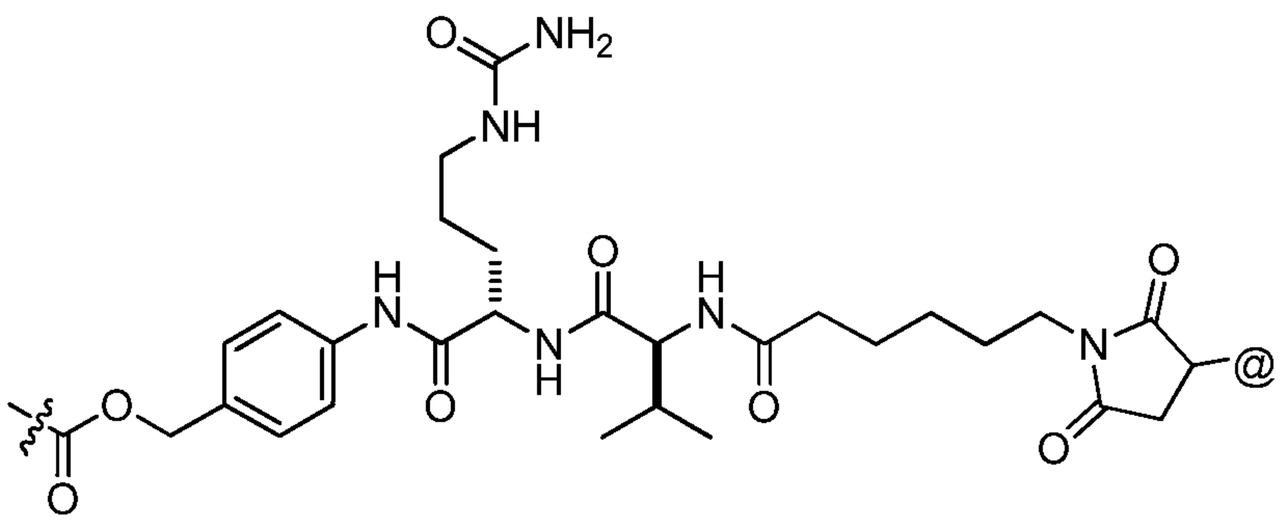


IVc.6 (closed form),

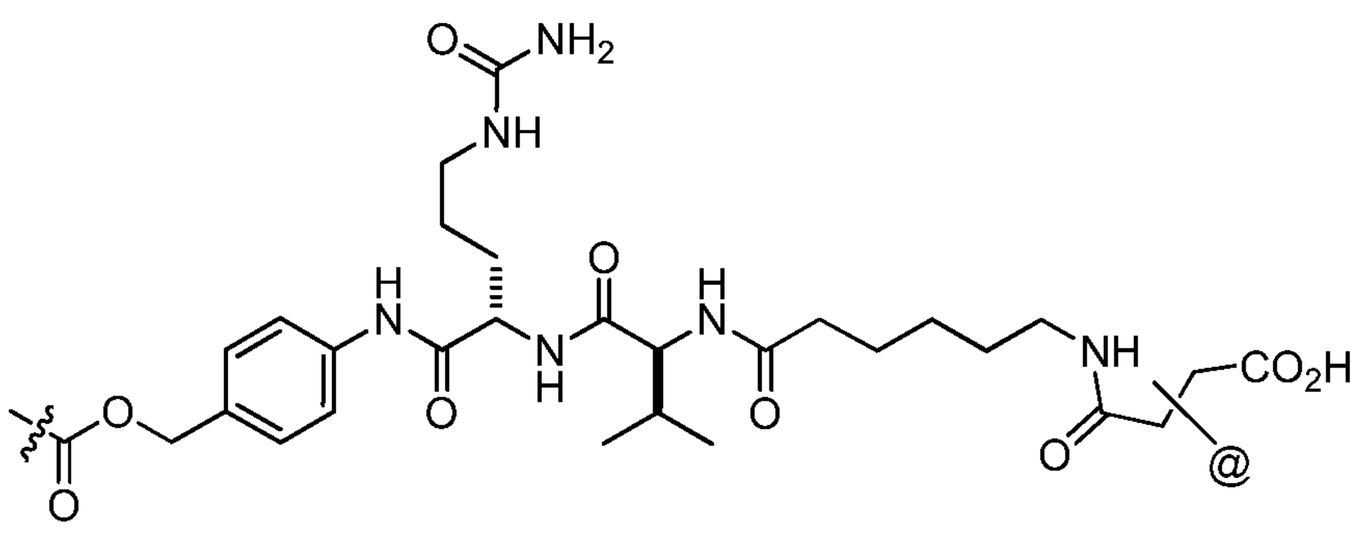
5



IVc.6 (open form)



IVb.2 (closed form), and



IVb.2 (open form)

Bcl-xL Linker Selection Considerations

As is known by skilled artisans, the linker selected for a particular ADC may be influenced by a variety of factors, including but not limited to, the site of attachment to the antibody (*e.g.*, lys, cys or other amino acid residues), structural constraints of the drug pharmacophore and the lipophilicity of the drug. The specific linker selected for an ADC should seek to balance these different factors for the specific antibody/drug combination. For a review of the factors that are influenced by choice of linkers in ADCs, *see* Nolting, Chapter 5 "Linker Technology in Antibody-Drug Conjugates," *In: Antibody-Drug Conjugates: Methods in Molecular Biology*, vol. 1045, pp. 71-100, Laurent Ducry (Ed.), Springer Science & Business Medica, LLC, 2013.

For example, ADCs have been observed to effect killing of bystander antigen-negative cells present in the vicinity of the antigen-positive tumor cells. The mechanism of bystander cell killing by

ADCs has indicated that metabolic products formed during intracellular processing of the ADCs may play a role. Neutral cytotoxic metabolites generated by metabolism of the ADCs in antigen-positive cells appear to play a role in bystander cell killing while charged metabolites may be prevented from diffusing across the membrane into the medium and therefore cannot affect bystander killing. In certain embodiments, the linker is selected to attenuate the bystander killing effect caused by cellular metabolites of the ADC. In certain embodiments, the linker is selected to increase the bystander killing effect.

The properties of the linker may also impact aggregation of the ADC under conditions of use and/or storage. Typically, ADCs reported in the literature contain no more than 3-4 drug molecules per antibody molecule (*see*, *e.g.*, Chari, 2008, *Acc Chem Res* 41:98-107). Attempts to obtain higher drug-to-antibody ratios ("DAR") often failed, particularly if both the drug and the linker were hydrophobic, due to aggregation of the ADC (*see* King *et al.*, 2002, *J Med Chem* 45:4336-4343; Hollander *et al.*, 2008, *Bioconjugate Chem* 19:358-361; Burke *et al.*, 2009 *Bioconjugate Chem* 20:1242-1250). In many instances, DARs higher than 3-4 could be beneficial as a means of increasing potency. In instances where the Bcl-xL inhibitor is hydrophobic in nature, it may be desirable to select linkers that are relatively hydrophilic as a means of reducing ADC aggregation, especially in instances where DARS greater than 3-4 are desired. Thus, in certain embodiments, the linker incorporates chemical moieties that reduce aggregation of the ADCs during storage and/or use. A linker may incorporate polar or hydrophilic groups such as charged groups or groups that become charged under physiological pH to reduce the aggregation of the ADCs. For example, a linker may incorporate charged groups such as salts or groups that deprotonate, *e.g.*, carboxylates, or protonate, *e.g.*, amines, at physiological pH.

Exemplary polyvalent linkers that have been reported to yield DARs as high as 20 that may be used to link numerous Bcl-xL inhibitors to an antibody are described in U.S. Patent No 8,399,512; U.S. Published Application No. 2010/0152725; U.S. Patent No. 8,524,214; U.S. Patent No. 8,349,308; U.S. Published Application No. 2013/189218; U.S. Published Application No. 2014/017265; WO 2014/093379; WO 2014/093394; WO 2014/093640, the content of which are incorporated herein by reference in their entireties.

In particular embodiments, the aggregation of the ADCs during storage or use is less than about 40% as determined by size-exclusion chromatography (SEC). In particular embodiments, the aggregation of the ADCs during storage or use is less than 35%, such as less than about 30%, such as less than about 25%, such as less than about 20%, such as less than about 15%, such as less than about 10%, such as less than about 5%, such as less than about 4%, or even less, as determined by size-exclusion chromatography (SEC).

III.A.3. Bcl-xL ADC Synthons

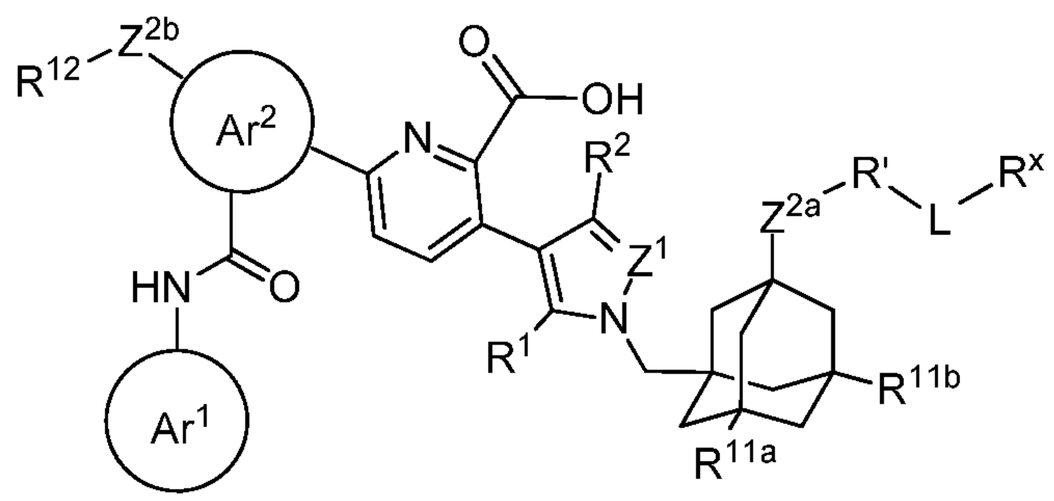
Antibody-Drug Conjugate synthons are synthetic intermediates used to form ADCs. The synthons are generally compounds according to structural formula (III):

(III) D——L——R^x

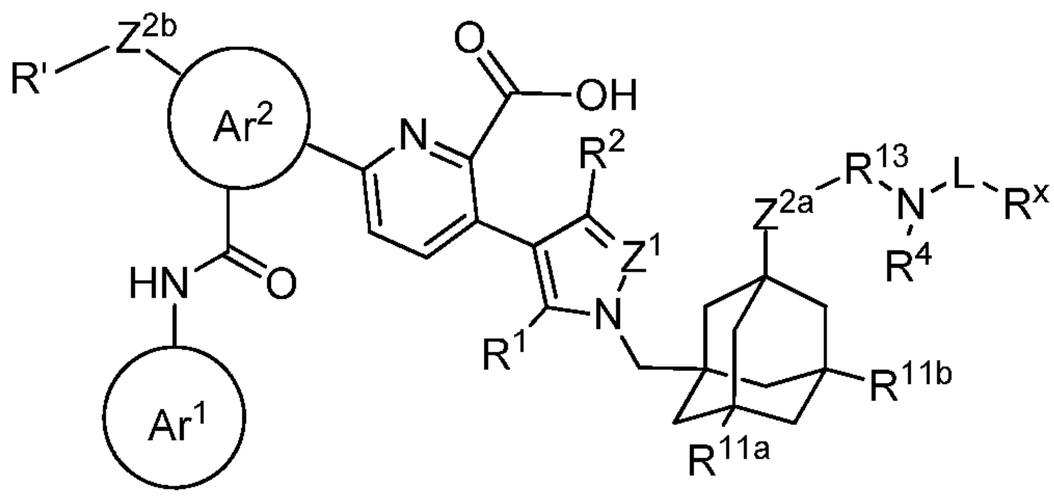
or a pharmaceutically acceptable salt thereof, wherein D is a Bcl-xL inhibitor as previously described, L is a linker as previously described, and R^x is a reactive group suitable for linking the synthon to an antibody.

In specific embodiments, the intermediate synthons are compounds according to structural formulae (IIIa), (IIIb), (IIIc) and (IIId), below, or a pharmaceutically acceptable salt thereof, where the various substituents Ar^1, Ar^2, Z^1, Z^{2a}, Z^{2b}, R', R^1, R^2, R^4, R^{11a}, R^{11b}, R^{12} and R^{13} are as previously defined for structural formulae (IIa), (IIb), (IIc) and (IId), respectively, L is a linker as previously described and R^x is a functional group as described above:

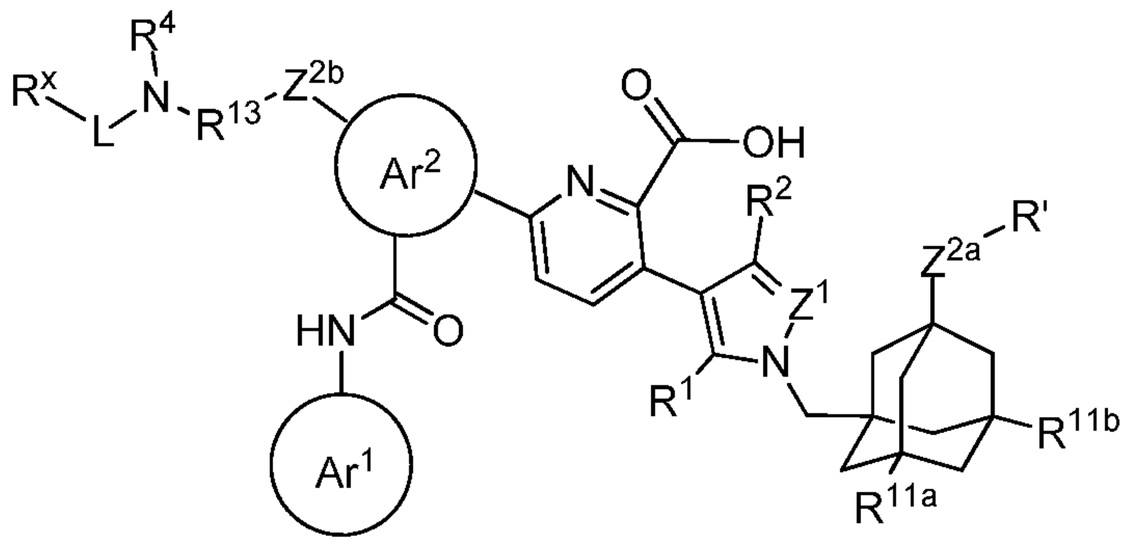
(IIIa)



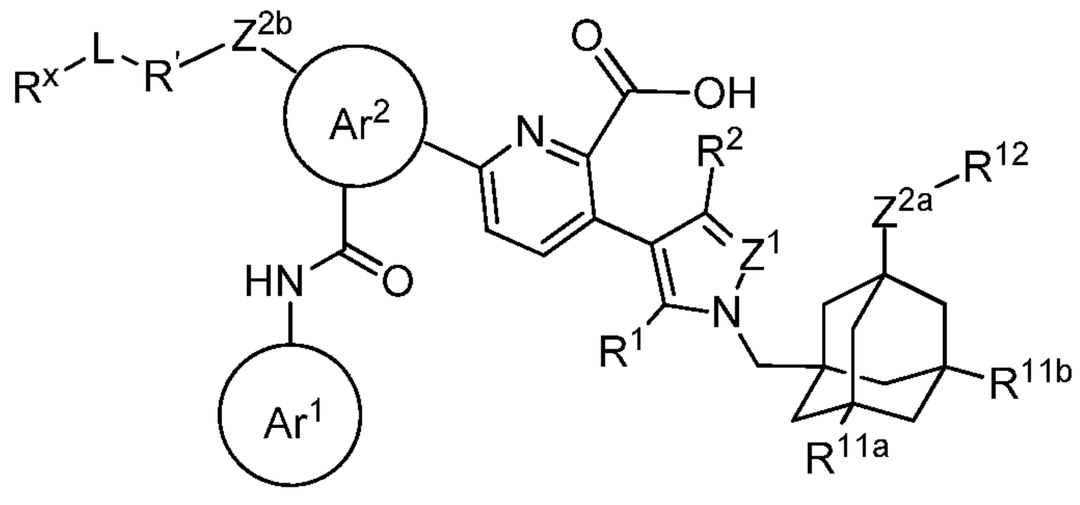
(IIIb)



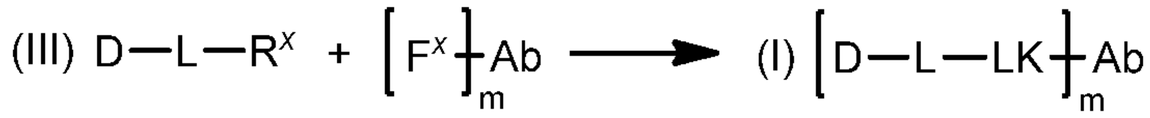
(IIIc)



(IIId)



To synthesize an ADC, an intermediate synthon according to structural formula (III), or a salt thereof, is contacted with an antibody of interest under conditions in which functional group R^x reacts with a "complementary" functional group on the antibody, F^x, to form a covalent linkage.



The identities of groups R^x and F^x will depend upon the chemistry used to link the synthon to the antibody. Generally, the chemistry used should not alter the integrity of the antibody, for example its ability to bind its target. Preferably, the binding properties of the conjugated antibody will closely resemble those of the unconjugated antibody. A variety of chemistries and techniques for conjugating molecules to biological molecules such as antibodies are known in the art and in particular to antibodies, are well-known. *See*, *e.g.*, Amon *et al.*, "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy," in: *Monoclonal Antibodies And Cancer Therapy*, Reisfeld *et al.* Eds., Alan R. Liss, Inc., 1985; Hellstrom *et al.*, "Antibodies For Drug Delivery," in: *Controlled Drug Delivery*, Robinson *et al.*, Eds., Marcel Dekker, Inc., 2nd Ed. 1987; Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review," in: *Monoclonal Antibodies '84: Biological And Clinical Applications*, Pinchera *et al.*, Eds., 1985; "Analysis, Results, and Future Prospective of the Therapeutic Use of Radiolabeled Antibody In Cancer Therapy," in: *Monoclonal Antibodies For Cancer Detection And Therapy*, Baldwin *et al.*, Eds., Academic Press, 1985; Thorpe *et al.*, 1982, *Immunol. Rev.* 62:119-58; PCT publication WO 89/12624**.** Any of these chemistries may be used to link the synthons to an antibody.

Typically, the synthons are linked to the side chains of amino acid residues of the antibody, including, for example, the primary amino group of accessible lysine residues or the sulfhydryl group of accessible cysteine residues. Free sulfhydryl groups may be obtained by reducing interchain disulfide bonds. In certain embodiments, LK is a linkage formed with an amino group on the anti-hB7-H3 antibody Ab. In certain embodiments, LK is an amide, thioether, or thiourea. In certain embodiments, LK is an amide or thiourea. In certain embodiments, LK is a linkage formed with a sulfhydryl group on the anti-hB7-H3 antibody Ab. In certain embodiments, LK is a thioether. In certain embodiments, LK is an amide, thioether, or thiourea; and m is an integer ranging from 1 to 8.

A number of functional groups R^x and chemistries useful for linking synthons to accessible lysine residues are known, and include by way of example and not limitation NHS-esters and isothiocyanates.

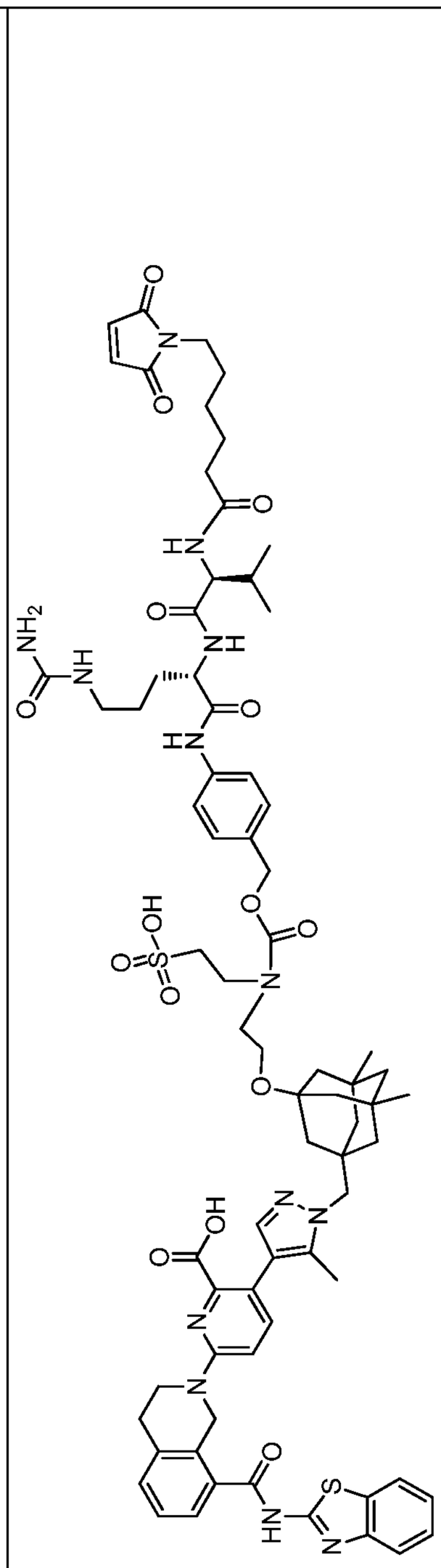
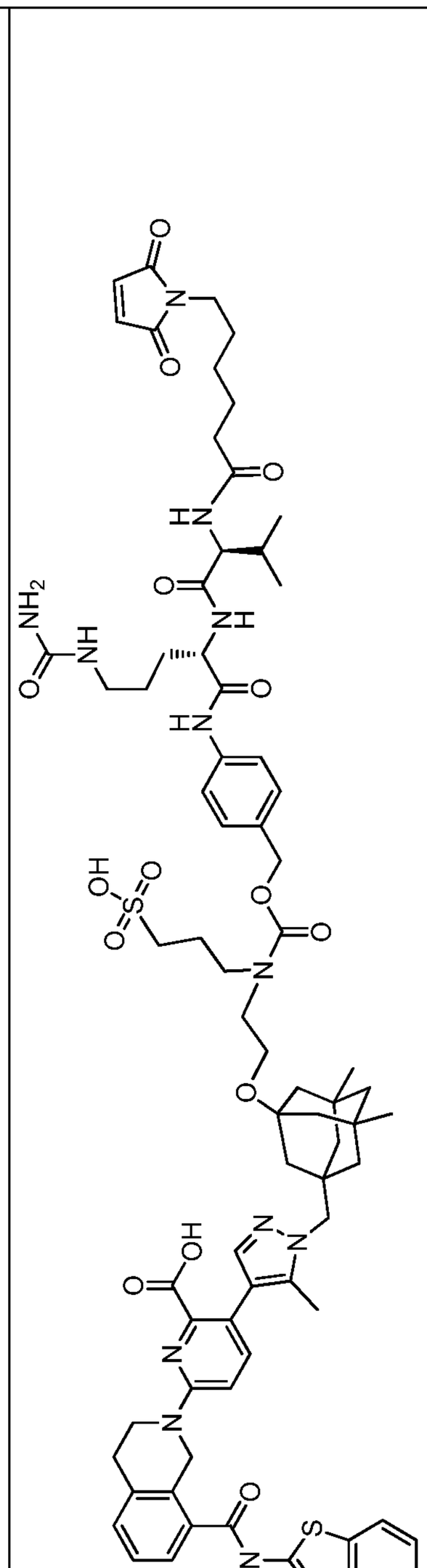
A number of functional groups R^x and chemistries useful for linking synthons to accessible free sulfhydryl groups of cysteine residues are known, and include by way of example and not limitation haloacetyls and maleimides.

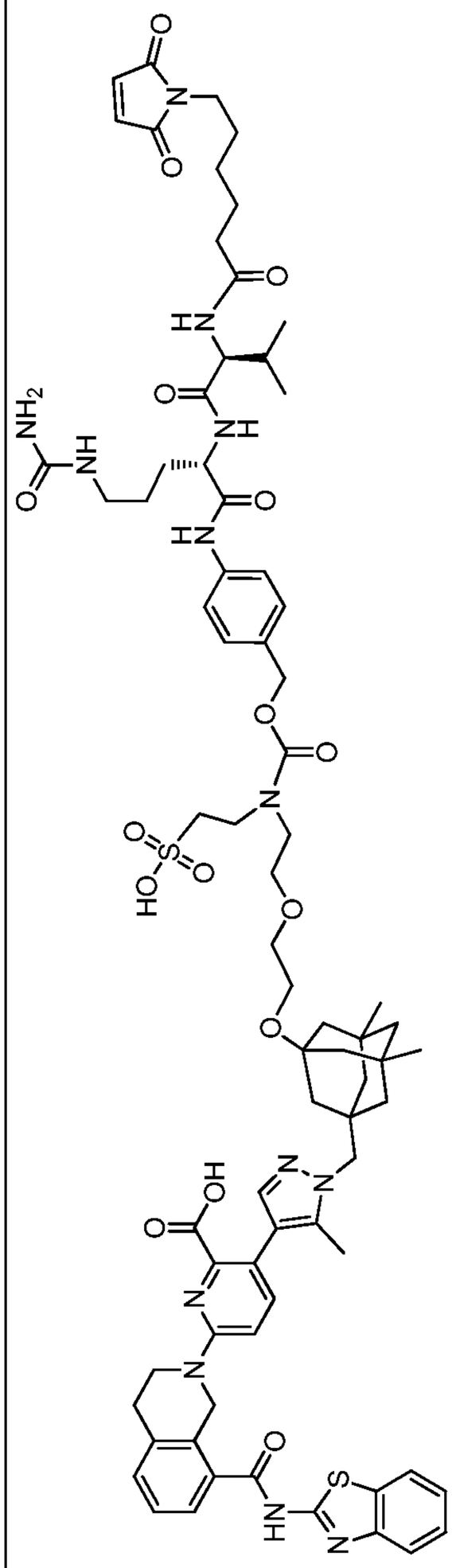
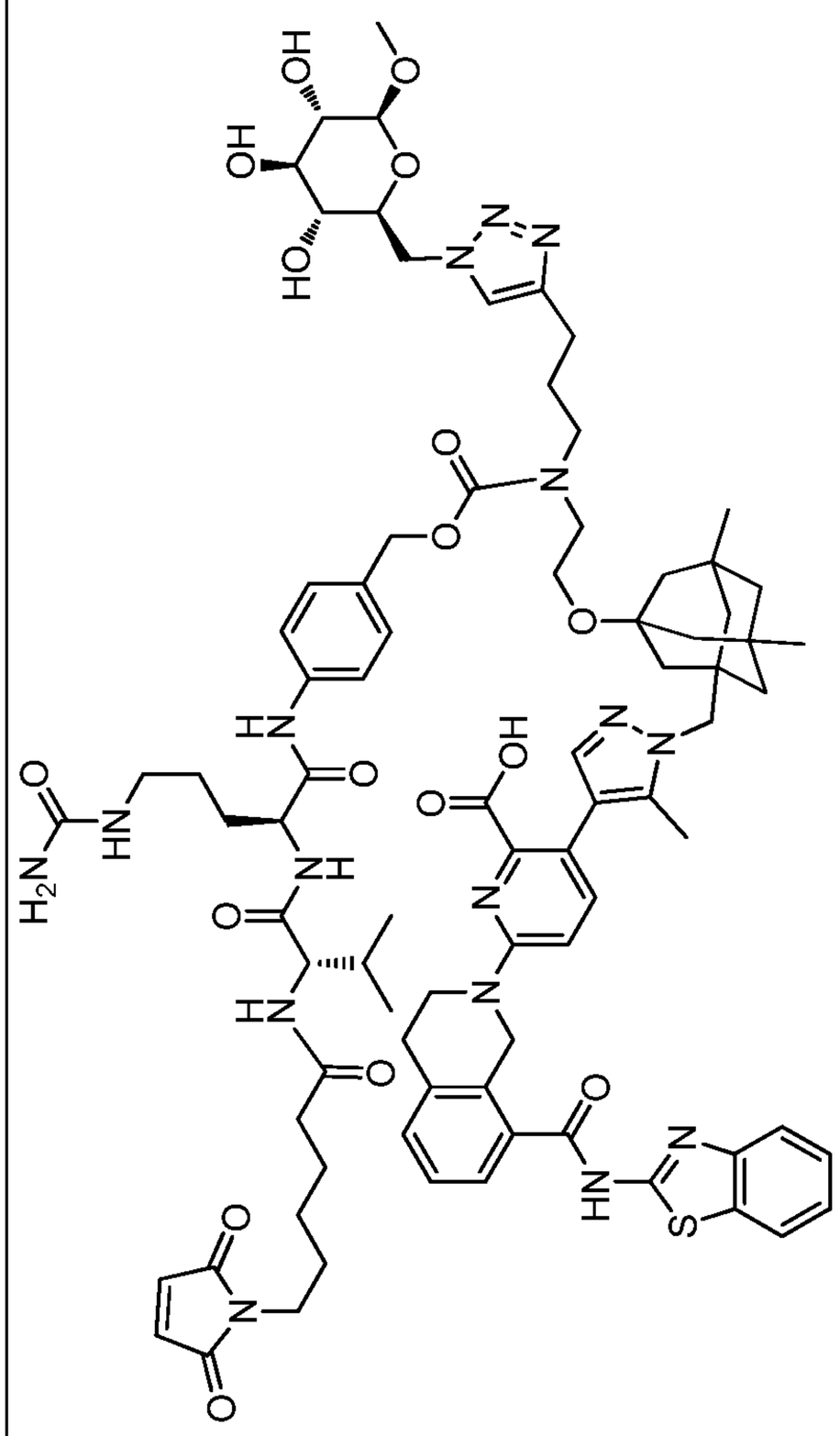
However, conjugation chemistries are not limited to available side chain groups. Side chains such as amines may be converted to other useful groups, such as hydroxyls, by linking an appropriate small molecule to the amine. This strategy can be used to increase the number of available linking sites on the antibody by conjugating multifunctional small molecules to side chains of accessible amino acid residues of the antibody. Functional groups R^x suitable for covalently linking the synthons to these "converted" functional groups are then included in the synthons.

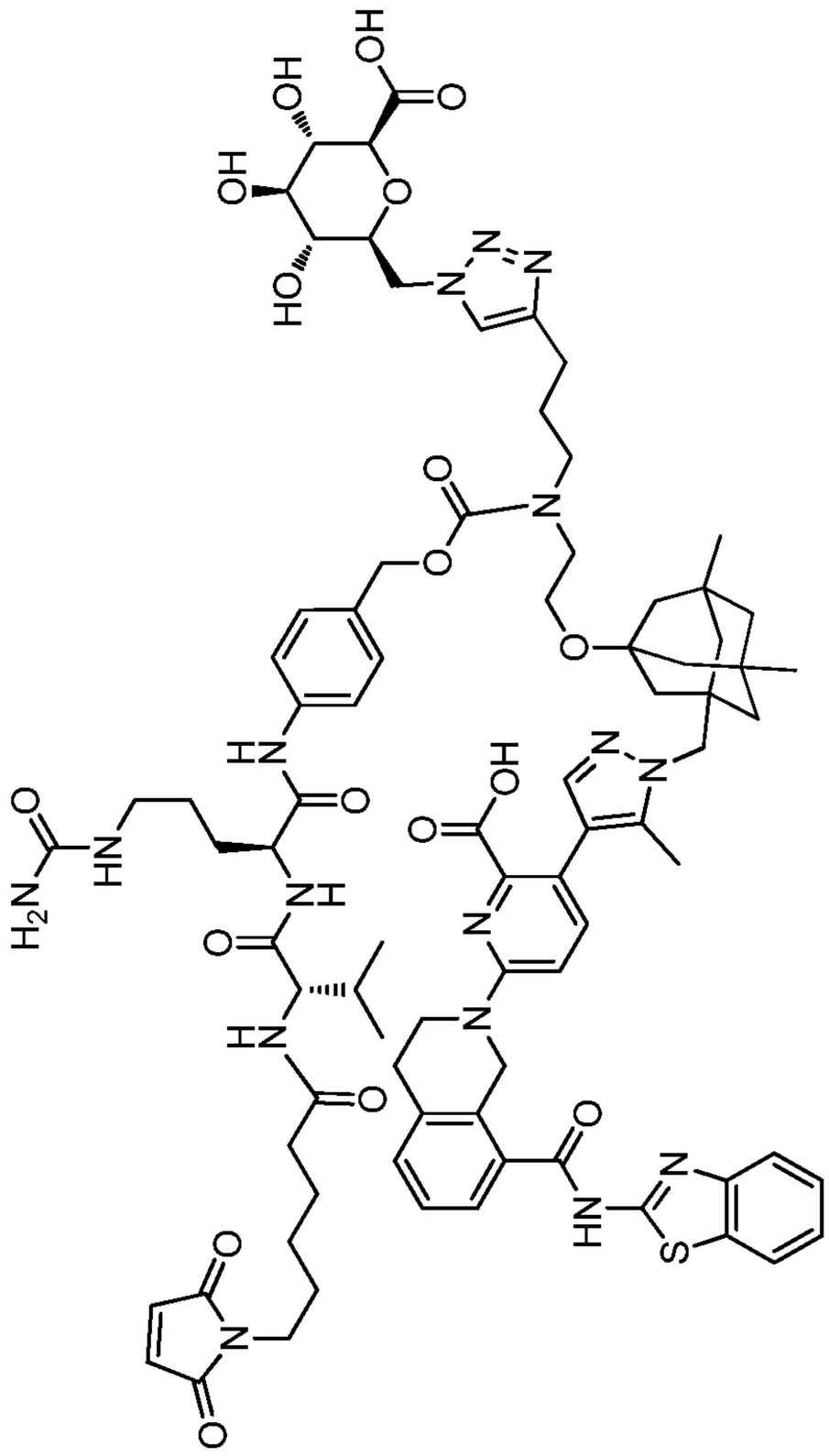
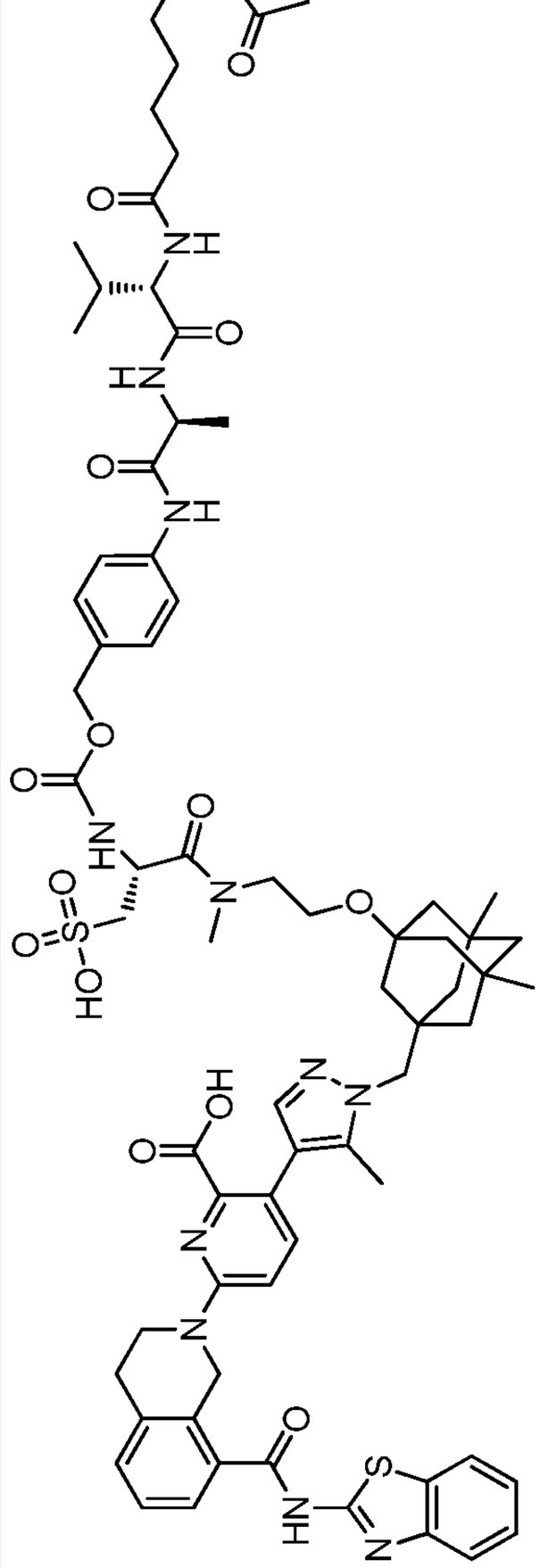
The antibody may also be engineered to include amino acid residues for conjugation. An approach for engineering antibodies to include non-genetically encoded amino acid residues useful for conjugating drugs in the context of ADCs is described in Axup *et al.*, 2003, *Proc Natl Acad Sci* 109:16101-16106 and Tian *et al.*, 2014, *Proc Natl Acad Sci* 111:1776-1771 as are chemistries and functional groups useful for linking synthons to the non-encoded amino acids.

Exemplary synthons useful for making ADCs described herein include, but are not limited to, the following synthons listed below in Table B.

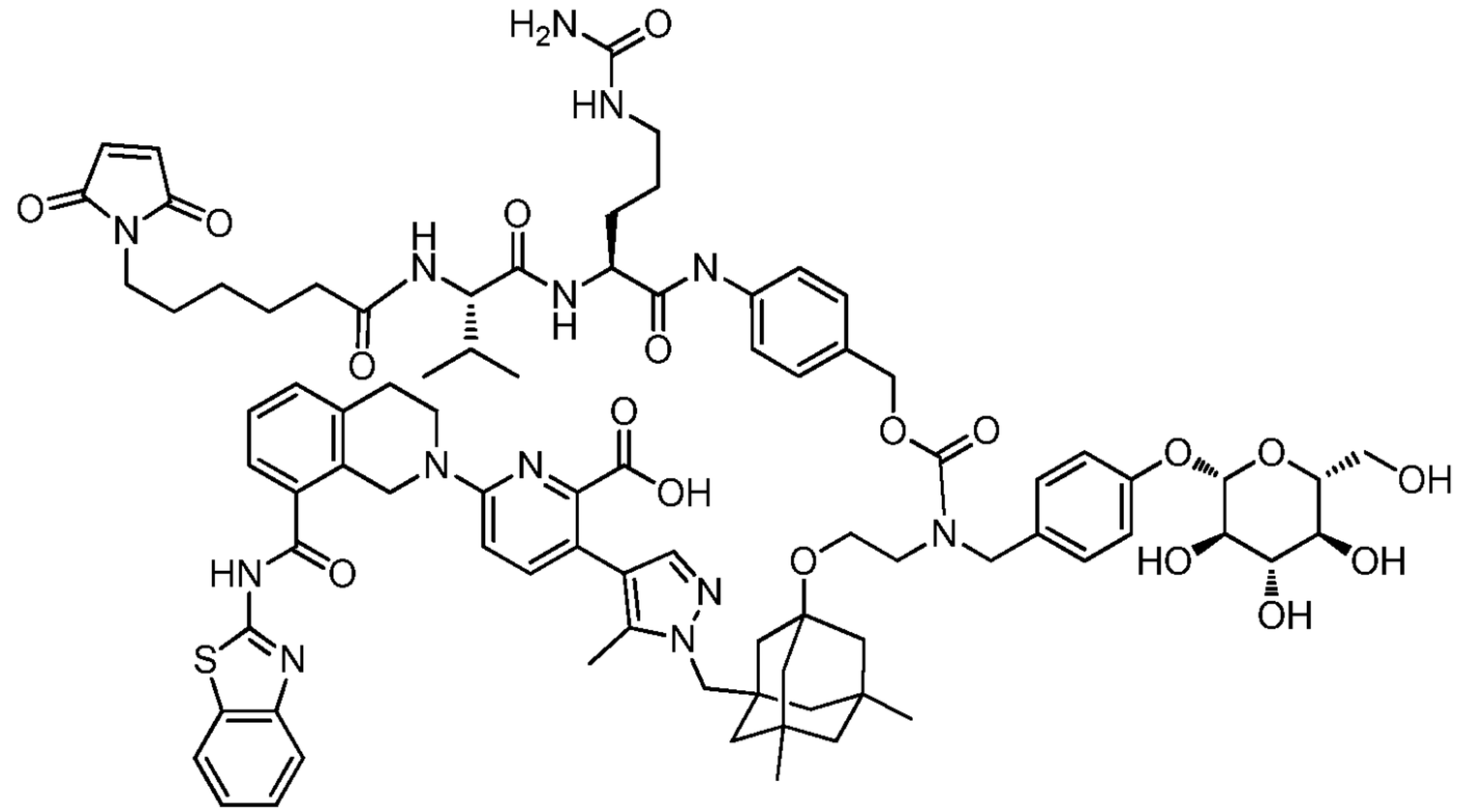
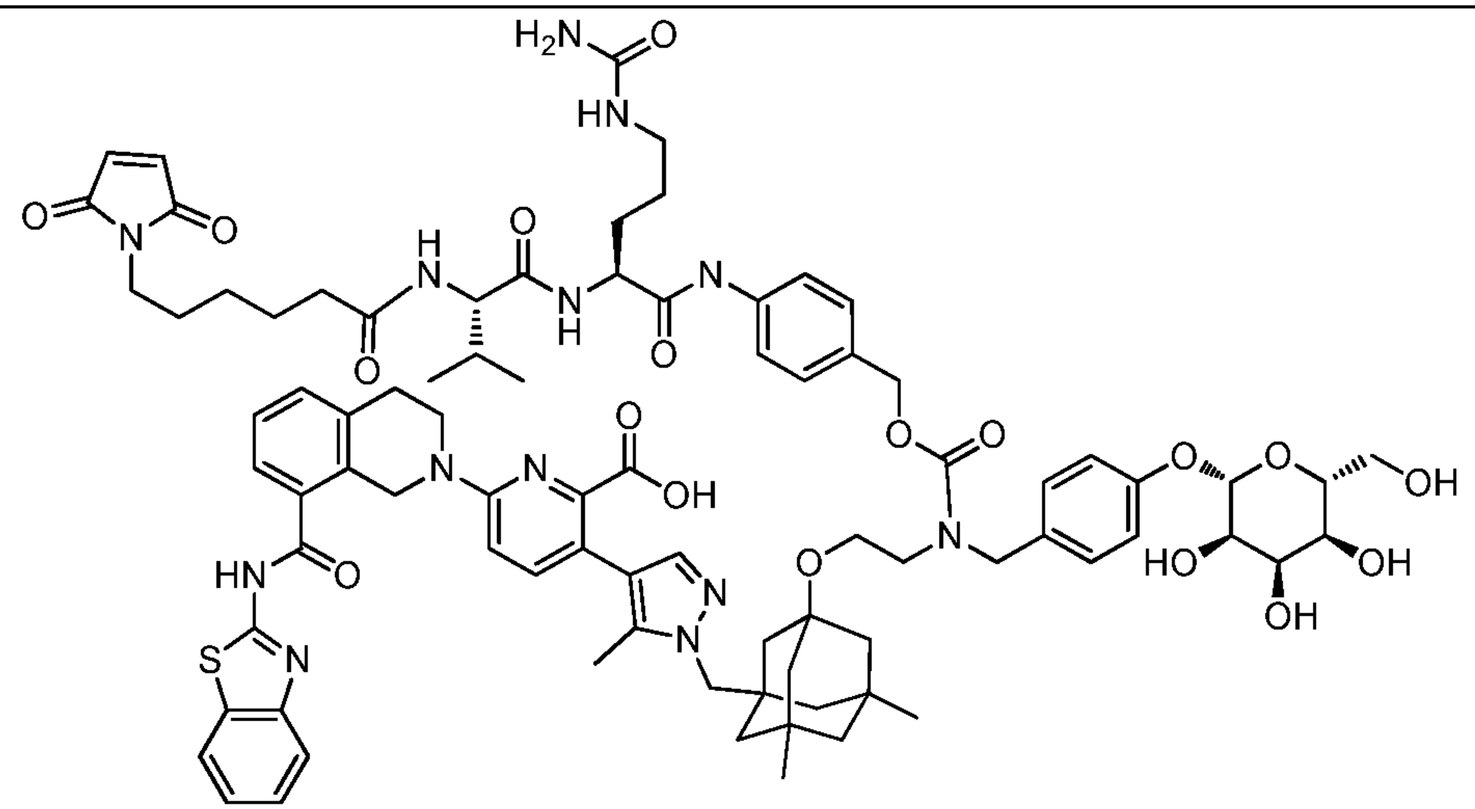
Table B

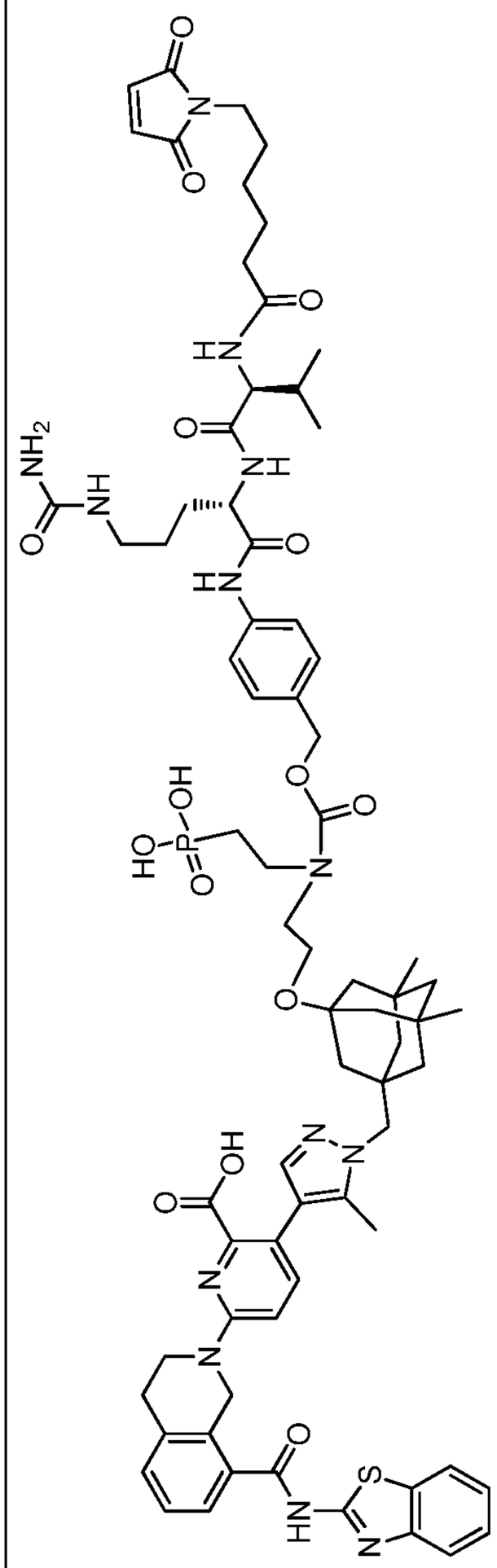
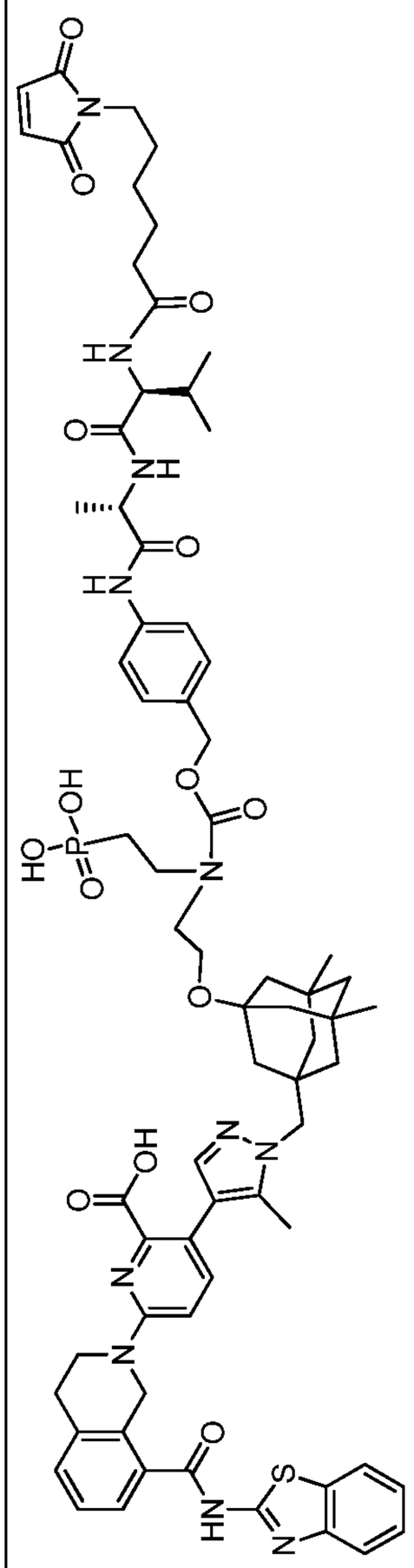
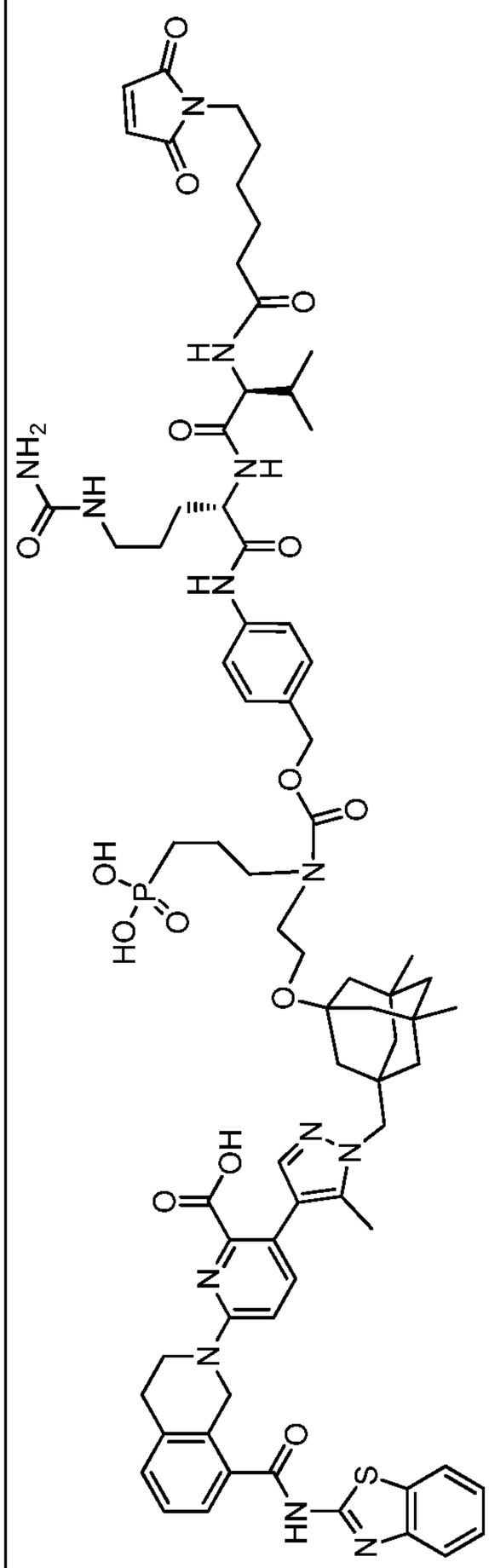
Example No.	Synthon Code	Synthon Structure
2.1	CZ	
2.2	DH	

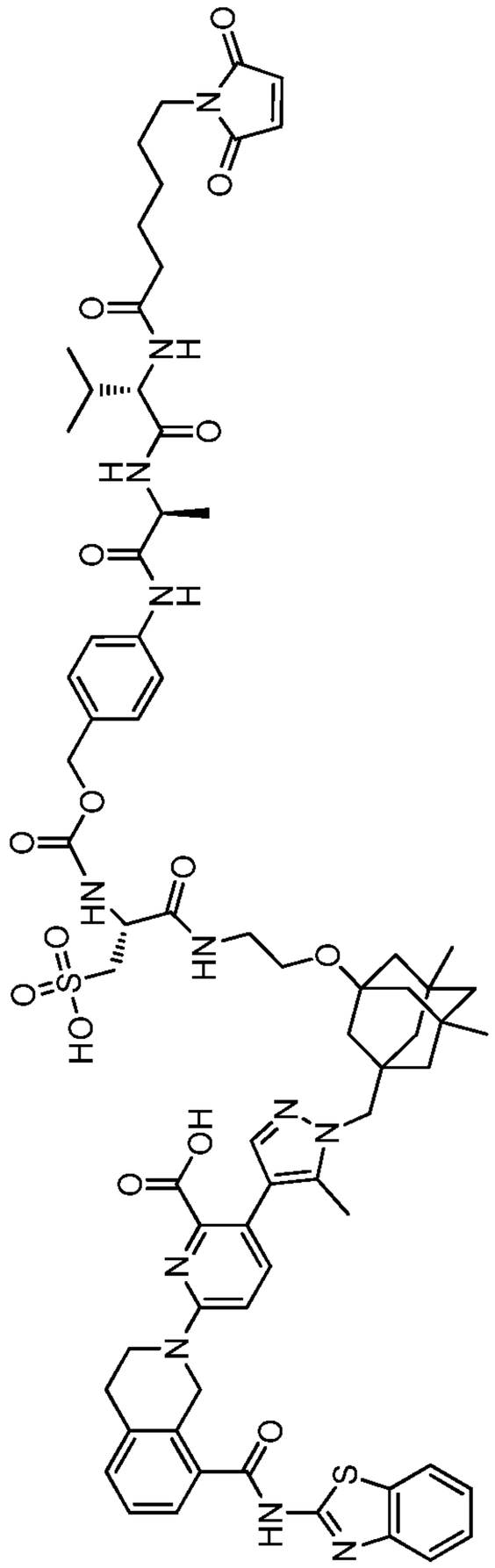
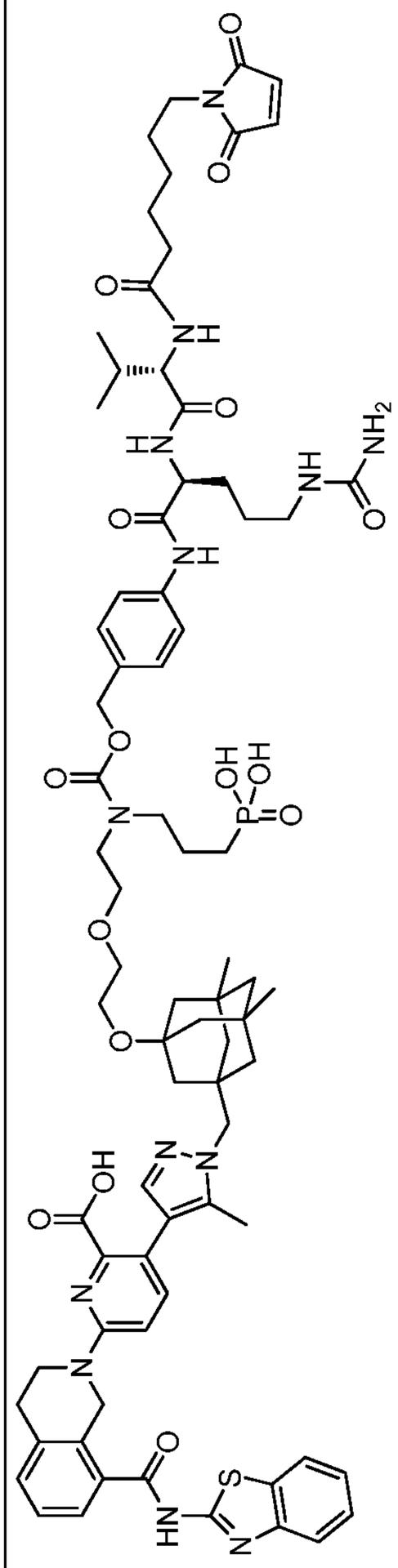
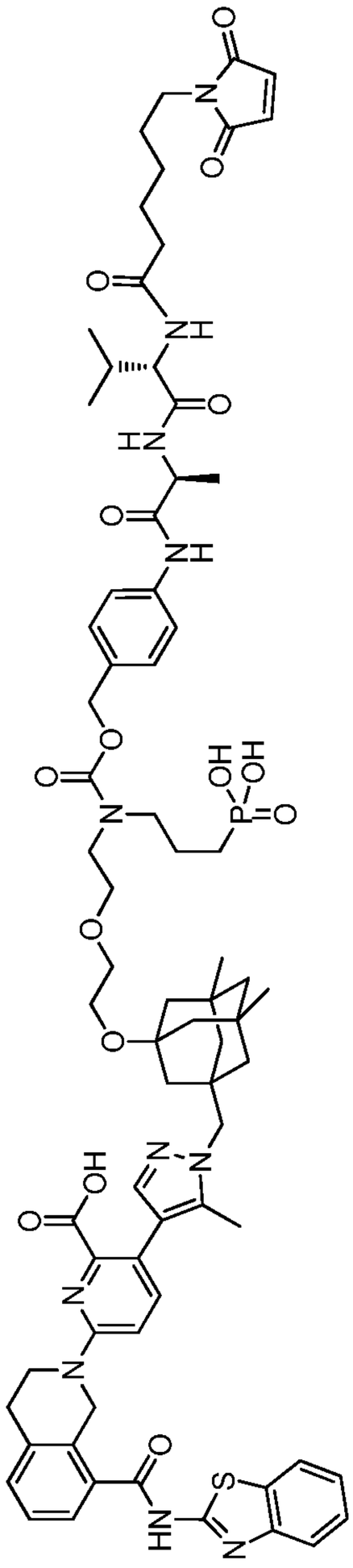
Example No.	Synthon Code	Synthon Structure
2.4	EP	
2.5	EF	

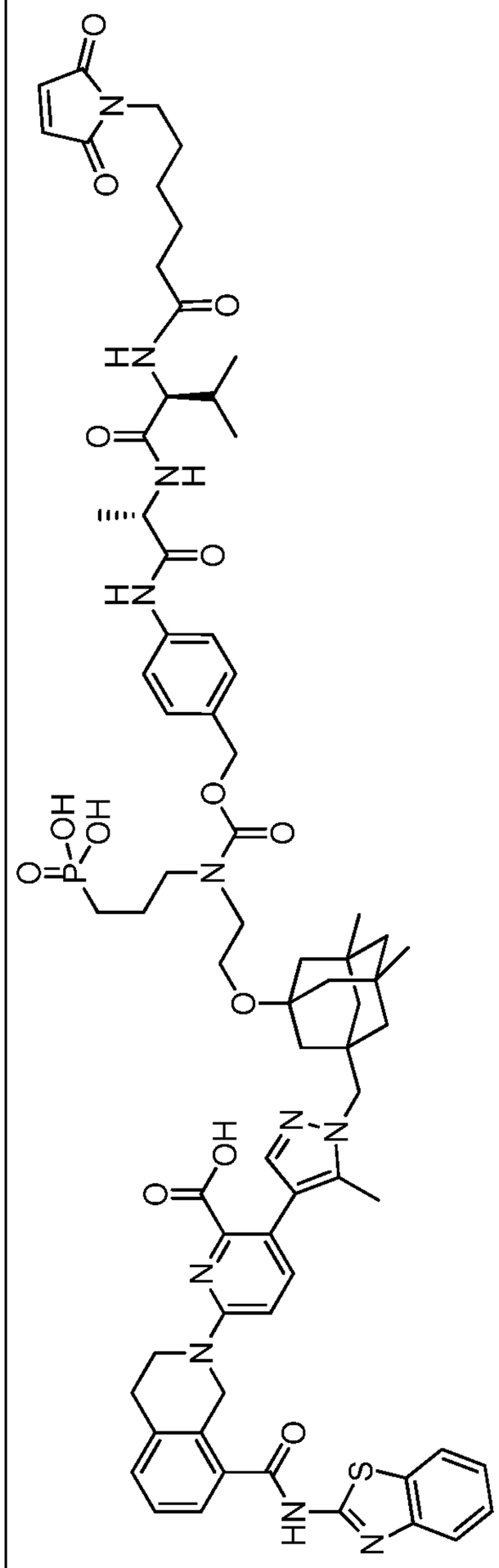
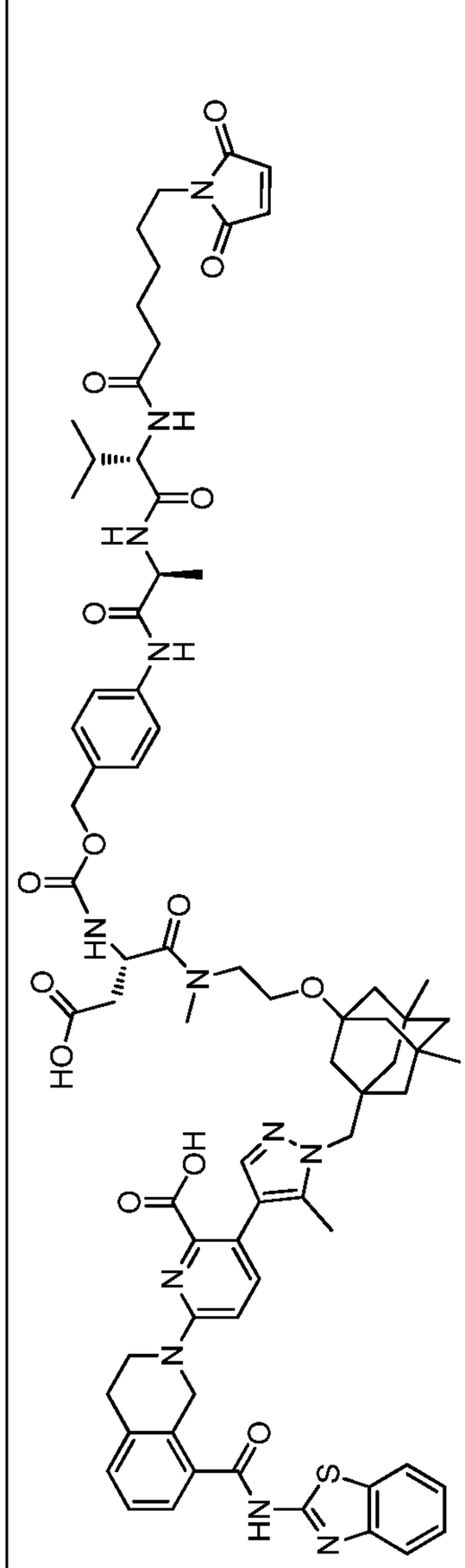
Example No.	Synthon Code	Synthon Structure
2.6	EG	
2.7	EH	

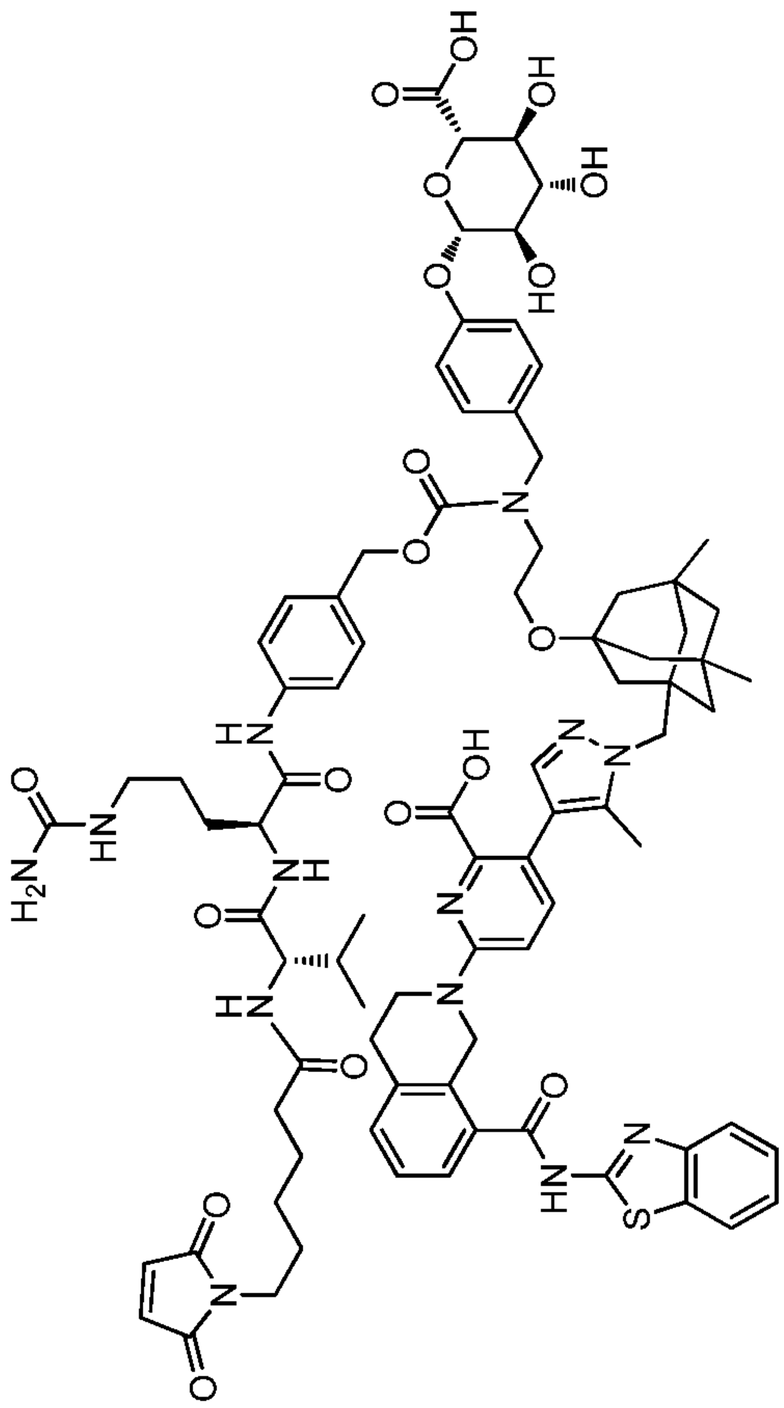
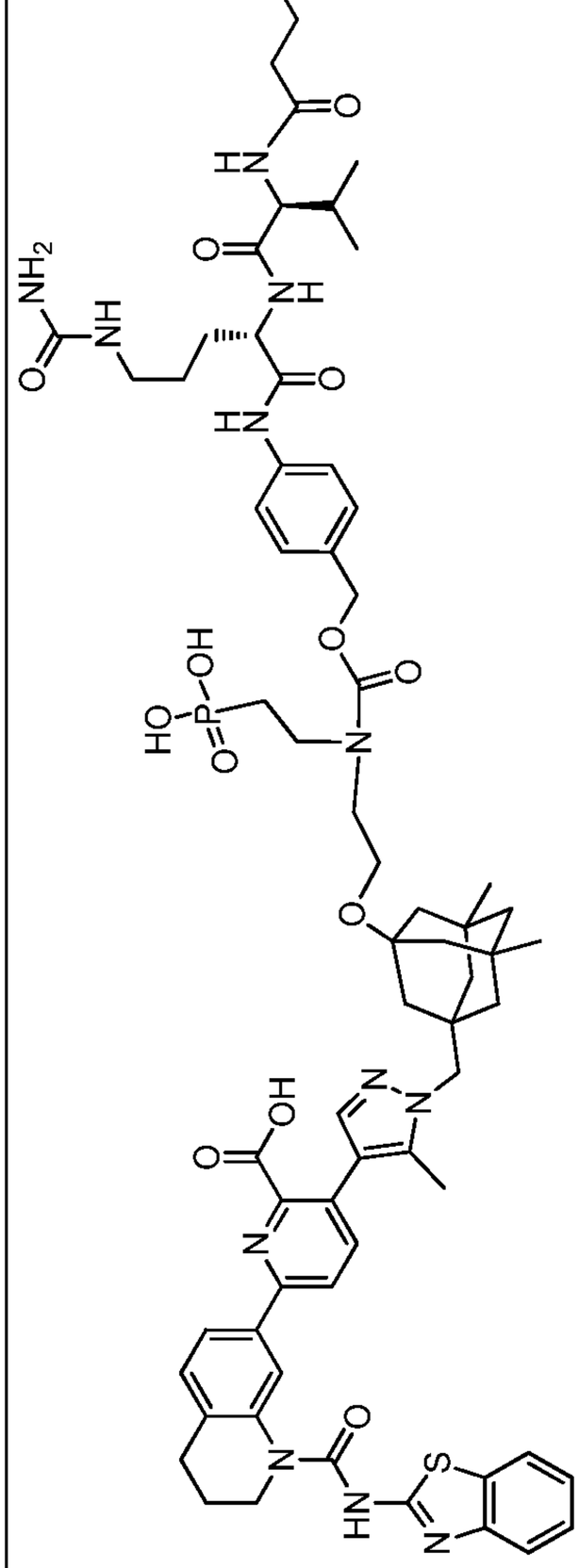
CA 03027045 2018-12-07

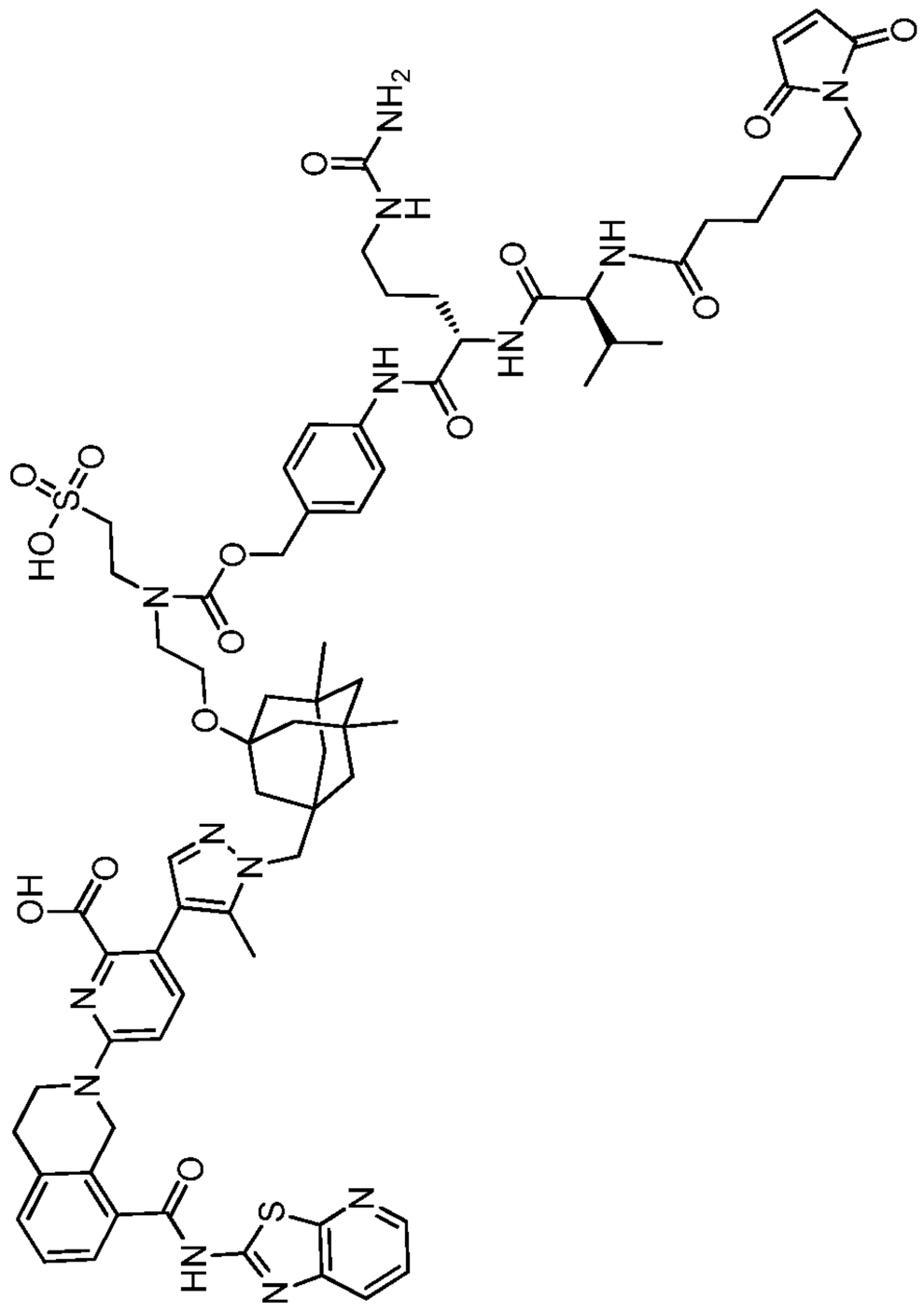
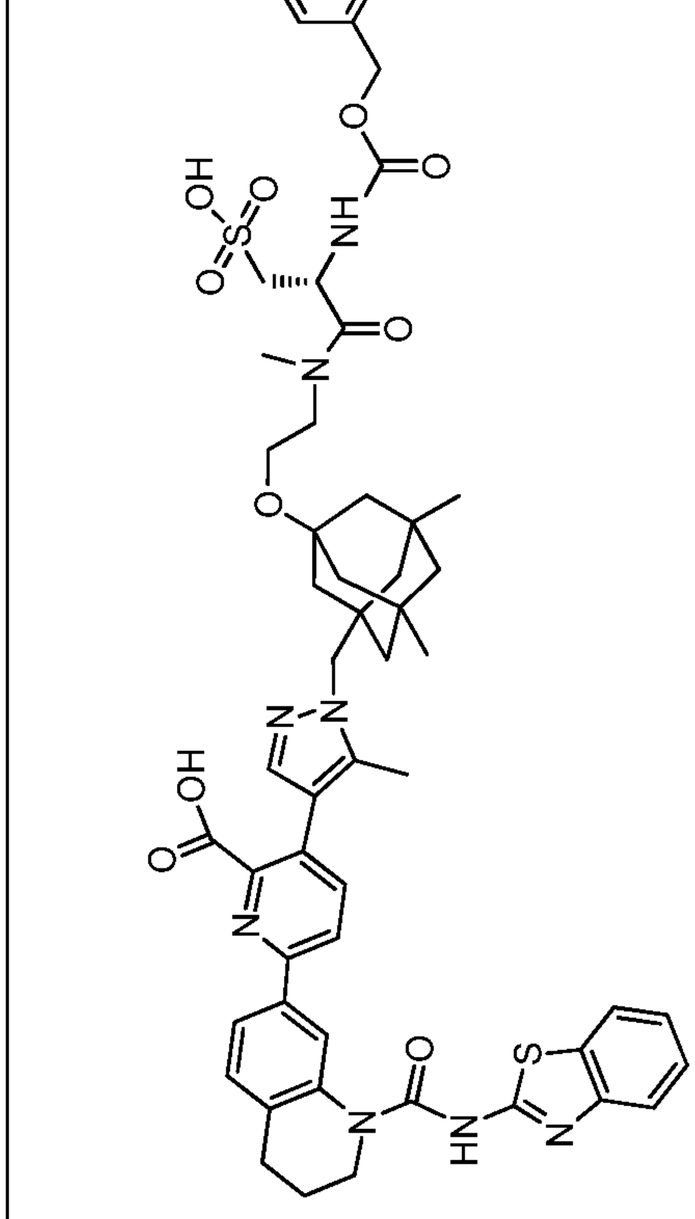
Example No.	Synthon Code	Synthon Structure
2.8	ER	
2.9	ES	

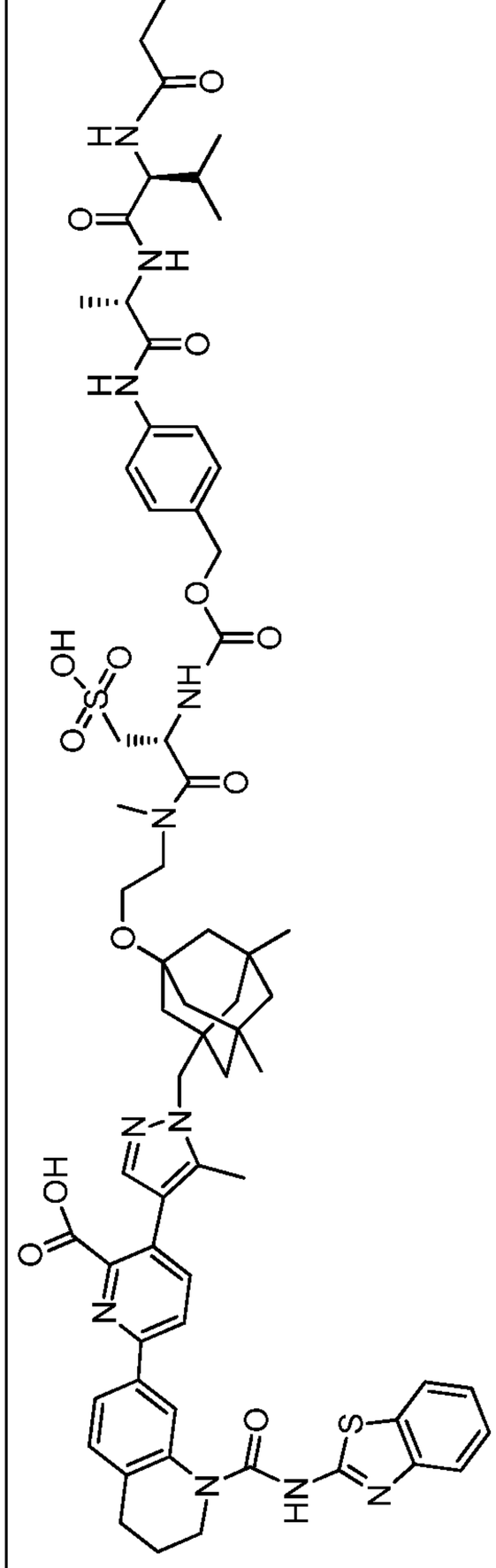
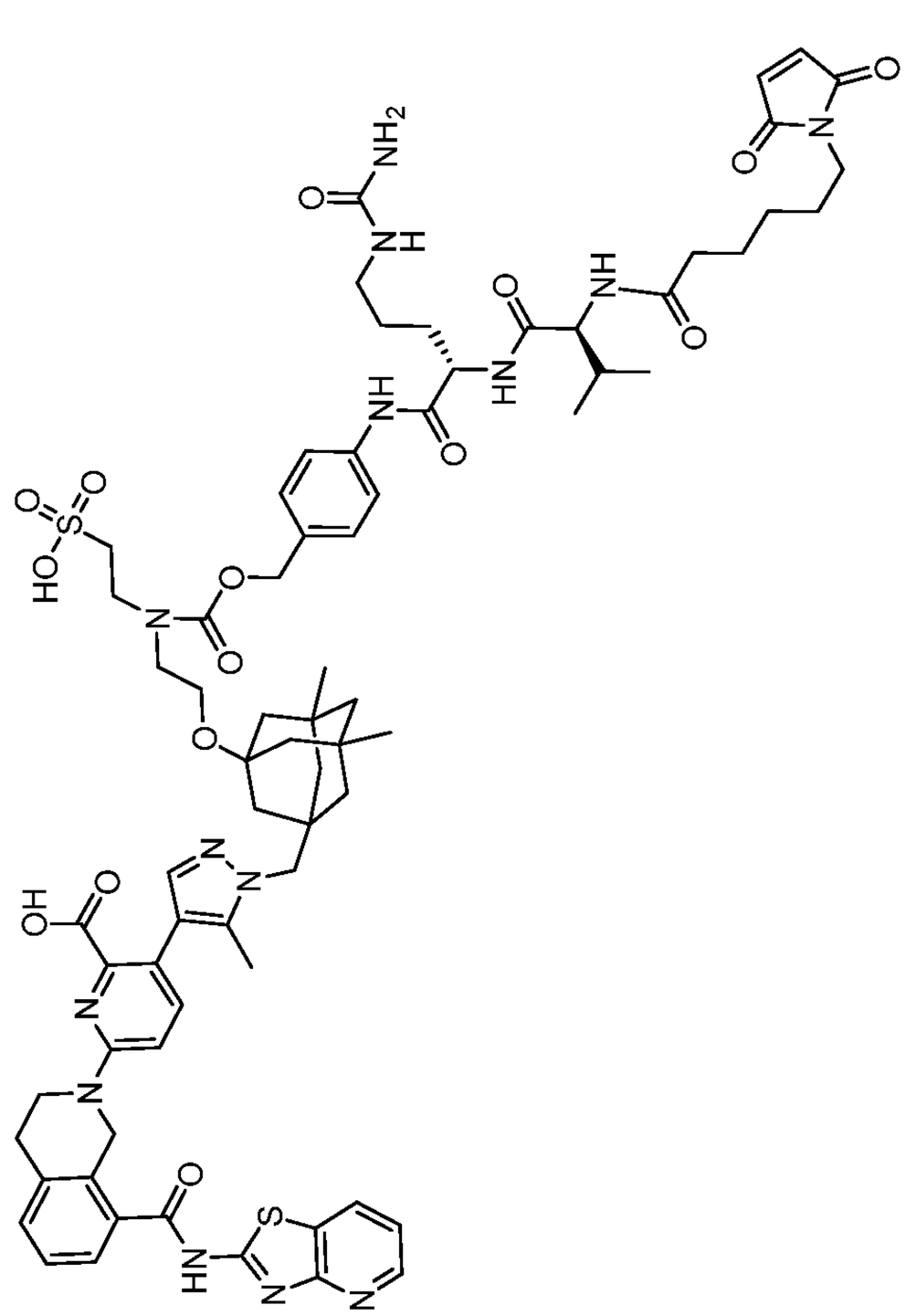
Example No.	Synthon Code	Synthon Structure
2.10	EQ	
2.11	EU	
2.12	EV	

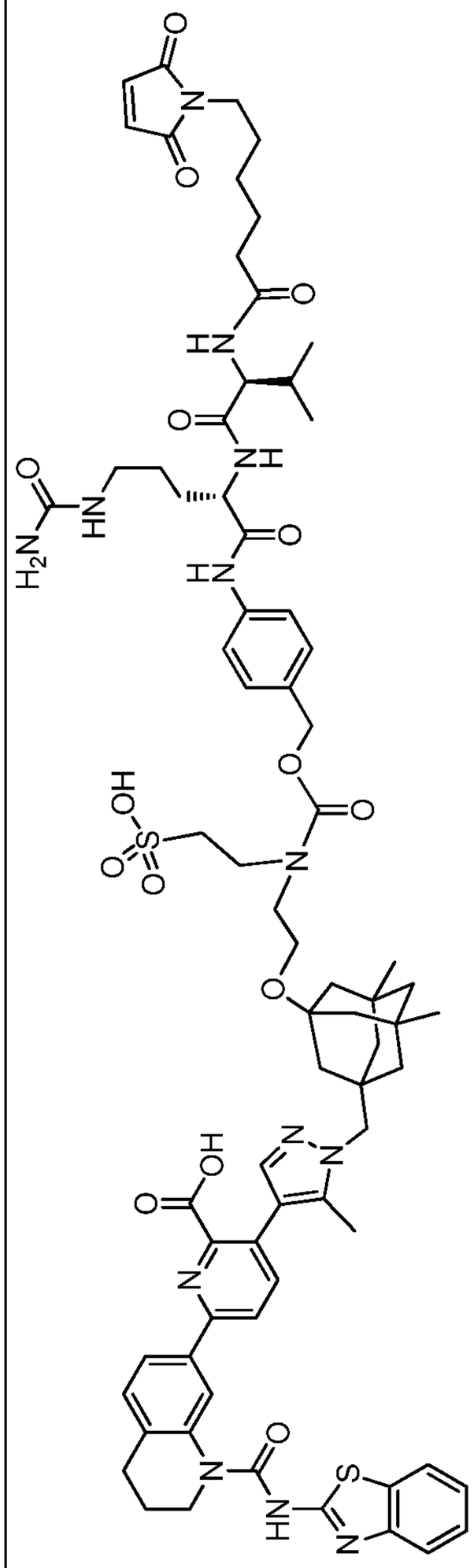
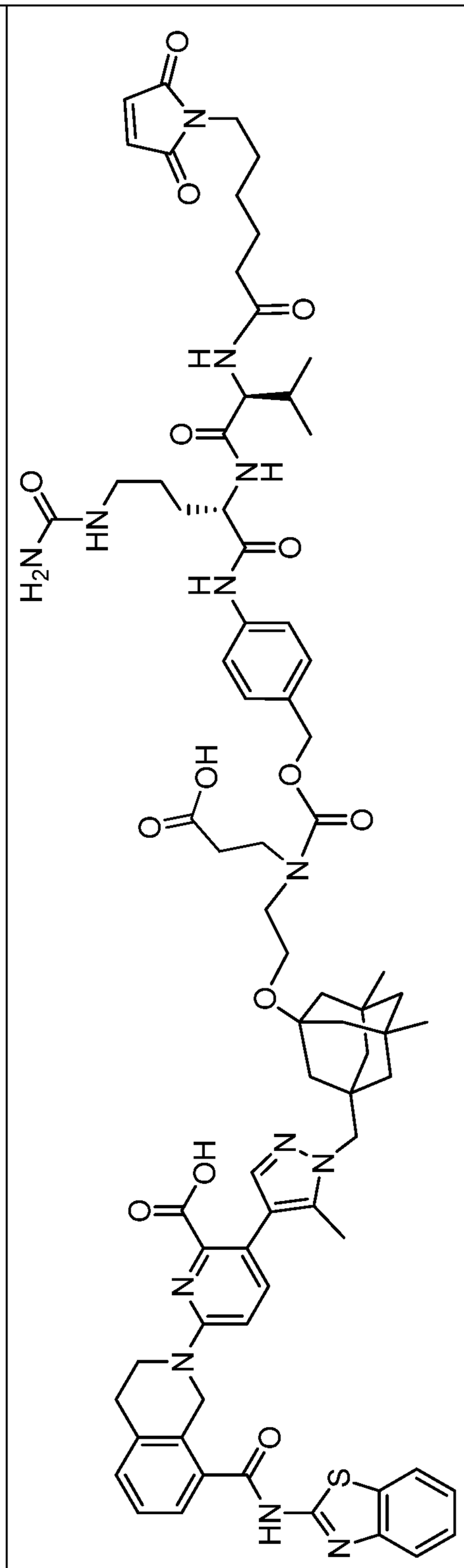
Example No.	Synthon Code	Synthon Structure
2.13	EW	
2.14	EX	
2.15	EY	

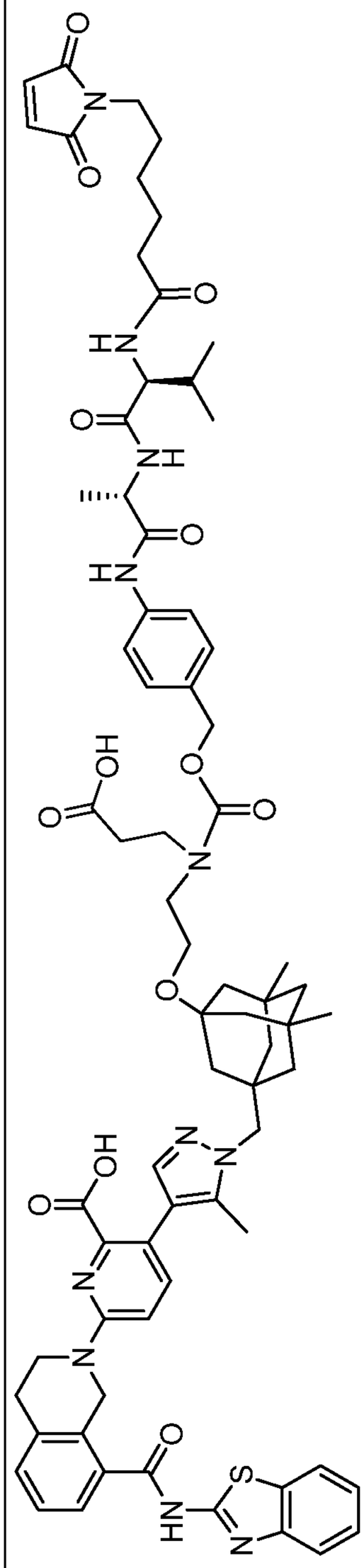
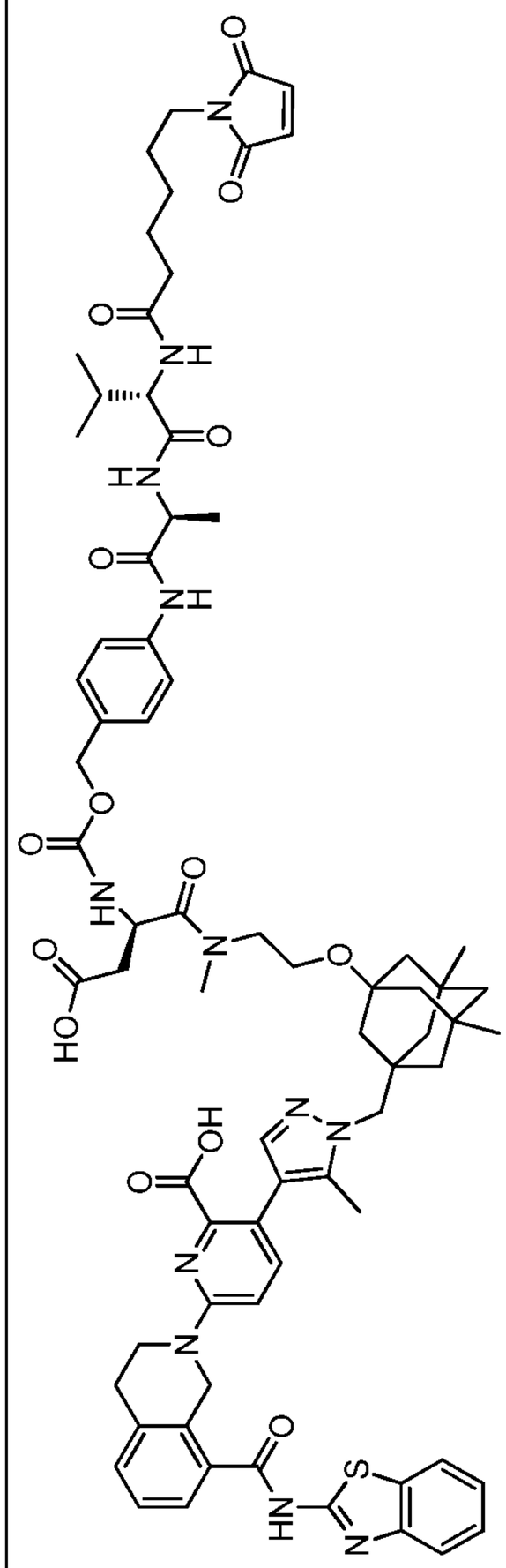
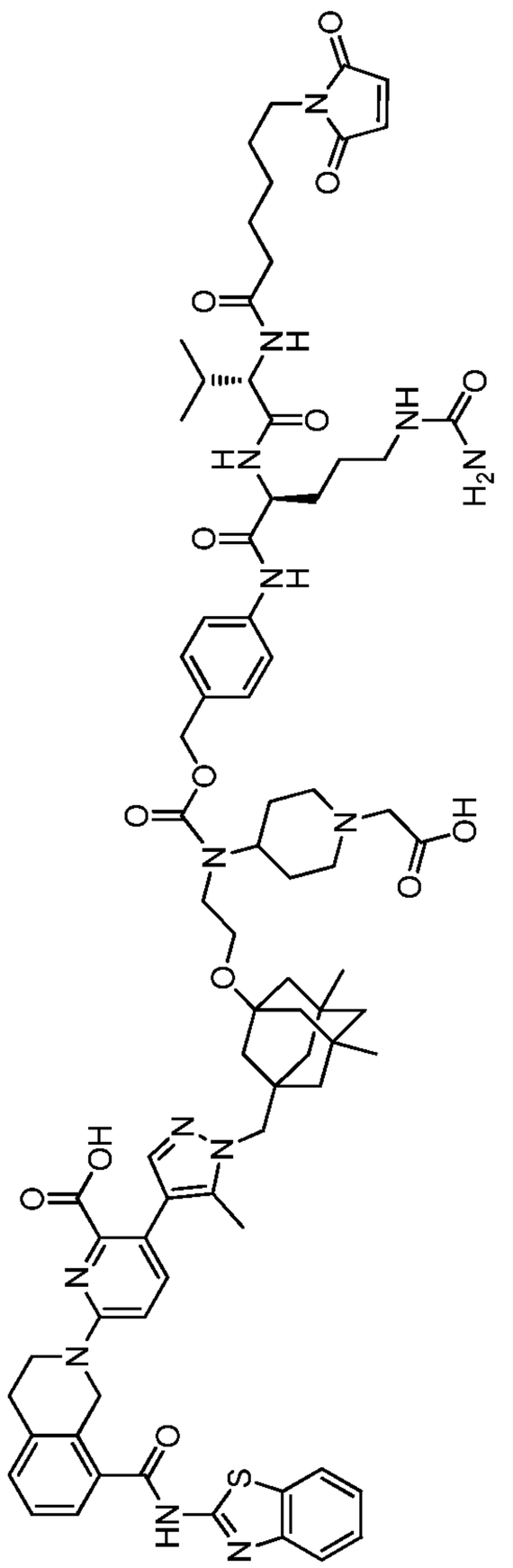
Example No.	Synthon Code	Synthon Structure
2.16	EZ	
2.17	FD	

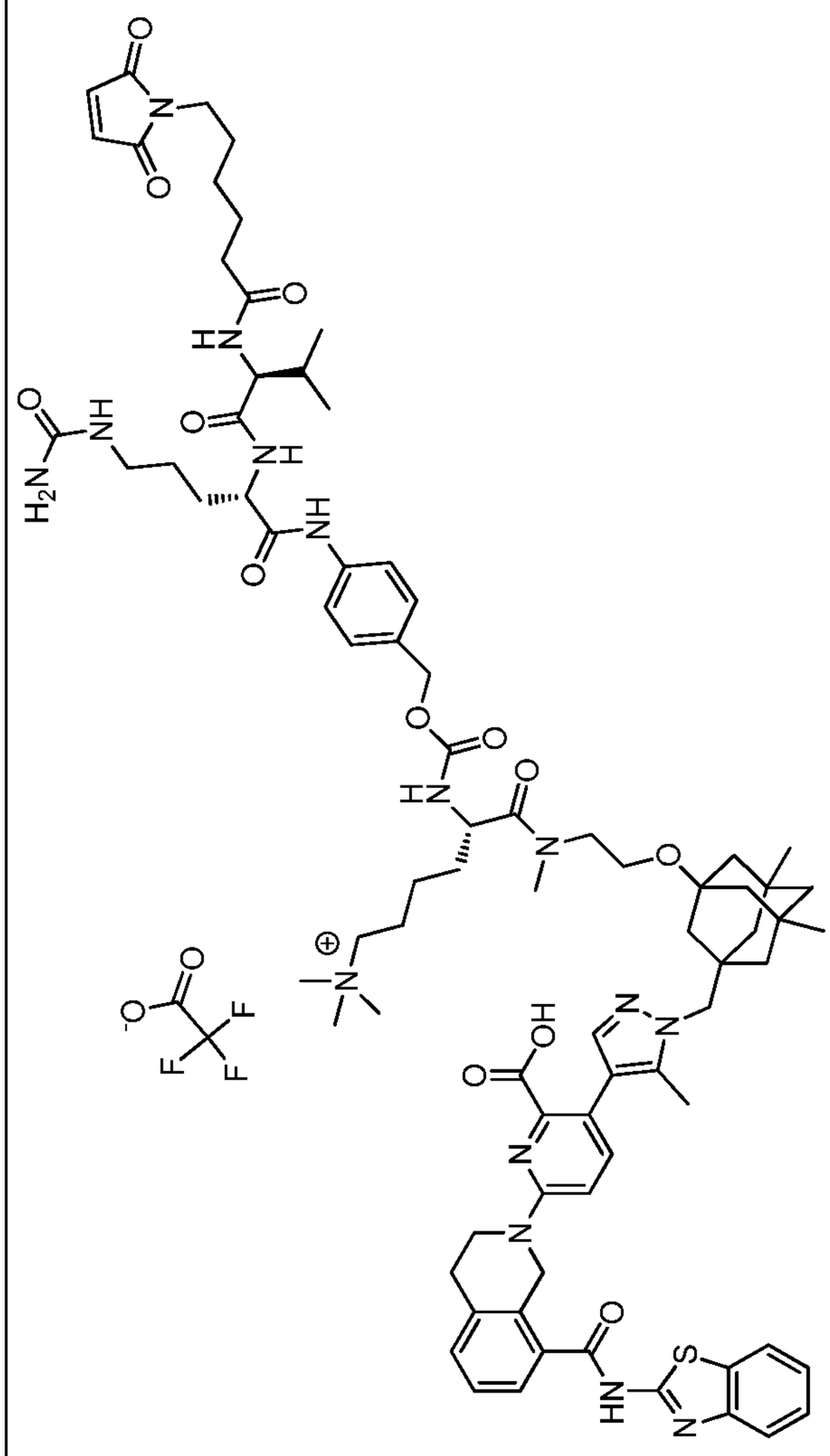
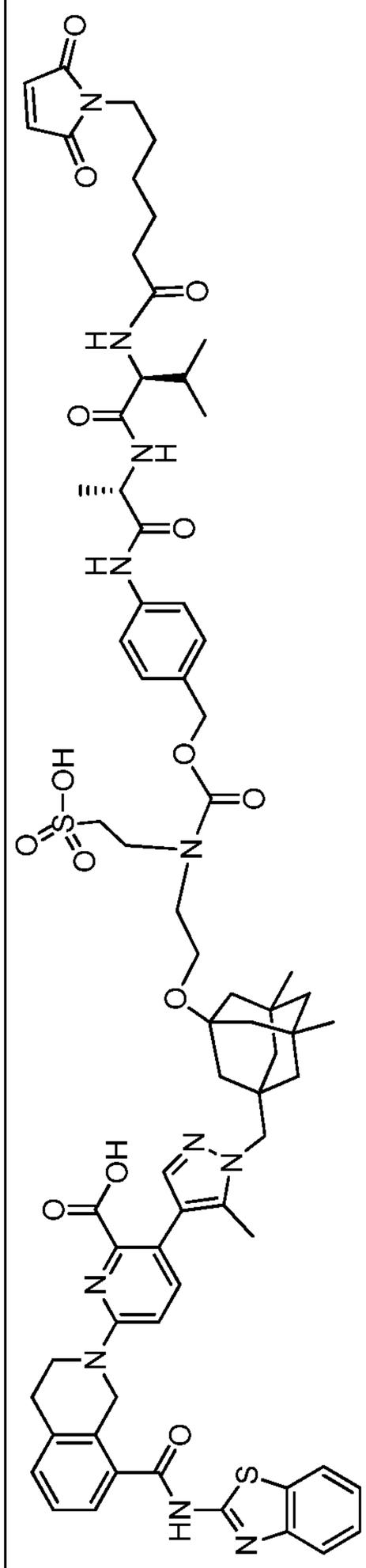
Example No.	Synthon Code	Synthon Structure
2.18	FS	
2.19	FI	

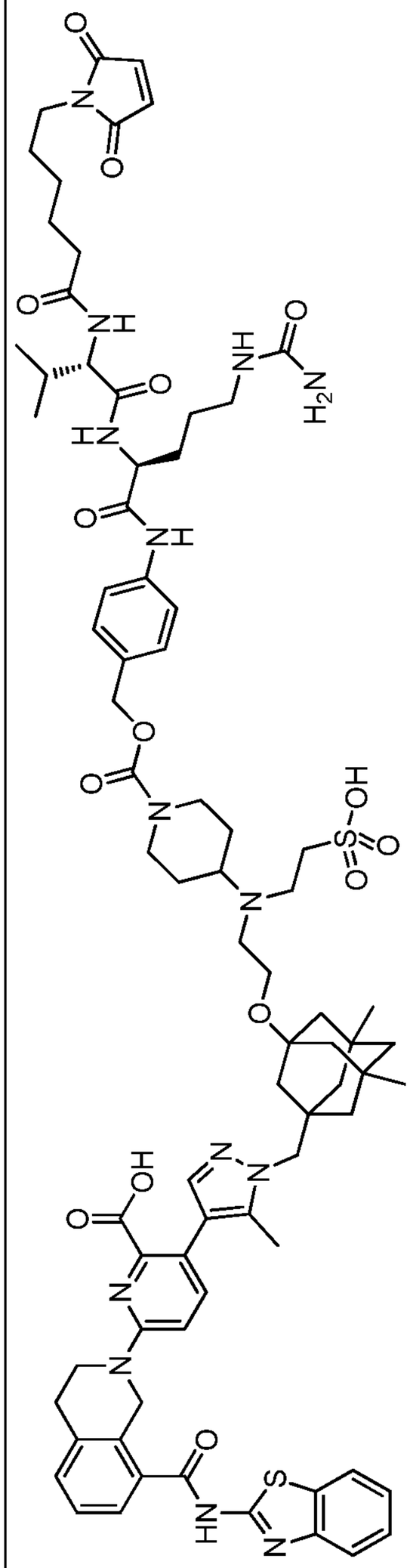
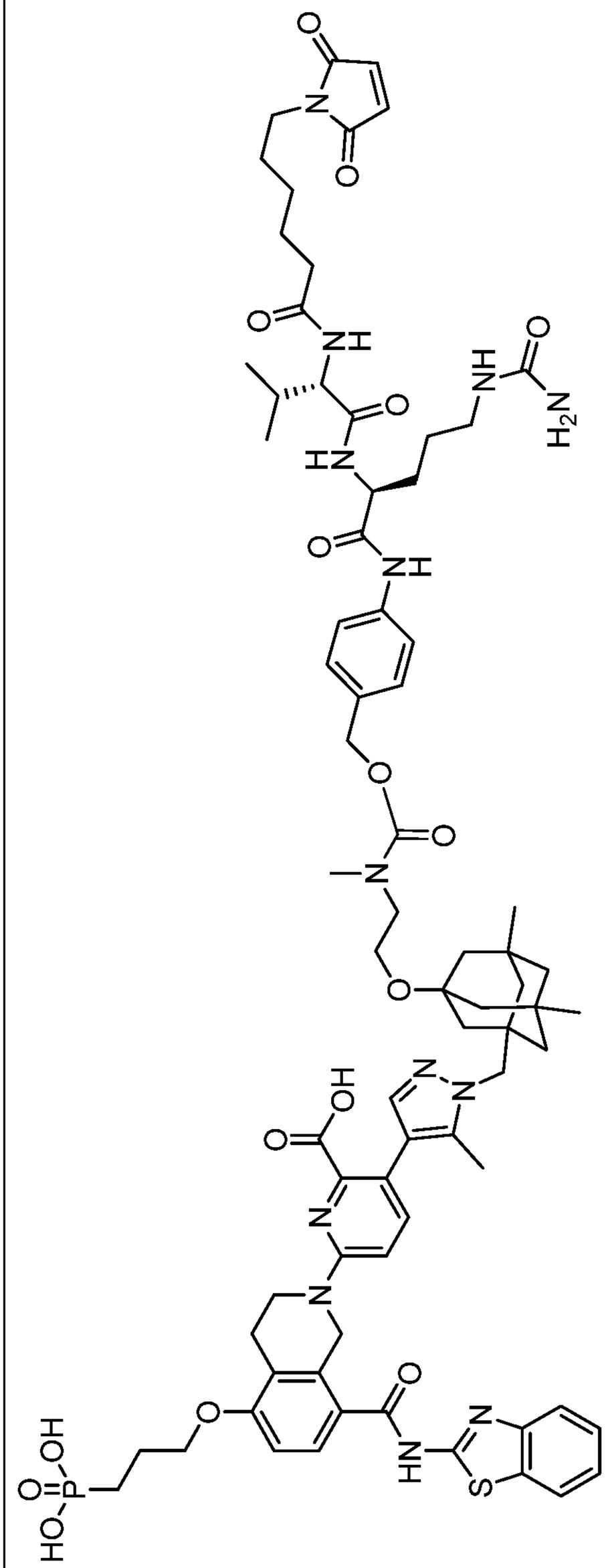
Example No.	Synthon Code	Synthon Structure
2.20	FV	
2.21	GC	

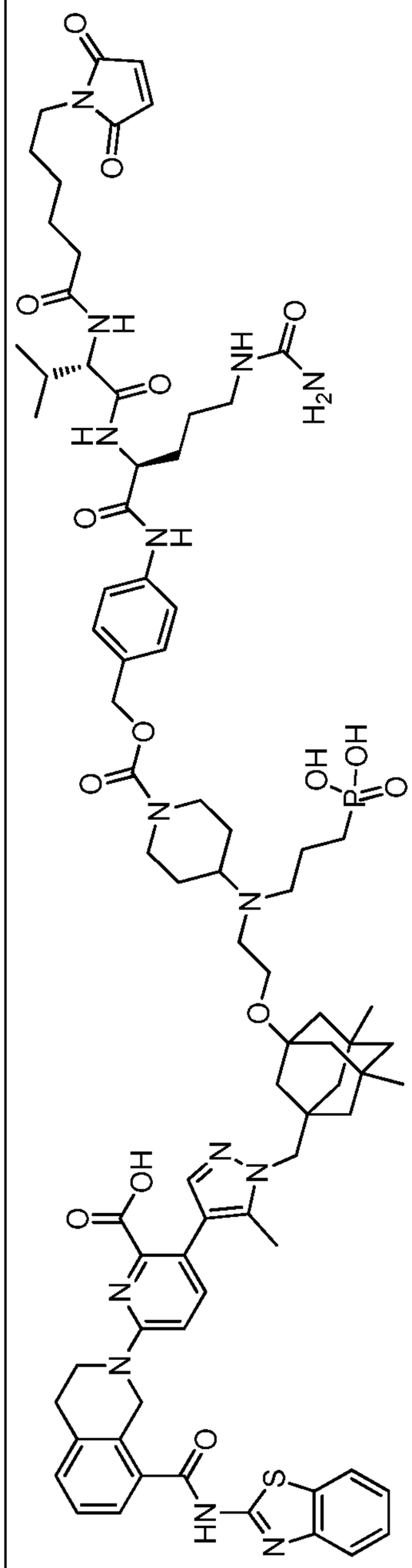
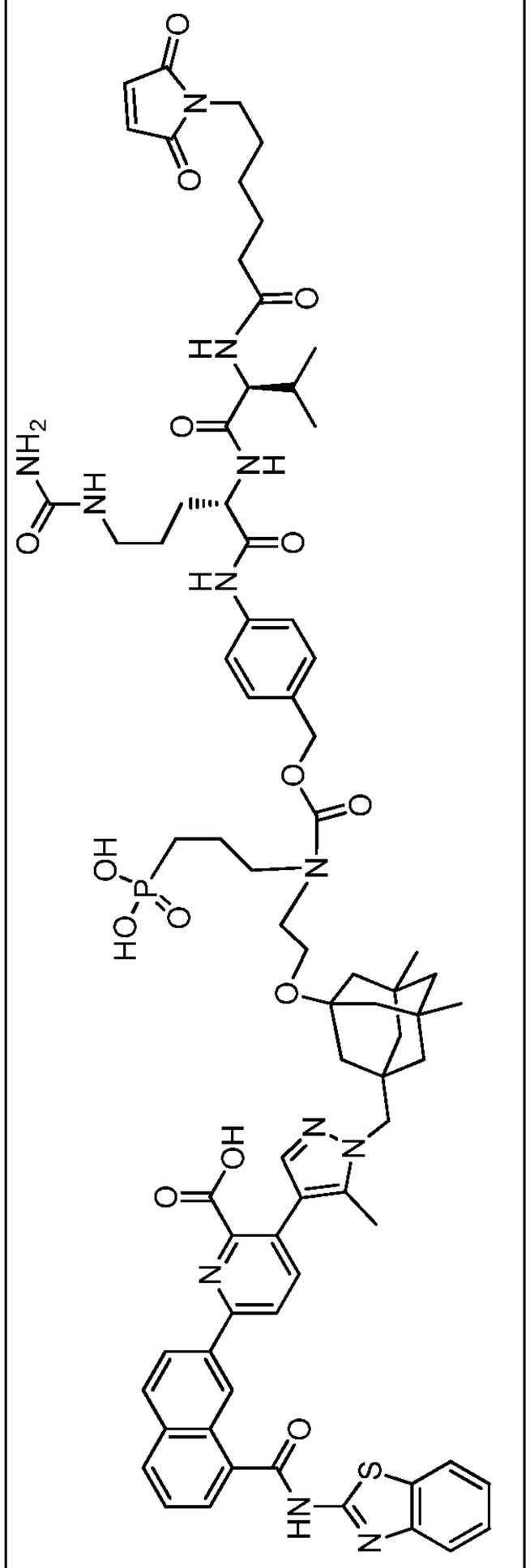
Example No.	Synthon Code	Synthon Structure
2.22	GB	
2.23	FW	

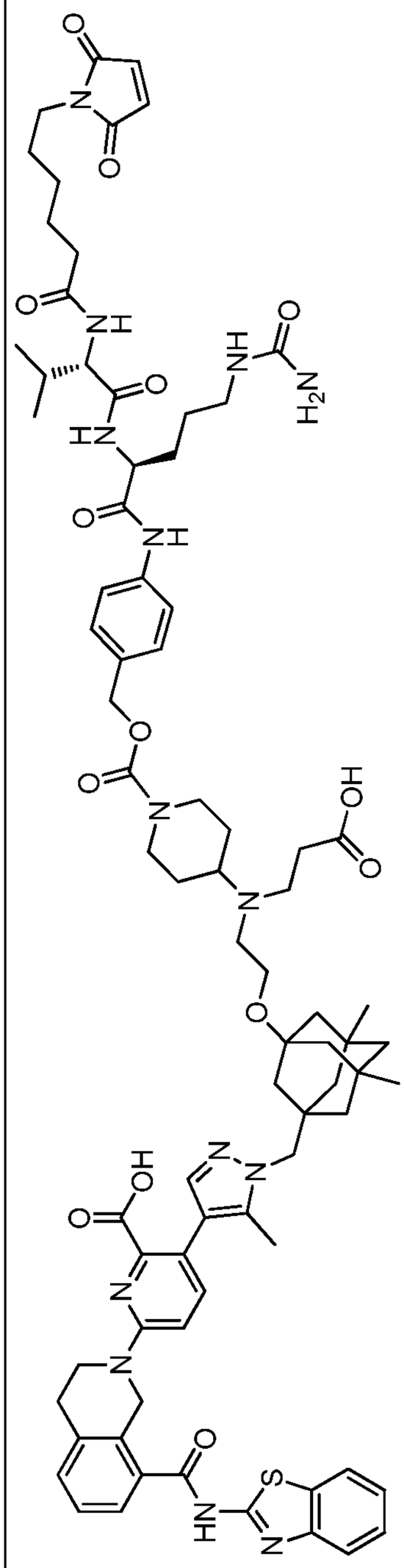
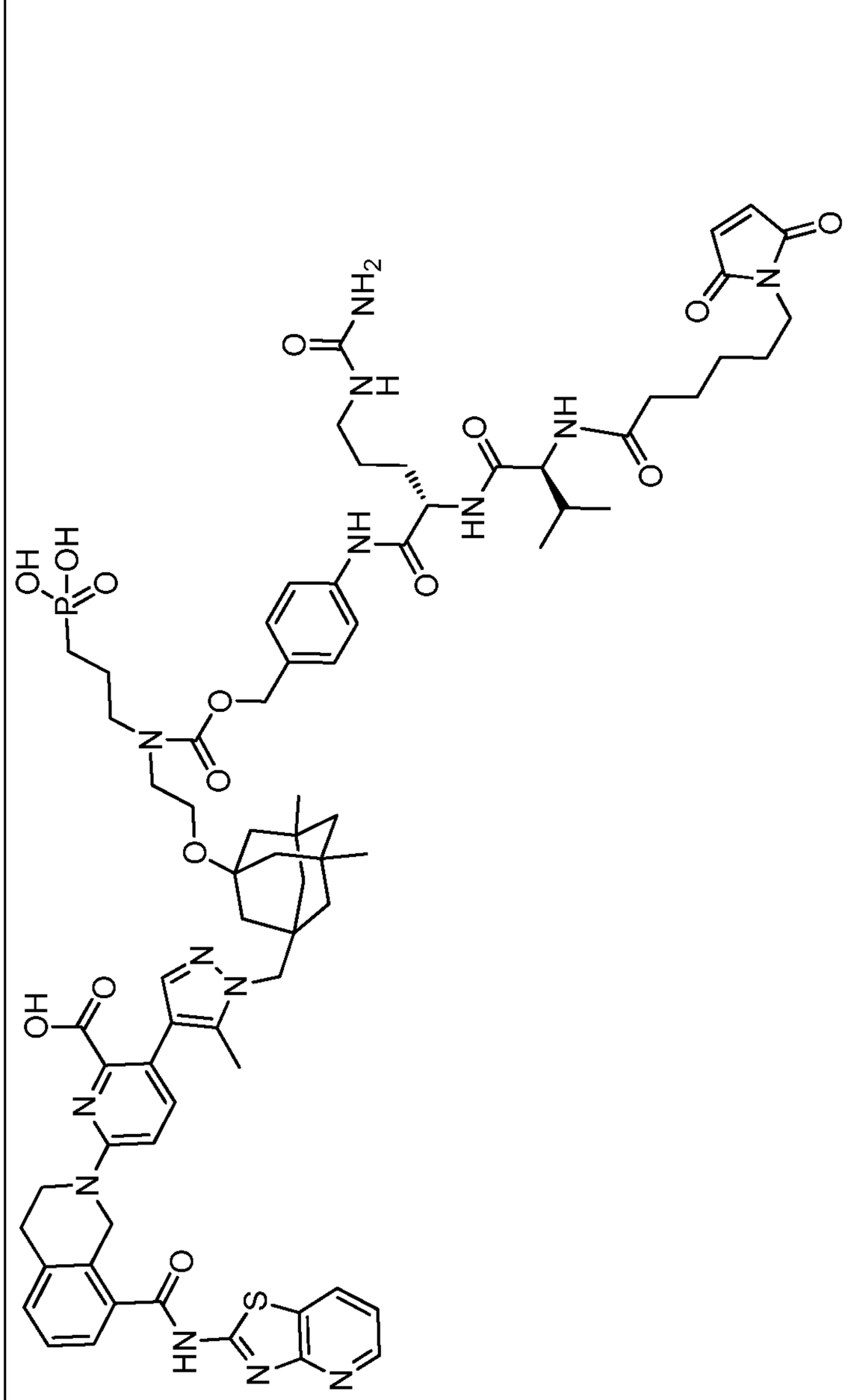
Example No.	Synthon Code	Synthon Structure
2.24	GD	
2.25	GK	

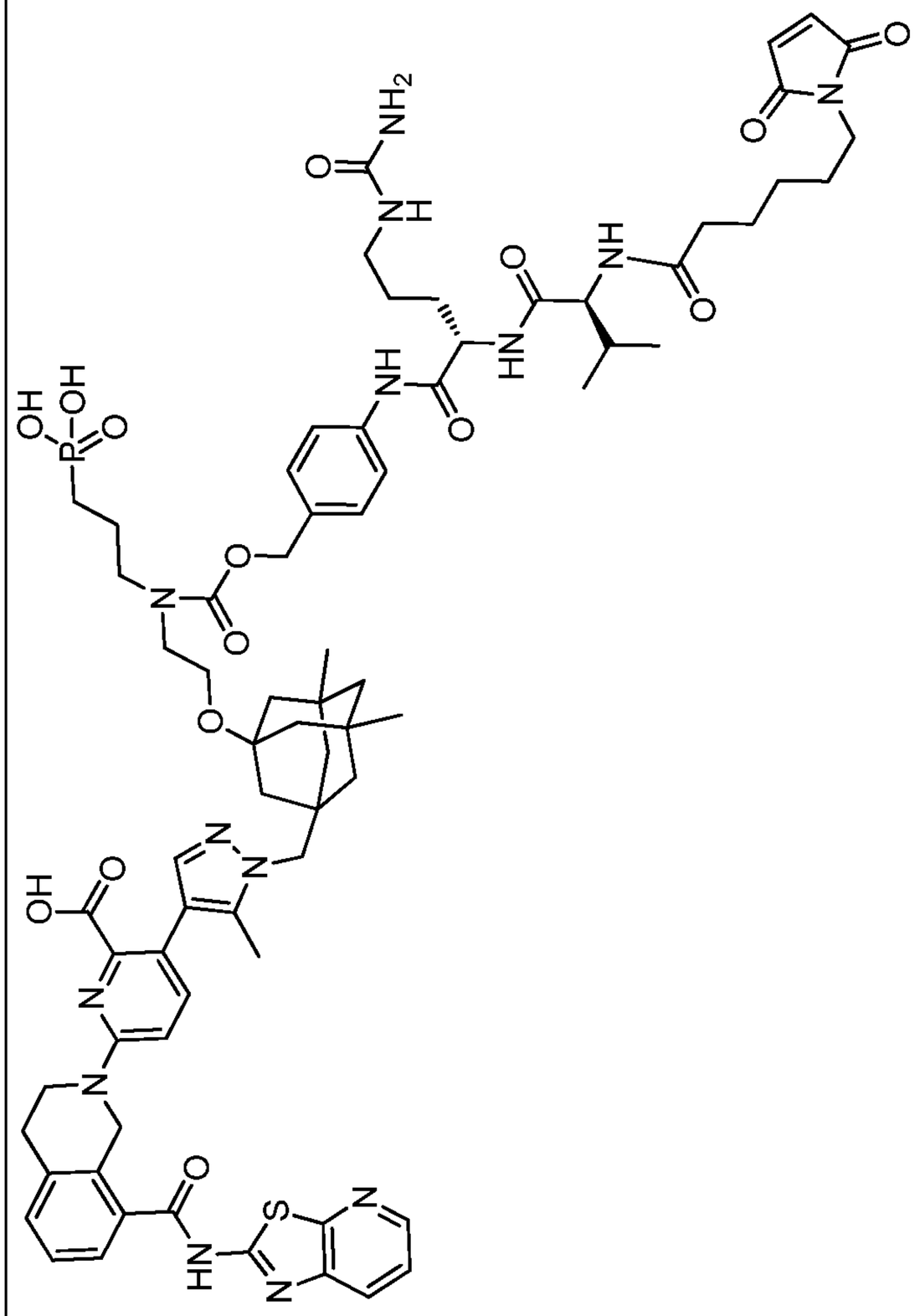
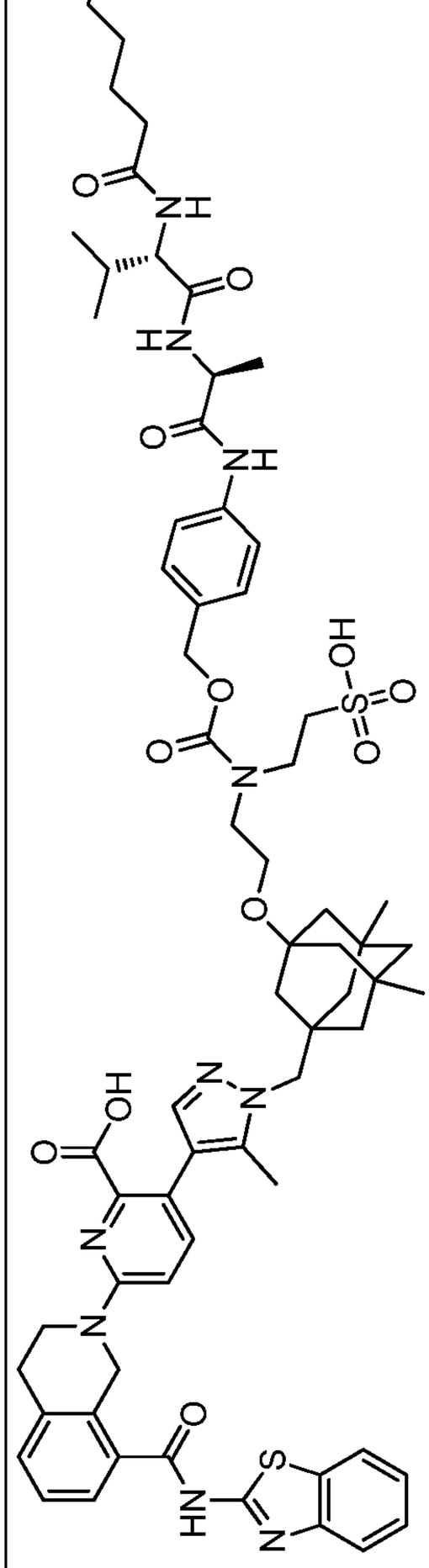
Example No.	Synthon Code	Synthon Structure
2.26	GJ	
2.27	GW	
2.28	HF	

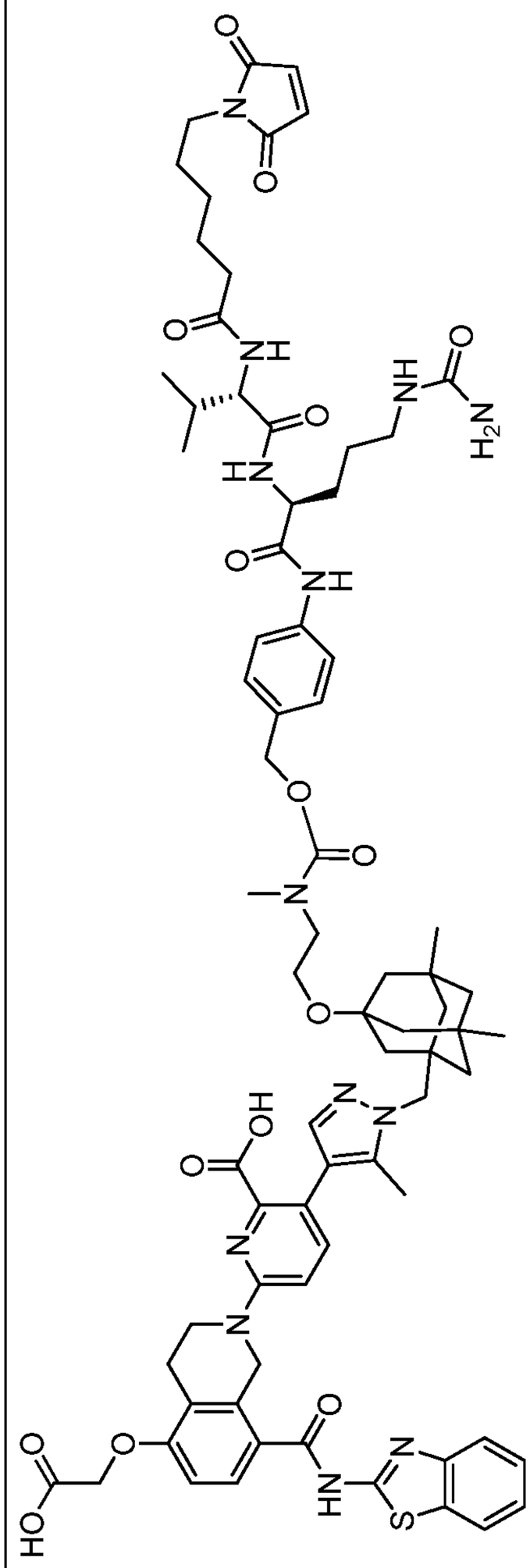
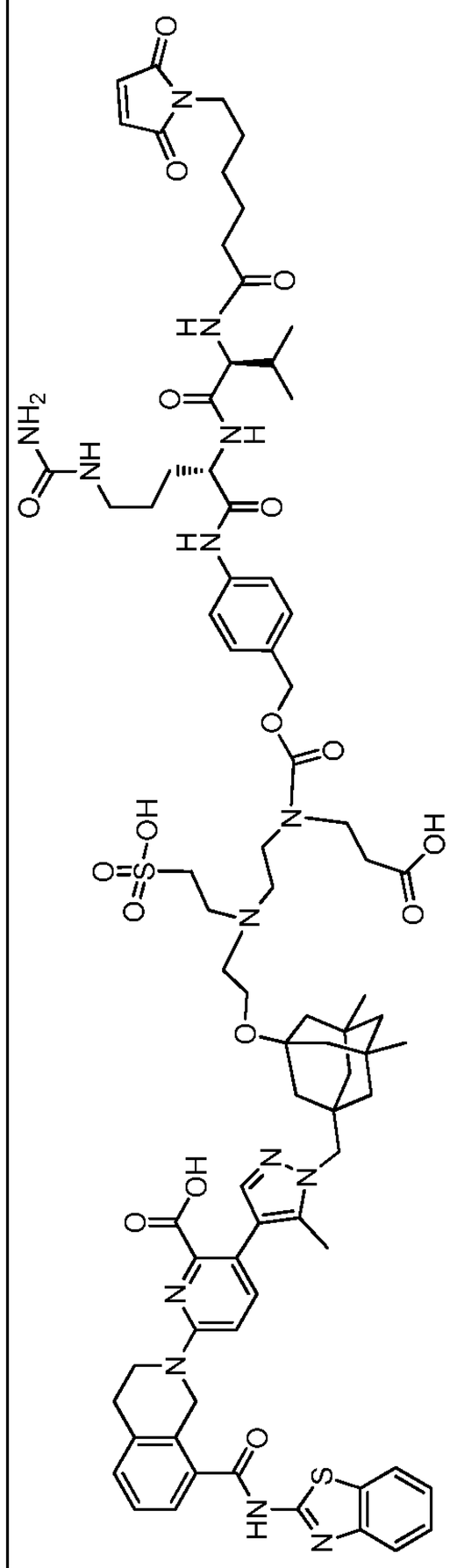
Example No.	Synthon Code	Synthon Structure
2.29	HG	
2.30	HP	

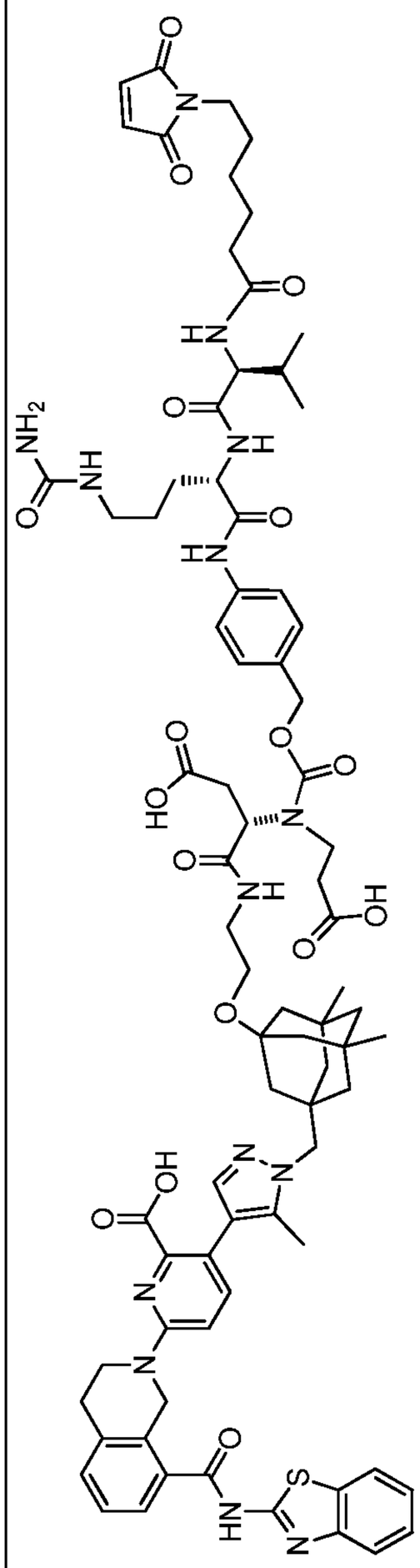
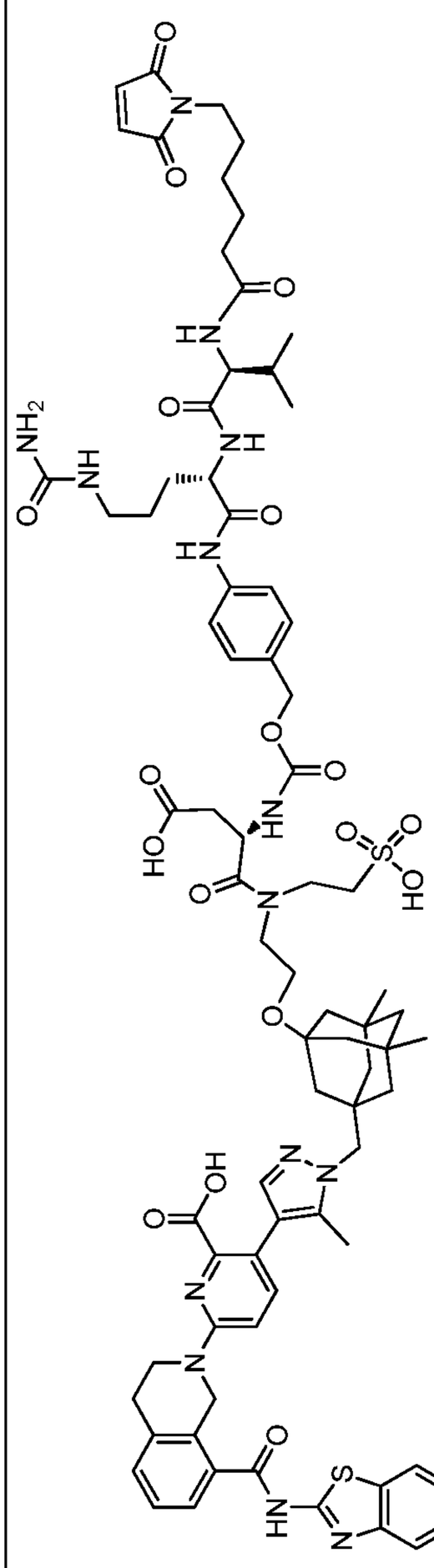
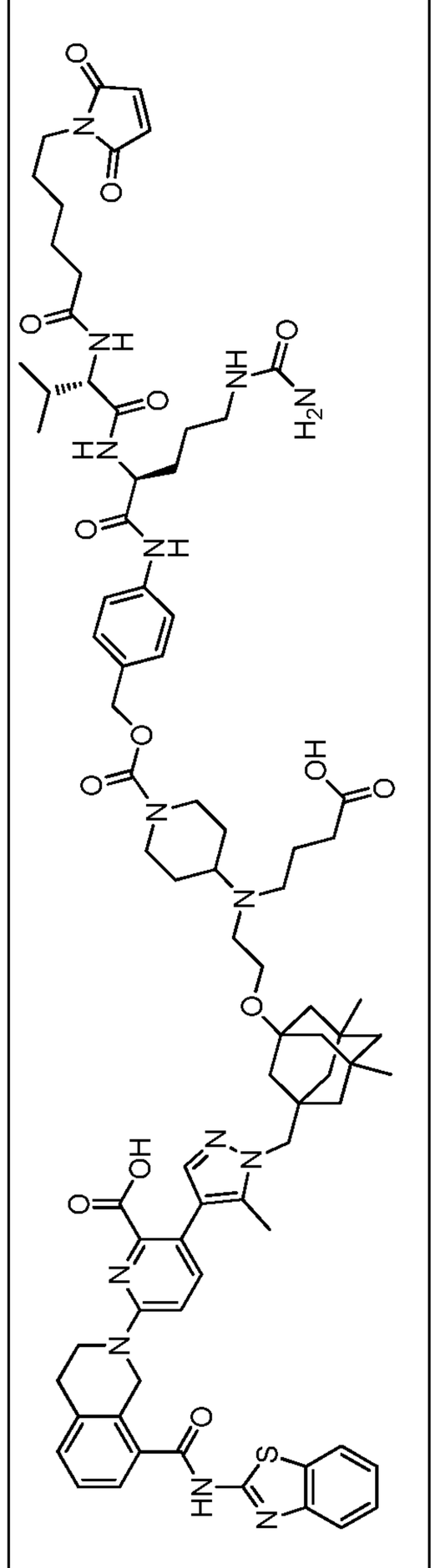
Example No.	Synthon Code	Synthon Structure
2.31	HR	
2.32	HU	

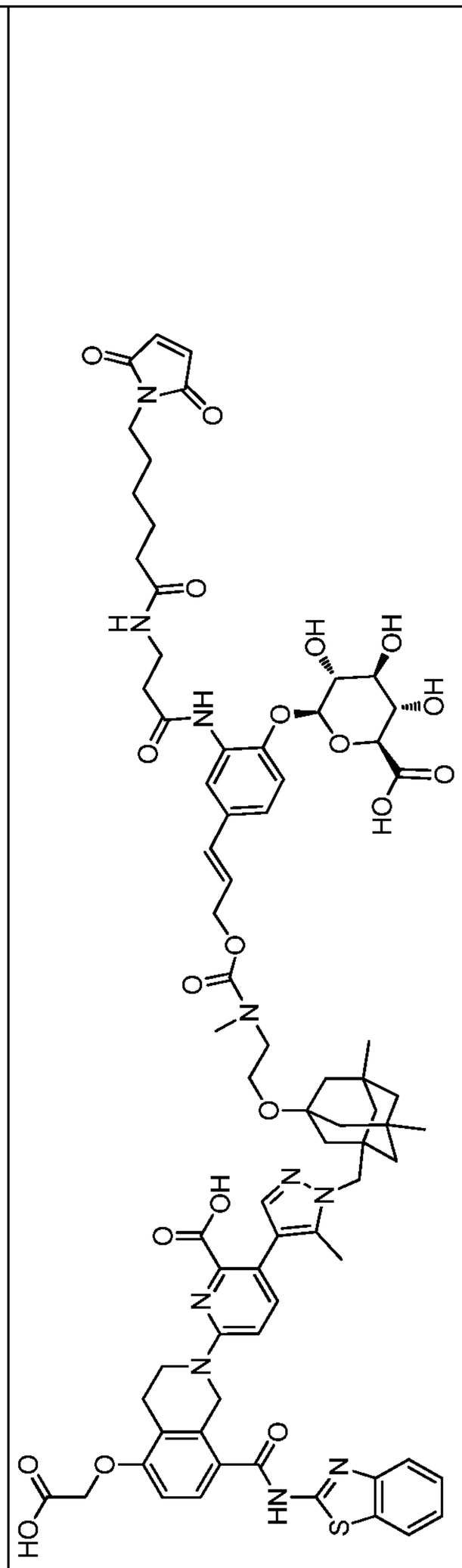
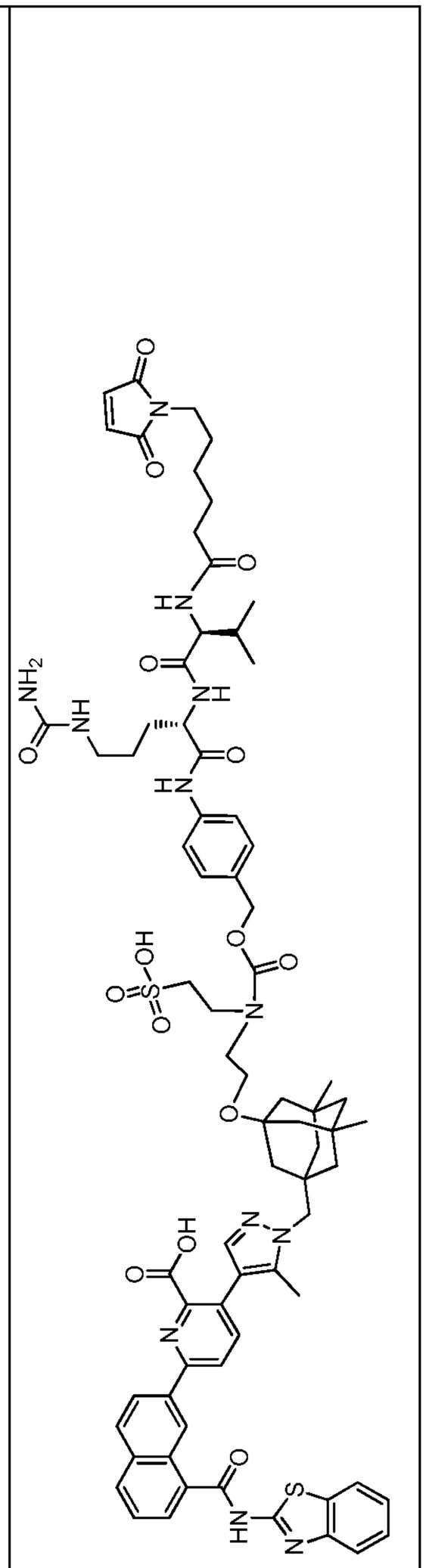
Example No.	Synthon Code	Synthon Structure
2.33	HT	
2.34	HV	

Example No.	Synthon Code	Synthon Structure
2.35	HZ	
2.36	IA	

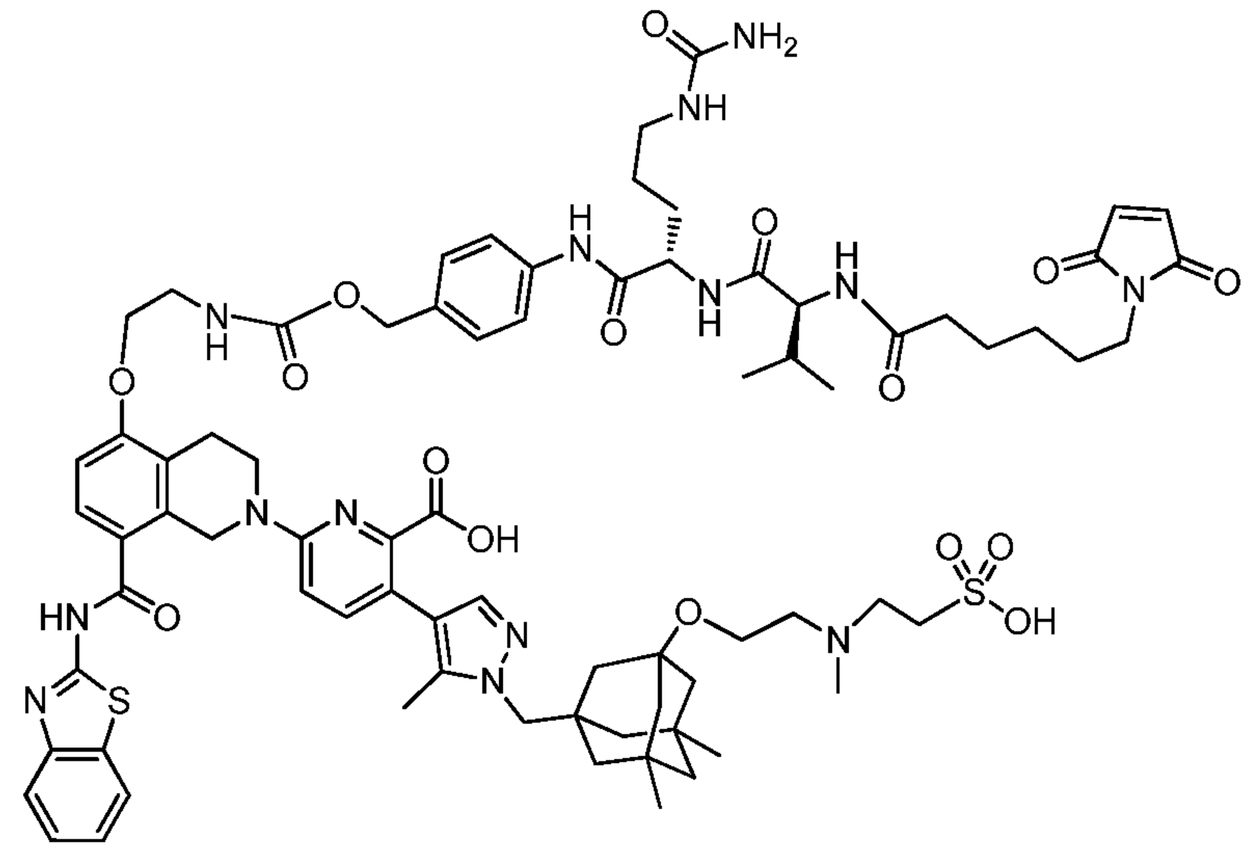
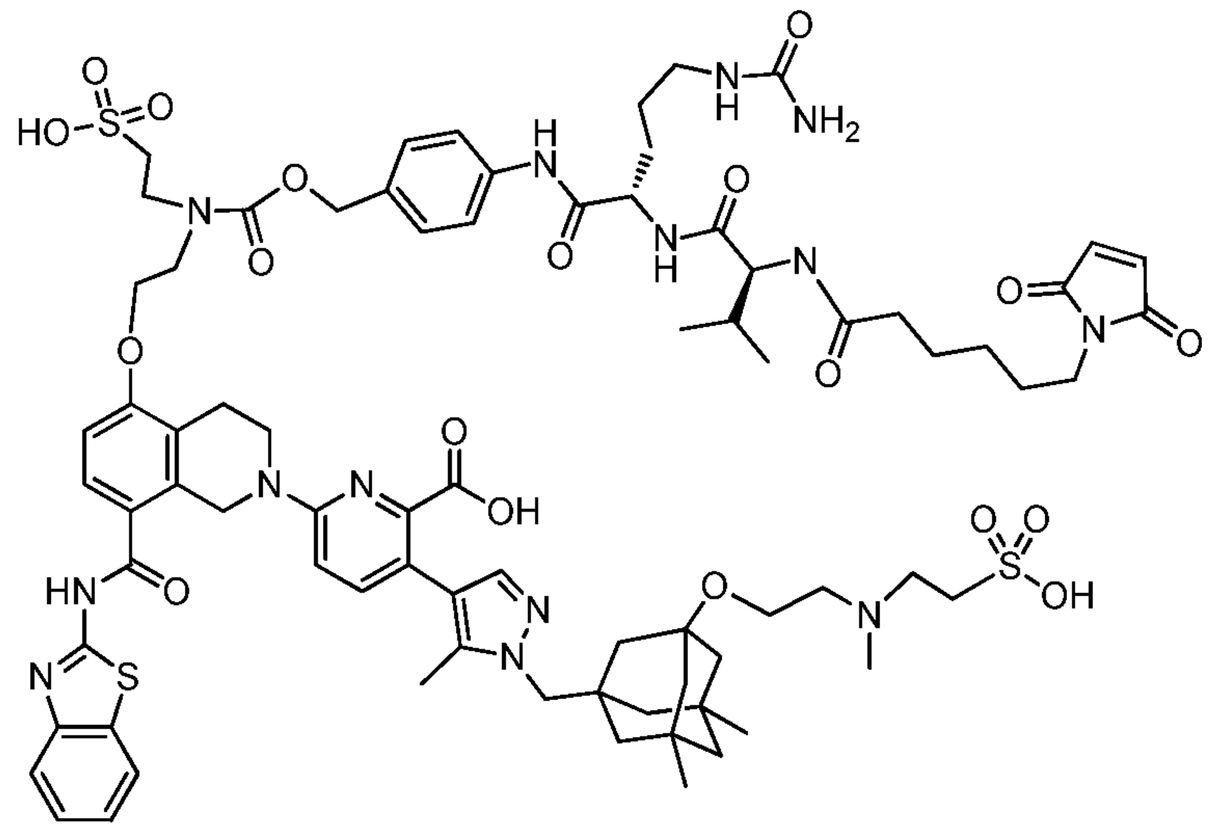
Example No.	Synthon Code	Synthon Structure
2.37	IF	
2.38	IG	

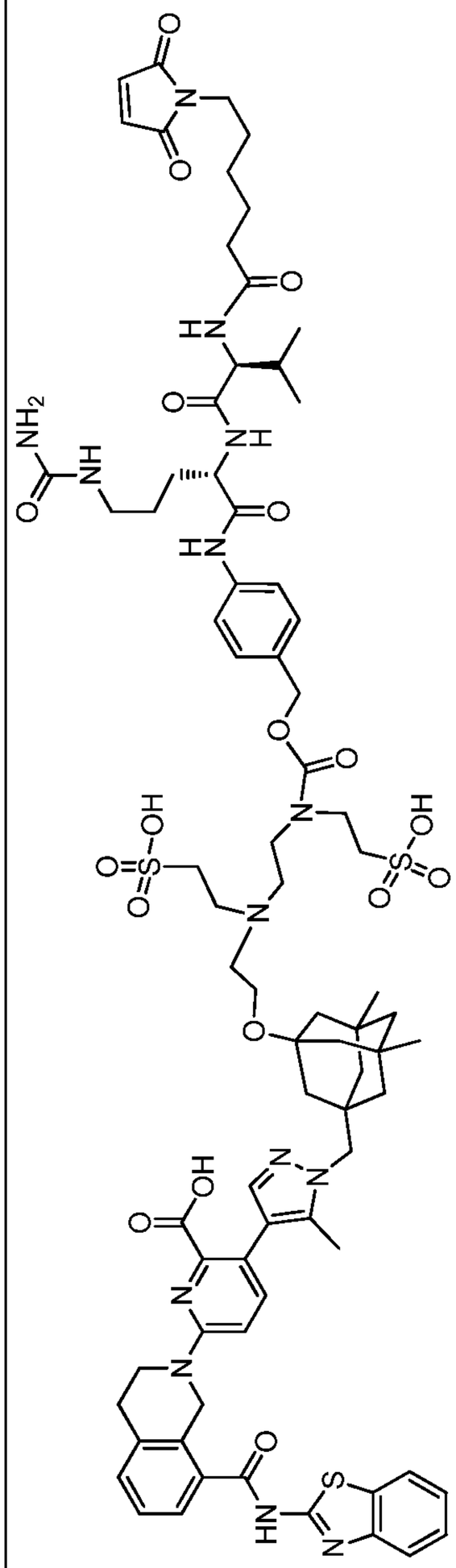
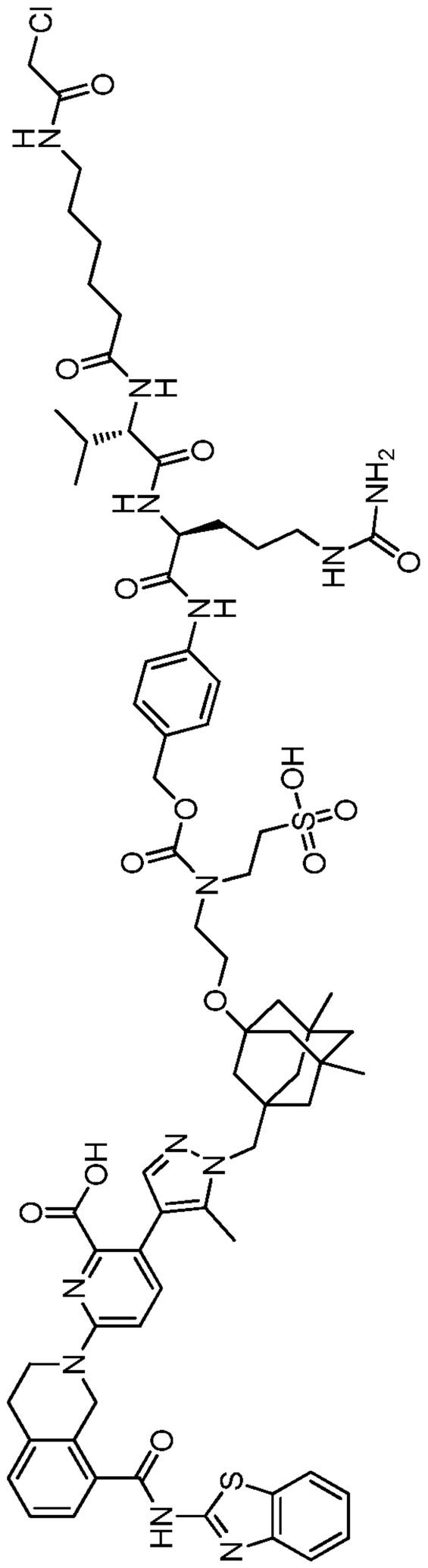
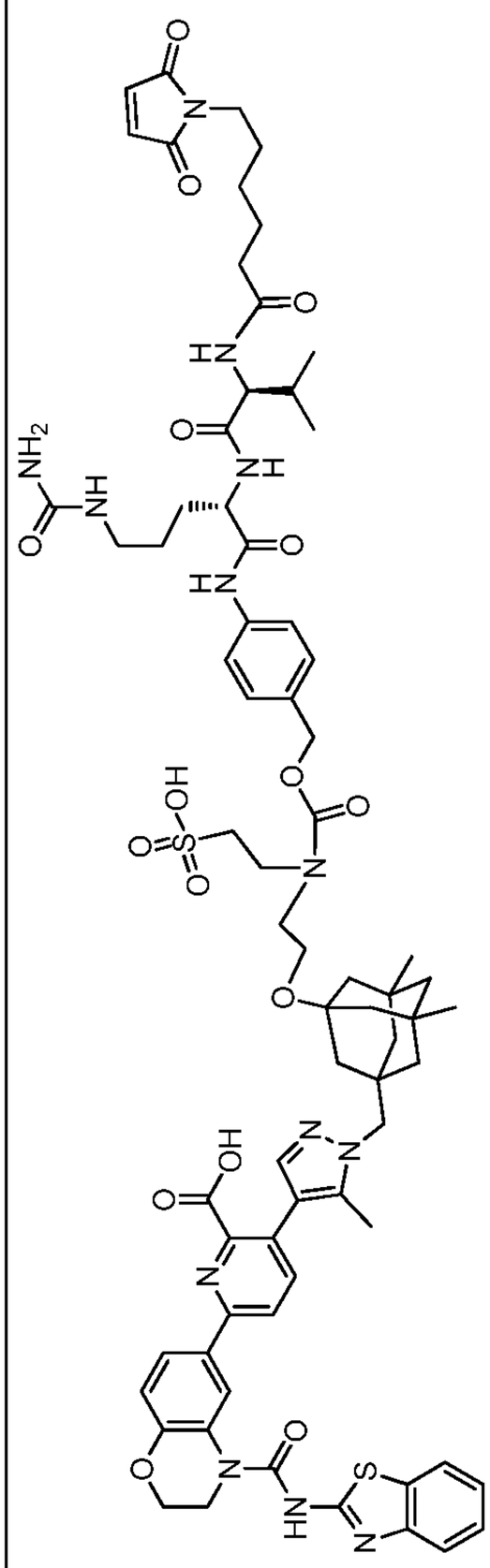
Example No.	Synthon Code	Synthon Structure
2.39	IH	
2.40	IJ	

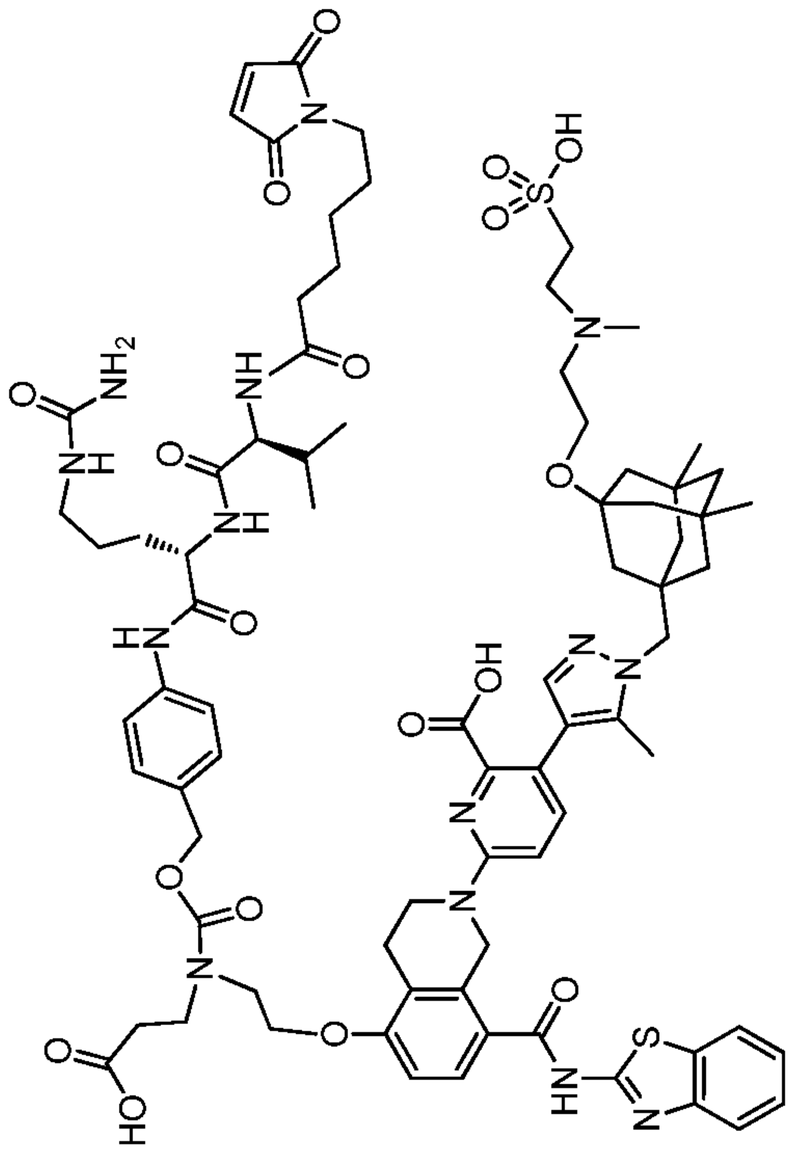
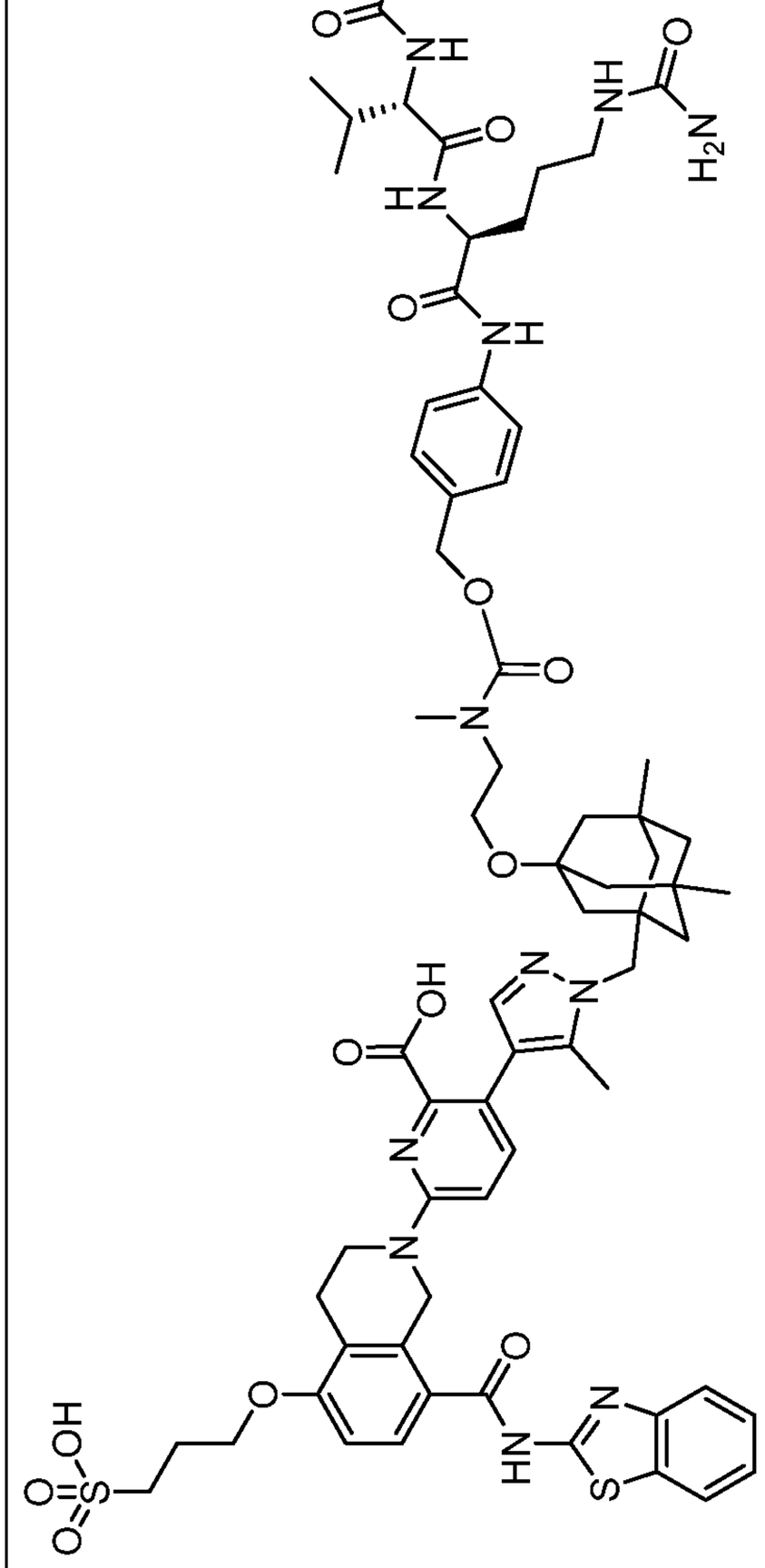
Example No.	Synthon Code	Synthon Structure
2.41	IK	
2.42	IL	
2.43	IM	

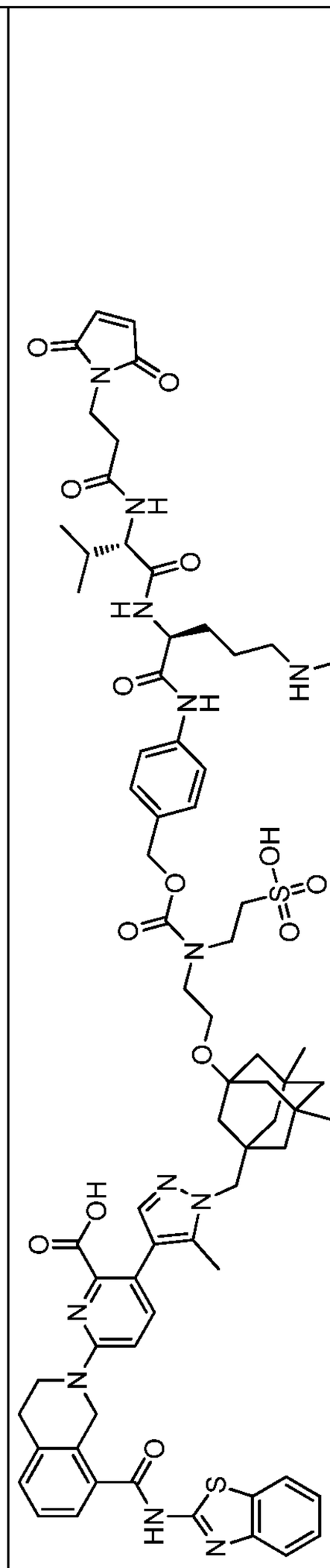
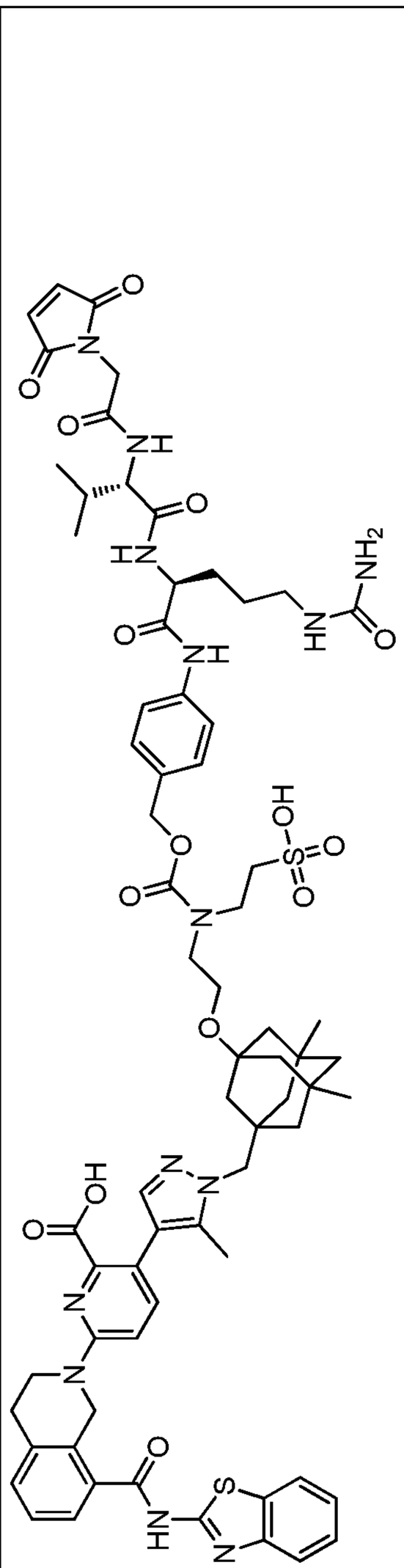
Example No.	Synthon Code	Synthon Structure
2.44	IO	
2.45	IP	

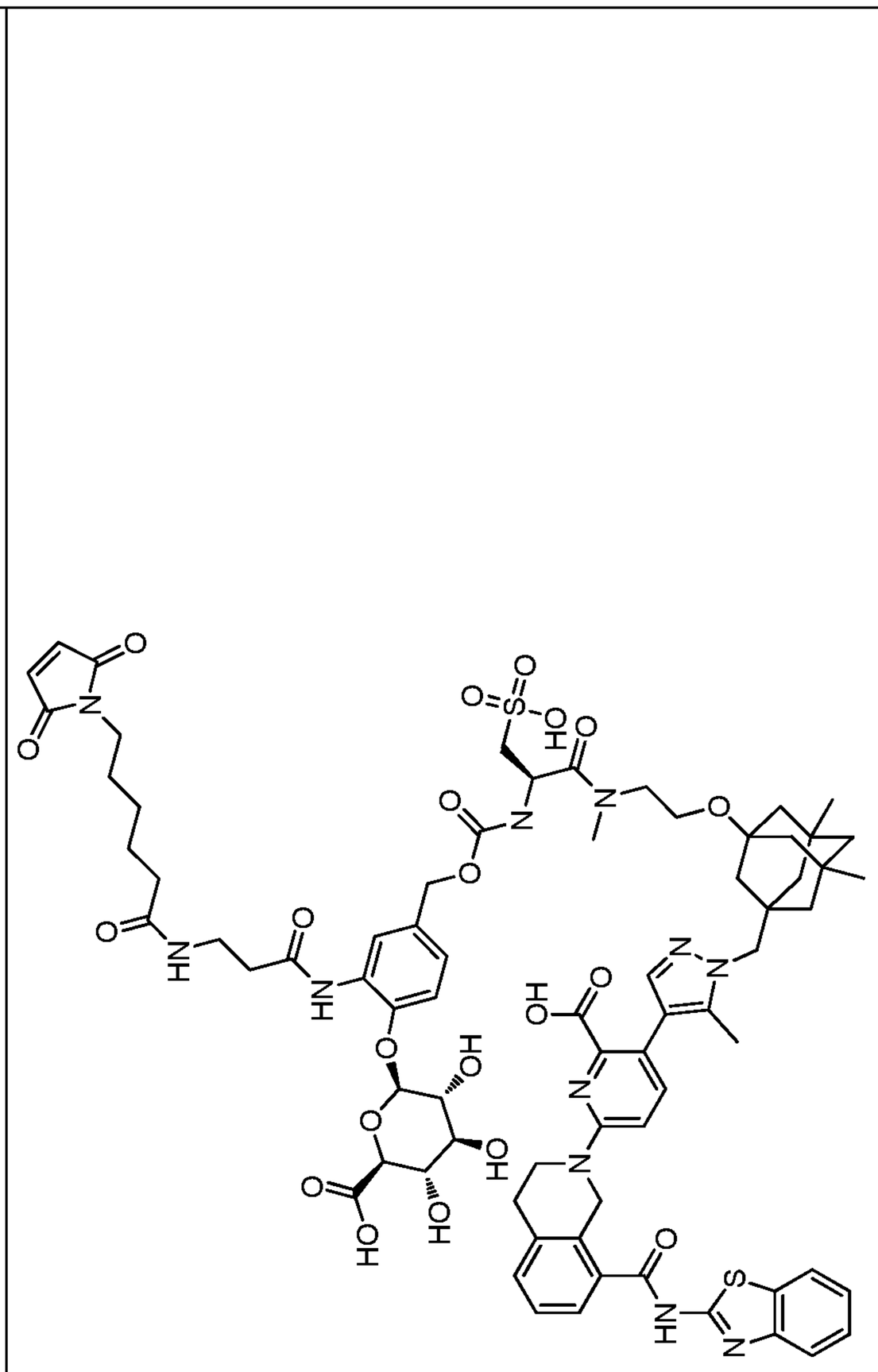
CA 03027045 2018-12-07

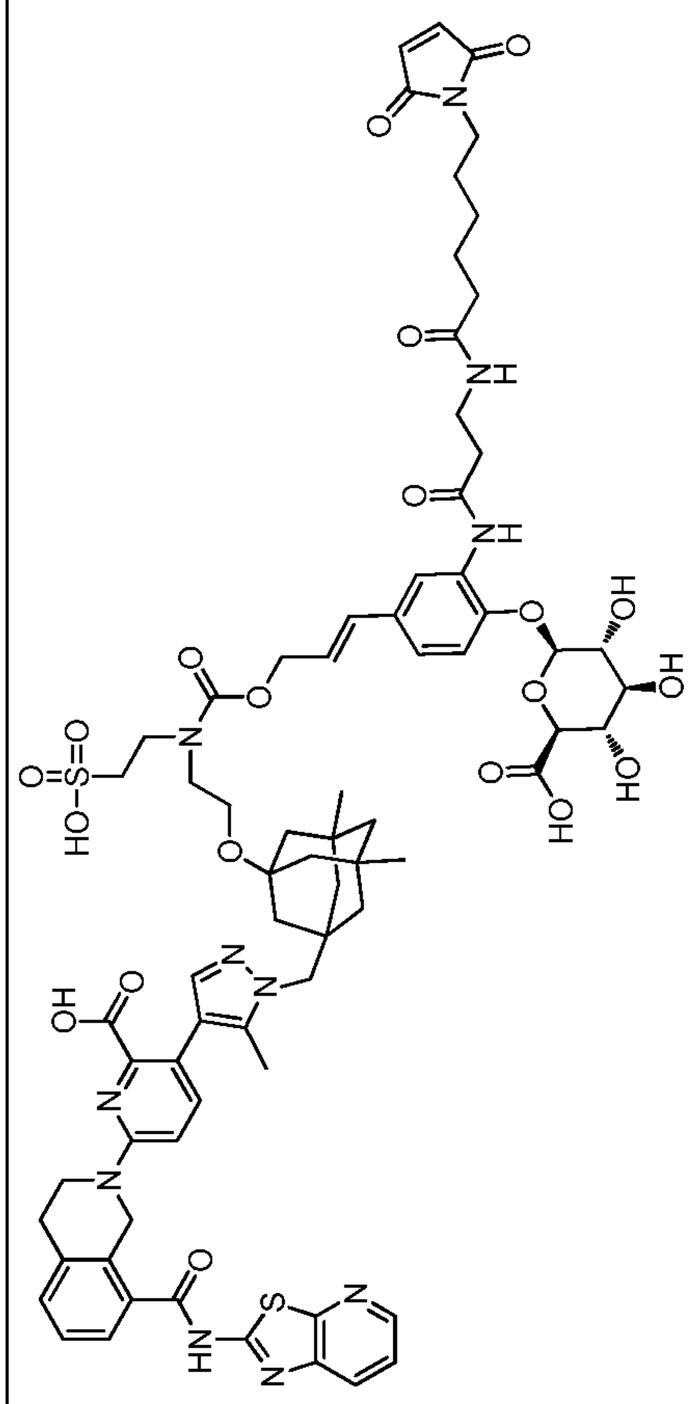
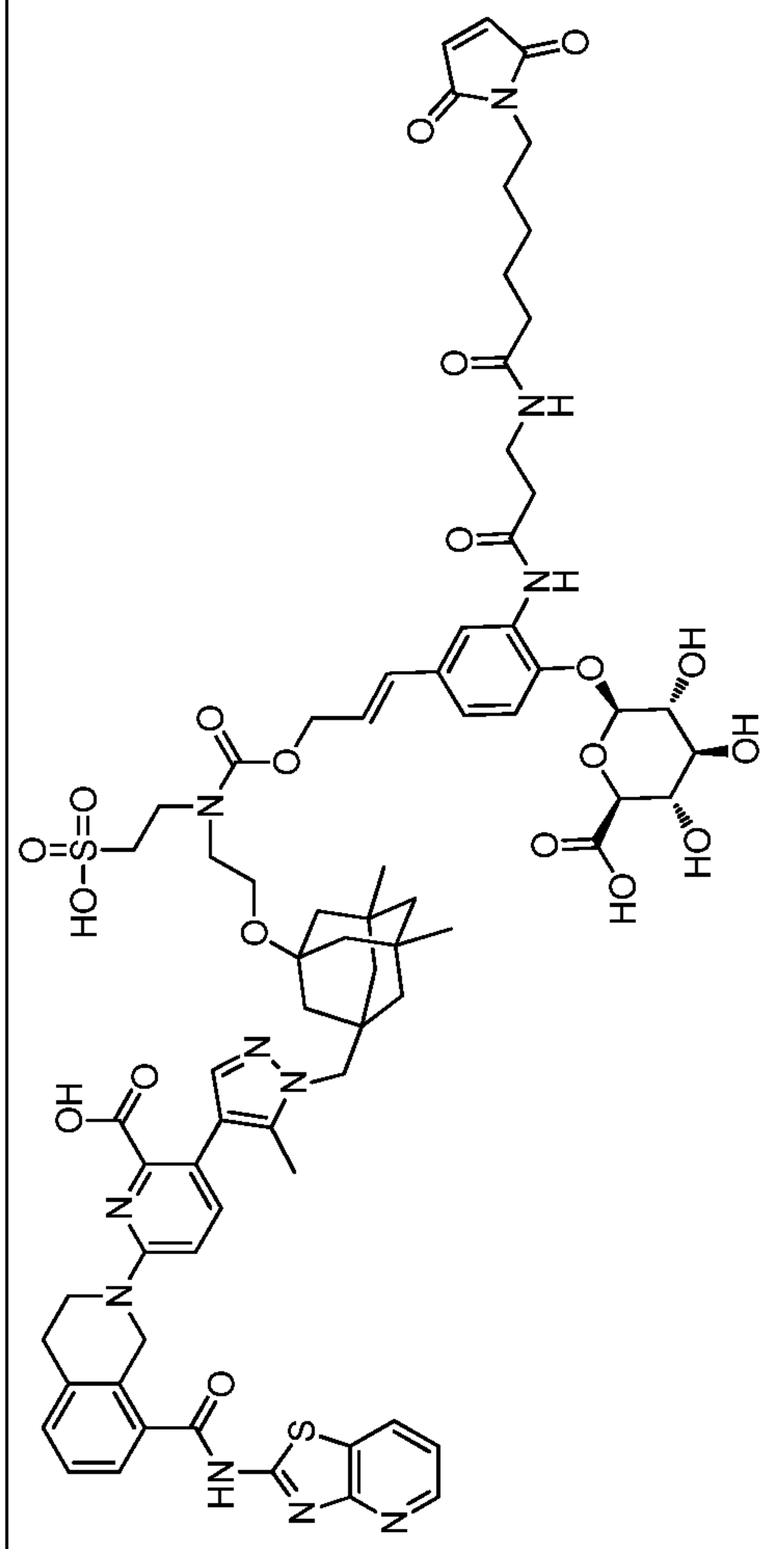
Example No.	Synthon Code	Synthon Structure
2.46	IS	
2.47	IU	

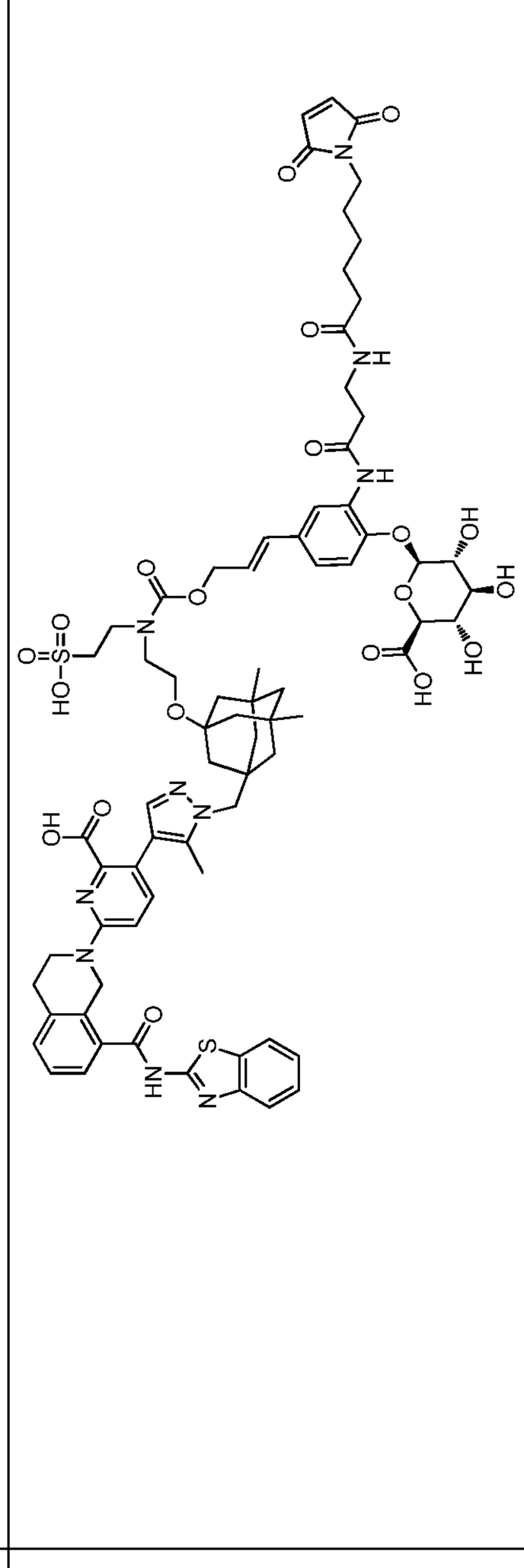
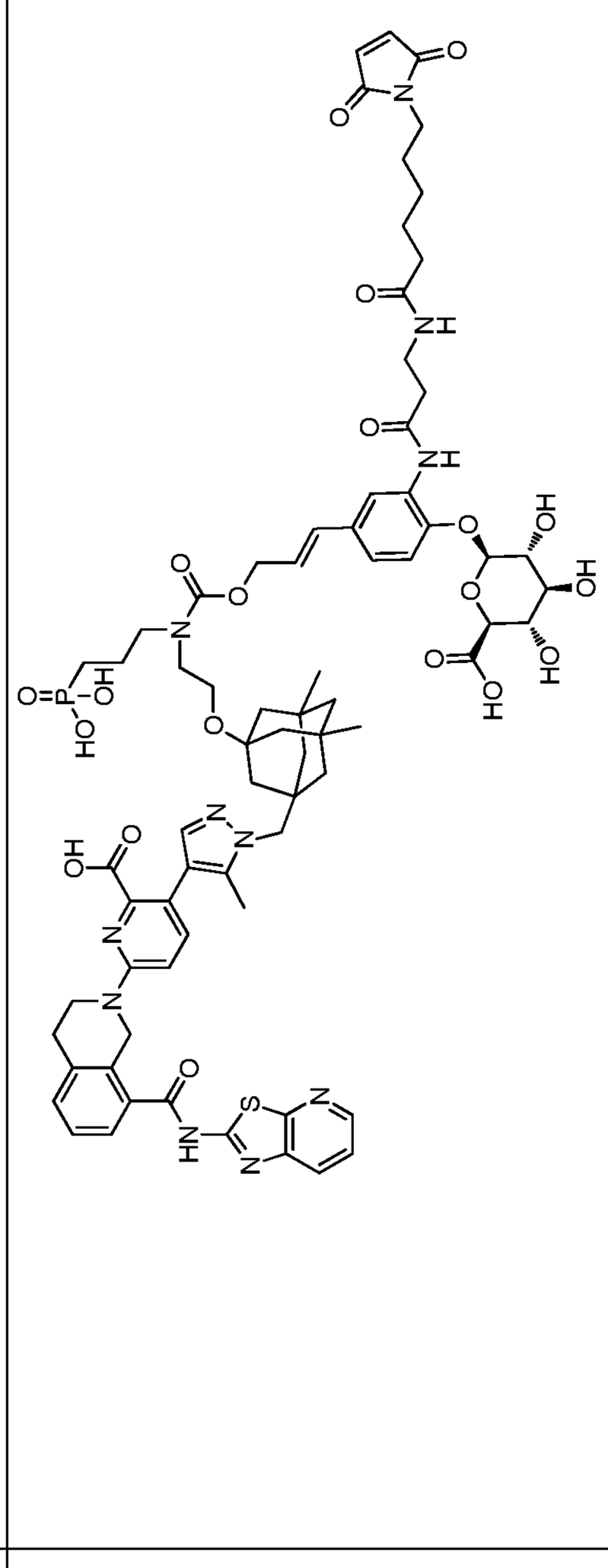
Example No.	Synthon Code	Synthon Structure
2.48	IV	
2.49	IZ	
2.50	JD	

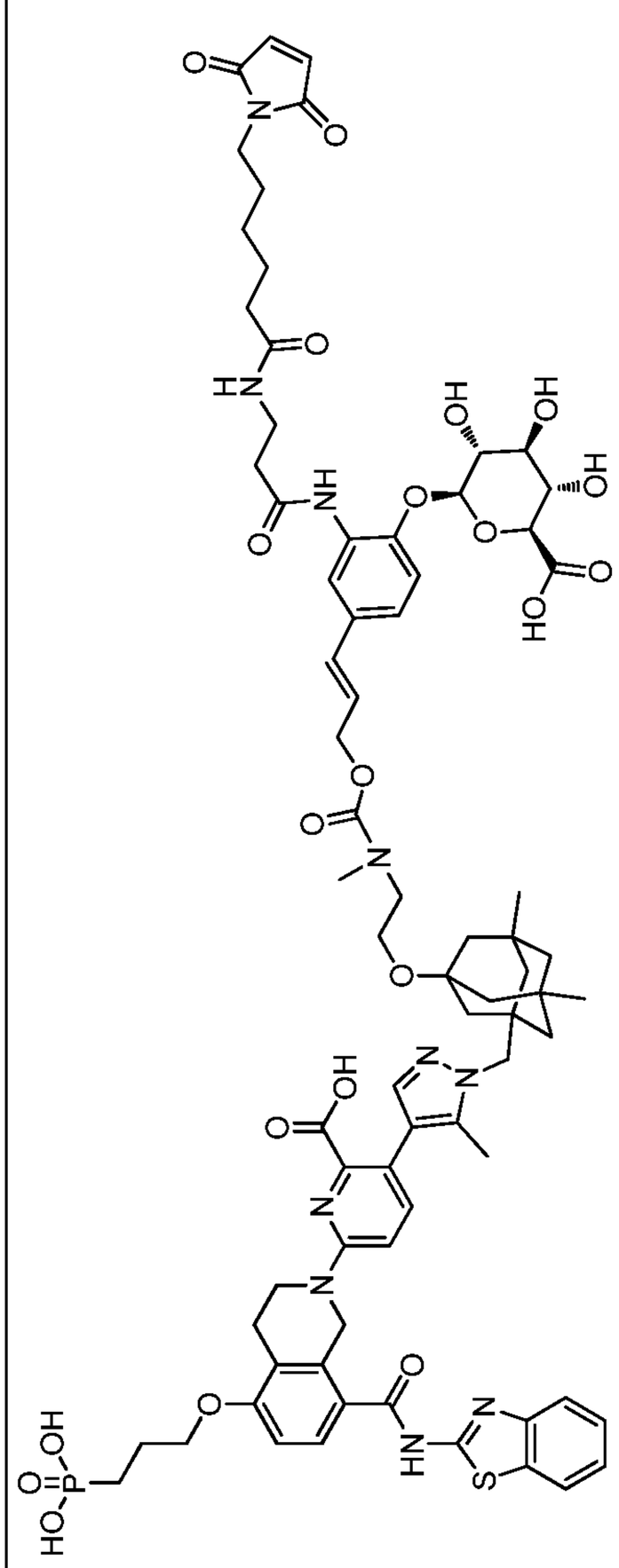
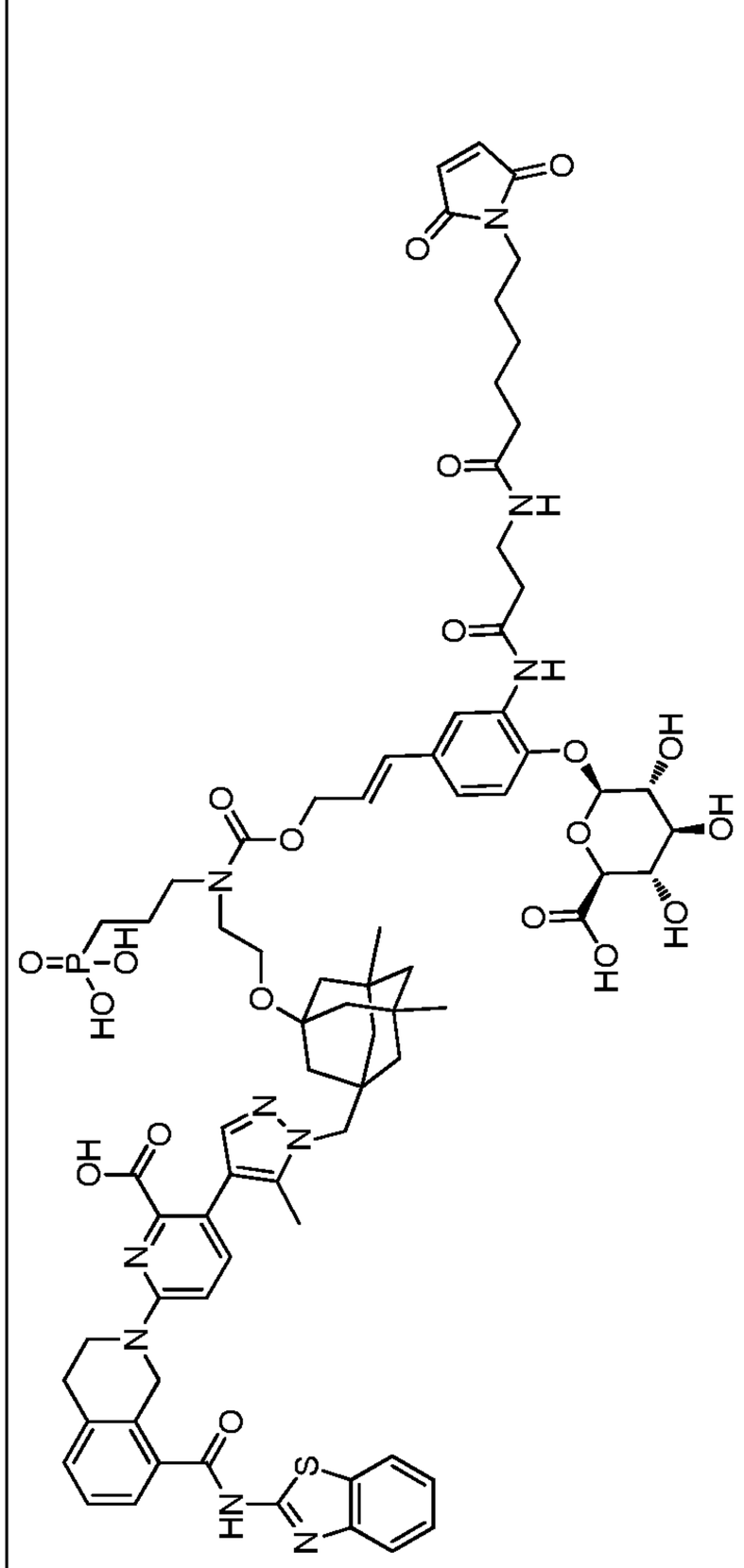
Example No.	Synthon Code	Synthon Structure
2.51	JF	
2.52	JK	

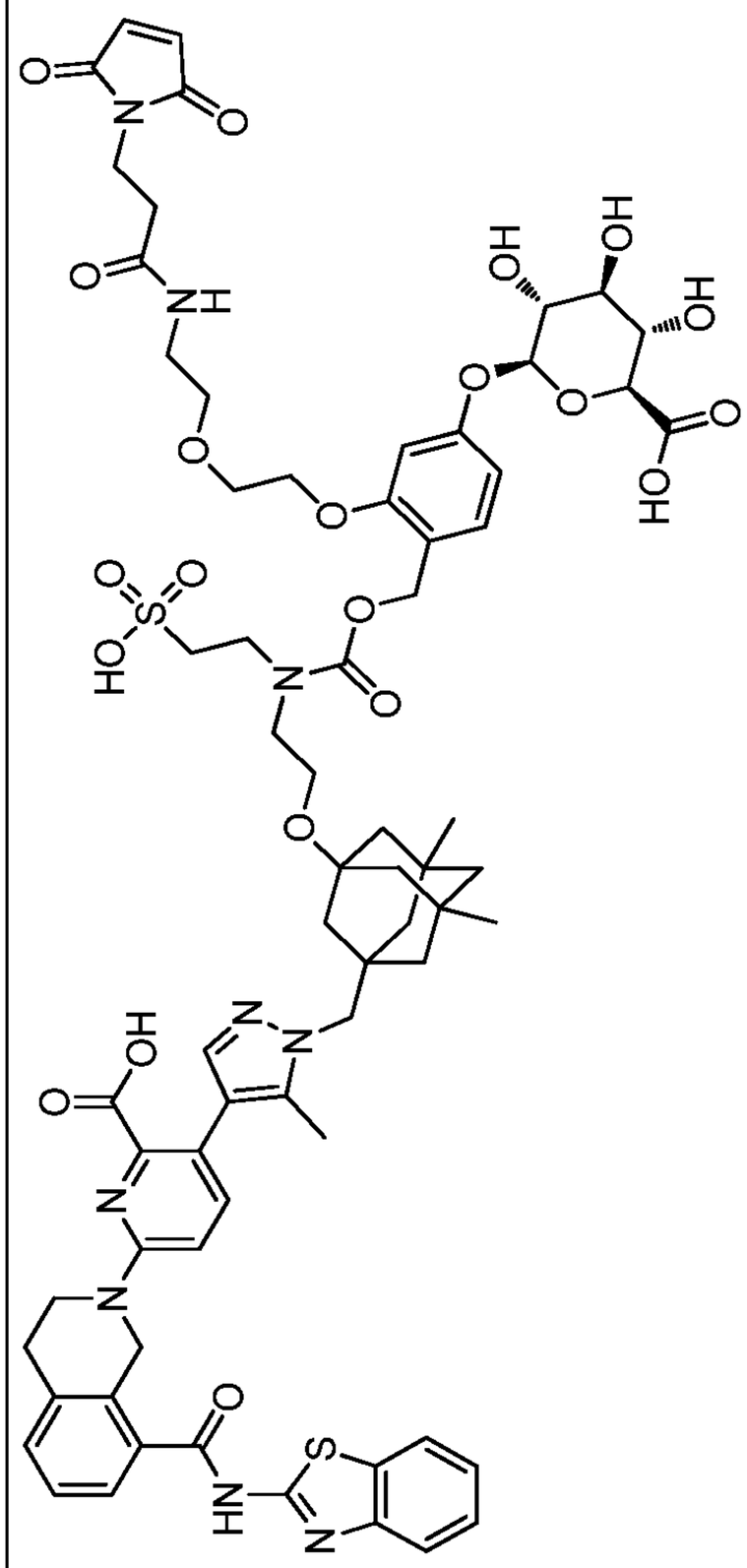
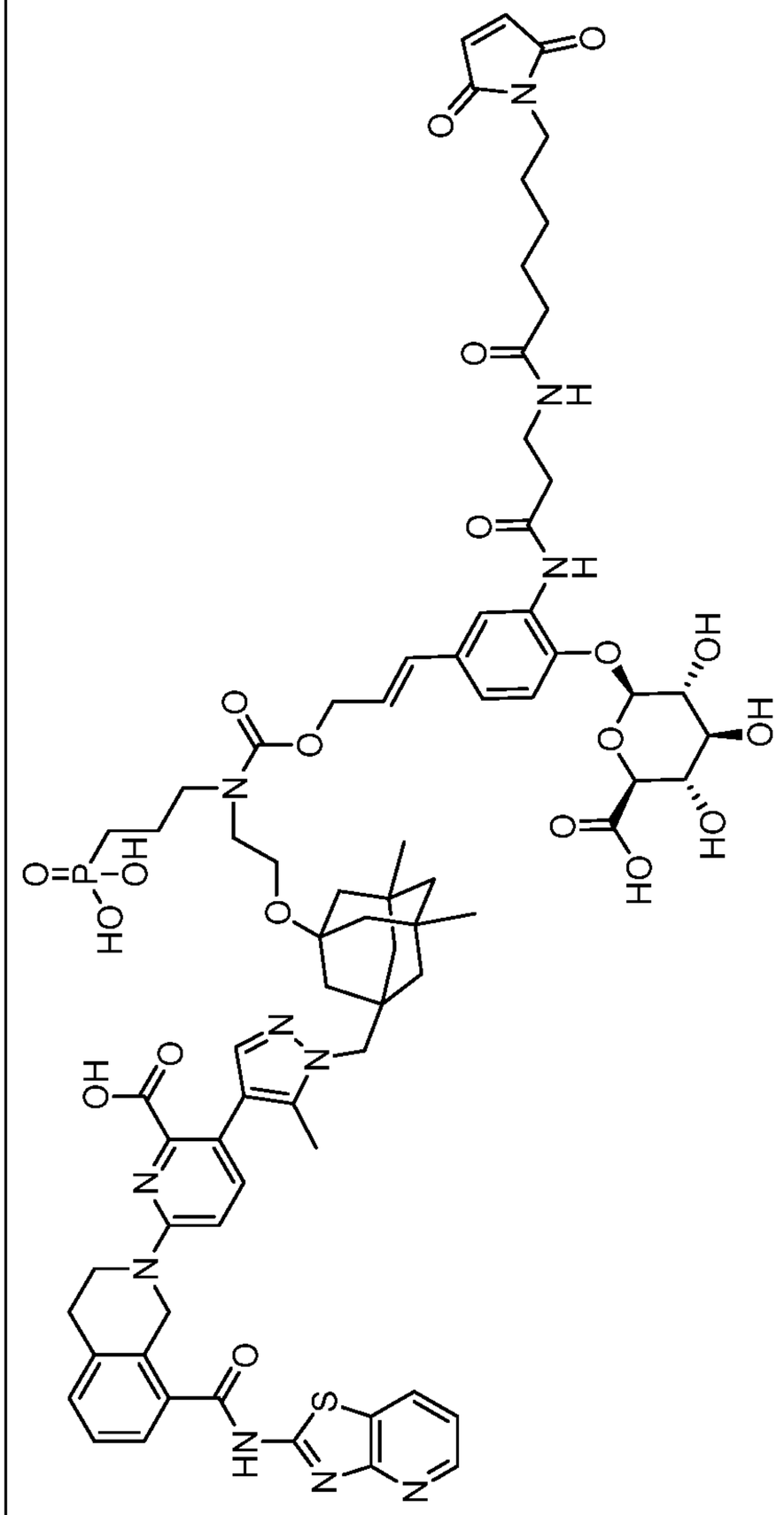
Example No.	Synthon Code	Synthon Structure
2.53	JJ	
2.54	JL	

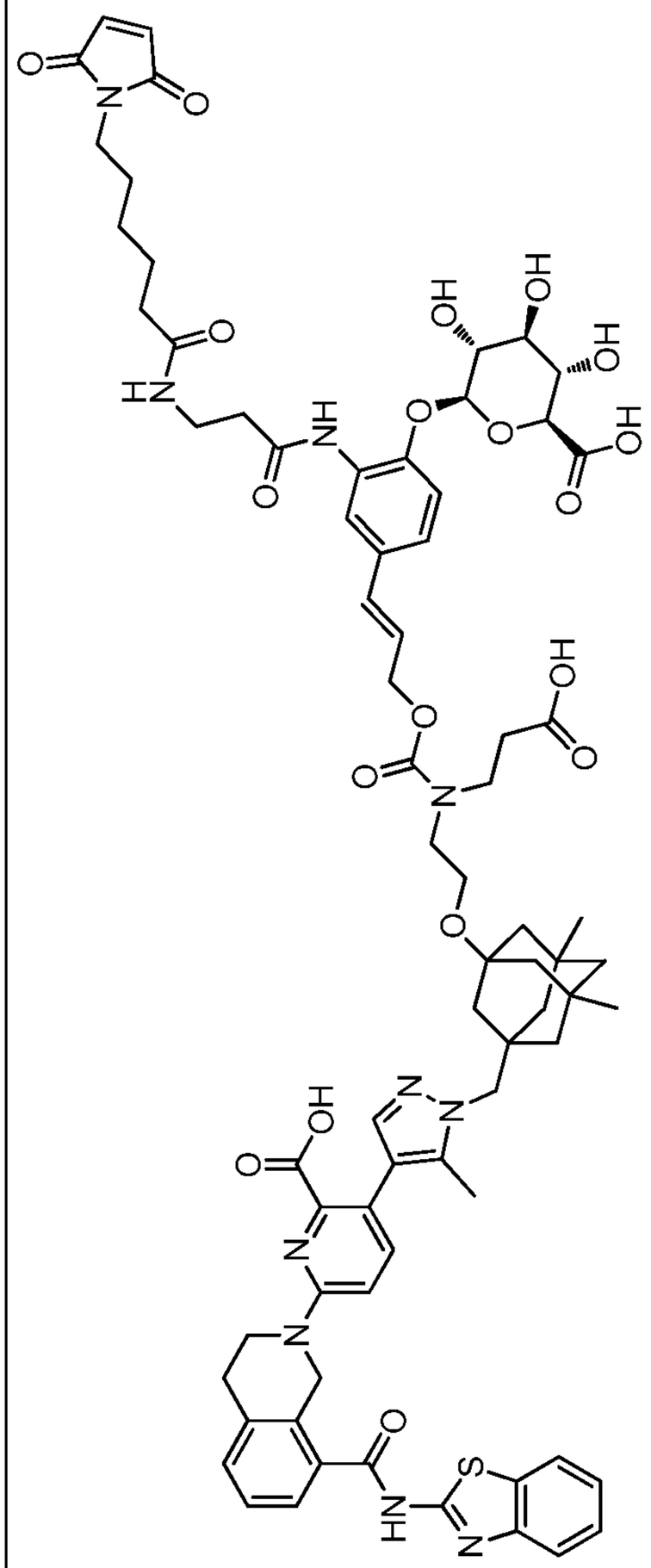
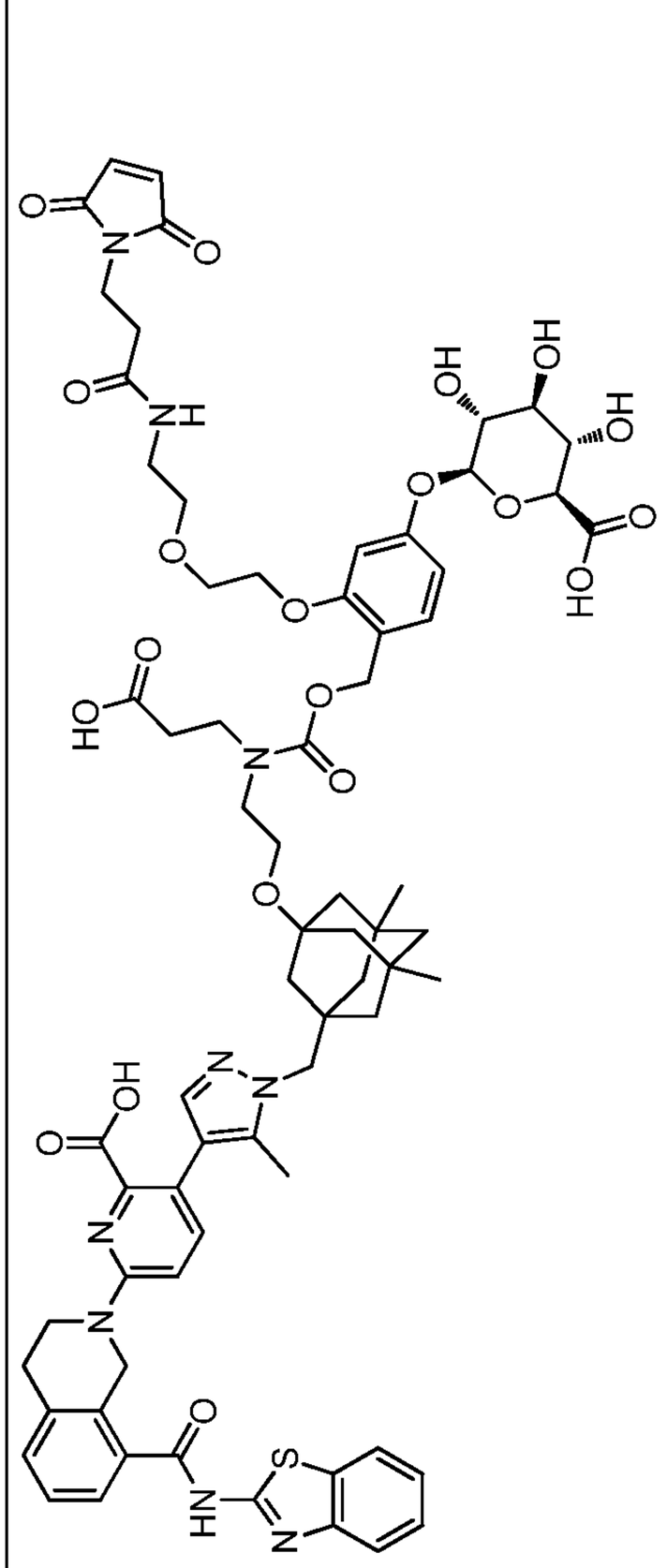
Example No.	Synthon Code	Synthon Structure
2.55	FE	

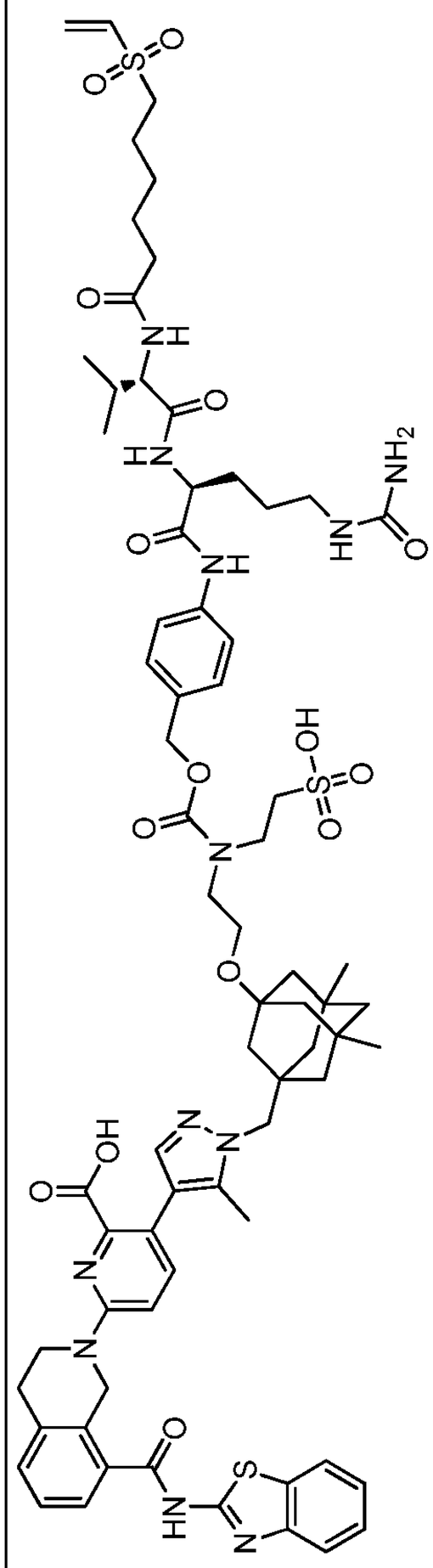
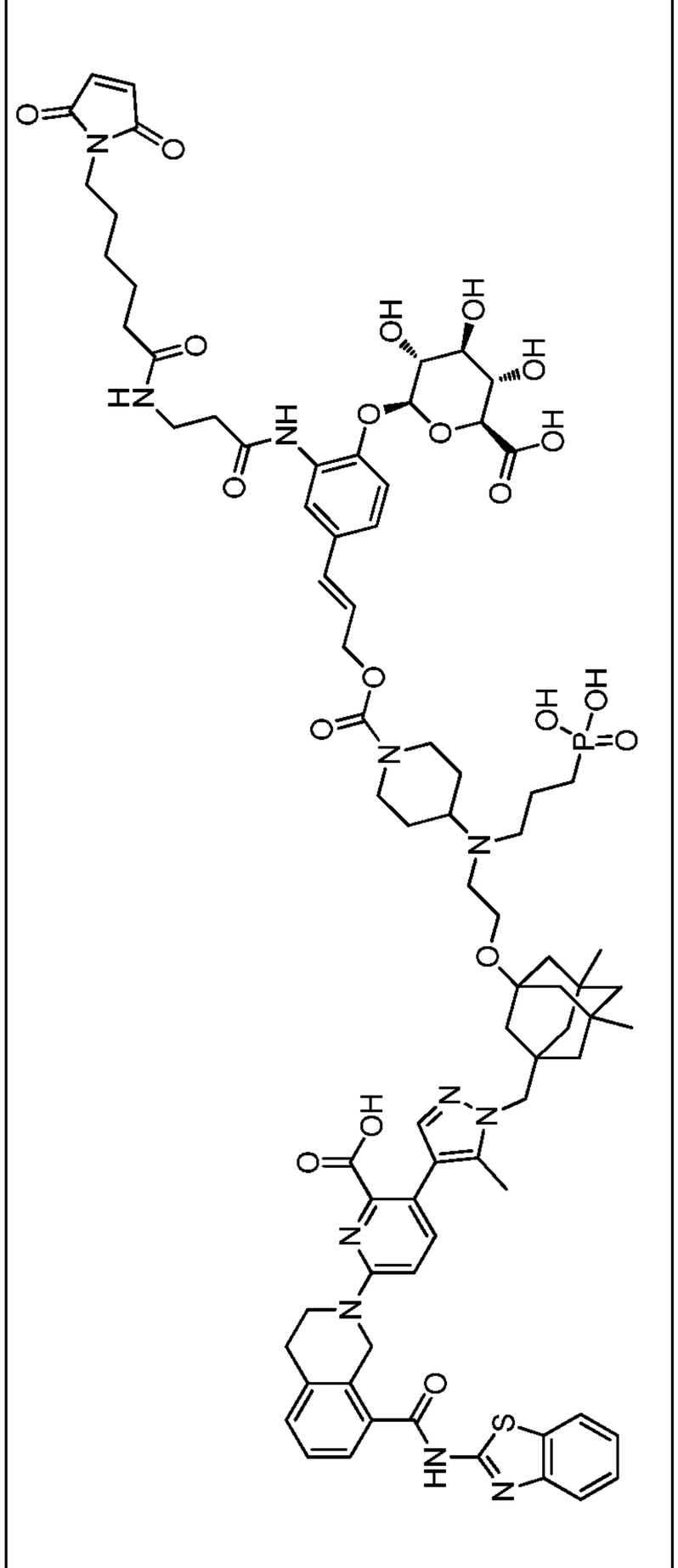
Example No.	Synthon Code	Synthon Structure
2.56	GG	
2.57	GM	

Example No.	Synthon Code	Synthon Structure
2.58	HD	
2.59	HS	

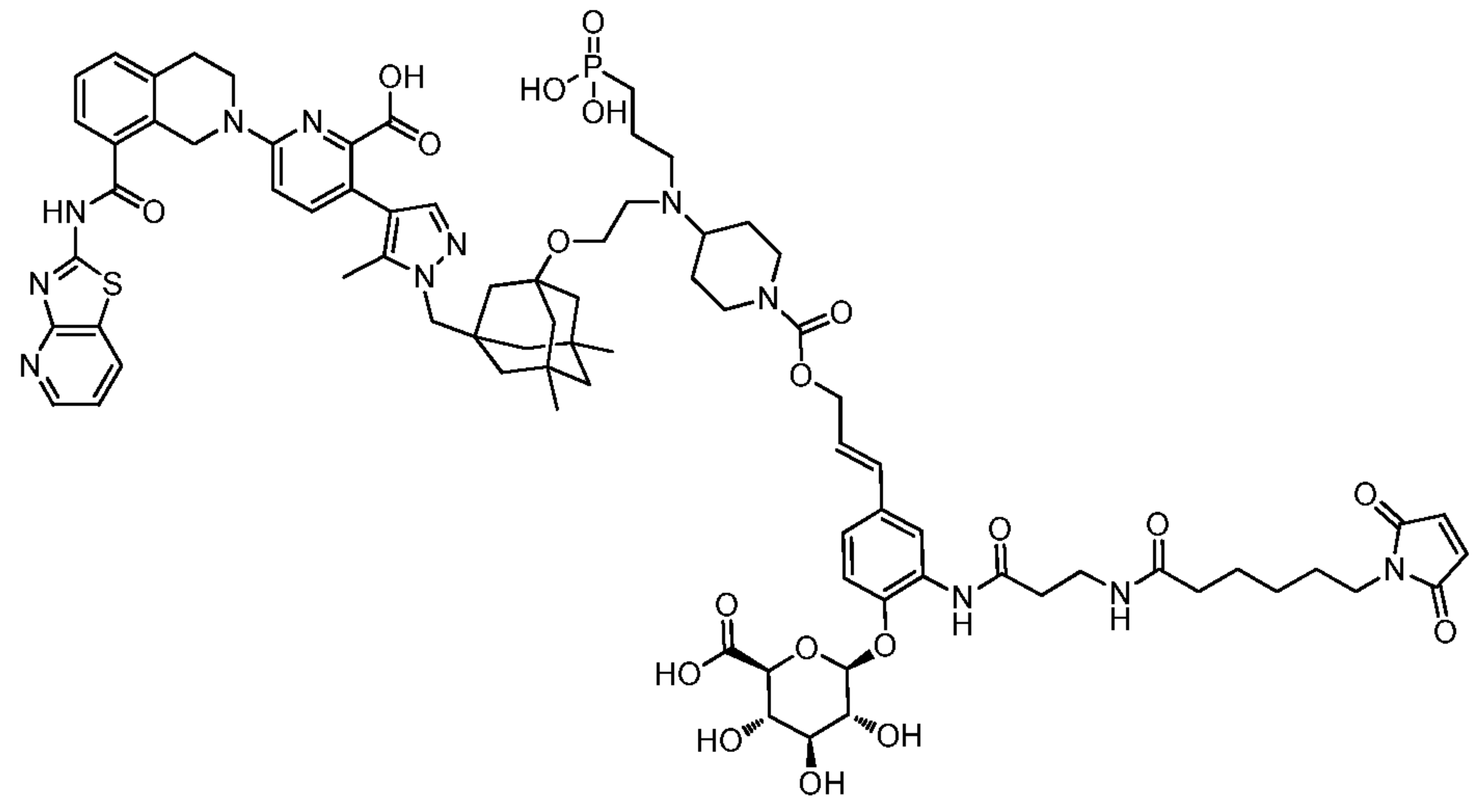
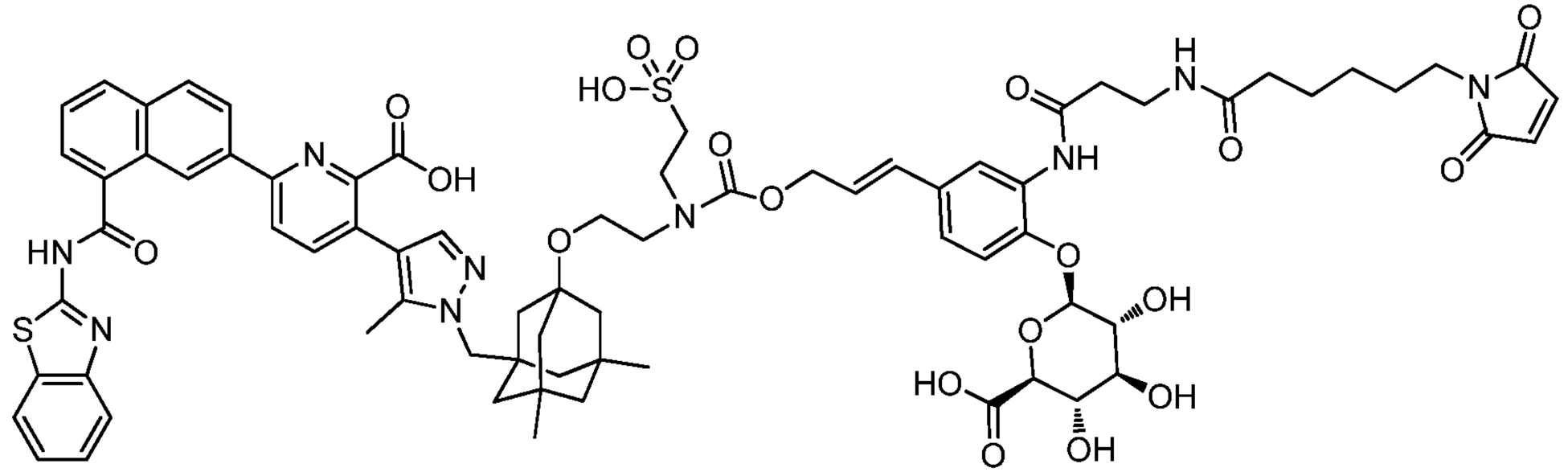
Example No.	Synthon Code	Synthon Structure
2.60	HW	
2.61	HX	

Example No.	Synthon Code	Synthon Structure
2.62	HY	
2.63	IB	

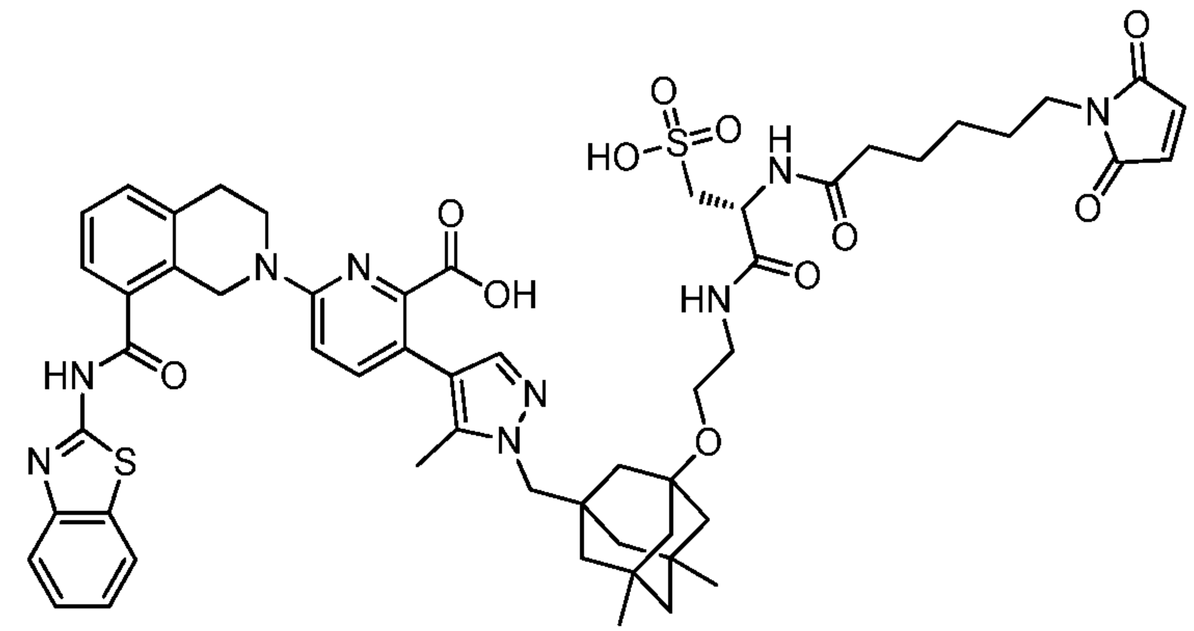
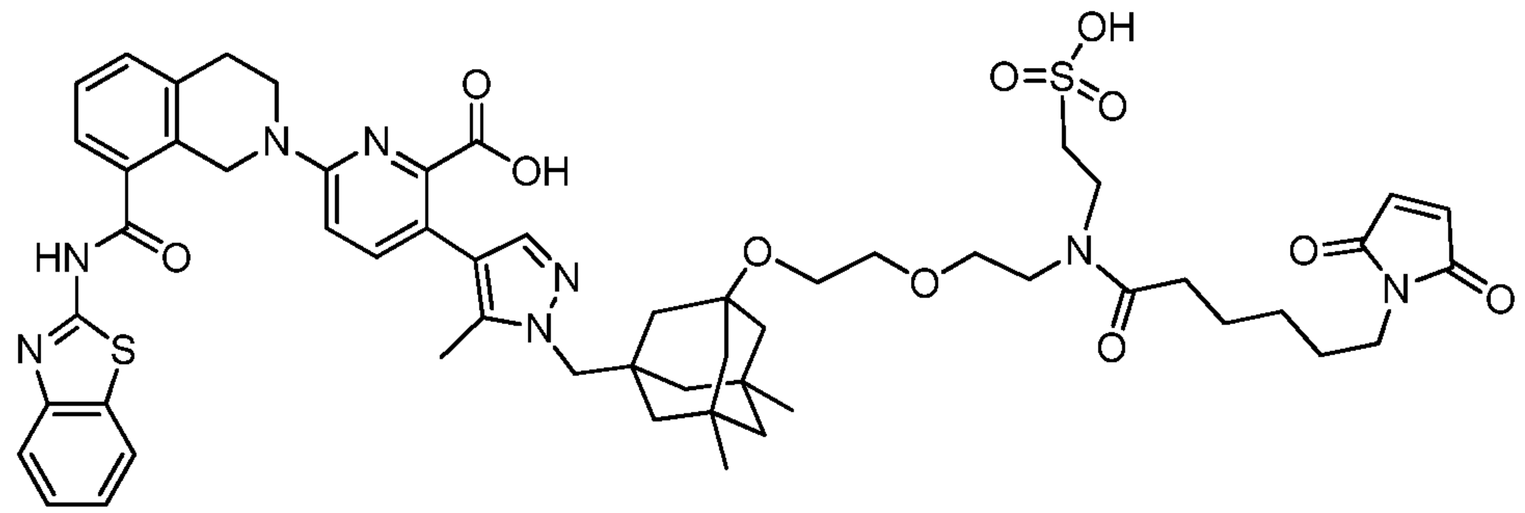
Example No.	Synthon Code	Synthon Structure
2.64	IE	
2.65	II	

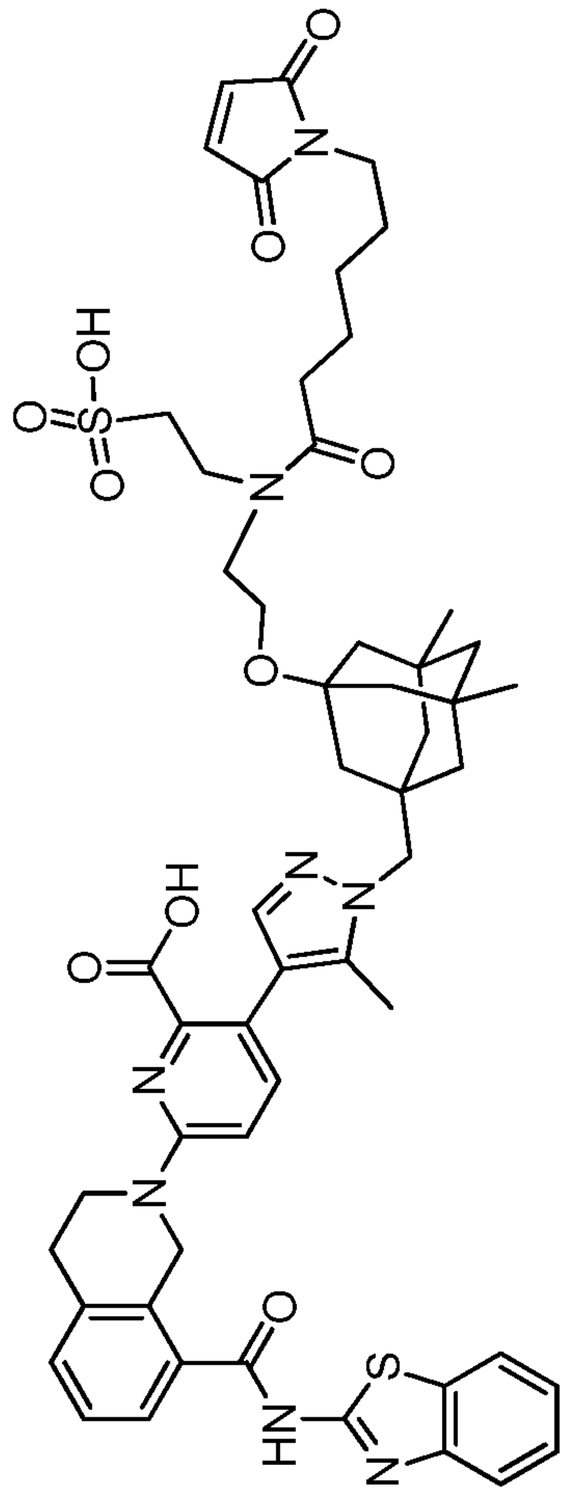
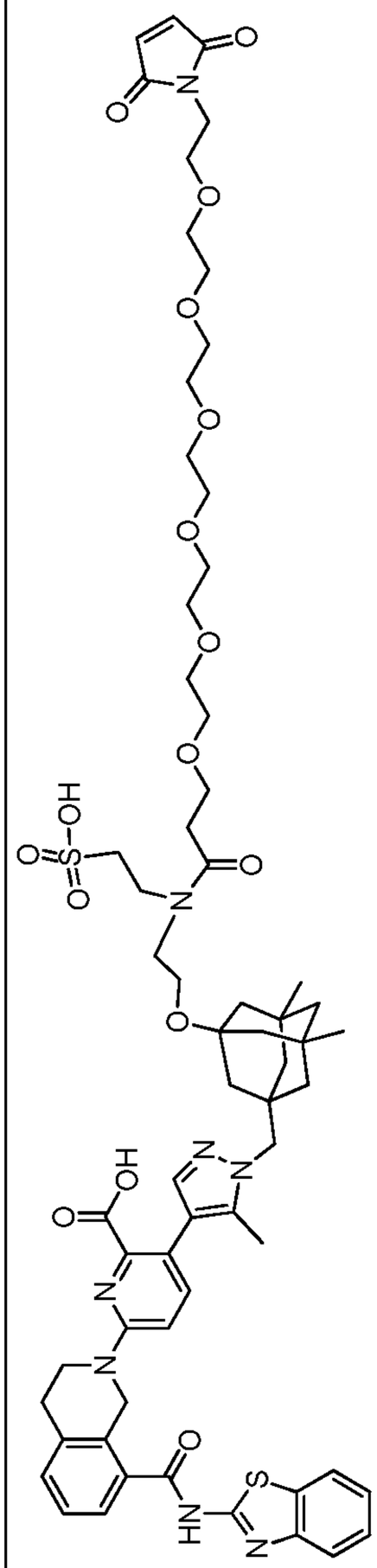
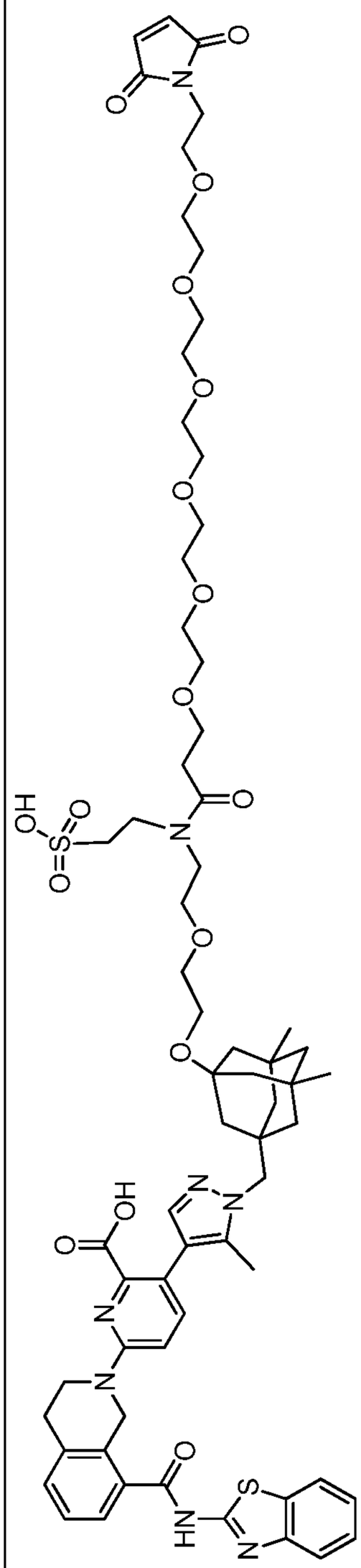
Example No.	Synthon Code	Synthon Structure
2.66	KY	
2.67	IW	

CA 03027045 2018-12-07

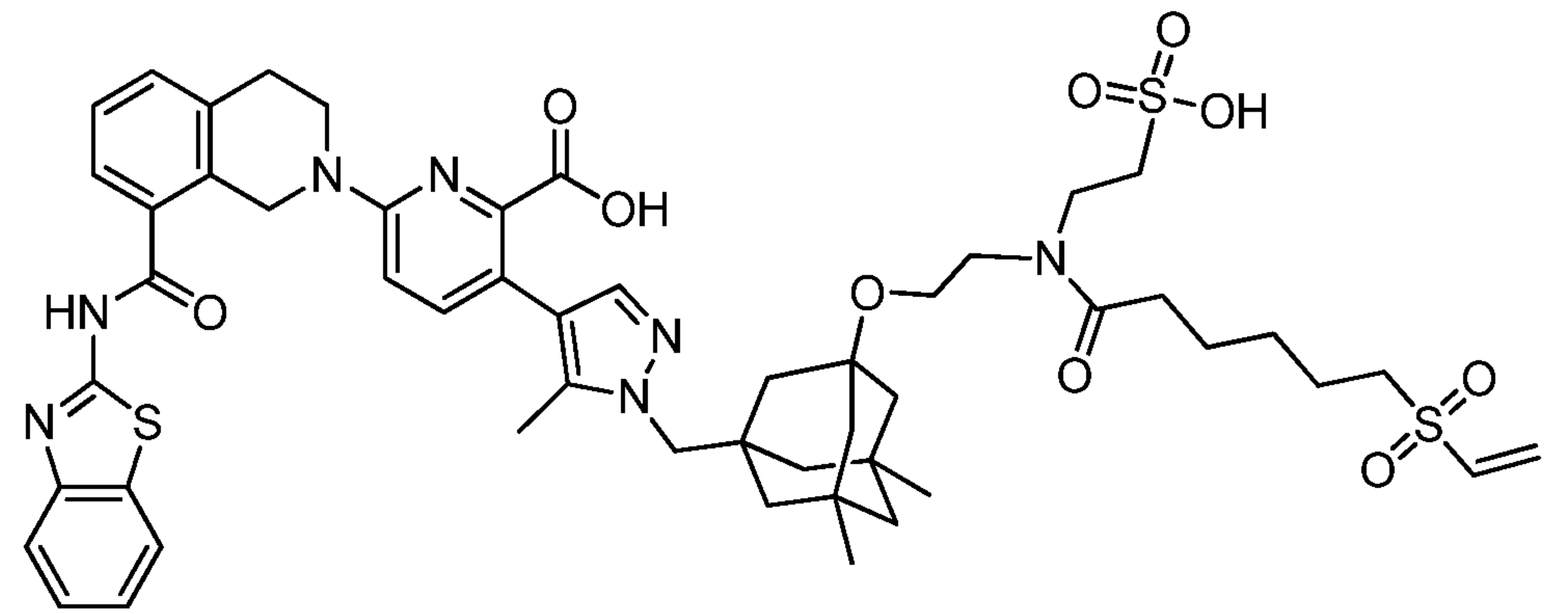
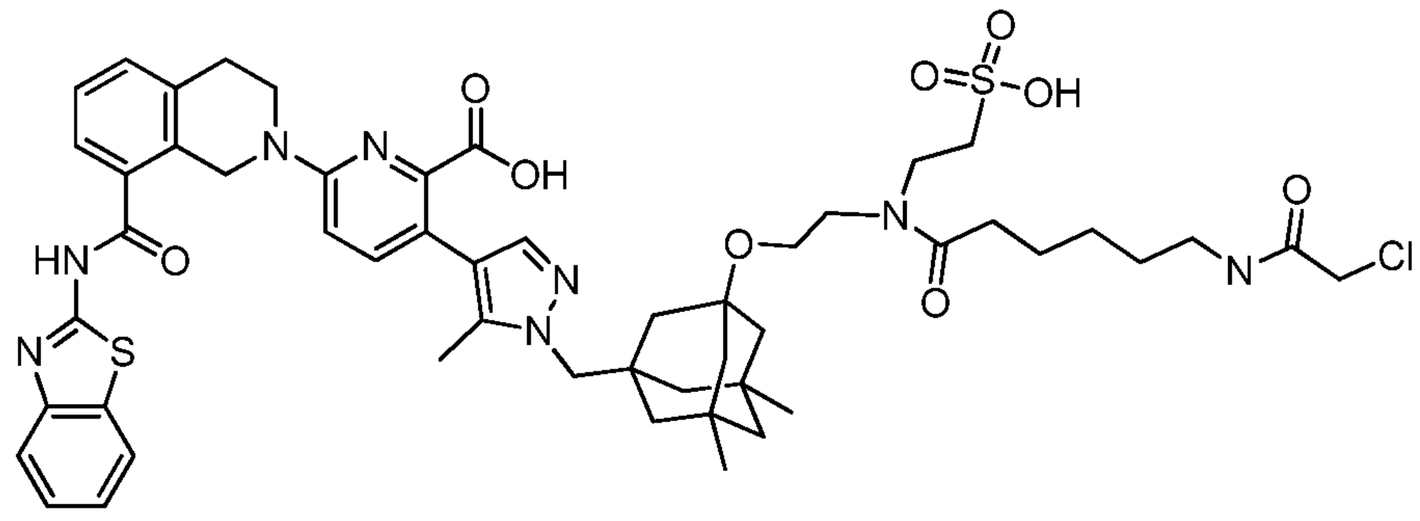
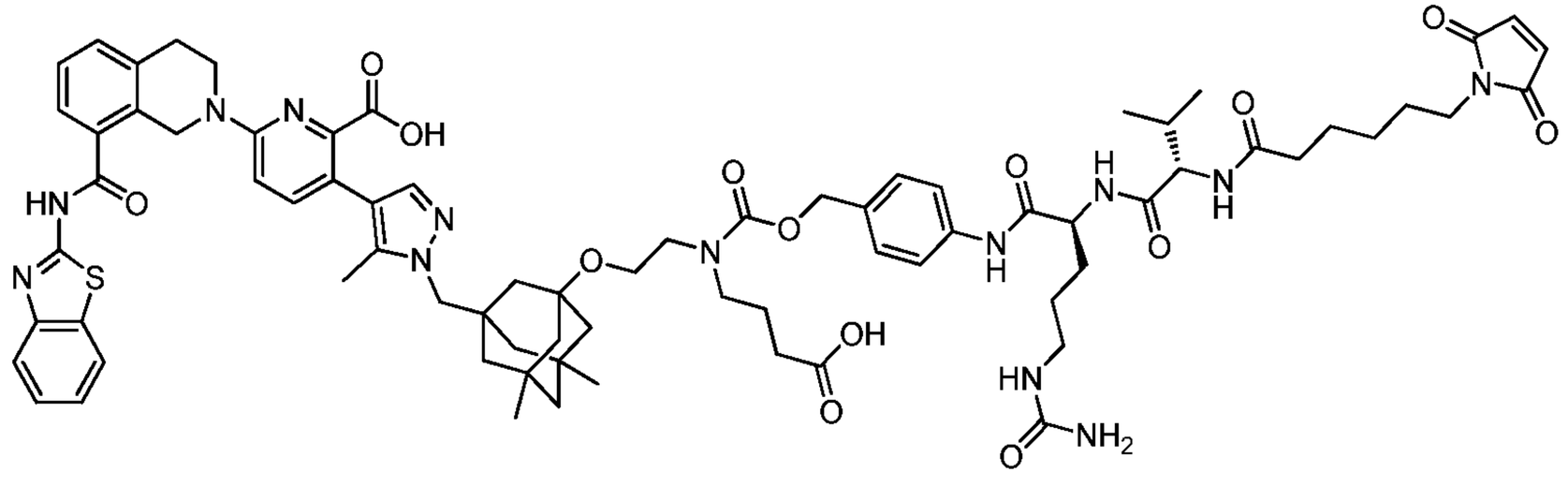
Example No.	Synthon Code	Synthon Structure
2.68	IY	
2.69	JA	

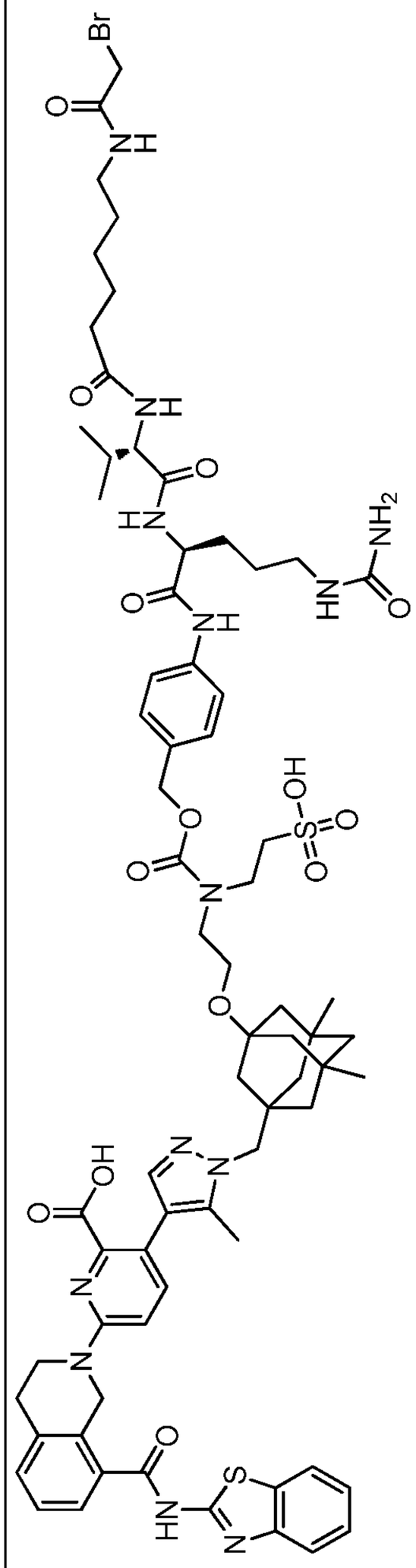
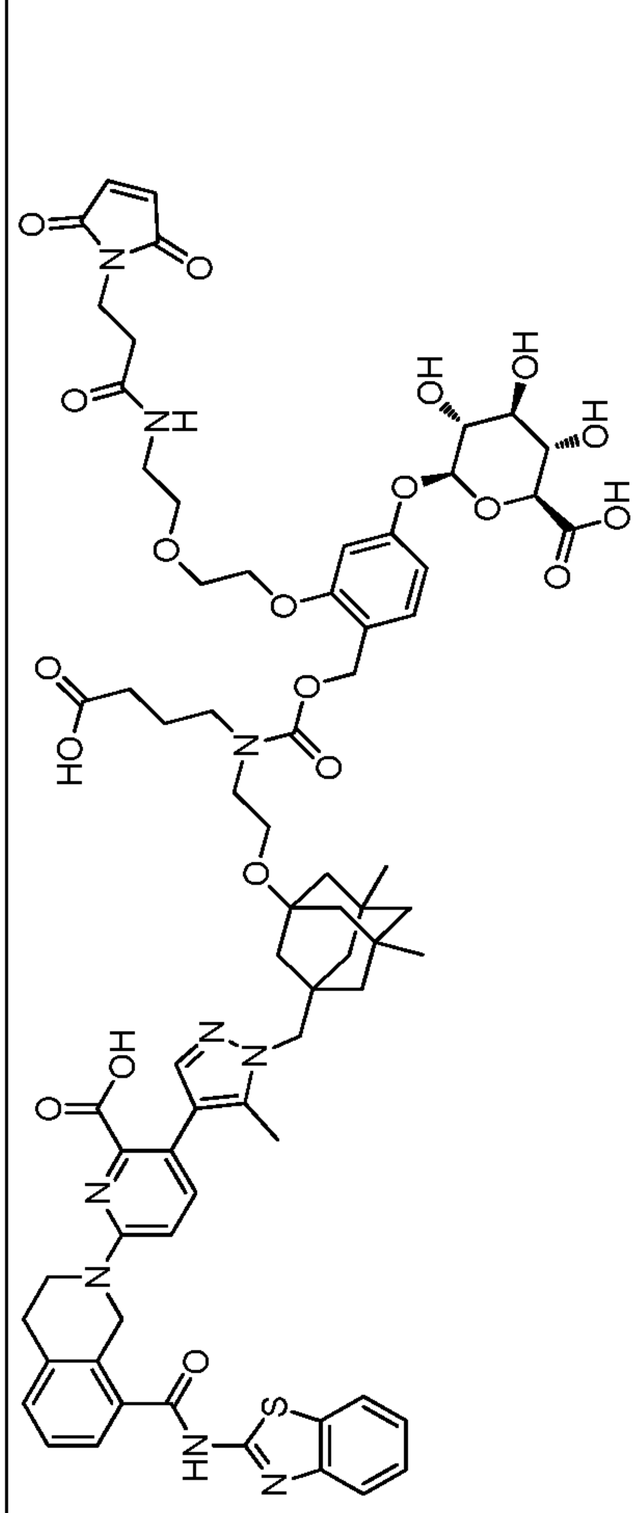
CA 03027045 2018-12-07

Example No.	Synthon Code	Synthon Structure
2.77	FA	
2.78	FJ	

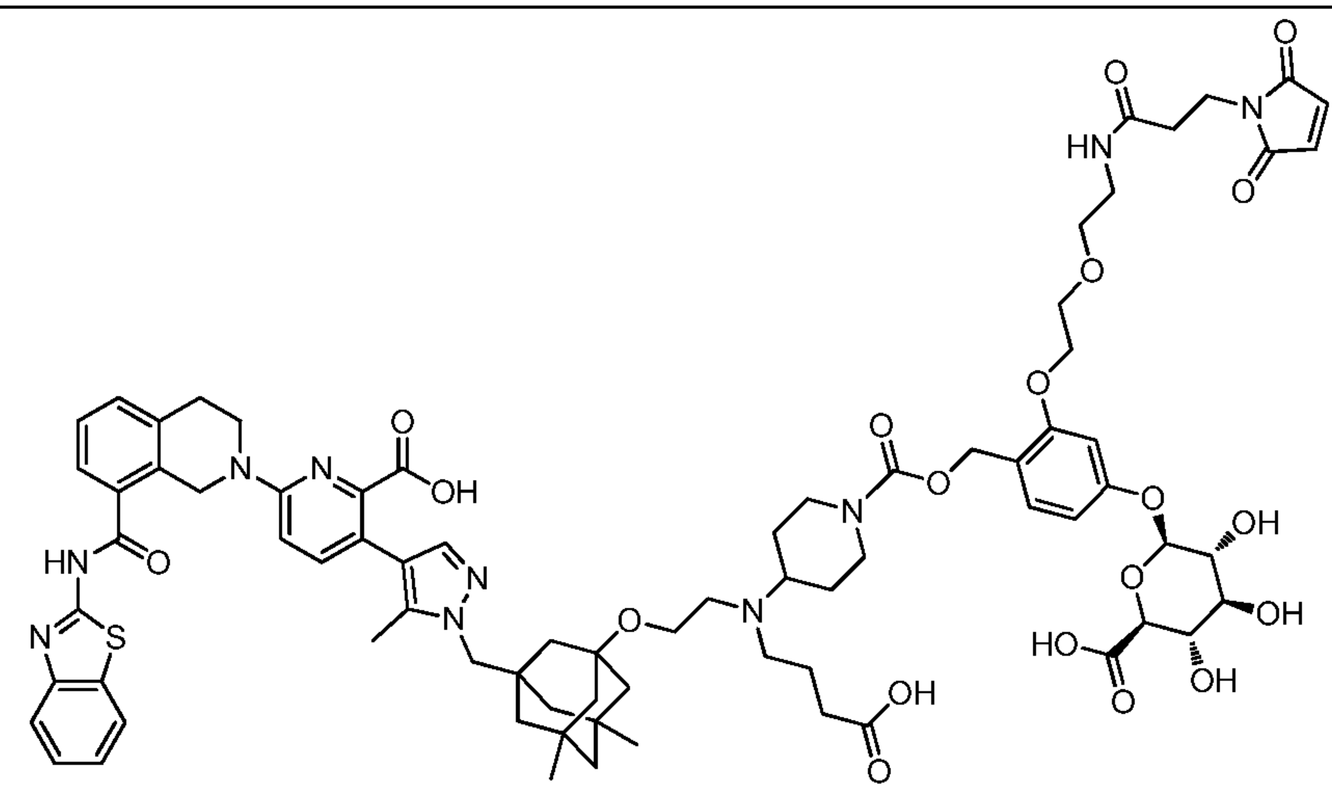
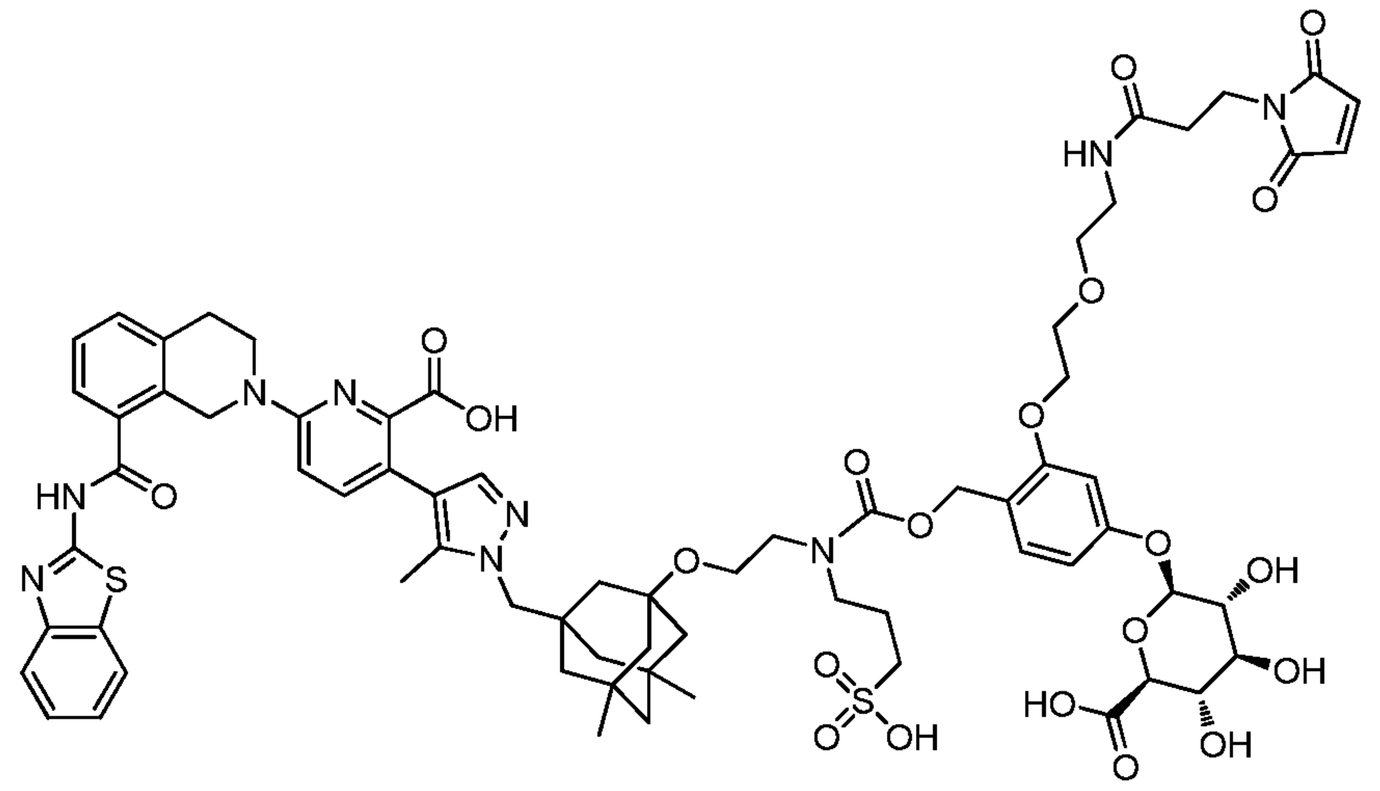
Example No.	Synthon Code	Synthon Structure
2.79	FK	
2.80	FQ	
2.81	FR	

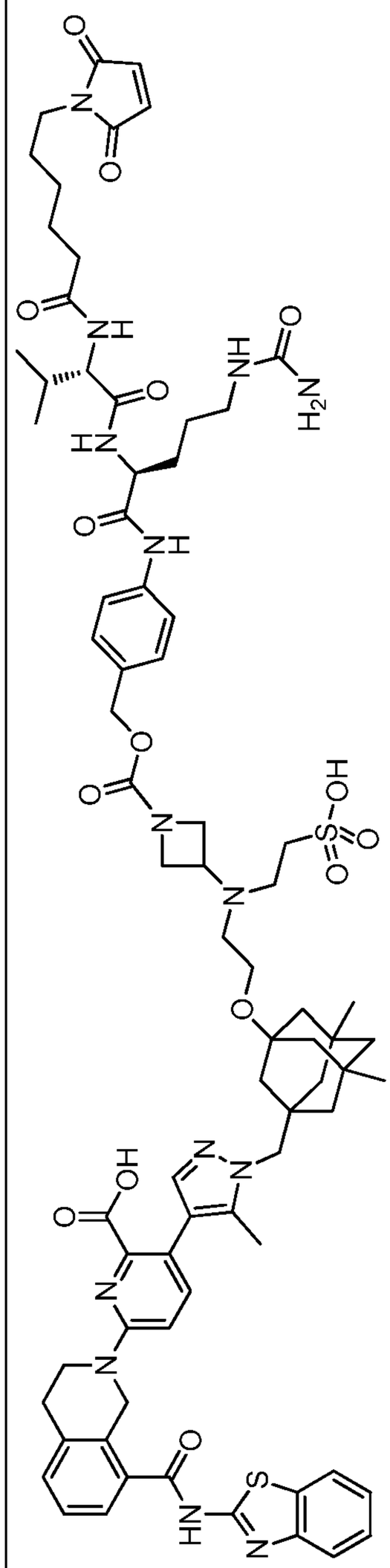
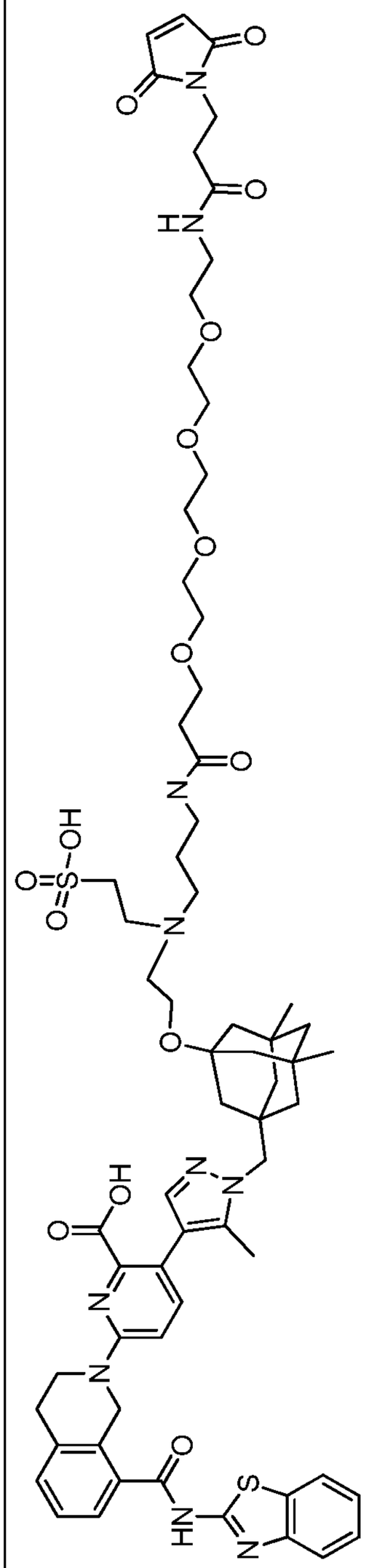
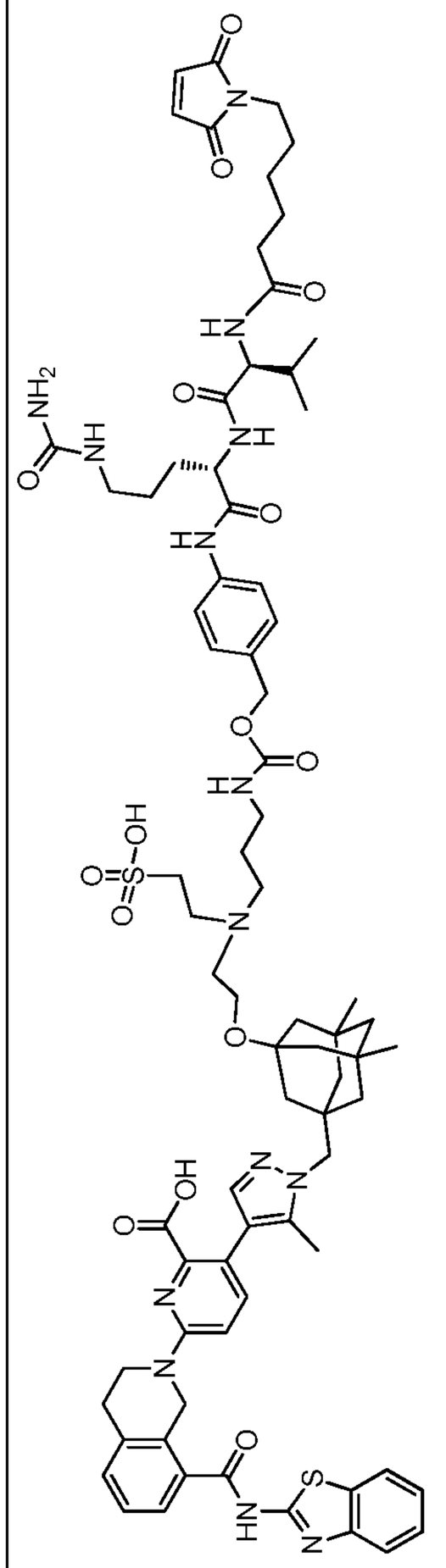
CA 03027045 2018-12-07

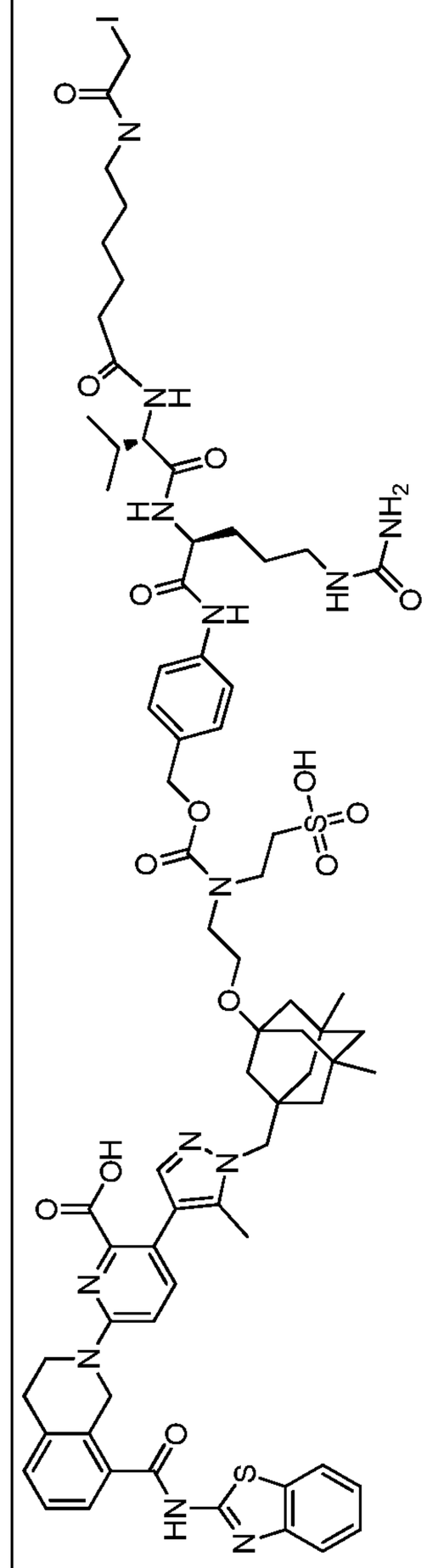
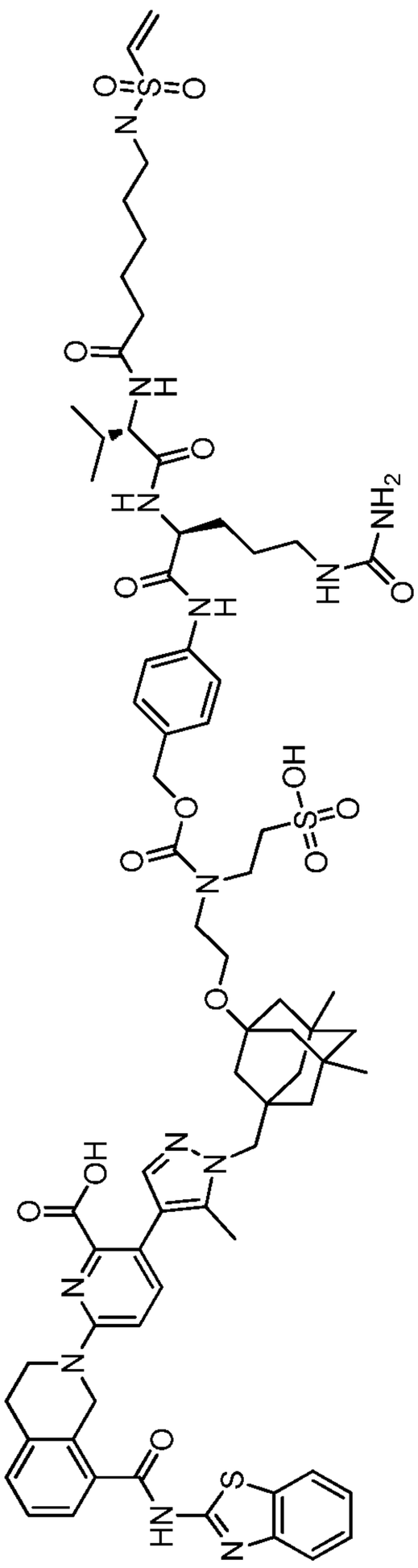
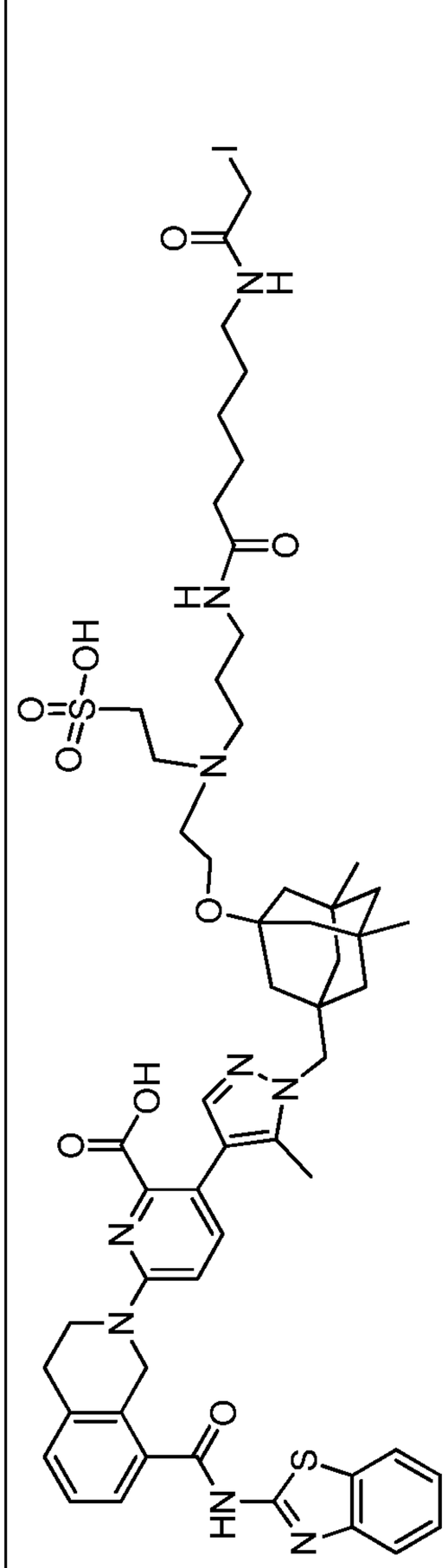
Example No.	Synthon Code	Synthon Structure
2.82	JE	
2.83	JM	
2.84	LE	

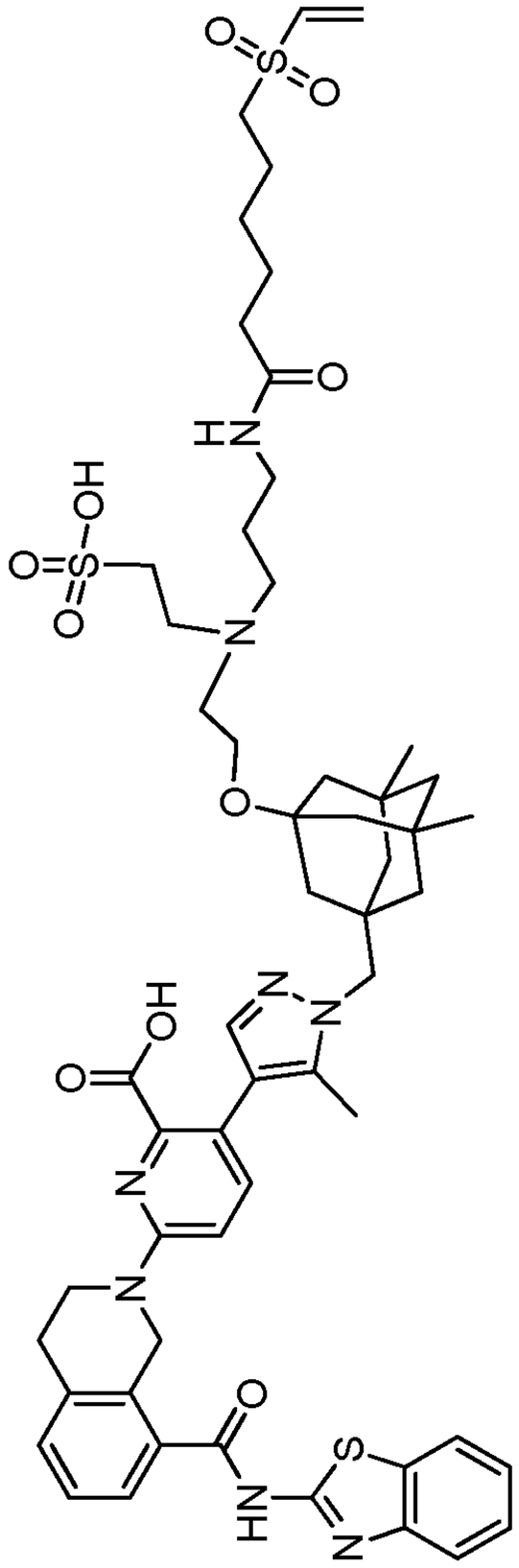
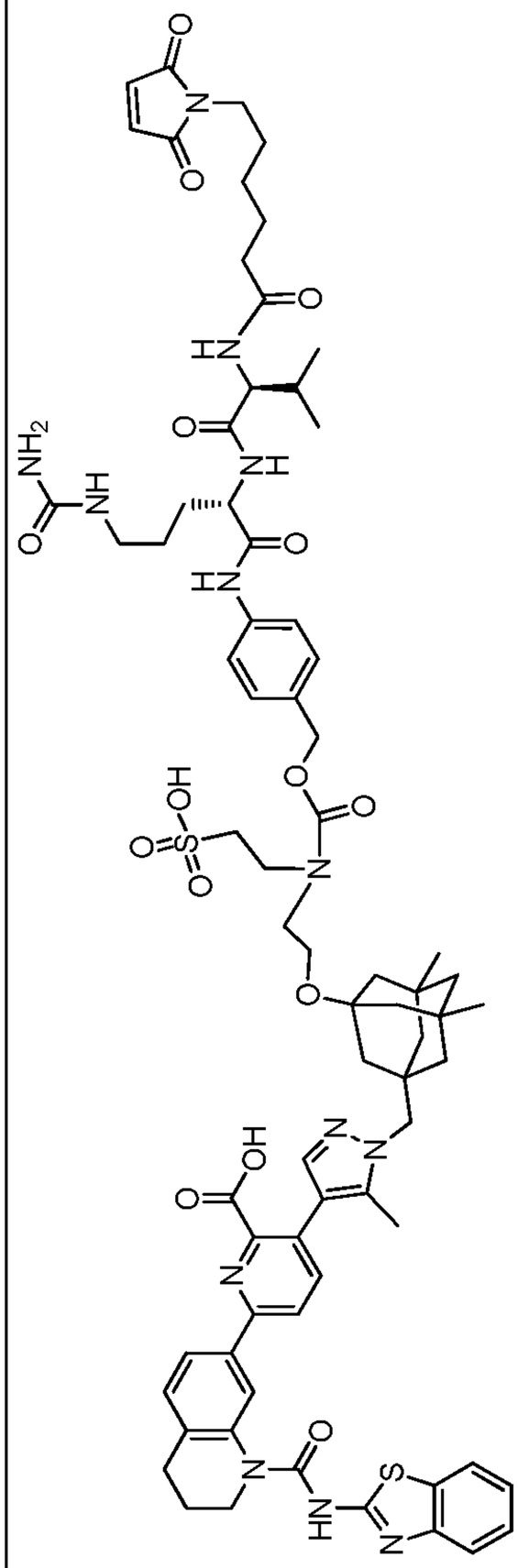
Example No.	Synthon Code	Synthon Structure
2.85	LH	
2.86	LJ	

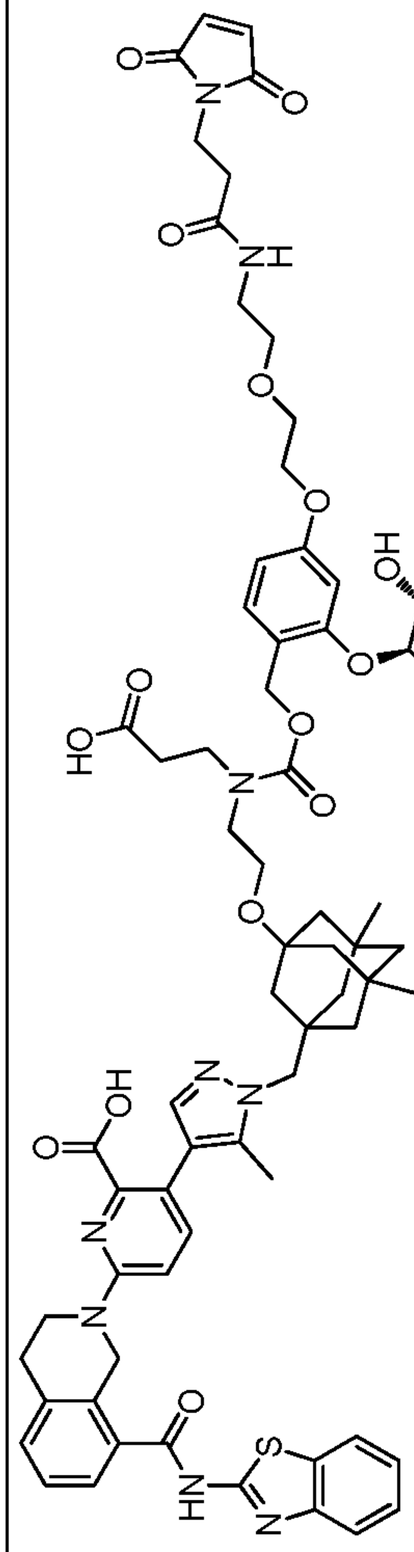
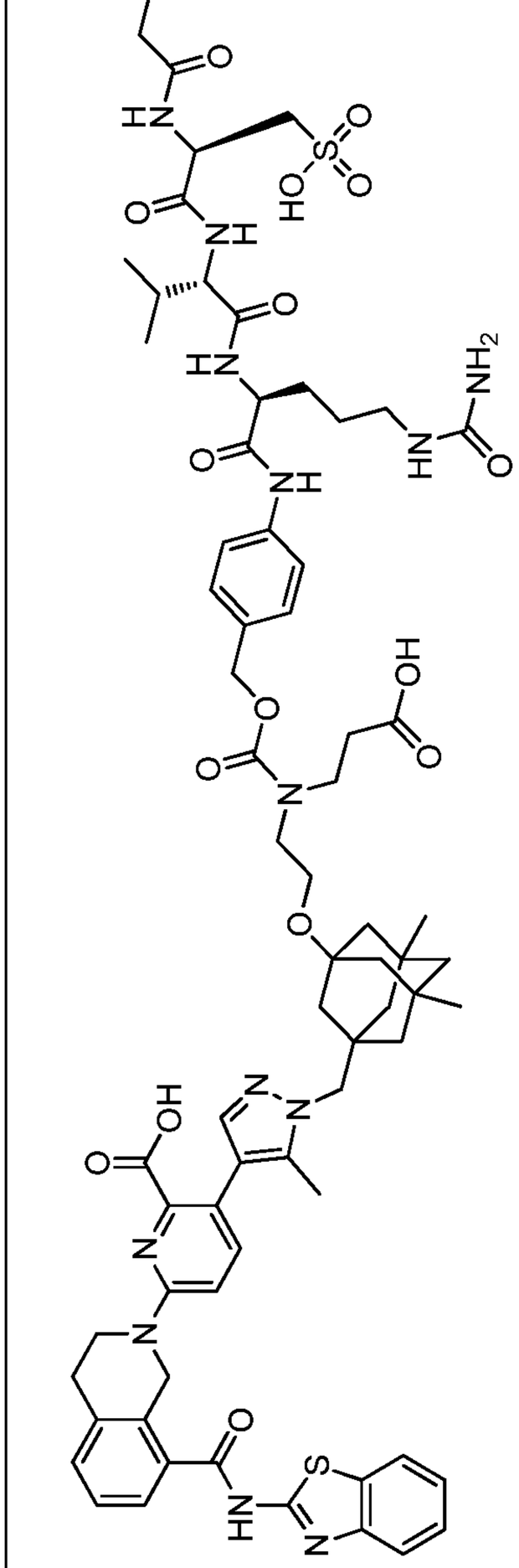
CA 03027045 2018-12-07

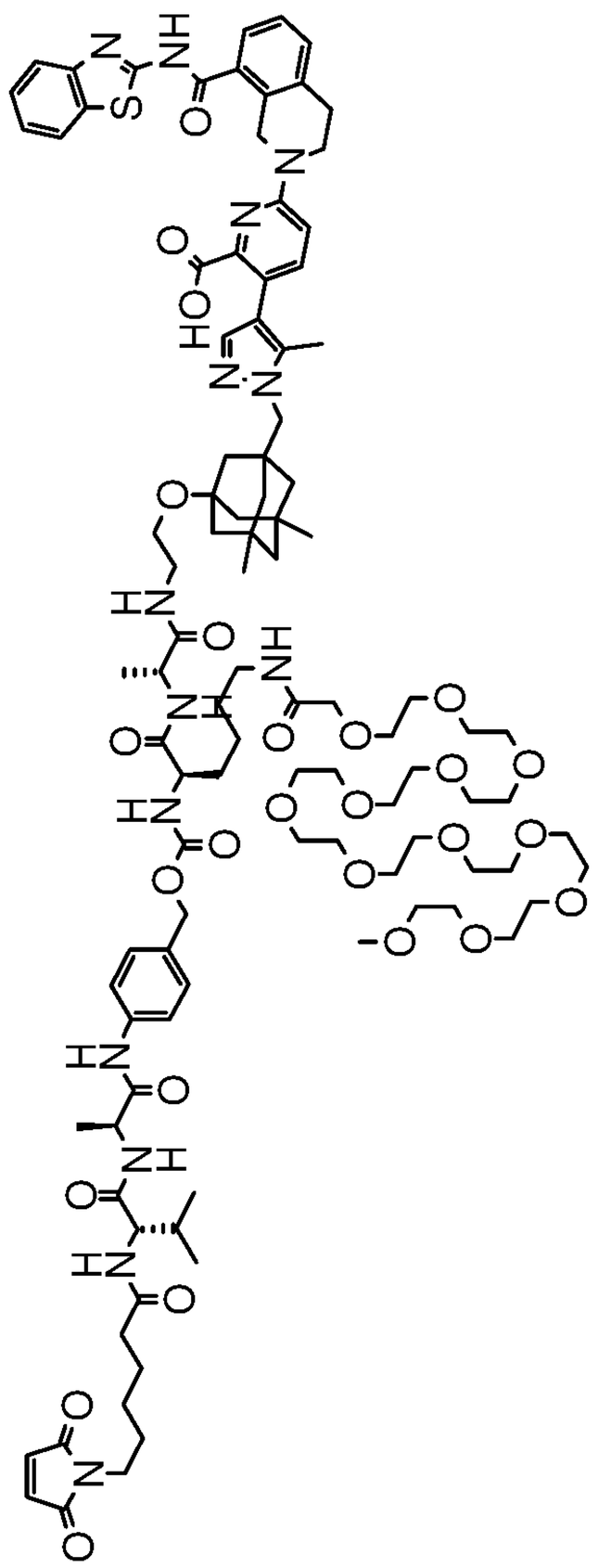
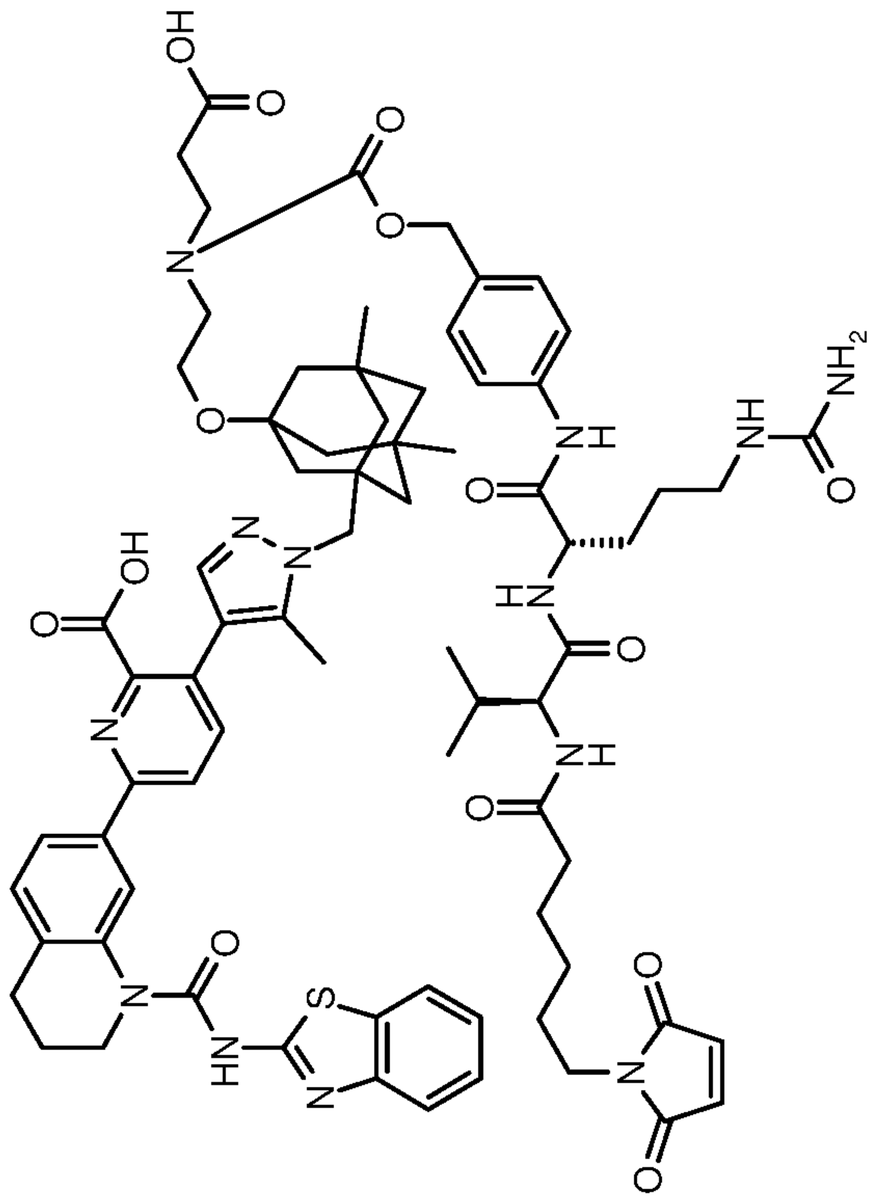
Example No.	Synthon Code	Synthon Structure
2.87	MA	
2.88	MD	

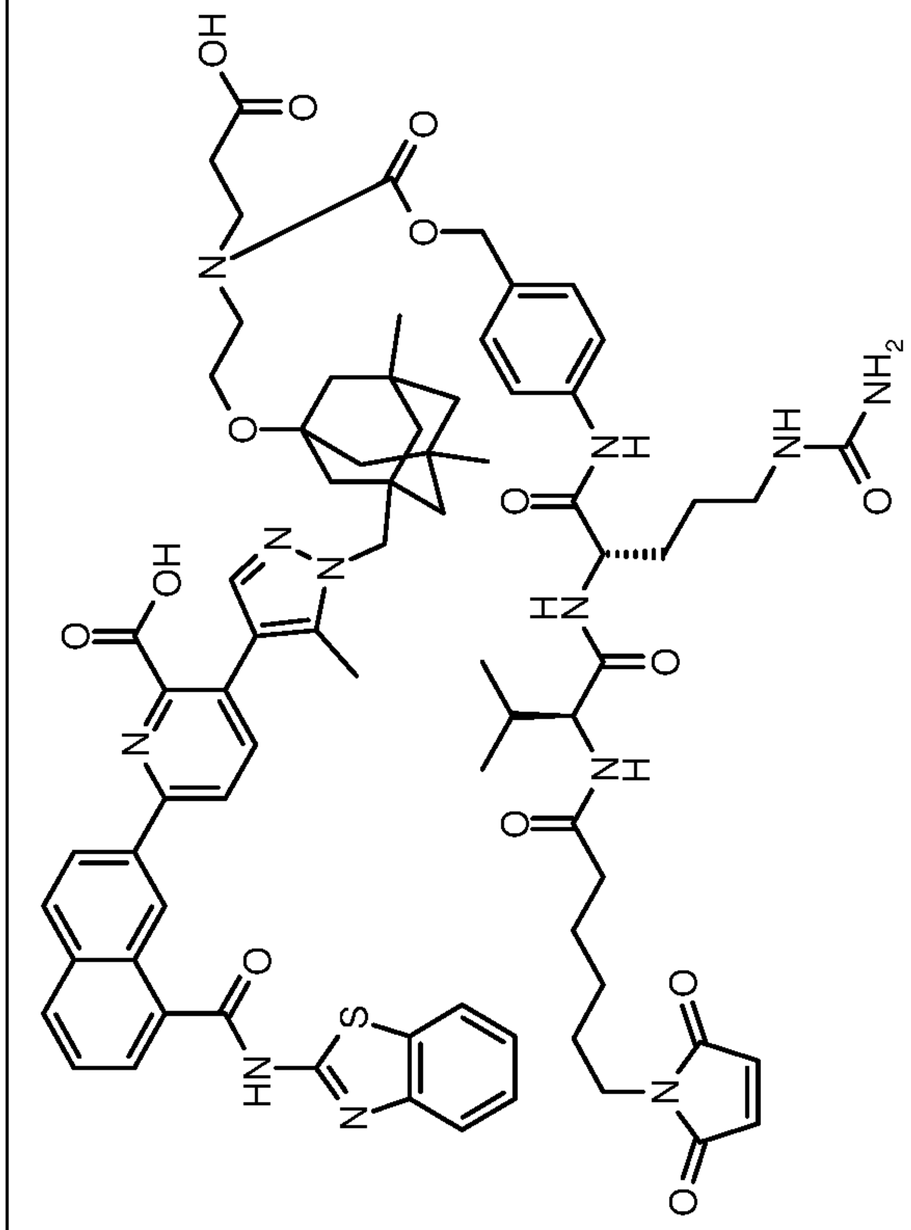
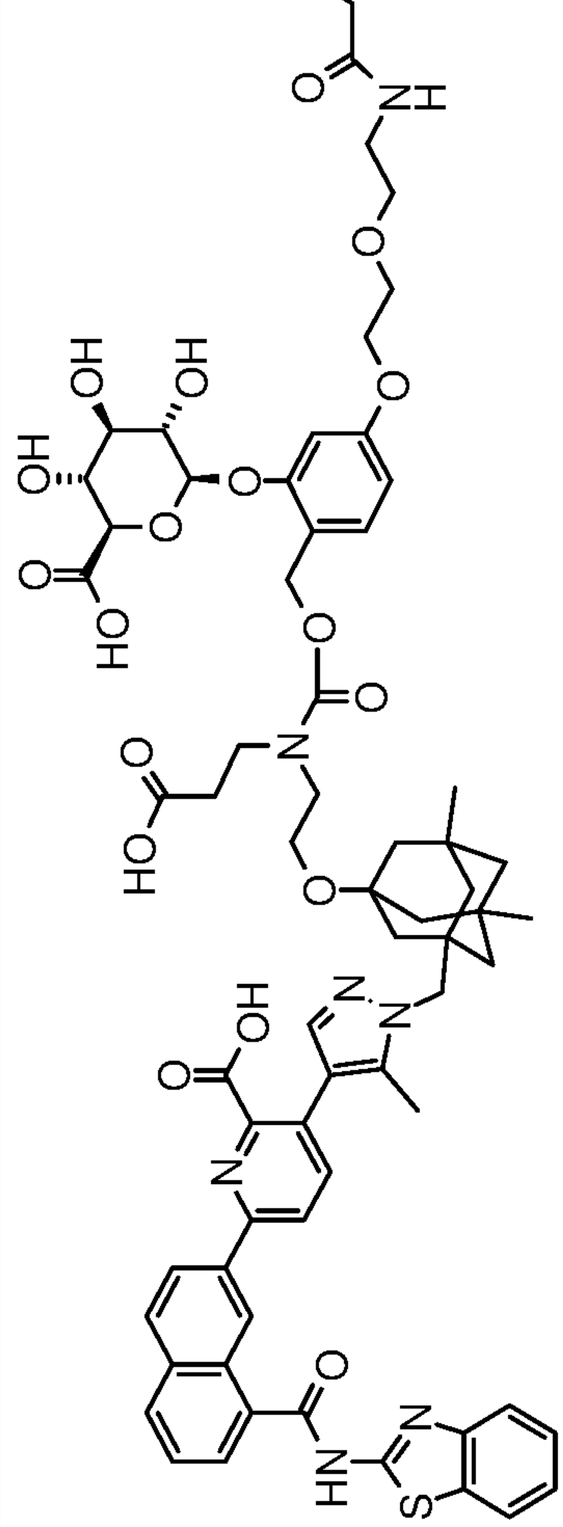
Example No.	Synthon Code	Synthon Structure
2.89	MG	
2.90	MS	
2.91	MR	

Example No.	Synthon Code	Synthon Structure
2.92	MQ	
2.93	MZ	
2.94	NA	

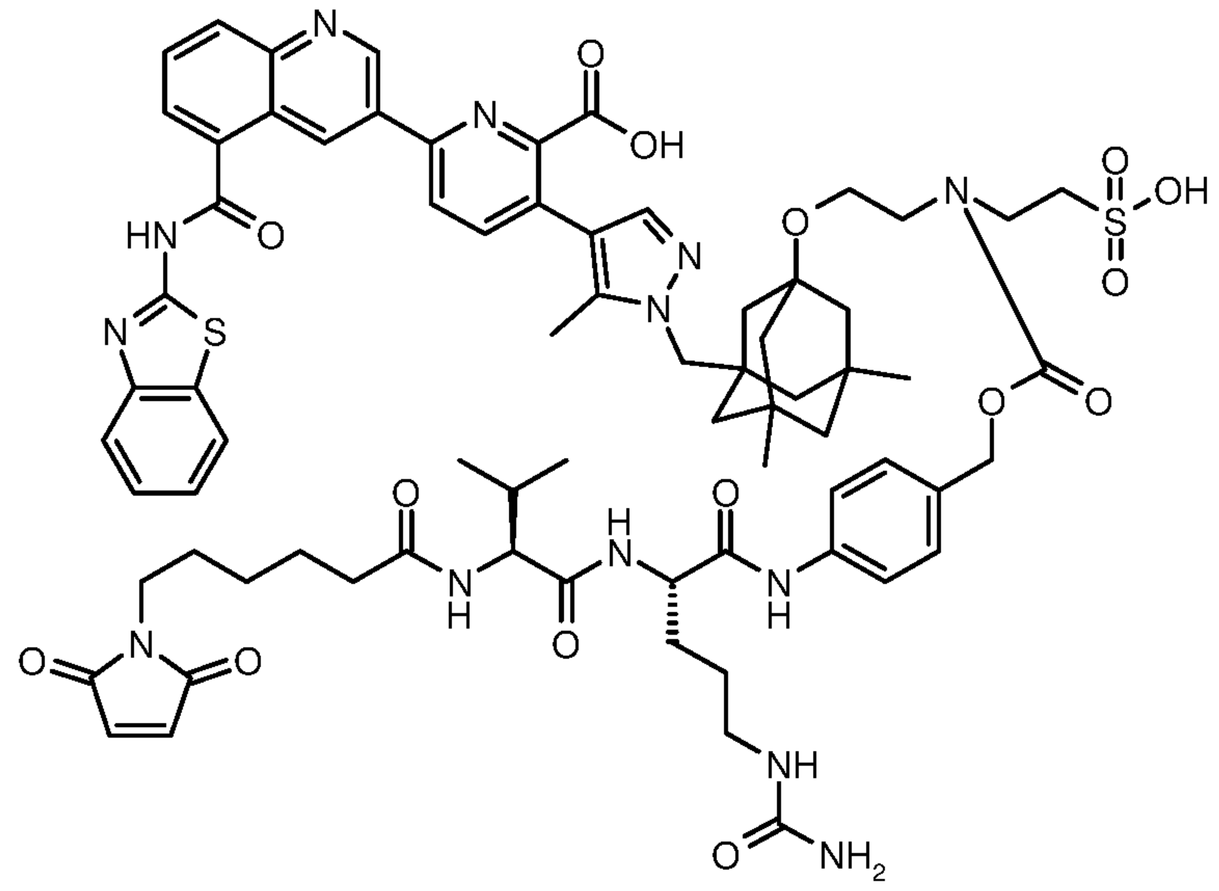
Example No.	Synthon Code	Synthon Structure	
2.95	NB		
2.96	NP		

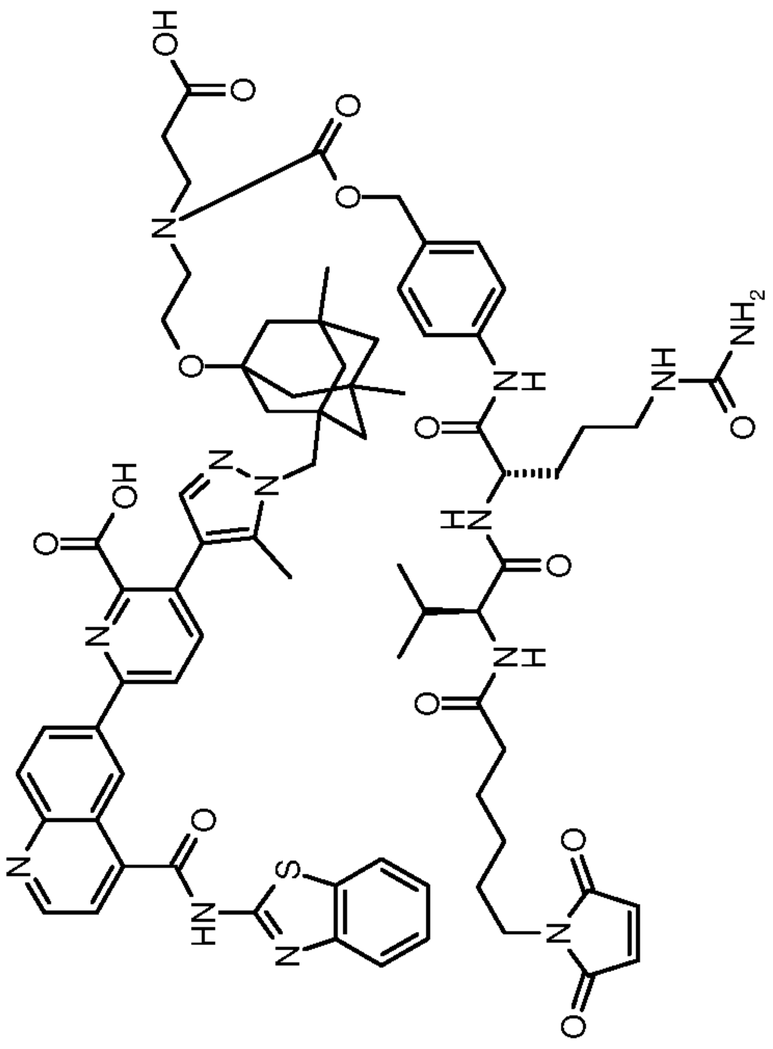
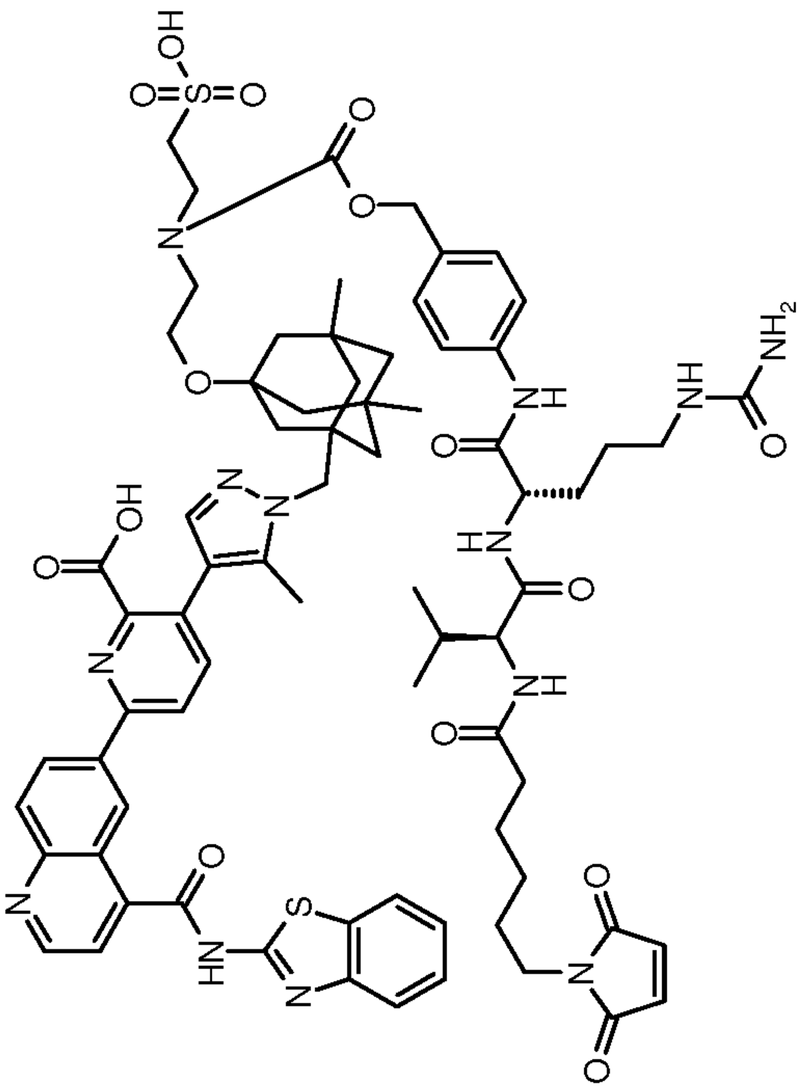
Example No.	Synthon Code	Synthon Structure
2.97	NN	
2.98	NO	

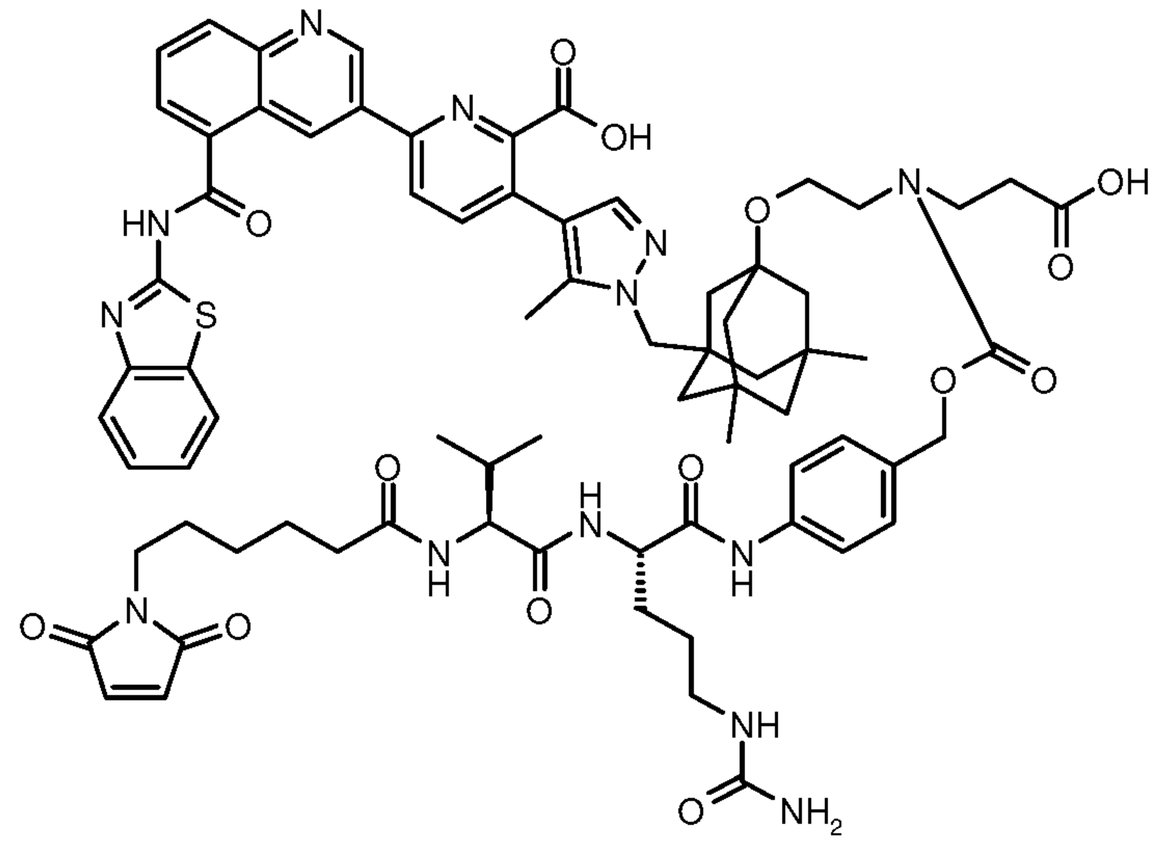
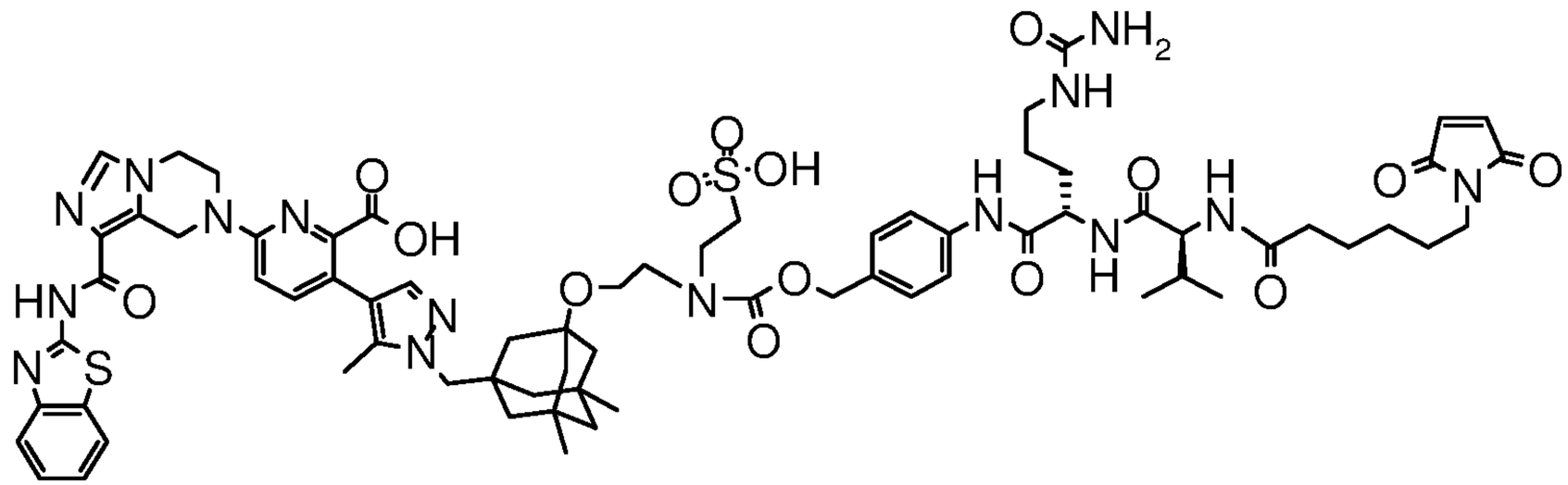
Example No.	Synthon Code	Synthon Structure
2.101	OK	
2.102	OW	

Example No.	Synthon Code	Synthon Structure
2.103	PC	
2.104	PI	

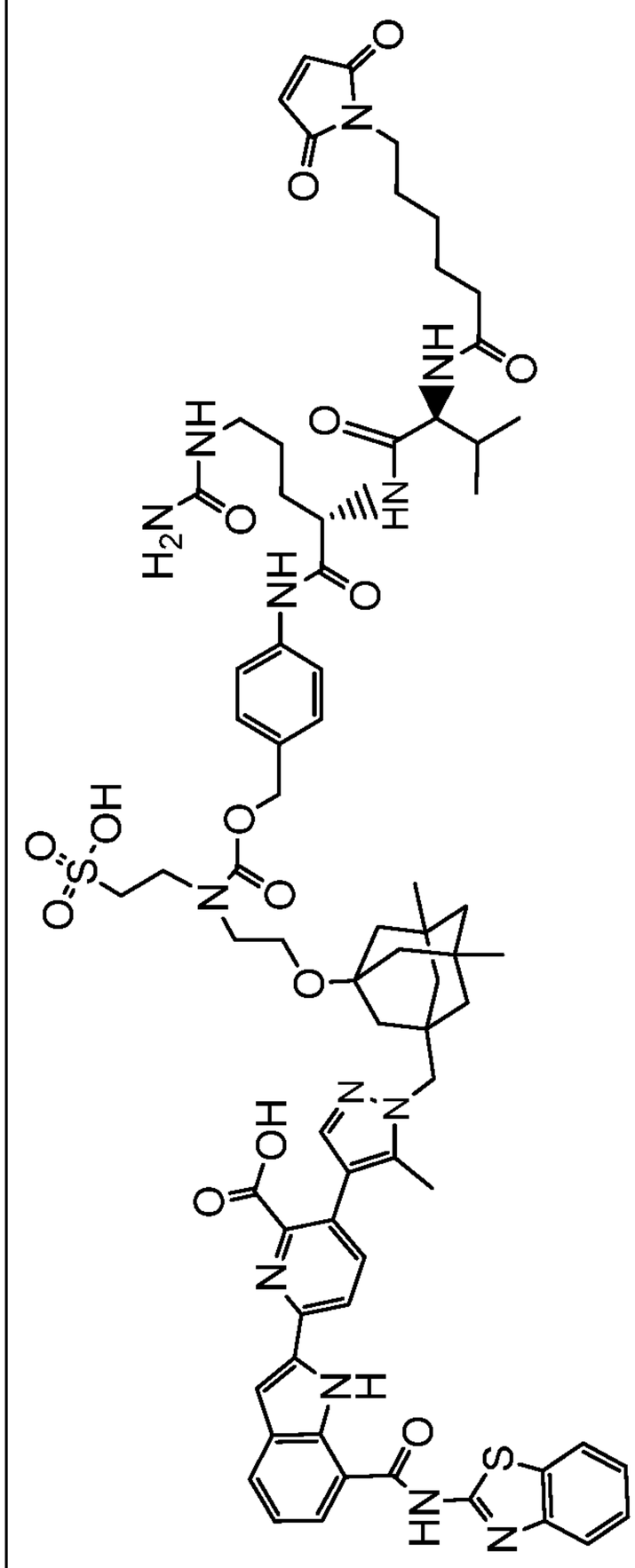
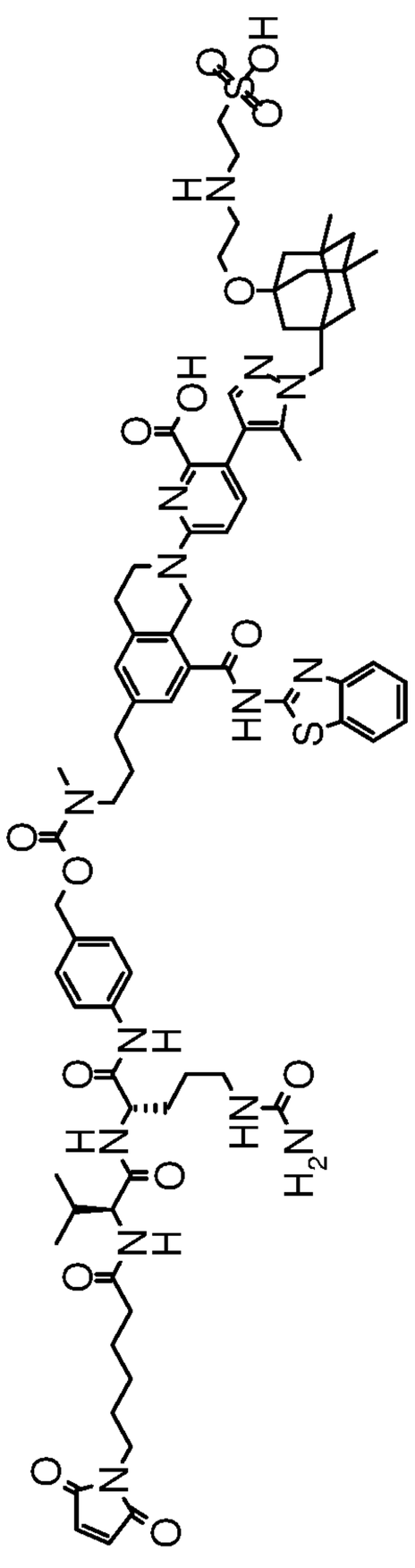
CA 03027045 2018-12-07

Example No.	Synthon Code	Synthon Structure
2.105	PJ	

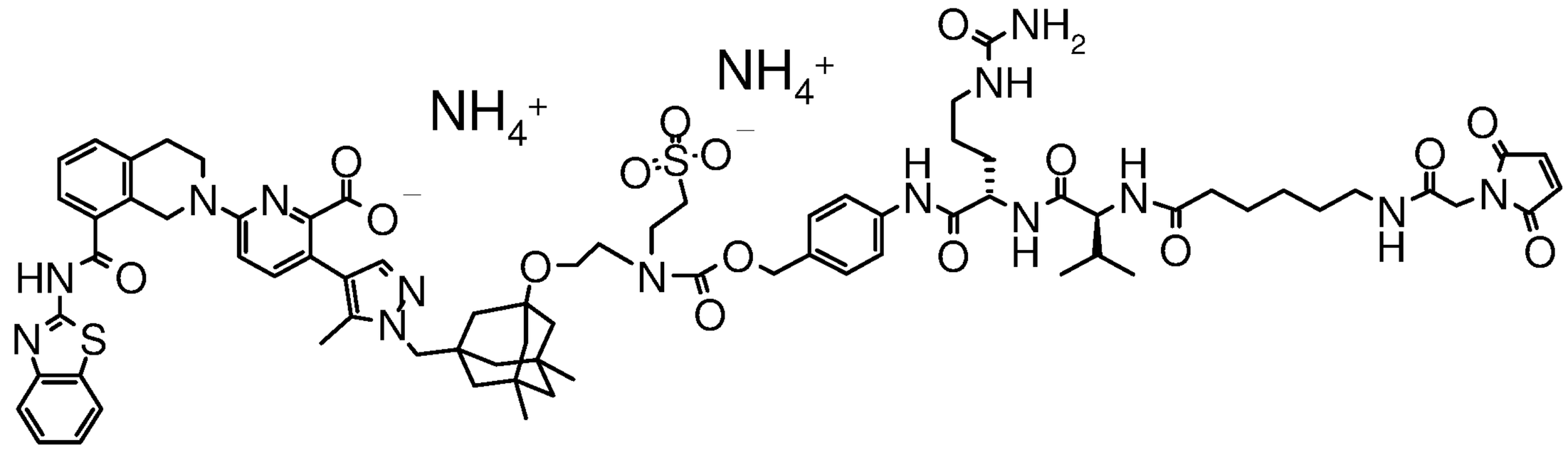
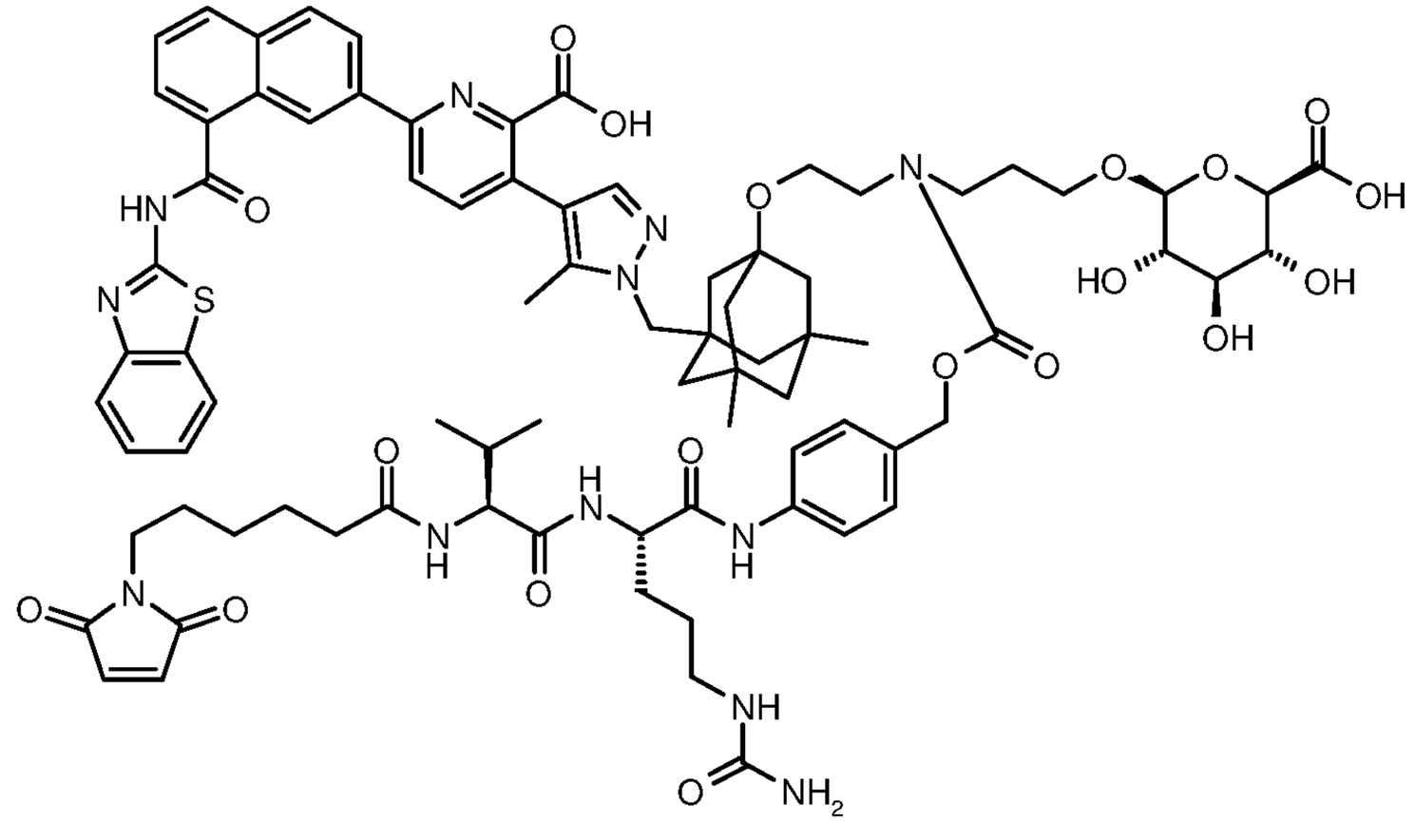
Example No.	Synthon Code	Synthon Structure
2.106	PU	
2.107	PV	

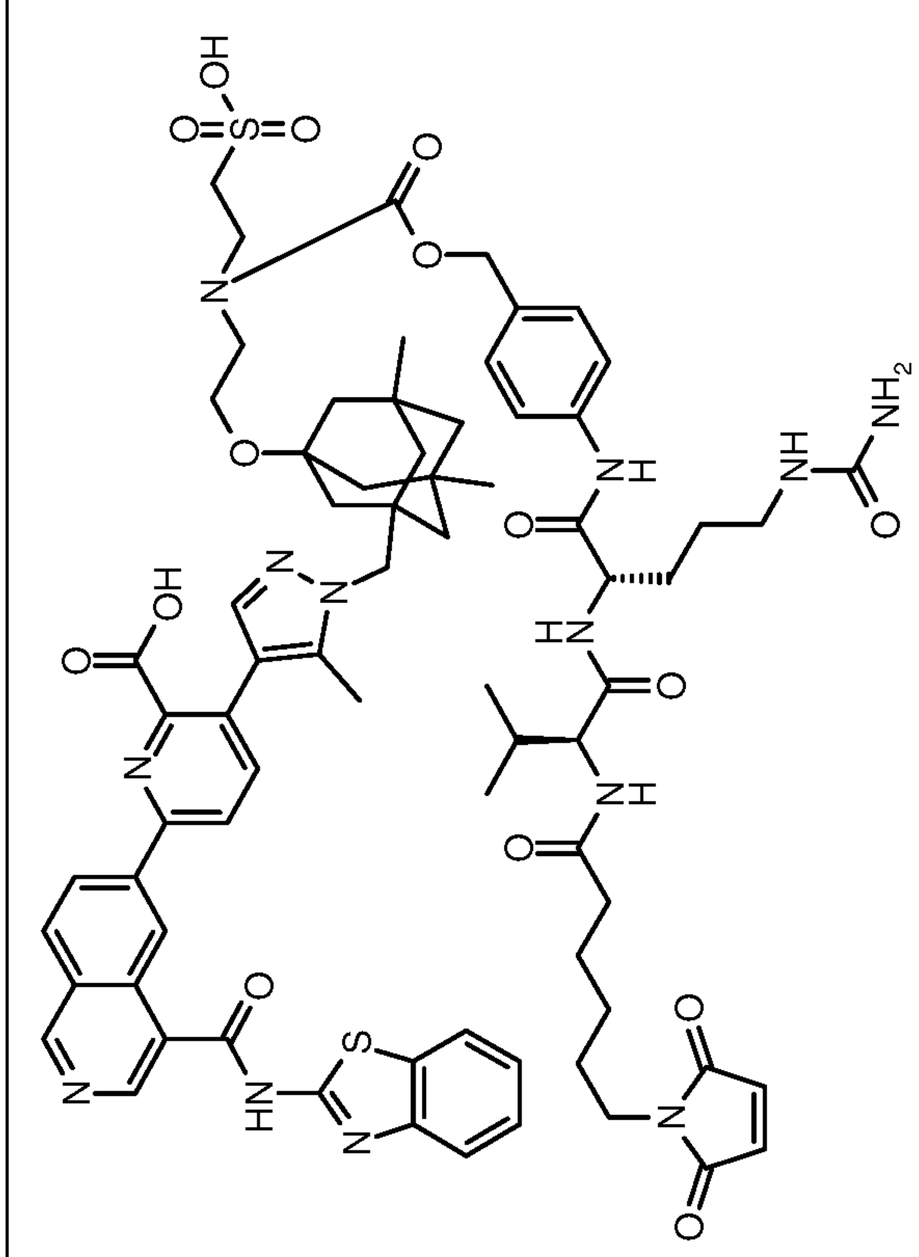
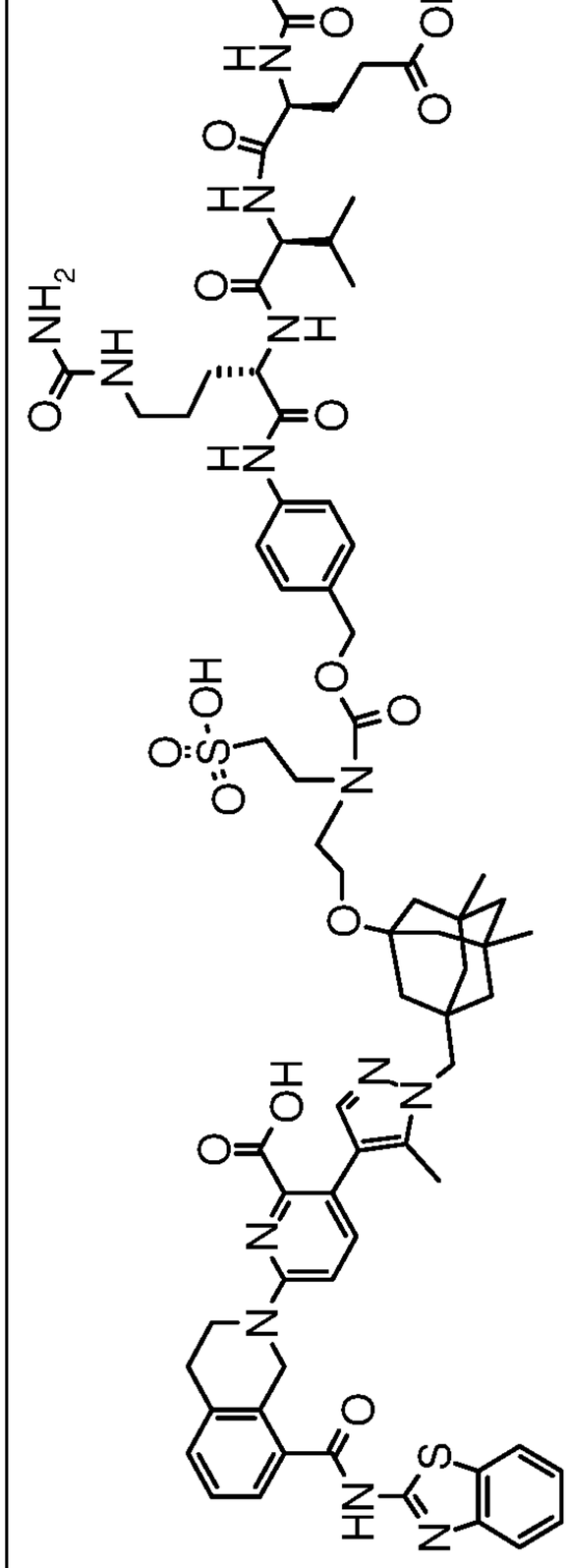
Example No.	Synthon Code	Synthon Structure
2.108	PW	
2.109	QW	

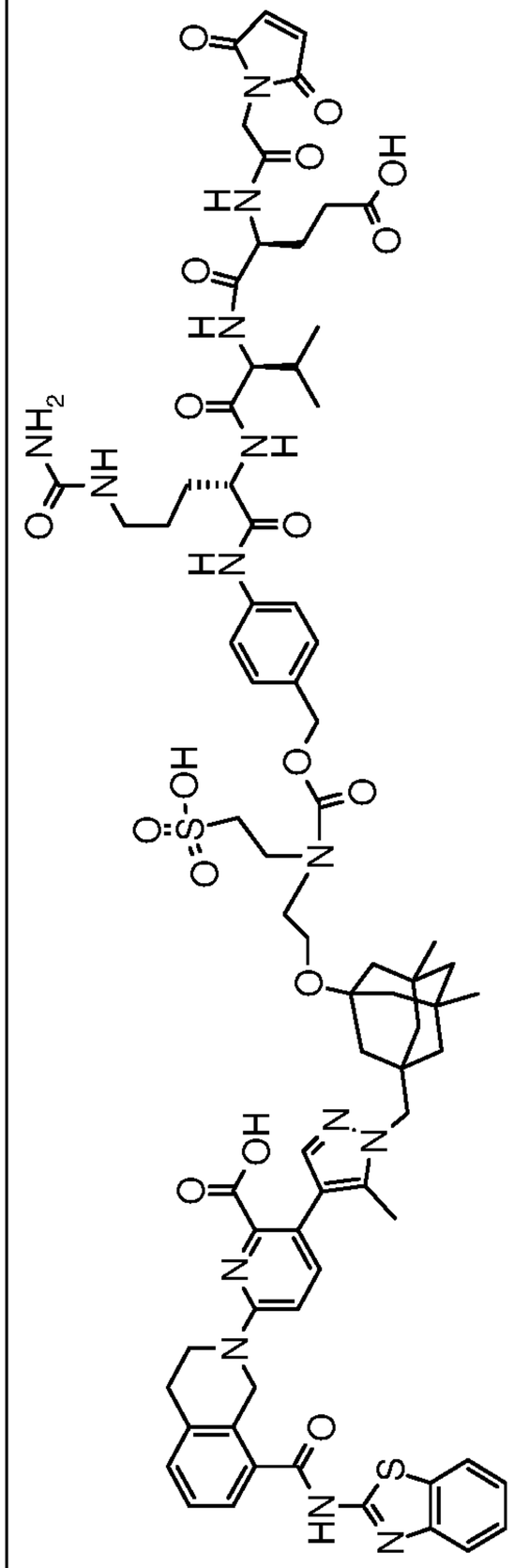
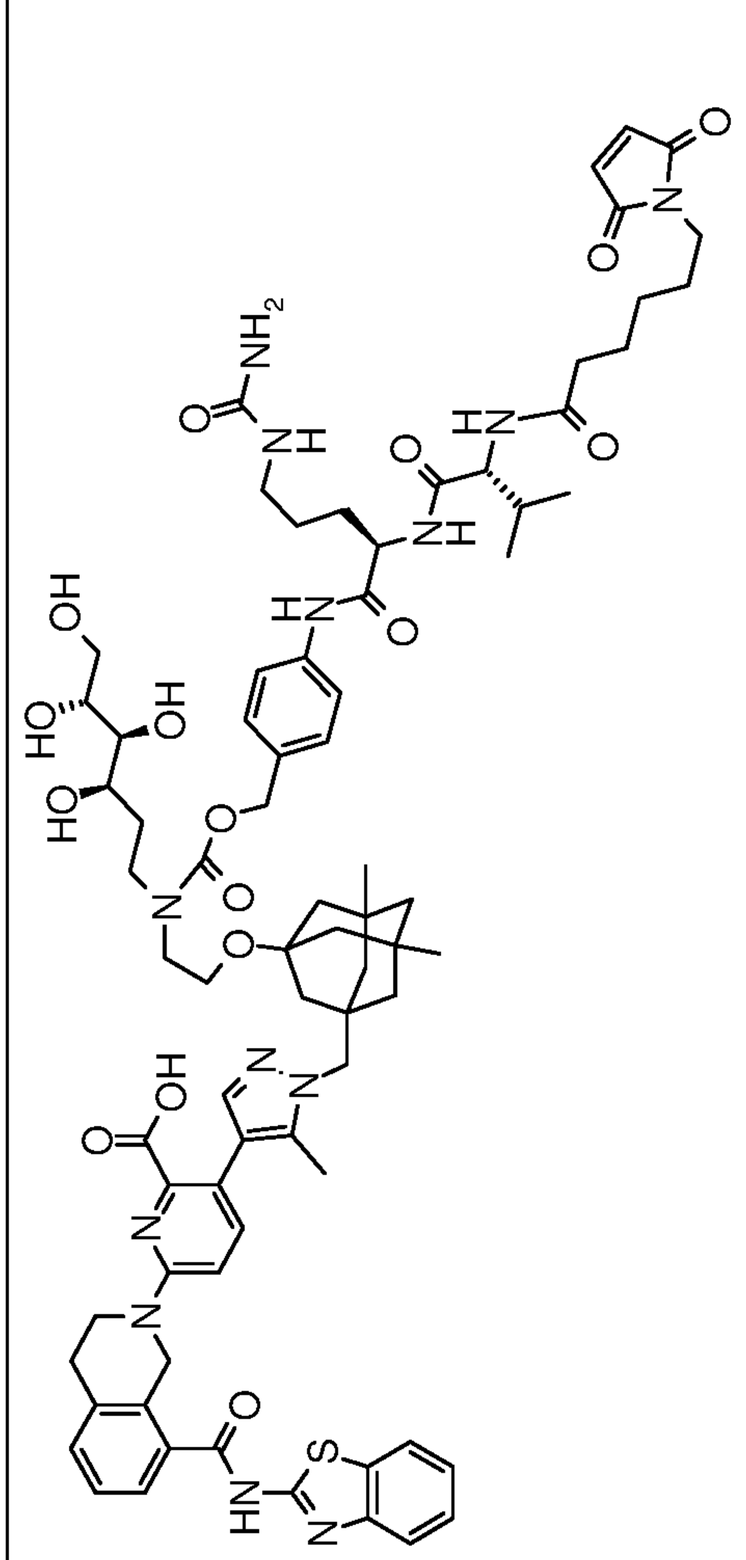
CA 03027045 2018-12-07

Example No.	Synthon Code	Synthon Structure
2.110	RM	
2.111	RR	

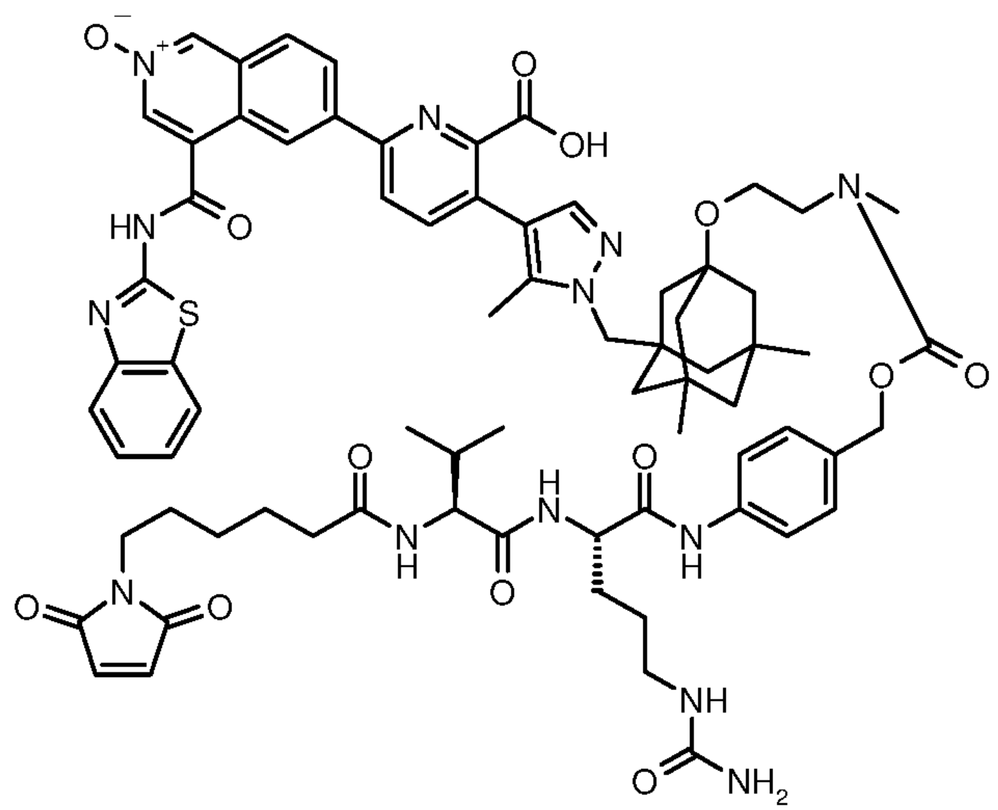
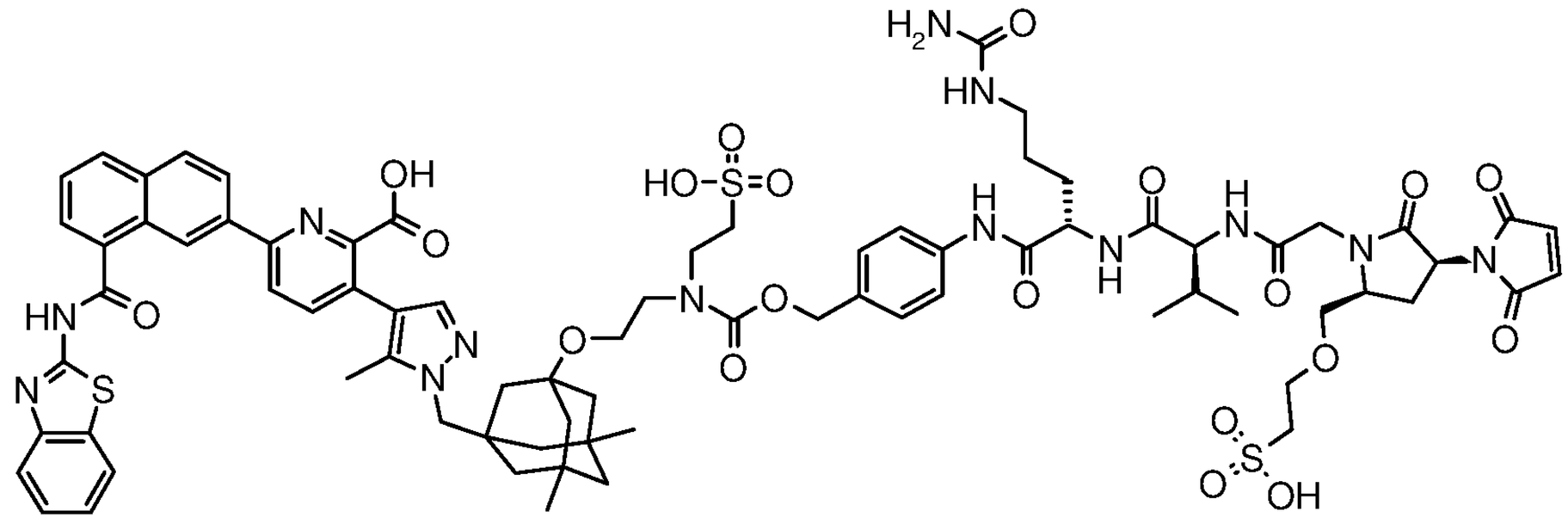
CA 03027045 2018-12-07

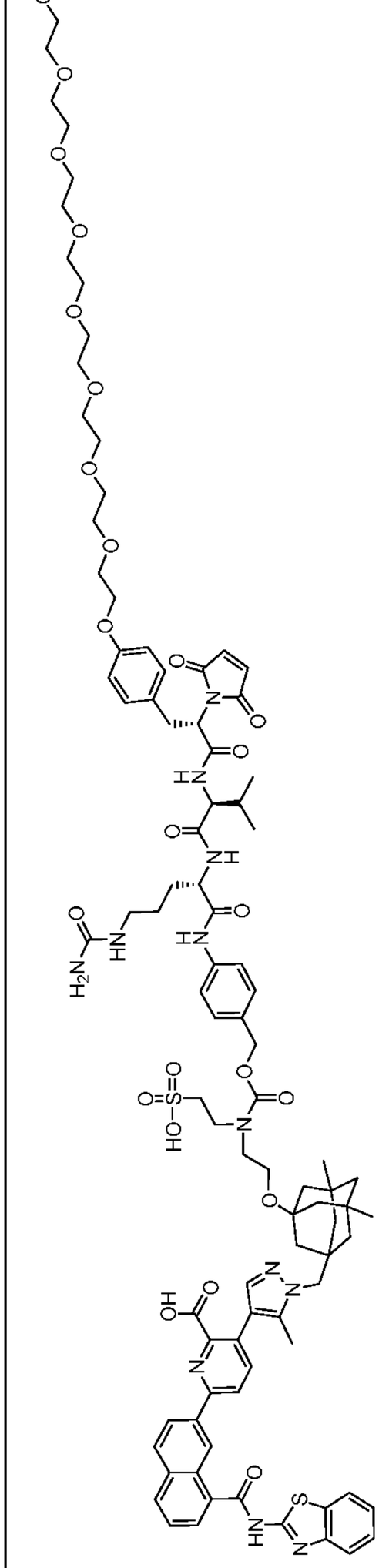
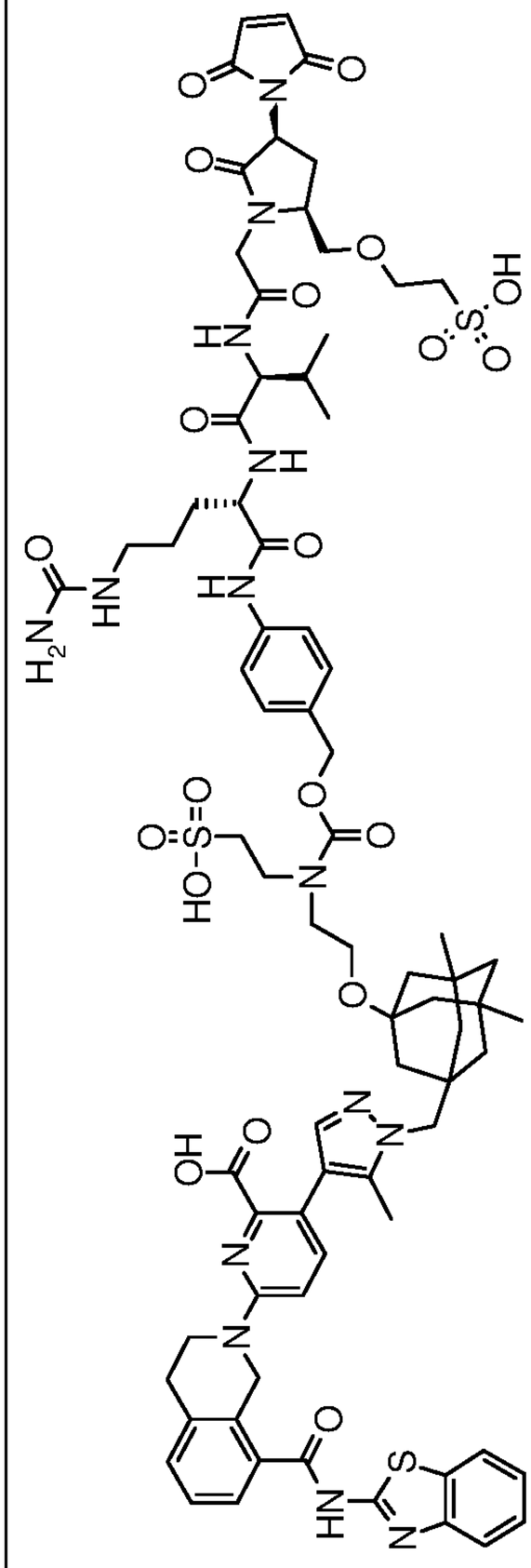
Example No.	Synthon Code	Synthon Structure
2.112	SJ	
2.113	SM	

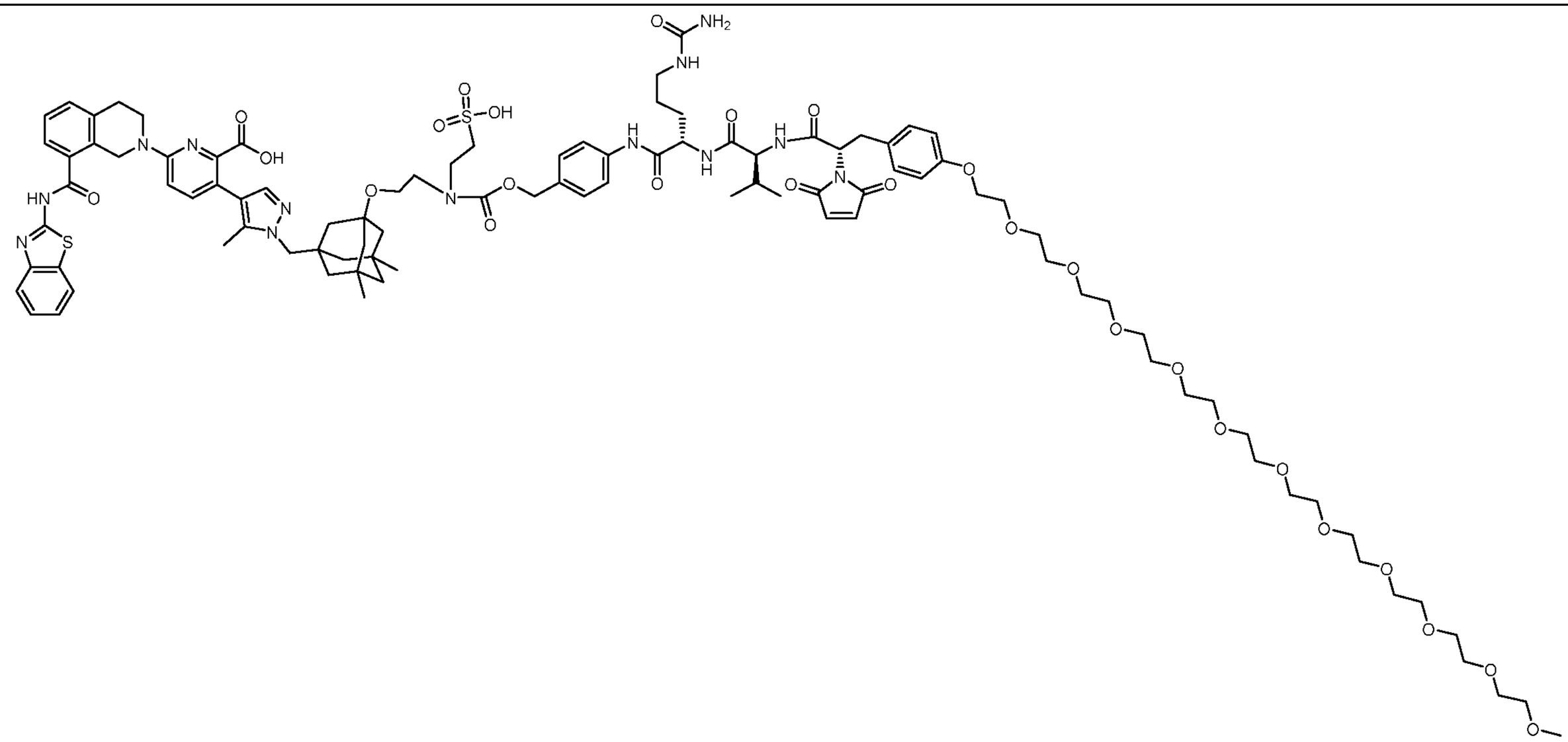
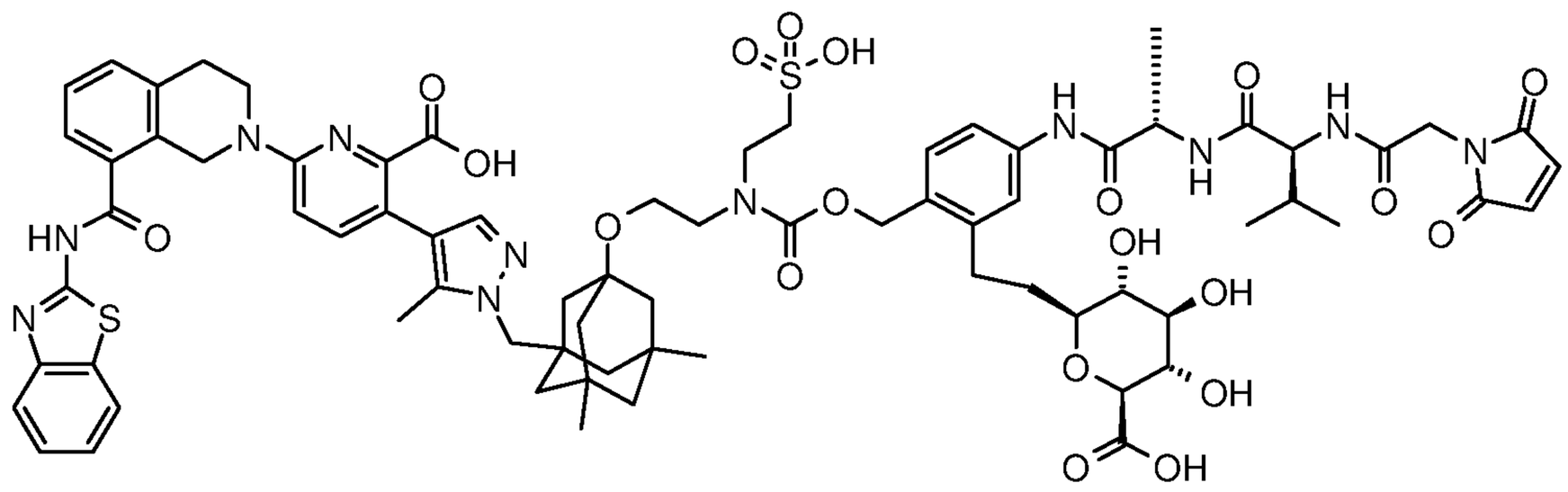
Example No.	Synthon Code	Synthon Structure
2.114	SN	
2.115	SS	

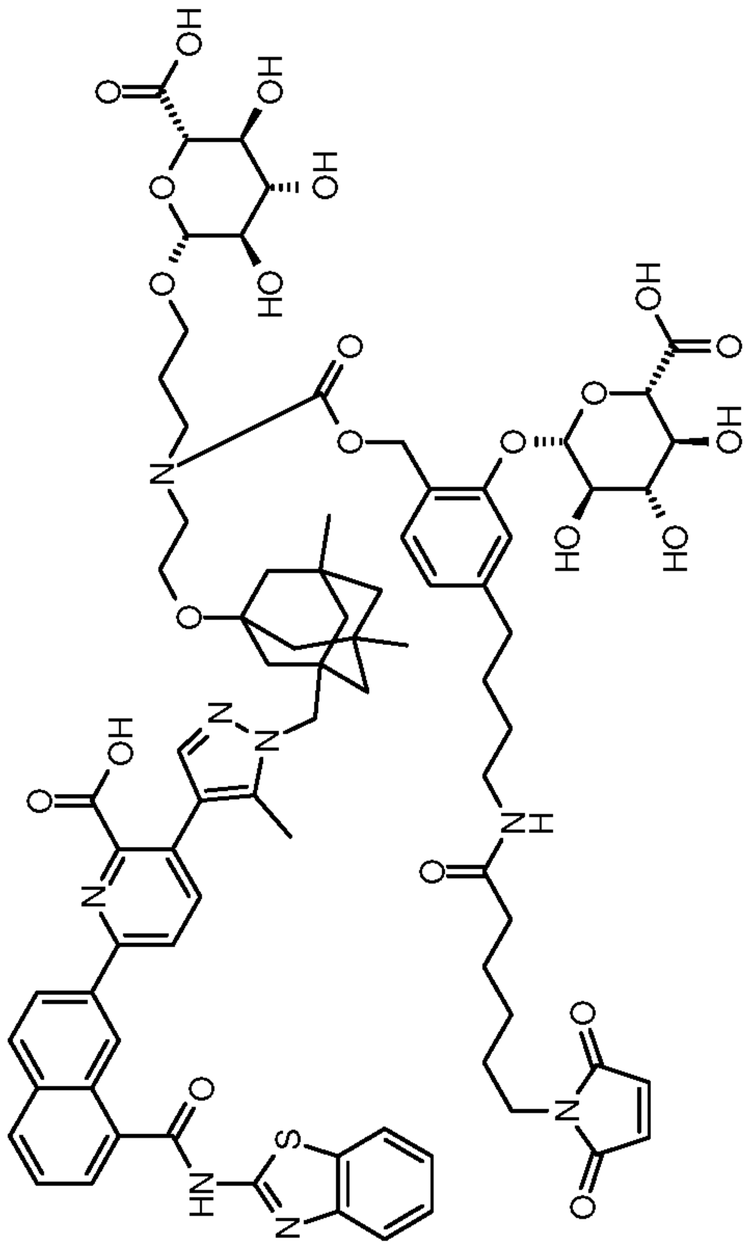
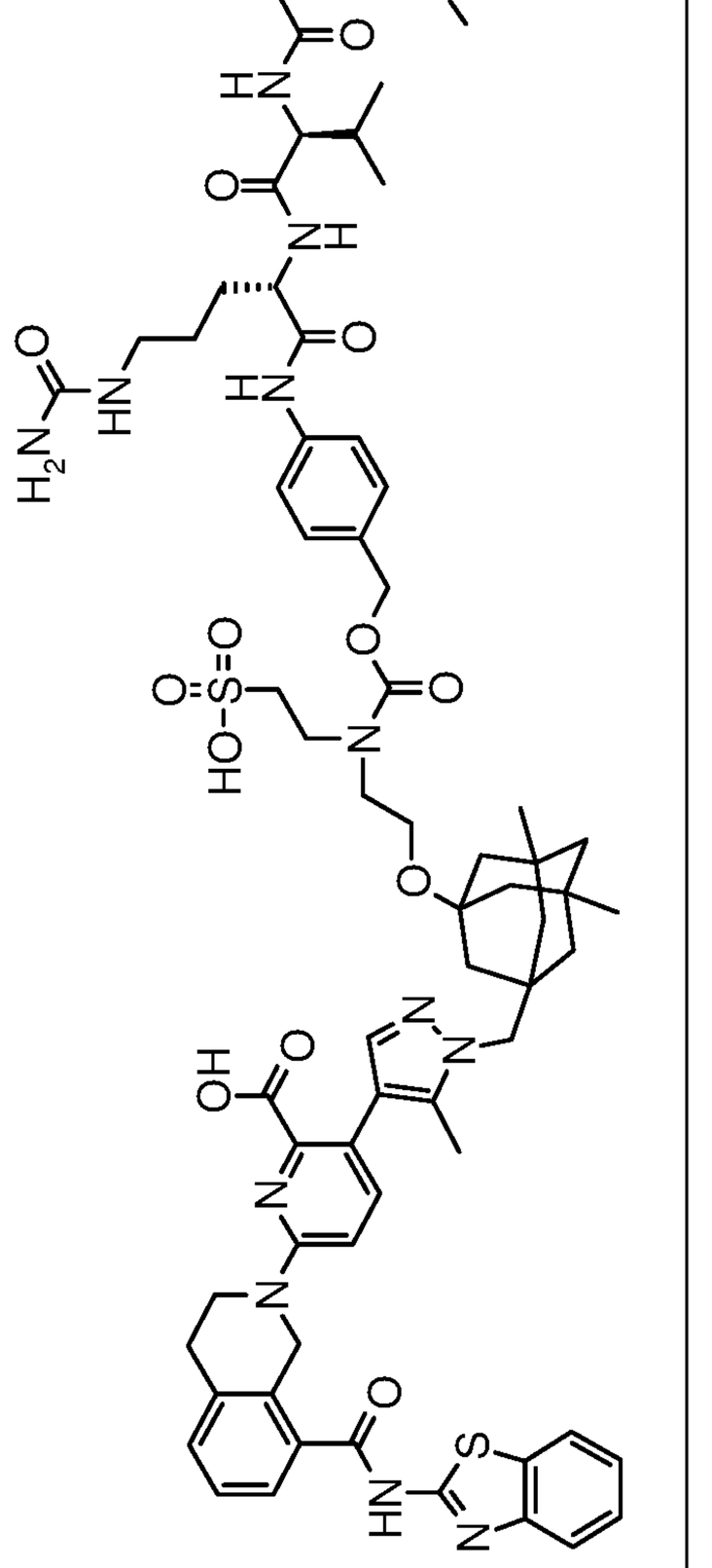
Example No.	Synthon Code	Synthon Structure
2.116	TA	
2.117	TW	

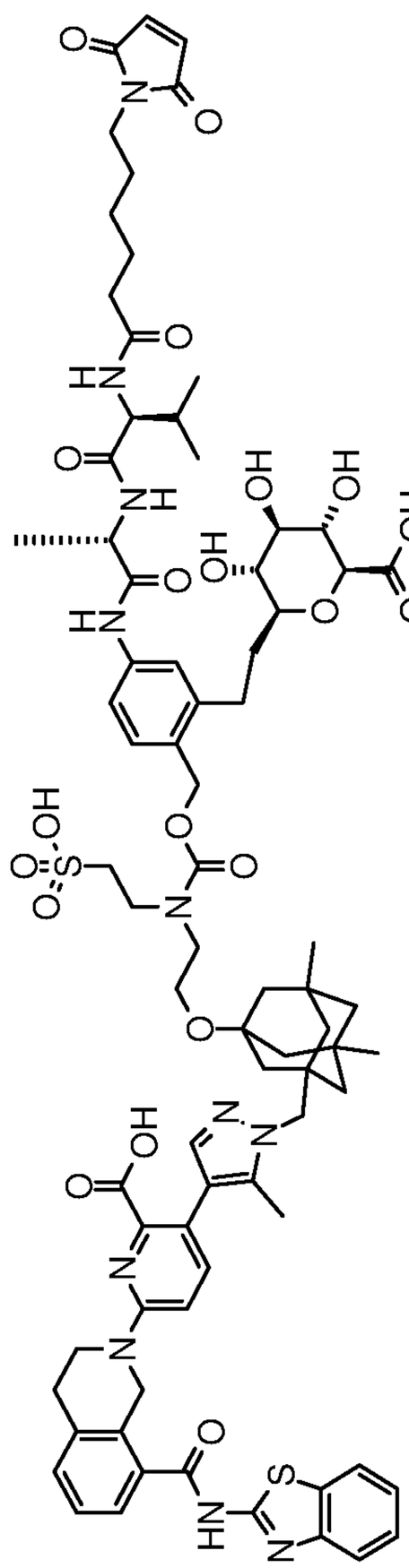
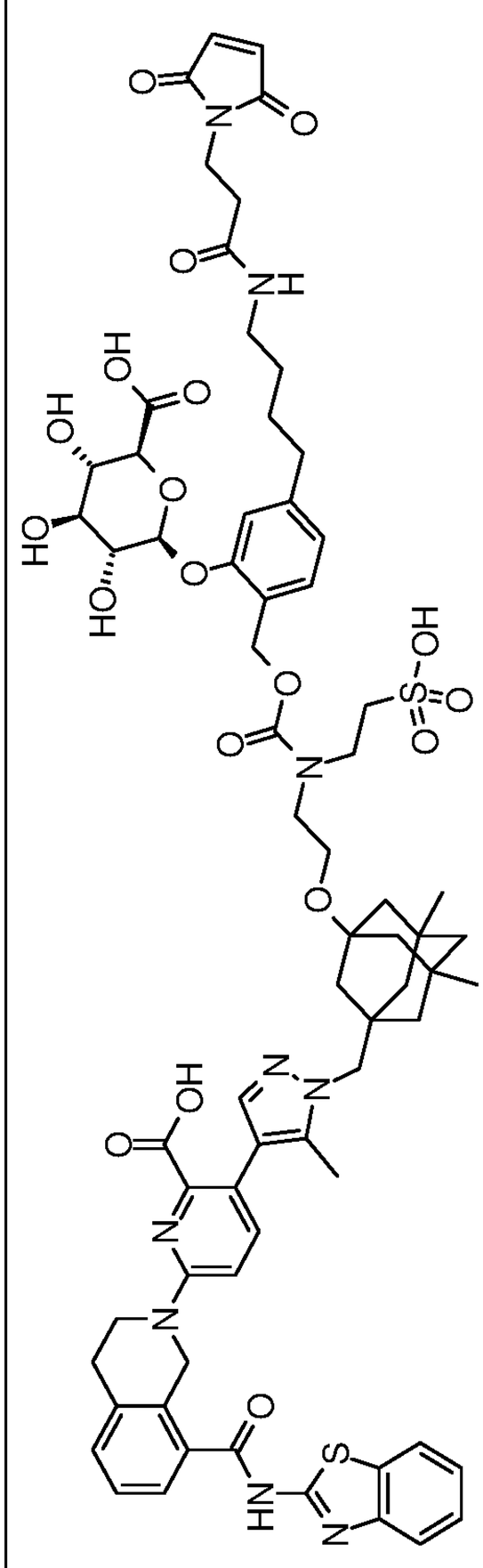
CA 03027045 2018-12-07

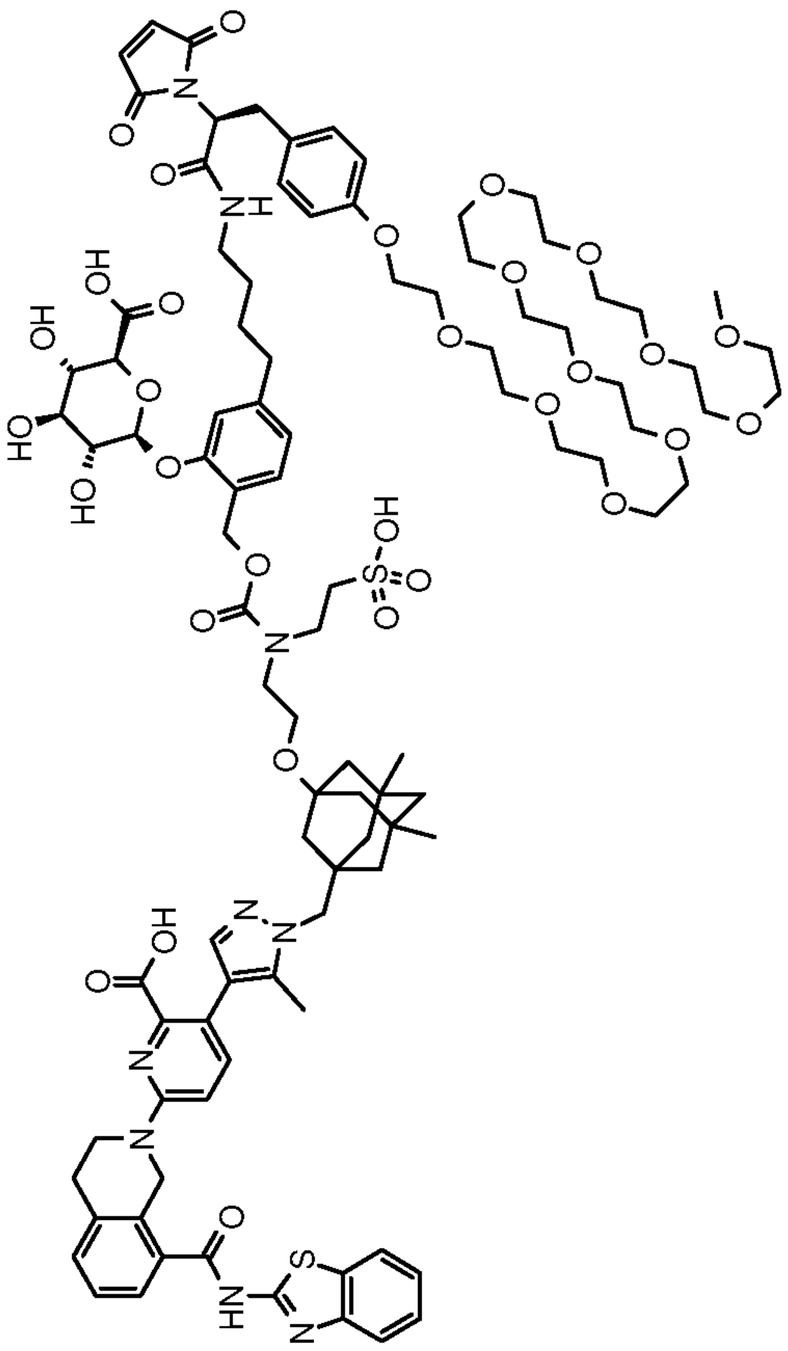
Example No.	Synthon Code	Synthon Structure
2.118	ST	
2.119	ZL	

Example No.	Synthon Code	Synthon Structure
2.120	SX	
2.121	SW	

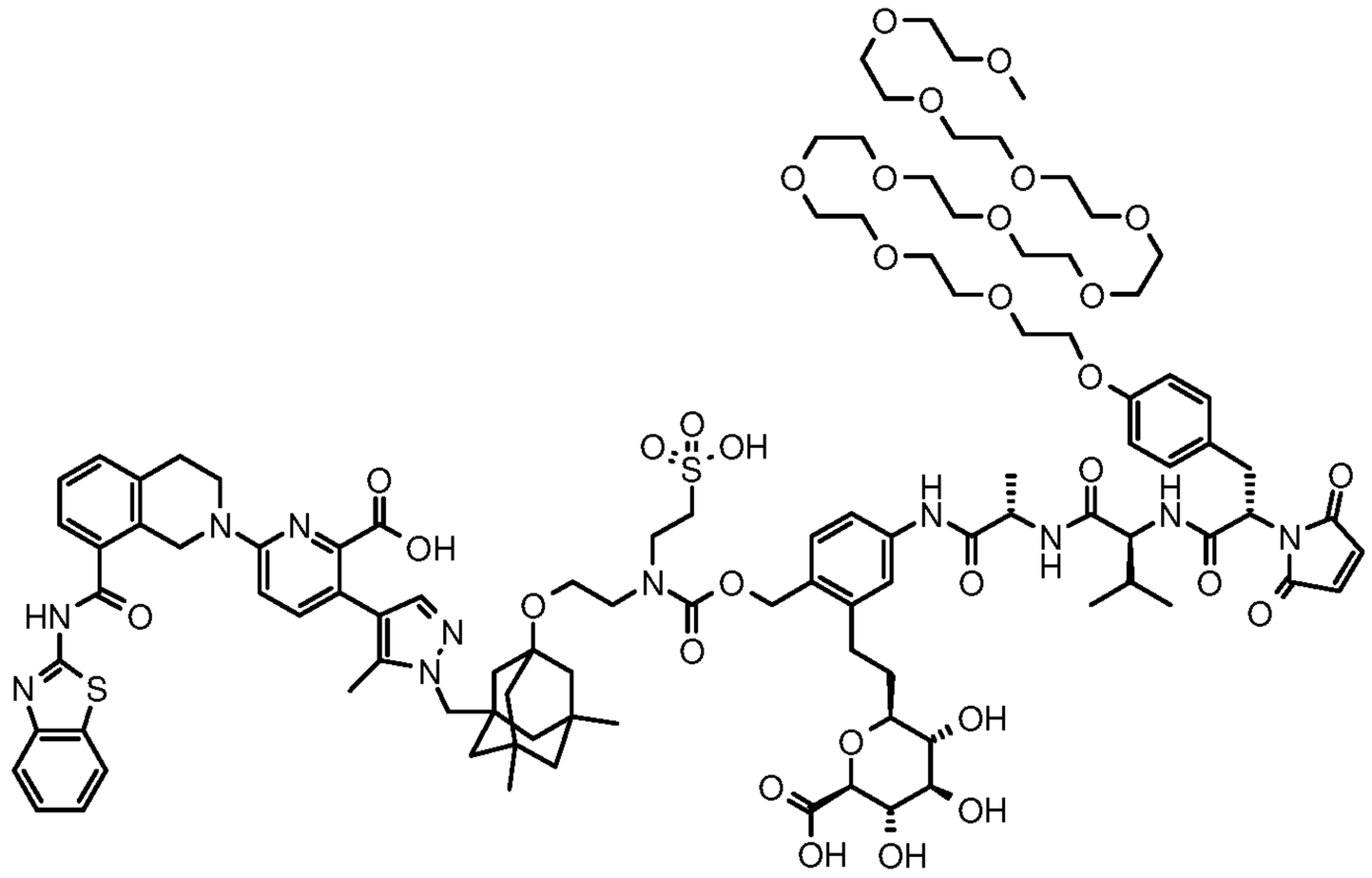
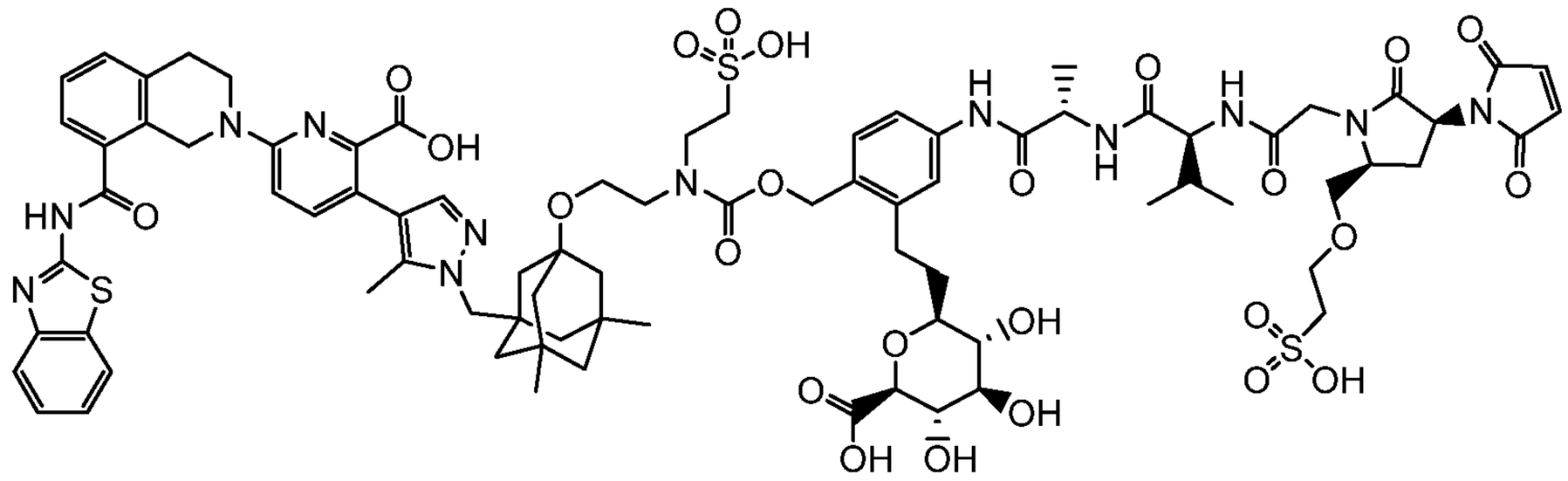
Example No.	Synthon Code	Synthon Structure
2.122	TV	
2.123	SZ	

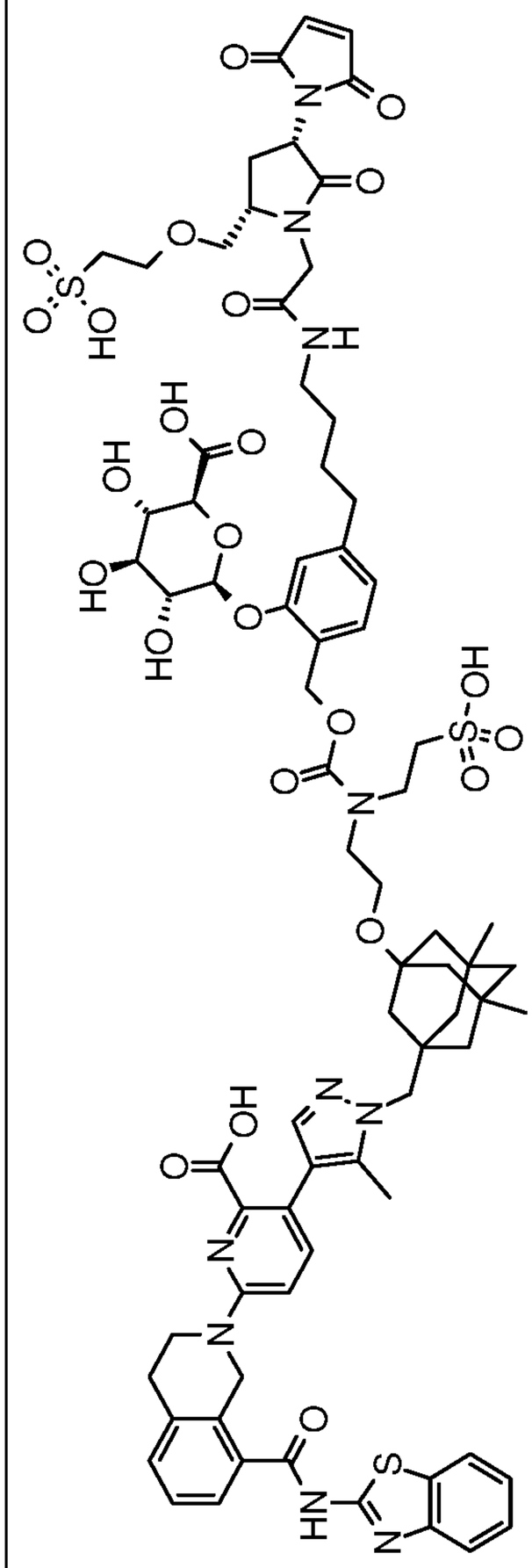
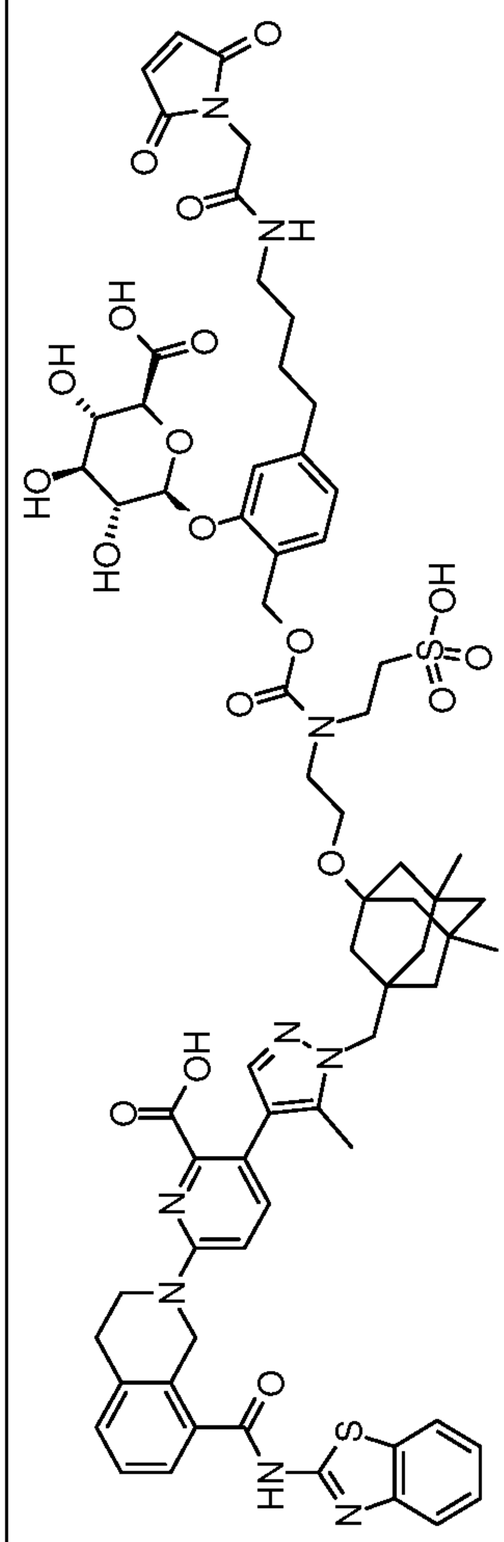
Example No.	Synthon Code	Synthon Structure
2.124	ZM	
2.125	SV	

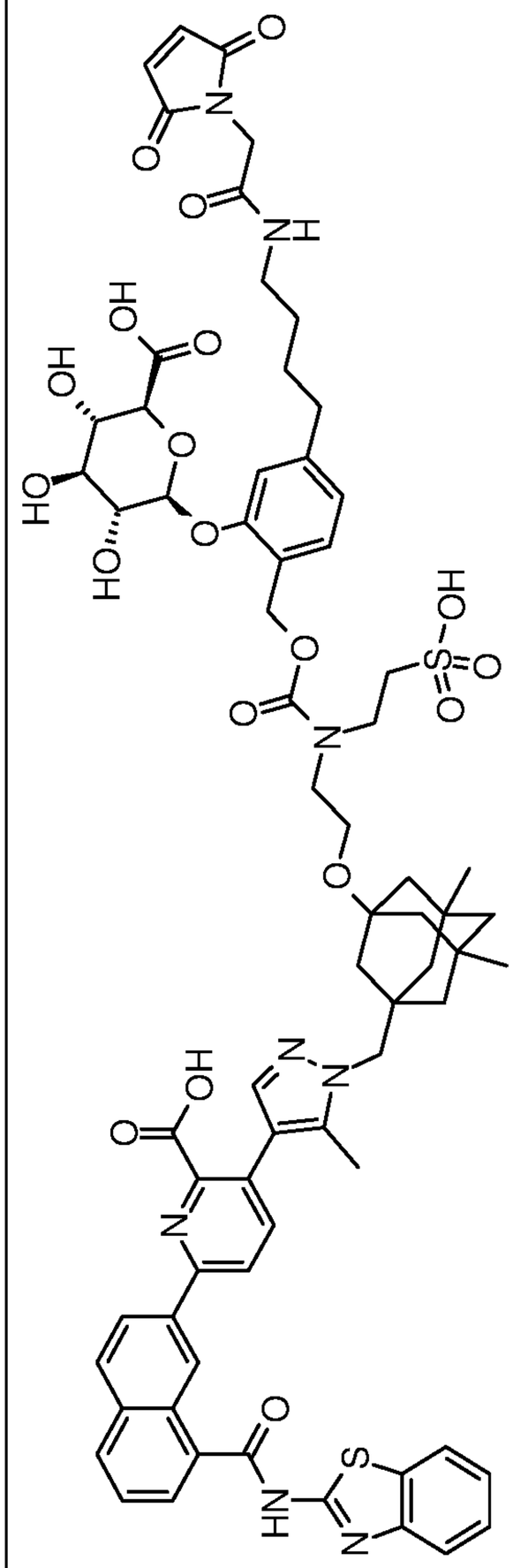
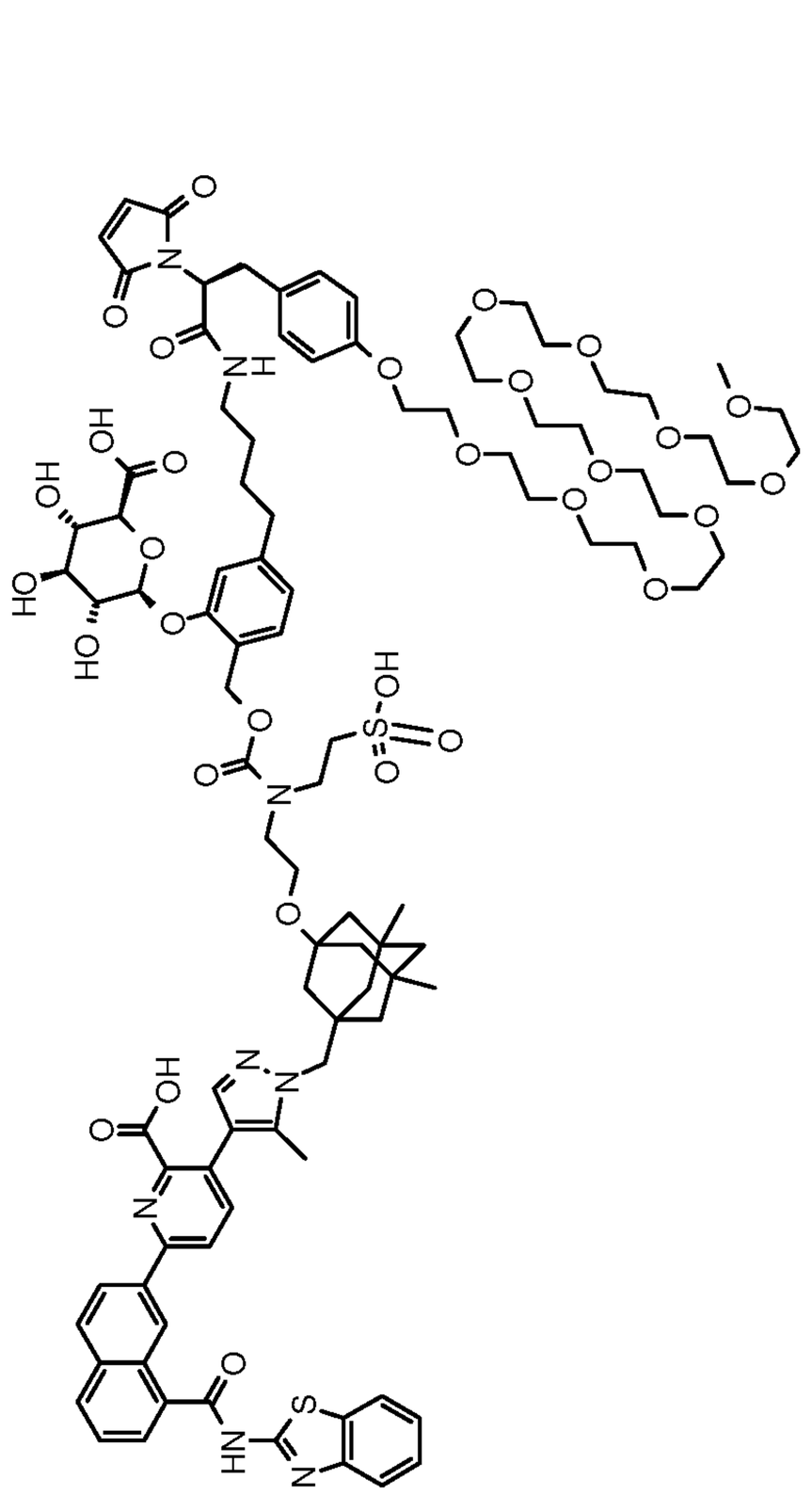
Example No.	Synthon Code	Synthon Structure
2.126	SY	
2.127	TK	

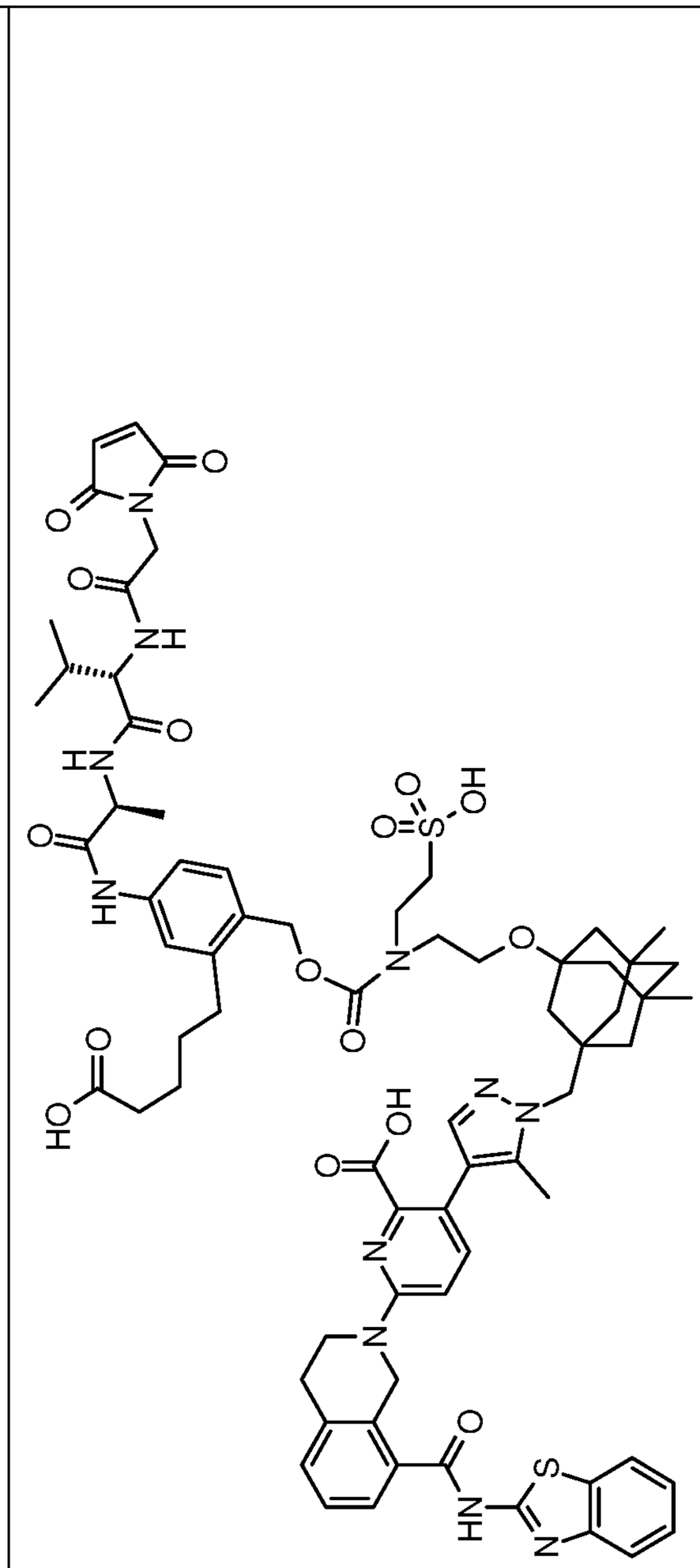
Example No.	Synthon Code	Synthon Structure
2.128	TR	

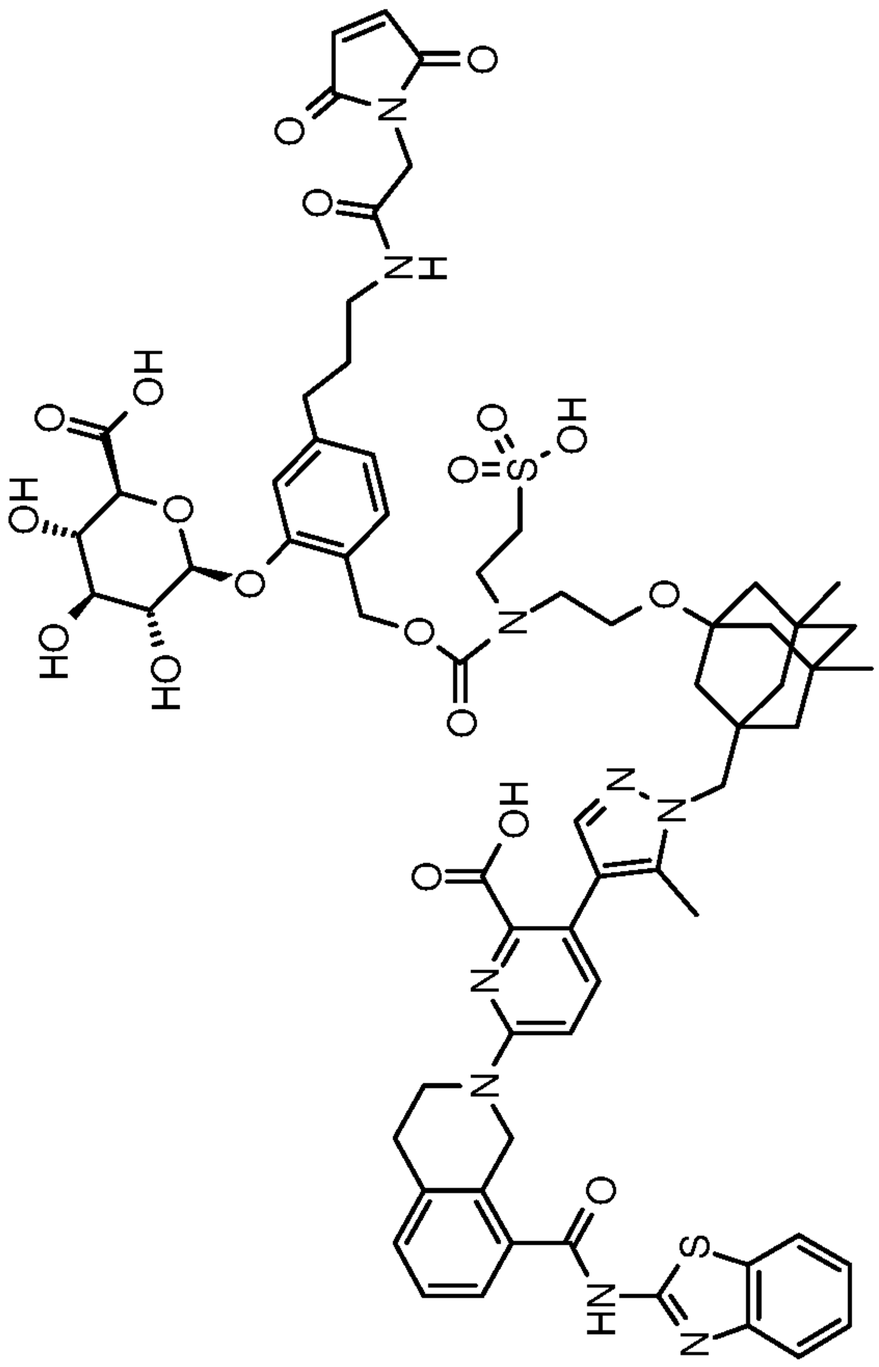
CA 03027045 2018-12-07

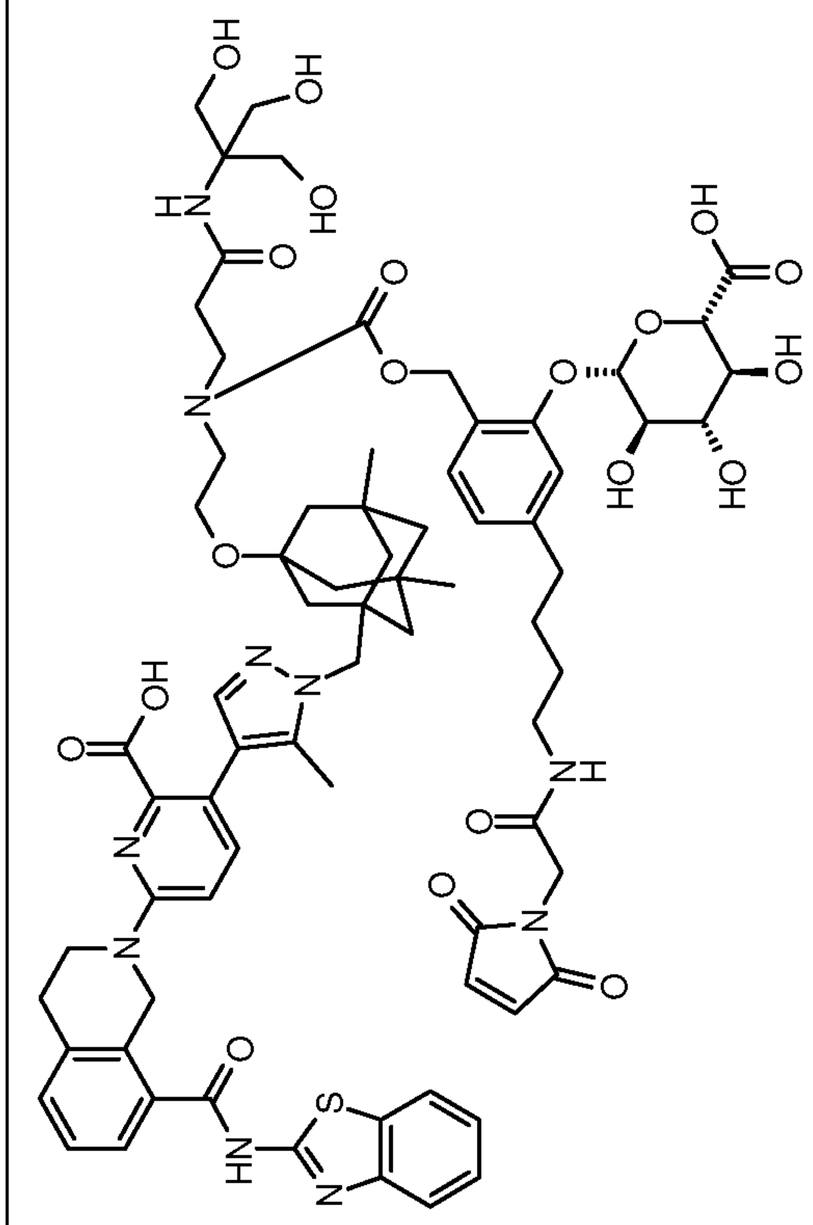
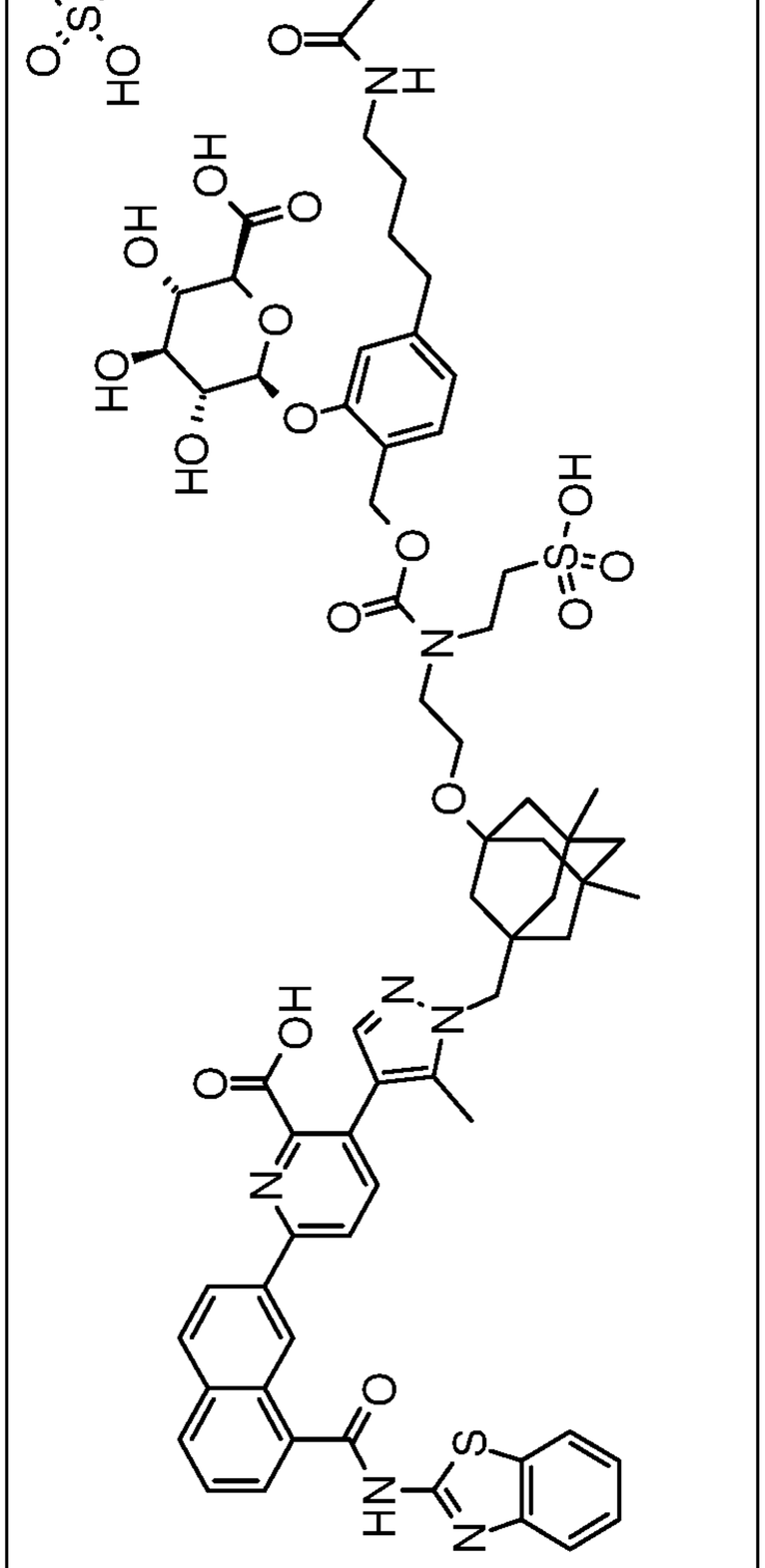
Example No.	Synthon Code	Synthon Structure
2.129	TY	
2.130	TX	

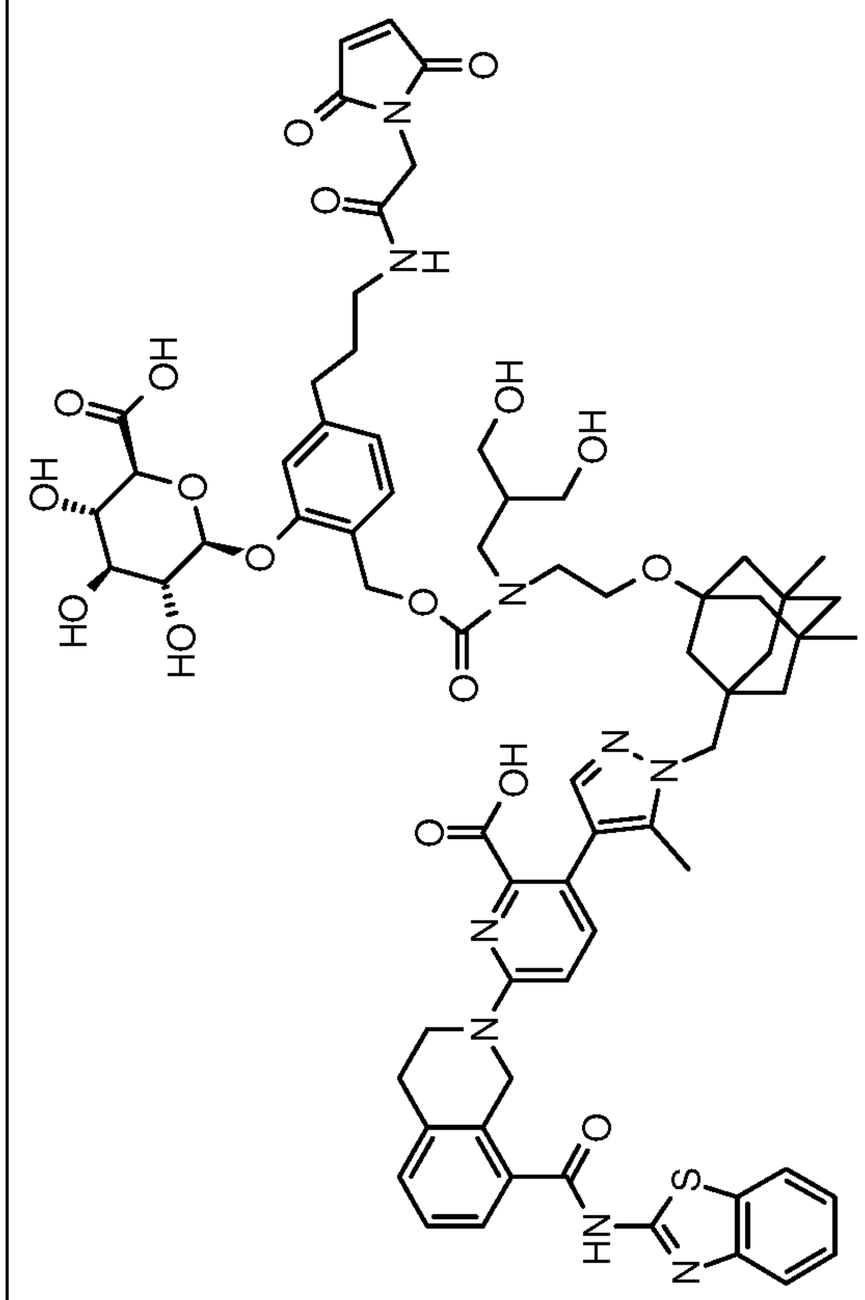
Example No.	Synthon Code	Synthon Structure
2.131	TZ	
2.132	UA	

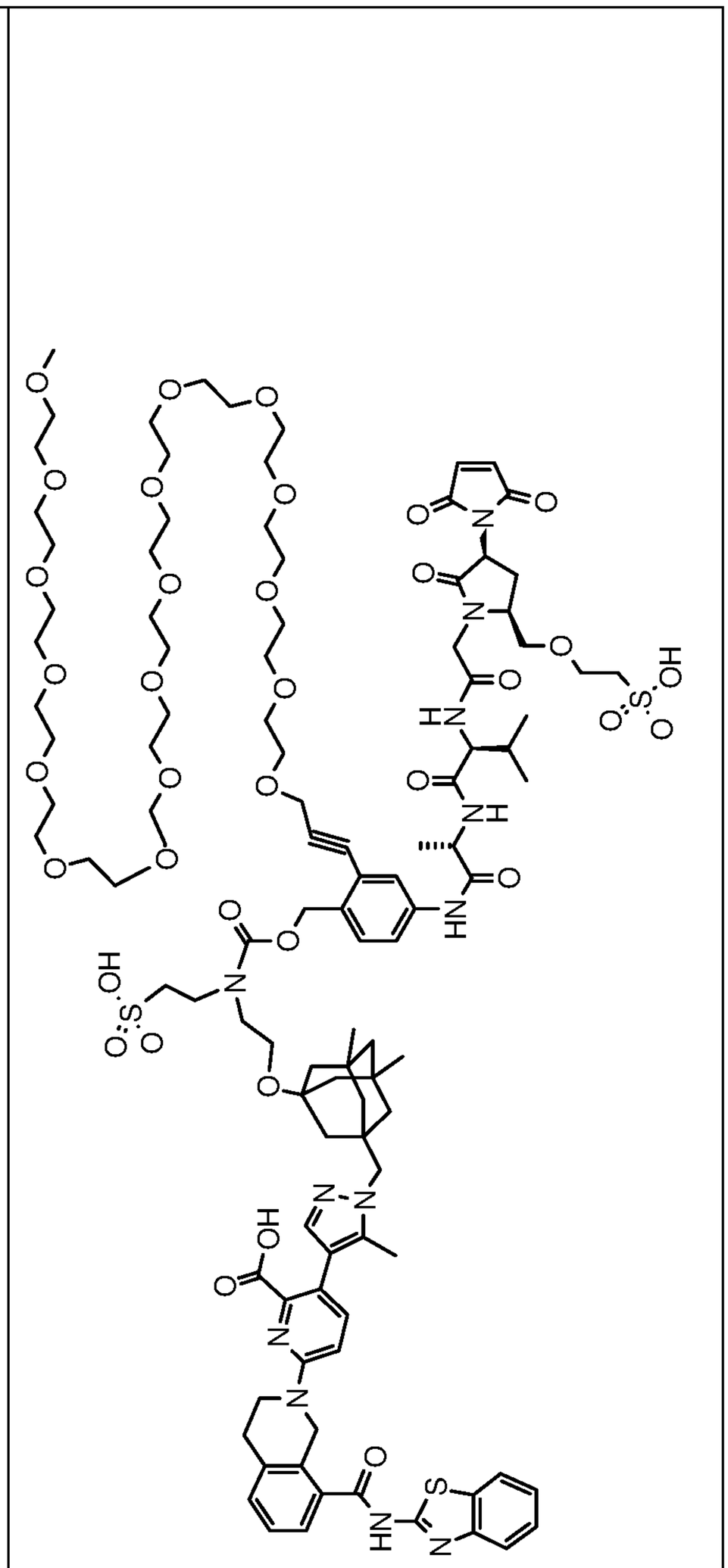
Example No.	Synthon Code	Synthon Structure
2.133	UJ	
2.134	UK	

Example No.	Synthon Code	Synthon Structure
2.135	UU	

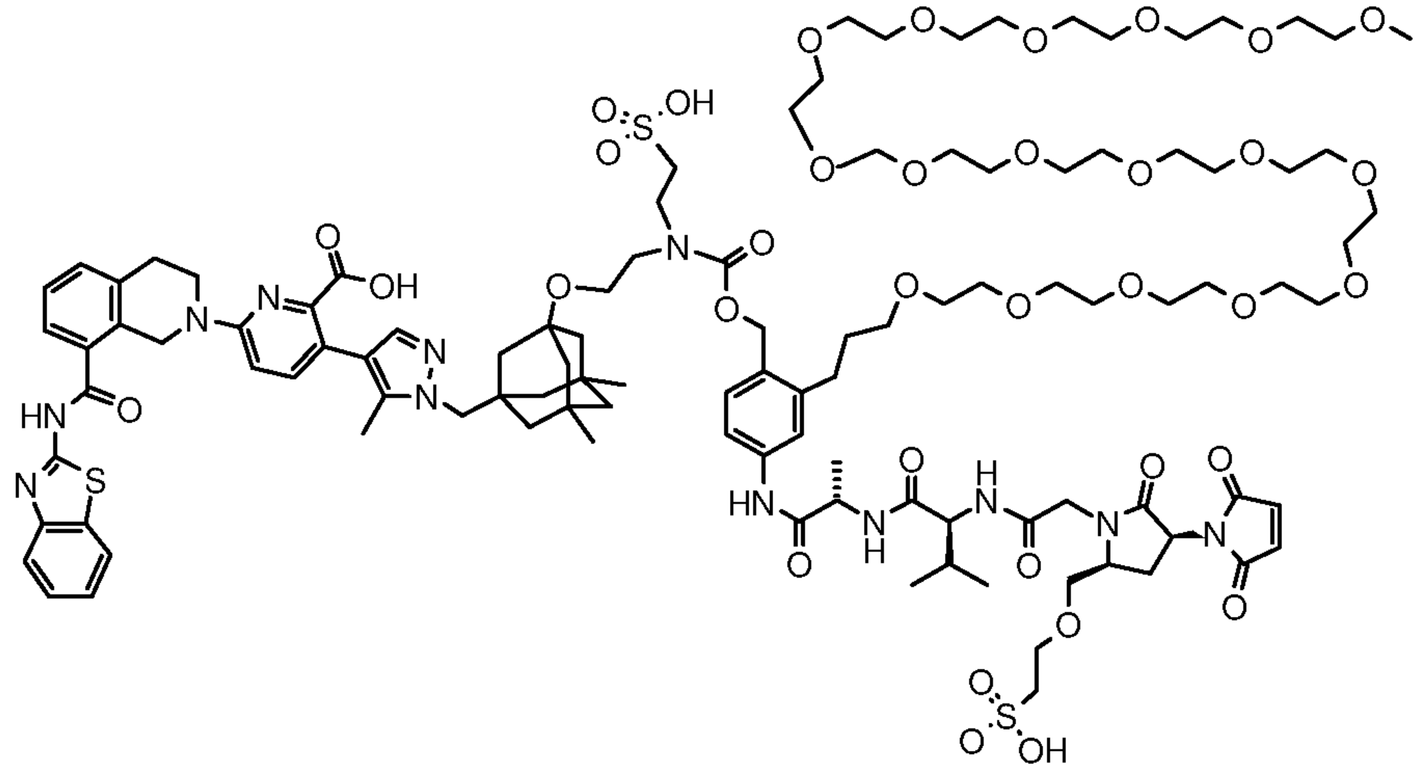
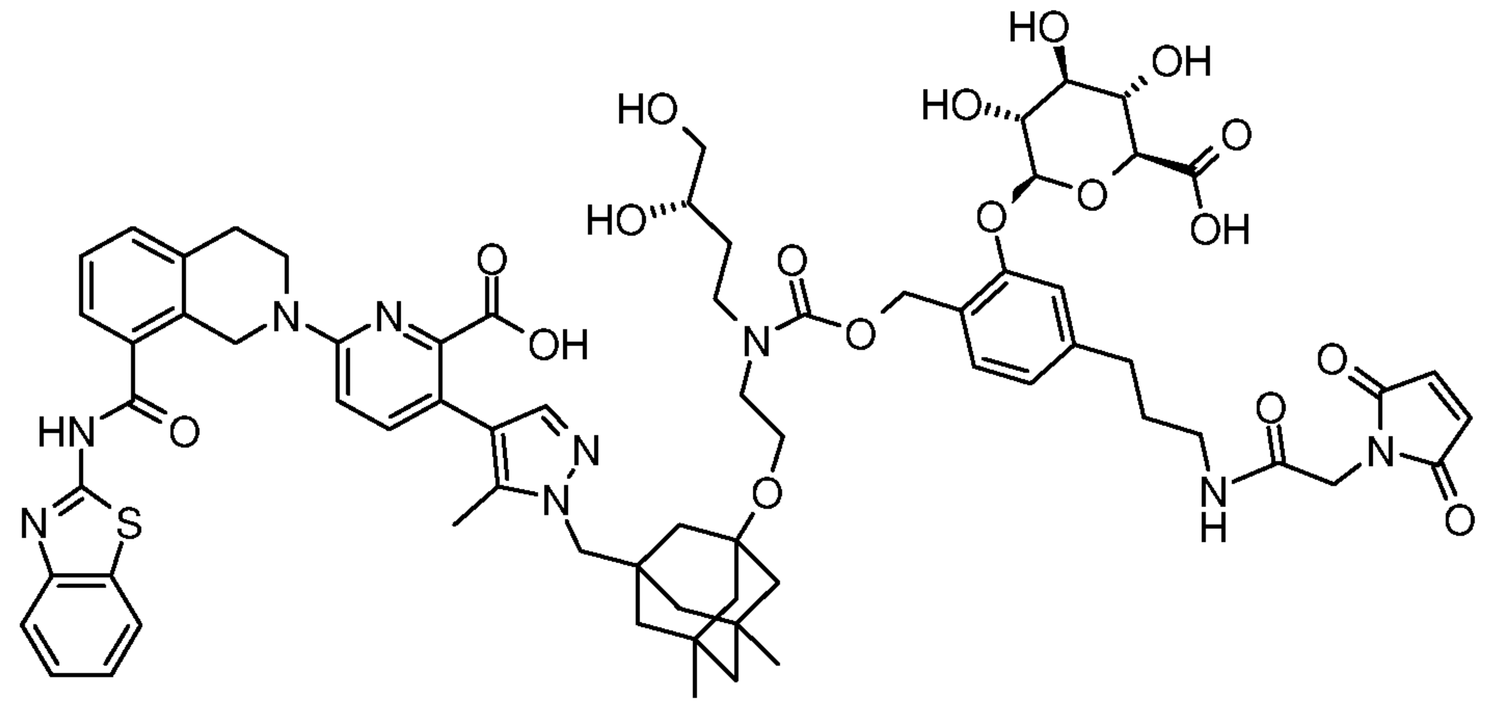
Example No.	Synthon Code	Synthon Structure
2.136	UV	

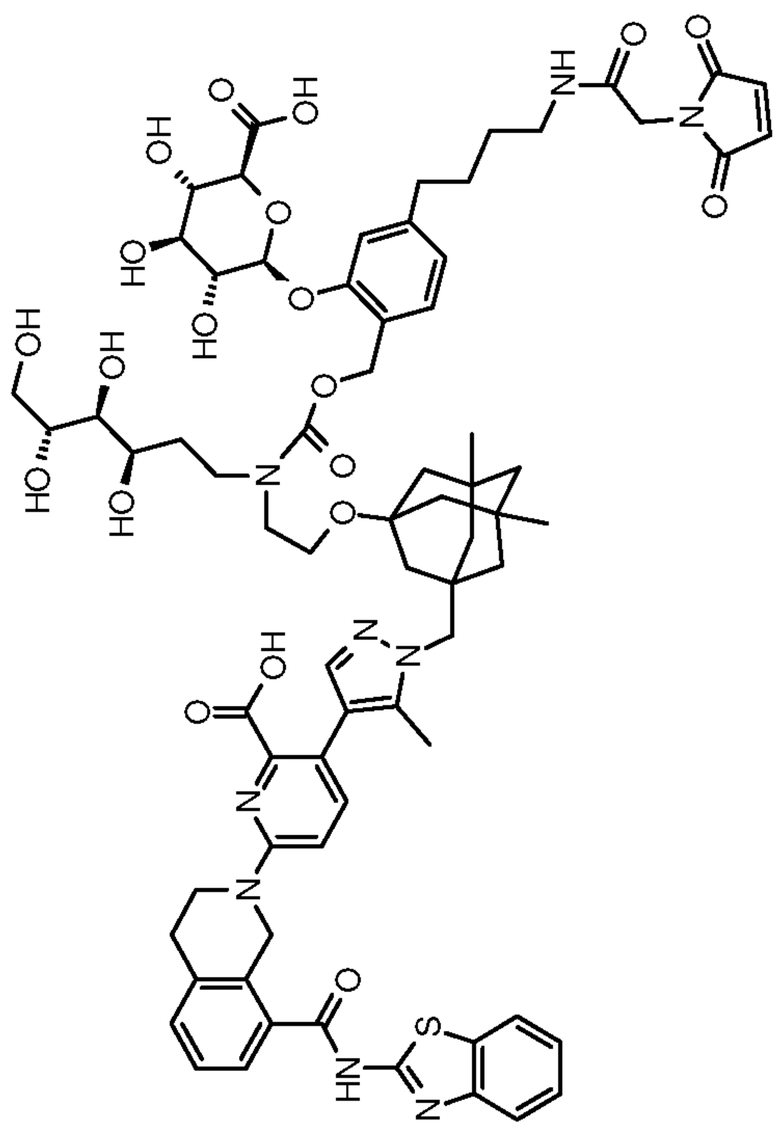
Example No.	Synthon Code	Synthon Structure
2.137	UZ	
2.138	VB	

Example No.	Synthon Code	Synthon Structure
2.139	VC	

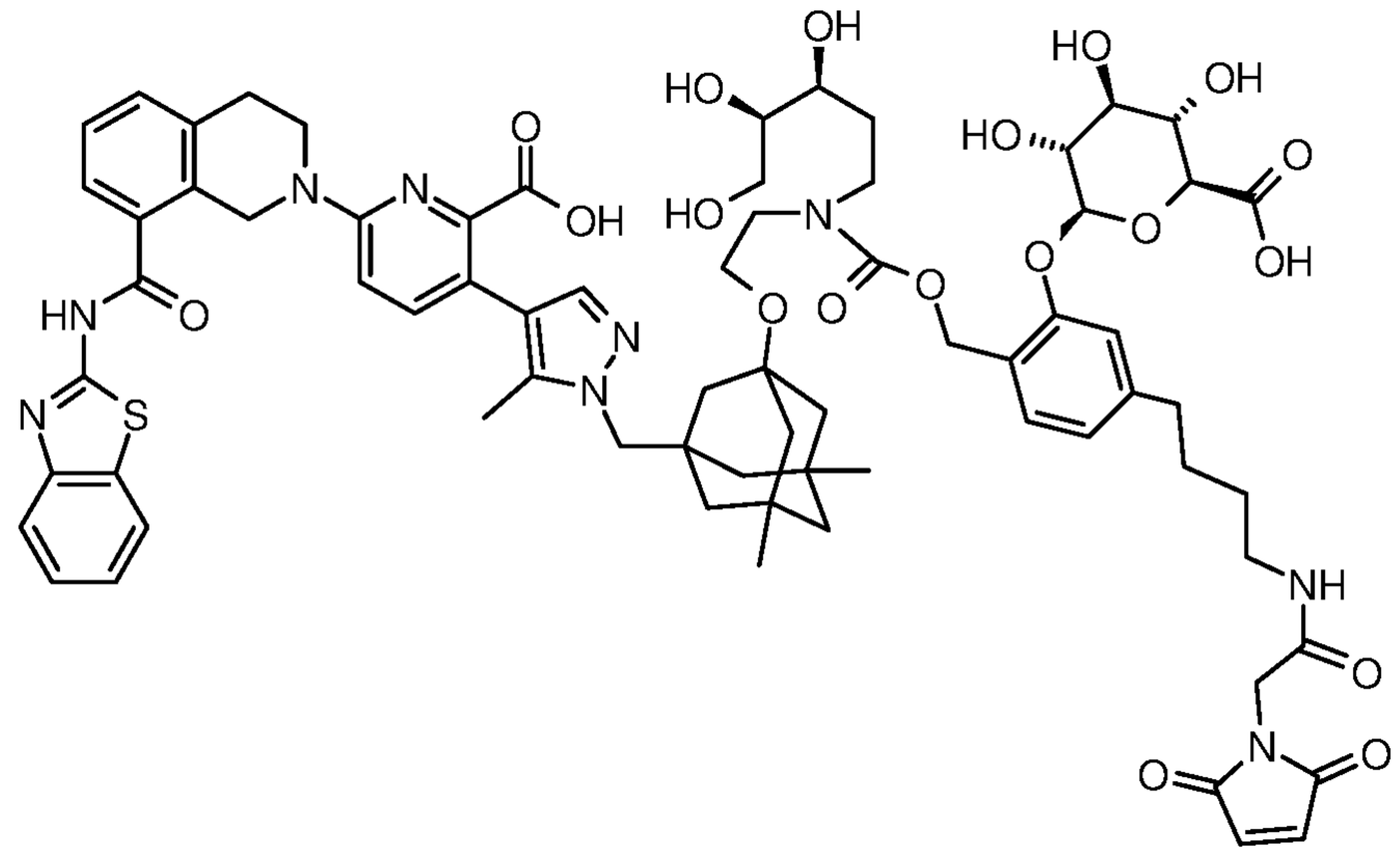
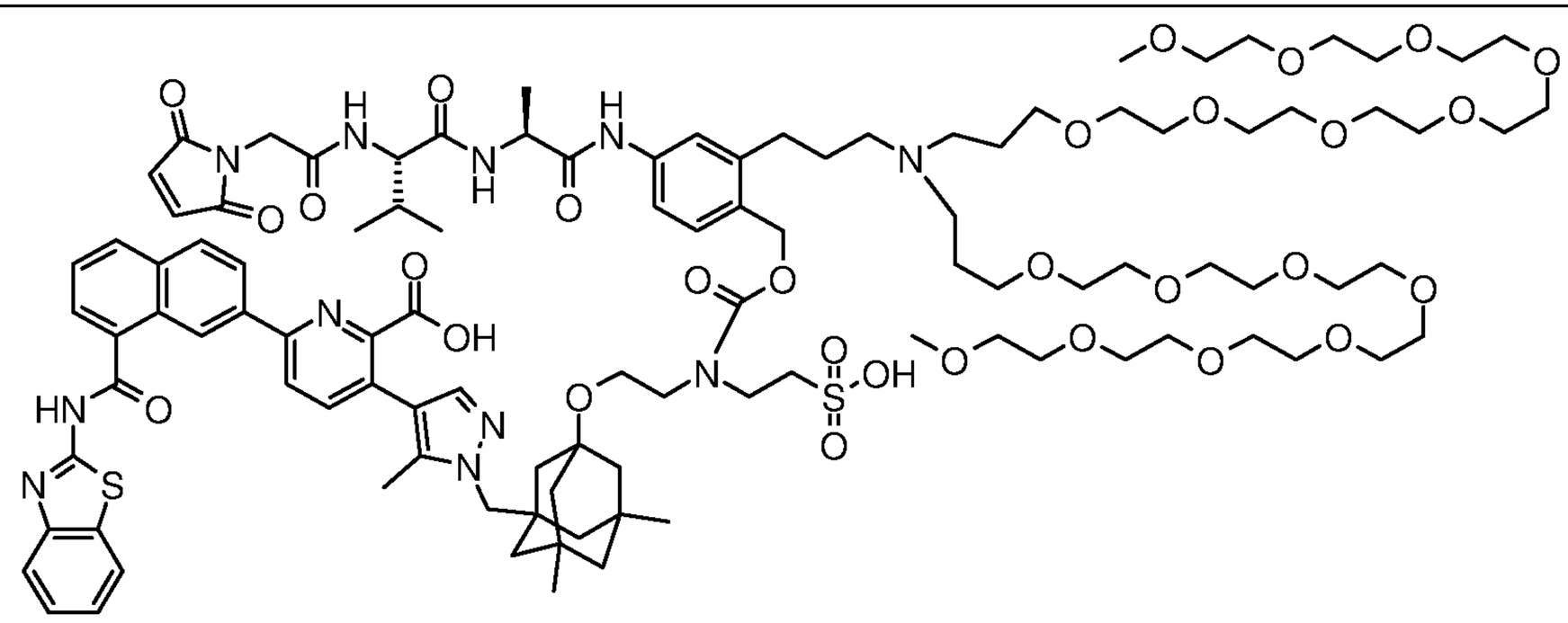
Example No.	Synthon Code	Synthon Structure
2.140	VS	

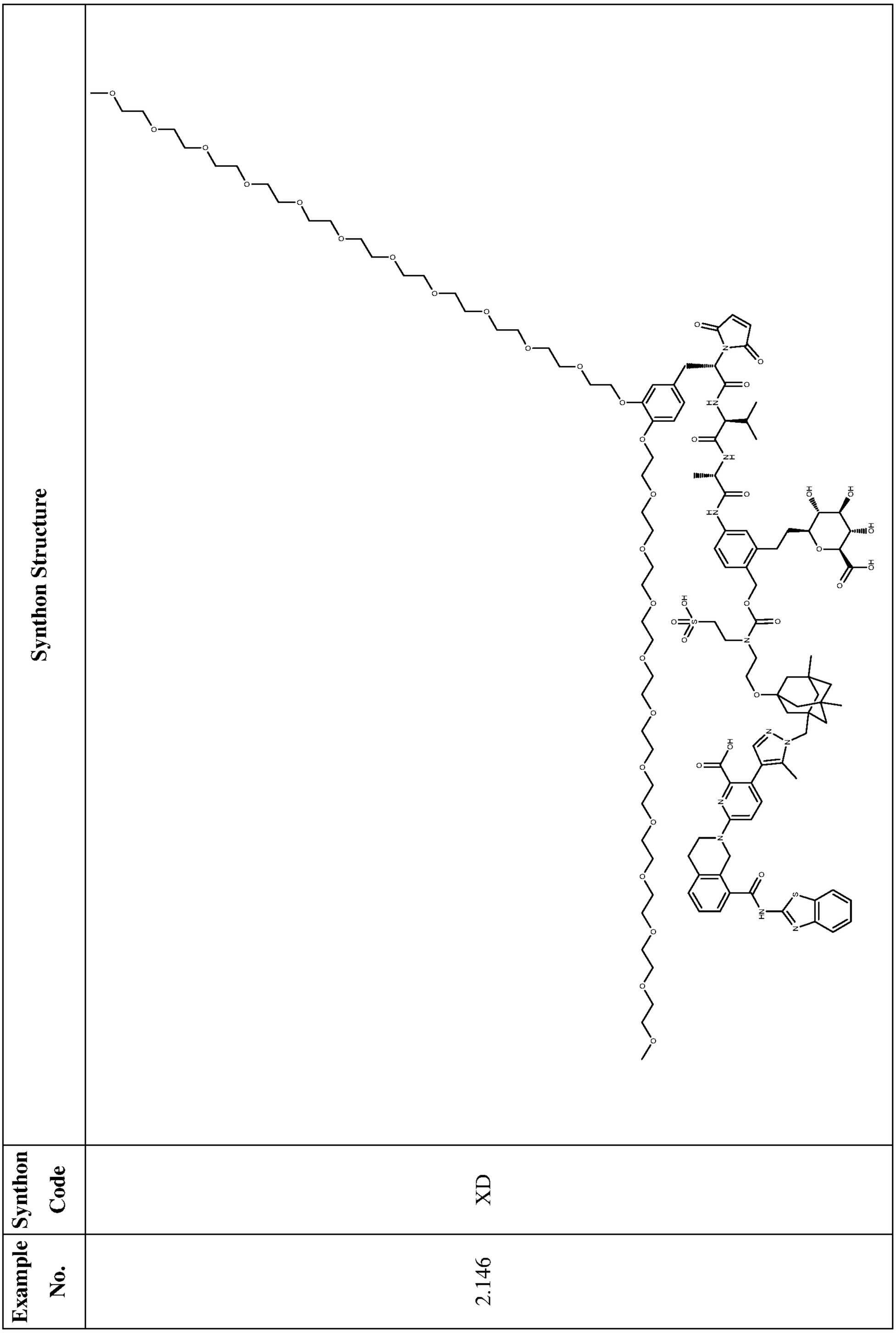
CA 03027045 2018-12-07

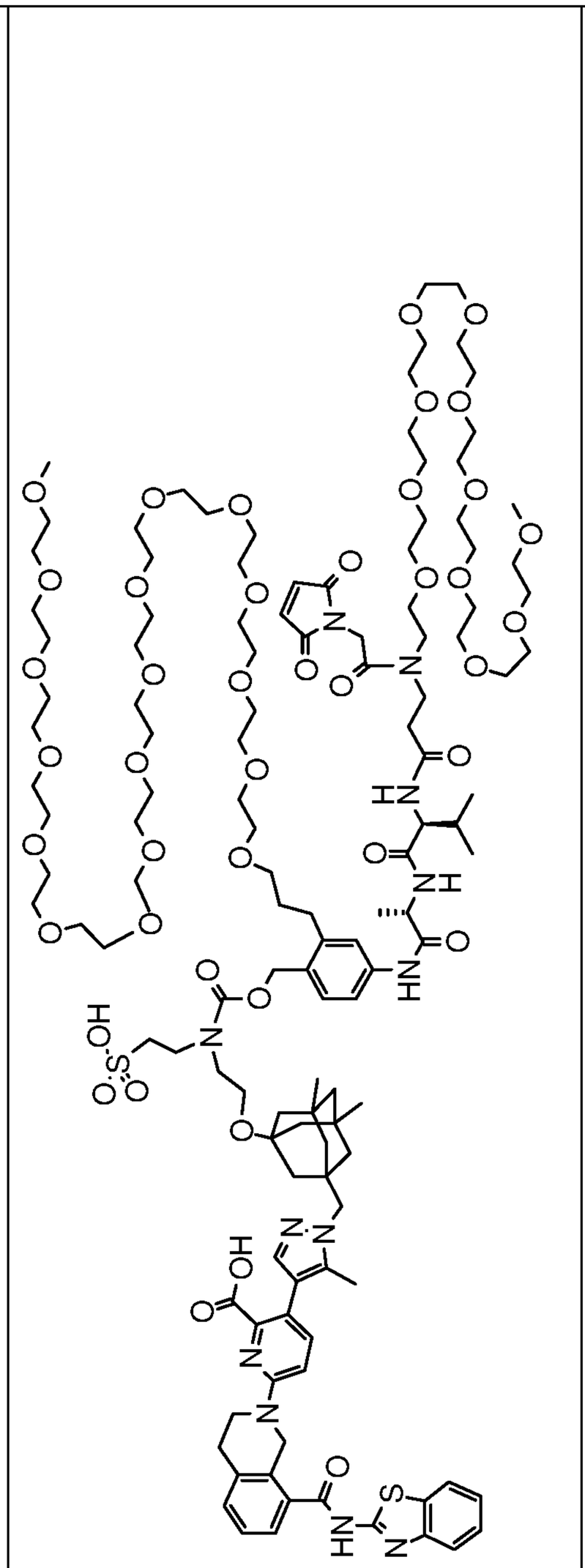
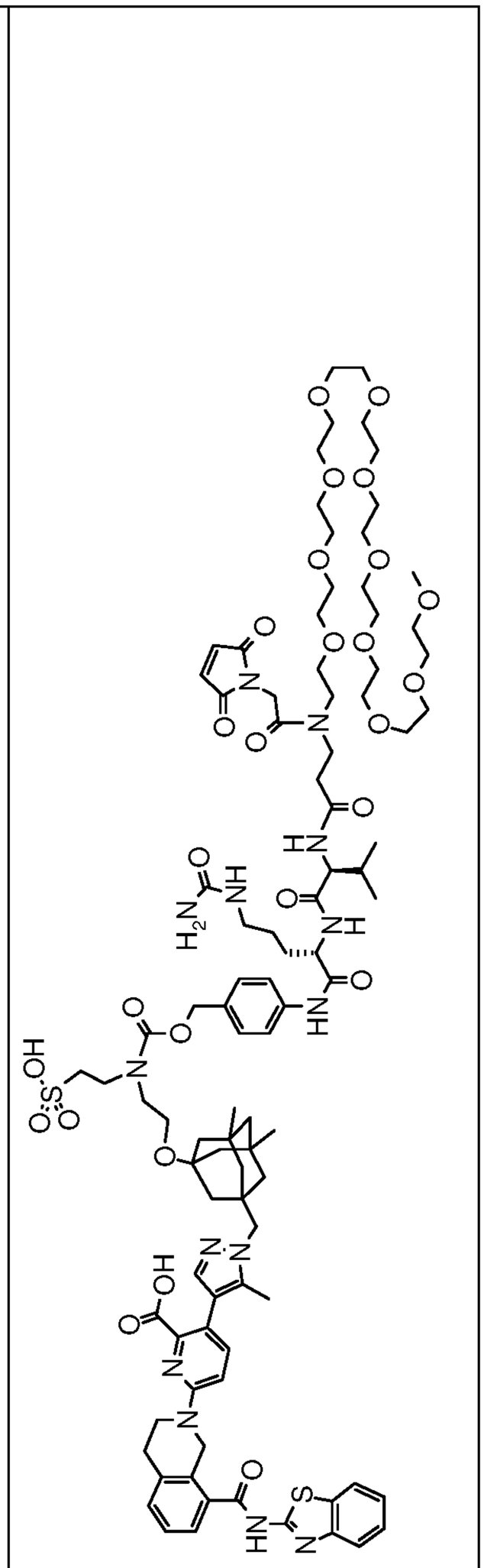
Example No.	Synthon Code	Synthon Structure
2.141	VT	
2.142	VY	

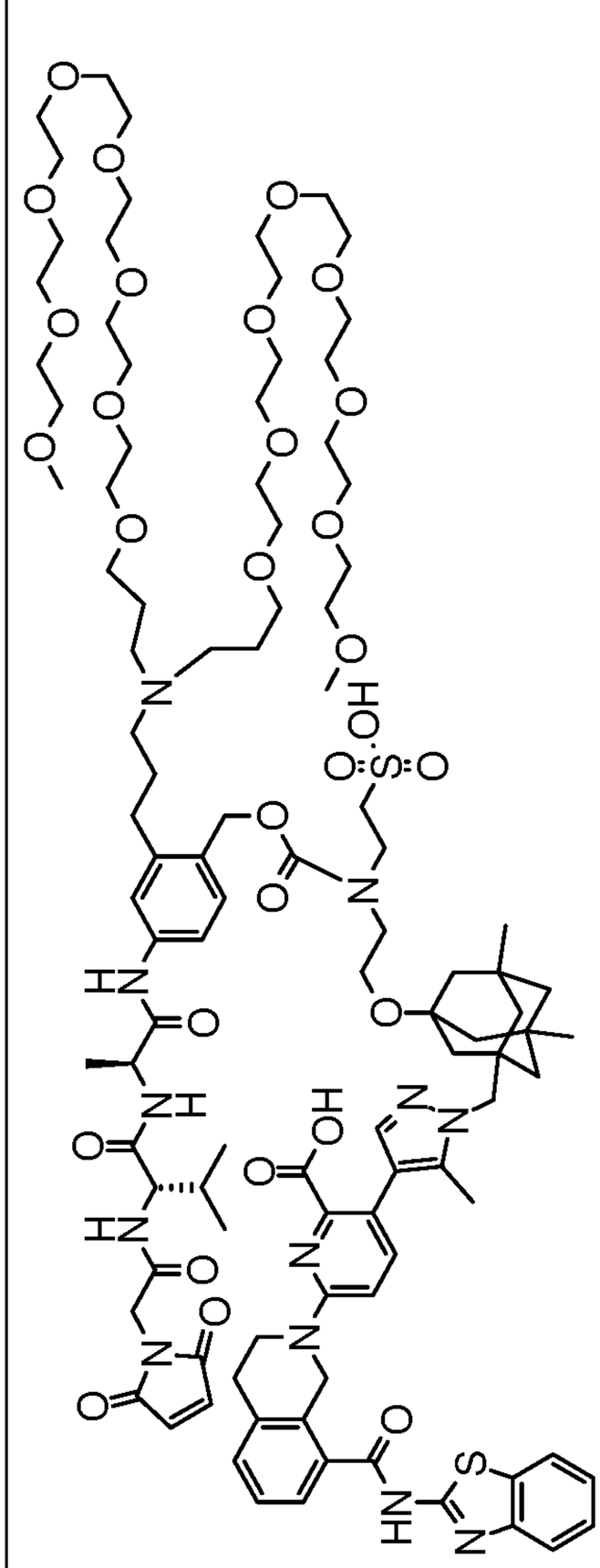
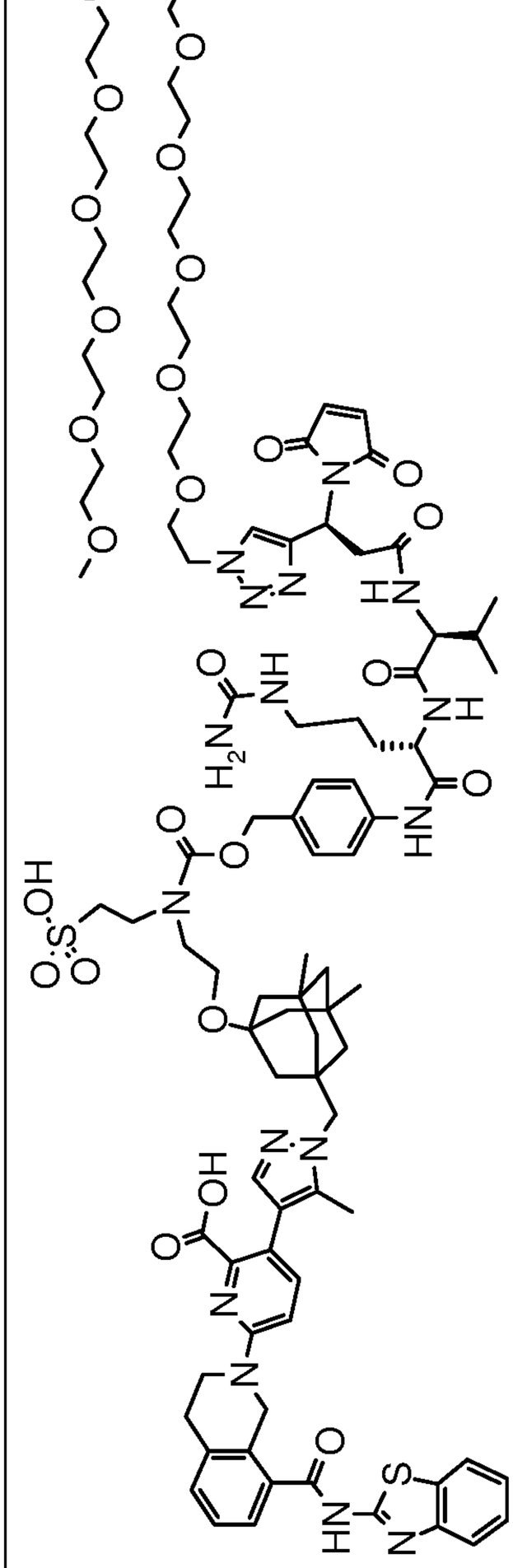
Example No.	Synthon Code	Synthon Structure
2.143	WI	

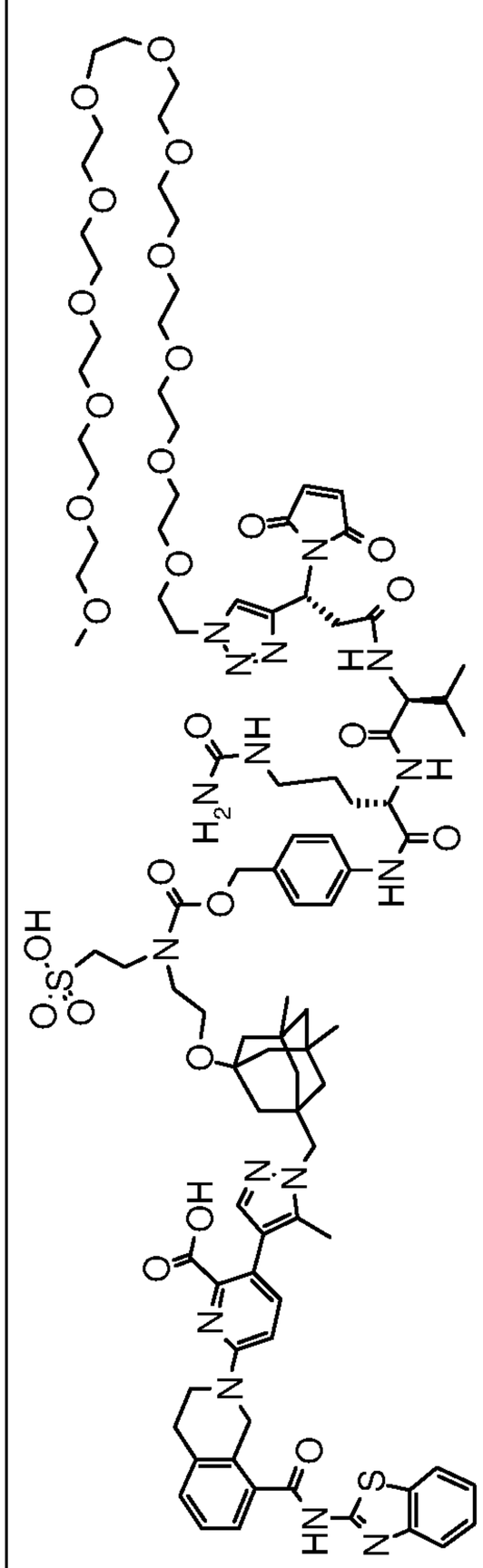
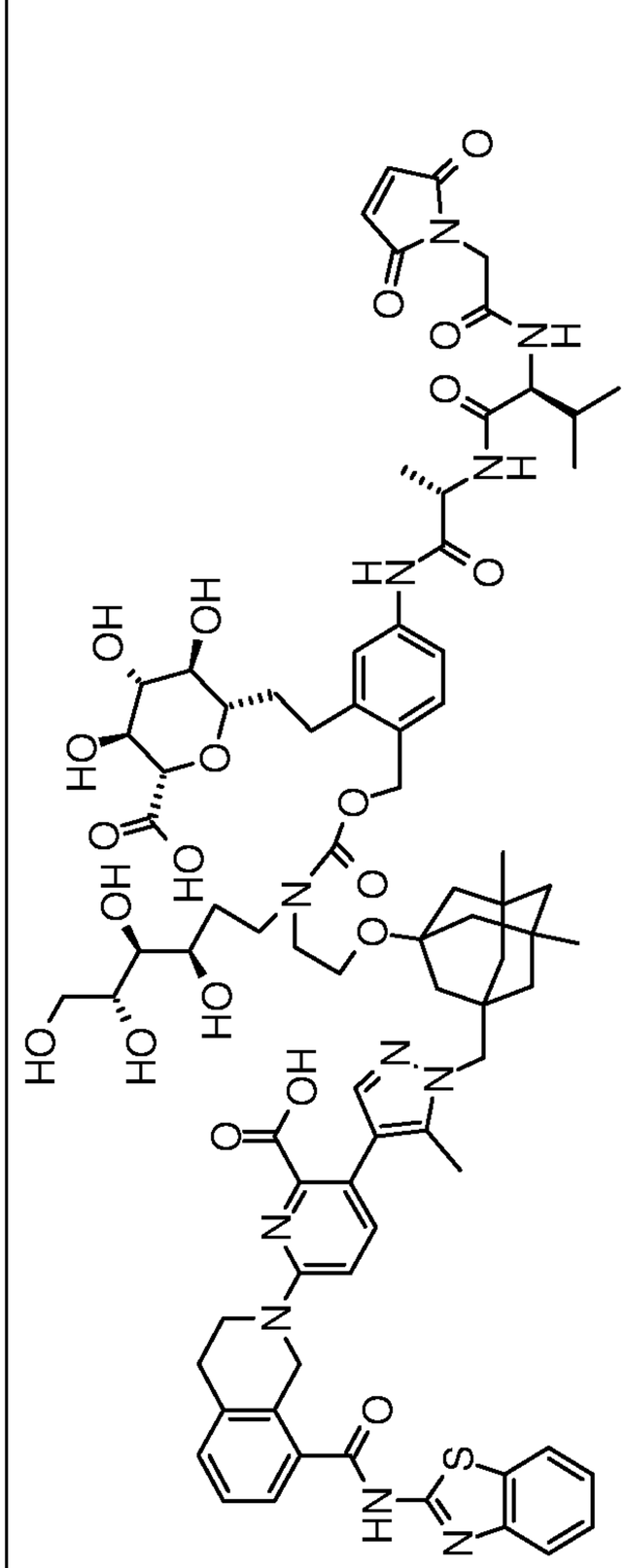
CA 03027045 2018-12-07

Example No.	Synthon Code	Synthon Structure
2.144	WK	
2.145	WP	

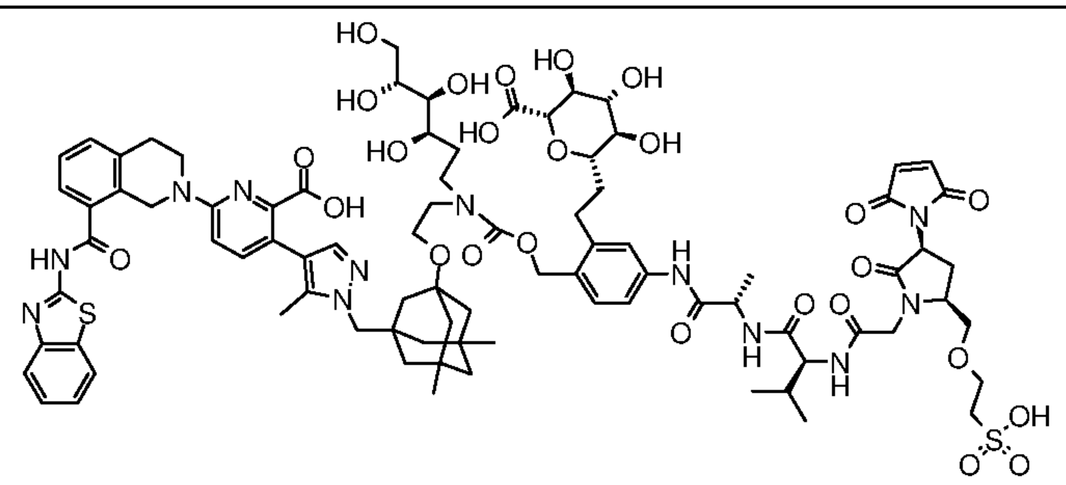
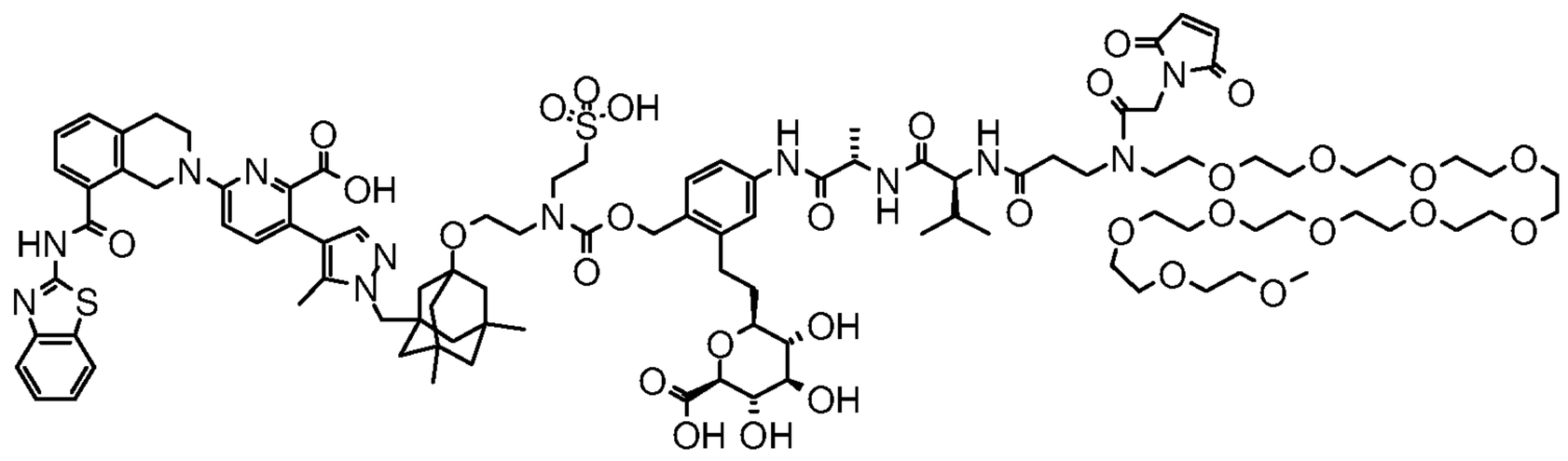
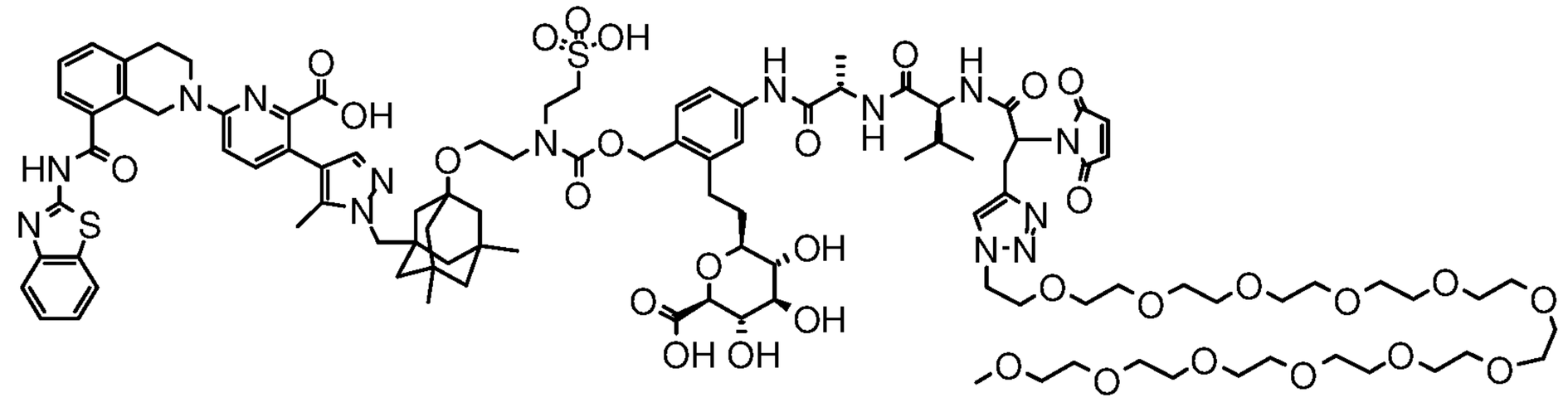
Example No.	Synthon Code	Synthon Structure
2.146	XD	

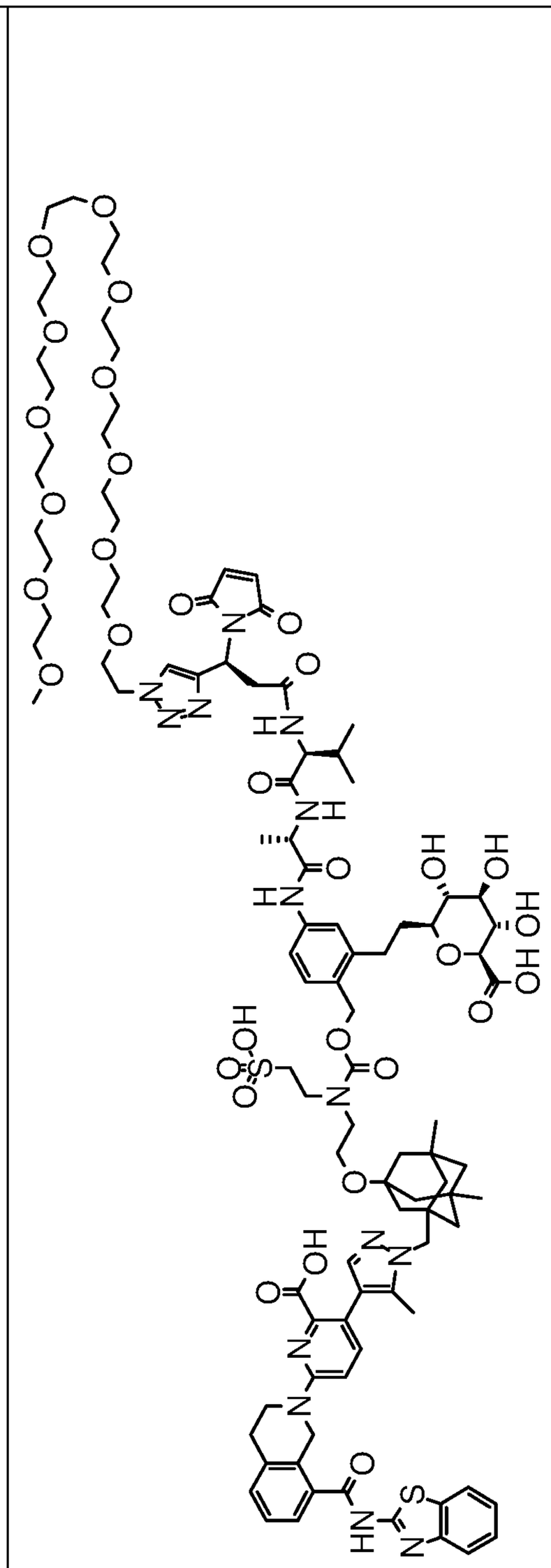
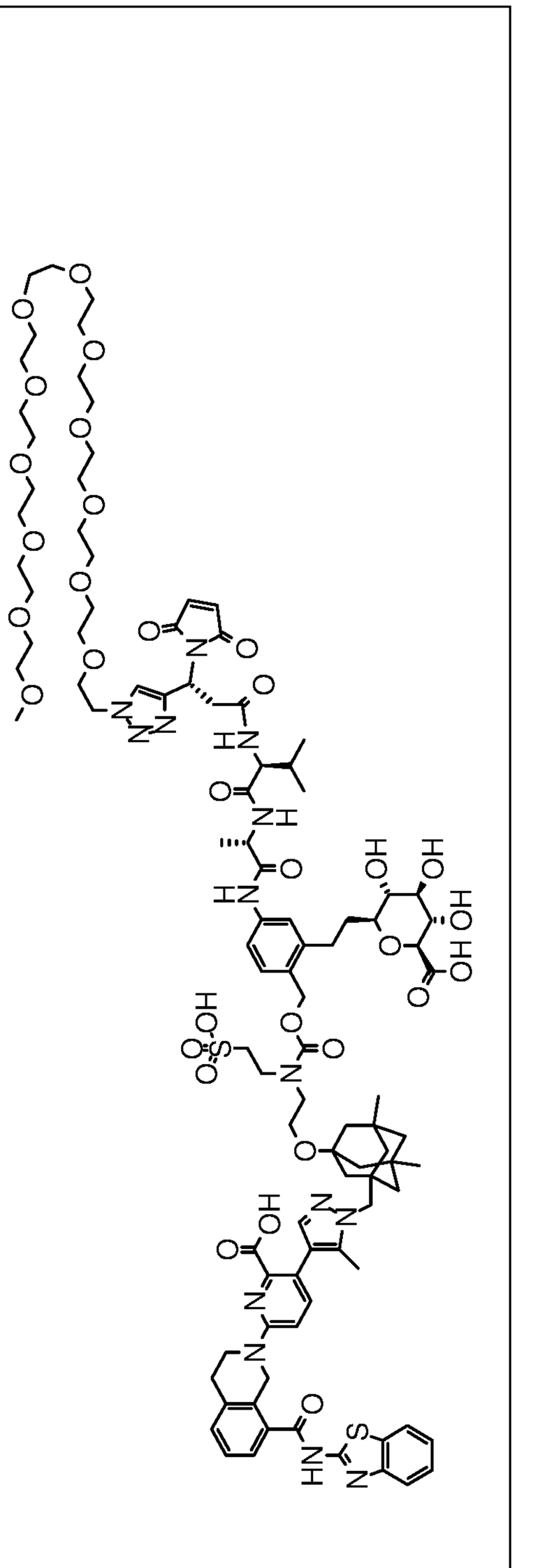
Example No.	Synthon Code	Synthon Structure
2.147	XK	
2.148	XL	

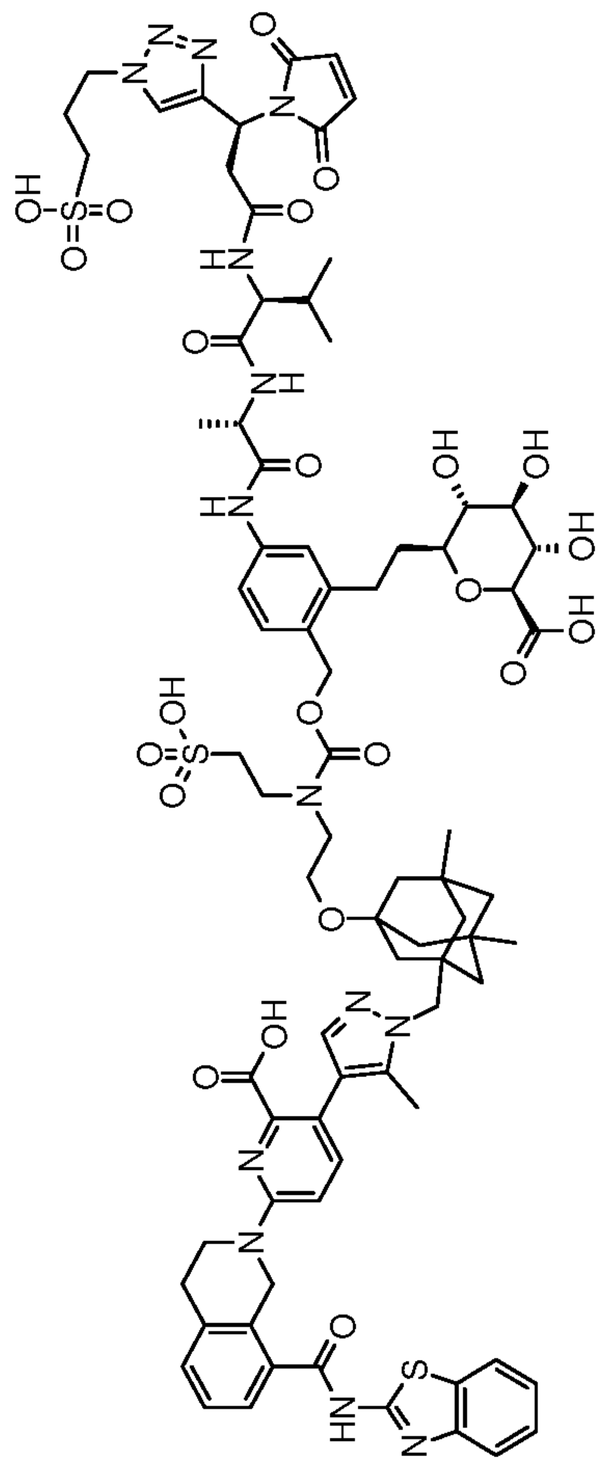
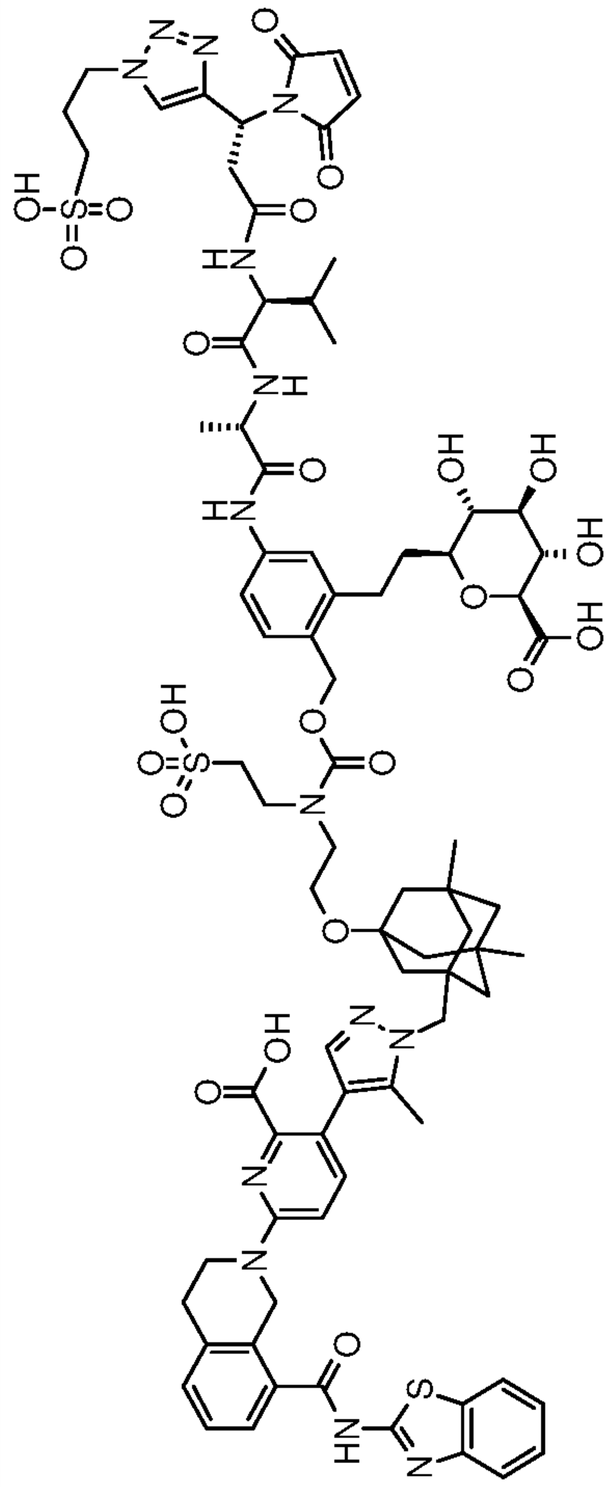
Example No.	Synthon Code	Synthon Structure
2.149	YJ	
2.150	YQ	

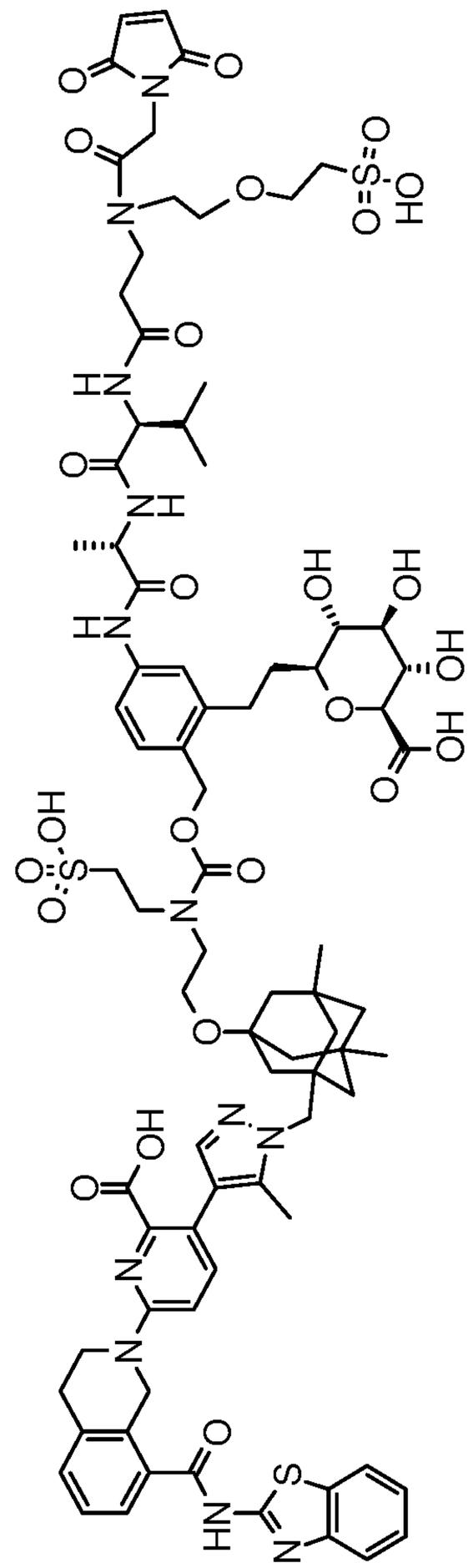
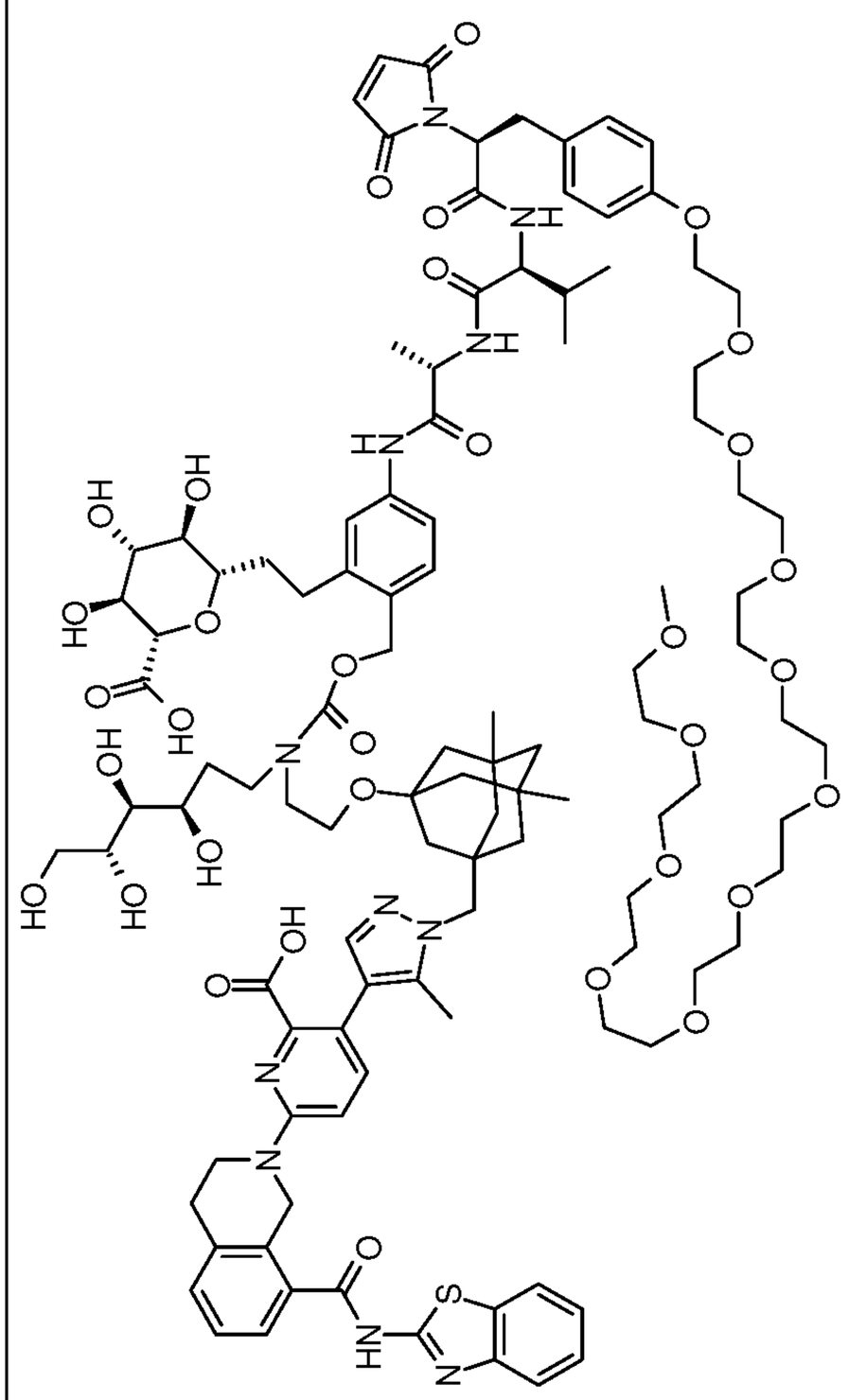
Example No.	Synthon Code	Synthon Structure
2.151	YR	
2.152	YS	

CA 03027045 2018-12-07

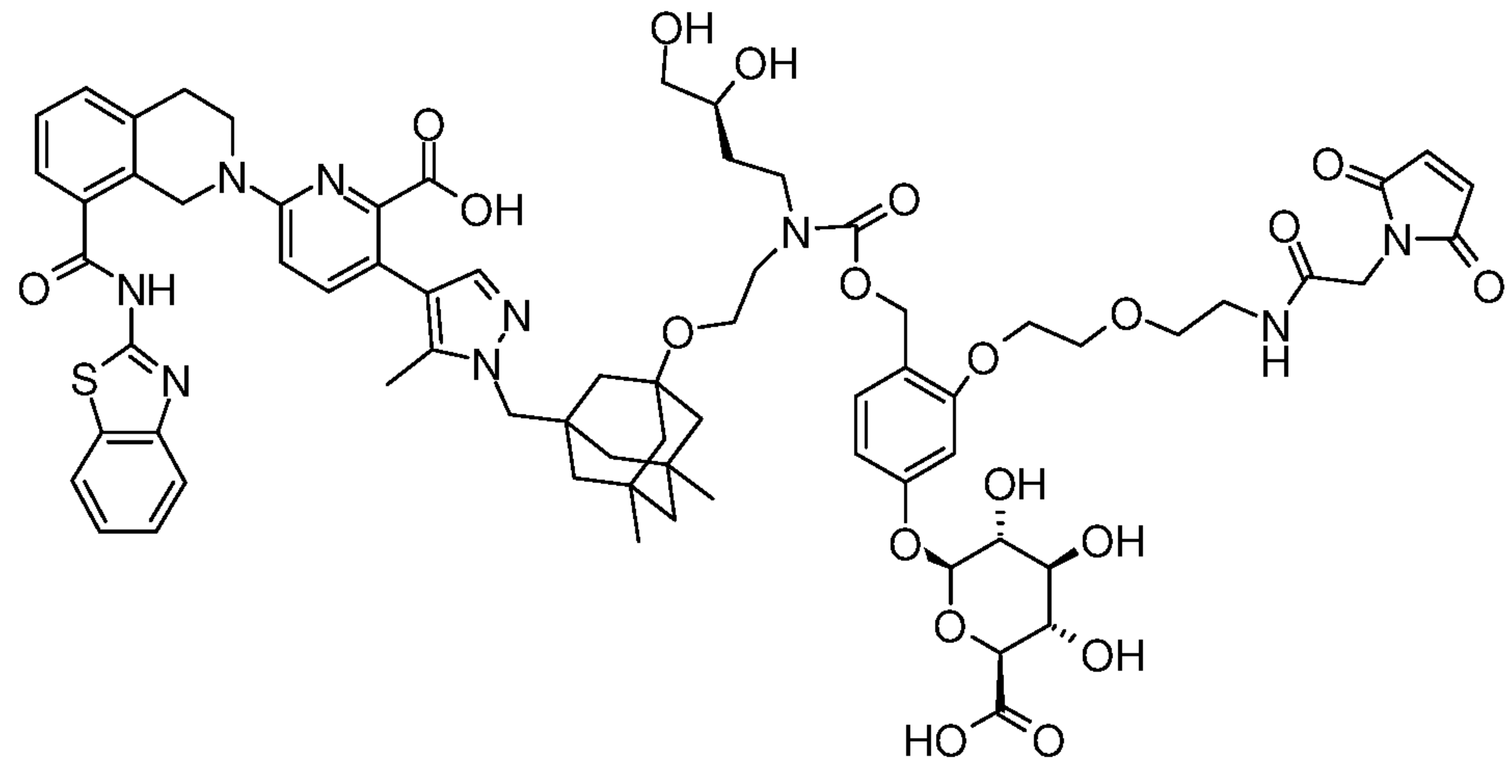
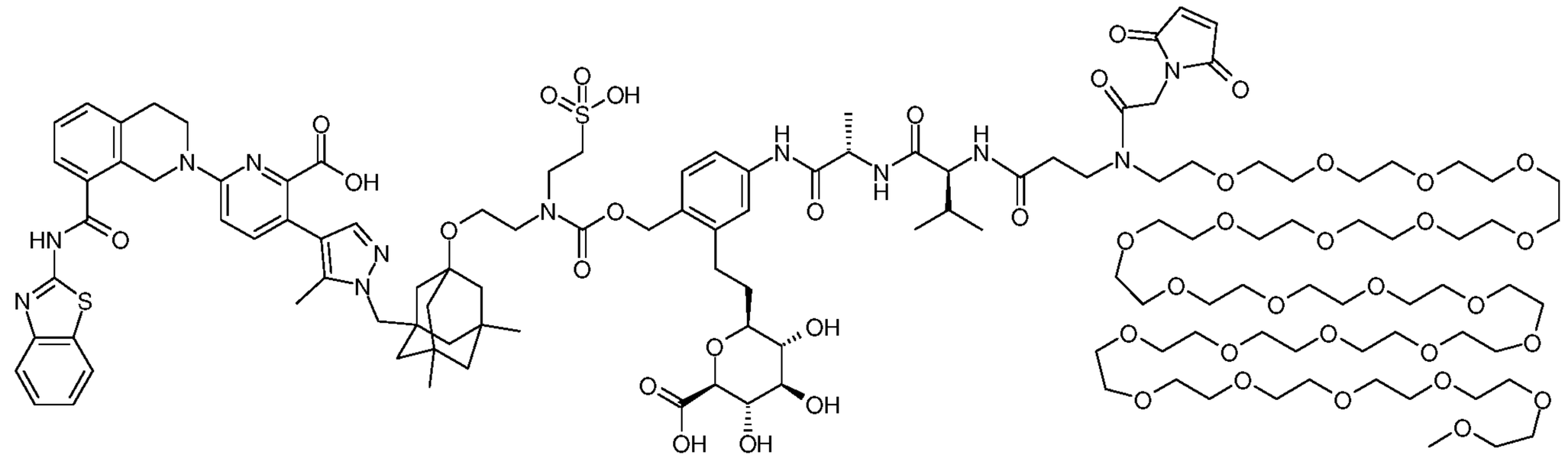
Example No.	Synthon Code	Synthon Structure
2.153	YY	
2.154	YT	
2.155	YU	

Example No.	Synthon Code	Synthon Structure
2.156	YV	
2.157	YW	

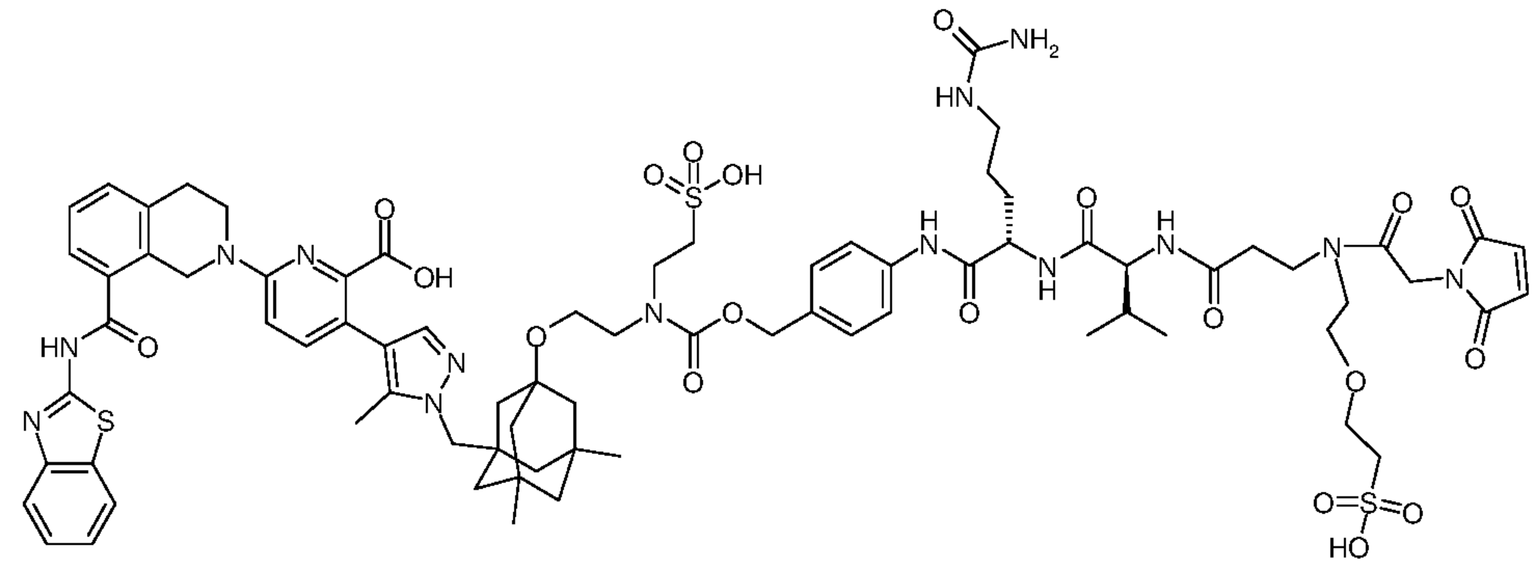
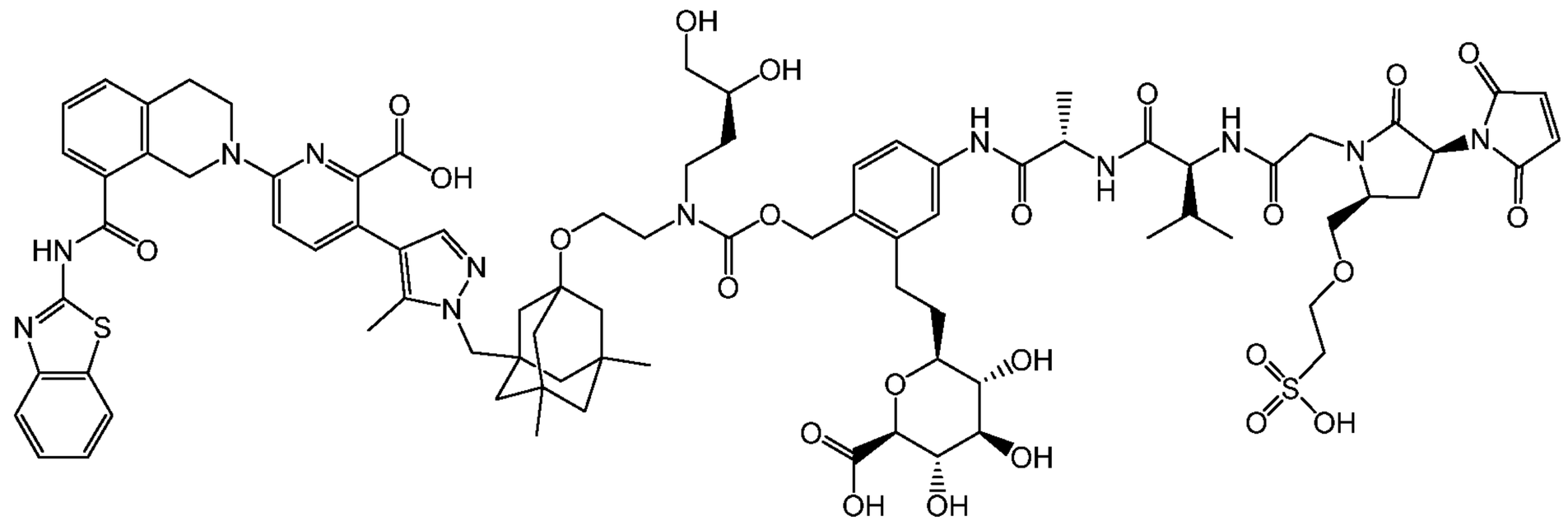
Example No.	Synthon Code	Synthon Structure
2.158	ZB	
2.159	ZC	

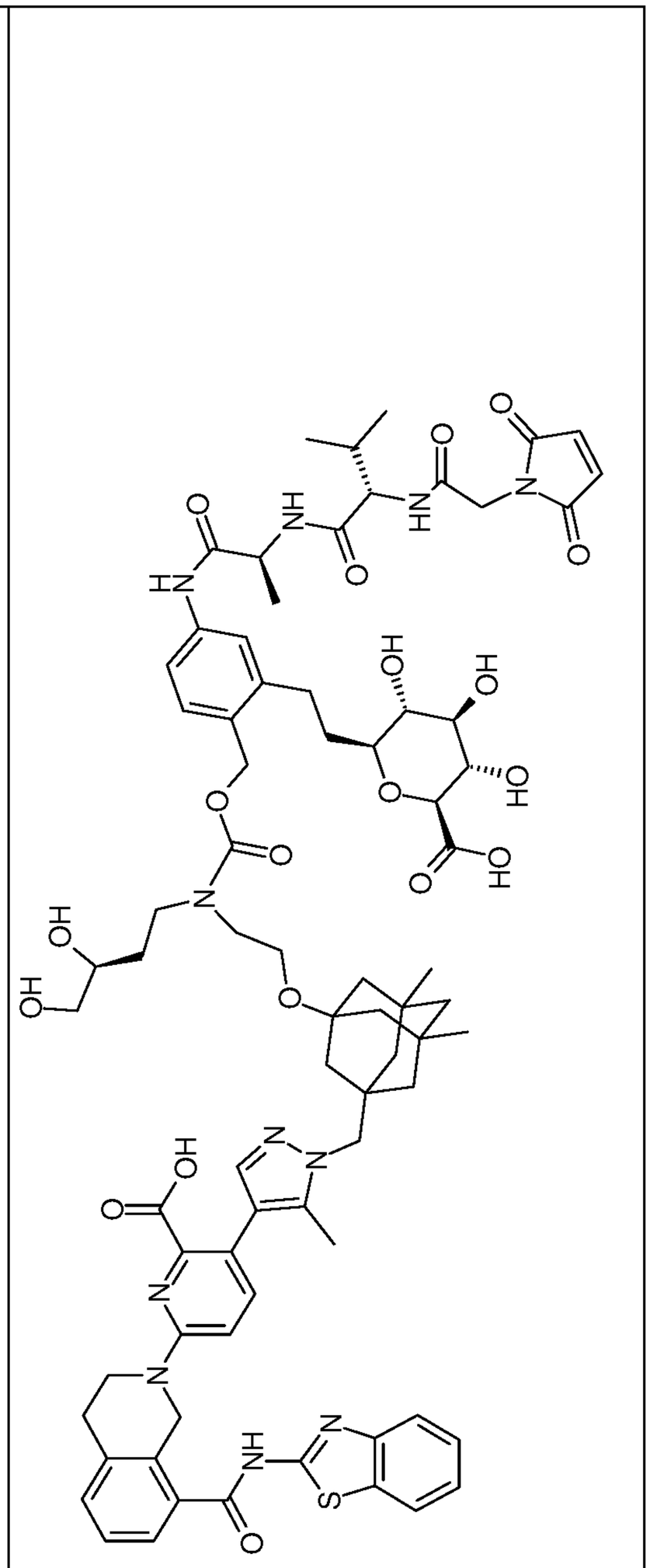
Example No.	Synthon Code	Synthon Structure
2.160	ZJ	
2.161	ZE	

CA 03027045 2018-12-07

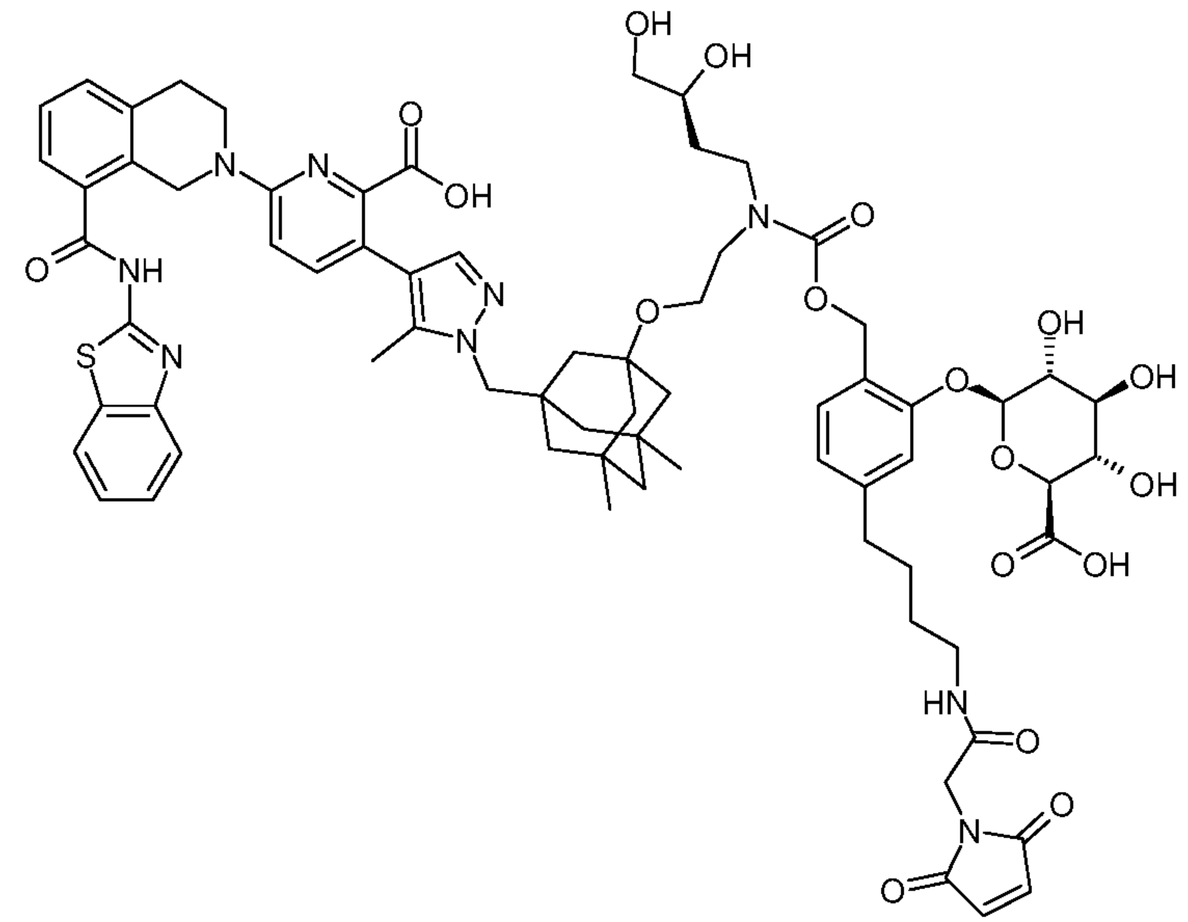
Example No.	Synthon Code	Synthon Structure
2.162	ZS	
2.163	ZW	

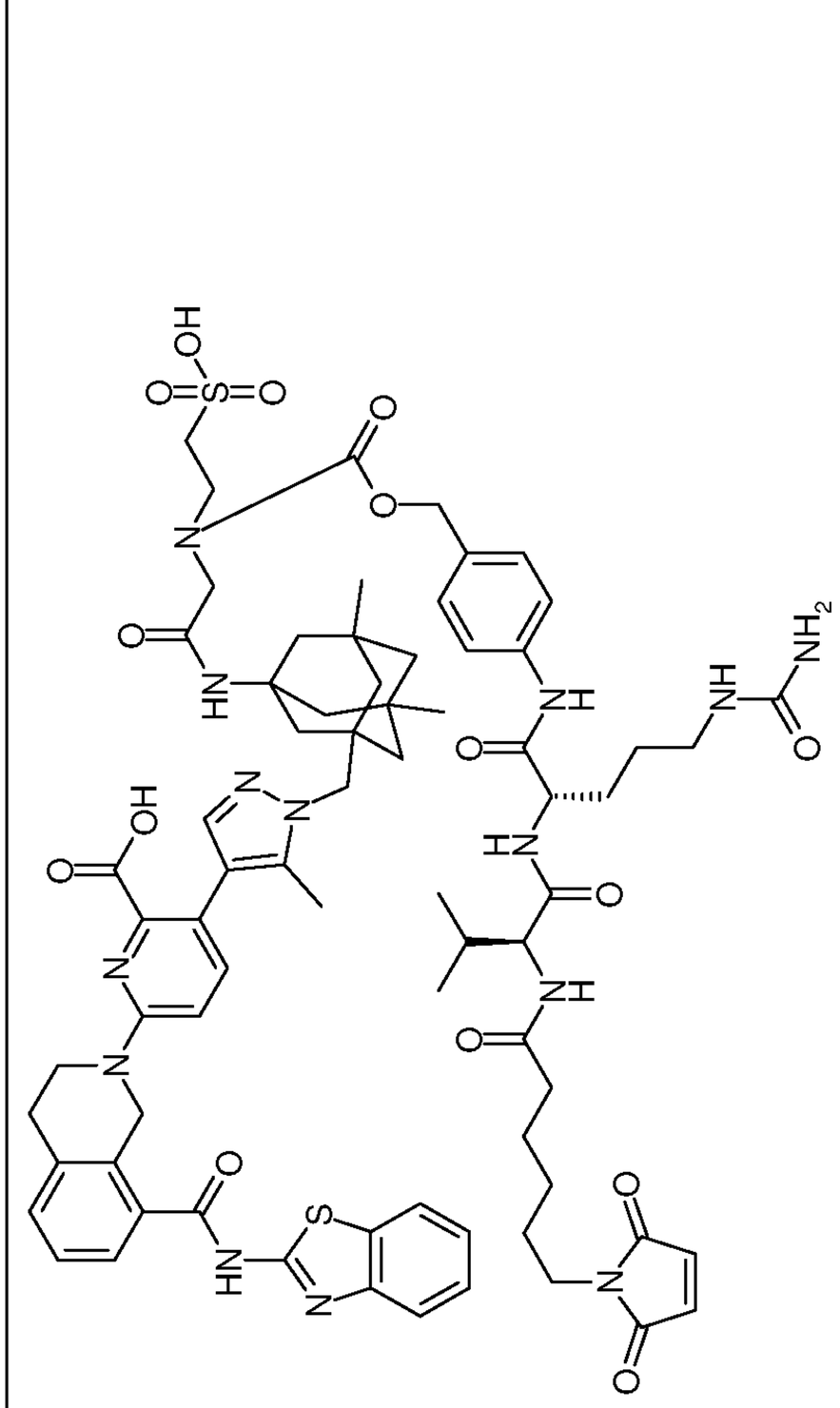
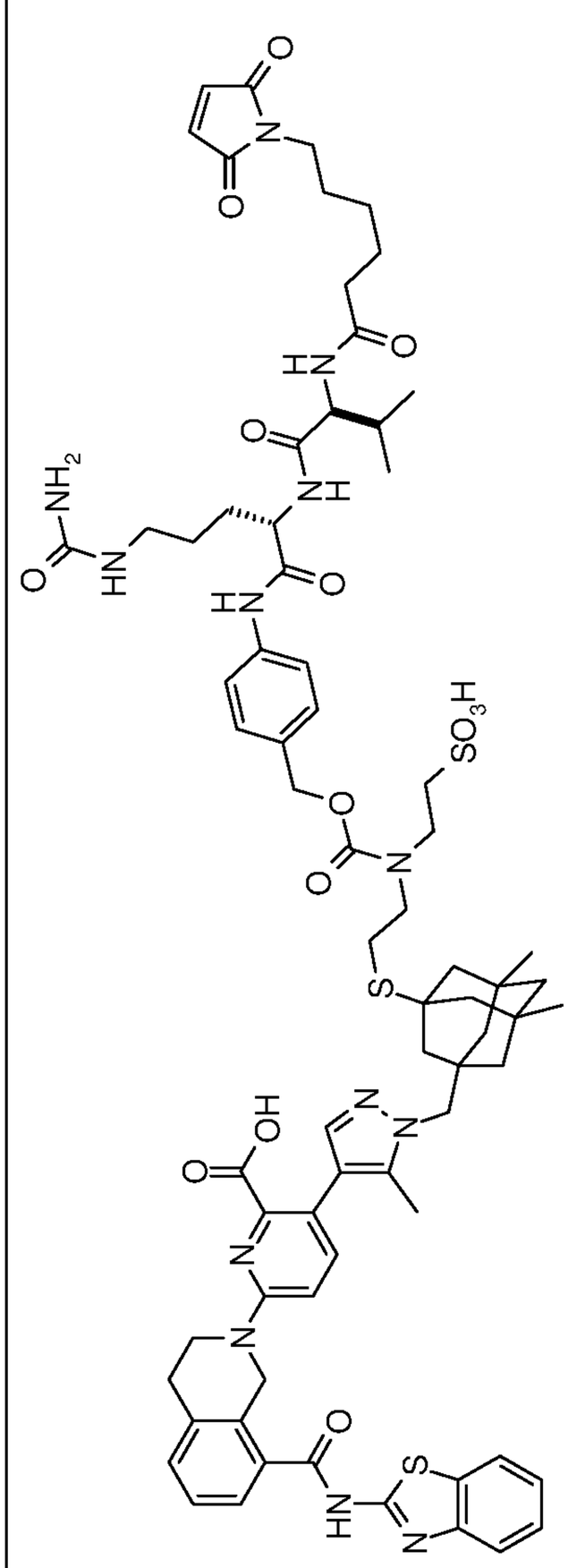
CA 03027045 2018-12-07

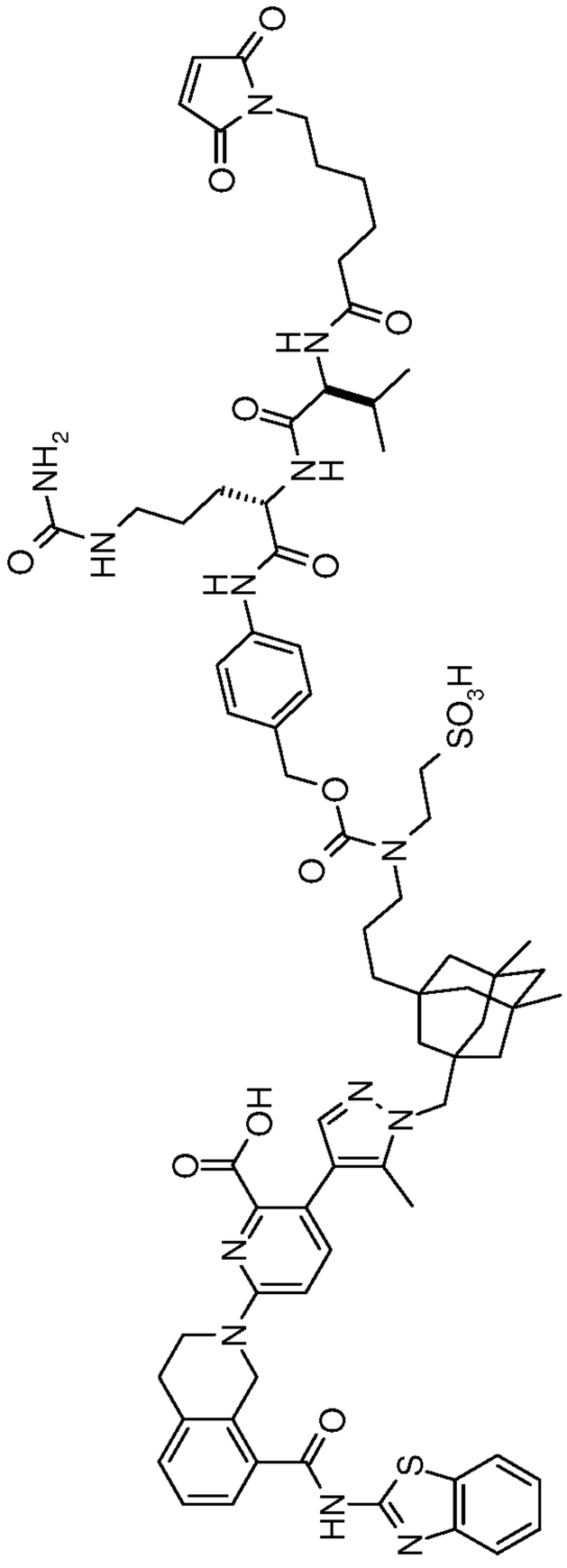
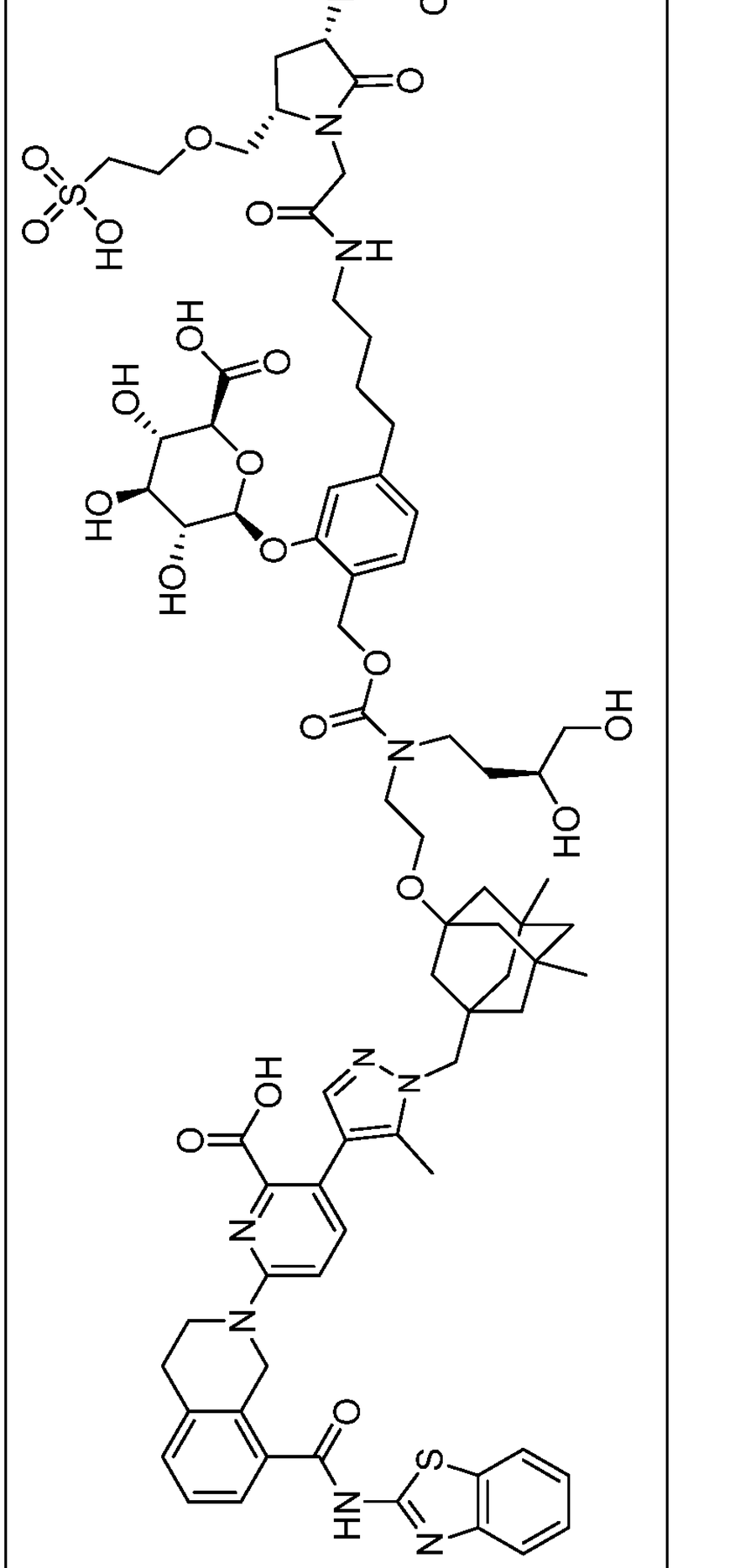
Example No.	Synthon Code	Synthon Structure
2.164	ZX	
2.166	AAA	

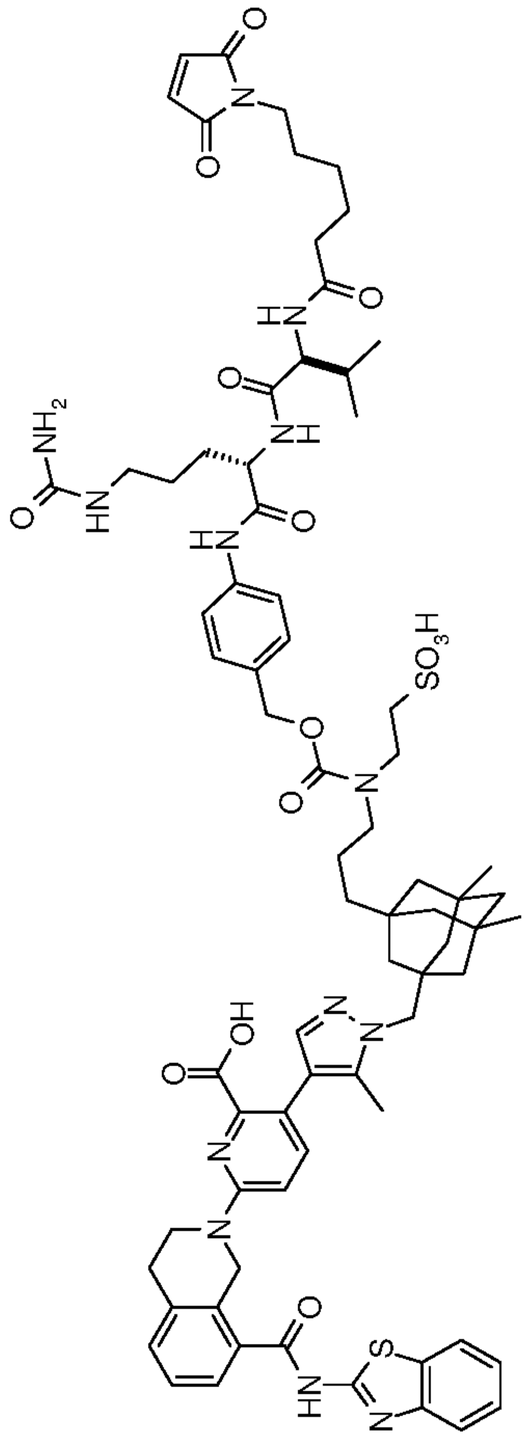
Example No.	Synthon Code	Synthon Structure
2.167	AAD	

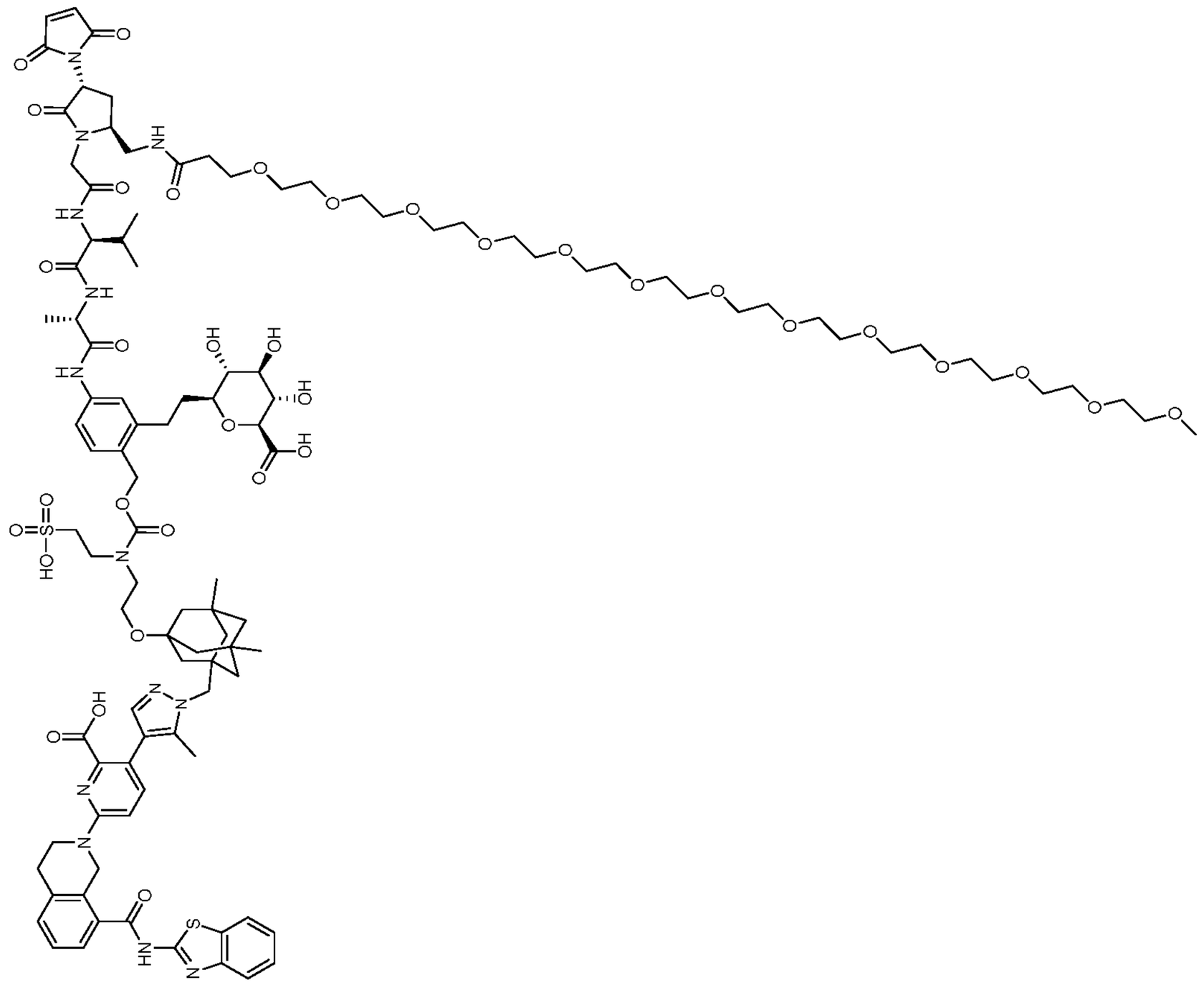
CA 03027045 2018-12-07

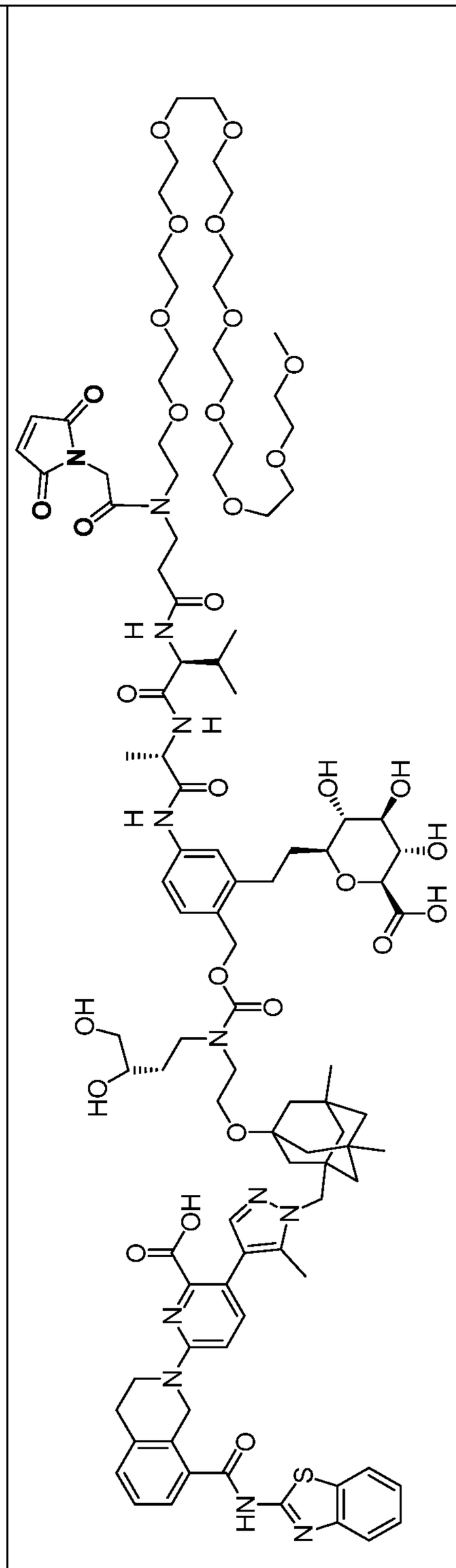
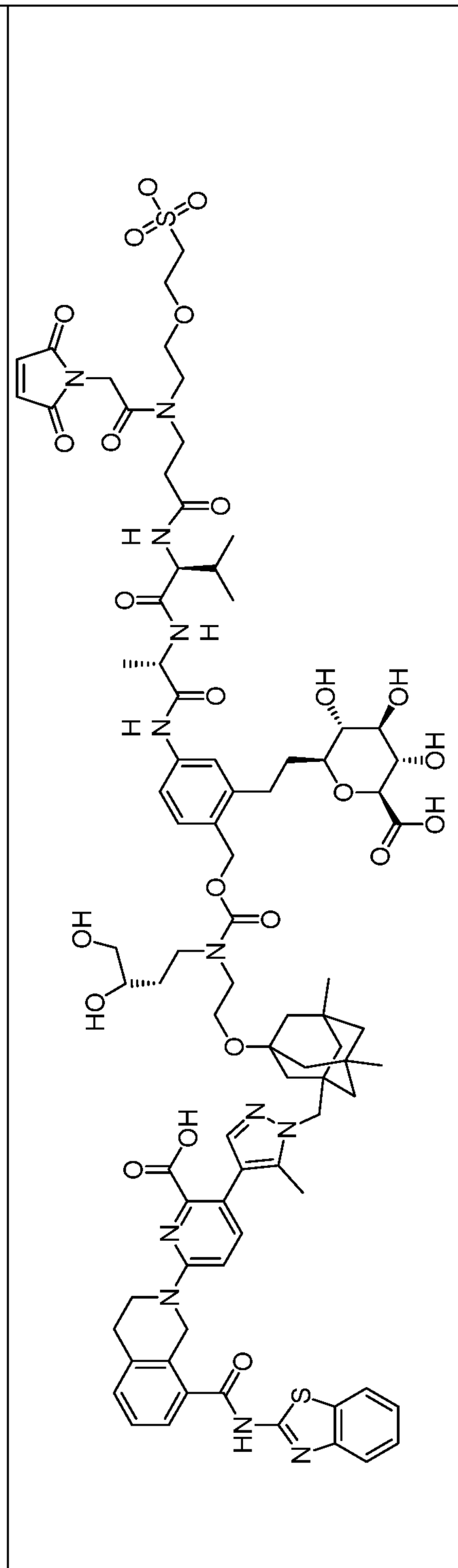
Example No.	Synthon Code	Synthon Structure
2.168	AAE	

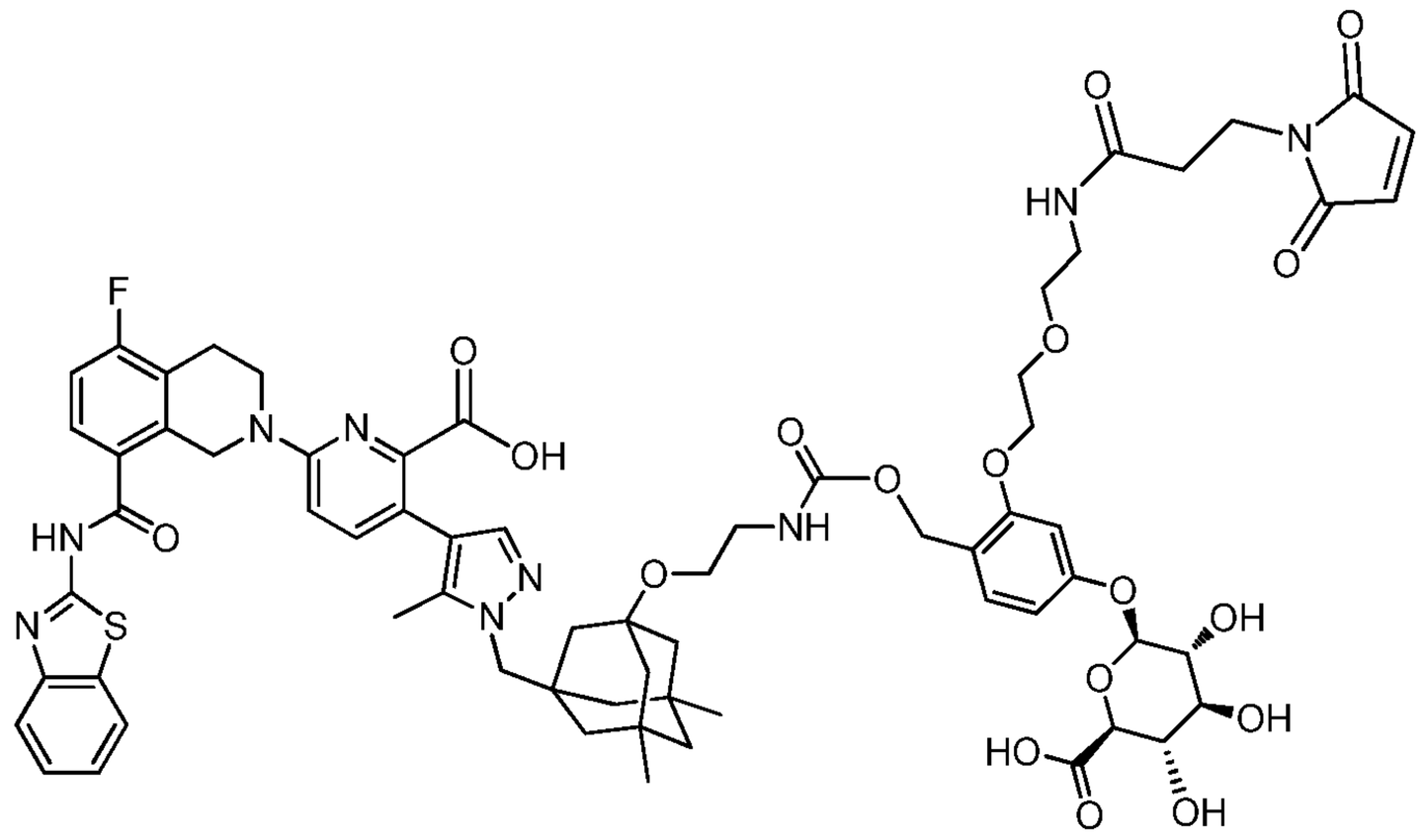
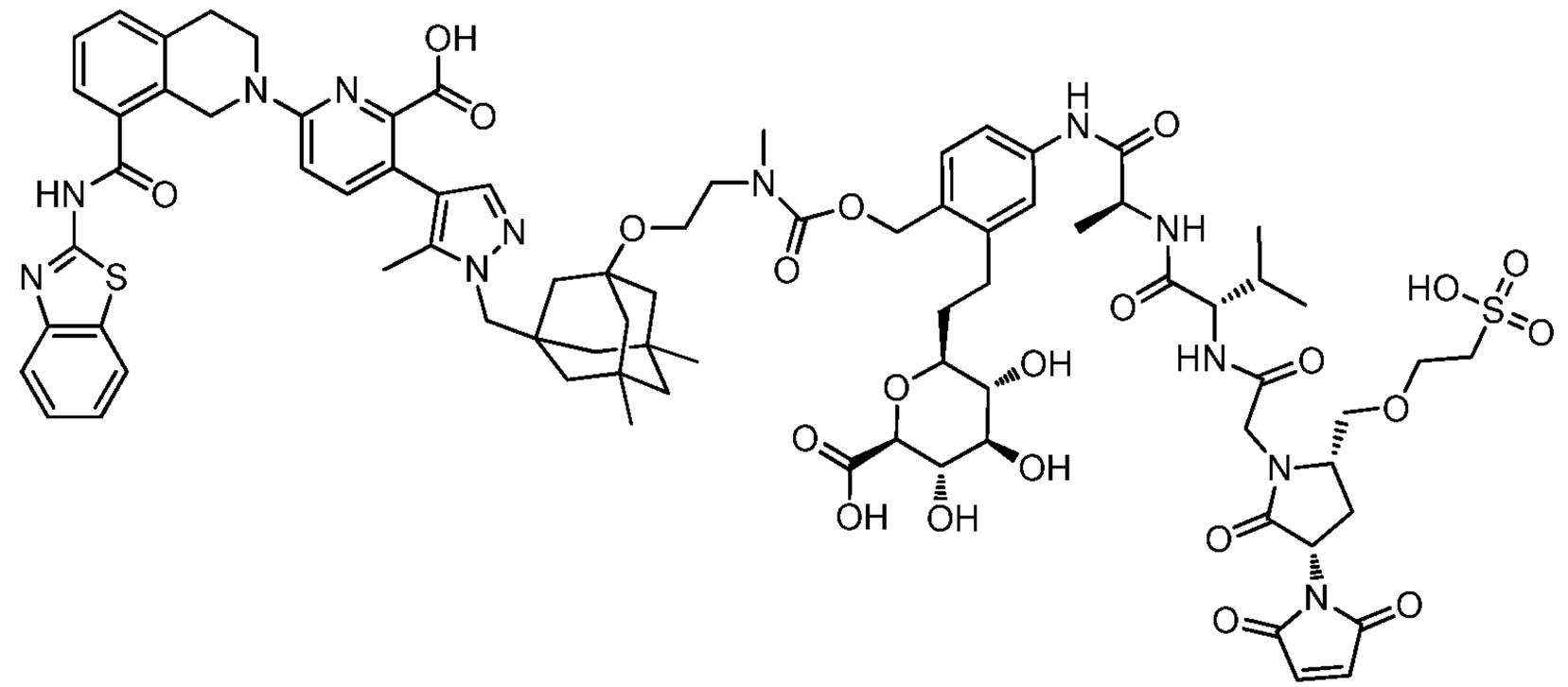
Example No.	Synthon Code	Synthon Structure
2.169	ABG	
2.170	ABL	

Example No.	Synthon Code	Synthon Structure
2.171	ABN	
2.172	AAF	

Example No.	Synthon Code	Synthon Structure
2.173	ABO	

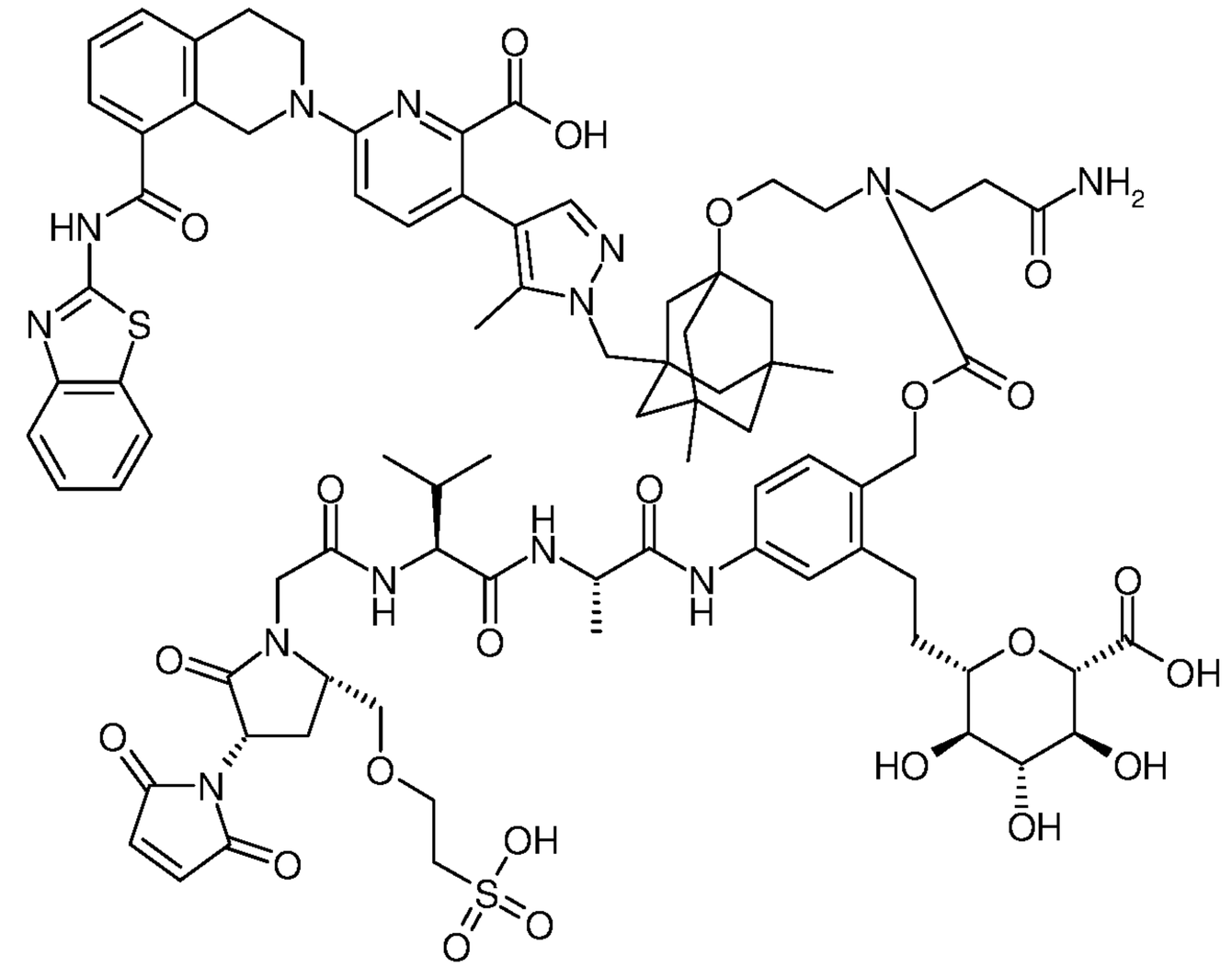
Example No.	Synthon Code	Synthon Structure
2.174	ABM	

Example No.	Synthon Code	Synthon Structure
2.175	ABU	
2.176	ABV	

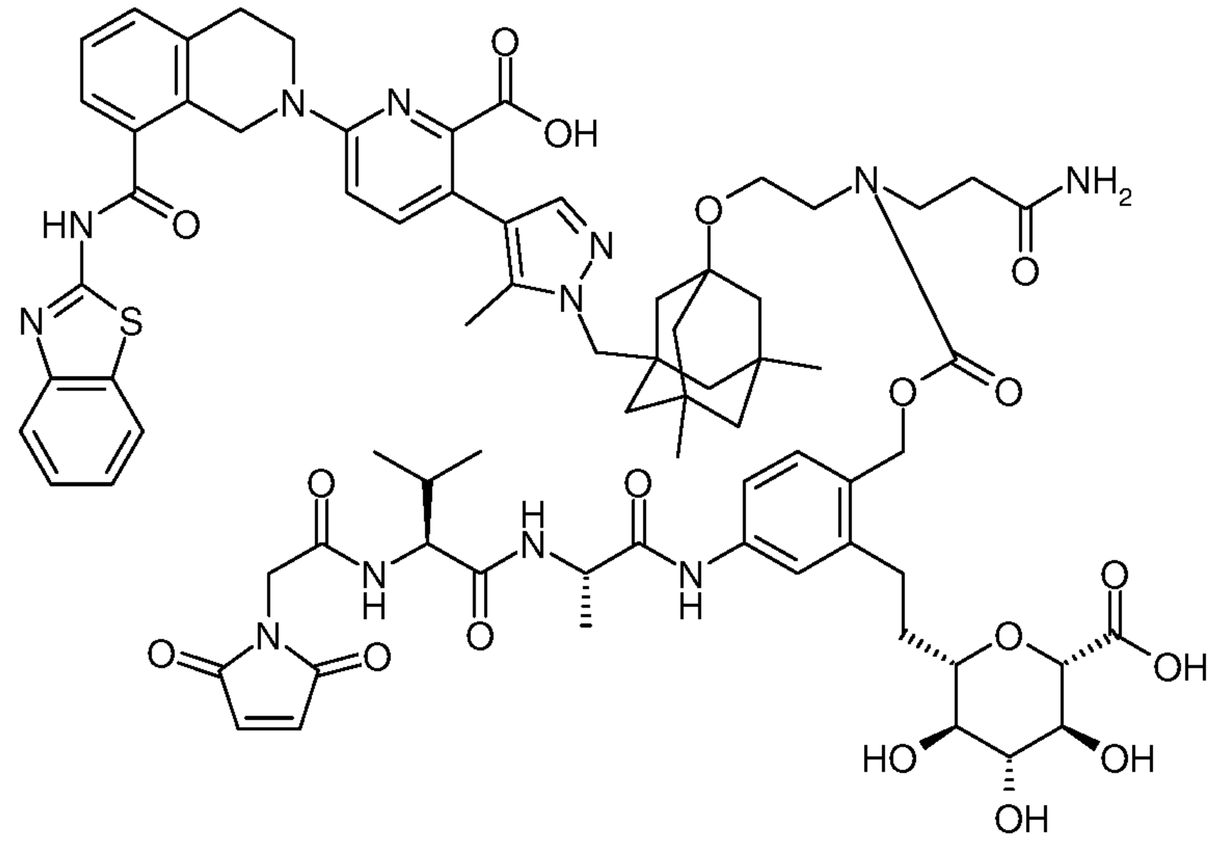
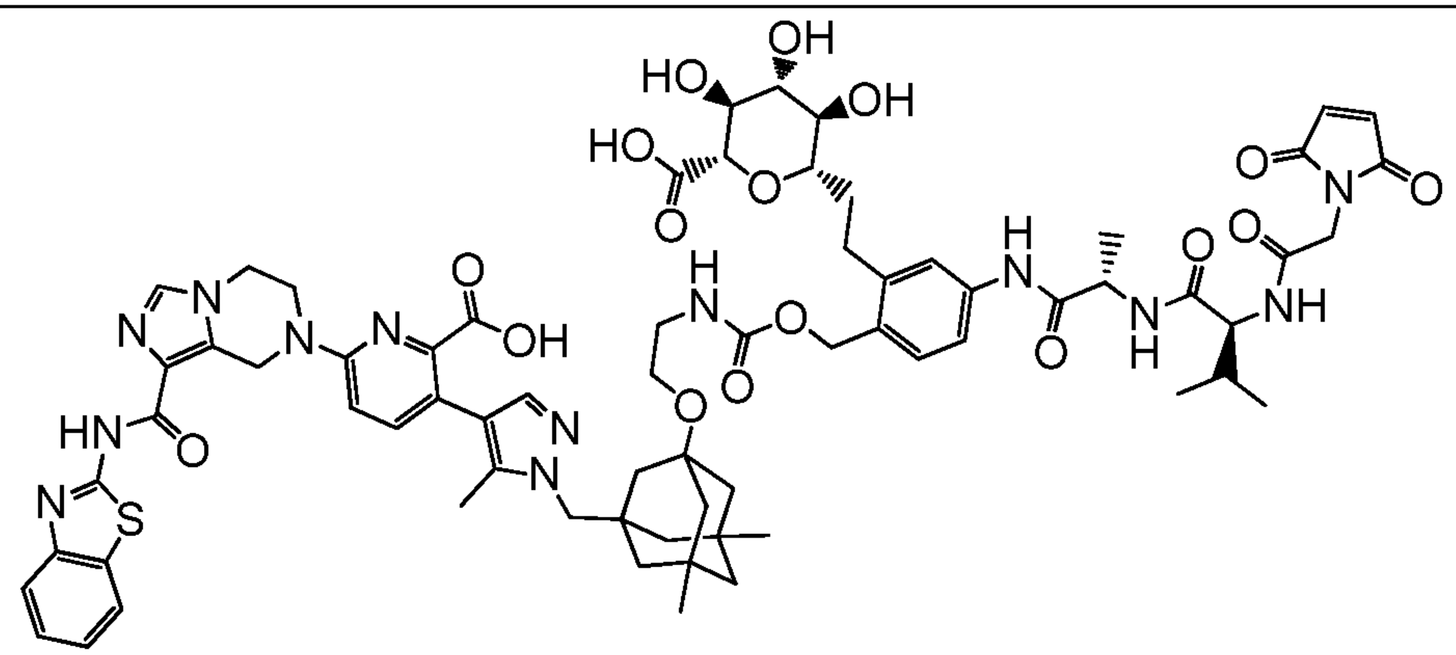
Example No.	Synthon Code	Synthon Structure
2.177 (control)	LB	
2.178 (control)	WD	

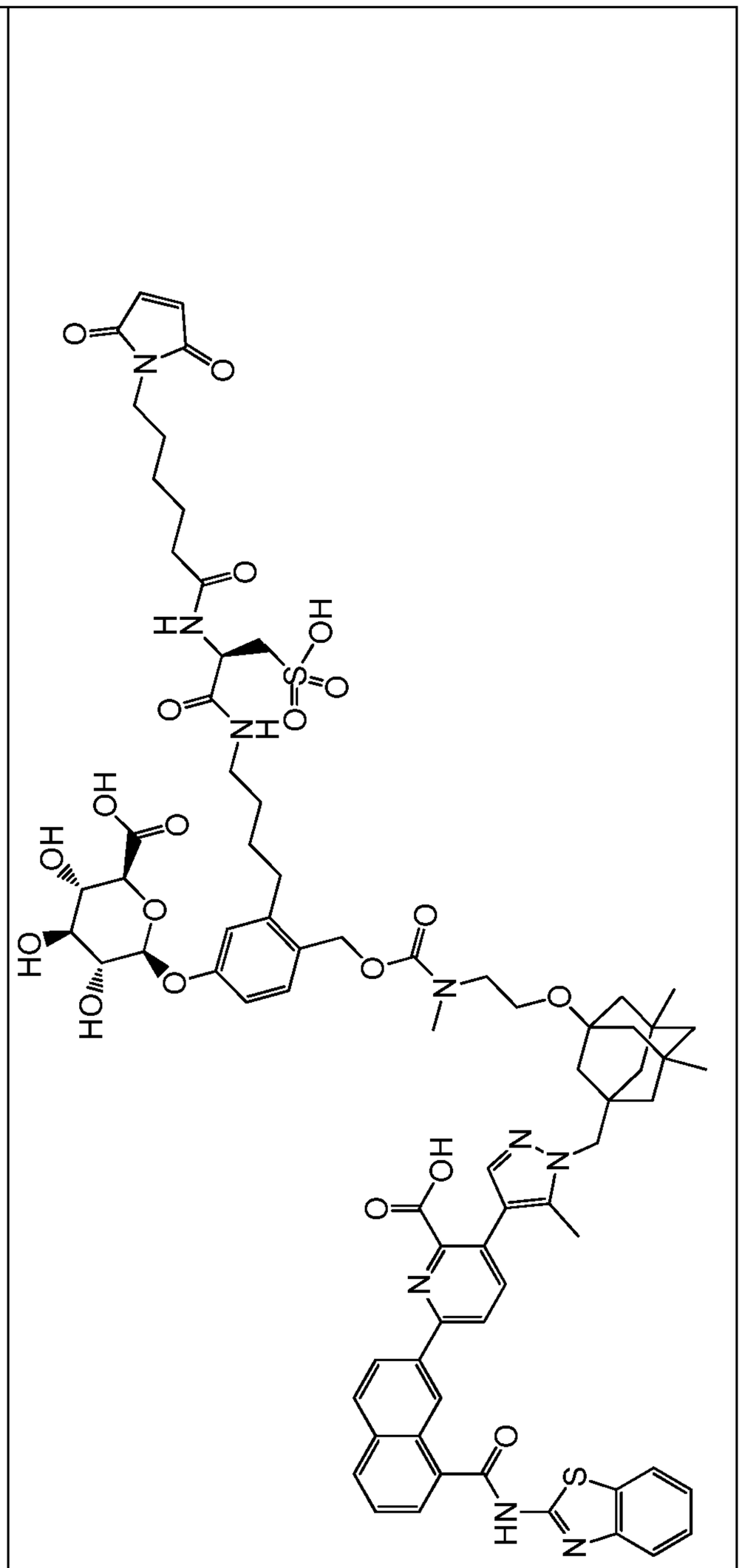
CA 03027045 2018-12-07

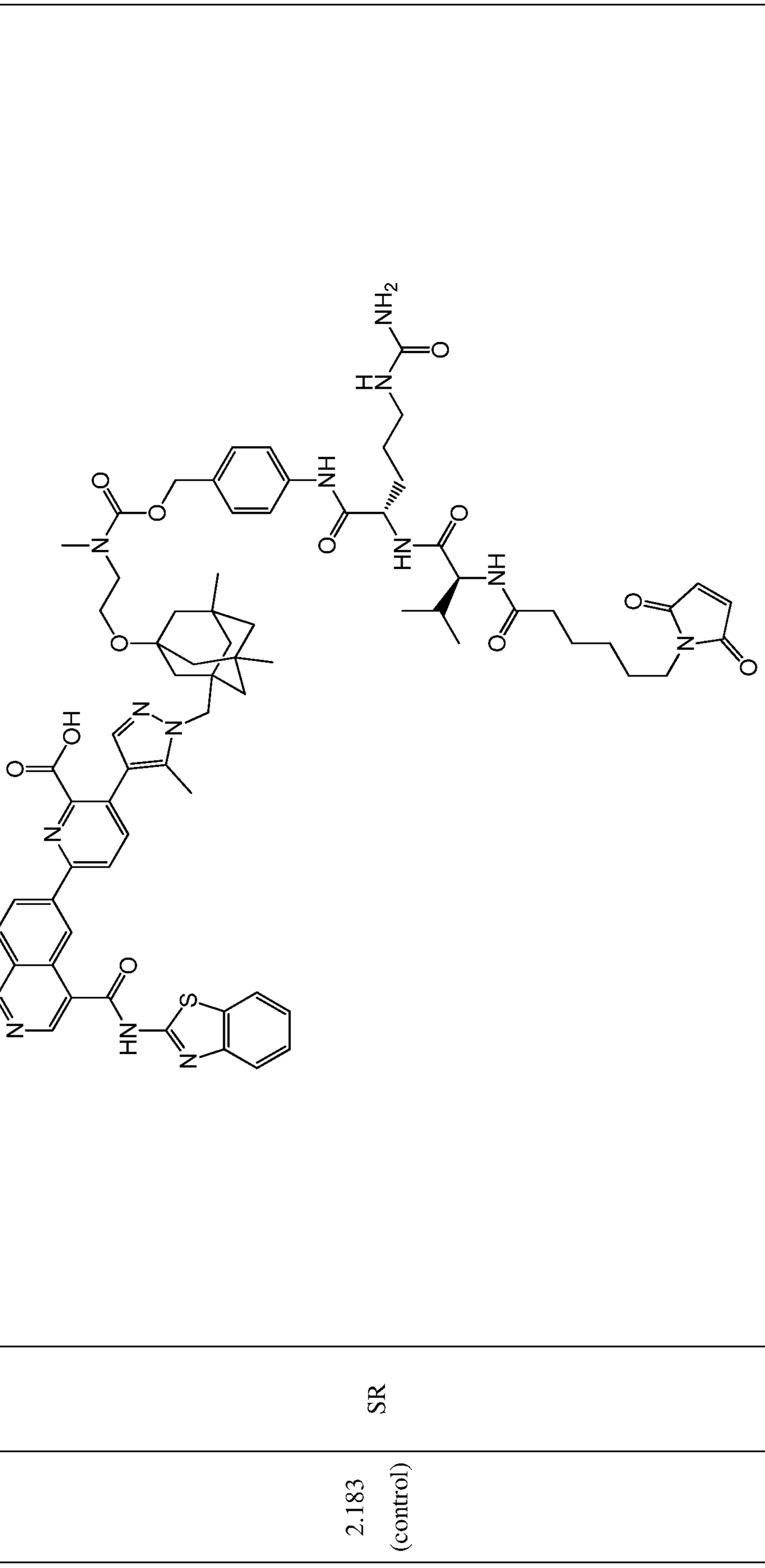
CA 03027045 2018-12-07

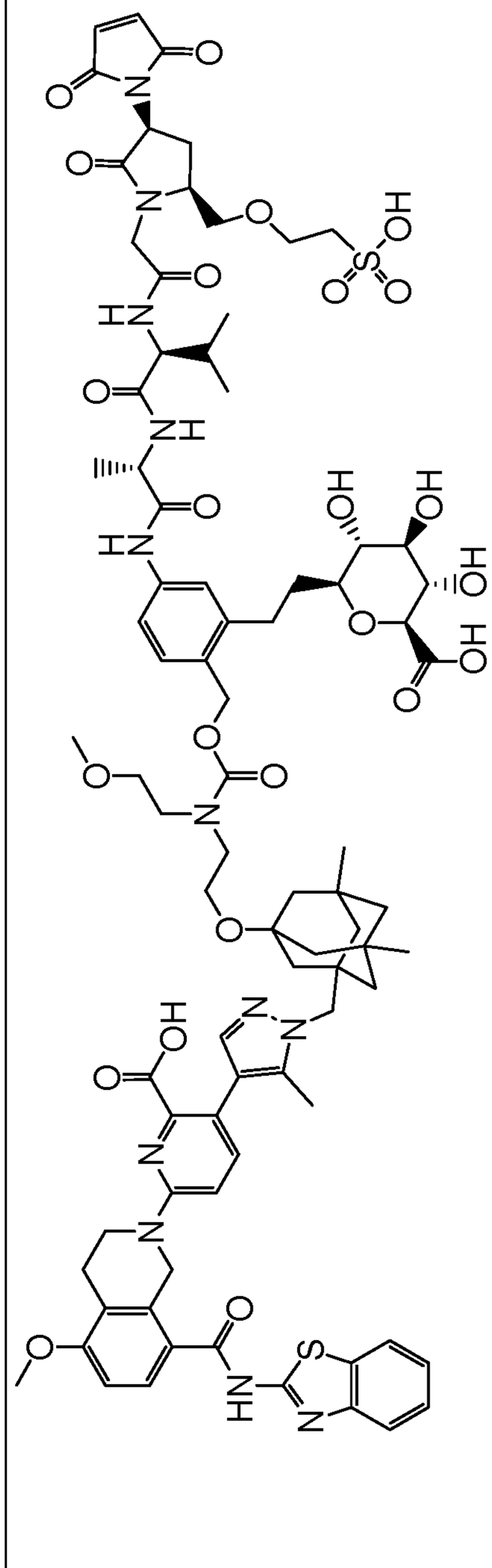
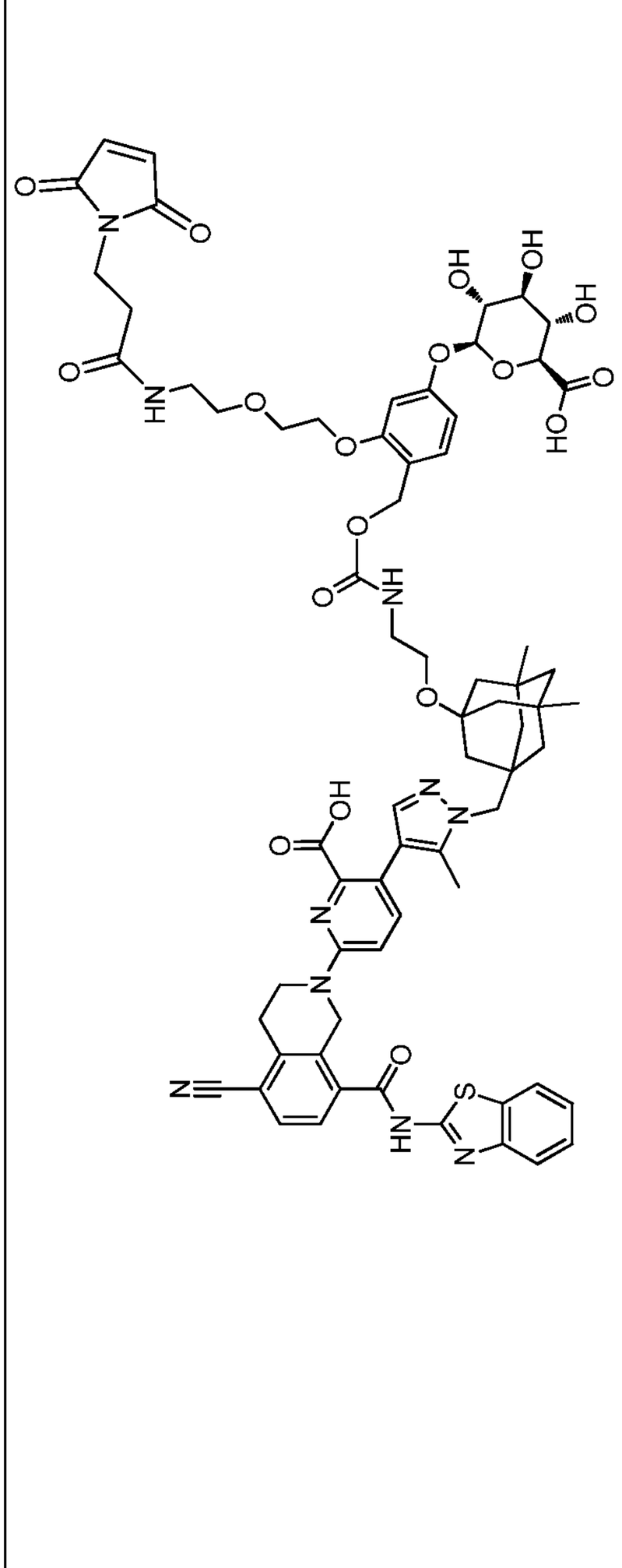
Example No.	Synthon Code	Synthon Structure
2.179 (control)	ZZ	

CA 03027045 2018-12-07

Example No.	Synthon Code	Synthon Structure
2.180 (control)	ZT	
2.181 (control)	XW	

Example No.	Synthon Code	Synthon Structure
2.182 (control)	SE	

Example No.	Synthon Code	Synthon Structure
2.183 (control)	SR	

Example No.	Synthon Code	Synthon Structure
2.184 (control)	YG	
2.185 (control)	KZ	

In certain embodiments, the synthon is selected from the group consisting of synthon examples 2.1, 2.2, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 2.10, 2.11, 2.12, 2.13, 2.14, 2.15, 2.16, 2.17, 2.18, 2.19, 2.20, 2.21, 2.22, 2.23, 2.24, 2.25, 2.26, 2.27, 2.28, 2.29, 2.30, 2.31, 2.32, 2.33, 2.34, 2.35, 2.36, 2.37, 2.38, 2.39, 2.40, 2.41, 2.42, 2.43, 2.44, 2.45, 2.46, 2.47, 2.48, 2.49, 2.50, 2.51, 2.52, 2.53, 2.54, 2.55, 2.56, 2.57, 2.58, 2.59, 2.60, 2.61, 2.62, 2.63, 2.64, 2.65, 2.66, 2.67, 2.68, 2.69, 2.77, 2.78, 2.79, 2.80, 2.81, 2.82, 2.83, 2.84, 2.85, 2.86, 2.87, 2.88, 2.89, 2.90, 2.91, 2.92, 2.93, 2.94, 2.95, 2.96, 2.97, 2.98, 2.101, 2.102, 2.103, 2.104, 2.105, 2.106, 2.107, 2.108, 2.109, 2.110, 2.111, 2.112, 2.113, 2.114, 2.115, 2.116, 2.117, 2.118, 2.119, 2.120, 2.121, 2.122, 2.123, 2.124, 2.125, 2.126, 2.127, 2.128, 2.129, 2.130, 2.131, 2.132, 2.133, 2.134, 2.135, 2.136, 2.137, 2.138, 2.139, 2.140, 2.141, 2.142, 2.143, 2.144, 2.145, 2.146, 2.147, 2.148, 2.149, 2.150, 2.151, 2.152, 2.153, 2.154, 2.155, 2.156, 2.157, 2.158, 2.159, 2.160, 2.161, 2.162, 2.163, 2.164, 2.166, 2.167, 2.168, 2.169, 2.170, 2.171, 2.172, 2.173, 2.174, 2.175, and 2.176, or a pharmaceutically acceptable salt thereof. The compound names of these synthon are provided below:

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N-{4-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]phenyl}-N^5-carbamoyl-L-ornithinamide;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N-{4-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](3-sulfopropyl)carbamoyl}oxy)methyl]phenyl}-N^5-carbamoyl-L-ornithinamide;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N-[4-({[{2-[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethoxy]ethyl}(2-sulfoethyl)carbamoyl]oxy}methyl)phenyl]-N^5-carbamoyl-L-ornithinamide;

methyl 6-[4-(3-{[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl]({[4-({N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N^5-carbamoyl-L-ornithyl}amino)benzyl]oxy}carbonyl)amino}propyl)-1H-1,2,3-triazol-1-yl]-6-deoxy-beta-L-glucopyranoside;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N-(4-{[([2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl]{3-[1-(beta-D-glucopyranuronosyl)-1H-1,2,3-triazol-4-yl]propyl}carbamoyl) oxy]methyl}phenyl)-N^5-carbamoyl-L-ornithinamide;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N-{4-[({[(2R)-1-{[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](methyl)amino}-1-oxo-3-sulfopropan-2-yl]carbamoyl}oxy)methyl]phenyl}-L-alaninamide;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N-{4-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl][4-(beta-D-glucopyranosyloxy)benzyl]carbamoyl}oxy)methyl]phenyl}-N^5-carbamoyl-L-ornithinamide;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N-{4-[({[4-(beta-D-allopyranosyloxy)benzyl][2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl]carbamoyl}oxy)methyl]phenyl}-N^5-carbamoyl-L-ornithinamide;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N-{4-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-phosphonoethyl)carbamoyl}oxy)methyl]phenyl}-N^5-carbamoyl-L-ornithinamide;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N-{4-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-phosphonoethyl)carbamoyl}oxy)methyl]phenyl}-L-alaninamide;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N-{4-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](3-phosphonopropyl)carbamoyl}oxy)methyl]phenyl}-N^5-carbamoyl-L-ornithinamide;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N-{4-[({[(2R)-1-{[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl]amino}-1-oxo-3-sulfopropan-2-yl]carbamoyl}oxy)methyl]phenyl}-L-alaninamide;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N-[4-({[{2-[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethoxy]ethyl}(3-phosphonopropyl)carbamoyl]oxy}methyl)phenyl]-N^5-carbamoyl-L-ornithinamide;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N-[4-({[{2-[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethoxy]ethyl}(3-phosphonopropyl)carbamoyl]oxy}methyl)phenyl]-L-alaninamide;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N-{4-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](3-phosphonopropyl)carbamoyl}oxy)methyl]phenyl}-L-alaninamide;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-(1-{[3-(2-{[(2S)-3-carboxy-2-({[(4-{[(2S)-2-{[(2S)-2-{[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]amino}-3-methylbutanoyl]amino}propanoyl]amino}benzyl)oxy]carbonyl}amino)propanoyl](methyl)amino}eth oxy)-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl]methyl}-5-methyl-1H-pyrazol-4-yl)pyridine-2-carboxylic acid;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N-{4-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl][4-(beta-D-glucopyranuronosyloxy)benzyl]carbamoyl}oxy)methyl]phenyl}-N^5-carbamoyl-L-ornithinamide;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N-{4-[({[2-({3-[(4-{6-[1-(1,3-benzothiazol-2-ylcarbamoyl)-1,2,3,4-tetrahydroquinolin-7-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-phosphonoethyl)carbamoyl}oxy)methyl]phenyl}-N^5-carbamoyl-L-ornithinamide;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N^5-carbamoyl-N-{4-[({[2-({3-[(4-{2-carboxy-6-[8-([1,3]thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]pyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]phenyl}-L-ornithinamide;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N-{4-[({[(2R)-1-{[2-({3-[(4-{6-[1-(1,3-benzothiazol-2-ylcarbamoyl)-1,2,3,4-tetrahydroquinolin-7-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](methyl)amino}-1-oxo-3-sulfopropan-2-yl]carbamoyl}oxy)methyl]phenyl}-N^5-carbamoyl-L-ornithinamide;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N-{4-[({[(2R)-1-{[2-({3-[(4-{6-[1-(1,3-benzothiazol-2-ylcarbamoyl)-1,2,3,4-tetrahydroquinolin-7-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](methyl)amino}-1-oxo-3-sulfopropan-2-yl]carbamoyl}oxy)methyl]phenyl}-L-alaninamide;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N^5-carbamoyl-N-{4-[({[2-({3-[(4-{2-carboxy-6-[8-([1,3]thiazolo[4,5-b]pyridin-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]pyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]phenyl}-L-ornithinamide;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N-{4-[({[2-({3-[(4-{6-[1-(1,3-benzothiazol-2-ylcarbamoyl)-1,2,3,4-tetrahydroquinolin-7-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]phenyl}-N^5-carbamoyl-L-ornithinamide;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N-{4-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-carboxyethyl)carbamoyl}oxy)methyl]phenyl}-N^5-carbamoyl-L-ornithinamide;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N-{4-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-carboxyethyl)carbamoyl}oxy)methyl]phenyl}-L-alaninamide;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-(1-{[3-(2-{[(2R)-3-carboxy-2-({[(4-{[(2S)-2-{[(2S)-2-{[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]amino}-3-methylbutanoyl]amino}propanoyl]amino}benzyl)oxy]carbonyl}amino)propanoyl](methyl)amino}ethoxy)-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl]methyl}-5-methyl-1H-pyrazol-4-yl)pyridine-2-carboxylic acid;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N-{4-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl][1-(carboxymethyl)piperidin-4-yl]carbamoyl}oxy)methyl]phenyl}-N^5-carbamoyl-L-ornithinamide;

(S)-6-((2-((3-((4-(6-(8-(benzo[d]thiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl)-2-carboxypyridin-3-yl)-5-methyl-1H-pyrazol-1-yl)methyl)-5,7-dimethyladamantan-1-yl)oxy)ethyl)(methyl)amino)-5-((((4-((S)-2-((S)-2-(6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanamido)-3-methylbutanamido)-5-ureidopentanamido)benzyl)oxy)carbonyl)amino)-N,N,N-trimethyl-6-oxohexan-1-aminium salt;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N-{4-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]phenyl}-L-alaninamide;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N-[4-({[(4-{[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)amino}piperidin-1-yl)carbonyl]oxy}methyl)phenyl]-N^5-carbamoyl-L-ornithinamide;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N-{4-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-5-(3-phosphonopropoxy)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](methyl)carbamoyl}oxy)methyl]phenyl}-N^5-carbamoyl-L-ornithinamide;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N-[4-({[(4-{[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](3-

phosphonopropyl)amino}piperidin-1-yl)carbonyl]oxy}methyl)phenyl]-N^5-carbamoyl-L-ornithinamide;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N-{4-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)naphthalen-2-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.$1^{3,7}$]dec-1-yl}oxy)ethyl](3-phosphonopropyl)carbamoyl}oxy)methyl]phenyl}-N^5-carbamoyl-L-ornithinamide;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N-[4-({[(4-{[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.$1^{3,7}$]dec-1-yl}oxy)ethyl](2-carboxyethyl)amino}piperidin-1-yl)carbonyl]oxy}methyl)phenyl]-N^5-carbamoyl-L-ornithinamide;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N^5-carbamoyl-N-{4-[({[2-({3-[(4-{2-carboxy-6-[8-([1,3]thiazolo[4,5-b]pyridin-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]pyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.$1^{3,7}$]dec-1-yl}oxy)ethyl](3-phosphonopropyl)carbamoyl}oxy)methyl]phenyl}-L-ornithinamide;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N^5-carbamoyl-N-{4-[({[2-({3-[(4-{2-carboxy-6-[8-([1,3]thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]pyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.$1^{3,7}$]dec-1-yl}oxy)ethyl](3-phosphonopropyl)carbamoyl}oxy)methyl]phenyl}-L-ornithinamide;

N-{6-[(chloroacetyl)amino]hexanoyl}-L-valyl-N-{4-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.$1^{3,7}$]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]phenyl}-L-alaninamide;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N-{4-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-5-(carboxymethoxy)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.$1^{3,7}$]dec-1-yl}oxy)ethyl](methyl)carbamoyl}oxy)methyl]phenyl}-N^5-carbamoyl-L-ornithinamide;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N-[4-({[(2-{[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.$1^{3,7}$]dec-1-yl}oxy)ethyl](2-sulfoethyl)amino}ethyl)(2-carboxyethyl)carbamoyl]oxy}methyl)phenyl]-N^5-carbamoyl-L-ornithinamide;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-[1-({3-[2-({(2S)-2-[{[(4-{[(2S)-5-(carbamoylamino)-2-{[(2S)-2-{[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]amino}-3-methylbutanoyl]amino}pentanoyl]amino}benzyl)oxy]carbonyl}(2-carboxyethyl)amino]-3-carboxypropanoyl}amino)ethoxy]-5,7-dimethyltricyclo[3.3.1.$1^{3,7}$]dec-1-yl}methyl)-5-methyl-1H-pyrazol-4-yl]pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-(1-{[3-(2-{[(2S)-2-({[(4-{[(2S)-5-(carbamoylamino)-2-{[(2S)-2-{[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]amino}-3-methylbutanoyl]amino}pentanoyl]amino}benzyl)oxy]carbonyl}amino)-3-carboxypropanoyl](2-sulfoethyl)amino}ethoxy)-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl]methyl}-5-methyl-1H-pyrazol-4-yl)pyridine-2-carboxylic acid;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N-[4-({[(4-{[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](3-carboxypropyl)amino}piperidin-1-yl)carbonyl]oxy}methyl)phenyl]-N^5-carbamoyl-L-ornithinamide;

4-[(1E)-3-({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-5-(carboxymethoxy)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](methyl)carbamoyl}oxy)prop-1-en-1-yl]-2-({N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-beta-alanyl}amino)phenyl beta-D-glucopyranosiduronic acid;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N-{4-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)naphthalen-2-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]phenyl}-N^5-carbamoyl-L-ornithinamide;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N-[4-({[(2-{[8-(1,3-benzothiazol-2-ylcarbamoyl)-2-(6-carboxy-5-{1-[(3,5-dimethyl-7-{2-[methyl(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridin-2-yl)-1,2,3,4-tetrahydroisoquinolin-5-yl]oxy}ethyl)carbamoyl]oxy}methyl)phenyl]-N^5-carbamoyl-L-ornithinamide;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N-[4-({[(2-{[8-(1,3-benzothiazol-2-ylcarbamoyl)-2-(6-carboxy-5-{1-[(3,5-dimethyl-7-{2-[methyl(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridin-2-yl)-1,2,3,4-tetrahydroisoquinolin-5-yl]oxy}ethyl)(2-sulfoethyl)carbamoyl]oxy}methyl)phenyl]-N^5-carbamoyl-L-ornithinamide;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N-[4-({[(2-{[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)amino}ethyl)(2-sulfoethyl)carbamoyl]oxy}methyl)phenyl]-N^5-carbamoyl-L-ornithinamide;

N-{6-[(chloroacetyl)amino]hexanoyl}-L-valyl-N-{4-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]phenyl}-N^5-carbamoyl-L-ornithinamide;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N-{4-[({[2-({3-[(4-{6-[4-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydro-2H-1,4-benzoxazin-6-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]phenyl}-N^5-carbamoyl-L-ornithinamide;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N-[4-({[(2-{[8-(1,3-benzothiazol-2-ylcarbamoyl)-2-(6-carboxy-5-{1-[(3,5-dimethyl-7-{2-[methyl(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridin-2-yl)-1,2,3,4-tetrahydroisoquinolin-5-yl]oxy}ethyl)(2-carboxyethyl)carbamoyl]oxy}methyl)phenyl]-N^5-carbamoyl-L-ornithinamide;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N-{4-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-5-(3-sulfopropoxy)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](methyl)carbamoyl}oxy)methyl]phenyl}-N^5-carbamoyl-L-ornithinamide;

N-[3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanoyl]-L-valyl-N-{4-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]phenyl}-N^5-carbamoyl-L-ornithinamide;

N-[(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)acetyl]-L-valyl-N-{4-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]phenyl}-N^5-carbamoyl-L-ornithinamide;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-(1-{[3-(2-{[(2S)-2-({[(4-{[(2S,3R,4S,5S,6S)-6-carboxy-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl]oxy}-3-[(3-{[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]amino}propanoyl)amino]benzyl)oxy]carbonyl}amino)-3-sulfopropanoyl](methyl)amino}ethoxy)-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl]methyl}-5-methyl-1H-pyrazol-4-yl)pyridine-2-carboxylic acid;

4-[(1E)-3-({[2-({3-[(4-{2-carboxy-6-[8-([1,3]thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]pyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)prop-1-en-1-yl]-2-({N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-beta-alanyl}amino)phenyl beta-D-glucopyranosiduronic acid;

4-[(1E)-3-({[2-({3-[(4-{2-carboxy-6-[8-([1,3]thiazolo[4,5-b]pyridin-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]pyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)prop-1-en-1-yl]-2-({N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-beta-alanyl}amino)phenyl beta-D-glucopyranosiduronic acid;

4-[(1E)-3-({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)prop-1-en-1-yl]-2-({N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-beta-alanyl}amino)phenyl beta-D-glucopyranosiduronic acid;

4-[(1E)-3-({[2-({3-[(4-{2-carboxy-6-[8-([1,3]thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]pyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](3-phosphonopropyl)carbamoyl}oxy)prop-1-en-1-yl]-2-({N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-beta-alanyl}amino)phenyl beta-D-glucopyranosiduronic acid;

4-[(1E)-3-({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-5-(3-phosphonopropoxy)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](methyl)carbamoyl}oxy)prop-1-en-1-yl]-2-({N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-beta-alanyl}amino)phenyl beta-D-glucopyranosiduronic acid;

4-[(1E)-3-({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](3-phosphonopropyl)carbamoyl}oxy)prop-1-en-1-yl]-2-({N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-beta-alanyl}amino)phenyl beta-D-glucopyranosiduronic acid;

4-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]-3-[2-(2-{[3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanoyl]amino}ethoxy)ethoxy]phenyl beta-D-glucopyranosiduronic acid;

4-[(1E)-3-({[2-({3-[(4-{2-carboxy-6-[8-([1,3]thiazolo[4,5-b]pyridin-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]pyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](3-phosphonopropyl)carbamoyl}oxy)prop-1-en-1-yl]-2-({N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-beta-alanyl}amino)phenyl beta-D-glucopyranosiduronic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3-{2-[(2-carboxyethyl)({[(2E)-3-(4-{[(2S,3R,4S,5S,6S)-6-carboxy-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl]oxy}-3-[(3-{[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]amino}propanoyl)amino]phenyl)prop-2-en-1-yl]oxy}carbonyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3-{2-[(2-carboxyethyl){[(4-{[(2S,3R,4S,5S,6S)-6-carboxy-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl]oxy}-2-[2-(2-{[3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-

yl)propanoyl]amino}ethoxy)ethoxy]benzyl)oxy]carbonyl}amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

N-[6-(ethenylsulfonyl)hexanoyl]-L-valyl-N-{4-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]phenyl}-N^5-carbamoyl-L-ornithinamide;

4-[(1E)-3-{[(4-{[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](3-phosphonopropyl)amino}piperidin-1-yl)carbonyl]oxy}prop-1-en-1-yl]-2-({N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-beta-alanyl}amino)phenyl beta-D-glucopyranosiduronic acid;

4-[(1E)-3-{[(4-{[2-({3-[(4-{2-carboxy-6-[8-([1,3]thiazolo[4,5-b]pyridin-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]pyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](3-phosphonopropyl)amino}piperidin-1-yl)carbonyl]oxy}prop-1-en-1-yl]-2-({N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-beta-alanyl}amino)phenyl beta-D-glucopyranosiduronic acid;

4-[(1E)-3-({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)naphthalen-2-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)prop-1-en-1-yl]-2-({N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-beta-alanyl}amino)phenyl beta-D-glucopyranosiduronic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-[1-({3-[2-({N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-3-sulfo-L-alanyl}amino)ethoxy]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}methyl)-5-methyl-1H-pyrazol-4-yl]pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-[1-({3-[2-(2-{[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl](2-sulfoethyl)amino}ethoxy)ethoxy]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}methyl)-5-methyl-1H-pyrazol-4-yl]pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-(1-{[3-(2-{[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl](2-sulfoethyl)amino}ethoxy)-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl]methyl}-5-methyl-1H-pyrazol-4-yl)pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3-{[1-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-21-oxo-22-(2-sulfoethyl)-3,6,9,12,15,18-hexaoxa-22-azatetracosan-24-yl]oxy}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3-{[1-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-21-oxo-22-(2-sulfoethyl)-3,6,9,12,15,18,25-heptaoxa-22-azaheptacosan-27-yl]oxy}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-(1-{[3-(2-{[6-(ethenylsulfonyl)hexanoyl](2-sulfoethyl)amino}ethoxy)-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl]methyl}-5-methyl-1H-pyrazol-4-yl)pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3-{2-[{6-[(chloroacetyl)amino]hexanoyl}(2-sulfoethyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N-{4-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](3-carboxypropyl)carbamoyl}oxy)methyl]phenyl}-N^5-carbamoyl-L-ornithinamide;

N-{6-[(bromoacetyl)amino]hexanoyl}-L-valyl-N-{4-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]phenyl}-N^5-carbamoyl-L-ornithinamide;

4-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](3-carboxypropyl)carbamoyl}oxy)methyl]-3-[2-(2-{[3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanoyl]amino}ethoxy)ethoxy]phenyl beta-D-glucopyranosiduronic acid;

4-({[(4-{[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](3-carboxypropyl)amino}piperidin-1-yl)carbonyl]oxy}methyl)-3-[2-(2-{[3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanoyl]amino}ethoxy)ethoxy]phenyl beta-D-glucopyranosiduronic acid;

4-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](3-sulfopropyl)carbamoyl}oxy)methyl]-3-[2-(2-{[3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanoyl]amino}ethoxy)ethoxy]phenyl beta-D-glucopyranosiduronic acid;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N-[4-({[(3-{[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)amino}azetidin-1-yl)carbonyl]oxy}methyl)phenyl]-N^5-carbamoyl-L-ornithinamide;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3-{[26-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-8,24-dioxo-3-(2-sulfoethyl)-11,14,17,20-tetraoxa-3,7,23-triazahexacos-1-yl]oxy}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N-[4-({[(3-{[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-

methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)amino}propyl)carbamoyl]oxy}methyl)phenyl]-N^5-carbamoyl-L-ornithinamide;

N-{6-[(iodoacetyl)amino]hexanoyl}-L-valyl-N-{4-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]phenyl}-N^5-carbamoyl-L-ornithinamide;

N-{6-[(ethenylsulfonyl)amino]hexanoyl}-L-valyl-N-{4-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]phenyl}-N^5-carbamoyl-L-ornithinamide;

N-{6-[(ethenylsulfonyl)amino]hexanoyl}-L-valyl-N-{4-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]phenyl}-N^5-carbamoyl-L-ornithinamide;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3-{2-[(3-{[6-(ethenylsulfonyl)hexanoyl]amino}propyl)(2-sulfoethyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

N-[3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanoyl]-L-valyl-N-{4-[({[2-({3-[(4-{6-[1-(1,3-benzothiazol-2-ylcarbamoyl)-1,2,3,4-tetrahydroquinolin-7-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]phenyl}-N^5-carbamoyl-L-ornithinamide;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3-{2-[(2-carboxyethyl){[(2-{[(2S,3R,4S,5S,6S)-6-carboxy-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl]oxy}-4-[2-(2-{[3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanoyl]amino}ethoxy)ethoxy]benzyl)oxy]carbonyl}amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-3-sulfo-L-alanyl-L-valyl-N-{4-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-carboxyethyl)carbamoyl}oxy)methyl]phenyl}-N^5-carbamoyl-L-ornithinamide;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3-{[(43S,46S)-43-({[(4-{[(2S)-2-{[(2S)-2-{[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]amino}-3-methylbutanoyl]amino}propanoyl]amino}benzyl)oxy]carbonyl}amino)-46-methyl-37,44,47-trioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-38,45,48-triazapentacontan-50-yl]oxy}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N-{4-[({[2-({3-[(4-{6-[1-(1,3-benzothiazol-2-ylcarbamoyl)-1,2,3,4-tetrahydroquinolin-7-yl]-2-carboxypyridin-3-yl}-5-methyl-

1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-carboxyethyl)carbamoyl}oxy)methyl]phenyl}-N^5-carbamoyl-L-ornithinamide;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N-{4-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)naphthalen-2-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-carboxyethyl)carbamoyl}oxy)methyl]phenyl}-N^5-carbamoyl-L-ornithinamide;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)naphthalen-2-yl]-3-{1-[(3-{2-[(2-carboxyethyl){[(2-{[(2R,3S,4R,5R,6R)-6-carboxy-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl]oxy}-4-[2-(2-{[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]amino}ethoxy)ethoxy]benzyl)oxy]carbonyl}amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N-{4-[({[2-({3-[(4-{6-[5-(1,3-benzothiazol-2-ylcarbamoyl)quinolin-3-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]phenyl}-N^5-carbamoyl-L-ornithinamide;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N-{4-[({[2-({3-[(4-{6-[4-(1,3-benzothiazol-2-ylcarbamoyl)quinolin-6-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-carboxyethyl)carbamoyl}oxy)methyl]phenyl}-N^5-carbamoyl-L-ornithinamide;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N-{4-[({[2-({3-[(4-{6-[4-(1,3-benzothiazol-2-ylcarbamoyl)quinolin-6-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]phenyl}-N^5-carbamoyl-L-ornithinamide;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N-{4-[({[2-({3-[(4-{6-[5-(1,3-benzothiazol-2-ylcarbamoyl)quinolin-3-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-carboxyethyl)carbamoyl}oxy)methyl]phenyl}-N^5-carbamoyl-L-ornithinamide;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N-{4-[({[2-({3-[(4-{6-[1-(1,3-benzothiazol-2-ylcarbamoyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]phenyl}-N^5-carbamoyl-L-ornithinamide;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N-{4-[({[2-({3-[(4-{6-[7-(1,3-benzothiazol-2-ylcarbamoyl)-1H-indol-2-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]phenyl}-N^5-carbamoyl-L-ornithinamide;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N-[4-({[{3-[8-(1,3-benzothiazol-2-ylcarbamoyl)-2-(6-carboxy-5-{1-[(3,5-dimethyl-7-{2-[(2-

sulfoethyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridin-2-yl)-1,2,3,4-tetrahydroisoquinolin-6-yl]propyl}(methyl)carbamoyl]oxy}methyl)phenyl]-N^5-carbamoyl-L-ornithinamide;

N-(6-{[(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)acetyl]amino}hexanoyl)-L-valyl-N-{4-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]phenyl}-N^5-carbamoyl-L-ornithinamide;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N-{4-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)naphthalen-2-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl][3-(beta-L-glucopyranuronosyloxy)propyl]carbamoyl}oxy)methyl]phenyl}-N^5-carbamoyl-L-ornithinamide;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N-{4-[({[2-({3-[(4-{6-[4-(1,3-benzothiazol-2-ylcarbamoyl)isoquinolin-6-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]phenyl}-N^5-carbamoyl-L-ornithinamide;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-alpha-glutamyl-L-valyl-N-{4-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]phenyl}-N^5-carbamoyl-L-ornithinamide;

N-[(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)acetyl]-L-alpha-glutamyl-L-valyl-N-{4-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]phenyl}-N^5-carbamoyl-L-ornithinamide;

1-{[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl]({[4-({N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-D-valyl-N^5-carbamoyl-D-ornithyl}amino)benzyl]oxy}carbonyl)amino}-1,2-dideoxy-D-arabino-hexitol;

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-N-{4-[({[2-({3-[(4-{6-[4-(1,3-benzothiazol-2-ylcarbamoyl)-2-oxidoisoquinolin-6-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](methyl)carbamoyl}oxy)methyl]phenyl}-N^5-carbamoyl-L-ornithinamide;

N-({(3S,5S)-3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-2-oxo-5-[(2-sulfoethoxy)methyl]pyrrolidin-1-yl}acetyl)-L-valyl-N-{4-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)naphthalen-2-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]phenyl}-N^5-carbamoyl-L-ornithinamide;

N-{(2S)-2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-3-[4-(2,5,8,11,14,17,20,23,26,29,32-undecaoxatetratriacontan-34-yloxy)phenyl]propanoyl}-L-valyl-N-{4-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)naphthalen-2-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]phenyl}-N^5-carbamoyl-L-ornithinamide;

N-({(3S,5S)-3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-2-oxo-5-[(2-sulfoethoxy)methyl]pyrrolidin-1-yl}acetyl)-L-valyl-N-{4-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]phenyl}-N^5-carbamoyl-L-ornithinamide;

N-{(2S)-2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-3-[4-(2,5,8,11,14,17,20,23,26,29,32-undecaoxatetratriacontan-34-yloxy)phenyl]propanoyl}-L-valyl-N-{4-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]phenyl}-N^5-carbamoyl-L-ornithinamide;

(6S)-2,6-anhydro-6-(2-{2-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]-5-({N-[(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)acetyl]-L-valyl-L-alanyl}amino)phenyl}ethyl)-L-gulonic acid;

3-{[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)naphthalen-2-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl]({[4-(4-{[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]amino}butyl)-2-(beta-D-glucopyranuronosyloxy)benzyl]oxy}carbonyl)amino}propyl beta-D-glucopyranosiduronic acid;

N-{[(3S,5S)-3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-5-(methoxymethyl)-2-oxopyrrolidin-1-yl]acetyl}-L-valyl-N-{4-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]phenyl}-N^5-carbamoyl-L-ornithinamide;

(6S)-2,6-anhydro-6-(2-{2-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]-5-({N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-L-valyl-L-alanyl}amino)phenyl}ethyl)-L-gulonic acid;

2-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]-5-(4-{[3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanoyl]amino}butyl)phenyl beta-D-glucopyranosiduronic acid;

2-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]-5-[4-({(2S)-2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-3-[4-(2,5,8,11,14,17,20,23,26,29,32-undecaoxatetratriacontan-34-yloxy)phenyl]propanoyl}amino)butyl]phenyl beta-D-glucopyranosiduronic acid;

(6S)-2,6-anhydro-6-(2-{2-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]-5-[(N-{(2S)-2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-3-[4-(2,5,8,11,14,17,20,23,26,29,32-undecaoxatetratriacontan-34-yloxy)phenyl]propanoyl}-L-valyl-L-alanyl)amino]phenyl}ethyl)-L-gulonic acid;

6-(8-(benzo[d]thiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl)-3-(1-((3-(2-((((2-(2-((2S,3R,4R,5S,6S)-6-carboxy-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl)ethyl)-4-((S)-2-((S)-2-(2-((3S,5S)-3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-2-oxo-5-((2-sulfoethoxy)methyl)pyrrolidin-1-yl)acetamido)-3-methylbutanamido)propanamido)benzyl)oxy)carbonyl)(2-sulfoethyl)amino)ethoxy)-5,7-dimethyladamantan-1-yl)methyl)-5-methyl-1H-pyrazol-4-yl)picolinic acid;

6-(8-(benzo[d]thiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl)-3-(1-((3-(2-((((2-(((2S,3R,4S,5S,6S)-6-carboxy-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl)oxy)-4-(4-(2-((3S,5S)-3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-2-oxo-5-((2-sulfoethoxy)methyl)pyrrolidin-1-yl)acetamido)butyl)benzyl)oxy)carbonyl)(2-sulfoethyl)amino)ethoxy)-5,7-dimethyladamantan-1-yl)methyl)-5-methyl-1H-pyrazol-4-yl)picolinic acid;

2-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]-5-(4-{[(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)acetyl]amino}butyl)phenyl beta-D-glucopyranosiduronic acid;

2-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)naphthalen-2-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]-5-(4-{[(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)acetyl]amino}butyl)phenyl beta-D-glucopyranosiduronic acid;

2-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)naphthalen-2-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]-5-[4-({(2S)-2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-3-[4-(2,5,8,11,14,17,20,23,26,29,32-undecaoxatetratriacontan-34-yloxy)phenyl]propanoyl}amino)butyl]phenyl beta-D-glucopyranosiduronic acid;

N-[(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)acetyl]-L-valyl-N-{4-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-

pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]-3-(4-carboxybutyl)phenyl}-L-alaninamide;

2-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]-5-(3-{[(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)acetyl]amino}propyl)phenyl beta-D-glucopyranosiduronic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3-{2-[({[2-{[(2S,3R,4S,5S,6S)-6-carboxy-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl]oxy}-4-(4-{[(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)acetyl]amino}butyl)benzyl]oxy}carbonyl)(3-{[1,3-dihydroxy-2-(hydroxymethyl)propan-2-yl]amino}-3-oxopropyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-(8-(benzo[d]thiazol-2-ylcarbamoyl)naphthalen-2-yl)-3-(1-((3-(2-((((2-(((2S,3R,4S,5S,6S)-6-carboxy-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl)oxy)-4-(4-(2-((3S,5S)-3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-2-oxo-5-((2-sulfoethoxy)methyl)pyrrolidin-1-yl)acetamido)butyl)benzyl)oxy)carbonyl)(2-sulfoethyl)amino)ethoxy)-5,7-dimethyladamantan-1-yl)methyl)-5-methyl-1H-pyrazol-4-yl)picolinic acid;

2-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl][3-hydroxy-2-(hydroxymethyl)propyl]carbamoyl}oxy)methyl]-5-(3-{[(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)acetyl]amino}propyl)phenyl beta-D-glucopyranosiduronic acid;

N-({(3S,5S)-3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-2-oxo-5-[(2-sulfoethoxy)methyl]pyrrolidin-1-yl}acetyl)-L-valyl-N-{4-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]-3-(2,5,8,11,14,17,20,23,26,29,32,35,38,41,44,47,50-heptadecaoxatripentacont-52-yn-53-yl)phenyl}-L-alaninamide;

N-({(3S,5S)-3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-2-oxo-5-[(2-sulfoethoxy)methyl]pyrrolidin-1-yl}acetyl)-L-valyl-N-{4-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]-3-(2,5,8,11,14,17,20,23,26,29,32,35,38,41,44,47,50-heptadecaoxatripentacontan-53-yl)phenyl}-L-alaninamide;

2-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl][(3S)-3,4-dihydroxybutyl]carbamoyl}oxy)methyl]-5-(3-{[(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)acetyl]amino}propyl)phenyl beta-D-glucopyranosiduronic acid;

1-{[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl]({[4-(4-{[(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)acetyl]amino}butyl)-2-(beta-D-glucopyranuronosyloxy)benzyl]oxy}carbonyl)amino}-1,2-dideoxy-D-arabino-hexitol;

1-{[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl]({[4-(4-{[(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)acetyl]amino}butyl)-2-(beta-D-glucopyranuronosyloxy)benzyl]oxy}carbonyl)amino}-1,2-dideoxy-D-erythro-pentitol;

N-[(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)acetyl]-L-valyl-N-{4-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)naphthalen-2-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]-3-[27-(2,5,8,11,14,17,20,23-octaoxahexacosan-26-yl)-2,5,8,11,14,17,20,23-octaoxa-27-azatriacontan-30-yl]phenyl}-L-alaninamide;

(6S)-2,6-anhydro-6-(2-{2-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]-5-({N-[(2S)-3-[3,4-bis(2,5,8,11,14,17,20,23,26,29,32-undecaoxatetratriacontan-34-yloxy)phenyl]-2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanoyl]-L-valyl-L-alanyl}amino)phenyl}ethyl)-L-gulonic acid;

N-[(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)acetyl]-N-(2,5,8,11,14,17,20,23,26,29,32-undecaoxatetratriacontan-34-yl)-beta-alanyl-L-valyl-N-{4-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]-3-(2,5,8,11,14,17,20,23,26,29,32,35,38,41,44,47,50-heptadecaoxatripentacontan-53-yl)phenyl}-L-alaninamide;

N-[(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)acetyl]-N-(2,5,8,11,14,17,20,23,26,29,32-undecaoxatetratriacontan-34-yl)-beta-alanyl-L-valyl-N-{4-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]phenyl}-N^5-carbamoyl-L-ornithinamide;

N-[(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)acetyl]-L-valyl-N-{4-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]-3-[27-(2,5,8,11,14,17,20,23-octaoxahexacosan-26-yl)-2,5,8,11,14,17,20,23-octaoxa-27-azatriacontan-30-yl]phenyl}-L-alaninamide;

N-{(3S)-3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-3-[1-(2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxaheptatriacontan-37-yl)-1H-1,2,3-triazol-4-yl]propanoyl}-L-valyl-N-{4-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-

methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]phenyl}-N^5-carbamoyl-L-ornithinamide;

N-{(3R)-3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-3-[1-(2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxaheptatriacontan-37-yl)-1H-1,2,3-triazol-4-yl]propanoyl}-L-valyl-N-{4-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]phenyl}-N^5-carbamoyl-L-ornithinamide;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-[1-({3-[2-({[(2-{2-[(2S,3R,4R,5S,6S)-6-carboxy-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl]ethyl}-4-{[(2S)-2-{[(2S)-2-{[(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)acetyl]amino}-3-methylbutanoyl]amino}propanoyl]amino}benzyl)oxy]carbonyl}[(3R,4S,5R)-3,4,5,6-tetrahydroxyhexyl]amino)ethoxy]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}methyl)-5-methyl-1H-pyrazol-4-yl]pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-[1-({3-[2-({[(2-{2-[(2S,3R,4R,5S,6S)-6-carboxy-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl]ethyl}-4-{[(2S)-2-({(2S)-2-[({(3S,5S)-3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-2-oxo-5-[(2-sulfoethoxy)methyl]pyrrolidin-1-yl}acetyl)amino]-3-methylbutanoyl}amino)propanoyl]amino}benzyl)oxy]carbonyl}[(3R,4S,5R)-3,4,5,6-tetrahydroxyhexyl]amino)ethoxy]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}methyl)-5-methyl-1H-pyrazol-4-yl]pyridine-2-carboxylic acid;

(6S)-2,6-anhydro-6-(2-{2-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]-5-({N-[(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)acetyl]-N-(2,5,8,11,14,17,20,23,26,29,32-undecaoxatetratriacontan-34-yl)-beta-alanyl-L-valyl-L-alanyl}amino)phenyl}ethyl)-L-gulonic acid;

(6S)-2,6-anhydro-6-(2-{2-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]-5-[(N-{2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-3-[1-(2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxaheptatriacontan-37-yl)-1H-1,2,3-triazol-4-yl]propanoyl}-L-valyl-L-alanyl)amino]phenyl}ethyl)-L-gulonic acid;

(6S)-2,6-anhydro-6-(2-{2-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]-5-[(N-{(3S)-3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-3-[1-(2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxaheptatriacontan-37-yl)-1H-1,2,3-triazol-4-yl]propanoyl}-L-valyl-L-alanyl)amino]phenyl}ethyl)-L-gulonic acid;

(6S)-2,6-anhydro-6-(2-{2-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-

dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]-5-[(N-{(3R)-3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-3-[1-(2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxaheptatriacontan-37-yl)-1H-1,2,3-triazol-4-yl]propanoyl}-L-valyl-L-alanyl)amino]phenyl}ethyl)-L-gulonic acid;

(6S)-2,6-anhydro-6-(2-{2-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]-5-[(N-{(3S)-3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-3-[1-(3-sulfopropyl)-1H-1,2,3-triazol-4-yl]propanoyl}-L-valyl-L-alanyl)amino]phenyl}ethyl)-L-gulonic acid;

(6S)-2,6-anhydro-6-(2-{2-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]-5-[(N-{(3R)-3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-3-[1-(3-sulfopropyl)-1H-1,2,3-triazol-4-yl]propanoyl}-L-valyl-L-alanyl)amino]phenyl}ethyl)-L-gulonic acid;

(6S)-2,6-anhydro-6-(2-{2-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]-5-({N-[(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)acetyl]-N-[2-(2-sulfoethoxy)ethyl]-beta-alanyl-L-valyl-L-alanyl}amino)phenyl}ethyl)-L-gulonic acid;

6-{8-[(1,3-benzothiazol-2-yl)carbamoyl]-3,4-dihydroisoquinolin-2(1H)-yl}-3-[1-({3-[2-({[(2-{2-[(2S,3R,4R,5S,6S)-6-carboxy-3,4,5-trihydroxyoxan-2-yl]ethyl}-4-{[(2S)-2-{[(2S)-2-{[(2S)-2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-3-{4-[(2,5,8,11,14,17,20,23,26,29,32-undecaoxatetratriacontan-34-yl)oxy]phenyl}propanoyl]amino}-3-methylbutanoyl]amino}propanoyl]amino}phenyl)methoxy]carbonyl}[(3R,4S,5R)-3,4,5,6-tetrahydroxyhexyl]amino)ethoxy]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]decan-1-yl}methyl)-5-methyl-1H-pyrazol-4-yl]pyridine-2-carboxylic acid;

4-{[({2-[(3-{[4-(6-{8-[(1,3-benzothiazol-2-yl)carbamoyl]-3,4-dihydroisoquinolin-2(1H)-yl}-2-carboxypyridin-3-yl)-5-methyl-1H-pyrazol-1-yl]methyl}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]decan-1-yl)oxy]ethyl}[(3S)-3,4-dihydroxybutyl]carbamoyl)oxy]methyl}-3-(2-{2-[2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)acetamido]ethoxy}ethoxy)phenyl beta-D-glucopyranosiduronic acid;

2,6-anhydro-8-[2-({[{2-[(3-{[4-(6-{8-[(1,3-benzothiazol-2-yl)carbamoyl]-3,4-dihydroisoquinolin-2(1H)-yl}-2-carboxypyridin-3-yl)-5-methyl-1H-pyrazol-1-yl]methyl}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]decan-1-yl)oxy]ethyl}(2-sulfoethyl)carbamoyl]oxy}methyl)-5-{[(79S,82S)-74-[(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)acetyl]-82-methyl-77,80,83-trioxo-79-(propan-2-yl)-2,5,8,11,14,17,20,23,26,29,32,35,38,41,44,47,50,53,56,59,62,65,68,71-tetracosaoxa-74,78,81-triazatrioctacontan-83-yl]amino}phenyl]-7,8-dideoxy-L-glycero-L-gulo-octonic acid;

6-{8-[(1,3-benzothiazol-2-yl)carbamoyl]-3,4-dihydroisoquinolin-2(1H)-yl}-3-{1-[(3-{2-[{[(4-{[(2S,5S)-2-[3-(carbamoylamino)propyl]-10-[(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)acetyl]-4,7-dioxo-5-(propan-2-yl)-15-sulfo-13-oxa-3,6,10-triazapentadecanan-1-oyl]amino}phenyl)methoxy]carbonyl}(2-sulfoethyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]decan-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-(8-(benzo[d]thiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl)-3-(1-((3-(2-((((2-(2-((2S,3R,4R,5S,6S)-6-carboxy-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl)ethyl)-4-((S)-2-((S)-2-(2-((3S,5S)-3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-2-oxo-5-((2-sulfoethoxy)methyl)pyrrolidin-1-yl)acetamido)-3-methylbutanamido)propanamido)benzyl)oxy)carbonyl)((S)-3,4-dihydroxybutyl)amino)ethoxy)-5,7-dimethyladamantan-1-yl)methyl)-5-methyl-1H-pyrazol-4-yl)picolinic acid;

2,6-anhydro-8-(2-{[({2-[(3-{[4-(6-{8-[(1,3-benzothiazol-2-yl)carbamoyl]-3,4-dihydroisoquinolin-2(1H)-yl}-2-carboxypyridin-3-yl)-5-methyl-1H-pyrazol-1-yl]methyl}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]decan-1-yl)oxy]ethyl}[(3S)-3,4-dihydroxybutyl]carbamoyl)oxy]methyl}-5-{[(2S)-2-({(2S)-2-[2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)acetamido]-3-methylbutanoyl}amino)propanoyl]amino}phenyl)-7,8-dideoxy-L-glycero-L-gulo-octonic acid;

2-{[({2-[(3-{[4-(6-{8-[(1,3-benzothiazol-2-yl)carbamoyl]-3,4-dihydroisoquinolin-2(1H)-yl}-2-carboxypyridin-3-yl)-5-methyl-1H-pyrazol-1-yl]methyl}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]decan-1-yl)oxy]ethyl}[(3S)-3,4-dihydroxybutyl]carbamoyl)oxy]methyl}-5-{4-[2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)acetamido]butyl}phenyl beta-D-glucopyranosiduronic acid;

6-{8-[(1,3-benzothiazol-2-yl)carbamoyl]-3,4-dihydroisoquinolin-2(1H)-yl}-3-{1-[(3-{2-[{[(4-{[(2S)-5-(carbamoylamino)-2-{[(2S)-2-{[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]amino}-3-methylbutanoyl]amino}pentanoyl]amino}phenyl)methoxy]carbonyl}(2-sulfoethyl)amino]acetamido}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]decan-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

N-[6-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)hexanoyl]-L-valyl-*N*-{4-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]-2-carboxypyridin-3-yl}-5-methyl-1*H*-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}sulfanyl)ethyl](2-sulfoethyl)carbamoyl}oxy)methyl]phenyl}-N^5-carbamoyl-L-ornithinamide;

N-[6-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)hexanoyl]-L-valyl-*N*-[4-({[(3-{3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]-2-carboxypyridin-3-yl}-5-methyl-1*H*-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}propyl)(2-sulfoethyl)carbamoyl]oxy}methyl)phenyl]-N^5-carbamoyl-L-ornithinamide;

2-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]-2-carboxypyridin-3-yl}-5-methyl-1*H*-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl][(3*S*)-3,4-dihydroxybutyl]carbamoyl}oxy)methyl]-5-{4-[({(3*S*,5*S*)-3-(2,5-dioxo-2,5-

dihydro-1*H*-pyrrol-1-yl)-2-oxo-5-[(2-sulfoethoxy)methyl]pyrrolidin-1-yl}acetyl)amino]butyl}phenyl beta-D-glucopyranosiduronic acid;

2,6-anhydro-8-[2-({[{2-[(3-{[4-(6-{8-[(1,3-benzothiazol-2-yl)carbamoyl]-3,4-dihydroisoquinolin-2(1*H*)-yl}-2-carboxypyridin-3-yl)-5-methyl-1*H*-pyrazol-1-yl]methyl}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]decan-1-yl)oxy]ethyl}(2-sulfoethyl)carbamoyl]oxy}methyl)-5-{[*N*-({(3*R*,5*S*)-3-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)-2-oxo-5-[(2-sulfoethoxy)methyl]pyrrolidin-1-yl}acetyl)-L-valyl-L-alanyl]amino}phenyl]-7,8-dideoxy-L-*glycero*-L-*gulo*-octonic acid;

2,6-anhydro-8-{2-({[{2-[(3-{[4-(6-{8-[(1,3-benzothiazol-2-yl)carbamoyl]-3,4-dihydroisoquinolin-2(1*H*)-yl}-2-carboxypyridin-3-yl)-5-methyl-1*H*-pyrazol-1-yl]methyl}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]decan-1-yl)oxy]ethyl}(2-sulfoethyl)carbamoyl]oxy}methyl)-5-[(*N*-{[(3*R*,5*S*)-3-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)-2-oxo-5-(41-oxo-2,5,8,11,14,17,20,23,26,29,32,35,38-tridecaoxa-42-azatritetracontan-43-yl)pyrrolidin-1-yl]acetyl}-L-valyl-L-alanyl)amino]phenyl}-7,8-dideoxy-L-*glycero*-L-*gulo*-octonic acid;

(6*S*)-2,6-anhydro-6-(2-{2-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]-2-carboxypyridin-3-yl}-5-methyl-1*H*-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl][(3*S*)-3,4-dihydroxybutyl]carbamoyl}oxy)methyl]-5-({*N*-[(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)acetyl]-*N*-(2,5,8,11,14,17,20,23,26,29,32-undecaoxatetratriacontan-34-yl)-b-alanyl-L-valyl-L-alanyl}amino)phenyl}ethyl)-L-gulonic acid; and

(6*S*)-2,6-anhydro-6-(2-{2-[({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]-2-carboxypyridin-3-yl}-5-methyl-1*H*-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl][(3*S*)-3,4-dihydroxybutyl]carbamoyl}oxy)methyl]-5-({*N*-[(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)acetyl]-*N*-[2-(2-sulfoethoxy)ethyl]-b-alanyl-L-valyl-L-alanyl}amino)phenyl}ethyl)-L-gulonic acid.

In certain embodiments, the ADC, or a pharmaceutically acceptable salt thereof,

D is the Bcl-xL inhibitor selected from the group consisting of the following compounds modified in that the hydrogen corresponding to the # position of structural formula (IIa), (IIb), (IIc), or (IId) is not present, forming a monoradical:

W2.01, W2.02, W2.03, W2.04, W2.05, W2.06, W2.07, W2.08, W2.09, W2.10, W2.11, W2.12, W2.13, W2.14, W2.15, W2.16, W2.17, W2.18, W2.19, W2.20, W2.21, W2.22, W2.23, W2.24, W2.25, W2.26, W2.27, W2.28, W2.29, W2.30, W2.31, W2.32, W2.33, W2.34, W2.35, W2.36, W2.37, W2.38, W2.39, W2.40, W2.41, W2.42, W2.43, W2.44, W2.45, W2.46, W2.47, W2.48, W2.49, W2.50, W2.51, W2.52, W2.53, W2.54, W2.55, W2.56, W2.57, W2.58, W2.59, W2.60, W2.61, W2.62, W2.63, W2.64, W2.65, W2.66, W2.67, W2.68, W2.69, W2.70, W2.71, W2.72, W2.73, W2.74, W2.75, W2.76, W2.77, W2.78, W2.79, W2.80, W2.81, W2.82, W2.83, W2.84, W2.85, W2.86, W2.87, W2.88, W2.89, W2.90, and W2.91, and a pharmaceutically acceptable salt thereof;

L is selected from the group consisting of linkers IVa.1-IVa.8, IVb.1-IVb.19, IVc.1-IVc.7, IVd.1-IVd.4, Va.1-Va.12, Vb.1-Vb.10, Vc.1-Vc.11, Vd.1-Vd.6, Ve.1-Ve.2, VIa.1, VIc.1-V1c.2, VId.1-VId.4, VIIa.1-VIIa.4, VIIb.1-VIIb.8, VIIc.1-VIIc.6, wherein each linker has reacted with the antibody, Ab, forming a covalent attachment;

LK is thioether; and

m is an integer ranging from 1 to 8.

In certain embodiments, the ADC, or a pharmaceutically acceptable salt thereof,

D is the Bcl-xL inhibitor selected from the group consisting of the following compounds modified in that the hydrogen corresponding to the # position of structural formula (IIa), (IIb), (IIc), or (IId) is not present, forming a monoradical:

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3,5-dimethyl-7-{2-[(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3-{2-[(2-carboxyethyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)naphthalen-2-yl]-3-{1-[(3,5-dimethyl-7-{2-[(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.1^{3,7}]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

1-{[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl}oxy)ethyl]amino}-1,2-dideoxy-D-arabino-hexitol;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-(1-{[3-(2-{[3-hydroxy-2-(hydroxymethyl)propyl]amino}ethoxy)-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl]methyl}-5-methyl-1H-pyrazol-4-yl)pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]-3-(1-{[3-(2-{[(3*S*)-3,4-dihydroxybutyl]amino}ethoxy)-5,7-dimethyltricyclo[3.3.1.1^{3,7}]dec-1-yl]methyl}-5-methyl-1*H*-pyrazol-4-yl)pyridine-2-carboxylic acid;

and pharmaceutically acceptable salts thereof;

L is selected from the group consisting of linkers IVb.2, IVc.5, IVc.6, IVc.7, IVd.4, Vb.9, Vc.11, VIIa.1, VIIa.3, VIIc.1, VIIc.4, and VIIc.5 in either closed or open forms and a pharmaceutically acceptable salt thereof;

LK is thioether; and

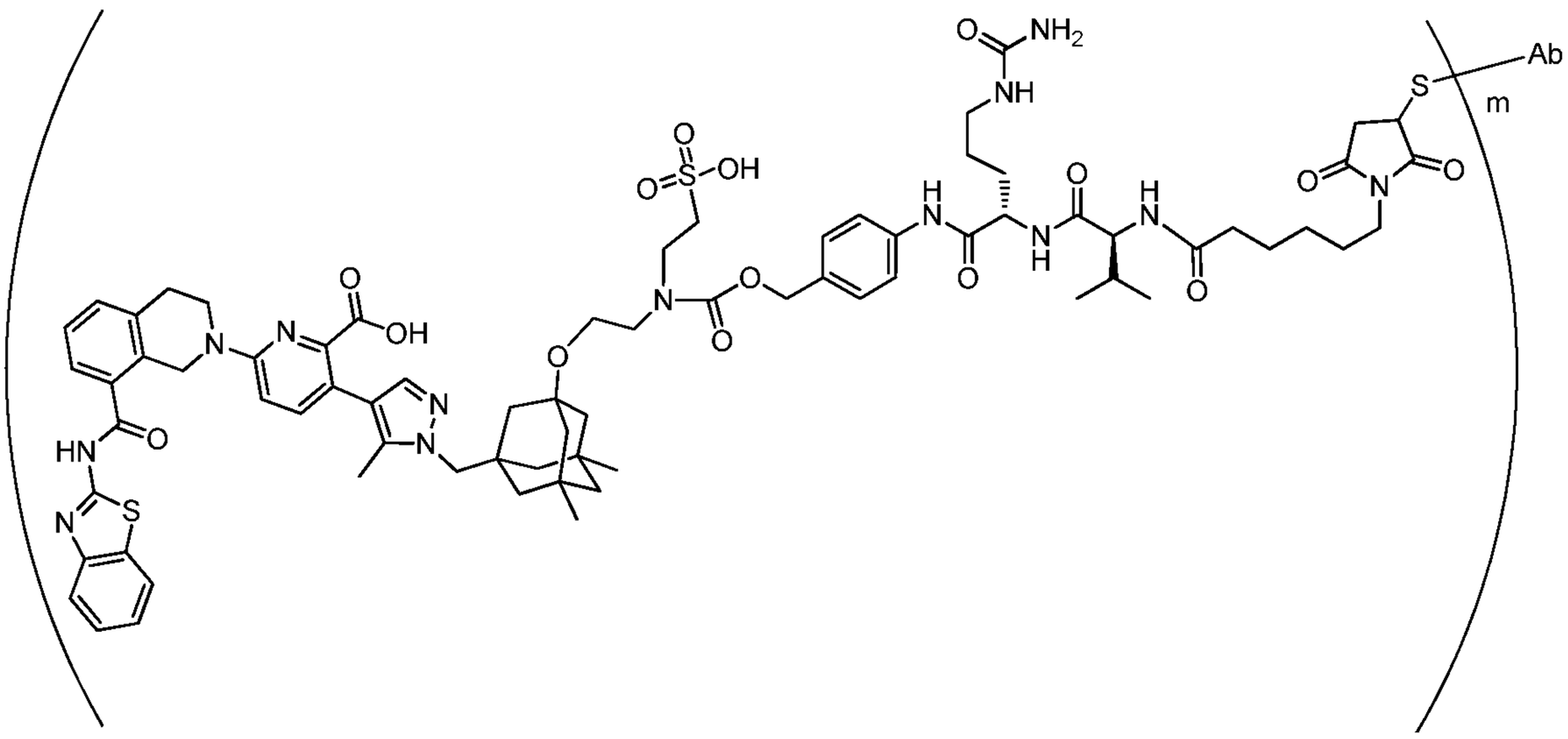
m is an integer ranging from 2 to 4.

To form an ADC, the maleimide ring of a synthon (for example, the synthons listed in Table B) may react with an antibody Ab, forming a covalent attachment as either a succinimide (closed

form) or succinamide(open form). Similarly, other functional groups, e.g. acetyl halide or vinyl sulfone may react with an antibody, Ab, forming a covalent attachment.

In certain embodiments, the ADC, or a pharmaceutically acceptable salt thereof, is selected from the group consisting of AbA-CZ, AbA-TX, AbA-TV, AbA-YY, AbA-AAA, AbA-AAD, AbB-CZ, AbB-TX, AbB-TV, AbB-YY, AbB-AAD, AbG-CZ, AbG-TX, AbG-TV, AbG-YY, AbG-AAA, AbG-AAD, AbK-CZ, AbK-TX, AbK-TV, AbK-YY, AbK-AAA, AbK-AAD, wherein CZ, TX, TV, YY, AAA, and AAD are synthons disclosed in Table B, and wherein the conjugated synthons are either in open or closed form.

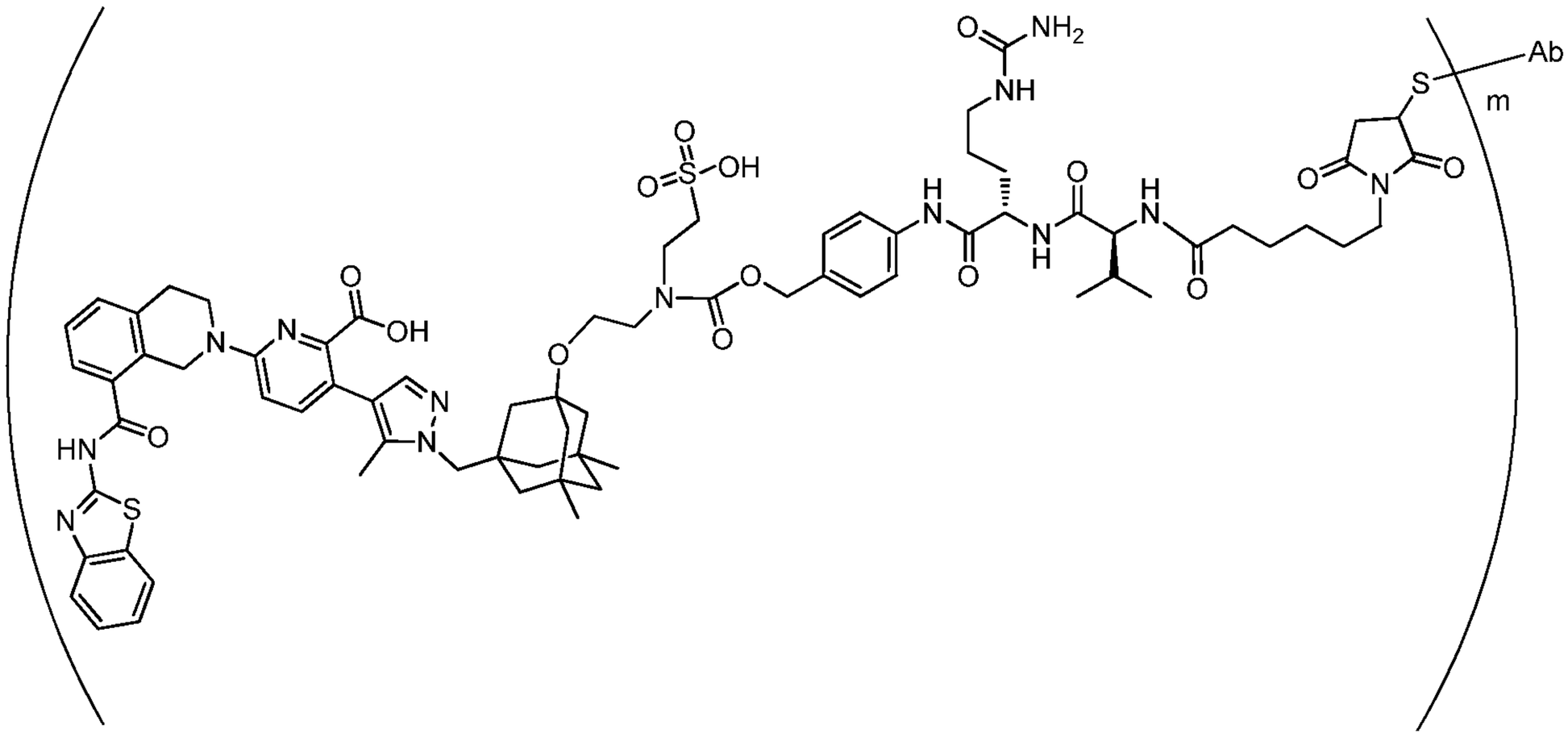
In one embodiment, the ADC, or a pharmaceutically acceptable salt thereof, is:



(i),

wherein m is 2, Ab is either an anti-hB7-H3 antibody, wherein the anti-hB7-H3 antibody comprises a heavy chain CDR3 domain comprising the amino acid sequence set forth in SEQ ID NO: 35, a heavy chain CDR2 domain comprising the amino acid sequence set forth in SEQ ID NO: 34, and a heavy chain CDR1 domain comprising the amino acid sequence set forth in SEQ ID NO: 33; and a light chain CDR3 domain comprising the amino acid sequence set forth in SEQ ID NO: 39, a light chain CDR2 domain comprising the amino acid sequence set forth in SEQ ID NO: 38, and a light chain CDR1 domain comprising the amino acid sequence set forth in SEQ ID NO: 37; or an anti-hB7-H3 antibody, wherein the anti-hB7H3 antibody comprises a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 147, and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 144; or an anti-hB7-H3 antibody, wherein the anti-hB7-H3 antibody comprises a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 168, and a light chain comprising the amino acid sequence set forth in SEQ ID NO: 169.

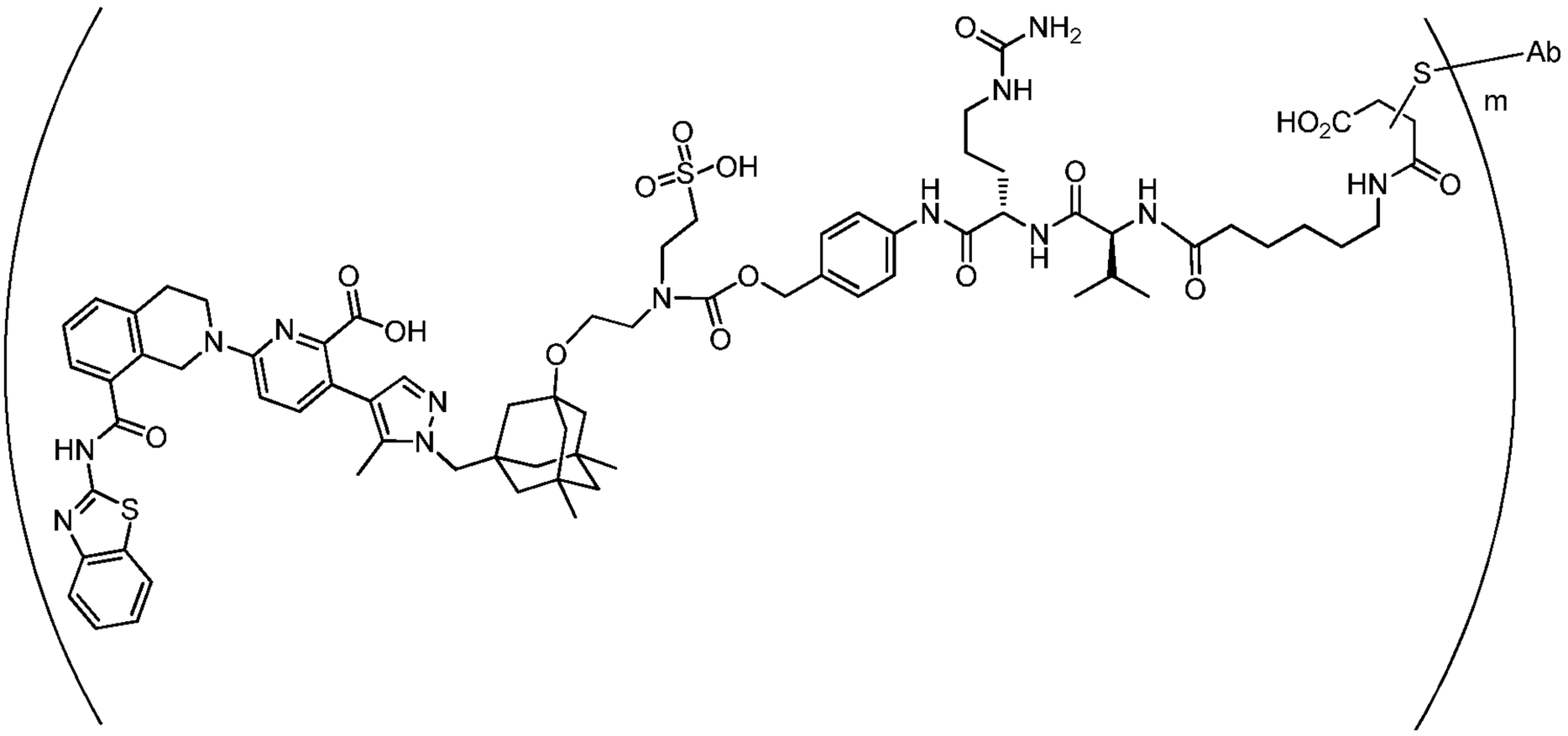
In one embodiment, the ADC, or a pharmaceutically acceptable salt thereof, is:



(i),

wherein m is 2, Ab is either an anti-hB7-H3 antibody, wherein the anti-hB7-H3 antibody comprises a heavy chain CDR3 domain comprising the amino acid sequence set forth in SEQ ID NO: 12, a heavy chain CDR2 domain comprising the amino acid sequence set forth in SEQ ID NO: 140, and a heavy chain CDR1 domain comprising the amino acid sequence set forth in SEQ ID NO: 10; and a light chain CDR3 domain comprising the amino acid sequence set forth in SEQ ID NO: 15, a light chain CDR2 domain comprising the amino acid sequence set forth in SEQ ID NO: 7, and a light chain CDR1 domain comprising the amino acid sequence set forth in SEQ ID NO: 136; or an anti-hB7-H3 antibody, wherein the anti-hB7H3 antibody comprises a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 139, and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 135; or an anti-hB7-H3 antibody, wherein the anti-hB7-H3 antibody comprises a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 170, and a light chain comprising the amino acid sequence set forth in SEQ ID NO: 171.

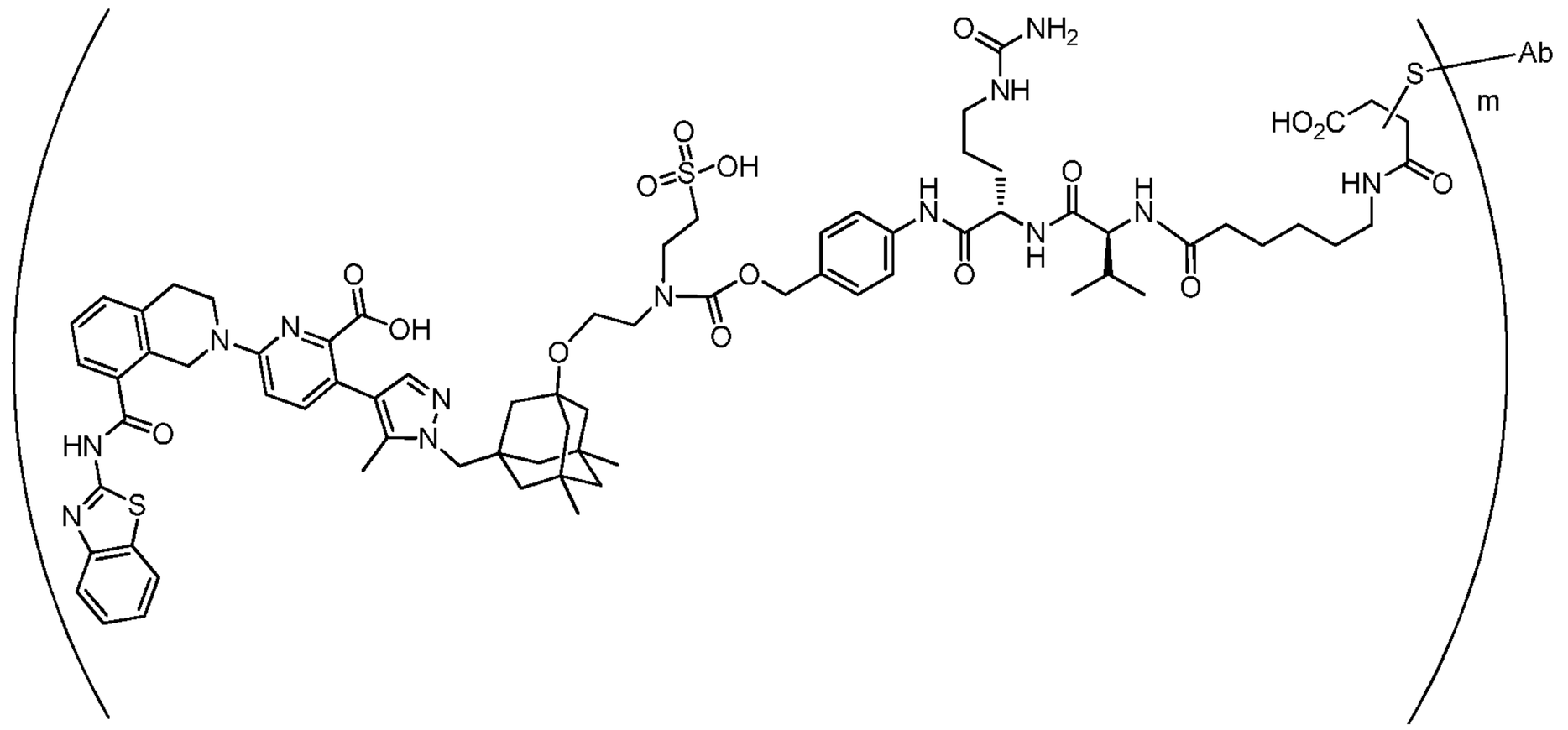
In one embodiment, the ADC, or a pharmaceutically acceptable salt thereof, is:



(ii),

wherein m is 2, Ab is either an anti-hB7-H3 antibody, wherein the anti-hB7-H3 antibody comprises a heavy chain CDR3 domain comprising the amino acid sequence set forth in SEQ ID NO: 35, a heavy chain CDR2 domain comprising the amino acid sequence set forth in SEQ ID NO: 34, and a heavy chain CDR1 domain comprising the amino acid sequence set forth in SEQ ID NO: 33; and a light chain CDR3 domain comprising the amino acid sequence set forth in SEQ ID NO: 39, a light chain CDR2 domain comprising the amino acid sequence set forth in SEQ ID NO: 38, and a light chain CDR1 domain comprising the amino acid sequence set forth in SEQ ID NO: 37; or an anti-hB7-H3 antibody, wherein the anti-hB7H3 antibody comprises a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 147, and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 144; or an anti-hB7-H3 antibody, wherein the anti-hB7-H3 antibody comprises a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 168, and a light chain comprising the amino acid sequence set forth in SEQ ID NO: 169.

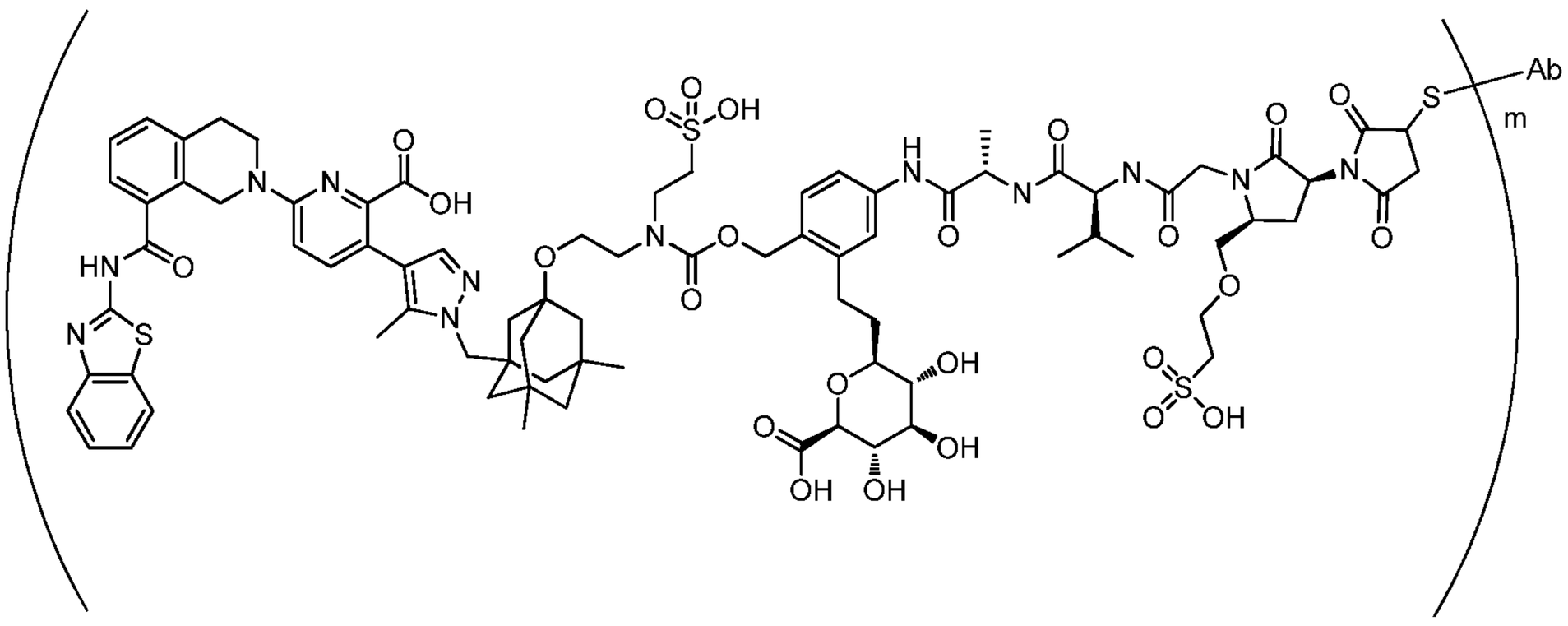
In one embodiment, the ADC, or a pharmaceutically acceptable salt thereof, is:



(ii),

wherein m is 2, Ab is either an anti-hB7-H3 antibody, wherein the anti-hB7-H3 antibody comprises a heavy chain CDR3 domain comprising the amino acid sequence set forth in SEQ ID NO: 12, a heavy chain CDR2 domain comprising the amino acid sequence set forth in SEQ ID NO: 140, and a heavy chain CDR1 domain comprising the amino acid sequence set forth in SEQ ID NO: 10; and a light chain CDR3 domain comprising the amino acid sequence set forth in SEQ ID NO: 15, a light chain CDR2 domain comprising the amino acid sequence set forth in SEQ ID NO: 7, and a light chain CDR1 domain comprising the amino acid sequence set forth in SEQ ID NO: 136; or an anti-hB7-H3 antibody, wherein the anti-hB7H3 antibody comprises a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 139, and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 135; or an anti-hB7-H3 antibody, wherein the anti-hB7-H3 antibody comprises a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 170, and a light chain comprising the amino acid sequence set forth in SEQ ID NO: 171.

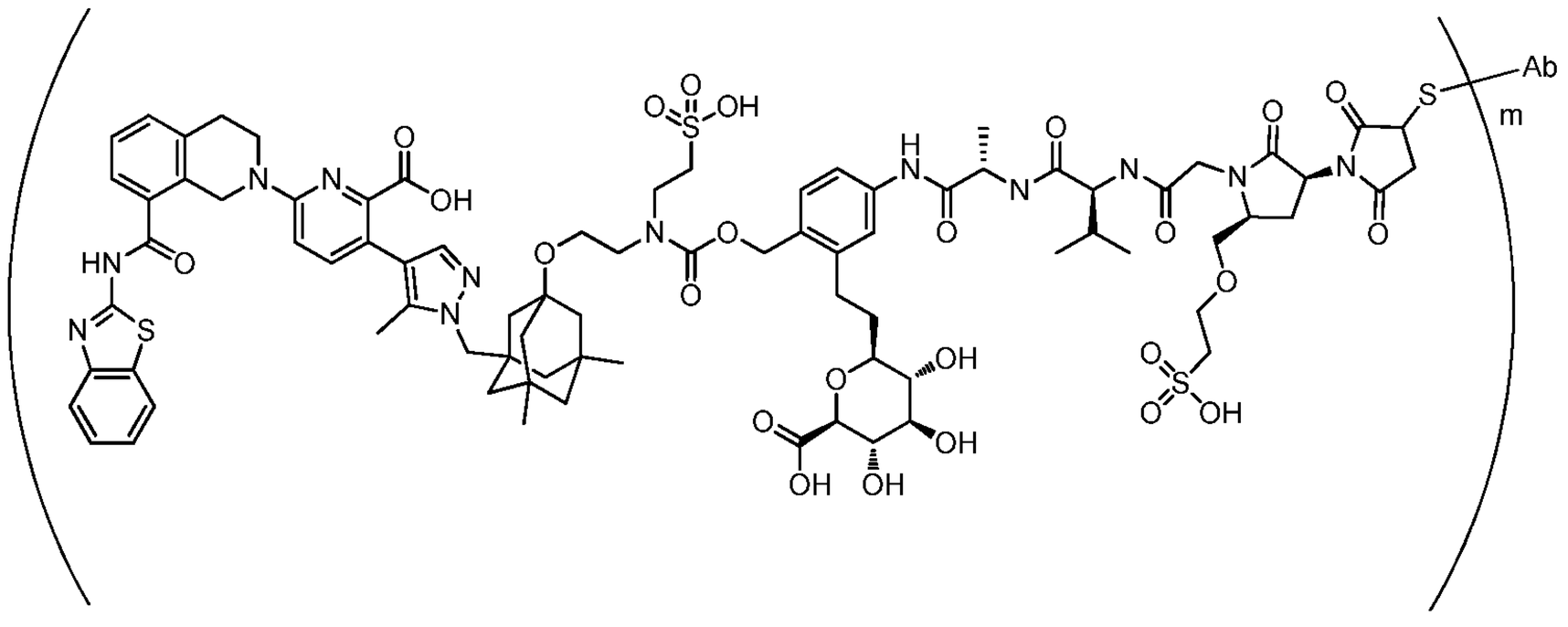
In one embodiment, the ADC, or a pharmaceutically acceptable salt thereof, is:



(iii),

wherein m is 2, Ab is either an anti-hB7-H3 antibody, wherein the anti-hB7-H3 antibody comprises a heavy chain CDR3 domain comprising the amino acid sequence set forth in SEQ ID NO: 35, a heavy chain CDR2 domain comprising the amino acid sequence set forth in SEQ ID NO: 34, and a heavy chain CDR1 domain comprising the amino acid sequence set forth in SEQ ID NO: 33; and a light chain CDR3 domain comprising the amino acid sequence set forth in SEQ ID NO: 39, a light chain CDR2 domain comprising the amino acid sequence set forth in SEQ ID NO: 38, and a light chain CDR1 domain comprising the amino acid sequence set forth in SEQ ID NO: 37; or an anti-hB7-H3 antibody, wherein the anti-hB7H3 antibody comprises a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 147, and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 144; or an anti-hB7-H3 antibody, wherein the anti-hB7-H3 antibody comprises a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 168, and a light chain comprising the amino acid sequence set forth in SEQ ID NO: 169.

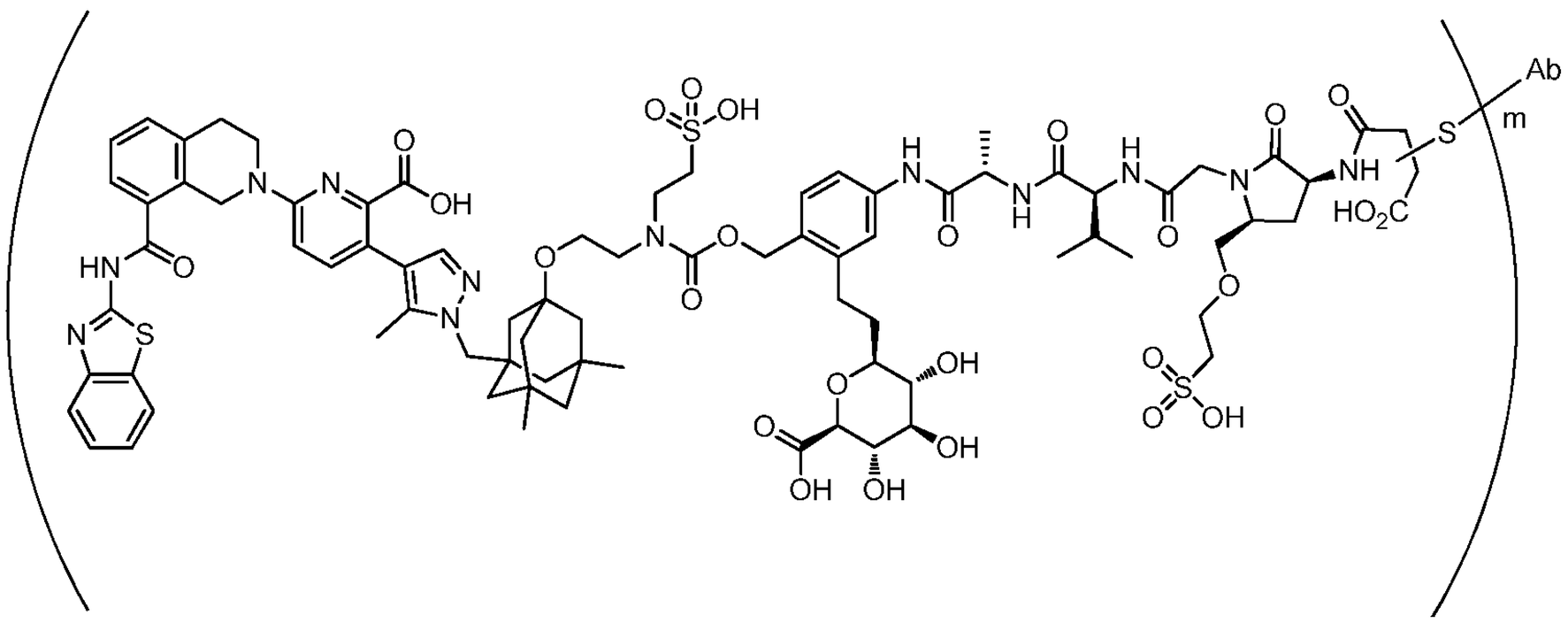
In one embodiment, the ADC, or a pharmaceutically acceptable salt thereof, is:



(iii),

wherein m is 2, Ab is either an anti-hB7-H3 antibody, wherein the anti-hB7-H3 antibody comprises a heavy chain CDR3 domain comprising the amino acid sequence set forth in SEQ ID NO: 12, a heavy chain CDR2 domain comprising the amino acid sequence set forth in SEQ ID NO: 140, and a heavy chain CDR1 domain comprising the amino acid sequence set forth in SEQ ID NO: 10; and a light chain CDR3 domain comprising the amino acid sequence set forth in SEQ ID NO: 15, a light chain CDR2 domain comprising the amino acid sequence set forth in SEQ ID NO: 7, and a light chain CDR1 domain comprising the amino acid sequence set forth in SEQ ID NO: 136; or an anti-hB7-H3 antibody, wherein the anti-hB7H3 antibody comprises a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 139, and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 135; or an anti-hB7-H3 antibody, wherein the anti-hB7-H3 antibody comprises a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 170, and a light chain comprising the amino acid sequence set forth in SEQ ID NO: 171.

In one embodiment, the ADC, or a pharmaceutically acceptable salt thereof, is:

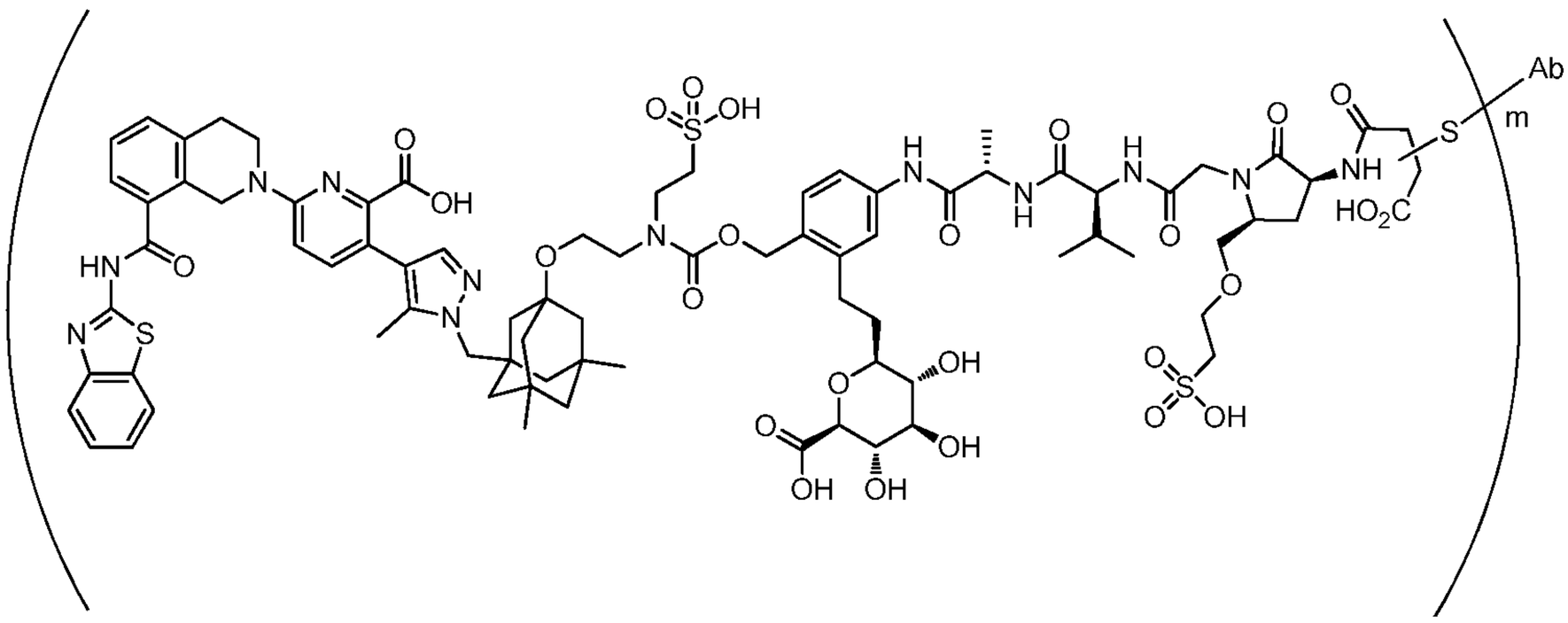


(iv),

wherein m is 2, Ab is either an anti-hB7-H3 antibody, wherein the anti-hB7-H3 antibody comprises a heavy chain CDR3 domain comprising the amino acid sequence set forth in SEQ ID NO: 35, a heavy chain CDR2 domain comprising the amino acid sequence set forth in SEQ ID NO: 34, and a heavy chain CDR1 domain comprising the amino acid sequence set forth in SEQ ID NO: 33; and a light chain CDR3 domain comprising the amino acid sequence set forth in SEQ ID NO: 39, a light chain

CDR2 domain comprising the amino acid sequence set forth in SEQ ID NO: 38, and a light chain CDR1 domain comprising the amino acid sequence set forth in SEQ ID NO: 37; or an anti-hB7-H3 antibody, wherein the anti-hB7H3 antibody comprises a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 147, and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 144; or an anti-hB7-H3 antibody, wherein the anti-hB7-H3 antibody comprises a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 168, and a light chain comprising the amino acid sequence set forth in SEQ ID NO: 169.

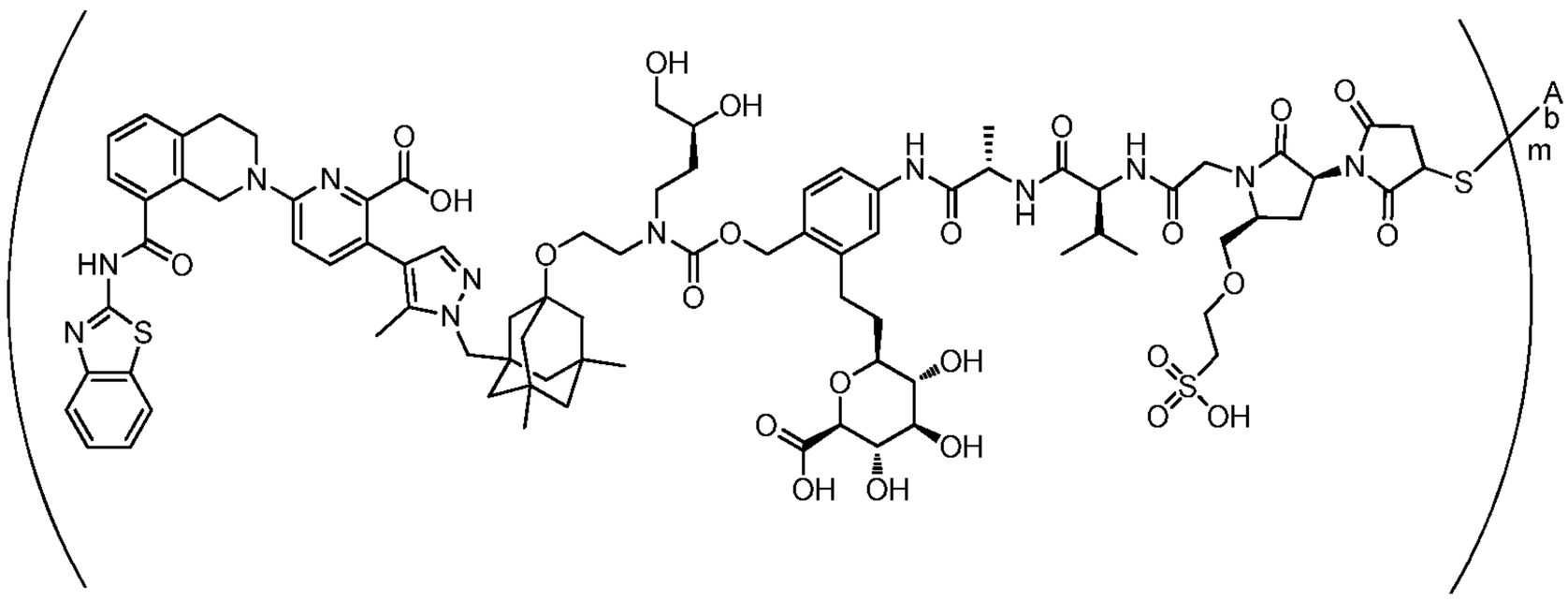
In one embodiment, the ADC, or a pharmaceutically acceptable salt thereof, is:



(iv),

wherein m is 2, Ab is either an anti-hB7-H3 antibody, wherein the anti-hB7-H3 antibody comprises a heavy chain CDR3 domain comprising the amino acid sequence set forth in SEQ ID NO: 12, a heavy chain CDR2 domain comprising the amino acid sequence set forth in SEQ ID NO: 140, and a heavy chain CDR1 domain comprising the amino acid sequence set forth in SEQ ID NO: 10; and a light chain CDR3 domain comprising the amino acid sequence set forth in SEQ ID NO: 15, a light chain CDR2 domain comprising the amino acid sequence set forth in SEQ ID NO: 7, and a light chain CDR1 domain comprising the amino acid sequence set forth in SEQ ID NO: 136; or an anti-hB7-H3 antibody, wherein the anti-hB7H3 antibody comprises a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 139, and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 135; or an anti-hB7-H3 antibody, wherein the anti-hB7-H3 antibody comprises a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 170, and a light chain comprising the amino acid sequence set forth in SEQ ID NO: 171.

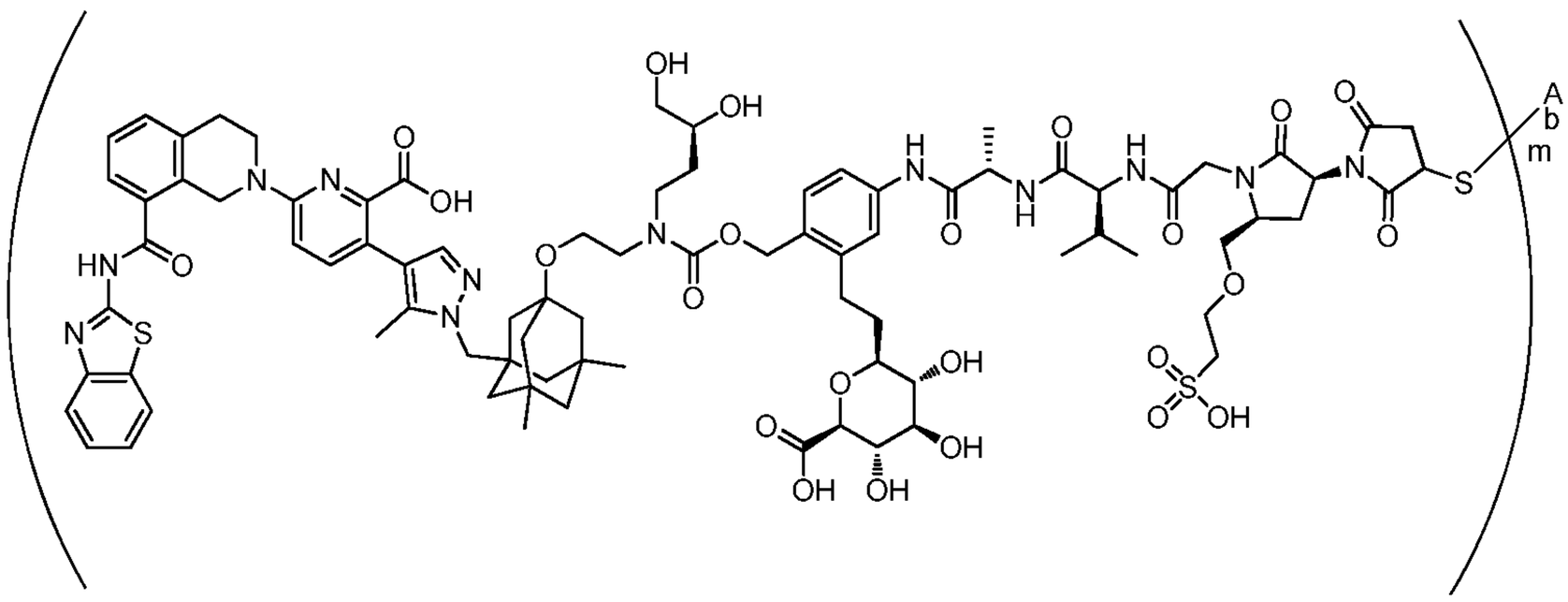
In one embodiment, the ADC, or a pharmaceutically acceptable salt thereof, is:



(v),

wherein m is 2, Ab is either an anti-hB7-H3 antibody, wherein the anti-hB7-H3 antibody comprises a heavy chain CDR3 domain comprising the amino acid sequence set forth in SEQ ID NO: 35, a heavy chain CDR2 domain comprising the amino acid sequence set forth in SEQ ID NO: 34, and a heavy chain CDR1 domain comprising the amino acid sequence set forth in SEQ ID NO: 33; and a light chain CDR3 domain comprising the amino acid sequence set forth in SEQ ID NO: 39, a light chain CDR2 domain comprising the amino acid sequence set forth in SEQ ID NO: 38, and a light chain CDR1 domain comprising the amino acid sequence set forth in SEQ ID NO: 37; or an anti-hB7-H3 antibody, wherein the anti-hB7H3 antibody comprises a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 147, and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 144; or an anti-hB7-H3 antibody, wherein the anti-hB7-H3 antibody comprises a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 168, and a light chain comprising the amino acid sequence set forth in SEQ ID NO: 169.

In one embodiment, the ADC, or a pharmaceutically acceptable salt thereof, is:

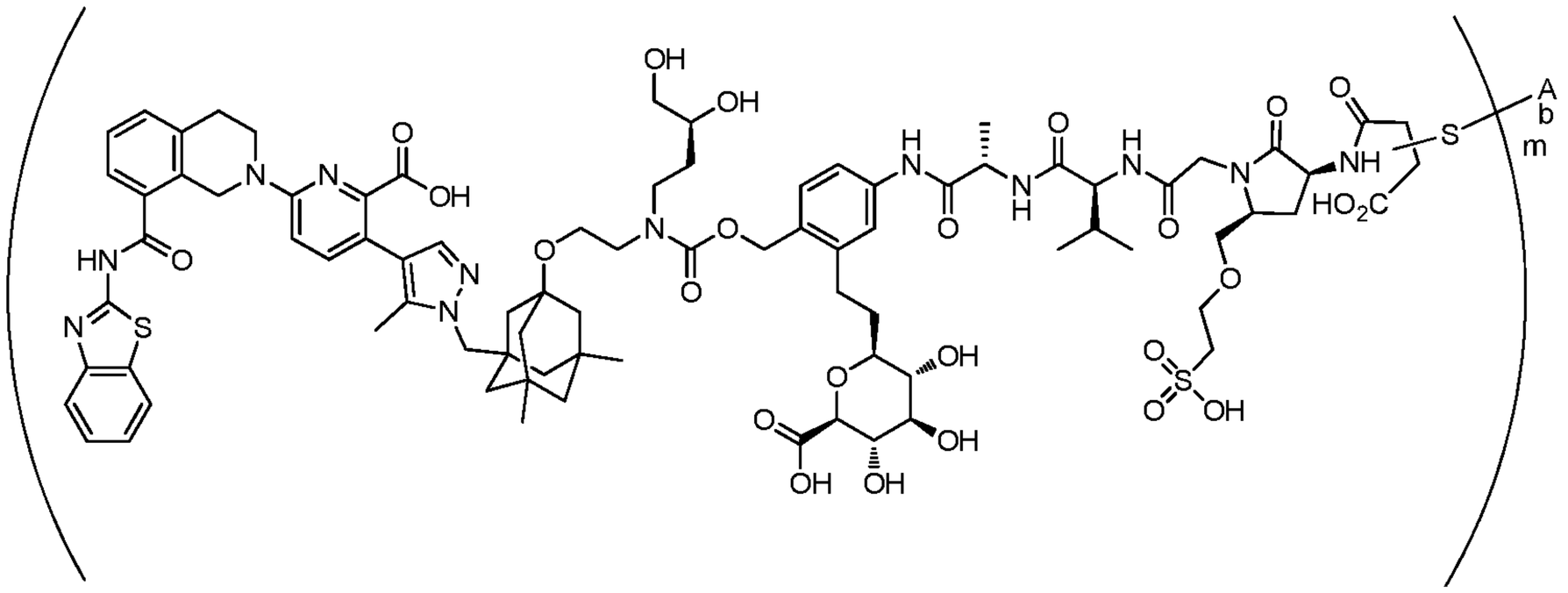


(v),

wherein m is 2, Ab is either an anti-hB7-H3 antibody, wherein the anti-hB7-H3 antibody comprises a heavy chain CDR3 domain comprising the amino acid sequence set forth in SEQ ID NO: 12, a heavy chain CDR2 domain comprising the amino acid sequence set forth in SEQ ID NO: 140, and a heavy chain CDR1 domain comprising the amino acid sequence set forth in SEQ ID NO: 10; and a light chain CDR3 domain comprising the amino acid sequence set forth in SEQ ID NO: 15, a light chain CDR2 domain comprising the amino acid sequence set forth in SEQ ID NO: 7, and a light chain

CDR1 domain comprising the amino acid sequence set forth in SEQ ID NO: 136; or an anti-hB7-H3 antibody, wherein the anti-hB7H3 antibody comprises a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 139, and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 135; or an anti-hB7-H3 antibody, wherein the anti-hB7-H3 antibody comprises a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 170, and a light chain comprising the amino acid sequence set forth in SEQ ID NO: 171.

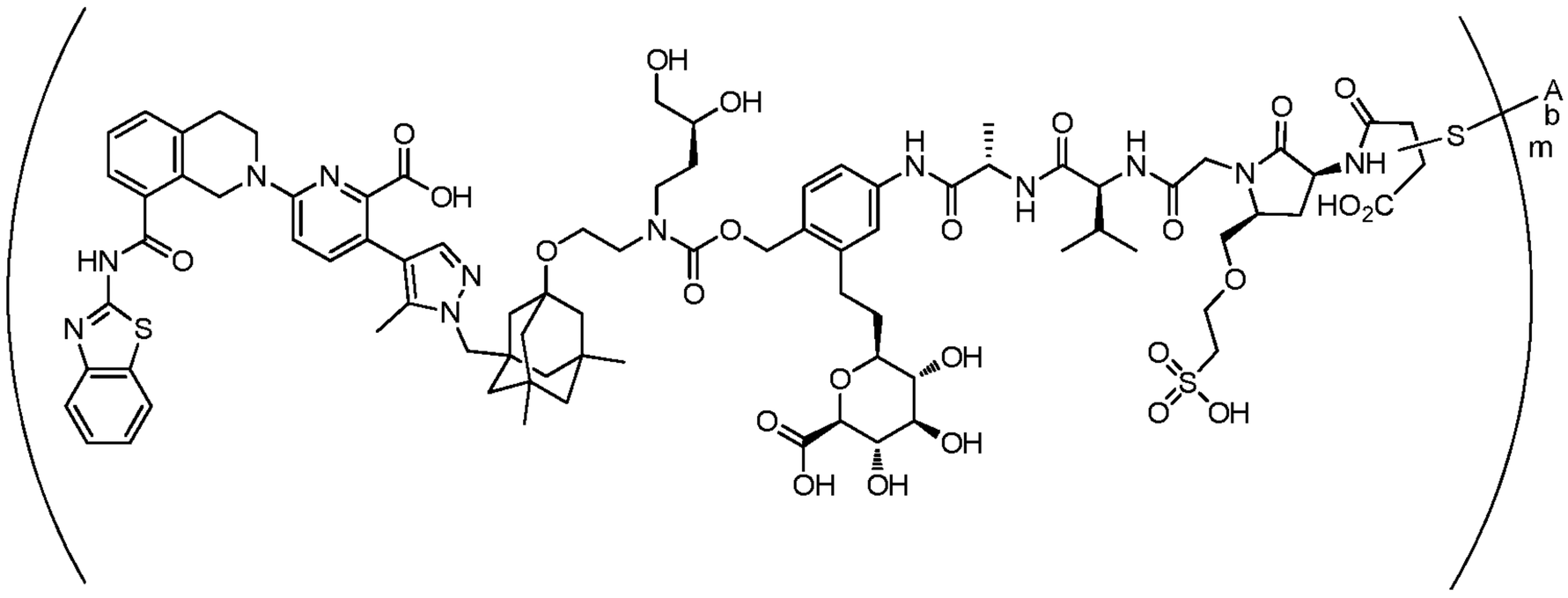
In one embodiment, the ADC, or a pharmaceutically acceptable salt thereof, is:



(vi),

wherein m is 2, Ab is either an anti-hB7-H3 antibody, wherein the anti-hB7-H3 antibody comprises a heavy chain CDR3 domain comprising the amino acid sequence set forth in SEQ ID NO: 35, a heavy chain CDR2 domain comprising the amino acid sequence set forth in SEQ ID NO: 34, and a heavy chain CDR1 domain comprising the amino acid sequence set forth in SEQ ID NO: 33; and a light chain CDR3 domain comprising the amino acid sequence set forth in SEQ ID NO: 39, a light chain CDR2 domain comprising the amino acid sequence set forth in SEQ ID NO: 38, and a light chain CDR1 domain comprising the amino acid sequence set forth in SEQ ID NO: 37; or an anti-hB7-H3 antibody, wherein the anti-hB7H3 antibody comprises a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 147, and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 144; or an anti-hB7-H3 antibody, wherein the anti-hB7-H3 antibody comprises a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 168, and a light chain comprising the amino acid sequence set forth in SEQ ID NO: 169.

In one embodiment, the ADC, or a pharmaceutically acceptable salt thereof, is:



(vi),

wherein m is 2, Ab is either an anti-hB7-H3 antibody, wherein the anti-hB7-H3 antibody comprises a heavy chain CDR3 domain comprising the amino acid sequence set forth in SEQ ID NO: 12, a heavy chain CDR2 domain comprising the amino acid sequence set forth in SEQ ID NO: 140, and a heavy chain CDR1 domain comprising the amino acid sequence set forth in SEQ ID NO: 10; and a light chain CDR3 domain comprising the amino acid sequence set forth in SEQ ID NO: 15, a light chain CDR2 domain comprising the amino acid sequence set forth in SEQ ID NO: 7, and a light chain CDR1 domain comprising the amino acid sequence set forth in SEQ ID NO: 136; or an anti-hB7-H3 antibody, wherein the anti-hB7H3 antibody comprises a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 139, and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 135; or an anti-hB7-H3 antibody, wherein the anti-hB7-H3 antibody comprises a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 170, and a light chain comprising the amino acid sequence set forth in SEQ ID NO: 171.

Bcl-xL inhibitors, including warheads and synthons, and methods of making the same, are described in US 2016/0339117 (AbbVie Inc.), which is incorporated by reference herein.

III.A.4. Methods of Synthesis of Bcl-xL ADCs

The Bcl-xL inhibitors and synthons described herein may be synthesized using standard, known techniques of organic chemistry. General schemes for synthesizing Bcl-xL inhibitors and synthons that may be used as-is or modified to synthesize the full scope of Bcl-xL inhibitors and synthons described herein are provided below. Specific methods for synthesizing exemplary Bcl-xL inhibitors and synthons that may be useful for guidance are provided in the Examples section. ADCs may likewise be prepared by standard methods, such as methods analogous to those described in Hamblett *et al.*, 2004, "Effects of Drug Loading on the Antitumor Activity of a Monoclonal Antibody Drug Conjugate", *Clin. Cancer Res.* 10:7063-7070; Doronina *et al.*, 2003, "Development of potent and highly efficacious monoclonal antibody auristatin conjugates for cancer therapy," *Nat. Biotechnol.* 21(7):778-784; and Francisco *et al.*, 2003, *Blood* 102:1458-1465. For example, ADCs with four drugs per antibody may be prepared by partial reduction of the antibody with an excess of a

reducing reagent such as DTT or TCEP at 37 °C for 30 min, then the buffer exchanged by elution through SEPHADEX® G-25 resin with 1 mM DTPA in DPBS. The eluent is diluted with further DPBS, and the thiol concentration of the antibody may be measured using 5,5'-dithiobis(2-nitrobenzoic acid) [Ellman's reagent]. An excess, for example 5-fold, of a linker-drug synthon is added at 4 °C for 1 hr, and the conjugation reaction may be quenched by addition of a substantial excess, for example 20-fold, of cysteine. The resulting ADC mixture may be purified on SEPHADEX G-25 equilibrated in PBS to remove unreacted synthons, desalted if desired, and purified by size-exclusion chromatography. The resulting ADC may then be then sterile filtered, for example, through a 0.2 μm filter, and lyophilized if desired for storage. In certain embodiments, all of the interchain cysteine disulfide bonds are replaced by linker-drug conjugates. One embodiment pertains to a method of making an ADC, comprising contacting a synthon described herein with an antibody under conditions in which the synthon covalently links to the antibody

Examples of the foregoing Bcl-xL inhibtors, linkers, and synthons thereof, as well as methods of making the same, can be found in US Patent Publication No. US 2016/0339117, the entire contents of which are incorporated by reference herein.

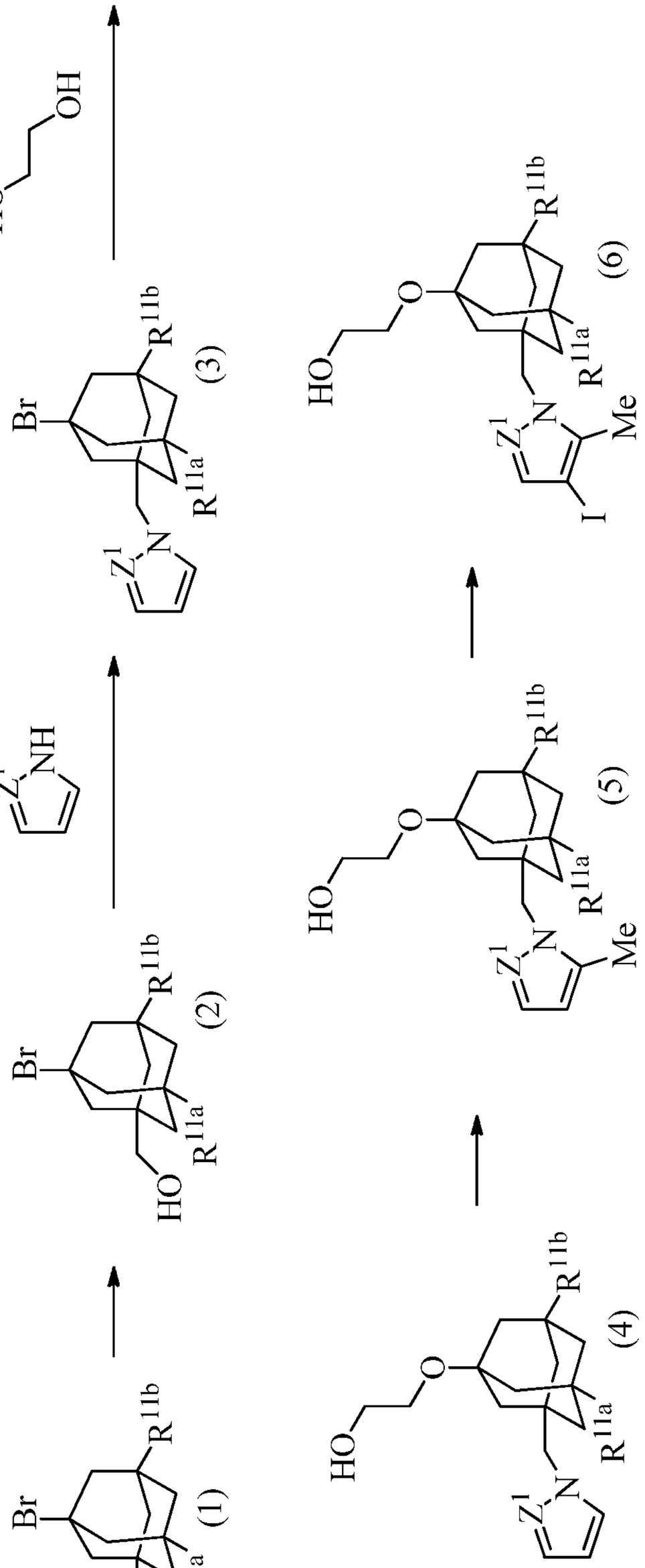
Specific methods for synthesizing exemplary ADCs that may be used to synthesize the full range of ADCs described herein are provided in the Examples section.

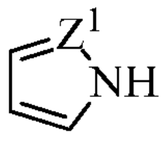
III.A.5. General Methods for Synthesizing Bcl-xL Inhibitors

In the schemes below, the various substituents Ar^1, Ar^2, Z^1, R^4, R^{10}, R^{11a} and R^{11b} are as defined in the Detailed Description section.

5.1.1. Synthesis of Compound (6)

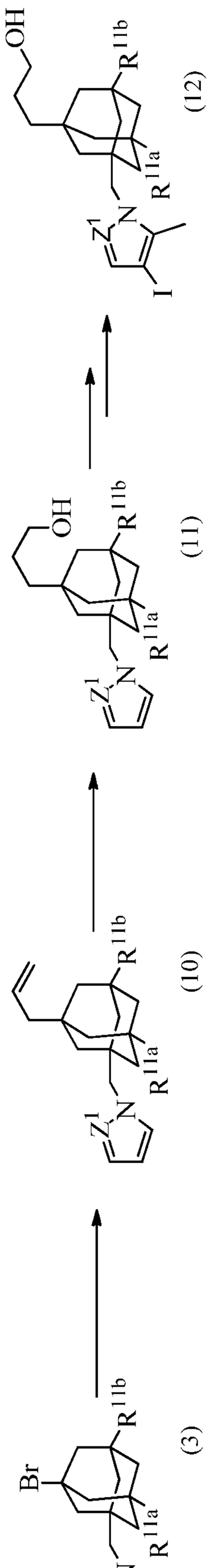
Scheme 1



The synthesis of an intermediate (6) is described in Scheme 1. Compound (1) can be treated with $BH_3 \cdot THF$ to provide compound (2). The reaction is typically performed at ambient temperature in a solvent, such as, but not limited to, tetrahydrofuran. Compound (3) can be prepared by treating compound (2) with  in the presence of cyanomethylenetributylphosphorane. The reaction is typically performed at an elevated temperature in a solvent such as, but not limited to, toluene. Compound (3) can be treated with ethane-1,2-diol in the presence of a base such as, but not limited to, triethylamine, to provide compound (4). The reaction is typically performed at an elevated temperature, and the reaction may be performed under microwave conditions. Compound (4) can be treated with a strong base, such as, but not limited to, n-butyllithium, followed by the addition of iodomethane, to provide compound (5). The addition and reaction is typically performed in a solvent such as, but not limited to, tetrahydrofuran, at a reduced temperature before warming up to ambient temperature for work up. Compound (5) can be treated with N-iodosuccinimide to provide compound (6). The reaction is typically performed at ambient temperature is a solvent such as, but not limited to, N,N-dimethylformamide.

5.1.2. Synthesis of Compound (12)

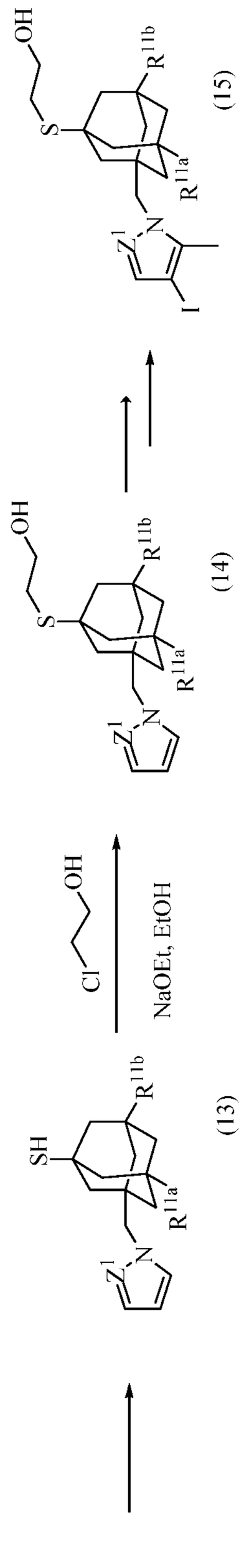
Scheme 2



The synthesis of intermediate (12) is described in Scheme 2. Compound (3) can be treated with tri-n-butyl-allylstannane in the presence of $ZnCl_2 \cdot Et_2O$ or N, N'-azoisobutyronitrile (AIBN) to provide compound (10) (Yamamoto e*t al.*, 1998, *Heterocycles* 47:765-780). The reaction is typically performed at -78 °C in a solvent, such as, but not limited to dichloromethane. Compound (10) can be treated under standard conditions known in the art for hydroboration/oxidation to provide compound (11). For example, treatment of compound (10) with a reagent such as $BH_3 \cdot THF$ in a solvent such as, but not limited to, tetrahydrofuran followed by treatment of the intermediate alkylborane adduct with an oxidant such as, but not limited to, hydrogen peroxide in the presence of a base such as, but not limited to, sodium hydroxide would provide compound (11) (Brown *et al.*, 1968, *J. Am. Chem. Soc.* 86:397). Typically the addition of $BH_3 \cdot THF$ is performed at low temperature before warming to ambient temperature, which is followed by the addition of hydrogen peroxide and sodium hydroxide to generate the alcohol product. Compound (12) can be generated according to Scheme 1, as previously described for compound (6).

5.1.3. Synthesis of Compound (15)

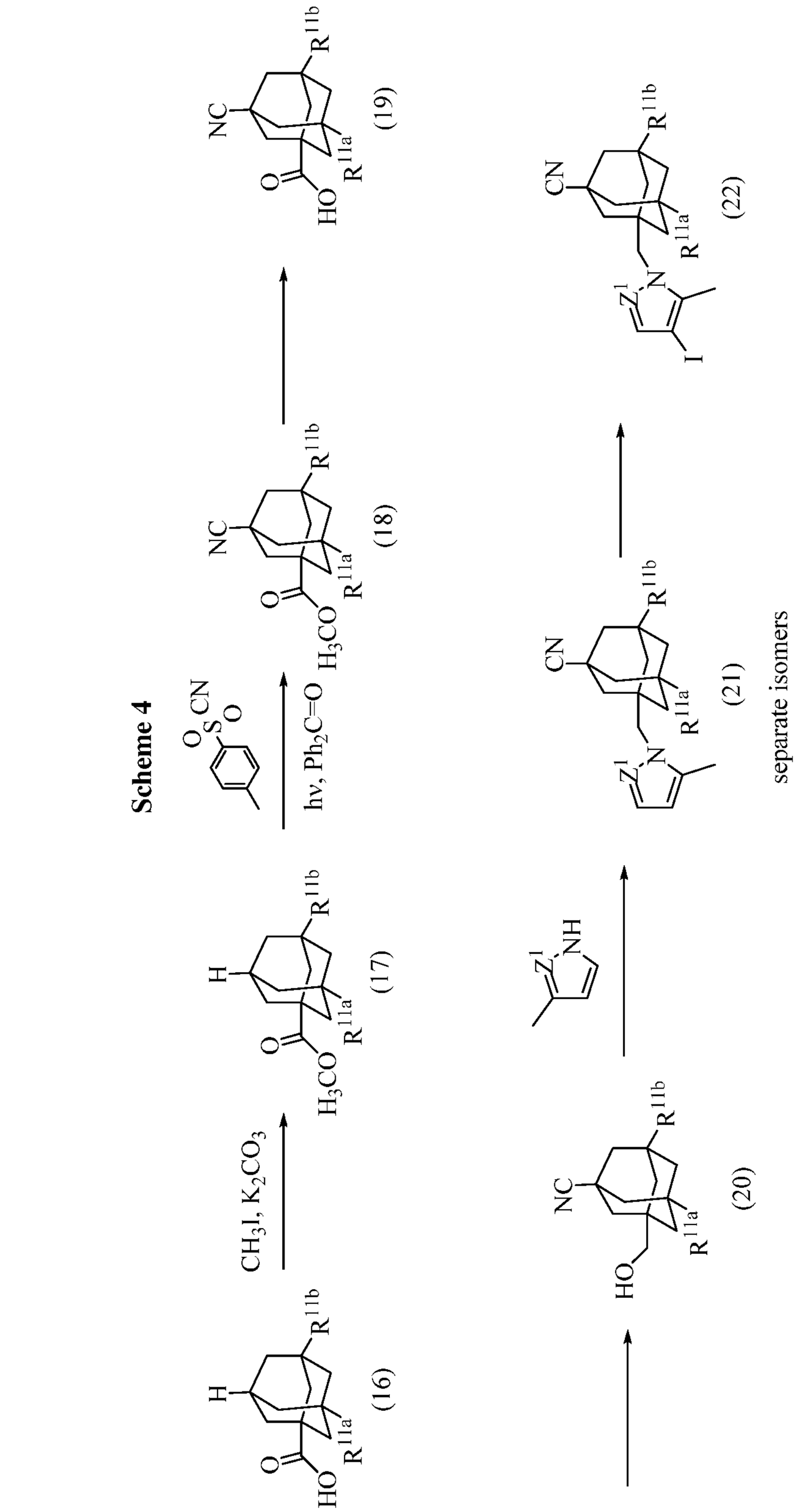
Scheme 3

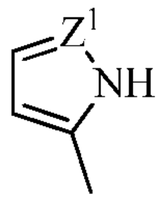


The synthesis of intermediate (15) is described in Scheme 3. Compound (3) can be reacted with thiourea in a solvent mixture of acetic acid and 48% aqueous HBr solution at 100 °C to yield an intermediate that can be subsequently treated with sodium hydroxide in a solvent mixture such as, but not limited to, 20% v/v ethanol in water to provide compound (13). Compound (13) can be reacted with 2-chloroethanol in the presence of a base such as, but not limited to, sodium ethoxide to provide compound (14). The reaction is typically performed at ambient or elevated temperatures in a solvent such as, but not limited to, ethanol. Compound (15) can be generated according to Scheme 1, as previously described for compound (6).

5.1.4. Synthesis of Compound (22)

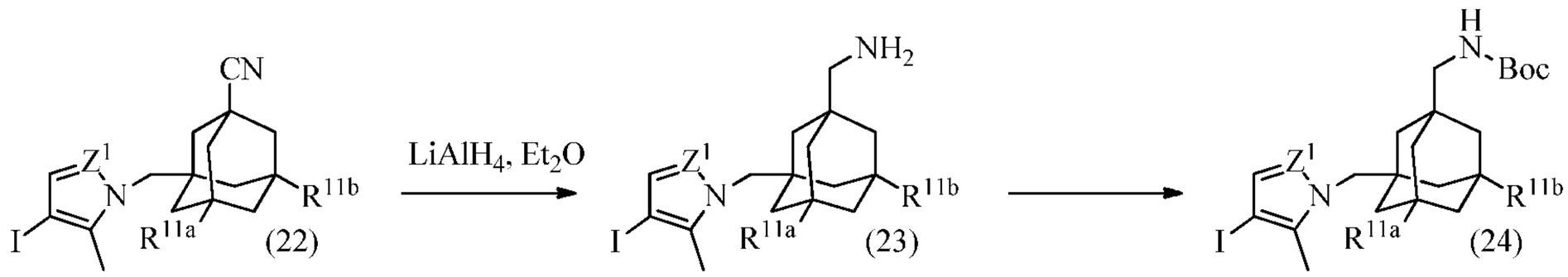
Scheme 4



The synthesis of compound (22) is described in Scheme 4. Compound (16) can be reacted with iodomethane in the presence of a base such as, but not limited to, potassium carbonate to provide compound (17). The reaction is typically conducted at ambient or elevated temperature in a solvent such as, but not limited to, acetone or N,N-dimethylformamide. Compound (17) can be reacted under photochemical conditions with tosyl cyanide in the presence of benzophenone to provide compound (18) (*see* Kamijo *et al.*, 2011, *Org. Lett.*, 13:5928-5931). The reaction is typically run at ambient temperature in a solvent such as, but not limited to, acetonitrile or benzene using a Riko 100W medium pressure mercury lamp as the light source. Compound (18) can be reacted with lithium hydroxide in a solvent system such as, but not limited to, mixtures of water and tetrahydrofuran or water and methanol to provide compound (19). Compound (19) can be treated with $BH_3 \cdot THF$ to provide compound (20). The reaction is typically performed at ambient temperature in a solvent, such as, but not limited to, tetrahydrofuran. Compound (21) can be prepared by treating compound (20) with  in the presence of cyanomethylenetributylphosphorane. The reaction is typically performed at an elevated temperature in a solvent such as, but not limited to, toluene. Compound (21) can be treated with N-iodosuccinimide to provide compound (22). The reaction is typically performed at ambient temperature is a solvent such as, but not limited to, N,N-dimethylformamide.

5.1.5. Synthesis of Compound (24)

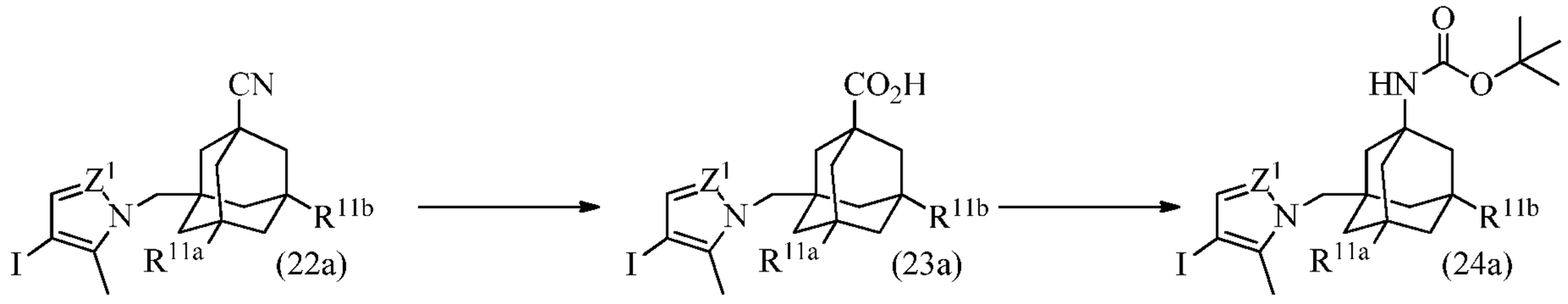
Scheme 5



The synthesis of pyrazole compound (24), is described in Scheme 5. Compound (22) can be treated with a reducing agent such as, but not limited to, lithium aluminum hydride in a solvent such as, but not limited to, diethyl ether or tetrahydrofuran to provide compound (23). Typically the reaction is performed at 0 °C before warming to ambient or elevated temperature. Compound (23) can be reacted with di-tert-butyl dicarbonate under standard conditions described herein or in the literature to provide compound (24).

5.1.6. Synthesis of Compound (24a)

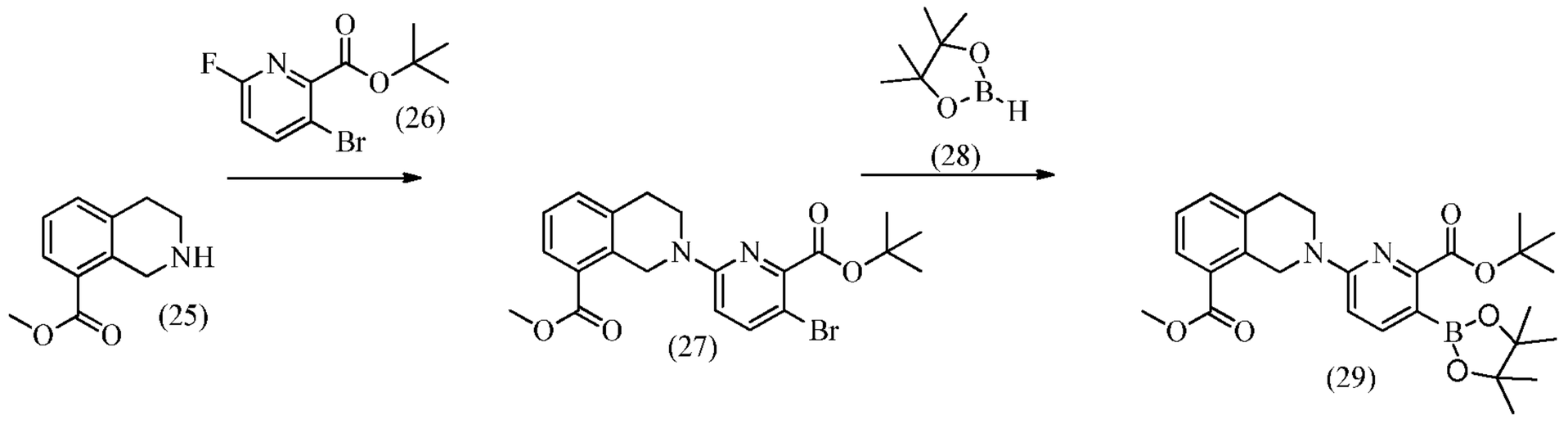
Scheme 6



The synthesis of intermediate (24a) is described in Scheme 6. Compound (22a) can be hydrolyzed using conditions described in the literature to provide compound (23a). Typically the reaction is run in the presence of potassium hydroxide in a solvent such as, but not limited to, ethylene glycol at elevated temperatures (*see* Roberts *et al.*, 1994, *J. Org. Chem.* *59*:6464-6469; Yang *et al*, 2013, *Org. Lett.*, 15:690-693). Compound (24a) can be made from compound (23a) by Curtius rearrangement using conditions described in the literature. For example, compound (23a) can be reacted with sodium azide in the presence of tetrabutylammonium bromide, zinc(II) triflate and di-tert-butyl dicarbonate to provide compound (24a) (*see* Lebel *et al.*, *Org. Lett.*, 2005, 7:4107-4110). Typically the reaction is run at elevated temperatures, preferably from 40-50°C, in a solvent such as, but not limited to, tetrahydrofuran.

5.1.7. Synthesis of Compound (29)

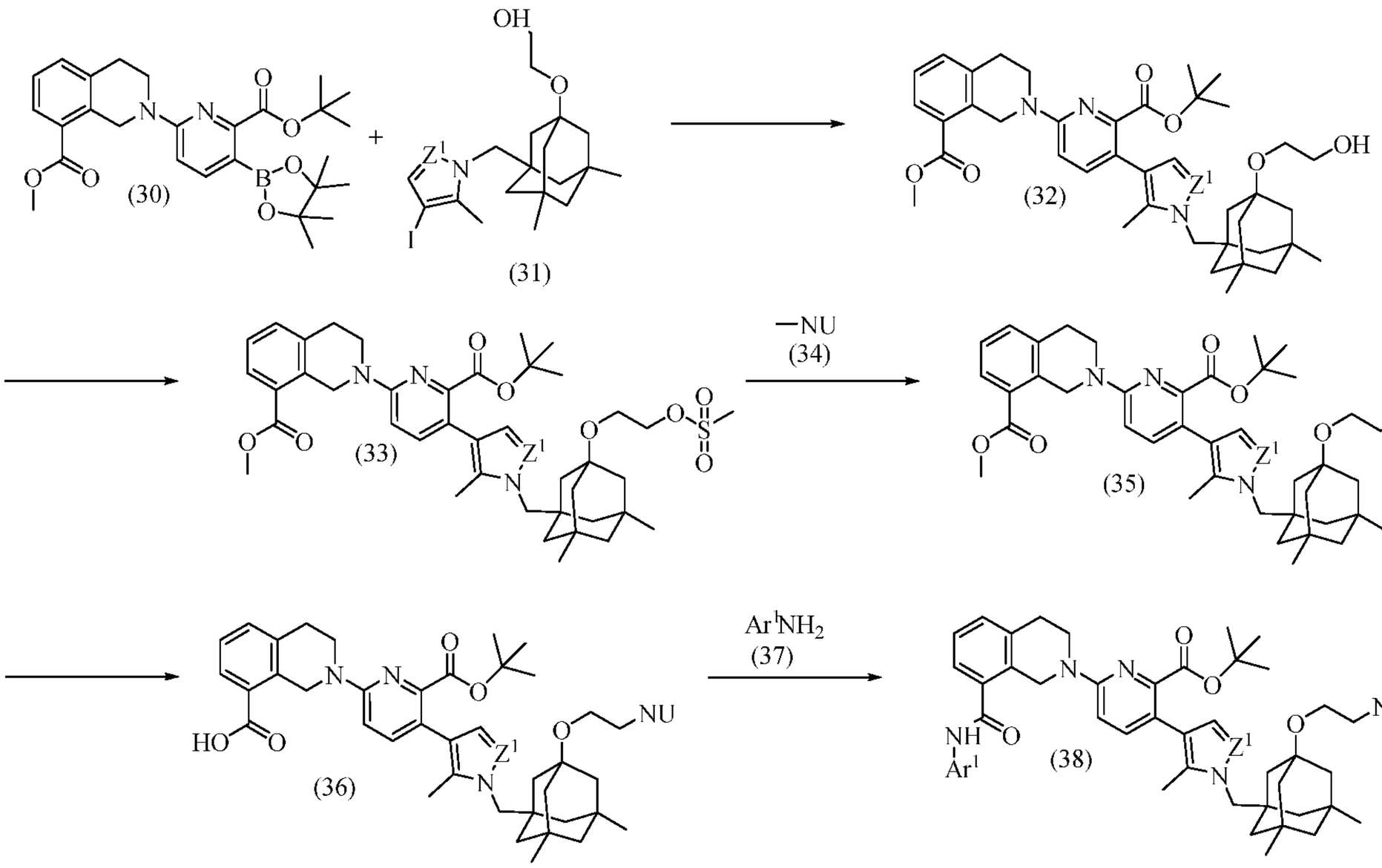
Scheme 7



As shown in Scheme 7, compounds of formula (27) can be prepared by reacting compounds of formula (25) with *tert*-butyl 3-bromo-6-fluoropicolinate (26) in the presence of a base, such as, but not limited to, N,N-diisopropylethylamine, or triethylamine. The reaction is typically performed under an inert atmosphere at an elevated temperature in a solvent, such as, but not limited to, dimethyl sulfoxide. Compounds of formula (27) can be reacted with 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (28), under borylation conditions described herein or in the literature to provide compounds of formula (29).

5.1.8. Synthesis of Compound (38)

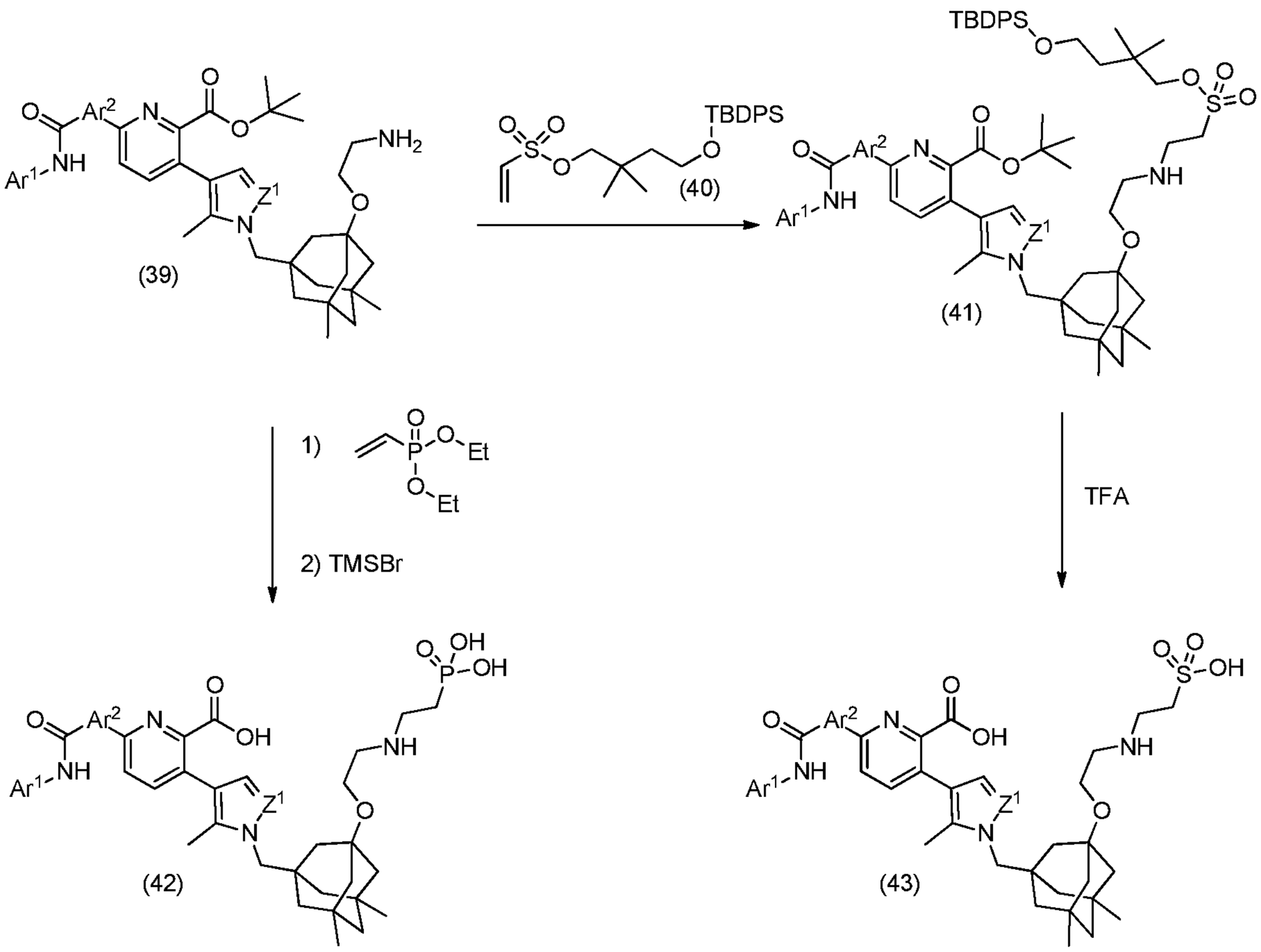
Scheme 8



Scheme 8 describes a method to make intermediates which contain -Nu (nucleophile) tethered to an adamantane and picolinate protected as a t-butyl ester. Compound (30) can be reacted with compound (31) under Suzuki Coupling conditions described herein or in the literature to provide methyl compound (32). Compound (32) can be treated with a base such as but not limited to triethylamine, followed by methanesulfonyl chloride to provide compound (33). The addition is typically performed at low temperature before warming up to ambient temperature in a solvent, such as, but not limited to, dichloromethane. Compound (33) can be reacted with a nucleophile (Nu) of formula (34) to provide compound (35). Examples of nucleophiles include, but are not limited to, sodium azide, methylamine, ammonia and di-tert-butyl iminodicarbonate. Compound (17) can be reacted with lithium hydroxide to provide compound (36). The reaction is typically performed at ambient temperature in a solvent such as but not limited to tetrahydrofuran, methanol, water, or mixtures thereof. Compound (36) can be reacted with compound (37) under amidation conditions described herein or readily available in the literature to provide compounds of formula (38).

5.1.9. Synthesis of Compounds (42) and (43)

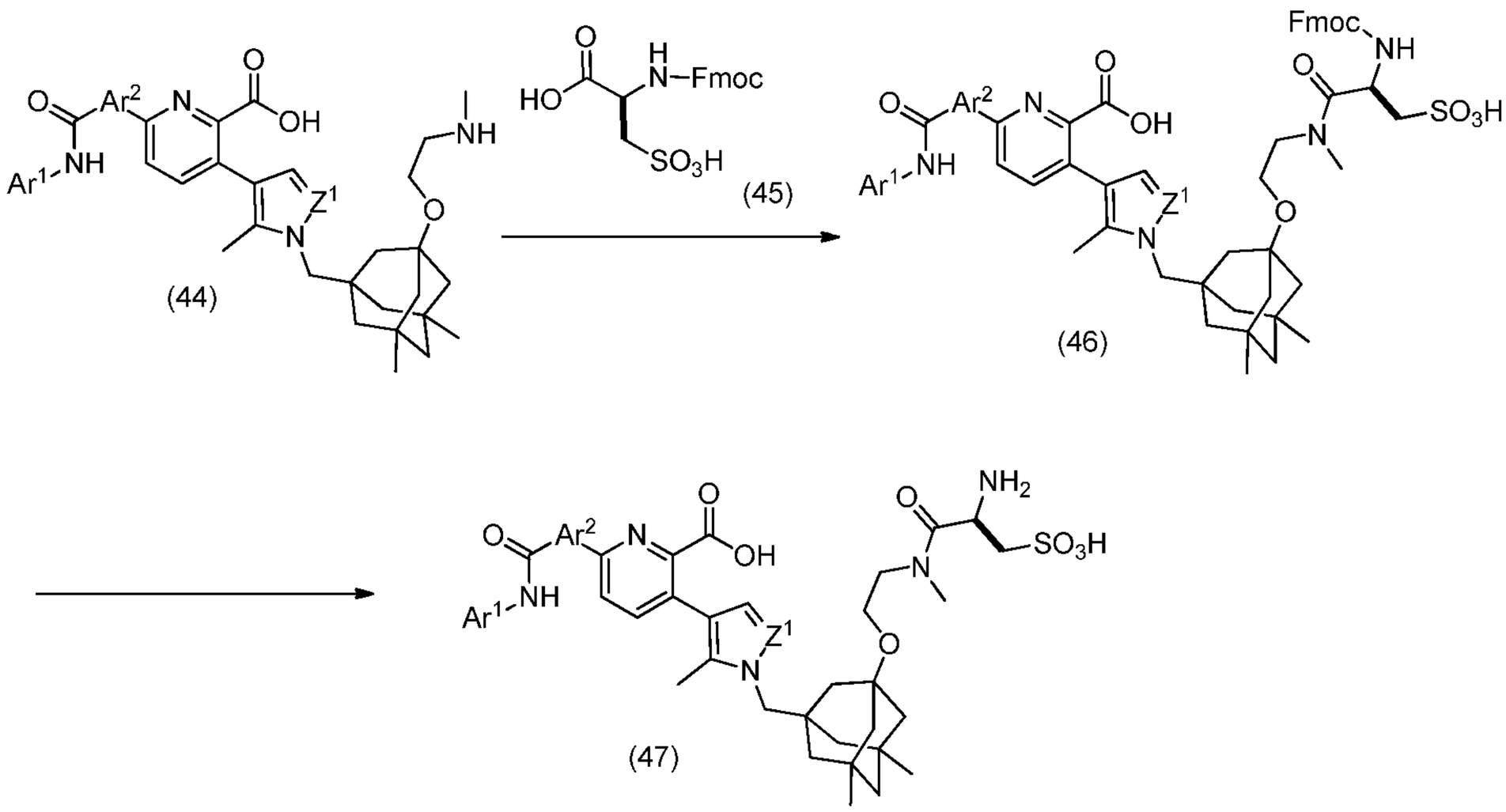
Scheme 9



Scheme 9 shows representative methods used to make solubilized Bcl-xL inhibitors. Bcl-xL inhibitors can be synthesized using the general approach of modifying a primary amine with a solubilizing group and then attaching the resulting secondary amine to a linker as described in later schemes. For example, compound (41) can be prepared by reacting compound (39) with compound (40). The reaction is typically performed at ambient temperature in a solvent such as but not limited to N,N-dimethylformamide. Compound (41) can be reacted with trifluoroacetic acid to provide compound (43). The reaction is typically performed at ambient temperature in a solvent such as but not limited to dichloromethane. Another example shown in Scheme 9 is the reaction of compound (39) with diethyl vinylphosphonate, followed by reaction with bromotrimethylsilane and allyltrimethylsilane to provide compound (42). Other examples to introduce solubilizing groups on the Bcl-xL inhibitors described herein include, but are not limited to, reductive amination reactions, alkylations, and amidation reactions.

5.1.10. Synthesis of Compound (47)

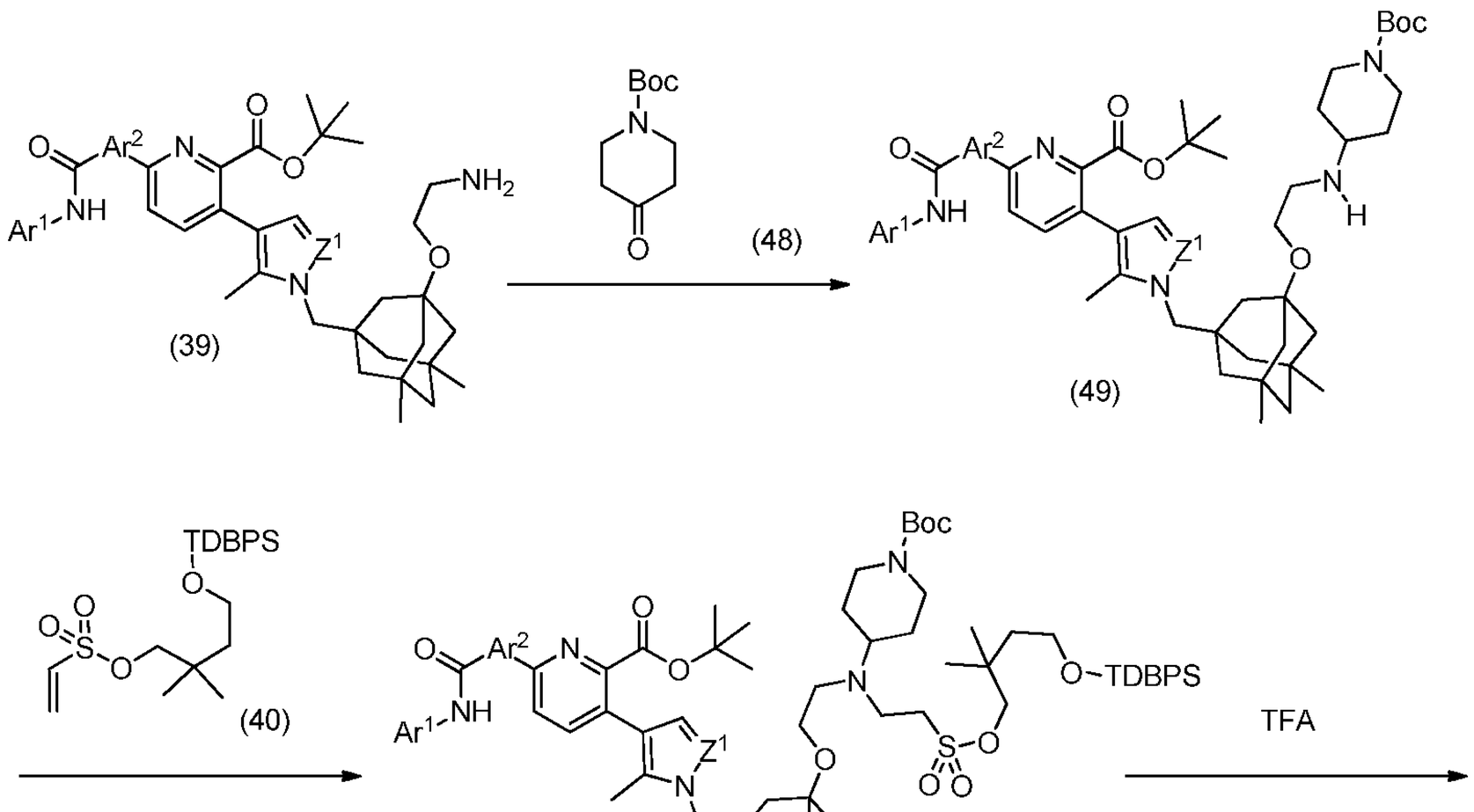
Scheme 10



Scheme 10 shows introduction of a solubilizing group by amidation reaction. Bcl-xL inhibitors can be synthesized using the general approach of modifying a primary or secondary amine with a solubilizing group and then attaching the resulting amine to a linker as described in later schemes. For example, compound (45) can be treated sequentially with HATU and compound (44), to provide compound (46). Compound (46) can be treated with diethylamine in solvents such as, but not limited to, N,N-dimethylformamide to give compound (47).

5.1.11. Synthesis of Compound (51)

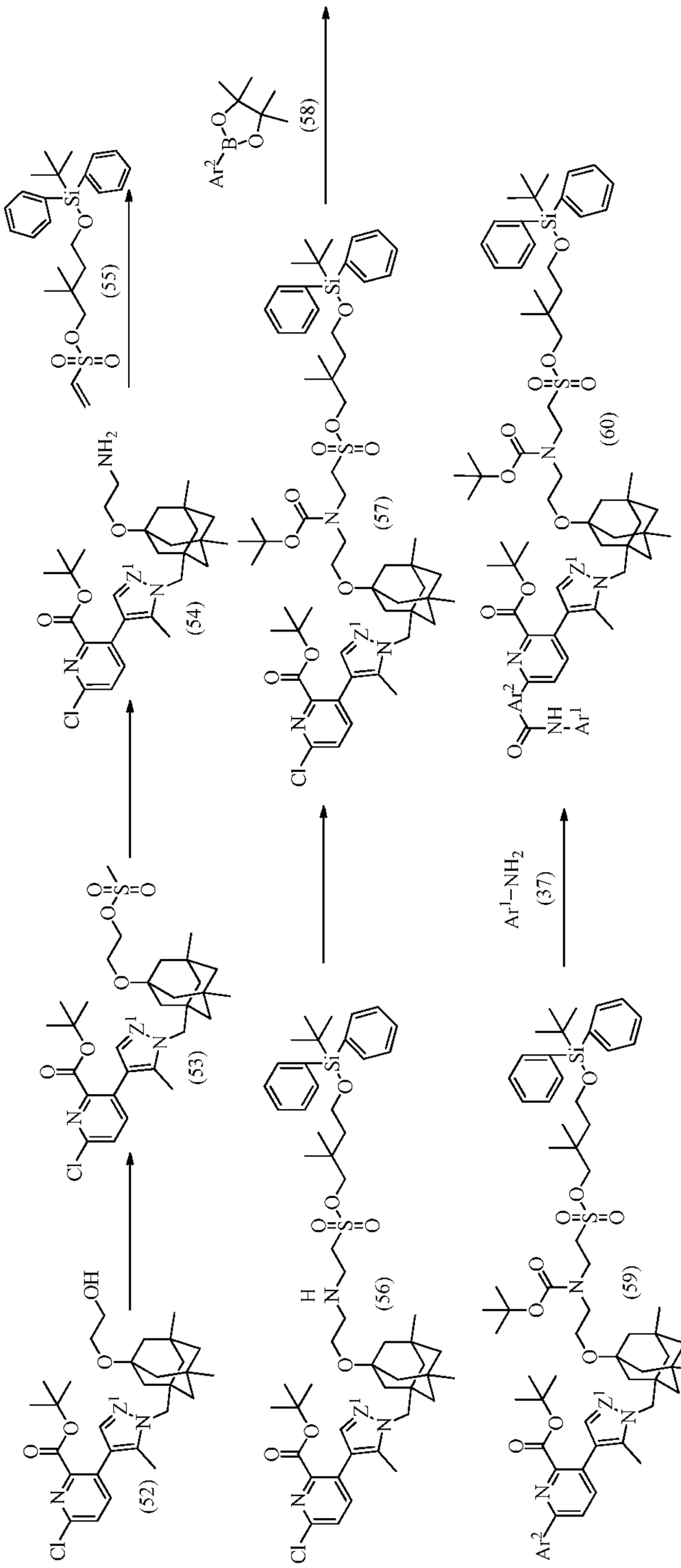
Scheme 11



Scheme 11 shows representative methods to make solubilized Bcl-xL inhibitors. Bcl-xL inhibitors can be synthesized using the general approach of modifying a primary amine with a spacer to give a differentially protected diamine. The unprotected secondary amine can be modified with a solubilizing group. Deprotection of a protected amine them reveals a site for linker attachment, as described in later schemes. For example, compound (39) can be reductively alkylated with reagents such as, but not limited to tert-butyl 4-oxopiperidine-1-carboxylate (48), under conditions known in the art, to provide a secondary amine (49). Compound (50) can be prepared by reacting compound (49) with 4-((*tert*-butyldiphenylsilyl)oxy)-2,2-dimethylbutyl ethenesulfonate (40). The reaction is typically performed at ambient temperature in a solvent such as but not limited to N,N-dimethylformamide. Compound (40) can be reacted with trifluoroacetic acid to provide compound (51). The reaction is typically performed at ambient temperature in a solvent such as but not limited to dichloromethane.

5.1.12. Synthesis of Compound (61)

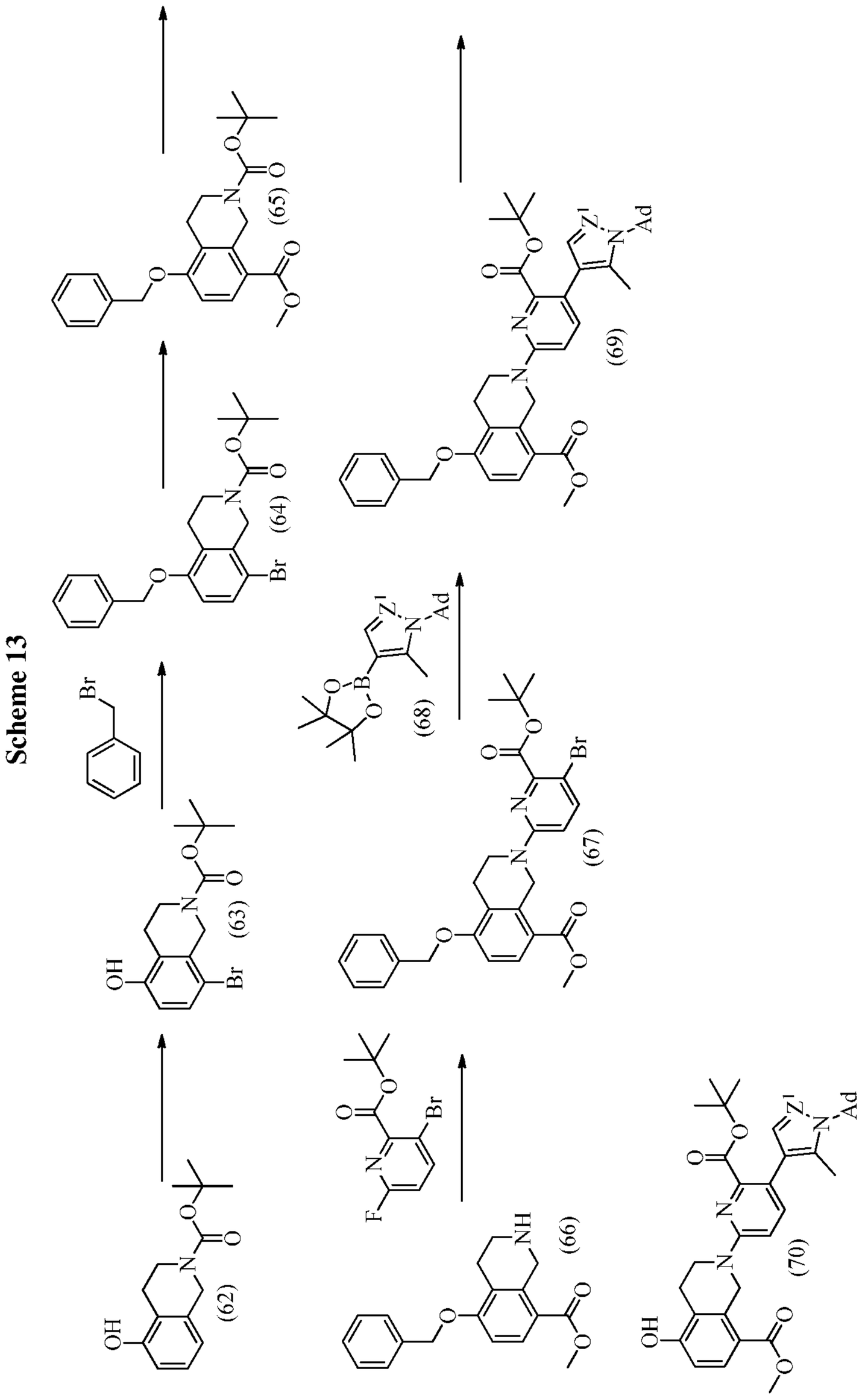
Scheme 12



Scheme 12 describes a method to synthesize solubilized Bcl-xL inhibitors. Compound (52) can be reacted with methanesulfonyl chloride, in the presence of a base, such as, but not limited to, triethylamine, to provide compound (53). The reaction is typically performed at a low temperature in a solvent such as but not limited to dichloromethane. Compound (53) can be treated with ammonia in methanol to provide compound (54). The reaction is typically performed at an elevated temperature, and the reaction may be performed under microwave conditions. Compound (56) can be prepared by reacting compound (55) in the presence of a base such as but not limited to N,N-diisopropylethylamine. The reaction is typically performed at ambient temperature in a solvent such as but not limited to N,N-dimethylformamide. Compound (56) can be treated with di-t-butyldicarbonate and 4-(dimethylamino)pyridine to provide compound (57). The reaction is typically performed at ambient temperature in a solvent such as but not limited to tetrahydrofuran. Compound (59) can be prepared by reacting compound (57) with a boronate ester (or the equivalent boronic acid) of formula (58), under Suzuki Coupling conditions described herein or in the literature. Bis(2,5-dioxopyrrolidin-1-yl) carbonate can be reacted with compound (37), followed by reaction with compound (59), to provide compound (60). The reaction is typically performed at ambient temperature in a solvent such as, but not limited to, acetonitrile. Compound (61) can be prepared by treating compound (60) with trifluoroacetic acid. The reaction is typically performed at ambient temperature in a solvent such as but not limited to dichloromethane.

5.1.13. Synthesis of Compound (70)

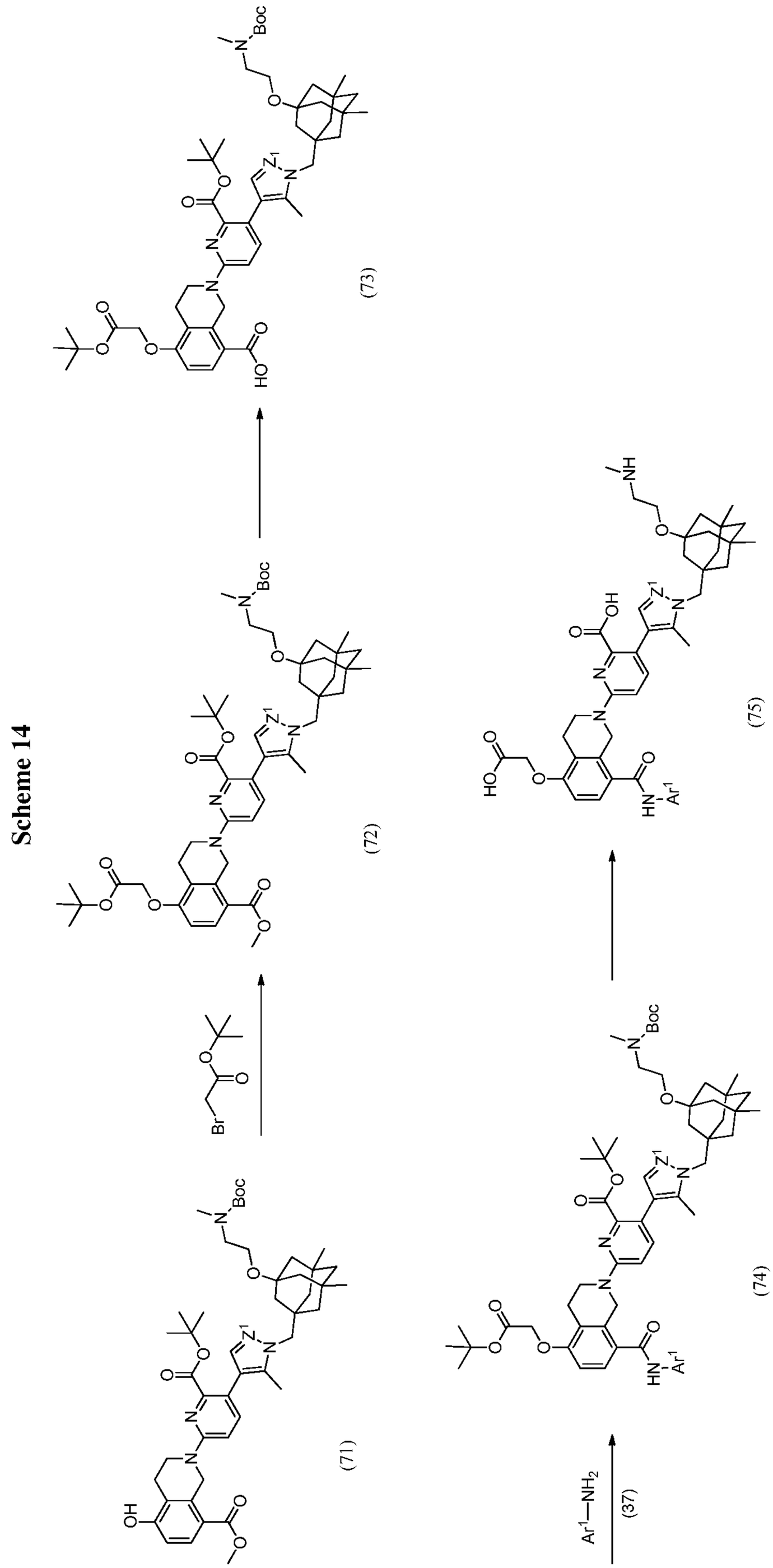
Scheme 13



Scheme 13 describes the synthesis of 5-hydroxy tetrahydroisoquinoline intermediates. Compound (63) can be prepared by treating compound (62) with N-bromosuccinimide. The reaction is typically performed at ambient temperature is a solvent such as, but not limited to, N,N-dimethylformamide. Compound (63) can be reacted with benzyl bromide in the presence of a base, such as, but not limited to, potassium carbonate, to provide compound (64). The reaction is typically performed at an elevated temperature, in a solvent such as, but not limited to, acetone. Compound (64) can be treated with carbon monoxide and methanol in the presence of a base, such as, but not limited to, triethylamine, and a catalyst, such as, but not limited to, compound (65). The reaction is typically performed at an elevated temperature under an inert atmosphere. Compound (65) can be treated with an acid, such as, but not limited to, hydrochloric acid in dioxane, to provide compound (66). The reaction is typically performed at ambient temperature in a solvent, such as, but not limited to, tetrahydrofuran. Compound (67) can be prepared by reacting compound (66) with *tert*-butyl 3-bromo-6-fluoropicolinate in the presence of a base, such as, but not limited to, triethylamine. The reaction is typically performed under an inert atmosphere at an elevated temperature in a solvent, such as, but not limited to, dimethyl sulfoxide. Compound (67) can be reacted with a boronic acid of formula (68), wherein Ad is the methyladamantane moiety of the compounds of the disclosure (*e.g.*, the compounds of formulae (IIa)-(IId)), under Suzuki Coupling conditions described herein or in the literature to provide compound (69). Compound (70) can be prepared by reacting compound (69) with hydrogen in the presence of $Pd(OH)_2$. The reaction is typically performed at an elevated temperature in a solvent such as, but not limited to tetrahydrofuran.

5.1.14. Synthesis of Compound (75)

Scheme 14



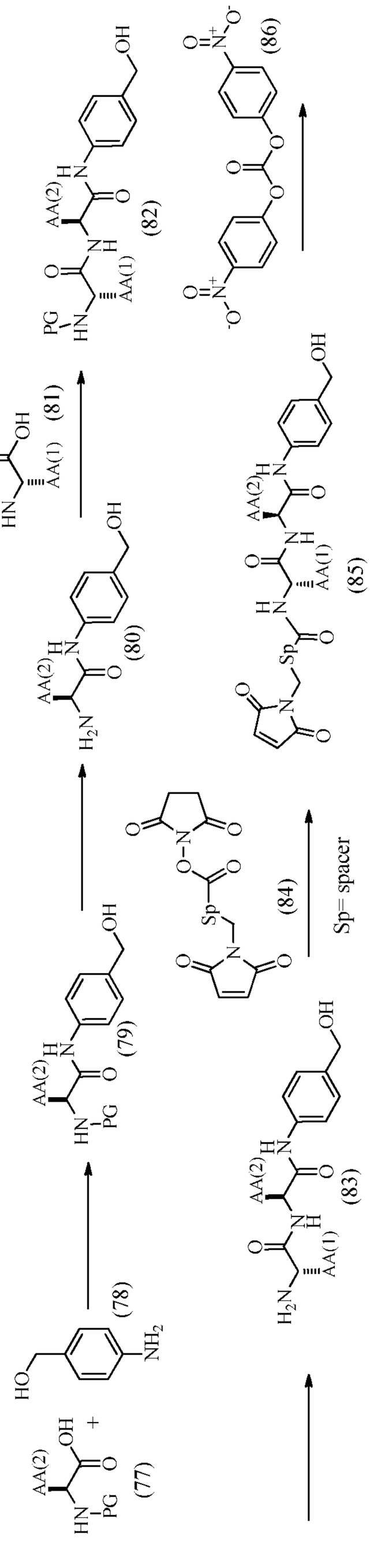
Scheme 14 shows representative methods used to make solubilized Bcl-xL inhibitors. Bcl-xL inhibitors can be synthesized using the general approach of modifying an Ar^2 substituent with a solubilizing group and then attaching an amine to a linker as described in later schemes. For example, compound (71) can be reacted with tert-butyl 2-bromoacetate in the presence of a base such as, but not limited to, potassium carbonate in a solvent such as, but not limited, to N,N-dimethylformamide. Compound (72) can be treated with aqueous lithium hydroxide in a solvent such as, but not limited to, methanol, tetrahydrofuran or mixtures thereof to provide compound (73). Compound (74) can be obtained by amidation of compound (73) with compound (37) under conditions previously described. Compound (74) can be treated with acids such as, but not limited to trifluoroacetic acid or HCl, to provide a Bcl-xL inhibitor of the formula (75). The reaction is typically performed at ambient temperature in solvents such as, but not limited to, dichloromethane or 1,4-dioxane.

III.A.6. General Methods for Synthesizing Bcl-xL Synthons

In the schemes below, the various substituents Ar^1, Ar^2, Z^1, Y, G, R^{11a} and R^{11b} are as defined in the Detailed Description section.

5.2.1. Synthesis of Compound (89)

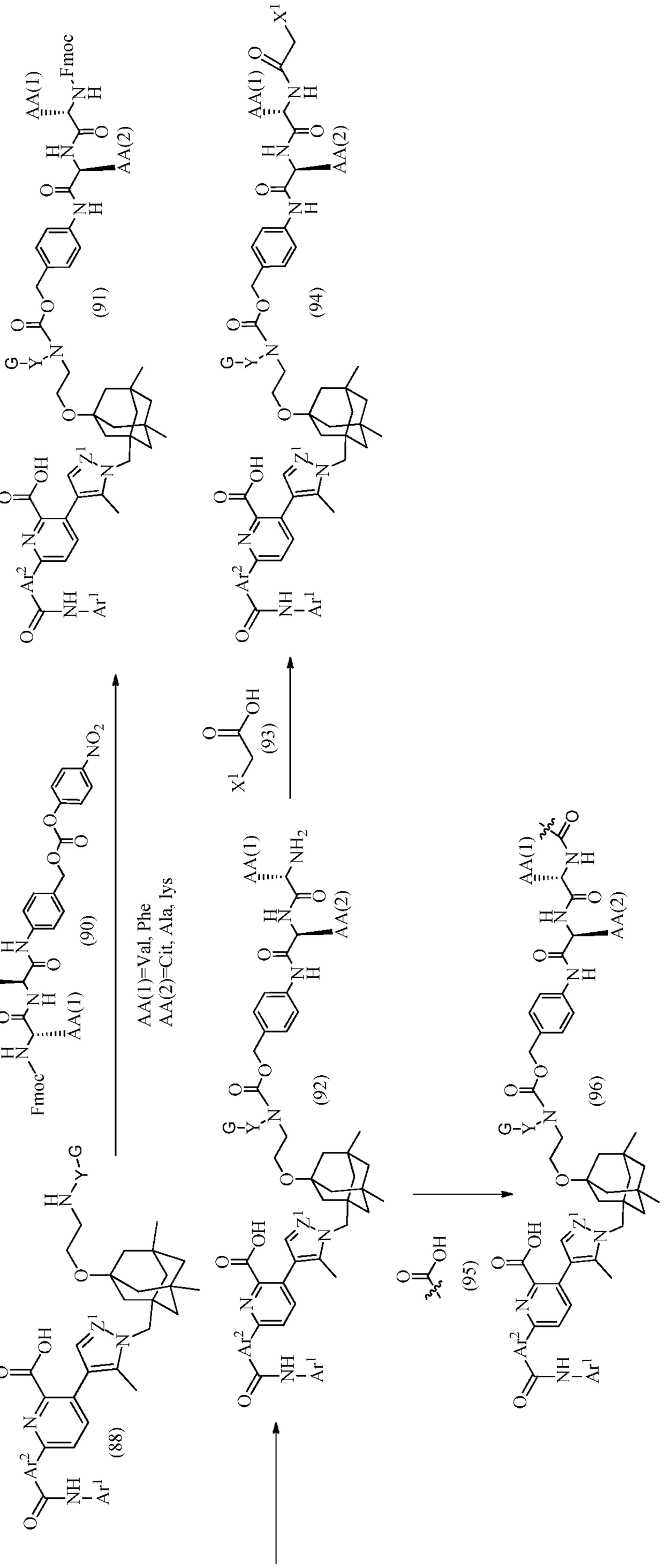
Scheme 15



As shown in scheme 15, compounds of formula (77), wherein PG is an appropriate base labile protecting group and AA(2) is Cit, Ala, or Lys, can be reacted with 4-(aminophenyl)methanol (78), under amidation conditions described herein or readily available in the literature to provide compound (79). Compound (80) can be prepared by reacting compound (79) with a base such as, but not limited to, diethylamine. The reaction is typically performed at ambient temperature in a solvent such as but not limited to N,N-dimethylformamide. Compound (81), wherein PG is an appropriate base or acid labile protecting group and AA(1) is Val or Phe, can be reacted with compound (80), under amidation conditions described herein or readily available in the literature to provide compound (82). Compound (83) can be prepared by treating compound (82) with diethylamine or trifluoroacetic acid, as appropriate. The reaction is typically performed at ambient temperature in a solvent such as but not limited to dichloromethane. Compound (84), wherein Sp is a spacer, can be reacted with compound (83) to provide compound (85). The reaction is typically performed at ambient temperature in a solvent such as but not limited to N,N-dimethylformamide. Compound (85) can be reacted with bis(4-nitrophenyl) carbonate (86) in the presence of a base such as, but not limited to N,N-diisopropylethylamine, to provide compounds (87). The reaction is typically performed at ambient temperature in a solvent such as but not limited to N,N-dimethylformamide. Compounds (87) can be reacted with compound (88) in the presence of a base such as, but not limited to, N,N-diisopropylethylamine, to provide compound (89). The reaction is typically performed at ambient temperature in a solvent such as, but not limited to, N,N-dimethylformamide.

5.2.2. Synthesis of Compounds (94) and (96)

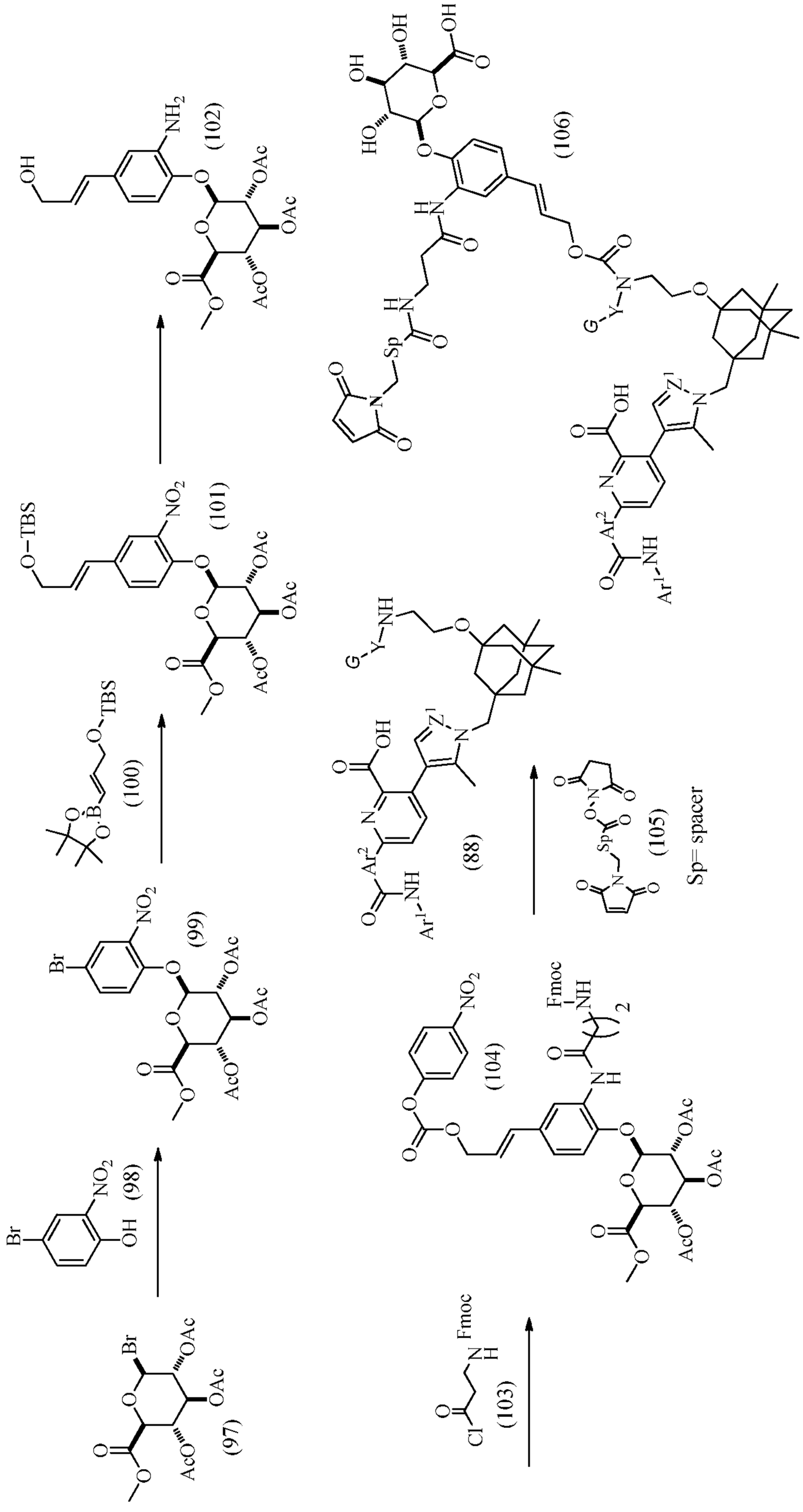
Scheme 16



Scheme 16 describes the installment of alternative mAb-linker attachments to dipeptide Synthons. Compound (88) can be reacted with compound (90) in the presence of a base such as, but not limited to, N,N-diisopropylamine to provide compound (91). The reaction is typically performed at ambient temperature in a solvent such as but not limited to N,N-dimethylformamide. Compound (92) can be prepared by reacting compound (91) with diethylamine. The reaction is typically performed at ambient temperature in a solvent such as but not limited to N,N-dimethylformamide. Compound (93), wherein X^1 is Cl, Br, or I, can be reacted with compound (92), under amidation conditions described herein or readily available in the literature to provide compound (94). Compound (92) can be reacted with compounds of formula (95) under amidation conditions described herein or readily available in the literature to provide compound (96).

5.2.3. Synthesis of Compound (106)

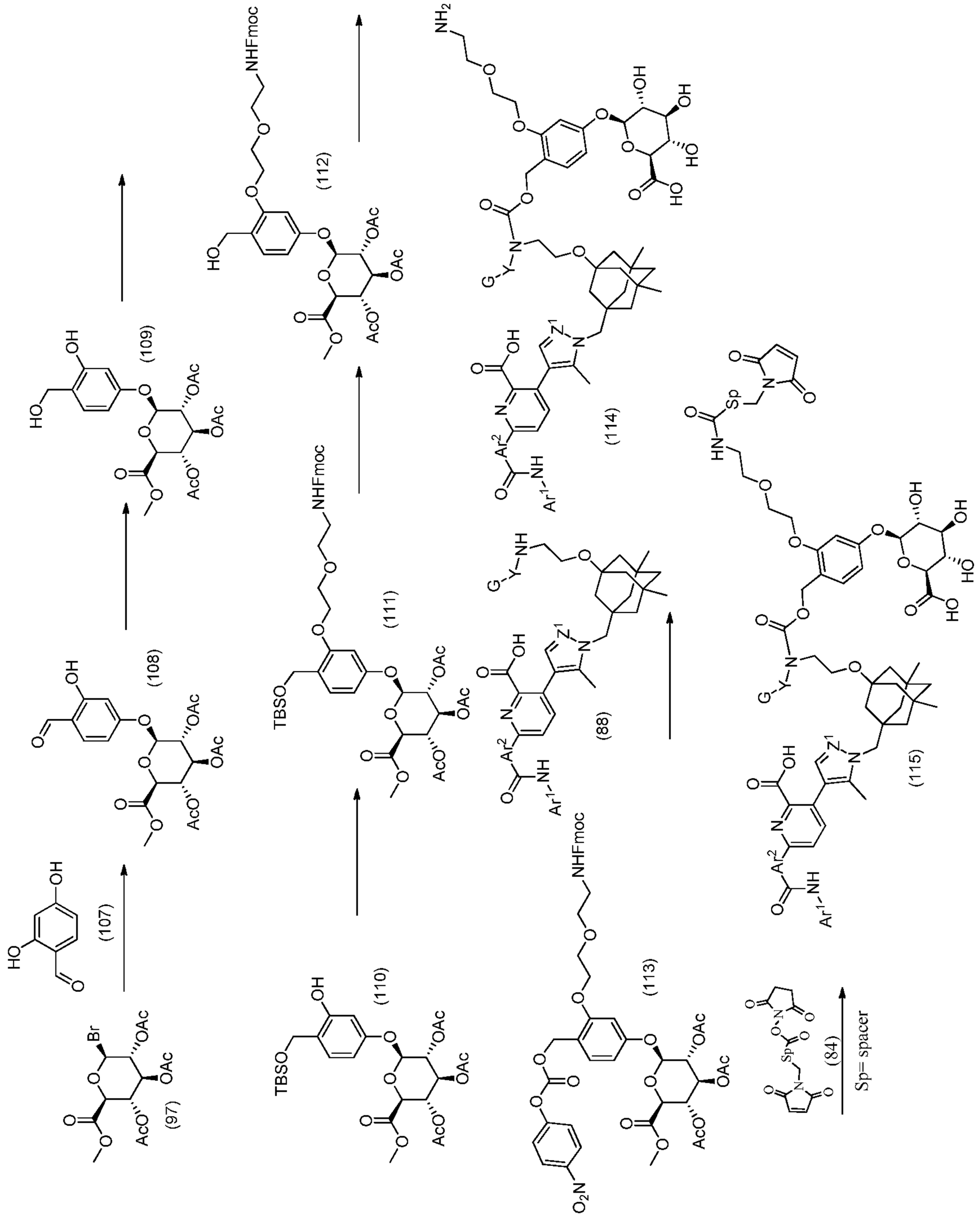
Scheme 17



Scheme 17 describes the synthesis of vinyl glucuronide linker intermediates and synthons. (2R,3R,4S,5S,6S)-2-Bromo-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (97) can be treated with silver oxide, followed by 4-bromo-2-nitrophenol (98) to provide (2S,3R,4S,5S,6S)-2-(4-bromo-2-nitrophenoxy)-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (99). The reaction is typically performed at ambient temperature in a solvent, such as, but not limited to, acetonitrile. (2S,3R,4S,5S,6S)-2-(4-Bromo-2-nitrophenoxy)-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (99) can be reacted with (E)-*tert*-butyldimethyl((3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)oxy)silane (100) in the presence of a base such as, but not limited to, sodium carbonate, and a catalyst such as but not limited to tris(dibenzylideneacetone)dipalladium ($Pd_2(dba)_3$), to provide (2S,3R,4S,5S,6S)-2-(4-((E)-3-((*tert*-butyldimethylsilyl)oxy)prop-1-en-1-yl)-2-nitrophenoxy)-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (101). The reaction is typically performed at an elevated temperature in a solvent, such as, but not limited to, tetrahydrofuran. (2S,3R,4S,5S,6S)-2-(2-amino-4-((E)-3-hydroxyprop-1-en-1-yl)phenoxy)-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (102) can be prepared by reacting (2S,3R,4S,5S,6S)-2-(4-((E)-3-((*tert*-butyldimethylsilyl)oxy)prop-1-en-1-yl)-2-nitrophenoxy)-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (101) with zinc in the presence of an acid such as, but not limited to, hydrochloric acid. The addition is typically performed at low temperature before warming to ambient temperature in a solvent such as, but not limited to, tetrahydrofuran, water, or mixtures thereof. (2S,3R,4S,5S,6S)-2-(2-amino-4-((E)-3-hydroxyprop-1-en-1-yl)phenoxy)-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (102) can be reacted with (9H-fluoren-9-yl)methyl (3-chloro-3-oxopropyl)carbamate (103), in the presence of a base such as, but not limited to, N,N-diisopropylethylamine, to provide (2S,3R,4S,5S,6S)-2-(2-(3-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)propanamido)-4-((E)-3-hydroxyprop-1-en-1-yl)phenoxy)-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (104). The addition is typically performed at low temperature before warming to ambient temperature in a solvent such as, but not limited to, dichloromethane. Compound (88) can be reacted with (2S,3R,4S,5S,6S)-2-(2-(3-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)propanamido)-4-((E)-3-hydroxyprop-1-en-1-yl)phenoxy)-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (104) in the presence of a base such as, but not limited to, N-ethyl-N-isopropylpropan-2-amine, followed by work up and reaction with compound (105) in the presence of a base such as, but not limited to, N,N-diisopropylethylamine to provide compound (106). The reactions are typically performed at ambient temperature in a solvent such as, but not limited to N,N- dimethylformamide.

5.2.4. Synthesis of Compound (115)

Scheme 18

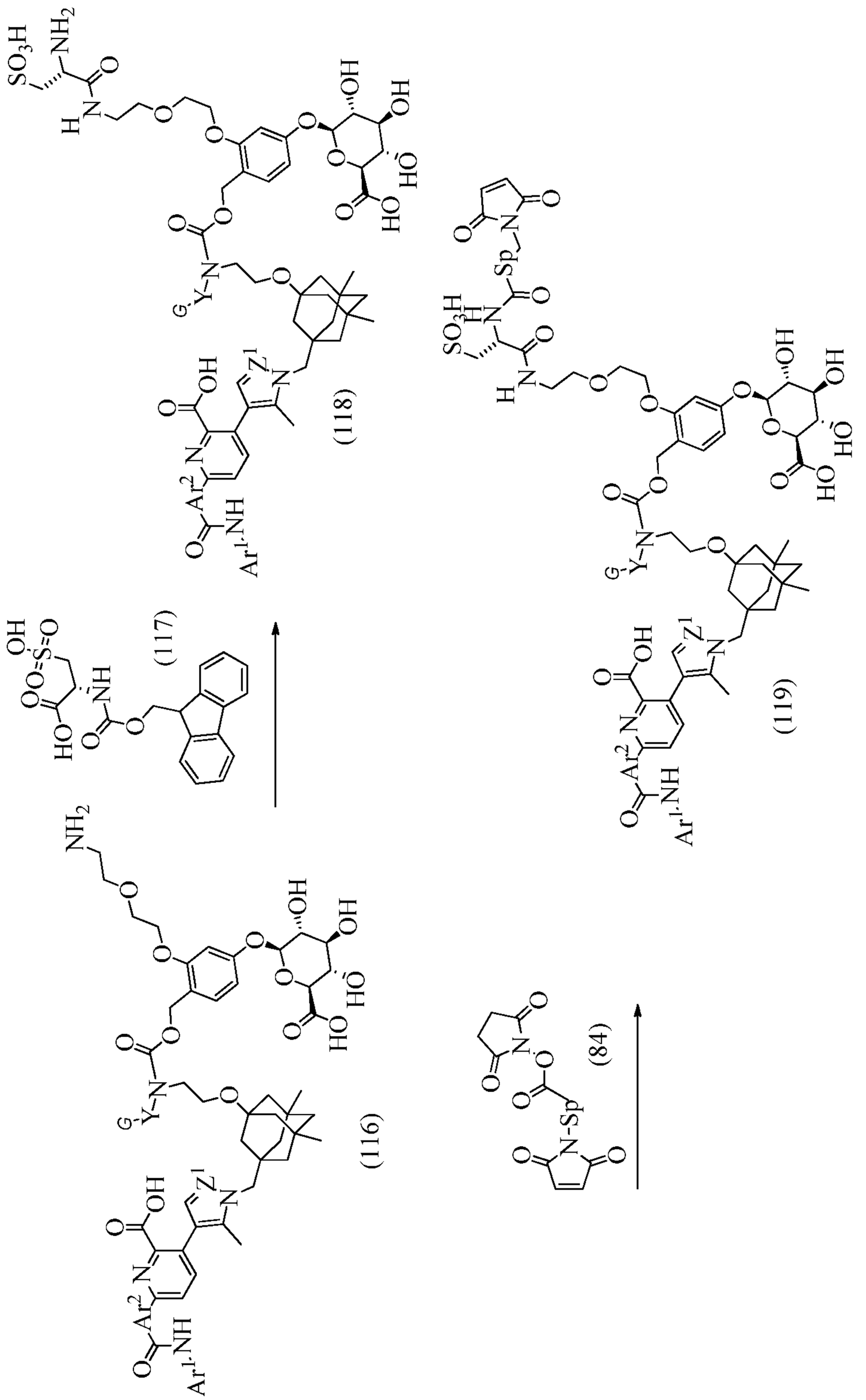


Scheme 18 describes the synthesis of a representative 2-ether glucuronide linker intermediate and synthon. (2S,3R,4S,5S,6S)-2-Bromo-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (97) can be reacted with 2,4-dihydroxybenzaldehyde (107) in the presence of silver carbonate to provide (2S,3R,4S,5S,6S)-2-(4-formyl-3-hydroxyphenoxy)-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (108). The reaction is typically performed at an elevated temperature in a solvent, such as, but not limited to, acetonitrile. (2S,3R,4S,5S,6S)-2-(4-Formyl-3-hydroxyphenoxy)-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (108) can be treated with sodium borohydride to provide (2S,3R,4S,5S,6S)-2-(3-hydroxy-4-(hydroxymethyl)phenoxy)-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (109). The addition is typically performed at low temperature before warming to ambient temperature in a solvent such as but not limited to tetrahydrofuran, methanol, or mixtures thereof. (2S,3R,4S,5S,6S)-2-(4-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-hydroxyphenoxy)-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (110) can be prepared by reacting (2S,3R,4S,5S,6S)-2-(3-hydroxy-4-(hydroxymethyl)phenoxy)-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (109) with *tert*-butyldimethylsilyl chloride in the presence of imidazole. The reaction is typically performed at low temperature in a solvent, such as, but not limited to, dichloromethane. (2S,3R,4S,5S,6S)-2-(3-(2-(2-((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)ethoxy)ethoxy)-4-(((*tert*-butyldimethylsilyl)oxy)methyl)phenoxy)-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (111) can be prepared by reacting (2S,3R,4S,5S,6S)-2-(4-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-hydroxyphenoxy)-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (110) with (9H-fluoren-9-yl)methyl (2-(2-hydroxyethoxy)ethyl)carbamate in the presence of triphenylphosphine and a azodicarboxylate such as, but not limited to, di-*tert*-butyl diazene-1,2-dicarboxylate. The reaction is typically performed at ambient temperature in a solvent such as but not limited to toluene. (2S,3R,4S,5S,6S)-2-(3-(2-(2-((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)ethoxy)ethoxy)-4-(((*tert*-butyldimethylsilyl)oxy)methyl)phenoxy)-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (111) can be treated with acetic acid to provide (2S,3R,4S,5S,6S)-2-(3-(2-(2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)ethoxy)ethoxy)-4-(hydroxymethyl)phenoxy)-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (112). The reaction is typically performed at ambient temperature in a solvent such as but not limited to water, tetrahydrofuran, or mixtures thereof. (2S,3R,4S,5S,6S)-2-(3-(2-(2-((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)ethoxy)ethoxy)-4-((((4-nitrophenoxy)carbonyl)oxy)methyl)phenoxy)-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (113) can be prepared by reacting (2S,3R,4S,5S,6S)-2-(3-(2-(2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)ethoxy)ethoxy)-4-(hydroxymethyl)phenoxy)-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (112) with bis(4-nitrophenyl) carbonate in the presence of a base such as but not limited to N-ethyl-N-

isopropylpropan-2-amine. The reaction is typically performed at ambient temperature in a solvent such as but not limited to N,N-dimethylformamide. (2S,3R,4S,5S,6S)-2-(3-(2-(2-((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)ethoxy)ethoxy)-4-((((4-nitrophenoxy)carbonyl)oxy)methyl)phenoxy)-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (113) can be treated with compound (88) in the presence of a base such as but not limited to N-ethyl-N-isopropylpropan-2-amine, followed by treatment with lithium hydroxide to provide a compound (114). The reaction is typically performed at ambient temperature in a solvent such as but not limited to N,N-dimethylformamide, tetrahydrofuran, methanol, or mixtures thereof. Compound (115) can be prepared by reacting compound (114) with compound (84) in the presence of a base such as but not limited to N-ethyl-N-isopropylpropan-2-amine. The reaction is typically performed at ambient temperature in a solvent such as but not limited to N,N-dimethylformamide.

5.2.5. Synthesis of Compound (119)

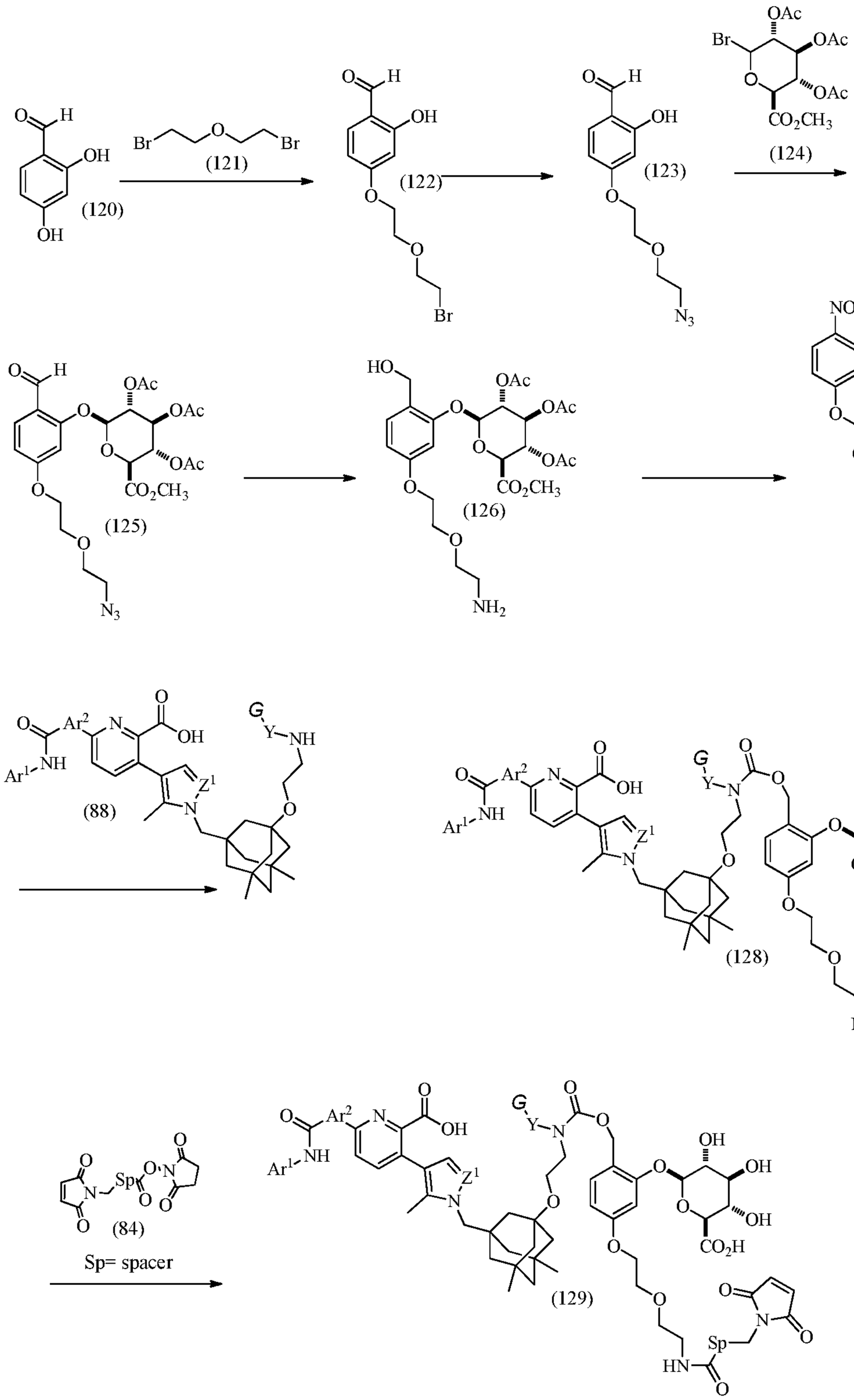
Scheme 19



Scheme 19 describes the introduction of a second solubilizing group to a sugar linker. Compound (116) can be reacted with (R)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-sulfopropanoic acid (117), under amidation conditions described herein or readily available in the literature, followed by treatment with a base such as but not limited to diethylamine, to provide compound (118). Compound (118) can be reacted with compound (84), wherein Sp is a spacer, under amidation conditions described herein or readily available in the literature, to provide compound (119).

5.2.6. Synthesis of Compound (129)

Scheme 20

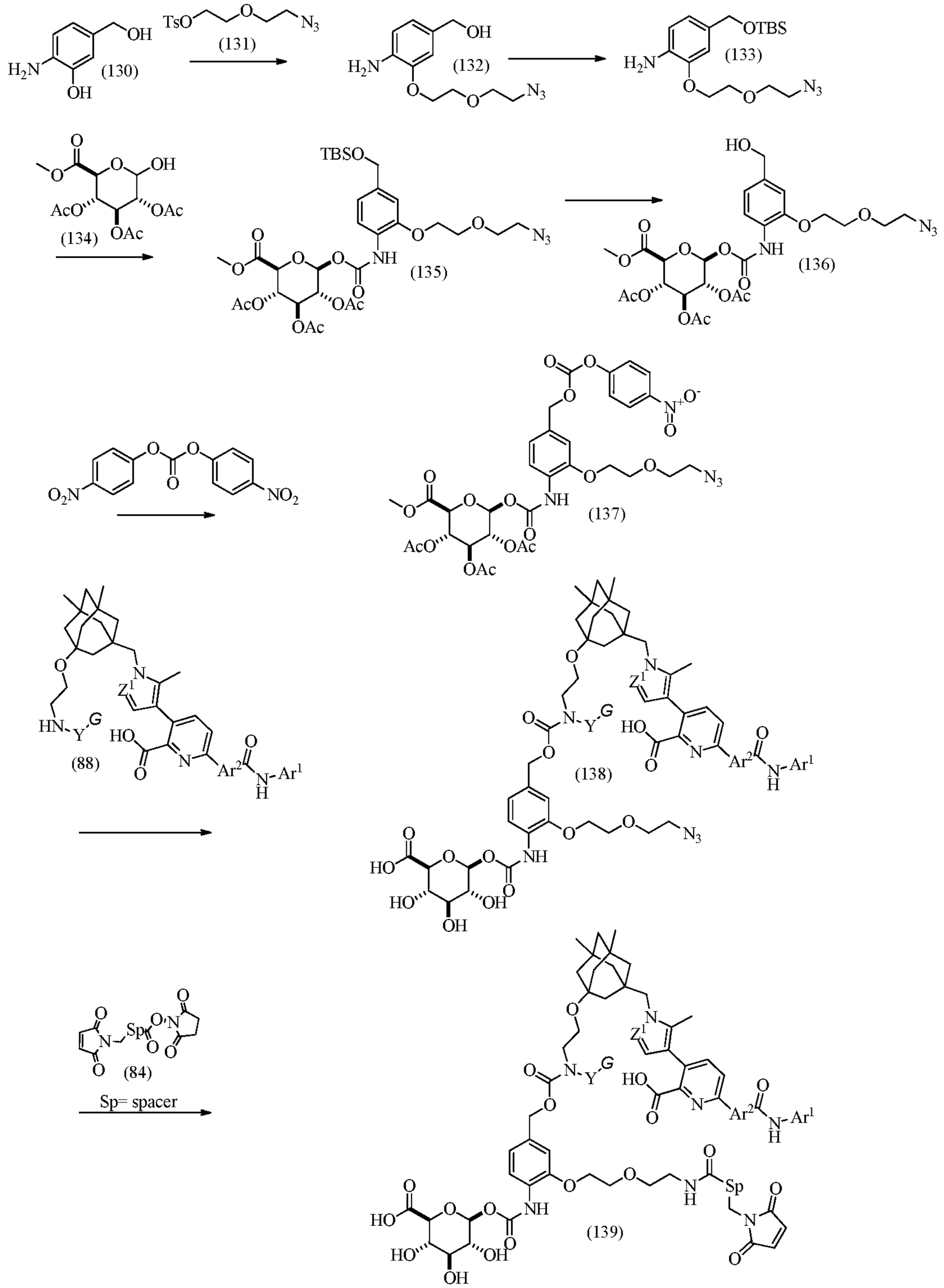


Scheme 20 describes the synthesis of 4-ether glucuronide linker intermediates and synthons. 4-(2-(2-Bromoethoxy)ethoxy)-2-hydroxybenzaldehyde (122) can be prepared by reacting 2,4-dihydroxybenzaldehyde (120) with 1-bromo-2-(2-bromoethoxy)ethane (121) in the presence of a base such as, but not limited to, potassium carbonate. The reaction is typically performed at an

elevated temperature in a solvent such as but not limited to acetonitrile. 4-(2-(2-Bromoethoxy)ethoxy)-2-hydroxybenzaldehyde (122) can be treated with sodium azide to provide 4-(2-(2-azidoethoxy)ethoxy)-2-hydroxybenzaldehyde (123). The reaction is typically performed at ambient temperature in a solvent such as but not limited to N,N-dimethylformamide. (2S,3R,4S,5S,6S)-2-(5-(2-(2-Azidoethoxy)ethoxy)-2-formylphenoxy)-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (125) can be prepared by reacting 4-(2-(2-azidoethoxy)ethoxy)-2-hydroxybenzaldehyde (123) with (3R,4S,5S,6S)-2-bromo-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (124) in the presence of silver oxide. The reaction is typically performed at ambient temperature in a solvent such as, but not limited to, acetonitrile. Hydrogenation of (2S,3R,4S,5S,6S)-2-(5-(2-(2-azidoethoxy)ethoxy)-2-formylphenoxy)-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (125) in the presence of Pd/C will provide (2S,3R,4S,5S,6S)-2-(5-(2-(2-aminoethoxy)ethoxy)-2-(hydroxymethyl)phenoxy)-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (126). The reaction is typically performed at ambient temperature in a solvent such as, but not limited to, tetrahydrofuran. (2S,3R,4S,5S,6S)-2-(5-(2-(2-((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)ethoxy)ethoxy)-2-(hydroxymethyl)phenoxy)-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (127) can be prepared by treating (2S,3R,4S,5S,6S)-2-(5-(2-(2-aminoethoxy)ethoxy)-2-(hydroxymethyl)phenoxy)-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (126) with (9H-fluoren-9-yl)methyl carbonochloridate in the presence of a base, such as, but not limited to, N-ethyl-N-isopropylpropan-2-amine. The reaction is typically performed at low temperature in a solvent such as, but not limited to, dichloromethane. Compound (88) can be reacted with (2S,3R,4S,5S,6S)-2-(5-(2-(2-((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)ethoxy)ethoxy)-2-(hydroxymethyl)phenoxy)-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (127) in the presence of a base, such as, but not limited to, N-ethyl-N-isopropylpropan-2-amine, followed by treatment with lithium hydroxide to provide compound (128). The reaction is typically performed at low temperature in a solvent such as, but not limited to, N,N-dimethylformamide. Compound (129) can be prepared by reacting compound (128) with compound (84) in the presence of a base such as, but not limited to, N-ethyl-N-isopropylpropan-2-amine. The reaction is typically performed at ambient temperature in a solvent such as but not limited to N,N-dimethylformamide.

5.2.7. Synthesis of Compound (139)

Scheme 21



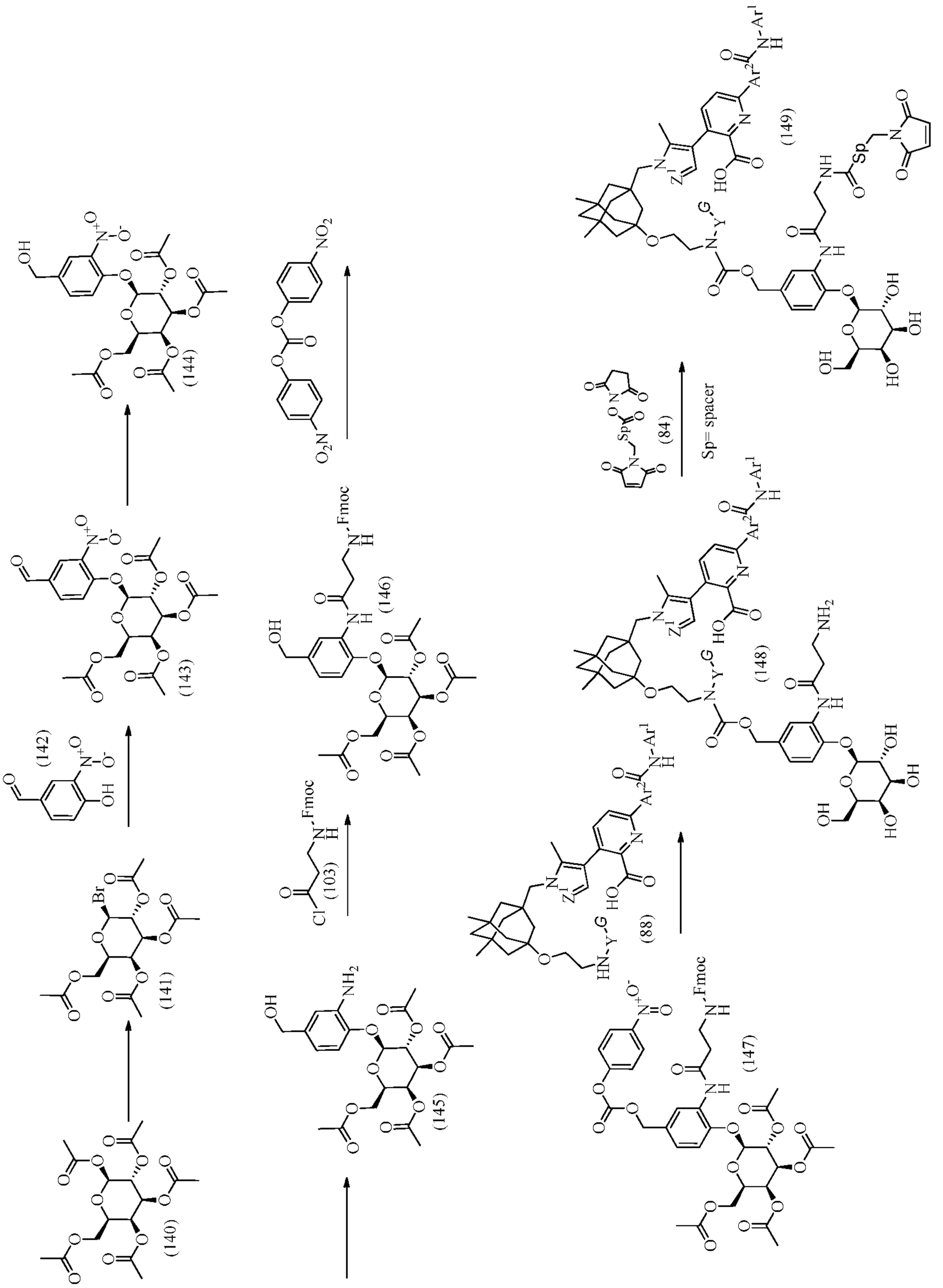
Scheme 21 describes the synthesis of carbamate glucuronide intermediates and synthons. 2-Amino-5-(hydroxymethyl)phenol (130) can be treated with sodium hydride and then reacted with 2-(2-azidoethoxy)ethyl 4-methylbenzenesulfonate (131) to provide (4-amino-3-(2-(2-azidoethoxy)ethoxy)phenyl)methanol (132). The reaction is typically performed at an elevated temperature in a solvent such as, but not limited to N,N-dimethylformamide. 2-(2-(2-

Azidoethoxy)ethoxy)-4-(((tert-butyldimethylsilyl)oxy)methyl)aniline (133) can be prepared by reacting (4-amino-3-(2-(2-azidoethoxy)ethoxy)phenyl)methanol (132) with tert-butyldimethylchlorosilane in the presence of imidazole. The reaction is typically performed at ambient temperature in a solvent such as, but not limited to tetrahydrofuran. 2-(2-(2-Azidoethoxy)ethoxy)-4-(((tert-butyldimethylsilyl)oxy)methyl)aniline (133) can be treated with phosgene, in the presence of a base such as but not limited to triethylamine, followed by reaction with (3R,4S,5S,6S)-2-hydroxy-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (134) in the presence of a base such as but not limited to triethylamine, to provide 2S,3R,4S,5S,6S)-2-(((2-(2-(2-azidoethoxy)ethoxy)-4-(((tert-butyldimethylsilyl)oxy)methyl)phenyl)carbamoyl)oxy)-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (135). The reaction is typically performed in a solvent such as, but not limited to, toluene, and the additions are typically performed at low temperature, before warming up to ambient temperature after the phosgene addition and heating at an elevated temperature after the (3R,4S,5S,6S)-2-hydroxy-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (134) addition. (2S,3R,4S,5S,6S)-2-(((2-(2-(2-Azidoethoxy)ethoxy)-4-(hydroxymethyl)phenyl)carbamoyl)oxy)-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (136) can be prepared by reacting 2S,3R,4S,5S,6S)-2-(((2-(2-(2-azidoethoxy)ethoxy)-4-(((tert-butyldimethylsilyl)oxy)methyl)phenyl)carbamoyl)oxy)-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (135) with p-toluenesulfonic acid monohydrate. The reaction is typically performed at ambient temperature in a solvent such as, but not limited to methanol. (2S,3R,4S,5S,6S)-2-(((2-(2-(2-Azidoethoxy)ethoxy)-4-(hydroxymethyl)phenyl)carbamoyl)oxy)-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (136) can be reacted with bis(4-nitrophenyl)carbonate in the presence of a base such as, but not limited to, N,N-diisopropylethylamine, to provide (2S,3R,4S,5S,6S)-2-(((2-(2-(2-azidoethoxy)ethoxy)-4-((((4-nitrophenoxy)carbonyl)oxy)methyl)phenyl)carbamoyl)oxy)-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (137). The reaction is typically performed at ambient temperature in a solvent such as, but not limited to, N,N-dimethylformamide. (2S,3R,4S,5S,6S)-2-(((2-(2-(2-Azidoethoxy)ethoxy)-4-((((4-nitrophenoxy)carbonyl)oxy)methyl)phenyl)carbamoyl)oxy)-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (137) can be reacted with compound in the presence of a base such as, but not limited to, N,N-diisopropylethylamine, followed by treatment with aqueous lithium hydroxide, to provide compound (138). The first step is typically conducted at ambient temperature in a solvent such as, but not limited to N,N-dimethylformamide, and the second step is typically conducted at low temperature in a solvent such as but not limited to methanol. Compound (138) can be treated with tris(2-carboxyethyl))phosphine hydrochloride, followed by reaction with compound (84) in the presence of a base such as, but not limited to, N,N-diisopropylethylamine, to provide compound (139). The reaction with tris(2-carboxyethyl))phosphine hydrochloride is typically performed at ambient temperature in a solvent such as, but not limited to, tetrahydrofuran, water, or mixtures thereof, and the reaction with N-succinimidyl 6-

maleimidohexanoate is typically performed at ambient temperature in a solvent such as, but not limited to, N,N-dimethylformamide.

5.2.8. Synthesis of Compound (149)

Scheme 22

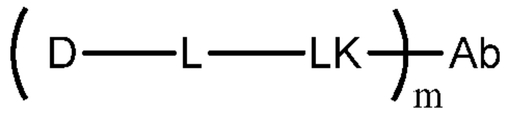

(140)
(141)
(142)
(143)
(144)
(145)
(146)
(147)
(148)
(149)
(84)
(88)
(103)
Sp= spacer
Fmoc
Sp
G
Y
Z1
Ar1
Ar2

Scheme 22 describes the synthesis of galactoside linker intermediates and synthons. (2S,3R,4S,5S,6R)-6-(Acetoxymethyl)tetrahydro-2H-pyran-2,3,4,5-tetrayl tetraacetate (140) can be treated with HBr in acetic acid to provide (2R,3S,4S,5R,6S)-2-(acetoxymethyl)-6-bromotetrahydro-2H-pyran-3,4,5-triyl triacetate (141). The reaction is typically performed at ambient temperature under a nitrogen atmosphere. (2R,3S,4S,5R,6S)-2-(Acetoxymethyl)-6-(4-formyl-2-nitrophenoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (143) can be prepared by treating (2R,3S,4S,5R,6S)-2-(acetoxymethyl)-6-bromotetrahydro-2H-pyran-3,4,5-triyl triacetate (141) with silver(I) oxide in the presence of 4-hydroxy-3-nitrobenzaldehyde (142). The reaction is typically performed at ambient temperature in a solvent such as, but not limited to, acetonitrile. (2R,3S,4S,5R,6S)-2-(Acetoxymethyl)-6-(4-formyl-2-nitrophenoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (143) can be treated with sodium borohydride to provide (2R,3S,4S,5R,6S)-2-(acetoxymethyl)-6-(4-(hydroxymethyl)-2-nitrophenoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (144). The reaction is typically performed at low temperature in a solvent such as but not limited to tetrahydrofuran, methanol, or mixtures thereof. (2R,3S,4S,5R,6S)-2-(Acetoxymethyl)-6-(2-amino-4-(hydroxymethyl)phenoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (145) can be prepared by treating (2R,3S,4S,5R,6S)-2-(acetoxymethyl)-6-(4-(hydroxymethyl)-2-nitrophenoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (144) with zinc in the presence of hydrochloric acid. The reaction is typically performed at low temperature, under a nitrogen atmosphere, in a solvent such as, but not limited to, tetrahydrofuran. (2S,3R,4S,5S,6R)-2-(2-(3-((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)propanamido)-4-(hydroxymethyl)phenoxy)-6-(acetoxymethyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (146) can be prepared by reacting (2R,3S,4S,5R,6S)-2-(acetoxymethyl)-6-(2-amino-4-(hydroxymethyl)phenoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (145) with (9H-fluoren-9-yl)methyl (3-chloro-3-oxopropyl)carbamate (103) in the presence of a base such as, but not limited to, N,N-diisopropylethylamine. The reaction is typically performed at low temperature, in a solvent such as, but not limited to, dichloromethane. (2S,3R,4S,5S,6R)-2-(2-(3-((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)propanamido)-4-(hydroxymethyl)phenoxy)-6-(acetoxymethyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (146) can be reacted with bis(4-nitrophenyl)carbonate in the presence of a base such as, but not limited to, N,N-diisopropylethylamine, to provide (2S,3R,4S,5S,6R)-2-(2-(3-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)propanamido)-4-((((4-nitrophenoxy)carbonyl)oxy)methyl)phenoxy)-6-(acetoxymethyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (147). The reaction is typically performed at low temperature, in a solvent such as, but not limited to, N,N-dimethylformamide. (2S,3R,4S,5S,6R)-2-(2-(3-((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)propanamido)-4-((((4-nitrophenoxy)carbonyl)oxy)methyl)phenoxy)-6-(acetoxymethyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (147) can be reacted with compound (88) in the presence of a base such as, but not limited to N,N-diisopropylethylamine, followed by treatment with lithium hydroxide, to provide compound

(148). The first step is typically performed at low temperature, in a solvent such as, but not limited to, N,N-dimethylformamide, and the second step is typically performed at ambient temperature, in a solvent such as, but not limited to, methanol. Compound (148) can be treated with compound (84), wherein Sp is a spacer, in the presence of a base, such as, but not limited to N,N-diisopropylethylamine, to provide compound (149). The reaction is typically performed at ambient temperature, in a solvent such as, but not limited to, N,N-dimethylformamide.

III.A.7. General Methods for Synthesizing Anti-B7-H3 ADCs

The present invention also discloses a process to prepare an anti-B7-H3 ADC according to structural formula (I):

(I) 

wherein D, L, LK, Ab and m are as defined in the Detailed Description section. The process comprises:

treating an antibody in an aqueous solution with an effective amount of a disulfide reducing agent at 30-40 °C for at least 15 minutes, and then cooling the antibody solution to 20-27 °C;

adding to the reduced antibody solution a solution of water/dimethyl sulfoxide comprising a synthon selected from the group of 2.1 to 2.176 (Table B);

adjusting the pH of the solution to a pH of 7.5 to 8.5;

allowing the reaction to run for 48 to 80 hours to form the ADC;

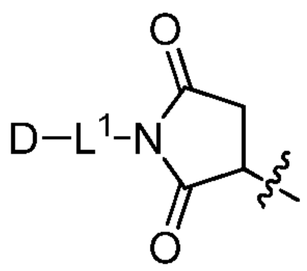
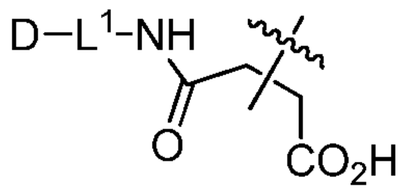
wherein the mass is shifted by 18 ± 2 amu for each hydrolysis of a succinimide to a succinamide as measured by electron spray mass spectrometry; and

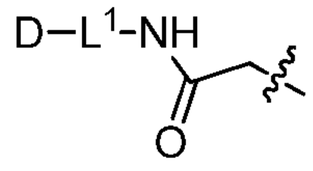
wherein the ADC is optionally purified by hydrophobic interaction chromatography.

In certain embodiments, the antibody is an hB7-H3 antibody, wherein the hB7-H3 antibody comprises the heavy and light chain CDRs of huAb3v2.5, huAb3v2.6, or huAb13v1.

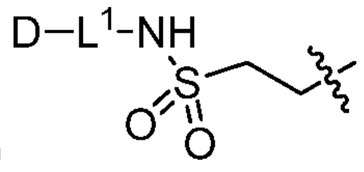
The present invention is also directed to an anti-B7-H3 ADC prepared by the above-described process.

In certain embodiments, the anti-B7-H3 ADC disclosed in the present application is formed by contacting an antibody that binds an hB7-H3 cell surface receptor or tumor associated antigen expressed on a tumor cell with a drug-linker synthon under conditions in which the drug-linker synthon covalently links to the antibody through a maleimide moiety as shown in formulae (IIe) and (IIf), or through an acetyl halide as shown in(IIg), or through a vinyl sulfone as shown in (IIh).

(IIe)  , (IIf)  ,



(IIg) ,



(IIh)

wherein D is the Bcl-xL inhibitor drug according to structural formula (IIa), (IIb), (IIc) or (IId) as described above and L^1 is the portion of the linker not formed from the maleimide, acetyl halide or vinyl sulfone upon attachment of the synthon to the antibody; and wherein the drug-linker synthon is selected from the group consisting of synthon examples 2.1 to 2.176 (Table B), or a pharmaceutically acceptable salt thereof.

In certain embodiments, the contacting step is carried out under conditions such that the anti-B7-H3 ADC has a DAR of 2, 3 or 4.

III.B. Anti-B7-H3 ADCs: Other Exemplary Drugs for Conjugation

Anti-B7-H3 antibodies may be used in ADCs to target one or more drug(s) to a cell of interest, *e.g.*, a cancer cell expressing B7-H3. The anti-B7-H3 ADCs of the invention provide a targeted therapy that may, for example, reduce the side effects often seen with anti-cancer therapies, as the one or more drug(s) is delivered to a specific cell.

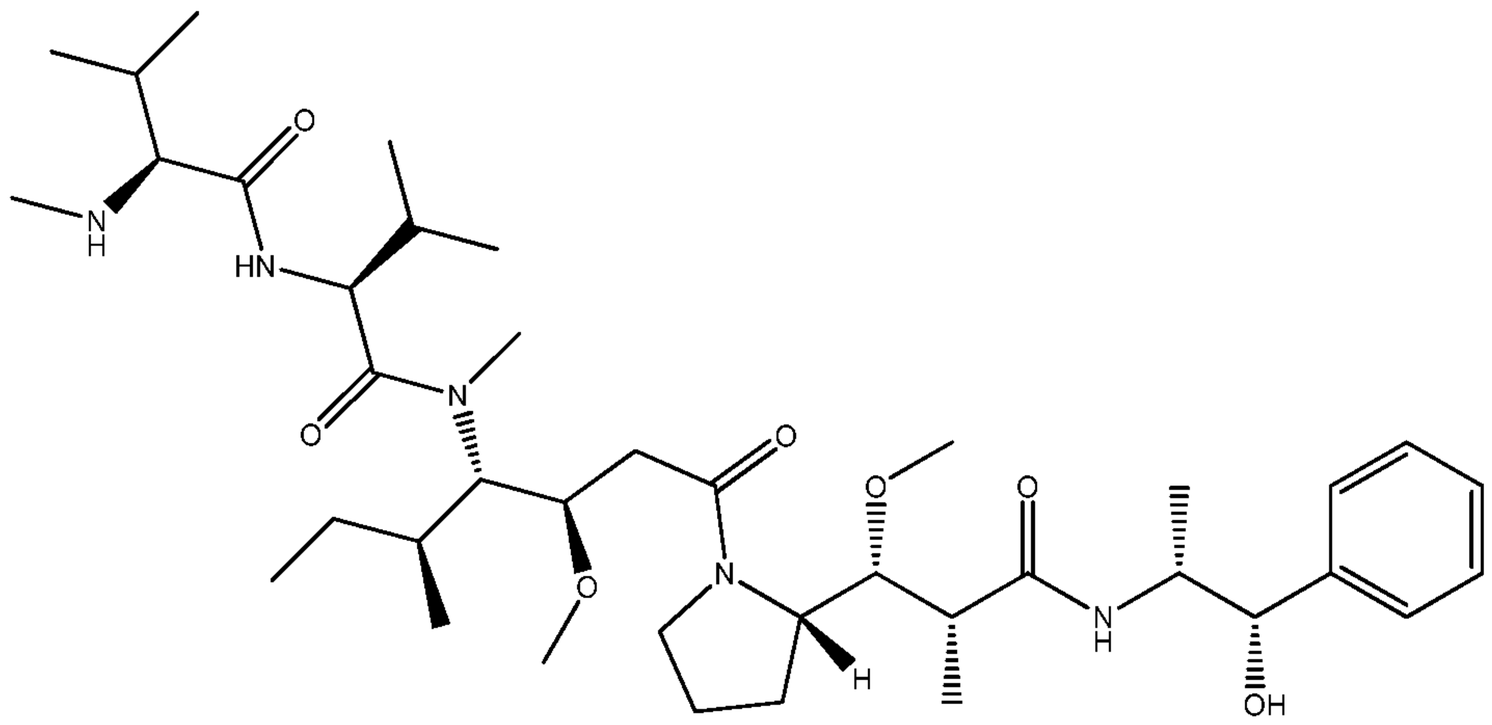
Auristatins

Anti-B7-H3 antibodies of the invention, *e.g.*, the huAb13v1, huAb3v2.5, or huAb3v2.6 antibody, may be conjugated to at least one auristatin. Auristatins represent a group of dolastatin analogs that have generally been shown to possess anticancer activity by interfering with microtubule dynamics and GTP hydrolysis, thereby inhibiting cellular division. For example, auristatin E (U.S. Patent No. 5,635,483) is a synthetic analogue of the marine natural product dolastatin 10, a compound that inhibits tubulin polymerization by binding to the same site on tubulin as the anticancer drug vincristine (G. R. Pettit, Prog. Chem. Org. Nat. Prod, 70: 1-79 (1997)). Dolastatin 10, auristatin PE, and auristatin E are linear peptides having four amino acids, three of which are unique to the dolastatin class of compounds. Exemplary embodiments of the auristatin subclass of mitotic inhibitors include, but are not limited to, monomethyl auristatin D (MMAD or auristatin D derivative), monomethyl auristatin E (MMAE or auristatin E derivative), monomethyl auristatin F (MMAF or auristatin F derivative), auristatin F phenylenediamine (AFP), auristatin EB (AEB), auristatin EFP (AEFP), and 5-benzoylvaleric acid-AE ester (AEVB). The synthesis and structure of auristatin derivatives are described in U.S. Patent Application Publication Nos. 2003-0083263, 2005-0238649 and 2005-0009751; International Patent Publication No. WO 04/010957, International Patent Publication No. WO 02/088172, and U.S. Pat. Nos. 6,323,315; 6,239,104; 6,034,065; 5,780,588; 5,665,860; 5,663,149; 5,635,483; 5,599,902; 5,554,725; 5,530,097; 5,521,284; 5,504,191; 5,410,024; 5,138,036; 5,076,973; 4,986,988; 4,978,744; 4,879,278; 4,816,444; and 4,486,414, each of which is incorporated by reference herein.

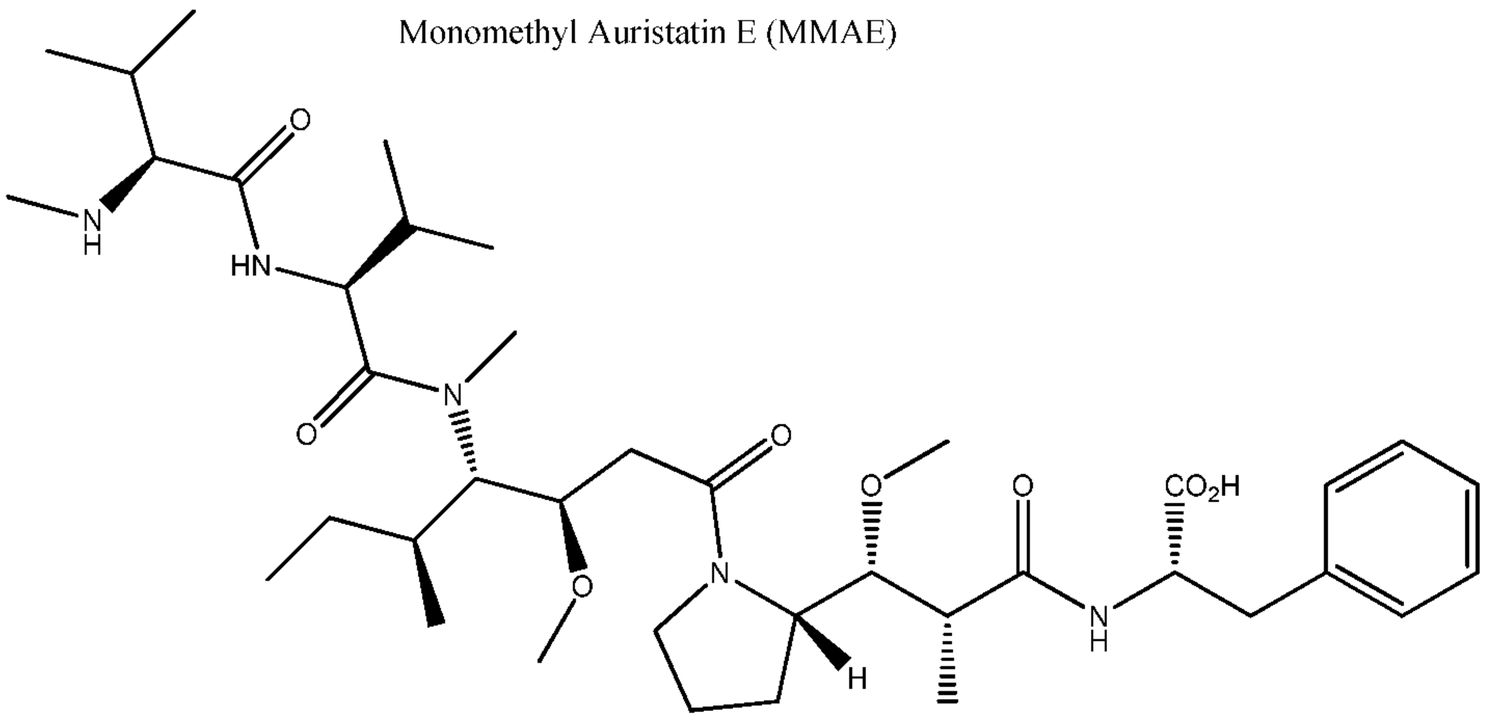
In one embodiment, anti-B7-H3 antibodies of the invention, *e.g.*, huAb13v1, huAb3v2.5, or huAb3v2.6, are conjugated to at least one MMAE (mono-methyl auristatin E). Monomethyl auristatin E (MMAE, vedotin) inhibits cell division by blocking the polymerization of tubulin. However, due to its super toxicity, auristatin E cannot be used as a drug itself. Auristatin E can be linked to a monoclonal antibody (mAb) that recognizes a specific marker expression in cancer cells and directs MMAE to the cancer cells. In one embodiment, the linker linking MMAE to the anti-B7-H3 antibody is stable in extracellular fluid (*i.e.*, the medium or environment that is external to cells), but is cleaved by cathepsin once the ADC has bound to the specific cancer cell antigen and entered the cancer cell, thus releasing the toxic MMAE and activating the potent anti-mitotic mechanism.

In one embodiment, an anti-B7-H3 antibody described herein, *e.g.*, huAb13v1, huAb3v2.5, or huAb3v2.6, is conjugated to at least one MMAF (monomethylauristatin F). Monomethyl auristatin F (MMAF) inhibits cell division by blocking the polymerization of tubulin. It has a charged C-terminal phenylalanine residue that attenuates its cytotoxic activity compared to its uncharged counterpart MMAE. However, due to its super toxicity, auristatin F cannot be used as a drug itself, but can be linked to a monoclonal antibody (mAb) that directs it to the cancer cells. In one embodiment, the linker to the anti-B7-H3 antibody is stable in extracellular fluid, but is cleaved by cathepsin once the conjugate has entered a tumor cell, thus activating the anti-mitotic mechanism.

The structures of MMAF and MMAE are provided below.



Monomethyl Auristatin E (MMAE)



Monomethyl Auristatin F (MMAF)

An example of huAb13v1, huAb3v2.5, or huAb3v2.6-vcMMAE is also provided in Figure 3. Notably, Figure 3 describes a situation where the antibody (*e.g.*, huAb13v1, huAb3v2.5, or huAb3v2.6) is coupled to a single drug and, therefore, has a DAR of 1. In certain embodiments, the ADC will have a DAR of 2 to 8, or, alternatively, 2 to 4.

Other Drugs for Conjugation

Examples of drugs that may be used in ADCs, *i.e.*, drugs that may be conjugated to the anti-B7-H3 antibodies of the invention, are provided below, and include mitotic inhibitors, antitumor antibiotics, immunomodulating agents, gene therapy vectors, alkylating agents, antiangiogenic agents, antimetabolites, boron-containing agents, chemoprotective agents, hormone agents, glucocorticoids, photoactive therapeutic agents, oligonucleotides, radioactive isotopes, radiosensitizers, topoisomerase inhibitors, kinase inhibitors, and combinations thereof.

1. Mitotic Inhibitors

In one aspect, anti-B7-H3 antibodies may be conjugated to one or more mitotic inhibitor(s) to form an ADC for the treatment of cancer. The term "mitotic inhibitor", as used herein, refers to a cytotoxic and/or therapeutic agent that blocks mitosis or cell division, a biological process particularly important to cancer cells. A mitotic inhibitor disrupts microtubules such that cell division is prevented, often by effecting microtubule polymerization (e.g., inhibiting microtubule polymerization) or microtubule depolymerization (e.g., stabilizing the microtubule cytoskeleton against depolymerization). Thus, in one embodiment, an anti-B7-H3 antibody of the invention is conjugated to one or more mitotic inhibitor(s) that disrupts microtubule formation by inhibiting tubulin polymerization. In another embodiment, an anti-B7-H3 antibody of the invention is conjugated to one or more mitotic inhibitor(s) that stabilizes the microtubule cytoskeleton from depolymerization. In one embodiment, the mitotic inhibitor used in the ADCs of the invention is Ixempra (ixabepilone). Examples of mitotic inhibitors that may be used in the anti-B7-H3 ADCs of the invention are provided below. Included in the genus of mitotic inhibitors are auristatins, described above.

a. Dolastatins

The anti-B7-H3 antibodies of the invention may be conjugated to at least one dolastatin to form an ADC. Dolastatins are short peptidic compounds isolated from the Indian Ocean sea hare *Dolabella auricularia* (see Pettit *et al.*, J. Am. Chem. Soc., 1976, 98, 4677). Examples of dolastatins include dolastatin 10 and dolastatin 15. Dolastatin 15, a seven-subunit depsipeptide derived from *Dolabella auricularia*, and is a potent antimitotic agent structurally related to the antitubulin agent dolastatin 10, a five-subunit peptide obtained from the same organism. Thus, in one embodiment, the anti-B7-H3 ADC of the invention comprises an anti-B7-H3 antibody, as described herein, and at least one dolastatin. Auristatins, described above, are synthetic derivatives of dolastatin 10.

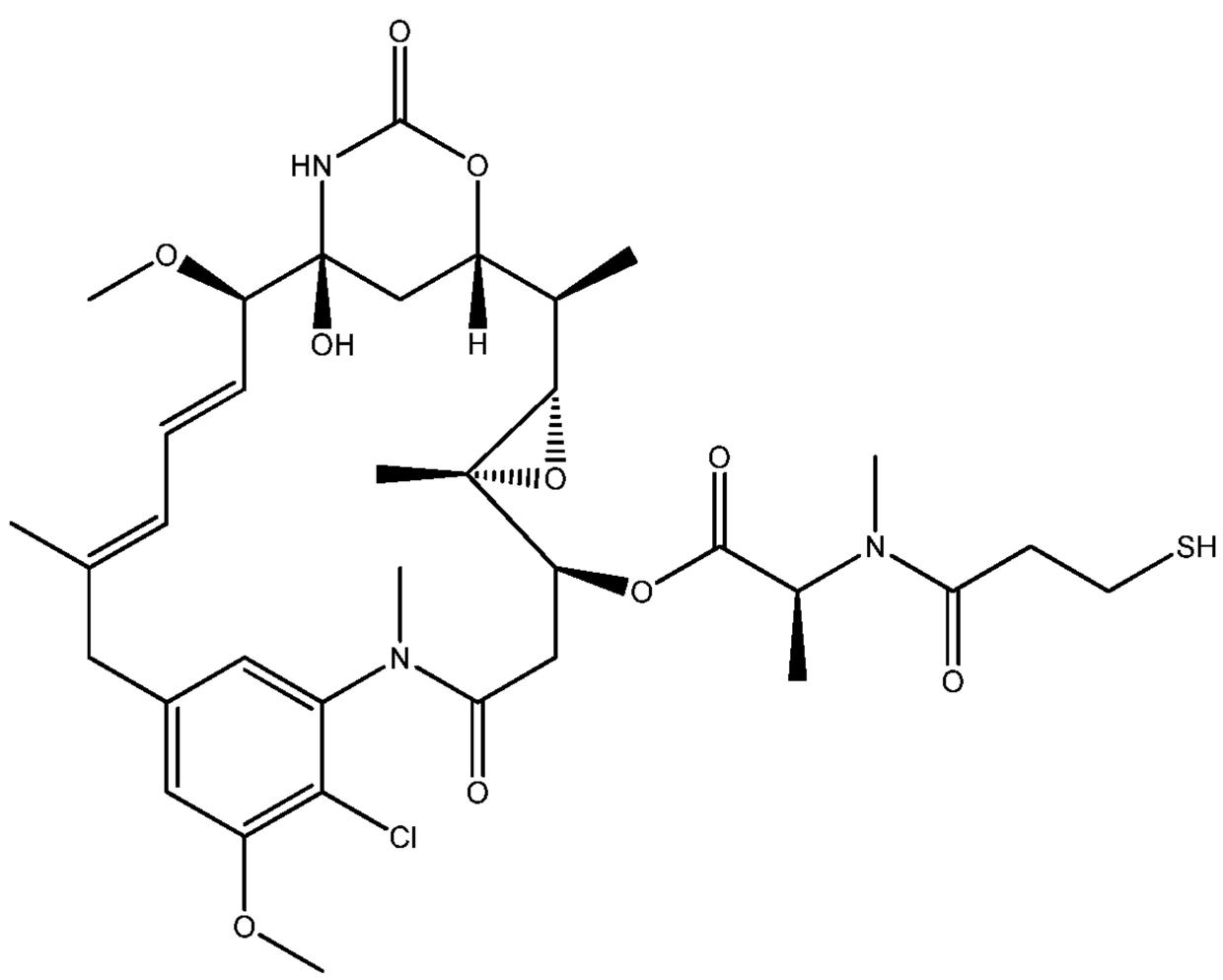
b. Maytansinoids

The anti-B7-H3 antibodies of the invention may be conjugated to at least one maytansinoid to form an ADC. Maytansinoids are potent antitumor agents that were originally isolated from members of the higher plant families *Celastraceae*, *Rhamnaceae*, and *Euphorbiaceae*, as well as some species of mosses (Kupchan et al, J. Am. Chem. Soc. 94:1354-1356 [1972]; Wani et al, J. Chem. Soc. Chem. Commun. 390: [1973]; Powell et al, J. Nat. Prod. 46:660-666 [1983]; Sakai et al, J. Nat. Prod. 51 :845-850 [1988]; and Suwanborirux et al, Experientia 46:117-120 [1990]). Evidence suggests that maytansinoids inhibit mitosis by inhibiting polymerization of the microtubule protein tubulin, thereby preventing formation of microtubules (see, *e.g.*, U.S. Pat. No. 6,441,163 and Remillard *et al.*, Science, 189, 1002-1005 (1975)). Maytansinoids have been shown to inhibit tumor cell growth *in vitro* using

cell culture models, and *in vivo* using laboratory animal systems. Moreover, the cytotoxicity of maytansinoids is 1,000-fold greater than conventional chemotherapeutic agents, such as, for example, methotrexate, daunorubicin, and vincristine (see, *e.g.*, U.S. Pat. No. 5,208,020).

Maytansinoids to include maytansine, maytansinol, C-3 esters of maytansinol, and other maytansinol analogues and derivatives (see, *e.g.*, U.S. Pat. Nos. 5,208,020 and 6,441,163, each of which is incorporated by reference herein). C-3 esters of maytansinol can be naturally occurring or synthetically derived. Moreover, both naturally occurring and synthetic C-3 maytansinol esters can be classified as a C-3 ester with simple carboxylic acids, or a C-3 ester with derivatives of N-methyl-L-alanine, the latter being more cytotoxic than the former. Synthetic maytansinoid analogues are described in, for example, Kupchan *et al.*, J. Med. Chem., 21, 31-37 (1978).

Suitable maytansinoids for use in ADCs of the invention can be isolated from natural sources, synthetically produced, or semi-synthetically produced. Moreover, the maytansinoid can be modified in any suitable manner, so long as sufficient cytotoxicity is preserved in the ultimate conjugate molecule. In this regard, maytansinoids lack suitable functional groups to which antibodies can be linked. A linking moiety desirably is utilized to link the maytansinoid to the antibody to form the conjugate, and is described in more detail in the linker section below. The structure of an exemplary maytansinoid, mertansine (DM1), is provided below.



Mertansine (DM1)

Representative examples of maytansinoids include, but are not limited, to DM1 ($N^{2'}$-deacetyl-$N^{2'}$-(3-mercapto-1-oxopropyl)-maytansine; also referred to as mertansine, drug maytansinoid 1;

ImmunoGen, Inc.; see also Chari *et al.* (1992) *Cancer Res* 52:127), DM2, DM3 ($N^{2'}$-deacetyl-$N^{2'}$-(4-mercapto-1-oxopentyl)-maytansine), DM4 (4-methyl-4-mercapto-1-oxopentyl)-maytansine), and maytansinol (a synthetic maytansinoid analog). Other examples of maytansinoids are described in US Patent No. 8,142,784, incorporated by reference herein.

Ansamitocins are a group of maytansinoid antibiotics that have been isolated from various bacterial sources. These compounds have potent antitumor activities. Representative examples include, but are not limited to ansamitocin P1, ansamitocin P2, ansamitocin P3, and ansamitocin P4.

In one embodiment of the invention, an anti-B7-H3 antibody is conjugated to at least one DM1. In one embodiment, an anti-B7-H3 antibody is conjugated to at least one DM2. In one embodiment, an anti-B7-H3 antibody is conjugated to at least one DM3. In one embodiment, an anti-B7-H3 antibody is conjugated to at least one DM4.

d. Plant Alkaloids

The anti-B7-H3 antibodies of the invention may be conjugated to at least one plant alkaloid, *e.g.*, a taxane or vinca alkaloid. Plant alkaloids are chemotherapy treatments derived made from certain types of plants. The vinca alkaloids are made from the periwinkle plant (*catharanthus rosea*), whereas the taxanes are made from the bark of the Pacific Yew tree (*taxus*). Both the vinca alkaloids and taxanes are also known as antimicrotubule agents, and are described in more detail below.

Taxanes

Anti-B7-H3 antibodies described herein may be conjugated to at least one taxane. The term "taxane" as used herein refers to the class of antineoplastic agents having a mechanism of microtubule action and having a structure that includes the taxane ring structure and a stereospecific side chain that is required for cytostatic activity. Also included within the term "taxane" are a variety of known derivatives, including both hydrophilic derivatives, and hydrophobic derivatives. Taxane derivatives include, but not limited to, galactose and mannose derivatives described in International Patent Application No. WO 99/18113; piperazino and other derivatives described in WO 99/14209; taxane derivatives described in WO 99/09021, WO 98/22451, and U.S. Pat. No. 5,869,680; 6-thio derivatives described in WO 98/28288; sulfenamide derivatives described in U.S. Pat. No. 5,821,263; and taxol derivative described in U.S. Pat. No. 5,415,869, each of which is incorporated by reference herein. Taxane compounds have also previously been described in U.S. Pat. Nos. 5,641,803, 5,665,671, 5,380,751, 5,728,687, 5,415,869, 5,407,683, 5,399,363, 5,424,073, 5,157,049, 5,773,464, 5,821,263, 5,840,929, 4,814,470, 5,438,072, 5,403,858, 4,960,790, 5,433,364, 4,942,184, 5,362,831, 5,705,503, and 5,278,324, all of which are expressly incorporated by reference. Further examples of taxanes include, but are not limited to, docetaxel (Taxotere; Sanofi Aventis), paclitaxel (Abraxane or Taxol; Abraxis Oncology), carbazitaxel, tesetaxel, opaxio, larotaxel, taxoprexin, BMS-184476, hongdoushan A, hongdoushan B, and hongdoushan C, and nanoparticle paclitaxel (ABI-007 / Abraxene; Abraxis

Bioscience).

In one embodiment, the anti-B7-H3 antibody of the invention is conjugated to at least one docetaxel molecule. In one embodiment, the anti-B7-H3 antibody of the invention is conjugated to at least one paclitaxel molecule.

Vinca alkaloids

In one embodiment, the anti-B7-H3 antibody is conjugated to at least one vinca alkaloid. Vinca alkaloids are a class of cell-cycle-specific drugs that work by inhibiting the ability of cancer cells to divide by acting upon tubulin and preventing the formation of microtubules. Examples of vinca alkaloids that may be used in the ADCs of the invention include, but are not limited to, vindesine sulfate, vincristine, vinblastine, and vinorelbine.

2. Antitumor Antibiotics

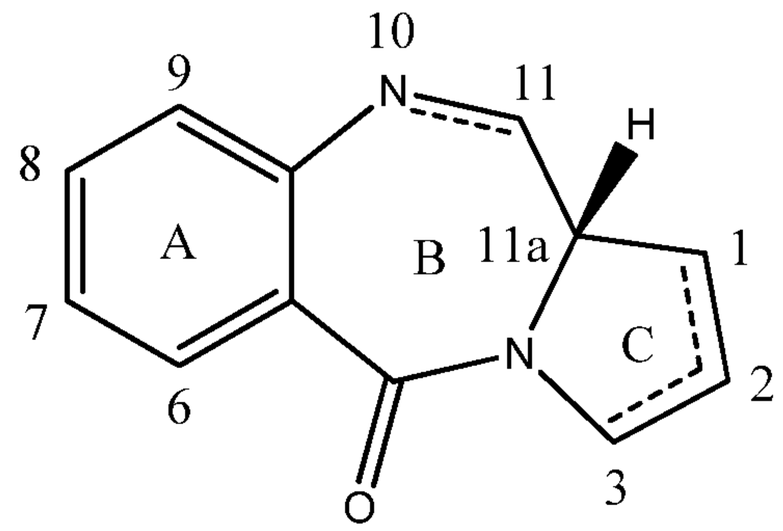
Anti-B7-H3 antibodies of the invention may be conjugated to one or more antitumor antibiotic(s) for the treatment of cancer. As used herein, the term "antitumor antibiotic" means an antineoplastic drug that blocks cell growth by interfering with DNA and is made from a microorganism. Often, antitumor antibiotics either break up DNA strands or slow down or stop DNA synthesis. Examples of antitumor antibiotics that may be included in the anti-B7-H3 ADCs of the invention include, but are not limited to, actinomycines (*e.g.*, pyrrolo[2,1-c][1,4]benzodiazepines), anthracyclines, calicheamicins, and duocarmycins, described in more detail below.

a. Actinomycins

The anti-B7-H3 antibodies of the invention may be conjugated to at least one actinomycin. Actinomycins are a subclass of antitumor antibiotics isolated from bacteria of the genus *Streptomyces*. Representative examples actinomycins include, but are not limited to, actinomycin D (Cosmegen [also known as actinomycin, dactinomycin, actinomycin IV, actinomycin C1], Lundbeck, Inc.), anthramycin, chicamycin A, DC-81, mazethramycin, neothramycin A, neothramycin B, porothramycin, prothracarcin B, SG2285, sibanomicin, sibiromycin, and tomaymycin. In one embodiment, the anti-B7-H3 antibody of the invention is conjugated to at least one pyrrolobenzodiazepine (PBD). Examples of PBDs include, but are not limited to, anthramycin, chicamycin A, DC-81, mazethramycin, neothramycin A, neothramycin B, porothramycin, prothracarcin B, SG2000 (SJG-136), SG2202 (ZC-207), SG2285 (ZC-423), sibanomicin, sibiromycin and tomaymycin. Thus, in one embodiment, anti-B7-H3 antibodies of the invention are conjugated to at least one actinomycin, *e.g.*, actinomycin D, or at least one PBD, *e.g.*, a pyrrolobenzodiazepine (PBD) dimer.

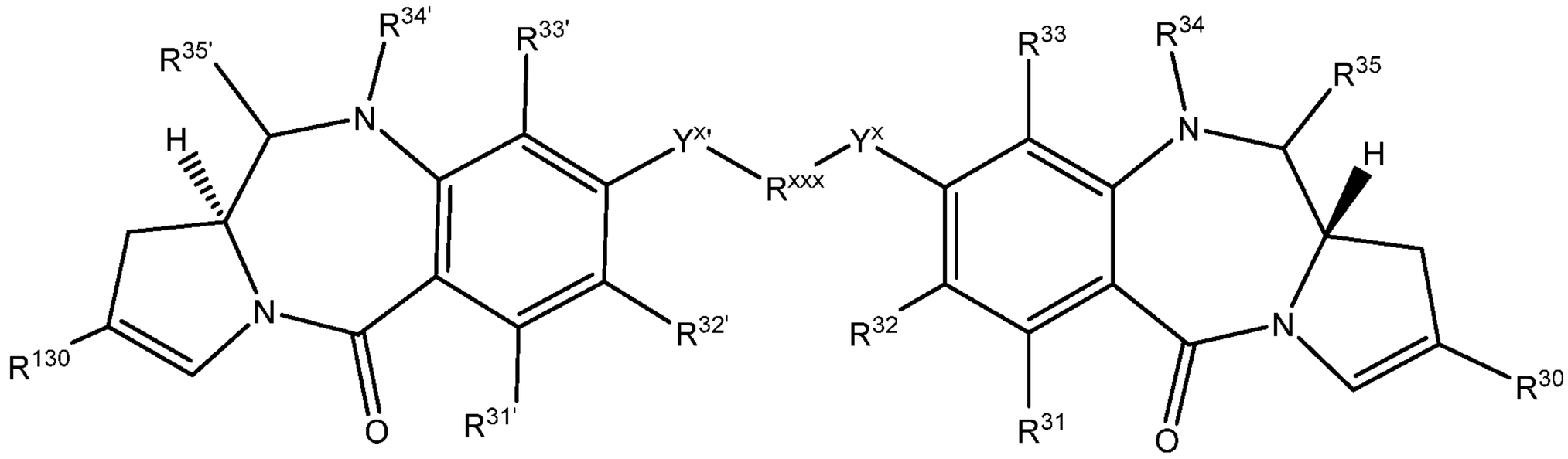
The structures of PBDs can be found, for example, in U.S. Patent Application Pub. Nos. 2013/0028917 and 2013/0028919, and in WO 2011/130598 A1, each of which are incorporated herein

by reference in their entirety. The generic structure of a PBD is provided below.



PBDs differ in the number, type and position of substituents, in both their aromatic A rings and pyrrolo C rings, and in the degree of saturation of the C ring. In the B-ring, there is generally an imine (N=C), a carbinolamine (NH-CH(OH)), or a carbinolamine methyl ether (NH-CH(OMe)) at the N10-C11 position which is the electrophilic center responsible for alkylating DNA. All of the known natural products have an (*S*)-configuration at the chiral C11α position which provides them with a right-handed twist when viewed from the C ring towards the A ring. The PBD examples provided herein may be conjugated to the anti-B7-H3 antibodies of the invention. Further examples of PBDs which may be conjugated to the anti-B7-H3 antibodies of the invention can be found, for example, in U.S. Patent Application Publication Nos. 2013/0028917 A1 and 2013/0028919 A1, in U.S. Patent Nos. 7,741,319 B2 , and in WO 2011/130598 A1 and WO 2006/111759 A1, each of which are incorporated herein by reference in their entirety.

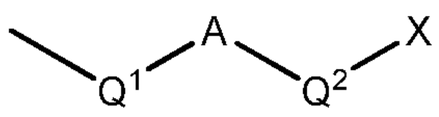
A representative PBD dimer having the following formula XXX may be conjugated to the anti-B7-H3 antibodies of the invention:



(XXX)

wherein:

R^{30} is of formula XXXI:



(XXXI)

where A is a C_{5-7} aryl group, X is a group conjugated to the Linker unit selected from the group consisting of —O—, —S—, —C(O)O—, —C(O)—, —NH(C=O)—, and —N(R^N)—, wherein R^N is selected from the group consisting of H, C_{1-4} alkyl and $(C_2H_4O)_mCH_3$, where s is 1 to 3, and either:

(i) Q^1 is a single bond, and Q^2 is selected from the group consisting of a single bond and —Z—$(CH_2)_n$—, where Z is selected from the group consisting of a single bond, O, S and NH and n is from 1 to 3; or

(ii) Q^1 is —CH=CH—, and Q^2 is a single bond;

R^{130} is a C_{5-10} aryl group, optionally substituted by one or more substituents selected from the group consisting of halo, nitro, cyano, C_{1-12} alkoxy, C_{3-20} heterocycloalkoxy, C_{5-20} aryloxy, heteroaryloxy, alkylalkoxy, arylalkoxy, alkylaryloxy, heteroarylalkoxy, alkylheteroaryloxy, C_{1-7} alkyl, C_{3-7} heterocyclyl and bis-oxy-C_{1-3} alkylene;

R^{31} and R^{33} are independently selected from the group consisting of H, R^x, OH, OR^x, SH, SR^x, NH_2, NHR^x, $NR^xR^{xx\prime}$, nitro, Me_3Sn and halo;

where R and R′ are independently selected from the group consisting of optionally substituted C_{1-12} alkyl, C_{3-20} heterocyclyl and C_{5-20} aryl groups;

R^{32} is selected from the group consisting of H, R^x, OH, OR^x, SH, SR^x, NH_2, NHR^x, NHR^xR^{xx}, nitro, Me_3Sn and halo;

either:

(a) R^{34} is H, and R^{11} is OH, OR^{xA}, where R^{xA} is C_{1-4} alkyl;

(b) R^{34} and R^{35} form a nitrogen-carbon double bond between the nitrogen and carbon atoms to which they are bound; or

(c) $R^{34}$is H and R^{35} is SO_zM, where z is 2 or 3;

R^{xxx} is a C_{3-12} alkylene group, which chain may be interrupted by one or more heteroatoms, selected from the group consisting of O, S, NH, and an aromatic ring;

Y^x and $Y^{x\prime}$ are is selected from the group consisting of O, S, and NH;

$R^{31\prime}$, $R^{32\prime}$, $R^{33\prime}$ are selected from the same groups as R^{31}, R^{32} and R^{33} respectively and $R^{34\prime}$ and $R^{35\prime}$ are the same as R^{34} and R^{35}, and each M is a monovalent pharmaceutically acceptable cation or both M groups together are a divalent pharmaceutically acceptable cation.

C_{1-12} alkyl: The term "C_{1-12} alkyl" as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a carbon atom of a hydrocarbon compound having from 1 to 12 carbon atoms, which may be aliphatic or alicyclic, and which may be saturated or unsaturated (e.g. partially unsaturated, fully unsaturated). Thus, the term "alkyl" includes the sub-classes alkenyl, alkynyl, cycloalkyl, etc., discussed below.

Examples of saturated alkyl groups include, but are not limited to, methyl (C_1), ethyl (C_2), propyl (C_3), butyl (C_4), pentyl (C_5), hexyl (C_6) and heptyl (C_7).

Examples of saturated linear alkyl groups include, but are not limited to, methyl (C_1), ethyl (C_2), n-propyl (C_3), n-butyl (C_4), n-pentyl (amyl) (C_5), n-hexyl (C_6) and n-heptyl (C_7).

Examples of saturated branched alkyl groups include iso-propyl (C_3), iso-butyl (C_4), sec-butyl (C_4), tert-butyl (C_4), iso-pentyl (C_5), and neo-pentyl (C_5).

C_{3-20} heterocyclyl: The term "C_{3-20} heterocyclyl" as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a ring atom of a heterocyclic compound, which moiety has from 3 to 20 ring atoms, of which from 1 to 10 are ring heteroatoms. Preferably, each ring has from 3 to 7 ring atoms, of which from 1 to 4 are ring heteroatoms.

In this context, the prefixes (e.g. C_{3-20}, C_{3-7}, C_{5-6}, etc.) denote the number of ring atoms, or range of number of ring atoms, whether carbon atoms or heteroatoms. For example, the term "C_{5-6}heterocyclyl", as used herein, pertains to a heterocyclyl group having 5 or 6 ring atoms.

Examples of monocyclic heterocyclyl groups include, but are not limited to, those derived from:

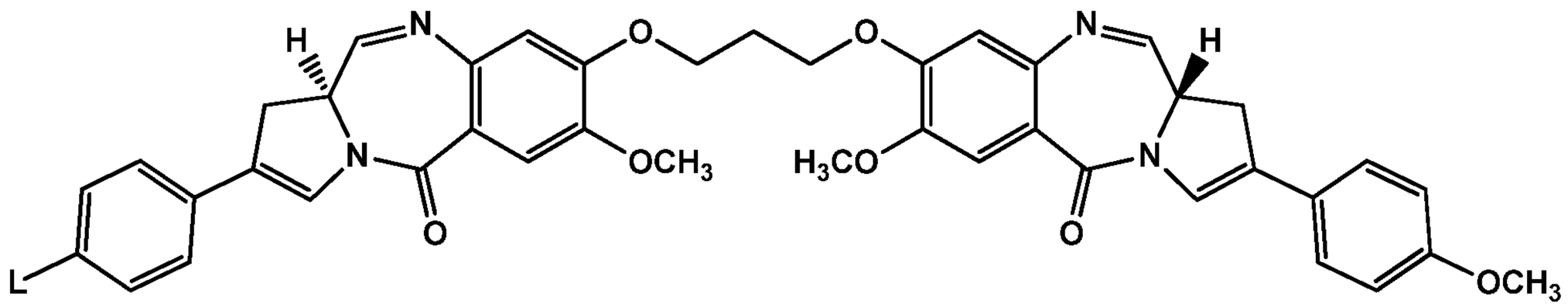
N_1: aziridine (C_3), azetidine (C_4), pyrrolidine (tetrahydropyrrole) (C_5), pyrroline (e.g., 3-pyrroline, 2,5-dihydropyrrole) (C_5), 2H-pyrrole or 3H-pyrrole (isopyrrole, isoazole) (C_5), piperidine (C_6), dihydropyridine (C_6), tetrahydropyridine (C_6), azepine (C_7); O_1: oxirane (C_3), oxetane (C_4), oxolane (tetrahydrofuran) (C_5), oxole (dihydrofuran) (C_5), oxane (tetrahydropyran) (C_6), dihydropyran (C_6), pyran (C_6), oxepin (C_7); S_1: thiirane (C_3), thietane (C_4), thiolane (tetrahydrothiophene) (C_5), thiane (tetrahydrothiopyran) (C_6), thiepane (C_7); O_2: dioxolane (C_5), dioxane (C_6), and dioxepane (C_7); O_3: trioxane (C_6); N_2: imidazolidine (C_5), pyrazolidine (diazolidine) (C_5), imidazoline (C_5), pyrazoline (dihydropyrazole) (C_5), piperazine (C_6); N_1O_1: tetrahydrooxazole (C_5), dihydrooxazole (C_5), tetrahydroisoxazole (C_5), dihydroisoxazole (C_5), morpholine (C_6), tetrahydrooxazine (C_6), dihydrooxazine (C_6), oxazine (C_6); N_1S_1: thiazoline (C_5), thiazolidine (C_5), thiomorpholine (C_6); N_2O_1: oxadiazine (C_6); O_1S_1: oxathiole (C_5) and oxathiane (thioxane) (C_6); and, $N_1O_1S_1$: oxathiazine (C_6).

Examples of substituted monocyclic heterocyclyl groups include those derived from saccharides, in cyclic form, for example, furanoses (C_5), such as arabinofuranose, lyxofuranose, ribofuranose, and xylofuranse, and pyranoses (C_6), such as allopyranose, altropyranose, glucopyranose, mannopyranose, gulopyranose, idopyranose, galactopyranose, and talopyranose.

C_{5-20} aryl: The term "C_{5-20} aryl", as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from an aromatic ring atom of an aromatic compound, which moiety has from 3 to 20 ring atoms. Preferably, each ring has from 5 to 7 ring atoms.

In this context, the prefixes (e.g. C_{3-20}, C_{5-7}, C_{5-6}, etc.) denote the number of ring atoms, or range of number of ring atoms, whether carbon atoms or heteroatoms. For example, the term "C_{5-6} aryl" as used herein, pertains to an aryl group having 5 or 6 ring atoms.

In one embodiment, the anti-B7-H3 antibodies of the invention may be conjugated to a PBD dimer having the following formula XXXIa:



(XXXIa)

wherein the above structure describes the PBD dimer SG2202 (ZC-207) and is conjugated to the anti-B7-H3 antibody of the invention via a linker L. SG2202 (ZC-207) is disclosed in, for example, U.S. Patent App. Pub. No. 2007/0173497, which is incorporated herein by reference in its entirety.

In another embodiment, a PBD dimer, SGD-1882, is conjugated to anti-B7-H3 antibody of the invention via a drug linker, as depicted in Figure 4. SGD-1882 is disclosed in Sutherland *et al.* (2013) *Blood* 122(8):1455 and in U.S Patent App. Pub. No. 2013/0028919, which is incorporated herein by reference in its entirety. As described in Figure 4, the PBD dimer SGD-1882 may be conjugated to an antibody via an mc-val-ala-dipeptide linker (collectively referred to as SGD-1910 in Figure 4). In a certain embodiment, an anti-B7-H3 antibody, as disclosed herein, is conjugated to the PBD dimer described in Figure 4. Thus, in a further embodiment, the invention includes an anti-B7-H3 antibody, as disclosed herein, conjugated to a PBD dimer via a mc-val-ala-dipeptide linker, as described in Figure 4. In certain embodiments, the invention includes an anti-B7-H3 antibody comprising a heavy chain variable region comprising a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 35, a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 34, and a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 33, and a light chain variable region comprising a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 39, a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 38, and a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 37, conjugated to a PBD, including, but not limited to, the PBD dimer described in Figure 4. In certain embodiments, the invention includes an anti-B7-H3 antibody comprising a heavy chain variable region comprising a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 12, a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 140, and a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 10, and a light chain variable region comprising a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 15, a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 7, and a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 136, conjugated to a PBD, including, but not limited to, the PBD dimer described in Figure 4. In certain embodiments, the invention includes an anti-B7-H3 antibody comprising a heavy chain variable region comprising a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 12, a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 140, and a CDR1 domain comprising the amino acid

sequence of SEQ ID NO: 10, and a light chain variable region comprising a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 15, a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 7, and a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 138, conjugated to a PBD, including, but not limited to, the PBD dimer described in Figure 4. In certain embodiments, the invention includes an anti-B7-H3 antibody comprising the heavy chain variable region of huAb13v1 as defined by the amino acid sequence set forth in SEQ ID NO: 147, or huAb3v2.5 or huAb3v2.6 as defined by the amino acid sequence set forth in SEQ ID NO: 139, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 144, 135, or 137 corresponding to huAb13v1, huAb3v2.5, or huAb3v2.6, respectively, wherein the antibody is conjugated to a PBD, such as, but not limited to, the exemplary PBD dimer of Figure 4.

b. Anthracyclines

Anti-B7-H3 antibodies of the invention may be conjugated to at least one anthracycline. Anthracyclines are a subclass of antitumor antibiotics isolated from bacteria of the genus *Streptomyces*. Representative examples include, but are not limited to daunorubicin (Cerubidine, Bedford Laboratories), doxorubicin (Adriamycin, Bedford Laboratories; also referred to as doxorubicin hydrochloride, hydroxydaunorubicin, and Rubex), epirubicin (Ellence, Pfizer), and idarubicin (Idamycin; Pfizer Inc.). Thus, in one embodiment, the anti-B7-H3 antibody of the invention is conjugated to at least one anthracycline, *e.g.*, doxorubicin.

c. Calicheamicins

The anti-B7-H3 antibodies of the invention may be conjugated to at least one calicheamicin. Calicheamicins are a family of enediyne antibiotics derived from the soil organism *Micromonospora echinospora.* Calicheamicins bind the minor groove of DNA and induce double-stranded DNA breaks, resulting in cell death with a 100 fold increase over other chemotherapeutics (Damle *et al.* (2003) *Curr Opin Pharmacol* 3:386). Preparation of calicheamicins that may be used as drug conjugates in the invention have been described, see U.S. Pat. Nos. 5,712,374; 5,714,586; 5,739,116; 5,767,285; 5,770,701; 5,770,710; 5,773,001; and 5,877,296. Structural analogues of calicheamicin which may be used include, but are not limited to, γ_1^I, α_2^I, α_3^I, N-acetyl-γ_1^I, PSAG and θ^I_1 (Hinman *et al.*, Cancer Research 53:3336-3342 (1993), Lode *et al.*, Cancer Research 58:2925-2928 (1998) and the aforementioned U.S. Patent Nos. 5,712,374; 5,714,586; 5,739,116; 5,767,285; 5,770,701; 5,770,710; 5,773,001; and 5,877,296). Thus, in one embodiment, the anti-B7-H3 antibody of the invention is conjugated to at least one calicheamicin.

d. Duocarmycins

Anti-B7-H3 antibodies of the invention may be conjugated to at least one duocarmycin. Duocarmycins are a subclass of antitumor antibiotics isolated from bacteria of the genus *Streptomyces*. (see Nagamura and Saito (1998) *Chemistry of Heterocyclic Compounds*, Vol. 34, No. 12). Duocarmycins bind to the minor groove of DNA and alkylate the nucleobase adenine at the N3 position (Boger (1993) *Pure and Appl Chem* 65(6):1123; and Boger and Johnson (1995) *PNAS USA* 92:3642). Synthetic analogs of duocarmycins include, but are not limited to, adozelesin, bizelesin, and carzelesin. Thus, in one embodiment, the anti-B7-H3 antibody of the invention is conjugated to at least one duocarmycin.

e. Other antitumor antibiotics

In addition to the foregoing, additional antitumor antibiotics that may be used in the anti-B7-H3 ADCs of the invention include bleomycin (Blenoxane, Bristol-Myers Squibb), mitomycin, and plicamycin (also known as mithramycin).

3. Immunomodulating Agents

In one aspect, anti-B7-H3 antibodies of the invention may be conjugated to at least one immunomodulating agent. As used herein, the term "immunomodulating agent" refers to an agent that can stimulate or modify an immune response. In one embodiment, an immunomodulating agent is an immunostimulator that enhances a subject's immune response. In another embodiment, an immunomodulating agent is an immunosuppressant that prevents or decreases a subject's immune response. An immunomodulating agent may modulate myeloid cells (monocytes, macrophages, dendritic cells, megakaryocytes and granulocytes) or lymphoid cells (T cells, B cells and natural killer (NK) cells) and any further differentiated cell thereof. Representative examples include, but are not limited to, bacillus calmette-guerin (BCG) and levamisole (Ergamisol). Other examples of immunomodulating agents that may be used in the ADCs of the invention include, but are not limited to, cancer vaccines, cytokines, and immunomodulating gene therapy.

a. Cancer vaccines

Anti-B7-H3 antibodies of the invention may be conjugated to a cancer vaccine. As used herein, the term "cancer vaccine" refers to a composition (*e.g.*, a tumor antigen and a cytokine) that elicits a tumor-specific immune response. The response is elicited from the subject's own immune system by administering the cancer vaccine, or, in the case of the instant invention, administering an ADC comprising an anti-B7-H3 antibody and a cancer vaccine. In preferred embodiments, the immune response results in the eradication of tumor cells in the body (*e.g.*, primary or metastatic tumor cells). The use of cancer vaccines generally involves the administration of a particular antigen or group of antigens that are, for example, present on the surface a particular cancer cell, or present on

the surface of a particular infectious agent shown to facilitate cancer formation. In some embodiments, the use of cancer vaccines is for prophylactic purposes, while in other embodiments, the use is for therapeutic purposes. Non-limiting examples of cancer vaccines that may be used in the anti-B7-H3 ADCs of the invention include, recombinant bivalent human papillomavirus (HPV) vaccine types 16 and 18 vaccine (Cervarix, GlaxoSmithKline), recombinant quadrivalent human papillomavirus (HPV) types 6, 11, 16, and 18 vaccine (Gardasil, Merck & Company), and sipuleucel-T (Provenge, Dendreon). Thus, in one embodiment, the anti-B7-H3 antibody of the invention is conjugated to at least one cancer vaccine that is either an immunostimulator or is an immunosuppressant.

b. Cytokines

The anti-B7-H3 antibodies of the invention may be conjugated to at least one cytokine. The term "cytokine" generally refers to proteins released by one cell population which act on another cell as intercellular mediators. Cytokines directly stimulate immune effector cells and stromal cells at the tumor site and enhance tumor cell recognition by cytotoxic effector cells (Lee and Margolin (2011) *Cancers* 3:3856). Numerous animal tumor model studies have demonstrated that cytokines have broad anti-tumor activity and this has been translated into a number of cytokine-based approaches for cancer therapy (Lee and Margoli, *supra*). Recent years have seen a number of cytokines, including GM-CSF, IL-7, IL-12, IL-15, IL-18 and IL-21, enter clinical trials for patients with advanced cancer (Lee and Margoli, *supra*).

Examples of cytokines that may be used in the ADCs of the invention include, but are not limited to, parathyroid hormone; thyroxine; insulin; proinsulin; relaxin; prorelaxin; glycoprotein hormones such as follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), and luteinizing hormone (LH); hepatic growth factor; fibroblast growth factor; prolactin; placental lactogen; tumor necrosis factor; mullerian-inhibiting substance; mouse gonadotropin-associated peptide; inhibin; activin; vascular endothelial growth factor; integrin; thrombopoietin (TPO); nerve growth factors such as NGF; platelet-growth factor; transforming growth factors (TGFs); insulin-like growth factor-I and -II; erythropoietin (EPO); osteoinductive factors; interferons such as interferon α, β,and γ, colony stimulating factors (CSFs); granulocyte-macrophage-C-SF (GM-CSF); and granulocyte-CSF (G-CSF); interleukins (ILs) such as IL-1, IL-1α, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-11, IL-12; tumor necrosis factor; and other polypeptide factors including LIF and kit ligand (KL). As used herein, the term cytokine includes proteins from natural sources or from recombinant cell culture and biologically active equivalents of the native sequence cytokines. Thus, in one embodiment, the invention provides an ADC comprising an anti-B7-H3 antibody described herein and a cytokine.

c. Colony-stimulating factors (CSFs)

The anti-B7-H3 antibodies of the invention may be conjugated to at least one colony stimulating factor (CSF). Colony stimulating factors (CSFs) are growth factors that assist the bone marrow in making white blood cells. Some cancer treatments (*e.g.*, chemotherapy) can affect white blood cells (which help fight infection); therefore, colony-stimulating factors may be introduced to help support white blood cell levels and strengthen the immune system. Colony-stimulating factors may also be used following a bone marrow transplant to help the new marrow start producing white blood cells. Representative examples of CSFs that may be used in the anti-B7-H3 ADCs of the invention include, but are not limited to erythropoietin (Epoetin), filgrastim (Neopogen (also known as granulocyte colony-stimulating factor (G-CSF); Amgen, Inc.), sargramostim (leukine (granulocyte-macrophage colony-stimulating factor and GM-CSF); Genzyme Corporation), promegapoietin, and Oprelvekin (recombinant IL-11; Pfizer, Inc.). Thus, in one embodiment, the invention provides an ADC comprising an anti-B7-H3 antibody described herein and a CSF.

4. Gene Therapy

The anti-B7-H3 antibody of the invention may be conjugated to at least one nucleic acid (directly or indirectly via a carrier) for gene therapy. Gene therapy generally refers to the introduction of genetic material into a cell whereby the genetic material is designed to treat a disease. As it pertains to immunomodulatory agents, gene therapy is used to stimulate a subject's natural ability to inhibit cancer cell proliferation or kill cancer cells. In one embodiment, the anti-B7-H3 ADC of the invention comprises a nucleic acid encoding a functional, therapeutic gene that is used to replace a mutated or otherwise dysfunctional (*e.g.* truncated) gene associated with cancer. In other embodiments, the anti-B7-H3 ADC of the invention comprises a nucleic acid that encodes for or otherwise provides for the production of a therapeutic protein to treat cancer. The nucleic acid that encodes the therapeutic gene may be directly conjugated to the anti-B7-H3 antibody, or alternatively, may be conjugated to the anti-B7-H3 antibody through a carrier. Examples of carriers that may be used to deliver a nucleic acid for gene therapy include, but are not limited to, viral vectors or liposomes.

5. Alkylating Agents

The anti-B7-H3 antibodies of the invention may be conjugated to one or more alkylating agent(s). Alkylating agents are a class of antineoplastic compounds that attaches an alkyl group to DNA. Examples of alkylating agents that may be used in the ADCs of the invention include, but are not limited to, alkyl sulfonates, ethylenimimes, methylamine derivatives, epoxides, nitrogen mustards, nitrosoureas, triazines, and hydrazines.

a. Alkyl Sulfonates

The anti-B7-H3 antibodies of the invention may be conjugated to at least one alkyl sulfonate. Alkyl sulfonates are a subclass of alkylating agents with a general formula: $R\text{-}SO_2\text{-}O\text{-}R^1$, wherein R and R^1 are typically alkyl or aryl groups. A representative example of an alkyl sulfonate includes, but is not limited to, busulfan (Myleran, GlaxoSmithKline; Busulfex IV, PDL BioPharma, Inc.).

b. Nitrogen Mustards

The anti-B7-H3 antibodies of the invention may be conjugated to at least one nitrogen mustard. Representative examples of this subclass of anti-cancer compounds include, but are not limited to chlorambucil (Leukeran, GlaxoSmithKline), cyclophosphamide (Cytoxan, Bristol-Myers Squibb; Neosar, Pfizer, Inc.), estramustine (estramustine phosphate sodium or Estracyt), Pfizer, Inc.), ifosfamide (Ifex, Bristol-Myers Squibb), mechlorethamine (Mustargen, Lundbeck Inc.), and melphalan (Alkeran or L-Pam or phenylalanine mustard; GlaxoSmithKline).

c. Nitrosoureas

The anti-B7-H3 antibody of the invention may be conjugated to at least one nitrosourea. Nitrosoureas are a subclass of alkylating agents that are lipid soluble. Representative examples include, but are not limited to, carmustine (BCNU [also known as BiCNU, *N,N*-Bis(2-chloroethyl)-*N*-nitrosourea, or 1, 3-bis (2-chloroethyl)-*l*-nitrosourea], Bristol-Myers Squibb), fotemustine (also known as Muphoran), lomustine (CCNU or 1-(2-chloro-ethyl)-3-cyclohexyl-1-nitrosourea, Bristol-Myers Squibb), nimustine (also known as ACNU), and streptozocin (Zanosar, Teva Pharmaceuticals).

d. Triazines and Hydrazines

The anti-B7-H3 antibody of the invention may be conjugated to at least one triazine or hydrazine. Triazines and hydrazines are a subclass of nitrogen-containing alkylating agents. In some embodiments, these compounds spontaneously decompose or can be metabolized to produce alkyl diazonium intermediates that facilitate the transfer of an alkyl group to nucleic acids, peptides, and/or polypeptides, thereby causing mutagenic, carcinogenic, or cytotoxic effects. Representative examples include, but are not limited to dacarbazine (DTIC-Dome, Bayer Healthcare Pharmaceuticals Inc.), procarbazine (Mutalane, Sigma-Tau Pharmaceuticals, Inc.), and temozolomide (Temodar, Schering Plough).

e. Other Alkylating Agents

The anti-B7-H3 antibodies of the invention may be conjugated to at least one ethylenimine, methylamine derivative, or epoxide. Ethylenimines are a subclass of alkylating agents that typically containing at least one aziridine ring. Epoxides represent a subclass of alkylating agents that are characterized as cyclic ethers with only three ring atoms.

Representatives examples of ethylenimines include, but are not limited to thiopeta (Thioplex, Amgen), diaziquone (also known as aziridinyl benzoquinone (AZQ)), and mitomycin C. Mitomycin C is a natural product that contains an aziridine ring and appears to induce cytoxicity through cross-linking DNA (Dorr RT, *et al. Cancer Res*. 1985;45:3510; Kennedy KA, et al *Cancer Res*. 1985;45:3541). Representative examples of methylamine derivatives and their analogs include, but are not limited to, altretamine (Hexalen, MGI Pharma, Inc.), which is also known as hexamethylamine and hexastat. Representative examples of epoxides of this class of anti-cancer compound include, but are not limited to dianhydrogalactitol. Dianhydrogalactitol (1,2:5,6-dianhydrodulcitol) is chemically related to the aziridines and generally facilitate the transfer of an alkyl group through a similar mechanism as described above. Dibromodulcitol is hydrolyzed to dianhydrogalactitol and thus is a pro-drug to an epoxide (Sellei C, *et al. Cancer Chemother Rep*. 1969;53:377).

6. Antiangiogenic Agents

In one aspect, the anti-B7-H3 antibodies described herein are conjugated to at least one antiangiogenic agent. Antiangiogenic agents inhibit the growth of new blood vessels. Antiangiogenic agents exert their effects in a variety of ways. In some embodiments, these agents interfere with the ability of a growth factor to reach its target. For example, vascular endothelial growth factor (VEGF) is one of the primary proteins involved in initiating angiogenesis by binding to particular receptors on a cell surface. Thus, certain antiangiogenic agents, that prevent the interaction of VEGF with its cognate receptor, prevent VEGF from initiating angiogenesis. In other embodiments, these agents interfere with intracellular signaling cascades. For example, once a particular receptor on a cell surface has been triggered, a cascade of other chemical signals is initiated to promote the growth of blood vessels. Thus, certain enzymes, for example, some tyrosine kinases, that are known to facilitate intracellular signaling cascades that contribute to, for example, cell proliferation, are targets for cancer treatment. In other embodiments, these agents interfere with intercellular signaling cascades. Yet, in other embodiments, these agents disable specific targets that activate and promote cell growth or by directly interfering with the growth of blood vessel cells. Angiogenesis inhibitory properties have been discovered in more than 300 substances with numerous direct and indirect inhibitory effects.

Representative examples of antiangiogenic agents that may be used in the ADCs of the invention include, but are not limited to, angiostatin, ABX EGF, C1-1033, PKI-166, EGF vaccine, EKB-569, GW2016, ICR-62, EMD 55900, CP358, PD153035, AG1478, IMC-C225 (Erbitux, ZD1839 (Iressa), OSI-774, Erlotinib (tarceva), angiostatin, arrestin, endostatin, BAY 12-9566 and w/fluorouracil or doxorubicin, canstatin, carboxyamidotriozole and with paclitaxel, EMD121974, S-24, vitaxin, dimethylxanthenone acetic acid, IM862, Interleukin-12, Interleukin-2, NM-3, HuMV833, PTK787, RhuMab, angiozyme (ribozyme), IMC-1C11, Neovastat, marimstat, prinomastat, BMS-275291,COL-3, MM1270, SU101, SU6668, SU11248, SU5416, with paclitaxel, with gemcitabine and cisplatin, and with irinotecan and cisplatin and with radiation, tecogalan, temozolomide and PEG

interferon α2b, tetrathiomolybdate, TNP-470, thalidomide, CC-5013 and with taxotere, tumstatin, 2-methoxyestradiol, VEGF trap, mTOR inhibitors (deforolimus, everolimus (Afinitor, Novartis Pharmaceutical Corporation), and temsirolimus (Torisel, Pfizer, Inc.)), kinase inhibitors (*e.g.*, erlotinib (Tarceva, Genentech, Inc.), imatinib (Gleevec, Novartis Pharmaceutical Corporation), gefitinib (Iressa, AstraZeneca Pharmaceuticals), dasatinib (Sprycel, Brystol-Myers Squibb), sunitinib (Sutent, Pfizer, Inc.), nilotinib (Tasigna, Novartis Pharmaceutical Corporation), lapatinib (Tykerb, GlaxoSmithKline Pharmaceuticals), sorafenib (Nexavar, Bayer and Onyx), phosphoinositide 3-kinases (PI3K), Osimertinib, Cobimetinib, Trametinib, Dabrafenib, Dinaciclib).

7. Antimetabolites

The anti-B7-H3 antibodies of the invention may be conjugated to at least one antimetabolite. Antimetabolites are types of chemotherapy treatments that are very similar to normal substances within the cell. When the cells incorporate an antimetabolite into the cellular metabolism, the result is negative for the cell, *e.g.*, the cell is unable to divide. Antimetabolites are classified according to the substances with which they interfere. Examples of antimetabolites that may be used in the ADCs of the invention include, but are not limited to, a folic acid antagonist (*e.g.*, methotrexate), a pyrimidine antagonist (*e.g.*, 5-Fluorouracil, Foxuridine, Cytarabine, Capecitabine, and Gemcitabine), a purine antagonist (*e.g.*, 6-Mercaptopurine and 6-Thioguanine) and an adenosine deaminase inhibitor (*e.g.*, Cladribine, Fludarabine, Nelarabine and Pentostatin), as described in more detail below.

a. Antifolates

The anti-B7-H3 antibodies of the invention may be conjugated to at least one antifolate. Antifolates are a subclass of antimetabolites that are structurally similar to folate. Representative examples include, but are not limited to, methotrexate, 4-amino-folic acid (also known as aminopterin and 4-aminopteroic acid), lometrexol (LMTX), pemetrexed (Alimpta, Eli Lilly and Company), and trimetrexate (Neutrexin, Ben Venue Laboratories, Inc.)

b. Purine Antagonists

The anti-B7-H3 antibodies of the invention may be conjugated to at least one purine antagonist. Purine analogs are a subclass of antimetabolites that are structurally similar to the group of compounds known as purines. Representative examples of purine antagonists include, but are not limited to, azathioprine (Azasan, Salix; Imuran, GlaxoSmithKline), cladribine (Leustatin [also known as 2-CdA], Janssen Biotech, Inc.), mercaptopurine (Purinethol [also known as 6-mercaptoethanol], GlaxoSmithKline), fludarabine (Fludara, Genzyme Corporation), pentostatin (Nipent, also known as 2'-deoxycoformycin (DCF)), 6-thioguanine (Lanvis [also known as thioguanine], GlaxoSmithKline).

c. Pyrimidine Antagonists

The anti-B7-H3 antibodies of the invention may be conjugated to at least one pyrimidine antagonist. Pyrimidine antagonists are a subclass of antimetabolites that are structurally similar to the group of compounds known as purines. Representative examples of pyrimidine antagonists include, but are not limited to azacitidine (Vidaza, Celgene Corporation), capecitabine (Xeloda, Roche Laboratories), Cytarabine (also known as cytosine arabinoside and arabinosylcytosine, Bedford Laboratories), decitabine (Dacogen, Eisai Pharmaceuticals), 5-fluorouracil (Adrucil, Teva Pharmaceuticals; Efudex, Valeant Pharmaceuticals, Inc), 5-fluoro-2'-deoxyuridine 5'-phosphate (FdUMP), 5-fluorouridine triphosphate, and gemcitabine (Gemzar, Eli Lilly and Company).

8. Boron-Containing Agents

The anti-B7-H3 antibody of the invention may be conjugated to at least one boron containing agent. Boron-containing agents comprise a class of cancer therapeutic compounds which interfere with cell proliferation. Representative examples of boron containing agents include, but are not limited, to borophycin and bortezomib (Velcade, Millenium Pharmaceuticals).

9. Chemoprotective Agents

The anti-B7-H3 antibodies of the invention may be conjugated to at least one chemoprotective agent. Chemoprotective drugs are a class of compounds, which help protect the body against specific toxic effects of chemotherapy. Chemoprotective agents may be administered with various chemotherapies in order to protect healthy cells from the toxic effects of chemotherapy drugs, while simultaneously allowing the cancer cells to be treated with the administered chemotherapeutic. Representative chemoprotective agents include, but are not limited to amifostine (Ethyol, Medimmune, Inc.), which is used to reduce renal toxicity associated with cumulative doses of cisplatin, dexrazoxane (Totect, Apricus Pharma; Zinecard), for the treatment of extravasation caused by the administration of anthracycline (Totect), and for the treatment of cardiac-related complications caused by the administration of the antitumor antibiotic doxorubicin (Zinecard), and mesna (Mesnex, Bristol-Myers Squibb), which is used to prevent hemorrhagic cystitis during chemotherapy treatment with ifocfamide.

10. Hormone agents

The anti-B7-H3 antibody of the invention may be conjugated to at least one hormone agent. A hormone agent (including synthetic hormones) is a compound that interferes with the production or activity of endogenously produced hormones of the endocrine system. In some embodiments, these compounds interfere with cell growth or produce a cytotoxic effect. Non-limiting examples include androgens, estrogens, medroxyprogesterone acetate (Provera, Pfizer, Inc.), and progestins.

11. Antihormone Agents

The anti-B7-H3 antibodies of the invention may be conjugated to at least one antihormone agent. An "antihormone" agent is an agent that suppresses the production of and/or prevents the function of certain endogenous hormones. In one embodiment, the antihormone agent interferes with the activity of a hormone selected from the group comprising androgens, estrogens, progesterone, and goanadotropin-releasing hormone, thereby interfering with the growth of various cancer cells. Representative examples of antihormone agents include, but are not limited to, aminoglutethimide, anastrozole (Arimidex, AstraZeneca Pharmaceuticals), bicalutamide (Casodex, AstraZeneca Pharmaceuticals), cyproterone acetate (Cyprostat, Bayer PLC), degarelix (Firmagon, Ferring Pharmaceuticals), exemestane (Aromasin, Pfizer Inc.), flutamide (Drogenil, Schering-Plough Ltd), fulvestrant (Faslodex, AstraZeneca Pharmaceuticals), goserelin (Zolodex, AstraZeneca Pharmaceuticals), letrozole (Femara, Novartis Pharmaceuticals Corporation), leuprolide (Prostap), lupron, medroxyprogesterone acetate (Provera, Pfizer Inc.), Megestrol acetate (Megace, Bristol-Myers Squibb Company), tamoxifen (Nolvadex, AstraZeneca Pharmaceuticals), and triptorelin (Decapetyl, Ferring).

12. Corticosteroids

The anti-B7-H3 antibodies of the invention may be conjugated to at least one corticosteroid. Corticosteroids may be used in the ADCs of the invention to decrease inflammation. An example of a corticosteroid includes, but is not limited to, a glucocorticoid, for example, prednisone (Deltasone, Pharmacia & Upjohn Company, a division of Pfizer, Inc.).

13. Photoactive Therapeutic Agents

The anti-B7-H3 antibodies of the invention may be conjugated to at least one photoactive therapeutic agent. Photoactive therapeutic agents include compounds that can be deployed to kill treated cells upon exposure to electromagnetic radiation of a particular wavelength. Therapeutically relevant compounds absorb electromagnetic radiation at wavelengths which penetrate tissue. In preferred embodiments, the compound is administered in a non-toxic form that is capable of producing a photochemical effect that is toxic to cells or tissue upon sufficient activation. In other preferred embodiments, these compounds are retained by cancerous tissue and are readily cleared from normal tissues. Non-limiting examples include various chromagens and dyes.

14. Oligonucleotides

The anti-B7-H3 antibodies of the invention may be conjugated to at least one oligonucleotide. Oligonucleotides are made of short nucleic acid chains that work by interfering with the processing of genetic information. In some embodiments, the oligonucleotides for use in ADCs are unmodified single-stranded and/or double-stranded DNA or RNA molecules, while in other embodiments, these

therapeutic oligonucleotides are chemically-modified single-stranded and/or double-stranded DNA or RNA molecules. In one embodiment, the oligonulceotides used in the ADCs are relatively short (19–25 nucleotides) and hybridize to a unique nucleic acid sequence in the total pool of nucleic acid targets present in cells. Some of the important oligonucleotide technologies include the antisense oligonucleotides (including RNA interference (RNAi)), aptamers, CpG oligonucleotides, and ribozymes.

a. Antisense oligonucleotides

The anti-B7-H3 antibody of the invention may be conjugated to at least one antisense oligonucleotide. Antisense oligonucleotides are designed to bind to RNA through Watson–Crick hybridization. In some embodiments the antisense oligonucleotide is complementary to a nucleotide encoding a region, domain, portion, or segment of B7-H3. In some embodiments, the antisense oligonucleotide comprises from about 5 to about 100 nucleotides, from about 10 to about 50 nucleotides, from about 12 to about 35, and from about 18 to about 25 nucleotides. In some embodiments, the oligonucleotide is at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% homologous to a region, portion, domain, or segment of the B7-H3 gene. In some embodiments there is substantial sequence homology over at least 15, 20, 25, 30, 35, 40, 50, or 100 consecutive nucleotides of the B7-H3 gene. In preferred embodiments, the size of these antisense oligonucleotides ranges from 12 to 25 nucleotides in length, with the majority of antisense oligonucleotides being 18 to 21 nucleotides in length. There are multiple mechanisms that can be exploited to inhibit the function of the RNA once the oligonucleotide binds to the target RNA (Crooke ST. (1999). *Biochim. Biophys. Acta*, 1489, 30–42). The best-characterized antisense mechanism results in cleavage of the targeted RNA by endogenous cellular nucleases, such as RNase H or the nuclease associated with the RNA interference mechanism. However, oligonucleotides that inhibit expression of the target gene by non-catalytic mechanisms, such as modulation of splicing or translation arrest, can also be potent and selective modulators of gene function.

Another RNase-dependent antisense mechanism that has recently received much attention is RNAi (Fire *et al.* (1998). *Nature*, 391, 806–811.; Zamore PD. (2002). *Science*, 296, 1265–1269.). RNA interference (RNAi) is a post-transcriptional process where a double stranded RNA inhibits gene expression in a sequence specific fashion. In some embodiments, the RNAi effect is achieved through the introduction of relatively longer double-stranded RNA (dsRNA), while in preferred embodiments, this RNAi effect is achieved by the introduction of shorter double-stranded RNAs, *e.g.* small interfering RNA (siRNA) and/or microRNA (miRNA). In yet another embodiment, RNAi can also be achieved by introducing of plasmid that generate dsRNA complementary to target gene. In each of the foregoing embodiments, the double-stranded RNA is designed to interfere with the gene expression of a particular the target sequence within cells. Generally, the mechanism involves

conversion of dsRNA into short RNAs that direct ribonucleases to homologous mRNA targets (summarized, Ruvkun, *Science* 2294:797 (2001)), which then degrades the corresponding endogenous mRNA, thereby resulting in the modulation of gene expression. Notably, dsRNA has been reported to have anti-proliferative properties, which makes it possible also to envisage therapeutic applications (Aubel *et al.*, *Proc. Natl. Acad. Sci., USA* 88:906 (1991)). For example, synthetic dsRNA has been shown to inhibit tumor growth in mice (Levy *et al. Proc. Nat. Acad. Sci. USA,* 62:357-361 (1969)), is active in the treatment of leukemic mice (Zeleznick *et al.*, *Proc. Soc. Exp. Biol. Med.* 130:126-128 (1969)), and inhibits chemically induced tumorigenesis in mouse skin (Gelboin *et al.*, *Science* 167:205-207 (1970)). Thus, in a preferred embodiment, the invention provides for the use of antisense oligonucleotides in ADCs for the treatment of breast cancer. In other embodiments, the invention provides compositions and methods for initiating antisense oligonucleotide treatment, wherein dsRNA interferes with target cell expression of B7-H3 at the mRNA level. dsRNA, as used above, refers to naturally-occurring RNA, partially purified RNA, recombinantly produced RNA, synthetic RNA, as well as altered RNA that differs from naturally-occurring RNA by the inclusion of non-standard nucleotides, non-nucleotide material, nucleotide analogs (*e.g.* locked nucleic acid (LNA)), deoxyribonucleotides, and any combination thereof. RNA of the invention need only be sufficiently similar to natural RNA that it has the ability to mediate the antisense oligonucleotide-based modulation described herein.

b. Aptamers

The anti-B7-H3 antibodies of the invention may be conjugated to at least one aptamer. An aptamer is a nucleic acid molecule that has been selected from random pools based on its ability to bind other molecules. Like antibodies, aptamers can bind target molecules with extraordinary affinity and specificity. In many embodiments, aptamers assume complex, sequence-dependent, three-dimensional shapes that allow them to interact with a target protein, resulting in a tightly bound complex analogous to an antibody-antigen interaction, thereby interfering with the function of said protein. The particular capacity of aptamers to bind tightly and specifically to their target protein underlines their potential as targeted molecular therapies.

c. CpG oligonucleotides

The anti-B7-H3 antibodies of the invention may be conjugated to at least one CpG oligonucleotide. Bacterial and viral DNA are known to be a strong activators of both the innate and specific immunity in humans. These immunologic characteristics have been associated with unmethylated CpG dinucleotide motifs found in bacterial DNA. Owing to the fact that these motifs are rare in humans, the human immune system has evolved the ability to recognize these motifs as an early indication of infection and subsequently initiate immune responses. Therefore, oligonucleotides containing this CpG motif can be exploited to initiate an antitumor immune response.

d. Ribozymes

The anti-B7-H3 antibody of the invention may be conjugated to at least one ribozyme. Ribozymes are catalytic RNA molecules ranging from about 40 to 155 nucleotides in length. The ability of ribozymes to recognize and cut specific RNA molecules makes them potential candidates for therapeutics. A representative example includes angiozyme.

15. Radionuclide Agents (Radioactive Isotopes)

The anti-B7-H3 antibodies of the invention may be conjugated to at least one radionuclide agent. Radionuclide agents comprise agents that are characterized by an unstable nucleus that is capable of undergoing radioactive decay. The basis for successful radionuclide treatment depends on sufficient concentration and prolonged retention of the radionuclide by the cancer cell. Other factors to consider include the radionuclide half-life, the energy of the emitted particles, and the maximum range that the emitted particle can travel. In preferred embodiments, the therapeutic agent is a radionuclide selected from the group consisting of ^{111}In, ^{177}Lu, ^{212}Bi, ^{213}Bi, ^{211}At, ^{62}Cu, ^{64}Cu, ^{67}Cu, ^{90}Y, ^{I25}I, ^{I31}I, ^{32}P, ^{33}P, ^{47}Sc, ^{111}Ag, ^{67}Ga, ^{142}Pr, ^{153}Sm, ^{161}Tb, ^{166}Dy, ^{166}Ho, ^{186}Re, ^{188}Re, ^{189}Re, ^{212}Pb, ^{223}Ra, ^{225}Ac, ^{59}Fe, ^{75}Se, ^{77}As, ^{89}Sr, ^{99}Mo, ^{105}Rh, ^{I09}Pd, ^{143}Pr, ^{149}Pm, ^{169}Er, ^{194}Ir, ^{198}Au, ^{199}Au, and ^{211}Pb. Also preferred are radionuclides that substantially decay with Auger-emitting particles. For example, Co-58, Ga-67, Br-80m, Tc-99m, Rh-103m, Pt-109, In-111 1, Sb-119, I-125, Ho-161, Os-189m and Ir-192. Decay energies of useful beta-particle-emitting nuclides are preferably Dy-152, At-211, Bi-212, Ra-223, Rn-219, Po-215, Bi-21 1, Ac-225, Fr-221, At-217, Bi-213 and Fm-255. Decay energies of useful alpha-particle-emitting radionuclides are preferably 2,000-10,000 keV, more preferably 3,000-8,000 keV, and most preferably 4,000-7,000 keV. Additional potential radioisotopes of use include ^{11}C, ^{13}N, ^{15}0, ^{75}Br, ^{198}Au, ^{224}Ac, ^{126}I, ^{133}I, ^{77}Br, ^{113m}In, ^{95}Ru, ^{97}Ru, ^{I03}Ru, ^{105}Ru, ^{107}Hg, ^{203}Hg, ^{121m}Te, ^{122m}Te, ^{125m}Te, ^{165}Tm, ^{I67}Tm, ^{168}Tm, ^{197}Pt, ^{109}Pd, ^{105}Rh, ^{142}Pr, ^{143}Pr, ^{161}Tb, $^{!66}$Ho, ^{199}Au, ^{57}Co, ^{58}Co, ^{51}Cr, ^{59}Fe, ^{75}Se, ^{201}Tl, ^{225}Ac, ^{76}Br, ^{I69}Yb, and the like.

16. Radiosensitizers

The anti-B7-H3 antibodies of the invention may be conjugated to at least one radiosensitizer. The term "radiosensitizer," as used herein, is defined as a molecule, preferably a low molecular weight molecule, administered to animals in therapeutically effective amounts to increase the sensitivity of the cells to be radiosensitized to electromagnetic radiation and/or to promote the treatment of diseases that are treatable with electromagnetic radiation. Radiosensitizers are agents that make cancer cells more sensitive to radiation therapy, while typically having much less of an effect on normal cells. Thus, the radiosensitizer can be used in combination with a radiolabeled antibody or ADC. The addition of the radiosensitizer can result in enhanced efficacy when compared to treatment with the radiolabeled antibody or antibody fragment alone. Radiosensitizers are

described in D. M. Goldberg (ed.), Cancer Therapy with Radiolabeled Antibodies, CRC Press (1995). Examples of radiosensitizers include gemcitabine, 5-fluorouracil, taxane, and cisplatin.

Radiosensitizers may be activated by the electromagnetic radiation of X-rays. Representative examples of X-ray activated radiosensitizers include, but are not limited to, the following: metronidazole, misonidazole, desmethylmisonidazole, pimonidazole, etanidazole, nimorazole, mitomycin C, RSU 1069, SR 4233, E09, RB 6145, nicotinamide, 5-bromodeoxyuridine (BUdR), 5-iododeoxyuridine (IUdR), bromodeoxycytidine, fluorodeoxyuridine (FUdR), hydroxyurea, cisplatin, and therapeutically effective analogs and derivatives of the same. Alternatively, radiosensitizers may be activated using photodynamic therapy (PDT). Representative examples of photodynamic radiosensitizers include, but are not limited to, hematoporphyrin derivatives, Photofrin(r), benzoporphyrin derivatives, NPe6, tin etioporphyrin (SnET2), pheoborbide a, bacteriochlorophyll a, naphthalocyanines, phthalocyanines, zinc phthalocyanine, and therapeutically effective analogs and derivatives of the same.

16. Topoisomerase Inhibitors

The anti-B7-H3 antibodies of the invention may be conjugated to at least one topoisomerase inhibitor. Topoisomerase inhibitors are chemotherapy agents designed to interfere with the action of topoisomerase enzymes (topoisomerase I and II), which are enzymes that control the changes in DNA structure by catalyzing then breaking and rejoining of the phosphodiester backbone of DNA strands during the normal cell cycle. Representative examples of DNA topoisomerase I inhibitors include, but are not limited to, camptothecins and its derivatives irinotecan (CPT-11, Camptosar, Pfizer, Inc.) and topotecan (Hycamtin, GlaxoSmithKline Pharmaceuticals). Representative examples of DNA topoisomerase II inhibitors include, but are not limited to, amsacrine, daunorubicin, doxotrubicin, epipodophyllotoxins, ellipticines, epirubicin, etoposide, razoxane, and teniposide.

17. Kinase Inhibitors

The anti-B7-H3 antibodies of the invention may be conjugated to at least one kinase inhibitor. By blocking the ability of protein kinases to function, tumor growth may be inhibited. Examples of kinase inhibitors that may be used in the ADCs of the invention include, but are not limited to, Axitinib, Bosutinib, Cediranib, Dasatinib, Erlotinib, Gefitinib, Imatinib, Lapatinib, Lestaurtinib, Nilotinib, Semaxanib, Sunitinib, Osimertinib, Cobimetinib, Trametinib, Dabrafenib, Dinaciclib, and Vandetanib.

18. Other Agents

Examples of other agents that may be used in the ADCs of the invention include, but are not limited to, abrin (*e.g.* abrin A chain), alpha toxin, Aleurites fordii proteins, amatoxin, crotin, curcin, dianthin proteins, diptheria toxin (*e.g.* diphtheria A chain and nonbinding active fragments of

diphtheria toxin), deoxyribonuclease (Dnase), gelonin, mitogellin, modeccin A chain, momordica charantia inhibitor, neomycin, onconase, phenomycin, Phytolaca americana proteins (PAPI, PAPII, and PAP-S), pokeweed antiviral protein, Pseudomonas endotoxin, Pseudomonas exotoxin (*e.g.* exotoxin A chain (from Pseudomonas aeruginosa)), restrictocin, ricin A chain, ribonuclease (Rnase), sapaonaria officinalis inhibitor, saporin, alpha-sarcin, Staphylcoccal enterotoxin-A, tetanus toxin, cisplatin, carboplatin, and oxaliplatin (Eloxatin, Sanofi Aventis), proteasome inhibitors (*e.g.* PS-341 [bortezomib or Velcade]), HDAC inhibitors (vorinostat (Zolinza, Merck & Company, Inc.)), belinostat, entinostat, mocetinostat, and panobinostat), COX-2 inhibitors, substituted ureas, heat shock protein inhibitors (*e.g.* Geldanamycin and its numerous analogs), adrenocortical suppressants, and the tricothecenes. (See, for example, WO 93/21232). Other agents also include asparaginase (Espar, Lundbeck Inc.), hydroxyurea, levamisole, mitotane (Lysodren, Bristol-Myers Squibb), and tretinoin (Renova, Valeant Pharmaceuticals Inc.).

III.C. Anti-B7-H3 ADCs: Other Exemplary Linkers

In addition to the linkers mentioned above, other exemplary linkers include, but are not limited to, 6-maleimidocaproyl, maleimidopropanoyl ("MP"), valine-citrulline ("val-cit" or "vc"), alanine-phenylalanine ("ala-phe"), p-aminobenzyloxycarbonyl (a "PAB"), N-Succinimidyl 4-(2-pyridylthio) pentanoate ("SPP"), and 4-(N-maleimidomethyl)cyclohexane-1 carboxylate ("MCC").

In one aspect, an anti-B7-H3 antibody is conjugated to a drug, (such as auristatin, *e.g.*, MMAE), via a linker comprising maleimidocaproyl ("mc"), valine citrulline (val-cit or "vc"), and PABA (referred to as a "mc-vc-PABA linker"). Maleimidocaproyl acts as a linker to the anti-B7-H3 antibody and is not cleavable. Val-cit is a dipeptide that is an amino acid unit of the linker and allows for cleavage of the linker by a protease, specifically the protease cathepsin B. Thus, the val-cit component of the linker provides a means for releasing the auristatin from the ADC upon exposure to the intracellular environment. Within the linker, p-aminobenzylalcohol (PABA) acts as a spacer and is self immolative, allowing for the release of the MMAE. The structure of the mc-vc-PABA-MMAE linker is provided in Figure 3.

As described above, suitable linkers include, for example, cleavable and non-cleavable linkers. A linker may be a "cleavable linker," facilitating release of a drug. Nonlimiting exemplary cleavable linkers include acid-labile linkers (e.g., comprising hydrazone), protease-sensitive (e.g., peptidase-sensitive) linkers, photolabile linkers, or disulfide-containing linkers (Chari et al., Cancer Research 52:127-131 (1992); U.S. Pat. No. 5,208,020). A cleavable linker is typically susceptible to cleavage under intracellular conditions. Suitable cleavable linkers include, for example, a peptide linker cleavable by an intracellular protease, such as lysosomal protease or an endosomal protease. In exemplary embodiments, the linker can be a dipeptide linker, such as a valine-citrulline (val-cit) or a phenylalanine-lysine (phe-lys) linker.

Linkers are preferably stable extracellularly in a sufficient manner to be therapeutically effective. Before transport or delivery into a cell, the ADC is preferably stable and remains intact, *i.e.* the antibody remains conjugated to the drug moiety. Linkers that are stable outside the target cell may be cleaved at some efficacious rate once inside the cell. Thus, an effective linker will: (i) maintain the specific binding properties of the antibody; (ii) allow delivery, *e.g.*, intracellular delivery, of the drug moiety; and (iii) maintain the therapeutic effect, *e.g.,* cytotoxic effect, of a drug moiety.

In one embodiment, the linker is cleavable under intracellular conditions, such that cleavage of the linker sufficiently releases the drug from the antibody in the intracellular environment to be therapeutically effective. In some embodiments, the cleavable linker is pH-sensitive, *i.e.*, sensitive to hydrolysis at certain pH values. Typically, the pH-sensitive linker is hydrolyzable under acidic conditions. For example, an acid-labile linker that is hydrolyzable in the lysosome (*e.g.*, a hydrazone, semicarbazone, thiosemicarbazone, cis-aconitic amide, orthoester, acetal, ketal, or the like) can be used. (See, *e.g.*, U.S. Pat. Nos. 5,122,368; 5,824,805; 5,622,929; Dubowchik and Walker, 1999, *Pharm. Therapeutics* 83:67-123; Neville *et al.*, 1989, *Biol. Chem.* 264:14653-14661.) Such linkers are relatively stable under neutral pH conditions, such as those in the blood, but are unstable at below pH 5.5 or 5.0, the approximate pH of the lysosome. In certain embodiments, the hydrolyzable linker is a thioether linker (such as, *e.g.*, a thioether attached to the therapeutic agent via an acylhydrazone bond (see, *e.g.*, U.S. Pat. No. 5,622,929).

In other embodiments, the linker is cleavable under reducing conditions (*e.g.*, a disulfide linker). A variety of disulfide linkers are known in the art, including, for example, those that can be formed using SATA (N-succinimidyl-5-acetylthioacetate), SPDP (N-succinimidyl-3-(2-pyridyldithio)propionate), SPDB (N-succinimidyl-3-(2-pyridyldithio)butyrate) and SMPT (N-succinimidyloxycarbonyl-alpha-methyl-alpha-(2-pyridyl-dithio)toluene), SPDB and SMPT. (See, *e.g.*, Thorpe *et al.*, 1987, Cancer Res. 47:5924-5931; Wawrzynczak *et al.*, In *Immunoconjugates: Antibody Conjugates in Radioimagery and Therapy of Cancer* (C. W. Vogel ed., Oxford U. Press, 1987. See also U.S. Pat. No. 4,880,935.).

In some embodiments, the linker is cleavable by a cleaving agent, *e.g.*, an enzyme, that is present in the intracellular environment (*e.g.*, within a lysosome or endosome or caveolea). The linker can be, *e.g.*, a peptidyl linker that is cleaved by an intracellular peptidase or protease enzyme, including, but not limited to, a lysosomal or endosomal protease. In some embodiments, the peptidyl linker is at least two amino acids long or at least three amino acids long. Cleaving agents can include cathepsins B and D and plasmin, all of which are known to hydrolyze dipeptide drug derivatives resulting in the release of active drug inside target cells (see, *e.g.*, Dubowchik and Walker, 1999, Pharm. Therapeutics 83:67-123). Most typical are peptidyl linkers that are cleavable by enzymes that are present in B7-H3-expressing cells. Examples of such linkers are described, *e.g.*, in U.S. Pat. No. 6,214,345, incorporated herein by reference in its entirety and for all purposes. In a specific embodiment, the peptidyl linker cleavable by an intracellular protease is a Val-Cit linker or a Phe-Lys

linker (see, *e.g.*, U.S. Pat. No. 6,214,345, which describes the synthesis of doxorubicin with the val-cit linker). One advantage of using intracellular proteolytic release of the therapeutic agent is that the agent is typically attenuated when conjugated and the serum stabilities of the conjugates are typically high.

In other embodiments, the linker is a malonate linker (Johnson *et al.*, 1995, Anticancer Res. 15:1387-93), a maleimidobenzoyl linker (Lau *et al.*, 1995, *Bioorg-Med-Chem.* 3(10):1299-1304), or a 3'-N-amide analog (Lau *et al.*, 1995, *Bioorg-Med-Chem.* 3(10): 1305-12).

In yet other embodiments, the linker unit is not cleavable and the drug is released, for example, by antibody degradation. See U.S. Publication No. 20050238649 incorporated by reference herein in its entirety. An ADC comprising a non-cleavable linker may be designed such that the ADC remains substantially outside the cell and interacts with certain receptors on a target cell surface such that the binding of the ADC initiates (or prevents) a particular cellular signaling pathway.

In some embodiments, the linker is substantially hydrophilic linker (*e.g.*, PEG4Mal and sulfo-SPDB). A hydrophilic linker may be used to reduce the extent to which the drug may be pumped out of resistant cancer cells through MDR (multiple drug resistance) or functionally similar transporters.

In other embodiments, upon cleavage, the linker functions to directly or indirectly inhibit cell growth and/or cell proliferation. For example, in some embodiments, the linker, upon cleavage, can function as an intercalating agent, thereby inhibiting macromolecular biosynthesis (*e.g.* DNA replication, RNA transcription, and/or protein synthesis).

In other embodiments, the linker is designed to facilitate bystander killing (the killing of neighboring cells) through diffusion of the linker-drug and/or the drug alone to neighboring cells. In other, embodiments, the linker promotes cellular internalization.

The presence of a sterically hindered disulfide can increase the stability of a particular disulfide bond, enhancing the potency of the ADC. Thus, in one embodiment, the linker includes a sterically hindered disulfide linkage. A sterically hindered disulfide refers to a disulfide bond present within a particular molecular environment, wherein the environment is characterized by a particular spatial arrangement or orientation of atoms, typically within the same molecule or compound, which prevents or at least partially inhibits the reduction of the disulfide bond. Thus, the presence of bulky (or sterically hindering) chemical moieties and/or bulky amino acid side chains proximal to the disulfide bond prevents or at least partially inhibits the disulfide bond from potential interactions that would result in the reduction of the disulfide bond.

Notably, the aforementioned linker types are not mutually exclusive. For example, in one embodiment, the linker used in the anti-B7-H3 ADCs described herein is a non-cleavable linker that promotes cellular internalization.

In some embodiments, a linker component comprises a "stretcher unit" that links an antibody to another linker component or to a drug moiety. An illustrative stretcher unit described in U.S. 8,309,093, incorporated by reference herein. In certain embodiments, the stretcher unit is linked to

the anti-B7-H3 antibody via a disulfide bond between a sulfur atom of the anti-B7-H3 antibody unit and a sulfur atom of the stretcher unit. A representative stretcher unit of this embodiment is depicted in U.S. 8,309,093, incorporated by reference herein. In yet other embodiments, the stretcher contains a reactive site that can form a bond with a primary or secondary amino group of an antibody. Examples of these reactive sites include but are not limited to, activated esters such as succinimide esters, 4 nitrophenyl esters, pentafluorophenyl esters, tetrafluorophenyl esters, anhydrides, acid chlorides, sulfonyl chlorides, isocyanates and isothiocyanates. Representative stretcher units of this embodiment are depicted in U.S. 8,309,093, incorporated by reference herein.

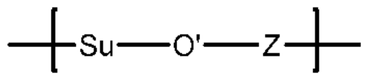
In some embodiments, the stretcher contains a reactive site that is reactive to a modified carbohydrate's (—CHO) group that can be present on an antibody. For example, a carbohydrate can be mildly oxidized using a reagent such as sodium periodate and the resulting (—CHO) unit of the oxidized carbohydrate can be condensed with a Stretcher that contains a functionality such as a hydrazide, an oxime, a primary or secondary amine, a hydrazine, a thiosemicarbazone, a hydrazine carboxylate, and an arylhydrazide such as those described by Kaneko *et al.*, 1991, *Bioconjugate Chem.* 2:133-41. Representative Stretcher units of this embodiment are depicted in U.S. 8,309,093, incorporated by reference herein.

In some embodiments, a linker component comprises an "amino acid unit". In some such embodiments, the amino acid unit allows for cleavage of the linker by a protease, thereby facilitating release of the drug from the immunoconjugate upon exposure to intracellular proteases, such as lysosomal enzymes (Doronina et al. (2003) Nat. Biotechnol. 21:778-784). Exemplary amino acid units include, but are not limited to, dipeptides, tripeptides, tetrapeptides, and pentapeptides. Exemplary dipeptides include, but are not limited to, valine-citrulline (vc or val-cit), alanine-phenylalanine (af or ala-phe); phenylalanine-lysine (fk or phe-lys); phenylalanine-homolysine (phe-homolys); and N-methyl-valine-citrulline (Me-val-cit). Exemplary tripeptides include, but are not limited to, glycine-valine-citrulline (gly-val-cit) and glycine-glycine-glycine (gly-gly-gly). An amino acid unit may comprise amino acid residues that occur naturally and/or minor amino acids and/or non-naturally occurring amino acid analogs, such as citrulline Amino acid units can be designed and optimized for enzymatic cleavage by a particular enzyme, for example, a tumor-associated protease, cathepsin B, C and D, or a plasmin protease.

In one embodiment, the amino acid unit is valine-citrulline (vc or val-cit). In another aspect, the amino acid unit is phenylalanine-lysine (*i.e.*, fk). In yet another aspect of the amino acid unit, the amino acid unit is N-methylvaline-citrulline. In yet another aspect, the amino acid unit is 5-aminovaleric acid, homo phenylalanine lysine, tetraisoquinolinecarboxylate lysine, cyclohexylalanine lysine, isonepecotic acid lysine, beta-alanine lysine, glycine serine valine glutamine and isonepecotic acid.

Alternatively, in some embodiments, the amino acid unit is replaced by a glucuronide unit that links a stretcher unit to a spacer unit if the stretcher and spacer units are present, links a stretcher

unit to the drug moiety if the spacer unit is absent, and links the linker unit to the drug if the stretcher and spacer units are absent. The glucuronide unit includes a site that can be cleaved by a β-glucuronidase enzyme (See also US 2012/0107332, incorporated by reference herein). In some embodiments, the glucuronide unit comprises a sugar moiety (Su) linked via a glycoside bond (—O'—) to a self-immolative group (Z) of the formula as depicted below (See also US 2012/0107332, incorporated by reference herein).



The glycosidic bond (—O'—) is typically a β-glucuronidase-cleavage site, such as a bond cleavable by human, lysosomal β-glucuronidase. In the context of a glucuronide unit, the term "self-immolative group" refers to a di- or tri-functional chemical moiety that is capable of covalently linking together two or three spaced chemical moieties (*i.e.*, the sugar moiety (via a glycosidic bond), a drug moiety (directly or indirectly via a spacer unit), and, in some embodiments, a linker (directly or indirectly via a stretcher unit) into a stable molecule. The self-immolative group will spontaneously separate from the first chemical moiety (*e.g.*, the spacer or drug unit) if its bond to the sugar moiety is cleaved.

In some embodiments, the sugar moiety (Su) is cyclic hexose, such as a pyranose, or a cyclic pentose, such as a furanose. In some embodiments, the pyranose is a glucuronide or hexose. The sugar moiety is usually in the β-D conformation. In a specific embodiment, the pyranose is a β-D-glucuronide moiety (*i.e.*, β-D-glucuronic acid linked to the self-immolative group —Z— via a glycosidic bond that is cleavable by β-glucuronidase). In some embodiments, the sugar moiety is unsubstituted (*e.g.*, a naturally occurring cyclic hexose or cyclic pentose). In other embodiments, the sugar moiety can be a substituted β-D-glucuronide (*i.e.*, glucuronic acid substituted with one or more group, such hydrogen, hydroxyl, halogen, sulfur, nitrogen or lower alkyl. In some embodiments, the glucuronide unit has one of the formulas as described in US 2012/0107332, incorporated by reference herein.

In some embodiments, the linker comprises a spacer unit (—Y—), which, when present, links an amino acid unit (or Glucuronide unit, see also US 2012/0107332, incorporated by reference herein) to the drug moiety when an amino acid unit is present. Alternately, the spacer unit links the stretcher unit to the drug moiety when the amino acid unit is absent. The spacer unit may also links the drug unit to the antibody unit when both the amino acid unit and stretcher unit are absent.

Spacer units are of two general types: non self-immolative or self-immolative. A non self-immolative spacer unit is one in which part or all of the spacer unit remains bound to the drug moiety after cleavage, particularly enzymatic, of an amino acid unit (or glucuronide unit) from the antibody-drug conjugate. Examples of a non self-immolative spacer unit include, but are not limited to a (glycine-glycine) spacer unit and a glycine spacer unit (see U.S. 8,309,093, incorporated by reference

herein)).Other examples of self-immolative spacers include, but are not limited to, aromatic compounds that are electronically similar to the PAB group such as 2-aminoimidazol-5-methanol derivatives (Hay *et al.*, 1999, Bioorg. Med. Chem. Lett. 9:2237) and ortho or para-aminobenzylacetals. Spacers can be used that undergo cyclization upon amide bond hydrolysis, such as substituted and unsubstituted 4-aminobutyric acid amides (Rodrigues *et al.*, 1995, Chemistry Biology 2:223), appropriately substituted bicyclo[2.2.1] and bicyclo[2.2.2] ring systems (Storm *et al.*, 1972, J. Amer. Chem. Soc. 94:5815) and 2-aminophenylpropionic acid amides (Amsberry *et al.*, 1990, J. Org. Chem. 55:5867). Elimination of amine-containing drugs that are substituted at the α-position of glycine (Kingsbury *et al.*, 1984, J. Med. Chem. 27:1447) are also examples of self-immolative spacers. .

Other examples of self-immolative spacers include, but are not limited to, aromatic compounds that are electronically similar to the PAB group such as 2-aminoimidazol-5-methanol derivatives (see, *e.g.*, Hay *et al.*, 1999, *Bioorg. Med. Chem. Lett.* 9:2237) and ortho or para-aminobenzylacetals. Spacers can be used that undergo cyclization upon amide bond hydrolysis, such as substituted and unsubstituted 4-aminobutyric acid amides (see, *e.g.*, Rodrigues *et al.*, 1995, *Chemistry Biology* 2:223), appropriately substituted bicyclo[2.2.1] and bicyclo[2.2.2] ring systems (see, *e.g.*, Storm *et al.*, 1972, *J. Amer. Chem. Soc.* 94:5815) and 2-aminophenylpropionic acid amides (see, *e.g.*, Amsberry *et al.*, 1990, J. Org. Chem. 55:5867). Elimination of amine-containing drugs that are substituted at the a-position of glycine (see, *e.g.*, Kingsbury *et al.*, 1984, *J. Med. Chem.* 27:1447) are also examples of self-immolative spacers.

Other suitable spacer units are disclosed in Published U.S. Patent Application No. 2005-0238649, the disclosure of which is incorporated by reference herein.

Another approach for the generation of ADCs involves the use of heterobifunctional cross-linkers which link the anti-B7-H3 antibody to the drug moiety. Examples of cross-linkers that may be used include N-succinimidyl 4-(5-nitro-2-pyridyldithio)-pentanoate or the highly water-soluble analog N-sulfosuccinimidyl 4-(5-nitro-2-pyridyldithio)-pentanoate, N-succinimidyl-4-(2-pyridyldithio) butyrate (SPDB), N-succinimidyl-4-(5-nitro-2-pyridyldithio) butyrate (SNPB), and N-sulfosuccinimidyl-4-(5-nitro-2-pyridyldithio) butyrate (SSNPB), N-succinimidyl-4-methyl-4-(5-nitro-2-pyridyldithio)pentanoate (SMNP), N-succinimidyl-4-(5-N,N-dimethylcarboxamido-2-pyridyldithio) butyrate (SCPB) or N-sulfosuccinimidyl4-(5-N,N-dimethylcarboxamido-2-pyridyldithio) butyrate (SSCPB)). The antibodies of the invention may be modified with the cross-linkers N-succinimidyl 4-(5-nitro-2-pyridyldithio)-pentanoate, N-sulfosuccinimidyl 4-(5-nitro-2-pyridyldithio)-pentanoate, SPDB, SNPB, SSNPB, SMNP, SCPB, or SSCPB can then react with a small excess of a particular drug that contains a thiol moiety to give excellent yields of an ADC. Preferably, the cross-linkers are compounds of the formula as depicted in U.S. Patent No. 6,913,748, incorporated by reference herein.

In one embodiment, charged linkers (also referred to as pro-charged linkers) are used to conjugate anti-B7-H3 antibodies to drugs to form ADCs. Charged linkers include linkers that become

charged after cell processing. The presence of a charged group(s) in the linker of a particular ADC or on the drug after cellular processing provides several advantages, such as (i) greater water solubility of the ADC, (ii) ability to operate at a higher concentration in aqueous solutions, (iii) ability to link a greater number of drug molecules per antibody, potentially resulting in higher potency, (iv) potential for the charged conjugate species to be retained inside the target cell, resulting in higher potency, and (v) improved sensitivity of multidrug resistant cells, which would be unable to export the charged drug species from the cell. Examples of some suitable charged or pro-charged cross-linkers and their synthesis are shown in Figures 1 to 10 of U.S. Patent No. 8,236, 319, and are incorporated by reference herein. Preferably, the charged or pro-charged cross-linkers are those containing sulfonate, phosphate, carboxyl or quaternary amine substituents that significantly increase the solubility of the ADCs, especially for ADCs with 2 to 20 conjugated drugs. Conjugates prepared from linkers containing a pro-charged moiety would produce one or more charged moieties after the conjugate is metabolized in a cell.

Additional examples of linkers that can be used with the compositions and methods include valine-citrulline; maleimidocaproyl; amino benzoic acids; p-aminobenzylcarbamoyl (PAB); lysosomal enzyme-cleavable linkers; maleimidocaproyl-polyethylene glycol (MC(PEG)6-OH); N-methyl-valine citrulline; N-succinimidyl 4-(N-maleimidomethyl)cyclohexane-1-carboxylate (SMCC); N-Succinimidyl 4-(2-pyridyldithio)butanoate (SPDB); and N-Succinimidyl 4-(2-pyridylthio)pentanoate (SPP) (See also US 2011/0076232). Another linker for use in the invention includes an avidin-biotin linkage to provide an avidin-biotin-containing ADC (See also U.S. Patent No. 4,676,980, PCT publication Nos. WO1992/022332A2, WO1994/016729A1, WO1995/015770A1, WO1997/031655A2, WO1998/035704A1, WO1999/019500A1, WO2001/09785A2, WO2001/090198A1, WO2003/093793A2, WO2004/050016A2, WO2005/081898A2, WO2006/083562A2, WO2006/089668A1, WO2007/150020A1, WO2008/135237A1, WO2010/111198A1, WO2011/057216A1, WO2011/058321A1, WO2012/027494A1, and EP77671B1), wherein some such linkers are resistant to biotinidase cleavage. Additional linkers that may be used in the invention include a cohesin/dockerin pair to provide a cohesion-dockerin-containing ADC (See PCT publication Nos. WO2008/097866A2, WO2008/097870A2, WO2008/103947A2, and WO2008/103953A2).

Additional linkers for use in the invention may contain non-peptide polymers (examples include, but are not limited to, polyethylene glycol, polypropylene glycol, polyoxyethylated polyols, polyvinyl alcohol, polysaccharides, dextran, polyvinyl ethyl ether, PLA (poly(lactic acid)), PLGA (poly(lactic acid-glycolic acid)), and combinations thereof, wherein a preferred polymer is polyethylene glycol) (See also PCT publication No. WO2011/000370). Additional linkers are also described in WO 2004-010957, U.S. Publication No. 20060074008, U.S. Publication No. 20050238649, and U.S. Publication No. 20060024317, each of which is incorporated by reference herein in its entirety).

For an ADC comprising a maytansinoid, many positions on maytansinoids can serve as the position to chemically link the linking moiety. In one embodiment, maytansinoids comprise a linking moiety that contains a reactive chemical group are C-3 esters of maytansinol and its analogs where the linking moiety contains a disulfide bond and the chemical reactive group comprises a N-succinimidyl or N-sulfosuccinimidyl ester. For example, the C-3 position having a hydroxyl group, the C-14 position modified with hydroxymethyl, the C-15 position modified with hydroxy and the C-20 position having a hydroxy group are all useful. The linking moiety most preferably is linked to the C-3 position of maytansinol.

The conjugation of the drug to the antibody via a linker can be accomplished by any technique known in the art. A number of different reactions are available for covalent attachment of drugs and linkers to antibodies. This may be accomplished by reaction of the amino acid residues of the antibody, including the amine groups of lysine, the free carboxylic acid groups of glutamic and aspartic acid, the sulfhydryl groups of cysteine and the various moieties of the aromatic amino acids. One of the most commonly used non-specific methods of covalent attachment is the carbodiimide reaction to link a carboxy (or amino) group of a compound to amino (or carboxy) groups of the antibody. Additionally, bifunctional agents such as dialdehydes or imidoesters have been used to link the amino group of a compound to amino groups of an antibody. Also available for attachment of drugs to antibodies is the Schiff base reaction. This method involves the periodate oxidation of a drug that contains glycol or hydroxy groups, thus forming an aldehyde which is then reacted with the binding agent. Attachment occurs via formation of a Schiff base with amino groups of the antibody. Isothiocyanates can also be used as coupling agents for covalently attaching drugs to antibodies. Other techniques are known to the skilled artisan and within the scope of the invention.

In certain embodiments, an intermediate, which is the precursor of the linker, is reacted with the drug under appropriate conditions. In certain embodiments, reactive groups are used on the drug or the intermediate. The product of the reaction between the drug and the intermediate, or the derivatized drug, is subsequently reacted with the anti-B7-H3 antibody under appropriate conditions. The synthesis and structure of exemplary linkers, stretcher units, amino acid units, self-immolative spacer units are described in U.S. Patent Application Publication Nos. 20030083263, 20050238649 and 20050009751, each if which is incorporated herein by reference.

Stability of the ADC may be measured by standard analytical techniques such as mass spectroscopy, HPLC, and the separation/analysis technique LC/MS.

IV. Purification of Anti-B7-H3 ADCs

Purification of the ADCs may be achieved in such a way that ADCs having certain DARs are collected. For example, HIC resin may be used to separate high drug loaded ADCs from ADCs having optimal drug to antibody ratios (DARs), *e.g.* a DAR of 4 or less. In one embodiment, a hydrophobic resin is added to an ADC mixture such that undesired ADCs, *i.e.,* higher drug loaded

ADCs, bind the resin and can be selectively removed from the mixture. In certain embodiments, separation of the ADCs may be achieved by contacting an ADC mixture (*e.g.,* a mixture comprising a drug loaded species of ADC of 4 or less and a drug loaded species of ADC of 6 or more) with a hydrophobic resin, wherein the amount of resin is sufficient to allow binding of the drug loaded species which is being removed from the ADC mixture. The resin and ADC mixture are mixed together, such that the ADC species being removed (*e.g.,* a drug loaded species of 6 or more) binds to the resin and can be separated from the other ADC species in the ADC mixture. The amount of resin used in the method is based on a weight ratio between the species to be removed and the resin, where the amount of resin used does not allow for significant binding of the drug loaded species that is desired. Thus, methods may be used to reduce the average DAR to less than 4. Further, the purification methods described herein may be used to isolate ADCs having any desired range of drug loaded species, *e.g.,* a drug loaded species of 4 or less, a drug loaded species of 3 or less, a drug loaded species of 2 or less, a drug loaded species of 1 or less.

Certain species of molecule(s) binds to a surface based on hydrophobic interactions between the species and a hydrophobic resin. In one embodiment, method of the invention refers to a purification process that relies upon the intermixing of a hydrophobic resin and a mixture of ADCs, wherein the amount of resin added to the mixture determines which species (*e.g.*, ADCs with a DAR of 6 or more) will bind. Following production and purification of an antibody from an expression system (e.g., a mammalian expression system), the antibody is reduced and coupled to a drug through a conjugation reaction. The resulting ADC mixture often contains ADCs having a range of DARs, *e.g.,* 1 to 8. In one embodiment, the ADC mixture comprises a drug loaded species of 4 or less and a drug loaded species of 6 or more. According to the methods of the invention, the ADC mixture may be purified using a process, such as, but not limited to, a batch process, such that ADCs having a drug loaded species of 4 or less are selected and separated from ADCs having a higher drug load (e.g., ADCs having a drug loaded species of 6 or more). Notably, the purification methods described herein may be used to isolate ADCs having any desired range of DAR, *e.g.,* a DAR of 4 or less, a DAR of 3 or less, or a DAR of 2 or less.

Thus, in one embodiment, an ADC mixture comprising a drug loaded species of 4 or less and a drug loaded species of 6 or more may be contacted with a hydrophobic resin to form a resin mixture, wherein the amount of hydrophobic resin contacted with the ADC mixture is sufficient to allow binding of the drug loaded species of 6 or more to the resin but does not allow significant binding of the drug load species of 4 or less; and removing the hydrophobic resin from the ADC mixture, such that the composition comprising ADCs is obtained, wherein the composition comprises less than 15% of the drug loaded species of 6 or more, and wherein the ADC comprises an antibody conjugated to a Bcl-xL inhibitor. In a separate embodiment, the method of the invention comprises contacting an ADC mixture comprising a drug loaded species of 4 or less and a drug loaded species of 6 or more with a hydrophobic resin to form a resin mixture, wherein the amount of hydrophobic resin contacted

with the ADC mixture is sufficient to allow binding of the drug loaded species of 6 or more to the resin but does not allow significant binding of the drug load species of 4 or less; and removing the hydrophobic resin from the ADC mixture, such that the composition comprising ADCs is obtained, wherein the composition comprises less than 15% of the drug loaded species of 6 or more, and wherein the ADC comprises an antibody conjugated to a Bcl-xL inhibitor, wherein the hydrophobic resin weight is 3 to 12 times the weight of the drug loaded species of 6 or more in the ADC mixture.

The ADC separation method described herein method may be performed using a batch purification method. The batch purification process generally includes adding the ADC mixture to the hydrophobic resin in a vessel, mixing, and subsequently separating the resin from the supernatant. For example, in the context of batch purification, a hydrophobic resin may be prepared in or equilibrated to the desired equilibration buffer. A slurry of the hydrophobic resin may thus be obtained. The ADC mixture may then be contacted with the slurry to adsorb the specific species of ADC(s) to be separated by the hydrophobic resin. The solution comprising the desired ADCs that do not bind to the hydrophobic resin material may then be separated from the slurry, e.g., by filtration or by allowing the slurry to settle and removing the supernatant. The resulting slurry can be subjected to one or more washing steps. In order to elute bound ADCs, the salt concentration can be decreased. In one embodiment, the process used in the invention includes no more than 50 g of hydrophobic resin.

Thus, a batch method may be used to contact an ADC mixture comprising a drug loaded species of 4 or less and a drug loaded species of 6 or more with a hydrophobic resin to form a resin mixture, wherein the amount of hydrophobic resin contacted with the ADC mixture is sufficient to allow binding of the drug loaded species of 6 or more to the resin but does not allow significant binding of the drug load species of 4 or less; and removing the hydrophobic resin from the ADC mixture, such that the composition comprising ADCs is obtained, wherein the composition comprises less than 15% of the drug loaded species of 6 or more, and wherein the ADC comprises an antibody conjugated to a Bcl-xL inhibitor. In a separate embodiment, a batch method is used to contact an ADC mixture comprising a drug loaded species of 4 or less and a drug loaded species of 6 or more with a hydrophobic resin to form a resin mixture, wherein the amount of hydrophobic resin contacted with the ADC mixture is sufficient to allow binding of the drug loaded species of 6 or more to the resin but does not allow significant binding of the drug load species of 4 or less; and removing the hydrophobic resin from the ADC mixture, such that the composition comprising ADCs is obtained, wherein the composition comprises less than 15% of the drug loaded species of 6 or more, and wherein the ADC comprises an antibody conjugated to a Bcl-xL inhibitor, wherein the hydrophobic resin weight is 3 to 12 times the weight of the drug loaded species of 6 or more in the ADC mixture.

Alternatively, in a separate embodiment, purification may be performed using a circulation process, whereby the resin is packed in a container and the ADC mixture is passed over the hydrophobic resin bed until the specific species of ADC(s) to be separated have been removed. The

supernatant (containing the desired ADC species) is then pumped from the container and the resin bed may be subjected to washing steps.

A circulation process may be used to contact an ADC mixture comprising a drug loaded species of 4 or less and a drug loaded species of 6 or more with a hydrophobic resin to form a resin mixture, wherein the amount of hydrophobic resin contacted with the ADC mixture is sufficient to allow binding of the drug loaded species of 6 or more to the resin but does not allow significant binding of the drug load species of 4 or less; and removing the hydrophobic resin from the ADC mixture, such that the composition comprising ADCs is obtained, wherein the composition comprises less than 15% of the drug loaded species of 6 or more, and wherein the ADC comprises an antibody conjugated to a Bcl-xL inhibitor. In a separate embodiment, a circulation process is used to contact an ADC mixture comprising a drug loaded species of 4 or less and a drug loaded species of 6 or more with a hydrophobic resin to form a resin mixture, wherein the amount of hydrophobic resin contacted with the ADC mixture is sufficient to allow binding of the drug loaded species of 6 or more to the resin but does not allow significant binding of the drug load species of 4 or less; and removing the hydrophobic resin from the ADC mixture, such that the composition comprising ADCs is obtained, wherein the composition comprises less than 15% of the drug loaded species of 6 or more, and wherein the ADC comprises an antibody conjugated to a Bcl-xL inhibitor, wherein the hydrophobic resin weight is 3 to 12 times the weight of the drug loaded species of 6 or more in the ADC mixture.

Alternatively, a flow through process may be used to purify an ADC mixture to arrive at a composition comprising a majority of ADCs having a certain desired DAR. In a flow through process, resin is packed in a container, *e.g.,* a column, and the ADC mixture is passed over the packed resin such that the desired ADC species does not substantially bind to the resin and flows through the resin, and the undesired ADC species is bound to the resin. A flow through process may be performed in a single pass mode (where the ADC species of interest are obtained as a result of a single pass through the resin of the container) or in a multi-pass mode (where the ADC species of interest are obtained as a result of multiple passes through the resin of the container). The flow through process is performed such that the weight of resin selected binds to the undesired ADC population, and the desired ADCs (*e.g.*, DAR 2-4) flow over the resin and are collected in the flow through after one or multiple passes.

A flow through process may be used to contact an ADC mixture comprising a drug loaded species of 4 or less and a drug loaded species of 6 or more with a hydrophobic resin, wherein the amount of hydrophobic resin contacted with the ADC mixture is sufficient to allow binding of the drug loaded species of 6 or more to the resin but does not allow significant binding of the drug load species of 4 or less, where the drug load species of 4 or less passes over the resin and is subsequently collected after one or multiple passes, such that the composition comprising the desired ADCs (e.g. DAR 2-4) is obtained, wherein the composition comprises less than 15% of the drug loaded species of 6 or more, and wherein the ADC comprises an antibody conjugated to a Bcl-xL inhibitor. In a

separate embodiment, a flow through process is used to contact an ADC mixture comprising a drug loaded species of 4 or less and a drug loaded species of 6 or more with a hydrophobic resin by passing the ADC mixture over the resin, wherein the amount of hydrophobic resin contacted with the ADC mixture is sufficient to allow binding of the drug loaded species of 6 or more to the resin but does not allow significant binding of the drug load species of 4 or less, where the drug load species of 4 or less passes over the resin and is subsequently collected, such that the composition comprising ADCs is obtained, wherein the composition comprises less than 15% of the drug loaded species of 6 or more, and wherein the ADC comprises an antibody conjugated to an a drug, *e.g.*, a Bcl-xL inhibitor, wherein the amount of hydrophobic resin weight is 3 to 12 times the weight of the drug loaded species of 6 or more in the ADC mixture.

Following a flow through process, the resin may be washed with a one or more washes following in order to further recover ADCs having the desired DAR range (found in the wash filtrate). For example, a plurality of washes having decreasing conductivity may be used to further recover ADCs having the DAR of interest. The elution material obtained from the washing of the resin may be subsequently combined with the filtrate resulting from the flow through process for improved recovery of ADCs having the DAR of interest.

The aforementioned batch, circulation, and flow through process purification methods are based on the use of a hydrophobic resin to separate high vs. low drug loaded species of ADC. Hydrophobic resin comprises hydrophobic groups which interact with the hydrophobic properties of the ADCs. Hydrophobic groups on the ADC interact with hydrophobic groups within the hydrophobic resin. The more hydrophobic a protein is the stronger it will interact with the hydrophobic resin.

Hydrophobic resin normally comprises a base matrix (e.g., cross-linked agarose or synthetic copolymer material) to which hydrophobic ligands (e.g., alkyl or aryl groups) are coupled. Many hydrophobic resins are available commercially. Examples include, but are not limited to, Phenyl Sepharose™ 6 Fast Flow with low or high substitution (Pharmacia LKB Biotechnology, AB, Sweden); Phenyl Sepharose™ High Performance (Pharmacia LKB Biotechnology, AB, Sweden); Octyl Sepharose™ High Performance (Pharmacia LKB Biotechnology, AB, Sweden); Fractogel™ EMD Propyl or Fractogel™ EMD Phenyl columns (E. Merck, Germany); Macro-Prep™ Methyl or Macro-Prep™. t-Butyl Supports (Bio-Rad, California); WP HI-Propyl (C_3)™ (J. T. Baker, New Jersey); and Toyopearl™ ether, hexyl, phenyl or butyl (TosoHaas, PA). In one embodiment, the hydrophobic resin is a butyl hydrophobic resin. In another embodiment, the hydrophobic resin is a phenyl hydrophobic resin. In another embodiment, the hydrophobic resin is a hexyl hydrophobic resin, an octyl hydrophobic resin, or a decyl hydrophobic resin. In one embodiment, the hydrophobic resin is a methacrylic polymer having n-butyl ligands (*e.g.* TOYOPEARL® Butyl-600M).

Further methods for purifying ADC mixtures to obtain a composition having a desired DAR are described in U.S. Application No. 14/210,602 (U.S. Patent Appln. Publication No. US 2014/0286968), incorporated by reference in its entirety.

In certain embodiments of the invention, ADCs described herein having a DAR2 are purified from ADCs having higher or lower DARs. Such purified DAR2 ADCs are referred to herein as "E2". Purification methods for achieving a composition having E2 anti-B7-H3 ADCs. In one embodiment, of the invention provides a composition comprising an ADC mixture, wherein at least 75% of the ADCs are anti-B7H3 ADCs (like those described herein) having a DAR2. In another embodiment, the invention provides a composition comprising an ADC mixture, wherein at least 80% of the ADCs are anti-B7H3 ADCs (like those described herein) having a DAR2. In another embodiment, the invention provides a composition comprising an ADC mixture, wherein at least 85% of the ADCs are anti-B7H3 ADCs (like those described herein) having a DAR2. In another embodiment, the invention provides a composition comprising an ADC mixture, wherein at least 90% of the ADCs are anti-B7H3 ADCs (like those described herein) having a DAR2.

V. Uses of Anti-B7-H3 Antibodies and Anti-B7-H3 ADCs

The antibodies and ADCs of the invention preferably are capable of neutralizing human B7-H3 activity both *in vivo* and *in vitro*. Accordingly, such antibodies and ADCs of the invention can be used to inhibit hB7-H3 activity, *e.g.,* in a cell culture containing hB7-H3, in human subjects or in other mammalian subjects having B7-H3 with which an antibody of the invention cross-reacts. In one embodiment, the invention provides a method for inhibiting hB7-H3 activity comprising contacting hB7-H3 with an antibody or ADC of the invention such that hB7-H3 activity is inhibited. For example, in a cell culture containing, or suspected of containing hB7-H3, an antibody or antibody portion of the invention can be added to the culture medium to inhibit hB7-H3 activity in the culture.

In another embodiment, of the invention a method for reducing hB7-H3 activity in a subject, advantageously from a subject suffering from a disease or disorder in which B7-H3 activity is detrimental. The invention provides methods for reducing B7-H3 activity in a subject suffering from such a disease or disorder, which method comprises administering to the subject an antibody or ADC of the invention such that B7-H3 activity in the subject is reduced. Preferably, the B7-H3 is human B7-H3, and the subject is a human subject. Alternatively, the subject can be a mammal expressing a B7-H3 to which antibodies of the invention are capable of binding. Still further the subject can be a mammal into which B7-H3 has been introduced (*e.g.*, by administration of B7-H3 or by expression of a B7-H3 transgene). Antibodies or ADCs of the invention can be administered to a human subject for therapeutic purposes. Moreover, antibodies or ADCS of the invention can be administered to a non-human mammal expressing a B7-H3 with which the antibody is capable of binding for veterinary purposes or as an animal model of human disease. Regarding the latter, such animal models may be

useful for evaluating the therapeutic efficacy of antibodies of the invention (*e.g.*, testing of dosages and time courses of administration).

As used herein, the term "a disorder in which B7-H3 expression is detrimental" is intended to include diseases and other disorders in which the presence of B7-H3 in a subject suffering from the disorder has been shown to be expressed, or has been shown to be or is suspected of being either responsible for the pathophysiology of the disorder or a factor that contributes to the disorder. For example, the ADCs of the invention may be used to target tumor cells that are expressing B7-H3. Non-limiting examples of disorders that can be treated with the ADCs of the invention, for example, an ADC comprising huAb13v1, include, but are not limited to, a variety of cancers including, but not limited to, small cell lung cancer, non small cell lunch cancer (NSCLC), breast cancer, ovarian cancer, lung cancer, a glioma, prostate cancer, pancreatic cancer, colon cancer, head and neck cancer, leukemia, e.g., acute myeloid leukemia (AML), lymphoma, e.g., non-Hodgkin's lymphoma (NHL), and kidney cancer. Other examples of cancer that may be treated using the compositions and methods disclosed herein include squamous cell carcinoma (*e.g.,* squamous lung cancer or squamous head and neck cancer), triple negative breast cancer, non-small cell lung cancer, colorectal cancer, and mesothelioma. In one embodiment, the antibodies or ADCs disclosed herein are used to treat a solid tumor, *e.g.,* inhibit growth of or decrease size of a solid tumor, overexpressing B7-H3 or which is B7-H3 positive. In one embodiment, the invention is directed to the treatment of squamous lung cancer associated with B7-H3 expression. In another embodiment, the antibodies and ADCs disclosed herein are used to treat triple negative breast cancer (TNBC). Diseases and disorders described herein may be treated by anti-B7-H3 antibodies or ADCs of the invention, as well as pharmaceutical compositions comprising such anti-B7-H3 antibodies or ADCs.

In certain embodiments, the cancer may be characterized as having EGFR overexpression. In one embodiment, the ADCs of the invention may be used to treating cancer associated with an activating EGFR mutation. Examples of such mutations include, but are not limited to, an exon 19 deletion mutation, a single-point substitution mutation L858R in exon 21, a T790M point mutation, and combinations thereof.

In certain embodiments, the antibodies or ADCs disclosed herein are administered to a subject in need thereof in order to treat advanced solid tumor types likely to exhibit elevated levels of B7-H3. Examples of such tumors include, but are not limited to, small cell lung cancer, breast cancer, ovarian cancer, head and neck squamous cell carcinoma, non-small cell lung cancer, triple negative breast cancer, colorectal carcinoma, and glioblastoma multiforme.

In certain embodiments, the invention includes a method for inhibiting or decreasing solid tumor growth in a subject having a solid tumor, said method comprising administering an anti-B7-H3 antibody or ADC described herein, to the subject having the solid tumor, such that the solid tumor growth is inhibited or decreased. In certain embodiments, the solid tumor is a non-small cell lung carcinoma or a glioblastoma. In further embodiments, the solid tumor is a B7-H3-expressing solid

tumors. In further embodiments, the solid tumor is an B7-H3 overexpressing solid tumors. In certain embodiments the anti-B7-H3 antibodies or ADCs described herein are administered to a subject having glioblastoma multiforme, alone or in combination with an additional agent, *e.g.,* radiation and/or temozolomide.

In certain embodiments the anti-B7-H3 ADCs described herein are are administered to a subject having small cell lung cancer, alone or in combination with an additional agent, *e.g.,* ABT-199 (venetoclax).

In certain embodiments the anti-B7-H3 ADCs described herein are administered to a subject having non-small cell lung cancer, alone or in combination with an additional agent, *e.g.,* a taxane. In certain embodiments the anti-B7-H3 antibodies or ADCs described herein are administered to a subject having breast cancer, alone or in combination with an additional agent, *e.g.,* a taxane. In certain embodiments the anti-B7-H3 antibodies or ADCs described herein are administered to a subject having ovarian cancer, alone or in combination with an additional agent, *e.g.,* a taxane.

Other combination therapies which are included in the invention are the administration of an anti-B7-H3 ADC with an agent selected from the group consisting of an anti-PD1 antibody (e.g. pembrolizumab), an anti-PD-L1 antibody (e.g., atezolizumab), an anti-CTLA-4 antibody (e.g. ipilimumab), a MEK inhibitor (e.g. trametinib), an ERK inhibitor, a BRAF inhibitor (e.g. dabrafenib), osimertinib, erlotinib, gefitinib, sorafenib, a CDK9 inhibitor (e.g. dinaciclib), a MCL-1 inhibitor, temozolomide, a Bcl-xL inhibitor, a Bcl-2 inhibitor (e.g. venetoclax), ibrutinib, a mTOR inhibitor (e.g. everolimus), a PI3K inhibitor (e.g. buparlisib), duvelisib, idelalisib, an AKT inhibitor, a HER2 inhibitor (e.g. lapatinib), a taxane (e.g., docetaxel, paclitaxel, nab-paclitaxel), venetoclax, an ADC comprising an auristatin, an ADC comprising a PBD (e.g. rovalpituzumab tesirine), an ADC comprising a maytansinoid (e.g. TDM1), a TRAIL agonist, a proteasome inhibitor (e.g. bortezomib), and a nicotinamide phosphoribosyltransferase (NAMPT) inhibitor.

Combination therapies include administration of an ADC of the invention prior to, concurrently with, or following administration of an additional therapeutic agent, including those described above.

In certain embodiments, the invention includes a method for inhibiting or decreasing solid tumor growth in a subject having a solid tumor which was identified as an B7-H3 expressing or B7-H3 overexpressing tumor, said method comprising administering an anti-B7-H3 antibody or ADC described herein, to the subject having the solid tumor, such that the solid tumor growth is inhibited or decreased. Methods for identifying B7-H3 expressing tumors (*e.g.*, B7-H3 overexpressing tumors) are known in the art, and include FDA-approved tests and validation assays. For example, the B7-H3 assay is a qualitative immunohistochemical (IHC) kit system used to identify B7-H3 expression in normal and neoplastic tissues routinely-fixed for histological evaluation. In addition, PCR-based assays may also be used for identifying B7-H3 overexpressing tumors. The amplified PCR products may be subsequently analyzed, for example, by gel electrophoresis using standard methods known in

the art to determine the size of the PCR products. Such tests may be used to identify tumors that may be treated with the methods and compositions described herein.

Any of the methods for gene therapy available in the art can be used according to the invention. For general reviews of the methods of gene therapy, see Goldspiel *et al.*, 1993, *Clinical Pharmacy* 12:488-505; Wu and Wu, 1991, *Biotherapy* 3:87-95; Tolstoshev, 1993, *Ann. Rev. Pharmacol. Toxicol.* 32:573-596; Mulligan, *Science* 260:926- 932 (1993); and Morgan and Anderson, 1993, *Ann. Rev. Biochem.* 62:191-217; May, 1993, *TIBTECH* 11(5):155-215. Methods commonly known in the art of recombinant DNA technology which can be used are described in Ausubel *et al.* (eds.), *Current Protocols in Molecular Biology*, John Wiley &Sons, NY (1993); and Kriegler, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990). Detailed description of various methods of gene therapy is provided in US20050042664 A1 which is incorporated herein by reference.

In another aspect, this application features a method of treating (*e.g.*, curing, suppressing, ameliorating, delaying or preventing the onset of, or preventing recurrence or relapse of) or preventing a B7-H3-associated disorder, in a subject. The method includes: administering to the subject an B7-H3 binding agent, *e.g.*, an anti-B7-H3 antibody or fragment thereof as described herein, in an amount sufficient to treat or prevent the B7-H3-associated disorder. The B7-H3 antagonist, *e.g.*, the anti-B7-H3 antibody or fragment thereof, can be administered to the subject, alone or in combination with other therapeutic modalities as described herein.

Antibodies or ADCs of the invention, or antigen binding portions thereof can be used alone or in combination to treat such diseases. It should be understood that the antibodies of the invention or antigen binding portion thereof can be used alone or in combination with an additional agent, *e.g.*, a therapeutic agent, said additional agent being selected by the skilled artisan for its intended purpose. For example, the additional agent can be a therapeutic agent art-recognized as being useful to treat the disease or condition being treated by the antibody of the invention. The additional agent also can be an agent that imparts a beneficial attribute to the therapeutic composition, *e.g.*, an agent which affects the viscosity of the composition.

It should further be understood that the combinations which are to be included within this invention are those combinations useful for their intended purpose. The agents set forth below are illustrative for purposes and not intended to be limited. The combinations, which are part of this invention, can be the antibodies of the invention and at least one additional agent selected from the lists below. The combination can also include more than one additional agent, *e.g.*, two or three additional agents if the combination is such that the formed composition can perform its intended function.

The combination therapy can include one or more B7-H3 antagonists, *e.g.*, anti-B7-H3 antibodies or fragments thereof, formulated with, and/or co-administered with, one or more additional therapeutic agents, *e.g.*, one or more cytokine and growth factor inhibitors, immunosuppressants, anti-

inflammatory agents (*e.g.*, systemic anti-inflammatory agents), anti-fibrotic agents, metabolic inhibitors, enzyme inhibitors, and/or cytotoxic or cytostatic agents, mitotic inhibitors, antitumor antibiotics, immunomodulating agents, vectors for gene therapy, alkylating agents, antiangiogenic agents, antimetabolites, boron-containing agents, chemoprotective agents, hormones, antihormone agents, corticosteroids, photoactive therapeutic agents, oligonucleotides, radionuclide agents, topoisomerase inhibitors, kinase inhibitors, or radiosensitizers, as described in more herein.

In a particular embodiment, the anti-B7-H3 binding proteins described herein, for example, anti-B7-H3 antibodies, are used in combination with an anti-cancer agent or an antineoplastic agent. The terms "anti-cancer agent" and "antineoplastic agent" refer to drugs used to treat malignancies, such as cancerous growths. Drug therapy may be used alone, or in combination with other treatments such as surgery or radiation therapy. Several classes of drugs may be used in cancer treatment, depending on the nature of the organ involved. For example, breast cancers are commonly stimulated by estrogens, and may be treated with drugs which inactive the sex hormones. Similarly, prostate cancer may be treated with drugs that inactivate androgens, the male sex hormone. Anti-cancer agents that may be used in conjunction with the anti-B7-H3 antibodies or ADCs of the invention include, among others, an anti-PD1 antibody (e.g., pembrolizumab), an anti-PD-L1 antibody (e.g., atezolizumab), an anti-CTLA-4 antibody (e.g., ipilimumab), a MEK inhibitor (e.g., trametinib), an ERK inhibitor, a BRAF inhibitor (e.g., dabrafenib), osimertinib (AZD9291), erlotinib, gefitinib, sorafenib, a CDK9 inhibitor (e.g., dinaciclib), a MCL-1 inhibitor, temozolomide, a Bcl-xL inhibitor, a Bcl-2 inhibitor (e.g., venetoclax), ibrutinib, a mTOR inhibitor (e.g., everolimus), a PI3K inhibitor (e.g., buparlisib), duvelisib, idelalisib, an AKT inhibitor, a HER2 inhibitor (e.g., lapatinib), Herceptin, a taxane (e.g., docetaxel, paclitaxel, nab-paclitaxel), an ADC comprising an auristatin, an ADC comprising a PBD (e.g., rovalpituzumab tesirine), an ADC comprising a maytansinoid (e.g., TDM1), a TRAIL agonist, a proteasome inhibitor (e.g., bortezomib), and a nicotinamide phosphoribosyltransferase (NAMPT) inhibitor, as well as the following agents:

Anti-Cancer Agent	Comments	Examples
Antibodies	Antibodies which bind IGF-1R (insulin-like growth factor type 1 receptor), which is expressed on the cell surface of most human cancers	A12 (fully humanized mAb) 19D12 (fully humanized mAb) Cp751-871 (fully humanized mAb) H7C10 (humanized mAb) alphaIR3 (mouse) ScFV/FC (mouse/human chimera) EM/164 (mouse)
	Antibodies which bind EGFR; Mutations affecting EGFR expression or activity could result in cancer	Matuzumab (EMD72000) Erbitux® / Cetuximab (Imclone) Vectibix® / Panitumumab (Amgen) mAb 806
	Antibodies which bind cMET (Mesechymal epithelial transition factor); a member of the MET family of receptor tyrosine kinases)	Nimotuxumab (TheraCIM) AVEO (AV299) (AVEO) AMG102 (Amgen) 5D5 (OA-5d5) (Genentech) H244G11 (Pierre Fabre)
	Anti-ErbB3 antibodies	Ab #14 (MM 121-14) Herceptin® (Trastuzumab; Genentech) 1B4C3; 2D1D12 (U3 Pharma AG)
Small Molecules Targeting IGF1R	Insulin-like growth factor type 1 receptor which is expressed on the cell surface of many human cancers	NVP-AEW541-A BMS-536,924 (1H-benzoimidazol-2-yl)-1H-pyridin-2-one) BMS-554,417 Cycloligan TAE226 PQ401
Small Molecules Targeting EGFR	EGFR; Overexpression or mutations affecting EGFR expression or activity could result in cancer	Iressa® / Gefitinib (AstraZeneca) CI-1033 (PD 183805) (Pfizer) Lapatinib (GW-572016) (GlaxoSmithKline) Tykerb® / Lapatinib Ditosylate (Smith Kline Beecham) Tarceva ® / Erlotinib HCL (OSI-774) (OSI Pharma) PKI-166 (Novartis) PD-158780 EKB-569 Tyrphostin AG 1478 (4-(3-Chloroanillino)-6,7-dimethoxyquinazoline)
Small Molecules Targeting cMET	cMET (Mesenchymal epithelial transition factor); a member of the MET family of receptor tyrosine kinases)	PHA665752 ARQ 197
Antimetabolites		Flourouracil (5-FU)

		Capecitabine / XELODA® (HLR Roche) 5-Trifluoromethyl-2'-deoxyuridine Methotrexate sodium (Trexall) (Barr) Raltitrexed/ Tomudex® (AstraZeneca) Pemetrexed / Alimta® (Lilly) Tegafur Cytosine Arabinoside (Cytarabine, Ara-C) / Thioguanine® (GlaxoSmithKline) 5-azacytidine 6-mercaptopurine (Mercaptopurine, 6-MP) Azathioprine / Azasan® (AAIPHARMA LLC) 6-thioguanine (6-TG) / Purinethol® (TEVA) Pentostatin / Nipent® (Hospira Inc.) Fludarabine phosphate / Fludara® (Bayer Health Care) Cladribine (2-CdA, 2-chlorodeoxyadenosine) / Leustatin® (Ortho Biotech)
Alkylating agents	An alkylating antineoplastic agent is an alkylating agent that attaches an alkyl group to DNA. Since cancer cells generally proliferate unrestrictively more than do healthy cells they are more sensitive to DNA damage, and alkylating agents are used clinically to treat a variety of tumors.	Ribonucleotide Reductase Inhibitor (RNR) Cyclophosphamide / Cytoxan (BMS) Neosar (TEVA) Ifosfamide / Mitoxana® (ASTA Medica) Thiotepa (Bedford, Abraxis, Teva) BCNU→ 1,3-bis(2-chloroethyl)-1-nitosourea CCNU→ 1, -(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (methyl CCNU) Hexamethylmelamine (Altretamine, HMM) / Hexalen® (MGI Pharma Inc.) Busulfan / Myleran (GlaxoSmithKline) Procarbazine HCL/ Matulane (Sigma Tau Pharmaceuticals, Inc.) Dacarbazine (DTIC) Chlorambucil / Leukara® (SmithKline Beecham) Melphalan / Alkeran® (GlaxoSmithKline) Cisplatin (Cisplatinum, CDDP) / Platinol (Bristol Myers) Carboplatin / Paraplatin (BMS) Oxaliplatin /Eloxitan® (Sanofi-Aventis US)
Topoisomerase inhibitors	Topoisomerase inhibitors are chemotherapy agents designed to interfere with the action of topoisomerase enzymes (topoisomerase I and II), which are enzymes that control the changes in DNA structure by catalyzing the breaking and rejoining of the phosphodiester backbone of DNA strands during the normal cell cycle.	Doxorubicin HCL / Doxil® (Alza) Daunorubicin citrate / Daunoxome® (Gilead) Mitoxantrone HCL / Novantrone (EMD Serono) Actinomycin D Etoposide / Vepesid® (BMS)/ Etopophos® (Hospira, Bedford, Teva Parenteral, Etc.) Topotecan HCL / Hycamtin® (GlaxoSmithKline) Teniposide (VM-26) / Vumon® (BMS) Irinotecan HCL(CPT-ll) / Camptosar® (Pharmacia & Upjohn)
Microtubule	Microtubules are one of the	Vincristine / Oncovin® (Lilly)

targeting agents	components of the cytoskeleton. They have diameter of ~24 nm and length varying from several micrometers to possibly millimeters in axons of nerve cells. Microtubules serve as structural components within cells and are involved in many cellular processes including mitosis, cytokinesis, and vesicular transport.	Vinblastine sulfate / Velban®(discontinued) (Lilly) Vinorelbine tartrate / Navelbine® (PierreFabre) Vindesine sulphate / Eldisine® (Lilly) Pac1itaxel / Taxol® (BMS) Docetaxel / Taxotere® (Sanofi Aventis US) Nanoparticle paclitaxel (ABI-007) / Abraxane® (Abraxis BioScience, Inc.) Ixabepilone / IXEMPRA™ (BMS)
Kinase inhibitors	Kinases are enzymes that catalyze the transfer of phosphate groups from high-energy, phosphate-donating molecules to specific substrates, and are utilized to transmit signals and regulate complex processes in cells.	Imatinib mesylate / Gleevec (Novartis) Sunitinib malate / Sutent® (Pfizer) Sorafenib tosylate / Nexavar® (Bayer) Nilotinib hydrochloride monohydrate / Tasigna® (Novartis), Osimertinib, Cobimetinib, Trametinib, Dabrafenib, Dinaciclib
Protein synthesis inhibitors	Induces cell apoptosis	L-asparaginase / Elspar® (Merck & Co.)
Immunotherapeutic agents	Induces cancer patients to exhibit immune responsiveness	Alpha interferon Angiogenesis Inhibitor / Avastin® (Genentech) IL-2→ Interleukin 2 (Aldesleukin) / Proleukin ® (Chiron) IL-12→ Interleukin 12
	Antibody / small molecule immune checkpoint modulators	Anti-CTLA-4 and PR-1 therapies Yervoy® (ipilimumab; Bristol-Myers Squibb) Opdivo® (nivolumab; Bristol-Myers Squibb) Keytrada® (pembrolizumab; Merck)
Hormones	Hormone therapies associated with menopause and aging seek to increase the amount of certain hormones in your body to compensate for age- or disease-related hormonal declines. Hormone therapy as a cancer treatment either reduces the level of specific hormones or alters the cancer's ability to use these hormones to grow and spread.	Toremifene citrate / Fareston® (GTX, Inc.) Fulvestrant / Faslodex® (AstraZeneca) Raloxifene HCL / Evista® (Lilly) Anastrazole / Arimidex® (AstraZeneca) Letrozole / Femara® (Novartis) Fadrozole (CGS 16949A) Exemestane / Aromasin® (Pharmacia & Upjohn) Leuprolide acetate / Eligard® (QTL USA) Lupron® (TAP Pharm) Goserelin acetate / Zoladex® (AstraZeneca) Triptorelin pamoate / Trelstar® (Watson Labs) Buserelin / Suprefact® (Sanofi Aventis) Nafarelin / Synarel® (Pfizer) Cetrorelix / Cetrotide® (EMD Serono) Bicalutamide / Casodex® (AstraZeneca) Nilutamide / Nilandron® (Aventis Pharm.)

		Megestrol acetate / Megace® (BMS) Somatostatin Analogs (Octreotide acetate / Sandostatin® (Novartis)
Glucocorticoids	Anti-inflammatory drugs used to reduce swelling that causes cancer pain.	Prednisolone Dexamethasone / Decadron® (Wyeth)
Aromatose inhibitors	Includes imidazoles	Ketoconazole
mTOR inhibitors	the mTOR signaling pathway was originally discovered during studies of the immunosuppressive agent rapamycin. This highly conserved pathway regulates cell proliferation and metabolism in response to environmental factors, linking cell growth factor receptor signaling via phosphoinositide-3-kinase(PI-3K) to cell growth, proliferation, and angiogenesis.	Sirolimus (Rapamycin) / Rapamune® (Wyeth) Temsirolimus (CCI-779) / Torisel® (Wyeth) Deforolimus (AP23573) / (Ariad Pharm.) Everolimus (RAD00I) / Certican® (Novartis)

In addition to the above anti-cancer agents, the anti-B7-H3 antibodies and ADCs described herein may be administered in combination with the agents described herein. Further, the aforementioned anti-cancer agents may also be used in the ADCs of the invention.

In particular embodiments, the anti-B7-H3 antibodies or ADCs can be administered alone or with another anti-cancer agent which acts in conjunction with or synergistically with the antibody to treat the disease associated with B7-H3 activity. Such anti-cancer agents include, for example, agents well known in the art (*e.g.*, cytotoxins, chemotherapeutic agents, small molecules and radiation). Examples of anti-cancer agents include, but are not limited to, Panorex (Glaxo-Welcome), Rituxan (IDEC/Genentech/Hoffman la Roche), Mylotarg (Wyeth), Campath (Millennium), Zevalin (IDEC and Schering AG), Bexxar (Corixa/GSK), Erbitux (Imclone/BMS), Avastin (Genentech) and Herceptin (Genentech/Hoffman la Roche). Other anti-cancer agents include, but are not limited to, those disclosed in U.S. Patent No. 7,598,028 and International Publication No. WO2008/100624, the contents of which are hereby incorporated by reference. One or more anti-cancer agents may be administered either simultaneously or before or after administration of an antibody or antigen binding portion thereof of the invention.

In particular embodiments of the invention, the anti-B7-H3 antibodies or ADCs described herein can be used in a combination therapy with an apoptotic agent, such as a Bcl-xL inhibitor or a Bcl-2 (B-cell lymphoma 2) inhibitor (*e.g.*, ABT-199 (venetoclax)) to treat cancer, such as leukemia, in a subject. In one embodiment, the anti-B7-H3 antibodies or ADCs described herein can be used in a combination therapy with a Bcl-xL inhibitor for treating cancer. In one embodiment, the anti-B7-H3

antibodies or ADCs described herein can be used in a combination therapy with venetoclax for treating cancer.

In particular embodiments of the invention, the anti-B7-H3 antibodies or ADCs described herein can be used in a combination therapy with an inhibitor of NAMPT (see examples of inhibitors in US 2013/0303509; AbbVie, Inc., incorporated by reference herein) to treat a subject in need thereof. NAMPT (also known as pre-B-cell-colony-enhancing factor (PBEF) and visfatin) is an enzyme that catalyzes the phosphoribosylation of nicotinamide and is the rate-limiting enzyme in one of two pathways that salvage NAD. In one embodiment of the invention, anti-B7-H3 antibodies and ADCs described herein are administered in combination with a NAMPT inhibitor for the treatment of cancer in a subject.

In particular embodiments of the invention, the anti-B7-H3 antibodies or ADCs described herein can be used in a combination therapy with SN-38, which is the active metabolite of the topoisomerase inhibitor irinotecan.

In other embodiments of the invention, the anti-B7-H3 antibodies or ADCs described herein can be used in a combination therapy with a PARP (poly ADP ribose polymerase) inhibitor, *e.g.*,veliparib, to treat cancer, including breast, ovarian and non-small cell lung cancers.

Further examples of additional therapeutic agents that can be co-administered and/or formulated with anti-B7-H3 antibodies or anti-B7-H3 ADCs described herein, include, but are not limited to, one or more of: inhaled steroids; beta-agonists, *e.g.*, short-acting or long- acting beta-agonists; antagonists of leukotrienes or leukotriene receptors; combination drugs such as ADVAIR; IgE inhibitors, *e.g.*, anti-IgE antibodies (*e.g.*, XOLAIR®, omalizumab); phosphodiesterase inhibitors (*e.g.*, PDE4 inhibitors); xanthines; anticholinergic drugs; mast cell-stabilizing agents such as cromolyn; IL-4 inhibitors; IL-5 inhibitors; eotaxin/CCR3 inhibitors; antagonists of histamine or its receptors including H1, H2, H3, and H4, and antagonists of prostaglandin D or its receptors (DP1 and CRTH2). Such combinations can be used to treat, for example, asthma and other respiratory disorders. Other examples of additional therapeutic agents that can be co-administered and/or formulated with anti-B7-H3 antibodies or anti-B7-H3 ADCs described herein, include, but are not limited to, one or more of, an anti-PD1 antibody (e.g., pembrolizumab), an anti-PD-L1 antibody (e.g., atezolizumab), an anti-CTLA-4 antibody (e.g., ipilimumab), a MEK inhibitor (e.g., trametinib), an ERK inhibitor, a BRAF inhibitor (e.g., dabrafenib), osimertinib (AZD9291), erlotinib, gefitinib, sorafenib, a CDK9 inhibitor (e.g., dinaciclib), a MCL-1 inhibitor, temozolomide, a Bcl-xL inhibitor, a Bcl-2 inhibitor (e.g., venetoclax), ibrutinib, a mTOR inhibitor (e.g., everolimus), a PI3K inhibitor (e.g., buparlisib), duvelisib, idelalisib, an AKT inhibitor, a HER2 inhibitor (e.g., lapatinib), Herceptin, a taxane (e.g., docetaxel, paclitaxel, nab-paclitaxel), an ADC comprising an auristatin, an ADC comprising a PBD (e.g., rovalpituzumab tesirine), an ADC comprising a maytansinoid (e.g., TDM1), a TRAIL agonist, a proteasome inhibitor (e.g., bortezomib), and a nicotinamide phosphoribosyltransferase (NAMPT) inhibitor. Additional examples of therapeutic agents that can be

co-administered and/or formulated with one or more anti-B7-H3 antibodies or fragments thereof include one or more of: TNF antagonists (*e.g.*, a soluble fragment of a TNF receptor, *e.g.*, p55 or p75 human TNF receptor or derivatives thereof, *e.g.*, 75 kD TNFR-IgG (75 kD TNF receptor-IgG fusion protein, ENBREL)); TNF enzyme antagonists, *e.g.*, TNF converting enzyme (TACE) inhibitors; muscarinic receptor antagonists; TGF-beta antagonists; interferon gamma; perfenidone; chemotherapeutic agents, *e.g.*, methotrexate, leflunomide, or a sirolimus (rapamycin) or an analog thereof, *e.g.*, CCI-779; COX2 and cPLA2 inhibitors; NSAIDs; immunomodulators; p38 inhibitors, TPL-2, MK-2 and NFkB inhibitors, among others.

Other preferred combinations are cytokine suppressive anti-inflammatory drug(s) (CSAIDs); antibodies to or antagonists of other human cytokines or growth factors, for example, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-15, IL-16, IL-18, IL-21, IL-31, interferons, EMAP-II, GM-CSF, FGF, EGF, PDGF, and edothelin-1, as well as the receptors of these cytokines and growth factors. Antibodies of the invention, or antigen binding portions thereof, can be combined with antibodies to cell surface molecules such as CD2, CD3, CD4, CD8, CD25, CD28, CD30, CD40, CD45, CD69, CD80 (B7.1), CD86 (B7.2), CD90, CTLA, CTLA-4, PD-1, or their ligands including CD154 (gp39 or CD40L).

Preferred combinations of therapeutic agents may interfere at different points in the inflammatory cascade; preferred examples include TNF antagonists like chimeric, humanized or human TNF antibodies, adalimumab, (HUMIRA; D2E7; PCT Publication No. WO 97/29131 and U.S. Patent No. 6,090,382, incorporated by reference herein), CA2 (RemicadeTM), CDP 571, and soluble p55 or p75 TNF receptors, derivatives, thereof, (p75TNFR1gG (EnbrelTM) or p55TNFR1gG (Lenercept), and also TNF converting enzyme (TACE) inhibitors; similarly IL-1 inhibitors (Interleukin-1-converting enzyme inhibitors, IL-1RA etc.) may be effective for the same reason. Other preferred combinations include Interleukin 4.

The pharmaceutical compositions of the invention may include a "therapeutically effective amount" or a "prophylactically effective amount" of an antibody or antibody portion of the invention. A "therapeutically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic result. A therapeutically effective amount of the antibody or antibody portion may be determined by a person skilled in the art and may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the antibody or antibody portion to elicit a desired response in the individual. A therapeutically effective amount is also one in which any toxic or detrimental effects of the antibody, or antibody portion, are outweighed by the therapeutically beneficial effects. A "prophylactically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired prophylactic result. Typically, since a prophylactic dose is used in subjects prior to or at an earlier stage of disease, the prophylactically effective amount will be less than the therapeutically effective amount.

Dosage regimens may be adjusted to provide the optimum desired response (*e.g.*, a therapeutic or prophylactic response). For example, a single bolus may be administered, several divided doses may be administered over time or the dose may be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation. It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the mammalian subjects to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the active compound and the particular therapeutic or prophylactic effect to be achieved, and (b) the limitations inherent in the art of compounding such an active compound for the treatment of sensitivity in individuals.

An exemplary, non-limiting range for a therapeutically or prophylactically effective amount of an ADC, an antibody or antibody portion of the invention is 0.1-20 mg/kg, more preferably 1-10 mg/kg. In one embodiment, the dose of the antibody or ADC described herein is 1 to 6 mg/kg, including the individual doses recited therein, *e.g.,* 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, and 6 mg/kg. In another embodiment, the dose of the antibody or ADC described herein is 1 to 200 µg/kg, including the individual doses recited therein, *e.g.,* 1 µg/kg, 2 µg/kg, 3 µg/kg, 4 µg/kg, 5 µg/kg, 10 µg/kg, 20 µg/kg, 30 µg/kg, 40 µg/kg, 50 µg/kg, 60 µg/kg, 80 µg/kg, 100 µg/kg, 120 µg/kg, 140 µg/kg, 160 µg/kg, 180 µg/kg and 200 µg/kg. It is to be noted that dosage values may vary with the type and severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that dosage ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed composition.

In one embodiment, an anti-B7-H3 ADC, including an ADC comprising antibody huAb13v1, huAb3v2.5, or huAb3v2.6, is administered to a subject in need thereof, *e.g.,* a subject having cancer, at a dose of 0.1 to 30 mg/kg. In another embodiment, the anti-B7-H3 antibody, *e.g.,* huAb13v1, huAb3v2.5, huAb3v2.6, or an antigen binding portion thereof, is administered to a subject in need thereof, *e.g.,* a subject having cancer, as an ADC at a dose of 1 to 15 mg/kg. In another embodiment, the anti-B7-H3 antibody, *e.g.,* huAb13v1, huAb3v2.5, huAb3v2.6, or an antigen binding portion thereof, is administered to a subject in need thereof, *e.g.,* a subject having cancer, as an ADC at a dose of 1 to 10 mg/kg. In another embodiment, the anti-B7-H3 antibody, *e.g.,* huAb13v1, huAb3v2.5, huAb3v2.6, or an antigen binding portion thereof, is administered to a subject in need thereof, *e.g.,* a subject having cancer, as an ADC at a dose of 2 to 3. In another embodiment, the anti-B7-H3 antibody, *e.g.,* huAb13v1, huAb3v2.5, huAb3v2.6, or an antigen binding portion thereof, is

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME	1	DE	3
CONTENANT LES PAGES	1	À	432

NOTE : Pour les tomes additionels, veuillez contacter le Bureau canadien des brevets

JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME	1	OF	3
CONTAINING PAGES	1	TO	432

NOTE: For additional volumes, please contact the Canadian Patent Office

NOM DU FICHIER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

AMENDED CLAIMS
received by the International Bureau on 20 January 2018 (20.01.2018)

1. An isolated anti-hB7H3 antibody, wherein the antibody comprises

a heavy chain variable region comprising

a CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NO: 12, SEQ ID NO: 35, and SEQ ID NO: 27,

a CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NO: 140, SEQ ID NO: 34, SEQ ID NO: 11, and SEQ ID NO: 26, and

a CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NO: 10, SEQ ID NO: 25, SEQ ID NO: 33; and

a light chain variable region comprising

a CDR3 having the amino acid sequence selected from the group consisting of SEQ ID NO: 15, SEQ ID NO: 39, and SEQ ID NO: 31;

a CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NO: 7, SEQ ID NO: 38, and SEQ ID NO: 30; and

a CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NO: 136, SEQ ID NO: 138, SEQ ID NO: 37, SEQ ID NO: 14, and SEQ ID NO: 29.

2. The antibody according to claim 1, wherein the antibody further comprises a human acceptor framework, said human acceptor framework comprises an amino acid sequence selected from the group consisting of SEQ ID Nos: 155, 156, 164, 165, 166, and 167.

3. The antibody according to claim 1, wherein the antibody further comprises a human acceptor framework, said human acceptor framework comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 155 to 158.

4. The anti-hB7-H3 antibody according to claim 1, wherein the antibody comprises a heavy chain variable domain comprising an amino acid sequence set forth in SEQ ID NO: 139 and a light chain variable domain comprising an amino acid sequence set forth in SEQ ID NO: 135.

5. The anti-hB7-H3 antibody according to claim 1, wherein the antibody comprises a heavy chain variable domain comprising an amino acid sequence set forth in SEQ ID NO: 139 and a light chain variable domain comprising an amino acid sequence set forth in SEQ ID NO: 137.

6. The anti-hB7-H3 antibody according to claim 1, wherein the antibody comprises a heavy chain variable domain comprising an amino acid sequence set forth in SEQ ID NO: 147 and a light chain variable domain comprising an amino acid sequence set forth in SEQ ID NO: 144.

7. A pharmaceutical composition comprising the anti-hB7-H3 antibody according to claim 1, and a pharmaceutically acceptable carrier.

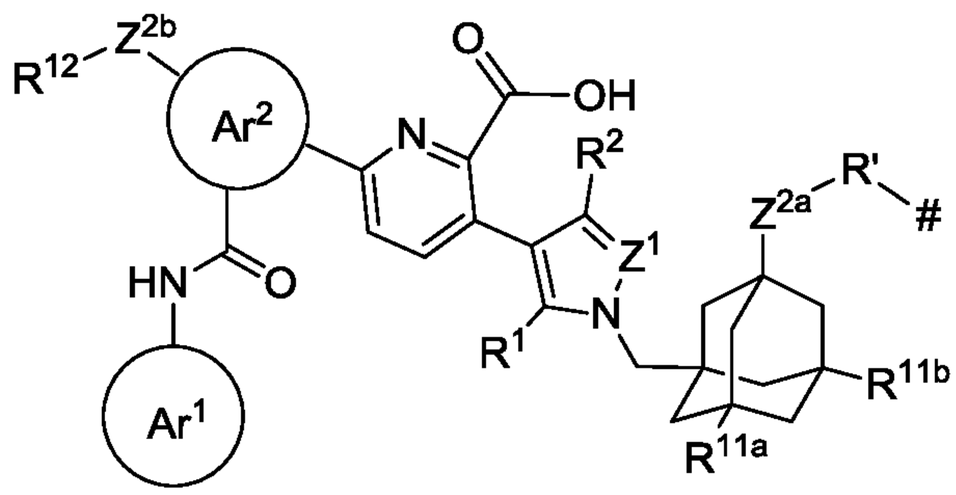
8. An anti-hB7-H3 Antibody Drug Conjugate (ADC) comprising the anti-hB7-H3 antibody according to claim 1 conjugated to one or more drugs via a linker.

9. The ADC of claim 8, wherein said one or more drugs is an auristatin or a pyrrolobenzodiazepine (PBD).

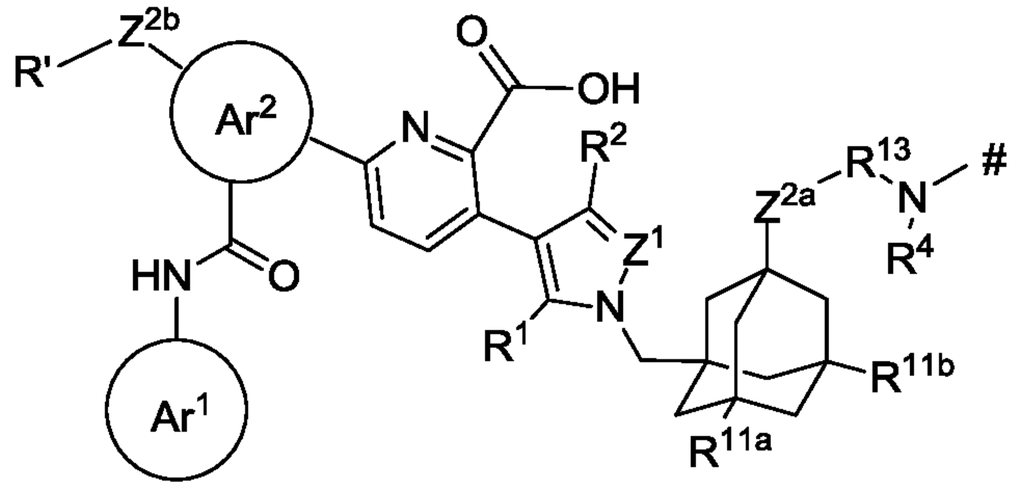
10. The ADC of claim 8, wherein said one or more drugs is a Bcl-xL inhibitor.

11. An anti-hB7-H3 antibody drug conjugate (ADC) comprising a drug linked to an anti-human B7-H3 (hB7-H3) antibody via a linker, wherein the drug is a Bcl-xL inhibitor according to structural formula (IIa), (IIb), (IIc), or (IId):

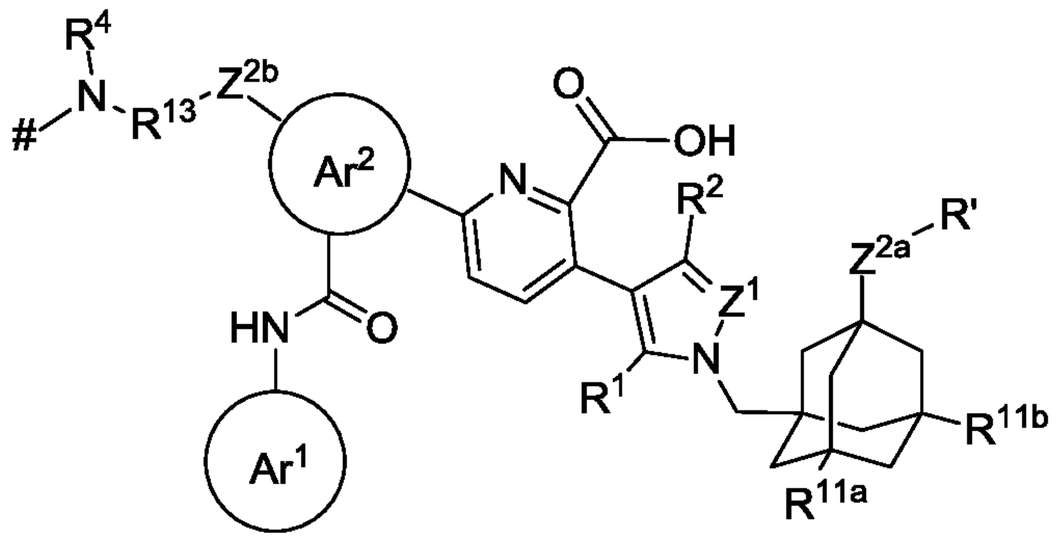
(IIa)



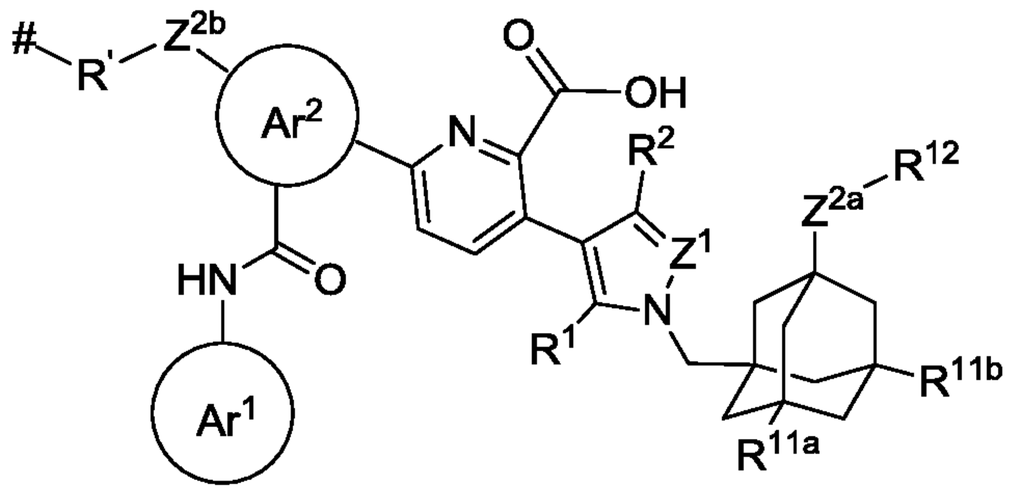
(IIb)



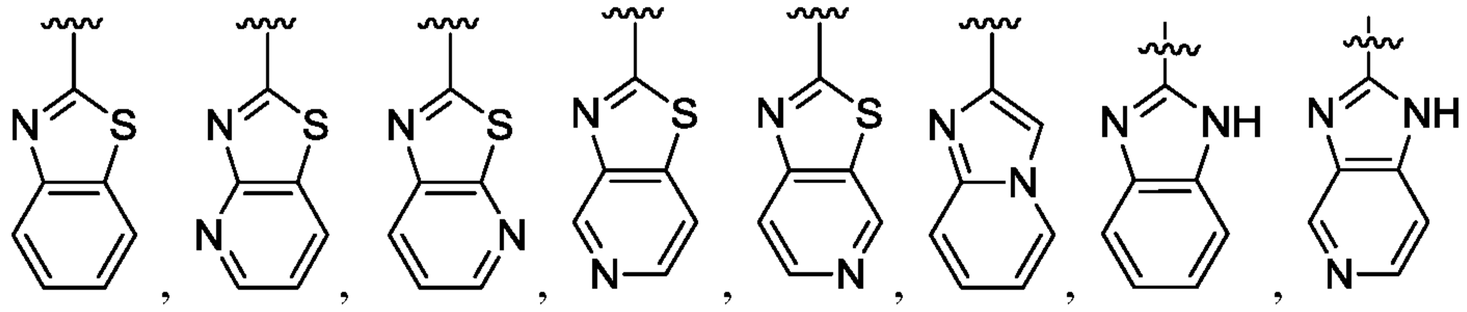
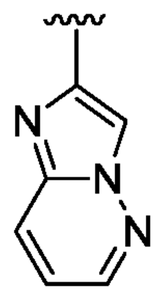
(IIc)

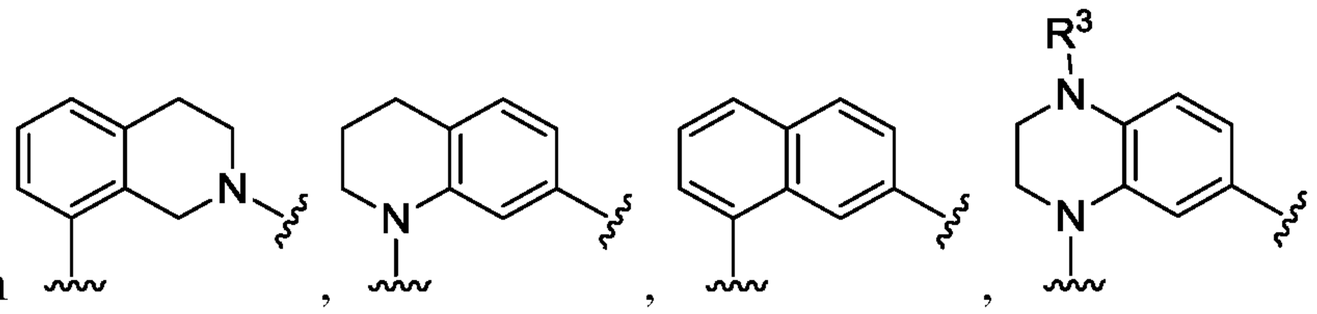
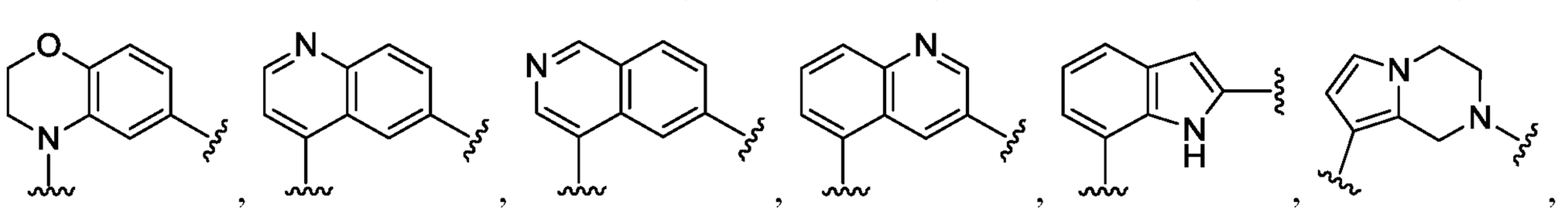
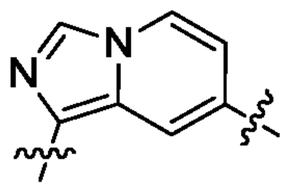


(IId)



wherein:

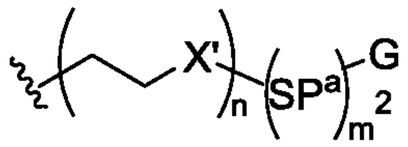
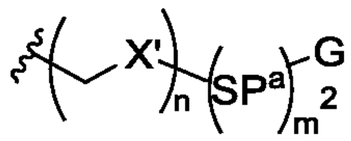
Ar^1 is selected from  , and  and is optionally substituted with one or more substituents independently selected from halo, hydroxy, nitro, lower alkyl, lower heteroalkyl, C_{1-4}alkoxy, amino, cyano and halomethyl;

Ar^2 is selected from  ,  , and  or an N-oxide thereof, and is optionally substituted with one or

more substituents independently selected from halo, hydroxy, nitro, lower alkyl, lower heteroalkyl, C_{1-4}alkoxy, amino, cyano and halomethyl, wherein the R^{12}-Z^{2b}-, R'-Z^{2b}-, #-N(R^4)-R^{13}-Z^{2b}-, or #-R'-Z^{2b}- substituents are attached to Ar^2 at any Ar^2 atom capable of being substituted;

Z^1 is selected from N, CH, C-halo, C-CH_3 and C-CN;

Z^{2a} and Z^{2b} are each , independently from one another, selected from a bond, NR^6, $CR^{6a}R^{6b}$, O, S, S(O), $S(O)_2$, -NR^6C(O)-,-NR^{6a}C(O)NR^{6b}-, and –NR^6C(O)O-;

R' is  or  , wherein #, where attached to R', is attached to R' at any R' atom capable of being substituted;

X' is selected at each occurrence from -N(R^{10})- , -N(R^{10})C(O)-, -N(R^{10})$S(O)_2$-, -$S(O)_2$N(R^{10})-, and -O-;

n is selected from 0-3;

R^{10} is independently selected at each occurrence from hydrogen, lower alkyl, heterocycle, aminoalkyl, G-alkyl, and -$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$-NH_2;

G at each occurrence is independently selected from a polyol, a polyethylene glycol with between 4 and 30 repeating units, a salt and a moiety that is charged at physiological pH;

SP^a is independently selected at each occurrence from oxygen, -$S(O)_2$N(H)-, -N(H)$S(O)_2$-, -N(H)C(O)-, -C(O)N(H) -, -N(H)- , arylene, heterocyclene, and optionally substituted methylene; wherein methylene is optionally substituted with one or more of -$NH(CH_2)_2$G, NH_2, C_{1-8}alkyl, and carbonyl;

m^2 is selected from 0-12;

R^1 is selected from hydrogen, methyl, halo, halomethyl, ethyl, and cyano;

R^2 is selected from hydrogen, methyl, halo, halomethyl and cyano;

R^3 is selected from hydrogen, methyl, ethyl, halomethyl and haloethyl;

R^4 is selected from hydrogen, lower alkyl and lower heteroalkyl or is taken together with an atom of R^{13} to form a cycloalkyl or heterocyclyl ring having between 3 and 7 ring atoms;

R^6, R^{6a} and R^{6b} are each, independent from one another, selected from hydrogen, optionally substituted lower alkyl, optionally substituted lower heteroalkyl, optionally substituted cycloalkyl and optionally substituted heterocyclyl, or are taken together with an atom from R^4 and an atom from R^{13} to form a cycloalkyl or heterocyclyl ring having between 3 and 7 ring atoms;

R^{11a} and R^{11b} are each, independently of one another, selected from hydrogen, halo, methyl, ethyl, halomethyl, hydroxyl, methoxy, CN, and SCH_3;

AMENDED SHEET (ARTICLE 19)

R^{12} is optionally R' or is selected from hydrogen, halo, cyano, optionally substituted alkyl, optionally substituted heteroalkyl, optionally substituted heterocyclyl, and optionally substituted cycloalkyl;

R^{13} is selected from optionally substituted C_{1-8} alkylene, optionally substituted heteroalkylene, optionally substituted heterocyclene, and optionally substituted cycloalkylene; and

represents a point of attachment to a linker.

12. The ADC of claim 11, wherein the Bcl-xL inhibitor is selected from the group consisting of the following compounds modified in that the hydrogen corresponding to the # position of structural formula (IIa), (IIb), (IIc), or (IId) is not present forming a monoradical:

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-[1-({3-[2-({2-[2-(carboxymethoxy)ethoxy]ethyl}amino)ethoxy]-5,7-dimethyltricyclo[3.3.1.13,7]dec-1-yl}methyl)-5-methyl-1H-pyrazol-4-yl]pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3,5-dimethyl-7-{2-[(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

2-{[(2-{[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.13,7]dec-1-yl}oxy)ethyl]amino}ethyl)sulfonyl]amino}-2-deoxy-D-glucopyranose;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3,5-dimethyl-7-{2-[(4-{[(3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl]methyl}benzyl)amino]ethoxy}tricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3,5-dimethyl-7-{2-[(3-sulfopropyl)amino]ethoxy}tricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3-{2-[(2,3-dihydroxypropyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

2-({[4-({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.13,7]dec-1-yl}oxy)ethyl]amino}methyl)phenyl]sulfonyl}amino)-2-deoxy-beta-D-glucopyranose;

8-(1,3-benzothiazol-2-ylcarbamoyl)-2-{6-carboxy-5-[1-({3-[2-({2-[1-(beta-D-glucopyranuronosyl)-1H-1,2,3-triazol-4-yl]ethyl}amino)ethoxy]-5,7-

AMENDED SHEET (ARTICLE 19)

dimethyltricyclo[3.3.1.13,7]dec-1-yl}methyl)-5-methyl-1H-pyrazol-4-yl]pyridin-2-yl}-1,2,3,4-tetrahydroisoquinoline;

3-[1-({3-[2-(2-{[4-(beta-D-allopyranosyloxy)benzyl]amino}ethoxy)ethoxy]-5,7-dimethyltricyclo[3.3.1.13,7]dec-1-yl}methyl)-5-methyl-1H-pyrazol-4-yl]-6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-(1-{[3,5-dimethyl-7-(2-{2-[(2-sulfoethyl)amino]ethoxy}ethoxy)tricyclo[3.3.1.13,7]dec-1-yl]methyl}-5-methyl-1H-pyrazol-4-yl)pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3,5-dimethyl-7-{2-[(2-phosphonoethyl)amino]ethoxy}tricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3,5-dimethyl-7-{2-[methyl(3-sulfo-L-alanyl)amino]ethoxy}tricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3,5-dimethyl-7-{2-[(3-phosphonopropyl)amino]ethoxy}tricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3,5-dimethyl-7-{2-[(3-sulfo-L-alanyl)amino]ethoxy}tricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-(1-{[3,5-dimethyl-7-(2-{2-[(3-phosphonopropyl)amino]ethoxy}ethoxy)tricyclo[3.3.1.13,7]dec-1-yl]methyl}-5-methyl-1H-pyrazol-4-yl)pyridine-2-carboxylic acid;

3-{1-[(3-{2-[L-alpha-aspartyl(methyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}-6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]pyridine-2-carboxylic acid;

6-{4-[({2-[2-(2-aminoethoxy)ethoxy]ethyl}[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.13,7]dec-1-yl}oxy)ethyl]amino)methyl]benzyl}-2,6-anhydro-L-gulonic acid;

4-({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.13,7]dec-1-yl}oxy)ethyl]amino}methyl)phenyl hexopyranosiduronic acid;

AMENDED SHEET (ARTICLE 19)

6-[1-(1,3-benzothiazol-2-ylcarbamoyl)-1,2,3,4-tetrahydroquinolin-7-yl]-3-{1-[(3,5-dimethyl-7-{2-[(2-phosphonoethyl)amino]ethoxy}tricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[1-(1,3-benzothiazol-2-ylcarbamoyl)-1,2,3,4-tetrahydroquinolin-7-yl]-3-{1-[(3,5-dimethyl-7-{2-[methyl(3-sulfo-L-alanyl)amino]ethoxy}tricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

3-{1-[(3,5-dimethyl-7-{2-[(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}-6-[8-([1,3]thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]pyridine-2-carboxylic acid;

3-{1-[(3,5-dimethyl-7-{2-[(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}-6-[8-([1,3]thiazolo[4,5-b]pyridin-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]pyridine-2-carboxylic acid;

6-[1-(1,3-benzothiazol-2-ylcarbamoyl)-1,2,3,4-tetrahydroquinolin-7-yl]-3-{1-[(3,5-dimethyl-7-{2-[(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3-{2-[(2-carboxyethyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3,5-dimethyl-7-{2-[(3-phosphonopropyl)(piperidin-4-yl)amino]ethoxy}tricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

3-{1-[(3-{2-[D-alpha-aspartyl(methyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}-6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-(1-{[3-(2-{[1-(carboxymethyl)piperidin-4-yl]amino}ethoxy)-5,7-dimethyltricyclo[3.3.1.13,7]dec-1-yl]methyl}-5-methyl-1H-pyrazol-4-yl)pyridine-2-carboxylic acid;

N-[(5S)-5-amino-6-{[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.13,7]dec-1-yl}oxy)ethyl](methyl)amino}-6-oxohexyl]-N,N-dimethylmethanaminium;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3,5-dimethyl-7-{2-[piperidin-4-yl(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

AMENDED SHEET (ARTICLE 19)

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-5-(3-phosphonopropoxy)-3,4-dihydroisoquinolin-2(1H)-yl]-3-[1-({3,5-dimethyl-7-[2-(methylamino)ethoxy]tricyclo[3.3.1.13,7]dec-1-yl}methyl)-5-methyl-1H-pyrazol-4-yl]pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-(1-{[3-(2-{[N-(2-carboxyethyl)-L-alpha-aspartyl]amino}ethoxy)-5,7-dimethyltricyclo[3.3.1.13,7]dec-1-yl]methyl}-5-methyl-1H-pyrazol-4-yl)pyridine-2-carboxylic acid;

3-{1-[(3-{2-[(2-aminoethyl)(2-sulfoethyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}-6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]pyridine-2-carboxylic acid;

6-[5-(2-aminoethoxy)-8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-[1-({3,5-dimethyl-7-[2-(methylamino)ethoxy]tricyclo[3.3.1.13,7]dec-1-yl}methyl)-5-methyl-1H-pyrazol-4-yl]pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)naphthalen-2-yl]-3-{1-[(3,5-dimethyl-7-{2-[(3-sulfopropyl)amino]ethoxy}tricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3-{2-[(2-carboxyethyl)(piperidin-4-yl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3,5-dimethyl-7-{2-[(3-sulfo-L-alanyl)(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3-{2-[{2-[(2-carboxyethyl)amino]ethyl}(2-sulfoethyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

3-{1-[(3,5-dimethyl-7-{2-[(3-phosphonopropyl)amino]ethoxy}tricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}-6-[8-([1,3]thiazolo[4,5-b]pyridin-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]pyridine-2-carboxylic acid;

3-{1-[(3,5-dimethyl-7-{2-[(3-phosphonopropyl)amino]ethoxy}tricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}-6-[8-([1,3]thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-5-(carboxymethoxy)-3,4-dihydroisoquinolin-2(1H)-yl]-3-[1-({3,5-dimethyl-7-[2-(methylamino)ethoxy]tricyclo[3.3.1.13,7]dec-1-yl}methyl)-5-methyl-1H-pyrazol-4-yl]pyridine-2-carboxylic acid;

AMENDED SHEET (ARTICLE 19)

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3-{2-[(3-carboxypropyl)(piperidin-4-yl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)naphthalen-2-yl]-3-{1-[(3,5-dimethyl-7-{2-[(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

3-{1-[(3-{2-[L-alpha-aspartyl(2-sulfoethyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}-6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3-{2-[(1,3-dihydroxypropan-2-yl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[5-(2-aminoethoxy)-8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3,5-dimethyl-7-{2-[methyl(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-5-{2-[(2-sulfoethyl)amino]ethoxy}-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3,5-dimethyl-7-{2-[methyl(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3,5-dimethyl-7-{2-[(2-sulfoethyl){2-[(2-sulfoethyl)amino]ethyl}amino]ethoxy}tricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-5-{2-[(2-carboxyethyl)amino]ethoxy}-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3,5-dimethyl-7-{2-[methyl(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

3-{1-[(3,5-dimethyl-7-{2-[(3-phosphonopropyl)(piperidin-4-yl)amino]ethoxy}tricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}-6-[8-([1,3]thiazolo[4,5-b]pyridin-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]pyridine-2-carboxylic acid;

6-[4-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydro-2H-1,4-benzoxazin-6-yl]-3-{1-[(3,5-dimethyl-7-{2-[(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

AMENDED SHEET (ARTICLE 19)

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-5-(3-sulfopropoxy)-3,4-dihydroisoquinolin-2(1H)-yl]-3-[1-({3,5-dimethyl-7-[2-(methylamino)ethoxy]tricyclo[3.3.1.13,7]dec-1-yl}methyl)-5-methyl-1H-pyrazol-4-yl]pyridine-2-carboxylic acid;

3-{1-[(3,5-dimethyl-7-{2-[(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}-6-[1-([1,3]thiazolo[4,5-b]pyridin-2-ylcarbamoyl)-1,2,3,4-tetrahydroquinolin-7-yl]pyridine-2-carboxylic acid;

3-{1-[(3,5-dimethyl-7-{2-[(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}-6-[8-([1,3]thiazolo[4,5-b]pyridin-2-ylcarbamoyl)naphthalen-2-yl]pyridine-2-carboxylic acid;

(1ξ)-1-({2-[5-(1-{[3-(2-aminoethoxy)-5,7-dimethyltricyclo[3.3.1.13,7]dec-1-yl]methyl}-5-methyl-1*H*-pyrazol-4-yl)-6-carboxypyridin-2-yl]-8-(1,3-benzothiazol-2-ylcarbamoyl)-1,2,3,4-tetrahydroisoquinolin-5-yl}methyl)-1,5-anhydro-D-glucitol;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3-{2-[(3-carboxypropyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)naphthalen-2-yl]-3-{1-[(3,5-dimethyl-7-{2-[(3-phosphonopropyl)amino]ethoxy}tricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-(1-{[3-(2-{[4-(beta-D-glucopyranosyloxy)benzyl]amino}ethoxy)-5,7-dimethyltricyclo[3.3.1.13,7]dec-1-yl]methyl}-5-methyl-1H-pyrazol-4-yl)pyridine-2-carboxylic acid;

3-(1-{[3-(2-{[4-(beta-D-allopyranosyloxy)benzyl]amino}ethoxy)-5,7-dimethyltricyclo[3.3.1.13,7]dec-1-yl]methyl}-5-methyl-1H-pyrazol-4-yl)-6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]pyridine-2-carboxylic acid;

3-{1-[(3-{2-[azetidin-3-yl(2-sulfoethyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}-6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]pyridine-2-carboxylic acid;

3-{1-[(3-{2-[(3-aminopropyl)(2-sulfoethyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}-6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]pyridine-2-carboxylic acid;

6-[1-(1,3-benzothiazol-2-ylcarbamoyl)-1,2,3,4-tetrahydroquinolin-7-yl]-3-{1-[(3-{2-[(2-carboxyethyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3-{2-[(N^6,N^6-dimethyl-L-lysyl)(methyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

3-{1-[(3-{2-[(3-aminopropyl)(methyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}-6-[1-(1,3-benzothiazol-2-ylcarbamoyl)-1,2,3,4-tetrahydroquinolin-7-yl]pyridine-2-carboxylic acid;

3-{1-[(3-{2-[azetidin-3-yl(methyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}-6-[1-(1,3-benzothiazol-2-ylcarbamoyl)-1,2,3,4-tetrahydroquinolin-7-yl]pyridine-2-carboxylic acid;

N^6-(37-oxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxaheptatriacontan-37-yl)-L-lysyl-N-[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.13,7]dec-1-yl}oxy)ethyl]-L-alaninamide;

methyl 6-[4-(3-{[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.13,7]dec-1-yl}oxy)ethyl]amino}propyl)-1H-1,2,3-triazol-1-yl]-6-deoxy-beta-L-glucopyranoside;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)naphthalen-2-yl]-3-{1-[(3-{2-[(2-carboxyethyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[5-(1,3-benzothiazol-2-ylcarbamoyl)quinolin-3-yl]-3-{1-[(3,5-dimethyl-7-{2-[(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[4-(1,3-benzothiazol-2-ylcarbamoyl)quinolin-6-yl]-3-{1-[(3,5-dimethyl-7-{2-[(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[5-(1,3-benzothiazol-2-ylcarbamoyl)quinolin-3-yl]-3-{1-[(3-{2-[(2-carboxyethyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[1-(1,3-benzothiazol-2-ylcarbamoyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl]-3-{1-[(3,5-dimethyl-7-{2-[(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

8-(1,3-benzothiazol-2-ylcarbamoyl)-2-{6-carboxy-5-[1-({3-[2-({3-[1-(beta-D-glucopyranuronosyl)-1H-1,2,3-triazol-4-yl]propyl}amino)ethoxy]-5,7-

AMENDED SHEET (ARTICLE 19)

dimethyltricyclo[3.3.1.13,7]dec-1-yl}methyl)-5-methyl-1H-pyrazol-4-yl]pyridin-2-yl}-1,2,3,4-tetrahydroisoquinoline;

6-[7-(1,3-benzothiazol-2-ylcarbamoyl)-1H-indol-2-yl]-3-{1-[(3,5-dimethyl-7-{2-[(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-6-[3-(methylamino)propyl]-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3,5-dimethyl-7-{2-[(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

5-{[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.13,7]dec-1-yl}oxy)ethyl]amino}-5-deoxy-D-arabinitol;

1-{[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.13,7]dec-1-yl}oxy)ethyl]amino}-1,2-dideoxy-D-arabino-hexitol;

6-[4-(1,3-benzothiazol-2-ylcarbamoyl)isoquinolin-6-yl]-3-{1-[(3,5-dimethyl-7-{2-[(2-sulfoethyl)amino]ethoxy}tricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-(1-{[3-(2-{[3-hydroxy-2-(hydroxymethyl)propyl]amino}ethoxy)-5,7-dimethyltricyclo[3.3.1.13,7]dec-1-yl]methyl}-5-methyl-1H-pyrazol-4-yl)pyridine-2-carboxylic acid;

1-{[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.13,7]dec-1-yl}oxy)ethyl]amino}-1,2-dideoxy-D-erythro-pentitol;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-(1-{[3,5-dimethyl-7-(2-{[(2S,3S)-2,3,4-trihydroxybutyl]amino}ethoxy)tricyclo[3.3.1.13,7]dec-1-yl]methyl}-5-methyl-1H-pyrazol-4-yl)pyridine-2-carboxylic acid;

6-[8 -(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-(1-{[3-(2-{[(2S,3S,4R,5R,6R)-2,3,4,5,6,7-hexahydroxyheptyl]amino}ethoxy)-5,7-dimethyltricyclo[3.3.1.13,7]dec-1-yl]methyl}-5-methyl-1H-pyrazol-4-yl)pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3-{2-[({3-[(1,3-dihydroxypropan-2-yl)amino]propyl}sulfonyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

AMENDED SHEET (ARTICLE 19)

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[(3-{2-[(3-{[1,3-dihydroxy-2-(hydroxymethyl)propan-2-yl]amino}-3-oxopropyl)amino]ethoxy}-5,7-dimethyltricyclo[3.3.1.13,7]dec-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]-3-(1-{[3-(2-{[(3*S*)-3,4-dihydroxybutyl]amino}ethoxy)-5,7-dimethyltricyclo[3.3.1.13,7]dec-1-yl]methyl}-5-methyl-1*H*-pyrazol-4-yl)pyridine-2-carboxylic acid;

4-({[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.13,7]dec-1-yl}oxy)ethyl]amino}methyl)phenyl beta-D-glucopyranosiduronic acid;

3-{[2-({3-[(4-{6-[8-(1,3-benzothiazol-2-ylcarbamoyl)naphthalen-2-yl]-2-carboxypyridin-3-yl}-5-methyl-1H-pyrazol-1-yl)methyl]-5,7-dimethyltricyclo[3.3.1.13,7]dec-1-yl}oxy)ethyl]amino}propyl beta-D-glucopyranosiduronic acid;

6-[4-(1,3-benzothiazol-2-ylcarbamoyl)-2-oxidoisoquinolin-6-yl]-3-[1-({3,5-dimethyl-7-[2-(methylamino)ethoxy]tricyclo[3.3.1.13,7]dec-1-yl}methyl)-5-methyl-1H-pyrazol-4-yl]pyridine-2-carboxylic acid;

6-{8-[(1,3-benzothiazol-2-yl)carbamoyl]-3,4-dihydroisoquinolin-2(1H)-yl}-3-{1-[(3,5-dimethyl-7-{2-[(2-sulfoethyl)amino]acetamido}tricyclo[3.3.1.13,7]decan-1-yl)methyl]-5-methyl-1H-pyrazol-4-yl}pyridine-2-carboxylic acid;

6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]-3-(1-{[3,5-dimethyl-7-({2-[(2-sulfoethyl)amino]ethyl}sulfanyl)tricyclo[3.3.1.13,7]dec-1-yl]methyl}-5-methyl-1*H*-pyrazol-4-yl)pyridine-2-carboxylic acid; and

6-{8-[(1,3-benzothiazol-2-yl)carbamoyl]-3,4-dihydroisoquinolin-2(1*H*)-yl}-3-{1-[(3,5-dimethyl-7-{3-[(2-sulfoethyl)amino]propyl}tricyclo[3.3.1.13,7]decan-1-yl)methyl]-5-methyl-1*H*-pyrazol-4-yl}pyridine-2-carboxylic acid.

13. A method for treating cancer, comprising administering a therapeutically effective amount of the ADC of claim 11 to a subject in need thereof.

14. A method for inhibiting or decreasing solid tumor growth in a subject having a solid tumor, said method comprising administering an effective amount of the ADC of claim 11 to the subject having the solid tumor, such that the solid tumor growth is inhibited or decreased.

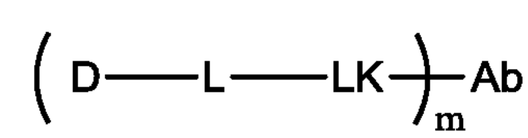
15. The method of claim 14, wherein the ADC is administered in combination with an additional agent or an additional therapy.

16. The isolated antibody according to claim 1, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 168 and a light chain comprising the amino acid sequence of SEQ ID NO: 169.

17. The isolated antibody according to claim 1, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 170 and a light chain comprising the amino acid sequence of SEQ ID NO: 171.

18. The isolated antibody according to claim 1 wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 172 and a light chain comprising the amino acid sequence of SEQ ID NO: 173.

19. A process for the preparation of an ADC according to structural formula (I):

(I) 

wherein:

D is the Bcl-xL inhibitor drug of formula (IIa), (IIb), (IIc), or (IId);

L is the linker;

Ab is an hB7-H3 antibody, wherein the hB7-H3 antibody comprises the heavy and light chain CDRs of huAb3v2.5, huAb3v2.6, or huAb13v1;

LK represents a covalent linkage linking linker L to antibody Ab; and

m is an integer ranging from 1 to 20;

the process comprising:

treating an antibody in an aqueous solution with an effective amount of a disulfide reducing agent at 30-40 °C for at least 15 minutes, and then cooling the antibody solution to 20-27 °C;

adding to the reduced antibody solution a solution of water/dimethyl sulfoxide comprising a synthon selected from the group of 2.1 to 2.176 (Table B);

adjusting the pH of the solution to a pH of 7.5 to 8.5;

allowing the reaction to run for 48 to 80 hours to form the ADC;

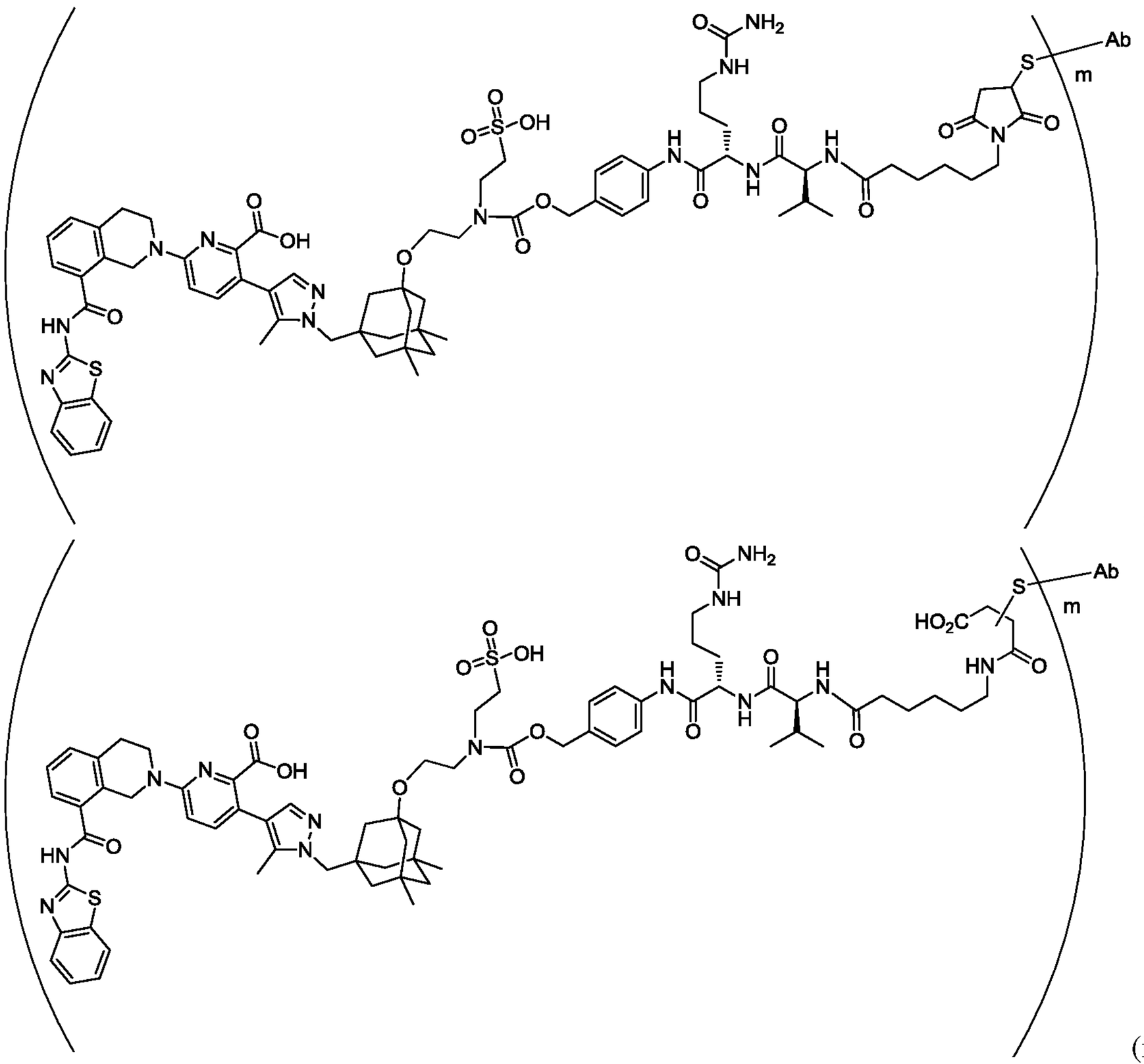
wherein the mass is shifted by 18 ± 2 amu for each hydrolysis of a succinimide to a succinamide as measured by electron spray mass spectrometry; and

wherein the ADC is optionally purified by hydrophobic interaction chromatography.

20. An ADC prepared by the process of claim 19.

21. An anti-human Epidermal Growth Factor Receptor (hEGFR) antibody drug conjugate (ADC) selected from the group consisting of

(1) formulae (i) or (ii):



(i), and

(ii),

wherein m is an integer from 1 to 6, optionally from 2 to 6; and

wherein Ab is an anti-hB7-H3 antibody comprising a heavy chain variable region and a light chain variable region selected from the group consisting of

a) a heavy chain CDR3 domain comprising the amino acid sequence set forth in SEQ ID NO: 35, a heavy chain CDR2 domain comprising the amino acid sequence set forth in SEQ ID NO: 34, and a heavy chain CDR1 domain comprising the amino acid sequence

AMENDED SHEET (ARTICLE 19)

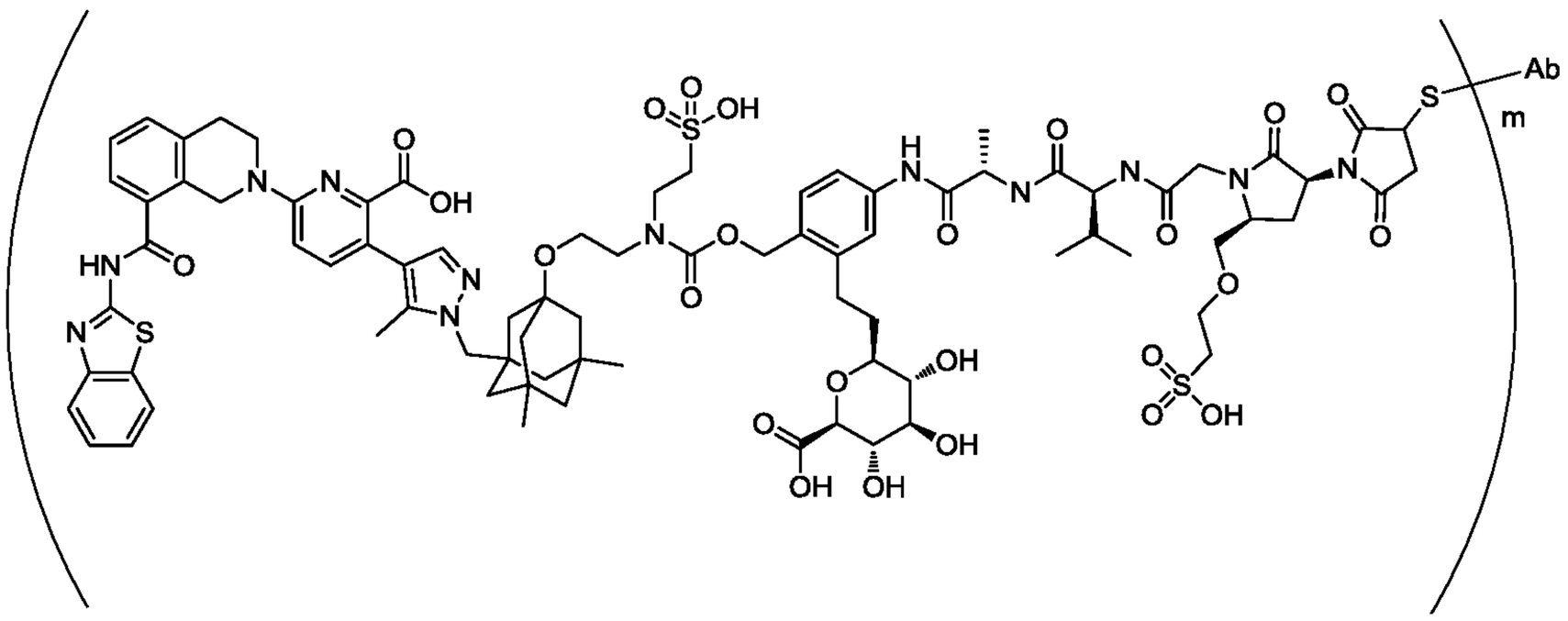
set forth in SEQ ID NO: 33; a light chain CDR3 domain comprising the amino acid sequence set forth in SEQ ID NO: 39, a light chain CDR2 domain comprising the amino acid sequence set forth in SEQ ID NO: 38, and a light chain CDR1 domain comprising the amino acid sequence set forth in SEQ ID NO: 37;

b) a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 147, and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 144;

c) a heavy chain CDR3 domain comprising the amino acid sequence set forth in SEQ ID NO: 12, a heavy chain CDR2 domain comprising the amino acid sequence set forth in SEQ ID NO: 140, and a heavy chain CDR1 domain comprising the amino acid sequence set forth in SEQ ID NO: 10; a light chain CDR3 domain comprising the amino acid sequence set forth in SEQ ID NO: 15, a light chain CDR2 domain comprising the amino acid sequence set forth in SEQ ID NO: 7, and a light chain CDR1 domain comprising the amino acid sequence set forth in SEQ ID NO: 136; and

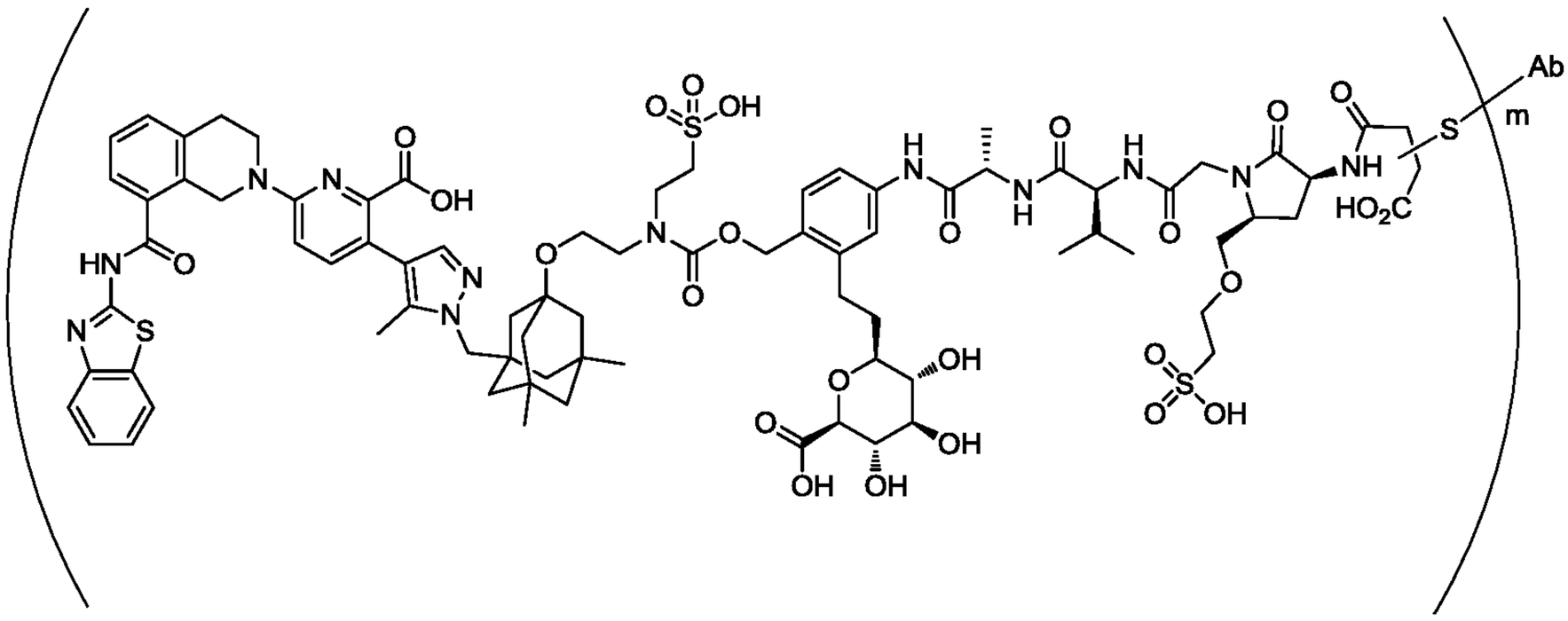
d) a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 139, and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 135;

(2) formulae (i) or (ii):



(i), and

AMENDED SHEET (ARTICLE 19)



(ii),

wherein m is an integer from 1 to 6, optionally from 2 to 6; and

wherein Ab is an anti-hB7-H3 antibody comprising a heavy chain variable region and a light chain variable region selected from the group consisting of

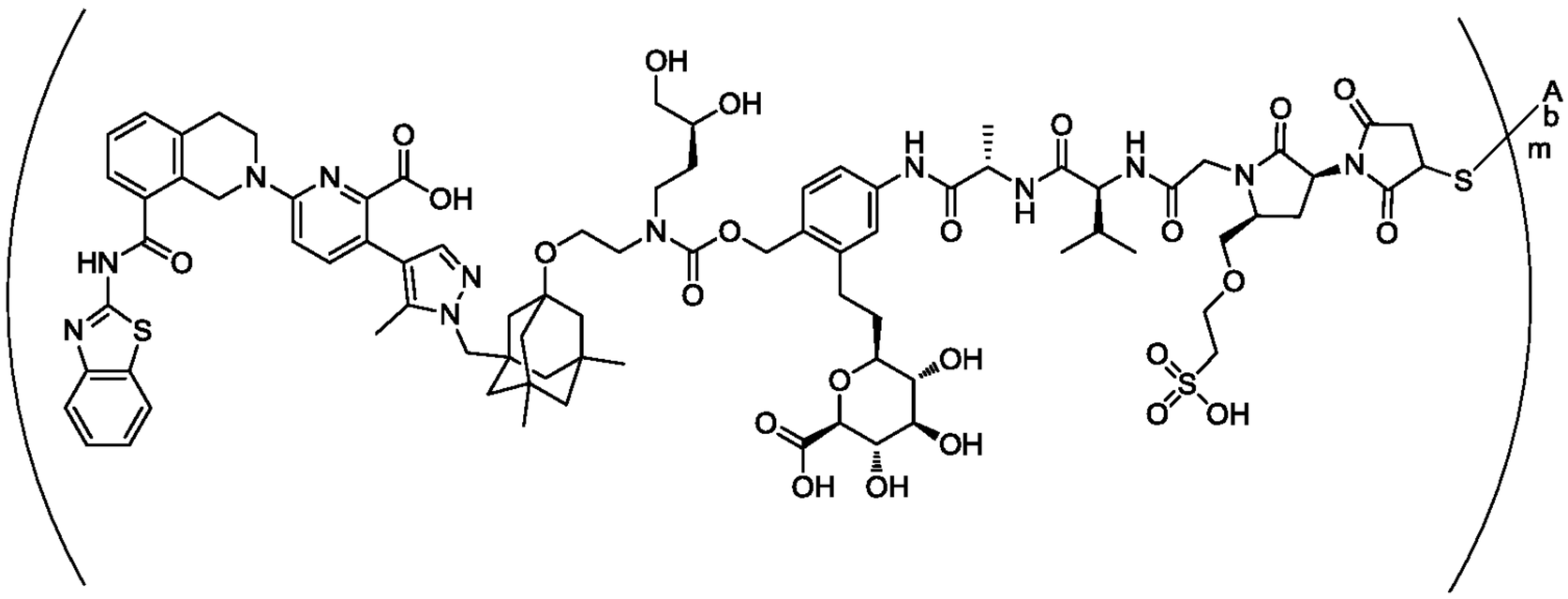
a) a heavy chain CDR3 domain comprising the amino acid sequence set forth in SEQ ID NO: 35, a heavy chain CDR2 domain comprising the amino acid sequence set forth in SEQ ID NO: 34, and a heavy chain CDR1 domain comprising the amino acid sequence set forth in SEQ ID NO: 33; a light chain CDR3 domain comprising the amino acid sequence set forth in SEQ ID NO: 39, a light chain CDR2 domain comprising the amino acid sequence set forth in SEQ ID NO: 38, and a light chain CDR1 domain comprising the amino acid sequence set forth in SEQ ID NO: 37;

b) a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 147, and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 144;

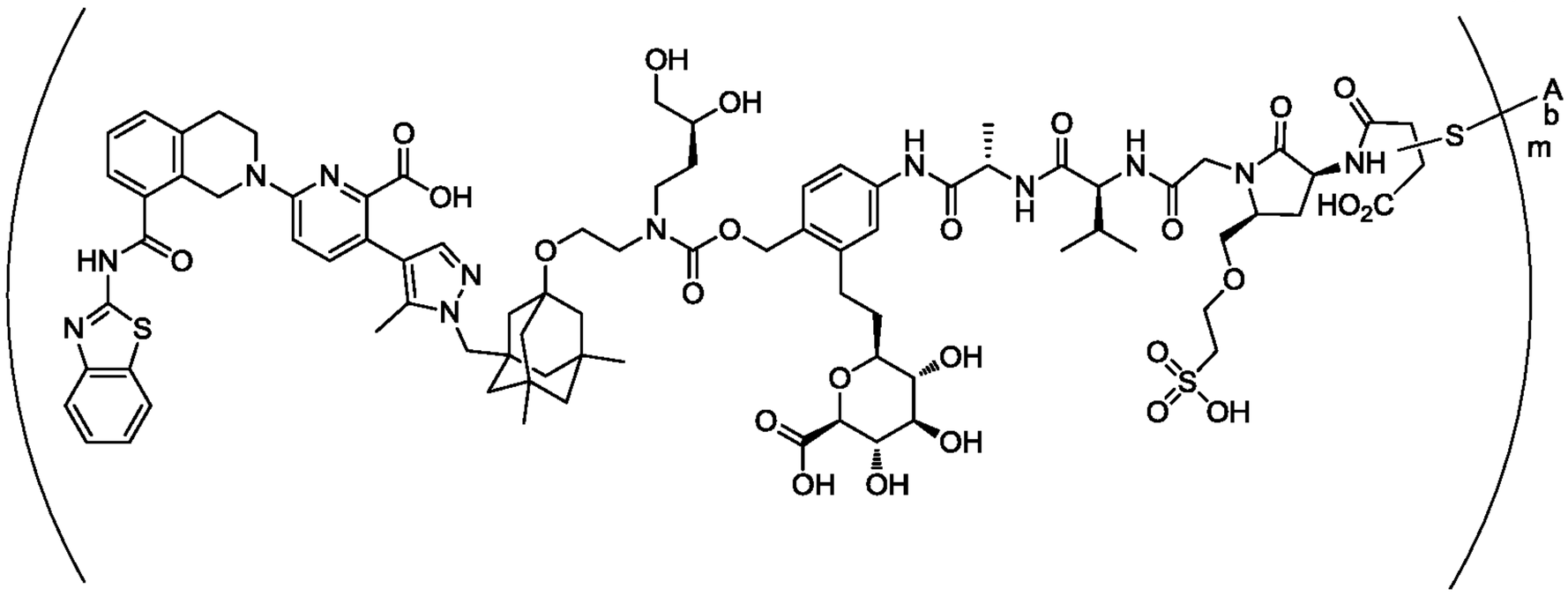
c) a heavy chain CDR3 domain comprising the amino acid sequence set forth in SEQ ID NO: 12, a heavy chain CDR2 domain comprising the amino acid sequence set forth in SEQ ID NO: 140, and a heavy chain CDR1 domain comprising the amino acid sequence set forth in SEQ ID NO: 10; a light chain CDR3 domain comprising the amino acid sequence set forth in SEQ ID NO: 15, a light chain CDR2 domain comprising the amino acid sequence set forth in SEQ ID NO: 7, and a light chain CDR1 domain comprising the amino acid sequence set forth in SEQ ID NO: 136; and

d) a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 139, and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 135; and

(3) formulae (i) or (ii):



(i), and



(ii),

wherein m is an integer from 1 to 6, optionally from 2 to 6; and

wherein Ab is an anti-hB7-H3 antibody comprising a heavy chain variable region and a light chain variable region selected from the group consisting of

a) a heavy chain CDR3 domain comprising the amino acid sequence set forth in SEQ ID NO: 35, a heavy chain CDR2 domain comprising the amino acid sequence set forth in SEQ ID NO: 34, and a heavy chain CDR1 domain comprising the amino acid sequence set forth in SEQ ID NO: 33; a light chain CDR3 domain comprising the amino acid sequence set forth in SEQ ID NO: 39, a light chain CDR2 domain comprising the amino acid sequence set forth in SEQ ID NO: 38, and a light chain CDR1 domain comprising the amino acid sequence set forth in SEQ ID NO: 37;

b) a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 147, and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 144;

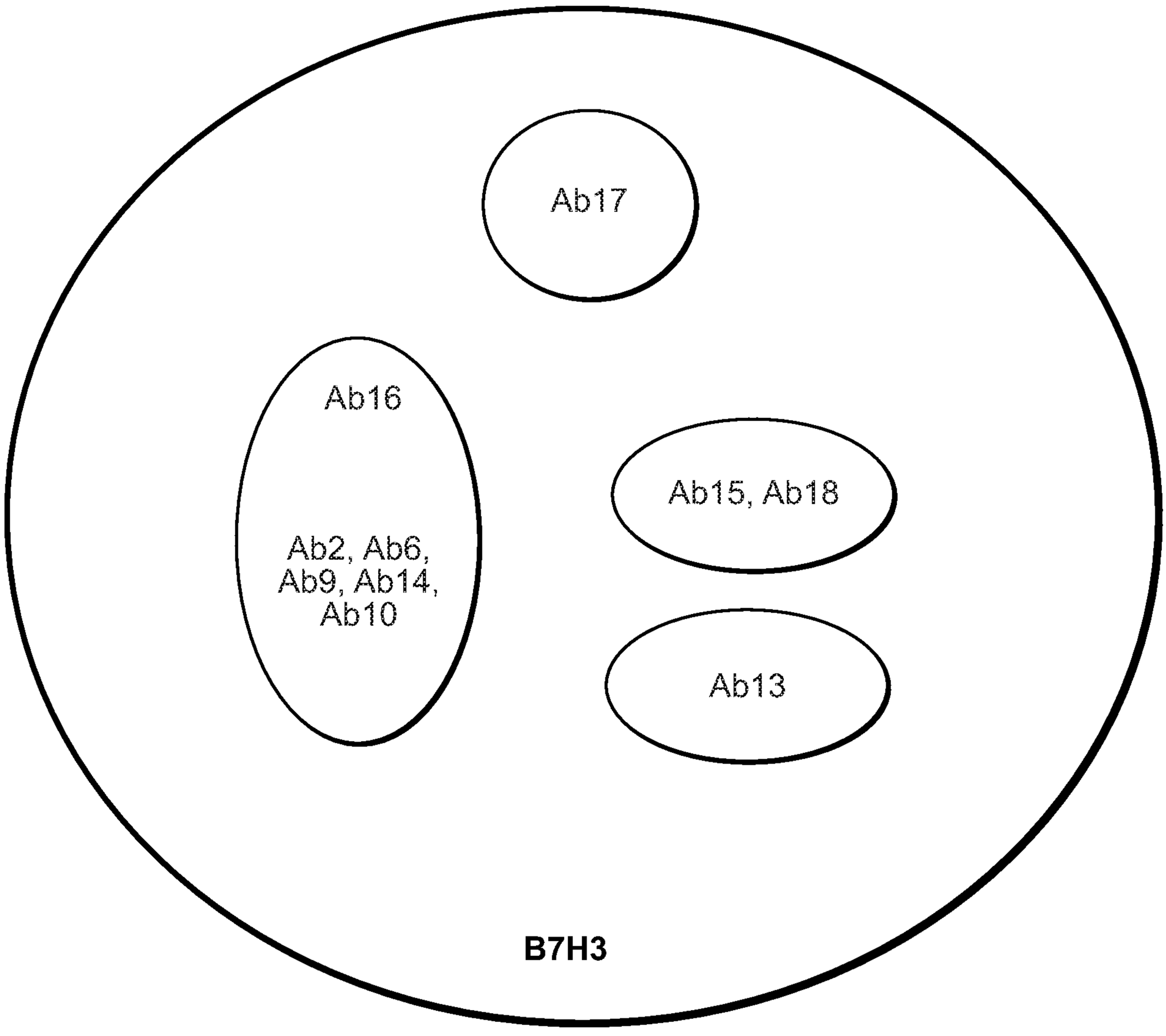
c) a heavy chain CDR3 domain comprising the amino acid sequence set forth in SEQ ID NO: 12, a heavy chain CDR2 domain comprising the amino acid sequence set forth in SEQ ID NO: 140, and a heavy chain CDR1 domain comprising the amino acid sequence set forth in SEQ ID NO: 10; a light chain CDR3 domain comprising the amino acid sequence set forth in SEQ ID NO: 15,

a light chain CDR2 domain comprising the amino acid sequence set forth in SEQ ID NO: 7, and a light chain CDR1 domain comprising the amino acid sequence set forth in SEQ ID NO: 136; and

d) a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 139, and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 135.

AMENDED SHEET (ARTICLE 19)

Figure 1



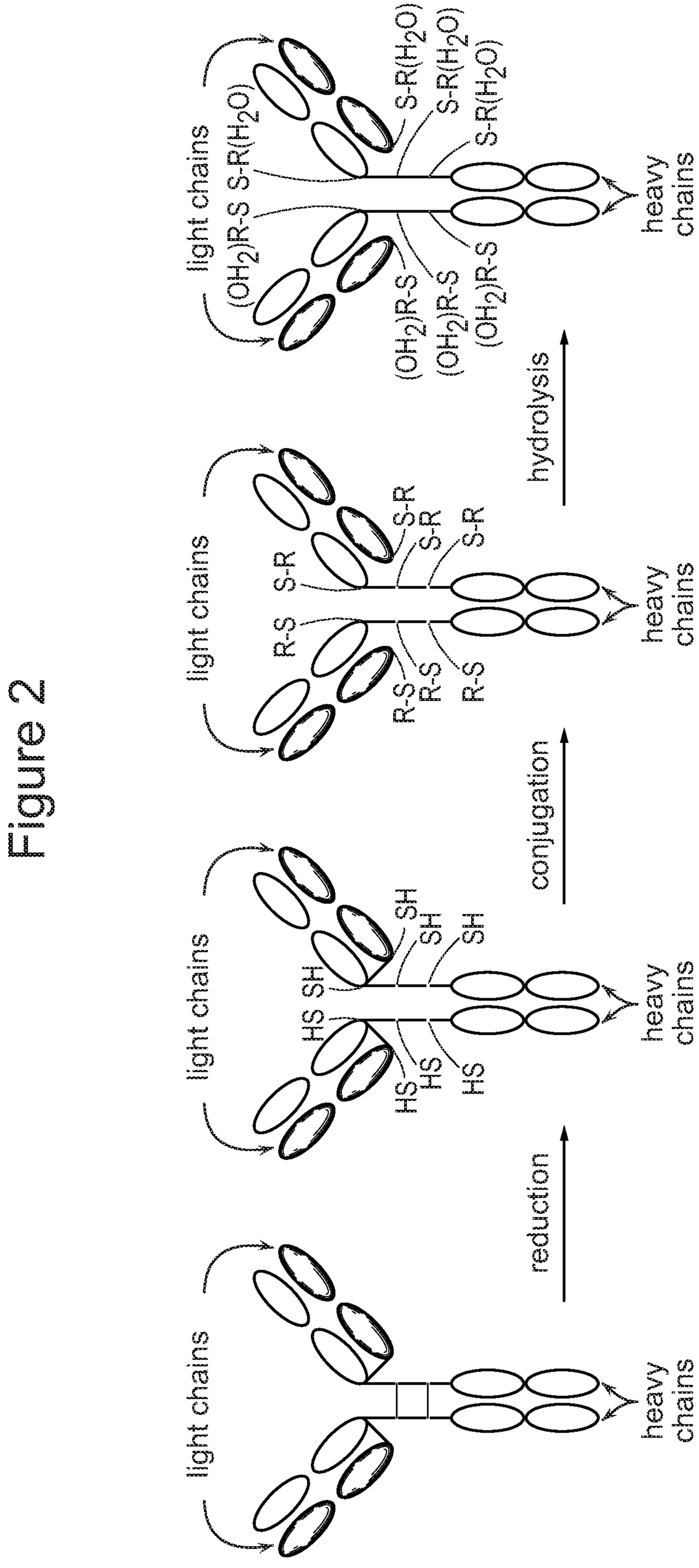
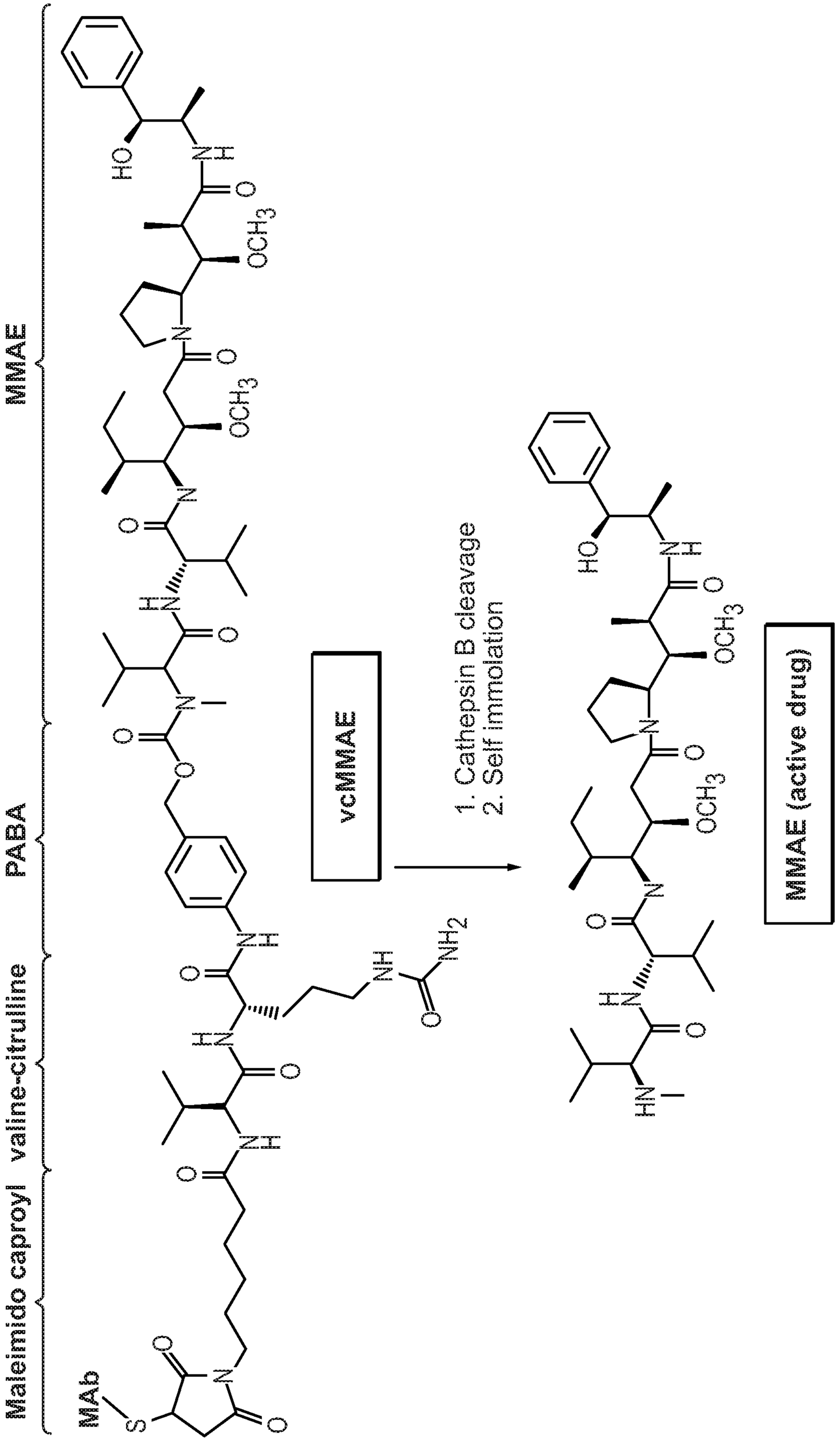

light chains
(OH2)R-S S-R(H2O)
(OH2)R-S
(OH2)R-S
(OH2)R-S
S-R(H2O)
S-R(H2O)
S-R(H2O)
heavy chains
hydrolysis
light chains
R-S S-R
R-S
R-S
R-S
S-R
S-R
S-R
heavy chains
conjugation
light chains
HS SH
HS
HS
HS
SH
SH
SH
heavy chains
reduction
light chains
heavy chains

Figure 2

Figure 3


MAE
PABA
valine-citrulline
Maleimido caproyl
vcMMAE
1. Cathepsin B cleavage
2. Self immolation
MMAE (active drug)
MAb

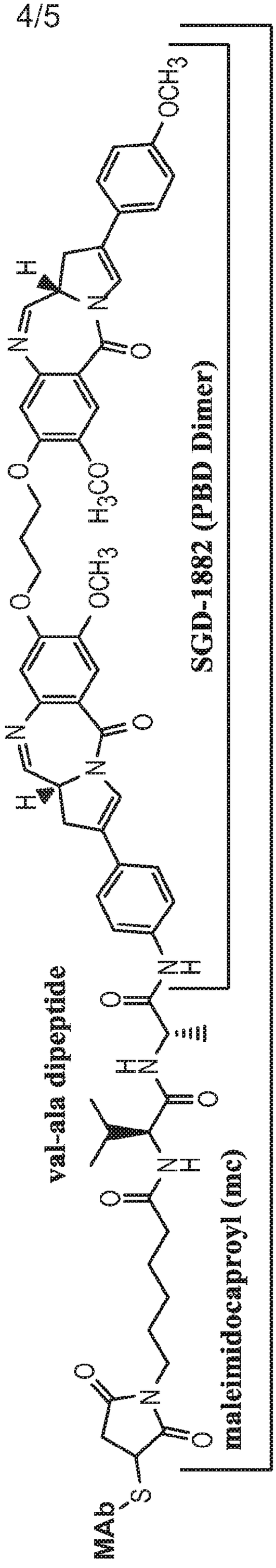

OCH3
H
N
N
O
O
H3CO
OCH3
O
O
N
H
N
O
O
N
H
N
O
O
N
O
MAb
S
SGD-1882 (PBD Dimer)
val-ala dipeptide
maleimidocaproyl (mc)
SGD-1910 (Drug Linker)

Figure 4

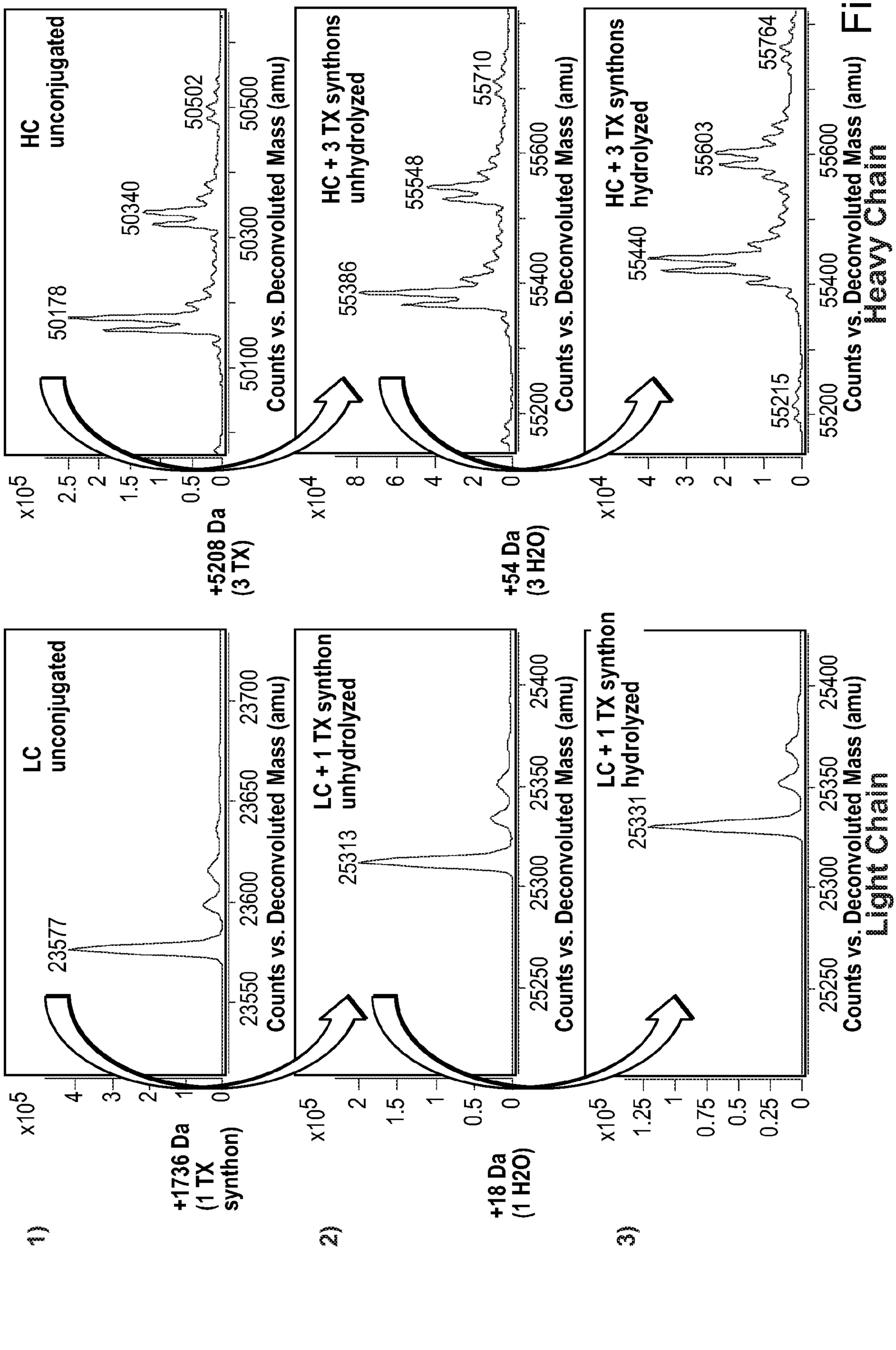

HC
unconjugated
50178
50340
50502
50100
50300
50500
Counts vs. Deconvoluted Mass (amu)
HC + 3 TX synthon
unhydrolyzed
55386
55548
55710
55200
55400
55600
Counts vs. Deconvoluted Mass (amu)
HC + 3 TX synthon
hydrolyzed
55440
55603
55764
55215
55400
55600
Counts vs. Deconvoluted Mass (amu)
Heavy Chain
+5208 Da
(3 TX)
+54 Da
(3 H2O)
LC
unconjugated
23577
23600
23650
23700
Counts vs. Deconvoluted Mass (amu)
LC + 1 TX synthon
unhydrolyzed
25313
25300
25350
25400
Counts vs. Deconvoluted Mass (amu)
LC + 1 TX synthon
hydrolyzed
25331
25300
25350
25400
Counts vs. Deconvoluted Mass (amu)
Light Chain
+1736 Da
(1 TX
synthon)
+18 Da
(1 H2O)
1)
2)
3)

Figure 5

Figure 1