MCL-1 INHIBITOR ANTIBODY-DRUG CONJUGATES AND METHODS OF USE

RELATED APPLICATION

[01] This application claims the benefit of and priority to the filing date under 35 U.S.C. §119(e) of US Provisional Application No. 62/850,098 filed on May 20, 2019, the entire content of which is incorporated herein by reference in its entirety.

SEQUENCE LISTING

[01a] The instant application contains a Sequence Listing which has been submitted as an amendment on 20 May 2022 and is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

[02] The present disclosure relates to antibody-drug conjugates (ADCs) comprising an Mcl-1 inhibitor and an anti-CD74 antibody or antigen-binding fragment thereof that binds an antigen target, e.g., an antigen expressed on a tumor or other cancer cell. The disclosure further relates to methods and compositions useful in the treatment and/or diagnosis of cancers that express the target antigen CD74 and/or are amenable to treatment by modulating Mcl-1 expression and/or activity, as well as methods of making those compositions. Linker-drug conjugates comprising an Mcl-1 inhibitor drug moiety and methods of making same are also disclosed.

BACKGROUND OF THE INVENTION

[03] Apoptosis, or programmed cell death, is a physiological process that is crucial for embryonic development and maintenance of tissue homeostasis. Apoptotic-type cell death generally involves morphological changes such as condensation of the nucleus and DNA fragmentation, as well as biochemical changes such as the activation of caspases that can cause damage to key structural components of the cell. Regulation of apoptosis is complex and typically involves the activation or repression of several intracellular signaling pathways (Cory et al. (2002) Nature Review Cancer 2:647-656).

[04] Deregulation of apoptosis is associated with certain pathologies. For instance, increased apoptosis is associated with neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, and ischemia. Conversely, deficits in apoptosis can play a role in the development of cancers and chemoresistance, autoimmune diseases, inflammatory diseases, and viral infections. The absence of apoptosis is one of the phenotypic signatures of cancer (Hanahan et al. (2000) Cell 100:57-70). Anti-apoptotic

[05] proteins of the Bcl-2 family are associated with numerous types of cancer, such as colon cancer, breast cancer, small cell lung cancer, non-small cell lung cancer, bladder cancer, ovarian cancer, prostate cancer, chronic lymphoid leukemia, lymphoma, myeloma, and pancreatic cancer.

[06] Myeloid cell leukemia 1 (Mcl-1), an anti-apoptotic Bcl-2 family member, is a regulator of cell survival. Amplification of the Mcl-1 gene and/or overexpression of the Mcl-1 protein has been observed in multiple cancer types and is commonly implicated in tumor development (Beroukhim et al. (2010) Nature 463(7283):899-905). Mcl-1 is one of the most frequently amplified genes in human cancer and is also a critical survival factor that has been shown to mediate drug resistance to a variety of anti-cancer agents.

[07] Mcl-1 is believed to promote cell survival by binding to and neutralizing the death-inducing activities of pro-apoptotic proteins such as Bim, Noxa, Bak, and Bax. Inhibition of Mcl-1 releases these pro-apoptotic proteins, often leading to the induction of apoptosis in tumor cells dependent on Mcl-1 for survival. Therapeutically targeting Mcl-1 or proteins upstream and/or downstream of it in an apoptotic signaling pathway, therefore, may represent promising strategies to treat various malignancies and to overcome drug resistance in certain human cancers.

[08] CD74 (DHLAG) is an established and attractive target for antibody drug conjugates due to its restricted expression on normal tissues and significant upregulation in a range of hematological malignancies. CD74 functions as a chaperone that is necessary for the assembly and trafficking of MHC class II complexes as well as a receptor for macrophage migration inhibitory receptor (MIF). In oncology, it has been well established that CD74 is significantly upregulated at both the RNA and protein level in a range of B-cell and myeloid cell malignancies including acute myeloid leukemia, multiple myeloma, and diffuse large B-cell lymphoma. Additionally CD74 is known to rapidly internalize upon antibody engagement and traffic to the lysosome as well as to to be rapidly repopulated on the surface of tumor cells following internalization. Antibodies and antibody drug conjugates targeting CD74 have been shown previously to demonstrate anti-tumor activity in preclinical models of cancer.

SUMMARY

[07a] In one aspect, the present disclosure provides an antibody-drug conjugate of Formula (1):

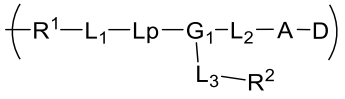
$$Ab\text{-}(L\text{-}D)_p \qquad (1)$$

wherein:

Ab is an anti-CD74 antibody or an antigen-binding fragment thereof;

p is an integer from 1 to 16; and

-(L-D) is of the formula (C):



(C),

wherein:

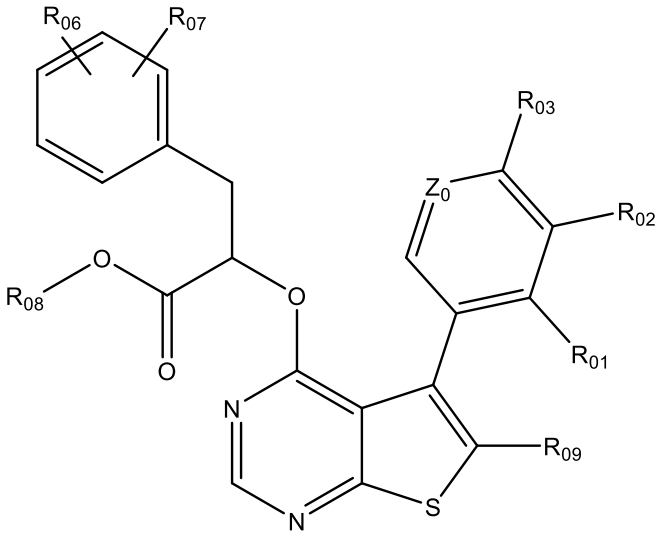
L is a linker;

R^1 is an attachment group;

L_1 is a bridging spacer;

L_p is a peptide group comprising 1 to 6 amino acids;

D is an Mcl-1 inhibitor; wherein the Mcl-1 inhibitor is a compound of Formula (II):



(II)

wherein:

Z_0 is a nitrogen atom or a C-R_{04} group,

R_{01} is a halogen atom, a linear or branched (C_1-C_6)alkyl group, a linear or branched (C_2-C_6)alkenyl group, a linear or branched (C_2-C_6)alkynyl group, a linear or branched (C_1-C_6)haloalkyl group, a hydroxy group, a linear or branched (C_1-C_6)alkoxy group, a -S-(C_1-C_6)alkyl group, a cyano group, -Cy_{08}, -$NR_{011}R_{011}$',

R_{02}, R_{03} and R_{04} independently of one another are a hydrogen atom, a halogen atom, a linear or branched (C_1-C_6)alkyl group, a linear or branched (C_2-C_6)alkenyl group, a linear or branched (C_2-C_6)alkynyl group, a linear or branched (C_1-C_6)haloalkyl, a hydroxy group, a linear or branched (C_1-C_6)alkoxy group, a -S-(C_1-C_6)alkyl group, a cyano group, a nitro group, -(C_0-C_6)alkyl-$NR_{011}R_{011}$', -O-Cy_{01}, -(C_0-C_6)alkyl-Cy_{01}, -(C_2-C_6)alkenyl-Cy_{01}, -(C_2-C_6)alkynyl-Cy_{01}, -O-(C_1-C_6)alkyl-$NR_{011}R_{011}$', -O-(C_1-C_6)alkyl-R_{031}, -C(O)-OR_{011}, -O-C(O)-R_{011}, -C(O)-$NR_{011}R_{011}$', -NR_{011}-C(O)-R_{011}', -NR_{011}-C(O)-OR_{011}', -(C_1-C_6)alkyl-NR_{011}-C(O)-R_{011}', -SO_2-$NR_{011}R_{011}$', or -SO_2-(C_1-C_6)alkyl,

or the pair (R_{02}, R_{03}) or (R_{03}, R_{04}) together with the carbon atoms to which they are attached form an aromatic or non-aromatic ring containing 5 to 7 ring members, which optionally contains 1 to 3 heteroatoms selected from O, S and N, wherein the ring is optionally substituted by a group selected from a linear or branched (C_1-C_6)alkyl, -$NR_{013}R_{013}$', -(C_0-C_6)alkyl-Cy_{01} and oxo,

R_{06} and R_{07} independently of one another are a hydrogen atom, a halogen atom, a linear or branched (C_1-C_6)alkyl group, a linear or branched (C_2-C_6)alkenyl group, a linear or branched (C_2-C_6)alkynyl group, a linear or branched (C_1-C_6)haloalkyl, a hydroxy group, a linear or branched (C_1-C_6)alkoxy group, a -S-(C_1-C_6)alkyl group, a cyano group, a nitro group, -(C_0-C_6)alkyl-$NR_{011}R_{011}$', -O-Cy_{01}, -(C_0-C_6)alkyl-Cy_{01}, -(C_2-C_6)alkenyl-Cy_{01}, -(C_2-C_6)alkynyl-Cy_{01}, -O-(C_1-C_6)alkyl-R_{012}, -C(O)-OR_{011}, -O-C(O)-R_{011}, -C(O)-$NR_{011}R_{011}$', -NR_{011}-C(O)-R_{011}', -NR_{011}-C(O)-OR_{011}', -(C_1-C_6)alkyl-NR_{011}-C(O)-R_{011}', -SO_2-$NR_{011}R_{011}$', or -SO_2-(C_1-C_6)alkyl,

or the pair (R_{06}, R_{07}), when fused with two adjacent carbon atoms, together with the carbon atoms to which they are attached form an aromatic or non-aromatic ring containing 5 to 7 ring members, which optionally contains 1 to 3 heteroatoms selected from O, S and N, and wherein the resulting ring is optionally substituted by a group selected from a linear or branched (C_1-C_6)alkyl group, -$NR_{013}R_{013}$', -(C_0-C_6)alkyl-Cy_{01} and an oxo,

R_{08} is a hydrogen atom, a linear or branched (C_1-C_8)alkyl group, an aryl group, a heteroaryl group, an aryl-(C_1-C_6)alkylgroup, or a heteroaryl(C_1-C_6)alkyl group,

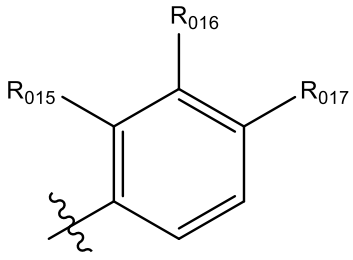
R_{09} is a linear or branched (C_1-C_6)alkyl group, a linear or branched (C_2-C_6)alkenyl group, a linear or branched (C_2-C_6)alkynyl group, -Cy_{02}, -(C_1-C_6)alkyl-Cy_{02}, -(C_2-C_6)alkenyl-Cy_{02}, -(C_2-C_6)alkynyl-Cy_{02}, -Cy_{02}-Cy_{03}, -(C_2-C_6)alkynyl-O-Cy_{02}, -Cy_{02}-(C_0-C_6)alkyl-O-(C_0-C_6)alkyl-Cy_{03}, a halogen atom, a cyano group, -C(O)-R_{014}, -C(O)-$NR_{014}R_{014}$',

R_{011} and R_{011}' independently of one another are a hydrogen atom, an optionally substituted linear or branched (C_1-C_6)alkyl group, or -(C_0-C_6)alkyl-Cy_{01}, or the pair (R_{011}, R_{011}') together with the nitrogen atom to which they are attached form an aromatic or non-aromatic ring containing 5 to 7 ring members, which optionally contains, in addition to the nitrogen atom, 1 to 3 heteroatoms selected from O, S and N, wherein the N atom is optionally substituted by a linear or branched (C_1-C_6)alkyl group, and wherein one or more of the carbon atoms of the linear or branched (C_1-C_6)alkyl group is optionally deuterated,

R_{012} is -Cy_{05}, -Cy_{05}-(C_0-C_6)alkyl-Cy_{06}, -Cy_{05}-(C_0-C_6)alkyl-O-(C_0-C_6)alkyl-Cy_{06}, -Cy_{05}-(C_0-C_6)alkyl-NR_{011}-(C_0-C_6)alkyl-Cy_{06}, -Cy_{05}-Cy_{06}-O-(C_0-C_6)alkyl-Cy_{07}, -Cy_{05}-(C_0-C_6)alkyl-Cy_{09}, -NH-C(O)-NH-R_{011}, -C(O)-$NR_{011}R_{011}$', -$NR_{011}R_{011}$', -OR_{011}, -NR_{011}-C(O)-R_{011}', -O-(C_1-C_6)alkyl-OR_{011}, -SO_2-R_{011}, or -C(O)-OR_{011},

R_{013}, R_{013}', R_{014} and R_{014}' independently of one another are a hydrogen atom, or an optionally substituted linear or branched (C_1-C_6)alkyl group,

Cy_{01}, Cy_{02}, Cy_{03}, Cy_{05}, Cy_{06}, Cy_{07} and Cy_{08} independently of one another, are a cycloalkyl group, a heterocycloalkyl group, an aryl group or a heteroaryl group, each of which is optionally substituted,

Cy_{09} is , wherein

R_{015} is a hydrogen atom; a $-(CH_2)_{p0}$-O-$(CHR_{018}$-CHR_{019}-O$)_{q0}$-R_{020} group; a linear or branched $(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkyl group; a $-U_0$-$(CH_2)_{q0}$-$NR_{021}R_{021}$' group; or a $-(CH_2)_{r0}$-U_0-$(CH_2)_{s0}$-heterocycloalkyl group,

R_{016} is a hydrogen atom; a hydroxy group; a hydroxy$(C_1$-$C_6)$alkyl group; a $-(CH_2)_{r0}$-U_0-$(CH_2)_{s0}$-heterocycloalkyl group; a $(CH_2)_{r0}$-U_0-V_0-O-P(O)$(OR_{020})_2$ group; a -O-P(O)$(O^-M^+)_2$ group; a -O-S(O)$_2OR_{020}$ group; a -S(O)$_2OR_{020}$ group; a $-(CH_2)_{p0}$-O-$(CHR_{018}$-CHR_{019}-O$)_{q0}$-R_{020} group; a $-(CH_2)_{p0}$-O-C(O)-$NR_{022}R_{023}$ group; or a $-U_0$-$(CH_2)_{q0}$-$NR_{021}R_{021}$' group,

R_{017} is a hydrogen atom; a $-(CH_2)_{p0}$-O-$(CHR_{018}$-CHR_{019}-O$)_{q0}$-R_{020} group; a -CH_2-P(O)$(OR_{020})_2$ group, a -O-P(O)$(OR_{020})_2$ group; a -O-P(O)$(O^-M^+)_2$ group; a hydroxy group; a hydroxy$(C_1$-$C_6)$alkyl group; a $-(CH_2)_{r0}$-U_0-$(CH_2)_{s0}$-heterocycloalkyl group; a $-U_0$-$(CH_2)_{q0}$-$NR_{021}R_{021}$' group; or an aldonic acid,

M^+ is a pharmaceutically acceptable monovalent cation,

U_0 is a bond or an oxygen atom,

V_0 is a $-(CH_2)_{s0}$- group or a -C(O)- group,

R_{018} is a hydrogen atom or a $(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkyl group,

R_{019} is a hydrogen atom or a hydroxy$(C_1$-$C_6)$alkyl group,

R_{020} is a hydrogen atom or a linear or branched $(C_1$-$C_6)$alkyl group,

R_{021} and R_{021}' independently of one are a hydrogen atom, a linear or branched $(C_1$-$C_6)$alkyl group, or a hydroxy$(C_1$-$C_6)$alkyl group,

or the pair (R_{021}, R_{021}') together with the nitrogen atom to which they are attached form an aromatic or non-aromatic ring containing 5 to 7 ring members, which optionally contains, in addition to the nitrogen atom, 1 to 3 heteroatoms selected from O, S and N, wherein the resulting ring is optionally substituted by a hydrogen atom or a linear or branched $(C_1$-$C_6)$alkyl group,

R_{022} is a $(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkyl group, a $-(CH_2)_{p0}$-$NR_{024}R_{024}$' group, or a $-(CH_2)_{p0}$-O-$(CHR_{018}$-CHR_{019}-O$)_{q0}$-R_{20} group,

R_{023} is a hydrogen atom or a $(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkyl group,

or the pair (R_{022}, R_{023}) together with the nitrogen atom to which they are attached form an aromatic or non-aromatic ring containing 5 to 18 ring members, which optionally contains, in addition to the nitrogen atom, 1 to 5 heteroatoms selected from O, S and N, wherein the resulting ring is optionally substituted by a hydrogen atom, a linear or branched (C_1-C_6)alkyl group or a heterocycloalkyl group,

R_{024} and R_{024}' independently of one another are a hydrogen atom or a linear or branched (C_1-C_6)alkyl group,

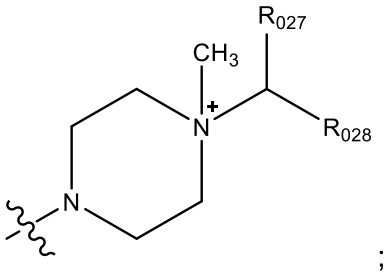
or the pair (R_{024}, R_{024}') together with the nitrogen atom to which they are attached form an aromatic or non-aromatic ring composed of from 5 to 7 ring members, which may contain in addition to the nitrogen atom from 1 to 3 heteroatoms selected from O, S and N, and wherein the resulting ring is optionally substituted by a hydrogen atom or a linear or branched (C_1-C_6)alkyl group,

R_{027} is a hydrogen atom or a linear or branched (C_1-C_6)alkyl group,

R_{028} is a -O-P(O)(O^-)(O^-) group, a -O-P(O)(O^-)(OR_{030}) group, a -O-P(O)(OR_{030})(OR_{030}') group, a -$(CH_2)_{p0}$-O-SO_2-O^- group, a -$(CH_2)_{p0}$-SO_2-O^- group, a -$(CH_2)_{p0}$-O-SO_2-OR_{030} group, -Cy_{010}, a -$(CH_2)_{p0}$-SO_2-OR_{030} group, a -O-C(O)-R_{029} group, a -O-C(O)-OR_{029} group or a -O-C(O)-$NR_{029}R_{029}$' group;

R_{029} and R_{029}' independently of one another are a hydrogen atom, a linear or branched (C_1-C_6)alkyl group or a linear or branched amino(C_1-C_6)alkyl group,

R_{030} and R_{030}' independently of one another are a hydrogen atom, a linear or branched (C_1-C_6)alkyl group or an aryl(C_1-C_6)alkylgroup,

R_{031} is 

;

p_0 is an integer equal to 0, 1, 2, or 3;

q_0 is an integer equal to 1, 2, 3 or 4;

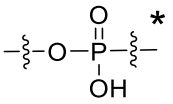
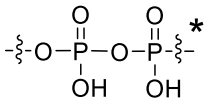
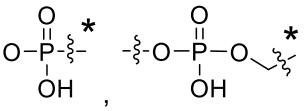
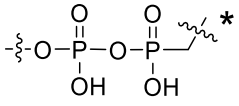
r_0 and s_0 are independently an integer equal to 0 or 1;

wherein one of the R_{03}, R_{09}, or R_{012} groups, if present, is covalently attached to the linker,

or an enantiomer, diastereoisomer, atropisomer, deuterated derivative, and/or pharmaceutically acceptable salt of any of the foregoing;

G_1-L_2-A is a self-immolative spacer;

L_2 is a bond, a methylene, a neopentylene or a C_2-C_3 alkenylene;

A is a bond, -OC(=O)-*,  ,  ,  ,  , -OC(=O)N(CH_3)CH_2CH_2N(CH_3)C(=O)-* or -OC(=O)N(CH_3)C(R^a)$_2$C(R^a)$_2$N(CH_3)C(=O)-*,

wherein each R^a is independently selected from H, C_1-C_6 alkyl, and C_3-C_8 cycloalkyl and the * of A indicates the point of attachment to D;

L_3 is a spacer moiety; and

R^2 is a hydrophilic moiety.

[07b] In another aspect, the present disclosure provides a composition comprising multiple copies of the antibody-drug conjugate as described herein, wherein the average p of the antibody-drug conjugates in the composition is from about 2 to about 16, e.g., about 2 to about 8, e.g., about 2 to about 4.

[07c] In another aspect, the present disclosure provides a pharmaceutical composition comprising the antibody-drug conjugate or the composition as described herein, and a pharmaceutically acceptable carrier.

[07d] In another aspect, the present disclosure provides a use of the antibody-drug conjugate, the composition, or the pharmaceutical composition as described herein in the manufacture of a medicament for treating a subject having or suspected of having a cancer, wherein a therapeutically effective amount of the antibody-drug conjugate, the composition, or the pharmaceutical composition as described herein is to be administered to the subject; preferably, wherein:

(1) the cancer expresses CD74; or

(2) the cancer is a tumor or a hematological cancer, preferably, the cancer is a breast cancer, multiple myeloma, plasma cell myeloma, leukemia, lymphoma, gastric cancer, acute myeloid leukemia, bladder cancer, brain cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell

lung cancer, chronic lymphocytic leukemia, prostate cancer, small cell lung cancer, or spleen cancer; and/or (3) at least one additional therapeutic agent is to be further administered to the subject in need thereof, preferably the one additional therapeutic agent is a Bcl-2 inhibitor, more preferably the one additional therapeutic agent is venetoclax, compound A1 or compound A2.

[07e] In another aspect, the present disclosure provides a use of the antibody-drug conjugate, the composition, or the pharmaceutical composition as described herein in the manufacture of a medicament for reducing or inhibiting the growth of a tumor or reducing or slowing the expansion of a cancer cell population in a subject, wherein a therapeutically effective amount of the antibody-drug conjugate, the composition, or the pharmaceutical composition as described herein is to be administered to the subject; preferably, wherein:
(1) the tumor or the cancer cell population expresses CD74;
(2) the tumor is a breast cancer, gastric cancer, bladder cancer, brain cancer, cervical cancer, colorectal cancer, esophageal cancer, hepatocellular cancer, melanoma, oral cancer, ovarian cancer, non-small cell lung cancer, prostate cancer, small cell lung cancer, or spleen cancer, or the cancer cell population is from a tumor or a hematological cancer, preferably the cancer cell population is from a breast cancer, multiple myeloma, plasma cell myeloma, leukemia, lymphoma, gastric cancer, acute myeloid leukemia, bladder cancer, brain cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, chronic lymphocytic leukemia, prostate cancer, small cell lung cancer, or spleen cancer; or
(3) administration of the antibody-drug conjugate, composition, or pharmaceutical composition reduces or inhibits the growth of the tumor or reduces the cancer cell population or slows the expansion of the cancer cell population by at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, or at least about 99%; and/or (4) at least one additional therapeutic agent is to be further administered to the subject in need thereof, preferably the one additional therapeutic agent is a Bcl-2 inhibitor, more preferably the one additional therapeutic agent is venetoclax, compound A1 or compound A2.

[07f] In another aspect, the present disclosure provides a method of determining whether a subject having or suspected of having a cancer will be responsive to treatment with the antibody-drug conjugate, the composition, or the pharmaceutical composition as described herein, comprising providing a biological sample obtained from the subject; contacting the

sample with the antibody-drug conjugate; and detecting binding of the antibody-drug conjugate to cancer cells in the sample, preferably wherein:

(1) the cancer cells in the sample express CD74;

(2) the cancer expresses CD74;

(3) the cancer is a tumor or a hematological cancer, preferably the cancer is a breast cancer, multiple myeloma, plasma cell myeloma, leukemia, lymphoma, gastric cancer, acute myeloid leukemia, bladder cancer, brain cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, chronic lymphocytic leukemia, prostate cancer, small cell lung cancer, or spleen cancer; and/or

(4) the sample is a tissue biopsy sample, a blood sample, or a bone marrow sample.

[07g] In another aspect, the present disclosure provides a method of producing the antibody-drug conjugate as described herein, comprising reacting an antibody or antigen-binding fragment with a cleavable linker joined to an MCL1 inhibitor under conditions that allow conjugation.

[07h] In another aspect, the present disclosure provides an antibody-drug conjugate of Formula (1):

$$Ab\text{-}(L\text{-}D)_p \qquad (1)$$

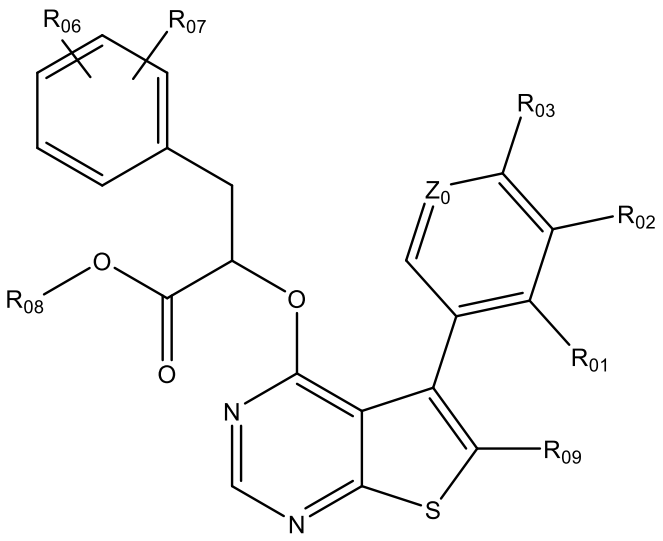
wherein:

Ab is an anti-CD74 antibody or an antigen-binding fragment thereof, optionally wherein the Ab is a Fc silent antibody;

p is an integer from 1 to 16;

L is a linker; and

D is an MCL1 inhibitor compound; wherein the Mcl-1 inhibitor is a compound of Formula (II):



(II)

wherein:

Z_0 is a nitrogen atom or a C-R_{04} group,

R_{01} is a halogen atom, a linear or branched (C_1-C_6)alkyl group, a linear or branched (C_2-C_6)alkenyl group, a linear or branched (C_2-C_6)alkynyl group, a linear or branched (C_1-C_6)haloalkyl group, a hydroxy group, a linear or branched (C_1-C_6)alkoxy group, a -S-(C_1-C_6)alkyl group, a cyano group, -Cy_{08}, -$NR_{011}R_{011}$',

R_{02}, R_{03} and R_{04} independently of one another are a hydrogen atom, a halogen atom, a linear or branched (C_1-C_6)alkyl group, a linear or branched (C_2-C_6)alkenyl group, a linear or branched (C_2-C_6)alkynyl group, a linear or branched (C_1-C_6)haloalkyl, a hydroxy group, a linear or branched (C_1-C_6)alkoxy group, a -S-(C_1-C_6)alkyl group, a cyano group, a nitro group, -(C_0-C_6)alkyl-$NR_{011}R_{011}$', -O-Cy_{01}, -(C_0-C_6)alkyl-Cy_{01}, -(C_2-C_6)alkenyl-Cy_{01}, -(C_2-C_6)alkynyl-Cy_{01}, -O-(C_1-C_6)alkyl-$NR_{011}R_{011}$', -O-(C_1-C_6)alkyl-R_{031}, -C(O)-OR_{011}, -O-C(O)-R_{011}, -C(O)-$NR_{011}R_{011}$', -NR_{011}-C(O)-R_{011}', -NR_{011}-C(O)-OR_{011}', -(C_1-C_6)alkyl-NR_{011}-C(O)-R_{011}', -SO_2-$NR_{011}R_{011}$', or -SO_2-(C_1-C_6)alkyl,

or the pair (R_{02}, R_{03}) or (R_{03}, R_{04}) together with the carbon atoms to which they are attached form an aromatic or non-aromatic ring containing 5 to 7 ring members, which optionally contains 1 to 3 heteroatoms selected from O, S and N, wherein the ring is optionally substituted by a group selected from a linear or branched (C_1-C_6)alkyl, -$NR_{013}R_{013}$', -(C_0-C_6)alkyl-Cy_{01} and oxo,

R_{06} and R_{07} independently of one another are a hydrogen atom, a halogen atom, a linear or branched (C_1-C_6)alkyl group, a linear or branched (C_2-C_6)alkenyl group, a linear or branched (C_2-C_6)alkynyl group, a linear or branched (C_1-C_6)haloalkyl, a hydroxy group, a linear or branched (C_1-C_6)alkoxy group, a -S-(C_1-C_6)alkyl group, a cyano group, a nitro group, -(C_0-C_6)alkyl-$NR_{011}R_{011}$',

-O-Cy_{01}, -(C_0-C_6)alkyl-Cy_{01}, -(C_2-C_6)alkenyl-Cy_{01}, -(C_2-C_6)alkynyl-Cy_{01}, -O-(C_1-C_6)alkyl-R_{012}, -C(O)-OR_{011}, -O-C(O)-R_{011}, -C(O)-$NR_{011}R_{011}$', -NR_{011}-C(O)-R_{011}', -NR_{011}-C(O)-OR_{011}', -(C_1-C_6)alkyl-NR_{011}-C(O)-R_{011}', -SO_2-$NR_{011}R_{011}$', or -SO_2-(C_1-C_6)alkyl,

or the pair (R_{06}, R_{07}), when fused with two adjacent carbon atoms, together with the carbon atoms to which they are attached form an aromatic or non-aromatic ring containing 5 to 7 ring members, which optionally contains 1 to 3 heteroatoms selected from O, S and N, and wherein the resulting ring is optionally substituted by a group selected from a linear or branched (C_1-C_6)alkyl group, -$NR_{013}R_{013}$', -(C_0-C_6)alkyl-Cy_{01} and an oxo,

R_{08} is a hydrogen atom, a linear or branched (C_1-C_8)alkyl group, an aryl group, a heteroaryl group, an aryl-(C_1-C_6)alkylgroup, or a heteroaryl(C_1-C_6)alkyl group,

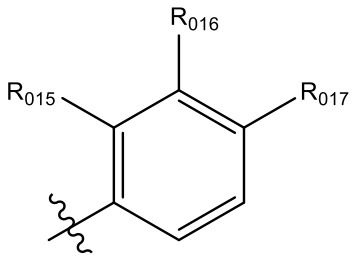
R_{09} is a linear or branched (C_1-C_6)alkyl group, a linear or branched (C_2-C_6)alkenyl group, a linear or branched (C_2-C_6)alkynyl group, -Cy_{02}, -(C_1-C_6)alkyl-Cy_{02}, -(C_2-C_6)alkenyl-Cy_{02}, -(C_2-C_6)alkynyl-Cy_{02}, -Cy_{02}-Cy_{03}, -(C_2-C_6)alkynyl-O-Cy_{02}, -Cy_{02}-(C_0-C_6)alkyl-O-(C_0-C_6)alkyl-Cy_{03}, a halogen atom, a cyano group, -C(O)-R_{014}, -C(O)-$NR_{014}R_{014}$',

R_{011} and R_{011}' independently of one another are a hydrogen atom, an optionally substituted linear or branched (C_1-C_6)alkyl group, or -(C_0-C_6)alkyl-Cy_{01}, or the pair (R_{011}, R_{011}') together with the nitrogen atom to which they are attached form an aromatic or non-aromatic ring containing 5 to 7 ring members, which optionally contains, in addition to the nitrogen atom, 1 to 3 heteroatoms selected from O, S and N, wherein the N atom is optionally substituted by a linear or branched (C_1-C_6)alkyl group, and wherein one or more of the carbon atoms of the linear or branched (C_1-C_6)alkyl group is optionally deuterated,

R_{012} is -Cy_{05}, -Cy_{05}-(C_0-C_6)alkyl-Cy_{06}, -Cy_{05}-(C_0-C_6)alkyl-O-(C_0-C_6)alkyl-Cy_{06}, -Cy_{05}-(C_0-C_6)alkyl-NR_{011}-(C_0-C_6)alkyl-Cy_{06}, -Cy_{05}-Cy_{06}-O-(C_0-C_6)alkyl-Cy_{07}, -Cy_{05}-(C_0-C_6)alkyl-Cy_{09}, -NH-C(O)-NH-R_{011}, -C(O)-$NR_{011}R_{011}$', -$NR_{011}R_{011}$', -OR_{011}, -NR_{011}-C(O)-R_{011}', -O-(C_1-C_6)alkyl-OR_{011}, -SO_2-R_{011}, or -C(O)-OR_{011},

R_{013}, R_{013}', R_{014} and R_{014}' independently of one another are a hydrogen atom, or an optionally substituted linear or branched (C_1-C_6)alkyl group,

Cy_{01}, Cy_{02}, Cy_{03}, Cy_{05}, Cy_{06}, Cy_{07} and Cy_{08} independently of one another, are a cycloalkyl group, a heterocycloalkyl group, an aryl group or a heteroaryl group, each of which is optionally substituted,

Cy_{09} is , wherein

R_{015} is a hydrogen atom; a $-(CH_2)_{p0}-O-(CHR_{018}-CHR_{019}-O)_{q0}-R_{020}$ group; a linear or branched (C_1-C_6)alkoxy(C_1-C_6)alkyl group; a $-U_0-(CH_2)_{q0}-NR_{021}R_{021}$' group; or a $-(CH_2)_{r0}-U_0-(CH_2)_{s0}$-heterocycloalkyl group,

R_{016} is a hydrogen atom; a hydroxy group; a hydroxy(C_1-C_6)alkyl group; a $-(CH_2)_{r0}-U_0-(CH_2)_{s0}$-heterocycloalkyl group; a $(CH_2)_{r0}-U_0-V_0-O-P(O)(OR_{020})_2$ group; a $-O-P(O)(O^-M^+)_2$ group; a $-O-S(O)_2OR_{020}$ group; a $-S(O)_2OR_{020}$ group; a $-(CH_2)_{p0}-O-(CHR_{018}-CHR_{019}-O)_{q0}-R_{020}$ group; a $-(CH_2)_{p0}-O-C(O)-NR_{022}R_{023}$ group; or a $-U_0-(CH_2)_{q0}-NR_{021}R_{021}$' group,

R_{017} is a hydrogen atom; a $-(CH_2)_{p0}-O-(CHR_{018}-CHR_{019}-O)_{q0}-R_{020}$ group; a $-CH_2-P(O)(OR_{020})_2$ group, a $-O-P(O)(OR_{020})_2$ group; a $-O-P(O)(O^-M^+)_2$ group; a hydroxy group; a hydroxy(C_1-C_6)alkyl group; a $-(CH_2)_{r0}-U_0-(CH_2)_{s0}$-heterocycloalkyl group; a $-U_0-(CH_2)_{q0}-NR_{021}R_{021}$' group; or an aldonic acid,

M^+ is a pharmaceutically acceptable monovalent cation,

U_0 is a bond or an oxygen atom,

V_0 is a $-(CH_2)_{s0}-$ group or a -C(O)- group,

R_{018} is a hydrogen atom or a (C_1-C_6)alkoxy(C_1-C_6)alkyl group,

R_{019} is a hydrogen atom or a hydroxy(C_1-C_6)alkyl group,

R_{020} is a hydrogen atom or a linear or branched (C_1-C_6)alkyl group,

R_{021} and R_{021}' independently of one are a hydrogen atom, a linear or branched (C_1-C_6)alkyl group, or a hydroxy(C_1-C_6)alkyl group,

or the pair (R_{021}, R_{021}') together with the nitrogen atom to which they are attached form an aromatic or non-aromatic ring containing 5 to 7 ring members, which optionally contains, in addition to the nitrogen atom, 1 to 3 heteroatoms selected from O, S and N, wherein the resulting ring is optionally substituted by a hydrogen atom or a linear or branched (C_1-C_6)alkyl group,

R_{022} is a (C_1-C_6)alkoxy(C_1-C_6)alkyl group, a $-(CH_2)_{p0}-NR_{024}R_{024}$' group, or a $-(CH_2)_{p0}-O-(CHR_{018}-CHR_{019}-O)_{q0}-R_{20}$ group,

R_{023} is a hydrogen atom or a (C_1-C_6)alkoxy(C_1-C_6)alkyl group,

or the pair (R_{022}, R_{023}) together with the nitrogen atom to which they are attached form an aromatic or non-aromatic ring containing 5 to 18 ring members, which optionally contains, in addition to the nitrogen atom, 1 to 5 heteroatoms

selected from O, S and N, wherein the resulting ring is optionally substituted by a hydrogen atom, a linear or branched (C_1-C_6)alkyl group or a heterocycloalkyl group,

R_{024} and R_{024}' independently of one another are a hydrogen atom or a linear or branched (C_1-C_6)alkyl group,

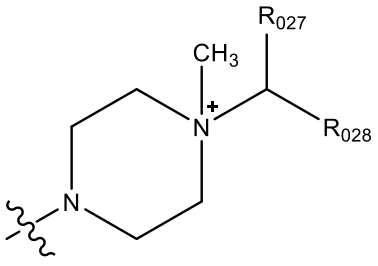
or the pair (R_{024}, R_{024}') together with the nitrogen atom to which they are attached form an aromatic or non-aromatic ring composed of from 5 to 7 ring members, which may contain in addition to the nitrogen atom from 1 to 3 heteroatoms selected from O, S and N, and wherein the resulting ring is optionally substituted by a hydrogen atom or a linear or branched (C_1-C_6)alkyl group,

R_{027} is a hydrogen atom or a linear or branched (C_1-C_6)alkyl group,

R_{028} is a -O-P(O)(O^-)(O^-) group, a -O-P(O)(O^-)(OR_{030}) group, a -O-P(O)(OR_{030})(OR_{030}') group, a -$(CH_2)_{p0}$-O-SO_2-O^- group, a -$(CH_2)_{p0}$-SO_2-O^- group, a -$(CH_2)_{p0}$-O-SO_2-OR_{030} group, -Cy_{010}, a -$(CH_2)_{p0}$-SO_2-OR_{030} group, a -O-C(O)-R_{029} group, a -O-C(O)-OR_{029} group or a -O-C(O)-$NR_{029}R_{029}$' group;

R_{029} and R_{029}' independently of one another are a hydrogen atom, a linear or branched (C_1-C_6)alkyl group or a linear or branched amino(C_1-C_6)alkyl group,

R_{030} and R_{030}' independently of one another are a hydrogen atom, a linear or branched (C_1-C_6)alkyl group or an aryl(C_1-C_6)alkylgroup,



R_{031} is ;

p_0 is an integer equal to 0, 1, 2, or 3;

q_0 is an integer equal to 1, 2, 3 or 4;

r_0 and s_0 are independently an integer equal to 0 or 1;

wherein one of the R_{03}, R_{09}, or R_{012} groups, if present, is covalently attached to the linker,

or an enantiomer, diastereoisomer, atropisomer, deuterated derivative, and/or pharmaceutically acceptable salt of any of the foregoing.

[07i] In another aspect, the present disclosure provides a use of the antibody-drug conjugate as described herein in the manufacture of a medicament for treating a disease or disorder, wherein the antibody-drug conjugate as described herein in combination with a Bcl-2 inhibitor is to be administered to a subject in need thereof, wherein the disease or disorder is mediated by CD74.

[07j] In yet another aspect, the present disclosure provides the antibody-drug conjugate, the composition, the pharmaceutical composition, or the antibody-drug conjugate as described herein for use in therapy.

[08] In some embodiments, the present disclosure provides, in part, novel antibody-drug conjugate (ADC) compounds with biological activity against cancer cells. The compounds may slow, inhibit, and/or reverse tumor growth in mammals, and/or may be useful for treating human cancer patients. The present disclosure more specifically relates, in some embodiments, to ADC compounds that are capable of binding and killing cancer cells. In some embodiments, the ADC compounds disclosed herein comprise a linker that attaches an Mcl-1 inhibitor to a full-length anti-CD74 antibody or an antigen-binding fragment. In some embodiments, the ADC compounds are also capable of internalizing into a target cell after binding.

[09] In some embodiments, ADC compounds may be represented by Formula (1):

CLAIMS

1. An antibody-drug conjugate of Formula (1):

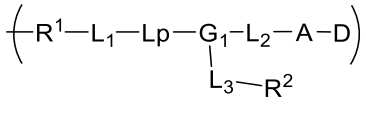
$$Ab\text{-}(L\text{-}D)_p \qquad (1)$$

wherein:

Ab is an anti-CD74 antibody or an antigen-binding fragment thereof;

p is an integer from 1 to 16; and

-(L-D) is of the formula (C):



(C),

wherein:

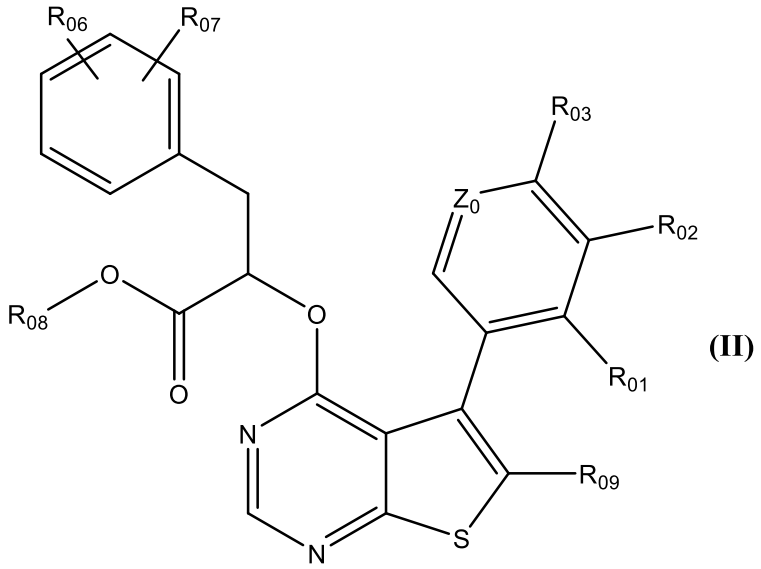
L is a linker;

R^1 is an attachment group;

L_1 is a bridging spacer;

L_p is a peptide group comprising 1 to 6 amino acids;

D is an Mcl-1 inhibitor; wherein the Mcl-1 inhibitor is a compound of Formula (II):



(II)

wherein:

Z_0 is a nitrogen atom or a C-R_{04} group,

R_{01} is a halogen atom, a linear or branched (C_1-C_6)alkyl group, a linear or branched (C_2-C_6)alkenyl group, a linear or branched (C_2-C_6)alkynyl group, a linear or branched (C_1-C_6)haloalkyl group, a hydroxy group, a linear or branched (C_1-C_6)alkoxy group, a -S-(C_1-C_6)alkyl group, a cyano group, -$Cy_{08,}$ -$NR_{011}R_{011}$',

R_{02}, R_{03} and R_{04} independently of one another are a hydrogen atom, a halogen atom, a linear or branched $(C_1\text{-}C_6)$alkyl group, a linear or branched $(C_2\text{-}C_6)$alkenyl group, a linear or branched $(C_2\text{-}C_6)$alkynyl group, a linear or branched $(C_1\text{-}C_6)$haloalkyl, a hydroxy group, a linear or branched $(C_1\text{-}C_6)$alkoxy group, a -S-$(C_1\text{-}C_6)$alkyl group, a cyano group, a nitro group, -$(C_0\text{-}C_6)$alkyl-$NR_{011}R_{011}$', -O-Cy_{01}, -$(C_0\text{-}C_6)$alkyl-Cy_{01}, -$(C_2\text{-}C_6)$alkenyl-Cy_{01}, -$(C_2\text{-}C_6)$alkynyl-Cy_{01}, -O-$(C_1\text{-}C_6)$alkyl-$NR_{011}R_{011}$', -O-$(C_1\text{-}C_6)$alkyl-R_{031}, -C(O)-OR_{011}, -O-C(O)-R_{011}, -C(O)-$NR_{011}R_{011}$', -NR_{011}-C(O)-R_{011}', -NR_{011}-C(O)-OR_{011}', -$(C_1\text{-}C_6)$alkyl-NR_{011}-C(O)-R_{011}', -SO_2-$NR_{011}R_{011}$', or -SO_2-$(C_1\text{-}C_6)$alkyl, or the pair (R_{02}, R_{03}) or (R_{03}, R_{04}) together with the carbon atoms to which they are attached form an aromatic or non-aromatic ring containing 5 to 7 ring members, which optionally contains 1 to 3 heteroatoms selected from O, S and N, wherein the ring is optionally substituted by a group selected from a linear or branched $(C_1\text{-}C_6)$alkyl, -$NR_{013}R_{013}$', -$(C_0\text{-}C_6)$alkyl-Cy_{01} and oxo,

R_{06} and R_{07} independently of one another are a hydrogen atom, a halogen atom, a linear or branched $(C_1\text{-}C_6)$alkyl group, a linear or branched $(C_2\text{-}C_6)$alkenyl group, a linear or branched $(C_2\text{-}C_6)$alkynyl group, a linear or branched $(C_1\text{-}C_6)$haloalkyl, a hydroxy group, a linear or branched $(C_1\text{-}C_6)$alkoxy group, a -S-$(C_1\text{-}C_6)$alkyl group, a cyano group, a nitro group, -$(C_0\text{-}C_6)$alkyl-$NR_{011}R_{011}$', -O-Cy_{01}, -$(C_0\text{-}C_6)$alkyl-Cy_{01}, -$(C_2\text{-}C_6)$alkenyl-Cy_{01}, -$(C_2\text{-}C_6)$alkynyl-Cy_{01}, -O-$(C_1\text{-}C_6)$alkyl-R_{012}, -C(O)-OR_{011}, -O-C(O)-R_{011}, -C(O)-$NR_{011}R_{011}$', -NR_{011}-C(O)-R_{011}', -NR_{011}-C(O)-OR_{011}', -$(C_1\text{-}C_6)$alkyl-NR_{011}-C(O)-R_{011}', -SO_2-$NR_{011}R_{011}$', or -SO_2-$(C_1\text{-}C_6)$alkyl,
or the pair (R_{06}, R_{07}), when fused with two adjacent carbon atoms, together with the carbon atoms to which they are attached form an aromatic or non-aromatic ring containing 5 to 7 ring members, which optionally contains 1 to 3 heteroatoms selected from O, S and N, and wherein the resulting ring is optionally substituted by a group selected from a linear or branched $(C_1\text{-}C_6)$alkyl group, -$NR_{013}R_{013}$', -$(C_0\text{-}C_6)$alkyl-Cy_{01} and an oxo,

R_{08} is a hydrogen atom, a linear or branched $(C_1\text{-}C_8)$alkyl group, an aryl group, a heteroaryl group, an aryl-$(C_1\text{-}C_6)$alkylgroup, or a heteroaryl$(C_1\text{-}C_6)$alkyl group,

R_{09} is a linear or branched $(C_1\text{-}C_6)$alkyl group, a linear or branched $(C_2\text{-}C_6)$alkenyl group, a linear or branched $(C_2\text{-}C_6)$alkynyl group, -Cy_{02}, -$(C_1\text{-}C_6)$alkyl-Cy_{02}, -$(C_2\text{-}C_6)$alkenyl-Cy_{02}, -$(C_2\text{-}C_6)$alkynyl-Cy_{02}, -Cy_{02}-Cy_{03}, -$(C_2\text{-}C_6)$alkynyl-O-Cy_{02}, -Cy_{02}-$(C_0\text{-}C_6)$alkyl-O-$(C_0\text{-}C_6)$alkyl-Cy_{03}, a halogen atom,

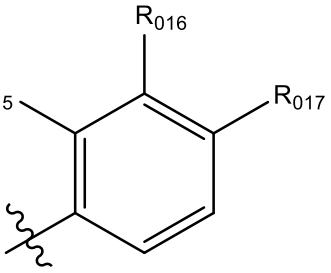
a cyano group, -C(O)-R_{014}, -C(O)-$NR_{014}R_{014}$',

R_{011} and R_{011}' independently of one another are a hydrogen atom, an optionally substituted linear or branched (C_1-C_6)alkyl group, or -(C_0-C_6)alkyl-Cy_{01},
or the pair (R_{011}, R_{011}') together with the nitrogen atom to which they are attached form an aromatic or non-aromatic ring containing 5 to 7 ring members, which optionally contains, in addition to the nitrogen atom, 1 to 3 heteroatoms selected from O, S and N, wherein the N atom is optionally substituted by a linear or branched (C_1-C_6)alkyl group, and wherein one or more of the carbon atoms of the linear or branched (C_1-C_6)alkyl group is optionally deuterated,

R_{012} is -Cy_{05}, -Cy_{05}-(C_0-C_6)alkyl-Cy_{06}, -Cy_{05}-(C_0-C_6)alkyl-O-(C_0-C_6)alkyl-Cy_{06}, -Cy_{05}-(C_0-C_6)alkyl-NR_{011}-(C_0-C_6)alkyl-Cy_{06}, -Cy_{05}-Cy_{06}-O-(C_0-C_6)alkyl-Cy_{07}, -Cy_{05}-(C_0-C_6)alkyl-Cy_{09}, -NH-C(O)-NH-R_{011}, -C(O)-$NR_{011}R_{011}$', -$NR_{011}R_{011}$', -OR_{011}, -NR_{011}-C(O)-R_{011}', -O-(C_1-C_6)alkyl-OR_{011}, -SO_2-R_{011}, or -C(O)-OR_{011},

R_{013}, R_{013}', R_{014} and R_{014}' independently of one another are a hydrogen atom, or an optionally substituted linear or branched (C_1-C_6)alkyl group,

Cy_{01}, Cy_{02}, Cy_{03}, Cy_{05}, Cy_{06}, Cy_{07} and Cy_{08} independently of one another, are a cycloalkyl group, a heterocycloalkyl group, an aryl group or a heteroaryl group, each of which is optionally substituted,

Cy_{09} is 

, wherein

R_{015} is a hydrogen atom; a -(CH_2)$_{p0}$-O-(CHR_{018}-CHR_{019}-O)$_{q0}$-R_{020} group; a linear or branched (C_1-C_6)alkoxy(C_1-C_6)alkyl group; a -U_0-(CH_2)$_{q0}$-$NR_{021}R_{021}$' group; or a -(CH_2)$_{r0}$-U_0-(CH_2)$_{s0}$-heterocycloalkyl group,

R_{016} is a hydrogen atom; a hydroxy group; a hydroxy(C_1-C_6)alkyl group; a -(CH_2)$_{r0}$-U_0-(CH_2)$_{s0}$-heterocycloalkyl group; a (CH_2)$_{r0}$-U_0-V_0-O-P(O)(OR_{020})$_2$ group; a -O-P(O)(O^-M^+)$_2$ group; a -O-S(O)$_2$$OR_{020}$ group; a -S(O)$_2$$OR_{020}$ group; a -(CH_2)$_{p0}$-O-(CHR_{018}-CHR_{019}-O)$_{q0}$-R_{020} group; a -(CH_2)$_{p0}$-O-C(O)-$NR_{022}R_{023}$ group; or a -U_0-(CH_2)$_{q0}$-$NR_{021}R_{021}$' group,

R_{017} is a hydrogen atom; a -(CH_2)$_{p0}$-O-(CHR_{018}-CHR_{019}-O)$_{q0}$-R_{020} group; a -CH_2-P(O)(OR_{020})$_2$ group, a -O-P(O)(OR_{020})$_2$ group; a -O-P(O)(O^-M^+)$_2$ group; a hydroxy group;

a hydroxy(C_1-C_6)alkyl group; a -$(CH_2)_{r0}$-U_0-$(CH_2)_{s0}$-heterocycloalkyl group; a -U_0-$(CH_2)_{q0}$-$NR_{021}R_{021}$' group; or an aldonic acid,

M^+ is a pharmaceutically acceptable monovalent cation,

U_0 is a bond or an oxygen atom,

V_0 is a -$(CH_2)_{s0}$- group or a -C(O)- group,

R_{018} is a hydrogen atom or a (C_1-C_6)alkoxy(C_1-C_6)alkyl group,

R_{019} is a hydrogen atom or a hydroxy(C_1-C_6)alkyl group,

R_{020} is a hydrogen atom or a linear or branched (C_1-C_6)alkyl group,

R_{021} and R_{021}' independently of one are a hydrogen atom, a linear or branched (C_1-C_6)alkyl group, or a hydroxy(C_1-C_6)alkyl group,

or the pair (R_{021}, R_{021}') together with the nitrogen atom to which they are attached form an aromatic or non-aromatic ring containing 5 to 7 ring members, which optionally contains, in addition to the nitrogen atom, 1 to 3 heteroatoms selected from O, S and N, wherein the resulting ring is optionally substituted by a hydrogen atom or a linear or branched (C_1-C_6)alkyl group,

R_{022} is a (C_1-C_6)alkoxy(C_1-C_6)alkyl group, a -$(CH_2)_{p0}$-$NR_{024}R_{024}$' group, or a -$(CH_2)_{p0}$-O-$(CHR_{018}$-CHR_{019}-O$)_{q0}$-R_{20} group,

R_{023} is a hydrogen atom or a (C_1-C_6)alkoxy(C_1-C_6)alkyl group,

or the pair (R_{022}, R_{023}) together with the nitrogen atom to which they are attached form an aromatic or non-aromatic ring containing 5 to 18 ring members, which optionally contains, in addition to the nitrogen atom, 1 to 5 heteroatoms selected from O, S and N, wherein the resulting ring is optionally substituted by a hydrogen atom, a linear or branched (C_1-C_6)alkyl group or a heterocycloalkyl group,

R_{024} and R_{024}' independently of one another are a hydrogen atom or a linear or branched (C_1-C_6)alkyl group,

or the pair (R_{024}, R_{024}') together with the nitrogen atom to which they are attached form an aromatic or non-aromatic ring composed of from 5 to 7 ring members, which may contain in addition to the nitrogen atom from 1 to 3 heteroatoms selected from O, S and N, and wherein the resulting ring is optionally substituted by a hydrogen atom or a linear or branched (C_1-C_6)alkyl group,

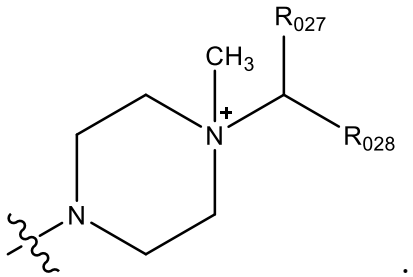
R_{027} is a hydrogen atom or a linear or branched (C_1-C_6)alkyl group,

R_{028} is a -O-P(O)(O^-)(O^-) group, a -O-P(O)(O^-)(OR_{030}) group, a -O-P(O)(OR_{030})(OR_{030}') group, a -$(CH_2)_{p0}$-O-SO_2-O^- group, a -$(CH_2)_{p0}$-SO_2-O^- group, a -

$(CH_2)_{p0}$-O-SO_2-OR_{030} group, -Cy_{010}, a -$(CH_2)_{p0}$-SO_2-OR_{030} group, a -O-C(O)-R_{029} group, a -O-C(O)-OR_{029} group or a -O-C(O)-$NR_{029}R_{029}$' group;

R_{029} and R_{029}' independently of one another are a hydrogen atom, a linear or branched (C_1-C_6)alkyl group or a linear or branched amino(C_1-C_6)alkyl group,

R_{030} and R_{030}' independently of one another are a hydrogen atom, a linear or branched (C_1-C_6)alkyl group or an aryl(C_1-C_6)alkylgroup,

R_{031} is 

;

p_0 is an integer equal to 0, 1, 2, or 3;

q_0 is an integer equal to 1, 2, 3 or 4;

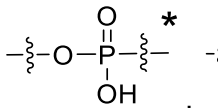
r_0 and s_0 are independently an integer equal to 0 or 1;

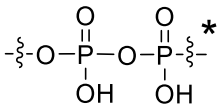
wherein one of the R_{03}, R_{09}, or R_{012} groups, if present, is covalently attached to the linker,

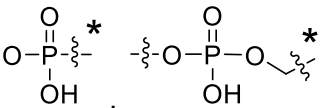
or an enantiomer, diastereoisomer, atropisomer, deuterated derivative, and/or pharmaceutically acceptable salt of any of the foregoing;

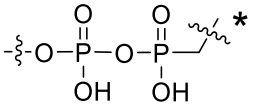
G_1-L_2-A is a self-immolative spacer;

L_2 is a bond, a methylene, a neopentylene or a C_2-C_3 alkenylene;

A is a bond, -OC(=O)-*, 

, 

, 

, 

, -OC(=O)N(CH_3)CH_2CH_2N(CH_3)C(=O)-* or

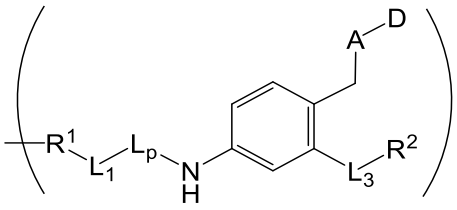
-OC(=O)N(CH_3)C(R^a)$_2$C(R^a)$_2$N(CH_3)C(=O)-*,

wherein each R^a is independently selected from H, C_1-C_6 alkyl, and C_3-C_8 cycloalkyl and the * of A indicates the point of attachment to D;

L_3 is a spacer moiety; and

R^2 is a hydrophilic moiety.

2. The antibody-drug conjugate of claim 1, or pharmaceutically acceptable salt thereof, wherein -(L-D) is of Formula (D):

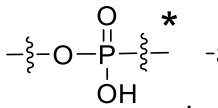
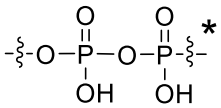
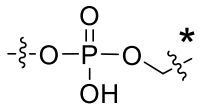
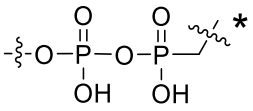

(D)

wherein:

R^1 is an attachment group;

L_1 is a bridging spacer;

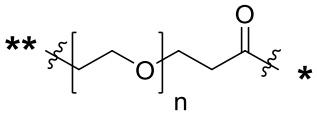
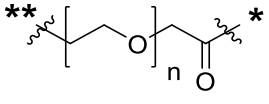
Lp is a peptide group comprising 1 to 6 amino acids;

A is a bond, -OC(=O)-*, , , , , -OC(=O)N(CH_3)CH_2CH_2N(CH_3)C(=O)-* or -OC(=O)N(CH_3)C(R^a)$_2$C(R^a)$_2$N(CH_3)C(=O)-*,

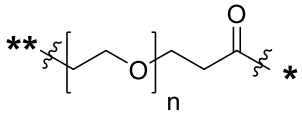
wherein each R^a is independently selected from H, C_1-C_6 alkyl, and C_3-C_8 cycloalkyl and the * of A indicates the point of attachment to D;

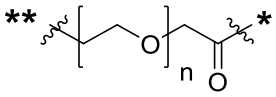
L_3 is a spacer moiety; and

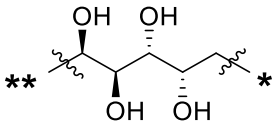
R^2 is a hydrophilic moiety.

3. The antibody-drug conjugate of claim 1 or 2, wherein (1) L_1 comprises: , , or *-CH(OH)CH(OH)CH(OH)CH(OH)-**,

wherein each n is an integer from 1 to 12, wherein the * of L_1 indicates the point of direct or indirect attachment to Lp, and the ** of L_1 indicates the point of direct or indirect attachment to R^1;

(2) L_1 is , and n is an integer from 1 to 12 or n is 1 or n is 12, wherein the * of L_1 indicates the point of direct or indirect attachment to Lp, and the ** of L_1 indicates the point of direct or indirect attachment to R^1;

(3) L_1 is , and n is an integer from 1 to 12, wherein the * of L_1 indicates the point of direct or indirect attachment to Lp, and the ** of L_1 indicates the point of direct or indirect attachment to R^1;

(4) L_1 comprises , wherein the * of L_1 indicates the point of direct or indirect attachment to Lp, and the ** of L_1 indicates the point of direct or indirect attachment to R^1; or

(5) L_1 is a bridging spacer comprising:

*-C(=O)$(CH_2)_m$O$(CH_2)_m$-**; *-C(=O)(($(CH_2)_m$O)$_t$$(CH_2)_n$-**; *-C(=O)$(CH_2)_m$-**;

*-C(=O)NH(($(CH_2)_m$O)$_t$$(CH_2)_n$-**;

*-C(=O)O$(CH_2)_m$SSC$(R^3)_2$$(CH_2)_m$C(=O)N$R^3$$(CH_2)_mNR^3$C(=O)$(CH_2)_m$-**;

*-C(=O)O$(CH_2)_m$C(=O)NH$(CH_2)_m$-**; *-C(=O)$(CH_2)_m$NH$(CH_2)_m$-**;

*-C(=O)$(CH_2)_m$NH$(CH_2)_n$C(=O)-**; *-C(=O)$(CH_2)_m$$X_1$$(CH_2)_m$-**;

*-C(=O)(($(CH_2)_m$O)$_t$$(CH_2)_n$$X_1$$(CH_2)_n$-**; *-C(=O)$(CH_2)_m$NHC(=O)$(CH_2)_n$-**;

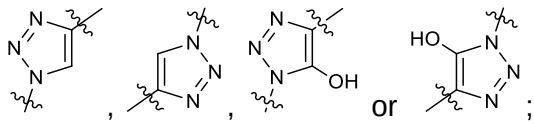
*-C(=O)(($(CH_2)_m$O)$_t$$(CH_2)_n$NHC(=O)$(CH_2)_n$-**;

*-C(=O)$(CH_2)_m$NHC(=O)$(CH_2)_n$$X_1$$(CH_2)_n$-**;

*-C(=O)(($(CH_2)_m$O)$_t$$(CH_2)_n$NHC(=O)$(CH_2)_n$$X_1$$(CH_2)_n$-**;

*-C(=O)(($(CH_2)_m$O)$_t$$(CH_2)_n$C(=O)NH$(CH_2)_m$-**; *-C(=O)$(CH_2)_mC(R^3)_2$-** or

*-C(=O)$(CH_2)_m$C(=O)NH$(CH_2)_m$-**, wherein the * of L_1 indicates the point of direct or indirect attachment to Lp, and the ** of L_1 indicates the point of direct or indirect attachment to R^1;

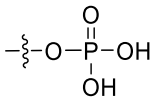
X_1 is ; and

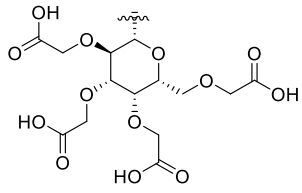
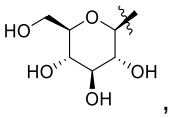
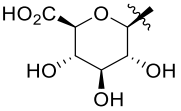
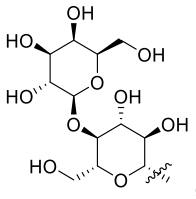
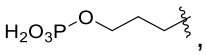
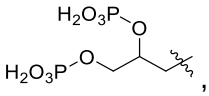
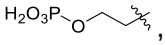
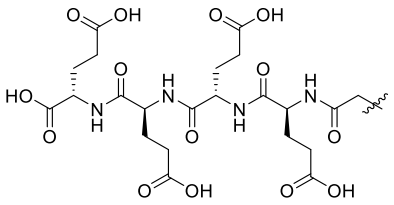
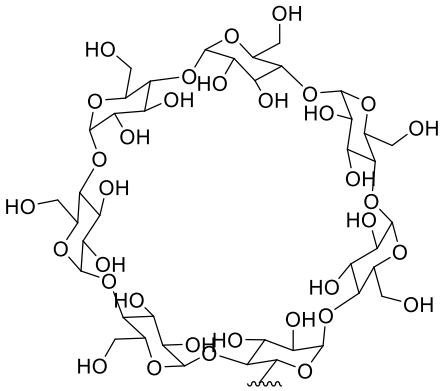
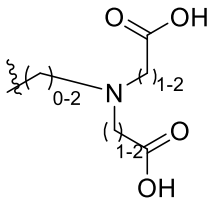
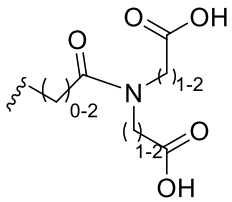
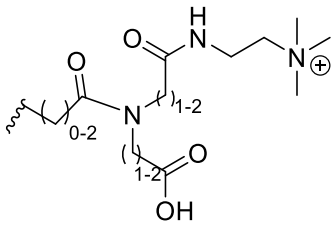
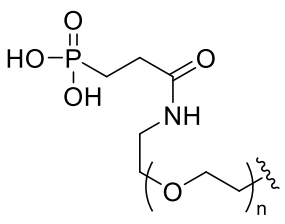
each m is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10;

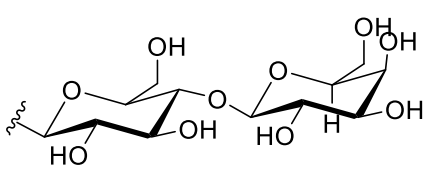
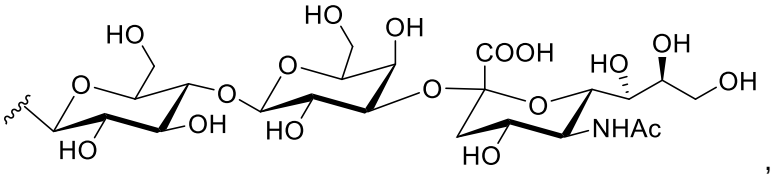
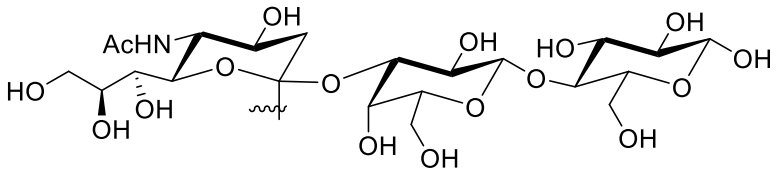
each n is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10; and

each t is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 and 30;

and each R^3 is independently selected from H and C_1-C_6alkyl.

4. The antibody-drug conjugate of any one of claims 1 to 3, wherein: (1) R^2 is a hydrophilic moiety comprising polyethylene glycol, polyalkylene glycol, a polyol, a polysarcosine, a sugar, an oligosaccharide, a polypeptide, or C_2-C_6 alkyl substituted with 1 to 3  groups;

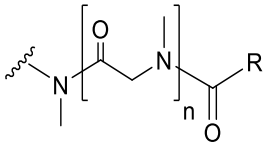
(2) R^2 is , , , , , , , , , , , , , wherein n is an interger between 1 and 6,

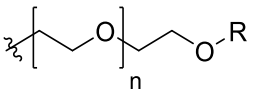
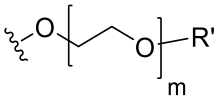
or ;

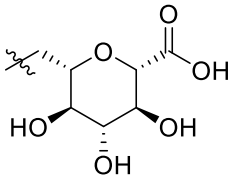
(3) the hydrophilic moiety represented by R^2 comprises:

(i) a polysarcosine, e.g., with the following moiety:



, wherein n is an integer between 3 and 25; and R is H, $–CH_3$ or -$CH_2CH_2C(=O)OH$; or

(ii) a polyethylene glycol of formula:  or , wherein R is H, -CH_3, $CH_2CH_2NHC(=O)OR_a$, -$CH_2CH_2NHC(=O)R_a$, or -$CH_2CH_2C(=O)OR_a$, R’ is OH, -OCH_3, -$CH_2CH_2NHC(=O)OR_a$, -$CH_2CH_2NHC(=O)R_a$, or -$OCH_2CH_2C(=O)OR_a$, in which R_a is H or C_{1-4} alkyl optionally substiltuted with either OH or C_{1-4} alkoxyl, and each of m and n is independently an integer between 2 and 25; or

(4) the hydrophilic moiety represented by R^2 comprises .

5. The antibody-drug conjugate of any one of claims 1 to 4, wherein:

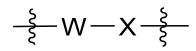
(i) L_3 is a spacer moiety having the structure ,

wherein:

W is -CH_2-, -CH_2O-, -$CH_2N(R^b)C(=O)O$-, -$NHC(=O)C(R^b)_2NHC(=O)O$-, -$NHC(=O)C(R^b)_2NH$-, -$NHC(=O)C(R^b)_2NHC(=O)$-, -$CH_2N(X\text{-}R^2)C(=O)O$-, -$C(=O)N(X\text{-}R^2)$-, -

$CH_2N(X\text{-}R^2)C(=O)$-, -$C(=O)NR^b$-, -$C(=O)NH$-, -$CH_2N\ R^b\ C(=O)$-, -$CH_2N\ R^b\ C(=O)NH$-, -$CH_2NR^bC(=O)NR^b$-, -$NHC(=O)$-, -$NHC(=O)O$-, -$NHC(=O)NH$-, -$OC(=O)NH$-, -$S(O)_2NH$-, -$NHS(O)_2$-, -$C(=O)$-, -$C(=O)O$- or -NH-, wherein each R^b is independently selected from H, C_1-C_6alkyl, and C_3-C_8 cycloalkyl; and

X is a bond, triazolyl, or -CH_2-triazolyl-; or

(ii) L_3 is a spacer moiety having the structure ,

wherein:

W is -CH_2-, -CH_2O-, -$CH_2N(R^b)C(=O)O$-, -$NHC(=O)C(R^b)_2NHC(=O)O$-, -$NHC(=O)C(R^b)_2NH$-, -$NHC(=O)C(R^b)_2NHC(=O)$-, -$CH_2N(X\text{-}R^2)C(=O)O$-, -$C(=O)N(X\text{-}R^2)$-, -$CH_2N(X\text{-}R^2)C(=O)$-, -$C(=O)NR^b$-, -$C(=O)NH$-, -$CH_2NR^bC(=O)$-, -$CH_2NR^bC(=O)NH$-, -$CH_2NR^bC(=O)NR^b$-, -$NHC(=O)$-, -$NHC(=O)O$-, -$NHC(=O)NH$-, -$OC(=O)NH$-, -$S(O)_2NH$-, -$NHS(O)_2$-, -$C(=O)$-, -$C(=O)O$- or -$NH$-, wherein each R^b is independently selected from H, C_1-C_6alkyl, and C_3-C_8 cycloalkyl; and

X is -CH_2-triazolyl-$C_{1\text{-}4}$ alkylene-$OC(O)NHS(O)_2NH$-, -$C_{4\text{-}6}$ cycloalkylene-$OC(O)NHS(O)_2NH$-, -$(CH_2CH_2O)_n$-$C(O)NHS(O)_2NH$-, -$(CH_2CH_2O)_n$-$C(O)NHS(O)_2NH$-$(CH_2CH_2O)_n$-, or -CH_2-triazolyl-$C_{1\text{-}4}$ alkylene-$OC(O)NHS(O)_2NH$-$(CH_2CH_2O)_n$-, wherein each n independently is 1, 2, or 3.

6. The antibody-drug conjugate of any one of claims 1 to 5, wherein: (1) the attachment group is formed by a reaction comprising at least one reactive group;

(2) the attachment group is formed by reacting:

a first reactive group that is attached to the linker, and

a second reactive group that is attached to the antibody or is an amino acid residue of the antibody;

(3) the attachment group is formed by reaction comprising at least one reactive group, wherein the at least one of the reactive groups comprises:

a thiol,

a maleimide,

a haloacetamide,

an azide,

an alkyne,

a cyclooctene,

a triaryl phosphine,

an oxanorbornadiene,

a cyclooctyne,

a diaryl tetrazine,

a monoaryl tetrazine,

a norbornene,

an aldehyde,

a hydroxylamine,

a hydrazine,

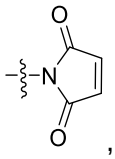
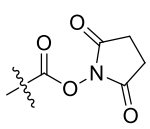
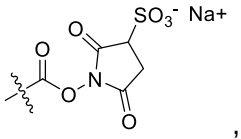
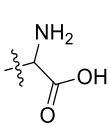
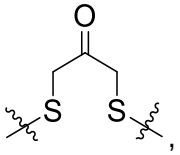
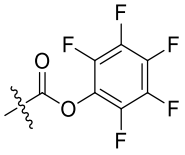
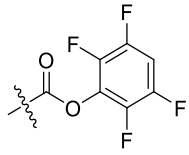
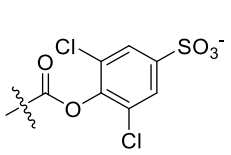
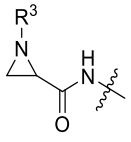
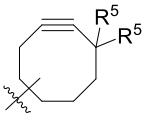
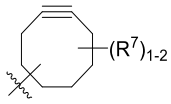
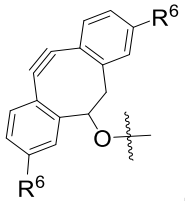
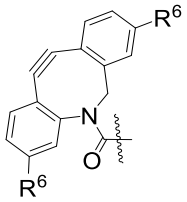
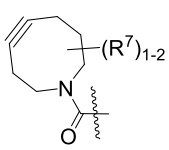
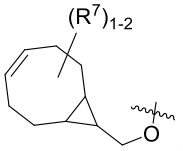
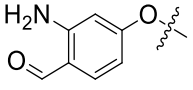
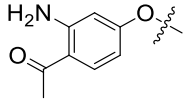
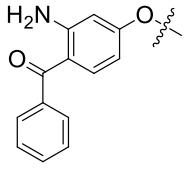
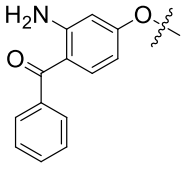
NH_2-NH-C(=O)-,

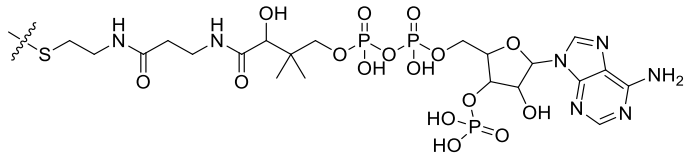
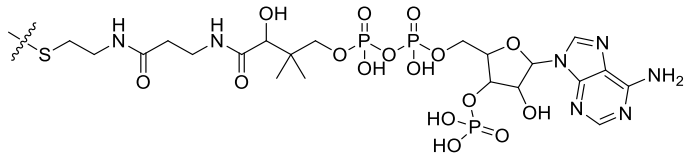
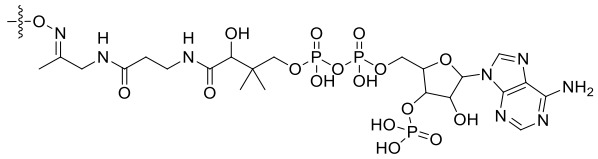
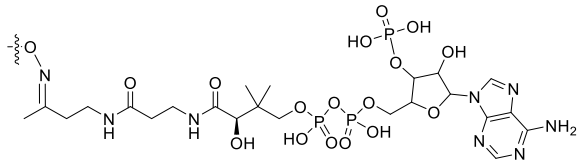
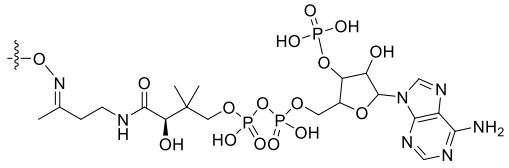
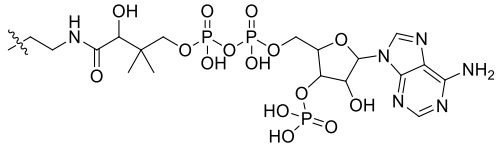
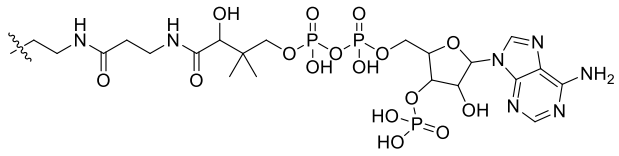
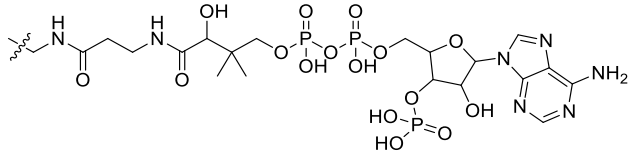
a ketone,

a vinyl sulfone,

an aziridine,

an amino acid residue,

, -ONH_2, -NH_2, , , , , , , , -N_3, , -SH, -SR^3, -SSR^4, -$S(=O)_2(CH=CH_2)$, -$(CH_2)_2S(=O)_2(CH=CH_2)$, -$NHS(=O)_2(CH=CH_2)$, -$NHC(=O)CH_2Br$, -$NHC(=O)CH_2I$, , -$C(O)NHNH_2$, , , , , , , , , , ,


,

,

,

,

,

,

, or

;

wherein:

each R^3 is independently selected from H and C_1-C_6alkyl;

each R^4 is 2-pyridyl or 4-pyridyl;

each R^5 is independently selected from H, C_1-C_6alkyl, F, Cl, and –OH;

each R^6 is independently selected from H, C_1-C_6alkyl, F, Cl, -NH_2, -OCH_3, -OCH_2CH_3, -$N(CH_3)_2$, -CN, -NO_2 and –OH;

each R^7 is independently selected from H, C_{1-6}alkyl, fluoro, benzyloxy substituted with –C(=O)OH, benzyl substituted with –C(=O)OH, C_{1-4}alkoxy substituted with –C(=O)OH and C_{1-4}alkyl substituted with –C(=O)OH;

(4) the attachment group is formed by reacting:

a first reactive group that is attached to the linker, and

a second reactive group that is attached to the antibody or is an amino acid residue of the antibody, wherein the first reactive group and second reactive group comprise:

a thiol and a maleimide,

a thiol and a haloacetamide,

a thiol and a vinyl sulfone,

a thiol and an aziridine,

an azide and an alkyne,

an azide and a cyclooctyne,

an azide and a cyclooctene,

an azide and a triaryl phosphine,

an azide and an oxanorbornadiene,

a diaryl tetrazine and a cyclooctene,

a monoaryl tetrazine and a norbornene,

an aldehyde and a hydroxylamine,

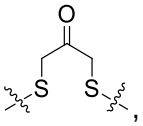
an aldehyde and a hydrazine,

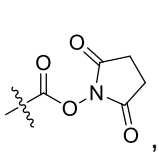
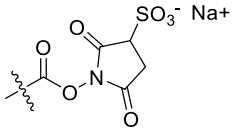
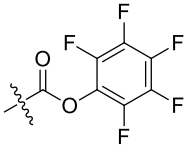
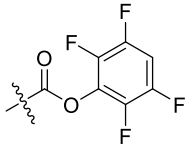
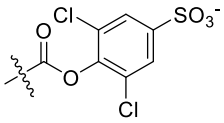
an aldehyde and NH_2-NH-C(=O)-,

a ketone and a hydroxylamine,

a ketone and a hydrazine,

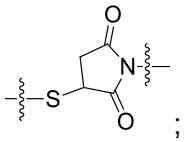
a ketone and NH_2-NH-C(=O)-,

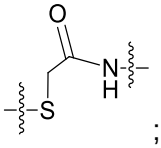
a hydroxylamine and ,

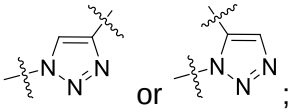
an amine and , , , , or , or

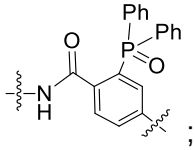
a CoA or CoA analogue and a serine residue; or

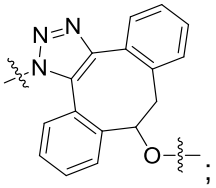
(5) the attachment group comprises a group selected from:

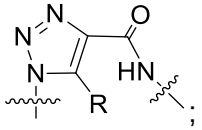

;

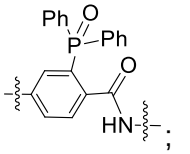

;

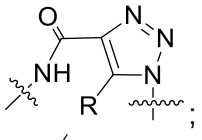

;

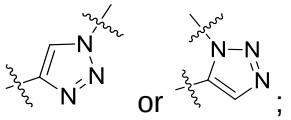

;

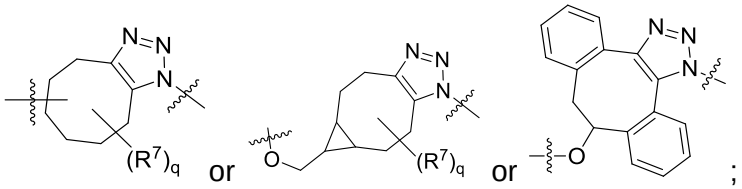

;

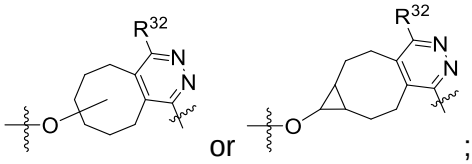

;

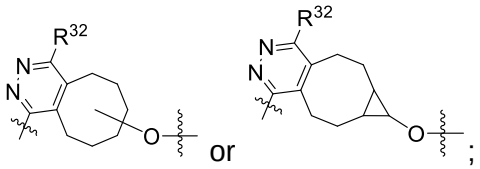
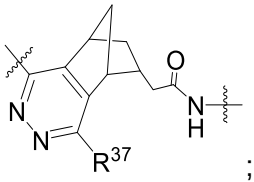
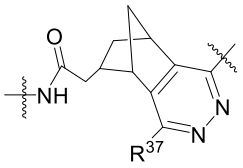
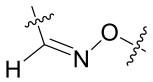
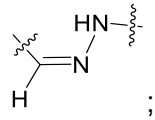
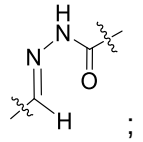
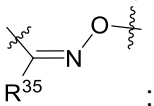
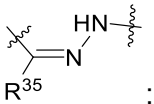
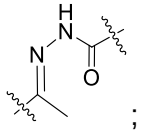
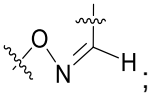
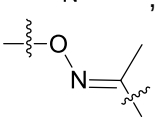
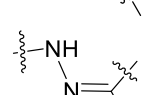
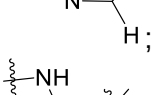
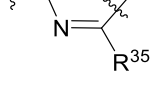
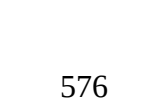

;

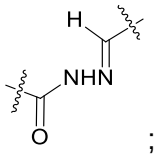

;

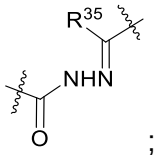

;

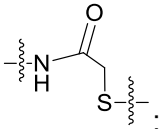

;

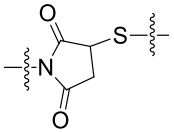

;

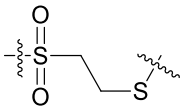

or

;

;

;

;

;

;

;

;

;

;

;

;

;

;

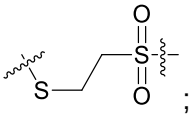

;

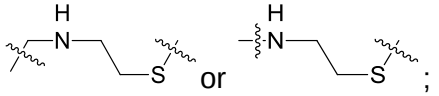

;

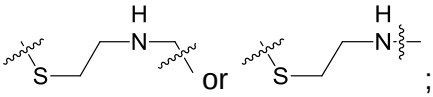

;

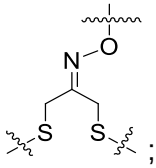

;


;

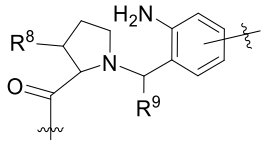

;

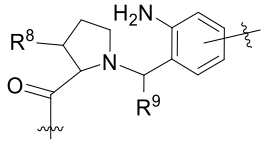

;

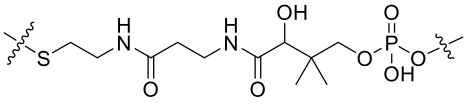

;

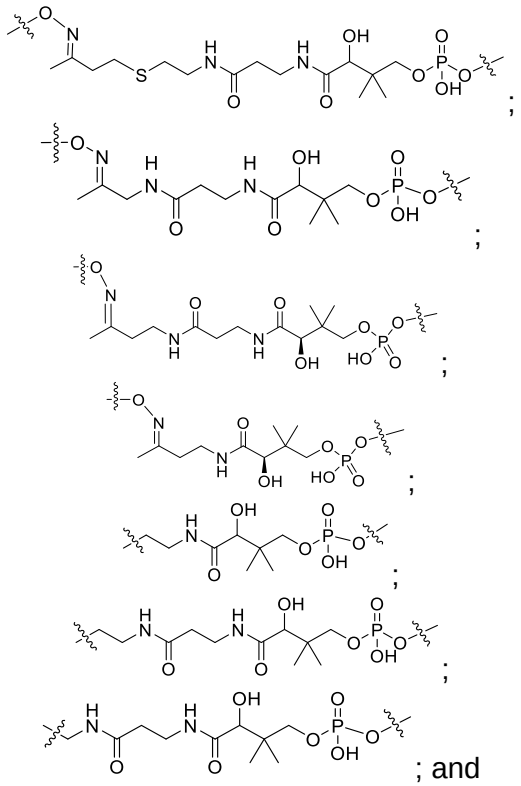

;

amide;


;


;


;



disulfide,

wherein:

R^{32} is H, C_{1-4} alkyl, phenyl, pyrimidine or pyridine;

R^{35} is H, C_{1-6} alkyl, phenyl or C_{1-4} alkyl substituted with 1 to 3 –OH groups;

each R^7 is independently selected from H, C_{1-6} alkyl, fluoro, benzyloxy substituted with –C(=O)OH, benzyl substituted with –C(=O)OH, C_{1-4} alkoxy substituted with –C(=O)OH and C_{1-4} alkyl substituted with –C(=O)OH;

R^{37} is independently selected from H, phenyl and pyridine;

q is 0, 1, 2 or 3;

R^8 is H or methyl; and

R^9 is H, $-CH_3$ or phenyl.

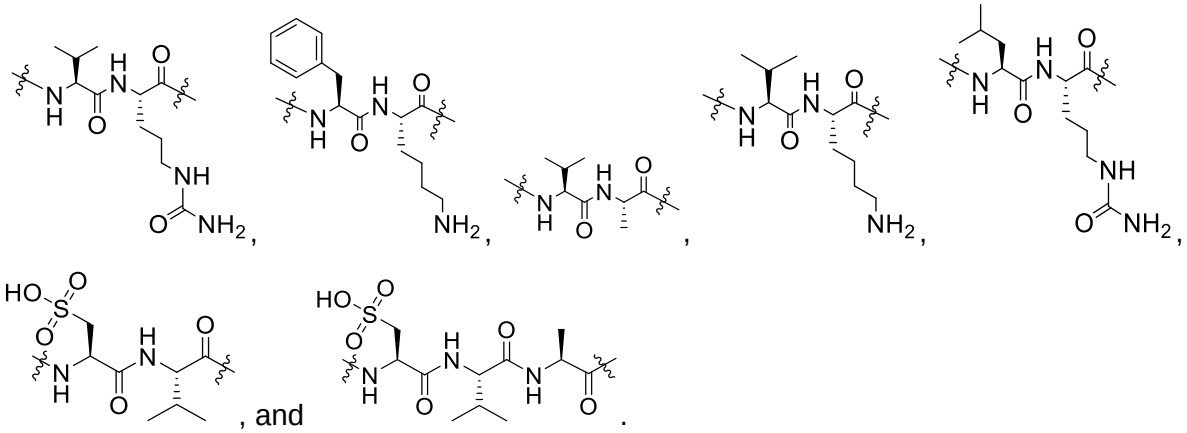
7. The antibody-drug conjugate of any one of claims 1 to 6, wherein: (1) the peptide group represented by Lp comprises 1 to 4 amino acid residues, 1 to 3 amino acid residues, or 1 to 2 amino acid residues, optionally wherein

the amino acid residues are selected from L-glycine (Gly), L-valine (Val), L-citrulline (Cit), L-cysteic acid (sulfo-Ala), L-lysine (Lys), L-isoleucine (Ile), L-phenylalanine (Phe), L-methionine

(Met), L-asparagine (Asn), L-proline (Pro), L-alanine (Ala), L-leucine (Leu), L-tryptophan (Trp), and L-tyrosine (Tyr);

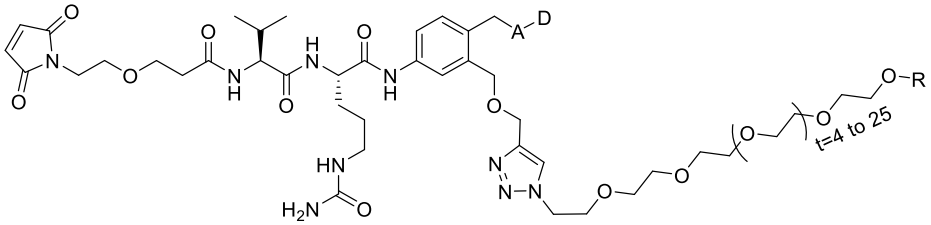
(2) the peptide group comprises Val-Cit, Phe-Lys, Val-Ala, Val-Lys, Leu-Cit, sulfo-Ala-Val, and/or sulfo-Ala-Val-Ala; or

(3) Lp is selected from:

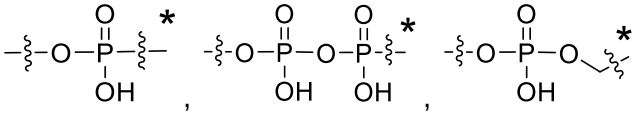


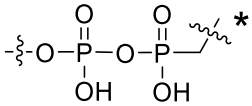
, and .

8. The antibody-drug conjugate of any one of claims 1 to 7, wherein -(L-D) comprises or is formed from a compound of formula:

(1) , wherein:

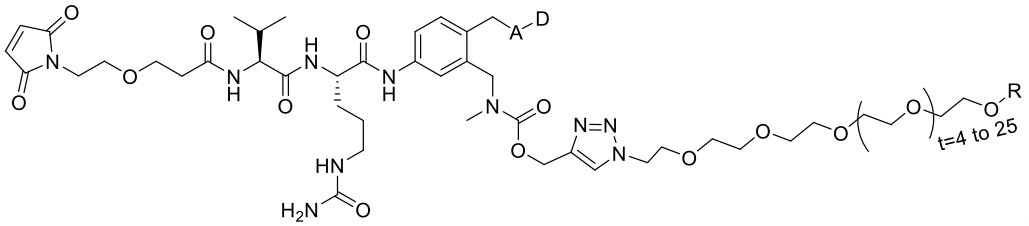
R is H, $-CH_3$ or $-CH_2CH_2C(=O)OH$;

A is a bond, -OC(=O)-*, ,

, $-OC(=O)N(CH_3)CH_2CH_2N(CH_3)C(=O)$-* or $-OC(=O)N(CH_3)C(R^a)_2C(R^a)_2N(CH_3)C(=O)$-*,

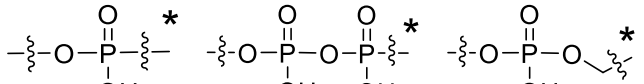
wherein each R^a is independently selected from H, C_1-C_6 alkyl, and C_3-C_8 cycloalkyl and the * of A indicates the point of attachment to D; and

D is an Mcl-1 inhibitor;

(2) 

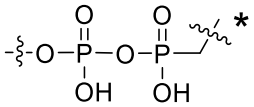
, wherein:

R is H, -CH_3 or -$CH_2CH_2C(=O)OH$;

A is a bond, -OC(=O)-*, 

,

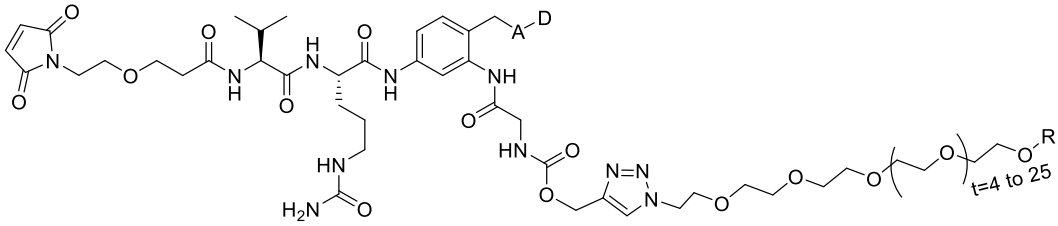
,

, 

, -OC(=O)$N(CH_3)CH_2CH_2N(CH_3)C(=O)$-* or -OC(=O)$N(CH_3)C(R^a)_2C(R^a)_2N(CH_3)C(=O)$-*,

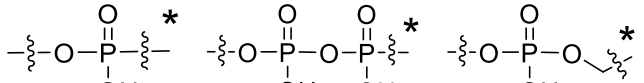
wherein each R^a is independently selected from H, C_1-C_6 alkyl, and C_3-C_8 cycloalkyl and the * of A indicates the point of attachment to D; and

D is an Mcl-1 inhibitor;

(3) 

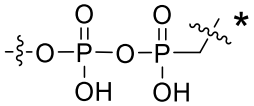
, wherein:

R is H, -CH_3 or -$CH_2CH_2C(=O)OH$;

A is a bond, -OC(=O)-*, 

,

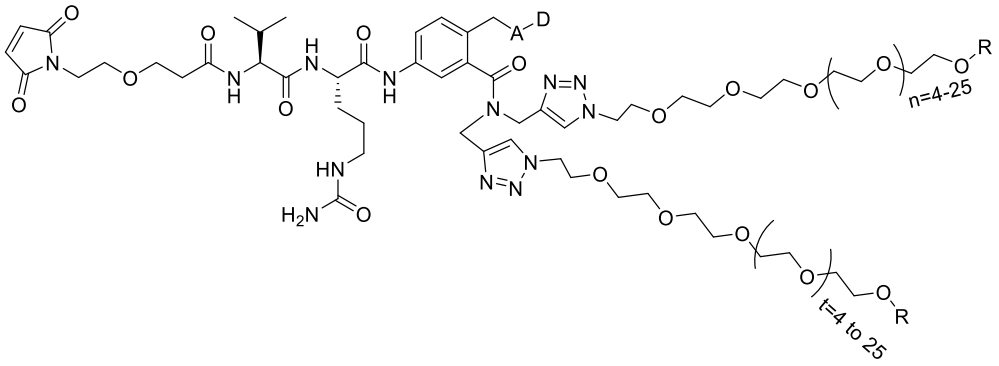
,

, 

, -OC(=O)$N(CH_3)CH_2CH_2N(CH_3)C(=O)$-* or -OC(=O)$N(CH_3)C(R^a)_2C(R^a)_2N(CH_3)C(=O)$-*,

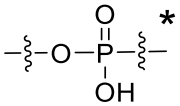
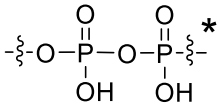
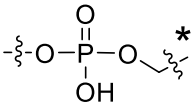
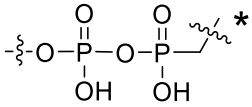
wherein each R^a is independently selected from H, C_1-C_6 alkyl, and C_3-C_8 cycloalkyl and the * of A indicates the point of attachment to D; and

D is an Mcl-1 inhibitor;



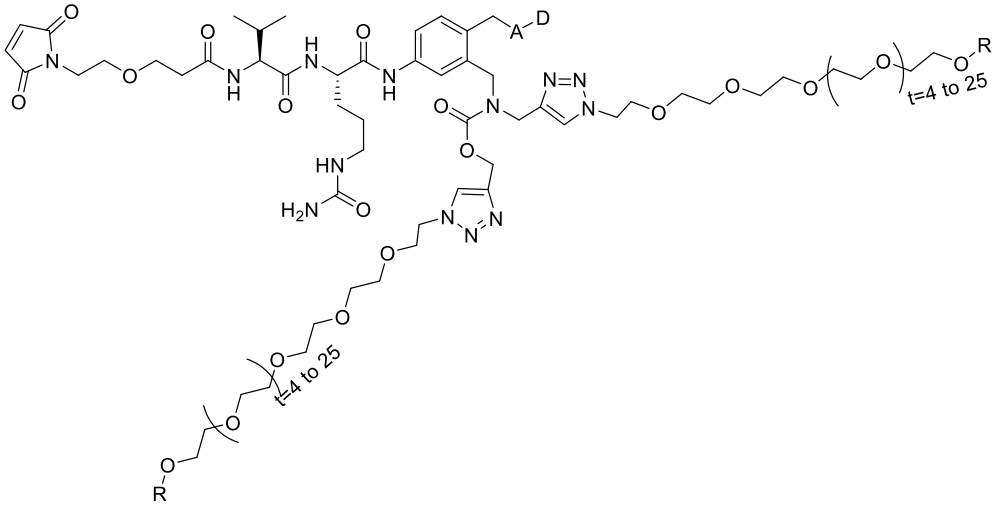
(4) , wherein:

each R is independently selected from H, $-CH_3$, and $-CH_2CH_2C(=O)OH$;

A is a bond, $-OC(=O)-*$,  ,  ,  ,  , $-OC(=O)N(CH_3)CH_2CH_2N(CH_3)C(=O)-*$ or $-OC(=O)N(CH_3)C(R^a)_2C(R^a)_2N(CH_3)C(=O)-*$,

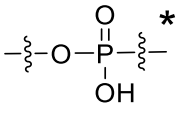
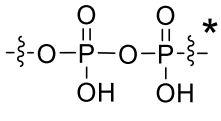
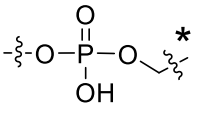
wherein each R^a is independently selected from H, C_1-C_6 alkyl, and C_3-C_8 cycloalkyl and the * of A indicates the point of attachment to D; and

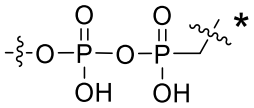
D is an Mcl-1 inhibitor;



(5) , wherein:

each R is independently selected from H, $-CH_3$, and $-CH_2CH_2C(=O)OH$;

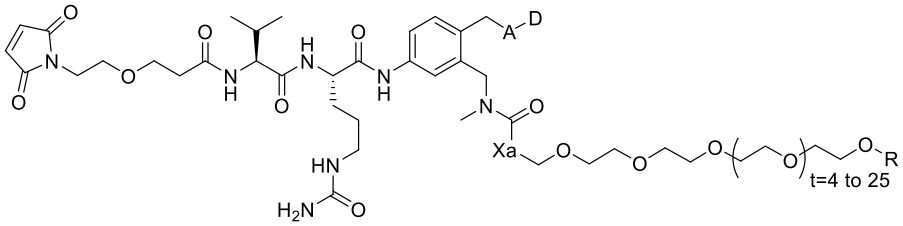
A is a bond, -OC(=O)-*,  ,  ,  ,

 , -OC(=O)N(CH_3)CH_2CH_2N(CH_3)C(=O)-* or

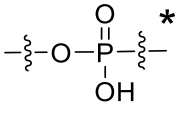
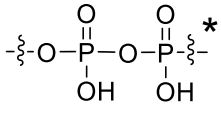
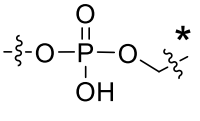
-OC(=O)N(CH_3)C(R^a)$_2$C(R^a)$_2$N(CH_3)C(=O)-*,

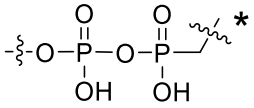
wherein each R^a is independently selected from H, C_1-C_6 alkyl, and C_3-C_8 cycloalkyl and the * of A indicates the point of attachment to D; and

D is an Mcl-1 inhibitor;

(6)  , wherein:

Xa is –CH_2-, -OCH_2-, -$NHCH_2$- or –$NRCH_2$- and each R independently is H, -CH_3 or -CH_2CH_2C(=O)OH;

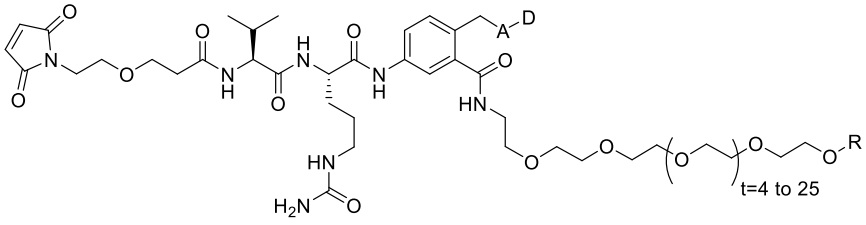
A is a bond, -OC(=O)-*,  ,  ,  ,

 , -OC(=O)N(CH_3)CH_2CH_2N(CH_3)C(=O)-* or

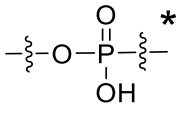
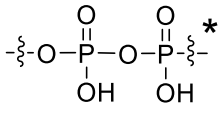
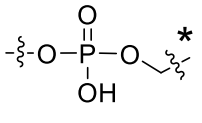
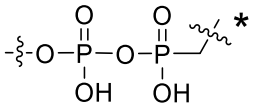
-OC(=O)N(CH_3)C(R^a)$_2$C(R^a)$_2$N(CH_3)C(=O)-*,

wherein each R^a is independently selected from H, C_1-C_6 alkyl, and C_3-C_8 cycloalkyl and the * of A indicates the point of attachment to D; and

D is an Mcl-1 inhibitor;

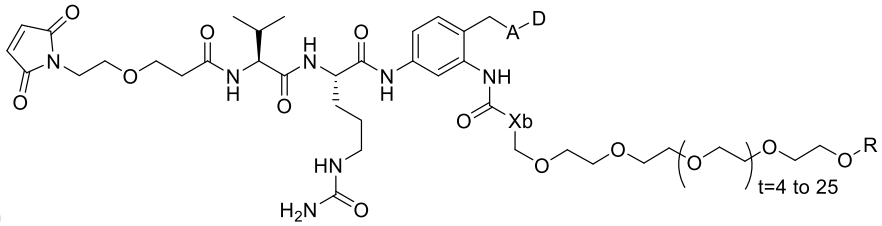
(7)  , wherein:

R is H, -CH_3 or -CH_2CH_2C(=O)OH;

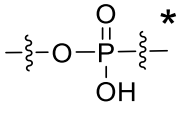
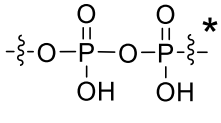
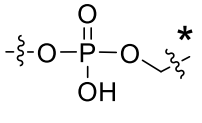
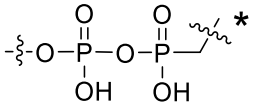
A is a bond, -OC(=O)-*,  ,  ,  ,  , -OC(=O)N(CH_3)CH_2CH_2N(CH_3)C(=O)-* or -OC(=O)N(CH_3)C(R^a)$_2$C(R^a)$_2$N(CH_3)C(=O)-*,

wherein each R^a is independently selected from H, C_1-C_6 alkyl, and C_3-C_8 cycloalkyl and the * of A indicates the point of attachment to D; and

D is an Mcl-1 inhibitor;

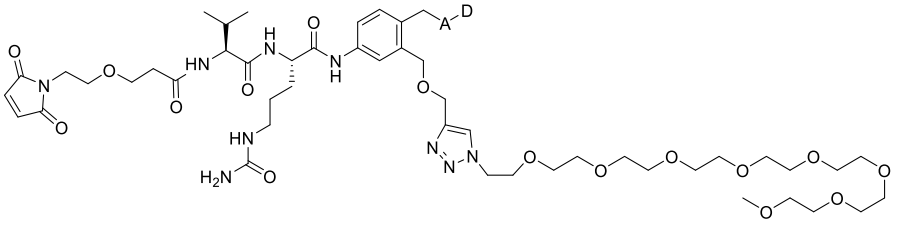
(8)  , wherein:

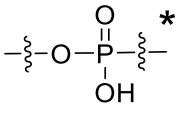
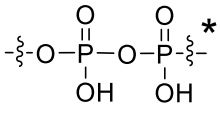
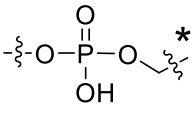
Xb is -CH_2-, -OCH_2-, -$NHCH_2$- or –$NRCH_2$- and each R independently is H, -CH_3 or -$CH_2CH_2C(=O)OH$;

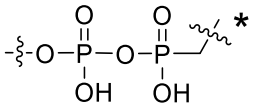
A is a bond, -OC(=O)-*,  ,  ,  ,  , -OC(=O)N(CH_3)CH_2CH_2N(CH_3)C(=O)-* or -OC(=O)N(CH_3)C(R^a)$_2$C(R^a)$_2$N(CH_3)C(=O)-*,

wherein each R^a is independently selected from H, C_1-C_6 alkyl, and C_3-C_8 cycloalkyl and the * of A indicates the point of attachment to D; and

D is an Mcl-1 inhibitor;

(9)  , wherein:

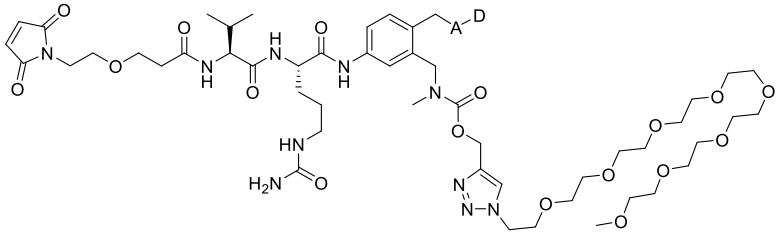
A is a bond, -OC(=O)-*,  ,  ,  ,

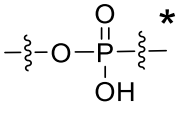
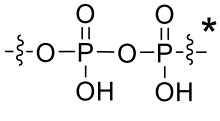
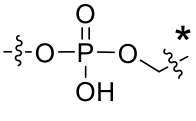
 , -OC(=O)N(CH_3)CH_2CH_2N(CH_3)C(=O)-* or

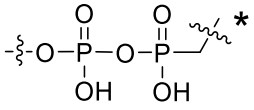
-OC(=O)N(CH_3)C(R^a)$_2$C(R^a)$_2$N(CH_3)C(=O)-*,

wherein each R^a is independently selected from H, C_1-C_6 alkyl, and C_3-C_8 cycloalkyl and the * of A indicates the point of attachment to D; and

D is an Mcl-1 inhibitor;

(10)  , wherein:

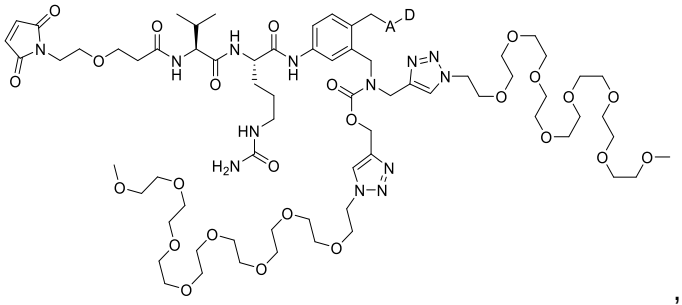
A is a bond, -OC(=O)-*,  ,  ,  ,

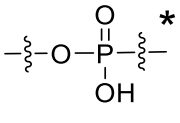
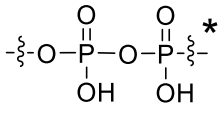
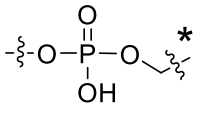
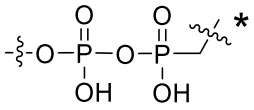
 , -OC(=O)N(CH_3)CH_2CH_2N(CH_3)C(=O)-* or

-OC(=O)N(CH_3)C(R^a)$_2$C(R^a)$_2$N(CH_3)C(=O)-*,

wherein each R^a is independently selected from H, C_1-C_6 alkyl, and C_3-C_8 cycloalkyl and the * of A indicates the point of attachment to D; and

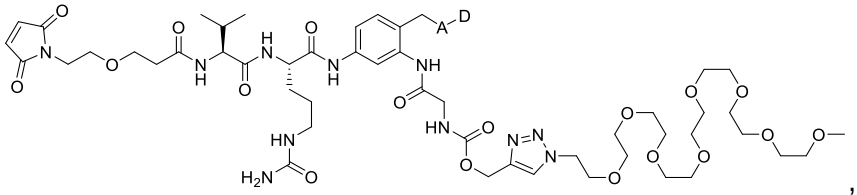
D is an Mcl-1 inhibitor;

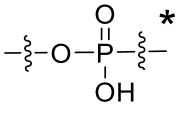
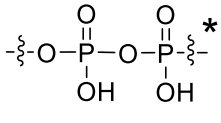
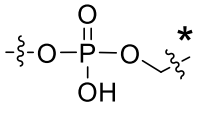
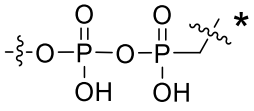
(11)  , wherein:

A is a bond, -OC(=O)-*,  ,  ,  ,  , -OC(=O)N(CH_3)CH_2CH_2N(CH_3)C(=O)-* or -OC(=O)N(CH_3)C(R^a)$_2$C(R^a)$_2$N(CH_3)C(=O)-*,

wherein each R^a is independently selected from H, C_1-C_6 alkyl, and C_3-C_8 cycloalkyl and the * of A indicates the point of attachment to D; and

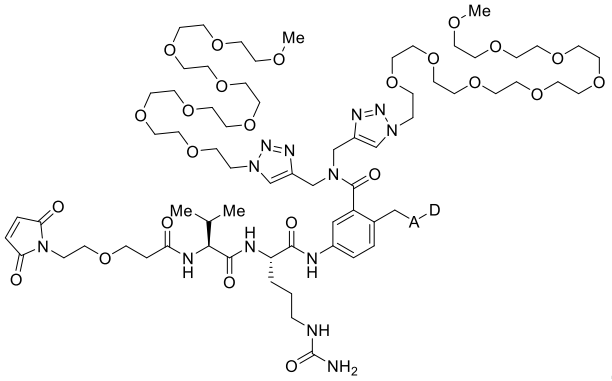
D is an Mcl-1 inhibitor;

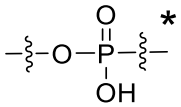
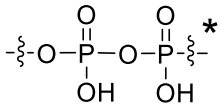
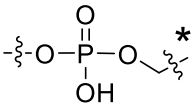
(12)  , wherein:

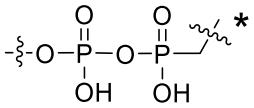
A is a bond, -OC(=O)-*,  ,  ,  ,  , -OC(=O)N(CH_3)CH_2CH_2N(CH_3)C(=O)-* or -OC(=O)N(CH_3)C(R^a)$_2$C(R^a)$_2$N(CH_3)C(=O)-*,

wherein each R^a is independently selected from H, C_1-C_6 alkyl, and C_3-C_8 cycloalkyl and the * of A indicates the point of attachment to D; and

D is an Mcl-1 inhibitor;

(13)  , wherein:

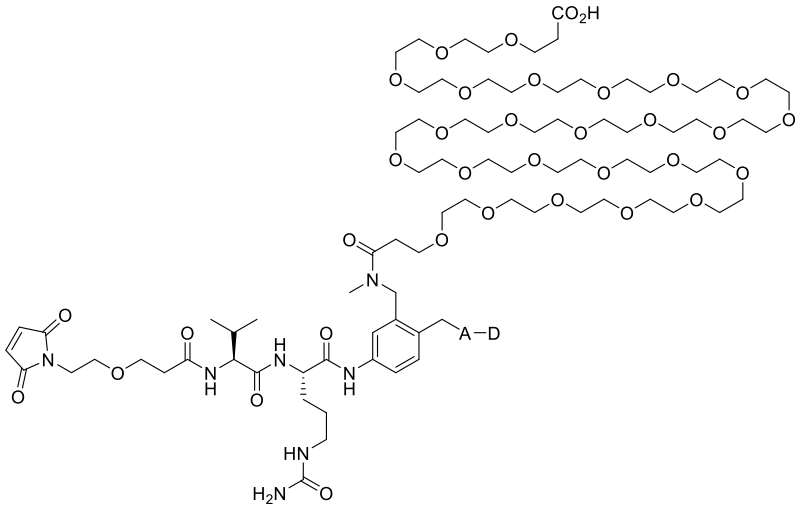
A is a bond, -OC(=O)-*,  ,  ,  ,

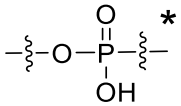
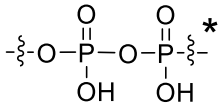
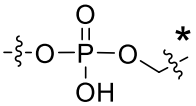
 , -OC(=O)N(CH_3)CH_2CH_2N(CH_3)C(=O)-* or

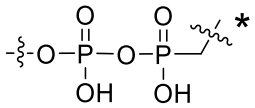
-OC(=O)N(CH_3)C(R^a)$_2$C(R^a)$_2$N(CH_3)C(=O)-*,

wherein each R^a is independently selected from H, C_1-C_6 alkyl, and C_3-C_8 cycloalkyl and the * of A indicates the point of attachment to D; and

D is an Mcl-1 inhibitor;

(14)  , wherein:

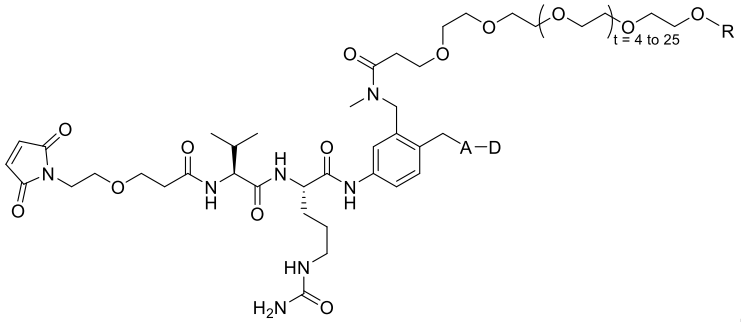
A is a bond, -OC(=O)-*,  ,  ,  ,

 , -OC(=O)N(CH_3)CH_2CH_2N(CH_3)C(=O)-* or

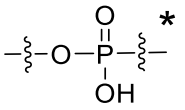
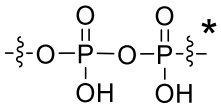
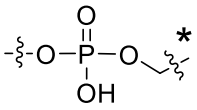
-OC(=O)N(CH_3)C(R^a)$_2$C(R^a)$_2$N(CH_3)C(=O)-*,

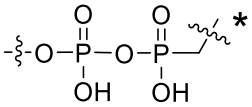
wherein each R^a is independently selected from H, C_1-C_6 alkyl, and C_3-C_8 cycloalkyl and the * of A indicates the point of attachment to D; and

D is an Mcl-1 inhibitor; or

(15)  , wherein:

each R independently is H, -CH_3 or -$CH_2CH_2C(=O)OH$;

A is a bond, -OC(=O)-*,  ,  ,  ,

 , -OC(=O)N(CH_3)CH_2CH_2N(CH_3)C(=O)-* or

-OC(=O)N(CH_3)C(R^a)$_2$C(R^a)$_2$N(CH_3)C(=O)-*,

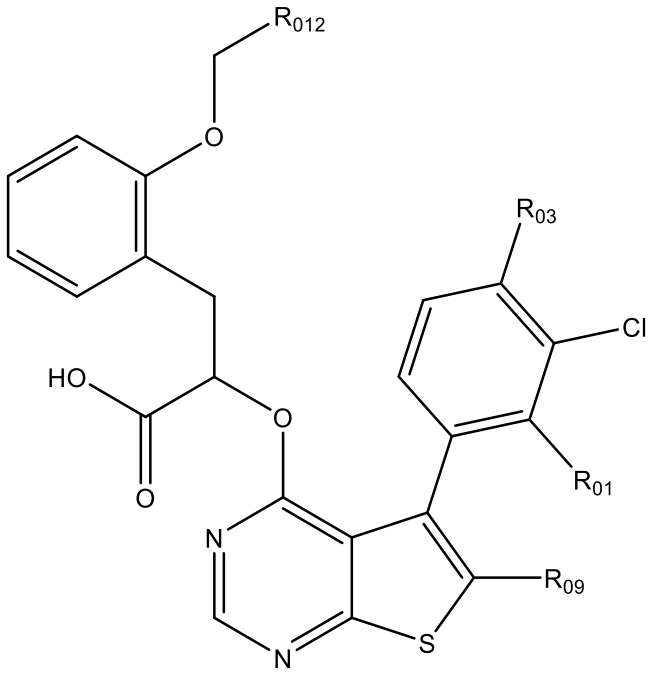
wherein each R^a is independently selected from H, C_1-C_6 alkyl, and C_3-C_8 cycloalkyl and the * of A indicates the point of attachment to D; and

D is an Mcl-1 inhibitor;

preferably for formulae (1) to (16), A is a bond and R is –CH_3.

9. The antibody-drug conjugate of any one of claims 1 to 8, wherein:

D comprises a compound of Formula (III):

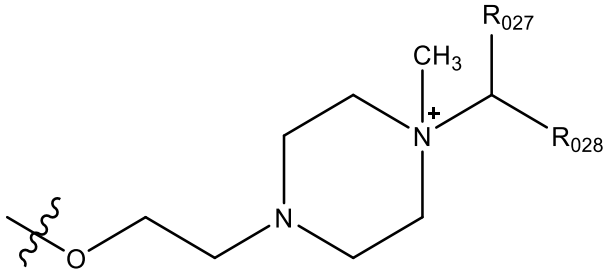


(III)

wherein:

R_{01} is a linear or branched $(C_1\text{-}C_6)$alkyl group,

R_{03} is $-O\text{-}(C_1\text{-}C_6)\text{alkyl-}NR_{011}R_{011}'$, or



,

wherein R_{011} and R_{011}' independently of one another are a hydrogen atom, an optionally substituted linear or branched $(C_1\text{-}C_6)$alkyl group, or $-(C_0\text{-}C_6)\text{alkyl-}Cy_{01}$;

or the pair (R_{011}, R_{011}') together with the nitrogen atom to which they are attached form an aromatic or non-aromatic ring containing 5 to 7 ring members, which optionally contains, in addition to the nitrogen atom, 1 to 3 heteroatoms selected from O, S and N, wherein the N atom may be substituted by 1 or 2 groups selected from a hydrogen atom or a linear or branched $(C_1\text{-}C_6)$alkyl group,

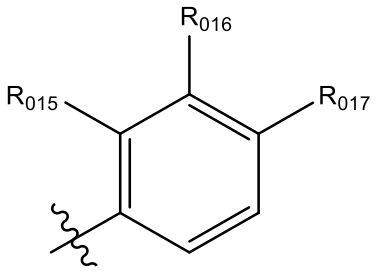
and wherein R_{027} is a hydrogen atom and R_{028} is a $-(CH_2)_{p0}\text{-}O\text{-}SO_2\text{-}O^-$ group or a $-(CH_2)_{p0}\text{-}SO_2\text{-}OR_{030}$ group;

R_{09} is a linear or branched $(C_2\text{-}C_6)$alkynyl group or $-Cy_{02}$,

R_{012} is $-Cy_{05}$, $-Cy_{05}\text{-}(C_0\text{-}C_6)\text{alkyl-}Cy_{06}$, or $-Cy_{05}\text{-}(C_0\text{-}C_6)\text{alkyl-}Cy_{09}$,

Cy_{01}, Cy_{02}, Cy_{05} and Cy_{06} independently of one another, are a cycloalkyl group, a

heterocycloalkyl group, an aryl group or a heteroaryl group, each of which is optionally substituted,

Cy_{09} is 

,

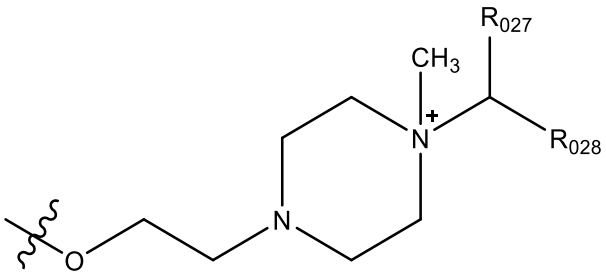
R_{015}, R_{016}, and R_{017} are as defined for formula (I),

wherein, at most, one of the R_{03}, R_{09}, or R_{012} groups, if present, is covalently attached to the linker,

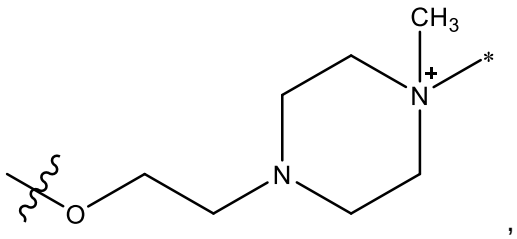
or the enantiomer, diastereoisomer, atropisomer, deuterated derivative, and/or pharmaceutically acceptable salt of any of the foregoing; preferably, wherein:

(i) R_{01} is methyl or ethyl;

(ii) R_{03} is -O-CH_2-CH_2-$NR_{011}R_{011}$' in which R_{011} and R_{011}' form, together with the nitrogen atom carrying them, a piperazinyl group which may be substituted by a substituted by a group areing a hydrogen atom or a linear or branched (C_1-C_6)alkyl group);

(iii) R_{03} comprises the formula: 

, wherein R_{027} is a hydrogen atom and R_{028} is a -$(CH_2)_{p0}$-SO_2-OR_{030} group;

(iv) R_{03} comprises the formula: 

,

wherein —* is a bond to the linker;

(v) R_{09} is Cy_{02}; preferably,

Cy_{02} is an optionally substituted aryl group;

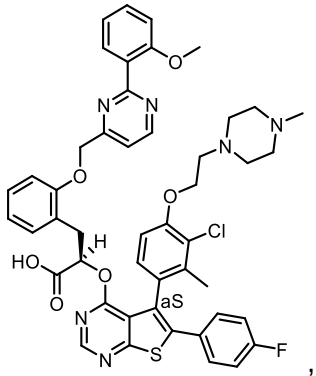
(vi) Cy_{05} comprises a heteroaryl group selected from a pyrazolyl group and a pyrimidinyl group; or

(vii) Cy_{05} is a pyrimidinyl group;

preferably, wherein the L is attached to D by a covalent bond from L to R_{03} of formula (I), (II), or (III); or the L is attached to D by a covalent bond from L to R_{09} of formula (I), (II), or (III).

10. The antibody-drug conjugate of any one of claims 1 to 9, wherein:

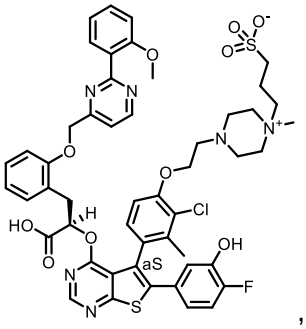
(1) D comprises:



,

or an enantiomer, diastereoisomer, atropisomer, deuterated derivative, and/or pharmaceutically acceptable salt of any of the foregoing;

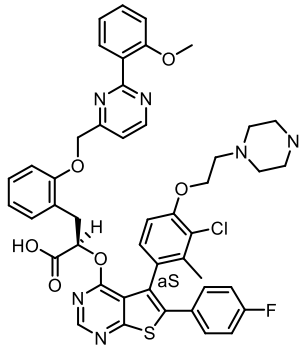
(2) D comprises:



,

or an enantiomer, diastereoisomer, atropisomer, deuterated derivative, and/or pharmaceutically acceptable salt of any of the foregoing;

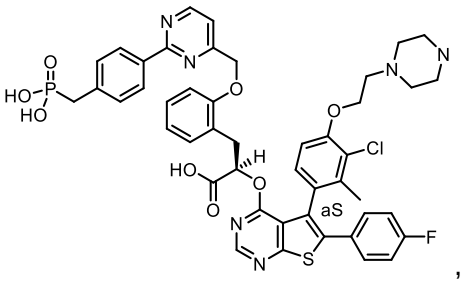
(3) D comprises:



,

or an enantiomer, diastereoisomer, atropisomer, deuterated derivative, and/or pharmaceutically acceptable salt of any of the foregoing;

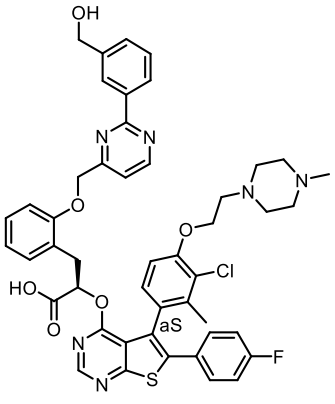
(4) D comprises:



,

or an enantiomer, diastereoisomer, atropisomer, deuterated derivative, and/or pharmaceutically acceptable salt of any of the foregoing;

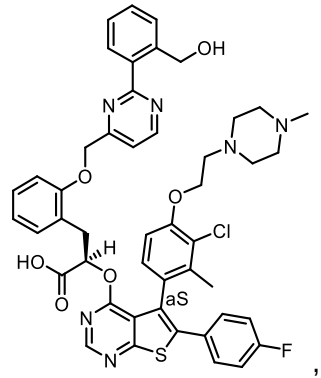
(5) D comprises:



,

or an enantiomer, diastereoisomer, atropisomer, deuterated derivative, and/or pharmaceutically acceptable salt of any of the foregoing;

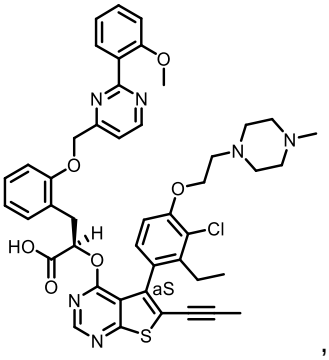
(6) D comprises:



,

or an enantiomer, diastereoisomer, atropisomer, deuterated derivative, and/or pharmaceutically acceptable salt of any of the foregoing;

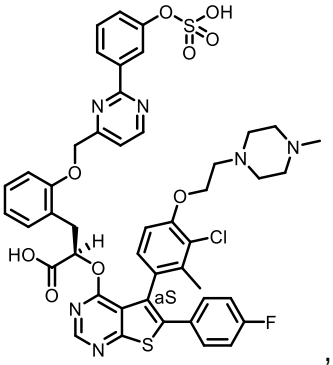
(7) D comprises:



,

or an enantiomer, diastereoisomer, atropisomer, deuterated derivative, and/or pharmaceutically acceptable salt of any of the foregoing;

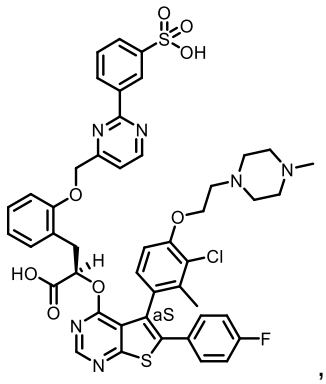
(8) D comprises:



,

or an enantiomer, diastereoisomer, atropisomer, deuterated derivative, and/or pharmaceutically acceptable salt of any of the foregoing;

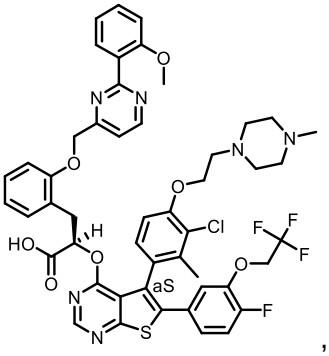
(9) D comprises:



,

or an enantiomer, diastereoisomer, atropisomer, deuterated derivative, and/or pharmaceutically acceptable salt of any of the foregoing;

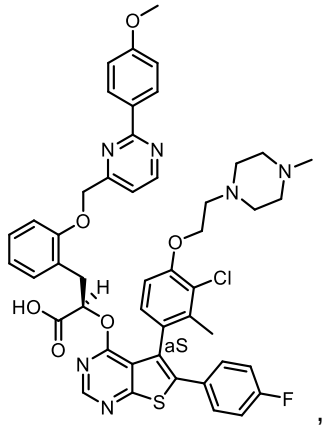
(10) D comprises:



,

or an enantiomer, diastereoisomer, atropisomer, deuterated derivative, and/or pharmaceutically acceptable salt of any of the foregoing;

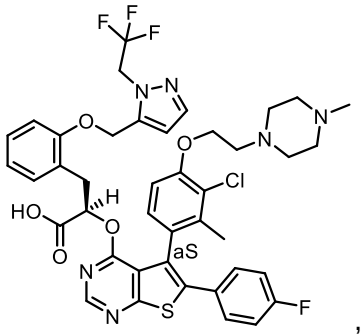
(11) D comprises:



,

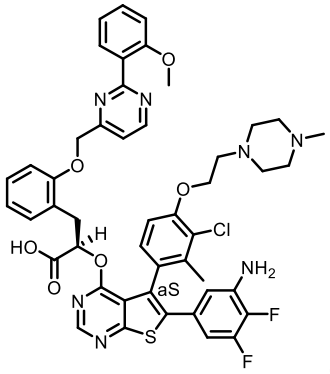
or an enantiomer, diastereoisomer, atropisomer, deuterated derivative, and/or pharmaceutically acceptable salt of any of the foregoing;

(12) D comprises:



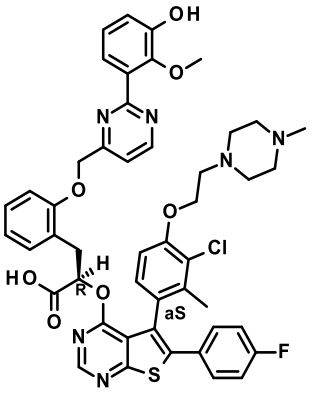
or an enantiomer, diastereoisomer, atropisomer, deuterated derivative, and/or pharmaceutically acceptable salt of any of the foregoing; or

(13) D comprises:



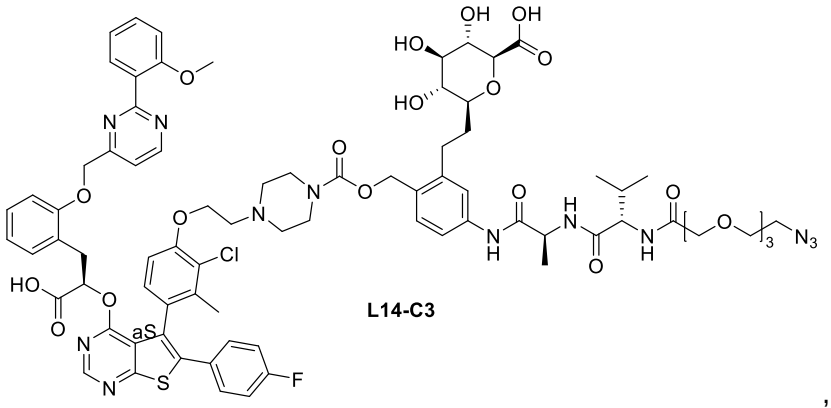
or an enantiomer, diastereoisomer, atropisomer, deuterated derivative, and/or pharmaceutically acceptable salt of any of the foregoing;

(14) D comprises:

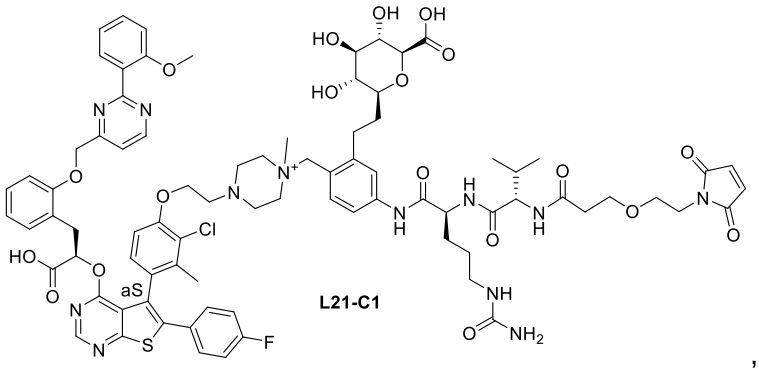


or an enantiomer, diastereoisomer, atropisomer, deuterated derivative, and/or pharmaceutically acceptable salt of any of the foregoing;

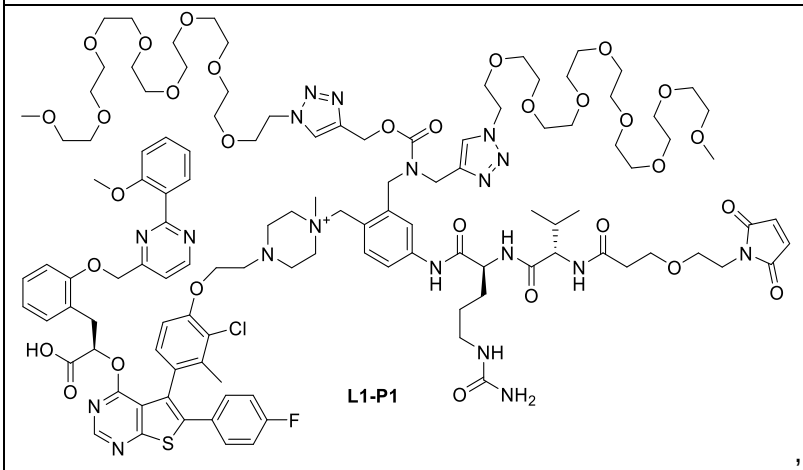
(15) -(L-D) is formed from a compound selected from table below or an enantiomer, diastereoisomer, atropisomer, deuterated derivative, and/or pharmaceutically acceptable salt thereof


L14-C3

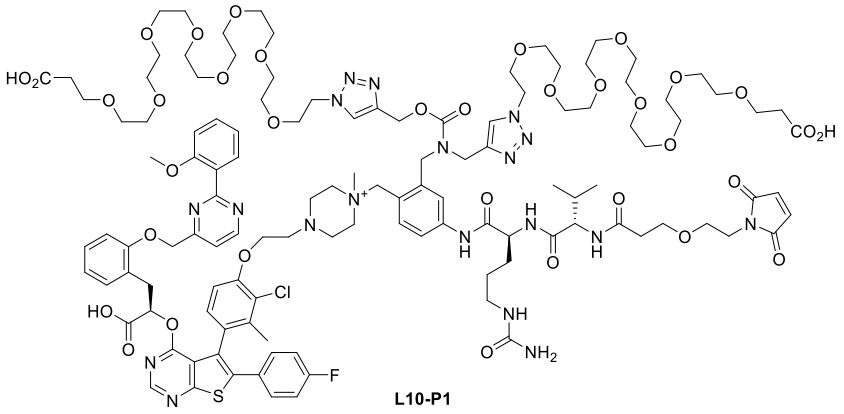
,


L21-C1

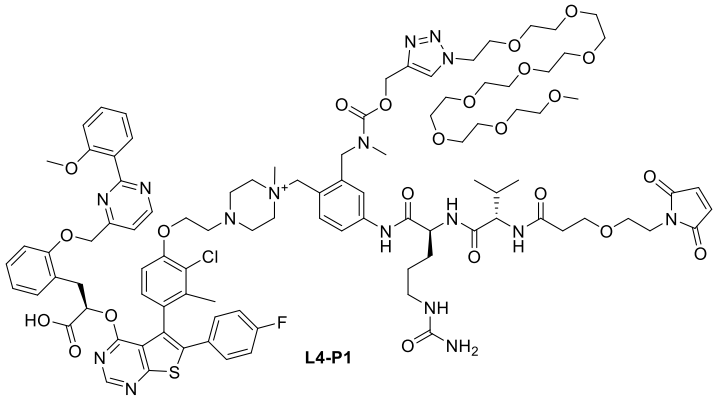
,


L1-P1

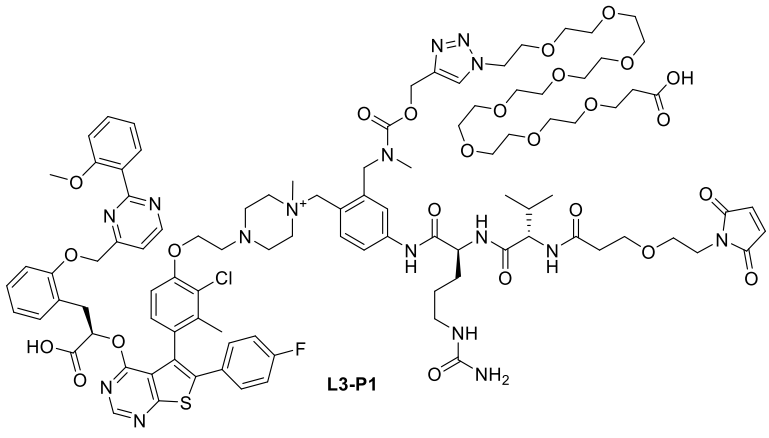
,



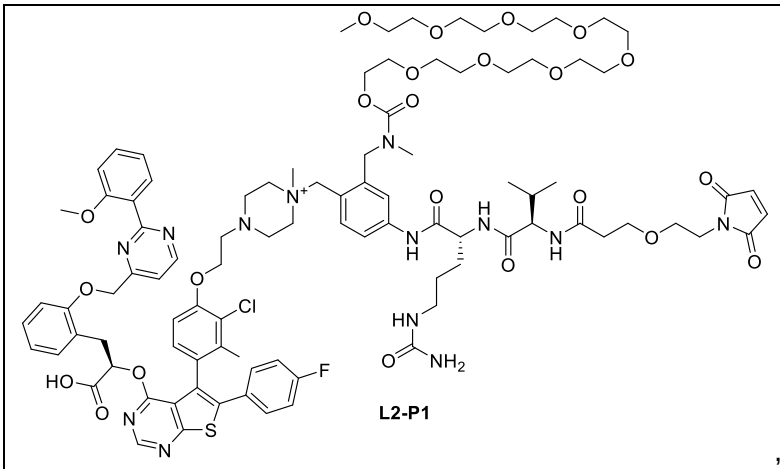
L10-P1 ,



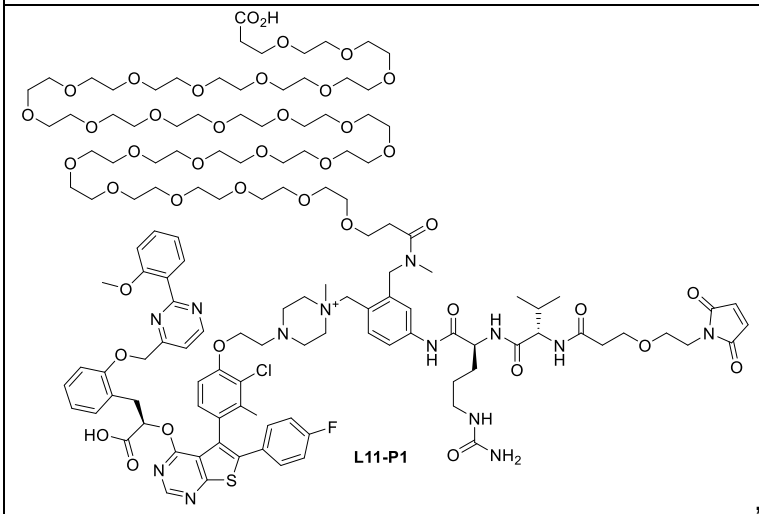
L4-P1 ,



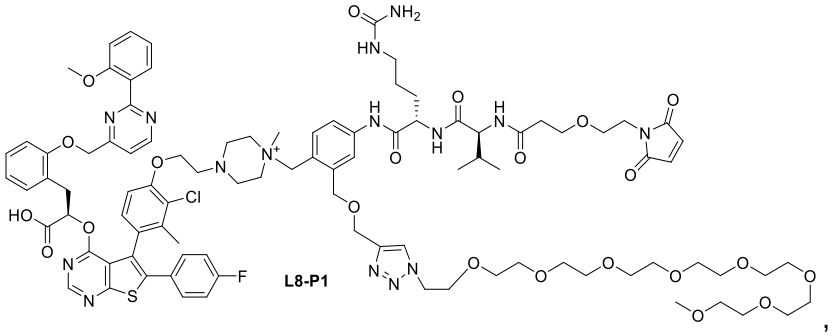
L3-P1 ,



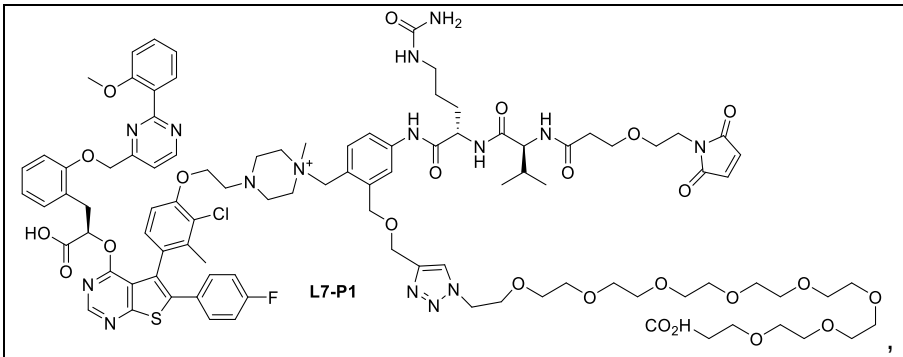
L2-P1 ,

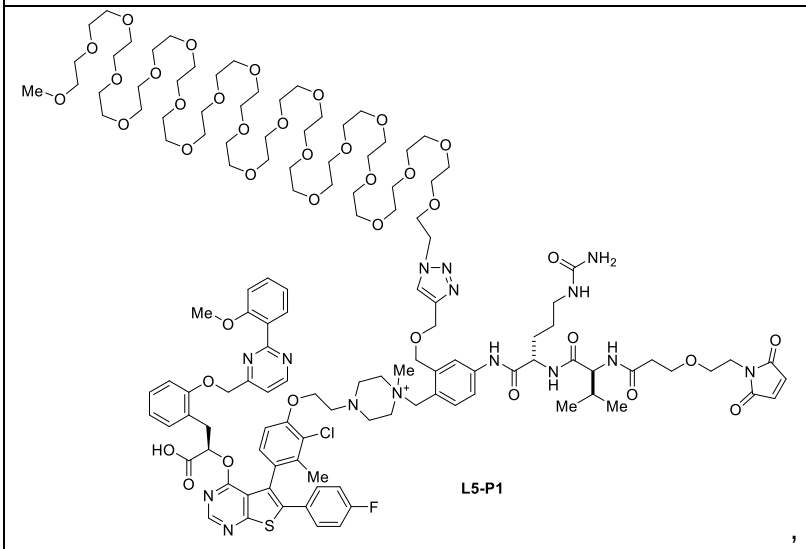


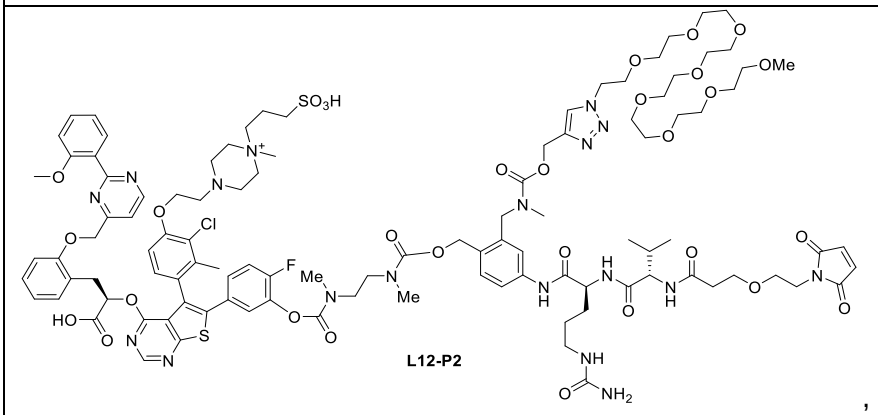
L11-P1 ,

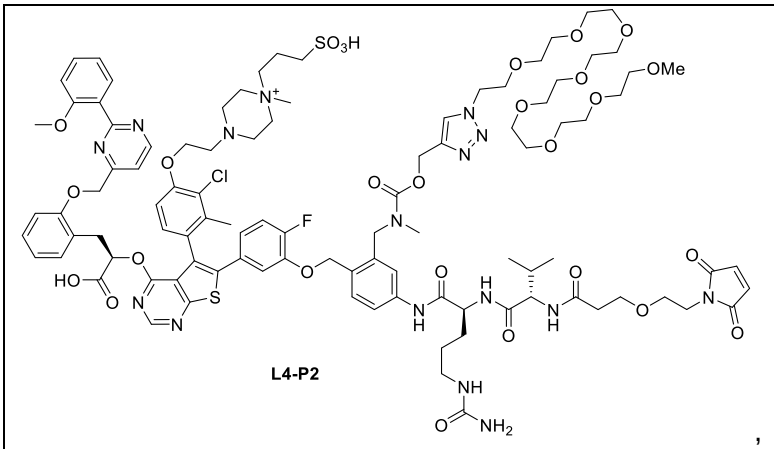


L8-P1 ,


L7-P1

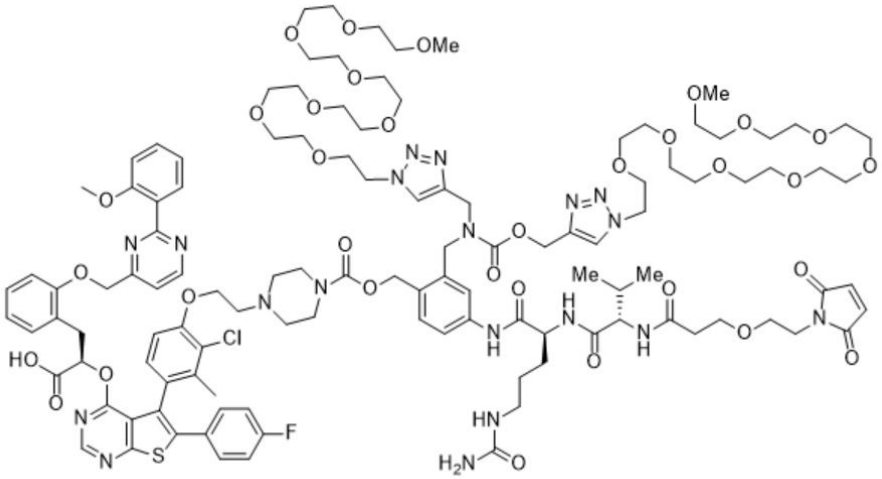

L5-P1


L12-P2

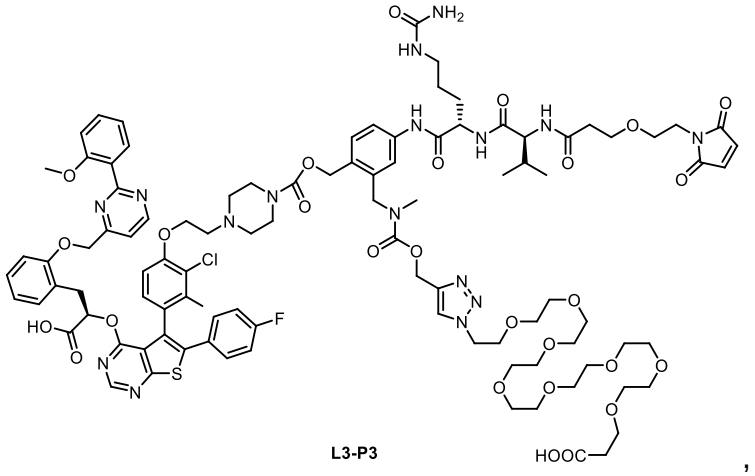


L4-P2

,

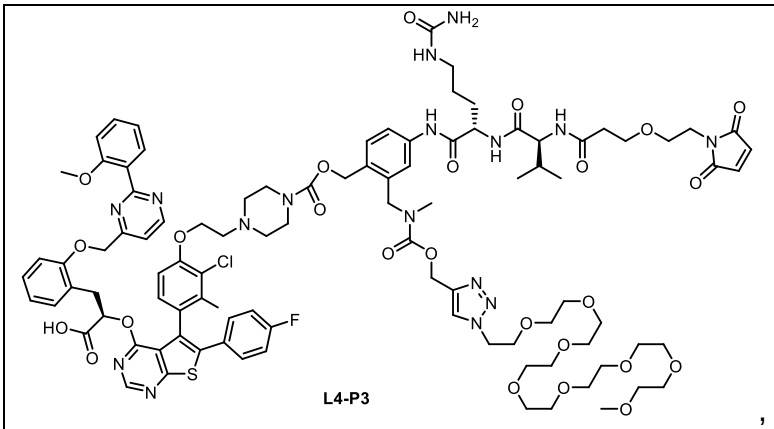


L1-P3,

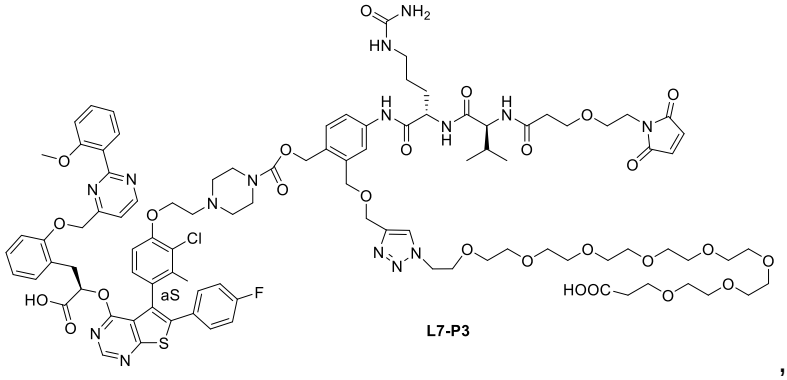


L3-P3

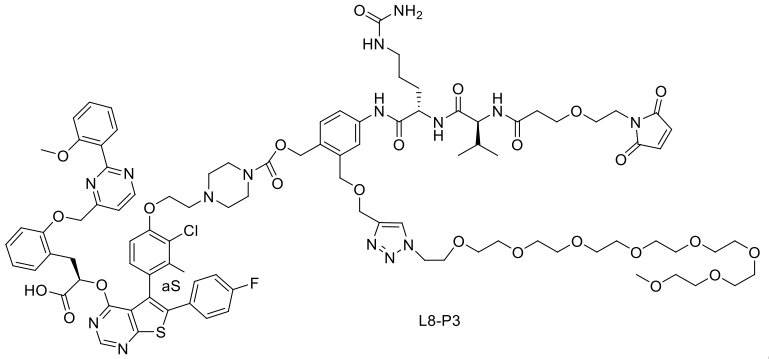
,



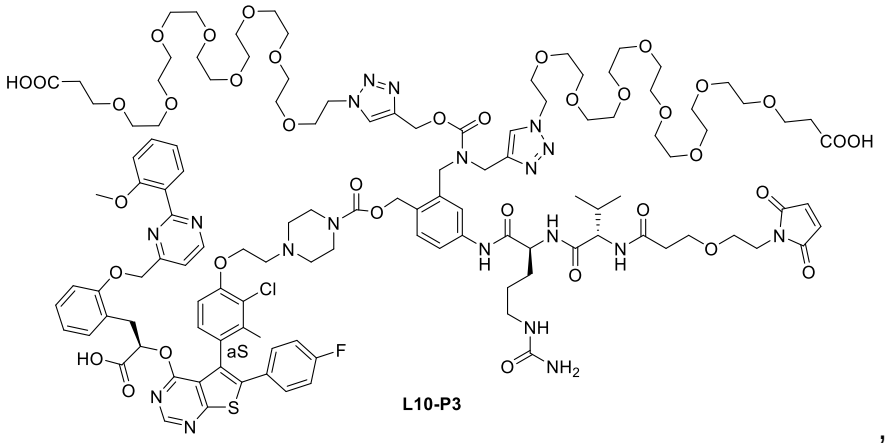
L4-P3 ,



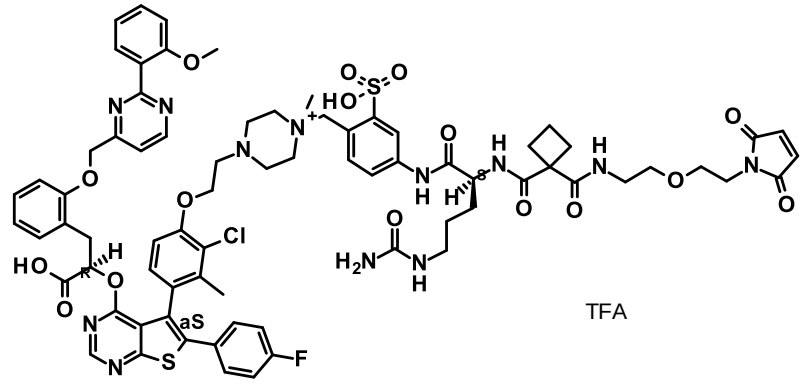
L7-P3 ,



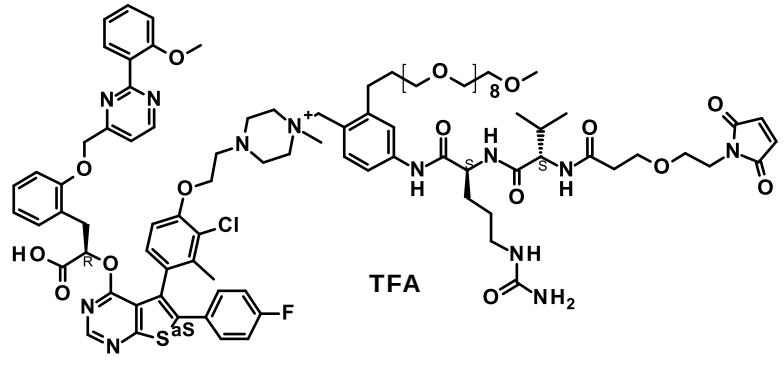
L8-P3 ,



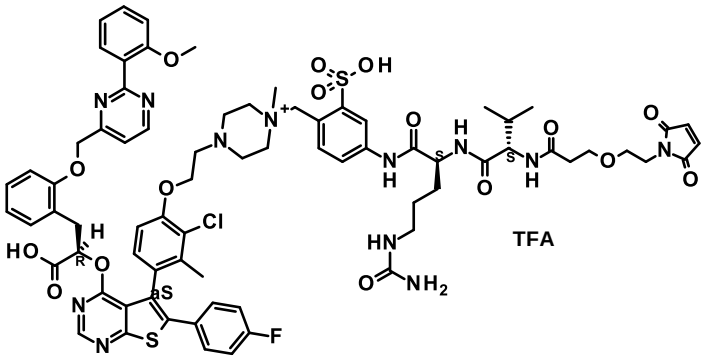
,



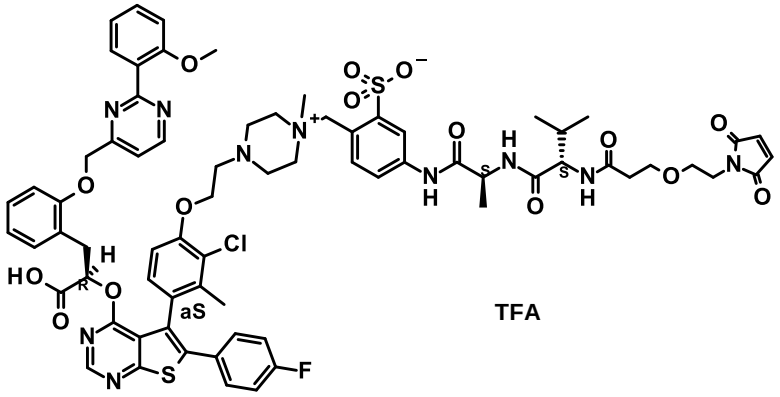
L25-P1.



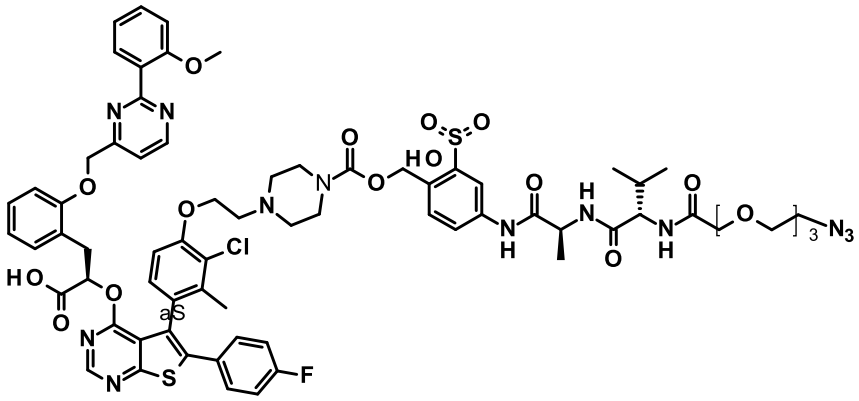
L26-P1,



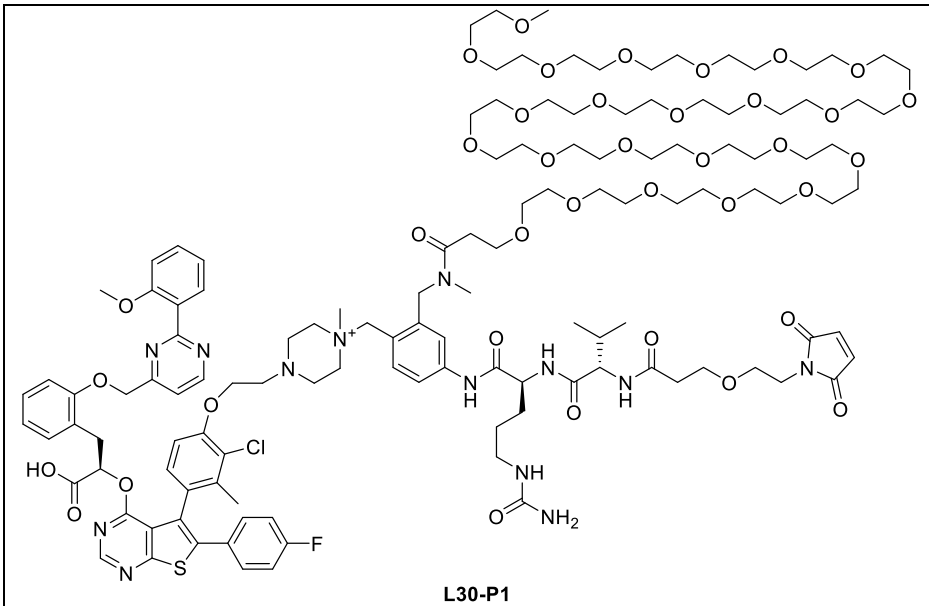
L27-P1,



L28-P1,

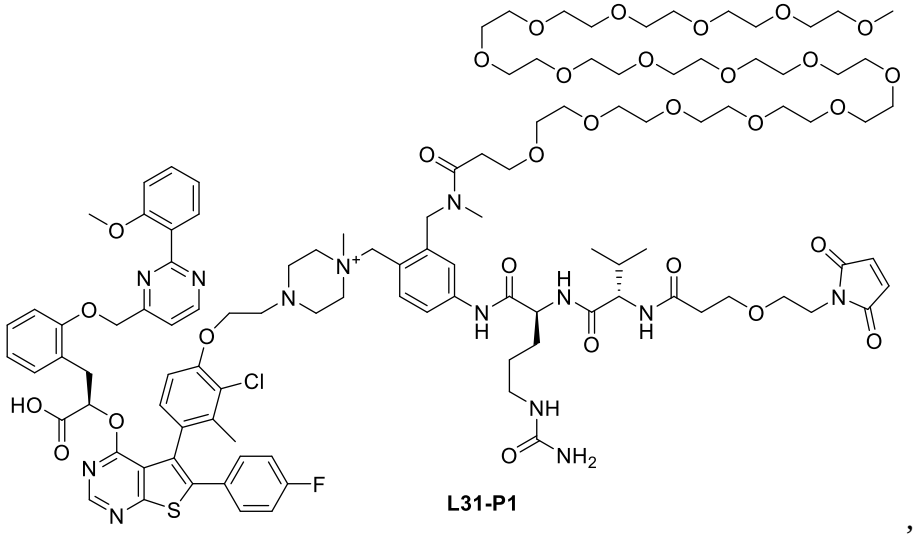


L29-C3,



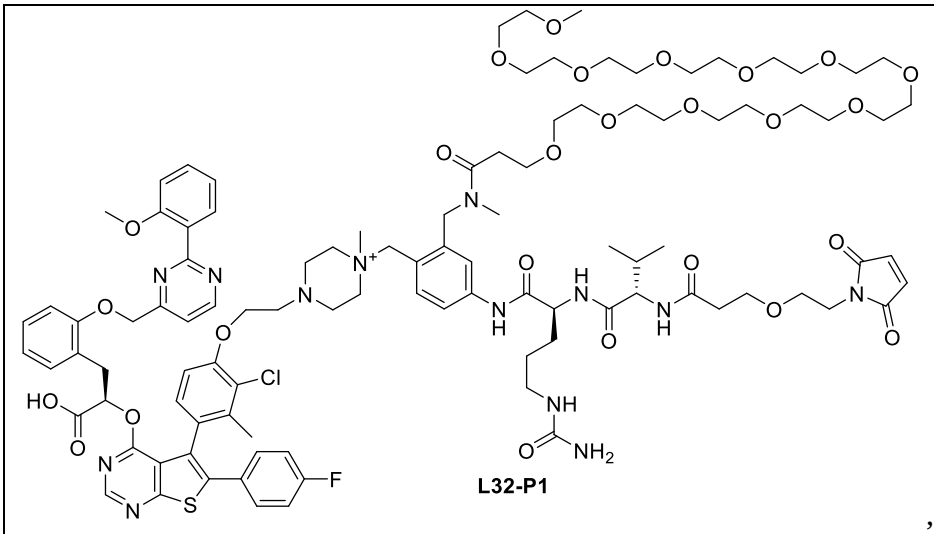
L30-P1

,



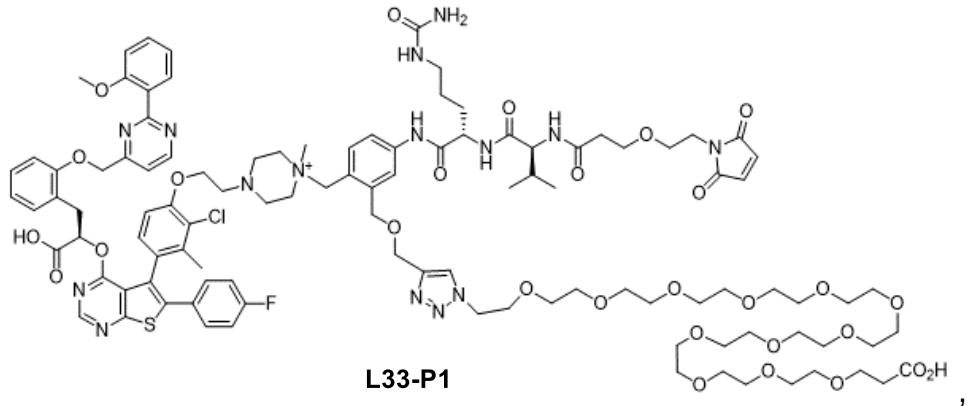
L31-P1

,



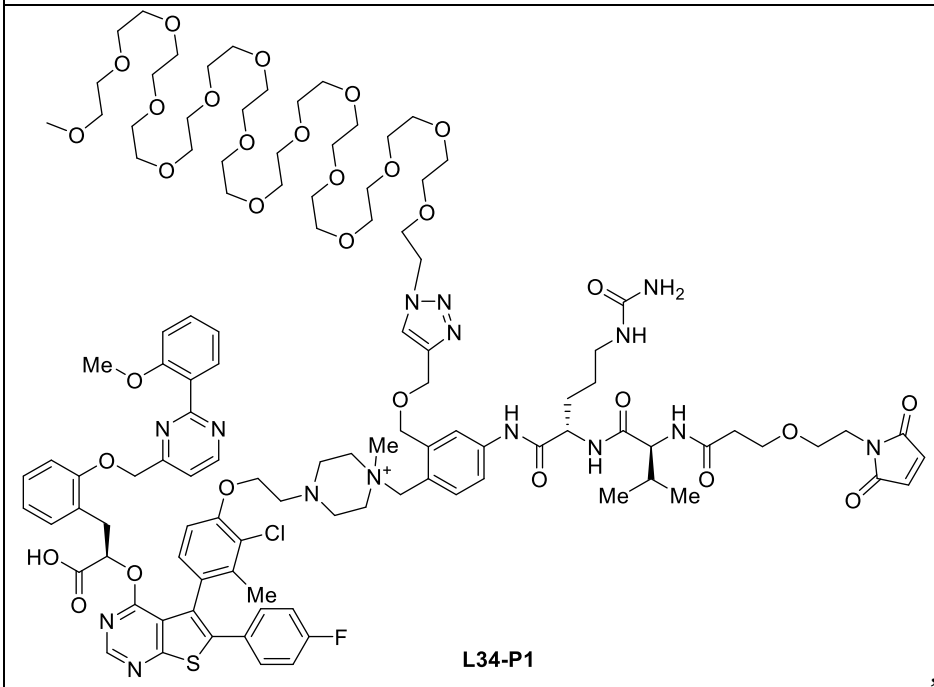
L32-P1

,



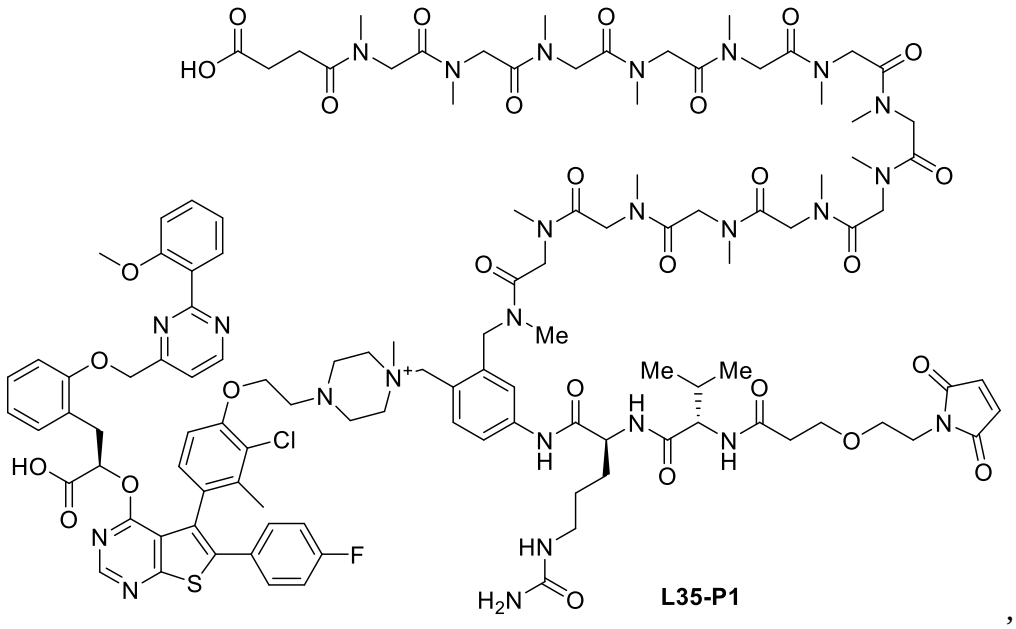
L33-P1

,



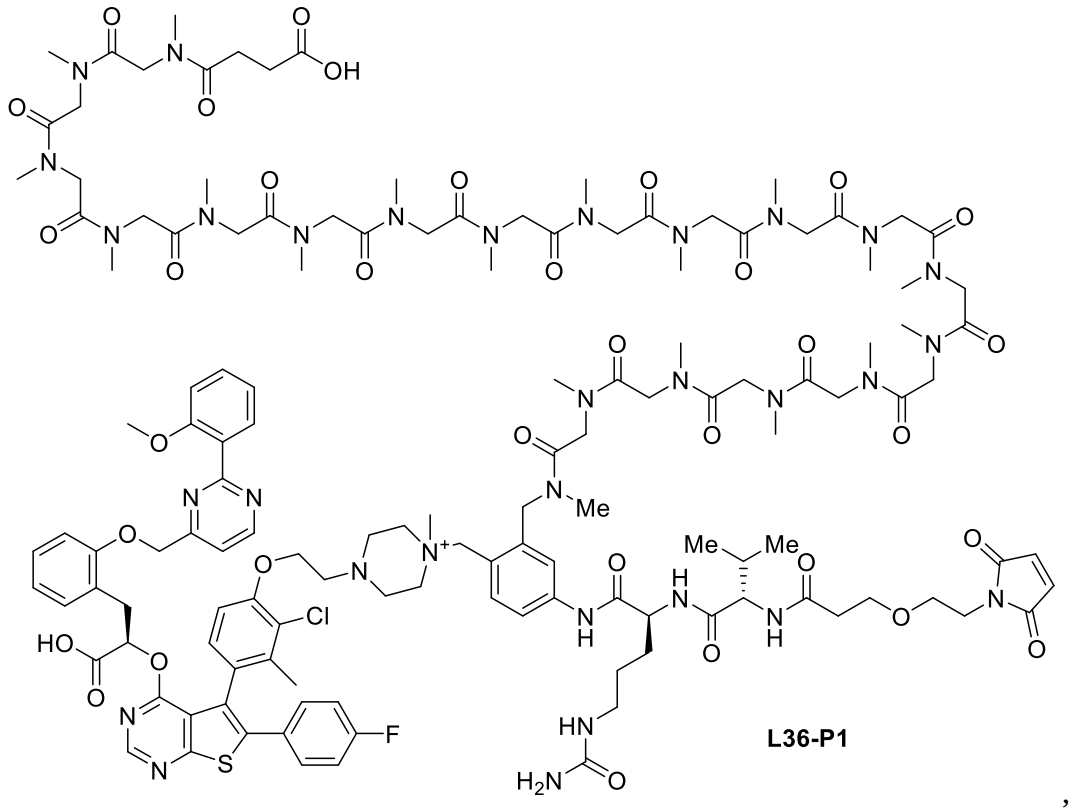
L34-P1

,



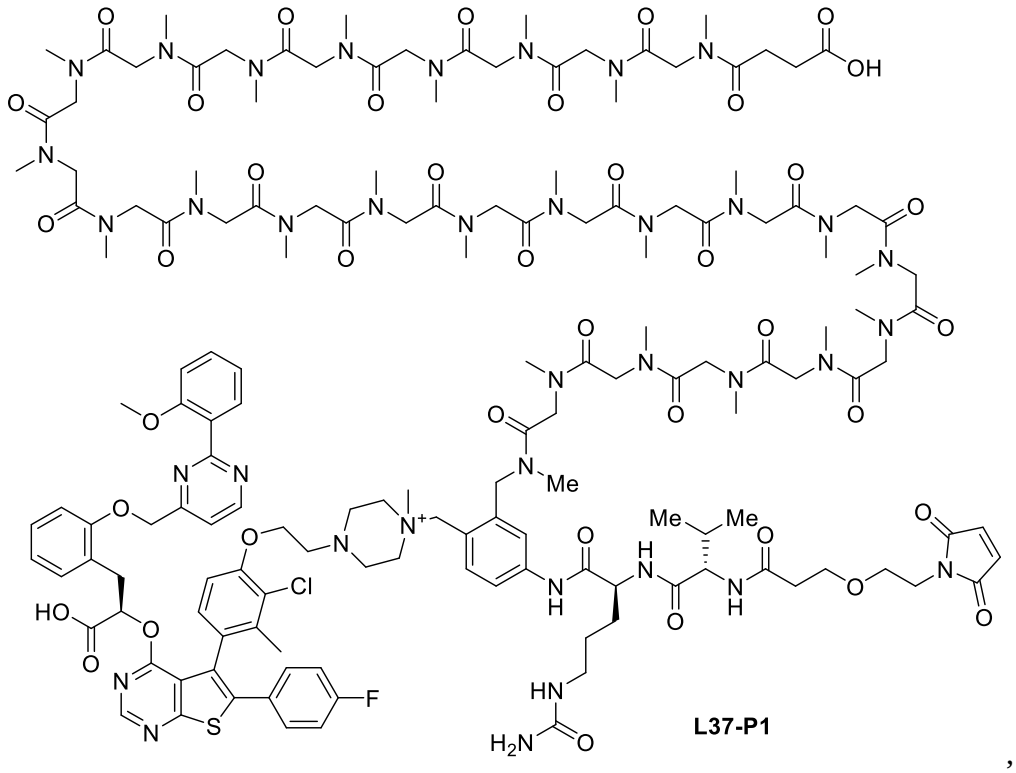
L35-P1

,



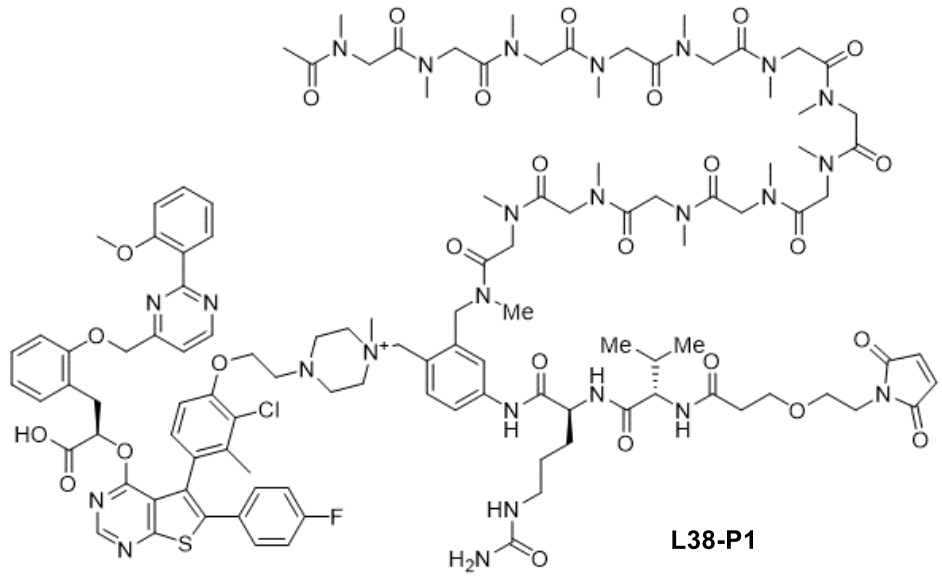
L36-P1

,



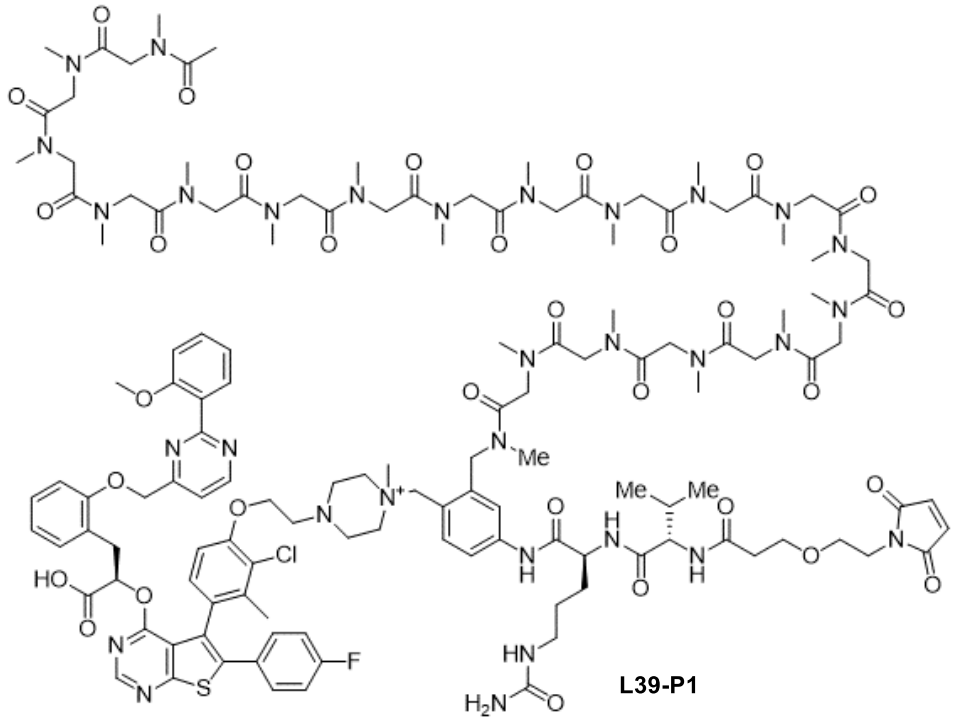
L37-P1

,



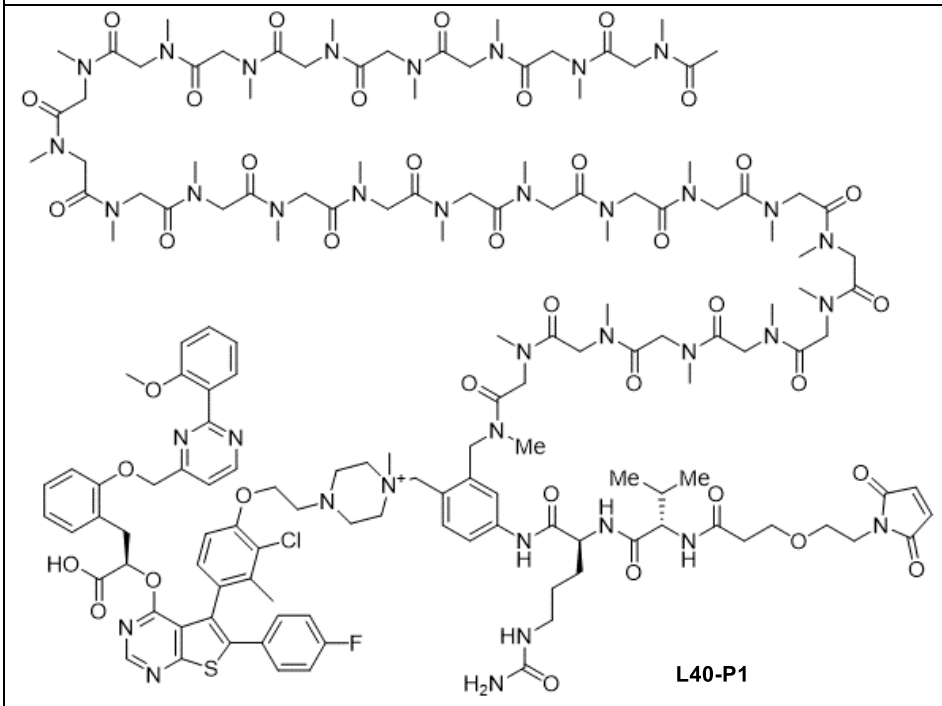
L38-P1

,



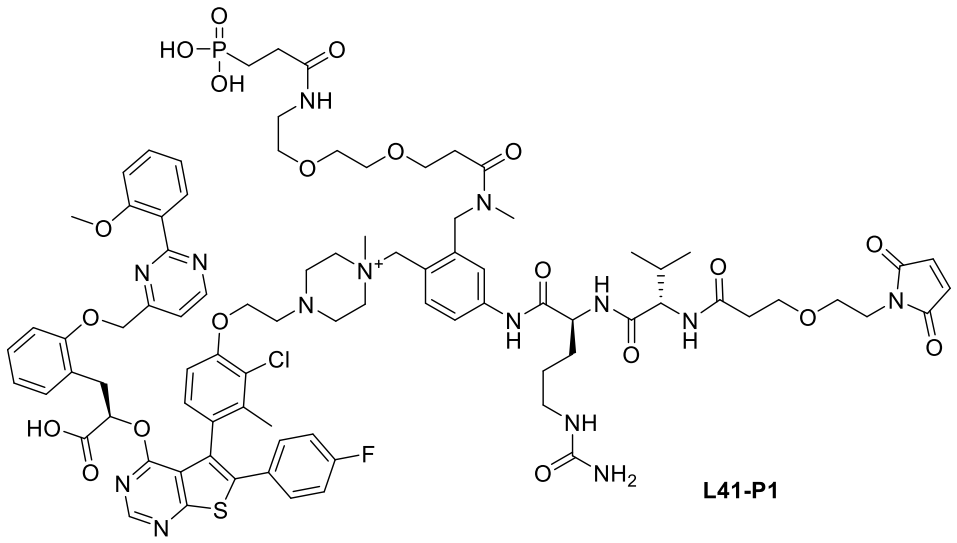
L39-P1

,



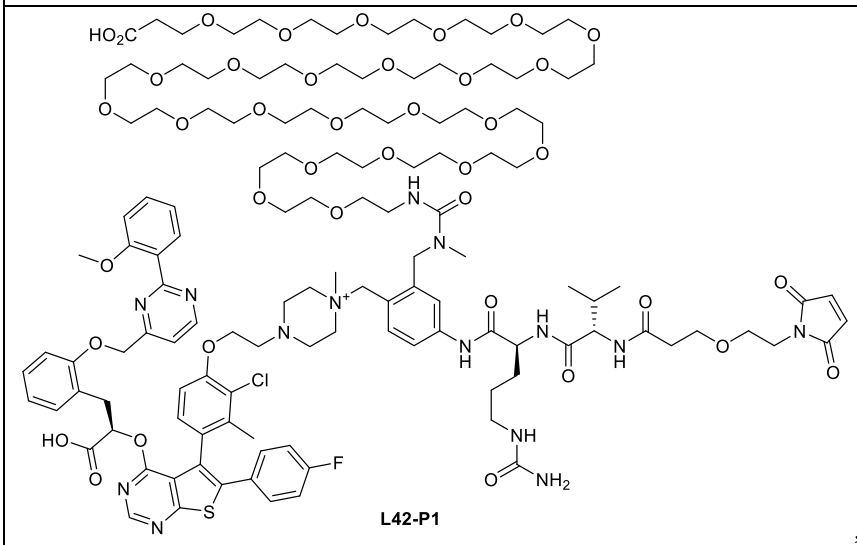
L40-P1

,



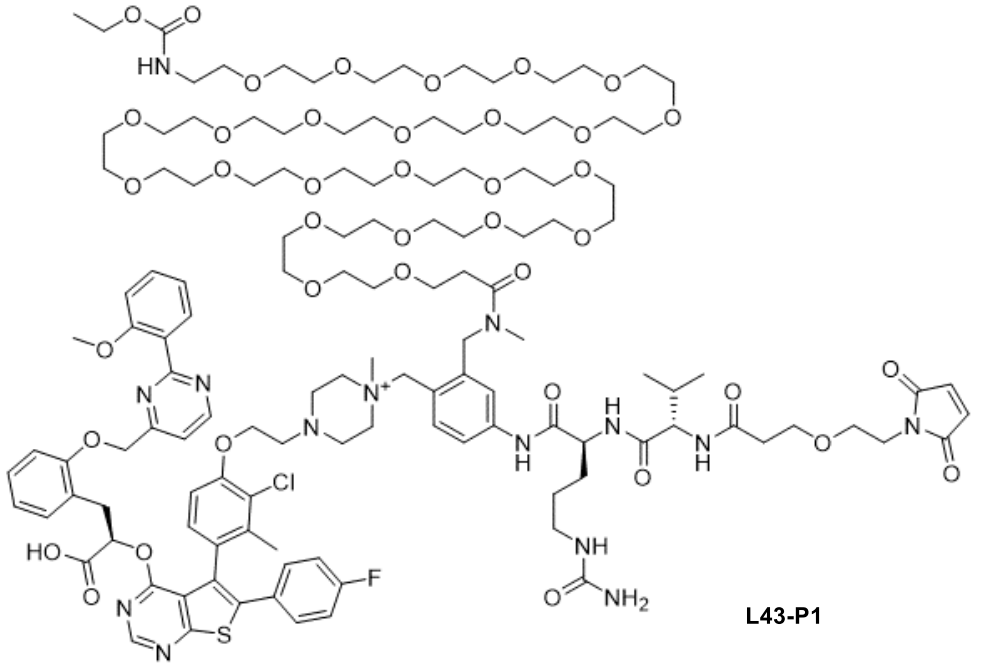
L41-P1

,



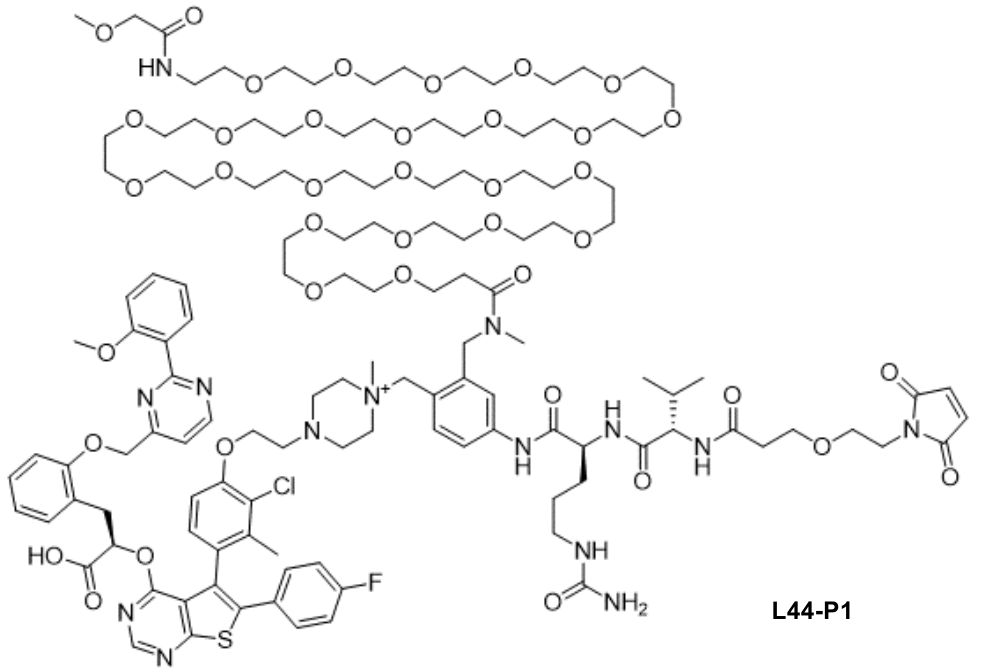
L42-P1

,



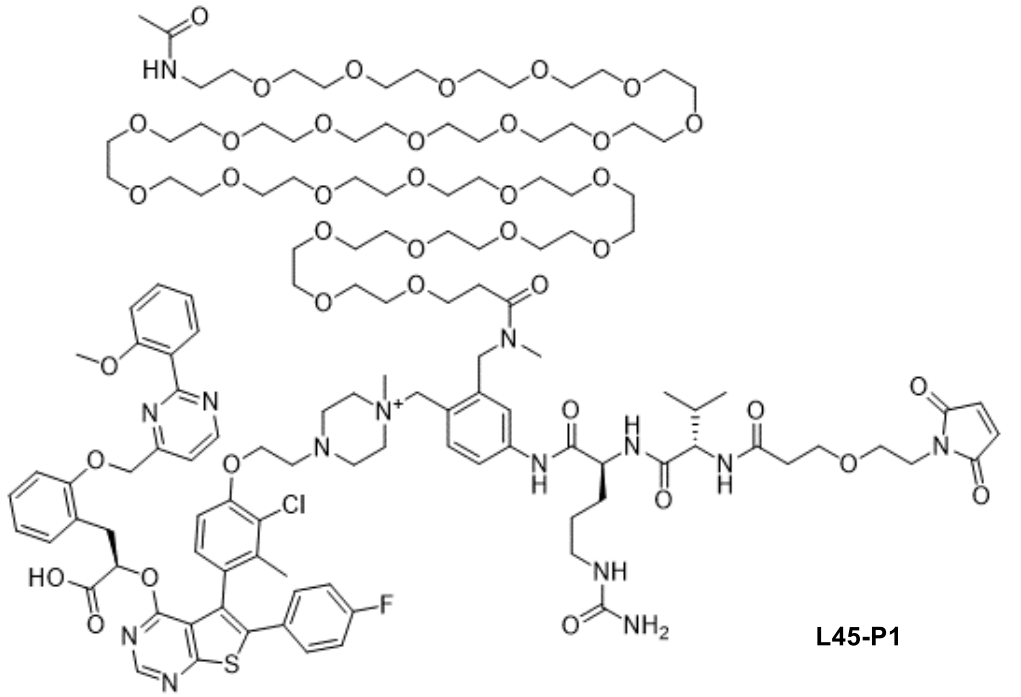
L43-P1

,



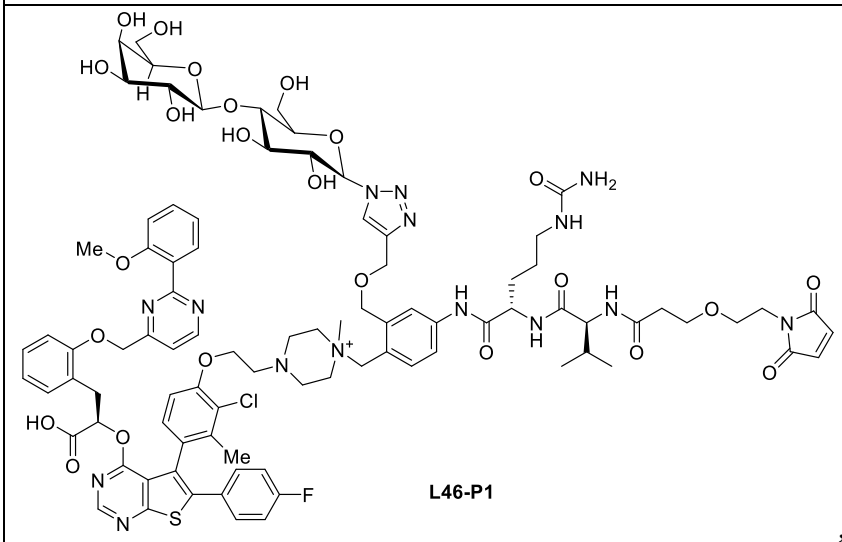
L44-P1

,



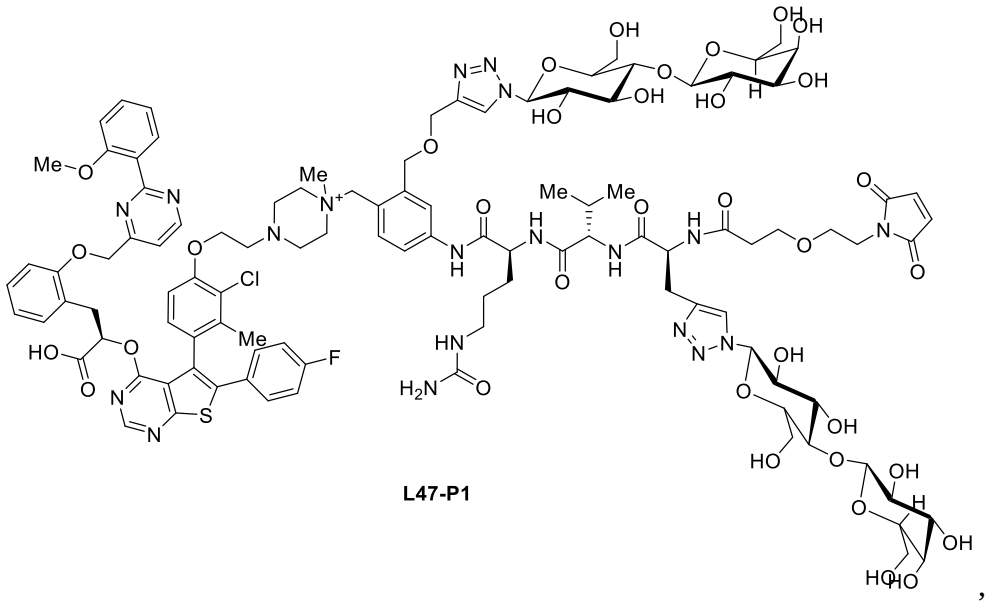
L45-P1

,



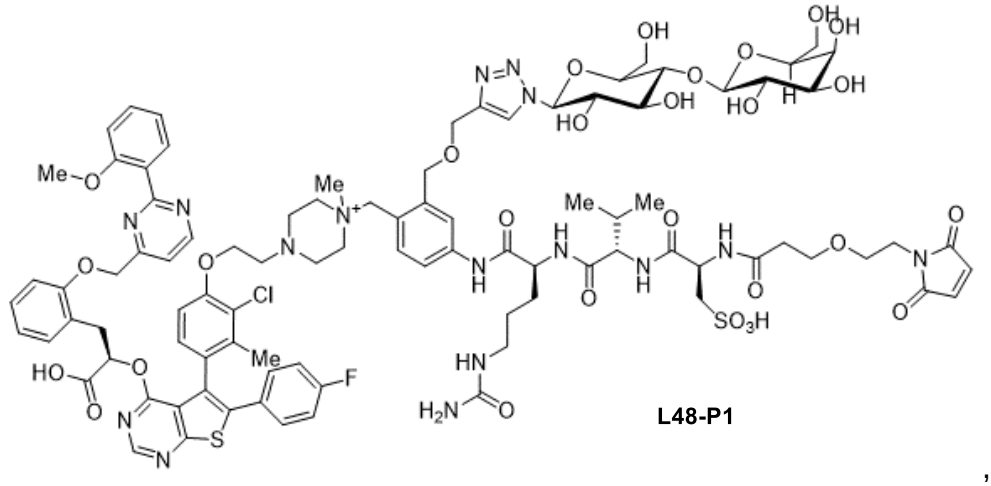
L46-P1

,



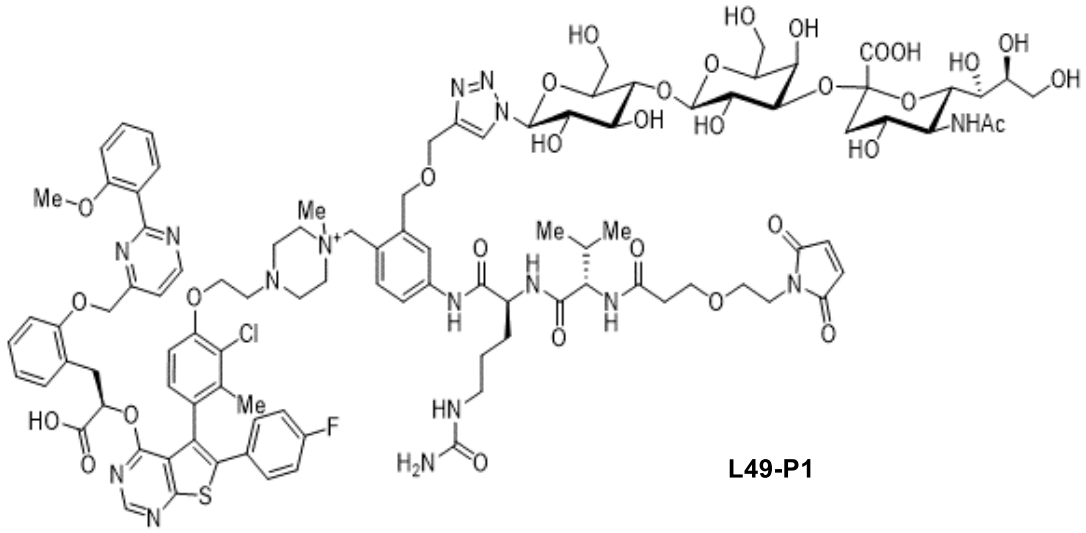
L47-P1

,



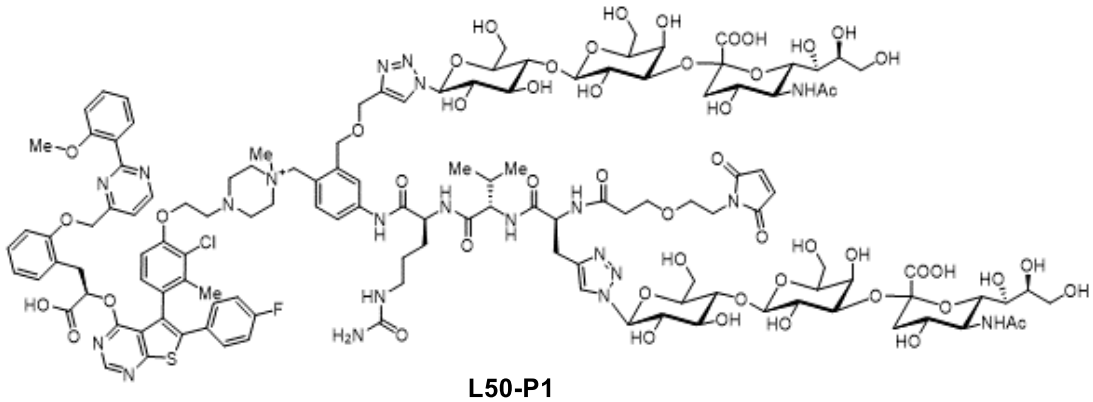
L48-P1

,



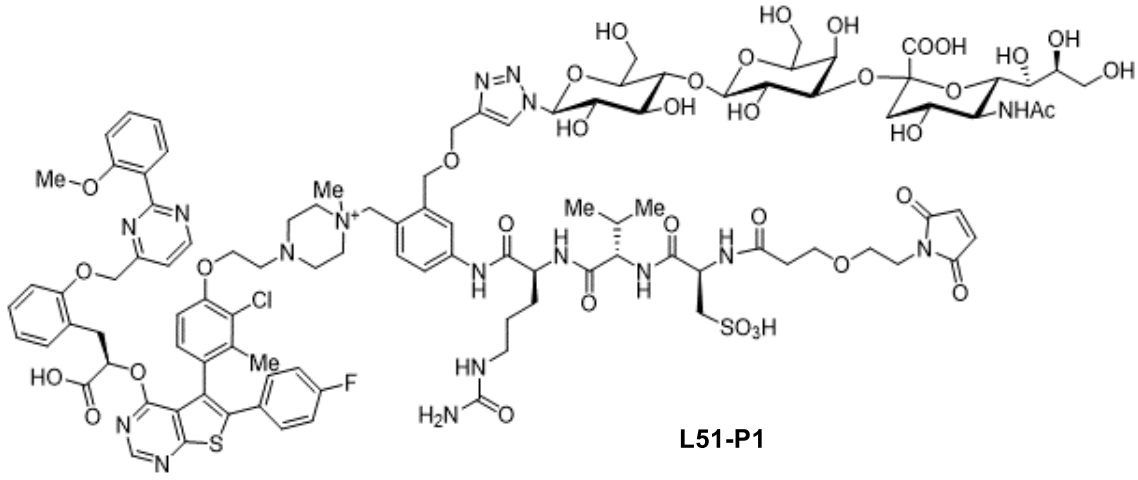
L49-P1

,



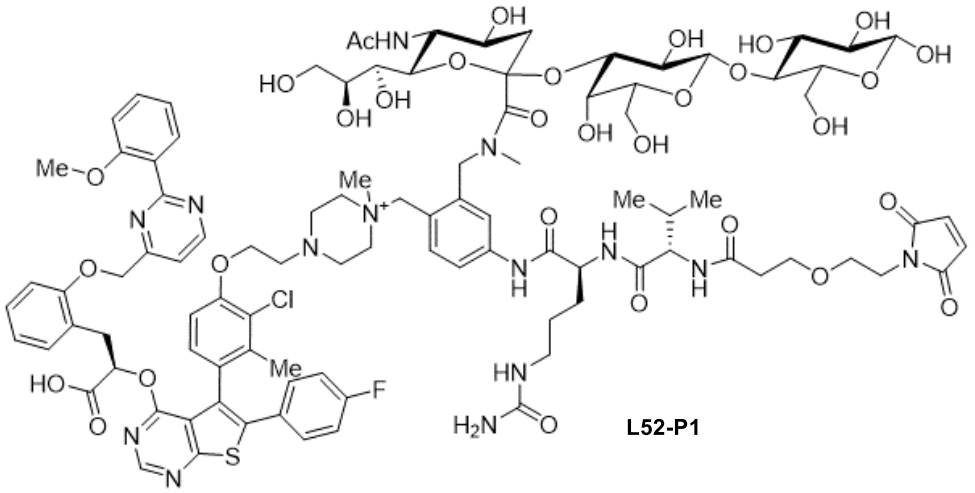
L50-P1

,



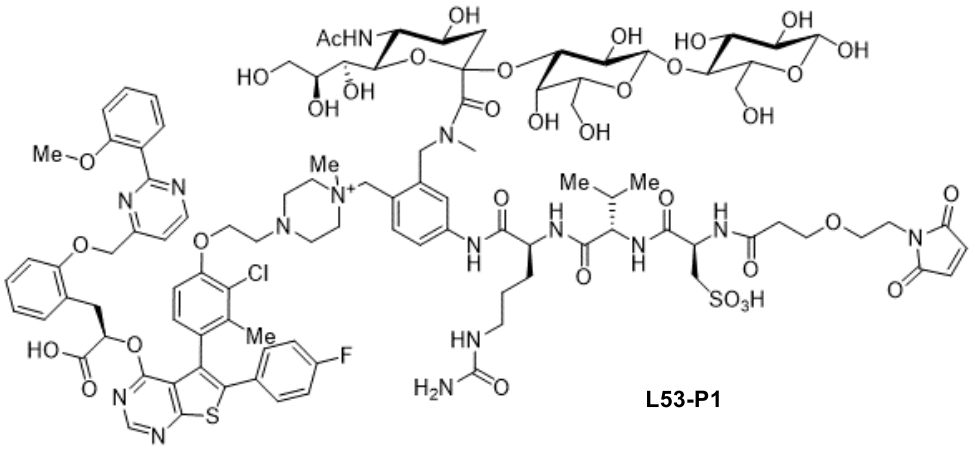
L51-P1

,



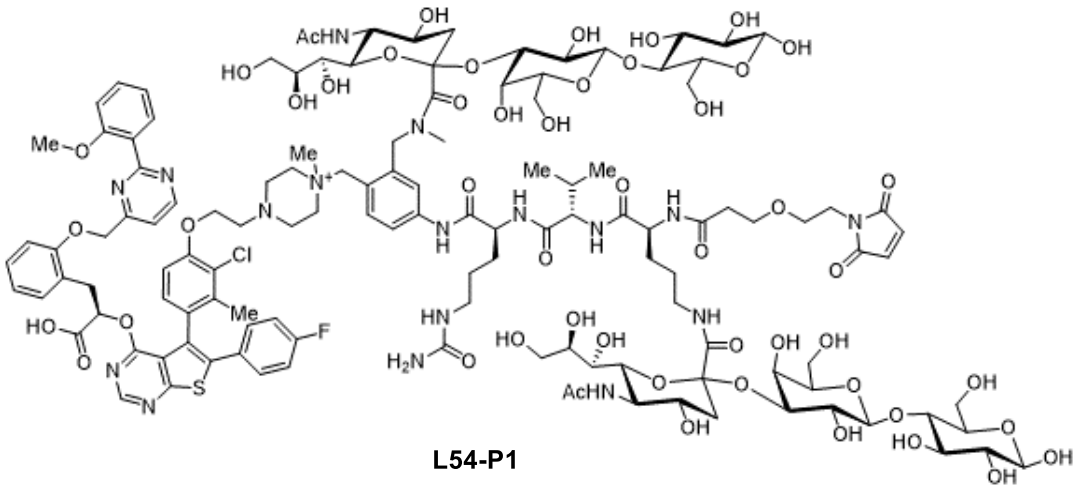
L52-P1

,



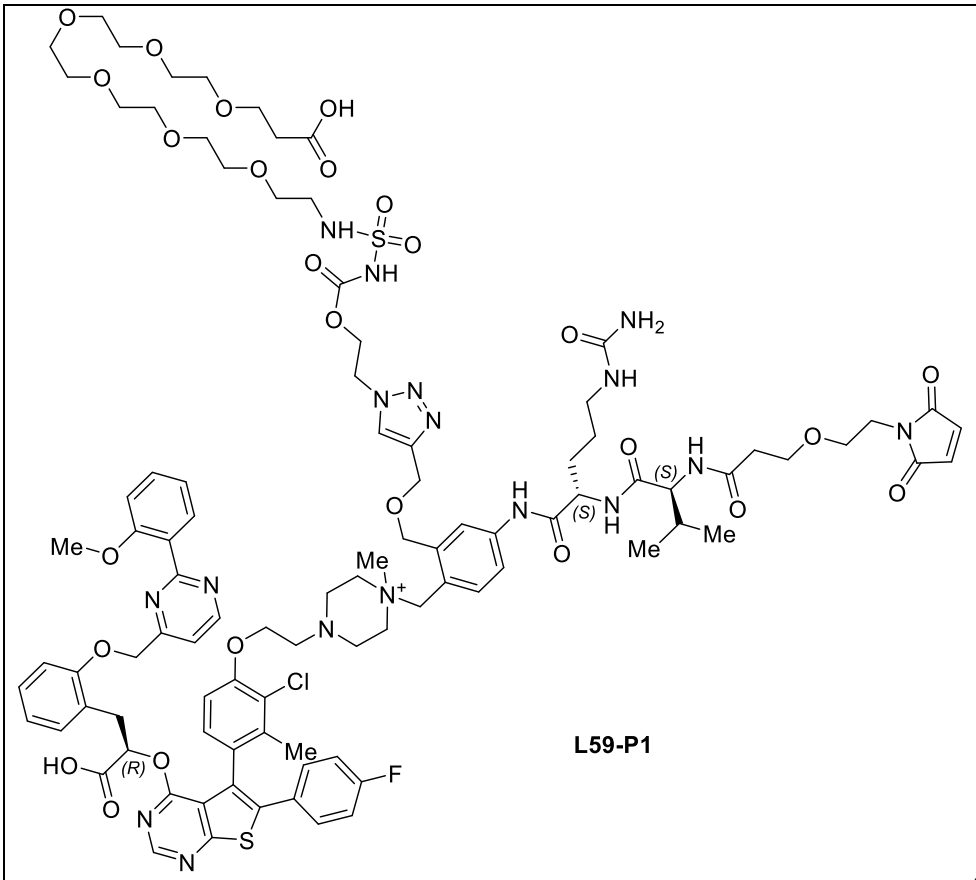
L53-P1

,



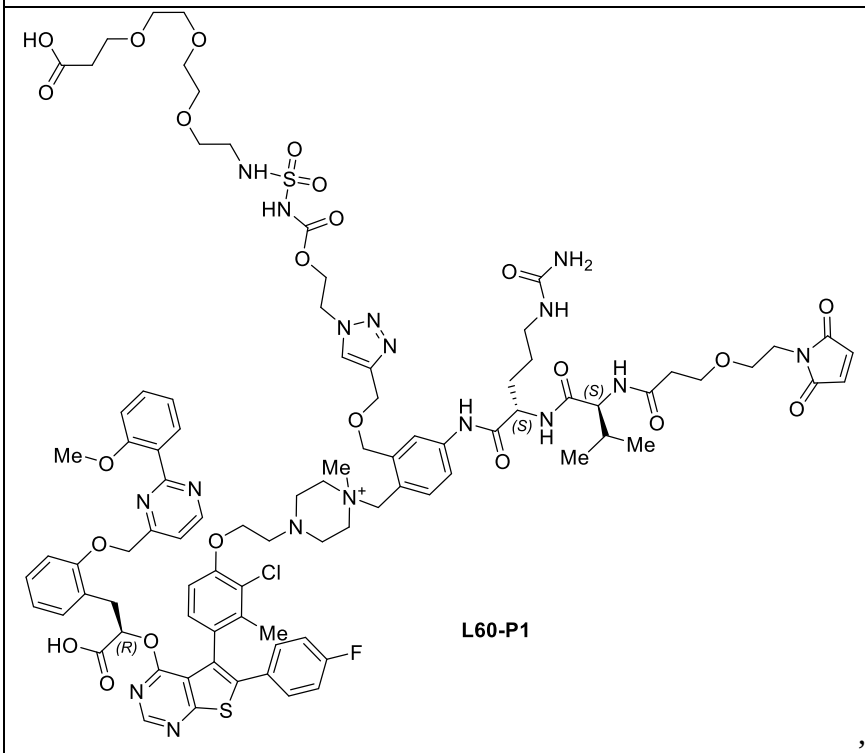
L54-P1

,



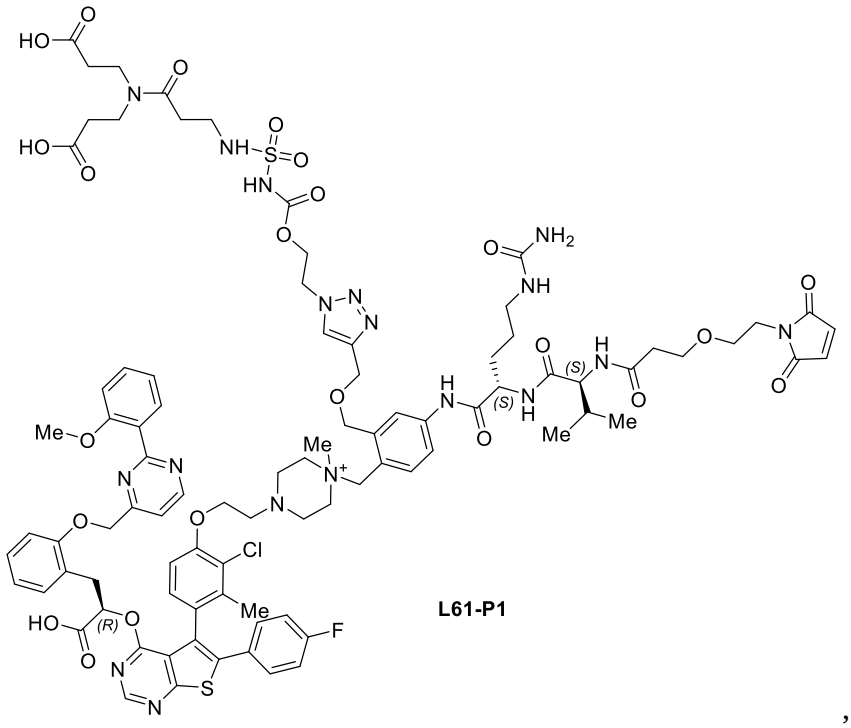
L59-P1

,



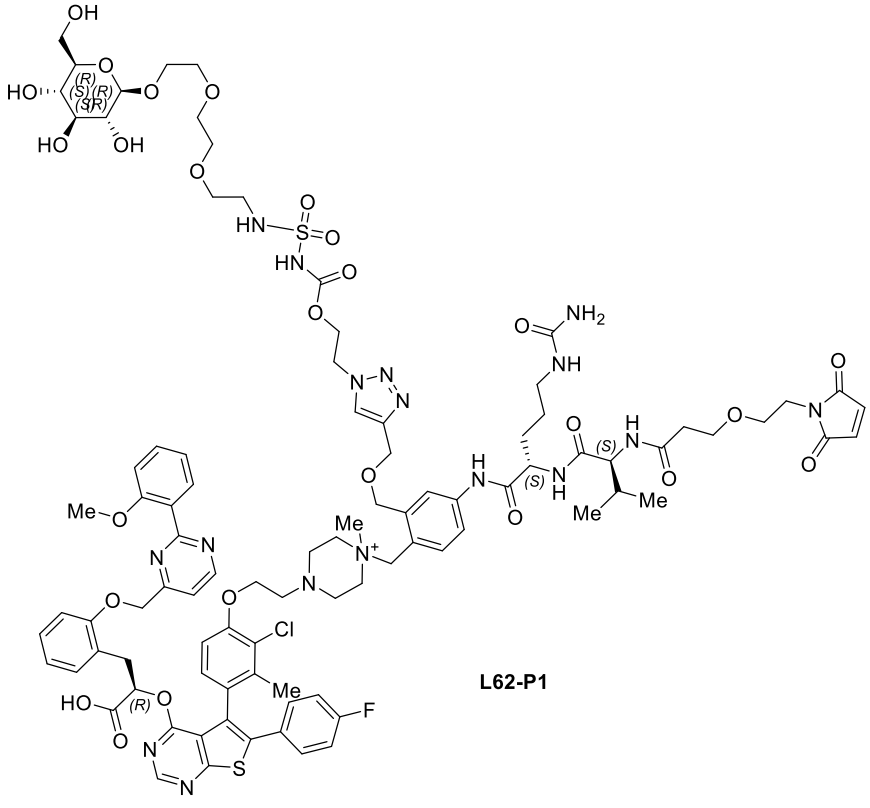
L60-P1

,



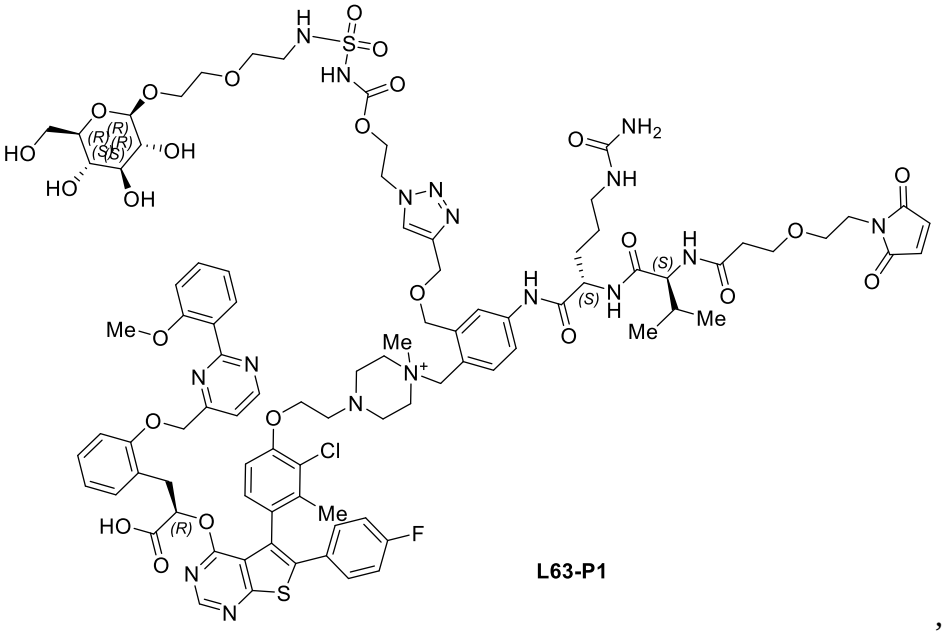
L61-P1

,



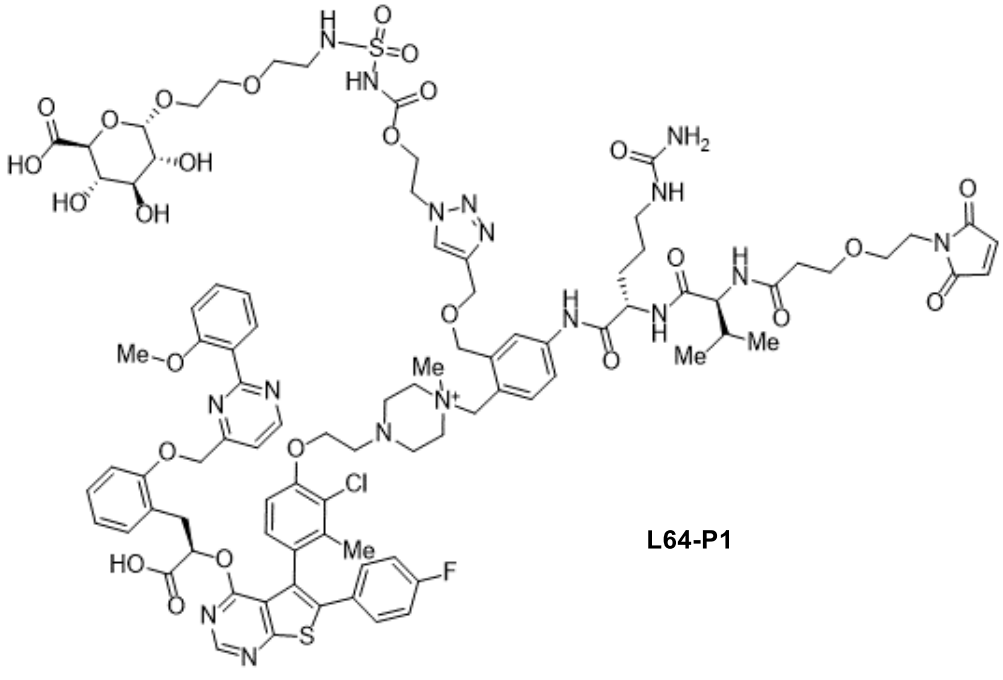
L62-P1

,



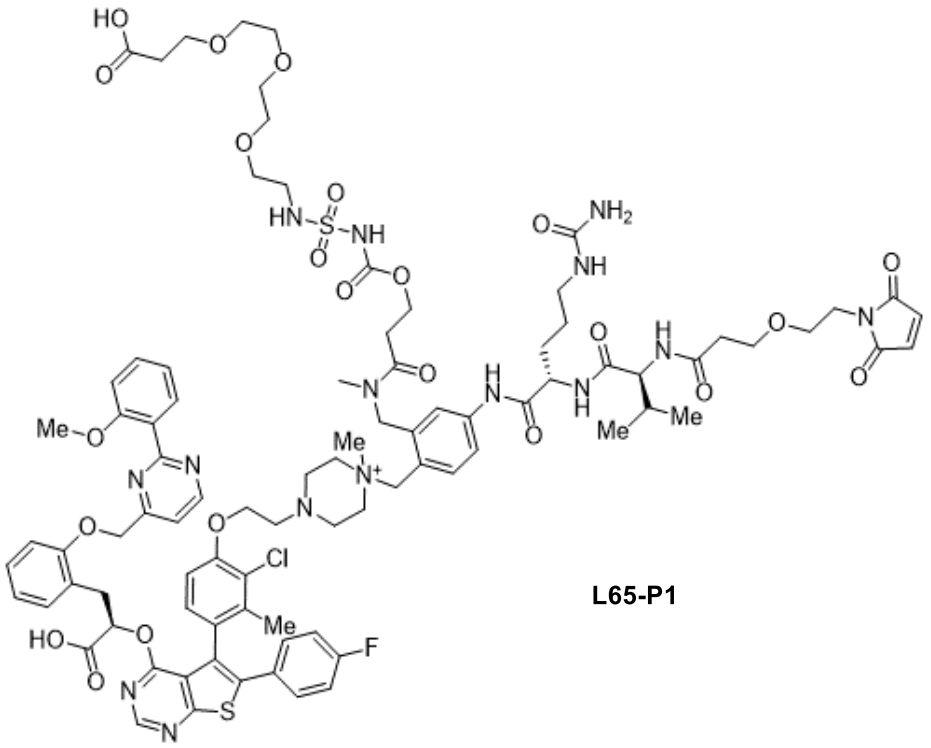
L63-P1

,



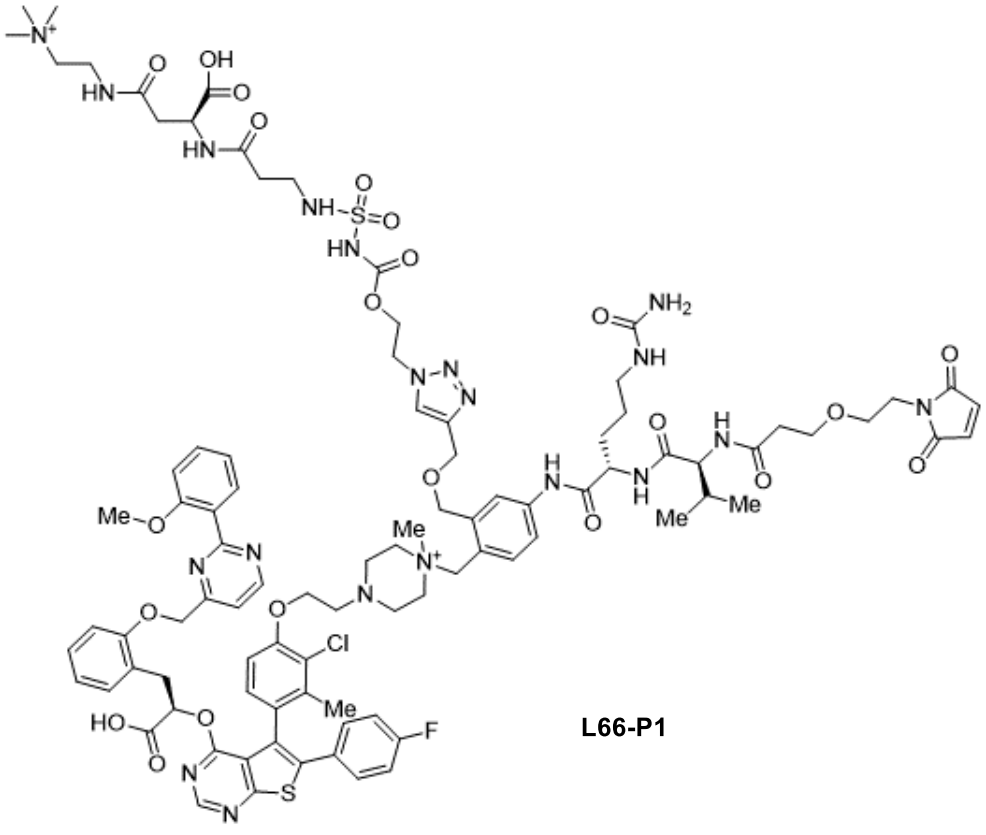
L64-P1

,



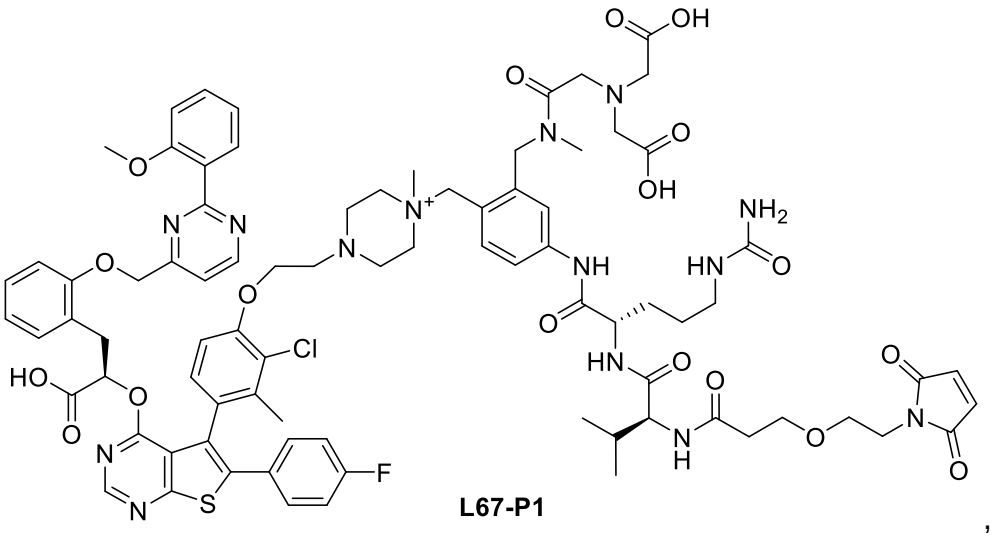
L65-P1

,



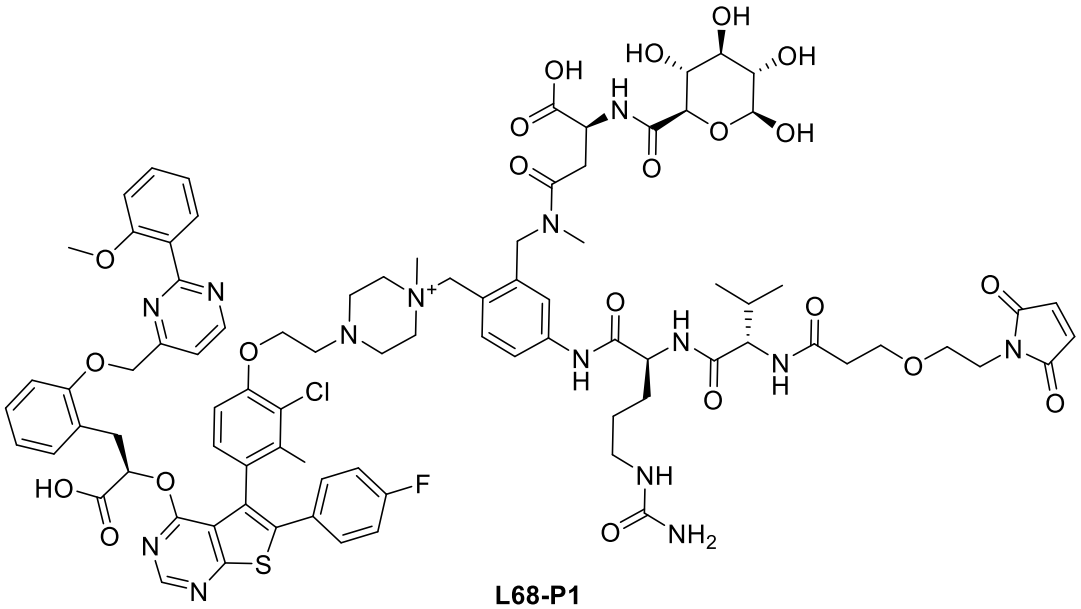
L66-P1

,



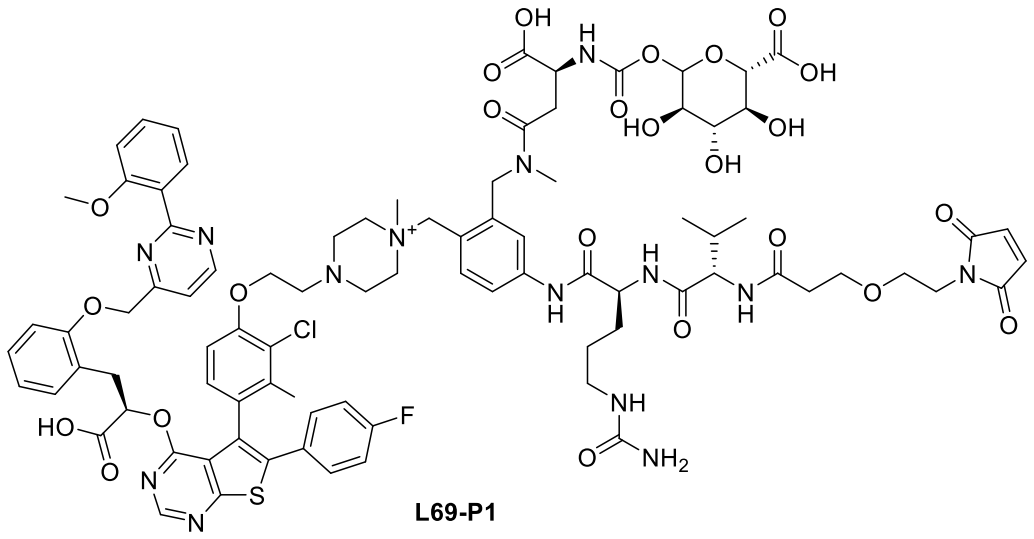
L67-P1

,



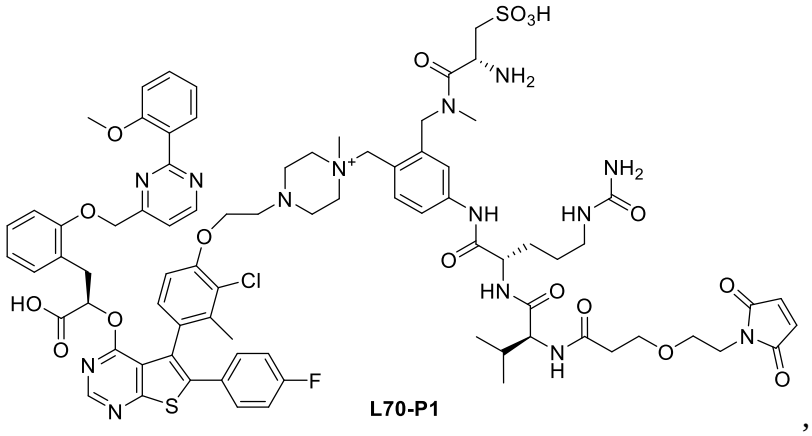
L68-P1

,



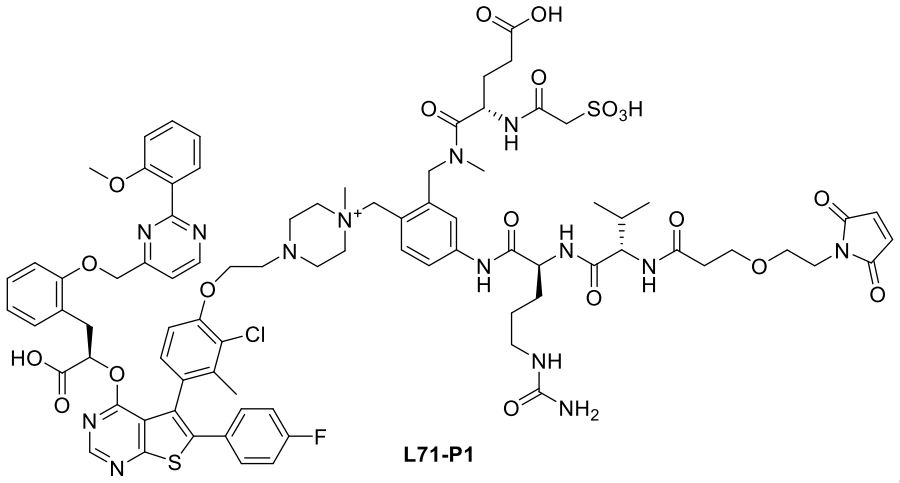
L69-P1

,



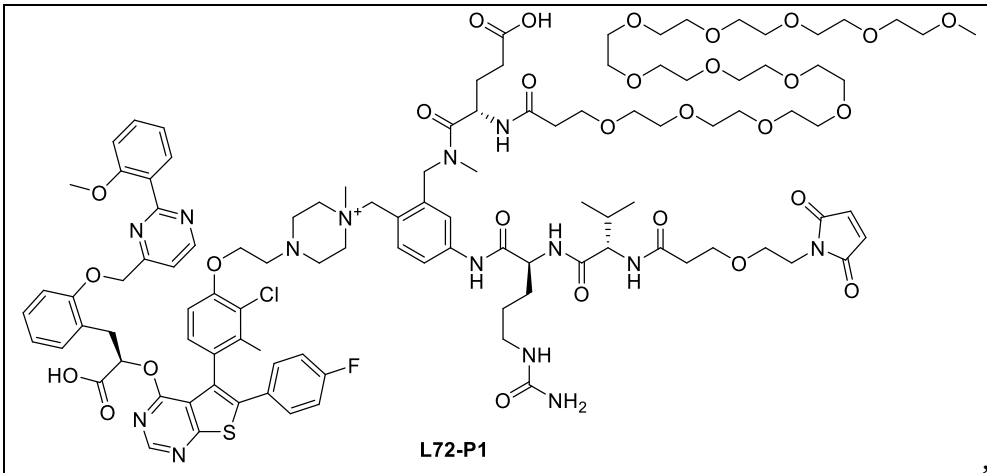
L70-P1

,



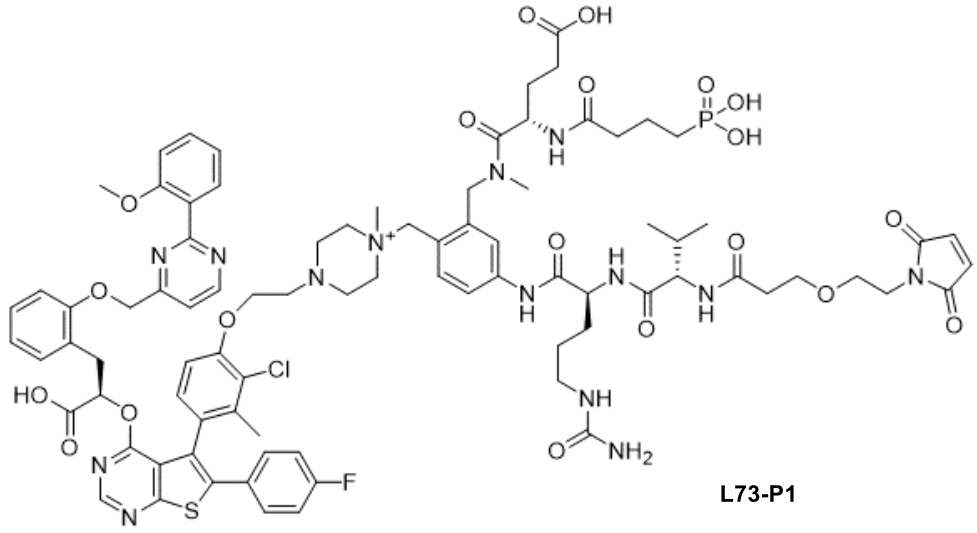
L71-P1

,



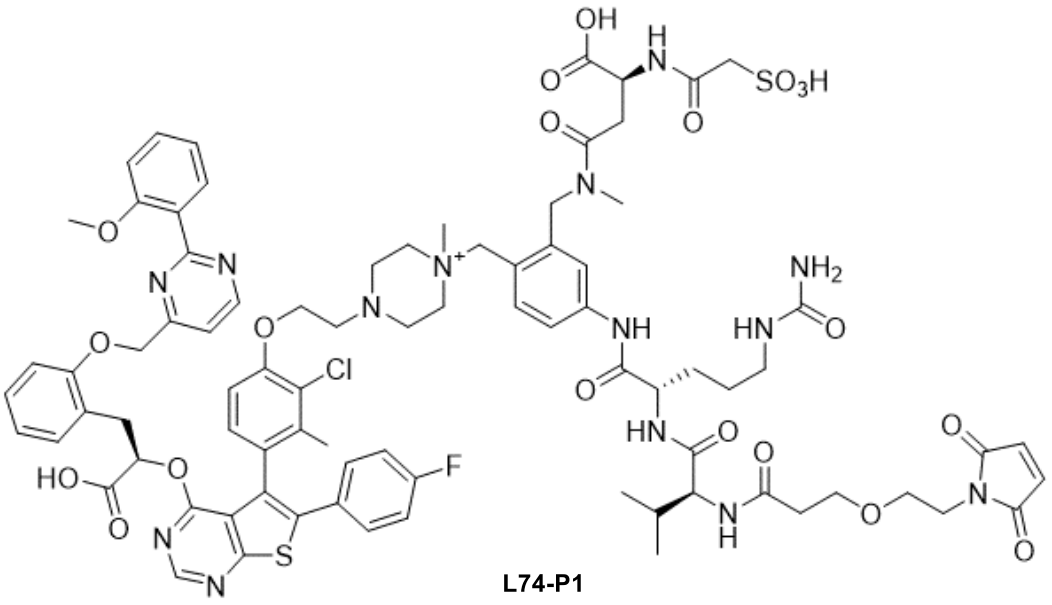
L72-P1

,



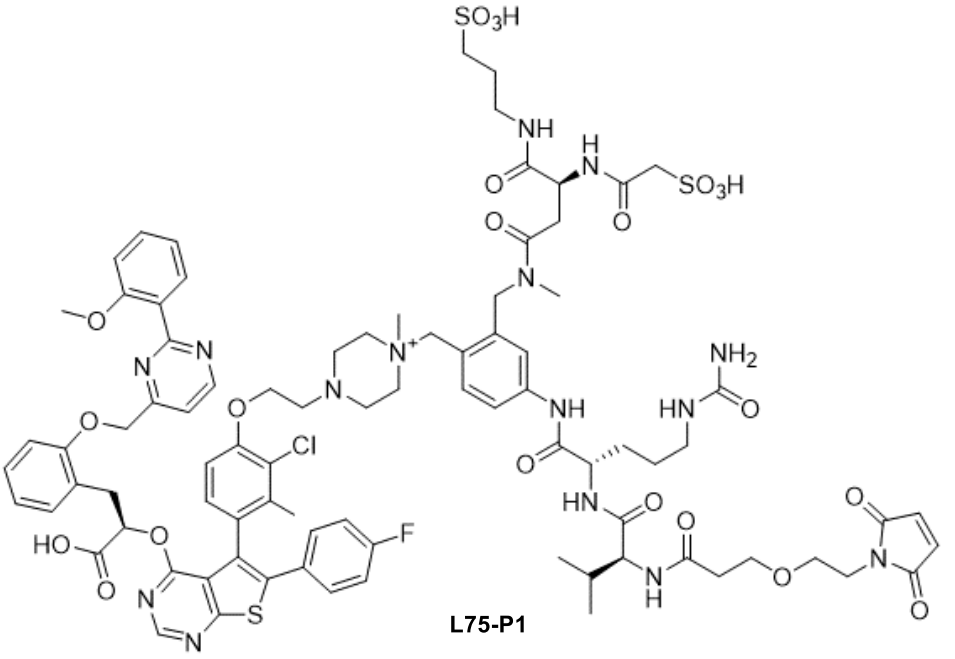
L73-P1

,



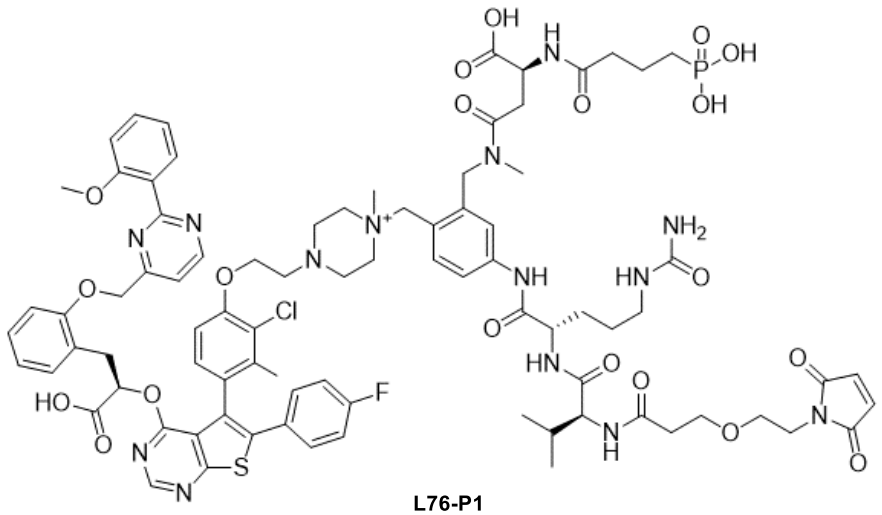
L74-P1

,



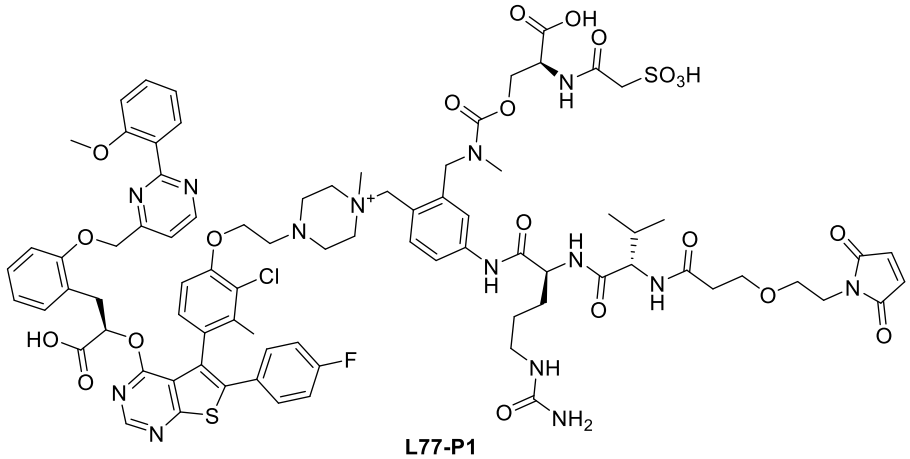
L75-P1

,



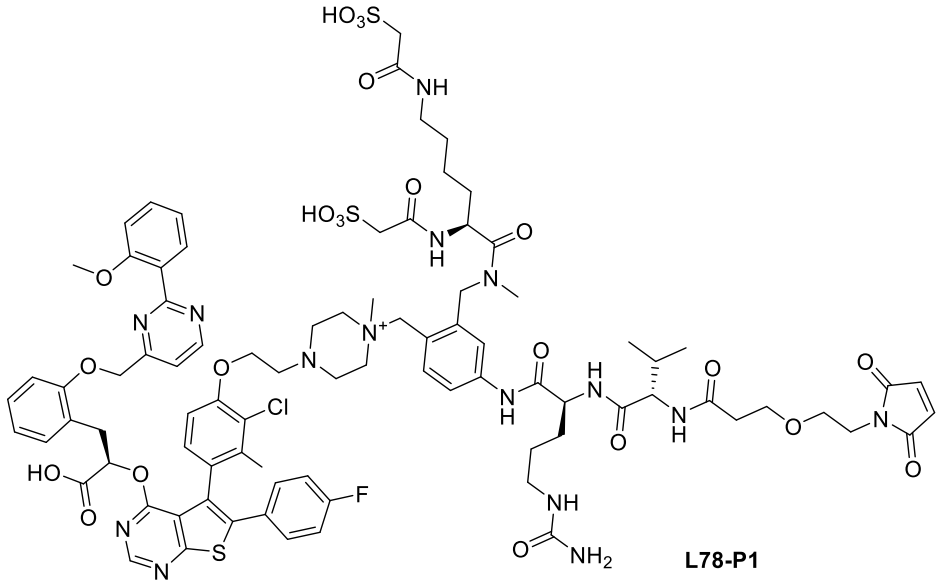
L76-P1

,



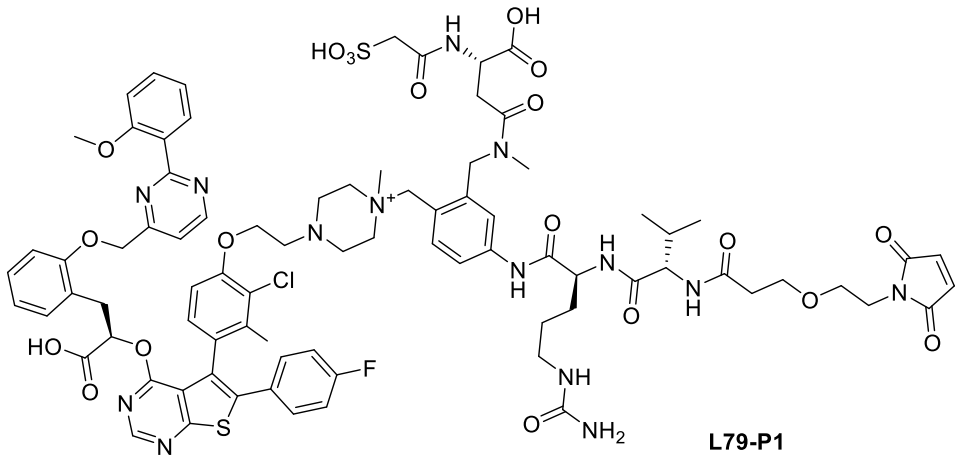
L77-P1

,



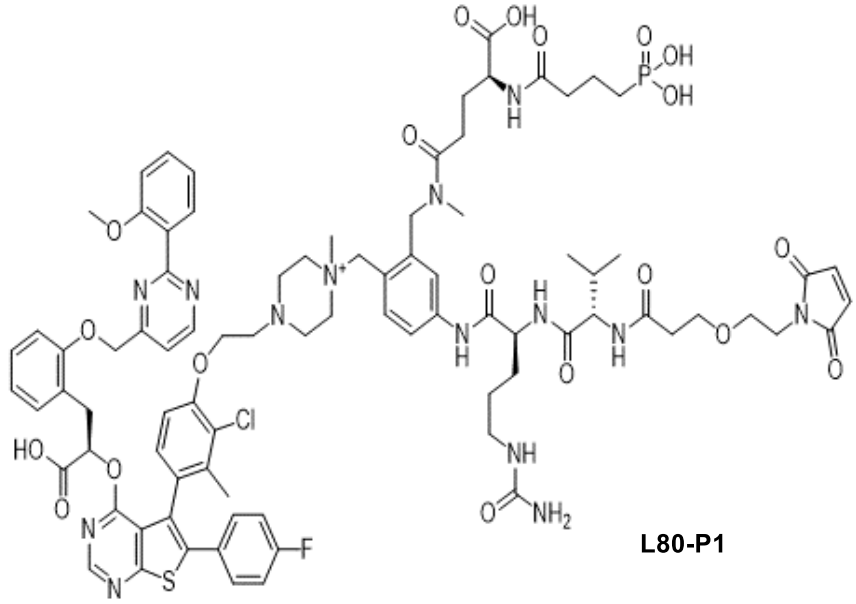
L78-P1

,



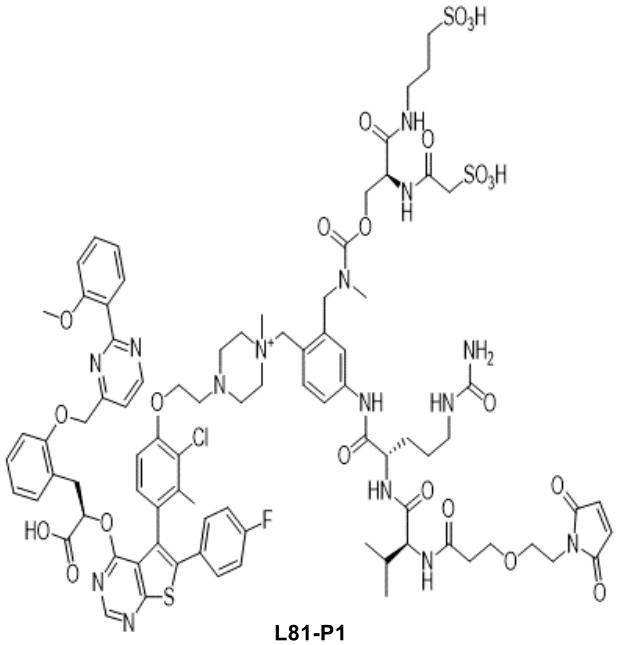
L79-P1

,



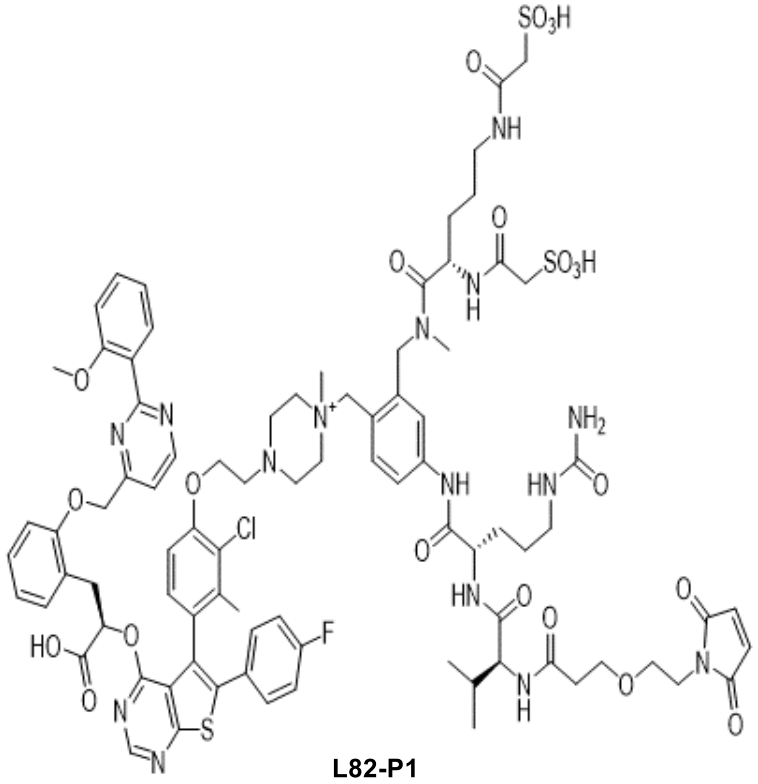
L80-P1

,



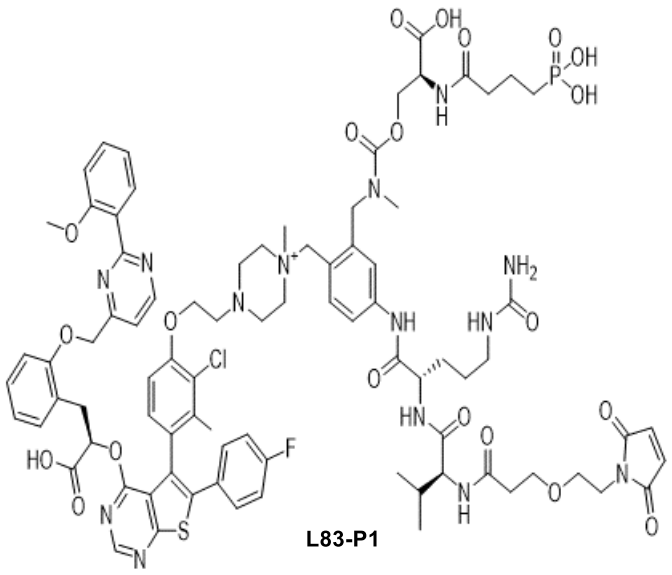
L81-P1

,



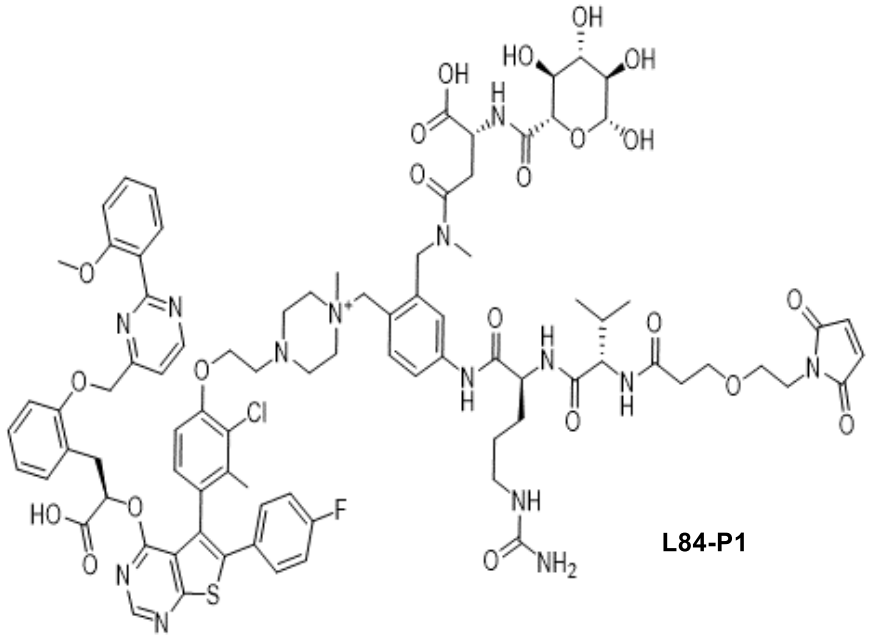
L82-P1

,



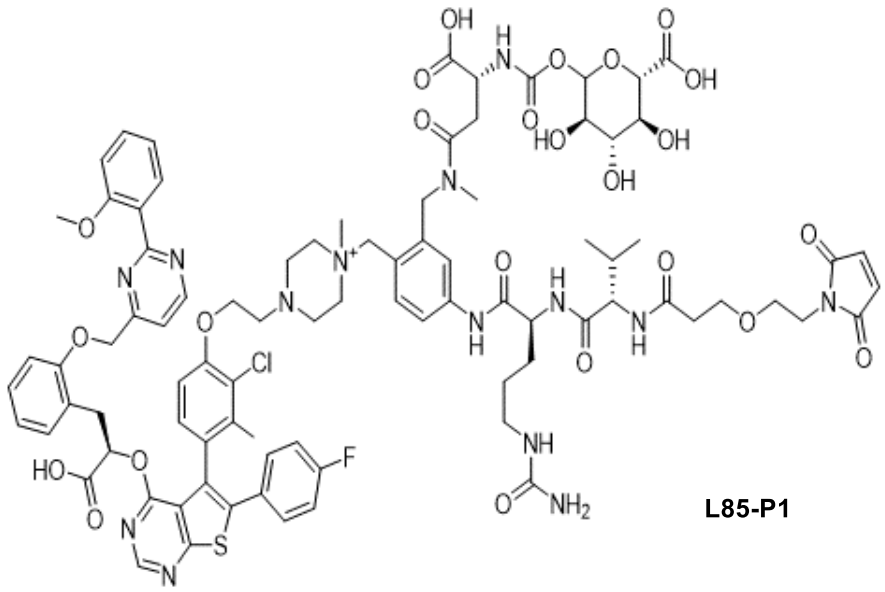
L83-P1

,



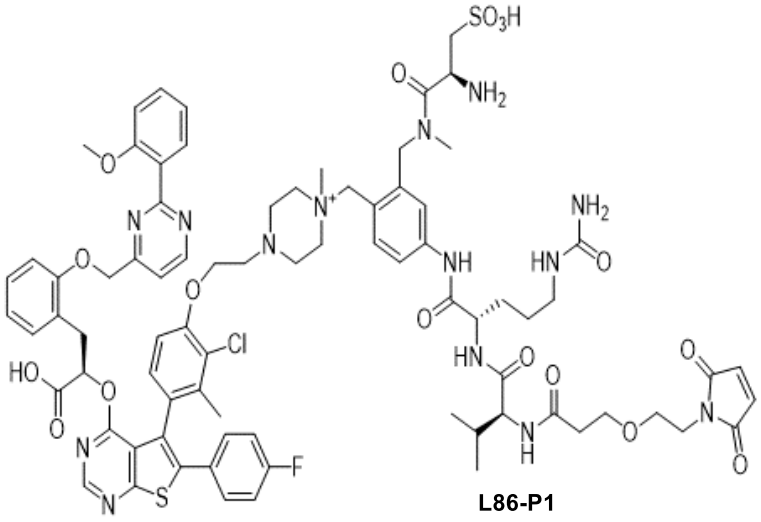
L84-P1

,



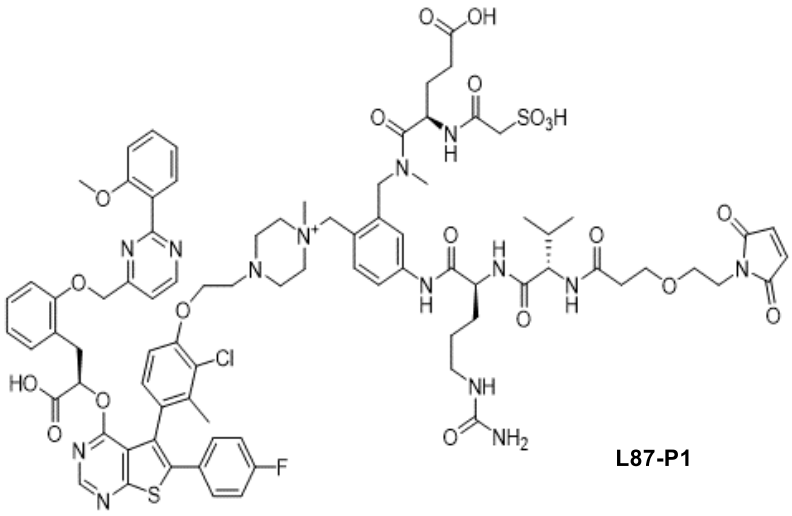
L85-P1

,



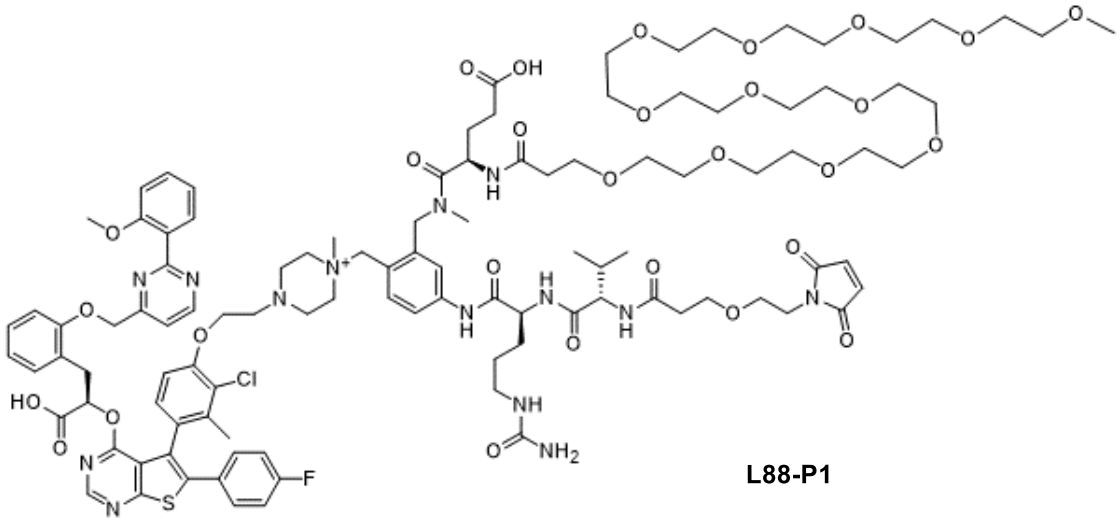
L86-P1

,



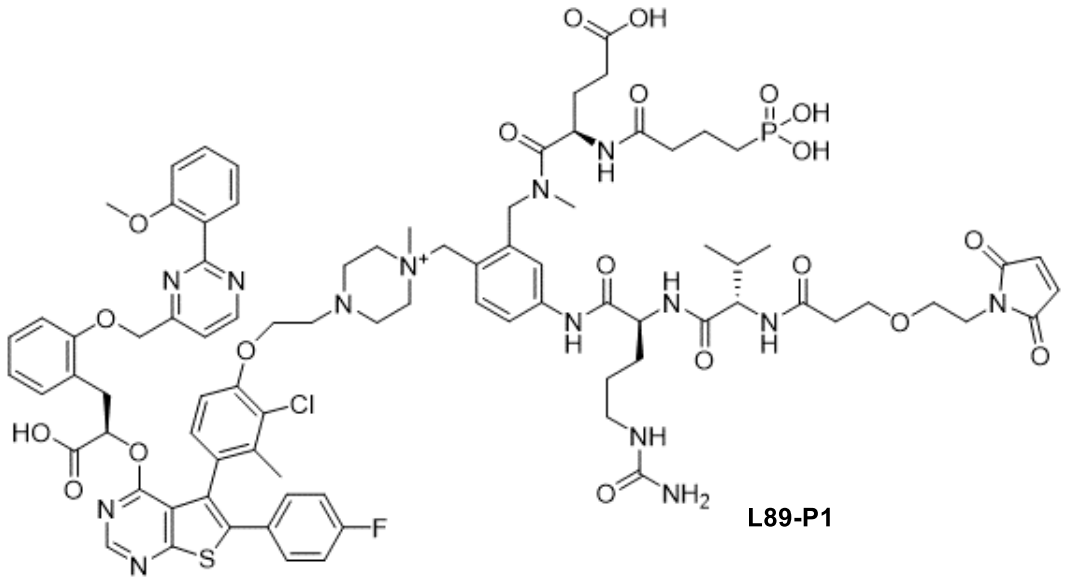
L87-P1

,



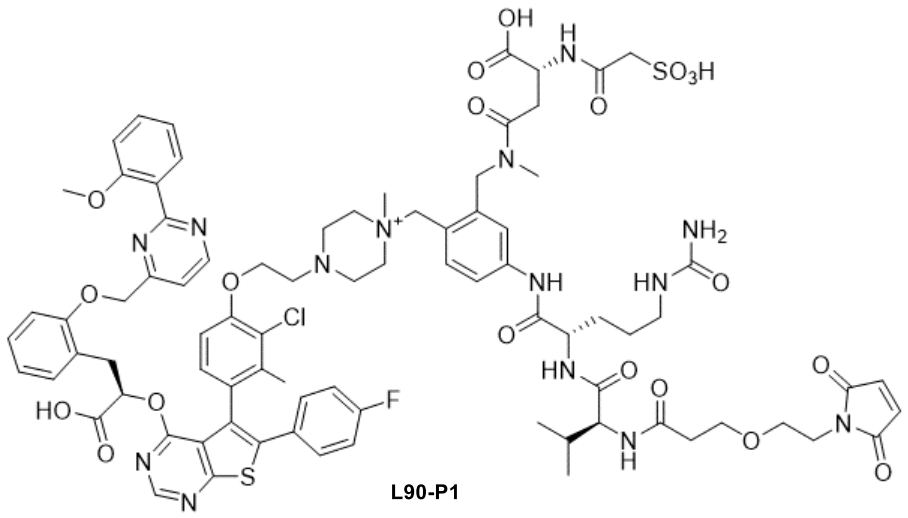
L88-P1

,



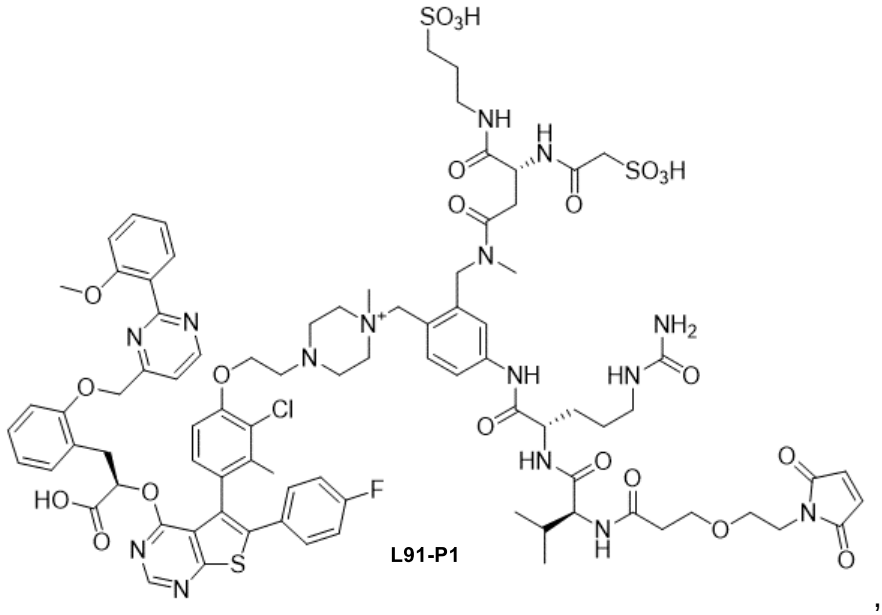
L89-P1

,

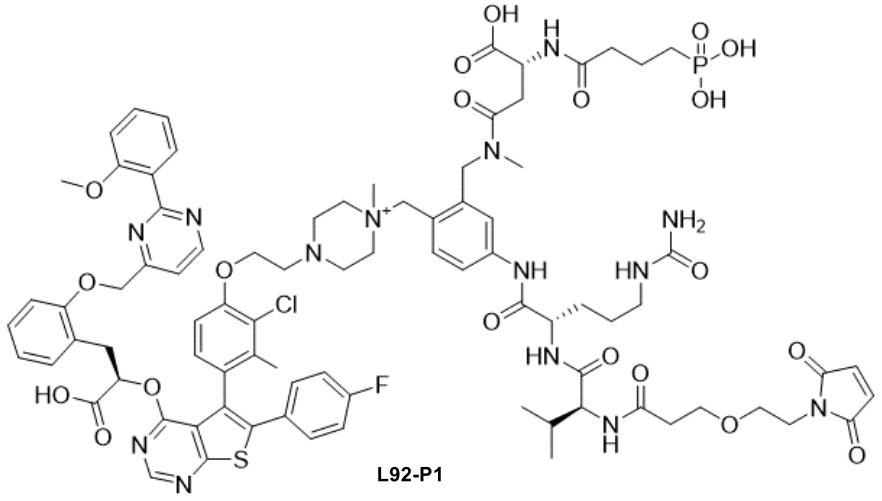


L90-P1

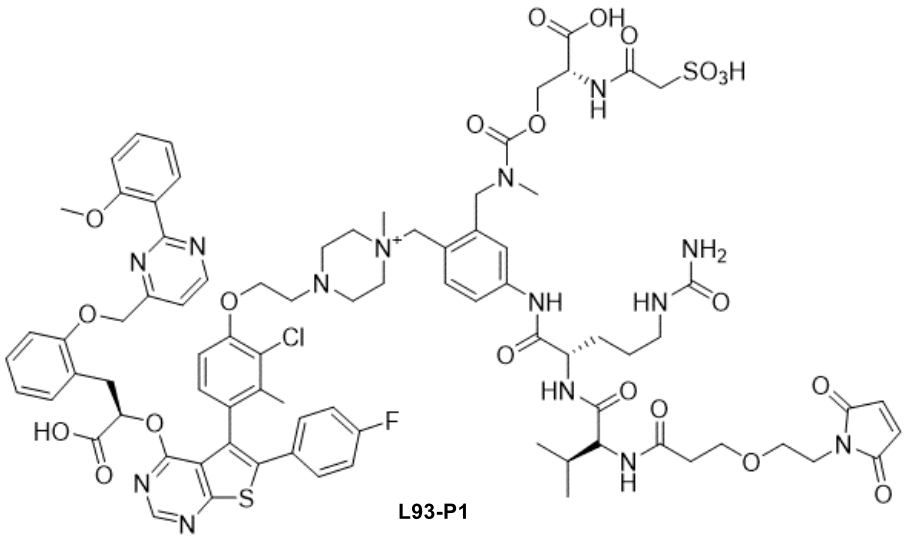
,


SO3H
NH
H
N
SO3H
O
O
O
N
O
N
N
N+
NH2
O
N
NH
HN
O
Cl
O
HN
O
O
HO
O
O
F
N
S
N
N
H
O
O
N
O
O

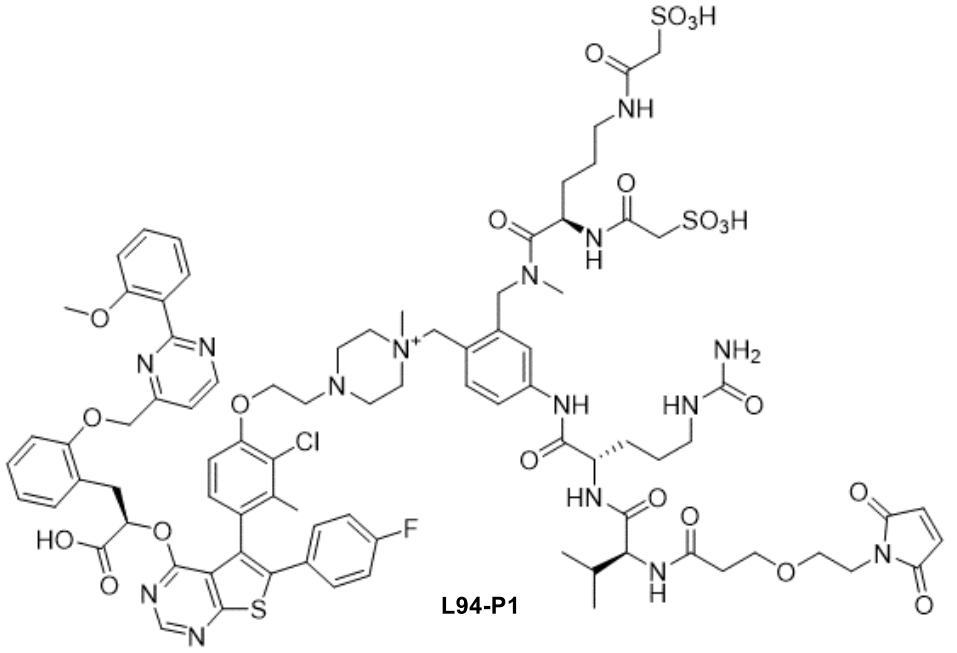
L91-P1 ,


OH
H
N
O
P
OH
O
OH
O
O
N
O
N
N
N+
NH2
O
N
NH
HN
O
Cl
O
HN
O
O
HO
O
O
F
N
S
N
N
H
O
O
N
O
O

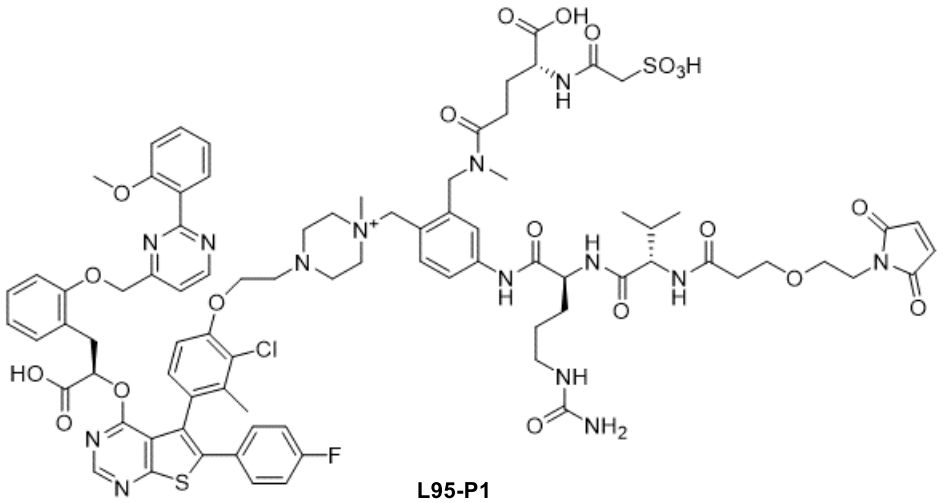
L92-P1 ,



L93-P1 ,

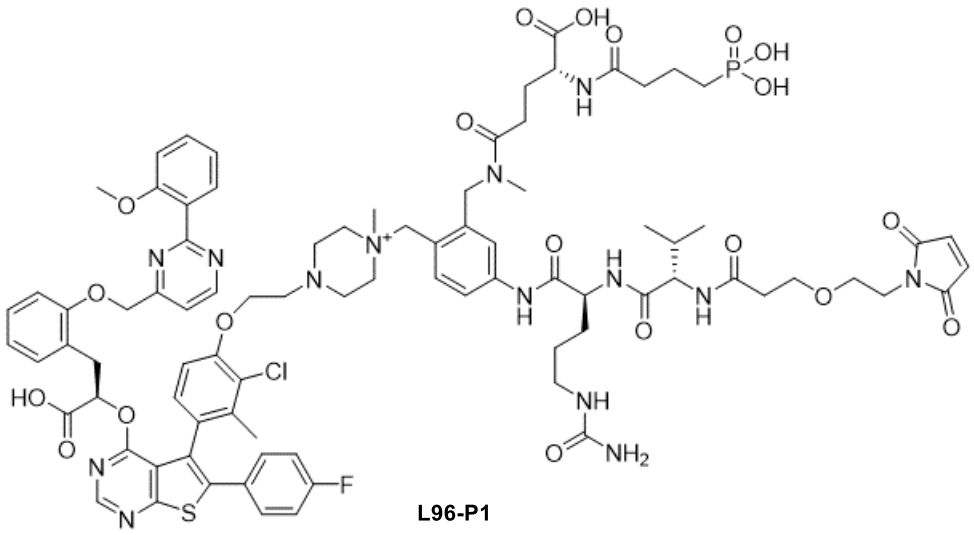


L94-P1 ,



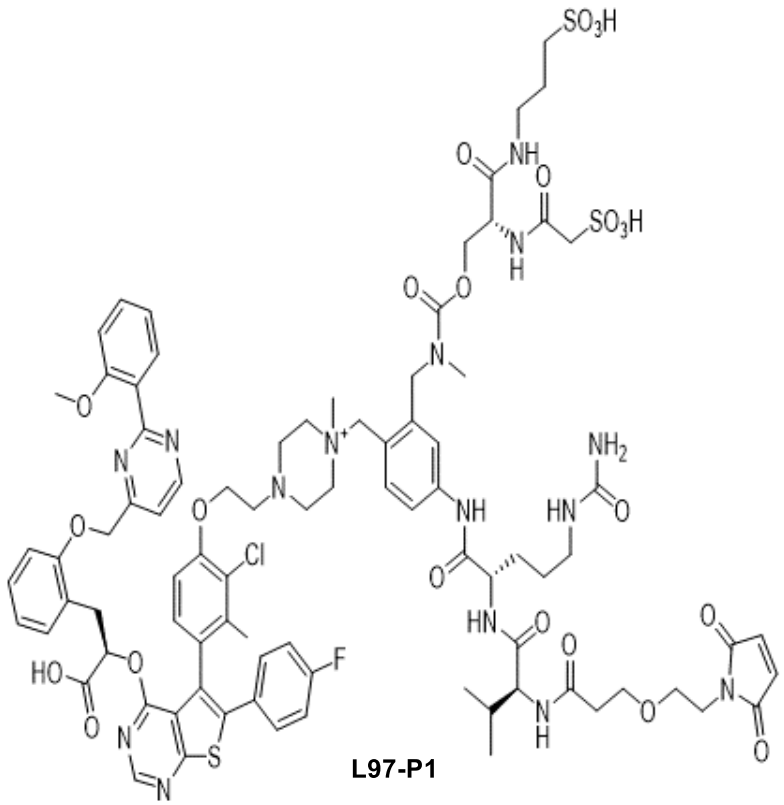
L95-P1

,



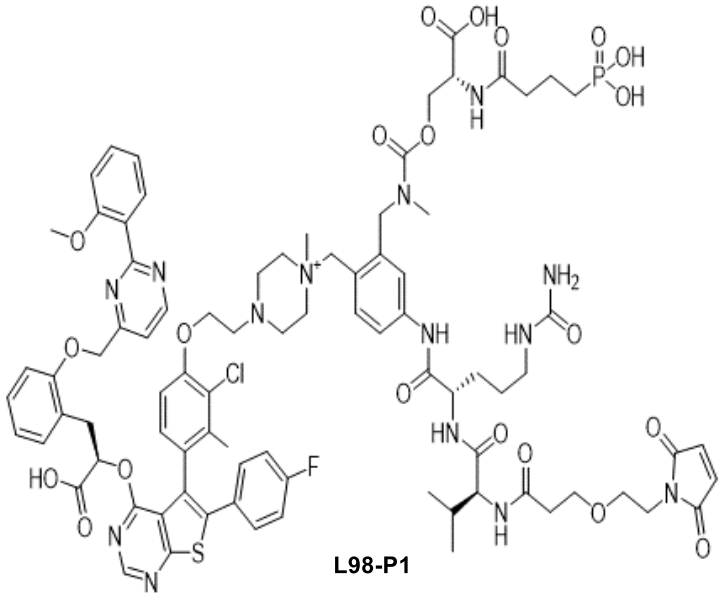
L96-P1

,



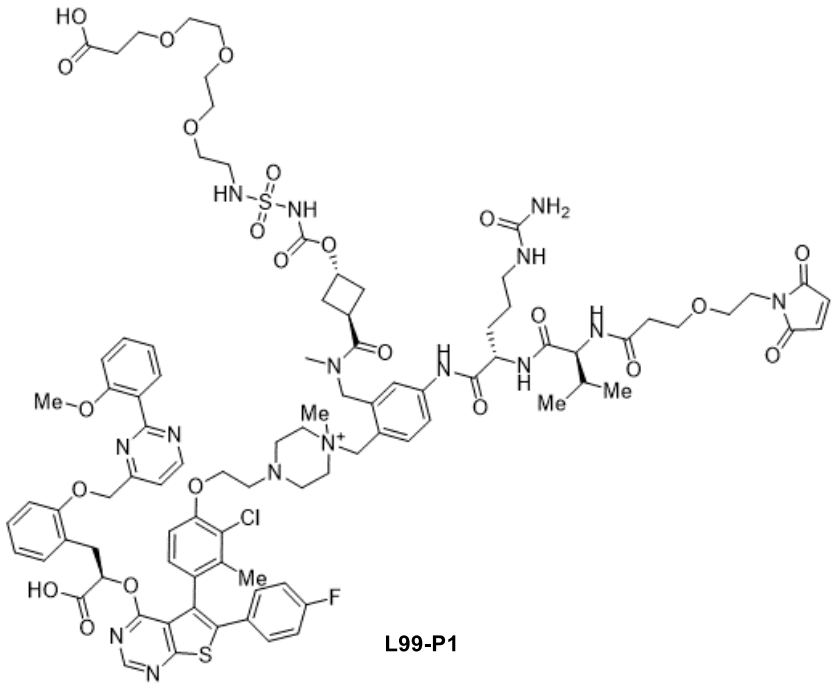
L97-P1

,



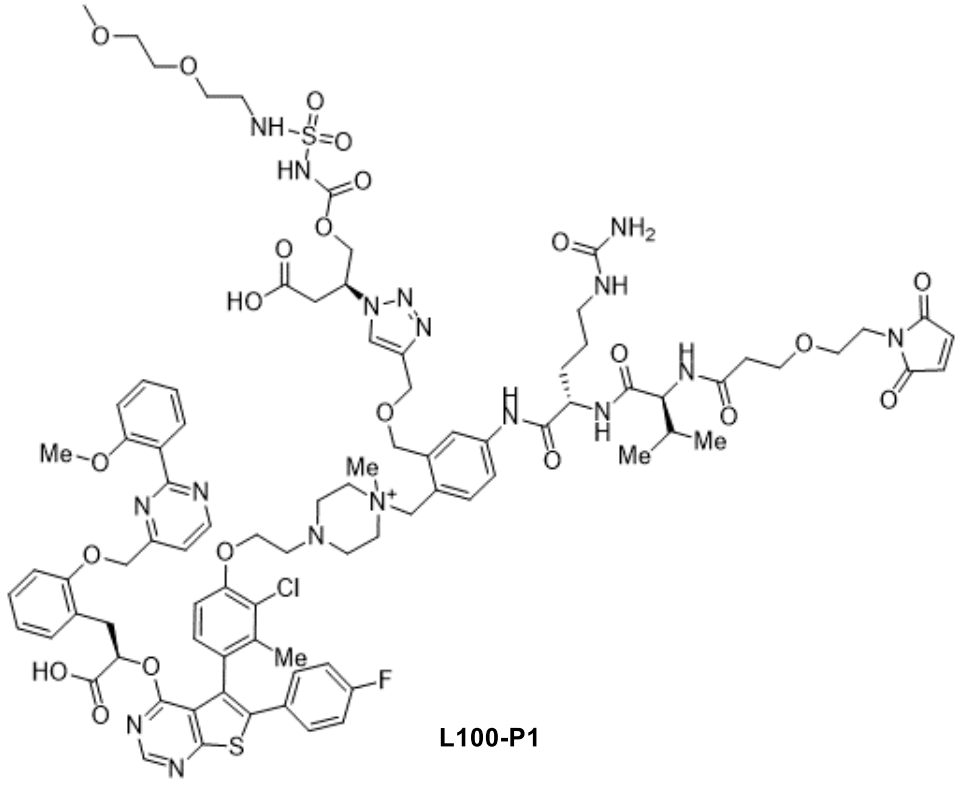
L98-P1

,



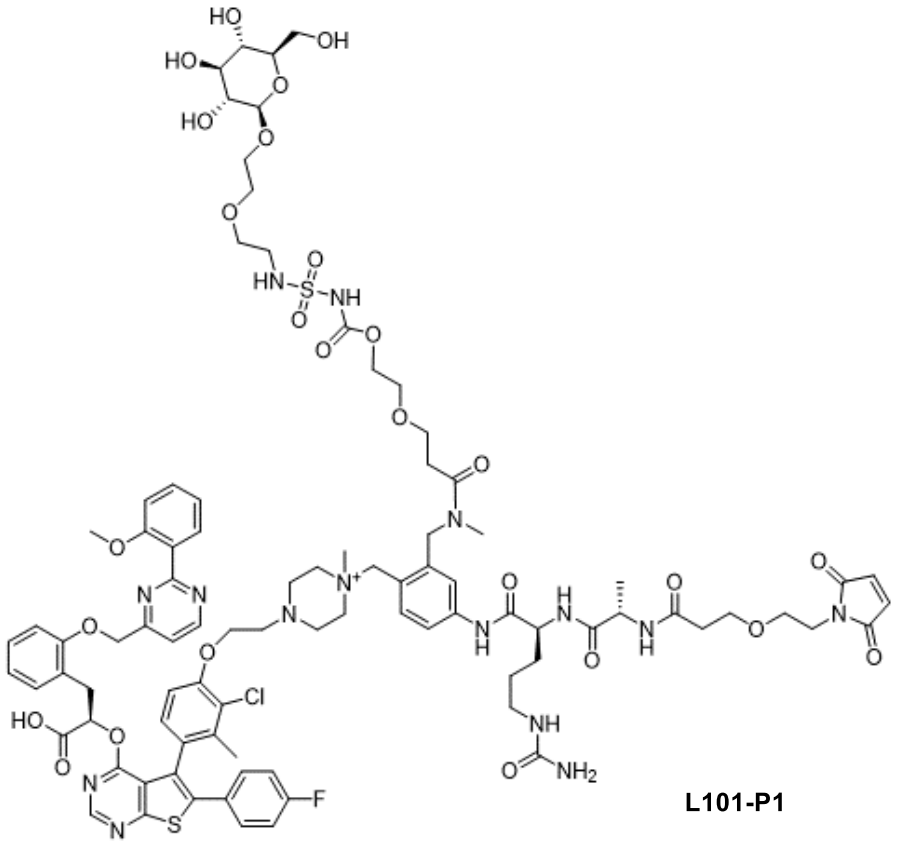
L99-P1

,



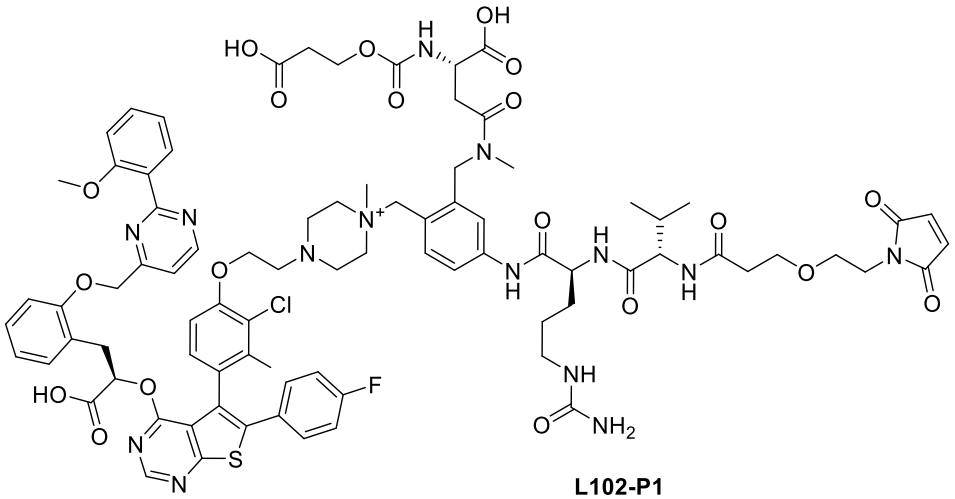
L100-P1

,



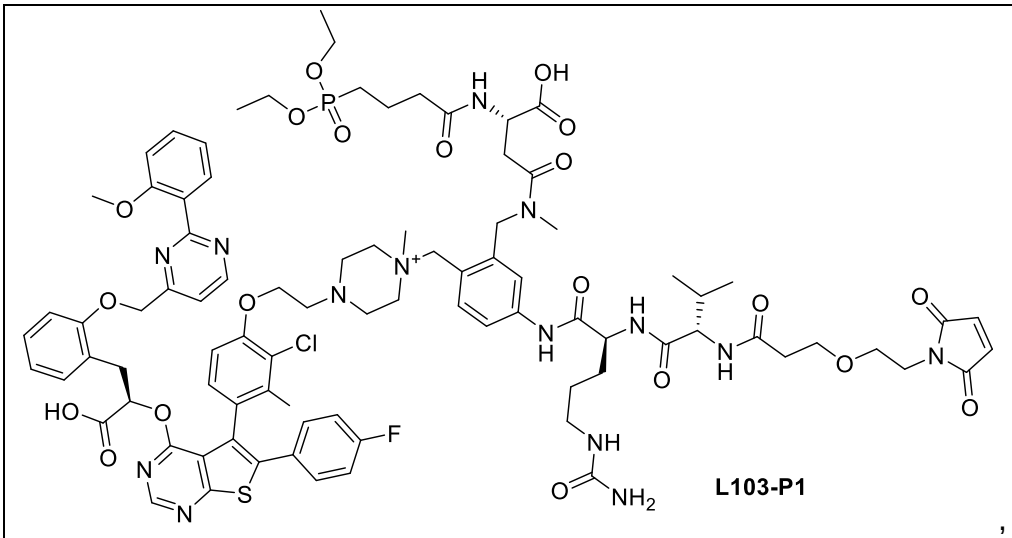
L101-P1

,



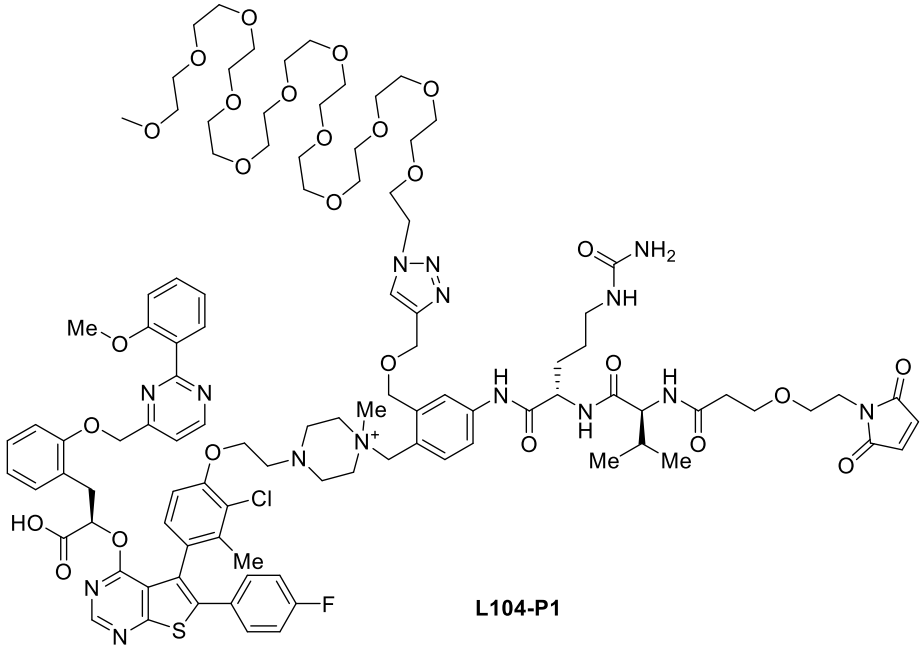
L102-P1

,



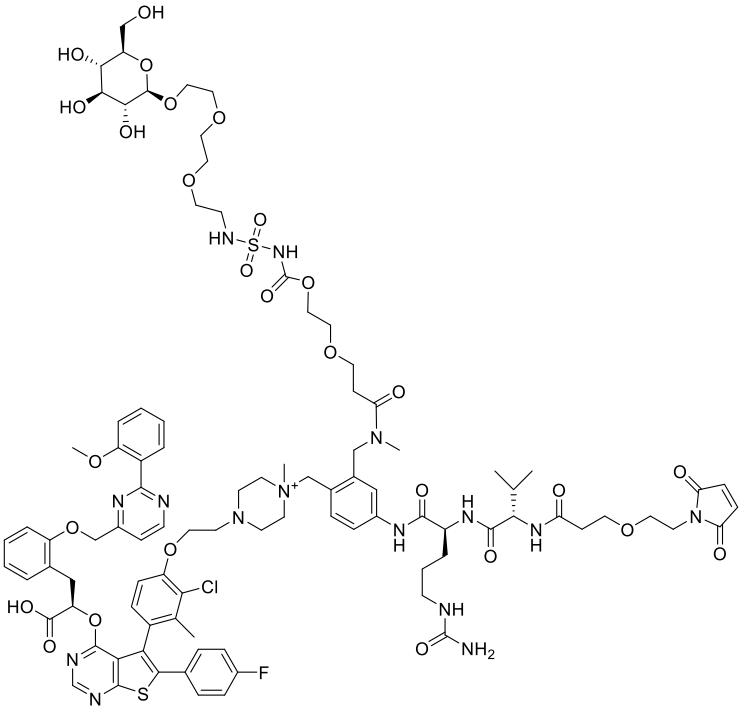
L103-P1

,



L104-P1

, and



L105-P1

.

.

11. The antibody drug conjugate of any one of claims 1-10, wherein the anti-CD74 antibody comprises three heavy chain CDRs and three light chain CDRs as follows:

(i) heavy chain CDR1 (HCDR1) consisting of SEQ ID NO:1, heavy chain CDR2 (HCDR2) consisting of SEQ ID NO:2, heavy chain CDR3 (HCDR3) consisting of SEQ ID NO:3; light chain CDR1 (LCDR1) consisting of SEQ ID NO:16, light chain CDR2 (LCDR2) consisting of SEQ ID NO:70, and light chain CDR3 (LCDR3) consisting of SEQ ID NO:18;

(ii) heavy chain CDR1 (HCDR1) consisting of SEQ ID NO:4, heavy chain CDR2 (HCDR2) consisting of SEQ ID NO:2, heavy chain CDR3 (HCDR3) consisting of SEQ ID NO:3; light chain CDR1 (LCDR1) consisting of SEQ ID NO:16, light chain CDR2 (LCDR2) consisting of SEQ ID NO:70, and light chain CDR3 (LCDR3) consisting of SEQ ID NO:18;

(iii) heavy chain CDR1 (HCDR1) consisting of SEQ ID NO:5, heavy chain CDR2 (HCDR2) consisting of SEQ ID NO:6, heavy chain CDR3 (HCDR3) consisting of SEQ ID NO:3; light chain CDR1 (LCDR1) consisting of SEQ ID NO:19, light chain CDR2 (LCDR2) consisting of SEQ ID NO:20, and light chain CDR3 (LCDR3) consisting of SEQ ID NO:21;

(iv) heavy chain CDR1 (HCDR1) consisting of SEQ ID NO:7, heavy chain CDR2 (HCDR2) consisting of SEQ ID NO:8, heavy chain CDR3 (HCDR3) consisting of SEQ ID NO:9;

light chain CDR1 (LCDR1) consisting of SEQ ID NO:22, light chain CDR2 (LCDR2) consisting of SEQ ID NO:20, and light chain CDR3 (LCDR3) consisting of SEQ ID NO:18;

(v) heavy chain CDR1 (HCDR1) consisting of SEQ ID NO:1, heavy chain CDR2 (HCDR2) consisting of SEQ ID NO:2, heavy chain CDR3 (HCDR3) consisting of SEQ ID NO:3; light chain CDR1 (LCDR1) consisting of SEQ ID NO:35, light chain CDR2 (LCDR2) consisting of SEQ ID NO:70, and light chain CDR3 (LCDR3) consisting of SEQ ID NO:18;

(vi) heavy chain CDR1 (HCDR1) consisting of SEQ ID NO:4, heavy chain CDR2 (HCDR2) consisting of SEQ ID NO:2, heavy chain CDR3 (HCDR3) consisting of SEQ ID NO:3; light chain CDR1 (LCDR1) consisting of SEQ ID NO:35, light chain CDR2 (LCDR2) consisting of SEQ ID NO:70, and light chain CDR3 (LCDR3) consisting of SEQ ID NO:18;

(vi) heavy chain CDR1(HCDR1) consisting of SEQ ID NO:4, heavy chain CDR2 (HCDR2) consisting of SEQ ID NO:2, heavy chain CDR3 (HCDR3) consisting of SEQ ID NO:3; light chain CDR1 (LCDR1) consisting of SEQ ID NO:35, light chain CDR2 (LCDR2) consisting of SEQ ID NO:70, and light chain CDR3 (LCDR3) consisting of SEQ ID NO:18.

(vii) heavy chain CDR1 (HCDR1) consisting of SEQ ID NO:5, heavy chain CDR2 (HCDR2) consisting of SEQ ID NO:6, heavy chain CDR3 (HCDR3) consisting of SEQ ID NO:3; light chain CDR1 (LCDR1) consisting of SEQ ID NO:71, light chain CDR2 (LCDR2) consisting of SEQ ID NO:20, and light chain CDR3 (LCDR3) consisting of SEQ ID NO:21.or

(viii) heavy chain CDR1 (HCDR1) consisting of SEQ ID NO:7, heavy chain CDR2 (HCDR2) consisting of SEQ ID NO:8, heavy chain CDR3 (HCDR3) consisting of SEQ ID NO:9; light chain CDR1 (LCDR1) consisting of SEQ ID NO:17, light chain CDR2 (LCDR2) consisting of SEQ ID NO:20, and light chain CDR3 (LCDR3) consisting of SEQ ID NO:18.

12. The antibody drug conjugate of claim 11, wherein the anti-CD74 antibody or antigen-binding fragment thereof comprises:

(i) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:10, and a light chain variable region comprising the amino acid sequence of SEQ ID NO:23;

(ii) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:10, and a light chain variable region comprising the amino acid sequence of SEQ ID NO:27;(iii) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:10, and a light chain variable region comprising the amino acid sequence of SEQ ID NO:31;

(iv) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:10, and a light chain variable region comprising the amino acid sequence of SEQ ID NO:36;

(v) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:10, and a light chain variable region comprising the amino acid sequence of SEQ ID NO:40; or

(vi) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:10, and a light chain variable region comprising the amino acid sequence of SEQ ID NO:44.

13. The antibody drug conjugate of claim 11 or 12, wherein the anti-CD74 antibody comprises:

(a) the heavy chain amino acid sequence of SEQ ID NO:12 and the light chain amino acid sequence of SEQ ID NO:25;

(b) the heavy chain amino acid sequence of SEQ ID NO:14 and the light chain amino acid sequence of SEQ ID NO:25;

(c) the heavy chain amino acid sequence of SEQ ID NO:15 and the light chain amino acid sequence of SEQ ID NO:25;

(d) the heavy chain amino acid sequence of SEQ ID NO:12 and the light chain amino acid sequence of SEQ ID NO:29;

(e) the heavy chain amino acid sequence of SEQ ID NO:14 and the light chain amino acid sequence of SEQ ID NO:29;

(f) the heavy chain amino acid sequence of SEQ ID NO:15 and the light chain amino acid sequence of SEQ ID NO:29;

(g) the heavy chain amino acid sequence of SEQ ID NO:12 and the light chain amino acid sequence of SEQ ID NO:33;

(h) the heavy chain amino acid sequence of SEQ ID NO:14 and the light chain amino acid sequence of SEQ ID NO:33;

(i) the heavy chain amino acid sequence of SEQ ID NO:15 and the light chain amino acid sequence of SEQ ID NO:33;

(j) the heavy chain amino acid sequence of SEQ ID NO:12 and the light chain amino acid sequence of SEQ ID NO:38;

(k) the heavy chain amino acid sequence of SEQ ID NO:14 and the light chain amino acid sequence of SEQ ID NO:38;

(l) the heavy chain amino acid sequence of SEQ ID NO:15 and the light chain amino acid sequence of SEQ ID NO:38;

(m) the heavy chain amino acid sequence of SEQ ID NO:12 and the light chain amino acid sequence of SEQ ID NO:42;

(n) the heavy chain amino acid sequence of SEQ ID NO:14 and the light chain amino acid sequence of SEQ ID NO:42;

(o) the heavy chain amino acid sequence of SEQ ID NO:15 and the light chain amino acid sequence of SEQ ID NO:42;

(p) the heavy chain amino acid sequence of SEQ ID NO:12 and the light chain amino acid sequence of SEQ ID NO:46;

(q) the heavy chain amino acid sequence of SEQ ID NO:14 and the light chain amino acid sequence of SEQ ID NO:46; or

(r) the heavy chain amino acid sequence of SEQ ID NO:15 and the light chain amino acid sequence of SEQ ID NO:46.

14. A composition comprising multiple copies of the antibody-drug conjugate of any one of claims 1 to 13, wherein the average *p* of the antibody-drug conjugates in the composition is from about 2 to about 16, e.g., about 2 to about 8, e.g., about 2 to about 4.

15. A pharmaceutical composition comprising the antibody-drug conjugate of any one of claims 1 to 13 or the composition of claim 14, and a pharmaceutically acceptable carrier.

16. Use of the antibody-drug conjugate of any one of claims 1 to 13, the composition of claim 14, or the pharmaceutical composition of claim 15 in the manufacture of a medicament for treating a subject having or suspected of having a cancer, wherein a therapeutically effective amount of the antibody-drug conjugate of any one of claims 1 to 13, the composition of claim 14, or the pharmaceutical composition of claim 15 is to be administered to the subject; preferably, wherein:
(1) the cancer expresses CD74; or
(2) the cancer is a tumor or a hematological cancer, preferably, the cancer is a breast cancer, multiple myeloma, plasma cell myeloma, leukemia, lymphoma, gastric cancer, acute myeloid leukemia, bladder cancer, brain cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, chronic lymphocytic leukemia, prostate cancer, small cell lung cancer, or spleen cancer; and/or (3) at least one additional therapeutic agent is to be further administered to the subject in

need thereof, preferably the one additional therapeutic agent is a Bcl-2 inhibitor, more preferably the one additional therapeutic agent is venetoclax, compound A1 or compound A2.

17. Use of the antibody-drug conjugate of any one of claims 1 to 13, the composition of claim 14, or the pharmaceutical composition of claim 15 in the manufacture of a medicament for reducing or inhibiting the growth of a tumor or reducing or slowing the expansion of a cancer cell population in a subject, wherein a therapeutically effective amount of the antibody-drug conjugate of any one of claims 1 to 13, the composition of claim 14, or the pharmaceutical composition of claim 15 is to be administered to the subject; preferably, wherein:
(1) the tumor or the cancer cell population expresses CD74;
(2) the tumor is a breast cancer, gastric cancer, bladder cancer, brain cancer, cervical cancer, colorectal cancer, esophageal cancer, hepatocellular cancer, melanoma, oral cancer, ovarian cancer, non-small cell lung cancer, prostate cancer, small cell lung cancer, or spleen cancer, or the cancer cell population is from a tumor or a hematological cancer, preferably the cancer cell population is from a breast cancer, multiple myeloma, plasma cell myeloma, leukemia, lymphoma, gastric cancer, acute myeloid leukemia, bladder cancer, brain cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, chronic lymphocytic leukemia, prostate cancer, small cell lung cancer, or spleen cancer; or
(3) administration of the antibody-drug conjugate, composition, or pharmaceutical composition reduces or inhibits the growth of the tumor or reduces the cancer cell population or slows the expansion of the cancer cell population by at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, or at least about 99%; and/or (4) at least one additional therapeutic agent is to be further administered to the subject in need thereof, preferably the one additional therapeutic agent is a Bcl-2 inhibitor, more preferably the one additional therapeutic agent is venetoclax, compound A1 or compound A2.

18. A method of determining whether a subject having or suspected of having a cancer will be responsive to treatment with the antibody-drug conjugate of any one of claims 1 to 13, the composition of claim 14, or the pharmaceutical composition of claim 15, comprising providing a biological sample obtained from the subject; contacting the sample with the antibody-drug

conjugate; and detecting binding of the antibody-drug conjugate to cancer cells in the sample, preferably wherein:

(1) the cancer cells in the sample express CD74;

(2) the cancer expresses CD74;

(3) the cancer is a tumor or a hematological cancer, preferably the cancer is a breast cancer, multiple myeloma, plasma cell myeloma, leukemia, lymphoma, gastric cancer, acute myeloid leukemia, bladder cancer, brain cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, chronic lymphocytic leukemia, prostate cancer, small cell lung cancer, or spleen cancer; and/or

(4) the sample is a tissue biopsy sample, a blood sample, or a bone marrow sample.

19. A method of producing the antibody-drug conjugate of any one of claims 1 to 13, comprising reacting an antibody or antigen-binding fragment with a cleavable linker joined to an MCL1 inhibitor under conditions that allow conjugation.

20. An antibody-drug conjugate of Formula (1):

$$Ab\text{-}(L\text{-}D)_p \qquad (1)$$

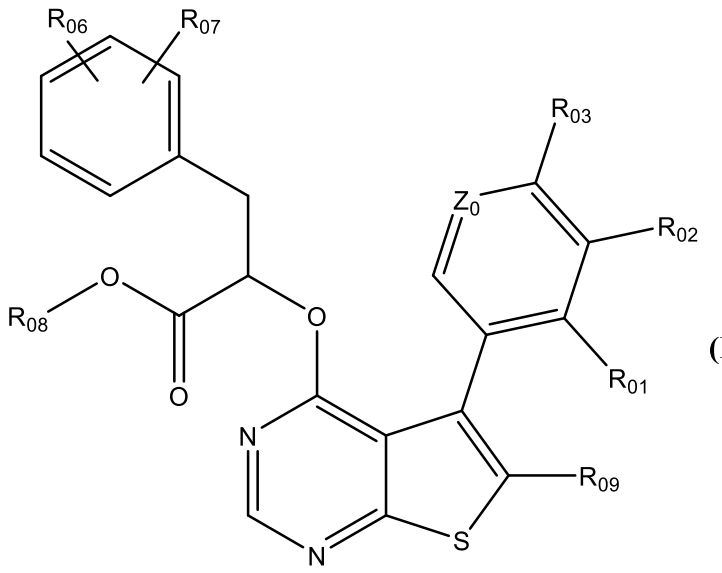
wherein:

Ab is an anti-CD74 antibody or an antigen-binding fragment thereof, optionally wherein the Ab is a Fc silent antibody;

p is an integer from 1 to 16;

L is a linker; and

D is an MCL1 inhibitor compound; wherein the Mcl-1 inhibitor is a compound of Formula (II):



(II)

wherein:

Z_0 is a nitrogen atom or a C-R_{04} group,

R_{01} is a halogen atom, a linear or branched (C_1-C_6)alkyl group, a linear or branched (C_2-C_6)alkenyl group, a linear or branched (C_2-C_6)alkynyl group, a linear or branched (C_1-C_6)haloalkyl group, a hydroxy group, a linear or branched (C_1-C_6)alkoxy group, a -S-(C_1-C_6)alkyl group, a cyano group, -Cy_{08}, -$NR_{011}R_{011}$',

R_{02}, R_{03} and R_{04} independently of one another are a hydrogen atom, a halogen atom, a linear or branched (C_1-C_6)alkyl group, a linear or branched (C_2-C_6)alkenyl group, a linear or branched (C_2-C_6)alkynyl group, a linear or branched (C_1-C_6)haloalkyl, a hydroxy group, a linear or branched (C_1-C_6)alkoxy group, a -S-(C_1-C_6)alkyl group, a cyano group, a nitro group, -(C_0-C_6)alkyl-$NR_{011}R_{011}$', -O-Cy_{01}, -(C_0-C_6)alkyl-Cy_{01}, -(C_2-C_6)alkenyl-Cy_{01}, -(C_2-C_6)alkynyl-Cy_{01}, -O-(C_1-C_6)alkyl-$NR_{011}R_{011}$', -O-(C_1-C_6)alkyl-R_{031}, -C(O)-OR_{011}, -O-C(O)-R_{011}, -C(O)-$NR_{011}R_{011}$', -NR_{011}-C(O)-R_{011}', -NR_{011}-C(O)-OR_{011}', -(C_1-C_6)alkyl-NR_{011}-C(O)-R_{011}', -SO_2-$NR_{011}R_{011}$', or -SO_2-(C_1-C_6)alkyl, or the pair (R_{02}, R_{03}) or (R_{03}, R_{04}) together with the carbon atoms to which they are attached form an aromatic or non-aromatic ring containing 5 to 7 ring members, which optionally contains 1 to 3 heteroatoms selected from O, S and N, wherein the ring is optionally substituted by a group selected from a linear or branched (C_1-C_6)alkyl, -$NR_{013}R_{013}$', -(C_0-C_6)alkyl-Cy_{01} and oxo,

R_{06} and R_{07} independently of one another are a hydrogen atom, a halogen atom, a linear or branched (C_1-C_6)alkyl group, a linear or branched (C_2-C_6)alkenyl group, a linear or branched (C_2-C_6)alkynyl group, a linear or branched

(C_1-C_6)haloalkyl, a hydroxy group, a linear or branched (C_1-C_6)alkoxy group, a -S-(C_1-C_6)alkyl group, a cyano group, a nitro group, -(C_0-C_6)alkyl-$NR_{011}R_{011}$', -O-Cy_{01}, -(C_0-C_6)alkyl-Cy_{01}, -(C_2-C_6)alkenyl-Cy_{01}, -(C_2-C_6)alkynyl-Cy_{01}, -O-(C_1-C_6)alkyl-R_{012}, -C(O)-OR_{011}, -O-C(O)-R_{011}, -C(O)-$NR_{011}R_{011}$', -NR_{011}-C(O)-R_{011}', -NR_{011}-C(O)-OR_{011}', -(C_1-C_6)alkyl-NR_{011}-C(O)-R_{011}', -SO_2-$NR_{011}R_{011}$', or -SO_2-(C_1-C_6)alkyl,

or the pair (R_{06}, R_{07}), when fused with two adjacent carbon atoms, together with the carbon atoms to which they are attached form an aromatic or non-aromatic ring containing 5 to 7 ring members, which optionally contains 1 to 3 heteroatoms selected from O, S and N, and wherein the resulting ring is optionally substituted by a group selected from a linear or branched (C_1-C_6)alkyl group, -$NR_{013}R_{013}$', -(C_0-C_6)alkyl-Cy_{01} and an oxo,

R_{08} is a hydrogen atom, a linear or branched (C_1-C_8)alkyl group, an aryl group, a heteroaryl group, an aryl-(C_1-C_6)alkylgroup, or a heteroaryl(C_1-C_6)alkyl group,

R_{09} is a linear or branched (C_1-C_6)alkyl group, a linear or branched (C_2-C_6)alkenyl group, a linear or branched (C_2-C_6)alkynyl group, -Cy_{02}, -(C_1-C_6)alkyl-Cy_{02}, -(C_2-C_6)alkenyl-Cy_{02}, -(C_2-C_6)alkynyl-Cy_{02}, -Cy_{02}-Cy_{03}, -(C_2-C_6)alkynyl-O-Cy_{02}, -Cy_{02}-(C_0-C_6)alkyl-O-(C_0-C_6)alkyl-Cy_{03}, a halogen atom, a cyano group, -C(O)-R_{014}, -C(O)-$NR_{014}R_{014}$',

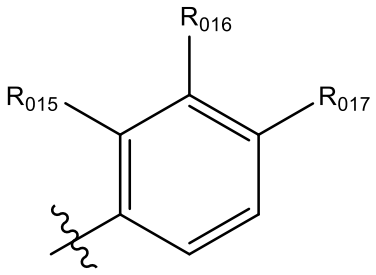
R_{011} and R_{011}' independently of one another are a hydrogen atom, an optionally substituted linear or branched (C_1-C_6)alkyl group, or -(C_0-C_6)alkyl-Cy_{01}, or the pair (R_{011}, R_{011}') together with the nitrogen atom to which they are attached form an aromatic or non-aromatic ring containing 5 to 7 ring members, which optionally contains, in addition to the nitrogen atom, 1 to 3 heteroatoms selected from O, S and N, wherein the N atom is optionally substituted by a linear or branched (C_1-C_6)alkyl group, and wherein one or more of the carbon atoms of the linear or branched (C_1-C_6)alkyl group is optionally deuterated,

R_{012} is -Cy_{05}, -Cy_{05}-(C_0-C_6)alkyl-Cy_{06}, -Cy_{05}-(C_0-C_6)alkyl-O-(C_0-C_6)alkyl-Cy_{06}, -Cy_{05}-(C_0-C_6)alkyl-NR_{011}-(C_0-C_6)alkyl-Cy_{06}, -Cy_{05}-Cy_{06}-O-(C_0-C_6)alkyl-Cy_{07}, -Cy_{05}-(C_0-C_6)alkyl-Cy_{09}, -NH-C(O)-NH-R_{011}, -C(O)-$NR_{011}R_{011}$', -$NR_{011}R_{011}$', -OR_{011}, -NR_{011}-C(O)-R_{011}', -O-(C_1-C_6)alkyl-OR_{011}, -SO_2-R_{011}, or -C(O)-OR_{011},

R_{013}, R_{013}', R_{014} and R_{014}' independently of one another are a hydrogen atom, or an optionally substituted linear or branched (C_1-C_6)alkyl group,

Cy_{01}, Cy_{02}, Cy_{03}, Cy_{05}, Cy_{06}, Cy_{07} and Cy_{08} independently of one another, are a

cycloalkyl group, a heterocycloalkyl group, an aryl group or a heteroaryl group, each of which is optionally substituted,

Cy_{09} is , wherein

R_{015} is a hydrogen atom; a $-(CH_2)_{p0}-O-(CHR_{018}-CHR_{019}-O)_{q0}-R_{020}$ group; a linear or branched (C_1-C_6)alkoxy(C_1-C_6)alkyl group; a $-U_0-(CH_2)_{q0}-NR_{021}R_{021}$' group; or a $-(CH_2)_{r0}-U_0-(CH_2)_{s0}$-heterocycloalkyl group,

R_{016} is a hydrogen atom; a hydroxy group; a hydroxy(C_1-C_6)alkyl group; a $-(CH_2)_{r0}-U_0-(CH_2)_{s0}$-heterocycloalkyl group; a $(CH_2)_{r0}-U_0-V_0-O-P(O)(OR_{020})_2$ group; a $-O-P(O)(O^-M^+)_2$ group; a $-O-S(O)_2OR_{020}$ group; a $-S(O)_2OR_{020}$ group; a $-(CH_2)_{p0}-O-(CHR_{018}-CHR_{019}-O)_{q0}-R_{020}$ group; a $-(CH_2)_{p0}-O-C(O)-NR_{022}R_{023}$ group; or a $-U_0-(CH_2)_{q0}-NR_{021}R_{021}$' group,

R_{017} is a hydrogen atom; a $-(CH_2)_{p0}-O-(CHR_{018}-CHR_{019}-O)_{q0}-R_{020}$ group; a $-CH_2-P(O)(OR_{020})_2$ group, a $-O-P(O)(OR_{020})_2$ group; a $-O-P(O)(O^-M^+)_2$ group; a hydroxy group; a hydroxy(C_1-C_6)alkyl group; a $-(CH_2)_{r0}-U_0-(CH_2)_{s0}$-heterocycloalkyl group; a $-U_0-(CH_2)_{q0}-NR_{021}R_{021}$' group; or an aldonic acid,

M^+ is a pharmaceutically acceptable monovalent cation,

U_0 is a bond or an oxygen atom,

V_0 is a $-(CH_2)_{s0}-$ group or a -C(O)- group,

R_{018} is a hydrogen atom or a (C_1-C_6)alkoxy(C_1-C_6)alkyl group,

R_{019} is a hydrogen atom or a hydroxy(C_1-C_6)alkyl group,

R_{020} is a hydrogen atom or a linear or branched (C_1-C_6)alkyl group,

R_{021} and R_{021}' independently of one are a hydrogen atom, a linear or branched (C_1-C_6)alkyl group, or a hydroxy(C_1-C_6)alkyl group,

or the pair (R_{021}, R_{021}') together with the nitrogen atom to which they are attached form an aromatic or non-aromatic ring containing 5 to 7 ring members, which optionally contains, in addition to the nitrogen atom, 1 to 3 heteroatoms selected from O, S and N, wherein the resulting ring is optionally substituted by a hydrogen atom or a linear or branched (C_1-C_6)alkyl group,

R_{022} is a $(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl group, a $\text{-}(CH_2)_{p0}\text{-}NR_{024}R_{024}$' group, or a $\text{-}(CH_2)_{p0}\text{-}O\text{-}(CHR_{018}\text{-}CHR_{019}\text{-}O)_{q0}\text{-}R_{20}$ group,

R_{023} is a hydrogen atom or a $(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl group,

or the pair (R_{022}, R_{023}) together with the nitrogen atom to which they are attached form an aromatic or non-aromatic ring containing 5 to 18 ring members, which optionally contains, in addition to the nitrogen atom, 1 to 5 heteroatoms selected from O, S and N, wherein the resulting ring is optionally substituted by a hydrogen atom, a linear or branched $(C_1\text{-}C_6)$alkyl group or a heterocycloalkyl group,

R_{024} and R_{024}' independently of one another are a hydrogen atom or a linear or branched $(C_1\text{-}C_6)$alkyl group,

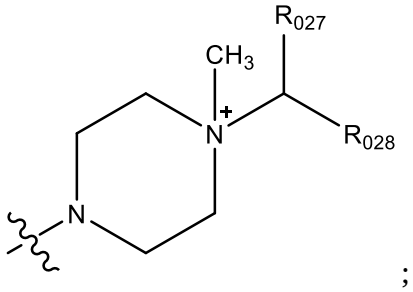
or the pair (R_{024}, R_{024}') together with the nitrogen atom to which they are attached form an aromatic or non-aromatic ring composed of from 5 to 7 ring members, which may contain in addition to the nitrogen atom from 1 to 3 heteroatoms selected from O, S and N, and wherein the resulting ring is optionally substituted by a hydrogen atom or a linear or branched $(C_1\text{-}C_6)$alkyl group,

R_{027} is a hydrogen atom or a linear or branched $(C_1\text{-}C_6)$alkyl group,

R_{028} is a $\text{-}O\text{-}P(O)(O^-)(O^-)$ group, a $\text{-}O\text{-}P(O)(O^-)(OR_{030})$ group, a $\text{-}O\text{-}P(O)(OR_{030})(OR_{030}')$ group, a $\text{-}(CH_2)_{p0}\text{-}O\text{-}SO_2\text{-}O^-$ group, a $\text{-}(CH_2)_{p0}\text{-}SO_2\text{-}O^-$ group, a $\text{-}(CH_2)_{p0}\text{-}O\text{-}SO_2\text{-}OR_{030}$ group, $\text{-}Cy_{010}$, a $\text{-}(CH_2)_{p0}\text{-}SO_2\text{-}OR_{030}$ group, a $\text{-}O\text{-}C(O)\text{-}R_{029}$ group, a $\text{-}O\text{-}C(O)\text{-}OR_{029}$ group or a $\text{-}O\text{-}C(O)\text{-}NR_{029}R_{029}$' group;

R_{029} and R_{029}' independently of one another are a hydrogen atom, a linear or branched $(C_1\text{-}C_6)$alkyl group or a linear or branched amino$(C_1\text{-}C_6)$alkyl group,

R_{030} and R_{030}' independently of one another are a hydrogen atom, a linear or branched $(C_1\text{-}C_6)$alkyl group or an aryl$(C_1\text{-}C_6)$alkylgroup,

R_{031} is 

;

p_0 is an integer equal to 0, 1, 2, or 3;

q_0 is an integer equal to 1, 2, 3 or 4;

r_0 and s_0 are independently an integer equal to 0 or 1;

wherein one of the R_{03}, R_{09}, or R_{012} groups, if present, is covalently attached to the linker,

or an enantiomer, diastereoisomer, atropisomer, deuterated derivative, and/or pharmaceutically acceptable salt of any of the foregoing.

21. Use of the antibody-drug conjugate of claim 20 in the manufacture of a medicament for treating a disease or disorder, wherein the antibody-drug conjugate of claim 20 in combination with a Bcl-2 inhibitor is to be administered to a subject in need thereof, wherein the disease or disorder is mediated by CD74.

22. The antibody-drug conjugate of any one of claims 1 to 13, the composition of claim 14, the pharmaceutical composition of claim 15, or the antibody-drug conjugate of claim 20 for use in therapy.