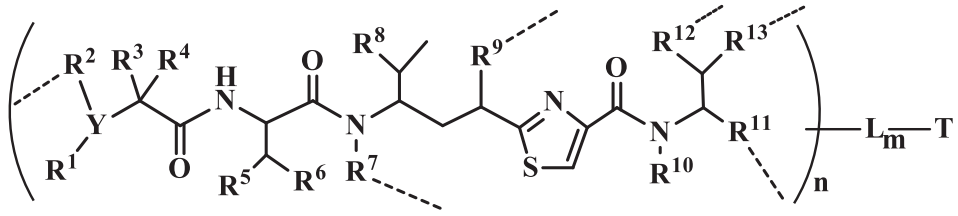
CLAIMS

What is claimed is:

1. A pharmaceutical composition of a liquid composition prior to lyophilization, or in a formulated lyophilized solid, or the reconstituted formulation from the lyophilized solid having the following compositions: a conjugate of a tubulysin analog to a cell-binding agent of Formula (I) may take up 0.01% ~ 99% by weight as major gradient in the formulation; 3% ~ 20.0% of one or more polyols selected from sucrose or trehalose; 0.01% ~ 2.0% of one or more surfactants selected from polysorbate; 0.0% ~ 5.0% of one or more preservatives; 0.0% ~ 30% of one or more amino acids; 0.0% ~ 5.0% of one or more antioxidants; 0.0% ~ 0.3% of one or more metal chelating agents; 0.0% ~ 30.0% of one or more buffer salts for adjusting pH of the formulation to pH 5 to 7; and 0.0% ~ 30.0% of one or more of isotonic agent for adjusting osmotic pressure between about 250 to 350 mOsm after reconstituted for administration to a patient;

wherein a tubulysin analog conjugate of Formula (I) illustrated as following:



(I)

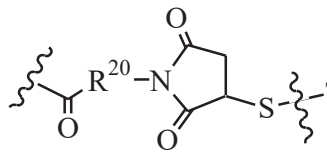
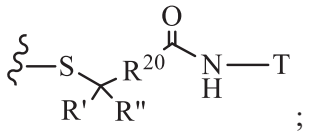
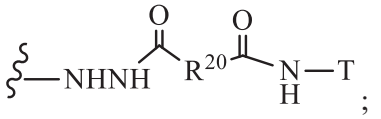
or their pharmaceutically acceptable salts, hydrates, or hydrated salts; or their isotopes, optical isomers, racemates, diastereomers or enantiomers thereof;

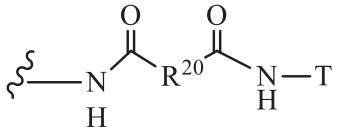
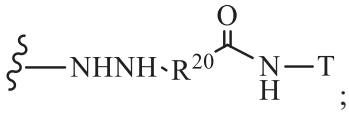
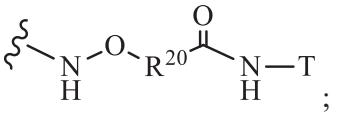
wherein T is a targeting or cell-binding molecule; L is a releasable linker; ----- is a linkage bond that L connects to an atom inside the bracket independently; n is 1~20 and m is 1~10;

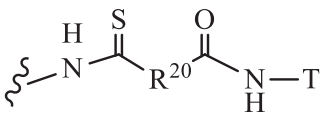
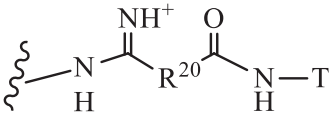
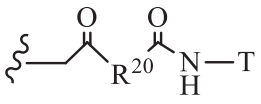
wherein T is an antibody; an antibody fragment; a lymphokine; a hormone; a vitamin; a growth factor; a colony stimulating factor; or a nutrient-transport molecule; a binding peptide, or antibody, or small molecule attached on albumin, polymers, dendrimers, liposomes, nanoparticles, vesicles, (viral) capsids;

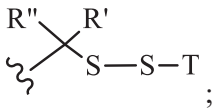
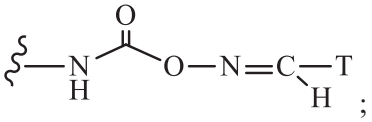
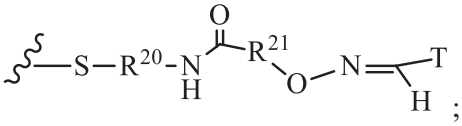
wherein the linker L has the formula: --Ww—(Aa)r--Vv—; wherein: --W-- is a Stretcher unit; w is 0 or 1; each --Aa-- is independently an Amino Acid unit; r is independently an integer ranging from 0 to 12; --V-- is a Spacer unit; and v is 0, 1 or 2; the Stretcher unit W may independently contain a self-immolative spacer, peptide units, a hydrazone bond, disulfide or thiolether bonds; the Stretcher unit (--W--), when present, links a targeted binding molecular unit (T) to an amino acid unit (--Aa--), or links V when an Aa is not present; the Stretcher unit W may independently contain a self-immolative spacer, a non self-immolative spacer, peptide units, a

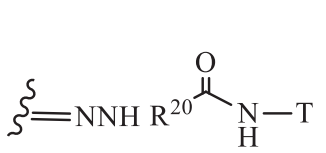
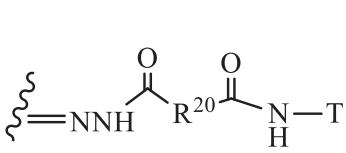
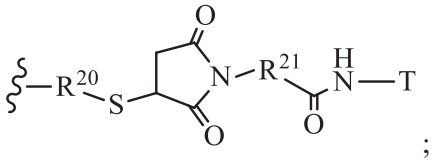
hydrazone bond, disulfide or thiolether bonds; W linked to T has the structures of:

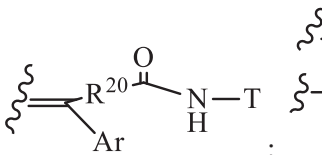
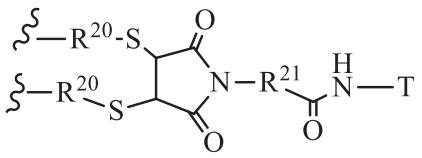
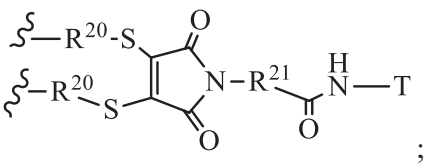

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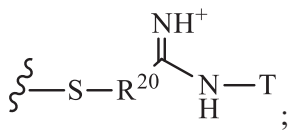
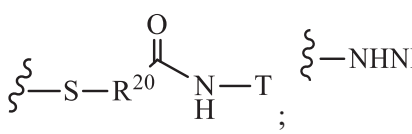
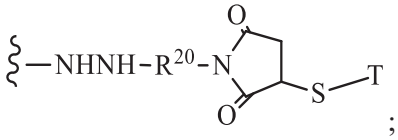

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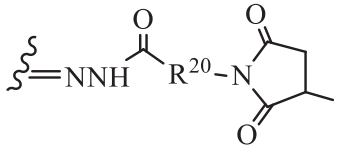
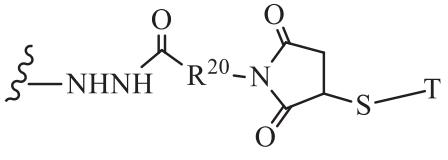

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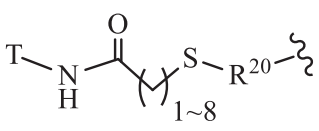
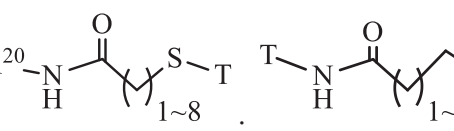

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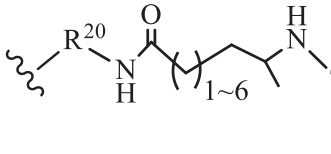
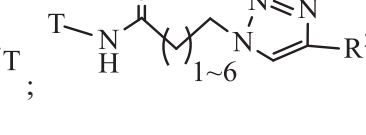
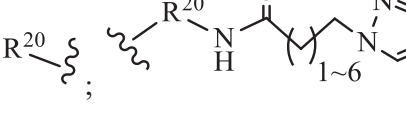

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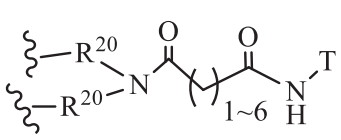
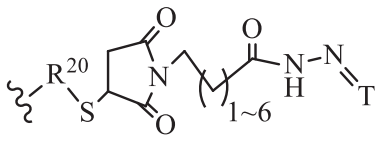
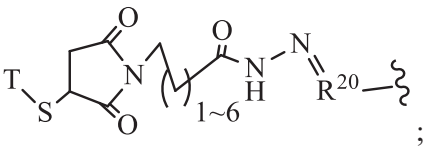
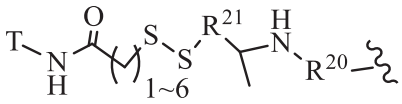
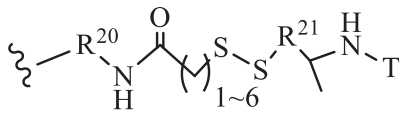

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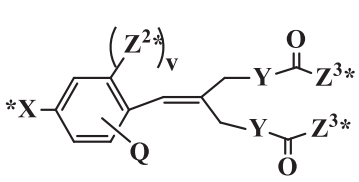
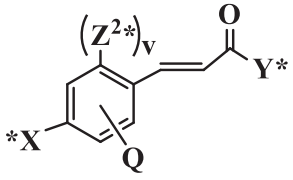
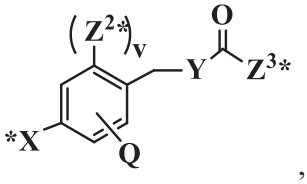
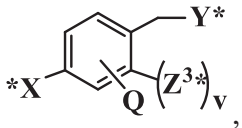
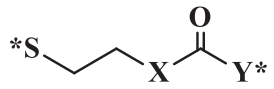
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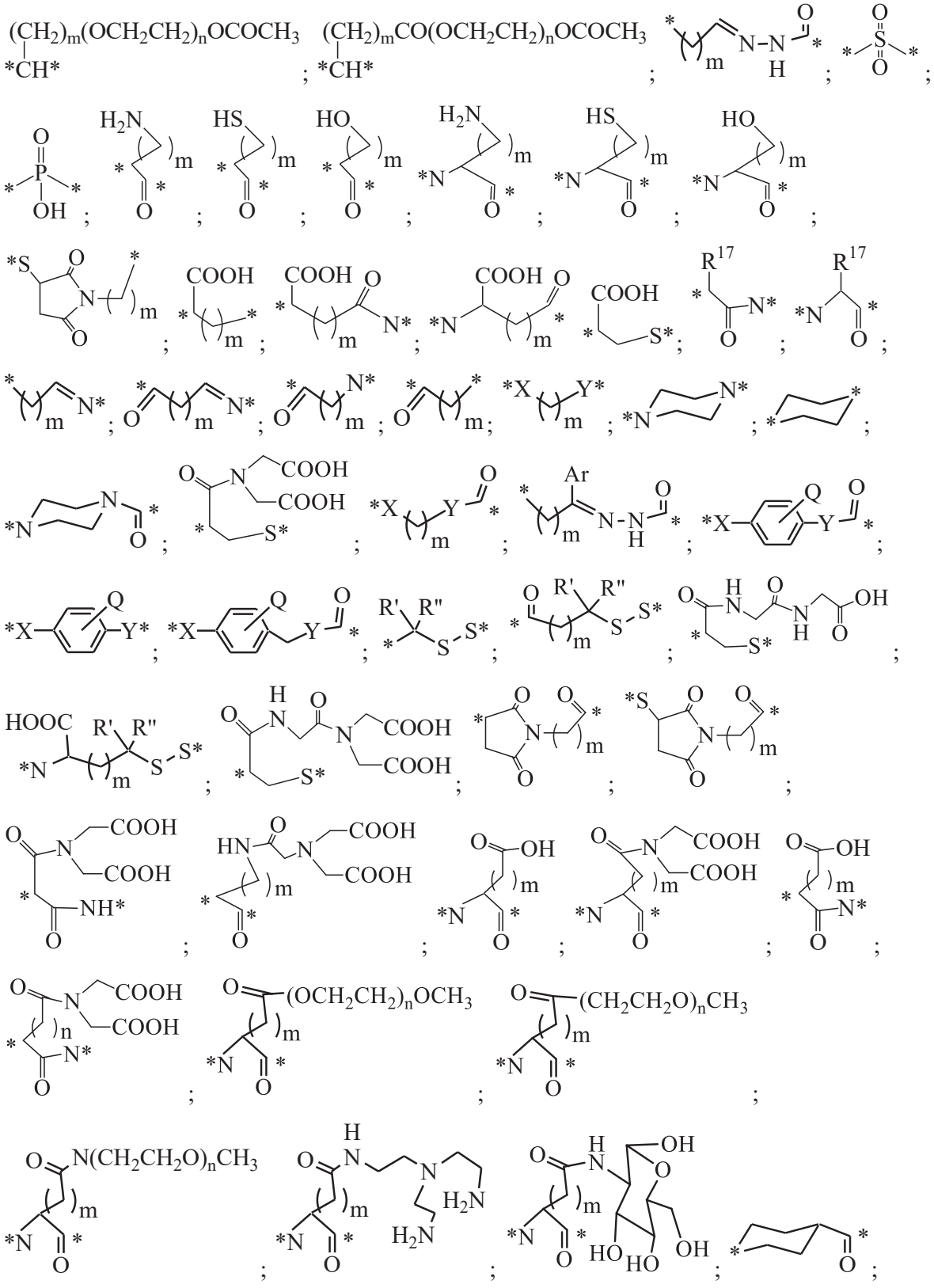

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wherein R^{20} and R^{21} are independently selected from –C_1~C_9 alkylene-, -C_1~C_7 carbocyclo-, -O-(C_1~C_8 alkyl)-, -arylene-, -C_1~C_9 alkylene-arylene-, -arylene, -C_1~C_9 alkylene-, -C_1~C_9 alkylene-(C_1~C_8 carbocyclo)-, -(C_3~C_7 carbocyclo)-C_1~C_9 alkylene-, -C_3~C_8 heterocyclo-, -C_1~C_{10} alkylene-(C_3~C_8 heterocyclo)-, -(C_3~C_8 heterocyclo)- C_1~C_9 alkylene-, -$(CH_2CH_2O)_k$-, -$(CH(CH_3)CH_2O)_k$-, and -$(CH_2CH_2O)_k$-CH_2-; k is an integer ranging from 1-20; R' and R'' are independently H or CH_3;

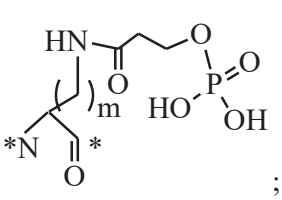
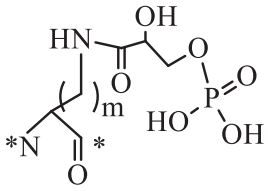
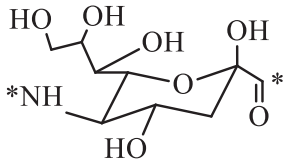
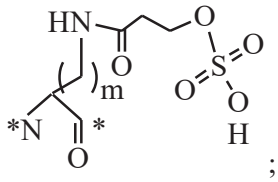
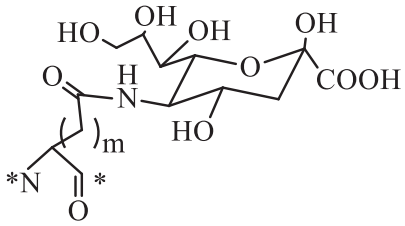
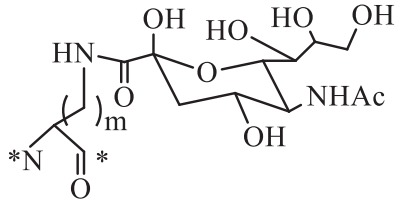
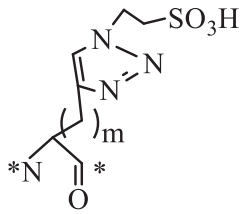
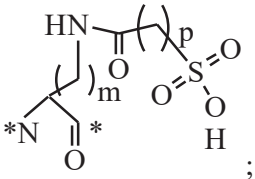
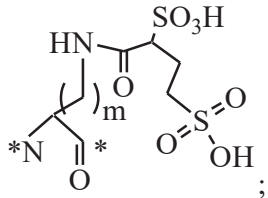
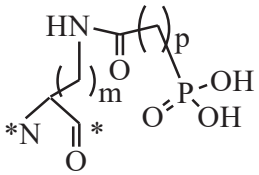
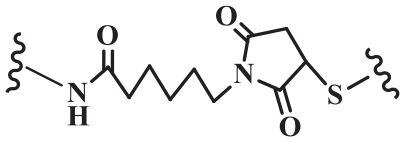
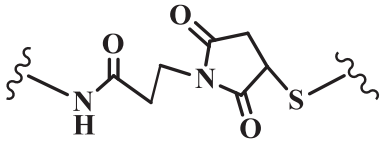
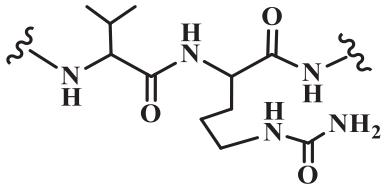
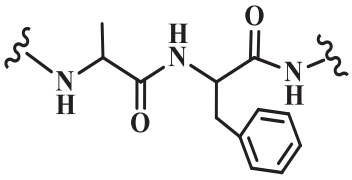
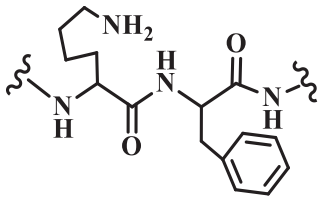
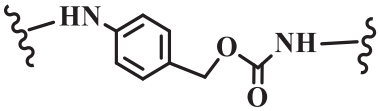
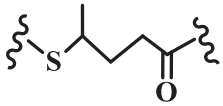
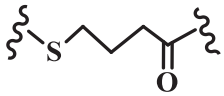
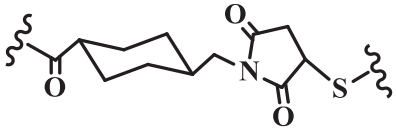
the self-immolative spacer includes aromatic compounds that are electronically similar to the para-aminobenzyl-carbamoyl (PAB) groups, 2-aminoimidazol-5-methanol derivatives, heterocyclic PAB analogs, beta-glucuronide, and ortho or para-aminobenzylacetals; or one of the following structures:

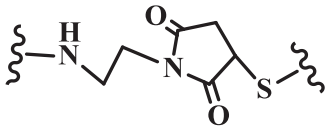

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,

,

; wherein the (*) atom is the point of attachment of additional spacer or releasable linker units, the tubulysin analog inside the bracket of the Formula (I), and/or the binding molecule (T); X, Y and $Z^3$are independently NH, O, or S; Z^2 is H, NH, O or S independently; v is 0 or 1; Q is independently H, OH, C_1~C_6 alkyl, $(OCH_2CH_2)_n$ F, Cl, Br, I, OR^{17}, or SR^{17}, $NR^{17}R^{18}$, $N{=}NR^{17}$, $N{=}R^{17}$, $NR^{17}R^{18}$, NO_2, $SOR^{17}R^{18}$, SO_2R^{17}, SO_3R^{17}, OSO_3R^{17}, $PR^{17}R^{18}$, $POR^{17}R^{18}$, $PO_2R^{17}R^{18}$, $OPO(OR^{17})(OR^{18})$, or $OCH_2PO(OR^{17}(OR^{18})$ wherein R^{17}, R^{18} are independently H, C_1~C_8 of alkyl; C_2~C_8 of alkenyl, alkynyl, heteroalkyl; C_3~C_8 of aryl, heterocyclic, carbocyclic, cycloalkyl, heterocycloalkyl, heteroaralkyl, alkylcarbonyl; or pharmaceutical cation salts;

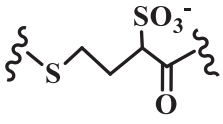
the non-self-immolative spacer having structure:

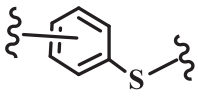
$*(CH_2CH_2O)_n*$; $*\underset{|}{C}H*(CH_2)_mCO(OCH_2CH_2)_nOCH_3$; $*\underset{|}{C}H*(CH_2)_mCON(CH_2CH_2O)_nCOCH_3$;

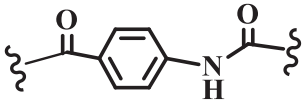


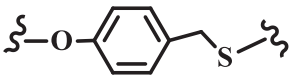

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6-maleimidocaproyl (MC),


maleimido propanoyl (MP),
valine-citrulline (val-cit),


alanine-phenylalanine (ala-phe),

lysine-phenylalanine (lys-phe),
p-aminobenzyloxycarbonyl

(PAB),
4-thio-pentanoate (SPP),

4-thio-butyrate (SPDB),

4-(N-maleimidomethyl)cyclo-hexane-1-carboxylate (MCC),

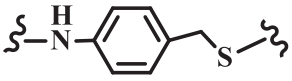


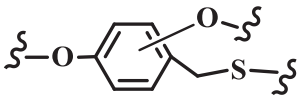
maleimidoethyl (ME),


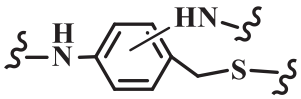
4-thio-2-hydroxysulfonyl-butyrate (2-Sulfo-SPDB),


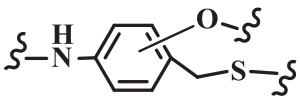
aryl-thiol (PySS),


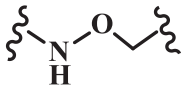
(4-acetyl)aminobenzoate (SIAB),


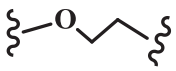
, oxylbenzylthio,


aminobenzylthio,


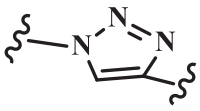
dioxylbenzylthio,


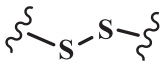
diamino-benzylthio,


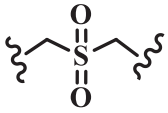
amino-oxylbenzylthio,


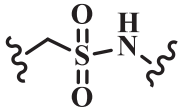
alkoxy amino (AOA),


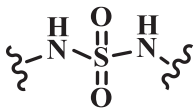
ethyleneoxy (EO),

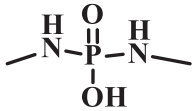

4-methyl-4-dithio-pentanoic (MPDP),


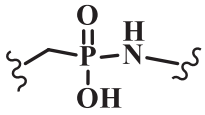
triazole,


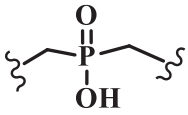
dithio,


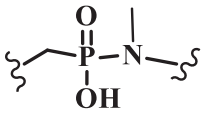
alkylsulfonyl,


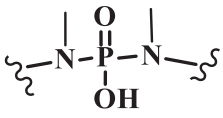
alkylsulfonamide,


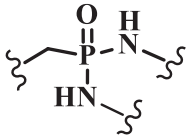
sulfon-bisamide,


Phosphondi-amide,


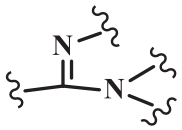
alkylphosphonamide,


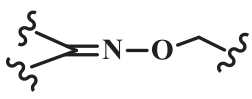
phosphinic acid,


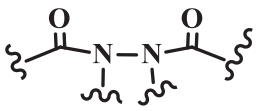
N-methylphosphonamidic acid,


N,N’-dimethylphosphon-amidic acid,


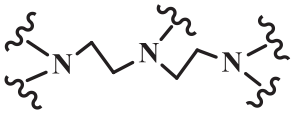
N,N’-dimethylphosphondiamide,


hydrazine,


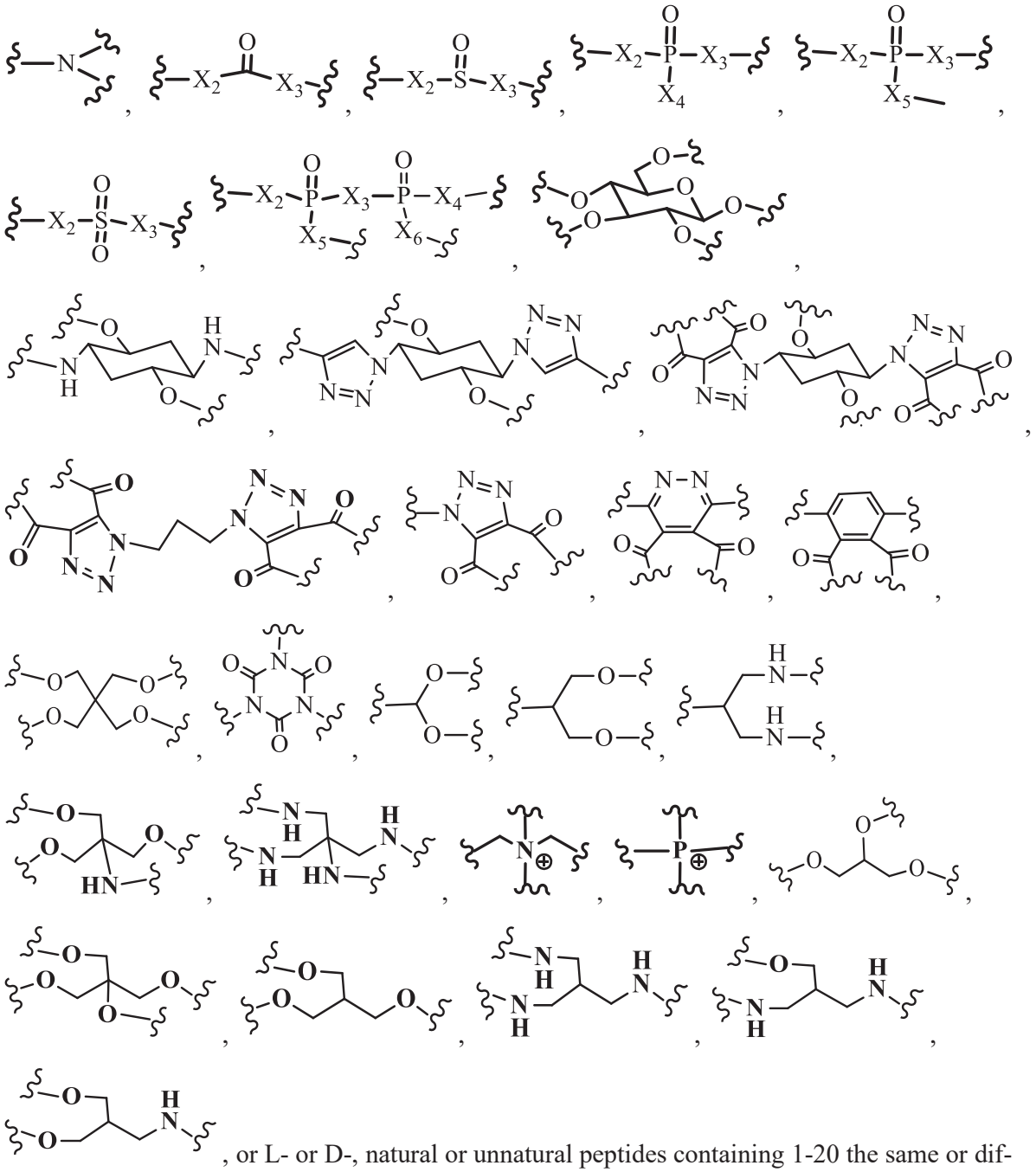
acetimidamide;


oxime,


acetylacetohydrazide,


aminoethyl-amine,


aminoethyl-aminoethyl-amine,



, or L- or D-, natural or unnatural peptides containing 1-20 the same or different amino acids;

wherein the "*" and " ∿ "atom are the point of attachment of additional spacer or releasable linkers, the tubulysin analog inside the bracket of the Formula (I), and/or the binding molecules; m is 1~10; n is 1~20; X_2, X_3, X_4, X_5, or X_6, are independently selected from NH; NHNH; N(R_{12}); N(R_{12})N($R_{12'}$); O; S; C_1-C_6 of alkyl; C_2-C_6 of heteroalkyl, alkylcycloalkyl, heterocycloalkyl; C_3-C_8 of aryl, Ar-alkyl, heterocyclic, carbocyclic, cycloalkyl, heteroalkylcycloalkyl, alkylcarbonyl, heteroaryl; CH_2OR_{12}, CH_2SR_{12}, CH_2NHR_{12}, or 1~8 amino acids; wherein R_{12} and $R_{12'}$ are independently H;C_1-C_8 of alkyl; C_2-C_8 of hetero-alkyl, alkylcycloalkyl, heterocycloalkyl; C_3-C_8

of aryl, Ar-alkyl, heterocyclic, carbocyclic, cycloalkyl, heteroalkylcycloalkyl, alkylcarbonyl, heteroaryl; or 1-8 carbon atoms of esters, ether, or amide; or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$ or $(OCH_2CH(CH_3))_p$, wherein p is an integer from 0 to about 1000, or combination above thereof;

A releasable component of the linker L that at least one bond in L can be broken under physiological conditions: a pH-labile, acid-labile, base-labile, oxidatively labile, metabolically labile, biochemically labile or enzyme-labile bond, which having one of the following structures: -$(CR_{15}R_{16})_m$(Aa)r$(CR_{17}R_{18})_n(OCH_2CH_2)_t$-, -$(CR_{15}R_{16})_m(CR_{17}R_{18})_n(Aa)_r(OCH_2CH_2)_t$-, -$(Aa)_r$-$(CR_{15}R_{16})_m(CR_{17}R_{18})_n(OCH_2CH_2)_t$-, -$(CR_{15}R_{16})_m(CR_{17}R_{18})_n(OCH_2CH_2)_r(Aa)_t$-, -$(CR_{15}R_{16})_m(CR_{17}{=}CR_{18})(CR_{19}R_{20})_n(Aa)_t(OCH_2CH_2)_r$-, -$(CR_{15}R_{16})_m(NR_{11}CO)(Aa)_t(CR_{19}R_{20})_n$-$(OCH_2CH_2)_r$-, -$(CR_{15}R_{16})_m(Aa)_t(NR_{21}CO)(CR_{19}R_{20})_n(OCH_2CH_2)_r$-, -$(CR_{15}R_{16})_m(OCO)(Aa)_t$-$(CR_{19}R_{20})_n(OCH_2CH_2)_r$-, -$(CR_{15}R_{16})_m(OCNR_{17})(Aa)_t(CR_{19}R_{20})_n(OCH_2CH_2)_r$-, -$(CR_{15}R_{16})_m$-$(CO)(Aa)_t$-$(CR_{19}R_{20})_n(OCH_2CH_2)_r$-, -$(CR_{15}R_{16})_m(NR_{21}CO)(Aa)_t(CR_{19}R_{20})_n(OCH_2CH_2)_r$-, -$(CR_{15}R_{16})_m$-$(OCO)(Aa)_t(CR_{19}R_{20})_n$-$(OCH_2CH_2)_r$-, -$(CR_{15}R_{16})_m(OCNR_{17})(Aa)_t(CR_{19}R_{20})_n$-$(OCH_2CH_2)_r$-, -$(CR_{15}R_{16})_m(CO)(Aa)_t(CR_{19}R_{20})_n$-$(OCH_2CH_2)_r$-, -$(CR_{15}R_{16})_m$-phenyl-$CO(Aa)_t$-$(CR_{17}R_{18})_n$-, -$(CR_{15}R_{16})_m$-furyl-$CO(Aa)_t(CR_{17}R_{18})_n$-, -$(CR_{15}R_6)_m$-oxazolyl-$CO(Aa)_t(CR_{17}R_{18})_n$-, -$(CR_{15}R_{16})_m$-thiazolyl-$CO(Aa)_t(CCR_{17}R_{18})_n$-, -$(CR_{15}R_{16})_t$-thienyl-$CO(CR_{17}R_{18})_n$-, -$(CR_{15}R_{16})_t$-imidazolyl-CO-$(CR_{17}R_{18})_n$-, -$(CR_{15}R_{16})_t$-morpholino-$CO(Aa)_t$-$(CR_{17}R_{18})_n$-, -$(CR_{15}R_{16})_t$-piperazino-$CO(Aa)_t(CR_{17}R_{18})_n$-, -$(CR_{15}R_{16})_t$-N-methylpiperazin-$CO(Aa)_t(CR_{17}R_{18})_n$-, -$(CR_{15}R_{16})_m$-$(Aa)_t$phenyl-, -$(CR_{15}R_{16})_m$-$(Aa)_t$furyl-, -$(CR_{15}R_{16})_m$-oxazolyl$(Aa)_t$-, -$(CR_{15}R_{16})_m$-thiazolyl$(Aa)_t$-, -$(CR_{15}R_{16})_m$-thienyl-$(Aa)_t$-, -$(CR_{15}R_{16})_m$-imidazolyl$(Aa)_t$-, -$(CR_{15}R_{16})_m$-morpholino-$(Aa)_t$-, -$(CR_{15}R_{16})_m$-piperazino-$(Aa)_t$-, -$(CR_{15}R_{16})_m$-N-methylpiperazino-$(Aa)_t$-
,-K$(CR_{15}R_{16})_m$(Aa)r$(CR_{17}R_{18})_n(OCH_2CH_2)_t$-, -K$(CR_{15}R_{16})_m(CR_{17}R_{18})_n(Aa)_r(OCH_2CH_2)_t$-
, -K$(Aa)_r$-$(CR_{15}R_{16})_m(CR_{17}R_{18})_n(OCH_2CH_2)_t$-, -K$(CR_{15}R_{16})_m(CR_{17}R_{18})_n(OCH_2CH_2)_r(Aa)_t$-
, -K$(CR_{15}R_{16})_m$-$(CR_{17}{=}CR_{18})(CR_{19}R_{20})_n(Aa)_t(OCH_2CH_2)_r$, -K$(CR_{15}R_{16})_m(NR_{11}CO)(Aa)_t$-$(CR_{19}R_{20})_n(OCH_2CH_2)_r$-, -K$(CR_5R_6)_m(Aa)_t(NR_{21}CO)(CR_{19}R_{20})_n(OCH_2CH_2)_r$-, -K$(CR_{15}R_{16})_m$-$(OCO)(Aa)_t(CR_{19}R_{20})_n$-$(OCH_2CH_2)_r$-, -K$(CR_{15}R_{16})_m(OCNR_{17})(Aa)_t(CR_{19}R_{20})_n$-$(OCH_2CH_2)_r$-
, -K$(CR_{15}R_{16})_m(CO)(Aa)_t$-$(CR_{19}R_{20})_n(OCH_2CH_2)_r$-, -K$(CR_{15}R_{16})_m(NR_{21}CO)(Aa)_t$-$(CR_{19}R_{20})_n$-$(OCH_2CH_2)_r$-, -K$(CR_{15}R_{16})_m$-$(OCO)(Aa)_t(CR_{19}R_{20})_n(OCH_2CH_2)_r$-, -K$(CR_{15}R_{16})_m$-$(OCNR_{17})(Aa)_t$-$(CR_{19}R_{20})_n(OCH_2CH_2)_r$-, -K-$(CR_{15}R_{16})_m(CO)(Aa)_t(CR_{19}R_{20})_n(OCH_2CH_2)_r$-, -K$(CR_{15}R_{16})_m$-phenyl-$CO(Aa)_t(CR_{17}R_{18})_n$-, -K-$(CR_{15}R_{16})_m$-furyl-$CO(Aa)_t(CR_{17}R_{18})_n$-, -K$(CR_{15}R_{16})_m$-oxazolyl-$CO(Aa)_t(CR_{17}R_{18})_n$-, -K$(CR_{15}R_{16})_m$-thiazolyl-$CO(Aa)_t$-$(CR_{17}R_{18})_n$-, -K$(CR_{15}R_{16})_t$-thienyl-$CO(CR_{17}R_{18})_n$-, -K$(CR_{15}R_{16})_t$imidazolyl-CO-$(CR_{17}R_{18})_n$-, -K$(CR_5R_6)_t$morpholino-$CO(Aa)_t$-$(CR_{17}R_{18})_n$-, -K$(CR_{15}R_{16})_t$-piperazino-$CO(Aa)_t$-$(CR_{17}R_{18})_n$-, -K$(CR_{15}R_{16})_t$-N-methylpiperazin-$CO(Aa)_t(CR_{17}R_{18})_n$-, -K$(CR_{15}R_{16})_m$-$(Aa)_t$phenyl, -K-$(CR_{15}R_{16})_m$-$(Aa)_t$furyl-, -K$(CR_{15}R_{16})_m$-

oxazolyl-$(Aa)_t$-, -$K(CR_{15}R_{16})_m$-thiazolyl$(Aa)_t$-, -$K(CR_{15}R_{16})_m$-thienyl-$(Aa)_t$-, -$K(CR_{15}R_{16})_m$-imidazolyl$(Aa)_t$-, -$K(CR_{15}R_{16})_m$-morpholino$(Aa)_t$-, -$K(CR_{15}R_{16})_m$piperazino$(Aa)_tG$, -$K(CR_5R_6)_m$-N-methyl-piperazino$(Aa)_t$-; wherein m, Aa, m, n, R_{13}, R_{14}, and R_{15} are described above; t and r here are 0 – 100 independently; R_{16}, R_{17}, R_{18}, R_{19}, and R_{20} are independently chosen from H; halide; C_1~C_8 of alkyl or heteroalkkyl, C_2~C_8 of aryl, alkenyl, alkynyl, ether, ester, amine or amide, C_3~C_8 of aryl, which optionally substituted by one or more halide, CN, $NR_{12}R_{12'}$, CF_3, OR_{12}, Aryl, heterocycle, $S(O)R_{12}$, SO_2R_{12}, $-CO_2H$, $-SO_3H$, $-OR_{12}$, $-CO_2R_{12}$, $-CONR_{12}$, $-PO_2R_{12}R_{13}$, $-PO_3H$ or $P(O)R_{12}R_{12'}R_{13}$; K is NR_{12}, -SS-, -C(=O)-, -C(=O)NH-, -C(=O)O-, -C=NH-O-, -C=N-NH-, -C(=O)NH-NH-, O, S, Se, B, Het (heterocyclic or heteroaromatic ring having C_3-C_{12}); or peptides containing the same or different 1- 20 amino acids;

Inside the bracket of the Formula (I) is a tubulysin analog wherein R^1, R^2, R^3, and R^4 are independently linear or branched C_1-C_8 of alkyl, alkyl alcohol; C_2-C_8 of heteroalkyl, alkylcycloalkyl, heterocycloalkyl, alkyl ether, alkyl carboxylate, alkyl amine, alkyl ester, alkyl amide; C_3-C_8 of aryl, Ar-alkyl, heterocyclic, carbocyclic, cycloalkyl, heteroalkylcycloalkyl, alkylcarbonyl; or two R's: R^1R^2, R^3R^4, R^5R^6, or $R^{12}R^{13}$ together form a 3~7 membered carbocyclic, cycloalkyl, heterocyclic, heterocycloalkyl, aromatic or heteroaromatic ring system; Y is N or C; In addition, R^1, R^2, R^3, and R^4 can be independently absent;

Wherein R^5, R^6, R^8 and R^{10} are independently selected from H and linear or branched C_1-C_4 of alkyl or C_2-C_4 of heteroalkyl;

Wherein R^7 is selected from H, R^{14}, or $-R^{14}C(=O)X^1R^{15}$; $-R^{14}X^1R^{15}$; X^1 is selected from O, S, S-S, NH, or NR^{14};

Wherein R^9 is H, -O-, $-OR^{14}$, $-OC(=O)R^{14}$-, $-OC(=O)NHR^{14}$-, $-OC(=O)NR^{14}R^{15}$-, $-OC(=O)R^{14}SSR^{15}$-, $OP(=O)(OR^{14})$-, or $OR^{14}OP(=O)(OR^{15})$;

Wherein R^{11} is H, R^{14}, $-R^{14}C(=O)R^{16}$, $-R^{14}C(=O)X^2R^{16}$, $-R^{14}X^2R^{16}$, $-R^{14}C(=O)X^2$, wherein X^2 is -O-, -S-, -NH-, $-NHS(O_2)$, -NHS(O), $-N(R^{14})$-, $-O-R^{14}$-, $-S-R^{14}$-, $-S(=O)-R^{14}$-, or $-NHR^{14}$-;

Wherein R^{12} is H, R^{14}, -O-, -S-, -N-, =N-, =NNH-, -OH, -SH, $-NH_2$, =NH, $=NNH_2$, $-NH(R^{14})$, $-OR^{14}$, -C(O)O-, $-C(O)OR^{16}$-,$-COR^{16}$, $-COOR^{14}$-, C(O)NH-, $C(O)NH_2$, $C(O)NHR^{14}$, $-SR^{14}$, $-S(=O)R^{14}$, $-P(=O)(OR^{16})_2$, $-OP(=O)(OR^{16})_2$, $-CH_2OP(=O)(OR^{16})_2$, $-SO_2R^{16}$;

Wherein R^{13} is linear or branched C_1-C_{10} of alkyl, alkyl acid, alkyl amide, alkyl amine; or C_2-C_{10} of heteroalkyl; or C_3-C_{10} of Ar; Ar refers to an aromatic or hetero aromatic group, composed of one or several rings, comprising four to ten carbon atoms; the term of hetero aromatic group refers to an aromatic group that has one or several carbon atoms replaced by hetero atoms; the term aryl or Ar also refers to an aromatic group, wherein one or several H atoms can be replaced independently by R^{17}, F, Cl, Br, I, OR^{16}, SR^{16}, $NR^{16}R^{17}$, $N=NR^{16}$, $N= R^{16}$, NR^{16} R^{17},

NO_2, $SOR^{16}R^{17}$, SO_2R^{16}, SO_3R^{16}, OSO_3R^{16}, $PR^{16}R^{17}$, $POR^{16}R^{17}$, $PO_2R^{16}R^{17}$, $OP(O)(OR^{17})_2$, $OCH_2OP(O)(OR^{17})_2$, $OC(O)OP(O)(OR^{17})_2$, $PO(OR^{16})(OR^{17})$, $OP(O)(OR^{17})OP(O)(OR^{17})_2$, $OC(O)R^{17}$ or $OC(O)NHR^{17}$;

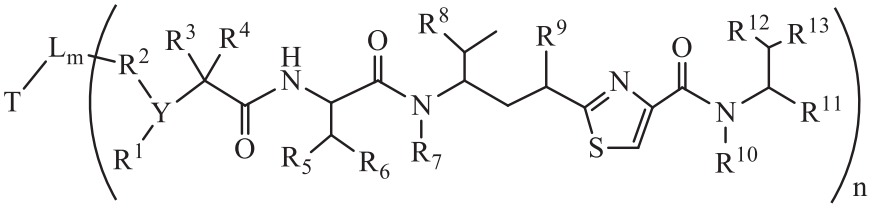
Wherein R^{14} and R^{15} are independently H; linear or branched C_1-C_8 of alkyl; C_2-C_8 of alkenyl, alkynyl, heteroalkyl, heterocyclic, carbocyclic; C_3-C_8 of aryl, cycloalkyl, alkylcycloalkyl, heterocycloalkyl, heteroaralkyl, heteroalkylcycloalkyl, alkylcarbonyl;

Wherein when R^{14} is bivalent, it is a R^{14} that is further connected to an additional functional group of one to four amino acid units, or $(CH_2CH_2O)_r$, r is an integer ranging from 0 to 12, or C_4-C_{12} of glycosides, or C_1-C_8 of carboxylic acid;

Wherein R^{16} is H, OH, R^{14} or one to four amino acid units;

Wherein R^{17} is H, linear or branched C_1-C_8 of alkyl; C_2-C_8 of alkenyl, alkynyl, heteroalkyl, heterocyclic; C_3-C_8 of aryl, carbocyclic, cycloalkyl, alkylcycloalkyl, heterocycloalkyl, heteroalkylcycloalkyl, heteroaralkyl, alkylcarbonyl or C_4-C_{12} of glycosides, or pharmaceutical salts.

2. The pharmaceutical composition according to Claim 1, wherein the conjugate of the tubulysin analog with a cell-binding agent of formula (I) have Formula (II):



(II)

or their pharmaceutically acceptable salts, hydrates, or hydrated salts; or the polymorphic crystal of these compounds; or their isotopes, optical isomers, racemates, diastereomers or enantiomers thereof;

Wherein T, L, n, m, Y, R^1, R^2, R^3, R^4, R^5, R^6, R^8, R^{10}, R^{13}, R^{14}, R^{15}, R^{16} and R^{17} are defined the same as in the Formula (I);

Wherein R^7 is selected from H, R^{14}, or $-R^{14}C(=O)X^1R^{15}$; $-R^{14}X^1R^{15}$; X^1 is selected from O, S, S-S, NH, or NR^{14};

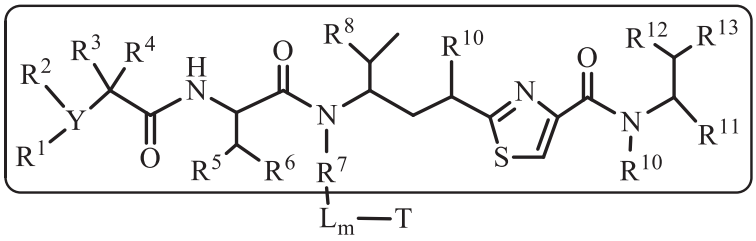
Wherein R^9 is H, -OH, $-OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)NHR^{14}$, $-OC(=O)NR^{14}R^{15}$, $-OC(=O)R^{14}SSR^{15}$, $OP(=O)(OR^{14})_2$, or $OR^{14}OP(=O)(OR^{15})$;

Wherein R^{11} is H, R^{14}, $-R^{14}C(=O)R^{16}$, $-R^{14}C(=O)X^2R^{16}$, $-R^{14}X^2R^{16}$, $-R^{14}C(=O)X^2$, wherein X^2 is -O-, -S-, -NH-, $-NHS(O_2)$, $-N(R^{14})$-, $-O-R^{14}$-, $-S-R^{14}$-, $-S(=O)-R^{14}$-, or $-NHR^{14}$-;

Wherein R^{12} is H, R^{14}, -O-, -S-, -N-, =N-, =NNH-, -OH, -SH, $-NH_2$, =NH, $=NNH_2$, -

$NH(R^{14})$, $-OR^{14}$, -C(O)O-, $-C(O)OR^{16}$-,$-COR^{16}$, $-COOR^{14}$-, C(O)NH-, $C(O)NH_2$, $C(O)NHR^{14}$, $-SR^{14}$, $-S(=O)R^{14}$, $-P(=O)(OR^{16})_2$, $-OP(=O)(OR^{16})_2$, $-CH_2OP(=O)(OR^{16})_2$, $-SO_2R^{16}$.

3. The pharmaceutical composition according to claim 1, wherein the conjugate of the tubulysin analog have Formula (III):



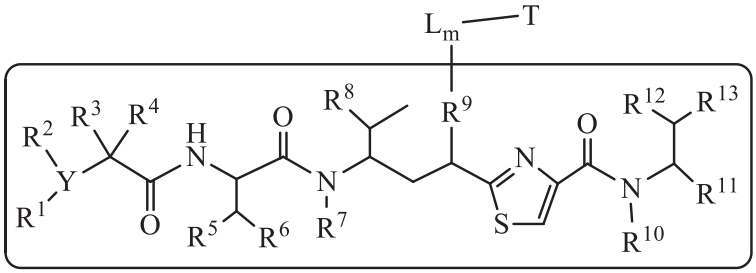
(III)

or their pharmaceutically acceptable salts, hydrates, or hydrated salts; or the polymorphic crystal of these compounds; or their isotopes, optical isomers, racemates, diastereomers or enantiomers thereof;

wherein T, L, m, Y, R^1, R^2, R^3, R^4, R^5, R^6, R^8, R^{10}, R^{11}, R^{12}, R^{13} and n are defined the same as in Formula (I);

wherein R^7 is independently selected from $-R^{14}$-, or $-R^{14}C(=O)X^1R^{15}$- or $-R^{14}X^1R^{15}$-, wherein R^{14} and R^{15} are independently linear or branched C_1~C_8 of alkyl, heteroalkyl; C_2~C_8 of alkenyl, alkynyl; C_3~C_8 of aryl, heterocyclic, carbocyclic, cycloalkyl, heterocycloalkyl, heteroaralkyl heteroalkylcycloalkyl, alkylcarbonyl; X^1 is selected from O, S, S-S, NH, or NR^{14}.

4. The pharmaceutical composition according to Claim 1, wherein the conjugate of the tubulysin analog have Formula (IV):



(IV)

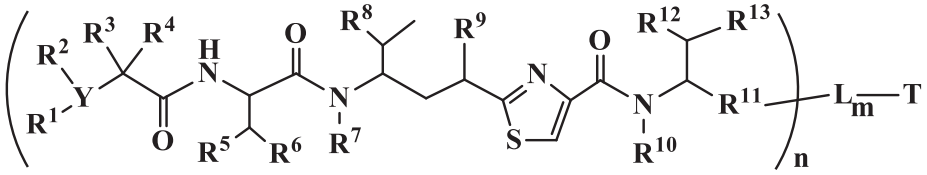
or their pharmaceutically acceptable salts, hydrates, or hydrated salts; or the polymorphic crystal of these compounds; or their isotopes, optical isomers, racemates, diastereomers or enantiomers thereof;

wherein T, L, m, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^{10}, R^{11}, R^{12}, R^{13} and n are defined the same as in Formula (I);

Wherein R^9 is independently H, -O-, $-OR^{14}$-, $-OC(=O)R^{14}$-, $-OC(=O)NHR^{14}$-, $-OC(=O)NR^{14}R^{15}$-, $-OC(=O)R^{14}SSR^{15}$-, $-OP(=O)(OR^{14})O$-, wherein R^{14}, R^{15} are independently H, C_1~C_8 of alkyl, heteroalkyl; C_3~C_8 of aryl, heteroaryl, heterocyclic, carbocyclic, cycloalkyl,

alkylcycloalkyl, heterocycloalkyl, heteroalkylcycloalkyl, heteroaralkyl, alkylcarbonyl or pharmaceutical salts.

5. The pharmaceutical composition according to Claim 1, wherein the conjugate of the tubulysin analog have Formula (V):



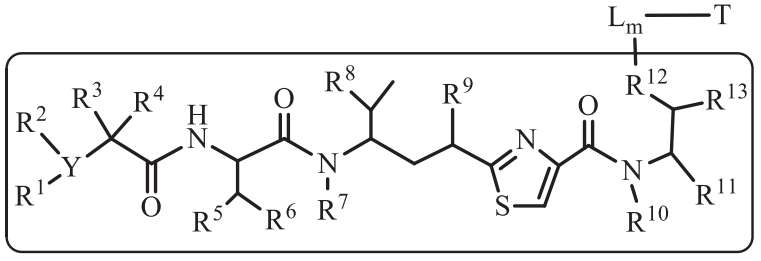
(V)

or their pharmaceutically acceptable salts, hydrates, or hydrated salts; or the polymorphic crystal of these compounds; or their isotopes, optical isomers, racemates, diastereomers or enantiomers thereof;

wherein T, L, m, Y, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{12}, R^{13} and n are defined the same as in Formula (II);

Wherein R^{11} is $-R^{14}-$, $-R^{14}C(=O)R^{17}-$, $-R^{14}C(=O)X^2R^{17}-$, $-R^{14}X^2R^{17}-$, $-R^{14}C(=O)X^2-$, wherein R^{17} is independently H, OH, C_1~C_8 of alkyl; C_2~C_8 of alkenyl, alkynyl, heteroalkyl; C_3~C_8 of aryl, arylene, heterocyclic, carbocyclic, heterocycloalkyl; or an amino acid, or two amino acid units; X^2 is -O-, -S-, -NH-, $-NHS(O_2)-$, -NHS(O)-, $-N(R^{14})-$, $-O-R^{14}-$, $-S-R^{14}-$, $-S(=O)-R^{14}-$, or $-NHR^{14}-$; R^{14} is H, C_1~C_8 of alkyl, heteroalkyl; C_2~C_8 of alkenyl, alkynyl; C_3~C_8 of aryl, heterocyclic, carbocyclic, cycloalkyl, alkylcycloalkyl, heterocycloalkyl, heteroalkylcycloalkyl, heteroaralkyl, alkylcarbonyl.

6. The pharmaceutical composition according to Claim 1, wherein the conjugate of the tubulysin analog have Formula (VI):



(VI)

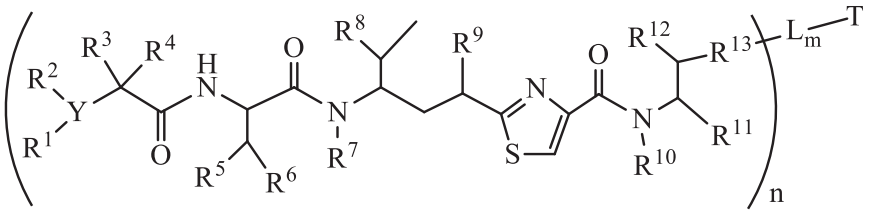
or their pharmaceutically acceptable salts, hydrates, or hydrated salts; or the polymorphic crystal of these compounds; or their isotopes, optical isomers, racemates, diastereomers or enantiomers thereof;

wherein T, L, m, Y, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10},R^{11}, R^{13} and n are defined the same as in Formula (II);

wherein R^{12} is independently R^{14}, -O-, -S-, -NH-, =N-, =NNH-, $-N(R^{14})-$, $-OR^{14}-$,C(O)O-, C(O)NH-, $C(O)NR^{14}-$, $-SR^{14}-$, $-S(=O)R^{14}-$, $-NHR^{14}-$, $-CH_2OP(=O)(OR^{15})-$, $-P(=O)(OR^{15})-$,. -

$OP(=O)(OR^{15})O$-, $-SO_2R^{14}$, R^{14}, R^{15} are independently C_1~C_8 of alkyl, heteroalkyl; C_2~C_8 of alkenyl, alkynyl; C_3~C_8 of aryl, heterocyclic, carbocyclic, cycloalkyl, alkylcycloalkyl, heterocycloalkyl, heteroaralkyl, heteroalkylcycloalkyl, alkylcarbonyl.

7. The pharmacentical composition according to Claim 1, wherein the conjugate of the tubulysin analog have Formula (VII):



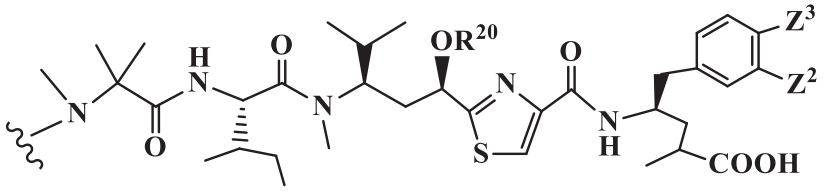
(VII)

or their pharmaceutically acceptable salts, hydrates, or hydrated salts; or the polymorphic crystal of these compounds; or their isotopes, optical isomers, racemates, diastereomers or enantiomers thereof,

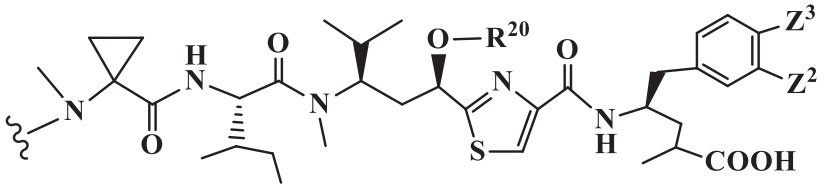
wherein T, L, n, m, Y, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are defined the same as in Formula (I);

wherein R^{13} is C_1~C_{10} of alkyl, heteroalkyl, alkyl acid, alkyl amide, alkyl amine, or Ar; Ar refers to a aromatic or hetero aromatic group, composed of one or several rings, comprising four to ten carbon. The term of hetero aromatic group refers one or several carbon on aromatic group, are replaced by O, N, Si, Se, P or S. The term aryl or Ar also refers to a aromatic group, wherein one or several H atoms are replaced independently by R^{18}, F, Cl, Br, I, OR^{16}, SR^{16}, $NR^{16}R^{18}$, $N{=}NR^{16}$, $N{=}R^{16}$, $NR^{16}R^{18}$, NO_2, $SOR^{16}R^{18}$, SO_2R^{16}, SO_3R^{16}, OSO_3R^{16}, $PR^{16}R^{18}$, $POR^{16}R^{18}$, $PO_2R^{16}R^{18}$, $OPO_3R^{16}R^{18}$, or $PO_3R^{16}R^{18}$ wherein R^{16}, R^{18} are independently H, C_1~C_8 of alkyl; C_2~C_8 of alkenyl, alkynyl, heteroalkyl; C_3~C_8 of aryl, heterocyclic, carbocyclic, cycloalkyl, alkylcycloalkyl, heterocycloalkyl, heteroaralkyl, heteroalkylcycloalkyl, alkylcarbonyl; or C_4 ~ C_{12} glycosides; or pharmaceutical salts.

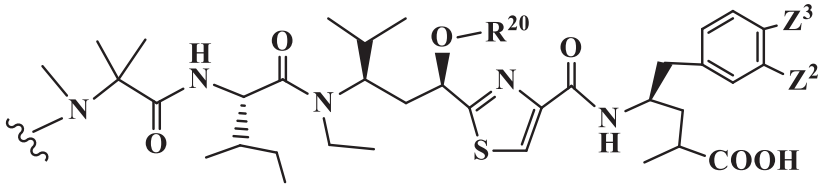
8. The pharmaceutical composition according to Claim **1**, wherein the tubulysin analog inside the bracket of Formula (I) have a structure represented by the following Formula II-01 ~II-73, III-01 ~III-71, IV-01 ~IV-71, V-01 ~V-71, VI-01 ~VI-16, and VII-01 ~VII-82, below:



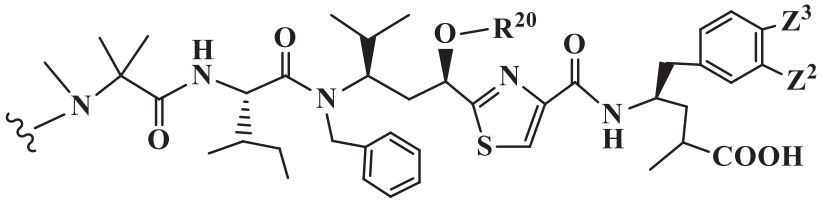
II-01,



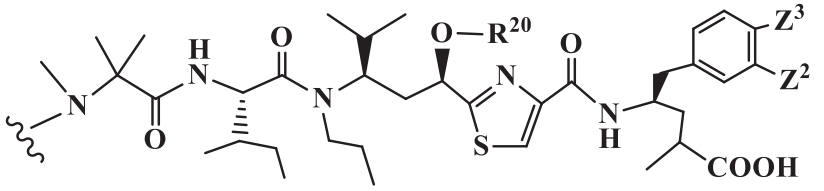
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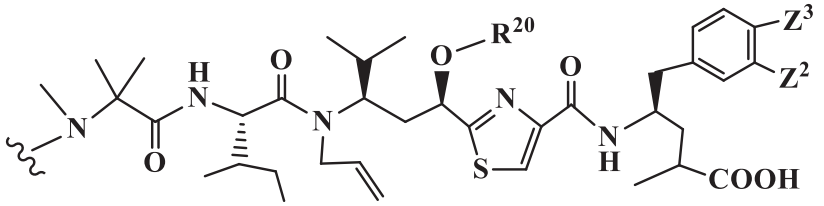
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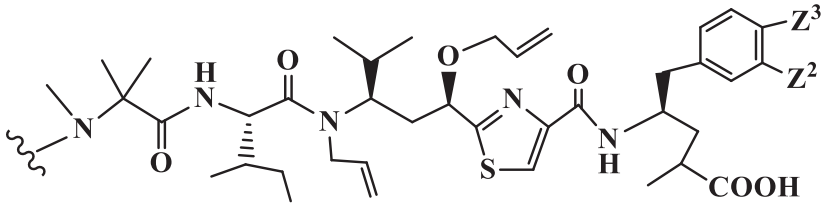
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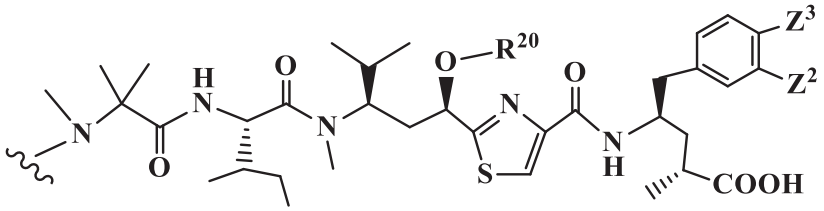
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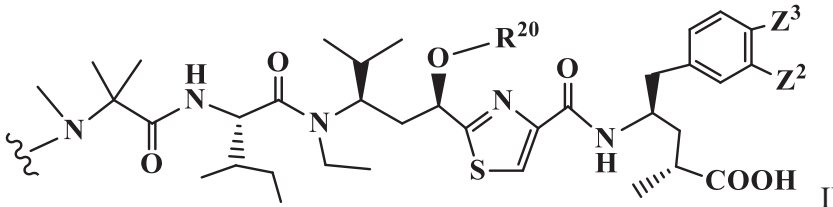
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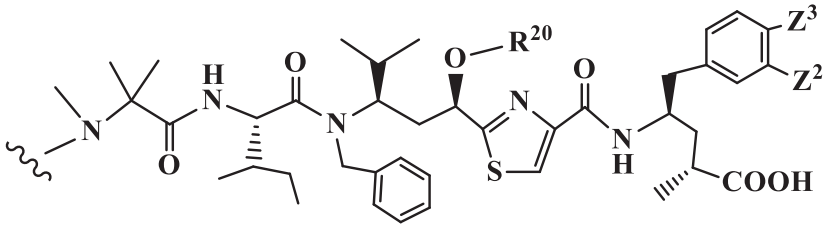
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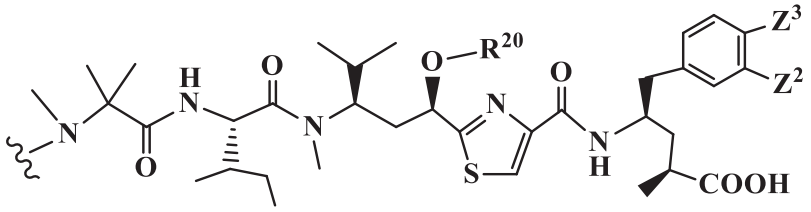
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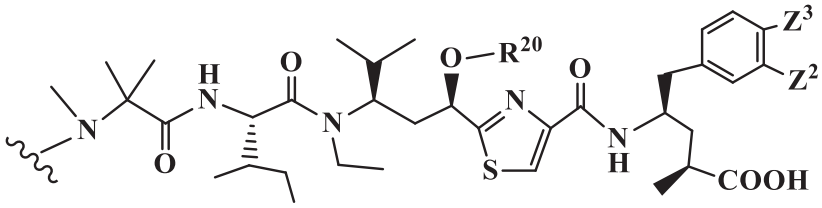
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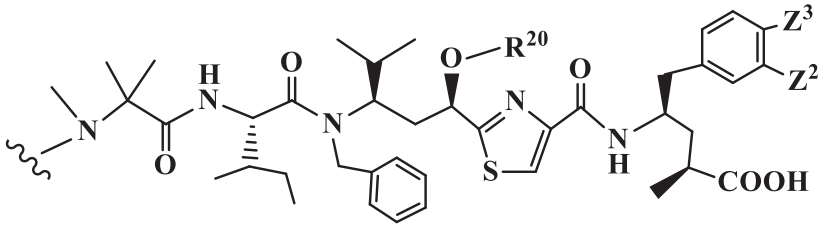
II-10,



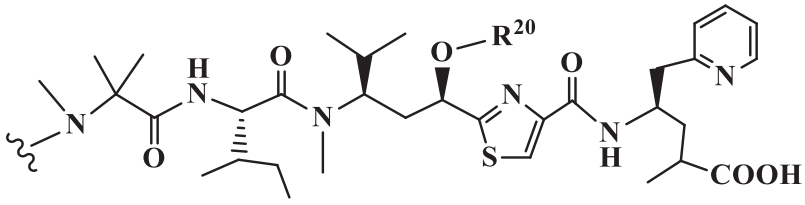
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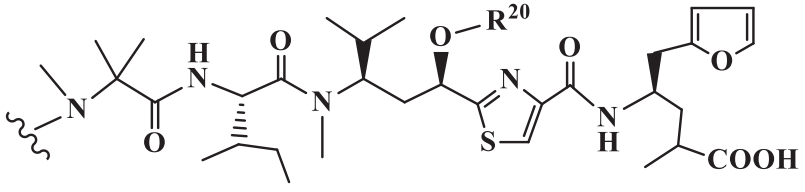
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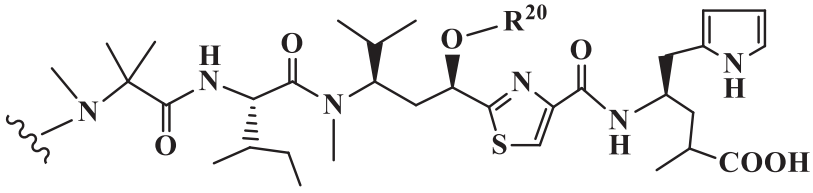
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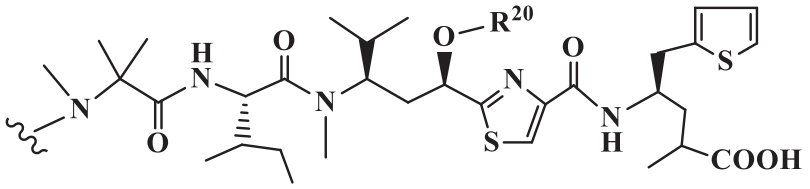
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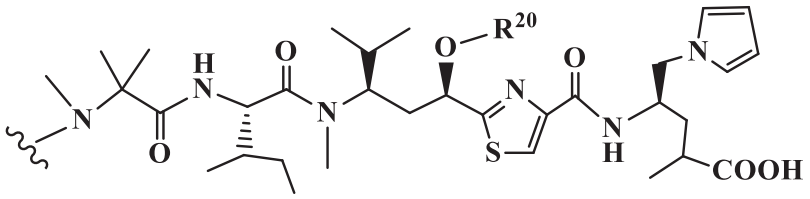


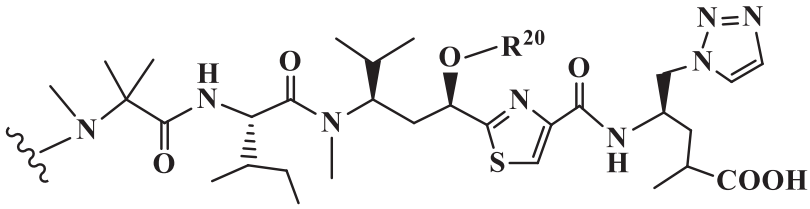
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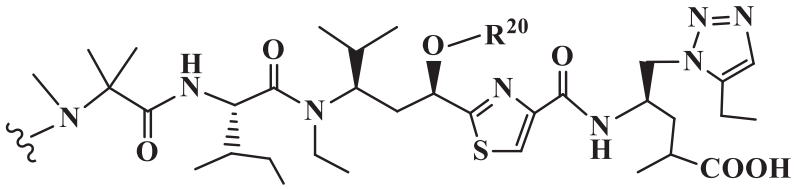


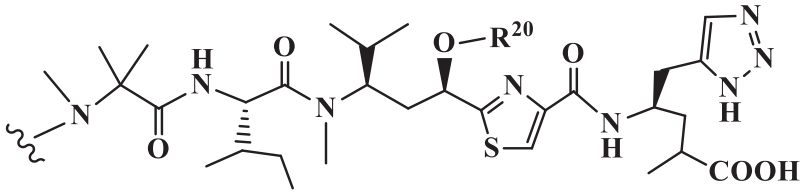
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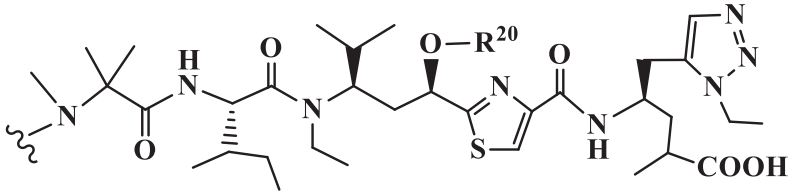

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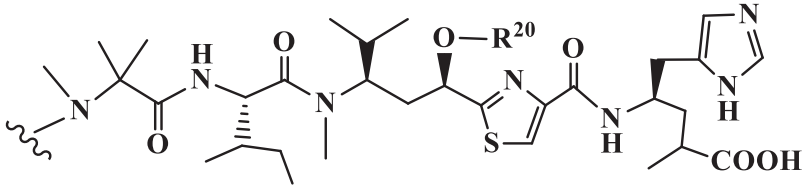

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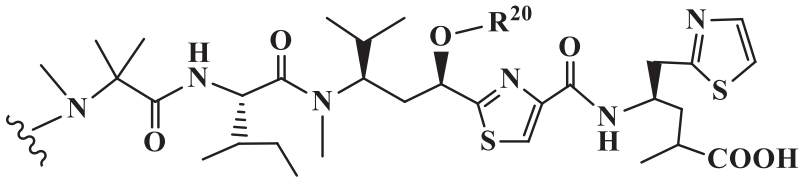

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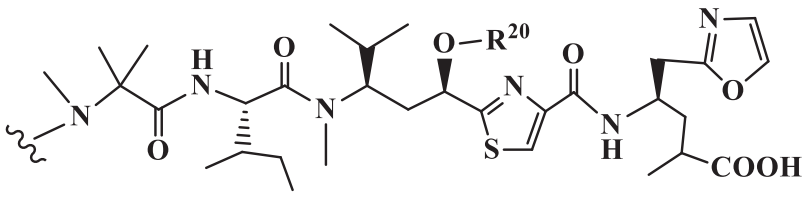

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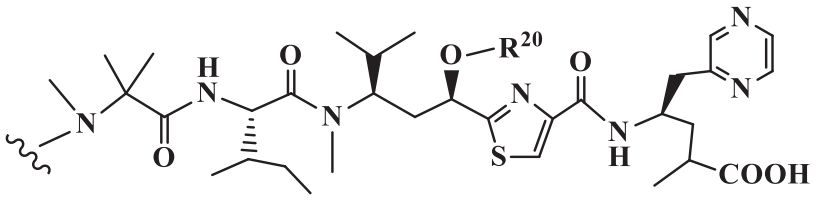

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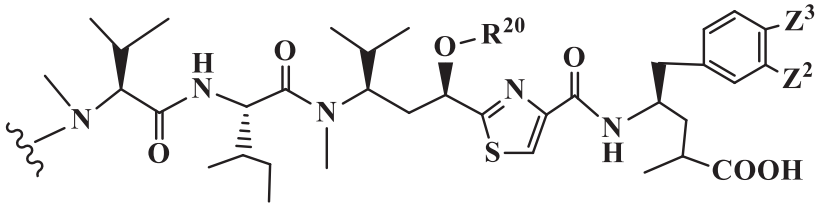

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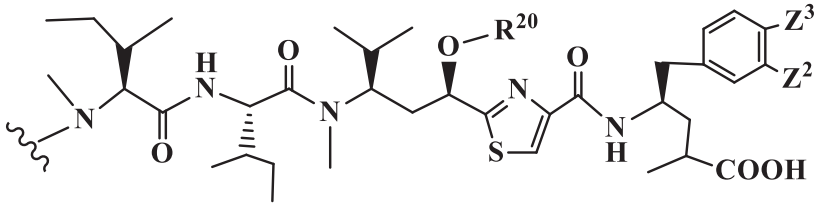
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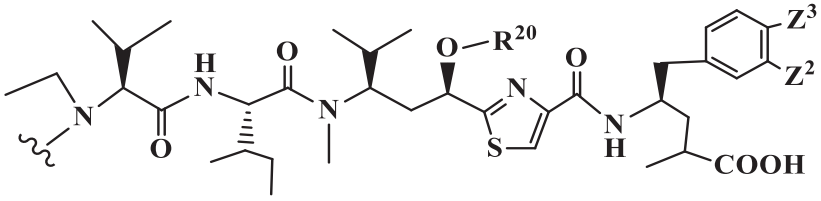
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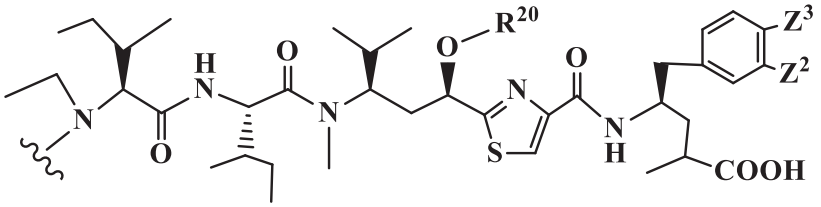
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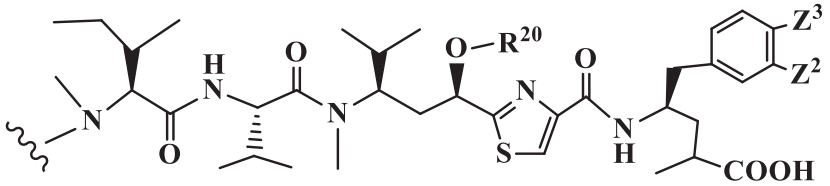
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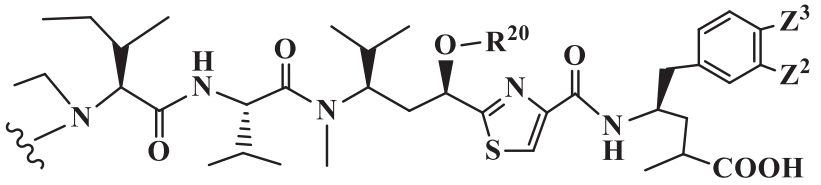
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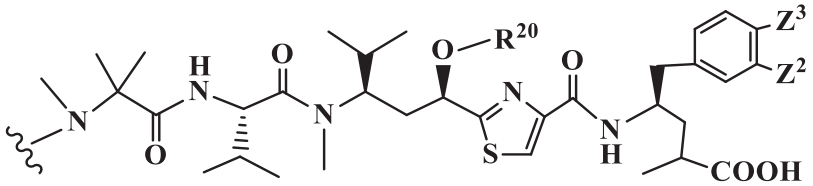
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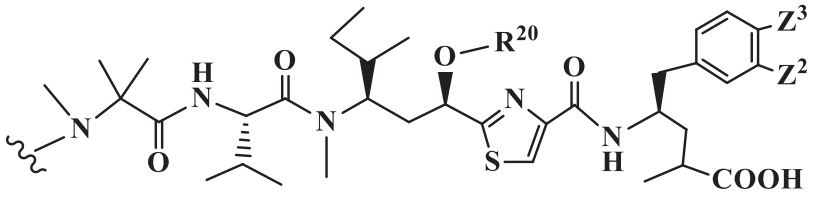


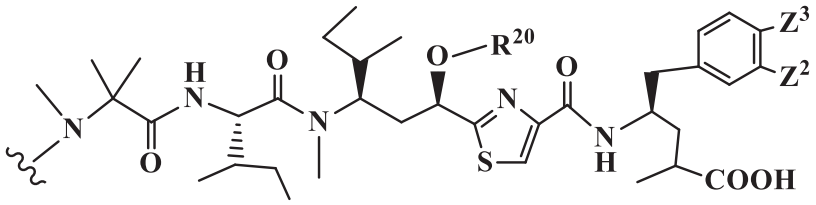
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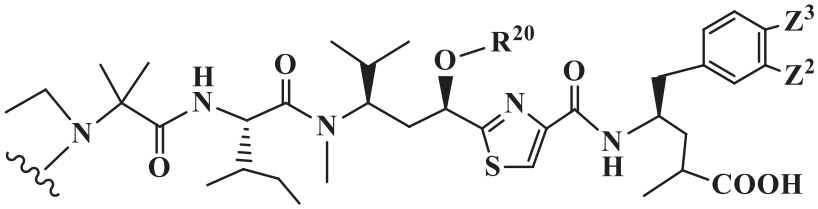


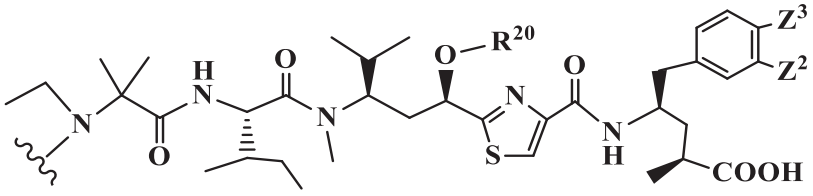
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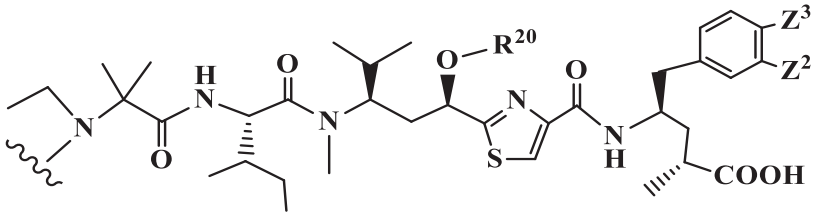

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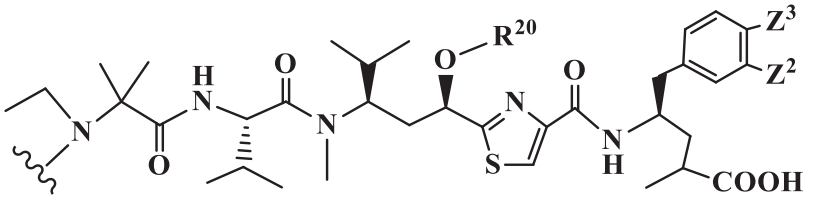

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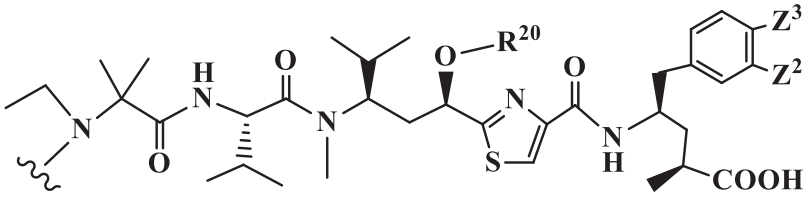

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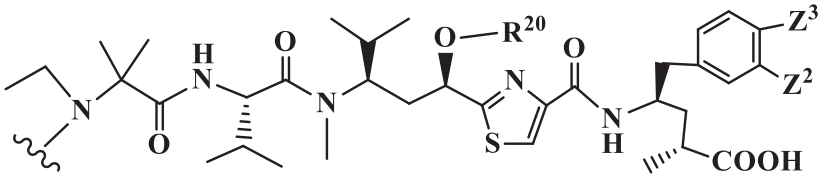

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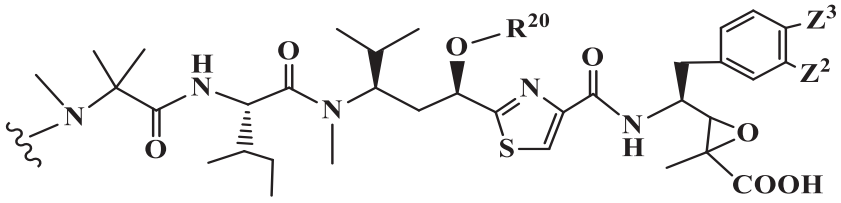

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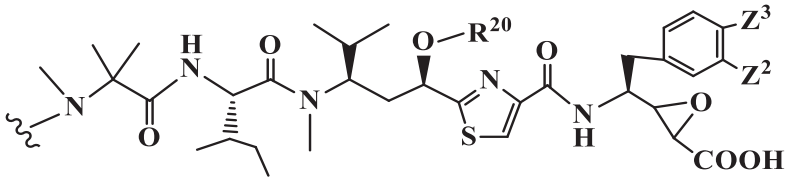

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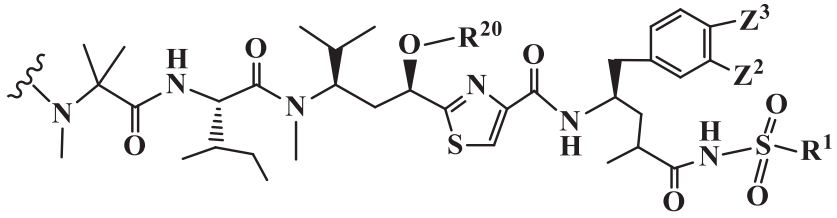

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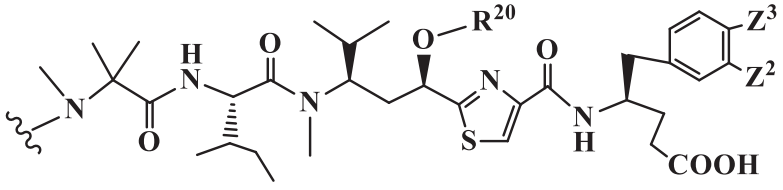

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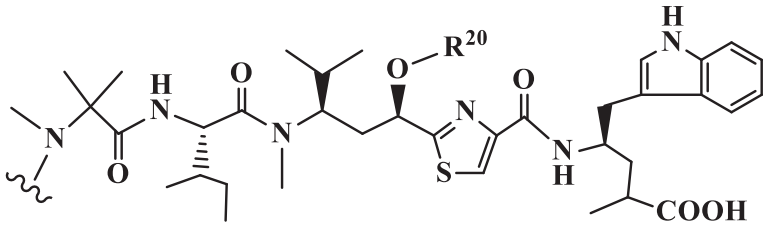

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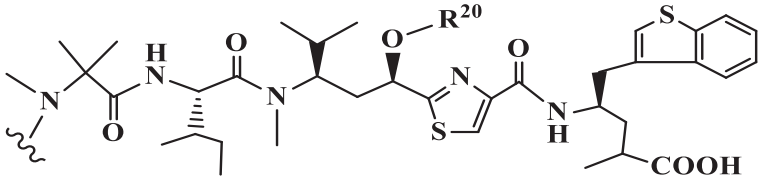

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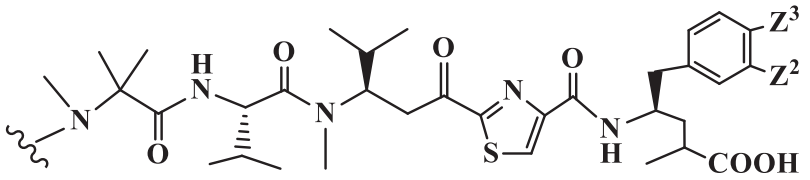

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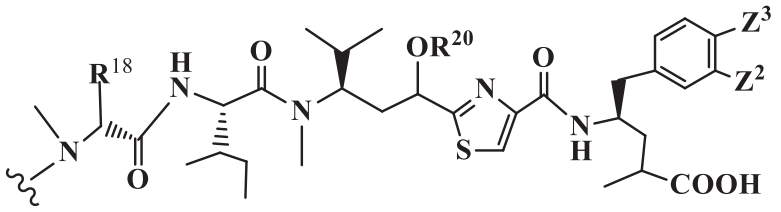

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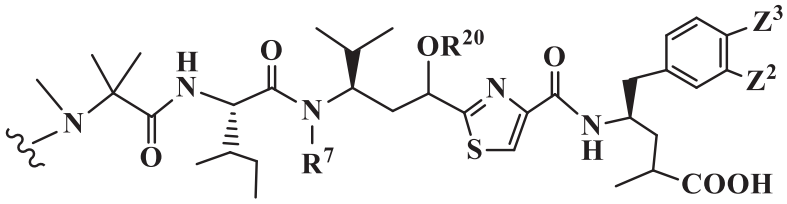

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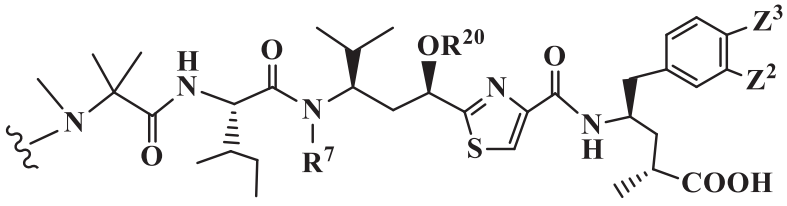

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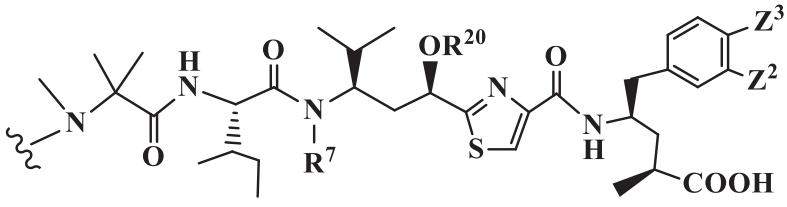

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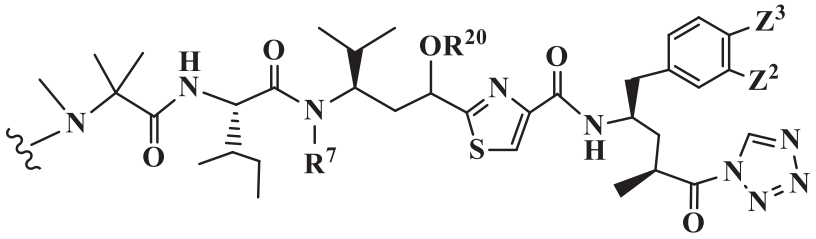

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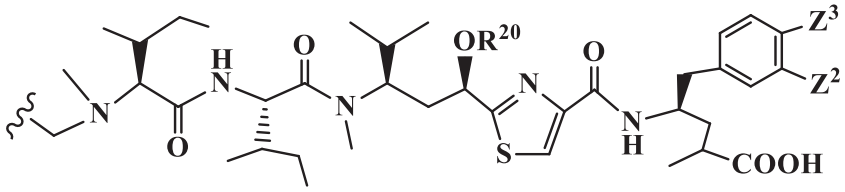

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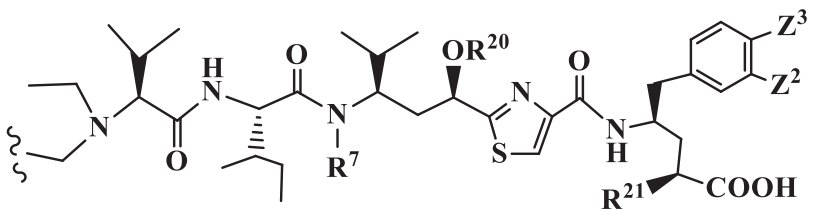

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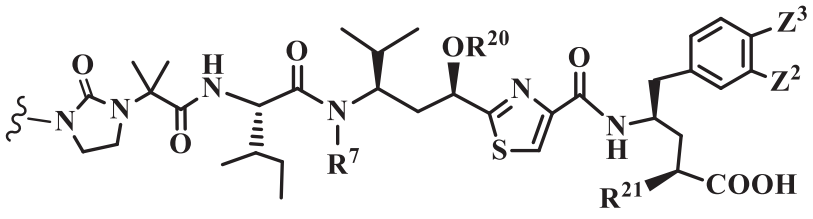

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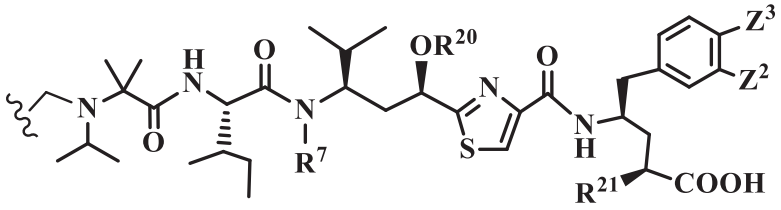

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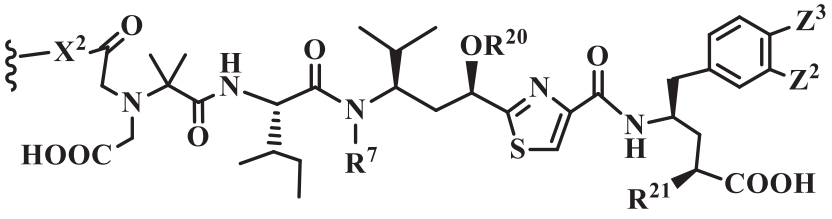

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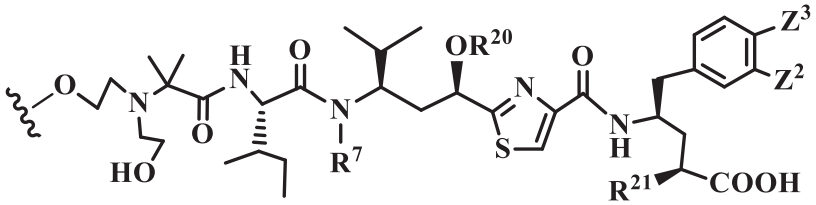

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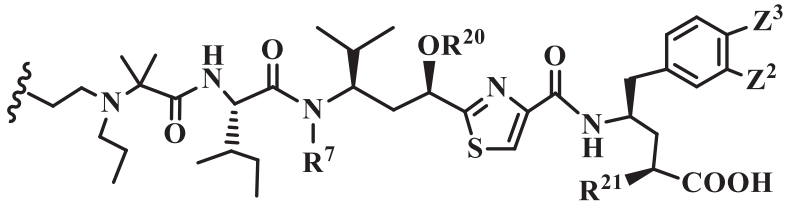

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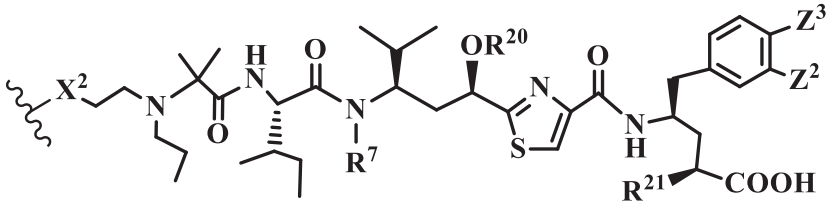

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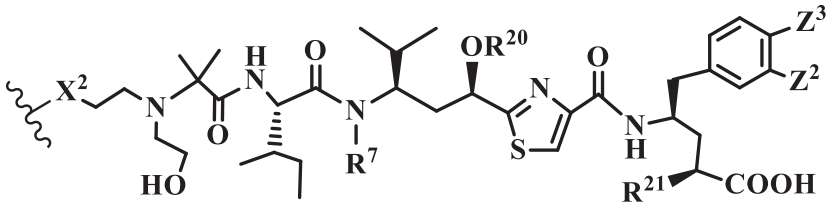

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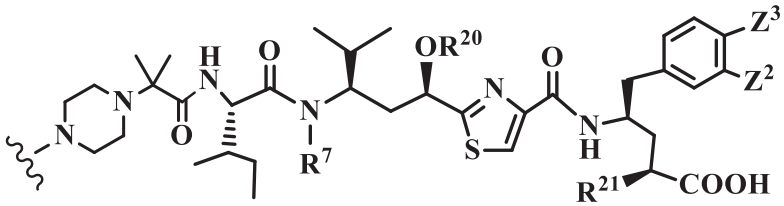

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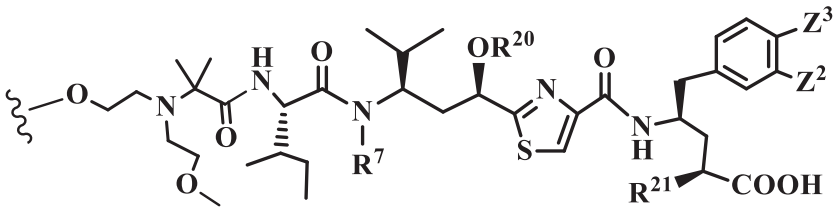

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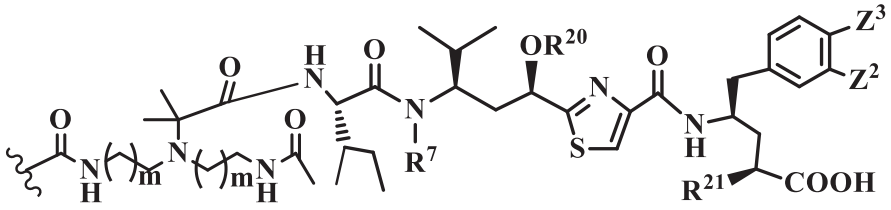
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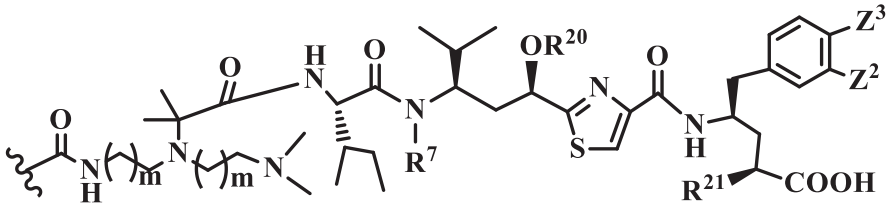
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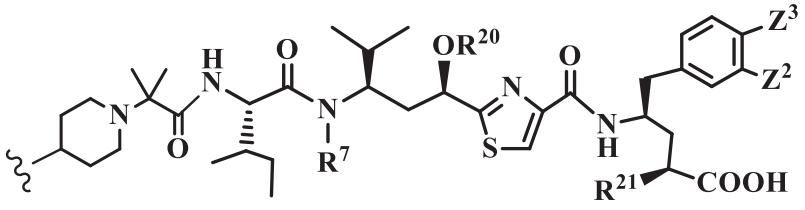
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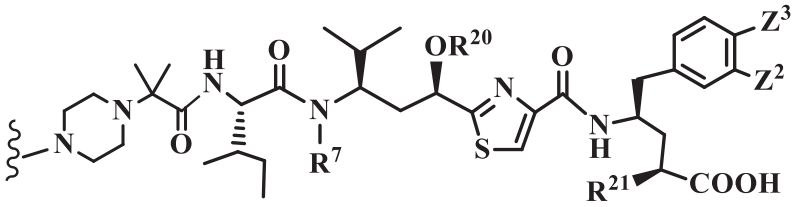
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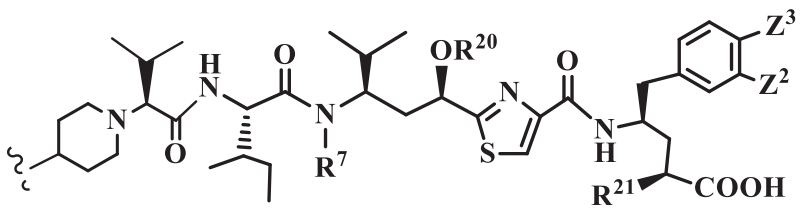
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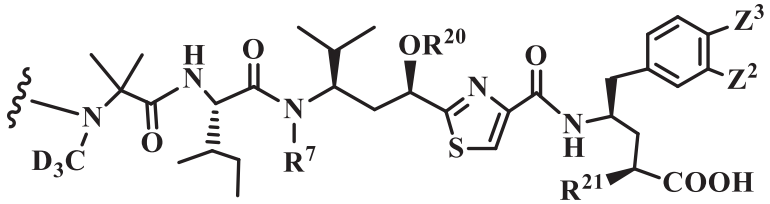


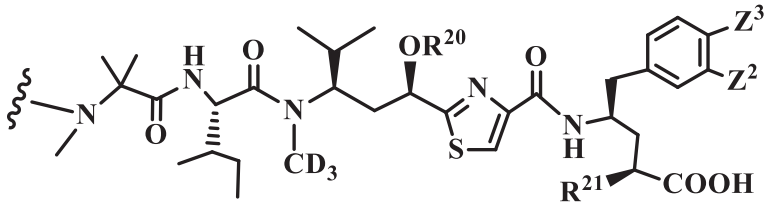
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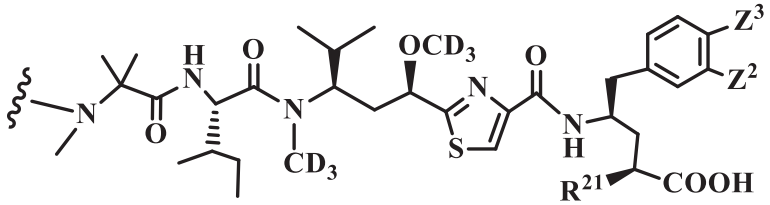


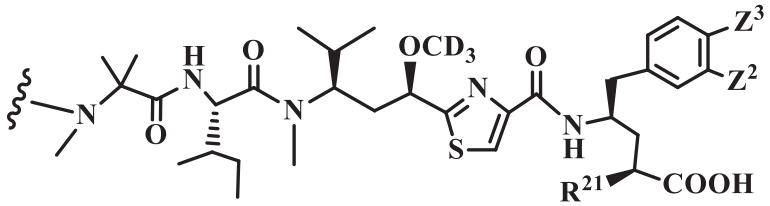
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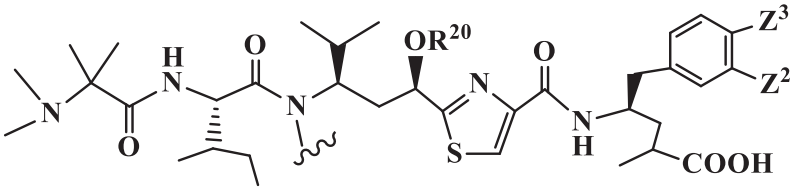

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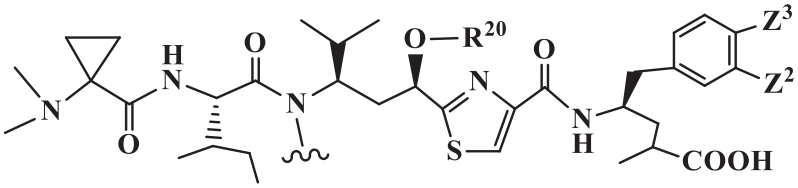

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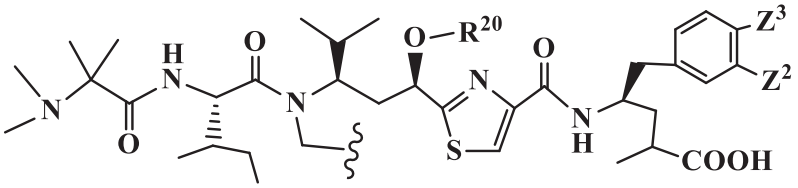

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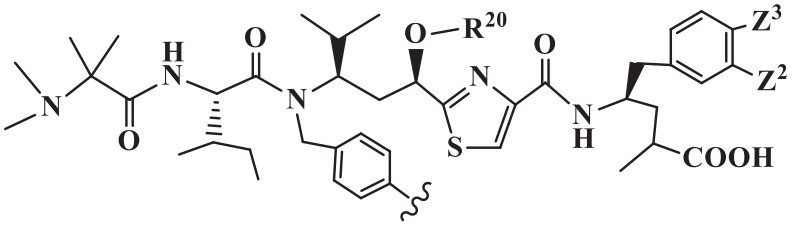

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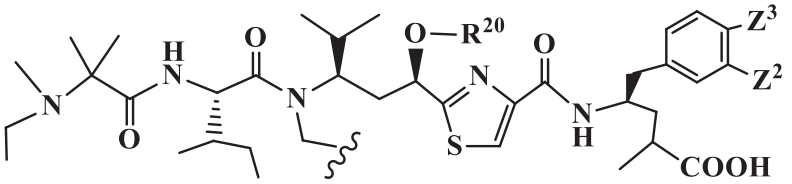

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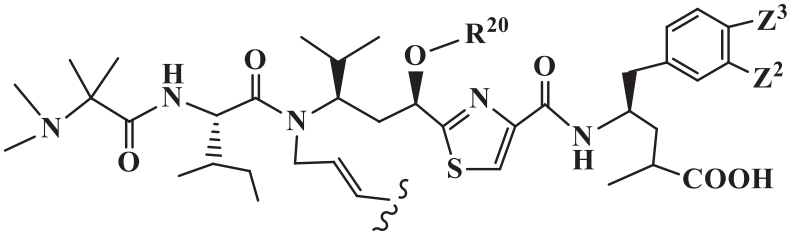

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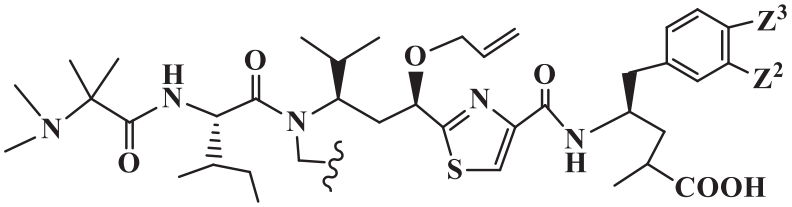
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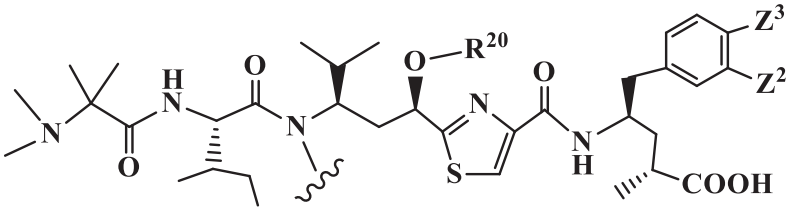
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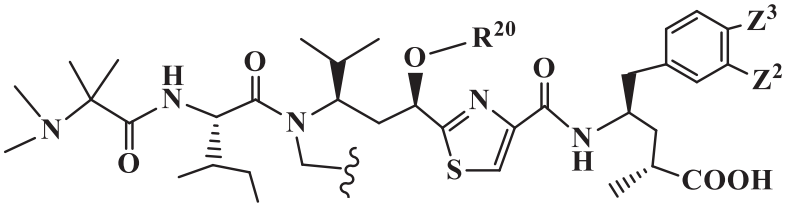
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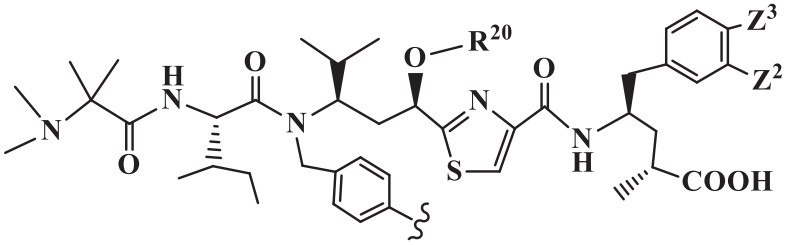
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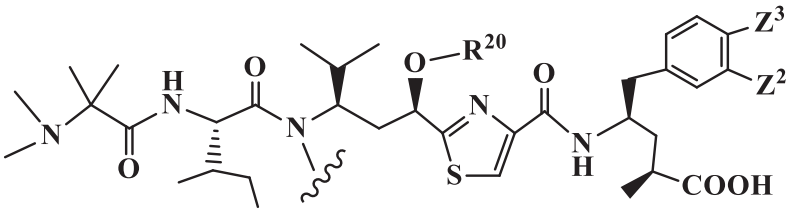
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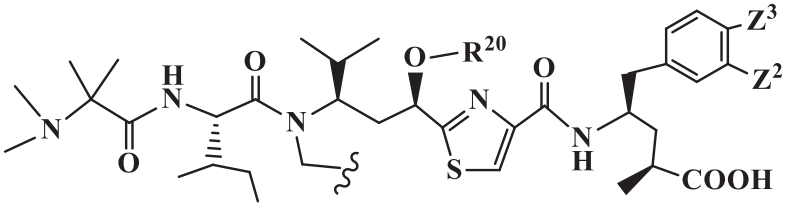
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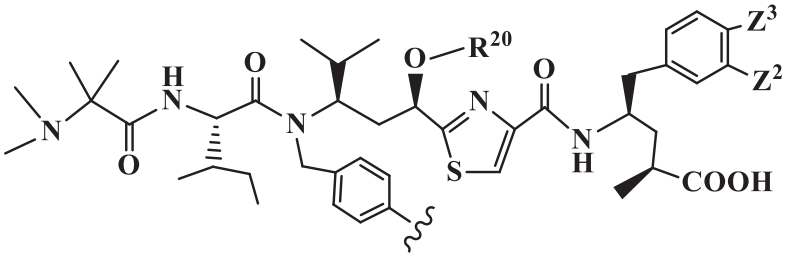
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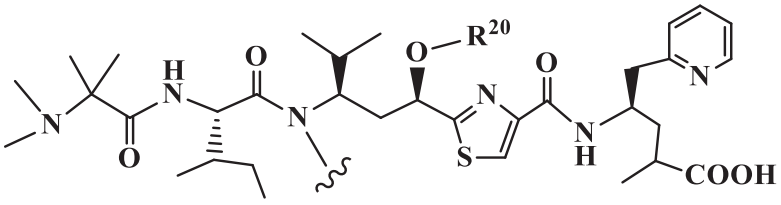
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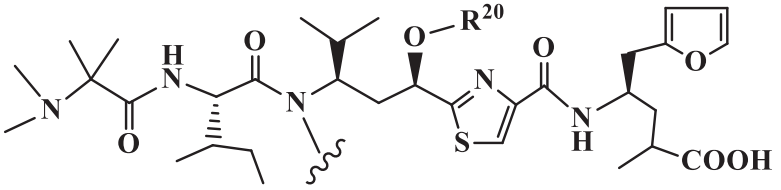
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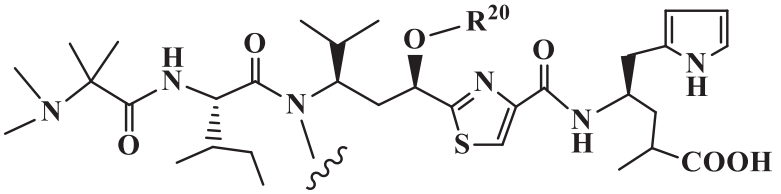
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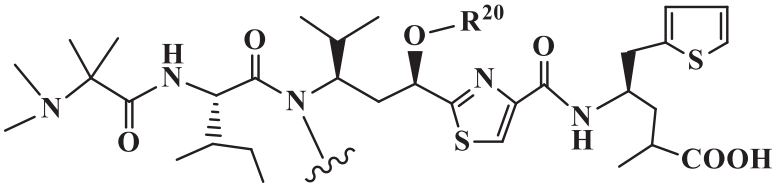
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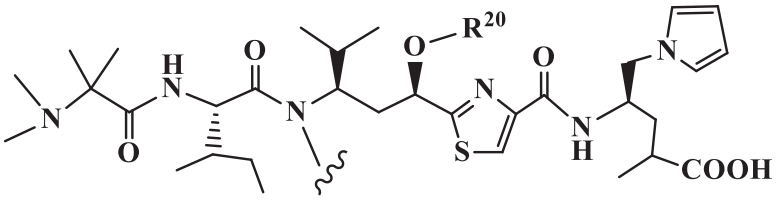
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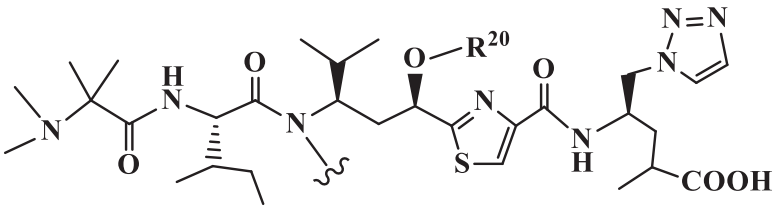


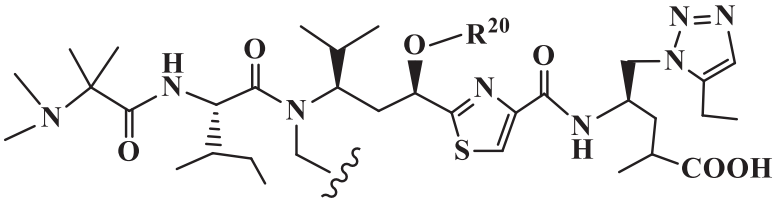
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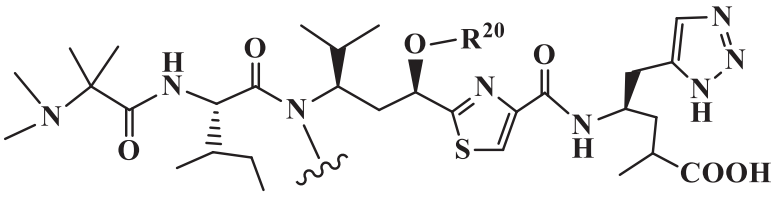


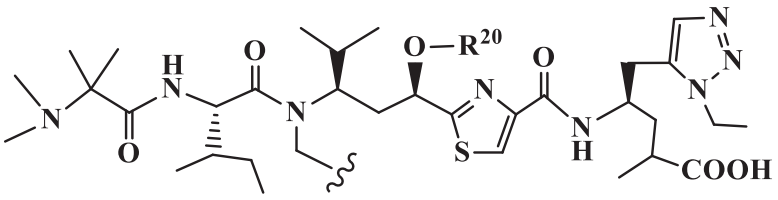
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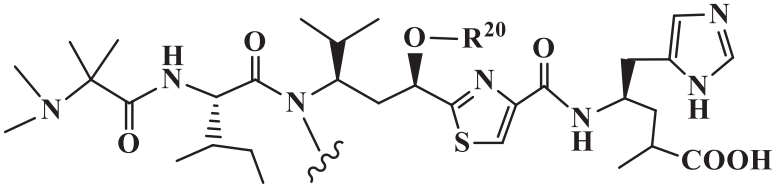

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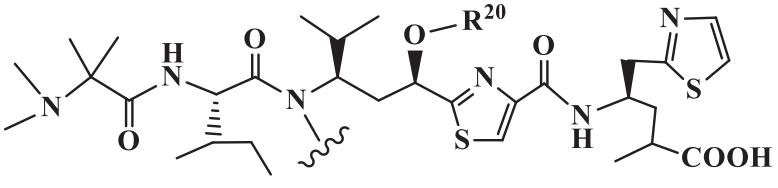

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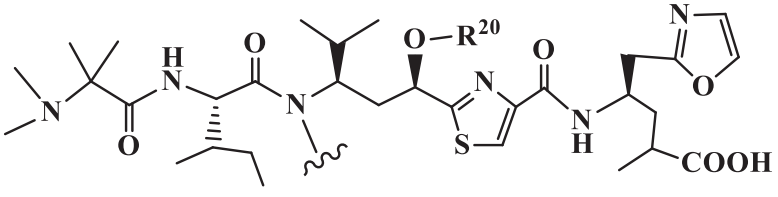

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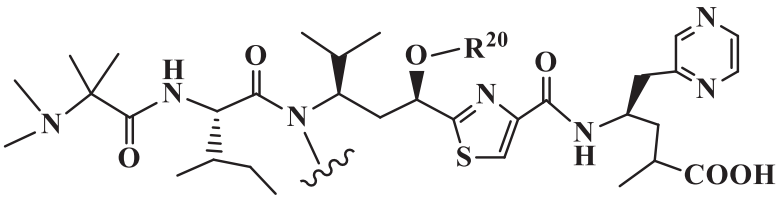

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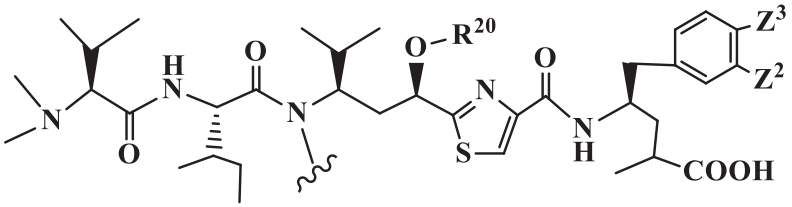

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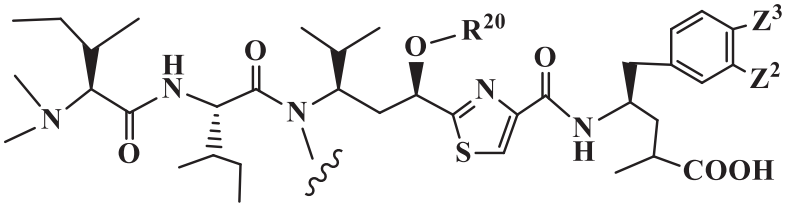

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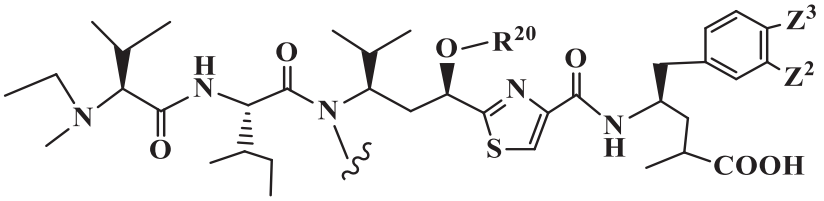
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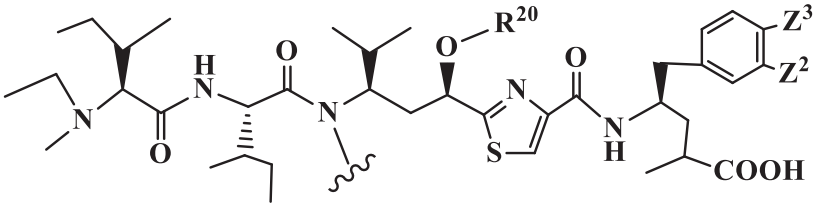
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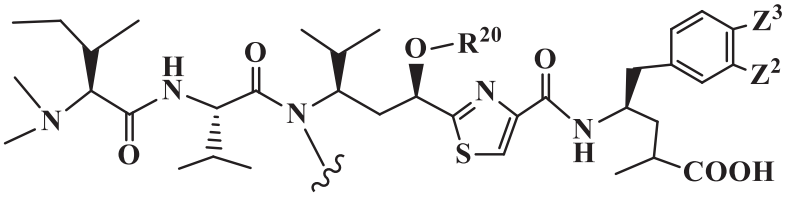
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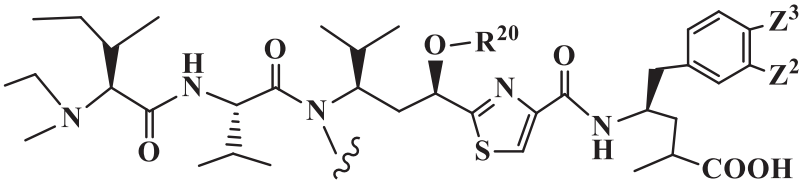
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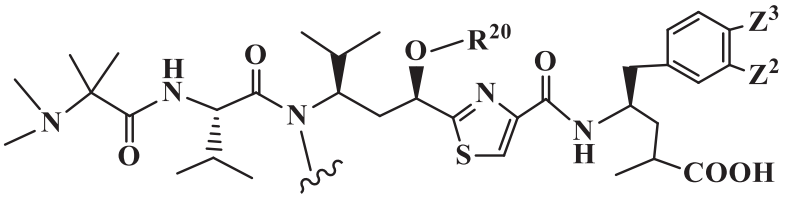
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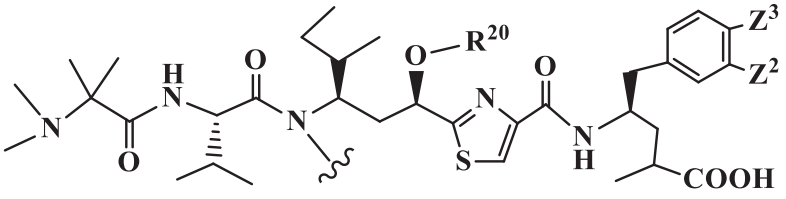


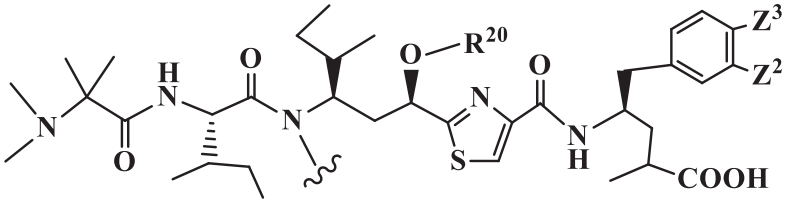
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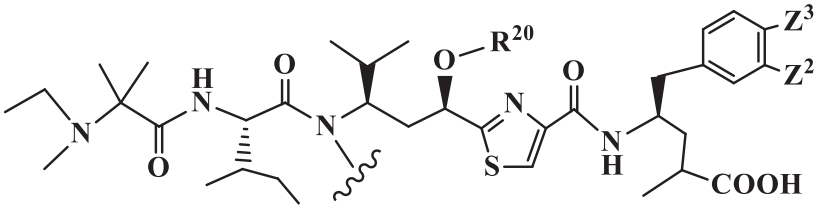


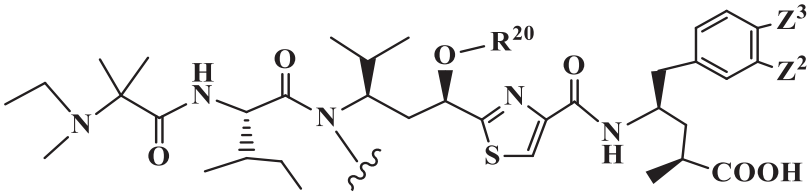
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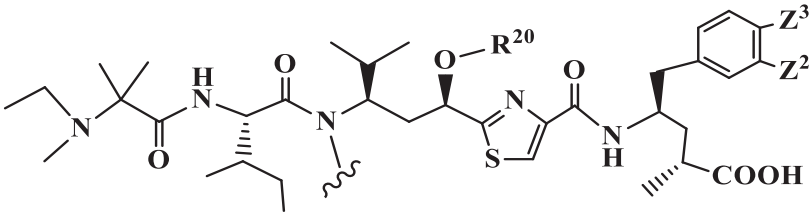

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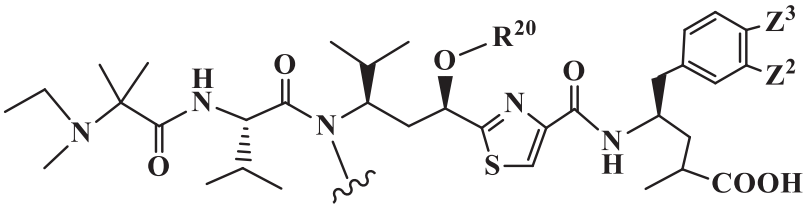

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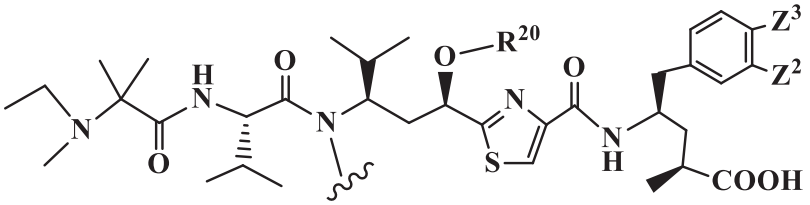

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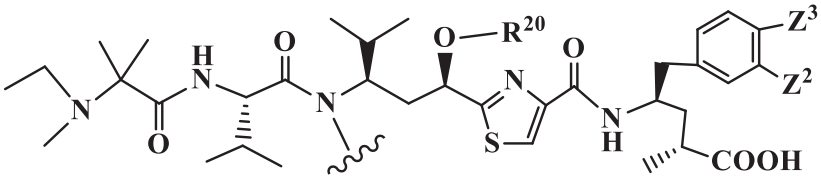

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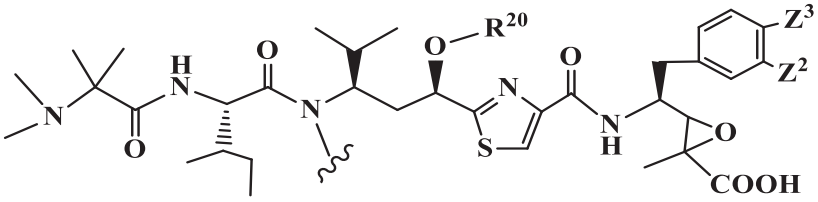

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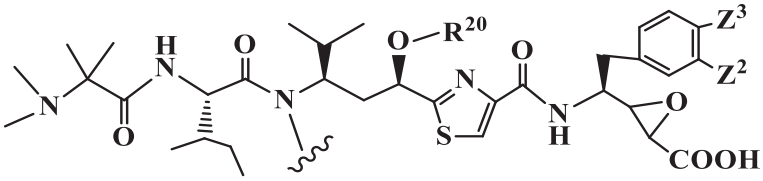
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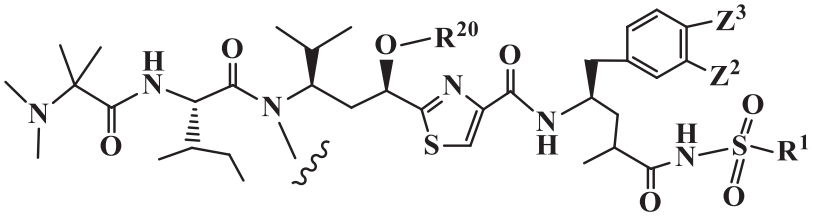
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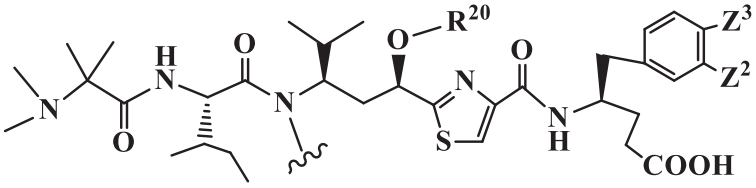
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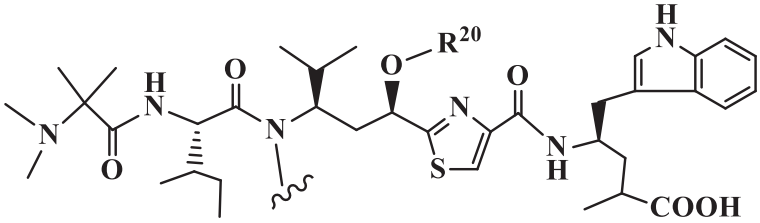
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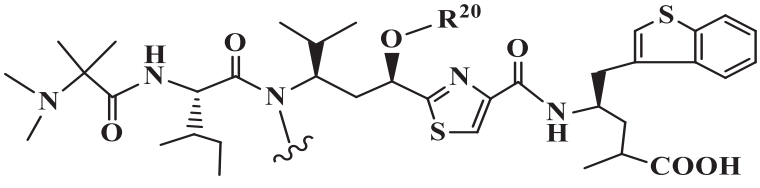
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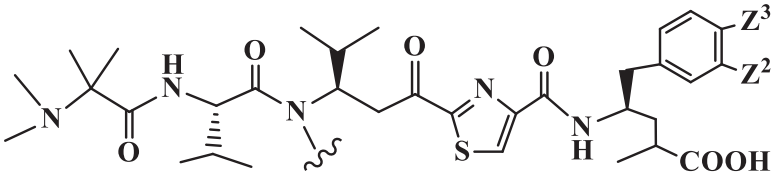
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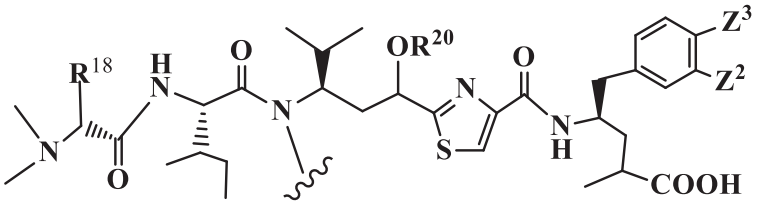


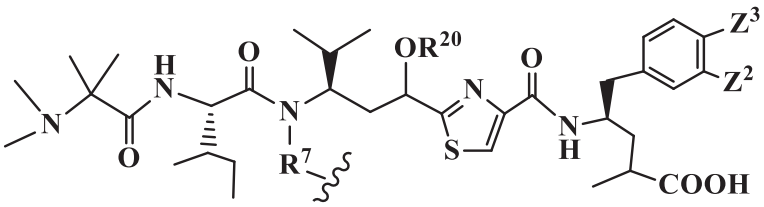
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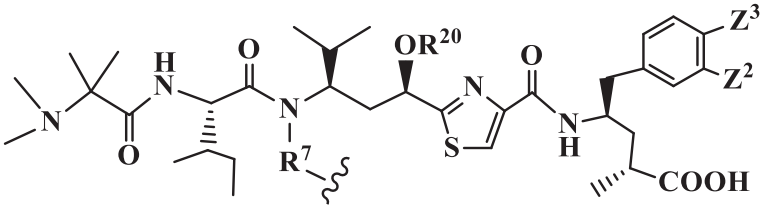


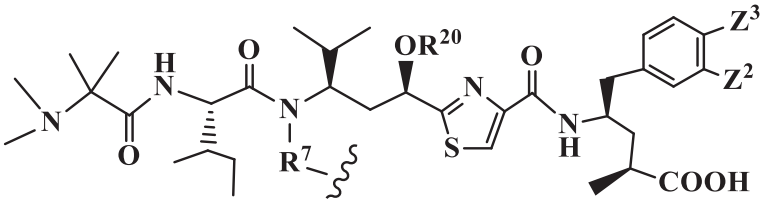
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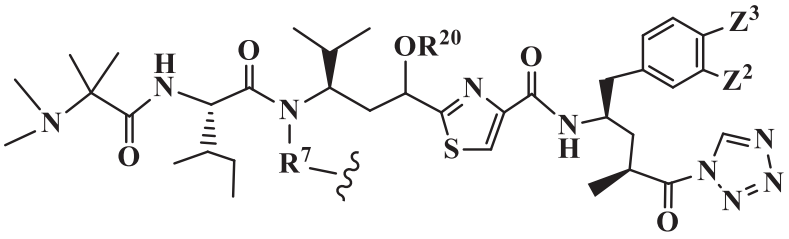

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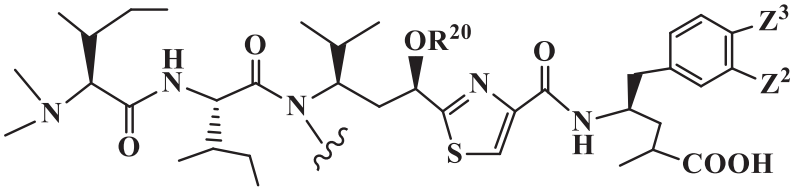

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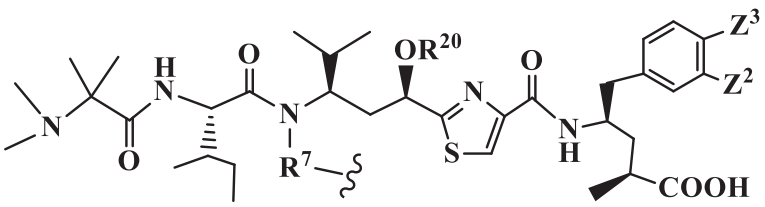

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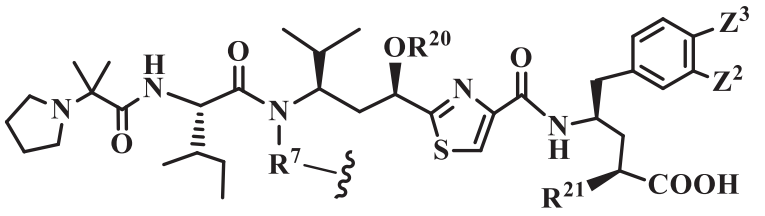

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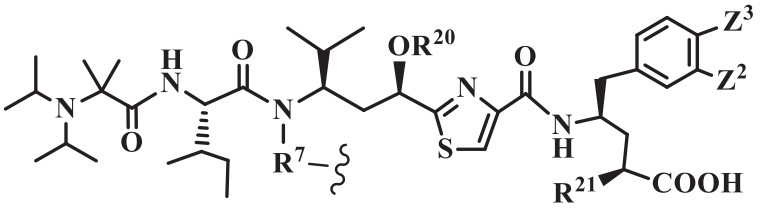

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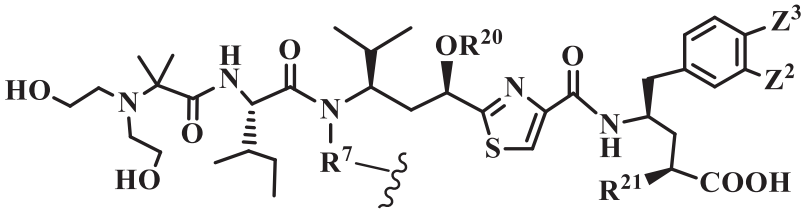

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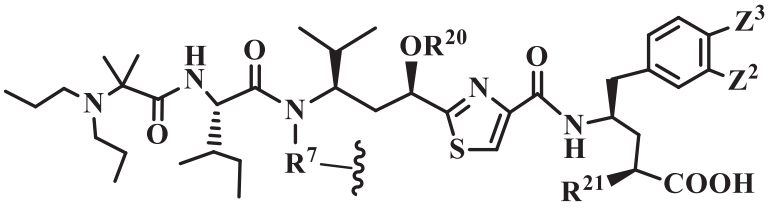

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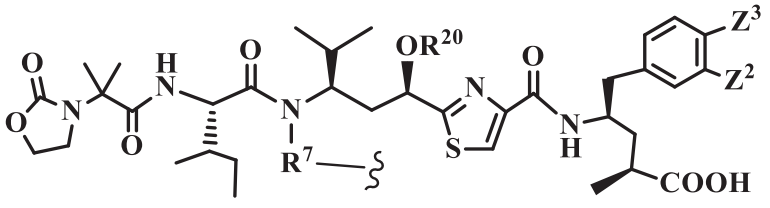

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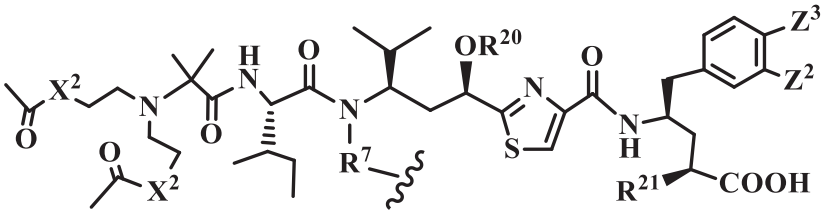

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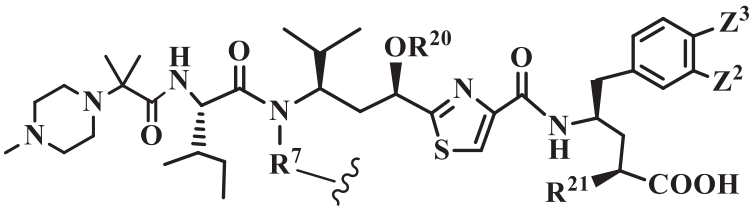

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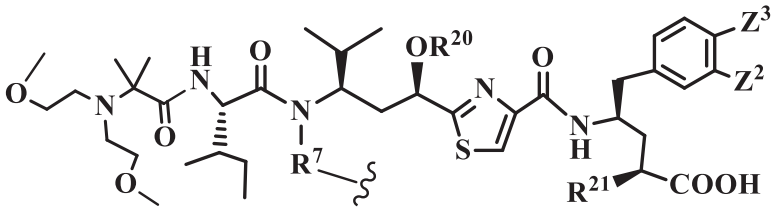

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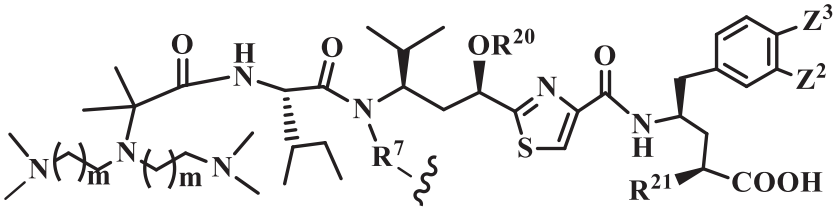

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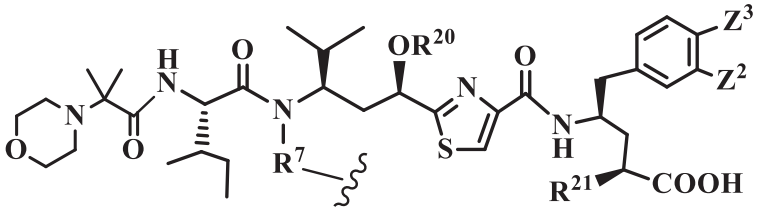
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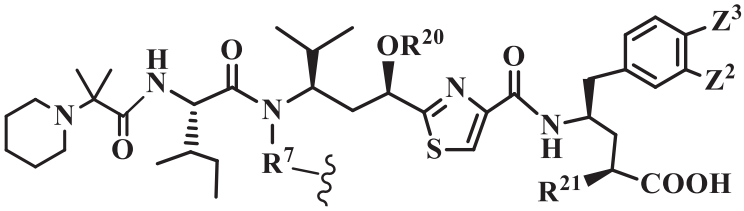
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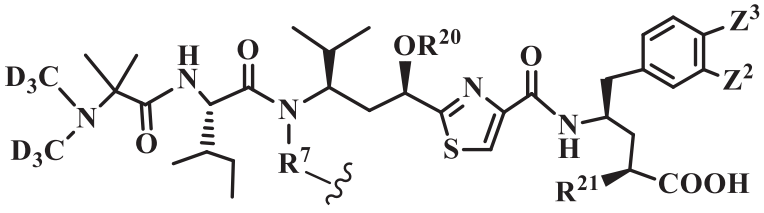
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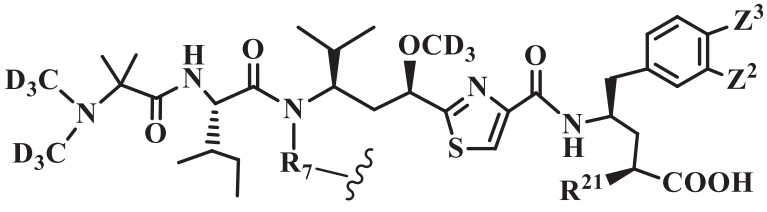
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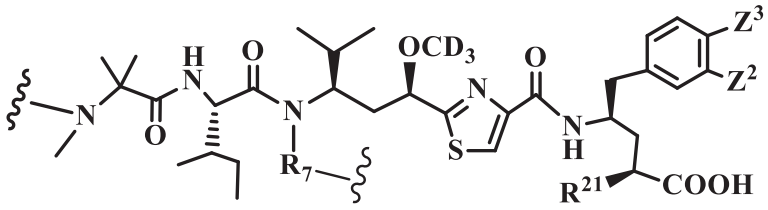
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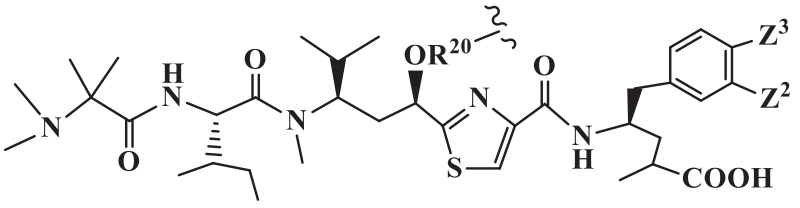
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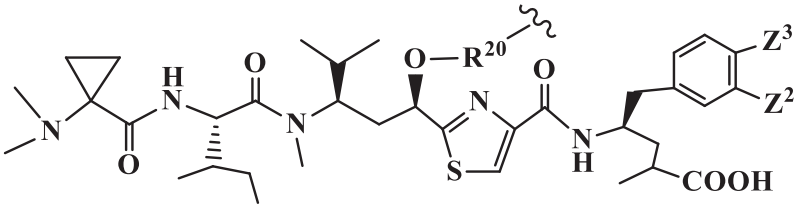
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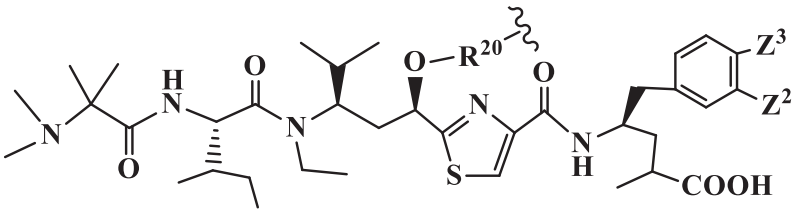
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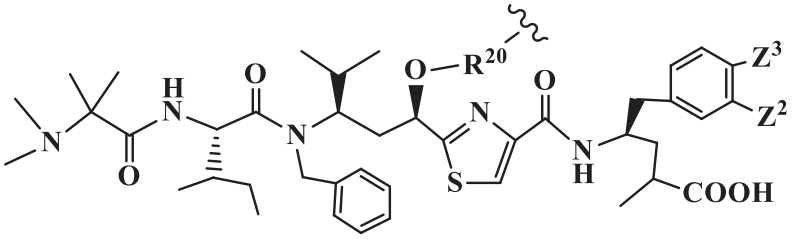
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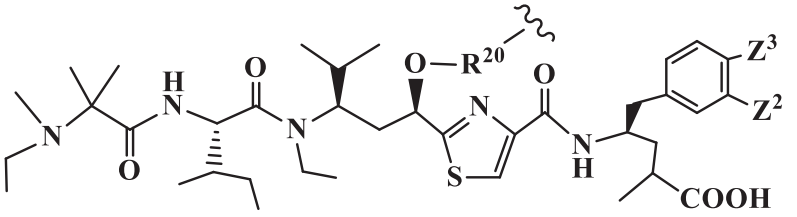
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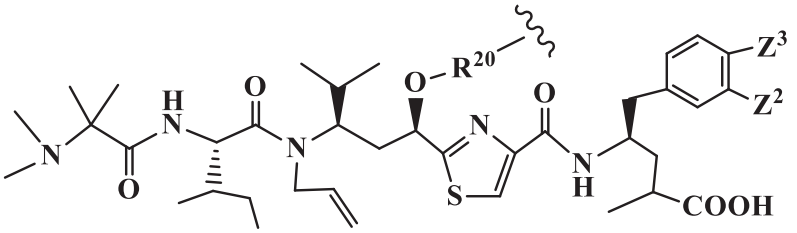
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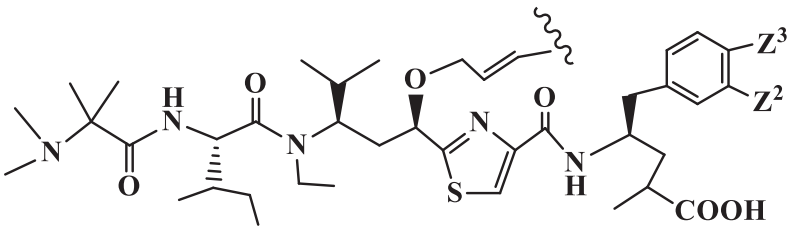
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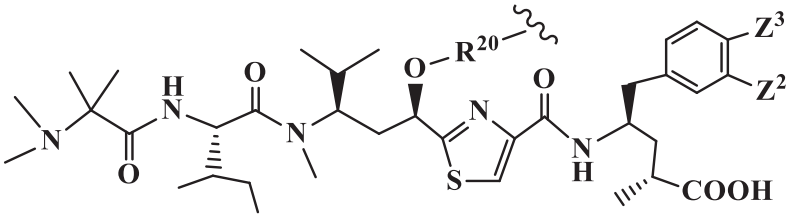
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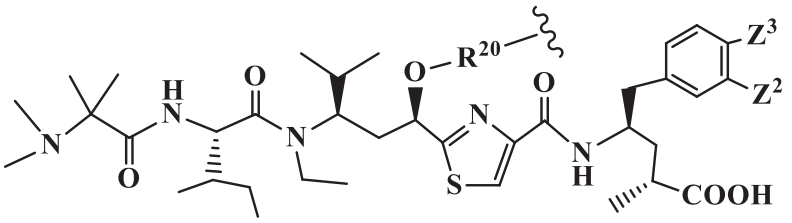
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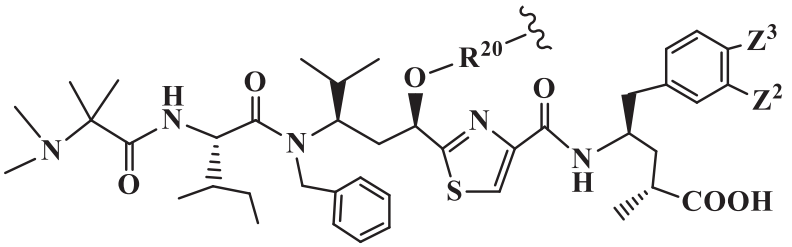
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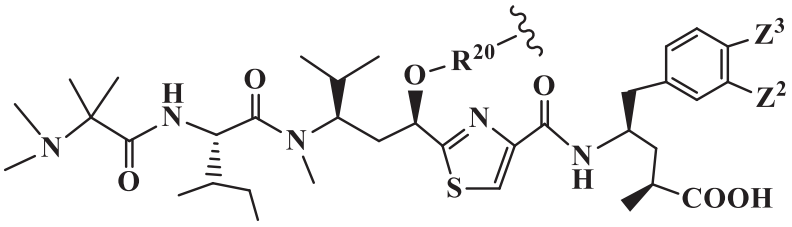
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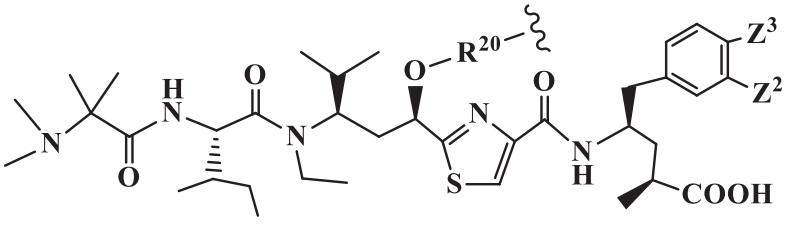
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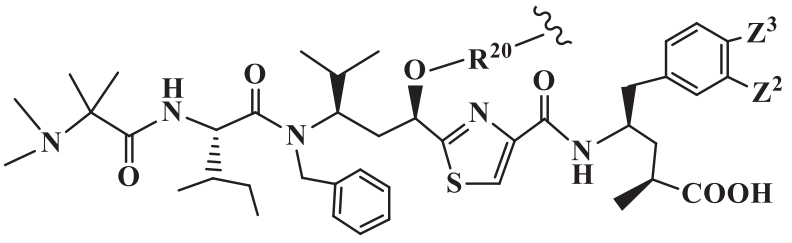
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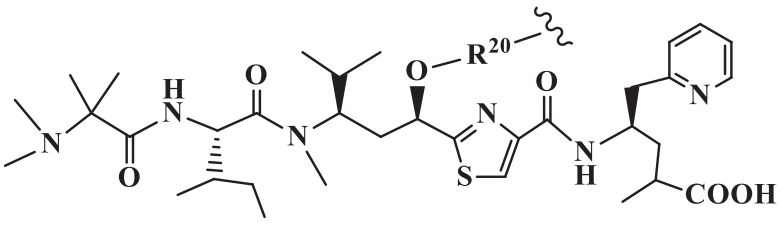
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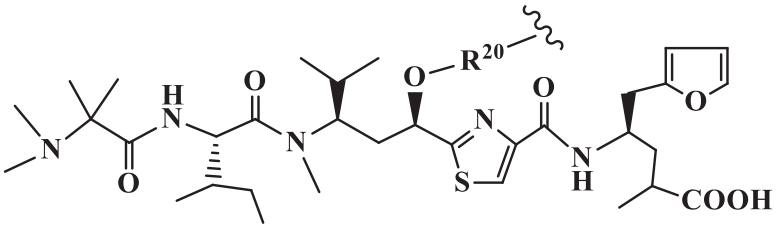


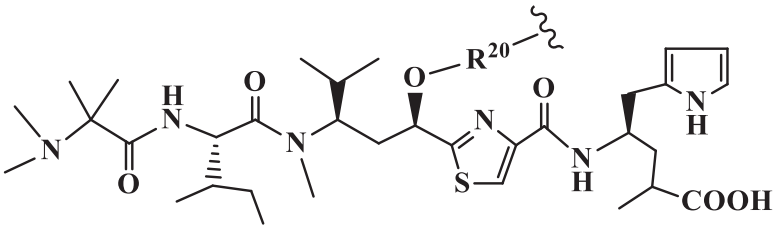
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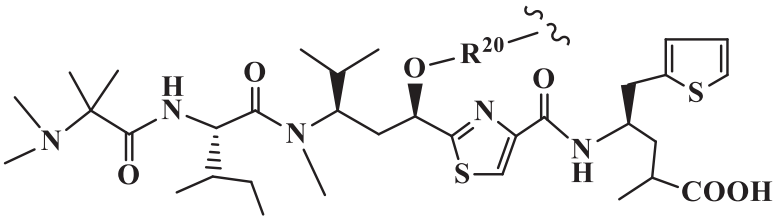


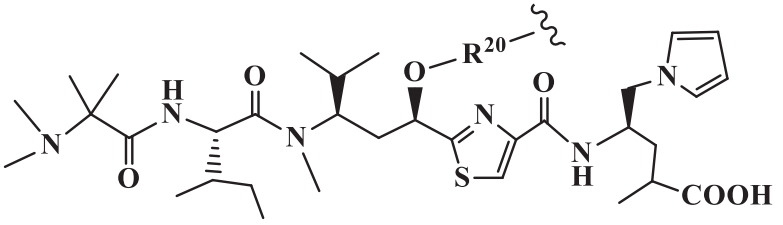
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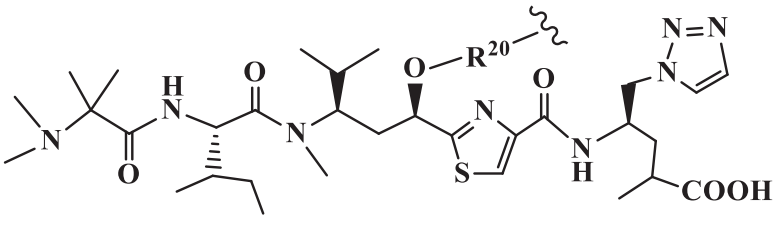

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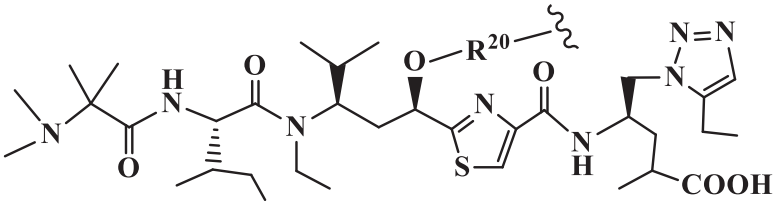

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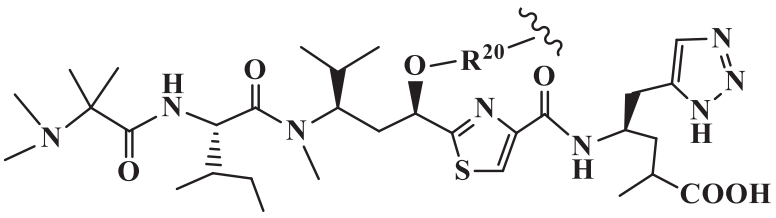

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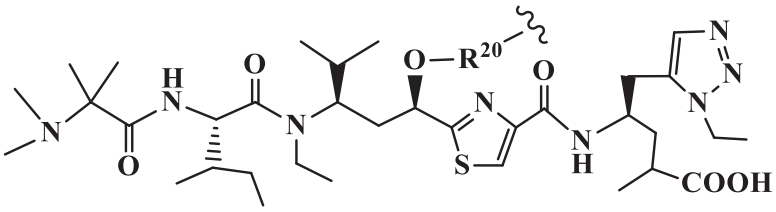

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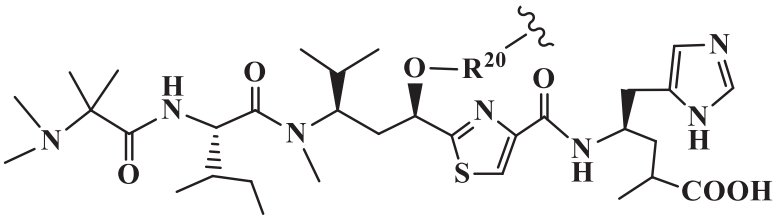

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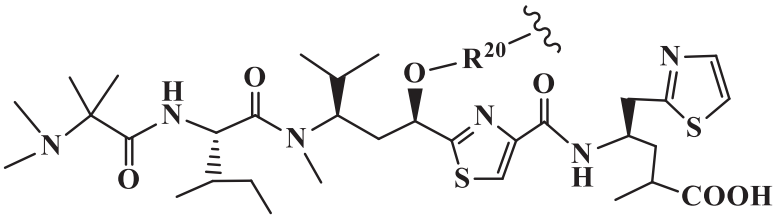
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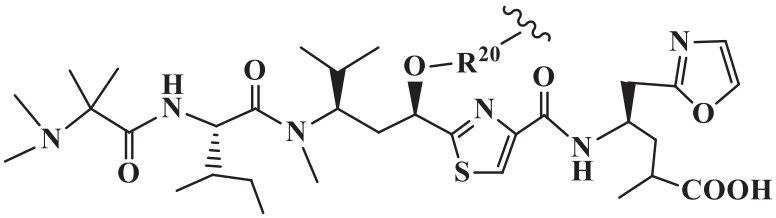
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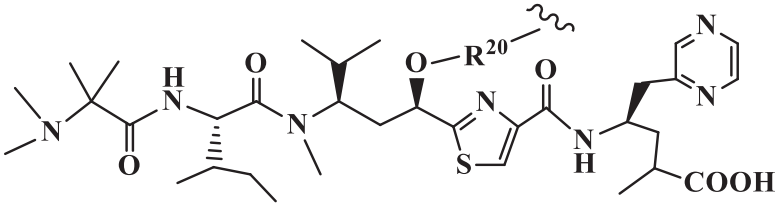
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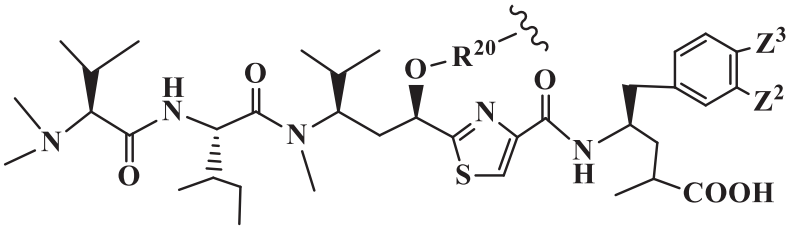
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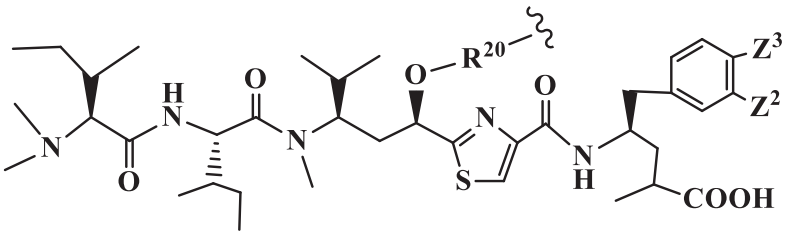
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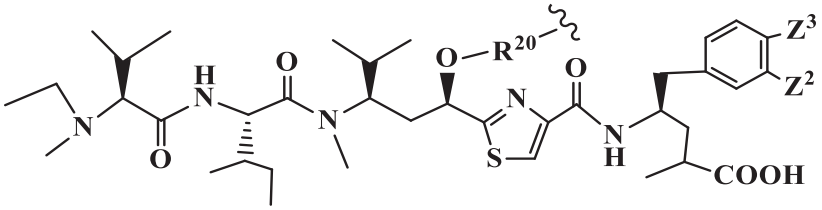


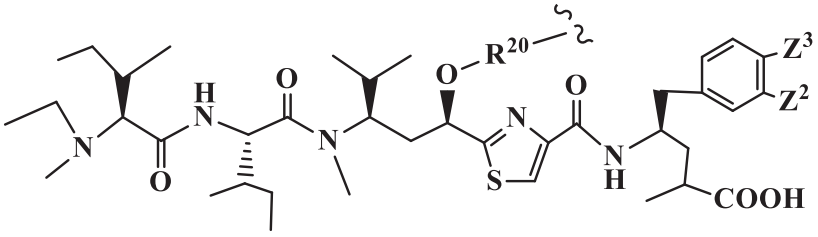
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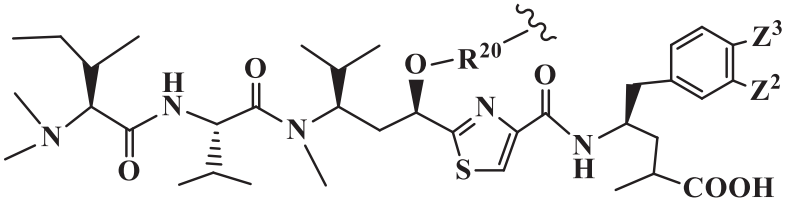


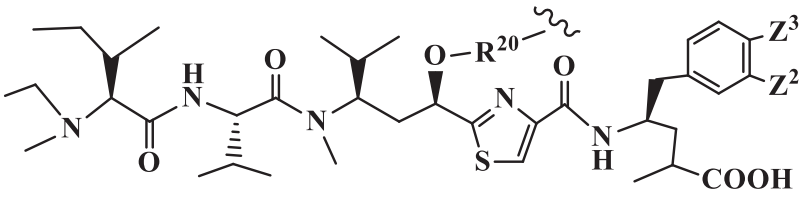
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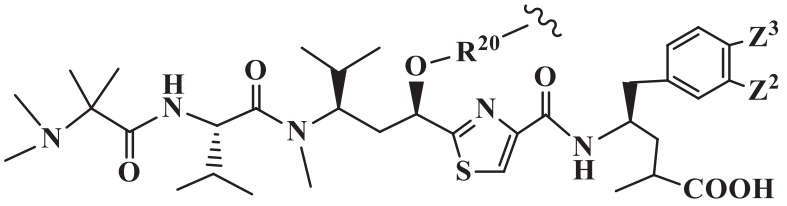

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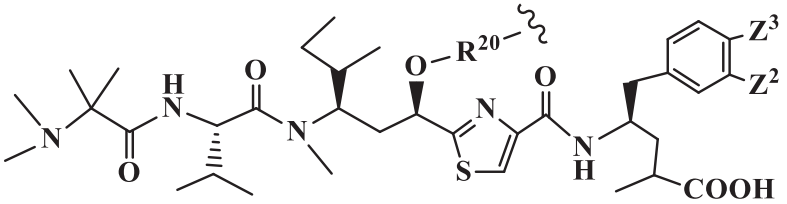

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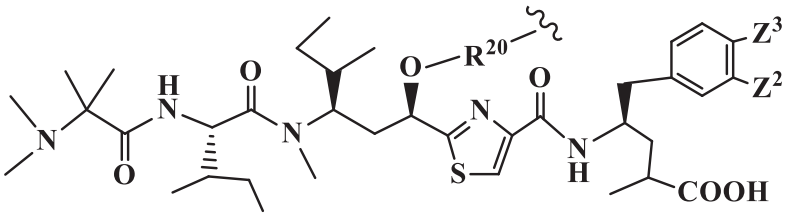

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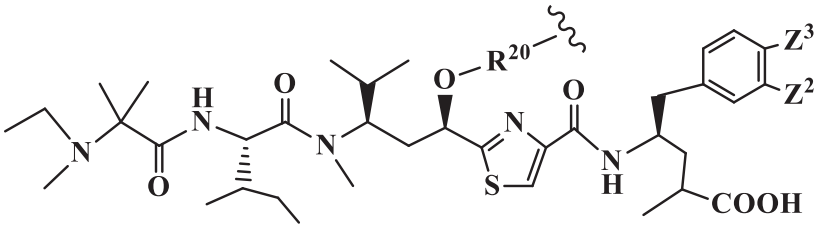

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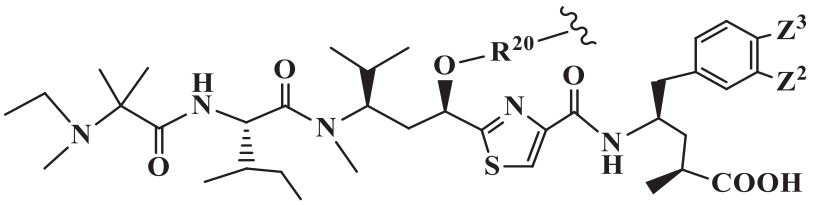

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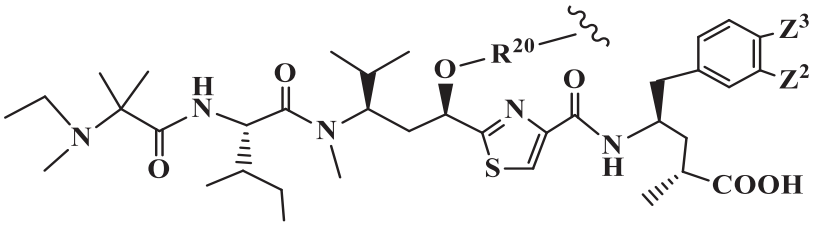

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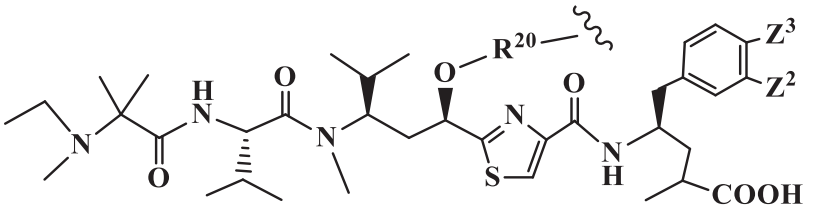

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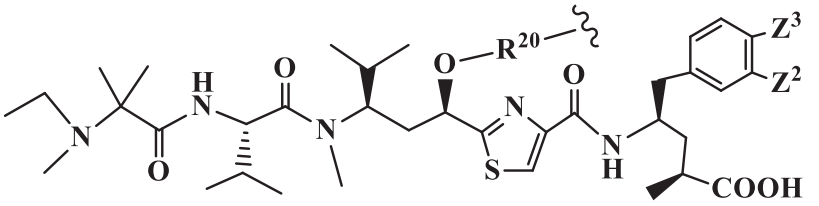

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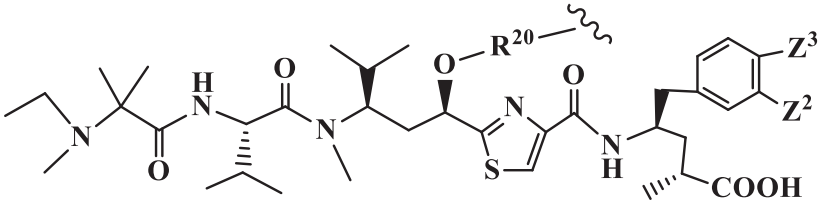

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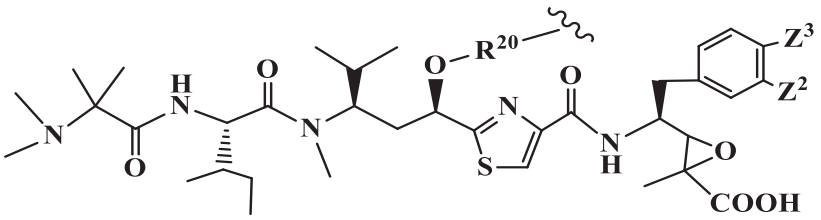

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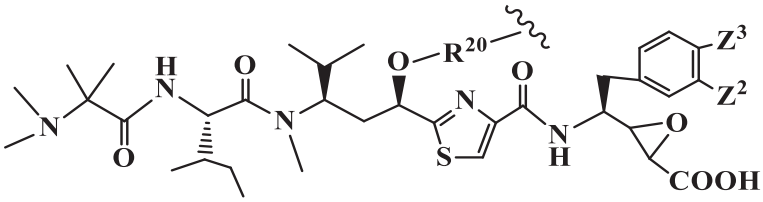

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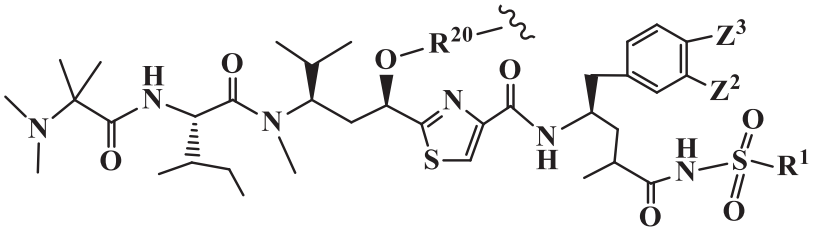

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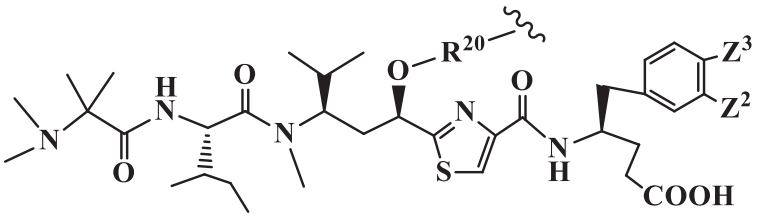
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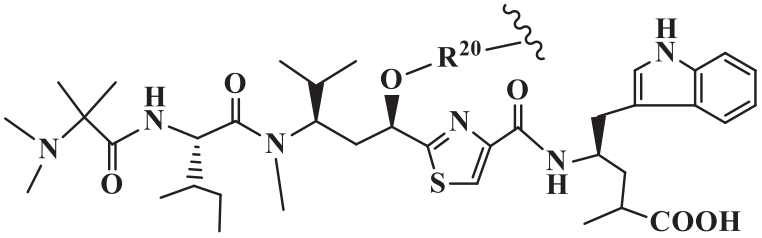
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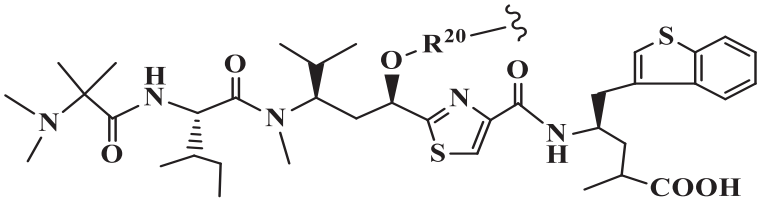
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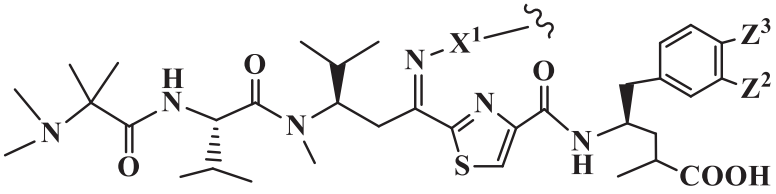
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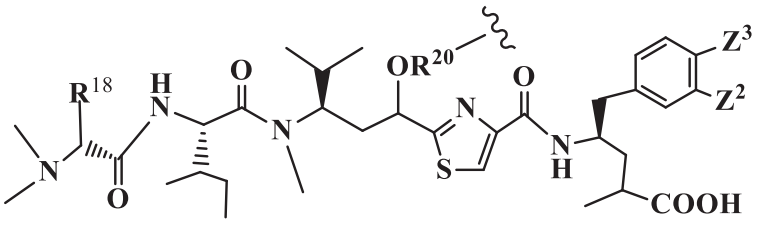
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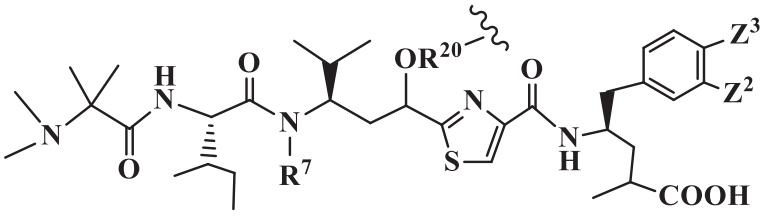


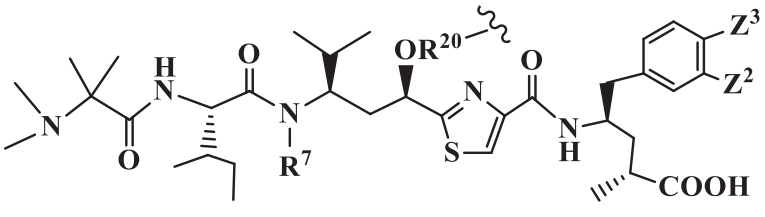
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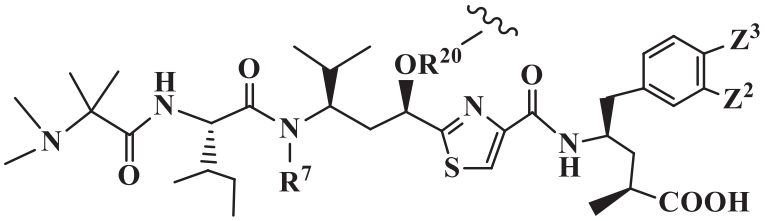


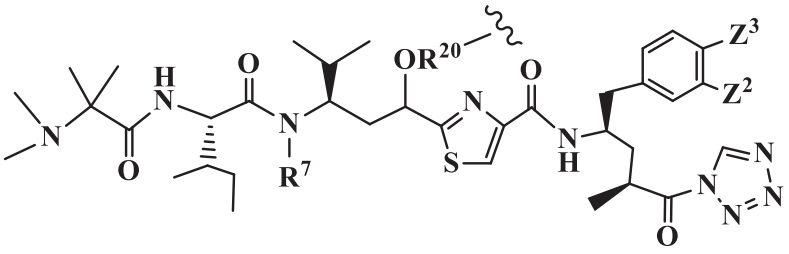
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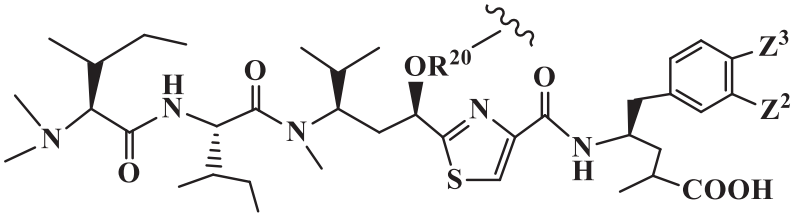

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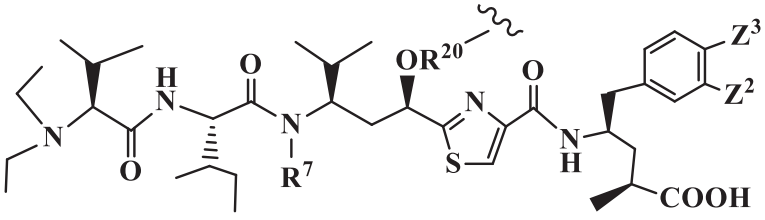

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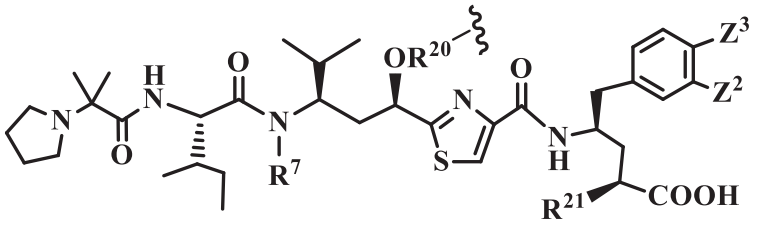

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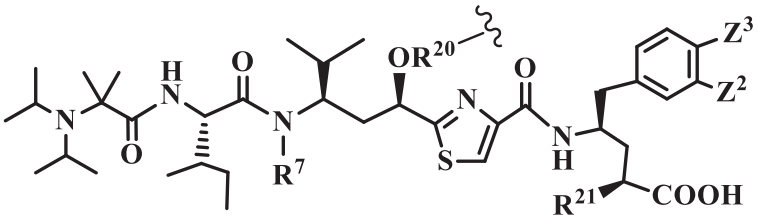

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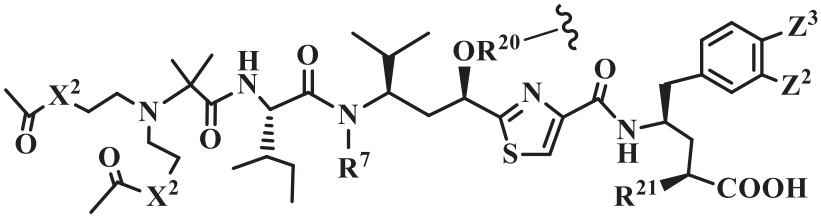

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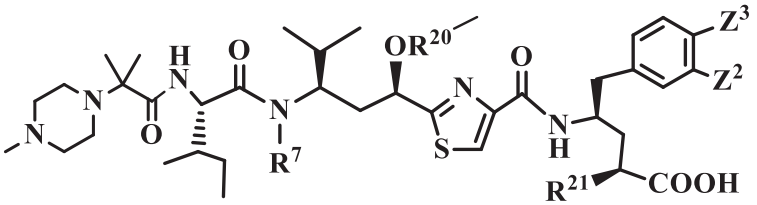
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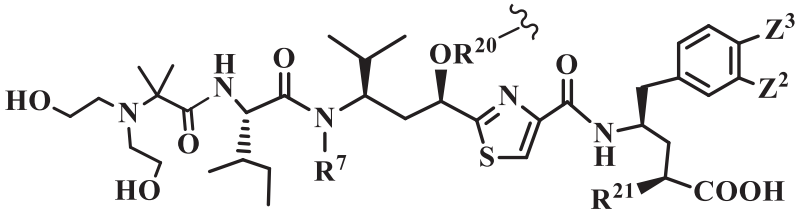
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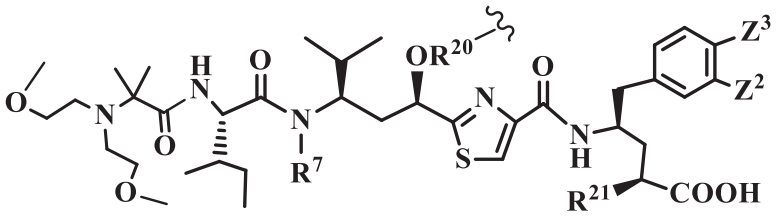
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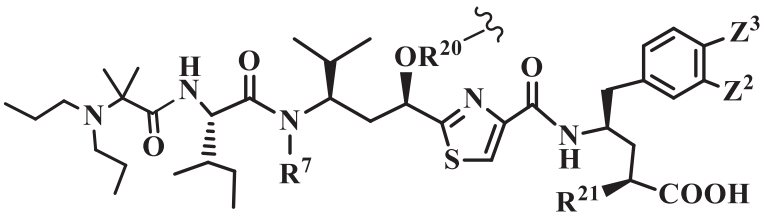
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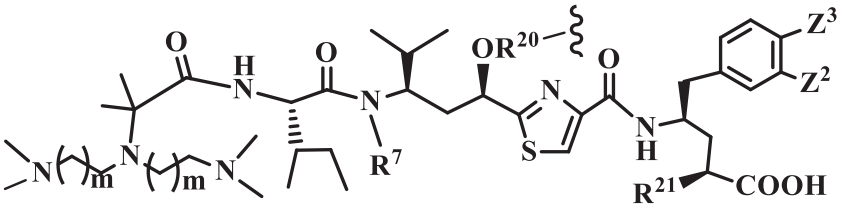
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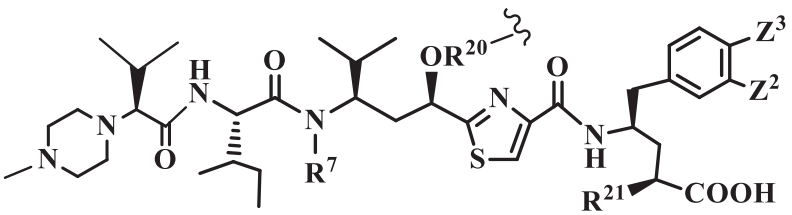
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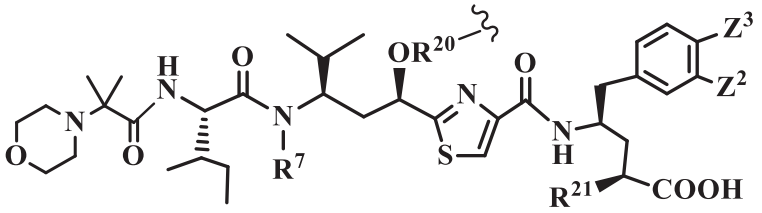
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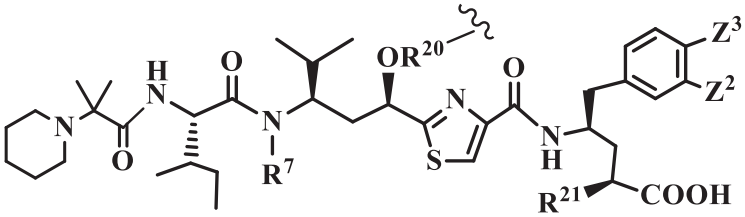
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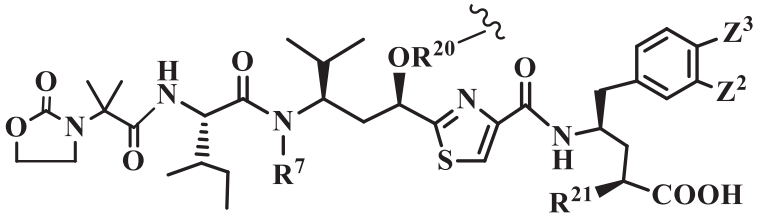
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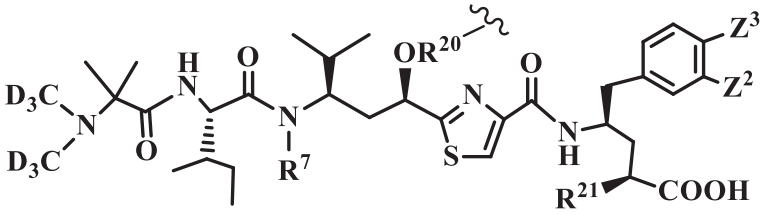
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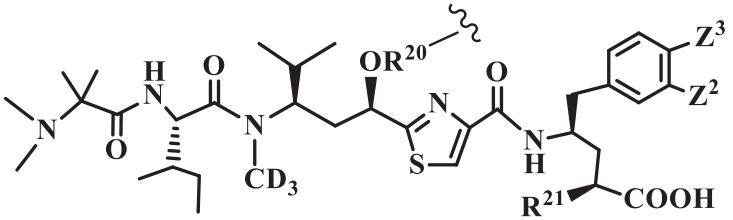
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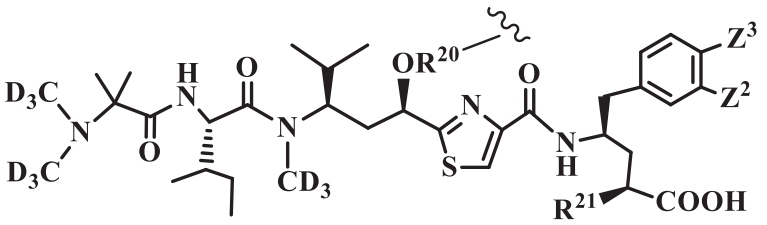
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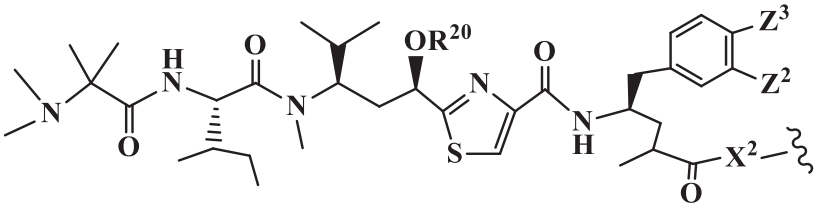
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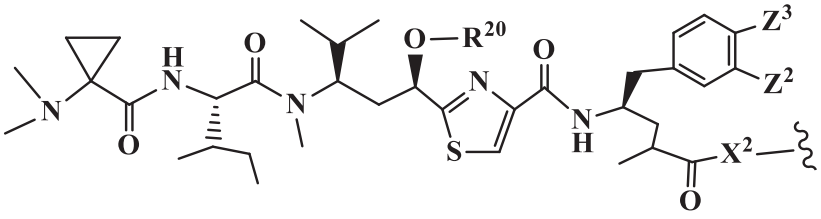
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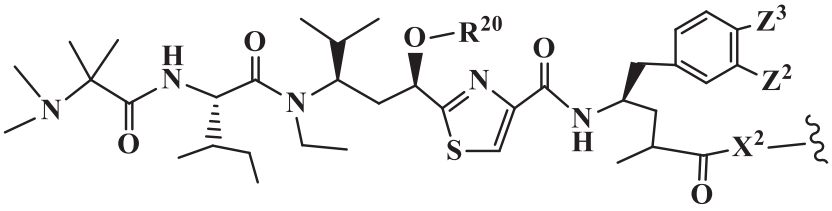
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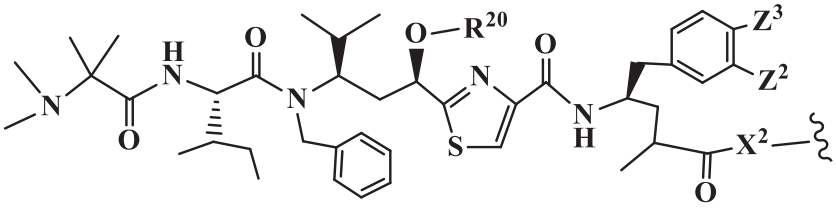
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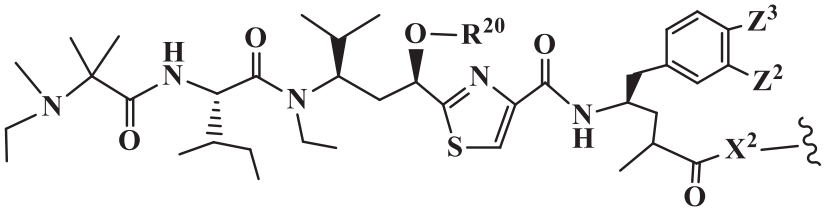
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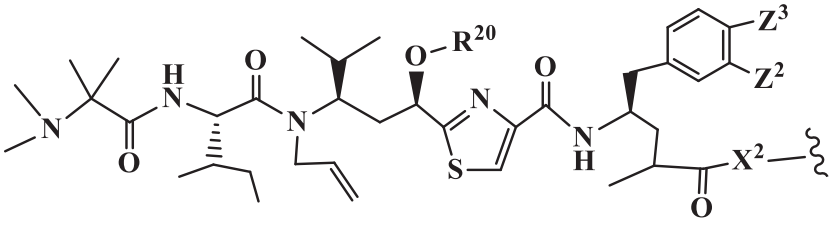
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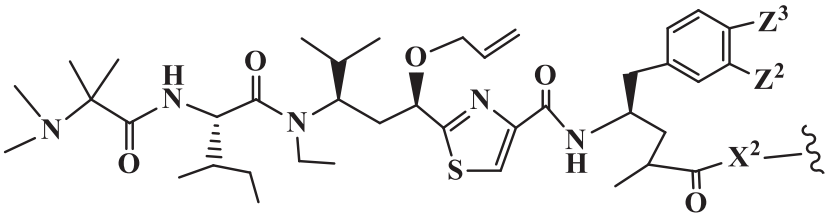
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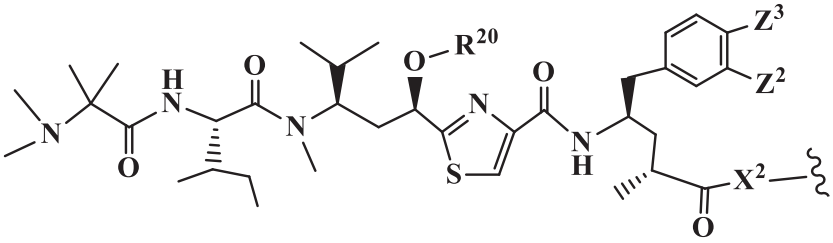
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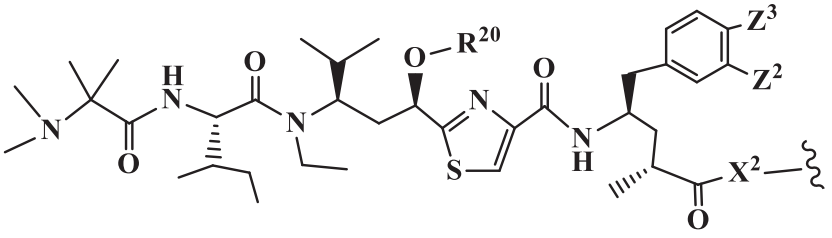
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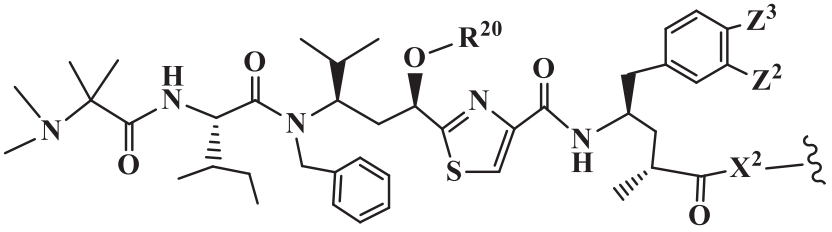
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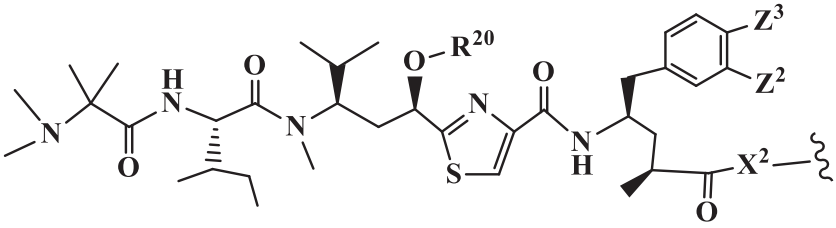
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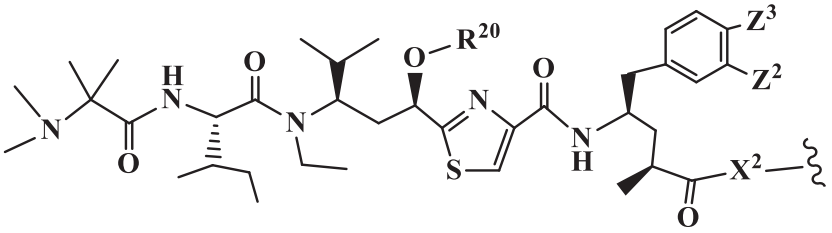
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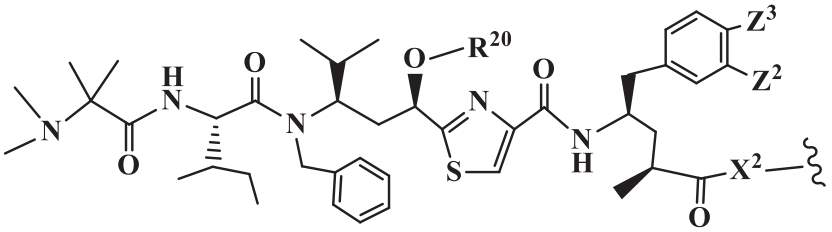
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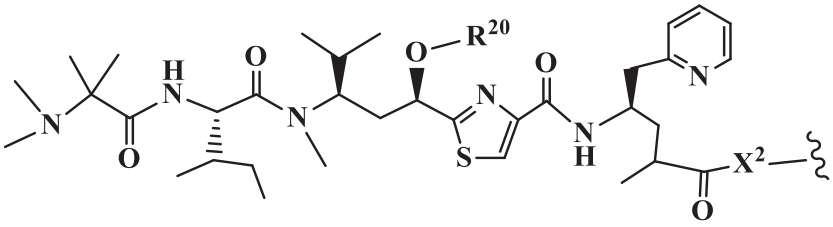
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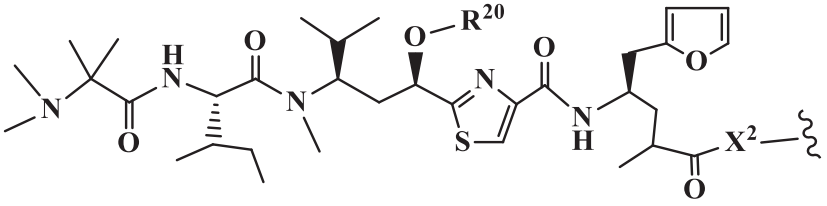
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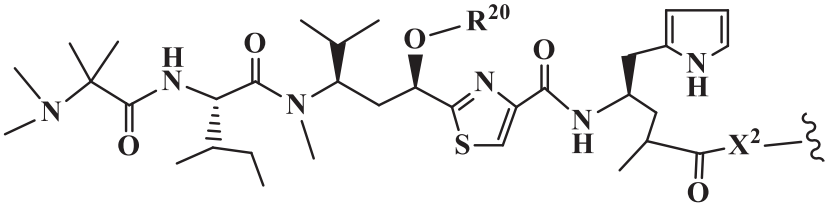
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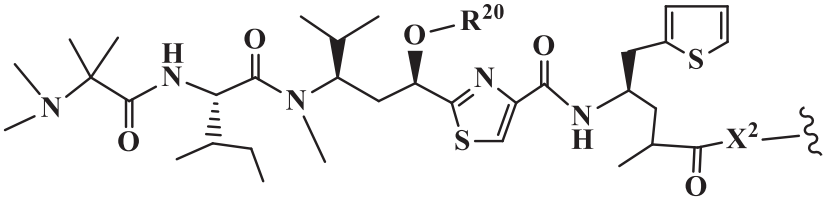
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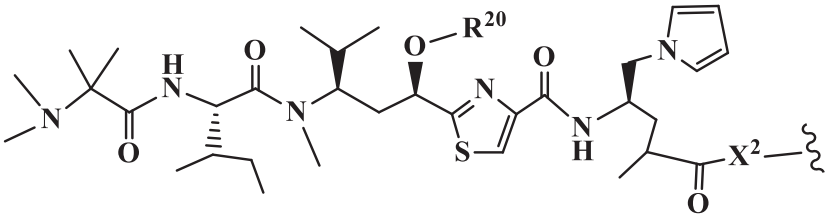
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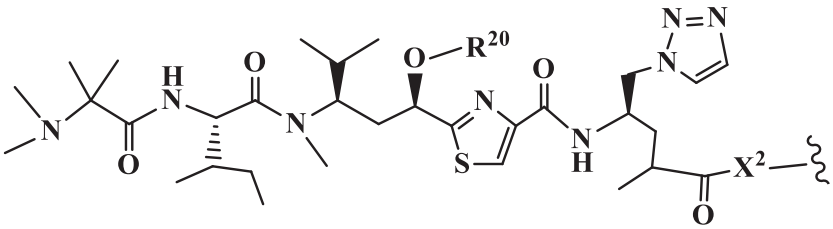
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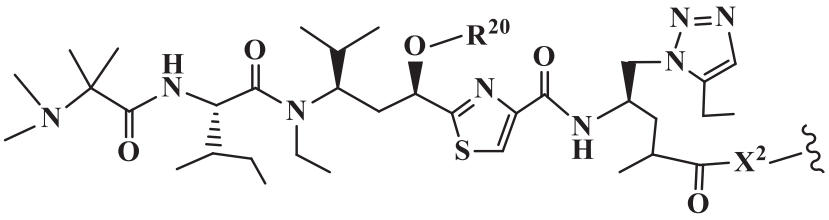
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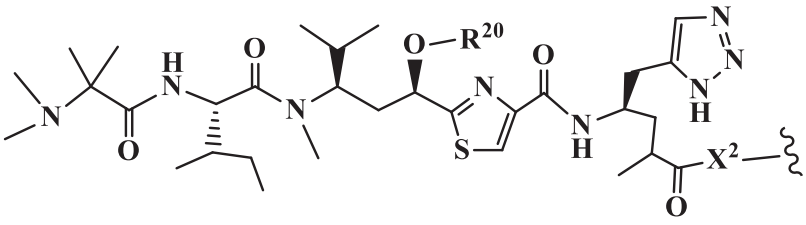
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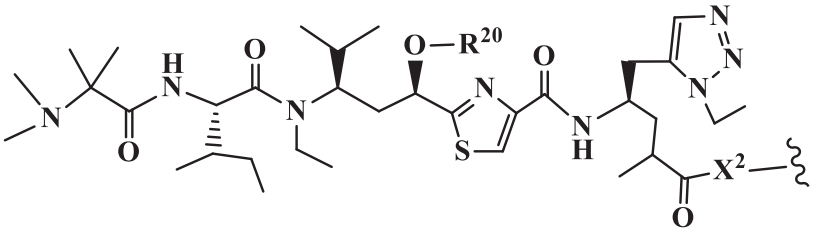
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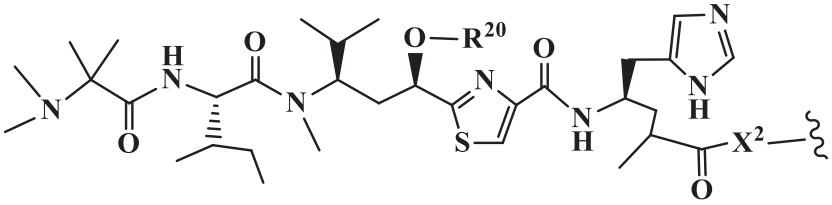
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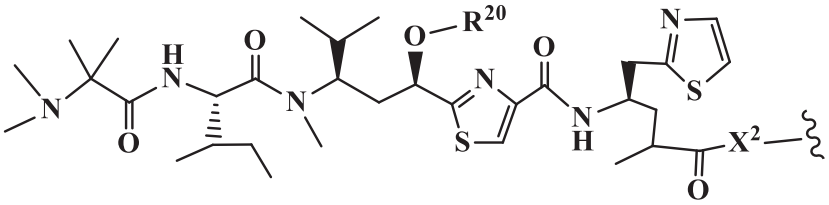
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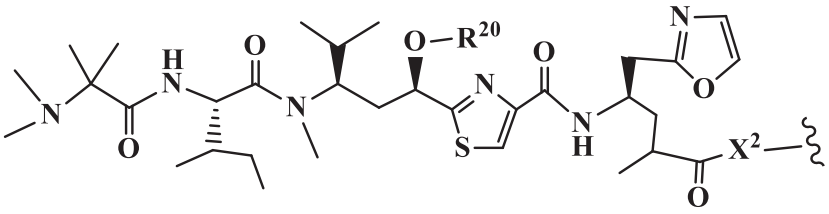
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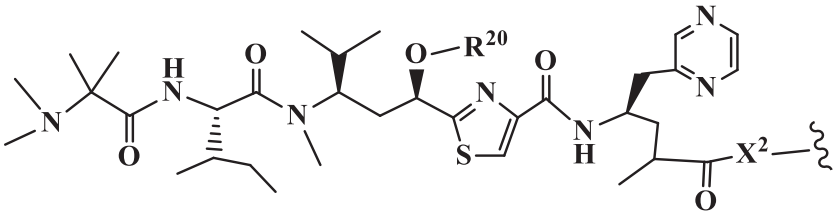
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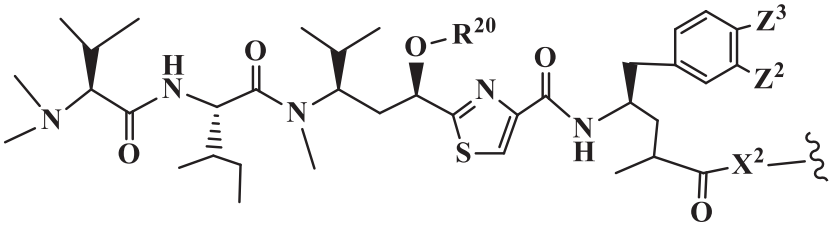
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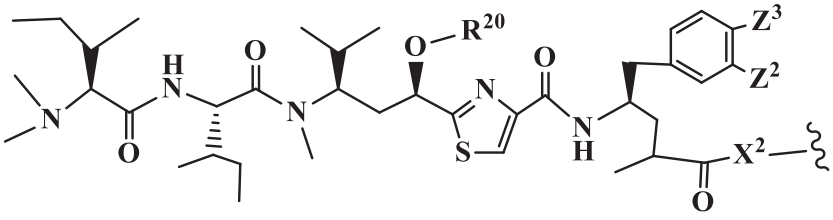
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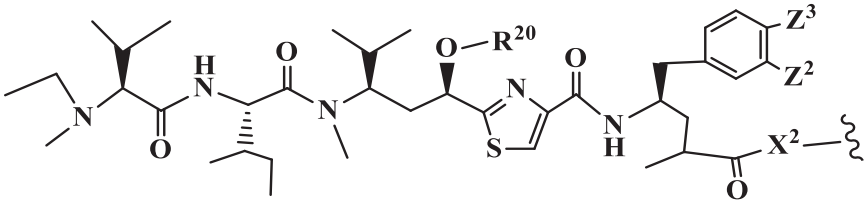
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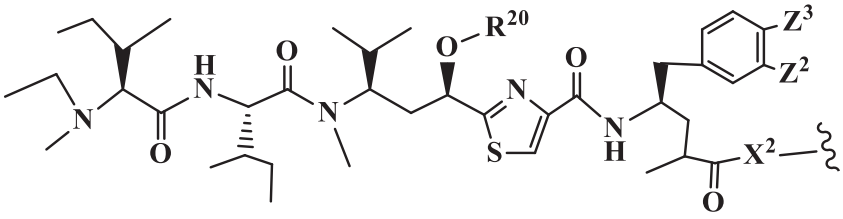
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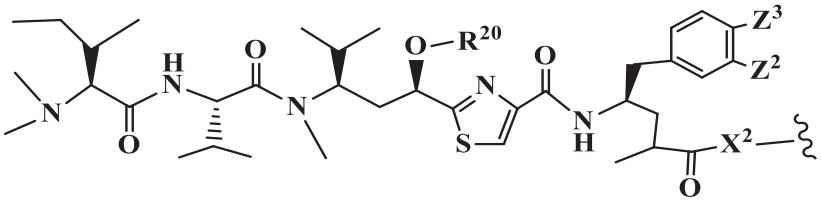
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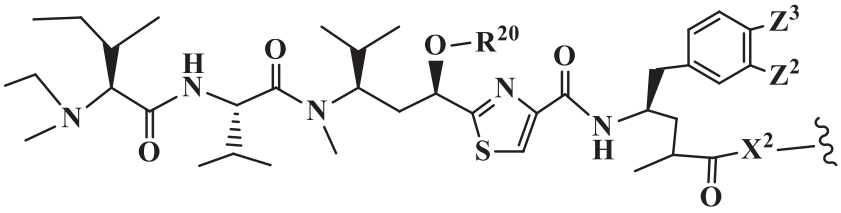
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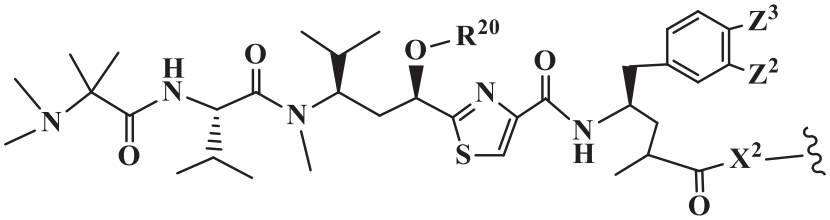
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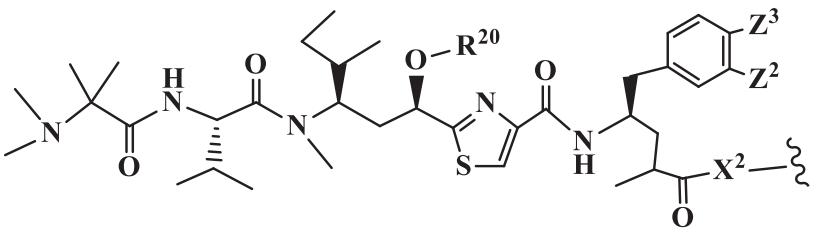
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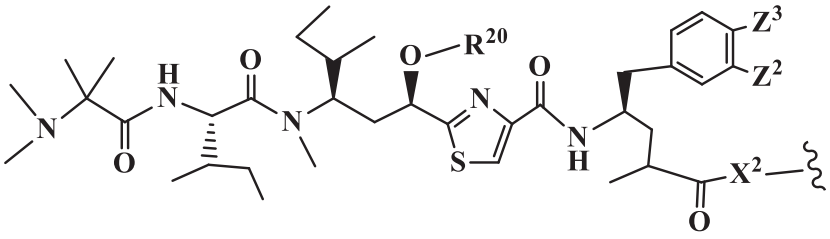
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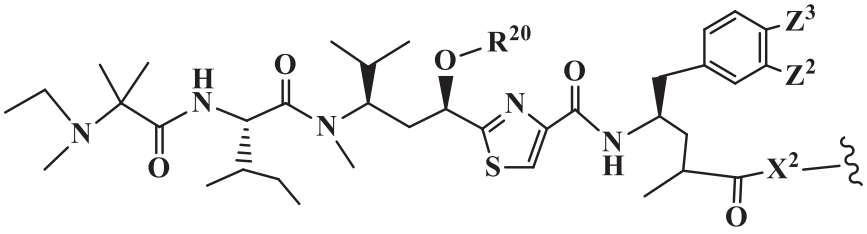
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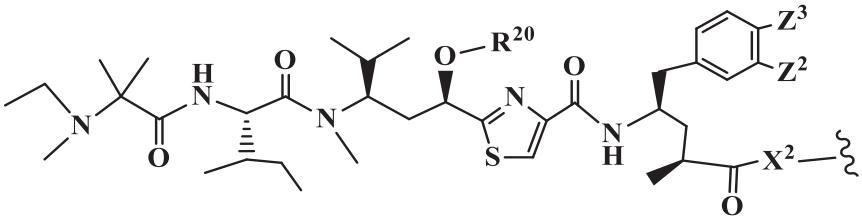
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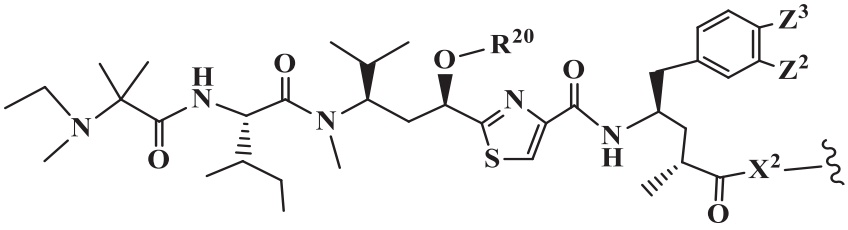
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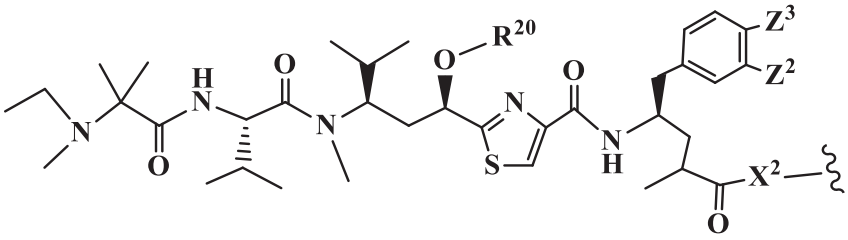
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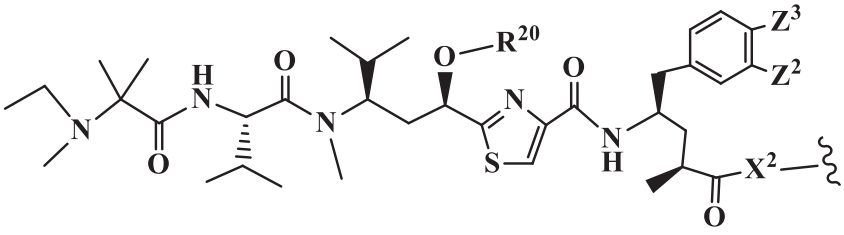
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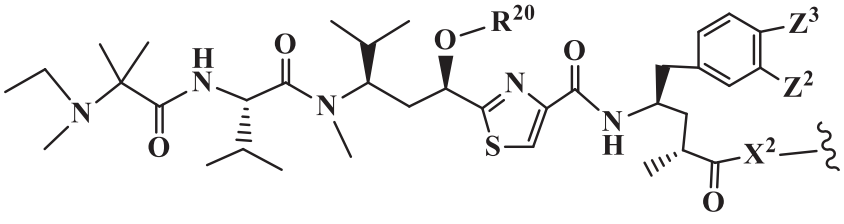
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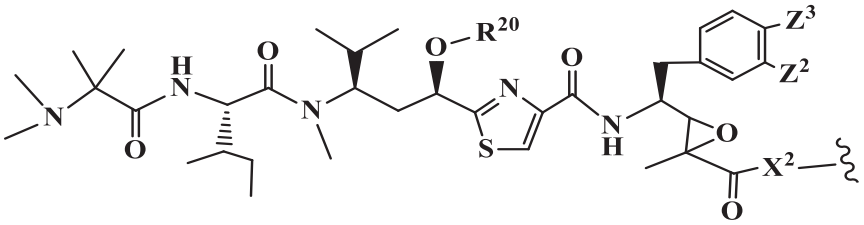
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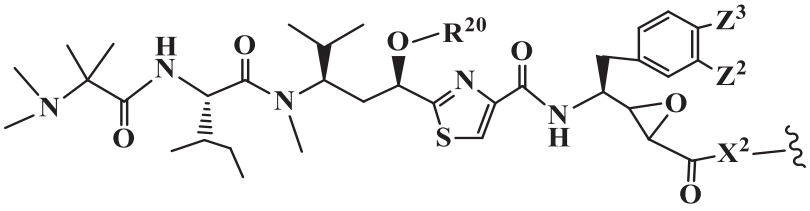
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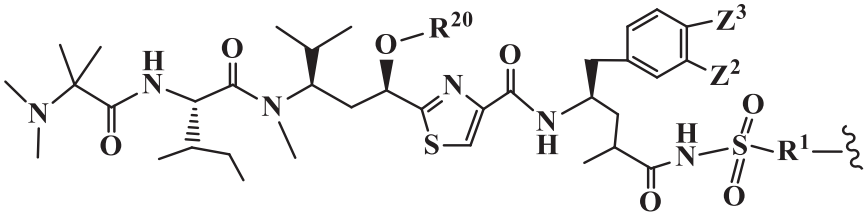
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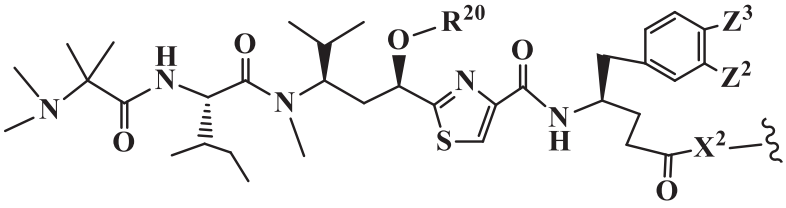
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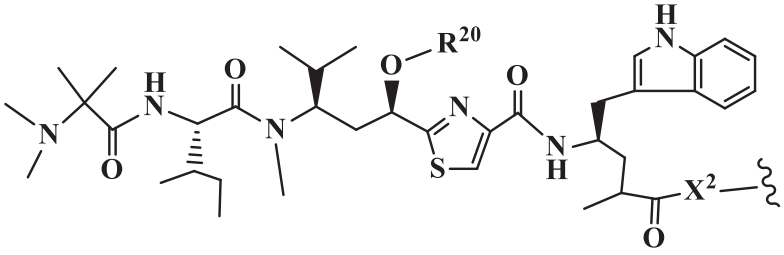
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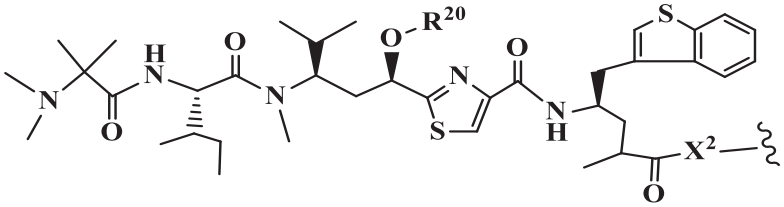
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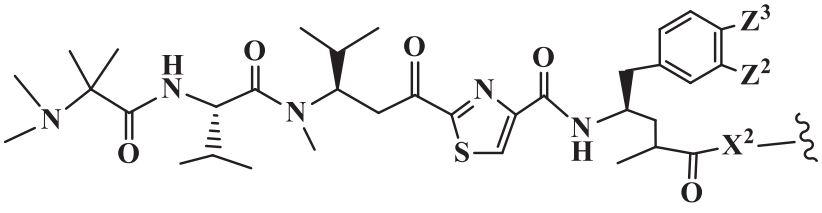
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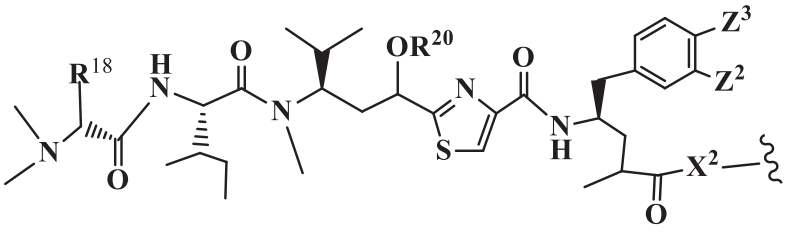
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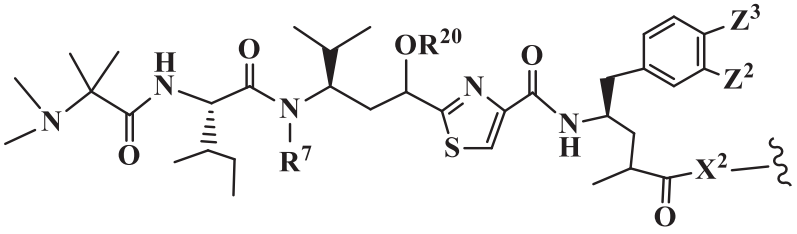
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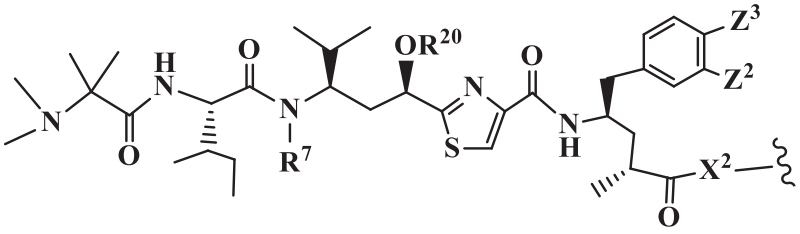
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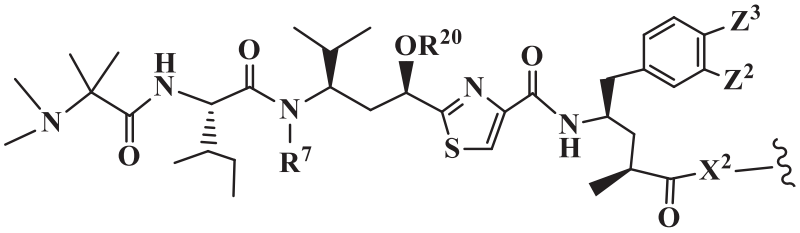
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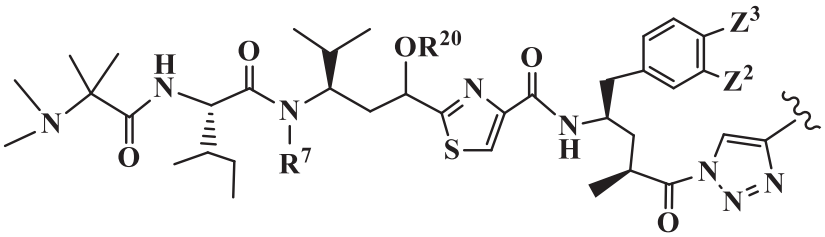
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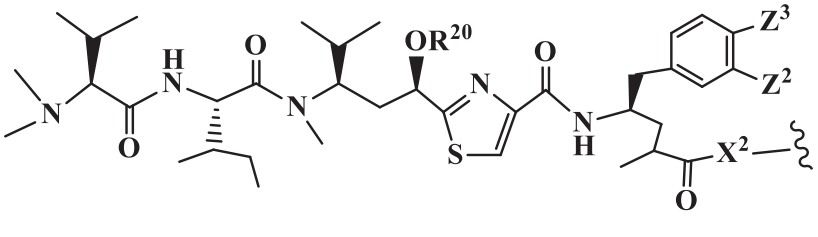
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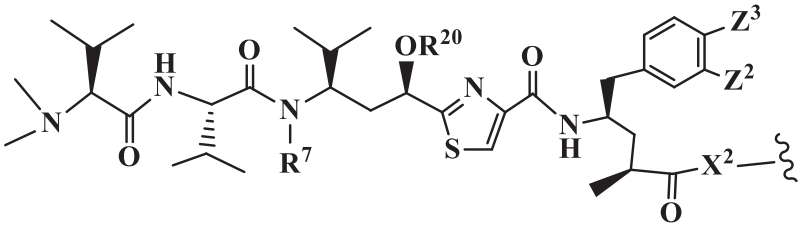
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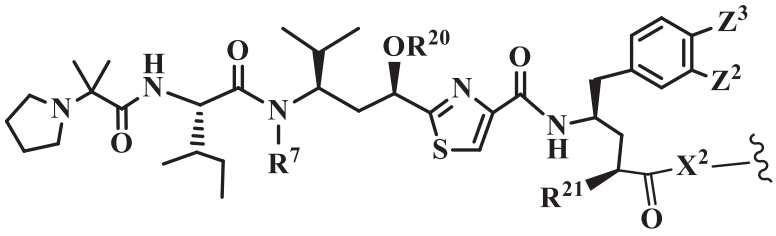
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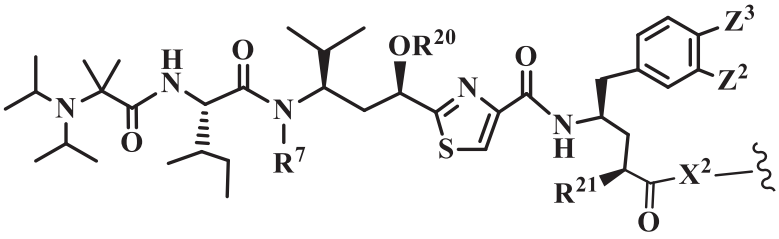
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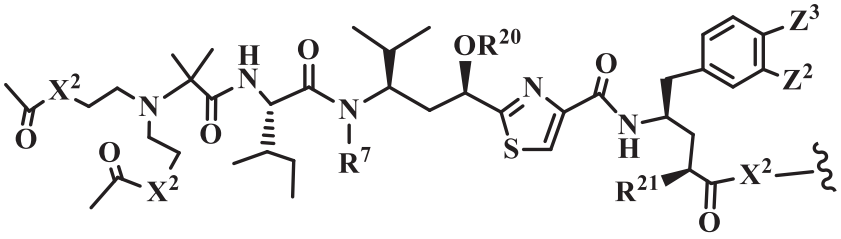
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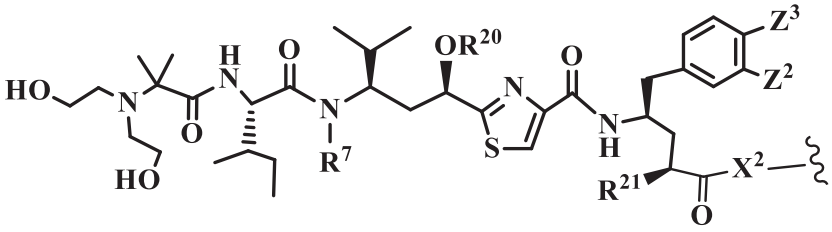
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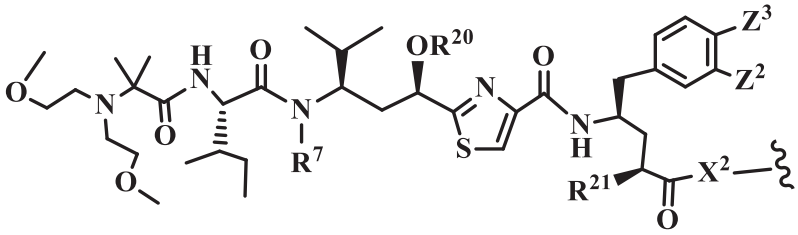
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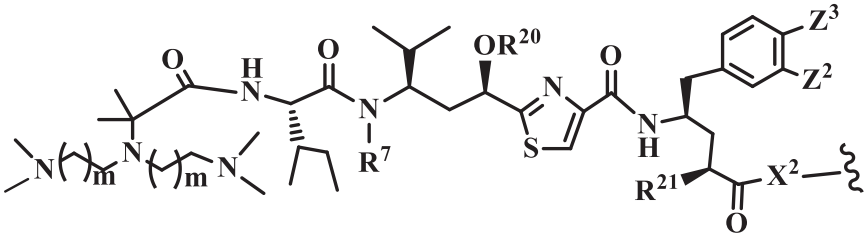
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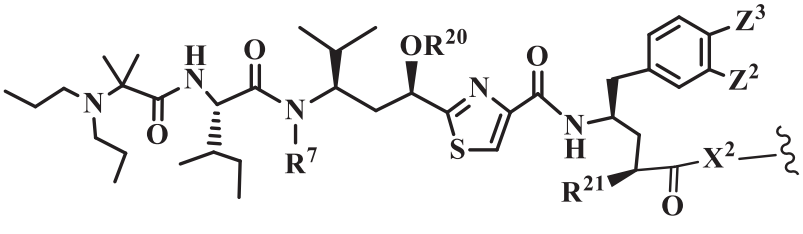
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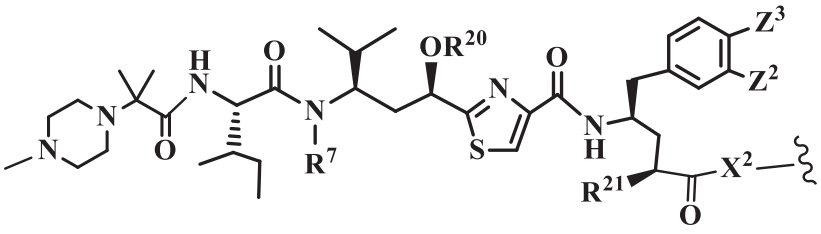
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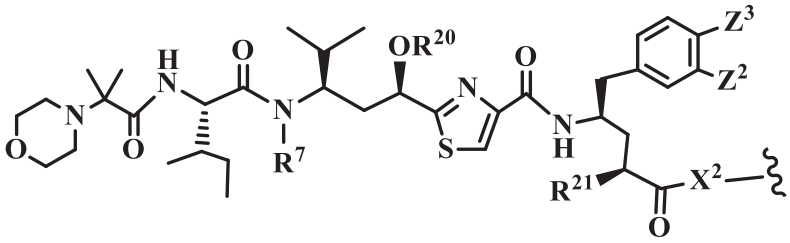
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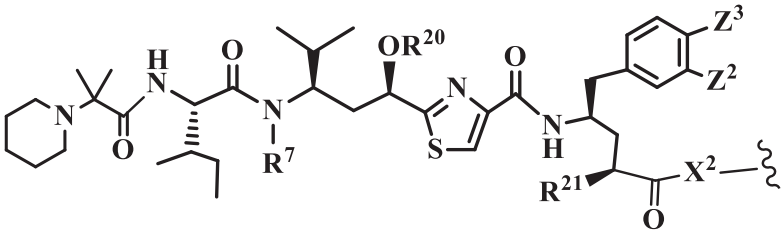
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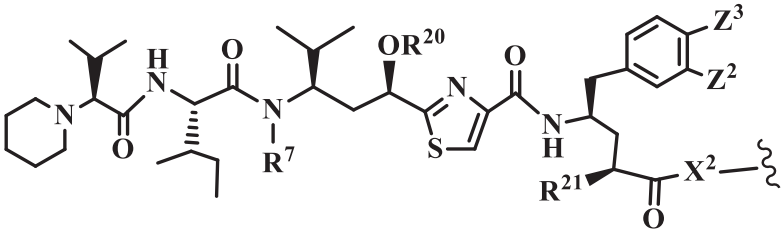
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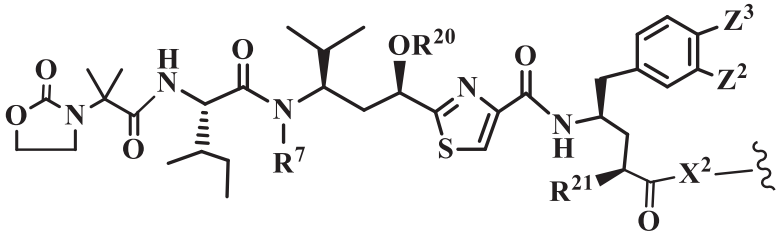
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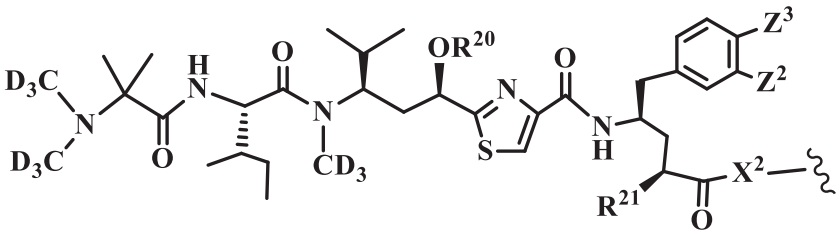
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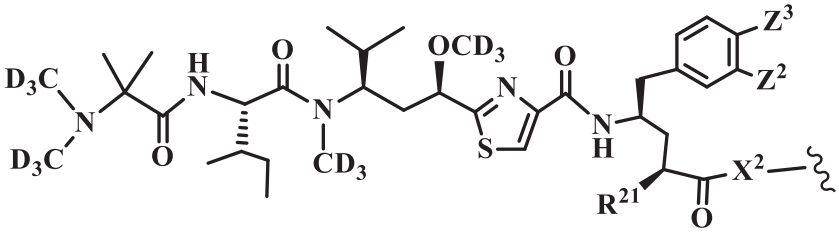
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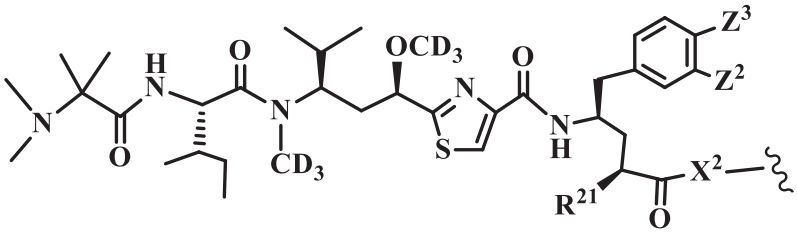
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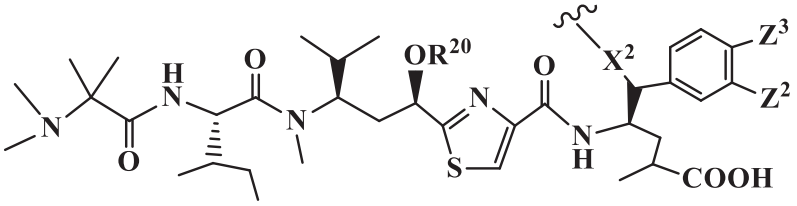
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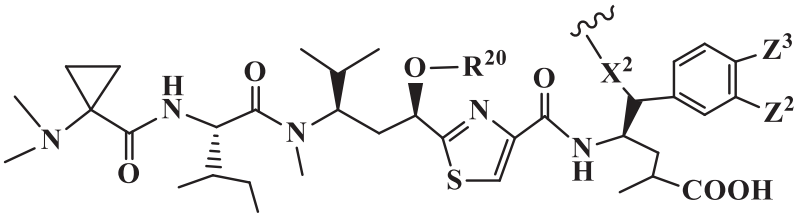
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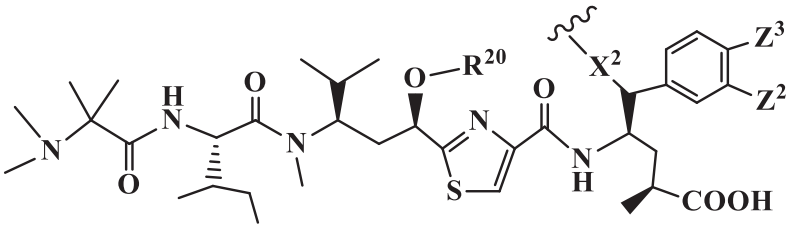
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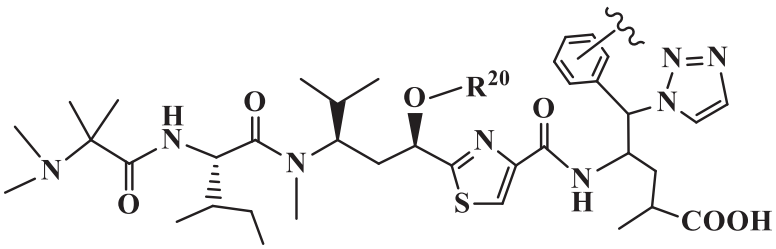
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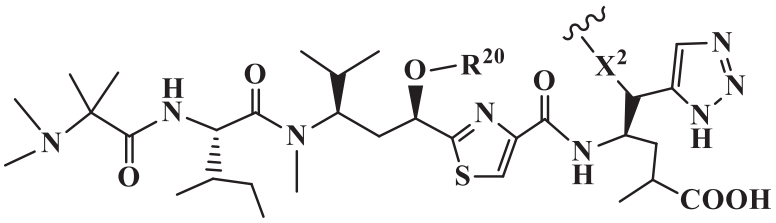
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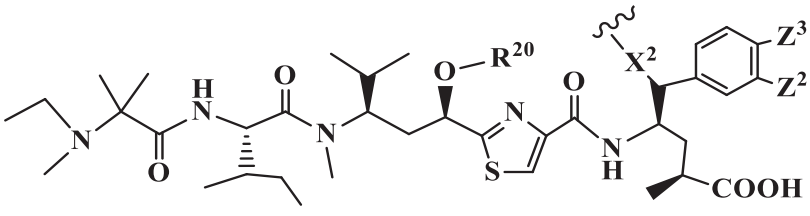
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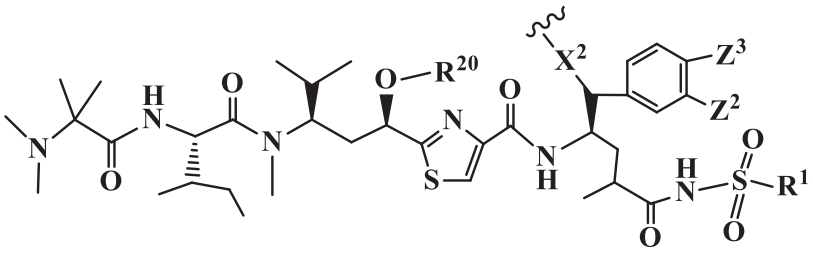
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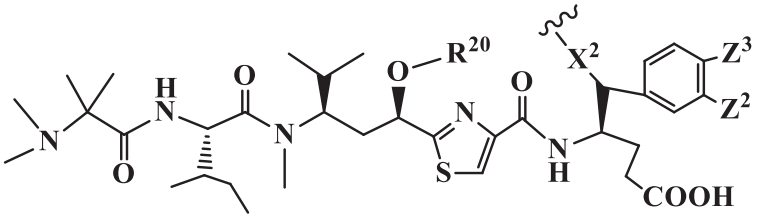
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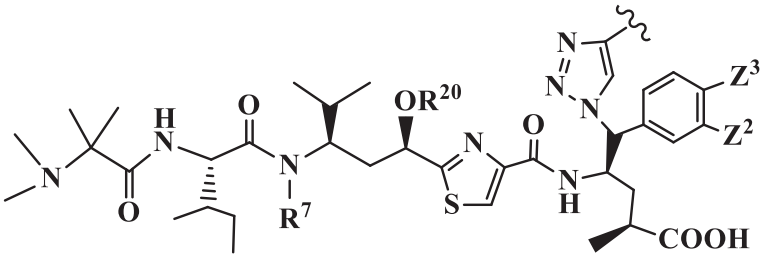
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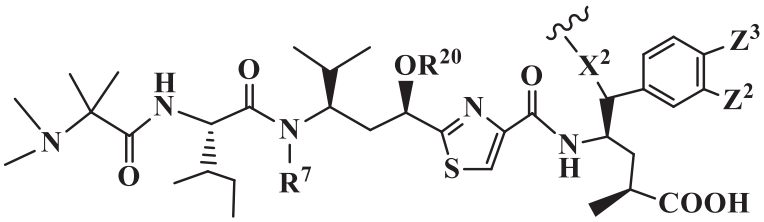
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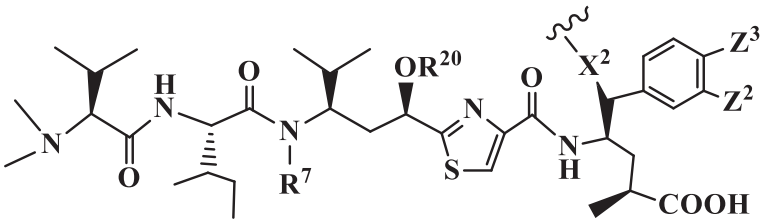
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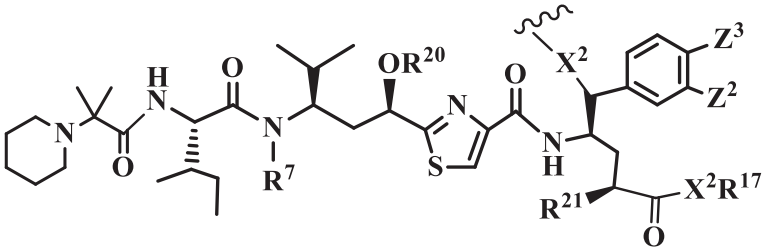
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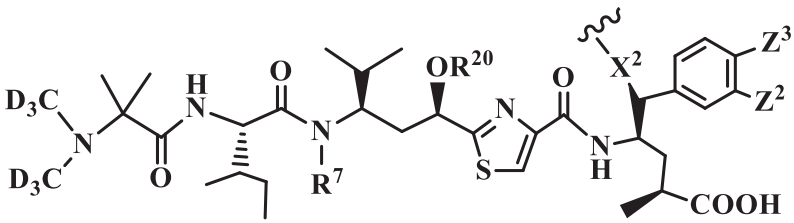
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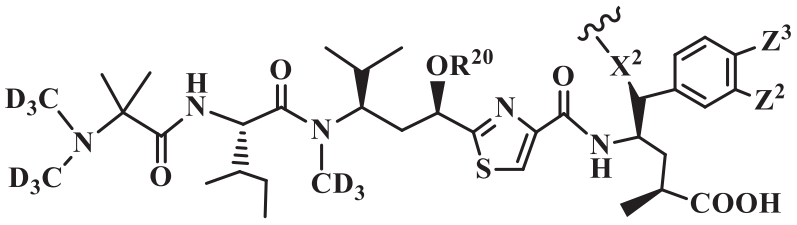
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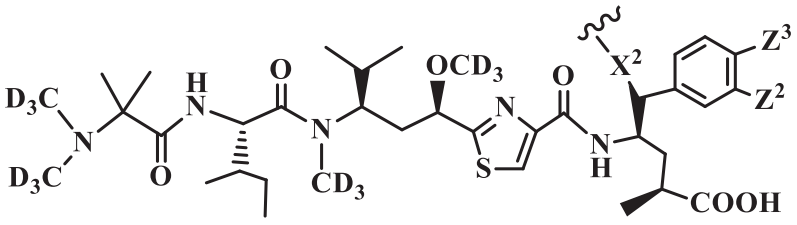
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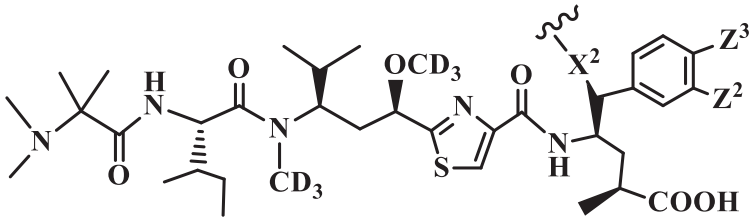
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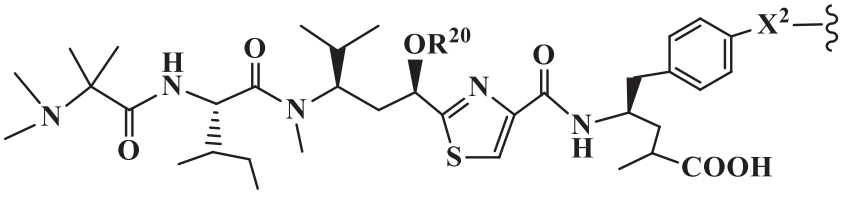
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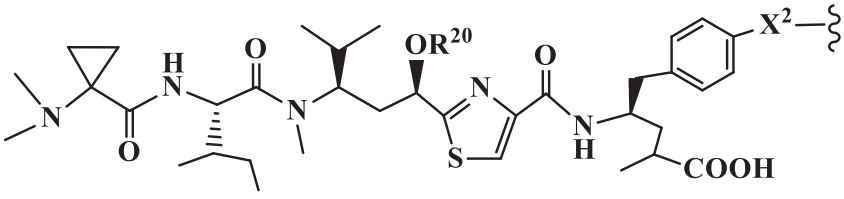
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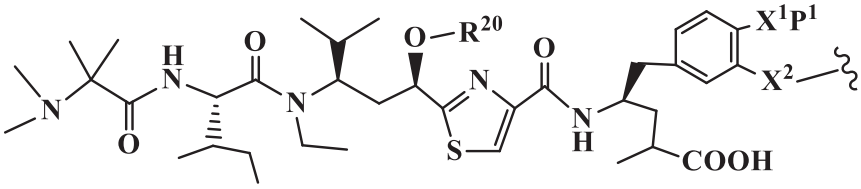
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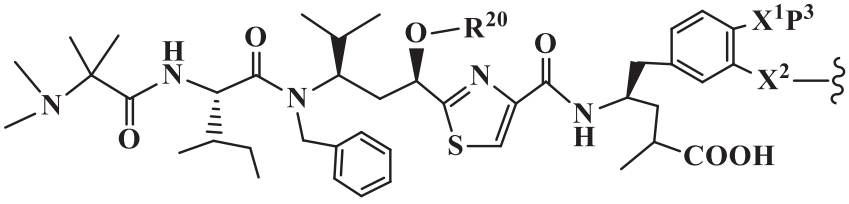
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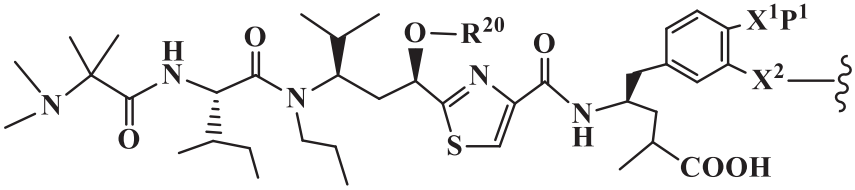
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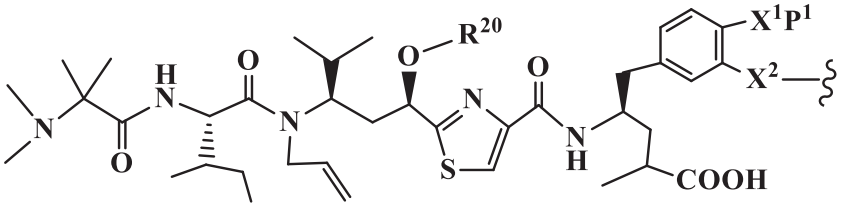
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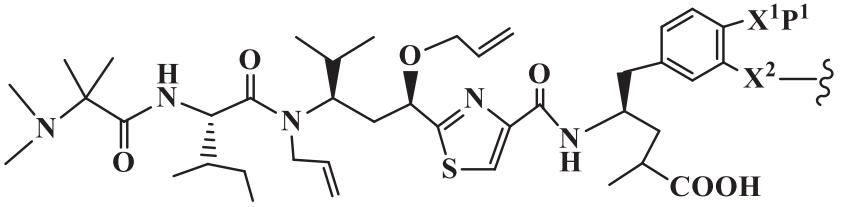
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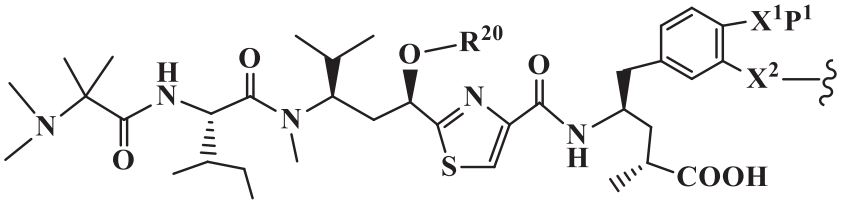
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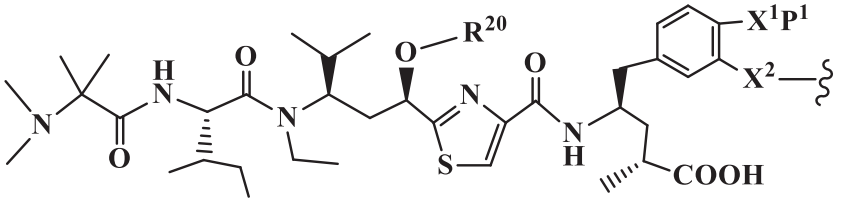
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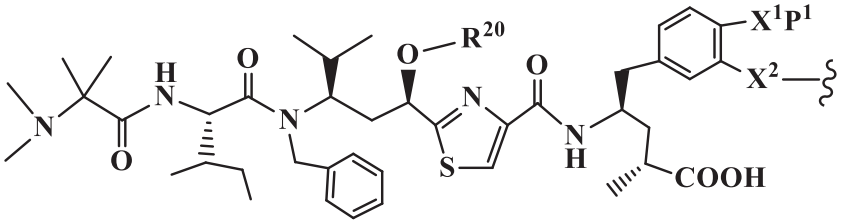
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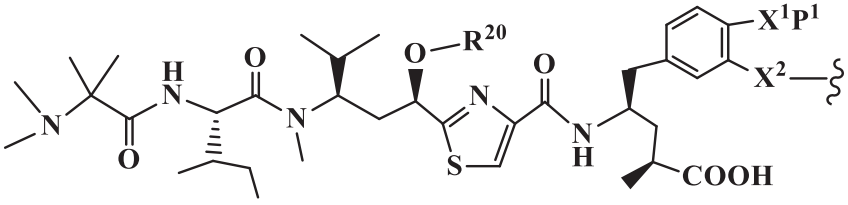
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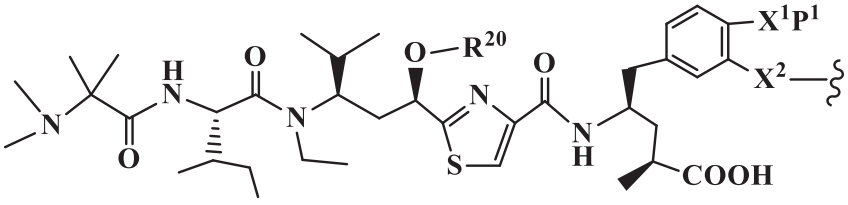
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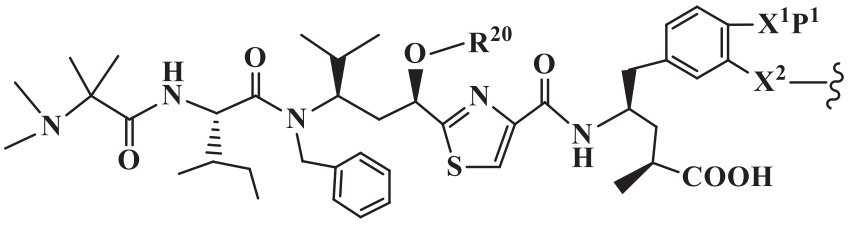
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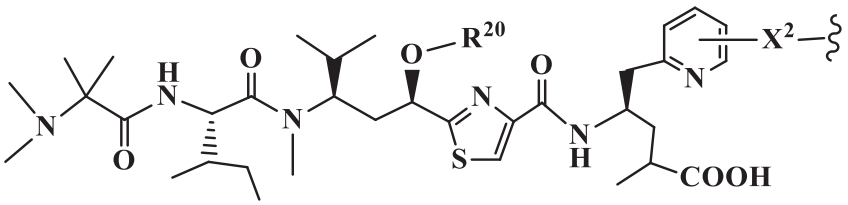
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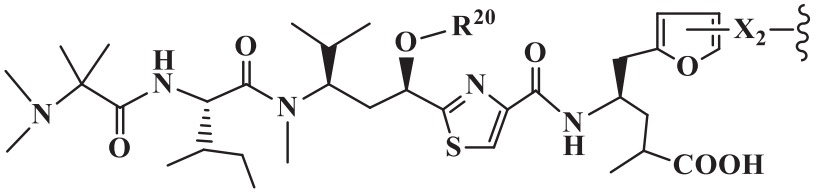
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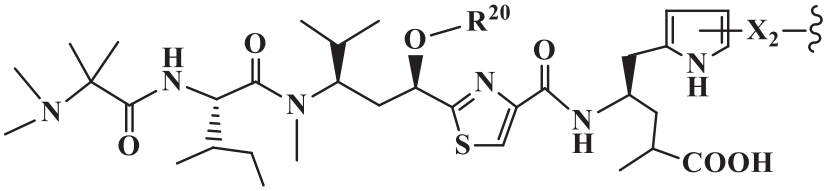
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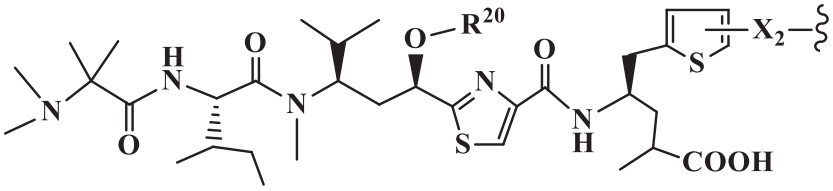
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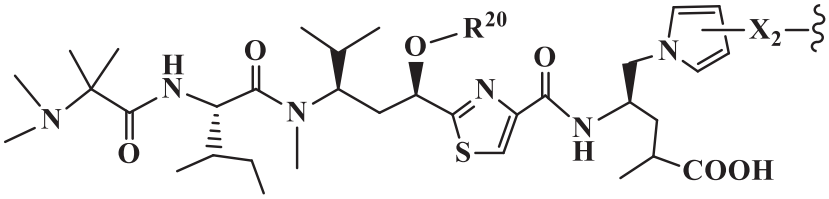
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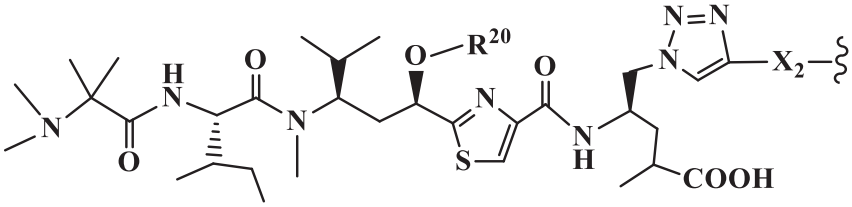
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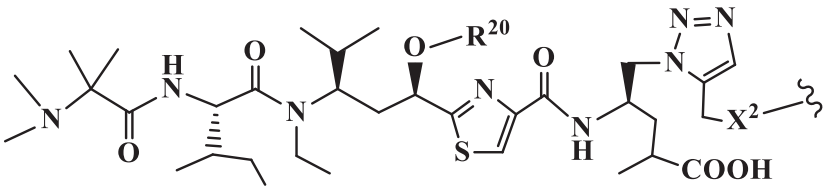
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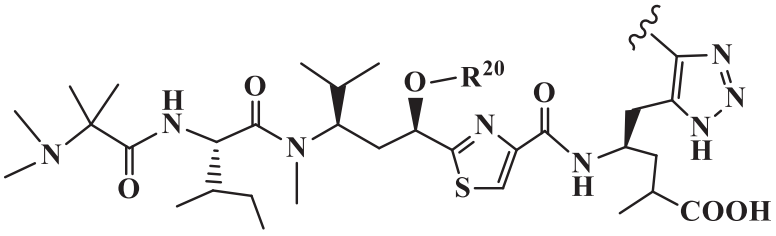
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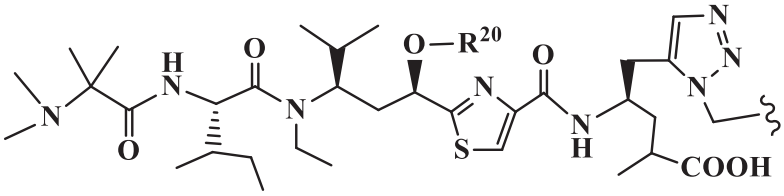
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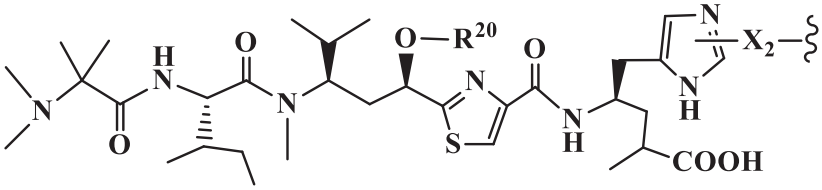
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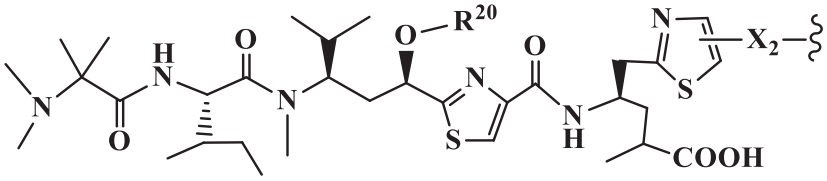
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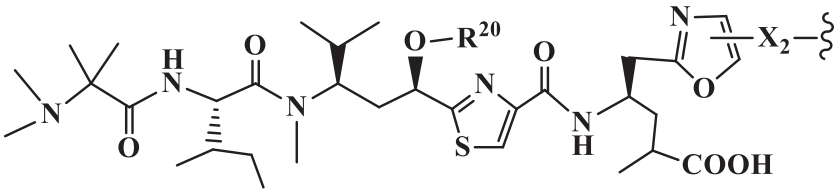
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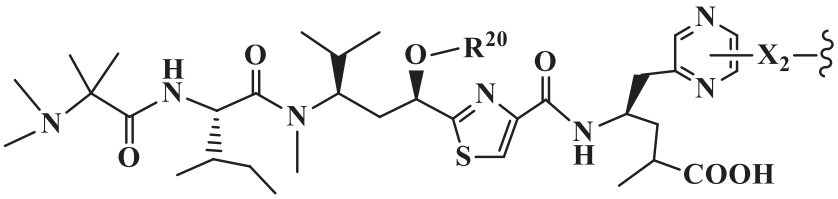
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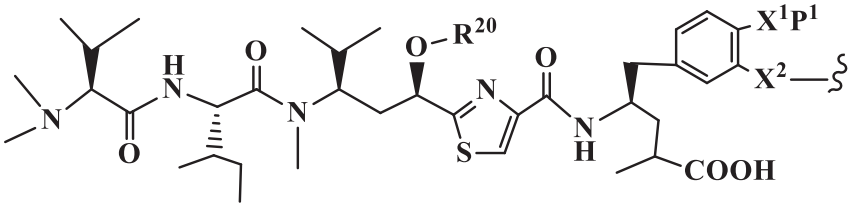
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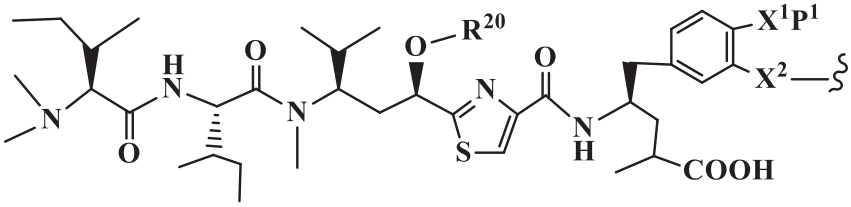
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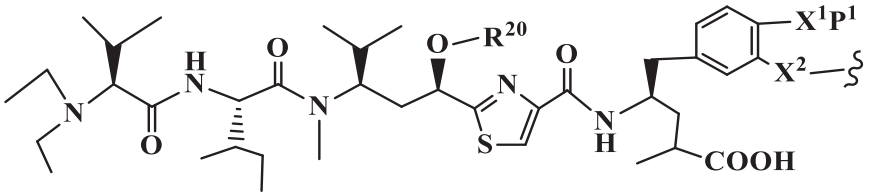
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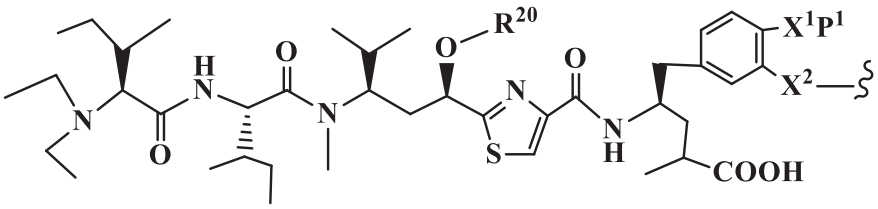
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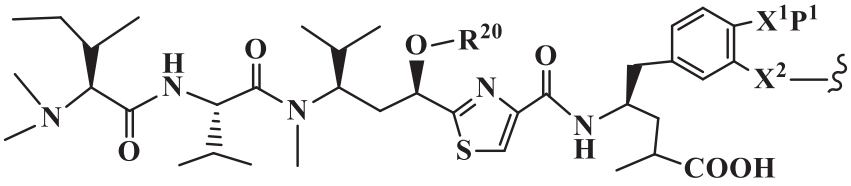
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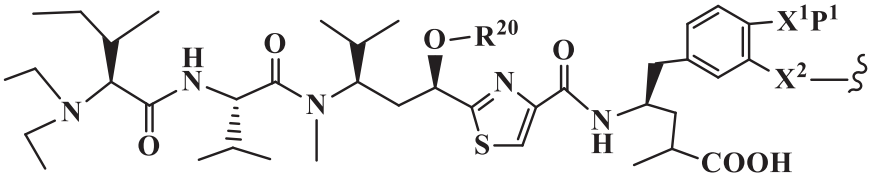
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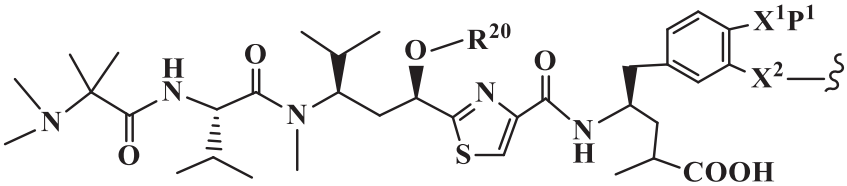
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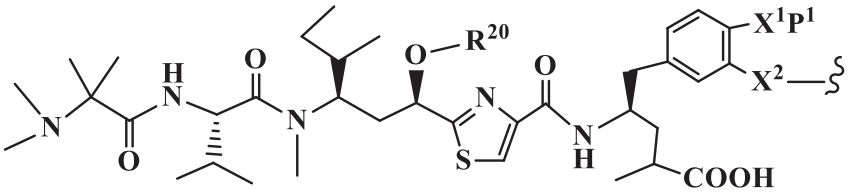
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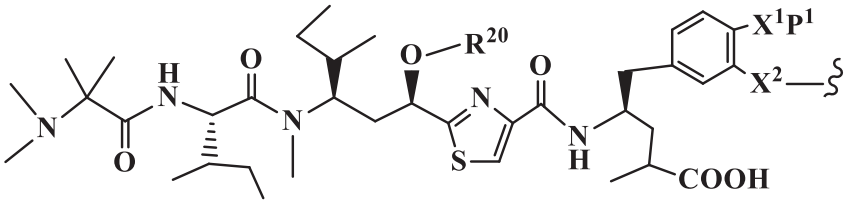
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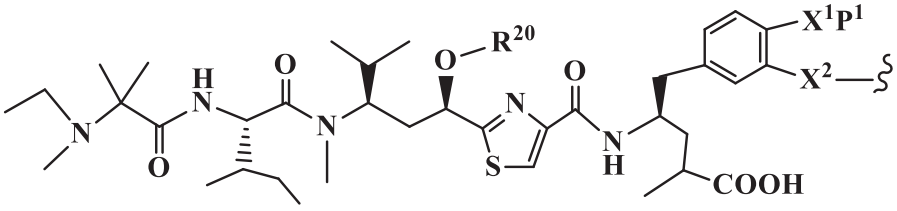
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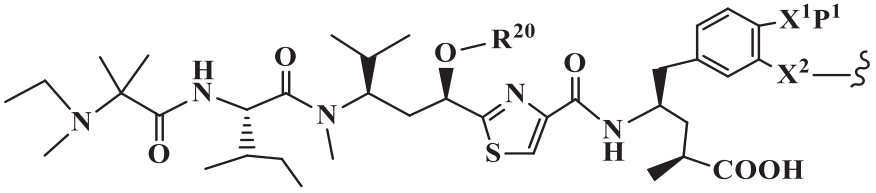
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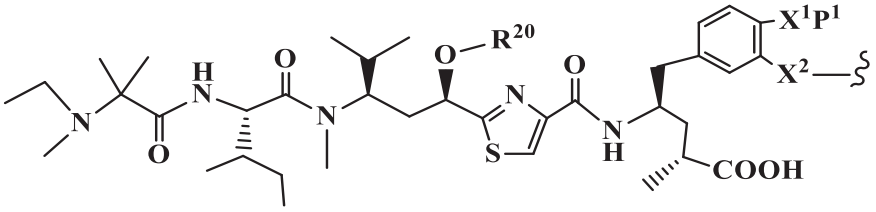
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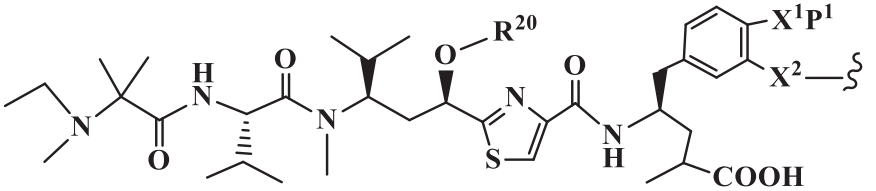
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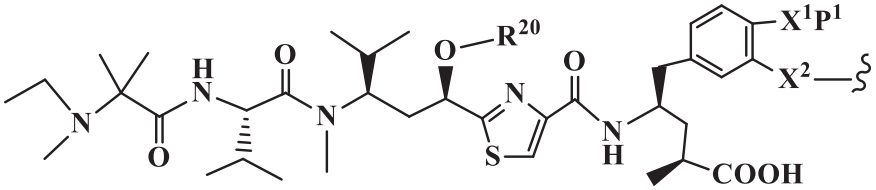
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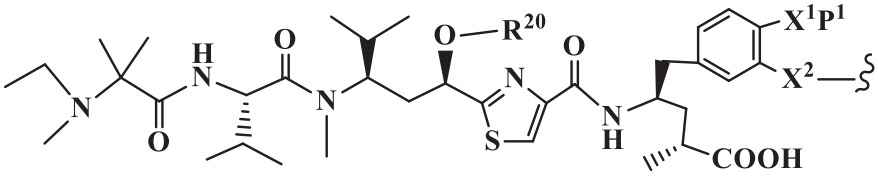
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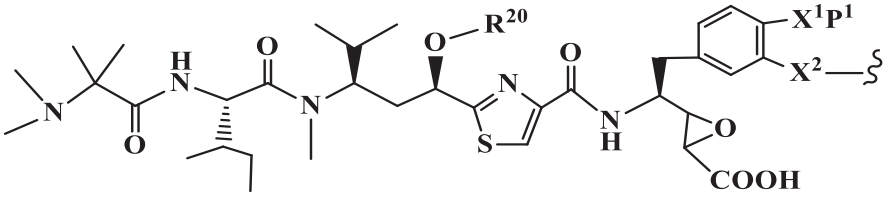
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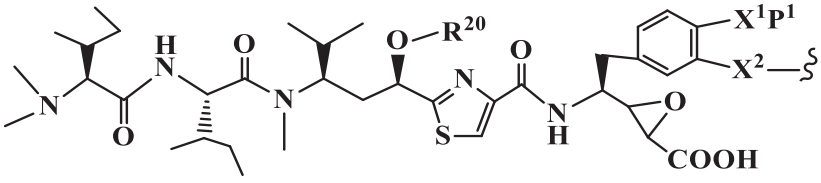
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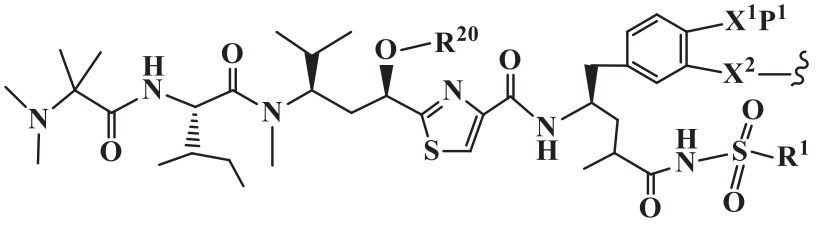
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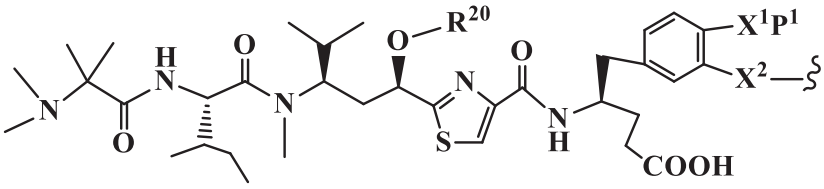
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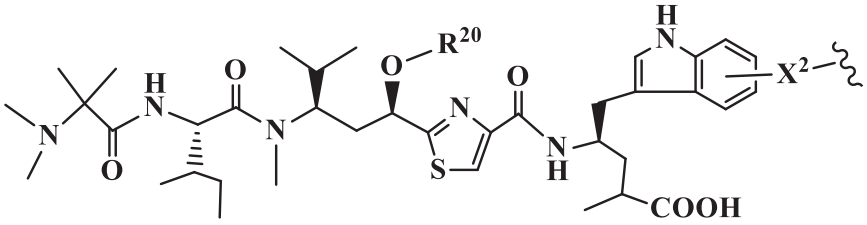
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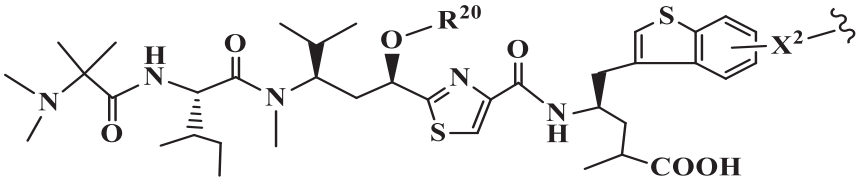
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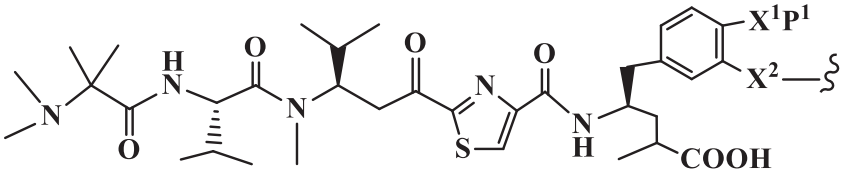
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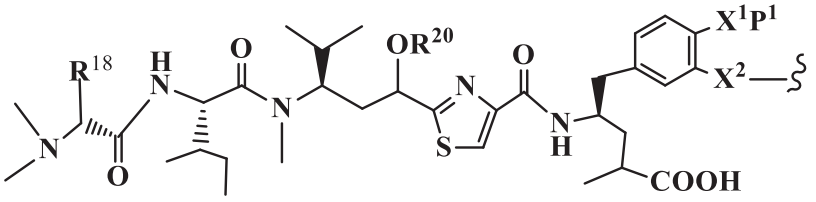
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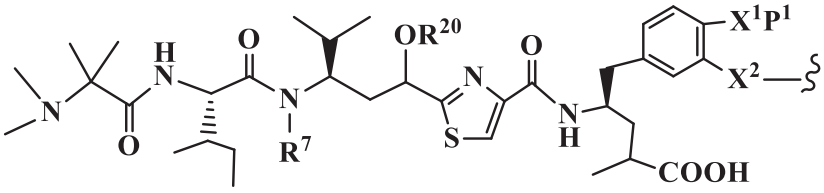
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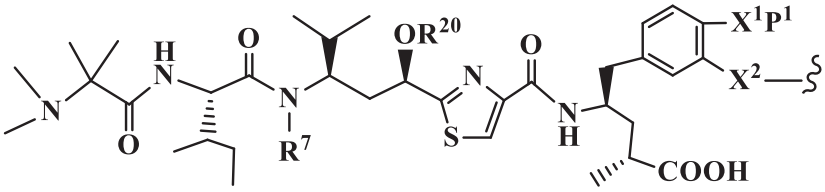
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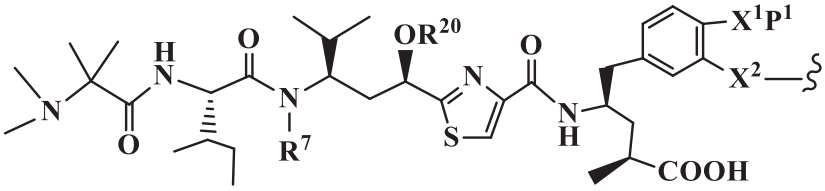
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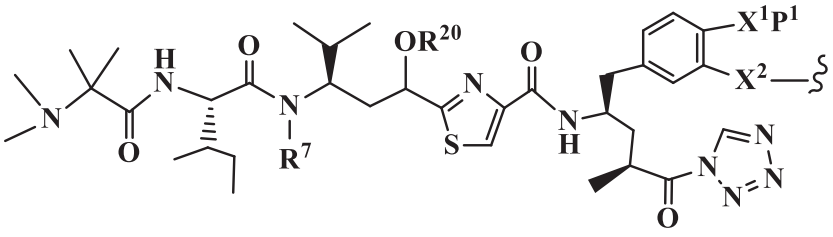
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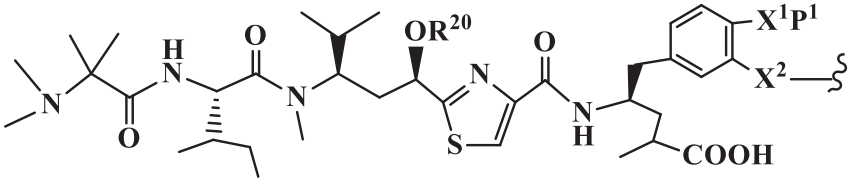
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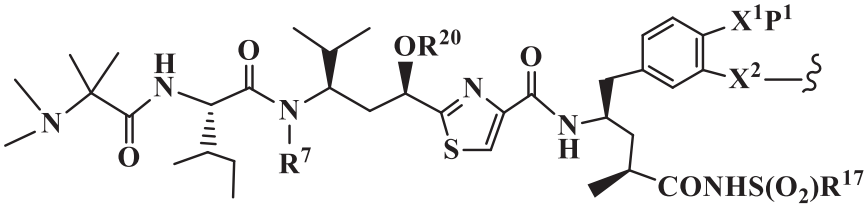
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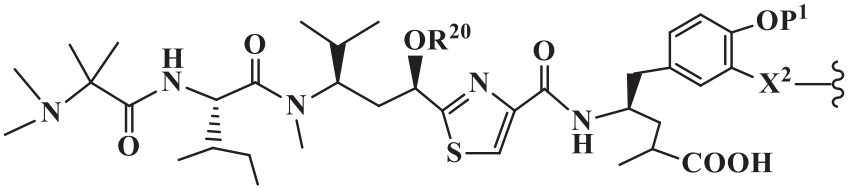
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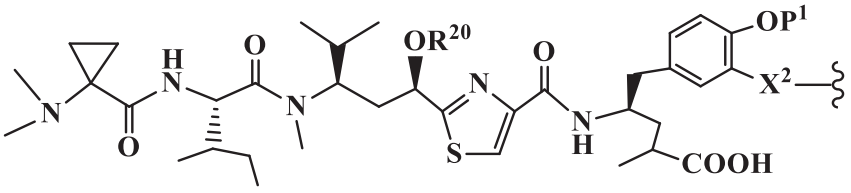
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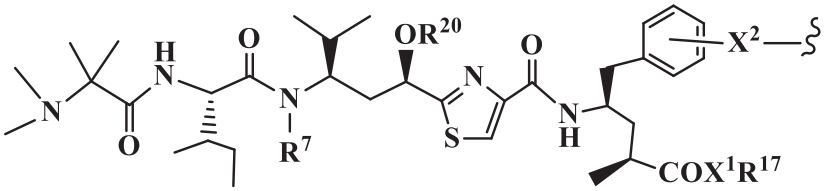
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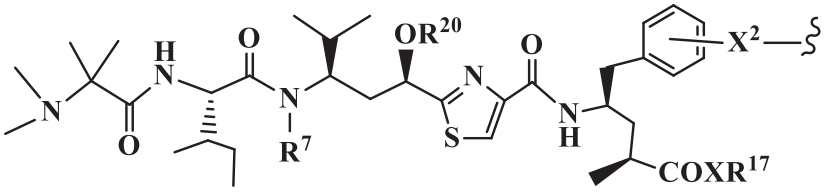
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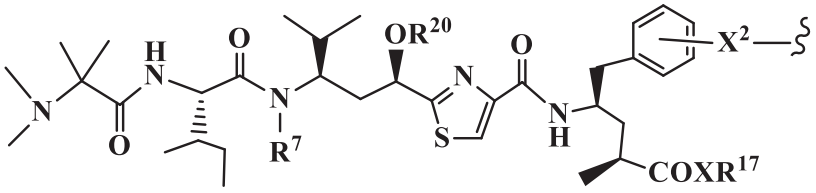
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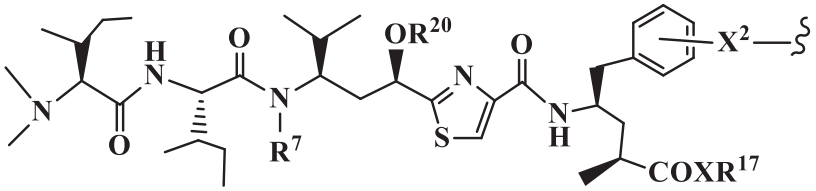
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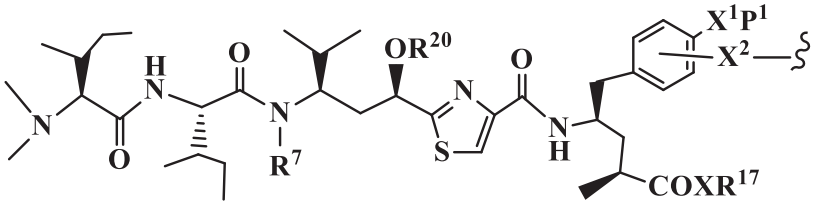
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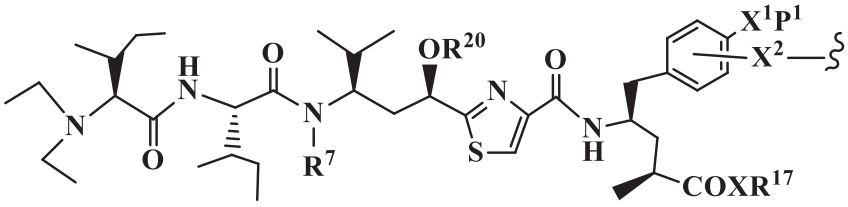
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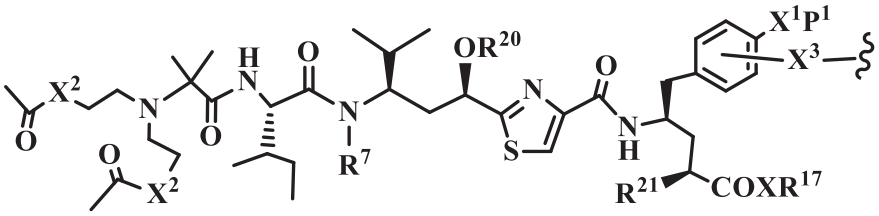
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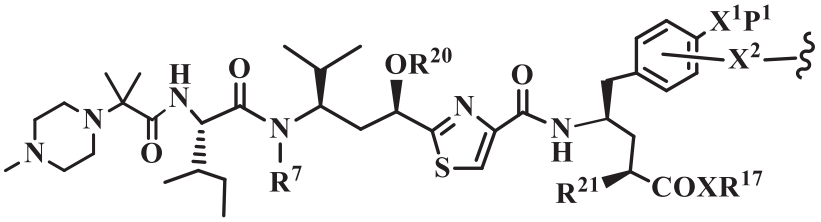
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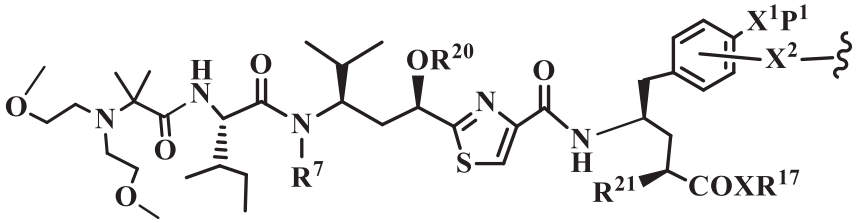
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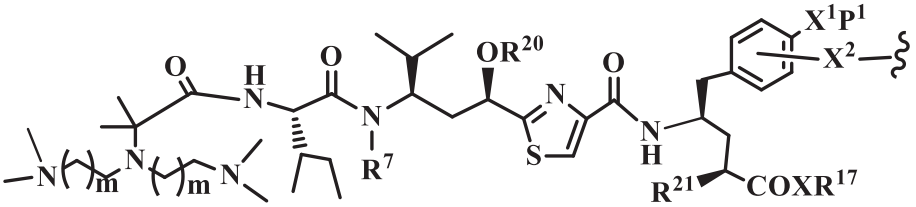
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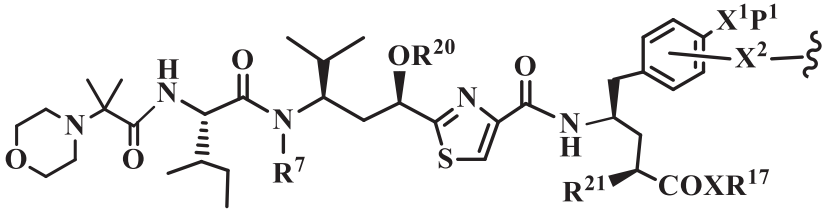
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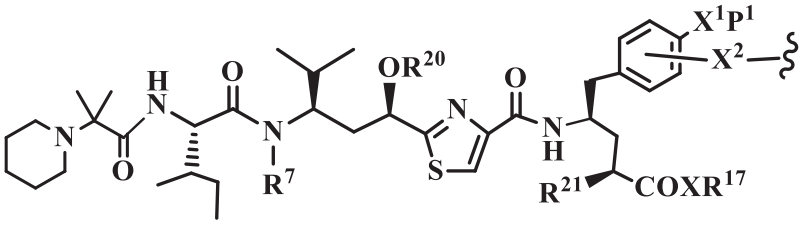
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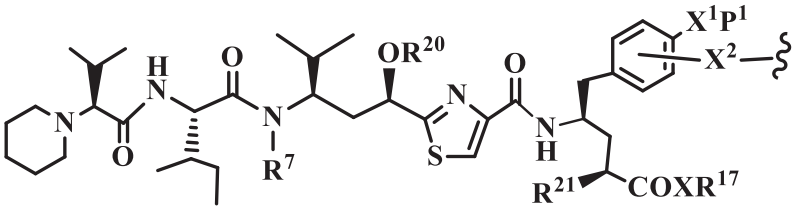
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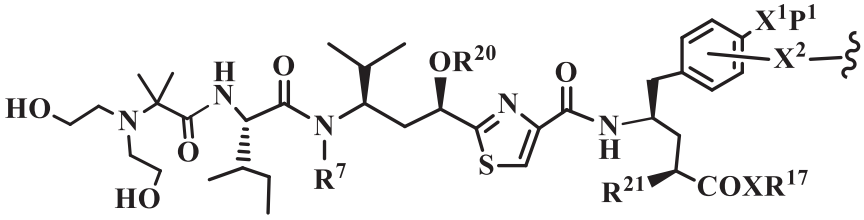
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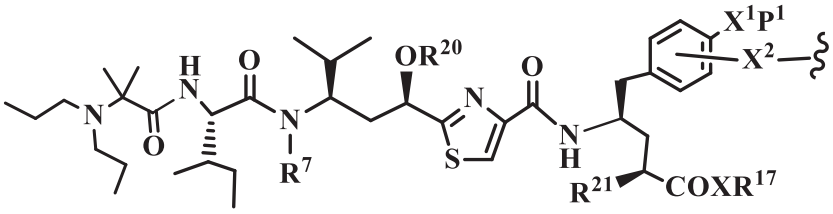
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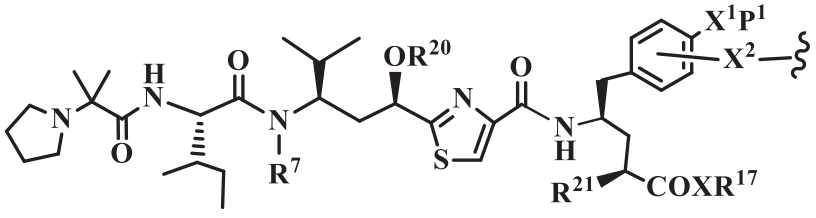
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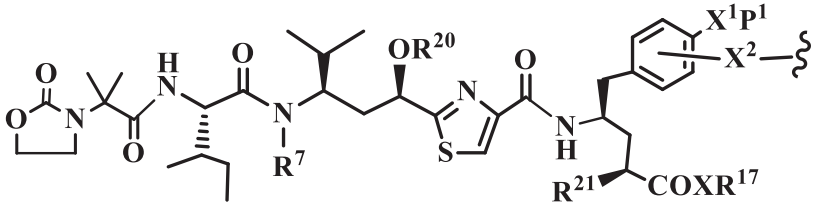
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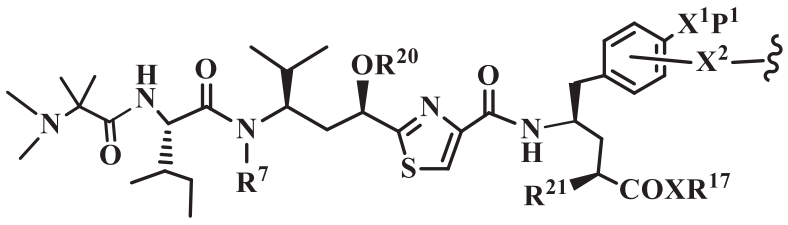
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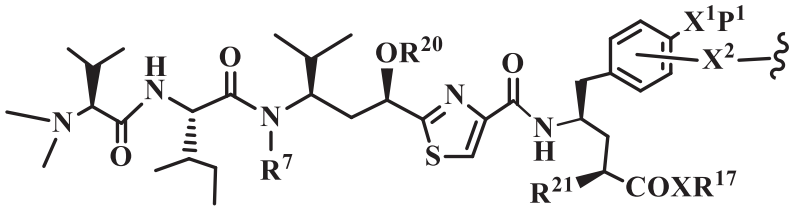
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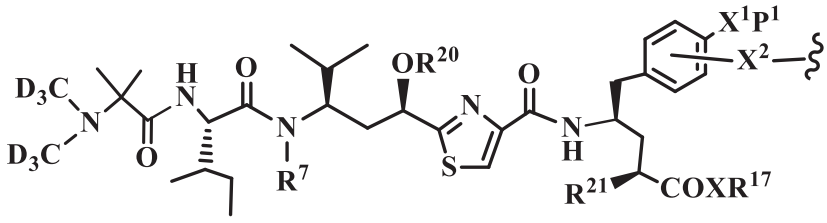
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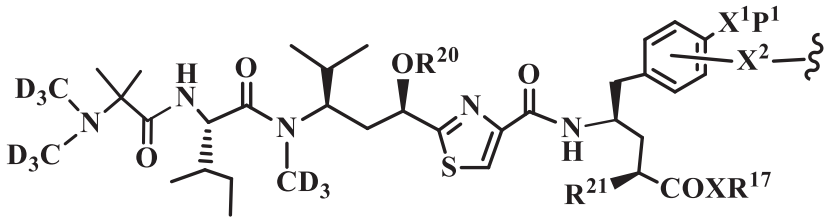
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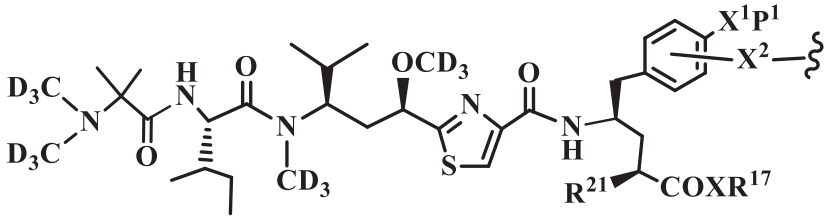
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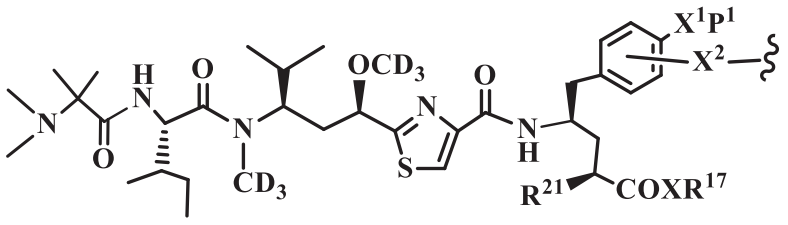
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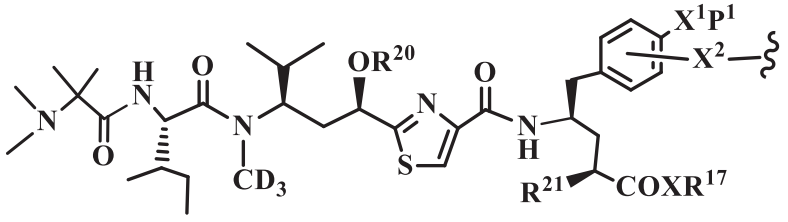
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VII-80,



VII-81,



VII-82,

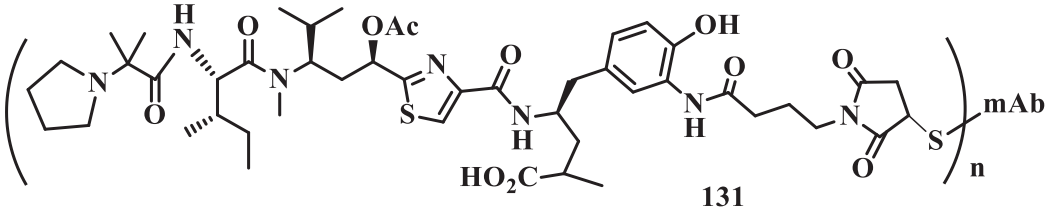
or their pharmaceutically acceptable salts, hydrates, or hydrated salts; or the polymorphic crystalline structures of these compounds; or their isotopes, optical isomers, racemates, diastereomers or enantiomers thereof;

wherein R^{20} is H; C_1-C_8 of linear or branched alkyl, heteroalkyl, or acyl (-C(O)R^{17}); C_2-C_8 of linear or branched alkenyl, alkynyl, alkylcycloalkyl, heterocycloalkyl; C_3-C_8 linear or branched of aryl, Ar-alkyl, heterocyclic, carbocyclic, cycloalkyl, heteroalkylcycloalkyl, alkylcarbonyl, heteroaryl; carbonate (-C(O)OR^{17}), carbamate (-C(O)N$R^{17}R^{18}$); or 1-8 carbon atoms of carboxylate, esters, ether, or amide; or 1~8 amino acids; or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$ or $(OCH_2CH(CH_3))_p$, wherein p is an integer from 0 to about 1000; or R^{20} is absent and the oxygen forms a ketone, or combination above thereof; wherein R^{21} is H, C_1-C_8 of linear or branched alkyl; X^1, X^2, and X^3, are independently O, S, NH, NHNH, NHR^{17}, CH_2 or absent; P^1 is H, R^{17}, $P(O)(OH)_2$, $P(O)(X^1R^{17})_2$, $CH_2P(O)(OH)_2$, $S(O^2)(X^1R^{17})$, $C_6H_{12}O_5$ (glycoside), $(CH_2CH_2O)_pR^{17}$, wherein p is selected from 0 -100,and R^{17} is defined above;

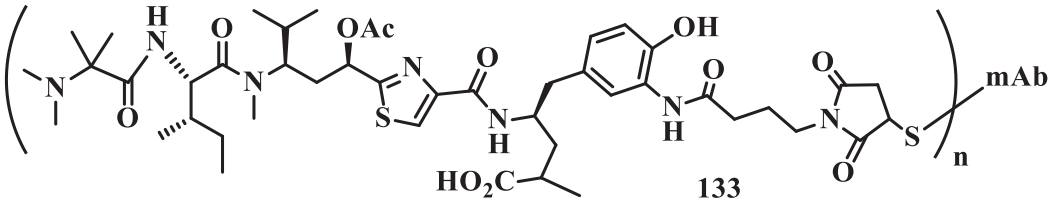
wherein $Z^2$and Z^3 are independently H, OH, NH_2, OR^{17}, NHR^{17}, COOH, COOR^{17}, C(O)R^{17}, C(O)NHR^{17}, C(O)N$HNHR^{17}$, C(O)NH_2, R^{18}, OCH_2OP(O)$(OR^{18})_2$, OC(O)OP(O)$(OR^{18})_2$, OP$O(OR^{18})_2$, NHP$O(OR^{18})_2$, OP(O)(OR^{18})OP(O)$(OR^{18})_2$, OC(O)R^{18}, OC(O)NHR^{18}, $OSO_2(OR^{18})$, O-(C_4-C_{12}-glycoside), C_1-C_8 of linear or branched alkyl or heteroalkyl; C_2-C_8 of linear or branched alkenyl, alkynyl, alkylcycloalkyl, heterocycloalkyl; C_3-C_8 linear or branched of aryl, Ar-alkyl, heterocyclic, carbocyclic, cycloalkyl, heteroalkylcycloalkyl, alkylcarbonyl, heteroaryl; carbonate (-C(O)OR^{17}), carbamate (-C(O)N$R^{17}R^{18}$); $R^{17}$and R^{18} are independently H, C_1-C_8 linear or branched alkyl or heteroalkyl; C_2-C_8 of linear or branched alkenyl, alkynyl, alkylcycloalkyl, heterocycloalkyl; C_3-C_8 linear or branched of aryl, Ar-alkyl, heterocyclic, carbocyclic, cycloalkyl, heteroalkylcycloalkyl, alkylcarbonyl, heteroaryl; carbonate (-C(O)OR^{17}), carbamate (-C(O)N$R^{17}R^{18}$); $R^{19}$is H, OH, NH_2, $OSO_2(OR^{18})$, XCH_2OP(O)$(OR^{18})_2$, XP$O(OR^{18})_2$, XC(O)OP(O)$(OR^{18})_2$, XC(O)R^{18}, XC(O)NHR^{18}, C_1~C_8 alkyl or carboxylate; C_2~C_8 alkenyl, alkynyl, alkylcycloalkyl, heterocycloalkyl; C_3~C_8 aryl or alkylcarbonyl; or pharmaceutical salts; X is O, S, NH, NHNH, NHR^{17}, or CH_2; R^1 and R^7 are defined in Claim 1; m is 1-10.

wherein "≀" is the site that linked to a linker L.

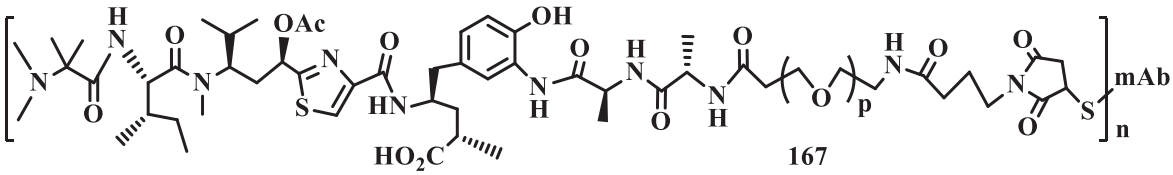
9. The pharmaceutical composition according to claims **1**, wherein the conjugate of tubulysin analog have the following structures:



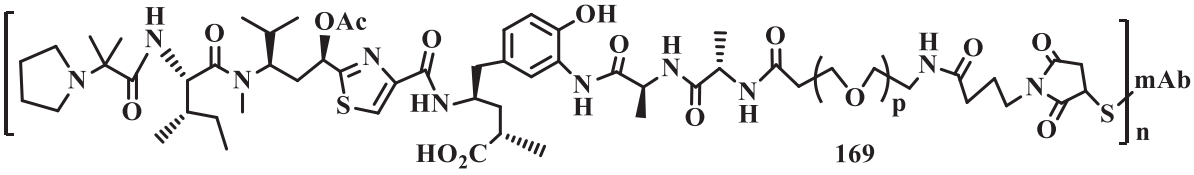
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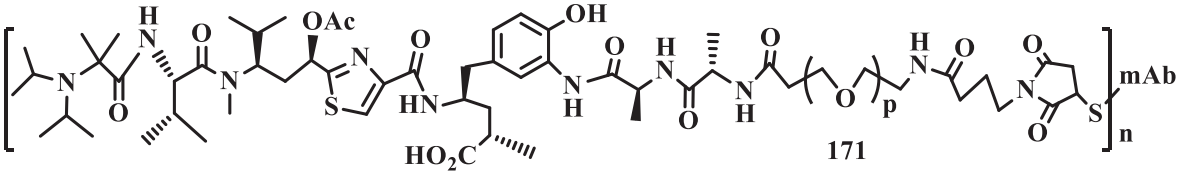
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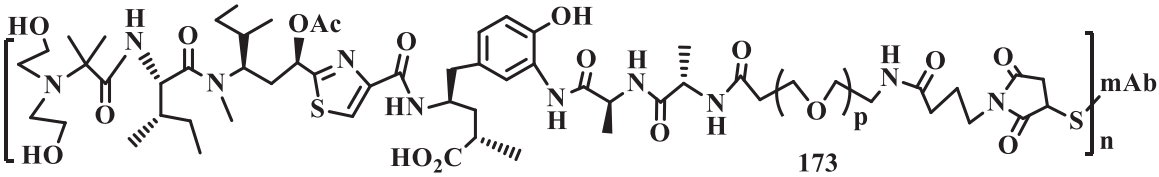
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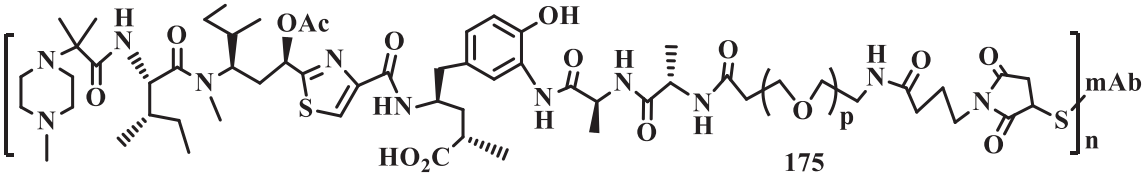
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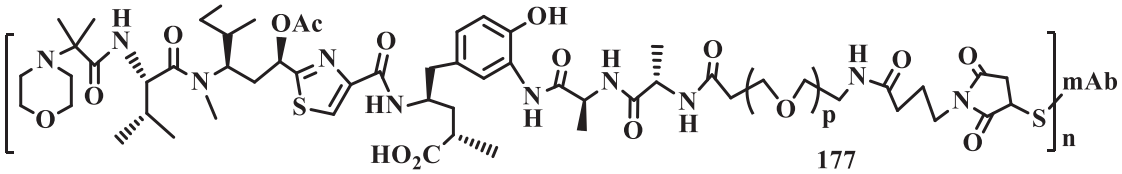
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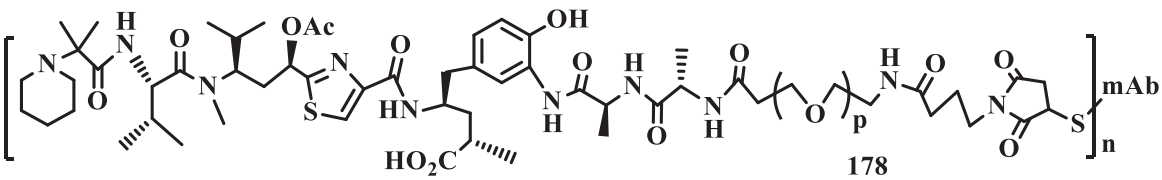
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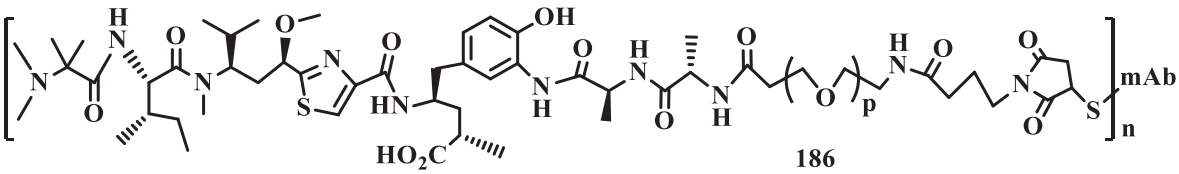
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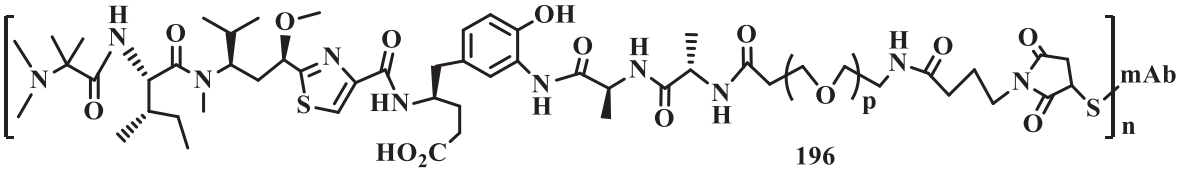
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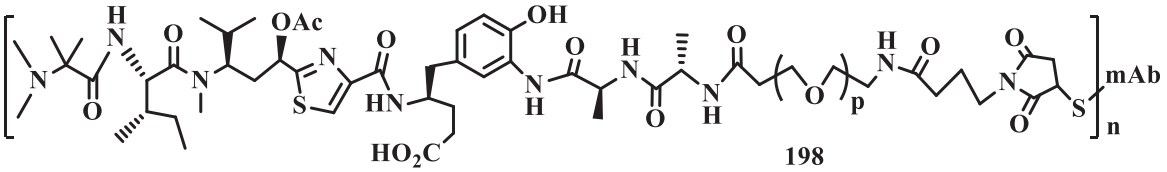
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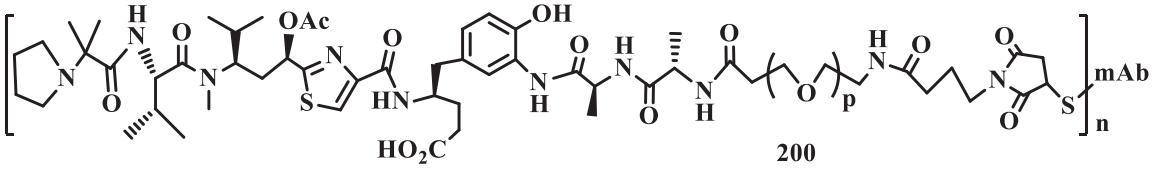
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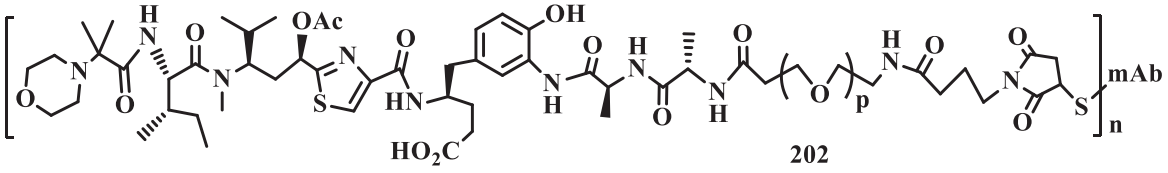
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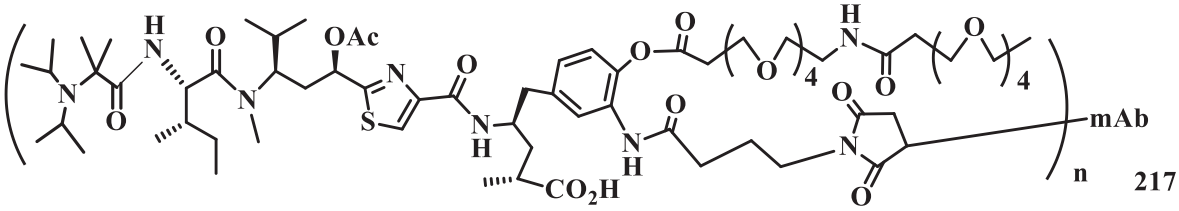
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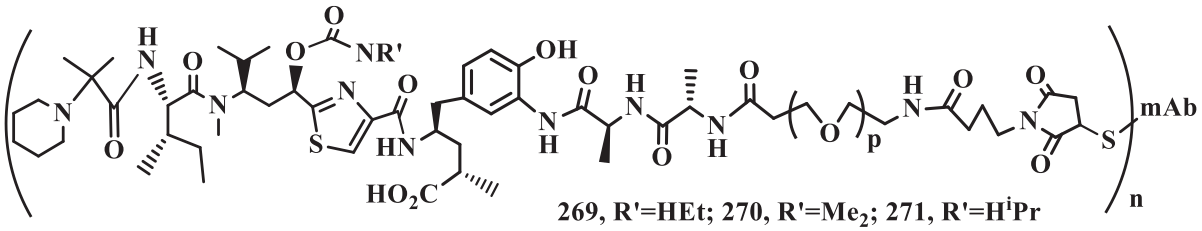
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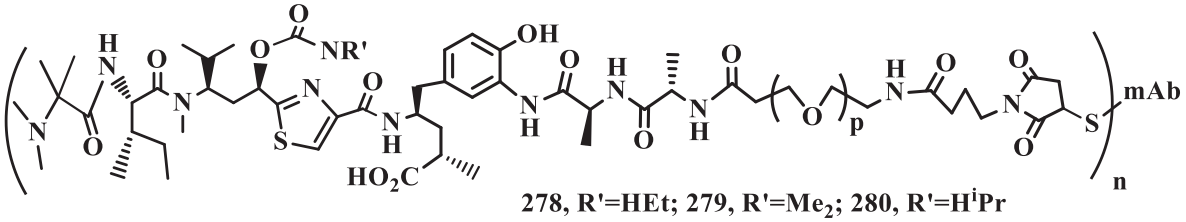
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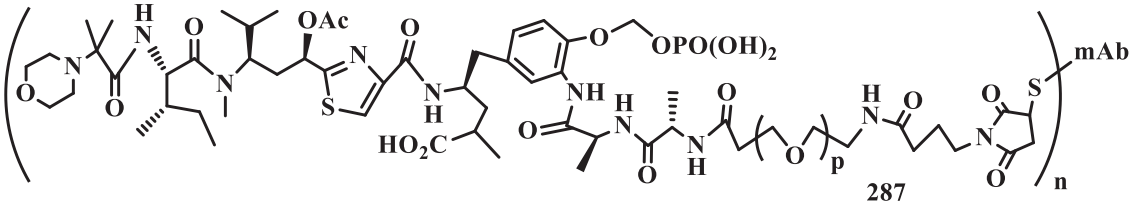
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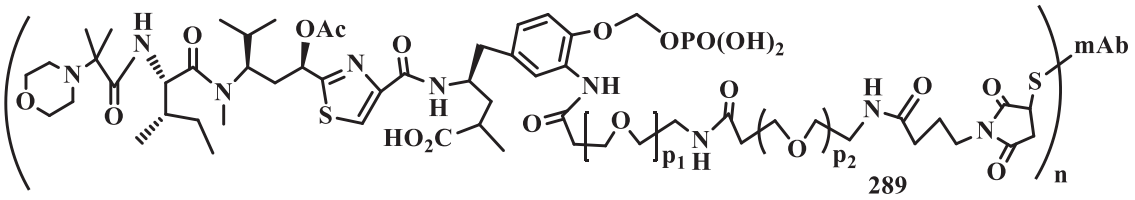
269, R'=HEt; 270, R'=Me_2; 271, R'=H^{i}Pr



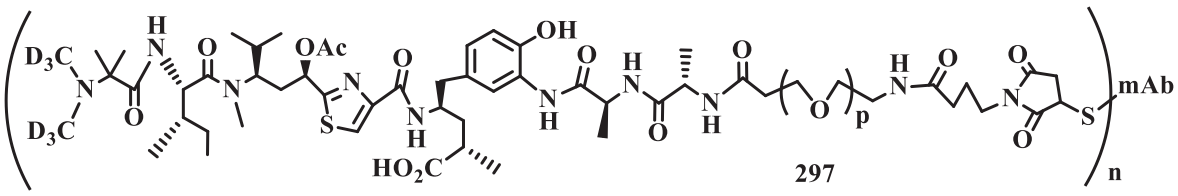
278, R'=HEt; 279, R'=Me_2; 280, R'=H^{i}Pr



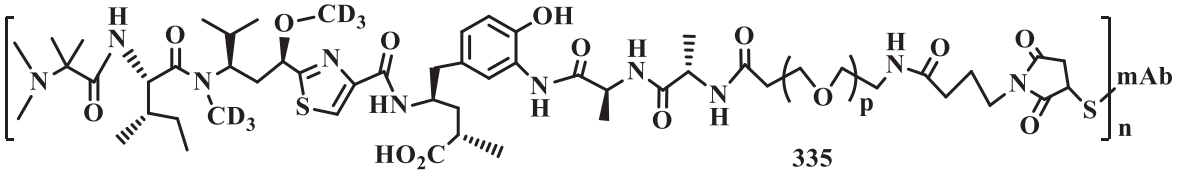
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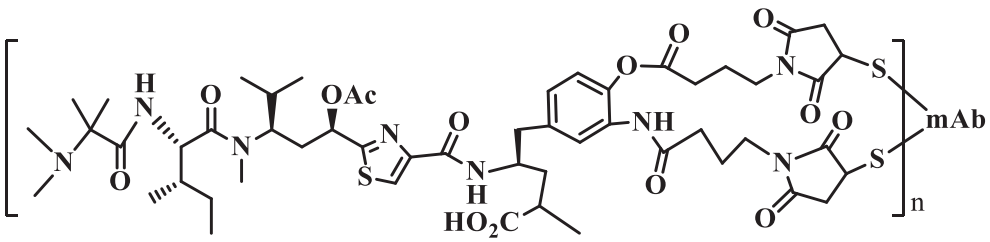
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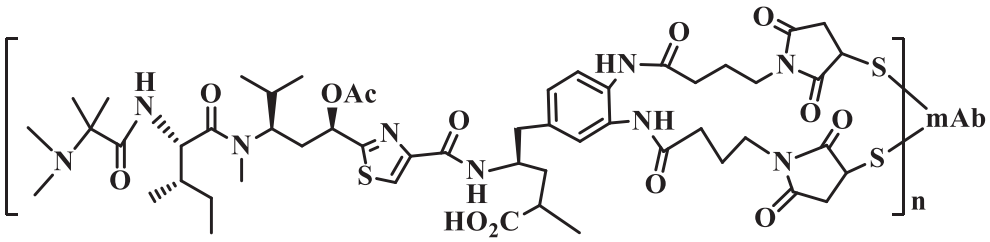
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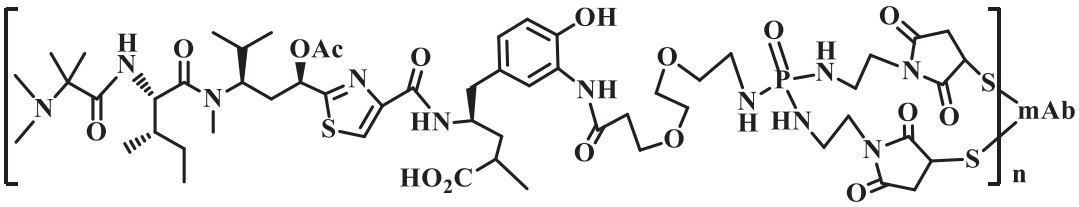
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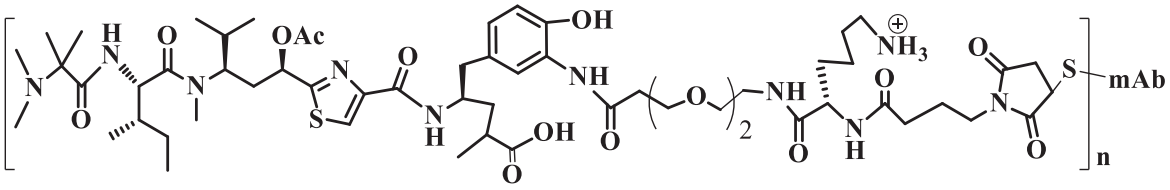
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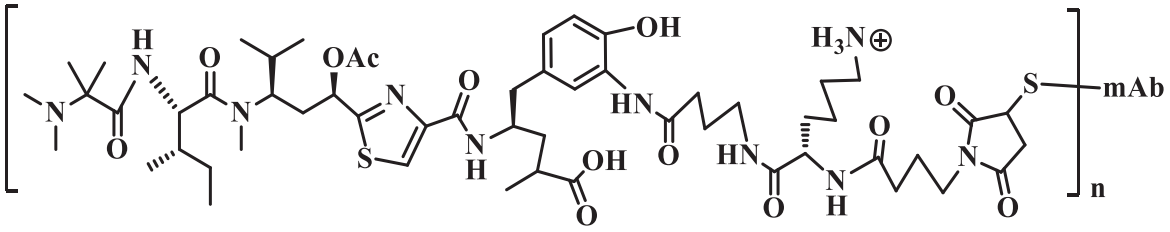
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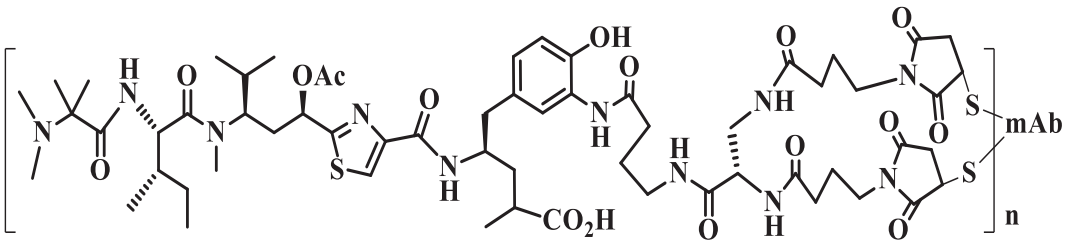
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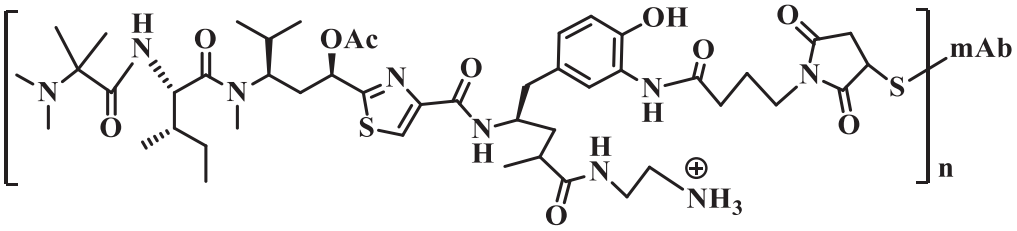
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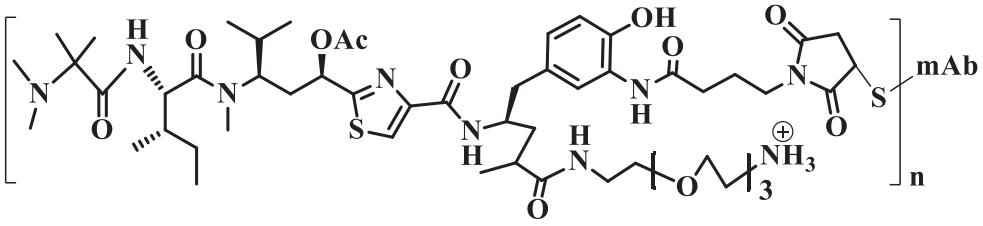
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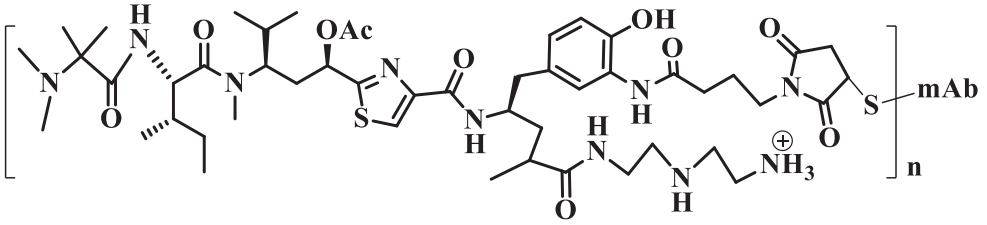
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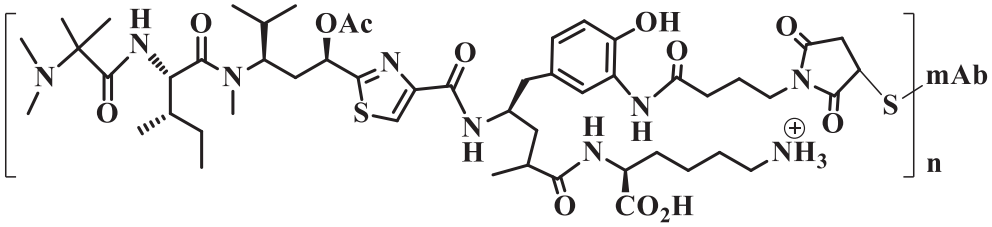
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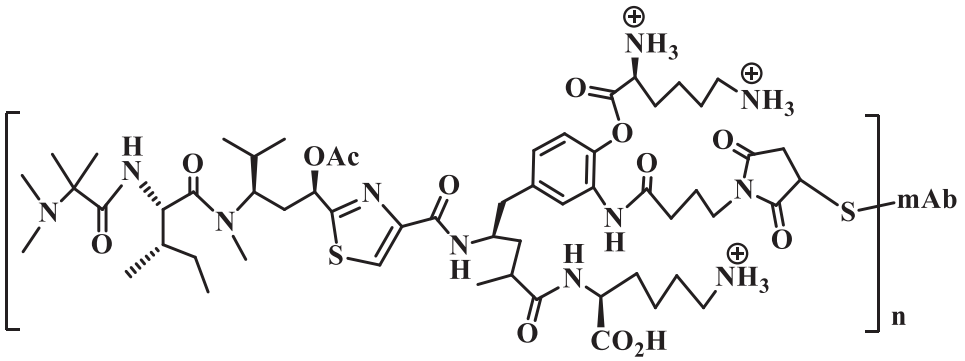
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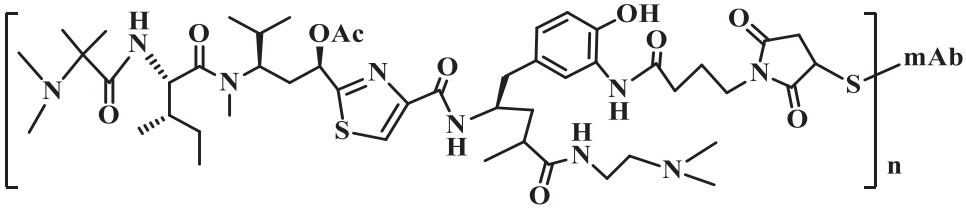
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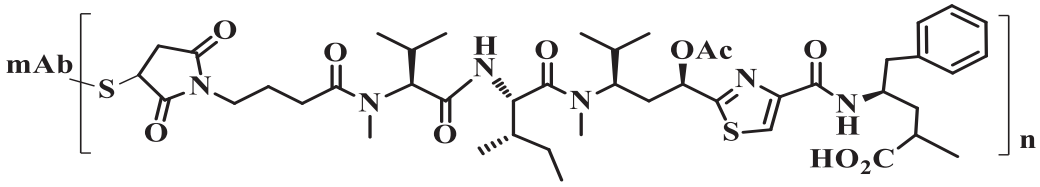
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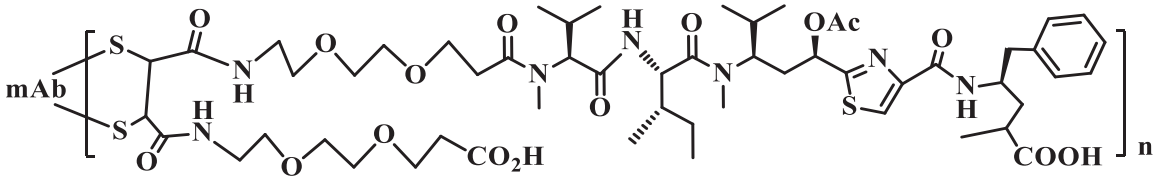
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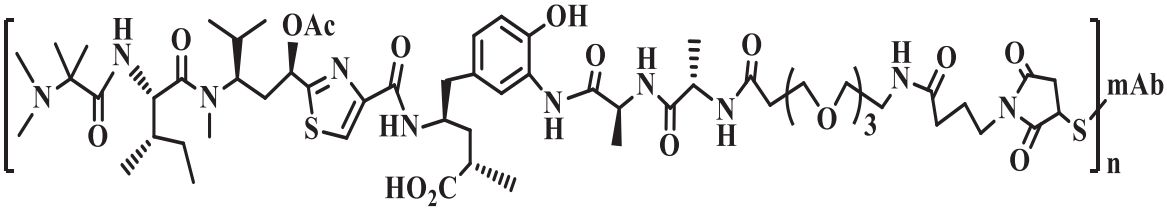
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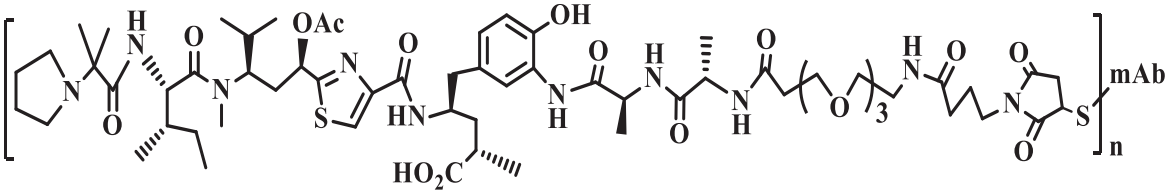
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C-712,



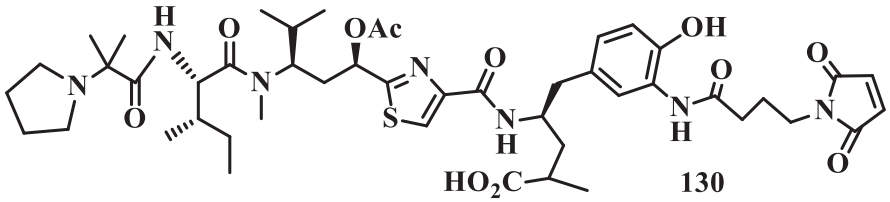
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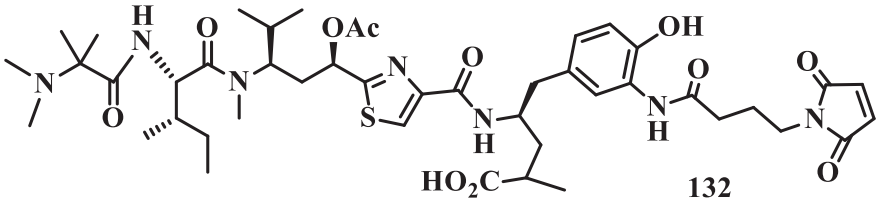
C-719,

wherein mAb is a a targeting or cell-binding molecule; n is 1 ~20; p, p1 and p2 is 0~100.

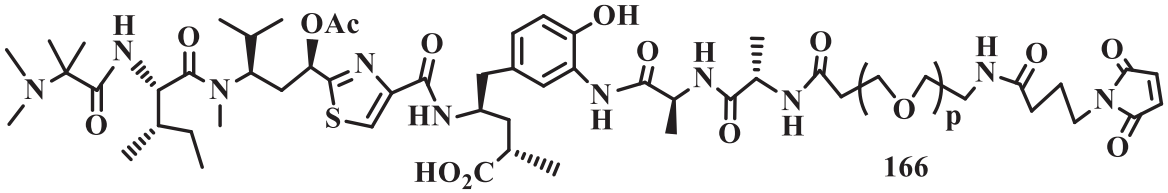
10. The pharmaceutical composition according to claim 9, wherein the conjugates of tubulysin analog are made from the following structures:



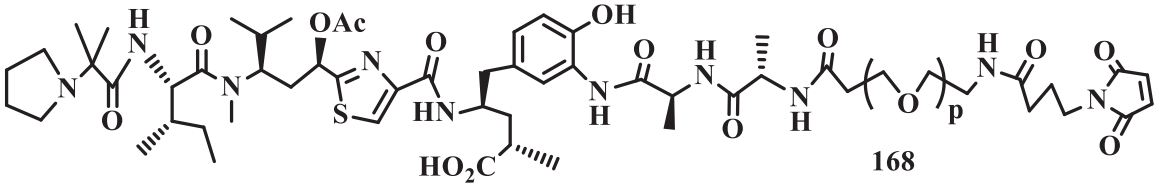
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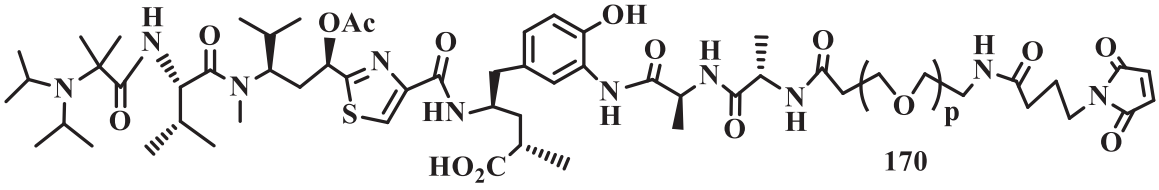
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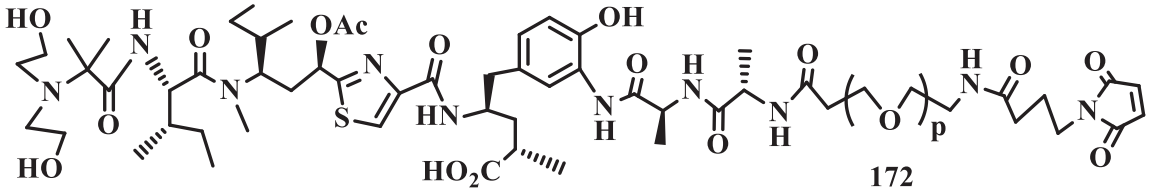
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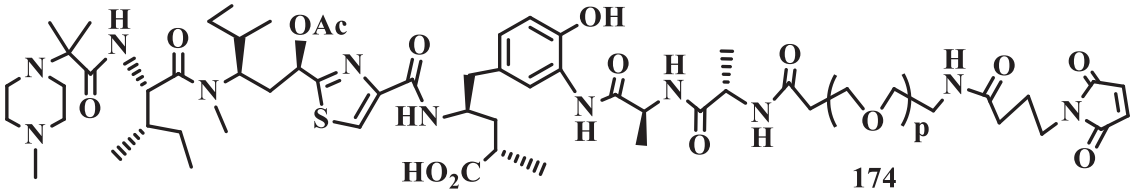
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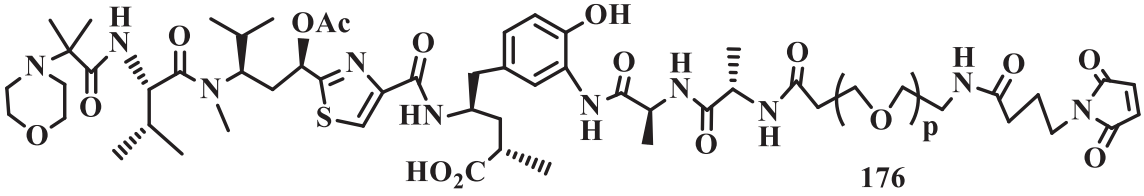
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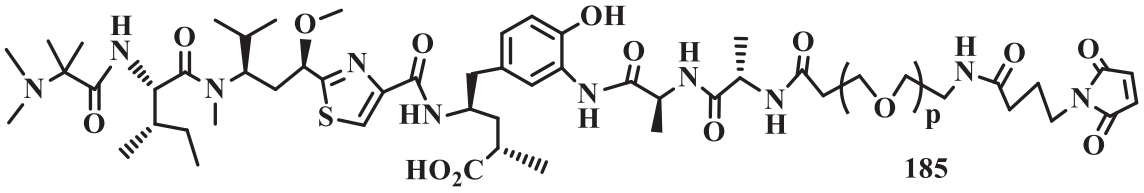
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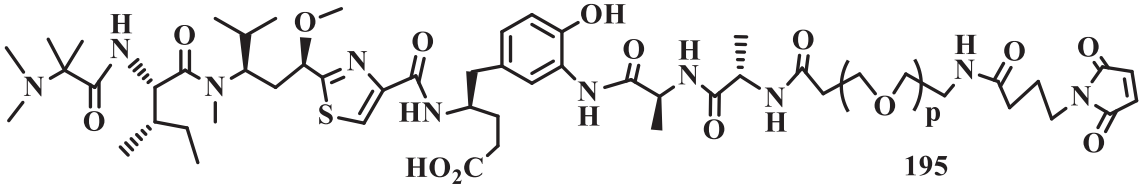
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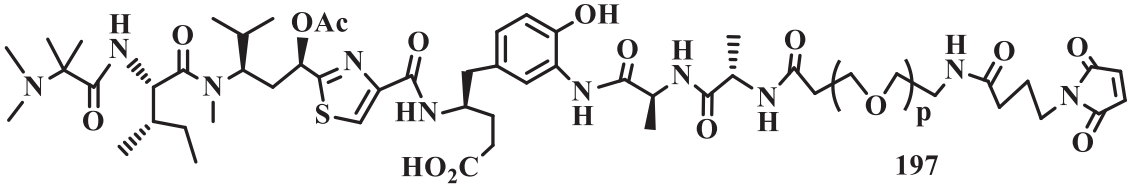
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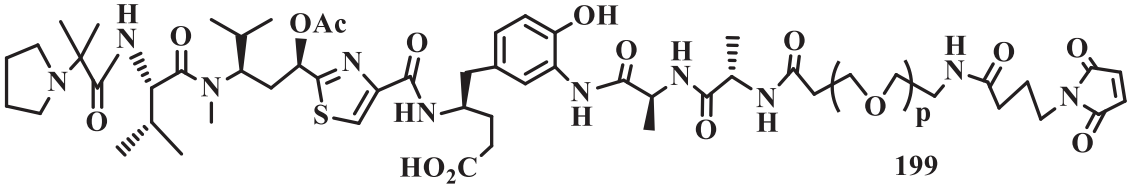
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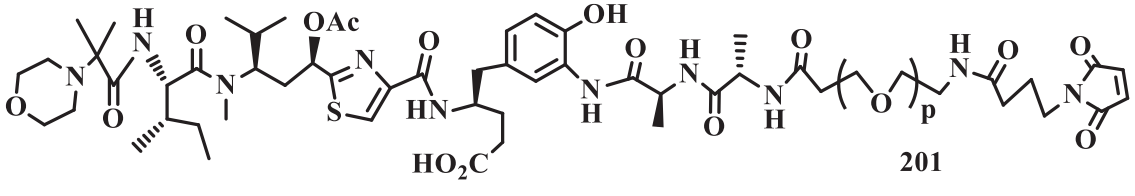
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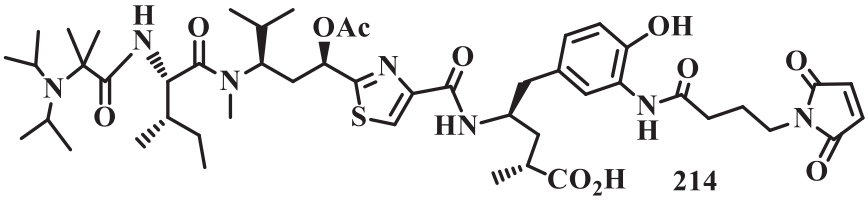
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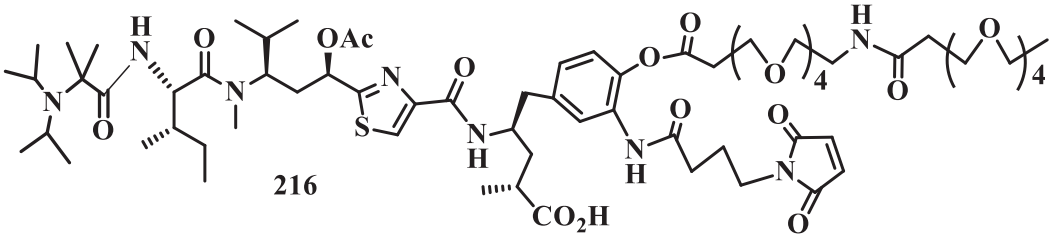
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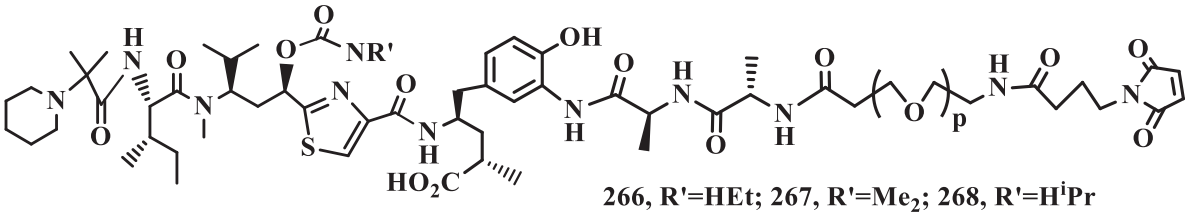
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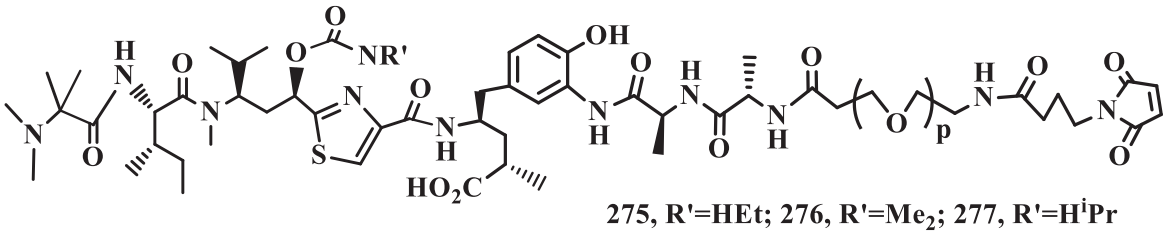
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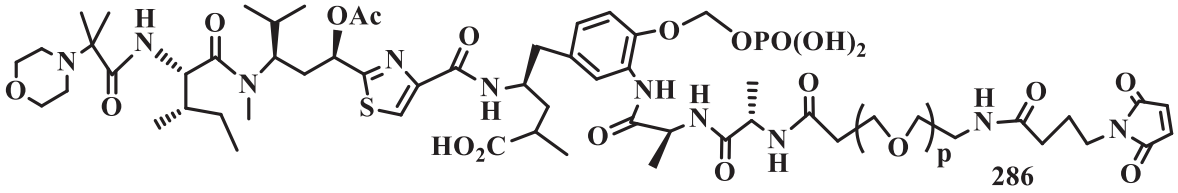
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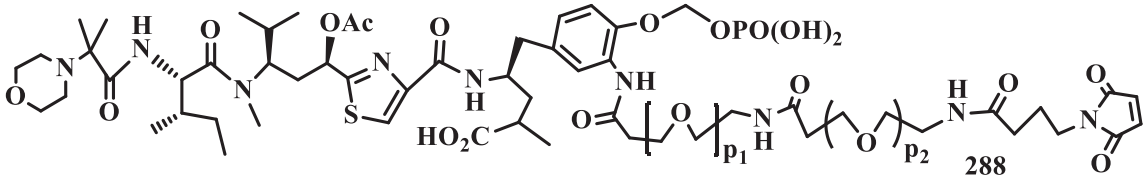
266, R'=HEt; 267, R'=Me_2; 268, R'=H^{i}Pr



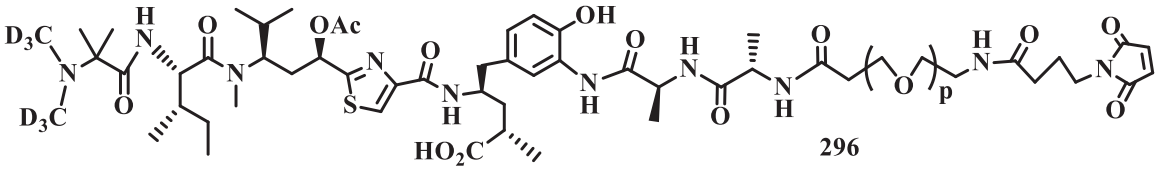
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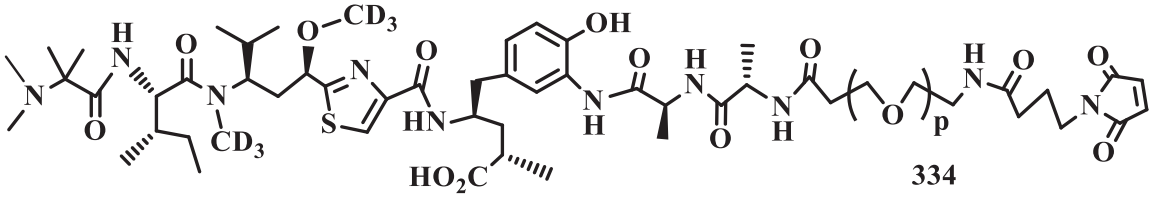
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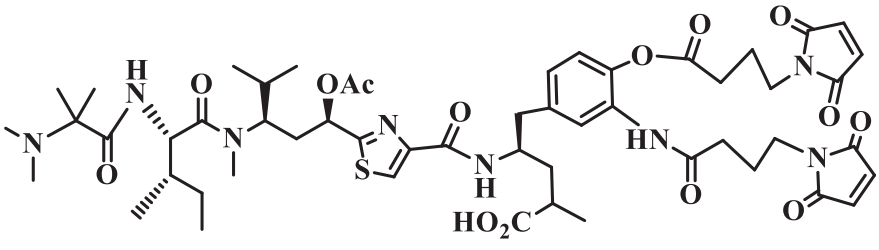
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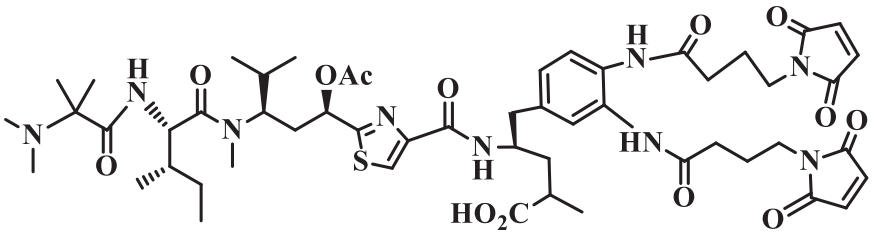
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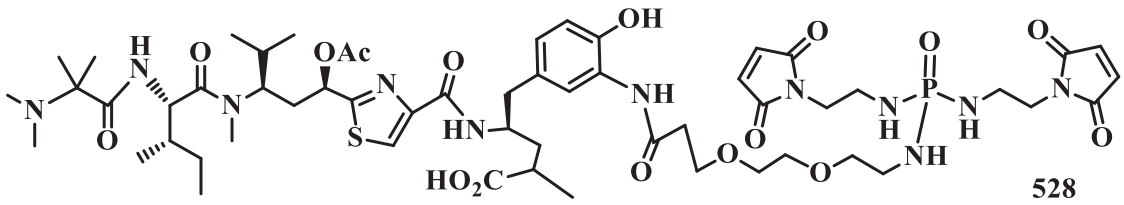
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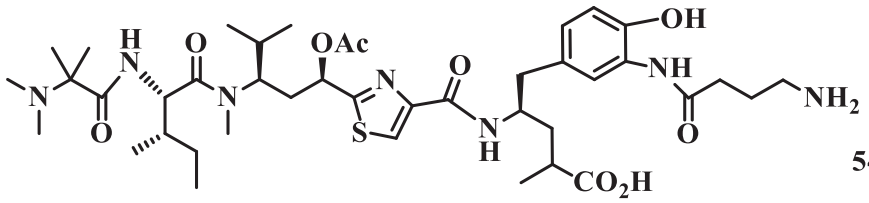
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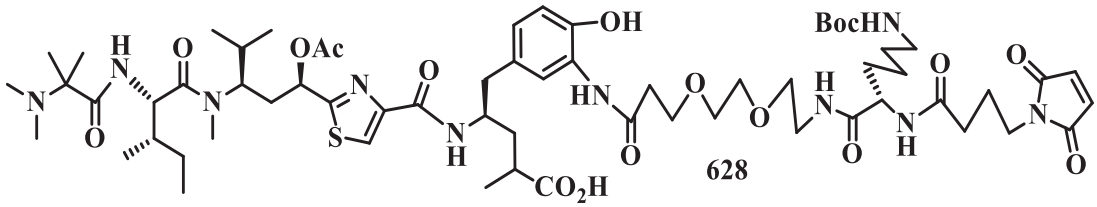
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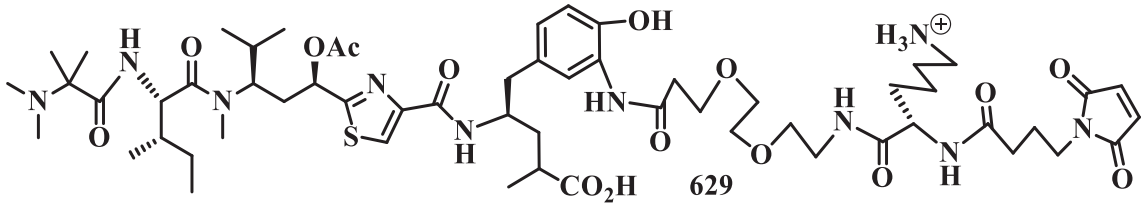
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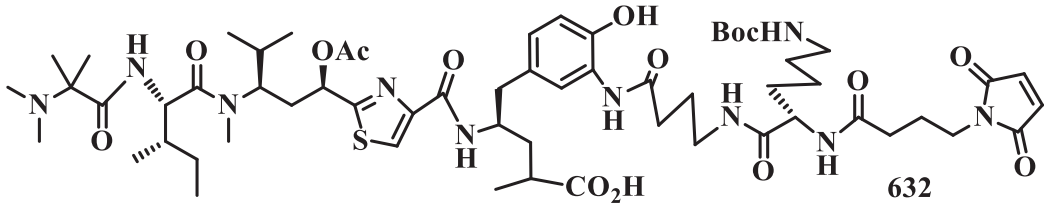
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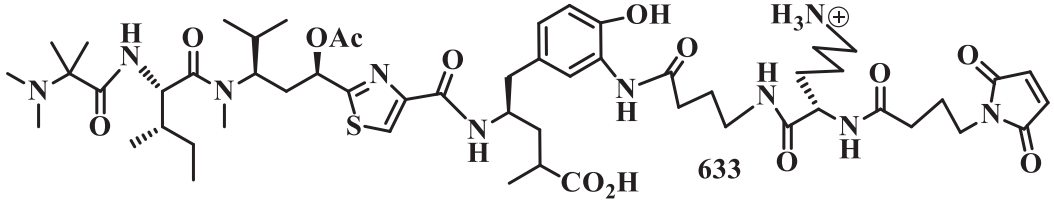
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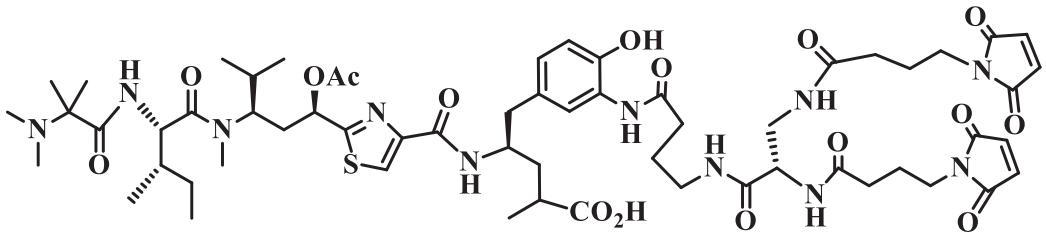
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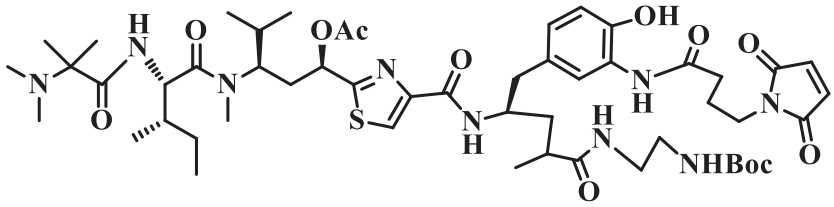
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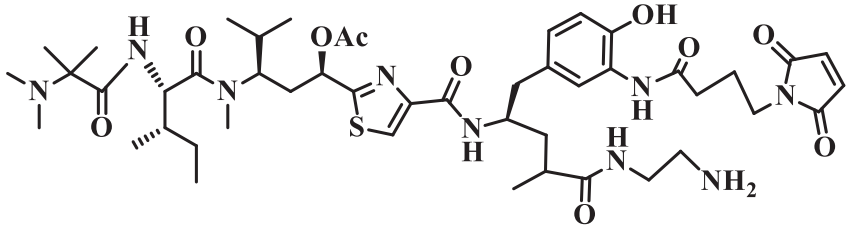
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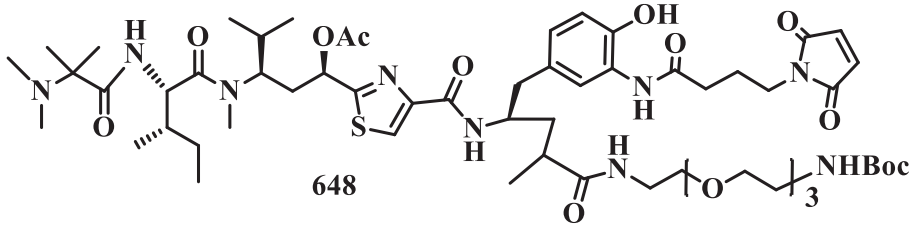
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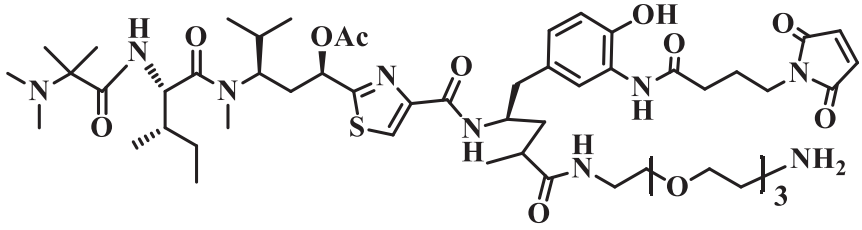
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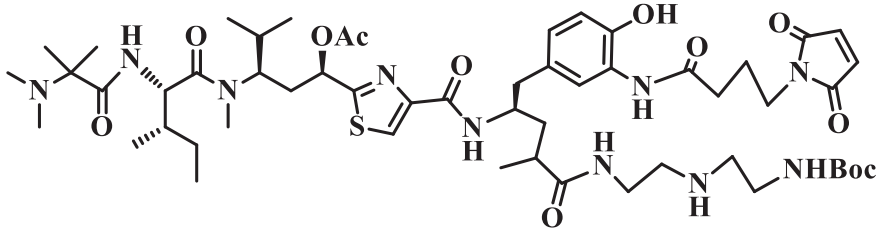
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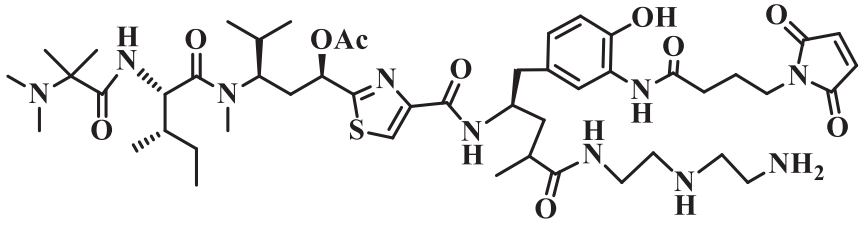
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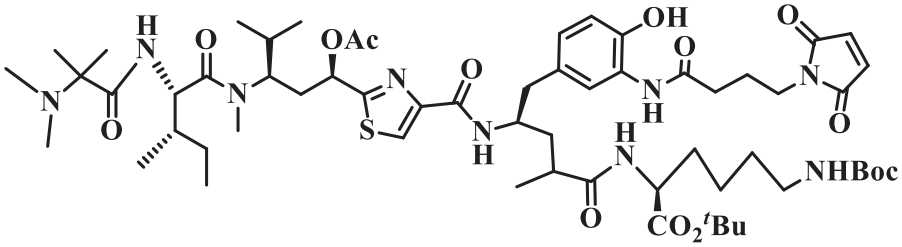
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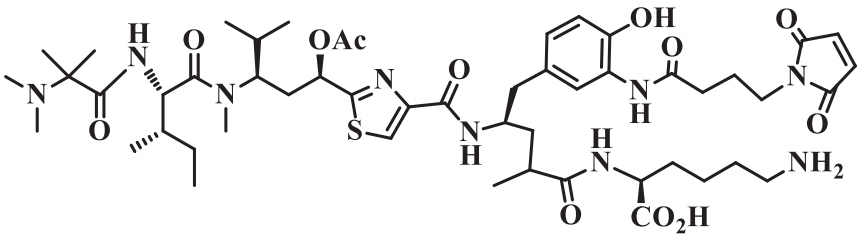
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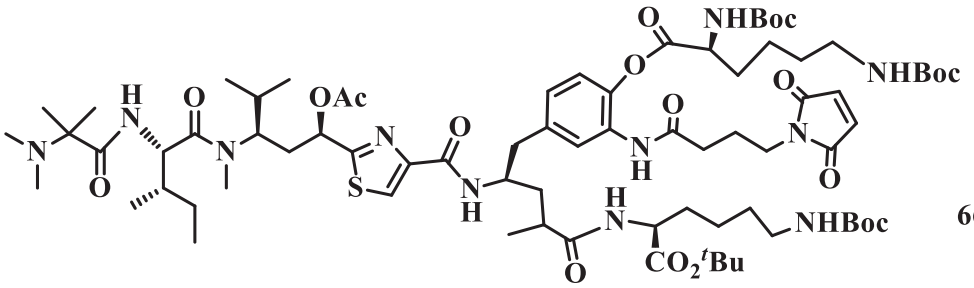
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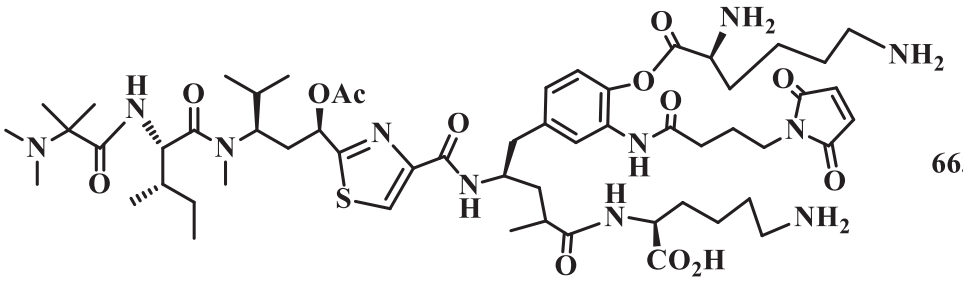
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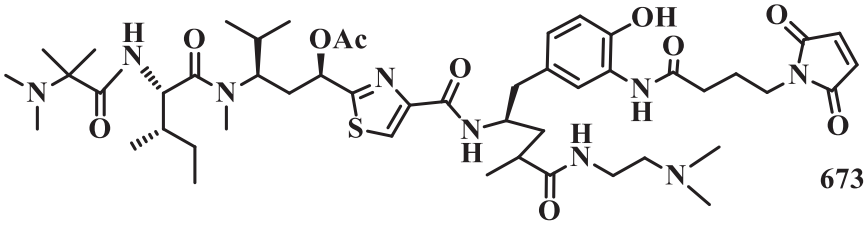
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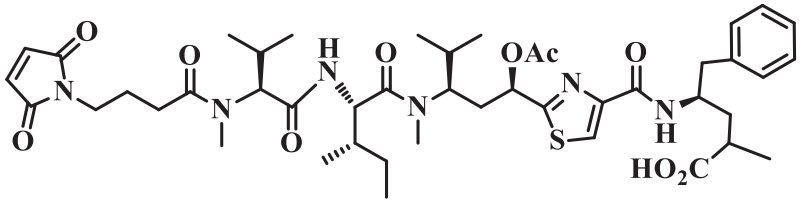
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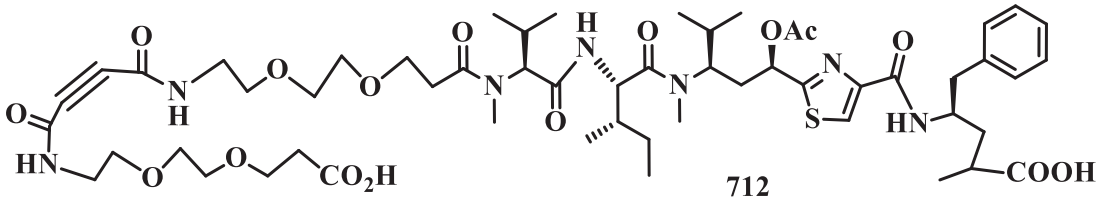
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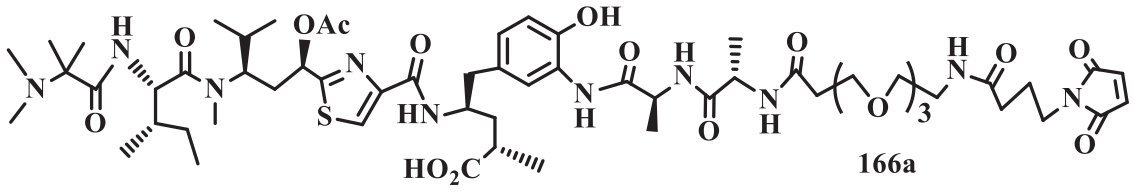
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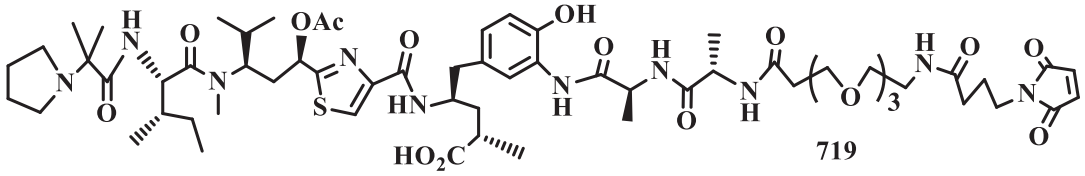
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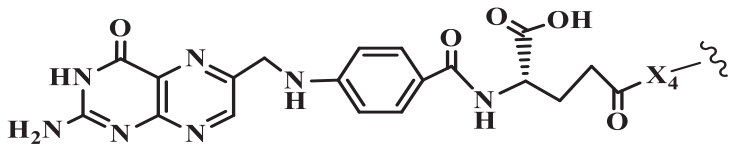


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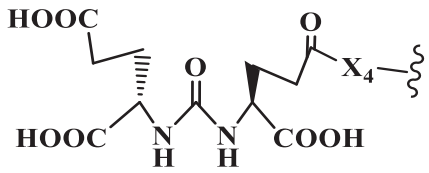


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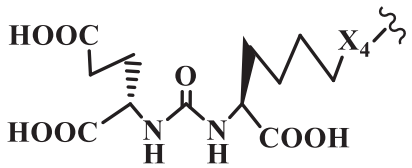
11. The pharmaceutical composition according to any one of claims **1, 2, 3, 4, 5, 6, 7,** or **9**, wherein the targeting or cell-binding molecule is an Ig-based protein scaffold molecule selected from Nanobody (a derivative of VHH (camelid Ig)), Domain antibodies (dAb, a derivative of VH or VL domain), Bispecific cell Engager (BiTE, a bispecific diabody), bispecific antibody, trispecific antibody, Dual Affinity ReTargeting (DART, a bispecific diabody); Tetravalent tandem antibodies (TandAb, a dimerized bispecific diabody); biparatopic antibody; a non-Ig-based protein scaffold molecule selected from Anticalin (a derivative of Lipocalins), Adnectins (10th FN3 (Fibronectin)), Designed Ankyrin Repeat Proteins (DARPins) (a derivative of ankrin repeat (AR) proteins), DARPin C9, DARPin Ec4 and DARPin E69_LZ3_E01, Avimers (a domain A/low-density lipoprotein (LDL) receptor); a small molecule itself or a small molecule coated on a protein, a nano particle, a polymer, a micelle or a lipid having the following structure LB01~LB54:



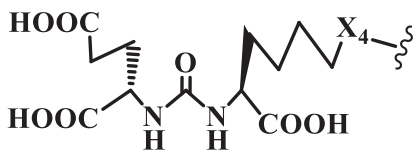
LB01 (Folate derivative),



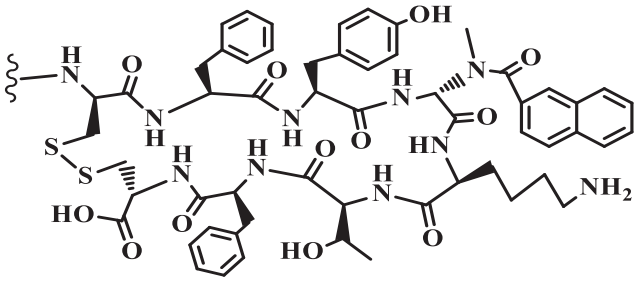
LB02 (PMSA ligand derivative),



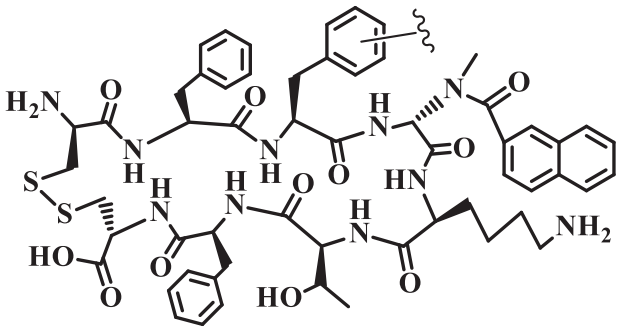
LB03 (PMSA ligand derivative),



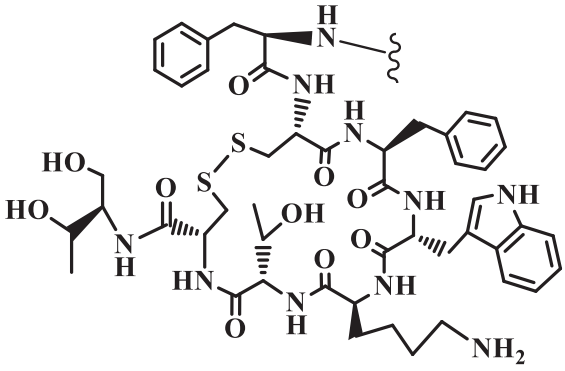
LB04 (PMSA ligand),



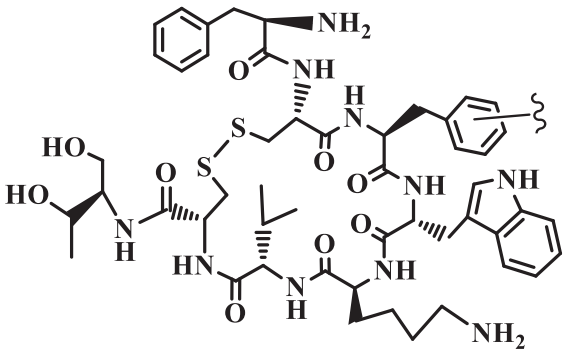
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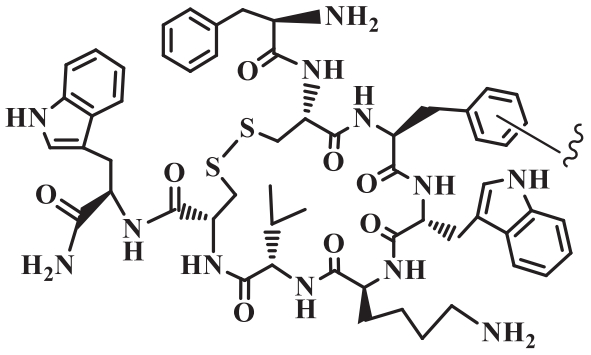
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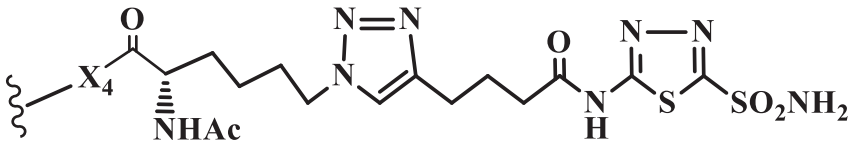
LB07 (Octreotide, a Somatostatin analog),



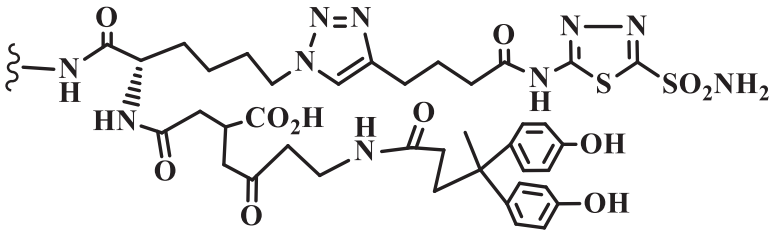
LB08 (Lanreotide, a Somatostatin analog),



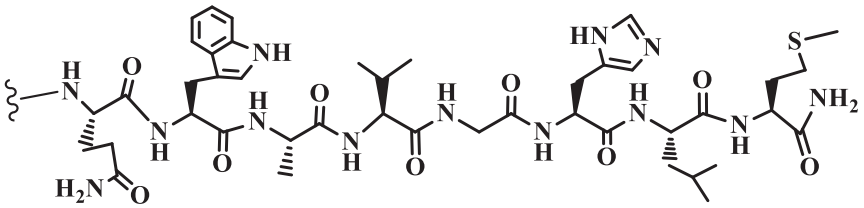
LB09 (Vapreotide (Sanvar), a Somatostatin analog),



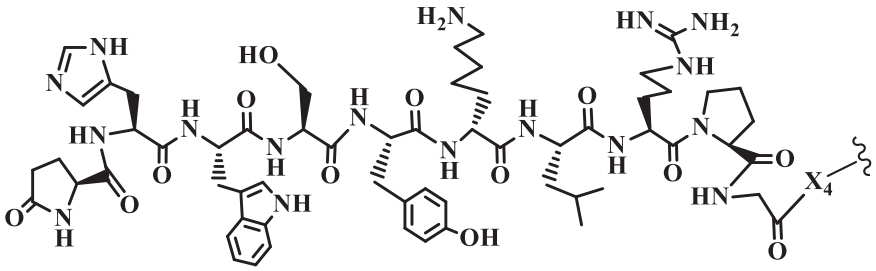
LB10 (CAIX ligand),



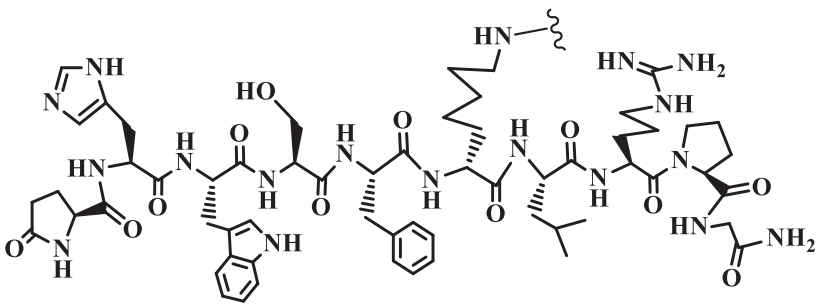
LB11 (CAIX ligand),



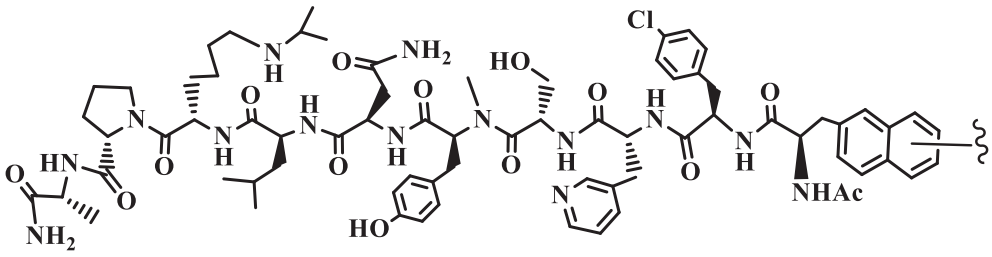
LB12 (Gastrin releasing peptide receptor (GRPr), MBA),



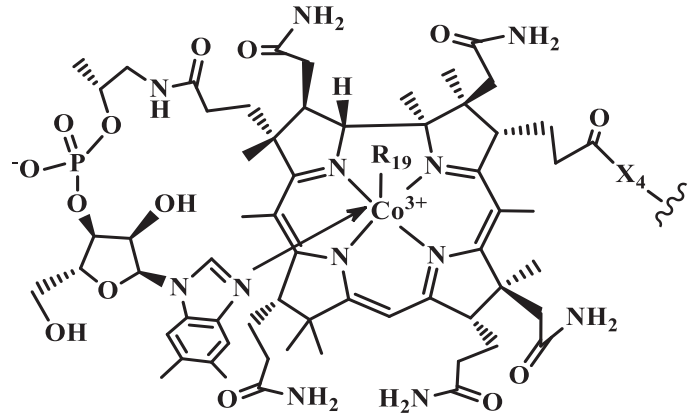
LB13 (luteinizing hormone-releasing hormone (LH-RH) ligand and GnRH),



LB14 (luteinizing hormone-releasing hormone (LH-RH) and GnRH ligand),

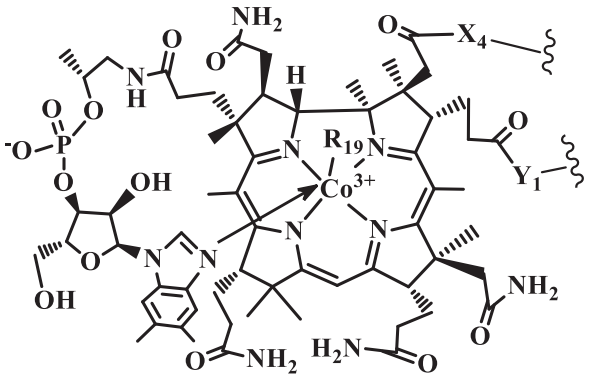


LB15 (GnRH antagonist, Abarelix),

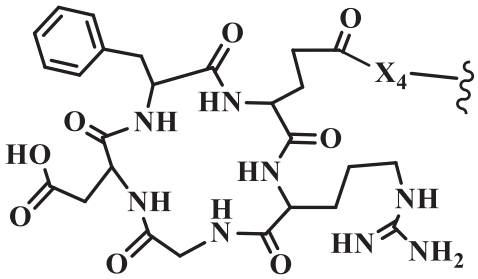


R_{19} is 5'deoxyadenosyl, Me, OH, CN;

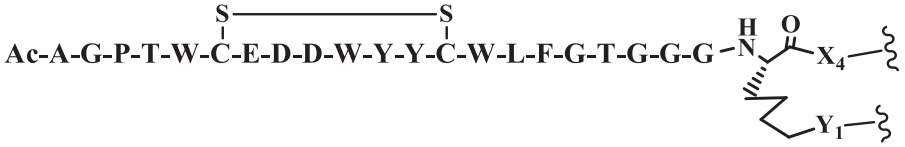
LB16 (cobalamin, vitamin B12 analog),



R_{19} is 5'deoxyadenosyl, Me, OH, CN; LB17 (cobalamin, vitamin B12 analog),



LB18 (for $\alpha_v\beta_3$ integrin receptor, cyclic RGD pentapeptide),



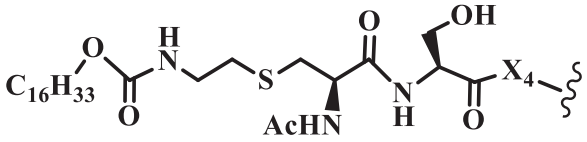
LB19 (hetero-bivalent peptide ligand conjugate for VEGF receptor),



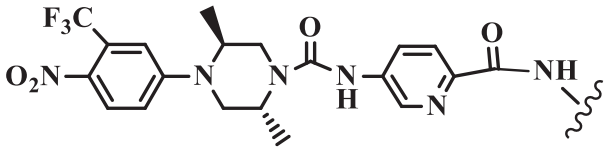
LB20 (Neuromedin B),



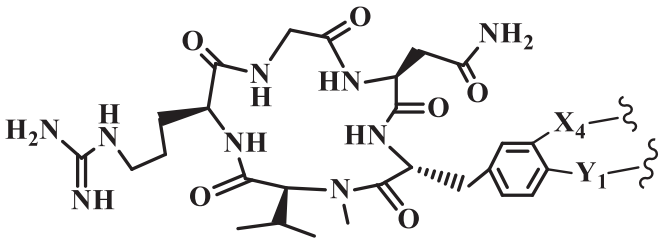
LB21 (bombesin conjugate for a G-protein coupled receptor),



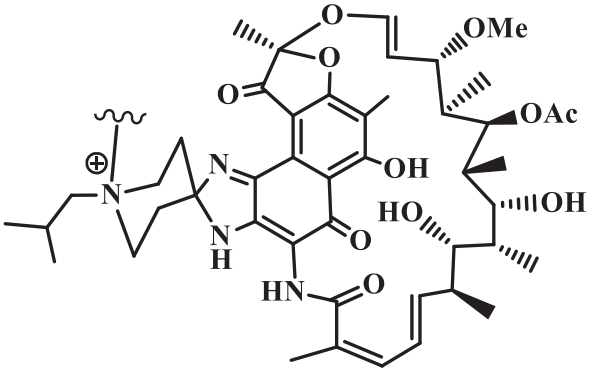
LB22 (TLR_2 conjugate for a Toll-like receptor),



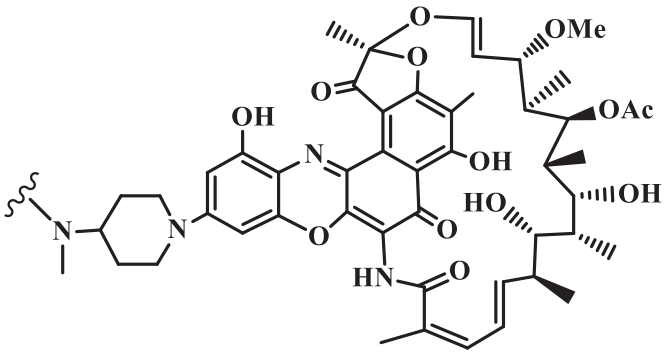
LB23



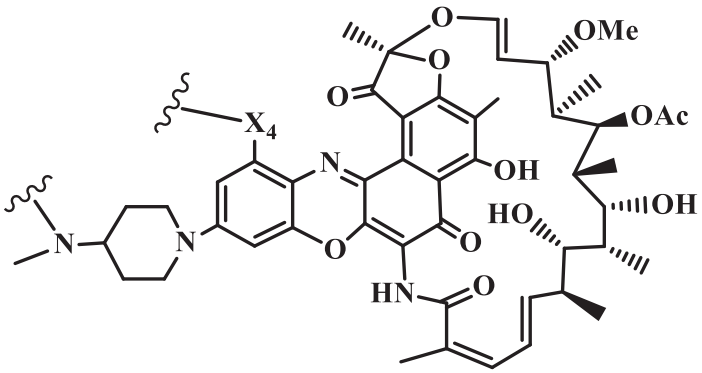
LB24 (Cilengitide/cyclo(-RGDfV-) derivative for an α_v intergrin receptor)



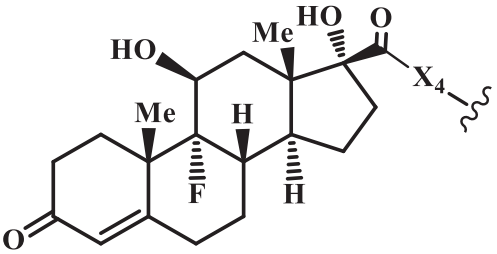
LB25 (Rifabutin analog),



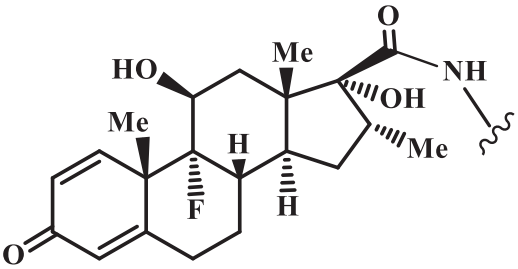
LB26 (Rifabutin analog),



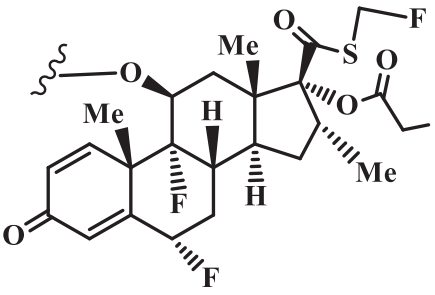
LB27 (Rifabutin analog),



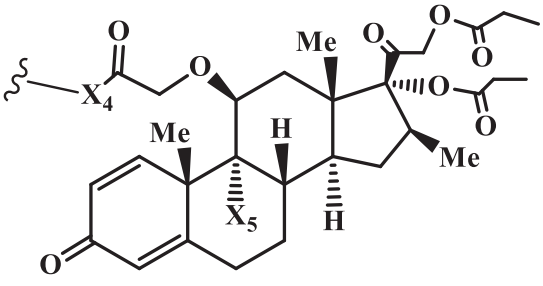
LB28 (Fludrocortisone),



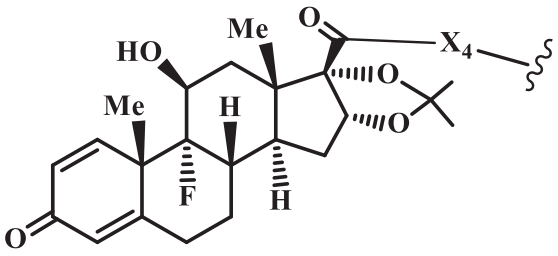
LB29 (Dexamethasone),



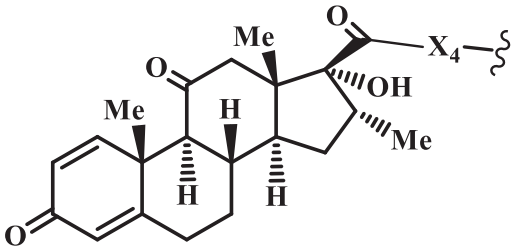
LB30 (fluticasone propionate),



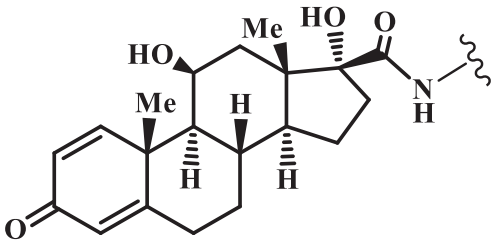
LB31 (Beclometasone dipropionate),



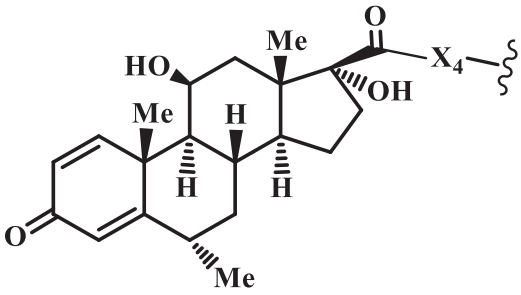
LB32 (Triamcinolone acetonide),



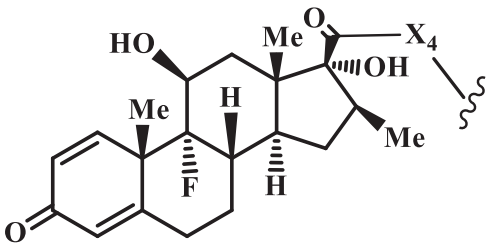
LB33 (Prednisone),



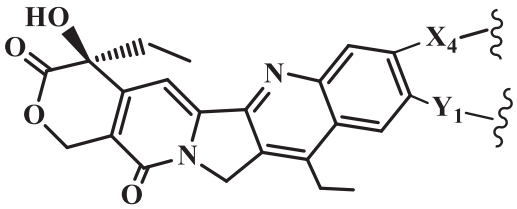
LB34 (Prednisolone),



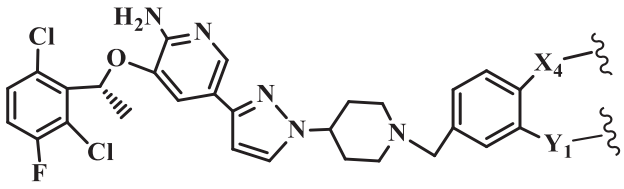
LB35 (Methylprednisolone),



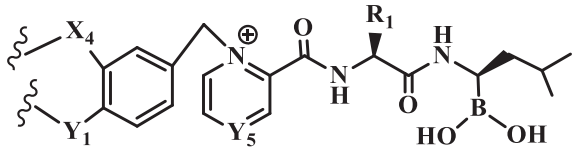
LB36 (Betamethasone),



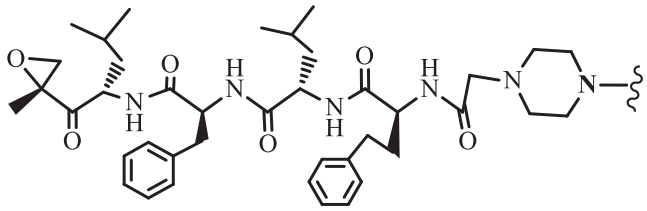
LB37 (Irinotecan analog),



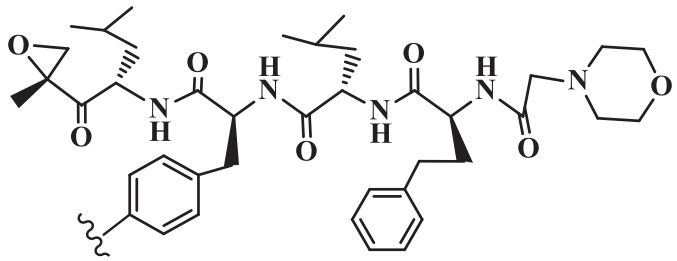
LB38 (Crizotinib analog**),**



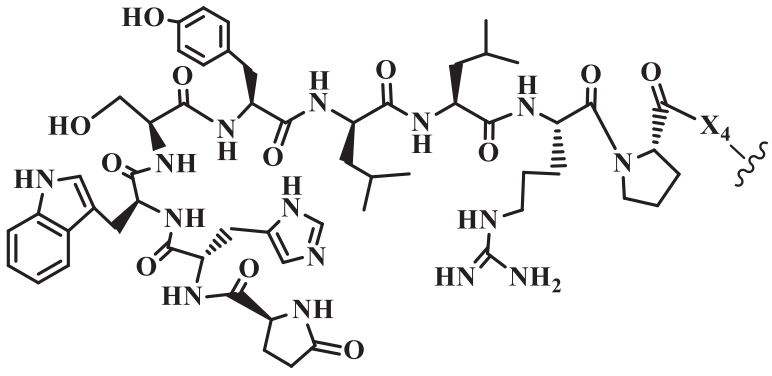
LB39 (Bortezomib analog), wherein Y_5, is N, CH, C(Cl), C(CH_3), or C($COOR_1$); R_1 is H, C_1-C_6 Alkyl, C_3-C_8 Ar;



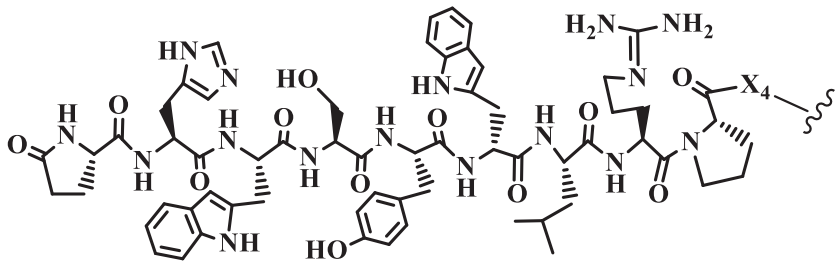
LB40 (Carfilzomib analog),



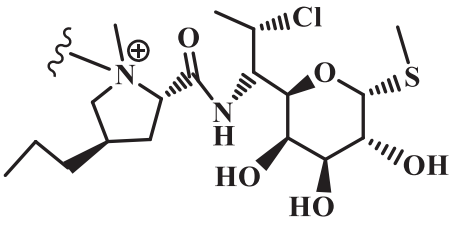
LB41 (Carfilzomib analog),



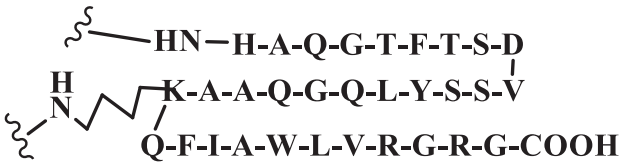
LB42 (Leuprolide analog),



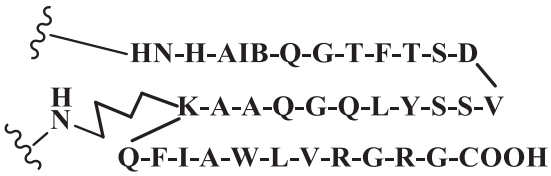
LB43 (Triptorelin analog),



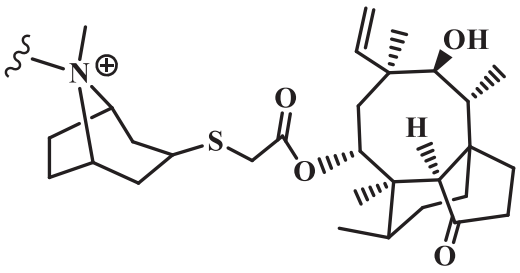
LB44 (Clindamycin),



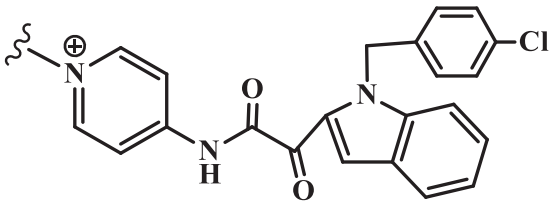
LB45 (Liraglutide analog),



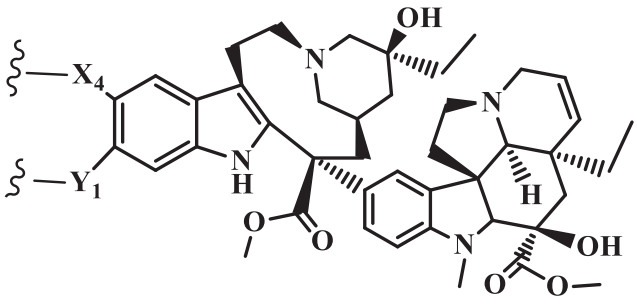
LB46 (Semaglutide analog),



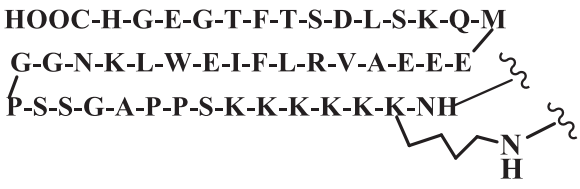
LB47 (Retapamulin analog),



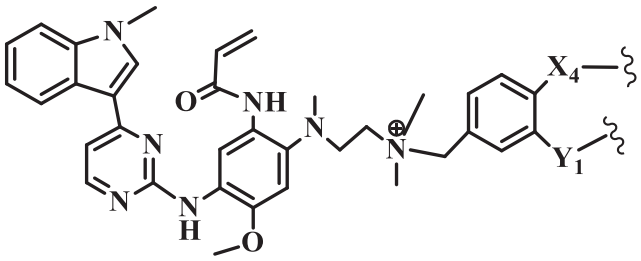
LB48 (Indibulin analog),



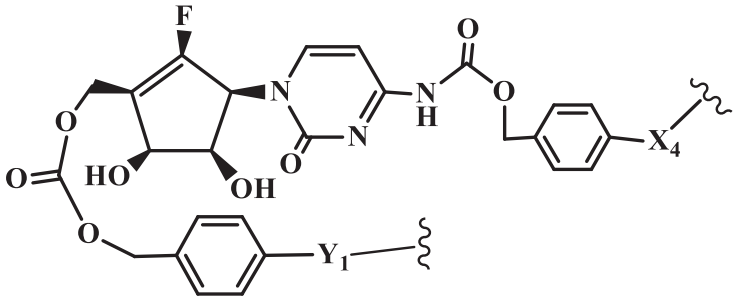
LB49 (Vinblastine analog),



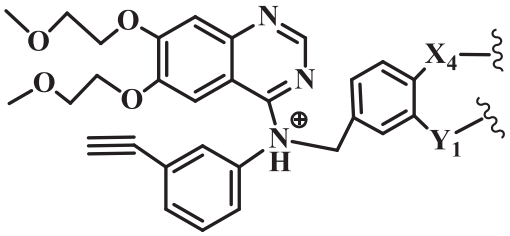
LB50 (Lixisenatide analog),



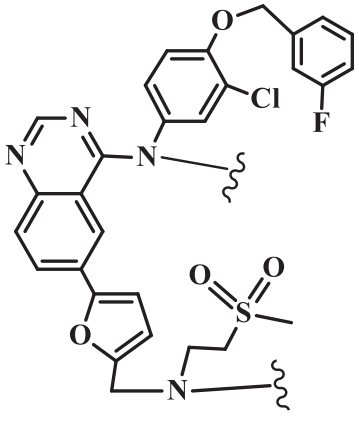
LB51 (Osimertinib analog),



LB52 (a neucleoside analog),



LB53 (Erlotinib analog),



LB54 (Lapatinib analog),

wherein " ∿∿ " is the site to link the linker L of the present patent; X_4,and Y_1 are independently O, NH, NHNH, NR_1, S, C(O)O, C(O)NH, OC(O)NH, OC(O)O, NHC(O)NH, NHC(O)S, OC(O)N(R^1), N(R^1)C(O)N(R^1), CH_2, C(O)NHNHC(O) and C(O)N R^1; X_5 is H, CH_3, F, or Cl; R^1, is defined in Formula (I) of Claim 1.

12. The pharmaceutical composition according to any one of claims **1, 2, 3, 4, 5, 6, 7,** or **9** wherein the targeting or cell-binding molecule is targeting against a tumor cell, a virus infected cell, a microorganism infected cell, a parasite infected cell, an autoimmune disease cell, an activated tumor cells, a myeloid cell, an activated T-cell, an affecting B cell, or a melanocyte, or any cells expressing any one of the following antigens or receptors: CD2, CD2R, CD3, CD3gd,

CD3e, CD4, CD5, CD6, CD7, CD8, CD8a, CD8b, CD9, CD10, CD11a, CD11b, CD11c, CD12, CD12w, CD13, CD14, CD15, CD15s, CD15u, CD16, CD16a, CD16b, CD17, CDw17, CD18, CD19, CD20, CD21, CD22, CD23, CD24, CD25, CD26, CD27, CD28, CD29, CD30, CD31, CD32, CD33, CD34, CD35, CD36, CD37, CD38, CD39, CD40, CD41, CD42, CD42a, CD42b, CD42c, CD42d, CD43, CD44, CD44R, CD45, CD45RA, CD45RB, CD45RO, CD46, CD47, CD47R, CD48, CD49a, CD49b, CD49c, CD49e, CD49f, CD50, CD51, CD52, CD53, CD54, CD55,CD56, CD57, CD58, CD59, CD60, CD60a, CD60b, CD60c, CD61, CD62E, CD62L, CD62P, CD63, CD64, CD65, CD65s, CD66, CD66a, CD66b, CD66c, CD66d, CD66e, CD66f, CD67, CD68, CD69, CD70, CD71, CD72, CD73, CD74, CD74, CD75, CD75s, CD76, CD77, CD78, CD79, CD79a, CD79b, CD80, CD81, CD82, CD83, CD84, CDw84, CD85, CD86, CD87, CD88, CD89, CD90, CD91, CD92, CDw92, CD93, CD94, CD95, CD96, CD97, CD98, CD99, CD99R, CD100, CD101, CD102, CD103, CD104, CD105, CD106, CD107, CD107a, CD107b, CD108, CD109, CD110, CD111, CD112, CD113, CDw113, CD114, CD115, CD116, CD117, CD118, CD119, CDw119, CD120a, CD120b, CD121a, CD121b, CDw121b, CD122, CD123, CDw123, CD124, CD125, CDw125, CD126, CD127, CD128, CDw128, CD129, CD130, CD131, CDw131, CD132, CD133, CD134, CD135, CD136, CDw136, CD137, CDw137, CD138, CD139, CD140a, CD140b, CD141, CD142, CD143, CD144, CD145, CDw145, CD146, CD147, CD148, CD149, CD150, CD151, CD152, CD153, CD154, CD155, CD156a, CD156b, CDw156c, CD157, CD158a, CD158b, CD159a, CD159b, CD159c, CD160, CD161, CD162, CD162R, CD163, CD164, CD165, CD166, CD167, CD167a, CD168, CD169, CD170, CD171, CD172a, CD172b, CD172g, CD173, CD174, CD175, CD175s, CD176, CD177, CD178, CD179, CD180, CD181, CD182, CD183, CD184, CD185, CD186, CDw186, CD187, CD188, CD189, CD190, Cd191, CD192, CD193, CD194, CD195, CD196, CD197, CD198, CDw198, CD199, CDw199, CD200, CD200a, CD200b, CD201, CD202, CD202b, CD203, CD203c, CD204, CD205, CD206, CD207, CD208, CD209, CD210, CDw210, CD212, CD213a1, CD213a2, CDw217, CDw218a, CDw218b, CD220, CD221, CD222, CD223, CD224, CD225, CD226, CD227, CD228, CD229, CD230, CD231, CD232, CD233, CD234, CD235a, CD235ab, CD235b, CD236, CD236R, CD238, CD239, CD240, CD240CE, CD240D, CD241, CD242, CD243, CD244, CD245, CD246, CD247, CD248, CD249, CD252, CD253, CD254, CD256, CD257, CD258, CD261, CD262, CD263, CD265, CD266, CD267, CD268, CD269, CD271, CD273, CD274, CD275, CD276 (B7-H3), CD277, CD278, CD279, CD280, CD281, CD282, CD283, CD284, CD289, CD292, CDw293, CD294, CD295, CD296, CD297, CD298, CD299, CD300a, CD300c, CD300e, CD301, CD302, CD303, CD304, CD305, CD306, CD309, CD312, CD314, CD315, CD316, CD317, CD318, CD319, CD320, CD321, CD322, CD324, CDw325, CD326, CDw327, CDw328, CDw329, CD331, CD332, CD333, CD334,

CD335, CD336, CD337, CDw338, CD339, CD340, CD341, CD342, CD343, CD344, CD345, CD346, CD347, CD348, CD349, CD350, CD351, CD352, CD353, CD354, CD355, CD356, CD357, CD358, CD359, CD360, CD361, CD362, CD363, CD364, CD365, CD366, CD367, CD368, CD369, CD370, CD371, CD372, CD373, CD374, CD375, CD376, CD377, CD378, CD379, CD381, CD382, CD383, CD384, CD385, CD386, CD387, CD388, CD389, CRIPTO, CRIPTO, CR, CR1, CRGF, CRIPTO, CXCR5, LY64, TDGF1, 4-1BB, APO2, ASLG659, BMPR1B, 4-1BB, 5AC, 5T4 (Trophoblastic glycoprotein, TPBG, 5T4, Wnt-Activated Inhibitory Factor 1 or WAIF1), Adenocarcinoma antigen, AGS-5, AGS-22M6, Activin receptor-like kinase 1, AFP, AKAP-4, ALK, Alpha integrin, Alpha v beta6, Amino-peptidase N, Amyloid beta, Androgen receptor, Angiopoietin 2, Angiopoietin 3, Annexin A1, Anthrax toxin protective antigen, Anti-transferrin receptor, AOC3 (VAP-1), B7-H3, Bacillus anthracis anthrax, BAFF (B-cell activating factor), BCMA, B-lymphoma cell, bcr-abl, Bombesin, BORIS, C5, C242 antigen, CA125 (carbohydrate antigen 125, MUC16), CA-IX (or CAIX, carbonic anhydrase 9), CALLA, CanAg, Canis lupus familiaris IL31, Carbonic anhydrase IX, Cardiac myosin, CCL11(C-C motif chemokine 11), CCR4 (C-C chemokine receptor type 4), CCR5, CD3E (epsilon), CEA (Carcinoembryonic antigen), CEACAM3, CEACAM5 (carcino-embryonic antigen), CFD (Factor D), Ch4D5, Cholecystokinin 2 (CCK2R), CLDN18 (Claudin-18), CLDN18.1 (Claudin-18.1), CLDN18.2 (Claudin-18.2), Clumping factor A, cMet, CRIPTO, FCSF1R (Colony stimulating factor 1 receptor), CSF2 (colony stimulating factor 2, Granulocyte-macrophage colony-stimulating factor (GM-CSF)), CSP4, CTLA4 (cytotoxic T-lymphocyte-associated protein 4), CTAA16.88 tumor antigen, CXCR4, C-X-C chemokine receptor type 4, cyclic ADP ribose hydrolase, Cyclin B1, CYP1B1, Cytomegalovirus, Cytomegalovirus glycoprotein B, Dabigatran, DLL3 (delta-like-ligand 3), DLL4 (delta-like-ligand 4), DPP4 (Dipeptidyl-peptidase 4), DR5 (Death receptor 5), E. coli shiga toxin type-1, E. coli shiga toxin type-2, ED-B, EGFL7 (EGF-like domain-containing protein 7), EGFR, EGFRII, EGFRvIII, Endoglin, Endothelin B receptor, Endotoxin, EpCAM (epithelial cell adhesion molecule), EphA2, Episialin, ERBB2 (Epidermal Growth Factor Receptor 2), ERBB3, ERG (TMPRSS2 ETS fusion gene), Escherichia coli, ETV6-AML, FAP (Fibroblast activation protein alpha), fibroblast surface antigen, FCGR1, alpha-Fetoprotein, Fibrin II, beta chain, Fibronectin extra domain-B, FOLR (folate receptor), Folate receptor alpha, Folate hydrolase, Fos-related antigen 1F protein of respiratory syncytial virus, Frizzled receptor, Fucosyl GM1, GD2 ganglioside, G-28 (a cell surface antigen glyvolipid), GD3 idiotype, GloboH, Glypican 3, N-glycolylneuraminic acid, GM3, GMCSF receptor α-chain, Growth differentiation factor, GP100, GPNMB (Trans-membrane glycoprotein NMB), GUCY2C (Guanylate cyclase 2C, guanylyl cyclase C(GC-C), intestinal Guanylate cyclase, Guanylate cyclase-C receptor, Heat-stable enterotoxin receptor (hSTAR)),

Heat shock proteins, Hemagglutinin, Hepatitis B surface antigen, Hepatitis B virus, HER1 (human epidermal growth factor receptor 1), HER2, HER2/neu, HER3 (ERBB-3), IgG4, HGF/SF (Hepatocyte growth factor/scatter factor), HHGFR, HIV-1, Histone complex, HLA-DR (human leukocyte antigen), HLA-DR10, HLA-DRB , HMWMAA, Human chorionic gonadotropin, HNGF, Human scatter factor receptor kinase, HPV E6/E7, Hsp90, hTERT, ICAM-1 (Intercellular Adhesion Molecule 1), Idiotype, IGF1R (IGF-1, insulin-like growth factor 1 receptor), IGHE, IFN-γ, Influenza hemagglutinin, IgE, IgE Fc region, IGHE, interleukins (comprising IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-6R, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-15, IL-17, IL-17A, IL-18, IL-19, IL-20, IL-21, IL-22, IL-23, IL-27, or IL-28), IL31RA, ILGF2 (Insulin-like growth factor 2), Integrins (α4, $\alpha_{IIb}\beta_3$, αvβ3, $\alpha_4\beta_7$, α5β1, α6β4, α7β7, αIIβ3, α5β5, αvβ5), Interferon gamma-induced protein, ITGA2, ITGB2, KIR2D, Kappa Ig, LCK, Le, Legumain, Lewis-Y antigen, LFA-1 (Lymphocyte function-associated antigen 1, CD11a), LHRH, LINGO-1, Lipoteichoic acid, LIV1A, LMP2, LTA, MAD-CT-1, MAD-CT-2, MAGE-1, MAGE-2, MAGE-3, MAGE A1, MAGE A3, MAGE 4, MART1, MCP-1, MIF (Macrophage migration inhibitory factor, or glycosylation-inhibiting factor (GIF)), MS4A1 (membrane-spanning 4-domains subfamily A member 1), MSLN (mesothelin), MUC1(Mucin 1, cell surface associated (MUC1) or polymorphic epithelial mucin (PEM)), MUC1-KLH, MUC16 (CA125), MCP1(monocyte chemotactic protein 1), MelanA/MART1, ML-IAP, MPG, MS4A1 (membrane-spanning 4-domains subfamily A), MYCN, Myelin-associated glycoprotein, Myostatin, NA17, NARP-1, NCA-90 (granulocyte antigen), Nectin-4 (ASG-22ME), NGF, Neural apoptosis-regulated proteinase 1, NOGO-A, Notch receptor, Nucleolin, Neu oncogene product, NY-BR-1, NY-ESO-1, OX-40, OxLDL (Oxidized low-density lipoprotein), OY-TES1, P21, p53 nonmutant, P97, Page4, PAP, Paratope of anti-(N-glycolylneuraminic acid), PAX3, PAX5, PCSK9, PDCD1 (PD-1, Programmed cell death protein 1), PDGF-Rα (Alpha-type platelet-derived growth factor receptor), PDGFR-β, PDL-1, PLAC1, PLAP-like testicular alkaline phosphatase, Platelet-derived growth factor receptor beta, Phosphate-sodium co-transporter, PMEL 17, Polysialic acid, Proteinase3 (PR1), Prostatic carcinoma, PS (Phosphatidylserine), Prostatic carcinoma cells, Pseudomonas aeruginosa, PSMA, PSA, PSCA, Rabies virus glycoprotein, RHD (Rh polypeptide 1 (RhPI)), Rhesus factor, RANKL, RhoC, Ras mutant, RGS5, ROBO4, Respiratory syncytial virus, RON, ROR1, Sarcoma translocation breakpoints, SART3, Sclerostin, SLAMF7 (SLAM family member 7), Selectin P, SDC1 (Syndecan 1), sLe(a), Somatomedin C, SIP (Sphingosine-1-phosphate), Somatostatin, Sperm protein 17, SSX2, STEAP1 (six-transmembrane epithelial antigen of the prostate 1), STEAP2, STn, TAG-72 (tumor associated glycoprotein 72), Survivin, T-cell receptor, T cell transmembrane protein, TEM1 (Tumor endothelial marker 1), TENB2, Tenascin C (TN-C), TGF-α, TGF-β (Transforming growth factor

beta), TGF-β1, TGF-β2 (Transforming growth factor-beta 2), Tie (CD202b), Tie2, TIM-1 (CDX-014), Tn, TNF, TNF-α, TNFRSF8, TNFRSF10B (tumor necrosis factor receptor super-family member 10B), TNFRSF-13B (tumor necrosis factor receptor superfamily member 13B), TPBG (trophoblast glycoprotein), TRAIL-R1 (Tumor necrosis apoptosis Inducing ligand Receptor 1), TRAILR2 (Death receptor 5 (DR5)), tumor-associated calcium signal transducer 2, tumor specific glycosylation of MUC1, TWEAK receptor, TYRP1(glycoprotein 75), TRP-1 (Trop1), TRP-2 (Trop2), Tyrosinase, VCAM-1, VEGF, VEGF-A, VEGF-2, VEGFR-1, VEGFR2, or vimentin, WT1, XAGE 1, or cells expressing any insulin growth factor receptors, or any epidermal growth factor receptors.

13. The pharmaceutical composition according to claim **12**, wherein the tumor cell is selected from the group consisting of lymphoma cells, myeloma cells, renal cells, breast cancer cells, prostate cancer cells, ovarian cancer cells, colorectal cancer cells, gastric cancer cells, squamous cancer cells, small-cell lung cancer cells, none small-cell lung cancer cells, testicular cancer cells, or malignant cells.

14. The pharmaceutical composition according to any one of claim **1, 2, 3, 4, 5, 6, 7,** or **9** for the treatment or prevention of a cancer, or an autoimmune disease, or an infectious disease.

15. The pharmaceutical composition according to Claim1 is further specific as: the amount of the conjugate of formula (I) is take up 1%-95% by weight as major gradient in the formulation, 0.0% -10% of one or more amino acids, 0.0% ~5% of preservative and 0.0% ~10% of buffuer salt for adjusting pH 4.5-8.5, or the amount of the conjugate of formula (I) is take up 1%-95% by weight as major gradient in the formulation, 0.0% -10% of one or more amino acids, 0.0% ~5% of preservative and 0.0% ~10% of buffuer salt for adjusting pH 4.5-8.5. and 0.0% -30.0% of one or more of isotonic agent for adjusting osmotic pressure between about 250 to 350 mOsm after reconstituted for administration to a patient;

wherein the preservative is selected from benzyl alcohol, octadecyldimethylbenzyl ammonium chloride, hexamethonium chloride, benzalkonium chloride, benzethonium chloride, phenol, butyl alcohol, alkyl parabens, catechol, resorcinol, cyclohexanol, 3-pentanol, or m-cresol;

wherein the amino acid is selected from arginine, cystine, glycine, lysine, histidine, ornithine, isoleucine, leucine, alanine, glycine, glutamic acid or aspartic acid;

wherein the buffer salt is selected from sodium, potassium, ammonium, or trihydroxyethylamino salts of citric acid, ascorbic acid, gluconic acid, carbonic acid, tartaric acid, succinic acid, acetic acid or phthalic acid; Tris or tromethamine hydrochloride, phosphate or sulfate; arginine, glycine, glycylglycine, or histidine with anionic acetate, chloride, phosphate, sulfate, or succinate salts;

wherein the tonicity agent is selected from mannitol, sorbitol, sodium acetate, potassium chloride, sodium phosphate, potassium phosphate, trisodium citrate, or sodium chloride.

16. The pharmaceutical composition according to Claim1 is further specific as: the amount of the conjugate of formula (I) is take up 10% ~ 85% by weight as major gradient in the formulation, 0.1% ~0.25% of surfactants selected from polysorbate 20 or polysorbate 80; 0.0% ~ 8.0% of one or more amino acids selected from arginine, histidine, ornithine, glycine or alanine, 0.0% ~5% of preservative selected from benzyl alcohol. and 1% ~10% of buffuer salt selected from sodium citrate or citric acid monohydrate for adjusting pH 5.0 ~ 6.5.

17. The pharmaceutical composition according to Claim **1, 15,** or **16** is held in a vial, bottle, pre-filled syringe, or pre-filled auto-injector syringe, in a form of a liquid or lyophilized solid.

18. The pharmaceutical composition of Claim **1, 2, 3, 4, 5, 6, 7, 9, 15,** or **16,** having in vitro, in vivo or ex vivo cell killing activity.

19. A pharmaceutical composition according to any one of Claim **1, 2, 3, 4, 5, 6, 7, 9, 15,** or **16,** administered concurrently with a synergistic agent selected from chemotherapeutic agent, a radiation therapy, an immunotherapy agent, an autoimmune disorder agent, an anti-infectious agents, a synergistic angent or the other conjugates for synergistically treatment or prevention of a cancer, or an autoimmune disease, or an infectious disease.

20. The pharmaceutical composition according to Claim **19**, wherein the synergistic agent is selected from one or more of the following agents:

(1). A chemotherapeutic agent selected from the group consisting of:

a). an alkylating agent: selected from the group consisting of nitrogen mustards: chlorambucil, chlornaphazine, cyclophosphamide, dacarbazine, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, mannomustine, mitobronitol, melphalan, mitolactol, pipobroman, novembichin, phenesterine, prednimustine, thiotepa, trofosfamide, uracil mustard; CC-1065 and adozelesin, carzelesin, bizelesin or their synthetic analogues; duocarmycin and its synthetic analogues, KW-2189, CBI-TMI, or CBI dimers; benzodiazepine dimers or pyrrolobenzodiazepine (PBD) dimers, tomaymycin dimers, indolinobenzodiazepine dimers, imidazobenzothiadiazepine dimers, or oxazolidinobenzodiazepine dimers; Nitrosoureas: comprising carmustine, lomustine, chlorozotocin, fotemustine, nimustine, ranimustine; Alkylsulphonates: comprising busulfan, treosulfan, improsulfan and piposulfan); Triazenes or dacarbazine; Platinum containing compounds: comprising carboplatin, cisplatin, and oxaliplatin; aziridines, benzodopa, carboquone, meturedopa, or uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, trietylenephosphoramide, triethylenethiophosphoramide and trimethylolomelamine];

b). A plant alkaloid: selected from the group consisting of Vinca alkaloids: comprising vincristine, vinblastine, vindesine, vinorelbine, and navelbin; Taxoids: comprising paclitaxel, docetaxol and their analogs, Maytansinoids comprising DM1, DM2, DM3, DM4, DM5, DM6, DM7, maytansine, ansamitocins and their analogs, cryptophycins (including the group consisting of cryptophycin 1 and cryptophycin 8); epothilones, eleutherobin, discodermolide, bryostatins, dolostatins, auristatins, tubulysins, cephalostatins; pancratistatin; a sarcodictyin; spongistatin;

c). A DNA Topoisomerase Inhibitor: selected from the groups of Epipodophyllins: comprising 9-aminocamptothecin, camptothecin, crisnatol, daunomycin, etoposide, etoposide phosphate, irinotecan, mitoxantrone, novantrone, retinoic acids (or retinols), teniposide, topotecan, 9-nitrocamptothecin or RFS 2000; and mitomycins and their analogs;

d). An antimetabolite: selected from the group consisting of {[Anti-folate: (DHFR inhibitors: comprising methotrexate, trimetrexate, denopterin, pteropterin, aminopterin (4-aminopteroic acid) or folic acid analogues); IMP dehydrogenase Inhibitors: (comprising mycophenolic acid, tiazofurin, ribavirin, EICAR); Ribonucleotide reductase Inhibitors: (comprising hydroxyurea, deferoxamine)]; [Pyrimidine analogs: Uracil analogs: (comprising ancitabine, azacitidine, 6-azauridine, capecitabine (Xeloda), carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, 5-Fluorouracil, floxuridine, ratitrexed (Tomudex)); Cytosine analogs: (comprising cytarabine, cytosine arabinoside, fludarabine); Purine analogs: (comprising azathioprine, fludarabine, mercaptopurine, thiamiprine, thioguanine)]; folic acid replenisher, frolinic acid};

e). A hormonal therapy: selected from the group consisting of {Receptor antagonists: [Anti-estrogen: (comprising megestrol, raloxifene, tamoxifen); LHRH agonists: (comprising goscrclin, leuprolide acetate); Anti-androgens: (comprising bicalutamide, flutamide, calusterone, dromostanolone propionate, epitiostanol, goserelin, leuprolide, mepitiostane, nilutamide, testolactone, trilostane and other androgens inhibitors)]; [Vitamin D3 analogs: (comprising CB 1093, EB 1089 KH 1060, cholecalciferol, ergocalciferol); Photodynamic therapies: (comprising verteporfin, phthalocyanine, photosensitizer Pc4, demethoxyhypocrellin A); Cytokines: (comprising Interferon-alpha, Interferon-gamma, tumor necrosis factor (TNFs), human proteins containing a TNF domain)]};

f). A kinase inhibitor, selected from the group consisting of BIBW 2992 (anti-EGFR/Erb2), imatinib, gefitinib, pegaptanib, sorafenib, dasatinib, sunitinib, erlotinib, nilotinib, lapatinib, axitinib, pazopanib. vandetanib, E7080 (anti-VEGFR2), mubritinib, ponatinib (AP24534), bafetinib (INNO-406), bosutinib (SKI-606), cabozantinib, vismodegib, iniparib, ruxolitinib,

CYT387, axitinib, tivozanib, sorafenib, bevacizumab, cetuximab, Trastuzumab, Ranibizumab, Panitumumab, ispinesib;

g). A poly (ADP-ribose) polymerase (PARP) inhibitors selected from the group consisting of olaparib, niraparib, iniparib, talazoparib, veliparib, CEP 9722 (Cephalon's), E7016 (Eisai's), BGB-290 (BeiGene's), or 3-aminobenzamide.

h). An antibiotic, selected from the group consisting of an enediyne antibiotic (selected from the group consisting of calicheamicin, calicheamicin γ1, δ1, α1 or β1; dynemicin, including dynemicin A and deoxydynemicin; esperamicin, kedarcidin, C-1027, maduropeptin, or neocarzinostatin chromophore and related chromoprotein enediyne antibiotic chromomophores), aclacinomycins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabicin, carminomycin, carzinophilin; chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin, morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin and deoxydoxorubicin, epirubicin, eribulin, esorubicin, idarubicin, marcellomycin, nitomycins, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin;

i). A polyketide (acetogenin), bullatacin and bullatacinone; gemcitabine, epoxomicins andcarfilzomib, bortezomib, thalidomide, lenalidomide, pomalidomide, tosedostat, zybrestat, PLX4032, STA-9090, Stimuvax, allovectin-7, Xegeva, Provenge, Yervoy, Isoprenylation inhibitors and Lovastatin, Dopaminergic neurotoxins and1-methyl-4-phenylpyridinium ion, Cell cycle inhibitors (selected from staurosporine), Actinomycins (comprising Actinomycin D, dactinomycin), amanitins, Bleomycins (comprising bleomycin A2, bleomycin B2, peplomycin), Anthracyclines (comprising daunorubicin, doxorubicin (adriamycin), idarubicin, epirubicin, pirarubicin, zorubicin, mtoxantrone, MDR inhibitors or verapamil, Ca^{2+}ATPase inhibitors or thapsigargin, Histone deacetylase inhibitors ((comprising Vorinostat, Romidepsin, Panobinostat, Valproic acid, Mocetinostat (MGCD0103), Belinostat, PCI-24781, Entinostat, SB939, Resminostat, Givinostat, AR-42, CUDC-101, sulforaphane, Trichostatin A) ; Thapsigargin, Celecoxib, glitazones, epigallocatechin gallate, Disulfiram, Salinosporamide A.; Anti-adrenals, selected from the group consisting of aminoglutethimide, mitotane, trilostane; aceglatone; aldophosphamide glycoside; aminolevulinic acid; amsacrine; arabinoside, bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; eflornithine (DFMO), elfomithine; elliptinium acetate, etoglucid; gallium nitrate; gacytosine, hydroxyurea; ibandronate, lentinan; lonidamine; mitoguazone; mitoxantrone; mopidamol; nitracrine; pentostatin; phenamet; pirarubicin; podophyllinic acid; 2-ethylhydrazide; procarbazine; razoxane; rhizoxin; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2, 2',2"-trichlorotriethylamine; trichothecenes

(including the group consisting ofT-2 toxin, verrucarin A, roridin A and anguidine); urethane, siRNA, antisense drugs;

(2). An anti-autoimmune disease agent: cyclosporine, cyclosporine A, aminocaproic acid, azathioprine, bromocriptine, chlorambucil, chloroquine, cyclophosphamide, corticosteroids (including the group consisting of amcinonide**,** betamethasone, budesonide**,** hydrocortisone, flunisolide, fluticasone propionate, fluocortolone danazol, dexamethasone, Triamcinolone acetonide, beclometasone dipropionate), DHEA, enanercept, hydroxychloroquine, infliximab, meloxicam, methotrexate, mofetil, mycophenylate, prednisone, sirolimus, tacrolimus.

(3). An anti-infectious disease agents comprising:

a). Aminoglycosides: amikacin, astromicin, gentamicin (netilmicin, sisomicin, isepamicin), hygromycin B, kanamycin (amikacin, arbekacin, bekanamycin, dibekacin, tobramycin), neomycin (framycetin, paromomycin, ribostamycin), netilmicin, spectinomycin, streptomycin, tobramycin, verdamicin;

b). Amphenicols: azidamfenicol, chloramphenicol, florfenicol, thiamphenicol;

c). Ansamycins: geldanamycin, herbimycin;

d). Carbapenems: biapenem, doripenem, ertapenem, imipenem/cilastatin, meropenem**,** panipenem;

e). Cephems: carbacephem (loracarbef), cefacetrile, cefaclor, cefradine, cefadroxil, cefalonium, cefaloridine, cefalotin or cefalothin, cefalexin, cefaloglycin, cefamandole, cefapirin, cefatrizine, cefazaflur, cefazedone, cefazolin, cefbuperazone, cefcapene, cefdaloxime, cefepime, cefminox, cefoxitin, cefprozil, cefroxadine, ceftezole, cefuroxime, cefixime, cefdinir, cefditoren, cefepime, cefetamet, cefmenoxime, cefodizime, cefonicid, cefoperazone, ceforanide, cefotaxime, cefotiam, cefozopran, cephalexin, cefpimizole, cefpiramide, cefpirome, cefpodoxime, cefprozil, cefquinome, cefsulodin, ceftazidime, cefteram, ceftibuten, ceftiolene, ceftizoxime, ceftobiprole, ceftriaxone, cefuroxime, cefuzonam, cephamycin (cefoxitin, cefotetan, cefmetazole), oxacephem (flomoxef, latamoxef);

f). Glycopeptides: bleomycin, vancomycin (oritavancin, telavancin), teicoplanin (dalbavancin), ramoplanin;

g). Glycylcyclines: tigecycline;

h). β-Lactamase inhibitors: penam (sulbactam, tazobactam), clavam (clavulanic acid);

i). Lincosamides: clindamycin, lincomycin;

j). Lipopeptides: daptomycin, A54145, calcium-dependent antibiotics (CDA);

k). Macrolides: azithromycin, cethromycin, clarithromycin, dirithromycin, erythromycin, flurithromycin, josamycin, ketolide (telithromycin, cethromycin), midecamycin, miocamycin,

oleandomycin, rifamycins (rifampicin, rifampin, rifabutin, rifapentine), rokitamycin, roxithromycin, spectinomycin, spiramycin, tacrolimus (FK506), troleandomycin, telithromycin;

l). Monobactams: aztreonam, tigemonam;

m). Oxazolidinones: linezolid;

n). Penicillins: amoxicillin, ampicillin, pivampicillin, hetacillin, bacampicillin, metampicillin, talampicillin, azidocillin, azlocillin, benzylpenicillin, benzathine benzylpenicillin, benzathine phenoxymethylpenicillin, clometocillin, procaine benzylpenicillin, carbenicillin (carindacillin), cloxacillin, dicloxacillin, epicillin, flucloxacillin, mecillinam (pivmecillinam)**,** mezlocillin, meticillin, nafcillin, oxacillin, penamecillin, penicillin, pheneticillin, phenoxymethylpenicillin, piperacillin, propicillin, sulbenicillin, temocillin, ticarcillin;

o). Polypeptides: bacitracin, colistin, polymyxin B;

p). Quinolones: alatrofloxacin, balofloxacin, ciprofloxacin, clinafloxacin, danofloxacin, difloxacin, enoxacin, enrofloxacin, floxin, garenoxacin, gatifloxacin, gemifloxacin, grepafloxacin, kano trovafloxacin, levofloxacin, lomefloxacin, marbofloxacin, moxifloxacin, nadifloxacin, norfloxacin, orbifloxacin, ofloxacin, pefloxacin, trovafloxacin, grepafloxacin, sitafloxacin, sparfloxacin, temafloxacin, tosufloxacin, trovafloxacin;

q). Streptogramins: pristinamycin, quinupristin/dalfopristin;

r). Sulfonamides: mafenide, prontosil, sulfacetamide, sulfamethizole, sulfanilimide, sulfasalazine, sulfisoxazole, trimethoprim, trimethoprim-sulfamethoxazole (co-trimoxazole);

s). Steroid antibacterials: selected from fusidic acid;

t). Tetracyclines: doxycycline, chlortetracycline, clomocycline, demeclocycline, lymecycline, meclocycline, metacycline, minocycline, oxytetracycline, penimepicycline, rolitetracycline, tetracycline, glycylcyclines (including tigecycline);

u). Other antibiotics: selected from the group consisting of annonacin, arsphenamine, bactoprenol inhibitors (Bacitracin), DADAL/AR inhibitors (cycloserine), dictyostatin, discodermolide, eleutherobin, epothilone, ethambutol, etoposide, faropenem, fusidic acid, furazolidone, isoniazid, laulimalide, metronidazole, mupirocin, mycolactone, NAM synthesis inhibitors (fosfomycin), nitrofurantoin, paclitaxel, platensimycin, pyrazinamide, quinupristin/dalfopristin, rifampicin (rifampin), tazobactam tinidazole, uvaricin;

(4). Anti-viral drugs comprising:

a). Entry/fusion inhibitors: aplaviroc, maraviroc, vicriviroc, *gp41* (enfuvirtide**),** PRO 140**,** CD4 (ibalizumab);

b). Integrase inhibitors: raltegravir, elvitegravir, globoidnan A;

c). Maturation inhibitors: bevirimat, vivecon;

d). Neuraminidase inhibitors**:** oseltamivir, zanamivir, peramivir;

e). Nucleosides & nucleotides: abacavir, aciclovir, adefovir, amdoxovir, apricitabine, brivudine, cidofovir, clevudine, dexelvucitabine, didanosine (ddI), elvucitabine, emtricitabine (FTC), entecavir, famciclovir, fluorouracil (5-FU), 3'-fluoro-substituted 2', 3'-dideoxynucleoside analogues (including the group consisting of3'-fluoro-2',3'-dideoxythymidine (FLT) and 3'-fluoro-2',3'-dideoxyguanosine (FLG), fomivirsen, ganciclovir**,** idoxuridine, lamivudine (3TC), l-nucleosides (including the group consisting of *β*-l-thymidine and *β*-l-2'-deoxycytidine), penciclovir, racivir, ribavirin, stampidine, stavudine (d4T), taribavirin (viramidine), telbivudine, tenofovir, trifluridine valaciclovir, valganciclovir, zalcitabine (ddC), zidovudine (AZT);

f). Non-nucleosides: amantadine, ateviridine, capravirine, diarylpyrimidines (etravirine, rilpivirine)**,** delavirdine, docosanol, emivirine, efavirenz, foscarnet (phosphonoformic acid), imiquimod, interferon alfa, loviride, lodenosine, methisazone, nevirapine, NOV-205, peginterferon alfa, podophyllotoxin, rifampicin, rimantadine, resiquimod (R-848), tromantadine;

g). Protease inhibitors: amprenavir**,** atazanavir**,** boceprevir, darunavir, fosamprenavir**,** indinavir, lopinavir**,** nelfinavir, pleconaril, ritonavir**,** saquinavir**,** telaprevir (VX-950), tipranavir;

h). Other types of anti-virus drugs: abzyme**,** arbidol, calanolide a, ceragenin, cyanovirin-n, diarylpyrimidines, epigallocatechin gallate (EGCG)**,** foscarnet**,** griffithsin, taribavirin (viramidine), hydroxyurea, KP-1461, miltefosine, pleconaril, portmanteau inhibitors, ribavirin, seliciclib.

(5). A radioisotope for radiotherapy that can be selected from the group consisting of (radionuclides) ^{3}H, ^{11}C, ^{14}C, ^{18}F, ^{32}P, ^{35}S, ^{64}Cu, ^{68}Ga, ^{86}Y, ^{99}Tc, ^{111}In, ^{123}I, ^{124}I, ^{125}I, ^{131}I, ^{133}Xe, ^{177}Lu, ^{211}At, or ^{213}Bi.

(6). Another cell-binding molecule-drug conjugate having a cytotoxic agent of a tubulysin analog, maytansinoid analog, taxanoid (taxane) analog, CC-1065 analog, daunorubicin and doxorubicin compound, amatoxin analog, benzodiazepine dimer (dimers of (pyrrolobenzodiazepine (PBD), tomaymycin, anthramycin, indolinobenzodiazepines, imidazobenzothiadiazepines, or oxazolidinobenzodiazepines)), calicheamicins and the enediyne antibiotic compound, actinomycin, azaserine, bleomycins, epirubicin, tamoxifen, idarubicin, dolastatins, auristatins (monomethyl auristatin E, MMAE , MMAF, auristatin PYE, auristatin TP, Auristatins 2-AQ, 6-AQ, EB (AEB), and EFP (AEFP)), duocarmycins, geldanamycins, methotrexates, thiotepa, vindesines, vincristines, hemiasterlins, nazumamides, microginins, radiosumins, topoisomerase I inhibitors, alterobactins, microsclerodermins, theonellamides, esperamicins, PNU-159682, and their analogues and derivatives above thereof;

(7). Other immunotheraphy drugs: selected from imiquimod, interferons (α or β), granulocyte colony-stimulating factors, cytokines, Interleukins (IL-1 ~ IL-35), antibodies (trastuzumab, pertuzumab, bevacizumab, cetuximab, panitumumab, infliximab, adalimumab, basiliximab,

daclizumab, omalizumab, PD-1 or PD-L1), Protein-bound drugs (Abraxane), an antibody conjugated with drugs selected from Trastuzumab-DM1, Trastuzumab deruxtecan (DS-8201a), Inotuzumab ozogamicin, Brentuximab vedotin, Sacituzumab govitecan, Glembatumumab vedotin, lorvotuzumab mertansine, AN-152 LMB2, TP-38, VB4-845, Cantuzumab mertansine, AVE9633, SAR3419, CAT-8015, IMGN388, Mirvetuximab soravtansine (IMGN853), Enfortumab vedotin, milatuzumab-doxorubicin, SGN-75 (anti-CD70), anti-Her3-exetecan, anti-Trop2-exetecan, nnti-CD79b-MMAE, anti-Her2-MMAE, anti-trop2-MMAE, anti-Her2-MMAF, anti-trop2-MMAF, anti-CD22-calicheamicin derivative, anti-CD22-MMAE, anti-Her2-auristatin derivatives, anti-Muc1- auristatin derivatives, anti-cMet- auristatin derivatives, or anti-Claudin18.2-auristatin derivatives.

(8). The pharmaceutically acceptable salts, acids or derivatives of any of the above drugs.

21. The pharmaceutical composition according to claim **20**, wherein the synergistic agent is selected from one or several of the following drugs: Abatacept, Abiraterone acetate, Abraxane, Acetaminophen/hydrocodone, Acalabrutinib, aducanumab, Adalimumab, ADXS31-142, ADXS-HER2, afatinib dimaleate, aldesleukin, alectinib, alemtuzumab, Alitretinoin, alpelisib, ado-trastuzumab emtansine, Amphetamine/ dextroamphetamine, analotinib, anastrozole, apalutamide, Aripiprazole, anthracyclines, Aripiprazole, Atazanavir, Atezolizumab, Atorvastatin, Avelumab, Axicabtagene ciloleucel, axitinib, belinostat, BCG Live, Bevacizumab, bexarotene, blinatumomab, Bortezomib, bosutinib, brentuximab vedotin, brigatinib, Budesonide, Budesonide/formoterol, Buprenorphine, Cabazitaxel, Cabozantinib, camrelizumab, capmatinib, Capecitabine, carfilzomib, chimeric antigen receptor-engineered T (CAR-T) cells, Celecoxib, ceritinib, Cetuximab, Chidamide, Ciclosporin, Cinacalcet, crizotinib, Cobimetinib, Cosentyx, crizotinib, CTL019, Dabigatran, dabrafenib, dacarbazine, daclizumab, dacomitinib, dacomotinib, daptomycin, Daratumumab, Darbepoetin alfa, darolutamide, Darunavir, dasatinib, denileukin diftitox, Denosumab, Depakote, Dexlansoprazole, Dexmethylphenidate, Dexamethasone, DigniCap Cooling System, Dinutuximab, Doxycycline, Duloxetine, Duvelisib, durvalumab, elotuzumab, Emtricitabine/ Rilpivirine/Tenofovir, disoproxil fumarate, Emtricitbine/ tenofovir/efavirenz, enfortumab vedotin-ejfv, Enoxaparin, ensartinib, entrectinib, Enzalutamide, Epoetin alfa, erlotinib, erdafitinib, Esomeprazole, Eszopiclone, Etanercept, Everolimus, exemestane, everolimus, exenatide ER, Ezetimibe, Ezetimibe/simvastatin, fam-trastuzumab deruxtecan, Fenofibrate, Filgrastim, fingolimod, flumatinib, Fluticasone propionate, Fluticasone/salmeterol, fulvestrant, gazyva, gefitinib, Glatiramer, Goserelin acetate, Icotinib, Imatinib, Ibritumomab tiuxetan, ibrutinib, idelalisib, ifosfamide, Infliximab, imiquimod, ImmuCyst, Immuno BCG, iniparib, Insulin aspart, Insulin detemir, Insulin glargine, Insulin lispro, Interferon alfa, Interferon alfa-1b,

Interferon alfa-2a, Interferon alfa-2b, Interferon beta, Interferon beta 1a, Interferon beta 1b, Interferon gamma-1a, lapatinib, Ipilimumab, Ipratropium bromide/salbutamol, Ixazomib, Kanuma, Lanreotide acetate, lenalidomide, lenaliomide, lenvatinib mesylate, letrozole, Levothyroxine, Levothyroxine, Lidocaine, Linezolid, Liraglutide, Lisdexamfetamine, LN-144, lorlatinib, Memantine, Methylphenidate, Metoprolol, Mekinist, mericitabine/Rilpivirine/ Tenofovir, Modafinil, Mometasone, Mycidac-C, Necitumumab, neratinib, Nilotinib, niraparib, Nivolumab, ofatumumab, obinutuzumab, olaparib, Olmesartan, Olmesartan/ hydrochlorothiazide, Omalizumab, Omega-3 fatty acid ethyl esters, Oncorine, Oseltamivir, Osimertinib, Oxycodone, palbociclib, Palivizumab, panitumumab, panobinostat, pazopanib, pembrolizumab, pexidartinib hydrochloride, PD-1 antibody, PD-L1 antibody, Pemetrexed, pertuzumab, Pneumococcal conjugate vaccine, polatuzumab vedotin, pomalidomide, Pregabalin, ProscaVax, Propranolol, Quetiapine, Rabeprazole, radium 223 chloride, Raloxifene, Raltegravir, ramucirumab, Ranibizumab, relugolix, regorafenib, Rituximab, Rivaroxaban, romidepsin, Rosuvastatin, ruxolitinib phosphate, Salbutamol, savolitinib, semaglutide, selinexor, Sevelamer, Sildenafil, siltuximab, Sipuleucel-T, Sitagliptin, Sitagliptin/metformin, Solifenacin, solanezumab, Sonidegib, Sorafenib, Sunitinib, tacrolimus, tacrimus, Tadalafil, tamoxifen, Tafinlar, Talimogene laherparepvec, talazoparib, Telaprevir, talazoparib, Temozolomide, temsirolimus, Tenofovir/emtricitabine, tenofovir disoproxil fumarate, Testosterone gel, Thalidomide, TICE BCG, Tiotropium bromide, Tisagenlecleucel, toremifene, trametinib, Trastuzumab, trastuzumab/hyaluronidase-oysk, Trabectedin (ecteinascidin 743), trametinib, tremelimumab, Trifluridine/tipiracil, Tretinoin, tislelizumab, Uro-BCG, Ustekinumab, Valsartan, veliparib, vandetanib, vemurafenib, venetoclax, vorinostat, zanubrutinib, ziv-aflibercept, Zostavaxor a combination above thereof.