CLAIMS

1. Use of an allosteric inhibitor of Chromodomain-helicase-DNA-binding protein 1-like (ALC1), in which the inhibitor specifically binds to an allosteric binding pocket formed by an amino acid stretch spanning amino acid residues 101 to 219 of SEQ ID NO: 1 in the preparation of a medicament for the treatment or amelioration of a proliferative disease in a patient in combination with and/or for enhancing the efficacy in treating a proliferative disease of

(a) an inhibitor of Topoisomerase I, Topoisomerase II, ATM, ATR, Wee1, BRD, and/or MEK,

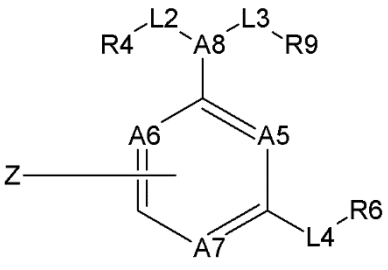
(b) mitomycin C or paclitaxel,

(c) ionizing radiation, or

(d) an antibody drug conjugate with a tumor specific antibody conjugated to a TOP1 inhibitor.

2. Use according to Claim 1, in which the allosteric binding pocket comprises or consists of L101, Y153, C156, L157, A160, L163, K164, V173, D174, E175, A176, H177, R178, L179, S183, L186, H187, T189, L190, F193, L200, L201, T202, N208, S209, E212, L213, L216, and F219 of SEQ ID NO: 1, preferably comprises or consists of Y153, C156, L157, A160, L163, V173, E175, R178, L186, H187, L190, F193, L200, and E212 of SEQ ID NO: 1.

3. Use according to Claim 1 or 2, in which the inhibitor of ALC1 (ALC1i) is according to Formula (I)



(I)

and isomers, salts, solvates, chemically protected forms, and prodrugs thereof, in which

(i) A5 and A8 are each independently selected from N or CH;

(ii) A6 is selected from N or CH, or when A6 takes part in the annulated carbo- or heterocycle Z, then A6 is C;

(iii) A7 is selected from N or CH, or when A7 takes part in the annulated carbo- or heterocycle Z, then A7 is C;

(iv) L2 is selected from the group consisting of -CH2-R4, –CF2– R4, -CH2-CH2- R4, -CH2-CH2-CH2-R4, -O-R4, -NH-R4, -N=R4;

(v) L3 is selected from the group consisting of CH2-R9, –CF2– R9, -CH2-CH2- R9, -CH2-CF2-R9, -CH2-CH2-CH2-R9, -O-R9, -NH-R9, -N=R9;

or

(vi) L2 and L3 together with the A8 to which they are connected form a 5- or 6-membered heterocycle substituted by R4 and/or R9;

(vii) L4 is CH2, –CF2–, CH2-CH2, CH2-CH2-CH2, O, N, and NH, or is absent;

(viii) Z is a 5-, 6- or 7-membered carbo- or heterocycle, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF3, Et, -OMe, -SMe, and -NO2; and can be annulated to the central core or connected via a covalent bond

(ix) R4 is 5-, 6- or 7-membered carbo- or heterocycle, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -CF3, Me, Et, -OMe, and -SMe, or R4 is hydrogen, methyl, or COOH;

(x) R9 is a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered carbo- or heterocycle, optionally substituted with one, two, or three (preferably one) substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF3, Et, -OMe, and -SMe;

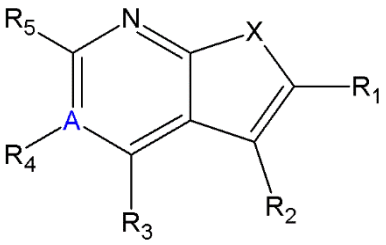
(xi) R6 is a 5-, 6- or 7-membered carbo- or heterocycle, optionally substituted with one, two, or three (preferably one) substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO2, Me, -CF3, Et, -OMe, and -SMe;

(xii) or R6 is H;

or

(xiii) when A7 takes part in the annulated carbo- or heterocycle Z then A5 and A6 are independently selected from -N or -CH and A8 is selected from -N, -CH, -CH2-N, -CH2-CH, or -NH-CH;

or according to Formula (II)



(II)

and isomers, salts, solvates, chemically protected forms, and prodrugs thereof, in which

(i) X is N or S;

(ii) A is C or N;

(iii) R_1 is –CO-OR_6, -CO-R_7, or -CO-NR_6R_A, preferably R_1 is –CO-OR_6;

(iv) R_2 is -R_7, -NHR_8, -O-R_7, -C-O-R_7, Br, -C_{3-8}-cycloalkyl (preferably cyclopropyl), or –C_{4-8}-cycloalkenyl (preferably cyclohexenyl);

or

(v) R_1 and R_2 together form a 5, 6 or 7 membered carbo- or heterocycle, optionally substituted, preferably with 1, 2 or 3 substituents independently selected from the group consisting of -OH, -NO_2, -CN, -Br, -Cl, -F, -I, -O-C_{1-3}-alkyl, =O, and [-O-CH_2-CH_2]-NH-CH(OH)-O-tBu;

(vi) R_3 is H, =O, -OH, -O-R_7, -R_7, or –$(CH_2)_m$-L, in which m is 0, 1 or 2, and L is a 5, 6 or 7 membered carbo- or heterocycle, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO_2, -CN, -Br, -Cl, -F, -I, -O-C_{1-3}-alkyl, -hydroxyC_{1-3}-alkyl and =O;

(vii) R_4 is H or -C_{1-3}-alkyl, preferably H;

(viii) R_5 is -$(CH_2)_m$-L, or -$(CH_2)_m$-(CH=CH)-L, in which m is 0, 1 or 2, preferably 0 or 1, and L is a 5, 6 or 7 membered carbo- or heterocycle, adamantyl, C_{1-4}-alkyl, or -$N(CH_3)_2$, optionally substituted, preferably with 1, 2, 3 or 4 substituents independently selected from the group consisting of -OH, -NO_2, -CN, -CO-OR_6, -Br, -Cl, -F, -I, -R_9, -

$O\text{-}R_9$, =O, and $[\text{-O-CH}_2\text{-CH}_2]_q$-NH-biotin with q being 1, 2, 3, or 4, or two adjacent substituents form a 5, 6 or 7 membered carbo- or heterocycle;

or

(ix) R_4 and R_5 together form a 5, 6, or 7 membered carbocycle, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, $-NO_2$, -CN, -Br, -Cl, -F, -I, $-O\text{-}R_9$, $-R_9$, $=CH\text{-}R_A$, and $–CH_2\text{-}R_A$, preferably R_4 and R_5 together form a $C_{5\text{-}7}$-cycloalkyl;

(x) R_6 is H, $-C_{1\text{-}6}$-alkyl, $-C_{2\text{-}6}$-alkenyl, $-C_{2\text{-}6}$-alkynyl, optionally substituted, preferably R_6 is H;

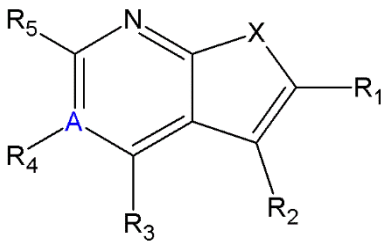
(xi) R_7 is $-C_{1\text{-}3}$-alkyl, $-C_{2\text{-}3}$-alkenyl, $-C_{2\text{-}3}$-alkynyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -Br, -Cl, -F, -I, $-CH_3$, $-OCH_3$, or $-SCH_3$;

(xii) R_8 is H or $C_{1\text{-}6}$-alkyl, preferably H,

(xiii) R_9 is $-C_{1\text{-}6}$-alkyl, $-C_{2\text{-}6}$-alkenyl, $-C_{2\text{-}6}$-alkynyl, $-C_{1\text{-}6}$-alkyl-aryl, or $C_{1\text{-}6}$-alkyl-heteroaryl (preferably isooxazole, thiazole, tetrazole, 1,2,4-thiadiazole, 1,2,3-thiadiazole, 1,2,5-thiadiazole, pyridine, 1,2,4-oxadiazole, pyrazine, or pyrazole), optionally substituted with 1, 2 or 3 substituents selected from the group consisting of -Br, -Cl, -F, -I, $-NO_2$, -CN, $-CONH_2$, $-CONH\text{-}C_{1\text{-}3}$-alkyl (preferably $–CONH\text{-}CH_3$), $-NH\text{-}CO\text{-}C_{1\text{-}3}$-alkyl (preferably $-NH\text{-}CO\text{-}CH_3$), $-C_{1\text{-}6}$-alkyl (preferably $-CH_3$, ethyl, propyl, t-butyl, or pentyl), $-C_{1\text{-}3}$-haloalkyl (preferably-CF_3, or $-CHF_2$), $-O\text{-}CHF_2$, $-O\text{-}CF_3$, carbocycle (preferably cyclopropyl, cyclohexyl or phenyl), -O-carbocycle (preferably phenoxy), heterocycle (preferably pyrazolyl), -CO-heterocycle (preferably –CO-(1-pyrrolidinyl)),$-SO_2\text{-}CH_3$, $-SO_2\text{-}N(CH_3)_2$, $-O\text{-}C_{1\text{-}4}$-alkyl (preferably $-OCH_3$), $-O\text{-}C_{1\text{-}3}$-alkyl-$O\text{-}C_{1\text{-}3}$-alkyl (preferably $–O\text{-}CH_2\text{-}O\text{-}CH_3$), $-SCH_3$, or when R_9 is $-C_{1\text{-}6}$-alkyl-aryl, then two adjacent substituents on the aryl moiety can form a 5, 6 or 7 membered carbo- or heterocycle, which is optionally substituted;

(xiv) R_A is H, carbo- or heterocycle, optionally substituted, preferably with 1, 2 or 3 substituents independently selected from the group consisting of -OH, $-NO_2$, -CN, -Br, -Cl, -F, -I, $-R_9$, $-O\text{-}R_7$, $-O\text{-}(CH_2)_o\text{-}R_9$, $-SO_2NH_2$, and =O, in which o is 0 or 1.

4. Use of an inhibitor of ALC1 (ALC1i) according to formula (II)



(II)

and isomers, salts, solvates, chemically protected forms, and prodrugs thereof, in which

(i) X is N or S;

(ii) A is C or N;

(iii) R_1 is –CO-OR_6, -CO-R_7, or -CO-NR_6R_A, preferably R_1 is –CO-OR_6;

(iv) R_2 is -R_7, -NHR_8, -O-R_7, -C-O-R_7, Br, -C_{3-8}-cycloalkyl (preferably cyclopropyl), or –C_{4-8}-cycloalkenyl (preferably cyclohexenyl);

or

(v) R_1 and R_2 together form a 5, 6 or 7 membered carbo- or heterocycle, optionally substituted, preferably with 1, 2 or 3 substituents independently selected from the group consisting of -OH, -NO_2, -CN, -Br, -Cl, -F, -I, -O-C_{1-3}-alkyl, =O, and [-O-CH_2-CH_2]-NH-CH(OH)-O-tBu;

(vi) R_3 is H, =O, -OH, -O-R_7, -R_7, or –$(CH_2)_m$-L, in which m is 0, 1 or 2, and L is a 5, 6 or 7 membered carbo- or heterocycle, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO_2, -CN, -Br, -Cl, -F, -I, -O-C_{1-3}-alkyl, -hydroxyC_{1-3}-alkyl and =O;

(vii) R_4 is H or -C_{1-3}-alkyl, preferably H;

(viii) R_5 is -$(CH_2)_m$-L, or -$(CH_2)_m$-(CH=CH)-L, in which m is 0, 1 or 2, preferably 0 or 1, and L is a 5, 6 or 7 membered carbo- or heterocycle, adamantyl, C_{1-4}-alkyl, or -$N(CH_3)_2$, optionally substituted, preferably with 1, 2, 3 or 4 substituents independently selected from the group consisting of -OH, -NO_2, -CN, -CO-OR_6, -Br, -Cl, -F, -I, -R_9, -O-R_9, =O, and [-O-CH_2-CH_2]$_q$-NH-biotin with q being 1, 2, 3, or 4, or two adjacent substituents form a 5, 6 or 7 membered carbo- or heterocycle;

or

(ix) R_4 and R_5 together form a 5, 6, or 7 membered carbocycle, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO_2, -CN, -Br, -Cl, -F, -I, -O-R_9, -R_9, =CH-R_A, and –CH_2-R_A, preferably R_4 and R_5 together form a C_{5-7}-cycloalkyl;

(x) R_6 is H, -C_{1-6}-alkyl, -C_{2-6}-alkenyl, -C_{2-6}-alkynyl, optionally substituted, preferably R_6 is H;

(xi) R_7 is -C_{1-3}-alkyl, -C_{2-3}-alkenyl, -C_{2-3}-alkynyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -Br, -Cl, -F, -I, -CH_3, -OCH_3, or -SCH_3;

(xii) R_8 is H or C_{1-6}-alkyl, preferably H,

(xiii) R_9 is -C_{1-6}-alkyl, -C_{2-6}-alkenyl, -C_{2-6}-alkynyl, -C_{1-6}-alkyl-aryl, or C_{1-6}-alkyl-heteroaryl (preferably isooxazole, thiazole, tetrazole, 1,2,4-thiadiazole, 1,2,3-thiadiazole, 1,2,5-thiadiazole, pyridine, 1,2,4-oxadiazole, pyrazine, or pyrazole), optionally substituted with 1, 2 or 3 substituents selected from the group consisting of -Br, -Cl, -F, -I, -NO_2, -CN, -$CONH_2$, -CONH-C_{1-3}-alkyl (preferably –CONH-CH_3), -NH-CO-C_{1-3}-alkyl (preferably -NH-CO-CH_3), -C_{1-6}-alkyl (preferably -CH_3, ethyl, propyl, t-butyl, or pentyl), -C_{1-3}-haloalkyl (preferably-CF_3, or -CHF_2), -O-CHF_2, -O-CF_3, carbocycle (preferably cyclopropyl, cyclohexyl or phenyl), -O-carbocycle (preferably phenoxy), heterocycle (preferably pyrazolyl), -CO-heterocycle (preferably –CO-(1-pyrrolidinyl)),-SO_2-CH_3, -SO_2-N(CH_3)$_2$, -O-C_{1-4}-alkyl (preferably -OCH_3), -O-C_{1-3}-alkyl-O-C_{1-3}-alkyl (preferably –O-CH_2-O-CH_3), -SCH_3, or when R_9 is -C_{1-6}-alkyl-aryl, then two adjacent substituents on the aryl moiety can form a 5, 6 or 7 membered carbo- or heterocycle, which is optionally substituted;

(xiv) R_A is H, carbo- or heterocycle, optionally substituted, preferably with 1, 2 or 3 substituents independently selected from the group consisting of -OH, -NO_2, -CN, -Br, -Cl, -F, -I, -R_9, -O-R_7, -O-(CH_2)$_o$-R_9, -SO_2NH_2, and =O, in which o is 0 or 1,

in the preparation of a medicament for the treatment or amelioration of pancreatic cancer or fallopian tube cancer in a patient in combination with an inhibitor of PARP, or for enhancing efficacy of an inhibitor of PARP in treating or ameliorating pancreatic cancer or fallopian tube cancer in a patient.

5. Use according to any preceding claim, in which the ALC1i has a structure of Formula (I), in which

A5 is N;

one of A6 and A7 is CH and the other one is N; or one of A6 and A7 is C and takes part in the annulated carbo- or heterocycle Z and the other one is N;

A8 is N or CH,

or

A5 is N;

one of A6 and A7 is C and takes part in the annulated 5-, 6- or 7-membered carbo- or heterocycle, preferably 5- or 6 membered aryl or heteroaryl Z and the other one is N;

A8 is N;

L2 is CH_2-CH_2-R4 and L3 is CH_2-CH_2-R9 or CH_2-CF_2-R9 or L2 and L3 together with the A8 to which they are connected form a 5- or 6-membered heterocycle, preferably piperidinyl or a pyrrolidinyl substituted by R4 and R9;

L4 is absent;

Z is any 6-membered carbo- or heterocycle, preferably 6-membered aryl or heteroaryl annulated to the central core, in which Z is optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF_3, Et, -OMe, -SMe, and NO_2;

R4 is COOH or tetrazolyl;

R9 is any 4-, 5-, 6-, or 7-membered carbo- or heterocycle, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF_3, Et, -OMe, and -SMe; and

R6 is any 5- or 6-membered carbo- or heterocycle, optionally substituted with one, two, or three (preferably one) substituents selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO_2, Me, -CF_3, Et, -OMe, and -SMe, or R6 is H,

or the ALC1i has a structure of Formula (II), in which:

X is N or S;

A is C or N;

R_1 is –CO-OR_6, -CO-R_7, or -CO-NR_6R_A, preferably R_1 is –CO-OR_6;

R_2 is -R_7, -NHR_8, -O-R_7, -C-O-R_7, Br, -C_{3-8}-cycloalkyl (preferably cyclopropyl), or –C_{4-8}-cycloalkenyl (preferably cyclohexenyl);

or

R_1 and R_2 together form a 5, 6 or 7 membered carbo- or heterocycle, optionally substituted, preferably with 1, 2 or 3 substituents independently selected from the group consisting of -OH, -NO_2, -CN, -Br, -Cl, -F, -I, -O-C_{1-3}-alkyl, =O, and [-O-CH_2-CH_2]-NH-CH(OH)-O-tBu;

R_3 is H, =O, -OH, -O-R_7, -R_7, or –$(CH_2)_m$-L, in which m is 0, 1 or 2, and L is a 5, 6 or 7 membered carbo- or heterocycle, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO_2, -CN, -Br, -Cl, -F, -I, -O-C_{1-3}-alkyl, -hydroxyC_{1-3}-alkyl and =O;

R_4 is H or -C_{1-3}-alkyl, preferably H;

R_5 is -$(CH_2)_m$-L, or -$(CH_2)_m$-(CH=CH)-L, in which m is 0, 1 or 2, preferably 0 or 1, and L is a 5, 6 or 7 membered carbo- or heterocycle, adamantyl, C_{1-4}-alkyl, or -$N(CH_3)_2$, optionally substituted, preferably with 1, 2, 3 or 4 substituents independently selected from the group consisting of -OH, -NO_2, -CN, -CO-OR_6, -Br, -Cl, -F, -I, -R_9, -O-R_9, =O, and [-O-CH_2-CH_2]$_q$-NH-biotin with q being 1, 2, 3, or 4, or two adjacent substituents form a 5, 6 or 7 membered carbo- or heterocycle;

or

R_4 and R_5 together form a 5, 6, or 7 membered carbocycle, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO_2, -CN, -Br, -Cl, -F, -I, -O-R_9, -R_9, =CH-R_A, and –CH_2-R_A, preferably R_4 and R_5 together form a C_{5-7}-cycloalkyl;

R_6 is H, -C_{1-6}-alkyl, -C_{2-6}-alkenyl, -C_{2-6}-alkynyl, optionally substituted, preferably R_6 is H;

R_7 is -C_{1-3}-alkyl, -C_{2-3}-alkenyl, -C_{2-3}-alkynyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -Br, -Cl, -F, -I, -CH_3, -OCH_3, or -SCH_3;

R_8 is H or C_{1-6}-alkyl, preferably H,

R_9 is -C_{1-6}-alkyl, -C_{2-6}-alkenyl, -C_{2-6}-alkynyl, -C_{1-6}-alkyl-aryl, or C_{1-6}-alkyl-heteroaryl (preferably isooxazole, thiazole, tetrazole, 1,2,4-thiadiazole, 1,2,3-thiadiazole, 1,2,5-thiadiazole, pyridine, 1,2,4-oxadiazole, pyrazine, or pyrazole), optionally substituted with 1, 2 or 3 substituents selected from the group consisting of -Br, -Cl, -F, -I, -NO_2, -CN, -$CONH_2$, -CONH-C_{1-3}-alkyl (preferably –CONH-CH_3), -NH-CO-C_{1-3}-alkyl (preferably -NH-CO-CH_3), -C_{1-6}-alkyl (preferably -CH_3, ethyl, propyl, t-butyl, or pentyl), -C_{1-3}-haloalkyl (preferably-CF_3, or -CHF_2), -O-CHF_2, -O-CF_3, carbocycle (preferably cyclopropyl, cyclohexyl or phenyl), -O-carbocycle (preferably phenoxy), heterocycle (preferably pyrazolyl), -CO-heterocycle (preferably –CO-(1-pyrrolidinyl)),-SO_2-CH_3, -SO_2-N(CH_3)$_2$, -O-C_{1-4}-alkyl (preferably -OCH_3), -O-C_{1-3}-alkyl-O-C_{1-3}-alkyl (preferably –O-CH_2-O-CH_3), -SCH_3, or when R_9 is -C_{1-6}-alkyl-aryl, then two adjacent substituents on the aryl moiety can form a 5, 6 or 7 membered carbo- or heterocycle, which is optionally substituted;

R_A is H, carbo- or heterocycle, optionally substituted, preferably with 1, 2 or 3 substituents independently selected from the group consisting of -OH, -NO_2, -CN, -Br, -Cl, -F, -I, -R_9, -O-R_7, -O-(CH_2)$_o$-R_9, -SO_2NH_2, and =O, in which o is 0 or 1.

6. Use according to any preceding claim , in which the ALC1i has a structure of formula (I), in which

each one of A5, A7 and A8 is N;

A6 is C and takes part in the annulated carbo- or heterocycle Z;

L3 is CH_2-CF_2-R9 or each one of L2 and L3 is CH_2-CH_2; or L2 and L3 together with the A8 to which they are connected form a piperidine ring or a pyrrolidine ring, substituted by R4 and R9;

L4 is absent;

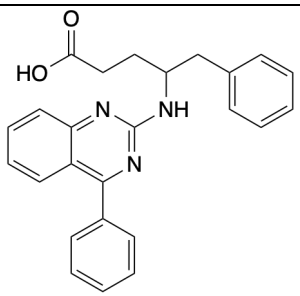
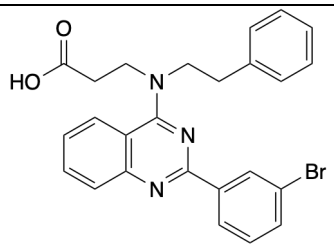
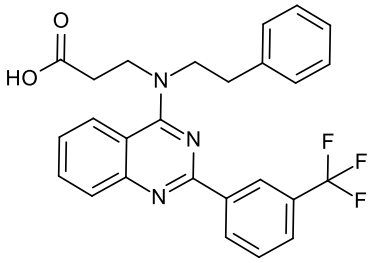
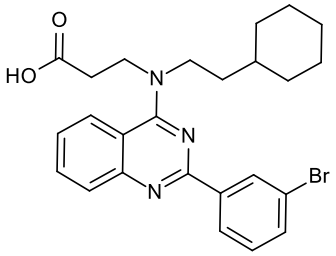
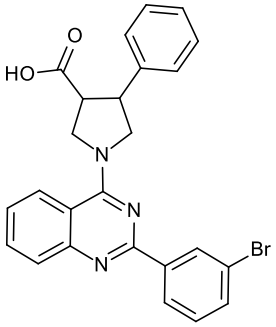
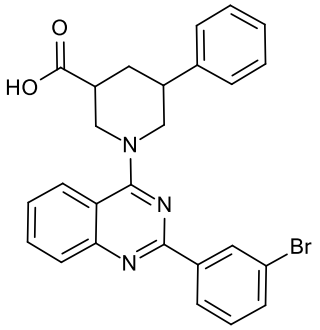
Z is phenyl or cyclohexyl annulated to the central core, in which Z is optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -OH, Me, -CF_3, -OMe, and -NO_2,

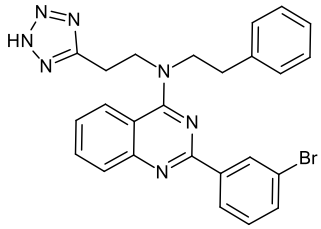
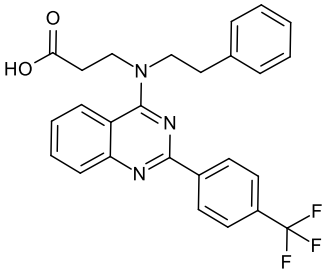
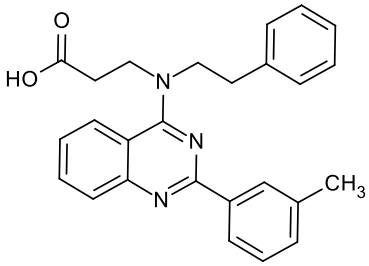
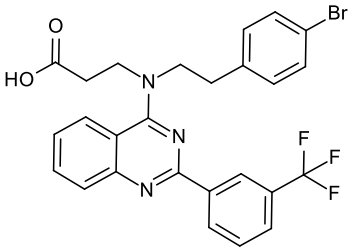
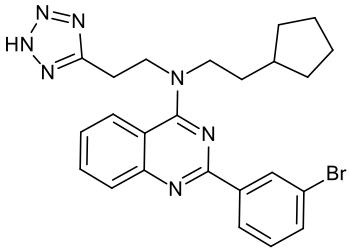
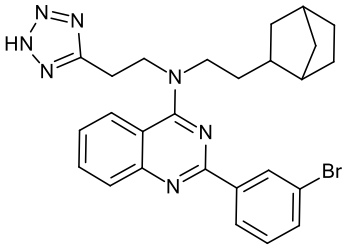
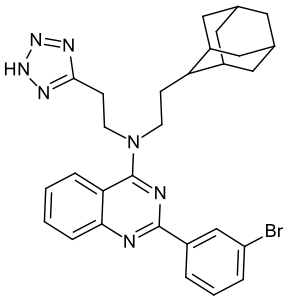
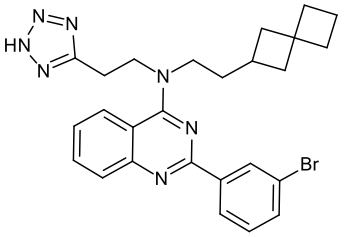
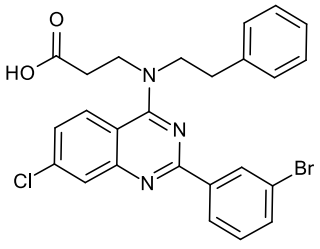
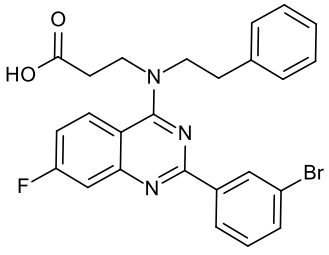
R4 is COOH or tetrazolyl;

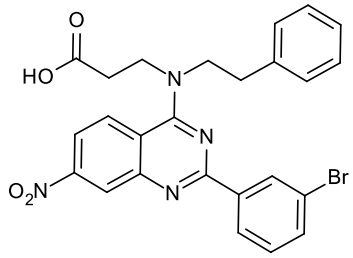
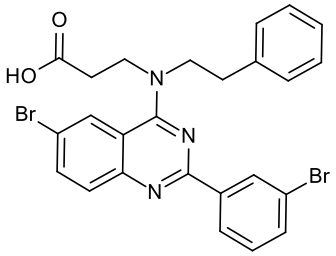
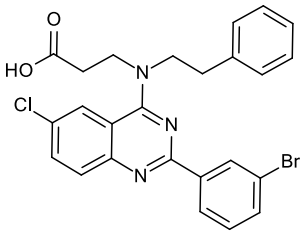
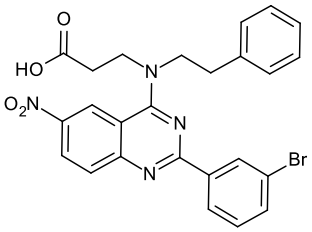
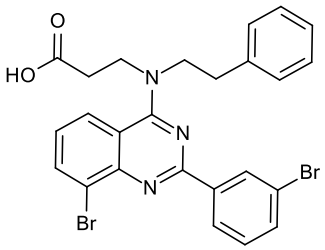
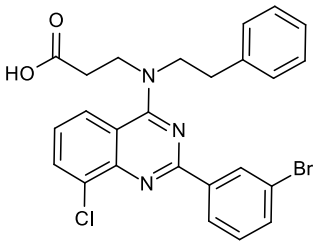
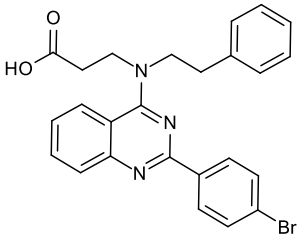
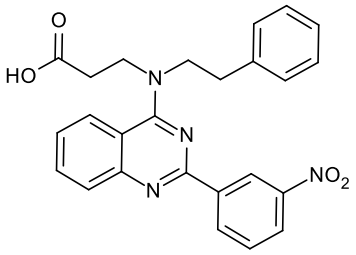
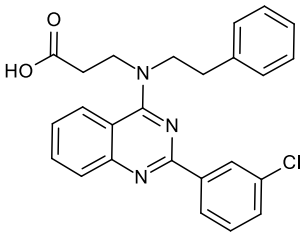
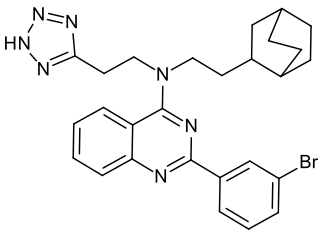
R9 is phenyl, cyclobutyl, cyclopentyl or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -CF_3, Me, -CH_2-CF_3, and –OMe;

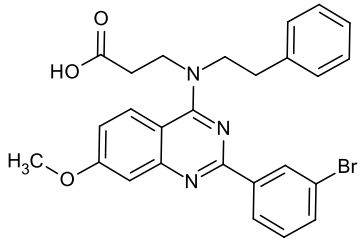
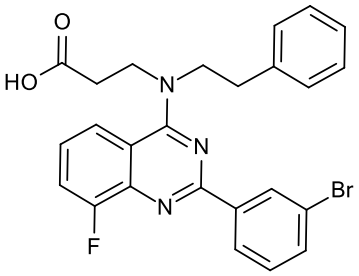
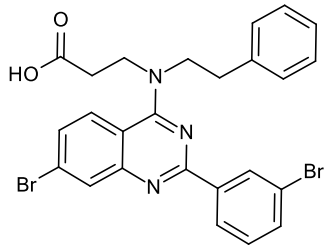
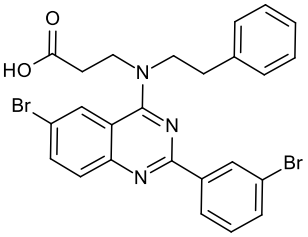
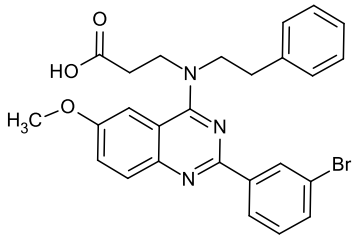
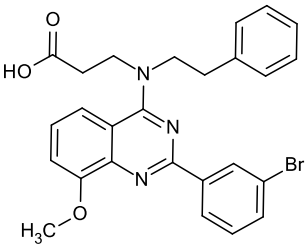
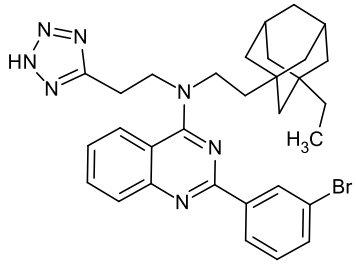
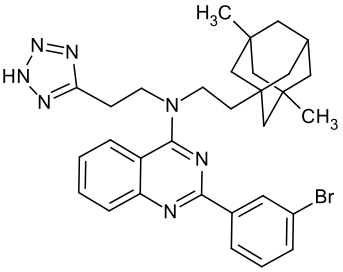
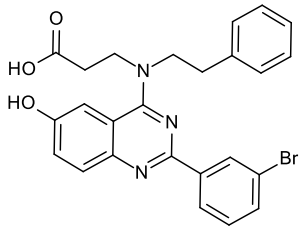
R6 is any 6-membered carbo- or heterocycle (preferably phenyl or cyclohexyl; more preferably phenyl), optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of Br, -Cl, -F, Me, -CF_3, -OMe, and -NO_2.

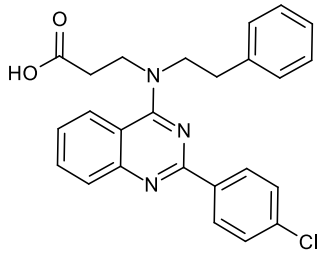
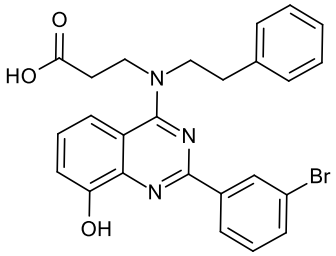
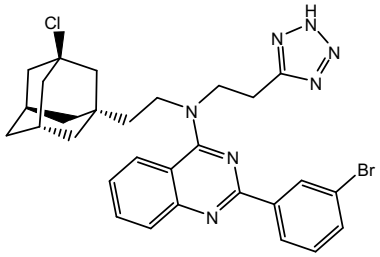
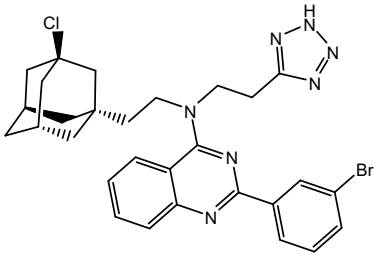
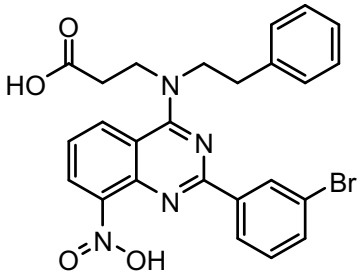
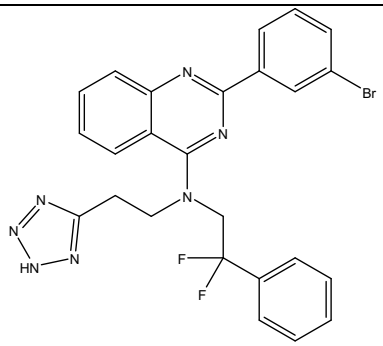
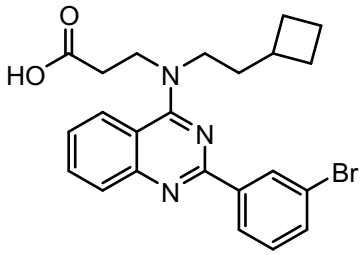
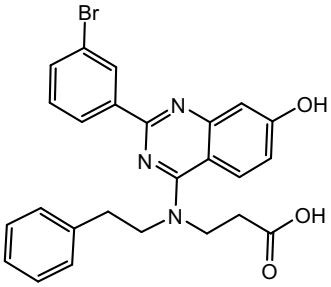
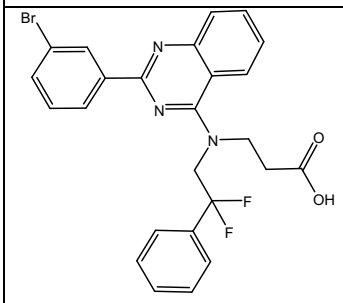
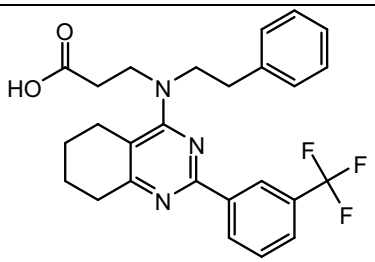
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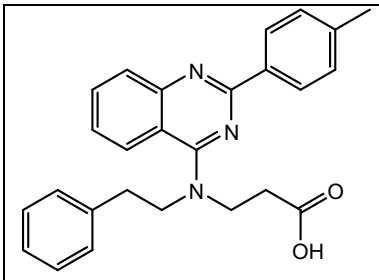
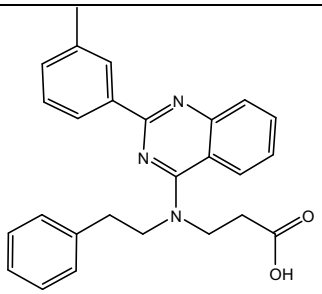
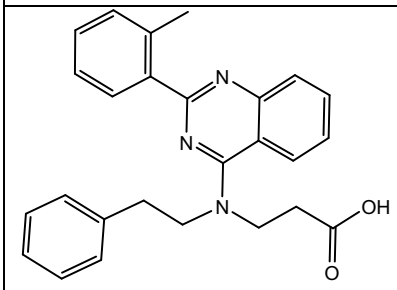
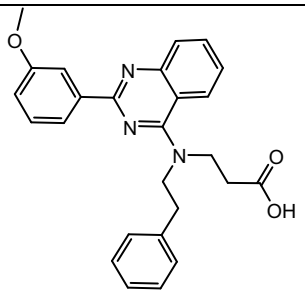
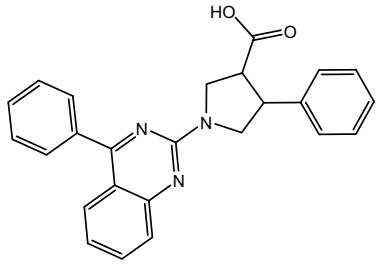
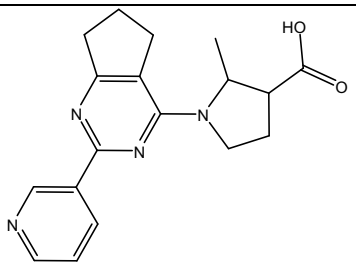
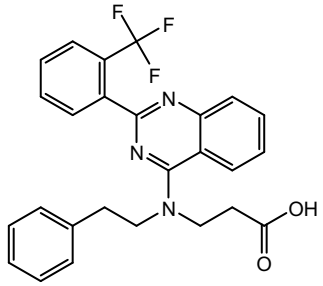
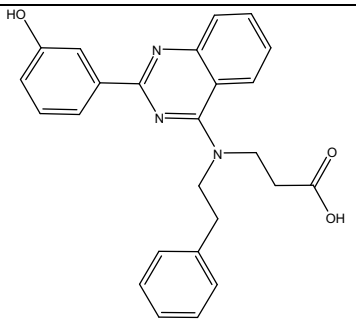
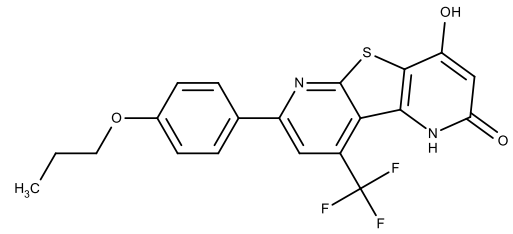
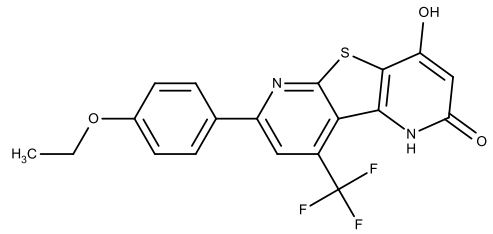
	
	
	

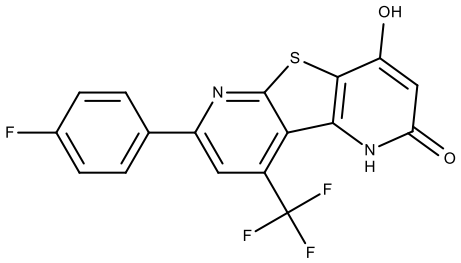
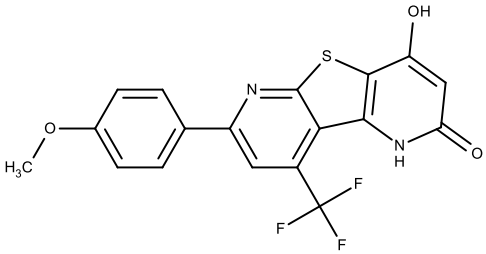
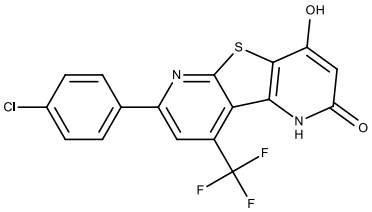
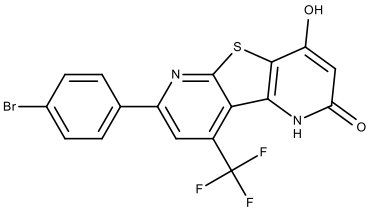
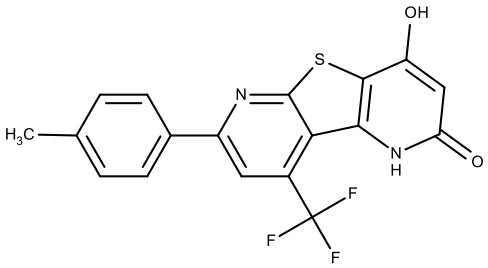
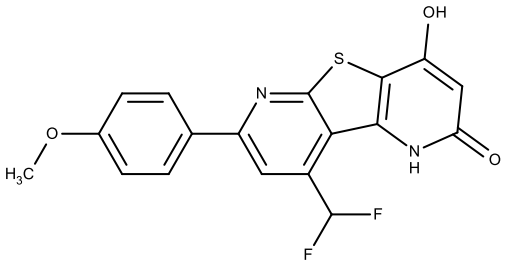
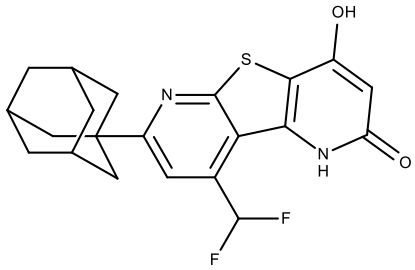
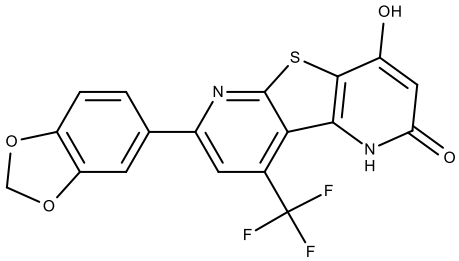
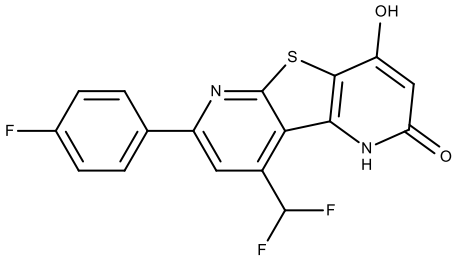
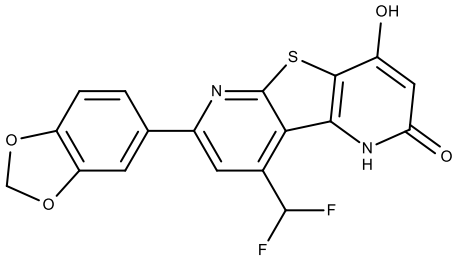
	
	
	
	
	

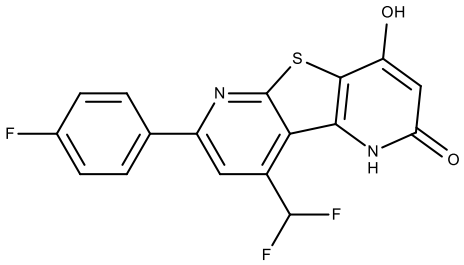
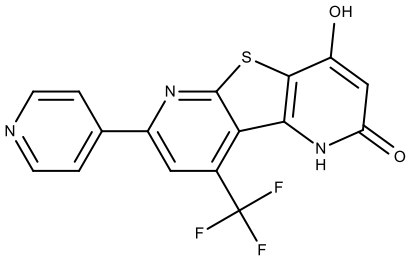
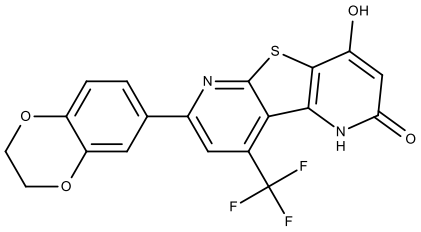
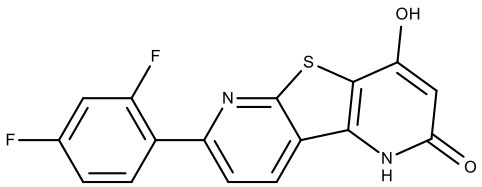
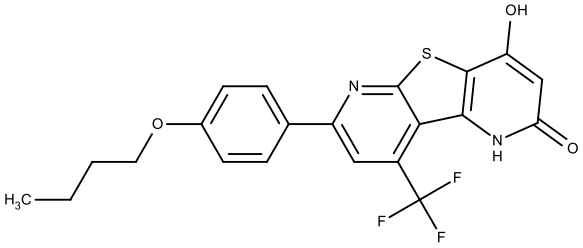
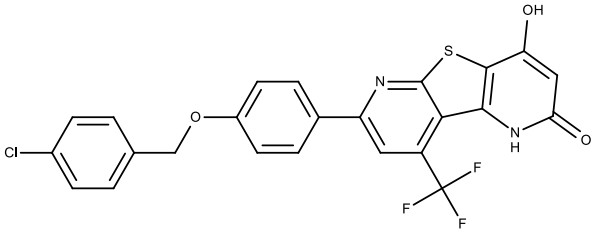
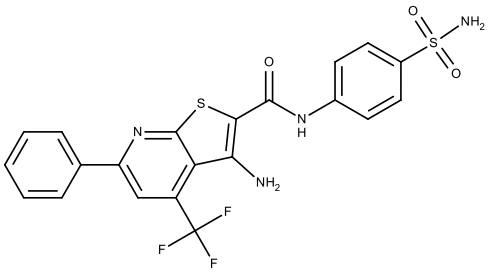
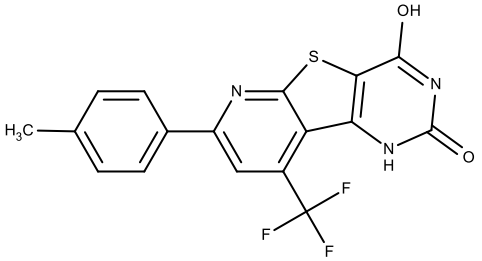
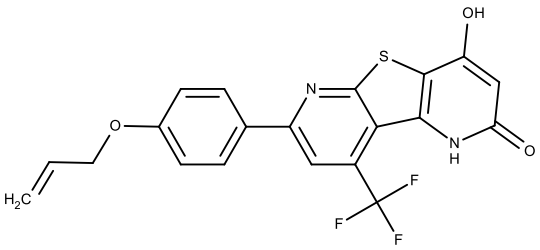
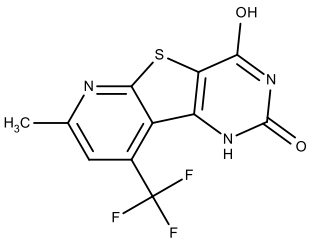
	
	
	
	
	

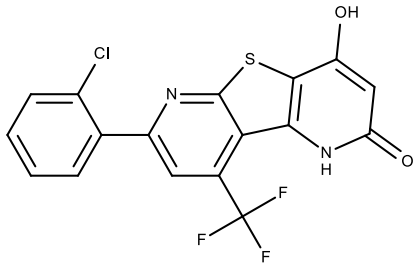
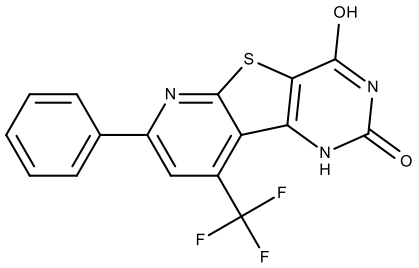
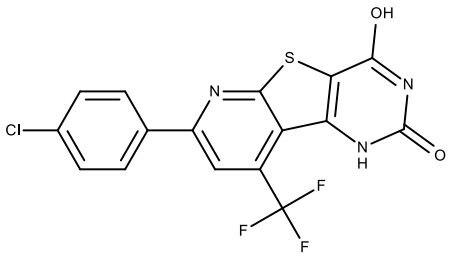
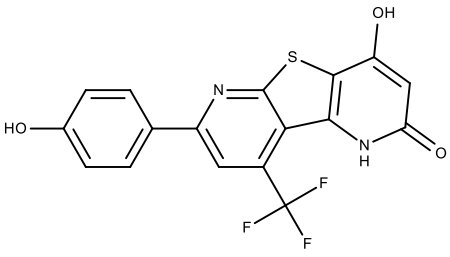
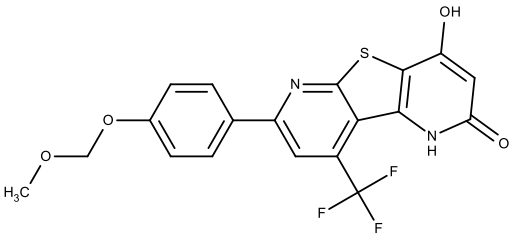
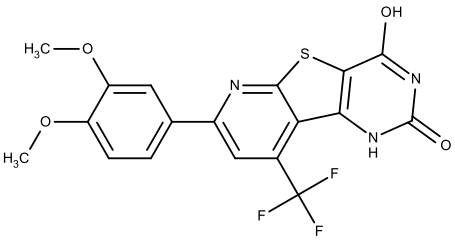
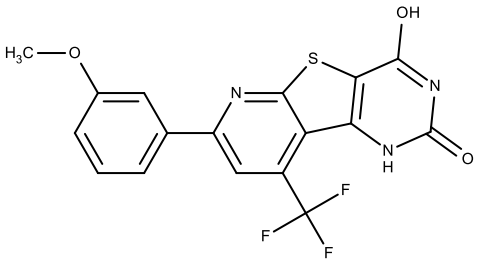
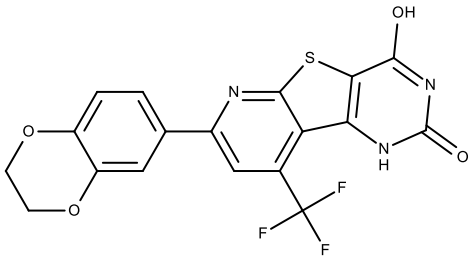
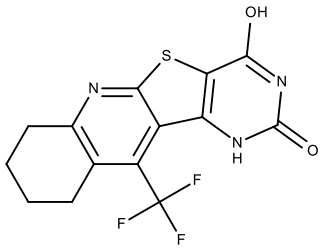
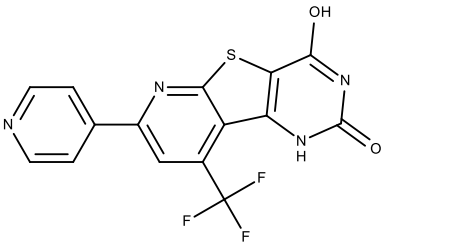
	
	
	
	
	

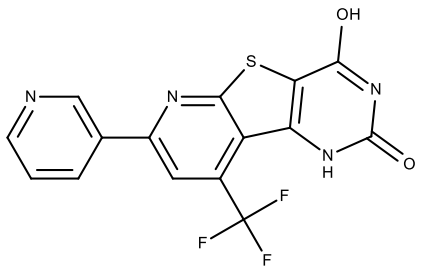
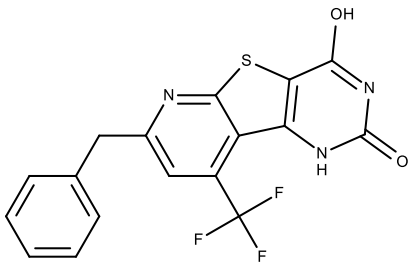
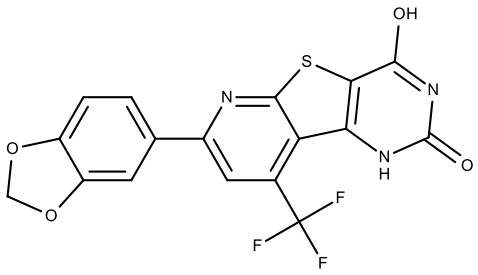
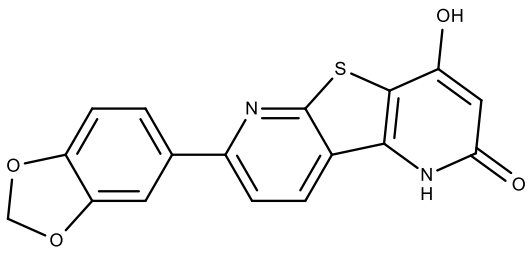
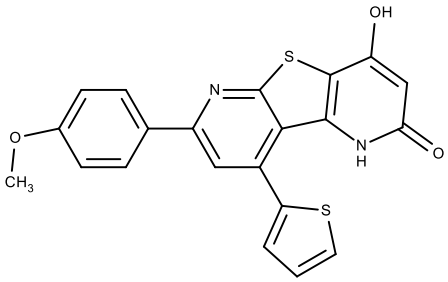
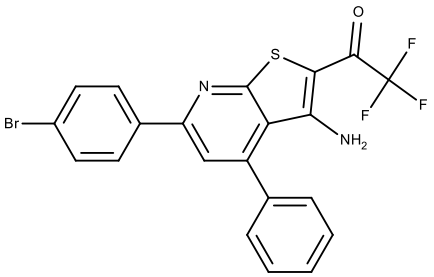
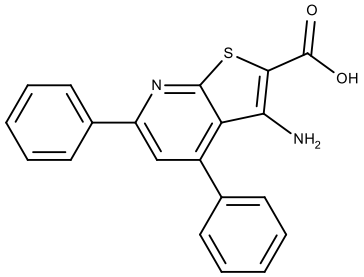
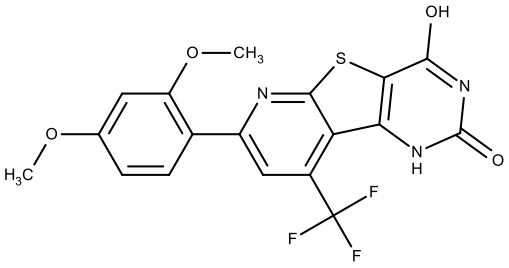
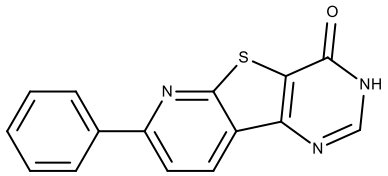
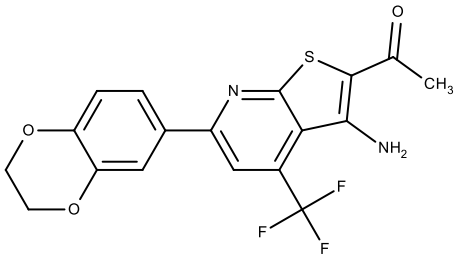
	
	
	
	
	

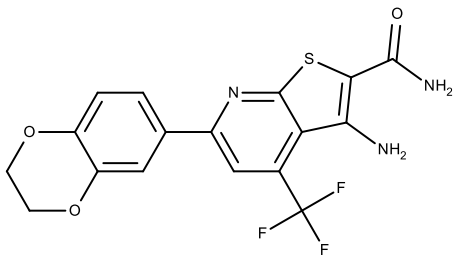
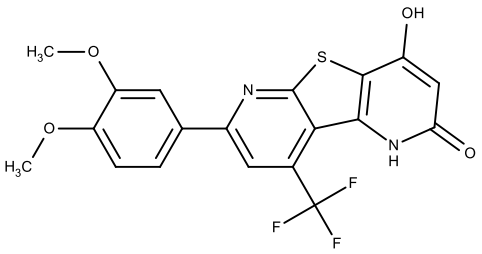
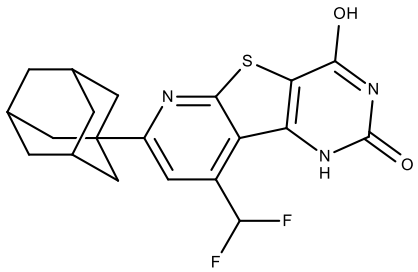
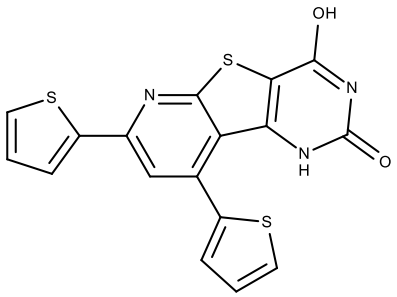
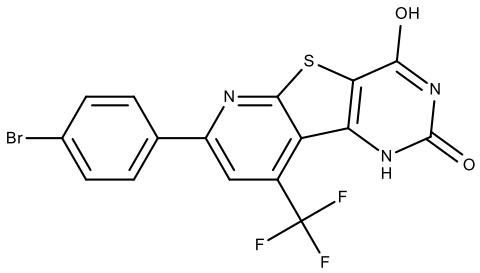
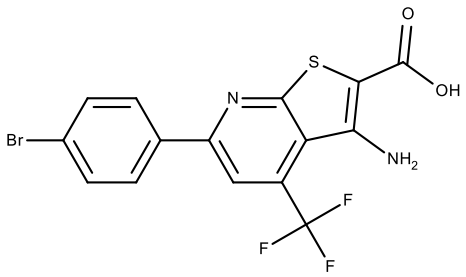
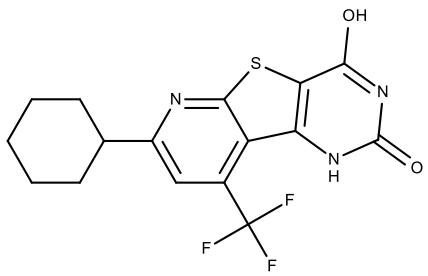
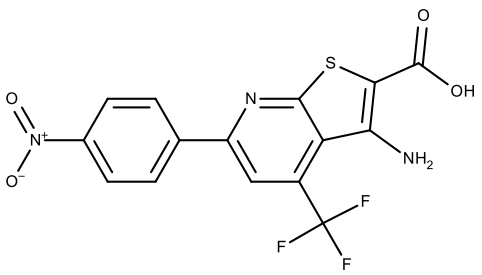
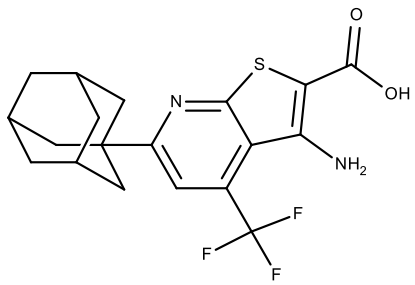
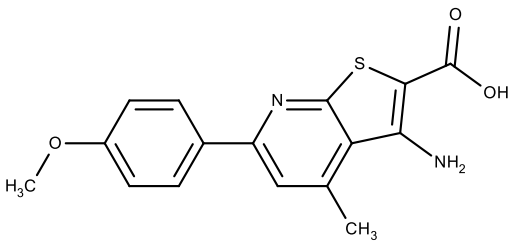
	
	
	
	
	

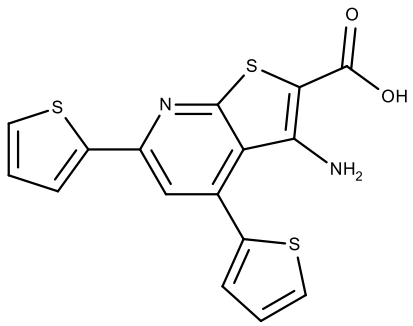
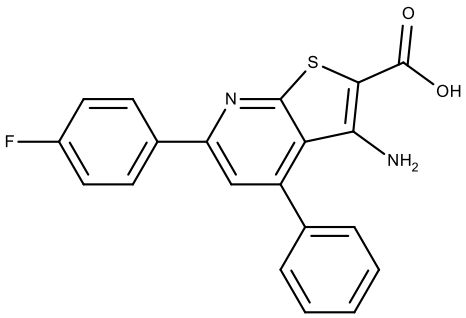
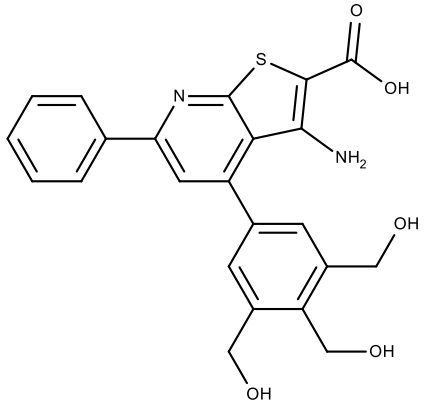
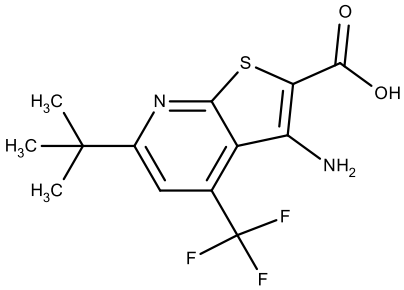
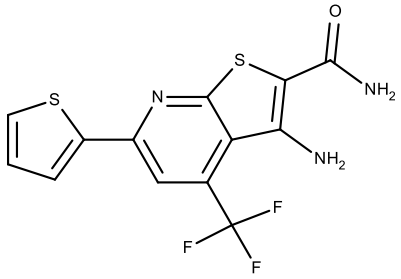
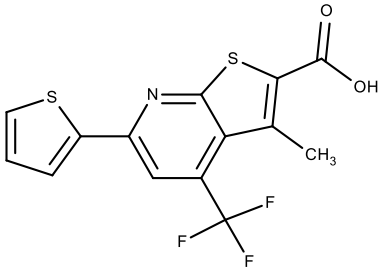
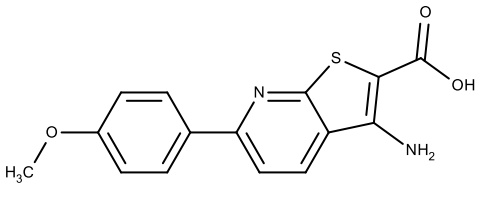
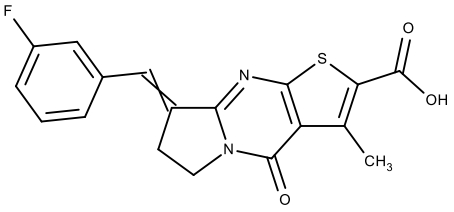
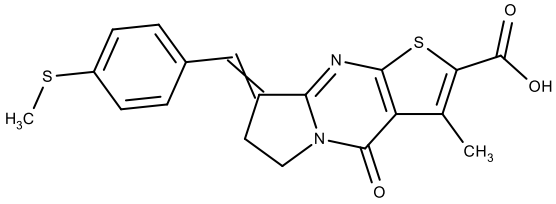
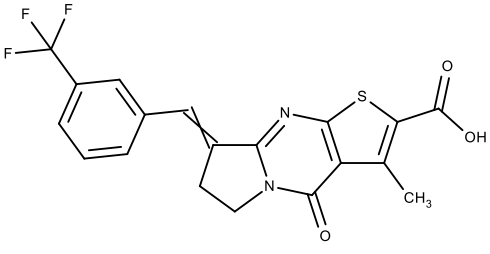
	
	
	
	
	

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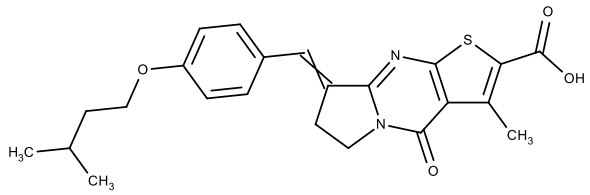
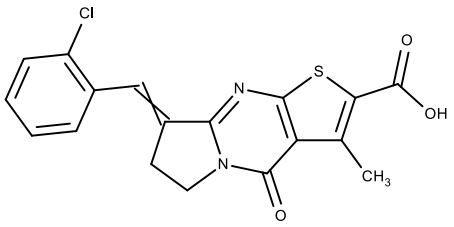
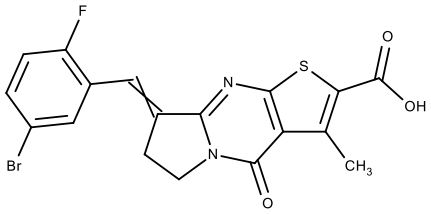
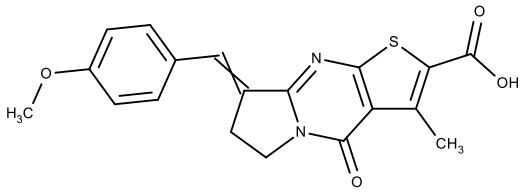
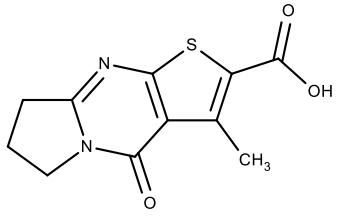
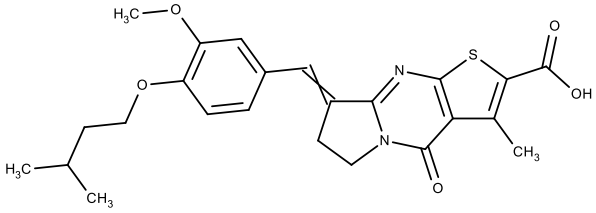
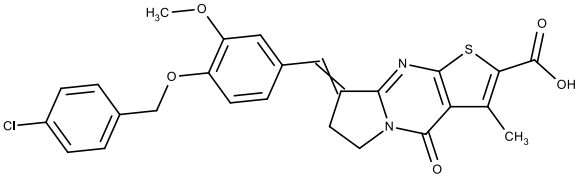
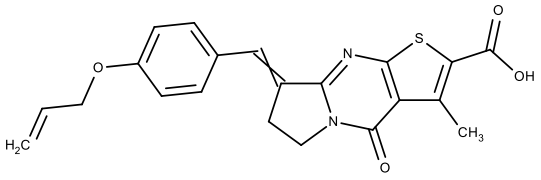
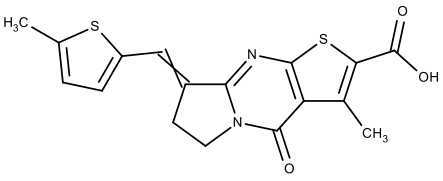
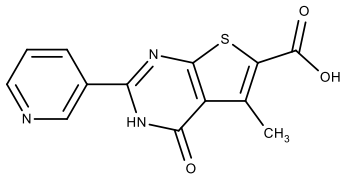
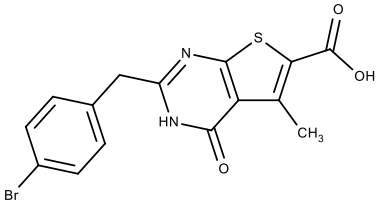
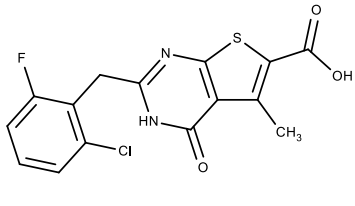
	
	
	
	
	

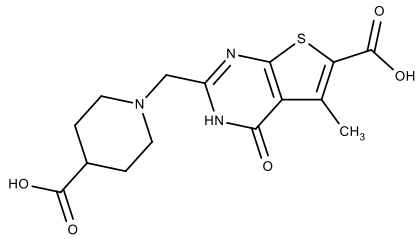
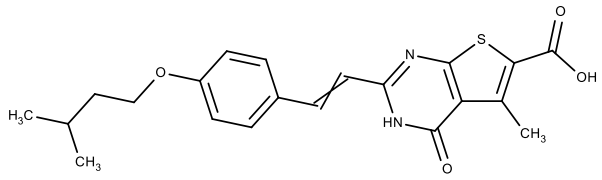
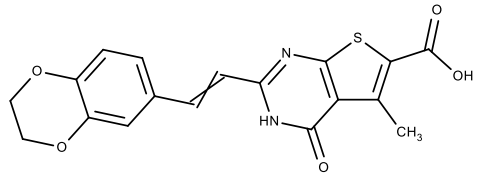
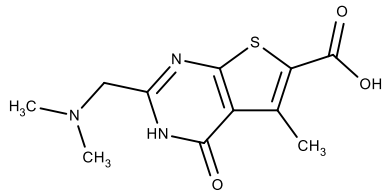
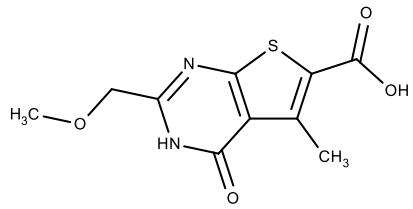
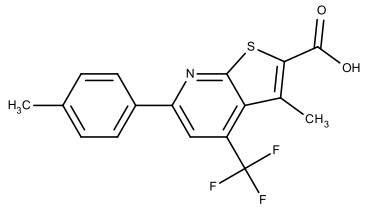
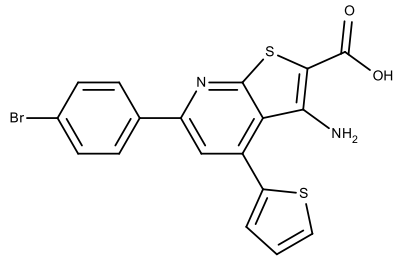
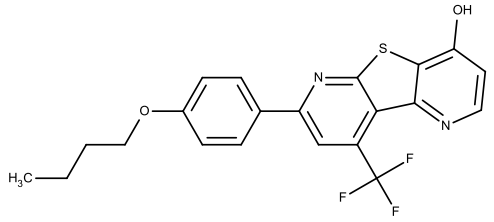
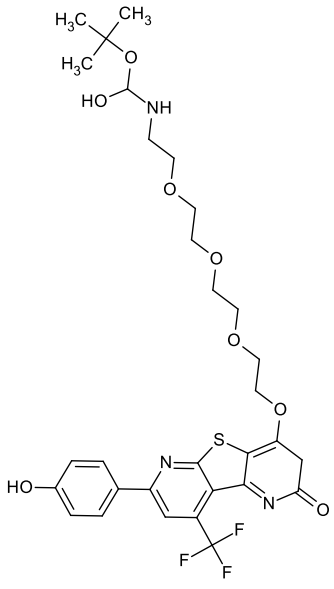
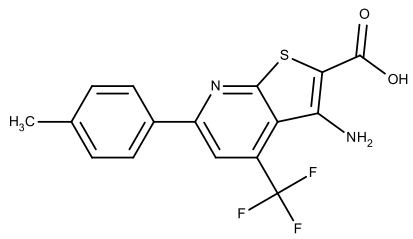
	
	
	
	
	

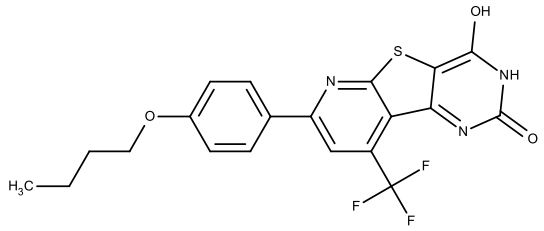
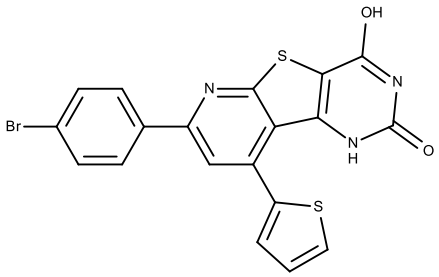
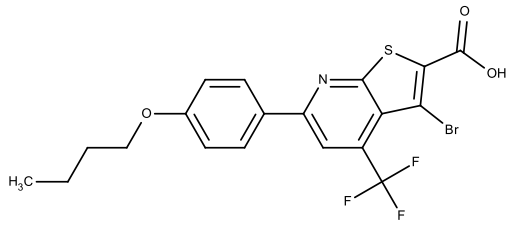
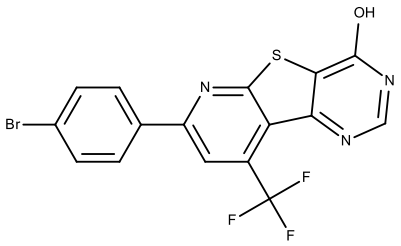
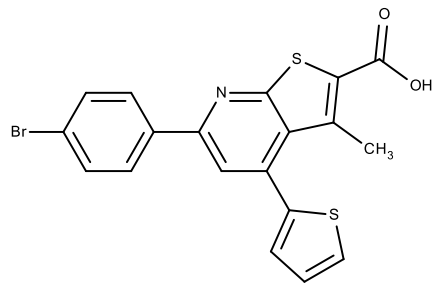
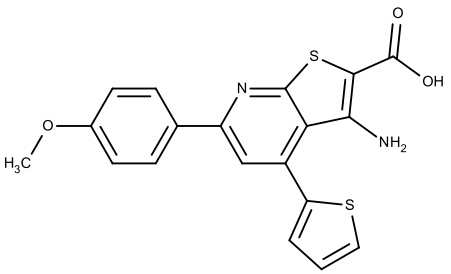
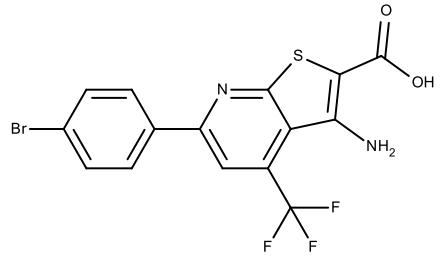
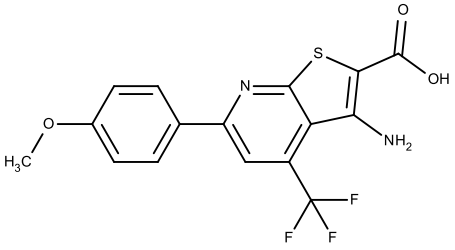
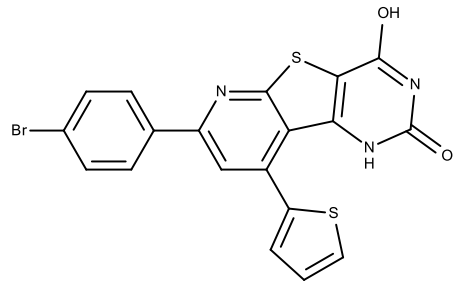
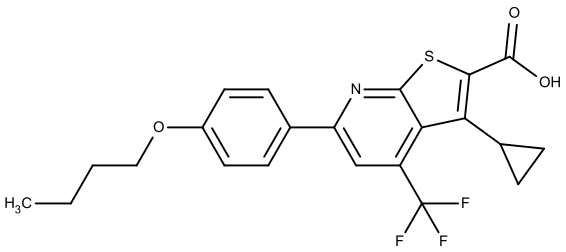
	
	
	
	
	

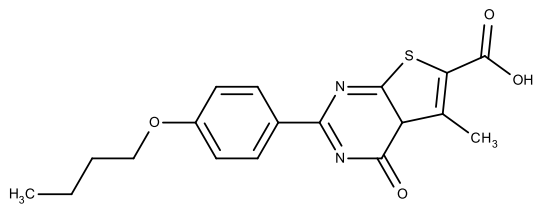
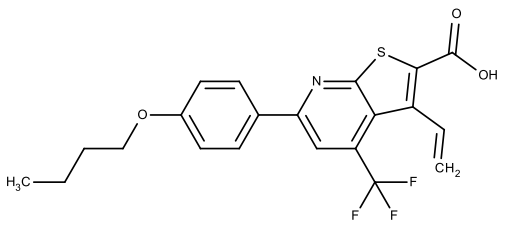
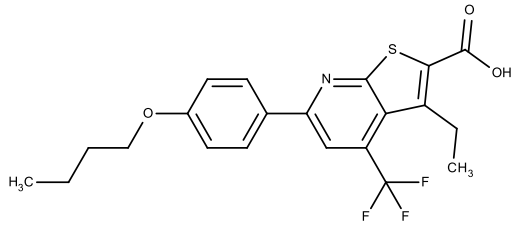
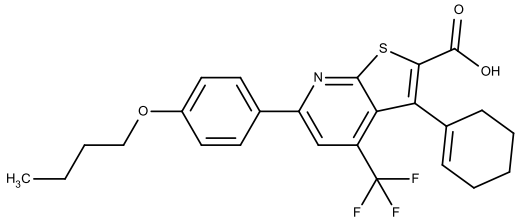
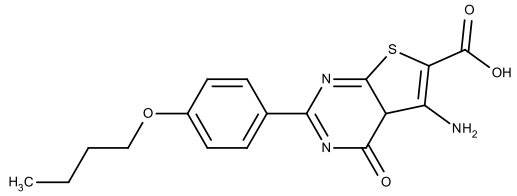
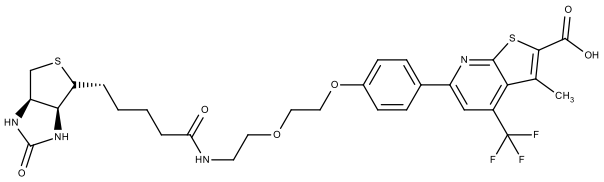
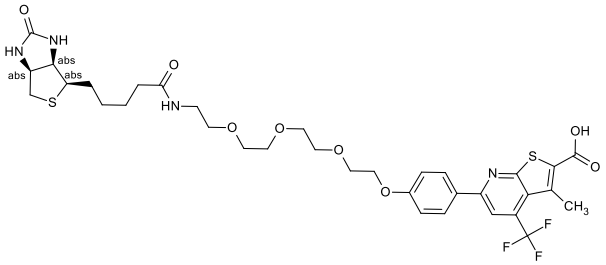
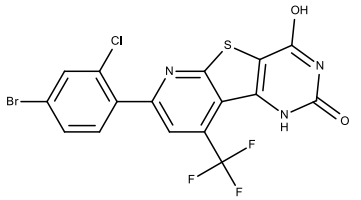
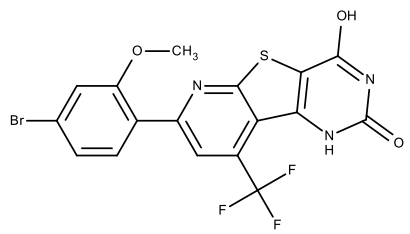
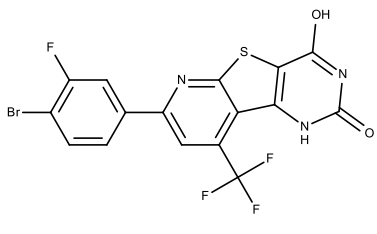
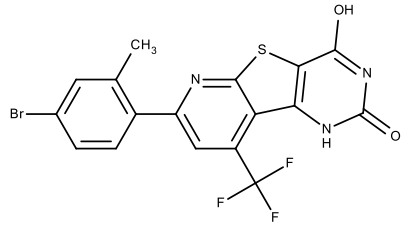
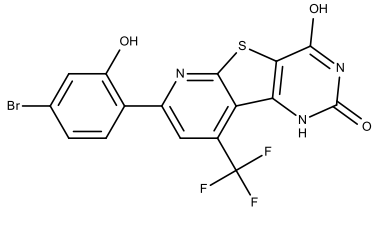
	
	
	
	
	

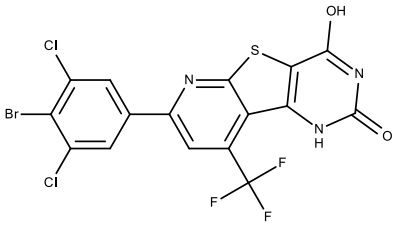
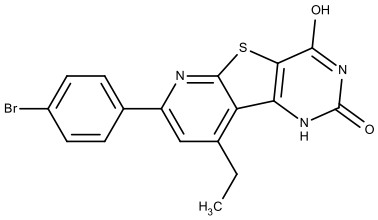
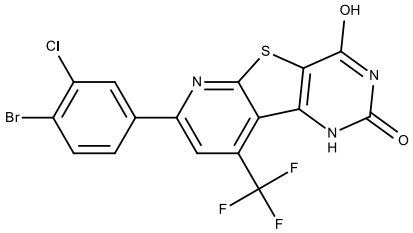
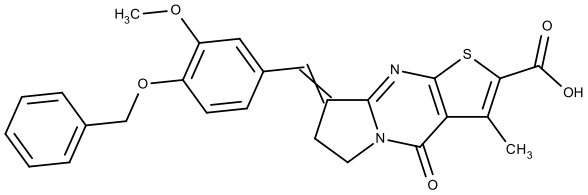
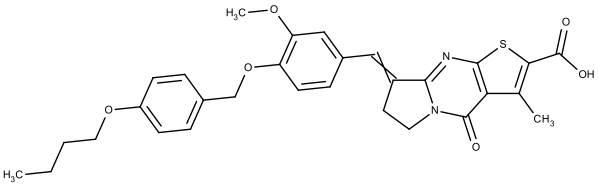
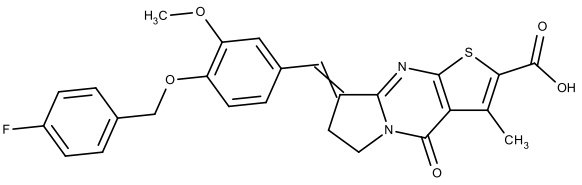
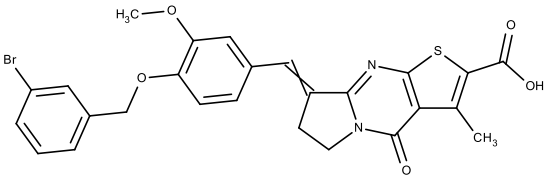
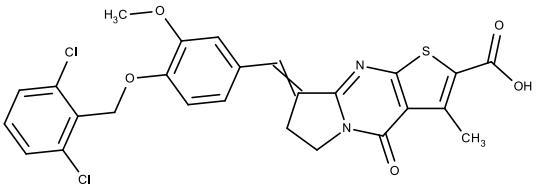
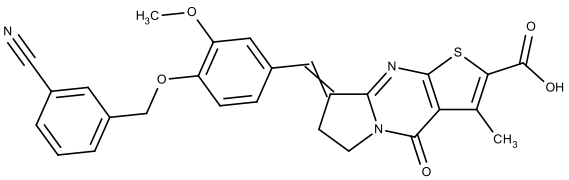
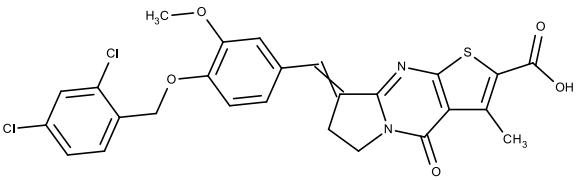
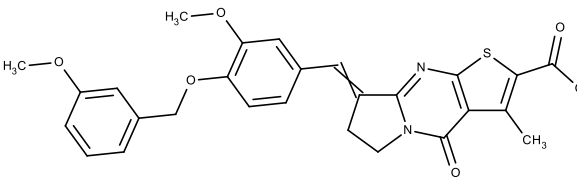
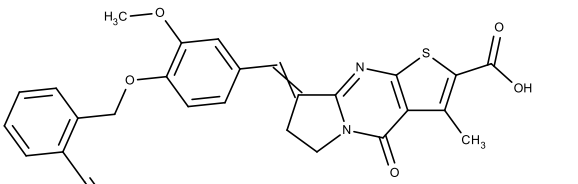
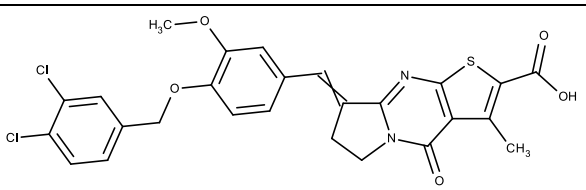
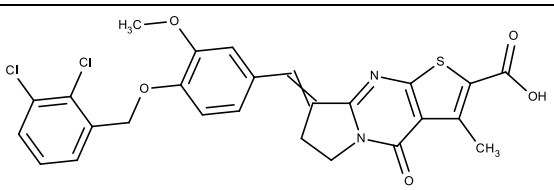
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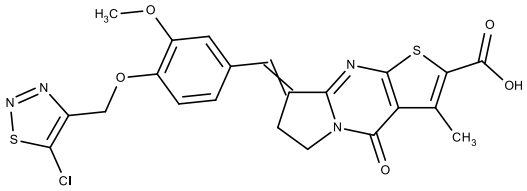
	
	
	
	
	
	

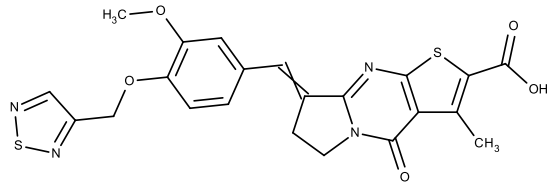
	
	
	
	
	

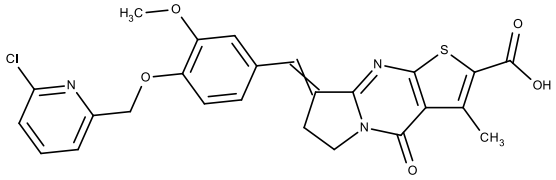
	
	
	
	
	

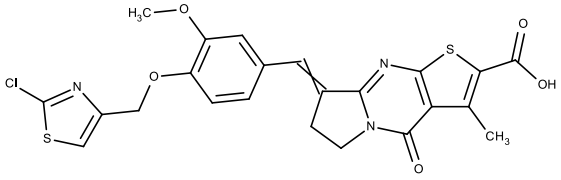
	
	
	
	
	
	

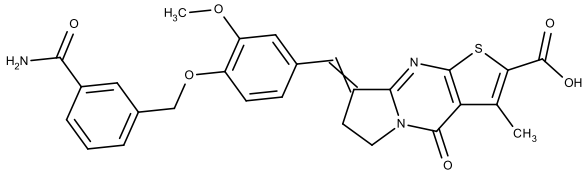
	
	
	
	
	
	
	

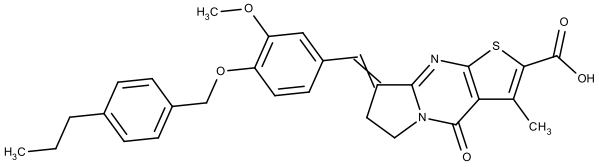


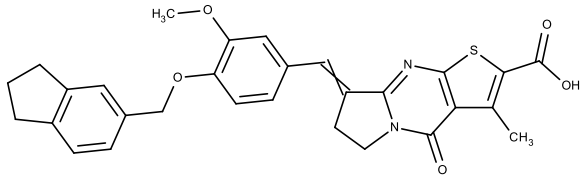


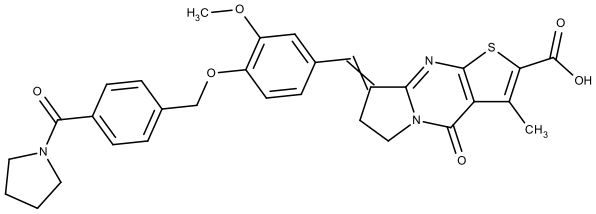


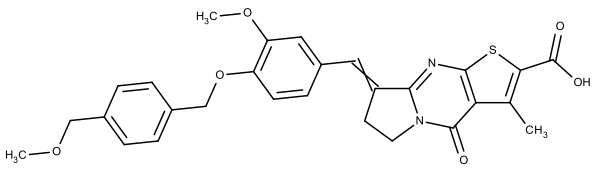


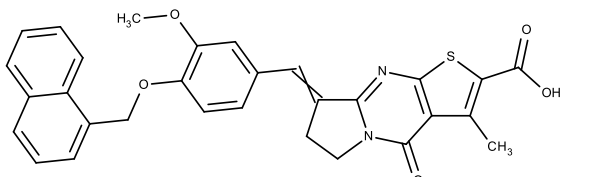


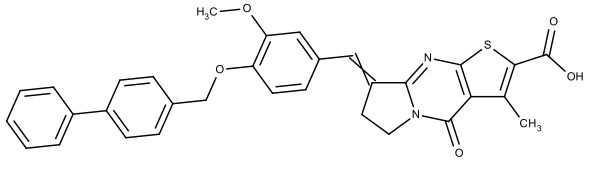


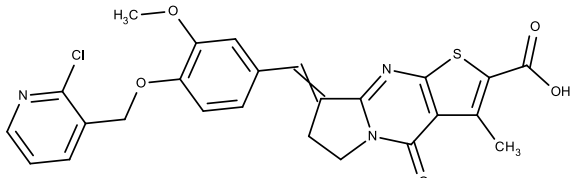


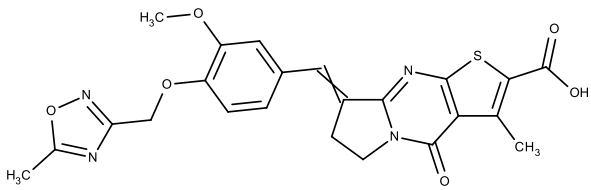


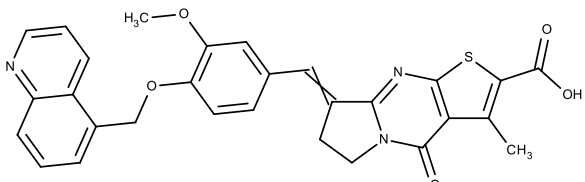


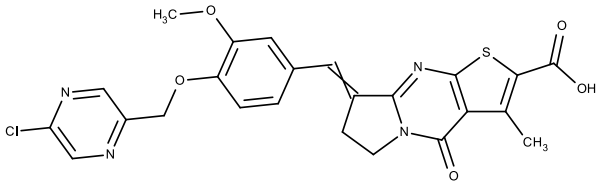


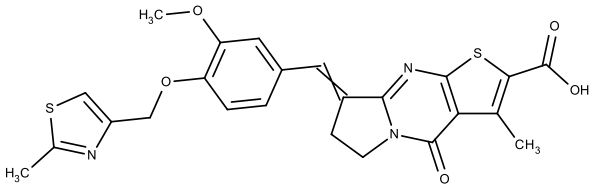


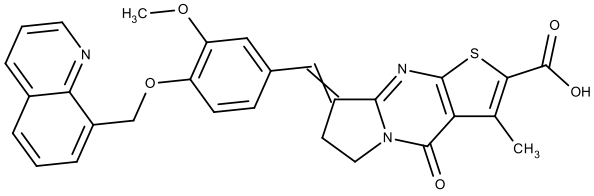


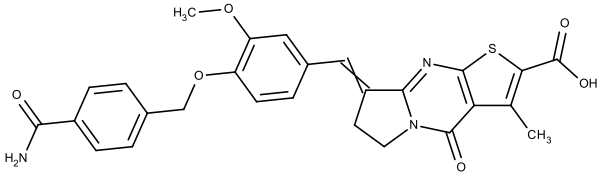


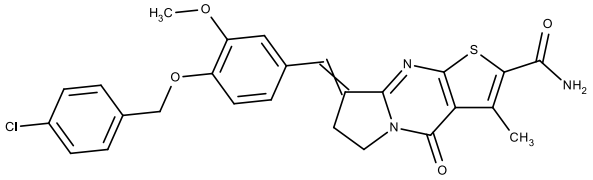


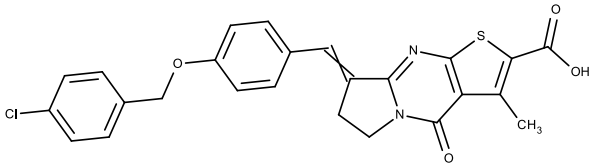


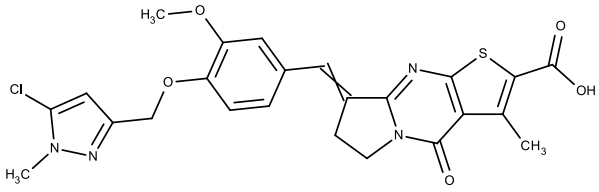


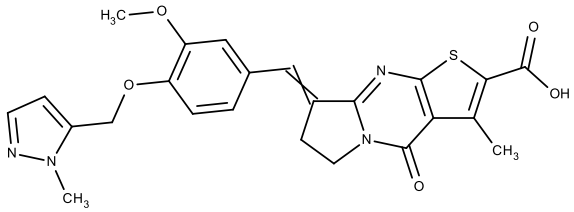


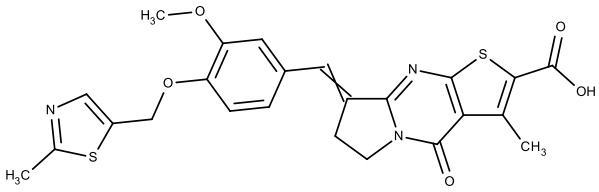


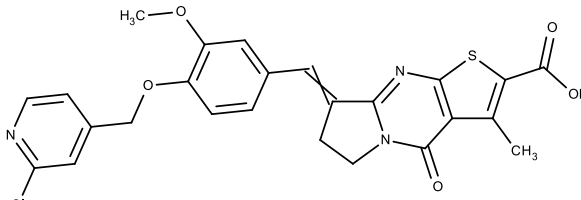


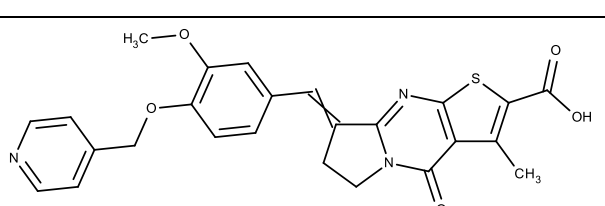


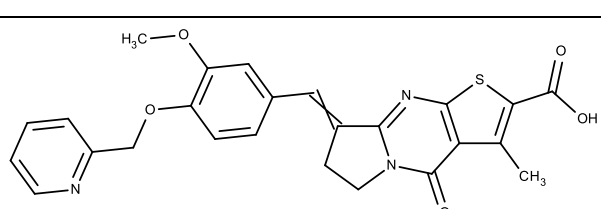


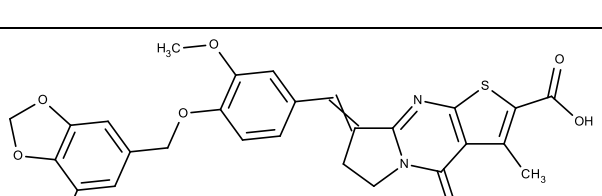


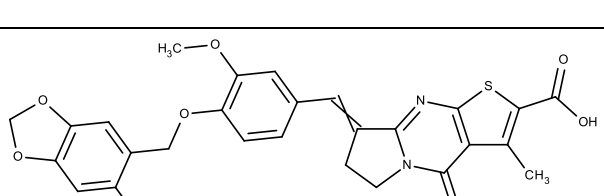


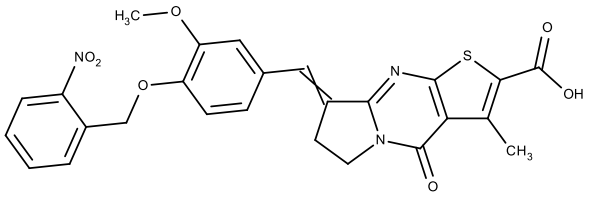
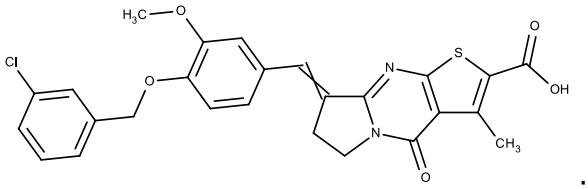
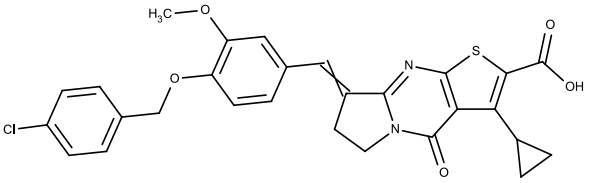










	 ; and
	

and isomers, pharmaceutically acceptable salts, solvates, chemically protected forms, and prodrugs thereof.

8. Use according to any preceding claim, in which the ALC1i and the inhibitor of Topoisomerase I, Topoisomerase II, ATM, ATR, Wee1, MEK, BRD, or of PARP, or mitomycin C, paclitaxel, or the antibody drug conjugate with a tumor specific antibody conjugated to a TOP1 inhibitor, such as trastuzumab deruxtecan, datopotamab deruxtecan, or sacituzumab govitecan, are to be administered simultaneously or subsequently.

9. Use according to any preceding claim, in which the proliferative disease is selected from a HR deficient cancer, preferably a BRCA-1 and/or BRCA-2-deficient tumor, and/or in which the proliferative disease is selected from hepatocellular carcinoma, breast cancer, ovarian cancer, fallopian tube cancer, primary peritoneal cancer, prostate cancer, colorectal cancer, or pancreatic cancer.

10. A pharmaceutical composition comprising an ALC1i as defined in any of Claims 1 to 7 and

(a) an inhibitor of Topoisomerase I, Topoisomerase II, ATM, ATR, Wee1, and/or BRD, MEK,

(b) mitomycin C or paclitaxel, or

(c) an antibody drug conjugate with a tumor specific antibody conjugated to a TOP1 inhibitor.

11. A pharmaceutical composition according to Claim 10, which is for use in treating or ameliorating a proliferative disease, preferably the proliferative disease is selected from a HR deficient cancer, preferably a BRCA-1 and/or BRCA-2-deficient tumor, and/or the proliferative disease is selected from hepatocellular carcinoma, breast cancer, ovarian cancer, fallopian tube cancer, primary peritoneal cancer, prostate cancer, colorectal cancer, or pancreatic cancer.

12. A kit of parts comprising

(i) an ALC1i as defined in any of Claims 1 to 7 with instructions to combine it with

(a) an inhibitor of Topoisomerase I, Topoisomerase II, ATM, ATR, Wee1, MEK, and/or BRD,

(b) mitomycin C or paclitaxel, or

(c) ionizing radiation; or

(d) an antibody drug conjugate with a tumor specific antibody conjugated to a TOP1 inhibitor, or

(ii) comprising

(a) an inhibitor of Topoisomerase I, Topoisomerase II, ATM, ATR, Wee1, MEK, and/or BRD, or

(b) mitomycin C, paclitaxel, or an antibody drug conjugate with a tumor specific antibody conjugated to a TOP1 inhibitor,

with instructions to combine it with an ALC1i as defined in any of Claims 1 to 5, or

(iii) comprising separately packaged an ALC1i as defined in any of Claims 1 to 5 and

(a) an inhibitor of Topoisomerase I, Topoisomerase II, ATM, ATR, Wee1, MEK, and/or BRD, or

(b) mitomycin C or paclitaxel, or

(c) an antibody drug conjugate with a tumor specific antibody conjugated to a TOP1 inhibitor,

optionally with instructions for use in treating or ameliorating a proliferative disease.

13. Use of a kit of parts according to Claim 12 in the preparation of a medicament for the treatment or amelioration of a proliferative disease, preferably the proliferative disease is selected from a HR deficient cancer, preferably a BRCA-1 and/or BRCA-2-deficient tumor, and/or the proliferative disease is selected from hepatocellular carcinoma, breast cancer, ovarian cancer, fallopian tube cancer, primary peritoneal cancer, prostate cancer, colorectal cancer, or pancreatic cancer.

14. Use according to any of Claims 1 to 9 and 13, a pharmaceutical composition according to Claim 10 or 11 or a kit according to Claim 12, in which the ALC1i is combined with any one of adavosertib, AZ-32, AZD-1056, AZD-1390, BAY-299, ABBV-744, trametinib, ceralasertib, elimusertib, paclitaxel, Mitomycin C, teniposide, topotecan, AZD-5305, niraparib, olaparib, rucaparib, veliparib, talazoparib, trastuzumab deruxtecan, datopotamab deruxtecan, and/or sacituzumab govitecan.

15. Use of a pharmaceutical composition comprising ALC1i-101 or a salt thereof and trastuzumab deruxtecan in the preparation of a medicament for the treatment or amelioration of a proliferative disease, preferably the proliferative disease is selected from a HR deficient cancer, preferably a BRCA-1 and/or BRCA-2-deficient cancer, and/or the proliferative disease is selected from hepatocellular carcinoma, breast cancer, ovarian cancer, fallopian tube cancer, primary peritoneal cancer, prostate cancer, colorectal cancer, or pancreatic cancer.

16. Use of a pharmaceutical composition comprising ALC1i-101 or a salt thereof and trastuzumab deruxtecan in the preparation of a medicament for the treatment of advanced or metastatic cancer with homologous recombination deficiency (HRD) mutations.

17. Use according to any of Claims 1 to 9, 13, 15 and 16, a pharmaceutical composition according to Claim 10 or 11 or a kit according to Claim 12, in which the patient to be treated is receiving or received trastuzumab deruxtecan and does or did not show at least a partial response, preferably after several treatment cycles.