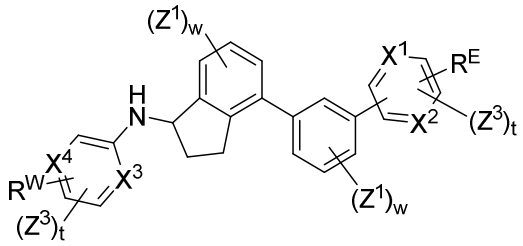
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound of formula (I):



(I)

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, solvate, or tautomer thereof, wherein:

each of X^1, X^2, X^3 and X^4 are independently N, CH or CZ^3;

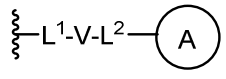
each Z^1 is independently is halo, $-OR^a$, $-NO_2$, cyano, $-NR^aR^b$, $-N_3$, $-S(O)_2R^a$, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$ alkynyl, $-O-C_{1-6}$ alkyl, $-O-C_{1-6}$ haloalkyl, $-C_{3-8}$ cycloalkyl, or $-C_{1-6}$ alkylC_{3-8} cycloalkyl; and

wherein each alkyl, alkenyl, alkynyl, and cycloalkyl is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, and cyano;

each w is independently 0, 1 or 2;

each Z^3 is independently halo, $-OR^a$, $-N_3$, $-NO_2$, cyano, $-NR^1R^2$, $-S(O)_2R^a$, $-S(O)_2NR^aR^b$, $-NR^aS(O)_2R^a$, $-NR^aC(O)R^a$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-NR^aC(O)OR^a$, $-NR^aC(O)NR^1R^2$, $-OC(O)NR^aR^b$, $-NR^aS(O)_2NR^aR^b$, $-C(O)NR^aS(O)_2NR^aR^b$, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-O-C_{1-6}$ alkyl, $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ haloalkyl, $-O-C_{1-6}$ cyanoalkyl, $-O-C_{1-6}$ haloalkyl, $-C_{3-8}$ cycloalkyl, $-C_{1-6}$ alkylC_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, and R^N; and

wherein the alkyl, alkenyl, alkynyl, C_{3-8} cycloalkyl, aryl, heteroaryl, or heterocyclyl group is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-O-C_{1-6}$cyanoalkyl, $-C(O)NR^aR^b$, $-NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-S(O)_2R^a$, $-NR^aS(O)_2R^b$, $-SO_2NR^aR^b$, $-NR^aS(O)_2NR^aR^b$, $-C(O)NR^aS(O)_2NR^aR^b$ and $-C_{3-8}$ cycloalkyl;

R^N is independently $-C_{1-6}$ alkylNR^1R^2, $-OC_{1-6}$ alkylNR^1R^2, $-C_{1-6}$ alkyl-$O-C_{1-6}$ alkylNR^1R^2, $-NR^aC_{1-6}$ alkylNR^1R^2, $-C_{1-6}$ alkyl$C(O)NR^1R^2$, $-O-C_{1-6}$ alkyl$C(O)NR^1R^2$, $-O-C_{1-6}$ alkyl$C(O)OR^1$, $-SC_{1-6}$ alkylNR^1R^2, $-C_{1-6}$ alkylOR^a, or ;

wherein:

L^1 is independently a bond, -O-, $-NR^a$-, -S-, -S(O)-, or $-S(O)_2$-;

V is independently selected from a bond, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

wherein each alkyl, alkenyl, or alkynyl is optionally independently substituted with $-OR^a$, halo, cyano, $-NR^aR^b$ or $-C_{3-8}$ cycloalkyl;

L^2 is independently a bond, -O-, $-NR^a-$, -S-, -S(O)-, or $-S(O)_2-$;

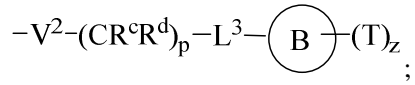
ring A is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

wherein each cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-O-C_{1-6}$ haloalkyl, $-NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-O-C_{1-6}$ cyanoalkyl, $-C(O)NR^aR^b$, $-NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-NR^aC(O)OR^a$, $-C(O)N(R^a)OR^b$, $-S(O)_2R^a$, $-S(O)_2NR^aR^b$, $-NR^aS(O)_2R^b$, $-NR^aS(O)_2NR^aR^b$, $-C(O)NR^aS(O)_2NR^aR^b$, C_{3-8} cycloalkyl, and $-C_{1-6}$ alkylC_{3-8} cycloalkyl; and

wherein the alkyl, alkenyl, or alkynyl group is optionally independently substituted with $-OR^a$, halo, cyano, $-NR^aR^b$ or $-C_{3-8}$ cycloalkyl;

each t is independently 0, 1 or 2;

R^E and R^W are each independently $-NR^1R^2$, $-C_{1-6}$ alkylNR^1R^2, $-O-C_{1-6}$ alkylNR^1R^2, $-C_{1-6}$ alkyl-O-C_{1-6}alkylNR^1R^2, $-NR^a-C_{1-6}$ alkylNR^1R^2, $-C_{1-6}$ alkyl$N^+R^1R^2R^3$, -S-C_{1-6} alkylNR^1R^2, $-C(O)NR^1R^2$, $-S(O)_2R^a$, $-(CH_2)_uS(O)_2NR^1R^2$, $-(CH_2)_uNR^aS(O)_2NR^aR^b$, $-S(O)_2NR^aC_{1-6}$ alkylNR^1R^2, $-NR^aS(O)_2C_{1-6}$ alkylNR^1R^2, $-(CH_2)_uC(O)NR^aS(O)_2NR^aR^b$, $-(CH_2)_uN^+R^1R^2O^-$, $-(CH_2)_uP^+R^bR^cR^d$, $-(CH_2)_uP^+R^cR^dO^-$, $-(CH_2)_uP^+O[NR^aR^b][NR^cR^d]$, $-(CH_2)_uNR^cP(O)(OR^c)_2$, $-(CH_2)_uCH_2OP(O)(OR^c)(OR^d)$, $-(CH_2)_uOP(O)(OR^c)(OR^d)$, $-(CH_2)_uOP(O)NR^aR^b)(OR^a)$, or



;

wherein:

V^2 is independently a bond, -O-, $-NR^a-$, -S-, -SO-, $-SO_2-$, $-C(O)NR^a-$, $-NR^aC(O)-$, $-S(O)_2NR^1-$, or $-NR^aS(O)_2-$;

L^3 is independently a bond, -O-, $-NR^a-$, -S-, -SO-, $-SO_2-$, $-C(O)NR^a-$, $-NR^aC(O)-$, $-S(O)_2NR^1-$, or $-NR^aS(O)_2-$;

ring B is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

T is independently hydrogen, $-OR^a$, $-(CH_2)_qNR^1R^2$, $-(CH_2)_qNR^aC(O)R^e$, or $-(CH_2)_qC(O)R^e$;

p is independently 0, 1, 2, 3, 4, or 5;

q is independently 0, 1, 2, 3, 4, or 5;

u is 0, 1, 2, 3, or 4;

z is 0, 1, 2, or 3; and

wherein the alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl of R^E or R^W is optionally substituted with 1 to 3 substituents independently selected from the group consisting of $-NR^aR^b$, halo, cyano, oxo, $-OR^a$, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ alkylNR^aR^b, $-C_{1-6}$ hydroxyalkyl, $-C_{3-8}$ cycloalkyl, and $-C_{1-3}$ alkylC_{3-8}cycloalkyl;

provided that at least one of V^2, L^3, ring B and T contains a nitrogen atom;

each R^1 is independently selected from hydrogen, $-C_{1-8}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-C_{3-6}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-C_{1-6}$ alkylheterocyclyl, $-C_{1-6}$ alkyl$C(O)OR^a$, $-C_{2-6}$ alkenyl$C(O)OR^a$, $-S(O)_2R^a$, $-S(O)_2NR^aR^b$, $-C(O)NR^aS(O)_2R^a$, and $-C_{1-6}$ alkylC_{3-8}cycloalkyl;

wherein each alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from $-OR^a$, cyano, halo, C_{1-6} alkyl, $-C_{1-6}$ alkylOR^a, $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ haloalkyl, C_{3-8} cycloalkyl, $-C_{1-3}$ alkylC_{3-8}cycloalkyl, $-C(O)R^a$, $-C_{1-6}$ alkyl$C(O)R^a$, $-C(O)OR^a$, $-C_{1-6}$ alkyl$C(O)OR^a$, $-NR^aR^b$, $-OC(O)NR^aR^b$, $NR^aC(O)OR^b$, $-C_{1-6}$ alkylNR^aR^b, $-C(O)NR^aR^b$, $-C_{1-6}$ alkyl$C(O)NR^aR^b$, $-S(O)_2R^a$, $-C_{1-6}$ alkyl$S(O)_2R^a$, $-S(O)_2NR^aR^b$, $-C_{1-6}$ alkyl$S(O)_2NR^aR^b$, $-C(O)NR^aS(O)_2R^b$, $-C_{1-6}$ alkyl$C(O)NR^aS(O)_2R^b$, $-NR^aC(O)R^b$, and $-C_{1-6}$alkyl$NR^aC(O)R^b$;

each R^2 is independently selected from hydrogen, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-C_{3-6}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-C_{1-6}$ alkylheterocyclyl, $-C_{2-6}$ alkyl-OR^a, $-C_{1-6}$ alkyl$C(O)OR^a$, and $-C_{2-6}$ alkenyl$C(O)OR^a$;

wherein each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from $-OR^a$, cyano, halo, C_{1-6}alkyl, $-C_{1-6}$ alkylOR^a, $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ haloalkyl, $-C_{3-8}$ cycloalkyl, $-C_{1-3}$ alkylC_{3-8}cycloalkyl, $-C(O)R^a$, $-C_{1-6}$ alkyl$C(O)R^a$, $-C(O)OR^a$, $-C_{1-6}$ alkyl$C(O)OR^a$, $-NR^aR^b$, $-C_{1-6}$ alkylNR^aR^b, $-C(O)NR^aR^b$, C_{1-6} alkyl$C(O)NR^aR^b$, $-S(O)_2R^a$, $-C_{1-6}$ alkyl$S(O)_2R^a$, $-S(O)_2NR^aR^b$, $-C_{1-6}$ alkyl$S(O)_2NR^aR^b$, $-C(O)NR^aS(O)_2R^{\mathbf{b}}$ and $-NR^aC(O)R^b$;

or R^1 and R^2 combine to form a heterocyclyl optionally substituted with 1 to 3 groups independently selected from oxo, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-OR^a$, $-C(O)OR^a$, $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ alkylOR^a, $-C_{1-6}$ haloalkyl, $-C_{1-3}$ alkylC_{3-8}cycloalkyl, $-C(O)R^a$, C_{1-6} alkyl$C(O)R^a$, $-C_{1-6}$ alkyl$C(O)OR^a$, $-NR^aR^b$, $-C_{1-6}$alkylNR^aR^b, $-C(O)NR^aR^b$, $-C_{1-6}$ alkyl$C(O)NR^aR^b$, $-S(O)_2R^a$, $-C_{1-6}$ alkyl$S(O)_2R^a$, $-S(O)_2NR^aR^b$, $-C(O)N{=}S(O)R^aNR^aR^b$, $-C(O)N{=}S(O)R^aNR^aC(O)R^b$, and $-C_{1-6}$ alkyl$S(O)_2NR^aR^b$;

each R^3 is independently hydrogen, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{3-6}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-C_{1-6}$ alkylheterocyclyl, $-C_{2-6}$ alkyl-OR^a, $-C_{1-6}$ alkyl$C(O)OR^a$, or $-C_{2-6}$ alkenyl$C(O)OR^a$;

each R^a is independently selected from hydrogen, -C_{1-6} alkyl, -C_{1-6} cyanoalkyl, -C_{1-6} haloalkyl, -C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, -C_{1-3} alkylC_{3-8}cycloalkyl, -C_{1-6} alkylaryl, -C_{1-6} alkylheteroaryl, and -C_{1-6}alkylheterocyclyl;

each R^b is independently selected from hydrogen, -C_{1-6} alkyl, -C_{1-6} cyanoalkyl, -C_{1-6} haloalkyl, -C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, -C_{1-3} alkylC_{3-8}cycloalkyl, -C_{1-6} alkylaryl, -C_{1-6} alkylheteroaryl, and -C_{1-6} alkylheterocyclyl;

or R^a and R^b may combine together to form a heterocyclyl optionally substituted with 1 to 4 groups independently selected from -OR^f, cyano, halo, -C_{1-6} alkylOR^f, -C_{1-6} cyanoalkyl, -C_{1-6} haloalkyl, -C_{3-8} cycloalkyl, -C_{1-3} alkylC_{3-8}cycloalkyl, -$C(O)R^f$, -C_{1-6} alkyl$C(O)R^f$, -$C(O)OR^f$, -C_{1-6} alkyl$C(O)OR^f$, -NR^fR^g, -C_{1-6} alkylNR^fR^g, -$C(O)NR^fR^g$, -C_{1-6} alkyl$C(O)NR^fR^g$, -$S(O)_2R^f$, -C_{1-6} alkyl$S(O)_2R^f$, -$S(O)_2NR^fR^g$, -C_{1-6} alkyl$S(O)_2NR^fR^g$, -$C(O)NR^fS(O)_2R^g$ and –$NR^fC(O)R^g$;

each R^c is independently selected from hydrogen, -OH, -C_{1-6} alkyl, -C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, -C_{1-3} alkylC_{3-8} cycloalkyl, -C_{1-6} alkylaryl, -C_{1-6} alkylheteroaryl, and -C_{1-6} alkylheterocyclyl;

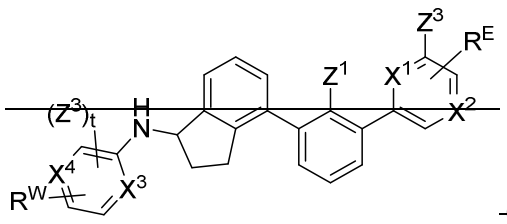
each R^d is independently selected from hydrogen, -C_{1-6} alkyl, -C_3-C_8cycloalkyl, aryl, heteroaryl, heterocyclyl, -C_{1-3} alkylC_{3-8}cycloalkyl, -C_{1-6} alkylaryl, -C_{1-6} alkylheteroaryl, and -C_{1-6} alkylheterocyclyl;

each R^e is independently selected from hydrogen, -C_{1-6} alkyl, -O-C_{1-6}alkyl, -C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, -O-C_{3-8} cycloalkyl, -O-aryl, -O-heteroaryl, -O-heterocyclyl, -C_{1-3} alkylC_{3-8}cycloalkyl, -C_{1-6} alkylaryl, -C_{1-6}alkylheteroaryl, -NR^fR^g, -C_{1-6} alkylNR^fR^g, -$C(O)NR^fR^g$, -C_{1-6} alkyl$C(O)NR^fR^g$, -$NHS(O)_2R^f$, -C_{1-6} alkyl$S(O)_2R^f$, and -C_{1-6} alkyl$S(O)_2NR^fR^g$;

each R^f is independently selected from hydrogen, -C_{1-6} alkyl, -C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, -C_{1-3} alkylC_{3-8} cycloalkyl, -C_{1-6} alkylaryl, -C_{1-6} alkylheteroaryl, and -C_{1-6} alkylheterocyclyl; and

each R^g is independently selected from hydrogen, -C_{1-6} alkyl, -C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, -C_{1-3} alkylC_{3-8} cycloalkyl, -C_{1-6} alkylaryl, -C_{1-6} alkylheteroaryl, and -C_{1-6} alkylheterocyclyl.

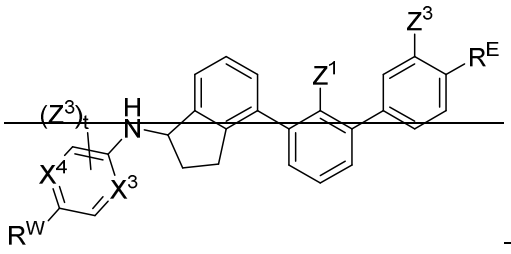
~~2. A compound of formula (IA):~~



~~(IA)~~

~~or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, solvate, or tautomer thereof, wherein X^1, X^2, X^3, X^4, Z^1, Z^3, t, R^W and R^E are as defined in claim 1.~~

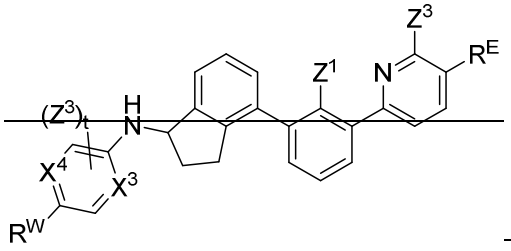
~~3. A compound of formula (IB):~~



~~(IB)~~

~~or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, solvate, or tautomer thereof, wherein X^3, X^4, Z^1, Z^3, t, R^W and R^E are as defined in claim 1.~~

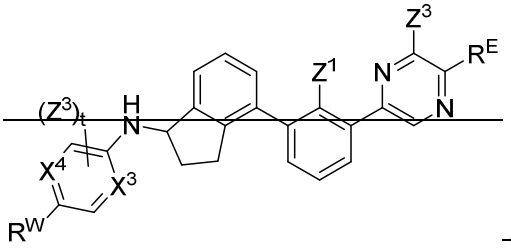
~~4. A compound of formula (IC):~~



~~(IC)~~

~~or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, solvate, or tautomer thereof, wherein X^3, X^4, Z^1, Z^3, t, R^W and R^E are as defined in claim 1.~~

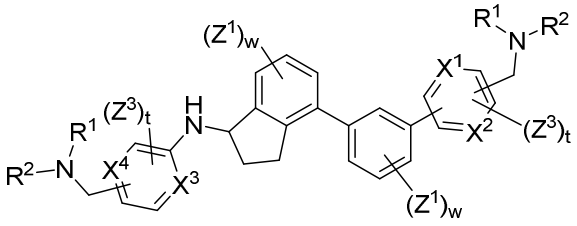
~~5. A compound of formula (ID):~~



~~(ID)~~

~~or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, solvate, or tautomer thereof, wherein X^3, X^4, Z^1, Z^3, t, R^W and R^E are as defined in claim 1.~~

~~6~~2. A compound of formula (II):



(II)

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, solvate, or tautomer thereof, wherein:

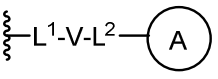
each of X^1, X^2, X^3 and X^4 are independently N, CH or CZ^3;

each Z^1 is independently halo, $-OR^a$, cyano, or $-C_{1-6}$ alkyl;

each w is independently 0, 1 or 2;

each Z^3 is independently halo, $-OR^a$, $-N_3$, $-NO_2$, cyano, $-NR^1R^2$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aSO_2R^a$, $-NR^aC(O)R^a$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-NR^aC(O)OR^a$, $-NR^aC(O)NR^1R^2$, $-OC(O)NR^aR^b$, $-NR^aS(O)_2NR^aR^b$, $-C(O)NR^aS(O)_2NR^aR^b$, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-O-C_{1-6}$ alkyl, $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ haloalkyl, $-O-C_{1-6}$ cyanoalkyl, $-O-C_{1-6}$ haloalkyl, $-C_{3-8}$ cycloalkyl, $-C_{1-6}$ alkylC_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, and R^N; and

wherein the alkyl, alkenyl, alkynyl, C_{3-8} cycloalkyl, aryl, heteroaryl, or heterocyclyl group is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-O-C_{1-6}$cyanoalkyl, $-C(O)NR^aR^b$, $NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-S(O)_2R^a$, $-NR^aS(O)_2R^b$, $-S(O)_2NR^aR^b$, $-NR^aS(O)_2NR^aR^b$, $-C(O)NR^aS(O)_2NR^aR^b$ and $-C_{3-8}$ cycloalkyl;

R^N is independently $-C_{1-6}$ alkylNR^1R^2, $-OC_{1-6}$ alkylNR^1R^2, $-C_{1-6}$ alkylOC_{1-6} alkylNR^1R^2, $-NR^a-C_{1-6}$ alkylNR^1R^2, $-C_{1-6}$ alkyl$C(O)NR^1R^2$, $-O-C_{1-6}$ alkyl$C(O)NR^1R^2$, $-O-C_{1-6}$ alkyl$C(O)OR^1$, $-S-C_{1-6}$ alkylNR^1R^2, $-C_{1-6}$ alkylOR^a, or 

;

wherein: L^1 is independently a bond, -O-, $-NR^a$-, -S-, -S(O)-, or $-S(O)_2$-;

V is independently selected from a bond, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

wherein each alkyl, alkenyl, or alkynyl is optionally independently substituted with $-OR^a$, halo, cyano, $-NR^aR^b$ or $-C_{3-8}$ cycloalkyl;

L^2 is independently a bond, -O-, $-NR^a$-, -S-, -S(O)-, or $-S(O)_2$-;

ring A is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

wherein each cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$ alkynyl, $-O-C_{1-6}$ haloalkyl, NR^aR^b, $-C(O)R^a$, $-C(O)OR^a$, $-OC_{1-6}$ alkylCN, $-C(O)NR^aR^b$, $-NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-NR^aC(O)OR^a$, $-C(O)N(R^a)OR^b$, $-S(O)_2R^a$, $-S(O)_2NR^aR^b$, $-NR^aS(O)_2R^b$, $-NR^aS(O)_2NR^aR^b$, $-C(O)NR^aS(O)_2NR^aR^b$, $-C_{3-8}$cycloalkyl, heteroaryl, and $-C_{1-6}$alkylC_{3-8} cycloalkyl; and

wherein the alkyl, alkenyl, or alkynyl group is optionally independently substituted with $-OR^a$, halo, cyano, $-NR^aR^b$ or $-C_{3-8}$ cycloalkyl;

each t is independently 0, 1 or 2;

each R^1 is independently selected from hydrogen, $-C_{1-8}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-C_{3-6}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl,

-C_{1-6} alkylheterocyclyl, -C_{1-6} alkylC(O)OR^a, -C_{2-6} alkenylC(O)OR^a, -$S(O)_2R^a$, -$S(O)_2NR^aR^b$, -$C(O)NR^aS(O)_2R^a$, and -C_{1-6} alkylC_{3-8}cycloalkyl;

wherein each alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from -OR^a, cyano, halo, C_{1-6}alkyl, -C_{1-6} alkylOR^a, -C_{1-6} cyanoalkyl, -C_{1-6} haloalkyl, C_{3-8} cycloalkyl, -C_{1-3} alkylC_{3-8}cycloalkyl, -$C(O)R^a$, -C_{1-6} alkylC(O)R^a, -C(O)OR^a, -C_{1-6} alkylC(O)OR^a, -NR^aR^b, -$OC(O)NR^aR^b$, -$NR^aC(O)OR^b$, -C_{1-6} alkylNR^aR^b, -$C(O)NR^aR^b$, -C_{1-6} alkylC(O)NR^aR^b, -SO_2R^a, -C_{1-6} alkylSO_2R^a, -$SO_2NR^aR^b$, -C_{1-6} alkyl$SO_2NR^aR^b$, -$C(O)NR^aSO_2R^b$, -C_{1-6} alkylC(O)$NR^aSO_2R^b$, -$NR^aC(O)R^b$, and -C_{1-6}alkyl$NR^aC(O)R^b$;

each R^2 is independently selected from hydrogen, -C_{1-6} alkyl, -C_{2-6} alkenyl, -C_{2-6} alkynyl, -C_{3-6} cycloalkyl, aryl, heteroaryl, heterocyclyl, -C_{1-6} alkylaryl, -C_{1-6} alkylheteroaryl, -C_{1-6} alkylheterocyclyl, -C_{2-6} alkyl-OR^a, -C_{1-6} alkylC(O)OR^a, and -C_{2-6} alkenylC(O)OR^a;

wherein each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from -OR^a, cyano, halo, C_{1-6} alkyl, -C_{1-6} alkylOR^a, -C_{1-6} cyanoalkyl, -C_{1-6} haloalkyl, -C_{3-8} cycloalkyl, -C_{1-3} alkylC_{3-8}cycloalkyl, -$C(O)R^a$, -C_{1-6} alkylC(O)R^a, -C(O)OR^a, -C_{1-6} alkylC(O)OR^a, -NR^aR^b, -C_{1-6} alkylNR^aR^b, -$C(O)NR^aR^b$, C_{1-6} alkylC(O)NR^aR^b, -$S(O)_2R^a$, -C_{1-6} alkyl$S(O)_2R^a$, -$S(O)_2NR^aR^b$, -C_{1-6} alkyl$S(O)_2NR^aR^b$, -$C(O)NR^aS(O)_2R^b$ and -$NR^aC(O)R^b$;

or R^1 and R^2 combine to form a heterocyclyl optionally substituted with 1 to 3 groups independently selected from oxo, -C_{1-6} alkyl, -C_{3-8} cycloalkyl, -C_{2-6} alkenyl, -C_{2-6} alkynyl, -OR^a, -C(O)OR^a, -C_{1-6} cyanoalkyl, -C_{1-6} alkylOR^a, -C_{1-6} haloalkyl, -C_{1-3} alkylC_{3-8}cycloalkyl, -$C(O)R^a$, -C_{1-6} alkylC(O)R^a, -C_{1-6} alkylC(O)OR^a, -NR^aR^b, -C_{1-6}alkylNR^aR^b, -$C(O)NR^aR^b$, -C_{1-6} alkylC(O)NR^aR^b, -$S(O)_2R^a$, -C_{1-6} alkyl$S(O)_2R^a$, -$S(O)_2NR^aR^b$, -C(O)N=S(O)$R^aNR^aR^b$, -C(O)N=S(O)$R^aNR^aC(O)R^b$, and -C_{1-6} alkyl$S(O)_2NR^aR^b$;

each R^3 is independently hydrogen, -C_{1-6} alkyl, -C_{2-6} alkenyl, -C_{3-6} cycloalkyl, aryl, heteroaryl, heterocyclyl, -C_{1-6} alkylaryl, -C_{1-6} alkylheteroaryl, -C_{1-6} alkylheterocyclyl, -C_{2-6} alkyl-OR^a, -C_{1-6} alkylC(O)OR^a, or -C_{2-6} alkenylC(O)OR^a;

each R^a is independently selected from hydrogen, -C_{1-6} alkyl, -C_{1-6} cyanoalkyl, -C_{1-6} haloalkyl, -C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, -C_{1-3} alkylC_{3-8}cycloalkyl, -C_{1-6} alkylaryl, -C_{1-6} alkylheteroaryl, and -C_{1-6}alkylheterocyclyl;

each R^b is independently selected from hydrogen, -C_{1-6} alkyl, -C_{1-6} cyanoalkyl, -C_{1-6} haloalkyl, -C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, -C_{1-3} alkylC_{3-8}cycloalkyl, -C_{1-6} alkylaryl, -C_{1-6} alkylheteroaryl, and -C_{1-6} alkylheterocyclyl;

or R^a and R^b may combine together to form a heterocyclyl optionally substituted with 1 to 4 groups independently selected from -OR^f, cyano, halo, -C_{1-6} alkylOR^f, -C_{1-6} cyanoalkyl, -C_{1-6} haloalkyl, -C_{3-8} cycloalkyl, -C_{1-3} alkylC_{3-8}cycloalkyl, -$C(O)R^f$, -C_{1-6} alkylC(O)R^f, -C(O)OR^f, -C_{1-6} alkylC(O)OR^f,

$-NR^fR^g$, $-C_{1-6}$ alkylNR^fR^g, $-C(O)NR^fR^g$, $-C_{1-6}$ alkyl$C(O)NR^fR^g$, $-S(O)_2R^f$, $-C_{1-6}$ alkyl$S(O)_2R^f$, $-S(O)_2NR^fR^g$, $-C_{1-6}$ alkyl$S(O)_2NR^fR^g$, $-C(O)NR^fS(O)_2R^g$ and $-NR^fC(O)R^g$;

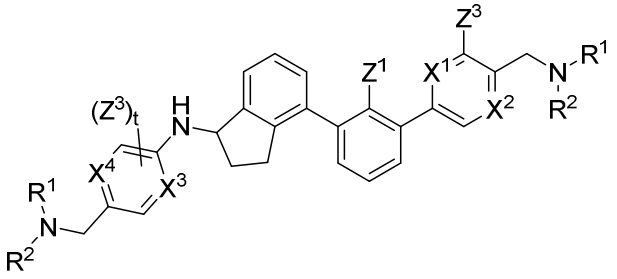
each R^c is independently selected from hydrogen, -OH, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkylC_{3-8} cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

R^d is independently selected from hydrogen, $-C_{1-6}$ alkyl, $-C_3-C_8$cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkylC_{3-8}cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

each R^f is independently selected from hydrogen, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkylC_{3-8} cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl; and

each R^g is independently selected from hydrogen, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkylC_{3-8} cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl.

~~7~~3. A compound of formula (IIA):



(IIA)

or a pharmaceutically acceptable salt~~, stereoisomer, mixture of stereoisomers, solvate, or tautomer~~ thereof, wherein:

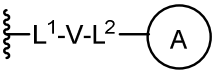
each of X^1, X^2, X^3 and X^4 are independently N, CH or CZ^3;

each Z^1 is independently halo, $-OR^a$, cyano, or $-C_{1-6}$ alkyl;

each w is independently 0, 1 or 2;

each Z^3 is independently halo, $-OR^a$, $-N_3$, $-NO_2$, cyano, $-NR^1R^2$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aSO_2R^a$, $-NR^aC(O)R^a$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-NR^aC(O)OR^a$, $-NR^aC(O)NR^1R^2$, $-OC(O)NR^aR^b$, $-NR^aS(O)_2NR^aR^b$, $-C(O)NR^aS(O)_2NR^aR^b$, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-O-C_{1-6}$ alkyl, $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ haloalkyl, $-O-C_{1-6}$ cyanoalkyl, $-O-C_{1-6}$ haloalkyl, $-C_{3-8}$ cycloalkyl, $-C_{1-6}$ alkylC_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, and R^N; and

wherein the alkyl, alkenyl, alkynyl, C_{3-8} cycloalkyl, aryl, heteroaryl, or heterocyclyl group is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-O-C_{1-6}$cyanoalkyl, $-C(O)NR^aR^b$, $NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-S(O)_2R^a$, $-NR^aS(O)_2R^b$, $-S(O)_2NR^aR^b$, $-NR^aS(O)_2NR^aR^b$, $-C(O)NR^aS(O)_2NR^aR^b$ and $-C_{3-8}$ cycloalkyl;

R^N is independently $-C_{1-6}$ alkylNR^1R^2, $-OC_{1-6}$ alkylNR^1R^2, $-C_{1-6}$ alkylOC_{1-6} alkylNR^1R^2, $-NR^a-C_{1-6}$ alkylNR^1R^2, $-C_{1-6}$ alkyl$C(O)NR^1R^2$, $-O-C_{1-6}$ alkyl$C(O)NR^1R^2$, $-O-C_{1-6}$ alkyl$C(O)OR^1$, $-S-C_{1-6}$ alkylNR^1R^2, $-C_{1-6}$ alkylOR^a, or ;

wherein: L^1 is independently a bond, -O-, $-NR^a-$, -S-, -S(O)-, or $-S(O)_2-$;

V is independently selected from a bond, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

wherein each alkyl, alkenyl, or alkynyl is optionally independently substituted with $-OR^a$, halo, cyano, $-NR^aR^b$ or $-C_{3-8}$ cycloalkyl;

L^2 is independently a bond, -O-, $-NR^a-$, -S-, -S(O)-, or $-S(O)_2-$;

ring A is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

wherein each cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$ alkynyl, $-O-C_{1-6}$ haloalkyl, NR^aR^b, $-C(O)R^a$, $-C(O)OR^a$, $-OC_{1-6}$ alkylCN, $-C(O)NR^aR^b$, $-NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-NR^aC(O)OR^a$, $-C(O)N(R^a)OR^b$, $-S(O)_2R^a$, $-S(O)_2NR^aR^b$, $-NR^aS(O)_2R^b$, $-NR^aS(O)_2NR^aR^b$, $-C(O)NR^aS(O)_2NR^aR^b$, $-C_{3-8}$cycloalkyl, heteroaryl, and $-C_{1-6}$alkylC_{3-8} cycloalkyl; and

wherein the alkyl, alkenyl, or alkynyl group is optionally independently substituted with $-OR^a$, halo, cyano, $-NR^aR^b$ or $-C_{3-8}$ cycloalkyl;

each t is independently 0, 1 or 2;

each R^1 is independently selected from hydrogen, $-C_{1-8}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-C_{3-6}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-C_{1-6}$ alkylheterocyclyl, $-C_{1-6}$ alkyl$C(O)OR^a$, $-C_{2-6}$ alkenyl$C(O)OR^a$, $-S(O)_2R^a$, $-S(O)_2NR^aR^b$, $-C(O)NR^aS(O)_2R^a$, and $-C_{1-6}$ alkylC_{3-8}cycloalkyl;

wherein each alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from $-OR^a$, cyano, halo, C_{1-6}alkyl, $-C_{1-6}$ alkylOR^a, $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ haloalkyl, C_{3-8} cycloalkyl, $-C_{1-3}$ alkylC_{3-8}cycloalkyl, $-C(O)R^a$, $-C_{1-6}$ alkyl$C(O)R^a$, $-C(O)OR^a$, $-C_{1-6}$ alkyl$C(O)OR^a$, $-NR^aR^b$, $-OC(O)NR^aR^b$, $-NR^aC(O)OR^b$, $-C_{1-6}$ alkylNR^aR^b, $-C(O)NR^aR^b$, $-C_{1-6}$ alkyl$C(O)NR^aR^b$, $-SO_2R^a$, $-C_{1-6}$ alkylSO_2R^a, $-SO_2NR^aR^b$, $-C_{1-6}$ alkyl$SO_2NR^aR^b$, $-C(O)NR^aSO_2R^b$, $-C_{1-6}$ alkyl$C(O)NR^aSO_2R^b$, $-NR^aC(O)R^b$, and $-C_{1-6}$alkyl$NR^aC(O)R^b$;

each R^2 is independently selected from hydrogen, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-C_{3-6}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-C_{1-6}$ alkylheterocyclyl, $-C_{2-6}$ alkyl-OR^a, $-C_{1-6}$ alkyl$C(O)OR^a$, and $-C_{2-6}$ alkenyl$C(O)OR^a$;

wherein each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from -OR^a, cyano, halo, C_{1-6} alkyl, -C_{1-6} alkylOR^a, -C_{1-6} cyanoalkyl, -C_{1-6} haloalkyl, -C_{3-8} cycloalkyl, -C_{1-3} alkylC_{3-8}cycloalkyl, -$C(O)R^a$, -C_{1-6} alkyl$C(O)R^a$, -$C(O)OR^a$, -C_{1-6} alkyl$C(O)OR^a$, -NR^aR^b, -C_{1-6} alkylNR^aR^b, -$C(O)NR^aR^b$, C_{1-6} alkyl$C(O)NR^aR^b$, -$S(O)_2R^a$, -C_{1-6} alkyl$S(O)_2R^a$, -$S(O)_2NR^aR^b$, -C_{1-6} alkyl$S(O)_2NR^aR^b$, -$C(O)NR^aS(O)_2R^b$ and -$NR^aC(O)R^b$;

or R^1 and R^2 combine to form a heterocyclyl optionally substituted with 1 to 3 groups independently selected from oxo, -C_{1-6} alkyl, -C_{3-8} cycloalkyl, -C_{2-6} alkenyl, -C_{2-6} alkynyl, -OR^a, -$C(O)OR^a$, -C_{1-6} cyanoalkyl, -C_{1-6} alkylOR^a, -C_{1-6} haloalkyl, -C_{1-3} alkylC_{3-8}cycloalkyl, -$C(O)R^a$, -C_{1-6} alkyl$C(O)R^a$, -C_{1-6} alkyl$C(O)OR^a$, -NR^aR^b, -C_{1-6}alkylNR^aR^b, -$C(O)NR^aR^b$, -C_{1-6} alkyl$C(O)NR^aR^b$, -$S(O)_2R^a$, -C_{1-6} alkyl$S(O)_2R^a$, -$S(O)_2NR^aR^b$, -$C(O)N=S(O)R^aNR^aR^b$, -$C(O)N=S(O)R^aNR^aC(O)R^b$, and -C_{1-6} alkyl$S(O)_2NR^aR^b$;

each R^3 is independently hydrogen, -C_{1-6} alkyl, -C_{2-6} alkenyl, -C_{3-6} cycloalkyl, aryl, heteroaryl, heterocyclyl, -C_{1-6} alkylaryl, -C_{1-6} alkylheteroaryl, -C_{1-6} alkylheterocyclyl, -C_{2-6} alkyl-OR^a, -C_{1-6} alkyl$C(O)OR^a$, or -C_{2-6} alkenyl$C(O)OR^a$;

each R^a is independently selected from hydrogen, -C_{1-6} alkyl, -C_{1-6} cyanoalkyl, -C_{1-6} haloalkyl, -C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, -C_{1-3} alkylC_{3-8}cycloalkyl, -C_{1-6} alkylaryl, -C_{1-6} alkylheteroaryl, and -C_{1-6}alkylheterocyclyl;

each R^b is independently selected from hydrogen, -C_{1-6} alkyl, -C_{1-6} cyanoalkyl, -C_{1-6} haloalkyl, -C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, -C_{1-3} alkylC_{3-8}cycloalkyl, -C_{1-6} alkylaryl, -C_{1-6} alkylheteroaryl, and -C_{1-6} alkylheterocyclyl;

or R^a and R^b may combine together to form a heterocyclyl optionally substituted with 1 to 4 groups independently selected from -OR^f, cyano, halo, -C_{1-6} alkylOR^f, -C_{1-6} cyanoalkyl, -C_{1-6} haloalkyl, -C_{3-8} cycloalkyl, -C_{1-3} alkylC_{3-8}cycloalkyl, -$C(O)R^f$, -C_{1-6} alkyl$C(O)R^f$, -$C(O)OR^f$, -C_{1-6} alkyl$C(O)OR^f$, -NR^fR^g, -C_{1-6} alkylNR^fR^g, -$C(O)NR^fR^g$, -C_{1-6} alkyl$C(O)NR^fR^g$, -$S(O)_2R^f$, -C_{1-6} alkyl$S(O)_2R^f$, -$S(O)_2NR^fR^g$, -C_{1-6} alkyl$S(O)_2NR^fR^g$, -$C(O)NR^fS(O)_2R^g$ and -$NR^fC(O)R^g$;

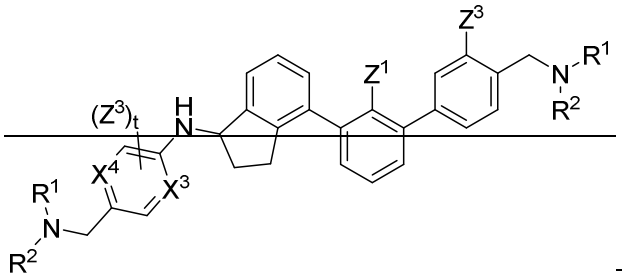
each R^c is independently selected from hydrogen, -OH, -C_{1-6} alkyl, -C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, -C_{1-3} alkylC_{3-8} cycloalkyl, -C_{1-6} alkylaryl, -C_{1-6} alkylheteroaryl, and -C_{1-6} alkylheterocyclyl;

R^d is independently selected from hydrogen, -C_{1-6} alkyl, -C_3-C_8cycloalkyl, aryl, heteroaryl, heterocyclyl, -C_{1-3} alkylC_{3-8}cycloalkyl, -C_{1-6} alkylaryl, -C_{1-6} alkylheteroaryl, and -C_{1-6} alkylheterocyclyl;

each R^f is independently selected from hydrogen, -C_{1-6} alkyl, -C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, -C_{1-3} alkylC_{3-8} cycloalkyl, -C_{1-6} alkylaryl, -C_{1-6} alkylheteroaryl, and -C_{1-6} alkylheterocyclyl; and

each R^g is independently selected from hydrogen, -C_{1-6} alkyl, -C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, -C_{1-3} alkylC_{3-8} cycloalkyl, -C_{1-6} alkylaryl, -C_{1-6} alkylheteroaryl, and -C_{1-6} alkylheterocyclyl~~X^1, X^2, X^3, X^4, Z^1, Z^3, t, R^1 and R^2 are as defined in claim 6~~.

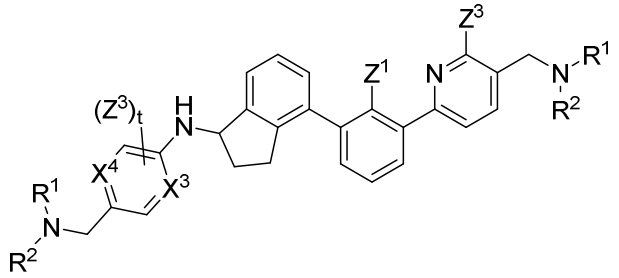
~~8. A compound of formula (IIB):~~



~~(IIB)~~

~~or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, solvate, or tautomer thereof, wherein X^3, X^4, Z^1, Z^3, t, R^1 and R^2 are as defined in claim 6.~~

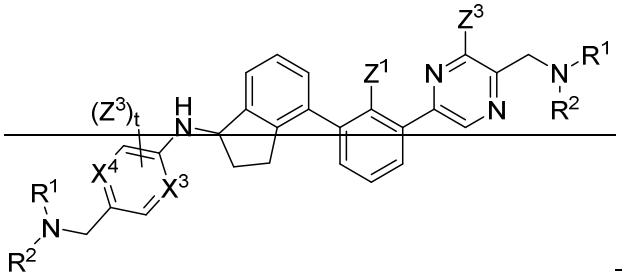
49. ~~A~~ The compound of claim 1, wherein the compound is of formula (IIC):



(IIC)

or a pharmaceutically acceptable salt~~, stereoisomer, mixture of stereoisomers, solvate, or tautomer~~ thereof~~, wherein X^3, X^4, Z^1, Z^3, t, R^1 and R^2 are as defined in claim 6~~.

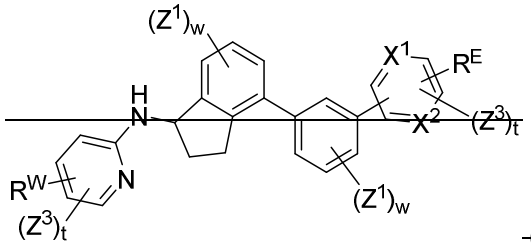
~~10. A compound of formula (IID):~~



~~(IID)~~

~~or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, solvate, or tautomer thereof, wherein X^3, X^4, Z^1, Z^3, t, R^1 and R^2 are as defined in claim 6.~~

~~11. A compound of formula (III):~~



(III)

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, solvate, or tautomer thereof, wherein:

each of X^1, X^2, X^3 and X^4 are independently N, CH or CZ^3;

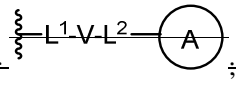
each Z^1 is independently is halo, $-OR^a$, $-NO_2$, cyano, $-NR^aR^b$, $-N_3$, $-S(O)_2R^a$, $-C_{1-6}$alkyl, $-C_{1-6}$haloalkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-O-C_{1-6}$alkyl, $-O-C_{1-6}$haloalkyl, $-C_{3-8}$cycloalkyl, or $-C_{1-6}$alkylC_{3-8}cycloalkyl; and

wherein each alkyl, alkenyl, alkynyl, and cycloalkyl is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, and cyano;

each w is independently 0, 1 or 2;

each Z^3 is independently halo, $-OR^a$, $-N_3$, $-NO_2$, cyano, $-NR^1R^2$, $-S(O)_2R^a$, $-S(O)_2NR^aR^b$, $-NR^aS(O)_2R^a$, $-NR^aC(O)R^a$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-NR^aC(O)OR^a$, $-NR^aC(O)NR^1R^2$, $-OC(O)NR^aR^b$, $-NR^aS(O)_2NR^aR^b$, $-C(O)NR^aS(O)_2NR^aR^b$, $-C_{1-6}$alkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-O-C_{1-6}$alkyl, $-C_{1-6}$cyanoalkyl, $-C_{1-6}$haloalkyl, $-O-C_{1-6}$cyanoalkyl, $-O-C_{1-6}$haloalkyl, $-C_{3-8}$cycloalkyl, $-C_{1-6}$alkylC_{3-8}cycloalkyl, aryl, heteroaryl, heterocyclyl, and R^N; and

wherein the alkyl, alkenyl, alkynyl, C_{3-8}cycloalkyl, aryl, heteroaryl, or heterocyclyl group is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-O-C_{1-6}$cyanoalkyl, $-C(O)NR^aR^b$, $-NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-S(O)_2R^a$, $-NR^aS(O)_2R^b$, $-SO_2NR^aR^b$, $-NR^aS(O)_2NR^aR^b$, $-C(O)NR^aS(O)_2NR^aR^b$ and $-C_{3-8}$cycloalkyl;

R^N is independently $-C_{1-6}$alkylNR^1R^2, $-OC_{1-6}$alkylNR^1R^2, $-C_{1-6}$alkyl$-O-C_{1-6}$alkylNR^1R^2, $-NR^aC_{1-6}$alkylNR^1R^2, $-C_{1-6}$alkyl$C(O)NR^1R^2$, $-O-C_{1-6}$alkyl$C(O)NR^1R^2$, $-O-C_{1-6}$alkyl$C(O)OR^1$, $-SC_{1-6}$alkylNR^1R^2, $-C_{1-6}$alkylOR^a, or ;

wherein:

L^1 is independently a bond, $-O-$, $-NR^a-$, $-S-$, $-S(O)-$, or $-S(O)_2-$;

V is independently selected from a bond, C_{1-6}alkyl, C_{2-6}alkenyl, and C_{2-6}alkynyl;

wherein each alkyl, alkenyl, or alkynyl is optionally independently substituted with $-OR^a$, halo, cyano, $-NR^aR^b$ or $-C_{3-8}$cycloalkyl;

L^2 is independently a bond, $-O-$, $-NR^a-$, $-S-$, $-S(O)-$, or $-S(O)_2-$;

ring A is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

wherein each cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-O-C_{1-6}$ haloalkyl, $-NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-O-C_{1-6}$ cyanoalkyl, $-C(O)NR^aR^b$, $-NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-NR^aC(O)OR^a$, $-C(O)N(R^a)OR^b$, $-S(O)_2R^a$, $-S(O)_2NR^aR^b$, $-NR^aS(O)_2R^b$, $-NR^aS(O)_2NR^aR^b$, $-C(O)NR^aS(O)_2NR^aR^b$, C_{3-8} cycloalkyl, and $-C_{1-6}$ alkylC_{3-8} cycloalkyl; and

wherein the alkyl, alkenyl, or alkynyl group is optionally independently substituted with $-OR^a$, halo, cyano, $-NR^aR^b$ or $-C_{3-8}$ cycloalkyl;

each t is independently 0, 1 or 2;

R^E and R^W are each independently $-NR^1R^2$, $-C_{1-6}$ alkylNR^1R^2, $-O-C_{1-6}$ alkylNR^1R^2, $-C_{1-6}$ alkyl-O-C_{1-6}alkylNR^1R^2, $-NR^a-C_{1-6}$ alkylNR^1R^2, $-C_{1-6}$ alkyl$N^+R^1R^2R^3$, $-S-C_{1-6}$ alkylNR^1R^2, $-C(O)NR^1R^2$, $-S(O)_2R^a$, $-(CH_2)_uS(O)_2NR^1R^2$, $-(CH_2)_uNR^aS(O)_2NR^aR^b$, $-S(O)_2NR^aC_{1-6}$ alkylNR^1R^2, $-NR^aS(O)_2C_{1-6}$ alkylNR^1R^2, $-(CH_2)_uC(O)NR^aS(O)_2NR^aR^b$, $-(CH_2)_uN^+R^1R^2O^-$, $-(CH_2)_uP^+R^bR^eR^d$, $-(CH_2)_uP^+R^eR^dO^-$, $-(CH_2)_uP^+O[NR^aR^b][NR^eR^d]$, $-(CH_2)_uNR^eP(O)(OR^e)_2$, $-(CH_2)_uCH_2OP(O)(OR^e)(OR^d)$, $-(CH_2)_uOP(O)(OR^e)(OR^d)$, $-(CH_2)_uOP(O)NR^aR^b)(OR^a)$, or

$$-V^2-(CR^cR^d)_p-L^3-\text{(B)}-(T)_z$$

;

wherein:

V^2 is independently a bond, $-O-$, $-NR^a-$, $-S-$, $-SO-$, $-SO_2-$, $-C(O)NR^a-$, $-NR^aC(O)-$, $-S(O)_2NR^1-$, or $-NR^aS(O)_2-$;

L^3 is independently a bond, $-O-$, $-NR^a-$, $-S-$, $-SO-$, $-SO_2-$, $-C(O)NR^a-$, $-NR^aC(O)-$, $-S(O)_2NR^1-$, or $-NR^aS(O)_2-$;

ring B is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

T is independently hydrogen, $-OR^a$, $-(CH_2)_qNR^1R^2$, $-(CH_2)_qNR^aC(O)R^e$, or $-(CH_2)_qC(O)R^e$;

p is independently 0, 1, 2, 3, 4, or 5;

q is independently 0, 1, 2, 3, 4, or 5;

u is 0, 1, 2, 3, or 4;

z is 0, 1, 2, or 3; and

wherein the alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl of R^E or R^W is optionally substituted with 1 to 3 substituents independently selected from the group consisting of $-NR^aR^b$, halo, cyano,

~~oxo, OR^a, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} cyanoalkyl, C_{1-6} alkylNR^aR^b, C_{1-6} hydroxyalkyl, C_{3-8} cycloalkyl, and C_{1-3} alkylC_{3-8}cycloalkyl;~~

~~provided that at least one of V^2, L^3, ring B and T contains a nitrogen atom;~~

~~each R^1 is independently selected from hydrogen, C_{1-8} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, aryl, heteroaryl, heterocyclyl, C_{1-6} alkylaryl, C_{1-6} alkylheteroaryl, C_{1-6} alkylheterocyclyl, C_{1-6} alkyl$C(O)OR^a$, C_{2-6} alkenyl$C(O)OR^a$, $S(O)_2R^a$, $S(O)_2NR^aR^b$, $C(O)NR^aS(O)_2R^a$, and C_{1-6} alkylC_{3-8}cycloalkyl;~~

~~wherein each alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from OR^a, cyano, halo, C_{1-6} alkyl, C_{1-6} alkylOR^a, C_{1-6} cyanoalkyl, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, C_{1-3} alkylC_{3-8}cycloalkyl, $C(O)R^a$, C_{1-6} alkyl$C(O)R^a$, $C(O)OR^a$, C_{1-6} alkyl$C(O)OR^a$, NR^aR^b, $OC(O)NR^aR^b$, $NR^aC(O)OR^b$, C_{1-6} alkylNR^aR^b, $C(O)NR^aR^b$, C_{1-6} alkyl$C(O)NR^aR^b$, $S(O)_2R^a$, C_{1-6} alkyl$S(O)_2R^a$, $S(O)_2NR^aR^b$, C_{1-6} alkyl$S(O)_2NR^aR^b$, $C(O)NR^aS(O)_2R^b$, C_{1-6} alkyl$C(O)NR^aS(O)_2R^b$, $NR^aC(O)R^b$, and C_{1-6}alkyl$NR^aC(O)R^b$;~~

~~each R^2 is independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, aryl, heteroaryl, heterocyclyl, C_{1-6} alkylaryl, C_{1-6} alkylheteroaryl, C_{1-6} alkylheterocyclyl, C_{2-6} alkyl OR^a, C_{1-6} alkyl$C(O)OR^a$, and C_{2-6} alkenyl$C(O)OR^a$;~~

~~wherein each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from OR^a, cyano, halo, C_{1-6}alkyl, C_{1-6} alkylOR^a, C_{1-6} cyanoalkyl, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, C_{1-3} alkylC_{3-8}cycloalkyl, $C(O)R^a$, C_{1-6} alkyl$C(O)R^a$, $C(O)OR^a$, C_{1-6} alkyl$C(O)OR^a$, NR^aR^b, C_{1-6} alkylNR^aR^b, $C(O)NR^aR^b$, C_{1-6} alkyl$C(O)NR^aR^b$, $S(O)_2R^a$, C_{1-6} alkyl$S(O)_2R^a$, $S(O)_2NR^aR^b$, C_{1-6} alkyl$S(O)_2NR^aR^b$, $C(O)NR^aS(O)_2R^b$ and $NR^aC(O)R^b$;~~

~~or R^1 and R^2 combine to form a heterocyclyl optionally substituted with 1 to 3 groups independently selected from oxo, C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^a, $C(O)OR^a$, C_{1-6} cyanoalkyl, C_{1-6} alkylOR^a, C_{1-6} haloalkyl, C_{1-3} alkylC_{3-8}cycloalkyl, $C(O)R^a$, C_{1-6} alkyl$C(O)R^a$, C_{1-6} alkyl$C(O)OR^a$, NR^aR^b, C_{1-6}alkylNR^aR^b, $C(O)NR^aR^b$, C_{1-6} alkyl$C(O)NR^aR^b$, $S(O)_2R^a$, C_{1-6} alkyl$S(O)_2R^a$, $S(O)_2NR^aR^b$, $C(O)N{=}S(O)R^aNR^aR^b$, $C(O)N{=}S(O)R^aNR^aC(O)R^b$, and C_{1-6} alkyl$S(O)_2NR^aR^b$;~~

~~each R^3 is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl, aryl, heteroaryl, heterocyclyl, C_{1-6} alkylaryl, C_{1-6} alkylheteroaryl, C_{1-6} alkylheterocyclyl, C_{2-6} alkyl OR^a, C_{1-6} alkyl$C(O)OR^a$, or C_{2-6} alkenyl$C(O)OR^a$;~~

~~each R^a is independently selected from hydrogen, C_{1-6} alkyl, C_{1-6} cyanoalkyl, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, C_{1-3} alkylC_{3-8}cycloalkyl, C_{1-6} alkylaryl, C_{1-6} alkylheteroaryl, and C_{1-6}alkylheterocyclyl;~~

each R^b is independently selected from hydrogen, C_{1-6} alkyl, C_{1-6} cyanoalkyl, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, C_{1-3} alkylC_{3-8}cycloalkyl, C_{1-6} alkylaryl, C_{1-6} alkylheteroaryl, and C_{1-6} alkylheterocyclyl;

or R^a and R^b may combine together to form a heterocyclyl optionally substituted with 1 to 4 groups independently selected from OR^f, cyano, halo, C_{1-6} alkylOR^f, C_{1-6} cyanoalkyl, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, C_{1-3} alkylC_{3-8}cycloalkyl, $C(O)R^f$, C_{1-6} alkyl$C(O)R^f$, $C(O)OR^f$, C_{1-6} alkyl$C(O)OR^f$, NR^fR^g, C_{1-6} alkylNR^fR^g, $C(O)NR^fR^g$, C_{1-6} alkyl$C(O)NR^fR^g$, $S(O)_2R^f$, C_{1-6} alkyl$S(O)_2R^f$, $S(O)_2NR^fR^g$, C_{1-6} alkyl$S(O)_2NR^fR^g$, $C(O)NR^fS(O)_2R^g$ and $NR^fC(O)R^g$;

each R^e is independently selected from hydrogen, -OH, C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, C_{1-3} alkylC_{3-8} cycloalkyl, C_{1-6} alkylaryl, C_{1-6} alkylheteroaryl, and C_{1-6} alkylheterocyclyl;

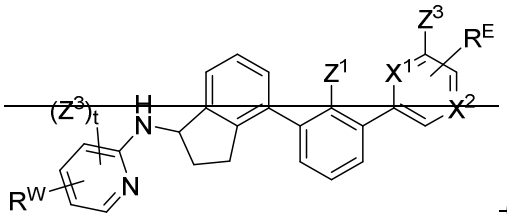
each R^d is independently selected from hydrogen, C_{1-6} alkyl, C_3-C_8cycloalkyl, aryl, heteroaryl, heterocyclyl, C_{1-3} alkylC_{3-8}cycloalkyl, C_{1-6} alkylaryl, C_{1-6} alkylheteroaryl, and C_{1-6} alkylheterocyclyl;

each R^e is independently selected from hydrogen, C_{1-6} alkyl, O C_{1-6}alkyl, C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, O C_{3-8} cycloalkyl, O aryl, O heteroaryl, O heterocyclyl, C_{1-3} alkylC_{3-8}cycloalkyl, C_{1-6} alkylaryl, C_{1-6}alkylheteroaryl, NR^fR^g, C_{1-6} alkylNR^fR^g, $C(O)NR^fR^g$, C_{1-6} alkyl$C(O)NR^fR^g$, $NHS(O)_2R^f$, C_{1-6} alkyl$S(O)_2R^f$, and C_{1-6} alkyl$S(O)_2NR^fR^g$;

each R^f is independently selected from hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, C_{1-3} alkylC_{3-8} cycloalkyl, C_{1-6} alkylaryl, C_{1-6} alkylheteroaryl, and C_{1-6} alkylheterocyclyl; and

each R^g is independently selected from hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, C_{1-3} alkylC_{3-8} cycloalkyl, C_{1-6} alkylaryl, C_{1-6} alkylheteroaryl, and C_{1-6} alkylheterocyclyl.

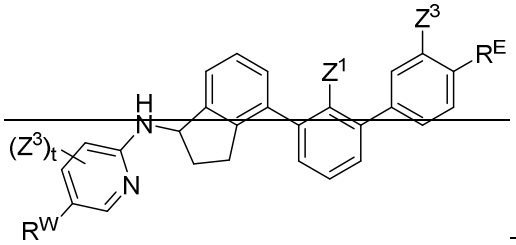
12. A compound of formula (IIIA):



(IIIA)

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, solvate, or tautomer thereof, wherein X^1, X^2, Z^1, Z^3, t, R^W and R^E are as in claim 11.

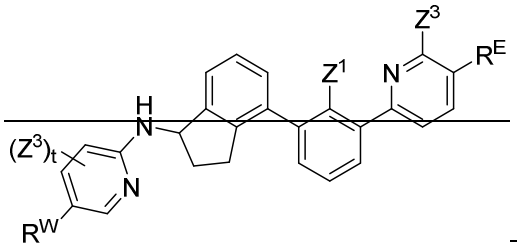
13. A compound of formula (IIIB):



(IIIB)

~~or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, solvate, or tautomer thereof, wherein Z^1, Z^3, t, R^W and R^E are as in claim 11.~~

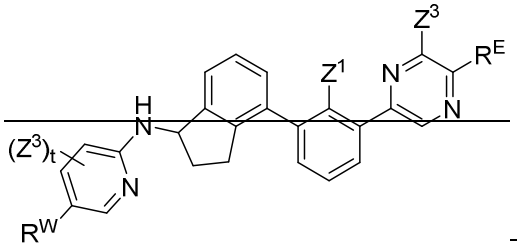
~~14. A compound of formula (IIIC):~~



~~(IIIC)~~

~~or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, solvate, or tautomer thereof, wherein Z^1, Z^3, t, R^W and R^E are as in claim 11.~~

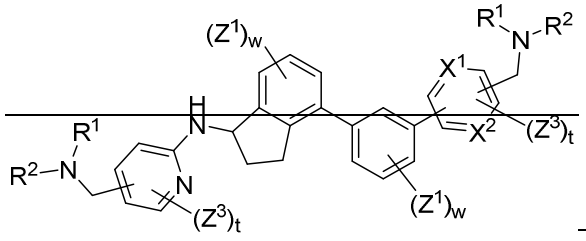
~~15. A compound of formula (IIID):~~



~~(IIID)~~

~~or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, solvate, or tautomer thereof, wherein Z^1, Z^3, t, R^W and R^E are as in claim 11.~~

~~16. A compound of formula (IV):~~



~~(IV)~~

~~or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, solvate, or tautomer thereof, wherein:~~

~~each of X^1 and X^2 are independently N, CH or CZ^3;~~

~~each Z^1 is independently halo, $-OR^a$, cyano, or $-C_{1-6}$ alkyl;~~

~~each w is independently 0, 1 or 2;~~

~~each Z^3 is independently halo, $-OR^a$, $-N_3$, $-NO_2$, cyano, $-NR^1R^2$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aSO_2R^a$, $-NR^aC(O)R^a$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-NR^aC(O)OR^a$, $-NR^aC(O)NR^1R^2$, $-OC(O)NR^aR^b$, $-NR^aS(O)_2NR^aR^b$, $-C(O)NR^aS(O)_2NR^aR^b$, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-O-C_{1-6}$ alkyl, $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ haloalkyl, $-O-C_{1-6}$ cyanoalkyl, $-O-C_{1-6}$ haloalkyl, $-C_{3-8}$ cycloalkyl, $-C_{1-6}$ alkylC_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, and R^N; and~~

wherein the alkyl, alkenyl, alkynyl, C_{3-8} cycloalkyl, aryl, heteroaryl, or heterocyclyl group is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-O-C_{1-6}$cyanoalkyl, $-C(O)NR^aR^b$, $NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-S(O)_2R^a$, $-NR^aS(O)_2R^b$, $-S(O)_2NR^aR^b$, $-NR^aS(O)_2NR^aR^b$, $-C(O)NR^aS(O)_2NR^aR^b$ and $-C_{3-8}$ cycloalkyl;

R^N is independently $-C_{1-6}$ alkylNR^1R^2, $-OC_{1-6}$ alkylNR^1R^2, $-C_{1-6}$ alkylOC_{1-6} alkylNR^1R^2, $-NR^a-C_{1-6}$ alkylNR^1R^2, $-C_{1-6}$ alkyl$C(O)NR^1R^2$, $-O-C_{1-6}$ alkyl$C(O)NR^1R^2$, $-O-C_{1-6}$ alkyl$C(O)OR^1$, $-S-C_{1-6}$ alkylNR^1R^2, $-C_{1-6}$ alkylOR^a, or ;

wherein: L^1 is independently a bond, $-O-$, $-NR^a-$, $-S-$, $-S(O)-$, or $-S(O)_2-$;

V is independently selected from a bond, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

wherein each alkyl, alkenyl, or alkynyl is optionally independently substituted with $-OR^a$, halo, cyano, $-NR^aR^b$ or $-C_{3-8}$ cycloalkyl;

L^2 is independently a bond, $-O-$, $-NR^a-$, $-S-$, $-S(O)-$, or $-S(O)_2-$;

ring A is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

wherein each cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$ alkynyl, $-O-C_{1-6}$ haloalkyl, NR^aR^b, $-C(O)R^a$, $-C(O)OR^a$, $-OC_{1-6}$ alkylCN, $-C(O)NR^aR^b$, $-NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-NR^aC(O)OR^a$, $-C(O)N(R^a)OR^b$, $-S(O)_2R^a$, $-S(O)_2NR^aR^b$, $-NR^aS(O)_2R^b$, $-NR^aS(O)_2NR^aR^b$, $-C(O)NR^aS(O)_2NR^aR^b$, $-C_{3-8}$cycloalkyl, heteroaryl, and $-C_{1-6}$alkylC_{3-8} cycloalkyl; and

wherein the alkyl, alkenyl, or alkynyl group is optionally independently substituted with $-OR^a$, halo, cyano, $-NR^aR^b$ or $-C_{3-8}$ cycloalkyl;

each t is independently 0, 1 or 2;

each R^1 is independently selected from hydrogen, $-C_{1-8}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-C_{3-6}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-C_{1-6}$ alkylheterocyclyl, $-C_{1-6}$ alkyl$C(O)OR^a$, $-C_{2-6}$ alkenyl$C(O)OR^a$, $-S(O)_2R^a$, $-S(O)_2NR^aR^b$, $-C(O)NR^aS(O)_2R^a$, and $-C_{1-6}$ alkylC_{3-8}cycloalkyl;

wherein each alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from $-OR^a$, cyano, halo, C_{1-6}alkyl, $-C_{1-6}$ alkylOR^a, $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ haloalkyl, C_{3-8} cycloalkyl, $-C_{1-3}$ alkylC_{3-8}cycloalkyl, $-C(O)R^a$, $-C_{1-6}$ alkyl$C(O)R^a$, $-C(O)OR^a$, $-C_{1-6}$ alkyl$C(O)OR^a$, $-NR^aR^b$, $-OC(O)NR^aR^b$, $-NR^aC(O)OR^b$, $-C_{1-6}$ alkylNR^aR^b, $-C(O)NR^aR^b$, $-C_{1-6}$ alkyl$C(O)NR^aR^b$, $-SO_2R^a$, $-C_{1-6}$ alkylSO_2R^a, $-SO_2NR^aR^b$,

~~C_{1-6} alkyl$SO_2NR^aR^b$, $C(O)NR^aSO_2R^b$, C_{1-6} alkyl$C(O)NR^aSO_2R^b$, $NR^aC(O)R^b$, and C_{1-6}alkyl$NR^aC(O)R^b$;~~

~~each R^2 is independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, aryl, heteroaryl, heterocyclyl, C_{1-6} alkylaryl, C_{1-6} alkylheteroaryl, C_{1-6} alkylheterocyclyl, C_{2-6} alkyl OR^a, C_{1-6} alkyl$C(O)OR^a$, and C_{2-6} alkenyl$C(O)OR^a$;~~

~~wherein each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from OR^a, cyano, halo, C_{1-6} alkyl, C_{1-6} alkylOR^a, C_{1-6} cyanoalkyl, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, C_{1-3} alkylC_{3-8}cycloalkyl, $C(O)R^a$, C_{1-6} alkyl$C(O)R^a$, $C(O)OR^a$, C_{1-6} alkyl$C(O)OR^a$, NR^aR^b, C_{1-6} alkylNR^aR^b, $C(O)NR^aR^b$, C_{1-6} alkyl$C(O)NR^aR^b$, $S(O)_2R^a$, C_{1-6} alkyl$S(O)_2R^a$, $S(O)_2NR^aR^b$, C_{1-6} alkyl$S(O)_2NR^aR^b$, $C(O)NR^aS(O)_2R^b$ and $NR^aC(O)R^b$;~~

~~or R^1 and R^2 combine to form a heterocyclyl optionally substituted with 1 to 3 groups independently selected from oxo, C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^a, $C(O)OR^a$, C_{1-6} cyanoalkyl, C_{1-6} alkylOR^a, C_{1-6} haloalkyl, C_{1-3} alkylC_{3-8}cycloalkyl, $C(O)R^a$, C_{1-6} alkyl$C(O)R^a$, C_{1-6} alkyl$C(O)OR^a$, NR^aR^b, C_{1-6}alkylNR^aR^b, $C(O)NR^aR^b$, C_{1-6} alkyl$C(O)NR^aR^b$, $S(O)_2R^a$, C_{1-6} alkyl$S(O)_2R^a$, $S(O)_2NR^aR^b$, $C(O)N=S(O)R^aNR^aR^b$, $C(O)N=S(O)R^aNR^aC(O)R^b$, and C_{1-6} alkyl$S(O)_2NR^aR^b$;~~

~~each R^3 is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl, aryl, heteroaryl, heterocyclyl, C_{1-6} alkylaryl, C_{1-6} alkylheteroaryl, C_{1-6} alkylheterocyclyl, C_{2-6} alkyl OR^a, C_{1-6} alkyl$C(O)OR^a$, or C_{2-6} alkenyl$C(O)OR^a$;~~

~~each R^a is independently selected from hydrogen, C_{1-6} alkyl, C_{1-6} cyanoalkyl, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, C_{1-3} alkylC_{3-8}cycloalkyl, C_{1-6} alkylaryl, C_{1-6} alkylheteroaryl, and C_{1-6}alkylheterocyclyl;~~

~~each R^b is independently selected from hydrogen, C_{1-6} alkyl, C_{1-6} cyanoalkyl, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, C_{1-3} alkylC_{3-8}cycloalkyl, C_{1-6} alkylaryl, C_{1-6} alkylheteroaryl, and C_{1-6} alkylheterocyclyl;~~

~~or R^a and R^b may combine together to form a heterocyclyl optionally substituted with 1 to 4 groups independently selected from OR^f, cyano, halo, C_{1-6} alkylOR^f, C_{1-6} cyanoalkyl, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, C_{1-3} alkylC_{3-8}cycloalkyl, $C(O)R^f$, C_{1-6} alkyl$C(O)R^f$, $C(O)OR^f$, C_{1-6} alkyl$C(O)OR^f$, NR^fR^g, C_{1-6} alkylNR^fR^g, $C(O)NR^fR^g$, C_{1-6} alkyl$C(O)NR^fR^g$, $S(O)_2R^f$, C_{1-6} alkyl$S(O)_2R^f$, $S(O)_2NR^fR^g$, C_{1-6} alkyl$S(O)_2NR^fR^g$, $C(O)NR^fS(O)_2R^g$ and $NR^fC(O)R^g$;~~

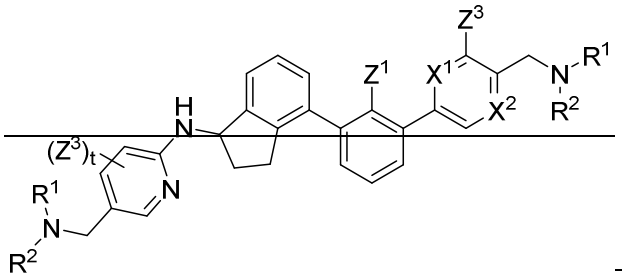
~~each R^e is independently selected from hydrogen, -OH, C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, C_{1-3} alkylC_{3-8} cycloalkyl, C_{1-6} alkylaryl, C_{1-6} alkylheteroaryl, and C_{1-6} alkylheterocyclyl;~~

~~R^d is independently selected from hydrogen, C_{1-6} alkyl, C_3-C_8cycloalkyl, aryl, heteroaryl, heterocyclyl, C_{1-3} alkylC_{3-8}cycloalkyl, C_{1-6} alkylaryl, C_{1-6} alkylheteroaryl, and C_{1-6} alkylheterocyclyl;~~

~~each R^f is independently selected from hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, C_{1-3} alkylC_{3-8} cycloalkyl, C_{1-6} alkylaryl, C_{1-6} alkylheteroaryl, and C_{1-6} alkylheterocyclyl; and~~

~~each R^g is independently selected from hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, C_{1-3} alkylC_{3-8} cycloalkyl, C_{1-6} alkylaryl, C_{1-6} alkylheteroaryl, and C_{1-6} alkylheterocyclyl.~~

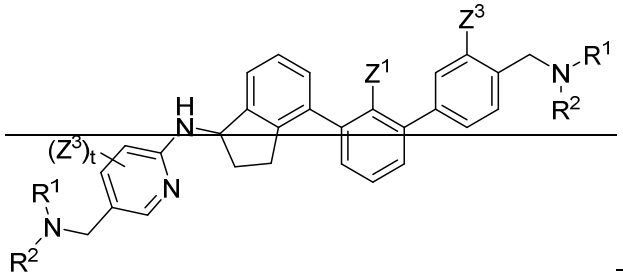
~~17. A compound of formula (IVA):~~



~~(IVA)~~

~~or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, solvate, or tautomer thereof, wherein X^1, X^2, Z^1, Z^3, t, R^1 and R^2 are as in claim 16.~~

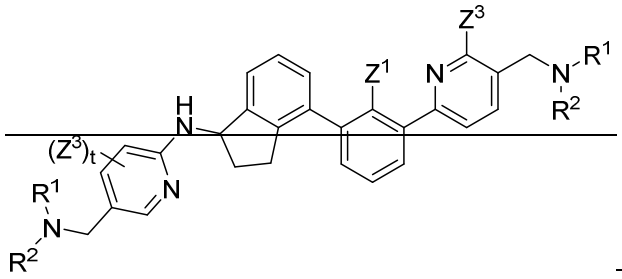
~~18. A compound of formula (IVB):~~



~~(IVB)~~

~~or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, solvate, or tautomer thereof, wherein Z^1, Z^3, t, R^1 and R^2 are as in claim 16.~~

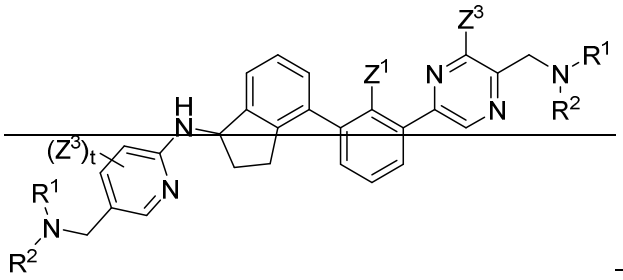
~~19. A compound of formula (IVC):~~



~~(IVC)~~

~~or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, solvate, or tautomer thereof, wherein Z^1, Z^3, t, R^1 and R^2 are as in claim 16.~~

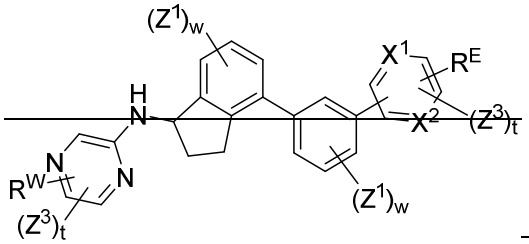
~~20. A compound of formula (IVD):~~



(IVD)

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, solvate, or tautomer thereof, wherein Z^1, Z^3, t, R^1 and R^2 are as in claim 16.

21. A compound of formula (V):



(V)

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, solvate, or tautomer thereof, wherein:

each of X^1, X^2, X^3 and X^4 are independently N, CH or CZ^3;

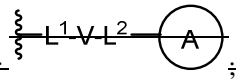
each Z^1 is independently is halo, $-OR^a$, $-NO_2$, cyano, $-NR^aR^b$, $-N_3$, $-S(O)_2R^a$, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$ alkynyl, $-O-C_{1-6}$ alkyl, $-O-C_{1-6}$ haloalkyl, $-C_{3-8}$ cycloalkyl, or $-C_{1-6}$ alkylC_{3-8} cycloalkyl; and

wherein each alkyl, alkenyl, alkynyl, and cycloalkyl is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, and cyano;

each w is independently 0, 1 or 2;

each Z^3 is independently halo, $-OR^a$, $-N_3$, $-NO_2$, cyano, $-NR^1R^2$, $-S(O)_2R^a$, $-S(O)_2NR^aR^b$, $-NR^aS(O)_2R^a$, $-NR^aC(O)R^a$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-NR^aC(O)OR^a$, $-NR^aC(O)NR^1R^2$, $-OC(O)NR^aR^b$, $-NR^aS(O)_2NR^aR^b$, $-C(O)NR^aS(O)_2NR^aR^b$, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-O-C_{1-6}$ alkyl, $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ haloalkyl, $-O-C_{1-6}$ cyanoalkyl, $-O-C_{1-6}$ haloalkyl, $-C_{3-8}$ cycloalkyl, $-C_{1-6}$ alkylC_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, and R^N; and

wherein the alkyl, alkenyl, alkynyl, C_{3-8} cycloalkyl, aryl, heteroaryl, or heterocyclyl group is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-O-C_{1-6}$cyanoalkyl, $-C(O)NR^aR^b$, $-NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-S(O)_2R^a$, $-NR^aS(O)_2R^b$, $-SO_2NR^aR^b$, $-NR^aS(O)_2NR^aR^b$, $-C(O)NR^aS(O)_2NR^aR^b$ and $-C_{3-8}$ cycloalkyl;

R^N is independently C_{1-6} alkylNR^1R^2, OC_{1-6} alkylNR^1R^2, C_{1-6} alkyl-O-C_{1-6} alkylNR^1R^2, NR^aC_{1-6} alkylNR^1R^2, C_{1-6} alkyl$C(O)NR^1R^2$, O-C_{1-6} alkyl$C(O)NR^1R^2$, O-C_{1-6} alkyl$C(O)OR^1$, SC_{1-6} alkylNR^1R^2, C_{1-6} alkylOR^a, or ;

wherein:

L^1 is independently a bond, O, NR^a, S, S(O), or $S(O)_2$;

V is independently selected from a bond, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

wherein each alkyl, alkenyl, or alkynyl is optionally independently substituted with OR^a, halo, cyano, NR^aR^b or C_{3-8} cycloalkyl;

L^2 is independently a bond, O, NR^a, S, S(O), or $S(O)_2$;

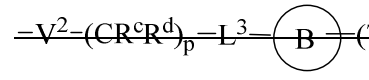
ring A is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

wherein each cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from oxo, NO_2, N_3, OR^a, halo, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, O-C_{1-6} haloalkyl, NR^aR^b, $C(O)R^a$, $C(O)OR^a$, O-C_{1-6} cyanoalkyl, $C(O)NR^aR^b$, $NR^aC(O)R^a$, $NR^aC(O)OR^a$, $NR^aC(O)OR^a$, $C(O)N(R^a)OR^b$, $S(O)_2R^a$, $S(O)_2NR^aR^b$, $NR^aS(O)_2R^b$, $NR^aS(O)_2NR^aR^b$, $C(O)NR^aS(O)_2NR^aR^b$, C_{3-8} cycloalkyl, and C_{1-6} alkylC_{3-8} cycloalkyl; and

wherein the alkyl, alkenyl, or alkynyl group is optionally independently substituted with OR^a, halo, cyano, NR^aR^b or C_{3-8} cycloalkyl;

each t is independently 0, 1 or 2;

R^E and R^W are each independently NR^1R^2, C_{1-6} alkylNR^1R^2, O-C_{1-6} alkylNR^1R^2, C_{1-6} alkyl-O-C_{1-6}alkylNR^1R^2, NR^a-C_{1-6} alkylNR^1R^2, C_{1-6} alkyl$N^+R^1R^2R^3$, S-C_{1-6} alkylNR^1R^2, $C(O)NR^1R^2$, $S(O)_2R^a$, $(CH_2)_uS(O)_2NR^1R^2$, $(CH_2)_uNR^aS(O)_2NR^aR^b$, $S(O)_2NR^aC_{1-6}$ alkylNR^1R^2, $NR^aS(O)_2C_{1-6}$ alkylNR^1R^2, $(CH_2)_uC(O)NR^aS(O)_2NR^aR^b$, $(CH_2)_uN^+R^1R^2O^-$, $(CH_2)_uP^+R^bR^eR^d$, $(CH_2)_uP^+R^eR^dO^-$, $(CH_2)_uP^+O[NR^aR^b][NR^eR^d]$, $(CH_2)_uNR^eP(O)(OR^e)_2$, $(CH_2)_uCH_2OP(O)(OR^e)(OR^d)$, $(CH_2)_uOP(O)(OR^e)(OR^d)$, $(CH_2)_uOP(O)NR^aR^b)(OR^a)$, or

;

wherein:

V^2 is independently a bond, O, NR^a, S, SO, SO_2, $C(O)NR^a$, $NR^aC(O)$, $S(O)_2NR^1$, or $NR^aS(O)_2$;

L^3 is independently a bond, O, NR^a, S, SO, SO_2, $C(O)NR^a$, $NR^aC(O)$, $S(O)_2NR^1$, or $NR^aS(O)_2$;

ring B is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

T is independently hydrogen, $-OR^a$, $-(CH_2)_qNR^1R^2$, $-(CH_2)_qNR^aC(O)R^e$, or $-(CH_2)_qC(O)R^e$;

p is independently 0, 1, 2, 3, 4, or 5;

q is independently 0, 1, 2, 3, 4, or 5;

u is 0, 1, 2, 3, or 4;

z is 0, 1, 2, or 3; and

wherein the alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl of R^E or R^W is optionally substituted with 1 to 3 substituents independently selected from the group consisting of $-NR^aR^b$, halo, cyano, oxo, $-OR^a$, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ alkylNR^aR^b, $-C_{1-6}$ hydroxyalkyl, $-C_{3-8}$ cycloalkyl, and $-C_{1-3}$ alkylC_{3-8}cycloalkyl;

provided that at least one of V^2, L^3, ring B and T contains a nitrogen atom;

each R^1 is independently selected from hydrogen, $-C_{1-8}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-C_{3-6}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-C_{1-6}$ alkylheterocyclyl, $-C_{1-6}$ alkyl$C(O)OR^a$, $-C_{2-6}$ alkenyl$C(O)OR^a$, $-S(O)_2R^a$, $-S(O)_2NR^aR^b$, $-C(O)NR^aS(O)_2R^a$, and $-C_{1-6}$ alkylC_{3-8}cycloalkyl;

wherein each alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from $-OR^a$, cyano, halo, C_{1-6} alkyl, $-C_{1-6}$ alkylOR^a, $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ haloalkyl, C_{3-8} cycloalkyl, $-C_{1-3}$ alkylC_{3-8}cycloalkyl, $-C(O)R^a$, $-C_{1-6}$ alkyl$C(O)R^a$, $-C(O)OR^a$, $-C_{1-6}$ alkyl$C(O)OR^a$, $-NR^aR^b$, $-OC(O)NR^aR^b$, $NR^aC(O)OR^b$, $-C_{1-6}$ alkylNR^aR^b, $-C(O)NR^aR^b$, $-C_{1-6}$ alkyl$C(O)NR^aR^b$, $-S(O)_2R^a$, $-C_{1-6}$ alkyl$S(O)_2R^a$, $-S(O)_2NR^aR^b$, $-C_{1-6}$ alkyl$S(O)_2NR^aR^b$, $-C(O)NR^aS(O)_2R^b$, $-C_{1-6}$ alkyl$C(O)NR^aS(O)_2R^b$, $-NR^aC(O)R^b$, and $-C_{1-6}$alkyl$NR^aC(O)R^b$;

each R^2 is independently selected from hydrogen, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-C_{3-6}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-C_{1-6}$ alkylheterocyclyl, $-C_{2-6}$ alkyl OR^a, $-C_{1-6}$ alkyl$C(O)OR^a$, and $-C_{2-6}$ alkenyl$C(O)OR^a$;

wherein each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from $-OR^a$, cyano, halo, C_{1-6}alkyl, $-C_{1-6}$ alkylOR^a, $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ haloalkyl, $-C_{3-8}$ cycloalkyl, $-C_{1-3}$ alkylC_{3-8}cycloalkyl, $-C(O)R^a$, $-C_{1-6}$ alkyl$C(O)R^a$, $-C(O)OR^a$, $-C_{1-6}$ alkyl$C(O)OR^a$, $-NR^aR^b$, $-C_{1-6}$ alkylNR^aR^b, $-C(O)NR^aR^b$, C_{1-6} alkyl$C(O)NR^aR^b$, $-S(O)_2R^a$, $-C_{1-6}$ alkyl$S(O)_2R^a$, $-S(O)_2NR^aR^b$, $-C_{1-6}$ alkyl$S(O)_2NR^aR^b$, $-C(O)NR^aS(O)_2R^b$ and $-NR^aC(O)R^b$;

or R^1 and R^2 combine to form a heterocyclyl optionally substituted with 1 to 3 groups independently selected from oxo, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-OR^a$, $-C(O)OR^a$, $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ alkylOR^a, $-C_{1-6}$ haloalkyl, $-C_{1-3}$ alkylC_{3-8}cycloalkyl, $-C(O)R^a$, C_{1-6} alkyl$C(O)R^a$,

~~C_{1-6} alkyl$C(O)OR^a$, NR^aR^b, C_{1-6}alkylNR^aR^b, $C(O)NR^aR^b$, C_{1-6} alkyl$C(O)NR^aR^b$, $S(O)_2R^a$, C_{1-6} alkyl$S(O)_2R^a$, $S(O)_2NR^aR^b$, $C(O)N=S(O)R^aNR^aR^b$, $C(O)N=S(O)R^aNR^aC(O)R^b$, and C_{1-6} alkyl$S(O)_2NR^aR^b$;~~

~~each R^3 is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl, aryl, heteroaryl, heterocyclyl, C_{1-6} alkylaryl, C_{1-6} alkylheteroaryl, C_{1-6} alkylheterocyclyl, C_{2-6} alkyl OR^a, C_{1-6} alkyl$C(O)OR^a$, or C_{2-6} alkenyl$C(O)OR^a$;~~

~~each R^a is independently selected from hydrogen, C_{1-6} alkyl, C_{1-6} cyanoalkyl, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, C_{1-3} alkylC_{3-8}cycloalkyl, C_{1-6} alkylaryl, C_{1-6} alkylheteroaryl, and C_{1-6}alkylheterocyclyl;~~

~~each R^b is independently selected from hydrogen, C_{1-6} alkyl, C_{1-6} cyanoalkyl, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, C_{1-3} alkylC_{3-8}cycloalkyl, C_{1-6} alkylaryl, C_{1-6} alkylheteroaryl, and C_{1-6} alkylheterocyclyl;~~

~~or R^a and R^b may combine together to form a heterocyclyl optionally substituted with 1 to 4 groups independently selected from OR^f, cyano, halo, C_{1-6} alkylOR^f, C_{1-6} cyanoalkyl, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, C_{1-3} alkylC_{3-8}cycloalkyl, $C(O)R^f$, C_{1-6} alkyl$C(O)R^f$, $C(O)OR^f$, C_{1-6} alkyl$C(O)OR^f$, NR^fR^g, C_{1-6} alkylNR^fR^g, $C(O)NR^fR^g$, C_{1-6} alkyl$C(O)NR^fR^g$, $S(O)_2R^f$, C_{1-6} alkyl$S(O)_2R^f$, $S(O)_2NR^fR^g$, C_{1-6} alkyl$S(O)_2NR^fR^g$, $C(O)NR^fS(O)_2R^g$ and $NR^fC(O)R^g$;~~

~~each R^e is independently selected from hydrogen, OH, C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, C_{1-3} alkylC_{3-8} cycloalkyl, C_{1-6} alkylaryl, C_{1-6} alkylheteroaryl, and C_{1-6} alkylheterocyclyl;~~

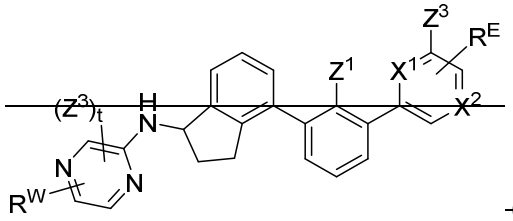
~~each R^d is independently selected from hydrogen, C_{1-6} alkyl, C_3-C_8cycloalkyl, aryl, heteroaryl, heterocyclyl, C_{1-3} alkylC_{3-8}cycloalkyl, C_{1-6} alkylaryl, C_{1-6} alkylheteroaryl, and C_{1-6} alkylheterocyclyl;~~

~~each R^e is independently selected from hydrogen, C_{1-6} alkyl, O C_{1-6}alkyl, C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, O C_{3-8} cycloalkyl, O aryl, O heteroaryl, O heterocyclyl, C_{1-3} alkylC_{3-8}cycloalkyl, C_{1-6} alkylaryl, C_{1-6}alkylheteroaryl, NR^fR^g, C_{1-6} alkylNR^fR^g, $C(O)NR^fR^g$, C_{1-6} alkyl$C(O)NR^fR^g$, $NHS(O)_2R^f$, C_{1-6} alkyl$S(O)_2R^f$, and C_{1-6} alkyl$S(O)_2NR^fR^g$;~~

~~each R^f is independently selected from hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, C_{1-3} alkylC_{3-8} cycloalkyl, C_{1-6} alkylaryl, C_{1-6} alkylheteroaryl, and C_{1-6} alkylheterocyclyl; and~~

~~each R^g is independently selected from hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, C_{1-3} alkylC_{3-8} cycloalkyl, C_{1-6} alkylaryl, C_{1-6} alkylheteroaryl, and C_{1-6} alkylheterocyclyl.~~

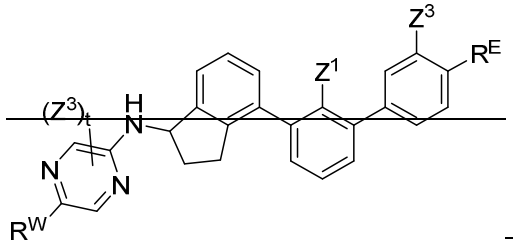
~~22. A compound of formula (VA):~~



~~(VA)~~

~~or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, solvate, or tautomer thereof, wherein X^1, X^2, Z^1, Z^3, t, R^W and R^E are as in claim 21.~~

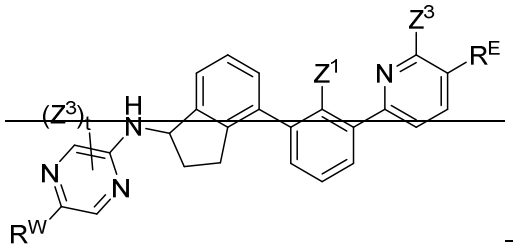
~~23. A compound of formula (VB):~~



~~(VB)~~

~~or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, solvate, or tautomer thereof, wherein Z^1, Z^3, t, R^W and R^E are as in claim 21.~~

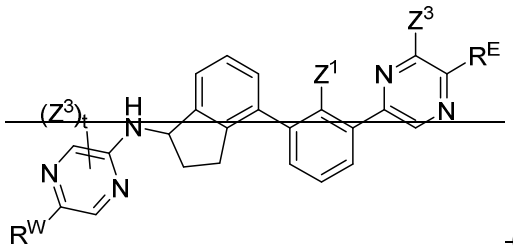
~~24. A compound of formula (VC):~~



~~(VC)~~

~~or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, solvate, or tautomer thereof, wherein Z^1, Z^3, t, R^W and R^E are as in claim 21.~~

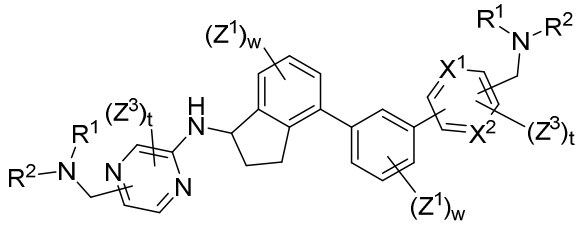
~~25. A compound of formula (VD):~~



~~(VD)~~

~~or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, solvate, or tautomer thereof, wherein Z^1, Z^3, t, R^W and R^E are as in claim 21.~~

~~26~~5. A compound of formula (VI):



(VI)

or a pharmaceutically acceptable salt~~, stereoisomer, mixture of stereoisomers, solvate, or tautomer~~ thereof, wherein:

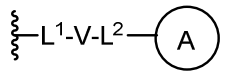
each of X^1 and X^2 are independently N, CH or CZ^3;

each Z^1 is independently halo, $-OR^a$, cyano, or $-C_{1-6}$ alkyl;

each w is independently 0, 1 or 2;

each Z^3 is independently halo, $-OR^a$, $-N_3$, $-NO_2$, cyano, $-NR^1R^2$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aSO_2R^a$, $-NR^aC(O)R^a$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-NR^aC(O)OR^a$, $-NR^aC(O)NR^1R^2$, $-OC(O)NR^aR^b$, $-NR^aS(O)_2NR^aR^b$, $-C(O)NR^aS(O)_2NR^aR^b$, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-O-C_{1-6}$ alkyl, $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ haloalkyl, $-O-C_{1-6}$ cyanoalkyl, $-O-C_{1-6}$ haloalkyl, $-C_{3-8}$ cycloalkyl, $-C_{1-6}$ alkylC_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, and R^N; and

wherein the alkyl, alkenyl, alkynyl, C_{3-8} cycloalkyl, aryl, heteroaryl, or heterocyclyl group is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-O-C_{1-6}$cyanoalkyl, $-C(O)NR^aR^b$, $NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-S(O)_2R^a$, $-NR^aS(O)_2R^b$, $-S(O)_2NR^aR^b$, $-NR^aS(O)_2NR^aR^b$, $-C(O)NR^aS(O)_2NR^aR^b$ and $-C_{3-8}$ cycloalkyl;

R^N is independently $-C_{1-6}$ alkylNR^1R^2, $-OC_{1-6}$ alkylNR^1R^2, $-C_{1-6}$ alkylOC_{1-6} alkylNR^1R^2, $-NR^a-C_{1-6}$ alkylNR^1R^2, $-C_{1-6}$ alkyl$C(O)NR^1R^2$, $-O-C_{1-6}$ alkyl$C(O)NR^1R^2$, $-O-C_{1-6}$ alkyl$C(O)OR^1$, $-S-C_{1-6}$ alkylNR^1R^2, $-C_{1-6}$ alkylOR^a, or ;

wherein: L^1 is independently a bond, -O-, $-NR^a$-, -S-, -S(O)-, or $-S(O)_2$-;

V is independently selected from a bond, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

wherein each alkyl, alkenyl, or alkynyl is optionally independently substituted with $-OR^a$, halo, cyano, $-NR^aR^b$ or $-C_{3-8}$ cycloalkyl;

L^2 is independently a bond, -O-, $-NR^a$-, -S-, -S(O)-, or $-S(O)_2$-;

ring A is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

wherein each cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$ alkynyl, $-O-C_{1-6}$ haloalkyl, NR^aR^b, $-C(O)R^a$, $-C(O)OR^a$, $-OC_{1-6}$ alkylCN, $-C(O)NR^aR^b$,

$-NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-NR^aC(O)OR^a$, $-C(O)N(R^a)OR^b$, $-S(O)_2R^a$, $-S(O)_2NR^aR^b$, $-NR^aS(O)_2R^b$, $-NR^aS(O)_2NR^aR^b$, $-C(O)NR^aS(O)_2NR^aR^b$, $-C_{3-8}$cycloalkyl, heteroaryl, and $-C_{1-6}$alkylC_{3-8} cycloalkyl; and

wherein the alkyl, alkenyl, or alkynyl group is optionally independently substituted with $-OR^a$, halo, cyano, $-NR^aR^b$ or $-C_{3-8}$ cycloalkyl;

each t is independently 0, 1 or 2;

each R^1 is independently selected from hydrogen, $-C_{1-8}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-C_{3-6}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-C_{1-6}$ alkylheterocyclyl, $-C_{1-6}$ alkyl$C(O)OR^a$, $-C_{2-6}$ alkenyl$C(O)OR^a$, $-S(O)_2R^a$, $-S(O)_2NR^aR^b$, $-C(O)NR^aS(O)_2R^a$, and $-C_{1-6}$ alkylC_{3-8}cycloalkyl;

wherein each alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from $-OR^a$, cyano, halo, C_{1-6}alkyl, $-C_{1-6}$ alkylOR^a, $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ haloalkyl, C_{3-8} cycloalkyl, $-C_{1-3}$ alkylC_{3-8}cycloalkyl, $-C(O)R^a$, $-C_{1-6}$ alkyl$C(O)R^a$, $-C(O)OR^a$, $-C_{1-6}$ alkyl$C(O)OR^a$, $-NR^aR^b$, $-OC(O)NR^aR^b$, $-NR^aC(O)OR^b$, $-C_{1-6}$ alkylNR^aR^b, $-C(O)NR^aR^b$, $-C_{1-6}$ alkyl$C(O)NR^aR^b$, $-SO_2R^a$, $-C_{1-6}$ alkylSO_2R^a, $-SO_2NR^aR^b$, $-C_{1-6}$ alkyl$SO_2NR^aR^b$, $-C(O)NR^aSO_2R^b$, $-C_{1-6}$ alkyl$C(O)NR^aSO_2R^b$, $-NR^aC(O)R^b$, and $-C_{1-6}$alkyl$NR^aC(O)R^b$;

each R^2 is independently selected from hydrogen, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-C_{3-6}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-C_{1-6}$ alkylheterocyclyl, $-C_{2-6}$ alkyl-OR^a, $-C_{1-6}$ alkyl$C(O)OR^a$, and $-C_{2-6}$ alkenyl$C(O)OR^a$;

wherein each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from $-OR^a$, cyano, halo, C_{1-6} alkyl, $-C_{1-6}$ alkylOR^a, $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ haloalkyl, $-C_{3-8}$ cycloalkyl, $-C_{1-3}$ alkylC_{3-8}cycloalkyl, $-C(O)R^a$, $-C_{1-6}$ alkyl$C(O)R^a$, $-C(O)OR^a$, $-C_{1-6}$ alkyl$C(O)OR^a$, $-NR^aR^b$, $-C_{1-6}$ alkylNR^aR^b, $-C(O)NR^aR^b$, C_{1-6} alkyl$C(O)NR^aR^b$, $-S(O)_2R^a$, $-C_{1-6}$ alkyl$S(O)_2R^a$, $-S(O)_2NR^aR^b$, $-C_{1-6}$ alkyl$S(O)_2NR^aR^b$, $-C(O)NR^aS(O)_2R^b$ and $-NR^aC(O)R^b$;

or R^1 and R^2 combine to form a heterocyclyl optionally substituted with 1 to 3 groups independently selected from oxo, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-OR^a$, $-C(O)OR^a$, $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ alkylOR^a, $-C_{1-6}$ haloalkyl, $-C_{1-3}$ alkylC_{3-8}cycloalkyl, $-C(O)R^a$, $-C_{1-6}$ alkyl$C(O)R^a$, $-C_{1-6}$ alkyl$C(O)OR^a$, $-NR^aR^b$, $-C_{1-6}$alkylNR^aR^b, $-C(O)NR^aR^b$, $-C_{1-6}$ alkyl$C(O)NR^aR^b$, $-S(O)_2R^a$, $-C_{1-6}$ alkyl$S(O)_2R^a$, $-S(O)_2NR^aR^b$, $-C(O)N{=}S(O)R^aNR^aR^b$, $-C(O)N{=}S(O)R^aNR^aC(O)R^b$, and $-C_{1-6}$ alkyl$S(O)_2NR^aR^b$;

each R^3 is independently hydrogen, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{3-6}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-C_{1-6}$ alkylheterocyclyl, $-C_{2-6}$ alkyl-OR^a, $-C_{1-6}$ alkyl$C(O)OR^a$, or $-C_{2-6}$ alkenyl$C(O)OR^a$;

each R^a is independently selected from hydrogen, -C_{1-6} alkyl, -C_{1-6} cyanoalkyl, -C_{1-6} haloalkyl, -C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, -C_{1-3} alkylC_{3-8}cycloalkyl, -C_{1-6} alkylaryl, -C_{1-6} alkylheteroaryl, and -C_{1-6}alkylheterocyclyl;

each R^b is independently selected from hydrogen, -C_{1-6} alkyl, -C_{1-6} cyanoalkyl, -C_{1-6} haloalkyl, -C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, -C_{1-3} alkylC_{3-8}cycloalkyl, -C_{1-6} alkylaryl, -C_{1-6} alkylheteroaryl, and -C_{1-6} alkylheterocyclyl;

or R^a and R^b may combine together to form a heterocyclyl optionally substituted with 1 to 4 groups independently selected from -OR^f, cyano, halo, -C_{1-6} alkylOR^f, -C_{1-6} cyanoalkyl, -C_{1-6} haloalkyl, -C_{3-8} cycloalkyl, -C_{1-3} alkylC_{3-8}cycloalkyl, -$C(O)R^f$, -C_{1-6} alkyl$C(O)R^f$, -$C(O)OR^f$, -C_{1-6} alkyl$C(O)OR^f$, -NR^fR^g, -C_{1-6} alkylNR^fR^g, -$C(O)NR^fR^g$, -C_{1-6} alkyl$C(O)NR^fR^g$, -$S(O)_2R^f$, -C_{1-6} alkyl$S(O)_2R^f$, -$S(O)_2NR^fR^g$, -C_{1-6} alkyl$S(O)_2NR^fR^g$, -$C(O)NR^fS(O)_2R^g$ and -$NR^fC(O)R^g$;

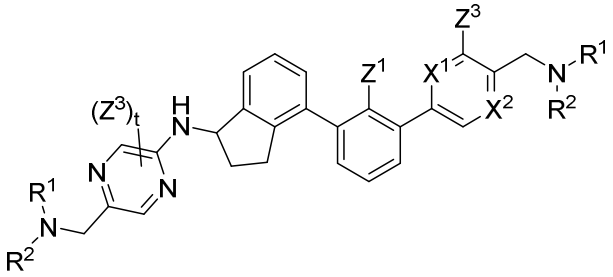
each R^c is independently selected from hydrogen, -OH, -C_{1-6} alkyl, -C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, -C_{1-3} alkylC_{3-8} cycloalkyl, -C_{1-6} alkylaryl, -C_{1-6} alkylheteroaryl, and -C_{1-6} alkylheterocyclyl;

R^d is independently selected from hydrogen, -C_{1-6} alkyl, -C_3-C_8cycloalkyl, aryl, heteroaryl, heterocyclyl, -C_{1-3} alkylC_{3-8}cycloalkyl, -C_{1-6} alkylaryl, -C_{1-6} alkylheteroaryl, and -C_{1-6} alkylheterocyclyl;

each R^f is independently selected from hydrogen, -C_{1-6} alkyl, -C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, -C_{1-3} alkylC_{3-8} cycloalkyl, -C_{1-6} alkylaryl, -C_{1-6} alkylheteroaryl, and -C_{1-6} alkylheterocyclyl; and

each R^g is independently selected from hydrogen, -C_{1-6} alkyl, -C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, -C_{1-3} alkylC_{3-8} cycloalkyl, -C_{1-6} alkylaryl, -C_{1-6} alkylheteroaryl, and -C_{1-6} alkylheterocyclyl.

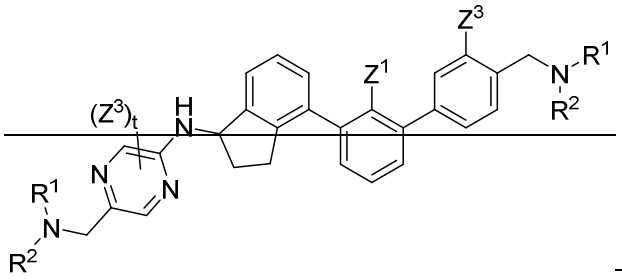
~~27~~6. ~~A~~ The compound of claim 1, wherein the compound is of formula (VIA):



(VIA)

or a pharmaceutically acceptable salt~~, stereoisomer, mixture of stereoisomers, solvate, or tautomer~~ thereof~~, wherein X^1, X^2, Z^1, Z^3, t, R^1 and R^2 are as in claim 26~~.

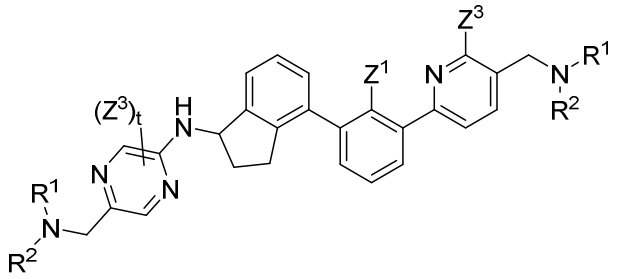
~~28. A compound of formula (VIB):~~



~~(VIB)~~

~~or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, solvate, or tautomer thereof, wherein Z^1, Z^3, t, R^1 and R^2 are as in claim 26.~~

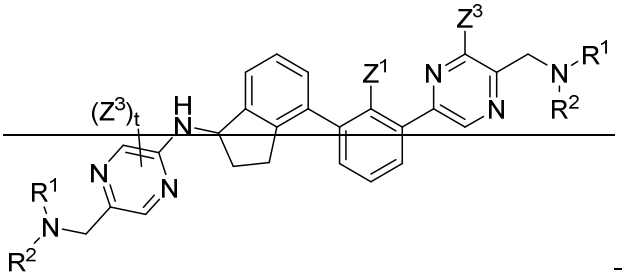
~~29~~7. ~~A~~ The compound of claim 1, wherein the compound is of formula (VIC):



(VIC)

or a pharmaceutically acceptable salt~~, stereoisomer, mixture of stereoisomers, solvate, or tautomer~~ thereof~~, wherein Z^1, Z^3, t, R^1 and R^2 are as in claim 26~~.

~~30. A compound of formula (VID):~~



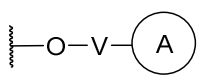
~~(VID)~~

~~or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, solvate, or tautomer thereof, wherein Z^1, Z^3, t, R^1 and R^2 are as in claim 26.~~

~~31~~8. The compound of any one of the preceding claims, wherein each Z^1 is independently halo.

~~32~~9. The compound of any one of the preceding claims, wherein at least one Z^3 is halo, -C_{1-6} alkyl, C_{1-6} haloalkyl, -O-cyanoalkyl, -O-C_{1-6} haloalkyl, or C_{1-6} alkoxy.

~~33~~10. The compound of any one of the preceding claims, wherein at least one Z^3 is of the formula:



V is independently selected from a bond, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

wherein each alkyl, alkenyl, or alkynyl is optionally independently substituted with -OR^a, halo, cyano, -NR^aR^b or -C_{3-8} cycloalkyl;

ring A is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

wherein each cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$ alkynyl, $-O-C_{1-6}$ haloalkyl, NR^aR^b, $-C(O)R^a$, $-C(O)OR^a$, $-OC_{1-6}$ alkylCN, $-C(O)NR^aR^b$, $-NR^aC(O)R^a$, $NR^aC(O)OR^a$, $-NR^aC(O)OR^a$, $-C(O)N(R^a)OR^b$, $-S(O)_2R^a$, $-S(O)_2NR^aR^b$, $-NR^aS(O)_2R^b$, $-NR^aS(O)_2NR^aR^b$, $-C(O)NR^aS(O)_2NR^aR^b$, $-C_{3-8}$ cycloalkyl, heteroaryl, and $-C_{1-6}$alkylC_{3-8} cycloalkyl.

~~34. The compound of claim 1, 11 or 21, wherein at least one of R^E and R^W is $-C_{1-6}$ alkylNR^{1}R^2.~~

~~35. The compound of claim 1, 11 or 21, wherein both of R^E and R^W are each independently $-C_{1-6}$ alkylNR^{1}R^2.~~

~~36~~11. The compound of <u>any one of the preceding</u> claim<u>s</u> ~~34 or 35~~, wherein R^1 and R^2 combine to form a heterocyclyl optionally substituted with 1 to 3 groups independently selected from oxo, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl,
$-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-OR^a$, $-C(O)OR^a$, $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ alkylOR^a,
$-C_{1-6}$ haloalkyl,
$-C_{1-3}$ alkylC_{3-8}cycloalkyl, $-C(O)R^a$, $-C_{1-6}$ alkyl$C(O)R^a$, $-C_{1-6}$ alkyl$C(O)OR^a$, $-NR^aR^b$,
$-C_{1-6}$alkylNR^aR^b,
$-C(O)NR^aR^b$, $-C_{1-6}$ alkyl$C(O)NR^aR^b$, $-S(O)_2R^a$, $-C_{1-6}$ alkyl$S(O)_2R^a$, $-S(O)_2NR^aR^b$,
$-C(O)N=S(O)R^aNR^aR^b$, $-C(O)N=S(O)R^aNR^aC(O)R^b$, and $-C_{1-6}$ alkyl$S(O)_2NR^aR^b$.

~~37~~12. The compound of <u>any one of</u> claim<u>s</u> ~~34 or 35~~1 to 10, wherein at least one of R^1 and R^2 is $-C_{1-6}$ alkylheteroaryl or $-C_{1-6}$ alkylheteocyclyl.

~~38. The compound of claim 1, 11 or 21, wherein:~~

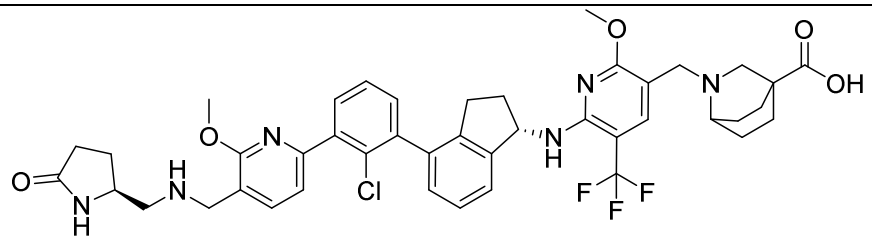
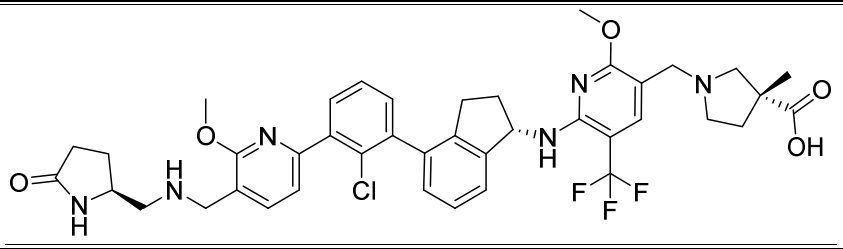
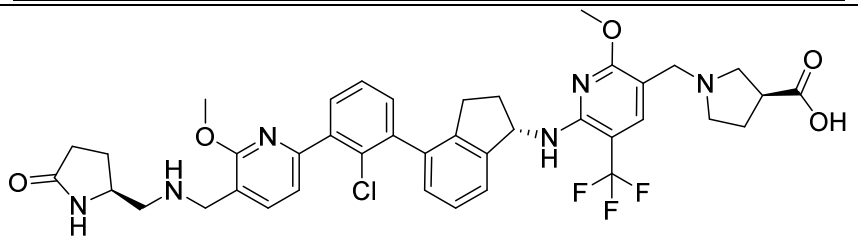
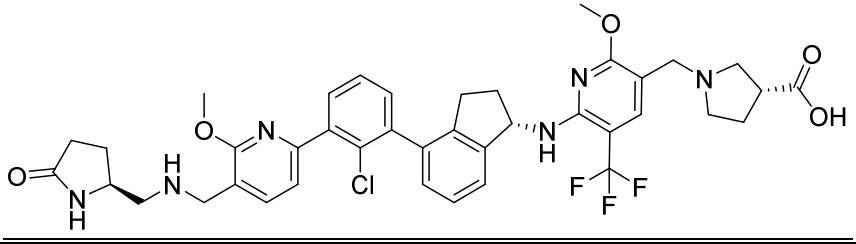
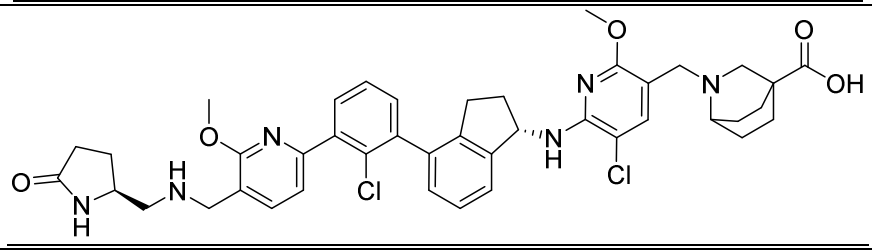
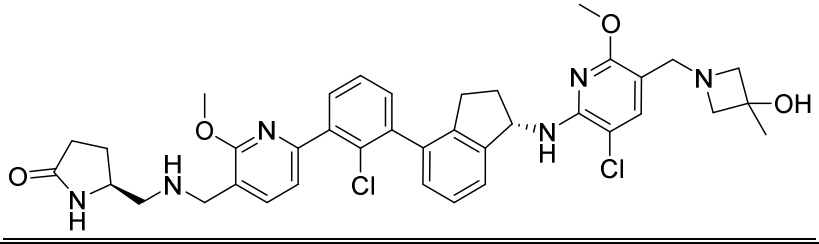
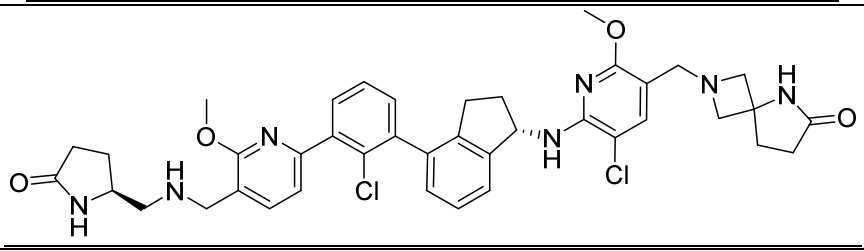
~~one of R^E and R^W is $-C_{1-6}$ alkylNR^{1}R^2, where R^1 and R^2 combine to form a heterocyclyl optionally substituted with 1 to 3 groups independently selected from oxo, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-OR^a$, $-C(O)OR^a$, $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ alkylOR^a, $-C_{1-6}$ haloalkyl, $-C_{1-3}$ alkylC_{3-8}cycloalkyl, $-C(O)R^a$, $-C_{1-6}$ alkyl$C(O)R^a$, $-C_{1-6}$ alkyl$C(O)OR^a$, $-NR^aR^b$, $-C_{1-6}$alkylNR^aR^b, $-C(O)NR^aR^b$, $-C_{1-6}$ alkyl$C(O)NR^aR^b$, $-S(O)_2R^a$, $-C_{1-6}$ alkyl$S(O)_2R^a$, $-S(O)_2NR^aR^b$, $-C(O)N=S(O)R^aNR^aR^b$, $-C(O)N=S(O)R^aNR^aC(O)R^b$, and $-C_{1-6}$ alkyl$S(O)_2NR^aR^b$; and~~

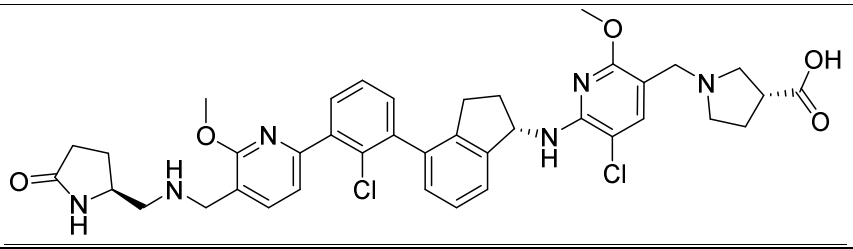
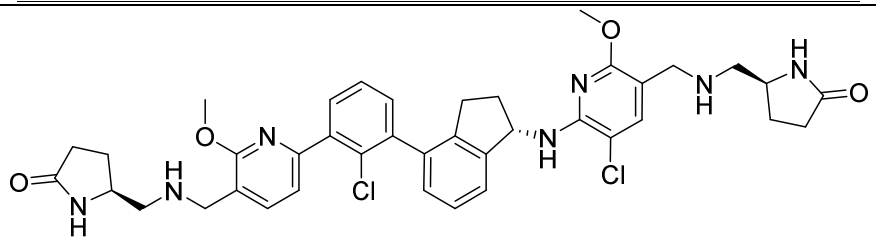
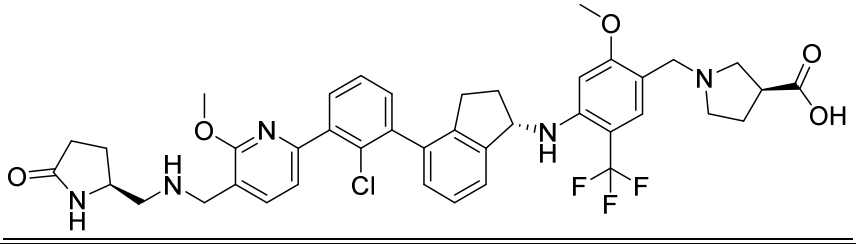
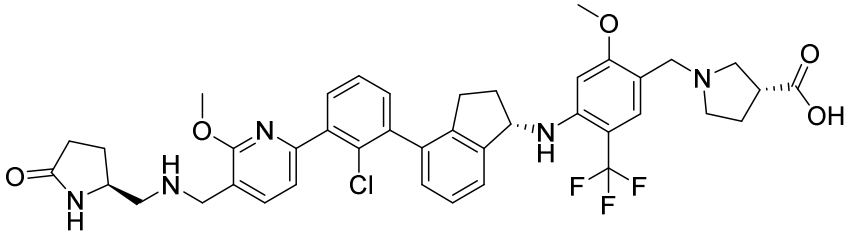
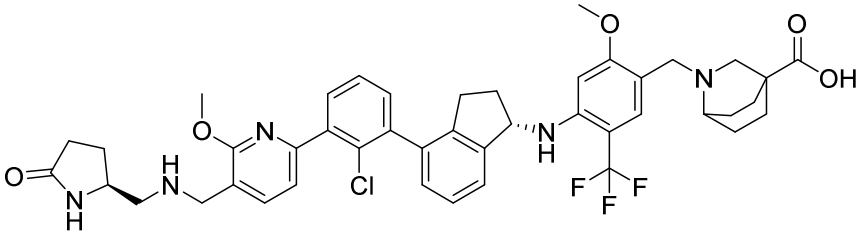
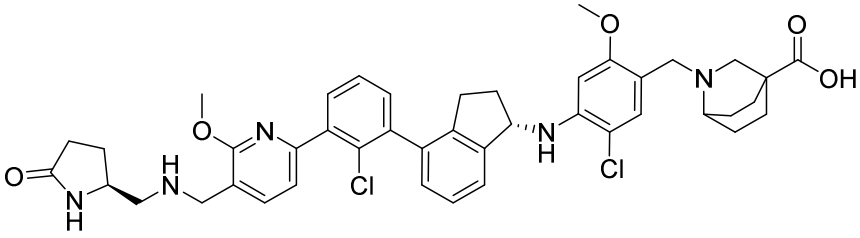
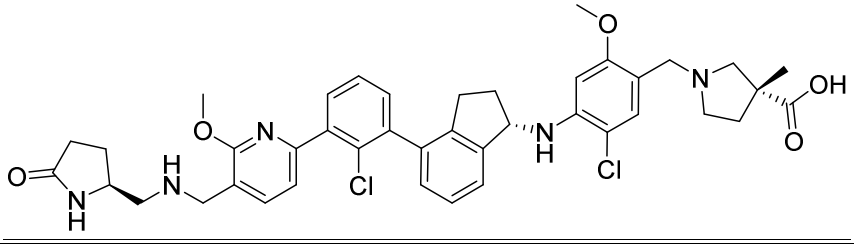
~~the other of R^E and R^W is $-C_{1-6}$ alkylNR^{1}R^2, where R^1 is hydrogen and R^2 is $-C_{1-6}$ alkylheteroaryl or $-C_{1-6}$ alkylheteocyclyl.~~

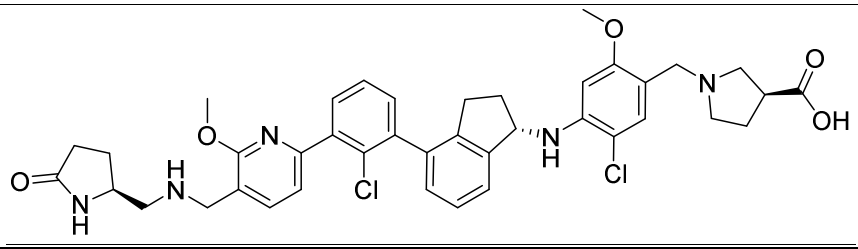
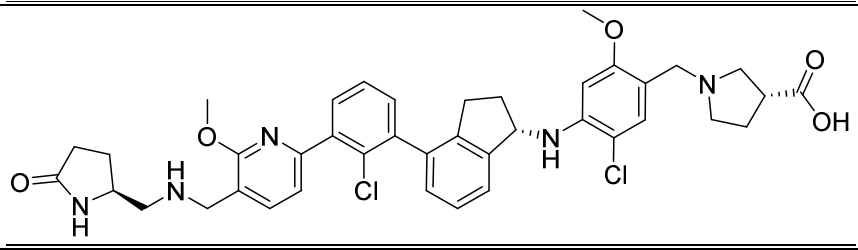
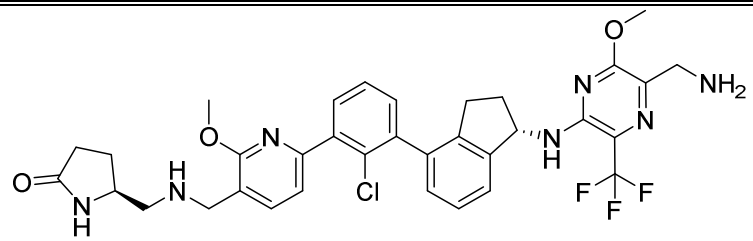
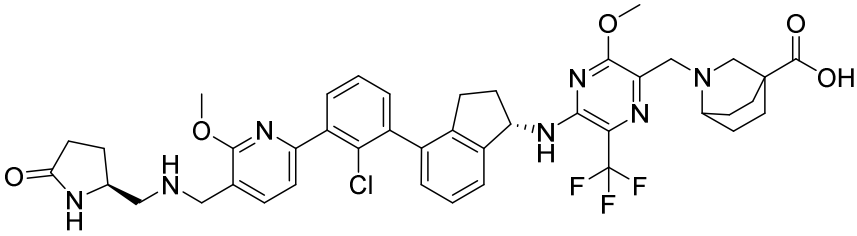
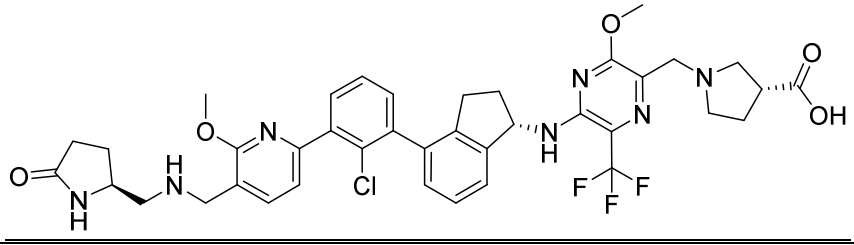
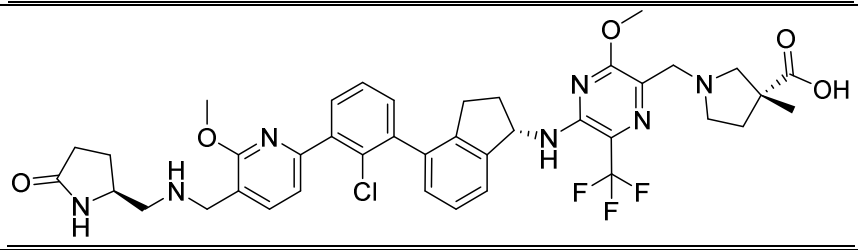
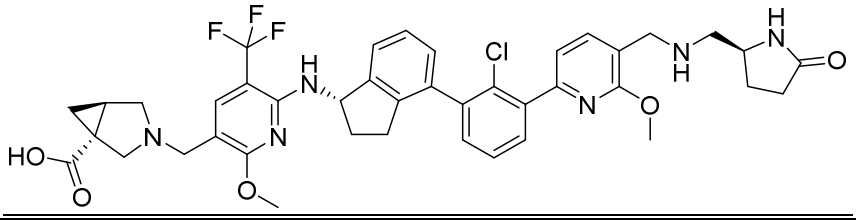
~~39~~13. A compound selected from Table 1A, or a pharmaceutically acceptable salt~~, stereoisomer, mixture of stereoisomers, solvate, or tautomer~~ thereof ~~.~~

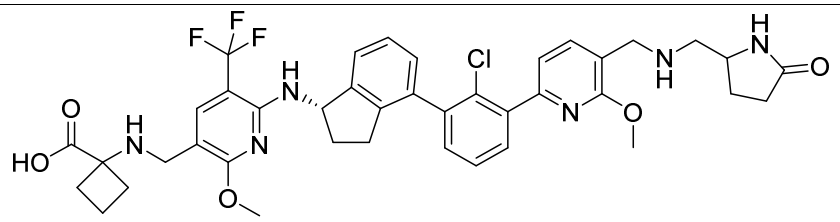
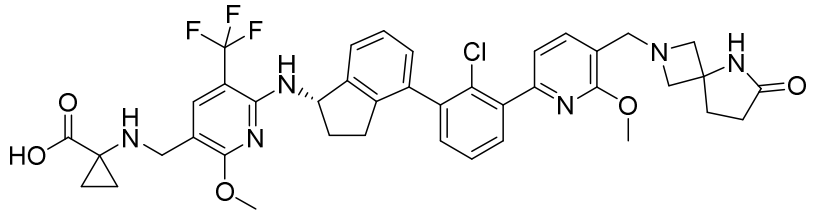
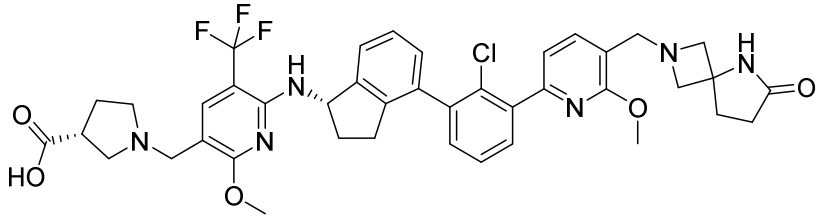
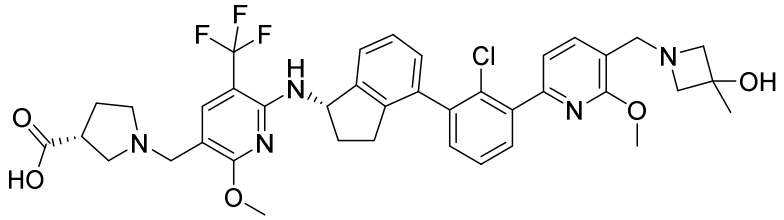
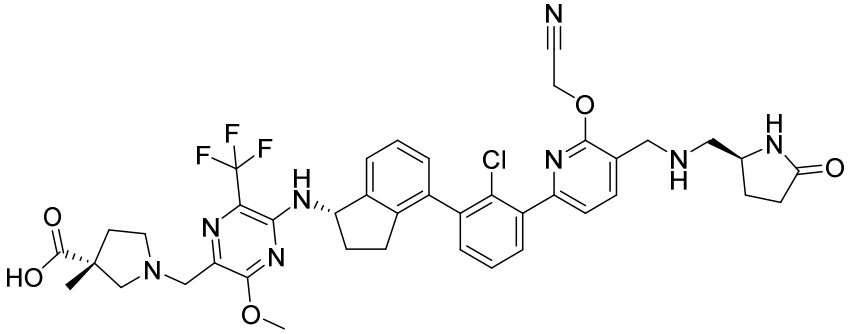
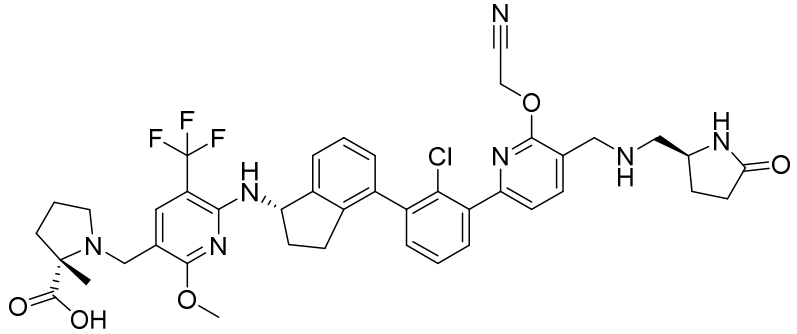
~~40.~~ A<u>or a</u> compound selected from Table 1B, or a pharmaceutically acceptable salt~~, stereoisomer, mixture of stereoisomers, solvate, or tautomer~~ thereof~~.~~<u>:</u>

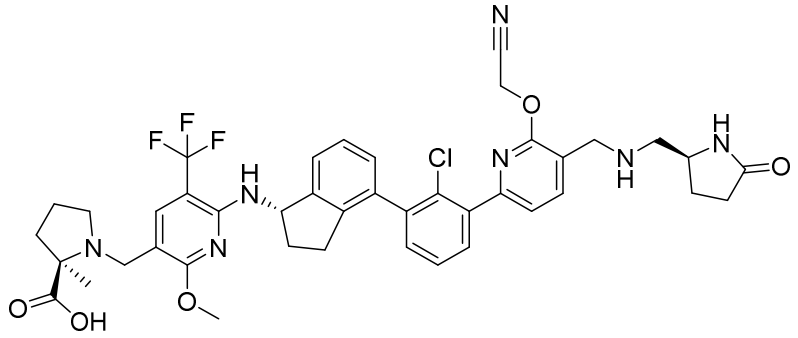
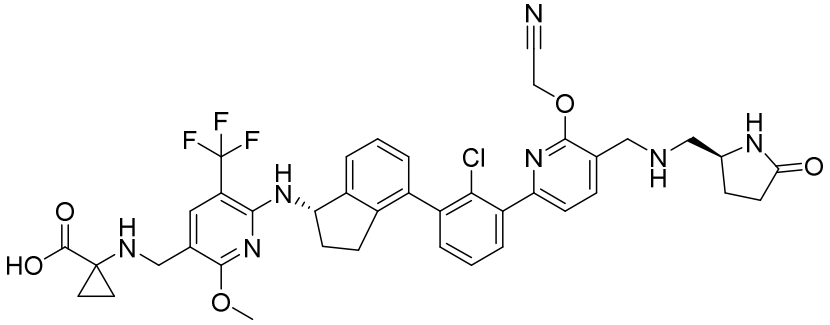
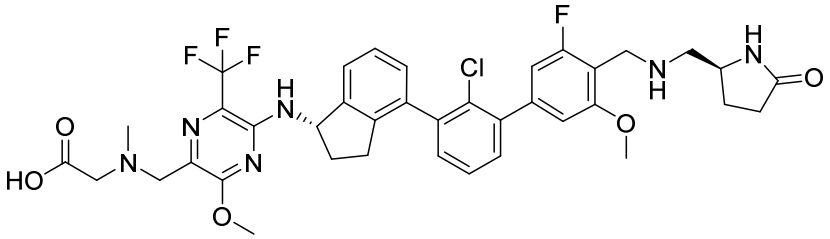
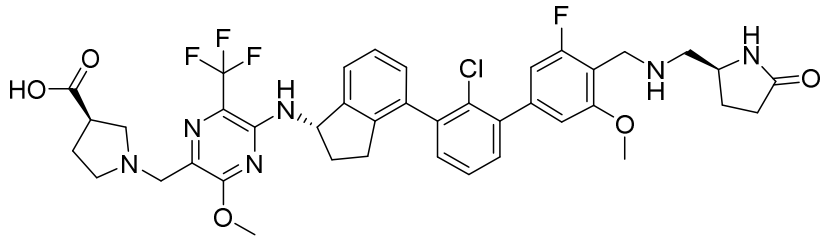
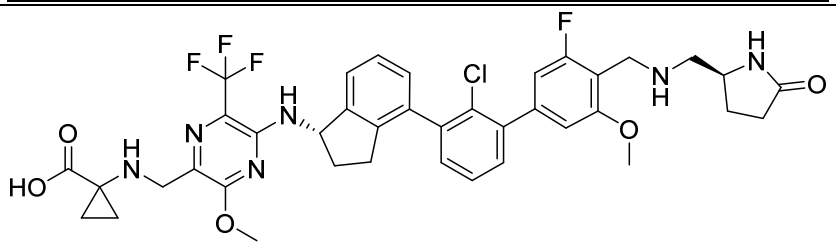
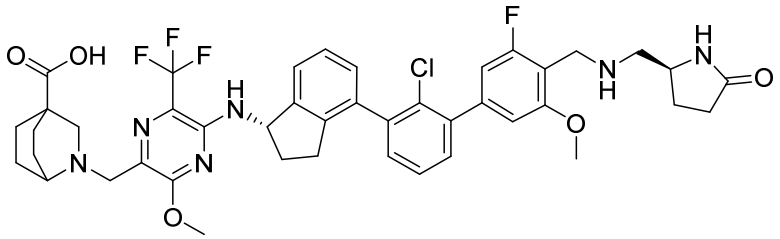
Table 1A

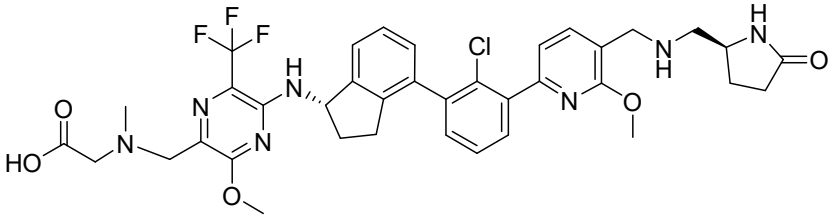
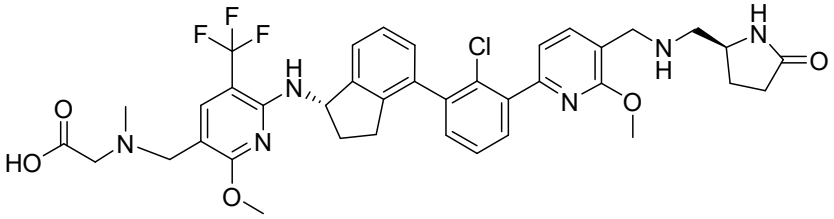
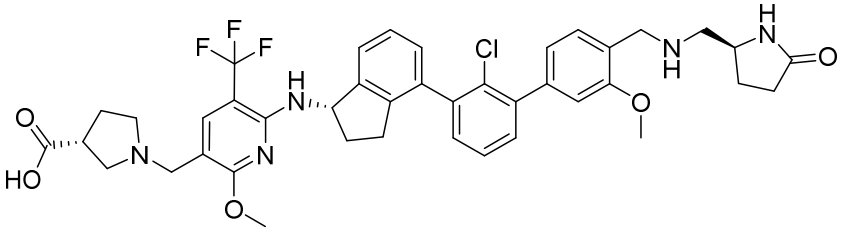
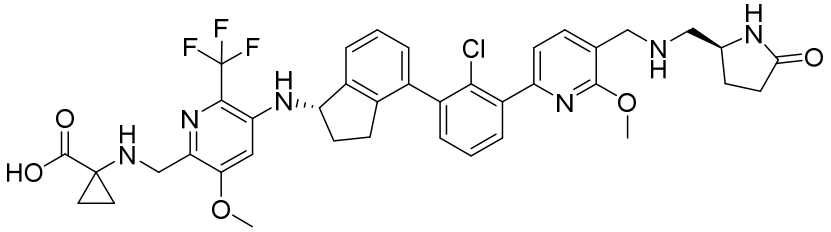
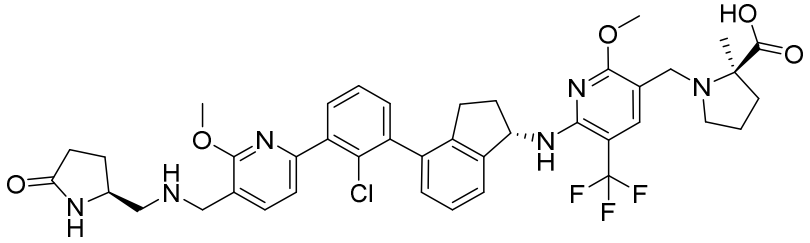
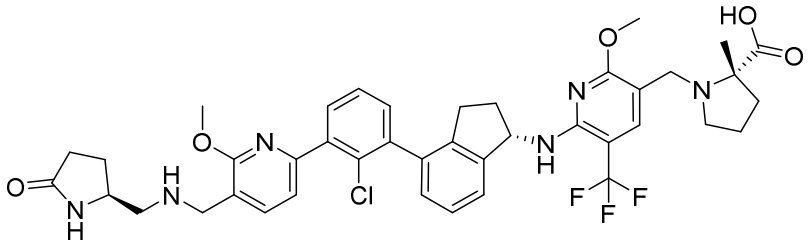
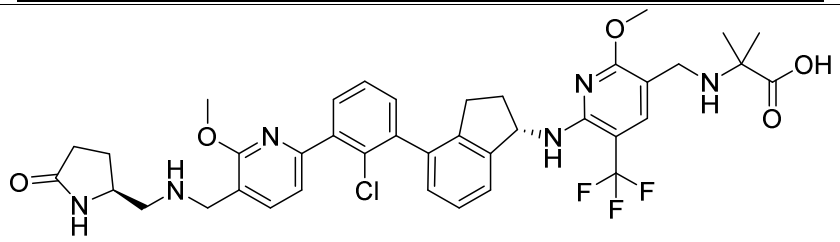
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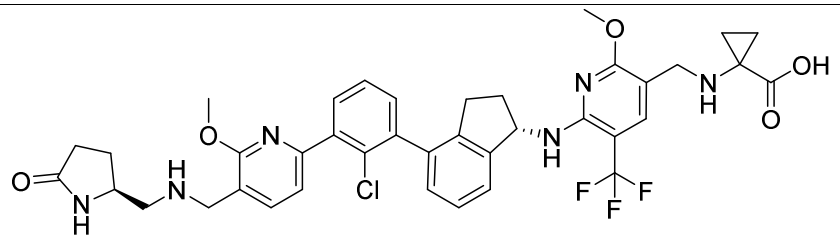
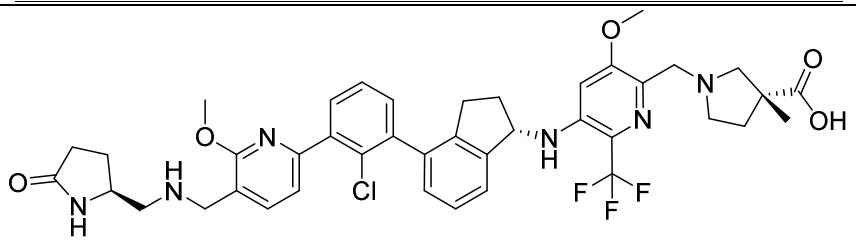
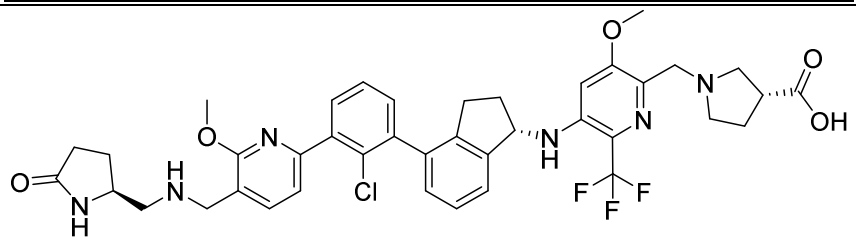
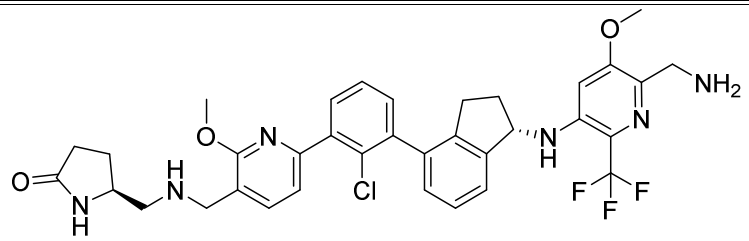
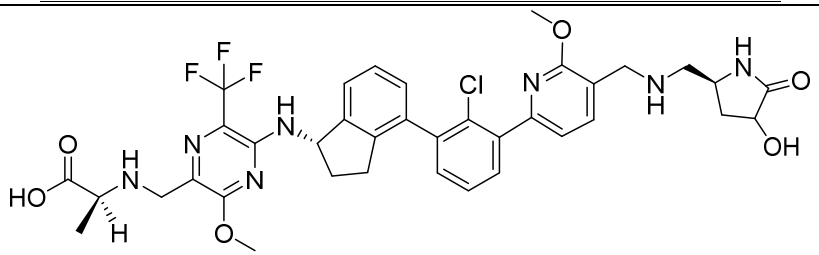
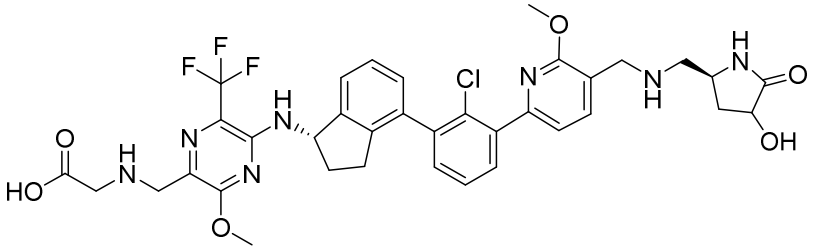
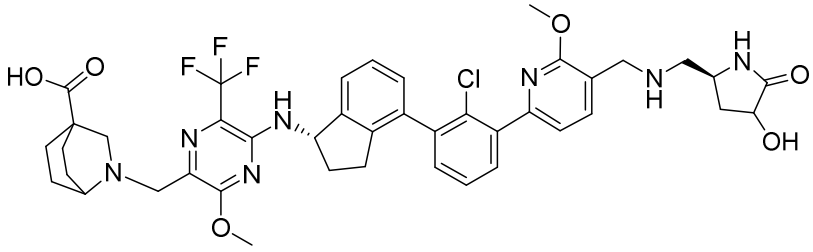
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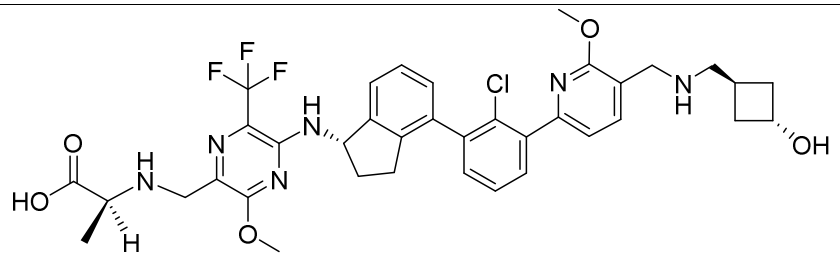
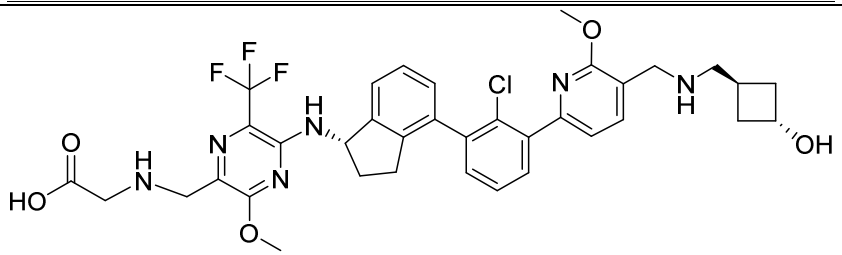
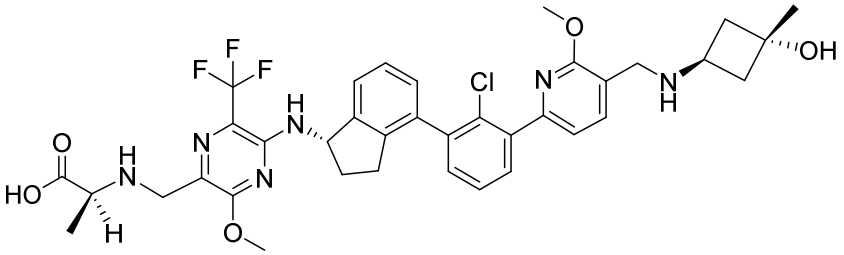
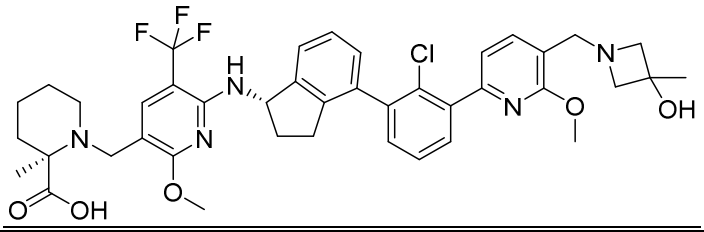
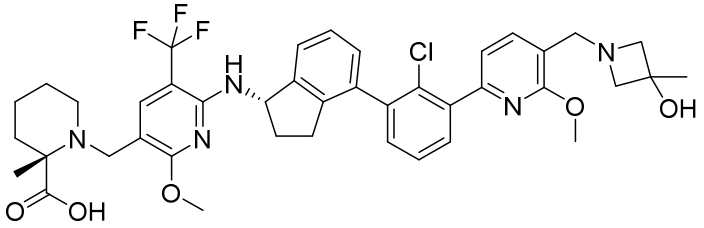
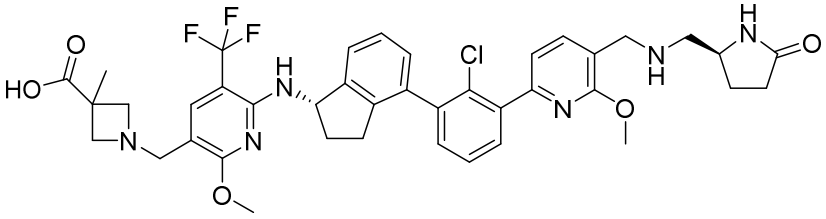
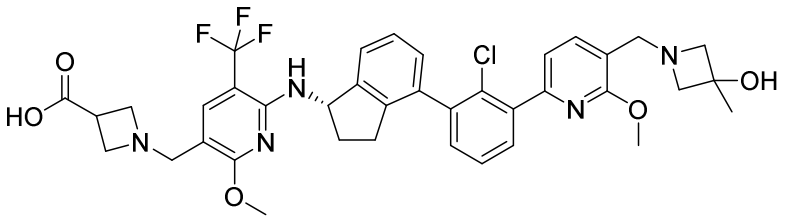
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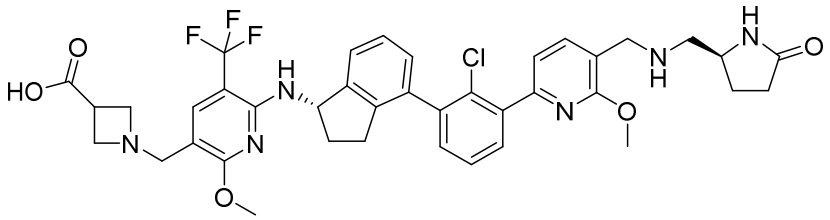
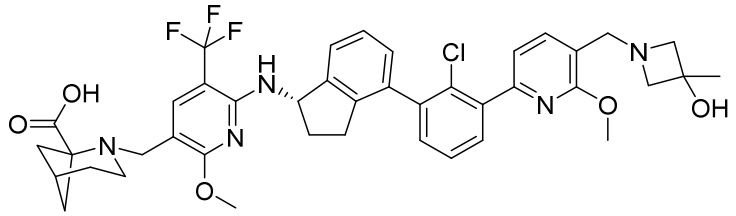
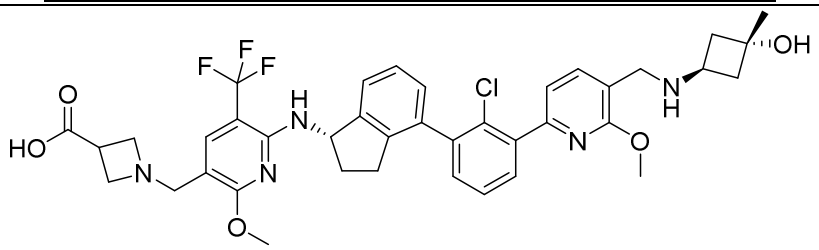
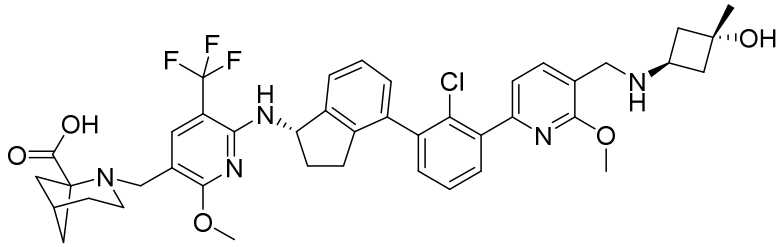
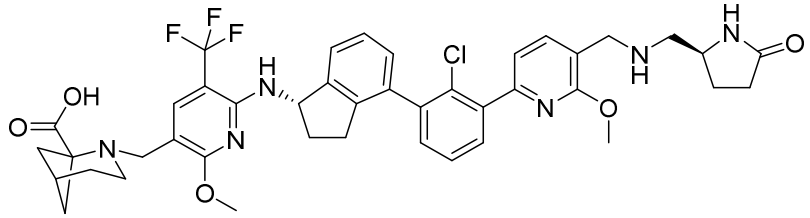
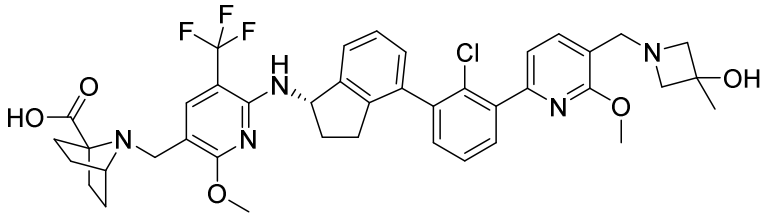
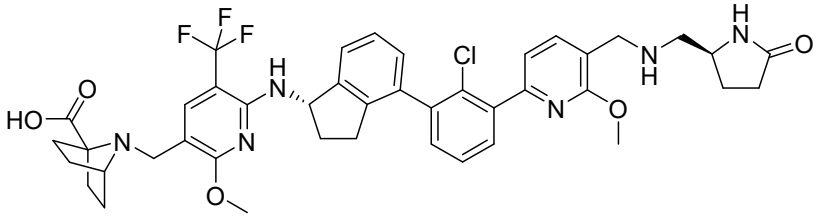
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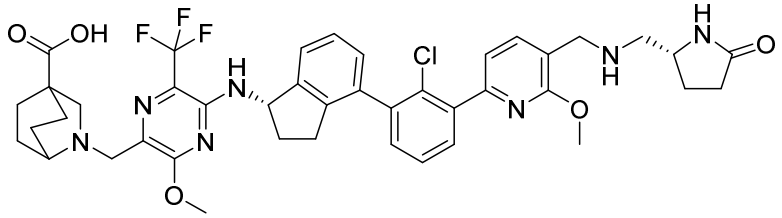
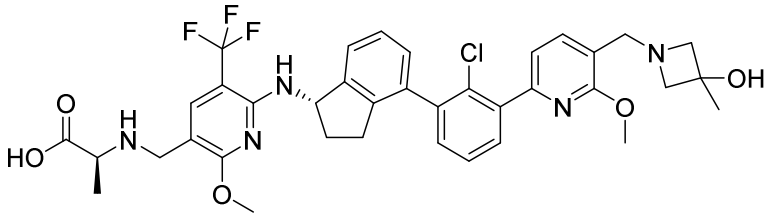
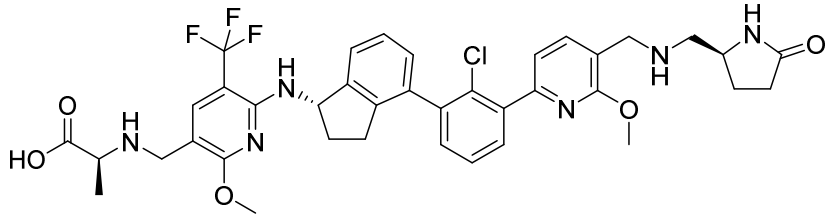
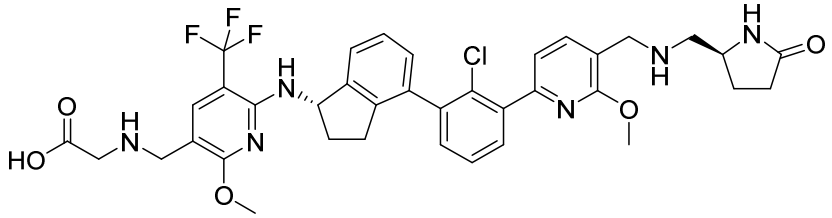
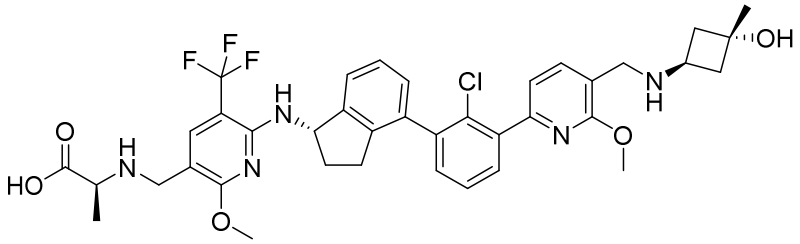
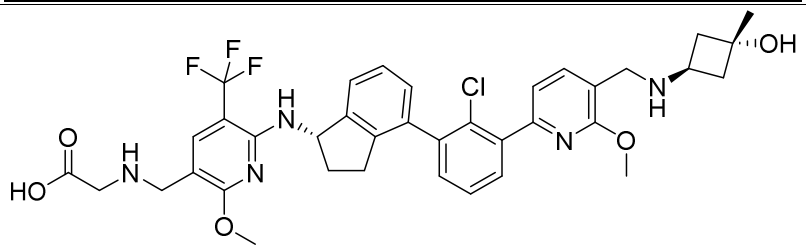
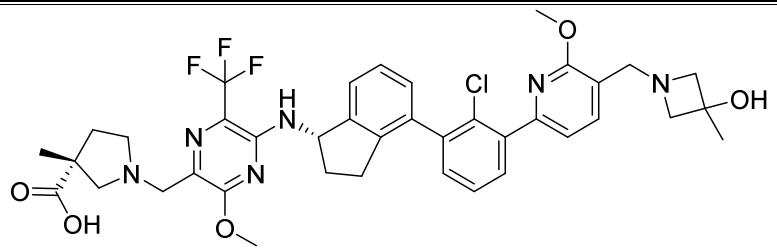
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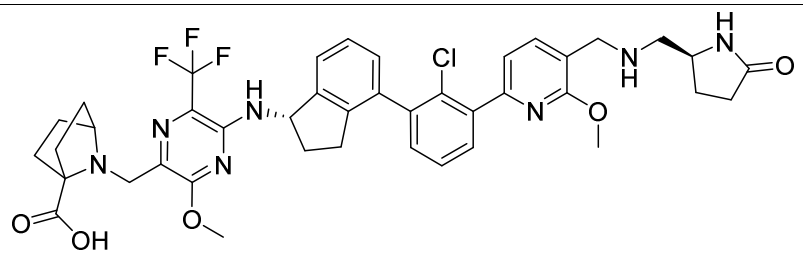
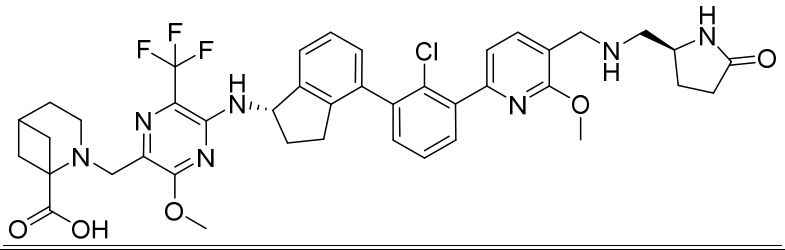
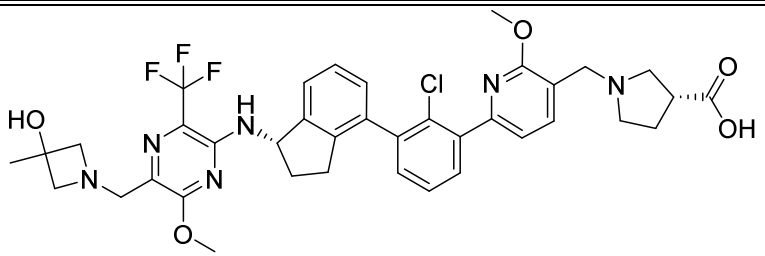
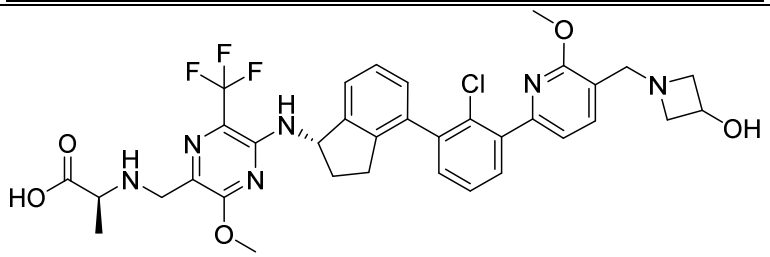
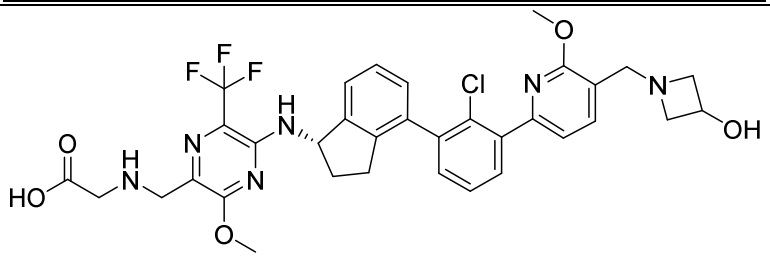
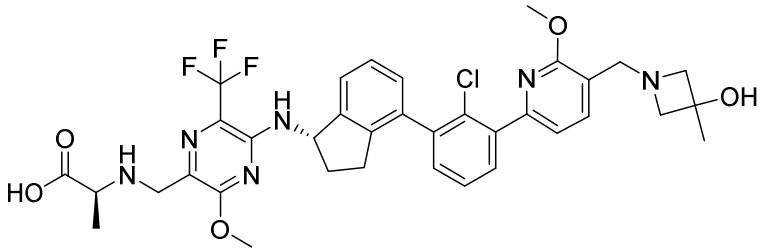
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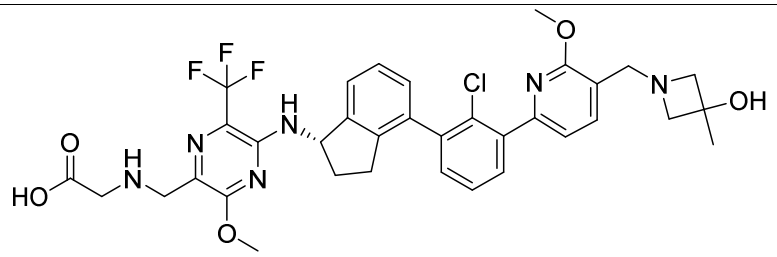
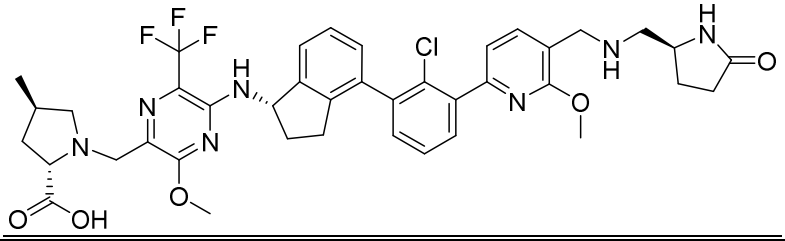
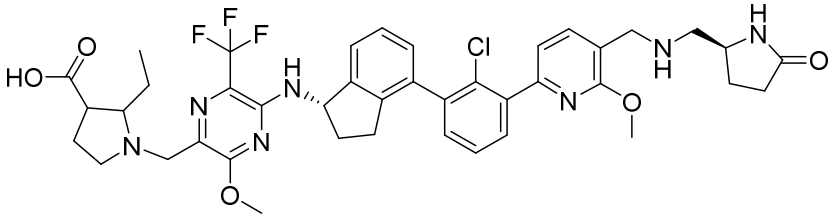
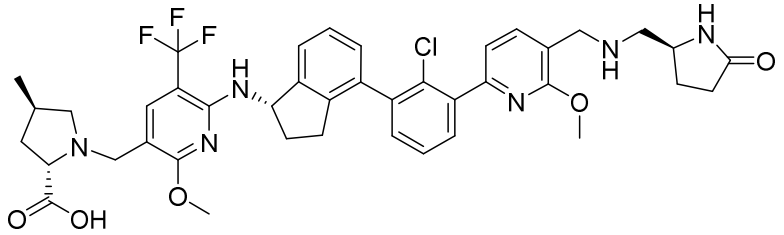
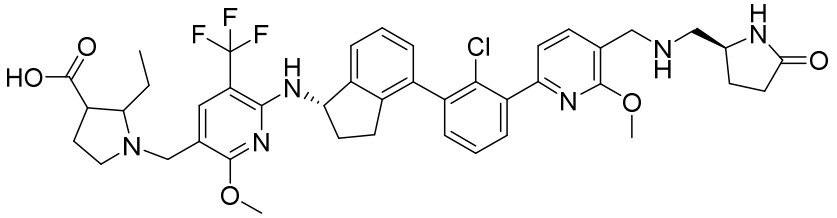
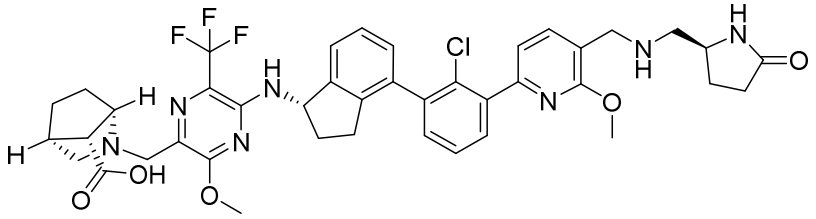
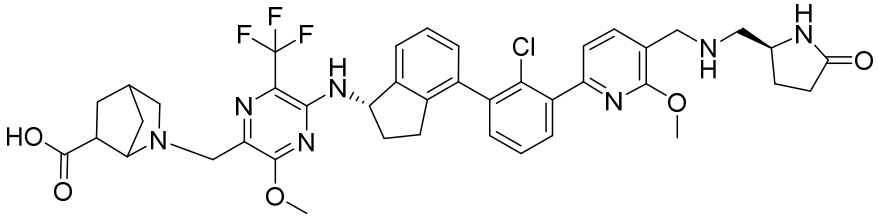
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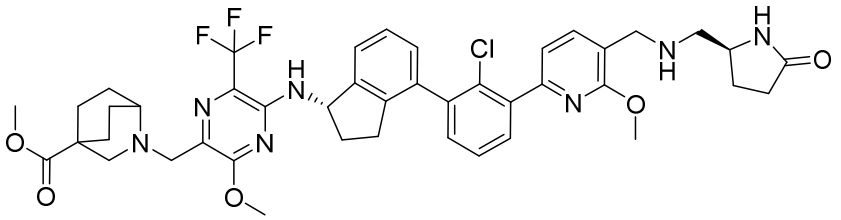
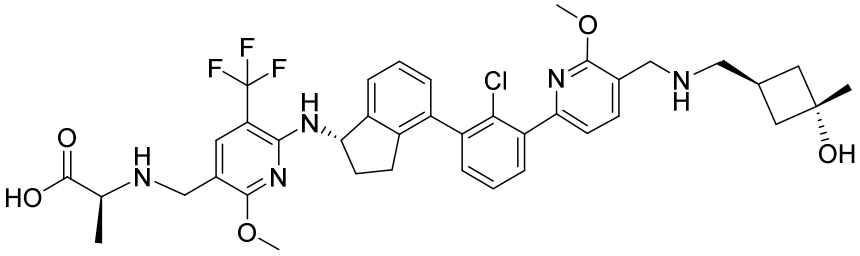
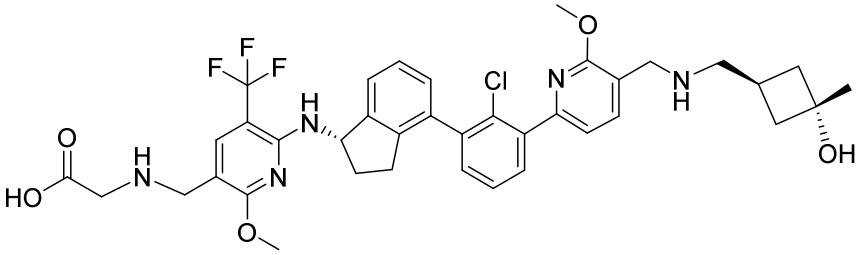
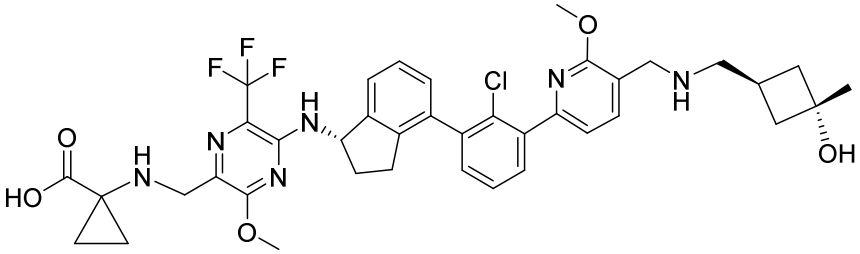
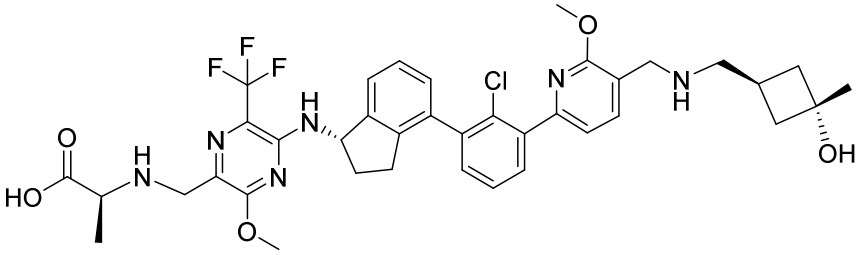
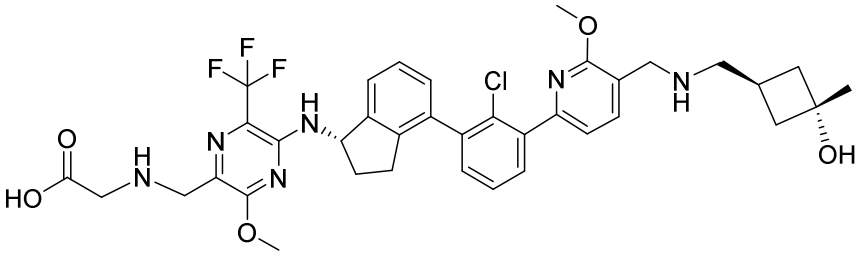
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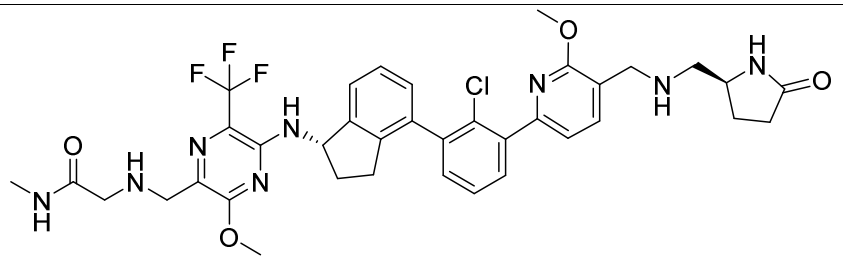
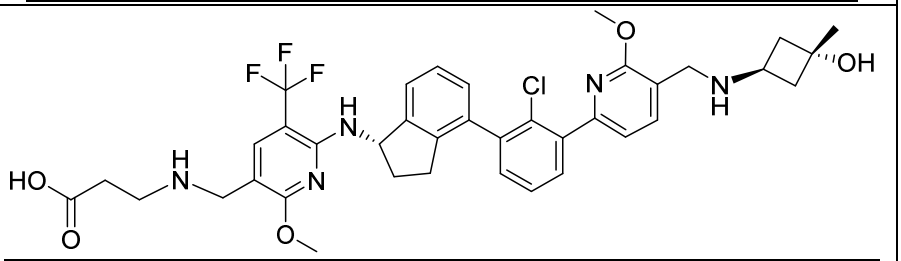
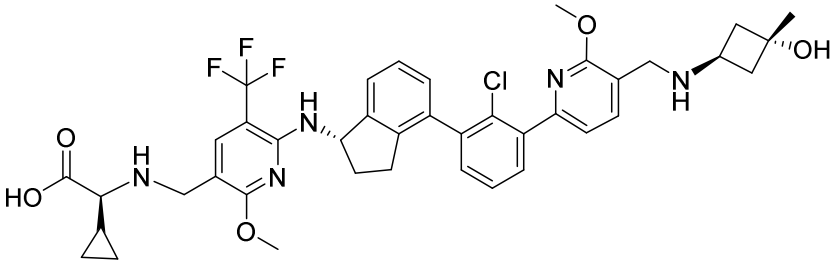
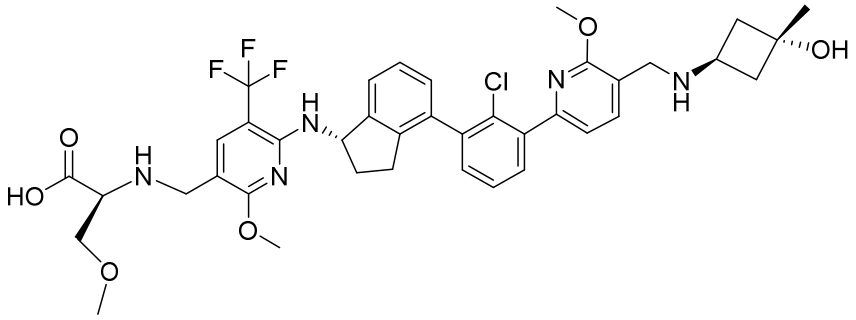
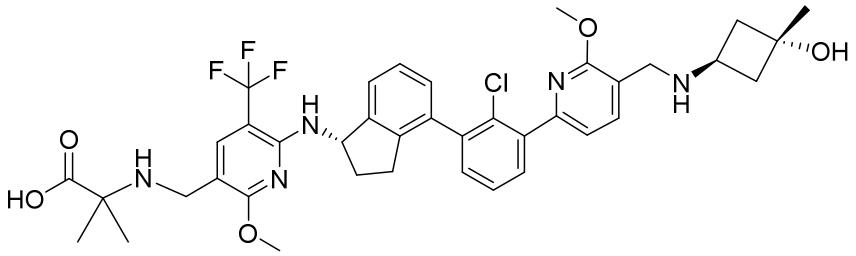
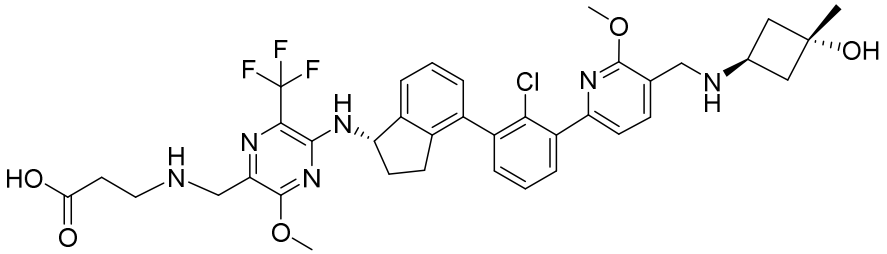
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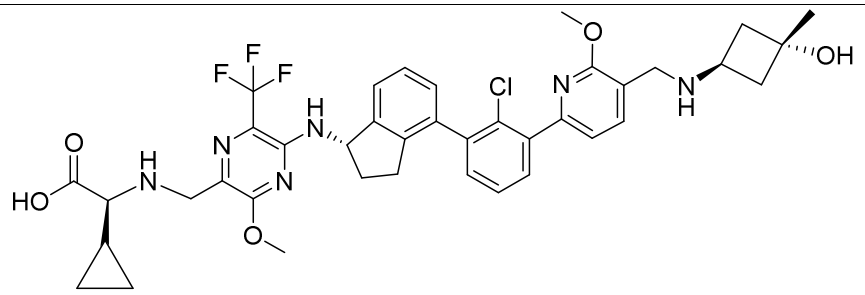
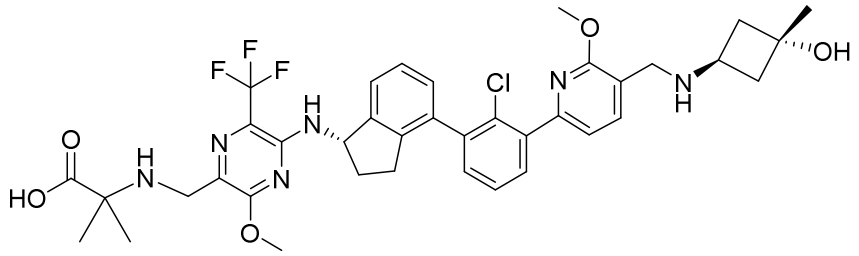
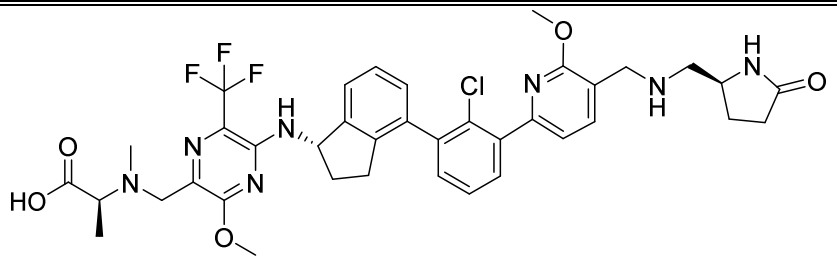
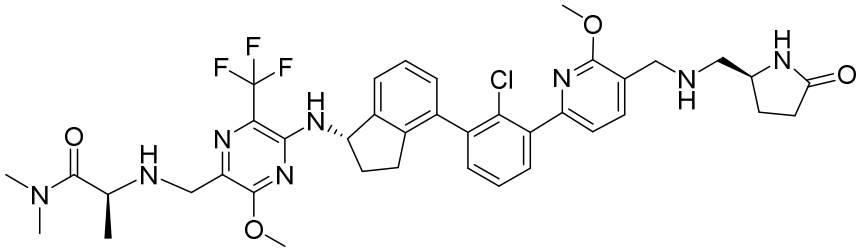
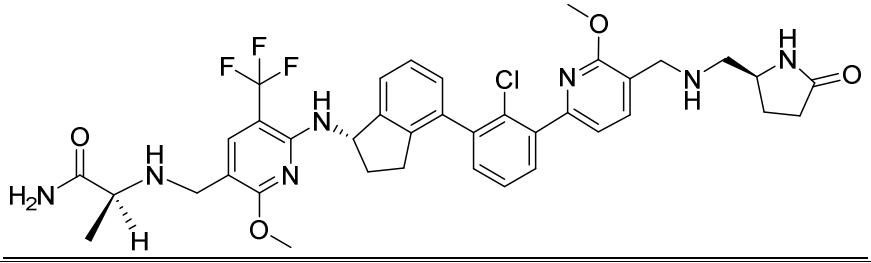
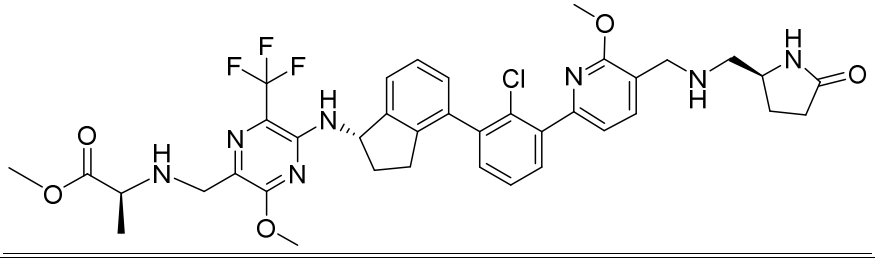
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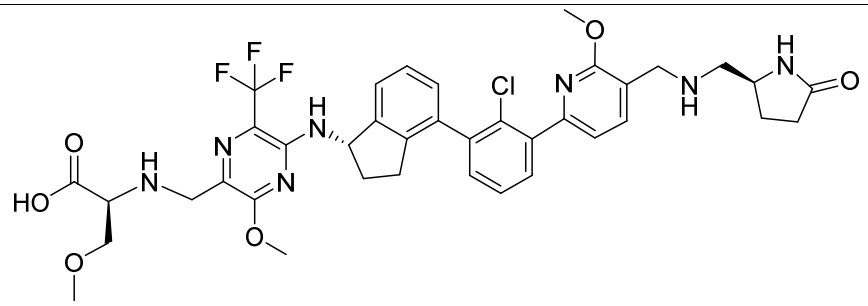
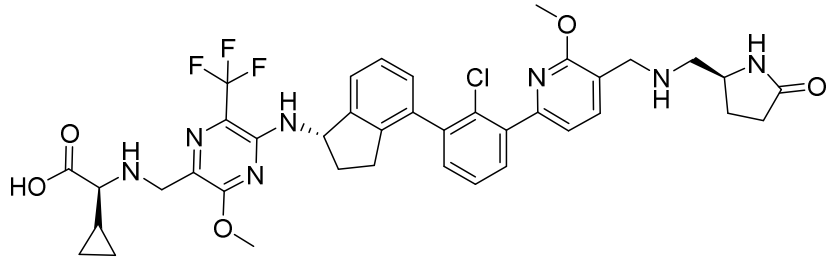
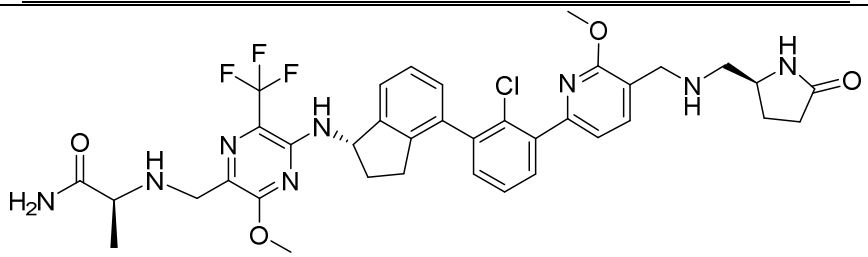
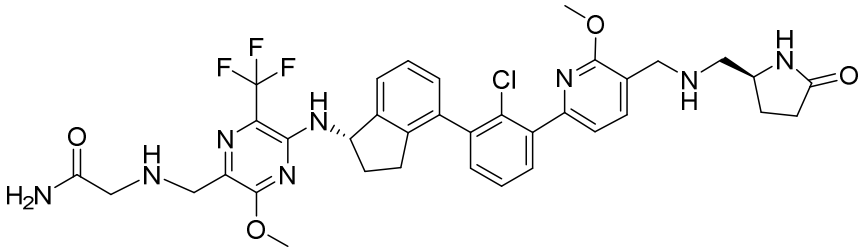
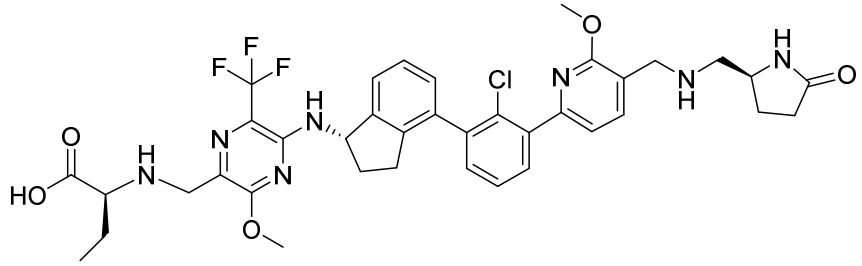
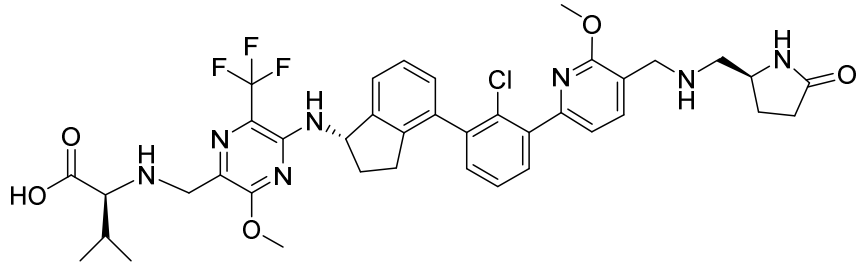
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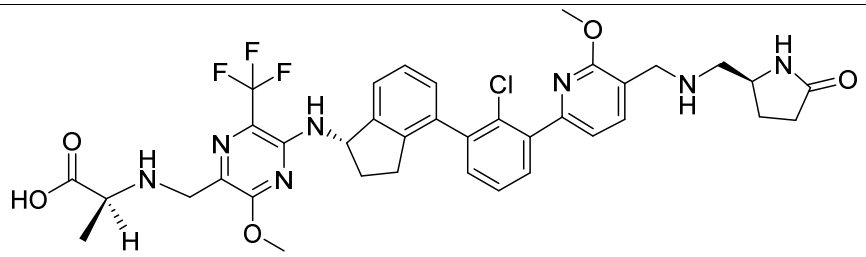
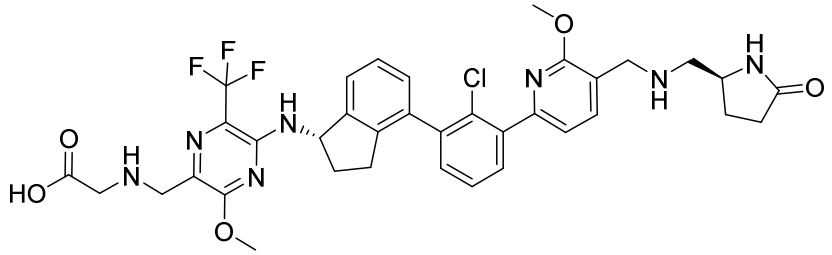
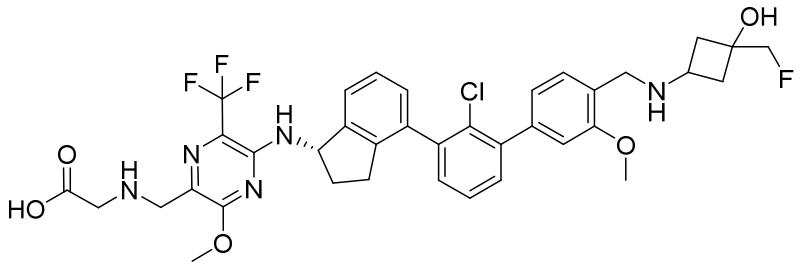
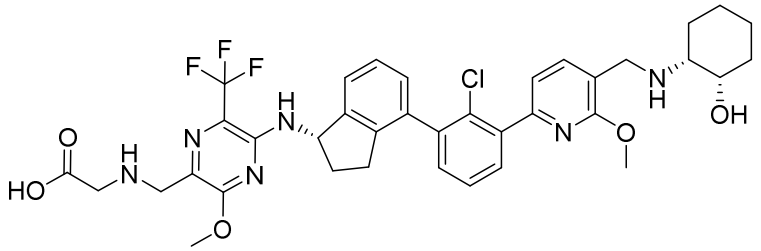
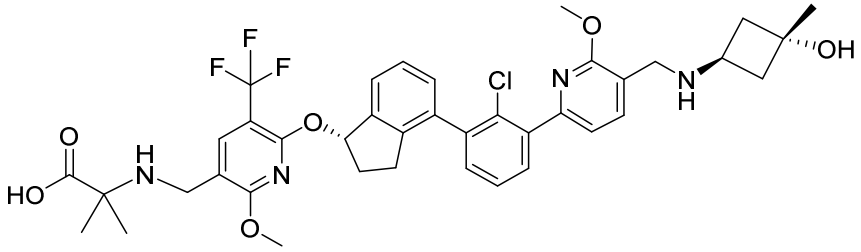
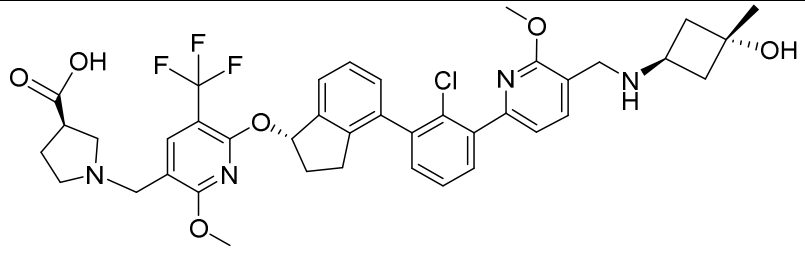
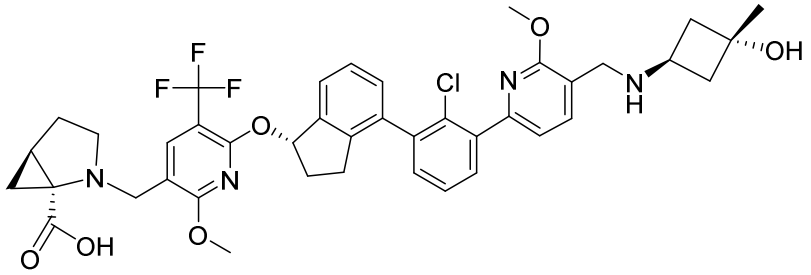
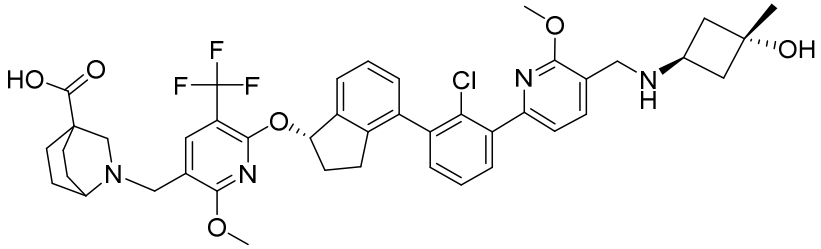
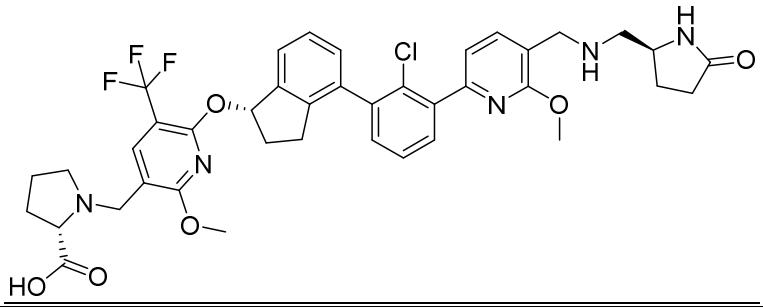
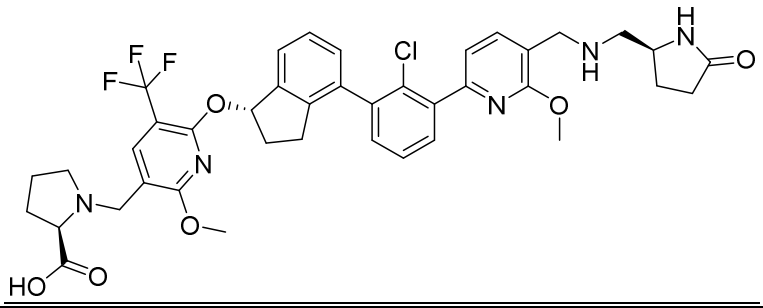
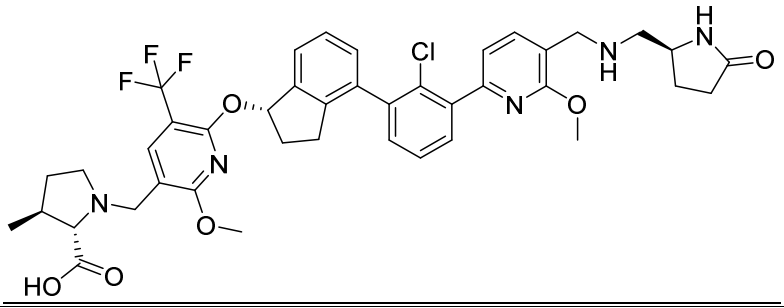
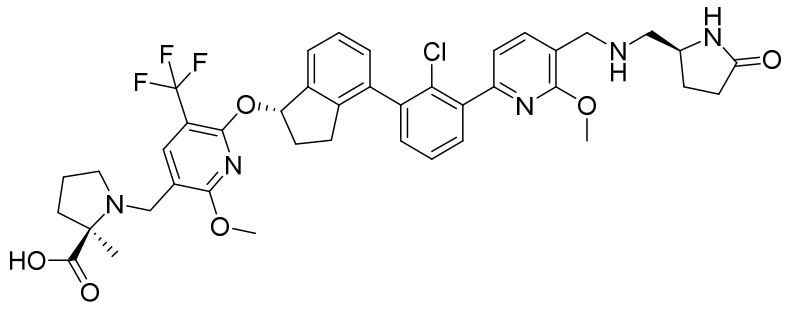
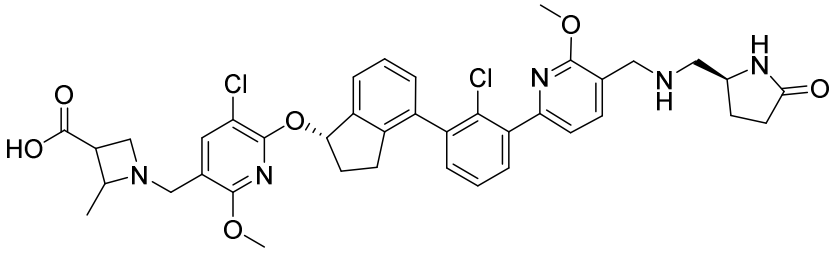
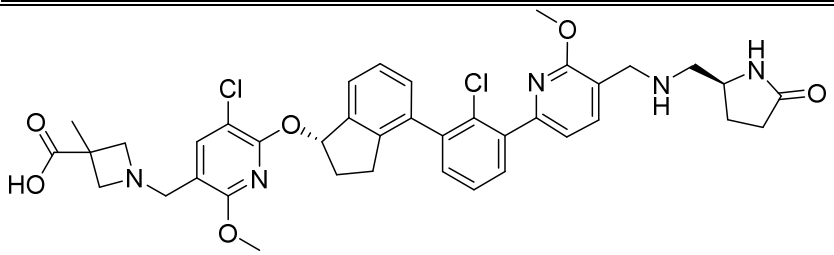
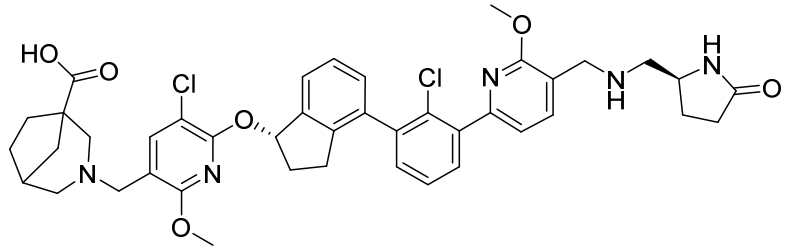
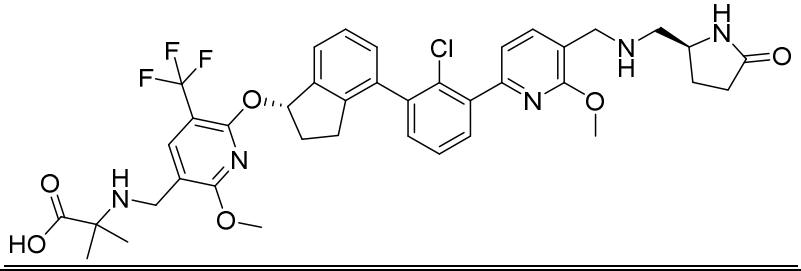
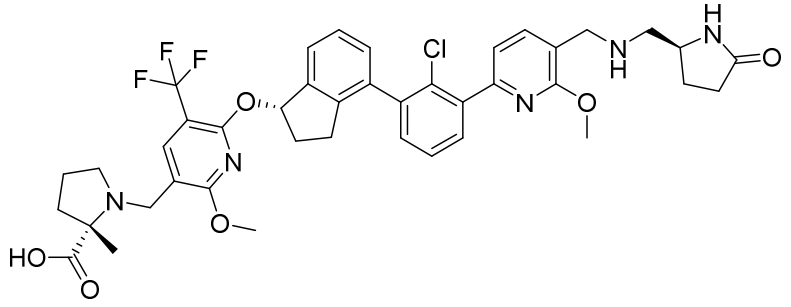
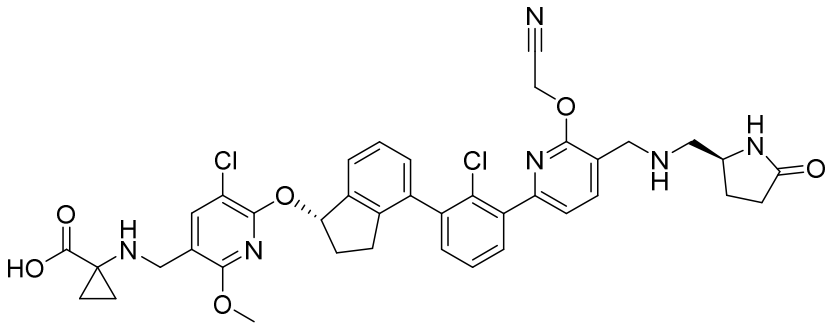
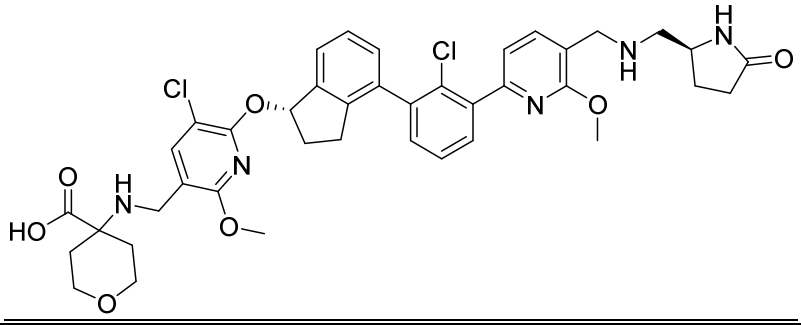
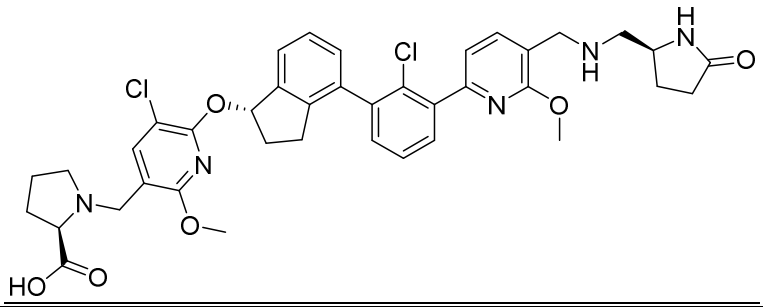
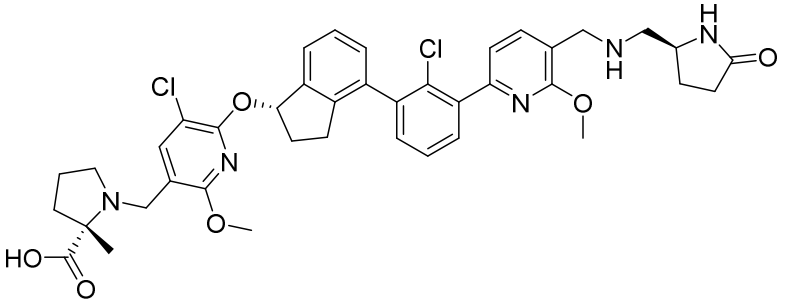
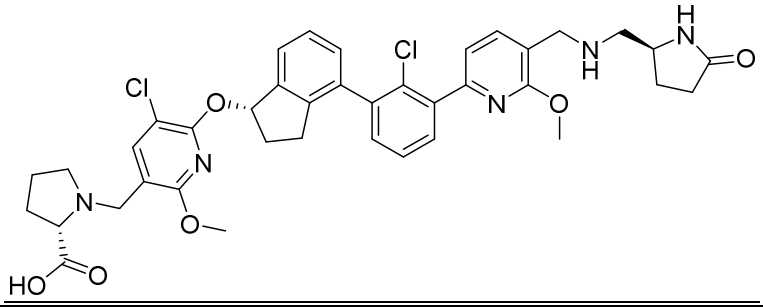
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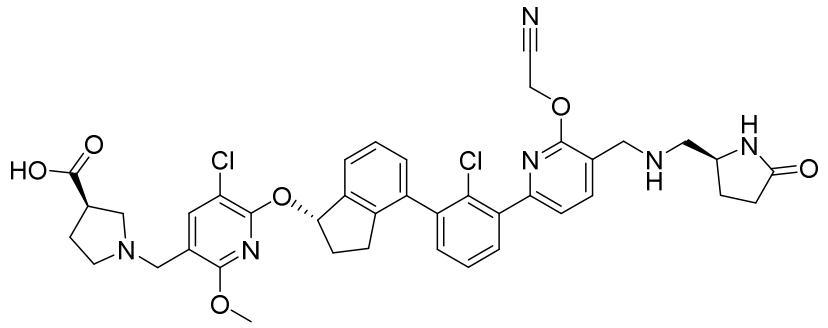
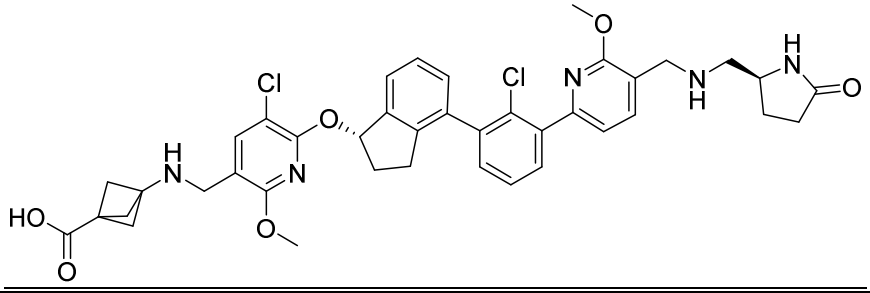
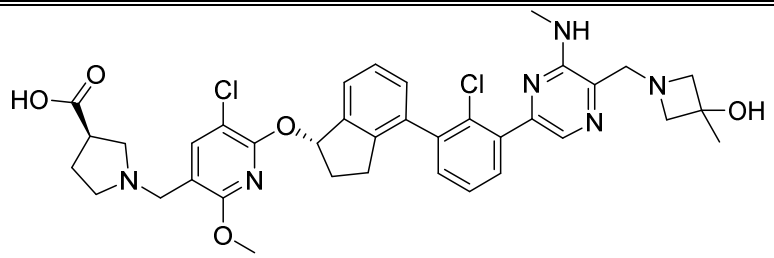
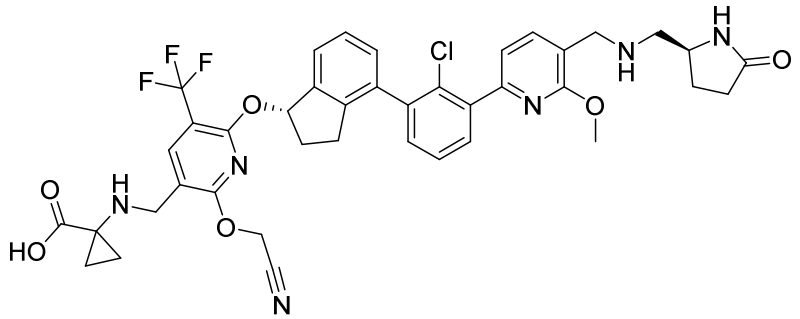
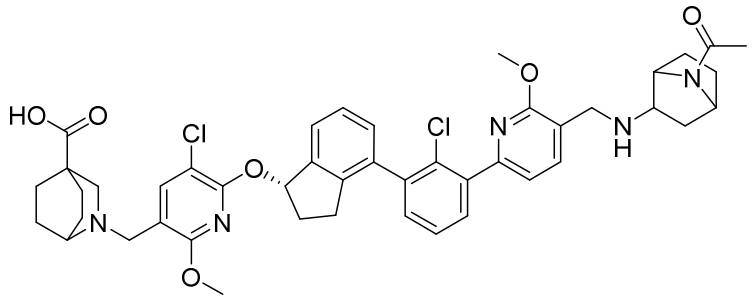
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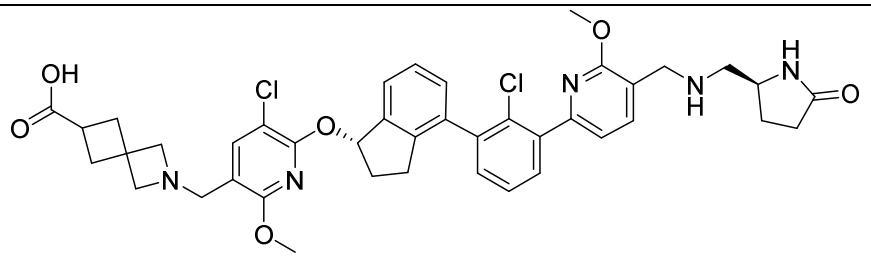
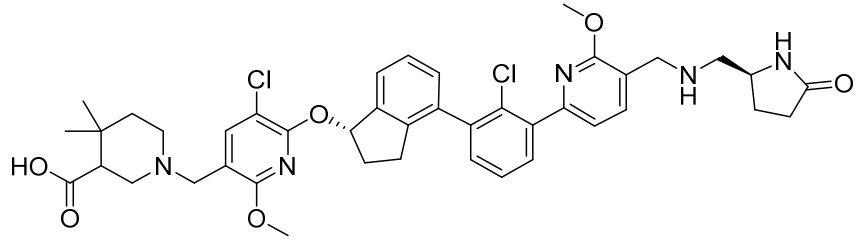
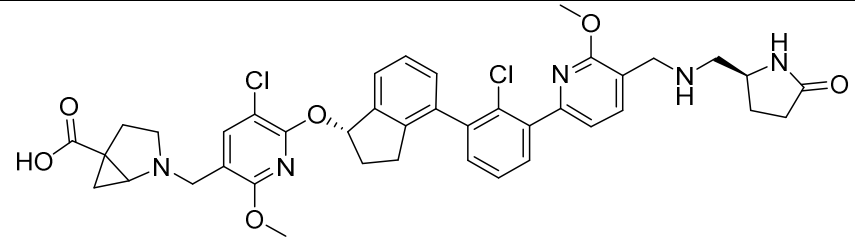
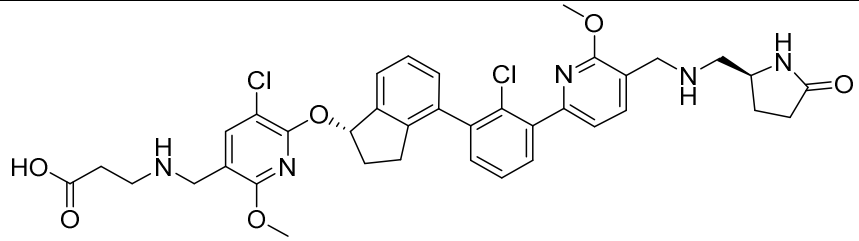
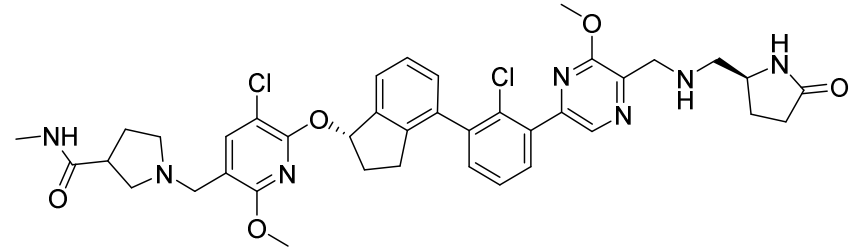
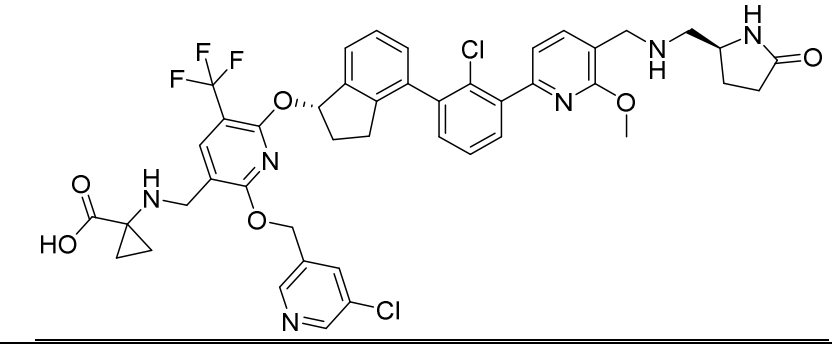
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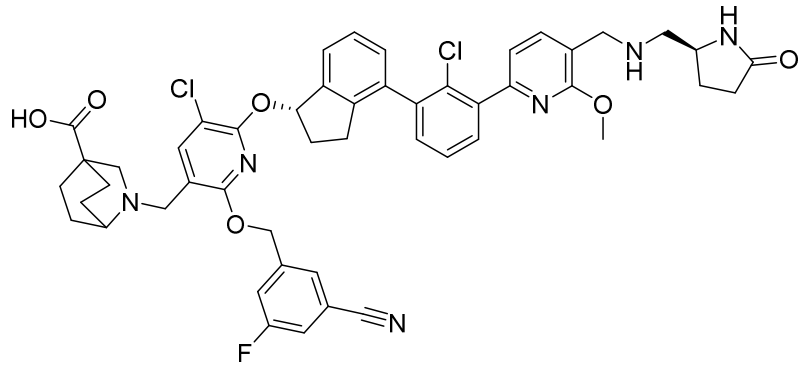
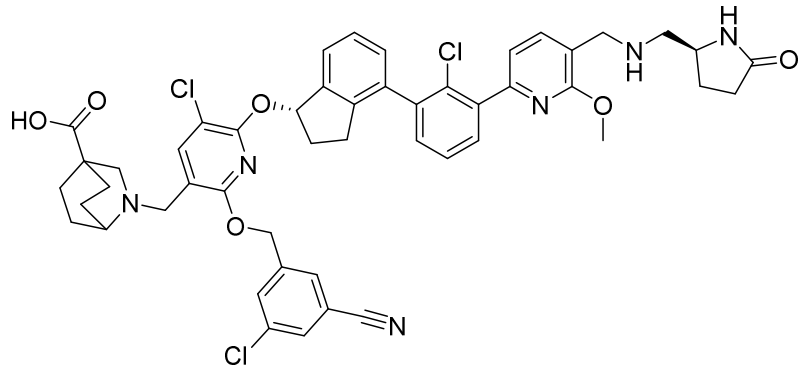
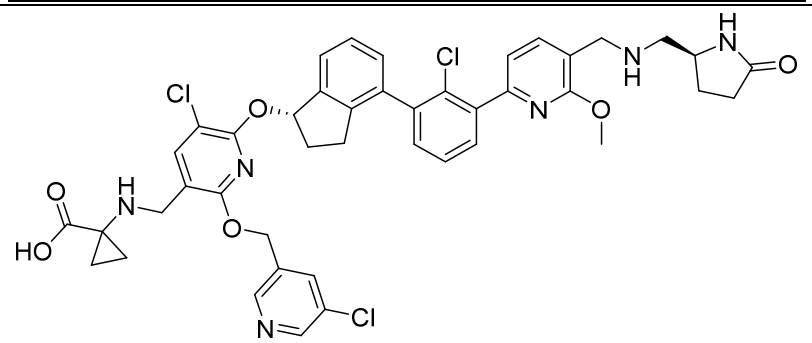
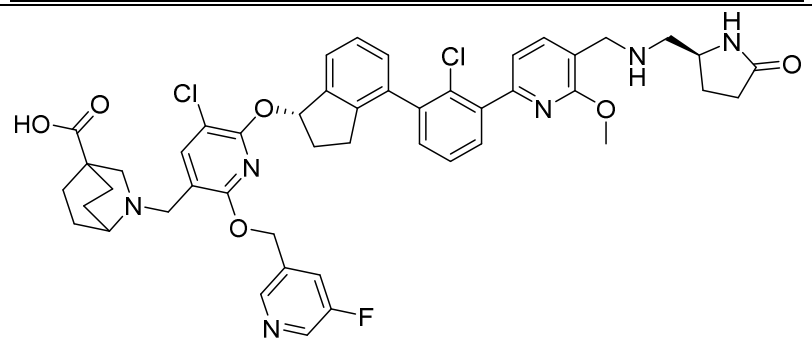
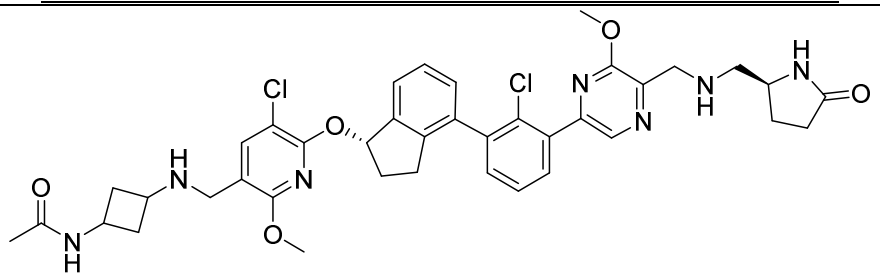
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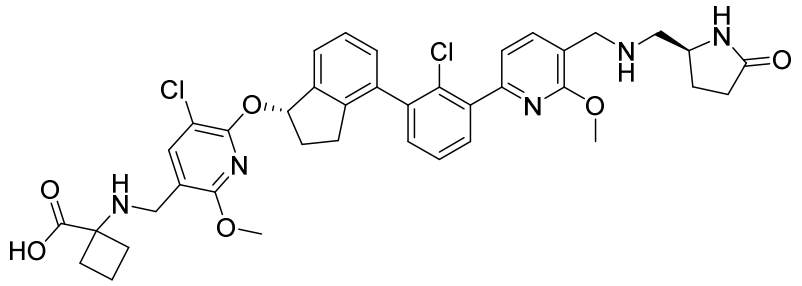
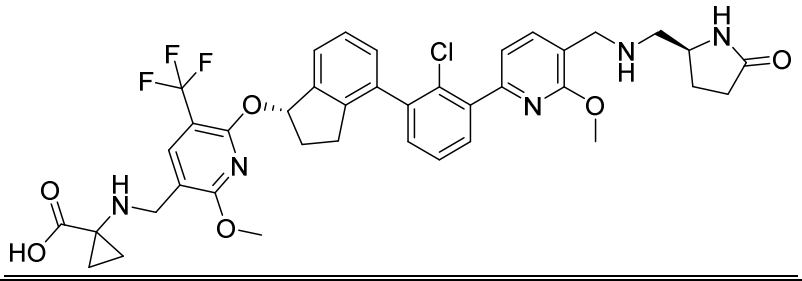
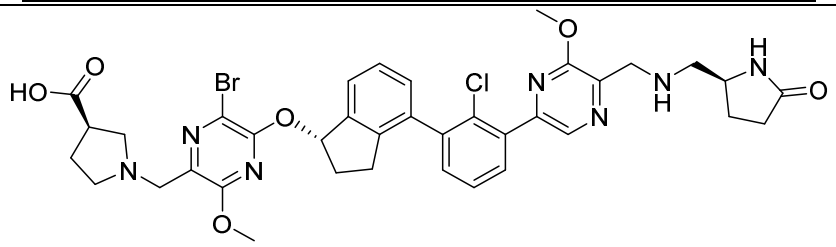
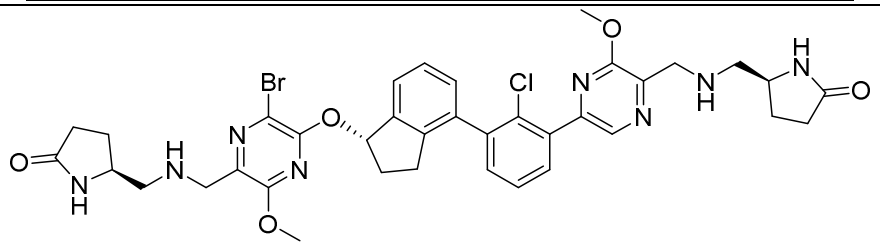
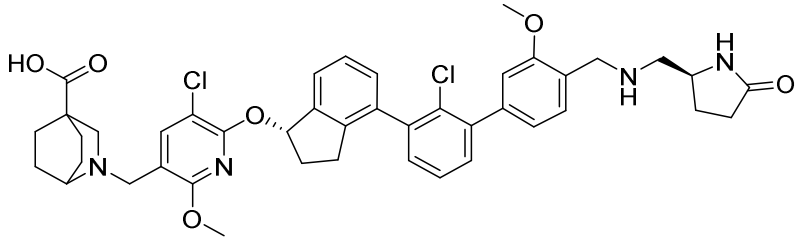
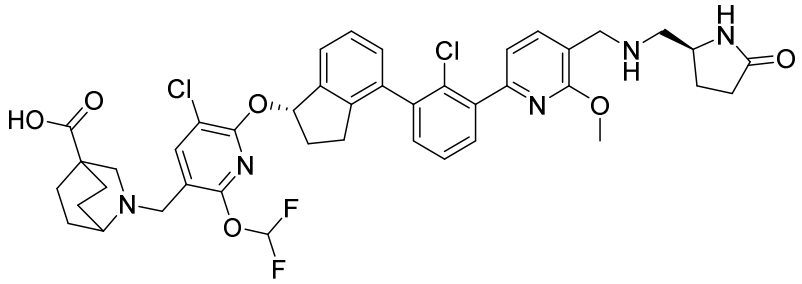
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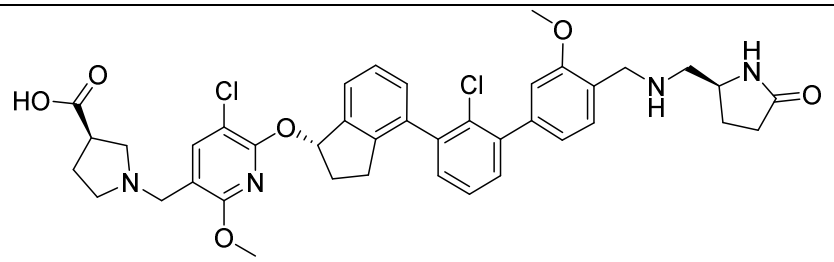
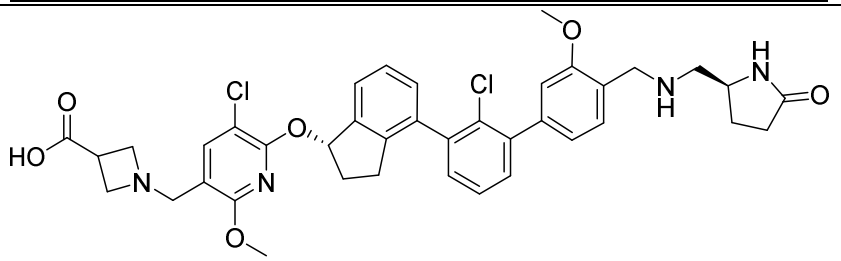
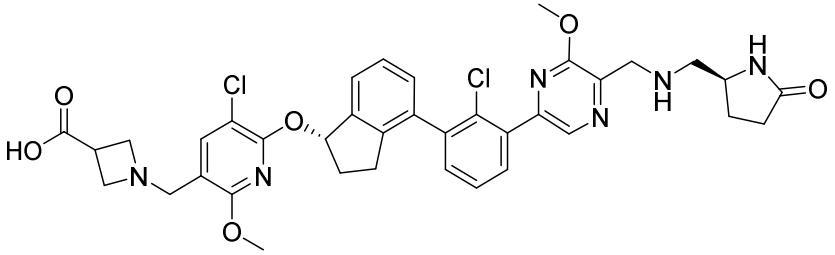
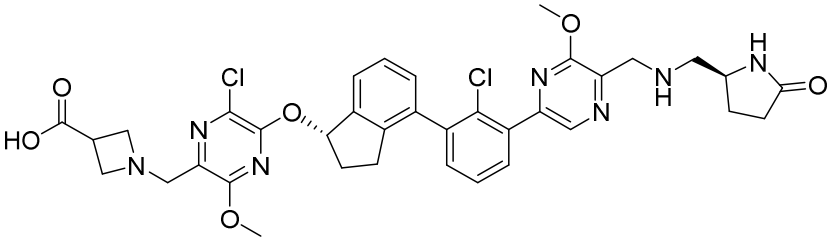
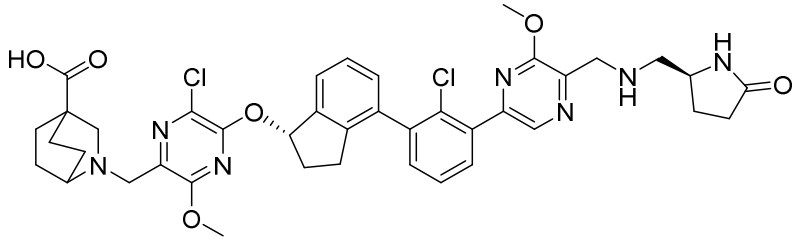
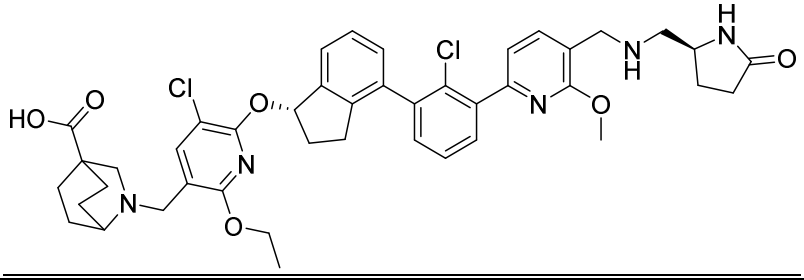
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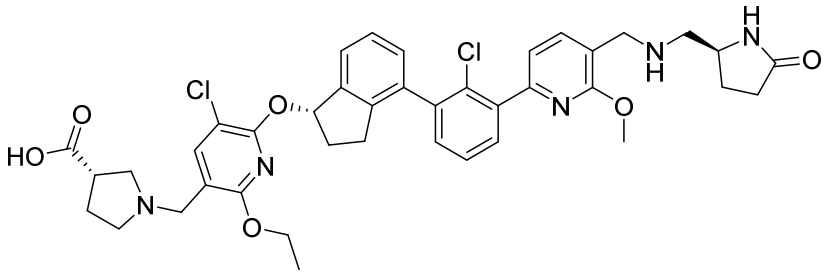
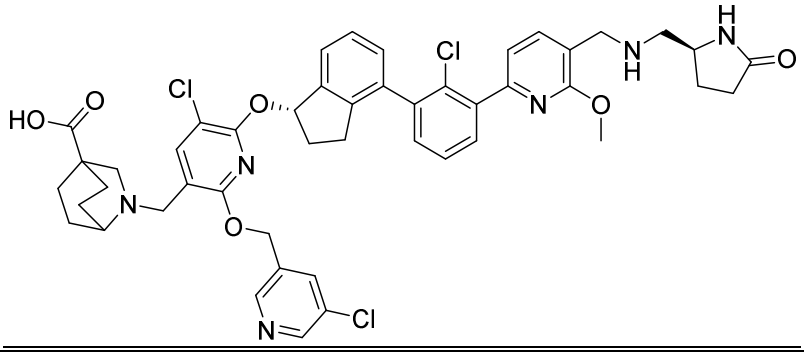
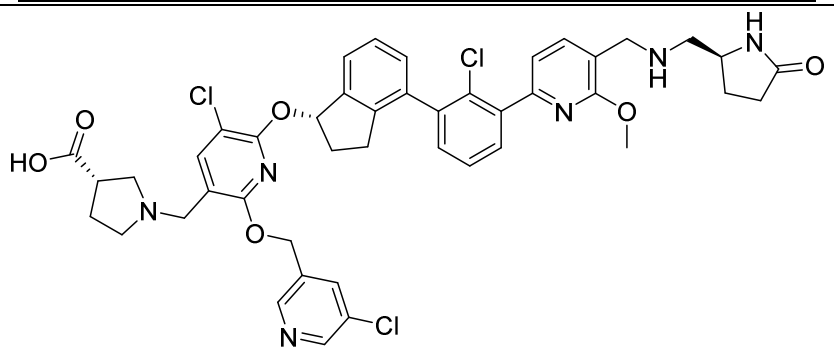
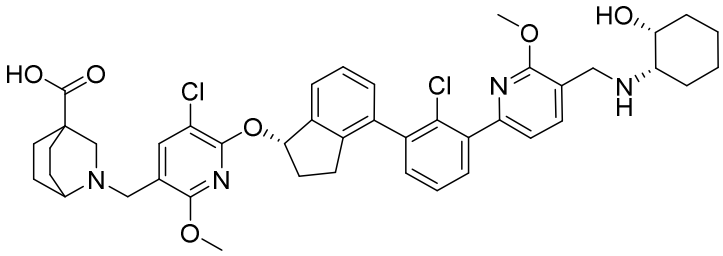
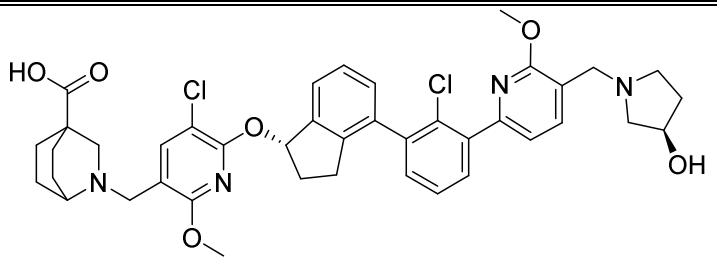
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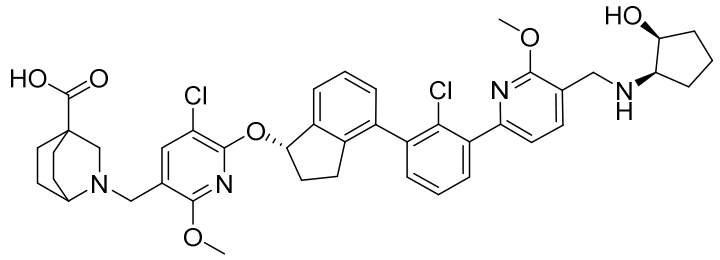
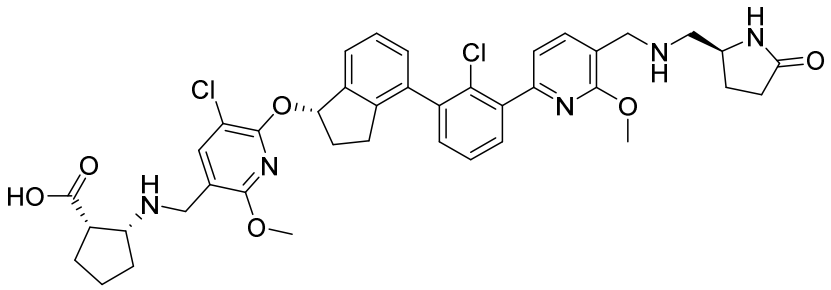
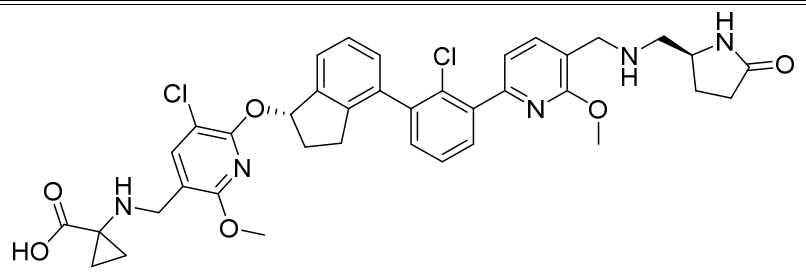
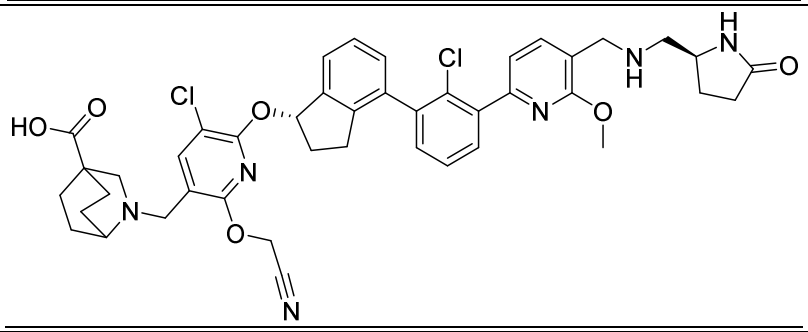
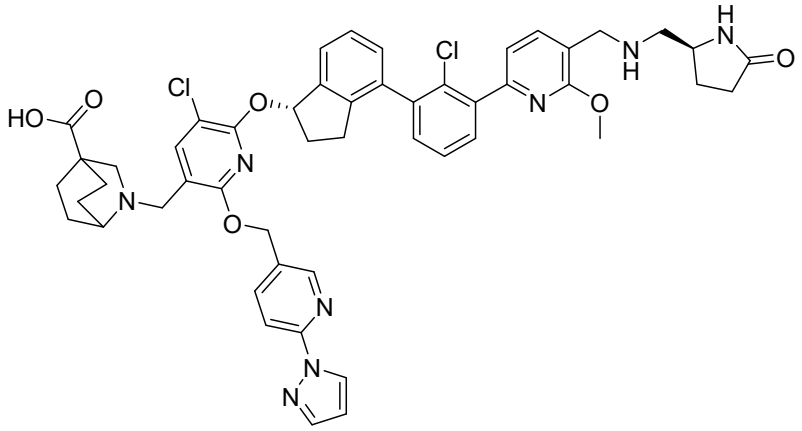
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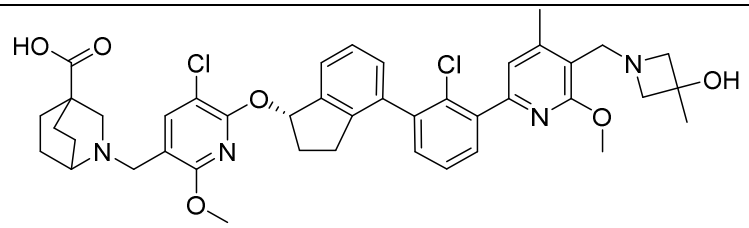
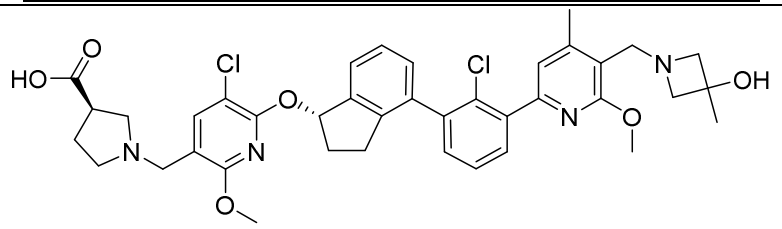
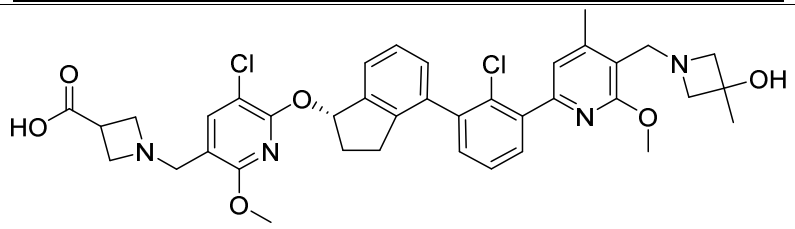
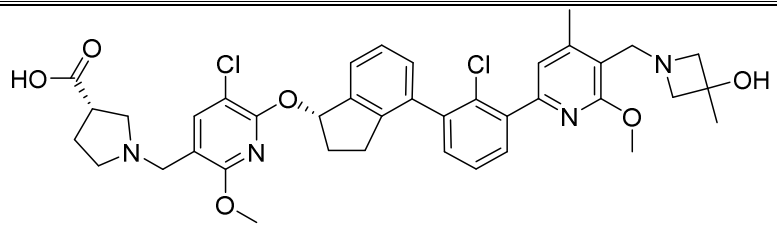
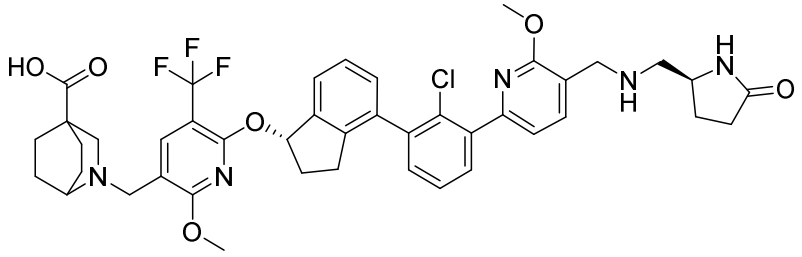
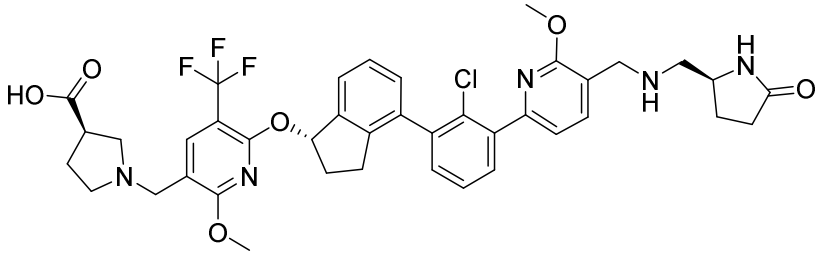
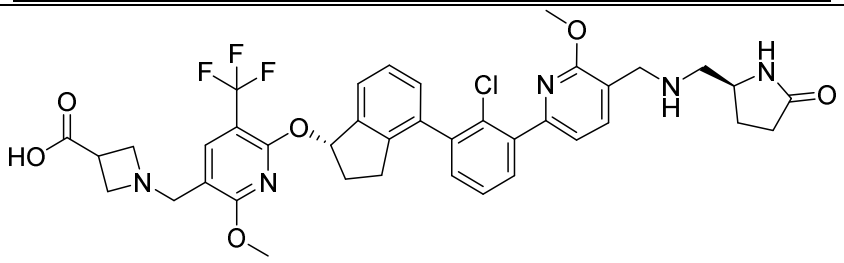
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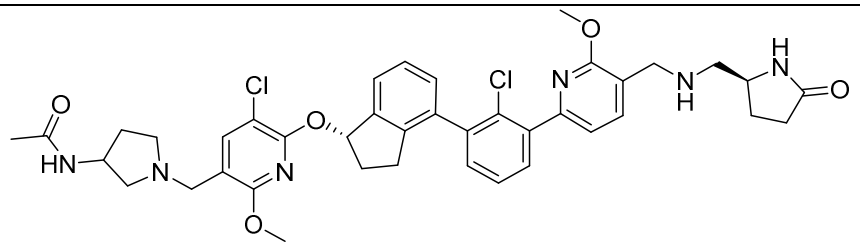
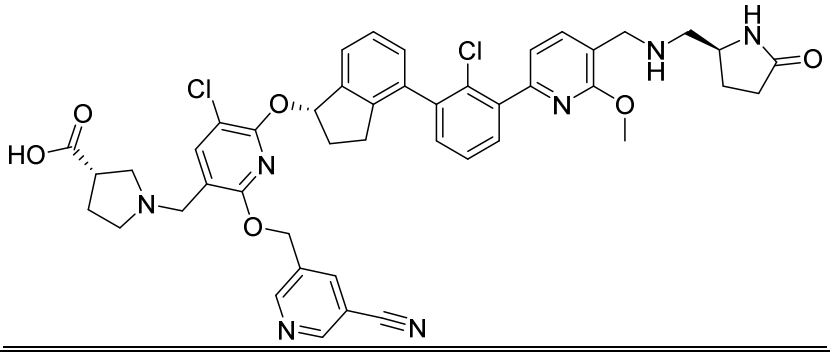
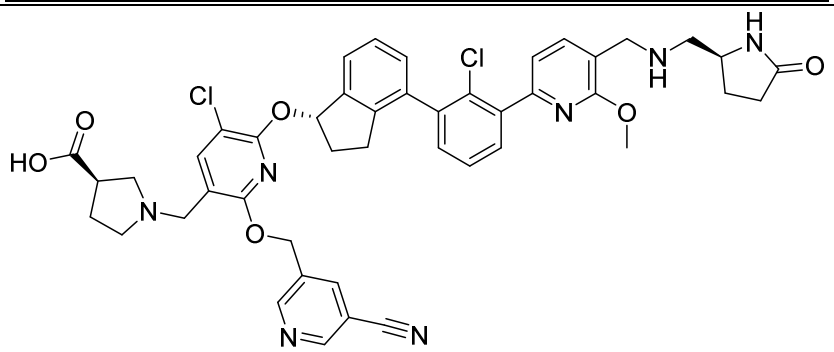
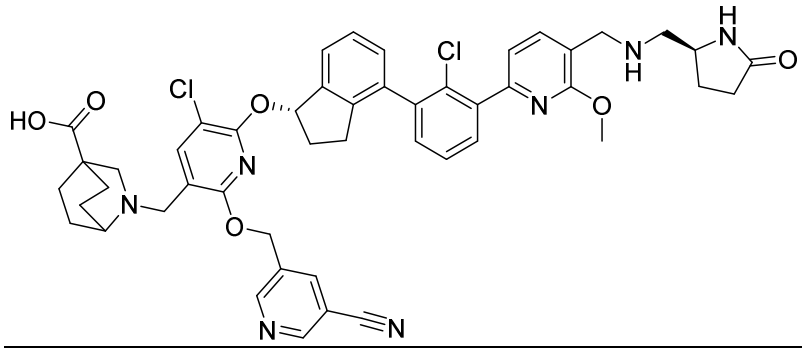
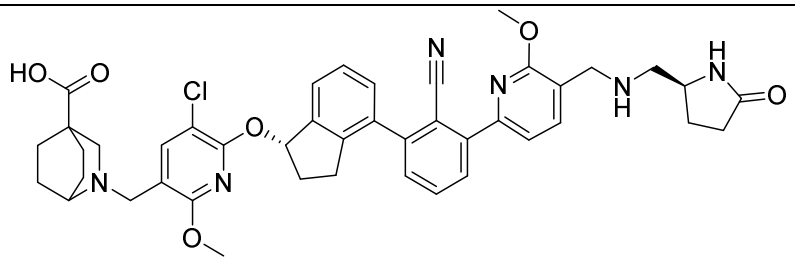
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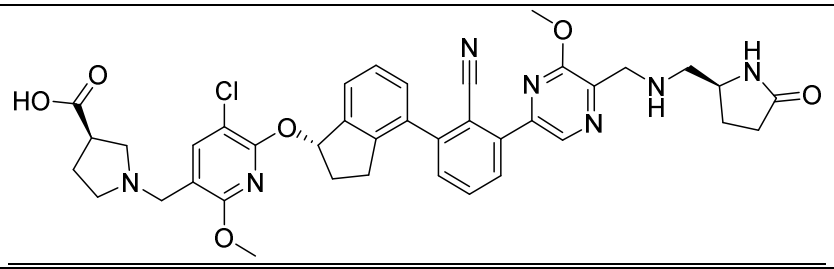
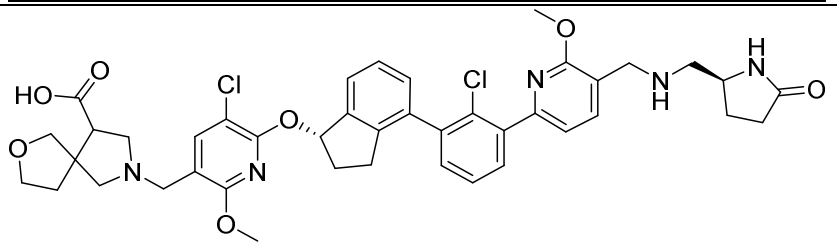
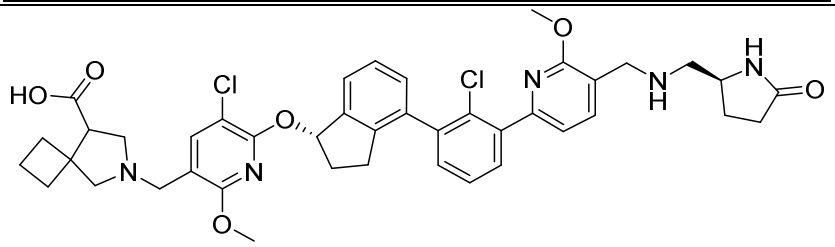
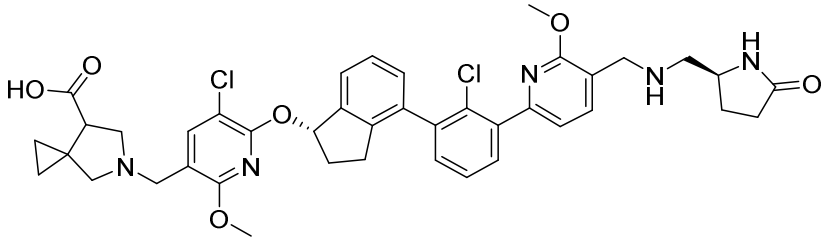
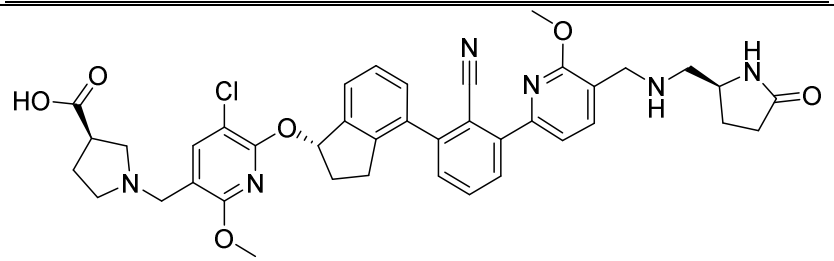
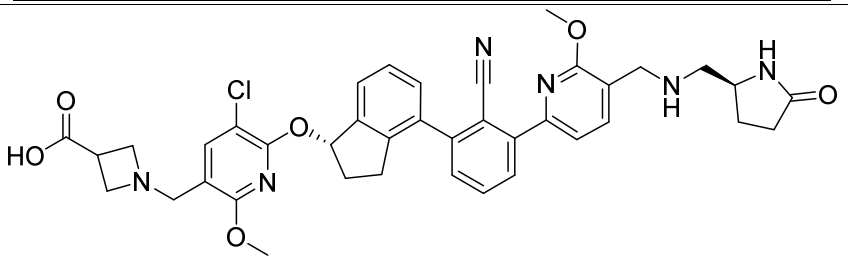
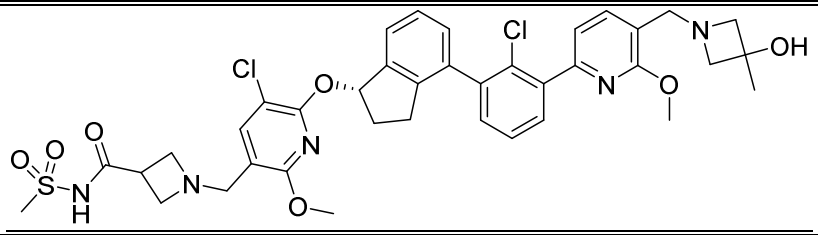
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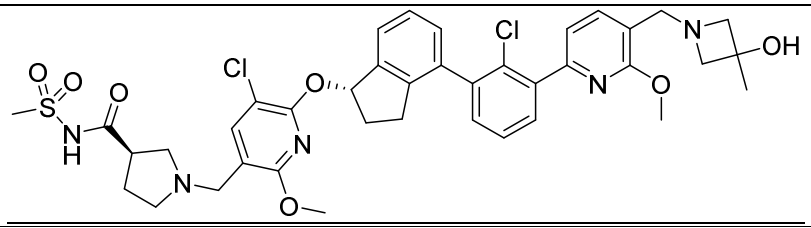
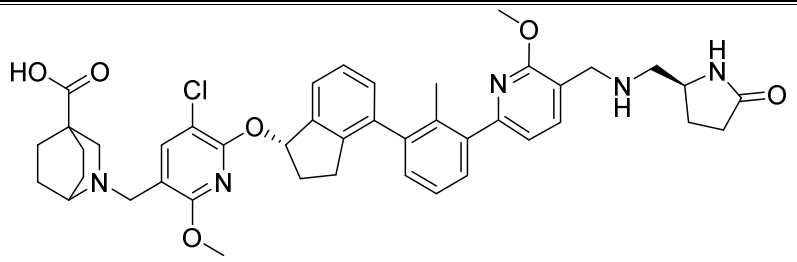
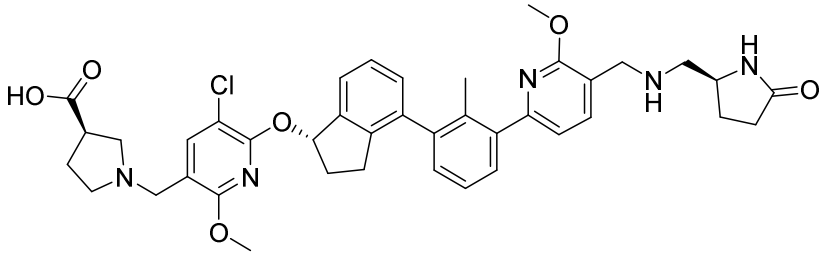
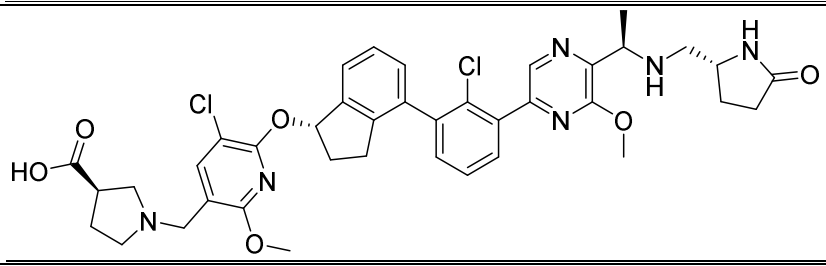
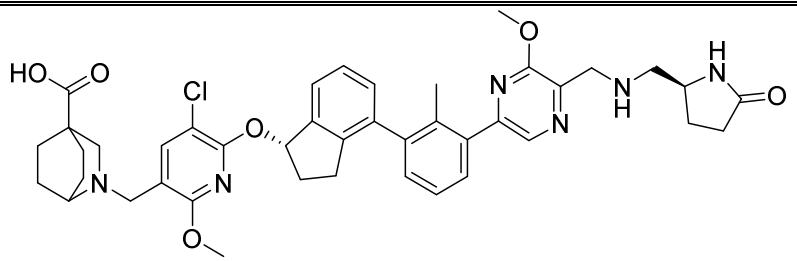
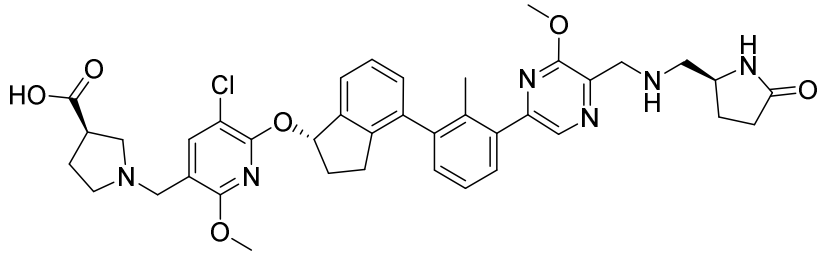
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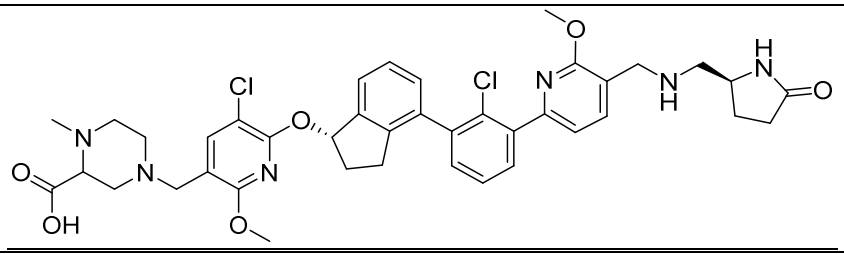
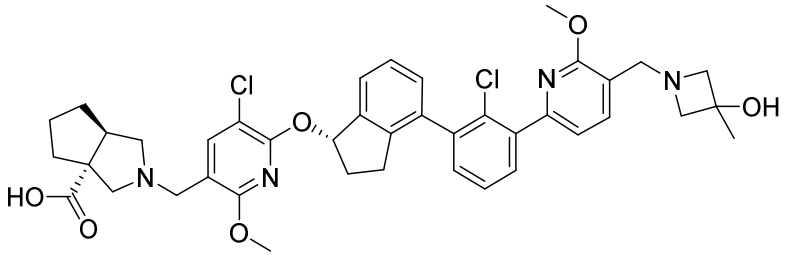
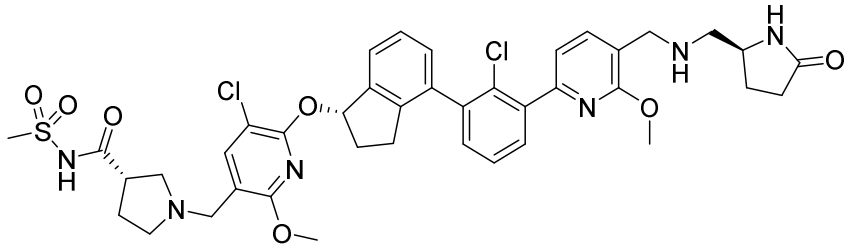
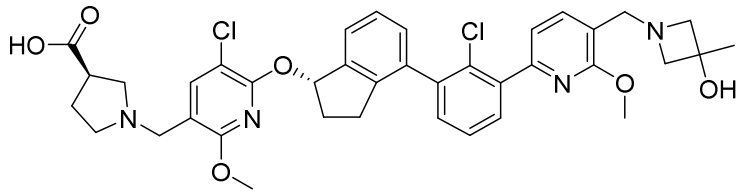
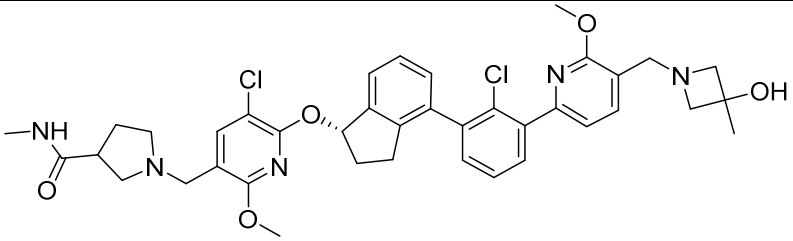
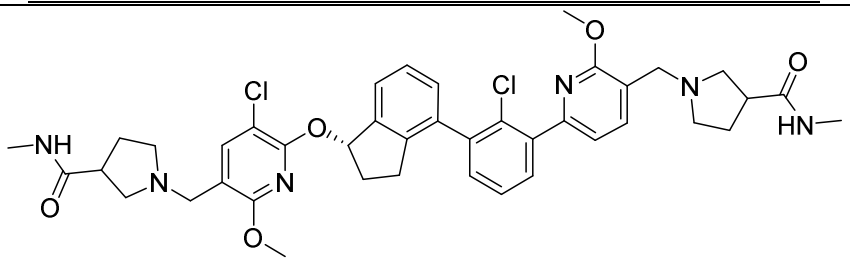
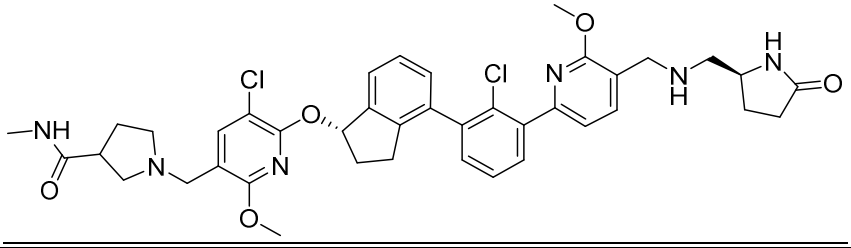
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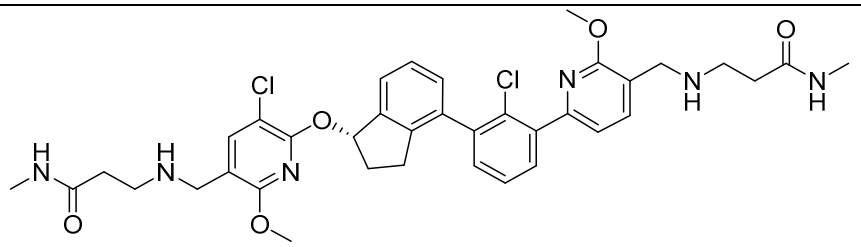
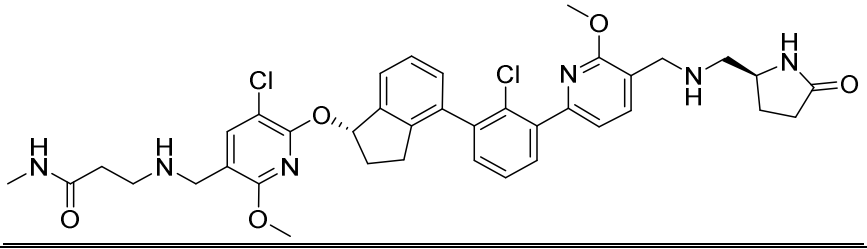
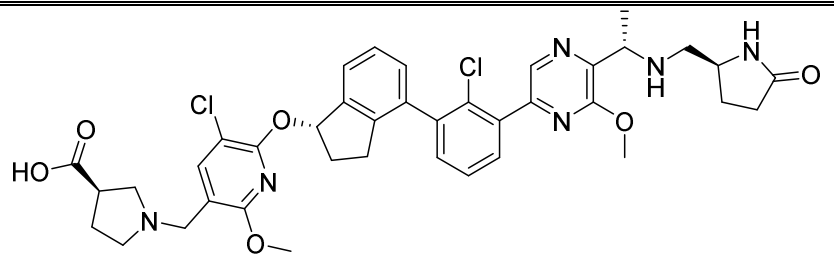
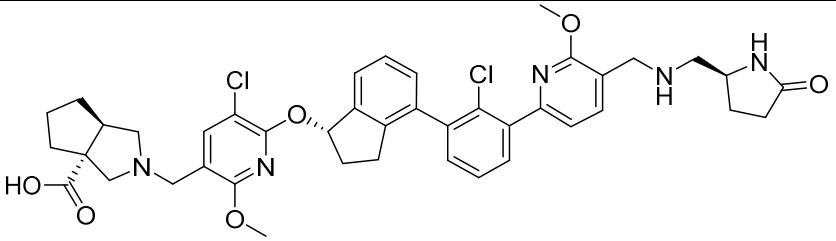
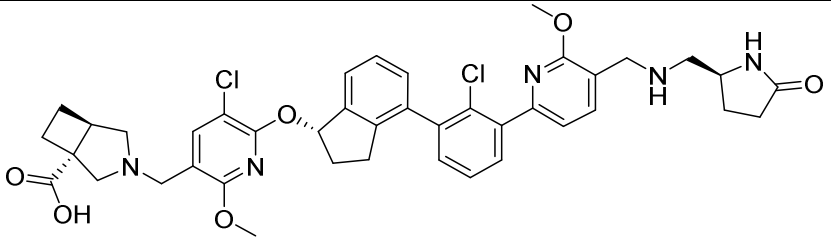
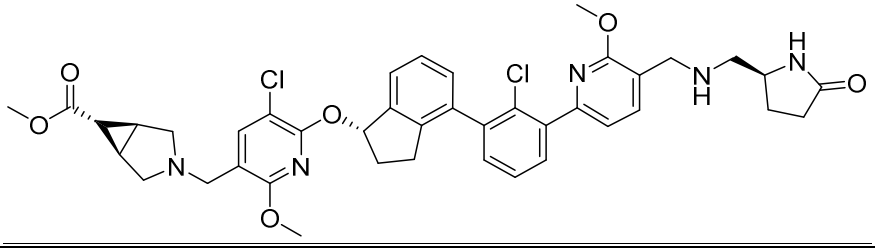
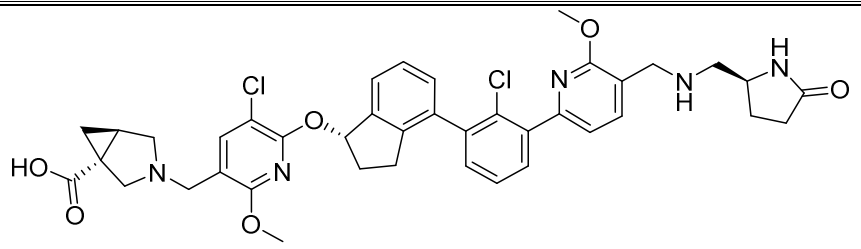
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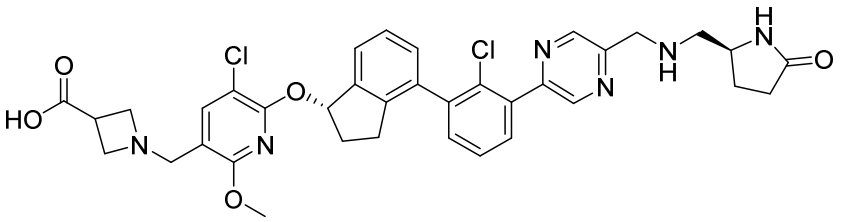
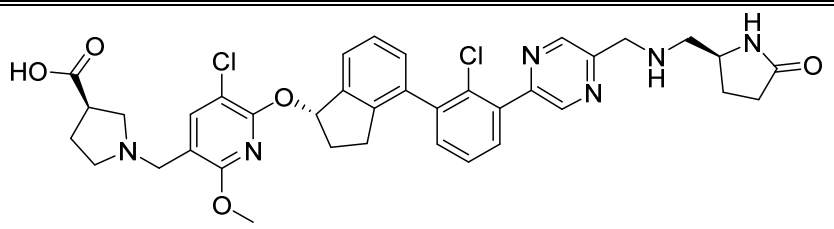
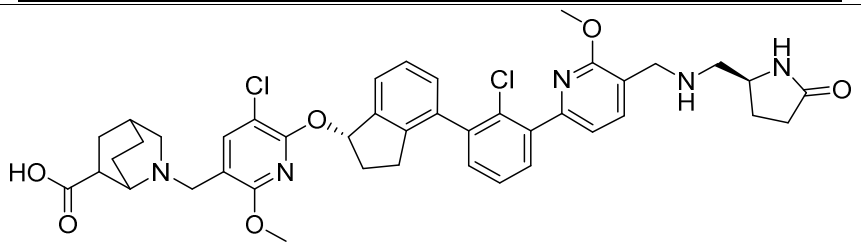
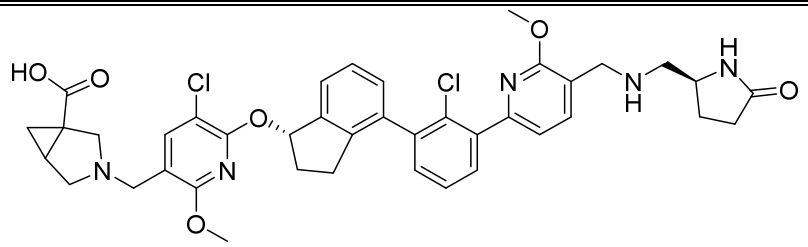
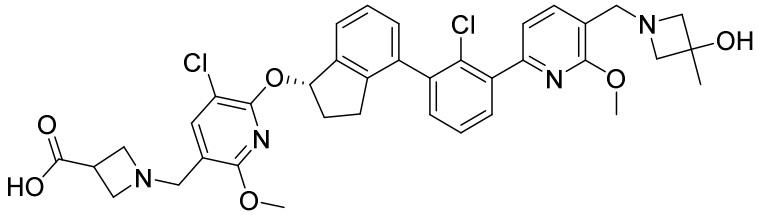
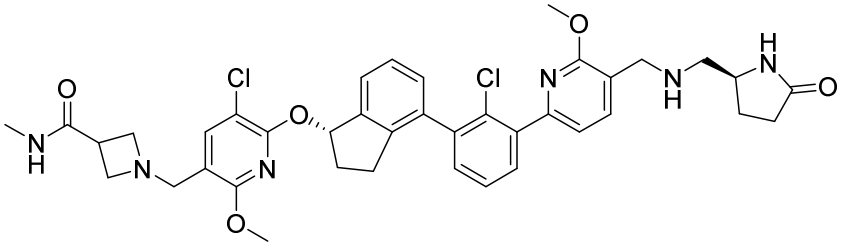
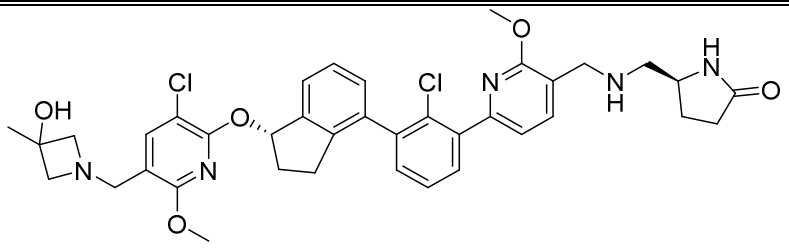
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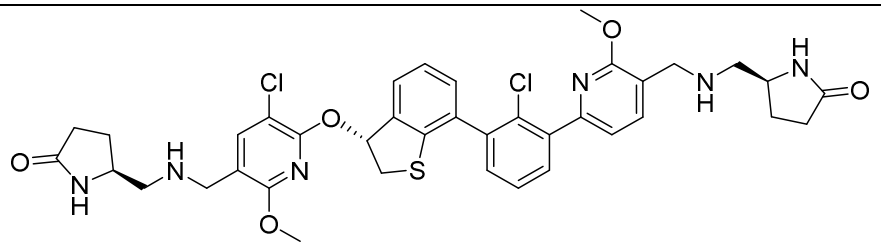
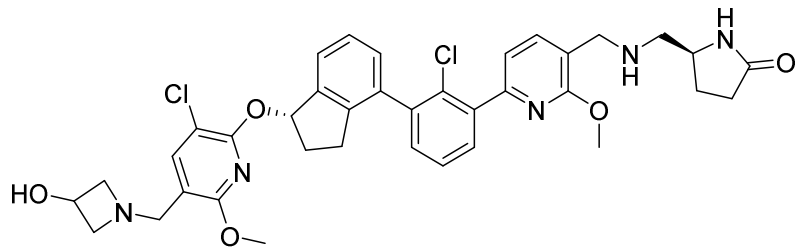
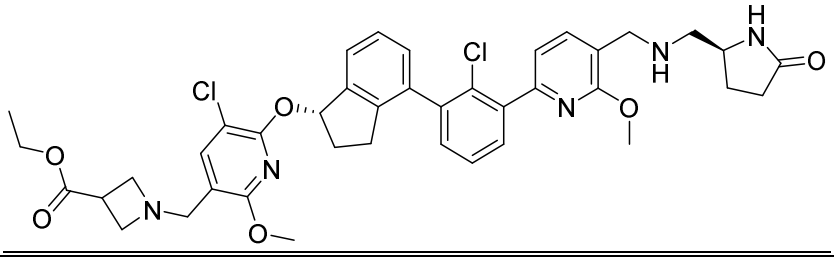
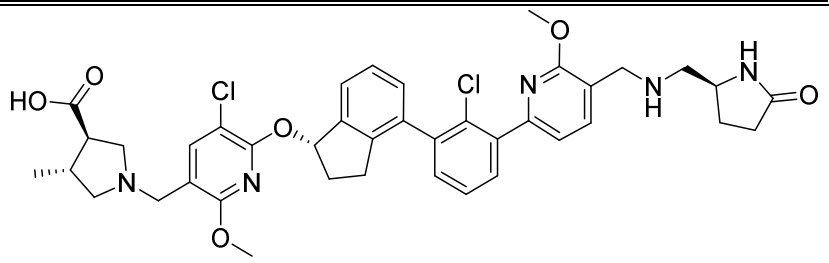
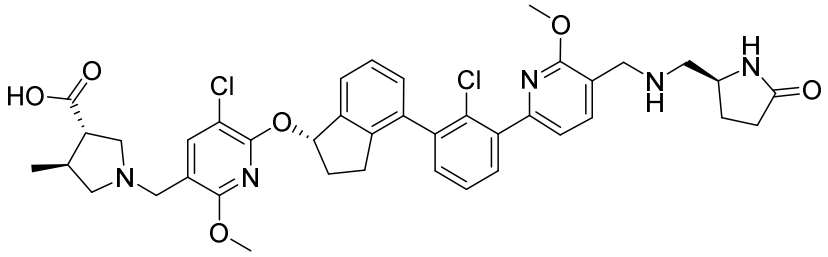
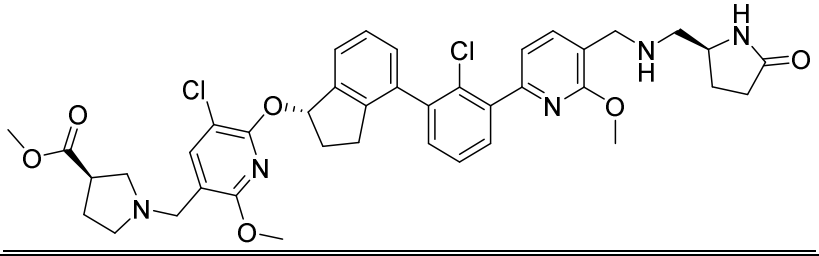
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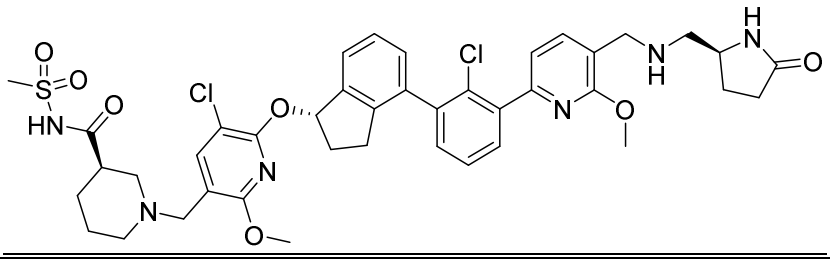
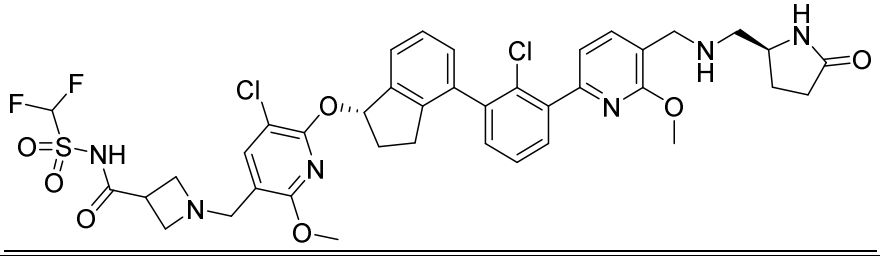
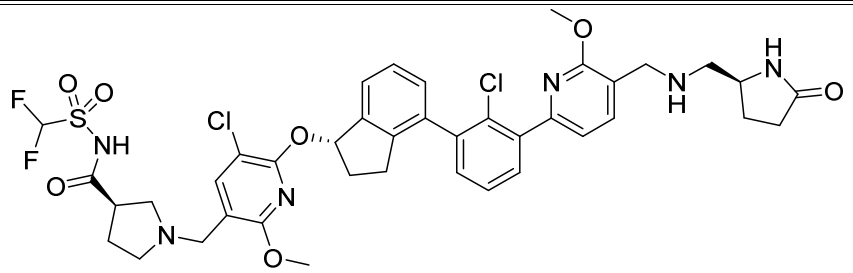
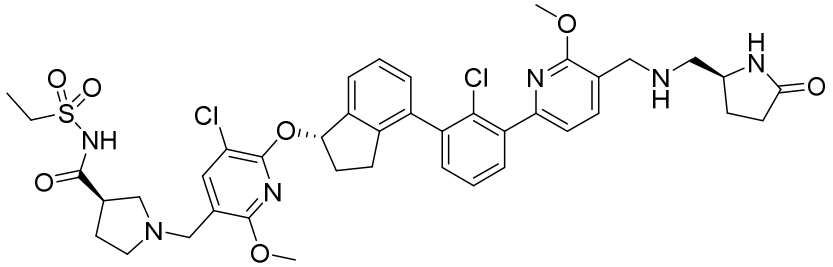
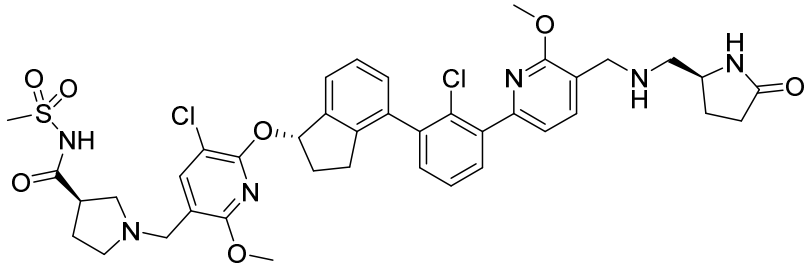
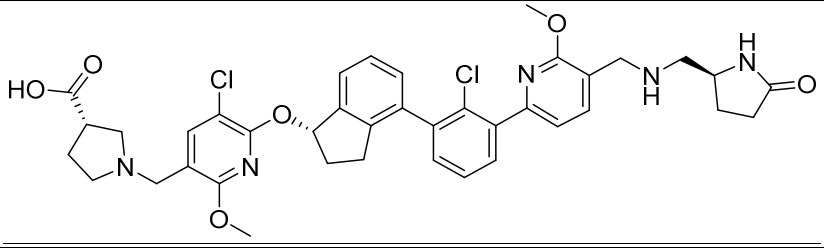
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B-81	

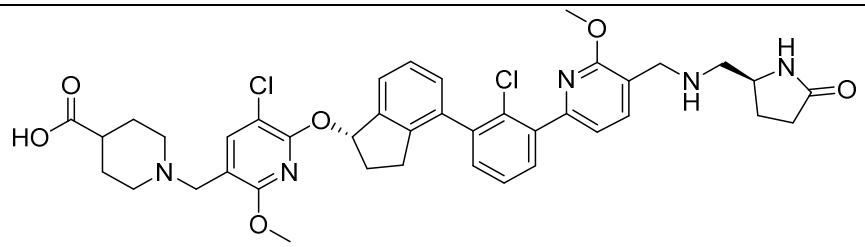
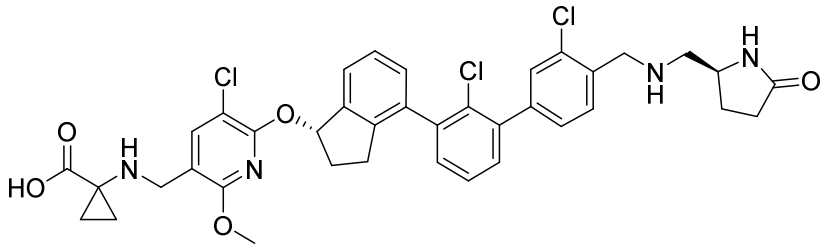
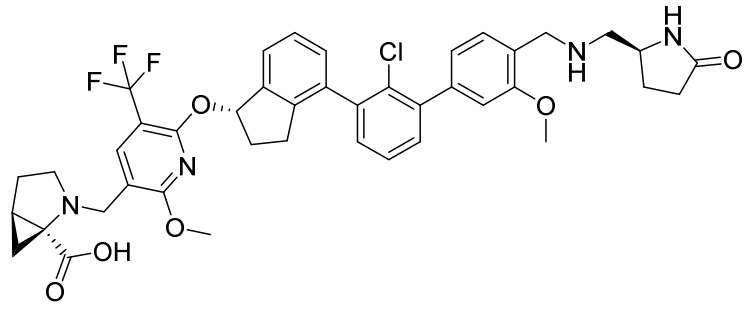
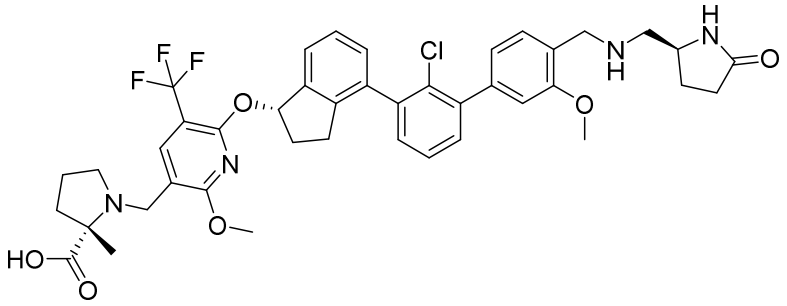
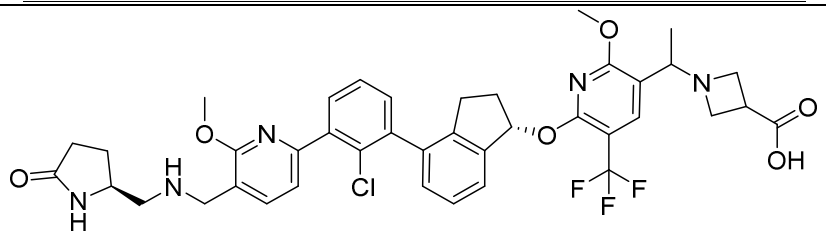
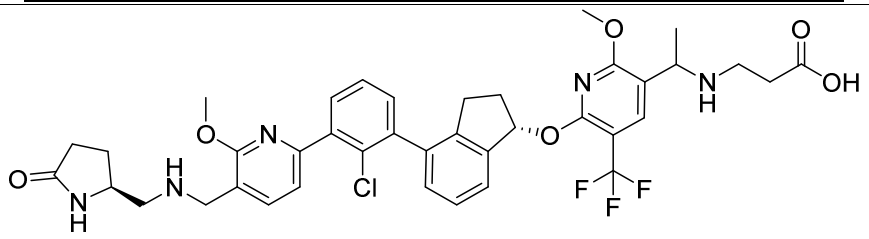
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B-88	

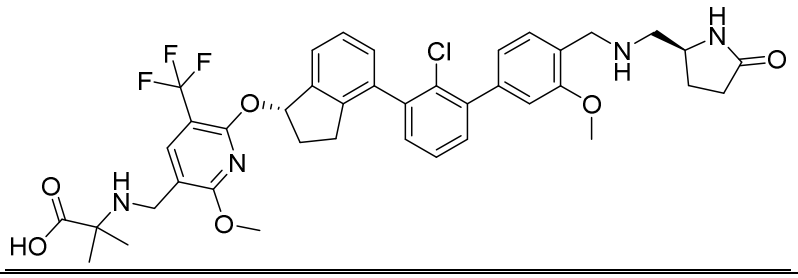
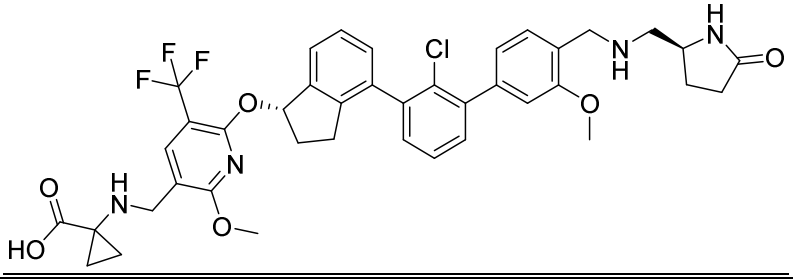
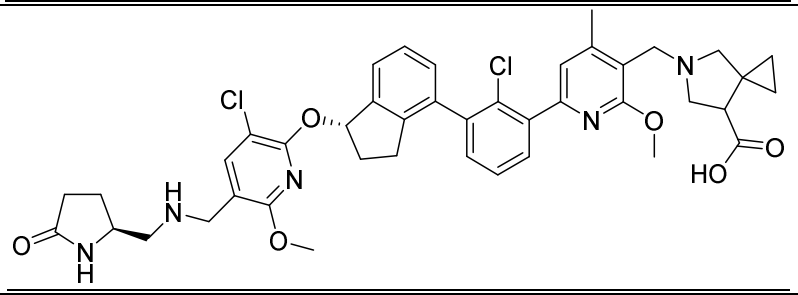
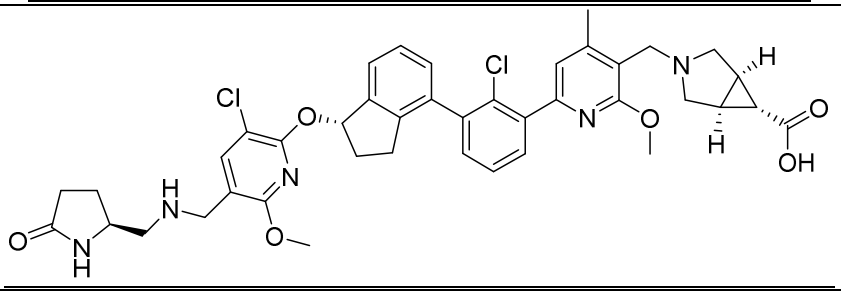
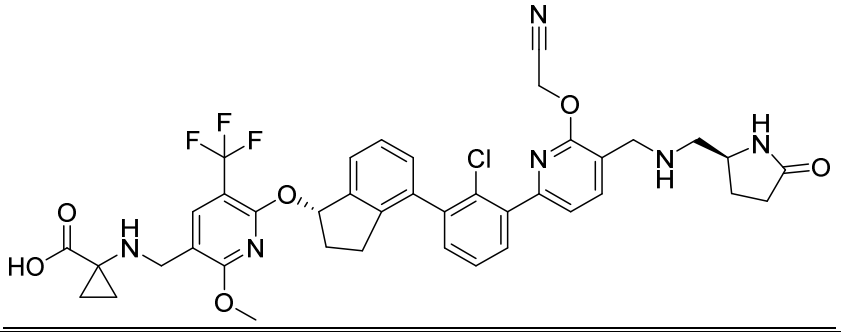
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B-95	

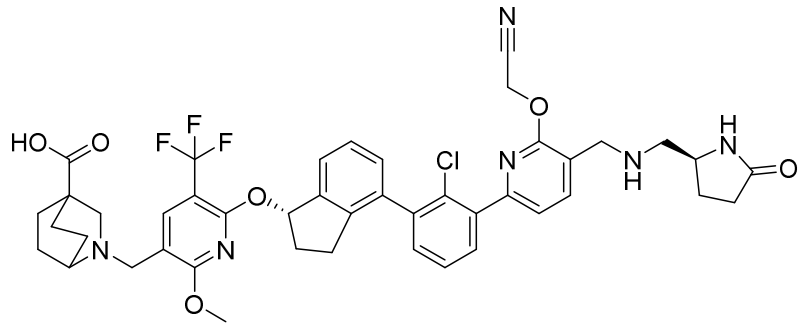
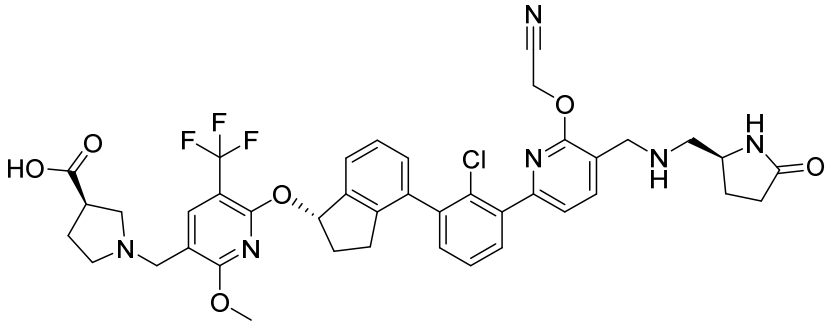
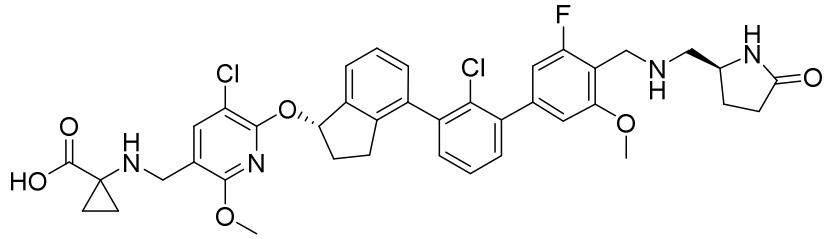
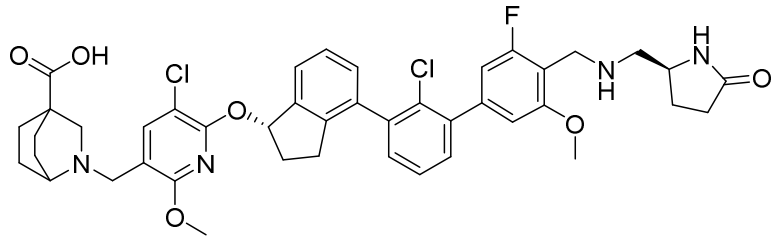
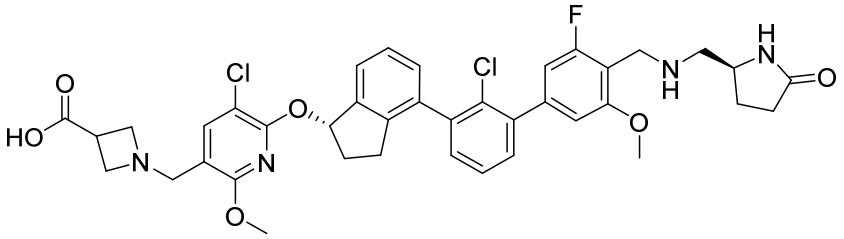
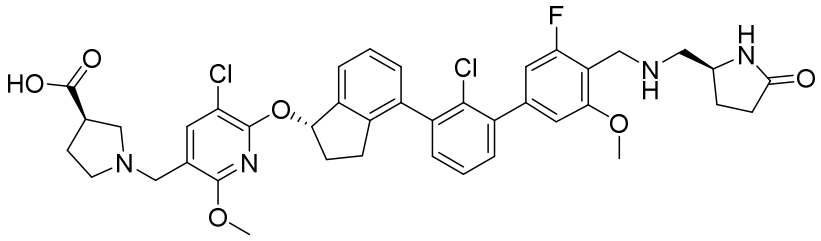
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B-102	

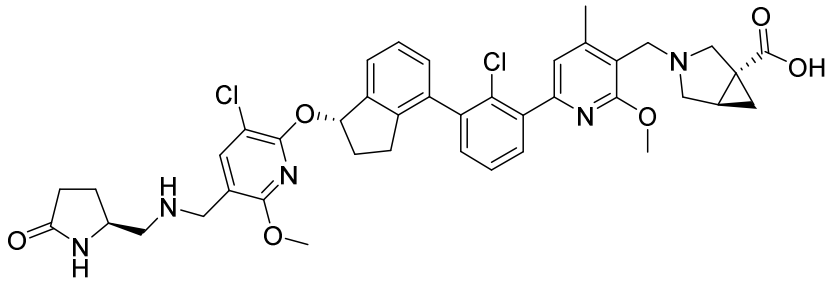
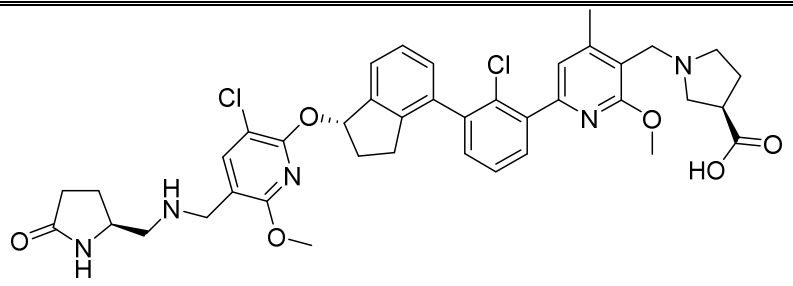
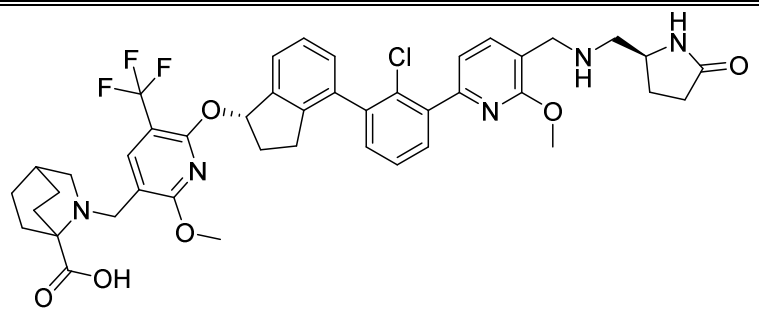
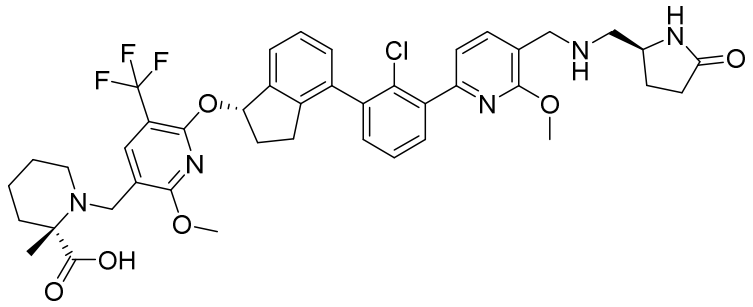
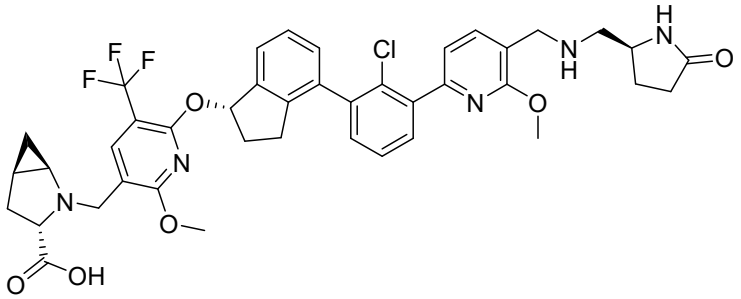
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B-108	

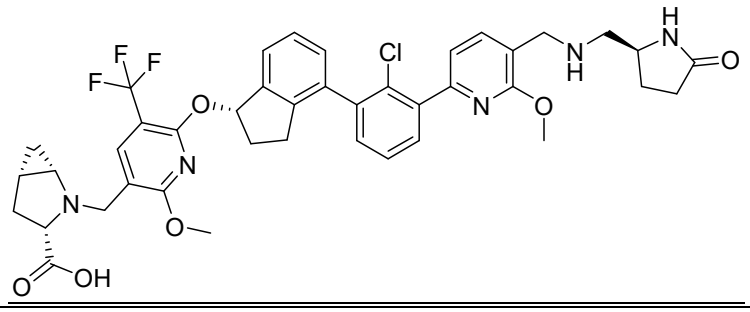
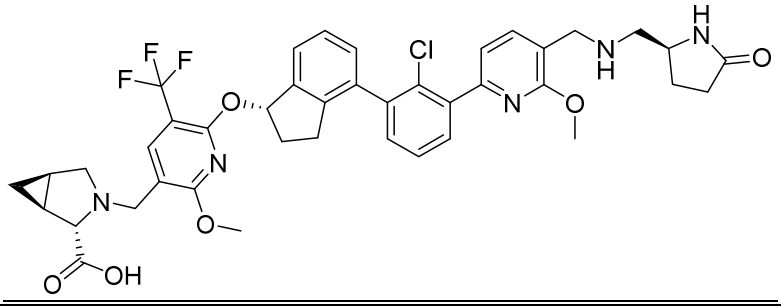
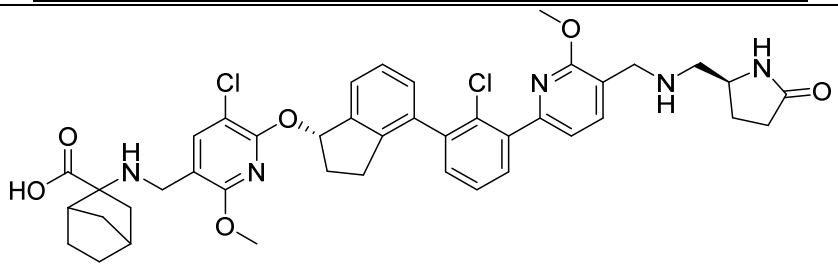
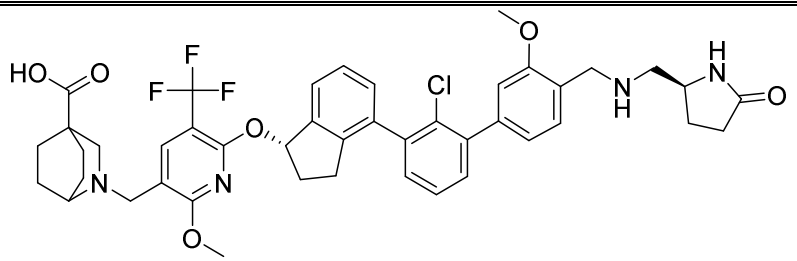
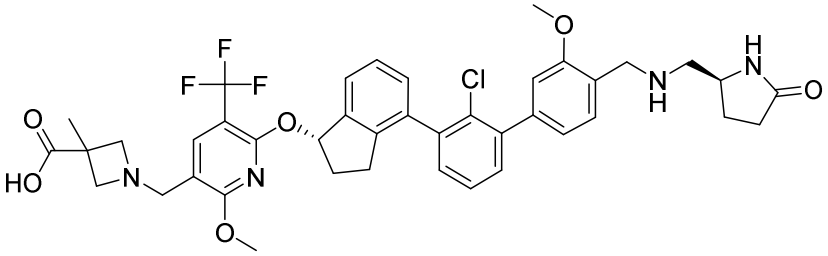
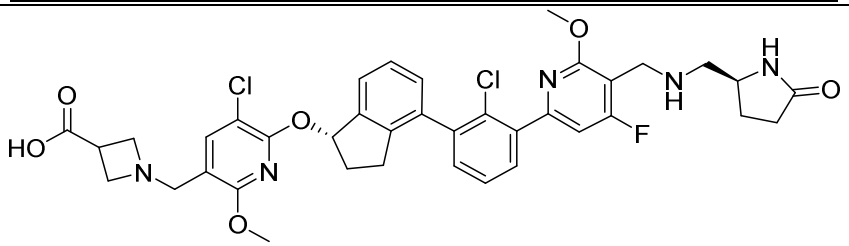
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B-114	

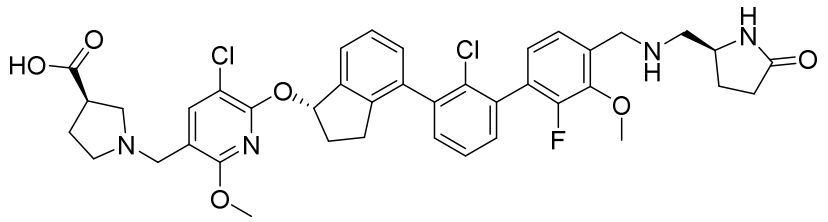
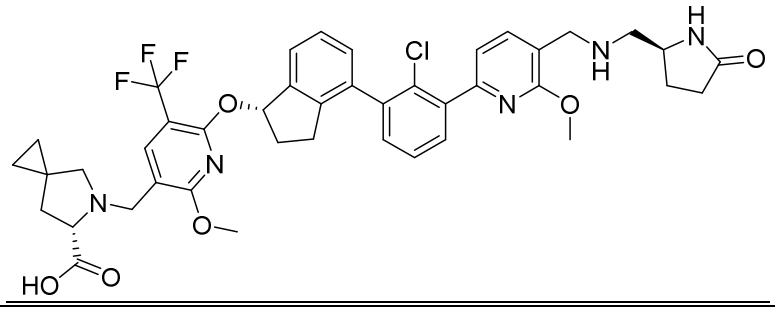
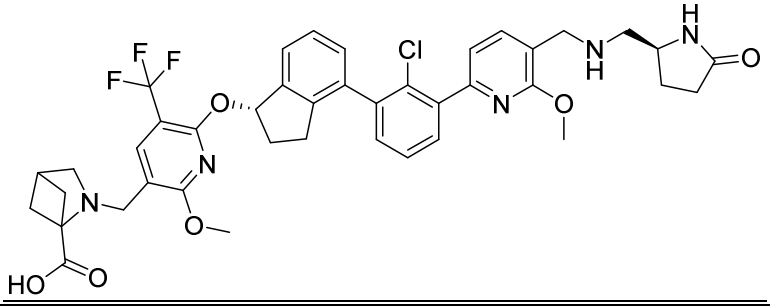
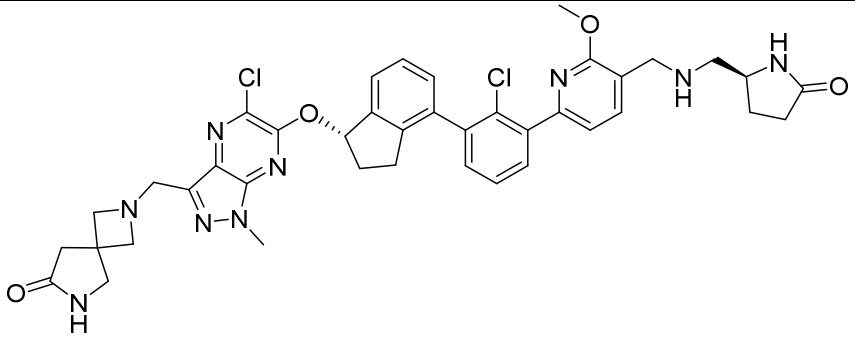
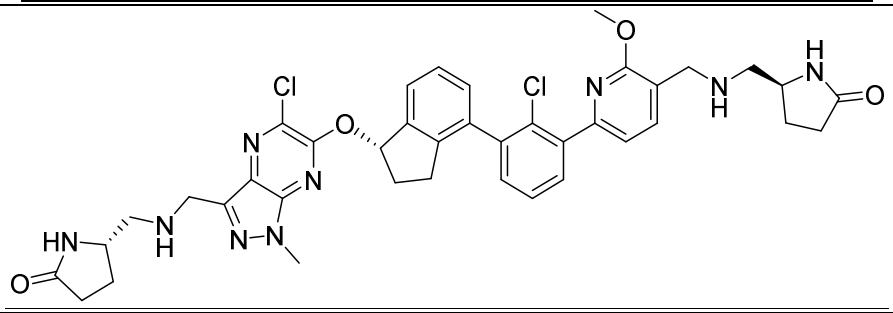
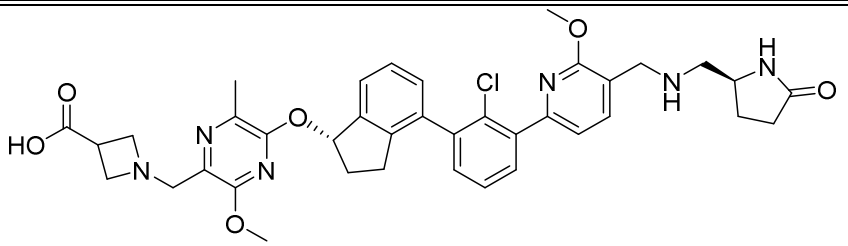
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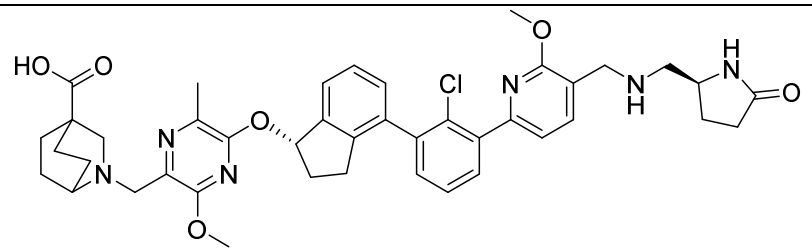
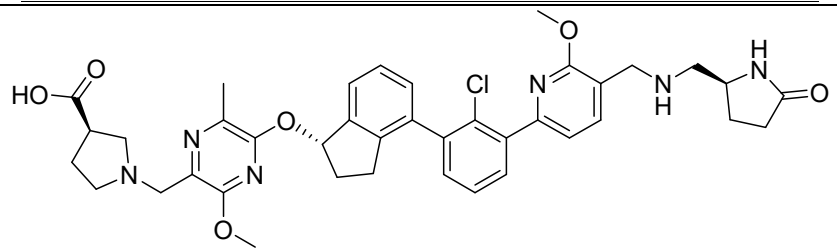
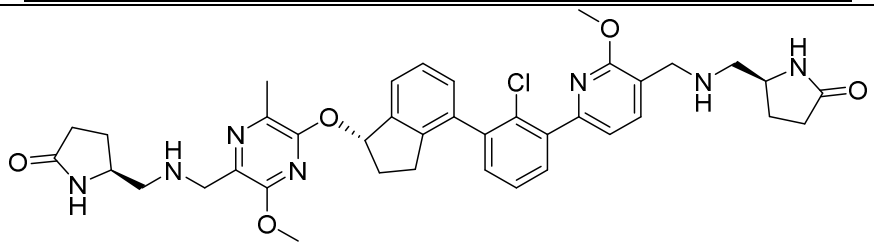
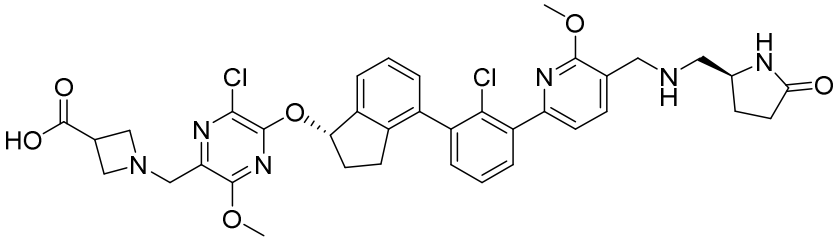
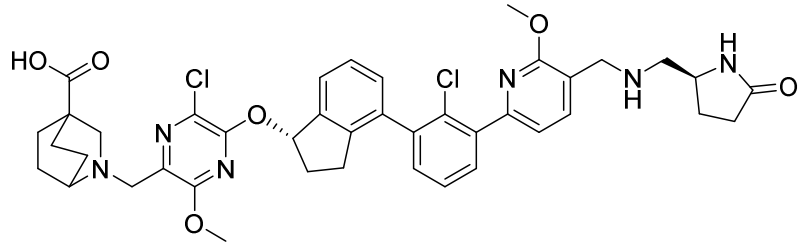
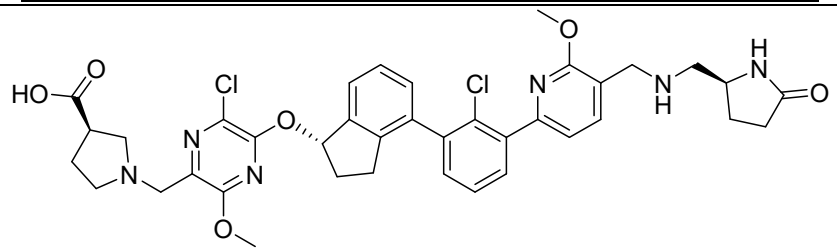
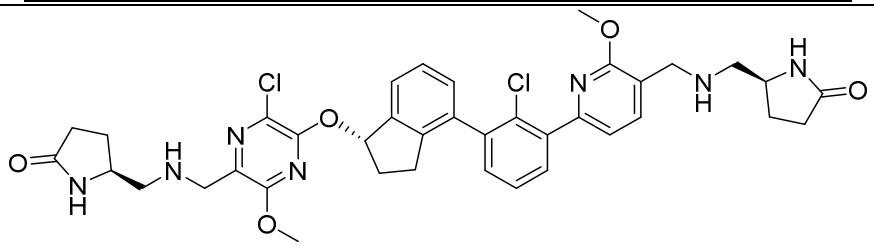
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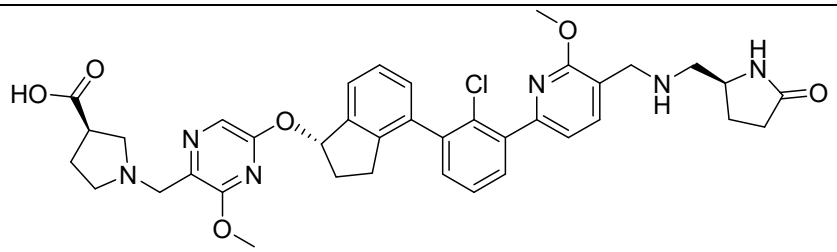
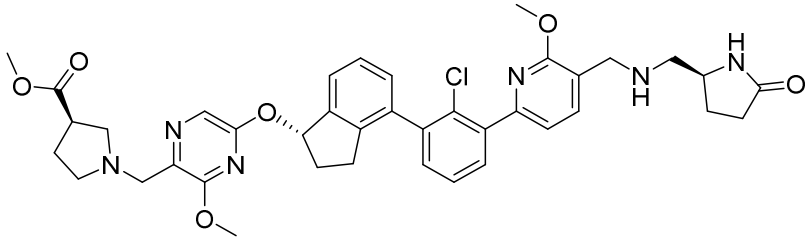
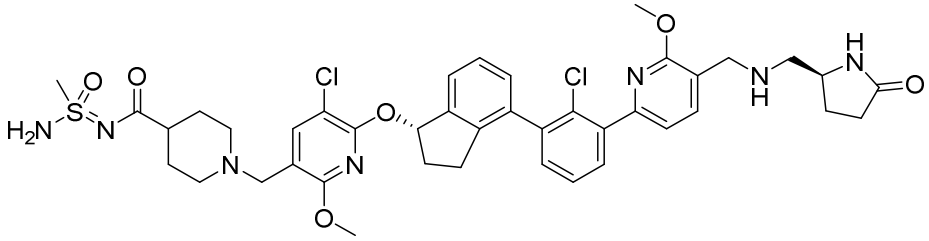
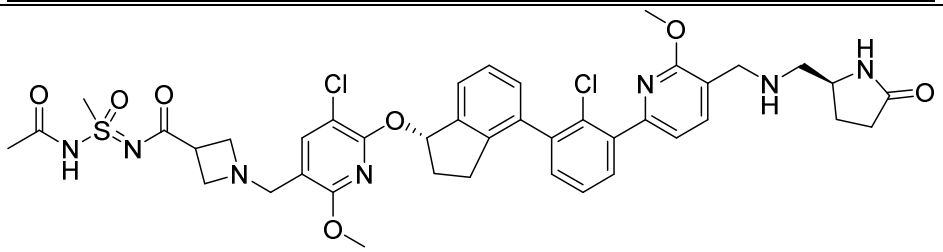
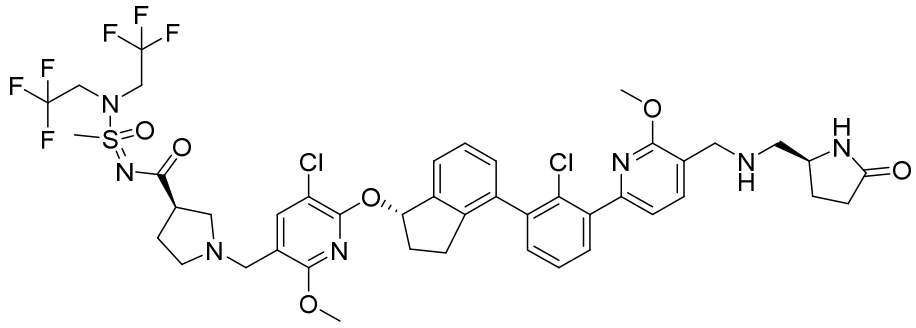
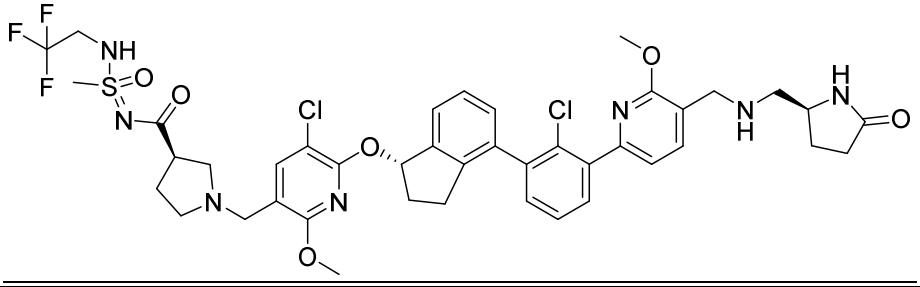
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B-131	

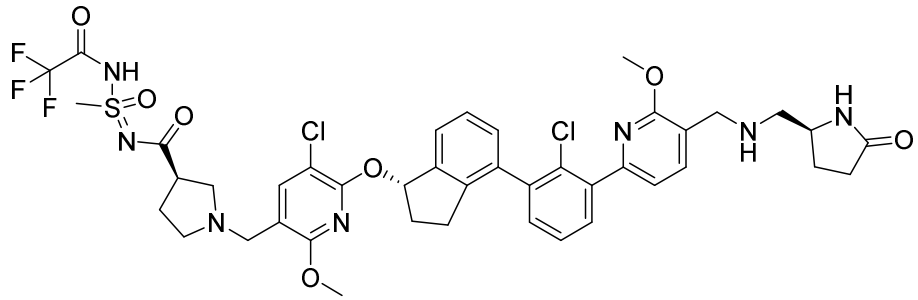
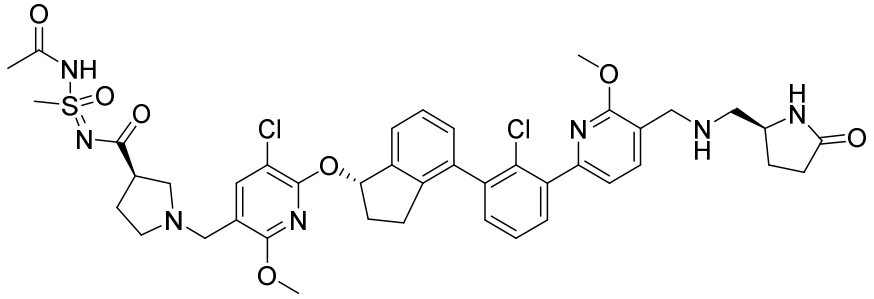
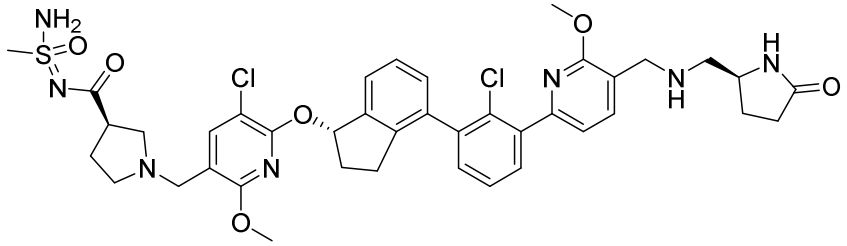
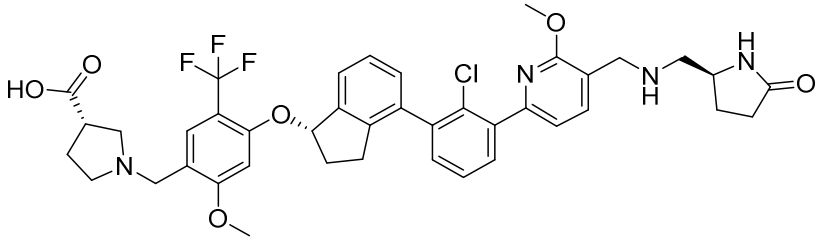
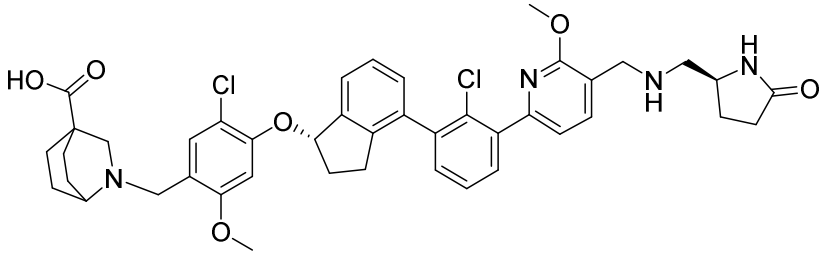
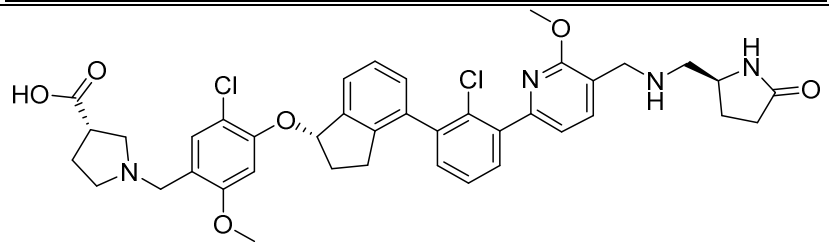
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B-136	

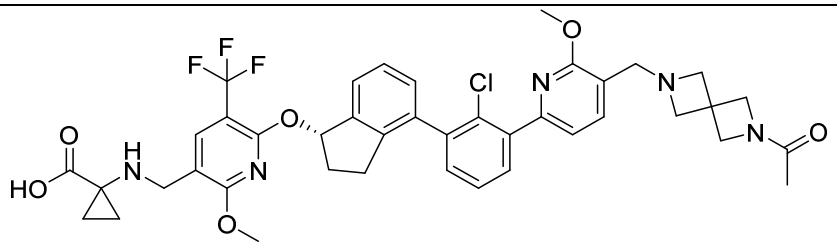
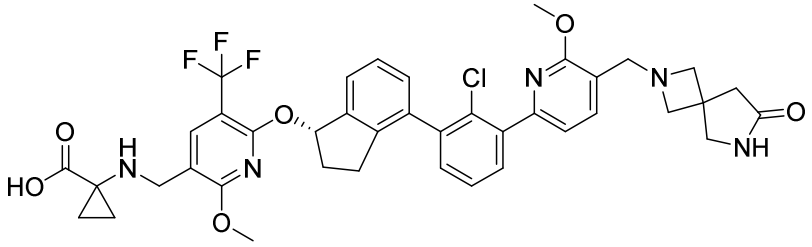
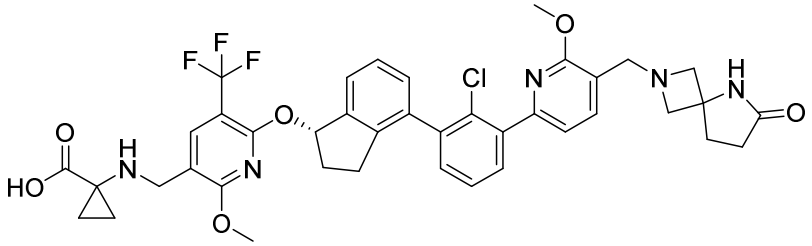
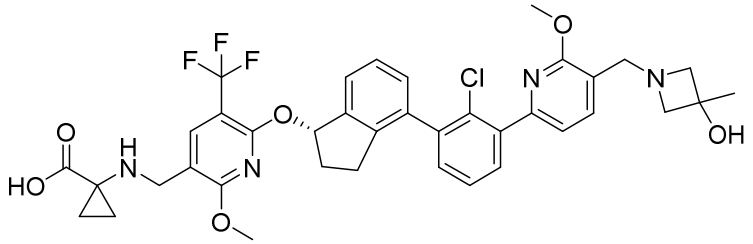
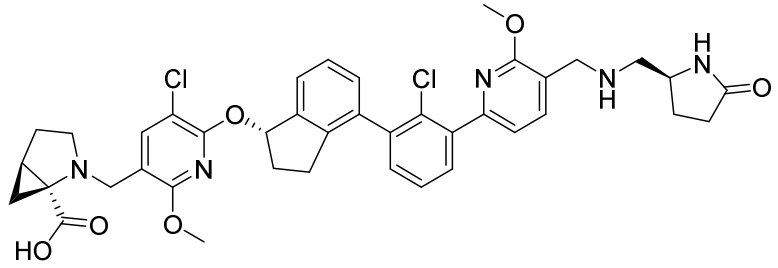
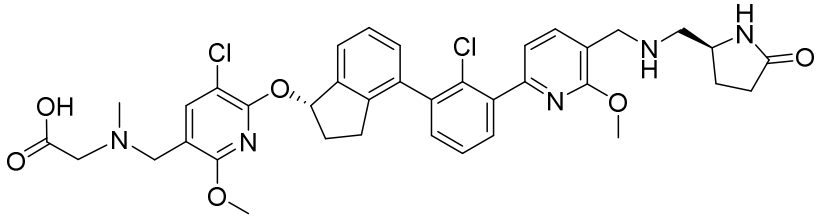
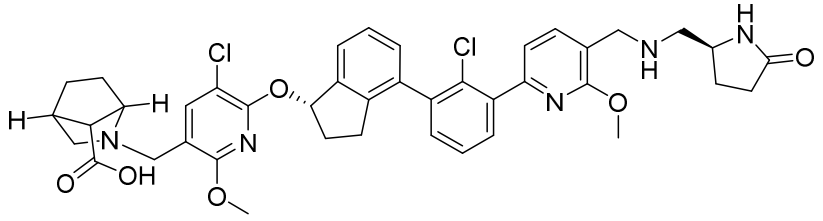
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B-142	

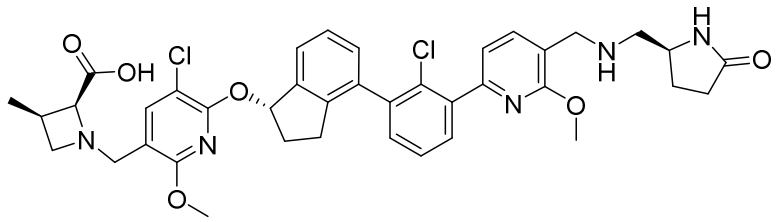
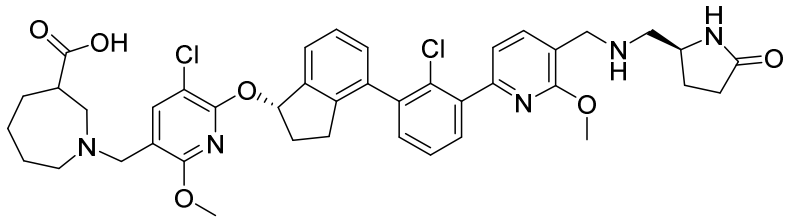
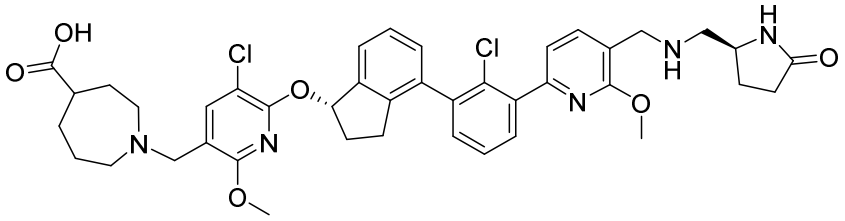
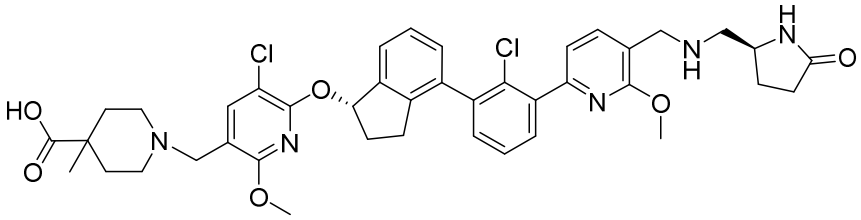
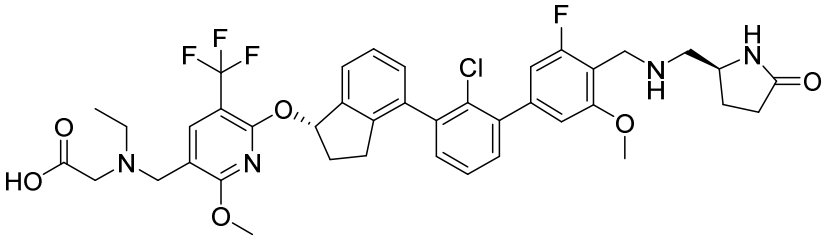
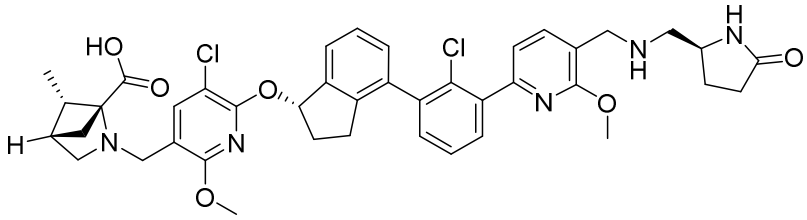
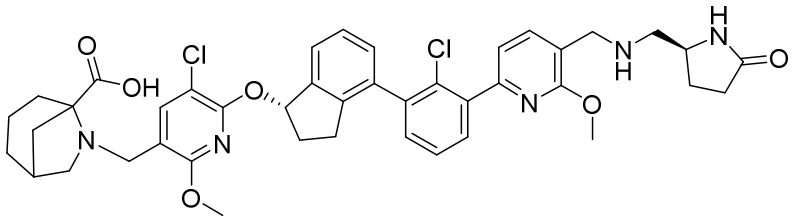
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B-148	

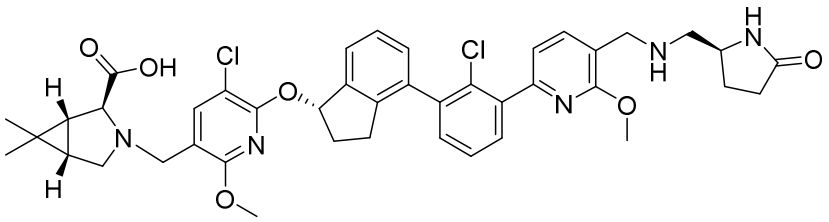
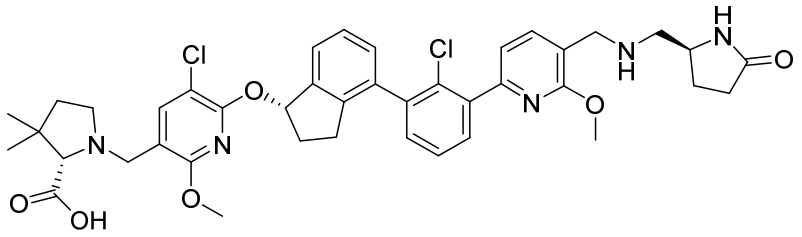
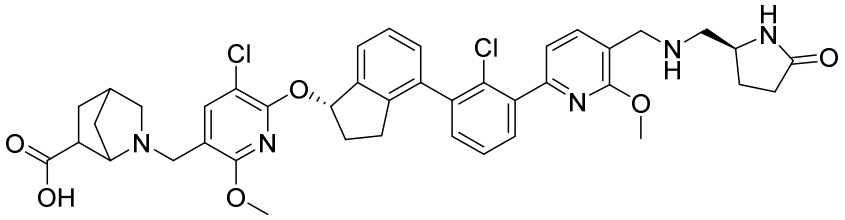
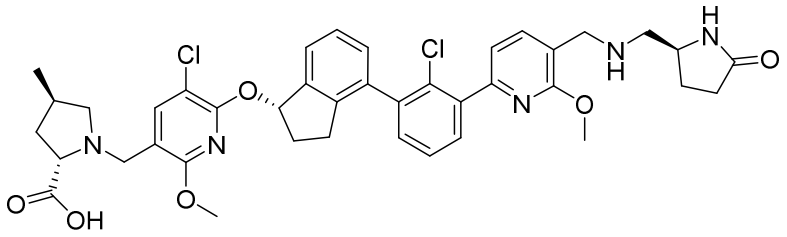
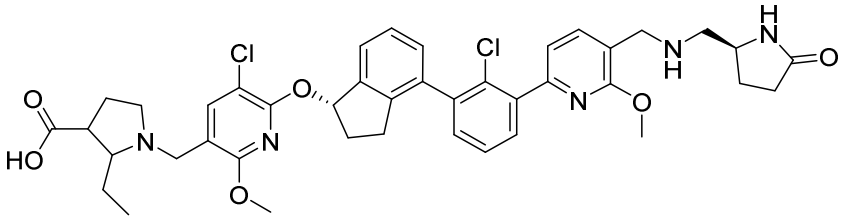
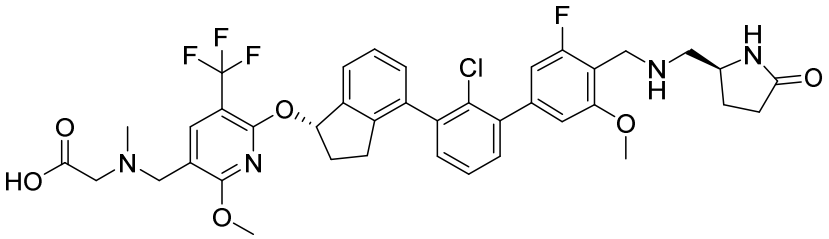
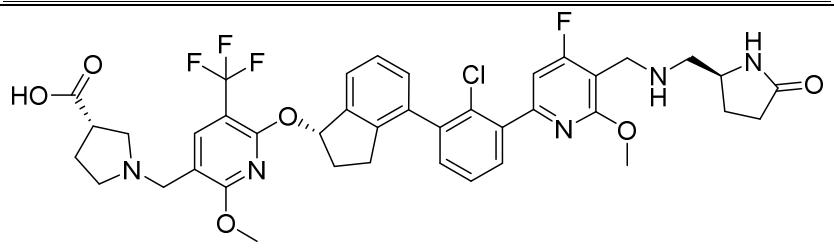
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B-155	

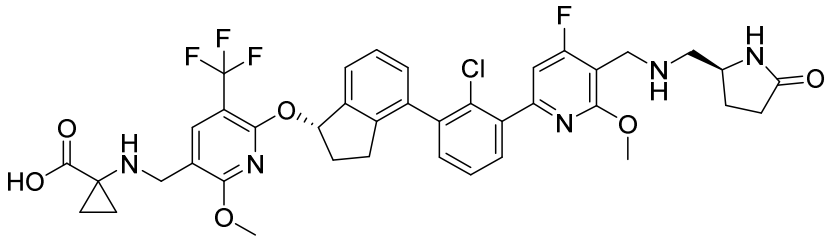
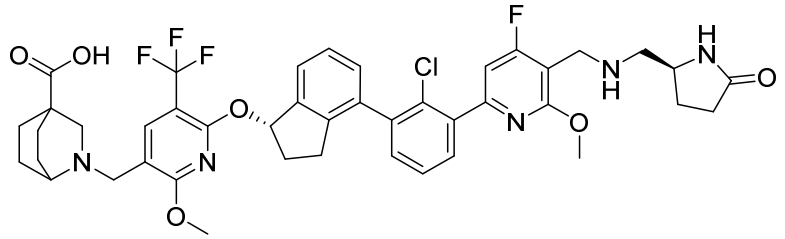
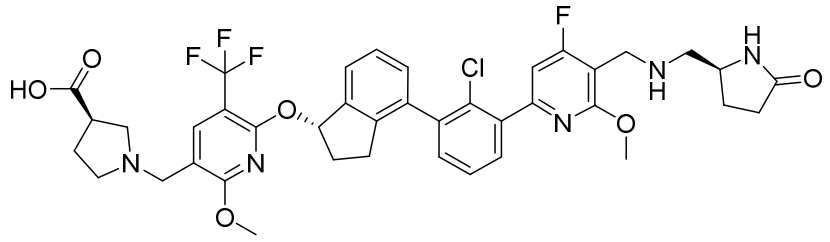
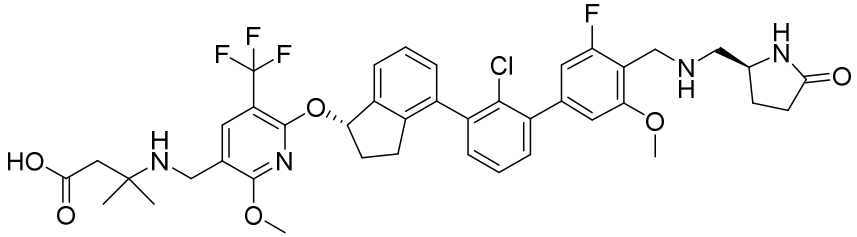
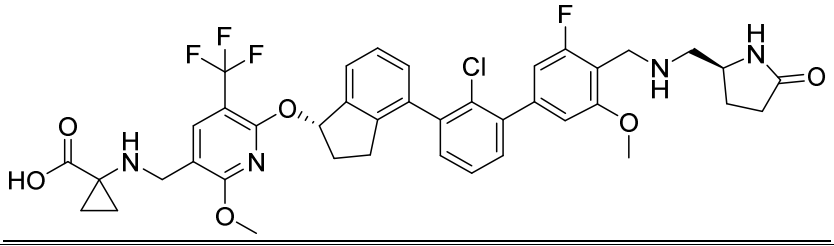
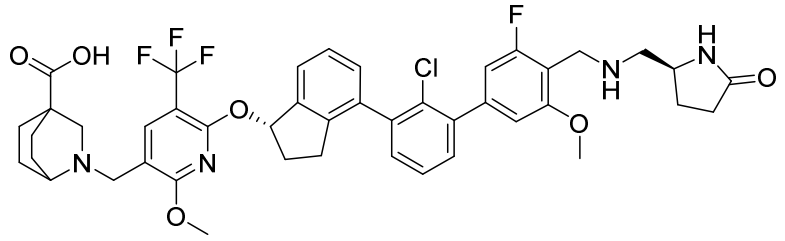
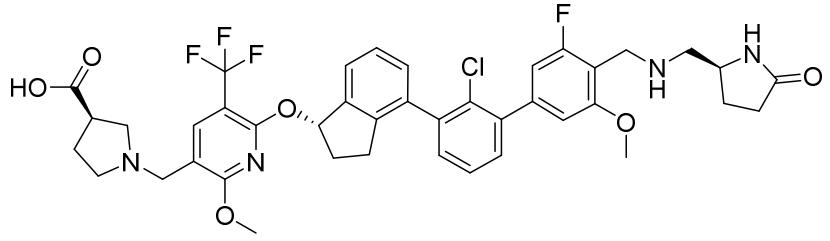
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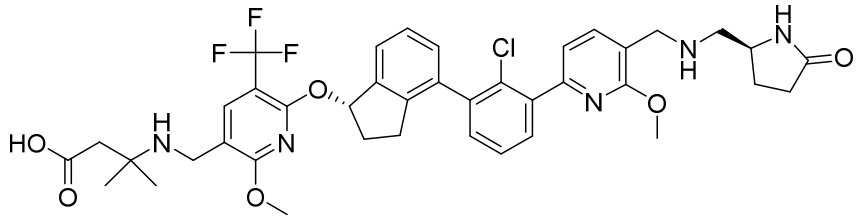
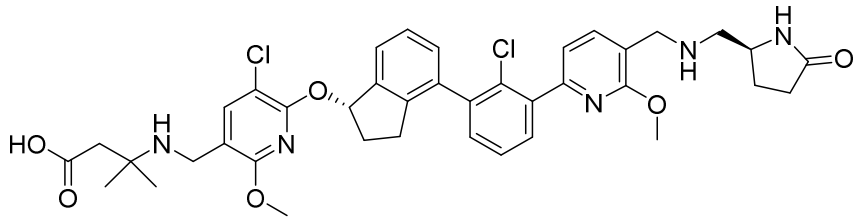
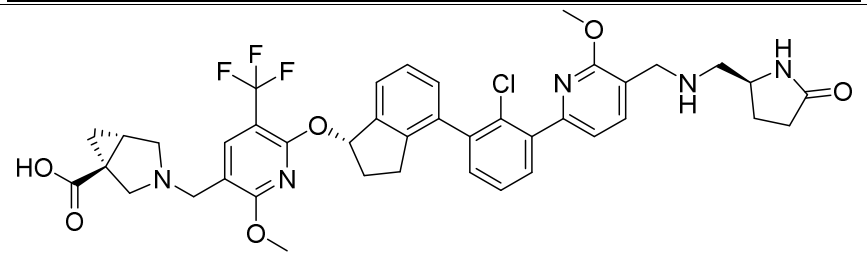
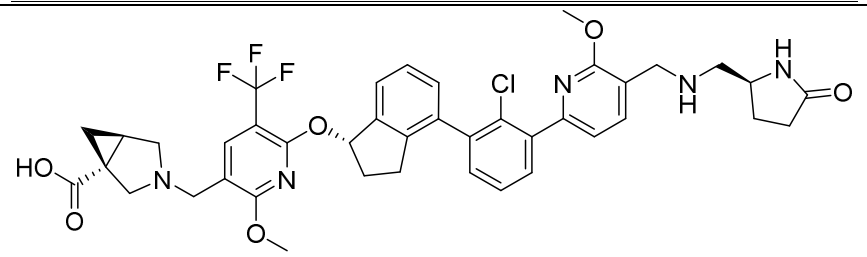
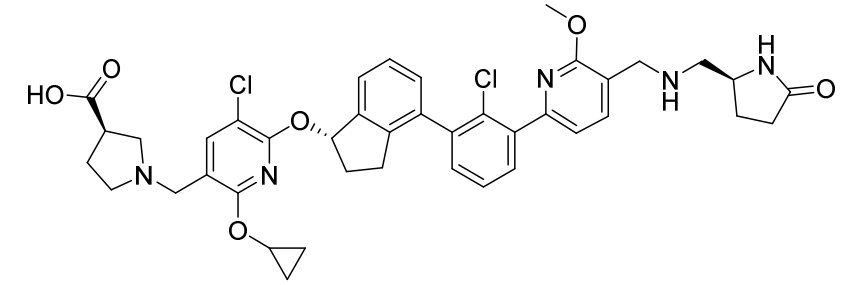
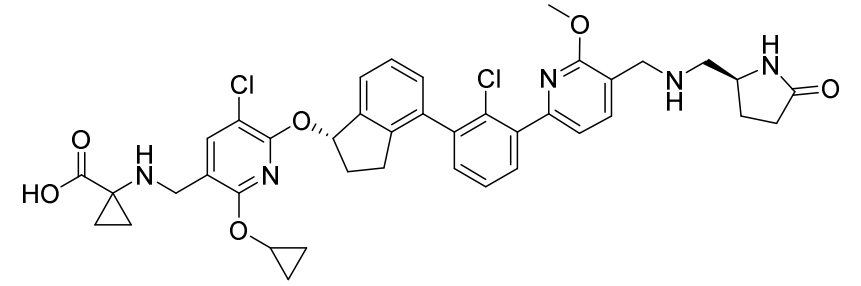
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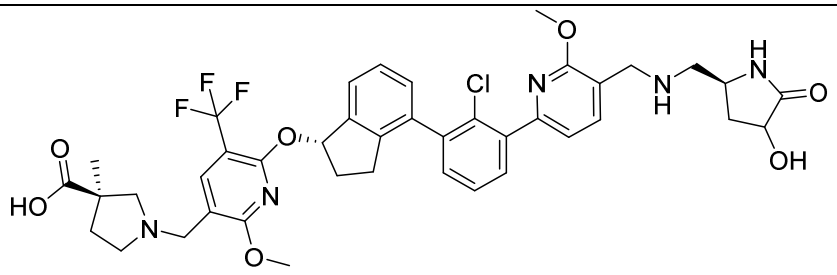
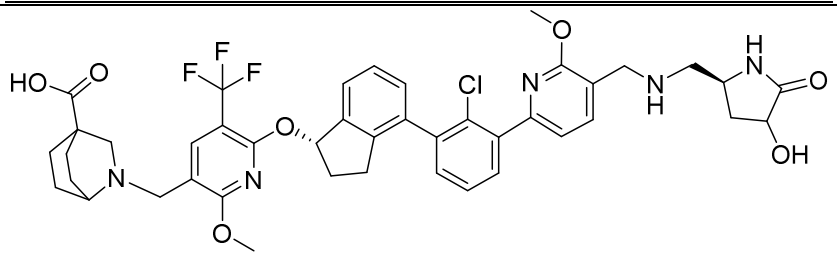
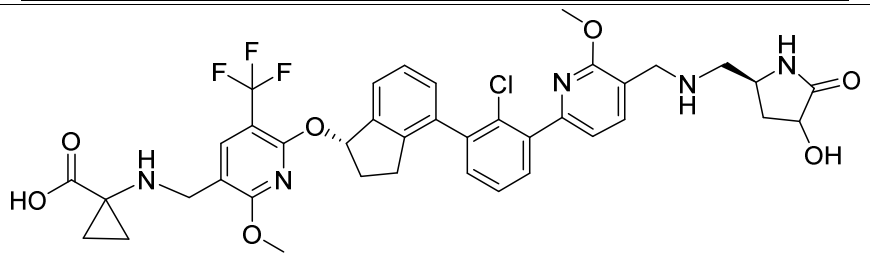
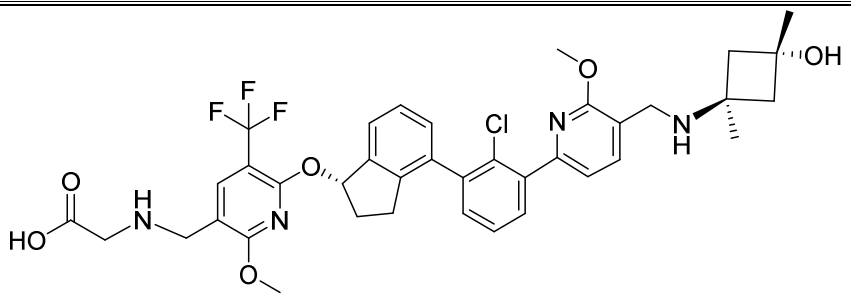
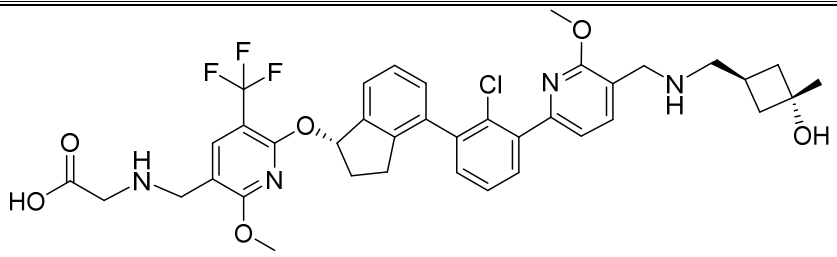
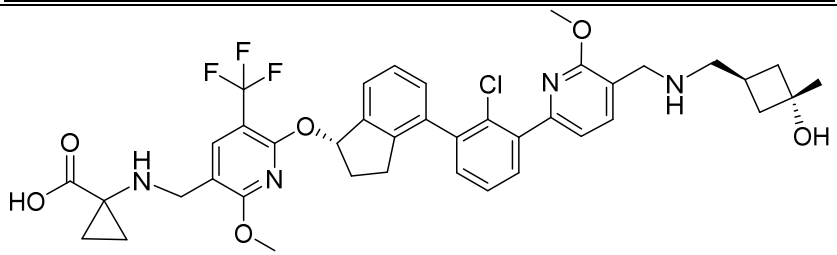
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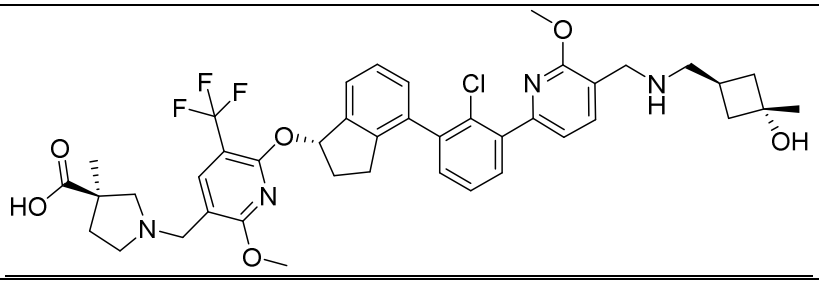
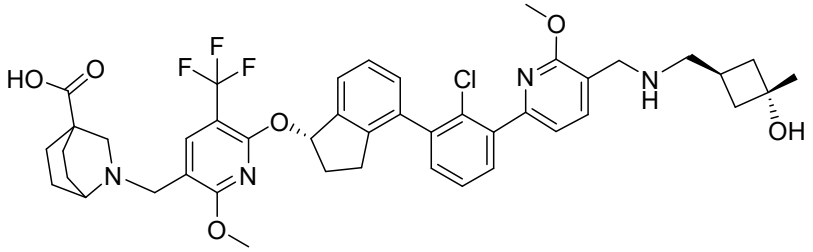
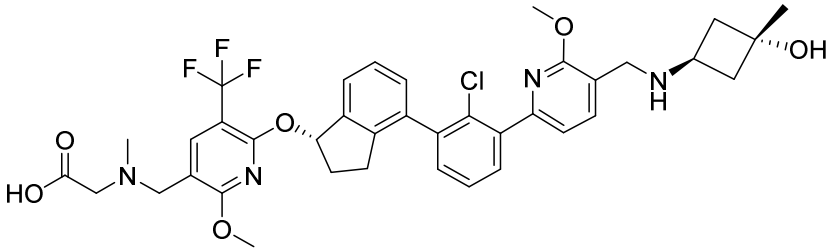
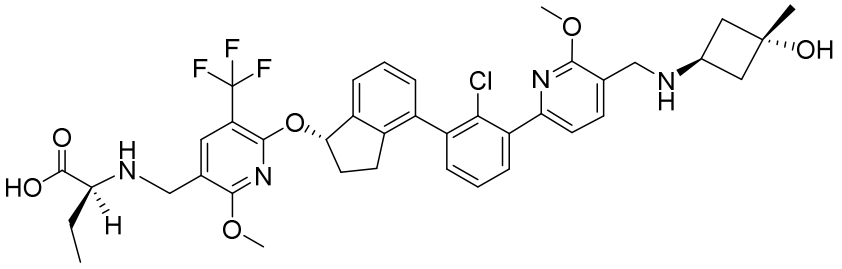
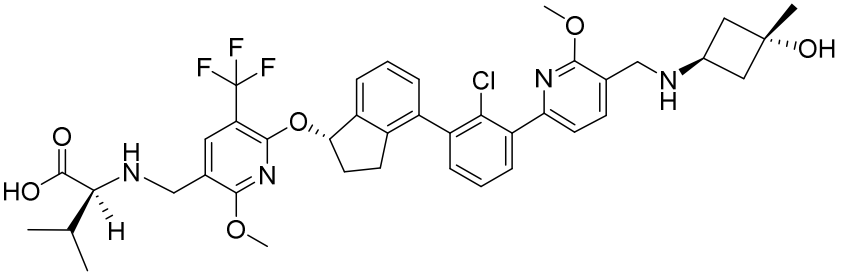
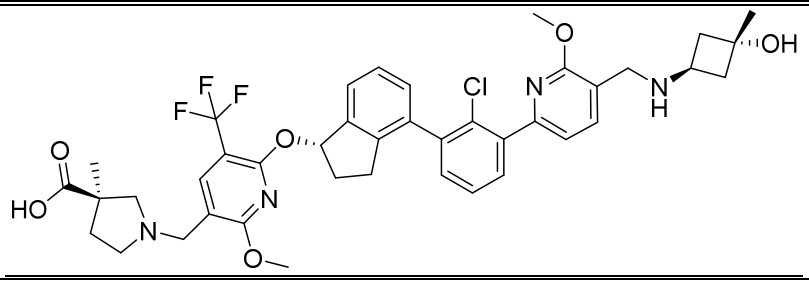
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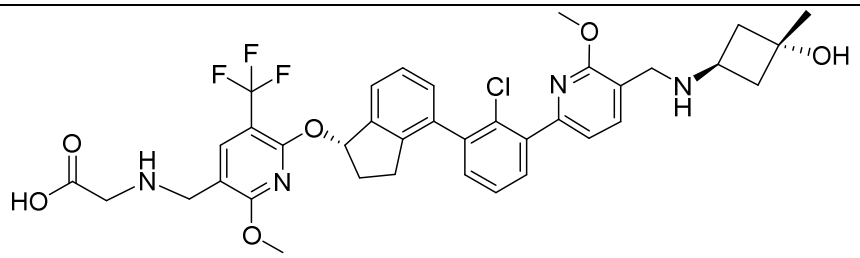
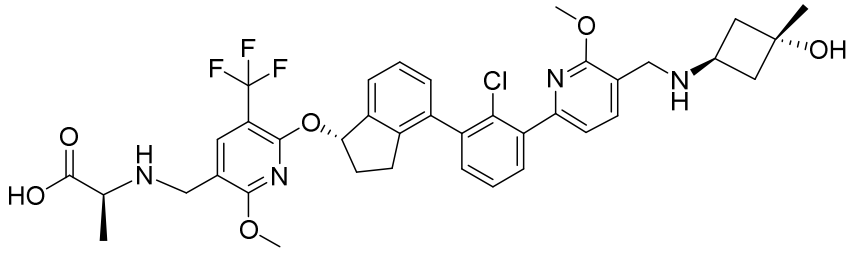
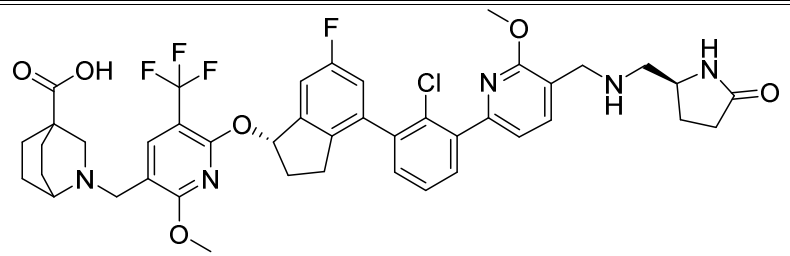
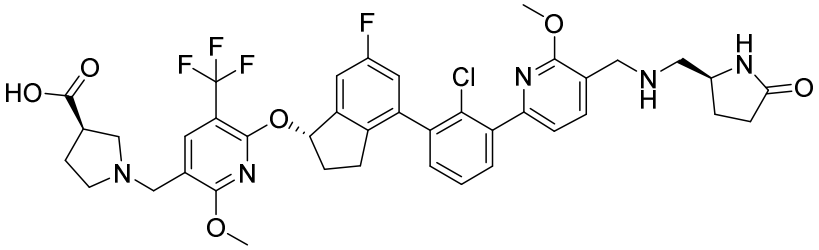
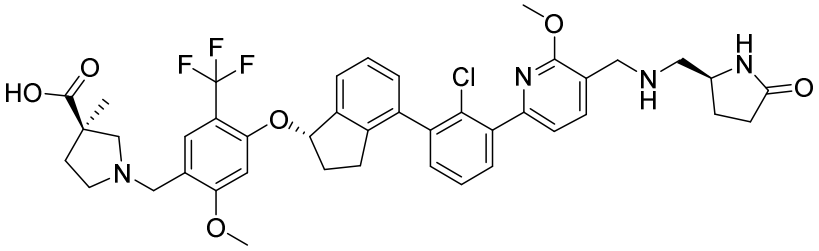
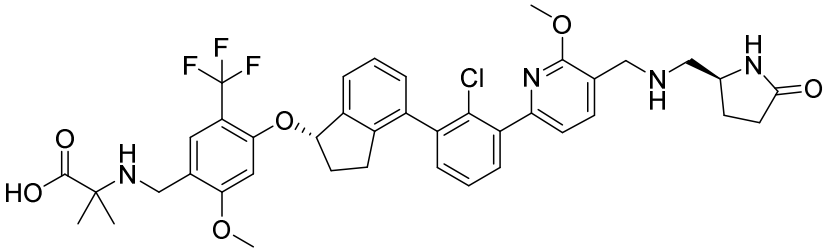
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B-188	

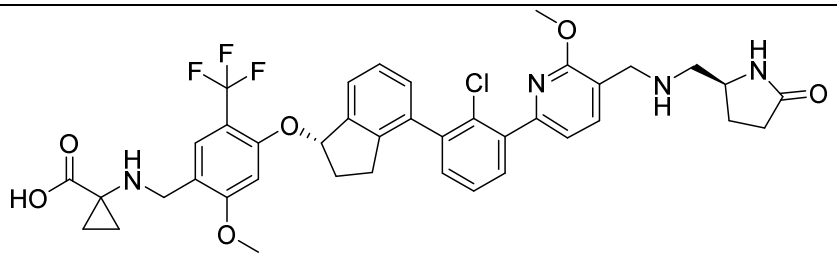
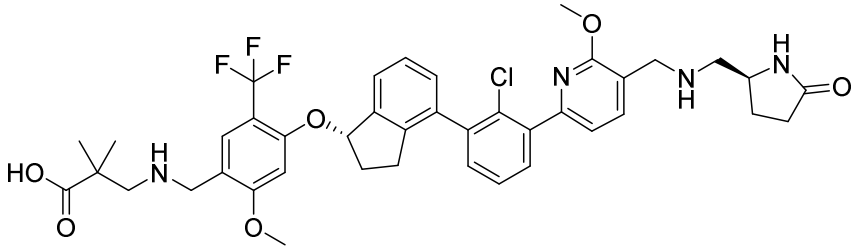
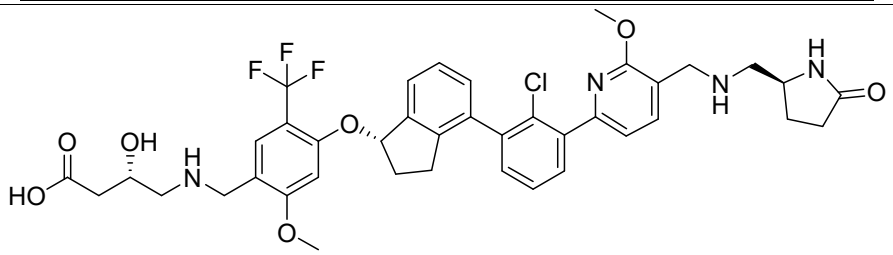
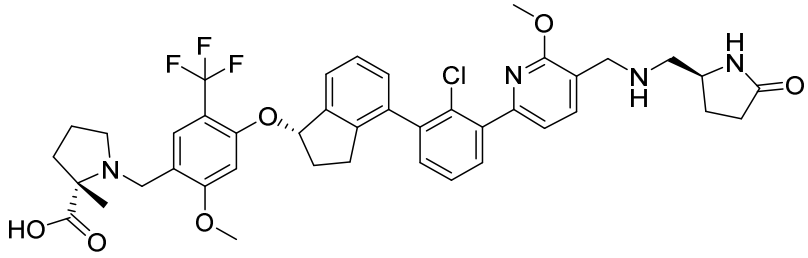
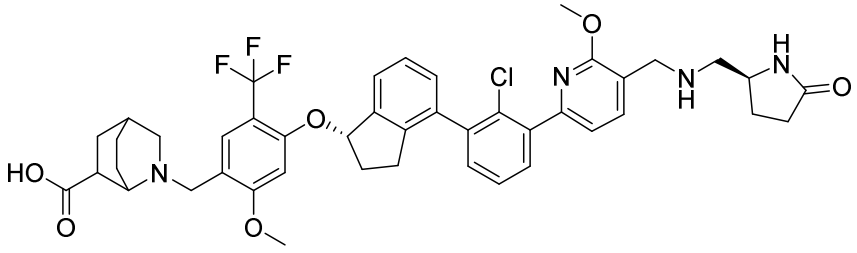
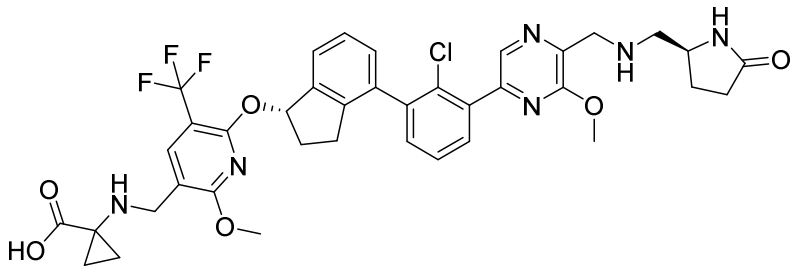
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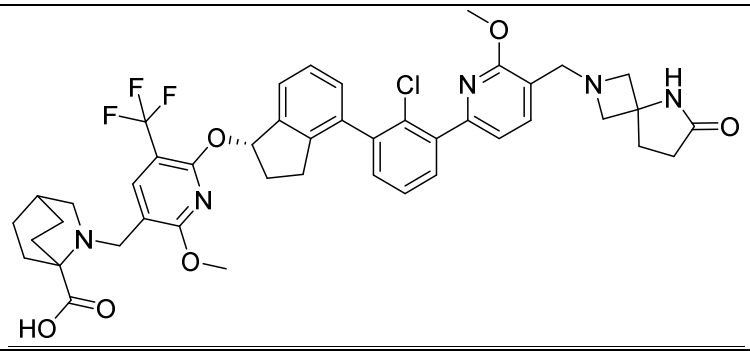
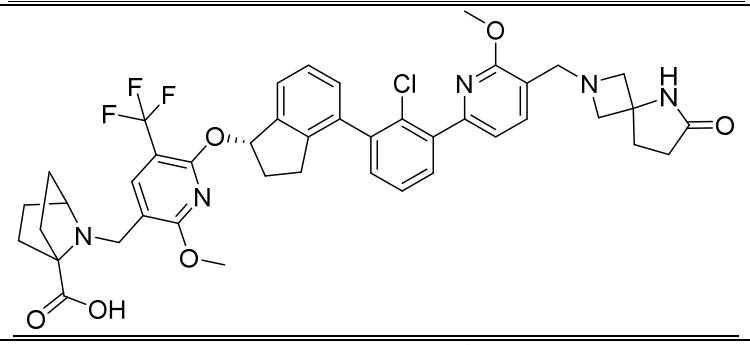
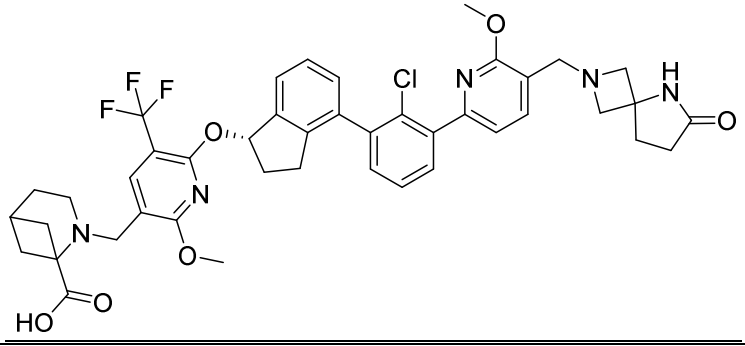
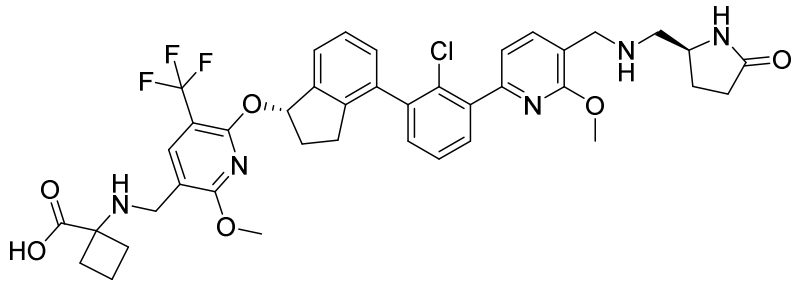
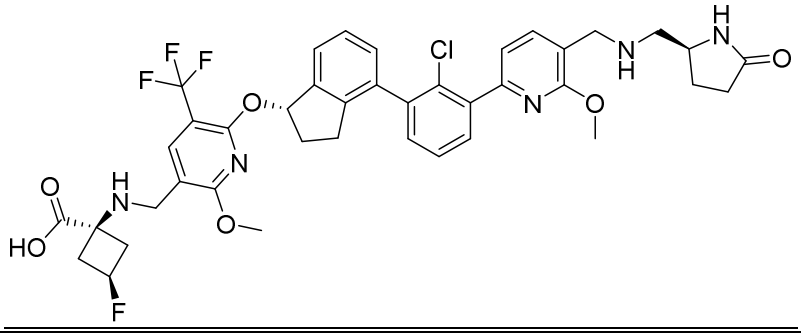
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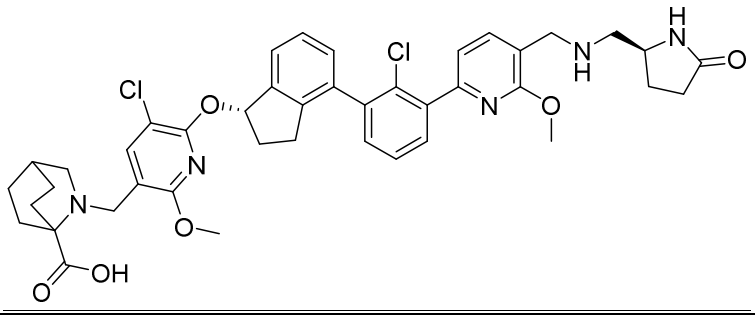
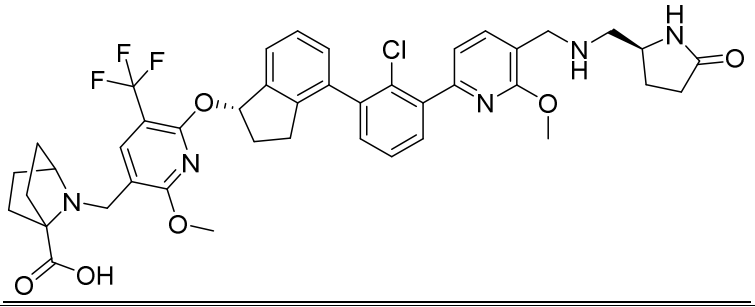
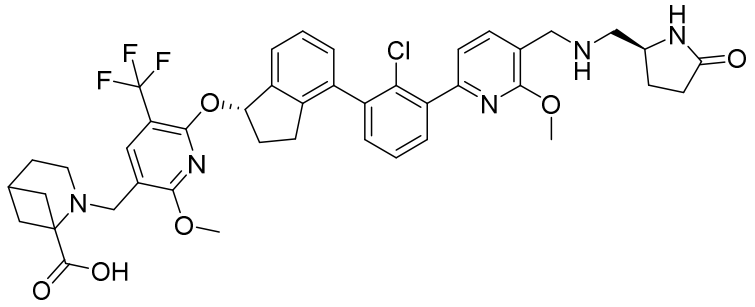
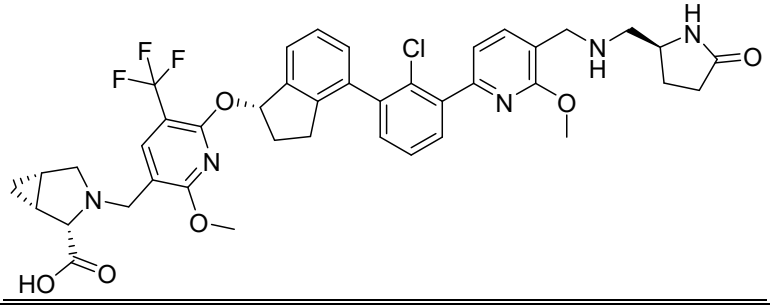
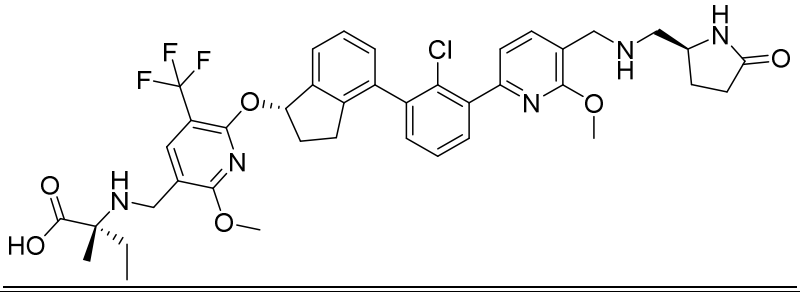
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B-207	

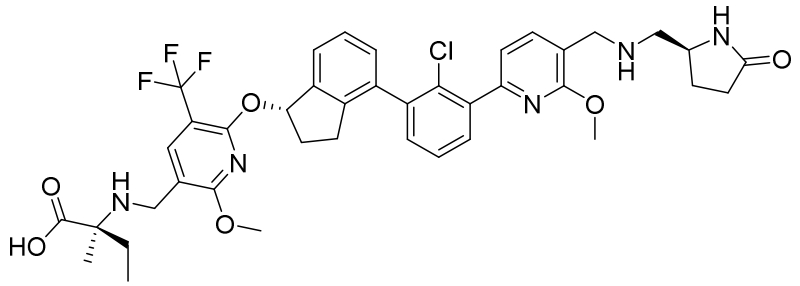
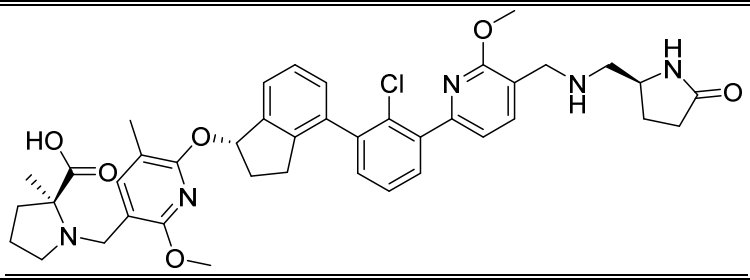
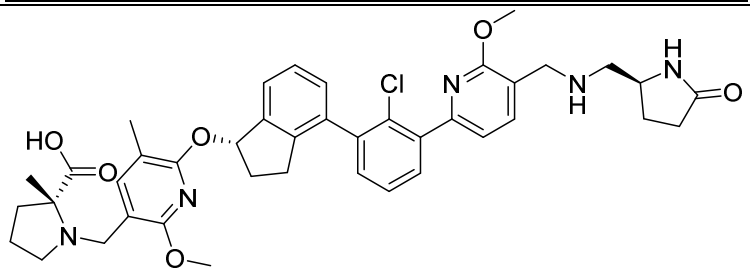
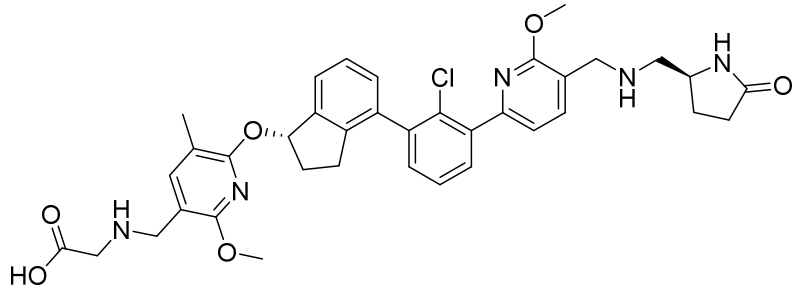
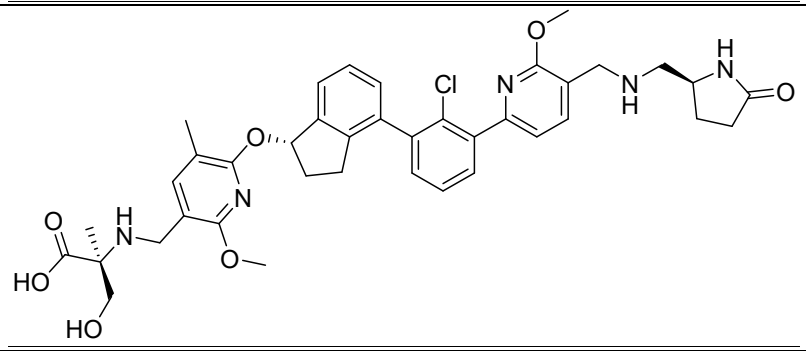
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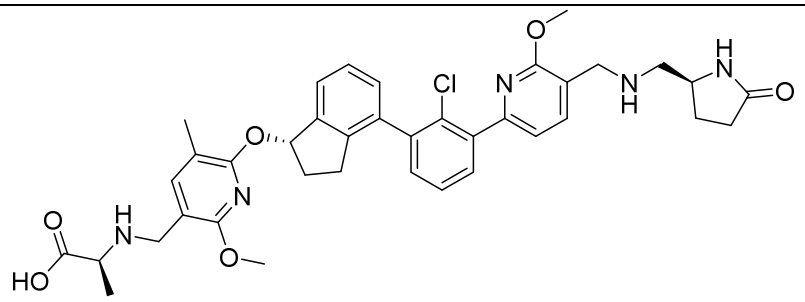
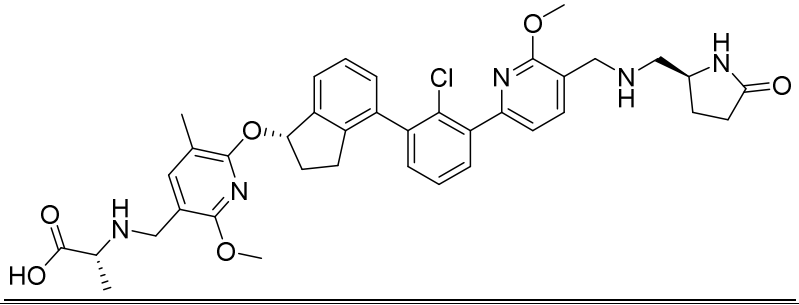
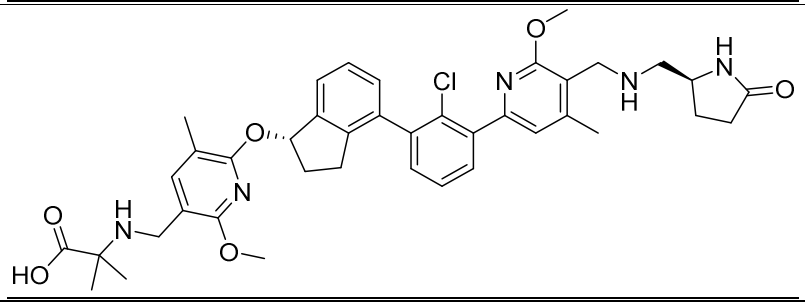
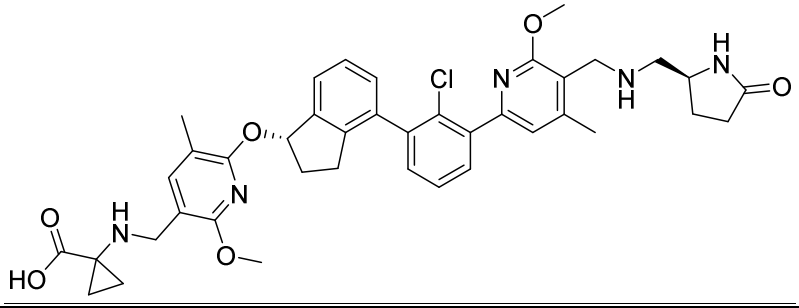
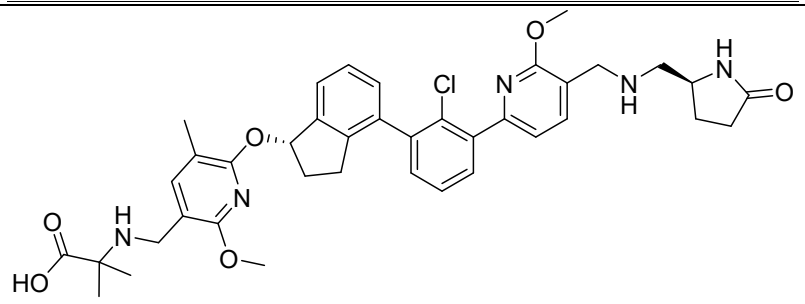
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B-219	

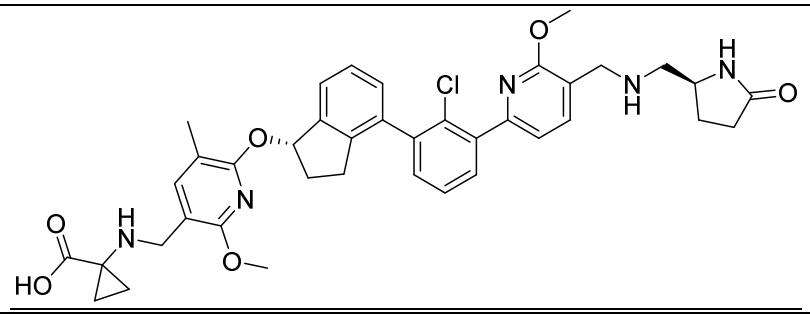
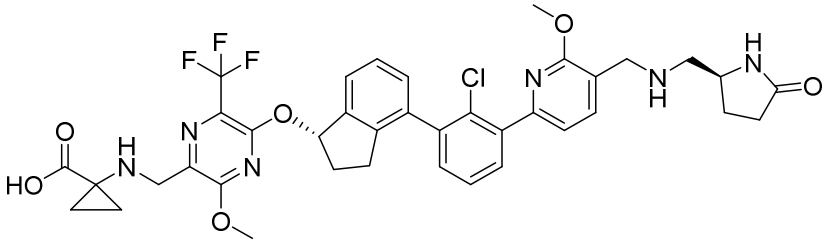
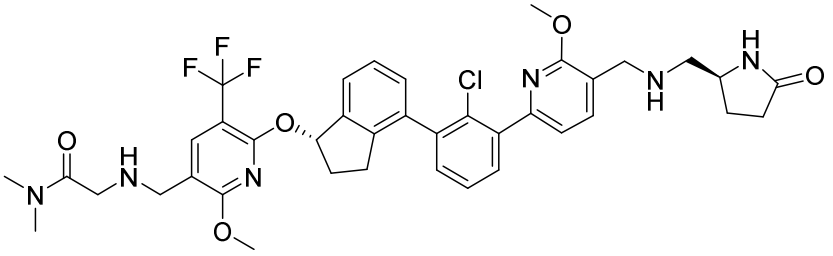
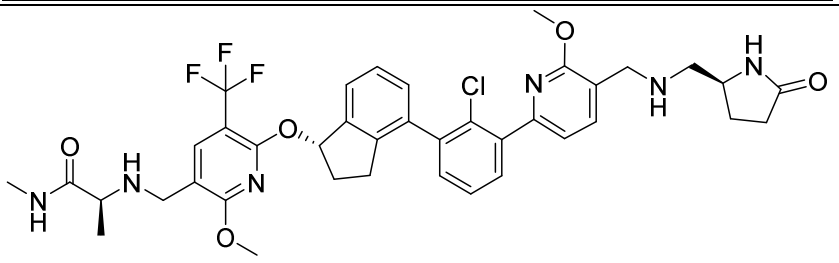
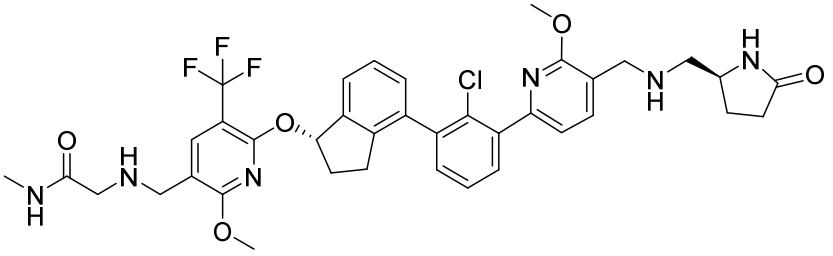
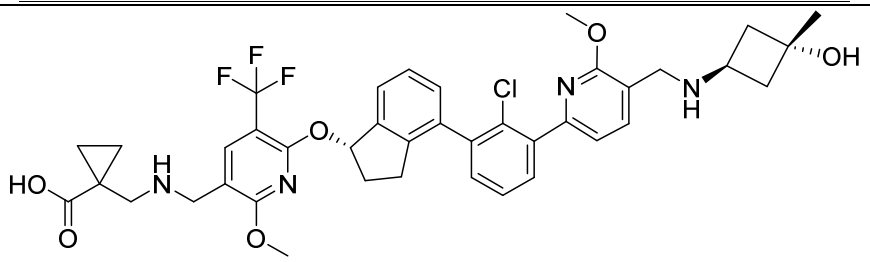
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B-225	

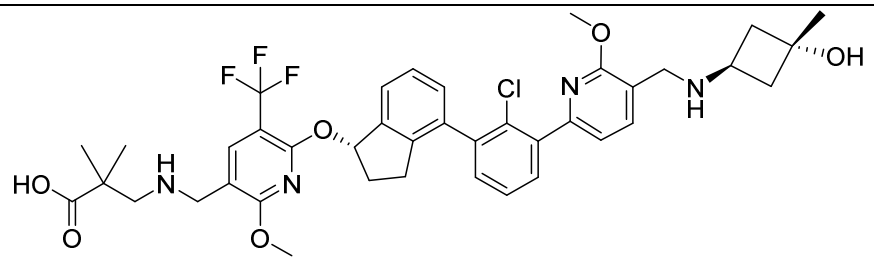
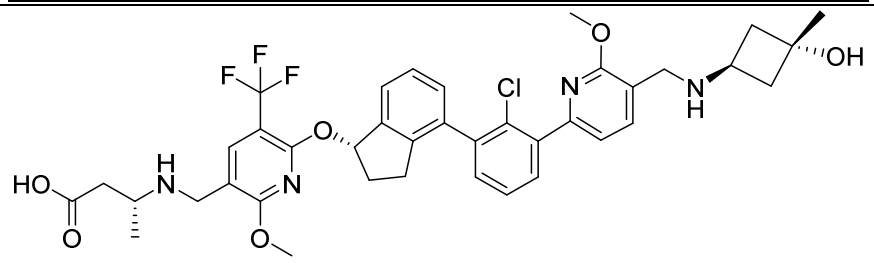
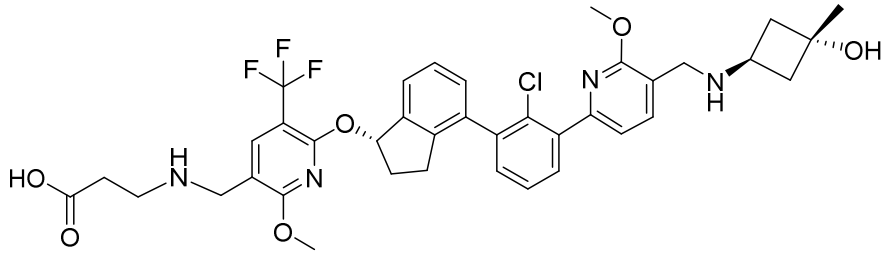
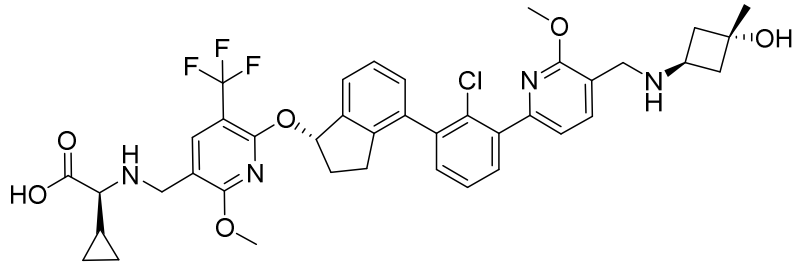
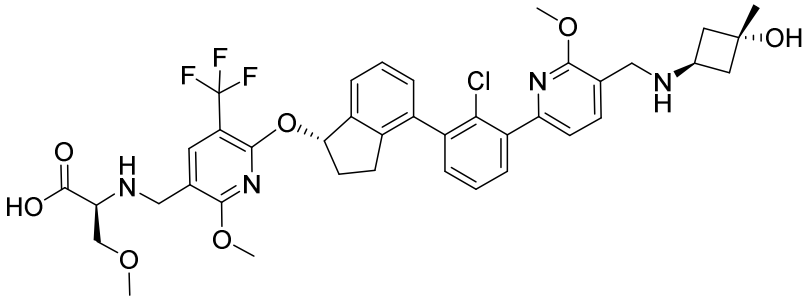
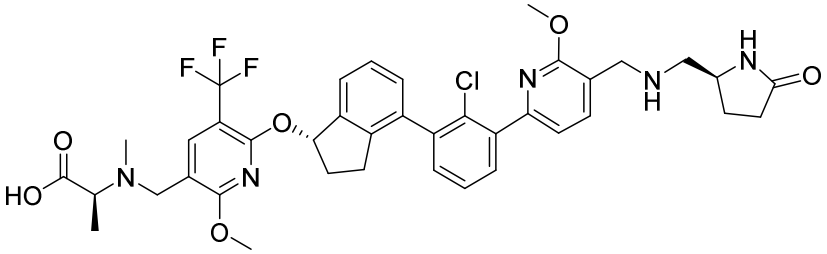
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B-230	

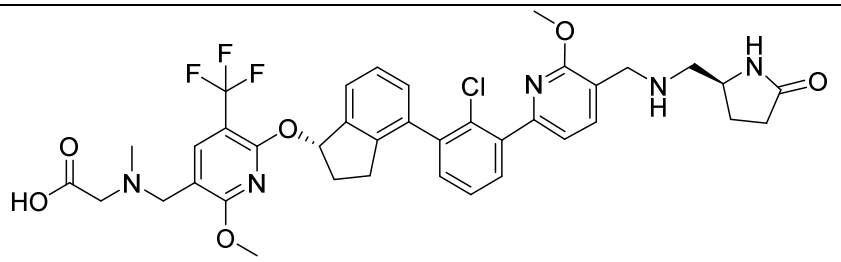
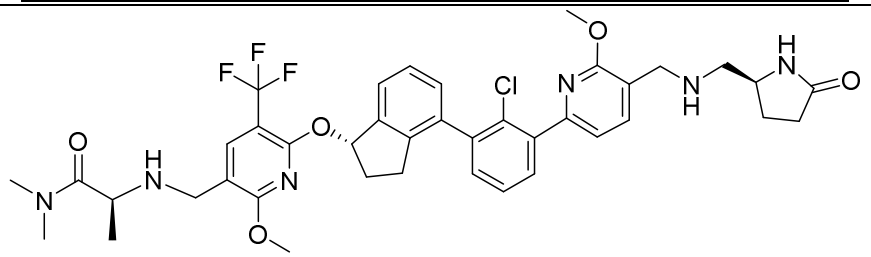
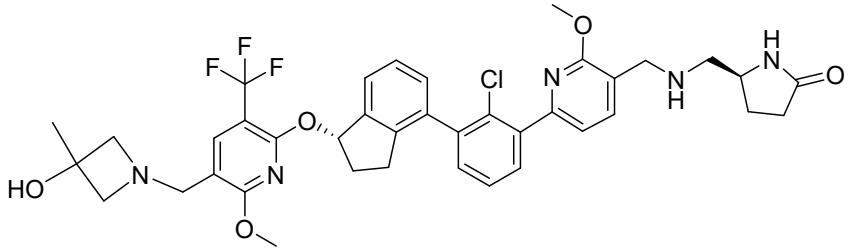
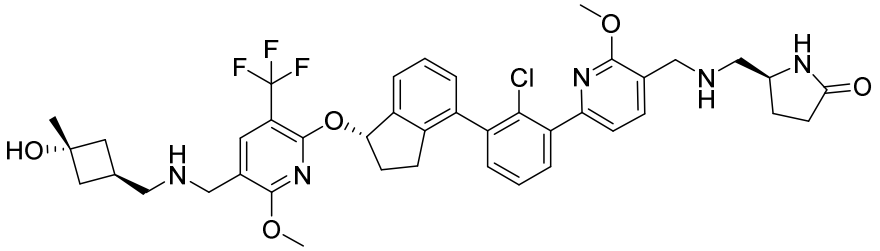
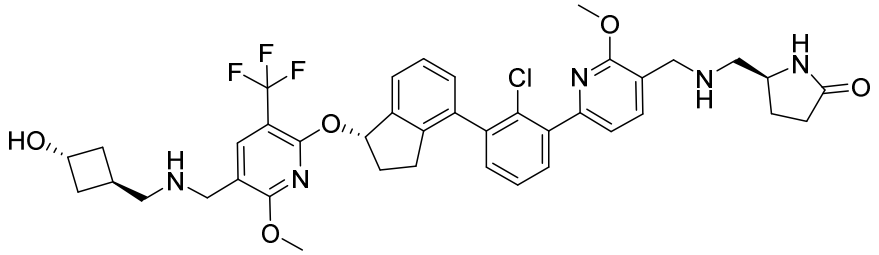
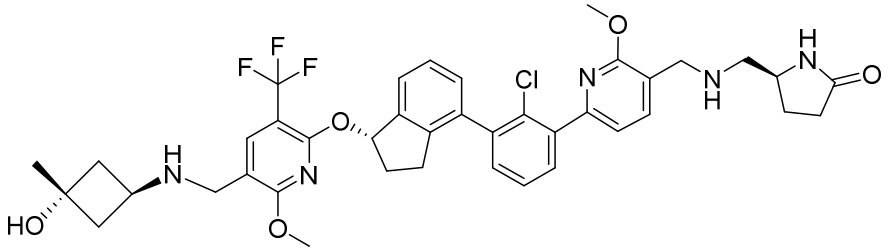
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B-235	

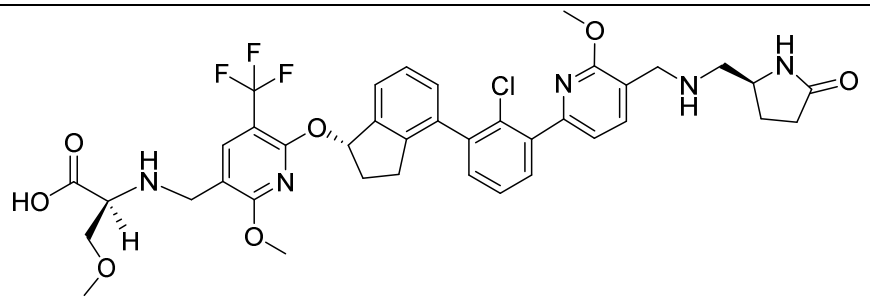
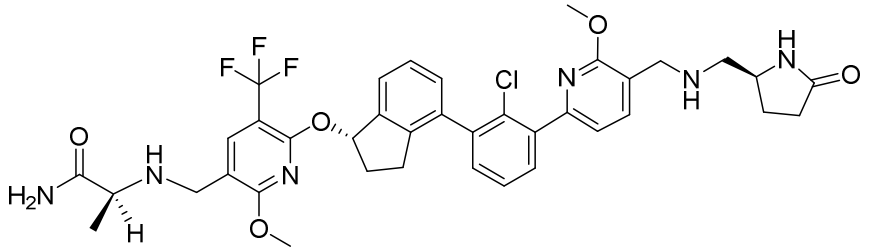
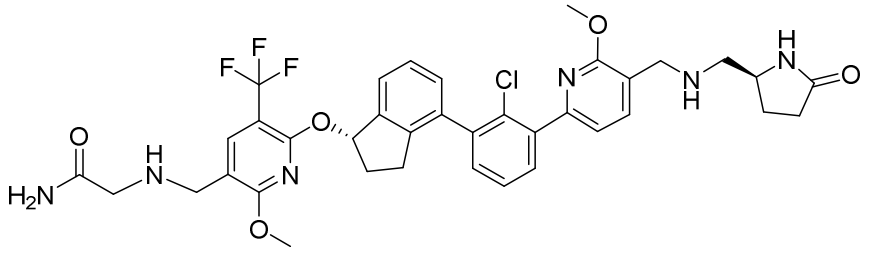
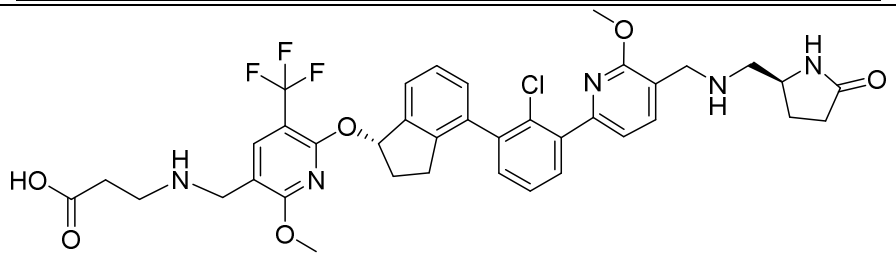
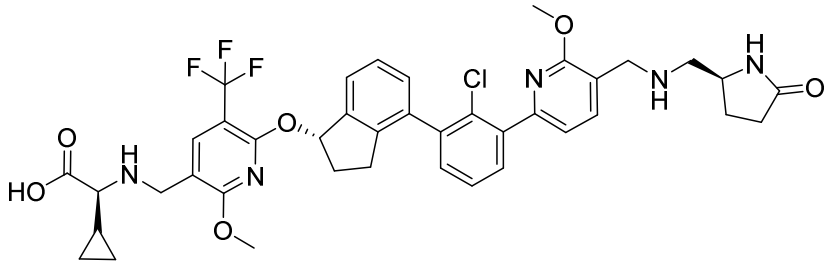
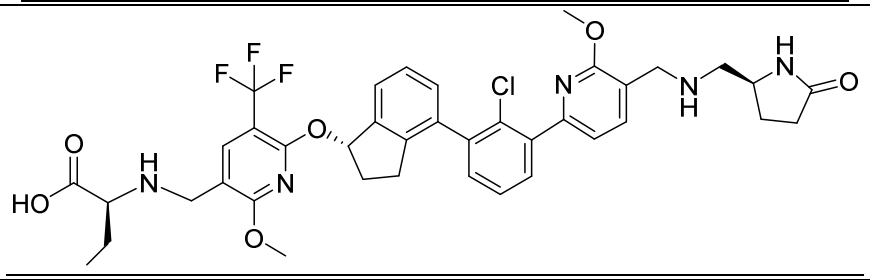
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B-240	

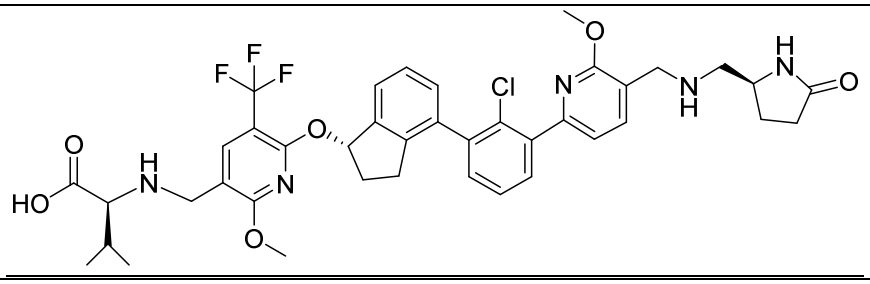
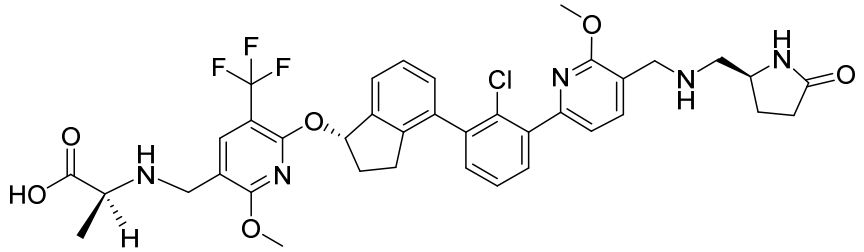
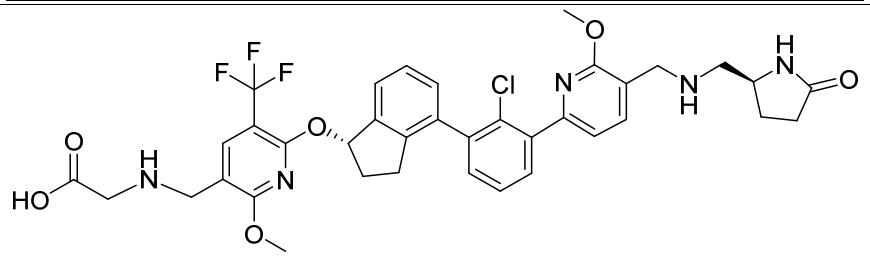
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B-245	

No.	Structure
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B-250	
B-251	

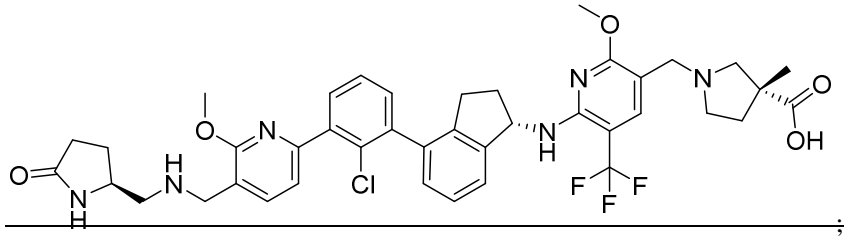
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B-255	
B-256	
B-257	

No.	Structure
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B-259	
B-260	
B-261	
B-262	
B-263	

No.	Structure
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B-266	
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B-268	
B-269	

No.	Structure
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B-271	
B-272	

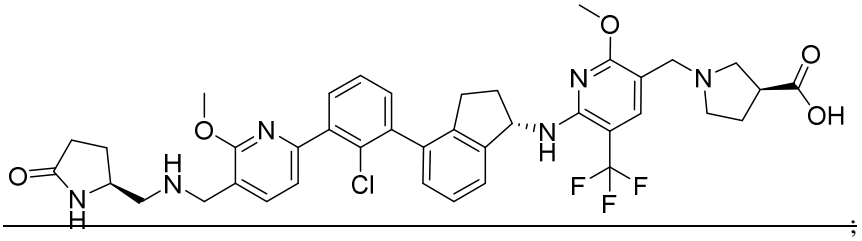
~~41. A compound which is:~~



~~;~~

~~or a pharmaceutically acceptable salt thereof.~~

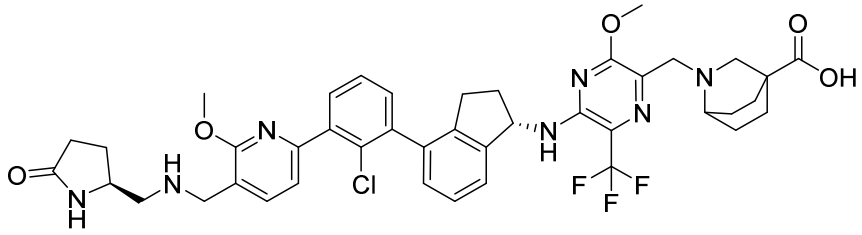
~~42. A compound which is:~~



~~;~~

~~or a pharmaceutically acceptable salt thereof.~~

~~43~~14. A compound which is:



;

or a pharmaceutically acceptable salt thereof.

~~44~~15. A pharmaceutical composition comprising a compound according to any one of claims 1-~~43~~-14 or a pharmaceutically acceptable salt~~, stereoisomer, mixture of stereoisomers, solvate, or tautomer~~ thereof, and at least one pharmaceutically acceptable excipient.

~~45~~16. The pharmaceutical composition according to claim ~~44~~15, further comprising at least one additional anticancer agent or therapy selected from rituxan, doxorubicin, gemcitabine, nivolumab, pembrolizumab, ~~and~~ ipilimumab, and atezolizumab, and at least one pharmaceutically acceptable excipient.

~~46. The pharmaceutical composition according to claim 44, wherein the additional anticancer agent is nivolumab, pembrolizumab, atezolizumab, or ipilimumab.~~

~~47. A method for inhibiting PD-1, PD-L1 and/or the PD-1/PD-L1 interaction comprising administering a compound according to any one of claims 1-43 or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, solvate, or tautomer thereof, to a patient in need thereof.~~

~~48. A method for treating cancer comprising administering a therapeutically effective amount of a compound according to any one of claims 1-43 or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, solvate, or tautomer thereof, to a patient in need thereof.~~

~~49. The method according to claim 48, wherein the cancer is pancreatic cancer, bladder cancer, colorectal cancer, breast cancer, prostate cancer, renal cancer, hepatocellular cancer, lung cancer, ovarian cancer, cervical cancer, gastric cancer, esophageal cancer, head and neck cancer, melanoma, neuroendocrine cancer, CNS cancer, brain cancer, bone cancer, soft tissue sarcoma, non-small cell lung cancer, small cell lung cancer or colon cancer.~~

~~50. The method according to claim 48, wherein the cancer is acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), myelodysplastic syndrome (MDS), myeloproliferative disease (MPD), chronic myeloid leukemia (CML), multiple myeloma (MM), non-Hodgkin's lymphoma (NHL), mantle cell lymphoma (MCL), follicular lymphoma, Waldestrom's macroglobulinemia (WM), T-cell lymphoma, B-cell lymphoma or diffuse large B-cell lymphoma (DLBCL).~~

17. Use of a compound according to any one of claims 1-14 or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer in a patient in need thereof.

51. The method according to claim 47 or 48, further comprising administering at least one additional anticancer agent or therapy selected from nivolumab, pembrolizumab, atezolizumab, ipilimumab, chemotherapy, radiation therapy, and resection therapy, to a patient in need thereof.

52. The method according to claim 47 or 48, wherein the additional anticancer agent or therapy is nivolumab, pembrolizumab, artezolizumab, nivolumab, pembrolizumab, atezolizumab, or ipilimumab.

53. A compound according to any one of claims 1-43 or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, solvate, or tautomer thereof, for use in therapy.

54. A compound according to any one of claims 1-43 or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, solvate, or tautomer thereof, for use in the manufacture of a medicament for treating cancer.

55. A compound according to any one of claims 1-43 or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, solvate, or tautomer thereof, and at least one additional anti-cancer agent selected from rituxan, doxorubicin, gemcitabine, nivolumab, pembrolizumab, and ipilimumab for use in the manufacture of a medicament for treating cancer.

56. A kit for treating or preventing cancer or a disease or condition that is amenable to treatment by inhibiting PD-1, PD-L1 and/or the PD-1/PD-L1 interaction in a patient in need thereof, comprising:

a) a compound according to any of claims 1-43, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, solvate, or tautomer thereof;

b) a monoclonal antibody checkpoint inhibitor or antigen binding fragment thereof; and optionally

c) a label or instructions for use.

57. A kit for treating or preventing cancer or a disease or condition that is amenable to treatment by inhibiting PD-1, PD-L1 and/or the PD-1/PD-L1 interaction in a patient in need thereof, comprising:

a) a compound according to any of claims 1-43, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, solvate, or tautomer thereof;

b) a monoclonal antibody checkpoint inhibitor or antigen binding fraction thereof; and optionally

c) an additional therapeutic agent; and optionally:

d) a label or instructions for use.

58. A kit for treating or preventing cancer or a disease or condition in a subject in need thereof, comprising:

a) a compound according to any of claims 1-43, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, solvate, or tautomer thereof;

b) an anti-MMP9 antibody or antigen binding fragment thereof; and optionally

c) an additional therapeutic agent; and optionally;

d) a label or instructions for use.