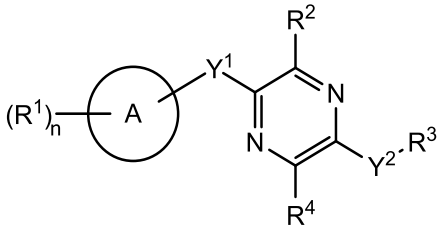
Claims:

1. A compound of Formula I-W:



I-W

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof, wherein:

A is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are 5- to 12-membered monocyclic or 5- to 12-membered polycyclic;

Y^1 is –S–, a direct bond, –NH–, $–S(O)_2–$, $–S(O)_2–NH–$, $–C(=CH_2)–$, $–CH_2–$, or –S(O)–;

Y^2 is $–NR^a–$, $–(CR^a_2)_m–$, –C(O)–, $–C(R^a)_2NH–$, $–(CR^a_2)_mO–$, $–C(O)N(R^a)–$, $–N(R^a)C(O)–$, $–S(O)_2N(R^a)–$, $–N(R^a)S(O)_2–$, $–N(R^a)C(O)N(R^a)–$, $–N(R^a)C(S)N(R^a)–$, –C(O)O–, –OC(O)–, $–OC(O)N(R^a)–$, $–N(R^a)C(O)O–$, $–C(O)N(R^a)O–$, $–N(R^a)C(S)–$, $–C(S)N(R^a)–$, or –OC(O)O–; wherein the bond on the left side of Y^2, as drawn, is bound to the pyrazine ring and the bond on the right side of the Y^2 moiety, as drawn, is bound to R^3;

R^1 is independently, at each occurrence, –H, –D, $–C_1$-C_6alkyl, $–C_2$-C_6alkenyl, $–C_4$-C_8cycloalkenyl, $–C_2$-C_6alkynyl, $–C_3$-C_8cycloalkyl, –OH, $–OR^6$, halogen, $–NO_2$, –CN, $–NR^5R^6$, $–SR^5$, $–S(O)_2NR^5R^6$, $–S(O)_2R^5$, $–NR^5S(O)_2NR^5R^6$, $–NR^5S(O)_2R^6$, $–S(O)NR^5R^6$, $–S(O)R^5$, $–NR^5S(O)NR^5R^6$, $–NR^5S(O)R^6$, $–C(O)R^5$,$–CO_2R^5$, $–C(O)NR^5R^6$, $–NR^5C(O)R^6$, monocyclic or polycyclic heterocyclyl, spiroheterocyclyl, heteroaryl, or oxo, wherein each alkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkyl, heterocyclyl, spiroheterocyclyl, or heteroaryl is optionally substituted with one or more –OH, $–NO_2$, oxo, –CN, $–R^5$, $–OR^5$, $–NR^5R^6$, $–SR^5$, $–S(O)_2NR^5R^6$, $–S(O)_2R^5$, $–NR^5S(O)_2NR^5R^6$, $–NR^5S(O)_2R^6$, $–S(O)NR^5R^6$, $–S(O)R^5$, $–NR^5S(O)NR^5R^6$, $–NR^5S(O)R^6$, heterocycle, aryl, or heteroaryl;

R^2 is independently –OH, –CN, $–C_1$-C_6alkyl, $–C_2$-C_6alkenyl, $–C_4$-C_8cycloalkenyl, $–C_2$-C_6alkynyl, F, Br, I, $–C_3$-C_8cycloalkyl, aryl, heterocyclyl containing 1-5 heteroatoms selected from the group consisting of N, S, P, and O, or heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, S, P, and O; wherein each alkyl,

alkenyl, cycloalkenyl, alkynyl, cycloalkyl, heterocyclyl, or heteroaryl is optionally substituted with one or more –OH, halogen, $–NO_2$, –CN, $–R^5$, $–OR^5$, $–NR^5R^6$, $–SR^5$, $–S(O)_2NR^5R^6$, $–S(O)_2R^5$, $–NR^5S(O)_2NR^5R^6$, $–NR^5S(O)_2R^6$, $–S(O)NR^5R^6$, $–S(O)R^5$, $–NR^5S(O)NR^5R^6$, $–NR^5S(O)R^6$, heterocycle, aryl, or heteroaryl; and wherein the heterocyclyl or heteroaryl is not attached via a nitrogen atom;

R^a is independently, at each occurrence, –H, –D, –OH, $–C_3$-C_8cycloalkyl, $–C_1$-C_6alkyl, 3- to 12-membered heterocyclyl, or $–(CH_2)_n$-aryl, wherein each alkyl or cycloalkyl is optionally substituted with one or more $–NH_2$, or wherein 2 R^a, together with the carbon atom to which they are both attached, can combine to form a 3- to 8-membered cycloalkyl;

R^b is independently, at each occurrence, –H, –D, –OH, $–C_1$-C_6alkyl, $–C_3$-C_8cycloalkyl, $–C_2$-C_6alkenyl, $–(CH_2)_n$-aryl, heterocyclyl containing 1-5 heteroatoms selected from the group consisting of N, S, P, and O, or heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, S, P, and O; wherein each alkyl, cycloalkyl, alkenyl, heterocycle, heteroaryl, or $–(CH_2)_n$-aryl is optionally substituted with one or more –OH, halogen, $–NO_2$, oxo, –CN, $–R^5$, $–OR^5$, $–NR^5R^6$, $–SR^5$, $–S(O)_2NR^5R^6$, $–S(O)_2R^5$, $–NR^5S(O)_2NR^5R^6$, $–NR^5S(O)_2R^6$, $–S(O)NR^5R^6$, $–S(O)R^5$, $–NR^5S(O)NR^5R^6$, $–NR^5S(O)R^6$, $–C(O)NR^5R^6$, $–NR^5C(O)R^6$, heterocycle, aryl, heteroaryl, $–(CH_2)_nOH$, $–C_1$-C_6alkyl, $–CF_3$, $–CHF_2$, or $–CH_2F$;

R^3 is independently –H, $–C_1$-C_6alkyl, a 3- to 12-membered monocyclic or polycyclic heterocycle, a 5- to 12-membered spiroheterocycle, C_3-C_8cycloalkyl, or $–(CH_2)_n$-R^b, wherein each alkyl, spiroheterocycle, heterocycle, or cycloalkyl is optionally substituted with one or more $–C_1$-C_6alkyl, –OH, $–NH_2$, $–OR^b$, $–NHR^b$, $–(CH_2)_nOH$, heterocyclyl, or spiroheterocyclyl; or

R^3 can combine with R^a to form a 3- to 12-membered monocyclic or polycyclic heterocycle or a 5- to 12-membered spiroheterocycle, wherein each heterocycle or spiroheterocycle is optionally substituted with one or more $–C_1$-C_6alkyl, halogen, –OH, $–OR^b$, $–NH_2$, $–NHR^b$, heteroaryl, heterocyclyl, $–(CH_2)_nNH_2$, $–(CH_2)_nOH$, $–COOR^b$, $–CONHR^b$, $–CONH(CH_2)_nCOOR^b$, $–NHCOOR^b$, $–CF_3$, $–CHF_2$, $–CH_2F$, or =O;

R^4 is independently –H, –D, $–C_1$-C_6alkyl, $–C_1$-C_6haloalkyl, $–C_1$-C_6hydroxyalkyl, $–CF_2OH$, –CHFOH, $–NH-NHR^5$, $–NH-OR^5$, $–O-NR^5R^6$, $–NHC(O)R^5$, $–NHC(O)NHR^5$, $–NHS(O)_2R^5$, $–NHS(O)_2NHR^5$, $–S(O)_2OH$, $–C(O)OR^5$, $–NH(CH_2)_nOH$, $–C(O)NH(CH_2)_nOH$, $–C(O)NH(CH_2)_nR^b$, $–C(O)R^b$, $–NH_2$, –OH, $–C(O)NR^5R^6$, $–S(O)_2NR^5R^6$, C_3-C_8cycloalkyl, aryl, or heterocyclyl containing 1-5 heteroatoms selected from the group consisting of N, S, P, and O, wherein each alkyl, cycloalkyl, or heterocyclyl is

optionally substituted with one or more –OH, –NH_2, –OR^b, halogen, or oxo; wherein each aryl is optionally substituted with one or more –OH, –NH_2, or halogen; or

R^a and R^4, together with the atom or atoms to which they are attached, can combine to form a monocyclic or polycyclic C_3-C_{12}cycloalkyl or a monocyclic or polycyclic 3- to 12-membered heterocycle, wherein the cycloalkyl or heterocycle is optionally substituted with oxo; wherein the heterocycle optionally comprises –$S(O)_2$– in the heterocycle;

R^5 is independently –H, –D, –C_1-C_6alkyl, –C_2-C_6alkenyl, –C_4-C_8cycloalkenyl, –C_2-C_6alkynyl, –C_3-C_8cycloalkyl, a monocyclic or polycyclic 3- to 12-membered heterocycle, –OR^7, –SR^7, –NR^7R^8, –NO_2, –CF_3, or –CN;

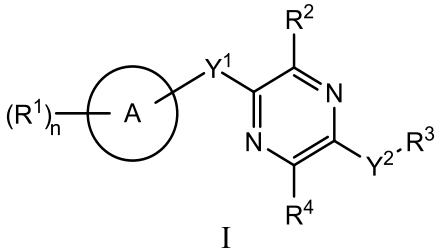
R^6 is independently –H, –D, –C_1-C_6alkyl, –C_2-C_6alkenyl, –C_4-C_8cycloalkenyl, –C_2-C_6alkynyl, –C_3-C_8cycloalkyl, a monocyclic or polycyclic 3- to 12-membered heterocycle, –OR^7, –SR^7, halogen, –NR^7R^8, –NO_2, –CF_3, or –CN;

R^7 and R^8 are independently, at each occurrence, –H, –D, –C_1-C_6alkyl, –C_2-C_6alkenyl, –C_4-C_8cycloalkenyl, –C_2-C_6alkynyl, –C_3-C_8cycloalkyl, –OR^b, or a monocyclic or polycyclic 3- to 12-membered heterocycle, wherein each alkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkyl, or heterocycle is optionally substituted with one or more –OH, –SH, –NH_2, –NO_2, or –CN;

m is independently, at each occurrence, 1, 2, 3, 4, 5 or 6; and

n is independently, at each occurrence, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.

2. The compound of claim 1, wherein the compound is Formula I:



I

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof, wherein:

A is 5- to 12-membered monocyclic or polycyclic heterocycloalkyl, aryl, or heteroaryl;

Y^1 is –S– or a direct bond;

Y^2 is –NR^a–, –$(CR^a_2)_m$–, –C(O)–, –$C(R^a)_2NH$–, –$(CR^a_2)_mO$–, –$C(O)N(R^a)$–, –$N(R^a)C(O)$–, –$S(O)_2N(R^a)$–, –$N(R^a)S(O)_2$–, –$N(R^a)C(O)N(R^a)$–, –$N(R^a)C(S)N(R^a)$–, –C(O)O–, –OC(O)–, –$OC(O)N(R^a)$–, –$N(R^a)C(O)O$–, –$C(O)N(R^a)O$–, –$N(R^a)C(S)$–,

–C(S)N(R^a)–, or –OC(O)O–; wherein the bond on the left side of Y^2, as drawn, is bound to the pyrazine ring and the bond on the right side of the Y^2 moiety is bound to R^3;

R^1 is independently, at each occurrence, –H, –D, –C_1-C_6alkyl, –C_2-C_6alkenyl, –C_4-C_8cycloalkenyl, –C_2-C_6alkynyl, –C_3-C_8cycloalkyl, –OH, halogen, –NO_2, –CN, –NR^5R^6, –SR^5, –$S(O)_2NR^5R^6$, –$S(O)_2R^5$, –$NR^5S(O)_2NR^5R^6$, –$NR^5S(O)_2R^6$, –$S(O)NR^5R^6$, –$S(O)R^5$, –$NR^5S(O)NR^5R^6$, –$NR^5S(O)R^6$, –$C(O)R^5$, or –CO_2R^5, wherein each alkyl, alkenyl, cycloalkenyl, alkynyl, or cycloalkyl is optionally substituted with one or more –OH, –NO_2, oxo, –CN, −R^5, –OR^5, –NR^5R^6, −SR^5, –$S(O)_2NR^5R^6$, –$S(O)_2R^5$, –$NR^5S(O)_2NR^5R^6$, –$NR^5S(O)_2R^6$, –$S(O)NR^5R^6$, –$S(O)R^5$, –$NR^5S(O)NR^5R^6$, –$NR^5S(O)R^6$, heterocycle, aryl, or heteroaryl;

R^2 is independently –OH, –CN, –C_1-C_6alkyl, –C_2-C_6alkenyl, –C_4-C_8cycloalkenyl, –C_2-C_6alkynyl, –C_3-C_8cycloalkyl, aryl, heterocyclyl containing 1-5 heteroatoms selected from the group consisting of N, S, P, and O, or heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, S, P, and O; wherein each alkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkyl, heterocyclyl, or heteroaryl is optionally substituted with one or more –OH, halogen, –NO_2, oxo, –CN, −R^5, –OR^5, –NR^5R^6, −SR^5, –$S(O)_2NR^5R^6$, –$S(O)_2R^5$, –$NR^5S(O)_2NR^5R^6$, –$NR^5S(O)_2R^6$, –$S(O)NR^5R^6$, –$S(O)R^5$, –$NR^5S(O)NR^5R^6$, –$NR^5S(O)R^6$, heterocycle, aryl, or heteroaryl; and wherein the heterocyclyl or heteroaryl is not attached via a nitrogen atom;

R^a is independently, at each occurrence, –H, –D, –OH, –C_3-C_8cycloalkyl, or –C_1-C_6alkyl, wherein each alkyl or cycloalkyl is optionally substituted with one or more –NH_2, wherein 2 R^a, together with the carbon atom to which they are both attached, can combine to form a 3- to 8-membered cycloalkyl;

R^b is independently, at each occurrence, –H, –D, –C_1-C_6alkyl, –C_3-C_8cycloalkyl, –C_2-C_6alkenyl, or heterocyclyl containing 1-5 heteroatoms selected from the group consisting of N, S, P, and O; wherein each alkyl, cycloalkyl, alkenyl, or heterocycle is optionally substituted with one or more –OH, halogen, –NO_2, oxo, –CN, −R^5, –OR^5, –NR^5R^6, −SR^5, –$S(O)_2NR^5R^6$, –$S(O)_2R^5$, –$NR^5S(O)_2NR^5R^6$, –$NR^5S(O)_2R^6$, –$S(O)NR^5R^6$, –$S(O)R^5$, –$NR^5S(O)NR^5R^6$, –$NR^5S(O)R^6$, heterocycle, aryl, or heteroaryl;

R^3 is independently –C_1-C_6alkyl or a 3- to 12-membered monocyclic or polycyclic heterocycle, wherein each alkyl or heterocycle is optionally substituted with one or more –C_1-C_6alkyl, –OH, or –NH_2; or

R^3 can combine with R^a to form a 3- to 12-membered monocyclic or polycyclic heterocycle or a 5- to 12-membered spiroheterocycle, wherein each heterocycle or spiroheterocycle is optionally substituted with $–C_1$-C_6alkyl, –OH, or $–NH_2$;

R^4 is independently –H, –D, or $–C_1$-C_6alkyl, wherein each alkyl is optionally substituted with one or more –OH, $–NH_2$, halogen, or oxo; or

R^a and R^4, together with the atom or atoms to which they are attached, can combine to form a monocyclic or polycyclic C_3-C_{12}cycloalkyl or a monocyclic or polycyclic 3- to 12-membered heterocycle, wherein the cycloalkyl or heterocycle is optionally substituted with oxo;

R^5 is independently –H, –D, $–C_1$-C_6alkyl, $–C_2$-C_6alkenyl, $–C_4$-C_8cycloalkenyl, $–C_2$-C_6alkynyl, $–C_3$-C_8cycloalkyl, a monocyclic or polycyclic 3- to 12-membered heterocycle, $–OR^7$, $–SR^7$, $–NR^7R^8$, $–NO_2$, or –CN;

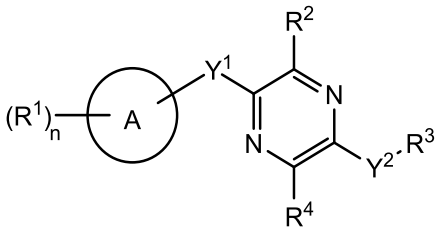
R^6 is independently –H, –D, $–C_1$-C_6alkyl, $–C_2$-C_6alkenyl, $–C_4$-C_8cycloalkenyl, $–C_2$-C_6alkynyl, $–C_3$-C_8cycloalkyl, a monocyclic or polycyclic 3- to 12-membered heterocycle, $–OR^7$, $–SR^7$, halogen, $–NR^7R^8$, $–NO_2$, or –CN;

R^7 and R^8 are independently, at each occurrence, –H, –D, $–C_1$-C_6alkyl, $–C_2$-C_6alkenyl, $–C_4$-C_8cycloalkenyl, $–C_2$-C_6alkynyl, $–C_3$-C_8cycloalkyl, or a monocyclic or polycyclic 3- to 12-membered heterocycle, wherein each alkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkyl, or heterocycle is optionally substituted with one or more –OH, –SH, $–NH_2$, $–NO_2$, or –CN;

m is independently, at each occurrence, 1, 2, 3, 4, 5 or 6; and

n is independently, at each occurrence, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.

3. The compound of claim 1, wherein the compound is Formula I-W6:



I-W6

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof, wherein:

A is a 5- to 12-membered monocyclic or polycyclic heteroaryl;

Y^1 is –S–;

Y^2 is $–NR^a–$; wherein the bond on the left side of Y^2, as drawn, is bound to the pyrazine ring and the bond on the right side of the Y^2 moiety, as drawn, is bound to R^3;

R^3 is combined with R^a to form a 3- to 12-membered monocyclic or polycyclic heterocycle or a 5- to 12-membered spiroheterocycle, wherein each heterocycle or spiroheterocycle is optionally substituted with one or more $–C_1$-C_6alkyl, –OH, $–NH_2$, heteroaryl, heterocyclyl, $-(CH_2)_nNH_2$, $-COOR^b$, $-CONHR^b$, $-CONH(CH_2)_nCOOR^b$, $-NHCOOR^b$, $-CF_3$, $-CHF_2$, or $-CH_2F$;

R^1 is independently, at each occurrence, –H, $–C_1$-C_6alkyl, –OH, halogen, $–NO_2$, –CN, $–NR^5R^6$, $–SR^5$, $–C(O)R^5$, or $–CO_2R^5$;

R^2 is $–C_1$-C_6alkyl;

R^b is independently, at each occurrence, –H or $–C_1$-C_6alkyl;

R^4 is –H, $–C_1$-C_6alkyl, $–C_1$-C_6haloalkyl, $–C_1$-C_6hydroxyalkyl, $–CF_2OH$, –CHFOH, $–C(O)NH(CH_2)_nOH$, $–C(O)NH(CH_2)_nR^b$, $-C(O)R^b$,$–C(O)NR^5R^6$, or –OH, wherein alkyl is optionally substituted with one or more –OH, $–NH_2$, halogen, or oxo; or

R^5 and R^6 are each independently, at each occurrence, –H or $–C_1$-C_6alkyl; and

n is independently, at each occurrence, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.

4. The compound of any of claims 1-2, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof, wherein Y^1 is –S–.

5. The compound of any of claims 1-2 or 4, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof, wherein Y^2 is $–(NR^a)–$.

6. The compound of claim 5, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof, wherein R^3 is $–C_1$-C_6alkyl, which is optionally substituted with one or more $–C_1$-C_6alkyl, –OH, $–NH_2$, $–OR^b$, $–NHR^b$, $–(CH_2)_nOH$, heterocyclyl, or spiroheterocyclyl.

7. The compound of claim 5, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof, wherein R^3 and R^a together with the atoms to which they are attached combine to form a 5- to 12-membered spiroheterocycle, which is optionally substituted with $–C_1$-C_6alkyl, –OH, $–NH_2$, heteroaryl, heterocyclyl, $-(CH_2)_nNH_2$, $-COOR^b$, $-CONHR^b$, $-CONH(CH_2)_nCOOR^b$, $-NHCOOR^b$, $-CF_3$, $-CHF_2$, or $-CH_2F$.

8. The compound of claim 7, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof, wherein 5- to 12-membered spiroheterocycle comprises piperidinyl.

9. The compound of claim 8, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof, wherein 5- to 12-membered spiroheterocycle comprises an oxygen.

10. The compound of claim 5, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof, wherein R^3 and R^a together with the atom to which they are attached combine to form a 3- to 12-membered monocyclic heterocycle, which is optionally substituted with $–C_1$-C_6alkyl, –OH, $–NH_2$, heteroaryl, heterocyclyl, $-(CH_2)_nNH_2$, $-COOR^b$, $-CONHR^b$, $-CONH(CH_2)_nCOOR^b$, $-NHCOOR^b$, $-CF_3$, $-CHF_2$, or $-CH_2F$.

11. The compound of claim 5, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof, wherein R^a and R^4 together with the atom to which they are attached combine to form a monocyclic or polycyclic 3- to 12-membered heterocycle.

12. The compound of any of claims 1-2 or 4, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof, wherein Y^2 is $–(CR^a{}_2)_m–$.

13. The compound of claim 12, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof, wherein R^3 and R^a together with the atoms to which they are attached combine to form a 3- to 12-membered monocyclic heterocycle, which is optionally substituted with $–C_1$-C_6alkyl, –OH, $–NH_2$, heteroaryl, heterocyclyl, $-(CH_2)_nNH_2$, $-COOR^b$, $-CONHR^b$, $-CONH(CH_2)_nCOOR^b$, $-NHCOOR^b$, $-CF_3$, $-CHF_2$, or $-CH_2F$.

14. The compound of any of claims 1-2 or 4, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof, wherein Y^2 is $–C(O)–$, $–C(R^a)_2NH–$, or $–C(O)N(R^a)–$.

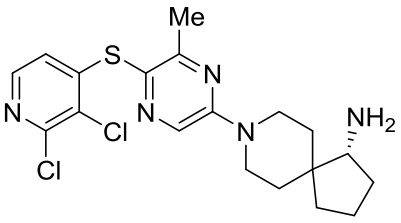
15. The compound of any of claims 1-2, 4, 12 or 14, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof, wherein R^3 and R^a together with the atoms to which they are attached combine to form a 3- to 12-membered polycyclic heterocycle,

which is optionally substituted with $–C_1$-C_6alkyl, –OH, $–NH_2$, heteroaryl, heterocyclyl, $-(CH_2)_nNH_2$, $-COOR^b$, $-CONHR^b$, $-CONH(CH_2)_nCOOR^b$, $-NHCOOR^b$, $-CF_3$, $-CHF_2$, or $-CH_2F$.

16. The compound of any of claims 1-2 or 4-15, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof, wherein A is heterocycloalkyl or aryl.

17. The compound of claim 1-2 or 4-15, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof, wherein A is heteroaryl.

18. The compound of claim 2, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof, selected from the group consisting of:



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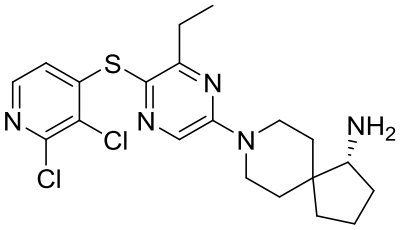

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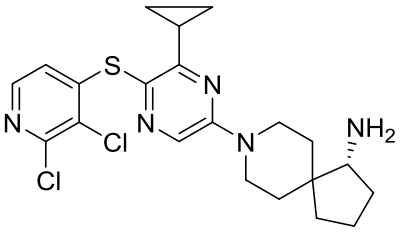

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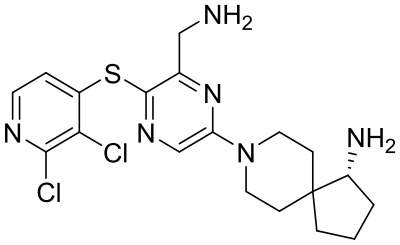

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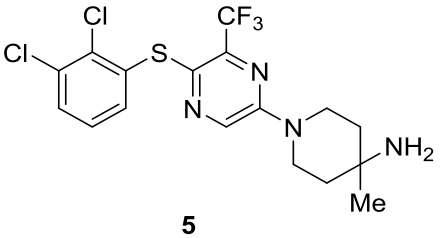

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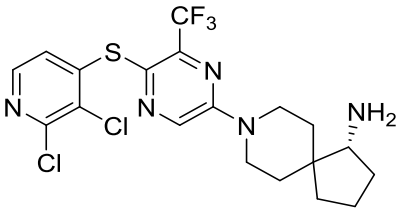

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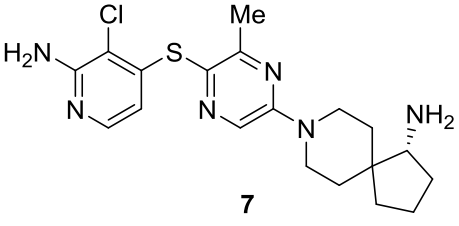

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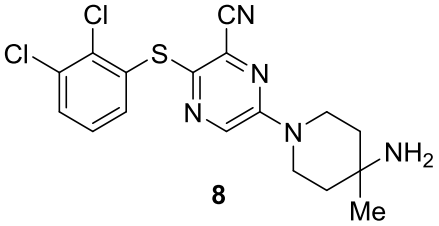

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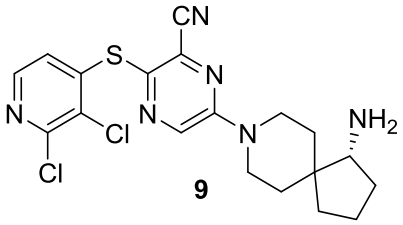

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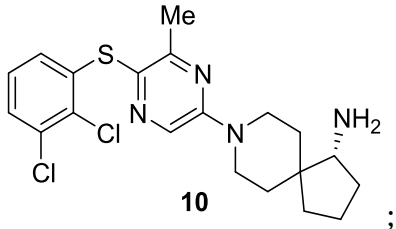

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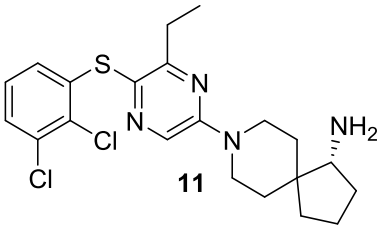

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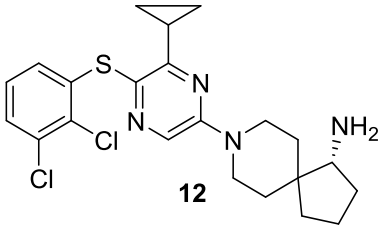

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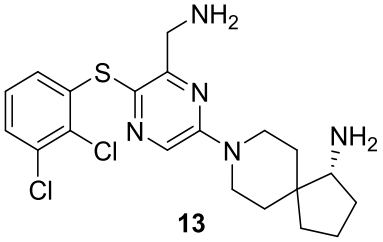

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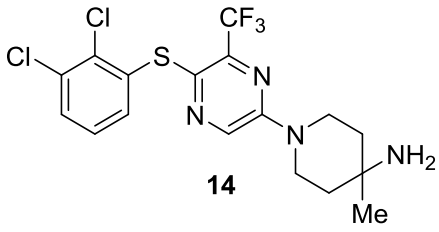

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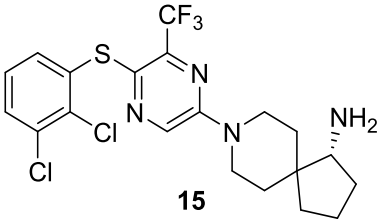

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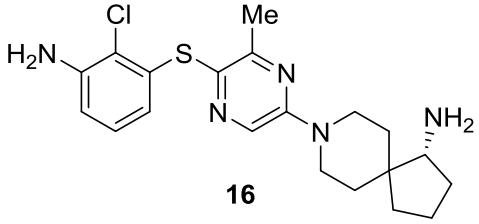

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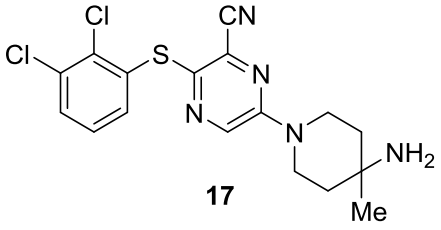

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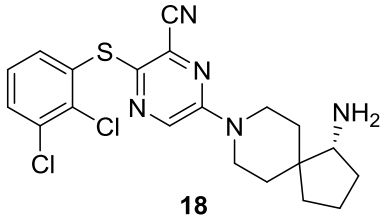

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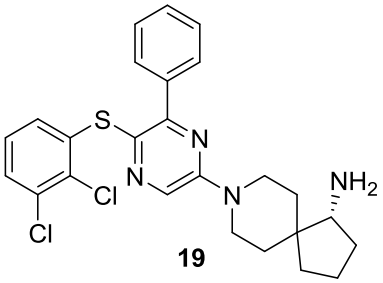

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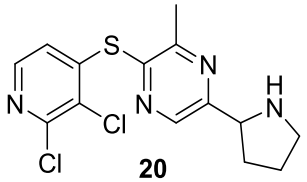

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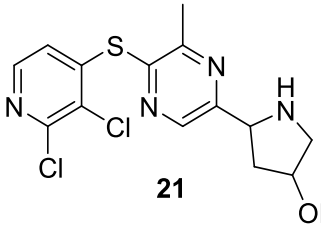

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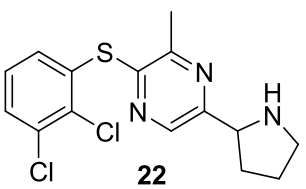

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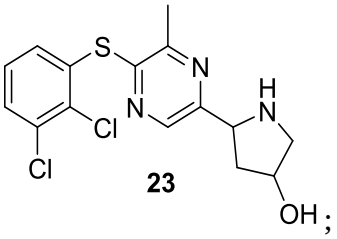

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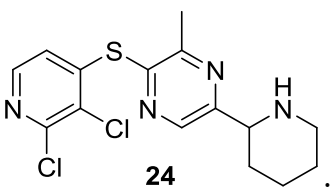

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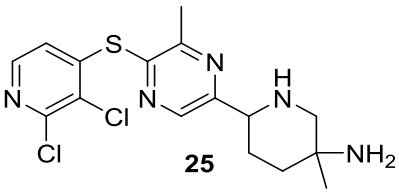

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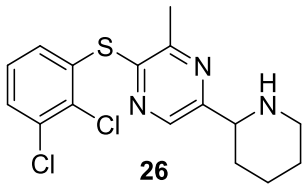

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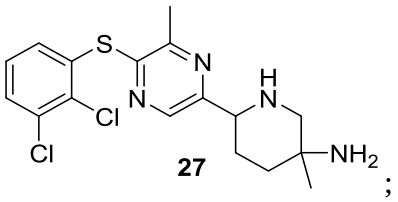

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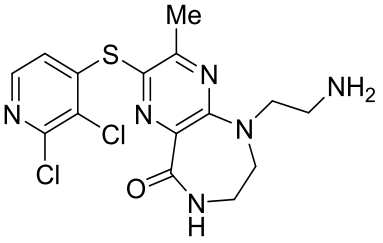

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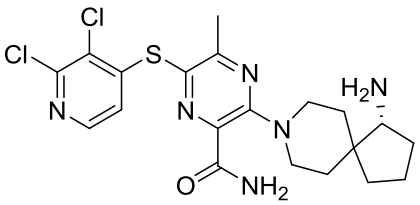

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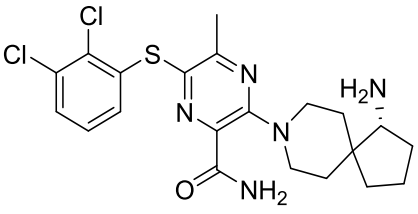

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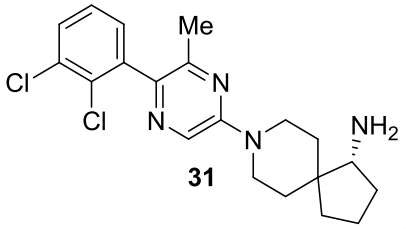

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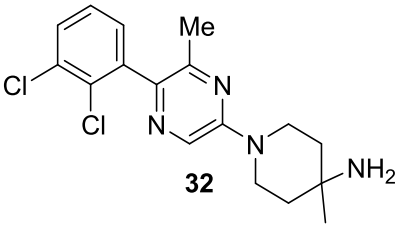

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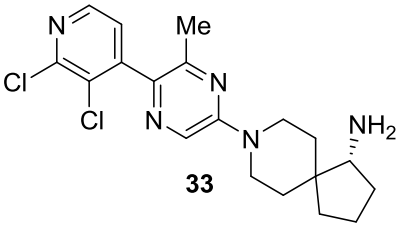

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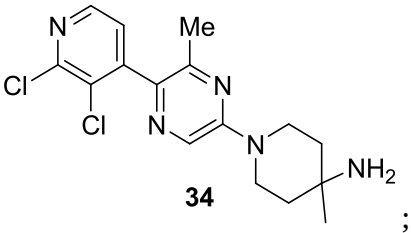

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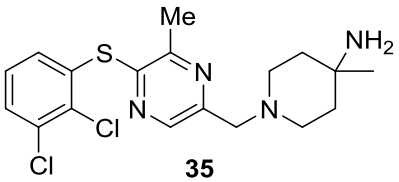

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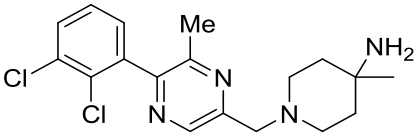

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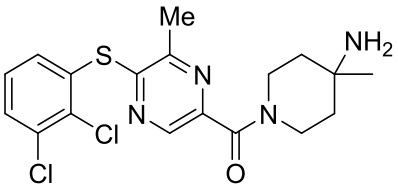

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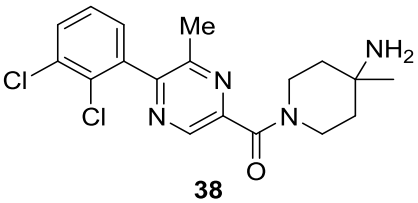

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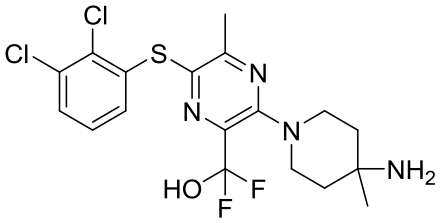

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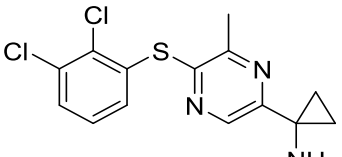

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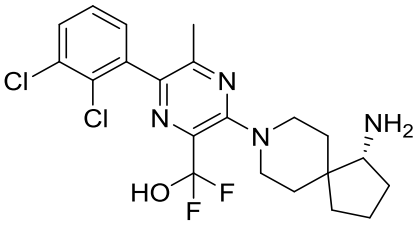

41

; and .

19. A compound of claim 1, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof, selected from the group consisting of:

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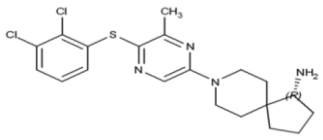
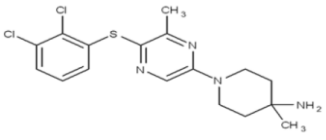
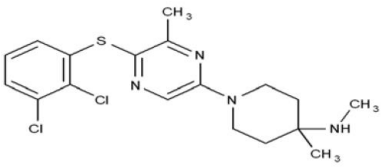
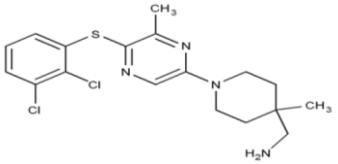
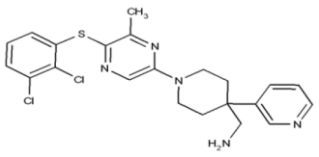
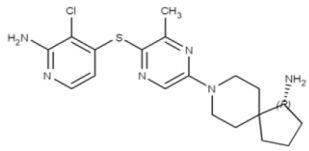
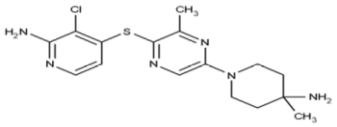
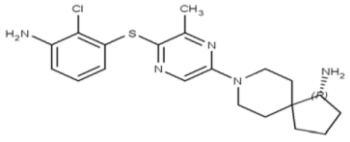
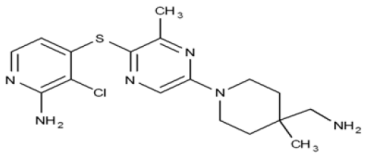
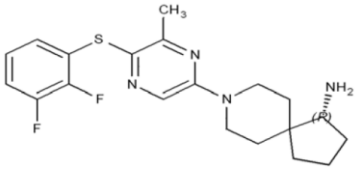
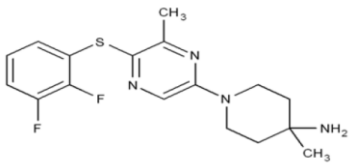
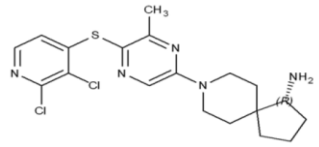
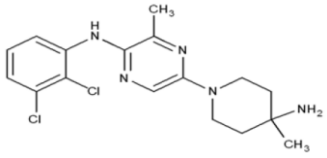
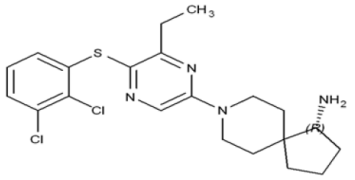
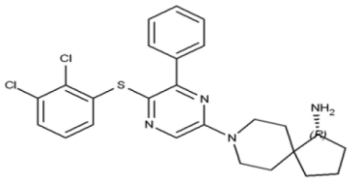
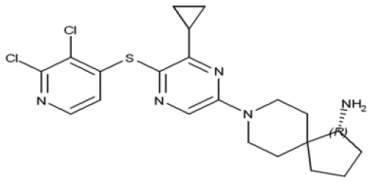
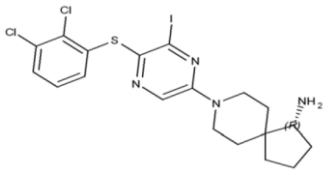
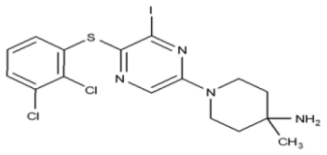
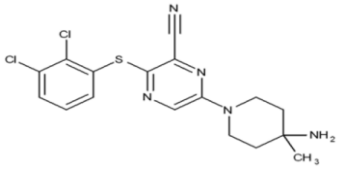
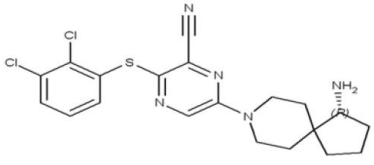
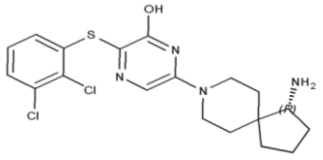
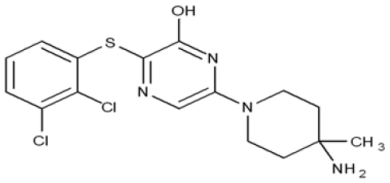
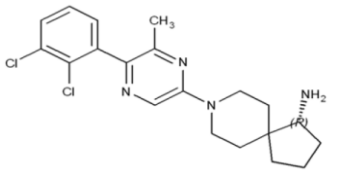
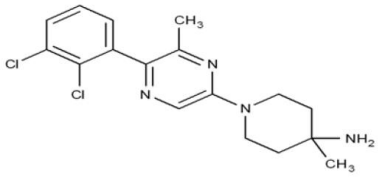
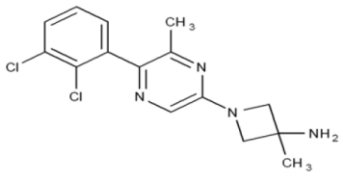
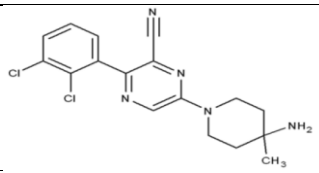
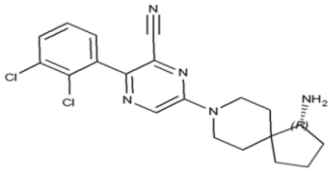
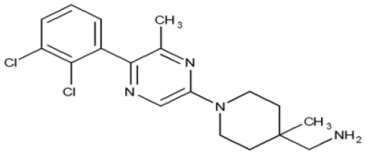
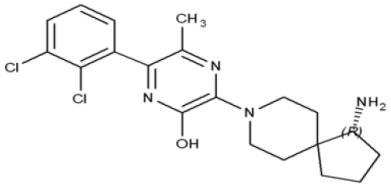
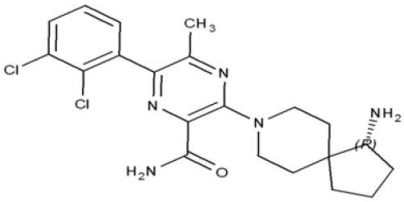
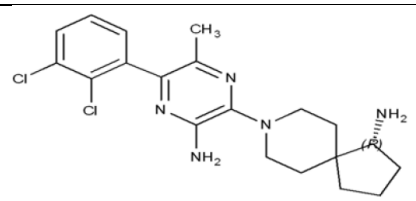
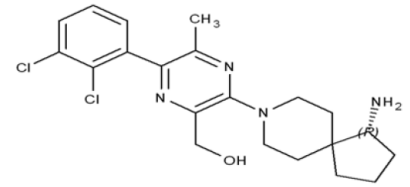
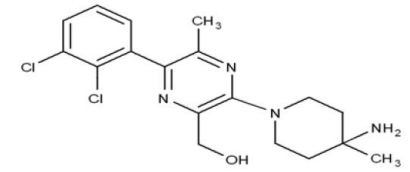
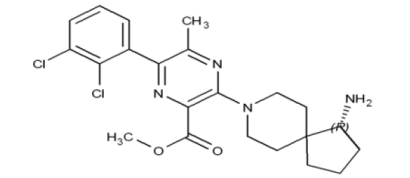
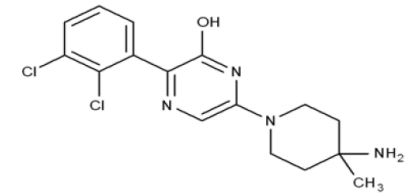
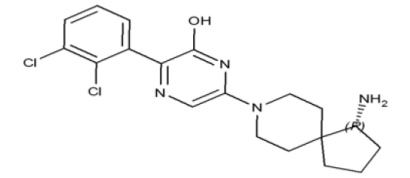
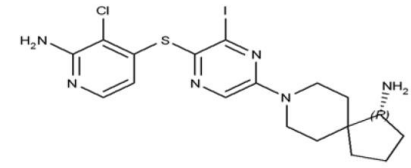
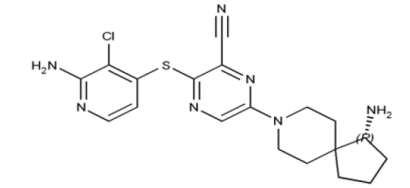
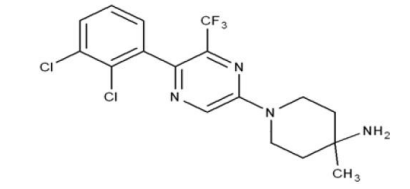
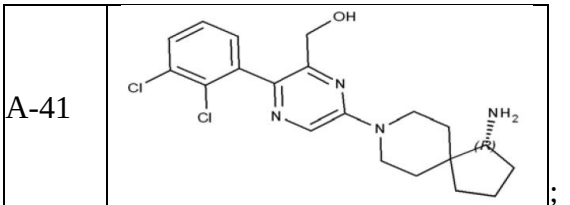
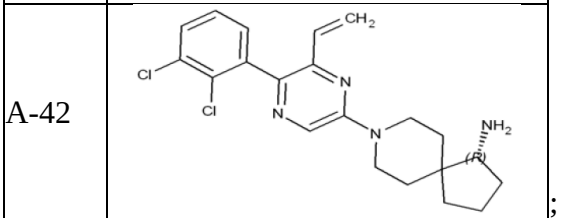
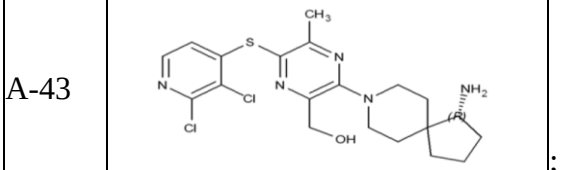
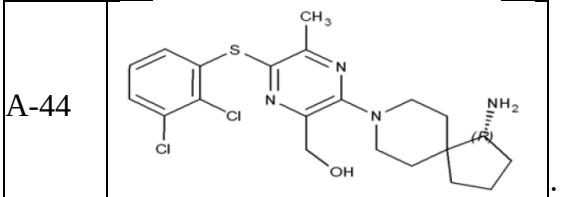
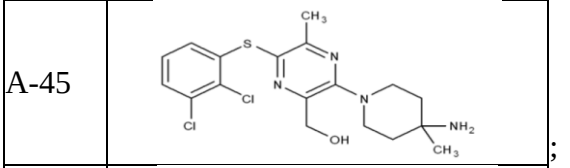
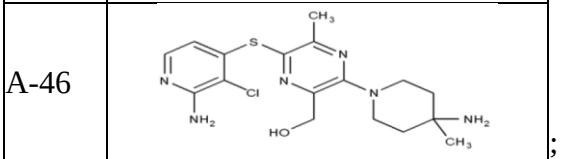
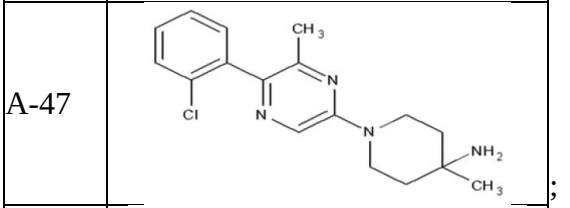
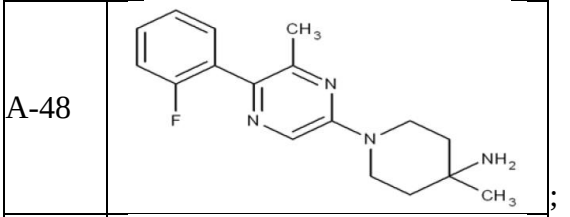
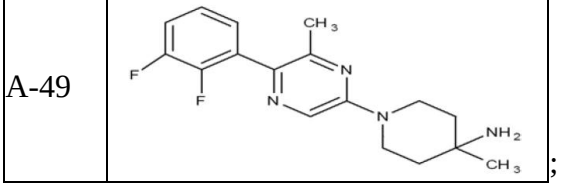
A-1	 ;
A-2	 ;
A-3	 ;
A-4	 ;
A-5	 ;

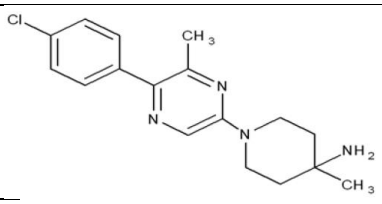
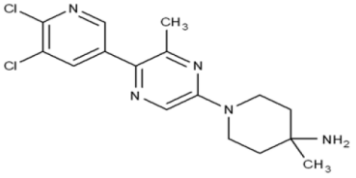
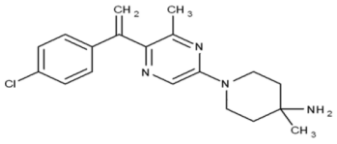
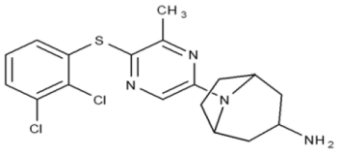
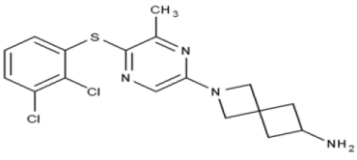
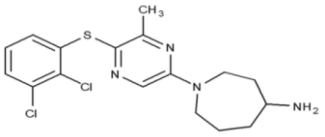
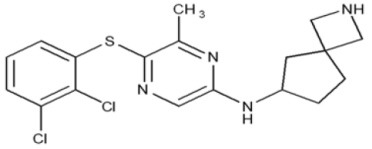
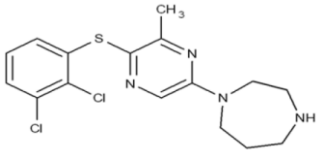
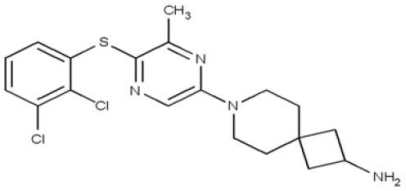
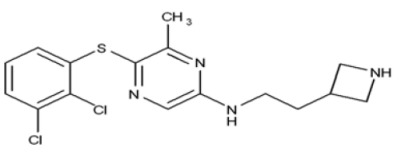
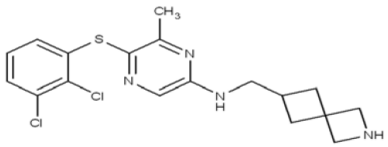
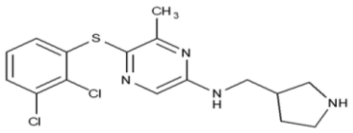
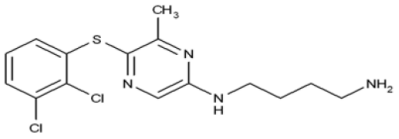
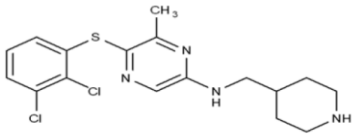
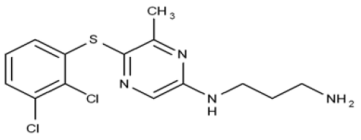
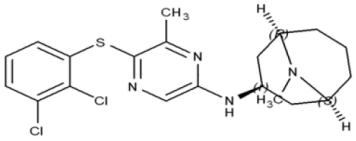
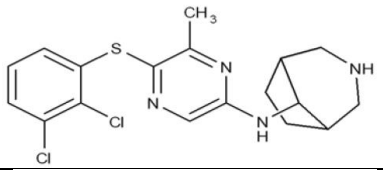
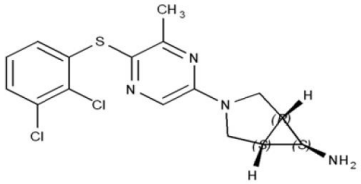
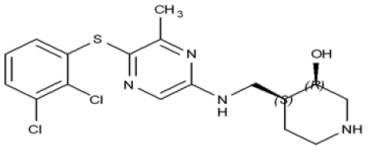
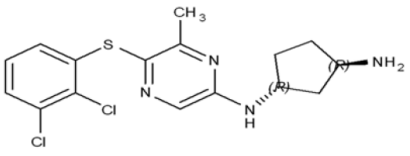
A-6	 ;
A-7	 ;
A-8	 ;
A-9	 ;
A-10	 ;
A-11	 ;

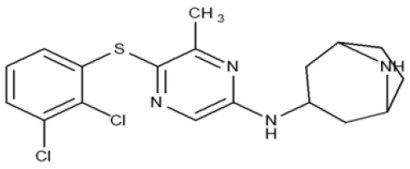
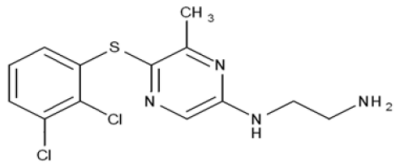
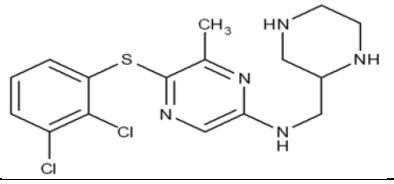
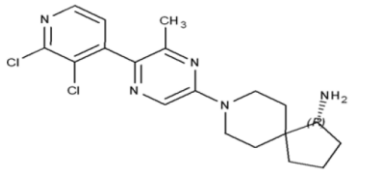
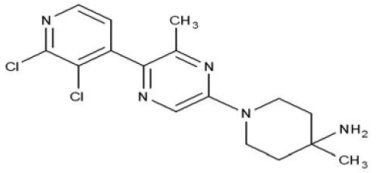
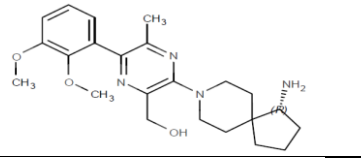
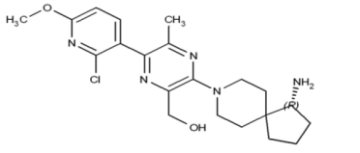
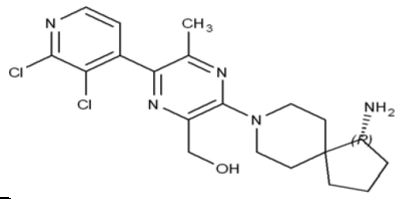
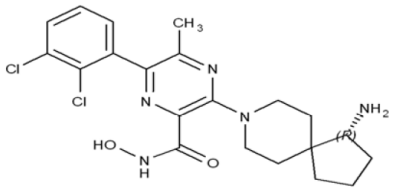
A-12	
A-13	
A-14	
A-15	
A-16	
A-17	
A-18	
A-19	
A-20	
A-21	

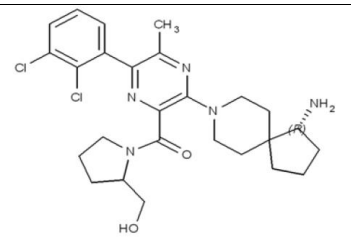
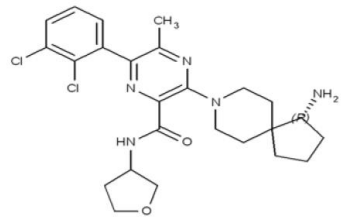
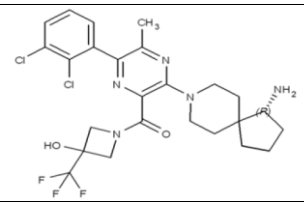
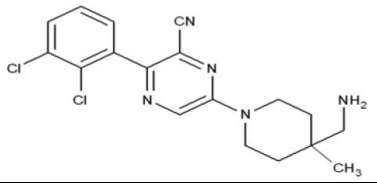
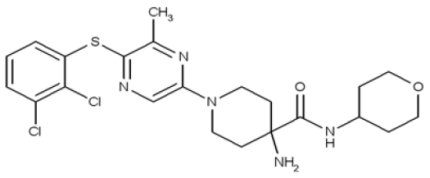
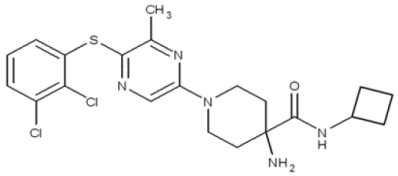
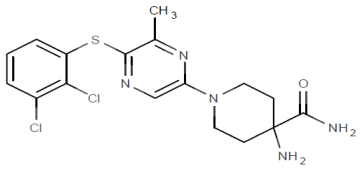
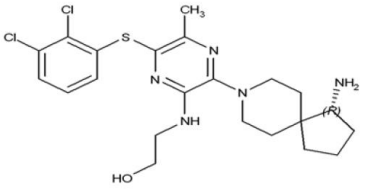
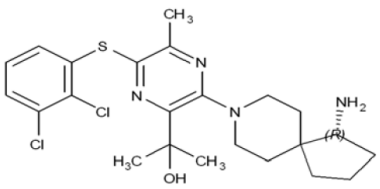
A-22	
A-23	
A-24	
A-25	
A-26	
A-27	
A-28	
A-29	
A-30	

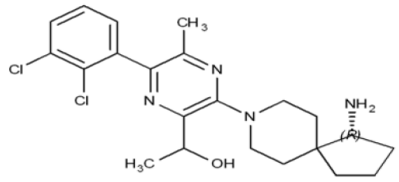
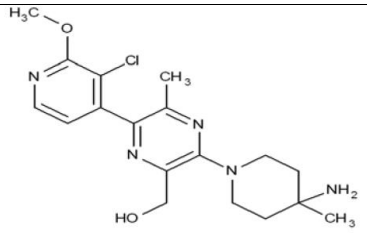
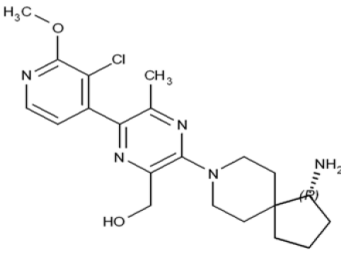
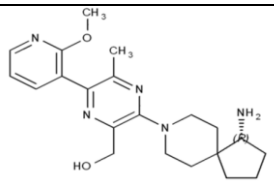
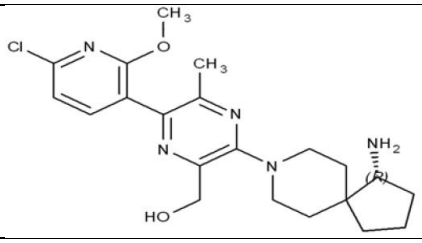
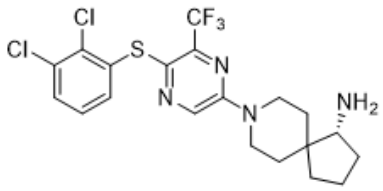
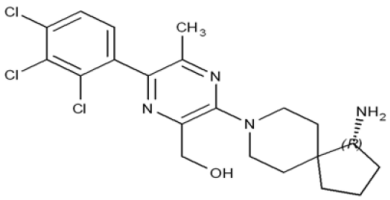
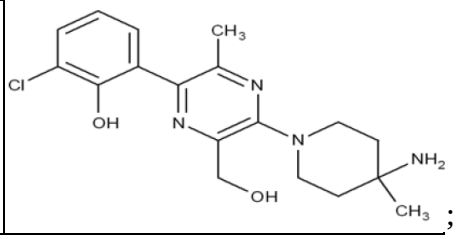
A-31	
A-32	
A-33	
A-35	
A-36	
A-37	
A-38	
A-39	
A-40	

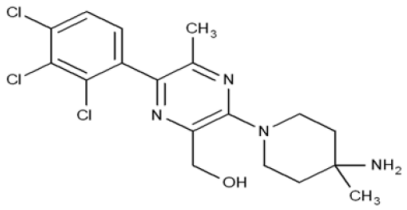
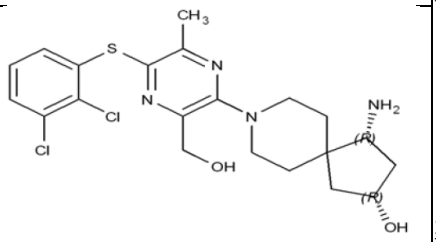
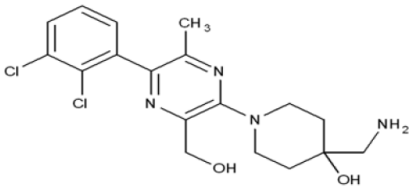
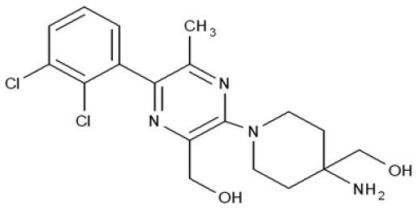
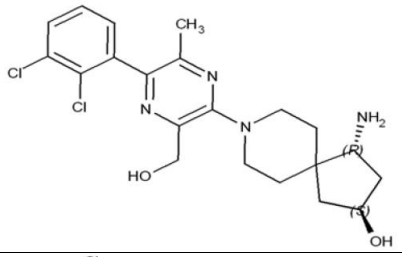
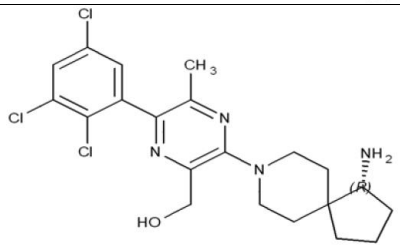
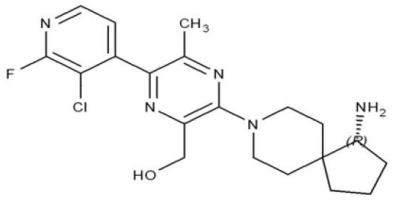
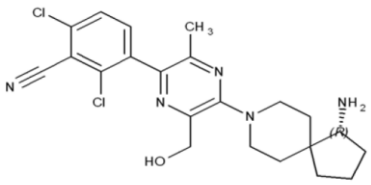
A-41	
A-42	
A-43	
A-44	
A-45	
A-46	
A-47	
A-48	
A-49	

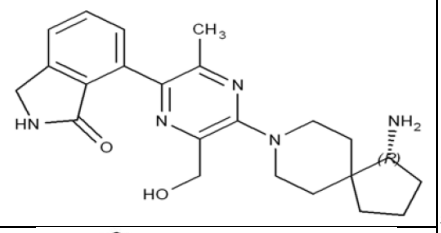
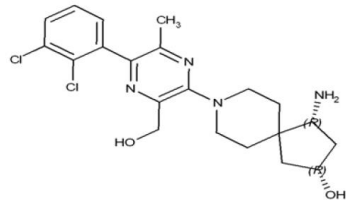
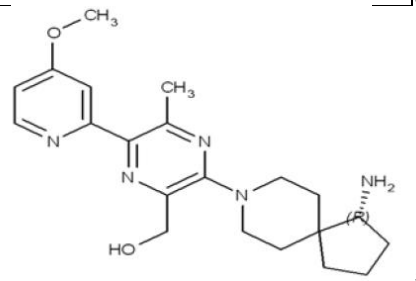
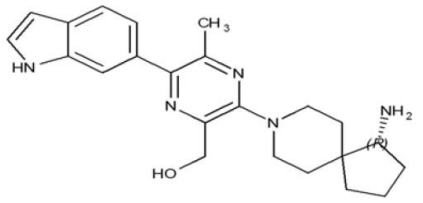
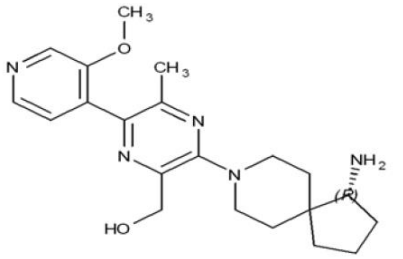
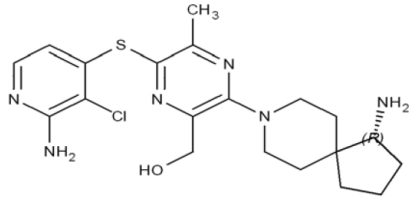
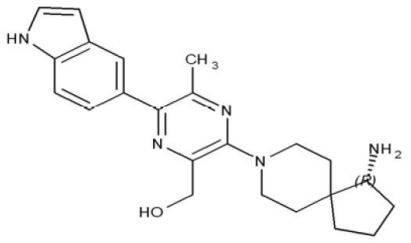
A-50	
A-51	
A-52	
A-53	
A-54	
A-55	
A-56	
A-57	
A-58	
A-59	
A-60	
A-61	
A-62	
A-63	
A-64	
A-65	
A-66	
A-67	
A-68	
A-69	

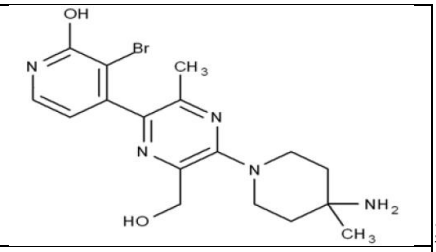
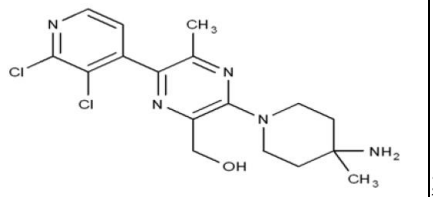
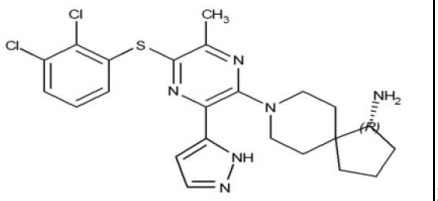
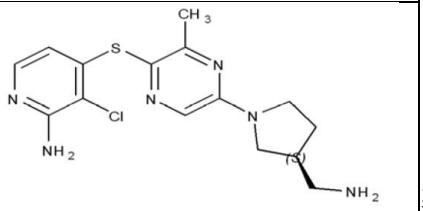
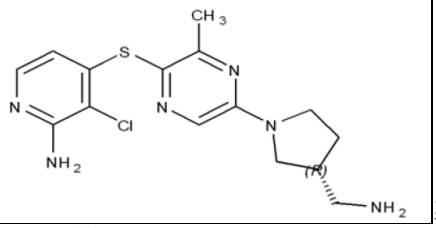
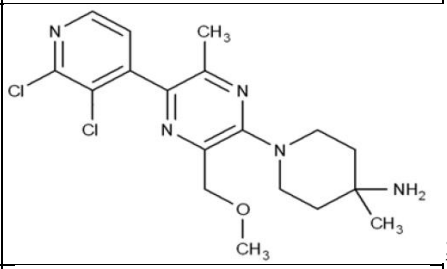
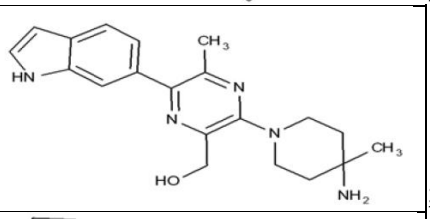
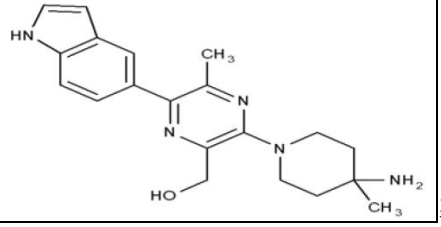
A-70	
A-71	
A-72	
A-73	
A-74	
A-75	
A-76	
A-77	
A-78	

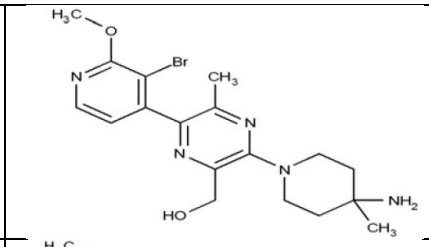
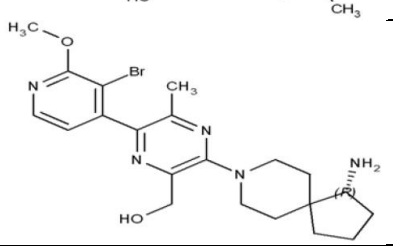
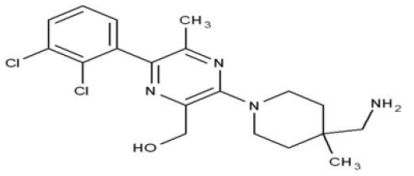
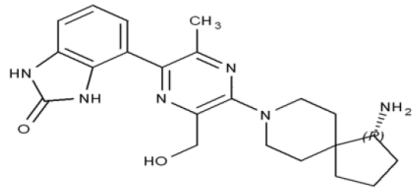
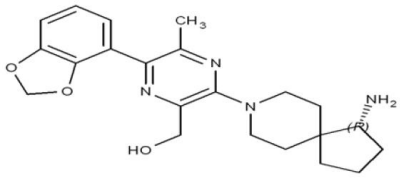
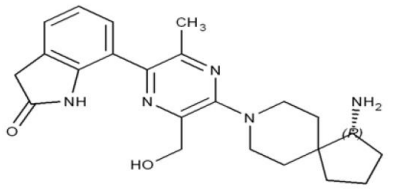
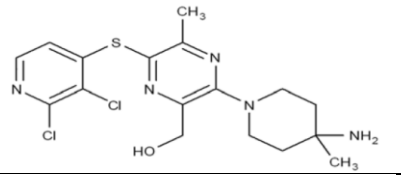
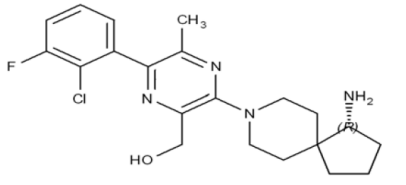
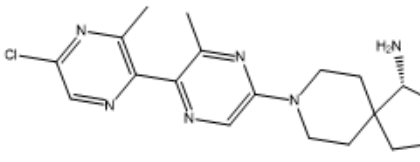
A-79	
A-80	
A-81	
A-82	
A-83	
A-84	
A-85	
A-86	
A-87	

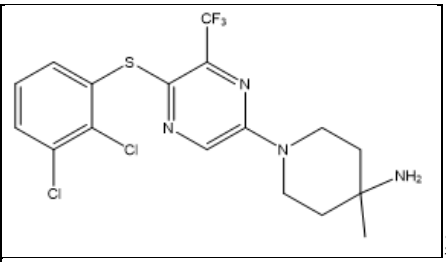
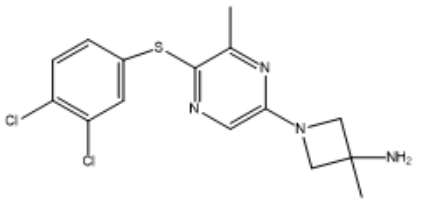
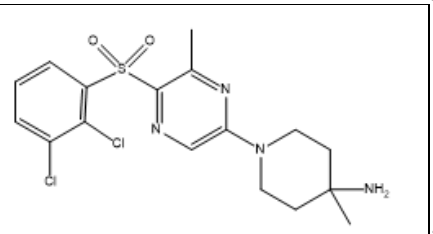
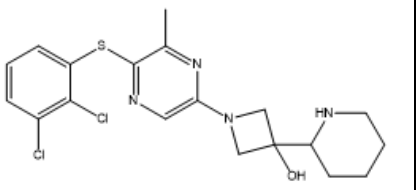
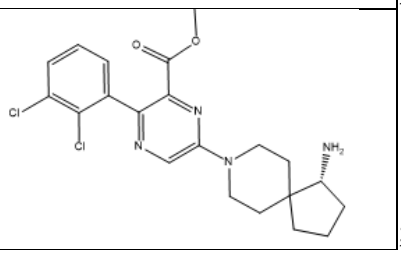
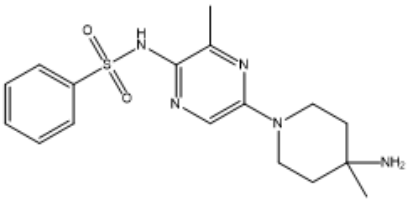
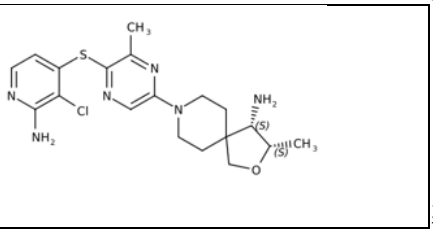
A-88	
A-89	
A-90	
A-91	
A-92	
A-93	
A-94	
A-95	

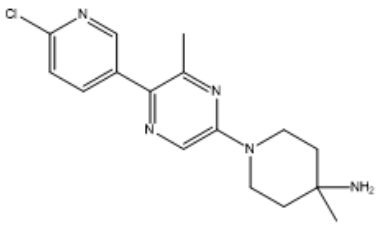
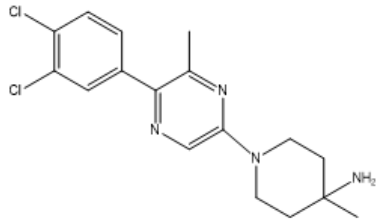
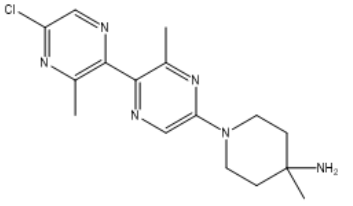
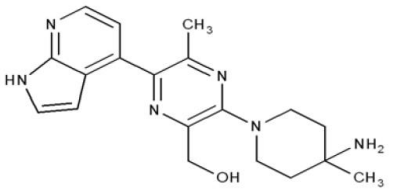
A-96	
A-97	
A-98	
A-99	
A-100	
A-101	
A-102	
A-103	

A-104	
A-105	
A-106	
A-107	
A-108	
A-109	
A-110	

A-111	
A-112	
A-113	
A-114	
A-115	
A-116	
A-117	
A-118	

A-119	
A-120	
A-121	
A-122	
A-123	
A-124	
A-125	
A-126	
A-127	

A-128	
A-129	
A-130	
A-131	
A- 132	
A-133	
A-134	

A-135	
A-136	
A-137	
A-138	

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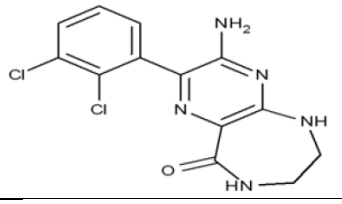
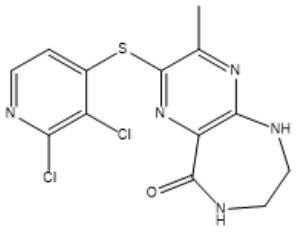
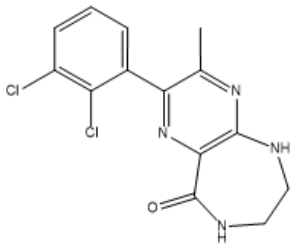
A-139	
A-140	
A-141	

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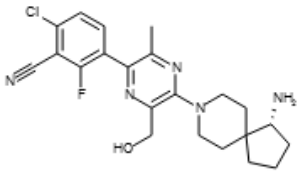
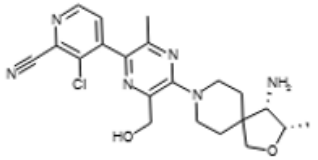
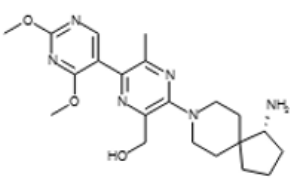
and

20. A compound of claim 1, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof, selected from the group consisting of:

Com-pound #	**Structure**
A-142	
A-143	
A-144	

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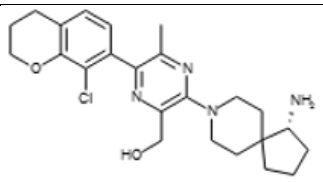
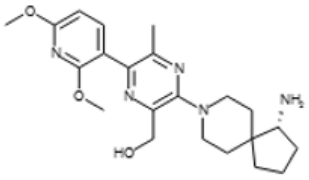
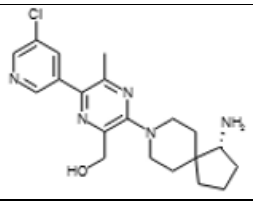
A-145	
A-146	
A-147	

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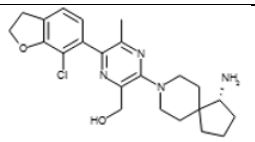
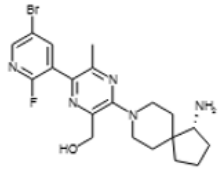
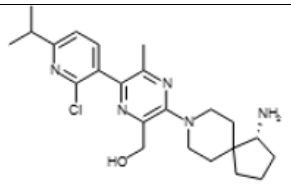
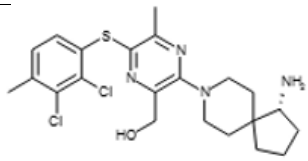
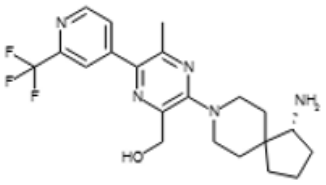
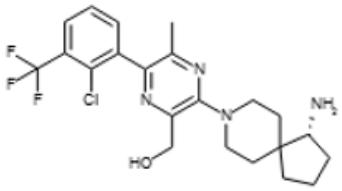
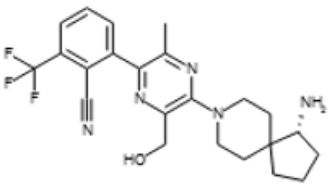
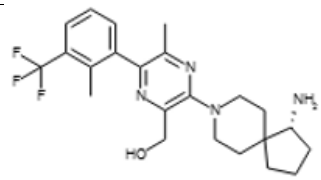
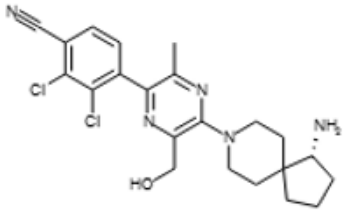
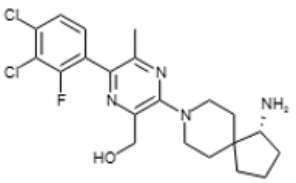
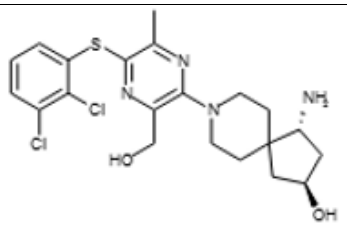
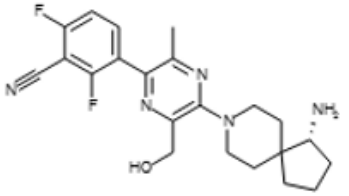
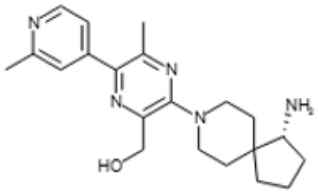
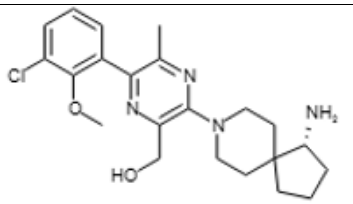
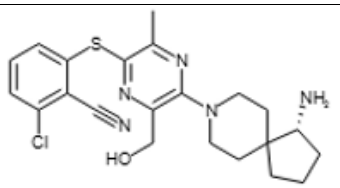
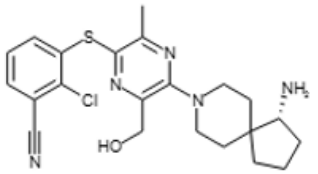
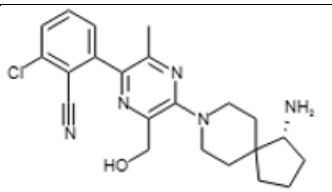
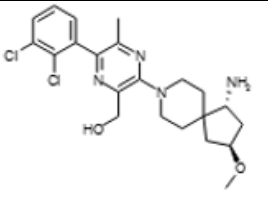
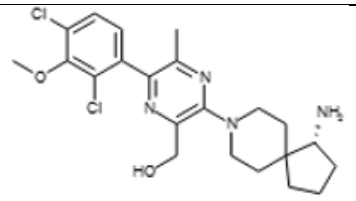
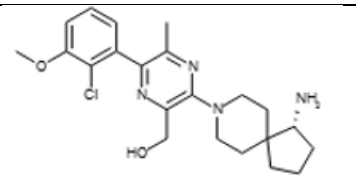
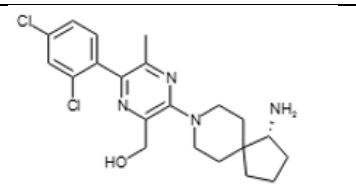
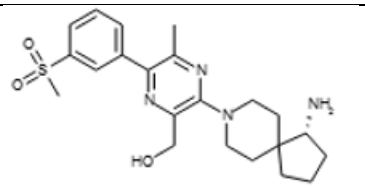
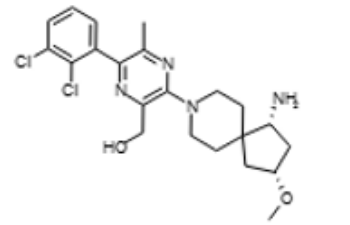
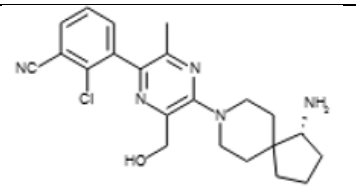
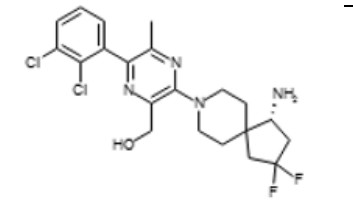
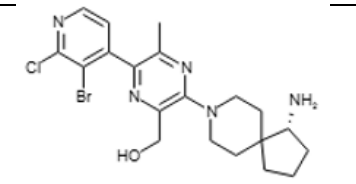
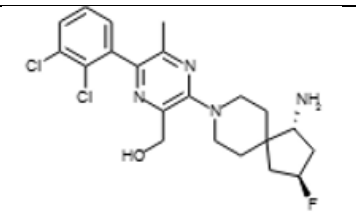
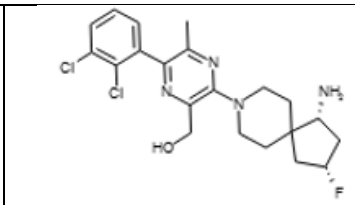
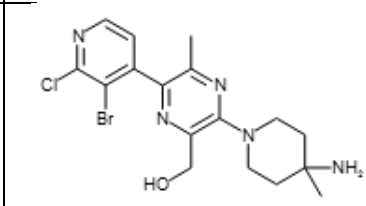
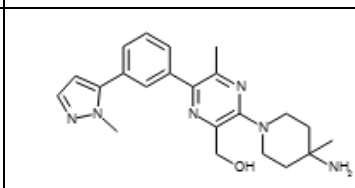
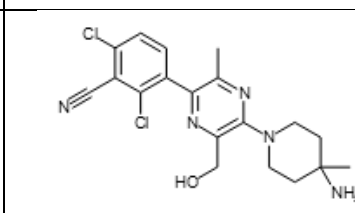
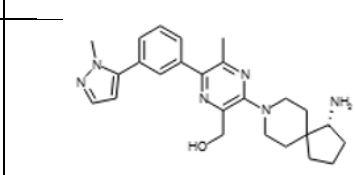
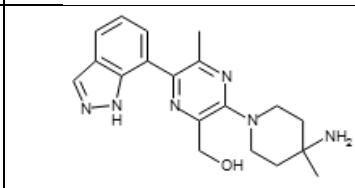
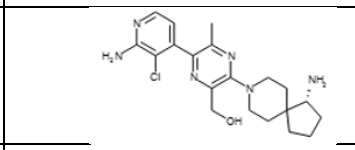
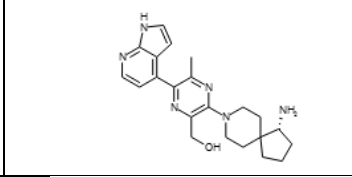
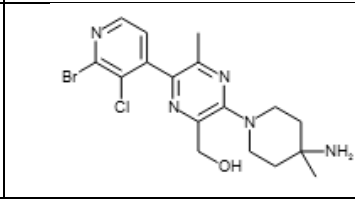
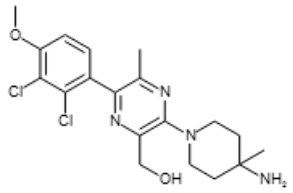
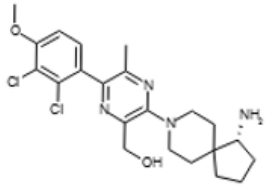
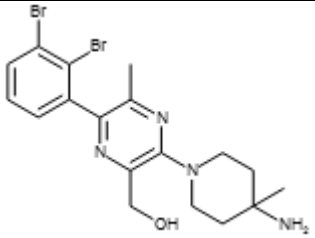
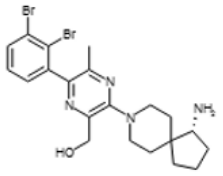
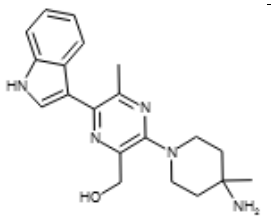
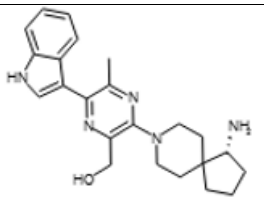
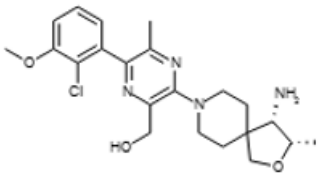
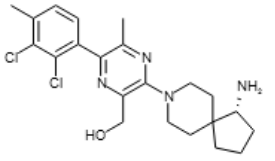
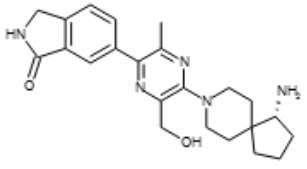
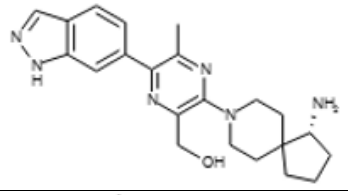
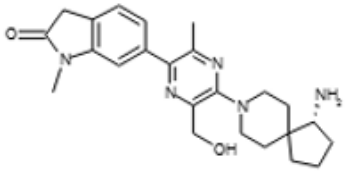
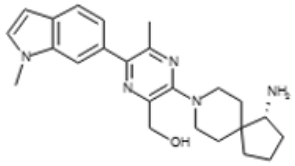
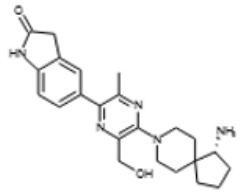
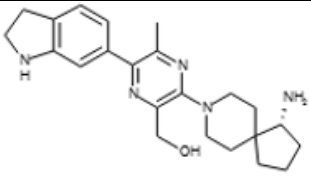
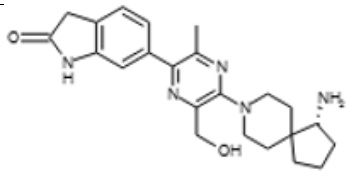
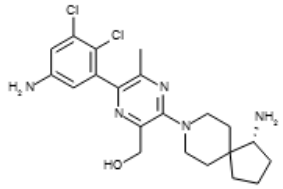
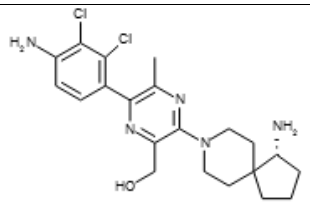
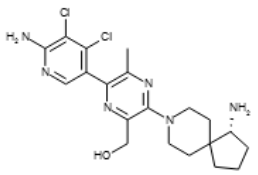
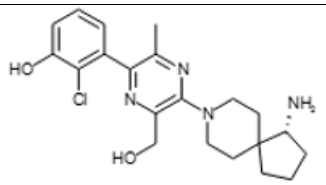
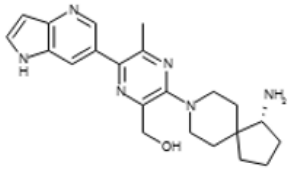
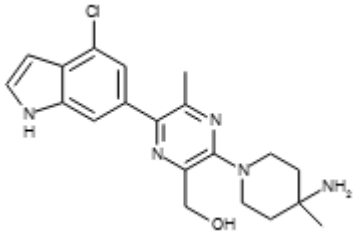
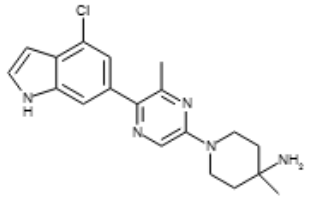
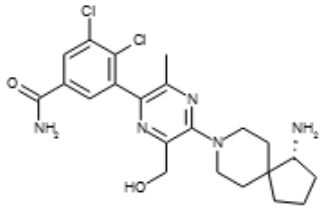
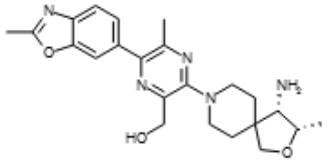
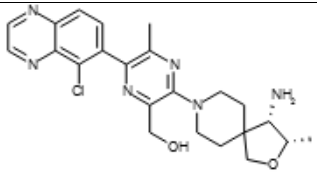
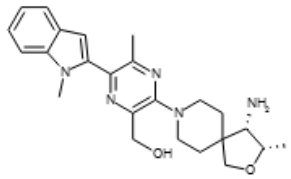
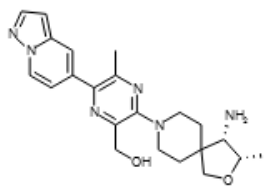
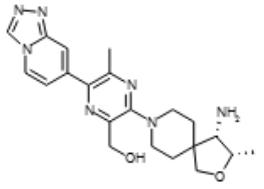
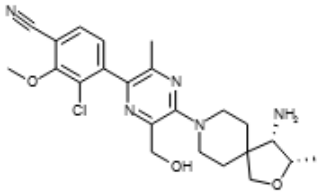
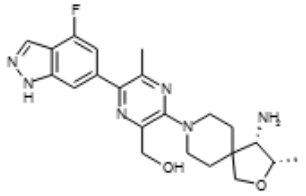
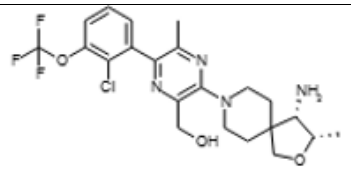
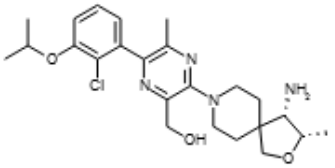
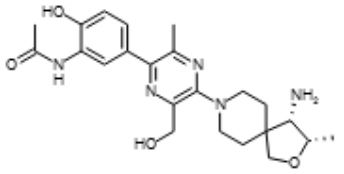
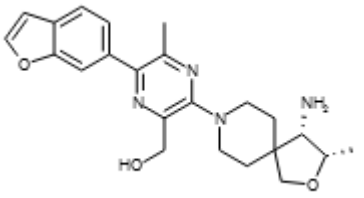
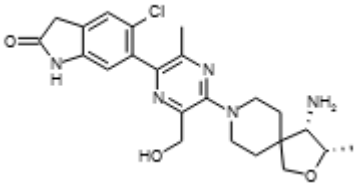
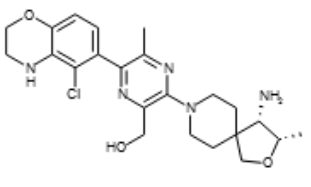
A-148	
A-149	
A-150	
A-151	
A-152	
A-153	
A-154	
A-155	
A-156	
A-157	
A-158	
A-159	
A-160	
A-161	
A-162	
A-163	
A-164	
A-165	

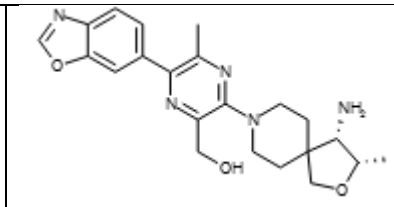
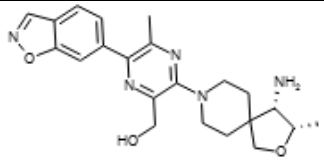
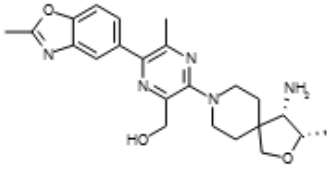
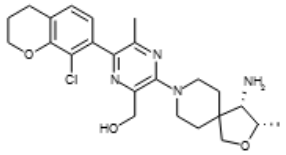
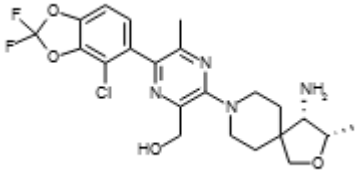
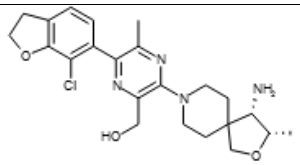
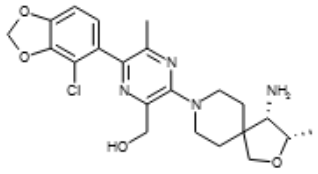
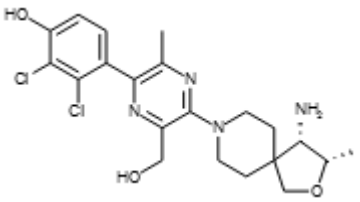
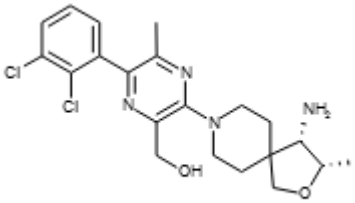
A-166	
A-167	
A-168	
A-169	
A-170	
A-171	
A-172	
A-173	
A-174	
A-175	
A-176	
A-177	
A-178	
A-179	
A-180	
A-181	
A-182	
A-183	

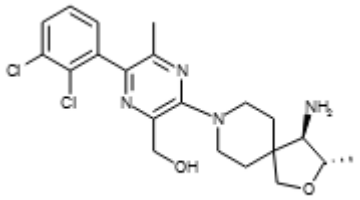
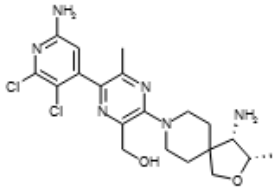
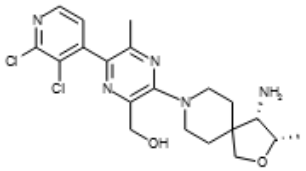
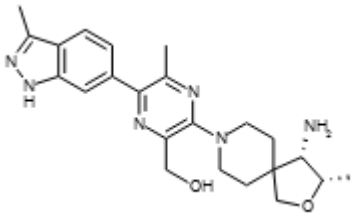
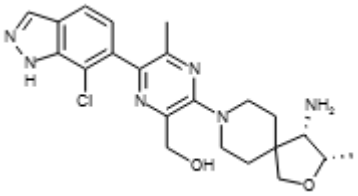
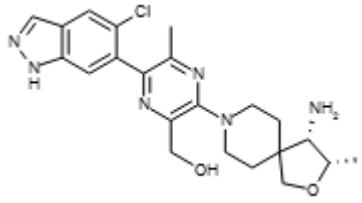
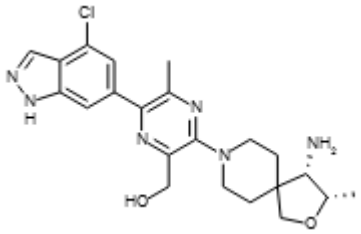
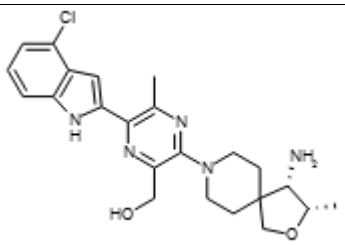
A-184	
A-185	
A-186	
A-187	
A-188	
A-189	
A-190	
A-191	
A-192	

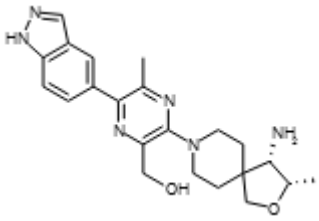
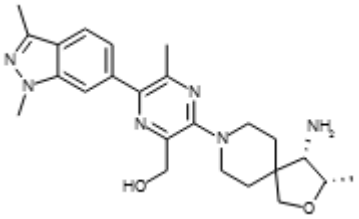
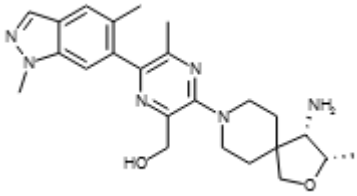
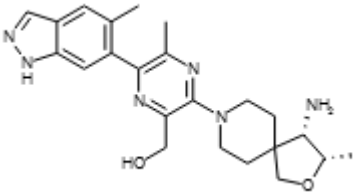
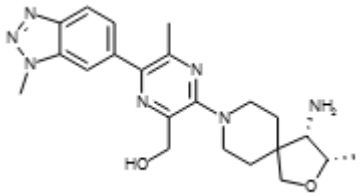
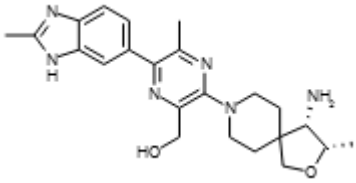
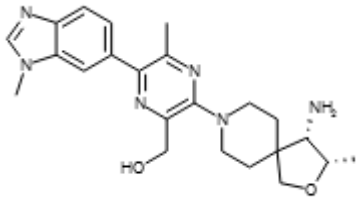
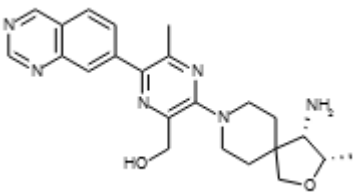
A-193	
A-194	
A-195	
A-196	
A-197	
A-198	
A-199	
A-200	
A-201	

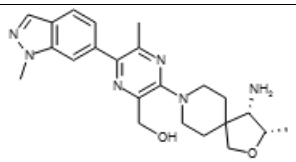
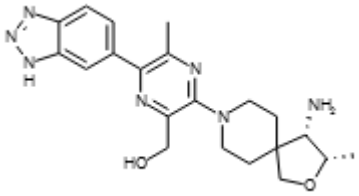
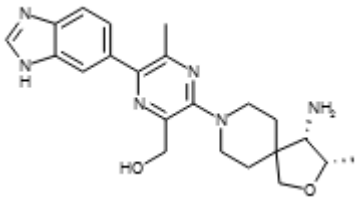
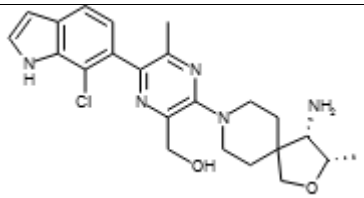
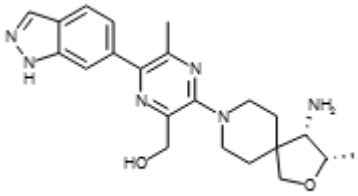
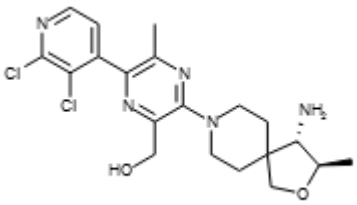
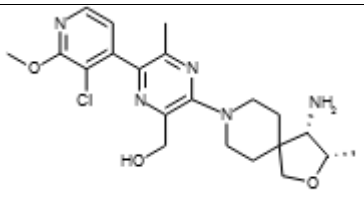
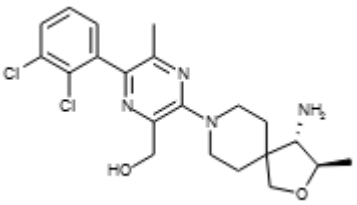
A-202	
A-203	
A-204	
A-205	
A-206	
A-207	
A-208	
A-209	
A-210	

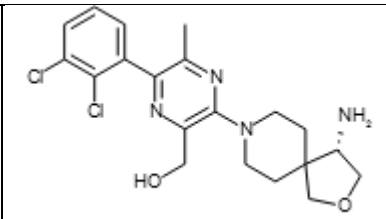
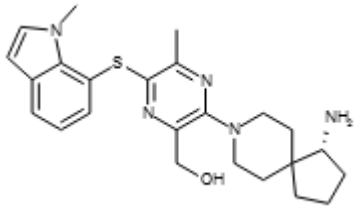
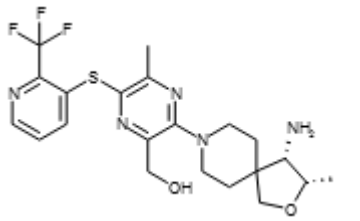
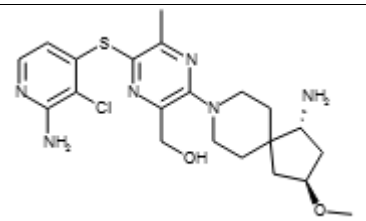
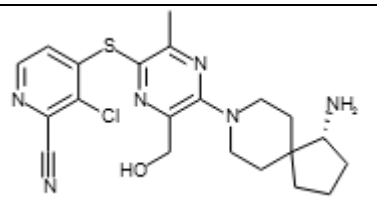
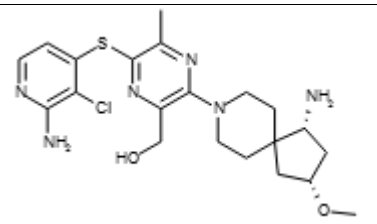
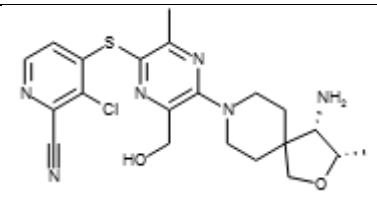
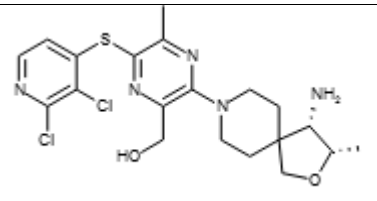
A-211	
A-212	
A-213	
A-214	
A-215	
A-216	
A-217	
A-218	
A-219	

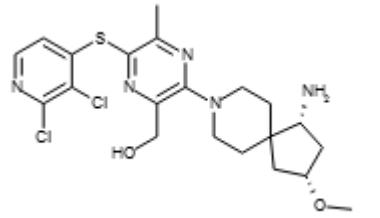
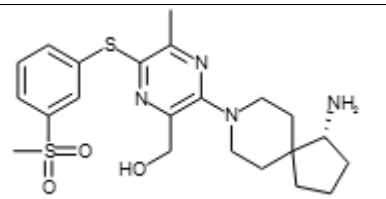
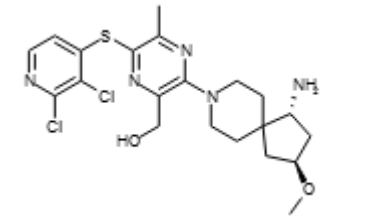
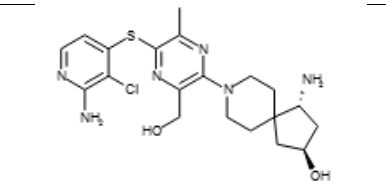
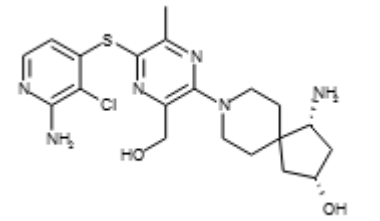
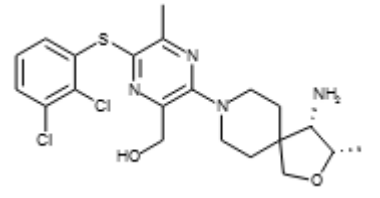
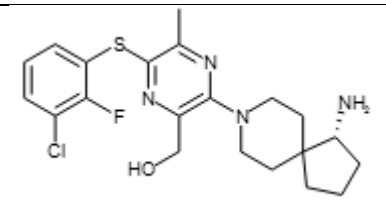
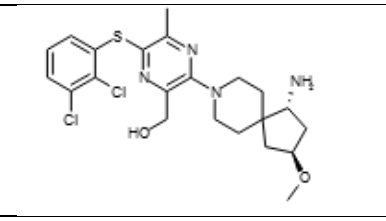
A-220	
A-221	
A-222	
A-223	
A-224	
A-225	
A-226	
A-227	
A-228	

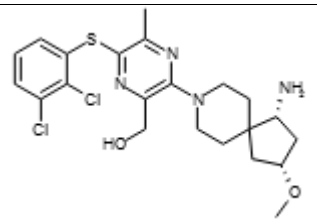
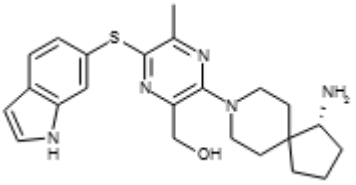
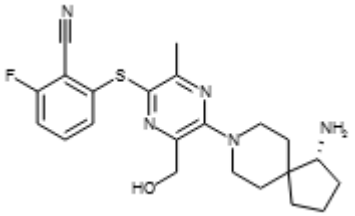
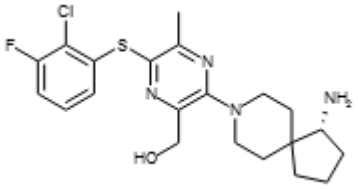
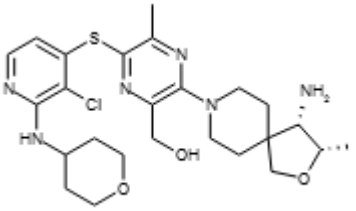
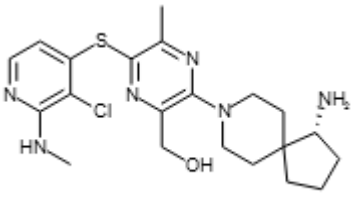
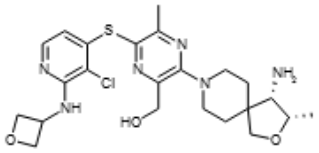
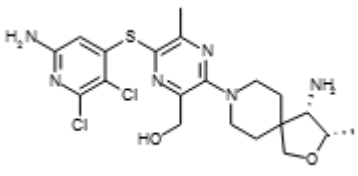
A-229	
A-230	
A-231	
A-232	
A-233	
A-234	
A-235	
A-236	

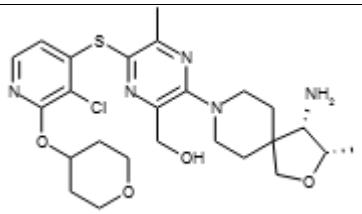
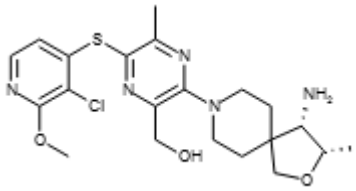
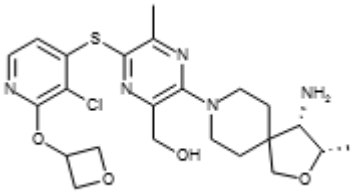
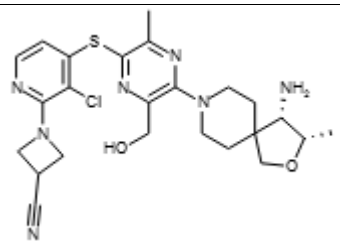
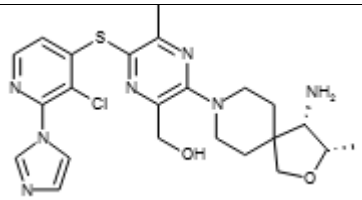
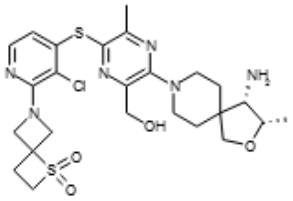
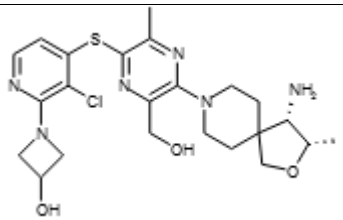
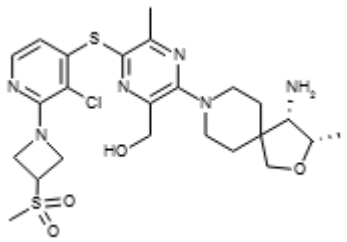
A-237	
A-238	
A-239	
A-240	
A-241	
A-242	
A-243	
A-244	

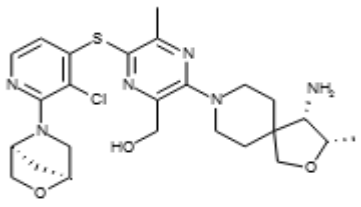
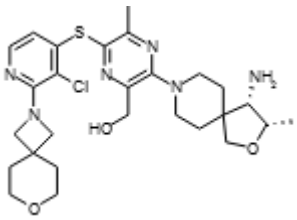
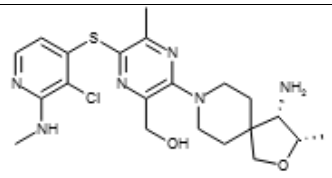
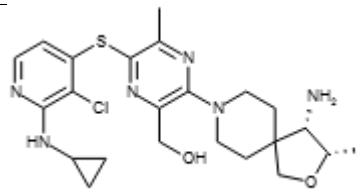
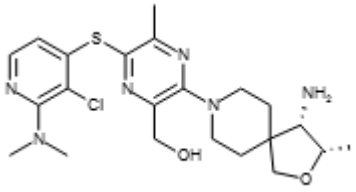
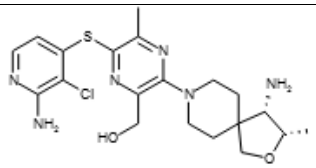
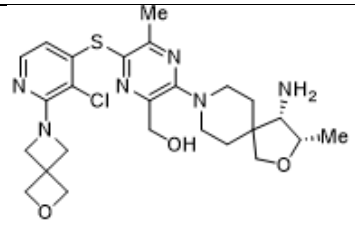
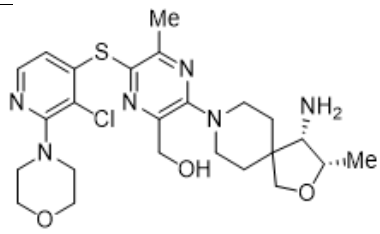
A-245	
A-246	
A-247	
A-248	
A-249	
A-250	
A-251	
A-252	

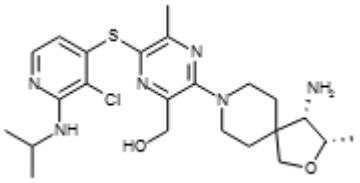
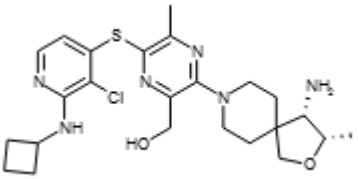
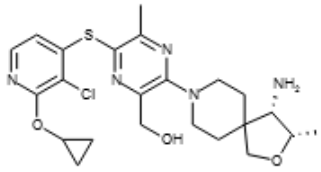
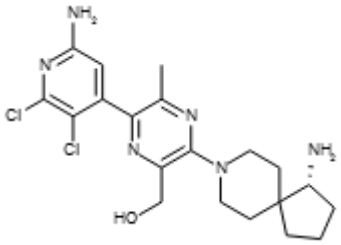
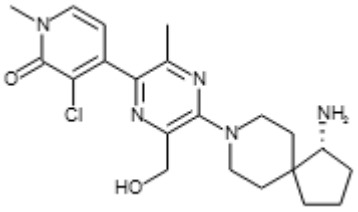
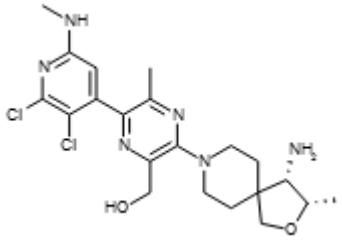
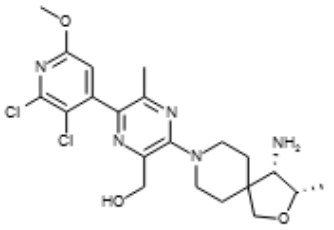
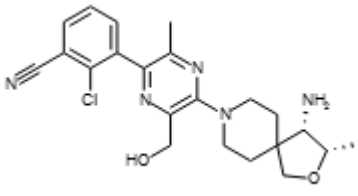
A-253	
A-254	
A-255	
A-256	
A-257	
A-258	
A-259	
A-260	

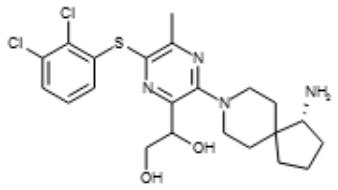
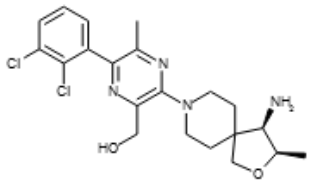
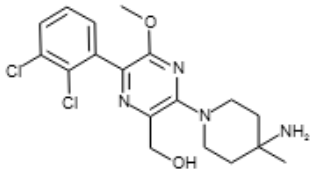
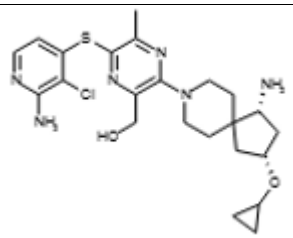
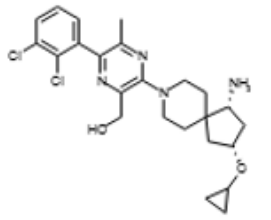
A-261	
A-262	
A-263	
A-264	
A-265	
A-266	
A-267	
A-268	

A-269	
A-270	
A-271	
A-272	
A-273	
A-274	
A-275	
A-276	

A-277	
A-278	
A-279	
A-280	
A-281	
A-282	
A-283	
A-284	

A-285	
A-286	
A-287	
A-288	
A-289	
A-290	
A-291	
A-292	

A-293	
A-294	
A-295	
A-296	
A-297	
A-298	
A-299	
A-300	

A-301	
A-302	
A-303	
A-304	
A-305	

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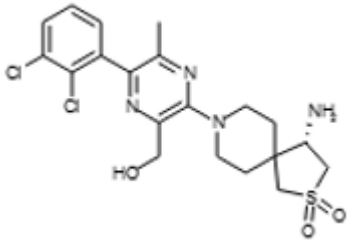
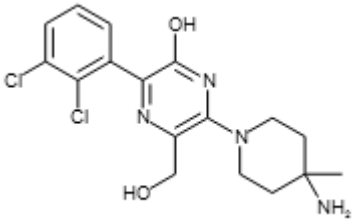
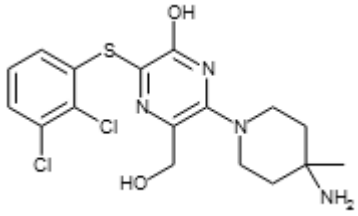
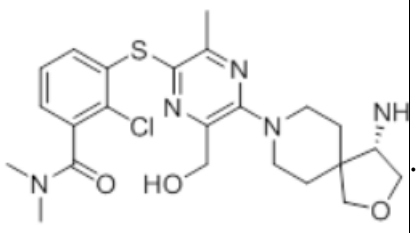
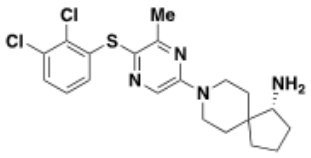
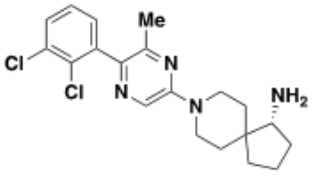
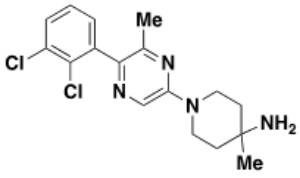
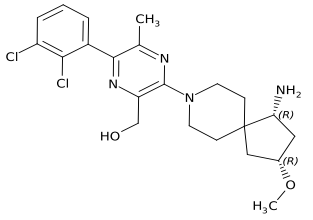
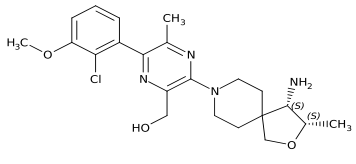
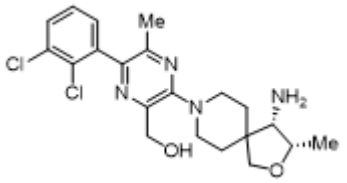
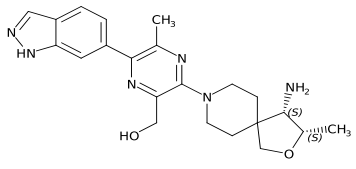
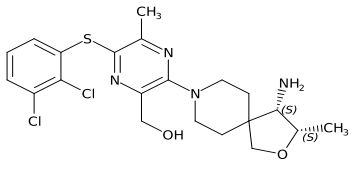
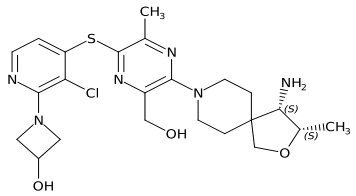
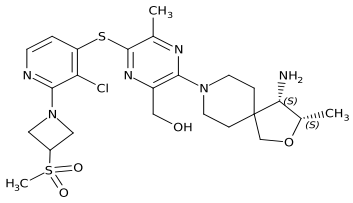
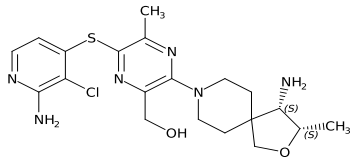
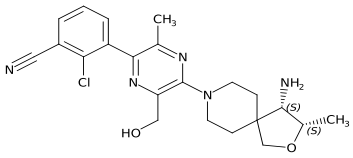
A-306	
A-307	
A-308	
A-309	

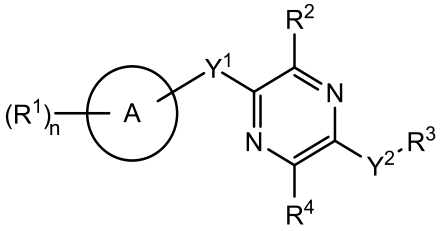
; ; ; and .

21. A compound of claim 1, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof, selected from the group consisting of:

22. A compound of Formula I-W:



I-W

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof, wherein:

A is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are 5- to 12-membered monocyclic or 5- to 12-membered polycyclic;

Y^1 is –S–, a direct bond, –NH–, $–S(O)_2–$, $–S(O)_2–NH–$, $–C(=CH_2)–$, $–CH_2–$, or –S(O)–;

Y^2 is $–NR^a–$, $–(CR^a_2)_m–$,$–C(R^a)_2NH–$, $–(CR^a_2)_mO–$, $–C(O)N(R^a)–$, $–N(R^a)C(O)–$, $–S(O)_2N(R^a)–$, $–N(R^a)S(O)_2–$, $–N(R^a)C(O)N(R^a)–$, $–N(R^a)C(S)N(R^a)–$, $–OC(O)N(R^a)–$, $–N(R^a)C(O)O–$, $–C(O)N(R^a)O–$, $–N(R^a)C(S)–$, or$–C(S)N(R^a)–$; wherein the bond on the left side of Y^2, as drawn, is bound to the pyrazine ring and the bond on the right side of the Y^2 moiety, as drawn, is bound to R^3;

R^1 is independently, at each occurrence, –H, –D, $–C_1$-C_6alkyl, $–C_2$-C_6alkenyl, $–C_4$-C_8cycloalkenyl, $–C_2$-C_6alkynyl, $–C_3$-C_8cycloalkyl, –OH, $–OR^6$, halogen, $–NO_2$, –CN, $–NR^5R^6$, $–SR^5$, $–S(O)_2NR^5R^6$, $–S(O)_2R^5$, $–NR^5S(O)_2NR^5R^6$, $–NR^5S(O)_2R^6$, $–S(O)NR^5R^6$, $–S(O)R^5$, $–NR^5S(O)NR^5R^6$, $–NR^5S(O)R^6$, $–C(O)R^5$,$–CO_2R^5$, $–C(O)NR^5R^6$, $–NR^5C(O)R^6$, monocyclic or polycyclic heterocyclyl, spiroheterocyclyl, heteroaryl, or oxo, wherein each alkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkyl, heterocyclyl, spiroheterocyclyl, or heteroaryl is optionally substituted with one or more –OH, halogen, $–NO_2$, oxo, –CN, $−R^5$, $–OR^5$, $–NR^5R^6$, $−SR^5$, $–S(O)_2NR^5R^6$, $–S(O)_2R^5$, $–NR^5S(O)_2NR^5R^6$, $–NR^5S(O)_2R^6$, $–S(O)NR^5R^6$, $–S(O)R^5$, $–NR^5S(O)NR^5R^6$, $–NR^5S(O)R^6$, heterocycle, aryl, or heteroaryl;

R^2 is independently –OH, –CN, $–C_1$-C_6alkyl, $–C_2$-C_6alkenyl, $–C_4$-C_8cycloalkenyl, $–C_2$-C_6alkynyl, F, Br, I, $–C(O)OR^b$, $–C_3$-C_8cycloalkyl, aryl, heterocyclyl containing 1-5 heteroatoms selected from the group consisting of N, S, P, and O, or heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, S, P, and O; wherein each alkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkyl, heterocyclyl, or heteroaryl is optionally substituted with one or more –OH, halogen, $–NO_2$, oxo, –CN, $−R^5$, $–OR^5$, $–NR^5R^6$, $−SR^5$, $–S(O)_2NR^5R^6$, $–S(O)_2R^5$, $–NR^5S(O)_2NR^5R^6$, $–NR^5S(O)_2R^6$, $–S(O)NR^5R^6$, $–S(O)R^5$, $–NR^5S(O)NR^5R^6$, $–NR^5S(O)R^6$, heterocycle, aryl, or heteroaryl; and wherein the heterocyclyl or heteroaryl is not attached via a nitrogen atom;

R^a is independently, at each occurrence, –H, –D, –OH, $–C_3$-C_8cycloalkyl, $–C_1$-C_6alkyl, 3- to 12-membered heterocyclyl, or $–(CH_2)_n$-aryl, wherein each alkyl or cycloalkyl is optionally substituted with one or more $–NH_2$, or wherein 2 R^a, together with the carbon atom to which they are both attached, can combine to form a 3- to 8-membered cycloalkyl;

R^b is independently, at each occurrence, –H, –D, –OH, $–C_1$-C_6alkyl, $–C_3$-C_8cycloalkyl, $–C_2$-C_6alkenyl, $–(CH_2)_n$-aryl, heterocyclyl containing 1-5 heteroatoms selected from the group consisting of N, S, P, and O, or heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, S, P, and O; wherein each alkyl, cycloalkyl, alkenyl, heterocycle, heteroaryl, or $–(CH_2)_n$-aryl is optionally substituted with one or more –OH, halogen, $–NO_2$, oxo, –CN, $−R^5$, $–OR^5$, $–NR^5R^6$, $−SR^5$, $–S(O)_2NR^5R^6$, $–S(O)_2R^5$, $–NR^5S(O)_2NR^5R^6$, $–NR^5S(O)_2R^6$, $–S(O)NR^5R^6$, $–S(O)R^5$, $–NR^5S(O)NR^5R^6$, $–NR^5S(O)R^6$,

–C(O)NR^{5}R^6, –NR^{5}C(O)R^6, heterocycle, aryl, heteroaryl, –(CH$_2$)$_n$OH, –C$_1$-C$_6$alkyl, –CF$_3$, –CHF$_2$, or –CH$_2$F;

R^3 is combined with R^a to form a 3- to 12-membered polycyclic heterocycle or a 5- to 12-membered spiroheterocycle, wherein each heterocycle or spiroheterocycle is optionally substituted with one or more –C$_1$-C$_6$alkyl, halogen, –OH, –OR^b, –NH$_2$, –NHR^b, heteroaryl, heterocyclyl, –(CH$_2$)$_n$NH$_2$, –(CH$_2$)$_n$OH, –COOR^b, –CONHR^b, –CONH(CH$_2$)$_n$COOR^b, –NHCOOR^b, –CF$_3$, –CHF$_2$, –CH$_2$F, or =O;

R^4 is independently –H, –D, –C$_1$-C$_6$alkyl, –C$_1$-C$_6$haloalkyl, –C$_1$-C$_6$hydroxyalkyl, –CF$_2$OH, –CHFOH, –NH-NHR^5, –NH-OR^5, –O-NR^{5}R^6, –NHC(O)R^5, –NHC(O)NHR^5, –NHS(O)$_2$R^5, –NHS(O)$_2$NHR^5, –S(O)$_2$OH, –C(O)OR^5, –NH(CH$_2$)$_n$OH, –C(O)NH(CH$_2$)$_n$OH, –C(O)NH(CH$_2$)$_n$R^b, –C(O)R^b, –NH$_2$, –OH, –C(O)NR^{5}R^6, –S(O)$_2$NR^{5}R^6, C$_3$-C$_8$cycloalkyl, aryl, heterocyclyl containing 1-5 heteroatoms selected from the group consisting of N, S, P, and O, or heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, S, P, and O, wherein each alkyl, cycloalkyl, or heterocyclyl is optionally substituted with one or more –OH, –NH$_2$, –OR^b, halogen, or oxo; wherein each aryl or heteroaryl is optionally substituted with one or more –OH, –NH$_2$, or halogen; or

R^a and R^4, together with the atom or atoms to which they are attached, can combine to form a monocyclic or polycyclic C$_3$-C$_{12}$cycloalkyl or a monocyclic or polycyclic 3- to 12-membered heterocycle, wherein the cycloalkyl or heterocycle is optionally substituted with oxo; wherein the heterocycle optionally comprises –S(O)$_2$– in the heterocycle;

R^5 and R^6 are independently, at each occurrence, –H, –D, –C$_1$-C$_6$alkyl, –C$_2$-C$_6$alkenyl, –C$_4$-C$_8$cycloalkenyl, –C$_2$-C$_6$alkynyl, –C$_3$-C$_8$cycloalkyl, a monocyclic or polycyclic 3- to 12-membered heterocycle, –OR^7, –SR^7, halogen, –NR^{7}R^8, –NO$_2$, –CF$_3$, or –CN;

R^7 and R^8 are independently, at each occurrence, –H, –D, –C$_1$-C$_6$alkyl, –C$_2$-C$_6$alkenyl, –C$_4$-C$_8$cycloalkenyl, –C$_2$-C$_6$alkynyl, –C$_3$-C$_8$cycloalkyl, –OR^b, or a monocyclic or polycyclic 3- to 12-membered heterocycle, wherein each alkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkyl, or heterocycle is optionally substituted with one or more –OH, –SH, –NH$_2$, –NO$_2$, or –CN;

m is independently, at each occurrence, 1, 2, 3, 4, 5 or 6; and

n is independently, at each occurrence, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.

23. A pharmaceutical composition comprising a compound of any of claims 1-22, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof, and a pharmaceutically acceptable carrier.

24. Use of a compound of any of claims 1-22, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof, in the manufacture of a medicament for the treatment of a disease associated with SHP2 modulation in a subject in need thereof.

25. The use of claim 24, wherein the disease is selected from Noonan Syndrome, Leopard Syndrome, juvenile myelomonocytic leukemias, neuroblastoma, melanoma, acute myeloid leukemia and cancers of the breast, lung and colon.

26. Use of a pharmaceutical composition of claim 23 in the manufacture of a medicament for the treatment of a disease associated with SHP2 modulation in a subject in need thereof.