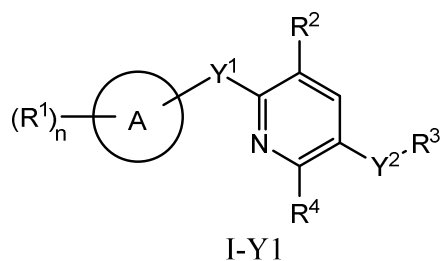


CLAIMS:

Claim 1. A compound of Formula I-Y1:



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

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

Y¹ is -S- or a direct bond;

Y² is -NR^a-, -(CR^a)_m-, -C(O)-, -C(R^a)₂NH-, -(CR^a)_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 Y², as drawn, is bound to the pyridine ring and the bond on the right side of the Y² moiety, as drawn, is bound to R³;

R¹ is independently, at each occurrence, -H, -D, -C₁-C₆alkyl, -C₂-C₆alkenyl, -C₄-C₈cycloalkenyl, -C₂-C₆alkynyl, -C₃-C₈cycloalkyl, -OH, halogen, -NO₂, -CN, -NH₂, -SR⁵, -S(O)₂NR⁵R⁶, -S(O)₂R⁵, -NR⁵S(O)₂NR⁵R⁶, -NR⁵S(O)₂R⁶, -S(O)NR⁵R⁶, -S(O)R⁵, -NR⁵S(O)NR⁵R⁶, -NR⁵S(O)R⁶, -C(O)R⁵, or -CO₂R⁵, wherein each alkyl, alkenyl, cycloalkenyl, alkynyl, or cycloalkyl is optionally substituted with one or more -OH, -NO₂, oxo, -CN, -OR⁵, -NR⁵R⁶, -SR⁵, -S(O)₂NR⁵R⁶, -S(O)₂R⁵, -NR⁵S(O)₂NR⁵R⁶, -NR⁵S(O)₂R⁶, -S(O)NR⁵R⁶, -S(O)R⁵, -NR⁵S(O)NR⁵R⁶, -NR⁵S(O)R⁶, heterocycle, aryl, or heteroaryl;

R² is -OH, -CN, -C₁-C₆alkyl, -C₂-C₆alkenyl, -C₄-C₈cycloalkenyl, -C₂-C₆alkynyl, -C₃-C₈cycloalkyl, 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, -NO₂, oxo, -CN, -R⁵, -OR⁵, -NR⁵R⁶, -SR⁵, -S(O)₂NR⁵R⁶, -S(O)₂R⁵, -NR⁵S(O)₂NR⁵R⁶,

$-\text{NR}^5\text{S}(\text{O})_2\text{R}^6$, $-\text{S}(\text{O})\text{NR}^5\text{R}^6$, $-\text{S}(\text{O})\text{R}^5$, $-\text{NR}^5\text{S}(\text{O})\text{NR}^5\text{R}^6$, $-\text{NR}^5\text{S}(\text{O})\text{R}^6$, heterocycle, aryl, or heteroaryl; and wherein the heterocyclyl or heteroaryl is not attached via a nitrogen atom;

R^a is independently, at each occurrence, $-\text{H}$, $-\text{D}$, $-\text{OH}$, $-\text{C}_3\text{-C}_8\text{cycloalkyl}$, or $-\text{C}_1\text{-C}_6\text{alkyl}$, wherein each alkyl or cycloalkyl is optionally substituted with one or more $-\text{NH}_2$, 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, $-\text{H}$, $-\text{D}$, $-\text{C}_1\text{-C}_6\text{alkyl}$, $-\text{C}_3\text{-C}_8\text{cycloalkyl}$, $-\text{C}_2\text{-C}_6\text{alkenyl}$, 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 $-\text{OH}$, halogen, $-\text{NO}_2$, oxo, $-\text{CN}$, $-\text{R}^5$, $-\text{OR}^5$, $-\text{NR}^5\text{R}^6$, $-\text{SR}^5$, $-\text{S}(\text{O})_2\text{NR}^5\text{R}^6$, $-\text{S}(\text{O})_2\text{R}^5$, $-\text{NR}^5\text{S}(\text{O})_2\text{NR}^5\text{R}^6$, $-\text{NR}^5\text{S}(\text{O})_2\text{R}^6$, $-\text{S}(\text{O})\text{NR}^5\text{R}^6$, $-\text{S}(\text{O})\text{R}^5$, $-\text{NR}^5\text{S}(\text{O})\text{NR}^5\text{R}^6$, $-\text{NR}^5\text{S}(\text{O})\text{R}^6$, heterocycle, aryl, heteroaryl, $-(\text{CH}_2)_n\text{OH}$, $-\text{C}_1\text{-C}_6\text{alkyl}$, $-\text{CF}_3$, $-\text{CHF}_2$, or $-\text{CH}_2\text{F}$;

R^3 is $-\text{H}$, $-\text{C}_1\text{-C}_6\text{alkyl}$, a 3- to 12-membered monocyclic or polycyclic heterocycle, $-\text{C}_3\text{-C}_8\text{cycloalkyl}$, or $-(\text{CH}_2)_n\text{-R}^b$, wherein each alkyl, heterocycle, or cycloalkyl is optionally substituted with one or more $-\text{C}_1\text{-C}_6\text{alkyl}$, $-\text{OH}$, $-\text{NH}_2$, $-\text{OR}^b$, $-\text{NHR}^b$, $-(\text{CH}_2)_n\text{OH}$, 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 $-\text{C}_1\text{-C}_6\text{alkyl}$, $-\text{OH}$, $-\text{NH}_2$, heteroaryl, heterocyclyl, $-(\text{CH}_2)_n\text{NH}_2$, $-\text{COOR}^b$, $-\text{CONHR}^b$, $-\text{CONH}(\text{CH}_2)_n\text{COOR}^b$, $-\text{NHCOOR}^b$, $-\text{CF}_3$, $-\text{CHF}_2$, or $-\text{CH}_2\text{F}$;

R^4 is $-\text{H}$, $-\text{D}$, $-\text{C}_1\text{-C}_6\text{alkyl}$, $-\text{NH-NHR}^5$, $-\text{NH-OR}^5$, $-\text{O-NR}^5\text{R}^6$, $-\text{NHC}(\text{O})\text{R}^5$, $-\text{NHC}(\text{O})\text{NHR}^5$, $-\text{NHS}(\text{O})_2\text{R}^5$, $-\text{NHS}(\text{O})_2\text{NHR}^5$, $-\text{S}(\text{O})_2\text{OH}$, $-\text{C}(\text{O})\text{OR}^5$, $-\text{NH}(\text{CH}_2)_n\text{OH}$, $-\text{C}(\text{O})\text{NH}(\text{CH}_2)_n\text{OH}$, $-\text{C}(\text{O})\text{NH}(\text{CH}_2)_n\text{R}^b$, $-\text{C}(\text{O})\text{R}^b$, $-\text{OH}$, $-\text{CN}$, $-\text{C}(\text{O})\text{NR}^5\text{R}^6$, $-\text{S}(\text{O})_2\text{NR}^5\text{R}^6$, $\text{C}_3\text{-C}_8\text{cycloalkyl}$, 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 $-\text{OH}$, $-\text{NH}_2$, halogen, or oxo; wherein each aryl is optionally substituted with one or more $-\text{OH}$, $-\text{NH}_2$, 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 $\text{C}_3\text{-C}_{12}\text{cycloalkyl}$ 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, $-NR^7R^8$, $-NO_2$, 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 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.

Claim 2. The compound of claim 1, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, tautomer, or isomer thereof, wherein Y^2 is $-NR^a-$.

Claim 3. The compound of any one of claims 1-2, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, tautomer, or isomer thereof, wherein Y^1 is $-S-$.

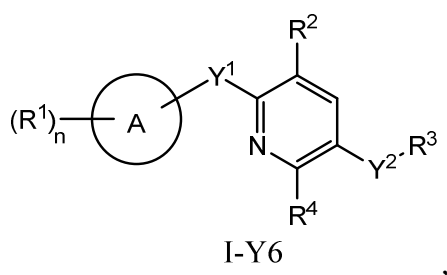
Claim 4. The compound of any one of claims 1-2, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, tautomer, or isomer thereof, wherein Y^1 is a direct bond.

Claim 5. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt, prodrug, 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 one or more $-C_1-C_6$ alkyl, $-OH$, $-NH_2$, heteroaryl, heterocyclyl, $-(CH_2)_nNH_2$, $-COOR^b$, $-CONHR^b$, $-CONH(CH_2)_nCOOR^b$, $-NHCOOR^b$, $-CF_3$, $-CHF_2$, or $-CH_2F$.

Claim 6. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt, prodrug, 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 one or more $-C_1-C_6$ alkyl, $-OH$, $-NH_2$, heteroaryl, heterocyclyl, $-(CH_2)_nNH_2$, $-COOR^b$, $-CONHR^b$, $-CONH(CH_2)_nCOOR^b$, $-NHCOOR^b$, $-CF_3$, $-CHF_2$, or $-CH_2F$.

Claim 7. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt, prodrug, 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 one or more $-C_1-C_6$ alkyl, $-OH$, $-NH_2$, heteroaryl, heterocyclyl, $-(CH_2)_nNH_2$, $-COOR^b$, $-CONHR^b$, $-CONH(CH_2)_nCOOR^b$, $-NHCOOR^b$, $-CF_3$, $-CHF_2$, or $-CH_2F$.

Claim 8. The compound of claim 1 or 2, wherein the compound is a compound of Formula I-Y6:



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

A is a 5- to 12-membered monocyclic or polycyclic aryl or 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 pyridine 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 $-C_1-C_6$ alkyl, $-OH$, $-NH_2$, $-CF_3$, $-CHF_2$, or $-CH_2F$;

R^1 is independently, at each occurrence, $-H$, $-C_1-C_6$ alkyl, $-OH$, halogen, or $-NH_2$;

R^2 is $-C_1-C_6$ alkyl or $-OH$;

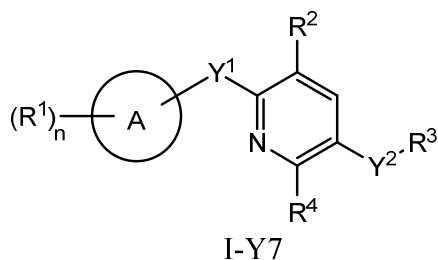
R^4 is $-H$, $-C_1-C_6$ alkyl, $-C_1-C_6$ haloalkyl, $-C_1-C_6$ hydroxyalkyl, $-CH_2OH$, $-CF_2OH$, or $-CHFOH$, wherein alkyl is optionally substituted with one or more $-OH$, $-NH_2$, halogen, or oxo;

or

R^5 and R^6 are each independently, at each occurrence, $-H$ or $-C_1-C_6$ alkyl; and

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

Claim 9. The compound of claim 1 or 2, wherein the compound is a compound of Formula I-Y7:



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

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

Y¹ is a direct bond;

Y² is -NR^a-; wherein the bond on the left side of Y², as drawn, is bound to the pyridine ring and the bond on the right side of the Y² moiety, as drawn, is bound to R³;

R³ 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 -C₁-C₆alkyl, -OH, -NH₂, -CF₃, -CHF₂, or -CH₂F;

R¹ is independently, at each occurrence, -H, -C₁-C₆alkyl, -OH, halogen, or -NH₂;

R² is -C₁-C₆alkyl or -OH;

R⁴ is -H, -C₁-C₆alkyl, -C₁-C₆haloalkyl, -C₁-C₆hydroxyalkyl, -CH₂OH, -CF₂OH, or -CHFOH, wherein alkyl is optionally substituted with one or more -OH, -NH₂, halogen, or oxo;
or

R⁵ and R⁶ are each independently, at each occurrence, -H or -C₁-C₆alkyl; and

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

Claim 10. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, tautomer, or isomer thereof, wherein A is a monocyclic or polycyclic heterocycloalkyl.

Claim 11. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, tautomer, or isomer thereof, wherein A is a monocyclic or polycyclic aryl.

Claim 12. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, tautomer, or isomer thereof, wherein A is a monocyclic or polycyclic heteroaryl.

Claim 13. The compound of any one of claims 1-12, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, tautomer, or isomer thereof, wherein R¹ is independently, at each occurrence, -H, -C₁-C₆alkyl, halogen, or -NH₂.

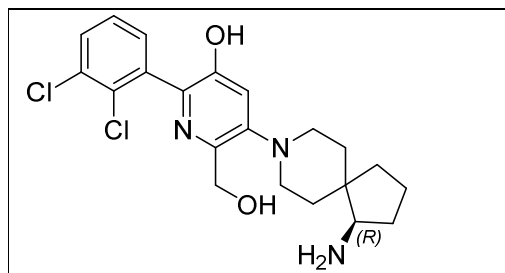
Claim 14. The compound of any one of claims 1-13, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, tautomer, or isomer thereof, wherein R² is -OH.

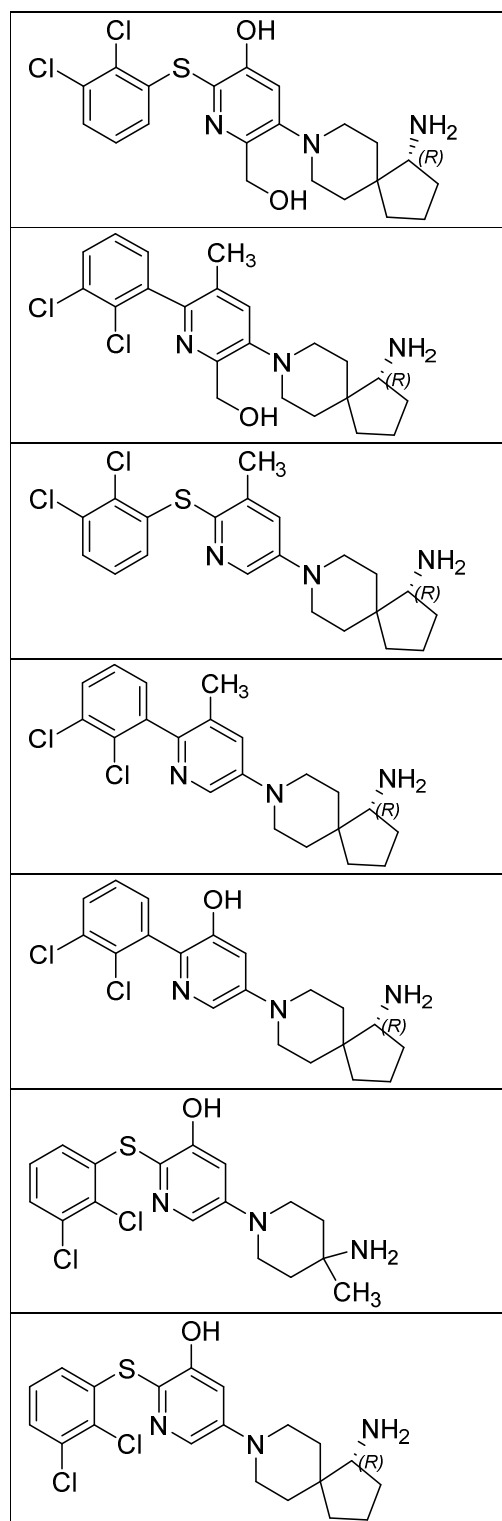
Claim 15. The compound of any one of claims 1-13, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, tautomer, or isomer thereof, wherein R² is -C₁-C₆alkyl.

Claim 16. The compound of any one of claims 1-15, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, tautomer, or isomer thereof, wherein R⁴ is -C₁-C₆alkyl, which is optionally substituted with one or more -OH, -NH₂, halogen, or oxo.

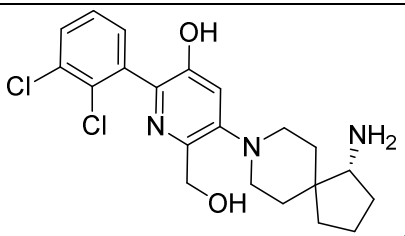
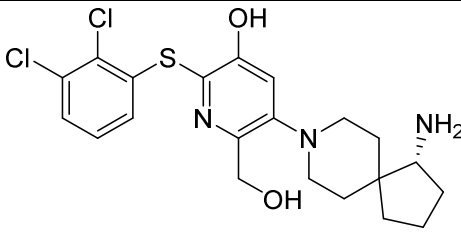
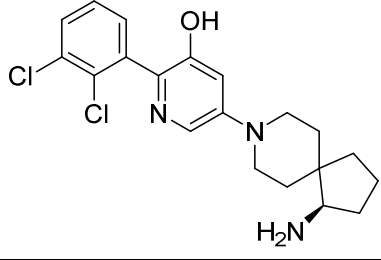
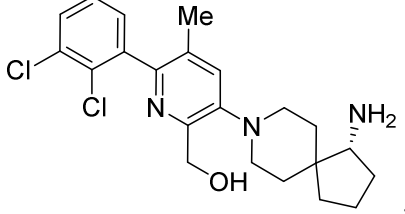
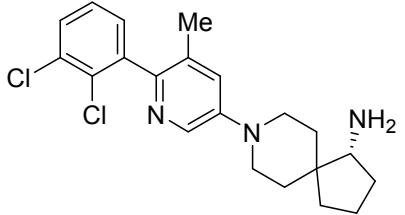
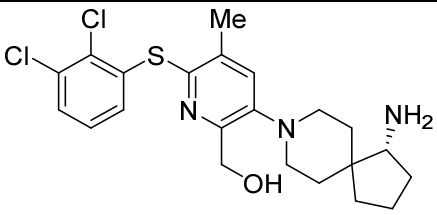
Claim 17. The compound of claim 16, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, tautomer, or isomer thereof, wherein R⁴ is -C₁-C₆alkyl, which is substituted with one or more -OH.

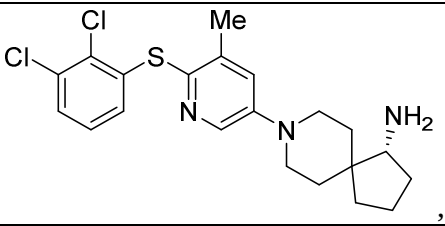
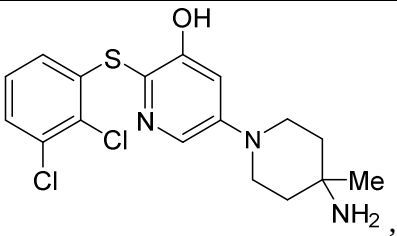
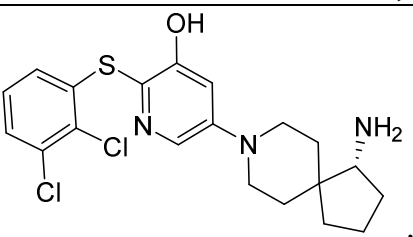
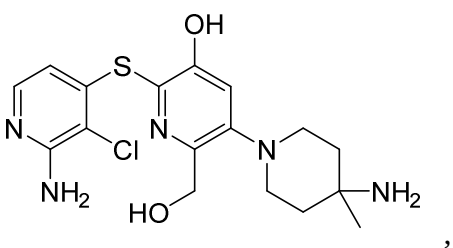
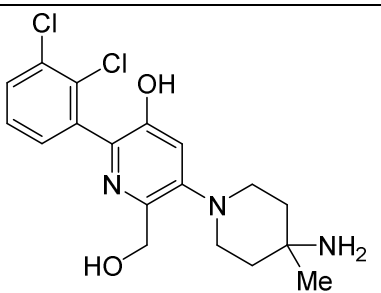
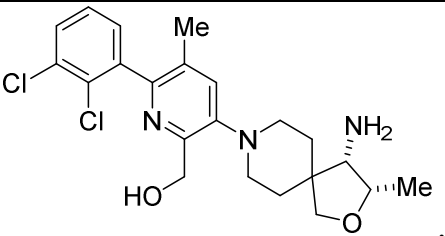
Claim 18. A compound, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, tautomer, or isomer thereof, selected from the group consisting of:

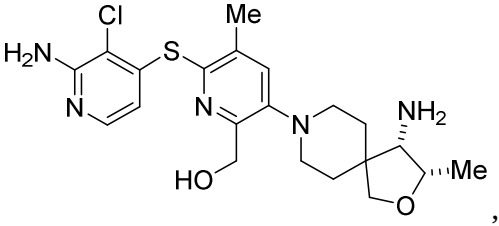
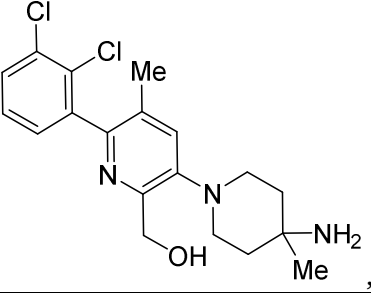
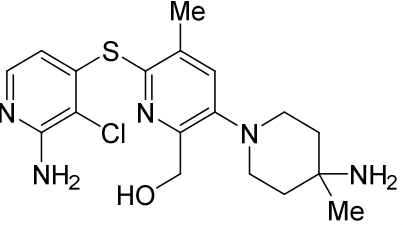
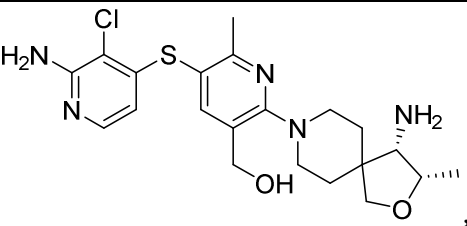
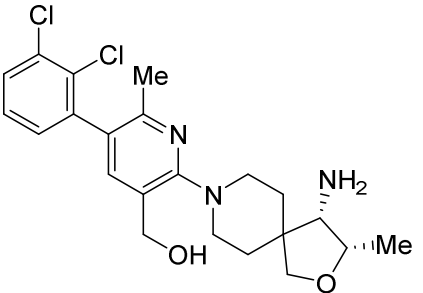
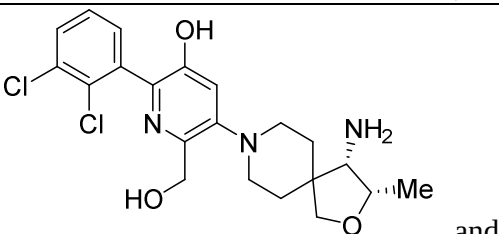


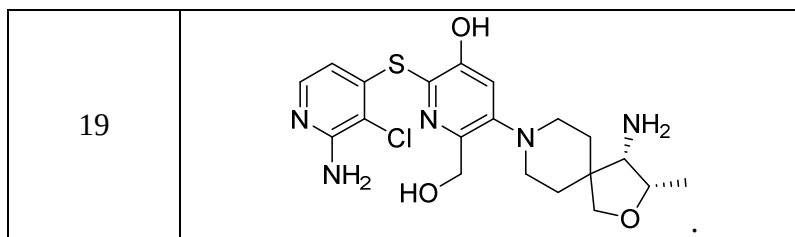


Claim 19. A compound, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, tautomer, or isomer thereof, selected from the group consisting of:

Example	
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18	 , and



Claim 20. A pharmaceutical composition comprising a compound of any one of claims 1-19, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, tautomer, or isomer thereof, and a pharmaceutically acceptable carrier.

Claim 21. Use of a compound of any one of claims 1-19, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, tautomer, or isomer thereof, and a pharmaceutically acceptable carrier, in the manufacture of a medicament for treating a disease associated with SHP2 modulation.

Claim 22. The use of claim 21, 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.

Claim 23. Use of a pharmaceutical composition of claim 20 in the manufacture of a medicament for treating a disease associated with SHP2 modulation.