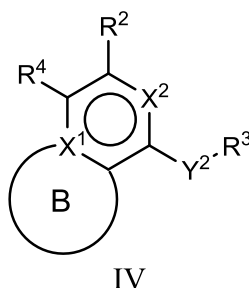
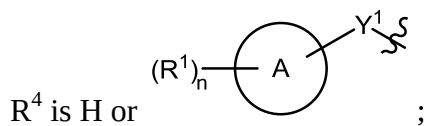


Claims:

Claim 1. A compound of the Formula IV:



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, provided that the heteroaryl is not  or  ;

R^1 is independently, at each occurrence, -H, -D, -C₁-C₆alkyl, -C₂-C₆alkenyl, -C₄-C₈cycloalkenyl, -C₂-C₆alkynyl, -C₃-C₈cycloalkyl, -OH, -OR⁵, halogen, -NO₂, -CN, -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, -C(O)R⁵, or -CO₂R⁵, wherein each alkyl, alkenyl, cycloalkenyl, alkynyl, or cycloalkyl 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, -NR⁵S(O)₂R⁶, -S(O)NR⁵R⁶, -S(O)R⁵, -NR⁵S(O)NR⁵R⁶, -NR⁵S(O)R⁶, heterocycle, aryl, or heteroaryl;

Y^1 is -S-, a direct bond, -NH-, -S(O)₂-, -S(O)₂-NH-, -C(=CH₂)-, -CH-, or -S(O)-;

X^1 is N or C;

X^2 is N or CH;

B, including the atoms at the points of attachment, is a monocyclic or polycyclic 5- to 12-membered heterocycle or a monocyclic or polycyclic 5- to 12-membered heteroaryl, wherein each heterocycle or heteroaryl is optionally substituted with one or more

$-\text{C}_1\text{-C}_6\text{alkyl}$, $-\text{OH}$, $-\text{NH}_2$, oxo, heteroaryl, heterocyclyl, $-(\text{CH}_2)_n\text{NH}_2$, $-(\text{CH}_2)_n\text{OH}$, $-\text{CF}_3$, $-\text{CHF}_2$, or $-\text{CH}_2\text{F}$;

R^2 is $-\text{H}$, $-\text{OH}$, $-\text{NR}^5\text{R}^6$, $-\text{C}_1\text{-C}_6\text{alkyl}$, $-\text{C}_2\text{-C}_6\text{alkenyl}$, $-\text{C}_4\text{-C}_8\text{cycloalkenyl}$, $-\text{C}_2\text{-C}_6\text{alkynyl}$, $-\text{NH}_2$, halogen, $-\text{C}_3\text{-C}_8\text{cycloalkyl}$, or heterocyclyl containing 1-5 heteroatoms selected from the group consisting of N, S, P, and O; wherein each alkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkyl, or heterocyclyl 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, or heteroaryl; and wherein the heterocyclyl is not attached via a nitrogen atom;

Y^2 is $-\text{NR}^a$ -, $-(\text{CR}^a_2)_m$ -, $-\text{C}(\text{O})$ -, $-\text{C}(\text{R}^a)_2\text{NH}$ -, $-(\text{CR}^a_2)_m\text{O}$ -, $-\text{C}(\text{O})\text{N}(\text{R}^a)$ -, $-\text{N}(\text{R}^a)\text{C}(\text{O})$ -, $-\text{S}(\text{O})_2\text{N}(\text{R}^a)$ -, $-\text{N}(\text{R}^a)\text{S}(\text{O})_2$ -, $-\text{N}(\text{R}^a)\text{C}(\text{O})\text{N}(\text{R}^a)$ -, $-\text{N}(\text{R}^a)\text{C}(\text{S})\text{N}(\text{R}^a)$ -, $-\text{C}(\text{O})\text{O}$ -, $-\text{OC}(\text{O})$ -, $-\text{OC}(\text{O})\text{N}(\text{R}^a)$ -, $-\text{N}(\text{R}^a)\text{C}(\text{O})\text{O}$ -, $-\text{C}(\text{O})\text{N}(\text{R}^a)\text{O}$ -, $-\text{N}(\text{R}^a)\text{C}(\text{S})$ -, $-\text{C}(\text{S})\text{N}(\text{R}^a)$ -, or $-\text{OC}(\text{O})\text{O}$ -; wherein the bond on the left side of Y^2 , as drawn, is bound to the ring and the bond on the right side of the Y^2 moiety, as drawn, is bound to R^3 ;

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 $-C_1-C_6$ alkyl, $-OH$, $-NH_2$, oxo, heteroaryl, heterocyclyl, $-(CH_2)_nNH_2$, $-(CH_2)_nOH$, $-CF_3$, $-CHF_2$, or $-CH_2F$, provided that the heterocycle formed by the combination of R^3 and R^a is not an optionally substituted piperazinyl;

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 $-NR^a-$.

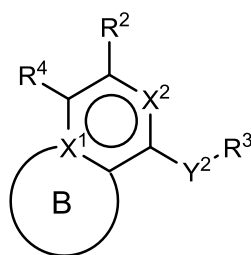
Claim 3. The compound of any one of claims 1-2, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, tautomer, or isomer thereof, wherein R^3 and R^a together with the atom to which they are attached combine to form a 3- to 12-membered monocyclic heterocycle or a 3- to 12-membered polycyclic heterocycle, wherein the heterocycle is optionally substituted with one or more $-C_1-C_6$ alkyl, $-OH$, $-NH_2$, $-(CH_2)_nNH_2$, $-(CH_2)_nOH$, $-CF_3$, $-CHF_2$, or $-CH_2F$.

Claim 4. The compound of any one of claims 1-3, 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, wherein the spiroheterocycle is optionally substituted with one or more $-C_1-C_6$ alkyl, $-OH$, $-NH_2$, $-(CH_2)_nNH_2$, $-(CH_2)_nOH$, $-CF_3$, $-CHF_2$, or $-CH_2F$.

Claim 5. The compound of claim 4, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, tautomer, or isomer thereof, wherein the spiroheterocycle is optionally substituted with one or more $-C_1-C_6$ alkyl.

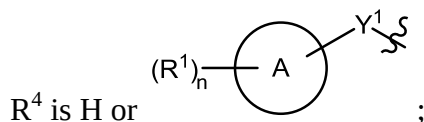
Claim 6. The compound of any one of claims 4 and 5, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, tautomer, or isomer thereof, wherein the spiroheterocycle is optionally substituted with one or more -NH_2 .

Claim 7. The compound of claim 1, wherein the compound of Formula IV is a compound of Formula IV-Q:

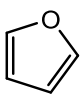
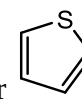


IV-Q

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, provided that the

heteroaryl is not  or  ;

R^1 is independently, at each occurrence, -H , -OR^5 , halogen, $\text{-C}_1\text{-C}_6$ alkyl, -CN , or $\text{-NR}^5\text{R}^6$;

Y^1 is -S- or a direct bond;

X^1 is N or C;

X^2 is N or CH;

B, including the atoms at the points of attachment, is a monocyclic or polycyclic 5- to 12-membered heterocycle or a monocyclic or polycyclic 5- to 12-membered heteroaryl, wherein each heterocycle or heteroaryl is optionally substituted with one or more $\text{-C}_1\text{-C}_6$ alkyl, -OH , -NH_2 , oxo, $\text{-(CH}_2)_n\text{NH}_2$, $\text{-(CH}_2)_n\text{OH}$, -CF_3 , -CHF_2 , or $\text{-CH}_2\text{F}$;

R^2 is -H , -OH , $\text{-NR}^5\text{R}^6$, $\text{-C}_1\text{-C}_6$ alkyl, or -NH_2 ; wherein each alkyl is optionally substituted with one or more -OH , halogen, -OR^5 , or $\text{-NR}^5\text{R}^6$;

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

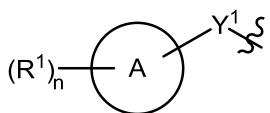
R^3 is combined with R^a to form a 3- to 12-membered monocyclic or polycyclic heterocycle or a 5- to 12-membered spiroheterocycle, wherein each heterocycle or spiroheterocycle is optionally substituted with one or more $-C_1-C_6$ alkyl, $-OH$, $-NH_2$, $-(CH_2)_nNH_2$, $-(CH_2)_nOH$, $-CF_3$, $-CHF_2$, or $-CH_2F$, provided that the heterocycle formed by the combination of R^3 and R^a is not an optionally substituted piperazinyl;

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

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 8. The compound any one of claims 1-7, or a pharmaceutically acceptable salt,

prodrug, solvate, hydrate, tautomer, or isomer thereof, wherein R^4 is  .

Claim 9. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, tautomer, or isomer thereof, wherein A is monocyclic or polycyclic aryl.

Claim 10. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, tautomer, or isomer thereof, wherein A is monocyclic or polycyclic heteroaryl.

Claim 11. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, tautomer, or isomer thereof, wherein Y^1 is $-S-$.

Claim 12. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, tautomer, or isomer thereof, wherein Y^1 is a direct bond.

Claim 13. The compound of any one of claims 1-12, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, tautomer, or isomer thereof, wherein R^1 is independently, at each occurrence, $-H$, halogen or $-NR^5R^6$.

Claim 14. The compound of any one of claims 1-13, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, tautomer, or isomer thereof, wherein R^2 is $-C_1-C_6$ alkyl, wherein the alkyl is optionally substituted with one or more $-OH$, halogen, $-OR^5$, or $-NR^5R^6$.

Claim 15. The compound of any one of claims 1-13, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, tautomer, or isomer thereof, wherein R^2 is methyl.

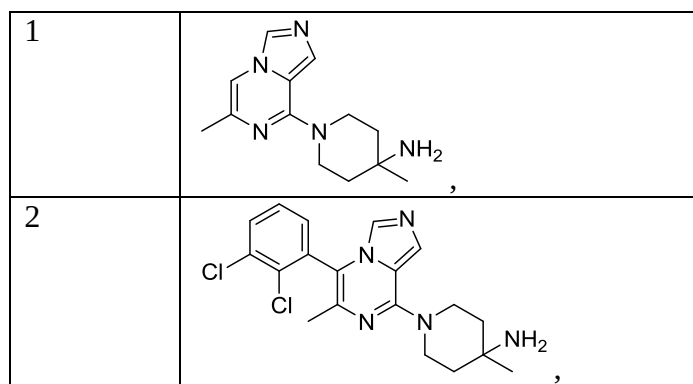
Claim 16. The compound of any one of claims 1-15, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, tautomer, or isomer thereof, wherein X^1 is N and X^2 is N.

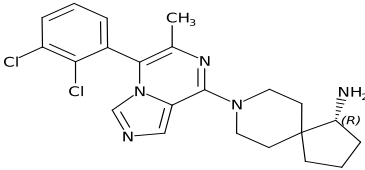
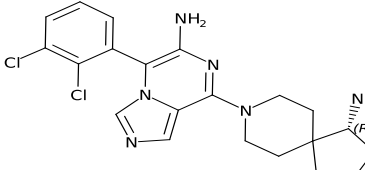
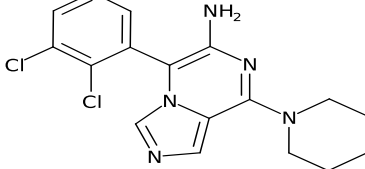
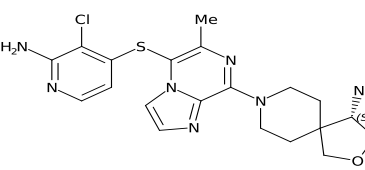
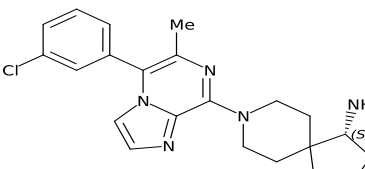
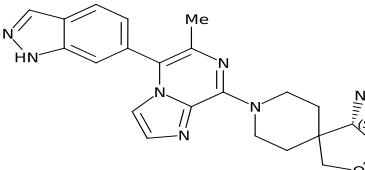
Claim 17. The compound of any one of claims 1-15, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, tautomer, or isomer thereof, wherein X^1 is C and X^2 is N.

Claim 18. The compound of any one of claims 1-17, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, tautomer, or isomer thereof, wherein B, including the atoms at the points of attachment, is a monocyclic 5- to 12-membered heterocycle or a polycyclic 5- to 12-membered heterocycle, wherein each heterocycle is optionally substituted with one or more $-C_1-C_6$ alkyl, $-OH$, $-NH_2$, oxo, $-(CH_2)_nNH_2$, $-(CH_2)_nOH$, $-CF_3$, $-CHF_2$, or $-CH_2F$.

Claim 19. The compound of any one of claims 1-17, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, tautomer, or isomer thereof, wherein B, including the atoms at the points of attachment, is a monocyclic 5- to 12-membered heteroaryl or a polycyclic 5- to 12-membered heteroaryl, wherein each heteroaryl is optionally substituted with one or more $-C_1-C_6$ alkyl, $-OH$, $-NH_2$, oxo, $-(CH_2)_nNH_2$, $-(CH_2)_nOH$, $-CF_3$, $-CHF_2$, or $-CH_2F$.

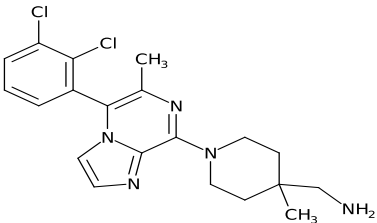
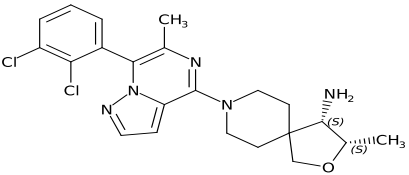
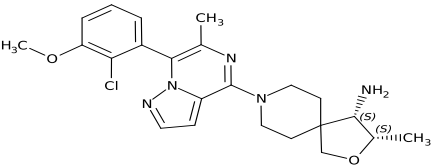
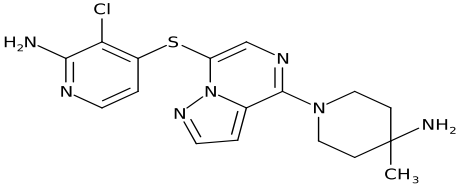
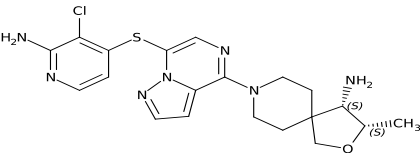
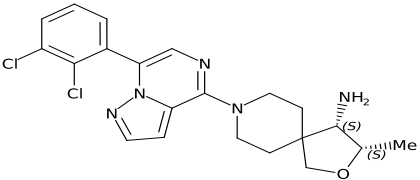
Claim 20. A compound selected from the group consisting of:

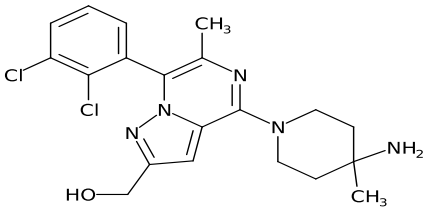
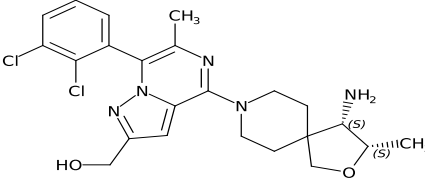
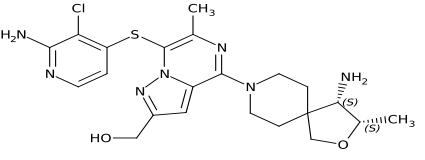
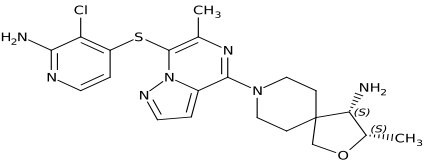
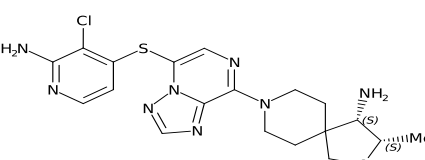
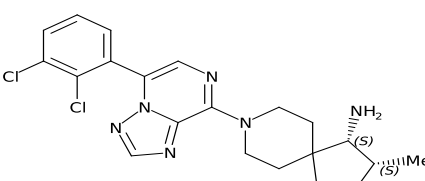


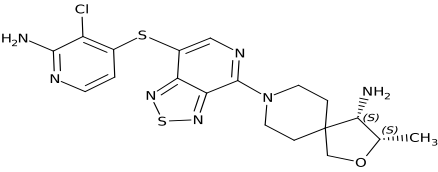
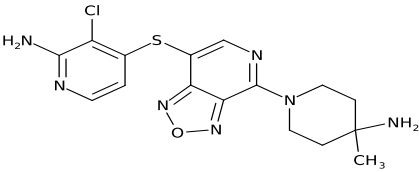
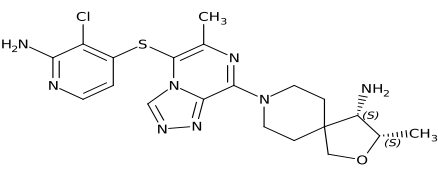
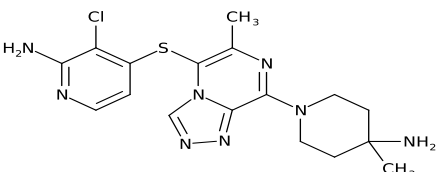
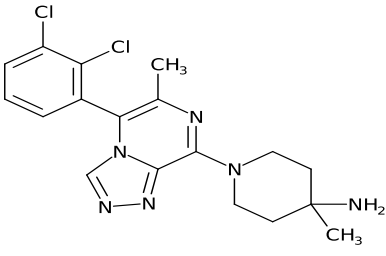
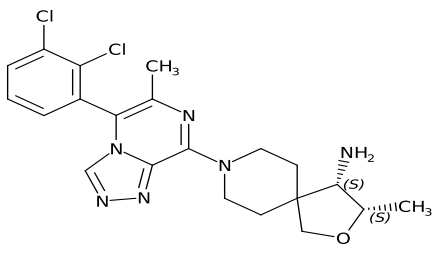
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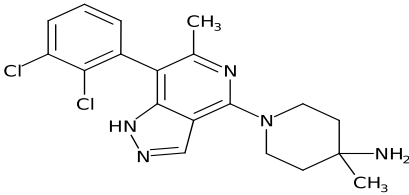
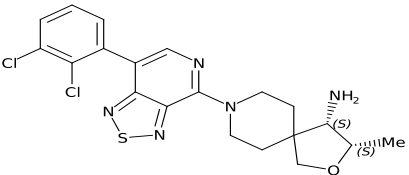
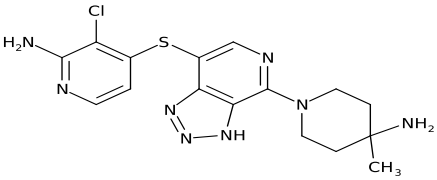
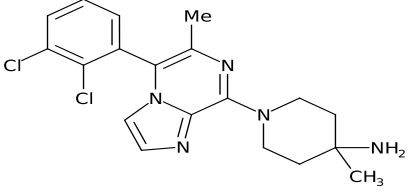
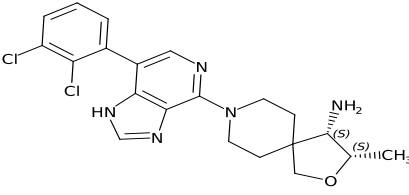
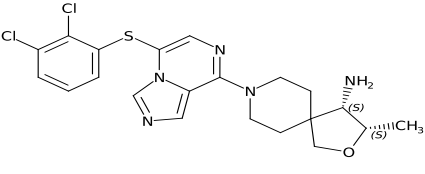
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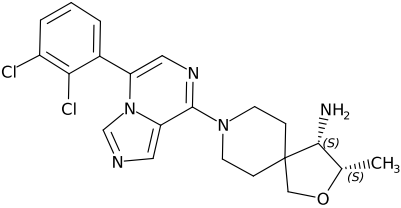
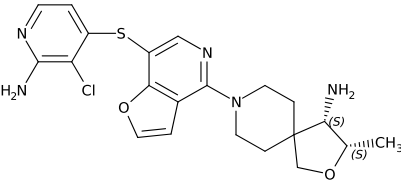
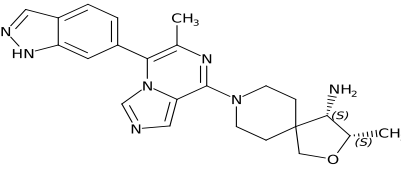
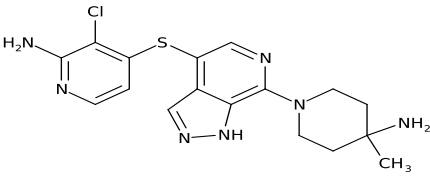
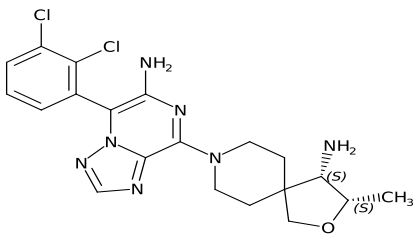
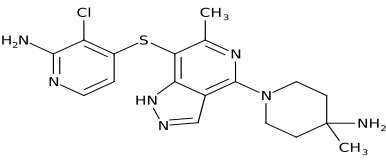
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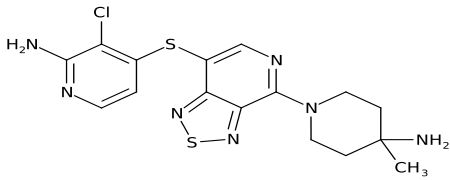
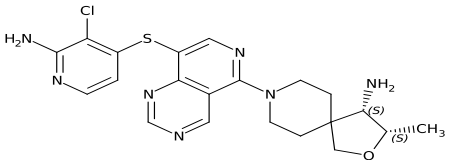
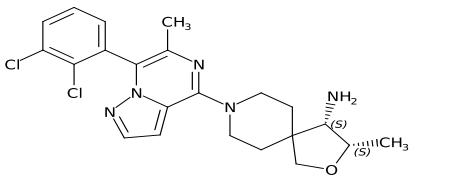
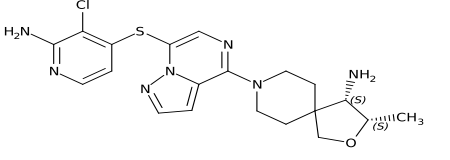
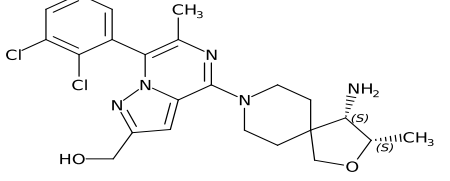
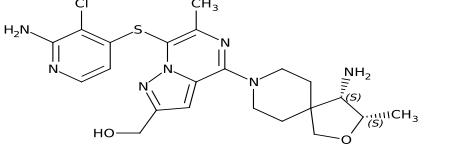
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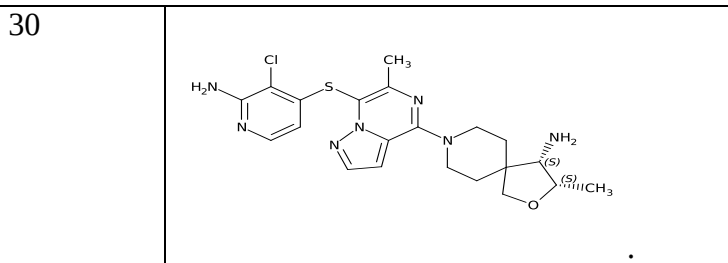
51	 , and
52	 ,

or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, tautomer, or isomer of any of the foregoing.

Claim 21. The compound of claim 20, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, tautomer, or isomer thereof, selected from the group consisting of:

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Claim 22. A pharmaceutical composition comprising a compound of any one of claims 1-21, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, tautomer, or isomer thereof, and a pharmaceutically acceptable carrier.

Claim 23. Use of a compound of any one of claims 1-21, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, tautomer, or isomer thereof, in the manufacture of a medicament for treating a disease associated with SHP2 modulation.

Claim 24. The use of claim 23, 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 25. Use of a pharmaceutical composition of claim 22 in the manufacture of a medicament for treating a disease associated with SHP2 modulation.