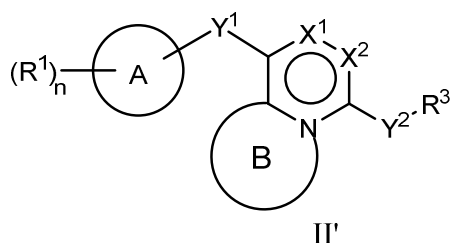


Claims:

1. A compound of the Formula II':



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;

R¹ is independently, at each occurrence, -H, -C₁-C₆alkyl, -C₂-C₆alkenyl, -C₄-C₈cycloalkenyl, -C₂-C₆alkynyl, -C₃-C₈cycloalkyl, -OH, -OR⁶, 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, -CO₂R⁵, -C(O)NR⁵R⁶, -NR⁵C(O)R⁶, 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, -NO₂, oxo, =O, -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;

Y¹ is -S-, a direct bond, -NH-, -S(O)₂-, -S(O)₂-NH-, -C(=CH₂)-, -CH₂-, or -S(O)-;

X¹ is N or CR²;

X² 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;

Y² is -NR^a-, -(CR^a)_m-, -O-, -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 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, –H, –OH, –C₃–C₈cycloalkyl, –C₁–C₆alkyl, 3- to 12-membered heterocyclyl, or –(CH₂)_n-aryl, wherein each alkyl or cycloalkyl is optionally substituted with one or more –NH₂, 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, –OH, –C₁–C₆alkyl, –C₃–C₈cycloalkyl, –C₂–C₆alkenyl, –(CH₂)_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 –(CH₂)_n-aryl 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, –C(O)NR⁵R⁶, –NR⁵C(O)R⁶, heterocycle, aryl, heteroaryl, –(CH₂)_nOH, –C₁–C₆alkyl, –CF₃, –CHF₂, or –CH₂F;

R^2 is independently –H, –NH₂, –OR^b, –CN, –C₁–C₆alkyl, –C₂–C₆alkenyl, –C₄–C₈cycloalkenyl, –C₂–C₆alkynyl, halogen, –C(O)OR^b, –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, aryl, or heteroaryl is optionally substituted with one or more –OH, halogen, –NO₂, oxo, –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;

R^3 is independently –H, –C₁–C₆alkyl, a 3- to 12-membered monocyclic or polycyclic heterocycle, a 5- to 12-membered spiroheterocycle, C₃–C₈cycloalkyl, –(CH₂)_n-R^b, or –(CH₂)_nC(O)NR⁵R⁶, wherein each alkyl, spiroheterocycle, heterocycle, or cycloalkyl is optionally substituted with one or more –C₁–C₆alkyl, –OH, –NH₂, –OR^b, –NHR^b, –(CH₂)_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 –C₁–C₆alkyl, halogen, –OH, –OR^b,

$-\text{NH}_2$, $-\text{NHR}^b$, optionally substituted heteroaryl, optionally substituted heterocyclyl, $-(\text{CH}_2)_n\text{NH}_2$, $-(\text{CH}_2)_n\text{OH}$, $-\text{COOR}^b$, $-\text{CONHR}^b$, $-\text{CONH}(\text{CH}_2)_n\text{COOR}^b$, $-\text{NHCOOR}^b$, $-\text{O}-\text{C}(\text{O})-\text{NR}^5\text{R}^6$, $-\text{CF}_3$, $-\text{CHF}_2$, $-\text{CH}_2\text{F}$, or $=\text{O}$; wherein the heteroaryl and heterocyclyl are optionally substituted with $-\text{CN}$;

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

R^7 and R^8 are independently, at each occurrence, $-\text{H}$, $-\text{C}_1\text{-C}_6\text{alkyl}$, $-\text{C}_2\text{-C}_6\text{alkenyl}$, $-\text{C}_4\text{-C}_8\text{cycloalkenyl}$, $-\text{C}_2\text{-C}_6\text{alkynyl}$, $-\text{C}_3\text{-C}_8\text{cycloalkyl}$, $-\text{OR}^b$, 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 $-\text{OH}$, $-\text{SH}$, $-\text{NH}_2$, $-\text{NO}_2$, or $-\text{CN}$;

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

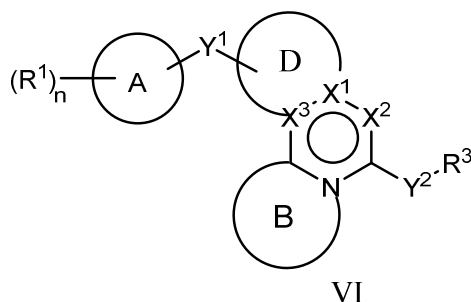
n is independently 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

provided that when X^2 is N and B ring is a monocyclic 5-membered heteroaryl containing

3-4 nitrogen atoms, then is not ; and

provided that when X^1 is N; X^2 is CH and Y^1 is NH; then R^1 is not $\text{C}_3\text{-C}_8\text{cycloalkyl}$ or heteroaryl.

2. A compound of the Formula VI:



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;

R^1 is independently, at each occurrence, $-H$, $-C_1-C_6$ alkyl, $-C_2-C_6$ alkenyl, $-C_4-C_8$ cycloalkenyl, $-C_2-C_6$ alkynyl, $-C_3-C_8$ cycloalkyl, $-OH$, $-OR^6$, 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, $=O$, $-CN$, $-R^5$, $-OR^5$, $-NR^5R^6$, $-SR^5$, $-S(O)_2NR^5R^6$, $-S(O)_2R^5$, $-NR^5S(O)_2NR^5R^6$, $-NR^5S(O)_2R^6$, $-S(O)NR^5R^6$, $-S(O)R^5$, $-NR^5S(O)NR^5R^6$, $-NR^5S(O)R^6$, heterocycle, aryl, or heteroaryl;

Y^1 is $-S-$, a direct bond, $-NH-$, $-S(O)_2-$, $-S(O)_2NH-$, $-C(=CH_2)-$, $-CH_2-$, or $-S(O)-$;

X^1 is N or C;

X^2 is N or CH;

X^3 is N or C;

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;

D, including the atoms at the points of attachment, is a monocyclic 5-to 7-membered heterocycle or a monocyclic 5-to 7-membered heteroaryl;

Y^2 is $-NR^a-$, $-(CR^a)_m-$, $-O-$, $-C(O)-$, $-C(R^a)_2NH-$, $-(CR^a)_mO-$, $-C(O)N(R^a)-$, $-N(R^a)C(O)-$, $-S(O)_2N(R^a)-$, $-N(R^a)S(O)_2-$, $-N(R^a)C(O)N(R^a)-$, $-N(R^a)C(S)N(R^a)-$, $-C(O)O-$, $-OC(O)-$, $-OC(O)N(R^a)-$, $-N(R^a)C(O)O-$, $-C(O)N(R^a)O-$, $-N(R^a)C(S)-$, $-C(S)N(R^a)-$, or $-OC(O)O-$; wherein the bond on the left side of 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, $-H$, $-OH$, $-C_3-C_8$ cycloalkyl, $-C_1-C_6$ alkyl, 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, -OH, -C₁-C₆alkyl, -C₃-C₈cycloalkyl, -C₂-C₆alkenyl, -(CH₂)_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 -(CH₂)_n-aryl 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, -C(O)NR⁵R⁶, -NR⁵C(O)R⁶, heterocycle, aryl, heteroaryl, -(CH₂)_nOH, -C₁-C₆alkyl, -CF₃, -CHF₂, or -CH₂F;

R² is independently -H, -NH₂, -OR^b, -CN, -C₁-C₆alkyl, -C₂-C₆alkenyl, -C₄-C₈cycloalkenyl, -C₂-C₆alkynyl, halogen, -C(O)OR^b, -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, aryl, 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, -NR⁵S(O)₂R⁶, -S(O)NR⁵R⁶, -S(O)R⁵, -NR⁵S(O)NR⁵R⁶, -NR⁵S(O)R⁶, heterocycle, aryl, or heteroaryl;

R³ is independently -H, -C₁-C₆alkyl, a 3- to 12-membered monocyclic or polycyclic heterocycle, a 5- to 12-membered spiroheterocycle, C₃-C₈cycloalkyl, or -(CH₂)_n-R^b, wherein each alkyl, spiroheterocycle, heterocycle, or cycloalkyl is optionally substituted with one or more -C₁-C₆alkyl, -OH, -NH₂, -OR^b, -NHR^b, -(CH₂)_nOH, -(CH₂)_nC(O)NR⁵R⁶, heterocyclyl, or spiroheterocyclyl; or

R³ 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 -C₁-C₆alkyl, halogen, -OH, -OR^b, -NH₂, -NHR^b, optionally substituted heteroaryl, optionally substituted heterocyclyl, -(CH₂)_nNH₂, -(CH₂)_nOH, -COOR^b, -CONHR^b, -CONH(CH₂)_nCOOR^b, -NHCOOR^b, -O-C(O)-NR⁵R⁶, -CF₃, -CHF₂, -CH₂F, or =O; wherein the heteroaryl and heterocyclyl are optionally substituted with -CN;

R⁵ and R⁶ are independently, at each occurrence, -H, -C₁-C₆alkyl, -C₂-C₆alkenyl, -C₄-C₈cycloalkenyl, -C₂-C₆alkynyl, -C₃-C₈cycloalkyl, a monocyclic or polycyclic 3- to 12-membered heterocycle, -OR⁷, -SR⁷, halogen, -NR⁷R⁸, -NO₂, -CF₃, or -CN;

R⁷ and R⁸ are independently, at each occurrence, -H, -C₁-C₆alkyl, -C₂-C₆alkenyl, -C₄-C₈cycloalkenyl, -C₂-C₆alkynyl, -C₃-C₈cycloalkyl, -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, -NH₂, -NO₂, or -CN;

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

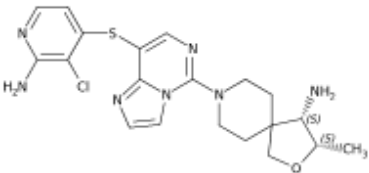
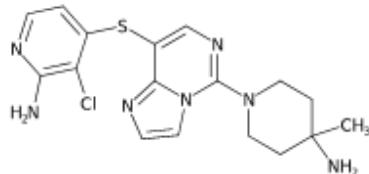
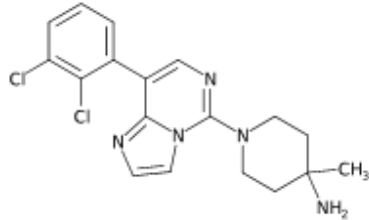
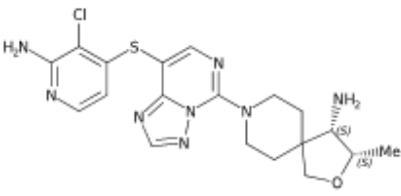
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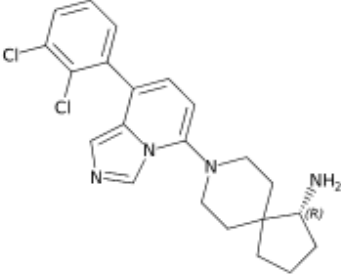
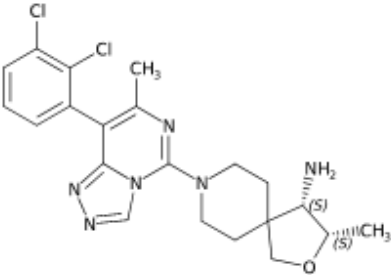
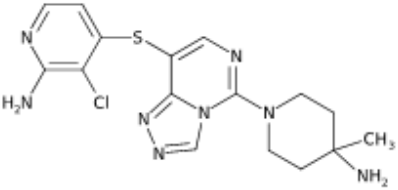
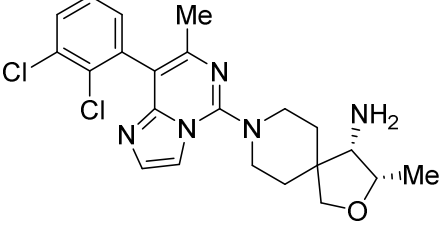
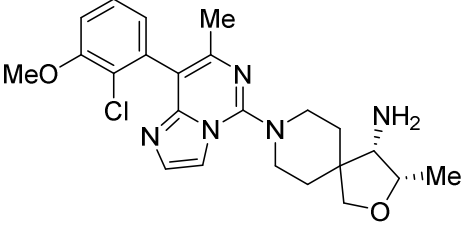
3. The compound of claim 1 or 2, wherein Y¹ is -S- or a direct bond.
4. The compound of any one of claims 1-3, wherein X¹ is N.
5. The compound of any one of claims 1-3, wherein X¹ is CR².
6. The compound of any one of claims 1-3, wherein X² is N.
7. The compound of any one of claims 1-3, wherein X² is CH.
8. The compound of any one of claims 1-7, wherein B, including the atoms at the points of attachment, is a monocyclic 5-to 12-membered heteroaryl.
9. The compound of any one of claims 1-8, wherein A is heterocycloalkyl.
10. The compound of any one of claims 1-8, wherein A is aryl or heteroaryl.
11. The compound of any one of claims 1-8, wherein A is phenyl or pyridyl.
12. The compound of any one of claims 1-11, wherein R¹ is independently -OH, -NO₂, -CN, halogen, or -NR⁵R⁶.
13. The compound of any one of claims 1-12, wherein Y² is -NR^a-.
14. The compound of any one of claims 1-13, wherein R^a is -H or C₁-C₆alkyl.
15. The compound of any one of claims 1-14, wherein R³ is -C₁-C₆alkyl, a 3-to 12-membered monocyclic heterocycle, or a 3-to 12-membered polycyclic heterocycle.

16. The compound of any of one of claims 1-13, 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, 3-to 12-membered polycyclic heterocycle, or 5- to 12-membered spiroheterocycle.

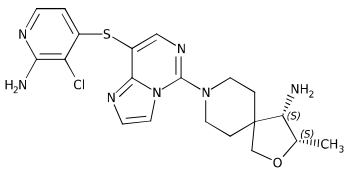
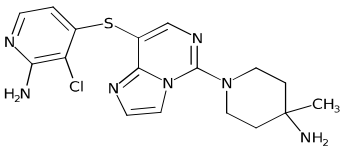
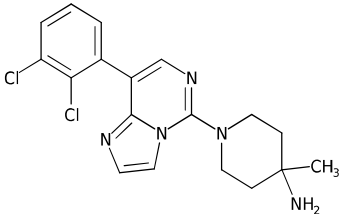
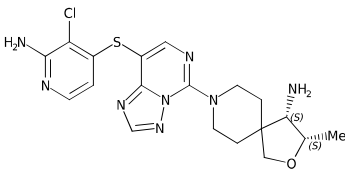
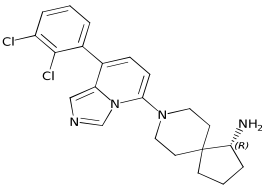
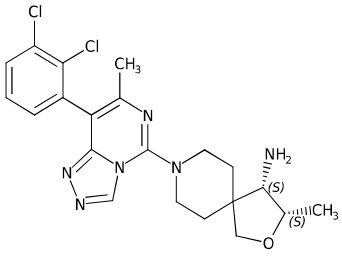
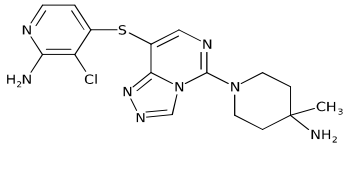
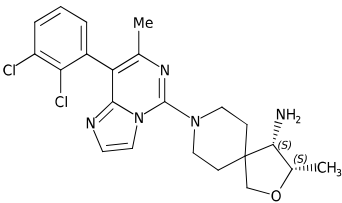
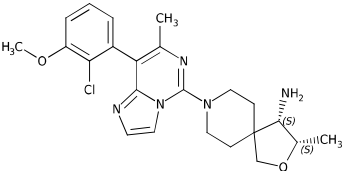
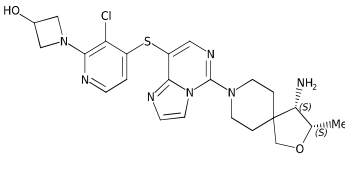
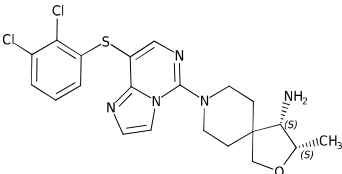
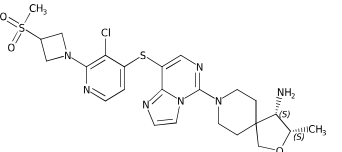
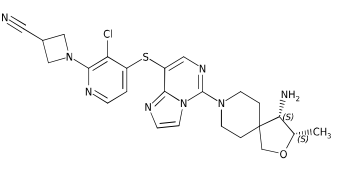
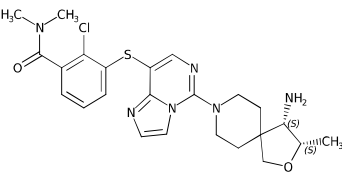
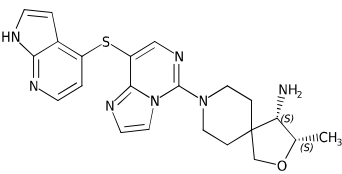
17. The compound of claim 16, wherein heterocycle or spirocycle formed by R^3 and R^a is substituted with one or more substituents selected from the group consisting of C_1 - C_6 alkyl, $-OH$, halogen, $-NH_2$, $-NHR^b$, $-CF_3$, $-CHF_2$, or $-CH_2F$.

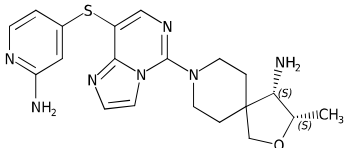
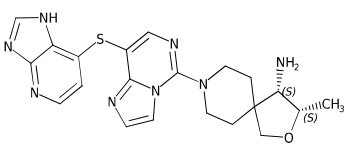
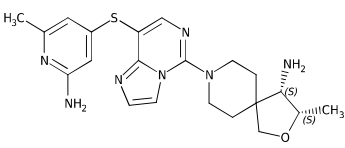
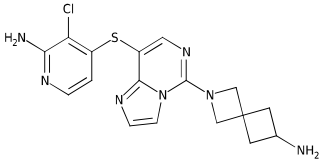
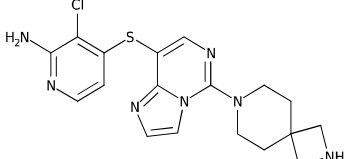
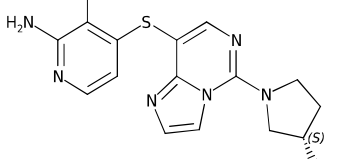
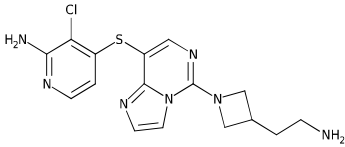
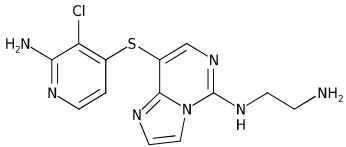
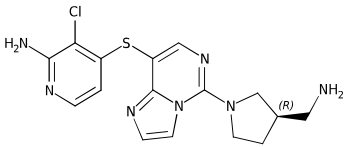
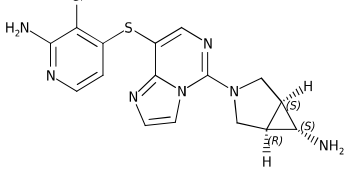
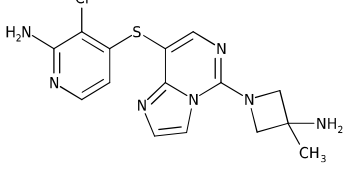
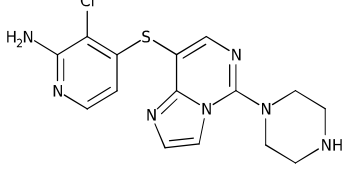
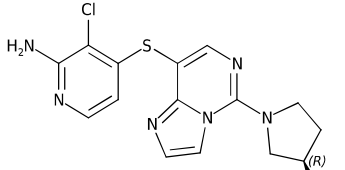
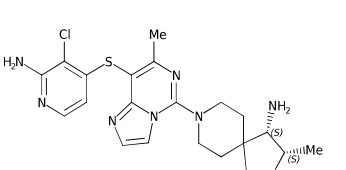
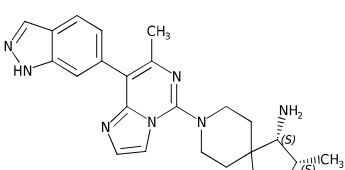
18. The compound of claim 1 or 2, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, selected from the group consisting of:

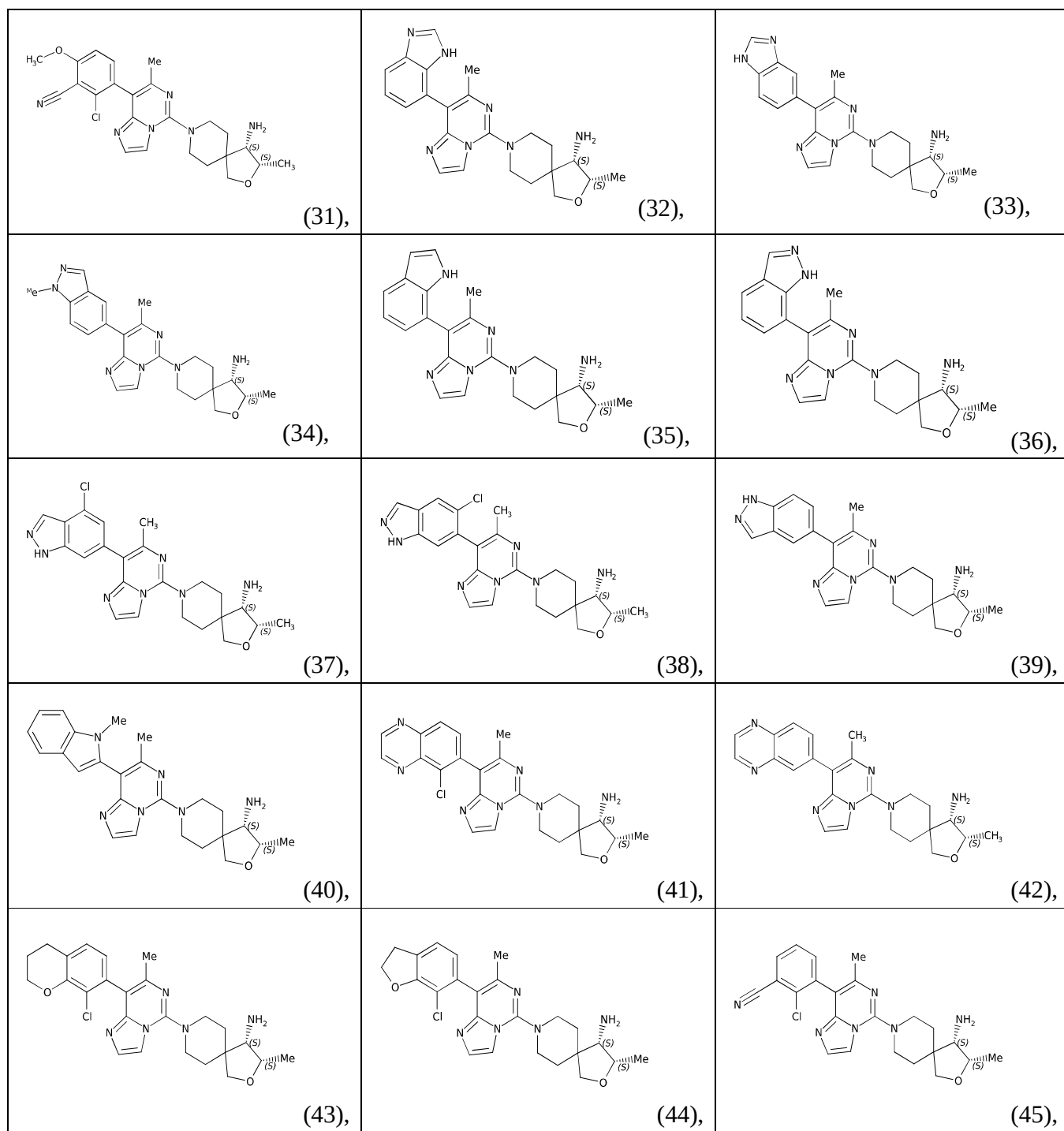
Compound	
1	
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3	
4	

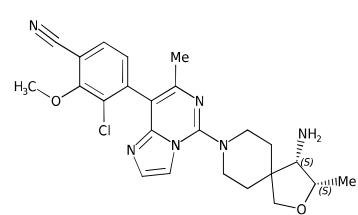
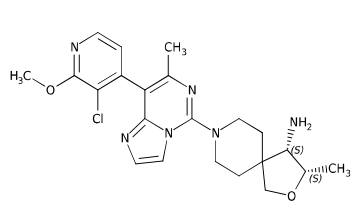
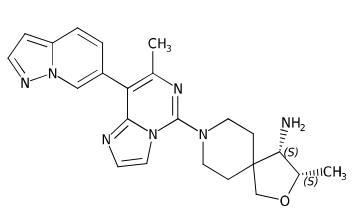
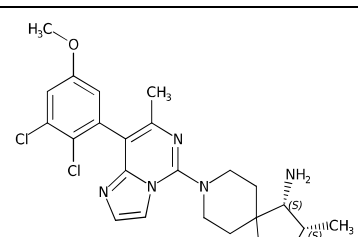
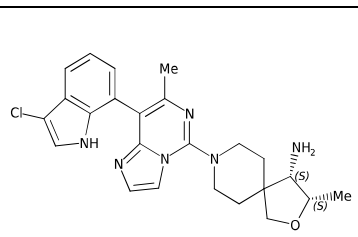
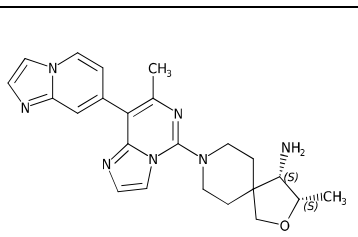
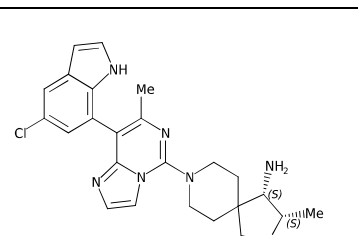
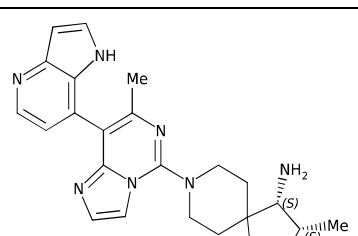
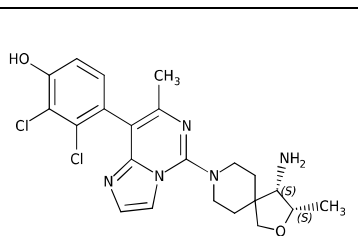
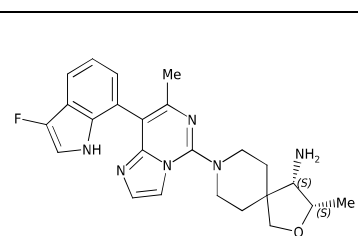
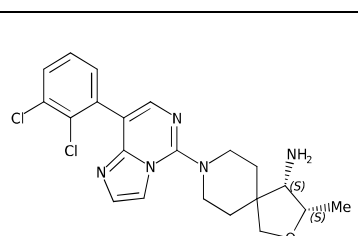
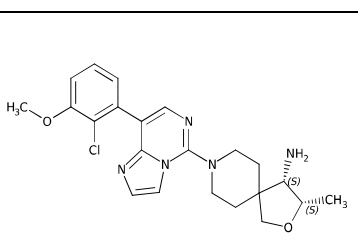
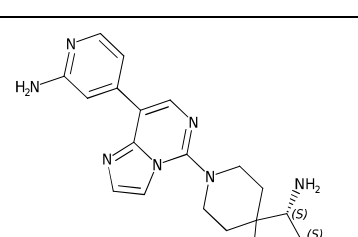
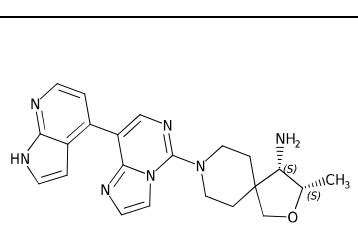
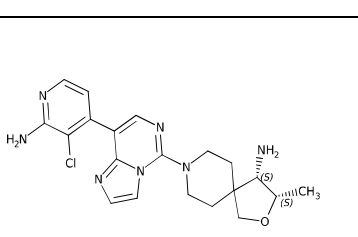
5	
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9	

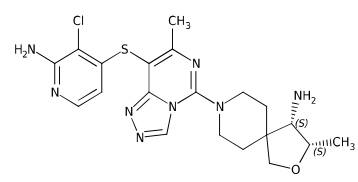
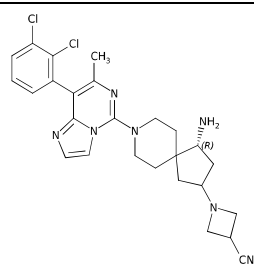
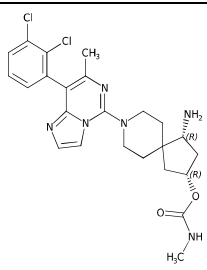
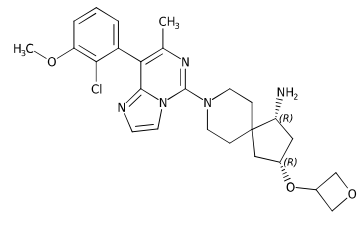
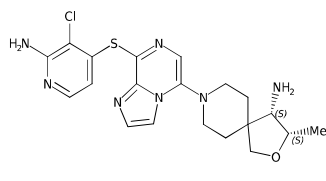
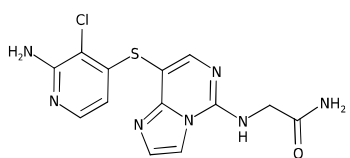
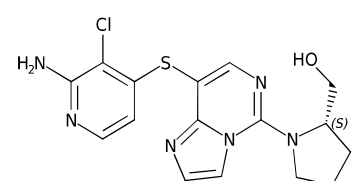
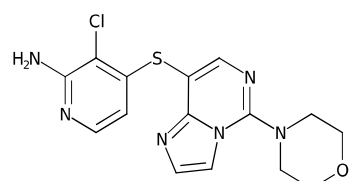
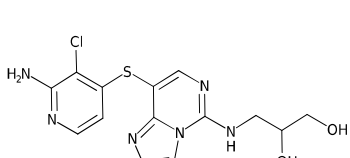
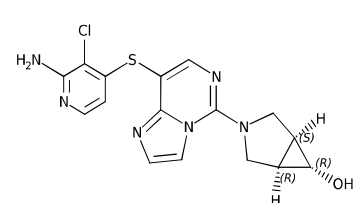
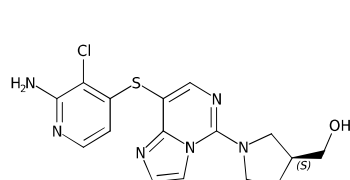
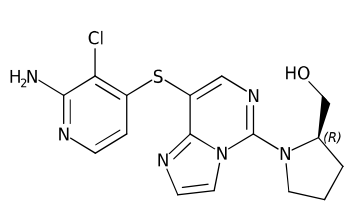
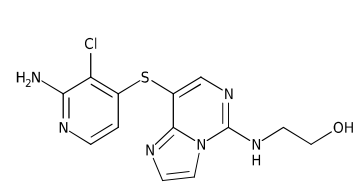
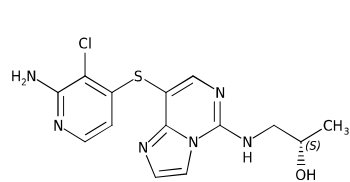
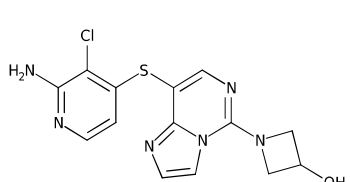
19. The compound of claim 1 or 2, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, selected from the group consisting of:

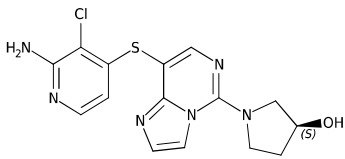
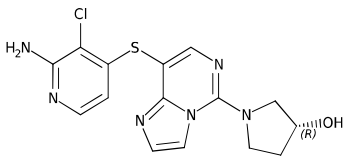
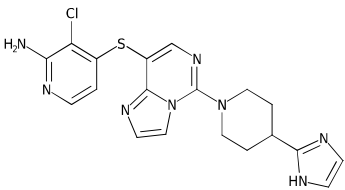
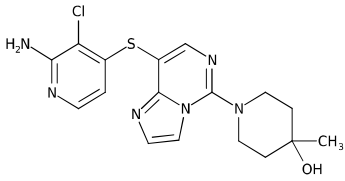
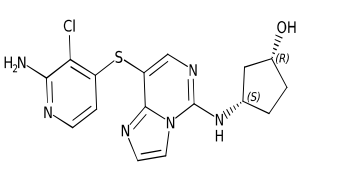
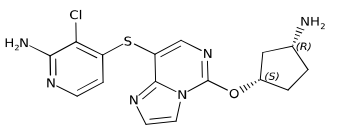
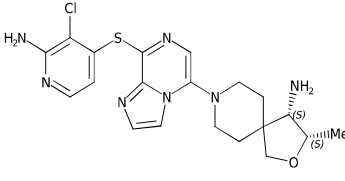
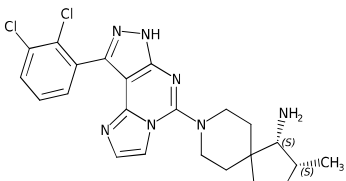
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 (10),	 (11),	 (12),
 (13),	 (14),	 (15),

 (16),	 (17),	 (18),
 (19),	 (20),	 (21),
 (22),	 (23),	 (24),
 (25),	 (26),	 (27),
 (28),	 (29),	 (30),



 (46),	 (47),	 (48),
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 (67),	 (68),	 (69),
 (70),	 (71),	 (72),
 (73),	 (74),	 (75),

 (76),	 (77),	 (78),
 (79),	 (80),	 (81)
 (82), and	 (83).	

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

21. Use of an effective amount of a compound of any one of claims 1-19, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof in the manufacture of a medicament for treating a disease associated with SHP2 modulation in a subject in need thereof.

22. The use of claim 21, wherein the disease is selected from the group consisting of Noonan Syndrome, Leopard Syndrome, juvenile myelomonocytic leukemias, neuroblastoma, melanoma, acute myeloid leukemia and cancers of the breast, lung and colon.

23. A compound of any one of claims 1-19, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof, for use in treating or preventing a disease associated with SHP2 modulation.

24. A compound of claim 23, wherein the disease is selected from the group consisting of Noonan Syndrome, Leopard Syndrome, juvenile myelomonocytic leukemias, neuroblastoma, melanoma, acute myeloid leukemia and cancers of the breast, lung and colon.

25. Use of an effective amount of a pharmaceutical composition of claim 20 in the manufacture of a medicament for treating a disease associated with SHP2 modulation in a subject in need thereof.