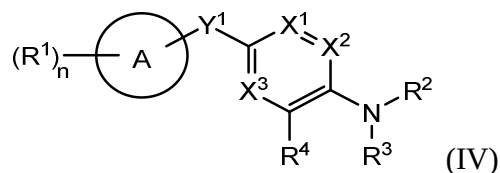


CLAIMS:

1. A compound of Formula IV:



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

X¹ is N or CH;

X² is N or CH;

X³ is N or CH;

wherein at least one of X¹, X², or X³ is N;

Y¹ is –S– or a direct bond,

A is selected from the group consisting of 5- to 12-membered monocyclic or polycyclic cycloalkyl, monocyclic or polycyclic heterocycloalkyl, monocyclic or polycyclic aryl, or monocyclic or polycyclic heteroaryl;

R¹ is independently, at each occurrence, –H, –D, –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, or 3-to 12-membered monocyclic or polycyclic heterocycle, wherein each alkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkyl or heterocycle 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;

R² and R³ are independently selected from the group consisting of –H, –D, –OH, –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, 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 combines with R^2 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, halogen, $-OH$, $-OR^b$, $-NH_2$, $-NHR^b$, optionally substituted heteroaryl, optionally substituted heterocyclyl, $-(CH_2)_nNH_2$, $-(CH_2)_nOH$, $-COOR^b$, $-CONHR^b$, $-CONH(CH_2)_nCOOR^b$, $-NHCOOR^b$, $-O-C(O)-NR^5R^6$, $-CF_3$, $-CHF_2$, $-CH_2F$, or $=O$; wherein the heteroaryl and heterocyclyl are optionally substituted with $-CN$;

R^4 is $-C_1-C_6$ alkyl, $-C_1-C_6$ haloalkyl, $-C_1-C_6$ hydroxyalkyl $-CF_2OH$, $-CHFOH$, $-NH-NHR^5$, $-NH-OR^5$, $-O-NR^5R^6$, $-NHR^5$, $-OR^5$, $-NHC(O)R^5$, $-NHC(O)NHR^5$, $-NHS(O)_2R^5$, $-NHS(O)_2NHR^5$, $-S(O)_2OH$, $-C(O)OR^5$, $-NH(CH_2)_nOH$, $-C(O)NH(CH_2)_nOH$, $-C(O)NH(CH_2)_nR^b$, $-C(O)R^b$, $-NH_2$, $-OH$, $-CN$, $-C(O)NR^5R^6$, $-S(O)_2NR^5R^6$, 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;

R^5 and R^6 are each independently, at each occurrence, selected from the group consisting of $-H$, $-D$, $-C_1-C_6$ 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, $-NR^7R^8$, $-NO_2$, and $-CN$;

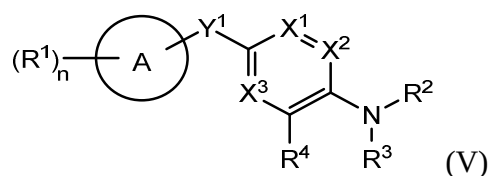
R^7 and R^8 are independently, at each occurrence, $-H$, $-D$, $-C_1-C_6$ alkyl, $-C_2-C_6$ alkenyl, $-C_4-C_8$ cycloalkenyl, $-C_2-C_6$ alkynyl, $-C_3-C_8$ cycloalkyl, a monocyclic or polycyclic 3-to 12-membered heterocycle, wherein each alkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkyl, or heterocycle is optionally substituted with one or more $-OH$, $-SH$, $-NH_2$, $-NO_2$, or $-CN$;

R^b is independently $-H$, $-D$, $-C_1-C_6$ alkyl, $-C_1-C_6$ cycloalkyl, $-C_2-C_6$ alkenyl, $-(CH_2)_n$ -aryl, heterocyclyl containing 1-5 heteroatoms selected from the group consisting of N, S, P, or 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, $-CN$, $-R^5$, $-OR^5$, $-NR^5R^6$, $-SR^5$, $-S(O)_2NR^5R^6$, $-S(O)_2R^5$, $-NR^5S(O)_2NR^5R^6$, $-NR^5S(O)_2R^6$, $-S(O)NR^5R^6$, $-S(O)R^5$,

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

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

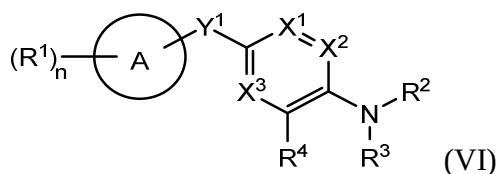
2. The compound of claim 1, wherein the compound is Formula V:



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

R^4 is $-\text{C}_1\text{-C}_6\text{alkyl}$, wherein alkyl is optionally substituted with one or more $-\text{OH}$, $-\text{NH}_2$, halogen, or oxo.

3. The compound of claim 1, wherein the compound is Formula VI:



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

R^3 combines with R^2 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 $-\text{C}_1\text{-C}_6\text{alkyl}$, halogen, $-\text{OH}$, $-\text{OR}^b$, $-\text{NH}_2$, $-\text{NHR}^b$, optionally substituted heteroaryl, optionally substituted heterocyclyl, $-(\text{CH}_2)_n\text{NH}_2$, $-(\text{CH}_2)_n\text{OH}$, $-\text{COOR}^b$, $-\text{CONHR}^b$, $-\text{CONH}(\text{CH}_2)_n\text{COOR}^b$, $-\text{NHCOOR}^b$, $-\text{O-C}(\text{O})-\text{NR}^5\text{R}^6$, $-\text{CF}_3$, $-\text{CHF}_2$, $-\text{CH}_2\text{F}$, or $=\text{O}$; wherein the heteroaryl and heterocyclyl are optionally substituted with $-\text{CN}$;

R^4 is $-\text{C}_1\text{-C}_6\text{alkyl}$, wherein alkyl is optionally substituted with one or more $-\text{OH}$, $-\text{NH}_2$, halogen, or oxo.

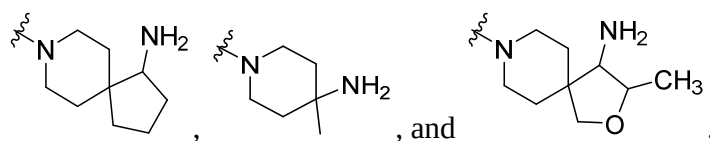
4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt, solvate, hydrate, or tautomer thereof, wherein X^1 is CH.
5. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt, solvate, hydrate, or tautomer thereof, wherein X^2 is N.
6. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt, solvate, hydrate, or tautomer thereof, wherein X^3 is N.
7. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt, solvate, hydrate, or tautomer thereof, wherein A is monocyclic or polycyclic aryl.
8. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt, solvate, hydrate, or tautomer thereof, wherein A is monocyclic heteroaryl, polycyclic heteroaryl, monocyclic heterocycloalkyl, or polycyclic heterocycloalkyl.
9. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt, solvate, hydrate, or tautomer thereof, wherein each R^1 is selected from the group consisting of -H, halogen, $-C_1-C_6$ alkyl, and $-NR^5R^6$.
10. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt, solvate, hydrate, or tautomer thereof, wherein R^4 is an optionally substituted $-C_1-C_6$ alkyl.
11. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt, solvate, hydrate, or tautomer thereof, wherein R^4 is $-CH_2-OH$.
12. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt, solvate, hydrate, or tautomer thereof, wherein R^4 is $-C_1-C_6$ alkyl substituted with one or more halogen.
13. The compound of any one of claims 1-12, or a pharmaceutically acceptable salt, solvate, hydrate, or tautomer thereof, wherein R^3 combines with R^2 to form a 3-to 12-membered monocyclic or polycyclic heterocycle, wherein the heterocycle is optionally substituted with $-C_1-C_6$ alkyl, 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 $=O$.

14. The compound of claim 13, or a pharmaceutically acceptable salt, solvate, hydrate, or tautomer thereof, wherein the heterocycle is unsubstituted or substituted with $-C_1-C_6$ alkyl, $-OR^b$, or $-NH_2$.

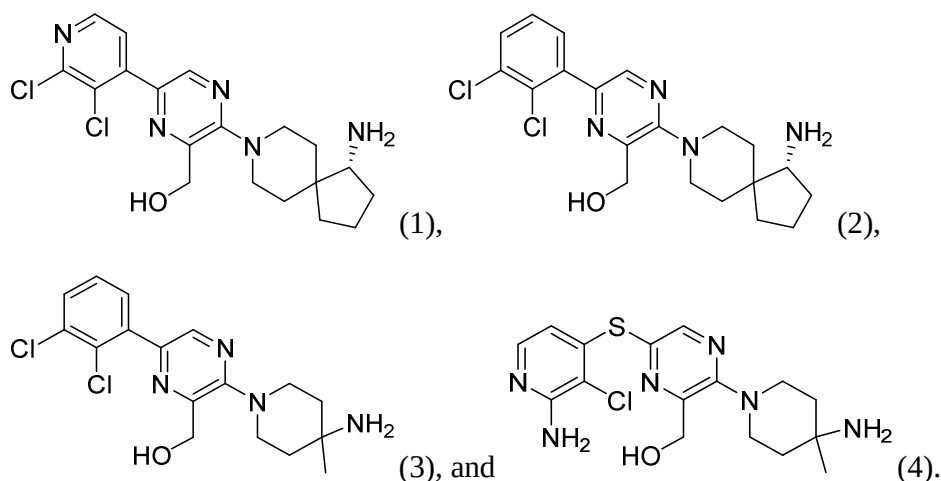
15. The compound of any one of claims 1-12, or a pharmaceutically acceptable salt, solvate, hydrate, or tautomer thereof, wherein R^3 combines with R^2 to form a 5-to 12-membered spiroheterocycle, wherein the spiroheterocycle is optionally substituted with $-C_1-C_6$ alkyl, halogen, $-OH$, $-OR^b$, $-NH_2$, $-NHR^b$, 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 $=O$.

16. The compound of claim 15, or a pharmaceutically acceptable salt, solvate, hydrate, or tautomer thereof, wherein the spiroheterocycle is unsubstituted or substituted with $-C_1-C_6$ alkyl, $-OR^b$, or $-NH_2$.

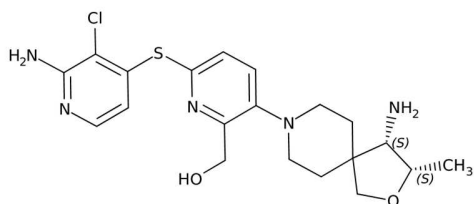
17. The compound of any one of claims 1-12, or a pharmaceutically acceptable salt, solvate, hydrate, or tautomer thereof, wherein R^3 combines with R^2 to form a moiety selected from:



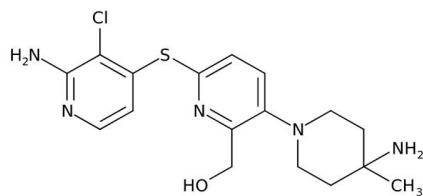
18. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof, selected from the group consisting of



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



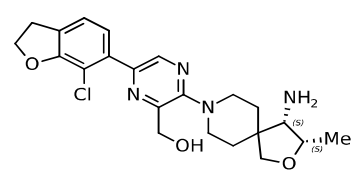
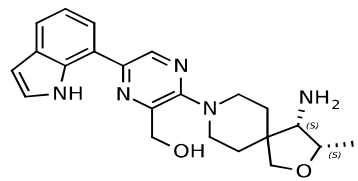
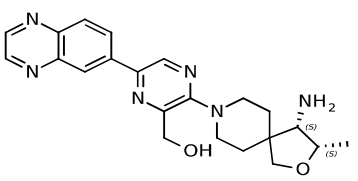
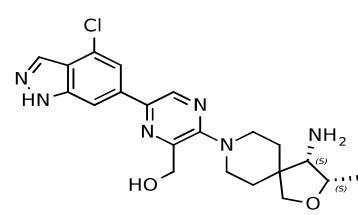
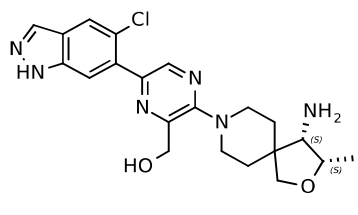
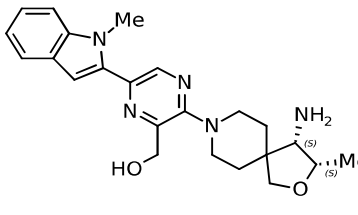
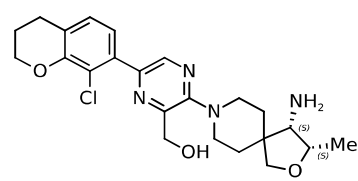
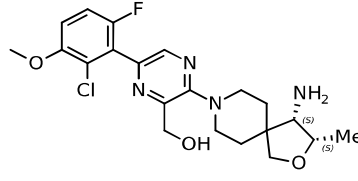
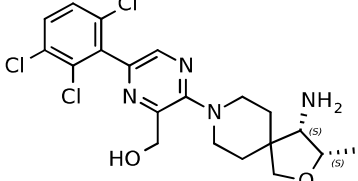
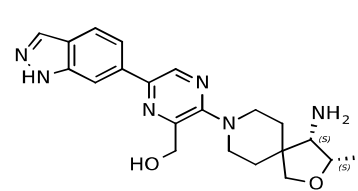
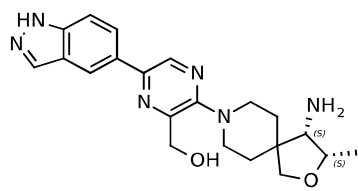
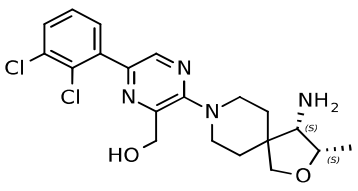
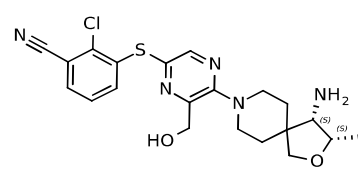
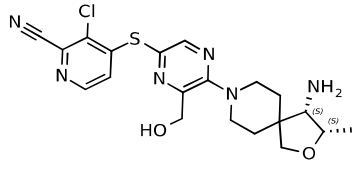
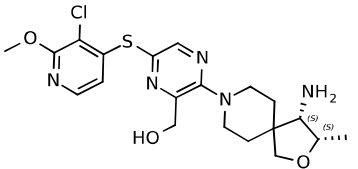
(5) and

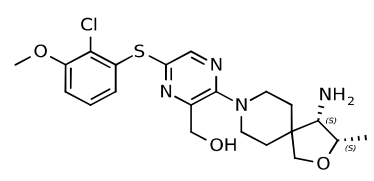
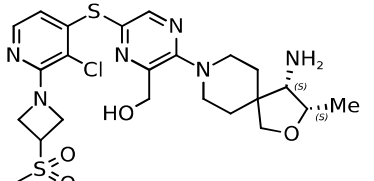
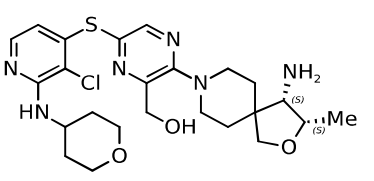
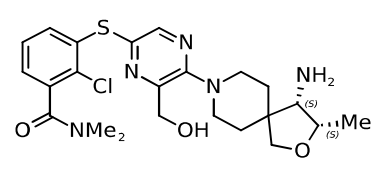
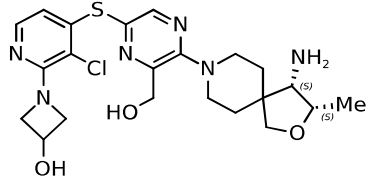
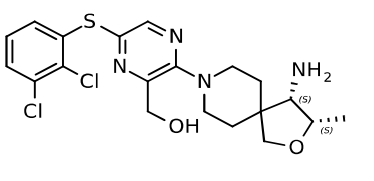
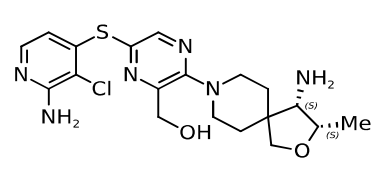
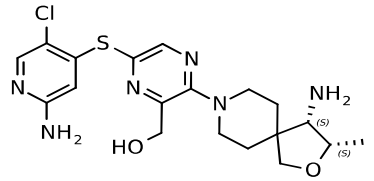
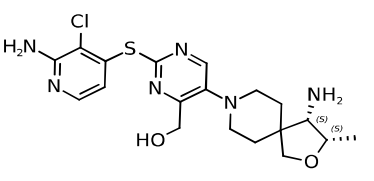


(5a).

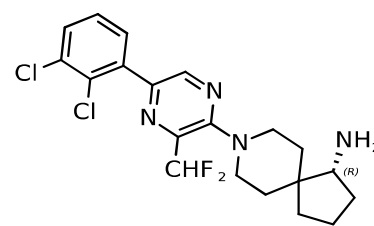
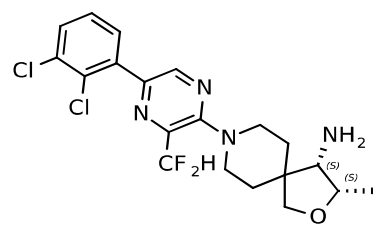
20. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof, selected from the group consisting of

(1),	(2),	(3),
(4),	(5),	(6),
(7),	(8),	(9),

 (10),	 (11),	 (12),
 (13),	 (14),	 (15),
 (16),	 (17),	 (18),
 (19),	 (20),	 (21),
 (22),	 (23),	 (24),

 (25),	 (26),	 (27),
 (28),	 (29),	 (30),
 (31),	 (32), and	 (33).

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

 (34) and	 (35).
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22. A pharmaceutical composition comprising a compound of any one of claims 1-21, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof, and a pharmaceutically acceptable carrier.
23. Use of an effective amount of a compound of any one of claims 1-21, 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.
24. The use 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 22, in the manufacture of a medicament for treating a disease associated with SHP2 modulation in a subject in need thereof.