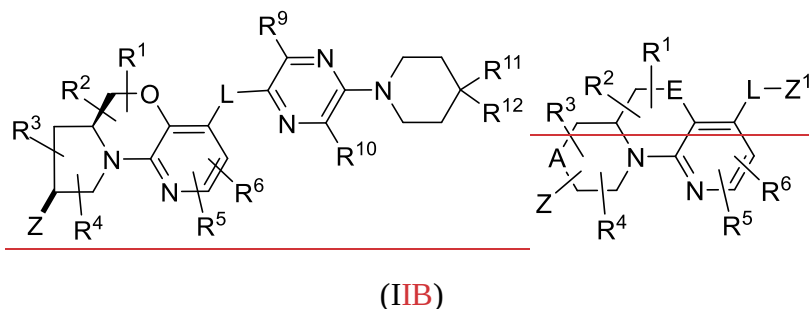


What is Claimed:

- 1 A compound of Formula (IIB):



- 5 wherein:

~~A and E are independently selected from a bond, CH₂, O, NH, S, and S(O)₂;~~

Z is hydrogen, alkyl, halo, haloalkyl, haloalkoxy, cyano, cycloalkyl, heterocyclyl, heteroaryl (wherein cycloalkyl, heterocyclyl, and heteroaryl are optionally substituted with one to three halo), $\text{O(alk)}_y\text{R}^a$, O(alk)OR^b , S(O)R^c , $\text{S(O)}_2\text{R}^d$, $\text{NR}^e\text{C(O)R}^f$, $\text{NR}^g\text{SO}_2\text{R}^h$, $\text{OC(O)NR}^i\text{R}^j$, $\text{C(O)NR}^k\text{R}^m$, $\text{S(O)}_2\text{NR}^n\text{R}^o$, NR^pR^q , $\text{NR}^r\text{C(O)C(O)R}^s$ or Y-M (wherein Y is bond, O, or SO_2 and M is alkyl, haloalkyl, cycloalkyl, heterocyclyl, or heteroaryl wherein alkyl, haloalkyl, cycloalkyl, heterocyclyl and heteroaryl are substituted with $\text{O(alk)}_y\text{R}^a$, O(alk)OR^b , S(O)R^c , $\text{S(O)}_2\text{R}^d$, $\text{NR}^e\text{C(O)R}^f$, $\text{NR}^g\text{SO}_2\text{R}^h$, $\text{OC(O)NR}^i\text{R}^j$, $\text{C(O)NR}^k\text{R}^m$, $\text{S(O)}_2\text{NR}^n\text{R}^o$, NR^pR^q , or $\text{NR}^r\text{C(O)C(O)R}^s$ and cycloalkyl, heterocyclyl, and heteroaryl are optionally further substituted with 1 to 3 halo); wherein each y is 0 or 1, each alk is alkylene, and each R^c , R^d , R^f , R^h , and R^s are independently alkyl, cycloalkyl, cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, or optionally substituted heteroaralkyl; and each R^a , R^b , R^e , R^g , R^i , R^j , R^k , R^m , R^n , R^o , R^p , R^q , R^r , and R^s are independently hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, or optionally substituted heteroaralkyl; or, independently of each other, each R^i and R^j , R^k and R^m , R^n and R^o , and R^p and R^q , together with the nitrogen atom to which they are attached form optionally substituted heterocyclyl;

(a) Z is -Y-M, wherein Y is bond and M is alkyl, haloalkyl, cycloalkyl, heterocyclyl, or heteroaryl, wherein alkyl, haloalkyl, cycloalkyl, heterocyclyl and heteroaryl are substituted with -O(alkylene)OR^a, wherein R^a is alkyl, cycloalkyl, cycloalkylalkyl, aminoalkyl,

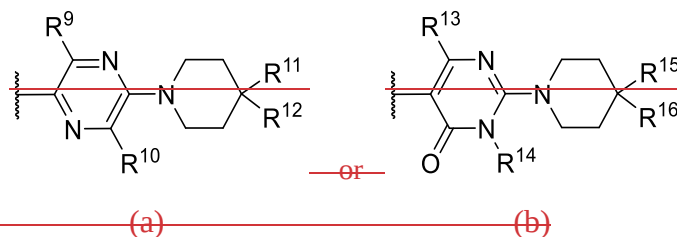
(b) Z is -Y-M, wherein Y is bond and M is alkyl, haloalkyl, cycloalkyl, heterocyclyl, or heteroaryl, wherein alkyl, haloalkyl, cycloalkyl, heterocyclyl and heteroaryl are substituted with -O-R^a, wherein R^a is alkyl, cycloalkyl, cycloalkylalkyl, aminoalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, or optionally substituted heteroaryl; or

(d) Z is -O(alkylene)OR^b, where R^b is alkyl, cycloalkyl, cycloalkylalkyl, aminoalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

R⁵ and R⁶ are independently selected from hydrogen, alkyl, cycloalkyl, halo, haloalkyl, haloalkoxy, alkoxy, hydroxy, cyano, hydroxylalkyl, amino, and aminoalkyl, or wherein one of R⁵ and R⁶ is optionally substituted heterocyclcyl and the other R⁵ and R⁶ is selected from hydrogen, alkyl, cycloalkyl, halo, haloalkyl, haloalkoxy, alkoxy, hydroxy, cyano, hydroxylalkyl, amino, and aminoalkyl;

L is bond, O, S, S(O), S(O)₂, or CR⁷R⁸ where R⁷ and R⁸ are independently hydrogen or alkyl;

~~$\mathbb{Z}^1$ is a group of formula (a) or (b):~~



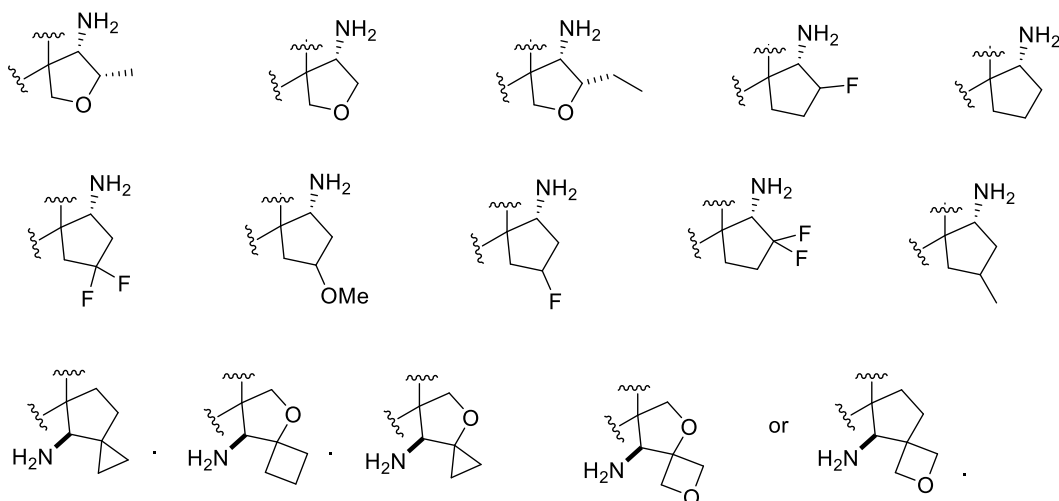
~~wherein:~~

R⁹ is hydrogen, alkyl, halo, hydroxy, amino, or haloalkyl;

R^{10} is hydrogen, alkyl, halo, hydroxy, hydroxyalkyl, $-CD_2OH$, alkylsulfoxide, alkylsulfonyl, amino, aminoalkyl, aminosulfonyl, aminocarbonyl, carboxy, cyano, or alkoxy carbonyl;

R^{11} and R^{12} together with the carbon atom to which they are attached form a ring of formula (c);

wherein ring of formula (c) is:



R^{13} is hydrogen, alkyl, halo, hydroxy, amino, or haloalkyl;

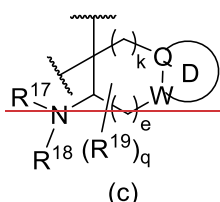
R^{14} is hydrogen, alkyl, or haloalkyl;

R^{11} and R^{15} are selected from amino and aminoalkyl;

R^{12} and R^{16} are selected from hydrogen, cyano, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, cycloalkyl, aryl, heterocyclyl, and heteroaryl, where alkyl, cycloalkyl, aryl, heterocyclyl and heteroaryl are optionally substituted with one to three substituents

independently selected from alkyl, halo, haloalkyl, haloalkoxy, alkoxy, and cyano;

or R^{11} and R^{12} , and R^{15} and R^{16} together with the carbon atom to which they are attached form a ring of formula (c):



wherein:

e is 0, 1, or 2;

k is 0, 1, or 2 provided $e + k$ is 1, 2, or 3;

~~— q is 0, 1, or 2, or 3;~~

~~R¹⁷ and R¹⁸ are independently selected from hydrogen, alkyl, cycloalkyl and haloalkyl;~~

~~each R¹⁹ is independently selected from hydrogen, alkyl, halo, haloalkyl, haloalkoxy, alkoxy, hydroxy, cyano, alkylsulfoxide, alkylsulfonyl, oxo, cycloalkyl, optionally substituted heterocyclyl, and optionally substituted heteroaryl; or~~

~~when two R¹⁹ groups are attached to the same carbon atom, the two R¹⁹ groups together with the carbon atom to which they are attached form cycloalkylene or heterocyclylene;~~

~~ring D is absent or present; wherein:~~

~~— (i) — when ring D is absent, then one of Q and W is CH₂, O, S, S(O), S(O)₂, or NH; and the other of Q and W is CH₂; and~~

~~— (ii) — when ring D is present, then Q and W are independently N or C provided only one of Q and W is N; and ring D is phenyl or a 5 or 6 membered heteroaryl ring which, including Q and W, contains one to three heteroatoms independently selected from N, O, and S and ring D is optionally be substituted with one or two substituents independently selected from alkyl, cycloalkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, hydroxyalkyl, cyano, amino, aminoalkyl, carboxy, and optionally substituted heterocyclyl; or a pharmaceutically acceptable salt thereof.~~

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof wherein Z is -Y-M₁ (wherein Y is bond and M is alkyl, haloalkyl, cycloalkyl, heterocyclyl, or heteroaryl wherein alkyl, haloalkyl, cycloalkyl, heterocyclyl and heteroaryl are substituted with -O(alkylene)OR^a where R^a is alkyl, cycloalkyl, cycloalkylalkyl, aminoalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, or optionally substituted heteroaryl.

~~3. — The compound of claim 1, or a pharmaceutically acceptable salt thereof wherein Z is -Y-M (wherein Y is bond or O and M is alkyl, haloalkyl, cycloalkyl, heterocyclyl, or heteroaryl wherein alkyl, haloalkyl, cycloalkyl, heterocyclyl and heteroaryl are substituted with -O(alk)OR^b, -S(O)₂R^d, -NR^eC(O)R^f, -NR^gSO₂R^h, -OC(O)NRⁱR^j, -C(O)NR^kR^m, or -S(O)₂NRⁿR^o;~~

34. The compound of claim 1, or a pharmaceutically acceptable salt thereof wherein Z is -Y-M₁ (wherein Y is bond and M is alkyl, haloalkyl, cycloalkyl, heterocyclyl, or heteroaryl wherein alkyl, haloalkyl, cycloalkyl, heterocyclyl and heteroaryl are substituted

with -O-R^a where R^a is alkyl, cycloalkyl, cycloalkylalkyl, aminoalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, or optionally substituted heteroaryl.

54. The compound of claim 1, or a pharmaceutically acceptable salt thereof
5 wherein Z is -OR^a where R^a is alkyl, cycloalkyl, cycloalkylalkyl, aminoalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, or optionally substituted heteroaryl.

56. The compound of claim 1, or a pharmaceutically acceptable salt thereof
10 wherein Z is -O(alkylene)OR^b where R^b is alkyl, cycloalkyl, cycloalkylalkyl, aminoalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, or optionally substituted heteroaryl.

~~7. The compound of claim 1, or a pharmaceutically acceptable salt thereof
wherein Z is hydrogen, alkyl, halo, haloalkyl, haloalkoxy, cyano, cycloalkyl, heterocyclyl,
heteroaryl (wherein cycloalkyl, heterocyclyl, and heteroaryl are optionally substituted with
one to three halo), O(alk)_yR^a, O(alk)OR^b, S(O)₂R^d,
15 -OC(O)NRⁱR^j, S(O)₂NR^aR^o, NR^pR^q, or Y-M (wherein Y is bond, O, or SO₂ and M is alkyl,
haloalkyl, cycloalkyl, heterocyclyl, or heteroaryl wherein alkyl, haloalkyl, cycloalkyl,
heterocyclyl and heteroaryl are substituted with O(alk)_yR^a, O(alk)OR^b, S(O)₂R^d, or NR^pR^q
and cycloalkyl, heterocyclyl, and heteroaryl are optionally further substituted with 1 to 3
20 halo).~~

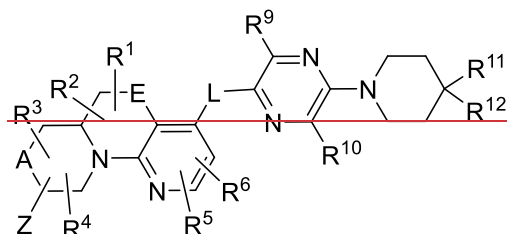
86. The compound of claim 21, or a pharmaceutically acceptable salt thereof
wherein Z is methoxymethyloxymethyl, ethoxymethyloxymethyl, methoxyethyloxymethyl,
cyclopropylmethyloxymethyl, or oxetan-3-ylmethyloxymethyl.

97. The compound of claim 31, or a pharmaceutically acceptable salt thereof
25 wherein Z is methoxymethyloxy, methoxyethyloxy, methoxymethyl,
methoxymethyloxymethyl, ethoxymethyloxymethyl, methoxyethyloxymethyl,
cyclopropylmethyloxy, or oxetan-3-ylmethyloxymethyl.

~~10. The compound of claim 7, or a pharmaceutically acceptable salt thereof
wherein Z is hydrogen, fluoro, cyano, methoxy, hydroxy, cyclopentyloxy, tetrahydrofuran-3-
30 yloxy, oxetan-3-yloxy, methoxymethyloxy, methoxyethyloxy, methylsulfonyl,
aminocarbonyloxy, pyrazol-1-yl, hydroxymethyl, methoxymethyl, ethoxymethyl,
methoxymethyloxymethyl, ethoxymethyloxymethyl, methoxyethyloxymethyl,
cyclopropylmethyloxy, or oxetan-3-ylmethyloxymethyl.~~

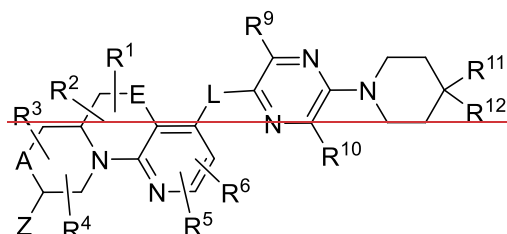
~~11. The compound of claim 1, or a pharmaceutically acceptable salt thereof wherein Z is fluoro.~~

~~12. The compound of any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof is wherein the compound has a structure of formula (II):~~



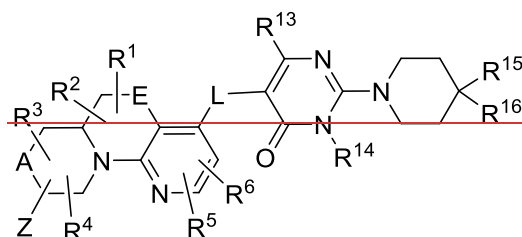
~~(II).~~

~~13. The compound of any one of claims 1 to 12, and or a pharmaceutically acceptable salt thereof is wherein the compound has a structure of Formula (IIA):~~



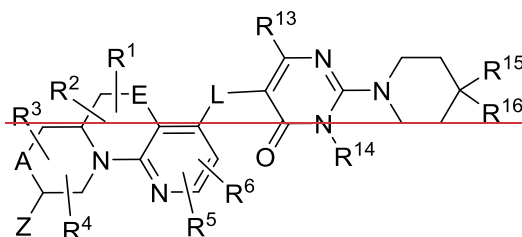
~~(IIA).~~

~~14. The compound of any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof is wherein the compound has a structure of formula (III):~~



~~(III).~~

~~15. The compound of claim 1 to 11 and 14, or a pharmaceutically acceptable salt thereof is wherein the compound has structure of Formula (IIIA):~~

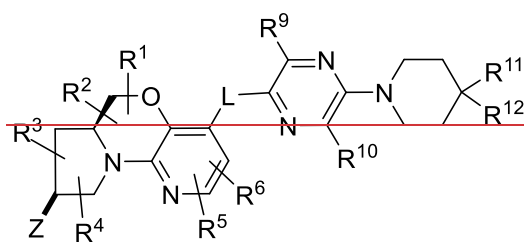


~~(IIIA).~~

~~16. The compound of claim any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof wherein E is O and A is CH₂ or bond.~~

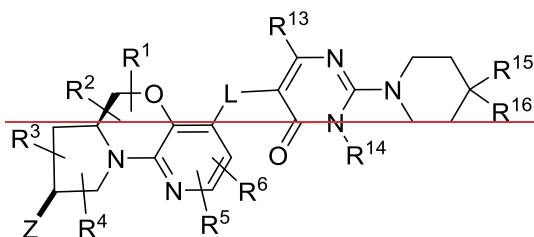
~~17. The compound of claim any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof wherein E is O and A is bond.~~

5 ~~18. The compound of any one of claims 2 to 13, or a pharmaceutically acceptable salt thereof has a structure of formula (HB):~~



~~(HB).~~

10 ~~19. The compound of any one of claim 2 to 11, 14, and 15, or a pharmaceutically acceptable salt thereof has the structure of formula (IIB):~~



~~(IIB).~~

15 ~~208. The compound of claim any one of claims 1 to 19, or a pharmaceutically acceptable salt thereof wherein R⁹ and R¹³ are is hydrogen.~~

~~219. The compound of claim any one of claims 1 to 19, or a pharmaceutically acceptable salt thereof wherein R⁹ and R¹³ are is amino.~~

~~2210. The compound of claim any one of claims 1 to 19, or a pharmaceutically acceptable salt thereof wherein R⁹ and R¹³ are is methyl.~~

20 ~~2311. The compound of claim any one of claims 1 to 19, or a pharmaceutically acceptable salt thereof wherein R⁹ and R¹³ are independently is hydrogen, alkyl, or amino.~~

~~2412. The compound of claim any one of claims 1 to 23, or a pharmaceutically acceptable salt thereof wherein L is S.~~

25 ~~2513. The compound of claim any one of claims 1 to 23, or a pharmaceutically acceptable salt thereof wherein L is S(O) or S(O)₂.~~

~~2614.~~ The compound of claim ~~any one of claims 1 to 23,~~ or a pharmaceutically acceptable salt thereof wherein L is bond.

~~2715.~~ The compound of claim ~~any one of claims 1 to 23,~~ or a pharmaceutically acceptable salt thereof wherein L is CR^7R^8 where R^5 and R^6 are independently hydrogen or alkyl.

~~2816.~~ The compound of claim ~~any one of claims 1 to 13, 16 to 18 and 20 to 27,~~ or a pharmaceutically acceptable salt thereof wherein R^{10} is hydroxyalkyl.

~~2917.~~ The compound of claim ~~any one of claims 1 to 13, 16 to 18 and 20 to 27,~~ or a pharmaceutically acceptable salt thereof wherein R^{10} is hydroxymethyl.

~~3018.~~ The compound of claim ~~any one of claims 1 to 13, 16 to 18 and 20 to 27,~~ or a pharmaceutically acceptable salt thereof wherein R^{10} is hydrogen.

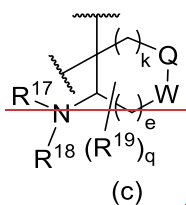
~~31.—The compound of claim any one of claims 1 to 11, 14 to 17, 19, and 20 to 28, or a pharmaceutically acceptable salt thereof is wherein R^{14} is hydrogen or methyl.~~

~~32.—The compound of claim any one of claims 1 to 31, or a pharmaceutically acceptable salt thereof wherein:~~

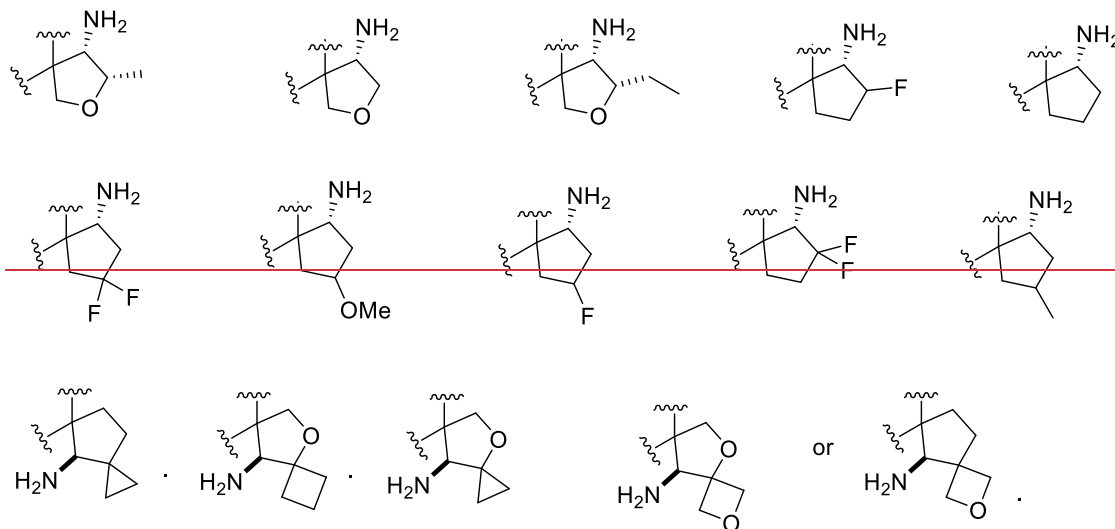
~~R^{11} and R^{15} are selected from amino and aminoalkyl; and R^{12} and R^{16} are independently selected from hydrogen, cyano, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, cycloalkyl, aryl, heterocyclyl, and heteroaryl, where alkyl, cycloalkyl, aryl, heterocyclyl and heteroaryl are optionally substituted with one to three substituents independently selected from alkyl, halo, haloalkyl, haloalkoxy, alkoxy, and cyano.~~

~~33.—The compound of claim 32, or a pharmaceutically acceptable salt thereof wherein R^{11} and R^{15} are aminomethyl and R^{12} and R^{16} are methyl.~~

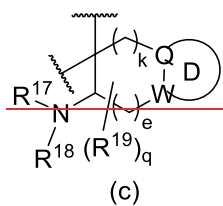
~~34.—The compound of claim any one of claims 1 to 31, or a pharmaceutically acceptable salt thereof wherein R^{11} and R^{12} , and R^{15} and R^{16} together with the carbon atom to which they are attached form a ring of formula (c):~~



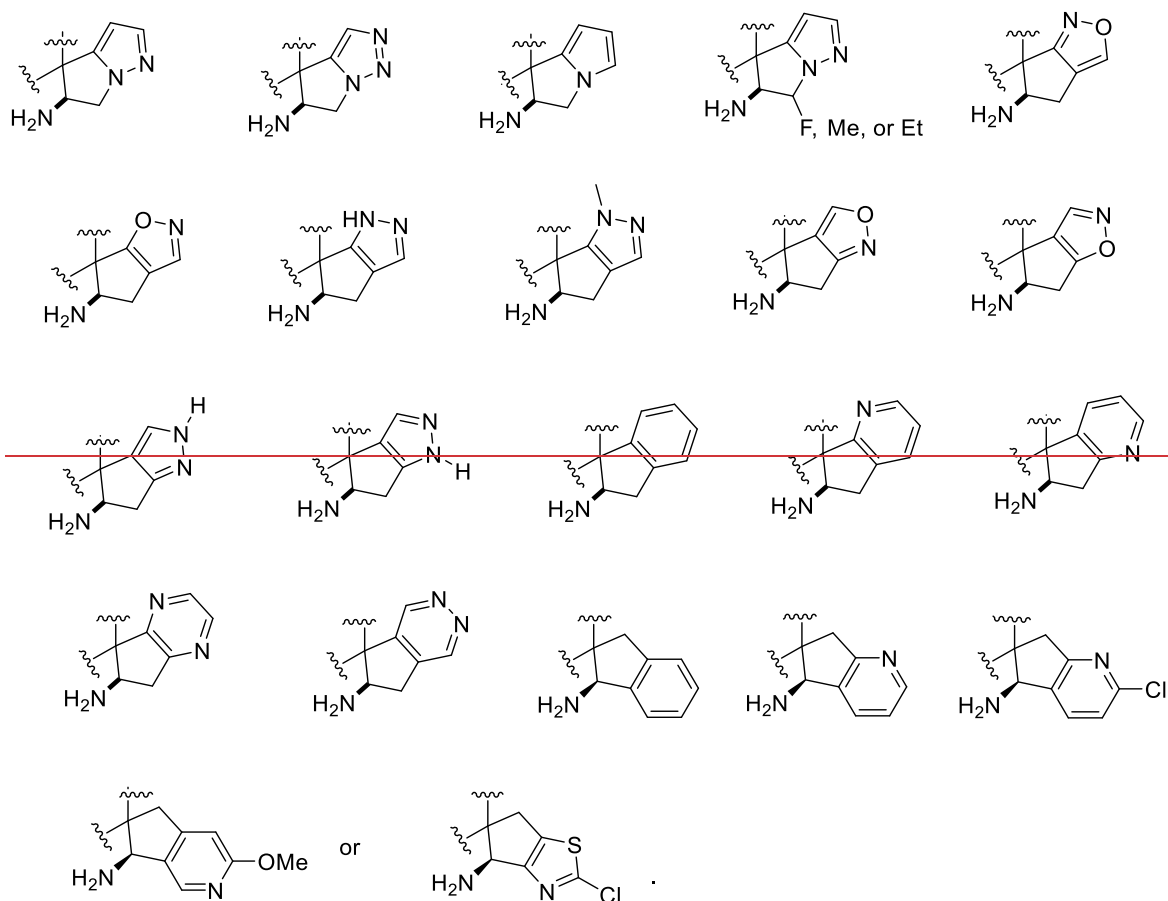
~~35. The compound of claim 32, or a pharmaceutically acceptable salt thereof wherein ring of formula (c) is:~~



5 ~~36. The compound of claim any one of claims 1 to 31, or a pharmaceutically acceptable salt thereof wherein R^{11} and R^{12} , and R^{15} and R^{16} together with the carbon atom to which they are attached form a ring of formula (c):~~



~~37. The compound of claim 36, or a pharmaceutically acceptable salt thereof wherein ring of formula (c) is:~~



3819. The compound of ~~any one of~~ claims ~~1 to 37~~, or a pharmaceutically acceptable salt thereof wherein R^1 , R^2 , R^3 , and R^4 are independently selected from hydrogen, alkyl, halo, haloalkyl, haloalkoxy, alkoxy, cyano, and hydroxy, amino.

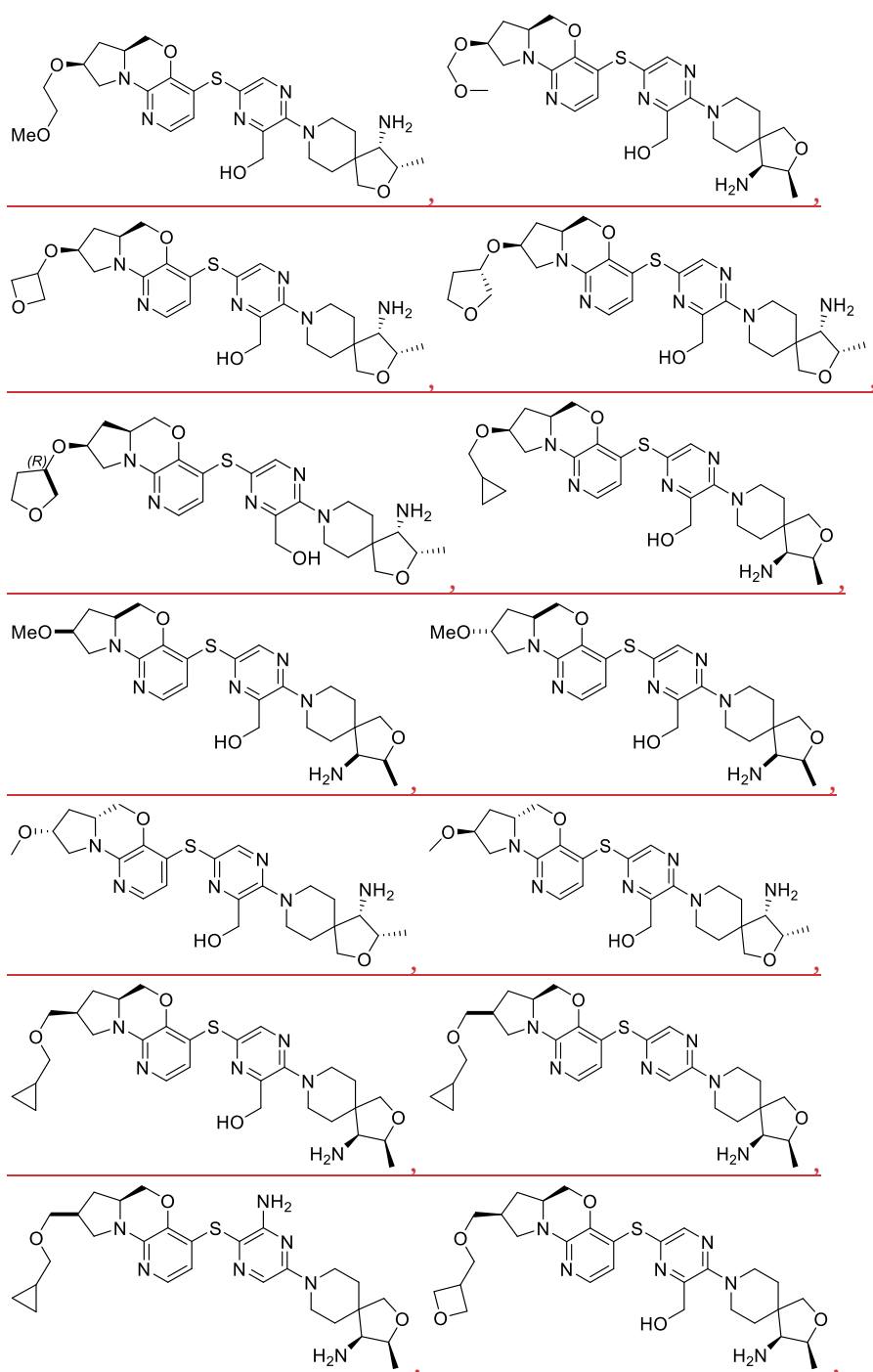
5 **3920.** The compound of claim **3819**, or a pharmaceutically acceptable salt thereof wherein one of R^1 , R^2 , R^3 , and R^4 is hydrogen and the remaining three of R^1 , R^2 , R^3 , and R^4 are independently selected from hydrogen, methyl, fluoro, methoxy, hydroxy, and amino.

4021. The compound of claim **3819**, or a pharmaceutically acceptable salt thereof wherein R^1 , R^2 , R^3 , and R^4 are hydrogen.

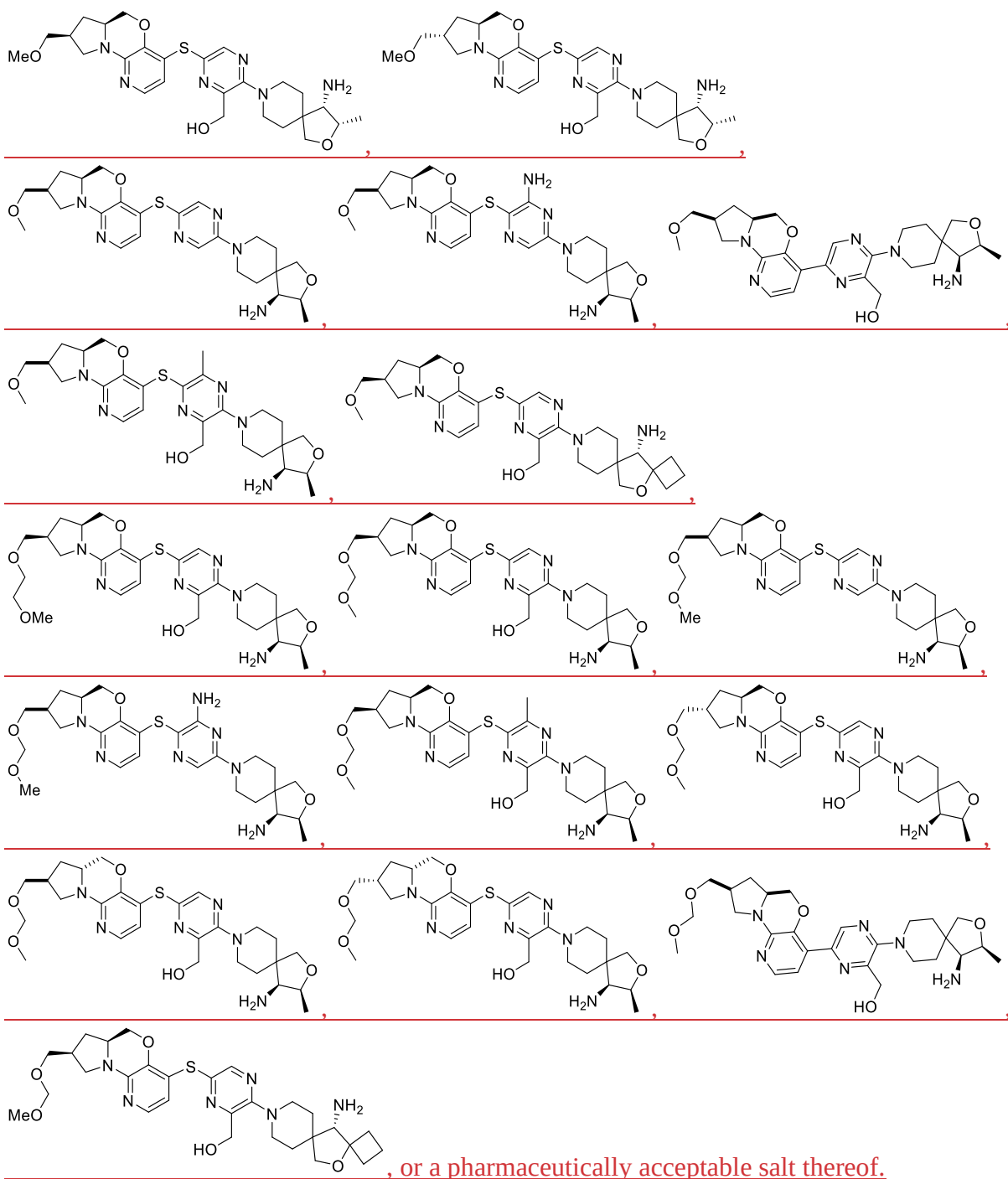
4122. The compound of ~~any one of~~ claims ~~1 to 40~~, or a pharmaceutically acceptable salt ~~thereof~~ wherein R⁵ is hydrogen, alkyl, halo, or amino and R⁶ is hydrogen, alkyl, halo, haloalkyl, haloalkoxy, alkoxy, hydroxy, or cyano.

4223. The compound of claim **4122**, or a pharmaceutically acceptable salt thereof
 5 wherein R⁵ and R⁶ are hydrogen.

4324. The compound of claim 1 selected from:



10



, or a pharmaceutically acceptable salt thereof.

~~(3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-(((S)-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-4-yl)thio)pyrazin-2-yl)methanol;~~

~~(3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-(((R)-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-4-yl)thio)pyrazin-2-yl)methanol;~~

~~(3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-(((6aS,8S)-8-fluoro-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-4-yl)thio)pyrazin-2-yl)methanol;~~

~~(3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-(((6aS,8R)-8-fluoro-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-4-yl)thio)pyrazin-2-yl)methanol;~~

5 ~~(3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-(((6aS,8S)-8-methoxy-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-4-yl)thio)pyrazin-2-yl)methanol;~~

~~(3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-(((6aS,8R)-8-methoxy-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-4-yl)thio)pyrazin-2-yl)methanol;~~

10 ~~(6aS,8S)-4-((5-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-(hydroxymethyl)pyrazin-2-yl)thio)-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-8-ol;~~

~~(6aS,8R)-4-((5-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-(hydroxymethyl)pyrazin-2-yl)thio)-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-8-ol;~~

15 ~~(3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-(((6aR,8R)-8-methoxy-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-4-yl)thio)pyrazin-2-yl)methanol;~~

20 ~~(3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-(((6aR,8S)-8-methoxy-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-4-yl)thio)pyrazin-2-yl)methanol;~~

~~(3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-(((6aS,8S)-8-(((S)-tetrahydrofuran-3-yl)oxy)-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-4-yl)thio)pyrazin-2-yl)methanol;~~

25 ~~(3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-(((6aS,8S)-8-(((R)-tetrahydrofuran-3-yl)oxy)-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-4-yl)thio)pyrazin-2-yl)methanol;~~

30 ~~(3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-(((6aS,8S)-8-(oxetan-3-yloxy)-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-4-yl)thio)pyrazin-2-yl)methanol;~~

~~(3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-(((6aS,8S)-8-(methoxymethoxy)-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-4-yl)thio)pyrazin-2-yl)methanol;~~

~~(3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-(((6aS,8S)-8-(2-methoxyethoxy)-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-4-yl)thio)pyrazin-2-yl)methanol;~~

~~(3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-(((6aS,8S)-8-(cyclopropylmethoxy)-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-4-yl)thio)pyrazin-2-yl)methanol;~~

~~(3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-(((S)-6a',7'-dihydro-6'H,9'H-spiro[cyclopropane-1,8'-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin]-4'-yl)thio)pyrazin-2-yl)methanol;~~

~~(6aS,8S)-4-((5-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-(hydroxymethyl)pyrazin-2-yl)thio)-8-methyl-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-8-ol;~~

~~-(6aS,8R)-4-((5-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-(hydroxymethyl)pyrazin-2-yl)thio)-8-methyl-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-8-ol;~~

~~(6aS,8S)-4-((5-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-(hydroxymethyl)pyrazin-2-yl)thio)-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazine-8-carbonitrile;~~

~~(3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-(((6aS,8S)-8-(methylsulfonyl)-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-4-yl)thio)pyrazin-2-yl)methanol;~~

~~(6aS,8S)-4-((5-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-(hydroxymethyl)pyrazin-2-yl)thio)-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-8-yl carbamate;~~

~~(6aS,8R)-4-((5-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-(hydroxymethyl)pyrazin-2-yl)thio)-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-8-yl carbamate;~~

~~(6-(((6aS,8S)-8-(1H-pyrazol-1-yl)-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-4-yl)thio)-3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)pyrazin-2-yl)methanol;~~

~~(6-(((6aS,8R)-8-(1H-pyrazol-1-yl)-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-4-yl)thio)-3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)pyrazin-2-yl)methanol;~~

~~(3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-(((R)-6a,7,9,10-tetrahydro-6H-[1,4]oxazino[4,3-d]pyrido[3,2-b][1,4]oxazin-4-yl)thio)pyrazin-2-yl)methanol;~~

~~(3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-(((S)-6a,7,9,10-tetrahydro-6H-[1,4]oxazino[4,3-d]pyrido[3,2-b][1,4]oxazin-4-yl)thio)pyrazin-2-yl)methanol;~~

5 ~~4-(((5-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-(hydroxymethyl)pyrazin-2-yl)thio)-6a,7,9,10-tetrahydro-6H-pyrido[3,2-b][1,4]thiazino[4,3-d][1,4]oxazine-8,8-dioxide;~~

10 ~~(3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-(((6aS,8S)-8-(methoxymethyl)-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-4-yl)thio)pyrazin-2-yl)methanol;~~

~~(3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-(((6aS,8R)-8-(methoxymethyl)-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-4-yl)thio)pyrazin-2-yl)methanol;~~

15 ~~(3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-(((6aS,8S)-8-((methoxymethoxy)methyl)-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-4-yl)thio)pyrazin-2-yl)methanol;~~

~~(3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-(((6aS,8S)-8-(2-methoxyethoxy)methyl)-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-4-yl)thio)pyrazin-2-yl)methanol;~~

20 ~~(3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-(((6aS,8S)-8-((cyclopropylmethoxy)methyl)-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-4-yl)thio)pyrazin-2-yl)methanol;~~

25 ~~(3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-(((6aS,8S)-8-((oxetan-3-ylmethoxy)methyl)-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-4-yl)thio)pyrazin-2-yl)methanol;~~

~~(3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-(((S)-2-amino-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-4-yl)thio)pyrazin-2-yl)methanol;~~

30 ~~(3-((S)-5-amino-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)-6-(((6aS,8S)-8-(methoxymethyl)-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-4-yl)thio)pyrazin-2-yl)methanol;~~

~~(3-((S)-5-amino-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)-6-(((6aS,8R)-8-(methoxymethyl)-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-4-yl)thio)pyrazin-2-yl)methanol;~~

~~(3-((S)-5-amino-13-oxa-9-azadispiro[3.1.56.24]tridecan-9-yl)-6-(((6aS,8S)-8-(methoxymethyl)-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-4-yl)thio)pyrazin-2-yl)methanol;~~

~~(3-((S)-5-amino-13-oxa-9-azadispiro[3.1.56.24]tridecan-9-yl)-6-(((6aS,8S)-8-((methoxymethoxy)methyl)-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-4-yl)thio)pyrazin-2-yl)methanol;~~

~~(3-((S)-5-amino-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)-6-(((6aS,8S)-8-((methoxymethoxy)methyl)-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-4-yl)thio)pyrazin-2-yl)methanol;~~

~~(3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-(((6aS,8S)-8-((methoxymethoxy)methyl)-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-4-yl)thio)-5-methylpyrazin-2-yl)methanol;~~

~~(3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-(((6aS,8R)-8-((methoxymethoxy)methyl)-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-4-yl)thio)pyrazin-2-yl)methanol;~~

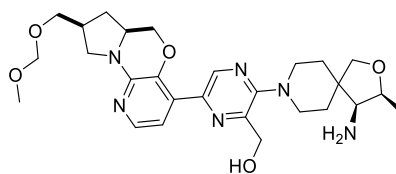
~~(3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-(((6aR,8S)-8-((methoxymethoxy)methyl)-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-4-yl)thio)pyrazin-2-yl)methanol;~~

~~(3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-(((6aR,8R)-8-((methoxymethoxy)methyl)-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-4-yl)thio)pyrazin-2-yl)methanol;~~

~~(3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-((6aS,8S)-8-(methoxymethyl)-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-4-yl)pyrazin-2-yl)methanol; and~~

~~(3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-((6aS,8S)-8-((methoxymethoxy)methyl)-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-4-yl)pyrazin-2-yl)methanol;~~

or a pharmaceutically acceptable salt thereof.



4425. The compound of claim 12 that is, or a pharmaceutically acceptable salt thereof, selected from:

~~(3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-(((6aS,8S)-8-((methoxymethoxy)methyl)-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-4-yl)thio)pyrazin-2-yl)methanol;~~

~~(3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-(((6aS,8S)-8-((2-methoxyethoxy)methyl)-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-4-yl)thio)pyrazin-2-yl)methanol;~~

~~(3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-(((6aS,8S)-8-((cyclopropylmethoxy)methyl)-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-4-yl)thio)pyrazin-2-yl)methanol;~~

~~(3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-(((6aS,8S)-8-((oxetan-3-ylmethoxy)methyl)-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-4-yl)thio)pyrazin-2-yl)methanol;~~

~~(3-((S)-5-amino-13-oxa-9-azadispiro[3.1.56.24]tridecan-9-yl)-6-(((6aS,8S)-8-((methoxymethoxy)methyl)-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-4-yl)thio)pyrazin-2-yl)methanol;~~

~~(3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-(((6aS,8S)-8-(((methoxymethoxy)methoxy)methyl)-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-4-yl)thio)pyrazin-2-yl)methanol;~~

~~(3S,4S)-8-(5-(((6aS,8S)-8-((methoxymethoxy)methyl)-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-4-yl)thio)pyrazin-2-yl)-3-methyl-2-oxa-8-azaspiro[4.5]decan-4-amine;~~

~~(3S,4S)-8-(6-amino-5-(((6aS,8S)-8-((methoxymethoxy)methyl)-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-4-yl)thio)pyrazin-2-yl)-3-methyl-2-oxa-8-azaspiro[4.5]decan-4-amine;~~

~~(S)-1'-(5-(((6aS,8S)-8-((methoxymethoxy)methyl)-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine;~~

~~(S)-1'-(6-amino-5-(((6aS,8S)-8-((methoxymethoxy)methyl)-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine;~~

~~(3-((S)-5-amino-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)-6-(((6aS,8S)-8-((methoxymethoxy)methyl)-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-4-yl)thio)pyrazin-2-yl)methanol;~~

~~(3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-(((6aS,8S)-8-((methoxymethoxy)methyl)-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-4-yl)thio)-5-methylpyrazin-2-yl)methanol;~~

~~(3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-(((6aS,8R)-8-((methoxymethoxy)methyl)-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-4-yl)thio)pyrazin-2-yl)methanol;~~

~~(3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-(((6aR,8S)-8-((methoxymethoxy)methyl)-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-4-yl)thio)pyrazin-2-yl)methanol;~~

~~(3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-(((6aR,8R)-8-((methoxymethoxy)methyl)-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-4-yl)thio)pyrazin-2-yl)methanol; and~~

~~(3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-((6aS,8S)-8-((methoxymethoxy)methyl)-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-4-yl)pyrazin-2-yl)methanol; or~~

~~a pharmaceutically acceptable salt thereof.~~

~~4526. A pharmaceutical composition comprising a compound, or pharmaceutically acceptable salt thereof, of any one of claims 1 to 44-25 and a pharmaceutically acceptable excipient.~~

~~4627. Use of a compound of any one of claims 1 to 25, or pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of cancerA method of treating a disease treatable by inhibition of SHP2 in a patient which method comprises administering to the patient, in need of such treatment, a therapeutically effective amount of a compound, or pharmaceutically acceptable salt thereof, of any one of claims 1 to 44 or which method comprises administering to the patient, in need of such treatment, a pharmaceutical composition comprising a compound, or pharmaceutically acceptable salt thereof, of any one of claims 1 to 44 and a pharmaceutically acceptable excipient.~~

~~47.—The method of claim 46 wherein the disease is cancer.~~

~~48~~28. The ~~method~~use of claim ~~27~~47 wherein the cancer is selected from lung cancer, stomach cancer, liver cancer, colon cancer, kidney cancer, breast cancer, pancreatictis cancer, juvenile myelomonocytic leukemias, neuroblastoma, melanoma, ~~and-or~~or acute myeloid leukemia.

~~49.—The method of claim 46 wherein the disease is selected from Noonan syndrome and Leopard syndrome.~~