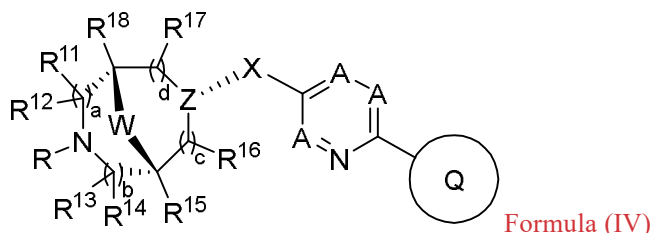


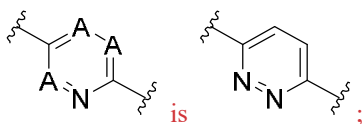
SUMMARY

[0005] The novel small molecule splicing modulators (SMSMs) described herein do not suffer from the limitations above, nor the structural and steric hindrances that greatly limit oligonucleotide therapies (e.g., by blocking hybridization to pre-mRNA targets). Small molecules have been essential in uncovering the mechanisms, regulations, and functions of many cellular processes, including DNA replication, transcription, and translation. While several recent reports have described screens for small molecule effectors of splicing, only a small number of constitutive or alternative splicing modulators have been identified and many of the small-molecule inhibitors lack specificity, lack selectivity, lack potency, exhibit toxicity, or are not orally available. Targeting the RNA transcriptome with small-molecule modulators represents an untapped therapeutic approach to treat a variety of RNA-mediated diseases. Accordingly, there remains a need to develop small-molecule RNA modulators useful as therapeutic agents. There is need in the art for novel modulators of splicing or splicing-dependent processes. Provided herein are small molecule splicing modulators and uses thereof that fulfill this need.

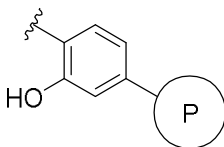
[0005a] In one aspect, provided herein is a compound that has the structure of Formula (IV), or a pharmaceutically acceptable salt thereof:



wherein:



ring Q is:



; wherein ring P is aryl or heteroaryl;

X is -O-;

each R¹ is independently H, D, C₁-C₆ alkyl, -CD₃, C₁-C₆ haloalkyl, C₁-C₆ heteroalkyl, C₃- C₂-C₇ heterocycloalkyl, aryl, or heteroaryl;

Z is CR⁷; and R⁷ is H;

W is C₁-C₄ alkylene;

R is H;

R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , and R^{18} are each independently selected from the group consisting of H, F, OR^1 , C_{1-6} alkyl, C_{1-6} fluoroalkyl, C_{1-6} heteroalkyl, wherein alkyl is optionally substituted with hydroxy, amino, methoxy, mono- C_{1-6} alkylamino or di- C_{1-6} alkylamino;

a and b are each 0;

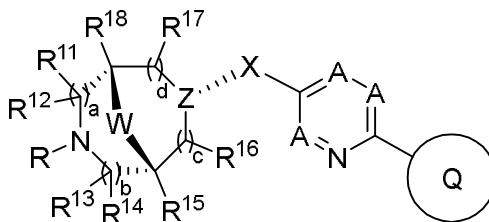
c and d are each 1; and

wherein the compound of Formula (IV) has a stereochemical purity of at least 80%.

[0005b] In another aspect, provided herein is a pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable diluent, carrier, or excipient.

[0005c] In another aspect, provided herein is a compound disclosed herein, or a pharmaceutically acceptable salt thereof, for use in the treatment, prevention and/or delay of progression of a disease or condition.

[0006] Provided herein is a compound that has the structure of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IV)

wherein,

each A is independently N or CR^A ;

each R^A is independently selected from H, D, halogen, -CN, -OH, - OR^1 , =O, =N- OR^1 , - SR^1 , -S(=O) R^1 , -S(=O) $_2R^1$, -N(R^1) $_2$, -NR ^{1} S(=O)(=NR ^{1}) R^2 , -NR ^{1} S(=O) $_2R^2$, -S(=O) $_2$ N(R^1) $_2$, -C(=O) R^1 , -OC(=O) R^1 , -C(=O)OR ^{1} , -OC(=O)OR ^{1} , -C(=O)N(R^1) $_2$, -OC(=O)N(R^1) $_2$, -NR ^{1} C(=O) R^1 , -P(=O)(R^2) $_2$, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} haloalkyl, substituted or unsubstituted C_{1-6} heteroalkyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{2-7} heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted monocyclic heteroaryl;

ring Q is monocyclic aryl, bicyclic aryl, monocyclic heteroaryl, or fused bicyclic heteroaryl;

X is -O-, -NR ^{3} -, -CR ^{4} R ^{5} -, -C(=O)-, -C(=CR ^{2})-, -S-, -S(=O)-, -S(=O) $_2$ -, or -S(=O)(=NR ^{1})-

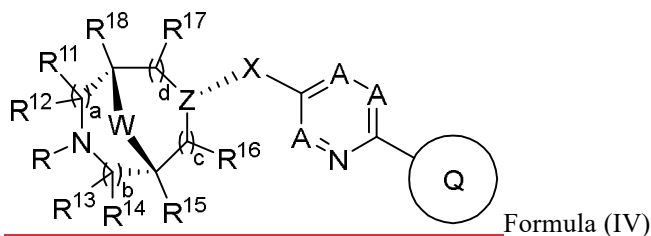
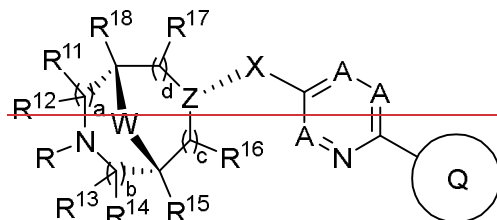
each R^1 is independently H, D, substituted or unsubstituted C_{1-6} alkyl, -CD $_3$, substituted or unsubstituted C_{1-6} haloalkyl, substituted or unsubstituted C_{1-6} heteroalkyl, substituted or unsubstituted C_{3-8}

cycloalkyl, substituted or unsubstituted C₂-C₇ heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

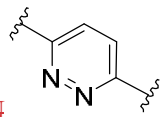
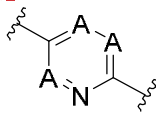
CLAIMS

What is claimed is:

1. 1. A compound that has the structure of Formula (IV), or a pharmaceutically acceptable salt ~~or solvate~~ thereof:

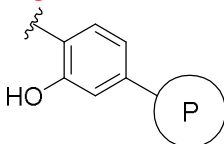


wherein:



each A is independently N;

ring Q is:



; wherein ring P is aryl or CR^Aheteroaryl;

X is -O-;

each R^AR¹ is independently selected from H, D, halogen, CN, OH, OR⁺, =O, =N-OR⁺, -SR¹, -S(=O)R¹, -S(=O)₂R¹, -N(R¹)₂, -NR¹S(=O)(=NR¹)R², -NR¹S(=O)₂R², -S(=O)₂N(R¹)₂, -C(=O)R⁺, -OC(=O)R⁺, -C(=O)OR⁺, -OC(=O)OR⁺, -C(=O)N(R¹)₂, -OC(=O)N(R¹)₂, -NR⁺C(=O)R⁺, -P(=O)(R²)₂, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted -CD₃, C₁-C₆ haloalkyl, substituted or unsubstituted C₁-C₆ heteroalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl, substituted or unsubstituted C₂-C₇ heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted monocyclic or heteroaryl; ring Q is monocyclic aryl, bicyclic aryl, monocyclic heteroaryl, or fused bicyclic heteroaryl; X is -O-, NR³, -CR⁴R⁵, -C(=O)-, C(=CR²)₂, -S-, S(=O)-, S(=O)₂-, or S(=O)(=NR⁺)-; each R⁺ is independently H, D, substituted or unsubstituted C₁-C₆ alkyl, CD₃, substituted or unsubstituted C₁-C₆ haloalkyl, substituted or unsubstituted C₁-C₆ heteroalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl, substituted or unsubstituted C₂-C₇ heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

each R^2 is independently H, D, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted monocyclic heteroaryl, $-OR^+$, $-N(R^+)_2$, $-CH_2OR^+$, $-C(=O)OR^+$, $-OC(=O)R^+$, $-C(=O)N(R^+)_2$, or $-NR^+C(=O)R^+$;

R^3 is $-OR^+$, $-N(R^+)_2$, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_8 cycloalkyl, or substituted or unsubstituted C_2 - C_7 heterocycloalkyl;

R^4 is H, D, F, $-CN$, $-OR^+$, $-SR^+$, $-N(R^+)_2$, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_1 - C_6 alkylene- OR^+ , substituted or unsubstituted C_3 - C_8 cycloalkyl, substituted or unsubstituted C_2 - C_7 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^5 is H, D, F, $-CN$, $-OR^+$, $-SR^+$, $-N(R^+)_2$, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_1 - C_6 alkylene- OR^+ , substituted or unsubstituted C_3 - C_8 cycloalkyl, substituted or unsubstituted C_2 - C_7 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or

R^4 and R^5 taken in combination with the carbon atom to which they attach, form a substituted or unsubstituted C_{3-8} cycloalkyl or a substituted or unsubstituted C_{2-7} heterocycloalkyl;

Z is $-CR^2$; and R^2 is independently H, D, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl or $-CH_2OR^+$;

W is substituted or unsubstituted C_1 - C_4 alkylene, substituted or unsubstituted C_2 - C_4 alkenylene, or substituted or unsubstituted C_1 - C_4 heteroalkylene;

R is selected from the group consisting of H, a substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} fluoroalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_8 cycloalkyl, substituted or unsubstituted C_2 - C_7 heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl, wherein alkyl is optionally substituted with hydroxy, amino, substituted or unsubstituted mono- C_{1-6} alkylamino, or substituted or unsubstituted di- C_{1-6} alkylamino;

 Z is CR^7 ; and R^7 is H;

 W is C_1 - C_4 alkylene;

 R is H;

 R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , and R^{18} are each independently selected from the group consisting of H, F, OR^1 , substituted or unsubstituted C_{1-6} alkyl, a substituted or unsubstituted C_{1-6} fluoroalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, wherein alkyl is optionally substituted with hydroxy, amino, methoxy, substituted or unsubstituted mono- C_{1-6} alkylamino or substituted or unsubstituted di- C_{1-6} alkylamino;

 R^{11} and R^{13} , taken in combination form a substituted or unsubstituted C_{1-3} alkylene group or a substituted or unsubstituted C_{1-3} heteroalkylene group; or

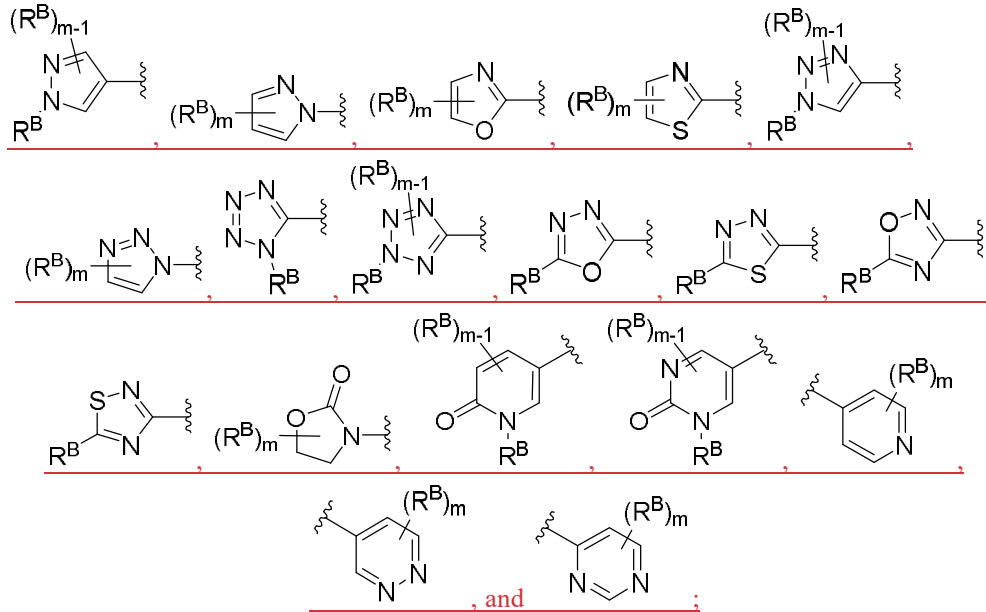
~~R¹⁴ and R¹⁵, taken in combination form a substituted or unsubstituted C₁₋₃ alkylene group; or~~
~~R¹⁶ and R¹⁷, taken in combination form a substituted or unsubstituted C₁₋₃ alkylene group; or~~
~~R¹³ and R¹⁴, taken in combination with the carbon atom to which they attach, form a spirocyclic C₃₋₈ cycloalkyl; or~~
~~R¹⁷ and R², taken in combination form a substituted or unsubstituted C₁₋₃ alkylene group; or~~
~~when X is -NR³-, then R³ and R² are optionally taken together with the intervening atoms to which they are attached to form a 4, 5, or 6-membered ring; or~~
~~when X is -NR³-, then R³ and R¹⁶ are optionally taken together with the intervening atoms to which they are attached to form a 4, 5, or 6-membered ring;~~

_____ a and b are each ~~independently selected from 0, 1, 2, or 3;~~

_____ c and d are each ~~independently selected from 1, 2, 3, or 4~~1; and

_____ wherein the compound of Formula (IV) has a stereochemical purity of at least 80%.

2. The compound of claim ~~1~~1, or a pharmaceutically acceptable salt ~~or solvate~~ thereof, wherein ~~W is substituted or unsubstituted C₁-C₄alkylene~~ ring P is heteroaryl selected from:



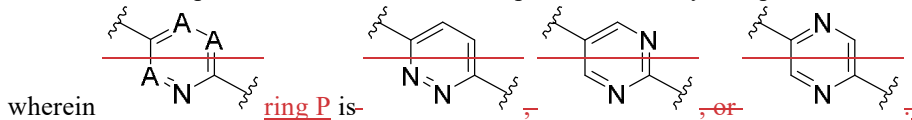
wherein:

R^B is independently selected from cyano, halogen, hydroxy, C₁-C₄ alkyl, -OCH₃, -OCD₃,

C₁-C₄ alkoxy, C₃-C₆ cycloalkyl;

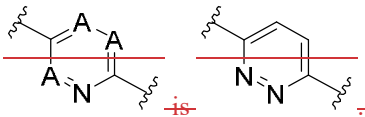
m is 0, 1, 2, or 3.

~~3.~~ 3. The compound of claim ~~1 or 2,~~2, or a pharmaceutically acceptable salt ~~or solvate~~ thereof,



~~The compound of any one of claims 1-3,~~

~~4.—4. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein~~



~~5. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt or solvate thereof,~~

wherein X is O , NR^3 , S , CR^4R^5 , $\text{C}(=\text{O})$, or $\text{C}(=\text{CR}^2_2)$.

~~6. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt or solvate thereof,~~

~~wherein X is O, NR³, or C(=O).~~

~~7. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt or solvate thereof;~~

~~wherein ring Q is substituted or unsubstituted aryl.~~

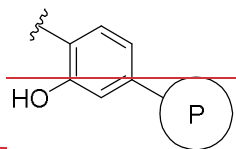
~~8. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt or solvate thereof,~~

~~wherein ring Q is 2 hydroxy phenyl substituted with:~~

~~0, 1, 2, or 3 substituents independently selected from C₁₋₆ alkyl, oxo, oxime, hydroxy, halo-C₁₋₆ alkyl, dihalo-C₁₋₆ alkyl, trihalo-C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkoxy-C₃₋₇ cycloalkyl, halo-C₁₋₆ alkoxy, dihalo-C₁₋₆ alkoxy, trihalo-C₁₋₆ alkoxy, hydroxy, cyano, halogen, amino, mono-C₁₋₆ alkylamino, di-C₁₋₆ alkylamino, aryl, heteroaryl, C₁₋₆ alkyl substituted with hydroxy, C₁₋₆ alkoxy substituted with aryl, amino, C(=O)NH-C₁₋₆ alkyl heteroaryl, NHC(=O)-C₁₋₆ alkyl heteroaryl, C₁₋₆ alkyl C(=O)NH heteroaryl, C₁₋₆ alkyl NHC(=O) heteroaryl, C₃₋₇ cycloalkyl, 5-7 membered cycloalkenyl, or 5, 6 or 9 membered heterocycle containing 1 or 2 heteroatoms independently, selected from S, O, and N; wherein two C₁₋₆ alkyl groups can combine with the atoms to which they are bound to form a 5-6 membered ring;~~

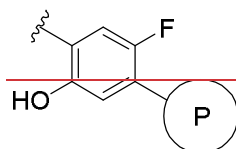
~~wherein heteroaryl has 5, 6, 9, or 10 ring atoms, 1, 2 or 3 ring heteroatoms selected from N, O, and S, and is substituted with 0, 1, or 2 substituents independently selected from oxo, hydroxy, nitro, halogen, C₁₋₆ alkyl, C₁₋₆ alkenyl, C₁₋₆ alkoxy, C₃₋₇ cycloalkyl, C₁₋₆ alkyl-OH, trihalo-C₁₋₆ alkyl, mono-C₁₋₆ alkylamino, di-C₁₋₆ alkylamino, C(=O)NH₂, NH₂, NO₂, hydroxy-C₁₋₆ alkylamino, hydroxy-C₁₋₆ alkyl, 4-7 membered heterocycle-C₁₋₆ alkyl, amino-C₁₋₆ alkyl, mono-C₁₋₆ alkylamino-C₁₋₆ alkyl, and di-C₁₋₆ alkylamino-C₁₋₆ alkyl.~~

9. ~~The compound of any one of claims 1-7, or a pharmaceutically acceptable salt or solvate thereof, wherein:~~



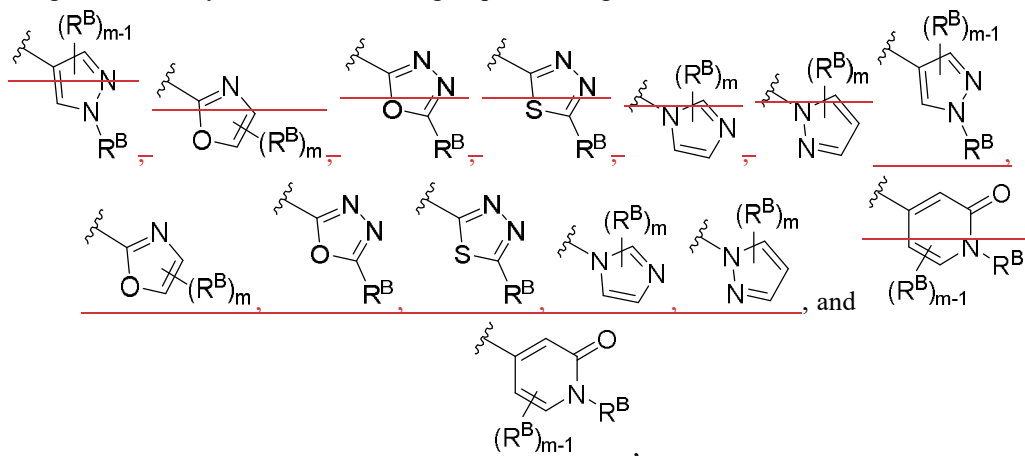
~~ring Q is~~, wherein ring P is aryl or heteroaryl.

10. ~~The compound of any one of claims 1-7, or a pharmaceutically acceptable salt or solvate thereof, wherein:~~



~~ring Q is~~, wherein ring P is aryl or heteroaryl.

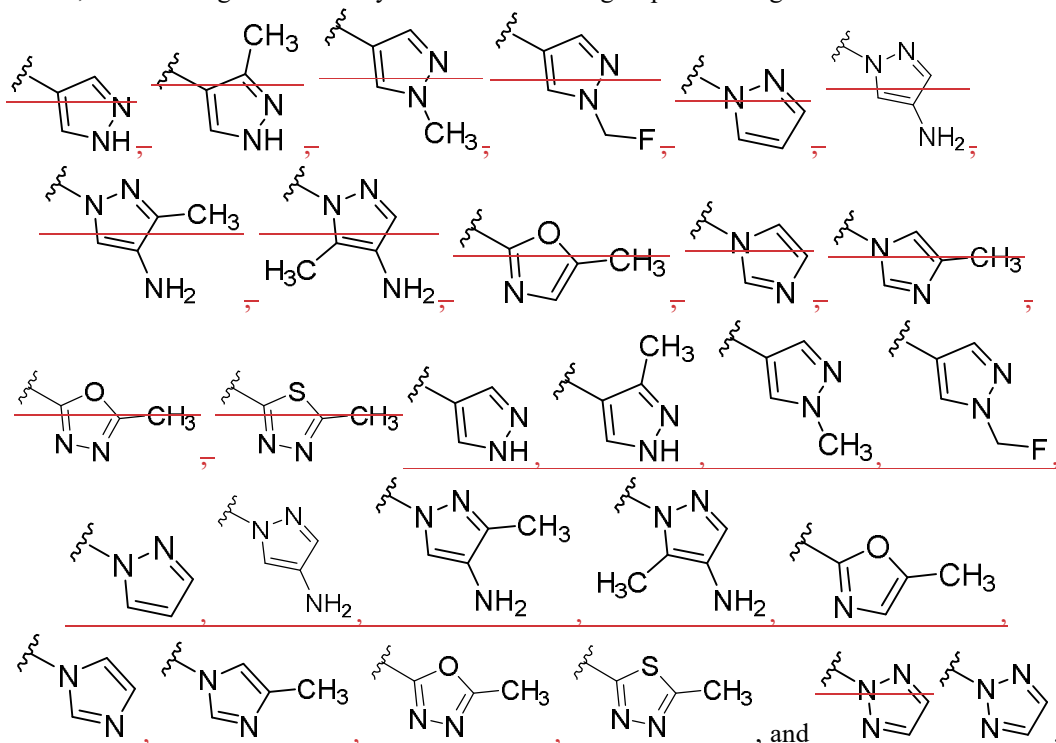
11. ~~The compound of claim 9 or 10, or a pharmaceutically acceptable salt or solvate thereof, wherein~~ ring P is heteroaryl selected from the group consisting of:



wherein each R^B is independently selected from cyano, halogen, hydroxy, ~~substituted or unsubstituted~~ C_{1-6} alkyl, $-OCH_3$, $-OCD_3$, ~~substituted or unsubstituted~~ C_{2-6} alkenyl, ~~substituted or unsubstituted~~ C_{2-6} alkynyl, ~~substituted or unsubstituted~~ C_{1-6} alkoxy, ~~substituted or unsubstituted~~ C_{3-7} cycloalkyl, ~~substituted or unsubstituted~~ C_{2-8} heterocycloalkyl, heteroaryl, ~~substituted or unsubstituted~~ heterocycloalkyl- C_{1-6} alkyl, ~~substituted or unsubstituted~~ C_{1-6} alkyl-aryl, ~~substituted or unsubstituted~~ C_{1-6} alkyl-heterocycloalkyl, ~~substituted or unsubstituted~~ C_{1-6} alkyl-heteroaryl, ~~substituted or unsubstituted~~ C_{1-6} alkoxy-aryl, ~~substituted or unsubstituted~~ C_{1-6} alkoxy-heterocycloalkyl, ~~substituted or unsubstituted~~ C_{1-6} alkoxy-heteroaryl, and C_{1-6} alkoxy substituted with hydroxy, C_{1-6} alkoxy, amino, mono- C_{1-6} alkylamino and di- C_{1-6} alkylamino;

and m is 0, 1, 2, or 3.

12. 5. ~~The compound of claim 9 or 10, 1, or a pharmaceutically acceptable salt or solvate thereof, wherein ring P is heteroaryl selected from the group consisting of:~~



- Chemical structures of various pyrazole, imidazole, and triazole derivatives are shown, including substituted pyrazoles, imidazoles, and triazoles, some with wavy lines indicating attachment points.

-

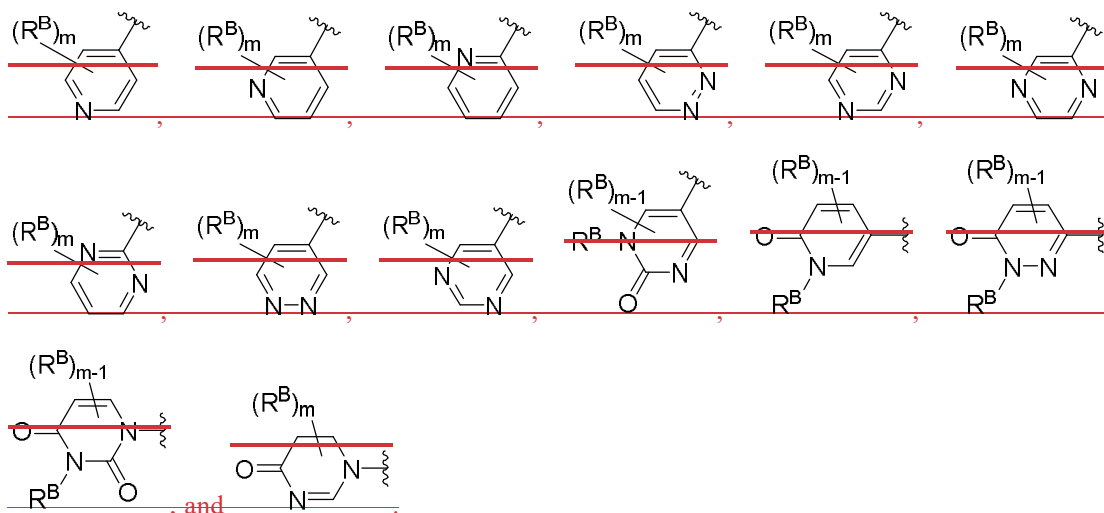
-

~~19. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt or solvate thereof, wherein ring Q is monocyclic heteroaryl or fused bicyclic heteroaryl.~~

~~20. The compound of claim 19, or a pharmaceutically acceptable salt or solvate thereof, wherein ring Q is a 5- or 6-membered monocyclic heteroaryl having 1-4 ring nitrogen atoms and which is substituted by phenyl or a heteroaryl having 5- or 6 ring atoms, 1- or 2 ring heteroatoms independently selected from N, O and S and is substituted with 0, 1, or 2 substituents independently selected from cyano, C₁₋₆ alkyl, mono-C₁₋₆ alkylamino, di-C₁₋₆ alkylamino, hydroxy-C₁₋₆ alkylamino, hydroxy-C₁₋₆ alkyl, amino-C₁₋₆ alkyl and mono-C₁₋₆ alkylamino-C₁₋₆ alkyl, and di-C₁₋₆ alkylamino-C₁₋₆ alkyl.~~

~~21. The compound of claim 19, or a pharmaceutically acceptable salt or solvate thereof, wherein ring Q is fused bicyclic heteroaryl having 8 to 10 ring atoms, 1, 2, or 3 ring heteroatoms independently selected from N, O or S, and which is substituted with 0, 1, or 2 substituents independently selected from cyano, oxime, halogen, hydroxy, C₁₋₆ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₆ alkoxy, C₁₋₆ alkoxy substituted with hydroxy, amino, mono-C₁₋₆ alkylamino, and di-C₁₋₆ alkylamino.~~

~~22. The compound of claim 19, or a pharmaceutically acceptable salt or solvate thereof, wherein ring Q is a monocyclic heterocycle selected from the group consisting of:~~

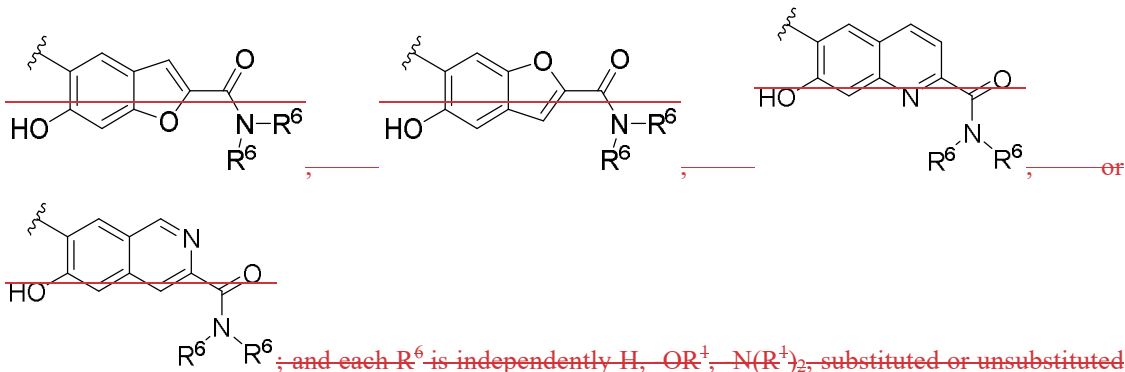


~~23. The compound of claim 19, or a pharmaceutically acceptable salt or solvate thereof, wherein: ring Q is a 6-5 fused heteroaryl, 6-6 fused heteroaryl, 5-6 fused heteroaryl, 5-5 fused heteroaryl, 7-5 fused heteroaryl, or 5-7 fused heteroaryl.~~

~~24. The compound of claim 23, or a pharmaceutically acceptable salt or solvate thereof, wherein ring Q is a 6-5 fused heteroaryl, 6-6 fused heteroaryl, or 5-6 fused heteroaryl, selected from the group consisting of:~~



25. ~~The compound of claim 23, or a pharmaceutically acceptable salt or solvate thereof, wherein ring-Q is~~



~~26. The compound of any one of claims 1-25, wherein X is -NR³-.~~

~~27. The compound of claim 26, wherein R³ is -OR¹, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted C₁-C₆ haloalkyl, substituted or unsubstituted C₁-C₆ heteroalkyl, or substituted or unsubstituted C₃-C₈ cycloalkyl.~~

~~28. The compound of claim 26, wherein R³ is C₃-C₈ cycloalkyl that is selected from cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.~~

~~29. The compound of claim 28, wherein R³ is cyclopropyl.~~

~~30. The compound of claim 26, wherein R³ is C₃-C₈ cycloalkyl that is selected from cyclopentenyl, or cyclohexenyl.~~

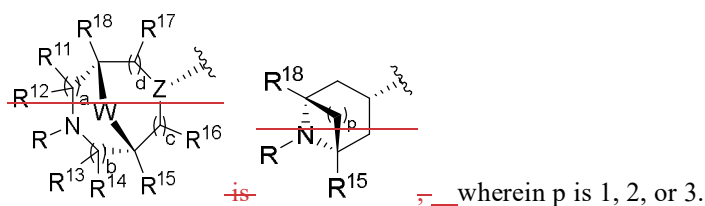
~~31. The compound of claim 26, wherein R³ is -CH₃ or -CF₃.~~

~~32. The compound of claim 26, wherein R³ is -CD₃.~~

~~33. The compound of claim 26, wherein R³ is -OCH₃, -OCH₂CH₃, -OCH₂CH₂OH or -OCH₂CH₂OCH₃.~~

~~34. The compound of claim 26, wherein R³ is -OCD₃.~~

~~35. The compound of any one of claims 1-34, or a pharmaceutically acceptable salt or solvate thereof, wherein~~



36. 11. The compound of claim ~~35,10~~, or a pharmaceutically acceptable salt ~~or solvate~~ thereof, wherein:
 R is H; R¹⁵ and R¹⁸ are H; and p is 2 or 3.

37. 12. The compound of claim ~~35,10~~, or a pharmaceutically acceptable salt ~~or solvate~~ thereof, wherein:
 R is H; R¹⁵ and R¹⁸ are H; and p is 2.

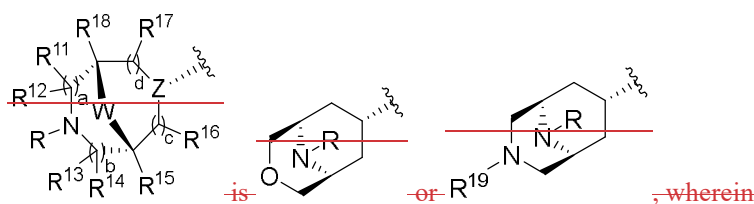
38. 13. The compound of claim ~~35,10~~, or a pharmaceutically acceptable salt ~~or solvate~~ thereof, wherein:
 R is H; R¹⁵ and R¹⁸ are H; and p is 3.

39. 14. The compound of claim ~~35,10~~, or a pharmaceutically acceptable salt ~~or solvate~~ thereof, wherein:
 R is H; R¹⁵ and R¹⁸ are CH₃; and p is 2 or 3.

40. 15. The compound of claim ~~35,10~~, or a pharmaceutically acceptable salt or solvate thereof, wherein:
 R is H; R¹⁵ and R¹⁸ are CH₃; and p is 2.

41. 16. The compound of claim ~~35,10~~, or a pharmaceutically acceptable salt or solvate thereof, wherein:
 R is H; R¹⁵ and R¹⁸ are CH₃; and p is 3.

42.—17. A pharmaceutical composition comprising a~~The~~ compound of any one of claims 1 to 16,
~~1-34,~~ or a pharmaceutically acceptable salt ~~or solvate~~ thereof, and a pharmaceutically acceptable
diluent, carrier, or excipient, ~~wherein~~



R¹⁹ ~~is~~ H, D, CN, OH, OR⁺, SR⁺, S(=O)R⁺, S(=O)₂R⁺, CH₂-N(R⁺)₂, S(=O)₂N(R⁺)₂, C(=O)R⁺, CO₂R⁺,
~~-C(=O)N(R⁺)₂, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted C₁-C₆ haloalkyl,
substituted or unsubstituted C₁-C₆ heteroalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl, or
substituted or unsubstituted C₂-C₈ heterocycloalkyl.~~

18. A compound of any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, for use
in the treatment, prevention and/or delay of progression of a disease or condition.

43.—The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, that is:

2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol;

2-(6-(((1R,3r,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol;

2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol;

2-(6-(((1R,3r,5S)-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol;

2-(6-(((1R,5S,8s)-3-azabicyclo[3.2.1]octan-8-yl)(methylamino)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol;

2-(6-(((1R,5S,8r)-3-azabicyclo[3.2.1]octan-8-yl)(methylamino)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol;

2-(6-(((1R,4R,5S)-2-azabicyclo[2.2.1]heptan-5-yl)(methylamino)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol;

2-(6-(((1S,4S,5R)-2-azabicyclo[2.2.1]heptan-5-yl)(methylamino)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol;

2-(6-(((1R,4R,5R)-2-azabicyclo[2.2.1]heptan-5-yl)(methylamino)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol;

2-(6-(((1S,4S,5S)-2-azabicyclo[2.2.1]heptan-5-yl)(methylamino)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol;

2-(6-(((1R,3r,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol;

2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol;

2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol;

2-(6-(((1R,3r,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol;

2-(6-(((1R,5S,7r)-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)(methylamino)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol;

2-(6-(((1R,5S,7s)-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)(methylamino)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol;

2-(6-(((1R,5S,7r)-1,5-dimethyl-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)(methylamino)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol;

2-(6-(((1R,5S,7s)-1,5-dimethyl-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)(methylamino)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol;

2-(6-(((1R,5S,7s)-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)oxy)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol;

2-(6-(((1R,5S,7r)-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)oxy)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol;

2-(6-(((1R,3s,5S)-9-azabicyclo[3.3.1]nonan-3-yl)(methylamino)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol;

~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-4-fluoro-5-(1H-pyrazol-4-yl)phenol;~~
~~6-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)quinolin-7-ol;~~
~~3-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-7-methoxynaphthalen-2-ol;~~
~~6-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-5-hydroxy-3-methylbenzo[d]oxazol-2(3H)-one;~~
~~3-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-7-(fluoromethoxy)naphthalen-2-ol;~~
~~3-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-7-(difluoromethoxy)naphthalen-2-ol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-4-fluoro-5-(1H-pyrazol-4-yl)phenol;~~
~~4-(4-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-3-hydroxyphenyl)-1-methylpyridin-2(1H)-one;~~
~~4-(4-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-2-fluoro-5-hydroxyphenyl)-1-methylpyridin-2(1H)-one;~~
~~5-(4-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-3-hydroxyphenyl)-2-methylpyridazin-3(2H)-one;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-5-(1-(methyl-d3)-1H-pyrazol-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-5-(2-(methoxy-d3)pyridin-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-5-(2-methoxypyridin-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-5-(1-(fluoromethyl)-1H-pyrazol-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-5-(4-fluoro-1H-pyrazol-1-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-5-(4-fluoro-1H-imidazol-1-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-5-(4-methyl-1H-imidazol-1-yl)phenol;~~
~~4-(4-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-5-hydroxy-2-methylphenyl)-1-methylpyridin-2(1H)-one;~~
~~5-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)phenol;~~

~~4-(4-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-3-hydroxyphenyl)-1-methylpyrimidin-2(1H)-one;~~
~~4-(4-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-3-hydroxyphenyl)-1-methyl-1,3,5-triazin-2(1H)-one;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-4-methyl-5-(1H-pyrazol-4-yl)phenol;~~
~~4-(4-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-3-hydroxyphenyl)pyridin-2(1H)-one;~~
~~4-(4-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-2-fluoro-5-hydroxyphenyl)pyridin-2(1H)-one;~~
~~5-(2-(difluoromethoxy)pyridin-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-5-(1-(trifluoromethyl)-1H-pyrazol-4-yl)phenol;~~
~~4-(4-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-3-hydroxyphenyl)-1-(fluoromethyl)pyridin-2(1H)-one;~~
~~6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-5-hydroxy-N-methylbenzofuran-2-carboxamide;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-5-(2-fluoro-6-methoxypyridin-4-yl)phenol;~~
~~4-(4-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-3-hydroxyphenyl)-6-fluoropyridin-2-ol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-5-(6-methoxypyridazin-4-yl)phenol;~~
~~5-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-6-hydroxy-N-methylbenzofuran-2-carboxamide;~~
~~4-(4-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-2-fluoro-5-hydroxyphenyl)-1-(fluoromethyl)pyridin-2(1H)-one;~~
~~6-(4-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-3-hydroxyphenyl)-3-methylpyrimidin-4(3H)-one;~~
~~4-(4-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-3-hydroxyphenyl)-1-methyl-1H-pyrrole-2-carbonitrile;~~
~~1-(4-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-3-hydroxyphenyl)-1H-imidazole-4-carbonitrile;~~
~~1-(4-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-2-fluoro-5-hydroxyphenyl)-1H-imidazole-4-carbonitrile;~~
~~6-(4-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-2-fluoro-5-hydroxyphenyl)-3-methylpyrimidin-4(3H)-one;~~

~~4-(4-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-3-hydroxyphenyl)picolinonitrile;~~
~~1-(4-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-3-hydroxyphenyl)-1H-pyrazole-4-carbonitrile;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(ethylamino)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(ethylamino)pyridazin-3-yl)-4-fluoro-5-(1H-pyrazol-4-yl)phenol;~~
~~1-(4-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-3-hydroxyphenyl)-1H-pyrrole-3-carbonitrile;~~
~~5-(2,6-difluoropyridin-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-5-(6-(methoxy-d3)pyridazin-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-4-fluoro-5-(6-(methoxy-d3)pyridazin-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-5-(2-fluoro-6-(methoxy-d3)pyridin-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-4-fluoro-5-(2-fluoro-6-(methoxy-d3)pyridin-4-yl)phenol;~~
~~4-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-3'-methoxy-[1,1'-biphenyl]-3-ol;~~
~~4-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-4'-fluoro-3'-methoxy-[1,1'-biphenyl]-3-ol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-5-(5-methoxypyridin-3-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-5-(6-fluoro-5-methoxypyridin-3-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-4-fluoro-5-(6-methoxypyridazin-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl d3)amino)pyridazin-3-yl)-4-fluoro-5-(1H-pyrazol-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-5-(6-methoxypyrimidin-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-4-fluoro-5-(6-methoxypyrimidin-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-5-(1H-imidazol-1-yl)phenol;~~

~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-5-(4-methyl-1H-imidazol-1-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-5-(5-methyl-1,3,4-oxadiazol-2-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-5-(1H-pyrazol-1-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-5-(4-methyl-1H-pyrazol-1-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-5-(3-methyl-1H-pyrazol-1-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-5-(2H-1,2,3-triazol-2-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-5-(1H-1,2,3-triazol-1-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-5-(4-methyl-1H-1,2,3-triazol-1-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-5-(1H-1,2,3-triazol-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-5-(1H-tetrazol-5-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-5-(2-methyloxazol-5-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-5-(3-methylisoxazol-5-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-5-(2-methyl-1H-imidazol-1-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-5-(2,4-dimethyl-1H-imidazol-1-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-5-(5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-5-(5-methyl-1H-tetrazol-1-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-5-(5-methyl-2H-tetrazol-2-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-5-(4H-1,2,4-triazol-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-5-(6-methylpyridin-3-yl)phenol;~~

~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-5-(2-methylpyrimidin-5-yl)phenol;~~
~~5-(4-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-3-hydroxyphenyl)-2-methylpyridazin-3(2H)-one;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-5-(6-methylpyridazin-3-yl)phenol;~~
~~4-(4-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-3-hydroxyphenyl)-1-methylpyridin-2(1H)-one;~~
~~5-(4-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-3-hydroxyphenyl)-1-methylpyridin-2(1H)-one;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-5-(4-(trifluoromethyl)-1H-imidazol-1-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-5-(1H-1,2,4-triazol-1-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-5-(3-methyl-1H-1,2,4-triazol-1-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-5-(1H-imidazol-1-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-5-(4-methyl-1H-imidazol-1-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-5-(5-methyl-1,3,4-oxadiazol-2-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-5-(1H-pyrazol-1-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-5-(4-methyl-1H-pyrazol-1-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-5-(3-methyl-1H-pyrazol-1-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-5-(2H-1,2,3-triazol-2-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-5-(1H-1,2,3-triazol-1-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-5-(1H-1,2,3-triazol-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-5-(1H-tetrazol-5-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-5-(2-methyloxazol-5-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-5-(3-methylisoxazol-5-yl)phenol;~~

~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-5-(5-methyl-1H-tetrazol-1-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-5-(5-methyl-2H-tetrazol-2-yl)phenol;~~
~~4-(4-(6-(((1R,3s,5S)-1,5-dimethyl-9-azabicyclo[3.3.1]nonan-3-yl)(methyl)amino)pyridazin-3-yl)-3-hydroxyphenyl)-1-methylpyridin-2(1H)-one;~~
~~5-(4-(6-(((1R,3s,5S)-1,5-dimethyl-9-azabicyclo[3.3.1]nonan-3-yl)(methyl)amino)pyridazin-3-yl)-3-hydroxyphenyl)-2-methylpyridazin-3(2H)-one;~~
~~5-(6-(((1R,3s,5S)-1,5-dimethyl-9-azabicyclo[3.3.1]nonan-3-yl)(methyl)amino)pyridazin-3-yl)-6-hydroxy-N-methylbenzofuran-2-carboxamide;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-9-azabicyclo[3.3.1]nonan-3-yl)oxy)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-9-azabicyclo[3.3.1]nonan-3-yl)oxy)pyridazin-3-yl)-4-fluoro-5-(1H-pyrazol-4-yl)phenol;~~
~~4-(4-(6-(((1R,3s,5S)-1,5-dimethyl-9-azabicyclo[3.3.1]nonan-3-yl)(methyl)amino)pyridazin-3-yl)-2-fluoro-5-hydroxyphenyl)-1-(fluoromethyl)pyridin-2(1H)-one;~~
~~4-(4-(6-(((1R,3s,5S)-1,5-dimethyl-9-azabicyclo[3.3.1]nonan-3-yl)(methyl)amino)pyridazin-3-yl)-2-fluoro-5-hydroxyphenyl)-1-methylpyridin-2(1H)-one;~~
~~6-(4-(6-(((1R,3s,5S)-1,5-dimethyl-9-azabicyclo[3.3.1]nonan-3-yl)(methyl)amino)pyridazin-3-yl)-3-hydroxyphenyl)-3-methylpyrimidin-4(3H)-one;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-9-azabicyclo[3.3.1]nonan-3-yl)(methyl)amino)pyridazin-3-yl)-5-(6-methoxypyridazin-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-9-azabicyclo[3.3.1]nonan-3-yl)(methyl)amino)pyridazin-3-yl)-5-(6-(methoxy-d3)pyridazin-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-9-azabicyclo[3.3.1]nonan-3-yl)(methyl)amino)pyridazin-3-yl)-4-fluoro-5-(6-(methoxy-d3)pyridazin-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-9-azabicyclo[3.3.1]nonan-3-yl)(methyl)amino)pyridazin-3-yl)-5-(6-methoxypyrimidin-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-9-azabicyclo[3.3.1]nonan-3-yl)(methyl)amino)pyridazin-3-yl)-4-fluoro-5-(1H-pyrazol-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-9-azabicyclo[3.3.1]nonan-3-yl)(methyl)amino)pyridazin-3-yl)-5-(1H-imidazol-1-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-9-azabicyclo[3.3.1]nonan-3-yl)(methyl)amino)pyridazin-3-yl)-5-(2-methyloxazol-5-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-9-azabicyclo[3.3.1]nonan-3-yl)(methyl)amino)pyridazin-3-yl)-4-fluoro-5-(2-methyloxazol-5-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-9-azabicyclo[3.3.1]nonan-3-yl)(methyl)amino)pyridazin-3-yl)-5-(2H-1,2,3-triazol-2-yl)phenol;~~

~~2-(6-(((1R,3s,5S)-9-azabicyclo[3.3.1]nonan-3-yl)oxy)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol;~~
~~2-(6-(((1R,3r,5S)-9-azabicyclo[3.3.1]nonan-3-yl)oxy)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-9-azabicyclo[3.3.1]nonan-3-yl)oxy)pyridazin-3-yl)-4-fluoro-5-(1H-pyrazol-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-9-azabicyclo[3.3.1]nonan-3-yl)(methylamino)pyridazin-3-yl)-5-(1H-1,2,3-triazol-1-yl)phenol;~~
~~5-(4-(6-(((1R,3s,5S)-9-azabicyclo[3.3.1]nonan-3-yl)(methylamino)pyridazin-3-yl)-3-hydroxyphenyl)-2-methylpyridazin-3(2H)-one;~~
~~5-(4-(6-(((1R,3s,5S)-9-azabicyclo[3.3.1]nonan-3-yl)(methylamino)pyridazin-3-yl)-3-hydroxyphenyl)-2-(methyl-d3)pyridazin-3(2H)-one;~~
~~5-(4-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-3-hydroxyphenyl)-2-(methyl-d3)pyridazin-3(2H)-one;~~
~~4-(4-(6-(((1R,3s,5S)-9-azabicyclo[3.3.1]nonan-3-yl)(methylamino)pyridazin-3-yl)-3-hydroxyphenyl)-1-methylpyridin-2(1H)-one;~~
~~4-(4-(6-(((1R,3s,5S)-9-azabicyclo[3.3.1]nonan-3-yl)(methylamino)pyridazin-3-yl)-3-hydroxyphenyl)-1-(methyl-d3)pyridin-2(1H)-one;~~
~~4-(4-(6-(((1R,3s,5S)-9-azabicyclo[3.3.1]nonan-3-yl)(methylamino)pyridazin-3-yl)-2-fluoro-5-hydroxyphenyl)-1-methylpyridin-2(1H)-one;~~
~~5-(4-(6-(((1R,3s,5S)-9-azabicyclo[3.3.1]nonan-3-yl)(methylamino)pyridazin-3-yl)-2-fluoro-5-hydroxyphenyl)-2-methylpyridazin-3(2H)-one;~~
~~2-(6-(((1R,3s,5S)-9-azabicyclo[3.3.1]nonan-3-yl)(methylamino)pyridazin-3-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-9-azabicyclo[3.3.1]nonan-3-yl)(methylamino)pyridazin-3-yl)-5-(1-(methyl-d3)-1H-pyrazol-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-9-azabicyclo[3.3.1]nonan-3-yl)(methylamino)pyridazin-3-yl)-5-(2-methoxypyridin-4-yl)phenol;~~
~~4-(4-(6-(((1R,3s,5S)-9-azabicyclo[3.3.1]nonan-3-yl)(methylamino)pyridazin-3-yl)-3-hydroxyphenyl)-1,6-dimethylpyridin-2(1H)-one;~~
~~4-(4-(6-(((1R,3s,5S)-9-azabicyclo[3.3.1]nonan-3-yl)(methylamino)pyridazin-3-yl)-3-hydroxyphenyl)-1-(fluoromethyl)pyridin-2(1H)-one;~~
~~4-(6-(((1R,3s,5S)-9-azabicyclo[3.3.1]nonan-3-yl)(methylamino)pyridazin-3-yl)-3'-methoxy-4'-methyl-[1,1'-biphenyl]-3-ol;~~
~~4-(4-(6-(((1R,3s,5S)-9-azabicyclo[3.3.1]nonan-3-yl)(methylamino)pyridazin-3-yl)-3-hydroxyphenyl)pyridin-2(1H)-one;~~
~~6-(6-(((1R,3s,5S)-9-azabicyclo[3.3.1]nonan-3-yl)(methylamino)pyridazin-3-yl)-5-hydroxy-N-methylbenzofuran-2-carboxamide;~~
~~6-(6-(((1R,3s,5S)-9-azabicyclo[3.3.1]nonan-3-yl)(methylamino)pyridazin-3-yl)-5-hydroxy-N,N-dimethylbenzofuran-2-carboxamide;~~

~~6-(6-(((1R,3s,5S)-9-azabicyclo[3.3.1]nonan-3-yl)(methyl)amino)pyridazin-3-yl)-N-cyclopropyl-5-hydroxybenzofuran-2-carboxamide;~~
~~5-(6-(((1R,3s,5S)-9-azabicyclo[3.3.1]nonan-3-yl)(methyl)amino)pyridazin-3-yl)-6-hydroxy-N-methylbenzofuran-2-carboxamide;~~
~~5-(6-(((1R,3s,5S)-9-azabicyclo[3.3.1]nonan-3-yl)(methyl)amino)pyridazin-3-yl)-6-hydroxy-N,N-dimethylbenzofuran-2-carboxamide;~~
~~5-(6-(((1R,3s,5S)-9-azabicyclo[3.3.1]nonan-3-yl)(methyl)amino)pyridazin-3-yl)-N-cyclopropyl-6-hydroxybenzofuran-2-carboxamide;~~
~~6-(4-(6-(((1R,3s,5S)-9-azabicyclo[3.3.1]nonan-3-yl)(methyl)amino)pyridazin-3-yl)-3-hydroxyphenyl)-3-methylpyrimidin-4(3H)-one;~~
~~2-(6-(((1R,3s,5S)-9-azabicyclo[3.3.1]nonan-3-yl)(methyl)amino)pyridazin-3-yl)-5-(1-(difluoromethyl)-1H-pyrazol-4-yl)phenol;~~
~~2-(6-(cyclopropyl((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)amino)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-5-(2-(methyl-d3)oxazol-5-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-4-fluoro-5-(2-(methyl-d3)oxazol-5-yl)phenol;~~
~~4-(4-(6-(((1R,3s,5S)-1,5-dimethyl-9-azabicyclo[3.3.1]nonan-3-yl)(methyl)amino)pyridazin-3-yl)-3-hydroxyphenyl)-1-methylpyrimidin-2(1H)-one;~~
~~4-(4-(6-(((1R,3s,5S)-1,5-dimethyl-9-azabicyclo[3.3.1]nonan-3-yl)(methyl)amino)pyridazin-3-yl)-3-hydroxyphenyl)pyridin-2(1H)-one;~~
~~4-(4-(6-(((1R,3s,5S)-1,5-dimethyl-9-azabicyclo[3.3.1]nonan-3-yl)(methyl)amino)pyridazin-3-yl)-2-fluoro-5-hydroxyphenyl)pyridin-2(1H)-one; and~~
~~5-(2-(difluoromethoxy)pyridin-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-9-azabicyclo[3.3.1]nonan-3-yl)(methyl)amino)pyridazin-3-yl)phenol.~~

44. ~~A compound, or a pharmaceutically acceptable salt or solvate thereof, that is:~~

~~(6-(2-hydroxy-4-(1H-pyrazol-4-yl)phenyl)pyridazin-3-yl)(piperazin-1-yl)methanone;~~
~~2-(6-(piperidin-4-ylthio)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol;~~
~~(3,6-diazabicyclo[3.1.1]heptan-3-yl)(6-(2-hydroxy-4-(1H-pyrazol-4-yl)phenyl)pyridazin-3-yl)methanone;~~
~~2-(6-((6-azabicyclo[3.1.1]heptan-3-yl)(2-fluoroethyl)amino)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol;~~
~~(3,8-diazabicyclo[3.2.1]octan-3-yl)(6-(2-hydroxy-4-(1H-pyrazol-4-yl)phenyl)pyridazin-3-yl)methanone;~~
~~2-(6-((8-azabicyclo[3.2.1]octan-3-yl)(2-fluoroethyl)amino)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol;~~
~~2-(6-(octahydro-1,6-naphthyridin-1(2H)-yl)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol;~~

~~2-(6-(methoxy(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol;~~
~~2-(6-(hydroxy(2,2,6,6-tetramethylpiperidin-4-yl)methyl)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol;~~
~~(6-(2-hydroxy-4-(1H-pyrazol-4-yl)phenyl)pyridazin-3-yl)(3,3,5,5-tetramethylpiperazin-1-yl)methanone;~~
~~(6-(2-hydroxy-4-(1H-pyrazol-4-yl)phenyl)pyridazin-3-yl)(2,2,6,6-tetramethylpiperidin-4-yl)methanone;~~
~~5-(1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)thio)pyridazin-3-yl)phenol;~~
~~2-(6-((2-methoxyethoxy)(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol;~~
~~5-(1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-ylidene)methyl)pyridazin-3-yl)phenol;~~
~~5-(1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)(trifluoromethyl)amino)pyridazin-3-yl)phenol;~~
~~2-(6-((2-fluoroethyl)(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol;~~
~~5-(1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)(2,2,2-trifluoroethyl)amino)pyridazin-3-yl)phenol;~~
~~2-(6-((3-fluoropropyl)(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol;~~
~~5-(1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)(3,3,3-trifluoropropyl)amino)pyridazin-3-yl)phenol;~~
~~3-(6-((2-fluoroethyl)(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-7-methoxynaphthalen-2-ol;~~
~~2-(6-((2-fluoroethyl)(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenol;~~
~~2-(6-((2-fluoroethyl)(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(5-methyl-1H-pyrazol-4-yl)phenol;~~
~~2-(6-((2-fluoroethyl)(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(5-methyloxazol-2-yl)phenol;~~
~~2-(6-((2-fluoroethyl)(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(1H-pyrazol-1-yl)phenol;~~
~~5-(4-(6-((2-fluoroethyl)(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-3-hydroxyphenyl)pyridin-2(1H)-one;~~
~~5-(4-(6-((2-fluoroethyl)(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-3-hydroxyphenyl)pyrimidin-2(1H)-one;~~
~~2-(6-((2-methoxyethoxy)(2,2,6,6-tetramethylpiperidin-4-yl)methyl)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol;~~
~~2-(6-(((1R,3S,5S)-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol;~~

~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-5-(5-methyloxazol-2-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-5-(4-methyl-1H-imidazol-1-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-5-(1H-imidazol-1-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-5-(3-methyl-1H-pyrazol-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-5-(1H-pyrazol-1-yl)phenol;~~
~~4-(4-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-3-hydroxyphenyl)pyridin-2(1H)-one;~~
~~4-(4-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-3-hydroxyphenyl)-1-methylpyridin-2(1H)-one;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-5-(4-amino-1H-pyrazol-1-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-5-(4-amino-5-methyl-1H-pyrazol-1-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-5-(4-amino-3-methyl-1H-pyrazol-1-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-5-(5-methyl-1,3,4-oxadiazol-2-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-5-(5-methyl-1,3,4-thiadiazol-2-yl)phenol;~~
~~3-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-7-methoxynaphthalen-2-ol;~~
~~3-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)naphthalene-2,7-diol;~~
~~6-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)isoquinolin-7-ol;~~
~~6-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-1-methylisoquinolin-7-ol;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)thio)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol;~~
~~((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(6-(2-hydroxy-4-(1H-pyrazol-4-yl)phenyl)pyridazin-3-yl)methanone;~~
~~2-(6-(1-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)vinyl)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-5-(5-methyloxazol-2-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-5-(4-methyl-1H-imidazol-1-yl)phenol;~~

~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-5-(1H-imidazol-1-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-5-(3-methyl-1H-pyrazol-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-5-(1H-pyrazol-1-yl)phenol;~~
~~4-(4-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-3-hydroxyphenyl)pyridin-2(1H)-one;~~
~~4-(4-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-3-hydroxyphenyl)-1-methylpyridin-2(1H)-one;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-5-(4-amino-1H-pyrazol-1-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-5-(4-amino-5-methyl-1H-pyrazol-1-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-5-(4-amino-3-methyl-1H-pyrazol-1-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-5-(5-methyl-1,3,4-oxadiazol-2-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-5-(5-methyl-1,3,4-thiadiazol-2-yl)phenol;~~
~~3-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-7-methoxynaphthalen-2-ol;~~
~~3-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)naphthalene-2,7-diol;~~
~~6-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)isoquinolin-7-ol;~~
~~6-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-1-methylisoquinolin-7-ol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-3-fluoro-5-(1H-pyrazol-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-3,4-difluoro-5-(1H-pyrazol-4-yl)phenol;~~
~~4-(4-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-3-fluoro-5-hydroxyphenyl)-1-methylpyridin-2(1H)-one;~~
~~4-(4-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-2,3-difluoro-5-hydroxyphenyl)-1-methylpyridin-2(1H)-one;~~

~~2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-3-fluoro-5-(2-methoxypyridin-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-3,4-difluoro-5-(2-methoxypyridin-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-3-fluoro-5-(6-methoxypyridazin-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-3,4-difluoro-5-(6-methoxypyridazin-4-yl)phenol;~~
~~5-(4-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-3-fluoro-5-hydroxyphenyl)-2-methylpyridazin-3(2H)-one;~~
~~5-(4-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-2,3-difluoro-5-hydroxyphenyl)-2-methylpyridazin-3(2H)-one;~~
~~2-(6-(cyclopropyl((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)amino)pyridazin-3-yl)-3-fluoro-5-(6-methoxypyridazin-4-yl)phenol;~~
~~2-(6-(cyclopropyl((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)amino)pyridazin-3-yl)-3,4-difluoro-5-(6-methoxypyridazin-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-3-fluoro-5-(6-methoxypyrimidin-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-3,4-difluoro-5-(6-methoxypyrimidin-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(2-fluoroethylamino)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(2-fluoroethylamino)pyridazin-3-yl)-4-fluoro-5-(1H-pyrazol-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(2-fluoroethylamino)pyridazin-3-yl)-3-fluoro-5-(1H-pyrazol-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(2-fluoroethylamino)pyridazin-3-yl)-3,4-difluoro-5-(1H-pyrazol-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-3-fluoro-5-(2-(methoxy-d3)pyridin-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-3,4-difluoro-5-(2-(methoxy-d3)pyridin-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-3-fluoro-5-(6-(methoxy-d3)pyridazin-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-3,4-difluoro-5-(6-(methoxy-d3)pyridazin-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl-d3)amino)pyridazin-3-yl)-3-fluoro-5-(2-(methoxy-d3)pyridin-4-yl)phenol;~~

~~2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl-d3)amino)pyridazin-3-yl)-3,4-difluoro-5-(2-(methoxy-d3)pyridin-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl-d3)amino)pyridazin-3-yl)-3-fluoro-5-(6-(methoxy-d3)pyridazin-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl-d3)amino)pyridazin-3-yl)-3,4-difluoro-5-(6-(methoxy-d3)pyridazin-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-3-fluoro-5-(1-methyl-1H-pyrazol-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-3,4-difluoro-5-(1-methyl-1H-pyrazol-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-4-fluoro-5-(1,2,3-triazin-5-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-3,4-difluoro-5-(1,2,3-triazin-5-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-3-fluoro-5-(1,2,3-triazin-5-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-9-azabicyclo[3.3.1]nonan-3-yl)(methyl)amino)pyridazin-3-yl)-4-fluoro-5-(6-methoxypyridazin-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-9-azabicyclo[3.3.1]nonan-3-yl)(methyl)amino)pyridazin-3-yl)-3,4-difluoro-5-(6-methoxypyridazin-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-9-azabicyclo[3.3.1]nonan-3-yl)(methyl)amino)pyridazin-3-yl)-3-fluoro-5-(6-methoxypyridazin-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-9-azabicyclo[3.3.1]nonan-3-yl)(methyl)amino)pyridazin-3-yl)-3,4-difluoro-5-(6-methoxypyrimidin-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-9-azabicyclo[3.3.1]nonan-3-yl)(methyl)amino)pyridazin-3-yl)-3-fluoro-5-(6-methoxypyrimidin-4-yl)phenol;~~
~~2-(6-(cyclopropyl)((1R,3s,5S)-1,5-dimethyl-9-azabicyclo[3.3.1]nonan-3-yl)amino)pyridazin-3-yl)-4-fluoro-5-(6-methoxypyridazin-4-yl)phenol;~~
~~2-(6-(cyclopropyl)((1R,3s,5S)-1,5-dimethyl-9-azabicyclo[3.3.1]nonan-3-yl)amino)pyridazin-3-yl)-3,4-difluoro-5-(6-methoxypyridazin-4-yl)phenol;~~
~~2-(6-(cyclopropyl)((1R,3s,5S)-1,5-dimethyl-9-azabicyclo[3.3.1]nonan-3-yl)amino)pyridazin-3-yl)-3-fluoro-5-(6-methoxypyridazin-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-9-azabicyclo[3.3.1]nonan-3-yl)(2-fluoroethyl)amino)pyridazin-3-yl)-4-fluoro-5-(6-methoxypyridazin-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-9-azabicyclo[3.3.1]nonan-3-yl)(2-fluoroethyl)amino)pyridazin-3-yl)-3,4-difluoro-5-(6-methoxypyridazin-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-9-azabicyclo[3.3.1]nonan-3-yl)(2-fluoroethyl)amino)pyridazin-3-yl)-3-fluoro-5-(6-methoxypyridazin-4-yl)phenol;~~

~~2-(6-(((1R,3s,5S)-1,5-dimethyl-9-azabicyclo[3.3.1]nonan-3-yl)oxy)pyridazin-3-yl)-4-fluoro-5-(6-methoxypyridazin-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-9-azabicyclo[3.3.1]nonan-3-yl)oxy)pyridazin-3-yl)-3,4-difluoro-5-(6-methoxypyridazin-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-9-azabicyclo[3.3.1]nonan-3-yl)oxy)pyridazin-3-yl)-3-fluoro-5-(6-methoxypyridazin-4-yl)phenol;~~
~~4-(4-(6-(((1R,3s,5S)-1,5-dimethyl-9-azabicyclo[3.3.1]nonan-3-yl)oxy)pyridazin-3-yl)-2-fluoro-5-hydroxyphenyl)-1-methylpyridin-2(1H)-one;~~
~~4-(4-(6-(((1R,3s,5S)-1,5-dimethyl-9-azabicyclo[3.3.1]nonan-3-yl)oxy)pyridazin-3-yl)-2,3-difluoro-5-hydroxyphenyl)-1-methylpyridin-2(1H)-one;~~
~~4-(4-(6-(((1R,3s,5S)-1,5-dimethyl-9-azabicyclo[3.3.1]nonan-3-yl)oxy)pyridazin-3-yl)-3-fluoro-5-hydroxyphenyl)-1-methylpyridin-2(1H)-one;~~
~~4-(4-(6-(((1R,3s,5S)-1,5-dimethyl-9-azabicyclo[3.3.1]nonan-3-yl)(methyl)amino)pyridazin-3-yl)-2-fluoro-5-hydroxyphenyl)-1-methylpyridin-2(1H)-one;~~
~~4-(4-(6-(((1R,3s,5S)-1,5-dimethyl-9-azabicyclo[3.3.1]nonan-3-yl)(methyl)amino)pyridazin-3-yl)-2,3-difluoro-5-hydroxyphenyl)-1-methylpyridin-2(1H)-one;~~
~~4-(4-(6-(((1R,3s,5S)-1,5-dimethyl-9-azabicyclo[3.3.1]nonan-3-yl)(methyl)amino)pyridazin-3-yl)-3-fluoro-5-hydroxyphenyl)-1-methylpyridin-2(1H)-one;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)-4-fluoropyridazin-3-yl)-4-fluoro-5-(1H-pyrazol-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)-5-fluoropyridazin-3-yl)-4-fluoro-5-(1H-pyrazol-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-9-azabicyclo[3.3.1]nonan-3-yl)(methyl)amino)-4-fluoropyridazin-3-yl)-4-fluoro-5-(1H-pyrazol-4-yl)phenol;~~
~~2-(6-(((1R,3s,5S)-1,5-dimethyl-9-azabicyclo[3.3.1]nonan-3-yl)(methyl)amino)-5-fluoropyridazin-3-yl)-4-fluoro-5-(1H-pyrazol-4-yl)phenol;~~
~~7-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6-hydroxy-N-methylisoquinoline-3-carboxamide;~~
~~7-(6-(((1R,3s,5S)-1,5-dimethyl-9-azabicyclo[3.3.1]nonan-3-yl)(methyl)amino)pyridazin-3-yl)-6-hydroxy-N-methylisoquinoline-3-carboxamide;~~
~~6-(6-(((1R,3s,5S)-1,5-dimethyl-9-azabicyclo[3.3.1]nonan-3-yl)(methyl)amino)pyridazin-3-yl)-7-hydroxy-N-methylquinoline-2-carboxamide;~~
~~6-(6-(((1R,3s,5S)-1,5-dimethyl-9-azabicyclo[3.3.1]nonan-3-yl)(methyl)amino)pyridazin-3-yl)-1-fluoro-7-hydroxy-N-methyl-2-naphthamide;~~
~~6-(6-(((1R,3s,5S)-1,5-dimethyl-9-azabicyclo[3.3.1]nonan-3-yl)(methyl)amino)pyridazin-3-yl)-3-fluoro-7-hydroxy-N-methyl-2-naphthamide;~~
~~6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-3-fluoro-7-hydroxy-N-methyl-2-naphthamide; and~~

~~6-(6-(((1R,3S,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-1-fluoro-7-hydroxy-N-methyl-2-naphthamide.~~

- ~~45. A composition comprising a small molecule splicing modulator compound (SMSM); wherein the SMSM interacts with an unpaired bulged nucleobase of an RNA duplex, and wherein the RNA duplex comprises a splice site.~~
- ~~46. A composition comprising a complex comprising a small molecule splicing modulator compound (SMSM) bound to an RNA duplex, wherein the SMSM interacts with an unpaired bulged nucleobase of an RNA duplex, and wherein the RNA duplex comprises a splice site.~~
- ~~47. The composition of claim 45 or 46, wherein the duplex RNA comprises an alpha helix.~~
- ~~48. The composition of any one of claims 45-47, wherein the unpaired bulged nucleobase is located on an external portion of a helix of the duplex RNA.~~
- ~~49. The composition of any one of claims 45-47, wherein the unpaired bulged nucleobase is located within an internal portion of the helix of the duplex RNA.~~
- ~~50. The composition of any one of claims 45-49, wherein the SMSM forms one or more intermolecular interactions with the duplex RNA.~~
- ~~51. The composition of any one of claims 45-50, wherein the SMSM forms one or more intermolecular interactions with the unpaired bulged nucleobase.~~
- ~~52. The composition of claim 50 or 51, wherein the intermolecular interaction is selected from the group comprising an ionic interaction, a hydrogen bond, a dipole-dipole interaction or a van der Waals interaction.~~
- ~~53. The composition of any one of claims 45-52, wherein a first portion of the SMSM interacts with the unpaired bulged nucleobase on a first RNA strand of the RNA duplex.~~
- ~~54. The composition of claims 53, wherein a second portion of the SMSM interacts with one or more nucleobases of a second RNA strand of the RNA duplex, wherein the first RNA strand is not the second RNA strand.~~
- ~~55. The composition of any one of claims 45-54, wherein a rate of exchange of the unpaired bulged nucleobase from within the interior of a helix of the duplex RNA to an exterior portion of the helix is reduced.~~
- ~~56. The composition of any one of claims 45-55, wherein the SMSM reduces a rate of rotation of the unpaired bulged nucleobase.~~
- ~~57. The composition of any one of claims 45-56, wherein the SMSM reduces a rate of rotation of the unpaired bulged nucleobase around a phosphate backbone of an RNA strand of the RNA duplex.~~
- ~~58. The composition of anyone of claims 45-57, wherein the SMSM modulates a distance of the unpaired bulged nucleobase from a second nucleobase of the duplex RNA.~~
- ~~59. The composition of claim 58, wherein the SMSM reduces the distance of the unpaired bulged nucleobase from a second nucleobase of the duplex RNA.~~
- ~~60. The composition of claim of anyone of claims 46-59, wherein the unpaired bulged nucleobase is located within the interior of a helix of the duplex RNA of the complex.~~

- ~~61. The composition of any one of claims 45-60, wherein the SMSM reduces a size of a bulge of the RNA duplex.~~
- ~~62. The composition of any one of claims 45-61, wherein the SMSM removes a bulge of the RNA duplex.~~
- ~~63. The composition of any one of claims 45-57, wherein the SMSM stabilizes a bulge of the RNA duplex.~~
- ~~64. The composition of any one of claims 45-63, wherein the SMSM modulates splicing at the splice site of the RNA duplex.~~
- ~~65. The composition of claim 64, wherein the SMSM increases splicing at the splice site of the RNA duplex.~~
- ~~66. The composition of claim 64, wherein the SMSM reduces splicing at the splice site of the RNA duplex.~~
- ~~67. The composition of any one of claims 45-66, wherein the unpaired bulged nucleobase has modulated base stacking within an RNA strand of the RNA duplex.~~
- ~~68. The composition of claim 67, wherein the unpaired bulged nucleobase has increased base stacking within an RNA strand of the RNA duplex.~~
- ~~69. The composition of claim 67, wherein the unpaired bulged nucleobase has decreased base stacking within an RNA strand of the RNA duplex.~~
- ~~70. The composition of any one of claims 45-69, wherein the SMSM is not an aptamer.~~
- ~~71. The composition of any one of claims 45-70, wherein the RNA duplex comprises pre-mRNA.~~
- ~~72. The composition of any one of claims 45-70, wherein the unpaired bulged nucleobase is free to rotate around a phosphate backbone of an RNA strand of the RNA duplex in the absence of the SMSM~~
- ~~73. A method of modulating splicing comprising contacting a small molecule splicing modulator compound (SMSM) to cells, wherein the SMSM kills the cells at an IC_{50} of less than 50 nM.~~
- ~~74. A method of modulating splicing comprising contacting a small molecule splicing modulator compound (SMSM) to cells, wherein the SMSM modulates splicing at a splice site sequence of a pre-mRNA that encodes a mRNA, wherein the mRNA encodes a target protein or a functional RNA, and wherein a total amount of the mRNA is increased at least about 10% compared to the total amount of the mRNA encoding the target protein or functional RNA produced in control cells.~~
- ~~75. A method of modulating splicing comprising contacting a small molecule splicing modulator compound (SMSM) to cells, wherein the SMSM modulates splicing at a splice site sequence of a pre-mRNA that encodes a mRNA, wherein the mRNA encodes a target protein or a functional RNA, and wherein a total amount of the mRNA, the target protein and/or the functional RNA is at least 10% lower than the total amount of the mRNA, the target protein and/or the functional RNA in control cells.~~
- ~~76. A method of modulating splicing comprising contacting a small molecule splicing modulator compound (SMSM) to cells, wherein the SMSM modulates splicing at a splice site sequence of a pre-mRNA that encodes a first mRNA isoform associated with a disease or condition and a second mRNA isoform, wherein~~

- (a) ~~a total amount of the first mRNA isoform is decreased by at least about 10% compared to the total amount of the first mRNA isoform in control cells, and/or~~
- (b) ~~a total amount of the second mRNA isoform is increased by at least about 10% compared to the total amount of the first mRNA isoform in control cells.~~

- ~~77. A method of modulating splicing comprising contacting a small molecule splicing modulator compound (SMSM) to cells comprising an amount of a first mRNA isoform and an amount of a second mRNA isoform present in the cells; wherein a ratio of the first mRNA isoform to the second mRNA isoform is decreased at least 1.2 fold; wherein the first and second mRNAs are encoded by a pre-mRNA comprising a splice site sequence, and wherein the first mRNA isoform is associated with a disease or condition and a second mRNA isoform.~~
- ~~78. A method of modulating splicing, comprising contacting a small molecule splicing modulator compound (SMSM) to a cell comprising a polynucleotide with a splice site sequence, wherein the SMSM modulates exon inclusion, exon exclusion, pseudoexon inclusion, intron retention, or splicing at a cryptic splice site of the polynucleotide, and wherein the SMSM modulates splicing of the splice site sequence.~~
- ~~79. A method of modulating splicing, comprising contacting a small molecule splicing modulator compound (SMSM) to a cell comprising a polynucleotide with a splice site sequence, thereby modulating splicing of the polynucleotide, wherein the splice site sequence comprises a splice site sequence selected from the group consisting of splice site sequences of Table 2A, Table 2B, Table 2C or Table 2D.~~
- ~~80. A method of modulating splicing, comprising contacting a small molecule splicing modulator compound (SMSM) to a cell comprising a polynucleotide with a splice site sequence, wherein the splice site sequence comprises a sequence selected from GGAguaag and AGAguaag.~~
- ~~81. A method of modulating splicing, comprising contacting a small molecule splicing modulator compound (SMSM) to a cell comprising a polynucleotide with a splice site sequence, wherein the splice site sequence comprises at least one bulged nucleotide at the -3, -2, -1, +1, +2, +3, +4, +5 or +6 position of the splice site sequence.~~
- ~~82. A method of modulating splicing, comprising contacting a small molecule splicing modulator compound (SMSM) to a cell comprising a polynucleotide with a splice site sequence, wherein the splice site sequence comprises a mutant nucleotide at the -3, -2, -1, +1, +2, +3, +4, +5 or +6 position of the splice site sequence.~~
- ~~83. A method of modulating splicing, comprising contacting a small molecule splicing modulator compound (SMSM) to a cell comprising a polynucleotide with a splice site sequence, thereby modulating splicing of the polynucleotide, wherein the splice site sequence comprises a sequence selected from the group consisting of NGAgunvrn, NHAddddn, NNBnnnnnn, and NHAdmrvk; wherein N or n is A, U, G or C; B is C, G, or U; H or h is A, C, or U; d is a, g, or u; m is a or e; r is a or g; v is a, c or g; k is g or u.~~

- ~~84. A method of modulating splicing, comprising contacting a small molecule splicing modulator compound (SMSM) to a cell comprising a polynucleotide with a splice site sequence, thereby modulating splicing of the polynucleotide, wherein the splice site sequence comprises a sequence selected from the group consisting of NNBgunnnn, NNBhunnnn, or NNBgvnnnn; wherein N or n is A, U, G or C; B is C, G, or U; H or h is A, C, or U; d is a, g, or u; m is a or c; r is a or g; v is a, c or g; k is g or u.~~
- ~~85. The method of claim 84, wherein the splice site sequence comprises a sequence selected from the group consisting of NNBgurrn, NNBguwvwn, NNBgumvn, NNBguvbn, NNBgukddn, NNBgubnbd, NNBhunngn, NNBhurhhd, or NNBgvdnvn; wherein N or n is A, U, G or C; B is C, G, or U; H or h is A, C, or U; d is a, g, or u; m is a or c; r is a or g; v is a, c or g; k is g or u.~~
- ~~86. The method of any one of claims 83-85, wherein the nucleotide at the -3, -2, -1, +1, +2, +3, +4, +5 or +6 position of the splice site sequence is a bulged nucleotide.~~
- ~~87. The method of any one of claims 83-86, wherein the nucleotide at the -3, -2, -1, +1, +2, +3, +4, +5 or +6 position of the splice site sequence is mutated nucleotide.~~
- ~~88. The method of any one of claims 74-87, wherein the splice site sequence comprises a sequence selected from the group consisting of splice site sequences of Table 2A, Table 2B, Table 2C or Table 2D.~~
- ~~89. A method of modulating splicing, comprising contacting a small molecule splicing modulator compound (SMSM) to a cell comprising a polynucleotide with a splice site sequence, thereby modulating splicing of the polynucleotide, wherein the polynucleotide is encoded by a gene selected from the group consisting of genes of Table 2A, Table 2B, Table 2C or Table 2D.~~
- ~~90. The method of claim 89, wherein the gene is SMN2.~~
- ~~91. The method of claim 90, wherein modulating splicing of the polynucleotide comprises inhibiting skipping of exon 7.~~
- ~~92. The method of claim 89, wherein the gene is DMD.~~
- ~~93. The method of claim 92, wherein modulating splicing of the polynucleotide comprises promoting skipping of exon 51.~~
- ~~94. A method of modulating splicing comprising
contacting a small molecule splicing modulator compound (SMSM) to a cell;
wherein the SMSM interacts with an unpaired bulged nucleobase of an RNA duplex in the cell;
wherein the duplex RNA comprises a splice site sequence; and
wherein the SMSM modulates splicing of the RNA duplex.~~
- ~~95. A method for modulating the relative position of a first nucleobase relative to a second nucleobase, wherein the first nucleobase and the second nucleobase are within a duplex RNA, the method comprising
contacting a small molecule splicing modulator compound (SMSM) to the duplex RNA, or a pharmaceutically acceptable salt thereof;
wherein the first nucleobase is an unpaired bulged nucleobase of the RNA duplex;~~

- ~~wherein the duplex RNA comprises a splice site sequence.~~
- ~~96. The method of claim 94 or 95, wherein the duplex RNA comprises a helix.~~
- ~~97. The method of any one of claims 94-96, wherein the unpaired bulged nucleobase is located on an external portion of a helix of the duplex RNA prior to contacting the SMSM.~~
- ~~98. The method of any one of claims 94-97, wherein the SMSM forms one or more intermolecular interactions with the duplex RNA.~~
- ~~99. The method of any one of claims 94-98, wherein the SMSM forms one or more intermolecular interactions with the unpaired bulged nucleobase.~~
- ~~100. The method of claim 98 or 99, wherein the intermolecular interaction is selected from the group comprising an ionic interaction, a hydrogen bond, a dipole-dipole interaction or a van der Waals interaction.~~
- ~~101. The method of any one of claims 94-100, wherein a rate of exchange of the unpaired bulged nucleobase from within the interior of a helix of the duplex RNA to an exterior portion of the helix is reduced.~~
- ~~102. The method of any one of claims 94-101, wherein a rate of rotation of the unpaired bulged nucleobase is reduced.~~
- ~~103. The method of any one of claims 94-102, wherein a rate of rotation of the unpaired bulged nucleobase around a phosphate backbone of an RNA strand of the RNA duplex is reduced.~~
- ~~104. The method of anyone of claims 94-103, wherein a distance of the unpaired bulged nucleobase from a second nucleobase of the duplex RNA is modulated after contacting the SMSM.~~
- ~~105. The method of claim 104, wherein the distance of the unpaired bulged nucleobase from a second nucleobase of the duplex RNA is reduced.~~
- ~~106. The method of claim of anyone of claims 94-105, wherein the unpaired bulged nucleobase is located within the interior of the helix of the duplex RNA.~~
- ~~107. The method of any one of claims 94-106, wherein a size of a bulge of the RNA duplex is reduced.~~
- ~~108. The method of any one of claims 94-107, wherein a bulge of the RNA duplex is removed or maintained.~~
- ~~109. The method of any one of claims 94-108, wherein splicing at the splice site of the RNA duplex is promoted.~~
- ~~110. The method of any one of claims 94-107, wherein base stacking of the unpaired bulged nucleobase within an RNA strand of the RNA duplex is increased after contacting the SMSM.~~
- ~~111. The method of anyone of claims 94-104, wherein the distance of the unpaired bulged nucleobase from a second nucleobase of the duplex RNA is increased or maintained.~~
- ~~112. The method of claim of anyone of claims 94-104 and 111 wherein a bulge of the RNA duplex is stabilized after contacting the SMSM.~~
- ~~113. The method of claim of anyone of claims 94-104, 111 and 112, wherein the unpaired bulged nucleobase is located on an exterior portion of a helix of the duplex RNA.~~

- ~~114. The method of anyone of claims 94-104 and 111-113, wherein a size of a bulge of the RNA duplex is increased.~~
- ~~115. The method of any one of claims 94-108, and 111-114, wherein splicing at the splice site of the RNA duplex is inhibited.~~
- ~~116. The method of any one of claims 94-100 and 111-115, wherein splicing is inhibited at the splice site~~
- ~~117. The method of any one of claims 94-100 and 111-116, wherein base stacking of the unpaired bulged nucleobase within an RNA strand of the RNA duplex is reduced after contacting the SMSM.~~
- ~~118. The method of any one of claims 94-118, wherein the RNA duplex comprises pre-mRNA.~~
- ~~119. A method of treating a subject with a tumor comprising administering a small molecule splicing modulator compound (SMSM) to the subject, wherein a size of the tumor is reduced.~~
- ~~120. A method of treating a subject with a tumor comprising administering a small molecule splicing modulator compound (SMSM) to the subject, wherein tumor growth is inhibited by at least 20~~
- ~~121. A method condition or disease comprising administering a small molecule splicing modulator compound (SMSM) to a subject, wherein the SMSM modulates splicing of a splice site of a polynucleotide in a cell of the subject, wherein the condition or disease is associated with splicing of the splice site.~~
- ~~122. The method of claim 121, wherein the subject has the disease or condition.~~
- ~~123. A method of treating a subject with a disease or condition comprising administering a small molecule splicing modulator compound (SMSM) to a subject with a disease or condition selected from the group consisting of diseases of Table 2A, Table 2B, Table 2C and Table 2D.~~
- ~~124. A method of treating a subject with a disease or condition comprising administering a small molecule splicing modulator compound (SMSM) to a subject with a disease or condition, wherein the SMSM is selected from the group consisting of the SMSMs of Table 1A, Table 1B or Table 1C.~~
- ~~125. A method of treating a subject with a disease or condition comprising administering a small molecule splicing modulator compound (SMSM) to a subject with a disease or condition, wherein the SMSM binds to a pre-mRNA comprising a splice site sequence selected from the group consisting of splice site sequences of Table 2A, Table 2B, Table 2C or Table 2D.~~
- ~~126. The method of any one of claims 121-125, wherein the disease or condition is spinal muscular atrophy.~~
- ~~127. The method of any one of claims 121-125, wherein the disease or condition is Duchenne's muscular dystrophy.~~
- ~~128. The method of any one of claims 73-127, wherein the SMSM is selected from the group consisting of SMSMs of Table 1A, Table 1B and Table 1C.~~
- ~~129. The method of any one of claims 73-128, wherein the SMSM is the compound of any one of claims 1-72.~~
- ~~130. The method of any one of claims 78-129, wherein the method further comprises administering an additional therapeutic molecule to the subject.~~
- ~~131. The method of any one of claims 78-130, wherein the subject is a mammal.~~
- ~~132. The method of claim 131, wherein the mammal is a human.~~
- ~~133. The method of any one of claims 73-132, wherein the polynucleotide is a pre-mRNA.~~

- ~~134. The method of any one of claims 73-133, wherein modulating splicing comprises preventing, inhibiting or reducing splicing at the splice site sequence of the polynucleotide.~~
- ~~135. The method of any one of claims 73-134, wherein modulating splicing comprises enhancing, promoting or increasing splicing at the splice site sequence of the polynucleotide.~~
- ~~136. The method of any one of claims 73-135, wherein the splice site sequence is a 5' splice site sequence, a 3' splice site sequence, a branch point splice site sequence or a cryptic splice site sequence.~~
- ~~137. The method of any one of claims 73-136, wherein:~~
- ~~(a) the splice site comprises a mutation,~~
 - ~~(b) the splice site comprises a bulge,~~
 - ~~(c) the splice site comprises a mutation and a bulge,~~
 - ~~(d) the splice site does not comprises a mutation,~~
 - ~~(e) the splice site does not comprises a bulge, or~~
 - ~~(f) the splice site does not comprises a mutation and does not comprise a bulge.~~
- ~~138. The method of claim 137, wherein the bulge is a bulge caused by the mutation.~~
- ~~139. The method of claim 137, wherein a bulged nucleotide is a mutant nucleotide.~~
- ~~140. The method of claim 137, wherein a bulged nucleotide is not a mutant nucleotide.~~
- ~~141. The method of any one of claims 73-140, wherein the SMSM decreases a K_D of splicing complex component to the polynucleotide.~~
- ~~142. The method of any one of claims 73-140, wherein the SMSM increases a K_D of splicing complex component to the polynucleotide.~~
- ~~143. The method of any one of claims 73-142, wherein the SMSM inhibits binding of a splicing complex component to the polynucleotide at the splice site sequence, upstream of the splice site sequence or downstream of the splice site sequence.~~
- ~~144. The method of any one of claims 73-142, wherein the SMSM promotes binding of a splicing complex component to the polynucleotide at the splice site sequence, upstream of the splice site sequence or downstream of the splice site sequence.~~
- ~~145. The method of any one of claims 73-144, wherein the polynucleotide is RNA.~~
- ~~146. The method of claim 145, wherein the RNA is a pre-mRNA.~~
- ~~147. The method of claim 145, wherein the RNA is a heterogeneous nuclear RNA.~~
- ~~148. The The method of any one of claims 73-147, wherein the splice site sequence is a 5' splice site sequence, a 3' splice site sequence, a branch point (BP) splice site sequence, an exonic splicing enhancer (ESE) sequence, an exonic splicing silencer (ESS) sequence, an intronic splicing enhancer (ISE) sequence, an intronic splicing silencer (ISS) sequence, a polypyrimidine tract sequence, or any combination thereof.~~
- ~~149. The The method of any one of claims 73-148, wherein the polynucleotide is at least 5, 6, 7, 8, 9, 10, 15, 20, 25, 50, 100, 250, 500, 750, 1,000, 2,000, 5,000, 10,000, 50,000, 100,000, 500,000, or 1,000,000 nucleotides in length.~~

- ~~150. The method of any one of claims 73-149, wherein the SMSM binds to the splice site sequence of the polynucleotide.~~
- ~~151. The method of any one of claims 73-149, wherein the SMSM interacts with a bulge of the splice site sequence of the polynucleotide.~~
- ~~152. The method of claim 150, wherein the polynucleotide comprises a cis-acting element sequence.~~
- ~~153. The method of claim 152, wherein the cis-acting element sequence does not comprise a bulge.~~
- ~~154. The method of claim 152, wherein the cis-acting element sequence does not comprise a mutation.~~
- ~~155. The method of claim 152, wherein the cis-acting element sequence comprises a mutation, a bulge, or a combination thereof, at the cis-acting element sequence, 1-1000 nucleobases upstream of the cis-acting element sequence or 1-1000 nucleobases downstream of the cis-acting element sequence.~~
- ~~156. The method of any one of claims 152-155, wherein the cis-acting element sequence comprises a regulatory element sequence that modulates recruitment of a splicing complex component to the polynucleotide.~~
- ~~157. The method of any one of claims 152-155, wherein the cis-acting element sequence comprises a regulatory element sequence that modulates recruitment of a spliceosome to the polynucleotide.~~
- ~~158. The method of claim 156 or 157, wherein the regulatory element sequence comprises an exonic splicing enhancer (ESE) sequence, an exonic splicing silencer (ESS) sequence, an intronic splicing enhancer (ISE) sequence, an intronic splicing silencer (ISS) sequence, and combinations thereof.~~
- ~~159. The method of any one of claims 73-158, wherein the SMSM binds to the splicing complex component.~~
- ~~160. The method claim 159, wherein the splicing complex component is 9G8, A1 hnRNP, A2 hnRNP, ASD 1, ASD 2b, ASF, B1 hnRNP, C1 hnRNP, C2 hnRNP, CBP20, CBP80, CELF, F hnRNP, FBP11, Fox-1, Fox-2, G hnRNP, H hnRNP, hnRNP 1, hnRNP 3, hnRNP C, hnRNP G, hnRNP K, hnRNP M, hnRNP U, Hu, HUR, I hnRNP, K hnRNP, KH type splicing regulatory protein (KSRP), L hnRNP, M hnRNP, mBBP, muscle-blind like (MBNL), NF45, NFAR, Nova 1, Nova 2, nPTB, P54/SFRS11, polypyrimidine tract binding protein (PTB), PRP19 complex proteins, R hnRNP, RNPC1, SAM68, SC35, SF, SF1/BBP, SF2, SF3a, SF3B, SFRS10, Sm proteins, SR proteins, SRm300, SRp20, SRp30e, SRP35C, SRP36, SRP38, SRp40, SRp55, SRp75, SRSF, STAR, GSG, SUP 12, TASR 1, TASR 2, TIA, TIAR, TRA2, TRA2a/b, U hnRNP, U1 snRNP, U11 snRNP, U12 snRNP, U1-C, U2 snRNP, U2AF1-RS2, U2AF35, U2AF65, U4 snRNP, U5 snRNP, U6 snRNP, Urp, YB1, or any combination thereof.~~
- ~~161. The method of claim 159, wherein the splicing complex component comprises a RNA.~~
- ~~162. The method of claim 159, wherein the splicing complex component is a small nuclear RNA (snRNA).~~
- ~~163. The method of claim 162, wherein the snRNA comprises U1 snRNA, U2 snRNA, U4 snRNA, U5 snRNA, U6 snRNA, U11 snRNA, U12 snRNA, U4atac snRNA, U5 snRNA, U6atac snRNA, or any combination thereof.~~
- ~~164. The method of claim 159, wherein the splicing complex component comprises a protein.~~

- ~~165. The method of claim 159, wherein the splicing complex component comprises a small nuclear ribonucleoprotein (snRNP).~~
- ~~166. The method of claim 165, wherein the snRNP comprises U1 snRNP, U2 snRNP, U4 snRNP, U5 snRNP, U6 snRNP, U11 snRNP, U12 snRNP, U4atac snRNP, U5 snRNP, U6 atac snRNP, or any combinations thereof.~~
- ~~167. The method of 164, wherein the protein is a serine/arginine-rich (SR) protein.~~
- ~~168. The method of any one of claims 73-167, wherein the splice site sequence comprises a base that is mismatched to a base of a snRNA sequence.~~
- ~~169. The method of any one of claims 73-168, wherein a bulge is due to mismatched base pairing between the splice site sequence and a snRNA sequence.~~
- ~~170. A compound, or a pharmaceutically acceptable salt or solvate thereof, that is:~~
- ~~6-chloro-N-(2,2,6,6-tetramethylpiperidin-4-yl)pyridazin-3-amine;~~
 - ~~6-chloro-N-cyclopropyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)pyridazin-3-amine;~~
 - ~~6-(4-chloro-2-methoxyphenyl)-N-cyclopropyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)pyridazin-3-amine;~~
 - ~~N-cyclopropyl-6-(2-methoxy-4-(1H-pyrazol-4-yl)phenyl)-N-(2,2,6,6-tetramethylpiperidin-4-yl)pyridazin-3-amine;~~
 - ~~tert-butyl(1R,3S,5S)-3-((6-chloropyridazin-3-yl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate;~~
 - ~~tert-butyl(1R,3s,5S)-3-((6-chloropyridazin-3-yl)(methyl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate;~~
 - ~~tert-butyl(1R,3s,5S)-3-((6-(4-chloro-2-methoxyphenyl)pyridazin-3-yl)(methyl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate;~~
 - ~~tert-butyl(1R,3s,5S)-3-((6-(2-methoxy-4-(1H-pyrazol-4-yl)phenyl)pyridazin-3-yl)(methyl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate;~~
 - ~~tert-butyl(1R,3s,5S)-3-((6-(2-hydroxy-4-(1H-pyrazol-4-yl)phenyl)pyridazin-3-yl)(methyl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate;~~
 - ~~tert-butyl(1R,3s,5S)-3-((6-chloropyridazin-3-yl)(methyl)amino)-9-azabicyclo[3.3.1]nonane-9-carboxylate;~~
 - ~~tert-butyl(1R,3s,5S)-3-((6-(2-(methoxymethoxy)-4-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)phenyl)pyridazin-3-yl)(methyl)amino)-9-azabicyclo[3.3.1]nonane-9-carboxylate;~~
 - ~~(1R,3s,5S)-N-(6-chloropyridazin-3-yl)-9-(4-methoxybenzyl)-1,5-dimethyl-9-azabicyclo[3.3.1]nonan-3-amine;~~
 - ~~(1R,3s,5S)-N-(6-chloropyridazin-3-yl)-9-(4-methoxybenzyl)-N,1,5-trimethyl-9-azabicyclo[3.3.1]nonan-3-amine;~~
 - ~~(1R,3s,5S)-9-(4-methoxybenzyl)-N-(6-(2-(methoxymethoxy)-4-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)phenyl)pyridazin-3-yl)-N,1,5-trimethyl-9-azabicyclo[3.3.1]nonan-3-amine;~~
 - ~~tert-butyl(1R,3s,5S)-3-((6-(4-chloro-5-fluoro-2-(methoxymethoxy)phenyl)pyridazin-3-yl)(methyl)amino)-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate;~~

~~tert-butyl(1R,3s,5S)-3-((6-(5-fluoro-2-(methoxymethoxy)-4-(1H-pyrazol-4-yl)phenyl)pyridazin-3-yl)(methylamino)-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate;~~
~~(1R,3s,5S)-N-(6-chloropyridazin-3-yl)-9-(4-methoxybenzyl)-N,1,5-trimethyl-9-azabicyclo[3.3.1]nonan-3-amine;~~
~~(1R,3s,5S)-N-(6-(4-chloro-5-fluoro-2-(methoxymethoxy)phenyl)pyridazin-3-yl)-9-(4-methoxybenzyl)-N,1,5-trimethyl-9-azabicyclo[3.3.1]nonan-3-amine;~~
~~(1R,3s,5S)-N-(6-(5-fluoro-2-(methoxymethoxy)-4-(1H-pyrazol-4-yl)phenyl)pyridazin-3-yl)-9-(4-methoxybenzyl)-N,1,5-trimethyl-9-azabicyclo[3.3.1]nonan-3-amine;~~
~~tert-butyl(1R,3s,5S)-3-((6-(2-(methoxymethoxy)-4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)pyridazin-3-yl)(methylamino)-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate;~~
~~tert-butyl(1R,3s,5S)-3-((6-(4-chloro-5-fluoro-2-(methoxymethoxy)phenyl)pyridazin-3-yl)(methylamino)-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate;~~
~~2tert-butyl(1R,3s,5S)-3-((6-(5-fluoro-2-(methoxymethoxy)-4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)pyridazin-3-yl)(methylamino)-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate;~~
~~(1R,3s,5S)-3-(6-chloropyridazin-3-yloxy)-1,5-dimethyl-8-azabicyclo[3.2.1]octane; or~~
~~(1R,3s,5S)-3-((6-(2-(methoxymethoxy)-4-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)phenyl)pyridazin-3-yl)oxy)-1,5-dimethyl-8-azabicyclo[3.2.1]octane.~~