

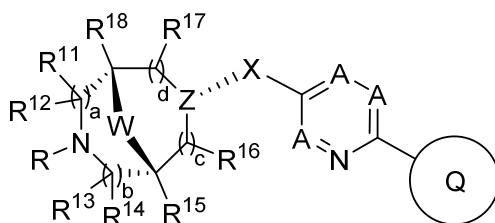
[0169] In some embodiments, the snRNP comprises U1 snRNP, U2 snRNP, U4 snRNP, U5 snRNP, U6 snRNP, U11 snRNP, U12 snRNP, U4atac snRNP, U5 snRNP, U6 atac snRNP, or any combinations thereof.

[0170] The method of 164, wherein the protein is a serine/arginine-rich (SR) protein.

[0171] In some embodiments, the splice site sequence comprises a base that is mismatched to a base of a snRNA sequence.

[0172] In some embodiments, a bulge is due to mismatched base pairing between the splice site sequence and a snRNA sequence.

[0172a] Provided herein is a compound 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, -OR¹, =O, =N-OR¹, -SR¹, -S(=O)R¹, -S(=O)₂R¹, -N(R¹)₂, -NR¹S(=O)(=NR¹)R², -NR¹S(=O)₂R², -S(=O)₂N(R¹)₂, -C(=O)R¹, -OC(=O)R¹, -C(=O)OR¹, -OC(=O)OR¹, -C(=O)N(R¹)₂, -OC(=O)N(R¹)₂, -NR¹C(=O)R¹, -P(=O)(R²)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, substituted or unsubstituted C₂-C₇ heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted monocyclic heteroaryl;

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

X is -NR³-, -CR⁴R⁵-, -C(=O)-, or -C(=CR²)₂-;

each R¹ 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 R² is independently H, D, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted C₁-C₆ haloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted monocyclic heteroaryl, -OR¹, -N(R¹)₂, -CH₂OR¹, -C(=O)OR¹, -OC(=O)R¹, -C(=O)N(R¹)₂, or -NR¹C(=O)R¹;

R³ is -OR¹, -N(R¹)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-C₇ heterocycloalkyl;

R⁴ is H, D, F, -CN, -OR¹, -SR¹, -N(R¹)₂, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted C₁-C₆ haloalkyl, substituted or unsubstituted C₁-C₆ heteroalkyl, substituted or unsubstituted C₁-C₆ alkylene-OR¹, substituted or unsubstituted C₃-C₈ cycloalkyl, substituted or unsubstituted C₂-C₇ heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R⁵ is H, D, F, -CN, -OR¹, -SR¹, -N(R¹)₂, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted C₁-C₆ haloalkyl, substituted or unsubstituted C₁-C₆ heteroalkyl, substituted or unsubstituted C₁-C₆ alkylene-OR¹, substituted or unsubstituted C₃-C₈ cycloalkyl, substituted or unsubstituted C₂-C₇ heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or

R⁴ and R⁵ taken in combination with the carbon atom to which they attach, form a substituted or unsubstituted C₃₋₈ cycloalkyl or a substituted or unsubstituted C₂₋₇ heterocycloalkyl;

Z is CR⁷; and R⁷ is H, D, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted C₁-C₆ haloalkyl or -CH₂OR¹;

W is substituted or unsubstituted C₁-C₄ alkylene, substituted or unsubstituted C₂-C₄ alkenylene, or substituted or unsubstituted C₁-C₄ heteroalkylene;

R is selected from the group consisting of H, a substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₁₋₆ fluoroalkyl, 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 heteroaryl, wherein alkyl is optionally substituted with hydroxy, amino, substituted or unsubstituted mono-C₁₋₆ alkylamino, or substituted or unsubstituted di-C₁₋₆ alkylamino;

R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, and R¹⁸ are each independently selected from the group consisting of H, F, OR¹, substituted or unsubstituted C₁₋₆ alkyl, a substituted or unsubstituted C₁₋₆ fluoroalkyl, and substituted or unsubstituted C₁-C₆ heteroalkyl, wherein alkyl is optionally substituted with hydroxy, amino, methoxy, substituted or unsubstituted mono-C₁₋₆ alkylamino or substituted or unsubstituted di-C₁₋₆ alkylamino;

R¹¹ and R¹³, taken in combination form a substituted or unsubstituted C₁₋₃ alkylene group or a substituted or unsubstituted C₁₋₃ heteroalkylene group; or

R¹¹ 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

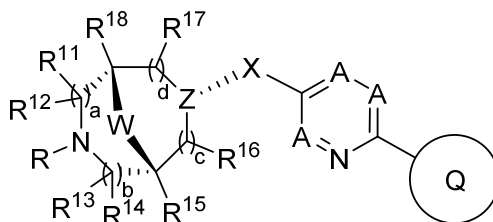
when X is -NR³-, then R³ and R¹⁶ are optionally taken together with the intervening atoms to which they are attached to form a 4, 5, or 6-membered ring;

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; and

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

[0172b] Provided herein is a compound 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, -OR¹, =O, =N-OR¹, -SR¹, -S(=O)R¹, -S(=O)₂R¹, -N(R¹)₂, -NR¹S(=O)(=NR¹)R², -NR¹S(=O)₂R², -S(=O)₂N(R¹)₂, -C(=O)R¹, -OC(=O)R¹, -C(=O)OR¹, -OC(=O)OR¹, -C(=O)N(R¹)₂, -OC(=O)N(R¹)₂, -NR¹C(=O)R¹, -P(=O)(R²)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, substituted or unsubstituted C₂-C₇ heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted monocyclic heteroaryl;

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

X is -O- or -S-;

each R¹ 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 R² is independently H, D, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted C₁-C₆ haloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted monocyclic heteroaryl, -OR¹, -N(R¹)₂, -CH₂OR¹, -C(=O)OR¹, -OC(=O)R¹, -C(=O)N(R¹)₂, or -NR¹C(=O)R¹;

Z is CR⁷; and R⁷ is H, D, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted C₁-C₆ haloalkyl or -CH₂OR¹;

W is substituted or unsubstituted C₁-C₄ alkylene, substituted or unsubstituted C₂-C₄ alkenylene, or substituted or unsubstituted C₁-C₄heteroalkylene;

R is selected from the group consisting of H, a substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₁₋₆ fluoroalkyl, 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 heteroaryl, wherein alkyl is optionally substituted with hydroxy, amino, substituted or unsubstituted mono-C₁₋₆ alkylamino, or substituted or unsubstituted di-C₁₋₆ alkylamino;

R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, and R¹⁸ are each independently selected from the group consisting of H, F, OR¹, substituted or unsubstituted C₁₋₆ alkyl, a substituted or unsubstituted C₁₋₆ fluoroalkyl, and substituted or unsubstituted C₁-C₆ heteroalkyl, wherein alkyl is optionally substituted with hydroxy, amino, methoxy, substituted or unsubstituted mono-C₁₋₆ alkylamino or substituted or unsubstituted di-C₁₋₆ alkylamino;

R¹¹ and R¹³, taken in combination form a substituted or unsubstituted C₁₋₃ alkylene group or a substituted or unsubstituted C₁₋₃ heteroalkylene group; or

R¹¹ 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

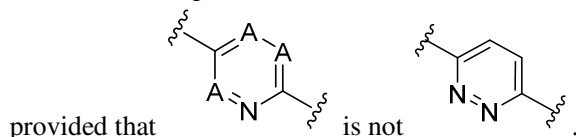
R¹³ and R¹⁴, taken in combination with the carbon atom to which they attach, form a spirocyclic C₃₋₈ cycloalkyl; or

R¹⁷ and R², taken in combination form a substituted or unsubstituted C₁₋₃ alkylene group;

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; and

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



[0172c] Provided herein is a pharmaceutical composition comprising a compound as described herein, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable diluent, carrier, or excipient.

[0172d] Provided herein is a compound as described herein, or a pharmaceutically acceptable salt or solvate thereof, for use as a medicament.

INCORPORATION BY REFERENCE

[0173] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0174] **FIG. 1** depicts a diagram of alternative splicing of an exemplary pre-mRNA. One mRNA isoform depicted encodes a protein that enhances or promotes cell proliferation and/or cancer. The other mRNA isoform depicted encodes a protein that enhances or inhibits cell proliferation and/or cancer. The two isoforms differ by a single exon.

[0175] **FIG. 2** depicts a diagram of an RNA (left), the RNA with a mutation (middle), and a small molecule bound to the RNA with the mutation (right). The mutation depicted disrupts a stem-loop that contains the mutated base increasing 5'ss accessibility. Access to the 5' splice site can be decreased by the depicted stem loop-stabilizing small molecule splicing modulator. In this case the resulting mRNA isoform has skipped one exon by a small molecule splicing modulator.

[0176] **FIG. 3** depicts diagrams of an exemplary primary RNA structure (top), exemplary secondary RNA structures (middle) and exemplary tertiary RNA structures (bottom).

[0177] **FIG. 4** depicts a diagram of an exemplary small molecule splicing modulator bound to a complex comprising a polynucleotide and splicing complex protein.

[0178] **FIG. 5** depicts a diagram of alternative splicing of exemplary pre-mRNAs transcribed from the indicated genes. mRNA isoforms depicted on the left are normal; mRNA isoforms depicted on the right promote cancer.

[0179] **FIG. 6A** depicts an exemplary SMN2 pre-mRNA sequence with a bulge.

[0180] **FIG. 6B** depicts an exemplary pre-mRNA sequence with a bulge.

[0181] **FIG. 6C** depicts an exemplary pre-mRNA sequence with a bulge.

[0182] **FIG. 6D** depicts an exemplary pre-mRNA sequence with a bulge.

[0183] **FIG. 6E** depicts an exemplary pre-mRNA sequence without a bulge.

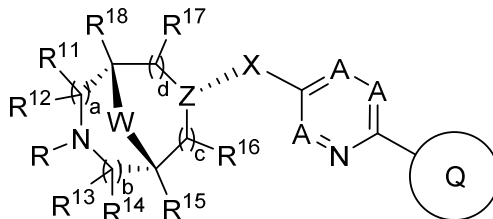
[0184] **FIG. 7** depicts a graph of relative transcript levels of FOXM1 isoform A (represses cancer) and FOXM1 isoform B (promotes cancer) in A-673 cells incubated with the indicated concentrations of an SMSM.

[0185] **FIG. 8** depicts a plot of the measured IC₅₀ of cell viability of an SMSM for the indicated cells.

CLAIMS

What is claimed is:

1. A compound 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, -OR¹, =O, =N-OR¹, -SR¹, -S(=O)R¹, -S(=O)₂R¹, -N(R¹)₂, -NR¹S(=O)(=NR¹)R², -NR¹S(=O)₂R², -S(=O)₂N(R¹)₂, -C(=O)R¹, -OC(=O)R¹, -C(=O)OR¹, -OC(=O)OR¹, -C(=O)N(R¹)₂, -OC(=O)N(R¹)₂, -NR¹C(=O)R¹, -P(=O)(R²)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, substituted or unsubstituted C₂-C₇ heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted monocyclic heteroaryl;

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

X is -NR³-, -CR⁴R⁵-, -C(=O)-, or -C(=CR²)-

each R¹ 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 R² is independently H, D, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted C₁-C₆ haloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted monocyclic heteroaryl, -OR¹, -N(R¹)₂, -CH₂OR¹, -C(=O)OR¹, -OC(=O)R¹, -C(=O)N(R¹)₂, or -NR¹C(=O)R¹;

R³ is -OR¹, -N(R¹)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-C₇ heterocycloalkyl;

R⁴ is H, D, F, -CN, -OR¹, -SR¹, -N(R¹)₂, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted C₁-C₆ haloalkyl, substituted or unsubstituted C₁-C₆ heteroalkyl, substituted or

unsubstituted C₁-C₆ alkylene-OR¹, substituted or unsubstituted C₃-C₈ cycloalkyl, substituted or unsubstituted C₂-C₇ heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R⁵ is H, D, F, -CN, -OR¹, -SR¹, -N(R¹)₂, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted C₁-C₆ haloalkyl, substituted or unsubstituted C₁-C₆ heteroalkyl, substituted or unsubstituted C₁-C₆ alkylene-OR¹, substituted or unsubstituted C₃-C₈ cycloalkyl, substituted or unsubstituted C₂-C₇ heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or

R⁴ and R⁵ taken in combination with the carbon atom to which they attach, form a substituted or unsubstituted C₃₋₈ cycloalkyl or a substituted or unsubstituted C₂₋₇ heterocycloalkyl;

Z is CR⁷; and R⁷ is H, D, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted C₁-C₆ haloalkyl or -CH₂OR¹;

W is substituted or unsubstituted C₁-C₄ alkylene, substituted or unsubstituted C₂-C₄ alkenylene, or substituted or unsubstituted C₁-C₄ heteroalkylene;

R is selected from the group consisting of H, a substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₁₋₆ fluoroalkyl, 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 heteroaryl, wherein alkyl is optionally substituted with hydroxy, amino, substituted or unsubstituted mono-C₁₋₆ alkylamino, or substituted or unsubstituted di-C₁₋₆ alkylamino;

R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, and R¹⁸ are each independently selected from the group consisting of H, F, OR¹, substituted or unsubstituted C₁₋₆ alkyl, a substituted or unsubstituted C₁₋₆ fluoroalkyl, and substituted or unsubstituted C₁-C₆ heteroalkyl, wherein alkyl is optionally substituted with hydroxy, amino, methoxy, substituted or unsubstituted mono-C₁₋₆ alkylamino or substituted or unsubstituted di-C₁₋₆ alkylamino;

R¹¹ and R¹³, taken in combination form a substituted or unsubstituted C₁₋₃ alkylene group or a substituted or unsubstituted C₁₋₃ heteroalkylene group; or

R¹¹ 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

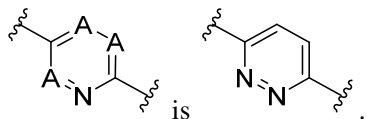
when X is -NR³-, then R³ and R¹⁶ are optionally taken together with the intervening atoms to which they are attached to form a 4, 5, or 6-membered ring;

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

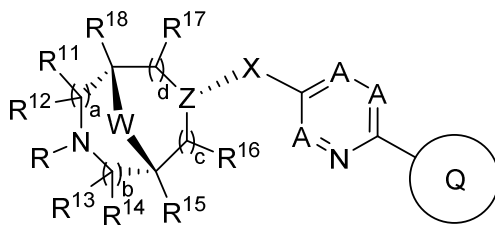
c and d are each independently selected from 1, 2, 3, or 4; and

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

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



3. A compound 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, -OR¹, =O, =N-OR¹, -SR¹, -S(=O)R¹, -S(=O)₂R¹, -N(R¹)₂, -NR¹S(=O)(=NR¹)R², -NR¹S(=O)₂R², -S(=O)₂N(R¹)₂, -C(=O)R¹, -OC(=O)R¹, -C(=O)OR¹, -OC(=O)OR¹, -C(=O)N(R¹)₂, -OC(=O)N(R¹)₂, -NR¹C(=O)R¹, -P(=O)(R²)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, substituted or unsubstituted C₂-C₇ heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted monocyclic heteroaryl;

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

X is -O- or -S-;

each R¹ 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 R² is independently H, D, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted C₁-C₆ haloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted monocyclic heteroaryl, -OR¹, -N(R¹)₂, -CH₂OR¹, -C(=O)OR¹, -OC(=O)R¹, -C(=O)N(R¹)₂, or -NR¹C(=O)R¹;

Z is CR⁷; and R⁷ is H, D, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted C₁-C₆ haloalkyl or -CH₂OR¹;

W is substituted or unsubstituted C₁-C₄ alkylene, substituted or unsubstituted C₂-C₄ alkenylene, or substituted or unsubstituted C₁-C₄heteroalkylene;

R is selected from the group consisting of H, a substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₁₋₆ fluoroalkyl, 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 heteroaryl, wherein alkyl is optionally substituted with hydroxy, amino, substituted or unsubstituted mono-C₁₋₆ alkylamino, or substituted or unsubstituted di-C₁₋₆ alkylamino;

R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, and R¹⁸ are each independently selected from the group consisting of H, F, OR¹, substituted or unsubstituted C₁₋₆ alkyl, a substituted or unsubstituted C₁₋₆ fluoroalkyl, and substituted or unsubstituted C₁-C₆ heteroalkyl, wherein alkyl is optionally substituted with hydroxy, amino, methoxy, substituted or unsubstituted mono-C₁₋₆ alkylamino or substituted or unsubstituted di-C₁₋₆ alkylamino;

R¹¹ and R¹³, taken in combination form a substituted or unsubstituted C₁₋₃ alkylene group or a substituted or unsubstituted C₁₋₃ heteroalkylene group; or

R¹¹ 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

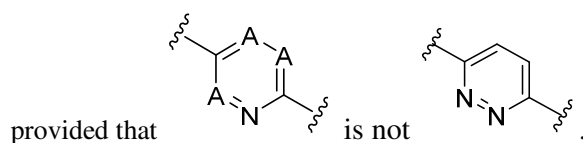
R¹³ and R¹⁴, taken in combination with the carbon atom to which they attach, form a spirocyclic C₃₋₈ cycloalkyl; or

R¹⁷ and R², taken in combination form a substituted or unsubstituted C₁₋₃ alkylene group;

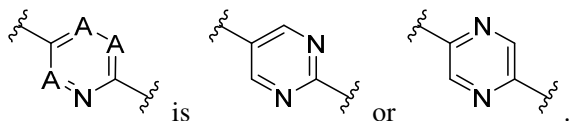
a and b are each independently selected from 0, 1, 2, or 3;

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

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



4. The compound of claim 1 or 3, or a pharmaceutically acceptable salt or solvate thereof, wherein



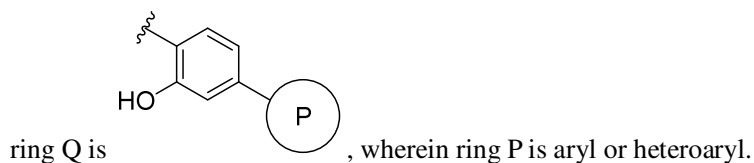
5. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt or solvate thereof, wherein ring Q is 2-hydroxy-phenyl substituted with:

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, -C(=O)NH-C₁₋₆ alkyl-heteroaryl, -NHC(=O)-C₁₋₆ alkylheteroaryl, 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,

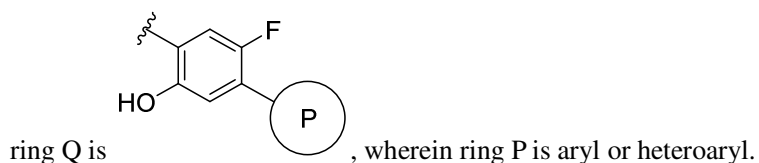
wherein two C₁₋₆ alkyl groups can combine with the atoms to which they are bound to form a 5-6 membered ring; and

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.

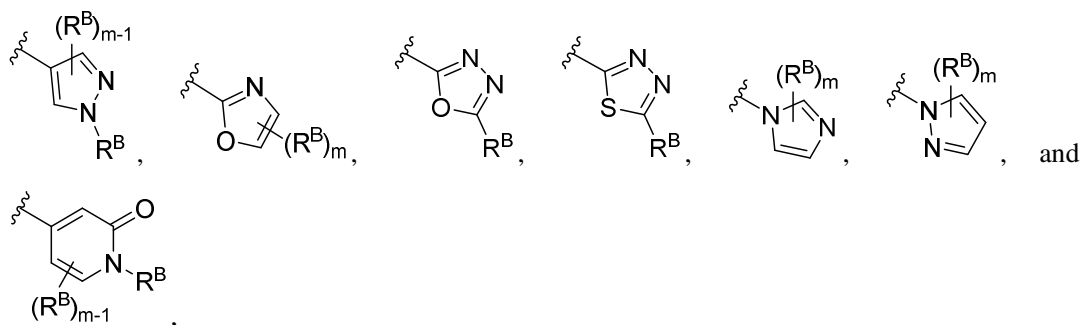
6. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt or solvate thereof, wherein:



7. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt or solvate thereof, wherein:

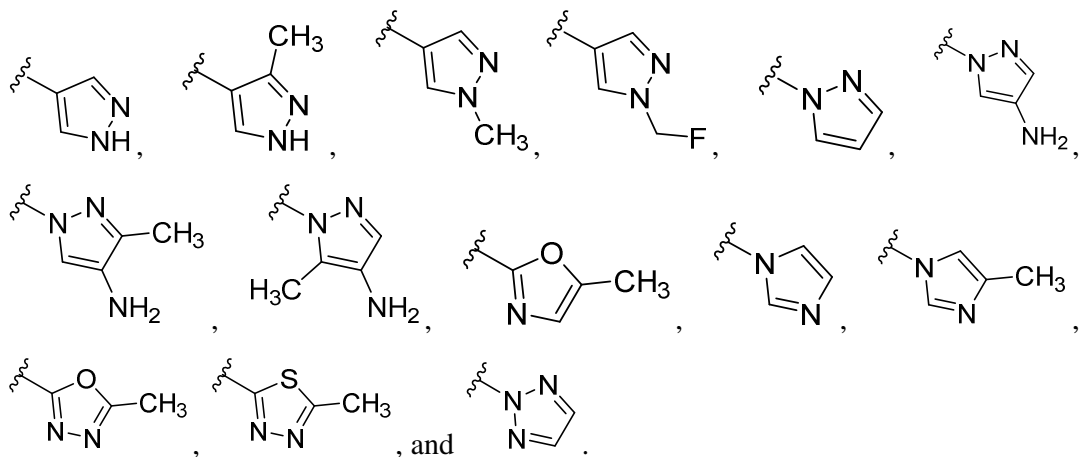


8. The compound of claim 6 or 7, or a pharmaceutically acceptable salt or solvate thereof, wherein ring P is heteroaryl selected from the group consisting of:



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.

9. The compound of claim 6 or 7, or a pharmaceutically acceptable salt or solvate thereof, wherein ring P is heteroaryl selected from the group consisting of:



10. The compound of claim 6 or 7, or a pharmaceutically acceptable salt or solvate thereof, wherein ring P is heteroaryl selected from the group consisting of:

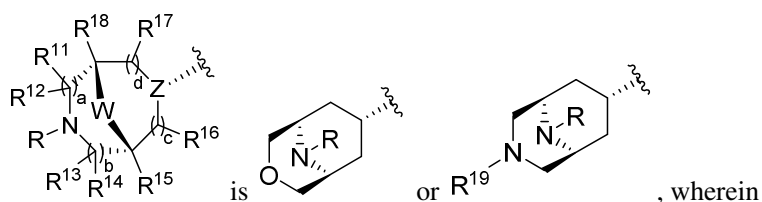
R is H; R¹⁵ and R¹⁸ are H; and p is 2.

18. The compound of claim 16, or a pharmaceutically acceptable salt or solvate thereof, wherein R is H; R¹⁵ and R¹⁸ are H; and p is 3.

19. The compound of claim 16, or a pharmaceutically acceptable salt or solvate thereof, wherein R is H; R¹⁵ and R¹⁸ are CH₃; and p is 2.

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

21. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt or solvate thereof, wherein



R¹⁹ is H, D, -CN, -OH, -OR¹, -SR¹, -S(=O)R¹, -S(=O)₂R¹, -CH₂-N(R¹)₂, -S(=O)₂N(R¹)₂, -C(=O)R¹, -CO₂R¹, -C(=O)N(R¹)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.

22. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt or solvate thereof, wherein R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, and R¹⁸ are each independently selected from the group consisting of H, F, and substituted or unsubstituted C₁-C₆ alkyl.

23. A pharmaceutical composition comprising a compound of any one of claims 1 to 22, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable diluent, carrier, or excipient.

24. A compound according to any one of claims 1-22, or a pharmaceutically acceptable salt or solvate thereof, for use as a medicament.