

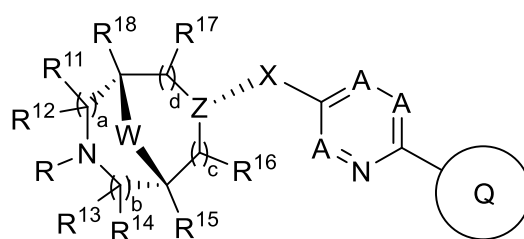
[0169] In some embodiments, the snRNP comprises U1 snRNP, U2 snRNP, U4 snRNP, U5 snRNP, U6 snRNP, U11 snRNP, U12 snRNP, U4atac snRNP, U5 snRNP, U6 atac snRNP, or any combinations thereof.

[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.

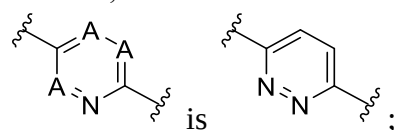
[0172] In some embodiments, a bulge is due to mismatched base pairing between the splice site sequence and a snRNA sequence.

[0172a] Provided herein is a compound of Formula (IV), or a pharmaceutically acceptable salt ~~or solvate~~ thereof:



Formula (IV)

wherein,



ring Q is 5-6 or 6-5 fused bicyclic heteroaryl having 1, 2, or 3 ring heteroatoms independently selected from N, O or S;

wherein ring Q is optionally substituted with one or more substituents selected from:

halogen, -CN, -NH₂, -NH(CH₃), -N(CH₃)₂, -OH, -CO₂H, -CO₂(C₁-C₄ alkyl), -C(=O)NH₂, -C(=O)NH(C₁-C₄ alkyl), -C(=O)N(C₁-C₄ alkyl)₂, -C(=O)NH(C3-C8 cycloalkyl), -S(=O)₂NH₂, -S(=O)₂NH(C₁-C₄ alkyl), -S(=O)₂N(C₁-C₄ alkyl)₂, C₁-C₄ alkyl, C₃-C₆ cycloalkyl, C₁-C₄ fluoroalkyl, C₁-C₄ heteroalkyl, C₁-C₄ alkoxy, C₁-C₄ fluoroalkoxy, -SC₁-C₄ alkyl, -S(=O)C₁-C₄ alkyl, -S(=O)₂(C₁-C₄ alkyl), -NH(cyclopropyl), -OCH₃, -OCF₃, and oxo;

X is -NR³-;

each R¹ is independently H, D, C₁-C₆ alkyl, -CD₃, C₁-C₆ haloalkyl, C₁-C₆ heteroalkyl, C₃-C₈ cycloalkyl, or C₂-C₇ heterocycloalkyl;

R³ is -OR¹, -N(R¹)₂, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ heteroalkyl, C₃-C₈ cycloalkyl, or C₂-C₇ heterocycloalkyl;

Z is CR⁷; and R⁷ is H;

W is C₁-C₄ alkylene;

R is H;

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

[0172b] 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.

[0172c] 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' splice site 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.

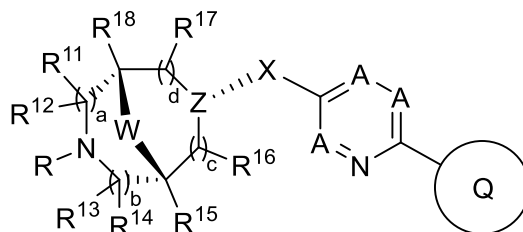
[0176] FIG. 3 depicts diagrams of an exemplary primary RNA structure (top), exemplary secondary RNA structures (middle) and exemplary tertiary RNA structures (bottom).

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

CLAIMS

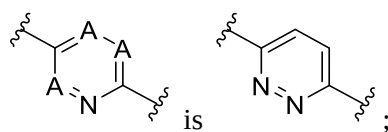
What is claimed is:

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



Formula (IV)

wherein,



ring Q is 5-6 or 6-5 fused bicyclic heteroaryl [having 1, 2, or 3 ring heteroatoms independently selected from N, O or S](#);

wherein ring Q is optionally substituted with one or more substituents selected from:

halogen, -CN, -NH₂, -NH(CH₃), -N(CH₃)₂, -OH, -CO₂H, -CO₂(C₁-C₄ alkyl), -C(=O)NH₂, -C(=O)NH(C₁-C₄ alkyl), -C(=O)N(C₁-C₄ alkyl)₂, [-C\(=O\)NH\(C₃-C₈ cycloalkyl\)](#), -S(=O)₂NH₂, -S(=O)₂NH(C₁-C₄ alkyl), -S(=O)₂N(C₁-C₄ alkyl)₂, C₁-C₄ alkyl, C₃-C₆ cycloalkyl, C₁-C₄ fluoroalkyl, C₁-C₄ heteroalkyl, C₁-C₄ alkoxy, C₁-C₄ fluoroalkoxy, -SC₁-C₄ alkyl, -S(=O)C₁-C₄ alkyl, -S(=O)₂(C₁-C₄ alkyl), -NH(cyclopropyl), -OCH₃, -OCF₃, and oxo;
X is -NR³-;

each R¹ is independently H, D, C₁-C₆ alkyl, -CD₃, C₁-C₆ haloalkyl, C₁-C₆ heteroalkyl, C₃-C₈ cycloalkyl, or C₂-C₇ heterocycloalkyl;

R³ is -OR¹, -N(R¹)₂, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ heteroalkyl, C₃-C₈ cycloalkyl, or C₂-C₇ heterocycloalkyl;

Z is CR⁷; and R⁷ is H;

W is C₁-C₄ alkylene;

R is H;

R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, and R¹⁸ are each independently selected from the group consisting of H, F, OR¹, C₁-C₆ alkyl, C₁-C₆ fluoroalkyl, and C₁-C₆ heteroalkyl, wherein the alkyl, fluoroalkyl, or heteroalkyl is optionally substituted with hydroxy, amino, methoxy, mono-C₁-C₆ alkylamino, and di-C₁-C₆ 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%.](#)

2. The compound of claim 1, or a pharmaceutically acceptable salt ~~or solvate~~ thereof, wherein R³ is -CH₃.

3. The compound of claim 1, or a pharmaceutically acceptable salt ~~or solvate~~ thereof, wherein R³ is C₃-C₈ cycloalkyl selected from cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

4. The compound of claim 1, or a pharmaceutically acceptable salt ~~or solvate~~ thereof, wherein R³ is -CH₃, -CD₃, -CF₃, -OCH₃, -OCD₃, -OCH₂CH₃, -OCH₂CH₂OH, or -OCH₂CH₂OCH₃.

5. The compound of claim 1, or a pharmaceutically acceptable salt ~~or solvate~~ thereof, wherein W is -CH₂CH₂-.

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

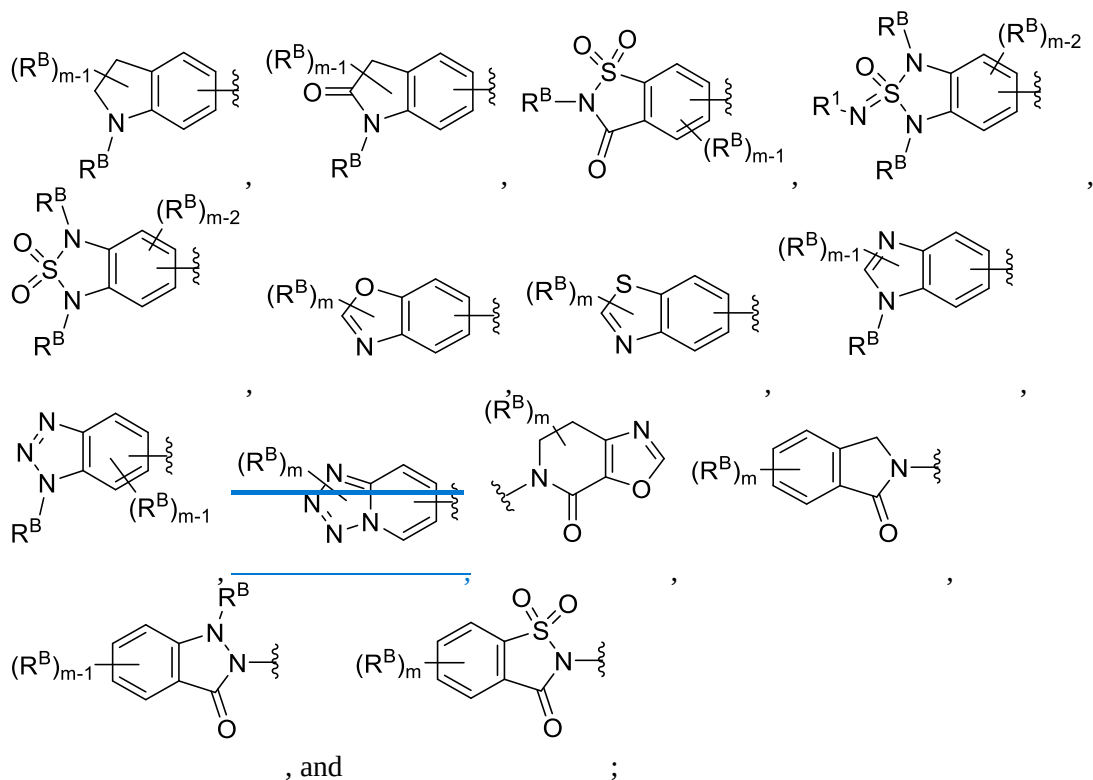
ring Q is optionally substituted 5-6 or 6-5 fused bicyclic heteroaryl having ~~8 to 10 ring atoms, and~~ 1, 2, or 3 ring heteroatoms independently selected from N, O or S, which is substituted with 0, 1, or 2 substituents independently selected from cyano, halogen, hydroxy, C₁₋₄ alkyl, and C₁₋₄ alkoxy.

7. The compound of any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein: ring Q is optionally substituted 5-6 or 6-5 fused bicyclic heteroaryl having 1, 2, or 3 ring heteroatoms independently selected from N and O.

8. The compound of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, wherein: ring Q is optionally substituted benzoxazolyl or benzofuranyl.

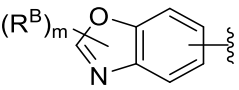
~~79.~~ The compound of any one of claims 1 to 5, or a pharmaceutically acceptable salt ~~or solvate~~ thereof, wherein:

ring Q is selected from the group consisting of:

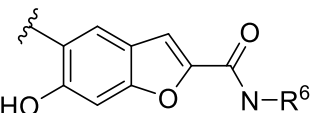
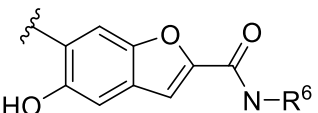


wherein each R^B is independently selected from cyano, halogen, hydroxy, C_1 - C_4 alkyl, $-OCH_3$, $-OCD_3$, C_1 - C_4 alkoxy, C_{3-6} cycloalkyl;
and m is ~~0~~, 1, 2, or 3.

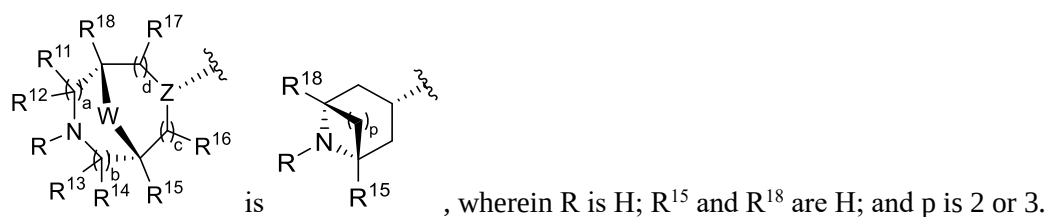
109. The compound of any one of claims 1 to 5~~claim 6 or 7~~, or a pharmaceutically acceptable salt ~~or~~

~~solvate~~ thereof, wherein ring Q is , wherein each R^B is independently selected from cyano, halogen, hydroxy, C_1 - C_4 alkyl, $-OCH_3$, $-OCD_3$, C_1 - C_4 alkoxy, C_{3-6} cycloalkyl; and m is ~~0~~, 1, 2, or 3.

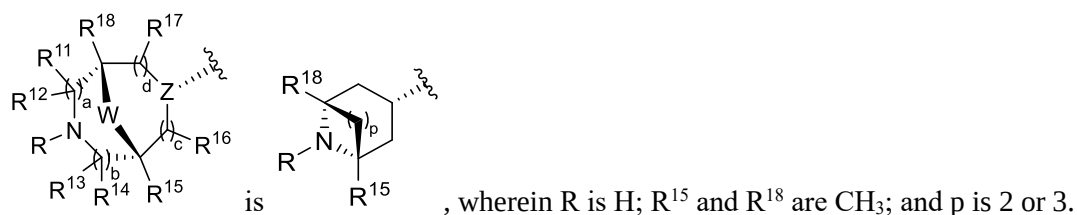
110. The compound of any one of claims 1 to 5~~claim 6 or 7~~, or a pharmaceutically acceptable salt ~~or~~

~~solvate~~ thereof, wherein ring Q is  or  ; and each R^6 is independently H or C_1 - C_4 alkyl.

111. The compound of any one of claims 1 to 4 or 6 to 110, or a pharmaceutically acceptable salt ~~or~~ ~~solvate~~ thereof, wherein



[4413](#). The compound of any one of claims 1 to [4 or 6 to 119](#), or a pharmaceutically acceptable salt ~~or solvate~~ thereof, wherein



[4214](#). The compound of claim [4012](#), or a pharmaceutically acceptable salt ~~or solvate~~ thereof, wherein p is 2.

[4315](#). The compound of claim [4012](#), or a pharmaceutically acceptable salt ~~or solvate~~ thereof, wherein p is 3.

[4416](#). The compound of claim [4413](#), or a pharmaceutically acceptable salt ~~or solvate~~ thereof, wherein p is 2.

[4517](#). The compound of claim [4413](#), or a pharmaceutically acceptable salt ~~or solvate~~ thereof, wherein p is 3.

[4618](#). The compound of any one of claims 1 to 9, or a pharmaceutically acceptable salt ~~or solvate~~ thereof, wherein R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, and R¹⁸ are each H.

[4719](#). A pharmaceutical composition comprising a compound of any one of claims 1 to 16, or a pharmaceutically acceptable salt ~~or solvate~~ thereof, and a pharmaceutically acceptable diluent, carrier, or excipient.

[20.](#) The pharmaceutical composition of claim 19, wherein the compound of Formula (IV) has a stereochemical purity of at least 80%.

~~4821~~. A compound according to any one of claims 1 to ~~46~~18, or a pharmaceutically acceptable salt ~~or solvate~~ thereof, for use as a medicament.