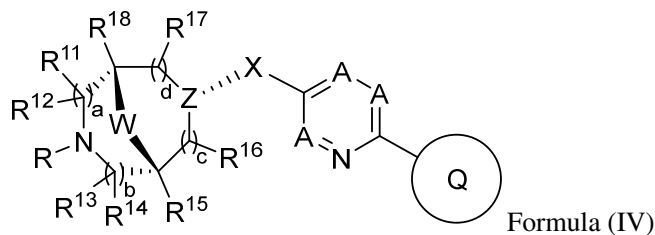


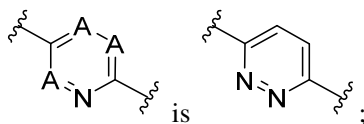
SUMMARY

[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.

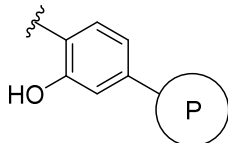
[0005a] In one aspect, provided herein is a compound that has the structure of Formula (IV), or a pharmaceutically acceptable salt thereof:



wherein:



ring Q is:



; wherein ring P is aryl or heteroaryl;

X is -O-;

each R^1 is independently H, D, C_1 - C_6 alkyl, $-CD_3$, C_1 - C_6 haloalkyl, or C_1 - C_6 heteroalkyl;

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 , C_{1-6} alkyl, C_{1-6} fluoroalkyl, and C_1 - C_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;

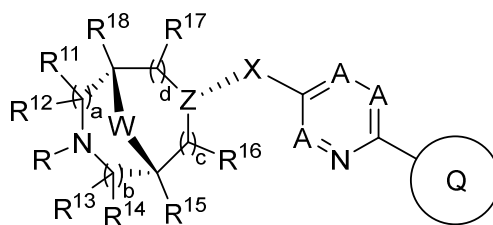
c and d are each 1; and

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 , -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 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, substituted or unsubstituted C_2 - C_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-, -NR³-, -CR⁴R⁵-, -C(=O)-, -C(=CR²)₂-, -S-, -S(=O)-, -S(=O)₂-, or -S(=O)(=NR¹)₂-;

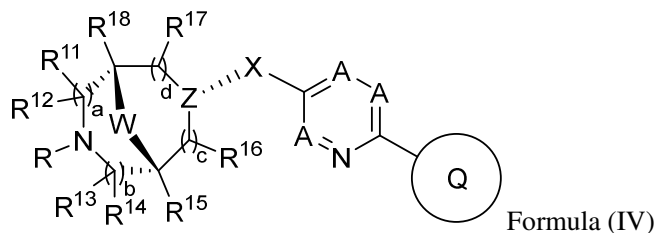
each R^1 is independently H, D, substituted or unsubstituted C_1 - C_6 alkyl, -CD₃, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_8

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

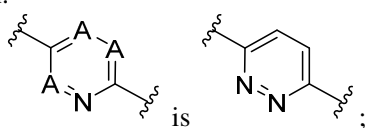
CLAIMS

What is claimed is:

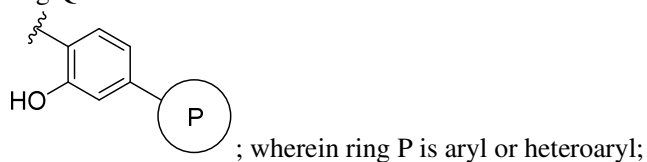
1. A compound that has the structure of Formula (IV), or a pharmaceutically acceptable salt thereof:



wherein:



ring Q is:



X is -O-;

each R¹ is independently H, D, C₁-C₆ alkyl, -CD₃, C₁-C₆ haloalkyl, or C₁-C₆ heteroalkyl;

Z is $\mathbb{C}R^7$; and R^7 is H ;

W is C₁-C₄ alkylene;

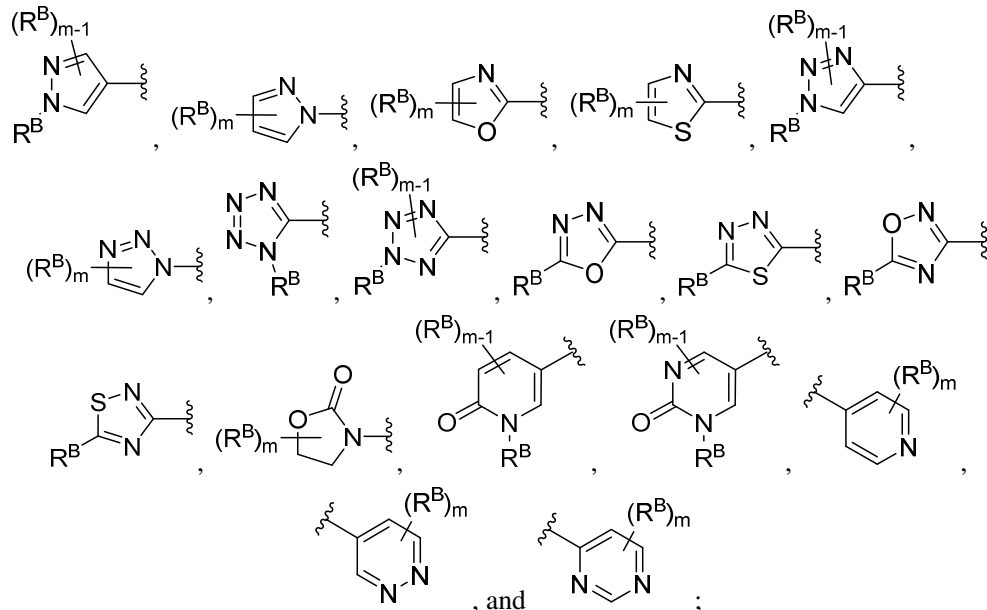
R is H;

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, and C_1 - C_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%.

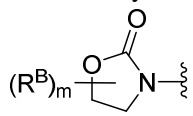
2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein ring P is heteroaryl selected from:



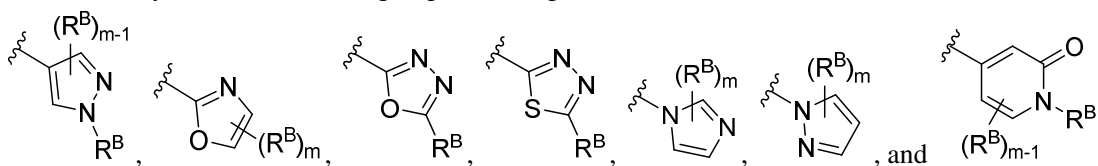
wherein:

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 - C_6 cycloalkyl;
 m is 0, 1, 2, or 3.

3. The compound of claim 2, or a pharmaceutically acceptable salt thereof, wherein ring P is:

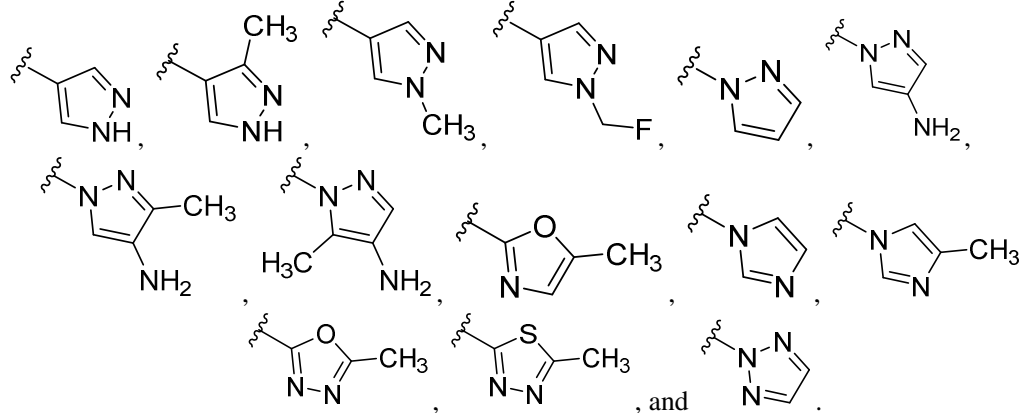


4. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein ring P is heteroaryl selected from the group consisting of:

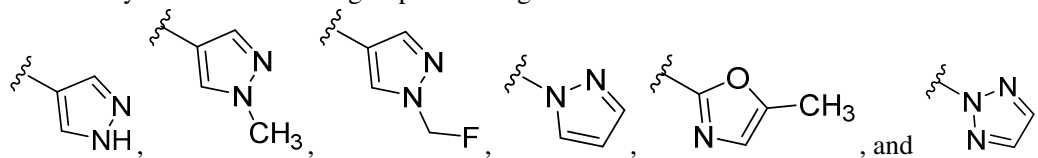


wherein each R^B is independently selected from cyano, halogen, hydroxy, C_{1-6} alkyl, $-OCH_3$, $-OCD_3$, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1 - C_4 alkoxy, C_{3-7} cycloalkyl, C_{2-8} heterocycloalkyl, heteroaryl, heterocycloalkyl- C_{1-6} alkyl, C_{1-6} alkyl-aryl, C_{1-6} alkyl-heterocycloalkyl, C_{1-6} alkyl-heteroaryl, C_{1-6} alkoxy-heterocycloalkyl, 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.

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

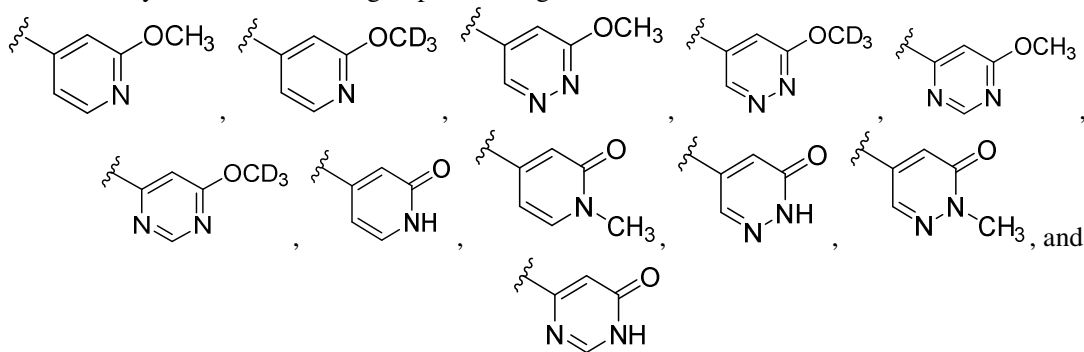


6. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein ring P is heteroaryl selected from the group consisting of:

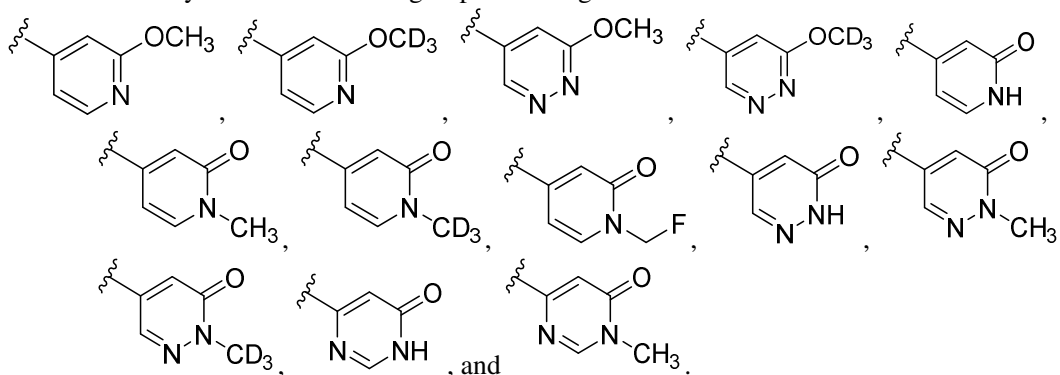


7. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein ring P is heteroaryl having 5 ring atoms, two ring heteroatoms selected from N and O, and is substituted with 0, 1, or 2 substituents independently selected from oxo and C₁₋₆ alkyl.

8. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein ring P is heteroaryl selected from the group consisting of:

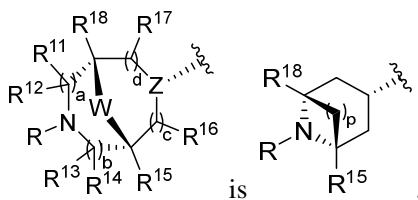


9. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein ring P is heteroaryl selected from the group consisting of:



10. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein ring P is phenyl, naphthyl, 5-membered heteroaryl, or 6-membered heteroaryl;
and wherein ring P is optionally substituted with one or more substituents selected from: oxo, 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, -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, and -OCF₃.

11. The compound of any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, wherein:



wherein p is 1, 2, or 3.

12. The compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein:
R is H; R¹⁵ and R¹⁸ are H; and p is 2 or 3.
13. The compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein:
R is H; R¹⁵ and R¹⁸ are H; and p is 2.
14. The compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein:
R is H; R¹⁵ and R¹⁸ are H; and p is 3.
15. The compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein:
R is H; R¹⁵ and R¹⁸ are CH₃; and p is 2 or 3.
16. The compound of claim 11, or a pharmaceutically acceptable salt or solvate thereof, wherein:
R is H; R¹⁵ and R¹⁸ are CH₃; and p is 2.
17. The compound of claim 11, or a pharmaceutically acceptable salt or solvate thereof, wherein:
R is H; R¹⁵ and R¹⁸ are CH₃; and p is 3.
18. A pharmaceutical composition comprising a compound of any one of claims 1 to 17, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable diluent, carrier, or excipient.
19. A compound of any one of claims 1 to 17, or a pharmaceutically acceptable salt thereof, for use in the treatment, prevention and/or delay of progression of a disease or condition.