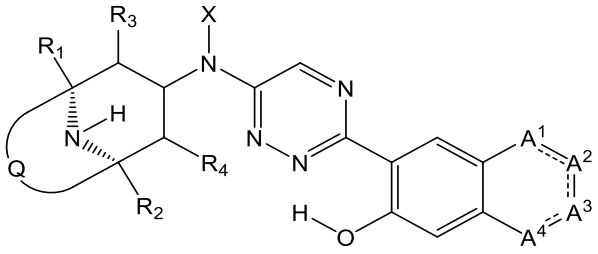
complex components) can create additional two-dimensional and three-dimensional complexity (*e.g.*, by binding to the pre-mRNA). These features can be potency-and efficacy-limiting for oligonucleotide therapies.

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 an aspect of the present disclosure, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof:



Formula (I)

wherein

Q is substituted or unsubstituted C_1-C_7 alkylene or substituted or unsubstituted C_1-C_7 heteroalkylene;

X is hydrogen, CH_3, or substituted or unsubstituted C_3–C_6 cycloalkyl;

each R_1 and R_2 is independently hydrogen, halogen, or CH_3;

each R_3 and R_4 is independently hydrogen or halogen;

each A^1, A^2, A^3, and A^4 is independently N, -NR^{Y1}-, -O-, -S-, or CR^{A1};

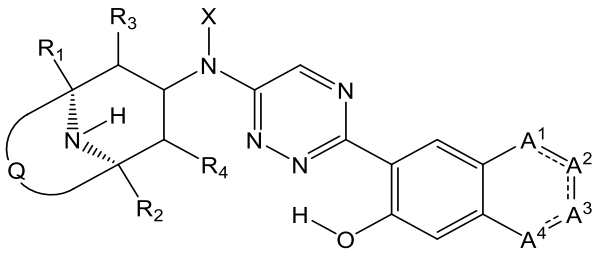
each ---- is independently a single or double bond;

each R^{A1} is independently hydrogen, halogen, =O, or substituted or unsubstituted C_1-C_6 alkyl; and each R^{Y1} is independently hydrogen or substituted or unsubstituted C_1–C_6 alkyl.

[0005b] In another aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutically acceptable salt thereof, for modulating splicing, wherein the compound, or a pharmaceutically acceptable salt thereof, is to be administered to cells, and wherein the compound 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.

[0005c] In a further aspect of the present disclosure, there is provided a compound disclosed herein for use in treating a disease or condition.

[0006] In one example, described herein is a compound of Formula (I):



Formula (I)

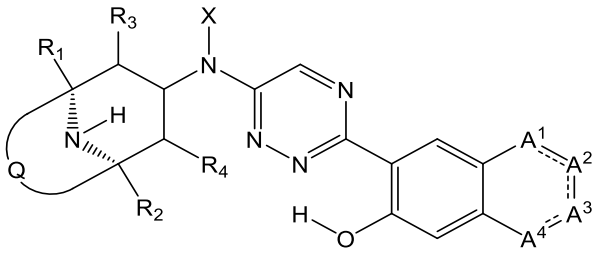
wherein, Q is substituted or unsubstituted C_1-C_7 alkylene or substituted or unsubstituted C_1-C_7 heteroalkylene; X is hydrogen, CH_3, or substituted or unsubstituted C_3–C_6 cycloalkyl; each R_1 and R_2 is independently hydrogen, halogen, or CH_3; each R_3 and R_4 is independently hydrogen or halogen; each A^1, A^2, A^3, and A^4 is independently N, -NR^{Y1}-, -O-, -S-, or CR^{A1}; each $\overline{\text{- - - -}}$ is independently a single or double bond; each R^{A1} is independently hydrogen, halogen, =O, or substituted or unsubstituted C_1-C_6 alkyl; and each R^{Y1} is independently hydrogen or substituted or unsubstituted C_1–C_6 alkyl; or a pharmaceutically acceptable salt or pharmaceutically acceptable solvate thereof.

[0007] Also provided herein are pharmaceutical compositions comprising a compound disclosed herein, or a pharmaceutically acceptable salt or pharmaceutically acceptable solvate thereof, and a pharmaceutically acceptable excipient or carrier.

CLAIMS

What is claimed is:

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



Formula (I)

wherein

Q is substituted or unsubstituted C_1-C_7 alkylene or substituted or unsubstituted C_1-C_7 heteroalkylene;

X is hydrogen, CH_3, or substituted or unsubstituted C_3–C_6 cycloalkyl;

each R_1 and R_2 is independently hydrogen, halogen, or CH_3;

each R_3 and R_4 is independently hydrogen or halogen;

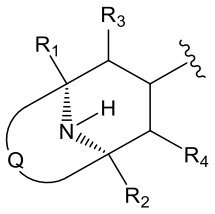
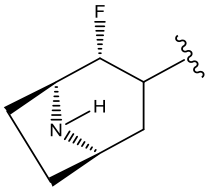
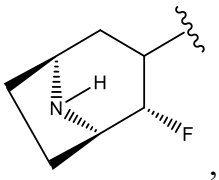
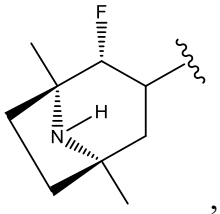
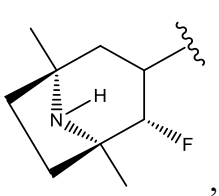
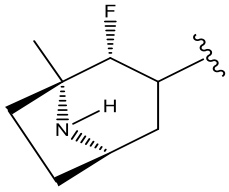
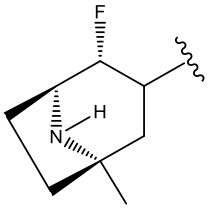
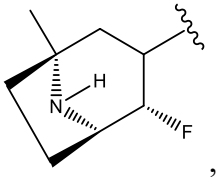
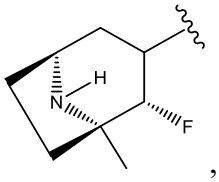
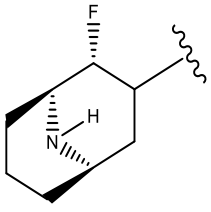
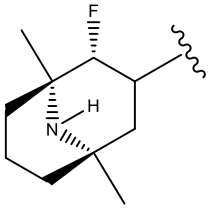
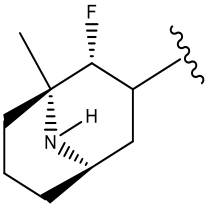
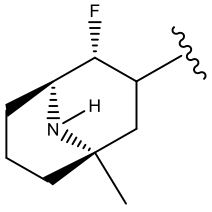
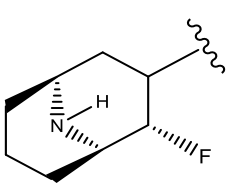
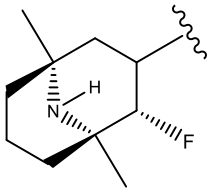
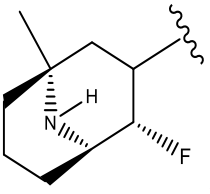
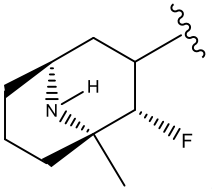
each A^1, A^2, A^3, and A^4 is independently N, -NR^{Y1}-, -O-, -S-, or CR^{A1};

each ---- is independently a single or double bond;

each R^{A1} is independently hydrogen, halogen, =O, or substituted or unsubstituted C_1-C_6 alkyl; and

each R^{Y1} is independently hydrogen or substituted or unsubstituted C_1–C_6 alkyl.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein at least one of R_3 or R_4 is fluorine.
3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R_3 is fluorine and R_4 is hydrogen.
4. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R_3 is hydrogen and R_4 is fluorine.
5. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein A^1 is CH, CF, $C(CH_3)$, N, O, or C(=O).
6. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein A^2 is CH, $C(CH_3)$, N, or $C(CH_3)$.
7. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein A^3 is CH, $C(CH_3)$, N, or $C(CH_3)$.
8. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein A^4 is CH, $C(CH_3)$, N, O, or C(=O).

9. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound comprises at least 20 carbon atoms, 5 nitrogen atoms and 1 fluorine atom.
10. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein one of A^1, A^2, A^3, and A^4 is C(=O).
11. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt thereof, wherein R_1 is hydrogen or CH_3.
12. The compound of any one of claims 1-11, or a pharmaceutically acceptable salt thereof, wherein R_2 is hydrogen or CH_3.
13. The compound of any one of claims 1-12, or a pharmaceutically acceptable salt thereof, wherein Q is substituted or unsubstituted C_1-C_7 alkylene.
14. The compound of claim 13, or a pharmaceutically acceptable salt thereof, wherein Q is substituted or unsubstituted C_2-C_4 alkylene.
15. The compound of any one of claims 1-14, or a pharmaceutically acceptable salt thereof, wherein  is selected from the group consisting of , , , , , , , , , , , , , , , and .
16. The compound of any one of claims 1-15, or a pharmaceutically acceptable salt thereof, wherein X is substituted or unsubstituted C_3–C_6 cycloalkyl.
17. The compound of claim 16, or a pharmaceutically acceptable salt thereof, wherein X is cyclopropyl.

18. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from Table 1 or Table 2.
19. A compound of any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof, for modulating splicing, wherein the compound, or a pharmaceutically acceptable salt thereof, is to be administered to cells, and wherein the compound 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.
20. The compound of any one of claims 1 to 18 for use in treating a disease or condition.