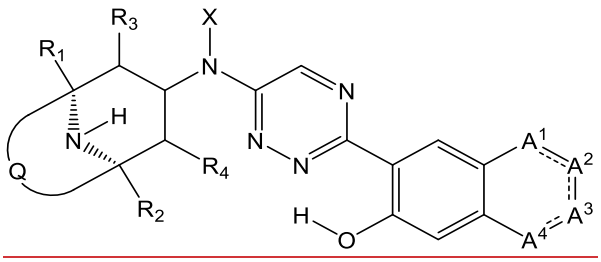
complex components) can create additional two-dimensional and three-dimensional complexity (*e.g.*, by binding to the pre-mRNA). These features can be potency-and efficacy-limiting for oligonucleotide therapies.

## 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 $CR^{A1}$;

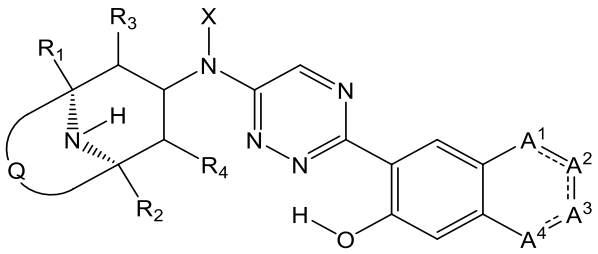
each ---- is independently a single or double bond;

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 ~~aspect~~example, described herein is a compound of Formula (I):




Formula (I)

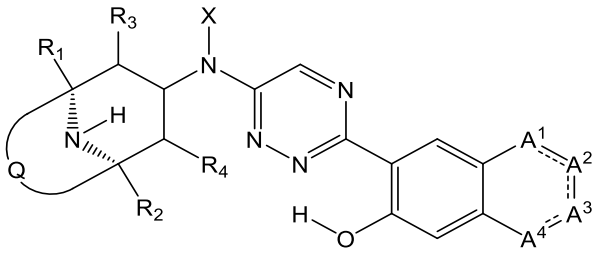
wherein, Q is substituted or unsubstituted $C_1$-$C_7$ alkylene or substituted or unsubstituted $C_1$-$C_7$ heteroalkylene; X is hydrogen, $CH_3$, or substituted or unsubstituted $C_3$–$C_6$ cycloalkyl; each $R_1$ and $R_2$ is independently hydrogen, halogen, or $CH_3$; each $R_3$ and $R_4$ is independently hydrogen or halogen; each $A^1$, $A^2$, $A^3$, and $A^4$ is independently N, -$NR^{Y1}$-, -O-, -S-, or $CR^{A1}$; each ---- 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;

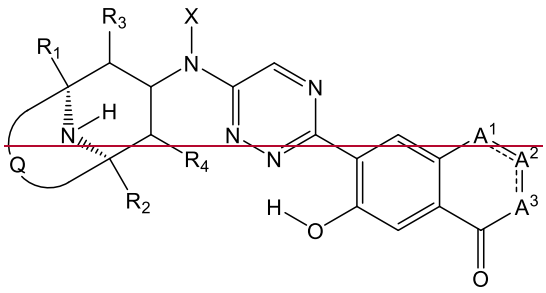
each $A^1$, $A^2$, $A^3$, and $A^4$ is independently N, -$NR^{Y1}$-, -O-, -S-, or $CR^{A1}$;

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

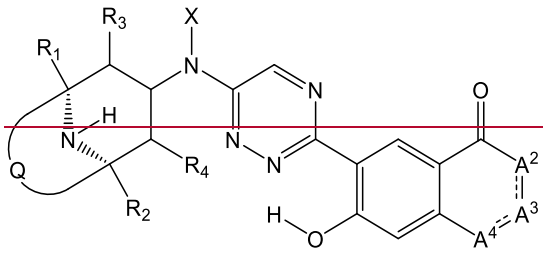
each $R^{Y1}$ is independently hydrogen or substituted or unsubstituted $C_1$–$C_6$ alkyl.

~~2. The compound of claim 1, wherein the compound has a structure of Formula (Ia):~~



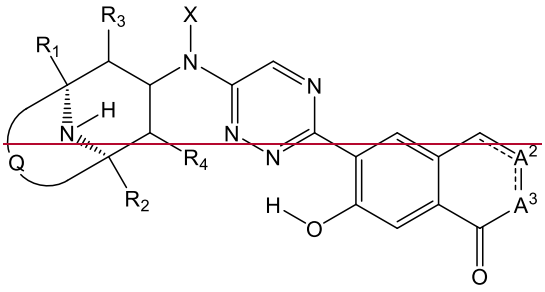
~~Formula (Ia).~~

~~3. The compound of claim 1, wherein the compound has a structure of Formula (Ib):~~



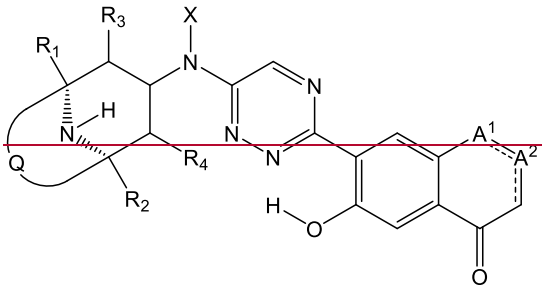
~~Formula (Ib).~~

~~4. The compound of claim 1, wherein the compound has a structure of Formula (Ic):~~



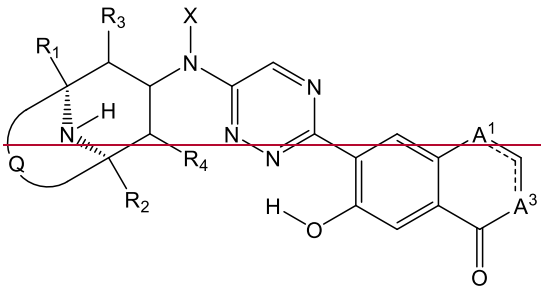
~~Formula (Ic).~~

~~5. The compound of claim 1, wherein the compound has a structure of Formula (Id):~~



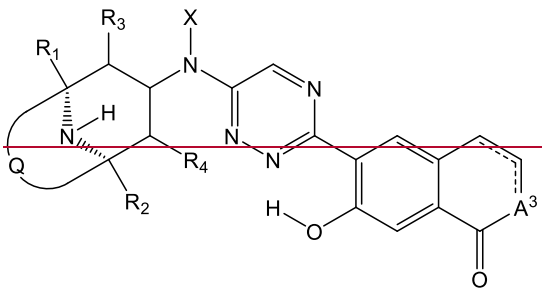
~~Formula (Id).~~

~~6. The compound of claim 1, wherein the compound has a structure of Formula (Ie):~~



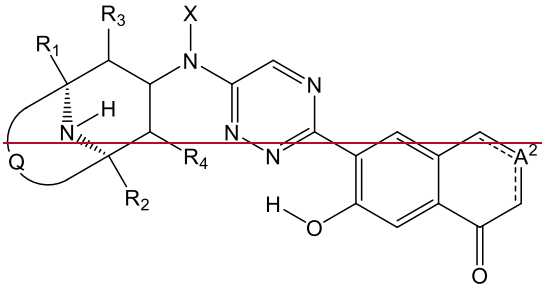
~~Formula (Ie).~~

~~7. The compound of claim 1, wherein the compound has a structure of Formula (If):~~



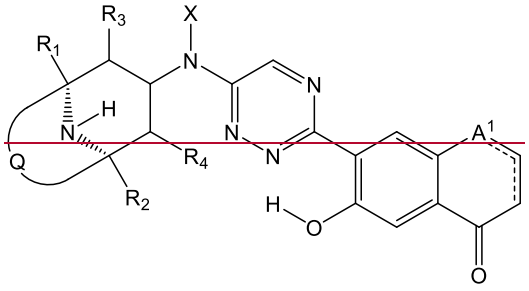
~~Formula (If).~~

~~8. The compound of claim 1, wherein the compound has a structure of Formula (Ig):~~



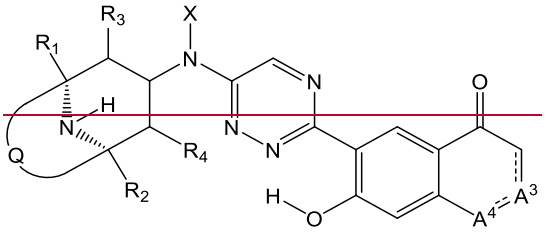
~~Formula (Ig).~~

~~9. The compound of claim 1, wherein the compound has a structure of Formula (Ih):~~



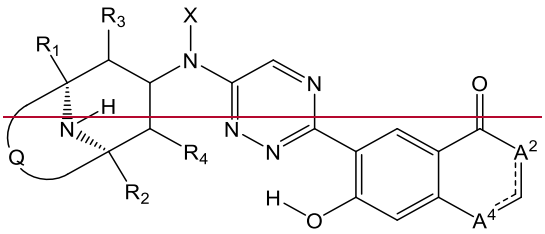
~~Formula (Ih).~~

~~10. The compound of claim 1, wherein the compound has a structure of Formula (Ii):~~



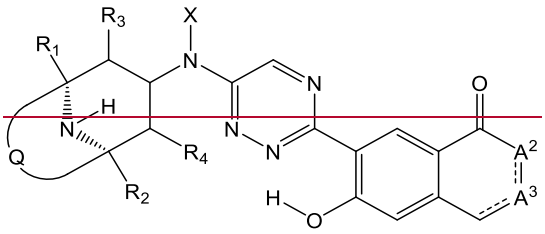
~~Formula (Ii).~~

~~11. The compound of claim 1, wherein the compound has a structure of Formula (Ij):~~



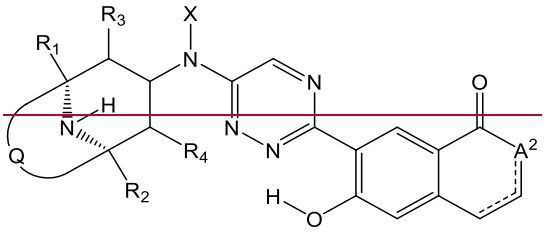
~~Formula (Ij).~~

~~12. The compound of claim 1, wherein the compound has a structure of Formula (Ik):~~



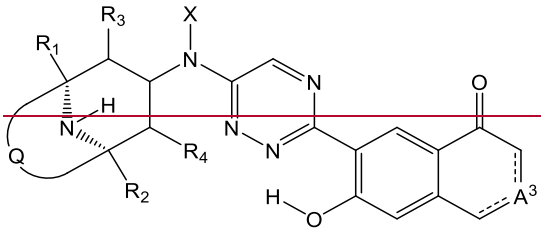
~~Formula (Ik).~~

~~13. The compound of claim 1, wherein the compound has a structure of Formula (Il):~~



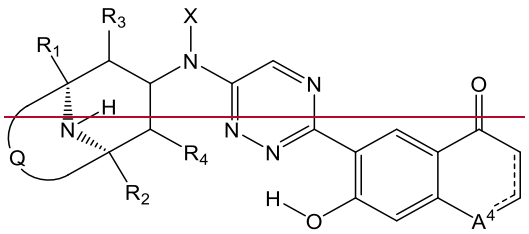
~~Formula (Il).~~

~~14. The compound of claim 1, wherein the compound has a structure of Formula (Im):~~



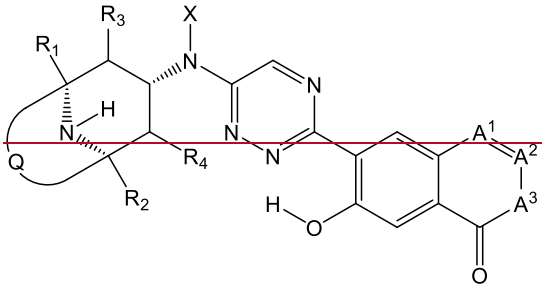
~~Formula (Im).~~

~~15. The compound of claim 1, wherein the compound has a structure of Formula (In):~~



~~Formula (In).~~

~~16. The compound of claim 1, wherein the compound has the structure of Formula (Iaa*):~~



~~Formula (Iaa*).~~

~~17.~~2. The compound of ~~any one of claims 1-16~~claim 1, or a pharmaceutically acceptable salt thereof, wherein at least one of $R_3$ or $R_4$ is fluorine.

~~18.~~3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof~~any one of claims 1-17~~, wherein $R_3$ is fluorine and $R_4$ is hydrogen.

~~19.~~4. The compound of ~~any one of claims 1-17~~claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein $R_3$ is hydrogen and $R_4$ is fluorine.

~~20.~~5. The compound of ~~any one of claims 1, 2, 5, 6, or 9~~ claim 1, or a pharmaceutically acceptable salt thereof, wherein $A^1$ is CH, CF, $C(CH_3)$, N, O, or C(=O).

~~21.~~6. The compound of ~~any one of claims 1-5, 8, or 11-13~~ claim 1, or a pharmaceutically acceptable salt thereof, wherein $A^2$ is CH, $C(CH_3)$, N, or $C(CH_3)$.

~~22.~~7. The compound of ~~any one of claims 1-4, 6, 7, 10, 12, or 14~~ claim 1, or a pharmaceutically acceptable salt thereof, wherein $A^3$ is CH, $C(CH_3)$, N, or $C(CH_3)$.

~~23.~~8. The compound of ~~any one of claims 1, 3, 10, 11, or 15~~ claim 1, or a pharmaceutically acceptable salt thereof, wherein $A^4$ is CH, $C(CH_3)$, N, O, or C(=O).

~~24.~~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.

~~25.~~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).

~~26.~~11. The compound of any one of claims 1-10~~25~~, or a pharmaceutically acceptable salt thereof, wherein $R_1$ is hydrogen or $CH_3$.

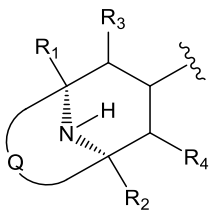
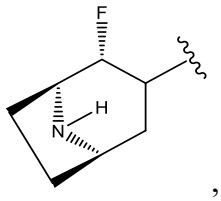
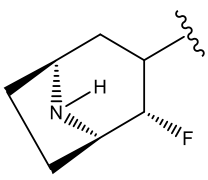
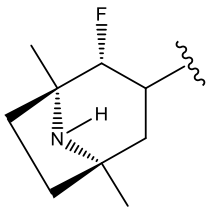
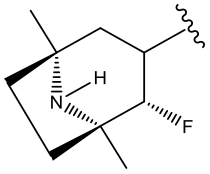
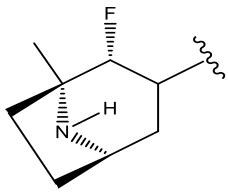
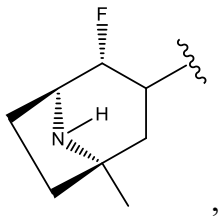
~~27.~~12. The compound of any one of claims 1-11~~26~~, or a pharmaceutically acceptable salt thereof, wherein $R_2$ is hydrogen or $CH_3$.

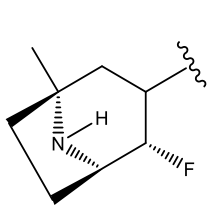
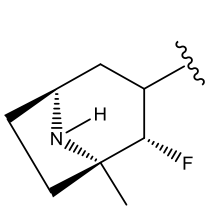
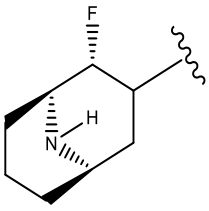
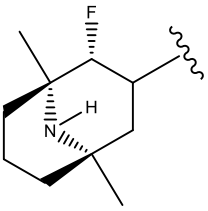
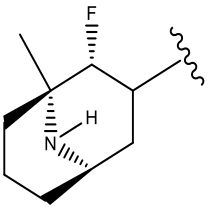
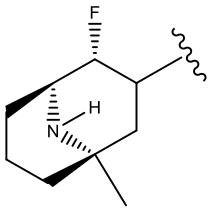
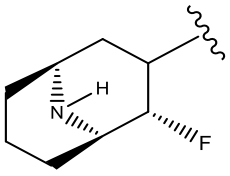
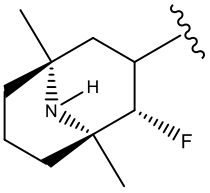
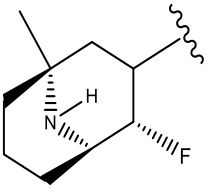
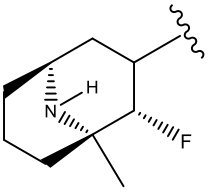
~~28.~~13. The compound of any one of claims 1-12~~27~~, or a pharmaceutically acceptable salt thereof, wherein Q is substituted or unsubstituted $C_1$-$C_7$ alkylene.

~~29.~~14. The compound of claim 13~~28~~, or a pharmaceutically acceptable salt thereof, wherein Q is substituted or unsubstituted $C_2$-$C_4$ alkylene.

~~30. The compound of claim 29, wherein Q is $-CH_2CH_2-$.~~

~~31. The compound of claim 29, wherein Q is $-CH_2CH_2CH_2-$.~~

~~32.~~15. The compound of any one of claims 1-14~~29~~, or a pharmaceutically acceptable salt thereof, wherein  is selected from the group consisting of , , , , , ,

, , , , , , , , , and .

~~33. The compound of any one of claims 1-32, wherein X is hydrogen.~~

~~34. The compound of any one of claims 1-32, wherein X is $-CH_3$.~~

~~35.~~16. The compound of any one of claims 1-~~32~~15, or a pharmaceutically acceptable salt thereof, wherein X is substituted or unsubstituted $C_3$–$C_6$ cycloalkyl.

~~36.~~17. The compound of claim 16~~35~~, or a pharmaceutically acceptable salt thereof, wherein X is cyclopropyl.

~~37.~~18. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from Table 1 or Table 2.

~~38. A pharmaceutically acceptable salt or solvate of a compound of any of the preceding claims.~~

~~39. A pharmaceutical composition comprising a compound of any one of claims 1-37, or a pharmaceutically acceptable salt or pharmaceutically acceptable solvate thereof, and a pharmaceutically acceptable excipient or carrier.~~

~~40.~~19. A compound of any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof, for ~~method of~~ modulating splicing, ~~comprising administering to cells a~~ wherein the compound ~~of any one of claims 1 to 38 or a pharmaceutical composition of claim 39~~, 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.

~~41.~~20. ~~A method of~~ The compound of any one of claims 1 to 18 for use in treating a disease or condition ~~comprising administering a compound of any one of claims 1 to 38 or a pharmaceutical composition of claim 39, to a subject in need thereof~~.

~~42. Use of a compound of any one of claims 1 to 38 or a pharmaceutical composition of claim 39, in the manufacture of a medicament for the treatment of a condition or disease.~~