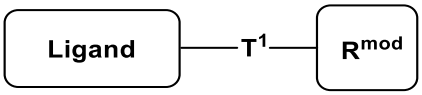
[0005] All endogenous mammalian diseases are ultimately mediated by the transcriptome. Insofar as messenger mRNA (mRNA) is part of the transcriptome, and all protein expression derives from mRNAs, there is the potential to intervene in protein-mediated diseases by modulating the expression of the relevant protein and by, in turn, modulating the translation of the corresponding upstream mRNA. But mRNA is only a small portion of the transcriptome: other transcribed RNAs also regulate cellular biology either directly by the structure and function of RNA structures (e.g., ribonucleoproteins) as well as via protein expression and action, including (but not limited to) miRNA, lncRNA, lincRNA, snoRNA, snRNA, scaRNA, piRNA, ceRNA, and pseudo-genes. Drugs that intervene at this level have the potential of modulating any and all cellular processes. Existing therapeutic modalities such as antisense RNA or siRNA, in most cases, have yet to overcome significant challenges such as drug delivery, absorption, distribution to target organs, pharmacokinetics, and cell penetration. In contrast, small molecules have a long history of successfully surmounting these barriers and these qualities, which make them suitable as drugs, are readily optimized through a series of analogues to overcome such challeges. In sharp contrast, there are no validated, general methods of screening small molecules for binding to RNA targets in general, much less inside cells. The application of small molecules as ligands for RNA that yield therapeutic benefit has received little to no attention from the drug discovery community.

[0006] 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.

SUMMARY

[0006a] In an aspect of the present disclosure, there is provided a compound of Formula **I**:



I

or a pharmaceutically acceptable salt thereof; wherein:

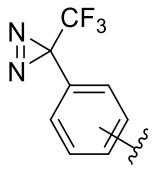
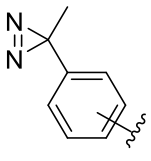
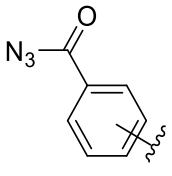
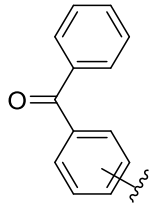
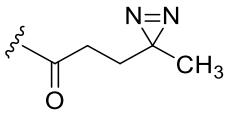
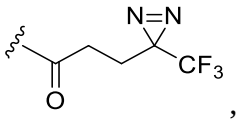
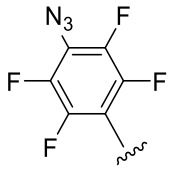
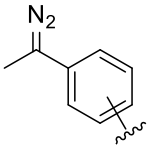
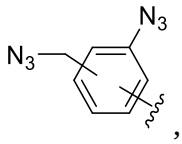
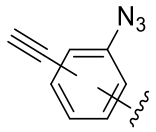
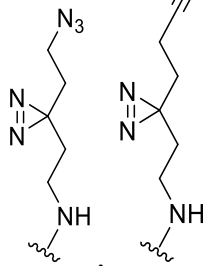
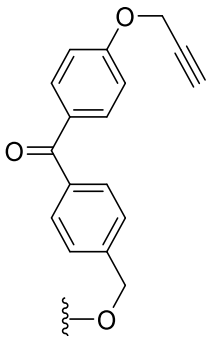
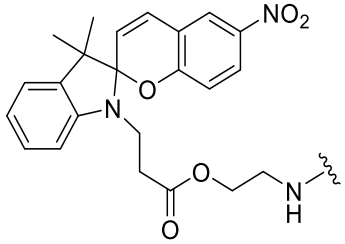
Ligand is a small molecule RNA binder;

T^1 is a bivalent tethering group selected from a C_{1-20} bivalent straight or branched hydrocarbon chain wherein 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 methylene units of the chain are independently and

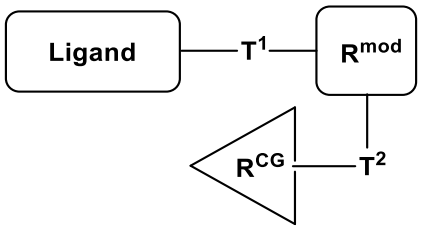
optionally replaced with a natural or non-natural amino acid, -O-, -C(O)-, -C(O)O-, -OC(O)-, -N(R)-, -C(O)N(R)-, -(R)NC(O)-, -OC(O)N(R)-, -(R)NC(O)O-, -N(R)C(O)N(R)-, -S-, -SO-, -SO_2-, -SO_2N(R)-, -(R)NSO_2-, -C(S)-, -C(S)O-, -OC(S)-, -C(S)N(R)-, -(R)NC(S)-, -(R)NC(S)N(R)-, or -Cy-; and 1-20 of the methylene units of the chain are independently and optionally replaced with -OCH_2CH_2-;

wherein each -Cy- is independently a bivalent optionally substituted 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, optionally substituted phenylene, an optionally substituted 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, an optionally substituted 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, an optionally substituted 8-10 membered bicyclic or bridged bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an optionally substituted 8-10 membered bicyclic or bridged bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring, a 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

R^{mod} is a photoactivatable group selected from , , , , , , , , , , , , .

[0006b] In another aspect of the present disclosure, there is provided a compound of Formula **II**:



II

or a pharmaceutically acceptable salt thereof; wherein:

Ligand is a small molecule RNA binder;

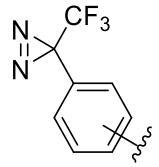
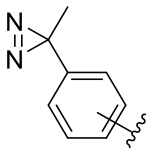
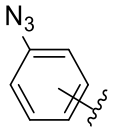
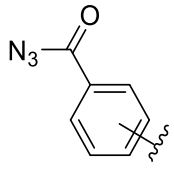
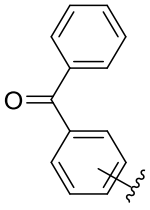
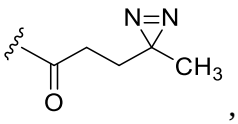
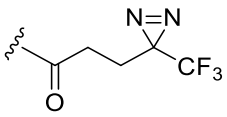
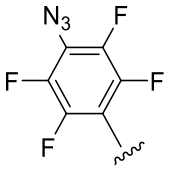
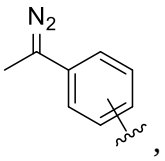
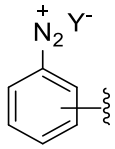
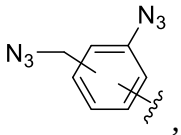
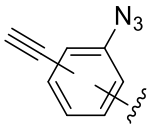
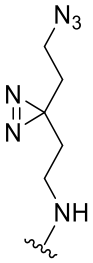
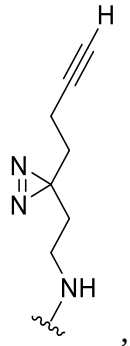
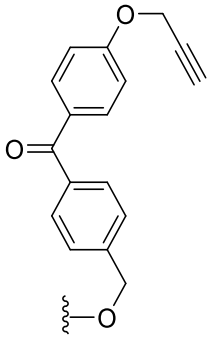
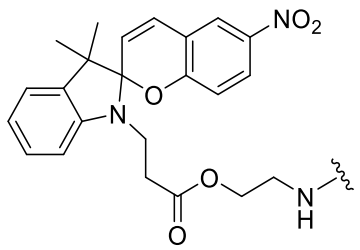
T^1 is a bivalent tethering group selected from a C_{1-20} bivalent straight or branched hydrocarbon chain wherein 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 methylene units of the chain are independently and optionally replaced with a natural or non-natural amino acid, -O-, -C(O)-, -C(O)O-, -OC(O)-, -N(R)-, -C(O)N(R)-, -(R)NC(O)-, -OC(O)N(R)-, -(R)NC(O)O-, -N(R)C(O)N(R)-, -S-, -SO-, -SO_2-, -SO_2N(R)-, -(R)NSO_2-, -C(S)-, -C(S)O-, -OC(S)-, -C(S)N(R)-, -(R)NC(S)-, -(R)NC(S)N(R)-, or -Cy-; and 1-20 of the methylene units of the chain are independently and optionally replaced with -OCH_2CH_2-;

wherein each -Cy- is independently a bivalent optionally substituted 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, optionally substituted phenylene, an optionally substituted 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, an optionally substituted 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, an optionally substituted 8-10 membered bicyclic or bridged bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an optionally substituted 8-10 membered bicyclic or bridged bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring, a 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

T^2 is a covalent bond or a bivalent tethering group selected from a C_{1-20} bivalent straight or branched hydrocarbon chain wherein 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 methylene units of the chain are independently and optionally replaced with a natural or non-natural amino acid, -O-, -C(O)-, -C(O)O-, -OC(O)-, -N(R)-, -C(O)N(R)-, -(R)NC(O)-, -OC(O)N(R)-, -(R)NC(O)O-, -N(R)C(O)N(R)-, -S-, -SO-, $-SO_2-$, $-SO_2N(R)-$, $-(R)NSO_2-$, -C(S)-, -C(S)O-, -OC(S)-, -C(S)N(R)-, -(R)NC(S)-, -(R)NC(S)N(R)-, or -Cy-; and 1-20 of the methylene units of the chain are independently and optionally replaced with $-OCH_2CH_2-$;

R^{CG} is a click-ready group selected from an azide, an alkyne, 4-dibenzocyclooctynol (DIBO), *gem*-difluorinated cyclooctynes (DIFO or DFO), biarylazacyclooctynone (BARAC), bicyclononyne (BCN), a strained cyclooctyne, an oxime, and oxanorbornadiene; or a pull-down group selected from a hapten and a ^{14}C, ^{32}P, or ^{3}H radiolabel; and

R^{mod} is a photoactivatable group selected from , , , , , , , , , , , , , , , or ; wherein Y^- is a pharmaceutically acceptable anion.

[0006c] In a further aspect of the present disclosure, there is provided a RNA conjugate, comprising a target RNA and a compound disclosed herein, wherein R^{mod} forms a covalent bond to the target RNA.

BRIEF DESCRIPTION OF THE FIGURES

[0007] FIG. 1 shows structures of theophylline ligands with points of attachment for the tethering groups.

[0008] FIG. 2 shows structures of tetracycline ligands with points of attachment for the tethering groups.

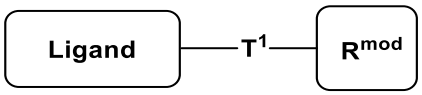
[0009] FIG. 3 shows structures of triptycene ligands with points of attachment for the tethering groups.

[0010] FIG. 4 shows structures of triptycene ligands with points of attachment for the tethering groups. X = CH, N, or C-OH; Y = CH or N; R1, R2, R3 = each independently selected from halo,

CLAIMS

We claim:

1. A compound of Formula **I**:



I

or a pharmaceutically acceptable salt thereof; wherein:

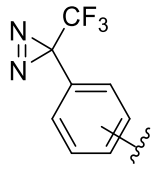
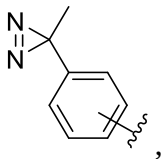
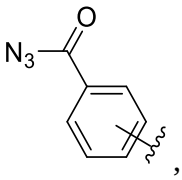
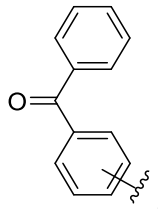
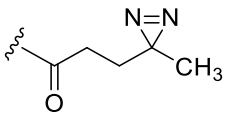
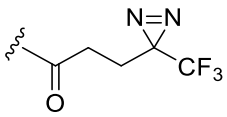
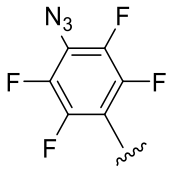
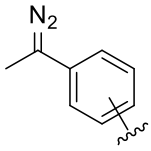
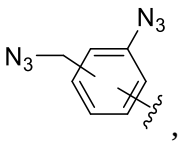
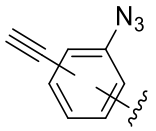
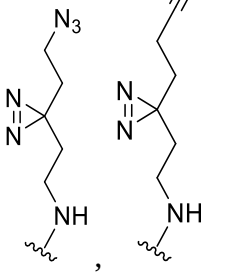
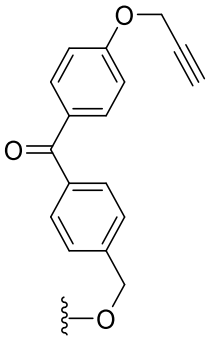
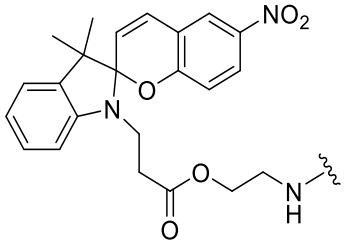
Ligand is a small molecule RNA binder;

T^1 is a bivalent tethering group selected from a C_{1-20} bivalent straight or branched hydrocarbon chain wherein 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 methylene units of the chain are independently and optionally replaced with a natural or non-natural amino acid, -O-, -C(O)-, -C(O)O-, -OC(O)-, -N(R)-, -C(O)N(R)-, -(R)NC(O)-, -OC(O)N(R)-, -(R)NC(O)O-, -N(R)C(O)N(R)-, -S-, -SO-, -SO_2-, -SO_2N(R)-, -(R)NSO_2-, -C(S)-, -C(S)O-, -OC(S)-, -C(S)N(R)-, -(R)NC(S)-, -(R)NC(S)N(R)-, or -Cy-; and 1-20 of the methylene units of the chain are independently and optionally replaced with -OCH_2CH_2-;

wherein each -Cy- is independently a bivalent optionally substituted 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, optionally substituted phenylene, an optionally substituted 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, an optionally substituted 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, an optionally substituted 8-10 membered bicyclic or bridged bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an optionally substituted 8-10 membered bicyclic or bridged bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring, a 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen,

oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

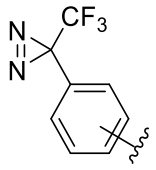
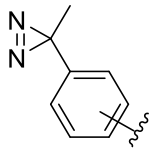
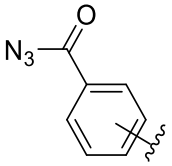
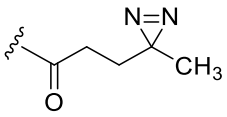
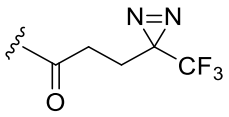
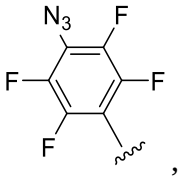
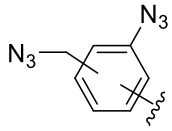
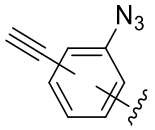
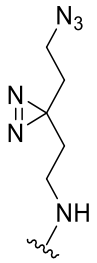
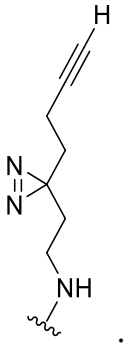
R^{mod} is a photoactivatable group selected from , , , , , , , , , , , , , or .

2. The compound of claim 1, wherein **Ligand** is selected from a heteroaryldihydropyrimidine (HAP), a macrolide, an alkaloid, an aminoglycoside, a tetracycline, a SMN2 ligand, a pleuromutilin, theophylline, ribocil, a substituted anthracene, a substituted triptycene, an oxazolidinone, or CPNQ; wherein **Ligand** may be optionally substituted with one or more substituents.

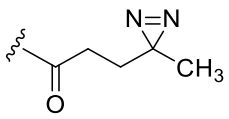
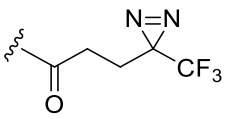
3. The compound of claim 1, wherein **Ligand** is selected from an optionally substituted heteroaryldihydropyrimidine (HAP), erythromycin, azithromycin, berberine, palmatine, a paromomycin, a neomycin, a kanamycin, doxycycline, oxytetracycline, pleuromutilin, theophylline, ribocil, LMI070 (NVS-SM1), a substituted triptycene, linezolid, tedizolid, or CPNQ; wherein **Ligand** may be optionally substituted with 1, 2, 3, or 4 substituents.

4. The compound of claim 1, wherein T^1 is selected from a C_{1-10} bivalent straight or branched hydrocarbon chain wherein 1, 2, 3, 4, or 5 methylene units of the chain are independently and optionally replaced with a natural or non-natural amino acid, -O-, -C(O)-, -C(O)O-, -OC(O)-, -N(R)-, -C(O)N(R)-, -(R)NC(O)-, -OC(O)N(R)-, -(R)NC(O)O-, -N(R)C(O)N(R)-, -S-, -SO-, $-SO_2-$, $-SO_2N(R)-$, $-(R)NSO_2-$, -C(S)-, -C(S)O-, -OC(S)-, -C(S)N(R)-, -(R)NC(S)-, -(R)NC(S)N(R)-, or -Cy-; and 1, 2, 3, 4, or 5, of the methylene units of the chain are independently and optionally replaced with $-OCH_2CH_2-$.

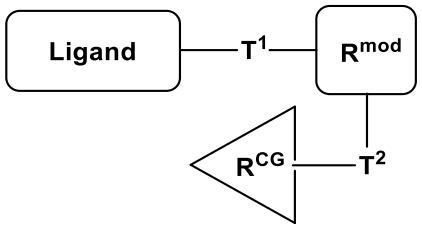
5. The compound of claim 1, wherein R^{mod} is selected from










, or .

6. An RNA conjugate, comprising a target RNA and a compound of claim 1, wherein R^{mod} forms a covalent bond to the target RNA.

7. The compound of claim 5, wherein R^{mod} is  or .

8. A compound of Formula **II**:



II

or a pharmaceutically acceptable salt thereof; wherein:

Ligand is a small molecule RNA binder;

T^1 is a bivalent tethering group selected from a C_{1-20} bivalent straight or branched hydrocarbon chain wherein 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 methylene units of the chain are independently and optionally replaced with a natural or non-natural amino acid, -O-, -C(O)-, -C(O)O-, -OC(O)-, -N(R)-, -C(O)N(R)-, -(R)NC(O)-, -OC(O)N(R)-, -(R)NC(O)O-, -N(R)C(O)N(R)-, -S-, -SO-, -SO_2-, -SO_2N(R)-, -(R)NSO_2-, -C(S)-, -C(S)O-, -OC(S)-, -C(S)N(R)-, -(R)NC(S)-, -(R)NC(S)N(R)-, or -Cy-; and 1-20 of the methylene units of the chain are independently and optionally replaced with -OCH_2CH_2-;

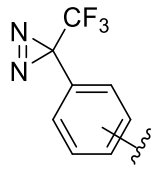
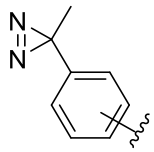
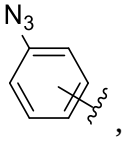
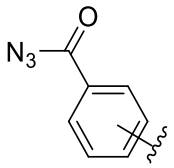
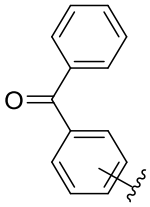
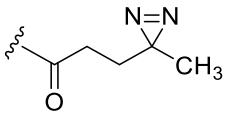
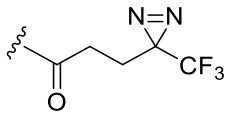
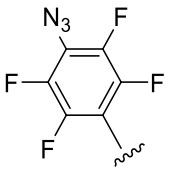
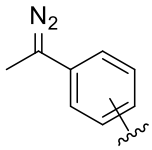
wherein each -Cy- is independently a bivalent optionally substituted 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, optionally substituted phenylene, an optionally substituted 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, an optionally substituted 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, an optionally substituted 8-10 membered bicyclic or bridged bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an optionally substituted 8-10 membered bicyclic or bridged bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

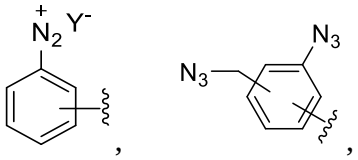
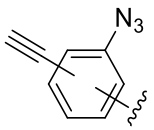
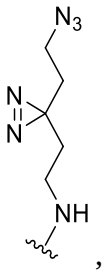
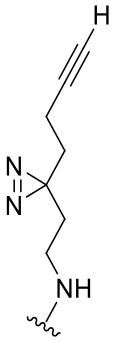
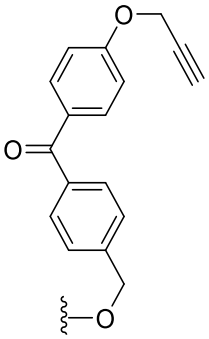
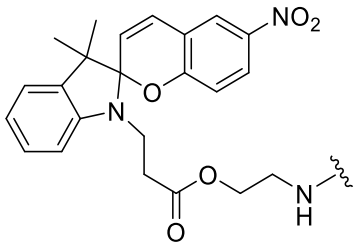
each R is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring, a 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered

bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

T^2 is a covalent bond or a bivalent tethering group selected from a C_{1-20} bivalent straight or branched hydrocarbon chain wherein 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 methylene units of the chain are independently and optionally replaced with a natural or non-natural amino acid, -O-, -C(O)-, -C(O)O-, -OC(O)-, -N(R)-, -C(O)N(R)-, -(R)NC(O)-, -OC(O)N(R)-, -(R)NC(O)O-, -N(R)C(O)N(R)-, -S-, -SO-, $-SO_2-$, $-SO_2N(R)-$, $-(R)NSO_2-$, -C(S)-, -C(S)O-, -OC(S)-, -C(S)N(R)-, -(R)NC(S)-, -(R)NC(S)N(R)-, or -Cy-; and 1-20 of the methylene units of the chain are independently and optionally replaced with $-OCH_2CH_2-$;

R^{CG} is a click-ready group selected from an azide, an alkyne, 4-dibenzocyclooctynol (DIBO), *gem*-difluorinated cyclooctynes (DIFO or DFO), biarylazacyclooctynone (BARAC), bicyclononyne (BCN), a strained cyclooctyne, an oxime, and oxanorbornadiene; or a pull-down group selected from a hapten and a ^{14}C, ^{32}P, or ^{3}H radiolabel; and

R^{mod} is a photoactivatable group selected from , , , , , , , , ,

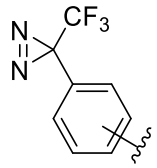
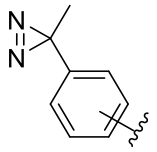
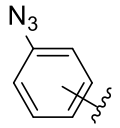
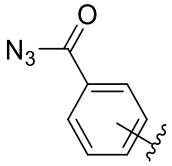
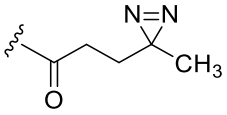
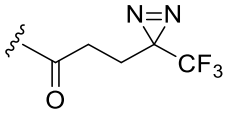
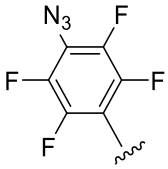
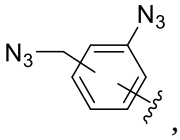
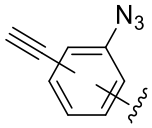
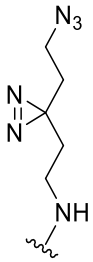
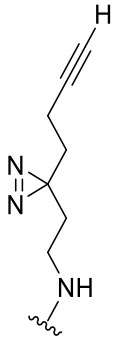

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, 
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, 
, 
, or 
; wherein Y^- is a pharmaceutically acceptable anion.

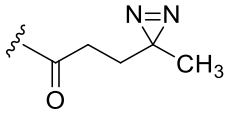
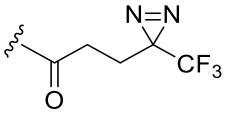
9. The compound of claim 8, wherein **Ligand** is selected from a heteroaryldihydropyrimidine (HAP), a macrolide, an alkaloid, an aminoglycoside, a tetracycline, a SMN2 ligand, a pleuromutilin, theophylline, ribocil, a substituted anthracene, a substituted triptycene, an oxazolidinone, or CPNQ; wherein **Ligand** may be optionally substituted with one or more substituents.

10. The compound of claim 8, wherein **Ligand** is selected from an optionally substituted heteroaryldihydropyrimidine (HAP), erythromycin, azithromycin, berberine, palmatine, a paromomycin, a neomycin, a kanamycin, doxycycline, oxytetracycline, pleuromutilin, theophylline, ribocil, LMI070 (NVS-SM1), a substituted triptycene, linezolid, tedizolid, or CPNQ; wherein **Ligand** may be optionally substituted with 1, 2, 3, or 4 substituents.

11. The compound of claim 8, wherein T^1 is selected from a C_{1-10} bivalent straight or branched hydrocarbon chain wherein 1, 2, 3, 4, or 5 methylene units of the chain are independently and optionally replaced with a natural or non-natural amino acid, -O-, -C(O)-, -C(O)O-, -OC(O)-, -N(R)-, -C(O)N(R)-, -(R)NC(O)-, -OC(O)N(R)-, -(R)NC(O)O-, -N(R)C(O)N(R)-, -S-, -SO-, $-SO_2-$, $-SO_2N(R)-$, $-(R)NSO_2-$, -C(S)-, -C(S)O-, -OC(S)-, -C(S)N(R)-

, -(R)NC(S)-, -(R)NC(S)N(R)-, or -Cy-; and 1, 2, 3, 4, or 5, of the methylene units of the chain are independently and optionally replaced with -OCH_2CH_2-.

12. The compound of claim 8, wherein R^{mod} is selected from , , , , , , , , , , or .

13. The compound of claim 8, wherein R^{mod} is  or .

14. The compound of claim 8, wherein R^{CG} is an azide, an alkyne, 4-dibenzocyclooctynol (DIBO), *gem*-difluorinated cyclooctynes (DIFO or DFO), biarylazacyclooctynone (BARAC), bicyclononyne (BCN), or biotin.

15. The compound of claim 8, wherein R^{CG} is an azide or an alkyne.

16. An RNA conjugate, comprising a target RNA and a compound of claim 8, wherein R^{mod} forms a covalent bond to the target RNA.