CLAIMS

1. A compound comprising a homo-bivalent covalent linker substituted on one end by a substituent X, wherein X comprises a biological moiety other than a nucleic acid, wherein the other end of the homo-bivalent linker is unsubstituted, and wherein the compound is at least 75% pure.

2. The compound of claim 1, wherein the compound comprises Structure 1:

X – R1 – R2 – A – R3 – B (Structure 1)

wherein:

X is a substituent comprising a biological moiety other than a nucleic acid, optionally, X is a peptide, protein, lipid, carbohydrate, carboxylic acid, vitamin, steroid, lignin, small molecule, organometallic compound, or a derivative of any of the foregoing;

R1 is a group comprising phosphodiester, thiophosphodiester, sulfate, amide, triazole, heteroaryl, ester, ether, thioether, disulfide, thiopropionate, acetal, glycol, or is absent;

R2 is a spacer group or is absent, optionally, the spacer group comprises C_2-C_{10} alkyl, C_2-C_{10} alkoxy, or C_1-C_{10} aryl;

A is a group comprising the reaction product of a first nucleophile and a first electrophile, optionally, the first nucleophile and first electrophile of A comprise (i) a thiol and a maleimide, optionally wherein the reaction product of the thiol and maleimide is a derivative of succinamic acid; (ii) a thiol and a vinylsulfone; (iii) a thiol and a pyridyldisulfide; (iv) a thiol and an iodoacetamide; (v) a thiol and an acrylate; (vi) an azide and an alkyne; or (vii) an amine and a carboxyl;

R3 is a group comprising a C_2-C_{10} alkyl, C_2-C_{10} alkoxy, C_1-C_{10} aryl, C_2-C_{10} alkyldithio, amide, ether, thioether, ester, oligonucleotide, oligopeptide, thiopropionate, or disulfide, optionally, R3 comprises thiopropionate or disulfide, an oligonucleotide, or an oligopeptide; and

B is a group comprising a second nucleophile or a second electrophile, wherein the second nucleophile is the same as the first nucleophile, and the second electrophile is the same as the first electrophile.

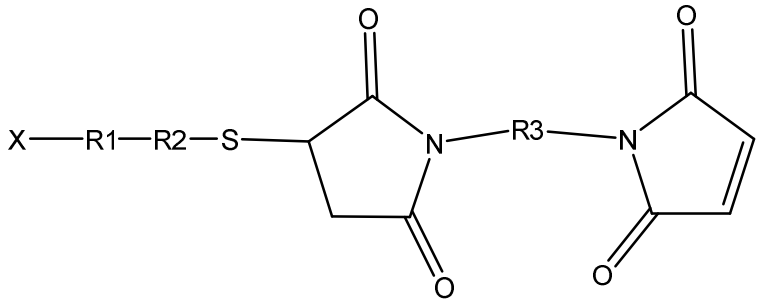
~~3. The compound of claim 2, wherein R2 comprises a C_2-C_{10} alkyl, C_2-C_{10} alkoxy, or C_1-C_{10} aryl, or is absent.~~

~~4. The compound of any of claims 2 or 3, wherein the first nucleophile and first electrophile of A comprise (i) a thiol and a maleimide, optionally wherein the reaction product of the thiol and maleimide is a derivative of succinamic acid; (ii) a thiol and a vinylsulfone; (iii) a thiol and a pyridyldisulfide; (iv) a thiol and an iodoacetamide; (v) a thiol and an acrylate; (vi) an azide and an alkyne; or (vii) an amine and a carboxyl.~~

~~5. The compound of any of claims 2 to 4, wherein A is a group comprising the reaction product of a thiol and a maleimide, optionally wherein the reaction product of the thiol and maleimide is a derivative of succinamic acid.~~

~~6. The compound of any of claims 2 to 5, wherein R3 is a group comprising a thiopropionate or disulfide, an oligonucleotide, or an oligopeptide.~~

~~7.~~3. The compound of claim 2, wherein the compound comprises Structure 2 or a pyrrolidinedione ring-opened derivative thereof, optionally wherein the pyrrolidinedione ring-opened derivative of Structure 2 is a derivative of succinamic acid:



(Structure 2).

~~8. The compound of claim 7, wherein R2 is a spacer group comprising a C_2-C_{10} alkyl, C_2-C_{10} alkoxy, or C_1-C_{10} aryl.~~

~~9.~~4. The compound of claim 3~~7~~, wherein:

X is a peptide or protein, or a derivative thereof;

R1 and R2 are absent; and

R3 is a group comprising a thiopropionate, disulfide, or oligonucleotide;

optionally, X is an organometallic compound, or a derivative thereof;

R1 is an ester group;

R2 is a spacer group comprising a C_2-C_{10} alkyl; and

R3 is a group comprising a thiopropionate, a disulfide, an oligonucleotide, or an oligopeptide; or

optionally, X is a small molecule, or a derivative thereof;

R1 is an ester group;

R2 is a spacer group comprising a C_2-C_{10} alkyl; and

R3 is a group comprising a thiopropionate, a disulfide, an oligonucleotide, or an oligopeptide.

~~10. The compound of claim 7, wherein:~~

~~X is an organometallic compound, or a derivative thereof;~~

~~R1 is an ester group;~~

~~R2 is a spacer group comprising a C_2-C_{10} alkyl; and~~

~~R3 is a group comprising a thiopropionate, a disulfide, an oligonucleotide, or an oligopeptide.~~

~~11. The compound of claim 7, wherein:~~

~~X is a small molecule, or a derivative thereof;~~

~~R1 is an ester group;~~

~~R2 is a spacer group comprising a C_2-C_{10} alkyl; and~~

~~R3 is a group comprising a thiopropionate, a disulfide, an oligonucleotide, or an oligopeptide.~~

~~12. The compound of claim 1, wherein the homo-bivalent covalent linker comprises a linker that is cleavable under intracellular conditions.~~

~~13.~~5. The compound of any of claims 2 to ~~11~~4, wherein the R3 group comprises a linker that is cleavable under intracellular conditions.

~~14.~~6. The compound of any of claims 1 to 3~~8~~, wherein the substituent X is a peptide, protein, lipid, carbohydrate, carboxylic acid, vitamin, steroid, lignin, small molecule, organometallic compound, or a derivative of any of the foregoing.

~~15.~~7. The compound of claim ~~14~~6, wherein the substituent X is a peptide, or a derivative thereof.

~~16.~~8. The compound of claim ~~14~~6, wherein the peptide is the transduction domain of HIV-1TAT protein, a Centyrin, a constrained peptide, a pHLIP peptide, or derivatives thereof.

~~17.~~9. The compound of claim ~~14~~6, wherein the substituent X is an antibody or antibody fragment, or a derivative thereof.

~~18.~~10. The compound of claim ~~17~~9, wherein the antibody fragment is a single-chain variable fragment, or derivative thereof.

~~19.~~11. The compound of claim ~~14~~6, wherein the substituent X is a carbohydrate, or a derivative thereof.

~~20.~~12. The compound of claim ~~14~~6, wherein the substituent X is a fatty acid, or a derivative thereof.

~~21.~~13. The compound of claim ~~14~~6, wherein the substituent X is a vitamin, or a derivative thereof.

~~22.~~14. The compound of claim ~~21~~13, wherein the substituent X is tocopherol or folate, or a derivative thereof.

~~23.~~15. The compound of claim ~~14~~6, wherein the substituent X is a cholesterol, or a derivative thereof.

~~24.~~16. The compound of claim ~~14~~6, wherein the substituent X is (2S,2'S)-2,2'-(Carbonyldiimino)dipentanedioic acid (DUPA), or a derivative thereof.

~~25.~~17. The compound of claim ~~14~~6, wherein the substituent X is anisamide, or a derivative thereof.

~~26.~~18. The compound of claim ~~14~~6, wherein the substituent X is an organometallic compound, or a derivative thereof.

~~27.~~19. The compound of claim ~~26~~18, wherein the organometallic compound is ferrocene, or a derivative thereof.

~~28.~~20. The compound of claim ~~14~~6, wherein substituent X is a small molecule, or a derivative thereof.

~~29.~~21. The compound of claim ~~28~~20, wherein the small molecule is lenalidomide, or a derivative thereof.

~~30.~~22. The compound of any of claims 1 to ~~29~~21, where in the compound is at least 80, 85, 90, 95, 96, 97, 98, 99, or 100 % pure.

31. A method for synthesizing a compound according to any of claims 1 to 30, the method comprising coupling the homo-bivalent covalent linker to the substituent X under reaction conditions that substantially favor the formation of the compound and substantially prevent dimerization of the substituent X.

32. The method of claim 31, wherein the method further comprises reacting the homo-bivalent covalent linker with a functionalized substituent X that comprises a functional group reactive with the homo-bivalent covalent linker.

33. The method of claim 32, wherein:

the functionalized substituent X comprises Structure 3:

X – R1 – R2 – A' (Structure 3); and

the homo-bivalent covalent linker comprises Structure 4:

A" – R3- B (Structure 4);

wherein:

X is a substituent comprising a biological moiety other than a nucleic acid;

R1 is a group comprising phosphodiester, thiophosphodiester, sulfate, amide, triazole, heteroaryl, ester, ether, thioether, disulfide, thiopropionate, acetal, glycol, or is absent;

R2 is a spacer group, or is absent;

R3 is a group comprising a C_2-C_{10} alkyl, C_2-C_{10} alkoxy, C_1-C_{10} aryl, C_2-C_{10} alkyldithio, amide, ether, thioether, ester, oligonucleotide, oligopeptide, thiopropionate, or disulfide;

A' and A" together comprise a first nucleophile and a first electrophile that react together to form A; and

B is a group comprising a second nucleophile or a second electrophile, wherein the second nucleophile is the same as the first nucleophile, and the second electrophile is the same as the first electrophile; and

wherein the resulting compound is Structure 1: X – R1 – R2 – A – R3 – B.

34. The method of claim 31, wherein the method further comprises reacting the homo-bivalent covalent linker with a functionalized R2 end group to form an intermediate, and then reacting the functionalized R2 end group of the intermediate with a functionalized

substituent X that comprises a functional group reactive with the functionalized R2 end group to form R1; wherein:

R1 is a group comprising phosphodiester, thiophosphodiester, sulfate, amide, triazole, heteroaryl, ester, ether, thioether, disulfide, thiopropionate, acetal, or glycol; and

R2 is a spacer group.

35. The method of claim 34, wherein:

the homo-bivalent covalent linker comprises Structure 4:

A"-R3-B (Structure 4)

the functionalized R2 end group comprises Structure 5:

R1'-R2-A' (Structure 5)

the functionalized substituent X comprises Structure 6:

X-R1" (Structure 6)

wherein:

X is a substituent comprising a biological moiety other than a nucleic acid;

R1' and R1" are functional groups that react to form R1;

R1 is a group comprising phosphodiester, thiophosphodiester, sulfate, amide, triazole, heteroaryl, ester, ether, thioether, disulfide, thiopropionate, acetal, or glycol;

R2 is a spacer group;

R3 is a group comprising a C_2-C_{10} alkyl, C_2-C_{10} alkoxy, C_1-C_{10} aryl, C_2-C_{10} alkyldithio, amide, ether, thioether, ester, oligonucleotide, oligopeptide, thiopropionate, or disulfide; and

A' and A" together comprise a first nucleophile and a first electrophile that react to form A;

B is a group comprising a second nucleophile or a second electrophile, wherein the second nucleophile is the same as the first nucleophile, and the second electrophile is the same as the first electrophile; and

wherein the resulting compound is Structure 1: X-R1-R2-A-R3-B.

~~36. The method of any of claims 31 to 35, wherein the coupling of the homo-bivalent covalent linker to the substituent X is carried out in a dilute solution of the functionalized substituent X with a stoichiometric excess of the homo-bivalent covalent linker.~~

~~37. The method of any of claims 31 to 35, wherein the coupling of the homo-bivalent covalent linker to the substituent X is carried out with a molar excess of the homo-bivalent covalent linker of at least about 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, or 100.~~

~~38. The method of claim 37, wherein the coupling of the homo-bivalent covalent linker to the substituent X is carried out with a molar excess of the homo-bivalent covalent linker of about 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, or 100.~~

~~39. The method of any of claims 31 to 38, wherein the coupling of the homo-bivalent covalent linker to the substituent X is carried out at a pH of below about 7, 6, 5, or 4.~~

~~40. The method of any one of claims 31 to 38, wherein the coupling of the homo-bivalent covalent linker to the substituent X is carried out at a pH of about 7, 6, 5, or 4.~~

~~41. The method of any one of claims 31 to 40, wherein the coupling of the homo-bivalent covalent linker to the substituent X is carried out in a solution comprising water and a water miscible organic co-solvent.~~

~~42. The method of claim 41, wherein the water miscible organic co-solvent comprises DMF, NMP, DMSO, alcohol, or acetonitrile.~~

~~43. The method of claim 42, wherein the water miscible organic co-solvent comprises acetonitrile.~~

~~44. The method of any of claims 41 to 42, wherein the water miscible organic co-solvent comprises about 10, 15, 20, 25, 30, 40, or 50 % (v/v) of the solution.~~

~~45. The method of any of claims 31 to 38, wherein the coupling of the homo-bivalent covalent linker to the substituent X is carried out in a solution comprising an anhydrous organic solvent.~~

~~46. The method of claim 45, wherein the anhydrous organic solvent comprises dichloromethane, DMF, DMSO, THF, dioxane, pyridine, alcohol, or acetonitrile~~

47. The method of any of claims 31 to 46, wherein the yield of the compound is at least 75, 80, 85, 90, 95, 96, 97, 98, 99, or 100 %.

48. The method of any of claims 31 to 46, wherein the purity of the compound is at least 80, 85, 90, 95, 96, 97, 98, 99, or 100 %.

49. A multi-conjugate comprising Structure 7:

X●Y (Structure 7)

wherein:

X is a first substituent comprising a biological moiety other than a nucleic acid;
Y is a second substituent that is the same as or different from X; and
● is a covalent linker joining X and Y, and comprising Structure 8:

- R1 - R2 - A - R3 - A - R2 - R1 - (Structure 8)

wherein:

each R1 is independently a group comprising phosphodiester, thiophosphodiester, sulfate, amide, triazole, heteroaryl, ester, ether, thioether, disulfide, thiopropionate, acetal, glycol, or is absent;
each R2 is independently a spacer group, or is absent;
each A is the same and is a group comprising the reaction product of a nucleophile and an electrophile; and
R3 is a group comprising a C_2-C_{10} alkyl, C_2-C_{10} alkoxy, C_1-C_{10} aryl, C_2-C_{10} alkyldithio, amide, ether, thioether, ester, oligonucleotide, oligopeptide, thiopropionate, or disulfide.

50. The multi-conjugate of claim 49, wherein Y is different from X.

51. The multi-conjugate of claim 49 or 50, wherein X is a peptide, protein, lipid, carbohydrate, carboxylic acid, vitamin, steroid, lignin, small molecule, organometallic compound, or a derivative of any of the foregoing.

52. The multi-conjugate of any of claims 49 to 52, wherein Y is a nucleic acid, peptide, protein, lipid, carbohydrate, carboxylic acid, vitamin, steroid, lignin, small molecule, organometallic compound, or a derivative of any of the foregoing.

53. The multi-conjugate of any of claims 49 to 52, wherein X is a peptide, antibody (or fragment thereof), small molecule, organometallic compound, or derivative of any of the foregoing.

54. The multi-conjugate of claim 53, wherein the peptide is the transduction domain of HIV-1TAT protein, a Centyrin, a constrained peptide, a pHLIP peptide, or derivatives thereof.

55. The multi-conjugate of claim 53, wherein the antibody fragment is a single-chain variable fragment, or derivative thereof.

56. The multi-conjugate of claim 53, wherein the small molecule is lenalidomide, or a derivative thereof.

57. The multi-conjugate of claim 53, wherein the organometallic compound is ferrocene, or a derivative thereof.

58. The multi-conjugate of any of claims 49 to 57, wherein Y is nucleic acid, or a derivative thereof.

59. The multi-conjugate of claim 58, wherein Y is RNA or a derivative thereof.

60. The multi-conjugate of claim 59, wherein Y is siRNA, saRNA, or miRNA, or derivatives thereof.

61. The multi-conjugate of claim 60, wherein Y is siRNA or a derivative thereof.

62. The multi-conjugate of any of claims 49 to 61, wherein R3 is cleavable under intracellular conditions.

63. The multi-conjugate of any of claims 49 to 62, wherein the multi-conjugate is at least 75, 80, 85, 90, 95, 96, 97, 98, 99, or 100 % pure.

64. A method for synthesizing a multi-conjugate of Structure 7:

X●Y (Structure 7)

wherein:

X is a first substituent comprising a biological moiety other than a nucleic acid;

Y is a second substituent that is the same or different from X; and

● is a covalent linker joining X and Y;

the method comprising the steps of:

(a) reacting X-R4 with a homo-bivalent linker ○ to produce a mono-substituted product X-○, wherein R4 is a functional group capable of reacting with ○ under conditions that produce the mono-substituted product X-○ and substantially prevent dimerization of X; and

(b) reacting X-○ with R5-Y, wherein R5 is a functional group capable of reacting with ○, thereby forming X●Y.

65. A method for synthesizing a multi-conjugate of Structure 7:

X●Y (Structure 7)

wherein:

X is a first substituent comprising a biological moiety other than a nucleic acid;

Y is a second substituent that is the same or different from X; and

● is a covalent linker joining X and Y;

the method comprising the steps of:

(a) reacting R4-Y with a homo-bivalent linker ○ to produce a mono-substituted product ○-Y, wherein R4 is a functional group capable of reacting with ○ under conditions that produce the mono-substituted product ○-Y and substantially prevent dimerization of Y; and

(b) reacting ○-Y with X-R5, wherein R5 is a functional group capable of reacting with ○, thereby forming X●Y.

66. The method of claim 64, wherein step (a) is carried out with a stoichiometric excess of the homo-bivalent linker ○ relative to X-R4.

67. The method of claim 65, wherein step (a) is carried out with a stoichiometric excess of the homo-bivalent linker ○ relative to R4-Y.

68. The method of claim 64 or 65, wherein step (a) is carried out with a molar excess of the homo-bivalent linker ○ of about 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, or 100.

69. The method of any of claims 64 to 68, wherein step (a) is carried out in a solution comprising water and, optionally, a water miscible organic co-solvent.

70. The method of claim 69, wherein step (a) is carried out at a pH of about 7, 6, 5, or 4.

71. The method of claim 69, wherein the water miscible organic co-solvent comprises DMF, DMSO, THF, dioxane, pyridine, alcohol, or acetonitrile.

72. The method of claim 71, wherein the water miscible organic co-solvent comprises acetonitrile.

73. The method of any of claims 69 to 72, wherein the water miscible organic co-solvent comprises about 10, 15, 20, 25, 30, 40, or 50 % (v/v) of the solution.

74. The method of claim 64 or 65, wherein step (a) is carried out in a solution comprising an anhydrous organic solvent.

75. The method of claim 74, wherein the anhydrous organic solvent comprises dichloromethane, DMF, DMSO, THF, dioxane, pyridine, alcohol, or acetonitrile.

76. The method of claim 75, wherein the anhydrous organic solvent comprises dioxane.

77. The method of claim 75, wherein the anhydrous organic solvent comprises DMF.

78. The method of claim 75, wherein the anhydrous organic solvent comprises pyridine.

79. The method of any of claims 64 to 78, wherein X is a peptide, protein, lipid, carbohydrate, carboxylic acid, vitamin, steroid, lignin, small molecule, organometallic compound, or a derivative of any of the foregoing.

80. The method of any of claims 64 to 77, wherein Y is a nucleic acid, peptide, protein, lipid, carbohydrate, carboxylic acid, vitamin, steroid, lignin, small molecule, or a derivative of any of the foregoing.

81. The method of any of claims 64 to 80, wherein X is a peptide, antibody (or fragment thereof), small molecule, organometallic compound, or a derivative of any of the foregoing.

82. The method of claim 81, wherein the peptide is the transduction domain of HIV-1TAT protein, a Centyrin, a constrained peptide, a pHLIP peptide, or derivatives thereof.

83. The method of claim81, wherein the antibody fragment is a single-chain variable fragment, or derivative thereof.

84. The method of claim 81, wherein the small molecule is lenalidomide, or a derivative thereof.

85. The method of claim 81, wherein the organometallic compound is ferrocene, or a derivative thereof.

86. The method of any of claims 64 to 85, wherein Y is a nucleic acid, or a derivative thereof.

87. The method of claim 86, wherein Y is RNA or a derivative thereof.

88. The method of claim 87, wherein Y is siRNA, saRNA, or miRNA, or derivatives thereof.

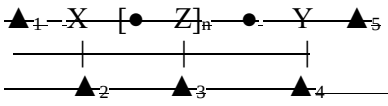
89. The method of claim 88, wherein Y is siRNA or a derivative thereof.

90. The method of any of claims 64 to 89, wherein the covalent linker ● is cleavable under intracellular conditions.

91. The method of any of claims 64 to 90, wherein the yield of the multi-conjugate X●Y is at least 75, 80, 85, 90, 95, 96, 97, 98, 99 or 100 %.

92. The method of any of claims 64 to 91, wherein the purity of the multi-conjugate X●Y is at least 75, 80, 85, 90, 95, 96, 97, 98, 99 or 100 %.

93. A multi-conjugate comprising substituents X, Y and Z, wherein each of the substituents, independently, is a biological moiety, and is joined to another substituent by a covalent linker ●; wherein the multi-conjugate comprises Structure 9:



(Structure 9)

wherein:

each of ▲1, ▲2, ▲3, ▲4 and ▲5 is, independently, absent or comprises a biological moiety covalently linked to its respective substituent;

n is an integer that is greater than or equal to zero; and

at least one of the substituents present in Structure 9 is not a nucleic acid.

94. The multi-conjugate of claim 93, wherein n is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.

95. The multi-conjugate of claim 93 or 94, wherein at least one covalent linker ● is a homo-bivalent covalent linker.

96. The multi-conjugate of any of claims 93 to 95, wherein X is not a nucleic acid.

97. The multi-conjugate of any of claims 93 to 96, wherein Y is not a nucleic acid.

98. The multi-conjugate of any of claims 93 to 97, wherein at least one ▲ is present.

99. The multi-conjugate of claim 98, wherein the at least one ▲ that is present is a targeting ligand; or wherein at least two ▲ are present and each of the at least two ▲ that are present are a targeting ligand; or wherein at least two ▲ are present and each of the at least two ▲ that are present are the same targeting ligand; or wherein $▲_1$ and $▲_5$ are present and are the same targeting ligand.

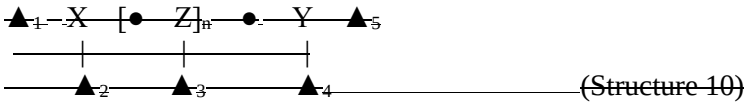
100. The multi-conjugate of any of claims 93 to 99, wherein at least one covalent linker ● is a sulfur-containing covalent linker; and at least one of $▲_1$, $▲_2$, $▲_3$, $▲_4$ and $▲_5$ comprises a sulfur-containing end group Q.

101. The multi-conjugate of claim 100, wherein the sulfur-containing end group Q comprises a protected thiol group that is deprotectable under a deprotection condition; and the sulfur-containing covalent linker ● is stable under the deprotection condition.

102. The multi-conjugate of claim 100 or 101, wherein the sulfur-containing covalent linker ● comprises a cleavable group that is cleavable under a cleavage condition that is not the deprotection condition.

103. The multi-conjugate of any of claims 100 to 102, wherein the sulfur-containing end group Q comprises a protected thiol group of the formula S-PG.

104. A method for synthesizing a multi-conjugate comprising Structure 10:



(Structure 10)

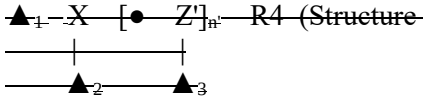
the method comprising:

reacting a compound of Structure 10a with a homo-bivalent linker to form a compound of Structure 10b under conditions that produce the mono-substituted product (Structure 10b) and substantially prevent dimerization of Structure 10a;

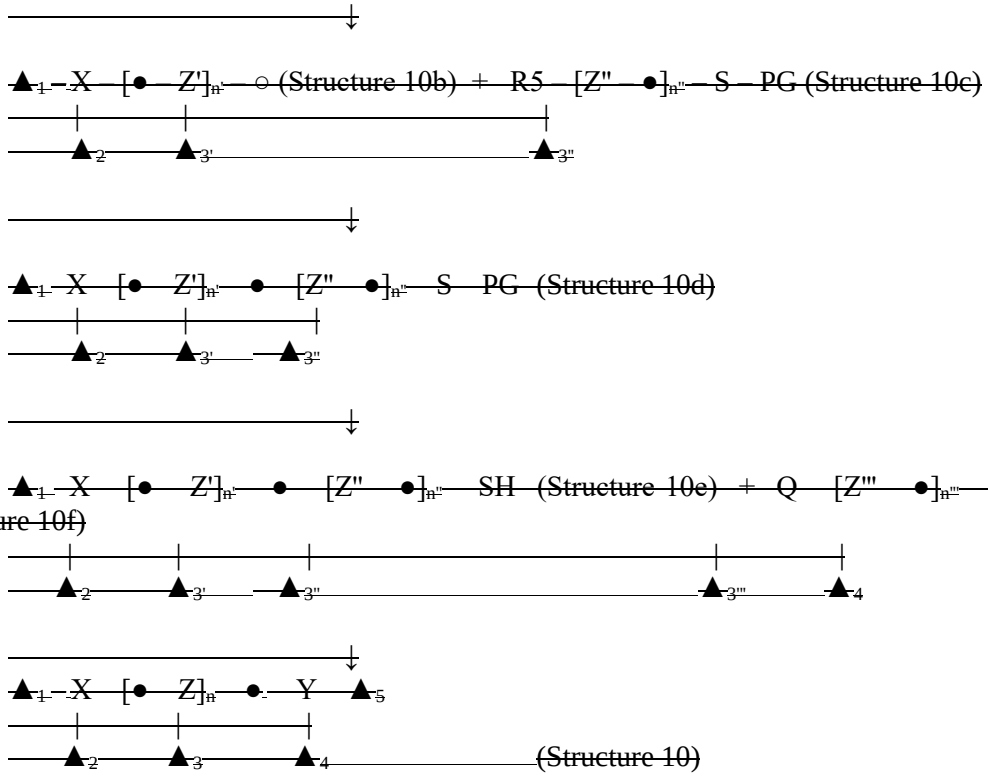
reacting the compound of Structure 10b with a compound of Structure 10c to form a compound of Structure 10d;

deprotecting the compound of Structure 10d to form a compound of Structure 10e; and

reacting the compound of Structure 10e with a compound of Structure 10f to form Structure 10; as follows:



(Structure 10a) + homo-bivalent linker ○



wherein:

● is a covalent linker

○ is a homo-bivalent linker;

R4 is a functional group selected to react with the homo-bivalent linker ○ under conditions that produce the mono-substituted product of Structure 10b and substantially prevent dimerization of Structure 10a;

R5 is a functional group selected to react with the homo-bivalent linker ○;

S — PG is a protected thiol group comprising a sulfur-containing group that is different from any sulfur-containing group residing within any of the covalent linkers ● within Structures 10b, 10c and 10d;

Q is a reactive group selected to react with the —SH group of Structure 10e to form a covalent linker ●;

X, Y, and Z are substituents of the multi-conjugate, and each is a biological moiety; optionally wherein at least one of X, Y, and Z that is present in the multi-conjugate is not a nucleic acid;

Z', Z", and Z'" are substituents of the multi-conjugate, and each is a biological moiety;

each of ▲1, ▲2, ▲3, ▲4 and ▲5 is, independently, absent or comprises a biological moiety covalently linked to its respective substituent;

each of ▲$_{3'}$, ▲$_{3''}$, and ▲$_{3'''}$ is, independently, absent or comprises a biological moiety covalently linked to its respective substituent;

n is an integer that is greater than or equal to 1, and optionally n is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; and

n', n", and n'" are each an integer greater than or equal to zero, with the proviso that the sum of n' + n" + n'" is n.

105. A composition comprising the multi-conjugate of any of claims 49-63 or 93-103, and a pharmaceutically acceptable excipient.

106. A composition comprising the multi-conjugate of any of claims 49-63 or 93-103, for use in the manufacture of a medicament.

107. A method for treating a subject comprising administering to the subject an effective amount of the multi-conjugate of any of claims 49-63 or 93-103 or the composition of claim 105.

108. A method of modulating an activity of one or more target genes in a cell, the method comprising introducing to the cell a multi-conjugate according to any of claims 49-63 or 93-100 and maintaining the cell under conditions in which the multi-conjugate enters the cell and the activity of the target gene or genes is modulated.

109. A method of observing an activity of a multi-conjugate in a cell, the method comprising introducing to the cell a multi-conjugate according to any of claims 49-63 or 93-100 and maintaining the cell under conditions in which the multi-conjugate enters the cell and the activity of the multi-conjugate is observed.