

METHODS AND COMPOUNDS FOR MODULATING INHERITED GENETIC DISEASES**CROSS REFERENCE**

[0001] This application claims the benefit of U.S. Provisional Application No. 63/564,707 filed on March 13, 2024 and U.S. Provisional Application No. 63/607,832 filed on December 8, 2023, which are hereby incorporated by reference in their entirety.

FIELD OF THE DISCLOSURE

[0002] Disclosed herein are heterocyclic polyamide compounds and compositions and their application as pharmaceuticals for the treatment of myotonic dystrophy type 1 (“DM1”) or Fuchs’ endothelial dystrophy or Fuchs’ endothelial corneal dystrophy (“FECD”).

BACKGROUND OF THE DISCLOSURE

[0003] The disclosure relates to the treatment of inherited genetic diseases characterized by overproduction of mRNA.

[0004] Myotonic dystrophy (“DM”), a member of the class of ailments known as muscular dystrophy, affects approximately 1 in 8000 people. DM is the most common form of muscular dystrophy among adult-onset patients, with most DM cases being diagnosed after age 20. DM is characterized by the persistence of muscular contraction, and is associated with several symptoms, including muscular disorders and cataracts, and cardiac and respiratory disorders, both of which typically are seen later in the progression of the disease. Although treatment is available for the amelioration of associated symptoms, no cure is currently employed that can stop or reverse the progression of DM. Respiratory failure and cardiac dysrhythmia account for the most common causes of death amongst DM patients.

[0005] The most severe form of DM is myotonic dystrophy type 1 (“DM1”). DM1 is an autosomal dominant genetic disease, caused by a mutation of the *dmpk* gene. This gene codes for the myotonic dystrophy protein kinase (MDPK) protein, also known as myotonin-protein kinase. The MDPK protein can be found in muscular, cardiac, and neural tissue.

[0006] DM1 is induced by transcription of the defective *dmpk* gene in DM1 subjects. Normally, this gene contains a 3’ untranslated region with a count of 5-37 CTG trinucleotide repeats. In the DM1 genotype, this trinucleotide is expanded to a count of 50 to over 3,000 repeats, with most having over 1,000 repeats of the CTG sequence. The count tends to increase in descendants, resulting in an earlier age of onset for later generations. Furthermore, the count has been observed to increase in a subject’s lifetime, due possibly to aberrant DNA repair.

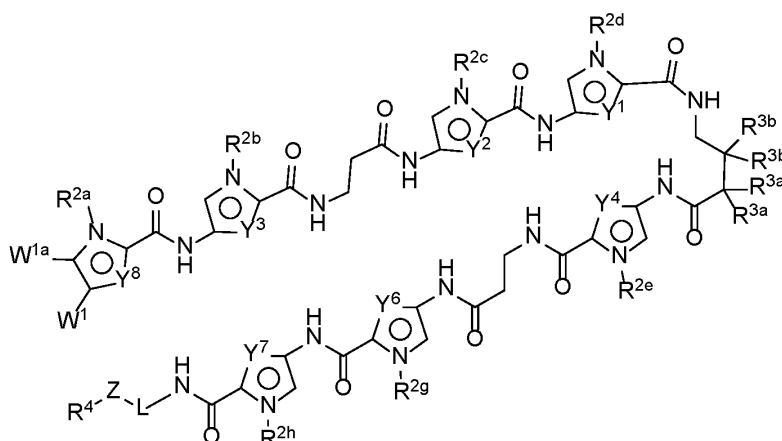
[0007] The progression of DM1 is attributed to “RNA toxicity” from *dmpk* mRNA having the expanded CTG region. This mRNA forms aggregates with certain proteins, and these aggregates interfere with the normal cellular function. Binding of defective mRNA to muscle blind proteins is perhaps a mechanism

leading to the symptoms of DM1, particularly since muscle blind protein activity is required for proper muscle development in flies.

[0008] Fuchs' endothelial dystrophy or Fuchs' endothelial corneal dystrophy ("FECD") is a non-inflammatory, sporadic or autosomal dominant, dystrophy involving the endothelial layer of the cornea. With Fuchs' dystrophy the cornea begins to swell causing glare, halos, and reduced visual acuity. The damage to the cornea in Fuchs' endothelial dystrophy can be so severe as to cause corneal blindness. Fuchs' dystrophy has been classified into early-onset (first decade) and late-onset (fourth to the fifth decade) with a predominance of females in the latter. Early-onset Fuchs' has Collagen type 8 $\alpha 2$ chain involvement. Late-onset is characterized by Transcription factor 4 (TCF4), Transcription factor 8 (TCF8), ATP/GTP binding protein-like 1 (AGBL1), lipoxigenase homology domain 1 (LOXHD1), solute carrier family 4 member 11 (SLC4A11) gene and Transforming growth factor- β -induced and clusterin involvement.

SUMMARY OF THE DISCLOSURE

[0009] In an aspect, provided herein is a transcription modulator molecule having the structure of Formula (I), or a pharmaceutically acceptable salt thereof:



Formula (I),

wherein:

each Y^1 , Y^2 , Y^3 , Y^4 , Y^5 , Y^6 , Y^7 , and Y^8 is independently CH or N;

W^1 and W^{1a} are each independently hydrogen, C_1 - C_3 haloalkyl, or $-N=C(N(R^{1e}))_2$, wherein each R^{1e} is independently hydrogen or C_1 - C_3 alkyl;

L is absent, C_1 - C_{20} alkylene, or C_2 - C_{20} heteroalkylene;

Z is absent, $-C(O)-$, or $-C(=NH)-$;

R^4 is C_1 - C_8 alkyl, C_3 - C_{10} cycloalkyl, 4 to 12-membered heterocycloalkyl, $-OR^{4b}$, or $-NR^{4a}R^{4b}$; wherein

R^{4a} is hydrogen, optionally substituted C_1 - C_{20} alkyl, optionally substituted C_1 - C_{20} haloalkyl, or optionally substituted C_1 - C_{20} heteroalkyl, each of which is optionally substituted with one or more R^5 ;

R^{4b} is hydrogen, optionally substituted C₁-C₂₀ alkyl, optionally substituted C₂-C₂₀ alkenyl, optionally substituted C₂-C₂₀ alkynyl, optionally substituted C₁-C₂₀ aminoalkyl, optionally substituted C₁-C₂₀ haloalkyl, optionally substituted C₁-C₂₀ heteroalkyl, optionally substituted C₁-C₂₀ hydroxyalkyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted 4 to 12-membered heterocycloalkyl, optionally substituted phenyl, or optionally substituted 5 to 10-membered heteroaryl, each of which is optionally substituted with one or more R⁵; or

R^{4a} and R^{4b} together with the nitrogen to which they are attached form an optionally substituted 4 to 12-membered heterocycloalkyl which is optionally substituted with one or more R⁵;

each R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^{2e}, R^{2g}, and R^{2h} is independently hydrogen, optionally substituted C₁-C₅₀ alkyl, optionally substituted C₂-C₅₀ alkenyl, optionally substituted C₂-C₅₀ alkynyl, optionally substituted C₁-C₅₀ heteroalkyl, optionally substituted C₂-C₅₀ heteroalkenyl, optionally substituted C₂-C₅₀ heteroalkynyl, optionally substituted C₁-C₅₀ haloalkyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted 3 to 8-membered heterocycloalkyl, or optionally substituted PEG₁₋₅₀; each of which is optionally substituted with one or more R⁶;

each R^{3a} and R^{3b} is independently hydrogen, halogen, C₁-C₆ alkyl, -NR^{3c}R^{3d}, -NHC(O)OR^{3c}, or -NHC(O)R^{3c}, or two R^{3a} or two R^{3b} together with the carbon atom to which they are attached form a C₃-C₆ cycloalkyl or 4 to 6-membered heterocycloalkyl;

or one of R^{3a} and one of R^{3b} together with the atoms to which they are attached form a C₃-C₆ cycloalkyl or 4 to 6-membered heterocycloalkyl; wherein

R^{3c} and R^{3d} are each independently hydrogen, C₁-C₂₀ alkyl, C₁-C₃ alkyl(phenyl), or PEG₁₋₂₀;

R^{3e} is C₁-C₂₀ alkyl, PEG₁₋₂₀, C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;

each R⁵ is independently halogen, -CN, -OH, -OR^{5a}, -N₃, -NR^{5a}R^{5b}, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted 4 to 8-membered heterocycloalkyl, or optionally substituted phenyl, each of which is optionally substituted with one or more R^{5c}, wherein

R^{5a} and R^{5b} are each independently hydrogen, C₁-C₂₀ alkyl, or PEG₁₋₂₀;

each R^{5c} is independently C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;

each R⁶ is independently halogen, -CN, -OH, -OR^{6a}, -N₃, -NR^{6a}R^{6b}, -CO(O)R^{6c}, -C(O)OR^{6c}, -C(O)NR^{6a}R^{6b}, -NHC(O)R^{6c}, -NHC(O)OR^{6c}, -OC(O)NR^{6a}R^{6b}, C₃-C₆ cycloalkyl, or 4 to 6 membered heterocycloalkyl; wherein

R^{6a} and R^{6b} are each independently hydrogen, C₁-C₂₀ alkyl, or PEG₁₋₂₀; and

R^{6c} is C₁-C₂₀ alkyl, PEG₁₋₂₀, C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl.

[0010] In some embodiments, the transcription modulator molecule is selected from Table 1, or a pharmaceutically acceptable salt thereof.

[0011] In another aspect, provided herein is a pharmaceutical composition comprising a transcription modulator molecule disclosed herein or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient.

[0012] In another aspect, provided herein is a method of treating Fuchs' endothelial dystrophy or Fuchs' endothelial corneal dystrophy (FECD) in a subject in need thereof, the method comprising administering to the subject an effective amount of a transcription modulator molecule disclosed herein or a pharmaceutically acceptable salt thereof.

[0013] In another aspect, provided herein is a method of treating myotonic dystrophy type 1 (DM1) in a subject in need thereof, the method comprising administering to the subject an effective amount of a transcription modulator molecule or a pharmaceutically acceptable salt thereof.

[0014] It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments, are given by way of illustration only, since various changes and modifications within the spirit and scope of the instant disclosure will become apparent to those skilled in the art from this detailed description.

INCORPORATION BY REFERENCE

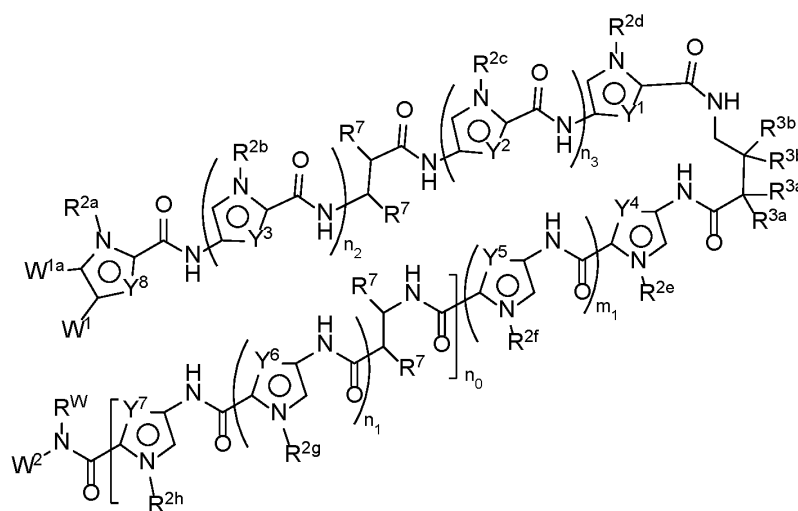
[0015] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

DETAILED DESCRIPTION

[0016] Disclosed here are transcription modulator molecules and method of treating DM1 and FECD.

Compounds – Transcription modulator molecules

[0017] In an aspect, provided herein is a transcription modulator molecule having the structure of Formula (A-1), or a pharmaceutically acceptable salt thereof:



Formula (A-1),

wherein:

each Y^1 , Y^2 , Y^3 , Y^4 , Y^5 , Y^6 , Y^7 , and Y^8 is independently CH or N;

W^1 and W^{1a} are each independently hydrogen, C_1 - C_3 haloalkyl, or $-N=C(N(R^{1e}))_2$, wherein each R^{1e} is independently hydrogen or C_1 - C_3 alkyl;

W^2 is optionally substituted C_1 - C_{20} alkyl or optionally substituted C_1 - C_{20} heteroalkyl; or W^2 is $-L-Z-R^4$, wherein

L is absent, C_1 - C_{20} alkylene, or C_2 - C_{20} heteroalkylene;

Z is absent, $-C(O)-$, or $-C(=NH)-$;

R^4 is C_1 - C_8 alkyl, C_3 - C_{10} cycloalkyl, 4 to 12-membered heterocycloalkyl, $-OR^{4b}$, or $-NR^{4a}R^{4b}$,

wherein

R^{4a} is hydrogen, optionally substituted C_1 - C_{20} alkyl, optionally substituted C_1 - C_{20} haloalkyl, or optionally substituted C_1 - C_{20} heteroalkyl, each of which is optionally substituted with one or more R^5 ;

R^{4b} is hydrogen, optionally substituted C_1 - C_{20} alkyl, optionally substituted C_2 - C_{20} alkenyl, optionally substituted C_2 - C_{20} alkynyl, optionally substituted C_1 - C_{20} aminoalkyl, optionally substituted C_1 - C_{20} haloalkyl, optionally substituted C_1 - C_{20} heteroalkyl, optionally substituted C_1 - C_{20} hydroxyalkyl, optionally substituted C_3 - C_{10} cycloalkyl, optionally substituted 4 to 10-membered heterocycloalkyl, optionally substituted phenyl, or optionally substituted 5 to 12-membered heteroaryl, each of which is optionally substituted with one or more R^5 ; or

R^{4a} and R^{4b} together with the nitrogen to which they are attached form an optionally substituted 4 to 12-membered heterocycloalkyl which is optionally substituted with one or more R^5 ;

R^W is hydrogen, optionally substituted C_1 - C_{20} alkyl or optionally substituted C_1 - C_{20} heteroalkyl; or

W^2 and R^W together with the nitrogen atom to which they are attached form an optionally substituted 4 to 10-membered heterocycloalkyl which is optionally substituted with one or more R^5 ;

each R^{2a} , R^{2b} , R^{2c} , R^{2d} , R^{2e} , R^{2f} , R^{2g} , and R^{2h} is independently hydrogen, optionally substituted C_1 - C_{50} alkyl, optionally substituted C_2 - C_{50} alkenyl, optionally substituted C_2 - C_{50} alkynyl, optionally substituted C_1 - C_{50} heteroalkyl, optionally substituted C_2 - C_{50} heteroalkenyl, optionally substituted C_2 - C_{50} heteroalkynyl, optionally substituted C_1 - C_{50} haloalkyl, optionally substituted C_3 - C_8 cycloalkyl, optionally substituted 3 to 8-membered heterocycloalkyl, or optionally substituted PEG₁₋₅₀; each of which is optionally substituted with one or more R^6 ;

each R^{3a} and R^{3b} is independently hydrogen, halogen, C_1 - C_6 alkyl, $-NR^{3c}R^{3d}$, $-NHC(O)OR^{3c}$, or $-NHC(O)R^{3e}$, or two R^{3a} or two R^{3b} together with the carbon atom to which they are attached form a C_3 - C_6 cycloalkyl or 4 to 6-membered heterocycloalkyl;

or one of R^{3a} and one of R^{3b} together with the atoms to which they are attached form a C_3 - C_6 cycloalkyl or 4 to 6-membered heterocycloalkyl; wherein

R^{3c} and R^{3d} are each independently hydrogen, C_1 - C_{20} alkyl, C_1 - C_3 alkyl(phenyl), or PEG₁₋₂₀;

R^{3e} is C_1 - C_{20} alkyl, PEG₁₋₂₀, C_3 - C_8 cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;

each R^5 is independently halogen, -CN, -OH, -OR^{5a}, -N₃, -NR^{5a}R^{5b}, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted 4 to 8-membered heterocycloalkyl, or optionally substituted phenyl, each of which is optionally substituted with one or more R^{5c}, wherein

R^{5a} and R^{5b} are each independently hydrogen, C₁-C₂₀ alkyl, or PEG₁₋₂₀;

each R^{5c} is independently C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;

each R⁶ is independently halogen, -CN, -OH, -OR^{6a}, -N₃, -NR^{6a}R^{6b}, -CO(O)R^{6c}, -C(O)OR^{6c}, -C(O)NR^{6a}R^{6b}, -NHC(O)R^{6c}, -NHC(O)OR^{6c}, -OC(O)NR^{6a}R^{6b}, C₃-C₆ cycloalkyl, or 4 to 6 membered heterocycloalkyl; wherein

R^{6a} and R^{6b} are each independently hydrogen, C₁-C₂₀ alkyl, or PEG₁₋₂₀;

R^{6c} is C₁-C₂₀ alkyl, PEG₁₋₂₀, C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;

each R⁷ is independently hydrogen, halogen, -OH, or C₁-C₃ alkyl;

n₁ and n₂ are each independently 0 or 1;

n₃ is 1 or 2;

m₁ is 0, 1, 2, or 3; and

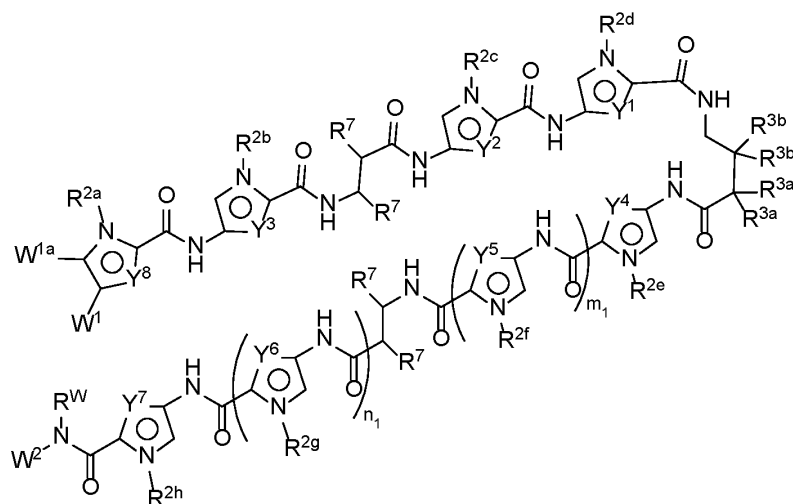
n₀ is 0 or 1, wherein n₀ and m₁ are both not 0.

[0018] In some embodiments of Formula (A-1), n₀ is 1. In some embodiments of Formula (A-1), n₀ is 0.

[0019] In some embodiments of Formula (A-1), n₂ is 1. In some embodiments of Formula (A-1), n₂ is 0.

[0020] In some embodiments of Formula (A-1), n₃ is 1. In some embodiments of Formula (A-1), n₃ is 0.

[0021] In another aspect, provided herein is a transcription modulator molecule having the structure of Formula (A-2), or a pharmaceutically acceptable salt thereof:



Formula (A-2),

wherein:

each Y¹, Y², Y³, Y⁴, Y⁵, Y⁶, Y⁷, and Y⁸ is independently CH or N;

W¹ and W^{1a} are each independently hydrogen, C₁-C₃ haloalkyl, or -N=C(N(R^{1e})₂)₂, wherein each R^{1e} is independently hydrogen or C₁-C₃ alkyl;

W² is optionally substituted C₁-C₂₀ alkyl or optionally substituted C₁-C₂₀ heteroalkyl; or W² is -L-Z-R⁴, wherein

L is absent, C₁-C₂₀ alkylene, or C₂-C₂₀ heteroalkylene;

Z is absent, -C(O)-, or -C(=NH)-;

R⁴ is C₁-C₈ alkyl, C₃-C₁₀ cycloalkyl, 4 to 12-membered heterocycloalkyl, -OR^{4b}, or -NR^{4a}R^{4b}, wherein

R^{4a} is hydrogen, optionally substituted C₁-C₂₀ alkyl, optionally substituted C₁-C₂₀ haloalkyl, or optionally substituted C₁-C₂₀ heteroalkyl, each of which is optionally substituted with one or more R⁵;

R^{4b} is hydrogen, optionally substituted C₁-C₂₀ alkyl, optionally substituted C₂-C₂₀ alkenyl, optionally substituted C₂-C₂₀ alkynyl, optionally substituted C₁-C₂₀ aminoalkyl, optionally substituted C₁-C₂₀ haloalkyl, optionally substituted C₁-C₂₀ heteroalkyl, optionally substituted C₁-C₂₀ hydroxyalkyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted 4 to 12-membered heterocycloalkyl, optionally substituted phenyl, or optionally substituted 5 to 10-membered heteroaryl, each of which is optionally substituted with one or more R⁵; or

R^{4a} and R^{4b} together with the nitrogen to which they are attached form an optionally substituted 4 to 12-membered heterocycloalkyl which is optionally substituted with one or more R⁵;

R^W is hydrogen, optionally substituted C₁-C₂₀ alkyl or optionally substituted C₁-C₂₀ heteroalkyl; or

W² and R^W together with the nitrogen atom to which they are attached form an optionally substituted 4 to 10-membered heterocycloalkyl which is optionally substituted with one or more R⁵;

each R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^{2e}, R^{2f}, R^{2g}, and R^{2h} is independently hydrogen, optionally substituted C₁-C₅₀ alkyl, optionally substituted C₂-C₅₀ alkenyl, optionally substituted C₂-C₅₀ alkynyl, optionally substituted C₁-C₅₀ heteroalkyl, optionally substituted C₂-C₅₀ heteroalkenyl, optionally substituted C₂-C₅₀ heteroalkynyl, optionally substituted C₁-C₅₀ haloalkyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted 3 to 8-membered heterocycloalkyl, or optionally substituted PEG₁₋₅₀; each of which is optionally substituted with one or more R⁶;

each R^{3a} and R^{3b} is independently hydrogen, halogen, C₁-C₆ alkyl, -NR^{3c}R^{3d}, -NHC(O)OR^{3e}, or -NHC(O)R^{3e}, or two R^{3a} or two R^{3b} together with the carbon atom to which they are attached form a C₃-C₆ cycloalkyl or 4 to 6-membered heterocycloalkyl;

or one of R^{3a} and one of R^{3b} together with the atoms to which they are attached form a C₃-C₆ cycloalkyl or 4 to 6-membered heterocycloalkyl; wherein

R^{3c} and R^{3d} are each independently hydrogen, C₁-C₂₀ alkyl, C₁-C₃ alkyl(phenyl), or PEG₁₋₂₀;

R^{3e} is C₁-C₂₀ alkyl, PEG₁₋₂₀, C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;

each R^5 is independently halogen, -CN, -OH, -OR^{5a}, -N₃, -NR^{5a}R^{5b}, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted 4 to 8-membered heterocycloalkyl, or optionally substituted phenyl, each of which is optionally substituted with one or more R^{5c}, wherein

R^{5a} and R^{5b} are each independently hydrogen, C₁-C₂₀ alkyl, or PEG₁₋₂₀;

each R^{5c} is independently C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;

each R⁶ is independently halogen, -CN, -OH, -OR^{6a}, -N₃, -NR^{6a}R^{6b}, -CO(O)R^{6c}, -C(O)OR^{6c}, -C(O)NR^{6a}R^{6b}, -NHC(O)R^{6c}, -NHC(O)OR^{6c}, -OC(O)NR^{6a}R^{6b}, C₃-C₆ cycloalkyl, or 4 to 6 membered heterocycloalkyl; wherein

R^{6a} and R^{6b} are each independently hydrogen, C₁-C₂₀ alkyl, or PEG₁₋₂₀;

R^{6c} is C₁-C₂₀ alkyl, PEG₁₋₂₀, C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;

each R⁷ is independently hydrogen, halogen, -OH, or C₁-C₃ alkyl; and

n₁ and m₁ are each independently 0 or 1.

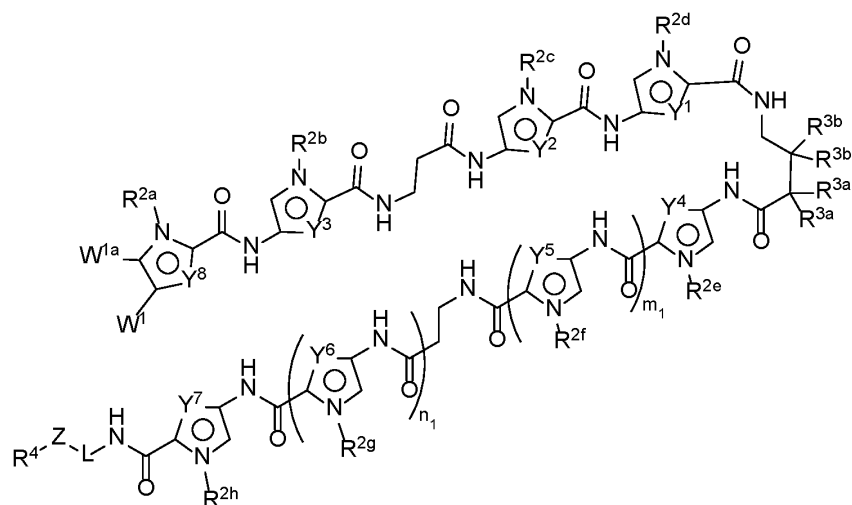
[0022] In some embodiments of Formula (A-1) or (A-2), W² is optionally substituted C₁-C₂₀ alkyl or optionally substituted C₁-C₂₀ heteroalkyl. In some embodiments of Formula (A-1) or (A-2), W² is optionally substituted C₁-C₁₀ alkyl or optionally substituted C₁-C₁₀ heteroalkyl. In some embodiments of Formula (A-1) or (A-2), W² is optionally substituted C₁-C₁₀ alkyl. In some embodiments of Formula (A-1) or (A-2), W² is optionally substituted C₁-C₁₀ heteroalkyl.

[0023] In some embodiments of Formula (A-1) or (A-2), W² is -L-Z-R⁴.

[0024] In some embodiments of Formula (A-1) or (A-2), R^W is optionally substituted C₁-C₂₀ alkyl or optionally substituted C₁-C₂₀ heteroalkyl. In some embodiments of Formula (A-1) or (A-2), R^W is optionally substituted C₁-C₁₀ alkyl or optionally substituted C₁-C₁₀ heteroalkyl. In some embodiments of Formula (A-1) or (A-2), R^W is optionally substituted C₁-C₁₀ alkyl. In some embodiments of Formula (A-1) or (A-2), R^W is optionally substituted C₁-C₁₀ heteroalkyl. In some embodiments of Formula (A-1) or (A-2), R^W is hydrogen.

[0025] In some embodiments of Formula (A-1) or (A-2), W² and R^W together with the nitrogen atom to which they are attached form an optionally substituted 4 to 10-membered heterocycloalkyl which is optionally substituted with one or more R⁵. In some embodiments of Formula (A-1) or (A-2), W² and R^W together with the nitrogen atom to which they are attached form an optionally substituted 4 to 6-membered heterocycloalkyl. In some embodiments of Formula (A-1) or (A-2), W² and R^W together with the nitrogen atom to which they are attached form an optionally substituted 4-membered heterocycloalkyl. In some embodiments of Formula (A-1) or (A-2), W² and R^W together with the nitrogen atom to which they are attached form an optionally substituted 5-membered heterocycloalkyl. In some embodiments of Formula (A-1) or (A-2), W² and R^W together with the nitrogen atom to which they are attached form an optionally substituted 6-membered heterocycloalkyl.

[0026] In another aspect, provided herein is a transcription modulator molecule having the structure of Formula (A-3), or a pharmaceutically acceptable salt thereof:



Formula (A-3),

wherein:

each Y¹, Y², Y³, Y⁴, Y⁵, Y⁶, Y⁷, and Y⁸ is independently CH or N;

W¹ and W^{1a} are each independently hydrogen, C₁-C₃ haloalkyl, or -N=C(N(R^{1e}))₂, wherein each R^{1e} is independently hydrogen or C₁-C₃ alkyl;

L is absent, C₁-C₂₀ alkylene, or C₂-C₂₀ heteroalkylene;

Z is absent, -C(O)-, or -C(=NH)-;

R⁴ is C₁-C₈ alkyl, C₃-C₁₀ cycloalkyl, 4 to 12-membered heterocycloalkyl, -OR^{4b}, or -NR^{4a}R^{4b}; wherein

R^{4a} is hydrogen, optionally substituted C₁-C₂₀ alkyl, optionally substituted C₁-C₂₀ haloalkyl, or optionally substituted C₁-C₂₀ heteroalkyl, each of which is optionally substituted with one or more R⁵;

R^{4b} is hydrogen, optionally substituted C₁-C₂₀ alkyl, optionally substituted C₂-C₂₀ alkenyl, optionally substituted C₂-C₂₀ alkynyl, optionally substituted C₁-C₂₀ aminoalkyl, optionally substituted C₁-C₂₀ haloalkyl, optionally substituted C₁-C₂₀ heteroalkyl, optionally substituted C₁-C₂₀ hydroxyalkyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted 4 to 12-membered heterocycloalkyl, optionally substituted phenyl, or optionally substituted 5 to 10-membered heteroaryl, each of which is optionally substituted with one or more R⁵; or

R^{4a} and R^{4b} together with the nitrogen to which they are attached form an optionally substituted 4 to 12-membered heterocycloalkyl which is optionally substituted with one or more R⁵;

each R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^{2e}, R^{2f}, R^{2g}, and R^{2h} is independently hydrogen, optionally substituted C₁-C₅₀ alkyl, optionally substituted C₂-C₅₀ alkenyl, optionally substituted C₂-C₅₀ alkynyl, optionally substituted C₁-C₅₀ heteroalkyl, optionally substituted C₂-C₅₀ heteroalkenyl, optionally substituted C₂-C₅₀ heteroalkynyl, optionally substituted C₁-C₅₀ haloalkyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted 3 to 8-membered heterocycloalkyl, or optionally substituted PEG₁₋₅₀; each of which is optionally substituted with one or more R⁶;

each R^{3a} and R^{3b} is independently hydrogen, halogen, C_1 - C_6 alkyl, $-NR^{3c}R^{3d}$, $-NHC(O)OR^{3c}$, or $-NHC(O)R^{3c}$,
or

two R^{3a} or two R^{3b} together with the carbon atom to which they are attached form a C_3 - C_6 cycloalkyl or 4 to 6-membered heterocycloalkyl; or

one of R^{3a} and one of R^{3b} together with the atoms to which they are attached form a C_3 - C_6 cycloalkyl or 4 to 6-membered heterocycloalkyl; wherein

R^{3c} and R^{3d} are each independently hydrogen, C_1 - C_{20} alkyl, C_1 - C_3 alkyl(phenyl), or PEG_{1-20} ;

R^{3e} is C_1 - C_{20} alkyl, PEG_{1-20} , C_3 - C_8 cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;

each R^5 is independently halogen, $-CN$, $-OH$, $-OR^{5a}$, $-N_3$, $-NR^{5a}R^{5b}$, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 alkynyl, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 haloalkyl, optionally substituted C_3 - C_8 cycloalkyl, optionally substituted 4 to 8-membered heterocycloalkyl, or optionally substituted phenyl, each of which is optionally substituted with one or more R^{5c} , wherein

R^{5a} and R^{5b} are each independently hydrogen, C_1 - C_{20} alkyl, or PEG_{1-20} ;

each R^{5c} is independently C_3 - C_8 cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;

each R^6 is independently halogen, $-CN$, $-OH$, $-OR^{6a}$, $-N_3$, $-NR^{6a}R^{6b}$, $-CO(O)R^{6c}$, $-C(O)OR^{6c}$, $-C(O)NR^{6a}R^{6b}$, $-NHC(O)R^{6c}$, $-NHC(O)OR^{6c}$, $-OC(O)NR^{6a}R^{6b}$, C_3 - C_6 cycloalkyl, or 4 to 6 membered heterocycloalkyl; wherein

R^{6a} and R^{6b} are each independently hydrogen, C_1 - C_{20} alkyl, or PEG_{1-20} ;

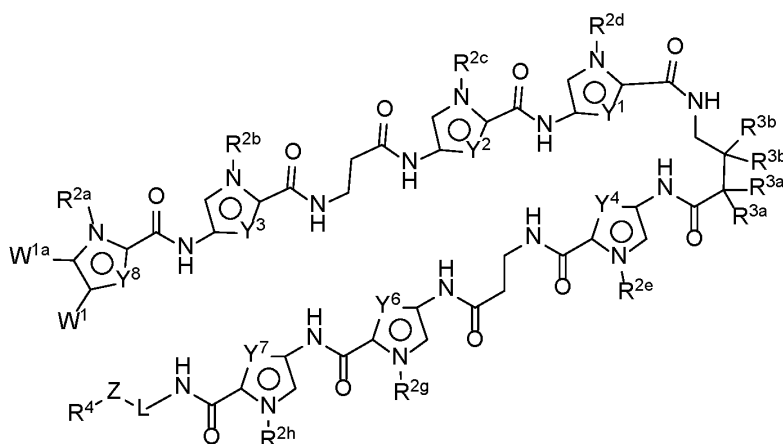
R^{6c} is C_1 - C_{20} alkyl, PEG_{1-20} , C_3 - C_8 cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl; and

n_1 and m_1 are each independently 0 or 1.

[0027] In some embodiments of Formula (A-1), (A-2), or (A-3), n_1 is 1. In some embodiments of Formula (A-1), (A-2), or (A-3), n_1 is 0.

[0028] In some embodiments of Formula (A-1), m_1 is 1, 2, or 3. In some embodiments of (A-1), m_1 is 1 or 2. In some embodiments of (A-1), (A-2), or (A-3), m_1 is 0 or 1. In some embodiments of Formula (A-1), (A-2), or (A-3), m_1 is 0. In some embodiments of Formula (A-1), (A-2), or (A-3), m_1 is 1.

[0029] In some embodiments, provided herein is a transcription modulator molecule having a structure of Formula (I), or a pharmaceutically acceptable salt thereof.



Formula (I),

wherein:

each Y¹, Y², Y³, Y⁴, Y⁶, Y⁷, and Y⁸ is independently CH or N;

W¹ and W^{1a} are each independently hydrogen, C₁-C₃ haloalkyl, or -N=C(N(R^{1e}))₂, wherein each R^{1e} is independently hydrogen or C₁-C₃ alkyl;

L is absent, C₁-C₂₀ alkylene, or C₂-C₂₀ heteroalkylene;

Z is absent, -C(O)-, or -C(=NH)-;

R⁴ is C₁-C₈ alkyl, C₃-C₁₀ cycloalkyl, 4 to 12-membered heterocycloalkyl, -OR^{4b}, or -NR^{4a}R^{4b}; wherein

R^{4a} is hydrogen, optionally substituted C₁-C₂₀ alkyl, optionally substituted C₁-C₂₀ haloalkyl, or optionally substituted C₁-C₂₀ heteroalkyl, each of which is optionally substituted with one or more R⁵;

R^{4b} is hydrogen, optionally substituted C₁-C₂₀ alkyl, optionally substituted C₂-C₂₀ alkenyl, optionally substituted C₂-C₂₀ alkynyl, optionally substituted C₁-C₂₀ aminoalkyl, optionally substituted C₁-C₂₀ haloalkyl, optionally substituted C₁-C₂₀ heteroalkyl, optionally substituted C₁-C₂₀ hydroxyalkyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted 4 to 12-membered heterocycloalkyl, optionally substituted phenyl, or optionally substituted 5 to 10-membered heteroaryl, each of which is optionally substituted with one or more R⁵; or

R^{4a} and R^{4b} together with the nitrogen to which they are attached form an optionally substituted 4 to 10-membered heterocycloalkyl which is optionally substituted with one or more R⁵;

each R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^{2e}, R^{2g}, and R^{2h} is independently hydrogen, optionally substituted C₁-C₅₀ alkyl, optionally substituted C₂-C₅₀ alkenyl, optionally substituted C₂-C₅₀ alkynyl, optionally substituted C₁-C₅₀ heteroalkyl, optionally substituted C₂-C₅₀ heteroalkenyl, optionally substituted C₂-C₅₀ heteroalkynyl, optionally substituted C₁-C₅₀ haloalkyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted 3 to 8-membered heterocycloalkyl, or optionally substituted PEG₁₋₅₀; each of which is optionally substituted with one or more R⁶;

each R^{3a} and R^{3b} is independently hydrogen, halogen, C₁-C₆ alkyl, -NR^{3c}R^{3d}, -NHC(O)OR^{3c}, or -NHC(O)R^{3e},

or two R^{3a} or two R^{3b} together with the carbon atom to which they are attached form a C₃-C₆ cycloalkyl or 4 to 6-membered heterocycloalkyl; or

one of R^{3a} and one of R^{3b} together with the atoms to which they are attached form a C₃-C₆ cycloalkyl or 4 to 6-membered heterocycloalkyl; wherein

R^{3c} and R^{3d} are each independently hydrogen, C₁-C₂₀ alkyl, C₁-C₃ alkyl(phenyl), or PEG₁₋₂₀;

R^{3e} is C₁-C₂₀ alkyl, PEG₁₋₂₀, C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;

each R⁵ is independently halogen, -CN, -OH, -OR^{5a}, -N₃, -NR^{5a}R^{5b}, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted 4 to 8-membered heterocycloalkyl, or optionally substituted phenyl, each of which is optionally substituted with one or more R^{5c}, wherein

R^{5a} and R^{5b} are each independently hydrogen, C₁-C₂₀ alkyl, or PEG₁₋₂₀;

each R^{5c} is independently C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;

each R⁶ is independently halogen, -CN, -OH, -OR^{6a}, -N₃, -NR^{6a}R^{6b}, -CO(O)R^{6c}, -C(O)OR^{6c}, -C(O)NR^{6a}R^{6b}, -NHC(O)R^{6c}, -NHC(O)OR^{6c}, -OC(O)NR^{6a}R^{6b}, C₃-C₆ cycloalkyl, or 4 to 6 membered heterocycloalkyl; wherein

R^{6a} and R^{6b} are each independently hydrogen, C₁-C₂₀ alkyl, or PEG₁₋₂₀; and

R^{6c} is C₁-C₂₀ alkyl, PEG₁₋₂₀, C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl.

[0030] In some embodiments of Formula (A-1), (A-2), (A-3), or (I), Y¹ is CH. In some embodiments of Formula (A-1), (A-2), (A-3), or (I), Y¹ is N.

[0031] In some embodiments of Formula (A-1), (A-2), (A-3), or (I), Y² is CH. In some embodiments of Formula (A-1), (A-2), (A-3), or (I), Y² is N.

[0032] In some embodiments of Formula (A-1), (A-2), (A-3), or (I), Y³ is CH. In some embodiments of Formula (A-1), (A-2), (A-3), or (I), Y³ is N.

[0033] In some embodiments of Formula (A-1), (A-2), (A-3), or (I), Y⁴ is CH. In some embodiments of Formula (A-1), (A-2), (A-3), or (I), Y⁴ is N.

[0034] In some embodiments of Formula (A-1), (A-2), or (A-3), each Y⁵ is independently CH. In some embodiments of Formula (A-1), (A-2), or (A-3), each Y⁵ is independently N.

[0035] In some embodiments of Formula (A-1), (A-2), (A-3), or (I), each Y⁶ is CH. In some embodiments of Formula (A-1), (A-2), (A-3), or (I), each Y⁶ is independently N.

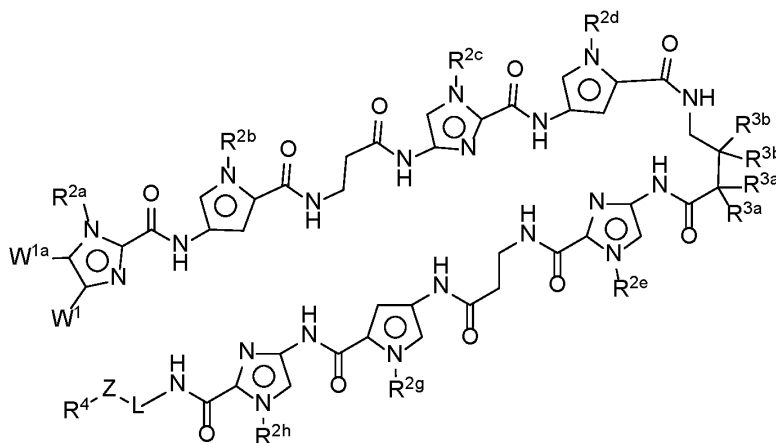
[0036] In some embodiments of Formula (A-1), (A-2), (A-3), or (I), Y⁷ is CH. In some embodiments of Formula (A-1), (A-2), (A-3), or (I), Y⁷ is N.

[0037] In some embodiments of Formula (A-1), (A-2), (A-3), or (I), Y⁸ is CH. In some embodiments of Formula (A-1), (A-2), (A-3), or (I), Y⁸ is N.

[0038] In some embodiments of Formula (A-1), (A-2), (A-3), or (I), Y², Y⁴, Y⁷, and Y⁸ are each N and Y¹, Y³, and Y⁶ are each CH.

[0039] In some embodiments of Formula (A-1), (A-2), (A-3), or (I), Y¹, Y², Y³, and Y⁸ are each N and Y⁴, Y⁶, and Y⁷ are each CH.

[0040] In some embodiments, provided herein is a transcription modulator molecule having a structure of Formula (II), or a pharmaceutically acceptable salt thereof:



Formula (II),

wherein:

W¹ and W^{1a} are each independently hydrogen, C₁-C₃ haloalkyl, or -N=C(N(R^{1e}))₂, wherein each R^{1e} is independently hydrogen or C₁-C₃ alkyl;

L is absent, C₁-C₂₀ alkylene, or C₂-C₂₀ heteroalkylene;

Z is absent, -C(O)-, or -C(=NH)-;

R⁴ is C₁-C₈ alkyl, C₃-C₁₀ cycloalkyl, 4 to 12-membered heterocycloalkyl, -OR^{4b}, or -NR^{4a}R^{4b}; wherein

R^{4a} is hydrogen, optionally substituted C₁-C₂₀ alkyl, optionally substituted C₁-C₂₀ haloalkyl, or optionally substituted C₁-C₂₀ heteroalkyl, each of which is optionally substituted with one or more R⁵;

R^{4b} is hydrogen, optionally substituted C₁-C₂₀ alkyl, optionally substituted C₂-C₂₀ alkenyl, optionally substituted C₂-C₂₀ alkynyl, optionally substituted C₁-C₂₀ aminoalkyl, optionally substituted C₁-C₂₀ haloalkyl, optionally substituted C₁-C₂₀ heteroalkyl, optionally substituted C₁-C₂₀ hydroxyalkyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted 4 to 12-membered heterocycloalkyl, optionally substituted phenyl, or optionally substituted 5 to 10-membered heteroaryl, each of which is optionally substituted with one or more R⁵; or

R^{4a} and R^{4b} together with the nitrogen to which they are attached form an optionally substituted 4 to 12-membered heterocycloalkyl which is optionally substituted with one or more R⁵;

each R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^{2e}, R^{2g}, and R^{2h} is independently hydrogen, optionally substituted C₁-C₅₀ alkyl, optionally substituted C₂-C₅₀ alkenyl, optionally substituted C₂-C₅₀ alkynyl, optionally substituted C₁-C₅₀ heteroalkyl, optionally substituted C₂-C₅₀ heteroalkenyl, optionally substituted C₂-C₅₀ heteroalkynyl, optionally substituted C₁-C₅₀ haloalkyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted 3

Z is absent, -C(O)-, or -C(=NH)-;

R⁴ is C₁-C₈ alkyl, C₃-C₁₀ cycloalkyl, 4 to 12-membered heterocycloalkyl, -OR^{4b}, or -NR^{4a}R^{4b}; wherein

R^{4a} is hydrogen, optionally substituted C₁-C₂₀ alkyl, optionally substituted C₁-C₂₀ haloalkyl, or optionally substituted C₁-C₂₀ heteroalkyl, each of which is optionally substituted with one or more R⁵;

R^{4b} is hydrogen, optionally substituted C₁-C₂₀ alkyl, optionally substituted C₂-C₂₀ alkenyl, optionally substituted C₂-C₂₀ alkynyl, optionally substituted C₁-C₂₀ aminoalkyl, optionally substituted C₁-C₂₀ haloalkyl, optionally substituted C₁-C₂₀ heteroalkyl, optionally substituted C₁-C₂₀ hydroxyalkyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted 4 to 12-membered heterocycloalkyl, optionally substituted phenyl, or optionally substituted 5 to 10-membered heteroaryl, each of which is optionally substituted with one or more R⁵; or

R^{4a} and R^{4b} together with the nitrogen to which they are attached form an optionally substituted 4 to 12-membered heterocycloalkyl which is optionally substituted with one or more R⁵;

each R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^{2e}, R^{2g}, and R^{2h} is independently hydrogen, optionally substituted C₁-C₅₀ alkyl, optionally substituted C₂-C₅₀ alkenyl, optionally substituted C₂-C₅₀ alkynyl, optionally substituted C₁-C₅₀ heteroalkyl, optionally substituted C₂-C₅₀ heteroalkenyl, optionally substituted C₂-C₅₀ heteroalkynyl, optionally substituted C₁-C₅₀ haloalkyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted 3 to 8-membered heterocycloalkyl, or optionally substituted PEG₁₋₅₀; each of which is optionally substituted with one or more R⁶;

each R^{3b} is independently hydrogen, C₁-C₆ alkyl, -NR^{3c}R^{3d}, -NHC(O)OR^{3c}, or -NHC(O)R^{3e},

or two R^{3b} together with the carbon atom to which they are attached form a C₃-C₆ cycloalkyl or 4 to 6-membered heterocycloalkyl, wherein

R^{3c} and R^{3d} are each independently hydrogen, C₁-C₂₀ alkyl, C₁-C₃ alkyl(phenyl), or PEG₁₋₂₀;

R^{3e} is C₁-C₂₀ alkyl, PEG₁₋₂₀, C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;

each R⁵ is independently halogen, -CN, -OH, -OR^{5a}, -N₃, -NR^{5a}R^{5b}, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted 4 to 8-membered heterocycloalkyl, or optionally substituted phenyl, each of which is optionally substituted with one or more R^{5c}, wherein

R^{5a} and R^{5b} are each independently hydrogen, C₁-C₂₀ alkyl, or PEG₁₋₂₀;

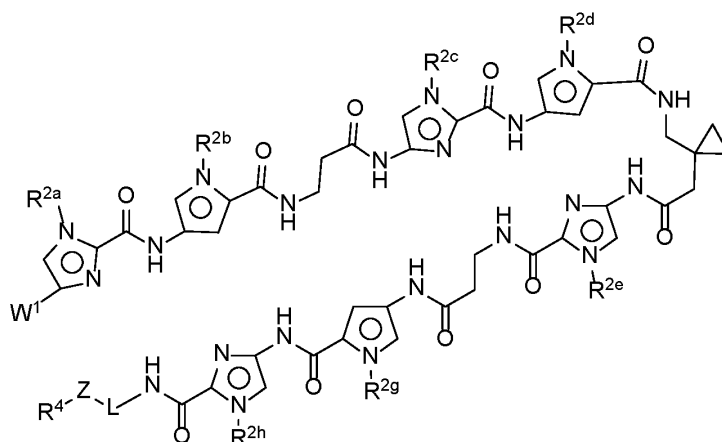
each R^{5c} is independently C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;

each R⁶ is independently halogen, -CN, -OH, -OR^{6a}, -N₃, -NR^{6a}R^{6b}, -CO(O)R^{6c}, -C(O)OR^{6c}, -C(O)NR^{6a}R^{6b}, -NHC(O)R^{6c}, -NHC(O)OR^{6c}, -OC(O)NR^{6a}R^{6b}, C₃-C₆ cycloalkyl, or 4 to 6 membered heterocycloalkyl; wherein

R^{6a} and R^{6b} are each independently hydrogen, C₁-C₂₀ alkyl, or PEG₁₋₂₀; and

R^{6c} is C₁-C₂₀ alkyl, PEG₁₋₂₀, C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl.

[0042] In some embodiments, provided herein is a transcription modulator molecule having a structure of Formula (IIIa), or a pharmaceutically acceptable salt thereof:



Formula (IIIa),

wherein:

W¹ is hydrogen or -N=C(N(R^{1e}))₂, wherein each R^{1e} is independently hydrogen or C₁-C₃ alkyl;

L is absent, ₁-C₂₀ alkylene or C₂-C₂₀ heteroalkylene;

Z is absent, -C(O)-, or -C(=NH)-;

R⁴ is C₁-C₈ alkyl, C₃-C₁₀ cycloalkyl, 4 to 12-membered heterocycloalkyl, -OR^{4b}, or -NR^{4a}R^{4b}; wherein

R^{4a} is hydrogen, optionally substituted C₁-C₂₀ alkyl, optionally substituted C₁-C₂₀ haloalkyl, or optionally substituted C₁-C₂₀ heteroalkyl, each of which is optionally substituted with one or more R⁵;

R^{4b} is hydrogen, optionally substituted C₁-C₂₀ alkyl, optionally substituted C₂-C₂₀ alkenyl, optionally substituted C₂-C₂₀ alkynyl, optionally substituted C₁-C₂₀ aminoalkyl, optionally substituted C₁-C₂₀ haloalkyl, optionally substituted C₁-C₂₀ heteroalkyl, optionally substituted C₁-C₂₀ hydroxyalkyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted 4 to 12-membered heterocycloalkyl, optionally substituted phenyl, or optionally substituted 5 to 10-membered heteroaryl, each of which is optionally substituted with one or more R⁵; or

R^{4a} and R^{4b} together with the nitrogen to which they are attached form an optionally substituted 4 to 12-membered heterocycloalkyl which is optionally substituted with one or more R⁵;

each R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^{2e}, R^{2g}, and R^{2h} is independently hydrogen, optionally substituted C₁-C₅₀ alkyl, optionally substituted C₂-C₅₀ alkenyl, optionally substituted C₂-C₅₀ alkynyl, optionally substituted C₁-C₅₀ heteroalkyl, optionally substituted C₂-C₅₀ heteroalkenyl, optionally substituted C₂-C₅₀ heteroalkynyl, optionally substituted C₁-C₅₀ haloalkyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted 3 to 8-membered heterocycloalkyl, or optionally substituted PEG₁₋₅₀; each of which is optionally substituted with one or more R⁶;

each R⁵ is independently halogen, -CN, -OH, -OR^{5a}, -N₃, -NR^{5a}R^{5b}, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆

haloalkyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted 4 to 8-membered heterocycloalkyl, or optionally substituted phenyl, each of which is optionally substituted with one or more R^{5c}, wherein

R^{5a} and R^{5b} are each independently hydrogen, C₁-C₂₀ alkyl, or PEG₁₋₂₀;

each R^{5c} is independently C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;

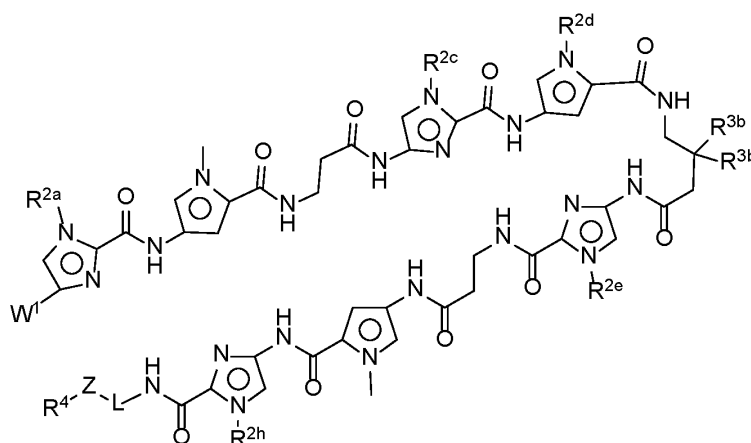
each R⁶ is independently halogen, -CN, -OH, -OR^{6a}, -N₃, -NR^{6a}R^{6b}, -CO(O)R^{6c}, -C(O)OR^{6c}, -C(O)NR^{6a}R^{6b}, -NHC(O)R^{6c}, -NHC(O)OR^{6c}, -OC(O)NR^{6a}R^{6b}, C₃-C₆ cycloalkyl, or 4 to 6 membered heterocycloalkyl; wherein

R^{6a} and R^{6b} are each independently hydrogen, C₁-C₂₀ alkyl, or PEG₁₋₂₀; and

R^{6c} is C₁-C₂₀ alkyl, PEG₁₋₂₀, C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl.

[0043] In some embodiments of Formula (I), (II), (III), or (IIIa), at least one of R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^{2e}, R^{2g}, or R^{2h} is not unsubstituted C₁-C₂₀ alkyl. In some embodiments of Formula (I), (II), (III), or (IIIa), at least one of R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^{2e}, R^{2g}, or R^{2h} is not methyl.

[0044] In some embodiments, provided herein is a transcription modulator molecule having a structure of Formula (IV), or a pharmaceutically acceptable salt thereof:



Formula (IV),

wherein:

W¹ is hydrogen or -N=C(N(R^{1c}))₂, wherein each R^{1c} is independently hydrogen or C₁-C₃ alkyl;

L is absent, C₁-C₂₀ alkylene, or C₂-C₂₀ heteroalkylene;

Z is absent, -C(O)-, or -C(=NH)-;

R⁴ is C₁-C₈ alkyl, C₃-C₁₀ cycloalkyl, 4 to 12-membered heterocycloalkyl, -OR^{4b}, or -NR^{4a}R^{4b}; wherein

R^{4a} is hydrogen, optionally substituted C₁-C₂₀ alkyl, optionally substituted C₁-C₂₀ haloalkyl, or optionally substituted C₁-C₂₀ heteroalkyl, each of which is optionally substituted with one or more R⁵;

R^{4b} is hydrogen, optionally substituted C₁-C₂₀ alkyl, optionally substituted C₂-C₂₀ alkenyl, optionally substituted C₂-C₂₀ alkynyl, optionally substituted C₁-C₂₀ aminoalkyl, optionally substituted C₁-C₂₀ haloalkyl, optionally substituted C₁-C₂₀ heteroalkyl, optionally substituted C₁-C₂₀ hydroxyalkyl,

optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted 4 to 12-membered heterocycloalkyl, optionally substituted phenyl, or optionally substituted 5 to 10-membered heteroaryl, each of which is optionally substituted with one or more R⁵; or

R^{4a} and R^{4b} together with the nitrogen to which they are attached form an optionally substituted 4 to 12-membered heterocycloalkyl which is optionally substituted with one or more R⁵;

each R^{2a}, R^{2c}, R^{2d}, R^{2e}, and R^{2h} is independently hydrogen, optionally substituted C₁-C₅₀ alkyl, optionally substituted C₂-C₅₀ alkenyl, optionally substituted C₂-C₅₀ alkynyl, optionally substituted C₁-C₅₀ heteroalkyl, optionally substituted C₂-C₅₀ heteroalkenyl, optionally substituted C₂-C₅₀ heteroalkynyl, optionally substituted C₁-C₅₀ haloalkyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted 3 to 8-membered heterocycloalkyl, or optionally substituted PEG₁₋₅₀; each of which is optionally substituted with one or more R⁶;

each R^{3b} is independently hydrogen, halogen, C₁-C₆ alkyl, -NR^{3c}R^{3d}, -NHC(O)OR^{3c}, or -NHC(O)R^{3e}, or two R^{3b} together with the carbon atom to which they are attached form a C₃-C₆ cycloalkyl or 4 to 6-membered heterocycloalkyl, wherein

R^{3c} and R^{3d} are each independently hydrogen, C₁-C₂₀ alkyl, C₁-C₃ alkyl(phenyl), or PEG₁₋₂₀;

R^{3e} is C₁-C₂₀ alkyl, PEG₁₋₂₀, C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;

each R⁵ is independently halogen, -CN, -OH, -OR^{5a}, -N₃, -NR^{5a}R^{5b}, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted 4 to 8-membered heterocycloalkyl, or optionally substituted phenyl, each of which is optionally substituted with one or more R^{5c}, wherein

R^{5a} and R^{5b} are each independently hydrogen, C₁-C₂₀ alkyl, or PEG₁₋₂₀;

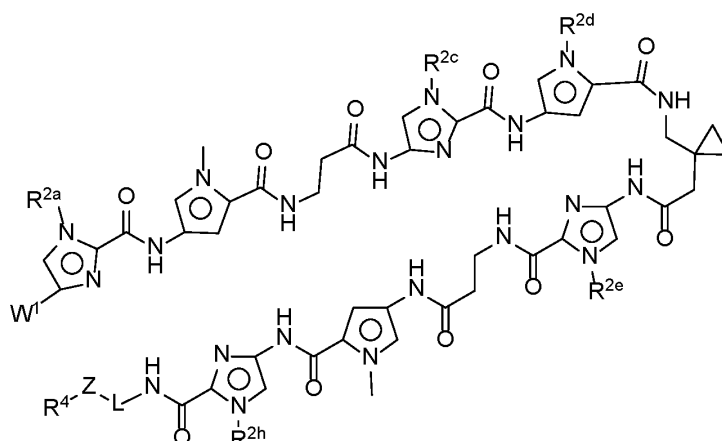
each R^{5c} is independently C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;

each R⁶ is independently halogen, -CN, -OH, -OR^{6a}, -N₃, -NR^{6a}R^{6b}, -CO(O)R^{6c}, -C(O)OR^{6c}, -C(O)NR^{6a}R^{6b}, -NHC(O)R^{6c}, -NHC(O)OR^{6c}, -OC(O)NR^{6a}R^{6b}, C₃-C₆ cycloalkyl, or 4 to 6 membered heterocycloalkyl; wherein

R^{6a} and R^{6b} are each independently hydrogen, C₁-C₂₀ alkyl, or PEG₁₋₂₀; and

R^{6c} is C₁-C₂₀ alkyl, PEG₁₋₂₀, C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl.

[0045] In some embodiments, provided herein is a transcription modulator molecule having a structure of Formula (IVa), or a pharmaceutically acceptable salt thereof:



Formula (IVa),

wherein:

W^1 is hydrogen or $-N=C(N(R^{1e}))_2$, wherein each R^{1e} is independently hydrogen or C_1 - C_3 alkyl;

L is absent, C_1 - C_{20} alkylene, or C_2 - C_{20} heteroalkylene;

Z is absent, $-C(O)-$, or $-C(=NH)-$;

R^4 is C_1 - C_8 alkyl, C_3 - C_{10} cycloalkyl, 4 to 12-membered heterocycloalkyl, $-OR^{4b}$, or $-NR^{4a}R^{4b}$; wherein

R^{4a} is hydrogen, optionally substituted C_1 - C_{20} alkyl, optionally substituted C_1 - C_{20} haloalkyl, or optionally substituted C_1 - C_{20} heteroalkyl, each of which is optionally substituted with one or more R^5 ;

R^{4b} is hydrogen, optionally substituted C_1 - C_{20} alkyl, optionally substituted C_2 - C_{20} alkenyl, optionally substituted C_2 - C_{20} alkynyl, optionally substituted C_1 - C_{20} aminoalkyl, optionally substituted C_1 - C_{20} haloalkyl, optionally substituted C_1 - C_{20} heteroalkyl, optionally substituted C_1 - C_{20} hydroxyalkyl, optionally substituted C_3 - C_{10} cycloalkyl, optionally substituted 4 to 12-membered heterocycloalkyl, optionally substituted phenyl, or optionally substituted 5 to 10-membered heteroaryl, each of which is optionally substituted with one or more R^5 ; or

R^{4a} and R^{4b} together with the nitrogen to which they are attached form an optionally substituted 4 to 12-membered heterocycloalkyl which is optionally substituted with one or more R^5 ;

each R^{2a} , R^{2c} , R^{2d} , R^{2e} , and R^{2h} is independently hydrogen, optionally substituted C_1 - C_{50} alkyl, optionally substituted C_2 - C_{50} alkenyl, optionally substituted C_2 - C_{50} alkynyl, optionally substituted C_1 - C_{50} heteroalkyl, optionally substituted C_2 - C_{50} heteroalkenyl, optionally substituted C_2 - C_{50} heteroalkynyl, optionally substituted C_1 - C_{50} haloalkyl, optionally substituted C_3 - C_8 cycloalkyl, optionally substituted 3 to 8-membered heterocycloalkyl, or optionally substituted PEG_{1-50} ; each of which is optionally substituted with one or more R^6 ;

each R^5 is independently halogen, $-CN$, $-OH$, $-OR^{5a}$, $-N_3$, $-NR^{5a}R^{5b}$, optionally substituted C_1 - C_6 alkyl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 alkynyl, optionally substituted C_1 - C_6 haloalkyl, optionally substituted C_3 - C_8 cycloalkyl, optionally substituted 4 to 8-membered

heterocycloalkyl, or optionally substituted phenyl, each of which is optionally substituted with one or more R^{5c} , wherein

R^{5a} and R^{5b} are each independently hydrogen, C_1 - C_{20} alkyl, or PEG_{1-20} ;

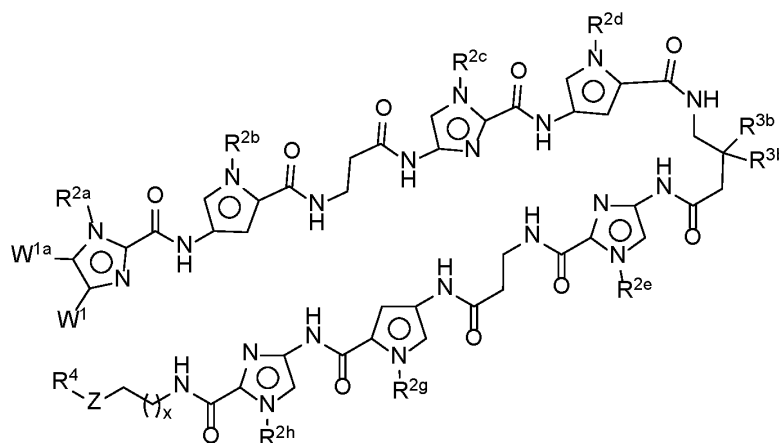
each R^{5c} is independently C_3 - C_8 cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;

each R^6 is independently halogen, -CN, -OH, -OR^{6a}, -N₃, -NR^{6a}R^{6b}, -CO(O)R^{6c}, -C(O)OR^{6c}, -C(O)NR^{6a}R^{6b}, -NHC(O)R^{6c}, -NHC(O)OR^{6c}, -OC(O)NR^{6a}R^{6b}, C_3 - C_6 cycloalkyl, or 4 to 6 membered heterocycloalkyl; wherein

R^{6a} and R^{6b} are each independently hydrogen, C_1 - C_{20} alkyl, or PEG_{1-20} ; and

R^{6c} is C_1 - C_{20} alkyl, PEG_{1-20} , C_3 - C_8 cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl.

[0046] In another aspect, provided herein is a transcription modulator molecule having a structure of Formula (V), or a pharmaceutically acceptable salt thereof:



Formula (V),

wherein:

W^1 and W^{1a} are each independently is hydrogen, C_1 - C_3 haloalkyl, or -N=C(N(R^{1e}))₂, wherein each R^{1e} is independently hydrogen or C_1 - C_3 alkyl;

Z is absent, -C(O)-, or -C(=NH)-;

R^4 is C_1 - C_8 alkyl, C_3 - C_{10} cycloalkyl, 4 to 12-membered heterocycloalkyl, or -NR^{4a}R^{4b}; wherein

R^{4a} is hydrogen, optionally substituted C_1 - C_{20} alkyl, optionally substituted C_1 - C_{20} haloalkyl, or optionally substituted C_1 - C_{20} heteroalkyl, each of which is optionally substituted with one or more R^5 ;

R^{4b} is hydrogen, optionally substituted C_1 - C_{20} alkyl, optionally substituted C_1 - C_{20} haloalkyl, optionally substituted C_1 - C_{20} heteroalkyl, optionally substituted C_3 - C_{10} cycloalkyl, optionally substituted 4 to 12-membered heterocycloalkyl, or optionally substituted 5 to 10-membered heteroaryl, each of which is optionally substituted with one or more R^5 ; or

R^{4a} and R^{4b} together with the nitrogen to which they are attached form an optionally substituted 4 to 12-membered heterocycloalkyl which is optionally substituted with one or more R^5 ;

R^{2a} , R^{2b} , R^{2c} , R^{2d} , R^{2e} , R^{2g} , and R^{2h} are each independently hydrogen, optionally substituted C_1 - C_{20} alkyl, C_1 - C_{20} heteroalkyl, optionally substituted C_1 - C_{20} haloalkyl, or optionally substituted PEG_{1-20} ; each of which is optionally substituted with one or more R^6 ;

each R^{3b} is hydrogen;

or two R^{3b} together with the carbon atom to which they are attached form a C_3 - C_6 cycloalkyl or 4 to 6-membered heterocycloalkyl;

each R^5 is independently halogen, -CN, -OH, -OR^{5a}, -N₃, -NR^{5a}R^{5b}, optionally substituted C_1 - C_6 alkyl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 alkynyl, optionally substituted C_1 - C_6 haloalkyl, optionally substituted C_3 - C_8 cycloalkyl, optionally substituted 4 to 8-membered heterocycloalkyl, or optionally substituted phenyl, each of which is optionally substituted with one or more R^{5c} , wherein

R^{5a} and R^{5b} are each independently hydrogen, C_1 - C_{20} alkyl, or PEG_{1-20} ;

each R^{5c} is independently C_3 - C_8 cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;

each R^6 is independently halogen, -CN, -OH, -OR^{6a}, -N₃, -NR^{6a}R^{6b}, -CO(O)R^{6c}, -C(O)OR^{6c}, -C(O)NR^{6a}R^{6b}, -NHC(O)R^{6c}, -NHC(O)OR^{6c}, -OC(O)NR^{6a}R^{6b}, C_3 - C_6 cycloalkyl, or 4 to 6 membered heterocycloalkyl; wherein

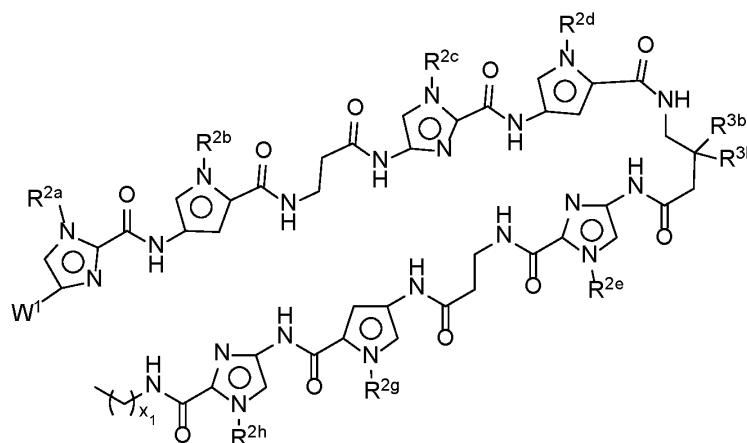
R^{6a} and R^{6b} are each independently hydrogen, C_1 - C_{20} alkyl, or PEG_{1-20} ;

R^{6c} is C_1 - C_{20} alkyl, PEG_{1-20} , C_3 - C_8 cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl; and

x is 0-10.

[0047] In some embodiments of Formula (V), at least one of R^{2a} , R^{2b} , R^{2c} , R^{2d} , R^{2e} , R^{2g} , or R^{2h} is not unsubstituted C_1 - C_{20} alkyl. In some embodiments of Formula (V), at least one of R^{2a} , R^{2b} , R^{2c} , R^{2d} , R^{2e} , R^{2g} , or R^{2h} is not methyl.

[0048] In another aspect, provided herein is a transcription modulator molecule having a structure of Formula (VI), or a pharmaceutically acceptable salt thereof:



Formula (VI),

wherein:

W^1 is hydrogen or -N=C(N(R^{1c}))₂, wherein each R^{1c} is independently hydrogen or C_1 - C_3 alkyl;

R^{2a} , R^{2b} , R^{2c} , R^{2d} , R^{2e} , R^{2g} , and R^{2h} are each independently hydrogen, optionally substituted C_1 - C_{50} alkyl, optionally substituted C_2 - C_{50} alkenyl, optionally substituted C_2 - C_{50} alkynyl, optionally substituted C_1 - C_{50} heteroalkyl, optionally substituted C_2 - C_{50} heteroalkenyl, optionally substituted C_2 - C_{50} heteroalkynyl, optionally substituted C_1 - C_{50} haloalkyl, optionally substituted C_3 - C_8 cycloalkyl, optionally substituted 3 to 8-membered heterocycloalkyl, or optionally substituted PEG_{1-50} ; each of which is optionally substituted with one or more R^6 ;

each R^{3b} is independently hydrogen, halogen, C_1 - C_6 alkyl, $-NR^{3c}R^{3d}$, $-NHC(O)OR^{3c}$, or $-NHC(O)R^{3e}$; or two R^{3b} together with the atoms to which they are attached form a C_3 - C_6 cycloalkyl or 4 to 6-membered heterocycloalkyl; wherein

R^{3c} and R^{3d} are each independently hydrogen, C_1 - C_{20} alkyl, C_1 - C_3 alkyl(phenyl), or PEG_{1-20} ;

R^{3e} is C_1 - C_{20} alkyl, PEG_{1-20} , C_3 - C_8 cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;

each R^6 is independently halogen, $-CN$, $-OH$, $-OR^{6a}$, $-N_3$, $-NR^{6a}R^{6b}$, $-CO(O)R^{6c}$, $-C(O)OR^{6c}$, $-C(O)NR^{6a}R^{6b}$, $-NHC(O)R^{6c}$, $-NHC(O)OR^{6c}$, $-OC(O)NR^{6a}R^{6b}$, C_3 - C_6 cycloalkyl, or 4 to 6 membered heterocycloalkyl; wherein

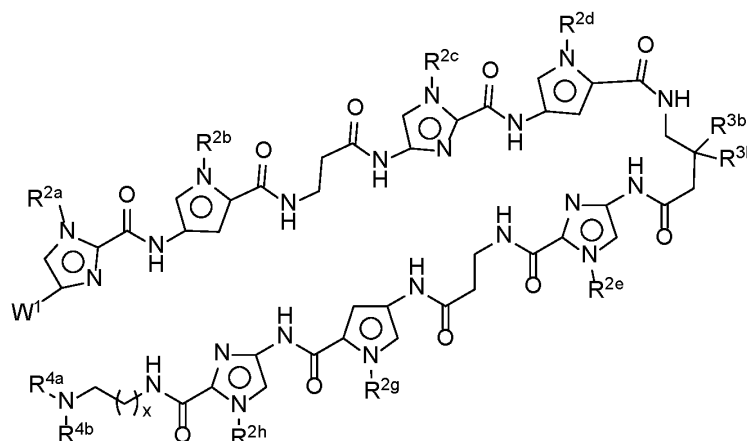
R^{6a} and R^{6b} are each independently hydrogen, C_1 - C_{20} alkyl, or PEG_{1-20} ;

R^{6c} is C_1 - C_{20} alkyl, PEG_{1-20} , C_3 - C_8 cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl; and

x_1 is 0-6.

[0049] In some embodiments of Formula (VI), x_1 is 0-6. In some embodiments of Formula (VI), x_1 is 0-3. In some embodiments of Formula (VI), x_1 is 1, 2, or 3. In some embodiments of Formula (VI), x_1 is 0. In some embodiments of Formula (VI), x_1 is 1. In some embodiments of Formula (VI), x_1 is 2. In some embodiments of Formula (VI), x_1 is 3. In some embodiments of Formula (VI), x_1 is 4. In some embodiments of Formula (VI), x_1 is 5. In some embodiments of Formula (VI), x_1 is 6.

[0050] In another aspect, provided herein is a transcription modulator molecule having a structure of Formula (VII), or a pharmaceutically acceptable salt thereof:



Formula (VII),

wherein:

W^1 is hydrogen or $-N=C(N(R^{1c}))_2$, wherein each R^{1c} is independently hydrogen or C_1 - C_3 alkyl;

R^{2a} , R^{2b} , R^{2c} , R^{2d} , R^{2e} , R^{2g} , and R^{2h} are each independently hydrogen, optionally substituted C_1 - C_{50} alkyl, optionally substituted C_2 - C_{50} alkenyl, optionally substituted C_2 - C_{50} alkynyl, optionally substituted C_1 - C_{50} heteroalkyl, optionally substituted C_2 - C_{50} heteroalkenyl, optionally substituted C_2 - C_{50} heteroalkynyl, optionally substituted C_1 - C_{50} haloalkyl, optionally substituted C_3 - C_8 cycloalkyl, optionally substituted 3 to 8-membered heterocycloalkyl, or optionally substituted PEG_{1-50} ; each of which is optionally substituted with one or more R^6 ;

each R^{3b} is independently hydrogen, halogen, C_1 - C_6 alkyl, $-NR^{3c}R^{3d}$, $-NHC(O)OR^{3c}$, or $-NHC(O)R^{3e}$; or two R^{3b} together with the atoms to which they are attached form a C_3 - C_6 cycloalkyl or 4 to 6-membered heterocycloalkyl; wherein

R^{3c} and R^{3d} are each independently hydrogen, C_1 - C_{20} alkyl, C_1 - C_3 alkyl(phenyl), or PEG_{1-20} ;

R^{3e} is C_1 - C_{20} alkyl, PEG_{1-20} , C_3 - C_8 cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;

R^{4a} and R^{4b} are each independently C_1 - C_3 alkyl or PEG_{1-10} ;

each R^6 is independently halogen, $-CN$, $-OH$, $-OR^{6a}$, $-N_3$, $-NR^{6a}R^{6b}$, $-CO(O)R^{6c}$, $-C(O)OR^{6c}$, $-C(O)NR^{6a}R^{6b}$, $-NHC(O)R^{6c}$, $-NHC(O)OR^{6c}$, $-OC(O)NR^{6a}R^{6b}$, C_3 - C_6 cycloalkyl, or 4 to 6 membered heterocycloalkyl; wherein

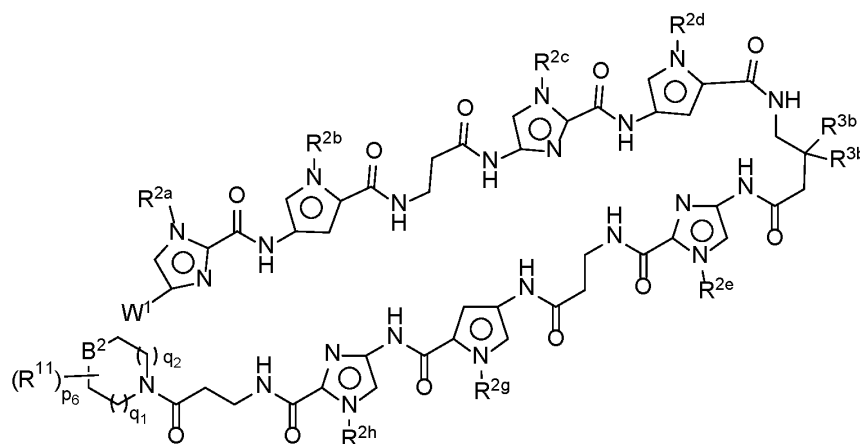
R^{6a} and R^{6b} are each independently hydrogen, C_1 - C_{20} alkyl, or PEG_{1-20} ;

R^{6c} is C_1 - C_{20} alkyl, PEG_{1-20} , C_3 - C_8 cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl; and

x is an integer from 0-10.

[0051] In some embodiments of Formula (VII), R^{4a} and R^{4b} are each independently C_1 - C_3 alkyl. In some embodiments of Formula (VII), R^{4a} and R^{4b} are each $-CH_3$. In some embodiments of Formula (VII), R^{4a} and R^{4b} are each independently PEG_{1-10} .

[0052] In another aspect, provided herein is a transcription modulator molecule having a structure of Formula (VIII), or a pharmaceutically acceptable salt thereof:



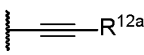
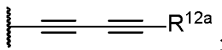
Formula (VIII),

wherein:

W^1 is hydrogen or $-N=C(N(R^{1e}))_2$, wherein each R^{1e} is independently hydrogen or C_1 - C_3 alkyl;

B^2 is NR^{10a} , or CHR^{12} ; wherein

R^{10a} is hydrogen or C₁-C₃ alkyl;

R¹² is an optionally substituted 4 to 6-membered heterocycloalkyl, , or ;

R^{12a} is an optionally substituted 4 to 6-membered heterocycloalkyl;

R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^{2e}, R^{2g}, and R^{2h} are each independently hydrogen, optionally substituted C₁-C₅₀ alkyl, optionally substituted C₂-C₅₀ alkenyl, optionally substituted C₂-C₅₀ alkynyl, optionally substituted C₁-C₅₀ heteroalkyl, optionally substituted C₂-C₅₀ heteroalkenyl, optionally substituted C₂-C₅₀ heteroalkynyl, optionally substituted C₁-C₅₀ haloalkyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted 3 to 10-membered heterocycloalkyl, or optionally substituted PEG₁₋₅₀; each of which is optionally substituted with one or more R⁶;

each R^{3b} is independently hydrogen, halogen, C₁-C₆ alkyl, -NR^{3c}R^{3d}, -NHC(O)OR^{3c}, or -NHC(O)R^{3e}; or two R^{3b} together with the atoms to which they are attached form a C₃-C₆ cycloalkyl or 4 to 6-membered heterocycloalkyl; wherein

R^{3c} and R^{3d} are each independently hydrogen, C₁-C₂₀ alkyl, C₁-C₃ alkyl(phenyl), or PEG₁₋₂₀;

R^{3e} is C₁-C₂₀ alkyl, PEG₁₋₂₀, C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;

each R⁶ is independently halogen, -CN, -OH, -OR^{6a}, -N₃, -NR^{6a}R^{6b}, -CO(O)R^{6c}, -C(O)OR^{6c}, -C(O)NR^{6a}R^{6b}, -NHC(O)R^{6c}, -NHC(O)OR^{6c}, -OC(O)NR^{6a}R^{6b}, C₃-C₆ cycloalkyl, or 4 to 6 membered heterocycloalkyl; wherein

R^{6a} and R^{6b} are each independently hydrogen, C₁-C₂₀ alkyl, or PEG₁₋₂₀;

R^{6c} is C₁-C₂₀ alkyl, PEG₁₋₂₀, C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;

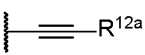
each R¹¹ is independently halogen, -CN, -OH, -N₃, or C₁-C₆ haloalkyl;

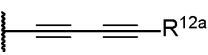
p₆ is 0, 1, 2, 3, or 4; and

q₁ and q₂ are each independently 0, 1, or 2.

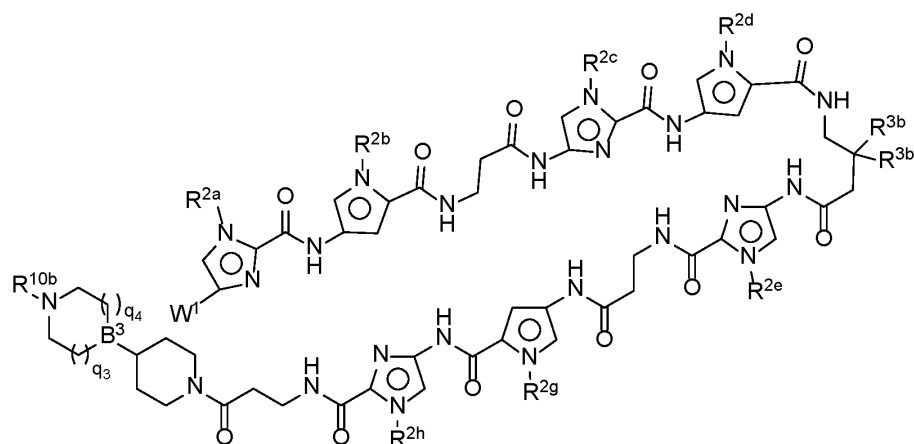
[0053] In some embodiments of Formula (VIII), B² is NR^{10a}. In some embodiments of Formula (VIII), CHR¹².

[0054] In some embodiments of Formula (VIII), R¹² is an optionally substituted 4 to 6-membered

heterocycloalkyl. In some embodiments of Formula (VIII), R¹² is . In some embodiments of

Formula (VIII), R¹² is .

[0055] In another aspect, provided herein is a transcription modulator molecule having a structure of Formula (VIIIa), or a pharmaceutically acceptable salt thereof.



Formula (VIIIa),

wherein:

W¹ is hydrogen or -N=C(N(R^{1e}))₂, wherein each R^{1e} is independently hydrogen or C₁-C₃ alkyl;

R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^{2e}, R^{2g}, and R^{2h} are each independently hydrogen, optionally substituted C₁-C₅₀ alkyl, optionally substituted C₂-C₅₀ alkenyl, optionally substituted C₂-C₅₀ alkynyl, optionally substituted C₁-C₅₀ heteroalkyl, optionally substituted C₂-C₅₀ heteroalkenyl, optionally substituted C₂-C₅₀ heteroalkynyl, optionally substituted C₁-C₅₀ haloalkyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted 3 to 8-membered heterocycloalkyl, or optionally substituted PEG₁₋₅₀; each of which is optionally substituted with one or more R⁶;

each R^{3b} is independently hydrogen, halogen, C₁-C₆ alkyl, -NR^{3c}R^{3d}, -NHC(O)OR^{3c}, or -NHC(O)R^{3e}; or two R^{3b} together with the atoms to which they are attached form a C₃-C₆ cycloalkyl or 4 to 6-membered heterocycloalkyl; wherein

R^{3c} and R^{3d} are each independently hydrogen, C₁-C₂₀ alkyl, C₁-C₃ alkyl(phenyl), or PEG₁₋₂₀;

R^{3e} is C₁-C₂₀ alkyl, PEG₁₋₂₀, C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;

each R⁶ is independently halogen, -CN, -OH, -OR^{6a}, -N₃, -NR^{6a}R^{6b}, -CO(O)R^{6c}, -C(O)OR^{6c}, -C(O)NR^{6a}R^{6b}, -NHC(O)R^{6c}, -NHC(O)OR^{6c}, -OC(O)NR^{6a}R^{6b}, C₃-C₆ cycloalkyl, or 4 to 6 membered heterocycloalkyl; wherein

R^{6a} and R^{6b} are each independently hydrogen, C₁-C₂₀ alkyl, or PEG₁₋₂₀;

R^{6c} is C₁-C₂₀ alkyl, PEG₁₋₂₀, C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl

B³ is N or CH;

R^{10b} is hydrogen or C₁-C₃ alkyl; and

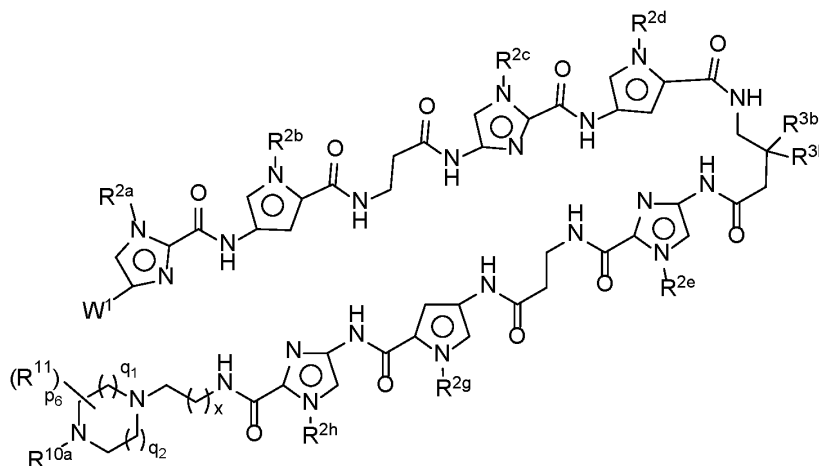
q₃ and q₄ are each independently 0, 1, or 2.

[0056] In some embodiments of Formula (VIIIa), B³ is N. In some embodiments of Formula (VIIIa), B³ is CH.

[0057] In some embodiments of Formula (VIIIa), R^{10b} is C₁-C₃ alkyl. In some embodiment of Formula (VIIIa), R^{10b} is methyl. In some embodiments of Formula (VIIIa), R^{10b} is hydrogen.

[0058] In some embodiments of Formula (VIIIa), q_3 and q_4 are each 0. In some embodiments of Formula (VIIIa), q_3 and q_4 are each 1.

[0059] In another aspect, provided herein is a transcription modulator molecule having a structure of Formula (VIIIb), or a pharmaceutically acceptable salt thereof:



Formula (VIIIb),

wherein:

W^1 is hydrogen or $-N=C(N(R^{1e}))_2$, wherein each R^{1e} is independently hydrogen or C_1 - C_3 alkyl;

R^{2a} , R^{2b} , R^{2c} , R^{2d} , R^{2e} , R^{2g} , and R^{2h} are each independently hydrogen, optionally substituted C_1 - C_{50} alkyl, optionally substituted C_2 - C_{50} alkenyl, optionally substituted C_2 - C_{50} alkynyl, optionally substituted C_1 - C_{50} heteroalkyl, optionally substituted C_2 - C_{50} heteroalkenyl, optionally substituted C_2 - C_{50} heteroalkynyl, optionally substituted C_1 - C_{50} haloalkyl, optionally substituted C_3 - C_8 cycloalkyl, optionally substituted 3 to 8-membered heterocycloalkyl, or optionally substituted PEG_{1-50} ; each of which is optionally substituted with one or more R^6 ;

each R^{3b} is independently hydrogen, halogen, C_1 - C_6 alkyl, $-NR^{3c}R^{3d}$, $-NHC(O)OR^{3c}$, or $-NHC(O)R^{3e}$;

or two R^{3b} together with the atoms to which they are attached form a C_3 - C_6 cycloalkyl or 4 to 6-membered heterocycloalkyl; wherein

R^{3c} and R^{3d} are each independently hydrogen, C_1 - C_{20} alkyl, C_1 - C_3 alkyl(phenyl), or PEG_{1-20} ;

R^{3e} is C_1 - C_{20} alkyl, PEG_{1-20} , C_3 - C_8 cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;

each R^6 is independently $-CN$, $-OH$, $-OR^{6a}$, $-N_3$, $-NR^{6a}R^{6b}$, $-CO(O)R^{6c}$, $-C(O)OR^{6c}$, $-C(O)NR^{6a}R^{6b}$, $-NHC(O)R^{6c}$, $-NHC(O)OR^{6c}$, or $-OC(O)NR^{6a}R^{6b}$; wherein

R^{6a} and R^{6b} are each independently hydrogen, C_1 - C_{20} alkyl, or PEG_{1-20} ;

R^{6c} is C_1 - C_{20} alkyl, PEG_{1-20} , C_3 - C_8 cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;

R^{10a} is hydrogen or C_1 - C_3 alkyl;

each R^{11} is independently halogen, $-CN$, $-OH$, $-N_3$, or C_1 - C_6 haloalkyl;

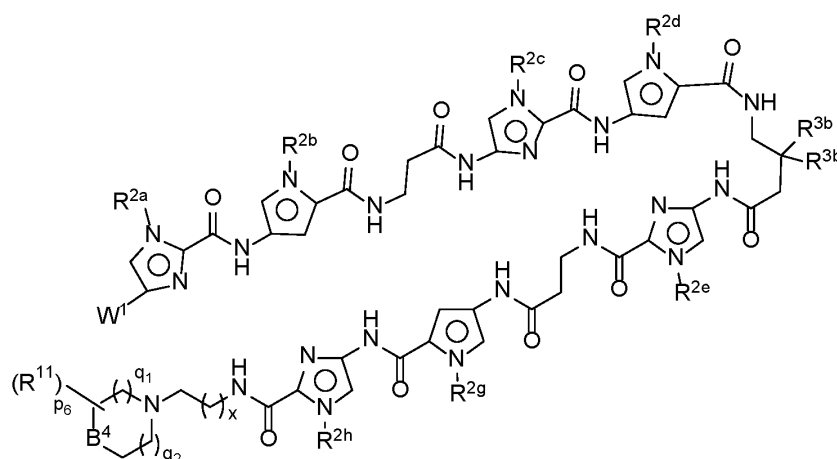
p_6 is 0, 1, 2, 3, or 4;

q_1 and q_2 are each independently 0, 1, or 2; and

x is an integer from 0-10.

[0060] In some embodiments of Formula (VIII) or (VIIIb), R^{10a} is C₁-C₃ alkyl. In some embodiments of Formula (VIII) or (VIIIb), R^{10a} is methyl or ethyl. In some embodiments of Formula (VIII) or (VIIIb), R^{10a} is methyl. In some embodiments of Formula (VIII) or (VIIIb), R^{10a} is hydrogen.

[0061] In another aspect, provided herein is a transcription modulator molecule having a structure of Formula (VIIIc), or a pharmaceutically acceptable salt thereof:



Formula (VIIIc).

wherein:

W¹ is hydrogen or -N=C(N(R^{1e})₂)₂, wherein each R^{1e} is independently hydrogen or C₁-C₃ alkyl;

R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^{2e}, R^{2g}, and R^{2h} are each independently hydrogen, optionally substituted C₁-C₅₀ alkyl, optionally substituted C₂-C₅₀ alkenyl, optionally substituted C₂-C₅₀ alkynyl, optionally substituted C₁-C₅₀ heteroalkyl, optionally substituted C₂-C₅₀ heteroalkenyl, optionally substituted C₂-C₅₀ heteroalkynyl, optionally substituted C₁-C₅₀ haloalkyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted 3 to 8-membered heterocycloalkyl, or optionally substituted PEG₁₋₅₀; each of which is optionally substituted with one or more R⁶;

each R^{3b} is independently hydrogen, halogen, C₁-C₆ alkyl, -NR^{3c}R^{3d}, -NHC(O)OR^{3c}, or -NHC(O)R^{3e};

or two R^{3b} together with the atoms to which they are attached form a C₃-C₆ cycloalkyl or 4 to 6-membered heterocycloalkyl; wherein

R^{3c} and R^{3d} are each independently hydrogen, C₁-C₂₀ alkyl, C₁-C₃ alkyl(phenyl), or PEG₁₋₂₀;

R^{3e} is C₁-C₂₀ alkyl, PEG₁₋₂₀, C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;

each R⁶ is independently halogen, -CN, -OH, -OR^{6a}, -N₃, -NR^{6a}R^{6b}, -CO(O)R^{6c}, -C(O)OR^{6c}, -C(O)NR^{6a}R^{6b}, -NHC(O)R^{6c}, -NHC(O)OR^{6c}, -OC(O)NR^{6a}R^{6b}, C₃-C₆ cycloalkyl, or 4 to 6 membered heterocycloalkyl;

wherein

R^{6a} and R^{6b} are each independently hydrogen, C₁-C₂₀ alkyl, or PEG₁₋₂₀;

R^{6c} is C₁-C₂₀ alkyl, PEG₁₋₂₀, C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;

each R¹¹ is independently halogen, -CN, -OH, -N₃, or C₁-C₆ haloalkyl;

B^4 is 0 or CH_2 :

p_6 is 0, 1, 2, 3, or 4;

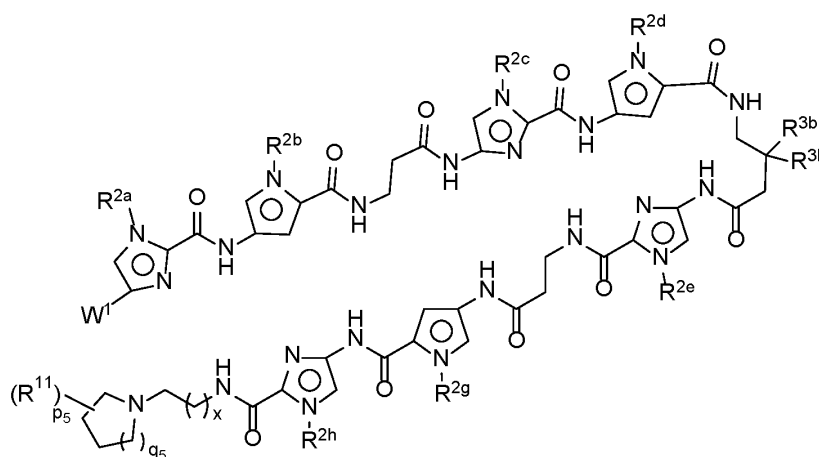
q_1 and q_2 are each independently 0, 1, or 2; and

x is an integer from 0-10.

[0062] In some embodiments of Formula (VIIIc), B^4 is O. In some embodiments of Formula (VIIIc), B^4 is CH_2 .

[0063] In some embodiments of Formula (VIII), (VIIIa), (VIIIb), or (VIIIc), p_6 is 1 or 2. In some embodiments of Formula (VIII), (VIIIa), (VIIIb), or (VIIIc), p_6 is 0. In some embodiments of Formula (VIII), (VIIIa), (VIIIb), or (VIIIc), p_6 is 1. In some embodiments of Formula (VIII), (VIIIa), (VIIIb), or (VIIIc), p_6 is 2.

[0064] In another aspect, provided herein is a transcription modulator molecule having a structure of Formula (VIIId), or a pharmaceutically acceptable salt thereof:



Formula (VIIId),

wherein:

W^1 is hydrogen or $-N=C(N(R^{1e})_2)_2$, wherein each R^{1e} is independently hydrogen or C_1 - C_3 alkyl;

R^{2a} , R^{2b} , R^{2c} , R^{2d} , R^{2e} , R^{2g} , and R^{2h} are each independently hydrogen, optionally substituted C_1 - C_{50} alkyl, optionally substituted C_2 - C_{50} alkenyl, optionally substituted C_2 - C_{50} alkynyl, optionally substituted C_1 - C_{50} heteroalkyl, optionally substituted C_2 - C_{50} heteroalkenyl, optionally substituted C_2 - C_{50} heteroalkynyl, optionally substituted C_1 - C_{50} haloalkyl, optionally substituted C_3 - C_8 cycloalkyl, optionally substituted 3 to 8-membered heterocycloalkyl, or optionally substituted PEG₁₋₅₀; each of which is optionally substituted with one or more R^6 ;

each R^{3b} is independently hydrogen, halogen, C_1 - C_6 alkyl, $-NR^{3c}R^{3d}$, $-NHC(O)OR^{3c}$, or $-NHC(O)R^{3e}$;

or two R^{3b} together with the atoms to which they are attached form a C_3 - C_6 cycloalkyl or 4 to 6-membered heterocycloalkyl; wherein

R^{3c} and R^{3d} are each independently hydrogen, C_1 - C_{20} alkyl, C_1 - C_3 alkyl(phenyl), or PEG₁₋₂₀;

R^{3e} is C_1 - C_{20} alkyl, PEG₁₋₂₀, C_3 - C_8 cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;

each R^6 is independently halogen, -CN, -OH, -OR^{6a}, -N₃, -NR^{6a}R^{6b}, -CO(O)R^{6c}, -C(O)OR^{6c}, -C(O)NR^{6a}R^{6b}, -NHC(O)R^{6c}, -NHC(O)OR^{6c}, -OC(O)NR^{6a}R^{6b}, C₃-C₆ cycloalkyl, or 4 to 6 membered heterocycloalkyl;

wherein

R^{6a} and R^{6b} are each independently hydrogen, C₁-C₂₀ alkyl, or PEG₁₋₂₀;

R^{6c} is C₁-C₂₀ alkyl, PEG₁₋₂₀, C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;

each R^{11} is independently halogen, -CN, -OH, -N₃, or C₁-C₆ haloalkyl;

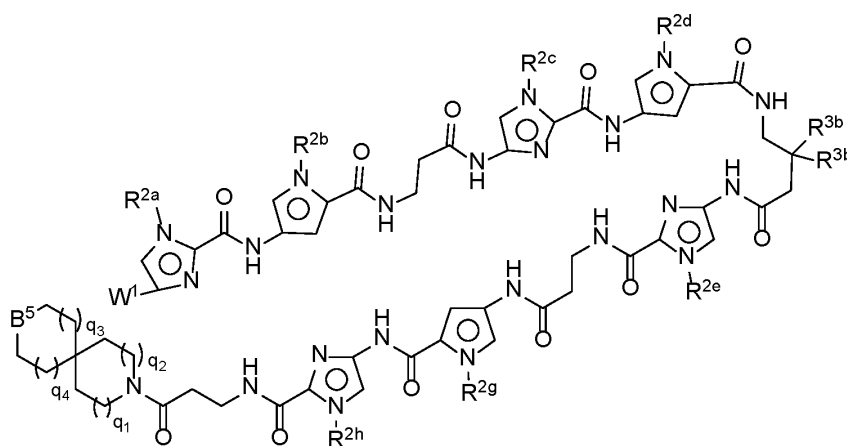
p_5 is 1, 2, 3, or 4;

q_5 is 0, 1, 2, or 3; and

x is an integer from 0-10;

[0065] In some embodiments of Formula (VIIId), p_5 is 1 or 2. In some embodiments of Formula (VIIId), p_5 is 1 and R^{11} is halogen or C₁-C₆ haloalkyl. In some embodiments of Formula (VIIId), p_5 is 2 and R^{11} is halogen or C₁-C₆ haloalkyl. In some embodiments of Formula (VIIId), p_5 is 1 and R^5 is -F or -CF₃.

[0066] In another aspect, provided herein is a transcription modulator molecule having a structure of Formula (IX), or a pharmaceutically acceptable salt thereof:



Formula (IX),

wherein:

W^1 is hydrogen or -N=C(N(R^{1e}))₂, wherein each R^{1e} is independently hydrogen or C₁-C₃ alkyl;

B^5 is NR^{10c} or O; wherein

R^{10c} is hydrogen or C₁-C₃ alkyl;

R^{2a} , R^{2b} , R^{2c} , R^{2d} , R^{2e} , R^{2g} , and R^{2h} are each independently hydrogen, optionally substituted C₁-C₅₀ alkyl, optionally substituted C₂-C₅₀ alkenyl, optionally substituted C₂-C₅₀ alkynyl, optionally substituted C₁-C₅₀ heteroalkyl, optionally substituted C₂-C₅₀ heteroalkenyl, optionally substituted C₂-C₅₀ heteroalkynyl, optionally substituted C₁-C₅₀ haloalkyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted 3 to 8-membered heterocycloalkyl, or optionally substituted PEG₁₋₅₀; each of which is optionally substituted with one or more R^6 ;

each R^{3b} is independently hydrogen, halogen, C₁-C₆ alkyl, -NR^{3c}R^{3d}, -NHC(O)OR^{3c}, or -NHC(O)R^{3c};

or two R^{3b} together with the atoms to which they are attached form a C₃-C₆ cycloalkyl or 4 to 6-membered heterocycloalkyl; wherein

R^{3c} and R^{3d} are each independently hydrogen, C₁-C₂₀ alkyl, C₁-C₃ alkyl(phenyl), or PEG₁₋₂₀;

R^{3e} is C₁-C₂₀ alkyl, PEG₁₋₂₀, C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;

each R⁶ is independently halogen, -CN, -OH, -OR^{6a}, -N₃, -NR^{6a}R^{6b}, -CO(O)R^{6c}, -C(O)OR^{6c}, -C(O)NR^{6a}R^{6b}, -NHC(O)R^{6c}, -NHC(O)OR^{6c}, -OC(O)NR^{6a}R^{6b}, C₃-C₆ cycloalkyl, or 4 to 6 membered heterocycloalkyl; wherein

R^{6a} and R^{6b} are each independently hydrogen, C₁-C₂₀ alkyl, or PEG₁₋₂₀;

R^{6c} is C₁-C₂₀ alkyl, PEG₁₋₂₀, C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl; and

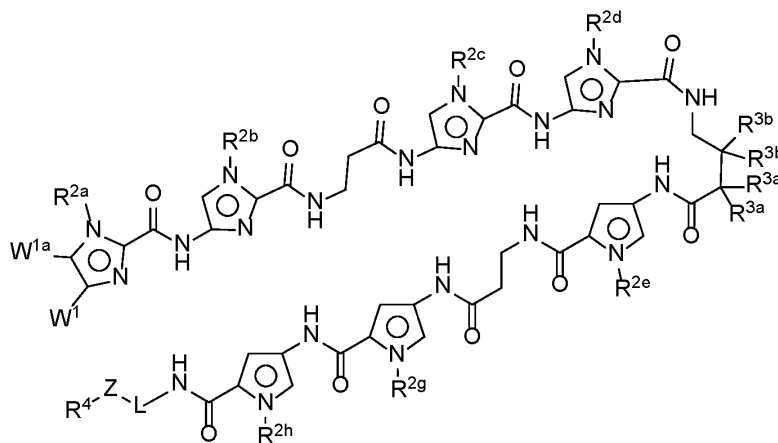
q₁, q₂, q₃, and q₄ are each independently 0, 1, or 2.

[0067] In some embodiments of Formula (IX), B⁵ is NR^{10c}. In some embodiments of Formula (IX), B⁵ is NCH₃. In some embodiments of Formula (IX), B⁵ is -NH-. In some embodiments of Formula (IX), B⁵ is -O-.

[0068] In some embodiments of Formula (VIII), (VIIIb), (VIIIc), or (IX), q₁ and q₂ are each 0. In some embodiments of Formula (VIII), (VIIIb), (VIIIc), or (IX), q₁ and q₂ are each 1. In some embodiments of Formula (VIII), (VIIIb), (VIIIc), or (IX), q₁ is 1 and q₂ is 0.

[0069] In some embodiments of Formula (VIIIa) or (IX), q₃ and q₄ are each 0. In some embodiments of Formula (VIIIa) or (IX), q₃ and q₄ are each 1. In some embodiments of Formula (VIIIa) or (IX), q₃ is 1 and q₄ is 0.

[0070] In another aspect, provided herein is a transcription modulator molecule having a structure of Formula (X), or a pharmaceutically acceptable salt thereof:



Formula (X),

wherein:

W¹ and W^{1a} are each independently hydrogen, C₁-C₃ haloalkyl, or -N=C(N(R^{1e}))₂, wherein each R^{1e} is independently hydrogen or C₁-C₃ alkyl;

L is absent, C₁-C₂₀ alkylene, or C₂-C₂₀ heteroalkylene;

Z is absent, -C(O)-, or -C(=NH)-;

R⁴ is C₁-C₈ alkyl, C₃-C₁₀ cycloalkyl, 4 to 12-membered heterocycloalkyl, -OR^{4b}, or -NR^{4a}R^{4b}; wherein

R^{4a} is hydrogen, optionally substituted C₁-C₂₀ alkyl, optionally substituted C₁-C₂₀ haloalkyl, or optionally substituted C₁-C₂₀ heteroalkyl, each of which is optionally substituted with one or more R⁵;

R^{4b} is hydrogen, optionally substituted C₁-C₂₀ alkyl, optionally substituted C₂-C₂₀ alkenyl, optionally substituted C₂-C₂₀ alkynyl, optionally substituted C₁-C₂₀ aminoalkyl, optionally substituted C₁-C₂₀ haloalkyl, optionally substituted C₁-C₂₀ heteroalkyl, optionally substituted C₁-C₂₀ hydroxyalkyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted 4 to 12-membered heterocycloalkyl, optionally substituted phenyl, or optionally substituted 5 to 10-membered heteroaryl, each of which is optionally substituted with one or more R⁵; or

R^{4a} and R^{4b} together with the nitrogen to which they are attached form an optionally substituted 4 to 12-membered heterocycloalkyl which is optionally substituted with one or more R⁵;

each R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^{2e}, R^{2g}, and R^{2h} is independently hydrogen, optionally substituted C₁-C₅₀ alkyl, optionally substituted C₂-C₅₀ alkenyl, optionally substituted C₂-C₅₀ alkynyl, optionally substituted C₁-C₅₀ heteroalkyl, optionally substituted C₂-C₅₀ heteroalkenyl, optionally substituted C₂-C₅₀ heteroalkynyl, optionally substituted C₁-C₅₀ haloalkyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted 3 to 8-membered heterocycloalkyl, or optionally substituted PEG₁₋₅₀; each of which is optionally substituted with one or more R⁶;

each R^{3a} and R^{3b} is independently hydrogen, C₁-C₆ alkyl, -NR^{3c}R^{3d}, -NHC(O)OR^{3e}, or -NHC(O)R^{3e}, or two R^{3a} or two R^{3b} together with the carbon atom to which they are attached form a C₃-C₆ cycloalkyl or 4 to 6-membered heterocycloalkyl;

or one of R^{3a} and one of R^{3b} together with the atoms to which they are attached form a C₃-C₆ cycloalkyl or 4 to 6-membered heterocycloalkyl; wherein

R^{3c} and R^{3d} are each independently hydrogen, C₁-C₂₀ alkyl, C₁-C₃ alkyl(phenyl), or PEG₁₋₂₀;

R^{3e} is C₁-C₂₀ alkyl, PEG₁₋₂₀, C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;

each R⁵ is independently halogen, -CN, -OH, -OR^{5a}, -N₃, -NR^{5a}R^{5b}, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted 4 to 8-membered heterocycloalkyl, or optionally substituted phenyl, each of which is optionally substituted with one or more R^{5c}, wherein

R^{5a} and R^{5b} are each independently hydrogen, C₁-C₂₀ alkyl, or PEG₁₋₂₀;

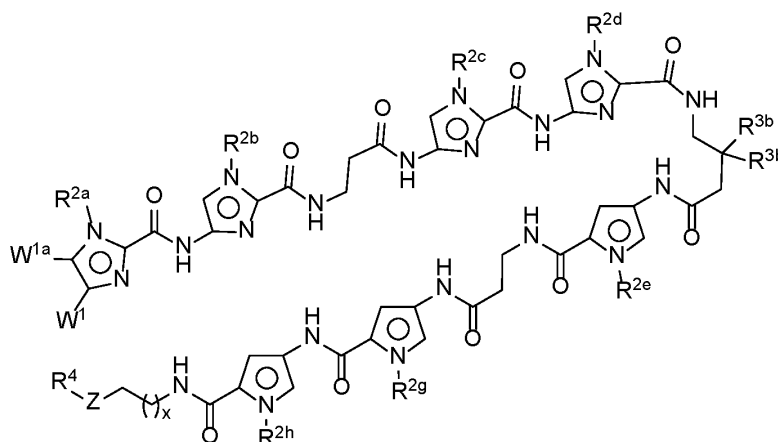
each R^{5c} is independently C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;

each R⁶ is independently halogen, -CN, -OH, -OR^{6a}, -N₃, -NR^{6a}R^{6b}, -CO(O)R^{6c}, -C(O)OR^{6c}, -C(O)NR^{6a}R^{6b}, -NHC(O)R^{6c}, -NHC(O)OR^{6c}, -OC(O)NR^{6a}R^{6b}, C₃-C₆ cycloalkyl, or 4 to 6 membered heterocycloalkyl; wherein

R^{6a} and R^{6b} are each independently hydrogen, C₁-C₂₀ alkyl, or PEG₁₋₂₀; and

R^{6c} is C₁-C₂₀ alkyl, PEG₁₋₂₀, C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl.

[0071] In another aspect, provided herein is a transcription modulator molecule having a structure of Formula (XI), or a pharmaceutically acceptable salt thereof:



Formula (XI),

wherein:

W¹ and W^{1a} are each independently hydrogen, C₁-C₃ haloalkyl, or -N=C(N(R^{1e})₂)₂, wherein each R^{1e} is independently hydrogen or C₁-C₃ alkyl;

Z is absent, -C(O)-, or -C(=NH)-;

R⁴ is C₁-C₈ alkyl, C₃-C₁₀ cycloalkyl, 4 to 12-membered heterocycloalkyl, or -NR^{4a}R^{4b}; wherein

R^{4a} is hydrogen, optionally substituted C₁-C₂₀ alkyl, optionally substituted C₁-C₂₀ haloalkyl, or optionally substituted C₁-C₂₀ heteroalkyl, each of which is optionally substituted with one or more R⁵;

R^{4b} is hydrogen, optionally substituted C₁-C₂₀ alkyl, optionally substituted C₁-C₂₀ haloalkyl, optionally substituted C₁-C₂₀ heteroalkyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted 4 to 12-membered heterocycloalkyl, or optionally substituted 5 to 10-membered heteroaryl, each of which is optionally substituted with one or more R⁵; or

R^{4a} and R^{4b} together with the nitrogen to which they are attached form an optionally substituted 4 to 12-membered heterocycloalkyl which is optionally substituted with one or more R⁵;

R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^{2e}, R^{2g}, and R^{2h} are each independently hydrogen, optionally substituted C₁-C₂₀ alkyl, C₁-C₂₀ heteroalkyl, optionally substituted C₁-C₂₀ haloalkyl, or optionally substituted PEG₁₋₂₀; each of which is optionally substituted with one or more R⁶;

each R^{3b} is hydrogen;

or two R^{3b} together with the carbon atom to which they are attached form a C₃-C₆ cycloalkyl or 4 to 6-membered heterocycloalkyl;

each R⁵ is independently halogen, -CN, -OH, -OR^{5a}, -N₃, -NR^{5a}R^{5b}, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted 4 to 8-membered

heterocycloalkyl, or optionally substituted phenyl, each of which is optionally substituted with one or more R^{5c} , wherein

R^{5a} and R^{5b} are each independently hydrogen, C_1 - C_{20} alkyl, or PEG_{1-20} ;

each R^{5c} is independently C_3 - C_8 cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;

each R^6 is independently halogen, -CN, -OH, -OR^{6a}, -N₃, -NR^{6a}R^{6b}, -CO(O)R^{6c}, -C(O)OR^{6c}, -C(O)NR^{6a}R^{6b}, -NHC(O)R^{6c}, -NHC(O)OR^{6c}, -OC(O)NR^{6a}R^{6b}, C_3 - C_6 cycloalkyl, or 4 to 6 membered heterocycloalkyl; wherein

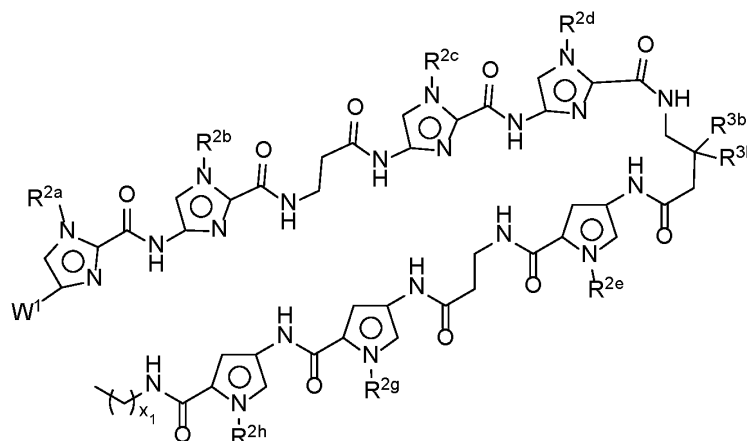
R^{6a} and R^{6b} are each independently hydrogen, C_1 - C_{20} alkyl, or PEG_{1-20} ;

R^{6c} is C_1 - C_{20} alkyl, PEG_{1-20} , C_3 - C_8 cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl; and

x is 0-10.

[0072] In some embodiments of Formula (V), (X), or (XI), at least one of R^{2a} , R^{2b} , R^{2c} , R^{2d} , R^{2e} , R^{2g} , or R^{2h} is not unsubstituted C_1 - C_{20} alkyl. In some embodiments of Formula (V), (X), or (XI), at least one of R^{2a} , R^{2b} , R^{2c} , R^{2d} , R^{2e} , R^{2g} , or R^{2h} is not methyl.

[0073] In another aspect, provided herein is a transcription modulator molecule having a structure of Formula (XII), or a pharmaceutically acceptable salt thereof:



Formula (XII),

wherein:

W^1 is hydrogen or $-N=C(N(R^{1e}))_2$, wherein each R^{1e} is independently hydrogen or C_1 - C_3 alkyl;

R^{2a} , R^{2b} , R^{2c} , R^{2d} , R^{2e} , R^{2g} , and R^{2h} are each independently hydrogen, optionally substituted C_1 - C_{50} alkyl, optionally substituted C_2 - C_{50} alkenyl, optionally substituted C_2 - C_{50} alkynyl, optionally substituted C_1 - C_{50} heteroalkyl, optionally substituted C_2 - C_{50} heteroalkenyl, optionally substituted C_2 - C_{50} heteroalkynyl, optionally substituted C_1 - C_{50} haloalkyl, optionally substituted C_3 - C_8 cycloalkyl, optionally substituted 3 to 8-membered heterocycloalkyl, or optionally substituted PEG_{1-50} ; each of which is optionally substituted with one or more R^6 ;

each R^{3b} is independently hydrogen, halogen, C_1 - C_6 alkyl, -NR^{3c}R^{3d}, -NHC(O)OR^{3c}, or -NHC(O)R^{3e};

or two R^{3b} together with the atoms to which they are attached form a C_3 - C_6 cycloalkyl or 4 to 6-membered heterocycloalkyl; wherein

R^{3c} and R^{3d} are each independently hydrogen, C_1 - C_{20} alkyl, C_1 - C_3 alkyl(phenyl), or PEG_{1-20} ;

R^{3e} is C_1 - C_{20} alkyl, PEG_{1-20} , C_3 - C_8 cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;

each R^6 is independently halogen, -CN, -OH, -OR^{6a}, -N₃, -NR^{6a}R^{6b}, -CO(O)R^{6c}, -C(O)OR^{6c}, -C(O)NR^{6a}R^{6b}, -NHC(O)R^{6c}, -NHC(O)OR^{6c}, -OC(O)NR^{6a}R^{6b}, C_3 - C_6 cycloalkyl, or 4 to 6 membered heterocycloalkyl; wherein

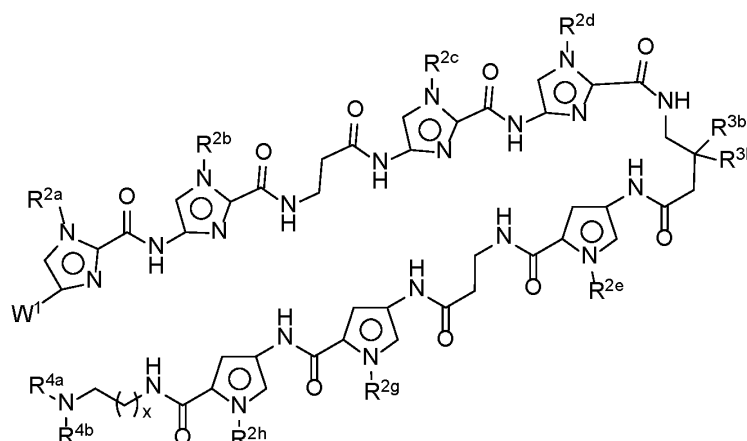
R^{6a} and R^{6b} are each independently hydrogen, C_1 - C_{20} alkyl, or PEG_{1-20} ;

R^{6c} is C_1 - C_{20} alkyl, PEG_{1-20} , C_3 - C_8 cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl; and

x_1 is 0-6.

[0074] In some embodiments of Formula (XII), x_1 is 0-6. In some embodiments of Formula (XII), x_1 is 0-3. In some embodiments of Formula (XII), x_1 is 1, 2, or 3. In some embodiments of Formula (XI), x_1 is 0. In some embodiments of Formula (XII), x_1 is 1. In some embodiments of Formula (XII), x_1 is 2. In some embodiments of Formula (XII), x_1 is 3. In some embodiments of Formula (XII), x_1 is 4. In some embodiments of Formula (XII), x_1 is 5. In some embodiments of Formula (XII), x_1 is 6.

[0075] In another aspect, provided herein is a transcription modulator molecule having a structure of Formula (XIII), or a pharmaceutically acceptable salt thereof:



Formula (XIII),

wherein:

W^1 is hydrogen or -N=C(N(R^{1e}))₂, wherein each R^{1e} is independently hydrogen or C_1 - C_3 alkyl;

R^{2a} , R^{2b} , R^{2c} , R^{2d} , R^{2e} , R^{2g} , and R^{2h} are each independently hydrogen, optionally substituted C_1 - C_{50} alkyl, optionally substituted C_2 - C_{50} alkenyl, optionally substituted C_2 - C_{50} alkynyl, optionally substituted C_1 - C_{50} heteroalkyl, optionally substituted C_2 - C_{50} heteroalkenyl, optionally substituted C_2 - C_{50} heteroalkynyl, optionally substituted C_1 - C_{50} haloalkyl, optionally substituted C_3 - C_8 cycloalkyl, optionally substituted 3 to 8-membered heterocycloalkyl, or optionally substituted PEG_{1-50} ; each of which is optionally substituted with one or more R^6 ;

each R^{3b} is independently hydrogen, halogen, C_1 - C_6 alkyl, -NR^{3c}R^{3d}, -NHC(O)OR^{3c}, or -NHC(O)R^{3e};

or two R^{3b} together with the atoms to which they are attached form a C_3 - C_6 cycloalkyl or 4 to 6-membered heterocycloalkyl; wherein

R^{3c} and R^{3d} are each independently hydrogen, C_1 - C_{20} alkyl, C_1 - C_3 alkyl(phenyl), or PEG_{1-20} ;

R^{3e} is C_1 - C_{20} alkyl, PEG_{1-20} , C_3 - C_8 cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;

R^{4a} and R^{4b} are each independently C_1 - C_3 alkyl or PEG_{1-10} ;

each R^6 is independently halogen, -CN, -OH, -OR^{6a}, -N₃, -NR^{6a}R^{6b}, -CO(O)R^{6c}, -C(O)OR^{6c}, -C(O)NR^{6a}R^{6b}, -NHC(O)R^{6c}, -NHC(O)OR^{6c}, -OC(O)NR^{6a}R^{6b}, C_3 - C_6 cycloalkyl, or 4 to 6 membered heterocycloalkyl;

wherein

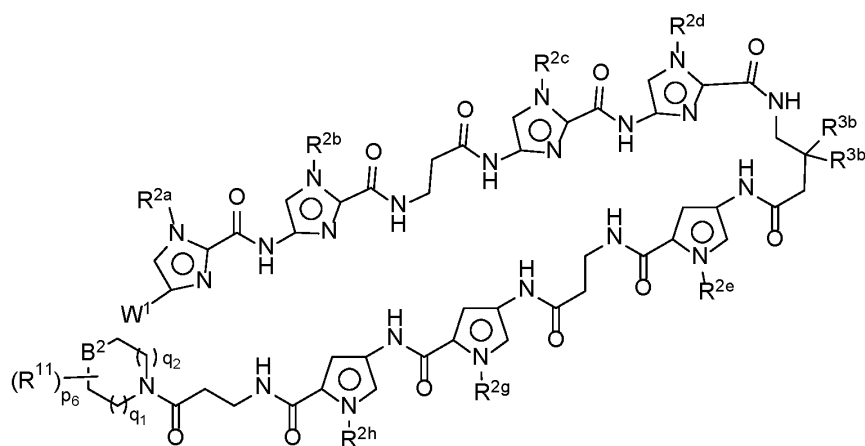
R^{6a} and R^{6b} are each independently hydrogen, C_1 - C_{20} alkyl, or PEG_{1-20} ;

R^{6c} is C_1 - C_{20} alkyl, PEG_{1-20} , C_3 - C_8 cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl; and

x is an integer from 0-10.

[0076] In some embodiments of Formula (XIII), R^{4a} and R^{4b} are each independently C_1 - C_3 alkyl. In some embodiments of Formula (XIII), R^{4a} and R^{4b} are each -CH₃. In some embodiments of Formula (XIII), R^{4a} and R^{4b} are each independently PEG_{1-10} .

[0077] In another aspect, provided herein is a transcription modulator molecule having a structure of Formula (XIV), or a pharmaceutically acceptable salt thereof:



Formula (XIV),

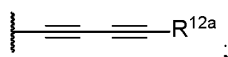
wherein:

W^1 is hydrogen or -N=C(N(R^{1e})₂)₂, wherein each R^{1e} is independently hydrogen or C_1 - C_3 alkyl;

B^2 is NR^{10a}, or CHR¹²; wherein

R^{10a} is hydrogen or C_1 - C_3 alkyl;

R¹² is an optionally substituted 4 to 6-membered heterocycloalkyl, $\text{---}R^{12a}$, or



R^{12a} is an optionally substituted 4 to 6-membered heterocycloalkyl;

R^{2a} , R^{2b} , R^{2c} , R^{2d} , R^{2e} , R^{2g} , and R^{2h} are each independently hydrogen, optionally substituted C_1 - C_{50} alkyl, optionally substituted C_2 - C_{50} alkenyl, optionally substituted C_2 - C_{50} alkynyl, optionally substituted C_1 - C_{50} heteroalkyl, optionally substituted C_2 - C_{50} heteroalkenyl, optionally substituted C_2 - C_{50} heteroalkynyl, optionally substituted C_1 - C_{50} haloalkyl, optionally substituted C_3 - C_{10} cycloalkyl, optionally substituted 3

to 10-membered heterocycloalkyl, or optionally substituted PEG₁₋₅₀; each of which is optionally substituted with one or more R⁶;

each R^{3b} is independently hydrogen, halogen, C₁-C₆ alkyl, -NR^{3c}R^{3d}, -NHC(O)OR^{3c}, or -NHC(O)R^{3e}; or two R^{3b} together with the atoms to which they are attached form a C₃-C₆ cycloalkyl or 4 to 6-membered heterocycloalkyl; wherein

R^{3c} and R^{3d} are each independently hydrogen, C₁-C₂₀ alkyl, C₁-C₃ alkyl(phenyl), or PEG₁₋₂₀;

R^{3e} is C₁-C₂₀ alkyl, PEG₁₋₂₀, C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;

each R⁶ is independently halogen, -CN, -OH, -OR^{6a}, -N₃, -NR^{6a}R^{6b}, -CO(O)R^{6c}, -C(O)OR^{6c}, -C(O)NR^{6a}R^{6b}, -NHC(O)R^{6c}, -NHC(O)OR^{6c}, -OC(O)NR^{6a}R^{6b}, C₃-C₆ cycloalkyl, or 4 to 6 membered heterocycloalkyl; wherein

R^{6a} and R^{6b} are each independently hydrogen, C₁-C₂₀ alkyl, or PEG₁₋₂₀;

R^{6c} is C₁-C₂₀ alkyl, PEG₁₋₂₀, C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;

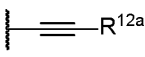
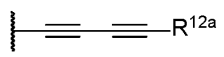
each R¹¹ is independently halogen, -CN, -OH, -N₃, or C₁-C₆ haloalkyl;

p₆ is 0, 1, 2, 3, or 4; and

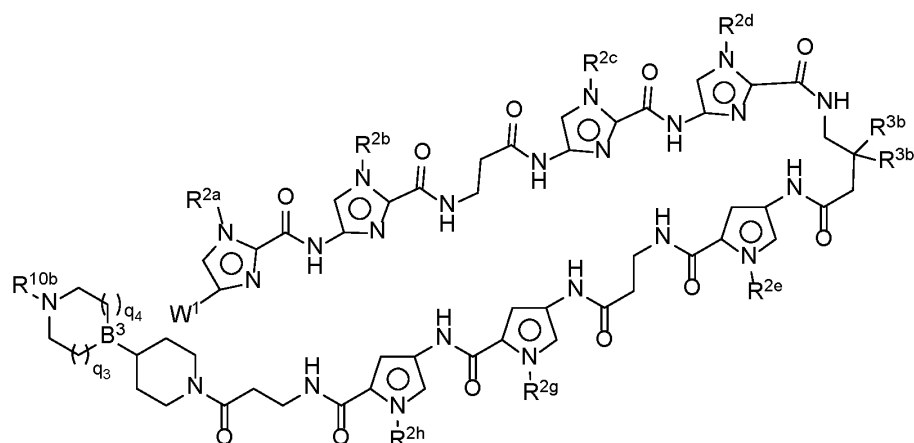
q₁ and q₂ are each independently 0, 1, or 2.

[0078] In some embodiments of Formula (XIV), B² is NR^{10a}. In some embodiments of Formula (XIV), CHR¹².

[0079] In some embodiments of Formula (XIV), R¹² is an optionally substituted 4 to 6-membered

heterocycloalkyl. In some embodiments of Formula (XIV), R¹² is . In some embodiments of Formula (XIV), R¹² is .

[0080] In another aspect, provided herein is a transcription modulator molecule having a structure of Formula (XIVa), or a pharmaceutically acceptable salt thereof:



Formula (XIVa),

wherein:

W¹ is hydrogen or -N=C(N(R^{1e}))₂, wherein each R^{1e} is independently hydrogen or C₁-C₃ alkyl;

R^{2a} , R^{2b} , R^{2c} , R^{2d} , R^{2e} , R^{2g} , and R^{2h} are each independently hydrogen, optionally substituted C_1 - C_{50} alkyl, optionally substituted C_2 - C_{50} alkenyl, optionally substituted C_2 - C_{50} alkynyl, optionally substituted C_1 - C_{50} heteroalkyl, optionally substituted C_2 - C_{50} heteroalkenyl, optionally substituted C_2 - C_{50} heteroalkynyl, optionally substituted C_1 - C_{50} haloalkyl, optionally substituted C_3 - C_8 cycloalkyl, optionally substituted 3 to 8-membered heterocycloalkyl, or optionally substituted PEG_{1-50} ; each of which is optionally substituted with one or more R^6 ;

each R^{3b} is independently hydrogen, halogen, C_1 - C_6 alkyl, $-NR^{3c}R^{3d}$, $-NHC(O)OR^{3c}$, or $-NHC(O)R^{3e}$; or two R^{3b} together with the atoms to which they are attached form a C_3 - C_6 cycloalkyl or 4 to 6-membered heterocycloalkyl; wherein

R^{3c} and R^{3d} are each independently hydrogen, C_1 - C_{20} alkyl, C_1 - C_3 alkyl(phenyl), or PEG_{1-20} ;

R^{3e} is C_1 - C_{20} alkyl, PEG_{1-20} , C_3 - C_8 cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;

each R^6 is independently halogen, $-CN$, $-OH$, $-OR^{6a}$, $-N_3$, $-NR^{6a}R^{6b}$, $-CO(O)R^{6c}$, $-C(O)OR^{6c}$, $-C(O)NR^{6a}R^{6b}$, $-NHC(O)R^{6c}$, $-NHC(O)OR^{6c}$, $-OC(O)NR^{6a}R^{6b}$, C_3 - C_6 cycloalkyl, or 4 to 6 membered heterocycloalkyl; wherein

R^{6a} and R^{6b} are each independently hydrogen, C_1 - C_{20} alkyl, or PEG_{1-20} ;

R^{6c} is C_1 - C_{20} alkyl, PEG_{1-20} , C_3 - C_8 cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl

B^3 is N or CH;

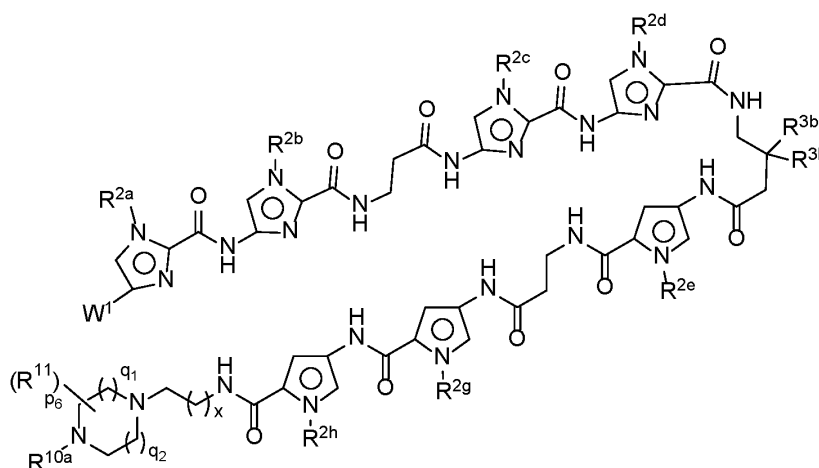
R^{10b} is hydrogen or C_1 - C_3 alkyl; and

q_3 and q_4 are each independently 0, 1, or 2.

[0081] In some embodiments of Formula (XIVa), B^3 is N. In some embodiments of Formula (XIVa), B^3 is CH.

[0082] In some embodiments of Formula (XIVa), R^{10b} is C_1 - C_3 alkyl. In some embodiment of Formula (XIVa), R^{10b} is methyl. In some embodiments of Formula (XIVa), R^{10b} is hydrogen.

[0083] In another aspect, provided herein is a transcription modulator molecule having a structure of Formula (XIVb), or a pharmaceutically acceptable salt thereof:



Formula (XIVb),

wherein:

W^1 is hydrogen or $-N=C(N(R^{1e}))_2$, wherein each R^{1e} is independently hydrogen or C_1 - C_3 alkyl;

R^{2a} , R^{2b} , R^{2c} , R^{2d} , R^{2e} , R^{2g} , and R^{2h} are each independently hydrogen, optionally substituted C_1 - C_{50} alkyl, optionally substituted C_2 - C_{50} alkenyl, optionally substituted C_2 - C_{50} alkynyl, optionally substituted C_1 - C_{50} heteroalkyl, optionally substituted C_2 - C_{50} heteroalkenyl, optionally substituted C_2 - C_{50} heteroalkynyl, optionally substituted C_1 - C_{50} haloalkyl, optionally substituted C_3 - C_8 cycloalkyl, optionally substituted 3 to 8-membered heterocycloalkyl, or optionally substituted PEG_{1-50} ; each of which is optionally substituted with one or more R^6 ;

each R^{3b} is independently hydrogen, halogen, C_1 - C_6 alkyl, $-NR^{3c}R^{3d}$, $-NHC(O)OR^{3c}$, or $-NHC(O)R^{3e}$;

or two R^{3b} together with the atoms to which they are attached form a C_3 - C_6 cycloalkyl or 4 to 6-membered heterocycloalkyl; wherein

R^{3c} and R^{3d} are each independently hydrogen, C_1 - C_{20} alkyl, C_1 - C_3 alkyl(phenyl), or PEG_{1-20} ;

R^{3e} is C_1 - C_{20} alkyl, PEG_{1-20} , C_3 - C_8 cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;

each R^6 is independently $-CN$, $-OH$, $-OR^{6a}$, $-N_3$, $-NR^{6a}R^{6b}$, $-CO(O)R^{6c}$, $-C(O)OR^{6c}$, $-C(O)NR^{6a}R^{6b}$, $-NHC(O)R^{6c}$, $-NHC(O)OR^{6c}$, or $-OC(O)NR^{6a}R^{6b}$; wherein

R^{6a} and R^{6b} are each independently hydrogen, C_1 - C_{20} alkyl, or PEG_{1-20} ;

R^{6c} is C_1 - C_{20} alkyl, PEG_{1-20} , C_3 - C_8 cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;

R^{10a} is hydrogen or C_1 - C_3 alkyl;

each R^{11} is independently halogen, $-CN$, $-OH$, $-N_3$, or C_1 - C_6 haloalkyl;

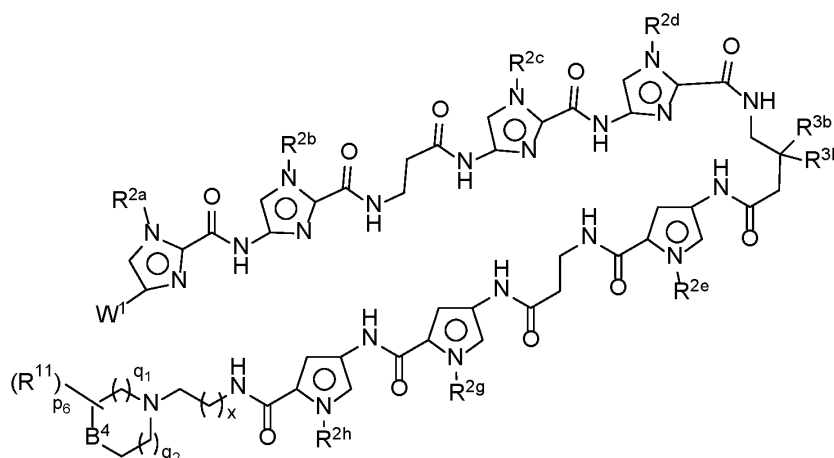
p_6 is 0, 1, 2, 3, or 4;

q_1 and q_2 are each independently 0, 1, or 2; and

x is an integer from 0-10.

[0084] In some embodiments of Formula (XIV) or (XIVb), R^{10a} is C_1 - C_3 alkyl. In some embodiments of Formula (XIV) or (XIVb), R^{10a} is methyl or ethyl. In some embodiments of Formula (XIV) or (XIVb), R^{10a} is methyl. In some embodiments of Formula (XIV) or (XIVb), R^{10a} is hydrogen.

[0085] In another aspect, provided herein is a transcription modulator molecule having a structure of Formula (XIVc), or a pharmaceutically acceptable salt thereof:



Formula (XIVc),

wherein:

W¹ is hydrogen or -N=C(N(R^{1e})₂), wherein each R^{1e} is independently hydrogen or C₁-C₃ alkyl;

R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^{2e}, R^{2g}, and R^{2h} are each independently hydrogen, optionally substituted C₁-C₅₀ alkyl, optionally substituted C₂-C₅₀ alkenyl, optionally substituted C₂-C₅₀ alkynyl, optionally substituted C₁-C₅₀ heteroalkyl, optionally substituted C₂-C₅₀ heteroalkenyl, optionally substituted C₂-C₅₀ heteroalkynyl, optionally substituted C₁-C₅₀ haloalkyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted 3 to 8-membered heterocycloalkyl, or optionally substituted PEG₁₋₅₀; each of which is optionally substituted with one or more R⁶;

each R^{3b} is independently hydrogen, halogen, C₁-C₆ alkyl, -NR^{3c}R^{3d}, -NHC(O)OR^{3c}, or -NHC(O)R^{3c};

or two R^{3b} together with the atoms to which they are attached form a C₃-C₆ cycloalkyl or 4 to 6-membered heterocycloalkyl; wherein

R^{3c} and R^{3d} are each independently hydrogen, C₁-C₂₀ alkyl, C₁-C₃ alkyl(phenyl), or PEG₁₋₂₀;

R^{3c} is C₁-C₂₀ alkyl, PEG₁₋₂₀, C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;

each R⁶ is independently halogen, -CN, -OH, -OR^{6a}, -N₃, -NR^{6a}R^{6b}, -CO(O)R^{6c}, -C(O)OR^{6c}, -C(O)NR^{6a}R^{6b}, -NHC(O)R^{6c}, -NHC(O)OR^{6c}, -OC(O)NR^{6a}R^{6b}, C₃-C₆ cycloalkyl, or 4 to 6 membered heterocycloalkyl;

wherein

R^{6a} and R^{6b} are each independently hydrogen, C₁-C₂₀ alkyl, or PEG₁₋₂₀;

R^{6c} is C₁-C₂₀ alkyl, PEG₁₋₂₀, C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;

each R¹¹ is independently halogen, -CN, -OH, -N₃, or C₁-C₆ haloalkyl;

B⁴ is O or CH₂;

p₆ is 0, 1, 2, 3, or 4;

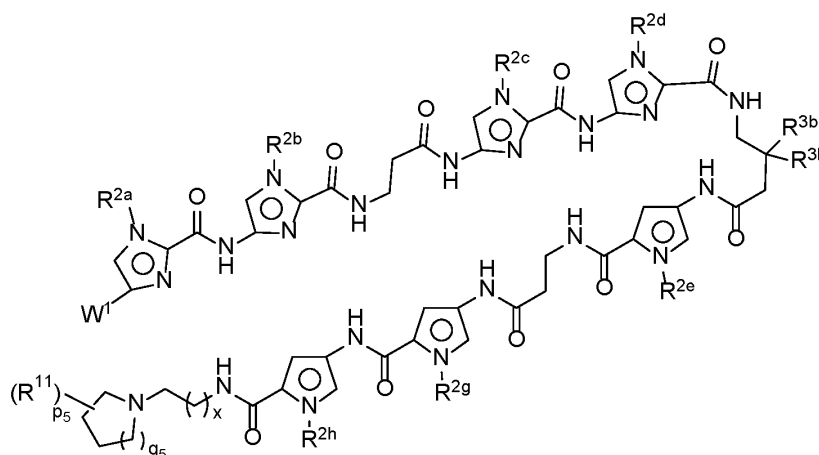
q₁ and q₂ are each independently 0, 1, or 2; and

x is an integer from 0-10.

[0086] In some embodiments of Formula (XIVc), B⁴ is O. In some embodiments of Formula (XIVc), B⁴ is CH₂.

[0087] In some embodiments of Formula (XIV), (XIVa), (XIVb), or (XIVc), p₆ is 1 or 2. In some embodiments of Formula (XIV), (XIVa), (XIVb), or (XIVc), p₆ is 0. In some embodiments of Formula (XIV), (XIVa), (XIVb), or (XIVc), p₆ is 1. In some embodiments of Formula (XIV), (XIVa), (XIVb), or (XIVc), p₆ is 2.

[0088] In another aspect, provided herein is a transcription modulator molecule having a structure of Formula (XIVd), or a pharmaceutically acceptable salt thereof:



Formula (XIVd),

wherein:

W¹ is hydrogen or -N=C(N(R^{1e})₂), wherein each R^{1e} is independently hydrogen or C₁-C₃ alkyl;

R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^{2e}, R^{2g}, and R^{2h} are each independently hydrogen, optionally substituted C₁-C₅₀ alkyl, optionally substituted C₂-C₅₀ alkenyl, optionally substituted C₂-C₅₀ alkynyl, optionally substituted C₁-C₅₀ heteroalkyl, optionally substituted C₂-C₅₀ heteroalkenyl, optionally substituted C₂-C₅₀ heteroalkynyl, optionally substituted C₁-C₅₀ haloalkyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted 3 to 8-membered heterocycloalkyl, or optionally substituted PEG₁₋₅₀; each of which is optionally substituted with one or more R⁶;

each R^{3b} is independently hydrogen, halogen, C₁-C₆ alkyl, -NR^{3c}R^{3d}, -NHC(O)OR^{3c}, or -NHC(O)R^{3e};

or two R^{3b} together with the atoms to which they are attached form a C₃-C₆ cycloalkyl or 4 to 6-membered heterocycloalkyl; wherein

R^{3c} and R^{3d} are each independently hydrogen, C₁-C₂₀ alkyl, C₁-C₃ alkyl(phenyl), or PEG₁₋₂₀;

R^{3e} is C₁-C₂₀ alkyl, PEG₁₋₂₀, C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;

each R⁶ is independently halogen, -CN, -OH, -OR^{6a}, -N₃, -NR^{6a}R^{6b}, -CO(O)R^{6c}, -C(O)OR^{6c}, -C(O)NR^{6a}R^{6b}, -NHC(O)R^{6c}, -NHC(O)OR^{6c}, -OC(O)NR^{6a}R^{6b}, C₃-C₆ cycloalkyl, or 4 to 6 membered heterocycloalkyl;

wherein

R^{6a} and R^{6b} are each independently hydrogen, C₁-C₂₀ alkyl, or PEG₁₋₂₀;

R^{6c} is C₁-C₂₀ alkyl, PEG₁₋₂₀, C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;

each R¹¹ is independently halogen, -CN, -OH, -N₃, or C₁-C₆ haloalkyl;

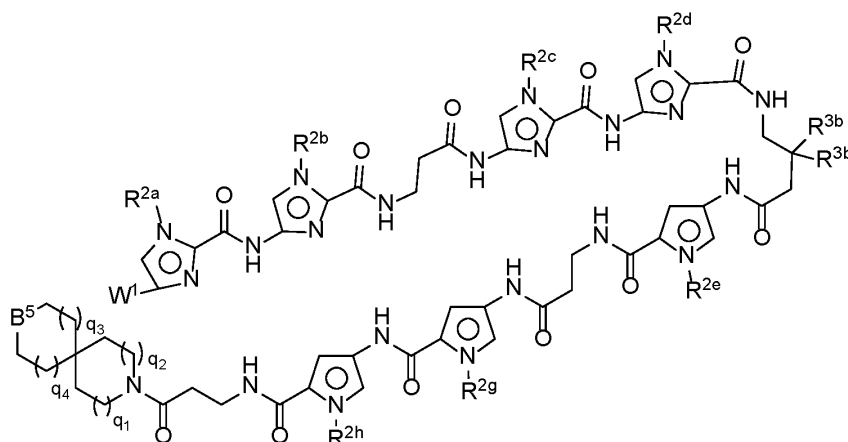
p₅ is 1, 2, 3, or 4;

q₅ is 0, 1, 2, or 3; and

x is an integer from 0-10.

[0089] In some embodiments of Formula (XIVd), p₅ is 1 or 2. In some embodiments of Formula (XIVd), p₅ is 1 and R¹¹ is halogen or C₁-C₆ haloalkyl. In some embodiments of Formula (XIVd), p₅ is 2 and R¹¹ is halogen or C₁-C₆ haloalkyl. In some embodiments of Formula (XIVd), p₅ is 1 and R⁵ is -F or -CF₃.

[0090] In another aspect, provided herein is a transcription modulator molecule having a structure of Formula (XV), or a pharmaceutically acceptable salt thereof:



Formula (XV),

wherein:

W¹ is hydrogen or -N=C(N(R^{1e}))₂, wherein each R^{1e} is independently hydrogen or C₁-C₃ alkyl;

B⁵ is NR^{10c} or O; wherein

R^{10c} is hydrogen or C₁-C₃ alkyl;

R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^{2e}, R^{2g}, and R^{2h} are each independently hydrogen, optionally substituted C₁-C₅₀ alkyl, optionally substituted C₂-C₅₀ alkenyl, optionally substituted C₂-C₅₀ alkynyl, optionally substituted C₁-C₅₀ heteroalkyl, optionally substituted C₂-C₅₀ heteroalkenyl, optionally substituted C₂-C₅₀ heteroalkynyl, optionally substituted C₁-C₅₀ haloalkyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted 3 to 8-membered heterocycloalkyl, or optionally substituted PEG₁₋₅₀; each of which is optionally substituted with one or more R⁶;

each R^{3b} is independently hydrogen, halogen, C₁-C₆ alkyl, -NR^{3c}R^{3d}, -NHC(O)OR^{3c}, or -NHC(O)R^{3e};

or two R^{3b} together with the atoms to which they are attached form a C₃-C₆ cycloalkyl or 4 to 6-membered heterocycloalkyl; wherein

R^{3c} and R^{3d} are each independently hydrogen, C₁-C₂₀ alkyl, C₁-C₃ alkyl(phenyl), or PEG₁₋₂₀;

R^{3e} is C₁-C₂₀ alkyl, PEG₁₋₂₀, C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;

each R⁶ is independently halogen, -CN, -OH, -OR^{6a}, -N₃, -NR^{6a}R^{6b}, -CO(O)R^{6c}, -C(O)OR^{6c}, -C(O)NR^{6a}R^{6b}, -NHC(O)R^{6c}, -NHC(O)OR^{6c}, -OC(O)NR^{6a}R^{6b}, C₃-C₆ cycloalkyl, or 4 to 6 membered heterocycloalkyl;

wherein

R^{6a} and R^{6b} are each independently hydrogen, C₁-C₂₀ alkyl, or PEG₁₋₂₀;

R^{6c} is C₁-C₂₀ alkyl, PEG₁₋₂₀, C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl; and

q₁, q₂, q₃, and q₄ are each independently 0, 1, or 2.

[0091] In some embodiments of Formula (XV), B⁵ is NR^{10c}. In some embodiments of Formula (XV), B⁵ is NCH₃. In some embodiments of Formula (XV), B⁵ is -NH-. In some embodiments of Formula (XV), B⁵ is -O-.

[0092] In some embodiments of Formula (XIV), (XIVb), (XIVc), or (XV), q_1 and q_2 are each 0. In some embodiments of Formula (XIV), (XIVb), (XIVc), or (XV), q_1 and q_2 are each 1. In some embodiments of Formula (XIV), (XIVb), (XIVc), or (XV), q_1 is 1 and q_2 is 0.

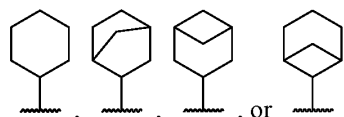
[0093] In some embodiments of Formula (XIVa) or (XV), q_3 and q_4 are each 0. In some embodiments of Formula (XIVa) or (XV), q_3 and q_4 are each 1. In some embodiments of Formula (XIVa) or (XV), q_3 is 1 and q_4 is 0.

[0094] In some embodiments of Formula (V), (VII), (VIIIb), (VIIIc), (VIId), (XI), (XIII), (XIVb), (XIVc), or (XIVd), x is 1-10. In some embodiments of Formula (V), (VII), (VIIIb), (VIIIc), (VIId), (XI), (XIII), (XIVb), (XIVc), or (XIVd), x is 1-8. In some embodiments of Formula (V), x is 1-6. In some embodiments of Formula (V), (VII), (VIIIb), (VIIIc), (VIId), (XI), (XIII), (XIVb), (XIVc), or (XIVd), x is 1, 2, 3, 4, or 5. In some embodiments of Formula (V), (VII), (VIIIb), (VIIIc), (VIId), (XI), (XIII), (XIVb), (XIVc), or (XIVd), x is 1, 2, 3, 4. In some embodiments of Formula (V), (VII), (VIIIb), (VIIIc), (VIId), (XI), (XIII), (XIVb), (XIVc), or (XIVd), x is 0. In some embodiments of Formula (V), (VII), (VIIIb), (VIIIc), (VIId), (XI), (XIII), (XIVb), (XIVc), or (XIVd), x is 1. In some embodiments of Formula (V), (VII), (VIIIb), (VIIIc), (VIId), (XI), (XIII), (XIVb), (XIVc), or (XIVd), x is 2. In some embodiments of Formula (V), (VII), (VIIIb), (VIIIc), (VIId), (XI), (XIII), (XIVb), (XIVc), or (XIVd), x is 3. In some embodiments of Formula (V), (VII), (VIIIb), (VIIIc), (VIId), (XI), (XIII), (XIVb), (XIVc), or (XIVd), x is 4. In some embodiments of Formula (V), (VII), (VIIIb), (VIIIc), (VIId), (XI), (XIII), (XIVb), (XIVc), or (XIVd), x is 5. In some embodiments of Formula (V), (VII), (VIIIb), (VIIIc), (VIId), (XI), (XIII), (XIVb), (XIVc), or (XIVd), x is 6. In some embodiments of Formula (V), (VII), (VIIIb), (VIIIc), (VIId), (XI), (XIII), (XIVb), (XIVc), or (XIVd), x is 7. In some embodiments of Formula (V), (VII), (VIIIb), (VIIIc), (VIId), (XI), (XIII), (XIVb), (XIVc), or (XIVd), x is 8. In some embodiments of Formula (V), (VII), (VIIIb), (VIIIc), (VIId), (XI), (XIII), (XIVb), (XIVc), or (XIVd), x is 9. In some embodiments of Formula (V), (VII), (VIIIb), (VIIIc), (VIId), (XI), (XIII), (XIVb), (XIVc), or (XIVd), x is 10.

[0095] In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), R^{2a} , R^{2b} , R^{2c} , R^{2d} , R^{2e} , R^{2g} , and R^{2h} are each independently hydrogen, optionally substituted C_1 - C_{20} alkyl, optionally substituted C_1 - C_{20} heteroalkyl, optionally substituted C_1 - C_{20} haloalkyl, optionally substituted C_3 - C_8 cycloalkyl, optionally substituted 3 to 8-membered heterocycloalkyl, or optionally substituted PEG₁₋₂₀; each of which is optionally substituted with one or more R^6 .

[0096] In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), R^{2a} , R^{2b} , R^{2c} , R^{2d} , R^{2e} , R^{2g} , and R^{2h} are each independently an optionally substituted C_3 - C_8 cycloalkyl or optionally substituted 3 to 8-membered heterocycloalkyl, wherein the cycloalkyl or heterocycloalkyl is a monocyclic, bridged, or spirocyclic cycloalkyl or heterocycloalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), R^{2a} , R^{2b} , R^{2c} , R^{2d} , R^{2e} , R^{2g} , and R^{2h} are each

independently an optionally substituted C₃-C₈ cycloalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^{2e}, R^{2g}, and R^{2h} are each independently cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^{2e}, R^{2g}, and R^{2h} are each



independently , , , or .

[0097] In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^{2e}, R^{2g}, and R^{2h} is independently an optionally substituted C₁-C₂₀ alkyl, C₁-C₂₀ heteroalkyl, optionally substituted C₁-C₂₀ haloalkyl, or optionally substituted PEG₁₋₂₀; each of which is optionally substituted with one or more R⁶. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^{2e}, R^{2g}, and R^{2h} are each independently PEG₁₋₂₀. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^{2e}, R^{2g}, and R^{2h} are each independently an optionally substituted C₁-C₂₀ alkyl or optionally substituted C₁-C₂₀ haloalkyl; each of which is optionally substituted with one or more R⁶. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^{2e}, R^{2g}, and R^{2h} are each independently C₁-C₂₀ alkyl, optionally substituted with one or more R⁶. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^{2e}, R^{2g}, and R^{2h} are each independently C₁-C₂₀ haloalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^{2e}, R^{2g}, and R^{2h} are each independently methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, cyclohexyl, -CF₃, or -CH₂CF₃. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^{2e}, R^{2g}, and R^{2h} are each independently methyl, ethyl, propyl, hexyl, cyclohexyl, -CF₃, or -CH₂CF₃. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^{2e}, R^{2g}, and R^{2h} are each independently methyl, ethyl, propyl, cyclohexyl, or -CH₂CF₃. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb),

(XIVc), (XIVd), or (XV), R^{2a} , R^{2b} , R^{2c} , R^{2d} , R^{2e} , R^{2g} , and R^{2h} are each methyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), R^{2a} , R^{2b} , R^{2c} , R^{2d} , R^{2e} , R^{2g} , and R^{2h} are each propyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), R^{2a} , R^{2b} , R^{2c} , R^{2d} , R^{2e} , R^{2g} , and R^{2h} are each cyclohexyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), R^{2a} , R^{2b} , R^{2c} , R^{2d} , R^{2e} , R^{2g} , and R^{2h} are each $-\text{CH}_2\text{CF}_3$.

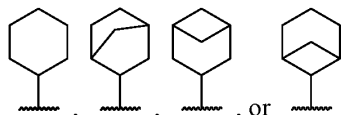
[0098] In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), at least one of R^{2a} , R^{2b} , R^{2c} , R^{2d} , R^{2e} , R^{2g} , or R^{2h} is not unsubstituted $\text{C}_1\text{-C}_{20}$ alkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), at least one of R^{2a} , R^{2b} , R^{2c} , R^{2d} , R^{2e} , R^{2g} , or R^{2h} is not methyl.

[0099] In some embodiments of Formula (IV) or (IVa), R^{2a} , R^{2c} , R^{2d} , R^{2e} , and R^{2h} are each independently hydrogen, optionally substituted $\text{C}_1\text{-C}_{20}$ alkyl, optionally substituted $\text{C}_1\text{-C}_{20}$ heteroalkyl, optionally substituted $\text{C}_1\text{-C}_{20}$ haloalkyl, optionally substituted $\text{C}_3\text{-C}_6$ cycloalkyl, or optionally substituted PEG_{1-20} ; each of which is optionally substituted with one or more R^6 . In some embodiments of Formula (IV) or (IVa), R^{2a} , R^{2c} , R^{2d} , R^{2e} , and R^{2h} are each independently an optionally substituted $\text{C}_1\text{-C}_{20}$ alkyl or optionally substituted $\text{C}_1\text{-C}_{20}$ haloalkyl; each of which is optionally substituted with one or more R^6 . In some embodiments of Formula (IV) or (IVa), R^{2a} , R^{2c} , R^{2d} , R^{2e} , and R^{2h} are each independently $\text{C}_1\text{-C}_{20}$ alkyl, optionally substituted with one or more R^6 . In some embodiments of Formula (IV) or (IVa), R^{2a} , R^{2c} , R^{2d} , R^{2e} , and R^{2h} are each independently methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, cyclohexyl, $-\text{CF}_3$, or $-\text{CH}_2\text{CF}_3$. In some embodiments of Formula (IV) or (IVa), R^{2a} , R^{2c} , R^{2d} , R^{2e} , and R^{2h} are each independently methyl, ethyl, propyl, cyclohexyl, or $-\text{CH}_2\text{CF}_3$. In some embodiments of Formula (IV) or (IVa), R^{2a} , R^{2c} , R^{2d} , R^{2e} , and R^{2h} are each independently methyl, ethyl, propyl, or $-\text{CH}_2\text{CF}_3$. In some embodiments of Formula (IV) or (IVa), R^{2a} , R^{2c} , R^{2d} , R^{2e} , and R^{2h} are each methyl. In some embodiments of Formula (IV) or (IVa), R^{2a} , R^{2c} , R^{2d} , R^{2e} , and R^{2h} are each propyl. In some embodiments of Formula (IV) or (IVa), R^{2a} , R^{2c} , R^{2d} , R^{2e} , and R^{2h} are each $-\text{CH}_2\text{CF}_3$. In some embodiments of Formula (IV) or (IVa), R^{2a} , R^{2c} , R^{2d} , R^{2e} , and R^{2h} are each cyclohexyl.

[00100] In some embodiments of Formula (IV) or (IVa), at least one of R^{2a} , R^{2c} , R^{2d} , R^{2e} , or R^{2h} is not unsubstituted $\text{C}_1\text{-C}_{20}$ alkyl. In some embodiments of Formula (IV) or (IVa), at least one of R^{2a} , R^{2c} , R^{2d} , R^{2e} , or R^{2h} is not methyl.

[00101] In some embodiments of Formula (A-1), (A-2), or (A-3), R^{2f} is hydrogen, optionally substituted $\text{C}_1\text{-C}_{20}$ alkyl, optionally substituted $\text{C}_1\text{-C}_{20}$ heteroalkyl, optionally substituted $\text{C}_1\text{-C}_{20}$ haloalkyl, optionally substituted $\text{C}_3\text{-C}_8$ cycloalkyl, optionally substituted 3 to 8-membered heterocycloalkyl, or optionally substituted PEG_{1-20} ; each of which is optionally substituted with one or more R^6 . In some embodiments of

Formula (A-1), (A-2), or (A-3), R^{2f} is an optionally substituted C_3 - C_8 cycloalkyl or optionally substituted 3 to 8-membered heterocycloalkyl, wherein the cycloalkyl or heterocycloalkyl is a monocyclic, bridged, or spirocyclic cycloalkyl or heterocycloalkyl. In some embodiments of Formula (A-1), (A-2), or (A-3), R^{2f} is an optionally substituted C_3 - C_8 cycloalkyl. In some embodiments of Formula (A-1), (A-2), or (A-3), R^{2f} is



. In some embodiments of Formula (A-1), (A-2), or (A-3), R^{2h} is an optionally substituted C_1 - C_{20} alkyl or optionally substituted C_1 - C_{20} haloalkyl; each of which is optionally substituted with one or more R^6 . In some embodiments of Formula (A-1), (A-2), or (A-3), R^{2h} is C_1 - C_{20} alkyl, optionally substituted with one or more R^6 . In some embodiments of Formula (A-1), (A-2), or (A-3), R^{2f} are each independently methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, cyclohexyl, $-CF_3$, or $-CH_2CF_3$. In some embodiments of Formula (A-1), (A-2), or (A-3), R^{2f} is methyl, ethyl, propyl, or $-CH_2CF_3$. In some embodiments of Formula (A-1), (A-2), or (A-3), R^{2f} is methyl. In some embodiments of Formula (A-1), (A-2), or (A-3), R^{2f} are each propyl. In some embodiments of Formula (A-1), (A-2), or (A-3), R^{2f} are each cyclohexyl. In some embodiments of Formula (A-1), (A-2), or (A-3), R^{2f} is $-CH_2CF_3$.

[00102] In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), or (X), each R^{3a} is independently hydrogen, $-NR^{3e}R^{3d}$, or $-NHC(O)R^{3e}$. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), or (X), each R^{3a} is independently hydrogen or $-NHC(O)R^{3e}$. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), or (X), each R^{3a} is hydrogen.

[00103] In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), each R^{3b} is independently hydrogen, $-NR^{3e}R^{3d}$, or $-NHC(O)R^{3e}$. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), each R^{3b} is independently hydrogen or $-NHC(O)R^{3e}$. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), each R^{3b} is hydrogen.

[00104] In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), or (X), two R^{3a} together with the carbon atom to which they are attached form a C_3 - C_6 cycloalkyl or 4 to 6-membered heterocycloalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), or (X), two R^{3a} together with the carbon atom to which they are attached form a C_3 - C_6 cycloalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), or (X), two R^{3a} together with the carbon atom to which they are attached form a cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), or (X), two R^{3a} together with the carbon atom to which they are attached form a cyclopropyl or cyclobutyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), or (X), two R^{3a} together with the carbon atom to which they are attached form a cyclopropyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), or (X), two R^{3a} together with the carbon atom to which they are attached form a cyclobutyl. In some

embodiments of Formula (A-1), (A-2), (A-3), (I), (II), or (X), two R^{3a} together with the carbon atom to which they are attached form a 4 to 6-membered heterocycloalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), or (X), two R^{3a} together with the carbon atom to which they are attached form a 4-membered heterocycloalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), or (X), two R^{3a} together with the carbon atom to which they are attached form a 5-membered heterocycloalkyl.

[00105] In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), two R^{3b} together with the carbon atom to which they are attached form a C_3 - C_6 cycloalkyl or 4 to 6-membered heterocycloalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), two R^{3b} together with the carbon atom to which they are attached form a C_3 - C_6 cycloalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), two R^{3b} together with the carbon atom to which they are attached form a cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), two R^{3b} together with the carbon atom to which they are attached form a cyclopropyl or cyclobutyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), two R^{3b} together with the carbon atom to which they are attached form a cyclopropyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), two R^{3b} together with the carbon atom to which they are attached form a cyclobutyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), two R^{3b} together with the carbon atom to which they are attached form a 4 to 6-membered heterocycloalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), two R^{3b} together with the carbon atom to which they are attached form a 4-membered heterocycloalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), two R^{3b} together with the carbon atom to which they are attached form a 5-membered heterocycloalkyl.

[00106] In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), or (X), one of R^{3a} and one of R^{3b} together with the atoms to which they are attached form a C_3 - C_6 cycloalkyl or 4 to 6-membered heterocycloalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), or (X), one of R^{3a} and one of R^{3b} together with the atoms to which they are attached form a C_3 - C_6 cycloalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), or (X), one of R^{3a} and one of R^{3b} together with the atoms to which they

are attached form a cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), or (X), one of R^{3a} and one of R^{3b} together with the atoms to which they are attached form a cyclopropyl or cyclobutyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), or (X), one of R^{3a} and one of R^{3b} together with the atoms to which they are attached form a cyclopropyl. In some embodiments of Formula (A-2), (A-3), (I), (II), or (X), one of R^{3a} and one of R^{3b} together with the atoms to which they are attached form a 4 to 6-membered heterocycloalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), or (X), one of R^{3a} and one of R^{3b} together with the atoms to which they are attached form a 4-membered heterocycloalkyl. In some embodiments of Formula (A-2), (A-3), (I), (II), or (X), one of R^{3a} and one of R^{3b} together with the atoms to which they are attached form a 5-membered heterocycloalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), or (X), one of R^{3a} and one of R^{3b} together with the atoms to which they are attached form a 6-membered heterocycloalkyl.

[00107] In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), Z is absent, -C(O)-, or -C(=NH)-. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), Z is absent or -C(O)-. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), Z is absent. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), Z is -C(O)-. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), Z is -C(=NH)-.

[00108] In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), or (X), L is C_1 - C_{20} alkylene or C_2 - C_{20} heteroalkylene. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), or (X), L is C_1 - C_{20} alkylene. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), or (X), L is C_1 - C_{10} alkylene. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), or (X), L is C_1 - C_8 alkylene. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), or (X), L is C_1 - C_6 alkylene. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), or (X), L is C_1 - C_4 alkylene. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), or (X), L is C_1 - C_3 alkylene. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), or (X), L is C_1 - C_2 alkylene. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), or (X), L is C_2 - C_{20} heteroalkylene. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), or (X), L is C_2 - C_{10} heteroalkylene. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), or (X), L is C_2 - C_8 heteroalkylene. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), or (X), L is C_2 - C_6 heteroalkylene. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), or (X), L is C_2 - C_4 heteroalkylene. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), or (X), the heteroalkylene is polyethylene glycol. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), or (X), L is $-(CH_2CH_2-O)_{y1}-$, wherein y_1 is an integer in the range of 1-10. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), or (X), the heteroalkylene comprises $-(CH_2)_{x3}N(R^a)(CH_2)_{x4}-$, wherein R^a is

hydrogen, optionally substituted C₁-C₆ alkyl, or optionally substituted C₁-C₆ haloalkyl; and each x₃ and x₄ is independently an integer in the range of 1-6. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), or (X), L is absent.

[00109] In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R⁴ is C₁-C₈ alkyl, C₃-C₁₀ cycloalkyl, 4 to 12-membered heterocycloalkyl, or -NR^{4a}R^{4b}; wherein

R^{4a} is hydrogen, optionally substituted C₁-C₂₀ alkyl, or optionally substituted C₁-C₂₀ heteroalkyl, each of which is optionally substituted with one or more R⁵;

R^{4b} is hydrogen, optionally substituted C₁-C₂₀ alkyl, optionally substituted C₁-C₂₀ haloalkyl, optionally substituted C₁-C₂₀ heteroalkyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted 4 to 12-membered heterocycloalkyl, or optionally substituted 5 to 10-membered heteroaryl, each of which is optionally substituted with one or more R⁵; or

R^{4a} and R^{4b} together with the nitrogen to which they are attached form an optionally substituted 4 to 12-membered heterocycloalkyl which is optionally substituted with one or more R⁵;

each R⁵ is independently halogen, -CN, -OH, -OR^{5a}, -N₃, -NR^{5a}R^{5b}, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted 4 to 8-membered heterocycloalkyl, or optionally substituted phenyl, each of which is optionally substituted with one or more R^{5c};

R^{5a} and R^{5b} are each independently hydrogen, C₁-C₂₀ alkyl, or PEG₁₋₂₀; and

each R^{5c} is independently C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl.

[00110] In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R⁴ is C₁-C₈ alkyl or -NR^{4a}R^{4b}; wherein

R^{4a} is hydrogen, optionally substituted C₁-C₂₀ alkyl, or optionally substituted C₁-C₂₀ heteroalkyl, each of which is optionally substituted with one or more R⁵;

R^{4b} is hydrogen, optionally substituted C₁-C₂₀ alkyl, optionally substituted C₁-C₂₀ haloalkyl, or optionally substituted C₁-C₂₀ heteroalkyl, each of which is optionally substituted with one or more R⁵; or

R^{4a} and R^{4b} together with the nitrogen to which they are attached form an optionally substituted 4 to 12-membered heterocycloalkyl which is optionally substituted with one or more R⁵;

each R⁵ is independently halogen, -CN, -OH, -OR^{5a}, -N₃, -NR^{5a}R^{5b}, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted 4 to 8-membered heterocycloalkyl, or optionally substituted phenyl, each of which is optionally substituted with one or more R^{5c};

R^{5a} and R^{5b} are each independently hydrogen, C₁-C₂₀ alkyl, or PEG₁₋₂₀; and

each R^{5c} is independently C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl.

[00111] In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R⁴ is C₁-C₈ alkyl or -NR^{4a}R^{4b}; wherein

R^{4a} is hydrogen, optionally substituted C₁-C₂₀ alkyl, or optionally substituted C₁-C₂₀ heteroalkyl, each of which is optionally substituted with one or more R⁵;

R^{4b} is optionally substituted C₁-C₂₀ alkyl, optionally substituted C₁-C₂₀ haloalkyl, or optionally substituted C₁-C₂₀ heteroalkyl, each of which is optionally substituted with one or more R⁵; or

R^{4a} and R^{4b} together with the nitrogen to which they are attached form an optionally substituted 4 to 12-membered heterocycloalkyl which is optionally substituted with one or more R⁵;

each R⁵ is independently halogen, -CN, -OH, -OR^{5a}, -N₃, -NR^{5a}R^{5b}, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted 4 to 8-membered heterocycloalkyl, or optionally substituted phenyl, each of which is optionally substituted with one or more R^{5c},

R^{5a} and R^{5b} are each independently hydrogen, C₁-C₂₀ alkyl, or PEG₁₋₂₀; and

each R^{5c} is independently C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl.

[00112] In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R⁴ is C₁-C₈ alkyl, C₃-C₁₀ cycloalkyl, or 4 to 12-membered heterocycloalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R⁴ is C₃-C₁₀ cycloalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R⁴ is 4 to 12-membered heterocycloalkyl, wherein the heterocycloalkyl is a monocyclic, bicyclic, bridge, or spirocyclic heterocycloalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R⁴ is C₃-C₁₀ cycloalkyl, wherein the cycloalkyl is a monocyclic, bicyclic, bridge, or spirocyclic cycloalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R⁴ is C₁-C₈ alkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R⁴ is C₁-C₆ alkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R⁴ is C₁-C₄ alkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R⁴ is methyl, ethyl, propyl, or butyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R⁴ is methyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R⁴ is ethyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R⁴ is propyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R⁴ is butyl.

[00113] In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R⁴ is -NR^{4a}R^{4b}.

[00114] In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), or (X), R⁴ is -OR^{4b}.

[00115] In some embodiments of

[00116] or (XI), q₈ and q₉ are each 0. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), q₈ and q₉ are each 1. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), q₈ is 0 and q₉ is 1.

[00117] In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), B¹ is -CR^{8a}R^{8a}-, -O-, or -NR^{8b}-. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), B¹ is -S-, -S(O)-, or -S(O)₂-. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), B¹ is -CR^{8a}R^{8a}-. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), B¹ is -O-. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), B¹ is -NR^{8b}-. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), B¹ is -NH-. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), B¹ is -NCH₃-. Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{4a} is hydrogen, optionally substituted C₁-C₂₀ alkyl, or optionally substituted C₁-C₂₀ heteroalkyl, each of which is optionally substituted with one or more R⁵. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{4a} is optionally substituted C₁-C₂₀ alkyl or optionally substituted C₁-C₂₀ heteroalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{4a} is optionally substituted C₁-C₁₀ alkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{4a} is optionally substituted C₁-C₈ alkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (VII), (X), or (XI), R^{4a} is optionally substituted C₁-C₆ alkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{4a} is optionally substituted C₁-C₁₀ heteroalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{4a} is optionally substituted C₁-C₈ heteroalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{4a} is optionally substituted C₁-C₆ heteroalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{4a} is hydrogen.

[00118] In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{4b} is optionally substituted C₁-C₂₀ alkyl, optionally substituted C₁-C₂₀ haloalkyl, optionally substituted C₁-C₂₀ heteroalkyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted 4 to 12-membered heterocycloalkyl, or optionally substituted 5 to 10-membered heteroaryl, each of which is optionally substituted with one or more R⁵. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{4b} is optionally substituted C₁-C₂₀ alkyl or optionally substituted C₁-C₂₀ heteroalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{4b} is optionally substituted C₁-C₁₀ alkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{4b} is optionally substituted C₁-C₈ alkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{4b} is optionally substituted C₁-C₆ alkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{4b} is optionally substituted C₁-C₁₀ heteroalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{4b} is optionally substituted C₁-C₈ heteroalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (VI), (X), or (XI), R^{4b} is optionally substituted C₁-C₆ heteroalkyl. In some embodiments of

Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{4b} is optionally substituted C₁-C₁₀ haloalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{4b} is optionally substituted C₁-C₈ haloalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{4b} is optionally substituted C₁-C₆ haloalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{4b} is hydrogen.

[00119] In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{4b} is optionally substituted C₃-C₁₀ cycloalkyl or optionally substituted 4 to 12-membered heterocycloalkyl.

[00120] In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (VII), (X), or (XI), R^{4b} is optionally substituted C₃-C₁₀ cycloalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{4b} is optionally substituted C₃-C₈ cycloalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{4b} is optionally substituted cyclopropyl, optionally substituted cyclobutyl, optionally substituted cyclopentyl, or optionally substituted cyclohexyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{4b} is optionally substituted cyclopropyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{4b} is optionally substituted cyclobutyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (VI), (X), or (XI), R^{4b} is optionally substituted cyclopentyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{4b} is optionally substituted cyclohexyl.

[00121] In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{4b} is optionally substituted 4 to 12-membered heterocycloalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{4b} is optionally substituted 4 to 10-membered heterocycloalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{4b} is optionally substituted 4 to 6-membered heterocycloalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{4b} is optionally substituted piperidine, optionally substituted piperazine, or optionally substituted morpholine. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (VI), (X), or (XI), R^{4b} is optionally substituted piperidine. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{4b} is optionally substituted piperazine. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{4b} is optionally substituted morpholine.

[00122] In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{4a} is optionally substituted C₁-C₂₀ alkyl or optionally substituted C₁-C₂₀ heteroalkyl; and R^{4b} is optionally substituted C₁-C₂₀ alkyl or optionally substituted C₁-C₂₀ heteroalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IVa), (IVa), (V), (X), or (XI), R^{4a} is C₁-C₂₀ alkyl; and R^{4b} is C₁-C₂₀ alkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V),

(VII), (X), or (XI), R^{4a} is methyl and R^{4b} is methyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{4a} is hydrogen and R^{4b} is hydrogen.

[00123] In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{4a} and R^{4b} together with the nitrogen to which they are attached form an optionally substituted 4 to 12-membered heterocycloalkyl which is optionally substituted with one or more R^5 and wherein the heterocycloalkyl is monocyclic, bicyclic, bridged, or spirocyclic. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{4a} and R^{4b} together with the nitrogen to which they are attached form an optionally substituted 6 to 12-membered monocyclic, bridged, or spirocyclic heterocycloalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{4a} and R^{4b} together with the nitrogen to which they are attached form an optionally substituted 4 to 10-membered heterocycloalkyl which is optionally substituted with one or more R^5 . In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (IX), or (X), R^{4a} and R^{4b} together with the nitrogen to which they are attached form an optionally substituted 4 to 6-membered heterocycloalkyl, which is optionally substituted with one or more R^5 . In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{4a} and R^{4b} together with the nitrogen to which they are attached form an optionally substituted piperidine, optionally substituted piperazine, or optionally substituted morpholine. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{4a} and R^{4b} together with the nitrogen to which they are attached form an optionally substituted piperidine. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{4a} and R^{4b} together with the nitrogen to which they are attached form an optionally substituted piperazine. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{4a} and R^{4b} together with the nitrogen to which they are attached form an optionally substituted morpholine.

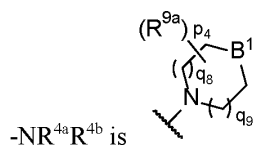
[00124] In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), each R^5 is independently halogen, -CN, -OH, -OR^{5a}, -N₃, -NR^{5a}R^{5b}, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted 4 to 8-membered heterocycloalkyl, or optionally substituted phenyl, each of which is optionally substituted with one or more R^{5c} . In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), each R^5 is independently halogen, -OH, -OR^{5a}, -NR^{5a}R^{5b}, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted 4 to 8-membered heterocycloalkyl, or optionally substituted phenyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), each R^5 is independently an optionally substituted C₂-C₆ alkenyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), each R^5 is independently an optionally substituted C₂-C₆ alkynyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), each R^5 is independently halogen. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), each

R^5 is independently optionally substituted C_3 - C_8 cycloalkyl, optionally substituted 4 to 8-membered heterocycloalkyl, or optionally substituted phenyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), each R^5 is independently C_3 - C_8 cycloalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), each R^5 is independently optionally substituted 4 to 8-membered heterocycloalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), each R^5 is independently optionally substituted phenyl.

[00125] In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{5a} and R^{5b} are each independently hydrogen, C_1 - C_{20} alkyl, or PEG_{1-20} . In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{5a} and R^{5b} are each independently C_1 - C_{20} alkyl or PEG_{1-20} . In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{5a} and R^{5b} are each independently C_1 - C_{10} alkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), (R^{5a} and R^{5b} are each independently PEG_{1-10} . In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{5a} and R^{5b} are each independently hydrogen.

[00126] In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), each R^{5c} is independently C_3 - C_8 cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), each R^{5c} is independently C_3 - C_8 cycloalkyl or 4 to 8-membered heterocycloalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), each R^{5c} is independently C_3 - C_8 cycloalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (VII), (X), or (XI), each R^{5c} is independently 4 to 8-membered heterocycloalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), each R^{5c} is independently phenyl.

[00127] In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI),



wherein:

q_8 and q_9 are each independently 0, 1, or 2;

p_4 is 0-4;

B^1 is $-CR^{8a}R^{8a}-$, $-O-$, $-NR^{8b}-$, $-S-$, $-S(O)-$, or $-S(O)_2-$; or B^1 is $\text{---}L^2\text{---}(\text{B})\text{---}(R^{9b})_{p_3}$, wherein

L^2 is absent, C_1 - C_4 alkylene, C_2 - C_4 alkenylene, C_2 - C_4 alkynylene, or phenylene;

ring B is absent, C_3 - C_6 cycloalkyl, 4 to 6-membered heterocycloalkyl, phenyl, or 5 to 10-membered heteroaryl;

R^{8a} is hydrogen, halogen, -OH, -NH₂, -N(CH₃)₂, optionally substituted C₁-C₁₀ alkyl, optionally substituted C₁-C₁₀ haloalkyl, optionally substituted C₁-C₁₀ heteroalkyl; or two R^{8a} together with the carbon atom to which they are attached form an optionally substituted C₃-C₆ cycloalkyl or optionally substituted 4 to 6-membered heterocycloalkyl;

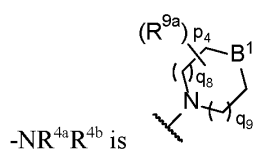
R^{8b} is hydrogen, optionally substituted C₁-C₁₀ alkyl, optionally substituted C₁-C₁₀ haloalkyl, optionally substituted C₁-C₁₀ heteroalkyl, -C(O)OR^{8c}, or -C(O)R^{8c}; or

R^{8c} is hydrogen, optionally substituted C₁-C₆ alkyl or optionally substituted C₁-C₆ haloalkyl;

each of R^{9a} or R^{9b} is independently halogen, -OH, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₃-C₆ cycloalkyl, or 4 to 6-membered heterocycloalkyl; and

p_3 is 0, 1, or 2.

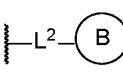
[00128] In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI),



wherein:

q_8 and q_9 are each independently 0 or 1;

p_4 is 0-4;

B^1 is -CR^{8a}R^{8a}-, -O-, -NR^{8b}-, or B^1 is , wherein

L^2 is absent or C₂-C₄ alkynylene;

ring B is absent, C₃-C₆ cycloalkyl, 4 to 6-membered heterocycloalkyl, phenyl, or 6-membered heteroaryl;

R^{8a} is hydrogen, halogen, optionally substituted C₁-C₁₀ alkyl, or optionally substituted C₁-C₁₀ haloalkyl; two R^{8a} together with the carbon atom to which they are attached form an optionally substituted 4 to 6-membered heterocycloalkyl;

R^{8b} is hydrogen, optionally substituted C₁-C₁₀ alkyl or optionally substituted C₁-C₁₀ haloalkyl;

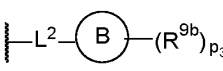
R^{8c} is hydrogen or optionally substituted C₁-C₆ alkyl;

each of R^{9a} or R^{9b} is independently halogen, -OH, C₁-C₃ alkyl, or C₁-C₃ haloalkyl; and

p_3 is 0 or 1.

[00129] In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X),

[00130] In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X),

or (XI), B^1 is .

[00131] In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), ring B is absent, C₃-C₆ cycloalkyl, 4 to 6-membered heterocycloalkyl, phenyl, or 5 to 6-membered heteroaryl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X),

or (XI), ring B is C₃-C₆ cycloalkyl or 4 to 6-membered heterocycloalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), ring B is phenyl or 6-membered heteroaryl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), ring B is phenyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), ring B is absent.

[00132] In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), L² is absent or C₂-C₄ alkynylene. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), L² is C₂-C₄ alkynylene. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), L² is C₂ alkynylene. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), L² is phenylene. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), L² is absent.

[00133] In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{8a} is hydrogen, halogen, -OH, optionally substituted C₁-C₁₀ alkyl, optionally substituted C₁-C₁₀ heteroalkyl, or optionally substituted C₁-C₁₀ haloalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{8a} is hydrogen, halogen, -OH, optionally substituted C₁-C₁₀ alkyl, or optionally substituted C₁-C₁₀ haloalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{8a} is halogen. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{8a} is optionally substituted C₁-C₁₀ alkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{8a} is optionally substituted C₁-C₁₀ heteroalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{8a} is optionally substituted C₁-C₁₀ haloalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{8a} is hydrogen.

[00134] In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), two R^{8a} together with the carbon atom to which they are attached form an optionally substituted C₃-C₆ cycloalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), two R^{8a} together with the carbon atom to which they are attached form an optionally substituted 4 to 6-membered heterocycloalkyl.

[00135] In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{8b} is optionally substituted C₁-C₁₀ alkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{8b} is optionally substituted C₁-C₁₀ heteroalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{8b} is optionally substituted C₁-C₁₀ haloalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{8b} is -C(O)OR^{8c} or -C(O)R^{8c}. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{8b} is hydrogen.

[00136] In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{8c} is optionally substituted C₁-C₆ alkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I),

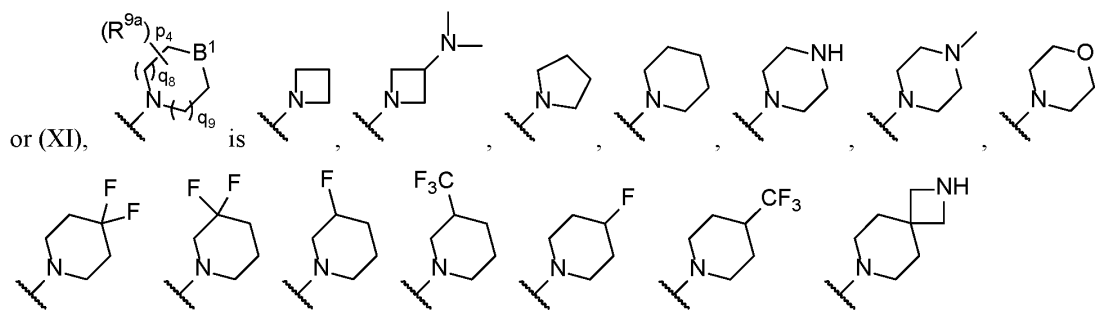
(II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{8c} is optionally substituted C_1 - C_6 haloalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (IIa), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), R^{8c} is hydrogen.

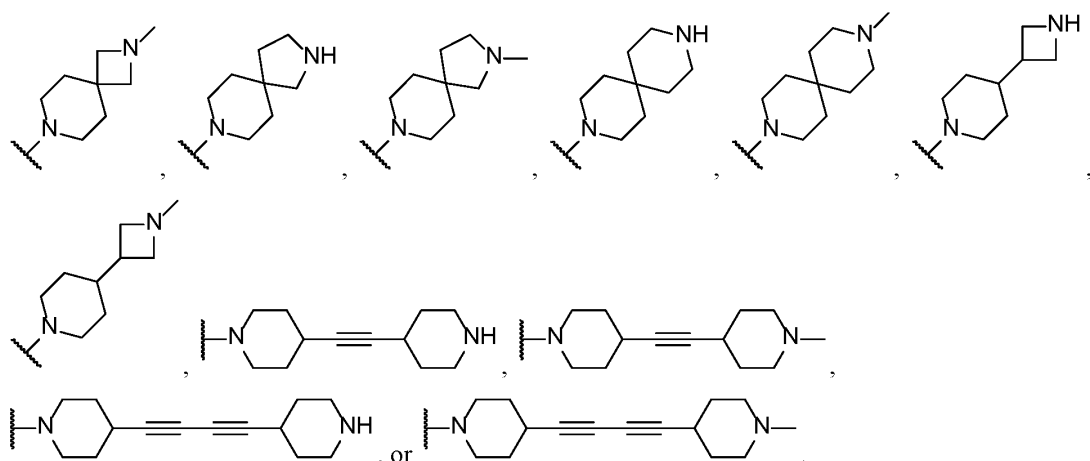
[00137] In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), each of R^{9a} or R^{9b} is independently halogen, -OH, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, C_3 - C_6 cycloalkyl, or 4 to 6-membered heterocycloalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), each of R^{9a} or R^{9b} is independently halogen, -OH, C_1 - C_3 alkyl, or C_1 - C_3 haloalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), each of R^{9a} or R^{9b} is independently C_3 - C_6 cycloalkyl or 4 to 6-membered heterocycloalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), each of R^{9a} or R^{9b} is independently C_3 - C_6 cycloalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), each of R^{9a} or R^{9b} is independently 4 to 6-membered heterocycloalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), each of R^{9a} or R^{9b} is independently halogen, -OH, -CH₃, or -CF₃. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), each of R^{9a} or R^{9b} is independently -F or -CF₃.

[00138] In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), p_3 is 0. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), p_3 is 1. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), p_3 is 2.

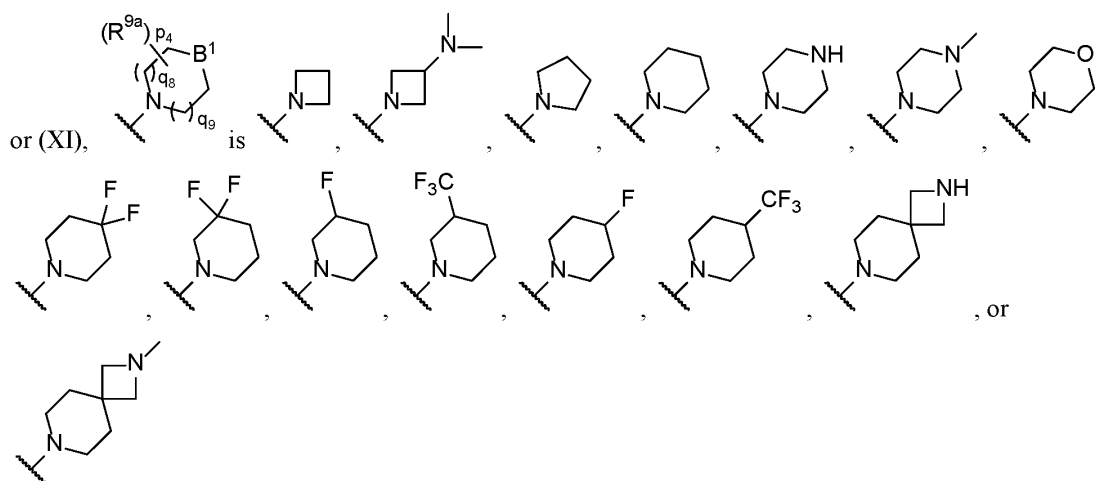
[00139] In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), p_4 is 0-4. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), p_4 is 0-3. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), p_4 is 1 or 2. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), p_4 is 0. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), p_4 is 1. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), p_4 is 2. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), p_4 is 3. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X), or (XI), p_4 is 4.

[00140] In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X),

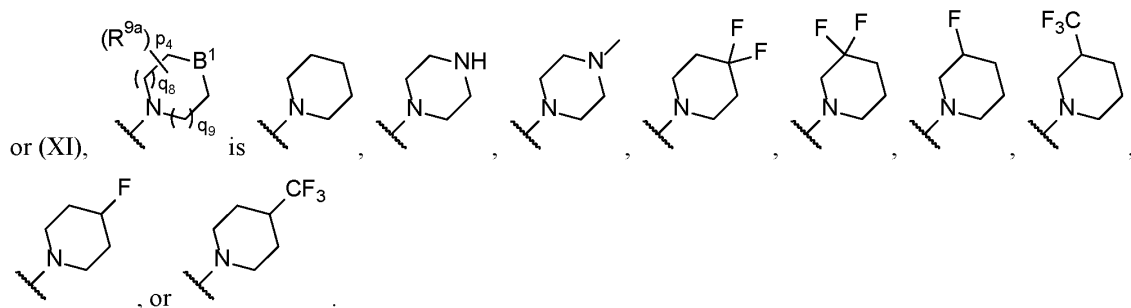




[00141] In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X),



[00142] In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (X),



[00143] In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), each R^6 is independently -CN, -OH, -OR^{6a}, -NHC(O)OR^{6a}, -OC(O)NR^{6a}R^{6b}, -N₃, -NR^{6a}R^{6b}, -CO(O)R^{6c}, -C(O)OR^{6c}, -C(O)NR^{6a}R^{6b}, -NHC(O)R^{6c}, C₃-C₆ cycloalkyl, or 4 to 6 membered heterocycloalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa),

(XIVb), (XIVc), (XIVd), or (XV), each R^6 is independently -CN, OH, OR^{6a} , $NHC(O)OR^{6a}$, $OC(O)NR^{6a}R^{6b}$, $-N_3$, $-NR^{6a}R^{6b}$, $-CO(O)R^{6c}$, $-C(O)OR^{6c}$, $-C(O)NR^{6a}R^{6b}$, or $-NHC(O)R^{6c}$. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), each R^6 is independently $-N_3$, $-NR^{6a}R^{6b}$, $-CO(O)R^{6c}$, $-C(O)OR^{6c}$, $-C(O)NR^{6a}R^{6b}$, or $-NHC(O)R^{6c}$. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), each R^6 is independently $-NR^{6a}R^{6b}$, $-C(O)NR^{6a}R^{6b}$, or $-NHC(O)R^{6c}$. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), each R^6 is independently $-NR^{6a}R^{6b}$. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), each R^6 is independently $-C(O)NR^{6a}R^{6b}$. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), each R^6 is independently $-NHC(O)R^{6c}$. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), each R^6 is independently $-NHC(O)R^{6c}$, wherein R^{6c} is PEG_{1-20} . In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), each R^6 is independently C_3-C_6 cycloalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), each R^6 is independently -CN, -OH, -OCH₃, -N₃, -NH₂, -NHCH₃, or -N(CH₃)₂. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), each R^6 is independently -OH, -NH₂, -NHCH₃, or -N(CH₃)₂.

[00144] In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), R^{6a} and R^{6b} are each independently hydrogen, C_1-C_{20} alkyl, or PEG_{1-20} . In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), R^{6a} and R^{6b} are each independently C_1-C_{20} alkyl or PEG_{1-20} . In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), R^{6a} and R^{6b} are each independently C_1-C_{10} alkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), R^{6a} and R^{6b} are each independently PEG_{1-10} . In some embodiments of

Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), R^{6a} and R^{6b} are each independently hydrogen.

[00145] In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), R^{6c} is C_1 - C_{20} alkyl, PEG_{1-20} , C_3 - C_8 cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), R^{6c} is C_1 - C_{20} alkyl or PEG_{1-20} . In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), R^{6c} is C_1 - C_{10} alkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), R^{6c} is PEG_{1-10} . In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), R^{6c} is C_3 - C_8 cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), R^{6c} is C_3 - C_8 cycloalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), R^{6c} is 4 to 8-membered heterocycloalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), R^{6c} is phenyl.

[00146] In some embodiments of Formula (A-1) or (A-2), each R^7 is independently hydrogen, halogen, -OH, or C_1 - C_3 alkyl. In some embodiments of Formula (A-1) or (A-2), each R^7 is independently hydrogen, halogen, -OH. In some embodiments of Formula (A-1) or (A-2), each R^7 is independently halogen. In some embodiments of Formula (A-1) or (A-2), each R^7 is independently -OH. In some embodiments of Formula (A-1) or (A-2), each R^7 is independently hydrogen.

[00147] In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), W^1 is $-N=C(N(R^{1e})_2)_2$, wherein each R^{1e} is independently hydrogen or C_1 - C_3 alkyl. In some embodiments, each R^{1e} is independently hydrogen. In some embodiments, each R^{1e} is independently C_1 - C_3 alkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), W^1 is $-N=C(N(CH_3)_2)_2$. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIId), (IX), (X), (XI), (XII),

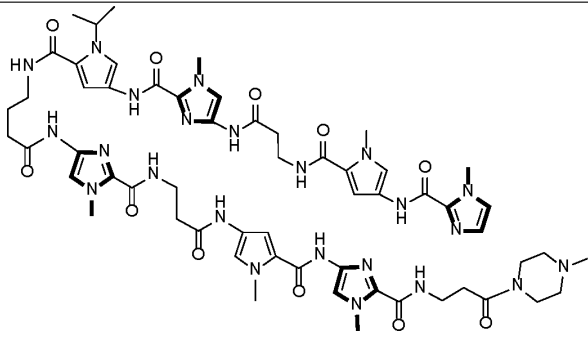
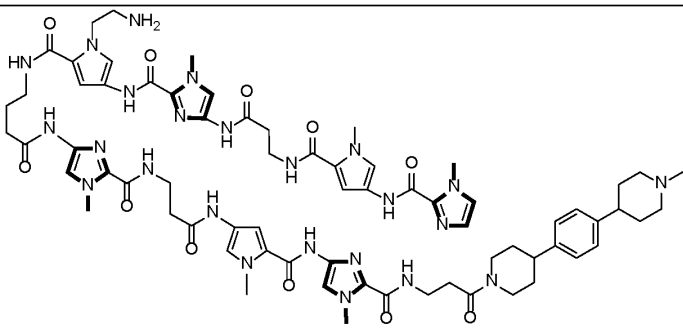
(XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), W^1 is $-N=C(NH_2)_2$. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), W^1 is C_1 - C_3 haloalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (III), (IIIa), (IV), (IVa), (V), (VI), (VII), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIId), (IX), (X), (XI), (XII), (XIII), (XIV), (XIVa), (XIVb), (XIVc), (XIVd), or (XV), W^1 is hydrogen.

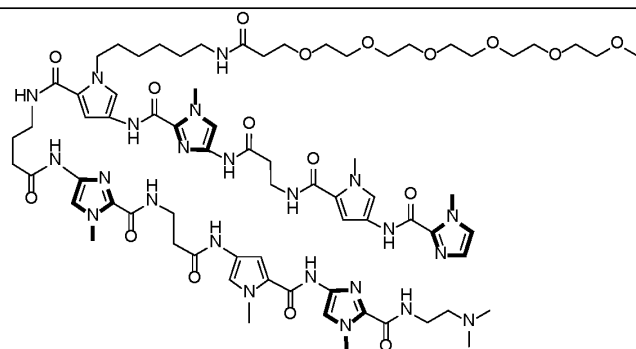
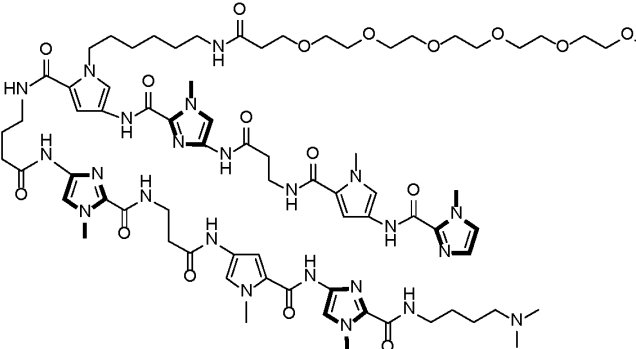
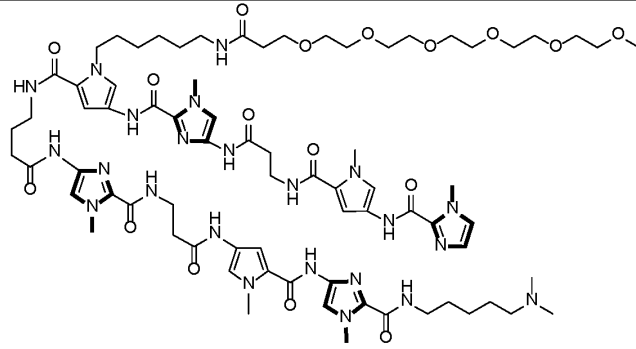
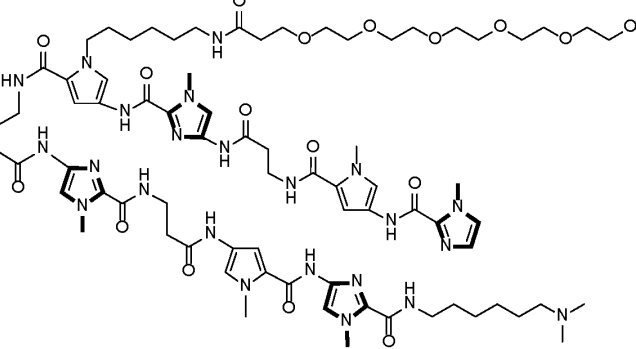
[00148] In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (V), (X), or (XI), W^{1a} is hydrogen, $-N=C(N(R^{1e})_2)_2$, or C_1 - C_3 haloalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (V), (X), or (XI), W^{1a} is hydrogen, or C_1 - C_3 haloalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (V), (X), or (XI), W^{1a} is C_1 - C_3 haloalkyl. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (V), (X), or (XI), W^{1a} is $-N=C(N(R^{1e})_2)_2$. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (V), (X), or (XI), W^{1a} is hydrogen.

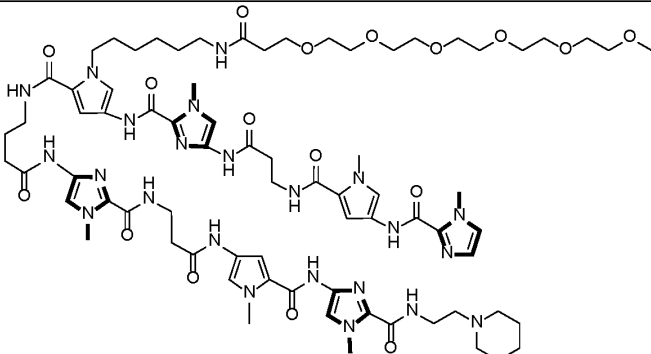
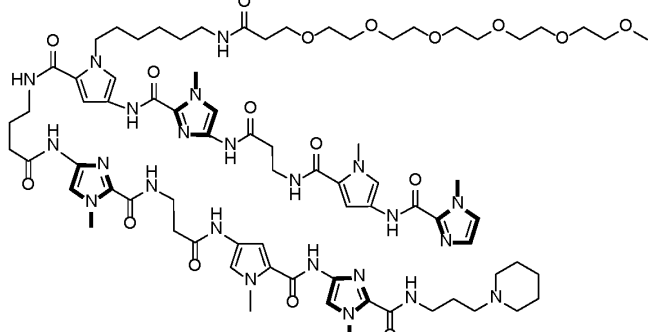
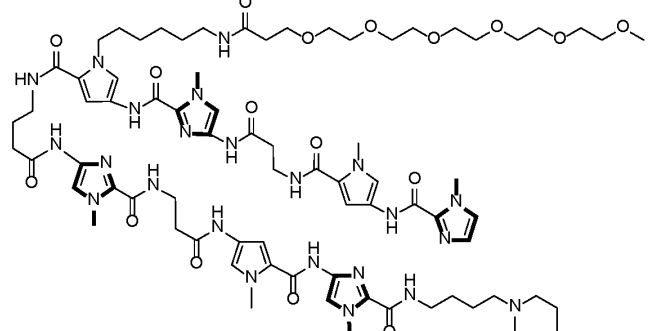
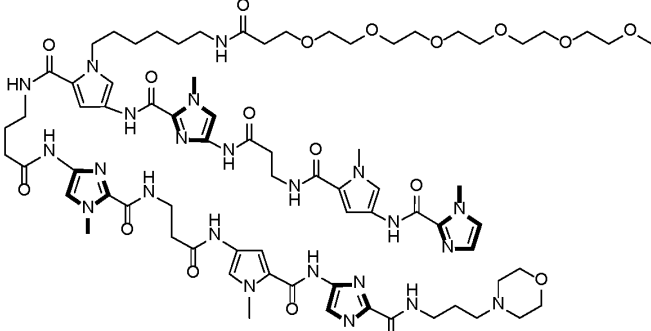
[00149] In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (V), (X), or (XI), W^1 is hydrogen and W^{1a} is $-CF_3$. In some embodiments of Formula (A-1), (A-2), (A-3), (I), (II), (V), (X), or (XI), W^1 is hydrogen and W^{1a} is hydrogen.

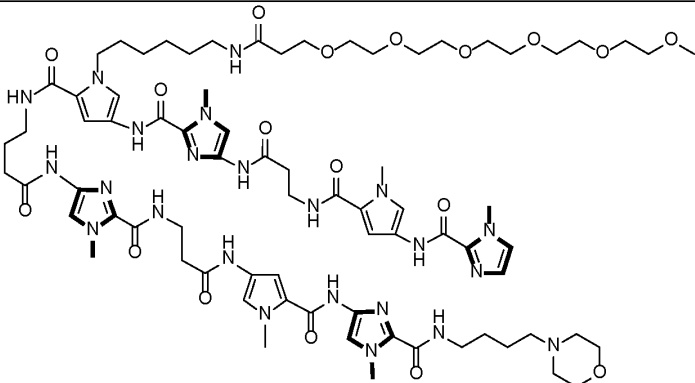
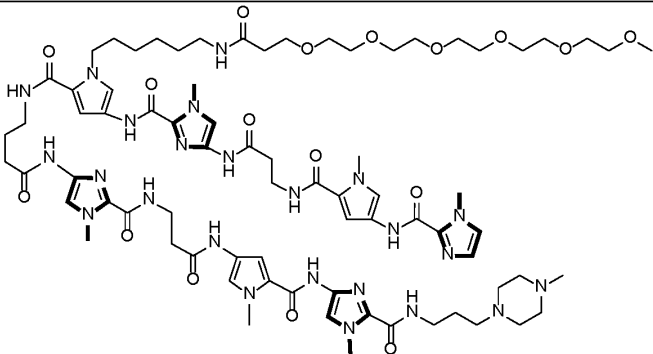
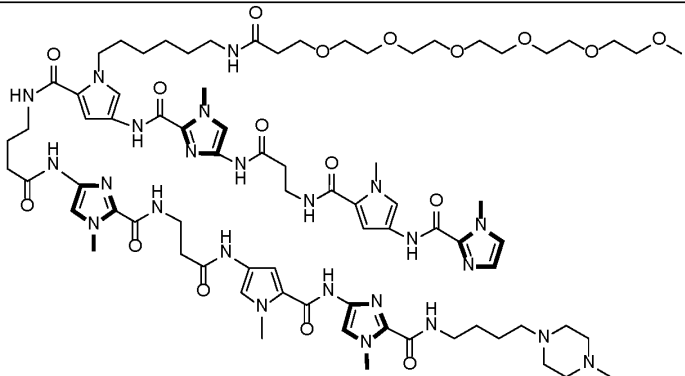
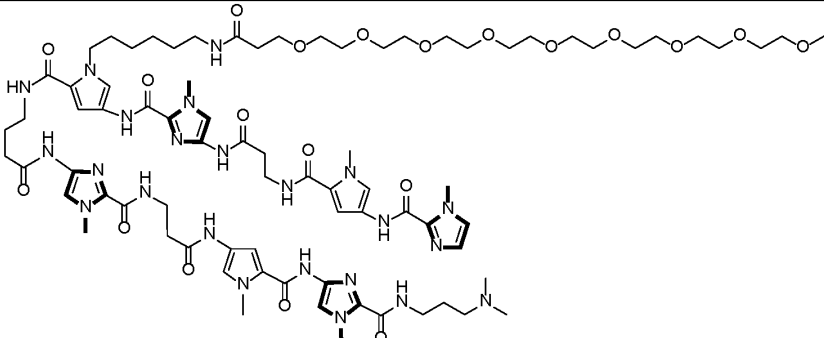
[00150] In some embodiments, non-limiting examples of the transcription modulator compounds described herein are presented in Table 1.

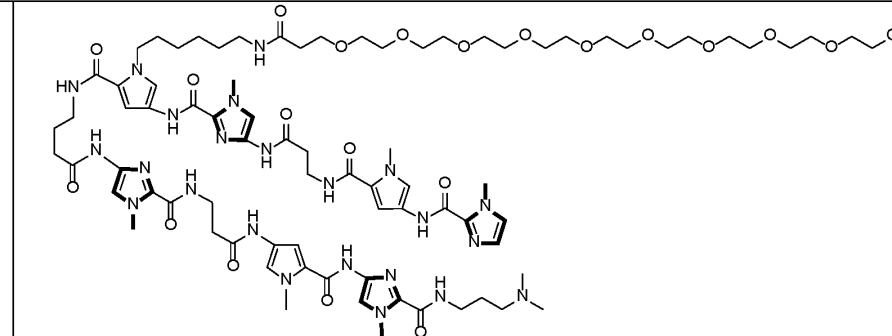
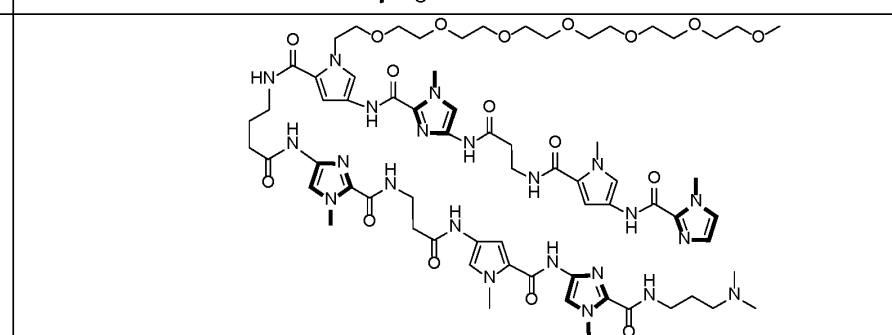
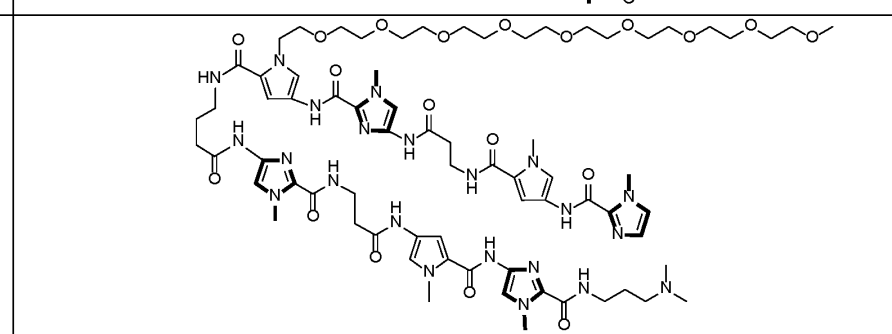
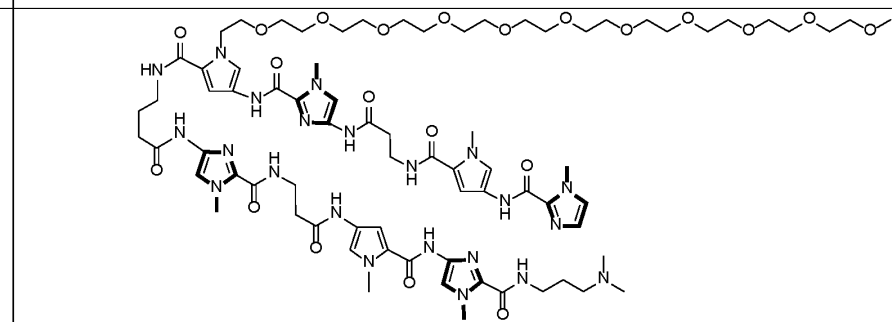
Table 1.

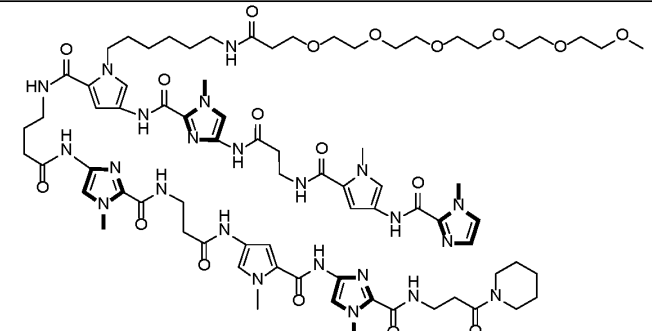
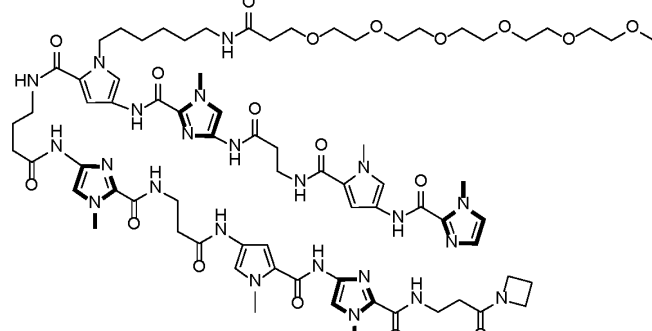
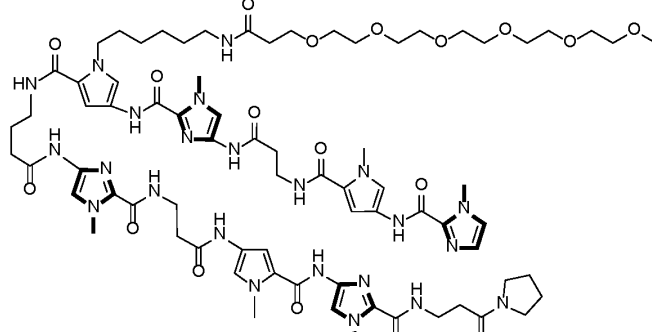
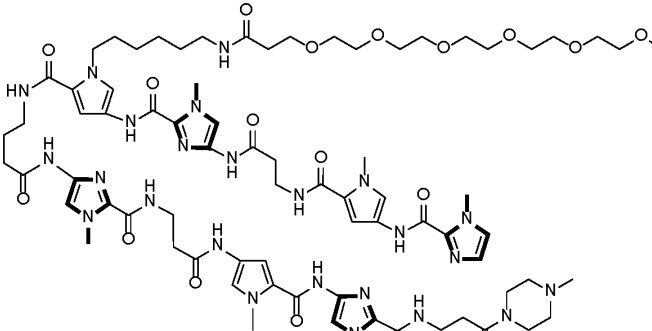
Cmpd. No.	Structure
A-1	
A-2	

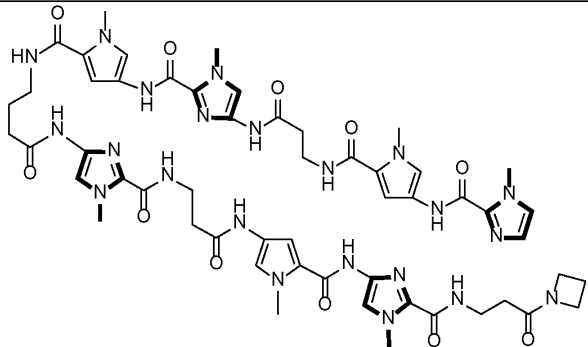
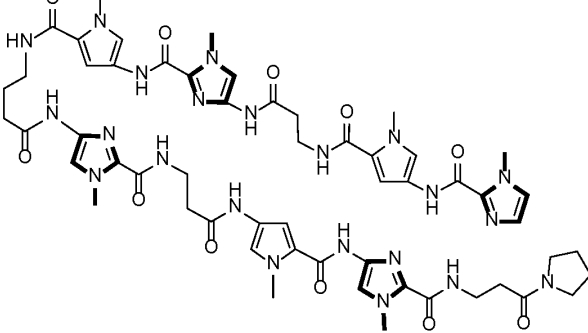
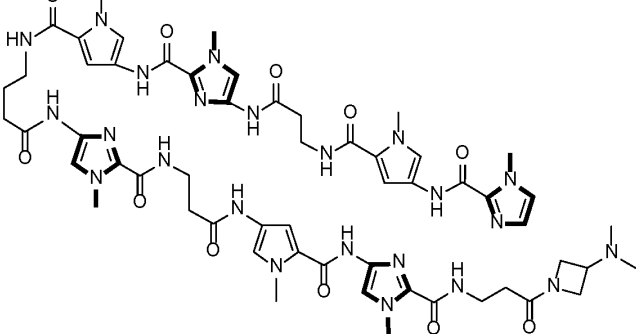
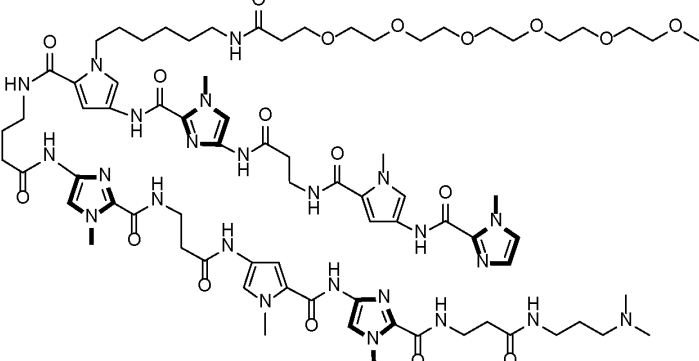
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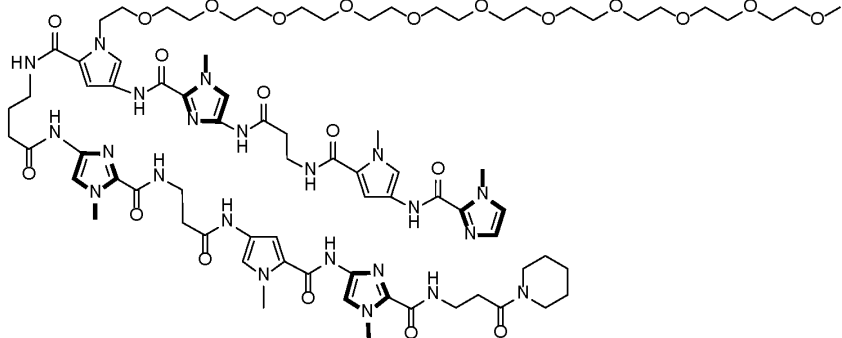
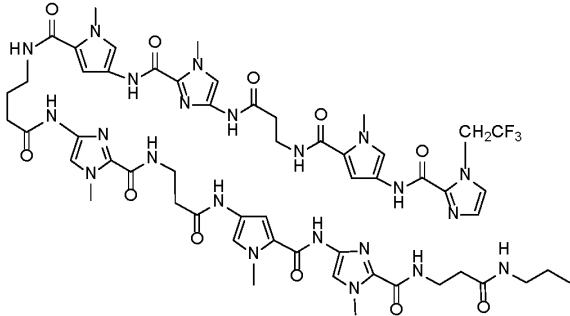
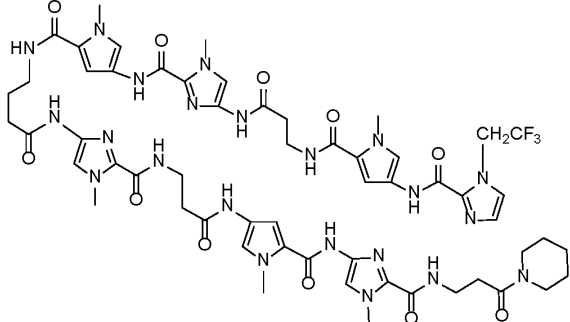
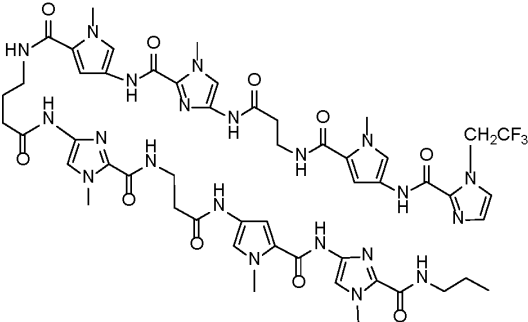
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A-13	
A-14	

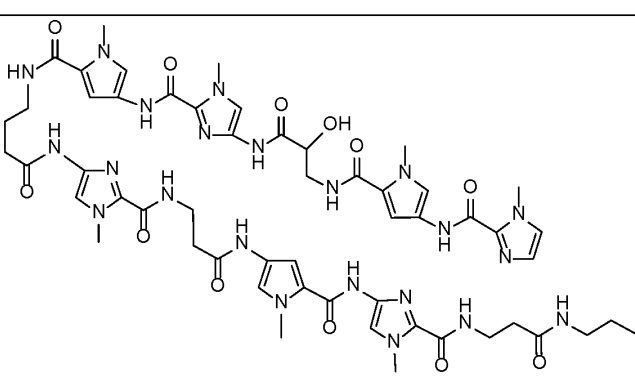
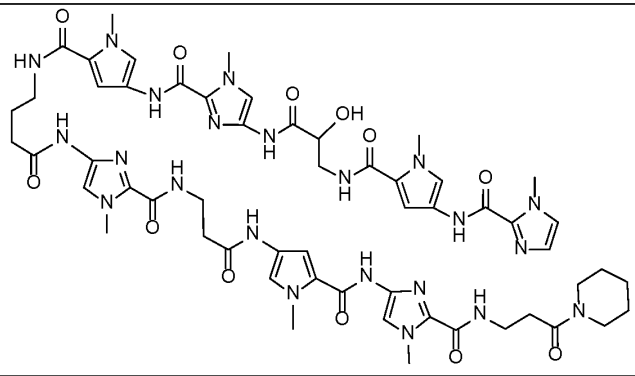
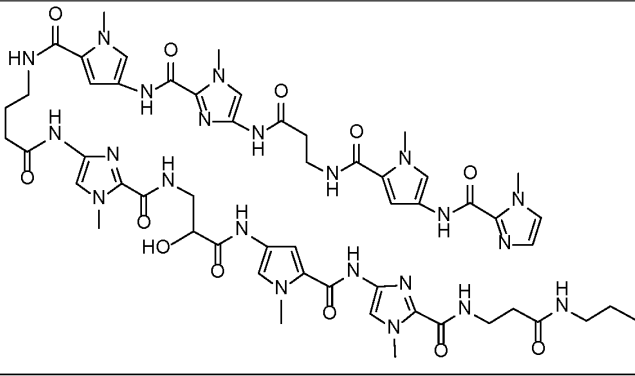
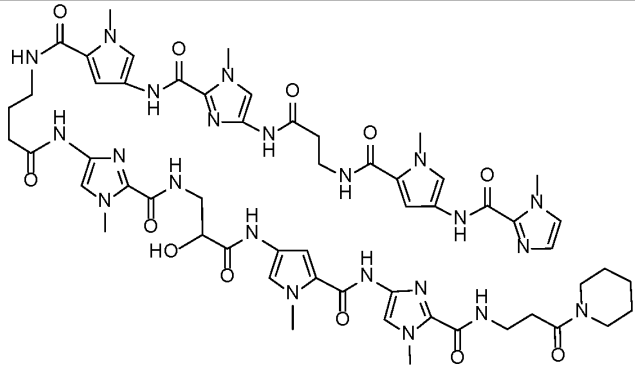
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A-16	
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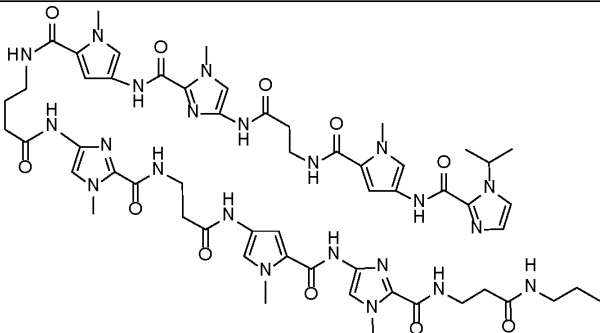
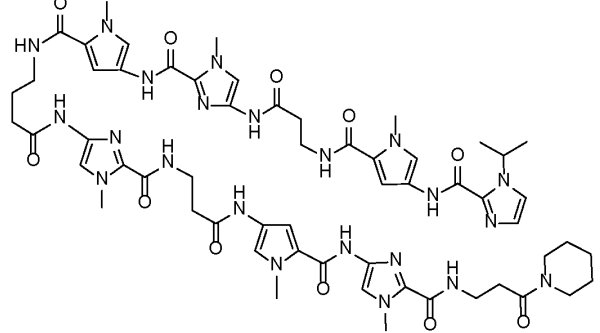
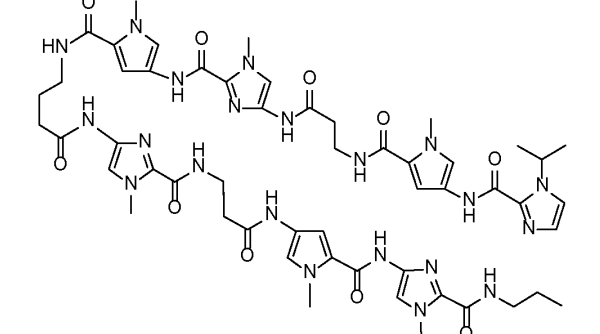
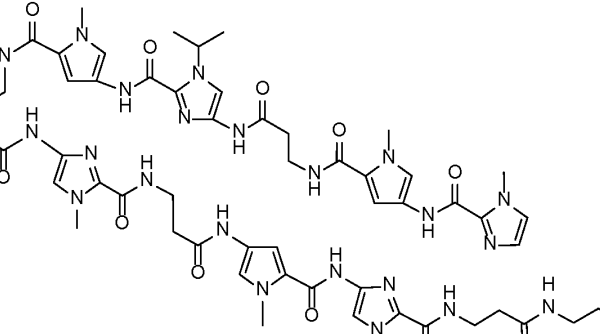
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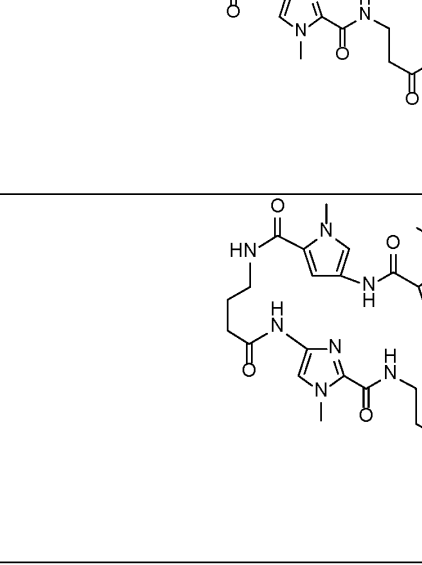
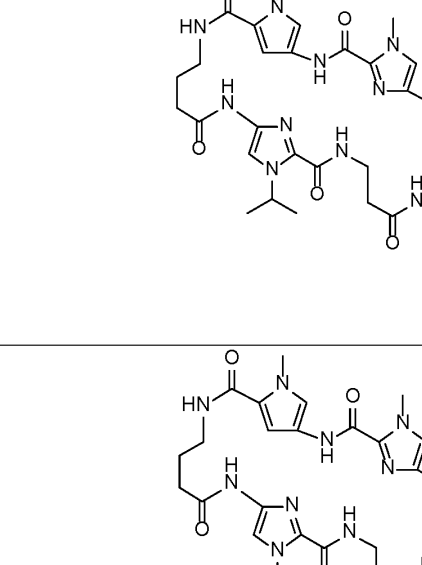
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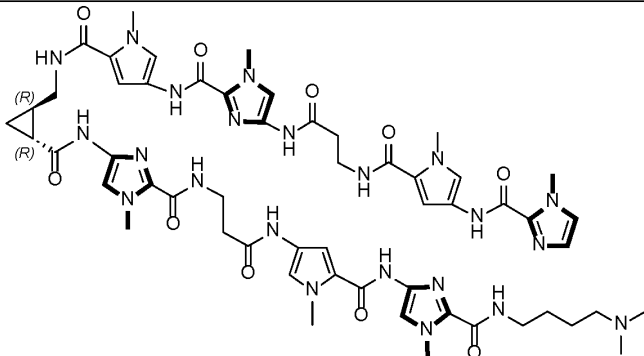
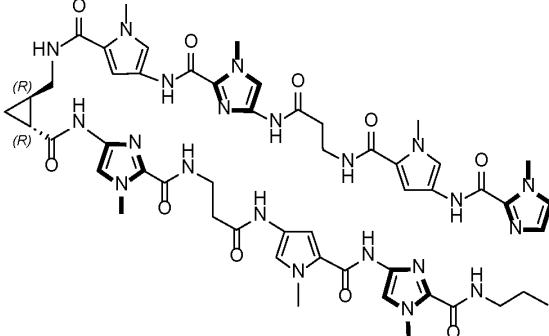
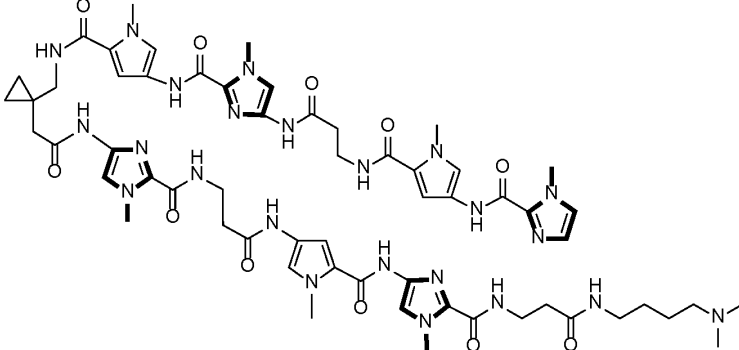
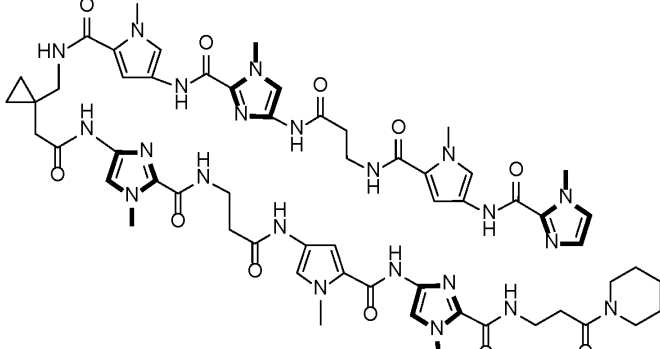
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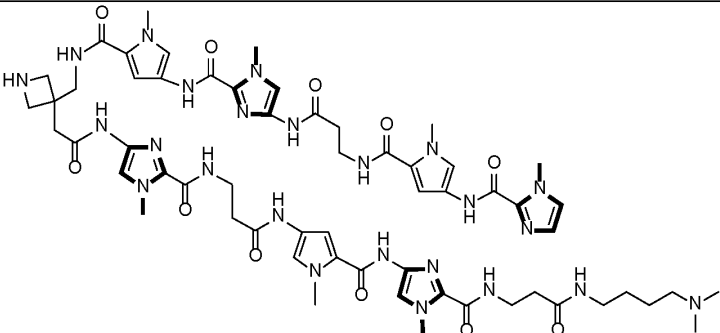
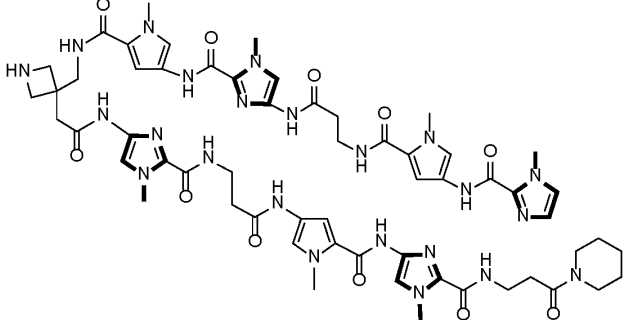
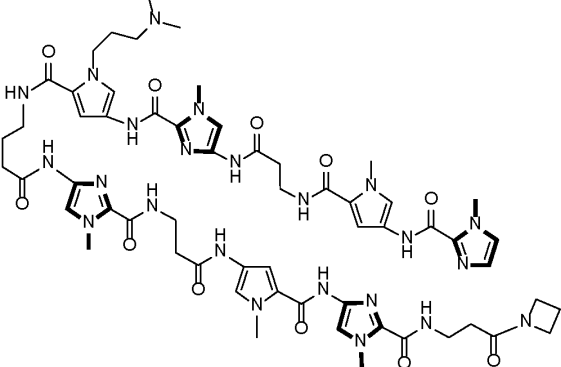
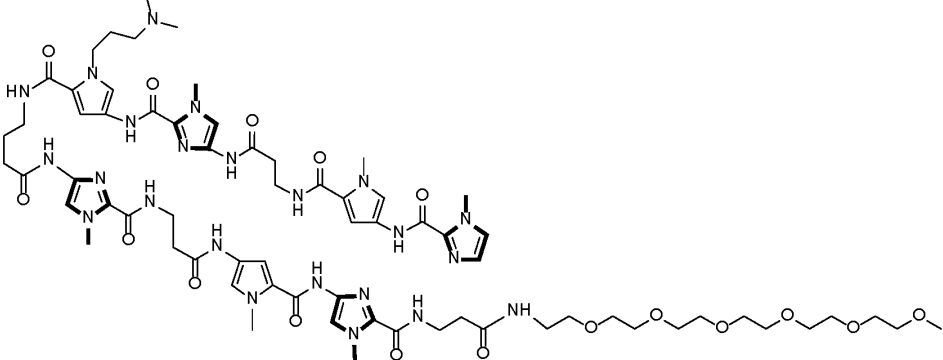
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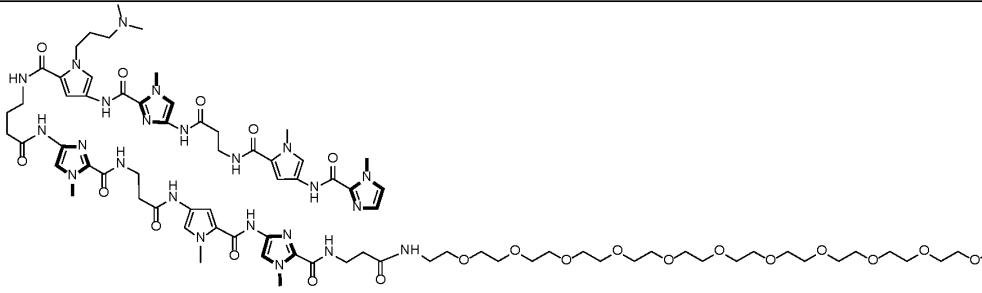
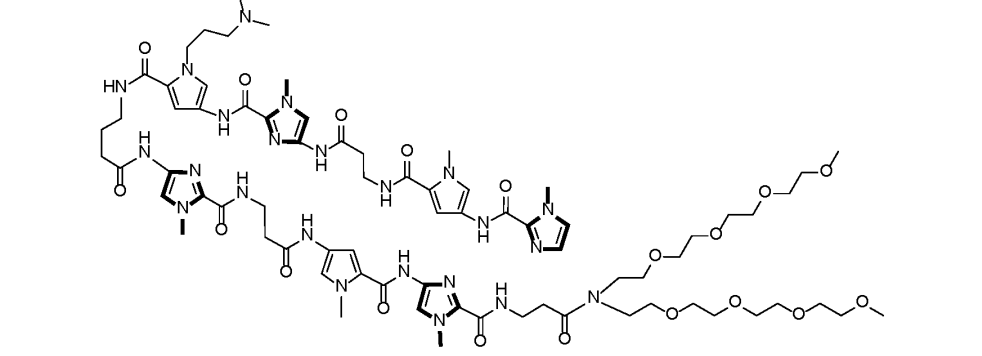
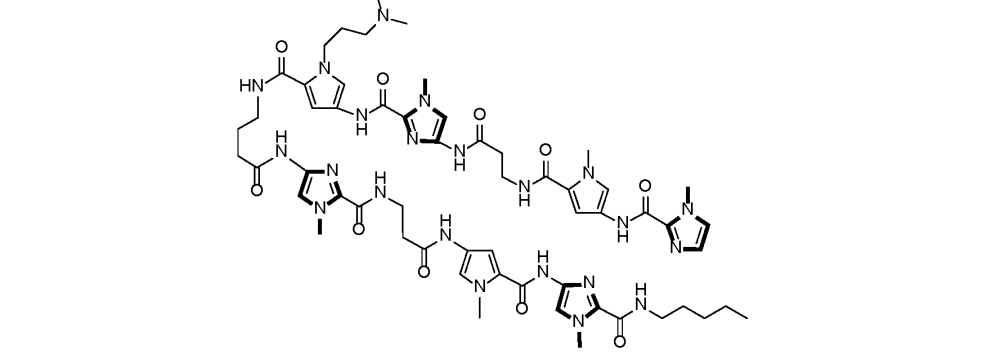
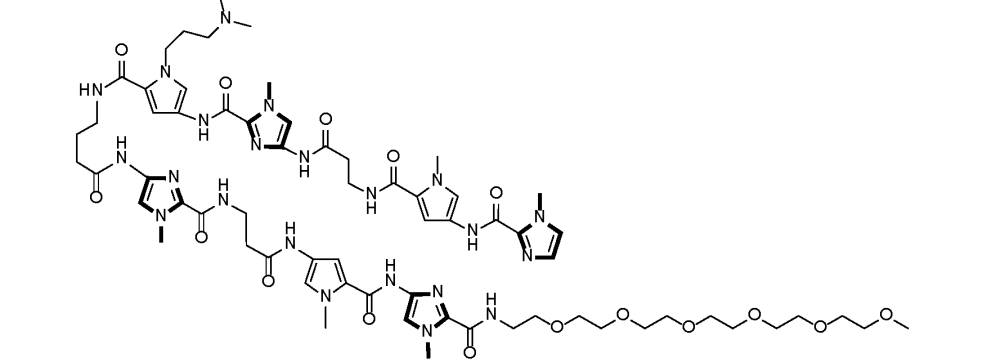
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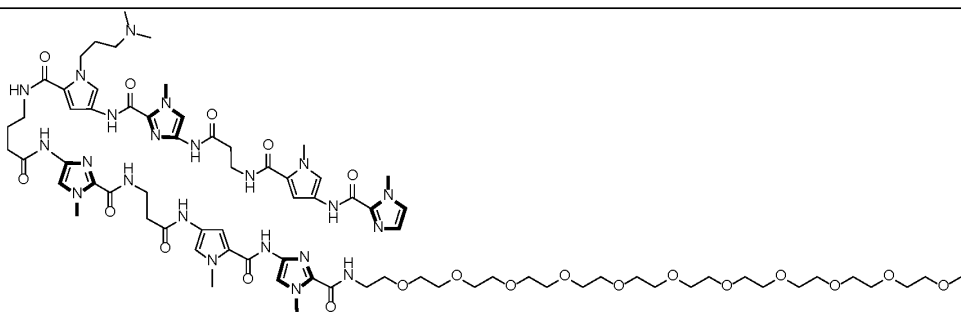
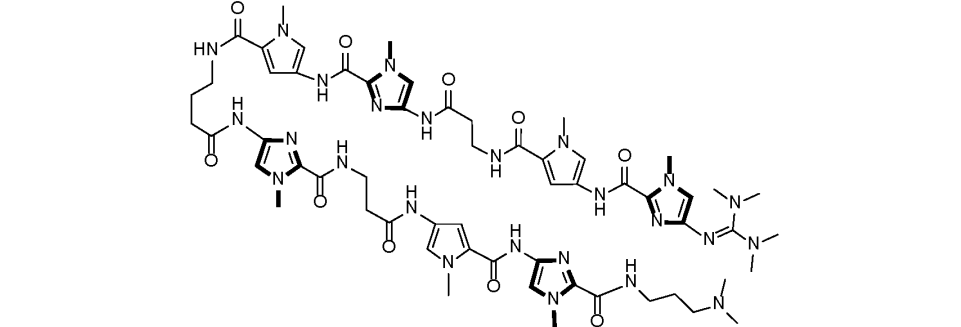
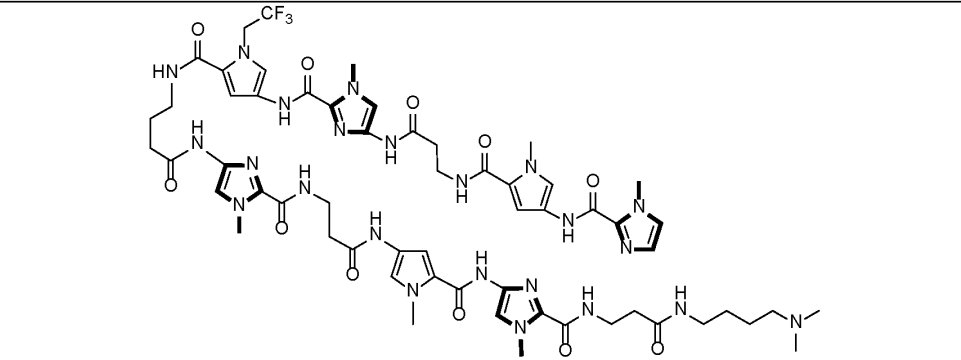
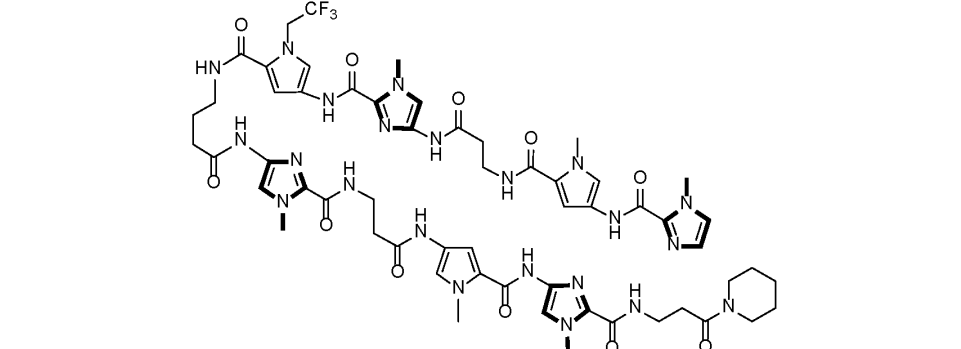
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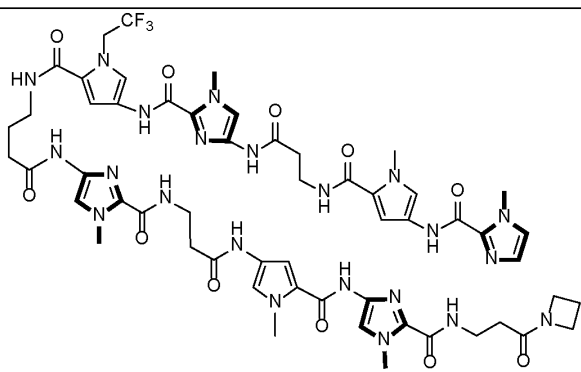
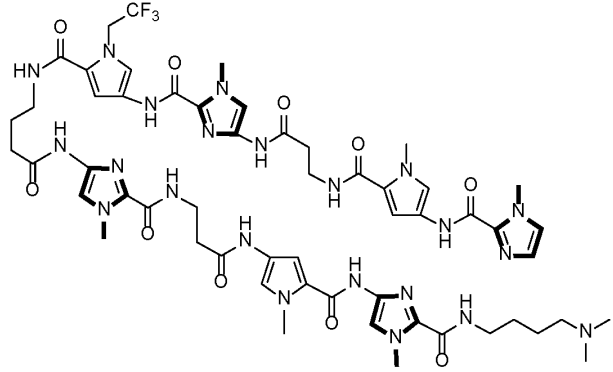
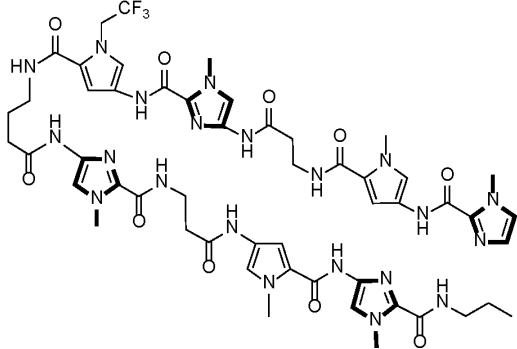
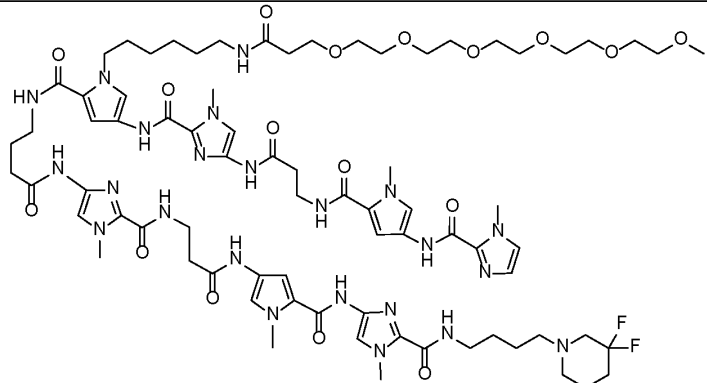
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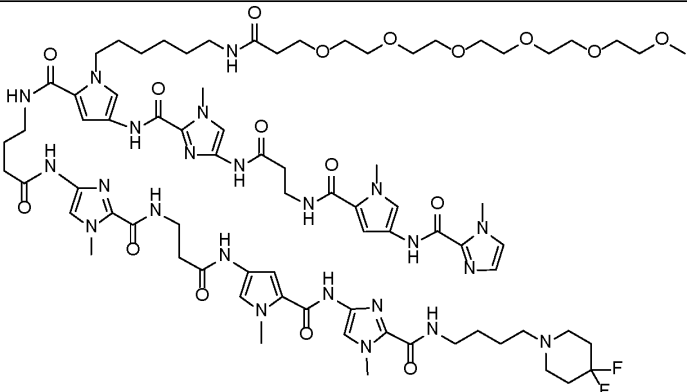
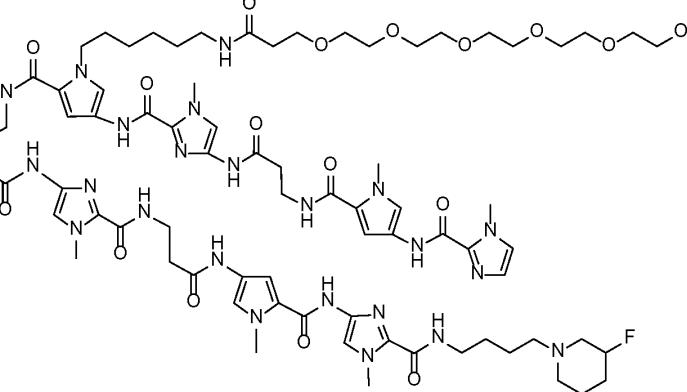
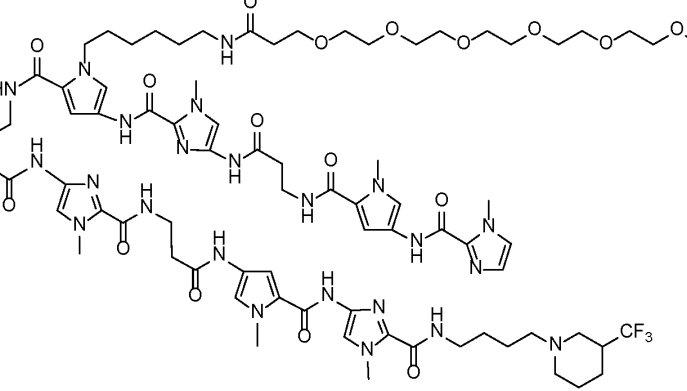
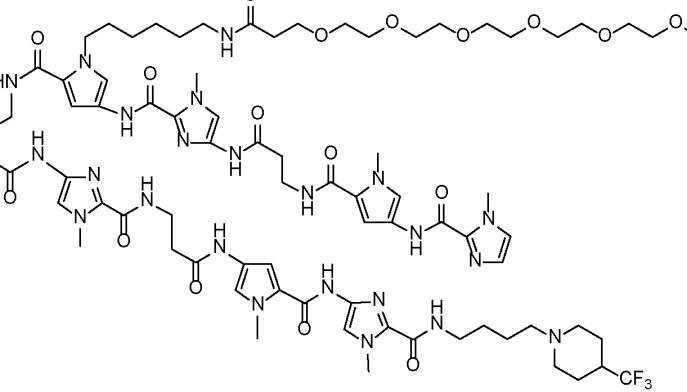
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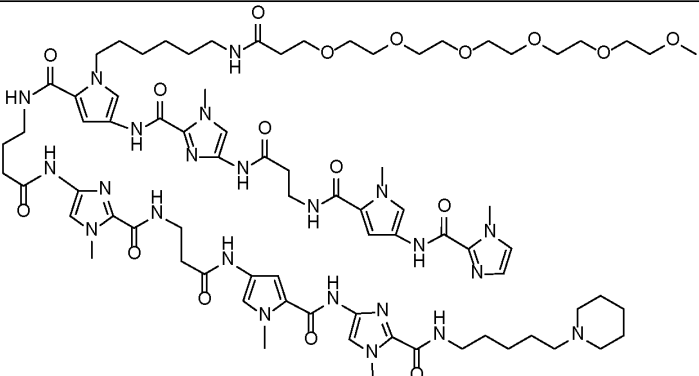
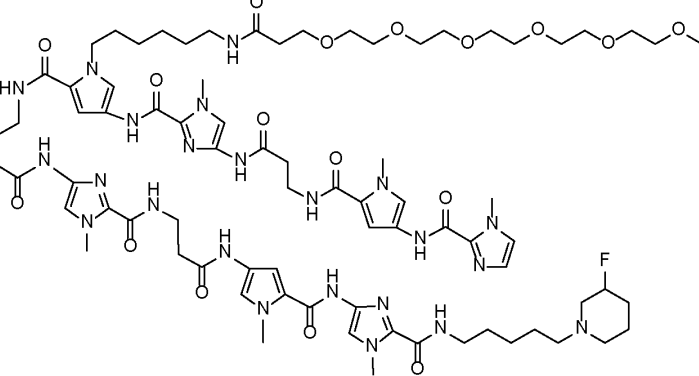
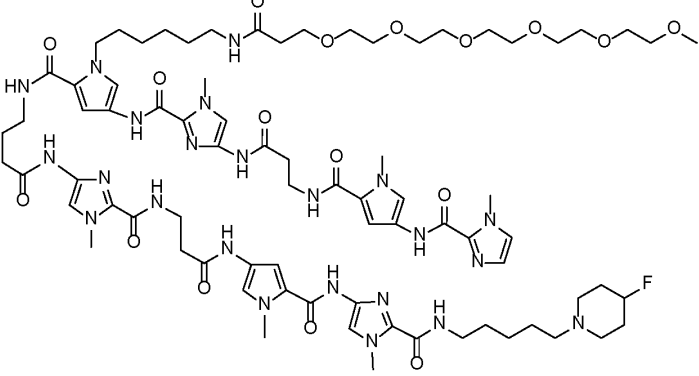
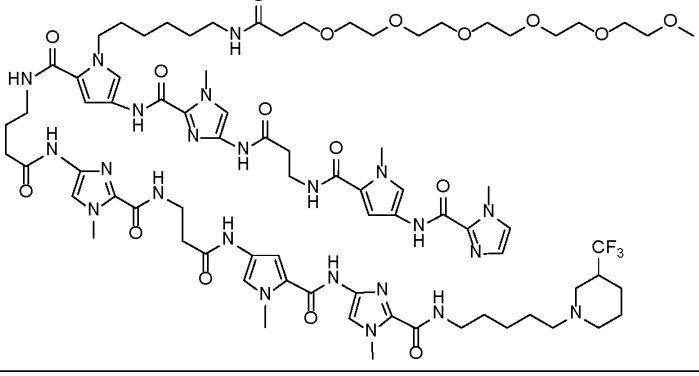
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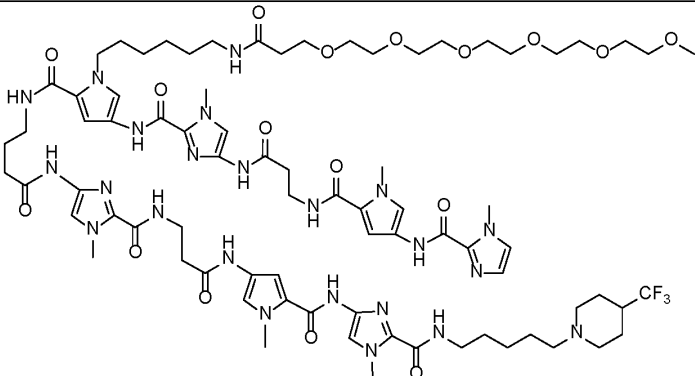
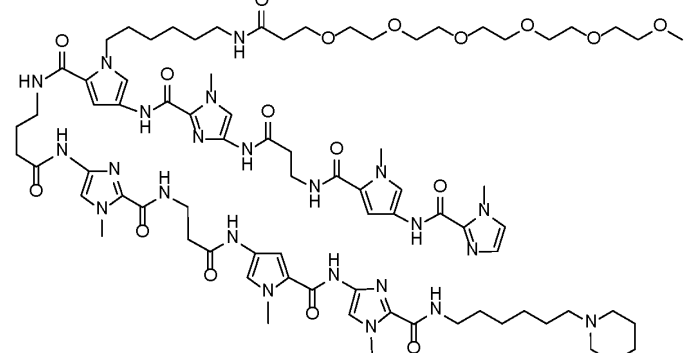
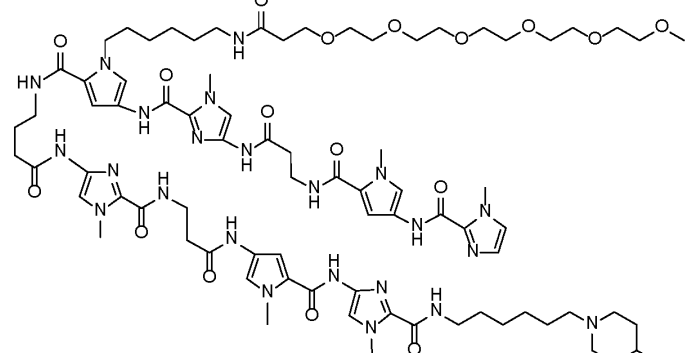
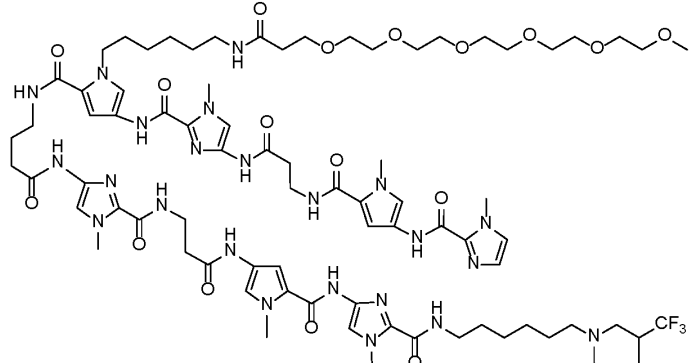
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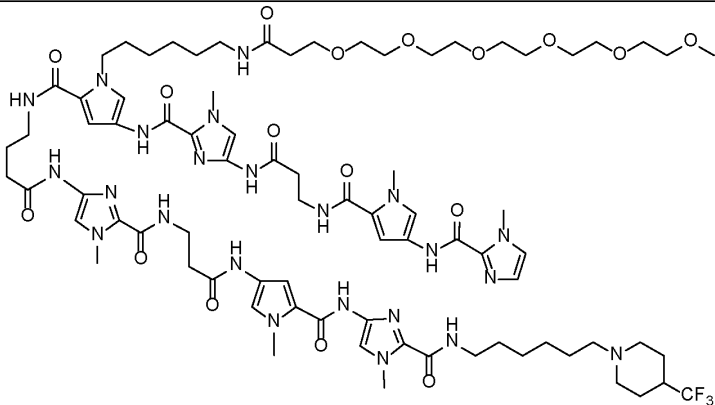
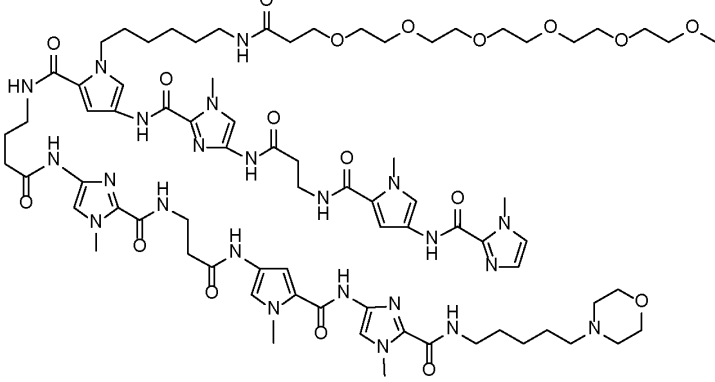
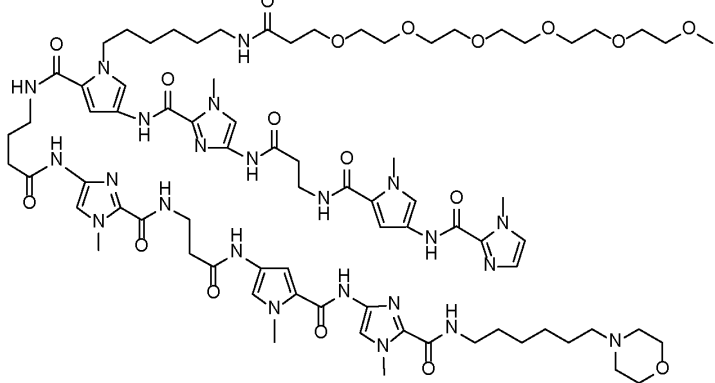
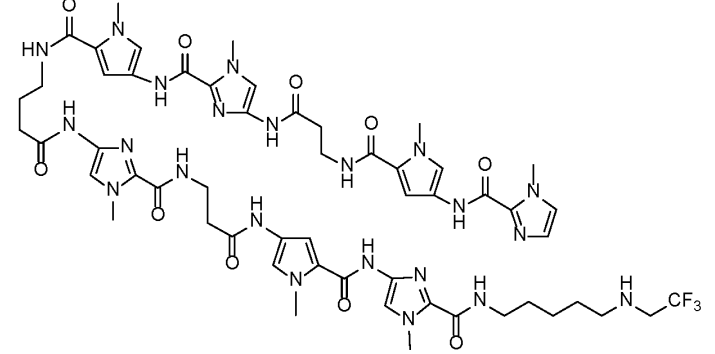
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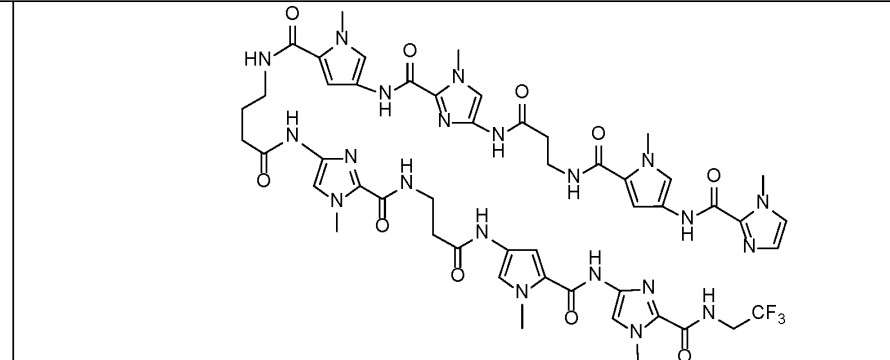
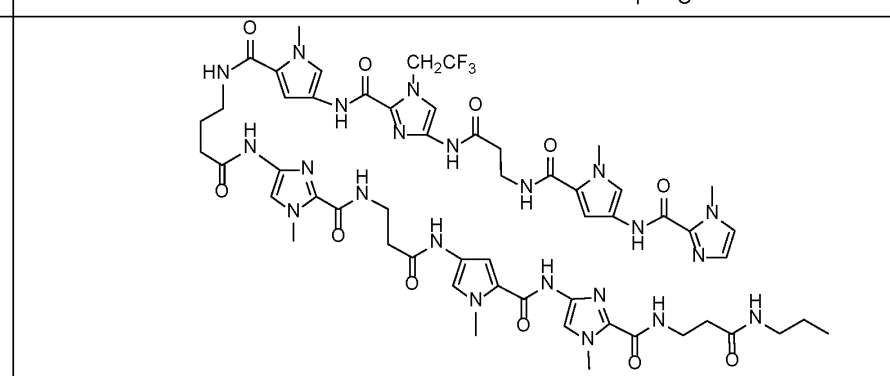
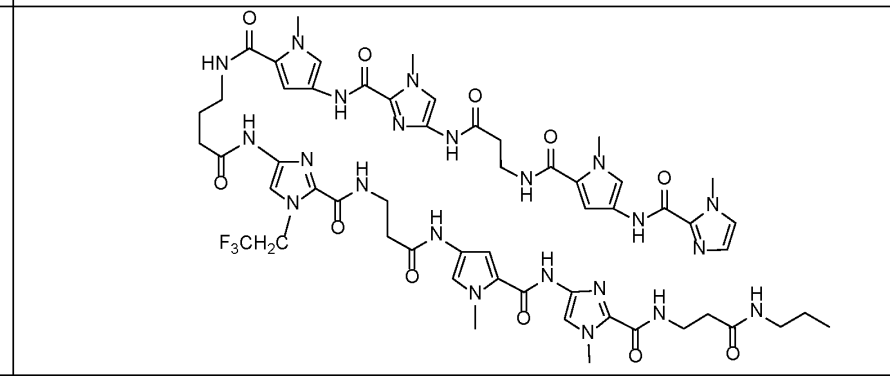
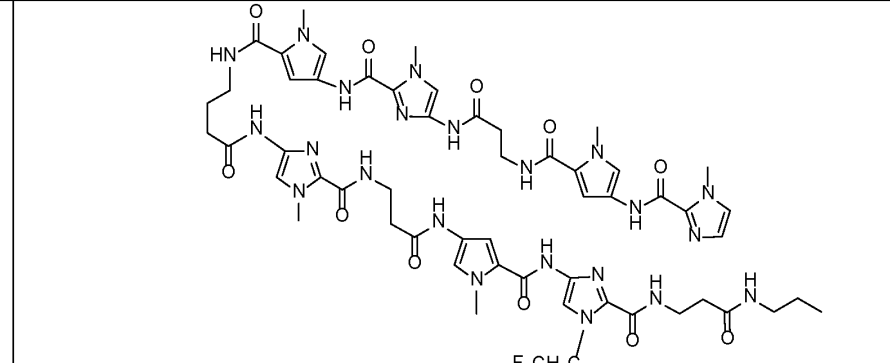
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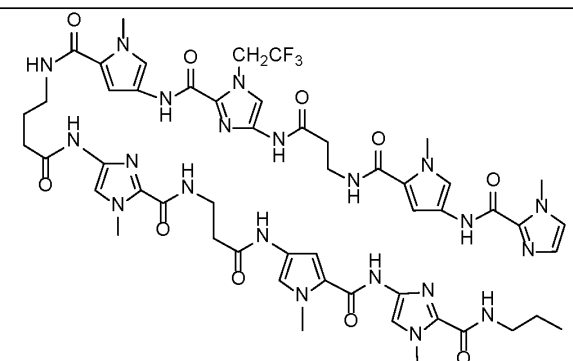
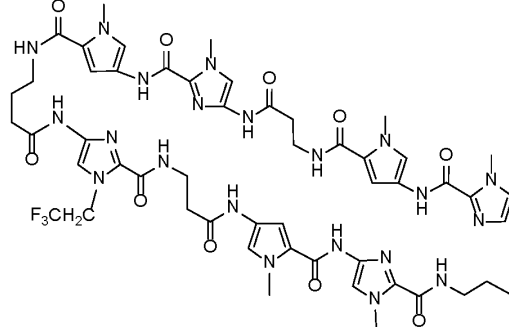
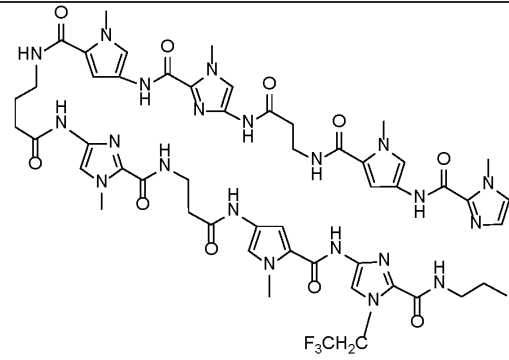
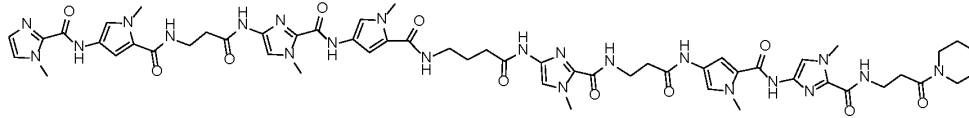
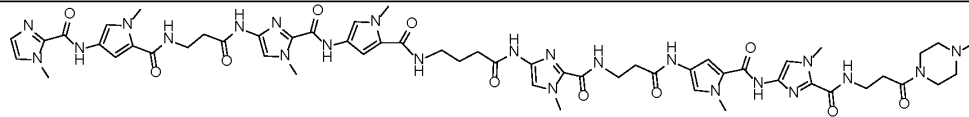
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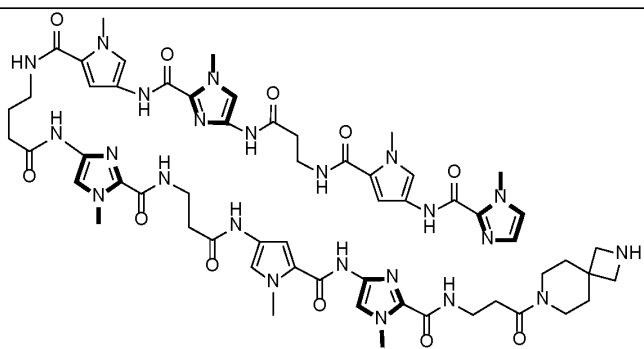
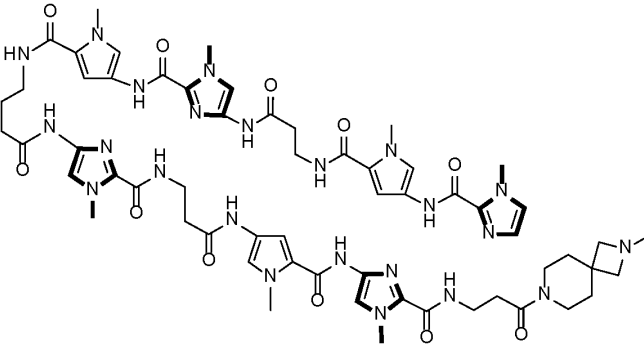
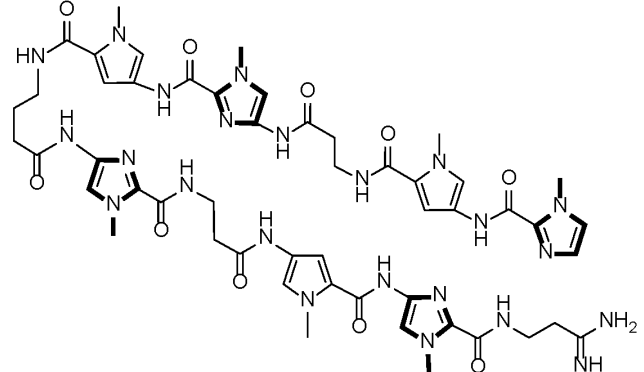
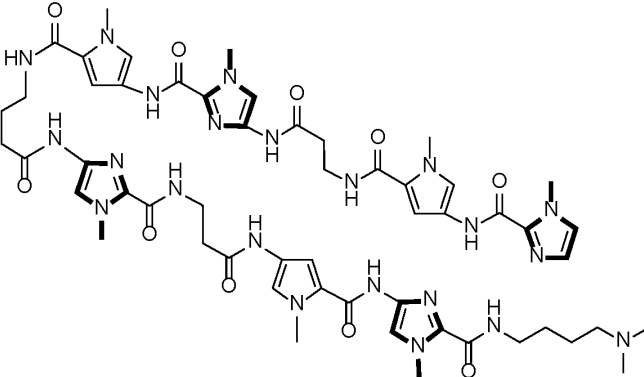
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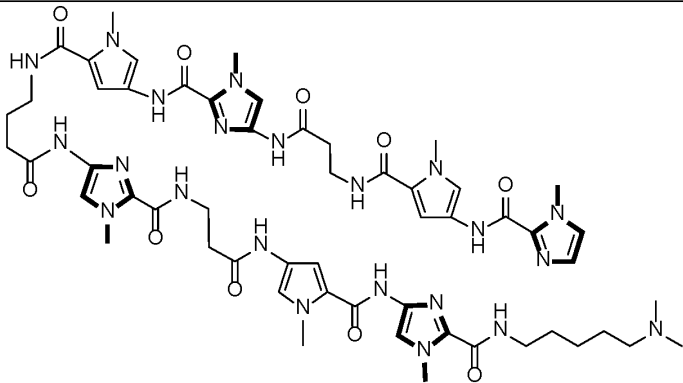
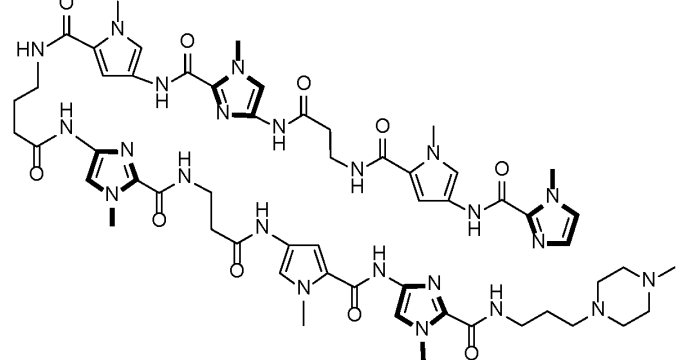
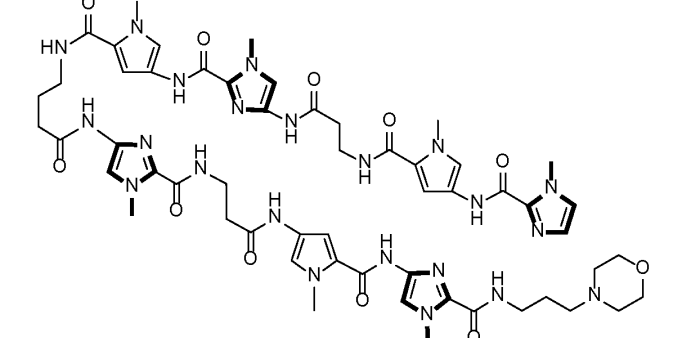
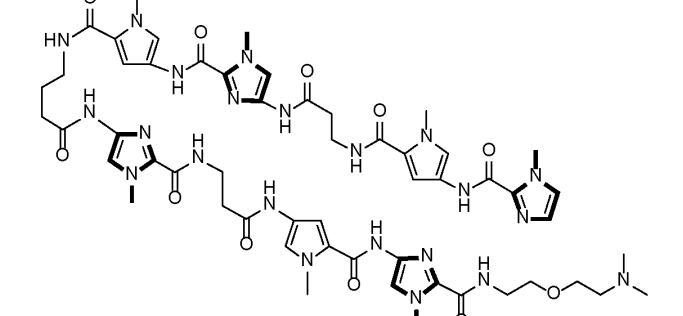
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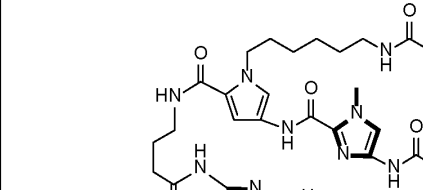
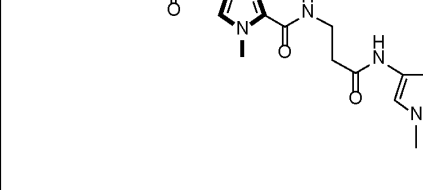
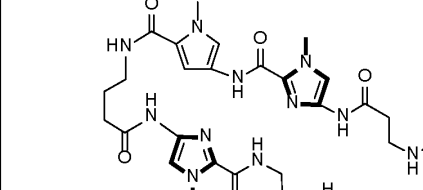
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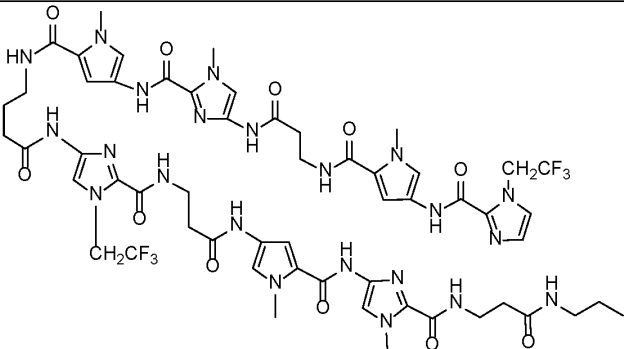
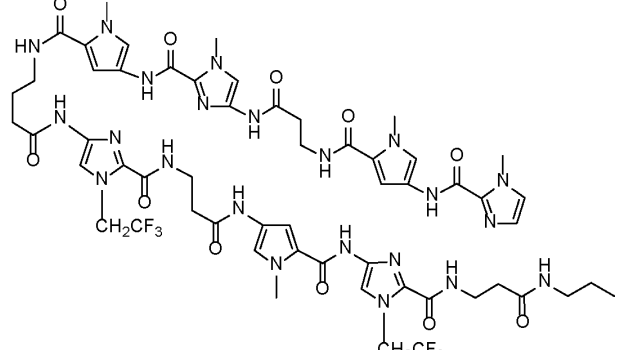
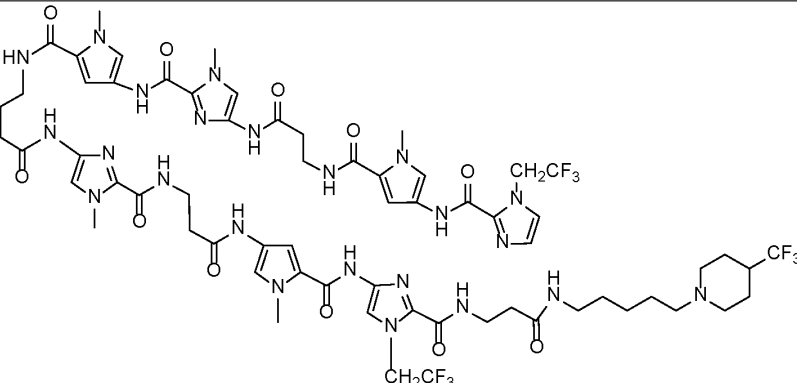
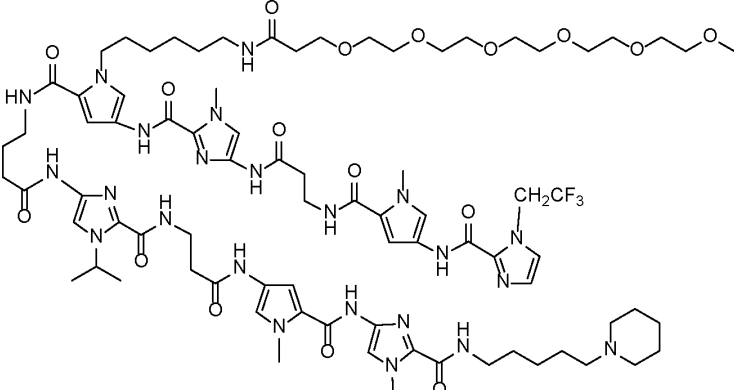
A-87	 Chemical structure of A-87, a macrocyclic peptide derivative. The structure features a long chain of amino acid residues linked by amide bonds, forming a macrocycle. A side chain contains a trifluoromethyl group (CF_3).
A-88	 Chemical structure of A-88, a macrocyclic peptide derivative. The structure features a long chain of amino acid residues linked by amide bonds, forming a macrocycle. A side chain contains a trifluoromethyl group (CH_2CF_3).
A-89	 Chemical structure of A-89, a macrocyclic peptide derivative. The structure features a long chain of amino acid residues linked by amide bonds, forming a macrocycle. A side chain contains a trifluoromethyl group ($\text{F}_3\text{CH}_2\text{C}$).
A-90	 Chemical structure of A-90, a macrocyclic peptide derivative. The structure features a long chain of amino acid residues linked by amide bonds, forming a macrocycle. A side chain contains a trifluoromethyl group ($\text{F}_3\text{CH}_2\text{C}$).

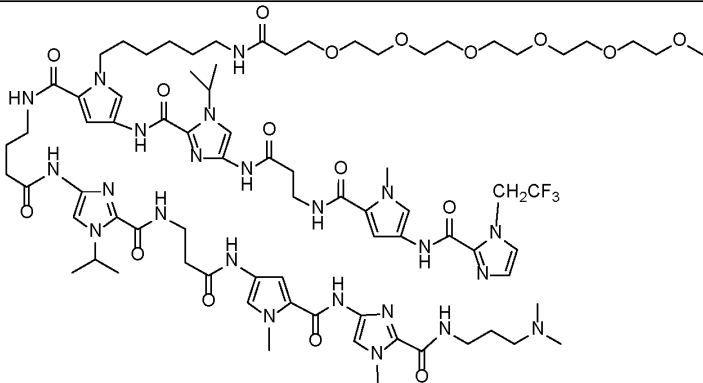
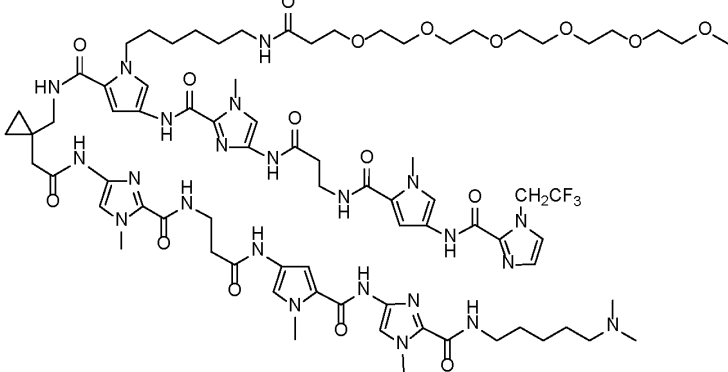
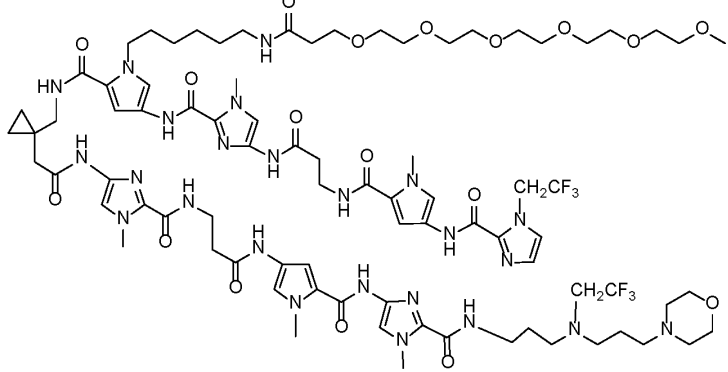
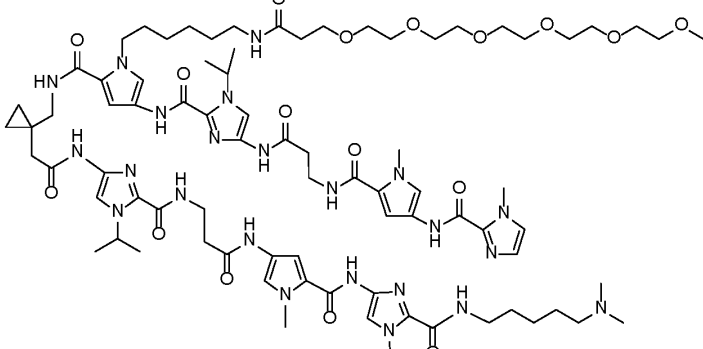
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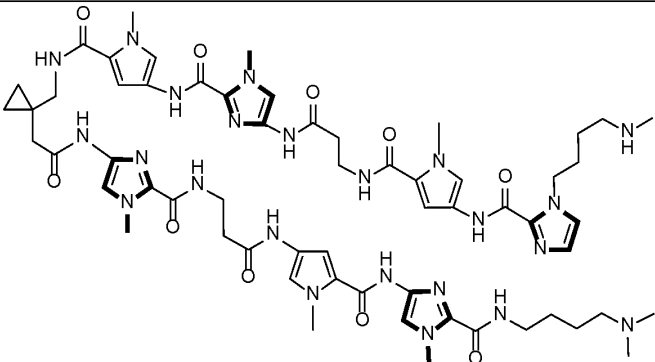
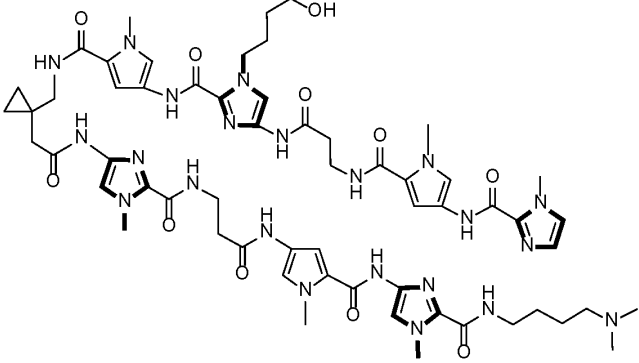
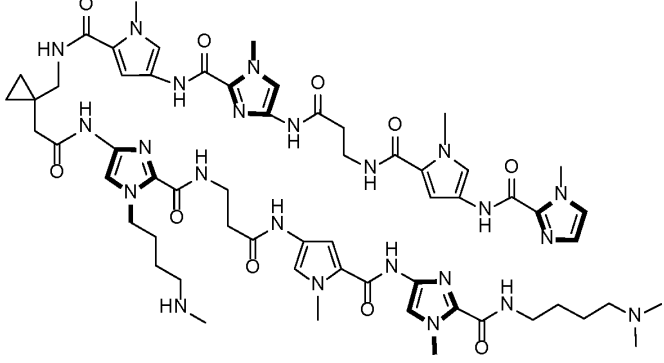
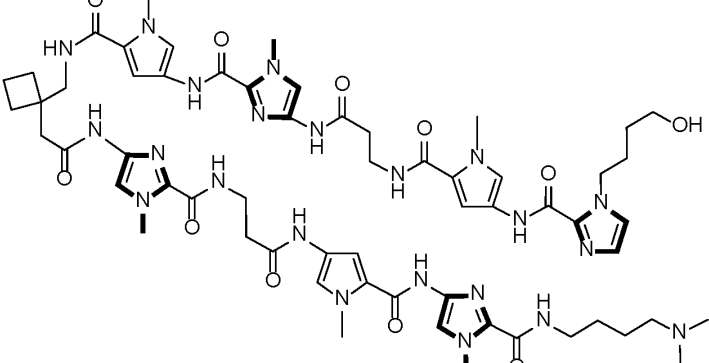
A-96	 Chemical structure A-96 is a complex molecule featuring a central chain of amide linkages connecting various heterocyclic rings, including pyrazoles, imidazoles, and a piperidine ring.
A-97	 Chemical structure A-97 is a complex molecule featuring a central chain of amide linkages connecting various heterocyclic rings, including pyrazoles, imidazoles, and a piperidine ring.
A-98	 Chemical structure A-98 is a complex molecule featuring a central chain of amide linkages connecting various heterocyclic rings, including pyrazoles, imidazoles, and a piperidine ring.
A-99	 Chemical structure A-99 is a complex molecule featuring a central chain of amide linkages connecting various heterocyclic rings, including pyrazoles, imidazoles, and a piperidine ring.

A-100	 Chemical structure A-100 is a complex molecule featuring a central chain of amide linkages connecting various heterocyclic rings, including pyrazoles, imidazoles, and thiazoles, with a terminal dimethylamino group.
A-101	 Chemical structure A-101 is a complex molecule featuring a central chain of amide linkages connecting various heterocyclic rings, including pyrazoles, imidazoles, and thiazoles, with a terminal dimethylpiperazine group.
A-102	 Chemical structure A-102 is a complex molecule featuring a central chain of amide linkages connecting various heterocyclic rings, including pyrazoles, imidazoles, and thiazoles, with a terminal morpholine group.
A-103	 Chemical structure A-103 is a complex molecule featuring a central chain of amide linkages connecting various heterocyclic rings, including pyrazoles, imidazoles, and thiazoles, with a terminal dimethylamino group.

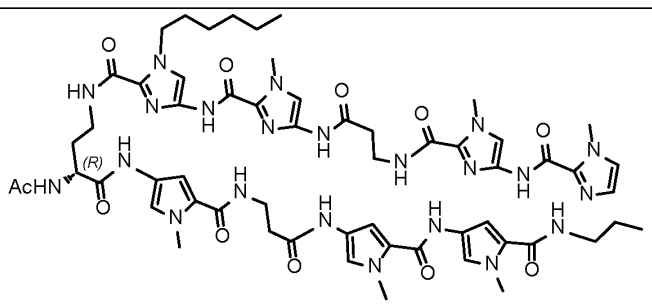
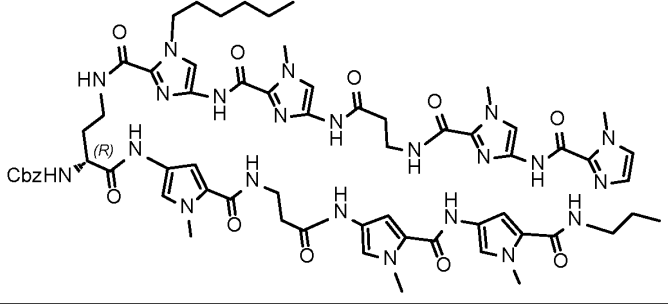
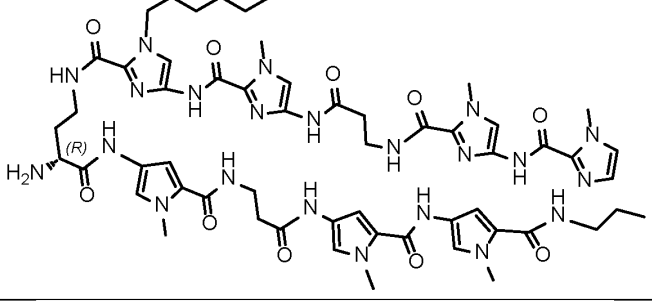
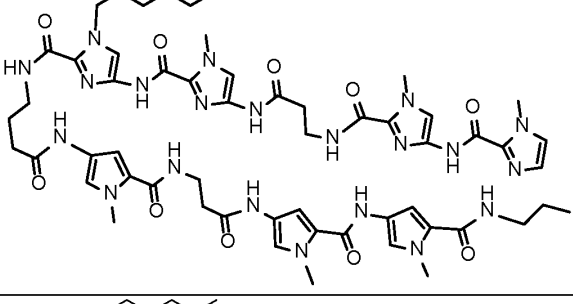
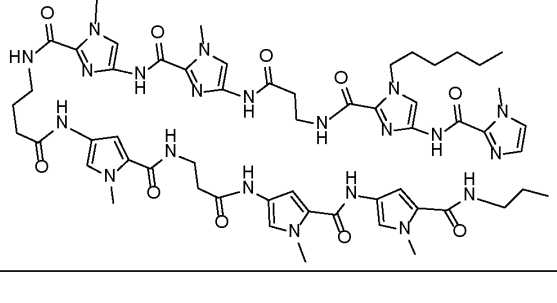
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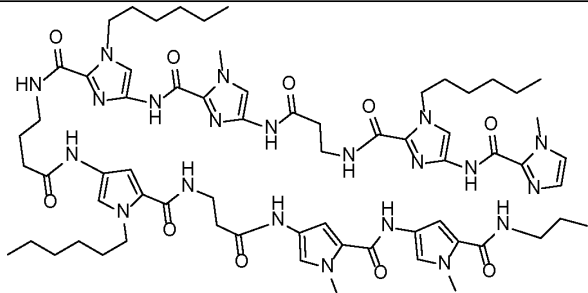
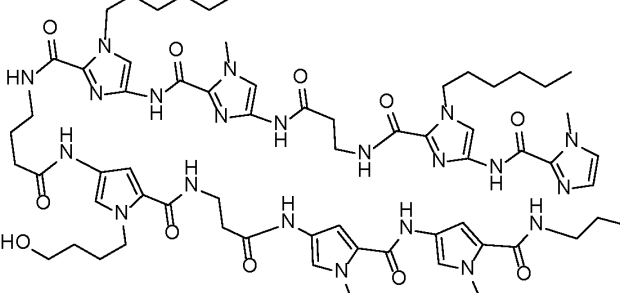
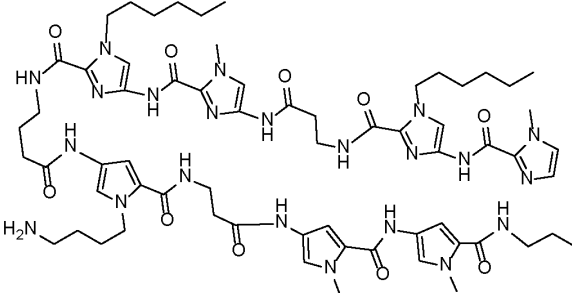
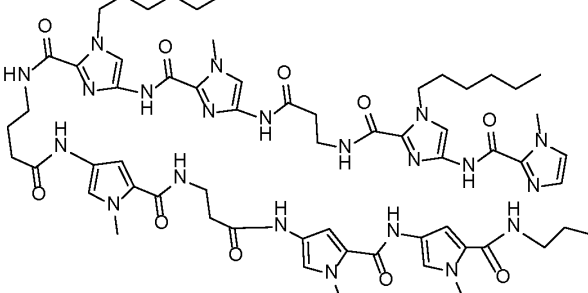
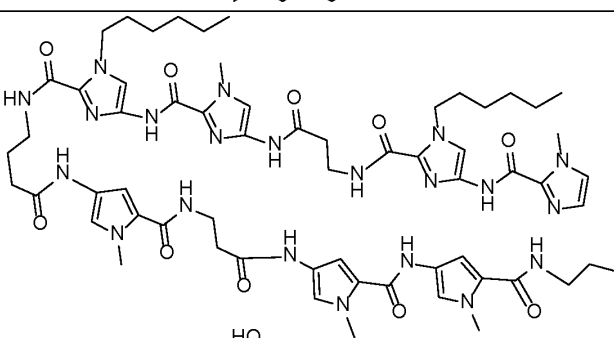
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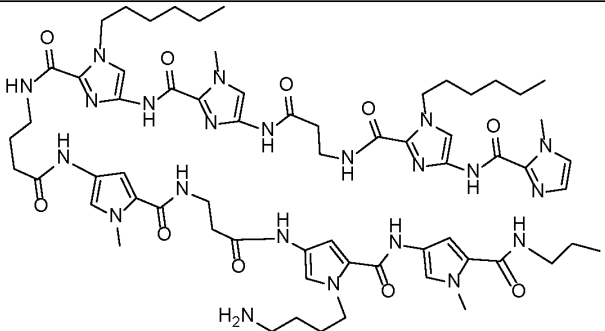
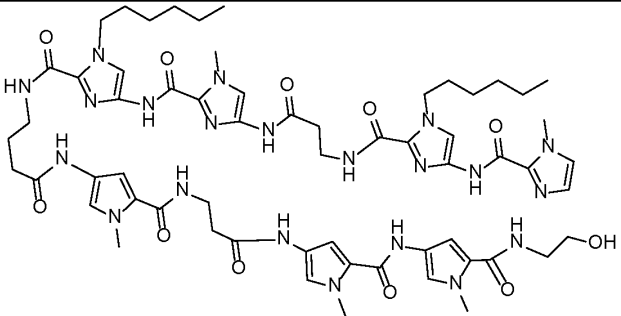
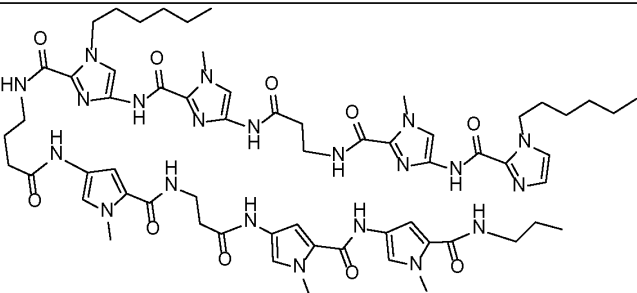
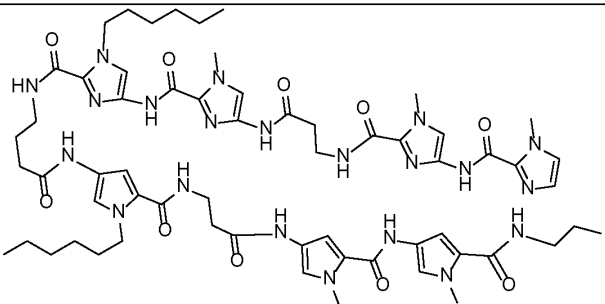
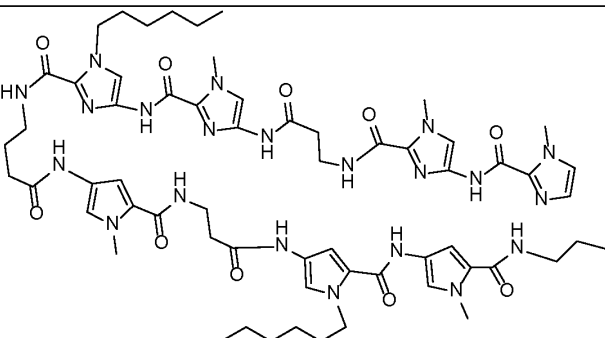
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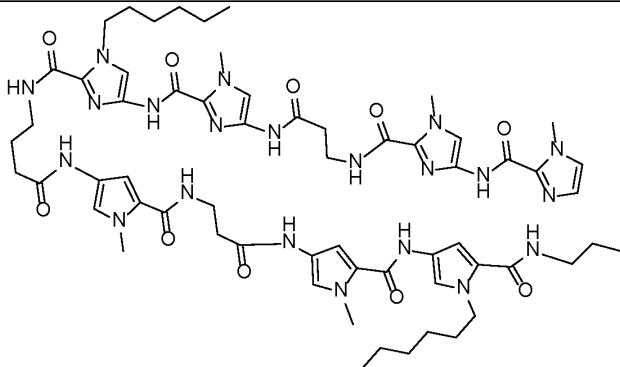
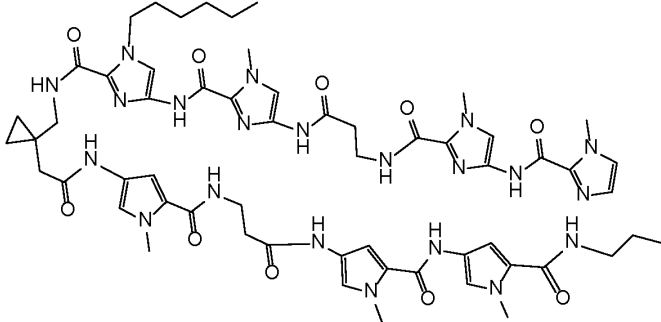
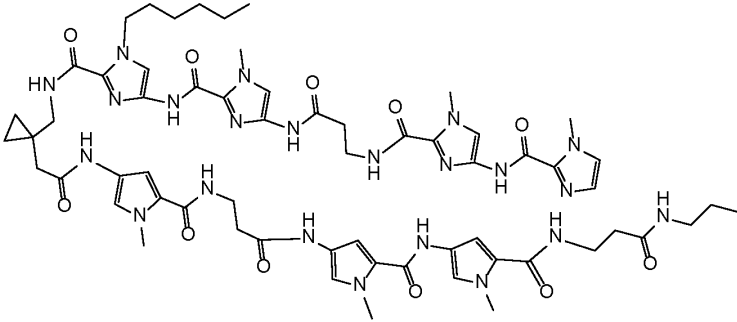
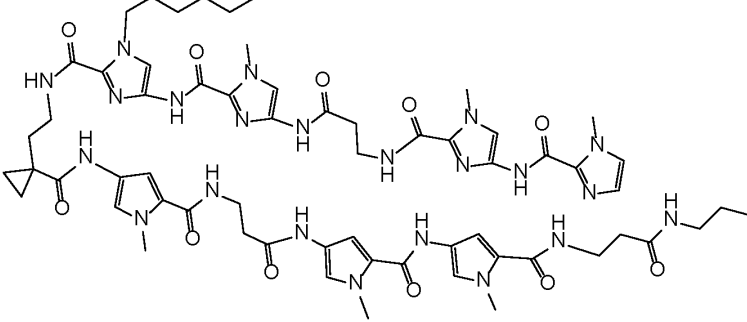
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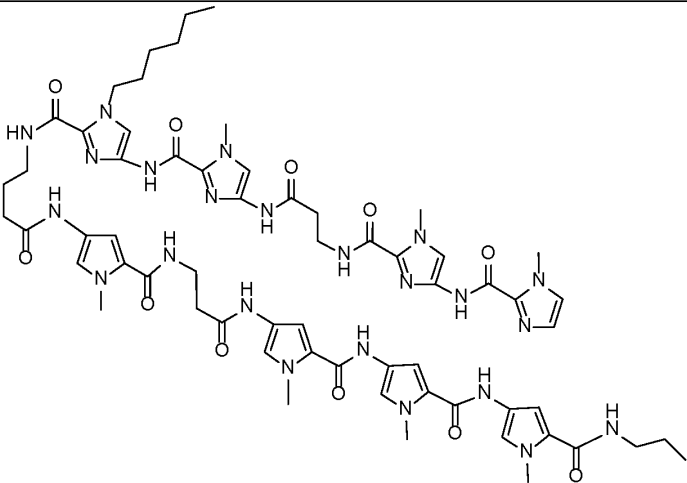
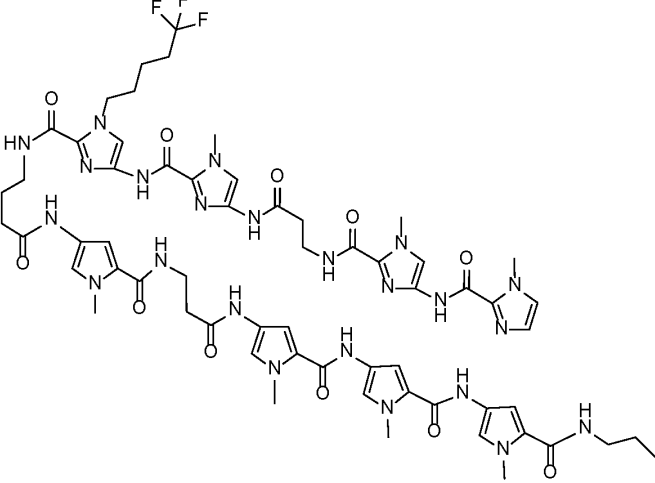
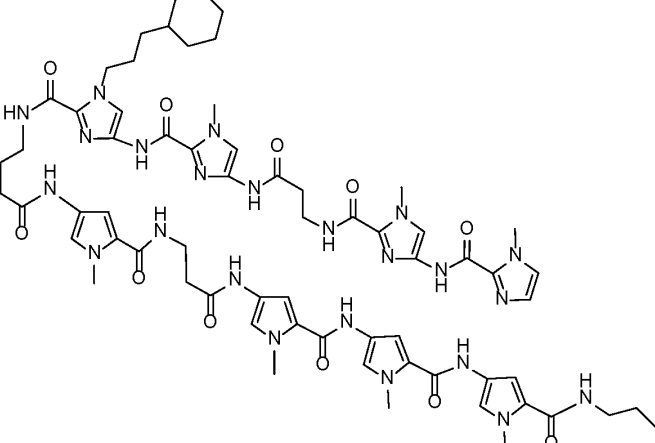
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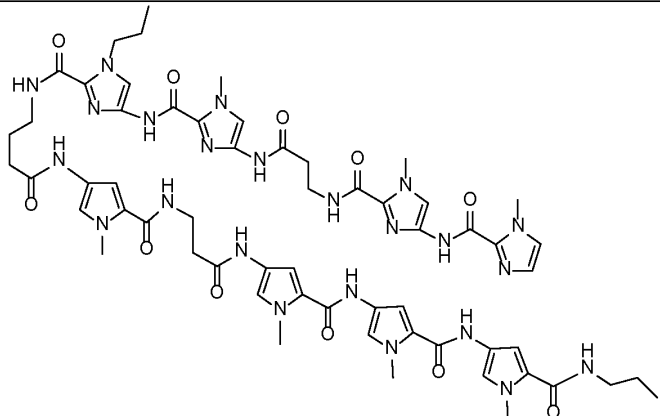
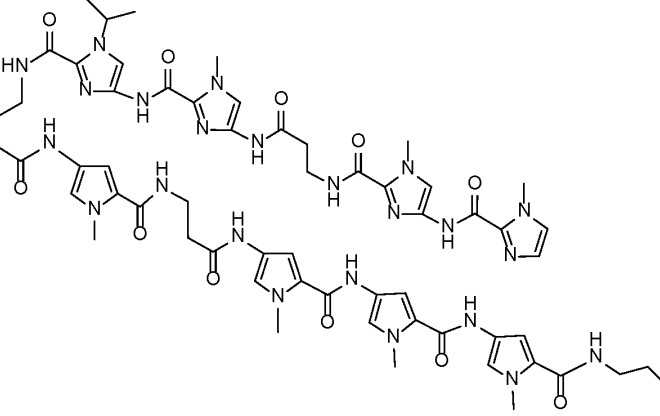
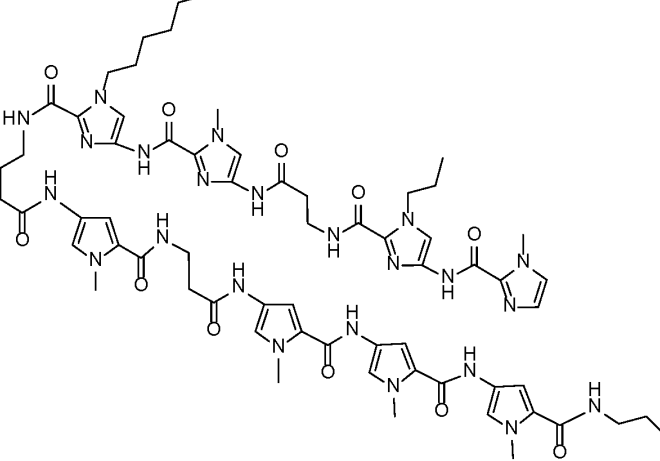
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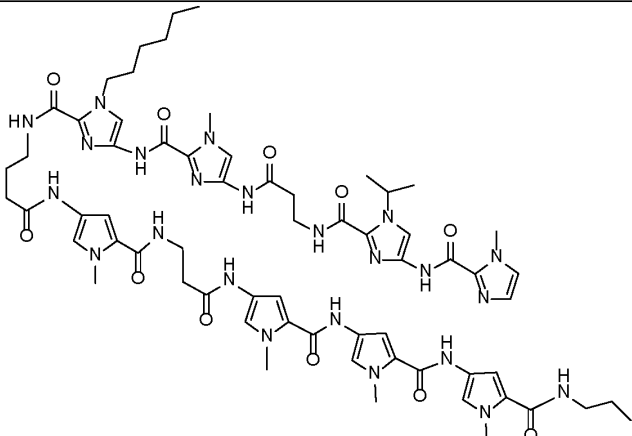
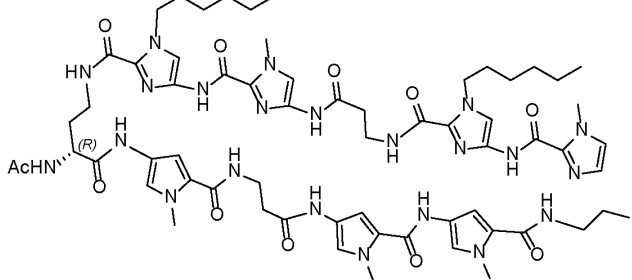
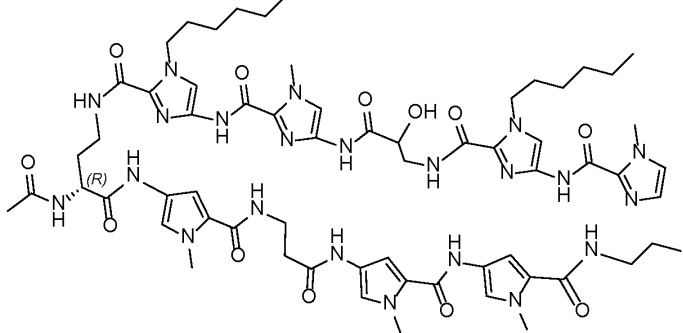
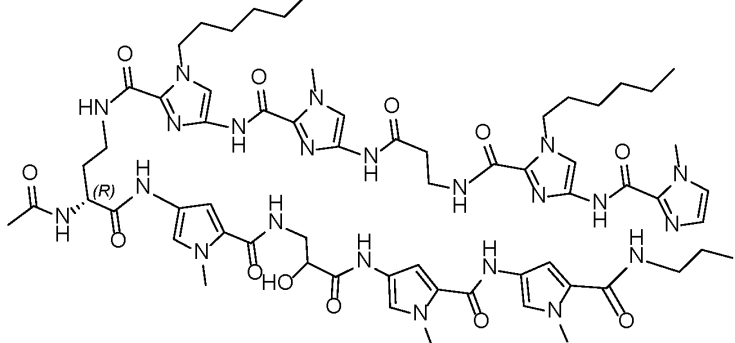
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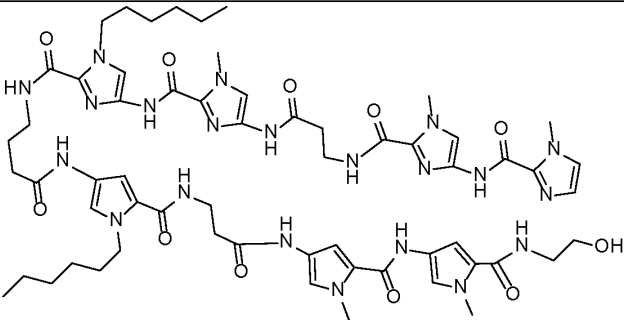
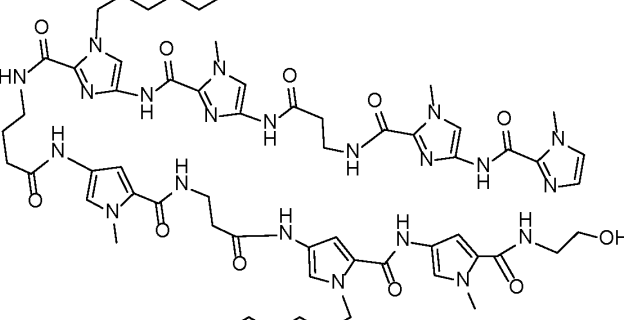
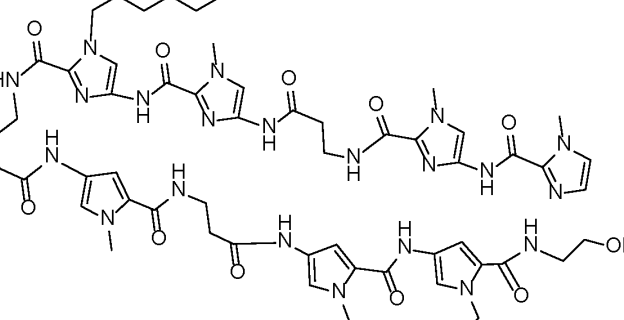
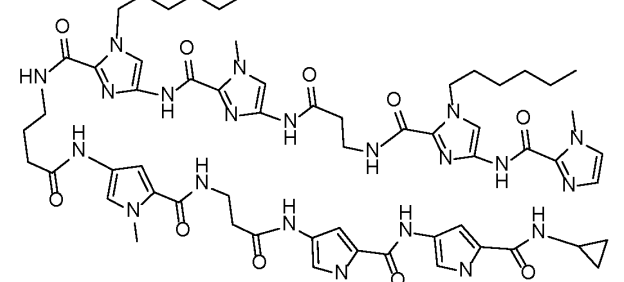
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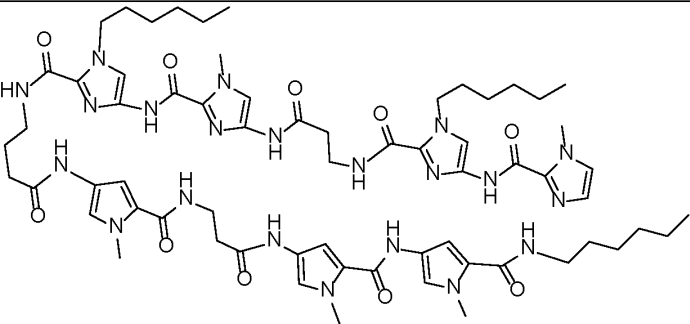
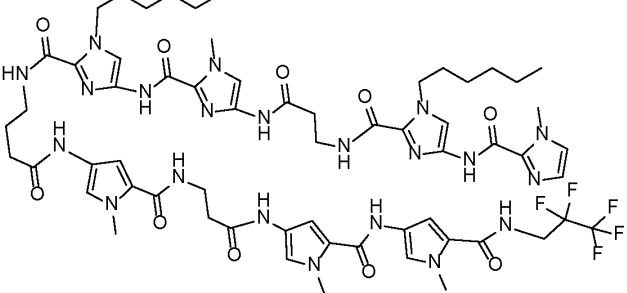
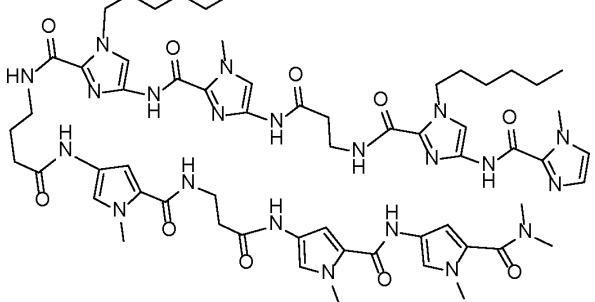
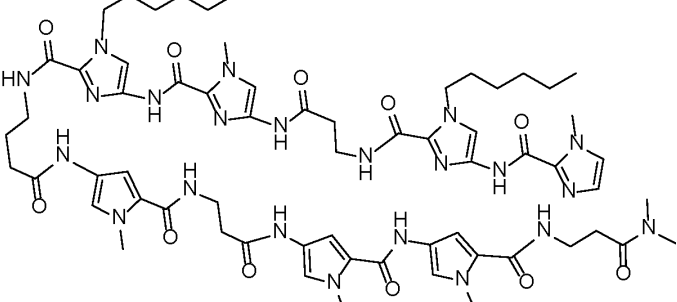
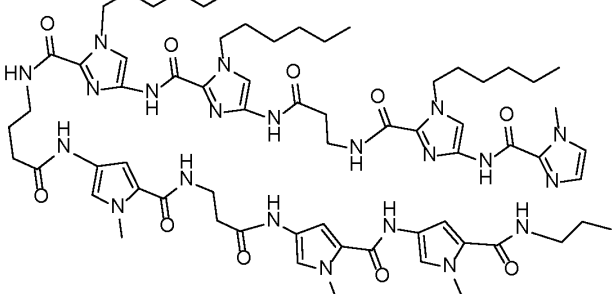
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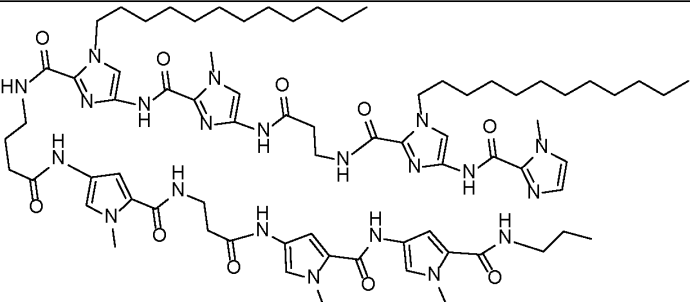
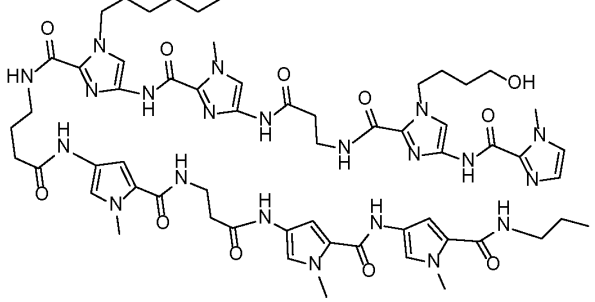
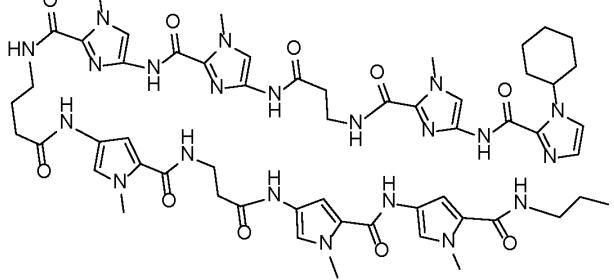
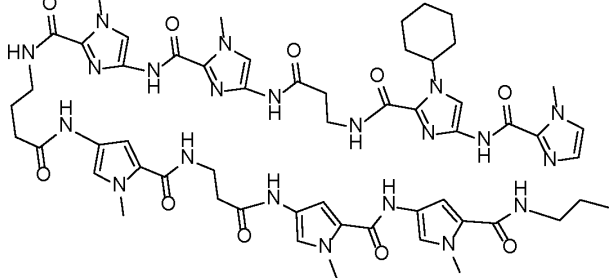
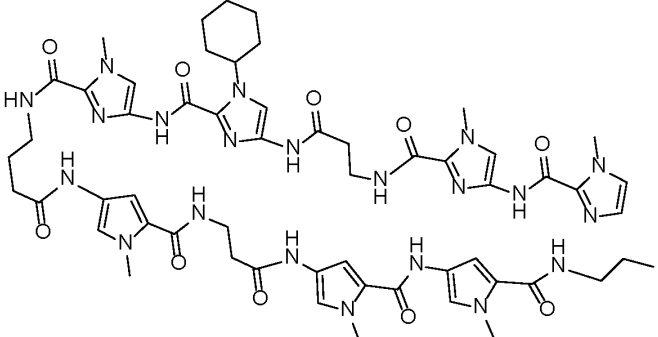
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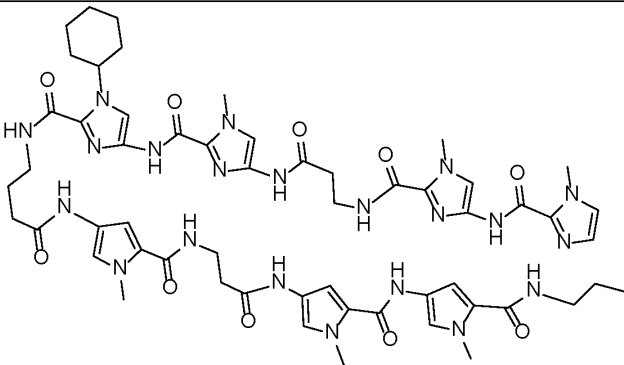
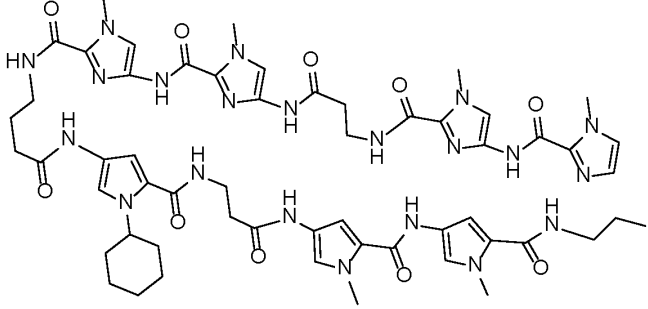
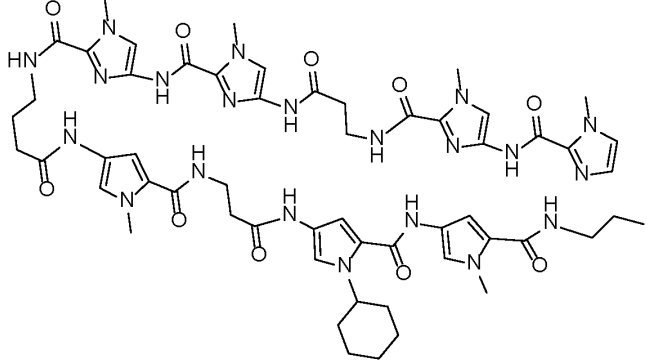
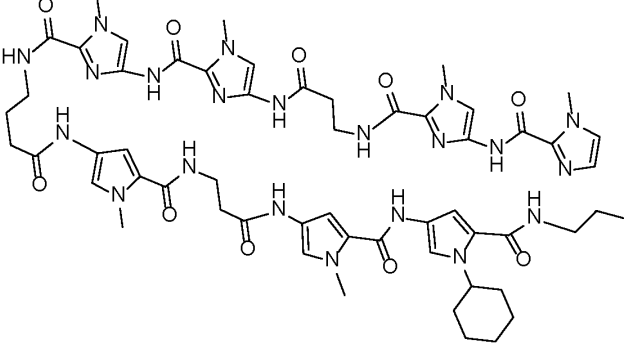
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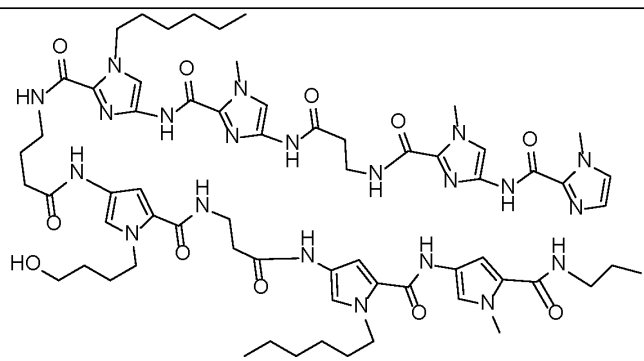
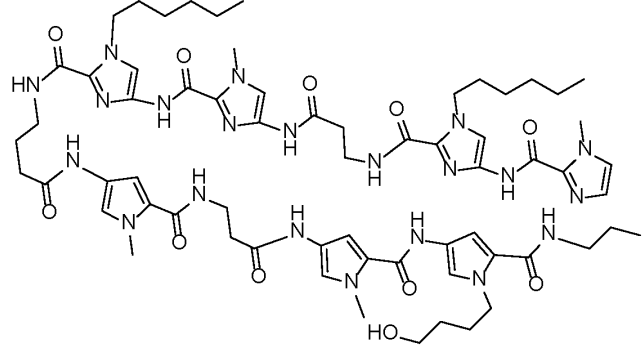
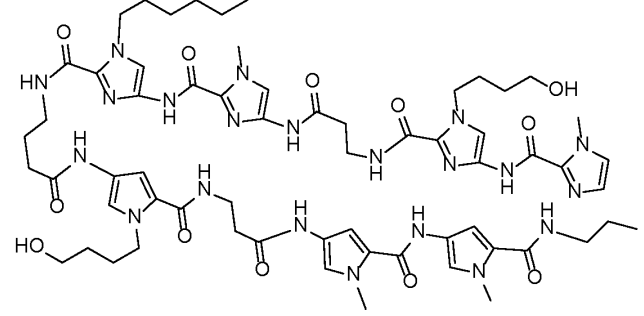
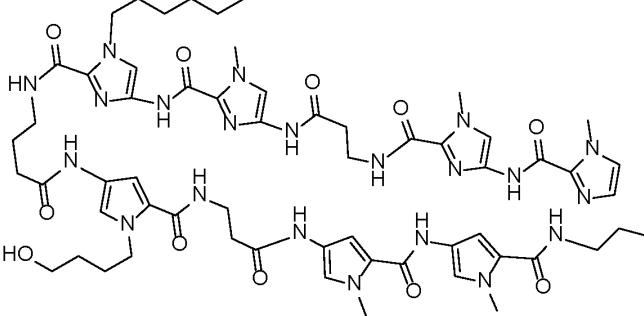
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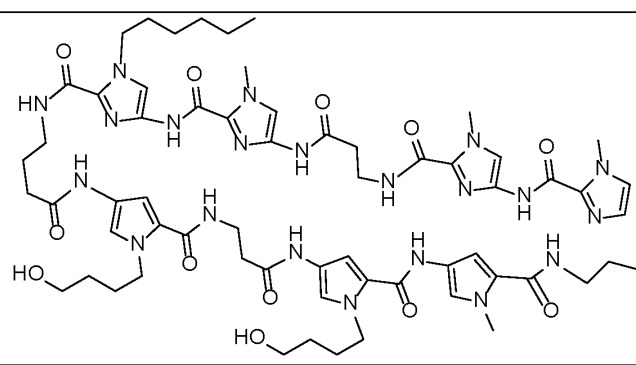
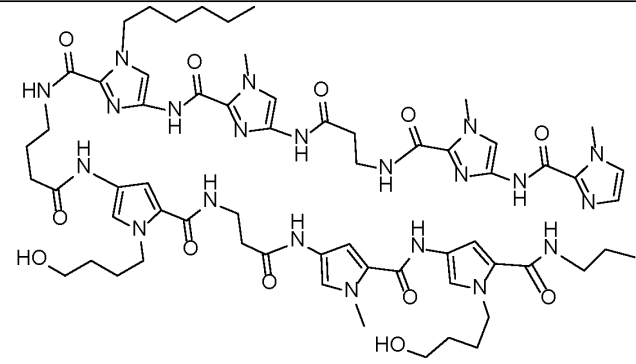
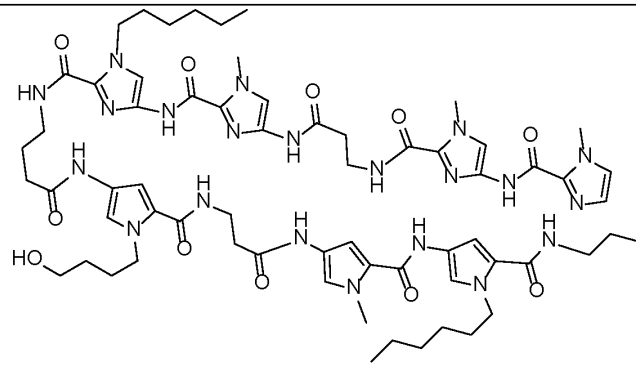
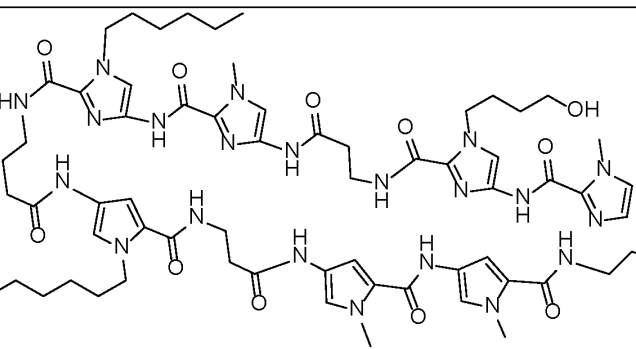
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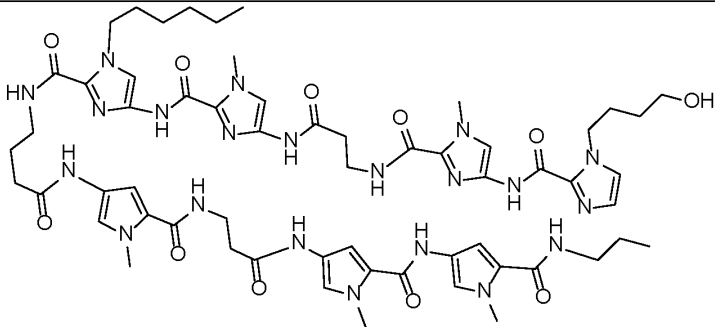
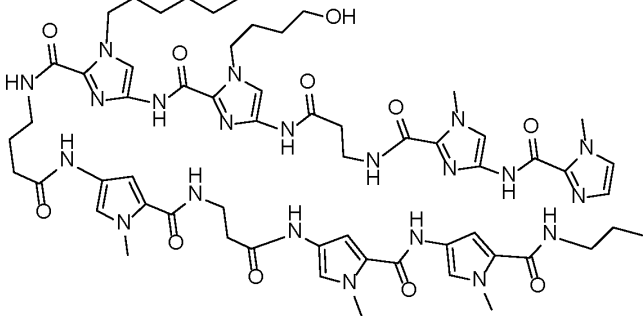
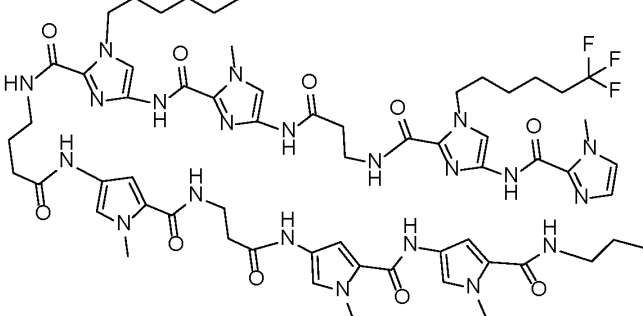
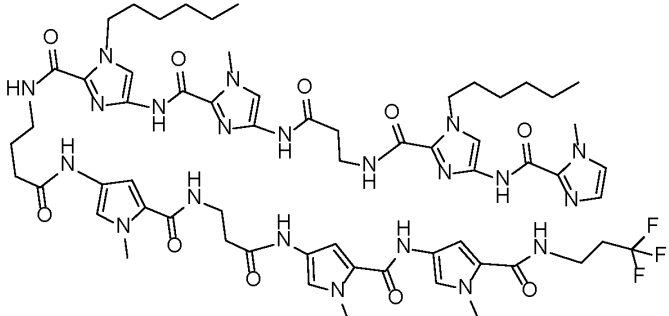
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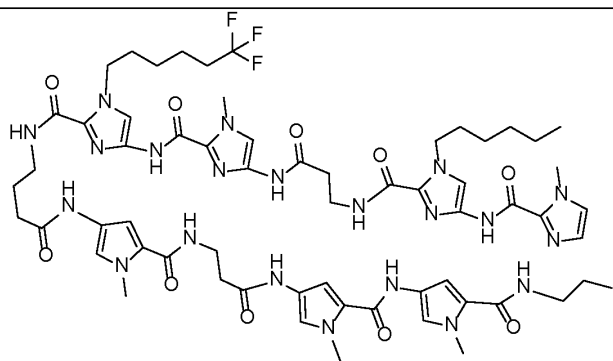
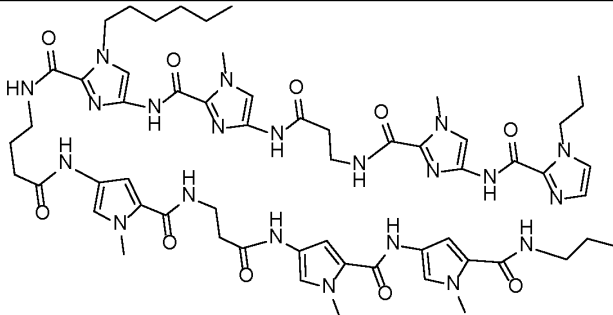
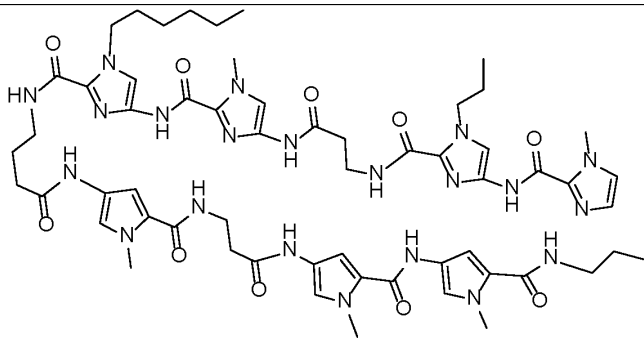
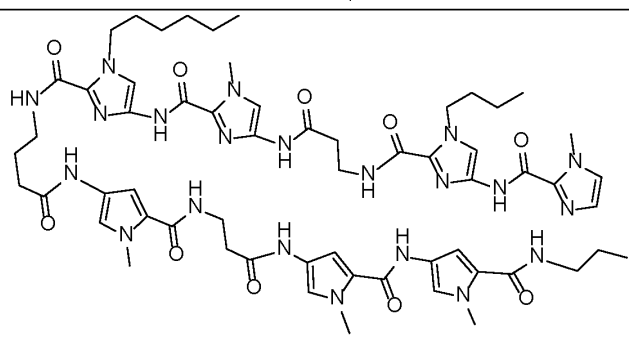
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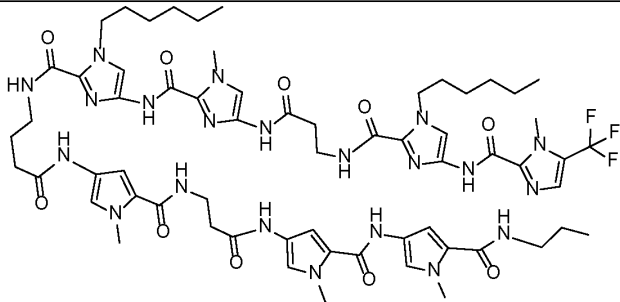
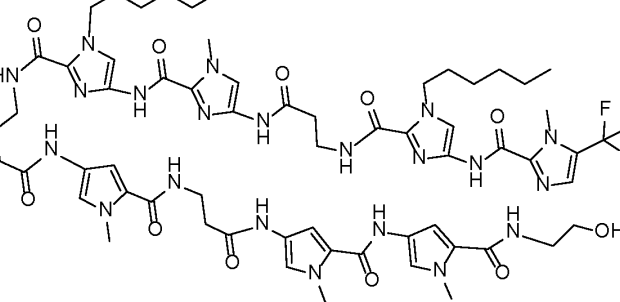
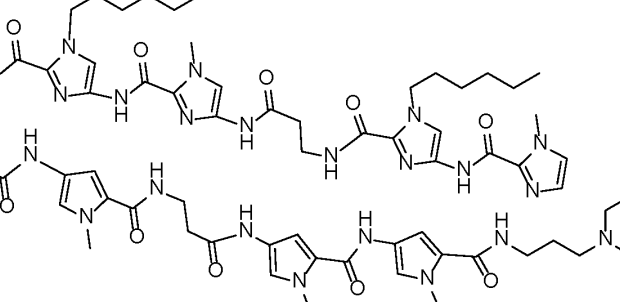
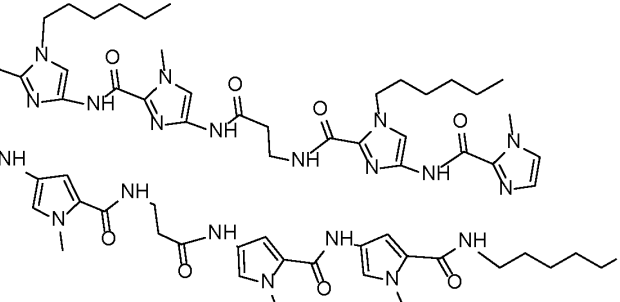
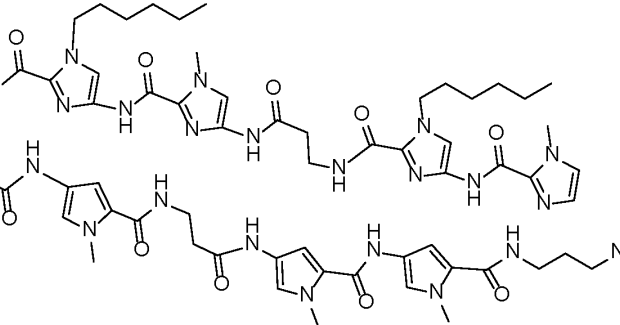
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A-169	 Chemical structure A-169 is a complex molecule featuring a central chain of amide linkages. The structure includes several heterocyclic rings, including pyridine, imidazole, and a cyclohexyl group. The molecule is highly branched and contains multiple amide bonds.
A-170	 Chemical structure A-170 is a complex molecule featuring a central chain of amide linkages. The structure includes several heterocyclic rings, including pyridine, imidazole, and a cyclohexyl group. The molecule is highly branched and contains multiple amide bonds.
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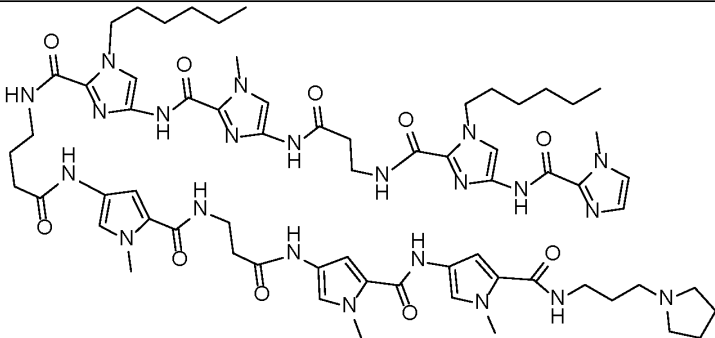
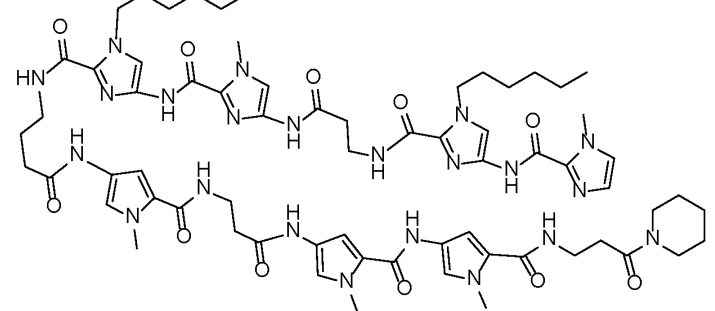
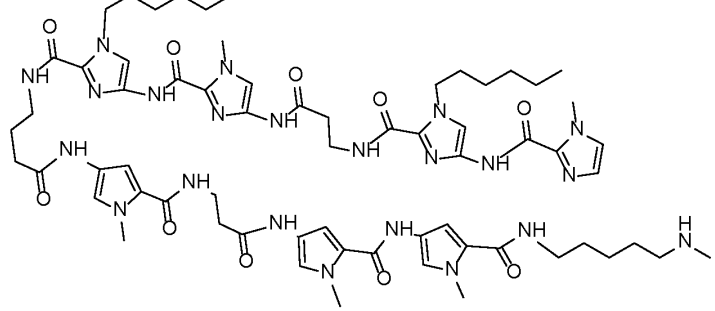
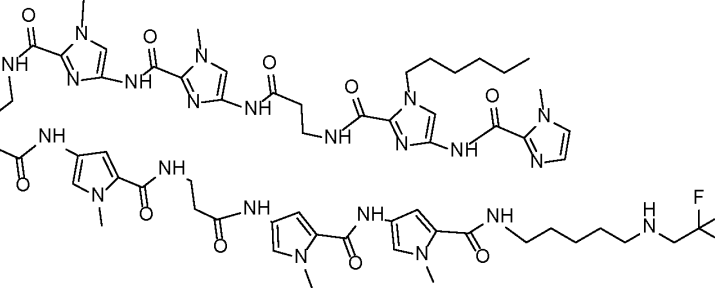
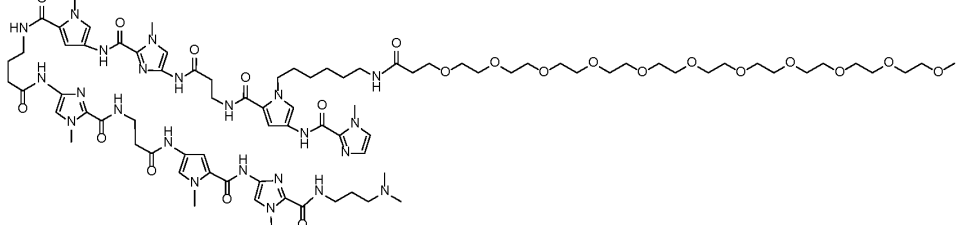
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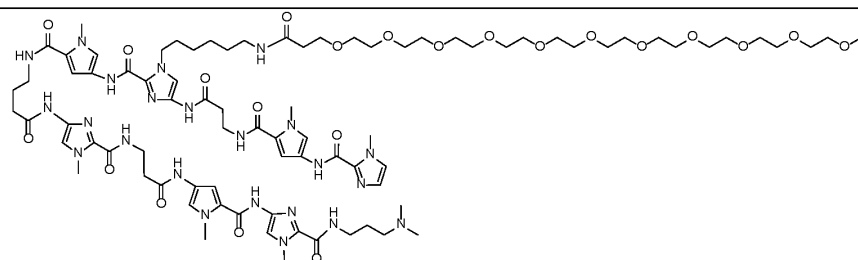
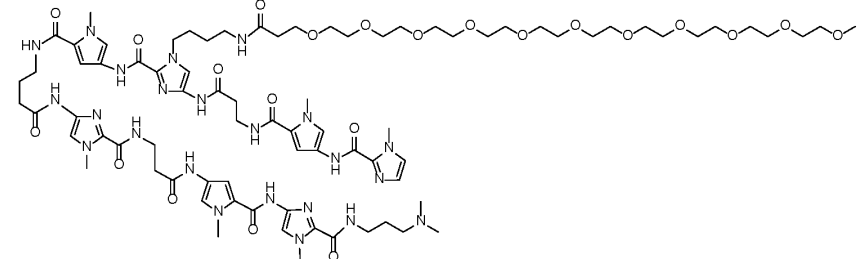
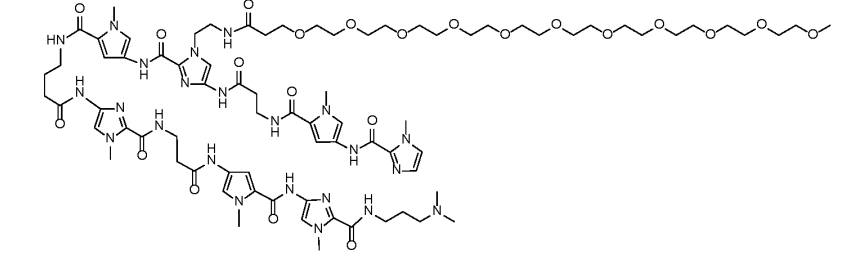
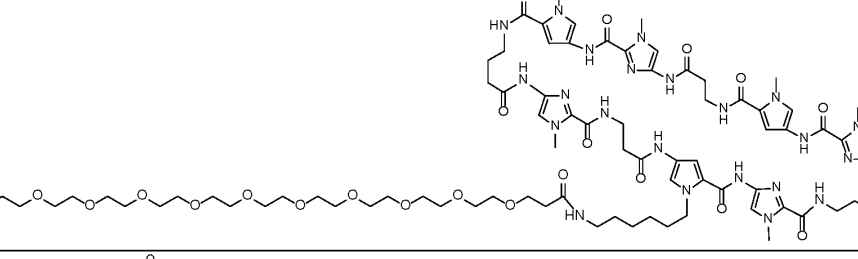
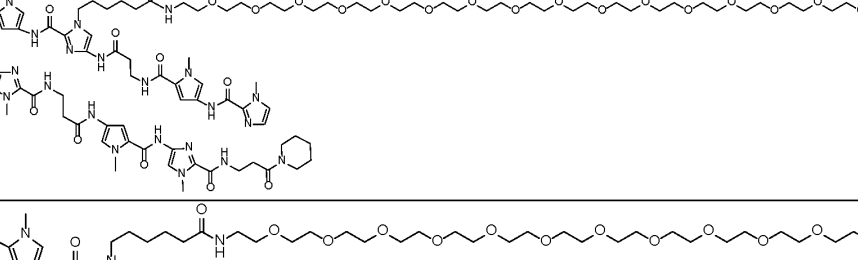
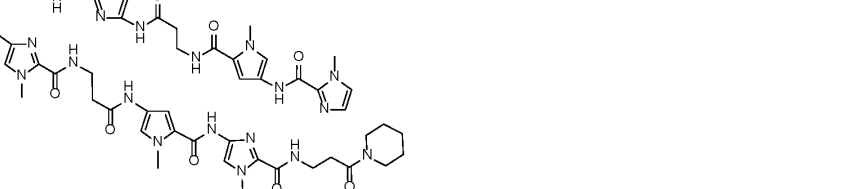
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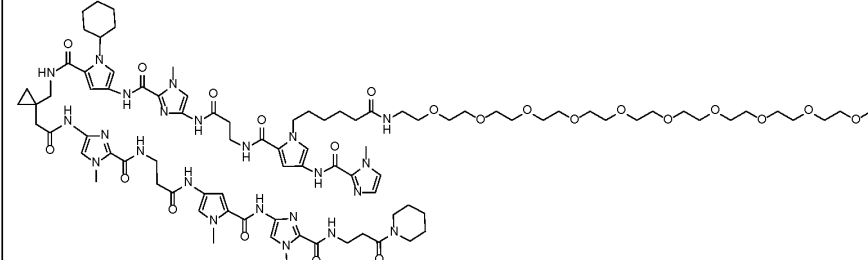
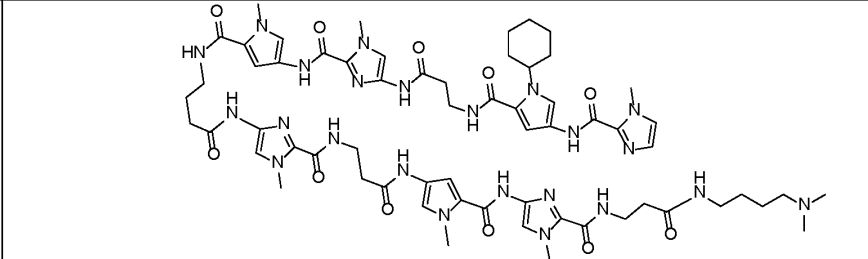
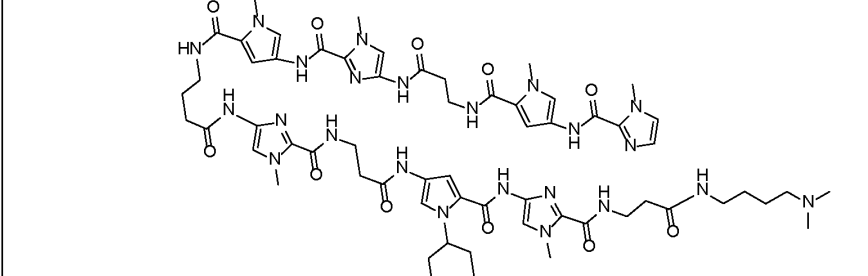
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Methods of Use

[00151] The present disclosure also relates to a method of modulating the transcription of *dmpk*, *atxn8*, *atxn80s*, or *tcf4*, the method comprising the step of contacting *dmpk*, *atxn8*, *atxn80s*, or *tcf4*, with a transcription modulator molecule as described herein, or a pharmaceutically acceptable salt thereof.

[00152] The cell phenotype, cell proliferation, transcription of *dmpk*, *atxn8*, *atxn80s*, or *tcf4*; production of mRNA from transcription of *dmpk*, *atxn8*, *atxn80s*, or *tcf4*; translation of *dmpk*, *atxn8*, *atxn80s*, or *tcf4*; change in biochemical output produced by the protein coded by *dmpk*, *atxn8*, *atxn80s*, or *tcf4*; or noncovalent binding of the protein coded by *dmpk*, *atxn8*, *atxn80s*, or *tcf4* with a natural binding partner may be monitored. Such methods may be modes of treatment of disease, biological assays, cellular assays, biochemical assays, or the like.

[00153] In some embodiments, the gene is *dmpk*. In some embodiments, the gene is *atxn8*. In some embodiments, the gene is *atxn80s*. In some embodiments, the gene is *tcf4*.

[00154] Also provided herein are methods of suppressing transcription of a *tcf4* gene having a nucleotide repeat sequence comprising CAG with a transcription modulator molecule as described herein, or a pharmaceutically acceptable salt thereof.

[00155] Also provided herein is a method of treatment of a disease mediated by transcription of *dmpk*, *atxn8*, *atxn80s*, or *tcf4* comprising the administration of a therapeutically effective amount of a transcription modulator molecule as disclosed herein, or a salt thereof, to a subject in need thereof.

[00156] In some embodiments, the methods of treatment reduce hairpin formation of mRNA. In some embodiments, the methods herein reduce formation of nuclear foci. In some embodiments, the methods herein reduce sequestration of Muscleblind-like (MBNL) protein, which in some cases leads to defective RNA splicing or spliceopathy.

[00157] In some cases, the defective RNA splicing or spliceopathy may lead to dysfunction and loss of corneal endothelial cells (CEC). In some cases, administration of a composition comprising a transcription modulator molecule as described herein, or a pharmaceutically acceptable salt thereof, restores CEC function and/or maintains the number of CECs in the cornea.

[00158] In some embodiments, the disease is selected from DM1 and FECD.

[00159] In some embodiments, the disease is DM1.

[00160] In some embodiments, the disease is Fuchs' Endothelial Corneal Dystrophy (FECD).

[00161] The binding affinity between the transcription modulator molecule and the target gene can be adjusted based on the composition of the molecule. In some embodiments, the molecule is capable of binding the DNA with an affinity of less than about 1 μ M, about 900 nM, about 800 nM, about 700 nM, about 600 nM, about 500 nM, about 400 nM, about 300 nM, about 250 nM, about 200 nM, about 150 nM, about 100 nM, about 50 nM, about 10 nM, or about 1 nM, about. In some embodiments, the molecule is capable of binding the DNA with an affinity in the range of about 0.1 nM – 1 μ M, 1-600 nM, 10-500 nM, 20-500 nM, 50-400 nM, or 100-300 nM.

[00162] In some embodiments, the molecule is capable of binding the DNA with an affinity of less than 500 nM. In some embodiments, the molecule capable of binding the DNA with an affinity of less than about 300 nM. In some embodiments, the molecule is capable of binding the DNA with an affinity of less than about 200 nM.

[00163] The binding affinity between the molecule and the target DNA can be determined using a quantitative footprint titration experiment. The experiment involves measuring the dissociation constant K_d of the molecule for the target sequence at either 24 °C or 37 °C, and using either standard assay solution conditions or approximate intracellular solution conditions.

[00164] In another aspect, provided herein is a method of treating myotonic dystrophy type 1 (DM1) in a subject in need thereof, the method comprising administering to the subject an effective amount of a molecule disclosed herein, or a pharmaceutically acceptable salt thereof.

[00165] In another aspect, provided herein is a method of treating Fuchs' endothelial dystrophy or Fuchs' endothelial corneal dystrophy (FECD) in a subject in need thereof, the method comprising administering to the subject an effective amount of a molecule disclosed herein, or a pharmaceutically acceptable salt thereof.

Pharmaceutical Compositions and Administration

[00166] The compounds described herein are administered to a subject in need thereof, either alone or in combination with pharmaceutically acceptable carriers, excipients, or diluents, in a pharmaceutical composition, according to standard pharmaceutical practice. In some embodiments, the compounds described herein are administered to animals.

[00167] In another aspect, provided herein are pharmaceutical compositions comprising a compound described herein, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient. Pharmaceutical compositions are formulated in a conventional manner using one or more pharmaceutically acceptable excipients that facilitate processing of the active compounds into preparations that can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. A summary of pharmaceutical compositions described herein can be found, for example, in Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, (N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins 1999), herein incorporated by reference for such disclosure.

[00168] In some embodiments, the pharmaceutically acceptable excipient is selected from carriers, binders, filling agents, suspending agents, flavoring agents, sweetening agents, disintegrating agents, dispersing agents, surfactants, lubricants, colorants, diluents, solubilizers, moistening agents, plasticizers, stabilizers, penetration enhancers, wetting agents, anti-foaming agents, antioxidants, preservatives, and any combinations thereof.

[00169] The dose of a pharmaceutical agent described herein for treating a disease or disorder may depend upon the subject's condition, that is, stage of the disease, severity of symptoms caused by the disease, general health status, as well as age, gender, and weight, and other factors apparent to a person skilled in the medical art. Pharmaceutical compositions may be administered in a manner appropriate to the disease to be treated as determined by persons skilled in the medical arts. In addition to the factors described herein and above related to use of pharmaceutical agent for treating a disease or disorder, suitable duration and frequency of administration of the pharmaceutical agent may also be determined or adjusted by such factors as the condition of the patient, the type and severity of the patient's disease, the particular form of the active ingredient, and the method of administration. Optimal doses of an agent may generally be determined using experimental models and/or clinical trials. The optimal dose may depend upon the body mass, weight, or blood volume of the subject. The use of the minimum dose that is sufficient to provide effective therapy is usually preferred. Design and execution of pre-clinical and clinical studies for a pharmaceutical agent, including when administered for prophylactic benefit, described herein are well within the skill of a person skilled in the relevant art. When two or more pharmaceutical agents are administered to treat a disease or disorder, the optimal dose of each pharmaceutical agent may be different, such as less than when either agent is administered alone as a single agent therapy. In certain particular embodiments, two pharmaceutical agents in combination may act synergistically or additively, and either agent may be used in a lesser amount

than if administered alone. An amount of a pharmaceutical agent that may be administered per day may be, for example, between about 0.01 mg/kg and 100 mg/kg, *e.g.*, between about 0.1 to 1 mg/kg, between about 1 to 10 mg/kg, between about 10-50 mg/kg, between about 50-100 mg/kg body weight. In other embodiments, the amount of a pharmaceutical agent that may be administered per day is between about 0.01 mg/kg and 1000 mg/kg, between about 100-500 mg/kg, or between about 500-1000 mg/kg body weight. The optimal dose, per day or per course of treatment, may be different for the disease or disorder to be treated and may also vary with the administrative route and therapeutic regimen.

Abbreviations and Definitions

[00170] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs.

[00171] Unless the context requires otherwise, throughout the specification and claims which follow, the word “comprise” and variations thereof, such as, “comprises” and “comprising” are to be construed in an open, inclusive sense, that is, as “including, but not limited to.” Further, headings provided herein are for convenience only and do not interpret the scope or meaning of the claimed invention.

[00172] As used in this specification and the appended claims, the singular forms “a,” “an,” and “the” include plural referents unless the content clearly dictates otherwise. It should also be noted that the term “or” is generally employed in its sense including “and/or” unless the content clearly dictates otherwise.

[00173] When ranges of values are disclosed, and the notation “from n_1 ... to n_2 ” or “between n_1 ... and n_2 ” is used, where n_1 and n_2 are the numbers, then unless otherwise specified, this notation is intended to include the numbers themselves and the range between them. This range may be integral or continuous between and including the end values. By way of example, the range “from 2 to 6 carbons” is intended to include two, three, four, five, and six carbons, since carbons come in integer units. Compare, by way of example, the range “from 1 to 3 μ M (micromolar),” which is intended to include 1 μ M, 3 μ M, and everything in between to any number of significant figures (*e.g.*, 1.255 μ M, 2.1 μ M, 2.9999 μ M, etc.).

[00174] The terms below, as used herein, have the following meanings, unless indicated otherwise:

[00175] “oxo” refers to =O.

[00176] “Carboxyl” refers to -COOH.

[00177] “Cyano” refers to -CN.

[00178] “Alkyl” refers to a straight-chain, or branched-chain saturated hydrocarbon monoradical having from one to about ten carbon atoms, more preferably one to six carbon atoms. Examples include, but are not limited to methyl, ethyl, n-propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, isopentyl, neopentyl, tert-amyl and hexyl, and longer alkyl groups, such as heptyl, octyl and the like. Whenever it appears herein, a numerical range such as “C₁-C₆ alkyl” or “C₁-alkyl”, means that the alkyl group may consist of 1 carbon atom, 2

carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms, although the present definition also covers the occurrence of the term “alkyl” where no numerical range is designated. In some embodiments, the alkyl is a C₁₋₁₀alkyl. In some embodiments, the alkyl is a C₁₋₆alkyl. In some embodiments, the alkyl is a C₁₋₅alkyl. In some embodiments, the alkyl is a C₁₋₄alkyl. In some embodiments, the alkyl is a C₁₋₃alkyl. Unless stated otherwise specifically in the specification, an alkyl group may be optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the alkyl is optionally substituted with oxo, halogen, -N₃, -CN, -C(O)OH, -C(O)OMe, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, the alkyl is optionally substituted with halogen, -CN, -OH, or -OMe. In some embodiments, the alkyl is optionally substituted with halogen.

[00179] “Alkenyl” refers to a straight-chain, or branched-chain hydrocarbon monoradical having one or more carbon-carbon double-bonds and having from two to about ten carbon atoms, more preferably two to about six carbon atoms. The group may be in either the *cis* or *trans* conformation about the double bond(s), and should be understood to include both isomers. Examples include, but are not limited to ethenyl (-CH=CH₂), 1-propenyl (-CH₂CH=CH₂), isopropenyl [-C(CH₃)=CH₂], butenyl, 1,3-butadienyl and the like. Whenever it appears herein, a numerical range such as “C₂-C₆ alkenyl” or “C₂₋₆alkenyl”, means that the alkenyl group may consist of 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms, although the present definition also covers the occurrence of the term “alkenyl” where no numerical range is designated. Unless stated otherwise specifically in the specification, an alkenyl group may be optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the alkenyl is optionally substituted with oxo, halogen, -N₃, -CN, -C(O)OH, -C(O)OMe, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, the alkenyl is optionally substituted with halogen, -CN, -OH, or -OMe. In some embodiments, the alkenyl is optionally substituted with halogen.

[00180] “Alkynyl” refers to a straight-chain or branched-chain hydrocarbon monoradical having one or more carbon-carbon triple-bonds and having from two to about ten carbon atoms, more preferably from two to about six carbon atoms. Examples include, but are not limited to ethynyl, 2-propynyl, 2-butyne, 1,3-butadiynyl and the like. Whenever it appears herein, a numerical range such as “C₂-C₆ alkynyl” or “C_{2-C6}alkynyl”, means that the alkynyl group may consist of 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms, although the present definition also covers the occurrence of the term “alkynyl” where no numerical range is designated. Unless stated otherwise specifically in the specification, an alkynyl group may be optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the alkynyl is optionally substituted with oxo, halogen, -N₃, -CN, -C(O)OH, -C(O)OMe, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, the alkynyl is optionally substituted with halogen, -CN, -OH, or -OMe. In some embodiments, the alkynyl is optionally substituted with halogen.

[00181] “Alkylene” refers to a straight or branched divalent hydrocarbon chain. Unless stated otherwise specifically in the specification, an alkylene group may be optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the alkylene is optionally substituted with oxo, halogen, $-N_3$, $-CN$, $-C(O)OH$, $C(O)OMe$, $-OH$, $-OMe$, $-NH_2$, or $-NO_2$. In some embodiments, the alkylene is optionally substituted with halogen, $-CN$, $-OH$, or $-OMe$. In some embodiments, the alkylene is optionally substituted with halogen.

[00182] “Alkoxy” refers to a radical of the formula $-OR_a$ where R_a is an alkyl radical as defined. Unless stated otherwise specifically in the specification, an alkoxy group may be optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the alkoxy is optionally substituted with halogen, $-N_3$, $-CN$, $-C(O)OH$, $C(O)OMe$, $-OH$, $-OMe$, $-NH_2$, or $-NO_2$. In some embodiments, the alkoxy is optionally substituted with halogen, $-CN$, $-OH$, or $-OMe$. In some embodiments, the alkoxy is optionally substituted with halogen.

[00183] “Aryl” refers to a radical derived from an aromatic monocyclic or aromatic multicyclic hydrocarbon ring system by removing a hydrogen atom from a ring carbon atom. The aromatic monocyclic or aromatic multicyclic hydrocarbon ring system can contain only hydrogen and carbon and from five to eighteen carbon atoms, where at least one of the rings in the ring system is aromatic, *i.e.*, it contains a cyclic, delocalized $(4n+2)$ π -electron system in accordance with the Hückel theory. The ring system from which aryl groups are derived include, but are not limited to, groups such as benzene, fluorene, indane, indene, tetralin and naphthalene. The aryl radical may be a monocyclic, bicyclic, tricyclic, or tetracyclic ring system, which may include fused (when fused with a cycloalkyl or heterocycloalkyl ring, the aryl is bonded through an aromatic ring atom) or bridged ring systems. In some embodiments, the aryl is a 6- to 10-membered aryl. In some embodiments, the aryl is a 6-membered aryl (phenyl). Aryl radicals include, but are not limited to, aryl radicals derived from the hydrocarbon ring systems of anthrylene, naphthylene, phenanthrylene, anthracene, azulene, benzene, chrysene, fluoranthene, fluorene, as-indacene, s-indacene, indane, indene, naphthalene, phenalene, phenanthrene, pleiadene, pyrene, and triphenylene. Unless stated otherwise specifically in the specification, an aryl may be optionally substituted, for example, with halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the aryl is optionally substituted with halogen, methyl, ethyl, $-N_3$, $-CN$, $-C(O)OH$, $C(O)OMe$, $-CF_3$, $-OH$, $-OMe$, $-NH_2$, or $-NO_2$. In some embodiments, the aryl is optionally substituted with halogen, methyl, ethyl, $-CN$, $-CF_3$, $-OH$, or $-OMe$. In some embodiments, the aryl is optionally substituted with halogen.

[00184] “Cycloalkyl” refers to a partially or fully saturated, monocyclic, or polycyclic carbocyclic ring, which may include fused (when fused with an aryl or a heteroaryl ring, the cycloalkyl is bonded through a non-aromatic ring atom), spiro, or bridged ring systems. In some embodiments, the cycloalkyl is fully saturated. Representative cycloalkyls include, but are not limited to, cycloalkyls having from three to fifteen

carbon atoms (*e.g.*, C₃-C₁₅ fully saturated cycloalkyl or C₃-C₁₅ cycloalkenyl), from three to ten carbon atoms (*e.g.*, C₃-C₁₀ fully saturated cycloalkyl or C₃-C₁₀ cycloalkenyl), from three to eight carbon atoms (*e.g.*, C₃-C₈ fully saturated cycloalkyl or C₃-C₈ cycloalkenyl), from three to six carbon atoms (*e.g.*, C₃-C₆ fully saturated cycloalkyl or C₃-C₆ cycloalkenyl), from three to five carbon atoms (*e.g.*, C₃-C₅ fully saturated cycloalkyl or C₃-C₅ cycloalkenyl), or three to four carbon atoms (*e.g.*, C₃-C₄ fully saturated cycloalkyl or C₃-C₄ cycloalkenyl). In some embodiments, the cycloalkyl is a 3- to 10-membered fully saturated cycloalkyl or a 3- to 10-membered cycloalkenyl. In some embodiments, the cycloalkyl is a 3- to 6-membered fully saturated cycloalkyl or a 3- to 6-membered cycloalkenyl. In some embodiments, the cycloalkyl is a 5- to 6-membered fully saturated cycloalkyl or a 5- to 6-membered cycloalkenyl. Monocyclic cycloalkyls include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic cycloalkyls include, for example, adamantyl, norbornyl, decalinyl, bicyclo[3.3.0]octane, bicyclo[4.3.0]nonane, cis-decalin, trans-decalin, bicyclo[2.1.1]hexane, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, bicyclo[3.2.2]nonane, and bicyclo[3.3.2]decane, and 7,7-dimethyl-bicyclo[2.2.1]heptanyl. Partially saturated cycloalkyls include, for example cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl. Unless stated otherwise specifically in the specification, a cycloalkyl is optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, a cycloalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -N₃, -CN, -C(O)OH, C(O)OMe, -CF₃, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, a cycloalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -CF₃, -OH, or -OMe. In some embodiments, the cycloalkyl is optionally substituted with halogen.

[00185] "Cycloalkenyl" refers to an unsaturated non-aromatic monocyclic or polycyclic hydrocarbon radical consisting solely of carbon and hydrogen atoms, which includes fused or bridged ring systems, preferably having from three to twelve carbon atoms and comprising at least one double bond. In certain embodiments, a cycloalkenyl comprises three to ten carbon atoms. In other embodiments, a cycloalkenyl comprises five to seven carbon atoms. The cycloalkenyl may be attached to the rest of the molecule by a single bond. Examples of monocyclic cycloalkenyls includes, *e.g.*, cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl.

[00186] "Halo" or "halogen" refers to bromo, chloro, fluoro or iodo. In some embodiments, halogen is fluoro or chloro. In some embodiments, halogen is fluoro.

[00187] As used herein, the term "haloalkyl" or "haloalkane" refers to an alkyl radical, as defined above, that is substituted by one or more halogen radicals, for example, trifluoromethyl, dichloromethyl, bromomethyl, 2,2,2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, and the like. In some embodiments, the alkyl part of the fluoroalkyl radical is optionally further substituted. Examples of halogen substituted alkanes ("haloalkanes") include halomethane (*e.g.*, chloromethane, bromomethane, fluoromethane, iodomethane), di- and trihalomethane (*e.g.*, trichloromethane, tribromomethane, trifluoromethane, triiodomethane), 1-haloethane, 2-haloethane, 1,2-dihaloethane, 1-halopropane, 2-halopropane, 3-halopropane, 1,2-

dihalopropane, 1,3-dihalopropane, 2,3-dihalopropane, 1,2,3-trihalopropane, and any other suitable combinations of alkanes (or substituted alkanes) and halogens (*e.g.*, Cl, Br, F, I, etc.). When an alkyl group is substituted with more than one halogen radicals, each halogen may be independently selected *e.g.*, 1-chloro,2-fluoroethane.

[00188] "Fluoroalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more fluoro radicals, for example, trifluoromethyl, difluoromethyl, fluoromethyl, 2,2,2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, and the like.

[00189] "Hydroxyalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more hydroxyls. In some embodiments, the alkyl is substituted with one hydroxyl. In some embodiments, the alkyl is substituted with one, two, or three hydroxyls. Hydroxyalkyl include, for example, hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, or hydroxypentyl. In some embodiments, the hydroxyalkyl is hydroxymethyl.

[00190] "Aminoalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more amines. In some embodiments, the alkyl is substituted with one amine. In some embodiments, the alkyl is substituted with one, two, or three amines. Aminoalkyl include, for example, aminomethyl, aminoethyl, aminopropyl, aminobutyl, or aminopentyl. In some embodiments, the aminoalkyl is aminomethyl.

[00191] "Heteroalkyl" refers to an alkyl group in which one or more skeletal atoms of the alkyl are selected from an atom other than carbon, *e.g.*, oxygen, nitrogen (*e.g.*, -NH-, -N(alkyl)-), sulfur, phosphorus, or combinations thereof. A heteroalkyl is attached to the rest of the molecule at a carbon atom of the heteroalkyl. In one aspect, a heteroalkyl is a C₁-C₆ heteroalkyl wherein the heteroalkyl is comprised of 1 to 6 carbon atoms and one or more atoms other than carbon, *e.g.*, oxygen, nitrogen (*e.g.* -NH-, -N(alkyl)-), sulfur, phosphorus, or combinations thereof wherein the heteroalkyl is attached to the rest of the molecule at a carbon atom of the heteroalkyl. Examples of such heteroalkyl are, for example, -CH₂OCH₃, -CH₂CH₂OCH₃, -CH₂CH₂OCH₂CH₂OCH₃, -CH(CH₃)OCH₃, -CH₂NHCH₃, -CH₂N(CH₃)₂, -CH₂CH₂NHCH₃, or -CH₂CH₂N(CH₃)₂. Unless stated otherwise specifically in the specification, a heteroalkyl is optionally substituted for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, a heteroalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -CF₃, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, a heteroalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -CF₃, -OH, or -OMe. In some embodiments, the heteroalkyl is optionally substituted with halogen.

[00192] "Heterocycloalkyl" refers to a 3- to 24-membered partially or fully saturated ring radical comprising 2 to 23 carbon atoms and from one to 8 heteroatoms selected from the group consisting of nitrogen, oxygen, phosphorous, silicon, and sulfur. In some embodiments, the heterocycloalkyl is fully saturated. In some embodiments, the heterocycloalkyl comprises one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur. In some embodiments, the heterocycloalkyl comprises one to three heteroatoms selected from the group consisting of nitrogen and oxygen. In some embodiments, the heterocycloalkyl comprises one to three nitrogens. In some embodiments, the heterocycloalkyl comprises

one or two nitrogens. In some embodiments, the heterocycloalkyl comprises one nitrogen. In some embodiments, the heterocycloalkyl comprises one nitrogen and one oxygen. Unless stated otherwise specifically in the specification, the heterocycloalkyl radical may be a monocyclic, bicyclic, tricyclic, or tetracyclic ring system, which may include fused (when fused with an aryl or a heteroaryl ring, the heterocycloalkyl is bonded through a non-aromatic ring atom), spiro, or bridged ring systems; and the nitrogen, carbon, or sulfur atoms in the heterocycloalkyl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized. Representative heterocycloalkyls include, but are not limited to, heterocycloalkyls having from two to fifteen carbon atoms (*e.g.*, C₂-C₁₅ fully saturated heterocycloalkyl or C₂-C₁₅ heterocycloalkenyl), from two to ten carbon atoms (*e.g.*, C₂-C₁₀ fully saturated heterocycloalkyl or C₂-C₁₀ heterocycloalkenyl), from two to eight carbon atoms (*e.g.*, C₂-C₈ fully saturated heterocycloalkyl or C₂-C₈ heterocycloalkenyl), from two to seven carbon atoms (*e.g.*, C₂-C₇ fully saturated heterocycloalkyl or C₂-C₇ heterocycloalkenyl), from two to six carbon atoms (*e.g.*, C₂-C₆ fully saturated heterocycloalkyl or C₂-C₆ heterocycloalkenyl), from two to five carbon atoms (*e.g.*, C₂-C₅ fully saturated heterocycloalkyl or C₂-C₅ heterocycloalkenyl), or two to four carbon atoms (*e.g.*, C₂-C₄ fully saturated heterocycloalkyl or C₂-C₄ heterocycloalkenyl). Examples of such heterocycloalkyl radicals include, but are not limited to, aziridinyl, azetidiny, oxetanyl, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, 1,1-dioxo-thiomorpholinyl, 1,3-dihydroisobenzofuran-1-yl, 3-oxo-1,3-dihydroisobenzofuran-1-yl, methyl-2-oxo-1,3-dioxol-4-yl, and 2-oxo-1,3-dioxol-4-yl. The term heterocycloalkyl also includes all ring forms of the carbohydrates, including but not limited to the monosaccharides, the disaccharides, and the oligosaccharides. In some embodiments, heterocycloalkyls have from 2 to 10 carbons in the ring. It is understood that when referring to the number of carbon atoms in a heterocycloalkyl, the number of carbon atoms in the heterocycloalkyl is not the same as the total number of atoms (including the heteroatoms) that make up the heterocycloalkyl (*i.e.* skeletal atoms of the heterocycloalkyl ring). In some embodiments, the heterocycloalkyl is a 3- to 8-membered fully saturated heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 3- to 7-membered fully saturated heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 3- to 6-membered fully saturated heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 4- to 6-membered fully saturated heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 5- to 6-membered fully saturated heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 3- to 8-membered heterocycloalkenyl. In some embodiments, the heterocycloalkyl is a 3- to 7-membered heterocycloalkenyl. In some embodiments, the heterocycloalkyl is a 3- to 6-membered heterocycloalkenyl. In some embodiments, the heterocycloalkyl is a 4- to 6-membered heterocycloalkenyl. In some embodiments, the heterocycloalkyl is a 5- to 6-membered heterocycloalkenyl. Unless stated otherwise specifically in the specification, a heterocycloalkyl may be optionally substituted as described below, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl,

alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the heterocycloalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -C(O)OH, C(O)OMe, -CF₃, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, the heterocycloalkyl is optionally substituted with halogen, methyl, ethyl, -CN, -CF₃, -OH, or -OMe. In some embodiments, the heterocycloalkyl is optionally substituted with halogen.

[00193] “Heteroaryl” refers to a 5- to 14-membered ring system radical comprising one to thirteen carbon atoms, one to six heteroatoms selected from the group consisting of nitrogen, oxygen, phosphorous, and sulfur, and at least one aromatic ring. In some embodiments, the heteroaryl comprises one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur. In some embodiments, the heteroaryl comprises one to three heteroatoms selected from the group consisting of nitrogen and oxygen. In some embodiments, the heteroaryl comprises one to three nitrogens. In some embodiments, the heteroaryl comprises one or two nitrogens. In some embodiments, the heteroaryl comprises one nitrogen. The heteroaryl radical may be a monocyclic, bicyclic, tricyclic, or tetracyclic ring system, which may include fused (when fused with a cycloalkyl or heterocycloalkyl ring, the heteroaryl is bonded through an aromatic ring atom) or bridged ring systems; and the nitrogen, carbon, or sulfur atoms in the heteroaryl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized. In some embodiments, the heteroaryl is a 5- to 10-membered heteroaryl. In some embodiments, the heteroaryl is a 5- to 6-membered heteroaryl. In some embodiments, the heteroaryl is a 6-membered heteroaryl. In some embodiments, the heteroaryl is a 5-membered heteroaryl. Examples include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzothiazolyl, benzindolyl, benzodioxolyl, benzofuranlyl, benzooxazolyl, benzothiazolyl, benzothiadiazolyl, benzo[b][1,4]dioxepinyl, 1,4-benzodioxanyl, benzonaphthofuranlyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranlyl, benzopyranonyl, benzofuranlyl, benzofuranonyl, benzothieryl (benzothiophenyl), benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, dibenzofuranlyl, dibenzothiophenyl, furanyl, furanonyl, isothiazolyl, imidazolyl, indazolyl, indolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indoliziny, isoxazolyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 1-oxidopyridinyl, 1-oxidopyrimidinyl, 1-oxidopyrazinyl, 1-oxidopyridazinyl, 1-phenyl-1H-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazolinyl, quinoxalinyl, quinolinyl, quinuclidinyl, isoquinolinyl, tetrahydroquinolinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl, and thiophenyl (i.e., thienyl). Unless stated otherwise specifically in the specification, a heteroaryl may be optionally substituted, for example, with halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the heteroaryl is optionally substituted with halogen, methyl, ethyl, -CN, -C(O)OH, C(O)OMe, -CF₃, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, the heteroaryl is optionally substituted with halogen, methyl, ethyl, -CN, -CF₃, -OH, or -OMe. In some embodiments, the heteroaryl is optionally substituted with halogen.

[00194] The term “transcription,” well known in the art, refers to the synthesis of RNA (*i.e.*, ribonucleic acid) by DNA-directed RNA polymerase. The term “modulate transcription” refers to a change in transcriptional level which can be measured by methods well known in the art, for example, assay of mRNA, the product of transcription. In certain embodiments, modulation is an increase in transcription. In other embodiments, modulation is a decrease in transcription.

[00195] The term “polyamide” refers to polymers of linkable units chemically bound by amide (*i.e.*, CONH) linkages; optionally, polyamides include chemical probes conjugated therewith. Polyamides may be synthesized by stepwise condensation of carboxylic acids (COOH) with amines (RR'NH) using methods known in the art. Alternatively, polyamides may be formed using enzymatic reactions *in vitro*, or by employing fermentation with microorganisms.

[00196] The term “linker” or “oligomeric backbone” refers to a chain of at least 10 contiguous atoms. In certain embodiments, the linker contains no more than 20 non-hydrogen atoms. The terms linker and oligomeric backbone can be used interchangeably. In some embodiments, the linker contains no more than 40 non-hydrogen atoms. In some embodiments, the linker contains no more than 60 non-hydrogen atoms. In certain embodiments, the linker contains atoms chosen from C, H, N, O, and S. In some embodiments, every non-hydrogen atom is chemically bonded either to 2 neighboring atoms in the linker, or one neighboring atom in the linker and a terminus of the linker. In some embodiments, the linker forms an amide bond with at least one of the two other groups to which it is attached. In certain embodiments, the linker forms an ester or ether bond with at least one of the two other groups to which it is attached. In some embodiments, the linker forms a thioester or thioether bond with at least one of the two other groups to which it is attached. In some embodiments, the linker forms a direct carbon-carbon bond with at least one of the two other groups to which it is attached. In some embodiments, the linker forms an amine or amide bond with at least one of the two other groups to which it is attached. In some embodiments, the linker comprises $-(CH_2OCH_2)-$ units. In some embodiments, the linker comprises $-(CH(CH_3)OCH_2)-$ units. In some embodiments, the linker comprises $-(CH_2NR_NCH_2)$ units, for $R_N = C_{1-4}alkyl$. In some embodiments, the linker comprises an arylene, cycloalkylene, or heterocycloalkylene moiety.

[00197] The term “bond” refers to a covalent linkage between two atoms, or two moieties when the atoms joined by the bond are considered to be part of larger substructure. A bond may be single, double, or triple unless otherwise specified. A dashed line between two atoms in a drawing of a molecule indicates that an additional bond may be present or absent at that position.

[00198] As used herein, “optionally substituted” is a substituted group is derived from the unsubstituted parent group in which there has been an exchange of one or more hydrogen atoms for another atom or group. Unless otherwise indicated, when a group is deemed to be “substituted” or “optionally substituted” it is meant that the group is substituted with one or more substituents independently selected from C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, C_1-C_6 heteroalkyl, C_3-C_7 carbocyclyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), C_3-C_7 -carbocyclyl- C_1-C_6 -alkyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), 3-10 membered

heterocyclyl (optionally substituted with halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, and C₁-C₆ haloalkoxy), 3-10 membered heterocyclyl-C₁-C₆-alkyl (optionally substituted with halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, and C₁-C₆ haloalkoxy), aryl (optionally substituted with halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, and C₁-C₆ haloalkoxy), aryl(C₁-C₆)alkyl (optionally substituted with halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, and C₁-C₆ haloalkoxy), 5-10 membered heteroaryl (optionally substituted with halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, and C₁-C₆ haloalkoxy), 5-10 membered heteroaryl(C₁-C₆)alkyl (optionally substituted with halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, and C₁-C₆ haloalkoxy), halo, cyano, hydroxy, C₁-C₆ alkoxy, C₁-C₆ alkoxy(C₁-C₆)alkyl (i.e., ether), aryloxy, sulfhydryl (mercapto), halo(C₁-C₆)alkyl (e.g., -CF₃), halo(C₁-C₆)alkoxy (e.g., -OCF₃), C₁-C₆ alkylthio, arylthio, amino, amino(C₁-C₆)alkyl, nitro, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, acyl, cyanato, isocyanato, thiocyanato, isothiocyanato, sulfinyl, sulfonyl, and oxo (=O). Wherever a group is described as “optionally substituted” that group can be substituted with the above substituents.

[00199] The term “one or more” when referring to an optional substituent means that the subject group is optionally substituted with one, two, three, or four substituents. In some embodiments, the subject group is optionally substituted with one, two, or three substituents. In some embodiments, the subject group is optionally substituted with one or two substituents. In some embodiments, the subject group is optionally substituted with one substituent. In some embodiments, the subject group is optionally substituted with two substituents.

[00200] Chemical entities having carbon-carbon double bonds or carbon-nitrogen double bonds may exist in *Z*- or *E*- form (or *cis*- or *trans*- form). Furthermore, some chemical entities may exist in various tautomeric forms. Unless otherwise specified, compounds described herein are intended to include all *Z*-, *E*- and tautomeric forms as well.

[00201] The compounds disclosed herein, in some embodiments, are used in different enriched isotopic forms, e.g., enriched in the content of ²H, ³H, ¹¹C, ¹³C and/or ¹⁴C. In one particular embodiment, the compound is deuterated in at least one position. Such deuterated forms can be made by the procedure described in U.S. Patent Nos. 5,846,514 and 6,334,997. As described in U.S. Patent Nos. 5,846,514 and 6,334,997, deuteration can improve the metabolic stability and or efficacy, thus increasing the duration of action of drugs.

[00202] Unless otherwise stated, compounds described herein are intended to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by ¹³C- or ¹⁴C-enriched carbon are within the scope of the present disclosure.

[00203] The compounds of the present disclosure optionally contain unnatural proportions of atomic isotopes at one or more atoms that constitute such compounds. For example, the compounds may be labeled with isotopes, such as for example, deuterium (²H), tritium (³H), iodine-125 (¹²⁵I) or carbon-14 (¹⁴C). Isotopic substitution with ²H, ¹¹C, ¹³C, ¹⁴C, ¹⁵C, ¹²N, ¹³N, ¹⁵N, ¹⁶N, ¹⁶O, ¹⁷O, ¹⁴F, ¹⁵F, ¹⁶F, ¹⁷F, ¹⁸F, ³³S, ³⁴S, ³⁵S,

³⁶S, ³⁵Cl, ³⁷Cl, ⁷⁹Br, ⁸¹Br, and ¹²⁵I are all contemplated. All isotopic variations of the compounds of the present invention, whether radioactive or not, are encompassed within the scope of the present invention. In some embodiments, where isotopic variations are illustrated, the remaining atoms of the compound may optionally contain unnatural portions of atomic isotopes.

[00204] In certain embodiments, the compounds disclosed herein have some or all of the ¹H atoms replaced with ²H atoms. The methods of synthesis for deuterium-containing compounds are known in the art and include, by way of non-limiting example only, the following synthetic methods.

[00205] Deuterium substituted compounds are synthesized using various methods such as described in: Dean, Dennis C.; Editor. Recent Advances in the Synthesis and Applications of Radiolabeled Compounds for Drug Discovery and Development. [In: Curr., Pharm. Des., 2000; 6(10)] **2000**, 110 pp; George W.; Varma, Rajender S. The Synthesis of Radiolabeled Compounds via Organometallic Intermediates, Tetrahedron, **1989**, 45(21), 6601-21; and Evans, E. Anthony. Synthesis of radiolabeled compounds, J. Radioanal. Chem., **1981**, 64(1-2), 9-32.

[00206] Deuterated starting materials are readily available and are subjected to the synthetic methods described herein to provide for the synthesis of deuterium-containing compounds. Large numbers of deuterium-containing reagents and building blocks are available commercially from chemical vendors, such as Aldrich Chemical Co.

[00207] In some embodiments of a compound disclosed herein, one or more of the substituent groups comprise deuterium at a percentage higher than the natural abundance of deuterium. In some embodiments of a compound disclosed herein, one or more hydrogens are replaced with one or more deuteriums.

[00208] In some embodiments of a compound disclosed herein, the abundance of deuterium in each of the substituents is independently at least 1%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or 100% of a total number of hydrogen and deuterium.

[00209] Compounds of the present disclosure also include crystalline and amorphous forms of those compounds, pharmaceutically acceptable salts, and active metabolites of these compounds having the same type of activity, including, for example, polymorphs, pseudopolymorphs, solvates, hydrates, unsolvated polymorphs (including anhydrides), conformational polymorphs, and amorphous forms of the compounds, as well as mixtures thereof.

[00210] The compounds described herein may in some cases exist as diastereomers, enantiomers, or other stereoisomeric forms. Where absolute stereochemistry is not specified, the compounds presented herein include all diastereomeric, enantiomeric, and epimeric forms as well as the appropriate mixtures thereof. Separation of stereoisomers may be performed by chromatography or by forming diastereomers and separating by recrystallization, or chromatography, or any combination thereof. (Jean Jacques, Andre Collet, Samuel H. Wilen, "Enantiomers, Racemates and Resolutions", John Wiley And Sons, Inc., 1981, herein incorporated by reference for this disclosure). Stereoisomers may also be obtained by stereoselective synthesis.

[00211] The term “salt” or “pharmaceutically acceptable salt” refers to salts derived from a variety of organic and inorganic counter ions well known in the art. Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids. Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, *p*-toluenesulfonic acid, salicylic acid, and the like. Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases. Inorganic bases from which salts can be derived include, for example, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum, and the like. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like, specifically such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine. In some embodiments, the pharmaceutically acceptable base addition salt is chosen from ammonium, potassium, sodium, calcium, and magnesium salts.

[00212] The phrase “pharmaceutically acceptable” is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[00213] The phrase “pharmaceutically acceptable excipient” or “pharmaceutically acceptable carrier” as used herein means a pharmaceutically acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, excipient, solvent, or encapsulating material. Each carrier must be “acceptable” in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations.

[00214] An “effective amount” or “therapeutically effective amount” refers to an amount of a compound administered to a mammalian subject, either as a single dose or as part of a series of doses, which is effective to produce a desired therapeutic effect.

[00215] The terms “treat,” “treating” or “treatment,” as used herein, include alleviating, abating, or ameliorating at least one symptom of a disease or condition, preventing additional symptoms, inhibiting the disease or condition, *e.g.*, arresting the development of the disease or condition, relieving the disease or condition, causing regression of the disease or condition, relieving a condition caused by the disease or condition, or stopping the symptoms of the disease or condition.

[00216] The term “patient” is generally synonymous with the term “subject” and includes all mammals including humans. Examples of patients include humans, livestock such as cows, goats, sheep, pigs, and rabbits, and companion animals such as dogs, cats, rabbits, and horses. Preferably, the patient is a human.

[00217] The term “contacting” refers to bringing the compound (*e.g.*, a transcription molecular molecule of the present disclosure) into proximity of the desired target gene. The contacting may result in the binding to or result in a conformational change of the target moiety.

EXAMPLES

[00218] The following examples are given for the purpose of illustrating various embodiments of the invention and are not meant to limit the present invention in any fashion. The present examples, along with the methods described herein are presently representative of preferred embodiments, are exemplary, and are not intended as limitations on the scope of the invention. Changes therein and other uses which are encompassed within the spirit of the invention as defined by the scope of the claims will occur to those skilled in the art.

Compound Synthesis

[00219] Compounds of the present disclosure can be prepared using methods illustrated in general synthetic schemes and experimental procedures detailed below. General synthetic schemes and experimental procedures are presented for purposes of illustration and are not intended to be limiting. Starting materials used to prepare compounds of the present disclosure are commercially available or can be prepared using routine methods known in the art.

[00220] Synthetic chemistry transformations and methodologies useful in synthesizing the compounds described herein are known in the art and include, for example, those described in R.

Larock, *Comprehensive Organic Transformations* (1989); T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 2d. Ed. (1991); L. Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis* (1994); and L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis* (1995).

List of Abbreviation

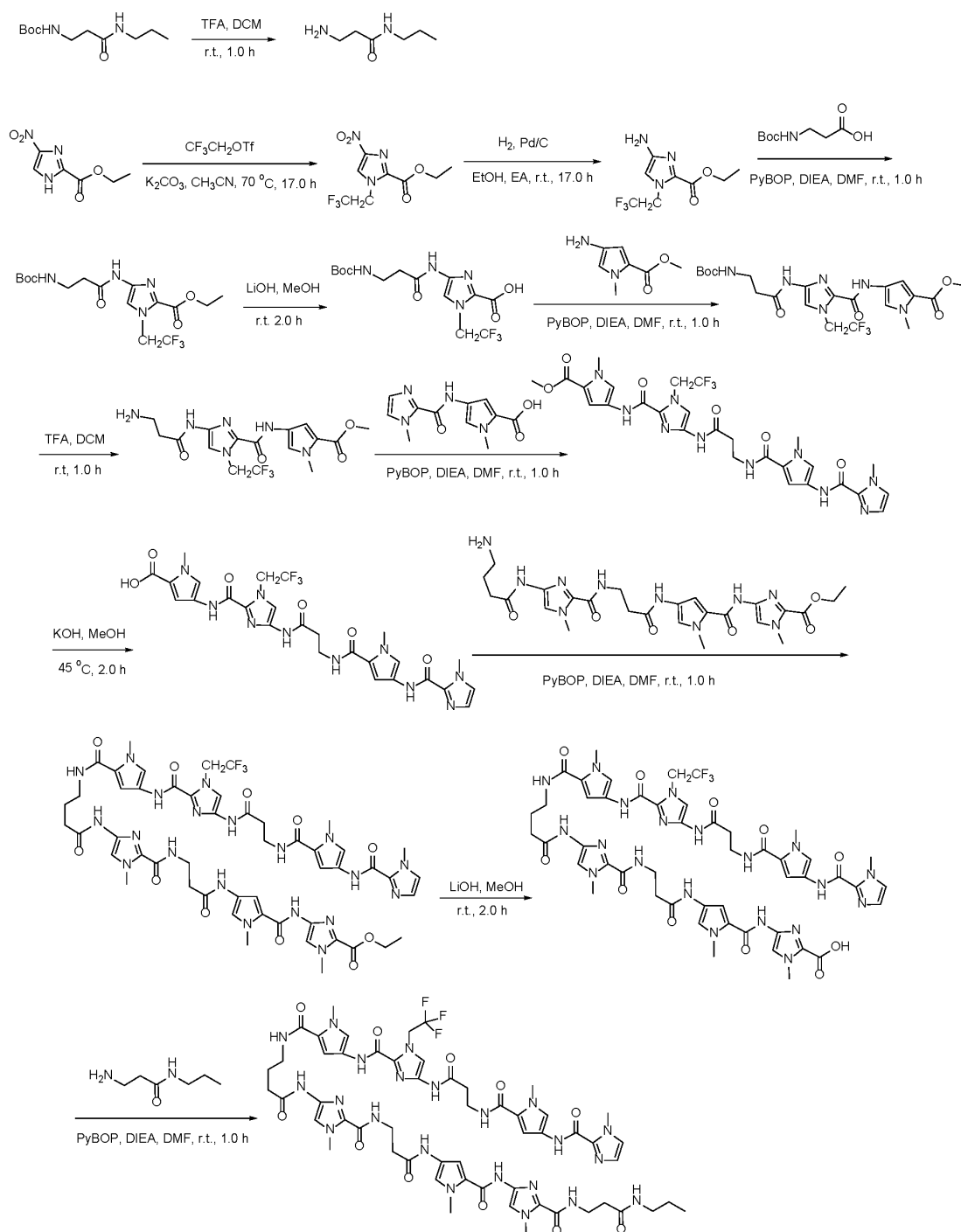
[00221] Ac₂O = acetic anhydride; AcCl = acetyl chloride; ACN = acetonitrile; AcOH = acetic acid; AIBN = azobisisobutyronitrile; aq. = aqueous; Bu₃SnH = tributyltin hydride; CD₃OD = deuterated methanol; CDCl₃ = deuterated chloroform; CDI = 1,1'-Carbonyldiimidazole; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; DCM = dichloromethane; DEAD = diethyl azodicarboxylate; DIBAL-H = di-iso-butyl aluminium hydride; DIEA = DIPEA = N,N-diisopropylethylamine; DMAP = 4-dimethylaminopyridine; DMF = N,N-dimethylformamide; DMSO-d₆ = deuterated dimethyl sulfoxide; DMSO = dimethyl sulfoxide; DPPA =

diphenylphosphoryl azide; EDC.HCl = EDCI.HCl = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride; Et₂O = diethyl ether; EA = ethyl acetate; EtOH = ethanol; h = hour; HATU=2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium; HMDS = hexamethyldisilazane; HOBT = 1-hydroxybenzotriazole; i-PrOH = isopropanol; LAH = lithium aluminium hydride; LiHMDS = Lithium bis(trimethylsilyl)amide; MeCN = acetonitrile; MeOH = methanol; MP-carbonate resin = macroporous triethylammonium methylpolystyrene carbonate resin; MsCl = mesyl chloride; MTBE = methyl tertiary butyl ether; MW = microwave irradiation ; n-BuLi = n-butyllithium; NaHMDS = Sodium bis(trimethylsilyl)amide; NaOMe = sodium methoxide; NaOtBu = sodium t-butoxide; NBS = N-bromosuccinimide; NCS = N-chlorosuccinimide; NMP = N-Methyl-2-pyrrolidone; Pd(Ph₃)₄ = tetrakis(triphenylphosphine)palladium(0); Pd₂(dba)₃ = tris(dibenzylideneacetone)dipalladium(0); PdCl₂(PPh₃)₂ = bis(triphenylphosphine)palladium(II) dichloride; PG = protecting group; prep-HPLC = preparative high-performance liquid chromatography; PyBop = (benzotriazol-1-yloxy)-tripyrrolidinophosphonium hexafluorophosphate; Pyr = pyridine; RT = room temperature; RuPhos = 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl; sat. = saturated; ss = saturated solution; t-BuOH = tert-butanol; T3P = Propylphosphonic Anhydride; TBS = TBDMS = *tert*-butyldimethylsilyl; TBSCl = TBDMSCl = *tert*-butyldimethylchlorosilane; TEA = Et₃N = triethylamine; TFA = trifluoroacetic acid; TFAA = trifluoroacetic anhydride; THF = tetrahydrofuran; Tol = toluene; TsCl = tosyl chloride; XPhos = 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl.

SYNTHESIS OF REPRESENTATIVE COMPOUNDS OF THE DISCLOSURE

[00222] Example 1. Synthesis of Compound A-88

[00223] Scheme 1.



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[00225] Step 2. To a solution of ethyl 4-nitro-1H-imidazole-2-carboxylate (9.74 g, 52.61 mmol, 1.00 equiv.) in CH₃CN (95.00 mL) was added 2,2,2-trifluoroethyl trifluoromethanesulfonate (15.87 g, 68.39 mmol, 1.30 equiv) and K₂CO₃ (21.81 g, 157.83 mmol, 3.00 equiv) and the resulting mixture was stirred for 17.0 h at 70 °C. The reaction mixture was filtered, concentrated under reduced pressure, and purified by silica gel column chromatography, eluted with PE/EA=1:1 to afford ethyl 4-nitro-1-(2,2,2-trifluoroethyl)imidazole-2-carboxylate (12.10 g, 79.20%) as a white solid. LC/MS: mass calcd. For C₈H₈F₃N₃O₄: 267.05, found: 268.10 [M+H]⁺.

[00226] Step 3. To a solution of ethyl 4-nitro-1-(2,2,2-trifluoroethyl) imidazole-2-carboxylate (12.10 g, 45.29 mmol, 1.00 equiv) in EtOH (50.00 mL) and EA (50.00 mL) was added Pd/C (4.82 g, 40% w/w) and the reaction mixture was stirred for 17.0 h at room temperature under H₂ atmosphere. The reaction mixture was filtered and concentrated to afford ethyl 4-amino-1-(2,2,2-trifluoroethyl) imidazole-2-carboxylate (9.50 g, 79.59%) as a white solid. LC/MS: mass calcd. For C₈H₁₀F₃N₃O₂: 237.07, found: 238.15 [M+H]⁺.

[00227] Step 4. To a stirred solution of ethyl 4-amino-1-(2,2,2-trifluoroethyl) imidazole-2-carboxylate (6.04 g, 25.47 mmol, 1.00 equiv) in DMF (45.00 mL) was added DIEA (19.75 g, 152.80 mmol, 6.00 equiv), 3-[(tert-butoxycarbonyl)amino]propanoic acid (5.30 g, 28.01 mmol, 1.10 equiv) and PyBOP (13.25 g, 25.47 mmol, 1.00 equiv) in portions at 0 °C and the resulting mixture was stirred for 1.0 h at room temperature. The reaction mixture was poured into ice water (150 mL). The precipitated solids were collected by filtration, washed with H₂O (3x50 mL), and dried under vacuum to yield ethyl 4-{3-[(tert-butoxycarbonyl)amino]propanamido}-1-(2,2,2-trifluoroethyl) imidazole-2-carboxylate (6.60 g, 57.12%) as a white solid. LC/MS: mass calcd. For C₁₆H₂₃F₃N₄O₅: 408.16, found: 409.25 [M+H]⁺.

[00228] Step 5. To a stirred solution of ethyl 4-{3-[(tert-butoxycarbonyl)amino]propanamido}-1-(2,2,2-trifluoroethyl) imidazole-2-carboxylate (9.27 g, 22.70 mmol, 1.00 equiv) in MeOH (70.00 mL) was added LiOH solution (2M in H₂O, 45.40 mL, 90.80 mmol, 4.00 equiv) dropwise and the reaction mixture was stirred for 2.0 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in H₂O (50 mL). The mixture was acidified to pH 3~5 with 2 M HCl. The precipitated solids were collected by filtration, washed with H₂O (3x30 mL), and dried under vacuum. The crude product was purified by reverse phase column with the following conditions: column, C18 silica gel; mobile phase, ACN in water (0.05% TFA), 10% to 50% gradient in 30 min; detector, UV 254 nm. The fractions were combined and concentrated to afford 4-{3-[(tert-butoxycarbonyl)amino]propanamido}-1-(2,2,2-trifluoroethyl)imidazole-2-carboxylic acid (4.10 g, 37.99%) as a yellow solid. LC/MS: mass calcd. For C₁₄H₁₉F₃N₄O₅: 380.13, found: 403.05 [M+Na]⁺.

[00229] Step 6. To a stirred solution of 4-{3-[(tert-butoxycarbonyl)amino]propanamido}-1-(2,2,2-trifluoroethyl) imidazole-2-carboxylic acid (2.20 g, 5.78 mmol, 1.00 equiv) in DMF (20.00 mL) was added DIEA (4.49 g, 34.71 mmol, 6.00 equiv), methyl 4-amino-1-methylpyrrole-2-carboxylate (0.89 g, 5.78 mmol, 1.00 equiv) and PyBOP (3.01 g, 5.78 mmol, 1.00 equiv) in portions at 0 °C. The resulting mixture was stirred for 1.0 h at room temperature. Next the reaction was poured into ice water (60 mL). The precipitated solids were collected by filtration, washed with H₂O (3x50 mL), and dried under vacuum to afford methyl 4-

(4-{3-[(tert-butoxycarbonyl)amino]propanamido}-1-(2,2,2-trifluoroethyl)imidazole-2-amido)-1-methylpyrrole-2-carboxylate (1.40 g, 42.17%) as a white solid. LC/MS: mass calcd. For $C_{21}H_{27}F_3N_6O_6$: 516.19, found: 517.15 $[M+H]^+$.

[00230] Step 7. To a stirred solution of methyl 4-(4-{3-[(tert-butoxycarbonyl)amino]propanamido}-1-(2,2,2-trifluoroethyl)imidazole-2-amido)-1-methylpyrrole-2-carboxylate (1.38 g, 2.67 mmol, 1.00 equiv) in DCM (14.00 mL) was added TFA (2.80 mL) dropwise and the resulting mixture was stirred for 1.0 h. The reaction mixture was concentrated under vacuum to afford ethyl 4-[4-(3-aminopropanamido)-1-(2,2,2-trifluoroethyl)imidazole-2-amido]-1-methylpyrrole-2-carboxylate (1.10 g crude) as a yellow oil. LC/MS: mass calcd. For $C_{16}H_{19}F_3N_6O_4$: 416.14, found: 417.10 $[M+H]^+$.

[00231] Step 8. To a stirred solution of methyl 4-[4-(3-aminopropanamido)-1-(2,2,2-trifluoroethyl)imidazole-2-amido]-1-methylpyrrole-2-carboxylate (660.00 mg, 1.58 mmol, 1.00 equiv) in DMF (7.00 mL) was added DIEA (1.23 g, 9.51 mmol, 6.00 equiv), 1-methyl-4-(1-methylimidazole-2-amido)pyrrole-2-carboxylic acid (393.50 mg, 1.58 mmol, 1.00 equiv) and PyBOP (824.92 mg, 1.58 mmol, 1.00 equiv) in portions at 0 °C. The resulting mixture was stirred for 1.0 h at room temperature. Next the reaction mixture was poured into ice water (21 mL). The precipitated solids were collected by filtration, washed with H_2O (3x50 mL), and dried under vacuum. The crude product was purified by silica gel column chromatography, eluted with $CH_2Cl_2/MeOH=10:1$ to afford methyl 1-methyl-4-[4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)-1-(2,2,2-trifluoroethyl)imidazole-2-amido]pyrrole-2-carboxylate (1.00 g, 87.81%) as a white solid. LC/MS: mass calcd. For $C_{27}H_{29}F_3N_{10}O_6$: 646.22, found: 647.40 $[M+H]^+$.

[00232] Step 9. To a stirred solution of methyl 1-methyl-4-[4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)-1-(2,2,2-trifluoroethyl)imidazole-2-amido]pyrrole-2-carboxylate (900.00 mg, 1.39 mmol, 1.00 equiv) in MeOH (10.00 mL) was added KOH solution (2 M in H_2O , 6.96 mL, 13.92 mmol, 10.00 equiv) dropwise at room temperature. The resulting mixture was stirred for 2.0 h at 45 °C. Then the resulting mixture was concentrated under reduced pressure and the residue was dissolved in H_2O (50.00 mL). The mixture was acidified to pH 3~5 with 2 M HCl. The precipitated solids were collected by filtration, washed with H_2O (3x30 mL), and dried under vacuum to afford 1-methyl-4-[4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)-1-(2,2,2-trifluoroethyl)imidazole-2-amido]pyrrole-2-carboxylic acid (800.00 mg, 90.86%) as a white solid. LC/MS: mass calcd. For $C_{26}H_{27}F_3N_{10}O_6$: 632.21, found: 633.35 $[M+H]^+$.

[00233] Step 10. To a stirred solution of ethyl 4-[4-(3-{[4-(4-aminobutanamido)-1-methylimidazol-2-yl]formamido}propanamido)-1-methylpyrrole-2-amido]-1-methylimidazole-2-carboxylate (400.00 mg, 0.70 mmol, 1.00 equiv) in DMF (5.00 mL) was added DIEA (543.62 mg, 4.21 mmol, 6.00 equiv), 1-methyl-4-[4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)-1-(2,2,2-trifluoroethyl)imidazole-2-amido]pyrrole-2-carboxylic acid (620.80 mg, 0.98 mmol, 1.40 equiv) and PyBOP (364.80 mg, 0.70 mmol, 1.00 equiv) in portions at 0 °C. The resulting mixture was stirred for 1.0 h at room temperature. Then the reaction was poured into ice water (15 mL). The precipitated solids were collected by filtration,

washed with H₂O (3x5 mL), and dried under vacuum to afford ethyl 1-methyl-4-{1-methyl-4-[3-({1-methyl-4-[4-({1-methyl-4-[4-(3-({1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)-1-(2,2,2-trifluoroethyl)imidazole-2-amido]pyrrol-2-yl}formamido)butanamido]imidazol-2-yl}formamido)propanamido]pyrrole-2-amido}imidazole-2-carboxylate (800.00 mg, 72.22%) as a white solid. LC/MS: mass calcd. For C₅₁H₅₉F₃N₂₀O₁₁: 1184.46, found: 593.65 [M/2+H]⁺.

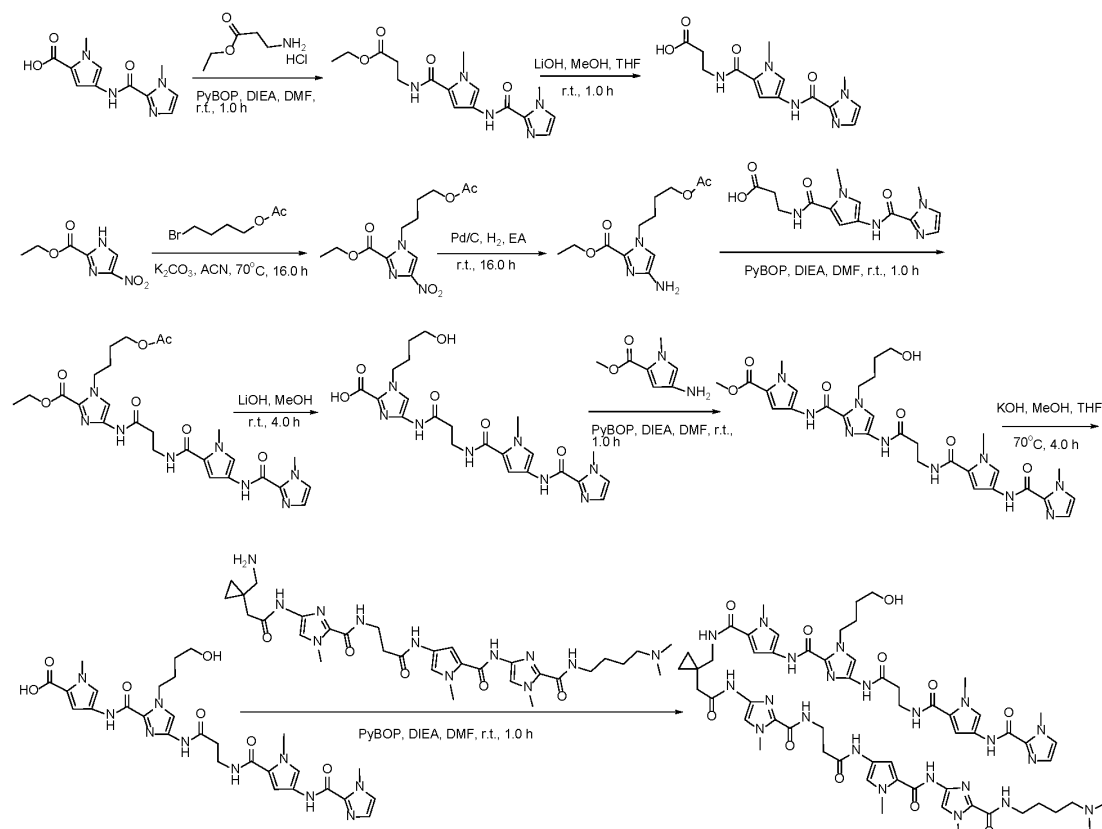
[00234] Step 11. To a stirred solution of ethyl 1-methyl-4-{1-methyl-4-[3-({1-methyl-4-[4-({1-methyl-4-[4-(3-({1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)-1-(2,2,2-trifluoroethyl)imidazole-2-amido]pyrrol-2-yl}formamido)butanamido]imidazol-2-yl}formamido)propanamido]pyrrole-2-amido}imidazole-2-carboxylate (700.00 mg, 0.59 mmol, 1.00 equiv) in MeOH (7.00 mL) was added LiOH solution (2 M in H₂O, 1.18 mL, 2.36 mmol, 4.00 equiv) dropwise at room temperature and the reaction mixture was stirred for 2.0 h. Then the reaction mixture was concentrated under reduced pressure. The residue was dissolved in H₂O (50 mL) and the mixture was acidified to pH 3~5 with 2M HCl. The precipitated solids were collected by filtration, washed with H₂O (3x30 mL), and dried under vacuum to afford 1-methyl-4-{1-methyl-4-[3-({1-methyl-4-[4-({1-methyl-4-[4-(3-({1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)-1-(2,2,2-trifluoroethyl)imidazole-2-amido]pyrrol-2-yl}formamido)butanamido]imidazol-2-yl}formamido)propanamido]pyrrole-2-amido}imidazole-2-carboxylic acid (700.00 mg, 87.06%) as a white solid. LC/MS: mass calcd. For C₄₉H₅₅F₃N₂₀O₁₁: 1156.43, found: 579.65 [M/2+H]⁺.

[00235] Step 12. To a stirred solution of 1-methyl-4-{1-methyl-4-[3-({1-methyl-4-[4-({1-methyl-4-[4-(3-({1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)-1-(2,2,2-trifluoroethyl)imidazole-2-amido]pyrrol-2-yl}formamido)butanamido]imidazol-2-yl}formamido)propanamido]pyrrole-2-amido}imidazole-2-carboxylic acid (100.00 mg, 0.09 mmol, 1.00 equiv) in DMF (1.00 mL) was added DIEA (111.70 mg, 0.86 mmol, 10.00 equiv), 3-amino-N-propylpropanamide (14.63 mg, 0.11 mmol, 1.30 equiv) and PyBOP (53.97 mg, 0.10 mmol, 1.20 equiv) in portions at 0 °C and the resulting mixture was stirred for 1.0 h at room temperature. The reaction was poured into ice water (3.00 mL). The precipitated solids were collected by filtration, washed with H₂O (3x3 mL), and dried under vacuum. The residue was purified by TLC-plate (DCM:MeOH=10:1) to afford 4-(3-({1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl}formamido}propanamido)-N-[1-methyl-5-({3-[(1-methyl-2-{2-({1-methyl-5-[(1-methyl-2-{2-(propylcarbamoyl)ethyl}carbamoyl}imidazol-4-yl)carbamoyl]pyrrol-3-yl}carbamoyl)ethyl}carbamoyl}imidazol-4-yl)carbamoyl]propyl}carbamoyl)pyrrol-3-yl]-1-(2,2,2-trifluoroethyl)imidazole-2-carboxamide (79.00 mg) as a white solid. The crude product was dissolved in DMF and filtered. The filtrate (2.0 mL) was purified by Prep-HPLC with the following conditions (Column: XBridge Shield RP18 OBD Column, 19*250 mm, 10 µm; Mobile Phase A: Water(10 mmol/L NH₄HCO₃+0.1% NH₃.H₂O), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 25% B to 40% B in 16 min, 40% B; Wave Length: 254 nm; RT1(min): 14.36). The fractions were combined and lyophilized to afford 4-(3-({1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl}formamido}propanamido)-N-[1-methyl-5-({3-[(1-methyl-2-{2-({1-methyl-5-[(1-methyl-2-{2-

(propylcarbamoyl)ethyl]carbamoyl]imidazol-4-yl)carbamoyl]pyrrol-3-yl}
carbamoyl)ethyl]carbamoyl]imidazol-4-yl)carbamoyl]propyl}carbamoyl]pyrrol-3-yl]-1-(2,2,2-
trifluoroethyl) imidazole-2-carboxamide (17.60 mg, 15.67%) as a white solid. LC/MS: mass calcd. For $C_{55}H_{67}F_3N_{22}O_{11}$: 1268.5312, found: 1269.5412 $[M+H]^+$.

[00236] Example 2. Synthesis of Compound A-117

[00237] Scheme 2.



[00238] Step 1. To a stirred solution of 1-methyl-4-(1-methylimidazole-2-amido)pyrrole-2-carboxylic acid (6.00 g, 24.17 mmol, 1.00 equiv) in DMF (50.00 mL) was added β-alanine ethyl ester (2.83 g, 24.17 mmol, 1.00 equiv), PyBOP (15.09 g, 29.00 mmol, 1.20 equiv) and DIEA (9.37 g, 72.51 mmol, 3.00 equiv) dropwise at room temperature and the resulting mixture was stirred for 1.0 h. The resulting mixture was poured into ice water (150 mL). The precipitated solids were collected by filtration, washed with water (100 mL), and dried to afford ethyl 3-([1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido)propanoate (6.90 g, 82.18%) as a yellow solid. LC/MS: mass calcd. For $C_{16}H_{21}N_5O_4$: 347.16, found: 348.10 $[M+H]^+$.

[00239] Step 2. To a stirred solution of ethyl 3-([1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido)propanoate (6.30 g, 18.13 mmol, 1.00 equiv) in MeOH (100.00 mL) and THF (50.00 mL) was added LiOH (36.27 mL, 72.54 mmol, 4.00 equiv, 2 M in H_2O) dropwise and the resulting mixture was stirred for 1.0 h at 25 °C. The resulting mixture was concentrated under vacuum. 100 mL H_2O was

added, the mixture was adjusted to pH 7~8 with 2 M HCl, and then the mixture was concentrated under reduced pressure. The residue was dissolved in H₂O (50 mL). The mixture was acidified to pH 3~5 with 2 M HCl. The precipitated solids were collected by filtration, washed with water (3x100 mL), and dried under vacuum to afford 3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanoic acid (5.30 g, 91.52%) as a white solid. LC/MS: mass calcd. For C₁₆H₂₃N₃O₃: 319.13, found: 320.10 [M+H]⁺.

[00240] Step 3. To a stirred solution of ethyl 4-nitro-1H-imidazole-2-carboxylate (1.00 g, 5.40 mmol, 1.00 equiv) in ACN (15.00 mL) was added 4-bromobutyl acetate (1.26 g, 6.48 mmol, 1.20 equiv) and K₂CO₃ (2.24 g, 16.20 mmol, 3.00 equiv) dropwise and the resulting mixture was stirred for 16.0 h at 70 °C. The reaction mixture was filtered and concentrated under vacuum. Next the reaction mixture was poured into ice-water (50 mL) and extracted with EA (3x50 mL). The combined organic phase was washed with H₂O (50 mL) and NaCl (50 mL), dried over anhydrous Na₂SO₄, and concentrated to afford ethyl 1-[4-(acetyloxy)butyl]-4-nitroimidazole-2-carboxylate (1.60 g, 98.98%) as a yellow solid. LC/MS: mass calcd. For C₁₂H₁₇N₃O₆: 299.11, found: 300.01 [M+H]⁺.

[00241] Step 4. To a stirred solution of ethyl 1-[4-(acetyloxy)butyl]-4-nitroimidazole-2-carboxylate (1.60 g, 5.35 mmol, 1.00 equiv) in EA (30.00 mL) was added Pd/C (160.00 mg, 10% w/w) dropwise and the resulting mixture was stirred for 16.0 h at 25 °C under H₂ atmosphere. Then the resulting mixture was filtered and concentrated to afford ethyl 1-[4-(acetyloxy)butyl]-4-aminoimidazole-2-carboxylate (1.30 g, 90.30%) as a yellow solid. LC/MS: mass calcd. For C₁₂H₁₉N₃O₄: 269.14, found: 270.10 [M+H]⁺.

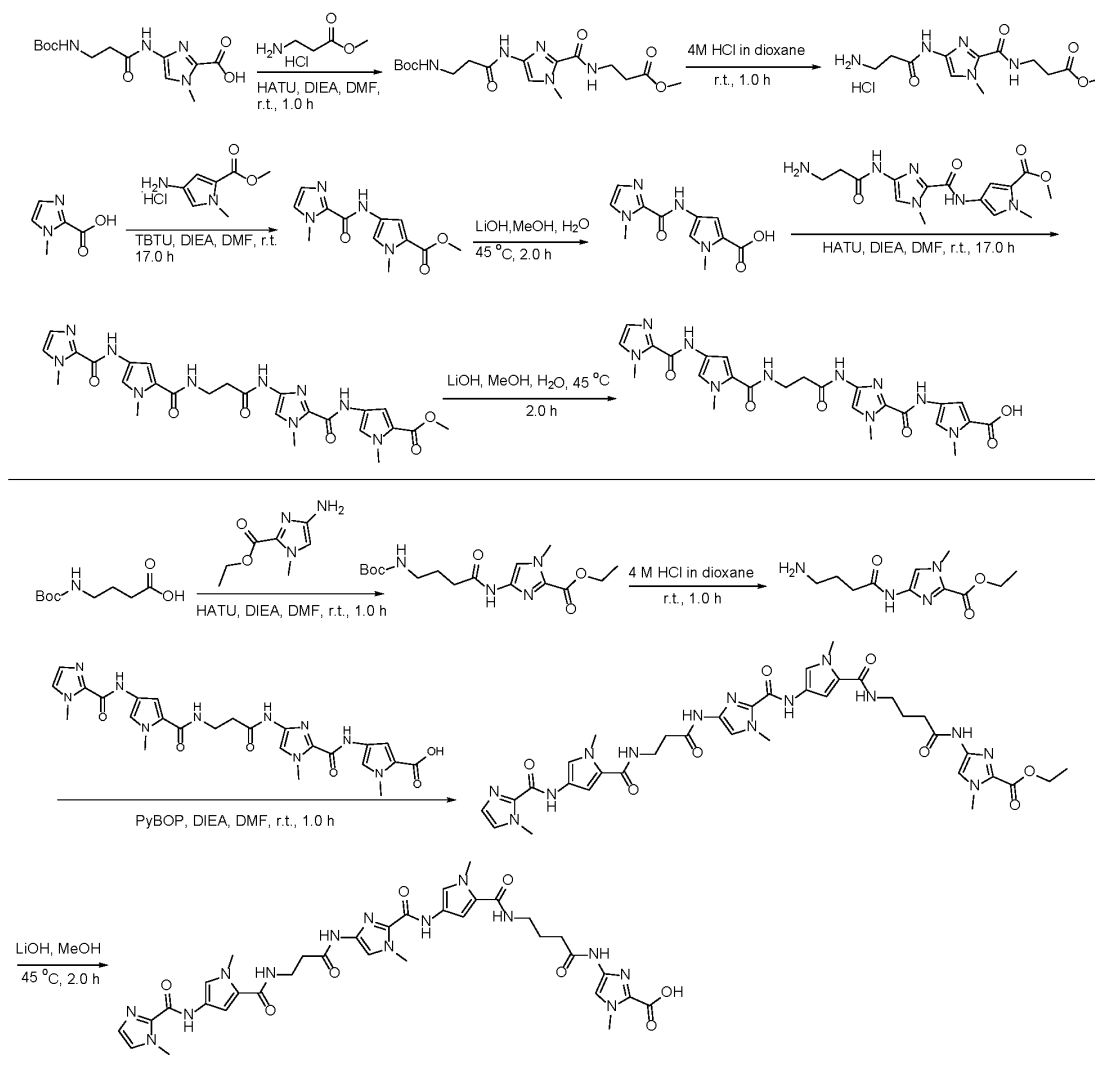
[00242] Step 5. To a stirred solution of ethyl 1-[4-(acetyloxy)butyl]-4-aminoimidazole-2-carboxylate (100.00 mg, 0.37 mmol, 1.00 equiv) in DMF (3.00 mL) was added 3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanoic acid (118.57 mg, 0.37 mmol, 1.00 equiv), PyBOP (231.89 mg, 0.45 mmol, 1.20 equiv) and DIEA (143.98 mg, 1.11 mmol, 3.00 equiv) dropwise and the resulting mixture was stirred for 1.0 h at 25 °C. Then the resulting mixture was poured into ice water (10 mL). The precipitated solids were collected by filtration, washed with water (10 mL), and dried under vacuum to afford ethyl 1-[4-(acetyloxy)butyl]-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-carboxylate (135.00 mg, 63.71%) as a yellow solid. LC/MS: mass calcd. For C₂₆H₃₄N₈O₇: 570.26, found: 571.30 [M+H]⁺.

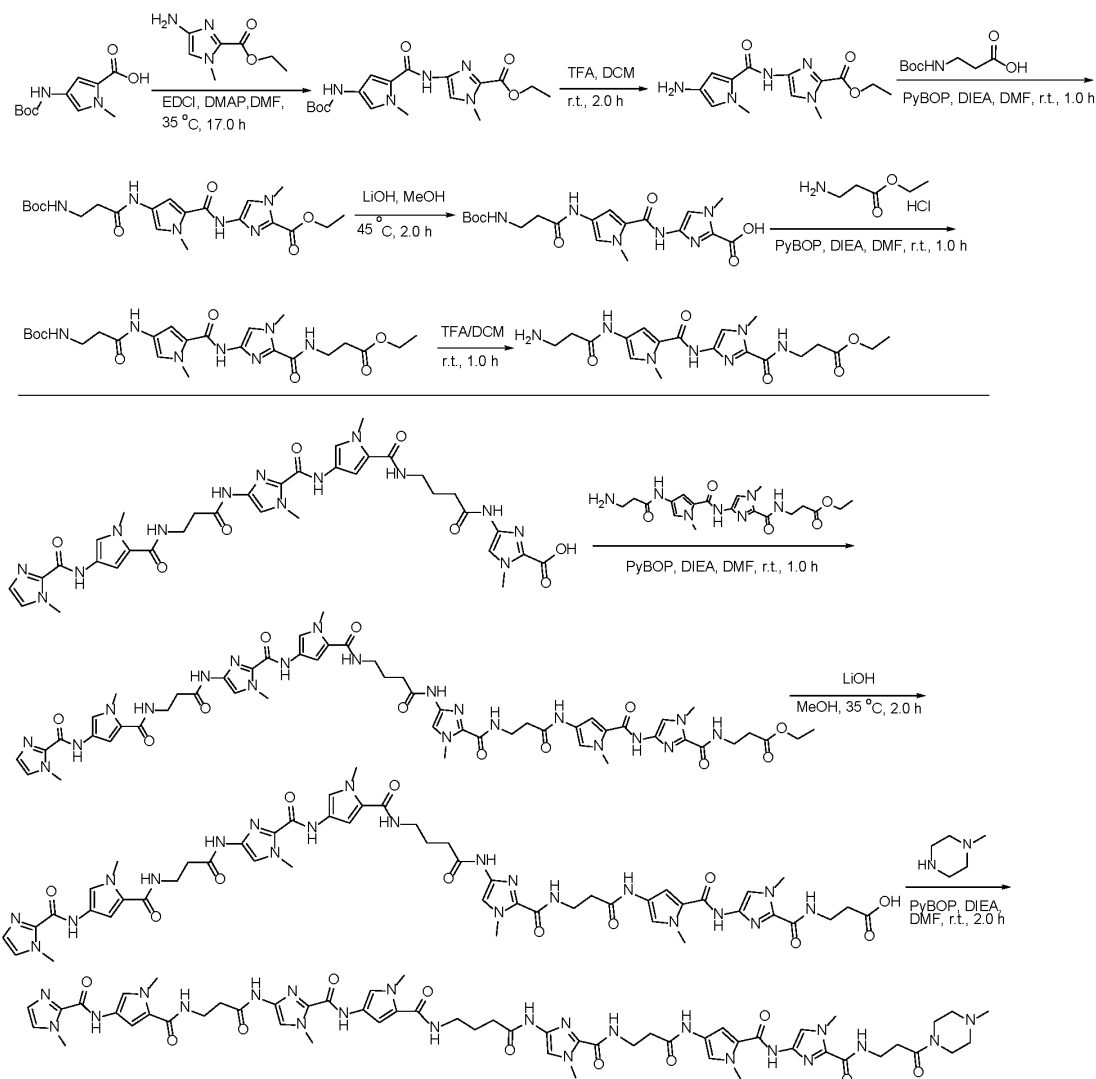
[00243] Step 6. To a stirred solution of ethyl 1-[4-(acetyloxy)butyl]-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-carboxylate (130.00 mg, 0.23 mmol, 1.00 equiv) in MeOH (3.00 mL) was added LiOH (0.46 mL, 0.91 mmol, 4.00 equiv, 2 M in H₂O) dropwise and the resulting mixture was stirred for 4.0 h at 25 °C. Next 10 mL H₂O was added, the mixture was adjusted to pH 7~8 with 2 M HCl, and the mixture was concentrated under reduced pressure. The residue was dissolved in H₂O (30 mL) and acidified to pH 3~5 with 2 M HCl. The precipitated solids were collected by filtration, washed with H₂O (3x20 mL), and dried under vacuum to afford 1-(4-hydroxybutyl)-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-carboxylic acid (110.00 mg, 96.46%) as a white solid. LC/MS: mass calcd. For C₂₂H₂₈N₈O₆: 500.21, found: 501.20 [M+H]⁺.

[00244] Step 7. To a stirred solution of 1-(4-hydroxybutyl)-4-(3-([1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido)propanamido)imidazole-2-carboxylic acid (100.00 mg, 0.20 mmol, 1.00 equiv) in DMF (3.00 mL) was added methyl 4-amino-1-methylpyrrole-2-carboxylate (30.80 mg, 0.20 mmol, 1.00 equiv), PyBOP (124.77 mg, 0.24 mmol, 1.20 equiv) and DIEA (77.47 mg, 0.60 mmol, 3.00 equiv) dropwise and the resulting mixture was stirred for 1.0 h at 25 °C. Then the resulting mixture was poured into ice water (20 mL). The precipitated solids were collected by filtration, washed with water (3x20 mL), and dried under vacuum to afford methyl 4-[1-(4-hydroxybutyl)-4-(3-([1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido)propanamido)imidazole-2-amido]-1-methylpyrrole-2-carboxylate (120.00 mg, 94.34%) as a yellow solid. LC/MS: mass calcd. For $C_{29}H_{36}N_{10}O_7$: 636.28, found: 637.25 $[M+H]^+$.

[00245] Step 8. To a stirred solution of methyl 4-[1-(4-hydroxybutyl)-4-(3-([1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido)propanamido)imidazole-2-amido]-1-methylpyrrole-2-carboxylate (110.00 mg, 0.17 mmol, 1.00 equiv) in MeOH (3.00 mL) and THF (1.50 mL) was added KOH (0.35 mL, 0.69 mmol, 4.00 equiv, 2 M in H_2O) dropwise at room temperature and the resulting mixture was stirred for 4.0 h at 70 °C. Then the mixture was adjusted to pH 7~8 with 2 M HCl. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in H_2O (20 mL) and acidified to pH 3~5 with 2 M HCl. The precipitated solids were collected by filtration washed with H_2O (3x20mL), and dried under vacuum to afford 4-[1-(4-hydroxybutyl)-4-(3-([1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido)propanamido)imidazole-2-amido]-1-methylpyrrole-2-carboxylic acid (85.00 mg, 79.01%) as a white solid. LC/MS: mass calcd. For $C_{28}H_{34}N_{10}O_7$: 622.26, found: 623.25 $[M+H]^+$.

[00246] Step 9. To a stirred solution of 4-[1-(4-hydroxybutyl)-4-(3-([1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido)propanamido)imidazole-2-amido]-1-methylpyrrole-2-carboxylic acid (75.00 mg, 0.12 mmol, 1.00 equiv) in DMF (2.00 mL) was added 4-(4-{3-[(4-{2-[1-(aminomethyl)cyclopropyl]acetamido}-1-methylimidazol-2-yl)formamido]propanamido}-1-methylpyrrole-2-amido)-N-[4-(dimethylamino)butyl]-1-methylimidazole-2-carboxamide (80.32 mg, 0.12 mmol, 1.00 equiv), DIEA (46.71 mg, 0.36 mmol, 3.00 equiv) and PyBOP (75.22 mg, 0.14 mmol, 1.20 equiv), and the reaction was stirred for 1.0 h at room temperature. The resulting mixture was poured into ice water (10 mL). The precipitated solids were collected by filtration, washed with water (3x10 mL), and dried under vacuum. The resulting residue was purified by Prep-HPLC: Column: YMC-Actus Triart C18 ExRS19*250mm, 5 μ m; Mobile Phase A: Water (10mmol/L NH_4HCO_3 +0.1% $NH_3.H_2O$), Mobile Phase B: 20mm NaOH+10%ACN; Flow rate: 25 mL/min mL/min; Gradient: 21% B to 46% B in 15min; Wave Length: 254 nm; RT1(min): 12.33. The fractions were combined and lyophilized to afford N-(5-[(1-[(2-[(5-[(2-[(4-(dimethylamino)butyl]carbamoyl)-1-methylimidazol-4-yl)carbamoyl]-1-methylpyrrol-3-yl]carbamoyl)ethyl]carbamoyl]-1-methylimidazol-4-yl)carbamoyl)methyl]cyclopropyl)methyl]carbamoyl)-1-methylpyrrol-3-yl)-1-(4-hydroxybutyl)-4-(3-([1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido)propanamido)imidazole-2-carboxamide (37.20 mg, 23.99%) as a white solid. HRMS: mass calcd. For $C_{61}H_{81}N_{23}O_{11}$: 1270.6220, found: 1271.6332 $[M+H]^+$.

[00247] Example 3. Synthesis of Compound A-95**[00248] Scheme 3.**



[00249] Step 1. Into a 1000 ml flask was added 4-[3-[(tert-butoxycarbonyl)amino]propanamido]-1-methylimidazole-2-carboxylic acid (11.00 g, 35.22 mmol, 1.00 equiv) and DMF (300.00 mL). The mixture was cooled to 0 °C and then HATU (20.09 g, 52.83 mmol, 1.50 equiv) and DIEA (18.21 g, 140.88 mmol, 4.00 equiv) were added dropwise. The mixture was stirred for 10 mins and then methyl 3-aminopropanoate (3.63 g, 35.22 mmol, 1.00 equiv) was added in portions. The reaction mixture was stirred at room temperature for 1.0 h. The reaction mixture was then poured into water/ice (600 mL), the solid was filtered out, and dried under vacuum. The aqueous phase was extracted by EA (3x200 mL), and the combined organic phase was washed with H₂O (1x200 mL) and NaCl (1x200 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The resulting residue was purified by silica gel column, eluted with pure EA to afford methyl 3-[(4-[3-[(tert-butoxycarbonyl)amino]propanamido]-1-methylimidazol-2-yl)formamido]propanoate (13.00 g, 87.95%) as a yellow solid. LC/MS: mass calcd. For C₁₇H₂₇N₅O₆: 397.20, found: 398.20 [M+H]⁺.

[00250] Step 2. A solution of methyl 3-[(4-[3-[(tert-butoxycarbonyl)amino]propanamido]-1-methylimidazol-2-yl]formamido]propanoate, (11g, 1.00 equiv) in HCl/1,4-dioxane (4M, 110.00 mL) was stirred for 1.0 h at room temperature. The resulting mixture was concentrated under vacuum to afford methyl 3-[[4-(3-aminopropanamido)-1-methylimidazol-2-yl] formamido]propanoate hydrochloride (11.00 g crude) as a yellow solid. LC/MS: mass calcd. For $C_{12}H_{19}N_5O_4$: 297.14, found: 298.20 $[M+H]^+$.

[00251] Step 3. To a stirred solution of 1-methylimidazole-2-carboxylic acid (10.00 g, 79.29 mmol, 7.00 equiv) in DMF (150.00 mL) was added TBTU (38.19 g, 118.94 mmol, 1.50 equiv), methyl 4-amino-1-methylpyrrole-2-carboxylate hydrochloride (16.63 g, 87.24 mmol, 1.10 equiv) and DIEA (30.74 g, 237.88 mmol, 3.00 equiv) in portions at 0 °C, and the resulting mixture was stirred for 17.0 h at room temperature. The reaction was poured into water/ice (450 mL). The precipitated solids were collected by filtration, washed with H_2O (3x50 mL), and dried under vacuum to afford ethyl 1-methyl-4-(1-methylimidazole-2-amido)pyrrole-2-carboxylate (16.5 g, 78.37%) as a white solid. LC/MS: mass calcd. For $C_{12}H_{14}N_4O_3$: 262.11, found: 263.15 $[M+H]^+$.

[00252] Step 4. To a stirred solution of ethyl methyl 1-methyl-4-(1-methylimidazole-2-amido)pyrrole-2-carboxylate (16.50 g, 1.00 equiv) in MeOH (100.00 mL) was added LiOH solution (2 M, 202 mL, 4.00 equiv) dropwise at room temperature and the resulting mixture was stirred for 2.0 h at 45 °C. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in H_2O (50 mL) and the mixture was acidified to pH 3~5 with 2M HCl. The precipitated solids were collected by filtration, washed with H_2O (3x30 mL), and dried under vacuum to afford 1-methyl-4-(1-methylimidazole-2-amido)pyrrole-2-carboxylic acid (12.00g, 76.84%) as white solid. LC/MS: mass calcd. For $C_{11}H_{12}N_4O_3$: 248.09, found: 249.10 $[M+H]^+$.

[00253] Step 5. The procedure was the same as Example 3 Step 1. 9.00 g of 1-methyl-4-(1-methylimidazole-2-amido)pyrrole-2-carboxylic acid was used and 14.00 g of the desired product (63.54% yield) was obtained as a yellow solid. LC/MS: mass calcd. For $C_{26}H_{30}N_{10}O_6$: 578.23, found: 579.10 $[M+H]^+$.

[00254] Step 6. The procedure was the same as Example 3 Step 4. 14.00 g of methyl 1-methyl-4-[1-methyl-4-(3-[[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido]propanamido)imidazole-2-amido]pyrrole-2-yl]formamidocarboxylate was used and 12.00 g of the desired product (81.49% yield) was obtained as a yellow solid. LC/MS: mass calcd. For $C_{25}H_{28}N_{10}O_6$: 564.22, found: 565.15 $[M+H]^+$.

[00255] Step 7. The procedure was the same as Example 3 Step 5. 7.80 g of 4-[(tert-butoxycarbonyl)amino]butanoic acid was obtained and 11.00 g of the desired product was obtained as little pink solid (80.70% yield). LC/MS: mass calcd. For $C_{16}H_{26}N_4O_5$: 354.19, found: 355.15 $[M+H]^+$.

[00256] Step 8. The procedure was the same as Example 3 Step 2. 9.40 g of ethyl 4-{4-[(tert-butoxycarbonyl)amino]butanamido}-1-methylimidazole-2-carboxylate was used and 6.20 g of the desired product was obtained as a white solid (90.89% yield). LCMS: mass calcd. For $C_{11}H_{18}N_4O_3$: 254.14, found: 255.15 $[M+H]^+$.

[00257] Step 9. To a stirred solution of 1-methyl-4-[1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-amido]pyrrole-2-carboxylic acid (18.20 g, 32.24

mmol, 1.00 equiv) in DMF (250.00 mL) was added DIEA (12.50 g, 96.71 mmol, 3.00 equiv), ethyl 4-(4-aminobutanamido)-1-methylimidazole-2-carboxylate (9.02 g, 35.46 mmol, 1.10 equiv) and PyBOP (20.13 g, 38.68 mmol, 1.20 equiv) at 0 °C, and the resulting mixture was stirred for 1.0 h at room temperature. Then the reaction was poured into ice/water (800 mL). The precipitated solids were collected by filtration, washed with H₂O (3x200 mL), and dried under vacuum to afford ethyl 1-methyl-4-[4-({1-methyl-4-[1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-amido]pyrrol-2-yl}formamido)butanamido]imidazole-2-carboxylate as a yellow solid (24.70 g, 95.74% yield). LC/MS: mass calcd. For C₃₆H₄₄N₁₄O₈: 800.35, found: 801.30 [M+H]⁺.

[00258] Step 10. The procedure was the same as Example 3 Step 4. 24.00 g of ethyl 1-methyl-4-[4-({1-methyl-4-[1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-amido]pyrrol-2-yl}formamido)butanamido]imidazole-2-carboxylate was used, and 23.10 g of the desired product was obtained as a yellow solid (99.36% yield). LC/MS: mass calcd. For C₃₄H₄₀N₁₄O₈: 772.32, found: 773.30 [M+H]⁺.

[00259] Step 11. To a stirred solution of 4-[(tert-butoxycarbonyl)amino]-1-methylpyrrole-2-carboxylic acid (11.50 g, 47.87 mmol, 1.00 equiv) in DMF (200.00 mL) was added EDCI (22.94 g, 119.66 mmol, 2.50 equiv), ethyl 4-amino-1-methylimidazole-2-carboxylate (8.10 g, 47.87 mmol, 1.00 equiv) and DMAP (14.62 g, 119.66 mmol, 2.50 equiv) at 0 °C, and the resulting mixture was stirred for 17.0 h at 35 °C. Next the reaction was poured into 500 mL ice/water. The precipitated solids were collected by filtration, washed with water (3x50 mL), and dried under vacuum to afford ethyl 4-{4-[(tert-butoxycarbonyl)amino]-1-methylpyrrole-2-amido}-1-methylimidazole-2-carboxylate (16.00 g, 85.48% yield) as a light yellow solid. LC/MS: mass calcd. For C₁₈H₂₅N₅O₅: 391.19, found: 392.30 [M+H]⁺.

[00260] Step 12. To a stirred solution of ethyl 4-{4-[(tert-butoxycarbonyl)amino]-1-methylpyrrole-2-amido}-1-methylimidazole-2-carboxylate (16.00 g, 40.88 mmol, 1.00 equiv) in DCM (135.00 mL) TFA (45.00 mL) was added dropwise and the resulting mixture was stirred for 2.0 h at room temperature. Then the resulting mixture was concentrated under vacuum and the residue was diluted with Et₂O (200 mL). The precipitated solids were collected by filtration, washed with Et₂O (2x100 mL), and dried under vacuum to afford ethyl 4-(4-amino-1-methylpyrrole-2-amido)-1-methylimidazole-2-carboxylate (16.00 g, crude) as a brown solid. LC/MS: mass calcd. For C₁₃H₁₇N₅O₃: 291.13, found: 292.15 [M+H]⁺.

[00261] Step 13. A solution of ethyl 4-(4-amino-1-methylpyrrole-2-amido)-1-methylimidazole-2-carboxylate (12.00 g, 41.19 mmol, 1.00 equiv) and 3-[(tert-butoxycarbonyl)amino] propanoic acid (7.50 g, 39.64 mmol, 0.96 equiv), PyBOP (22.00 g, 42.28 mmol, 1.03 equiv), DIEA (45.00 g, 348.18 mmol, 8.45 equiv) in DMF (120.00 mL) was stirred for 1.0 h at room temperature. Then the reaction mixture was poured into ice water (400 mL). The precipitated solids were collected by filtration, washed with water (3x150 mL), and dried under vacuum. The aqueous phase was extracted with EA (3x150 mL) and the combined organic phase was washed with H₂O (200 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography, eluted with PE/EA (1:8) to afford ethyl 4-(4-{3-[(tert-

butoxycarbonyl)amino]propanamido}-1-methylpyrrole-2-amido)-1-methylimidazole-2-carboxylate as a yellow solid (17.00 g, 89.28% yield). LC/MS: mass calcd. For $C_{21}H_{30}N_6O_6$: 462.22, found: 463.35 $[M+H]^+$.

[00262] Step 14. The procedure was the same as Example 3 Step 4. 12.00 g of ethyl 4-(4-{3-[(tert-butoxycarbonyl)amino]propanamido}-1-methylpyrrole-2-amido)-1-methylimidazole-2-carboxylate was used, and 10.00 g of the desired product was obtained as a white solid (88.81% yield). LC/MS: mass calcd. For $C_{19}H_{26}N_6O_6$: 434.19, found: 435.25 $[M+H]^+$.

[00263] Step 15. A solution of 4-(4-{3-[(tert-butoxycarbonyl)amino]propanamido}-1-methylpyrrole-2-amido)-1-methylimidazole-2-carboxylic acid (10.00 g, 23.02 mmol, 1.00 equiv) and β -alanine ethyl ester hydrochloride (4.90 g, 31.90 mmol, 1.39 equiv), PyBOP (12.50 g, 24.02 mmol, 1.04 equiv), DIEA (9.00 g, 69.64 mmol, 3.03 equiv) in DMF (120.00 mL) was stirred for 1.0 h at room temperature. The reaction was quenched with the addition of water (500 mL) at room temperature. The resulting mixture was extracted with EA (3x400 mL) and the combined organic layers were washed with brine (3x200 mL), dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography, eluted with PE/EA (1:8) to afford ethyl 3-{[4-(4-{3-[(tert-butoxycarbonyl)amino]propanamido}-1-methylpyrrole-2-amido)-1-methylimidazol-2-yl]formamido}propanoate (12.00 g, 93.80%) as a yellow solid. LC/MS: mass calcd. For $C_{24}H_{35}N_7O_7$: 533.26, found: 534.30 $[M+H]^+$.

[00264] Step 16. The procedure was the same as Example 3 Step 12. 12.00 g of ethyl 3-{[4-(4-{3-[(tert-butoxycarbonyl)amino]propanamido}-1-methylpyrrole-2-amido)-1-methylimidazol-2-yl]formamido}propanoate was used, and 12.00 g of the desired product was obtained as a white solid. LC/MS: mass calcd. For $C_{19}H_{27}N_7O_5$: 433.21, found: 434.25 $[M+H]^+$.

[00265] Step 17. The procedure was the same as Example 3 Step 9. 10.00 g of 1-methyl-4-[4-({1-methyl-4-[1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-amido]pyrrol-2-yl}formamido)butanamido)imidazole-2-carboxylic acid was used, and 13.60 g of the desired product was obtained as a yellow solid (88.61% yield). Pure product was obtained as light yellow solid after purification by Prep-HPLC. HRMS: mass calcd. For $C_{53}H_{65}N_{21}O_{12}$: 1187.5122, found: 1188.5153 $[M+H]^+$.

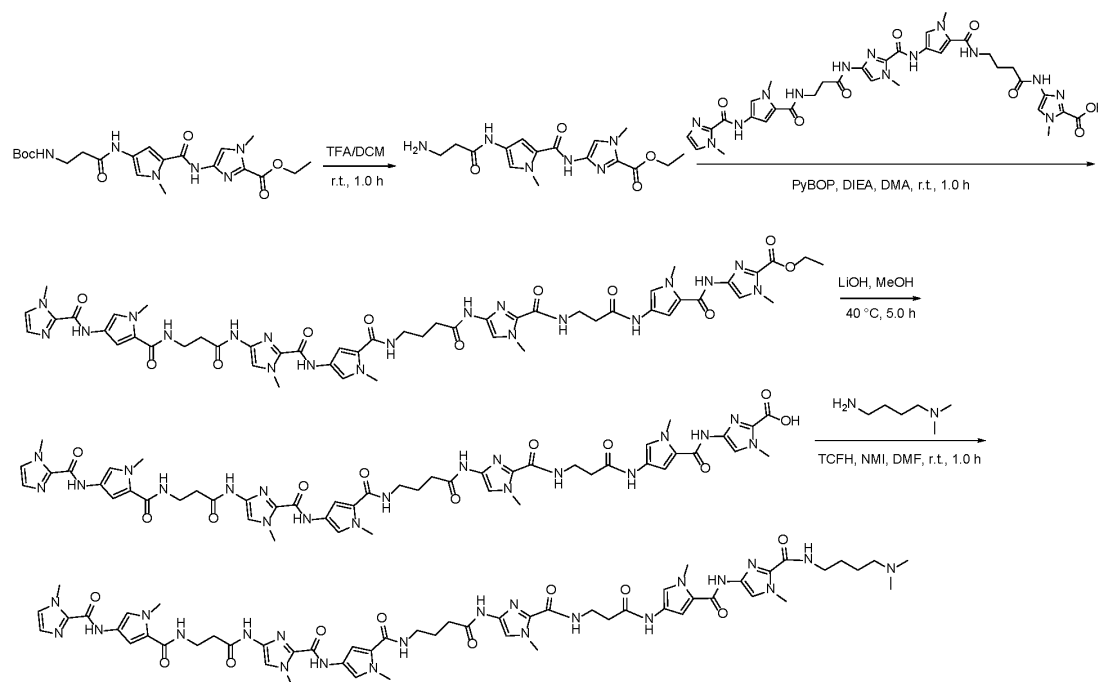
[00266] Step 18. The procedure was the same as Example 3 Step 4, but the reaction temperature was 35 °C. 10.60 g of ethyl 3-[(1-methyl-4-{1-methyl-4-[3-({1-methyl-4-[4-({1-methyl-4-[1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-amido]pyrrol-2-yl}formamido)butanamido)imidazol-2-yl}formamido)propanamido]pyrrole-2-amido)imidazol-2-yl]formamido]propanoate was used, and 10.00 g of the desired product was obtained as a yellow solid. LC/MS: mass calcd. For $C_{51}H_{61}N_{21}O_{12}$: 1159.48, found: 581.25 $[M/2+H]^+$.

[00267] Step 19. To a stirred solution of 3-[(1-methyl-4-{1-methyl-4-[3-({1-methyl-4-[4-({1-methyl-4-[1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-amido]pyrrol-2-yl}formamido)butanamido)imidazol-2-yl}formamido)propanamido]pyrrole-2-

amido}imidazol-2-yl)formamido]propanoic acid (100.00 mg, 0.09 mmol, 1.00 equiv) and 1-methylpiperazine (8.75 mg, 0.09 mmol, 1.00 equiv) in DMF (3.00 mL) were added PyBOP (68.22 mg, 0.13 mmol, 1.50 equiv) and DIEA (28.24 mg, 0.22 mmol, 2.50 equiv), and the reaction mixture was stirred at room temperature for 2.0 h. The reaction mixture was purified by Prep-HPLC with the following conditions: Column, Jupiter C18 300A, 21.2 mm X 250 mm, 5 μ m; Mobile Phase A: Water (0.05%TFA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 12% B to 27% B in 14 min, 27% B to 27% B in 16.5 min, 27% B; Wave Length: 254 nm; RT1(min): 15.22. The fractions were combined and lyophilized to afford 1-methyl-4-{1-methyl-4-[3-({1-methyl-4-[4-({1-methyl-4-[1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-amido]pyrrol-2-yl]formamido)butanamido]imidazol-2-yl}formamido)propanamido]pyrrole-2-amido}-N-[3-(4-methylpiperazin-1-yl)-3-oxopropyl]imidazole-2-carboxamide (56.90 mg, 51.75%) as a white solid. HRMS: mass calcd. For $C_{56}H_{71}N_{23}O_{11}$: 1241.5703, found: 1242.5785 $[M+H]^+$.

[00268] Example 4. Synthesis of Compound A-99

[00269] Scheme 4.



[00270] Step 1. The procedure was the same as Example 3 Step 12. 2.00 g of ethyl 4-(4-{3-[(tert-butoxycarbonyl)amino]propanamido}-1-methylpyrrole-2-amido)-1-methylimidazole-2-carboxylate was used, and 2.00 g of the desired product was obtained as a white solid. LC/MS: mass calcd. For $C_{16}H_{22}N_6O_4$: 362.17, found: 363.25 $[M+H]^+$.

[00271] Step 2. The procedure was the same as Example 3 Step 9, but the solvent was DMA. 3.00 g of 1-methyl-4-[4-({1-methyl-4-[1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-amido]pyrrol-2-yl}formamido)butanamido]imidazole-2-carboxylic

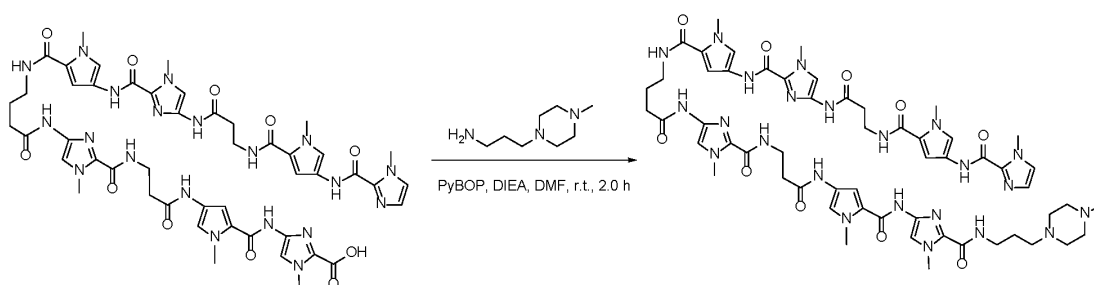
acid was used, and 4.30 g of the desired product was obtained as a yellow solid (96.84% yield). LC/MS: mass calcd. For $C_{50}H_{60}N_{20}O_{11}$: 1116.48, found: 1117.60 $[M+H]^+$.

[00272] Step 3. The procedure was the same as Example 3 Step 4, but the reaction temperature was 40 °C and the reaction time was 5.0 h. 4.20 g of ethyl 1-methyl-4-{1-methyl-4-[3-({1-methyl-4-[4-({1-methyl-4-[1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-amido]pyrrol-2-yl}formamido)butanamido]imidazol-2-yl}formamido)propanamido]pyrrole-2-amido}imidazole-2-carboxylate was used, and 4.00 g of the desired product was obtained as a yellow solid (97.97% yield). LC/MS: mass calcd. For $C_{48}H_{56}N_{20}O_{11}$: 1088.44, found: 1089.55 $[M+H]^+$.

[00273] Step 4. A solution of 1-methyl-4-{1-methyl-4-[3-({1-methyl-4-[4-({1-methyl-4-[1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-amido]pyrrol-2-yl}formamido)butanamido]imidazol-2-yl}formamido)propanamido]pyrrole-2-amido}imidazole-2-carboxylic acid (100.00 mg, 0.09 mmol, 1.00 equiv), (4-aminobutyl)dimethylamine (16.00 mg, 0.14 mmol, 1.50 equiv), TCFH (39.00 mg, 0.14 mmol, 1.51 equiv) and NMI (23.00 mg, 0.28 mmol, 3.05 equiv) in DMF (1.50 mL) were stirred for 1.0 h at room temperature. Next the reaction was poured into ice water (10 mL), and the mixture was stirred for 15 min. The precipitated solids were collected by filtration, washed with water (3 x 3 mL), and dried under vacuum. The crude product was purified by prep-HPLC: Column: XBridge Prep Phenyl OBD Column, 19*150 mm, 5 μ m; Mobile Phase A: water (10 mmol/L NH_4HCO_3 +0.1% $NH_3.H_2O$), Mobile Phase B: MeOH--HPLC; Flow rate: 25 mL/min; Gradient: 50% B to 70% B in 10 min, 70% B; Wave Length: 220 nm; RT1(min): 9.65. The fractions were combined and lyophilized to afford N-[5-({3-[(2-{[2-({5-[(2-{[4-(dimethylamino)butyl]carbamoyl}-1-methylimidazol-4-yl)carbamoyl]-1-methylpyrrol-3-yl}carbamoyl)ethyl]carbamoyl}-1-methylimidazol-4-yl)carbamoyl]propyl}carbamoyl)-1-methylpyrrol-3-yl]-1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-carboxamide (31.0 mg, 27.94%) as a white solid. HRMS: mass calcd. For $C_{54}H_{70}N_{22}O_{10}$: 1186.5645, found: 1187.5692 $[M+H]^+$.

[00274] Example 5. Synthesis of Compound A-101

[00275] Scheme 5.

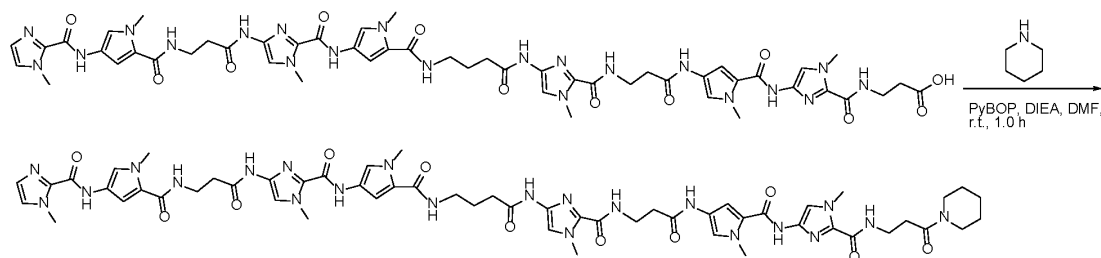


[00276] Into a 25 ml flask was added 1-methyl-4-{1-methyl-4-[3-({1-methyl-4-[4-({1-methyl-4-[1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-amido]pyrrol-2-yl}formamido)butanamido]imidazol-2-yl}formamido)propanamido]pyrrole-2-amido}imidazole-2-carboxylic acid (70.00 mg, 0.06 mmol, 1.00 equiv), DMF (1.5 mL), 3-(4-

methylpiperazin-1-yl)propan-1-amine (15 mg, 0.095 mmol, 1.48 equiv), DIEA (56.00 mg, 0.43 mmol, 6.74 equiv), and the mixture was stirred at room temperature for 5 mins. Then PyBOP (56.00 mg, 0.11 mmol, 1.67 equiv) was added and the reaction mixture was stirred at room temperature for 2.0 h. The reaction mixture was purified by Prep-HPLC: Column: XBridge Prep Phenyl OBD Column, 19*150 mm, 5um; Mobile Phase A: Water(10 mmol/L NH_4HCO_3 +0.1% $\text{NH}_3\cdot\text{H}_2\text{O}$), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 12% B to 36% B in 10 min, 36% B; Wave Length: 220 nm; RT1(min): 9.68. The fractions were combined and lyophilized to afford 1-methyl-4-(3-([1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido)propanamido)-N-[1-methyl-5-({3-([1-methyl-2-{2-([1-methyl-5-([1-methyl-2-{3-(4-methylpiperazin-1-yl)propyl}carbamoyl}imidazol-4-yl)carbamoyl]pyrrol-3-yl}carbamoyl)ethyl}carbamoyl}imidazol-4-yl)carbamoyl]propyl}carbamoyl)pyrrol-3-yl]imidazole-2-carboxamide (28.4 mg, 35.22% yield) as a white solid.

[00277] Example 6. Synthesis of Compound A-94

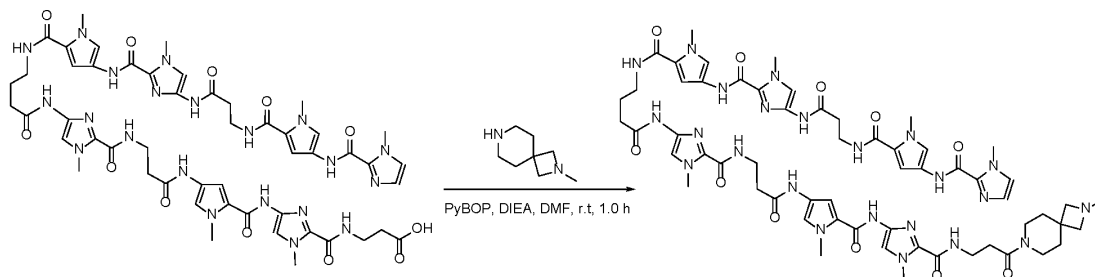
[00278] Scheme 6.



[00279] The procedure was the same as Example 3 Step 9. 100.00 mg of 3-[(1-methyl-4-{1-methyl-4-[3-({1-methyl-4-[4-({1-methyl-4-[1-methyl-4-(3-([1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido)propanamido)imidazole-2-amido]pyrrol-2-yl]formamido)butanamido]imidazol-2-yl}formamido)propanamido]pyrrole-2-amido}imidazol-2-yl]formamido]propanoic acid was used and 41.50 mg of the desired product was obtained as a white solid (38.42% yield). HRMS: mass calcd. For $\text{C}_{56}\text{H}_{70}\text{N}_{22}\text{O}_{11}$: 1226.56, found: 1227.57 $[\text{M}+\text{H}]^+$.

[00280] Example 7. Synthesis of Compound A-97

[00281] Scheme 7.

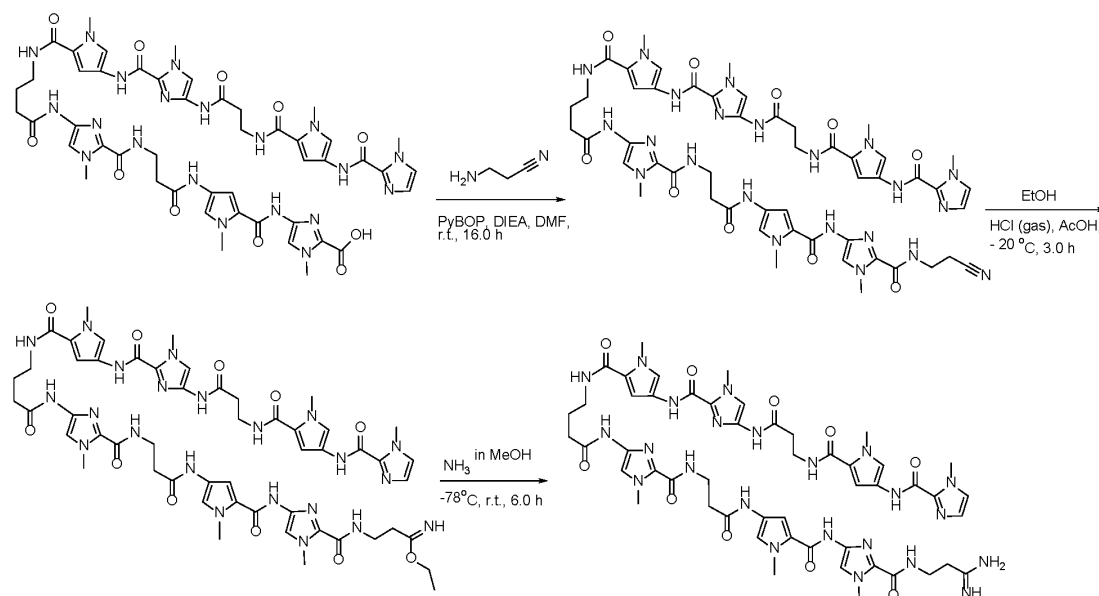


[00282] The procedure was the same as Example 3 Step 9. 70.00 mg of 3-[(1-methyl-4-{1-methyl-4-[3-({1-methyl-4-[4-({1-methyl-4-[1-methyl-4-(3-([1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-

yl]formamido}propanamido)imidazole-2-amido]pyrrol-2-yl]formamido)butanamido]imidazol-2-yl]formamido}propanamido]pyrrole-2-amido}imidazol-2-yl]formamido]propanoic acid was used and 20.00 mg of the desired product was obtained as a light yellow solid (24.30%, yield). HRMS: mass calcd. For $C_{59}H_{75}N_{23}O_{11}$: 1281.6016, found: 1282.6074 $[M+H]^+$.

[00283] Example 8. Synthesis of Compound A-98

[00284] Scheme 8.



[00285] Step 1. The procedure was the same as Example 3 Step 9. 150.00 mg of 1-methyl-4-{1-methyl-4-[3-({1-methyl-4-[4-({1-methyl-4-[1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-amido]pyrrol-2-yl]formamido)butanamido]imidazol-2-yl]formamido}propanamido]pyrrole-2-amido}imidazole-2-carboxylic acid was used, and 120.00 mg of the desired product was obtained as a light yellow solid (74.82% yield). HRMS: mass calcd. For $C_{51}H_{60}N_{22}O_{10}$: 1140.49, found: 1141.4911 $[M+H]^+$.

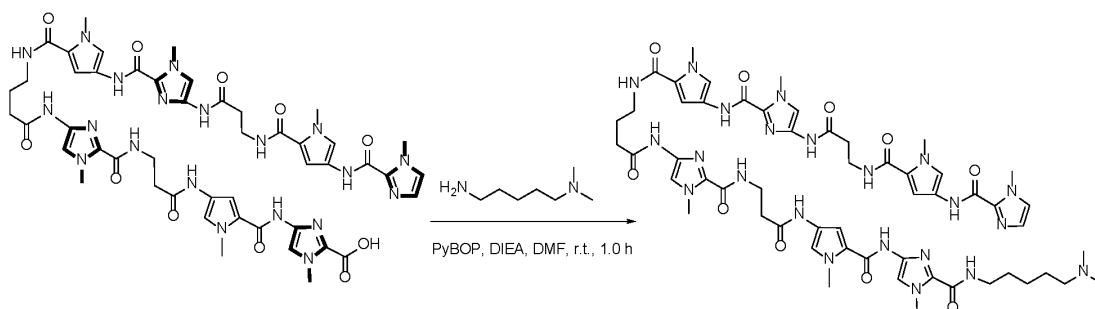
[00286] Step 2. A solution of N-(5-{[3-({2-[(2-{[5-({2-[(2-cyanoethyl)carbamoyl]-1-methylimidazol-4-yl}carbamoyl)-1-methylpyrrol-3-yl]carbamoyl}ethyl)carbamoyl]-1-methylimidazol-4-yl}carbamoyl)propyl]carbamoyl}-1-methylpyrrol-3-yl)-1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-carboxamide (110.00 mg, 0.10 mmol, 1.00 equiv) in ethyl alcohol (1.00 mL) was saturated with dry HCl(g) (17.57 mg, 0.48 mmol, 5.00 equiv) at -20 °C. The resultant mixture was stirred at room temperature for 3.0 h and was then concentrated under vacuum to yield the desired product (120.00 mg, 104.86% yield) as an off-white solid. LC/MS: mass calcd. For $C_{53}H_{66}N_{22}O_{11}$: 1186.53, found: 1187.65 $[M+H]^+$.

[00287] Step 3. To a solution of ethyl 3-[(1-methyl-4-{1-methyl-4-[3-({1-methyl-4-[4-({1-methyl-4-[1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-amido]pyrrol-2-yl]formamido)butanamido]imidazol-2-yl]formamido}propanamido]pyrrole-2-

amido}imidazol-2-yl)formamido]propanimidate (100.00 mg, 0.08 mmol, 1 equiv) in anhydrous ethanol (3 mL) was added NH₃ (2.87 mg, 0.17 mmol, 2 equiv) in MeOH (1 mL) at -78 °C and the resultant mixture was allowed to warm to room temperature for 6.0 h. The reaction was filtered and was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, ACN in water, 10% to 60% gradient in 10.0 min; detector, UV 254 nm. The fractions were combined and concentrated to afford the crude product (90.00 mg) which was dissolved in DMA (2 mL) and purified by Prep-HPLC with the following conditions (Column: Xselect CSH F-Phenyl OBD column, 19*250 mm, 5µm; Mobile Phase A: Water (0.05% TFA), Mobile Phase B: ACN; Flow rate: 20 mL/min; Gradient: 20% B to 30% B in 12 min, 30% B; Wave Length: 220 nm; RT1(min): 11; Number Of Runs: 5). This resulted in of the desired product as a white solid (14.50 mg, 14.69% yield). HRMS: mass calcd. For C₅₁H₆₃N₂₃O₁₀: 1157.51, found: 1158.5205 [M+H]⁺.

[00288] Example 9. Synthesis of Compound A-100

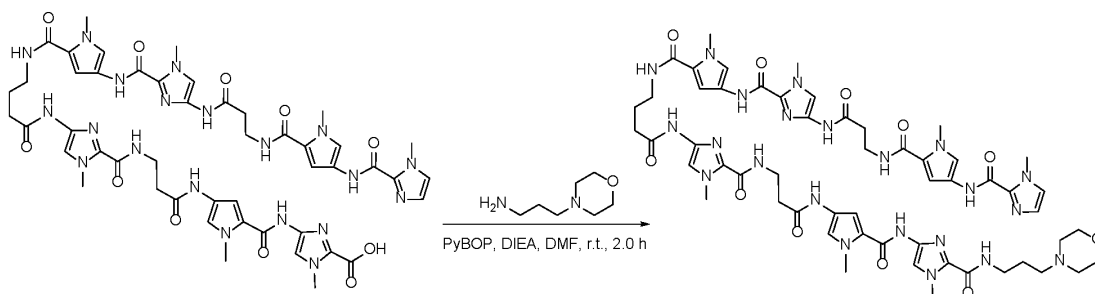
[00289] Scheme 9.



[00290] The procedure was the same as Example 3 Step 9. 100.00 mg of 1-methyl-4-{1-methyl-4-[3-({1-methyl-4-[4-({1-methyl-4-[1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-amido]pyrrol-2-yl}formamido)butanamido]imidazol-2-yl}formamido)propanamido]pyrrole-2-amido}imidazole-2-carboxylic acid was used and 53.30 mg of the desired product was obtained as a white solid (46.88% yield). HRMS: mass calcd. For $C_{55}H_{72}N_{22}O_{10}$: 1200.58, found: 1201.59 $[M+H]^+$.

[00291] Example 10. Synthesis of Compound A-102

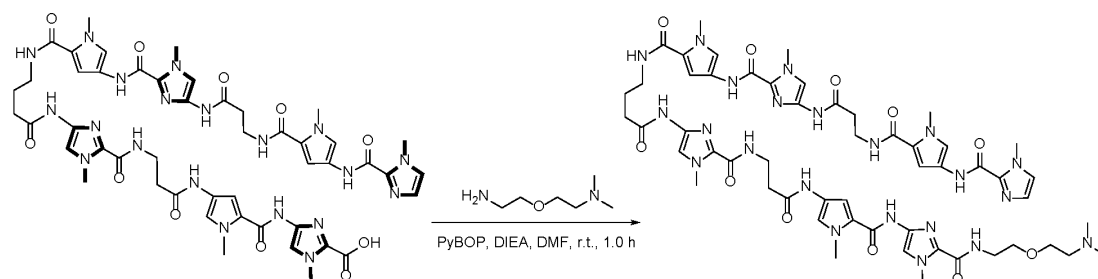
[00292] Scheme 10.



[00293] The procedure was the same as Example 3 Step 9. 80.00 mg of 1-methyl-4-{{1-methyl-4-[3-({1-methyl-4-[4-({1-methyl-4-[1-methyl-4-(3-{{1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl}formamido}propanamido)imidazole-2-amido]pyrrol-2-yl}formamido)butanamido]imidazol-2-yl}formamido)propanamido]pyrrole-2-amido}imidazole-2-carboxylic acid was used, and 27.00 mg of the desired product was obtained as a white solid (29.66% yield). LC/MS: mass calcd. $C_{55}H_{70}N_{22}O_{11}$: 1214.5594, found: 1215.5654 $[M+H]^+$.

[00294] **Example 11. Synthesis of Compound A-103**

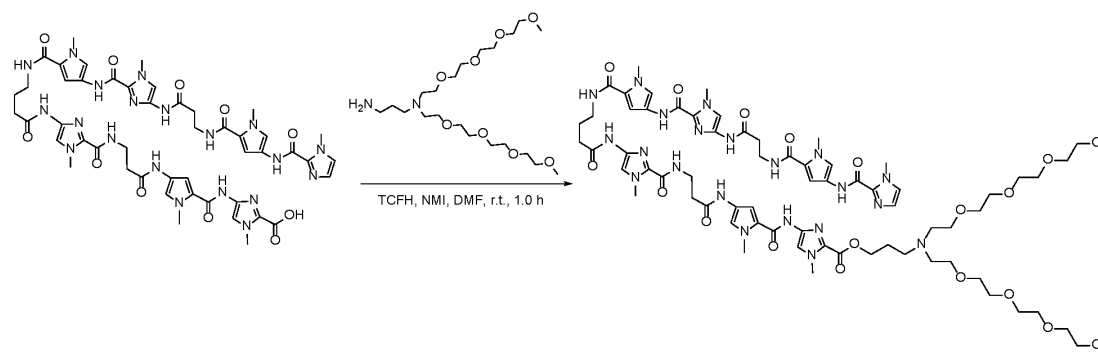
[00295] Scheme 11.



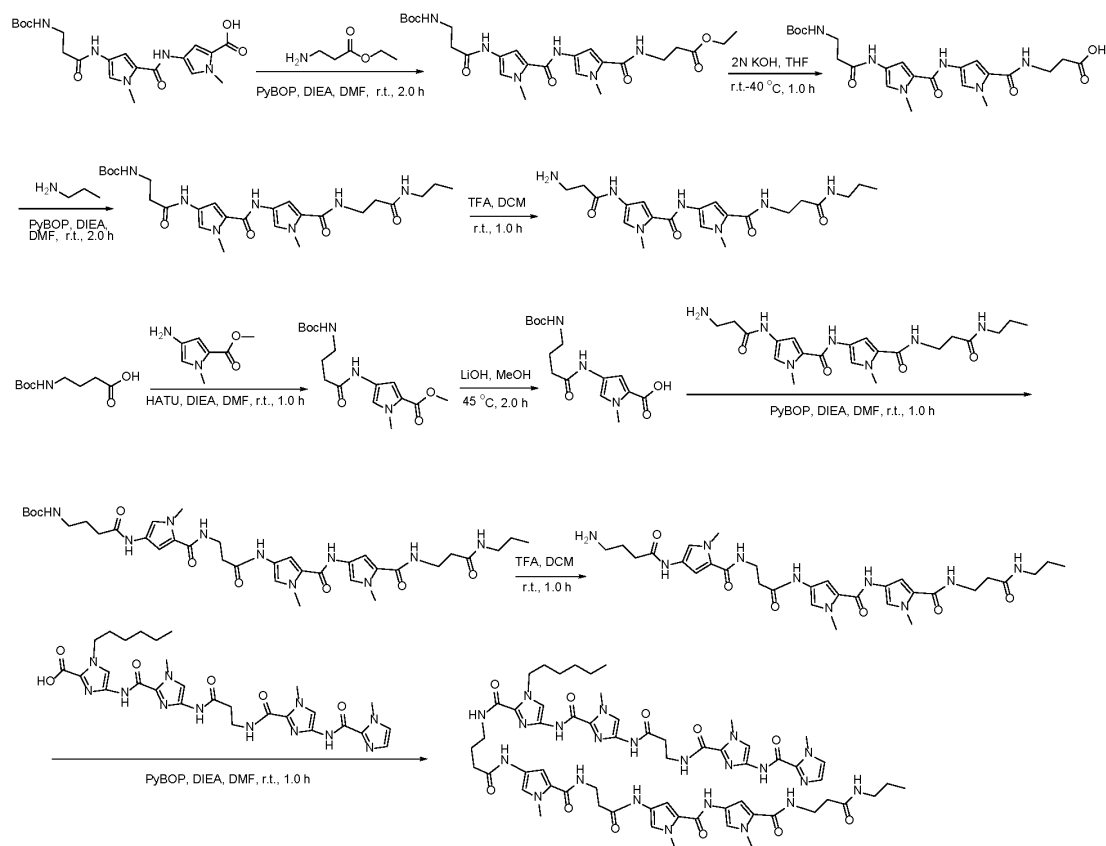
[00296] The procedure was the same as Example 3 Step 9. 100.00 mg of 1-methyl-4-{{1-methyl-4-[3-({1-methyl-4-[4-({1-methyl-4-[1-methyl-4-(3-{{1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl}formamido}propanamido)imidazole-2-amido]pyrrol-2-yl}formamido)butanamido]imidazol-2-yl}formamido)propanamido]pyrrole-2-amido}imidazole-2-carboxylic acid was used, and 22.30 mg of the desired product was obtained as a white solid. (19.94% yield). HRMS: mass calcd. For $C_{54}H_{70}N_{22}O_{11}$: 1202.5994, found: 1203.5638 $[M+H]^+$.

[00297] **Example 12. Synthesis of Compound A-106**

[00298] Scheme 12.



[00299] The procedure was the same as Example 4 Step 4. 41.00 mg of 14-(3-aminopropyl)-2,5,8,11,17,20,23,26-octa-14-azaheptacosane was used, and 37.20 mg (26.18% yield) of the desired product was obtained as white solid. HRMS: mass calcd. For $C_{69}H_{100}N_{22}O_{18}$: 1524.7586 found: 1525.7657 $[M+H]^+$.

[00300] Example 13. Synthesis of Compound A-124**[00301] Scheme 13.**

[00302] Step 1. To a stirred solution of 4-(4-{3-[(tert-butoxycarbonyl)amino]propanamido}-1-methylpyrrole-2-amido)-1-methylpyrrole-2-carboxylic acid (2.00 g, 4.61 mmol, 1.00 equiv) and β-alanine ethyl ester (0.65 g, 5.54 mmol, 1.20 equiv) in DMF (10.00 mL) were added PyBOP (3.12 g, 6.00 mmol, 1.30 equiv) and DIEA (1.79 g, 13.84 mmol, 3.00 equiv), and the resulting mixture was stirred for 2.0 h at room temperature. The resulting mixture was poured into ice water (20 mL). The precipitated solids were collected by filtration, washed with water (3x10 mL), and dried under vacuum to afford ethyl 3-{[4-(4-{3-[(tert-butoxycarbonyl)amino]propanamido}-1-methylpyrrole-2-amido)-1-methylpyrrol-2-yl]formamido}propanoate (2.10 g, 85.46%) as a yellow oil. LC/MS: mass calcd. For $C_{25}H_{36}N_6O_7$: 532.26, found: 555.30 $[M+Na]^+$.

[00303] Step 2. To a stirred solution of methyl 4-(4-{3-[(tert-butoxycarbonyl)amino]propanamido}-1-methylpyrrole-2-amido)-1-methylpyrrole-2-carboxylate (2.06 g, 4.60 mmol, 1.00 equiv) in THF (25.00 mL) was added KOH (2 M in H_2O , 23.02 mL, 46.03 mmol, 10.00 equiv), and the resulting mixture was stirred for 1.0 h at 40 °C. Next the resulting mixture was concentrated under reduced pressure. The residue was dissolved in H_2O (30.00 mL) and the mixture was acidified to pH = 4~5 with 2M HCl. The precipitated solids were collected by filtration, washed with H_2O (3x20.00 mL), and dried under vacuum to afford 4-(4-

{3-[(tert-butoxycarbonyl)amino]propanamido}-1-methylpyrrole-2-amido)-1-methylpyrrole-2-carboxylic acid (1.70 g, 85.19%) as a yellow oil. LC/MS: mass calcd. For $C_{23}H_{32}N_6O_7$: 504.23, found: 505.20 $[M+H]^+$.

[00304] Step 3. To a stirred solution of 3-{[4-(4-{3-[(tert-butoxycarbonyl)amino]propanamido}-1-methylpyrrole-2-amido)-1-methylpyrrol-2-yl]formamido}propanoic acid (1.66 g, 3.29 mmol, 1.00 equiv) and propylamine (0.23 g, 3.95 mmol, 1.20 equiv) in DMF (30.00 mL) were added PyBOP (2.23 g, 4.28 mmol, 1.30 equiv) and DIEA (1.28 g, 9.87 mmol, 3.00 equiv) and the resulting mixture was stirred for 2.0 h at room temperature. Next the reaction was diluted with water (30 mL) and the mixture was extracted with EA (3x30 mL). The combined organic layer was washed with brine (2x30 mL), dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 /MeOH (10:1) to afford tert-butyl N-[2-({1-methyl-5-[(1-methyl-5-{[2-(propylcarbamoyl)ethyl]carbamoyl}pyrrol-3-yl)carbamoyl]pyrrol-3-yl}carbamoyl)ethyl] carbamate (1.30 g, 72.41%) as a yellow solid. LC/MS: mass calcd. For $C_{26}H_{39}N_7O_6$: 545.30, found: 546.25 $[M+H]^+$.

[00305] Step 4. Into a 25 mL round-bottom flask were added tert-butyl N-[2-({1-methyl-5-[(1-methyl-5-{[2-(propylcarbamoyl)ethyl]carbamoyl}pyrrol-3-yl)carbamoyl]pyrrol-3-yl}carbamoyl)ethyl]carbamate (150.00 mg, 0.28 mmol, 1.00 equiv), TFA (1.00 mL) and DCM (5.00 mL) and the resulting mixture was stirred for 1.0 h at room temperature. Next the mixture was concentrated under vacuum to afford 4-(3-aminopropanamido)-1-methyl-N-(1-methyl-5-{[2-(propylcarbamoyl)ethyl]carbamoyl}pyrrol-3-yl)pyrrole-2-carboxamide (120.00 mg, 97.98%) as a yellow solid. LC/MS: mass calcd. For $C_{21}H_{31}N_7O_4$: 445.24, found: 468.30 $[M+Na]^+$.

[00306] Step 5. To a stirred solution of 4-[(tert-butoxycarbonyl)amino]butanoic acid (10.00 g, 49.20 mmol, 1.00 equiv) in DMF (200.00 mL) was added HATU (24.32 g, 63.96 mmol, 1.30 equiv), DIEA (19.04 g, 147.61 mmol, 3.00 equiv) and methyl 4-amino-1-methylpyrrole-2-carboxylate (9.10 g, 59.04 mmol, 1.20 equiv) at 0 °C, and the resulting mixture was stirred for 1.0 h at room temperature. Next the reaction was diluted with water (50 mL) and the mixture was extracted with EA (3x50 mL). The combined organic layer was washed with brine (2x50 mL), dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure to afford methyl 4-{4-[(tert-butoxycarbonyl)amino]butanamido}-1-methylpyrrole-2-carboxylate (11.00 g, 65.86%) as an orange solid. LC/MS: mass calcd. $C_{16}H_{25}N_3O_5$: 339.18, found: 340.15 $[M+H]^+$.

[00307] Step 6. To a stirred solution of methyl 4-{4-[(tert-butoxycarbonyl)amino]butanamido}-1-methylpyrrole-2-carboxylate (4.75 g, 13.99 mmol, 1.00 equiv) in MeOH (40.00 mL) was added LiOH (2 M in H_2O , 69.97 mL, 139.94 mmol, 10.00 equiv) dropwise at room temperature, and the resulting mixture was stirred for 2.0 h at 45 °C. Next the mixture was concentrated under reduced pressure. The residue was dissolved in H_2O (50.00 mL) and was acidified to pH = 4~5 with 2 M HCl. The precipitated solids were collected by filtration, washed with H_2O (3x40 mL), and dried under vacuum to afford 4-{4-[(tert-butoxycarbonyl)amino]butanamido}-1-methylpyrrole-2-carboxylic acid (4.00 g, 87.91%) as an orange solid. LC/MS: mass calcd. $C_{15}H_{23}N_3O_5$: 325.16, found: 326.05 $[M+H]^+$.

[00308] Step 7. To a stirred solution of 4-(3-aminopropanamido)-1-methyl-N-(1-methyl-5-{[2-(propylcarbamoyl)ethyl]carbamoyl}pyrrol-3-yl)pyrrole-2-carboxamide (110.00 mg, 0.23 mmol, 1.20 equiv)

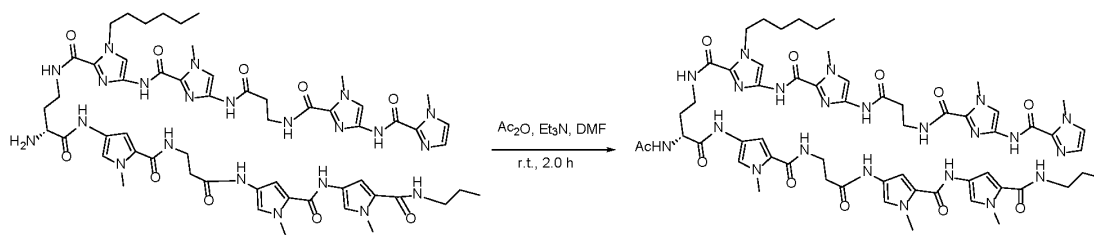
and 4-{4-[(tert-butoxycarbonyl)amino]butanamido}-1-methylpyrrole-2-carboxylic acid (66.94 mg, 0.21 mmol, 1.00 equiv) in DMF (3.00 mL) were added PyBOP (139.19 mg, 0.27 mmol, 1.30 equiv) and DIEA (79.78 mg, 0.62 mmol, 3.00 equiv), and the resulting mixture was stirred for 1.0 h at room temperature. The reaction mixture was purified by reverse-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (10mmol/L NH_4HCO_3), 10% to 50% gradient in 40 min; detector, UV 254 nm. The fractions were combined and concentrated under vacuum to afford tert-butyl N-{3-[(1-methyl-5-{[2-({1-methyl-5-[(1-methyl-5-{2-(propylcarbamoyl)ethyl]carbamoyl}pyrrol-3-yl)carbamoyl]pyrrol-3-yl}carbamoyl)ethyl]carbamoyl}pyrrol-3-yl)carbamoyl]propyl}carbamate (110.00 mg, 71.01%) as a white solid. LC/MS: mass calcd. $\text{C}_{36}\text{H}_{52}\text{N}_{10}\text{O}_8$: 752.40, found: 753.45 $[\text{M}+\text{H}]^+$.

[00309] Step 8. Into a 25 mL round-bottom flask were added tert-butyl N-{3-[(1-methyl-5-{[2-({1-methyl-5-[(1-methyl-5-{2-(propylcarbamoyl)ethyl]carbamoyl}pyrrol-3-yl)carbamoyl]pyrrol-3-yl}carbamoyl)ethyl]carbamoyl}pyrrol-3-yl)carbamoyl]propyl}carbamate (105.00 mg, 0.14 mmol, 1.00 equiv), TFA (1.00 mL) and DCM (5.00 mL), and the resulting mixture was stirred for 1.0 h at room temperature. The resulting mixture was concentrated under vacuum to afford 4-(3-{[4-(4-aminobutanamido)-1-methylpyrrol-2-yl]formamido}propanamido)-1-methyl-N-(1-methyl-5-{2-(propylcarbamoyl)ethyl}carbamoyl}pyrrol-3-yl)pyrrole-2-carboxamide (90.00 mg, 98.86%) as a colorless oil. LC/MS: mass calcd. For $\text{C}_{31}\text{H}_{44}\text{N}_{10}\text{O}_6$: 652.34, found: 653.50 $[\text{M}+\text{H}]^+$.

[00310] Step 9. To a stirred solution of 4-(3-{[4-(4-aminobutanamido)-1-methylpyrrol-2-yl]formamido}propanamido)-1-methyl-N-(1-methyl-5-{2-(propylcarbamoyl)ethyl}carbamoyl}pyrrol-3-yl)pyrrole-2-carboxamide (50.00 mg, 0.08 mmol, 1.20 equiv) and 1-hexyl-4-[1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)imidazol-2-yl]formamido}propanamido)imidazole-2-amido]imidazole-2-carboxylic acid (40.64 mg, 0.06 mmol, 1.00 equiv) in DMF (2.00 mL) were added PyBOP (43.18 mg, 0.09 mmol, 1.30 equiv) and DIEA (24.75 mg, 0.19 mmol, 3.00 equiv), and the resulting mixture was stirred for 1.0 h at room temperature. The reaction mixture was purified by Prep-HPLC with the following conditions: Column: XSelect CSH Phenyl-Hexyl, 19*250 mm, 5 μm ; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 22% B to 47% B in 12min; Wave Length: 254 nm; RT1(min): 11.4. The fractions were combined and lyophilized to afford N-[1-hexyl-2-({3-[(1-methyl-5-{[2-({1-methyl-5-[(1-methyl-5-{2-(propylcarbamoyl)ethyl]carbamoyl}pyrrol-3-yl)carbamoyl]pyrrol-3-yl}carbamoyl)ethyl]carbamoyl}pyrrol-3-yl)carbamoyl]propyl}carbamoyl)imidazol-4-yl]-1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)imidazol-2-yl]formamido}propanamido)imidazole-2-carboxamide formic acid (15.50 mg, 18.33%) as a white solid. HRMS: mass calcd. For $\text{C}_{59}\text{H}_{78}\text{N}_{22}\text{O}_{11}$: 1270.6220, found: 1271.6253 $[\text{M}+\text{H}]^+$. HPLC: 99.463% purity

[00311] Example 14. Synthesis of Compound A-125

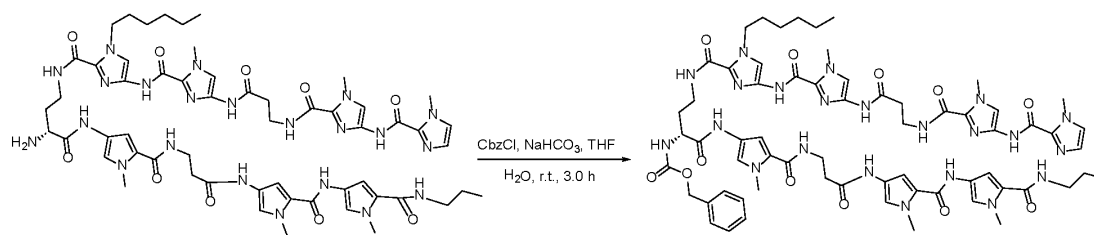
[00312] Scheme 14.



[00313] To a stirred solution of N-(2-{{(3R)-3-amino-3-{{[1-methyl-5-({2-[(1-methyl-5-{{[1-methyl-5-(propylcarbamoyl)pyrrol-3-yl]carbamoyl}pyrrol-3-yl]carbamoyl}ethyl}carbamoyl}pyrrol-3-yl]carbamoyl}propyl]carbamoyl}-1-hexylimidazol-4-yl)-1-methyl-4-(3-{{[1-methyl-4-(1-methylimidazole-2-amido)imidazol-2-yl]formamido}propanamido)imidazole-2-carboxamide (100.00 mg, 0.08 mmol, 1.00 equiv) in DMF (1.00 mL) were added Ac₂O (16.80 mg, 0.16 mmol, 2.00 equiv) and TEA (33.30 mg, 0.33 mmol, 4.00 equiv), and the resulting mixture was stirred for 2.0 h at room temperature. The reaction mixture was purified by reverse-phase flash chromatography with the following conditions: column, C18; MeCN in water (0.1% TFA), 10% to 50% gradient in 30 min; detector, UV 254 nm. The fractions were combined and dried under vacuum to afford the crude product. The crude product was further purified by Prep-HPLC: Column: XBridge Prep OBD C18 Column, 19*250 mm, 5µm; Mobile Phase A: Water (10mmol/L NH₄HCO₃), Mobile Phase B: ACN; Flow rate: 25 mL/min mL/min; Gradient: 28%B to 53%B in 12 min; Wave Length: 254 nm/220nm; RT1(min): 10.72. The fractions were combined and lyophilized to afford N-(2-{{(3R)-3-acetamido-3-{{[1-methyl-5-({2-[(1-methyl-5-{{[1-methyl-5-(propylcarbamoyl)pyrrol-3-yl]carbamoyl}pyrrol-3-yl]carbamoyl}ethyl}carbamoyl}pyrrol-3-yl]carbamoyl}propyl]carbamoyl}-1-hexylimidazol-4-yl)-1-methyl-4-(3-{{[1-methyl-4-(1-methylimidazole-2-amido)imidazol-2-yl]formamido}propanamido)imidazole-2-carboxamide (15.40 mg, 14.30%) as a white solid. HRMS: mass calcd. C₅₈H₇₆N₂₂O₁₁: 1256.6064, found: 1257.6129 [M+H]⁺.

[00314] Example 15. Synthesis of Compound A-126

[00315] Scheme 15.

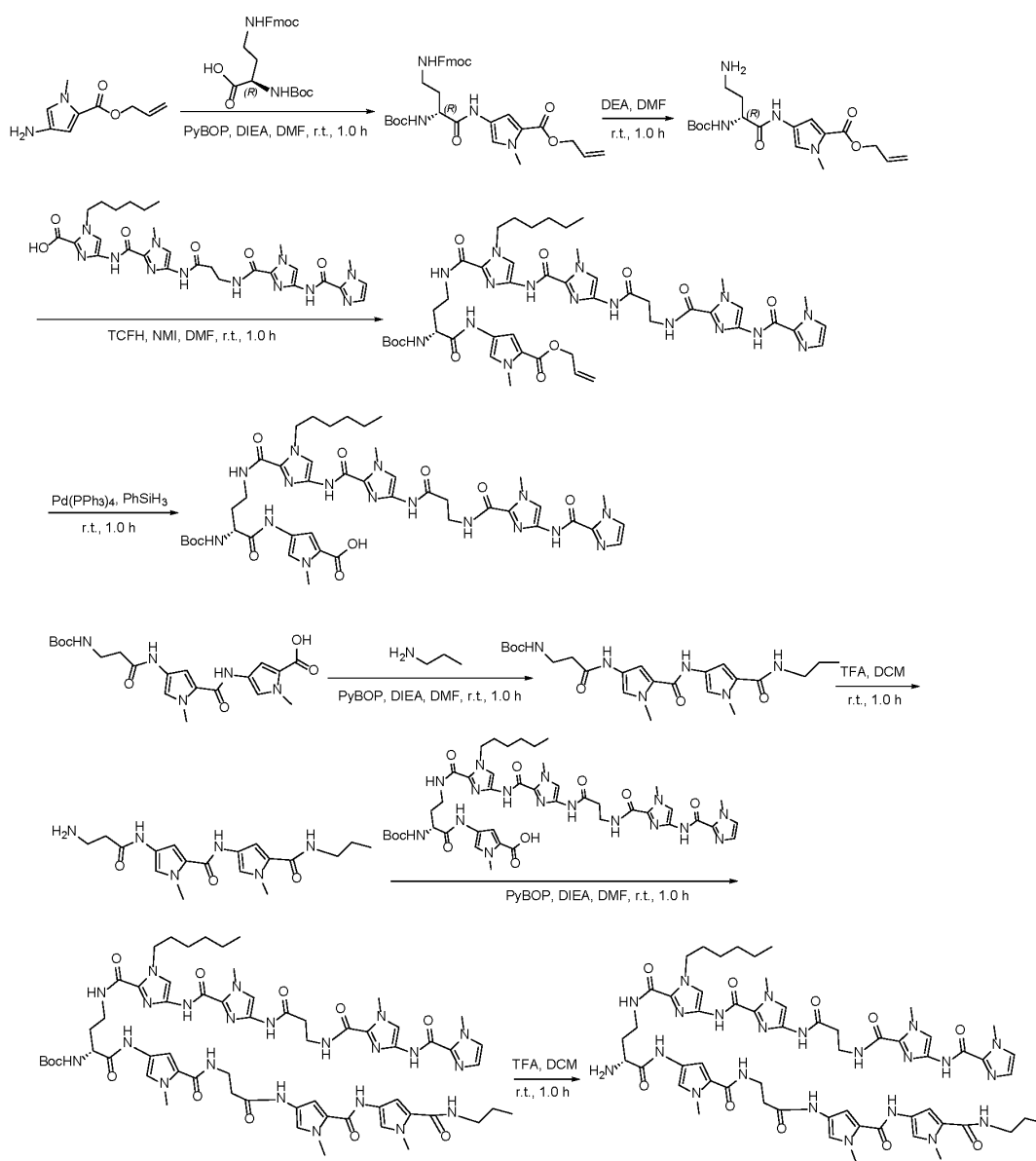


[00316] To a stirred solution of N-(2-{{(3R)-3-amino-3-{{[1-methyl-5-({2-[(1-methyl-5-{{[1-methyl-5-(propylcarbamoyl)pyrrol-3-yl]carbamoyl}pyrrol-3-yl]carbamoyl}ethyl}carbamoyl}pyrrol-3-yl]carbamoyl}propyl]carbamoyl}-1-hexylimidazol-4-yl)-1-methyl-4-(3-{{[1-methyl-4-(1-methylimidazole-2-amido)imidazol-2-yl]formamido}propanamido)imidazole-2-carboxamide (100.00 mg, 0.08 mmol, 1.00 equiv) in THF (2.00 mL) and H₂O (0.40 mL) was added benzyl chloroformate (16.84 mg, 0.10 mmol, 1.20 equiv) and NaHCO₃ (34.56 mg, 0.41 mmol, 5.00 equiv), and the resulting mixture was stirred for 3.0 h at room temperature. The reaction mixture was purified by reverse-phase flash chromatography with the following

conditions: column, C18; MeCN in water (0.1% TFA), 10% to 50% gradient in 30 min; detector, UV 254 nm. The fractions were combined and dried under vacuum to afford the crude product which was further purified by Prep-HPLC: Column: XBridge Prep OBD C18 Column, 19*250 mm, 5 μ m; Mobile Phase A: Water (10mmol/L NH₄HCO₃), Mobile Phase B: ACN; Flow rate: 25 mL/min mL/min; Gradient: 35%B to 60%B in 12 min; Wave Length: 254nm/220nm nm; RT1(min): 11.7. The fractions were combined and lyophilized to afford benzyl N-[(1R)-3-({1-hexyl-4-[1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)imidazol-2-yl]formamido}propanamido)imidazole-2-amido]imidazol-2-yl} formamido)-1-{[1-methyl-5-({2-[(1-methyl-5-{[1-methyl-5-(propylcarbamoyl)pyrrol-3-yl]carbamoyl} pyrrol-3-yl)carbamoyl]ethyl}carbamoyl)pyrrol-3-yl]carbamoyl}propyl]carbamate (4.60 mg, 4.04%) as a white solid. HRMS: mass calcd. C₆₄H₈₀N₂₂O₁₂: 1348.6326, found: 1349.6408[M+H]⁺.

[00317] Example 16. Synthesis of Compound A-127

[00318] Scheme 16.



[00319] Step 1. To a stirred solution of prop-2-en-1-yl 4-amino-1-methylpyrrole-2-carboxylate (4.50 g, 24.97 mmol, 1.00 equiv) in DMF (50.00 mL) was added (2R)-2-[(tert-butoxycarbonyl)amino]-4-[(9H-fluoren-9-ylmethoxy)carbonyl]amino}butanoic acid (11.00 g, 24.97 mmol, 1.00 equiv), PyBOP (15.62 g, 29.96 mmol, 1.20 equiv) and DIEA (13.05 mL, 74.91 mmol, 3.00 equiv), and the resulting mixture was stirred for 1.0 h at room temperature. Next the resulting mixture was poured into ice water (150 mL). The precipitated solids were collected by filtration, washed with water (2x80 mL), and dried under vacuum to afford prop-2-en-1-yl 4-[(2R)-2-[(tert-butoxycarbonyl)amino]-4-[(9H-fluoren-9-ylmethoxy)carbonyl]amino}butanamido]-1-methylpyrrole-2-carboxylate (5.30 g, 35.22%) as a yellow solid. LC/MS: mass calcd. For $\text{C}_{33}\text{H}_{38}\text{N}_4\text{O}_7$: 602.27, found: 603.35 $[\text{M}+\text{H}]^+$.

[00320] Step 2. To a stirred solution of prop-2-en-1-yl 4-[(2R)-2-[(tert-butoxycarbonyl)amino]-4-[(9H-fluoren-9-ylmethoxy)carbonyl]amino]butanamido]-1-methylpyrrole-2-carboxylate (5.75 g, 9.54 mmol, 1.00 equiv) in DMF (50.00 mL) was added DEA (10.00 mL), and the resulting mixture was stirred for 1.0 h at room temperature. The reaction was filtered, and the filtrate was purified by reverse phase column directly with the following conditions: column, C18 column; mobile phase, MeCN in water (0.05% TFA), 10% to 50% gradient in 50 min; detector, UV 254 nm. The fractions were combined and dried under vacuum to afford prop-2-en-1-yl 4-[(2R)-4-amino-2-[(tert-butoxycarbonyl)amino]butanamido]-1-methylpyrrole-2-carboxylate (2.80 g, 77.14%) as a white solid. LC/MS: mass calcd. For $C_{18}H_{28}N_4O_5$: 380.21, found: 381.20 $[M+H]^+$.

[00321] Step 3. To a stirred solution of prop-2-en-1-yl 4-[(2R)-4-amino-2-[(tert-butoxycarbonyl)amino]butanamido]-1-methylpyrrole-2-carboxylate (2.76 g, 7.25 mmol, 1.00 equiv) in DMF (20.00 mL) were added 1-hexyl-4-[1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)imidazol-2-yl]formamido}propanamido)imidazole-2-amido]imidazole-2-carboxylic acid (4.62 g, 7.25 mmol, 1.00 equiv), TCFH (2.44 g, 8.70 mmol, 1.20 equiv) and NMI (1.79 mL, 21.76 mmol, 3.00 equiv), and the resulting mixture was stirred for 1.0 h at room temperature. Next the resulting mixture was poured into ice water (60 mL). The precipitated solids were collected by filtration, washed with water (60 mL), and dried under vacuum. The crude product was purified by silica gel column chromatography, eluted with CH_2Cl_2 /MeOH (12:1) to afford prop-2-en-1-yl 4-[(2R)-2-[(tert-butoxycarbonyl)amino]-4-({1-hexyl-4-[1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)imidazol-2-yl]formamido}propanamido)imidazole-2-amido]imidazol-2-yl}formamido) butanamido]-1-methylpyrrole-2-carboxylate (2.70 g, 37.25%) as a white solid. LC/MS: mass calcd. For $C_{46}H_{62}N_{16}O_{10}$: 998.48, found: 999.50 $[M+H]^+$.

[00322] Step 4. To a stirred solution of prop-2-en-1-yl 4-[(2R)-2-[(tert-butoxycarbonyl)amino]-4-({1-hexyl-4-[1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)imidazol-2-yl]formamido}propanamido)imidazole-2-amido]imidazol-2-yl}formamido)butanamido]-1-methylpyrrole-2-carboxylate (2.60 g, 2.60 mmol, 1.00 equiv) in DMF (20.00 mL) was added phenylsilane (6.50 mL, 0.06 mmol, 2.00 equiv) and $Pd(PPh_3)_4$ (300.72 mg, 0.26 mmol, 0.10 equiv), and the resulting mixture was stirred for 1.0 h at room temperature. Next the reaction was filtered, and the filtrate was purified by reverse phase column with the following conditions: column, C18 column; mobile phase, MeCN in water (0.05% TFA), 10% to 70% gradient in 50 min; detector, UV 254 nm. The fractions were combined and dried under vacuum to afford 4-[(2R)-2-[(tert-butoxycarbonyl)amino]-4-({1-hexyl-4-[1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)imidazol-2-yl]formamido}propanamido)imidazole-2-amido]imidazol-2-yl}formamido)butanamido]-1-methylpyrrole-2-carboxylic acid (1.87 g, 74.93%) as a yellow solid. LC/MS: mass calcd. For $C_{43}H_{58}N_{16}O_{10}$: 958.45, found: 959.40 $[M+H]^+$.

[00323] Step 5. To the stirred solution of 4-(4-{3-[(tert-butoxycarbonyl)amino]propanamido}-1-methylpyrrole-2-amido)-1-methylpyrrole-2-carboxylic acid (1.00 g, 2.31 mmol, 1.00 equiv) in DMF (10.00 mL) were added DIEA (1.49 g, 11.54 mmol, 5.00 equiv), PyBOP (1.56 g, 3.00 mmol, 1.30 equiv) and propylamine (163.65 mg, 2.77 mmol, 1.20 equiv), and the reaction mixture was stirred at room temperature

for 1.0 h. The reaction mixture was purified by reverse-phase flash chromatography with the following conditions: column, C18 column; mobile phase, MeCN in water (0.1% TFA), 10% to 70% gradient in 30 min; detector, UV 254 nm. The fractions were combined and dried under vacuum to afford tert-butyl N-{2-[(1-methyl-5-{[1-methyl-5-(propylcarbamoyl)pyrrol-3-yl]carbamoyl}pyrrol-3-yl)carbamoyl]ethyl}carbamate (1.00 g, 91.34%) as a yellow oil. LCMS: mass calcd. $C_{23}H_{34}N_6O_5$ For: 474.26, found: 497.35 $[M+Na]^+$.

[00324] Step 6. To a stirred solution of ethyl tert-butyl N-{2-[(1-methyl-5-{[1-methyl-5-(propylcarbamoyl)pyrrol-3-yl]carbamoyl}pyrrol-3-yl)carbamoyl]ethyl}carbamate (350.00 mg, 0.738 mmol, 1.00 equiv) in DCM (5.00 mL) was added TFA (2.00 mL), and the reaction mixture was stirred at room temperature for 1.0 h. The reaction was concentrated under vacuum to afford 4-(3-aminopropanamido)-1-methyl-N-[1-methyl-5-(propylcarbamoyl)pyrrol-3-yl]pyrrole-2-carboxamide (350.00 mg, crude) as a light yellow oil. LCMS: mass calcd. $C_{18}H_{26}N_6O_3$ For: 374.21, found: 375.30 $[M+H]^+$.

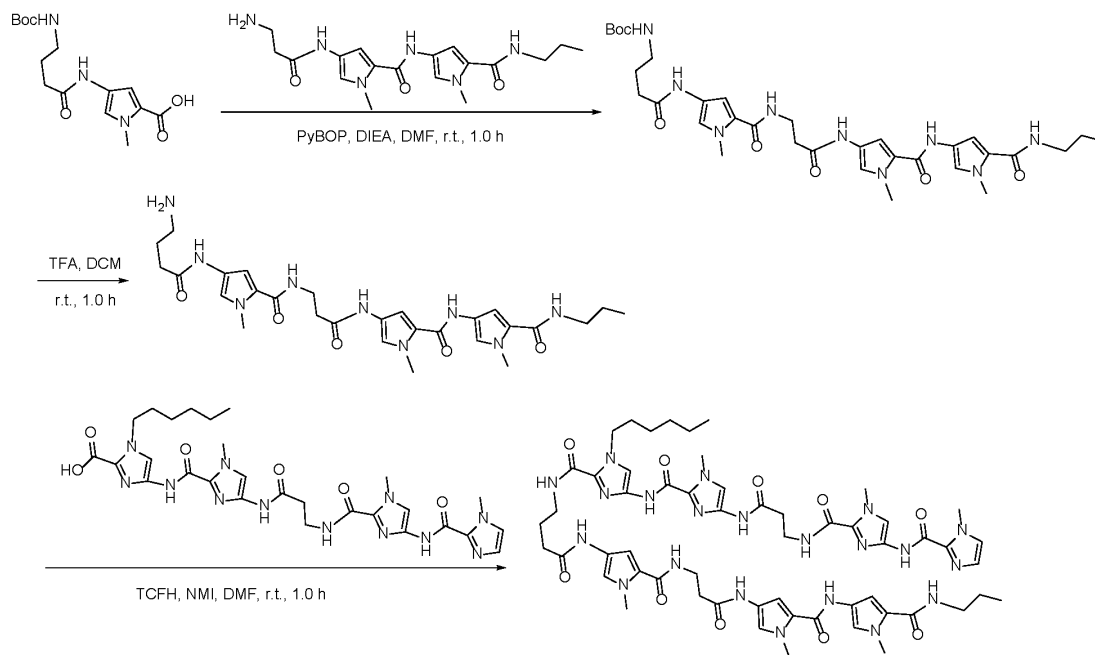
[00325] Step 7. To a stirred solution of 4-[(2R)-2-[(tert-butoxycarbonyl)amino]-4-(1-hexyl-4-[1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)imidazol-2-yl]formamido}propanamido)imidazole-2-amido]imidazol-2-yl}formamido)butanamido]-1-methylpyrrole-2-carboxylic acid (600.00 mg, 0.63 mmol, 1.00 equiv) in DMF (10.00 mL) were added 4-(3-aminopropanamido)-1-methyl-N-[1-methyl-5-(propylcarbamoyl)pyrrol-3-yl]pyrrole-2-carboxamide (468.53 mg, 1.25 mmol, 2.00 equiv), DIEA (326.93 μ L, 1.88 mmol, 3.00 equiv) and PyBOP (390.69 mg, 0.751 mmol, 1.20 equiv). The resulting mixture was stirred for 1.0 h at room temperature. The reaction mixture was purified by reverse-phase flash chromatography with the following conditions: column, C18 column; mobile phase, MeCN in water (0.1% TFA), 5% to 50% gradient in 30 min; detector, UV 254 nm. This resulted in tert-butyl N-[(1R)-3-(1-hexyl-4-[1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)imidazol-2-yl]formamido}propanamido)imidazole-2-amido]imidazol-2-yl}formamido)-1-{[1-methyl-5-(2-[(1-methyl-5-{[1-methyl-5-(propylcarbamoyl)pyrrol-3-yl]carbamoyl}pyrrol-3-yl)carbamoyl]ethyl}carbamoyl]pyrrol-3-yl]carbamoyl}propyl]carbamate (650.00 mg, 78.98%) as a yellow solid. LCMS: mass calcd. $C_{61}H_{82}N_{22}O_{12}$ For: 1314.65, found: 658.60 $[M/2+H]^+$.

[00326] Step 8. To a stirred solution of tert-butyl N-[(1R)-3-(1-hexyl-4-[1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)imidazol-2-yl]formamido}propanamido)imidazole-2-amido]imidazol-2-yl}formamido)-1-{[1-methyl-5-(2-[(1-methyl-5-{[1-methyl-5-(propylcarbamoyl)pyrrol-3-yl]carbamoyl}pyrrol-3-yl)carbamoyl]ethyl}carbamoyl]pyrrol-3-yl]carbamoyl}propyl]carbamate (80.00 mg, 0.06 mmol, 1.00 equiv) in DCM (1.00 mL) was added TFA (0.30 mL), and the reaction mixture was stirred at room temperature for 1.0 h. The resulting mixture was concentrated under vacuum and the residue was purified by Prep-HPLC: Column: XSelect CSH C18 Column, 19*250 mm, 5 μ m; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/min mL/min; Gradient: 19% B to 39% B in 9 min; Wave Length: 254 nm; RT1(min): 8. The fractions were combined and lyophilized to afford N-(2-{[(3R)-3-amino-3-{[1-methyl-5-(2-[(1-methyl-5-{[1-methyl-5-(propylcarbamoyl)pyrrol-3-yl]carbamoyl}pyrrol-3-yl)carbamoyl]ethyl}carbamoyl]pyrrol-3-yl]carbamoyl}propyl]carbamoyl}-1-hexylimidazol-4-yl)-1-methyl-

4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)imidazol-2-yl]formamido}propanamido)imidazole-2-carboxamide (16.9 mg, 22.77%) as a white solid. HRMS: mass calcd. $C_{56}H_{74}N_{22}O_{10}$: 1214.5958, found: 1215.6025 $[M+H]^+$.

[00327] Example 17. Synthesis of Compound A-128

[00328] Scheme 17.



[00329] Step 1. To a stirred solution of 4-{4-[(tert-butoxycarbonyl)amino]butanamido}-1-methylpyrrole-2-carboxylic acid (57.93 mg, 0.18 mmol, 1.00 equiv) and 4-(3-aminopropanamido)-1-methyl-N-[1-methyl-5-(propylcarbamoyl)pyrrol-3-yl]pyrrole-2-carboxamide (80.00 mg, 0.21 mmol, 1.20 equiv) in DMF (2.00 mL) were added PyBOP (120.45 mg, 0.23 mmol, 1.30 equiv) and DIEA (115.06 mg, 0.89 mmol, 5.00 equiv), and the resulting mixture was stirred for 1.0 h at room temperature. The reaction was diluted with water (10 mL) and the resulting mixture was extracted with EA (3x10 mL). The combined organic layer was washed with brine (2x10 mL), dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure to afford tert-butyl N-(3-{[1-methyl-5-({2-[(1-methyl-5-{[1-methyl-5-(propylcarbamoyl)pyrrol-3-yl]carbamoyl}pyrrol-3-yl)carbamoyl]ethyl}carbamoyl)pyrrol-3-yl]carbamoyl}propyl)carbamate (110.00 mg, 90.62%) as a yellow oil. LC/MS: mass calcd. For $C_{33}H_{47}N_9O_7$: 681.36, found: 704.50 $[M+Na]^+$.

[00330] Step 2. To a stirred solution of tert-butyl N-(3-{[1-methyl-5-({2-[(1-methyl-5-{[1-methyl-5-(propylcarbamoyl)pyrrol-3-yl]carbamoyl}pyrrol-3-yl)carbamoyl]ethyl}carbamoyl)pyrrol-3-yl]carbamoyl}propyl)carbamate (110.00 mg, 0.16 mmol, 1.00 equiv) in DCM (1.00 mL) was added TFA (0.30 mL) in portions at room temperature. The resulting mixture was stirred for 1.0 h at room temperature and was then concentrated under vacuum to afford 4-(3-{[4-(4-aminobutanamido)-1-methylpyrrol-2-yl]formamido}propanamido)-1-methyl-N-[1-methyl-5-(propylcarbamoyl)pyrrol-3-yl]pyrrole-2-

carboxamide (110.00 mg, crude) as a brown oil. LC/MS: mass calcd. For $C_{28}H_{39}N_9O_5$: 581.31, found: 582.25 $[M+H]^+$.

[00331] Step 3. To a stirred mixture of 4-(3-{[4-(4-aminobutanamido)-1-methylpyrrol-2-yl]formamido}propanamido)-1-methyl-N-(1-methyl-5-{[2-(propylcarbamoyl)ethyl]carbamoyl}pyrrol-3-yl)pyrrole-2-carboxamide (61.52 mg, 0.09 mmol, 1.00 equiv) and 1-hexyl-4-[1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)imidazol-2-yl]formamido}propanamido)imidazole-2-amido]imidazole-2-carboxylic acid (60.00 mg, 0.09 mmol, 1.00 equiv) in DMF (1.00 mL) were added TCFH (34.37 mg, 0.12 mmol, 1.30 equiv) and NMI (23.21 mg, 0.28 mmol, 3.00 equiv), and the resulting mixture was stirred for 1.0 h at room temperature. The reaction mixture was purified by Prep-HPLC with the following conditions: column XSelect CSH C18 Column, 19*250 mm, 5 μ m, Mobile Phase A: Water(0.1% FA), Mobile Phase B: ACN, Flow rate: 25 mL/min, Gradient: 30% B to 55% B in 12 min, RT1(min): 11.5. The fractions were combined and lyophilized to afford N-[1-hexyl-2-({3-[(1-methyl-5-{[2-({1-methyl-5-[(1-methyl-5-{[2-(propylcarbamoyl)ethyl]carbamoyl}pyrrol-3-yl)carbamoyl]pyrrol-3-yl}carbamoyl)ethyl]carbamoyl}pyrrol-3-yl)carbamoyl]propyl}carbamoyl)imidazol-4-yl]-1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)imidazol-2-yl]formamido}propanamido)imidazole-2-carboxamide; formic acid (2.30 mg, 1.77%) as a white solid. HRMS: mass calcd. For $C_{56}H_{73}N_{21}O_{10}$: 1199.5849, found: 1200.5885 $[M+H]^+$.

[00332] Example 18. Synthesis of Additional Compounds of the Disclosure

[00333] The compounds of the application were made by the methods similar to Examples 1-17. A summary of the analytical data is represented in Table 2.

Table 2. Mass spectrometry data for the compounds of the disclosure.

Cmpd. No.	Exact Mass	Observed $[M+H]^+$ from TOF-HRMS $[m/z]$
A-1	1269.6016	1270.6065
A-2	1428.7064	1429.7139
A-3	1549.7902	1550.8018
A-4	1577.8215	1578.8324
A-5	1591.8372	1592.8514
A-6	1605.8528	1606.8614
A-7	1589.8215	1590.8377
A-8	1603.8372	1604.8442
A-9	1617.8528	1618.8735
A-10	1605.8164	1628.8099 $[M+Na]$
A-11	1619.8321	1620.8477
A-12	1618.8481	1619.8582
A-13	1632.8637	1633.8785
A-14	1695.8845	1696.8922
A-15	1783.937	1784.948
A-16	1480.7324	1481.751
A-17	1568.7848	1569.7924

A-18	1656.8372	1657.8577
A-19	1617.8164	1618.8277
A-20	1589.7851	1590.7914
A-21	1603.8008	1604.8099
A-22	1632.8273	1633.8372
A-23	1198.5281	1199.5365
A-24	1212.5438	1213.5498
A-25	1241.5703	1242.5861
A-26	1634.843	1635.8531
A-27	1551.7695	1552.7795
A-28	1534.7429	1235.7527
A-29	1639.8219	1640.8362
A-30	1622.7954	1623.8105
A-31	1710.8478	1728.8944
A-32	1268.5312	1269.5373
A-33	1294.5468	1295.5529
A-34	1197.4941	1198.509
A-35	1216.5387	1217.5487
A-36	1242.5544	1243.5606
A-37	1216.5387	1217.5466
A-38	1242.5544	1243.5638
A-39	1228.5751	1229.5871
A-40	1254.5907	1255.5982
A-41	1157.538	1158.5529
A-42	1228.5751	1229.5864
A-43	1254.5907	1255.5994
A-44	1157.538	1158.546
A-45	1228.5751	1229.5863
A-46	1254.5907	1255.6021
A-47	1157.538	1158.5476
A-48	1228.5751	1229.585
A-49	1254.5907	1255.6017
A-50	1157.538	1158.5491
A-51	1198.5645	1199.5736
A-52	1141.5067	1142.5156
A-53	1283.6173	1284.6261
A-54	1252.5751	1253.5819
A-55	1298.6282	1299.634
A-56	1267.586	1268.5931
A-57	1269.6016	1270.6111
A-58	1507.7433	1508.7557
A-59	1727.8744	1728.8846
A-60	1609.8114	1610.8174
A-61	1228.6115	1229.6428
A-62	1436.7062	1437.7086
A-63	1656.8372	1657.851
A-64	1285.6442	1286.6565

A-65	1325.589	1326.5995
A-66	1294.5468	1295.5525
A-67	1266.5155	1267.5254
A-68	1254.5519	1255.5618
A-69	1197.4941	1198.5012
A-70	1653.834	1654.8406
A-71	1653.834	1654.8405
A-72	1635.8434	1636.8504
A-73	1685.8402	1686.848
A-74	1685.8402	1686.8484
A-75	1631.8685	1632.8768
A-76	1649.8591	1650.8616
A-77	1649.8591	1650.565
A-78	1699.8559	1700.8637
A-79	1699.8559	1700.8611
A-80	1645.8841	1646.8928
A-81	1663.8747	1664.8815
A-82	1713.8715	1714.8794
A-83	1713.8715	1714.8776
A-84	1633.8477	1634.8517
A-85	1647.8634	1648.871
A-86	1254.5519	1255.5588
A-87	1169.4628	1170.4708
A-88	1268.5312	1269.5412
A-89	1268.5312	1269.5415
A-90	1268.5312	1269.5411
A-91	1197.4941	1198.5037
A-92	1197.4941	1198.5042
A-93	1197.4941	1198.5033
A-94	1226.5594	1227.5663
A-95	1241.5703	1242.5785
A-96	1267.586	1268.5914
A-97	1281.6016	1282.6074
A-98	1157.5128	1158.5205
A-99	1186.5645	1187.5692
A-100	1200.5802	1201.5935
A-101	1227.5911	1228.5953
A-102	1214.5594	1215.5654
A-103	1202.5594	1203.5638
A-104	1283.6285	1284.6357
A-105	1563.8059	1564.8134
A-106	1524.7586	1525.7657
A-107	1242.602	1243.6057
A-108	1336.5186	1337.5253
A-109	1336.5186	1337.5282
A-110	1515.6107	1516.6255
A-111	1727.8872	1728.8938

A-112	1687.8559	1688.8714
A-113	1685.8402	1686.8455
A-114	1838.8804	1839.8952
A-115	1673.9154	1674.9221
A-116	1283.6540	1284.6676
A-117	1270.6220	1271.6332
A-118	1283.6540	1284.6611
A-119	1284.6377	1285.6479
A-120	1297.6693	1298.6783
A-121	1327.6435	1328.6493
A-123	1285.6329	1286.6356
A-124	1270.6220	1271.6253
A-125	1256.6064	1257.6129
A-126	1348.6326	1349.6408
A-127	1214.5958	1215.6025
A-128	1199.5849	1200.5885
A-129	1269.6632	1270.6704
A-130	1339.7414	1340.761
A-131	1327.705	1328.7178
A-132	1326.721	1327.7321
A-133	1339.7414	1340.7553
A-134	1327.705	1328.7158
A-135	1326.721	1327.7384
A-136	1271.6424	1272.6586
A-137	1269.6632	1270.6769
A-138	1269.6632	1270.6832
A-139	1269.6632	1270.6762
A-140	1269.6632	1270.6788
A-141	1225.6006	1226.6066
A-142	1296.6377	1297.6406
A-143	1296.6377	1297.6405
A-144	1321.6329	1322.6321
A-145	1361.589	1362.5956
A-146	1361.6642	1362.6717
A-147	1279.586	1280.5929
A-148	1279.586	1280.5917
A-149	1349.6642	1350.674
A-150	1349.6642	1350.6713
A-151	1326.6846	1327.6884
A-152	1342.6796	1343.6856
A-153	1342.6796	1343.6887
A-154	1271.6424	1272.6535
A-155	1271.6424	1272.6446
A-156	1271.6424	1272.6602
A-157	1267.6475	1268.6468
A-158	1311.7101	1312.7162
A-159	1359.6161	1360.6234

A-160	1255.6475	1256.6605
A-161	1326.6846	1327.6905
A-162	1339.7414	1340.7467
A-163	1437.851	1438.8566
A-164	1257.6268	1258.6329
A-165	1197.5693	1198.5777
A-166	1197.5693	1198.5763
A-167	1197.5693	1198.5745
A-168	1197.5693	1198.5707
A-169	1197.5693	1198.582
A-170	1197.5693	1198.5779
A-171	1197.5693	1198.5712
A-172	1327.705	1328.7132
A-173	1327.705	1328.7138
A-174	1315.6687	1316.6769
A-175	1257.6268	1258.6344
A-176	1315.6687	1316.6767
A-177	1315.6687	1316.6766
A-178	1327.705	1328.7123
A-179	1327.705	1328.7127
A-180	1257.6268	1258.6354
A-181	1257.6268	1258.6354
A-182	1323.6349	1324.6436
A-183	1323.6349	1324.6427
A-184	1323.6349	1324.6406
A-185	1227.6162	1228.6242
A-186	1227.6162	1228.6243
A-187	1241.6319	1242.6404
A-188	1337.6506	1338.6558
A-189	1339.6298	1340.6396
A-190	1352.7367	1353.7445
A-191	1380.768	1381.7726
A-192	1324.7054	1325.7123
A-193	1338.721	1339.7261
A-194	1366.7159	1367.7326
A-195	1326.721	1327.7267
A-196	1394.7084	1395.7137
A-197	1783.937	1784.9454
A-198	1783.937	1784.9453
A-199	1755.9057	1756.915
A-200	1727.8744	1728.8823
A-201	1783.937	1784.943
A-202	2131.095	2132.0909
A-203	1911.9843	1912.9931
A-204	2006.0625	2007.0717
A-205	1325.6642	1326.496
A-206	1325.6642	1326.496

BIOLOGICAL EXAMPLES

[00334] Example B-1. DM1 foci reduction assay methods

[00335] Myotonic Dystrophy 1 affected patient fibroblasts (Coriell GM04602; 1600 CTG repeats) and wild type fibroblasts (Coriell GM07492; control line) were cultured separately in Gibco DMEM (1X) + 4.5 g/L D-Glucose + L-Glutamine + 110 mg/L Sodium Pyruvate, supplemented with 10% FBS and 1x Pen/Strep. Cells were maintained in an incubator at 37 °C and 5% CO₂ with media refreshed every 48-72 hours.

[00336] At 90-95% confluency, both cell lines were harvested using Trypl-E then pelleted at 500 xg for 5 minutes and were resuspended in fresh media. DM1 fibroblasts were seeded in Agilent 96 well black plates at a density of 5,000 cells/well in 200 µL media; and 8 wells were reserved for control fibroblasts. Plates were returned to incubator for 24 hours at 37 °C and 5% CO₂.

[00337] Compounds were diluted from 10 mM stock to 1 mM in DMSO and then diluted once more to 6 µM (2x concentration) in media. Media was removed from all plates and cells were replenished with 100 µL media. Cells were treated in 8-point dose response, 1:3 fold dilution, 3 µM top dose via addition of 100 µL of 6 µM (2x concentration) compound to the 100 µL media with cells. Plates were returned to incubator for 48 hours at 37 °C and 5% CO₂.

[00338] Following treatment, compounds were removed, and plates were washed with PBS, then cells were fixed in 75 µL 4% PFA solution for 20 minutes at room temperature. Plates were washed twice with PBS and twice with cold 70% ethanol before permeabilization with 250 µL cold 70% ethanol for 24-72 hours at -20 °C.

[00339] After permeabilization, plates were washed once with a 30% formamide and 2X SSC buffer and rehydrated in that buffer for 15 minutes at room temperature. Cells were incubated overnight at 37 °C in 75 µL of a hybridization solution containing 30% formamide, 2X SSC, 25 mg/mL dextran sulfate, 2.5 mg/mL BSA, 0.2 µg/mL Herring sperm DNA, 2 mM vanadyl-ribonucleoside complex, and 5 nM CAG10-Cy3 probe.

[00340] Plates were washed once with 30% formamide in 2X SSC buffer, then twice with the buffer for 30 minutes at 37 °C, 300 RPM in an incubating plate shaker. Cells were stained with 75 µL of 2.5 µg/mL DAPI in PBS for 5 minutes at room temperature. Plates were then washed twice with PBS and stored in 250 µL PBS. Plates were sealed with adhesive foil and wiped down with 70% ethanol.

[00341] Cells were imaged on a Cytation5 with a 20x objective sampling from 4 areas of each well. Nuclei were captured under DAPI channel and foci under RFP channel. Plates were analyzed on an average foci per nucleus per well basis. Active compounds were defined as those that showed a significant decrease in foci per nucleus from the negative control cells in a dose-responsive manner.

[00342] Representative *in vitro* biochemical data is presented in Table 3A. A < 100 nM; B ≥100 nM to 500 nM; C ≥ 500 nM to 1000 nM; D > 1000 nM.

Table 3A. Representative DM1 biochemical data.

Cmpd. No.	IC _{50, 48h} (nM)
A-1	B
A-2	D
A-3	B
A-5	A
A-6	A
A-7	B
A-8	B
A-9	B
A-10	B
A-11	B
A-12	B
A-13	B
A-14	C
A-15	B
A-16	B
A-17	C
A-18	C
A-19	B
A-20	B
A-21	B
A-22	C
A-23	A
A-24	A
A-25	A
A-26	B
A-27	B
A-28	B
A-29	C
A-30	B
A-31	B
A-32	A
A-33	A
A-34	A
A-35	B
A-36	A
A-37	B
A-38	B
A-39	B
A-40	A
A-41	A
A-42	B
A-43	A
A-44	A
A-45	A
A-46	A

Cmpd. No.	IC _{50, 48h} (nM)
A-47	A
A-48	B
A-49	A
A-50	B
A-51	D
A-52	D
A-53	A
A-54	B
A-55	D
A-56	B
A-57	B
A-58	B
A-59	C
A-60	B
A-61	A
A-62	B
A-63	C
A-64	D
A-65	D
A-66	D
A-67	D
A-68	A
A-69	A
A-70	B
A-71	B
A-72	B
A-73	A
A-74	A
A-75	A
A-76	A
A-77	A
A-78	A
A-79	A
A-80	A
A-81	A
A-82	A
A-83	A
A-84	B
A-85	A
A-86	A
A-87	B
A-88	D
A-89	D
A-90	B
A-91	A

Cmpd. No.	IC _{50, 48h} (nM)
A-92	B
A-93	A
A-94	B
A-95	B
A-96	B
A-97	B
A-98	A
A-99	B

Cmpd. No.	IC _{50, 48h} (nM)
A-100	B
A-101	A
A-102	B
A-103	B
A-104	A
A-105	B
A-106	B
A-107	B

[00343] Example B-2. Foci reduction in FECD

[00344] F35T cells were cultured in media containing Opti-MEM (ThermoFisher) supplemented with 8% FBS, 20µg/mL ascorbic acid, 200 mg/mL CaCl₂, 0.08% chondroitin sulfate, 1X Pen/Strep, 100 µg/mL bovine pituitary extract, 5 ng/mL epidermal growth factor, and 20 ng/mL nerve growth factor. Throughout the culture, cells were maintained in an incubator at 37°C and 5% CO₂. Media was refreshed every 48 hours. Once cells reached adequate confluency, they were harvested and seeded in 96 well plates with a density of 5000 cells per well in 200 µL of the supplemented Opti-MEM media. Cells were returned to the incubator and left to settle for 24 hours at 37 °C and 5% CO₂. Cells were then treated in 8-point dose response with compounds or negative controls and incubated for 48 hours at 37 °C and 5% CO₂. After treatment, cells were fixed with 4% PFA for 20 minutes at room temperature, followed by permeabilization with 70% ethanol. Cells were incubated at -20 °C for a minimum of 1 hour and maximum of 72 hours, after which the ethanol was removed, and cells were washed with PBS. Cells were rehydrated with 30% formamide and 2XSSC buffer for 10 minutes at room temperature. Cells were then incubated overnight at 37 °C in the hybridization solution containing 30% formamide, 2XSSC, 55 mg/mL dextran sulfate, 2.75mg/mL bovine serum albumin, 0.2µg/mL Herring sperm DNA, 1% vanadyl-ribonucleoside complex, and 0.05% 10 µM CAG10-Cy3 probe. Cells were washed twice with 30% formamide in 2XSSC, incubating the cells while shaking with the second wash at 37 °C and 200rpm for 60 minutes. Cells were stained with 5 mg/mL DAPI 1:1000 in PBS, incubating at room temperature for 5 minutes. Cells were then washed with PBS and sealed with adhesive foil, with each well containing a final volume of 150 µL PBS. Cells were imaged on a Cytation 5 and analyzed on a foci per nucleus basis. Active compounds were defined as those that showed a significant decrease in foci per nucleus from the negative control cells in a dose-responsive manner.

[00345] Representative *in vitro* biochemical data is presented in Table 3B. A < 50 nM; B ≥50 nM to 100 nM; C ≥ 100 nM to 500 nM; D > 500 nM.

Table 3B. Representative FECD biochemical data.

Cmpd. No.	IC _{50, 48h} (nM)
A-1	B
A-2	C
A-3	C

Cmpd. No.	IC _{50, 48h} (nM)
A-5	C
A-6	A
A-7	C

Cmpd. No.	IC _{50, 48h} (nM)
A-8	B
A-9	A
A-10	C
A-11	C
A-12	B
A-13	B
A-14	C
A-15	C
A-16	B
A-17	C
A-18	C
A-19	B
A-20	C
A-21	C
A-22	C
A-23	A
A-24	A
A-25	B
A-26	B
A-27	B
A-28	B
A-29	C
A-30	C
A-31	B
A-32	A
A-33	A
A-34	A
A-35	B
A-36	A
A-37	C
A-38	C
A-39	A
A-40	A
A-41	A
A-42	A
A-43	A
A-44	A
A-45	A
A-46	A
A-47	A
A-48	A
A-49	A
A-50	B
A-51	D
A-52	D
A-53	D

Cmpd. No.	IC _{50, 48h} (nM)
A-54	A
A-55	D
A-56	A
A-57	A
A-58	A
A-59	C
A-60	B
A-61	A
A-62	A
A-63	C
A-64	D
A-65	A
A-66	A
A-67	A
A-68	B
A-69	B
A-70	A
A-71	A
A-72	A
A-73	A
A-74	A
A-75	D
A-76	A
A-77	A
A-78	A
A-79	A
A-80	A
A-81	A
A-82	A
A-83	A
A-84	A
A-85	A
A-86	A
A-87	A
A-88	A
A-89	A
A-90	A
A-91	D
A-92	A
A-93	A
A-94	A
A-95	B
A-96	C
A-97	C
A-98	C
A-99	A

Cmpd. No.	IC _{50, 48h} (nM)
A-100	C
A-101	B
A-102	C
A-103	C

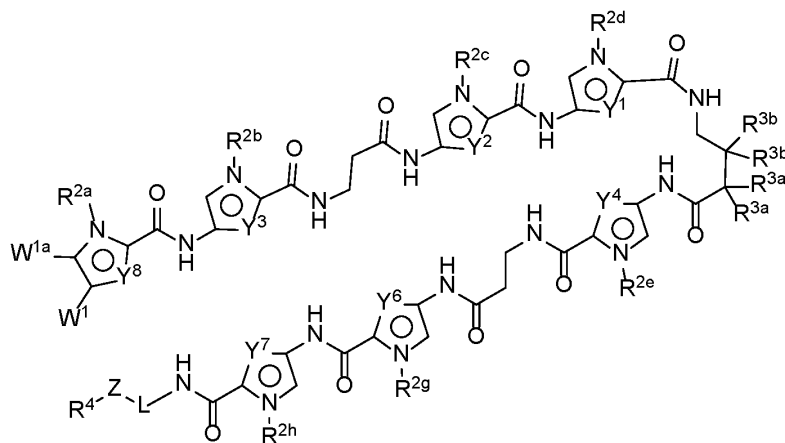
Cmpd. No.	IC _{50, 48h} (nM)
A-104	A
A-105	B
A-106	C
A-107	C

[00346] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby

CLAIMS

WHAT IS CLAIMED IS:

1. A transcription modulator molecule having the structure of Formula (I), or a pharmaceutically acceptable salt thereof:



Formula (I),

wherein:

W¹ and W^{1a} are each independently hydrogen, C₁-C₃ haloalkyl, or -N=C(N(R^{1e})₂)₂, wherein each R^{1e} is independently hydrogen or C₁-C₃ alkyl;

$\text{Y}^1, \text{Y}^2, \text{Y}^3, \text{Y}^4, \text{Y}^6, \text{Y}^7$, and Y^8 are each independently CH or N;

L is absent, C₁-C₂₀ alkylene, or C₂-C₂₀ heteroalkylene;

Z is absent, -C(O)-, or -C(=NH)-;

R^4 is C_1 - C_8 alkyl, C_3 - C_{10} cycloalkyl, 4 to 12-membered heterocycloalkyl, $-OR^{4b}$, or $-NR^{4a}R^{4b}$; wherein

R^{4a} is hydrogen, optionally substituted C₁-C₂₀ alkyl, optionally substituted C₁-C₂₀ haloalkyl, or optionally substituted C₁-C₂₀ heteroalkyl, each of which is optionally substituted with one or more R⁵;

R^{4b} is hydrogen, optionally substituted C₁-C₂₀ alkyl, optionally substituted C₂-C₂₀ alkenyl, optionally substituted C₂-C₂₀ alkynyl, optionally substituted C₁-C₂₀ aminoalkyl, optionally substituted C₁-C₂₀ haloalkyl, optionally substituted C₁-C₂₀ heteroalkyl, optionally substituted C₁-C₂₀ hydroxyalkyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted 4 to 12-membered heterocycloalkyl, optionally substituted phenyl, or optionally substituted 5 to 10-membered heteroarvl, each of which is optionally substituted with one or more R⁵; or

R^{4a} and R^{4b} together with the nitrogen to which they are attached form an optionally substituted 4 to 12-membered heterocycloalkyl which is optionally substituted with one or more R⁵;

each R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^{2e}, R^{2g}, and R^{2h} is independently hydrogen, optionally substituted C₁-C₅₀ alkyl, optionally substituted C₂-C₅₀ alkenyl, optionally substituted C₂-C₅₀ alkynyl, optionally substituted C₁-C₅₀ heteroalkyl, optionally substituted C₂-C₅₀ heteroalkenyl, optionally substituted C₂-C₅₀ heteroalkynyl, optionally substituted C₁-C₅₀ haloalkyl, optionally substituted C₃-C₈ cycloalkyl,

optionally substituted 3 to 8-membered heterocycloalkyl, or optionally substituted PEG₁₋₅₀; each of which is optionally substituted with one or more R⁶;
 each R^{3a} and R^{3b} is independently hydrogen, C₁-C₆ alkyl, -NR^{3c}R^{3d}, -NHC(O)OR^{3c}, or -NHC(O)R^{3e}, or two R^{3a} or two R^{3b} together with the carbon atom to which they are attached form a C₃-C₆ cycloalkyl or 4 to 6-membered heterocycloalkyl; or
 one of R^{3a} and one of R^{3b} together with the atoms to which they are attached form a C₃-C₆ cycloalkyl or 4 to 6-membered heterocycloalkyl; wherein

R^{3c} and R^{3d} are each independently hydrogen, C₁-C₂₀ alkyl, C₁-C₃ alkyl(phenyl), or PEG₁₋₂₀;

R^{3e} is C₁-C₂₀ alkyl, PEG₁₋₂₀, C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;

each R⁵ is independently halogen, -CN, -OH, -OR^{5a}, -N₃, -NR^{5a}R^{5b}, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted 4 to 8-membered heterocycloalkyl, or optionally substituted phenyl, each of which is optionally substituted with one or more R^{5c}, wherein

R^{5a} and R^{5b} are each independently hydrogen, C₁-C₂₀ alkyl, or PEG₁₋₂₀;

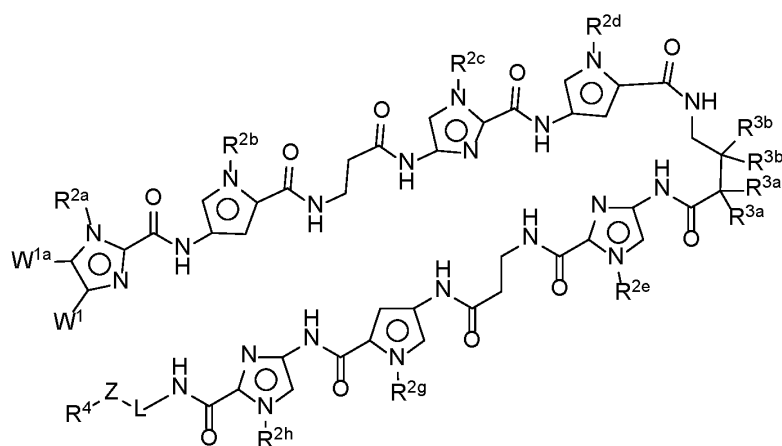
each R^{5c} is independently C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;

each R⁶ is independently halogen, -CN, -OH, -OR^{6a}, -N₃, -NR^{6a}R^{6b}, -CO(O)R^{6c}, -C(O)OR^{6c}, -C(O)NR^{6a}R^{6b}, -NHC(O)R^{6c}, -NHC(O)OR^{6c}, -OC(O)NR^{6a}R^{6b}, C₃-C₆ cycloalkyl, or 4 to 6 membered heterocycloalkyl; wherein

R^{6a} and R^{6b} are each independently hydrogen, C₁-C₂₀ alkyl, or PEG₁₋₂₀; and

R^{6c} is C₁-C₂₀ alkyl, PEG₁₋₂₀, C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl.

2. The molecule of claim 1, or a pharmaceutically acceptable salt thereof, wherein Y², Y⁴, Y⁷, and Y⁸ are each N and Y¹, Y³, and Y⁶ are each CH.
3. The molecule of claim 1 or 2, wherein the molecule has the structure of Formula (II), or a pharmaceutically acceptable salt thereof:



Formula (II),

wherein:

W^1 and W^{1a} are each independently hydrogen, C₁-C₃ haloalkyl, or -N=C(N(R^{1e})₂), wherein each R^{1e} is independently hydrogen or C₁-C₃ alkyl;

L is absent, C₁-C₂₀ alkylene, or C₂-C₂₀ heteroalkylene;

Z is absent, -C(O)-, or -C(=NH)-;

R⁴ is C₁-C₈ alkyl, C₃-C₁₀ cycloalkyl, 4 to 12-membered heterocycloalkyl, -OR^{4b}, or -NR^{4a}R^{4b}; wherein R^{4a} is hydrogen, optionally substituted C₁-C₂₀ alkyl, optionally substituted C₁-C₂₀ haloalkyl, or optionally substituted C₁-C₂₀ heteroalkyl, each of which is optionally substituted with one or more R⁵;

R^{4b} is hydrogen, optionally substituted C₁-C₂₀ alkyl, optionally substituted C₂-C₂₀ alkenyl, optionally substituted C₂-C₂₀ alkynyl, optionally substituted C₁-C₂₀ aminoalkyl, optionally substituted C₁-C₂₀ haloalkyl, optionally substituted C₁-C₂₀ heteroalkyl, optionally substituted C₁-C₂₀ hydroxyalkyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted 4 to 12-membered heterocycloalkyl, optionally substituted phenyl, or optionally substituted 5 to 10-membered heteroaryl, each of which is optionally substituted with one or more R⁵; or

R^{4a} and R^{4b} together with the nitrogen to which they are attached form an optionally substituted 4 to 12-membered heterocycloalkyl which is optionally substituted with one or more R⁵;

each R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^{2e}, R^{2g}, and R^{2h} is independently hydrogen, optionally substituted C₁-C₅₀ alkyl, optionally substituted C₂-C₅₀ alkenyl, optionally substituted C₂-C₅₀ alkynyl, optionally substituted C₁-C₅₀ heteroalkyl, optionally substituted C₂-C₅₀ heteroalkenyl, optionally substituted C₂-C₅₀ heteroalkynyl, optionally substituted C₁-C₅₀ haloalkyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted 3 to 8-membered heterocycloalkyl, or optionally substituted PEG₁₋₅₀; each of which is optionally substituted with one or more R⁶;

each R^{3a} and R^{3b} is independently hydrogen, C₁-C₆ alkyl, -NR^{3c}R^{3d}, -NHC(O)OR^{3c}, or -NHC(O)R^{3e}, or two R^{3a} or two R^{3b} together with the carbon atom to which they are attached form a C₃-C₆ cycloalkyl or 4 to 6-membered heterocycloalkyl; or

one of R^{3a} and one of R^{3b} together with the atoms to which they are attached form a C₃-C₆ cycloalkyl or 4 to 6-membered heterocycloalkyl; wherein

R^{3c} and R^{3d} are each independently hydrogen, C₁-C₂₀ alkyl, C₁-C₃ alkyl(phenyl), or PEG₁₋₂₀;

R^{3e} is C₁-C₂₀ alkyl, PEG₁₋₂₀, C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;

each R⁵ is independently halogen, -CN, -OH, -OR^{5a}, -N₃, -NR^{5a}R^{5b}, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted 4 to 8-membered heterocycloalkyl, or optionally substituted phenyl, each of which is optionally substituted with one or more R^{5c}, wherein

R^{5a} and R^{5b} are each independently hydrogen, C₁-C₂₀ alkyl, or PEG₁₋₂₀;

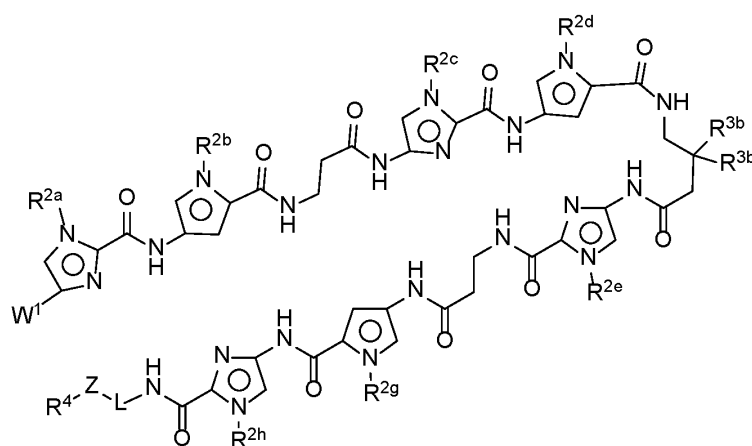
each R^{5c} is independently C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;

each R^6 is independently halogen, -CN, -OH, -OR^{6a}, -N₃, -NR^{6a}R^{6b}, -CO(O)R^{6c}, -C(O)OR^{6c}, -C(O)NR^{6a}R^{6b}, -NHC(O)R^{6c}, -NHC(O)OR^{6c}, -OC(O)NR^{6a}R^{6b}, C₃-C₆ cycloalkyl, or 4 to 6 membered heterocycloalkyl; wherein

R^{6a} and R^{6b} are each independently hydrogen, C₁-C₂₀ alkyl, or PEG₁₋₂₀; and

R^{6c} is C₁-C₂₀ alkyl, PEG₁₋₂₀, C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl.

4. The molecule of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein each R^{3a} and R^{3b} is independently hydrogen, -NR^{3c}R^{3d}, -NHC(O)OR^{3c}, or -NHC(O)R^{3e}.
5. The compound of claim 4, or a pharmaceutically acceptable salt thereof, wherein each R^{3a} and each R^{3b} is hydrogen.
6. The molecule of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein two R^{3a} together with the carbon atom to which they are attached form a C₃-C₆ cycloalkyl or 4 to 6-membered heterocycloalkyl.
7. The molecule of claim 6, or a pharmaceutically acceptable salt thereof, wherein each R^{3b} is hydrogen.
8. The molecule of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein two R^{3b} together with the carbon atom to which they are attached form a C₃-C₆ cycloalkyl or 4 to 6-membered heterocycloalkyl.
9. The molecule of claim 8, or a pharmaceutically acceptable salt thereof, wherein each R^{3a} is hydrogen.
10. The molecule of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein one of R^{3a} and one of R^{3b} together with the atoms to which they are attached form a C₃-C₆ cycloalkyl or 4 to 6-membered heterocycloalkyl.
11. The molecule of claim 3, wherein the molecule has the structure of Formula (III), or a pharmaceutically acceptable salt thereof:



Formula (III),

wherein:

W¹ is hydrogen or -N=C(N(R^{1e})₂)₂, wherein each R^{1e} is independently hydrogen or C₁-C₃ alkyl;

L is absent, C₁-C₂₀ alkylene, or C₂-C₂₀ heteroalkylene;

Z is absent, -C(O)-, or -C(=NH)-;

R⁴ is C₁-C₈ alkyl, C₃-C₁₀ cycloalkyl, 4 to 12-membered heterocycloalkyl, -OR^{4b}, or -NR^{4a}R^{4b}; wherein

R^{4a} is hydrogen, optionally substituted C₁-C₂₀ alkyl, optionally substituted C₁-C₂₀ haloalkyl, or optionally substituted C₁-C₂₀ heteroalkyl, each of which is optionally substituted with one or more R⁵;

R^{4b} is hydrogen, optionally substituted C₁-C₂₀ alkyl, optionally substituted C₂-C₂₀ alkenyl, optionally substituted C₂-C₂₀ alkynyl, optionally substituted C₁-C₂₀ aminoalkyl, optionally substituted C₁-C₂₀ haloalkyl, optionally substituted C₁-C₂₀ heteroalkyl, optionally substituted C₁-C₂₀ hydroxyalkyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted 4 to 12-membered heterocycloalkyl, optionally substituted phenyl, or optionally substituted 5 to 12-membered heteroaryl, each of which is optionally substituted with one or more R⁵; or

R^{4a} and R^{4b} together with the nitrogen to which they are attached form an optionally substituted 4 to 10-membered heterocycloalkyl which is optionally substituted with one or more R⁵;

each R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^{2e}, R^{2g}, and R^{2h} is independently hydrogen, optionally substituted C₁-C₅₀ alkyl, optionally substituted C₂-C₅₀ alkenyl, optionally substituted C₂-C₅₀ alkynyl, optionally substituted C₁-C₅₀ heteroalkyl, optionally substituted C₂-C₅₀ heteroalkenyl, optionally substituted C₂-C₅₀ heteroalkynyl, optionally substituted C₁-C₅₀ haloalkyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted 3 to 8-membered heterocycloalkyl, or optionally substituted PEG₁₋₅₀; each of which is optionally substituted with one or more R⁶;

each R^{3b} is independently hydrogen, C₁-C₆ alkyl, -NR^{3c}R^{3d}, -NHC(O)OR^{3c}, or -NHC(O)R^{3c}, or

two R^{3b} together with the carbon atom to which they are attached form a C₃-C₆ cycloalkyl or 4 to 6-membered heterocycloalkyl, wherein

R^{3c} and R^{3d} are each independently hydrogen, C₁-C₂₀ alkyl, C₁-C₃ alkyl(phenyl), or PEG₁₋₂₀;

R^{3e} is C₁-C₂₀ alkyl, PEG₁₋₂₀, C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;

each R⁵ is independently halogen, -CN, -OH, -OR^{5a}, -N₃, -NR^{5a}R^{5b}, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted 4 to 8-membered heterocycloalkyl, or optionally substituted phenyl, each of which is optionally substituted with one or more R^{5c}, wherein

R^{5a} and R^{5b} are each independently hydrogen, C₁-C₂₀ alkyl, or PEG₁₋₂₀;

each R^{5c} is independently C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;

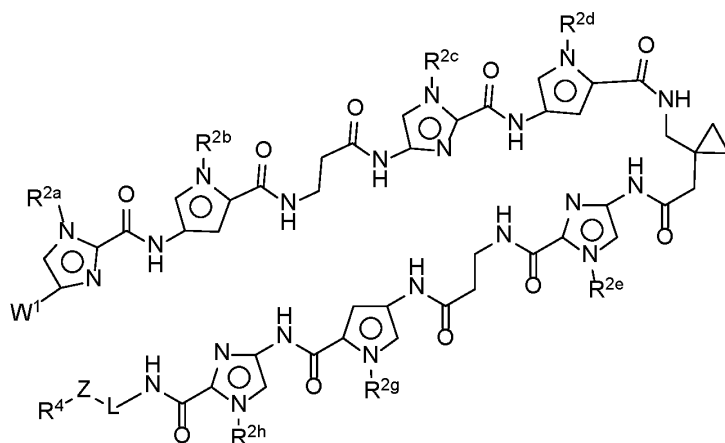
each R⁶ is independently halogen, -CN, -OH, -OR^{6a}, -N₃, -NR^{6a}R^{6b}, -CO(O)R^{6c}, -C(O)OR^{6c}, -

C(O)NR^{6a}R^{6b}, -NHC(O)R^{6c}, -NHC(O)OR^{6c}, -OC(O)NR^{6a}R^{6b}, C₃-C₆ cycloalkyl, or 4 to 6 membered heterocycloalkyl; wherein

R^{6a} and R^{6b} are each independently hydrogen, C₁-C₂₀ alkyl, or PEG₁₋₂₀; and

R^{6c} is C₁-C₂₀ alkyl, PEG₁₋₂₀, C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl.

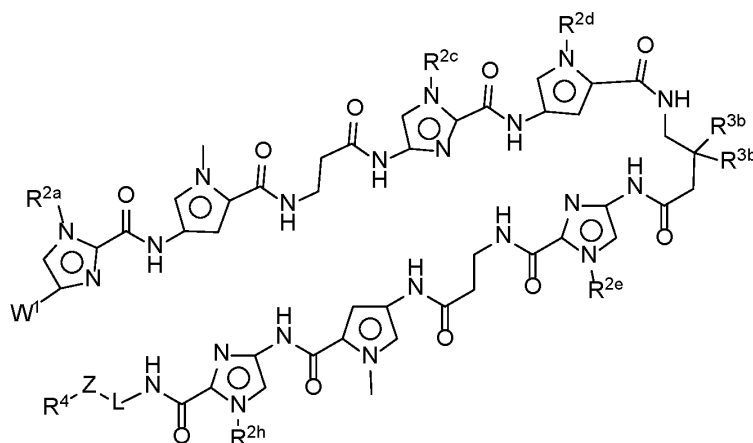
12. The molecule of claim 11, or a pharmaceutically acceptable salt thereof, wherein each R^{3b} is hydrogen.
13. The molecule of claim 11, or a pharmaceutically acceptable salt thereof, wherein or two R^{3b} together with the carbon atom to which they are attached form a C_3 - C_6 cycloalkyl or 4 to 6-membered heterocycloalkyl.
14. The molecule of claim 13, or a pharmaceutically acceptable salt thereof, wherein two R^{3b} together with the atom to which they are attached form a cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.
15. The molecule of claim 14, or a pharmaceutically acceptable salt thereof, wherein two R^{3b} together with the atom to which they are attached form a cyclopropyl.
16. The molecule of claim 11, wherein the molecule of Formula (III), has the structure of Formula (IIIa), or a pharmaceutically acceptable salt thereof:



Formula (IIIa).

17. The molecule of any one of claims 1-16, or a pharmaceutically acceptable salt thereof, wherein R^{2a} , R^{2b} , R^{2c} , R^{2d} , R^{2e} , R^{2g} , and R^{2h} are each independently hydrogen, optionally substituted C_1 - C_{20} alkyl, C_1 - C_{20} heteroalkyl, optionally substituted C_1 - C_{20} haloalkyl, optionally substituted C_3 - C_6 cycloalkyl, or optionally substituted PEG_{1-20} ; each of which is optionally substituted with one or more R^6 .
18. The molecule of claim 17, or a pharmaceutically acceptable salt thereof, wherein R^{2a} , R^{2b} , R^{2c} , R^{2d} , R^{2e} , R^{2g} , and R^{2h} are each independently C_1 - C_{20} alkyl, optionally substituted with one or more R^6 .
19. The molecule of claim 18, or a pharmaceutically acceptable salt thereof, wherein each R^6 is independently $-N_3$, $-NR^{6a}R^{6b}$, $-CO(O)R^{6c}$, $-C(O)OR^{6c}$, $-C(O)NR^{6a}R^{6b}$, or $-NHC(O)R^{6c}$.
20. The molecule of claim 18 or 19, or a pharmaceutically acceptable salt thereof, wherein each R^6 is independently $-NHC(O)R^{6c}$.
21. The molecule of any one of claims 1-16, or a pharmaceutically acceptable salt thereof, wherein R^{2a} , R^{2b} , R^{2c} , R^{2d} , R^{2e} , R^{2g} , and R^{2h} are each independently methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, cyclohexyl, $-CF_3$, or $-CH_2CF_3$.
22. The molecule of claim 19, or a pharmaceutically acceptable salt thereof, wherein R^{2a} , R^{2b} , R^{2c} , R^{2d} , R^{2e} , R^{2g} , and R^{2h} are each methyl.

23. The molecule of any one of claims 1-16, or a pharmaceutically acceptable salt thereof, wherein at least one of R^{2a} , R^{2b} , R^{2c} , R^{2d} , R^{2e} , R^{2g} , or R^{2h} is not unsubstituted C_1 - C_{20} alkyl.
24. The molecule of claim 23, or a pharmaceutically acceptable salt thereof, wherein at least one of R^{2a} , R^{2b} , R^{2c} , R^{2d} , R^{2e} , R^{2g} , or R^{2h} is not methyl.
25. The molecule of claim 11, wherein the molecule is of Formula (IV), or a pharmaceutically acceptable salt thereof:



Formula (IV),

wherein:

W^1 is hydrogen or $-N=C(N(R^{1e}))_2$, wherein each R^{1e} is independently hydrogen or C_1 - C_3 alkyl;

L is absent, C_1 - C_{20} alkylene, or C_2 - C_{20} heteroalkylene;

Z is absent, $-C(O)-$, or $-C(=NH)-$;

R^4 is C_1 - C_8 alkyl, C_3 - C_{10} cycloalkyl, 4 to 12-membered heterocycloalkyl, $-OR^{4b}$, or $-NR^{4a}R^{4b}$; wherein

R^{4a} is hydrogen, optionally substituted C_1 - C_{20} alkyl, optionally substituted C_1 - C_{20} haloalkyl, or optionally substituted C_1 - C_{20} heteroalkyl, each of which is optionally substituted with one or more R^5 ;

R^{4b} is hydrogen, optionally substituted C_1 - C_{20} alkyl, optionally substituted C_2 - C_{20} alkenyl, optionally substituted C_2 - C_{20} alkynyl, optionally substituted C_1 - C_{20} aminoalkyl, optionally substituted C_1 - C_{20} haloalkyl, optionally substituted C_1 - C_{20} heteroalkyl, optionally substituted C_1 - C_{20} hydroxyalkyl, optionally substituted C_3 - C_{10} cycloalkyl, optionally substituted 4 to 12-membered heterocycloalkyl, optionally substituted phenyl, or optionally substituted 5 to 10-membered heteroaryl, each of which is optionally substituted with one or more R^5 ; or

R^{4a} and R^{4b} together with the nitrogen to which they are attached form an optionally substituted 4 to 12-membered heterocycloalkyl which is optionally substituted with one or more R^5 ;

each R^{2a} , R^{2c} , R^{2d} , R^{2e} , and R^{2h} is independently hydrogen, optionally substituted C_1 - C_{50} alkyl, optionally substituted C_2 - C_{50} alkenyl, optionally substituted C_2 - C_{50} alkynyl, optionally substituted C_1 - C_{50} heteroalkyl, optionally substituted C_2 - C_{50} heteroalkenyl, optionally substituted C_2 - C_{50} heteroalkynyl, optionally substituted C_1 - C_{50} haloalkyl, optionally substituted C_3 - C_8 cycloalkyl, optionally

substituted 3 to 8-membered heterocycloalkyl, or optionally substituted PEG₁₋₅₀; each of which is optionally substituted with one or more R⁶;
 each R^{3b} is independently hydrogen, halogen, C₁-C₆ alkyl, -NR^{3c}R^{3d}, -NHC(O)OR^{3c}, or -NHC(O)R^{3e}, or two R^{3b} together with the carbon atom to which they are attached form a C₃-C₆ cycloalkyl or 4 to 6-membered heterocycloalkyl, wherein

R^{3c} and R^{3d} are each independently hydrogen, C₁-C₂₀ alkyl, C₁-C₃ alkyl(phenyl), or PEG₁₋₂₀;

R^{3e} is C₁-C₂₀ alkyl, PEG₁₋₂₀, C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;

each R⁵ is independently halogen, -CN, -OH, -OR^{5a}, -N₃, -NR^{5a}R^{5b}, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted 4 to 8-membered heterocycloalkyl, or optionally substituted phenyl, each of which is optionally substituted with one or more R^{5c}, wherein

R^{5a} and R^{5b} are each independently hydrogen, C₁-C₂₀ alkyl, or PEG₁₋₂₀;

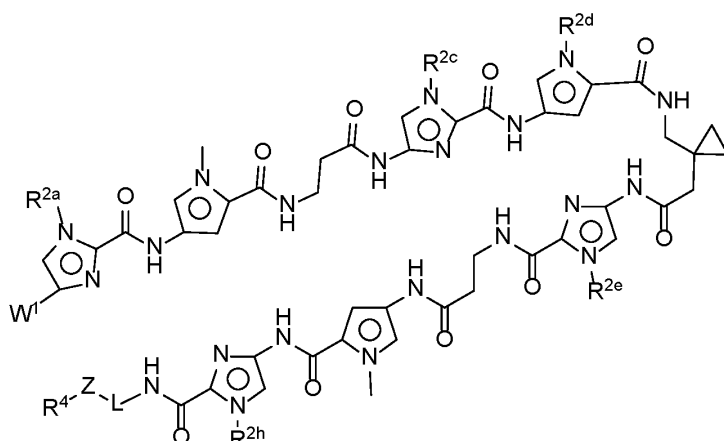
each R^{5c} is independently C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;

each R⁶ is independently halogen, -CN, -OH, -OR^{6a}, -N₃, -NR^{6a}R^{6b}, -CO(O)R^{6c}, -C(O)OR^{6c}, -C(O)NR^{6a}R^{6b}, -NHC(O)R^{6c}, -NHC(O)OR^{6c}, -OC(O)NR^{6a}R^{6b}, C₃-C₆ cycloalkyl, or 4 to 6 membered heterocycloalkyl; wherein

R^{6a} and R^{6b} are each independently hydrogen, C₁-C₂₀ alkyl, or PEG₁₋₂₀; and

R^{6c} is C₁-C₂₀ alkyl, PEG₁₋₂₀, C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl.

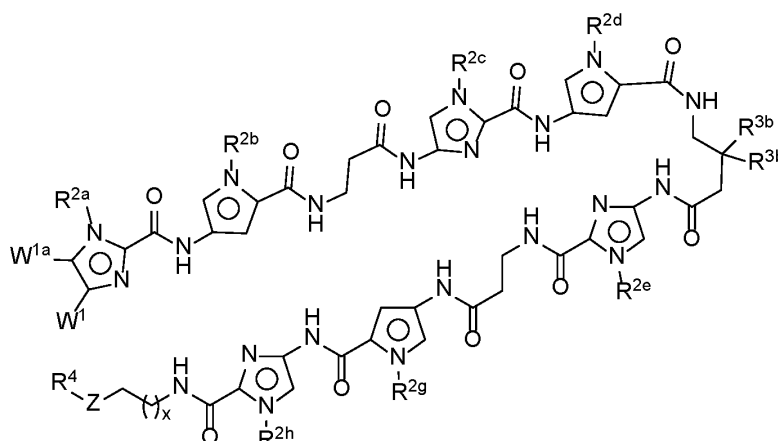
26. The molecule of claim 25, or a pharmaceutically acceptable salt thereof, wherein each R^{3b} is hydrogen.
27. The molecule of claim 26, or a pharmaceutically acceptable salt thereof, wherein two R^{3b} together with the carbon atom to which they are attached form a C₃-C₆ cycloalkyl or 4 to 6-membered heterocycloalkyl.
28. The molecule of claim 27, or a pharmaceutically acceptable salt thereof, wherein two R^{3b} together with the atom to which they are attached form a cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.
29. The molecule of claim 28, or a pharmaceutically acceptable salt thereof, wherein two R^{3b} together with the atom to which they are attached form a cyclopropyl.
30. The molecule of claim 25, wherein the molecule is of Formula (IV), has the structure of Formula (IVa), or a pharmaceutically acceptable salt thereof:



Formula (IVa).

31. The molecule of any one of claims 25-30, or a pharmaceutically acceptable salt thereof, wherein R^{2a} , R^{2c} , R^{2d} , R^{2e} , and R^{2h} are each independently hydrogen, optionally substituted C_1 - C_{20} alkyl, C_1 - C_{20} heteroalkyl, optionally substituted C_1 - C_{20} haloalkyl, or optionally substituted PEG_{1-20} ; each of which is optionally substituted with one or more R^6 .
32. The molecule of claim 31, or a pharmaceutically acceptable salt thereof, wherein R^{2a} , R^{2c} , R^{2d} , R^{2e} , and R^{2h} are each independently C_1 - C_{20} alkyl, optionally substituted with one or more R^6 .
33. The molecule of any one of claims 25-30, or a pharmaceutically acceptable salt thereof, wherein at least one of R^{2a} , R^{2c} , R^{2d} , R^{2e} , and R^{2h} is C_1 - C_{20} alkyl substituted with one or more R^6 and the others of R^{2a} , R^{2c} , R^{2d} , R^{2e} , and R^{2h} are each independently unsubstituted C_1 - C_{20} alkyl.
34. The molecule of any one of claims 25-30, or a pharmaceutically acceptable salt thereof, wherein R^{2a} is C_1 - C_{20} alkyl substituted with one or more R^6 and R^{2c} , R^{2d} , R^{2e} , and R^{2h} are each independently unsubstituted C_1 - C_{20} alkyl.
35. The molecule of any one of claims 25-30, or a pharmaceutically acceptable salt thereof, wherein R^{2c} is C_1 - C_{20} alkyl substituted with one or more R^6 and R^{2a} , R^{2d} , R^{2e} , and R^{2h} are each independently unsubstituted C_1 - C_{20} alkyl.
36. The molecule of any one of claims 25-30, or a pharmaceutically acceptable salt thereof, wherein R^{2d} is C_1 - C_{20} alkyl substituted with one or more R^6 and R^{2a} , R^{2c} , R^{2e} , and R^{2h} are each independently unsubstituted C_1 - C_{20} alkyl.
37. The molecule of any one of claims 25-30, or a pharmaceutically acceptable salt thereof, wherein R^{2e} is C_1 - C_{20} alkyl substituted with one or more R^6 and R^{2a} , R^{2c} , R^{2d} , and R^{2h} are each independently unsubstituted C_1 - C_{20} alkyl.
38. The molecule of any one of claims 25-30, or a pharmaceutically acceptable salt thereof, wherein R^{2h} is C_1 - C_{20} alkyl substituted with one or more R^6 and the others of R^{2a} , R^{2c} , R^{2d} , and R^{2e} are each independently unsubstituted C_1 - C_{20} alkyl.
39. The molecule of any one of claims 31-38, or a pharmaceutically acceptable salt thereof, wherein each R^6 is independently $-N_3$, $-NR^{6a}R^{6b}$, $-CO(O)R^{6c}$, $-C(O)OR^{6c}$, $-C(O)NR^{6a}R^{6b}$, or $-NHC(O)R^{6c}$.

40. The molecule of any one of claims 31-39, or a pharmaceutically acceptable salt thereof, wherein each R^6 is independently $-NHC(O)R^{6c}$.
41. The molecule of any one of any one of claims 1-40, or a pharmaceutically acceptable salt thereof, wherein L is C_1 - C_{10} alkylene or C_2 - C_{10} heteroalkylene.
42. The molecule of claim 41, or a pharmaceutically acceptable salt thereof, wherein L is C_1 - C_{10} alkylene.
43. The molecule of claim 41, or a pharmaceutically acceptable salt thereof, wherein L is C_2 - C_{10} heteroalkylene.
44. The molecule of any one of claims 1-40, or a pharmaceutically acceptable salt thereof, wherein L is absent.
45. The molecule of any of claims 1-44, or a pharmaceutically acceptable salt thereof, wherein R^4 is C_1 - C_8 alkyl or $-NR^{4a}R^{4b}$, wherein
- R^{4a} is hydrogen, optionally substituted C_1 - C_{20} alkyl, optionally substituted C_1 - C_{20} haloalkyl, or optionally substituted C_1 - C_{20} heteroalkyl, each of which is optionally substituted with one or more R^5 ;
 - R^{4b} is optionally substituted C_1 - C_{20} alkyl, optionally substituted C_1 - C_{20} haloalkyl, optionally substituted C_1 - C_{20} heteroalkyl, optionally substituted C_3 - C_{10} cycloalkyl, optionally substituted 4 to 12-membered heterocycloalkyl, or optionally substituted 5 to 10-membered heteroaryl, each of which is optionally substituted with one or more R^5 ; or
 - R^{4a} and R^{4b} together with the nitrogen to which they are attached form an optionally substituted 4 to 20-membered heterocycloalkyl which is optionally substituted with one or more R^5 ;
- each R^5 is independently halogen, $-CN$, $-OH$, $-OR^{5a}$, $-N_3$, $-NR^{5a}R^{5b}$, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 haloalkyl, optionally substituted C_3 - C_8 cycloalkyl, optionally substituted 4 to 8-membered heterocycloalkyl, or optionally substituted phenyl, each of which is optionally substituted with one or more R^{5c} , wherein
- R^{5a} and R^{5b} are each independently hydrogen, C_1 - C_{20} alkyl, or PEG_{1-20} ; and
 - each R^{5c} is independently C_3 - C_8 cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl.
46. The molecule of claim 11, wherein the molecule has the structure of Formula (V), or a pharmaceutically acceptable salt thereof:



Formula (V),

wherein:

W^1 and W^{1a} are each independently hydrogen, C_1 - C_3 haloalkyl, or $-N=C(N(R^{1e}))_2$, wherein each R^{1e} is independently hydrogen or C_1 - C_3 alkyl;

Z is absent, $-C(O)-$, or $-C(=NH)-$;

R^4 is C_1 - C_8 alkyl, C_3 - C_{10} cycloalkyl, 4 to 12-membered heterocycloalkyl, $-OR^{4b}$, or $-NR^{4a}R^{4b}$; wherein R^{4a} is hydrogen, optionally substituted C_1 - C_{20} alkyl, optionally substituted C_1 - C_{20} haloalkyl, or optionally substituted C_1 - C_{20} heteroalkyl, each of which is optionally substituted with one or more R^5 ;

R^{4b} is hydrogen, optionally substituted C_1 - C_{20} alkyl, optionally substituted C_1 - C_{20} haloalkyl, optionally substituted C_1 - C_{20} heteroalkyl, optionally substituted C_3 - C_{10} cycloalkyl, optionally substituted 4 to 12-membered heterocycloalkyl, or optionally substituted 5 to 10-membered heteroaryl, each of which is optionally substituted with one or more R^5 ; or

R^{4a} and R^{4b} together with the nitrogen to which they are attached form an optionally substituted 4 to 12-membered heterocycloalkyl which is optionally substituted with one or more R^5 ;

R^{2a} , R^{2b} , R^{2c} , R^{2d} , R^{2e} , R^{2g} , and R^{2h} are each independently hydrogen, optionally substituted C_1 - C_{20} alkyl, C_1 - C_{20} heteroalkyl, optionally substituted C_1 - C_{20} haloalkyl, or optionally substituted PEG_{1-20} ; each of which is optionally substituted with one or more R^6 ;

each R^{3b} is hydrogen; or

two R^{3b} together with the carbon atom to which they are attached form a C_3 - C_6 cycloalkyl or 4 to 6-membered heterocycloalkyl;

each R^5 is independently halogen, $-CN$, $-OH$, $-OR^{5a}$, $-N_3$, $-NR^{5a}R^{5b}$, optionally substituted C_1 - C_6 alkyl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 alkynyl, optionally substituted C_1 - C_6 haloalkyl, optionally substituted C_3 - C_8 cycloalkyl, optionally substituted 4 to 8-membered heterocycloalkyl, or optionally substituted phenyl, each of which is optionally substituted with one or more R^{5c} , wherein

R^{5a} and R^{5b} are each independently hydrogen, C_1 - C_{20} alkyl, or PEG_{1-20} ;

each R^{5c} is independently C_3 - C_8 cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl;
 each R^6 is independently halogen, -CN, -OH, -OR^{6a}, -N₃, -NR^{6a}R^{6b}, -CO(O)R^{6c}, -C(O)OR^{6c}, -C(O)NR^{6a}R^{6b}, -NHC(O)R^{6c}, -NHC(O)OR^{6c}, -OC(O)NR^{6a}R^{6b}, C_3 - C_6 cycloalkyl, or 4 to 6 membered heterocycloalkyl; wherein

R^{6a} and R^{6b} are each independently hydrogen, C_1 - C_{20} alkyl, or PEG₁₋₂₀;

R^{6c} is C_1 - C_{20} alkyl, PEG₁₋₂₀, C_3 - C_8 cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl; and
 x is 0-10.

47. The molecule of claim 46, or a pharmaceutically acceptable salt thereof, wherein each R^{3b} is hydrogen.
48. The molecule of claim 46 or 47, or a pharmaceutically acceptable salt thereof, wherein R^{2a} , R^{2b} , R^{2c} , R^{2d} , R^{2e} , R^{2g} , and R^{2h} are each independently optionally substituted C_1 - C_{20} alkyl or optionally substituted C_1 - C_{20} haloalkyl, each of which is optionally substituted with one or more R^6 .
49. The molecule of any one of claims 46-48, or a pharmaceutically acceptable salt thereof, wherein each R^6 is independently -N₃, -NR^{6a}R^{6b}, -CO(O)R^{6c}, -C(O)OR^{6c}, -C(O)NR^{6a}R^{6b}, or -NHC(O)R^{6c}.
50. The molecule of claim 49, or a pharmaceutically acceptable salt thereof, wherein each R^6 is independently -NHC(O)R^{6c}.
51. The molecule of any one of claims 46-48, or a pharmaceutically acceptable salt thereof, wherein R^{2a} , R^{2b} , R^{2c} , R^{2d} , R^{2e} , R^{2g} , and R^{2h} are each independently methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, -CF₃, or -CH₂CF₃.
52. The molecule of claim 51, or a pharmaceutically acceptable salt thereof, wherein R^{2a} , R^{2b} , R^{2c} , R^{2d} , R^{2e} , R^{2g} , and R^{2h} are each methyl.
53. The molecule of any one of claims 46 or 47, or a pharmaceutically acceptable salt thereof, wherein at least one of R^{2a} , R^{2b} , R^{2c} , R^{2d} , R^{2e} , R^{2g} , or R^{2h} is not unsubstituted C_1 - C_{20} alkyl.
54. The molecule of claim 53, or a pharmaceutically acceptable salt thereof, wherein at least one of R^{2a} , R^{2b} , R^{2c} , R^{2d} , R^{2e} , R^{2g} , or R^{2h} is not methyl.
55. The molecule of any one of claims 46-54, or a pharmaceutically acceptable salt thereof, wherein x is 0-6.
56. The molecule of claim 55, or a pharmaceutically acceptable salt thereof, wherein x is 1-4.
57. The molecule of claim 55 or 56, or a pharmaceutically acceptable salt thereof, wherein x is 1.
58. The molecule of any one of claims 46-57, or a pharmaceutically acceptable salt thereof, wherein R^4 is C_1 - C_8 alkyl.
59. The molecule of any one of claims 46-57, or a pharmaceutically acceptable salt thereof, wherein R^4 is -NR^{4a}R^{4b}.
60. The molecule of any one of claims 1-57 or 59, or a pharmaceutically acceptable salt thereof, wherein R^{4a} is hydrogen, optionally substituted C_1 - C_{20} alkyl, or optionally substituted C_1 - C_{20} heteroalkyl, each of which is optionally substituted with one or more R^5 ; and

R^{4b} is optionally substituted C₁-C₂₀ alkyl, optionally substituted C₁-C₂₀ haloalkyl, optionally substituted C₁-C₂₀ heteroalkyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted 4 to 12-membered heterocycloalkyl, or optionally substituted 5 to 10-membered heteroaryl, each of which is optionally substituted with one or more R⁵;

each R⁵ is independently halogen, -CN, -OH, -OR^{5a}, -N₃, -NR^{5a}R^{5b}, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted 4 to 8-membered heterocycloalkyl, or optionally substituted phenyl, each of which is optionally substituted with one or more R^{5c}, wherein

R^{5a} and R^{5b} are each independently hydrogen, C₁-C₂₀ alkyl, or PEG₁₋₂₀; and

each R^{5c} is independently C₃-C₈ cycloalkyl, 4 to 8-membered heterocycloalkyl, or phenyl.

61. The molecule of claim 60, or a pharmaceutically acceptable salt thereof, wherein R^{4a} is hydrogen, optionally substituted C₁-C₂₀ alkyl, or optionally substituted C₁-C₂₀ heteroalkyl; and R^{4b} is optionally substituted C₁-C₂₀ alkyl, optionally substituted C₁-C₂₀ haloalkyl, or optionally substituted C₁-C₂₀ heteroalkyl.
62. The molecule of claim 60 or 61, or a pharmaceutically acceptable salt thereof, wherein R^{4a} is C₁-C₂₀ alkyl and R^{4b} is C₁-C₂₀ alkyl.
63. The molecule of any one of claims 60-62, or a pharmaceutically acceptable salt thereof, wherein R^{4a} is methyl and R^{4b} is methyl.
64. The molecule of claim 60, or a pharmaceutically acceptable salt thereof, wherein R^{4b} is optionally substituted C₃-C₁₀ cycloalkyl or optionally substituted 4 to 12-membered heterocycloalkyl.
65. The molecule of claim 64, or a pharmaceutically acceptable salt thereof, wherein R^{4b} is optionally substituted C₃-C₁₀ cycloalkyl.
66. The molecule of claim 65, or a pharmaceutically acceptable salt thereof, wherein R^{4b} is optionally substituted cyclohexyl.
67. The molecule of claim 64, or a pharmaceutically acceptable salt thereof, wherein R^{4b} is optionally substituted 4 to 12-membered heterocycloalkyl.
68. The molecule of claim 67, or a pharmaceutically acceptable salt thereof, wherein R^{4b} is optionally substituted piperidine, optionally substituted piperazine, or optionally substituted morpholine.
69. The molecule of any one of claims 1-57 or 59, or a pharmaceutically acceptable salt thereof, wherein R^{4a} and R^{4b} together with the nitrogen to which they are attached form an optionally substituted 4 to 12-membered heterocycloalkyl which is optionally substituted with one or more R⁵, wherein the heterocycloalkyl is monocyclic, bicyclic, bridged, or spirocyclic.
70. The molecule of claim 69, or a pharmaceutically acceptable salt thereof, wherein R^{4a} and R^{4b} together with the nitrogen to which they are attached form an optionally substituted 4 to 6-membered heterocycloalkyl, which is optionally substituted with one or more R⁵.

71. The molecule of claim 70, or a pharmaceutically acceptable salt thereof, wherein R^{4a} and R^{4b} together with the nitrogen to which they are attached form an optionally substituted piperidine, optionally substituted piperazine, or optionally substituted morpholine.
72. The molecule of any one of claims 1-71, or a pharmaceutically acceptable salt thereof, wherein each R^5 is independently halogen, -OH, -OR^{5a}, -NR^{5a}R^{5b}, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted 4 to 8-membered heterocycloalkyl, or optionally substituted phenyl, each of which is optionally substituted with one or more R^{5c}.
73. The molecule of claim 72, or a pharmaceutically acceptable salt thereof, wherein each R^5 is independently halogen, -OH, -NH₂, -N(CH₃)₂, or -CF₃.
74. The molecule of any one of claims 1-72, or a pharmaceutically acceptable salt thereof, wherein Z is absent.
75. The molecule of any one of claims 1-72, or a pharmaceutically acceptable salt thereof, wherein Z is -C(O)-.
76. The molecule of any one of claims 1-72, or a pharmaceutically acceptable salt thereof, wherein Z - C(=NH)-;
77. The molecule of any one of claims 1-76, or a pharmaceutically acceptable salt thereof, wherein W¹ is hydrogen.
78. The molecule of any one of claims 1-10 or 46-77, or a pharmaceutically acceptable salt thereof, wherein W^{1a} is hydrogen.
79. A transcription modulator molecule selected from Table 1, or a pharmaceutically acceptable salt thereof.
80. A pharmaceutical composition comprising a molecule of any one of claims 1-79, or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable excipient.
81. A method of treating Fuchs' endothelial dystrophy or Fuchs' endothelial corneal dystrophy (FECD) in a subject in need thereof, the method comprising administering to the subject an effective amount of a molecule of any one of claims 1-79 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 80.
82. A method of treating myotonic dystrophy type 1 (DM1) in a subject in need thereof, the method comprising administering to the subject an effective amount of a molecule of any one of claims 1-79 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 80.