

METHODS AND COMPOUNDS FOR MODULATING HUNTINGTON'S DISEASE**CROSS REFERENCE**

[0001] This application claims the benefit of U.S. Provisional Application No. 63/587,625 filed on October 3, 2023 which is hereby incorporated by reference in its entirety.

FIELD OF THE DISCLOSURE

[0002] Disclosed herein are new chimeric heterocyclic polyamide compounds and compositions and their application as pharmaceuticals for the treatment of disease. Methods to modulate the expression of a target gene comprising the CAG trinucleotide repeat sequence in a subject are also provided for the treatment of diseases such as Huntington's disease ("HD").

BACKGROUND OF THE DISCLOSURE

[0003] Huntington's disease ("HD") was first identified in the late 19th century as an autosomal dominant, neurodegenerative disorder. The symptoms of HD, which include a range of movement, cognitive and psychiatric disorders, generally appear in adulthood. HD is associated with the presence of the CAG trinucleotide repeat sequence in the huntingtin gene (*HTT*), which codes for a protein termed huntingtin. Subjects with more than about 36 trinucleotide repeat sequences generally present with symptoms of HD, with a larger number of trinucleotide repeat sequences associated with an earlier onset of symptoms. Pathology stems from a cascade of steps: production of poly-Q huntingtin, followed by fragmentation of the elongated huntingtin into smaller peptides, which bind together and accumulate in neurons. The effects of this cascade are pronounced in the basal ganglia and cortex of the brain.

[0004] Huntington's disease-like syndrome refers to a group of ailments whose symptoms are similar to those of Huntington's disease, but which lack the characteristic mutation in the *HTT* gene. Huntington's disease-like 2 syndrome ("HDL2") is associated with a count of about 40 or more CAG trinucleotide repeat sequences in the junctophilin 3 (*Jph3*) gene. HDL2 is a genetic disorder that has been seen in subjects with African lineage. Age of onset is inversely correlated with the number of trinucleotide repeat sequences. Symptoms of this syndrome include dystonia and chorea (uncontrolled movements), emotional disruptions, dysarthria, bradykinesia, inability to incorporate new learning, and difficulty in making decisions. Life expectancy can range from a few years post diagnosis to over a decade. The current theory holds that a poly-Q protein that is coded by the *Jph3* gene forms aggregates in neuronal cells that is responsible for the pathology of the disease. However, evidence suggesting toxic gain-of-function of mRNA has also been uncovered, indicating a possible dual pathway for pathology.

[0005] In some embodiments, the mechanism set forth above provides opportunity for an effective treatment for a disease or disorder which is characterized by the presence of an excessive count of CAG trinucleotide repeat sequences in a target gene. In some embodiments, the pathology of the disease or disorder is due to the presence of mRNA containing an excessive count of CAG trinucleotide repeat sequences. In some embodiments, the pathology of the disease or disorder is due to the presence of a translation product containing an excessive count of glutamine amino acid residues. In some embodiments,

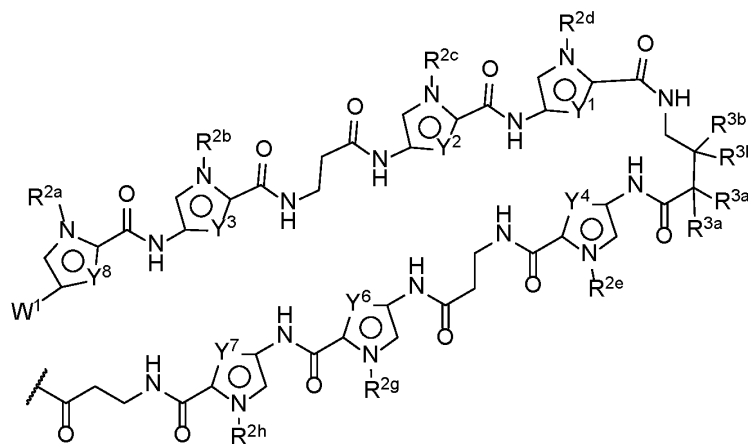
the pathology of the disease or disorder is due to a loss of function in the translation product. In some embodiments, the pathology of the disease or disorder is due to a gain of function in the translation product. In some embodiments, the pathology of the disease or disorder can be alleviated by increasing the rate of transcription of the defective gene. In some embodiments, the pathology of the disease or disorder can be alleviated by decreasing the rate of transcription of the defective gene.

SUMMARY OF THE DISCLOSURE

[0006] This disclosure utilizes regulatory molecules present in cell nuclei that control gene expression. Eukaryotic cells provide several mechanisms for controlling gene replication, transcription, and/or translation. Regulatory molecules that are produced by various biochemical mechanisms within the cell can modulate the various processes involved in the conversion of genetic information to cellular components. Several regulatory molecules are known to modulate the production of mRNA and, if directed to the target gene (such as, *HTT*), would modulate the production of the target gene mRNA that causes diseases such as, for example, Huntington's disease or Huntington's disease-like syndrome, and thus reverse the progress of these diseases.

[0007] Provided herein are transcription modulator molecules for recruiting a regulatory molecule into close proximity to the target gene. In some embodiments, provided herein is a transcription modulator molecule having a first terminus, a second terminus, and an oligomeric backbone moiety, or a pharmaceutically acceptable salt thereof, wherein:

- a) the first terminus comprises a DNA-binding moiety having the structure of Formula (A-8):



Formula (A-8),

wherein:

W¹ is hydrogen, -C₁-C₆ haloalkyl, or -N=C(N(R^{1e}))₂, wherein each R^{1e} is independently hydrogen or optionally substituted C₁-C₃ alkyl;

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

R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^{2e}, R^{2g}, and R^{2h} are each independently 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 heteroalkyl, optionally substituted C₂-C₂₀ heteroalkenyl, optionally substituted C₂-C₂₀ heteroalkynyl, optionally substituted C₁-C₂₀ haloalkyl, optionally substituted C₁-C₂₀ hydroxyalkyl, optionally substituted C₃-C₁₀ cycloalkyl, or optionally substituted 3 to 10-membered heterocycloalkyl; each of which is optionally substituted with one or more R^Z;

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

R^{3c} and R^{3d} are each independently hydrogen, alkyl, or PEG;

R^{3e} is alkyl, PEG, cycloalkyl, heterocycloalkyl, or phenyl;

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

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

each R^Z is independently halogen, -CN, -OH, -OR^{Za}, -N₃, -NR^{Za}R^{Zb}, -CO(O)R^{Zc}, -C(O)OR^{Zc}, -C(O)NR^{Za}R^{Zb}, C₁-C₁₀ alkyl, C₁-C₁₀ haloalkyl, C₁-C₁₀ heteroalkyl, C₃-C₁₀ cycloalkyl, 3 to 10-membered heterocycloalkyl, phenyl, or optionally 5 to 10-membered heteroaryl; wherein

R^{Za} and R^{Zb} are each independently hydrogen, alkyl, haloalkyl, or PEG; and

R^{Zc} is alkyl, haloalkyl, PEG, cycloalkyl, heterocycloalkyl, or phenyl;

- b) the second terminus comprises a protein-binding moiety capable of binding to a regulatory molecule that modulates expression of a gene; and
- c) the oligomeric backbone links the first terminus and the second terminus.

[0008] In some embodiments, the DNA binding moiety can bind selectively a trinucleotide repeat sequence of for example, *HTT*. The recruiting moiety, linked to the DNA binding moiety, will thus be held in proximity to the target gene; will recruit the regulatory molecule into proximity with the gene; and the regulatory molecule will modulate expression, and therefore counteract the production of defective target gene by direct interaction with the target gene. This mechanism may provide an effective treatment for HD, which is caused by the expression of defective *HTT*, where correction of the expression of the defective target gene thus represents an effective method for the treatment for these diseases.

[0009] The DNA binding moiety comprises a polyamide segment that will bind selectively to the target CAG sequence. Polyamides designed by for example Dervan (U.S. Patent Nos. 9,630,950 and 8,524,899) and others can selectively bind to selected DNA sequences. These polyamides sit in the minor groove of double helical DNA and form hydrogen bonding interactions with the Watson-Crick base pairs. Polyamides that selectively bind to particular DNA sequences can be designed by linking monoamide building blocks according to established chemical rules. One building block is provided for each DNA base pair, with each building block binding noncovalently and selectively to one of the DNA base pairs: A/T, T/A, G/C, and C/G. Following this guideline, trinucleotides bind to molecules with three amide units, i.e. tri-amides. In general, these polyamides can orient in either direction of a DNA sequence.

[0010] In principle, longer DNA sequences can be targeted with higher specificity and/or higher affinity by combining a larger number of monoamide building blocks into longer polyamide chains. Ideally, the binding affinity for a polyamide would simply be equal to the sum of each individual monoamide/DNA base pair interaction. In practice, however, due to the geometric mismatch between the fairly rigid polyamide and DNA structures, longer polyamide sequences do not bind to longer DNA sequences as tightly as would be expected from a simple additive contribution. The geometric mismatch between longer polyamide sequences and longer DNA sequences induces an unfavorable geometric strain that subtracts from the binding affinity than would be otherwise expected.

[0011] The disclosure provides for transcription modulator molecules that comprise a DNA binding moiety (for example a polyamide comprising multi-amine subunits) that is connected by a spacer (for example a linker moiety or oligomeric backbone) to a protein binding moiety. The spacer can alleviate the geometric strain that would otherwise decrease binding affinity of a larger polyamide sequence.

[0012] 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

[0013] 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. To the extent publications and patents or patent applications incorporated by reference contradict the disclosure contained in the specification, the specification is intended to supersede and/or take precedence over any such contradictory material.

DETAILED DESCRIPTION

[0014] The disclosure provides for transcription modulator molecules that comprise a DNA binding moiety (for example, a polyamide comprising multi-amine subunits) connected by spacers (for example, a linker moiety or oligomeric backbone) to a protein binding moiety. The spacers can alleviate the geometric strain that would otherwise decrease binding affinity of a larger polyamide sequences.

[0015] Treatment of a subject with these compounds will modulate the expression of the defective target gene, and this can reduce the occurrence, severity, or frequency of symptoms associated with genetic disease (such as for example HD). The compounds described herein recruit the regulatory molecule to modulate the expression of the defective target gene and effectively treat and alleviate the symptoms associated with diseases.

Compounds – Transcription modulator molecules

[0016] The compounds disclosed herein are transcription modulator molecules. They possess useful activity for modulating the transcription of a target gene (e.g., *HTT*) and may be used in the treatment or

prophylaxis of a disease or condition in which the target gene plays an active role. Thus, in broad aspects, some embodiments also provide pharmaceutical compositions comprising one or more compounds disclosed herein together with a pharmaceutically acceptable carrier, as well as methods of making and using the compounds and compositions.

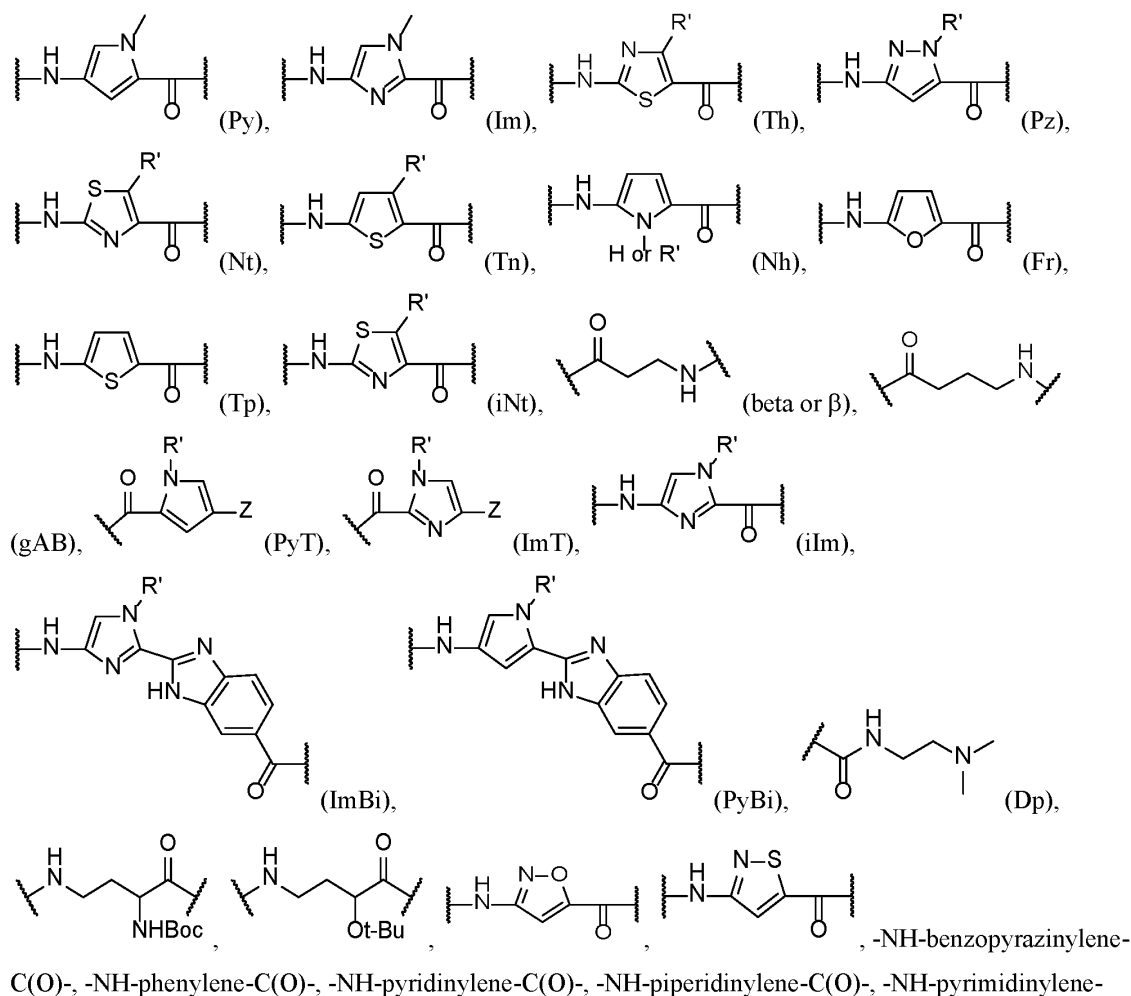
[0017] In an aspect, provided herein is a transcription modulator molecule having a first terminus, a second terminus, and a linker moiety, wherein:

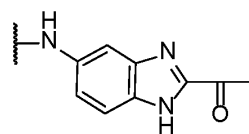
- a) the first terminus comprises a DNA-binding moiety;
- b) the second terminus comprises a protein-binding moiety capable of binding to a regulatory molecule that modulates expression of a gene; and
- c) the oligomeric backbone links the first terminus and the second terminus.

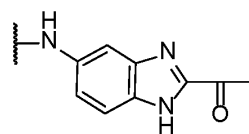
First terminus – DNA binding moiety

[0018] The first terminus interacts and binds with the gene, particularly with the minor grooves sequence. In an aspect, the molecules disclosed herein provide a polyamide sequence.

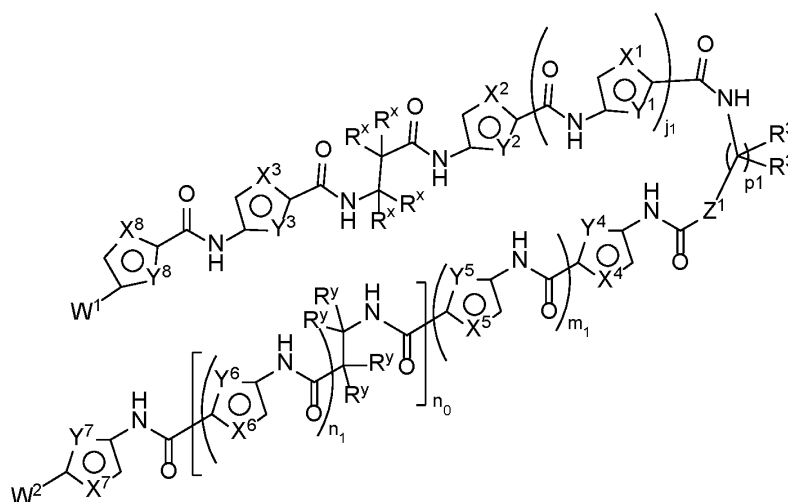
[0019] In some embodiments, the DNA-binding moiety comprises a polyamide of one or more of the following subunits selected from





C(O)-, -NH-anthracenylene-C(O)-, -NH-quinolinyne-C(O)-, and , wherein each R¹ is independently hydrogen, optionally substituted C₁-C₂₀ alkyl, optionally substituted C₁-C₂₀ heteroalkyl, optionally substituted C₁-C₂₀ haloalkyl, or optionally substituted C₁-C₂₀ alkylamino; and Z is H, NH₂, C₁-C₆ alkyl, C₁-C₆ haloalkyl, or C₁-C₆ alkyl-NH₂.

[0020] In some embodiments, the DNA-binding moiety comprises the structure of Formula (A-1), or a pharmaceutically acceptable salt thereof:



Formula (A-1),

wherein:

Z¹ is absent, -O- or -NH-;

W¹ is hydrogen, halogen, optionally substituted C₁-C₁₀ alkyl, optionally substituted C₁-C₁₀ haloalkyl, -

NR^{1e}R^{1f}, -NR^{1e}C(O)R^{1f}, -NR^{1e}C(O)NR^{1e}R^{1f}, -C(O)NR^{1e}R^{1f}, -OC(O)NR^{1e}R^{1f}, -NR^{1e}C(O)OR^{1f}, -

N=C(N(R^{1e})₂)₂, -Z_B-PO(OR^{1e})₂, -Z_B-(CH₂)_{p3}-PO(OR^{1e})₂, or -Z_B-(CH₂)_{p3}-O-PO(OR^{1e})₂, wherein

each R^{1e} is independently hydrogen or optionally substituted C₁-C₁₀ alkyl;

each R^{1f} is independently hydrogen, optionally substituted C₁-C₁₀ alkyl, optionally substituted C₁-C₁₀ heteroalkyl, AA_{p2}, or optionally substituted 5-membered heteroaryl, wherein each AA is an amino acid and p₂ is an integer from 1-10;

Z_B is N or O;

p₃ is 1-10;

W² is an optionally substituted C₁-C₆ alkyl, -C(O)NR^{1e}R^{1e}, or -C(O)NR^{1e}CH₂CH₂C(O)-, wherein each R^{1e} is independently hydrogen or optionally substituted C₁-C₁₀ alkyl;

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

each X¹, X², X³, X⁴, X⁵, X⁶, X⁷, and X⁸ is independently S, O, or NR²;

each R^2 is independently 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} heteroalkyl, optionally substituted C_2 - C_{20} heteroalkenyl, optionally substituted C_2 - C_{20} heteroalkynyl, optionally substituted C_1 - C_{20} haloalkyl, optionally substituted C_1 - C_{20} hydroxyalkyl, optionally substituted C_3 - C_{10} cycloalkyl, optionally substituted 3 to 10-membered heterocycloalkyl, optionally substituted phenyl, or optionally substituted 5 to 10-membered heteroaryl;

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

R^{3c} and R^{3d} are each independently hydrogen, alkyl, or PEG;

R^{3e} is alkyl, PEG, cycloalkyl, heterocycloalkyl, or phenyl;

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

each R^x and R^y is independently hydrogen, halogen, $-CN$, $-OH$, $-NH_2$, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl; or two R^x or two R^y together with the atoms to which they are attached form a C_3 - C_6 cycloalkyl or 3 to 6-membered heterocycloalkyl;

j_1 is 0 or 1;

m_1 is 0 or 1;

n_0 is 0 or 1; and

n_1 is 0 or 1;

p_1 is 2 or 3, provided that when Z^1 is $-O-$ or $-NH-$ then p_1 is 2, and when Z^1 is absent then p_1 is 3;

wherein one of W^1 or W^2 is attached to the oligomeric backbone.

[0021] In some embodiments of Formula (A-1), n_0 is 1. In some embodiments, n_0 is 0.

[0022] In some embodiments of Formula (A-1), p_1 is 3. In some embodiments, p_1 is 2.

[0023] In some embodiments of Formula (A-1), Z^1 is absent. In some embodiments, Z^1 is $-O-$. In some embodiments, Z^1 is $-NH-$.

[0024] In some embodiments of Formula (A-1), the DNA-binding moiety is connected to the oligomeric backbone through W^2 . In some embodiments of Formula (A-1), the DNA-binding moiety is connected to the oligomeric backbone through W^1 .

[0025] In some embodiments of Formula (A-1), W^2 is $-C(O)NR^{1c}R^{1e}$. In some embodiments, W^2 is $-C(O)NH-$. In some embodiments, W^2 is $-C(O)NR^{1c}CH_2CH_2C(O)-$. In some embodiments, W^2 is $-C(O)NHCH_2CH_2C(O)-$.

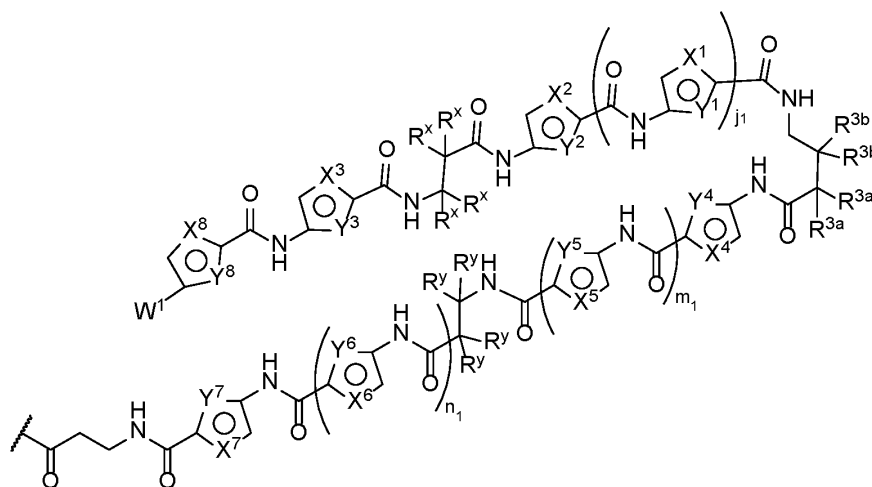
[0026] In some embodiments of Formula (A-1), W^2 is $-C(O)NH(CH_2)_2C(O)-^{**}$, wherein the oligomeric backbone is attached at ** . In some embodiments, W^2 is $-C(O)-NH-^{**}$, wherein the oligomeric backbone is attached at ** .

[0027] In some embodiments of Formula (A-1), each R^3 is independently hydrogen, halogen, C_1 - C_6 alkyl, $-NR^{3c}R^{3d}$, or $-NHC(O)R^{3e}$, wherein R^{3c} and R^{3d} are each independently hydrogen, alkyl, or PEG; and R^{3e} is alkyl, PEG, cycloalkyl, heterocycloalkyl, or phenyl. In some embodiments, each R^3 is independently -

$\text{NR}^{3c}\text{R}^{3d}$. In some embodiments, each R^3 is independently $-\text{NHC}(\text{O})\text{R}^{3e}$. In some embodiments, each R^3 is independently hydrogen.

[0028] In some embodiments of Formula (A-1), two R^3 together with the atoms to which they are attached form an optionally substituted C_3 - C_6 cycloalkyl or 3 to 6-membered heterocycloalkyl. In some embodiments, two R^3 together with the atom(s) to which they are attached form a C_3 - C_6 cycloalkyl. In some embodiments, two R^3 together with the atom(s) to which they are attached form a 4 to 6-membered heterocycloalkyl. In some embodiments, two R^3 together with the atom(s) to which they are attached form a 4-membered heterocycloalkyl. In some embodiments, two R^3 together with the atom(s) to which they are attached form a 5-membered heterocycloalkyl. In some embodiments, two R^3 together with the atom(s) to which they are attached form a 6-membered heterocycloalkyl. In some embodiments, two R^3 together with the atom(s) to which they are attached form a cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In some embodiments, two R^3 together with the atom(s) to which they are attached form a cyclopropyl. In some embodiments, two R^3 together with the atom(s) to which they are attached form a cyclobutyl. In some embodiments, two R^3 together with the atom(s) to which they are attached form a cyclopentyl. In some embodiments, two R^3 together with the atom(s) to which they are attached form a cyclohexyl.

[0029] In some embodiments, the DNA-binding moiety comprises the structure of Formula (A-2), or a pharmaceutically acceptable salt thereof:



Formula (A-2),

wherein:

W^1 is hydrogen, $-\text{C}_1$ - C_6 haloalkyl, or $-\text{N}=\text{C}(\text{N}(\text{R}^{1e})_2)_2$, wherein each R^{1e} is independently hydrogen or optionally substituted C_1 - C_3 alkyl;

each X^1 , X^2 , X^3 , X^4 , X^5 , X^6 , X^7 , and X^8 is independently S, O, or NR^2 ;

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

each R^2 is independently 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} heteroalkyl, optionally substituted C_2 - C_{20} heteroalkenyl, optionally substituted C_2 - C_{20}

heteroalkynyl, optionally substituted C₁-C₂₀ haloalkyl, optionally substituted C₁-C₂₀ hydroxyalkyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted 3 to 10-membered heterocycloalkyl, optionally substituted phenyl, or optionally substituted 5 to 10-membered heteroaryl;

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

R^{3e} is alkyl, PEG, cycloalkyl, heterocycloalkyl, or phenyl;

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

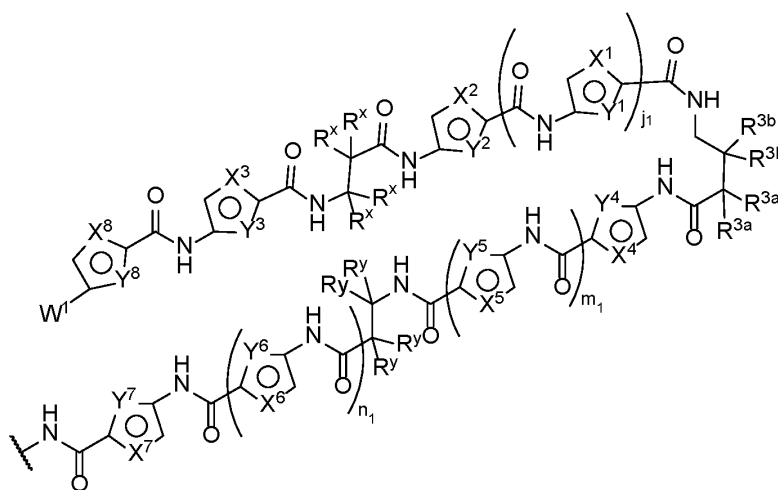
or one R^{3a} and one R^{3b} together with the atoms to which they are attached form a C₃-C₆ cycloalkyl or 4 to 6-membered heterocycloalkyl; and

each R^x and R^y is independently hydrogen, halogen, -CN, -OH, -NH₂, C₁-C₁₀ alkyl, or C₁-C₁₀ haloalkyl; or two R^x or two R^y together with the atoms to which they are attached to form a C₃-C₆ cycloalkyl or 3 to 6-membered heterocycloalkyl;

j₁ is 0 or 1; and

m₁ and n₁ are each independently 0 or 1.

[0030] In some embodiments, the DNA-binding moiety comprises the structure of Formula (A-3), or a pharmaceutically acceptable salt thereof:



Formula (A-3),

wherein:

W¹ is hydrogen, -C₁-C₆ haloalkyl, or -N=C(N(R^{1e}))₂, wherein each R^{1e} is independently hydrogen or optionally substituted C₁-C₃ alkyl;

each X¹, X², X³, X⁴, X⁵, X⁶, X⁷, and X⁸ is independently S, O, or NR²;

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

each R² is independently 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 heteroalkyl, optionally substituted C₂-C₂₀ heteroalkenyl, optionally substituted C₂-C₂₀

heteroalkynyl, optionally substituted C₁-C₂₀ haloalkyl, optionally substituted C₁-C₂₀ hydroxyalkyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted 3 to 10-membered heterocycloalkyl, optionally substituted phenyl, or optionally substituted 5 to 10-membered heteroaryl;

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

R^{3e} is alkyl, PEG, cycloalkyl, heterocycloalkyl, or phenyl;

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

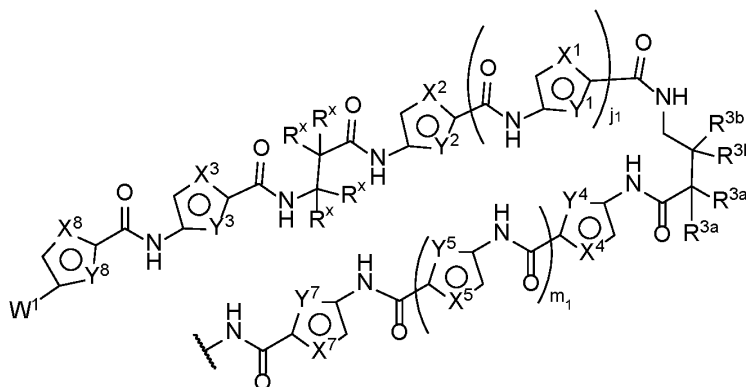
or one R^{3a} and one R^{3b} together with the atoms to which they are attached form a C₃-C₆ cycloalkyl or 4 to 6-membered heterocycloalkyl;

each R^x and R^y is independently hydrogen, halogen, -CN, -OH, -NH₂, C₁-C₁₀ alkyl, or C₁-C₁₀ haloalkyl; or two R^x or two R^y together with the atoms to which they are attached form a C₃-C₆ cycloalkyl or 3 to 6-membered heterocycloalkyl;

j₁ is 0 or 1; and

m₁ and n₁ are each independently 0 or 1.

[0031] In some embodiments, the DNA-binding moiety comprises the structure of Formula (A-4), or a pharmaceutically acceptable salt thereof:



Formula (A-4),

wherein:

W¹ is hydrogen, -C₁-C₆ haloalkyl, or -N=C(N(R^{1e}))₂, wherein each R^{1e} is independently hydrogen or optionally substituted C₁-C₃ alkyl;

each X¹, X², X³, X⁴, X⁵, X⁷, and X⁸ is independently S, O, or NR²;

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

each R² is independently 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 heteroalkyl, optionally substituted C₂-C₂₀ heteroalkenyl, optionally substituted C₂-C₂₀ heteroalkynyl, optionally substituted C₁-C₂₀ haloalkyl, optionally substituted C₁-C₂₀ hydroxyalkyl,

optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted 3 to 10-membered heterocycloalkyl, optionally substituted phenyl, or optionally substituted 5 to 10-membered heteroaryl;

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

R^{3e} is alkyl, PEG, cycloalkyl, heterocycloalkyl, or phenyl;

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

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

each R^x is independently hydrogen, halogen, -CN, -OH, -NH₂, C₁-C₁₀ alkyl, or C₁-C₁₀ haloalkyl; or two R^x together with the atoms to which they are attached form a C₃-C₆ cycloalkyl or 3 to 6-membered heterocycloalkyl;

j₁ is 0 or 1; and

m₁ is 0 or 1.

[0032] In some embodiments of Formula (A-1), (A-2), (A-3), or (A-4), each X¹, X², X³, X⁴, X⁵, X⁶, and X⁷ is independently -NR². In some embodiments, each X¹, X², X³, X⁴, X⁵, X⁶, X⁷, and X⁸ is independently O. In some embodiments, each X¹, X², X³, X⁴, X⁵, X⁶, X⁷, and X⁸ is independently S.

[0033] In some embodiments of Formula (A-1), (A-2), (A-3), or (A-4), each R² is independently 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 heteroalkyl, optionally substituted C₂-C₂₀ heteroalkenyl, optionally substituted C₂-C₂₀ heteroalkynyl, optionally substituted C₁-C₂₀ haloalkyl, optionally substituted C₁-C₂₀ hydroxyalkyl, optionally substituted C₃-C₁₀ cycloalkyl, or optionally substituted 3 to 10-membered heterocycloalkyl. In some embodiments, each R² is independently hydrogen, optionally substituted C₁-C₂₀ alkyl, optionally substituted C₁-C₂₀ aminoalkyl, optionally substituted C₁-C₂₀ heteroalkyl, optionally substituted C₁-C₂₀ haloalkyl, optionally substituted C₁-C₂₀ hydroxyalkyl, optionally substituted C₃-C₁₀ cycloalkyl, or optionally substituted 3 to 10-membered heterocycloalkyl. In some embodiments, each R² is independently an optionally substituted C₁-C₂₀ alkylamino. In some embodiments, each R² is independently an optionally substituted C₁-C₁₀ alkylamino. In some embodiments, each R² is independently an optionally substituted C₁-C₂₀ haloalkyl. In some embodiments, each R² is independently an optionally substituted C₁-C₁₀ haloalkyl. In some embodiments, each R² is independently an optionally substituted C₁-C₂₀ heteroalkyl. In some embodiments, each R² is independently an optionally substituted C₁-C₁₀ heteroalkyl. In some embodiments, each R² is independently an optionally substituted C₁-C₂₀ hydroxyalkyl. In some embodiments, each R² is independently an optionally substituted C₁-C₁₀ hydroxyalkyl. In some embodiments, each R² is independently optionally substituted C₃-C₁₀ cycloalkyl or optionally substituted 3 to 10-membered heterocycloalkyl. In some embodiments, each R² is independently optionally substituted C₃-C₁₀ cycloalkyl. In some embodiments, each R² is independently optionally substituted 3 to 10-membered heterocycloalkyl. In some embodiments, each R² is independently

optionally substituted phenyl. In some embodiments, each R^2 is independently optionally substituted 6-membered heteroaryl.

[0034] In some embodiments of Formula (A-1), (A-2), (A-3), or (A-4), each R^2 is independently an optionally substituted C_1 - C_{20} alkyl. In some embodiments, each R^2 is independently an optionally substituted C_1 - C_{10} alkyl. In some embodiments, each R^2 is independently methyl, ethyl, propyl, butyl, propyl, hexyl, heptyl, or octenyl. In some embodiments, each R^2 is independently methyl, ethyl, isopropyl, isobutyl, sec-butyl, tert-butyl, n-propyl, n-hexyl, n-heptyl, or n-octenyl. In some embodiments, each R^2 is methyl. In some embodiments, each R^2 is ethyl. In some embodiments, each R^2 is isopropyl. In some embodiments, each R^2 is butyl. In some embodiments, each R^2 is pentyl. In some embodiments, each R^2 is hexyl. In some embodiments, each R^2 is heptyl. In some embodiments, each R^2 is hydrogen.

[0035] In some embodiments of Formula (A-1), (A-2) or (A-3), each R^x and R^y is independently hydrogen, halogen, -CN, -OH, -NH₂, C_1 - C_{10} alkyl, or C_1 - C_{10} haloalkyl. In some embodiments, each R^x and R^y is independently hydrogen, -OH, C_1 - C_{10} alkyl, or C_1 - C_{10} haloalkyl. In some embodiments, each R^x and R^y is independently hydrogen.

[0036] In some embodiments of Formula (A-1), (A-2) or (A-3), two R^x or two R^y together with the atoms to which they are attached form a C_3 - C_6 cycloalkyl or 3 to 6-membered heterocycloalkyl. In some embodiments, two R^x or two R^y together with the atoms to which they are attached form a C_3 - C_6 cycloalkyl. In some embodiments, two R^x or two R^y together with the atoms to which they are attached form a 3 to 6-membered heterocycloalkyl.

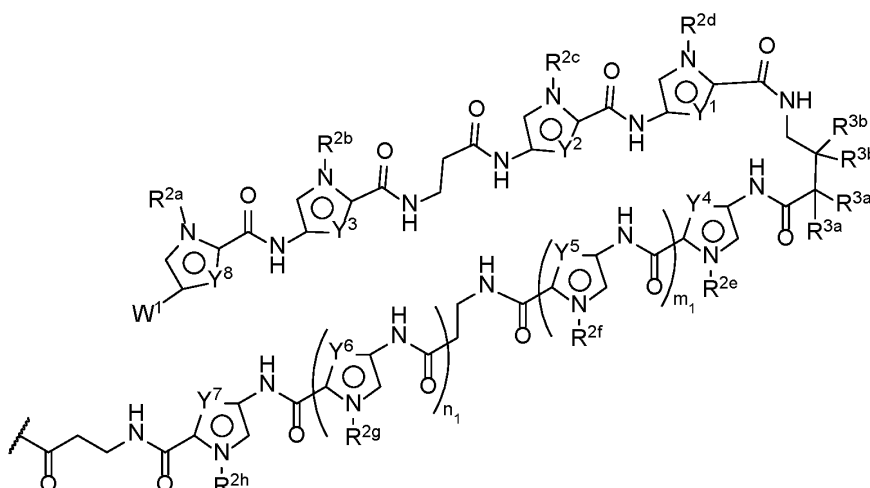
[0037] In some embodiments of Formula (A-4), each R^x is independently hydrogen, halogen, -CN, -OH, -NH₂, C_1 - C_{10} alkyl, or C_1 - C_{10} haloalkyl. In some embodiments, each R^x is independently hydrogen, -OH, C_1 - C_{10} alkyl, or C_1 - C_{10} haloalkyl. In some embodiments, each R^x is independently hydrogen.

[0038] In some embodiments of Formula (A-1), (A-2), (A-3), or (A-4), two R^x together with the atoms to which they are attached form a C_3 - C_6 cycloalkyl or 3 to 6-membered heterocycloalkyl. In some embodiments, two R^x together with the atoms to which they are attached form a C_3 - C_6 cycloalkyl. In some embodiments, two R^x together with the atoms to which they are attached form a 3 to 6-membered heterocycloalkyl.

[0039] In some embodiments of Formula (A-1), (A-2), or (A-3), two R^y together with the atoms to which they are attached form a C_3 - C_6 cycloalkyl or 3 to 6-membered heterocycloalkyl. In some embodiments, two R^y together with the atoms to which they are attached form a C_3 - C_6 cycloalkyl. In some embodiments, two R^y together with the atoms to which they are attached form a 3 to 6-membered heterocycloalkyl.

[0040] In some embodiments of Formula (A-1), (A-2), (A-3), or (A-4), j_1 is 1. In some embodiments, j_1 is 0.

[0041] In some embodiments, the DNA-binding moiety comprises the structure of Formula (A-5), or a pharmaceutically acceptable salt thereof.



Formula (A-5),

wherein:

W¹ is hydrogen, -C₁-C₆ haloalkyl, or -N=C(N(R^{1e})₂)₂, wherein each R^{1e} is independently hydrogen or optionally substituted C₁-C₃ alkyl;

$\text{Y}^1, \text{Y}^2, \text{Y}^3, \text{Y}^4, \text{Y}^5, \text{Y}^6, \text{Y}^7$, and Y^8 are each independently N or CH_3 ;

each R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^{2e}, R^{2f}, R^{2g}, and R^{2h} is independently 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 heteroalkyl, optionally substituted C₂-C₂₀ heteroalkenyl, optionally substituted C₂-C₂₀ heteroalkynyl, optionally substituted C₁-C₂₀ haloalkyl, optionally substituted C₁-C₂₀ hydroxyalkyl, optionally substituted C₃-C₁₀ cycloalkyl, or optionally substituted 3 to 10-membered heterocycloalkyl; each of which is optionally substituted with one or more R^Z.

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

R^{3e} is alkyl, PEG, cycloalkyl, heterocycloalkyl, or phenyl;

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

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

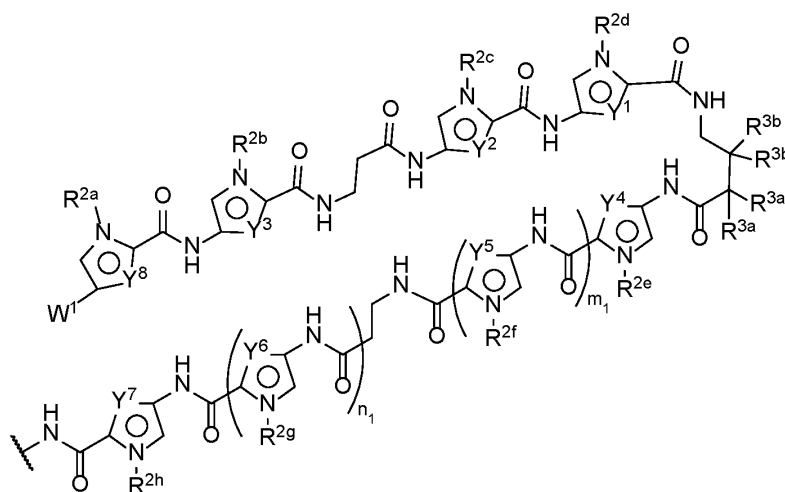
each R^Z is independently halogen, -CN, -OH, -OR^{Za}, -N₃, -NR^{Za}R^{Zb}, -CO(O)R^{Zc}, -C(O)OR^{Zc}, -C(O)NR^{Za}R^{Zb}, -NR^{Za}C(O)R^{Zc}, C₁-C₁₀ alkyl, C₁-C₁₀ haloalkyl, C₁-C₁₀ heteroalkyl, C₃-C₁₀ cycloalkyl, 3 to 10-membered heterocycloalkyl, phenyl, or optionally 5 to 10-membered heteroaryl; wherein

R^{Za} and R^{Zb} are each independently hydrogen, alkyl, haloalkyl, or PEG;

R^{Zc} is alkyl, haloalkyl, PEG, cycloalkyl, heterocycloalkyl, or phenyl; and

m_1 and n_1 are each independently 0 or 1.

[0042] In some embodiments, the DNA-binding moiety comprises the structure of Formula (A-6), or a pharmaceutically acceptable salt thereof:



Formula (A-6),

wherein:

W^1 is hydrogen, $-C_1-C_6$ haloalkyl, or $-N=C(N(R^{1e}))_2$, wherein each R^{1e} is independently hydrogen or optionally substituted C_1-C_3 alkyl;

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

each R^{2a} , R^{2b} , R^{2c} , R^{2d} , R^{2e} , R^{2g} , and R^{2h} is independently 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} heteroalkyl, optionally substituted C_2-C_{20} heteroalkenyl, optionally substituted C_2-C_{20} heteroalkynyl, optionally substituted C_1-C_{20} haloalkyl, optionally substituted C_1-C_{20} hydroxyalkyl, optionally substituted C_3-C_{10} cycloalkyl, or optionally substituted 3 to 10-membered heterocycloalkyl; each of which is optionally substituted with one or more R^Z ;

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

R^{3e} is alkyl, PEG, cycloalkyl, heterocycloalkyl, or phenyl;

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

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

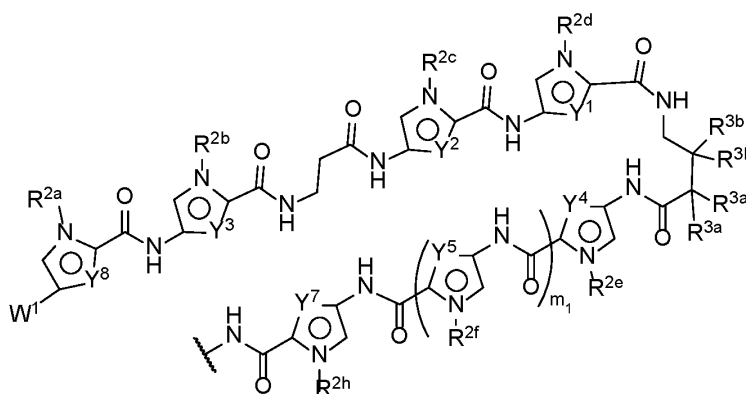
each R^Z is independently halogen, $-CN$, $-OH$, $-OR^{Za}$, $-N_3$, $-NR^{Za}R^{Zb}$, $-CO(O)R^{Zc}$, $-C(O)OR^{Zc}$, $-C(O)NR^{Za}R^{Zb}$, $-NR^{Za}C(O)R^{Zc}$, C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_1-C_{10} heteroalkyl, C_3-C_{10} cycloalkyl, 3 to 10-membered heterocycloalkyl, phenyl, or optionally 5 to 10-membered heteroaryl; wherein

R^{Za} and R^{Zb} are each independently hydrogen, alkyl, haloalkyl, or PEG;

R^{Zc} is alkyl, haloalkyl, PEG, cycloalkyl, heterocycloalkyl, or phenyl; and

m_1 and n_1 are each independently 0 or 1.

[0043] In some embodiments, the DNA-binding moiety comprises the structure of Formula (A-7), or a pharmaceutically acceptable salt thereof:



Formula (A-7),

wherein:

W^1 is hydrogen, $-C_1-C_6$ haloalkyl, or $-N=C(N(R^{1e}))_2$, wherein each R^{1e} is independently hydrogen or optionally substituted C_1-C_3 alkyl;

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

each R^{2a} , R^{2b} , R^{2c} , R^{2d} , R^{2e} , R^{2f} , and R^{2h} is independently 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} heteroalkyl, optionally substituted C_2-C_{20} heteroalkenyl, optionally substituted C_2-C_{20} heteroalkynyl, optionally substituted C_1-C_{20} haloalkyl, optionally substituted C_1-C_{20} hydroxyalkyl, optionally substituted C_3-C_{10} cycloalkyl, or optionally substituted 3 to 10-membered heterocycloalkyl; each of which is optionally substituted with one or more R^Z ;

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

R^{3e} is alkyl, PEG, cycloalkyl, heterocycloalkyl, or phenyl;

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

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

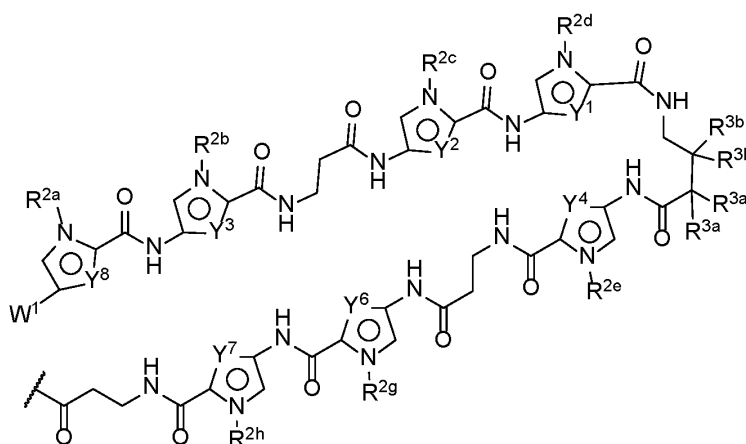
each R^Z is independently halogen, $-CN$, $-OH$, $-OR^{Za}$, $-N_3$, $-NR^{Za}R^{Zb}$, $-CO(O)R^{Zc}$, $-C(O)OR^{Zc}$, $-C(O)NR^{Za}R^{Zb}$, $-NR^{Za}C(O)R^{Zc}$, C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_1-C_{10} heteroalkyl, C_3-C_{10} cycloalkyl, 3 to 10-membered heterocycloalkyl, phenyl, or optionally 5 to 10-membered heteroaryl; wherein

R^{Za} and R^{Zb} are each independently hydrogen, alkyl, haloalkyl, or PEG;

R^{Zc} is alkyl, haloalkyl, PEG, cycloalkyl, heterocycloalkyl, or phenyl; and

m_1 is 0 or 1.

[0044] In some embodiments, the DNA-binding moiety comprises the structure of Formula (A-8), or a pharmaceutically acceptable salt thereof:



Formula (A-8),

wherein:

W¹ is hydrogen, -C₁-C₆ haloalkyl, or -N=C(N(R^{1e})₂), wherein each R^{1e} is independently hydrogen or optionally substituted C₁-C₃ alkyl;

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

R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^{2e}, R^{2g}, and R^{2h} are each independently 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 heteroalkyl, optionally substituted C₂-C₂₀ heteroalkenyl, optionally substituted C₂-C₂₀ heteroalkynyl, optionally substituted C₁-C₂₀ haloalkyl, optionally substituted C₁-C₂₀ hydroxyalkyl, optionally substituted C₃-C₁₀ cycloalkyl, or optionally substituted 3 to 10-membered heterocycloalkyl; each of which is optionally substituted with one or more R^Z;

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

R^{3e} is alkyl, PEG, cycloalkyl, heterocycloalkyl, or phenyl;

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

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

each R^Z is independently halogen, -CN, -OH, -OR^{Za}, -N₃, -NR^{Za}R^{Zb}, -CO(O)R^{Zc}, -C(O)OR^{Zc}, -C(O)NR^{Za}R^{Zb}, -NR^{Za}C(O)R^{Zc}, C₁-C₁₀ alkyl, C₁-C₁₀ haloalkyl, C₁-C₁₀ heteroalkyl, C₃-C₁₀ cycloalkyl, 3 to 10-membered heterocycloalkyl, phenyl, or optionally 5 to 10-membered heteroaryl; wherein

R^{Za} and R^{Zb} are each independently hydrogen, alkyl, haloalkyl, or PEG; and

R^{Zc} is alkyl, haloalkyl, PEG, cycloalkyl, heterocycloalkyl, or phenyl.

[0045] In some embodiments of any of Formulas (A-1) through (A-8), Y², Y⁴, Y⁷, and Y⁸ are each independently N; and Y¹, Y³, and Y⁶ are each independently CH. In some embodiments, Y², Y⁴, and Y⁷ are each independently N; and Y¹ and Y³ are each independently CH.

[0046] In some embodiments of any of Formulas (A-1) through (A-8), each Y^5 is independently CH. In some embodiments, each Y^5 is independently N.

[0047] In some embodiments of any of Formulas (A-1) through (A-8), each Y^6 is independently CH. In some embodiments, each Y^6 is independently N.

[0048] In some embodiments of any of Formulas (A-1) through (A-8), Y^8 is CH. In some embodiments, Y^8 is N.

[0049] In some embodiments of Formula (A-1), W^1 is hydrogen, halogen, optionally substituted C_1 - C_{10} alkyl, optionally substituted C_1 - C_{10} haloalkyl, $NR^{1e}R^{1f}$, $-NR^{1e}C(O)R^{1f}$, $-NR^{1e}C(O)NR^{1e}R^{1f}$, $-C(O)NR^{1e}R^{1f}$, $-OC(O)NR^{1e}R^{1f}$, or $-NR^{1e}C(O)OR^{1f}$. In some embodiments, W^1 is hydrogen or optionally substituted C_1 - C_{10} alkyl. In some embodiments, W^1 is $-NR^{1e}C(O)R^{1f}$, $-NR^{1e}C(O)NR^{1e}R^{1f}$, $-C(O)NR^{1e}R^{1f}$, $-OC(O)NR^{1e}R^{1f}$, or $-NR^{1e}C(O)OR^{1f}$.

[0050] In some embodiments of Formula (A-1), W^1 is $-Z_B-PO(OR^{1e})_2$, $-Z_B-(CH_2)_{p_3}-PO(OR^{1e})_2$, or $-Z_B-(CH_2)_{p_3}-O-PO_2(OR^{1e})_2$, wherein Z_B is O or N, and p_3 is 1-10.

[0051] In some embodiments of any of Formulas (A-1) through (A-8), 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. In some embodiments, W^1 is hydrogen or $-N=C(N(R^{1e})_2)_2$, wherein each R^{1e} is independently hydrogen or methyl.

[0052] In some embodiments of any of Formulas (A-1) through (A-8), W^1 is $-CF_3$.

[0053] In some embodiments of any of Formulas (A-1) through (A-8), W^1 is hydrogen.

[0054] In some embodiments of Formula (A-1), each AA is an unnatural or natural amino acid.

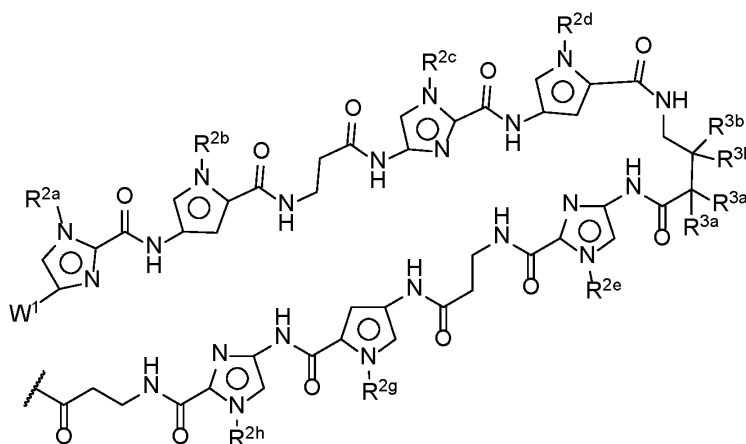
[0055] In some embodiments of any of Formula (A-1) through (A-8), each R^{1e} is independently hydrogen or C_1 - C_{10} alkyl. In some embodiments, each R^{1e} is independently hydrogen or C_1 - C_8 alkyl. In some embodiments, each R^{1e} is independently hydrogen or C_1 - C_6 alkyl. In some embodiments, each R^{1e} is independently hydrogen or C_1 - C_3 alkyl. In some embodiments, each R^{1e} is C_1 - C_3 alkyl. In some embodiments, each R^{1e} is independently methyl. In some embodiments, each R^{1e} is independently hydrogen.

[0056] In some embodiments of Formula (A-1), each R^{1f} is independently hydrogen, optionally substituted C_1 - C_{10} alkyl, optionally substituted C_1 - C_{10} heteroalkyl, optionally substituted 5-membered heteroaryl, or AA_{1-10} . In some embodiments, each R^{1f} is independently hydrogen or optionally substituted C_1 - C_{10} alkyl. In some embodiments, each R^{1f} is independently hydrogen or optionally substituted C_1 - C_8 alkyl. In some embodiments, each R^{1f} is independently hydrogen or optionally substituted C_1 - C_6 alkyl. In some embodiments, each R^{1f} is independently optionally substituted C_1 - C_6 alkyl. In some embodiments, each R^{1f} is independently methyl. In some embodiments, each R^{1f} is independently hydrogen. In some embodiments, R^{1f} is AA_{1-10} . In some embodiments, R^{1f} is AA_{1-4} . In some embodiments, R^{1f} is AA_{1-3} .

[0057] In some embodiments of any of Formulas (A-1) through (A-7), m_1 is 0. In some embodiments, m_1 is 1.

[0058] In some embodiments of any of Formulas (A-1), (A-2), (A-3), (A-5), or (A-6), n_1 is 0. In some embodiments, n_1 is 1.

[0059] In some embodiments, the DNA-binding moiety comprises the structure of Formula (A-9), or a pharmaceutically acceptable salt thereof:



Formula (A-9),

wherein:

W^1 is hydrogen;

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_2 - C_{20} alkenyl, optionally substituted C_2 - C_{20} alkynyl, optionally substituted C_1 - C_{20} aminoalkyl, optionally substituted C_1 - C_{20} heteroalkyl, optionally substituted C_2 - C_{20} heteroalkenyl, optionally substituted C_2 - C_{20} heteroalkynyl, optionally substituted C_1 - C_{20} haloalkyl, optionally substituted C_1 - C_{20} hydroxyalkyl, optionally substituted C_3 - C_{10} cycloalkyl, or optionally substituted 3 to 10-membered heterocycloalkyl; each of which is optionally substituted with one or more R^Z ;

each R^{3a} and R^{3b} is independently hydrogen, -OH, -NH₂, or C_1 - C_6 alkyl;

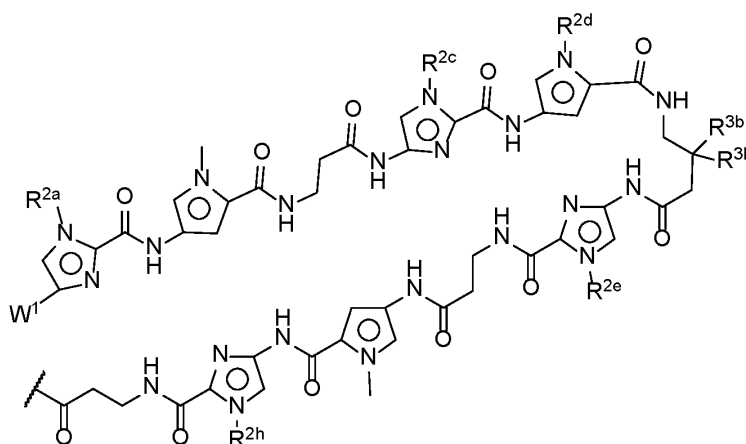
or two R^{3a} or two R^{3b} together with the atom to which they are attached form a C_3 - C_6 cycloalkyl or 4 to 6-membered heterocycloalkyl;

each R^Z is independently halogen, -CN, -OH, -OR^{Za}, -N₃, -NR^{Za}R^{Zb}, -CO(O)R^{Zc}, -C(O)OR^{Zc}, -C(O)NR^{Za}R^{Zb}, -NR^{Za}C(O)R^{Zc}, C_1 - C_{10} alkyl, C_1 - C_{10} haloalkyl, C_1 - C_{10} heteroalkyl, C_3 - C_{10} cycloalkyl, 3 to 10-membered heterocycloalkyl, phenyl, or optionally 5 to 10-membered heteroaryl; wherein

R^{Za} and R^{Zb} are each independently hydrogen, alkyl, haloalkyl, or PEG; and

R^{Zc} is alkyl, haloalkyl, PEG, cycloalkyl, heterocycloalkyl, or phenyl.

[0060] In some embodiments, the DNA-binding moiety comprises the structure of Formula (I), or a pharmaceutically acceptable salt thereof:



Formula (I),

wherein:

W^1 is hydrogen;

R^{2a} , R^{2c} , R^{2d} , R^{2e} , and R^{2h} are each independently 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} heteroalkyl, optionally substituted C_2 - C_{20} heteroalkenyl, optionally substituted C_2 - C_{20} heteroalkynyl, optionally substituted C_1 - C_{20} haloalkyl, optionally substituted C_1 - C_{20} hydroxyalkyl, optionally substituted C_3 - C_{10} cycloalkyl, or optionally substituted 3 to 10-membered heterocycloalkyl; each of which is optionally substituted with one or more R^Z ;

each R^{3b} is independently hydrogen, $-NH_2$, or C_1 - C_6 alkyl; or

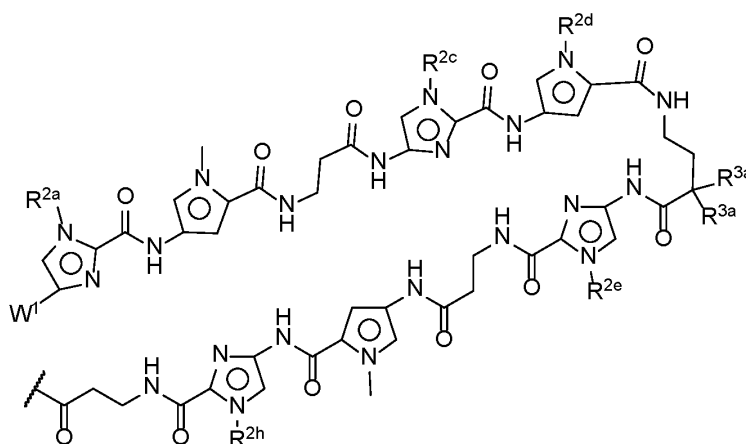
two R^{3b} together with the atom to which they are attached form a C_3 - C_6 cycloalkyl or 4 to 6-membered heterocycloalkyl;

each R^Z is independently halogen, $-CN$, $-OH$, $-OR^{Za}$, $-N_3$, $-NR^{Za}R^{Zb}$, $-CO(O)R^{Zc}$, $-C(O)OR^{Zc}$, $-C(O)NR^{Za}R^{Zb}$, $-NR^{Za}C(O)R^{Zc}$, C_1 - C_{10} alkyl, C_1 - C_{10} haloalkyl, C_1 - C_{10} heteroalkyl, C_3 - C_{10} cycloalkyl, 3 to 10-membered heterocycloalkyl, phenyl, or optionally 5 to 10-membered heteroaryl; wherein

R^{Za} and R^{Zb} are each independently hydrogen, alkyl, haloalkyl, or PEG; and

R^{Zc} is alkyl, haloalkyl, PEG, cycloalkyl, heterocycloalkyl, or phenyl.

[0061] In some embodiments, the DNA-binding moiety comprises the structure of Formula (I-A), or a pharmaceutically acceptable salt thereof:



Formula (I-A),

wherein:

W¹ is hydrogen;

R^{2a}, R^{2c}, R^{2d}, R^{2e}, and R^{2h} are each independently 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 heteroalkyl, optionally substituted C₂-C₂₀ heteroalkenyl, optionally substituted C₂-C₂₀ heteroalkynyl, optionally substituted C₁-C₂₀ haloalkyl, optionally substituted C₁-C₂₀ hydroxyalkyl, optionally substituted C₃-C₁₀ cycloalkyl, or optionally substituted 3 to 10-membered heterocycloalkyl; each of which is optionally substituted with one or more R^Z;

each R^{3a} is independently hydrogen, -NH₂, or C₁-C₆ alkyl; or

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

each R^Z is independently halogen, -CN, -OH, -OR^{Za}, -N₃, -NR^{Za}R^{Zb}, -CO(O)R^{Zc}, -C(O)OR^{Zc}, -C(O)NR^{Za}R^{Zb}, -NR^{Za}C(O)R^{Zc}, C₁-C₁₀ alkyl, or C₁-C₁₀ haloalkyl;

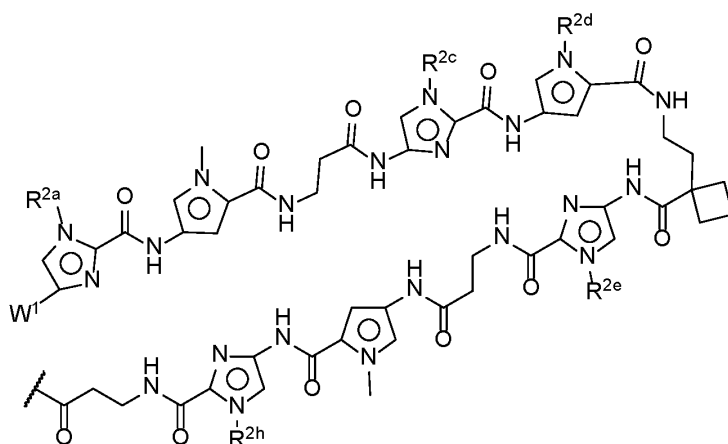
or two R^Z together with the atom(s) to which they are attached form a C₃-C₆ cycloalkyl, wherein

R^{Za} and R^{Zb} are each independently hydrogen, alkyl, haloalkyl, or PEG; and

R^{Zc} is alkyl, haloalkyl, PEG, cycloalkyl, heterocycloalkyl, or phenyl.

[0062] In some embodiments of Formula (I-A), two R^{3a} together with the atom to which they are attached form a C₃-C₆ cycloalkyl or 4 to 6-membered heterocycloalkyl. In some embodiments, two R^{3a} together with the atom to which they are attached form a C₃-C₆ cycloalkyl. two R^{3a} together with the atom to which they are attached form a cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

[0063] In some embodiments, the DNA-binding moiety of Formula (I-A) has the structure of Formula (I-A'), or a pharmaceutically acceptable salt thereof:



Formula (I-A').

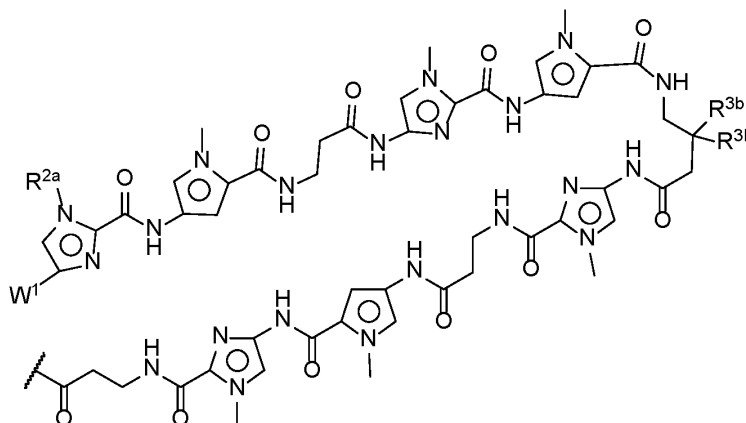
[0064] In some embodiments of Formula (I) or (I-A), R^{2a} , R^{2c} , R^{2d} , R^{2e} , or R^{2h} are each independently an optionally substituted C_1 - C_{20} alkyl, optionally substituted C_1 - C_{20} haloalkyl, or optionally substituted C_3 - C_8 cycloalkyl, each of which is optionally substituted with one or more R^Z . In some embodiments, R^{2a} , R^{2c} , R^{2d} , R^{2e} , or R^{2h} are each independently an optionally substituted C_3 - C_8 cycloalkyl. In some embodiments, R^{2a} , R^{2c} , R^{2d} , R^{2e} , or R^{2h} are each independently monocyclic, spirocycloalkyl, or bridged C_3 - C_8 cycloalkyl.

[0065] In some embodiments of Formula (I) or (I-A), one, two or three of R^{2a} , R^{2c} , R^{2d} , R^{2e} , or R^{2h} is substituted. In some embodiments, one or two of R^{2a} , R^{2c} , R^{2d} , R^{2e} , or R^{2h} is substituted. In some embodiments, one of R^{2a} , R^{2c} , R^{2d} , R^{2e} , or R^{2h} is substituted.

[0066] In some embodiments, of Formula (I) or (I-A) at least two of R^{2a} , R^{2c} , R^{2d} , R^{2e} , or R^{2h} is substituted. In some embodiments, at least one of R^{2a} , R^{2c} , R^{2d} , R^{2e} , or R^{2h} is substituted.

[0067] In some embodiments of Formula (I) or (I-A), at least two of R^{2a} , R^{2c} , R^{2d} , R^{2e} , or R^{2h} is not unsubstituted C_1 - C_{20} alkyl. In some embodiments, at least one of R^{2a} , R^{2c} , R^{2d} , R^{2e} , or R^{2h} is not unsubstituted C_1 - C_{20} alkyl. In some embodiments, at least two of R^{2a} , R^{2c} , R^{2d} , R^{2e} , or R^{2h} is not methyl. In some embodiments, at least one of R^{2a} , R^{2c} , R^{2d} , R^{2e} , or R^{2h} is not methyl.

[0068] In some embodiments, the DNA-binding moiety comprises the structure of Formula (Iaa), or a pharmaceutically acceptable salt thereof:



Formula (Iaa),

wherein:

 W^1 is hydrogen;

R^{2a} 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} heteroalkyl, optionally substituted C_2 - C_{20} heteroalkenyl, optionally substituted C_2 - C_{20} heteroalkynyl, optionally substituted C_1 - C_{20} haloalkyl, optionally substituted C_1 - C_{20} hydroxyalkyl, optionally substituted C_3 - C_{10} cycloalkyl, or optionally substituted 3 to 10-membered heterocycloalkyl; which is optionally substituted with one or more R^Z ;

each R^{3b} is independently hydrogen, $-NH_2$, or C_1 - C_6 alkyl; or

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

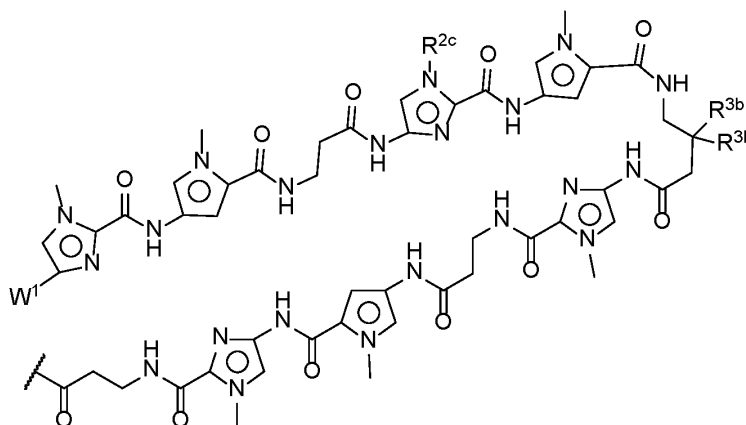
each R^Z is independently halogen, $-CN$, $-OH$, $-OR^{Za}$, $-N_3$, $-NR^{Za}R^{Zb}$, $-CO(O)R^{Zc}$, $-C(O)OR^{Zc}$, $-C(O)NR^{Za}R^{Zb}$, $-NR^{Za}C(O)R^{Zc}$, C_1 - C_{10} alkyl, C_1 - C_{10} haloalkyl, C_1 - C_{10} heteroalkyl, C_3 - C_{10} cycloalkyl, 3 to 10-membered heterocycloalkyl, phenyl, or optionally 5 to 10-membered heteroaryl; wherein

R^{Za} and R^{Zb} are each independently hydrogen, alkyl, haloalkyl, or PEG; and

R^{Zc} is alkyl, haloalkyl, PEG, cycloalkyl, heterocycloalkyl, or phenyl.

[0069] In some embodiments of Formula (Iaa), R^{2a} is an optionally substituted C_1 - C_{20} alkyl, optionally substituted C_1 - C_{20} haloalkyl, or optionally substituted C_3 - C_8 cycloalkyl, each of which is optionally substituted with one or more R^Z . In some embodiments, R^{2a} is an optionally substituted C_3 - C_8 cycloalkyl. In some embodiments, R^{2a} is a monocyclic, spirocycloalkyl, or bridged C_3 - C_8 cycloalkyl. In some embodiments, R^{2a} is not unsubstituted C_1 - C_{20} alkyl. In some embodiments, R^{2a} is not methyl.

[0070] In some embodiments, the DNA-binding moiety comprises the structure of Formula (Ibb), or a pharmaceutically acceptable salt thereof:



Formula (Ibb),

wherein:

 W^1 is hydrogen;

R^{2c} 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} heteroalkyl, optionally substituted C_2 - C_{20} heteroalkenyl, optionally substituted C_2 - C_{20} heteroalkynyl, optionally substituted C_1 - C_{20} haloalkyl, optionally substituted C_1 - C_{20} hydroxyalkyl, optionally substituted C_3 - C_{10} cycloalkyl, or optionally substituted 3 to 10-membered heterocycloalkyl; which is optionally substituted with one or more R^Z ;

each R^{3b} is independently hydrogen, $-NH_2$, or C_1 - C_6 alkyl; or

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

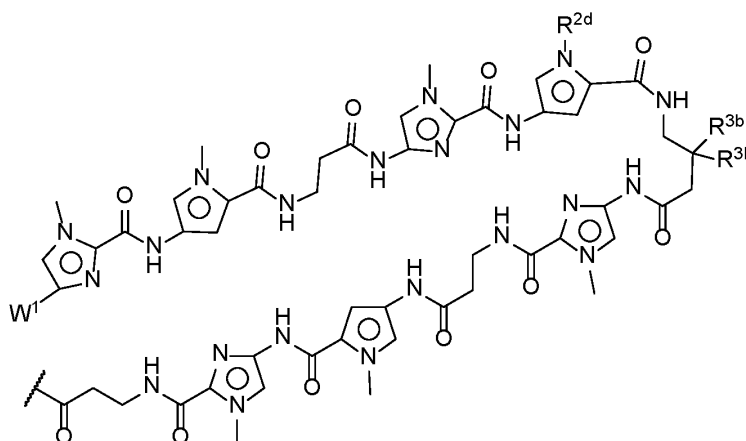
each R^Z is independently halogen, $-CN$, $-OH$, $-OR^{Za}$, $-N_3$, $-NR^{Za}R^{Zb}$, $-CO(O)R^{Zc}$, $-C(O)OR^{Zc}$, $-C(O)NR^{Za}R^{Zb}$, $-NR^{Za}C(O)R^{Zc}$, C_1 - C_{10} alkyl, C_1 - C_{10} haloalkyl, C_1 - C_{10} heteroalkyl, C_3 - C_{10} cycloalkyl, 3 to 10-membered heterocycloalkyl, phenyl, or optionally 5 to 10-membered heteroaryl; wherein

R^{Za} and R^{Zb} are each independently hydrogen, alkyl, haloalkyl, or PEG; and

R^{Zc} is alkyl, haloalkyl, PEG, cycloalkyl, heterocycloalkyl, or phenyl.

[0071] In some embodiments of Formula (Ibb), R^{2c} is an optionally substituted C_1 - C_{20} alkyl, optionally substituted C_1 - C_{20} haloalkyl, or optionally substituted C_3 - C_8 cycloalkyl, each of which is optionally substituted with one or more R^Z . In some embodiments, R^{2c} is an optionally substituted C_3 - C_8 cycloalkyl. In some embodiments, R^{2c} is a monocyclic, spirocycloalkyl, or bridged C_3 - C_8 cycloalkyl. In some embodiments, R^{2c} is not unsubstituted C_1 - C_{20} alkyl. In some embodiments, R^{2c} is not methyl.

[0072] In some embodiments, the DNA-binding moiety comprises the structure of Formula (Icc), or a pharmaceutically acceptable salt thereof:



Formula (Icc),

wherein:

W^1 is hydrogen;

R^{2d} 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} heteroalkyl, optionally substituted C_2 - C_{20} heteroalkenyl, optionally substituted C_2 - C_{20} heteroalkynyl,

optionally substituted C₁-C₂₀ haloalkyl, optionally substituted C₁-C₂₀ hydroxyalkyl, optionally substituted C₃-C₁₀ cycloalkyl, or optionally substituted 3 to 10-membered heterocycloalkyl; which is optionally substituted with one or more R^Z;

each R^{3b} is independently hydrogen, -NH₂, or C₁-C₆ alkyl; or

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

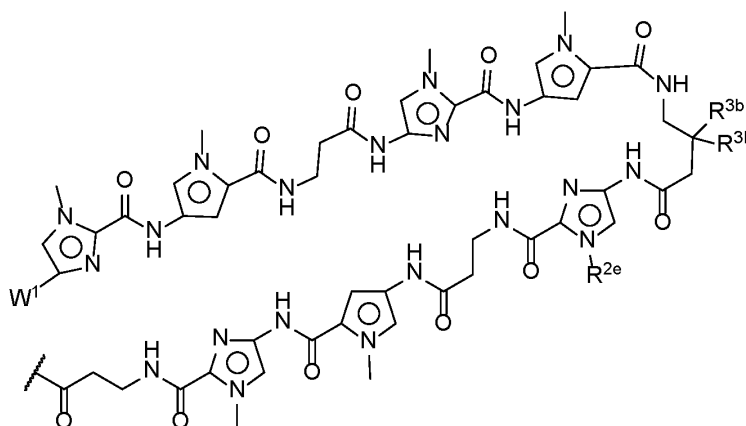
each R^Z is independently halogen, -CN, -OH, -OR^{Za}, -N₃, -NR^{Za}R^{Zb}, -CO(O)R^{Zc}, -C(O)OR^{Zc}, -C(O)NR^{Za}R^{Zb}, -NR^{Za}C(O)R^{Zc}, C₁-C₁₀ alkyl, C₁-C₁₀ haloalkyl, C₁-C₁₀ heteroalkyl, C₃-C₁₀ cycloalkyl, 3 to 10-membered heterocycloalkyl, phenyl, or optionally 5 to 10-membered heteroaryl; wherein

R^{Za} and R^{Zb} are each independently hydrogen, alkyl, haloalkyl, or PEG; and

R^{Zc} is alkyl, haloalkyl, PEG, cycloalkyl, heterocycloalkyl, or phenyl.

[0073] In some embodiments of Formula (Icc), R^{2d} is an optionally substituted C₁-C₂₀ alkyl, optionally substituted C₁-C₂₀ haloalkyl, or optionally substituted C₃-C₈ cycloalkyl, each of which is optionally substituted with one or more R^Z. In some embodiments, R^{2d} is an optionally substituted C₃-C₈ cycloalkyl. In some embodiments, R^{2d} is a monocyclic, spirocycloalkyl, or bridged C₃-C₈ cycloalkyl. In some embodiments, R^{2d} is not unsubstituted C₁-C₂₀ alkyl. In some embodiments, R^{2d} is not methyl.

[0074] In some embodiments, the DNA-binding moiety comprises the structure of Formula (Idd), or a pharmaceutically acceptable salt thereof:



Formula (Idd),

wherein:

W¹ is hydrogen;

R^{2e} 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 heteroalkyl, optionally substituted C₂-C₂₀ heteroalkenyl, optionally substituted C₂-C₂₀ heteroalkynyl, optionally substituted C₁-C₂₀ haloalkyl, optionally substituted C₁-C₂₀ hydroxyalkyl, optionally substituted C₃-C₁₀ cycloalkyl, or optionally substituted 3 to 10-membered heterocycloalkyl; which is optionally substituted with one or more R^Z;

each R^{3b} is independently hydrogen, $-NH_2$, or C_1 - C_6 alkyl; or

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

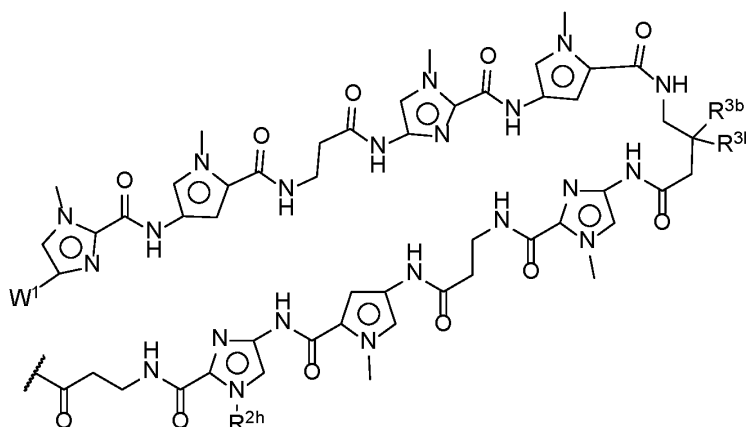
each R^Z is independently halogen, $-CN$, $-OH$, $-OR^{Za}$, $-N_3$, $-NR^{Za}R^{Zb}$, $-CO(O)R^{Zc}$, $-C(O)OR^{Zc}$, $-C(O)NR^{Za}R^{Zb}$, $-NR^{Za}C(O)R^{Zc}$, C_1 - C_{10} alkyl, C_1 - C_{10} haloalkyl, C_1 - C_{10} heteroalkyl, C_3 - C_{10} cycloalkyl, 3 to 10-membered heterocycloalkyl, phenyl, or optionally 5 to 10-membered heteroaryl; wherein

R^{Za} and R^{Zb} are each independently hydrogen, alkyl, haloalkyl, or PEG; and

R^{Zc} is alkyl, haloalkyl, PEG, cycloalkyl, heterocycloalkyl, or phenyl.

[0075] In some embodiments of Formula (Idd), R^{2e} is an optionally substituted C_1 - C_{20} alkyl, optionally substituted C_1 - C_{20} haloalkyl, or optionally substituted C_3 - C_8 cycloalkyl, each of which is optionally substituted with one or more R^Z . In some embodiments, R^{2e} is an optionally substituted C_3 - C_8 cycloalkyl. In some embodiments, R^{2e} is a monocyclic, spirocycloalkyl, or bridged C_3 - C_8 cycloalkyl. In some embodiments, R^{2e} is not unsubstituted C_1 - C_{20} alkyl. In some embodiments, R^{2e} is not methyl.

[0076] In some embodiments, the DNA-binding moiety comprises the structure of Formula (Iee), or a pharmaceutically acceptable salt thereof:



Formula (Iee),

wherein:

W^1 is hydrogen;

R^{2h} 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} heteroalkyl, optionally substituted C_2 - C_{20} heteroalkenyl, optionally substituted C_2 - C_{20} heteroalkynyl, optionally substituted C_1 - C_{20} haloalkyl, optionally substituted C_1 - C_{20} hydroxyalkyl, optionally substituted C_3 - C_{10} cycloalkyl, or optionally substituted 3 to 10-membered heterocycloalkyl; which is optionally substituted with one or more R^Z ;

each R^{3b} is independently hydrogen, $-NH_2$, or C_1 - C_6 alkyl; or

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

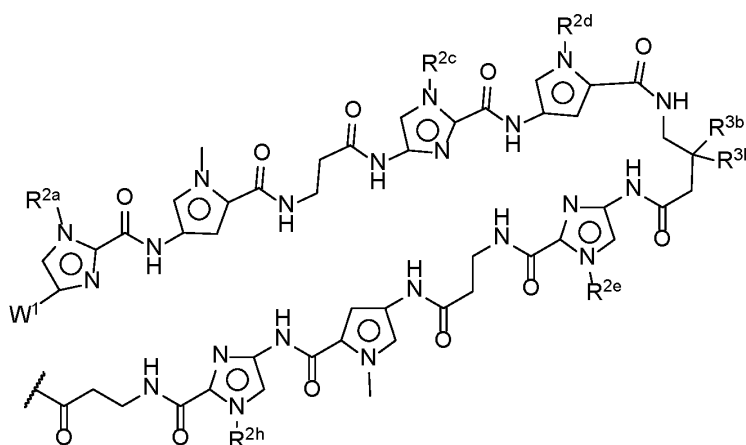
each R^Z is independently halogen, -CN, -OH, -OR^{Za}, -N₃, -NR^{Za}R^{Zb}, -CO(O)R^{Zc}, -C(O)OR^{Zc}, -C(O)NR^{Za}R^{Zb}, -NR^{Za}C(O)R^{Zc}, C₁-C₁₀ alkyl, C₁-C₁₀ haloalkyl, C₁-C₁₀ heteroalkyl, C₃-C₁₀ cycloalkyl, 3 to 10-membered heterocycloalkyl, phenyl, or optionally 5 to 10-membered heteroaryl; wherein

R^{Za} and R^{Zb} are each independently hydrogen, alkyl, haloalkyl, or PEG; and

R^{Zc} is alkyl, haloalkyl, PEG, cycloalkyl, heterocycloalkyl, or phenyl.

[0077] In some embodiments of Formula (Iee), R^{2h} is an optionally substituted C₁-C₂₀ alkyl, optionally substituted C₁-C₂₀ haloalkyl, or optionally substituted C₃-C₈ cycloalkyl, each of which is optionally substituted with one or more R^Z. In some embodiments, R^{2h} is an optionally substituted C₃-C₈ cycloalkyl. In some embodiments, R^{2h} is a monocyclic, spirocycloalkyl, or bridged C₃-C₈ cycloalkyl. In some embodiments, R^{2h} is not unsubstituted C₁-C₂₀ alkyl. In some embodiments, R^{2h} is not methyl.

[0078] In some embodiments, the DNA-binding moiety comprises the structure of Formula (I'), or a pharmaceutically acceptable salt thereof:



Formula (I'),

wherein:

W¹ is hydrogen;

R^{2a}, R^{2c}, R^{2e}, and R^{2h} are each independently an optionally substituted C₁-C₂₀ alkyl wherein each is optionally substituted with one or more R^Z;

R^{2d} is an optionally substituted C₁-C₂₀ alkyl or optionally substituted C₃-C₁₀ cycloalkyl, each of which is optionally substituted with one or more R^Z;

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

R^{3c} and R^{3d} are each independently hydrogen, alkyl, or PEG;

R^{3e} is alkyl, PEG, cycloalkyl, heterocycloalkyl, or phenyl;

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

each R^Z is independently halogen, -CN, -OH, -OR^{Za}, -N₃, -NR^{Za}R^{Zb}, -CO(O)R^{Zc}, -C(O)OR^{Zc}, -C(O)NR^{Za}R^{Zb}, -NR^{Za}C(O)R^{Zc}, C₁-C₁₀ alkyl, or C₁-C₁₀ haloalkyl;

or two R^Z together with the atom(s) to which they are attached form a C₃-C₆ cycloalkyl, wherein

R^{Za} and R^{Zb} are each independently hydrogen, alkyl, haloalkyl, or PEG; and

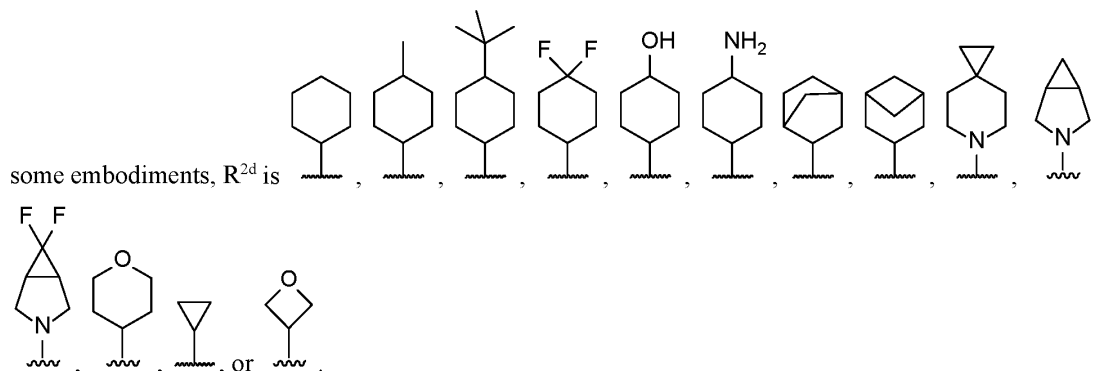
R^{Zc} is alkyl, haloalkyl, PEG, cycloalkyl, heterocycloalkyl, or phenyl;

with the proviso that when R^{2d} is an optionally substituted C_3 - C_{10} cycloalkyl, then each R^{3b} is hydrogen; or

when two R^{3b} form a C_3 - C_6 cycloalkyl, then R^{2d} is an optionally substituted C_1 - C_{20} alkyl.

[0079] In some embodiments of Formula (I'), R^{2d} is an optionally substituted C_3 - C_{10} cycloalkyl; and each R^{3b} is hydrogen.

[0080] In some embodiments of Formula (I'), R^{2d} is an optionally substituted monocyclic, spirocyclic, or bridged C_3 - C_8 cycloalkyl. In some embodiments, R^{2d} is a monocyclic C_6 - C_8 cycloalkyl optionally substituted with one or more R^Z , wherein each R^Z is independently halogen, $-OH$, $-OR^{Za}$, $-NR^{Za}R^{Zb}$, or C_1 - C_6 alkyl. In



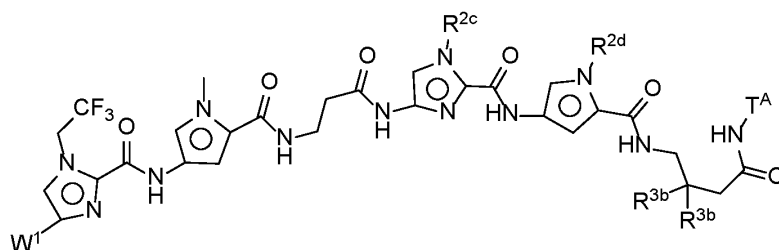
[0081] In some embodiments of Formula (I'), two R^{3b} together with the atom to which they are attached form a C_3 - C_6 cycloalkyl; and R^{2d} an optionally substituted C_1 - C_{20} alkyl.

[0082] In some embodiments of Formula (I'), two R^{3b} together with the atom to which they are attached form a cyclopropyl.

[0083] In some embodiments of Formula (I'), R^{2d} is an unsubstituted C_1 - C_8 alkyl. In some embodiments, R^{2d} is methyl, ethyl, isopropyl, n-butyl, isobutyl, pentyl, or hexyl. In some embodiments, R^{2d} is methyl, ethyl, or isopropyl. In some embodiments, R^{2d} is methyl. In some embodiments, R^{2d} is isopropyl.

[0084] In some embodiments of Formula (I'), R^{2a} , R^{2c} , R^{2e} , and R^{2h} are each independently an unsubstituted C_1 - C_8 alkyl. In some embodiments, R^{2a} , R^{2c} , R^{2e} , and R^{2h} are each independently methyl, ethyl, or isopropyl.

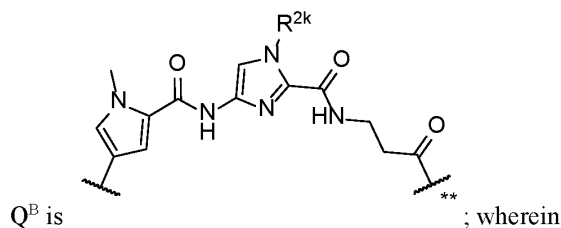
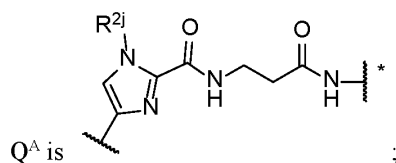
[0085] In some embodiments, the DNA-binding moiety comprises the structure of Formula (II), or a pharmaceutically acceptable salt thereof:



Formula (II),

wherein:

T^A is $-Q^A-Q^B$; wherein



R^{2j} is an optionally substituted C_1 - C_{20} alkyl, optionally substituted with one or more R^Z ;

R^{2k} is an optionally substituted C_1 - C_{20} alkyl or optionally substituted, C_3 - C_{10} cycloalkyl, each of which is optionally substituted with one or more R^Z ;

* is the attachment point of Q^A to Q^B ; and

** is the attachment point to the oligomeric linker;

W^1 is hydrogen;

R^{2c} and R^{2d} are each independently an optionally substituted C_1 - C_{20} alkyl, optionally substituted, C_3 - C_{10} cycloalkyl, or optionally substituted 3 to 10-membered heterocycloalkyl, each of which is optionally substituted with one or more R^Z ;

each R^{3b} is hydrogen or C_1 - C_6 alkyl;

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

each R^Z is independently halogen, -CN, -OH, -OR^{Za}, -N₃, -NR^{Za}R^{Zb}, -CO(O)R^{Zc}, -C(O)OR^{Zc}, -C(O)NR^{Za}R^{Zb}, -NR^{Za}C(O)R^{Zc}, C_1 - C_{10} alkyl, or C_1 - C_{10} haloalkyl;

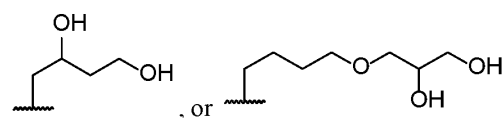
or two R^Z together with the atom(s) to which they are attached form a C_3 - C_6 cycloalkyl, wherein

R^{Za} and R^{Zb} are each independently hydrogen, alkyl, haloalkyl, or PEG; and

R^{Zc} is alkyl, haloalkyl, PEG, cycloalkyl, heterocycloalkyl, or phenyl.

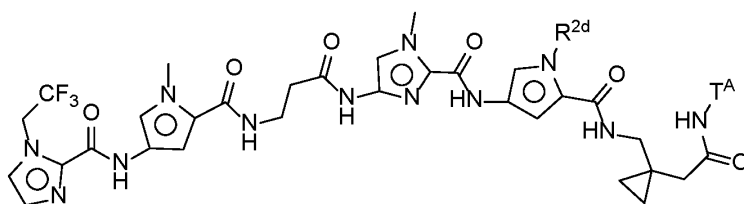
[0086] In some embodiments of Formula (II), each R^Z is independently halogen, -OH, -OR^{Za}, -NR^{Za}R^{Zb}, or C_1 - C_6 alkyl.

[0087] In some embodiments of Formula (II), R^{2c} is methyl, ethyl, isopropyl, , or



. In some embodiments, R^{2c} is methyl, ethyl, or isopropyl. In some embodiments, R^{2c} is methyl. In some embodiments, R^{2c} is isopropyl.

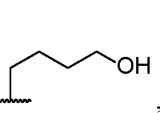
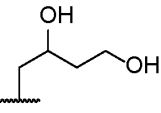
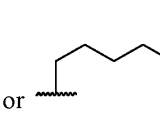
[0088] In some embodiments, the DNA-binding moiety of Formula (II) has the structure of Formula (IIa), or a pharmaceutically acceptable salt thereof:



Formula (IIa).

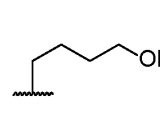
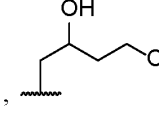
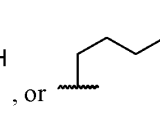
[0089] In some embodiments of Formula (II) or (IIa), R^{2d} is an optionally substituted C_1 - C_{20} alkyl, optionally substituted with one or more R^Z . In some embodiments, R^{2d} is an optionally substituted C_3 - C_{10} cycloalkyl, optionally substituted with one or more R^Z . In some embodiments, R^{2d} is an optionally substituted monocyclic, spirocyclic, or bridged C_3 - C_8 cycloalkyl, each of which is optionally substituted with one or more R^Z , wherein each R^Z is independently halogen, $-OH$, $-OR^{Za}$, $-NR^{Za}R^{Zb}$, or C_1 - C_6 alkyl.

[0090] In some embodiments of Formula (II) or (IIa), R^{2j} is an optionally substituted C_1 - C_{20} alkyl. In some embodiments, R^{2j} is an unsubstituted C_1 - C_{10} alkyl. In some embodiments, R^{2j} is methyl, ethyl,

isopropyl, , , or . In some embodiments, R^{2j} is methyl, ethyl, or isopropyl. In some embodiments, R^{2j} is methyl. In some embodiments, R^{2j} is isopropyl.

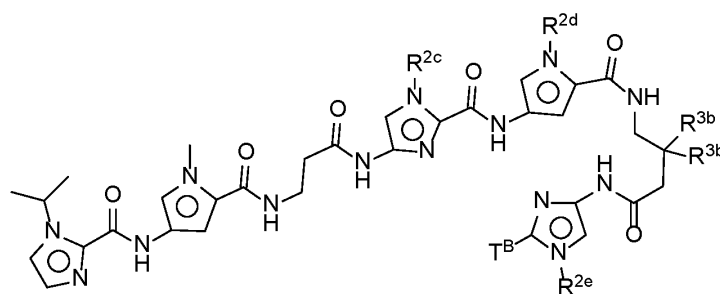
[0091] In some embodiments of Formula (II) or (IIa), R^{2k} is an optionally substituted C_3 - C_{10} cycloalkyl, optionally substituted with one or more R^Z . In some embodiments, R^{2k} is an optionally substituted monocyclic, spirocyclic, or bridged C_3 - C_8 cycloalkyl, each of which is optionally substituted with one or more R^Z , wherein each R^Z is independently halogen, $-OH$, $-OR^{Za}$, $-NR^{Za}R^{Zb}$, or C_1 - C_6 alkyl.

[0092] In some embodiments of Formula (II) or (IIa), R^{2k} is an optionally substituted C_1 - C_{10} alkyl. In some embodiments of Formula (II) or (IIa), R^{2k} is unsubstituted C_1 - C_{10} alkyl. In some embodiments, R^{2k} is

methyl, ethyl, isopropyl, , , or . In some embodiments, R^{2k} is methyl, ethyl, or isopropyl. In some embodiments, R^{2k} is methyl. In some embodiments, R^{2k} is isopropyl.

[0093] In some embodiments of Formula (II) or (IIa), R^{2j} is an unsubstituted C_1 - C_{10} alkyl and R^{2k} is unsubstituted C_1 - C_{10} alkyl. In some embodiments, R^{2j} is methyl and R^{2k} is methyl.

[0094] In some embodiments, the DNA-binding moiety comprises the structure of Formula (III), or a pharmaceutically acceptable salt thereof:

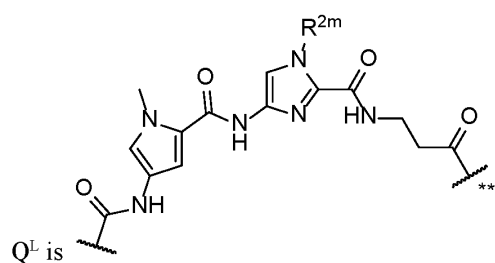


Formula (III),

wherein:

T^B is -S¹-Q^L; wherein

S¹ is -C(O)NH(CH₂)₂;



; wherein

R^{2m} is an optionally substituted C₁-C₂₀ alkyl which is optionally substituted with one or more R^Z; and

** is the attachment point to the oligomeric linker;

R^{2c} is an unsubstituted C₁-C₆ alkyl;

R^{2d} and R^{2e} are each independently an optionally substituted C₁-C₂₀ alkyl, optionally substituted C₃-C₁₀ cycloalkyl, or optionally substituted 3 to 10-membered heterocycloalkyl, each of which is optionally substituted with one or more R^Z;

each R^{3b} is hydrogen or C₁-C₆ alkyl;

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

each R^Z is independently halogen, -CN, -OH, -OR^{Za}, -N₃, -NR^{Za}R^{Zb}, -CO(O)R^{Zc}, -C(O)OR^{Zc}, -C(O)NR^{Za}R^{Zb}, -NR^{Za}C(O)R^{Zc}, C₁-C₁₀ alkyl, or C₁-C₁₀ haloalkyl;

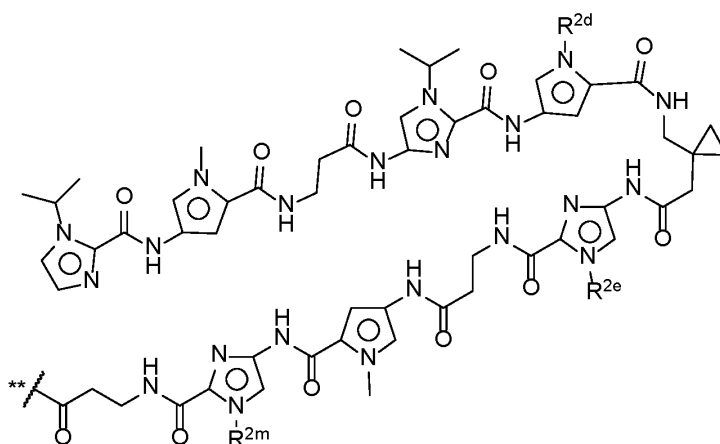
or two R^Z together with the atom(s) to which they are attached form a C₃-C₆ cycloalkyl, wherein

R^{Za} and R^{Zb} are each independently hydrogen, alkyl, haloalkyl, or PEG; and

R^{Zc} is alkyl, haloalkyl, PEG, cycloalkyl, heterocycloalkyl, or phenyl.

[0095] In some embodiments of Formula (III), R^{2c} is methyl, ethyl, or isopropyl. In some embodiments, R^{2c} is methyl. In some embodiments, R^{2c} is isopropyl.

[0096] In some embodiments, the DNA-binding moiety of Formula (III) has the structure of Formula (IIIa), or a pharmaceutically acceptable salt thereof:



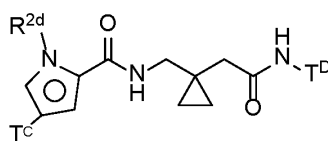
Formula (IIIa).

[0097] In some embodiments of Formula (III) or (IIIa), R^{2d} is an optionally substituted C_1 - C_{20} alkyl, optionally substituted with one or more R^Z . In some embodiments, R^{2d} is an optionally substituted C_3 - C_{10} cycloalkyl, optionally substituted with one or more R^Z . In some embodiments, R^{2d} is an optionally substituted monocyclic, spirocyclic, or bridged C_3 - C_8 cycloalkyl, each of which is optionally substituted with one or more R^Z , wherein each R^Z is independently halogen, $-OH$, $-OR^{Za}$, $-NR^{Za}R^{Zb}$, or C_1 - C_6 alkyl.

[0098] In some embodiments of Formula (III) or (IIIa), R^{2e} is an optionally substituted C_1 - C_{20} alkyl. In some embodiments, R^{2e} is methyl, ethyl, or isopropyl. In some embodiments, R^{2e} is methyl. In some embodiments, R^{2e} is isopropyl.

[0099] In some embodiments of Formula (III) or (IIIa), R^{2m} is an unsubstituted C_1 - C_6 alkyl. In some embodiments, R^{2m} is methyl, ethyl, or isopropyl. In some embodiments, R^{2m} is methyl. In some embodiments, R^{2m} is isopropyl.

[00100] In some embodiments, the DNA-binding moiety comprises the structure of Formula (IV), or a pharmaceutically acceptable salt thereof:



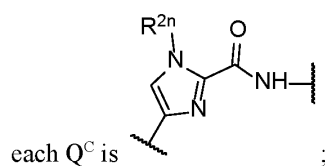
Formula (IV),

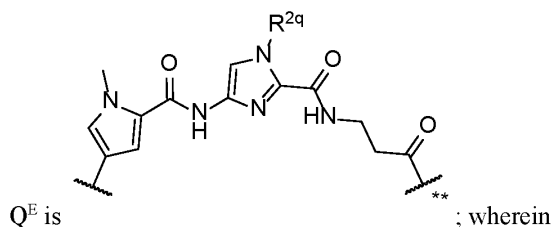
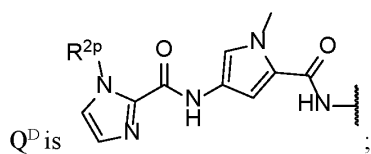
wherein:

T^C is $-Q^C-S^2-Q^D$;

T^D is $-Q^C-S^2-Q^E$; wherein

each S^2 is $-NHC(O)(CH_2)_2-$ or $-(CH_2)_2C(O)NH-$;





R^{2n} , R^{2p} , and R^{2q} are each independently an optionally substituted C_1 - C_{20} alkyl wherein each is optionally substituted with one or more R^Z ; and

** is the attachment point to the oligomeric linker;

R^{2d} is a C_3 - C_{10} cycloalkyl which is optionally substituted with one or more R^Z ;

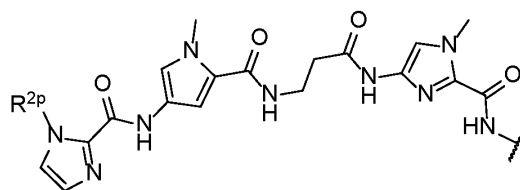
each R^Z is independently halogen, -CN, -OH, -OR^{Za}, -N₃, -NR^{Za}R^{Zb}, -CO(O)R^{Zc}, -C(O)OR^{Zc}, -C(O)NR^{Za}R^{Zb}, -NR^{Za}C(O)R^{Zc}, C_1 - C_{10} alkyl, or C_1 - C_{10} haloalkyl;

or two R^Z together with the atom(s) to which they are attached form a C_3 - C_6 cycloalkyl, wherein

R^{Za} and R^{Zb} are each independently hydrogen, alkyl, haloalkyl, or PEG; and

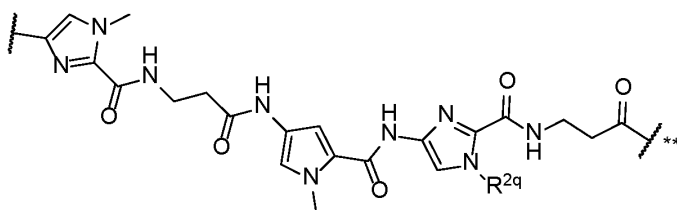
R^{Zc} is alkyl, haloalkyl, PEG, cycloalkyl, heterocycloalkyl, or phenyl.

[00101] In some embodiments of Formula (IV), each R^{2n} is independently unsubstituted C_1 - C_8 alkyl. In some embodiments, R^{2n} is methyl, ethyl, or isopropyl. In some embodiments, R^{2n} is methyl. In some embodiments, R^{2n} is isopropyl.



[00102] In some embodiments of Formula (IV), T^C is

[00103] In some embodiments of Formula (IV), T^D is



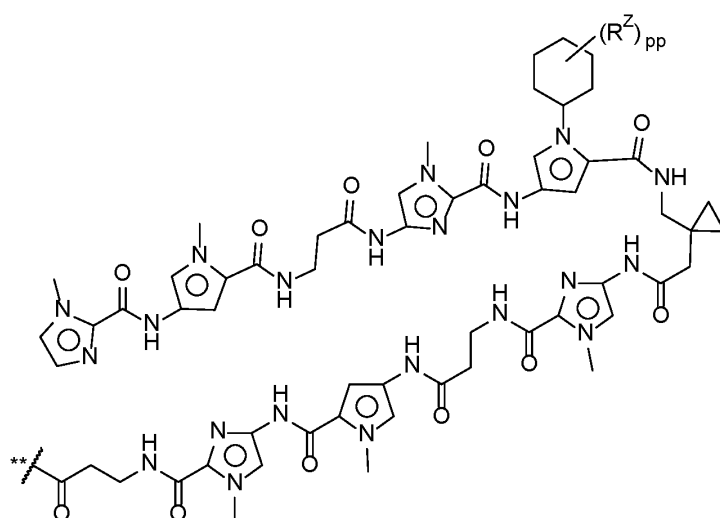
[00104] In some embodiments of Formula (IV), R^{2p} and R^{2q} are independently an optionally substituted C_1 - C_8 alkyl, each of which is optionally substituted with one or more R^Z ; wherein each R^Z is independently halogen, -OH, -OR^{Za}, or -NR^{Za}R^{Zb}.

[00105] In some embodiments of Formula (IV), each R^{2p} is independently unsubstituted C_1 - C_8 alkyl. In some embodiments, R^{2p} is methyl, ethyl, or isopropyl. In some embodiments, R^{2p} is methyl. In some embodiments, R^{2p} is isopropyl.

[00106] In some embodiments of Formula (IV), each R^{2q} is independently unsubstituted C_1 - C_8 alkyl. In some embodiments, R^{2q} is methyl, ethyl, or isopropyl. In some embodiments, R^{2q} is methyl. In some embodiments, R^{2q} is isopropyl.

[00107] In some embodiments of Formula (IV), R^{2d} is an optionally substituted monocyclic, spirocyclic, or bridge C_3 - C_8 cycloalkyl. In some embodiments, R^{2d} is an unsubstituted monocyclic C_6 - C_8 cycloalkyl.

[00108] In some embodiments, the DNA-binding moiety of Formula (IV) has the structure of Formula (IVa), or a pharmaceutically acceptable salt thereof:



Formula (IVa),

wherein:

each R^Z is independently halogen, -CN, -OH, -OR^{Za}, -N₃, -NR^{Za}R^{Zb}, -CO(O)R^{Zc}, -C(O)OR^{Zc}, -C(O)NR^{Za}R^{Zb}, -NR^{Za}C(O)R^{Zc}, C_1 - C_{10} alkyl, C_1 - C_{10} haloalkyl;

or two R^Z together with the atom(s) to which they are attached form a C_3 - C_6 cycloalkyl;

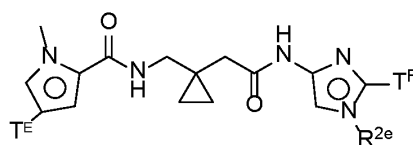
R^{Za} and R^{Zb} are each independently hydrogen, alkyl, haloalkyl, or PEG;

R^{Zc} is alkyl, haloalkyl, PEG, cycloalkyl, heterocycloalkyl, or phenyl; and

pp is 0, 1, or 2.

[00109] In some embodiments of Formula (IV) or (IVa), pp is 1 or 2. In some embodiments, pp is 0. In some embodiments, pp is 1. In some embodiments, pp is 2.

[00110] In some embodiments, the DNA-binding moiety comprises the structure of Formula (V), or a pharmaceutically acceptable salt thereof:



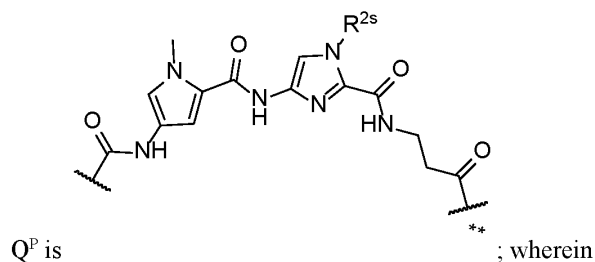
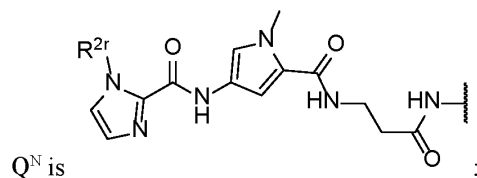
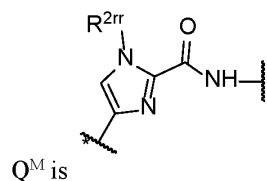
Formula (V),

wherein:

T^E is $-Q^M-Q^N$;

T^F is $-S^3-Q^P$; wherein

S^3 is $-C(O)NH(CH_2)_2-$;



R^{2r} , R^{2rr} , and R^{2s} are each independently an optionally substituted C_1 - C_{20} alkyl wherein each is optionally substituted with one or more R^Z ;

* is the attachment point of Q^M to Q^N ; and

** is the attachment point to the oligomeric linker;

R^{2e} is a C_3 - C_{10} cycloalkyl which is optionally substituted with one or more R^Z ;

each R^Z is independently halogen, $-CN$, $-OH$, $-OR^{Za}$, $-N_3$, $-NR^{Za}R^{Zb}$, $-CO(O)R^{Zc}$, $-C(O)OR^{Zc}$, $-C(O)NR^{Za}R^{Zb}$, $-NR^{Za}C(O)R^{Zc}$, C_1 - C_{10} alkyl, or C_1 - C_{10} haloalkyl;

or two R^Z together with the atom(s) to which they are attached form a C_3 - C_6 cycloalkyl, wherein

R^{Za} and R^{Zb} are each independently hydrogen, alkyl, haloalkyl, or PEG; and

R^{Zc} is alkyl, haloalkyl, PEG, cycloalkyl, heterocycloalkyl, or phenyl.

[00111] In some embodiments of Formula (V), R^{2e} is an optionally substituted monocyclic, spirocyclic, or bridge C_3 - C_8 cycloalkyl, each of which is optionally substituted with one or more R^Z . In some embodiments, R^{2e} is an unsubstituted monocyclic C_6 - C_8 cycloalkyl.

[00112] In some embodiments of Formula (V), R^{2r} , R^{2rr} , and R^{2s} are independently an optionally substituted C_1 - C_8 alkyl, each of which is optionally substituted with one or more R^Z ; wherein each R^Z is independently halogen, $-OH$, $-OR^{Za}$, or $-NR^{Za}R^{Zb}$.

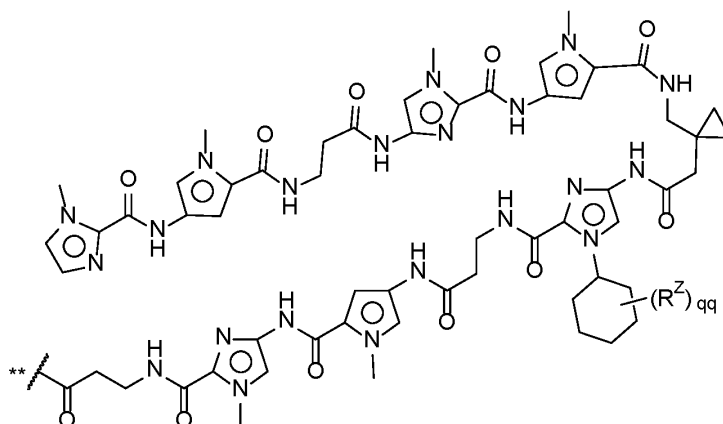
[00113] In some embodiments of Formula (V), R^{2r} , R^{2rr} , and R^{2s} are independently an unsubstituted C_1 - C_8 alkyl.

[00114] In some embodiments of Formula (V), R^{2r} is methyl, ethyl, or isopropyl. In some embodiments, R^{2r} is methyl. In some embodiments, R^{2r} is isopropyl.

[00115] In some embodiments of Formula (V), R^{2rr} is methyl, ethyl, or isopropyl. In some embodiments, R^{2rr} is methyl. In some embodiments, R^{2rr} is isopropyl.

[00116] In some embodiments of Formula (V), R^{2s} is methyl, ethyl, or isopropyl. In some embodiments, R^{2s} is methyl. In some embodiments, R^{2s} is isopropyl.

[00117] In some embodiments, the DNA-binding moiety comprises the structure of Formula (Va), or a pharmaceutically acceptable salt thereof:



Formula (Va),

wherein:

each R^Z is independently halogen, $-CN$, $-OH$, $-OR^{Za}$, $-N_3$, $-NR^{Za}R^{Zb}$, $-CO(O)R^{Zc}$, $-C(O)OR^{Zc}$, $-C(O)NR^{Za}R^{Zb}$, $-NR^{Za}C(O)R^{Zc}$, C_1 - C_{10} alkyl, C_1 - C_{10} haloalkyl;

or two R^Z together with the atom(s) to which they are attached form a C_3 - C_6 cycloalkyl;

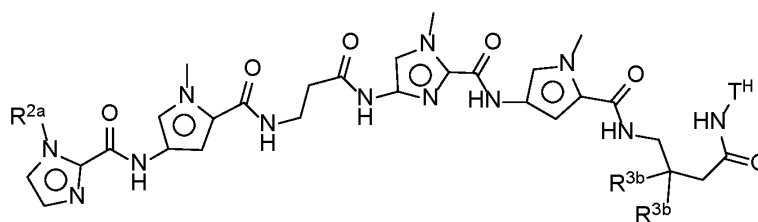
R^{Za} and R^{Zb} are each independently hydrogen, alkyl, haloalkyl, or PEG;

R^{Zc} is alkyl, haloalkyl, PEG, cycloalkyl, heterocycloalkyl, or phenyl; and

qq is 0, 1, or 2.

[00118] In some embodiments of Formula (V) or (Va), qq is 1 or 2. In some embodiments, qq is 0. In some embodiments, qq is 1. In some embodiments, qq is 2.

[00119] In some embodiments, the DNA-binding moiety comprises the structure of Formula (VI), or a pharmaceutically acceptable salt thereof:

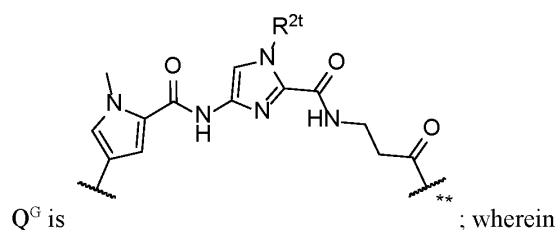
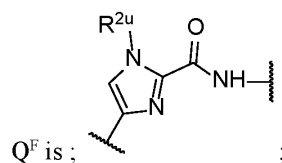


Formula (VI),

wherein:

T^H is $-Q^F-S^4-Q^G$; wherein

S^4 is $-NHC(O)(CH_2)_2-$;



R^{2u} and R^{2t} are each independently an optionally substituted C_1 - C_{20} alkyl wherein each is optionally substituted with one or more R^Z ; and

$**$ is the attachment point to the oligomeric linker;

R^{2a} is a C_3 - C_{10} cycloalkyl which is optionally substituted with one or more R^Z ;

each R^{3b} is hydrogen or C_1 - C_6 alkyl;

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

each R^Z is independently halogen, $-CN$, $-OH$, $-OR^{Za}$, $-N_3$, $-NR^{Za}R^{Zb}$, $-CO(O)R^{Zc}$, $-C(O)OR^{Zc}$, $-C(O)NR^{Za}R^{Zb}$, $-NR^{Za}C(O)R^{Zc}$, C_1 - C_{10} alkyl, or C_1 - C_{10} haloalkyl;

or two R^Z together with the atom(s) to which they are attached form a C_3 - C_6 cycloalkyl, wherein

R^{Za} and R^{Zb} are each independently hydrogen, alkyl, haloalkyl, or PEG; and

R^{Zc} is alkyl, haloalkyl, PEG, cycloalkyl, heterocycloalkyl, or phenyl.

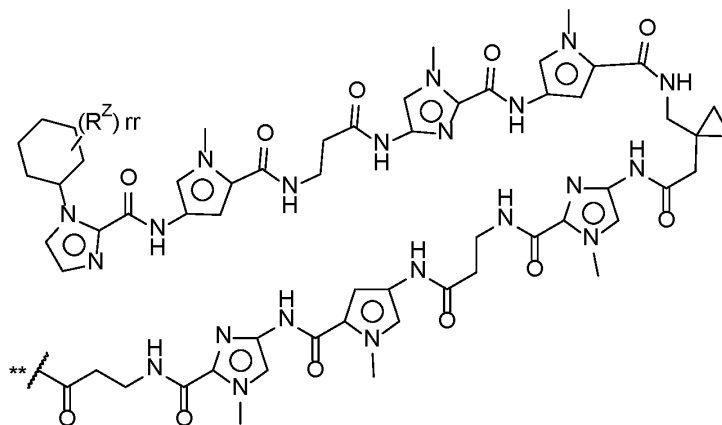
[00120] In some embodiments of Formula (VI), R^{2a} is an optionally substituted monocyclic, spirocyclic, or bridge C_3 - C_8 cycloalkyl, each of which is optionally substituted with one or more R^Z . In some embodiments, R^{2a} is an unsubstituted monocyclic C_6 - C_8 cycloalkyl.

[00121] In some embodiments of Formula (VI), R^{2u} and R^{2t} are independently an optionally substituted C_1 - C_8 alkyl, each of which is optionally substituted with one or more R^Z ; wherein each R^Z is independently halogen, $-OH$, $-OR^{Za}$, or $-NR^{Za}R^{Zb}$.

[00122] In some embodiments of Formula (VI), R^{2u} is an unsubstituted C_1 - C_8 alkyl. In some embodiments R^{2u} methyl, ethyl, or isopropyl. In some embodiments, R^{2u} is methyl. In some embodiments, R^{2u} is isopropyl.

[00123] In some embodiments of Formula (VI), R^{2t} is an unsubstituted C_1 - C_8 alkyl. In some embodiments, R^{2t} methyl, ethyl, or isopropyl. In some embodiments, R^{2t} is methyl. In some embodiments, R^{2t} is isopropyl.

[00124] In some embodiments, the DNA-binding moiety of Formula (VI) has the structure of Formula (VIa), or a pharmaceutically acceptable salt thereof:



Formula (VIa),

wherein:

each R^Z is independently halogen, -CN, -OH, -OR^{Za}, -N₃, -NR^{Za}R^{Zb}, -CO(O)R^{Zc}, -C(O)OR^{Zc}, -C(O)NR^{Za}R^{Zb},

-NR^{Za}C(O)R^{Zc}, C_1 - C_{10} alkyl, C_1 - C_{10} haloalkyl;

or two R^Z together with the atom(s) to which they are attached form a C_3 - C_6 cycloalkyl;

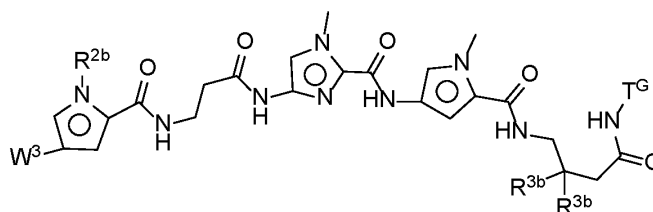
R^{Za} and R^{Zb} are each independently hydrogen, alkyl, haloalkyl, or PEG;

R^{Zc} is alkyl, haloalkyl, PEG, cycloalkyl, heterocycloalkyl, or phenyl; and

rr is 0, 1, or 2.

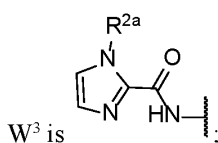
[00125] In some embodiments of Formula (VI) or (VIa), rr is 1 or 2. In some embodiments, rr is 0. In some embodiments, rr is 1. In some embodiments, rr is 2.

[00126] In some embodiments, the DNA-binding moiety comprises the structure of Formula (VII), or a pharmaceutically acceptable salt thereof:



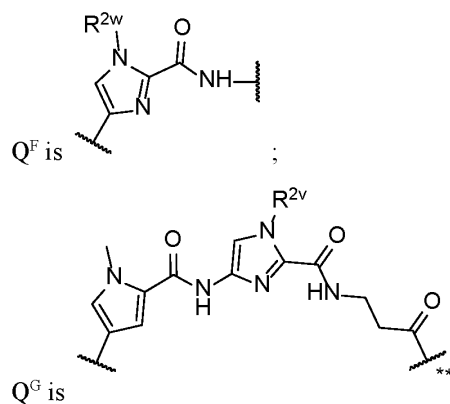
Formula (VII),

wherein:



T^G is $-Q^F-S^5-Q^G$; wherein

S^5 is $-\text{NHC(O)}(\text{CH}_2)_2-$;



R^{2a} , R^{2w} , and R^{2v} are each independently an optionally substituted C_1 - C_{20} alkyl wherein each is optionally substituted with one or more R^Z ; and

** is the attachment point to the oligomeric linker;

R^{2b} is a C_3 - C_{10} cycloalkyl which is optionally substituted with one or more R^Z ;

each R^{3b} is hydrogen or C_1 - C_6 alkyl;

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

each R^Z is independently halogen, $-\text{CN}$, $-\text{OH}$, $-\text{OR}^{Za}$, $-\text{N}_3$, $-\text{NR}^{Za}\text{R}^{Zb}$, $-\text{CO(O)}\text{R}^{Zc}$, $-\text{C(O)}\text{OR}^{Zc}$, $-\text{C(O)}\text{NR}^{Za}\text{R}^{Zb}$, $-\text{NR}^{Za}\text{C(O)}\text{R}^{Zc}$, C_1 - C_{10} alkyl, or C_1 - C_{10} haloalkyl;

or two R^Z together with the atom(s) to which they are attached form a C_3 - C_6 cycloalkyl, wherein

R^{Za} and R^{Zb} are each independently hydrogen, alkyl, haloalkyl, or PEG; and

R^{Zc} is alkyl, haloalkyl, PEG, cycloalkyl, heterocycloalkyl, or phenyl.

[00127] In some embodiments of Formula (VII), R^{2b} is an optionally substituted monocyclic, spirocyclic, or bridge C_3 - C_8 cycloalkyl, each of which is optionally substituted with one or more R^Z . In some embodiments, R^{2b} is an unsubstituted monocyclic C_6 - C_8 cycloalkyl

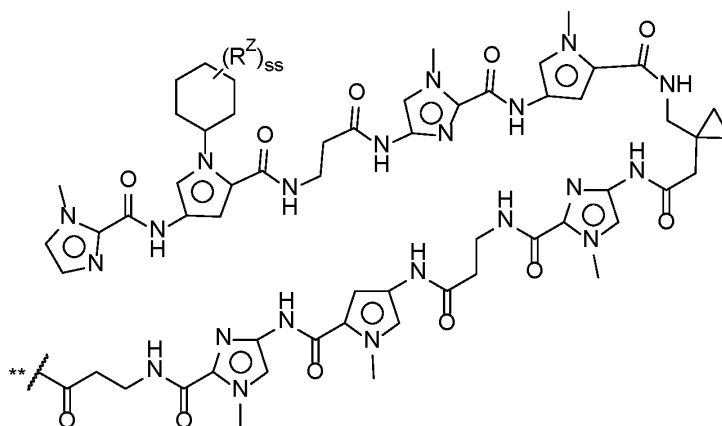
[00128] In some embodiments of Formula (VII), R^{2a} , R^{2w} , and R^{2v} are independently an optionally substituted C_1 - C_8 alkyl, each of which is optionally substituted with one or more R^Z ; wherein each R^Z is independently halogen, $-\text{OH}$, $-\text{OR}^{Za}$, or $-\text{NR}^{Za}\text{R}^{Zb}$.

[00129] In some embodiments of Formula (VII), R^{2a} is an unsubstituted C_1 - C_8 alkyl. In some embodiments R^{2a} methyl, ethyl, or isopropyl. In some embodiments, R^{2a} is methyl. In some embodiments, R^{2a} is isopropyl.

[00130] In some embodiments of Formula (VII), R^{2w} is an unsubstituted C_1 - C_8 alkyl. In some embodiments, R^{2w} methyl, ethyl, or isopropyl. In some embodiments, R^{2w} is methyl. In some embodiments, R^{2w} is isopropyl.

[00131] In some embodiments of Formula (VII), R^{2v} is an unsubstituted C_1 - C_8 alkyl. In some embodiments, R^{2v} methyl, ethyl, or isopropyl. In some embodiments, R^{2v} is methyl. In some embodiments, R^{2v} is isopropyl.

[00132] In some embodiments, the DNA-binding moiety of Formula (VII) has the structure of Formula (VIIa), or a pharmaceutically acceptable salt thereof:



Formula (VIIa),

wherein:

each R^Z is independently halogen, -CN, -OH, -OR^{Za}, -N₃, -NR^{Za}R^{Zb}, -CO(O)R^{Zc}, -C(O)OR^{Zc}, -C(O)NR^{Za}R^{Zb}, -NR^{Za}C(O)R^{Zc}, C₁-C₁₀ alkyl, C₁-C₁₀ haloalkyl;

or two R^Z together with the atom(s) to which they are attached form a C₃-C₆ cycloalkyl;

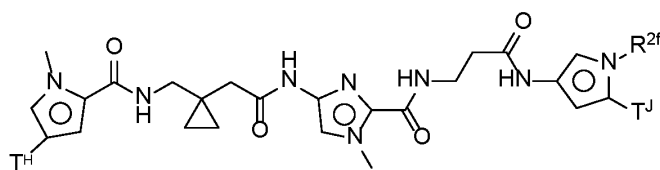
R^{Za} and R^{Zb} are each independently hydrogen, alkyl, haloalkyl, or PEG;

R^{Zc} is alkyl, haloalkyl, PEG, cycloalkyl, heterocycloalkyl, or phenyl; and

ss is 0, 1, or 2.

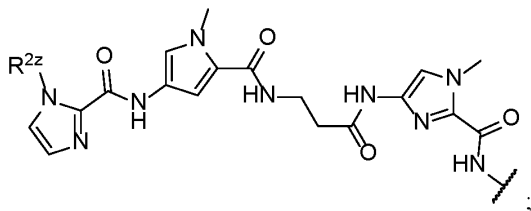
[00133] In some embodiments of Formula (VII) or (VIIa), ss is 1 or 2. In some embodiments, ss is 0. In some embodiments, ss is 1. In some embodiments, ss is 2.

[00134] In some embodiments, the DNA-binding moiety comprises the structure of Formula (VIII), or a pharmaceutically acceptable salt thereof:

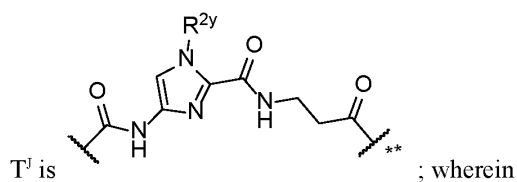


Formula (VIII),

wherein:



T^H is



R^{2y} and R^{2z} are each independently an optionally substituted C₁-C₂₀ alkyl wherein each is optionally substituted with one or more R^Z; and

** is the attachment point to the oligomeric linker;

R^{2f} is a C₃-C₁₀ cycloalkyl which is optionally substituted with one or more R^Z;

each R^Z is independently halogen, -CN, -OH, -OR^{Za}, -N₃, -NR^{Za}R^{Zb}, -CO(O)R^{Zc}, -C(O)OR^{Zc}, -C(O)NR^{Za}R^{Zb}, -NR^{Za}C(O)R^{Zc}, C₁-C₁₀ alkyl, or C₁-C₁₀ haloalkyl;

or two R^Z together with the atom(s) to which they are attached form a C₃-C₆ cycloalkyl, wherein

R^{Za} and R^{Zb} are each independently hydrogen, alkyl, haloalkyl, or PEG; and

R^{Zc} is alkyl, haloalkyl, PEG, cycloalkyl, heterocycloalkyl, or phenyl.

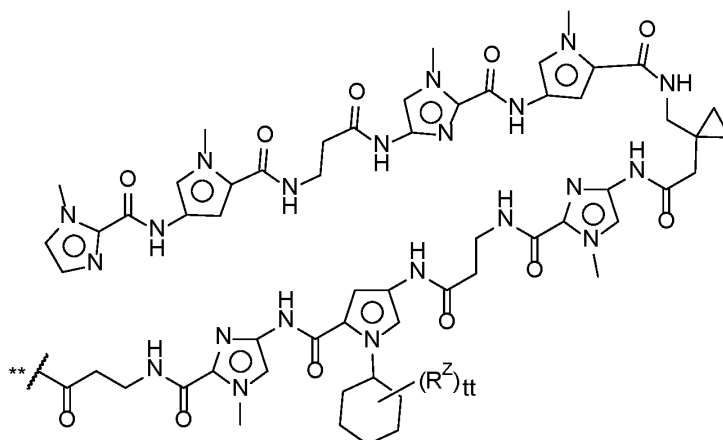
[00135] In some embodiments of Formula (VIII), R^{2f} is an optionally substituted monocyclic, spirocyclic, or bridge C₃-C₈ cycloalkyl, each of which is optionally substituted with one or more R^Z. In some embodiments, R^{2f} is an unsubstituted monocyclic C₆-C₈ cycloalkyl

[00136] In some embodiments of Formula (VIII), R^{2z} and R^{2y} are independently an optionally substituted C₁-C₈ alkyl, each of which is optionally substituted with one or more R^Z; wherein each R^Z is independently halogen, -OH, -OR^{Za}, or -NR^{Za}R^{Zb}.

[00137] In some embodiments of Formula (VIII), R^{2z} is an unsubstituted C₁-C₈ alkyl. In some embodiments R^{2z} methyl, ethyl, or isopropyl. In some embodiments, R^{2z} is methyl. In some embodiments, R^{2z} is isopropyl.

[00138] In some embodiments of Formula (VIII), R^{2y} is an unsubstituted C₁-C₈ alkyl. In some embodiments, R^{2y} methyl, ethyl, or isopropyl. In some embodiments, R^{2y} is methyl. In some embodiments, R^{2y} is isopropyl.

[00139] In some embodiments, the DNA-binding moiety of Formula (VIII) has the structure of Formula (VIIIa), or a pharmaceutically acceptable salt thereof:



Formula (VIIIa),

wherein:

each R^Z is independently halogen, -CN, -OH, -OR^{Za}, -N₃, -NR^{Za}R^{Zb}, -CO(O)R^{Zc}, -C(O)OR^{Zc}, -C(O)NR^{Za}R^{Zb}, -NR^{Za}C(O)R^{Zc}, C₁-C₁₀ alkyl, C₁-C₁₀ haloalkyl;

or two R^Z together with the atom(s) to which they are attached form a C₃-C₆ cycloalkyl;

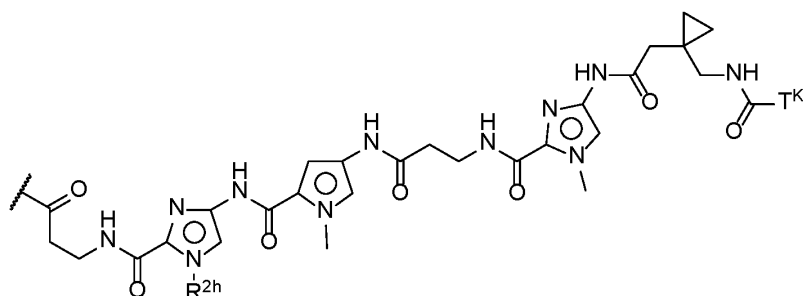
R^{Za} and R^{Zb} are each independently hydrogen, alkyl, haloalkyl, or PEG;

R^{Zc} is alkyl, haloalkyl, PEG, cycloalkyl, heterocycloalkyl, or phenyl; and

tt is 0, 1, or 2.

[00140] In some embodiments of Formula (VIII) or (VIIIa), tt is 1 or 2. In some embodiments, tt is 0. In some embodiments, tt is 1. In some embodiments, tt is 2.

[00141] In some embodiments, the DNA-binding moiety comprises the structure of Formula (IX), or a pharmaceutically acceptable salt thereof:

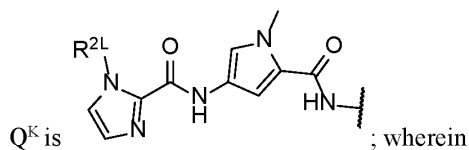
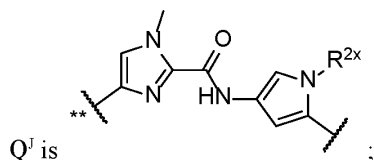


Formula (IX),

wherein:

T^K is $-Q^J-S^6-Q^K$; wherein

S⁶ is $\text{--NHC(O)(CH}_2\text{)}_2\text{--}$ or $\text{--(CH}_2\text{)}_2\text{C(O)NH--}$;



R^{2L} and R^{2X} are each independently an optionally substituted C₁-C₂₀ alkyl wherein each is optionally substituted with one or more R^Z; and

** is the attachment point to S group;

R^{2h} is a C₃-C₁₀ cycloalkyl which is optionally substituted with one or more R^Z ;

each R^Z is independently halogen, -CN, -OH, -OR^{Za}, -N₃, -NR^{Za}R^{Zb}, -CO(O)R^{Zc}, -C(O)OR^{Zc}, -C(O)NR^{Za}R^{Zb}, -NR^{Za}C(O)R^{Zc}, C₁-C₁₀ alkyl, or C₁-C₁₀ haloalkyl;

or two R^Z together with the atom(s) to which they are attached form a C₃-C₆ cycloalkyl, wherein

R^{Za} and R^{Zb} are each independently hydrogen, alkyl, haloalkyl, or PEG; and

R^{Zc} is alkyl, haloalkyl, PEG, cycloalkyl, heterocycloalkyl, or phenyl.

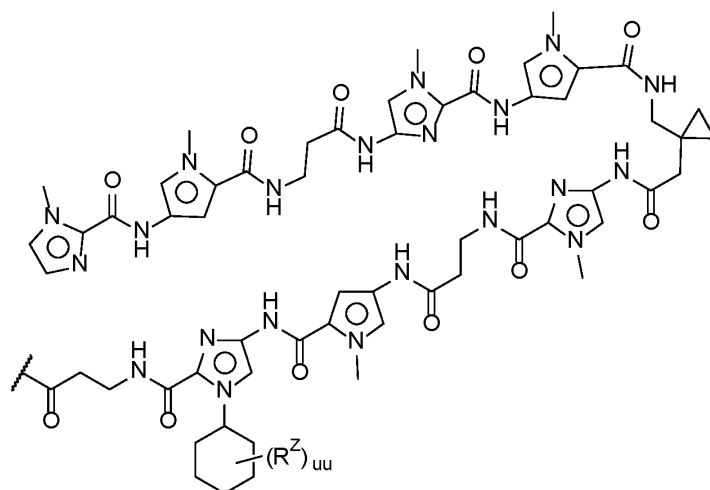
[00142] In some embodiments of Formula (IX), R^{2f} is an optionally substituted monocyclic, spirocyclic, or bridge C_3 - C_8 cycloalkyl, each of which is optionally substituted with one or more R^Z . In some embodiments, R^{2f} is an unsubstituted monocyclic C_6 - C_8 cycloalkyl.

[00143] In some embodiments of Formula (IX), R^{2x} and R^{2L} are independently an optionally substituted C_1 - C_8 alkyl, each of which is optionally substituted with one or more R^Z ; wherein each R^Z is independently halogen, -OH, -OR^{Za}, or -NR^{Za}R^{Zb}.

[00144] In some embodiments of Formula (IX), R^{2x} is an unsubstituted C_1 - C_8 alkyl. In some embodiments R^{2x} methyl, ethyl, or isopropyl. In some embodiments, R^{2x} is methyl. In some embodiments, R^{2x} is isopropyl.

[00145] In some embodiments of Formula (IX), R^{2L} is an unsubstituted C_1 - C_8 alkyl. In some embodiments, R^{2L} methyl, ethyl, or isopropyl. In some embodiments, R^{2L} is methyl. In some embodiments, R^{2L} is isopropyl.

[00146] In some embodiments, the DNA-binding moiety of Formula (IX) has the structure of Formula (IXa), or a pharmaceutically acceptable salt thereof



Formula (IXa),

wherein:

each R^Z is independently halogen, -CN, -OH, -OR^{Za}, -N₃, -NR^{Za}R^{Zb}, -CO(O)R^{Zc}, -C(O)OR^{Zc}, -C(O)NR^{Za}R^{Zb}, -NR^{Za}C(O)R^{Zc}, C_1 - C_{10} alkyl, C_1 - C_{10} haloalkyl;

or two R^Z together with the atom(s) to which they are attached form a C_3 - C_6 cycloalkyl;

R^{Za} and R^{Zb} are each independently hydrogen, alkyl, haloalkyl, or PEG;

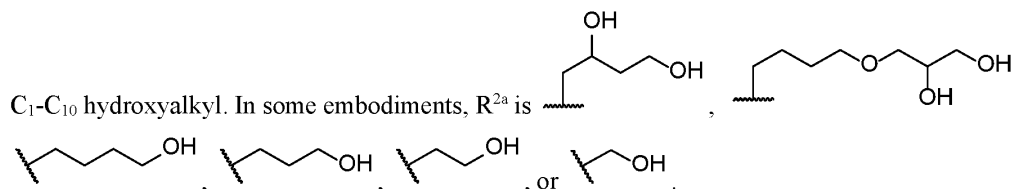
R^{Zc} is alkyl, haloalkyl, PEG, cycloalkyl, heterocycloalkyl, or phenyl; and

uu is 0, 1, or 2.

[00147] In some embodiments of Formula (IX) or (IXa), tt is 1 or 2. In some embodiments, tt is 0. In some embodiments, tt is 1. In some embodiments, tt is 2.

[00148] In some embodiments of any of Formulas (A-5) through (A-9), (I), (I-A), (I-A'), or (Iaa), R^{2a} 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} heteroalkyl, optionally substituted C_2 - C_{20} heteroalkenyl, optionally substituted C_2 - C_{20} heteroalkynyl, optionally substituted C_1 - C_{20} haloalkyl, optionally substituted C_1 - C_{20} hydroxyalkyl, optionally substituted C_3 - C_{10} cycloalkyl, or optionally substituted 3 to 10-membered heterocycloalkyl, each of which is optionally substituted with one or more R^Z . In some embodiments, R^{2a} is an optionally substituted C_1 - C_{10} alkylamino. In some embodiments, R^{2a} is an optionally substituted C_1 - C_{10} haloalkyl. In some embodiments, R^{2a} is an optionally substituted C_1 - C_{20} heteroalkyl. In some embodiments, R^{2a} is independently an optionally substituted C_1 - C_{10} heteroalkyl. In some embodiments, R^{2a} is an optionally substituted C_1 - C_{20} hydroxyalkyl. In some embodiments, R^{2a} is an optionally substituted C_1 - C_{10} hydroxyalkyl. In some embodiments, R^{2a} is an optionally substituted C_3 - C_{10} cycloalkyl or optionally substituted 3 to 10-membered heterocycloalkyl. In some embodiments, R^{2a} is hydrogen.

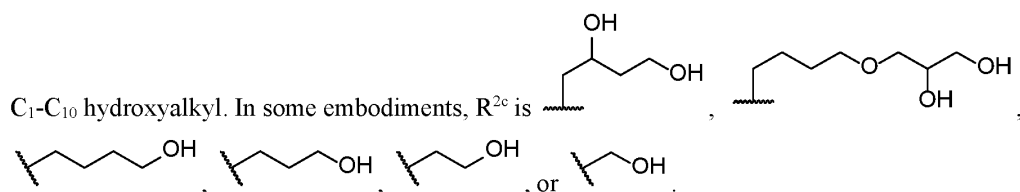
[00149] In some embodiments of any of Formulas (A-5) through (A-9), (I), (I'), (I-A), (Iaa), or (VII), R^{2a} is an optionally substituted C_1 - C_{20} alkyl. In some embodiments, R^{2a} is an optionally substituted C_1 - C_{10} alkyl. In some embodiments, R^{2a} is methyl, ethyl, propyl, butyl, propyl, hexyl, heptyl, or octyl. In some embodiments, R^{2a} is methyl, ethyl, isopropyl, isobutyl, sec-butyl, tert-butyl, n-propyl, n-hexyl, n-heptyl, or n-octyl. In some embodiments, R^{2a} is methyl. In some embodiments, R^{2a} is ethyl. In some embodiments, R^{2a} is isopropyl. In some embodiments, R^{2a} is butyl. In some embodiments, R^{2a} is pentyl. In some embodiments, R^{2a} is hexyl. In some embodiments, R^{2a} is heptyl. In some embodiments, R^{2a} is an optionally substituted C_1 - C_{20} haloalkyl. In some embodiments, R^{2a} is an optionally substituted C_1 - C_{10} haloalkyl. In some embodiments, R^{2a} is $-CF_3$, $-CH_2CF_3$, or $-CH_2CH_2CF_3$. In some embodiments, R^{2a} is an optionally substituted



[00150] In some embodiments of any of Formulas (A-5) through (A-9), R^{2b} 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} heteroalkyl, optionally substituted C_2 - C_{20} heteroalkenyl, optionally substituted C_2 - C_{20} heteroalkynyl, optionally substituted C_1 - C_{20} haloalkyl, optionally substituted C_1 - C_{20} hydroxyalkyl, optionally substituted C_3 - C_{10} cycloalkyl, or optionally substituted 3 to 10-membered heterocycloalkyl, each of which is optionally substituted with one or more R^Z . In some embodiments, R^{2b} is an optionally substituted C_1 - C_{10} alkylamino. In some embodiments, R^{2b} is an optionally substituted C_1 - C_{10} haloalkyl. In some embodiments, R^{2b} is an optionally substituted C_1 - C_{20} heteroalkyl. In some embodiments, R^{2b} is an optionally substituted C_1 - C_{10} heteroalkyl. In some embodiments, R^{2b} is an optionally substituted C_1 - C_{20} hydroxyalkyl. In some embodiments, R^{2b} is an

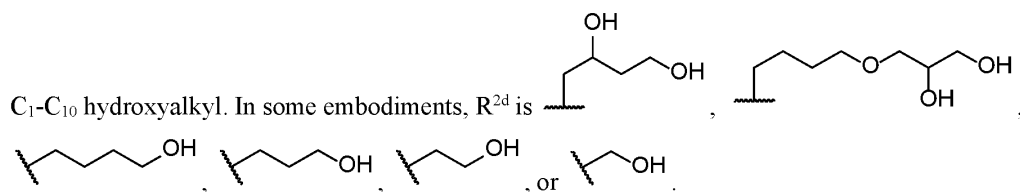
optionally substituted C₃-C₁₀ cycloalkyl or optionally substituted 3 to 10-membered heterocycloalkyl. In some embodiments, R^{2b} is hydrogen.

[00151] In some embodiments of any of Formulas (A-5) through (A-9), R^{2b} is an optionally substituted C₁-C₂₀ alkyl. In some embodiments, R^{2b} is an optionally substituted C₁-C₁₀ alkyl. In some embodiments, R^{2b} is methyl, ethyl, propyl, butyl, propyl, hexyl, heptyl, or octyl. In some embodiments, R^{2b} is methyl, ethyl, isopropyl, isobutyl, sec-butyl, tert-butyl, n-propyl, n-hexyl, n-heptyl, or n-octyl. In some embodiments, R^{2b} is methyl. In some embodiments, R^{2b} is ethyl. In some embodiments, R^{2b} is isopropyl. In some embodiments, R^{2b} is butyl. In some embodiments, R^{2b} is pentyl. In some embodiments, R^{2b} is hexyl. In some embodiments, R^{2b} is heptyl. In some embodiments, R^{2b} is an optionally substituted C₁-C₂₀ haloalkyl. In some embodiments, R^{2b} is an optionally substituted C₁-C₁₀ haloalkyl. In some embodiments, R^{2b} is -CF₃, -CH₂CF₃, or -CH₂CH₂CF₃. In some embodiments, R^{2b} is an optionally substituted C₁-C₁₀ hydroxyalkyl. In some



[00154] In some embodiments of any of Formulas (A-5) through (A-9), (I), (I'), (I-A), (I-A'), or (Icc), R^{2d} 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 heteroalkyl, optionally substituted C₂-C₂₀ heteroalkenyl, optionally substituted C₂-C₂₀ heteroalkynyl, optionally substituted C₁-C₂₀ haloalkyl, optionally substituted C₁-C₂₀ hydroxyalkyl, optionally substituted C₃-C₁₀ cycloalkyl, or optionally substituted 3 to 10-membered heterocycloalkyl, each of which is optionally substituted with one or more R^Z. In some embodiments, R^{2d} is an optionally substituted C₁-C₁₀ alkylamino. In some embodiments, R^{2d} is an optionally substituted C₁-C₁₀ haloalkyl. In some embodiments, R^{2d} is an optionally substituted C₁-C₂₀ heteroalkyl. In some embodiments, R^{2d} is independently an optionally substituted C₁-C₁₀ heteroalkyl. In some embodiments, R^{2d} is an optionally substituted C₁-C₂₀ hydroxyalkyl. In some embodiments, R^{2d} is an optionally substituted C₁-C₁₀ hydroxyalkyl. In some embodiments, R^{2d} is an optionally substituted C₃-C₁₀ cycloalkyl or optionally substituted 3 to 10-membered heterocycloalkyl. In some embodiments, R^{2d} is hydrogen.

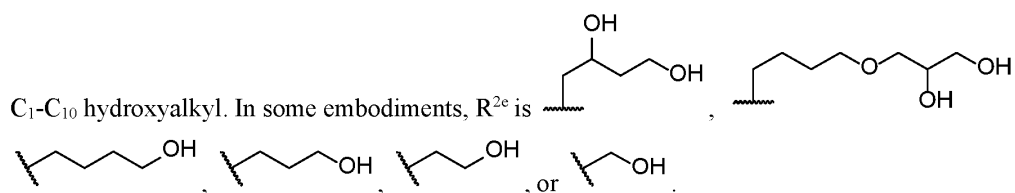
[00155] In some embodiments of any of Formulas (A-1) through (A-9), (I), (I'), (I-A), (Icc), (II), or (III), R^{2d} is an optionally substituted C₁-C₂₀ alkyl. In some embodiments, R^{2a} is an optionally substituted C₁-C₁₀ alkyl. In some embodiments, R^{2d} is methyl, ethyl, propyl, butyl, propyl, hexyl, heptyl, or octyl. In some embodiments, R^{2d} is methyl, ethyl, isopropyl, isobutyl, sec-butyl, tert-butyl, n-propyl, n-hexyl, n-heptyl, or n-octyl. In some embodiments, R^{2d} is methyl. In some embodiments, R^{2d} is ethyl. In some embodiments, R^{2d} is isopropyl. In some embodiments, R^{2d} is butyl. In some embodiments, R^{2d} is pentyl. In some embodiments, R^{2d} is hexyl. In some embodiments, R^{2d} is heptyl. In some embodiments, R^{2d} is an optionally substituted C₁-C₂₀ haloalkyl. In some embodiments, R^{2d} is an optionally substituted C₁-C₁₀ haloalkyl. In some embodiments, R^{2d} is -CF₃, -CH₂CF₃, or -CH₂CH₂CF₃. In some embodiments, R^{2d} is an optionally substituted



[00156] In some embodiments of any of Formulas (A-5) through (A-9), (I), (I-A), (I-A'), or (Idd), R^{2e} 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 heteroalkyl, optionally substituted C₂-C₂₀ heteroalkenyl, optionally substituted C₂-C₂₀ heteroalkynyl, optionally substituted C₁-C₂₀ haloalkyl, optionally substituted C₁-C₂₀ hydroxyalkyl, optionally substituted C₃-C₁₀ cycloalkyl, or optionally substituted 3 to 10-membered heterocycloalkyl, each of which is optionally

substituted with one or more R^Z . In some embodiments, R^{2e} is an optionally substituted C_1 - C_{10} alkylamino. In some embodiments, R^{2e} is an optionally substituted C_1 - C_{10} haloalkyl. In some embodiments, R^{2e} is an optionally substituted C_1 - C_{20} heteroalkyl. In some embodiments, R^{2e} is independently an optionally substituted C_1 - C_{10} heteroalkyl. In some embodiments, R^{2e} is an optionally substituted C_1 - C_{20} hydroxyalkyl. In some embodiments, R^{2e} is an optionally substituted C_1 - C_{10} hydroxyalkyl. In some embodiments, R^{2e} is an optionally substituted C_3 - C_{10} cycloalkyl or optionally substituted 3 to 10-membered heterocycloalkyl. In some embodiments, R^{2e} is hydrogen.

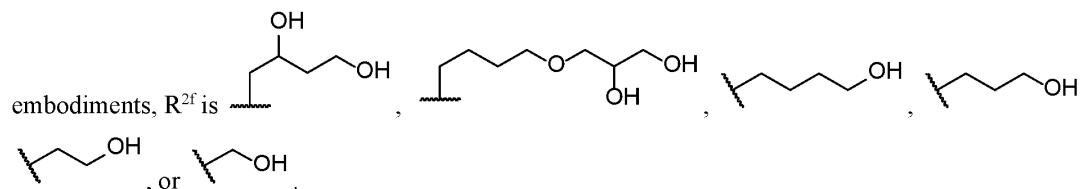
[00157] In some embodiments of any of Formulas (A-5) through (A-9), (I), (I'), (I-A), (I-A'), or (Idd), R^{2e} is an optionally substituted C_1 - C_{20} alkyl. In some embodiments, R^{2e} is an optionally substituted C_1 - C_{10} alkyl. In some embodiments, R^{2e} is methyl, ethyl, propyl, butyl, propyl, hexyl, heptyl, or octyl. In some embodiments, R^{2e} is methyl, ethyl, isopropyl, isobutyl, sec-butyl, tert-butyl, n-propyl, n-hexyl, n-heptyl, or n-octyl. In some embodiments, R^{2e} is methyl. In some embodiments, R^{2e} is ethyl. In some embodiments, R^{2e} is isopropyl. In some embodiments, R^{2e} is butyl. In some embodiments, R^{2e} is pentyl. In some embodiments, R^{2e} is hexyl. In some embodiments, R^{2e} is heptyl. In some embodiments, R^{2e} is an optionally substituted C_1 - C_{20} haloalkyl. In some embodiments, R^{2e} is an optionally substituted C_1 - C_{10} haloalkyl. In some embodiments, R^{2e} is $-CF_3$, $-CH_2CF_3$, or $-CH_2CH_2CF_3$. In some embodiments, R^{2e} is an optionally substituted



[00158] In some embodiments of any of Formulas (A-5), (A-6), or (A-7), R^{2f} 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} heteroalkyl, optionally substituted C_2 - C_{20} heteroalkenyl, optionally substituted C_2 - C_{20} heteroalkynyl, optionally substituted C_1 - C_{20} haloalkyl, optionally substituted C_1 - C_{20} hydroxyalkyl, optionally substituted C_3 - C_{10} cycloalkyl, or optionally substituted 3 to 10-membered heterocycloalkyl, each of which is optionally substituted with one or more R^Z . In some embodiments, R^{2f} is an optionally substituted C_1 - C_{10} alkylamino. In some embodiments, R^{2f} is an optionally substituted C_1 - C_{10} haloalkyl. In some embodiments, R^{2f} is an optionally substituted C_1 - C_{20} heteroalkyl. In some embodiments, R^{2f} is independently an optionally substituted C_1 - C_{10} heteroalkyl. In some embodiments, R^{2f} is an optionally substituted C_1 - C_{20} hydroxyalkyl. In some embodiments, R^{2f} is an optionally substituted C_1 - C_{10} hydroxyalkyl. In some embodiments, R^{2f} is an optionally substituted C_3 - C_{10} cycloalkyl or optionally substituted 3 to 10-membered heterocycloalkyl. In some embodiments, R^{2f} is hydrogen.

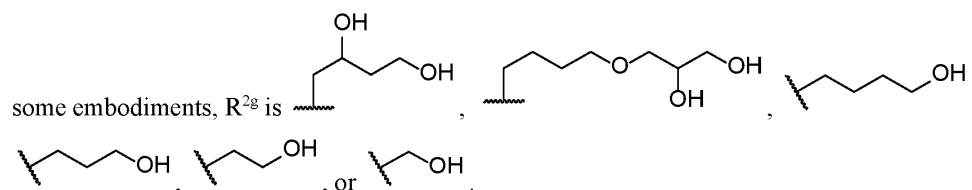
[00159] In some embodiments of any of Formulas (A-5), (A-6), or (A-7), R^{2f} is an optionally substituted C_1 - C_{20} alkyl. In some embodiments, R^{2f} is an optionally substituted C_1 - C_{10} alkyl. In some embodiments, R^{2f} is methyl, ethyl, propyl, butyl, propyl, hexyl, heptyl, or octyl. In some embodiments, R^{2f} is methyl, ethyl, isopropyl, isobutyl, sec-butyl, tert-butyl, n-propyl, n-hexyl, n-heptyl, or n-octyl. In some embodiments, R^{2f} is

methyl. In some embodiments, R^{2f} is ethyl. In some embodiments, R^{2f} is isopropyl. In some embodiments, R^{2f} is butyl. In some embodiments, R^{2f} is pentyl. In some embodiments, R^{2f} is hexyl. In some embodiments, R^{2f} is heptyl. In some embodiments, R^{2f} is an optionally substituted C₁-C₂₀ haloalkyl. In some embodiments, R^{2f} is an optionally substituted C₁-C₁₀ haloalkyl. In some embodiments, R^{2f} is -CF₃, -CH₂CF₃, or -CH₂CH₂CF₃. In some embodiments, R^{2f} is an optionally substituted C₁-C₁₀ hydroxyalkyl. In some



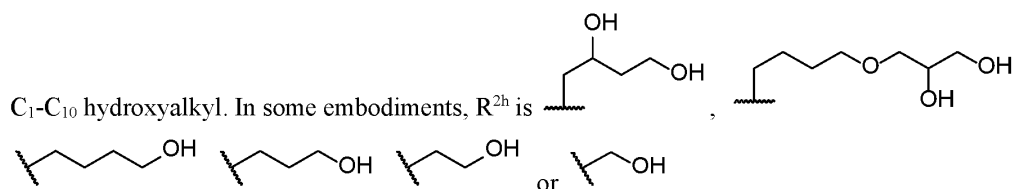
[00160] In some embodiments of any of Formulas (A-5), (A-6), (A-8), or (A-9), R^{2g} is hydrogen, optionally substituted C₁-C₂₀ alkyl, optionally substituted C₂-C₂₀ alkenyl, optionally substituted C₂-C₂₀ alkynyl, optionally substituted C₁-C₂₀ aminoalkyl, optionally substituted C₁-C₂₀ heteroalkyl, optionally substituted C₂-C₂₀ heteroalkenyl, optionally substituted C₂-C₂₀ heteroalkynyl, optionally substituted C₁-C₂₀ haloalkyl, optionally substituted C₁-C₂₀ hydroxyalkyl, optionally substituted C₃-C₁₀ cycloalkyl, or optionally substituted 3 to 10-membered heterocycloalkyl, each of which is optionally substituted with one or more R^Z. In some embodiments, R^{2g} is an optionally substituted C₁-C₁₀ alkylamino. In some embodiments, R^{2g} is an optionally substituted C₁-C₁₀ haloalkyl. In some embodiments, R^{2g} is an optionally substituted C₁-C₂₀ heteroalkyl. In some embodiments, R^{2g} is independently an optionally substituted C₁-C₁₀ heteroalkyl. In some embodiments, R^{2g} is an optionally substituted C₁-C₂₀ hydroxyalkyl. In some embodiments, R^{2g} is an optionally substituted C₁-C₁₀ hydroxyalkyl. In some embodiments, R^{2g} is an optionally substituted C₃-C₁₀ cycloalkyl or optionally substituted 3 to 10-membered heterocycloalkyl. In some embodiments, R^{2g} is hydrogen.

[00161] In some embodiments of any of Formulas (A-5), (A-6), (A-8), or (A-9), R^{2g} is an optionally substituted C₁-C₂₀ alkyl. In some embodiments, R^{2g} is an optionally substituted C₁-C₁₀ alkyl. In some embodiments, R^{2g} is methyl, ethyl, propyl, butyl, propyl, hexyl, heptyl, or octyl. In some embodiments, R^{2g} is methyl, ethyl, isopropyl, isobutyl, sec-butyl, tert-butyl, n-propyl, n-hexyl, n-heptyl, or n-octyl. In some embodiments, R^{2a} is methyl. In some embodiments, R^{2g} is ethyl. In some embodiments, R^{2g} is isopropyl. In some embodiments, R^{2g} is butyl. In some embodiments, R^{2g} is pentyl. In some embodiments, R^{2g} is hexyl. In some embodiments, R^{2g} is heptyl. In some embodiments, R^{2g} is an optionally substituted C₁-C₂₀ haloalkyl. In some embodiments, R^{2g} is an optionally substituted C₁-C₁₀ haloalkyl. In some embodiments, R^{2g} is -CF₃, -CH₂CF₃, or -CH₂CH₂CF₃. In some embodiments, R^{2g} is an optionally substituted C₁-C₁₀ hydroxyalkyl. In



[00162] In some embodiments of any of Formulas (A-5) through (A-9), (I), (I-A), (I-A'), or (Iee), R^{2h} 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} heteroalkyl, optionally substituted C_2 - C_{20} heteroalkenyl, optionally substituted C_2 - C_{20} heteroalkynyl, optionally substituted C_1 - C_{20} haloalkyl, optionally substituted C_1 - C_{20} hydroxyalkyl, optionally substituted C_3 - C_{10} cycloalkyl, or optionally substituted 3 to 10-membered heterocycloalkyl, each of which is optionally substituted with one or more R^Z . In some embodiments, R^{2h} is an optionally substituted C_1 - C_{10} alkylamino. In some embodiments, R^{2h} is an optionally substituted C_1 - C_{10} haloalkyl. In some embodiments, R^{2h} is an optionally substituted C_1 - C_{20} heteroalkyl. In some embodiments, R^{2h} is independently an optionally substituted C_1 - C_{10} heteroalkyl. In some embodiments, R^{2h} is an optionally substituted C_1 - C_{20} hydroxyalkyl. In some embodiments, R^{2h} is an optionally substituted C_1 - C_{10} hydroxyalkyl. In some embodiments, R^{2h} is an optionally substituted C_3 - C_{10} cycloalkyl or optionally substituted 3 to 10-membered heterocycloalkyl. In some embodiments, R^{2h} is hydrogen.

[00163] In some embodiments of any of Formulas (A-5) through (A-9), (I), (I'), (I-A), (I-A'), or (Iee), R^{2h} is an optionally substituted C_1 - C_{20} alkyl. In some embodiments, R^{2h} is an optionally substituted C_1 - C_{10} alkyl. In some embodiments, R^{2h} is methyl, ethyl, propyl, butyl, propyl, hexyl, heptyl, or octyl. In some embodiments, R^{2h} is methyl, ethyl, isopropyl, isobutyl, sec-butyl, tert-butyl, n-propyl, n-hexyl, n-heptyl, or n-octyl. In some embodiments, R^{2h} is methyl. In some embodiments, R^{2h} is ethyl. In some embodiments, R^{2h} is isopropyl. In some embodiments, R^{2h} is butyl. In some embodiments, R^{2h} is pentyl. In some embodiments, R^{2h} is hexyl. In some embodiments, R^{2h} is heptyl. In some embodiments, R^{2h} is an optionally substituted C_1 - C_{20} haloalkyl. In some embodiments, R^{2h} is an optionally substituted C_1 - C_{10} haloalkyl. In some embodiments, R^{2h} is $-CF_3$, $-CH_2CF_3$, or $-CH_2CH_2CF_3$. In some embodiments, R^{2h} is an optionally substituted



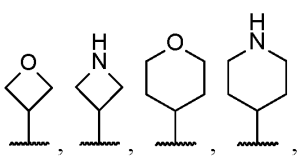
[00164] In some embodiments of any of Formulas (A-5) through (A-9), (I), (I-A), (I-A'), (Iaa), or (VI), R^{2a} is an optionally substituted C_3 - C_{10} cycloalkyl. In some embodiments, R^{2a} is optionally substituted C_3 - C_8 cycloalkyl. In some embodiments, R^{2a} is optionally substituted monocyclic, bicyclic, polycyclic, spirocyclic, or bridged cycloalkyl. In some embodiments, R^{2a} is optionally substituted monocyclic cycloalkyl. In some embodiments, R^{2a} is an optionally substituted spirocyclic cycloalkyl. In some embodiments, R^{2a} is an optionally substituted bridged cycloalkyl. In some embodiments, R^{2a} is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cyclohexyl. In some embodiments, R^{2a} is cyclopropyl. In some embodiments, R^{2a} is cyclobutyl. In some embodiments, R^{2a} is cyclopentyl. In some embodiments, R^{2a} is cyclohexyl. In some

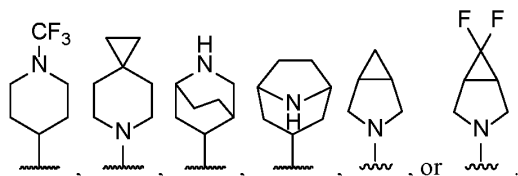
embodiments, R^{2a} is cyclohexyl. In some embodiments, R^{2a} is , , , , , , , , , , , , , , , or . In some embodiments, R^{2a} is an optionally substituted 3 to 10-membered heterocycloalkyl. In some embodiments, R^{2a} is an optionally substituted 3 to 8-membered heterocycloalkyl. In some embodiments, R^{2a} is a 3-membered, 4-membered, 5-

membered, or 6-membered heterocycloalkyl. In some embodiments, R^{2a} is , , , , , , , , , or .

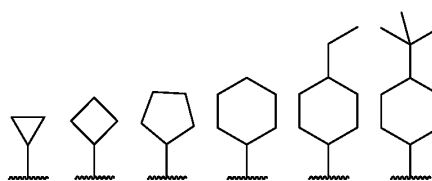
[00165] In some embodiments of any of Formulas (A-5) through (A-9), or (VII), R^{2b} is an optionally substituted C_3 - C_{10} cycloalkyl. In some embodiments, R^{2b} is optionally substituted C_3 - C_8 cycloalkyl. In some embodiments, R^{2b} is optionally substituted monocyclic, bicyclic, polycyclic, spirocyclic, or bridged cycloalkyl. In some embodiments, R^{2b} is optionally substituted monocyclic cycloalkyl. In some embodiments, R^{2b} is an optionally substituted spirocyclic cycloalkyl. In some embodiments, R^{2b} is an optionally substituted bridged cycloalkyl. In some embodiments, R^{2b} is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cyclohexyl. In some embodiments, R^{2b} is cyclopropyl. In some embodiments, R^{2b} is cyclobutyl. In some embodiments, R^{2b} is cyclopentyl. In some embodiments, R^{2b} is cyclohexyl. In some

embodiments, R^{2b} is cyclohexyl. In some embodiments, R^{2b} is , , , , , , , , , , , , , , , or . In some embodiments, R^{2b} is an optionally substituted 3 to 10-membered heterocycloalkyl. In some embodiments, R^{2b} is an optionally substituted 3 to 8-membered heterocycloalkyl. In some embodiments, R^{2b} is a 3-membered, 4-membered, 5-

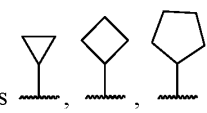
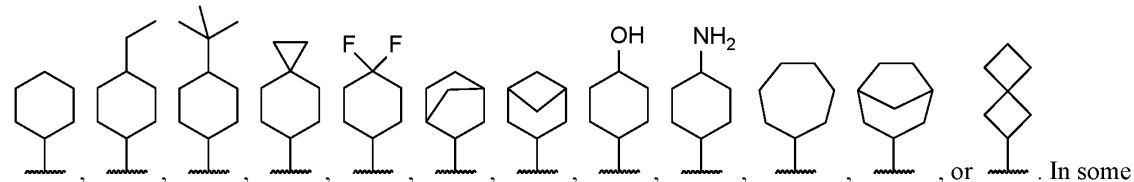
membered, or 6-membered heterocycloalkyl. In some embodiments, R^{2b} is ,

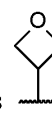


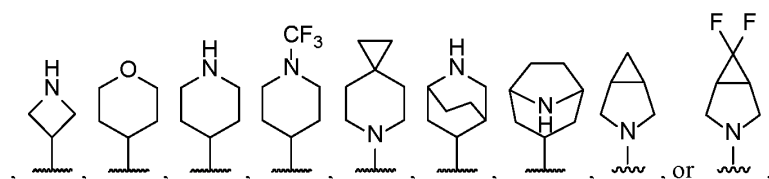
[00166] In some embodiments of any of Formulas (A-5) through (A-9), (I), (I'), (I-A), or (Ibb), R^{2c} is an optionally substituted C_3 - C_{10} cycloalkyl. In some embodiments, R^{2c} is optionally substituted C_3 - C_8 cycloalkyl. In some embodiments, R^{2c} is optionally substituted monocyclic, bicyclic, polycyclic, spirocyclic, or bridged cycloalkyl. In some embodiments, R^{2c} is optionally substituted monocyclic cycloalkyl. In some embodiments, R^{2c} is an optionally substituted spirocyclic cycloalkyl. In some embodiments, R^{2c} is an optionally substituted bridged cycloalkyl. In some embodiments, R^{2c} is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cyclohexyl. In some embodiments, R^{2c} is cyclopropyl. In some embodiments, R^{2c} is cyclobutyl. In some embodiments, R^{2c} is cyclopentyl. In some embodiments, R^{2c} is cyclohexyl. In some

embodiments, R^{2c} is cyclohexyl. In some embodiments, R^{2c} is , , , , , , , , , , , , ,

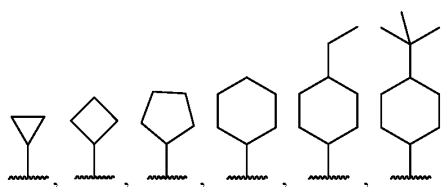
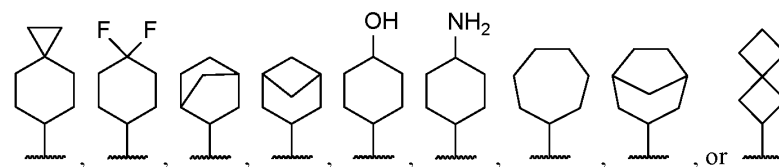
spirocyclic, or bridged cycloalkyl. In some embodiments, R^{2d} is optionally substituted monocyclic cycloalkyl. In some embodiments, R^{2d} is an optionally substituted spirocyclic cycloalkyl. In some embodiments, R^{2d} is an optionally substituted bridged cycloalkyl. In some embodiments, R^{2d} is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cyclohexyl. In some embodiments, R^{2d} is cyclopropyl. In some embodiments, R^{2d} is cyclobutyl. In some embodiments, R^{2d} is cyclopentyl. In some embodiments, R^{2d} is

cyclohexyl. In some embodiments, R^{2d} is cyclohexyl. In some embodiments, R^{2d} is , . In some embodiments, R^{2d} is an optionally substituted 3 to 10-membered heterocycloalkyl. In some embodiments, R^{2d} is an optionally substituted 3 to 8-membered heterocycloalkyl. In some embodiments, R^{2d} is a 3-

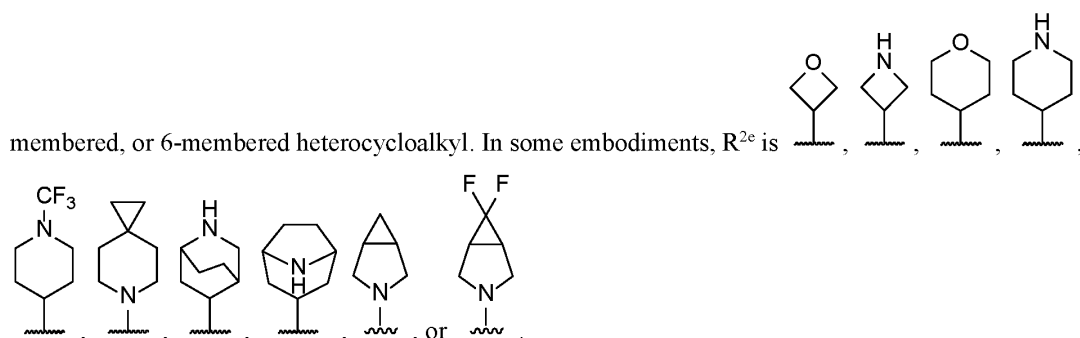
membered, 4-membered, 5-membered, or 6-membered heterocycloalkyl. In some embodiments, R^{2d} is 



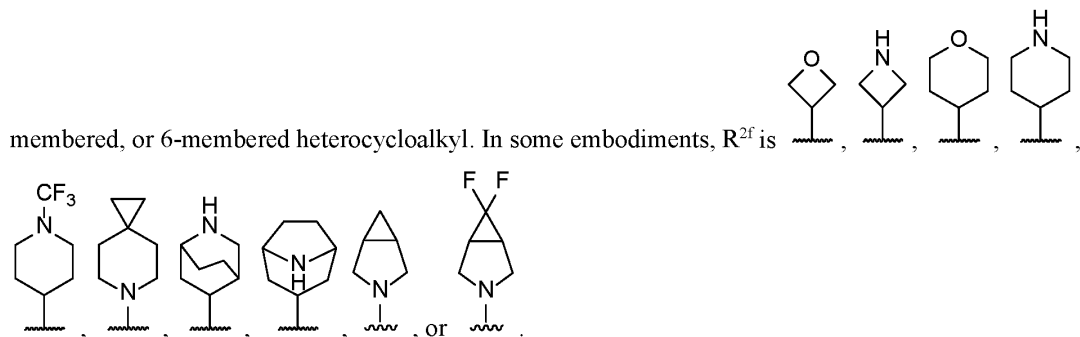
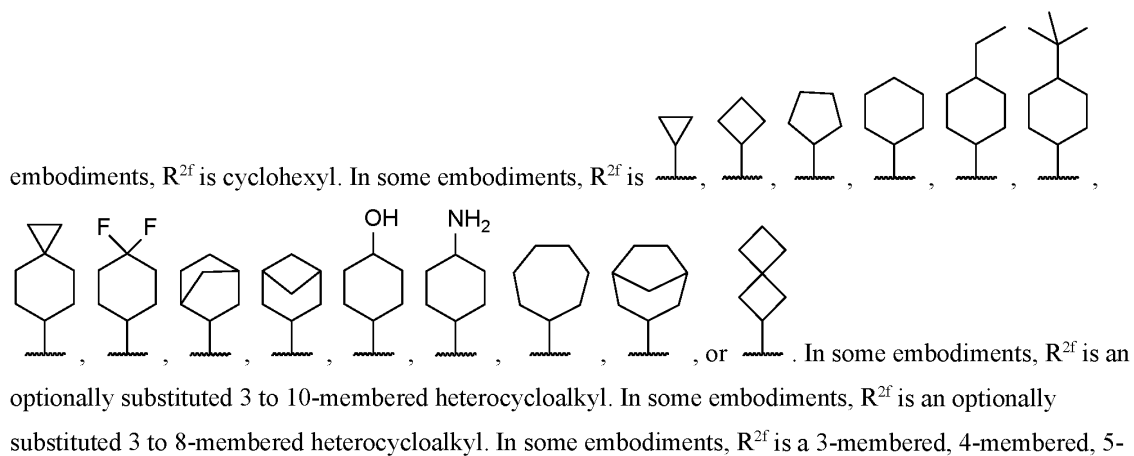
[00168] In some embodiments of any of Formulas (A-5) through (A-9), (I), (I'), (I-A), (Idd), or (V), R^{2e} is an optionally substituted C_3 - C_{10} cycloalkyl. In some embodiments, R^{2e} is optionally substituted C_3 - C_8 cycloalkyl. In some embodiments, R^{2e} is optionally substituted monocyclic, bicyclic, polycyclic, spirocyclic, or bridged cycloalkyl. In some embodiments, R^{2e} is optionally substituted monocyclic cycloalkyl. In some embodiments, R^{2e} is an optionally substituted spirocyclic cycloalkyl. In some embodiments, R^{2e} is an optionally substituted bridged cycloalkyl. In some embodiments, R^{2e} is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cyclohexyl. In some embodiments, R^{2e} is cyclopropyl. In some embodiments, R^{2e} is cyclobutyl. In some embodiments, R^{2e} is cyclopentyl. In some embodiments, R^{2e} is cyclohexyl. In some

embodiments, R^{2e} is cyclohexyl. In some embodiments, R^{2e} is , . In some embodiments, R^{2e} is an

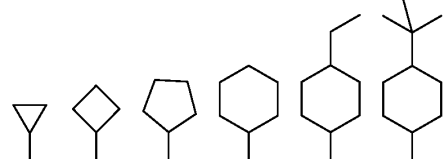
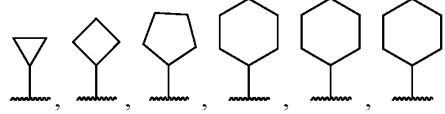
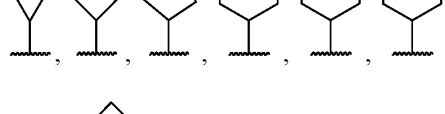
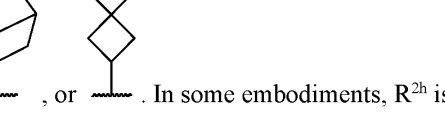
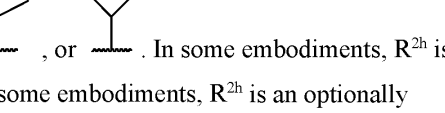
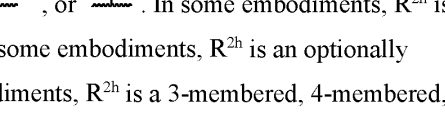
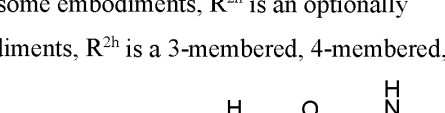
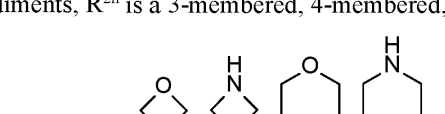
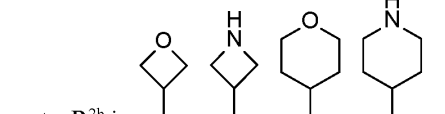
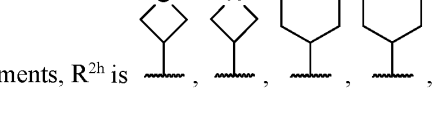
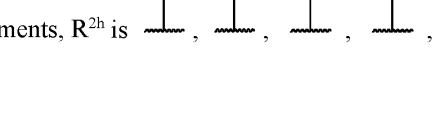
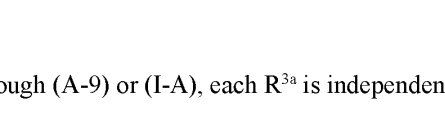
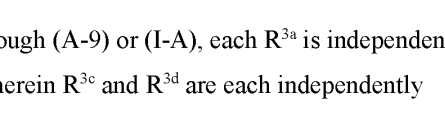
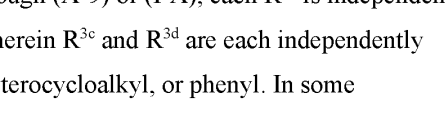
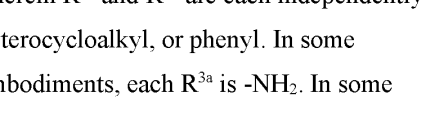
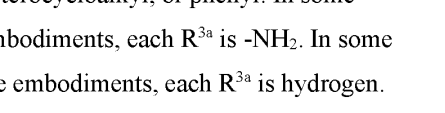
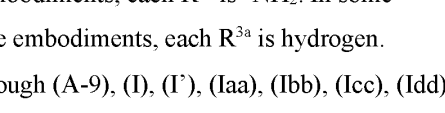
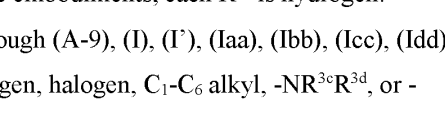
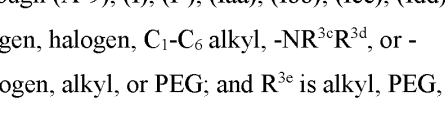
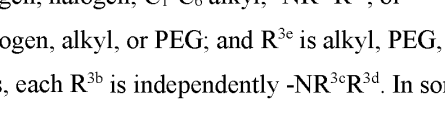
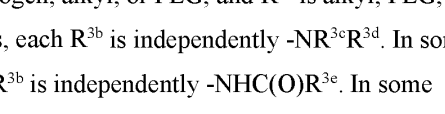
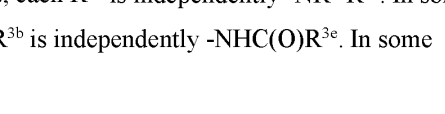
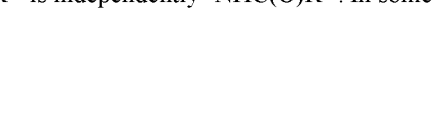
optionally substituted 3 to 10-membered heterocycloalkyl. In some embodiments, R^{2e} is an optionally substituted 3 to 8-membered heterocycloalkyl. In some embodiments, R^{2e} is a 3-membered, 4-membered, 5-

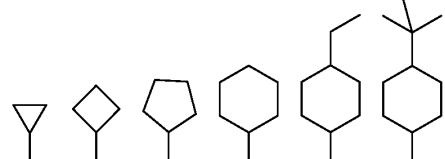
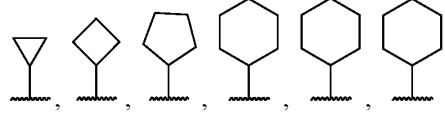
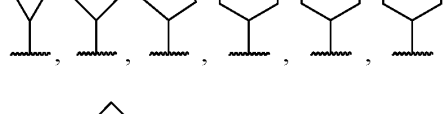
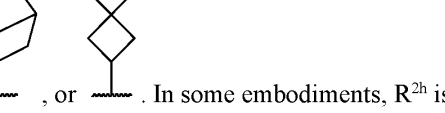
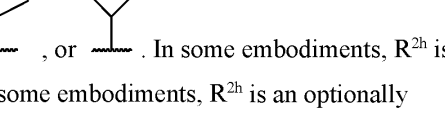
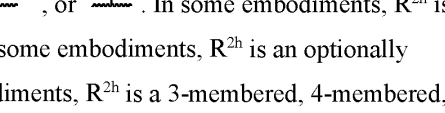
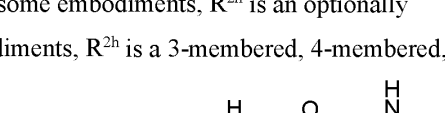
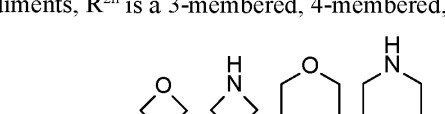
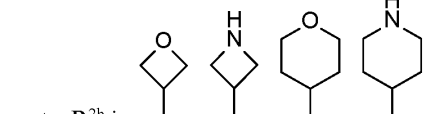
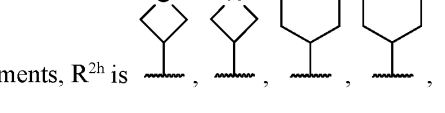
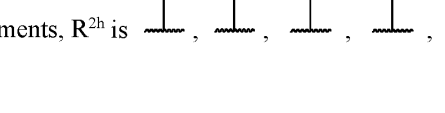
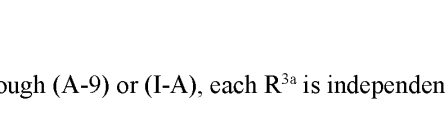
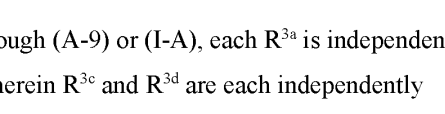
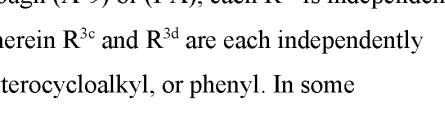
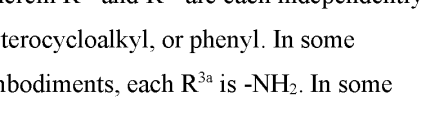
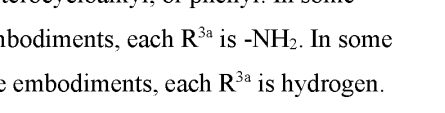
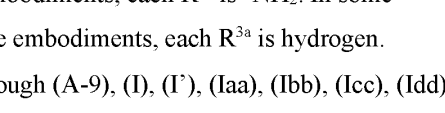
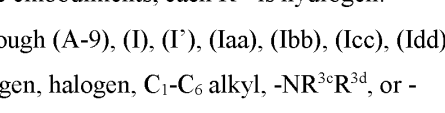
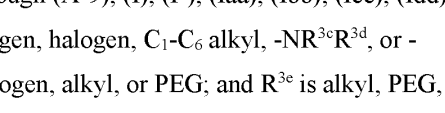
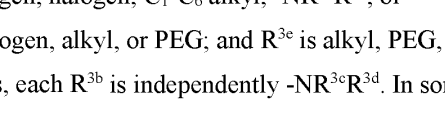
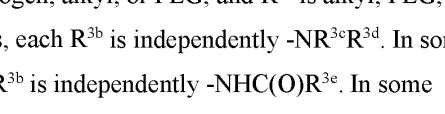
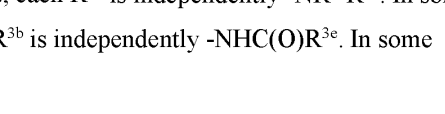
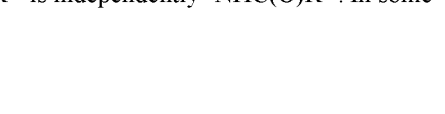


[00169] In some embodiments of any of Formulas (A-5) through (A-9), (I), (I'), (I-A), or (VIII), R^{2f} is an optionally substituted C_3 - C_{10} cycloalkyl. In some embodiments, R^{2f} is optionally substituted C_3 - C_8 cycloalkyl. In some embodiments, R^{2f} is optionally substituted monocyclic, bicyclic, polycyclic, spirocyclic, or bridged cycloalkyl. In some embodiments, R^{2f} is optionally substituted monocyclic cycloalkyl. In some embodiments, R^{2f} is an optionally substituted spirocyclic cycloalkyl. In some embodiments, R^{2f} is an optionally substituted bridged cycloalkyl. In some embodiments, R^{2f} is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cyclohexyl. In some embodiments, R^{2f} is cyclopropyl. In some embodiments, R^{2f} is cyclobutyl. In some embodiments, R^{2a} is cyclopentyl. In some embodiments, R^{2f} is cyclohexyl. In some



[00170] In some embodiments of any of Formulas (A-5) through (A-9), (I), (I-A), (I-A'), (Iee), or (IX), R^{2h} is an optionally substituted C_3 - C_{10} cycloalkyl. In some embodiments, R^{2h} is optionally substituted C_3 - C_8 cycloalkyl. In some embodiments, R^{2h} is optionally substituted monocyclic, bicyclic, polycyclic, spirocyclic, or bridged cycloalkyl. In some embodiments, R^{2h} is optionally substituted monocyclic cycloalkyl. In some embodiments, R^{2h} is an optionally substituted spirocyclic cycloalkyl. In some embodiments, R^{2h} is an optionally substituted bridged cycloalkyl. In some embodiments, R^{2h} is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cyclohexyl. In some embodiments, R^{2h} is cyclopropyl. In some embodiments, R^{2h} is cyclobutyl. In some embodiments, R^{2h} is cyclopentyl. In some embodiments, R^{2h} is cyclohexyl. In some

embodiments, R^{2h} is cyclohexyl. In some embodiments, R^{2h} is , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , . In some embodiments, R^{2h} is an optionally substituted 3 to 10-membered heterocycloalkyl. In some embodiments, R^{2h} is an optionally substituted 3 to 8-membered heterocycloalkyl. In some embodiments, R^{2h} is a 3-membered, 4-membered, 5-

membered, or 6-membered heterocycloalkyl. In some embodiments, R^{2h} is , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , 

[00171] In some embodiments of any of Formulas (A-2) through (A-9) or (I-A), each R^{3a} is independently hydrogen, halogen, C_1 - C_6 alkyl, $-NR^{3c}R^{3d}$, or $-NHC(O)R^{3e}$, wherein R^{3c} and R^{3d} are each independently hydrogen, alkyl, or PEG; and R^{3e} is alkyl, PEG, cycloalkyl, heterocycloalkyl, or phenyl. In some embodiments, each R^{3a} is independently $-NR^{3c}R^{3d}$. In some embodiments, each R^{3a} is $-NH_2$. In some embodiments, each R^{3a} is independently $-NHC(O)R^{3e}$. In some embodiments, each R^{3a} is hydrogen.

[00172] In some embodiments of any of Formulas (A-2) through (A-9), (I), (I'), (Iaa), (Ibb), (Icc), (Idd), (Iee), (II), (III), (VI) or (VII), each R^{3b} is independently hydrogen, halogen, C_1 - C_6 alkyl, $-NR^{3c}R^{3d}$, or $-NHC(O)R^{3e}$, wherein R^{3c} and R^{3d} are each independently hydrogen, alkyl, or PEG; and R^{3e} is alkyl, PEG, cycloalkyl, heterocycloalkyl, or phenyl. In some embodiments, each R^{3b} is independently $-NR^{3c}R^{3d}$. In some embodiments, each R^{3b} is $-NH_2$. In some embodiments, each R^{3b} is independently $-NHC(O)R^{3e}$. In some embodiments, each R^{3b} is hydrogen.

[00173] In some embodiments of any of Formulas (A-2) through (A-9), (I), (I'), (Iaa), (Ibb), (Icc), (Idd), (Iee), (II), (III), (VI), or (VII), each R^{3b} is independently hydrogen, -NH₂, or C₁-C₆ alkyl. In some embodiments, each R^{3b} is independently hydrogen or -NH₂. In some embodiments, each R^{3b} is hydrogen.

[00174] In some embodiments of any of Formulas (A-2) through (A-9) or (I-A), two R^{3a} together with the atoms to which they are attached form an optionally substituted C₃-C₆ cycloalkyl or 3 to 6-membered heterocycloalkyl. In some embodiments, two R^{3a} together with the atom(s) to which they are attached form a C₃-C₆ cycloalkyl. In some embodiments, two R^{3a} together with the atom(s) to which they are attached form a 4 to 6-membered heterocycloalkyl. In some embodiments, two R^{3a} together with the atom(s) to which they are attached form a 4-membered heterocycloalkyl. In some embodiments, two R^{3a} together with the atom(s) to which they are attached form a 5-membered heterocycloalkyl. In some embodiments, two R^{3a} together with the atom(s) to which they are attached form a 6-membered heterocycloalkyl. In some embodiments, two R^{3a} together with the atom(s) to which they are attached form a cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In some embodiments, two R^{3a} together with the atom(s) to which they are attached form a cyclopropyl. In some embodiments, two R^{3a} together with the atom(s) to which they are attached form a cyclobutyl. In some embodiments, two R^{3a} together with the atom(s) to which they are attached form a cyclopentyl. In some embodiments, two R^{3a} together with the atom(s) to which they are attached form a cyclohexyl.

[00175] In some embodiments of any of Formulas (A-2) through (A-9), (I), (I'), (Iaa), (Ibb), (Icc), (Idd), (Iee), (II), (III), (VI), or (VII), two R^{3b} together with the atoms to which they are attached form an optionally substituted C₃-C₆ cycloalkyl or 3 to 6-membered heterocycloalkyl. In some embodiments, two R^{3b} together with the atom(s) to which they are attached form a C₃-C₆ cycloalkyl. In some embodiments, two R^{3b} together with the atom(s) to which they are attached form a 4 to 6-membered heterocycloalkyl. In some embodiments, two R^{3b} together with the atom(s) to which they are attached form a 4-membered heterocycloalkyl. In some embodiments, two R^{3b} together with the atom(s) to which they are attached form a 5-membered heterocycloalkyl. In some embodiments, two R^{3b} together with the atom(s) to which they are attached form a 6-membered heterocycloalkyl. In some embodiments, two R^{3b} together with the atom(s) to which they are attached form a cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In some embodiments, two R^{3b} together with the atom(s) to which they are attached form a cyclopropyl. In some embodiments, two R^{3b} together with the atom(s) to which they are attached form a cyclobutyl. In some embodiments, two R^{3b} together with the atom(s) to which they are attached form a cyclopentyl. In some embodiments, two R^{3b} together with the atom(s) to which they are attached form a cyclohexyl.

[00176] In some embodiments of Formula (A-2), one R^{3a} and one R^{3b} together with the atoms to which they are attached form a C₃-C₆ cycloalkyl or 4 to 6-membered heterocycloalkyl. In some embodiments, one R^{3a} and one R^{3b} together with the atoms to which they are attached form a C₃-C₆ cycloalkyl. In some embodiments, one R^{3a} and one R^{3b} together with the atoms to which they are attached form a 4 to 6-membered heterocycloalkyl.

[00177] In some embodiments of any of Formulas (A-2) through (A-9), R^{3c} and R^{3d} are each independently hydrogen, alkyl, or PEG. In some embodiments, R^{3c} and R^{3d} are each independently hydrogen, C_1 - C_{20} alkyl, or PEG_{1-20} . In some embodiments, R^{3c} and R^{3d} are each independently C_1 - C_{20} alkyl. In some embodiments, R^{3c} and R^{3d} are each independently hydrogen.

[00178] In some embodiments of any of Formulas (A-2) through (A-9), R^{3e} is alkyl, PEG, cycloalkyl, heterocycloalkyl, or phenyl. In some embodiments, R^{3e} is C_1 - C_{20} alkyl, PEG_{1-20} , C_3 - C_6 cycloalkyl, 4 to 6-membered heterocycloalkyl, or phenyl. In some embodiments, R^{3e} is C_1 - C_{20} alkyl or PEG_{1-20} . In some embodiments, R^{3e} is C_3 - C_6 cycloalkyl, 4 to 6-membered heterocycloalkyl, or phenyl. In some embodiments, R^{3e} is C_1 - C_{20} alkyl.

[00179] In some embodiments of any of Formulas (A-5) through (A-9), (I), (I-A), (I-A'), (I'), (Iaa), (Ibb), (Icc), (Id), (Iee), (II), (IIa), (III), (IIIa), (IV), (IVa), (V), (Va), (VI), (VIa), (VII), (VIIa), (VIII), (VIIIa), (IX), or (IXa), each R^Z is independently halogen, -CN, -OH, -OR^{Za}, -N₃, -NR^{Za}R^{Zb}, -CO(O)R^{Zc}, -C(O)OR^{Zc}, -C(O)NR^{Za}R^{Zb}, -NR^{Za}C(O)R^{Zc}, C_1 - C_{10} alkyl, C_1 - C_{10} haloalkyl, C_1 - C_{10} heteroalkyl, C_3 - C_{10} cycloalkyl, 3 to 10-membered heterocycloalkyl, phenyl, or optionally 5 to 10-membered heteroaryl. In some embodiments, each R^Z is independently -CN, -OH, -OR^{Za}, -N₃, -NR^{Za}R^{Zb}, -CO(O)R^{Zc}, -C(O)OR^{Zc}, -C(O)NR^{Za}R^{Zb}, -NHC(O)R^{Zc}, -NHC(O)OR^{Zc}, -OC(O)NR^{Za}R^{Zb}, or optionally substituted 5 to 10-membered heteroaryl. In some embodiments, each R^Z is independently -CN, -OH, -OR^{Za}, -N₃, or -NR^{Za}R^{Zb}. In some embodiments, each R^Z is independently -C(O)NR^{Za}R^{Zb}, -NHC(O)R^{Zc}, or -OC(O)NR^{Za}R^{Zb}. In some embodiments, each R^Z is independently halogen, C_1 - C_{10} alkyl, or C_1 - C_{10} haloalkyl. In some embodiments, each R^Z is independently halogen. In some embodiments, each R^Z is independently C_1 - C_{10} alkyl. In some embodiments, each R^Z is independently C_1 - C_{10} haloalkyl.

[00180] In some embodiments of any of Formulas (A-5) through (A-9), (I), (I-A), (I-A'), (I'), (Iaa), (Ibb), (Icc), (Id), (Iee), (II), (IIa), (III), (IIIa), (IV), (IVa), (V), (Va), (VI), (VIa), (VII), (VIIa), (VIII), (VIIIa), (IX), or (IXa), each R^Z is independently halogen, -OH, -OR^{Za}, -NR^{Za}R^{Zb}, or C_1 - C_6 alkyl. In some embodiments, each R^Z is independently -F, -OH, -NH₂, -NHCH₃, -N(CH₃)₂, -CH₃, -CH₂CH₃, -CH(CH₃)₂, or -C(CH₃)₃. In some embodiments, each R^Z is independently -F, -OH, -NH₂, -NHCH₃, or -N(CH₃)₂. In some embodiments, each R^Z is independently -F or -OH. In some embodiments, each R^Z is independently -CH₃, -CH₂CH₃, -CH(CH₃)₂, or -C(CH₃)₃. In some embodiments, each R^Z is -F. In some embodiments, each R^Z is -OH.

[00181] In some embodiments of any of Formulas (A-5) through (A-9), (I), (I-A), (I-A'), (I'), (Iaa), (Ibb), (Icc), (Id), (Iee), (II), (IIa), (III), (IIIa), (IV), (IVa), (V), (Va), (VI), (VIa), (VII), (VIIa), (VIII), (VIIIa), (IX), or (IXa), each R^{Za} and R^{Zb} is independently hydrogen, alkyl, or PEG. In some embodiments, each R^{Za} and R^{Zb} is independently hydrogen, C_1 - C_{20} alkyl, or PEG_{1-20} . In some embodiments, each R^{Za} and R^{Zb} is independently C_1 - C_{20} alkyl. In some embodiments, each R^{Za} and R^{Zb} is independently hydrogen.

[00182] In some embodiments of any of Formulas (A-5) through (A-9), (I), (I-A), (I-A'), (I'), (Iaa), (Ibb), (Icc), (Id), (Iee), (II), (IIa), (III), (IIIa), (IV), (IVa), (V), (Va), (VI), (VIa), (VII), (VIIa), (VIII), (VIIIa), (IX), or (IXa), R^{Zc} is alkyl, PEG, cycloalkyl, heterocycloalkyl, or phenyl. In some embodiments, R^{Zc} is C_1 -

C₂₀ alkyl, PEG₁₋₂₀, C₃-C₆ cycloalkyl, 4 to 6-membered heterocycloalkyl, or phenyl. In some embodiments, R^{Zc} is C₁-C₂₀ alkyl or PEG₁₋₂₀. In some embodiments, R^{Zc} is C₁-C₂₀ alkyl.

[00183] The binding affinity between the polyamide and the target gene can be adjusted based on the composition of the polyamide. In some embodiments, the polyamide is capable of binding the DNA with an affinity of less than about 600 nM, about 500 nM, about 400 nM, about 300 nM, about 250 nM, about 200 nM, about 150 nM, about 100 nM, or about 50 nM. In some embodiments, the polyamide is capable of binding the DNA with an affinity of less than about 300 nM. In some embodiments, the polyamide is capable of binding the DNA with an affinity of less than about 200 nM. In some embodiments, the polyamide is capable of binding the DNA with an affinity of greater than about 200 nM, about 150 nM, about 100 nM, about 50 nM, about 10 nM, or about 1 nM. In some embodiments, the polyamide is capable of binding the DNA with an affinity in the range of about 1-600 nM, 10-500 nM, 20-500 nM, 50-400 nM, or 100-300 nM.

[00184] In some embodiments, the first terminus is capable of binding the DNA with an affinity of less than 500 nM.

[00185] The binding affinity between the polyamide and the target DNA can be determined using a quantitative footprint titration experiment. The experiment involves measuring the dissociation constant K_d of the polyamide for the target sequence at either 24 °C or 37 °C, and using either standard polyamide assay solution conditions or approximate intracellular solution conditions.

[00186] The binding affinity between the regulatory protein and the ligand on the second terminus can be determined using an assay suitable for the specific protein. The experiment involves measuring the dissociation constant K_d of the ligand for the protein and using either standard protein assay solution conditions or approximate intracellular solution conditions.

[00187] The polyamide composed of a pre-selected combination of subunits can selectively bind to the DNA in the minor groove. In their hairpin structure, antiparallel side-by-side pairings of two aromatic amino acids bind to DNA sequences, with a polyamide ring packed specifically against each DNA base.

Second Terminus – Regulatory Protein Binding Moiety

[00188] In some embodiments, the second terminus comprises a protein-binding moiety capable of binding to a regulatory molecule that modulates expression of a gene having an expanded nucleotide repeat.

[00189] In some embodiments, the second terminus comprises a bromodomain binding moiety.

[00190] In some embodiments, the second terminus comprises a moiety capable of binding to a bromodomain and extra terminal domain (BET) family member.

[00191] In some embodiments, the BET family member is BRD2, BRD3, BRD4, or BRDT. In some embodiments, the BET family member is BRD2. In some embodiments, the BET family member is BRD3. In some embodiments, the BET family member is BRD4. In some embodiments, the BET family member is BRDT.

[00192] In some embodiments, the protein-binding moiety binds to CBP/p300, PCAF (P300/CBP-Associated Factor), CECR2 (cat eye syndrome chromosome region candidate 2), BRPF (bromodomain and

PHD finger-containing protein), ATAD2/ATAD2B (chromatin remodeling proteins), TRIM24 (Tripartite motif-containing 24), BAZ2 (Bromodomain Adjacent to Zinc finger), TAF1 (TBP associated factors), BRD7/9, BPTF (Bromodomain PHD Finger Transcription Factor), SMARCA2/4, or PBRM1.

[00193] In some embodiments, the regulatory molecule is CBP/p300.

[00194] In some embodiments, the regulatory molecule is PCAF (P300/CBP-Associated Factor).

[00195] In some embodiments, the regulatory molecule is CECR2 (cat eye syndrome chromosome region candidate 2).

[00196] In some embodiments, the regulatory molecule is BRPF (bromodomain and PHD finger-containing protein).

[00197] In some embodiments, the regulatory molecule is a ATAD2 or ATAD2B chromatin remodeling protein.

[00198] In some embodiments, the regulatory molecule is BAZ2 (Bromodomain Adjacent Zinc Finger).

[00199] In some embodiments, the regulatory molecule is TAF1 (TBP associated factor).

[00200] In some embodiments, the regulatory molecule is TRIM24 (tripartite motif-containing 24).

[00201] In some embodiments, the regulatory molecule is BRD7/9.

[00202] In some embodiments, the regulatory molecule is BPTF (Bromodomain PHD Finger Transcription Factor).

[00203] In some embodiments, the regulatory molecule is SMARCA2/4.

[00204] In some embodiments, the regulatory molecule is PBRM1.

[00205] In some embodiments, the regulatory molecule modulates the rearrangement of histones.

[00206] In some embodiments, the regulatory molecule modulates the glycosylation, phosphorylation, alkylation, or acylation of histones.

[00207] In some embodiments, the regulatory molecule is a transcription factor.

[00208] In some embodiments, the regulatory molecule is an RNA polymerase.

[00209] In some embodiments, the regulatory molecule is a moiety that regulates the activity of RNA polymerase.

[00210] In some embodiments, the recruiting moiety binds to the regulatory molecule but does not inhibit the activity of the regulatory molecule. In some embodiments, the recruiting moiety binds to the regulatory molecule and inhibits the activity of the regulatory molecule. In some embodiments, the recruiting moiety binds to the regulatory molecule and increases the activity of the regulatory molecule.

[00211] In some embodiments, the recruiting moiety binds to the active site of the regulatory molecule. In certain embodiments, the recruiting moiety binds to a regulatory site of the regulatory molecule.

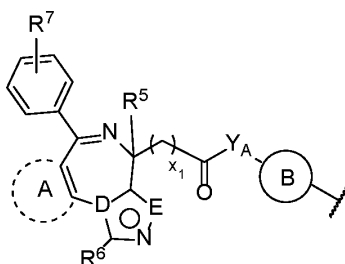
[00212] The binding affinity between the regulatory protein and the second terminus can be adjusted based on the composition of the molecule or type of protein. In some embodiments, the second terminus binds the regulatory molecule with an affinity of less than about 600 nM, about 500 nM, about 400 nM, about 300 nM, about 250 nM, about 200 nM, about 150 nM, about 100 nM, or about 50nM. In some embodiments, the

second terminus binds the regulatory molecule with an affinity of less than about 500 nM. In some embodiments, the second terminus binds the regulatory molecule with an affinity of less than about 400 nM. In some embodiments, the second terminus binds the regulatory molecule with an affinity of less than about 300 nM. In some embodiments, the second terminus binds the regulatory molecule with an affinity of less than about 250 nM. In some embodiments, the second terminus binds the regulatory molecule with an affinity of less than about 200 nM. In some embodiments, the second terminus binds the regulatory molecule with an affinity of less than about 150 nM. In some embodiments, the second terminus binds the regulatory molecule with an affinity of less than about 100 nM. In some embodiments, the second terminus binds the regulatory molecule with an affinity of less than about 50 nM.

[00213] In some embodiments, the second terminus comprises a diazine or diazepine ring, wherein the diazine or diazepine ring is fused with a C₆-C₁₀ aryl or a 5 to 10-membered heteroaryl ring comprising one or more heteroatoms selected from S, N and O. In some embodiments, the second terminus comprises an optionally substituted bicyclic or tricyclic structure.

[00214] In some embodiments, the second terminus has a triazolodiazepine structure. In some embodiments, the second terminus has a thiazolodiazepine structure.

[00215] In some embodiments, the second terminus comprises the structure of Formula (2-A), or a pharmaceutically acceptable salt thereof:



Formula (2-A),

wherein:

Ring A is an optionally substituted aryl or optionally substituted 5 to 6-membered heteroaryl;

Ring B is absent or an optionally substituted 6-membered monocyclic aryl or heteroaryl;

D is C or N;

E is O or N;

Y_A is -NH- or -O-;

R⁵ is hydrogen or C₁-C₆ alkyl;

R⁶ is selected from hydrogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ haloalkyl, and optionally substituted C₁-C₆ hydroxyalkyl;

R⁷ is selected from hydrogen, halogen, -NO₂, -CN, optionally substituted aryl, optionally substituted C₁-C₂₀ alkyl, optionally substituted C₁-C₂₀ heteroalkyl, optionally substituted C₁-C₆ haloalkyl, and optionally substituted C₁-C₆ hydroxyalkyl;

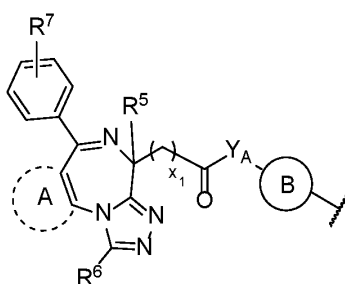
or R⁷ is -NR^{7A}R^{7B}, wherein

R^{7A} and R^{7B} are each independently hydrogen, optionally substituted C_1 - C_{20} alkyl, or optionally substituted C_1 - C_{20} heteroalkyl; and

x_1 is an integer from 1-6.

[00216] In some embodiments, D is N and E is N. In some embodiments, D is C and E is O.

[00217] In some embodiments, the second terminus comprises the structure of Formula (2-B), or a pharmaceutically acceptable salt thereof:



Formula (2-B),

wherein:

Ring A is an optionally substituted aryl or optionally substituted 5 to 6-membered heteroaryl;

Ring B is absent or an optionally substituted 6-membered monocyclic aryl or heteroaryl;

Y_A is -NH- or -O-;

R^5 is hydrogen or C_1 - C_6 alkyl;

R^6 is selected from hydrogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 haloalkyl, and optionally substituted C_1 - C_6 hydroxyalkyl;

R^7 is selected from hydrogen, halogen, -NO₂, -CN, optionally substituted aryl, optionally substituted C_1 - C_{20} alkyl, optionally substituted C_1 - C_{20} heteroalkyl, optionally substituted C_1 - C_6 haloalkyl, and optionally substituted C_1 - C_6 hydroxyalkyl;

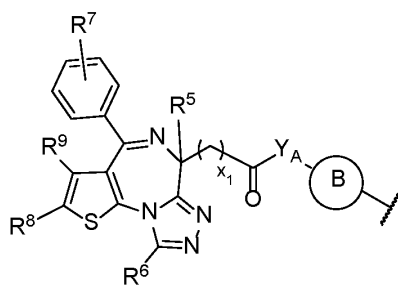
or R^7 is -NR^{7A}R^{7B}, wherein

R^{7A} and R^{7B} are each independently hydrogen, optionally substituted C_1 - C_{20} alkyl, or optionally substituted C_1 - C_{20} heteroalkyl; and

x_1 is an integer from 1-6.

[00218] In some embodiments, Ring A is an optionally substituted aryl ring. In some embodiments, Ring A is an optionally substituted phenyl. In some embodiments, Ring A is an optionally substituted 5 membered heteroaryl. In some embodiments, Ring A is an optionally substituted oxazoly. In some embodiments, Ring A is an optionally substituted furanyl. In some embodiments, Ring A is an optionally substituted thiophenyl.

[00219] In some embodiments, the second terminus comprising the structure of Formula (2-C), or a pharmaceutically acceptable salt thereof:



Formula (2-C),

wherein:

Ring B is absent or an optionally substituted 6-membered monocyclic aryl or heteroaryl;

Y_A is -NH- or -O-;

R^5 is hydrogen or C_1 - C_6 alkyl;

R^6 is selected from hydrogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 haloalkyl, and optionally substituted C_1 - C_6 hydroxyalkyl;

R^7 is selected from hydrogen, halogen, -NO₂, -CN, optionally substituted aryl, optionally substituted C_1 - C_{20} alkyl, optionally substituted C_1 - C_{20} heteroalkyl, optionally substituted C_1 - C_6 haloalkyl, and optionally substituted C_1 - C_6 hydroxyalkyl;

or R^7 is -NR^{7A}R^{7B}, wherein

R^{7A} and R^{7B} are each independently hydrogen, optionally substituted C_1 - C_{20} alkyl, or optionally substituted C_1 - C_{20} heteroalkyl;

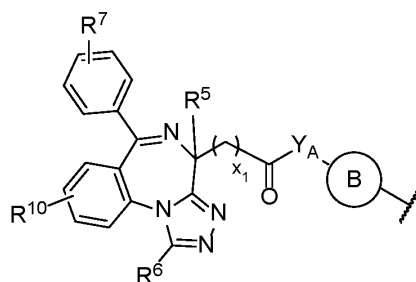
R^8 and R^9 are each independently selected from hydrogen, -C(O)OR^{8a}, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 haloalkyl, or optionally substituted C_1 - C_6 hydroxyalkyl; and

R^{8a} is hydrogen, C_1 - C_{20} alkyl, or C_1 - C_{20} heteroalkyl; and

x_1 is an integer from 1-6.

[00220] In some embodiments, R^8 and R^9 are each independently selected from optionally substituted C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, or C_1 - C_6 hydroxyalkyl. In some embodiments, R^8 and R^9 are each independently selected from optionally substituted C_1 - C_6 alkyl. In some embodiments, R^8 and R^9 are each independently methyl, ethyl, or propyl. In some embodiments, R^8 and R^9 are each independently methyl. In some embodiments, R^8 and R^9 are each independently ethyl. In some embodiments, R^8 and R^9 are each independently propyl.

[00221] In some embodiments, the second terminus comprising the structure of Formula (2-D), or a pharmaceutically acceptable salt thereof:



Formula (2-D),

wherein:

Ring B is absent or an optionally substituted 6-membered monocyclic aryl or heteroaryl;

Y_A is -NH- or -O-;

R^5 is hydrogen or C_1 - C_6 alkyl;

R^6 is selected from hydrogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 haloalkyl, and optionally substituted C_1 - C_6 hydroxyalkyl;

R^7 is selected from hydrogen, halogen, -NO₂, -CN, optionally substituted aryl, optionally substituted C_1 - C_{20} alkyl, optionally substituted C_1 - C_{20} heteroalkyl, optionally substituted C_1 - C_6 haloalkyl, and optionally substituted C_1 - C_6 hydroxyalkyl;

or R^7 is -NR^{7A}R^{7B}, wherein

R^{7A} and R^{7B} are each independently hydrogen, optionally substituted C_1 - C_{20} alkyl, or optionally substituted C_1 - C_{20} heteroalkyl;

R^{10} is selected from hydrogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 haloalkyl, or optionally substituted C_1 - C_6 hydroxyalkyl; and

x_1 is an integer from 1-6.

[00222] In some embodiments, R^5 is C_1 - C_6 alkyl. In some embodiments, R^5 is methyl or ethyl. In some embodiments, R^5 is methyl. In some embodiments, R^5 is ethyl. In some embodiments, R^5 is hydrogen.

[00223] In some embodiments, R^7 is selected from hydrogen, halogen, optionally substituted C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, or C_1 - C_6 hydroxyalkyl. In some embodiments, R^7 is halogen. In some embodiments, R^7 is Br, Cl, or F. In some embodiments, R^7 is Cl. In some embodiments, R^7 is F. In some embodiments, R^7 is Br.

[00224] In some embodiments, R^7 is -NR^{7A}R^{7B}, wherein R^{7A} and R^{7B} are each independently hydrogen or optionally substituted C_1 - C_6 alkyl.

[00225] In some embodiments, R^{10} is selected from optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 haloalkyl, or optionally substituted C_1 - C_6 hydroxyalkyl. In some embodiments, R^{10} is selected from optionally substituted C_1 - C_6 alkyl. In some embodiments, R^{10} is methyl, ethyl, or propyl. In some embodiments, R^{10} is methyl. In some embodiments, R^{10} is optionally substituted C_1 - C_6 hydroxyalkyl. In some embodiments, R^{10} is -OMe.

[00226] In some embodiments, R^6 is selected from optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 haloalkyl, or optionally substituted C_1 - C_6 hydroxyalkyl. In some embodiments, R^6 is an

optionally substituted C₁-C₆ alkyl. In some embodiments, R⁶ is methyl, ethyl, or propyl. In some embodiments, R⁶ is methyl. In some embodiments, R⁶ is ethyl. In some embodiments, R⁶ is propyl. In some embodiments, R⁶ is hydrogen.

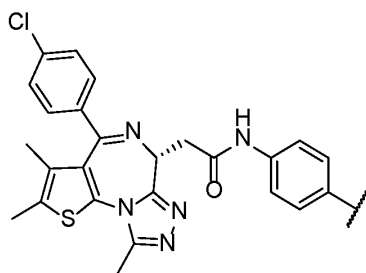
[00227] In some embodiments, Y_A is -NH-. In some embodiments, Y_A is -O-.

[00228] In some embodiments, Y_A is NH and x₁ is 1.

[00229] In some embodiments, x₁ is an integer from 1-5, 1-4, 1-3, or 1-2. In some embodiments, x₁ is 1. In some embodiments, x₁ is 2.

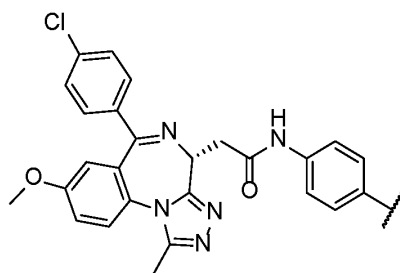
[00230] In some embodiments, Ring B is an optionally substituted 6-membered monocyclic aryl or heteroaryl, each of which is optionally substituted with alkyl, amino, halogen, hydroxy, hydroxyalkyl, or PEG. In some embodiments Ring B is phenyl. In some embodiments, Ring B is 6-membered monocyclic heteroaryl. In some embodiments, Ring B is pyridine or pyrimidine. In some embodiments, Ring B is absent.

[00231] In some embodiments, the second terminus comprises the structure of Formula (2-E), or a pharmaceutically acceptable salt thereof:



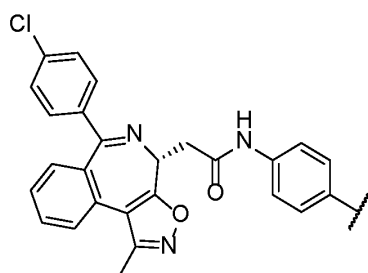
Formula (2-E).

[00232] In some embodiments, the second terminus comprises the structure of Formula (2-F), or a pharmaceutically acceptable salt thereof:



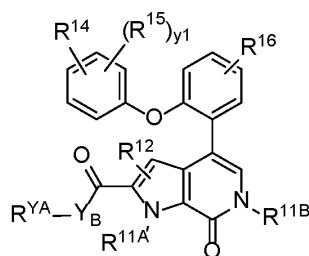
Formula (2-F).

[00233] In some embodiments, the second terminus comprises the structure of Formula (2-G), or a pharmaceutically acceptable salt thereof:



Formula (2-G).

[00234] In some embodiments, the second terminus comprises the structure of Formula (3-A), or a pharmaceutically acceptable salt thereof:



Formula (3-A),

wherein:

Y_B is $-CH_2NH-$, $-CH_2O-$, $-NH-$, or $-O-$;

R^{11A} and R^{11B} are each independently hydrogen or optionally substituted C_1-C_6 alkyl;

R^{12} is hydrogen, halogen, $-OH$, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 haloalkyl, or optionally substituted C_1-C_6 hydroxyalkyl;

R^{14} and R^{15} are each independently hydrogen, halogen, $-CN$, $-NO_2$, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 haloalkyl, or optionally substituted C_1-C_6 hydroxyalkyl;

or R^{14} is $-NR^A R^B$;

R^{16} is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted C_1-C_6 hydroxyalkyl, $-S(O)(=NH)R^A$, $-SO_2R^A$, or $-NHSO_2R^A$;

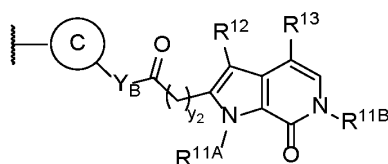
R^{YA} is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 haloalkyl, or optionally substituted 5-6-membered monocyclic aryl or heteroaryl;

each R^A and R^B is independently hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_1-C_6 haloalkyl, optionally substituted C_1-C_6 hydroxyalkyl, optionally substituted C_3-C_6 cycloalkyl, optionally substituted 4 to 6-membered heterocycloalkyl, or optionally substituted 5 to 6-membered heteroaryl; and

y_1 is 1-3;

wherein the attachment to the linker is at either R^{14} or at R^{YA} .

[00235] In some embodiments, the second terminus comprises the structure of Formula (3-B), or a pharmaceutically acceptable salt thereof:



Formula (3-B),

wherein:

Ring C is absent, optionally substituted 5 to 6-membered monocyclic aryl or heteroaryl or 4 to 8-membered heterocycle;

Y_B is -NH-, -CH₂NH-, -CH₂O-, or -O-;

R^{11A} and R^{11B} are each independently hydrogen or optionally substituted C₁-C₆ alkyl;

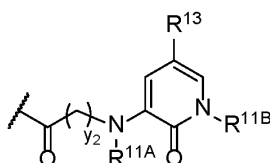
R^{12} is hydrogen, optionally substituted C₁-C₆ alkyl, C(O) R^A , or C(O)NR^A R^B ; wherein

each R^A and R^B is independently hydrogen, optionally substituted C₁-C₆ alkyl, or optionally substituted C₁-C₆ heteroalkyl;

R^{13} is hydrogen, substituted aryl, substituted heteroaryl, or substituted oxydibenzene; and

y_2 is an integer from 0-2.

[00236] In some embodiments, the second terminus comprises the structure of Formula (3-B1), or a pharmaceutically acceptable salt thereof:



Formula (3-B1),

wherein:

R^{11A} and R^{11B} are each independently hydrogen or optionally substituted C₁-C₆ alkyl;

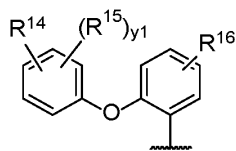
R^{13} is hydrogen, substituted aryl, substituted heteroaryl, or substituted oxydibenzene; and

y_2 is an integer from 0-2.

[00237] In some embodiments, y_2 is 0. In some embodiments, y_2 is 1. In some embodiments, y_2 is 2.

[00238] In some embodiments, R^{13} is substituted aryl or substituted heteroaryl. In some embodiments, R^{13} is hydrogen.

[00239] In some embodiments, R^{13} is substituted oxydibenzene.



[00240] In some embodiments, R^{13} is , wherein

R^{14} and R^{15} are each independently hydrogen, halogen, -CN, -NO₂, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ haloalkyl, or optionally substituted C₁-C₆ hydroxyalkyl;

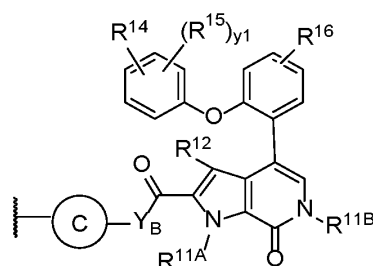
or R^{14} is -NR^A R^B ;

R^{16} is optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 alkynyl, optionally substituted C_1 - C_6 hydroxyalkyl, -
 $S(O)(=NH)R^A$, $-SO_2R^A$, or $-NHSO_2R^A$;

each R^A and R^B is independently hydrogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_1 - C_6 haloalkyl, optionally substituted C_1 - C_6 hydroxyalkyl, optionally substituted C_3 - C_6 cycloalkyl, optionally substituted 4 to 6-membered heterocycloalkyl, or optionally substituted 5 to 6-membered heteroaryl; and

y_1 is 1-3.

[00241] In some embodiments, the second terminus comprises the structure of Formula (3-C), or a pharmaceutically acceptable salt thereof:



Formula (3-C),

wherein:

Ring C is absent, optionally substituted 5 to 6-membered monocyclic aryl or heteroaryl or 4 to 8-membered heterocycle;

Y_B is $-CH_2NH-$, $-CH_2O-$, $-NH-$, or $-O-$;

R^{11A} and R^{11B} are each independently hydrogen or optionally substituted C_1 - C_6 alkyl;

R^{12} is hydrogen, halogen, $-OH$, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 haloalkyl, or optionally substituted C_1 - C_6 hydroxyalkyl;

R^{14} and R^{15} are each independently hydrogen, halogen, $-CN$, $-NO_2$, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 haloalkyl, or optionally substituted C_1 - C_6 hydroxyalkyl;

or R^{14} is $-NR^A R^B$;

R^{16} is optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 alkynyl, optionally substituted C_1 - C_6 hydroxyalkyl, -
 $S(O)(=NH)R^A$, $-SO_2R^A$, or $-NHSO_2R^A$;

each R^A and R^B is independently hydrogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_1 - C_6 haloalkyl, optionally substituted C_1 - C_6 hydroxyalkyl, optionally substituted C_3 - C_6 cycloalkyl, optionally substituted 4 to 6-membered heterocycloalkyl, or optionally substituted 5 to 6-membered heteroaryl; and

y_1 is an integer from 1-3.

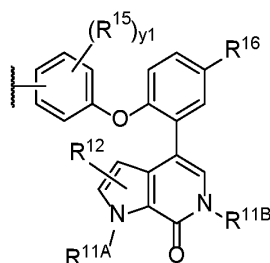
[00242] In some embodiments, Y_B is $-NH-$. In some embodiments, Y_B is $-CH_2NH-$. In some embodiments, Y_B is $-CH_2O-$. In some embodiments, Y_B is $-O-$.

[00243] In some embodiments, Ring C is an optionally substituted 5 or 6-membered monocyclic aryl or heteroaryl, each of which is optionally substituted with alkyl, amino, halogen, hydroxy, hydroxyalkyl, or PEG.

[00244] . In some embodiments, Ring C is phenyl. In some embodiments, Ring C is a 6-membered heteroaryl. In some embodiments, Ring C is pyridine, pyrazine, or triazine. In some embodiments, Ring C is pyridine. In some embodiments, Ring C is pyrazine. In some embodiments, Ring C is triazine. In some embodiments, Ring C is a 5-membered heteroaryl. In some embodiments, Ring C is a pyrazole. In some embodiments, Ring C is a triazole, pyrrole, imidazole, oxazole, oxadiazole, thiazole, or thiadiazole. In some embodiments, Ring C is a triazole. In some embodiments, Ring C is an imidazole or pyrrole. In some embodiments, an oxazole or oxadiazole. In some embodiments, Ring C is a thiazole or thiadiazole.

[00245] In some embodiments, Ring C is absent.

[00246] In some embodiments, the second terminus comprises the structure of Formula (3-D), or a pharmaceutically acceptable salt thereof:



Formula (3-D),

wherein:

R^{11A} and R^{11B} are each independently hydrogen or optionally substituted C_1 - C_6 alkyl;

R^{12} is hydrogen or an optionally substituted C_1 - C_6 alkyl;

each R^{15} is independently hydrogen, halogen, -CN, -NO₂, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 haloalkyl, or optionally substituted C_1 - C_6 hydroxyalkyl;

R^{16} is optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 alkynyl, optionally substituted C_1 - C_6 hydroxyalkyl, -S(O)(=NH) R^A , -SO₂ R^A , or -NHSO₂ R^A ;

R^A is hydrogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_1 - C_6 haloalkyl, optionally substituted C_1 - C_6 hydroxyalkyl, optionally substituted C_3 - C_6 cycloalkyl, optionally substituted 4 to 6-membered heterocycloalkyl, or optionally substituted 5 to 6-membered heteroaryl; and

y_1 is an integer from 1-3.

[00247] In some embodiments, R^{11A} and R^{11B} are each independently optionally substituted C_1 - C_6 alkyl. In some embodiments, R^{11A} and R^{11B} are each independently methyl, ethyl, propyl, or tert-butyl. In some embodiments, R^{11A} and R^{11B} are each independently methyl. In some embodiments, R^{11A} and R^{11B} are each independently hydrogen.

[00248] In some embodiments, R^{11A} is C_1 - C_6 alkyl, optionally substituted with haloalkyl or phosphorous hydroxide. In some embodiments, R^{11A} is C_1 - C_6 alkyl substituted with $-OP(O)(OH)_2$. In some embodiments, R^{11A} is unsubstituted C_1 - C_6 alkyl. In some embodiments, R^{11A} is methyl, ethyl, or tert-butyl. In some embodiments, R^{11A} is methyl. In some embodiments, R^{11A} is hydrogen.

[00249] In some embodiments, R^{12} is optionally substituted C_1 - C_6 alkyl. In some embodiments, R^{12} is hydrogen.

[00250] In some embodiments, R^{12} is $C(O)R^A$ or $C(O)NR^A R^B$. In some embodiments, R^{12} is $C(O)NR^A R^B$, wherein R^A and R^B are each independently hydrogen or optionally substituted C_1 - C_6 alkyl.

[00251] In some embodiments, R^{14} and R^{15} are each independently hydrogen, $-CN$, or $-NO_2$. In some embodiments, R^{14} and R^{15} are each independently halogen or optionally substituted C_1 - C_6 alkyl. In some embodiments, R^{14} and R^{15} are each independently Br, Cl, F, methyl, or ethyl. In some embodiments, R^{14} and R^{15} are each independently F or methyl.

[00252] In some embodiments, R^{16} is optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 alkynyl, or optionally substituted C_1 - C_6 hydroxyalkyl, each of which is optionally substituted with amido, alkyl, alkynyl, azido, amino, halogen, haloalkyl, hydroxy, nitro, oxo ($=O$), phosphorous hydroxide, or PEG.

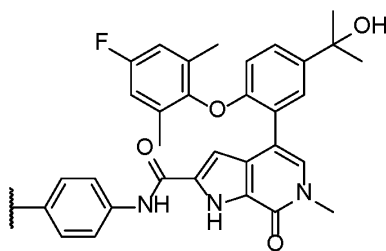
[00253] In some embodiments, R^{16} is optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, or optionally substituted C_1 - C_6 hydroxyalkyl. In some embodiments, R^{16} is C_1 - C_6 alkyl or C_1 - C_6 heteroalkyl, each or which optionally substituted with $-CN$, $-NH_2$, $-N_3$, $-OH$, CF_3 , or $-OP(O)(OH)_2$.

[00254] In some embodiments, R^{16} is $-SO_2R^A$, wherein R^A is C_1 - C_6 alkyl. In some embodiments, R^{16} is $-SO_2Et$. In some embodiments, R^{16} is $-SO_2Me$.

[00255] In some embodiments, R^{16} is $-NHSO_2R^A$, wherein R^A is C_1 - C_6 alkyl. In some embodiments, R^{16} is $-NHSO_2Et$. In some embodiments, R^{16} is $-NHSO_2Me$.

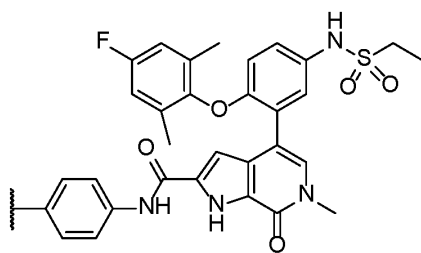
[00256] In some embodiments, y_1 is 1. In some embodiments, y_1 is 2. In some embodiments, y_1 is 3.

[00257] In some embodiments, the second terminus comprises the structure of Formula (3-E), or a pharmaceutically acceptable salt thereof:



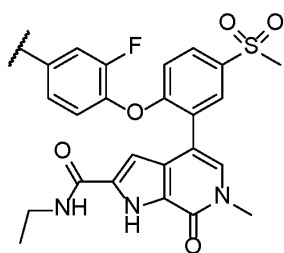
Formula (3-E).

[00258] In some embodiments, the second terminus comprising the structure of Formula (3-F), or a pharmaceutically acceptable salt thereof:

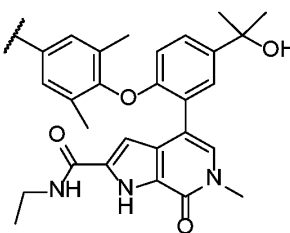


Formula (3-F).

[00259] In some embodiments, the second terminus comprising the structure of Formula (3-G) or Formula (3-H), or a pharmaceutically acceptable salt thereof:

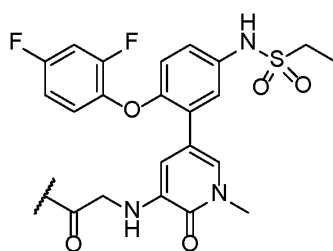


Formula (3-G) or



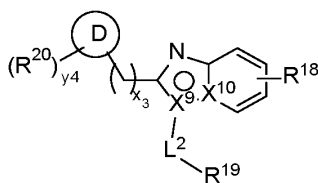
Formula (3-H).

[00260] In some embodiments, the second terminus comprising the structure of Formula (3-I), or a pharmaceutically acceptable salt thereof:



Formula (3-I).

[00261] In some embodiments, the second terminus comprises the structure of Formula (4-A), or a pharmaceutically acceptable salt thereof:



Formula (4-A),

wherein:

Ring D is absent, phenyl, or 5 to 6-membered heteroaryl;

X^9 and X^{10} are each independently C or N, wherein one of X^9 or X^{10} is N;

L² is absent, optionally substituted alkylene, -O-, or -NR^D-, wherein

R^D is hydrogen or optionally substituted C₁-C₃ alkyl;

R¹⁸ is an optionally substituted 5 to 6-membered heteroaryl;

R¹⁹ is an optionally substituted C₃-C₈ cycloalkyl or optionally substituted 4 to 7-membered heteroaryl;

each R^{20} is independently hydrogen, halogen, -CN, -NO₂, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ haloalkyl, or optionally substituted C₁-C₆ hydroxyalkyl;

x_3 is an integer from 1-3; and

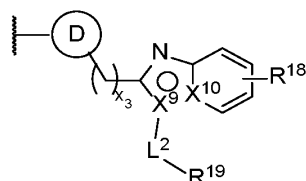
y_4 is an integer from 1-4;

wherein the attachment to the linker is at either R^{19} or at one of R^{20} .

[00262] In some embodiments, attachment to the linker is at R^{19} .

[00263] In some embodiments, attachment to the linker is at one of R^{20} .

[00264] In some embodiments, the second terminus comprises the structure of Formula (4-B), or a pharmaceutically acceptable salt thereof:



Formula (4-B),

wherein:

Ring D is absent, optionally substituted phenyl, or optionally substituted 5 to 6-membered heteroaryl;

X^9 and X^{10} are each independently C or N, wherein one of X^9 or X^{10} is N;

L^2 is absent, optionally substituted alkylene, -O-, or -NR^D-, wherein

R^D is hydrogen or optionally substituted C₁-C₃ alkyl;

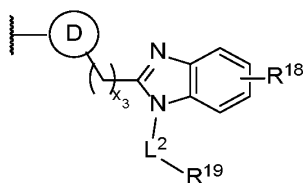
R^{18} is an optionally substituted 5 to 6-membered heteroaryl;

R^{19} is an optionally substituted C₃-C₈ cycloalkyl or optionally substituted 4 to 7-membered heteroaryl; and

x_3 is an integer from 1-3.

[00265] In some embodiments, X^9 is N; and X^{10} is C. In some embodiments, X^9 is C; and X^{10} is N.

[00266] In some embodiments, the second terminus comprises the structure of Formula (4-C), or a pharmaceutically acceptable salt thereof:

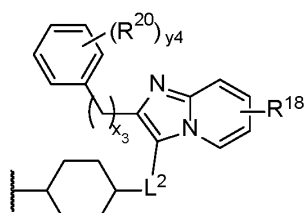


Formula (4-C).

[00267] In some embodiments, Ring D is an optionally substituted monocyclic 6-membered aryl or 5 to 6-membered heteroaryl. In some embodiments, Ring D is an optionally substituted monocyclic 6-membered aryl. In some embodiments, Ring D is an optionally substituted phenyl.

[00268] In some embodiments, R^{19} is an optionally substituted C₃-C₈ cycloalkyl. In some embodiments, R^{19} is optionally substituted 4 to 7-membered heteroaryl.

[00269] In some embodiments, the second terminus comprises the structure of Formula (4-D), or a pharmaceutically acceptable salt thereof:



Formula (4-D),

wherein:

L^2 is an optionally substituted alkylene, -O-, or -NR^D-, wherein

R^D is hydrogen or optionally substituted C₁-C₃ alkyl;

R¹⁸ is an optionally substituted 5 to 6-membered heteroaryl;

R²⁰ is hydrogen, halogen, -CN, -NO₂, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ haloalkyl, or optionally substituted C₁-C₆ hydroxyalkyl;

x₃ is an integer from 1-3; and

y₄ is an integer from 1-4.

[00270] In some embodiments, L^2 is an optionally substituted alkylene. In some embodiments, L^2 is C₂-C₄ alkylene, optionally substituted with one or more C₁-C₃ alkyl. In some embodiments, L^2 is absent.

[00271] In some embodiments, L^2 is -NR^D-. In some embodiments, L^2 is -NH-.

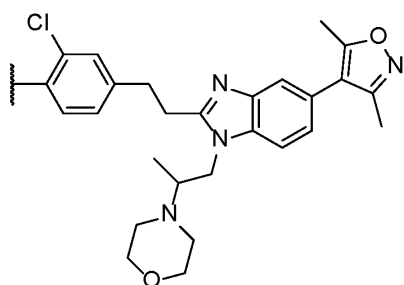
[00272] In some embodiments, R¹⁸ is an optionally substituted 5-membered heteroaryl. In some embodiments, R¹⁸ is optionally substituted oxazole, oxadiazole, thiazole, thiadiazole, pyrrole, or pyrazole. In some embodiments, R¹⁸ is optionally substituted oxazole.

[00273] In some embodiments, R²⁰ is halogen, -CN, -NO₂, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ haloalkyl, or optionally substituted C₁-C₆ hydroxyalkyl.

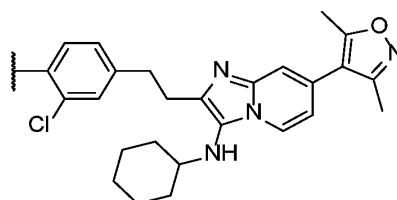
[00274] In some embodiments, x₃ is 1. In some embodiments, x₃ is 2. In some embodiments, x₃ is 3.

[00275] In some embodiments, y₄ is 1 or 2. In some embodiments, y₄ is 1. In some embodiments, y₄ is 2. In some embodiments, y₄ is 3. In some embodiments, y₄ is 4.

[00276] In some embodiments, the second terminus comprises the structure of Formula (4-E) or Formula (4-F), or a pharmaceutically acceptable salt thereof:

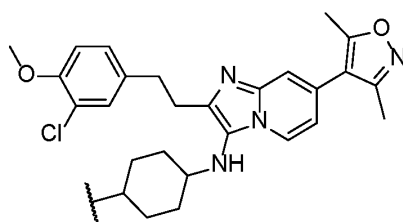


Formula (4-E) or



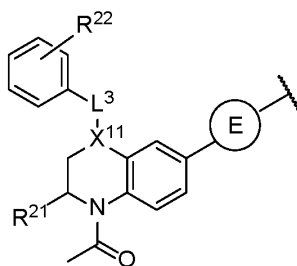
Formula (4F).

[00277] In some embodiments, the second terminus comprises the structure of Formula (4-G), or a pharmaceutically acceptable salt thereof:



Formula (4-G).

[00278] In some embodiments, the second terminus comprises the structure of Formula (5-A), or a pharmaceutically acceptable salt thereof:



Formula (5-A),

wherein:

Ring E is absent or an optionally substituted phenyl or optionally substituted 5 to 6-membered heteroaryl;

X¹¹ is CH or N;

L³ is -NR^E- or -CR^ER^E-, wherein

each R^E is independently hydrogen or optionally substituted C₁-C₃ alkyl;

R²¹ is C₁-C₆ alkyl or C₃-C₆ cycloalkyl; and

R²² is halogen, CN, NO₂, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ haloalkyl, or optionally substituted C₁-C₆ hydroxyalkyl.

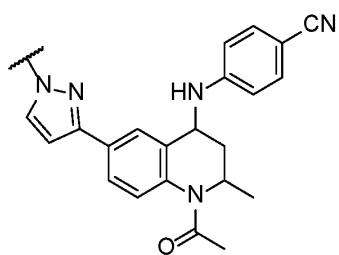
[00279] In some embodiments, Ring E is absent. In some embodiments, Ring E is an optionally substituted phenyl. In some embodiments, Ring E is an optionally substituted 5 to 6-membered heteroaryl. In some embodiments, Ring E is a 5-membered heteroaryl. In some embodiments, Ring E is a 6-membered heteroaryl.

[00280] In some embodiments, X¹¹ is CH and L³ is -NR^E-. In some embodiments, X¹¹ is N and L³ is -CR^ER^E-.

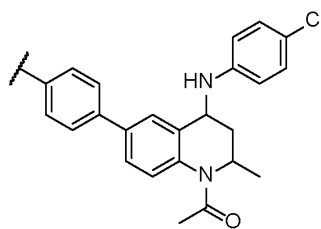
[00281] In some embodiments, R²¹ is C₁-C₆ alkyl. In some embodiments, R²¹ is methyl.

[00282] In some embodiments, R²² is halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ haloalkyl, or optionally substituted C₁-C₆ hydroxyalkyl. In some embodiments, R²² is CN, F, Cl, Br, or methyl.

[00283] In some embodiments, the second terminus comprises the structure of Formula (5-B) or Formula (5-C), or a pharmaceutically acceptable salt thereof:

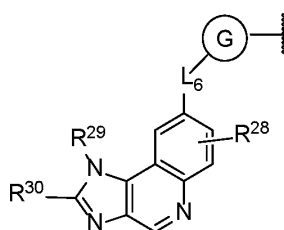


Formula (5-B) or



Formula (5-C).

[00284] In some embodiments, the second terminus comprises the structure of Formula (6-A), or a pharmaceutically acceptable salt thereof:



Formula (6-A),

wherein:

Ring G is absent or an optionally substituted C₃-C₆ cycloalkyl or optionally substituted 4 to 6-membered heterocycloalkyl;

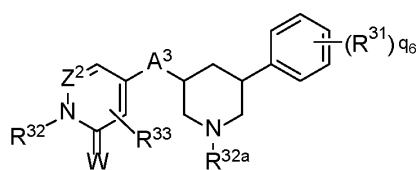
L⁶ is -O-(optionally substituted alkylene);

R²⁸ is an optionally substituted 5 to 6-membered heteroaryl;

R²⁹ is optionally substituted C₁-C₆ alkyl-(C₆-C₁₀ aryl) or optionally substituted C₁-C₆ alkyl-(6 to 10-membered heteroaryl); and

R³⁰ is optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₁-C₆ hydroxyalkyl, optionally substituted C₃-C₆ cycloalkyl, or optionally substituted 4 to 6-membered heterocycloalkyl.

[00285] In some embodiments, the second terminus comprises the structure of Formula (7-A), or a pharmaceutically acceptable salt thereof:



Formula (7-A),

wherein:

A³ is -O-, -NH-, or -CH₂-;

Z² is CH or N;

W is O or S;

each R^{31} is independently hydrogen, halogen, -OH, -CN, -NO₂, -NH₂, optionally substituted C₁-C₁₀ alkyl, optionally substituted C₁-C₁₀ haloalkyl, optionally substituted C₁-C₁₀ hydroxyalkyl, optionally substituted C₂-C₁₀ alkenyl, optionally substituted C₂-C₁₀ alkynyl, optionally substituted C₃-C₈ cycloalkyl, or optionally substituted 3 to 8-membered heterocycloalkyl;

or two R^{31} together with the atoms to which they are attached form an optionally substituted C₅-C₈ cycloalkyl or optionally substituted 5 to 8-membered heterocycloalkyl;

R^{32} is hydrogen or optionally substituted C₁-C₁₀ alkyl;

R^{32a} is hydrogen or optionally substituted C₁-C₁₀ alkyl;

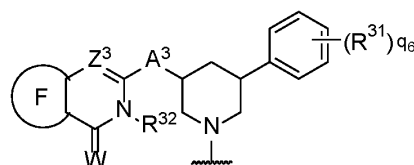
R^{33} is hydrogen, halogen, -OH, -CN, -NO₂, -NH₂, optionally substituted C₁-C₁₀ alkyl, optionally substituted C₁-C₁₀ haloalkyl, or optionally substituted C₁-C₁₀ hydroxyalkyl; and

q_6 is 0-4;

wherein Formula (7-A) is attached to the linker is at R^{32a} or at one of R^{31} .

[00286] In some embodiments, Z^2 is CH. In some embodiments, Z^2 is N.

[00287] In some embodiments, the second terminus comprises the structure of Formula (7-B), or a pharmaceutically acceptable salt thereof:



Formula (7-B),

wherein:

Ring F is an optionally substituted 5 to 6-membered heteroaryl;

A^3 is -O-, -NH-, or -CH₂-;

Z^3 is CH or N;

W is O or S;

each R^{31} is hydrogen, halogen, -OH, -CN, -NO₂, -NH₂, optionally substituted C₁-C₁₀ alkyl, optionally substituted C₁-C₁₀ haloalkyl, optionally substituted C₁-C₁₀ hydroxyalkyl, optionally substituted C₂-C₁₀ alkenyl, optionally substituted C₂-C₁₀ alkynyl, optionally substituted C₃-C₈-cycloalkyl, or optionally substituted 3- to 8-membered heterocycloalkyl;

or two R^{31} together with the atoms to which they are attached form an optionally substituted C₅-C₈ cycloalkyl or optionally substituted 5 to 8-membered heterocycloalkyl;

R^{32} is hydrogen or optionally substituted C₁-C₁₀ alkyl; and

q_6 is 1-4.

[00288] In some embodiments, A^3 is -O-. In some embodiments, A^3 is -NH-. In some embodiments, A^3 is -CH₂-.

[00289] In some embodiments, Z^3 is CH. In some embodiments, Z^3 is N.

[00290] In some embodiments, W is O. In some embodiments, W is S.

[00291] In some embodiments, Ring F is an optionally substituted 5-membered heteroaryl. In some embodiments, Ring F is an optionally substituted 6-membered heteroaryl.

[00292] In some embodiments, each R^{31} is independently an optionally substituted C_1 - C_{10} alkyl, optionally substituted C_1 - C_{10} haloalkyl, or optionally substituted C_1 - C_{10} hydroxyalkyl. In some embodiments, each R^{31} is independently an optionally substituted C_3 - C_8 -cycloalkyl or optionally substituted 3 to 8-membered heterocycloalkyl. In some embodiments, each R^{31} is independently hydrogen, halogen, -OH, -CN, -NO₂, or -NH₂. In some embodiments, each R^{31} is hydrogen.

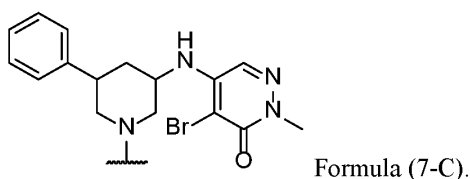
[00293] In some embodiments, R^{32} is an optionally substituted C_1 - C_{10} alkyl. In some embodiments, R^{32} is methyl. In some embodiments, R^{32} is hydrogen.

[00294] In some embodiments, R^{32a} is an optionally substituted C_1 - C_{10} alkyl. In some embodiments, R^{32a} is hydrogen.

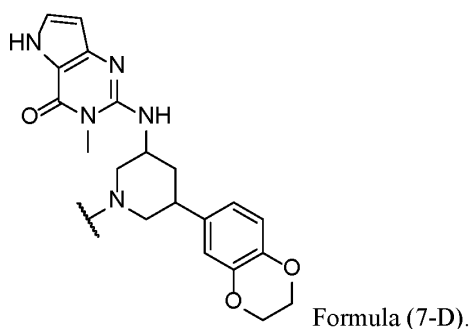
[00295] In some embodiments, R^{33} is hydrogen, halogen, -OH, -CN, -NO₂, or -NH₂. In some embodiments, R^{33} is an optionally substituted C_1 - C_{10} alkyl, optionally substituted C_1 - C_{10} haloalkyl, or optionally substituted C_1 - C_{10} hydroxyalkyl.

[00296] In some embodiments, Formula (7-A) is attached to the linker at R^{32a} . In some embodiments, Formula (7-A) is attached to the linker at one of R^{31} .

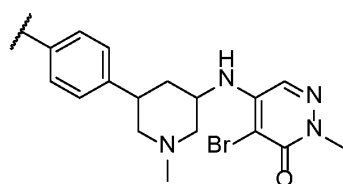
[00297] In some embodiments, the second terminus comprises the structure of Formula (7-C), or a pharmaceutically acceptable salt thereof:



[00298] In some embodiments, the second terminus comprise the structure of Formula (7-D), or a pharmaceutically acceptable salt thereof:

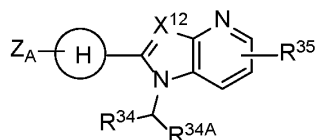


[00299] In some embodiments, the second terminus comprises the structure of Formula (7-E), or a pharmaceutically acceptable salt thereof:



Formula (7-E).

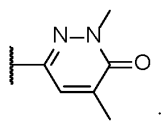
[00300] In some embodiments, the second terminus comprises the structure of Formula (8-A), or a pharmaceutically acceptable salt thereof:



Formula (8-A),

wherein:

Ring H is an optionally substituted phenyl or optionally substituted 6-membered heteroaryl;



or Ring H is

Z_A is absent or an optionally substituted phenyl formamide;

X^{12} is CH or N;

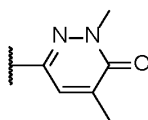
R^{34} is an optionally substituted phenyl or optionally substituted 6-membered heteroaryl;

R^{34A} is hydrogen, halogen, or optionally substituted C_1 - C_3 alkyl; and

R^{35} is independently halogen, optionally substituted C_1 - C_{10} alkyl, or optionally substituted 5 to 6-membered heteroaryl;

wherein the attachment to the linker is at R^{35} , Z_A , or Ring H.

[00301] In some embodiments, Ring H is an optionally substituted phenyl. In some embodiments, Ring H is an optionally substituted 6-membered heteroaryl.



[00302] In some embodiments, Ring H is

[00303] In some embodiments, Z_A is absent. In some embodiments, Z_A is an optionally substituted phenyl formamide. In some embodiments, Z_A is $-C(O)NH$ -phenyl.

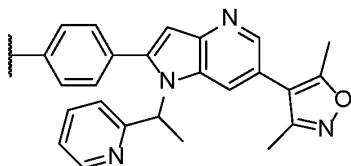
[00304] In some embodiments, X^{12} is CH. In some embodiments, X^{12} is N.

[00305] In some embodiments, R^{34} is an optionally substituted phenyl. In some embodiments, R^{34} is an optionally substituted 6-membered heteroaryl.

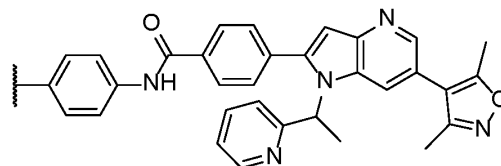
[00306] In some embodiments, R^{34A} is hydrogen or halogen. In some embodiments, R^{34A} is an optionally substituted C_1 - C_3 alkyl. In some embodiments, R^{34A} is methyl.

[00307] In some embodiments, Formula (8-A) is attachment to the linker is at R³⁵. In some embodiments, Formula (8-A) is attached to the linker at Z_A. In some embodiments, Formula (8-A) is attached to the linker at Ring H.

[00308] In some embodiments, the second terminus comprises the structure of Formula (8-B) or Formula (8-C), or a pharmaceutically acceptable salt thereof:

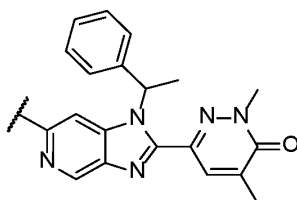


Formula (8-B) or



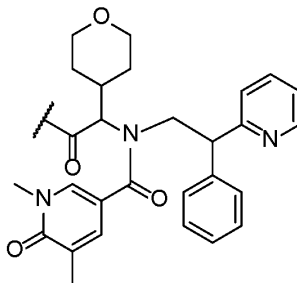
Formula (8-C).

[00309] In some embodiments, the second terminus comprises the structure of Formula (8-D), or a pharmaceutically acceptable salt thereof:



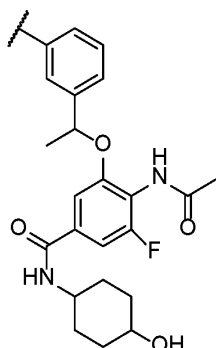
Formula (8-D).

[00310] In some embodiments, the second terminus comprises the structure of Formula (9-A), or a pharmaceutically acceptable salt thereof:

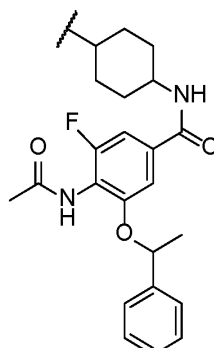


Formula (9-A).

[00311] In some embodiments, the second terminus comprises the structure of Formula (10-A) or Formula (10-B), or a pharmaceutically acceptable salt thereof:

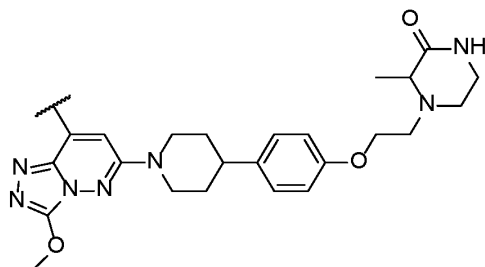


Formula (10-A) or



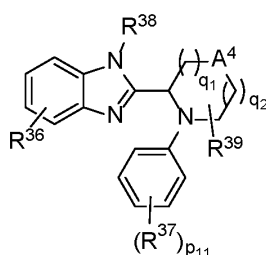
Formula (10-B).

[00312] In some embodiments, the second terminus comprises the structure of Formula (11-A), or a pharmaceutically acceptable salt thereof:



Formula (11-A).

[00313] In some embodiments, the second terminus comprises the structure of Formula (12-A), or a pharmaceutically acceptable salt thereof:



Formula (12-A),

wherein:

A^4 is $-CR^{40}R^{40}-$ or $-NR^{40}-$; wherein each R^{40} is independently hydrogen or optionally substituted C_1 - C_{10} alkyl;

R^{36} is an optionally substituted 5 to 6-membered heteroaryl;

each R^{37} is independently hydrogen, halogen, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl;

R^{38} is optionally substituted C_1 - C_{10} alkyl, optionally substituted C_3 - C_8 cycloalkyl, or optionally substituted 3 to 8-membered heterocycloalkyl;

R^{39} is hydrogen, halogen, $-OH$, $-CN$, $-NO_2$, $-NH_2$, oxo ($=O$), $=S$, C_1 - C_{10} haloalkyl, or C_1 - C_{10} hydroxyalkyl;

p_{11} is 1-4; and

q_1 and q_2 are each independently 0-2;

wherein the linker is attached to Formula (12-A) at either R^{38} or R^{40} .

[00314] In some embodiments, R^{36} is an optionally substituted 5-membered heteroaryl. In some embodiments, R^{36} is optionally substituted oxazole, oxadiazole, thiazole, thiadiazole, pyrrole, or pyrazole. In some embodiments, R^{36} is optionally substituted oxazole.

[00315] In some embodiments, each R^{37} is independently halogen, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl. In some embodiments, each R^{37} is independently halogen.

[00316] In some embodiments, R^{38} is an optionally substituted C_1 - C_{10} alkyl. In some embodiments, R^{38} is an optionally substituted C_3 - C_8 cycloalkyl or optionally substituted 3 to 8-membered heterocycloalkyl. In some embodiments, R^{38} is a 3 to 8-membered heterocycloalkyl.

[00317] In some embodiments, R^{39} is hydrogen, halogen, -OH, -CN, -NO₂, -NH₂, C₁-C₁₀ haloalkyl, or C₁-C₁₀ hydroxyalkyl. In some embodiments, R^{39} is oxo or =S. In some embodiments, R^{39} is oxo. In some embodiments, R^{39} is =S.

[00318] In some embodiments, A^4 is -NR⁴⁰. In some embodiments, A^4 is -NH. In some embodiments, A^4 is -NCH₃. In some embodiments, A^4 is -CR⁴⁰R⁴⁰. In some embodiments, A^4 is -CH₂-.

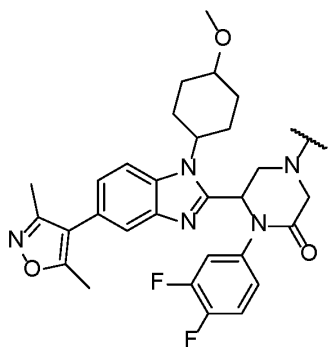
[00319] In some embodiments, each R⁴⁰ is independently optionally substituted C₁-C₁₀ alkyl. In some embodiments, each R⁴⁰ is independently hydrogen.

[00320] In some embodiments, p₁₁ is 3 or 4. In some embodiments, p₁₁ is 2. In some embodiments, p₁₁ is 1.

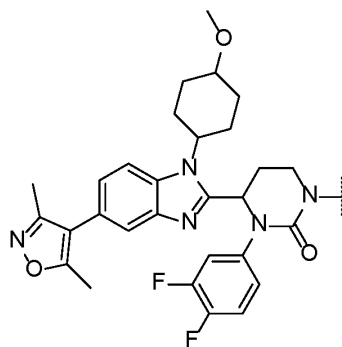
[00321] In some embodiments, q₁ is 1 and q₂ is 1. In some embodiments, q₁ is 2 and q₂ is 0.

[00322] In some embodiments, the linker is attached to Formula (12-A) through R³⁸. In some embodiments, the linker is attached to Formula (12-A) through R⁴⁰.

[00323] In some embodiments, the second terminus comprises Formula (12-B) or Formula (12-C), or a pharmaceutically acceptable salt thereof:

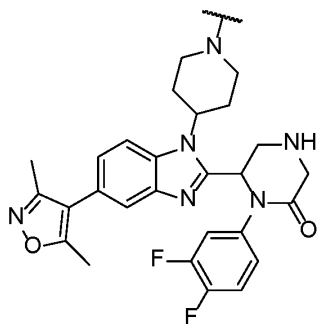


Formula (12-B) or

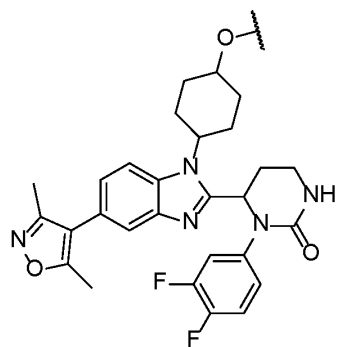


Formula (12-C).

[00324] In some embodiments, the second terminus comprises Formula (12-D) or Formula (12-E), or a pharmaceutically acceptable salt thereof:

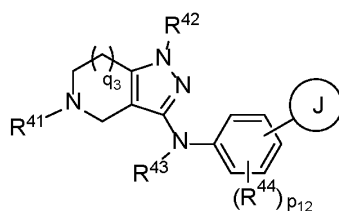


Formula (12-D) or



Formula (12-E).

[00325] In some embodiments, the second terminus comprises the structure of Formula (13-A), or a pharmaceutically acceptable salt thereof:



Formula (13-A),

wherein:

Ring J is absent or optionally substituted 5 to 6-membered heteroaryl;

R^{41} is optionally substituted C_1 - C_6 alkyl, optionally substituted C_3 - C_8 cycloalkyl, $-C(O)R^{41a}$, $-C(O)-$, or $-C(O)NR^{41a}R^{41b}$, wherein

R^{41a} and R^{41b} are each independently optionally substituted C_1 - C_{10} alkyl or optionally substituted C_3 - C_8 cycloalkyl;

R^{42} is an optionally substituted C_1 - C_{10} alkyl, optionally substituted C_1 - C_{10} haloalkyl, optionally substituted C_3 - C_8 cycloalkyl, or optionally substituted 3 to 8 membered heterocycloalkyl;

R^{43} is hydrogen or optionally substituted C_1 - C_{10} alkyl;

each R^{44} is independently hydrogen, halogen, $-OH$, $-CN$, $-NO_2$, $-NH_2$, optionally substituted C_1 - C_{10} alkyl, optionally substituted C_1 - C_{10} haloalkyl, C_1 - C_{10} hydroxyalkyl, optionally substituted C_2 - C_{10} alkenyl, optionally substituted C_2 - C_{10} alkynyl, optionally substituted C_3 - C_8 -cycloalkyl, or optionally substituted 3 to 8-membered heterocycloalkyl; or

R^{43} and one of R^{44} together with the atoms to which they are attached form an optionally substituted 5 to 8-membered heterocycloalkyl;

p_{12} is 1-4; and

q_3 is 0 or 1;

wherein Formula (13-A) is connected to the linker at Ring J, R^{41} , or R^{42} .

[00326] In some embodiments, R^{41} is optionally substituted C_1 - C_6 alkyl or optionally substituted C_3 - C_8 cycloalkyl. In some embodiments, R^{41} is $-C(O)R^{41a}$. In some embodiments, R^{41} is $-C(O)CH_3$ or $-C(O)CH_2CH_3$. In some embodiments, R^{41} is $-C(O)-NR^{41a}R^{41b}$.

[00327] In some embodiments, R^{41a} is optionally substituted C_1 - C_{10} alkyl. In some embodiments, R^{41a} is optionally substituted C_3 - C_8 cycloalkyl.

[00328] In some embodiments, R^{41b} is optionally substituted C_1 - C_{10} alkyl. In some embodiments, R^{41b} is optionally substituted C_3 - C_8 cycloalkyl.

[00329] In some embodiments, R^{42} is optionally substituted C_1 - C_{10} alkyl or optionally substituted C_1 - C_{10} haloalkyl. In some embodiments, R^{42} is optionally substituted C_3 - C_8 cycloalkyl or optionally substituted 3 to 8 membered heterocycloalkyl. In some embodiments, R^{42} is optionally substituted 3- to 8-membered heterocycloalkyl ring.

[00330] In some embodiments, R^{43} is optionally substituted C_1 - C_{10} alkyl. In some embodiments, R^{43} is hydrogen.

[00331] In some embodiments, each R^{44} is independently halogen, -OH, -CN, -NO₂, -NH₂, optionally substituted C₁-C₁₀ alkyl, optionally substituted C₁-C₁₀ haloalkyl, C₁-C₁₀ hydroxyalkyl, optionally substituted C₂-C₁₀ alkenyl, optionally substituted C₂-C₁₀ alkynyl, optionally substituted C₃-C₈-cycloalkyl, or optionally substituted 3 to 8-membered heterocycle. In some embodiments, each R^{44} is independently halogen or C₁-C₁₀ haloalkyl.

[00332] In some embodiments, R^{43} and one of R^{44} together with the atoms to which they are attached form an optionally substituted 5 to 8-membered heterocycloalkyl. In some embodiments, R^{43} and one of R^{44} together with the atoms to which they are attached form a 5, 6, 7, or 8-membered heterocycloalkyl.

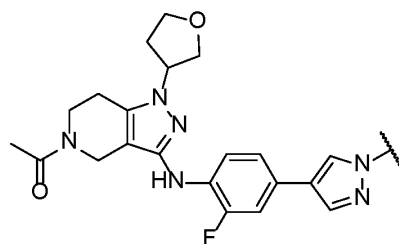
[00333] In some embodiments, p_{12} is 3 or 4. In some embodiments, p_{12} is 2. In some embodiments, p_{12} is 1.

[00334] In some embodiments, q_3 is 1. In some embodiments, q_3 is 0.

[00335] In some embodiments, Ring J is an optionally substituted 5-membered heteroaryl. In some embodiments, Ring J is absent.

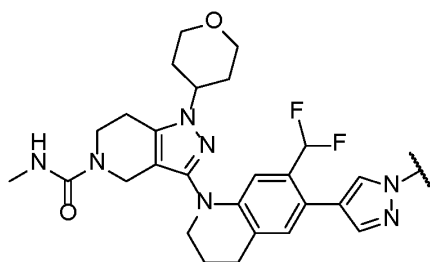
[00336] In some embodiments, Formula (13-A) is connected to the linker at Ring J. In some embodiments, Formula (13-A) is connected to the linker at R^{41} . In some embodiments, Formula (13-A) is connected to the linker at R^{42} .

[00337] In some embodiments, the second terminus comprises the structure of Formula (13-B), or a pharmaceutically acceptable salt thereof:

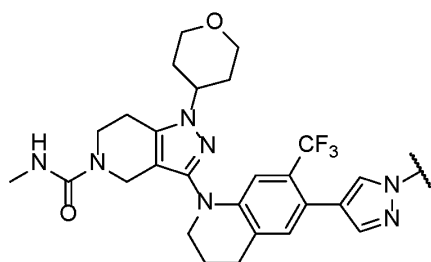


Formula (13-B).

[00338] In some embodiments, the second terminus comprises the structure of Formula (13-C1) or Formula (13-C2), or a pharmaceutically acceptable salt thereof:

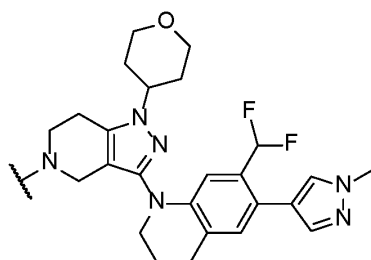


Formula (13-C1) or

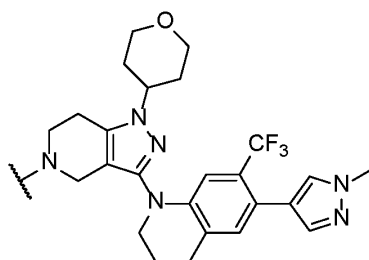


Formula (13-C2).

[00339] In some embodiments, the second terminus comprises the structure of Formula (13-D1) or Formula (13-D2), or a pharmaceutically acceptable salt thereof:

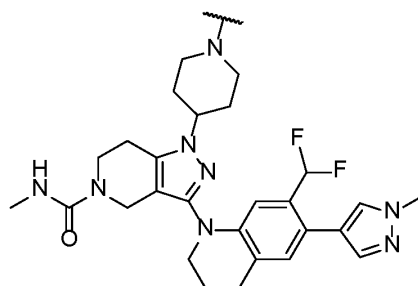


Formula (13-D1) or



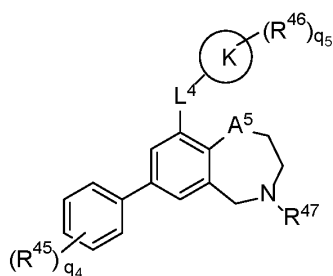
Formula (13-D2).

[00340] In some embodiments, the second terminus comprises the structure of Formula (13-E), or a pharmaceutically acceptable salt thereof:



Formula (13-E).

[00341] In some embodiments, the second terminus comprises the structure of Formula (14-A), or a pharmaceutically acceptable salt thereof:



Formula (14-A),

wherein:

Ring K is a 5 to 6-membered heterocycloalkyl;

A⁵ is absent, CH₂, -NH-, or -O-;

L⁴ is alkylene or heteroalkylene;

each R⁴⁵ is independently halogen, -OH, -CN, -NO₂, -NH₂, optionally substituted C₁-C₁₀ alkyl, optionally substituted C₁-C₁₀ haloalkyl, optionally substituted C₁-C₁₀ heteroalkyl, optionally substituted C₁-C₁₀ hydroxyalkyl, optionally substituted C₂-C₁₀ alkenyl, optionally substituted C₂-C₁₀ alkynyl, optionally substituted C₃-C₈-cycloalkyl, or optionally substituted 3 to 8-membered heterocycloalkyl;

each R⁴⁶ is independently hydrogen, halogen, -OH, -CN, -NO₂, -NH₂, optionally substituted C₁-C₁₀ alkyl, optionally substituted C₁-C₁₀ haloalkyl, optionally substituted C₁-C₁₀ hydroxyalkyl, optionally substituted C₂-C₁₀ alkenyl, optionally substituted C₂-C₁₀ alkynyl, optionally substituted C₃-C₈ cycloalkyl, or optionally substituted 3 to 8-membered heterocycloalkyl;

R⁴⁷ is optionally substituted C₁-C₁₀ alkyl, -C(O)R^{47a}, or -C(O)-NR^{47a}R^{47b}, wherein

R^{47a} and R^{47b} are each independently optionally substituted C₁-C₁₀ alkyl or optionally substituted C₃-C₈ cycloalkyl;

q₄ is 2-3; and

q₅ is 0-2;

wherein the Formula (14-A) is connected to the linker through Ring K or through one of R⁴⁵.

[00342] In some embodiments, A⁵ is absent. In some embodiments, A⁵ is -NH- or -O-. In some embodiments, A⁵ is -NH-. In some embodiments, A⁵ is -O-.

[00343] In some embodiments, L⁴ is alkylene. In some embodiments, In some embodiments, L⁴ is C₁-C₅ alkylene.

[00344] In some embodiments, L⁴ is heteroalkylene. In some embodiments, L⁴ is C₁-C₄ heteroalkylene-. In some embodiments, L⁴ is -O-CH₂- or -O-CH₂CH₂-.

[00345] In some embodiments, each R⁴⁵ is independently halogen, -OH, -CN, -NO₂, -NH₂, optionally substituted C₁-C₁₀ alkyl, optionally substituted C₁-C₁₀ haloalkyl, optionally substituted C₁-C₁₀ heteroalkyl, optionally substituted C₁-C₁₀ hydroxyalkyl, optionally substituted C₂-C₁₀ alkenyl, or optionally substituted C₂-C₁₀ alkynyl. In some embodiments, each R⁴⁵ is independently optionally substituted C₁-C₁₀ alkyl or

optionally substituted C₁-C₁₀ hydroxyalkyl. In some embodiments, each R⁴⁵ is independently C₁-C₁₀ hydroxyalkyl. In some embodiments, each R⁴⁵ is independently -OCH₃ or -OCH₂CH₃.

[00346] In some embodiments, each R⁴⁶ is independently hydrogen, halogen, -OH, -CN, -NO₂, -NH₂, optionally substituted C₁-C₁₀ alkyl, optionally substituted C₁-C₁₀ haloalkyl, or optionally substituted C₁-C₁₀ hydroxyalkyl. In some embodiments, each R⁴⁶ is independently hydrogen.

[00347] In some embodiments, R⁴⁷ is optionally substituted C₁-C₁₀ alkyl. In some embodiments, R⁴⁷ is -C(O)R^{47a}. In some embodiments, R⁴⁷ is -C(O)CH₃ or -C(O)CH₂CH₃. In some embodiments, -C(O)-NR^{47a}R^{47b}.

[00348] In some embodiments, R^{47a} is optionally substituted C₁-C₁₀ alkyl. In some embodiments, R^{47a} is optionally substituted C₃-C₈ cycloalkyl.

[00349] In some embodiments, R^{47b} is optionally substituted C₁-C₁₀ alkyl. In some embodiments, R^{47b} is an optionally substituted C₃-C₈ cycloalkyl.

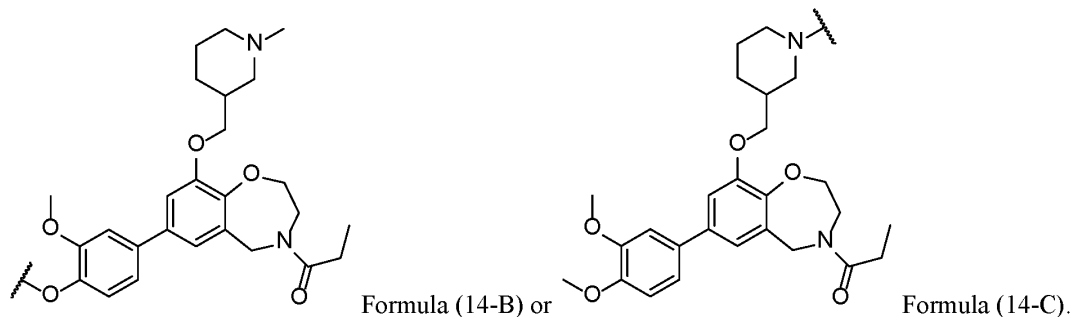
[00350] In some embodiments, Ring K is a 6-membered heterocycloalkyl.

[00351] In some embodiments, q₄ is 3. In some embodiments, q₄ is 2.

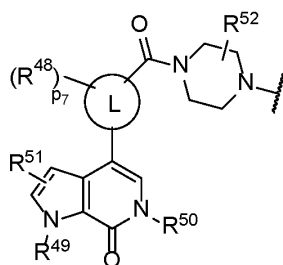
[00352] In some embodiments, q₅ is 2. In some embodiments, q₅ is 1. In some embodiments, q₅ is 0.

[00353] In some embodiments, Formula (14-A) is connected to the linker through Ring K. In some embodiments, Formula (14-A) is connected to the linker through one of R⁴⁵.

[00354] In some embodiments, the second terminus comprises the structure of Formula (14-B) or Formula (14-C), or a pharmaceutically acceptable salt thereof:



[00355] In some embodiments, the second terminus comprises the structure of Formula (15-A), or a pharmaceutically acceptable salt thereof:



Formula (15-A),

wherein:

Ring L is an aryl or heteroaryl;

each R^{48} is hydrogen, halogen, -OH, -CN, -NO₂, -NH₂, C₁-C₁₀ alkyl, C₁-C₁₀ haloalkyl, or C₁-C₁₀ hydroxyalkyl;

R^{49} and R^{50} are each independently hydrogen, optionally substituted C₁-C₁₀ alkyl, optionally substituted C₁-C₁₀ haloalkyl, optionally substituted C₂-C₁₀ alkenyl, or optionally substituted C₂-C₁₀ alkynyl;

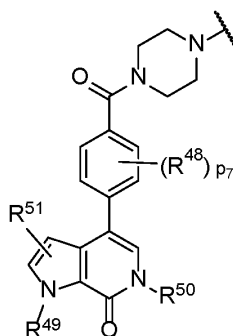
R^{51} is hydrogen, halogen, -OH, -CN, -NO₂, -NH₂, optionally substituted C₁-C₁₀ alkyl, optionally substituted C₁-C₁₀ haloalkyl, optionally substituted C₁-C₁₀ hydroxyalkyl, optionally substituted C₂-C₁₀ alkenyl, or optionally substituted C₂-C₁₀ alkynyl;

R^{52} is hydrogen, halogen, -OH, -CN, -NO₂, -NH₂, optionally substituted C₁-C₁₀ alkyl, optionally substituted C₁-C₁₀ haloalkyl, or optionally substituted C₁-C₁₀ hydroxyalkyl; and

p_7 is 1-4.

[00356] In some embodiments, Ring L is an aryl. In some embodiments, the aryl is phenyl. In some embodiments, Ring L is heteroaryl. In some embodiments, Ring L is a bicyclic heteroaryl comprising 1, 2, or 3 heteroatoms selected from N and O.

[00357] In some embodiments, wherein the second terminus comprises the structure of Formula (15-B), or a pharmaceutically acceptable salt thereof:



Formula (15-B),

wherein:

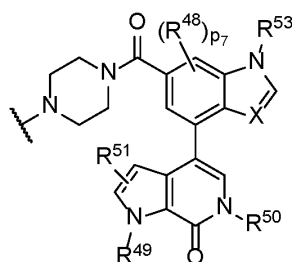
each R^{48} is hydrogen, halogen, -OH, -CN, -NO₂, -NH₂, C₁-C₁₀ alkyl, C₁-C₁₀ haloalkyl, or C₁-C₁₀ hydroxyalkyl;

R^{49} and R^{50} are each independently hydrogen, optionally substituted C₁-C₁₀ alkyl, optionally substituted C₁-C₁₀ haloalkyl, optionally substituted C₂-C₁₀ alkenyl, or optionally substituted C₂-C₁₀ alkynyl;

R^{51} is hydrogen, halogen, -OH, -CN, -NO₂, -NH₂, optionally substituted C₁-C₁₀ alkyl, optionally substituted C₁-C₁₀ haloalkyl, optionally substituted C₁-C₁₀ hydroxyalkyl, optionally substituted C₂-C₁₀ alkenyl, or optionally substituted C₂-C₁₀ alkynyl; and

p_7 is 1-4.

[00358] In some embodiments, wherein the second terminus comprises the structure of Formula (15-C), or a pharmaceutically acceptable salt thereof:



Formula (15-C),

wherein:

X is CR⁴⁸ or N;

each R⁴⁸ is hydrogen, halogen, -OH, -CN, -NO₂, -NH₂, C₁-C₁₀ alkyl, C₁-C₁₀ haloalkyl, or C₁-C₁₀ hydroxyalkyl;

R⁴⁹ and R⁵⁰ are each independently hydrogen, optionally substituted C₁-C₁₀ alkyl, optionally substituted C₁-C₁₀ haloalkyl, optionally substituted C₂-C₁₀ alkenyl, or optionally substituted C₂-C₁₀ alkynyl;

R⁵¹ is hydrogen, halogen, -OH, -CN, -NO₂, -NH₂, optionally substituted C₁-C₁₀ alkyl, optionally substituted C₁-C₁₀ haloalkyl, optionally substituted C₁-C₁₀ hydroxyalkyl, optionally substituted C₂-C₁₀ alkenyl, or optionally substituted C₂-C₁₀ alkynyl;

R⁵³ is hydrogen or optionally substituted C₁-C₁₀ alkyl; and

p₇ is 1-3.

[00359] In some embodiments, each R⁴⁸ is hydrogen, halogen, -OH, -CN, -NO₂, -NH₂, C₁-C₁₀ alkyl, C₁-C₁₀ haloalkyl, or optionally substituted C₁-C₁₀ hydroxyalkyl.

[00360] In some embodiments, R⁴⁹ is hydrogen, optionally substituted C₁-C₁₀ alkyl, optionally substituted C₁-C₁₀ haloalkyl, optionally substituted C₂-C₁₀ alkenyl, or optionally substituted C₂-C₁₀ alkynyl. In some embodiments, R⁴⁹ is an optionally substituted C₁-C₁₀ alkyl. In some embodiments, R⁴⁹ is methyl, ethyl, isopropyl, or tert-butyl. In some embodiments, R⁴⁹ is hydrogen.

[00361] In some embodiments, R⁵⁰ is hydrogen, optionally substituted C₁-C₁₀ alkyl, optionally substituted C₁-C₁₀ haloalkyl, optionally substituted C₂-C₁₀ alkenyl, or optionally substituted C₂-C₁₀ alkynyl. In some embodiments, R⁵⁰ is an optionally substituted C₁-C₁₀ alkyl or optionally substituted C₂-C₁₀ alkenyl. In some embodiments, R⁵⁰ is hydrogen.

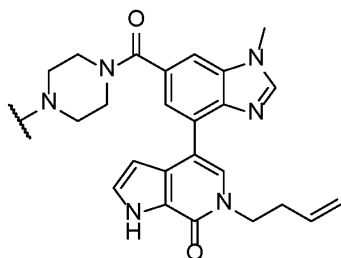
[00362] In some embodiments, R⁵¹ is hydrogen, halogen, -OH, -CN, -NO₂, -NH₂, optionally substituted C₁-C₁₀ alkyl, optionally substituted C₁-C₁₀ haloalkyl, optionally substituted C₁-C₁₀ hydroxyalkyl, optionally substituted C₂-C₁₀ alkenyl, or optionally substituted C₂-C₁₀ alkynyl.

[00363] In some embodiments, R⁵² is hydrogen, halogen, -OH, -CN, -NO₂, -NH₂, optionally substituted C₁-C₁₀ alkyl, optionally substituted C₁-C₁₀ haloalkyl, or optionally substituted C₁-C₁₀ hydroxyalkyl. In some embodiments, R⁵² is hydrogen.

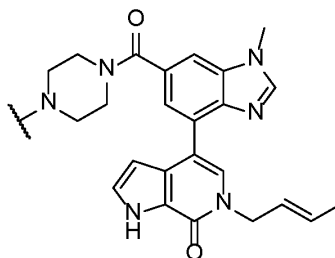
[00364] In some embodiments, R⁵³ is hydrogen or optionally substituted C₁-C₁₀ alkyl. In some embodiments, R⁵³ is an optionally substituted C₁-C₁₀ alkyl. In some embodiments, R⁵³ is methyl, ethyl, isopropyl, or tert-butyl. In some embodiments, R⁵³ is hydrogen.

[00365] In some embodiments, p_7 is 4. In some embodiments, p_7 is 3. In some embodiments, p_7 is 2. In some embodiments, p_7 is 1.

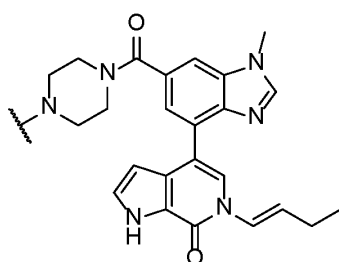
[00366] In some embodiments, the second terminus comprises the structure of Formula (15-D1), (15-D2), or (15-D3), or a pharmaceutically acceptable salt thereof:



Formula (15-D1),

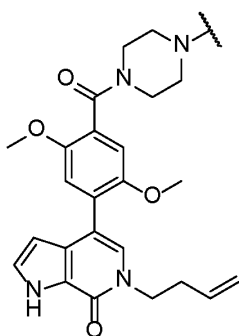


Formular (15-D2), or

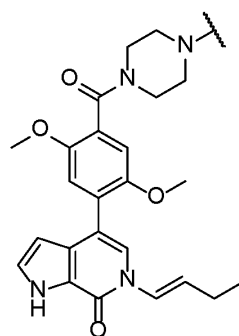


Formula (15-D3).

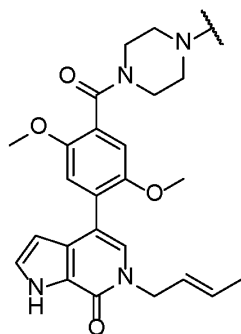
[00367] In some embodiments, the second terminus comprises the structure of Formula (15-E1), (15-E2), or (15-E3), or a pharmaceutically acceptable salt thereof:



Formula (15-E1),

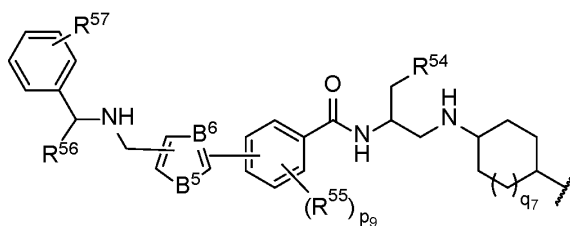


Formula (15-E2), or



Formula (15-E3).

[00368] In some embodiments, the second terminus comprises the structure of Formula (16-A), or a pharmaceutically acceptable salt thereof:



Formula (16-A),

wherein:

B⁵ is -O-, -NH-, or S;

B⁶ is N or CH;

R⁵⁴ is optionally substituted aryl or optionally substituted heteroaryl;

each R⁵⁵ is independently halogen, -OH, -CN, -NO₂, -NH₂, optionally substituted C₁-C₁₀ alkyl, optionally substituted C₁-C₁₀ haloalkyl, optionally substituted C₁-C₁₀ heteroalkyl, or optionally substituted C₁-C₁₀ hydroxyalkyl;

R⁵⁶ is hydrogen, optionally substituted C₁-C₁₀ alkyl, optionally substituted C₁-C₁₀ haloalkyl, or optionally substituted C₁-C₁₀ hydroxyalkyl;

R⁵⁷ is halogen, -OH, -CN, -NO₂, -NH₂, optionally substituted C₁-C₁₀ alkyl, optionally substituted C₁-C₁₀ haloalkyl, or optionally substituted C₁-C₁₀ hydroxyalkyl;

p₉ is 1-3; and

q₇ is 0-2.

[00369] In some embodiments, B⁵ is -O- or -S-. In some embodiments, B⁵ is -O-. In some embodiments, B⁵ is -S-.

[00370] In some embodiments, B⁶ is N. In some embodiments, B⁶ is CH.

[00371] In some embodiments, R⁵⁴ is an optionally substituted aryl. In some embodiments, R⁵⁴ is phenyl optionally substituted with one or more halogen, -CN, -NH₂, -OH, C₁-C₁₀ alkyl, C₁-C₁₀ haloalkyl, or C₁-C₁₀ hydroxyalkyl.

[00372] In some embodiments, each R⁵⁵ is independently halogen, -OH, -CN, -NH₂, optionally substituted C₁-C₁₀ alkyl, optionally substituted C₁-C₁₀ haloalkyl, or optionally substituted C₁-C₁₀ hydroxyalkyl.

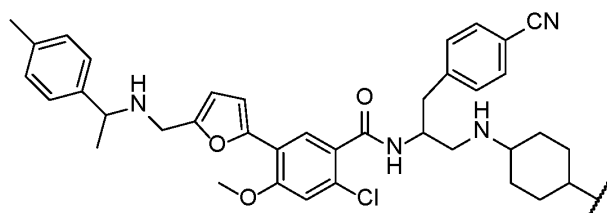
[00373] In some embodiments, R⁵⁶ is optionally substituted C₁-C₁₀ alkyl, optionally substituted C₁-C₁₀ haloalkyl, or optionally substituted C₁-C₁₀ hydroxyalkyl. In some embodiments, R⁵⁶ is optionally substituted C₁-C₁₀ alkyl.

[00374] In some embodiments, R⁵⁷ is halogen, -OH, -CN, -NO₂, -NH₂, or optionally substituted C₁-C₁₀ alkyl.

[00375] In some embodiments, p₉ is 3. In some embodiments, p₉ is 2. In some embodiments, p₉ is 1.

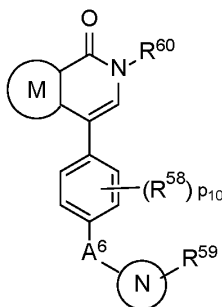
[00376] In some embodiments, q₇ is 2. In some embodiments, q₇ is 1. In some embodiments, q₇ is 0.

[00377] In some embodiments, the second terminus comprises the structure of Formula (16-B), or a pharmaceutically acceptable salt thereof:



Formula (16-B).

[00378] In some embodiments, the second terminus comprises the structure of Formula (17-A), or a pharmaceutically acceptable salt thereof:



Formula (17-A),

wherein:

Ring M is optionally substituted aryl or optionally substituted heteroaryl;

Ring N is absent or 4 to 8-membered heterocycloalkyl;

A⁶ is -O-, -NH-, or -CH₂-;

each R⁵⁸ is independently halogen, -OH, -CN, -NO₂, -NH₂, C₁-C₁₀ alkyl, C₁-C₁₀ haloalkyl, or C₁-C₁₀ hydroxyalkyl;

R⁵⁹ is hydrogen, -OH, -NH₂, C₁-C₁₀ alkyl, C₁-C₁₀ haloalkyl, C₁-C₁₀ hydroxyalkyl, or -NH-C₁-C₁₀ alkyl;

R⁶⁰ is hydrogen or optionally substituted C₁-C₁₀ alkyl; and

p₁₀ is 1-4;

wherein Formula (17-A) is connected to the linker through R⁵⁹.

[00379] In some embodiments, Ring M is an aryl, optionally substituted with one or more halogen, CN, NH₂, OH, C₁-C₁₀ alkyl, C₁-C₁₀ haloalkyl, or C₁-C₁₀ hydroxyalkyl. In some embodiments, Ring M is phenyl. In some embodiments, Ring M is an optionally substituted 6-membered heteroaryl, optionally substituted with one or more halogen, CN, NH₂, OH, C₁-C₁₀ alkyl, C₁-C₁₀ haloalkyl, or C₁-C₁₀ hydroxyalkyl. In some embodiments, Ring M is an optionally substituted pyridine.

[00380] In some embodiments, Ring N is 4 to 8-membered heterocycloalkyl. In some embodiment, Ring N is a 4-membered heterocycloalkyl. In some embodiments, Ring N is a 5-membered heterocycloalkyl. In some embodiments, Ring N is a 6-membered heterocycloalkyl. In some embodiments, Ring N is absent.

[00381] In some embodiments, A⁶ is -O- or -NH-. In some embodiments, A⁶ is -CH₂-.

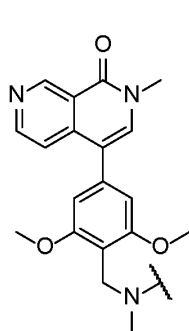
[00382] In some embodiments, each R⁵⁸ is independently -OH, -NH₂, C₁-C₁₀ alkyl, C₁-C₁₀ haloalkyl, or C₁-C₁₀ hydroxyalkyl. In some embodiments, each R⁵⁸ is independently C₁-C₁₀ alkyl, or C₁-C₁₀ hydroxyalkyl. In some embodiments, each R⁵⁸ is independently C₁-C₁₀ hydroxyalkyl.

[00383] In some embodiments, R^{59} is -OH, -NH₂, C₁-C₁₀ hydroxyalkyl, or -NH-C₁-C₁₀ alkyl. In some embodiments, R^{59} is hydrogen.

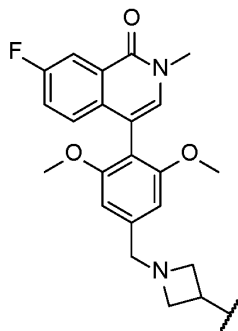
[00384] In some embodiments, R^{60} is optionally substituted C₁-C₁₀ alkyl. In some embodiments, R^{60} is methyl. In some embodiments, R^{60} is hydrogen.

[00385] In some embodiments, p_{10} is 3 or 4. In some embodiments, p_{10} is 2. In some embodiments, p_{10} is 1.

[00386] In some embodiments, the second terminus comprises the structure of Formula (17-B) or Formula (17-C), or a pharmaceutically acceptable salt thereof:

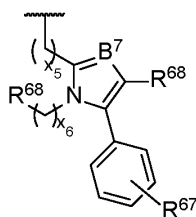


Formula (17-B) or



Formula (17-C).

[00387] In some embodiments, the second terminus comprises the structure of Formula (18-A), or a pharmaceutically acceptable salt thereof:



Formula (18-A),

wherein:

B^7 is N or CH;

R^{67} is hydrogen, halogen, -OH, -CN, -NO₂, -NH₂, optionally substituted C₁-C₁₀ alkyl, optionally substituted C₁-C₁₀ haloalkyl, optionally substituted C₁-C₁₀ heteroalkyl, or optionally substituted C₁-C₁₀ hydroxyalkyl;

R^{68} and R^{69} are each independently an optionally substituted 5-membered heteroaryl; and

x_5 and x_6 are each independently 0-4.

[00388] In some embodiments, B^7 is N. In some embodiments, B^7 is CH.

[00389] In some embodiments, R^{67} is halogen, -OH, -CN, -NO₂, -NH₂, optionally substituted C₁-C₁₀ alkyl, C₁-C₁₀ haloalkyl, or optionally substituted C₁-C₁₀ hydroxyalkyl. In some embodiments, R^{67} is halogen, -OH, -CN, -NO₂, -NH₂, or -CH₃.

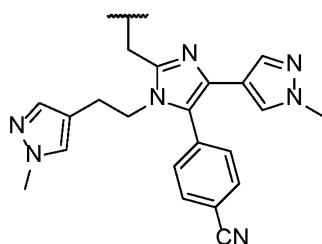
[00390] In some embodiments, R^{68} is optionally substituted oxazole, oxadiazole, thiazole, thiadiazole, pyrrole, or pyrazole. In some embodiments, R^{68} is pyrrole or pyrazole. In some embodiments, R^{68} is pyrrole. In some embodiments, R^{68} is pyrazole.

[00391] In some embodiments, R^{69} is optionally substituted oxazole, oxadiazole, thiazole, thiadiazole, pyrrole, or pyrazole. In some embodiments, R^{69} is pyrrole or pyrazole. In some embodiments, R^{69} is pyrrole. In some embodiments, R^{69} is pyrazole.

[00392] In some embodiments, x_5 is 2 or 3. In some embodiments, x_5 is 1. In some embodiments, x_5 is 0.

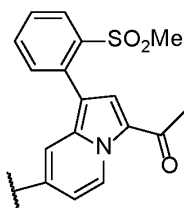
[00393] In some embodiments, x_6 is 3. In some embodiments, x_6 is 2. In some embodiments, x_6 is 1. In some embodiments, x_6 is 0.

[00394] In some embodiments, the second terminus comprise Formula (18-B), or a pharmaceutically acceptable salt thereof:



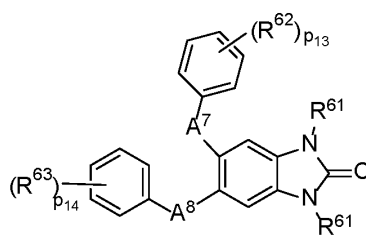
Formula (18-B).

[00395] In some embodiments, the second terminus comprises Formula (19-A), or a pharmaceutically acceptable salt thereof:



Formula (19-A).

[00396] In some embodiments, the second terminus comprises the structure of Formula (20-A), or a pharmaceutically acceptable salt thereof:



Formula (20-A),

wherein:

A^7 is $-NHC(O)-$ or $-NHS(O)_2-$;

A^8 is $-O-$ or $-NH-$;

each R^{61} is independently hydrogen or C_1-C_6 alkyl;

each R^{62} is independently halogen, $-CN$, $-NO_2$, $-OH$, $-OR^{62a}$, $-NR^{62a}R^{62b}$, $-C(O)R^{62a}$, optionally substituted C_1-C_{10} alkyl, optionally substituted C_1-C_{10} haloalkyl, optionally substituted C_1-C_{10} heteroalkyl, or optionally substituted C_1-C_{10} hydroxyalkyl; wherein

each R^{62a} and R^{62b} is independently hydrogen or C_1 - C_{10} alkyl, wherein each R^{63} is independently $-OR^{63a}$, $-NR^{63a}R^{63b}$, optionally substituted C_1 - C_{10} alkyl, optionally substituted C_1 - C_{10} haloalkyl, optionally substituted C_1 - C_{10} heteroalkyl, or optionally substituted C_1 - C_{10} hydroxyalkyl; wherein

each R^{63a} and R^{63b} is independently hydrogen, C_1 - C_{10} alkyl, C_1 - C_{10} alkylamino, C_1 - C_{10} haloalkyl, or C_1 - C_{10} hydroxyalkyl;

p_{13} is 1-3; and

p_{14} is 1-3;

wherein the linker is connected to Formula (20-A) through one of R^{62} or one of R^{63} .

[00397] In some embodiments, A^7 is $-NHC(O)-$. In some embodiments, A^7 is $-NHS(O)_2-$.

[00398] In some embodiments, A^8 is $-O-$. In some embodiments, A^8 is $-NH-$.

[00399] In some embodiments, each R^{61} is independently C_1 - C_6 alkyl. In some embodiments, each R^{61} is methyl. In some embodiments, each R^{61} is hydrogen.

[00400] In some embodiments, each R^{62} is independently optionally substituted C_1 - C_{10} alkyl, optionally substituted C_1 - C_{10} haloalkyl, optionally substituted C_1 - C_{10} heteroalkyl, or optionally substituted C_1 - C_{10} hydroxyalkyl. In some embodiments, each R^{62} is independently optionally substituted C_1 - C_{10} alkyl. In some embodiments, each R^{62} is independently optionally substituted C_1 - C_{10} haloalkyl. In some embodiments, each R^{62} is independently optionally substituted C_1 - C_{10} heteroalkyl. In some embodiments, each R^{62} is independently optionally substituted C_1 - C_{10} hydroxyalkyl.

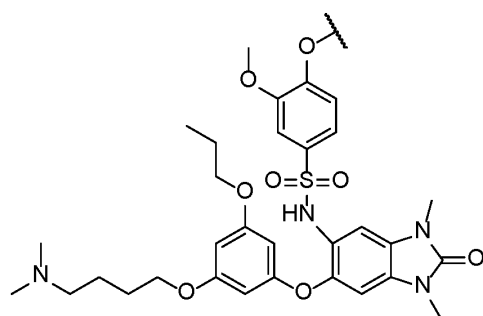
[00401] In some embodiments, each R^{63} is independently optionally substituted C_1 - C_{10} alkyl, optionally substituted C_1 - C_{10} haloalkyl, optionally substituted C_1 - C_{10} heteroalkyl, or optionally substituted C_1 - C_{10} hydroxyalkyl. In some embodiments, each R^{63} is independently optionally substituted C_1 - C_{10} alkyl. In some embodiments, each R^{66} is independently optionally substituted C_1 - C_{10} haloalkyl. In some embodiments, each R^{63} is independently optionally substituted C_1 - C_{10} heteroalkyl. In some embodiments, each R^{63} is independently optionally substituted C_1 - C_{10} hydroxyalkyl.

[00402] In some embodiments, p_{13} is 1. In some embodiments, p_{13} is 2. In some embodiments, p_{13} is 3.

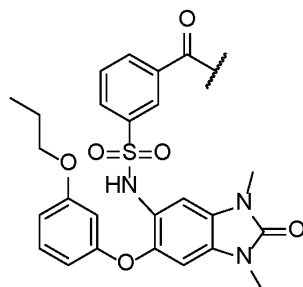
[00403] In some embodiments, p_{14} is 1. In some embodiments, p_{14} is 2. In some embodiments, p_{14} is 3.

[00404] In some embodiments, the linker is connected to Formula (20-A) through one of R^{62} . In some embodiments, the linker is connected to Formula (20-A) through one of R^{63} .

[00405] In some embodiments, the second terminus comprises the structure of Formula (20-B) or Formula (20-C), or a pharmaceutically acceptable salt thereof.

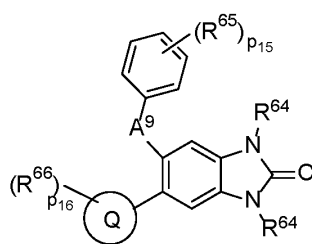


Formula (20-B) or



Formula (20-C).

[00406] In some embodiments, the second terminus comprises the structure of Formula (21-A), or a pharmaceutically acceptable salt thereof:



Formula (21-A),

wherein:

Ring Q is C₃-C₈ cycloalkyl or 4 to 8-membered heterocycloalkyl;

A⁹ is -O-, -NH-, or -NHC(O)-;

each R⁶⁴ is independently hydrogen or C₁-C₆ alkyl;

each R⁶⁵ is independently halogen, -CN, -NO₂, -OH, -OR^{62a}, -NR^{62a}R^{62b}, optionally substituted C₁-C₁₀ alkyl, optionally substituted C₁-C₁₀ haloalkyl, optionally substituted C₁-C₁₀ heteroalkyl, or optionally substituted C₁-C₁₀ hydroxyalkyl; wherein

each R^{62a} and R^{62b} is independently hydrogen or C₁-C₁₀ alkyl;

each R⁶⁶ is independently halogen, optionally substituted C₁-C₁₀ alkyl, optionally substituted C₁-C₁₀

haloalkyl, optionally substituted C₁-C₁₀ heteroalkyl, or optionally substituted C₁-C₁₀ hydroxyalkyl;

p_{15} is 0-3; and

p₁₆ is 1-3;

wherein Formula (21-A) is connected to the linker at one of R⁶⁵ or one of R⁶⁶.

[00407] In some embodiments, A⁹ is -O-. In some embodiments, A⁹ is -NH-. In some embodiments, A⁹ is -NHC(O)-.

[00408] In some embodiments, Ring Q is C₃-C₈ cycloalkyl. In some embodiments, Ring Q is 4 to 8-membered heterocycloalkyl.

[00409] In some embodiments, each R⁶⁴ is independently C₁-C₆ alkyl. In some embodiments, each R⁶⁴ is methyl. In some embodiments, each R⁶⁴ is hydrogen.

[00410] In some embodiments, each R⁶⁵ is independently optionally substituted C₁-C₁₀ alkyl, optionally substituted C₁-C₁₀ haloalkyl, optionally substituted C₁-C₁₀ heteroalkyl, or optionally substituted C₁-C₁₀ hydroxyalkyl. In some embodiments, each R⁶⁵ is independently optionally substituted C₁-C₁₀ alkyl. In some embodiments, each R⁶⁵ is independently optionally substituted C₁-C₁₀ haloalkyl. In some embodiments, each R⁶⁵ is independently optionally substituted C₁-C₁₀ heteroalkyl. In some embodiments, each R⁶⁵ is independently optionally substituted C₁-C₁₀ hydroxyalkyl.

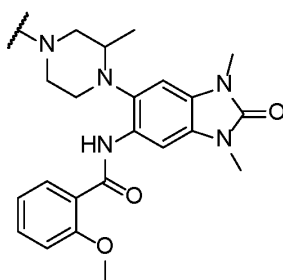
[00411] In some embodiments, each R⁶⁶ is independently optionally substituted C₁-C₁₀ alkyl, optionally substituted C₁-C₁₀ haloalkyl, optionally substituted C₁-C₁₀ heteroalkyl, or optionally substituted C₁-C₁₀ hydroxyalkyl. In some embodiments, each R⁶⁶ is independently optionally substituted C₁-C₁₀ alkyl. In some embodiments, each R⁶⁶ is independently optionally substituted C₁-C₁₀ haloalkyl. In some embodiments, each R⁶⁶ is independently optionally substituted C₁-C₁₀ heteroalkyl. In some embodiments, each R⁶⁶ is independently optionally substituted C₁-C₁₀ hydroxyalkyl.

[00412] In some embodiments, p₁₅ is 0. In some embodiments, p₁₅ is 1. In some embodiments, p₁₅ is 2. In some embodiments, p₁₅ is 3.

[00413] In some embodiments, p₁₆ is 1. In some embodiments, p₁₆ is 2. In some embodiments, p₁₆ is 3.

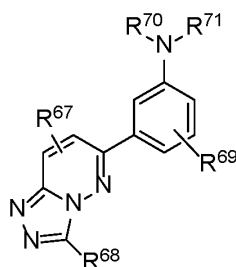
[00414] In some embodiments, Formula (21-A) is connected to the linker at one of R⁶⁵. In some embodiments, Formula (21-A) is connected to the linker at one of R⁶⁶.

[00415] In some embodiments, the second terminus comprises the structure of Formula (21-B), or a pharmaceutically acceptable salt thereof:



Formula (21-B).

[00416] In some embodiments, the second terminus comprises the structure of Formula (22-A), or a pharmaceutically acceptable salt thereof:



Formula (22-A),

wherein:

R^{67} is hydrogen, $-NH_2$, or $-NHSO_2CH_3$;

R^{68} and R^{69} are each independently halogen, $-CN$, $-NO_2$, $-OH$, optionally substituted C_1 - C_{10} alkyl, optionally substituted C_1 - C_{10} haloalkyl, or optionally substituted C_1 - C_{10} hydroxyalkyl;

R^{70} is $-S(O)R^{70a}$ or $-S(O)_2R^{70a}$, wherein R^{70a} is hydrogen or C_1 - C_{10} alkyl; and

R^{71} is hydrogen or C_1 - C_{10} alkyl;

wherein Formula (22-A) is attached to the linker at R^{67} or R^{71} .

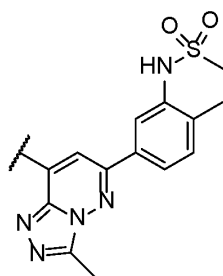
[00417] In some embodiments, R^{67} is hydrogen. In some embodiments, R^{67} is $-NH_2$, or $-NHSO_2CH_3$.

[00418] In some embodiments, R^{68} and R^{69} are each independently optionally substituted C_1 - C_{10} alkyl. In some embodiments, R^{68} and R^{69} are each methyl.

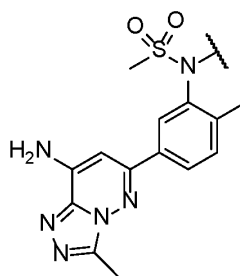
[00419] In some embodiments, R^{70} is $-S(O)_2R^{70a}$. In some embodiments, R^{70} is $-S(O)_2CH_3$.

[00420] In some embodiments, Formula (22-A) is attached to the linker at R^{67} . In some embodiments, Formula (22-A) is attached to the linker at R^{71} .

[00421] In some embodiments, the second terminus comprises the structure of Formula (22-B) or Formula (22-C), or a pharmaceutically acceptable salt thereof:

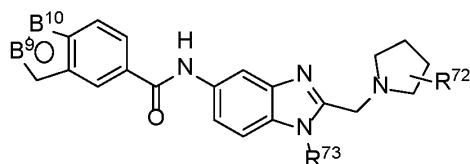


Formula (22-B) or



Formula (22-C).

[00422] In some embodiments, the second terminus comprises the structure of Formula (23-A), or a pharmaceutically acceptable salt thereof:



Formula (23-A)

wherein:

B^9 is $-\text{CH}-\text{CR}^{B9}-$, $-\text{N}-$, or NR^{B10} ;

B^{10} is $-\text{N}-$ or NR^{B10} , wherein

R^{B9} is hydrogen or halogen; and R^{B10} is hydrogen;

R^{72} is halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{OH}$, optionally substituted $\text{C}_1\text{-C}_{10}$ alkyl, optionally substituted $\text{C}_1\text{-C}_{10}$ haloalkyl, or optionally substituted $\text{C}_1\text{-C}_{10}$ hydroxyalkyl; and

R^{73} is hydrogen;

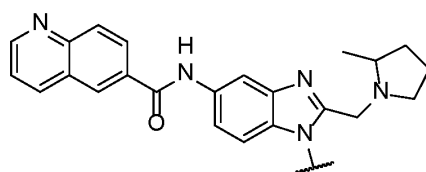
wherein Formula (23-A) is attached to the linker at R^{B9} , R^{B10} , or R^{73} .

[00423] In some embodiments, B^9 is $-\text{CH}-\text{CR}^{B9}-$ and B^{10} is $-\text{N}-$. In some embodiments, B^9 is $-\text{N}-$ and B^{10} is NR^{B10} . In some embodiments, B^9 is NR^{B10} and B^{10} is $-\text{N}-$.

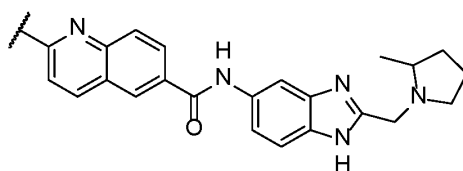
[00424] In some embodiments, R^{72} is an optionally substituted $\text{C}_1\text{-C}_{10}$ alkyl. In some embodiments, R^{72} is methyl.

[00425] In some embodiments, Formula (23-A) is attached to the linker at R^{B9} or R^{B10} . In some embodiments, Formula (23-A) is attached to the linker at R^{73} .

[00426] In some embodiments, the second terminus comprises the structure of Formula (23-B) or Formula (23-C), or a pharmaceutically acceptable salt thereof:

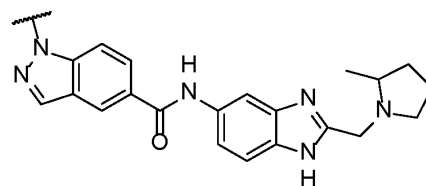


Formula (23-B), or

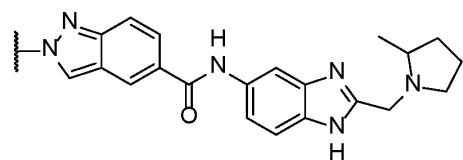


Formula (23-C).

[00427] In some embodiments, the second terminus comprises the structure of Formula (23-D) or Formula (23-E), or a pharmaceutically acceptable salt thereof:

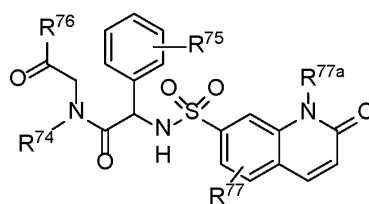


Formula (23-D) or



Formula (23-E).

[00428] In some embodiments, the second terminus comprises the structure of Formula (24-A), or a pharmaceutically acceptable salt thereof:



Formula (24-A),

wherein:

R^{74} is $-\text{CH}_2$ -(optionally substituted 5-membered heteroaryl);

R^{75} is $-\text{O}-(\text{C}_1\text{-C}_{10} \text{ alkyl})-\text{R}^{75a}$; wherein R^{75a} is $-\text{C}(\text{O})\text{O-alkyl}$;

R^{76} is $-\text{OR}^{76a}$, wherein R^{76a} is hydrogen or alkyl;

R^{77} is hydrogen or halogen; and

R^{77a} is hydrogen or $\text{C}_1\text{-C}_{10}$ alkyl;

wherein Formula (24-A) is attached to the linker at R^{75a} or R^{76a} .

[00429] In some embodiments, R^{75} is $-\text{O}-(\text{C}_1\text{-C}_{10} \text{ alkyl})-\text{C}(\text{O})\text{O-alkyl}$. In some embodiments, R^{75} is $-\text{O}-(\text{C}_1\text{-C}_4 \text{ alkyl})-\text{C}(\text{O})\text{O-}\text{C}_1\text{-C}_4 \text{ alkyl}$.

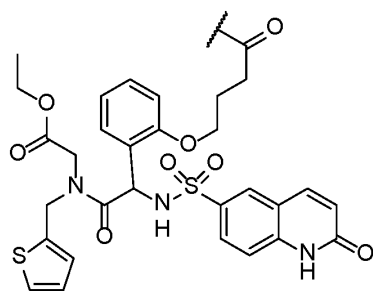
[00430] In some embodiments, R^{76} is $-\text{OH}$. In some embodiments, R^{76} is $-\text{OCH}_3$. In some embodiments, R^{76} is $-\text{O-CH}_2\text{CH}_3$.

[00431] In some embodiments, R^{77} is halogen. In some embodiments, R^{77} is hydrogen.

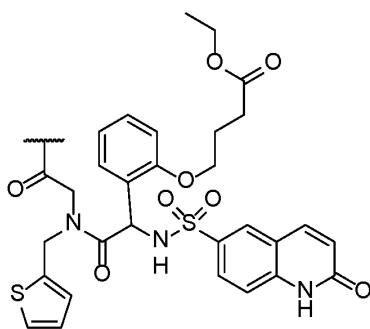
[00432] In some embodiments, R^{77a} is hydrogen or methyl. In some embodiments, R^{77a} is methyl. In some embodiments, R^{77a} is hydrogen.

[00433] In some embodiments, Formula (24-A) is attached to the linker at R^{75a} . In some embodiments, Formula (24-A) is attached to the linker at R^{76a} .

[00434] In some embodiments, the second terminus comprises the structure of Formula (24-B) or Formula (24-C), or a pharmaceutically acceptable salt thereof:

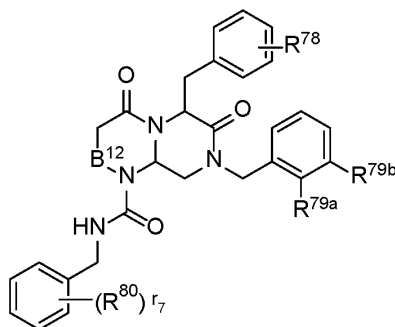


Formula (24-B) or



Formula (24-C).

[00435] In some embodiments, the second terminus comprises the structure of Formula (25-A), or a pharmaceutically acceptable salt thereof:



Formula (25-A),

wherein:

B^{12} is $-NR^{80a}-$ or $-C(R^{80b})_2-$;

R^{78} is halogen, $-CN$, $-NO_2$, $-OH$, or optionally substituted C_1 - C_{10} alkyl;

R^{79a} and R^{79b} are each independently halogen, $-CN$, $-NO_2$, $-NH_2$, $-N(CH_3)_2$, or optionally substituted C_1 - C_{10} alkyl;

or R^{79a} and R^{79b} together with the atoms to which they are attached form a 6-membered aryl;

each R^{80} is independently hydrogen, $-O-C_1-C_3$ alkyl, C_1 - C_{10} alkyl, or C_1 - C_{10} alkoxy;

R^{80a} is C_1 - C_6 alkyl;

each R^{80b} is independently hydrogen or C_1 - C_6 alkyl; and

r_7 is 1, 2, or 3;

wherein Formula (25-A) is attached to the linker at one of R^{80} .

[00436] In some embodiments, B^{12} is $-NR^{80a}-$. In some embodiments, B^{12} is $-C(R^{80b})_2-$.

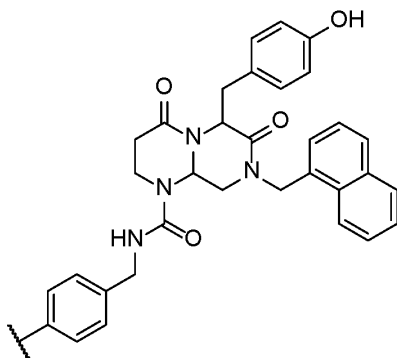
[00437] In some embodiments, R^{78} is $-CN$, $-NO_2$, or $-OH$. In some embodiments, R^{78} is $-OH$. In some embodiments, R^{78} is halogen. In some embodiments, R^{78} is an optionally substituted C_1 - C_{10} alkyl.

[00438] In some embodiments, R^{79a} and R^{79b} are each independently halogen, $-NH_2$, or $-N(CH_3)_2$.

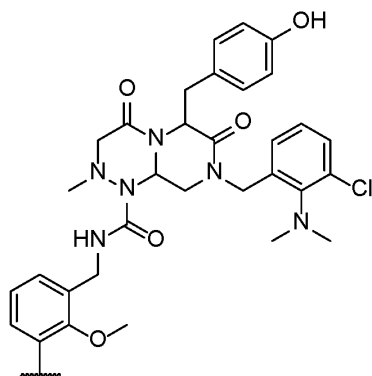
[00439] In some embodiments, R^{79a} and R^{79b} together with the atoms to which they are attached form a 6-membered aryl.

[00440] In some embodiments, each R^{80} is independently hydrogen. In some embodiments, each R^{80} is independently C_1 - C_{10} alkyl. In some embodiments, each R^{80} is independently C_1 - C_{10} alkoxy. In some embodiments, each R^{80} is independently $-OCH_3$.

[00441] In some embodiments, the second terminus comprises the structure of Formula (25-B) or Formula (25-C), or a pharmaceutically acceptable salt thereof:

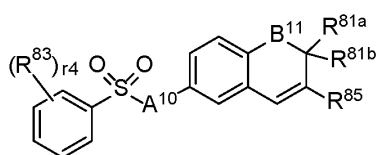


Formula (25-B) or



Formula (25-C).

[00442] In some embodiments, the second terminus comprises the structure of Formula (26-A), or a pharmaceutically acceptable salt thereof:



Formula (26-A),

wherein:

B^{11} is $-O-$ or $-NR^{82}-$;

A^{10} is $-NR^{84}-$ or $-NR^{84}CH_2-$;

R^{81a} and R^{81b} are each independently C_1 - C_{10} alkyl;

or R^{81a} and R^{81b} combine together to form oxo ($=O$);

R^{82} is hydrogen or C_1 - C_3 alkyl;

each R^{83} is independently halogen, $-CN$, $-NO_2$, $-OH$, $-OR^{83a}$, or optionally substituted C_1 - C_{10} alkyl; wherein

R^{83a} is C_1 - C_{10} alkyl;

R⁸⁴ is hydrogen, C₁-C₃ alkyl, C₃-C₆ cycloalkyl, or phenyl;

R⁸⁵ is hydrogen or C₁-C₁₀ alkyl; and

r₄ is 1, 2, or 3;

wherein Formula (26-A) is attached to the linker at one of R⁸³.

[00443] In some embodiments, B¹¹ is -O-. In some embodiments, B¹¹ is -NR⁸²-. In some embodiments, B¹¹ is NCH₃.

[00444] In some embodiments, A¹⁰ is -NR⁸⁴-. In some embodiments, A¹⁰ is -NR⁸⁴CH₂-.

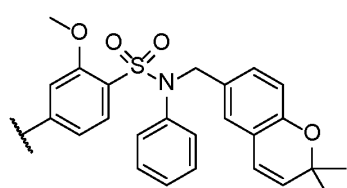
[00445] In some embodiments, R^{81a} and R^{81b} are each methyl. In some embodiments, R^{81a} and R^{81b} combine together to form oxo (=O).

[00446] In some embodiments, each R⁸³ is independently -CN, -OH, -OR^{83a}, or optionally substituted C₁-C₁₀ alkyl. In some embodiments, each R⁸³ is independently -OH or -OR^{83a}.

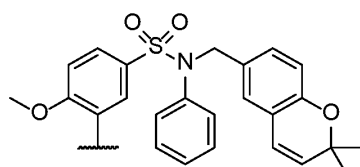
[00447] In some embodiments, R⁸⁴ is C₃-C₆ cycloalkyl or phenyl. In some embodiments, R⁸⁴ is phenyl.

[00448] In some embodiments, R⁸⁵ is C₁-C₁₀ alkyl. In some embodiments, R⁸⁵ is methyl. In some embodiments, R⁸⁵ is hydrogen.

[00449] In some embodiments, the second terminus comprises the structure of Formula (26-B) or Formula (26-C), or a pharmaceutically acceptable salt thereof:

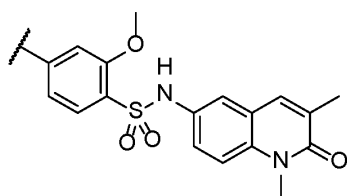


Formula (26-B) or

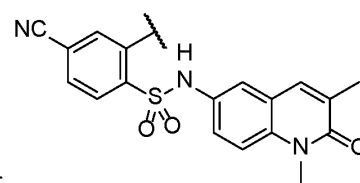


Formula (26-C).

[00450] In some embodiments, the second terminus comprises the structure of Formula (26-D) or Formula (26-E), or a pharmaceutically acceptable salt thereof:

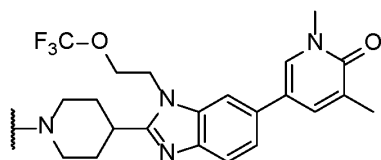


Formula (26-D) or



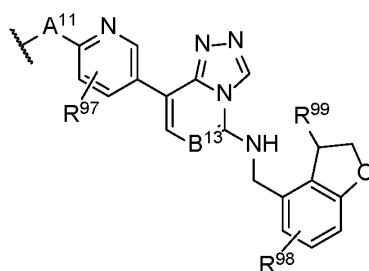
Formula (26-E).

[00451] In some embodiments, the second terminus comprises the structure of Formula (27-A), or a pharmaceutically acceptable salt thereof:



Formula (27-A).

[00452] In some embodiments, the second terminus comprises the structure of Formula (28-A), or a pharmaceutically acceptable salt thereof:



Formula (28-A),

wherein:

A¹¹ is C₁-C₆ alkylene;

B¹³ is N or CR¹⁰⁰;

R⁹⁷ is C₁-C₆ alkyl;

R⁹⁸ is halogen;

R⁹⁹ is hydrogen, halogen, or optionally substituted C₁-C₁₀ alkyl; and

R¹⁰⁰ is -OR^{100a} or optionally substituted C₁-C₁₀ alkyl; wherein R^{100a} is hydrogen or C₁-C₁₀ alkyl;

or R⁹⁹ and R¹⁰⁰ together with the atoms to which they are attached form a heterocycloalkyl.

[00453] In some embodiments, A¹¹ is C₁-C₄ alkylene. In some embodiments, A¹¹ is -CH₂CH₂-.

[00454] In some embodiments, B¹³ is N. In some embodiments, B¹³ is CR¹⁰⁰.

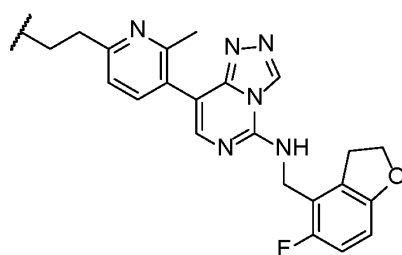
[00455] In some embodiments, R⁹⁷ is methyl.

[00456] In some embodiments, R⁹⁸ is -Cl.

[00457] In some embodiments, R¹⁰⁰ is -OR^{100a}. In some embodiments, R¹⁰⁰ is an optionally substituted C₁-C₁₀ alkyl.

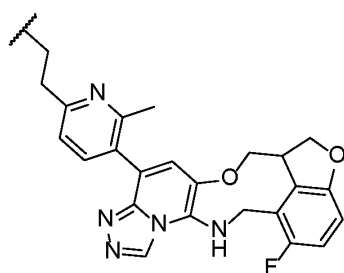
[00458] In some embodiments, R⁹⁹ and R¹⁰⁰ together with the atoms to which they are attached form a heterocycloalkyl.

[00459] In some embodiments, the second terminus comprises the structure of Formula (28-B), or a pharmaceutically acceptable salt thereof:



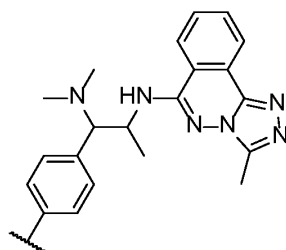
Formula (28-B).

[00460] In some embodiments, the second terminus comprises the structure of Formula (28-C), or a pharmaceutically acceptable salt thereof:



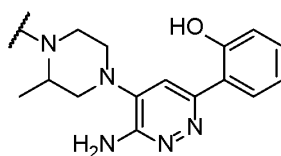
Formula (28-C).

[00461] In some embodiments, the second terminus comprises the structure of Formula (29-A), or a pharmaceutically acceptable salt thereof:



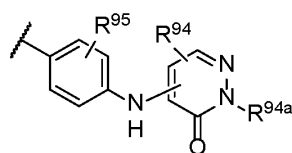
Formula (29-A).

[00462] In some embodiments, the second terminus comprises the structure of Formula (30-A), or a pharmaceutically acceptable salt thereof:



Formula (30-A).

[00463] In some embodiments, the second terminus comprises the structure of Formula (31-A), or a pharmaceutically acceptable salt thereof:



Formula (31-A),

wherein:

R^{94} is halogen;

R^{94a} is hydrogen or C_1 - C_3 alkyl; and

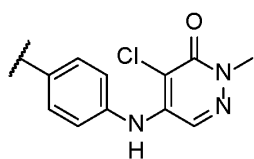
R^{95} is hydrogen, halogen, -OH, -OCH₃, or optionally substituted C_1 - C_{10} alkyl.

[00464] In some embodiments, R^{94} is -Cl.

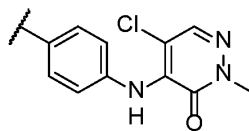
[00465] In some embodiments, R^{94a} is C_1 - C_3 alkyl. In some embodiments, R^{94a} is methyl. In some embodiments, R^{94a} is hydrogen.

[00466] In some embodiments, R^{95} is halogen, -OH, -OCH₃, or optionally substituted C_1 - C_{10} alkyl. In some embodiments, R^{95} is hydrogen.

[00467] In some embodiments, the second terminus comprises the structure of Formula (31-B) or Formula (31-C), or a pharmaceutically acceptable salt thereof:

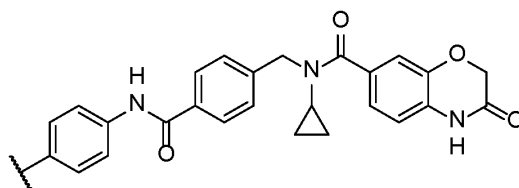


Formula (31-B) or



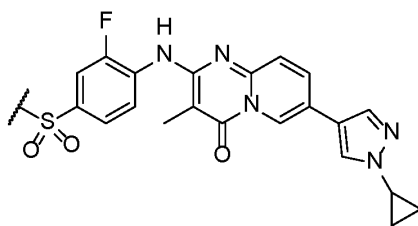
Formula (31-C).

[00468] In some embodiments, the second terminus comprises the structure of Formula (32-A), or a pharmaceutically acceptable salt thereof:



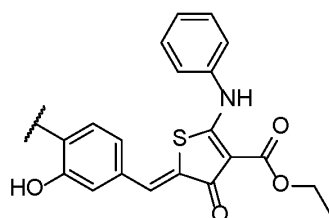
Formula (32-A).

[00469] In some embodiments, the second terminus comprises the structure of Formula (33-A), or a pharmaceutically acceptable salt thereof:



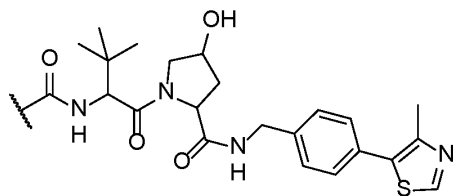
Formula (33-A).

[00470] In some embodiments, the second terminus comprises the structure of Formula (34-A), or a pharmaceutically acceptable salt thereof:



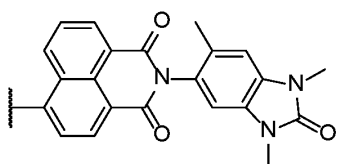
Formula (34-A).

[00471] In some embodiments, the second terminus comprises the structure of Formula (35-A), or a pharmaceutically acceptable salt thereof:

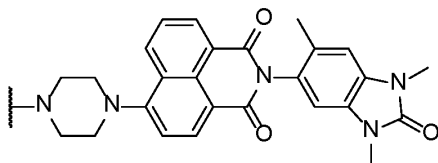


Formula (35-A).

[00472] In some embodiments, the second terminus comprises the structure of Formula (36-A) or Formula (36-B), or a pharmaceutically acceptable salt thereof:

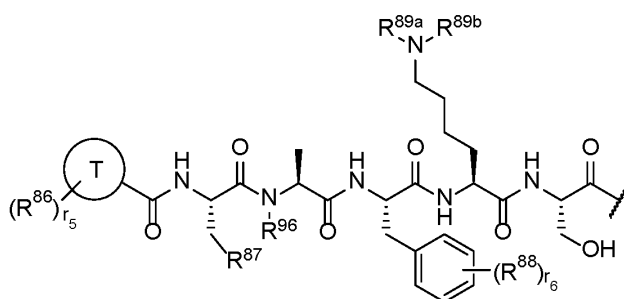


Formula (36-A) or



Formula (36-B).

[00473] In some embodiments, the second terminus comprises the structure of Formula (37-A), or a pharmaceutically acceptable salt thereof:



Formula (37-A),

wherein:

Ring T is a C₅-C₆ cycloalkyl, 5 to 6-membered heterocycloalkyl, or phenyl;

each R⁸⁶ is independently halogen, -CN, -NO₂, -OH, -OR^{86a}, -N(R^{86b})₂, or optionally substituted C₁-C₁₀ alkyl; wherein

each R^{86a} is independently C₁-C₁₀ alkyl;

each R^{86b} is independently hydrogen or C₁-C₁₀ alkyl;

R⁸⁷ is C₅-C₆ cycloalkyl or phenyl;

each R⁸⁸ is independently halogen, -CN, -NO₂, -OH, -OR^{88a}, -NR^{88b}R^{88b}, or optionally substituted C₁-C₁₀ alkyl; wherein

each R^{88a} is independently C₁-C₁₀ alkyl;

each R^{88b} is independently hydrogen or C₁-C₁₀ alkyl;

R^{89a} and R^{89b} are each independently hydrogen or C₁-C₁₀ alkyl;

or R^{89a} and R^{89b} together with the atom to which they are attached form a 5 to 6-membered heterocycloalkyl;

R⁹⁶ is hydrogen or -CH₃; and

r₅ and r₆ are each independently 0, 1, 2, or 3.

[00474] In some embodiments, Ring T is a C₅-C₆ cycloalkyl. In some embodiments, Ring T is a 5 to 6-membered heterocycloalkyl. In some embodiments, Ring T is phenyl.

[00475] In some embodiments, each R^{86} is independently halogen, $-OH$, $-OR^{86a}$, or $-N(R^{86b})_2$. In some embodiments, each R^{86} is independently halogen or $-N(R^{86b})_2$. In some embodiments, each R^{86} is independently $-N(R^{86b})_2$.

[00476] In some embodiments, R^{87} is C_5 - C_6 cycloalkyl. In some embodiments, R^{87} is phenyl.

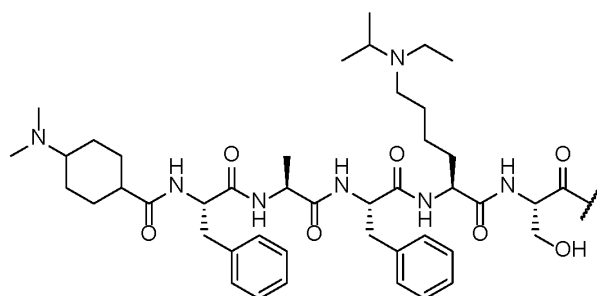
[00477] In some embodiments, R^{89a} and R^{89b} are each independently C_1 - C_{10} alkyl. In some embodiments, R^{89a} and R^{89b} are each hydrogen.

[00478] In some embodiments, R^{89a} and R^{89b} together with the atom to which they are attached form a 5 to 6-membered heterocycloalkyl.

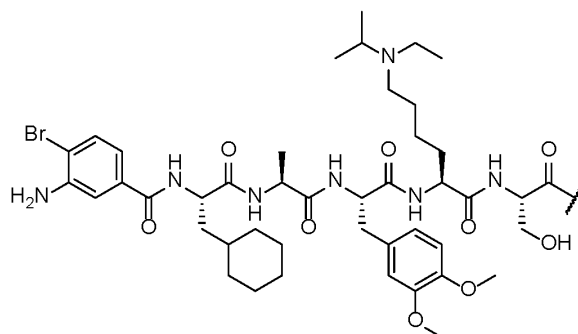
[00479] In some embodiments, R^{96} is $-CH_3$. In some embodiments, R^{96} is hydrogen.

[00480] In some embodiments, r_5 and r_6 are each independently 0, 1, or 2.

[00481] In some embodiments, the second terminus comprises the structure of Formula (37-B) or Formula (37-C), or a pharmaceutically acceptable salt thereof:

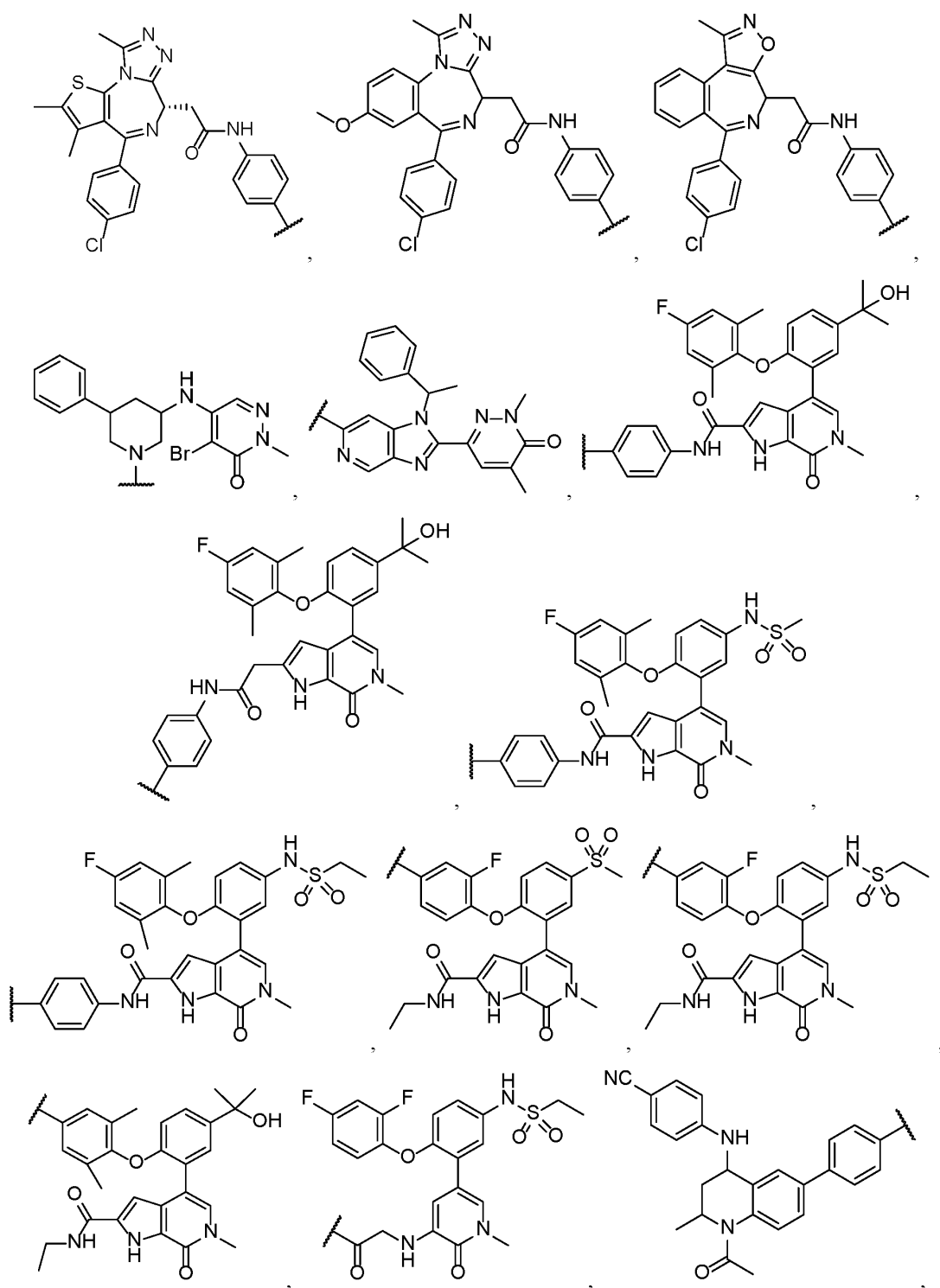


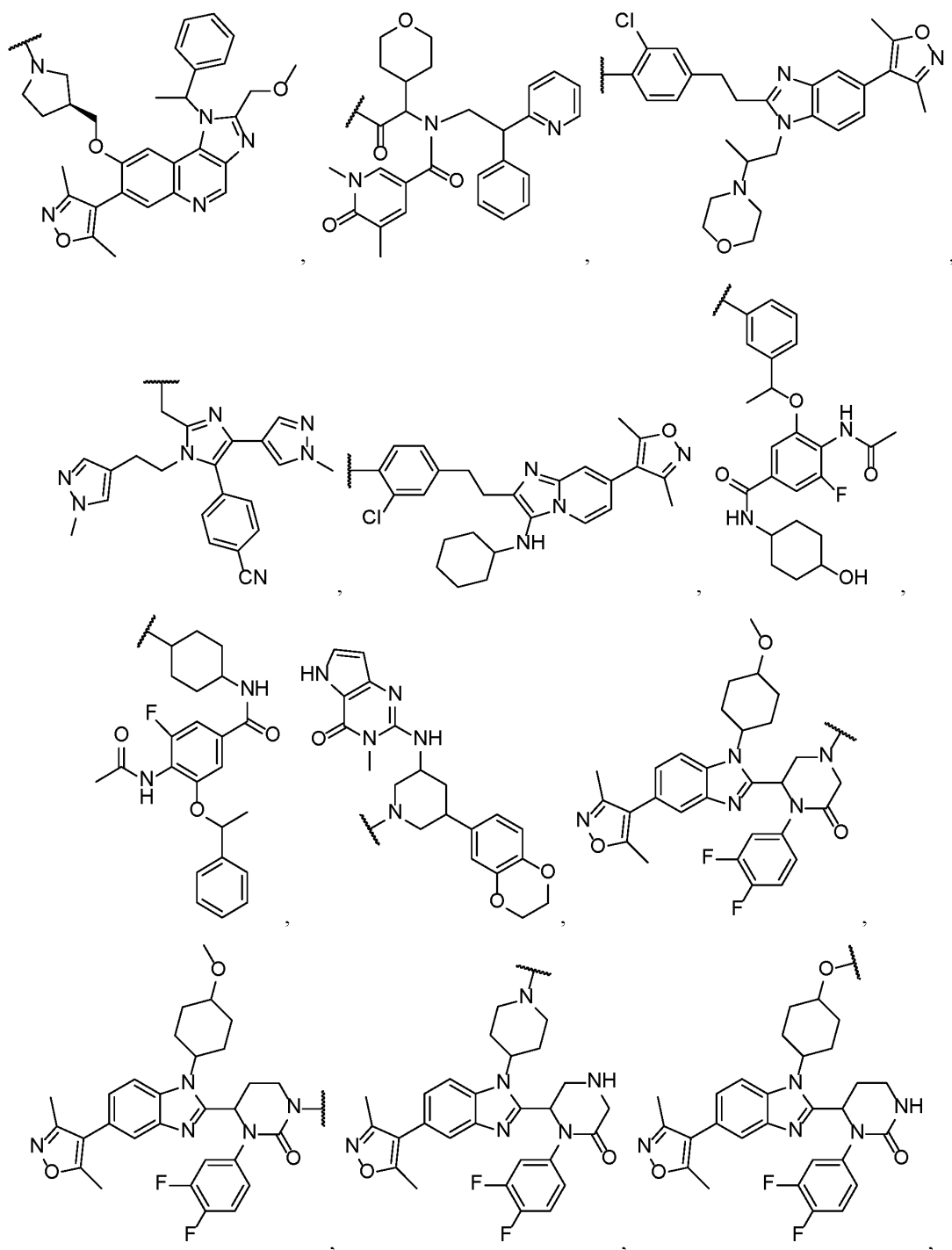
Formula (37-B) or

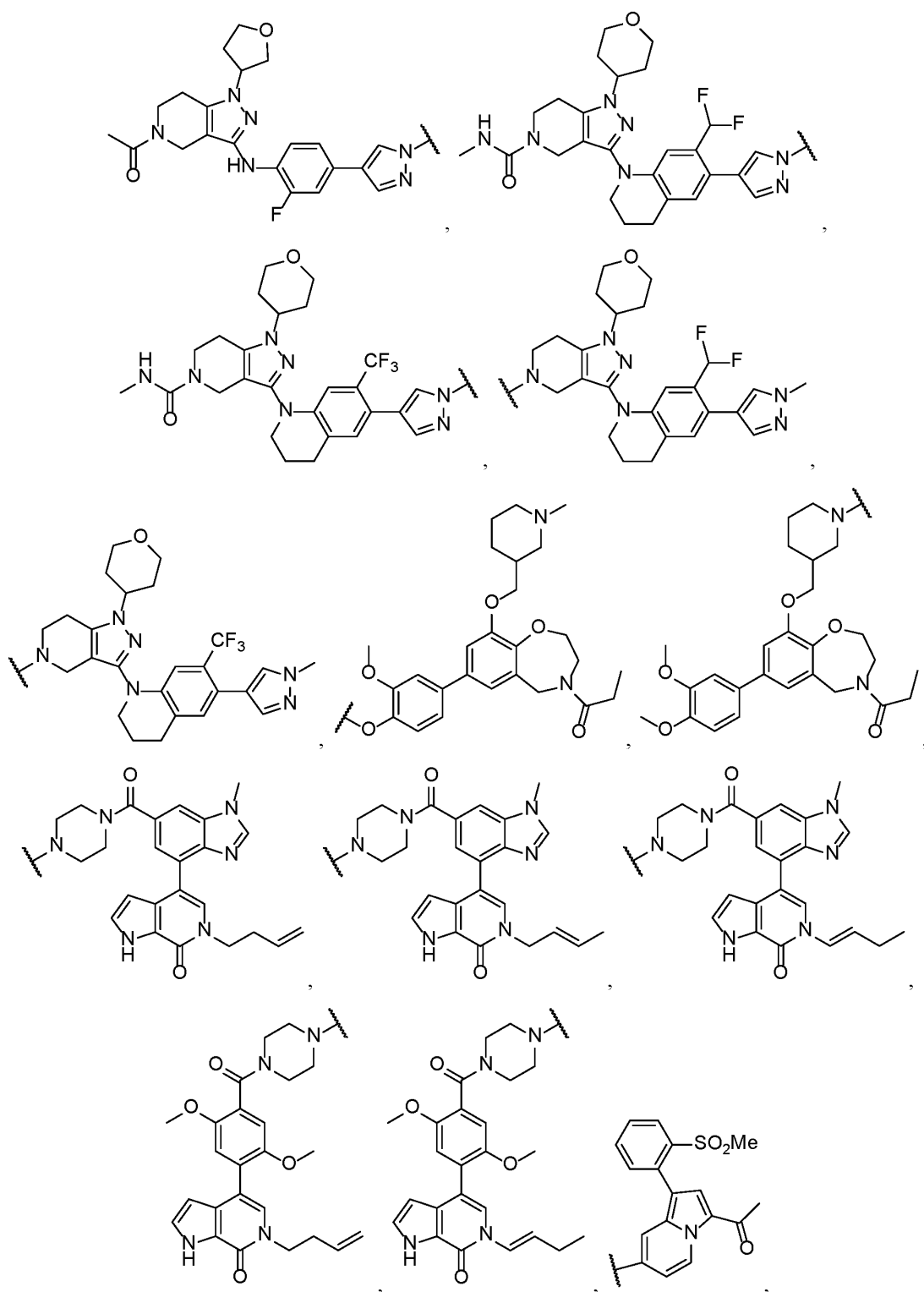


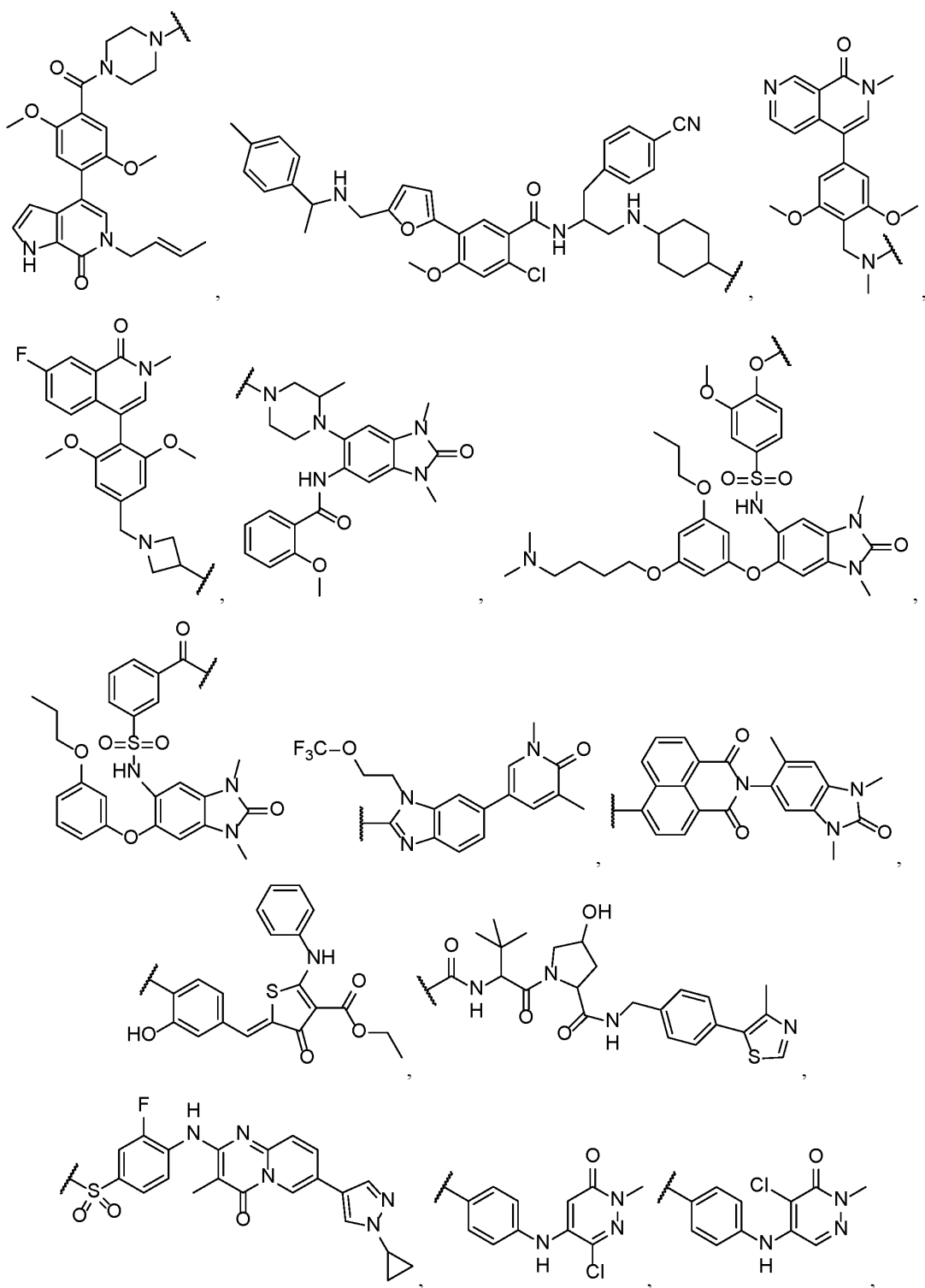
Formula (37-C).

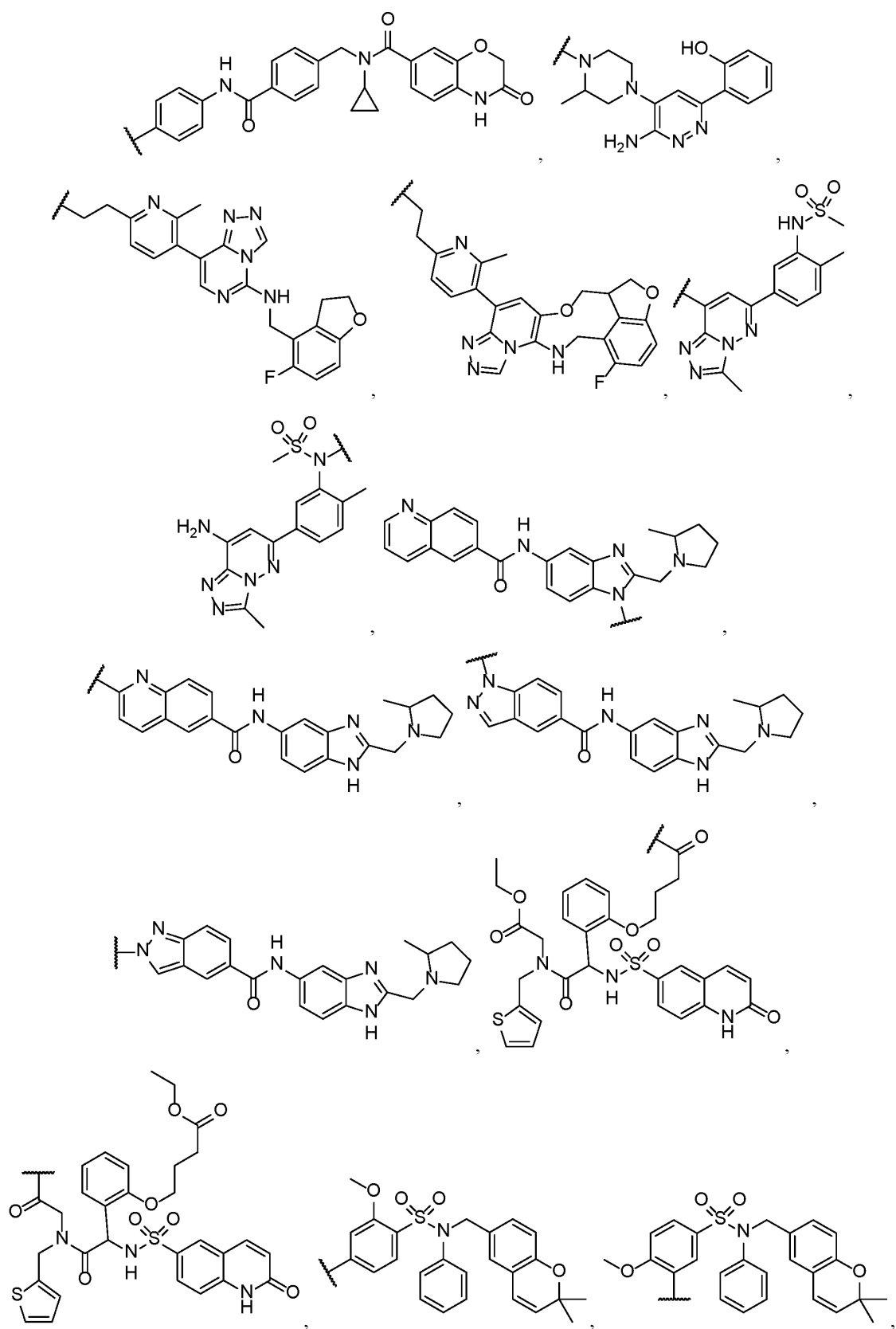
[00482] In some embodiments, the second terminus is selected from the group consisting of:

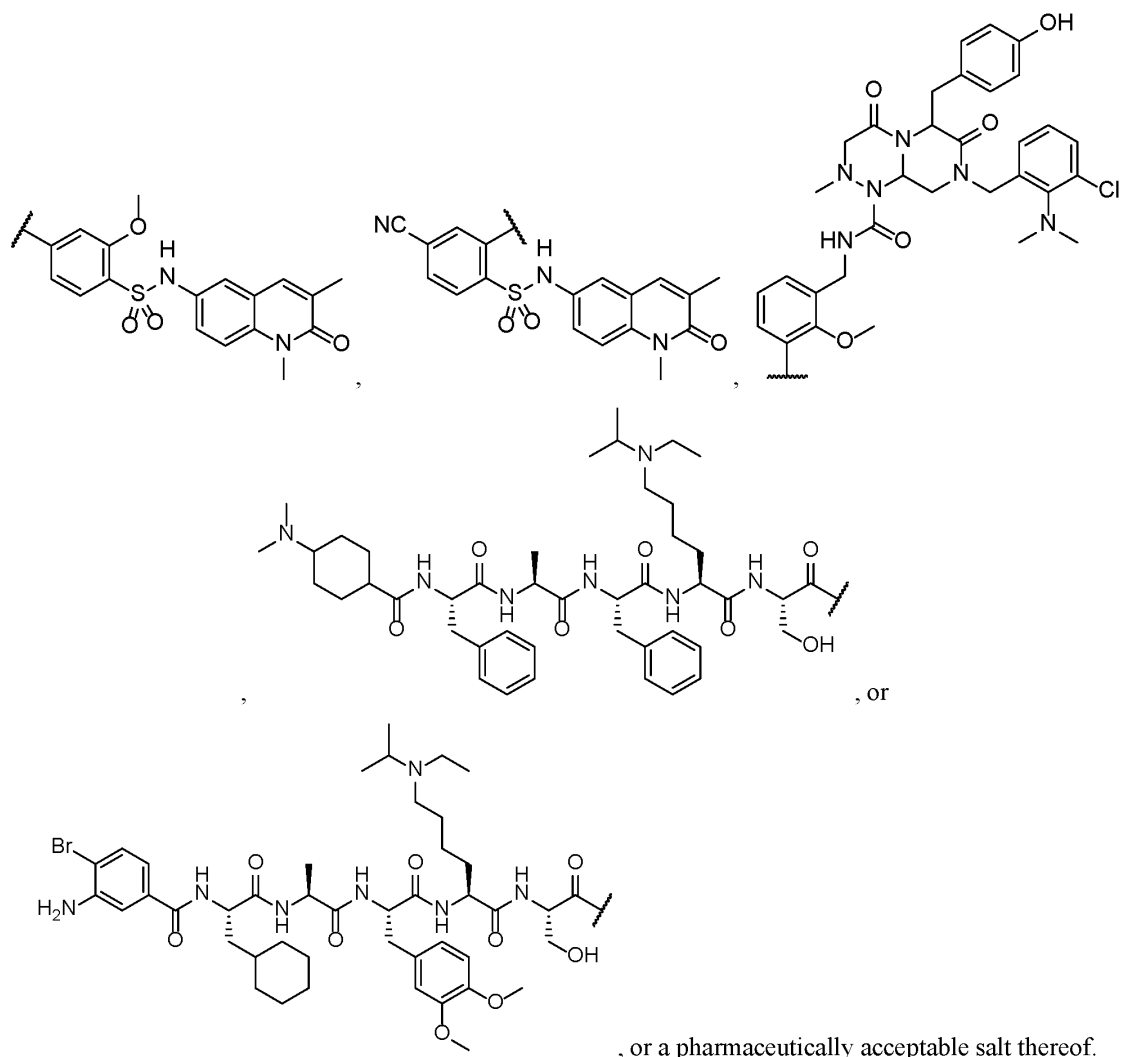








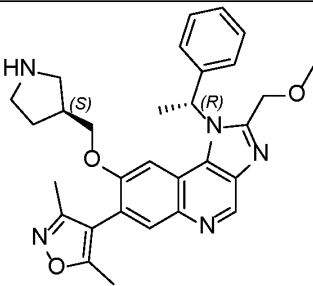
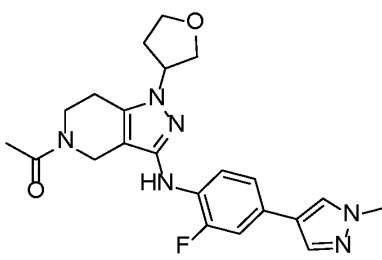
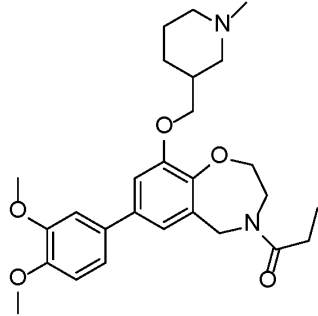
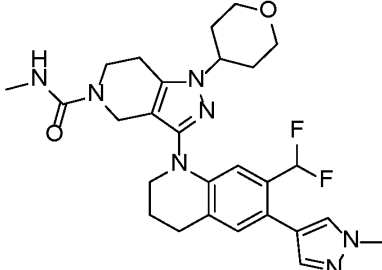
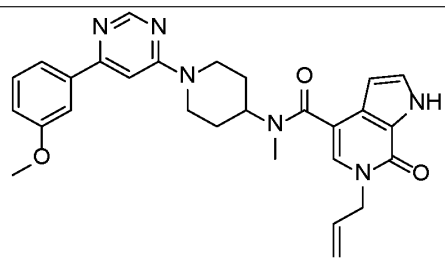


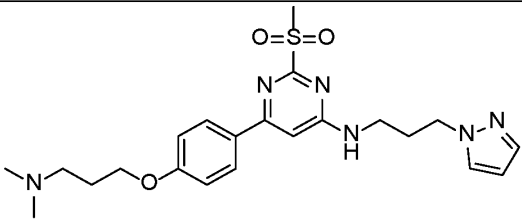
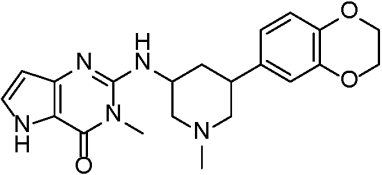
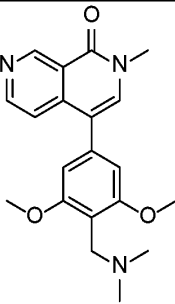
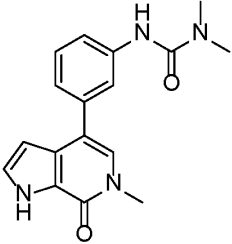
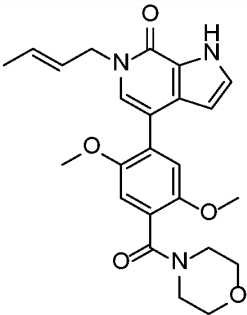
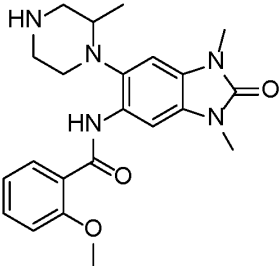


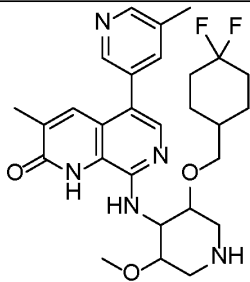
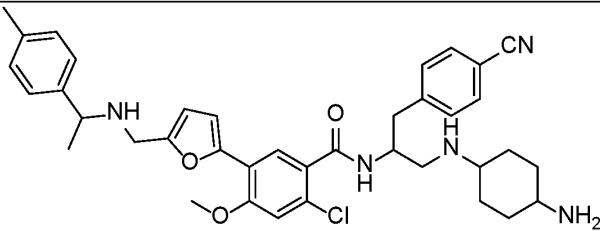
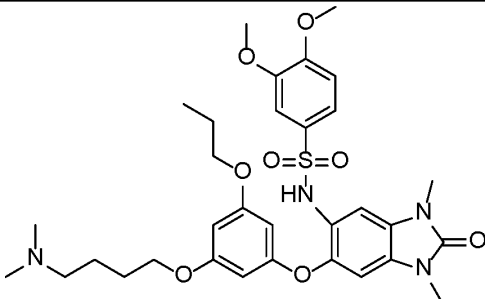
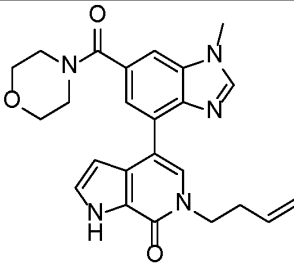
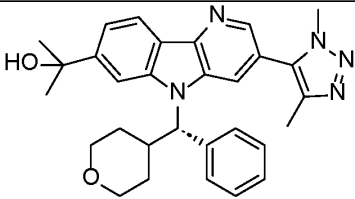
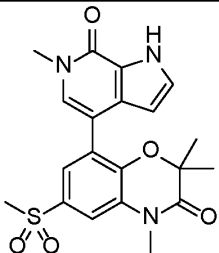
[00483] In some embodiments, the second terminus is selected from a moiety described in Table 1, or a pharmaceutically acceptable salt thereof.

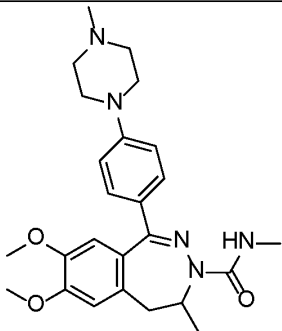
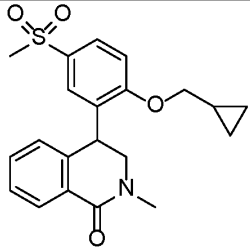
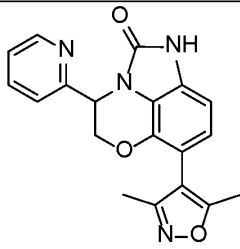
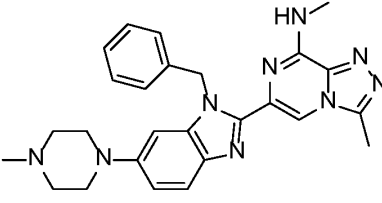
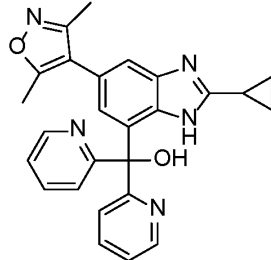
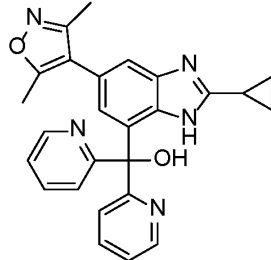
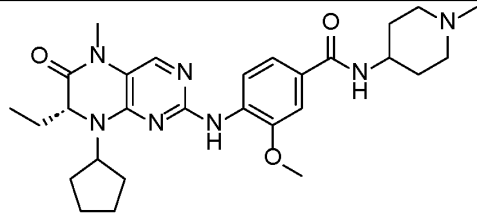
Table 1. Exemplary binding moieties.

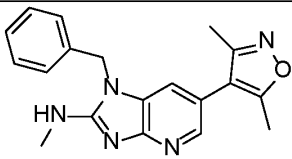
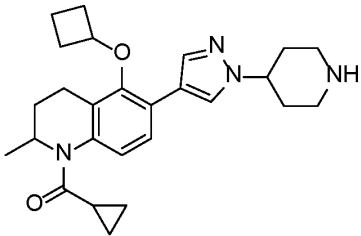
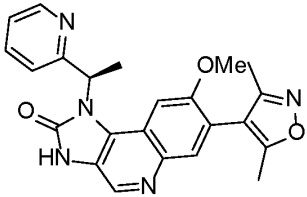
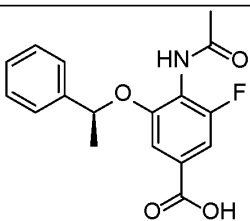
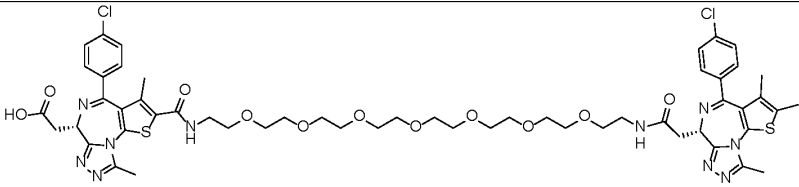
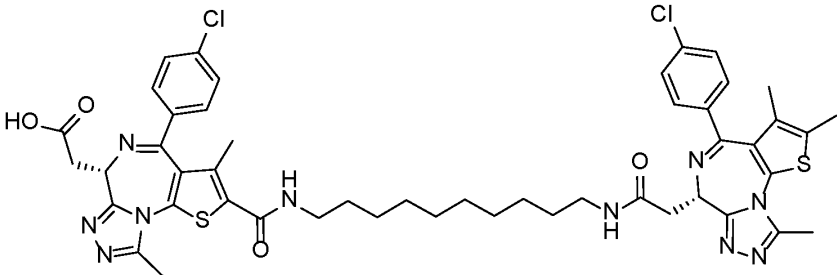
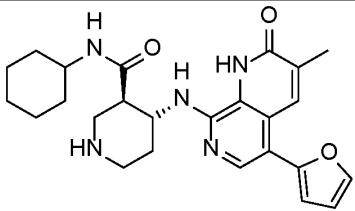
Structure	Target
The structure shows a central benzimidazole core. One nitrogen of the benzimidazole is substituted with a 4-chlorophenyl group. The other nitrogen is substituted with a 4-methoxyphenyl group. The benzimidazole core is also substituted with a 4-methoxyphenyl group and a 4-chlorophenyl group. The benzimidazole core is also substituted with a 4-methoxyphenyl group and a 4-chlorophenyl group.	CBP/P300

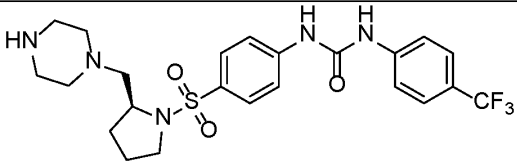
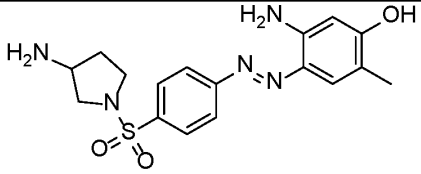
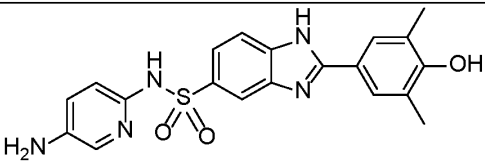
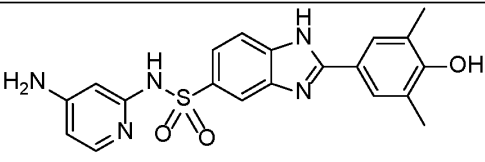
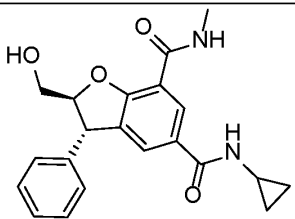
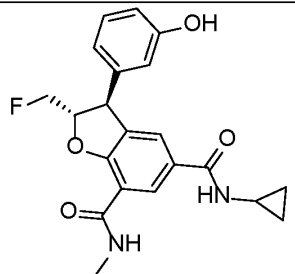
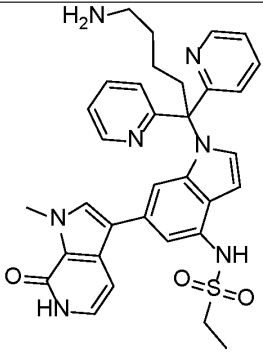
 Chemical structure of a BET(BD1) inhibitor. It features a quinoline core with a 2-methyl-5-isoxazolyl group at position 6, a 2-methoxy-1-phenyl-1H-imidazole-4-yl group at position 8, and a (S)-1-(2-methoxy-1-phenyl-1H-imidazole-4-yl)pyrrolidine group at position 4.	BET(BD1)
 Chemical structure of a PCAF inhibitor. It features a pyrazole core with a 2-methoxy-1-phenyl-1H-imidazole-4-yl group at position 3, a 2-methoxy-1-phenyl-1H-imidazole-4-yl group at position 5, and a 2-methoxy-1-phenyl-1H-imidazole-4-yl group at position 7.	PCAF
 Chemical structure of a CBP/P300 inhibitor. It features a pyrazole core with a 2-methoxy-1-phenyl-1H-imidazole-4-yl group at position 3, a 2-methoxy-1-phenyl-1H-imidazole-4-yl group at position 5, and a 2-methoxy-1-phenyl-1H-imidazole-4-yl group at position 7.	CBP/P300
 Chemical structure of a CBP/P300 inhibitor. It features a pyrazole core with a 2-methoxy-1-phenyl-1H-imidazole-4-yl group at position 3, a 2-methoxy-1-phenyl-1H-imidazole-4-yl group at position 5, and a 2-methoxy-1-phenyl-1H-imidazole-4-yl group at position 7.	CBP/P300
 Chemical structure of a CECR2 inhibitor. It features a pyrazole core with a 2-methoxy-1-phenyl-1H-imidazole-4-yl group at position 3, a 2-methoxy-1-phenyl-1H-imidazole-4-yl group at position 5, and a 2-methoxy-1-phenyl-1H-imidazole-4-yl group at position 7.	CECR2

	BPTF
	PCAF
	BRD7/9
	TAF1
	BRD7/9
	BRPF

	ATAD2/ATAD2B
	ATAD2/ATAD2B
	TRIM24
	TAF1
	BET
	BET

	BET
	BET
	BET
	BET
	BET
	BET
	BRD4

	BRD4
	BET
	BRD4
	BRD4
	BRD4
	BRD4
	BRD4

	BRDR; non-Kac
	BRD4
	BRD4
	BRD4
	BRD4
	BRD4
	BRD4; CBP/P300

Oligomeric Backbone – Linker Moiety

[00484] The oligomeric backbone is a linker that connects the first terminus and the second terminus and brings the regulatory molecule in proximity to the target gene to modulate gene expression.

[00485] The length of the linker depends on the type of regulatory protein and also the target gene. In some embodiments, the linker has a length of less than about 50 Angstroms. In some embodiments, the linker has a length of about 20 to 30 Angstroms.

[00486] In some embodiments, the oligomeric backbone comprises between 5 and 50 chain atoms.

[00487] In some embodiments, the oligomeric backbone comprises a multimer having 2 to 50 spacing moieties, wherein

each spacing moiety is independently selected from the group consisting of $-(\text{CR}^{1b}\text{R}^{1b})_x\text{-O}-$, $-(\text{CR}^{1b}\text{R}^{1b})_x\text{-NR}^{1a}-$, $-(\text{CR}^{1b}\text{R}^{1b})_x\text{-CH=CH-(CR}^{1b}\text{R}^{1b})_x\text{-O}-$, optionally substituted $\text{C}_1\text{-C}_{12}$ alkyl, optionally substituted $\text{C}_2\text{-C}_{10}$ alkenyl, optionally substituted $\text{C}_2\text{-C}_{10}$ alkynyl, optionally substituted $\text{C}_6\text{-C}_{10}$ arylene, optionally substituted $\text{C}_3\text{-C}_7$ cycloalkylene, optionally substituted 5 to 10-membered heteroarylene, optionally substituted 4- to 10-membered heterocycloalkylene, amino acid residue, $-\text{O}-$, $-\text{C}(\text{O})\text{NR}^{1a}-$, $-\text{NR}^{1a}\text{C}(\text{O})-$, $-\text{C}(\text{O})-$, $-\text{NR}^{1a}-$, $-\text{C}(\text{O})\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{S}(\text{O})_2\text{NR}^{1a}-$, $-\text{NR}^{1a}\text{S}(\text{O})_2-$, and $-\text{P}(\text{O})\text{OH}-$, and any combinations thereof; wherein

each x is independently 2-4;

each y is independently 1-10;

each R^{1a} is independently a hydrogen, optionally substituted $\text{C}_1\text{-C}_6$ alkyl, optionally substituted $\text{C}_1\text{-C}_6$ haloalkyl, $-\text{S}(\text{O})_2\text{-C}_1\text{-C}_6$ haloalkyl, $-\text{S}(\text{O})_2\text{-C}_1\text{-C}_6$ alkyl, $-\text{S}(\text{O})_2\text{-C}_3\text{-C}_6$ cycloalkyl, or $-\text{S}(\text{O})_2\text{N-(C}_1\text{-C}_6\text{ alkyl)}_2$; and

each R^{1b} is independently selected from hydrogen, halogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted amino, carboxyl, carboxyl ester, acyl, acyloxy, acyl amino, amino acyl, optionally substituted alkylamide, optionally substituted haloalkyl, sulfonyl, optionally substituted thioalkoxy, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, and optionally substituted heterocycl.

[00488] In some embodiments, the oligomeric backbone comprises a multimer having 2 to 50 spacing moieties, wherein each spacing moiety is independently selected from the group consisting of optionally substituted $\text{C}_1\text{-C}_{12}$ alkyl, $-(\text{CH}_2)_x\text{-O}-$, $-(\text{CH}_2)_x\text{-NH}-$, $-\text{O}-$, $-\text{C}(\text{O})\text{NH}-$, $-\text{NH}-$, and any combinations thereof.

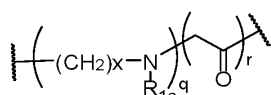
[00489] In some embodiments, the oligomeric backbone comprises $-(\text{T}^1\text{-V}^1)_a\text{-(T}^2\text{-V}^2)_b\text{-(T}^3\text{-V}^3)_c\text{-(T}^4\text{-V}^4)_d\text{-(T}^5\text{-V}^5)_e$, wherein

a, b, c, d and e are each independently 0 or 1, and where the sum of a, b, c, d and e is 1 to 5;

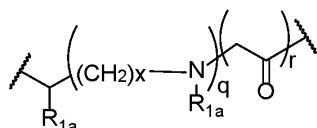
T^1 , T^2 , T^3 , T^4 and T^5 are each independently selected from an optionally substituted $\text{C}_1\text{-C}_{12}$ alkylene, optionally substituted alkenylene, optionally substituted alkynylene, $(\text{EA})_w$, $(\text{EDA})_m$, $(\text{PEG})_n$, (modified $\text{PEG})_n$, $(\text{AA})_p$, $-(\text{CR}^{2a}\text{OH})_h-$, optionally substituted $\text{C}_6\text{-C}_{10}$ arylene, optionally substituted $\text{C}_3\text{-C}_7$ cycloalkylene, optionally substituted 5- to 10-membered heteroarylene, optionally substituted 4- to 10-

membered heterocycloalkylene, an acetal group, a disulfide, a hydrazine, a carbohydrate, a beta-lactam, and an ester,

- (a) w is an integer from 1 to 20;
- (b) m is an integer from 1 to 20;
- (c) n is an integer from 1 to 30;
- (d) p is an integer from 1 to 20;
- (e) h is an integer from 1 to 12;
- (f) EA has the following structure



- (g) EDA has the following structure:



wherein each q is independently an integer from 1 to 6, each

x is independently an integer from 1 to 4, and each r is independently 0 or 1;

- (h) (PEG)_n has the structure of $\text{---}(\text{CR}^{1b}\text{R}^{1b}\text{---CR}^{1b}\text{R}^{1b}\text{---O})_n\text{---CR}^{1b}\text{R}^{1b}\text{---}$;
- (i) (modified PEG)_n has the structure of replacing at least one $\text{---}(\text{CR}^{1b}\text{R}^{1b}\text{---CR}^{1b}\text{R}^{1b}\text{---O})\text{---}$ in (PEG)_n with $\text{---}(\text{CH}_2\text{---CR}^{1b}\text{---CR}^{1b}\text{---CH}_2\text{---O})\text{---}$ or $\text{---}(\text{CR}^{1b}\text{R}^{1b}\text{---CR}^{1b}\text{R}^{1b}\text{---S})\text{---}$;

- (j) AA is an amino acid residue;

- (k) V¹, V², V³, V⁴ and V⁵ are each independently selected from the group consisting of a bond, C(O)-, -NR^{1a}-, -C(O)NR^{1a}-, -NR^{1a}C(O)-, -CONR^{1a}-C₁-C₄ alkyl-, -NR^{1a}C(O)-C₁-C₄ alkyl-, -C(O)O-, -OC(O)-, -O-, -S-, -S(O)-, -S(O)₂-, -S(O)₂NR^{1a}-, -NR^{1a}S(O)₂- and -P(O)OH-;

- (l) each R^{1a} is independently hydrogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ haloalkyl, -S(O)₂-C₁-C₆ haloalkyl, -S(O)₂-C₁-C₆ alkyl, -S(O)₂-C₃-C₆ cycloalkyl, or -S(O)₂N-(C₁-C₆ alkyl)₂; and

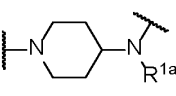
- (m) each R^{1b} is independently selected from hydrogen, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogen, alkoxy, substituted alkoxy, amino, substituted amino, optionally substituted haloalkyl, carboxyl, carboxyl ester, acyl, acyloxy, acyl amino, amino acyl, alkylamide, substituted alkylamide, sulfonyl, thioalkoxy, substituted thioalkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, and substituted heterocyclyl.

[00490] In some embodiments, the a, b, c, d and e are each independently 0 or 1, where the sum of a, b, c, d and e is 1. In some embodiments, the a, b, c, d and e are each independently 0 or 1, where the sum of a, b, c, d and e is 2. In some embodiments, the a, b, c, d and e are each independently 0 or 1, where the sum of a, b, c, d and e is 3. In some embodiments, the a, b, c, d and e are each independently 0 or 1, where the sum of

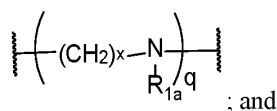
a, b, c, d and e is 4. In some embodiments, the a, b, c, d and e are each independently 0 or 1, where the sum of a, b, c, d and e is 5.

[00491] In some embodiments, n is 3-9. In some embodiments, n is 4-8. In some embodiments, n is 5 or 6.

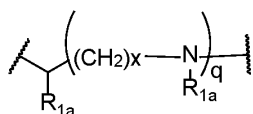
[00492] In some embodiments, T¹, T², T³, and T⁴, and T⁵ are each independently selected from C₁-C₁₂ alkyl, substituted C₁-C₁₂ alkyl, (EA)_w, (EDA)_m, (PEG)_n, (modified PEG)_n, (AA)_p, -(CR^{1b}OH)_h-, phenyl, substituted phenyl, piperidin-4-amino (P4A), para-amino-benzoyloxycarbonyl (PABC), meta-amino-benzoyloxycarbonyl (MABC), para-amino-benzoyloxy (PABO), meta-amino-benzoyloxy (MABO), para-aminobenzyl, an acetal group, a disulfide, a hydrazine, a carbohydrate, a beta-lactam, an ester, (AA)_p-MABC-(AA)_p, (AA)_p-MABO-(AA)_p, (AA)_p-PABO-(AA)_p and (AA)_p-PABC-(AA)_p. In some embodiments,

piperidin-4-amino (P4A) is , wherein R^{1a} is hydrogen or C₁-C₆ alkyl.

[00493] In some embodiments, T¹, T², T³, T⁴ and T⁵ are each independently selected from (C₁-C₁₂)alkyl, substituted C₁-C₁₂ alkyl, (EA)_w, (EDA)_m, (PEG)_n, (modified PEG)_n, (AA)_p-(CR^{2a}OH)_h-, optionally substituted C₆-C₁₀ arylene, 4 to 10-membered heterocycloalkene, optionally substituted 5 to 10-membered heteroarylene. In some embodiments, EA has the following structure:



EDA has the following structure:



[00494] In some embodiments, x is 2-3 and q is 1-3 for EA and EDA. In some embodiments, R^{1a} is hydrogen or C₁-C₆ alkyl.

[00495] In some embodiments, T⁴ or T⁵ is an optionally substituted C₆-C₁₀ arylene.

[00496] In some embodiments, T⁴ or T⁵ is phenylene or substituted phenylene. In some embodiments, T⁴ or T⁵ is phenylene or phenylene substituted with 1-3 substituents selected from C₁-C₆ alkyl, halogen, OH or amine. In some embodiments, T⁴ or T⁵ is 5 to 10-membered heteroarylene or substituted heteroarylene. In some embodiments, T⁴ or T⁵ is 4 to 10-membered heterocyclene or substituted heterocyclene. In some embodiments, T⁴ or T⁵ is heteroarylene or heterocyclene optionally substituted with 1-3 substituents selected from C₁-C₆ alkyl, halogen, OH or amine.

[00497] In some embodiments, T¹, T², T³, T⁴ and T⁵ and V¹, V², V³, V⁴ and V⁵ are selected from the following **Table 2**.

Table 2. Exemplary linker units.

T ¹	V ¹	T ²	V ²	T ³	V ³	T ⁴	V ⁴	T ⁵	V ⁵
C ₁ -C ₁₂ alkylene	C(O)NR ^{1a}	(EA) _w	CO	(PEG) _n	NR ^{1a} CO	----	----	----	----
C ₁ -C ₁₂ alkylene	C(O)NR ^{1a}	(EA) _w	CO	(PEG) _n	O	arylene	NR ^{1a} CO	----	----
C ₁ -C ₁₂ alkylene	C(O)NR ^{1a}	(EA) _w	CO	(PEG) _n	O	Subst. arylene	NR ^{1a} CO	----	----
C ₁ -C ₁₂ alkylene	C(O)NR ^{1a}	(EA) _w	CO	(PEG) _n	O	NR ^{1a} C O	C ₁ -C ₁₂ alkyl	Subst. arylene	NR ^{1a} CO
C ₁ -C ₁₂ alkylene	C(O)NR ^{1a}	(EA) _w	CO	C ₁ -C ₁₂ alkyl	NR ^{1a} CO- C ₁ -C ₄ alkyl	Subst. arylene	NR ¹¹	----	----
C ₁ -C ₁₂ alkylene	C(O)NR ^{1a}	(EA) _w	CO	(PEG) _n	O	Subst. arylene	---	----	----
(PEG) _n	C(O)NR ^{1a} - C ₁ -C ₄ alkyl	----	----	----	----	----	----	----	---
(EA) _w	CO	C ₁ -C ₁₂ alkyl	C(O)NR ^{1a} - C ₁ -C ₄ alkyl	----	----	----	----	----	---
C ₁ -C ₁₂ alkylene	C(O)NR ^{1a}	(EA) _w	CO	(PEG) _n	NR ^{1a} CO- C ₁ -C ₄ alkyl	----	----	----	----
(EA) _w	CO	(PEG) _n	O	phenyl	NR ^{1a} CO- C ₁ -C ₄ alkyl	----	----	----	----
C ₁ -C ₁₂ alkylene	C(O)NR ^{1a}	(PEG) _n	CO	----	----	----	----	----	---
C ₁ -C ₁₂ alkylene	C(O)NR ^{1a}	(EA) _w	CO	modifd. (PEG) _n	O	arylene	NR ^{1a} CO	----	----
(PEG) _n	(EA) _w	CO	(PEG) _n	----	----	----	----	----	----

[00498] In some embodiments, the oligomeric backbone comprises -N(R^{1a})(CH₂)_xN(R^{1a})(CH₂)_xN-, wherein each R^{1a} is independently selected from hydrogen or optionally substituted C₁-C₆ alkyl; and each x is independently an integer in the range of 1-10.

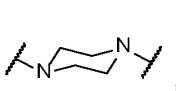
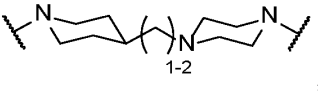
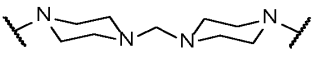
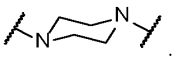
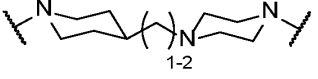
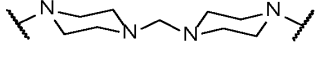
[00499] In some embodiments, the oligomeric backbone comprises -(CH₂-C(O)N(R^{1a})-(CH₂)_q-N(R^{1a})-(CH₂)_q-N(R^{1a})C(O)-(CH₂)_x-C(O)N(R^{1a})-A-, -(CH₂)_x-C(O)N(R^{1a})-(CH₂CH₂O)_y(CH₂)_x-C(O)N(R^{1a})-A-, or -C(O)N(R^{1a})-(CH₂)_q-N(R^{1a})-(CH₂)_q-N(R^{1a})C(O)-(CH₂)_x-A-; wherein each q is independently an integer from 2 to 10; each x is independently an integer from 1-6; and each A is independently selected from a bond, an optionally substituted C₁-C₁₂ alkyl, an optionally substituted C₆-C₁₀ arylene, optionally substituted C₃-C₇ cycloalkylene, optionally substituted 5 to 10-membered heteroarylene, and optionally substituted 4 to 10-membered heterocycloalkylene. In some embodiments, A is spiro-cycloalkylene or spiro-heterocycloalkylene

[00500] In some embodiments, the oligomeric backbone comprises -(CH₂CH₂-O)_{x7}- or -(CH₂CH₂-O)_{x8}-A-(CH₂CH₂-O)_{x9}-, wherein A is an optionally substituted 4 to 10-membered heterocycloalkylene or spirocycloalkylene, and each x₇, x₈, and x₉ is independently an integer from 1-15.

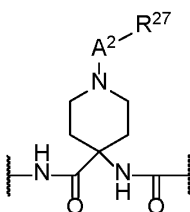
[00501] In some embodiments, the oligomeric backbone comprises $\text{-NR}^{1a}\text{-(CH}_2\text{CH}_2\text{O)}_y\text{(CH}_2\text{)}_x\text{-}$ or $\text{-NR}^{1a}\text{-(CH}_2\text{)}_q\text{-C(O)NR}^{1a}\text{(CH}_2\text{CH}_2\text{O)}_y\text{(CH}_2\text{)}_x\text{-}$, wherein q is 2-10, x is 1-4, y is 1-50, and each R^{1a} is independently hydrogen, optionally substituted $\text{C}_1\text{-C}_6$ alkyl, optionally substituted $\text{C}_1\text{-C}_6$ haloalkyl, $\text{-S(O)}_2\text{-C}_1\text{-C}_6$ haloalkyl, $\text{-S(O)}_2\text{-C}_1\text{-C}_6$ alkyl, $\text{-S(O)}_2\text{-C}_3\text{-C}_6$ cycloalkyl, or $\text{-S(O)}_2\text{N-(C}_1\text{-C}_6\text{ alkyl)}_2$. In some embodiments, the oligomeric backbone comprises $\text{-NR}^{1a}\text{-(CH}_2\text{CH}_2\text{O)}_y\text{(CH}_2\text{)}_x\text{-}$. In some embodiments, the oligomeric backbone comprises $\text{-NR}^{1a}\text{-(CH}_2\text{)}_q\text{-C(O)NR}^{1a}\text{(CH}_2\text{CH}_2\text{O)}_y\text{(CH}_2\text{)}_x\text{-}$.

[00502] In some embodiments, the oligomeric backbone comprises $\text{-(CH}_2\text{CH}_2\text{-O)}_x\text{-}$, $\text{-(CH}_2\text{CH}_2\text{-O)}_x\text{-(CH}_2\text{CH}_2\text{-NH-}$, $\text{-NR}^{1a}\text{-(CH}_2\text{CH}_2\text{-O)}_x\text{-}$, $\text{-NR}^{1a}\text{-(CH}_2\text{CH}_2\text{-O)}_x\text{-(CH}_2\text{CH}_2\text{)-NR}^{1a}\text{-}$, $\text{-(CH}_2\text{CH}_2\text{-O)}_x\text{-(CH}_2\text{CH}_2\text{)-NR}^{1a}\text{C(O)-}$, or $\text{-NR}^{1a}\text{-(CH}_2\text{CH}_2\text{-O)}_x\text{-(CH}_2\text{CH}_2\text{)-NR}^{1a}\text{C(O)-}$. In some embodiments, the oligomeric backbone comprises $\text{-(CH}_2\text{CH}_2\text{-O)}_x\text{-}$, $\text{-(CH}_2\text{CH}_2\text{-O)}_x\text{-(CH}_2\text{CH}_2\text{)-NH-}$, $\text{-NH-(CH}_2\text{CH}_2\text{-O)}_x\text{-}$, $\text{-NH-(CH}_2\text{CH}_2\text{-O)}_x\text{-(CH}_2\text{CH}_2\text{)-NH-}$, $\text{-(CH}_2\text{CH}_2\text{-O)}_x\text{-(CH}_2\text{CH}_2\text{)-NHC(O)-}$, or $\text{-NH-(CH}_2\text{CH}_2\text{-O)}_x\text{-(CH}_2\text{CH}_2\text{)-NHC(O)-}$. In some embodiments, the oligomeric backbone comprises $\text{-NH-(CH}_2\text{CH}_2\text{-O)}_x\text{-}$ or $\text{-NH-(CH}_2\text{CH}_2\text{-O)}_x\text{-(CH}_2\text{CH}_2\text{)-NH-}$. In some embodiments, the oligomeric backbone comprises $\text{-NH-(CH}_2\text{CH}_2\text{-O)}_x\text{-}$. In some embodiments, the oligomeric backbone comprises $\text{-NH-(CH}_2\text{CH}_2\text{-O)}_x\text{-(CH}_2\text{CH}_2\text{)-NH-}$.

[00503] In some embodiments, the oligomeric backbone comprises polyethylene glycol (PEG). In some embodiments, the oligomeric backbone comprises 1-20 PEG units. In some embodiments, the oligomeric backbone comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 PEG units.

[00504] In some embodiments, A is selected from , , or . In some embodiments, A is . In some embodiments, A is . In some embodiments, A is .

[00505] In some embodiments, A comprises a moiety having the structure, or a pharmaceutically acceptable salt thereof:



wherein:

A^2 is absent or -C(O)- ; and

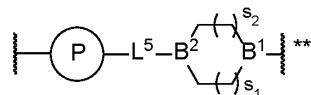
R^{27} is an optionally substituted $\text{C}_1\text{-C}_{50}$ alkyl or optionally substituted $\text{C}_1\text{-C}_{50}$ heteroalkyl.

[00506] In some embodiments, A^2 is -C(O)- . In some embodiments, A^2 is absent.

[00507] In some embodiments, R^{27} is $\text{C}_1\text{-C}_{50}$ alkyl. In some embodiments, R^{27} is $\text{C}_1\text{-C}_{40}$ alkyl. In some embodiments, R^{27} is $\text{C}_1\text{-C}_{30}$ alkyl. In some embodiments, R^{27} is $\text{C}_1\text{-C}_{20}$ alkyl. In some embodiments, R^{27} is $\text{C}_1\text{-C}_{10}$ alkyl. In some embodiments, R^{27} is $\text{C}_1\text{-C}_{50}$ heteroalkyl. In some embodiments, R^{26} is $\text{C}_1\text{-C}_{40}$

heteroalkyl. In some embodiments, R^{27} is C_1 - C_{30} heteroalkyl. In some embodiments, R^{27} is C_1 - C_{20} heteroalkyl. In some embodiments, R^{27} is C_1 - C_{10} heteroalkyl. In some embodiments, the heteroalkyl is polyethylene glycol (PEG).

[00508] In some embodiments, the oligomeric backbone comprises a moiety having a structure of Formula (C-1), or a pharmaceutically acceptable salt thereof:



Formula (C-1),

wherein:

Ring P is absent, arylene, or heterocycloalkylene;

L^5 is absent, optionally substituted alkylene, or optionally substituted alkynylene;

B^1 and B^2 are each independently CH or N;

s_1 and s_2 are each independently 0-3; and

** denotes attachment to the second terminus.

[00509] In some embodiments, Ring P is absent. In some embodiments, Ring P is C_4 - C_7 heterocycloalkylene.

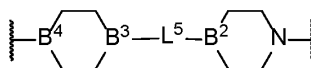
[00510] In some embodiments, B^1 is N. In some embodiments, B^1 is CH.

[00511] In some embodiments, B^2 is N. In some embodiments, B^2 is CH.

[00512] In some embodiments, L^5 is absent.

[00513] In some embodiments, L^5 is alkylene or alkynylene.

[00514] In some embodiments, the oligomeric backbone comprises a moiety having a structure of Formula (C-2), or a pharmaceutically acceptable salt thereof:



Formula (C-2),

wherein:

L^5 is absent, optionally substituted alkylene, or optionally substituted alkynylene; and

B^2 , B^3 and B^4 are each independently N or CH.

[00515] In some embodiments, each of B^3 and B^4 is independently N or CH; and B^2 is N.

[00516] In some embodiments, L^5 is C_1 - C_3 alkylene or C_1 - C_3 alkynylene. In some embodiments, L^5 is C_1 - C_3 alkylene. In some embodiments, L^5 is C_1 - C_3 alkynylene. In some embodiments, L^5 is $-CH_2-$, $-CH_2CH_2-$, $-C\equiv C-$, or $-C\equiv C-C\equiv C-$. In some embodiments, L^5 is $-CH_2-$ or $-CH_2CH_2-$. In some embodiments, L^5 is $-C\equiv C-$. In some embodiments, L^5 is $-C\equiv C-C\equiv C-$.

[00517] In some embodiments, L^5 is $-(C^{R^{1G}}R^{1G})_{x_{10}}-(alkylene)_2-(C^{R^{1G}}R^{1G})_{y_{10}}$; wherein x_{10} and y_{10} are each independently 0 or 1; and each R^{1G} is hydrogen or C_1 - C_3 alkyl.

[00524] In some embodiments, the oligomeric backbone is joined with the first terminus and/or with the second terminus with a group selected from -C(O)-, -NR^{1a}-, -C(O)NR^{1a}-, -NR^{1a}C(O)-, -C(O)NR^{1a}C₁-C₄alkyl-, -NR^{1a}C(O)-C₁-C₄alkyl-, -C(O)O-, -OC(O)-, -O-, -S-, -S(O)-, -S(O)₂-, -S(O)₂NR^{1a}-, -NR^{1a}S(O)₂-, -P(O)OH-, -((CH₂)_x-O)-, -((CH₂)_y-NR^{1a})-, optionally substituted C₁-C₁₂ alkylene, optionally substituted C₂-C₁₀ alkenylene, optionally substituted C₂-C₁₀ alkynylene, optionally substituted C₆-C₁₀ arylene, optionally substituted C₃-C₇ cycloalkylene, optionally substituted 5 to 10-membered heteroarylene, and optionally substituted 4 to 10-membered heterocycloalkylene, wherein each x is independently 1-4, each y is independently 1-4, and each R^{1a} is independently a hydrogen or optionally substituted C₁-C₆ alkyl.

[00525] In some embodiments, the oligomeric backbone is joined with the first terminus with a group selected from -O-, -C(O)-, -NR^{1a}-, C₁-C₁₂ alkyl, -C(O)NR^{1a}-, and -NR^{1a}C(O)-. In some embodiments, the oligomeric backbone is joined with the first terminus with a group selected from -O- or -NR^{1a}-.

[00526] In some embodiments, the oligomeric backbone is joined with the second terminus with a group selected from -C(O)-, -NR^{1a}-, -C(O)NR^{1a}-, -NR^{1a}C(O)-, -((CH₂)_x-O)-, -((CH₂)_y-NR^{1a})-, -O-, optionally substituted C₁-C₁₂ alkyl, optionally substituted C₆-C₁₀ arylene, optionally substituted C₃-C₇ cycloalkylene, optionally substituted 5- to 10-membered heteroarylene, and optionally substituted 4- to 10-membered heterocycloalkylene, wherein each x is independently 1-4, each y is independently 1-4, and each R^{1a} is independently a hydrogen, optionally substituted C₁-C₆ alkyl, or optionally substituted C₁-C₆ haloalkyl.

[00527] In some embodiments, the oligomeric backbone is joined with the second terminus with a group selected from -O-, -C(O)-, -NR^{1a}-, C₁-C₁₂ alkyl, -C(O)NR^{1a}-, and -NR^{1a}C(O)-. In some embodiments, the oligomeric backbone is joined with the second terminus with a group selected from -O- or -NR^{1a}-. In some embodiments, the oligomeric backbone is joined with the second terminus with -O-. In some embodiments, the oligomeric backbone is joined with the second terminus with -NR^{1a}-. In some embodiments, the oligomeric backbone is joined with the second terminus with -NH-.

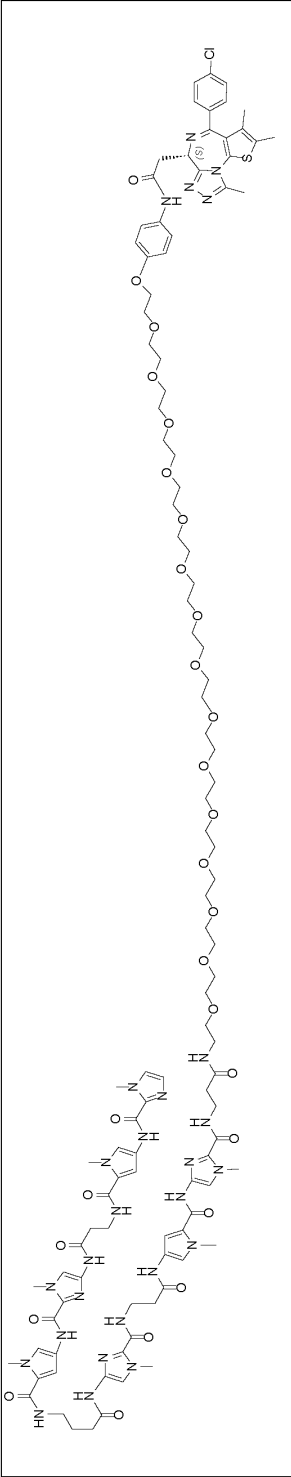
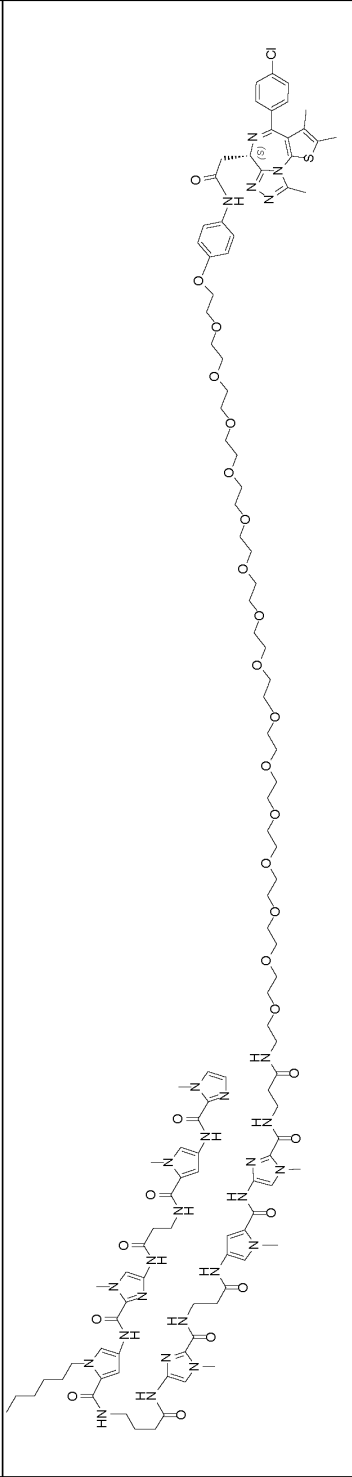
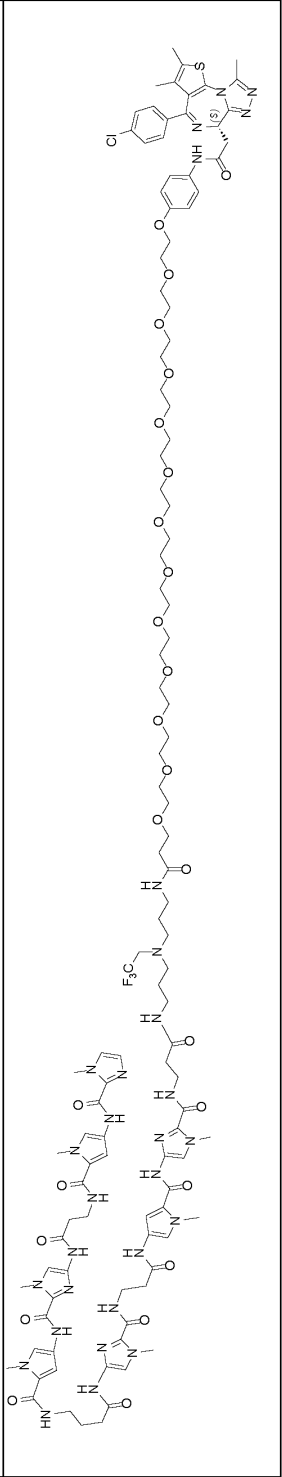
[00528] In some embodiments, each R^{1a} is independently hydrogen, -CH₃, -CF₃, -CH₂CF₃, -SO₂CH₃, -SO₂CH₂CH₃, -SO₂CF₃, -SO₂N(CH₃)₂, or -SO₂-cyclopropyl. In some embodiments, each R^{1a} is independently hydrogen, -CH₃, -CF₃, or -CH₂CF₃. In some embodiments, each R^{1a} is independently -SO₂CH₃, -SO₂CH₂CH₃, or -SO₂CF₃. In some embodiments, each R^{1a} is independently hydrogen. In some embodiments, each R^{1a} is independently -CH₃.

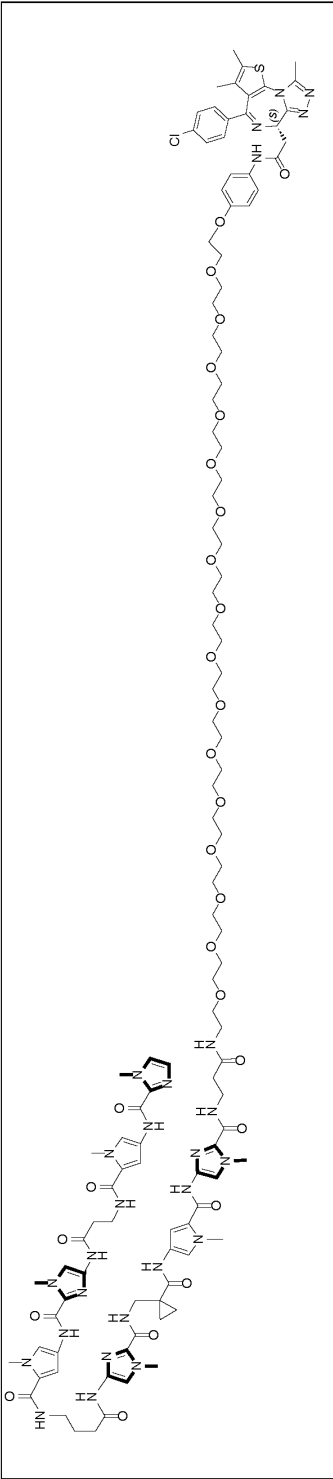
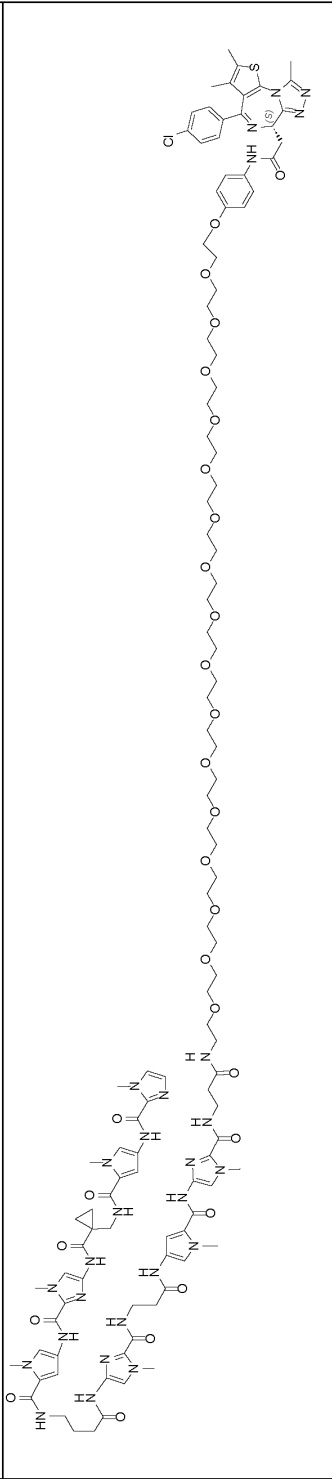
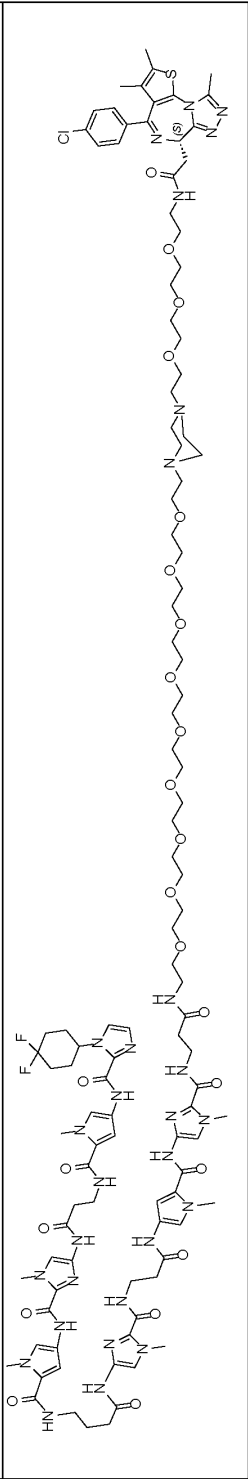
[00529] Any combination of the groups described above for the various variables is contemplated herein. Throughout the specification, groups and substituents thereof are chosen by one skilled in the field to provide stable moieties and compounds.

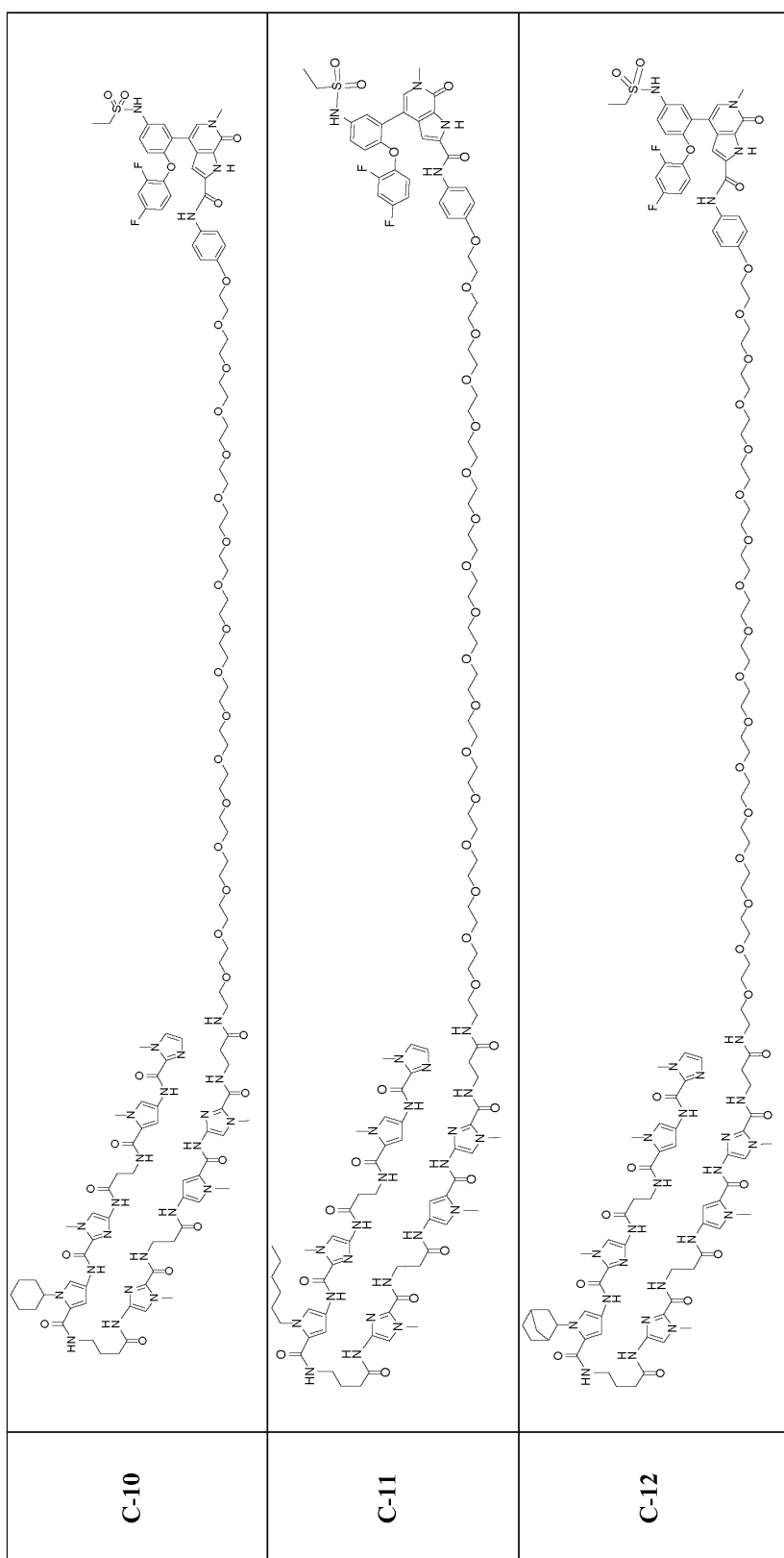
In some embodiments, non-limiting examples of the transcription modulator compounds described herein are presented below in **Table 3** (next page).

Table 3. Compounds of the disclosure.

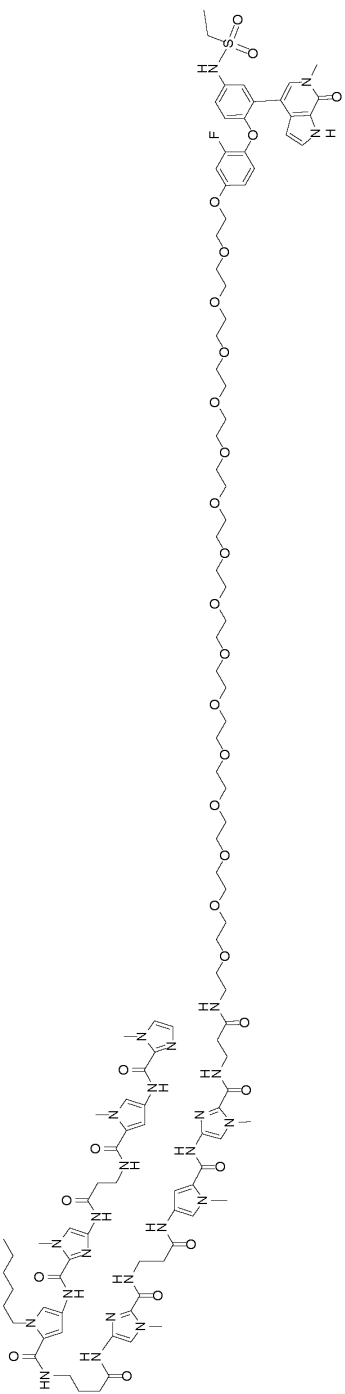
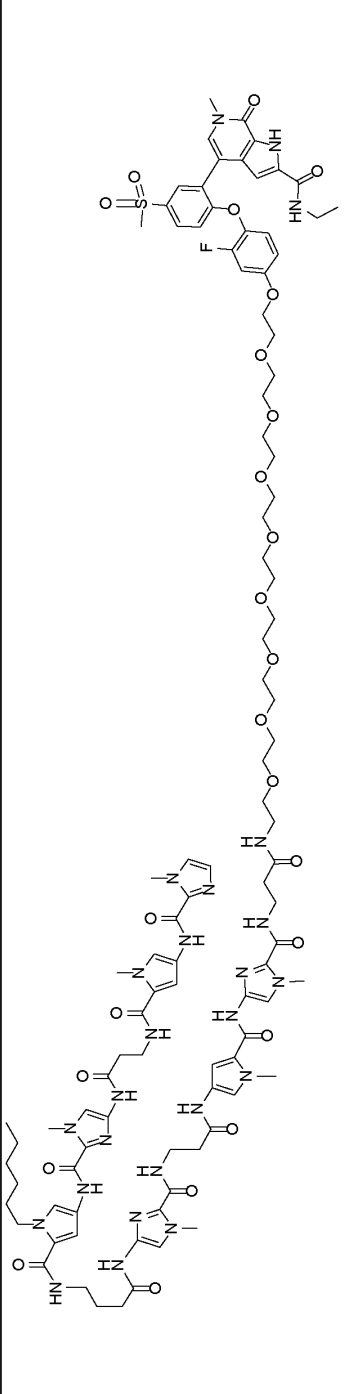
Cpd. No.	Structure
C-1	
C-2	
C-3	

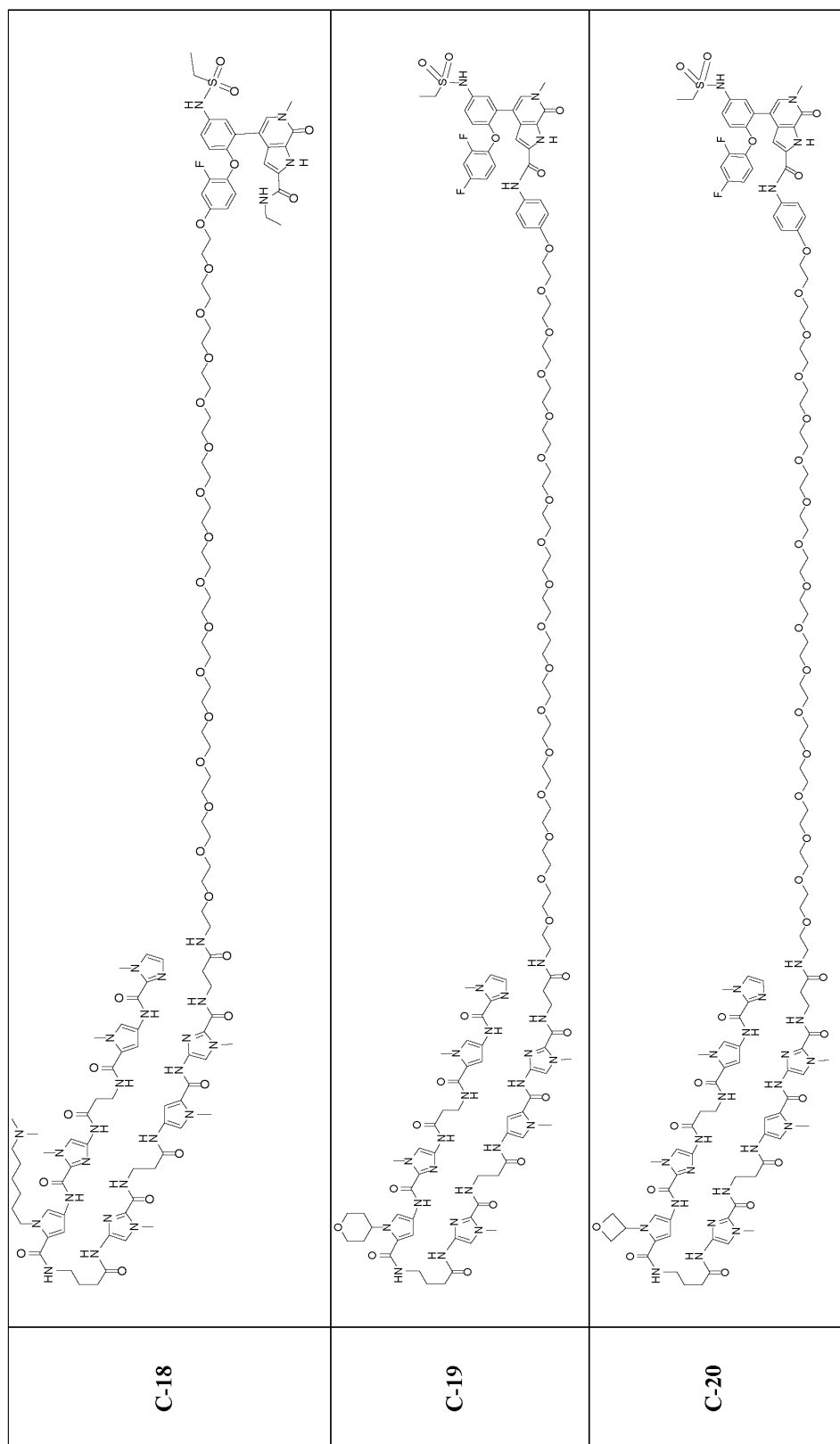
 Chemical structure of compound C-4. It features a 4-chlorophenyl group attached to a thiazole ring, which is linked via a carbonyl group to a long polyether chain. The chain terminates in a complex polycyclic aromatic system with multiple amide and carbonyl groups.	 Chemical structure of compound C-5. It is similar to C-4, but the polyether chain is shorter, and the terminal polycyclic aromatic system is more complex, featuring a central amide group and multiple carbonyl groups.	 Chemical structure of compound C-6. It features a 4-chlorophenyl group attached to a thiazole ring, which is linked via a carbonyl group to a long polyether chain. The chain terminates in a complex polycyclic aromatic system with multiple amide and carbonyl groups.
C-4	C-5	C-6

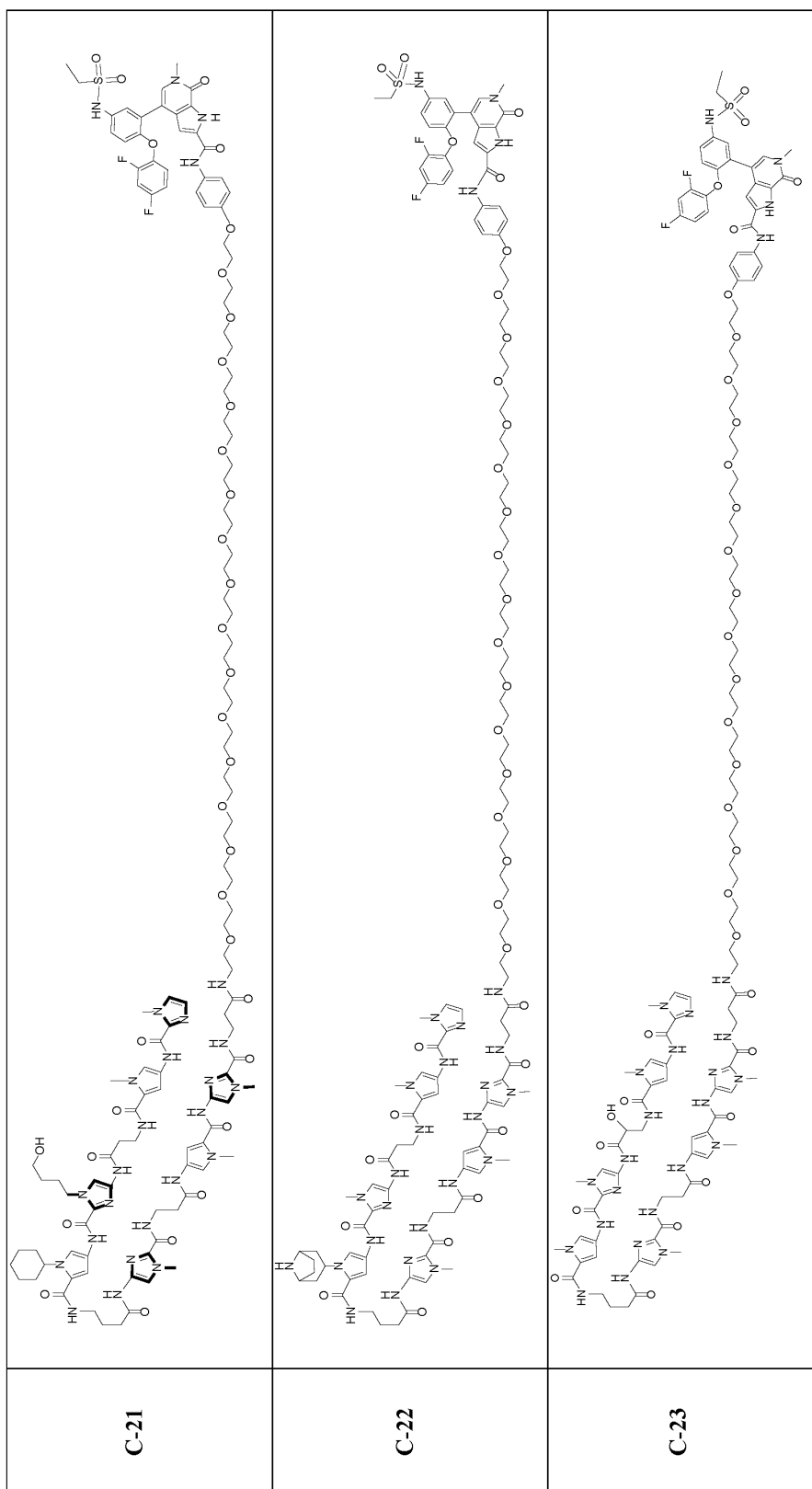
 Chemical structure of compound C-7, featuring a complex polycyclic aromatic system with a thiazole ring, a pyridine ring, and a benzimidazole ring, connected via a long polyether chain to a 4-chlorophenyl group.	 Chemical structure of compound C-8, featuring a complex polycyclic aromatic system with a thiazole ring, a pyridine ring, and a benzimidazole ring, connected via a long polyether chain to a 4-chlorophenyl group.	 Chemical structure of compound C-9, featuring a complex polycyclic aromatic system with a thiazole ring, a pyridine ring, and a benzimidazole ring, connected via a long polyether chain to a 4-chlorophenyl group.
C-7	C-8	C-9

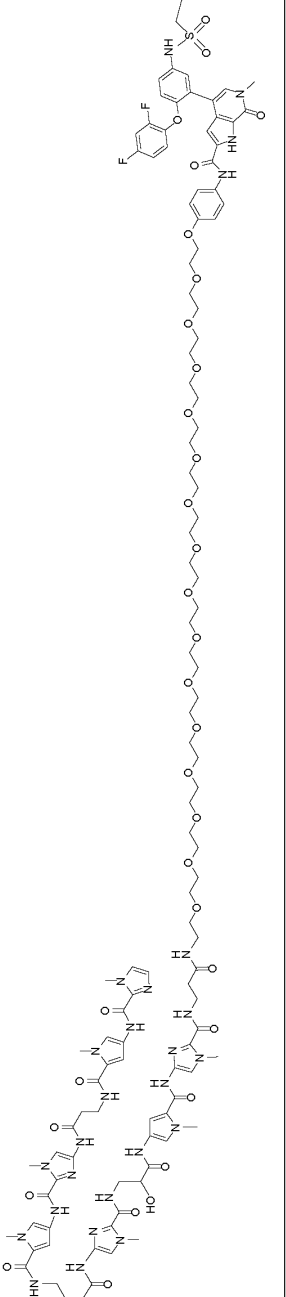
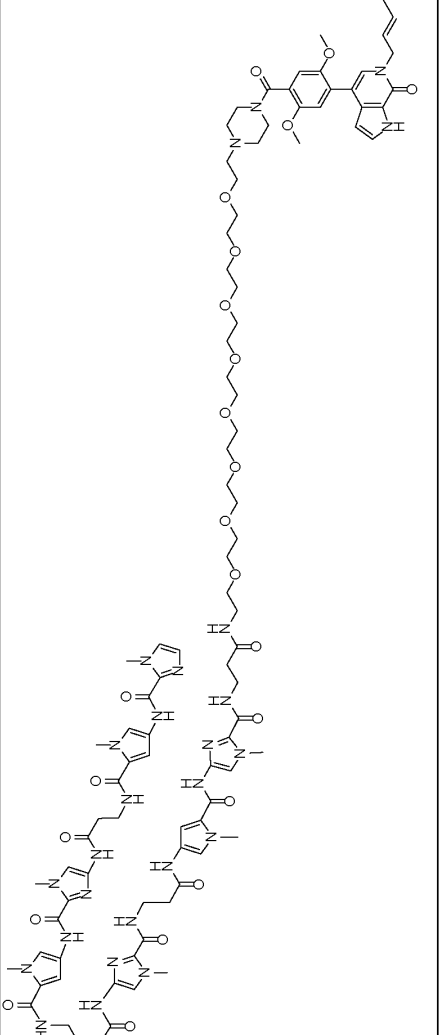


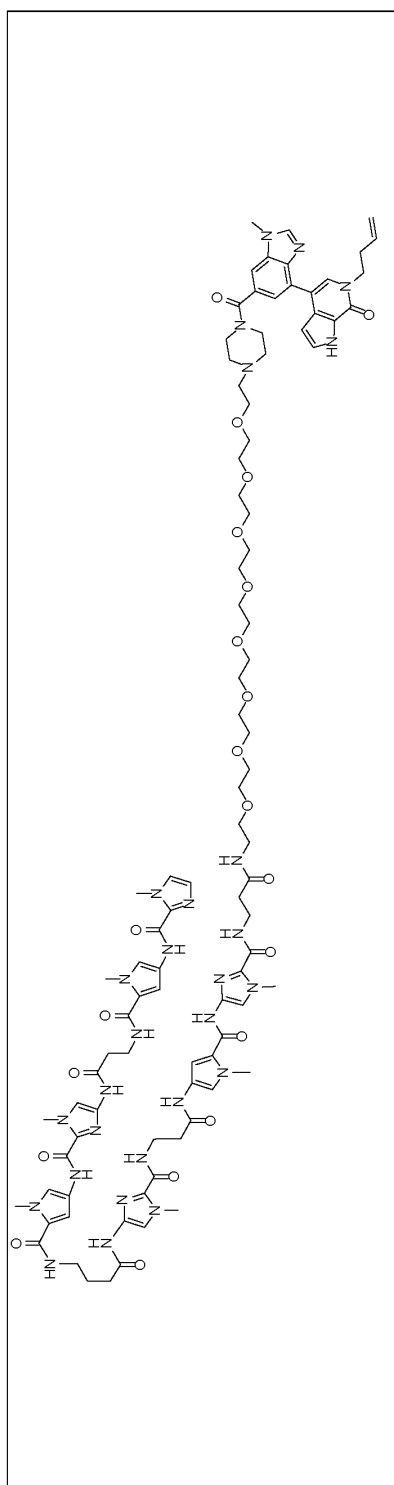
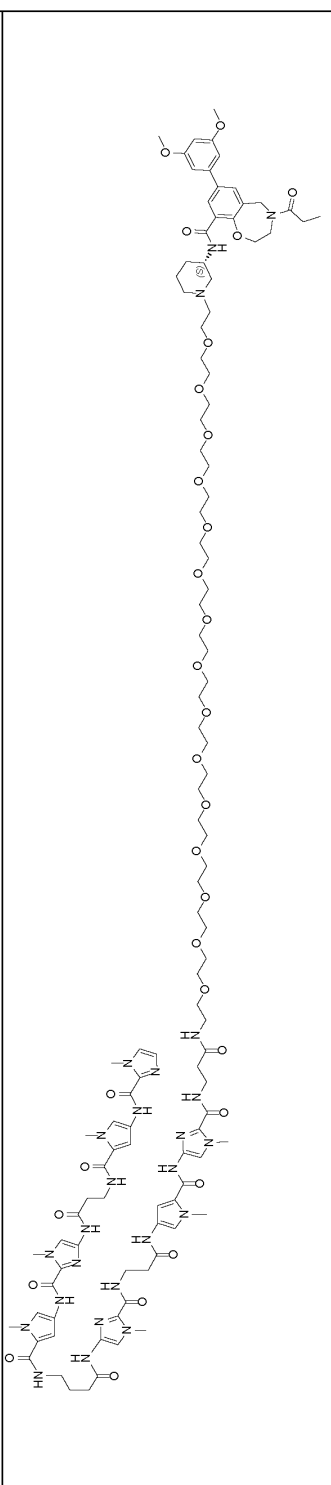


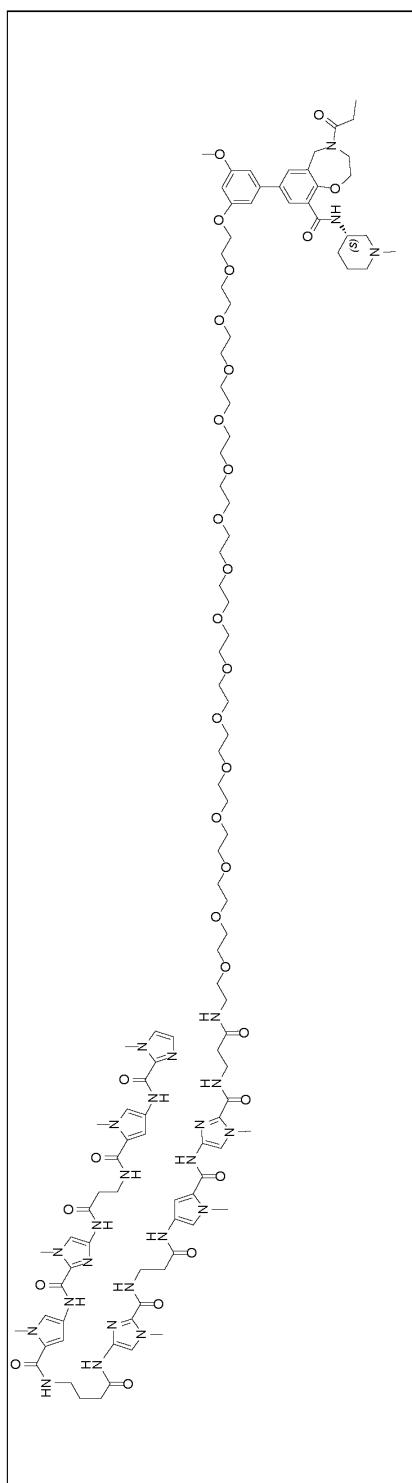
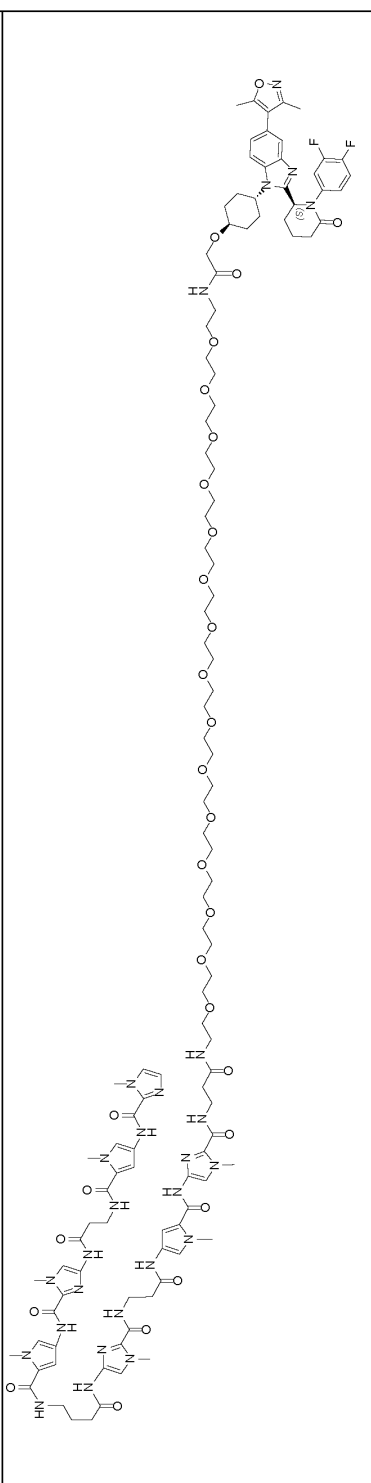
 Chemical structure of compound C-16. It features a central polyether chain consisting of 12 repeating units of -O-CH₂-CH₂-O-. The chain is terminated at both ends by a 4-fluorophenyl group. Each 4-fluorophenyl group is further substituted with a 2-ethylsulfonyl-5-methyl-1H-imidazo[4,5-b]pyridin-3-yl group.	 Chemical structure of compound C-17. It features a central polyether chain consisting of 12 repeating units of -O-CH₂-CH₂-O-. The chain is terminated at both ends by a 4-fluorophenyl group. Each 4-fluorophenyl group is further substituted with a 2-ethylsulfonyl-5-methyl-1H-imidazo[4,5-b]pyridin-3-yl group.
C-16	C-17

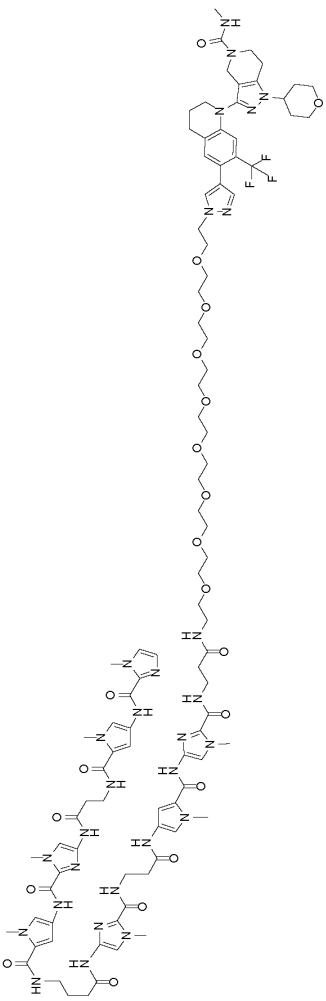
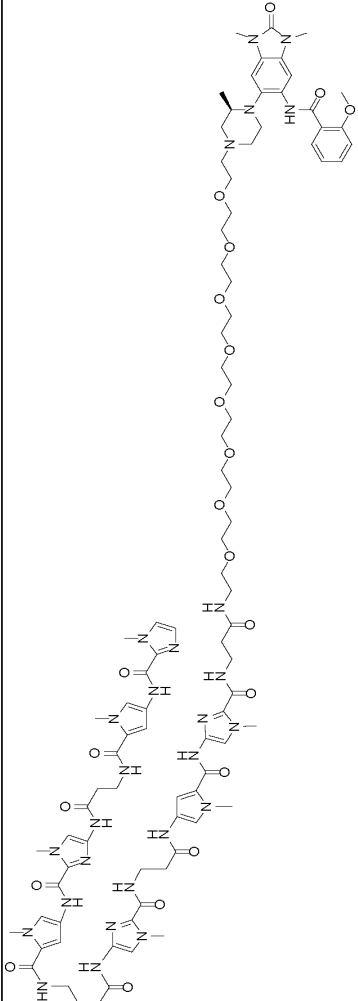


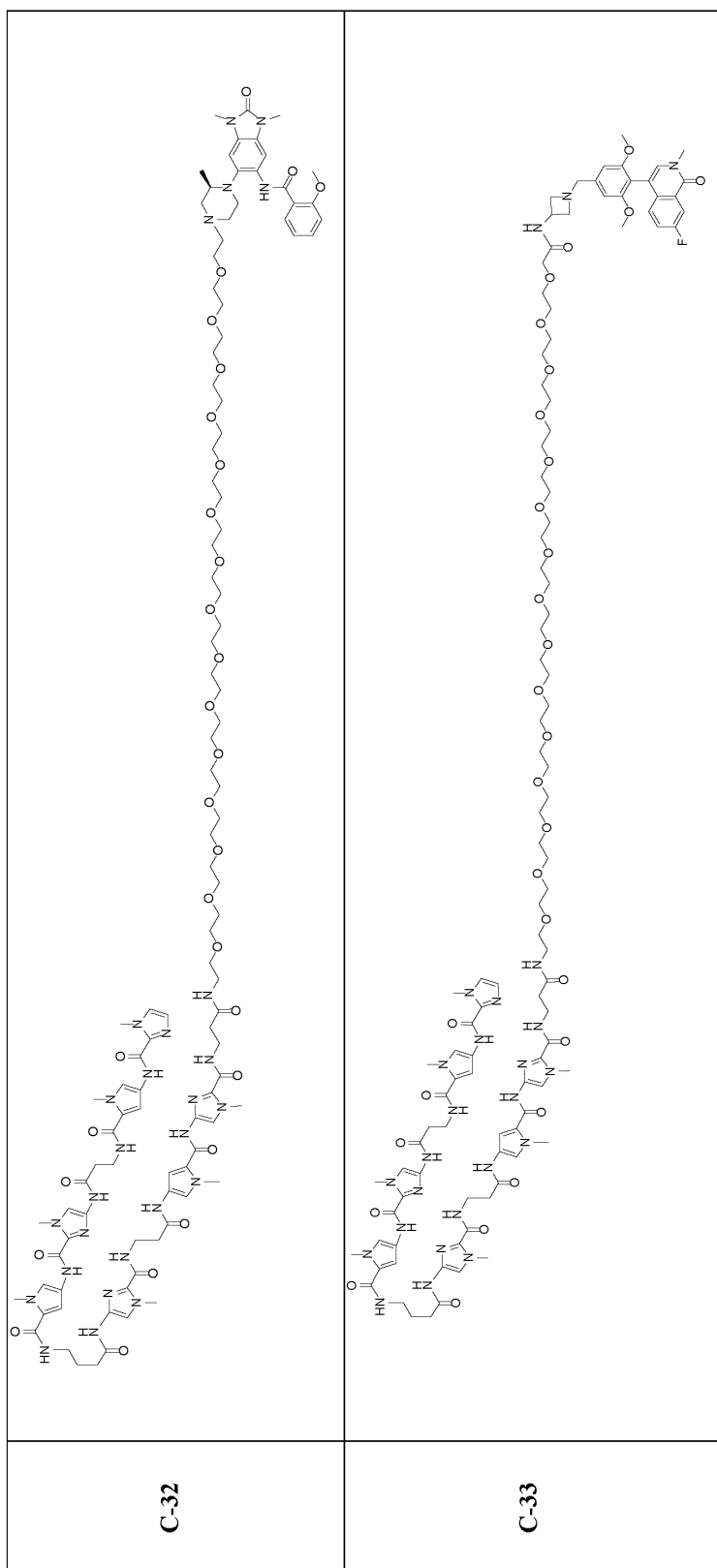


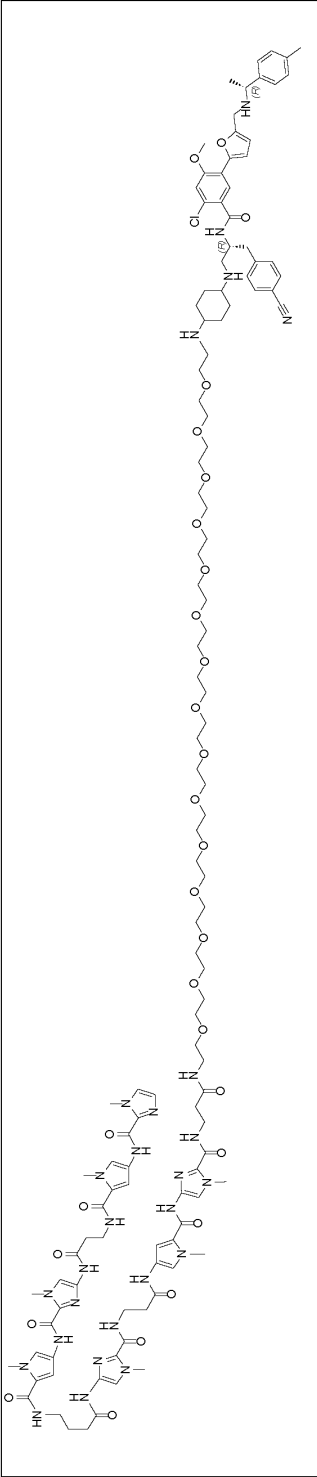
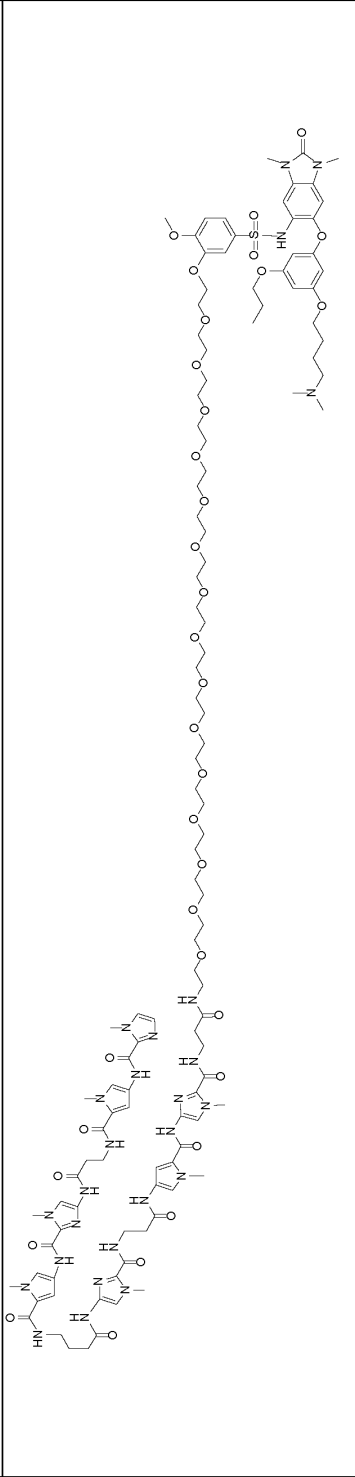
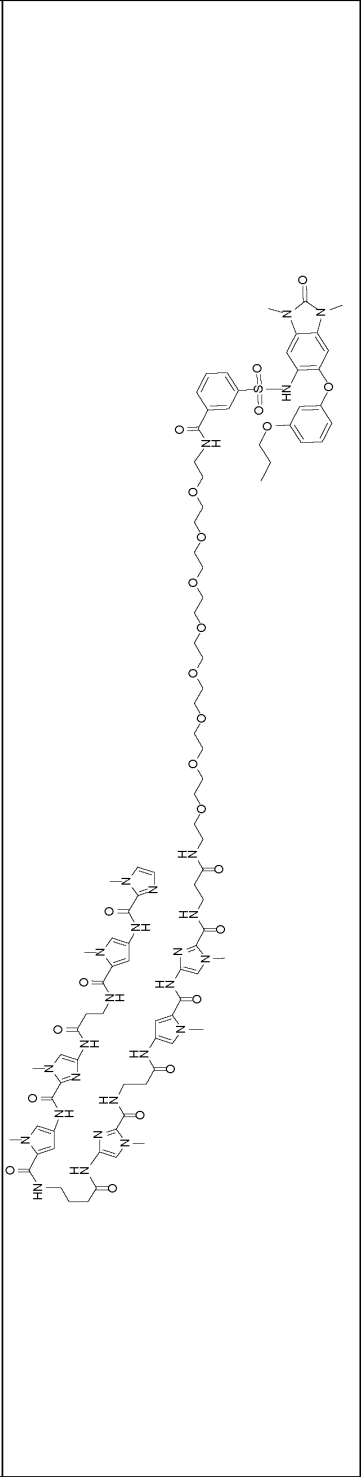
 Chemical structure of compound C-24. It features a long, flexible polyether chain (approximately 15 repeating units of -OCH₂CH₂O-) connecting two complex organic moieties. The left moiety is a substituted benzimidazole derivative with a fluorophenyl group and a sulfonamide group. The right moiety is a complex polycyclic structure containing multiple pyridine and imidazole rings, along with amide and ester linkages.	 Chemical structure of compound C-25. It features a long, flexible polyether chain (approximately 15 repeating units of -OCH₂CH₂O-) connecting two complex organic moieties. The left moiety is a substituted benzimidazole derivative with a fluorophenyl group and a sulfonamide group. The right moiety is a complex polycyclic structure containing multiple pyridine and imidazole rings, along with amide and ester linkages.
C-24	C-25

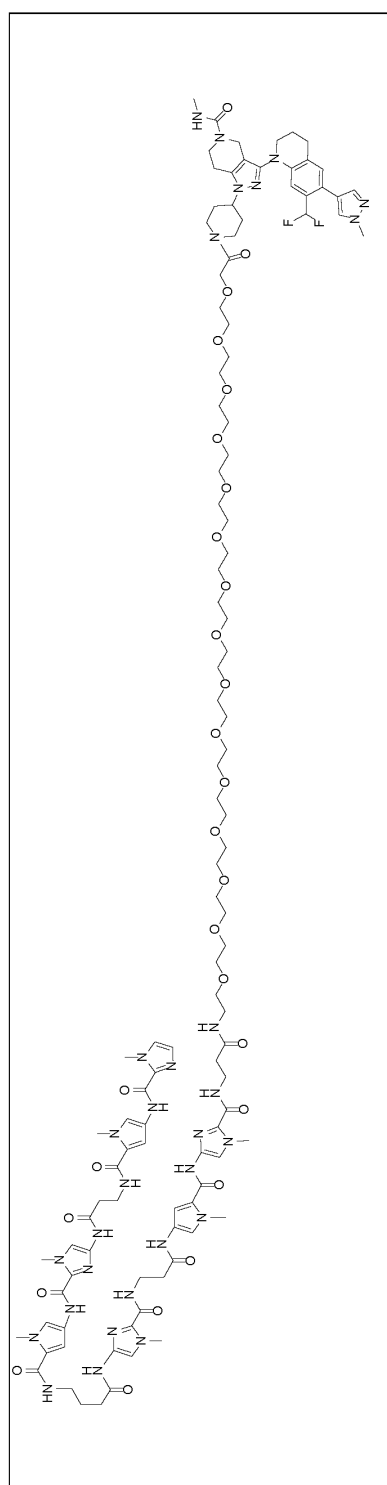
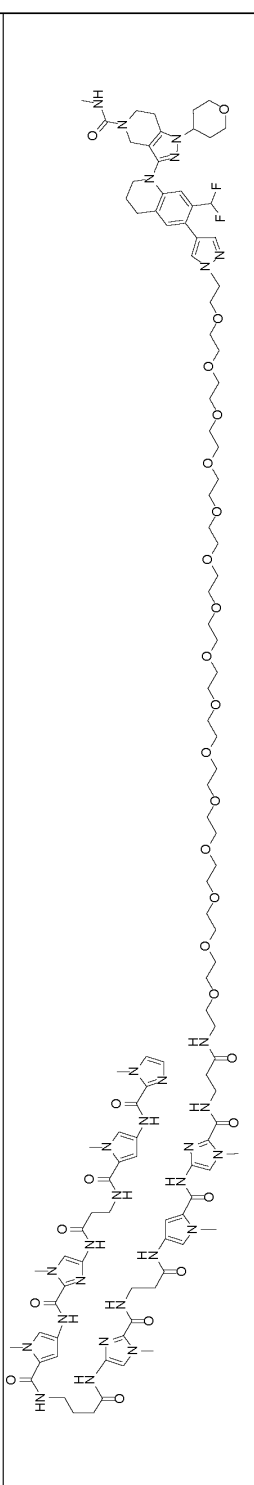
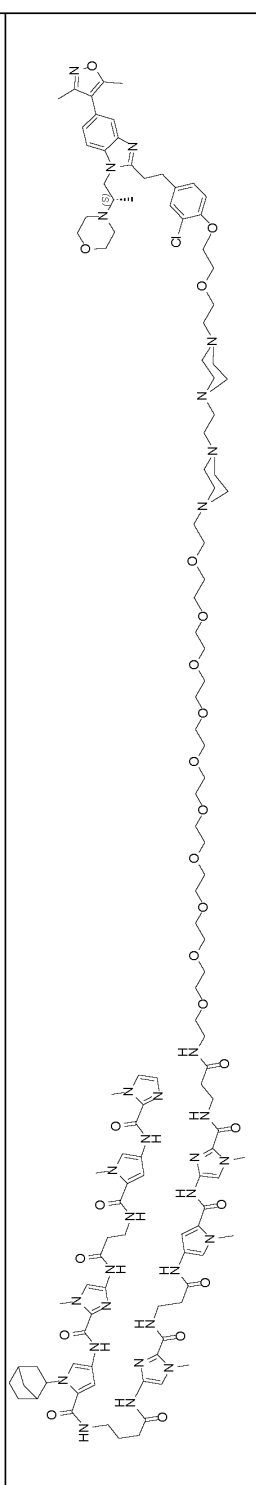
 Chemical structure of compound C-26. It features a central poly(ether) chain with multiple amide linkages. The structure includes a complex polycyclic aromatic system with a vinyl group, and a side chain containing a pyridine ring and a carboxylic acid group.	 Chemical structure of compound C-27. It features a central poly(ether) chain with multiple amide linkages. The structure includes a complex polycyclic aromatic system with a vinyl group, and a side chain containing a pyridine ring and a carboxylic acid group.
C-26	C-27

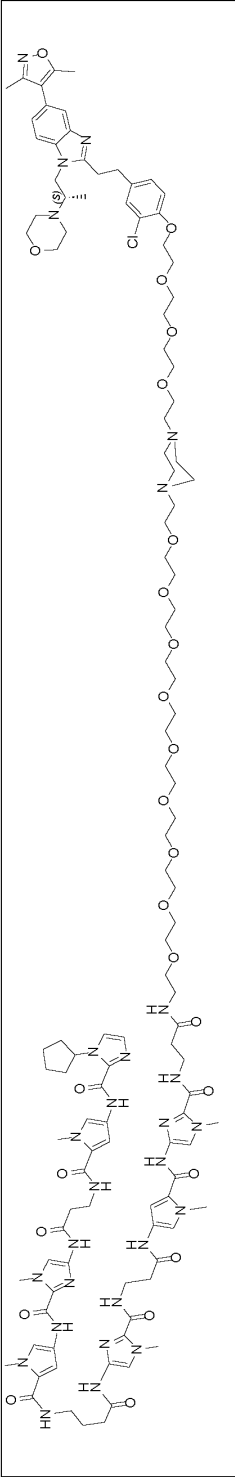
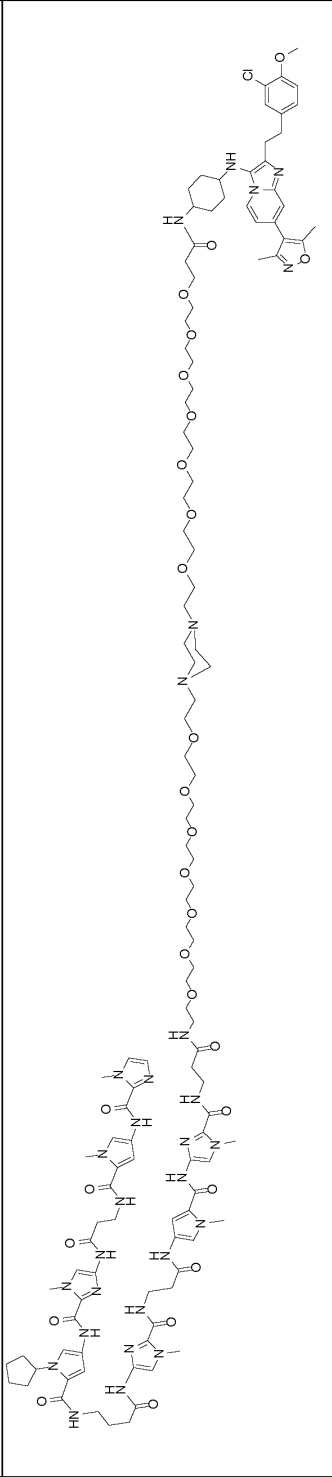
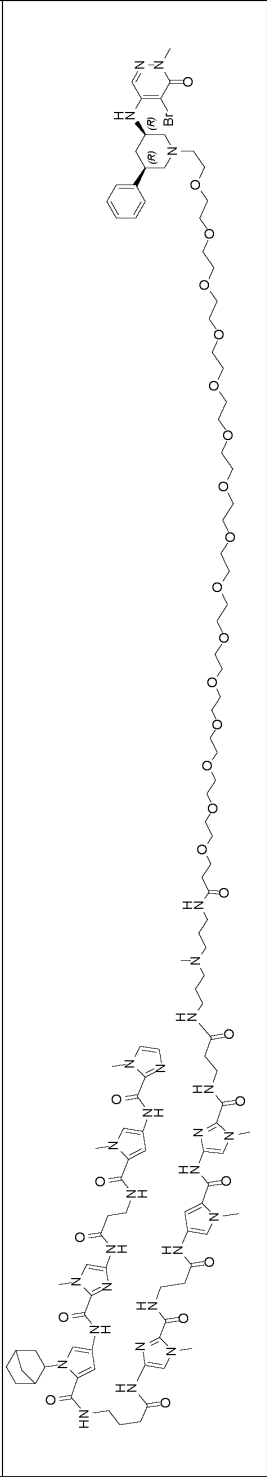
 Chemical structure of compound C-28. It features a long, flexible polyether chain (poly(ethylene glycol) derivative) with a terminal hydroxyl group. The other end of the chain is linked via an ester bond to a complex molecule. This complex molecule includes a benzimidazole core, a morpholine ring, and a pyridine ring. The pyridine ring is substituted with a methyl group and a methoxy group. The morpholine ring is substituted with a methyl group and a methoxy group. The benzimidazole core is substituted with a methyl group and a methoxy group.	 Chemical structure of compound C-29. It features a long, flexible polyether chain (poly(ethylene glycol) derivative) with a terminal hydroxyl group. The other end of the chain is linked via an ester bond to a complex molecule. This complex molecule includes a benzimidazole core, a morpholine ring, and a pyridine ring. The pyridine ring is substituted with a methyl group and a methoxy group. The morpholine ring is substituted with a methyl group and a methoxy group. The benzimidazole core is substituted with a methyl group and a methoxy group.
C-28	C-29

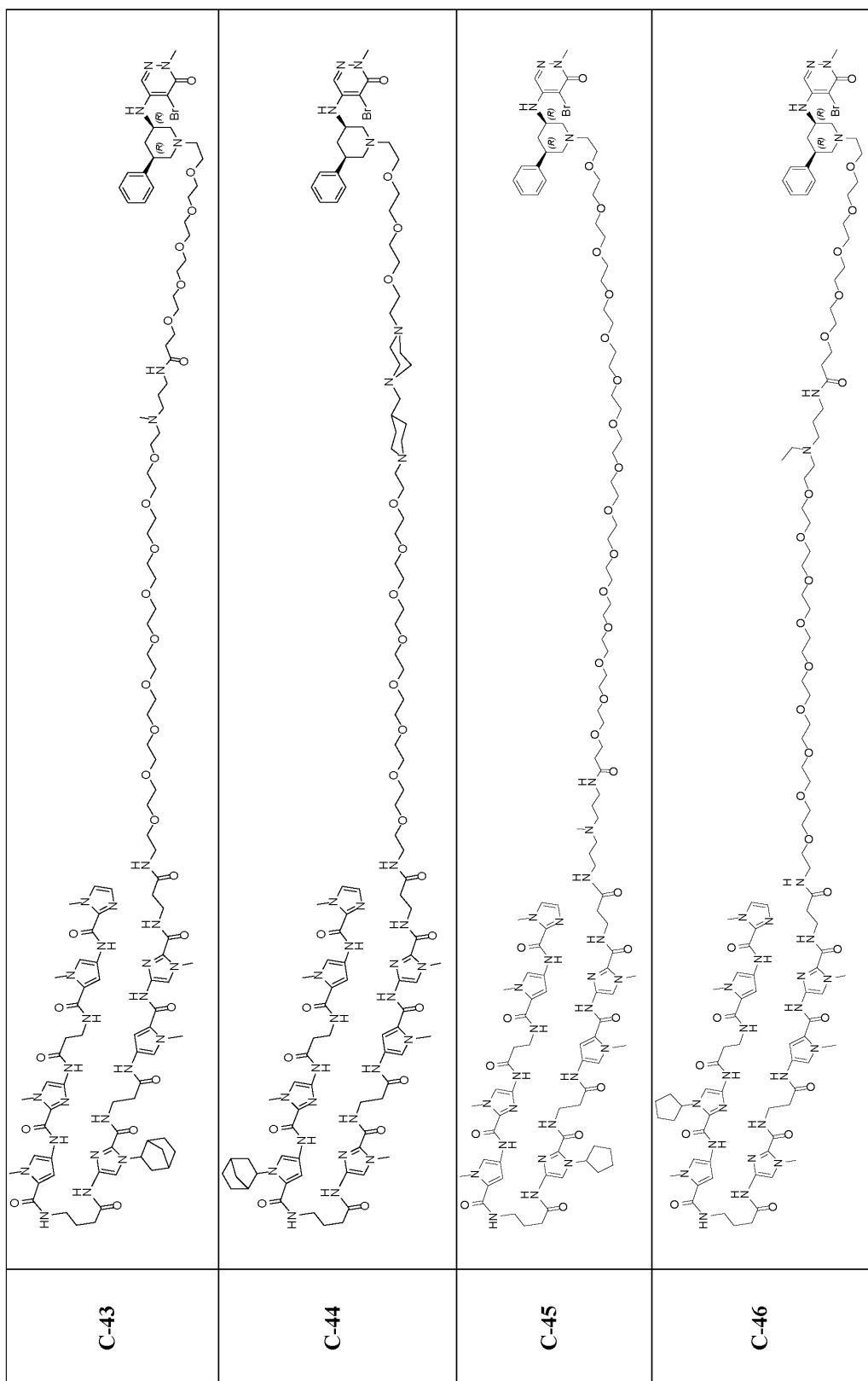
 Chemical structure of compound C-30. It features a central pyridine ring substituted with a 2,2,2-trifluoroethyl group, a 2-methyl-2-oxo-1,3-dioxolane-5-yl group, and a long polyether chain. The polyether chain is terminated by a complex heterocyclic system consisting of a pyrazole ring linked to a pyridine ring, which is further substituted with a methyl group and a 2-methyl-2-oxo-1,3-dioxolane-5-yl group.	 Chemical structure of compound C-31. It features a central pyridine ring substituted with a 2-methyl-2-oxo-1,3-dioxolane-5-yl group and a long polyether chain. The polyether chain is terminated by a complex heterocyclic system consisting of a pyrazole ring linked to a pyridine ring, which is further substituted with a methyl group and a 2-methyl-2-oxo-1,3-dioxolane-5-yl group.
C-30	C-31

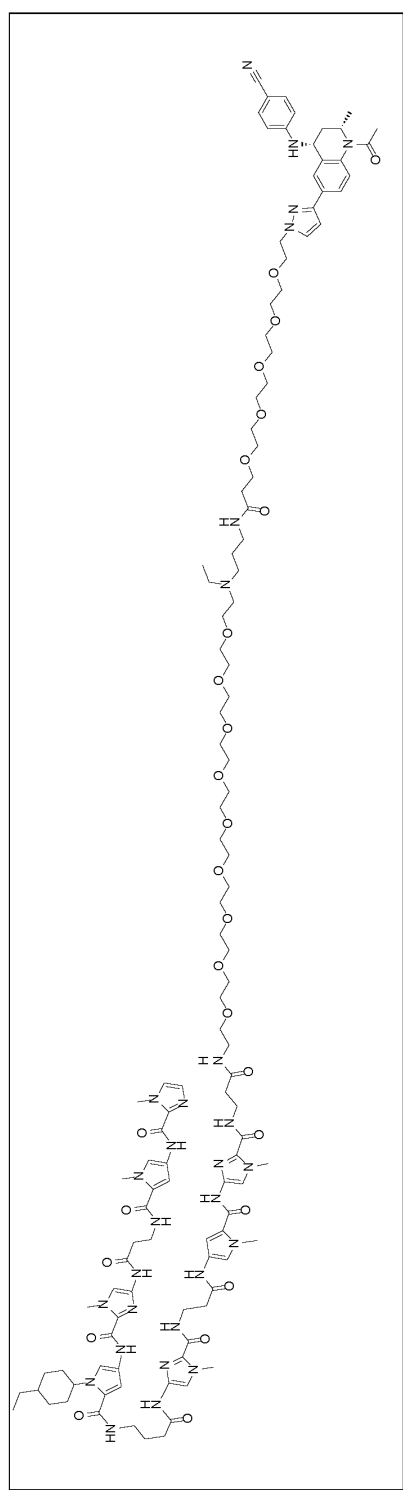
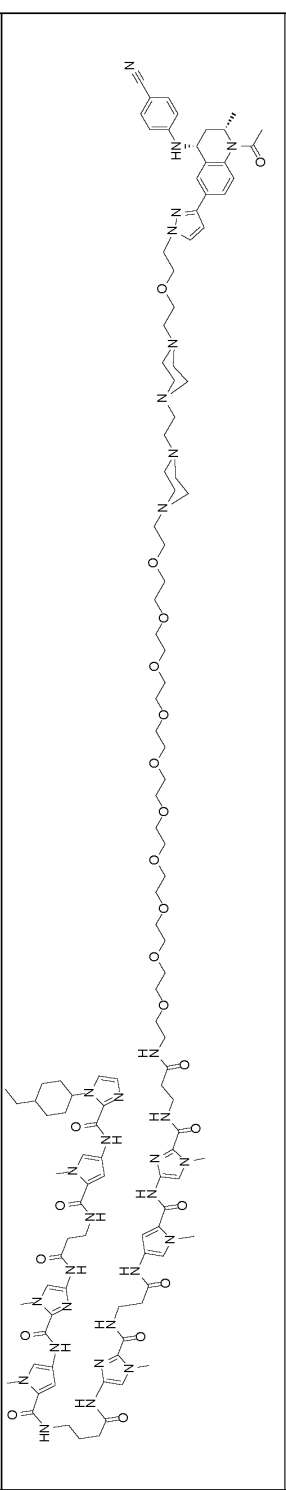
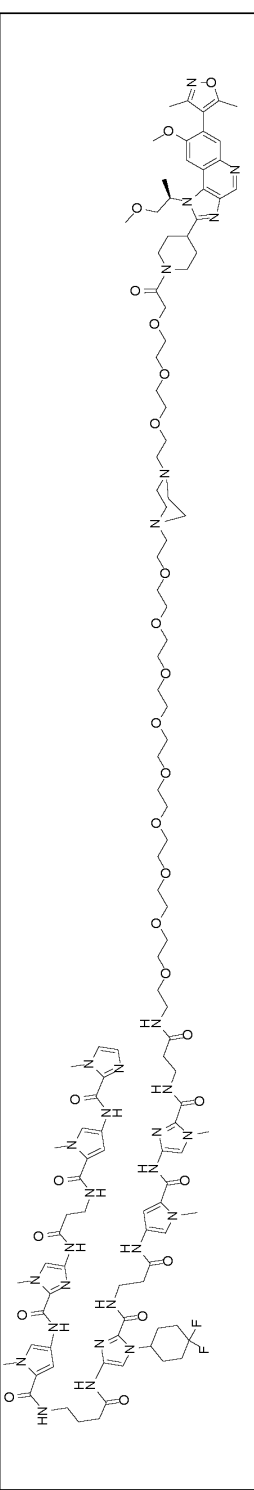


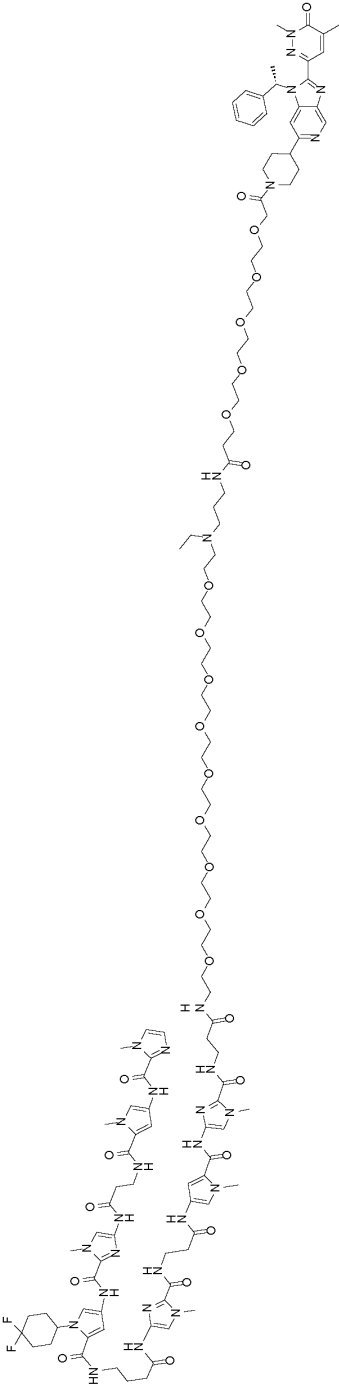
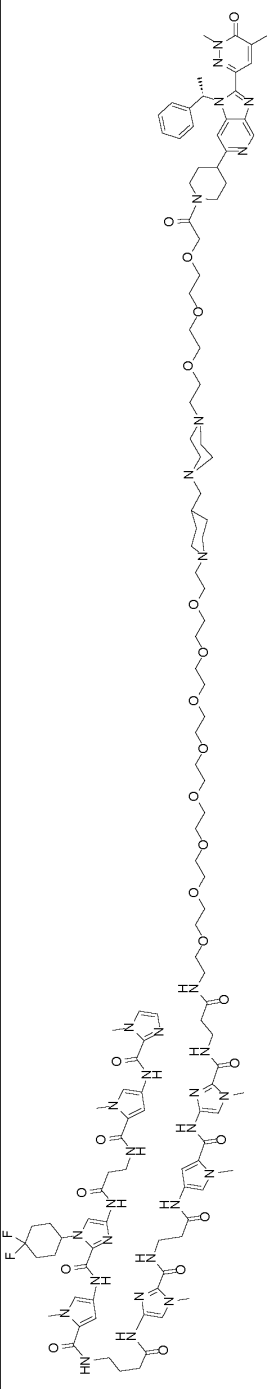
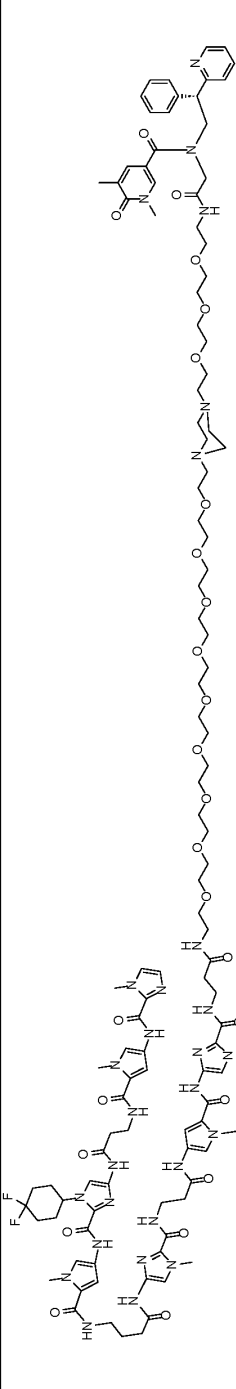
		
C-34	C-35	C-36

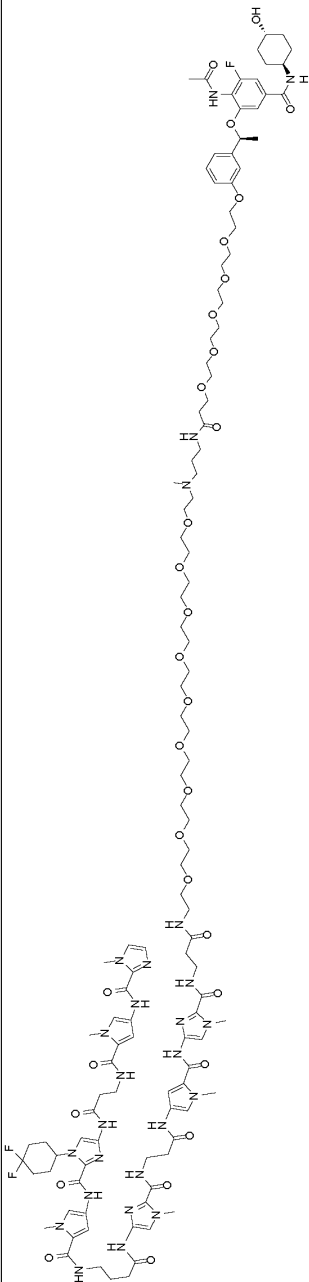
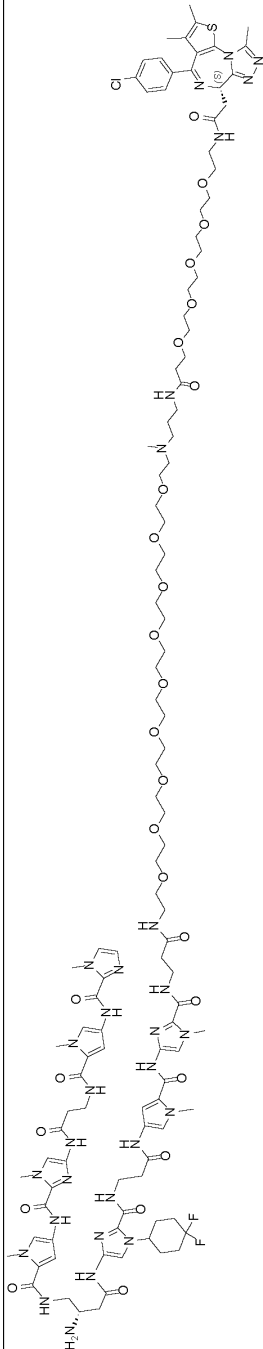
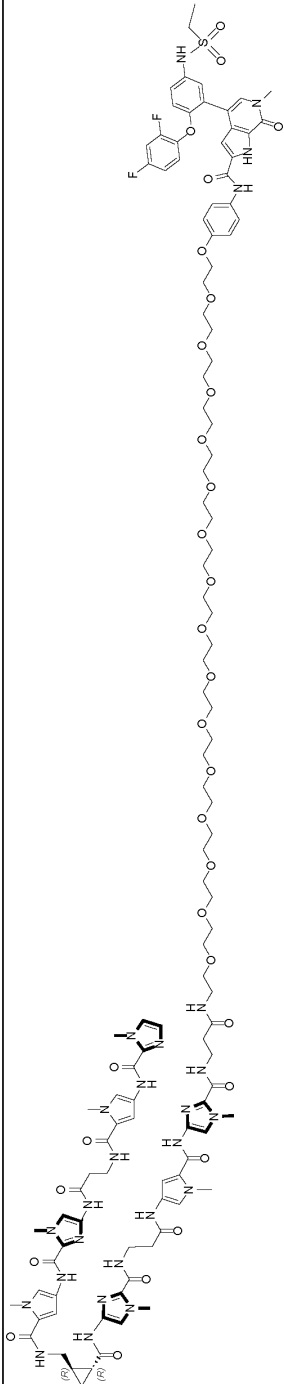
		
C-37	C-38	C-39

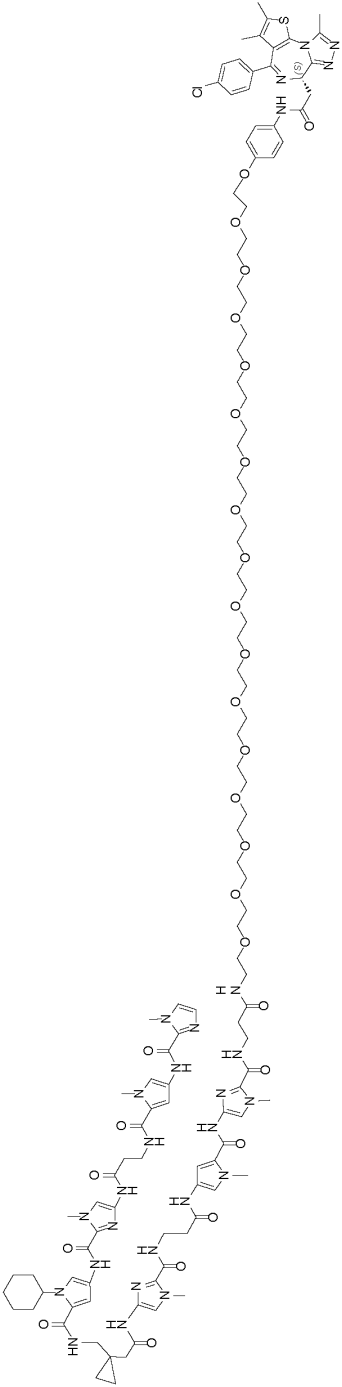
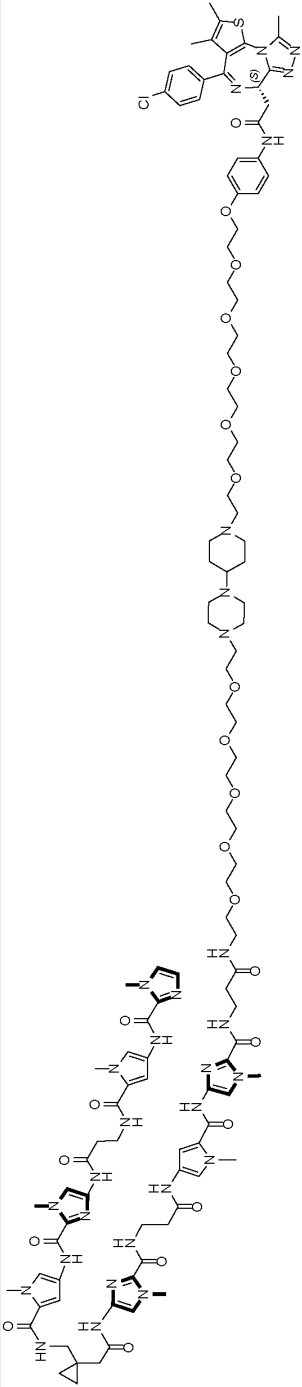
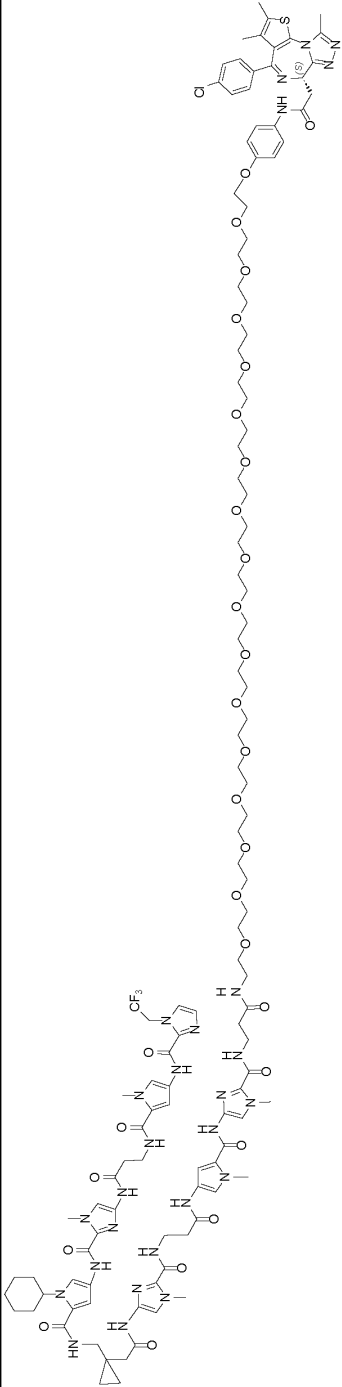
 Chemical structure of compound C-40. It features a complex molecule with a central core containing a pyrazole ring and a morpholine ring. This core is linked via a long, flexible polyether chain (containing multiple oxygen atoms) to a terminal group consisting of a pyrazole ring and a morpholine ring. The structure is highly symmetrical and includes various functional groups such as amides and ethers.	 Chemical structure of compound C-41. It features a complex molecule with a central core containing a pyrazole ring and a morpholine ring. This core is linked via a long, flexible polyether chain (containing multiple oxygen atoms) to a terminal group consisting of a pyrazole ring and a morpholine ring. The structure is highly symmetrical and includes various functional groups such as amides and ethers.	 Chemical structure of compound C-42. It features a complex molecule with a central core containing a pyrazole ring and a morpholine ring. This core is linked via a long, flexible polyether chain (containing multiple oxygen atoms) to a terminal group consisting of a pyrazole ring and a morpholine ring. The structure is highly symmetrical and includes various functional groups such as amides and ethers.
C-40	C-41	C-42

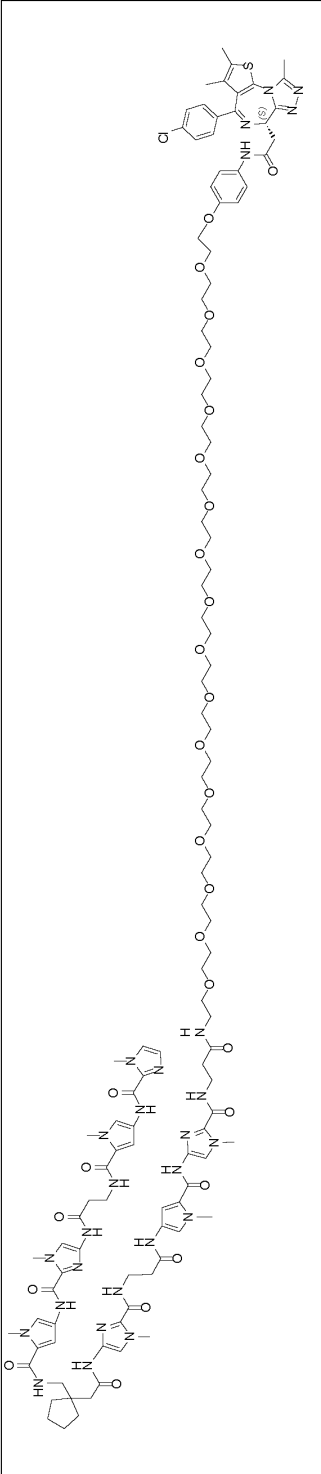
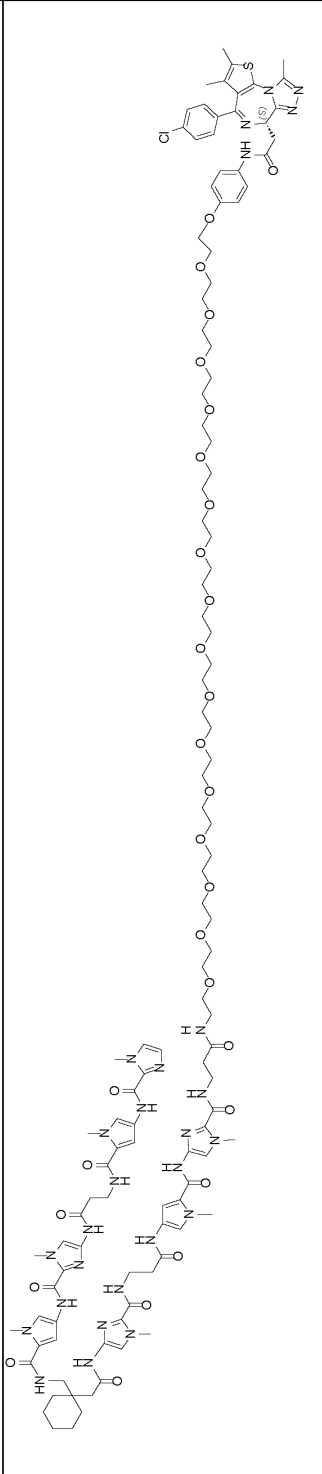
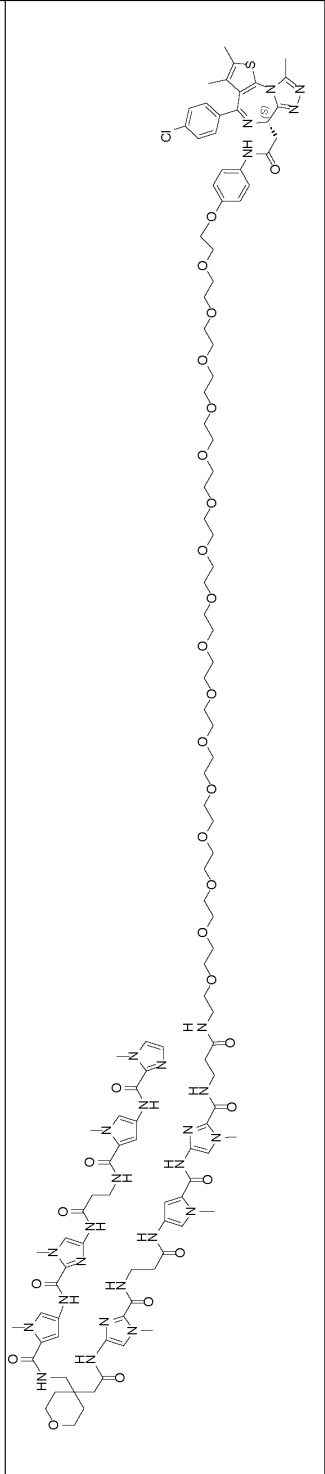


		
C-47	C-48	C-49

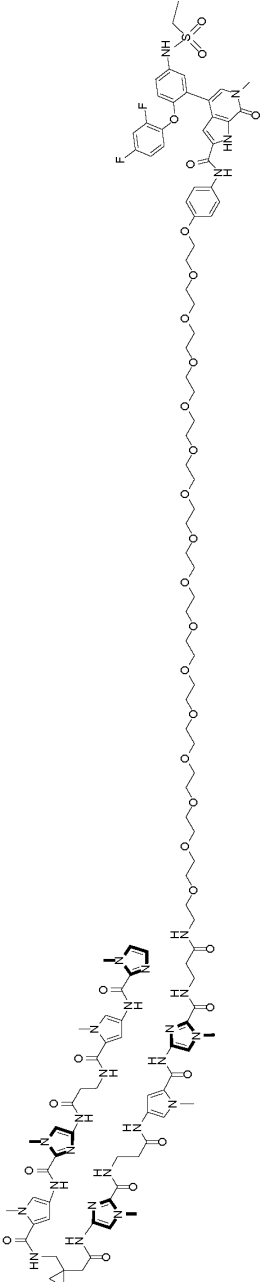
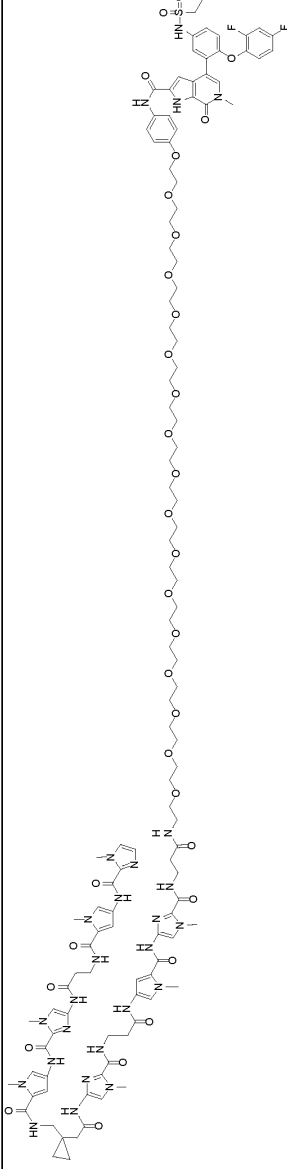
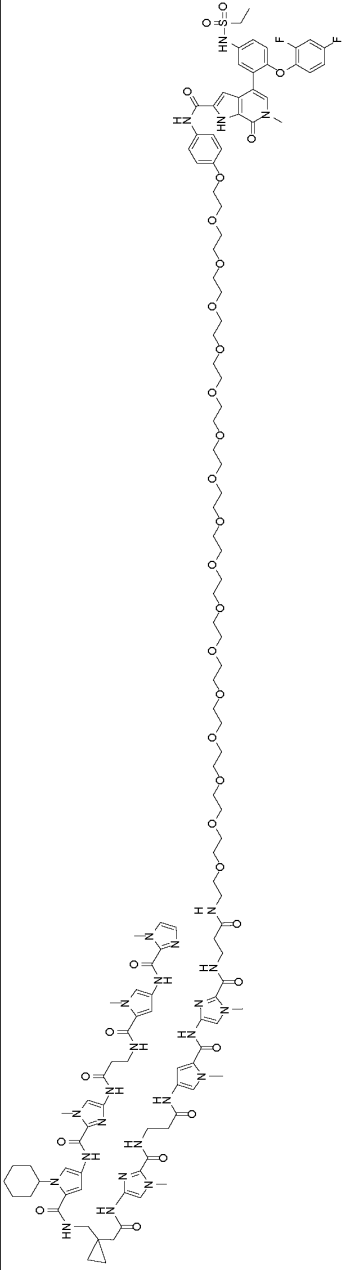
 Chemical structure of compound C-50, featuring a complex polycyclic aromatic system with multiple amide and ether linkages, and a long polyether chain.	 Chemical structure of compound C-51, featuring a complex polycyclic aromatic system with multiple amide and ether linkages, and a long polyether chain.	 Chemical structure of compound C-52, featuring a complex polycyclic aromatic system with multiple amide and ether linkages, and a long polyether chain.
C-50	C-51	C-52

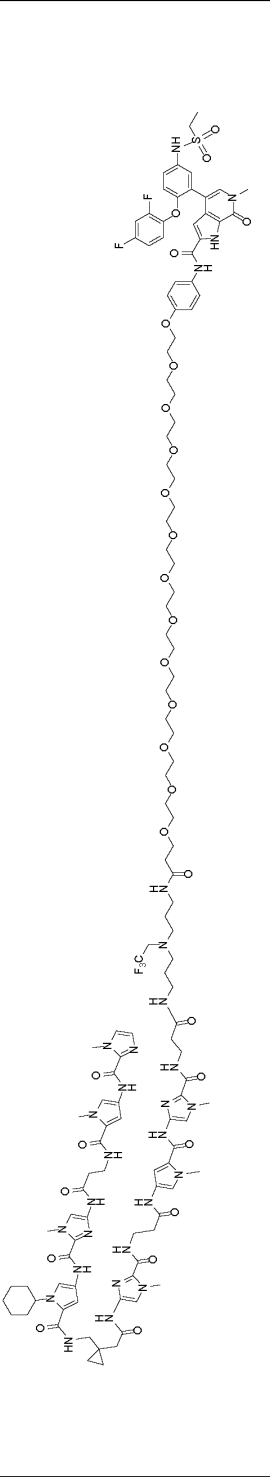
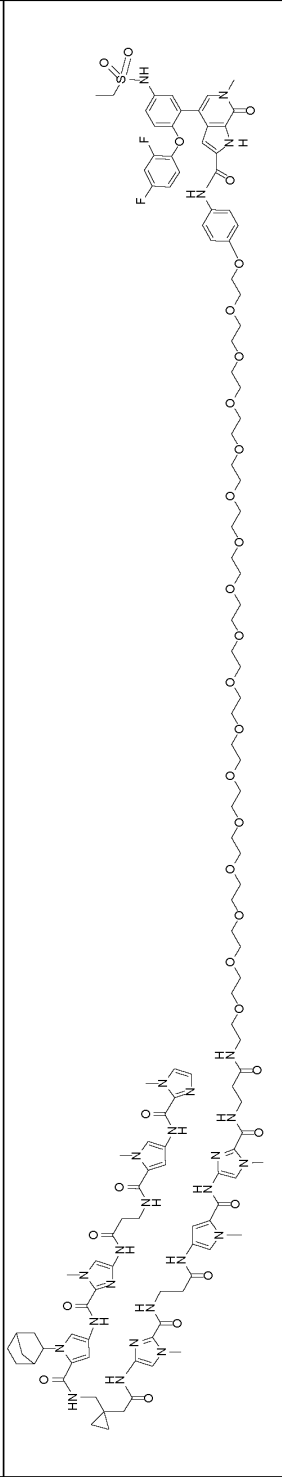
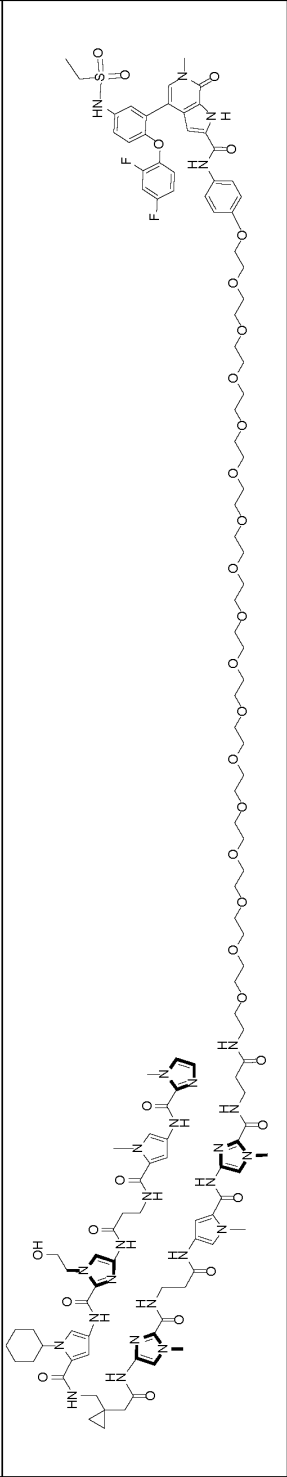
	C-53
	C-54
	C-55

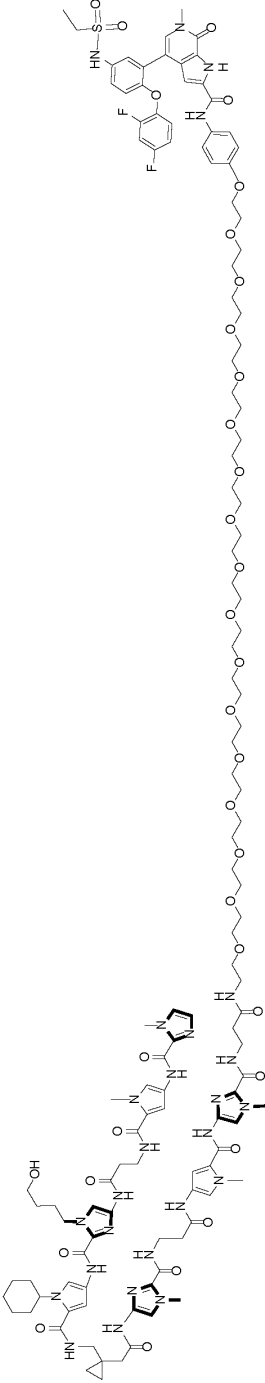
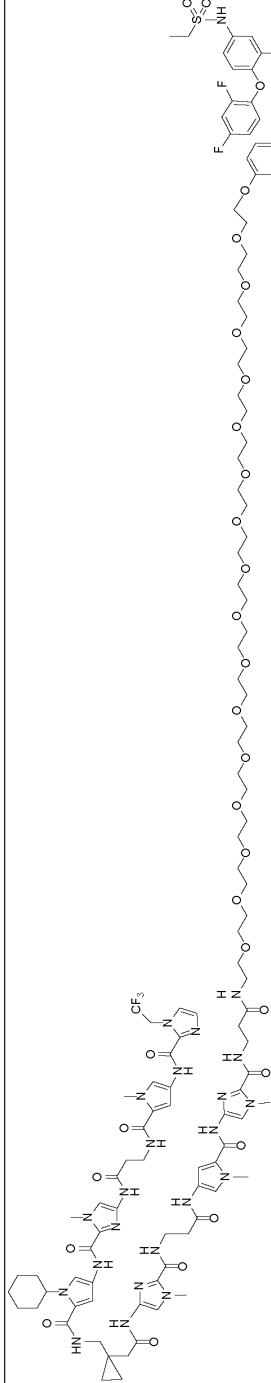
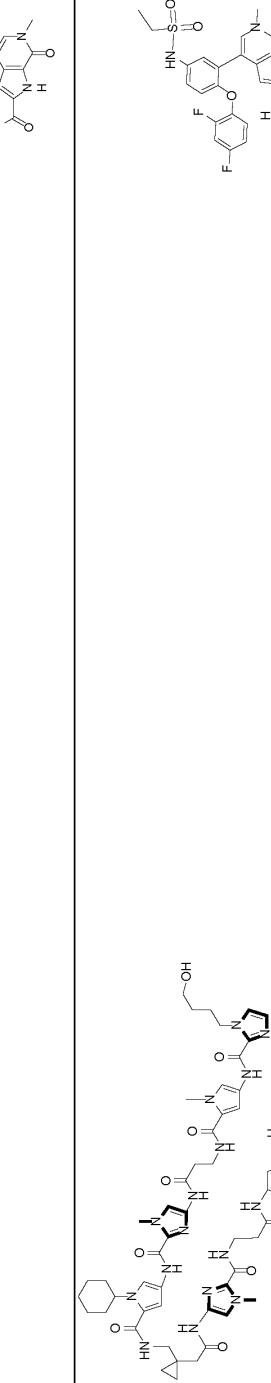
 Chemical structure of compound C-56. It features a complex polycyclic aromatic system with a thiazole ring, a pyridine ring, and a cyclohexyl group. The structure is linked via a long, flexible polyether chain to a terminal group consisting of a benzamide moiety and a thiazole ring.	 Chemical structure of compound C-57. It is similar to C-56 but includes a piperazine ring in the linker chain and a different terminal group configuration, including a thiazole ring and a pyridine ring.	 Chemical structure of compound C-58. It is similar to C-56 but includes a trifluoromethyl group (CF₃) in the linker chain and a different terminal group configuration, including a thiazole ring and a pyridine ring.
C-56	C-57	C-58

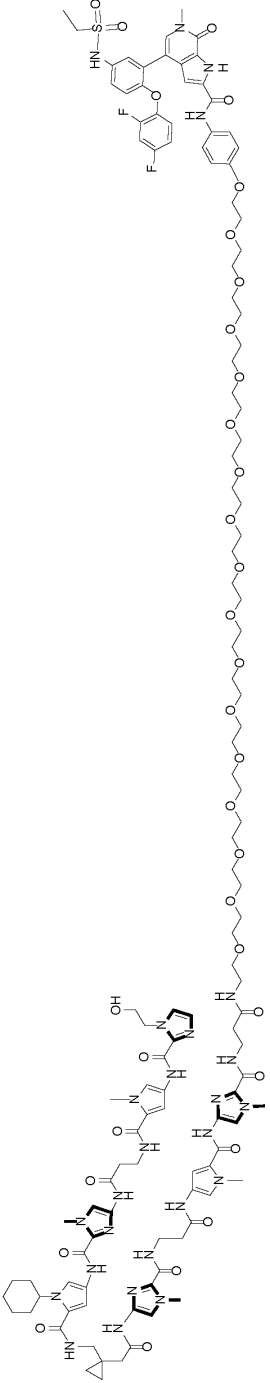
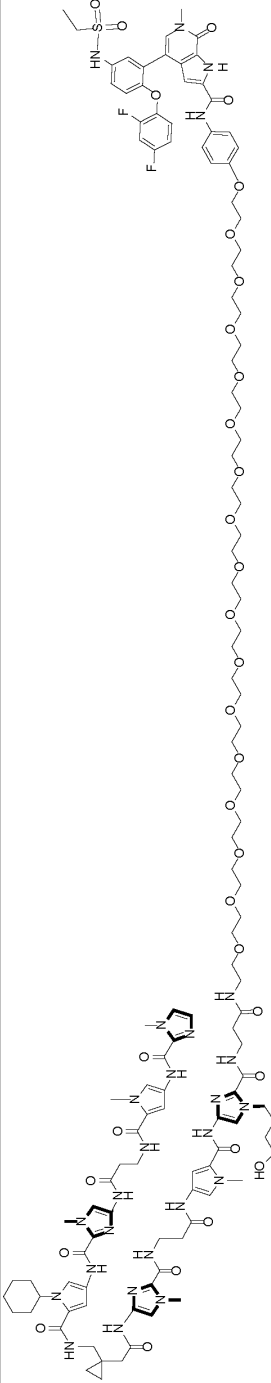
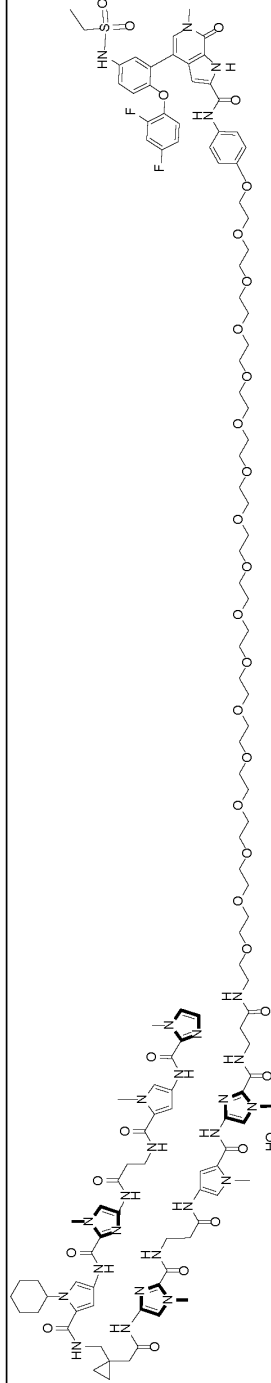
 Chemical structure of compound C-59. It features a 4-chlorophenyl group connected via an amide bond to a 4-((10,10-dimethyl-1,2,3,4,5,6-hexahydro-1,2,3,4-benzothiazol-5-yl)oxy)phenyl group. This is linked through a long polyether chain (10 repeating units of -OCH2CH2O-) to a 4-((10,10-dimethyl-1,2,3,4,5,6-hexahydro-1,2,3,4-benzothiazol-5-yl)oxy)phenyl group. The other end of the polyether chain is connected via an amide bond to a 4-chlorophenyl group.	 Chemical structure of compound C-60. It is similar to C-59 but the polyether chain consists of 12 repeating units of -OCH2CH2O-.	 Chemical structure of compound C-61. It is similar to C-59 but the polyether chain consists of 14 repeating units of -OCH2CH2O-.
C-59	C-60	C-61

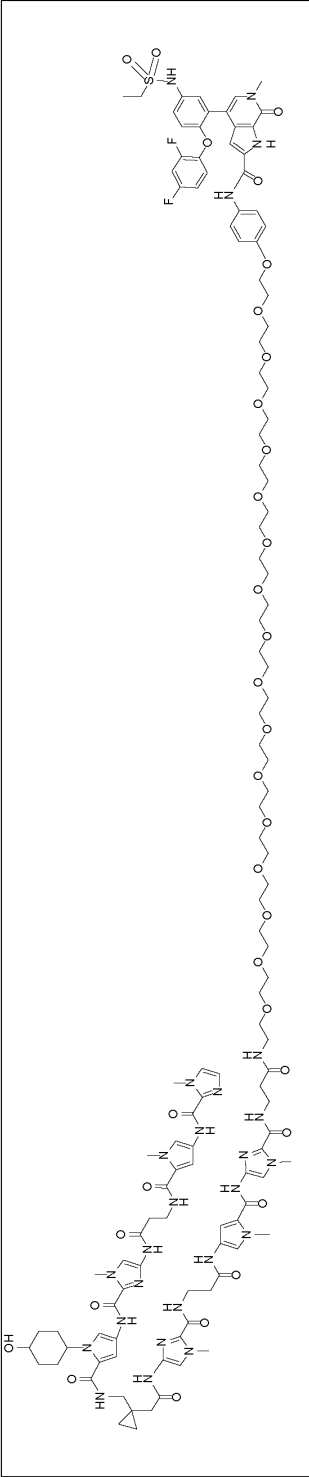
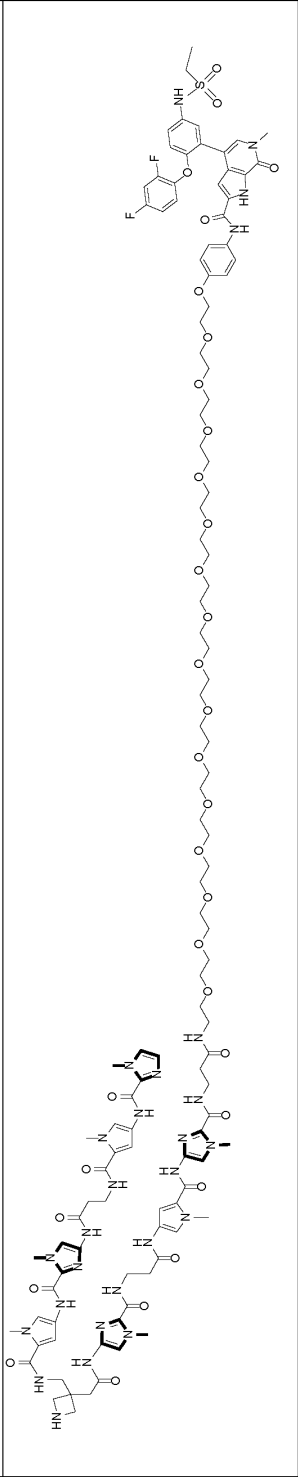
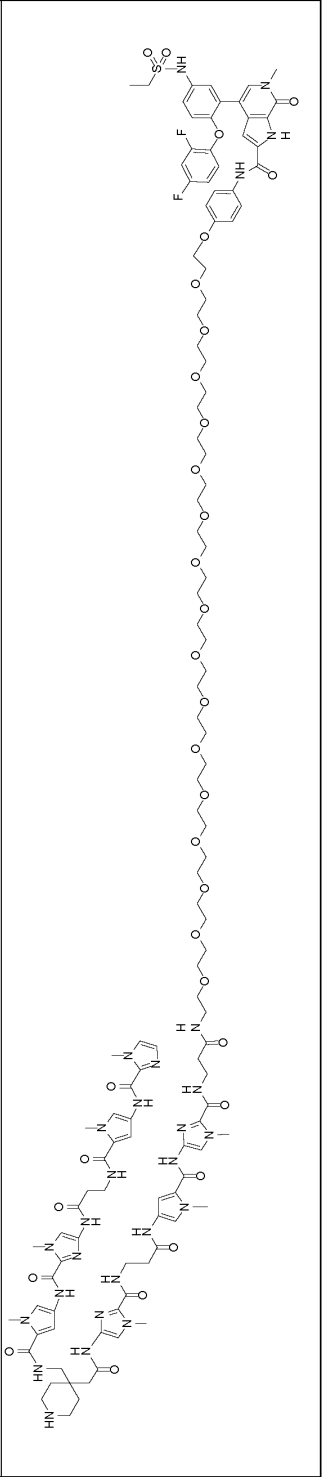
C-62	C-63	C-64
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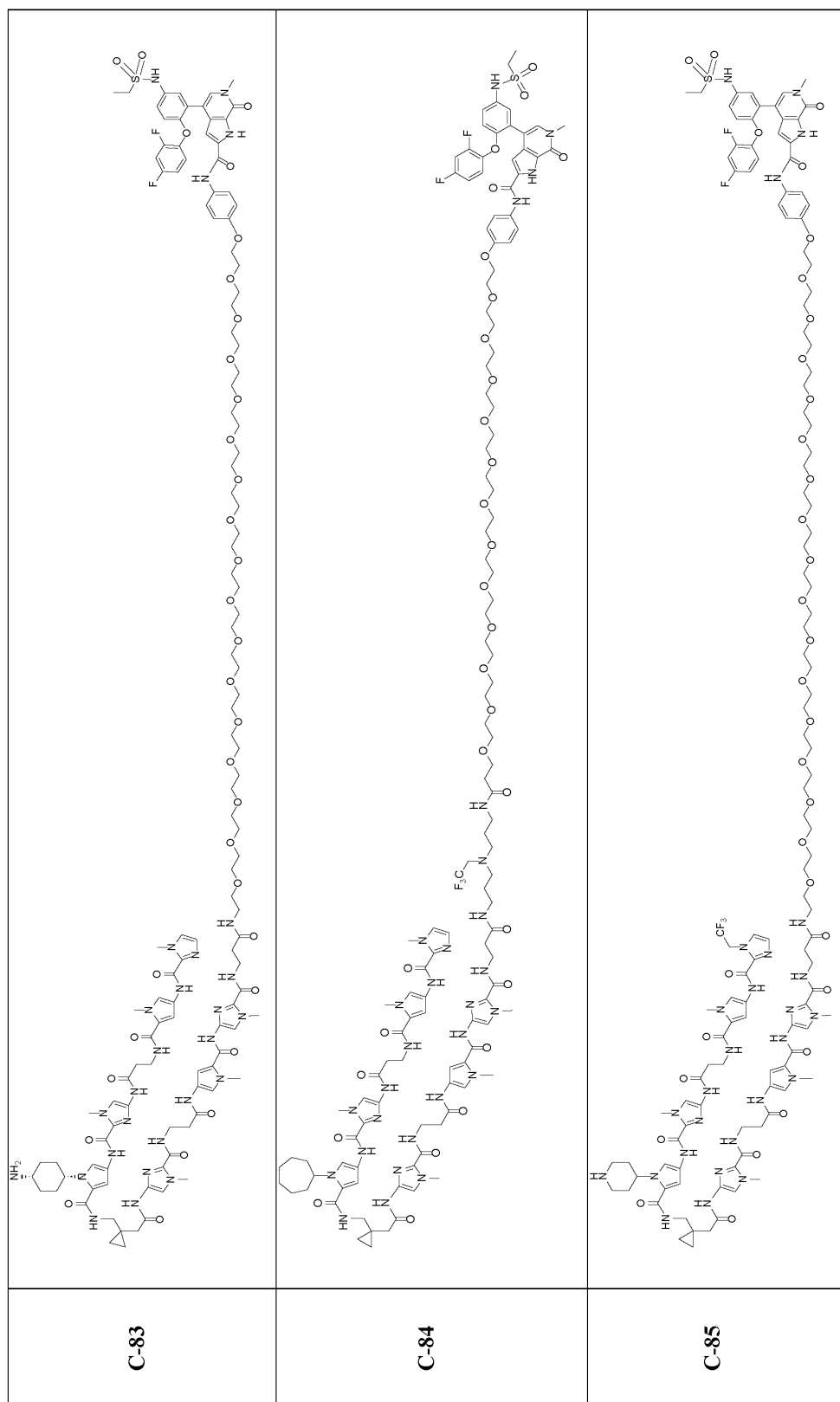
 Chemical structure of compound C-65. It features a long polyether chain (1,3-bis(2-methoxyethoxy)propane derivative) connected to a complex heterocyclic system. The system includes a pyrazole ring substituted with a 4-fluorophenyl group and a 4-(methylsulfonyl)phenyl group. The chain is also linked to a pyrazole ring substituted with a 4-(methylsulfonyl)phenyl group.	 Chemical structure of compound C-66. It features a long polyether chain (1,3-bis(2-methoxyethoxy)propane derivative) connected to a complex heterocyclic system. The system includes a pyrazole ring substituted with a 4-fluorophenyl group and a 4-(methylsulfonyl)phenyl group. The chain is also linked to a pyrazole ring substituted with a 4-(methylsulfonyl)phenyl group.	 Chemical structure of compound C-67. It features a long polyether chain (1,3-bis(2-methoxyethoxy)propane derivative) connected to a complex heterocyclic system. The system includes a pyrazole ring substituted with a 4-fluorophenyl group and a 4-(methylsulfonyl)phenyl group. The chain is also linked to a pyrazole ring substituted with a 4-(methylsulfonyl)phenyl group.
C-65	C-66	C-67

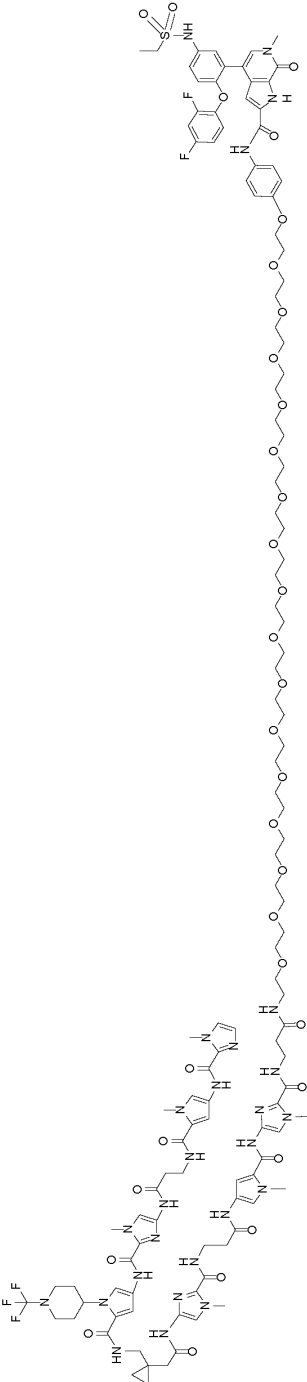
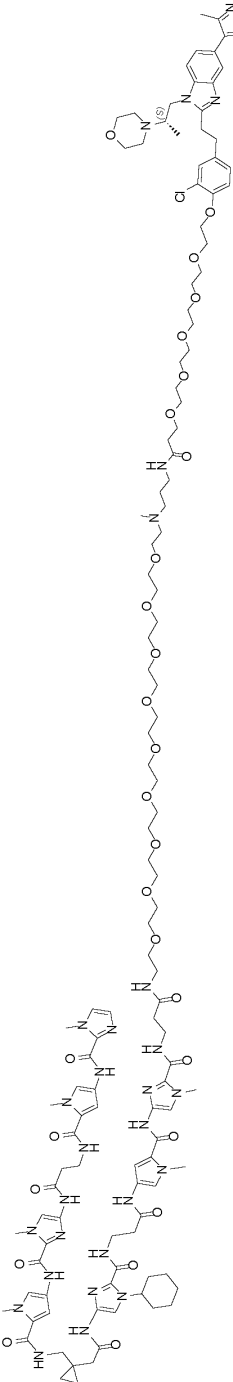
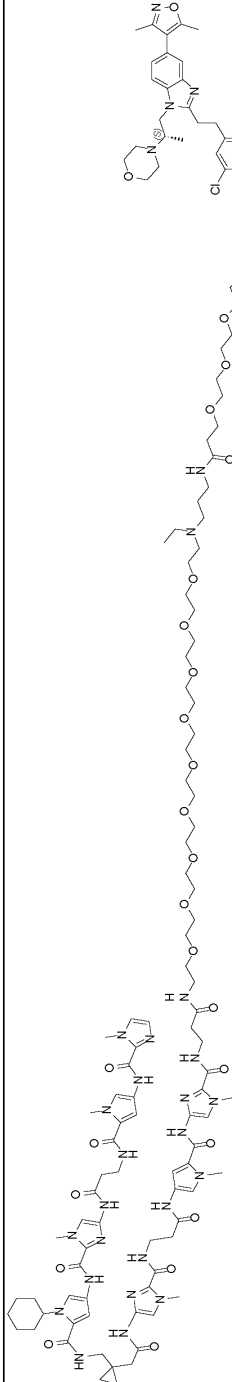
 Chemical structure of compound C-68. It features a complex polycyclic aromatic system with a central benzimidazole core. The structure is substituted with a 4-fluorophenyl group, a 4-ethanesulfonylphenyl group, and a long, flexible polyether chain (poly(ethylene glycol) derivative) that terminates in a 4-ethanesulfonylphenyl group. The molecule also contains a 4-fluorophenyl group and a 4-ethanesulfonylphenyl group.	 Chemical structure of compound C-69. It features a complex polycyclic aromatic system with a central benzimidazole core. The structure is substituted with a 4-fluorophenyl group, a 4-ethanesulfonylphenyl group, and a long, flexible polyether chain (poly(ethylene glycol) derivative) that terminates in a 4-ethanesulfonylphenyl group. The molecule also contains a 4-fluorophenyl group and a 4-ethanesulfonylphenyl group.	 Chemical structure of compound C-70. It features a complex polycyclic aromatic system with a central benzimidazole core. The structure is substituted with a 4-fluorophenyl group, a 4-ethanesulfonylphenyl group, and a long, flexible polyether chain (poly(ethylene glycol) derivative) that terminates in a 4-ethanesulfonylphenyl group. The molecule also contains a 4-fluorophenyl group and a 4-ethanesulfonylphenyl group.
C-68	C-69	C-70

 Chemical structure of compound C-71. It features a complex molecule with a central core containing a pyrazole ring and a fluorinated phenyl group. This core is linked via a long, flexible polyether chain (approximately 15 oxygen atoms) to a side chain. The side chain includes a carboxylic acid group, a pyrazole ring, and a cyclopropylmethyl group.	 Chemical structure of compound C-72. It is similar to C-71 but includes a trifluoromethyl (CF₃) group on the side chain, replacing the cyclopropylmethyl group.	 Chemical structure of compound C-73. It is similar to C-71 but includes a hydroxymethyl group on the side chain, replacing the cyclopropylmethyl group.
C-71	C-72	C-73

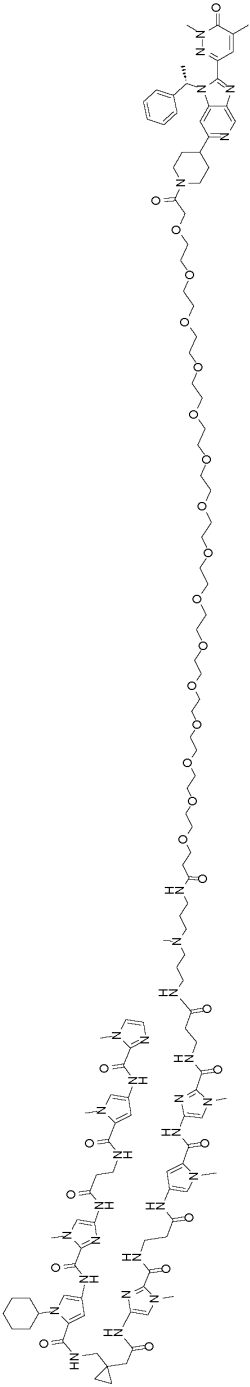
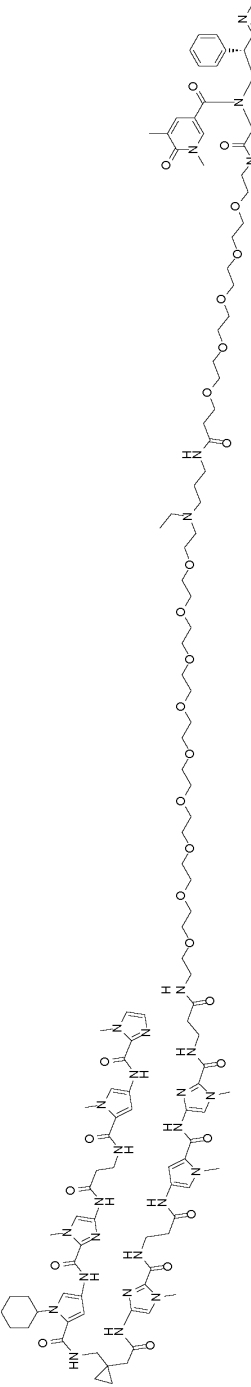
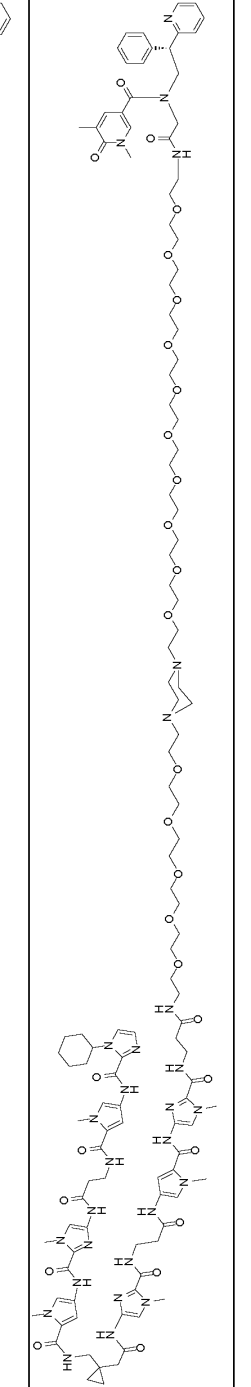
 Chemical structure of compound C-74. It features a complex molecule with a central pyrazole ring system. The molecule includes a 4-fluorophenyl group, a 4-ethanesulfonylphenyl group, and a long polyether chain (poly(ethylene glycol) derivative) attached to the pyrazole ring. The molecule also contains a 4-cyclohexylpyrazole group and a 4-(3-hydroxypropyl)pyrazole group.	 Chemical structure of compound C-75. It is similar to C-74 but with a different substitution pattern on the pyrazole ring, specifically a 4-(3-hydroxypropyl)pyrazole group instead of a 4-cyclohexylpyrazole group.	 Chemical structure of compound C-76. It is similar to C-74 but with a different substitution pattern on the pyrazole ring, specifically a 4-cyclohexylpyrazole group instead of a 4-(3-hydroxypropyl)pyrazole group.
C-74	C-75	C-76

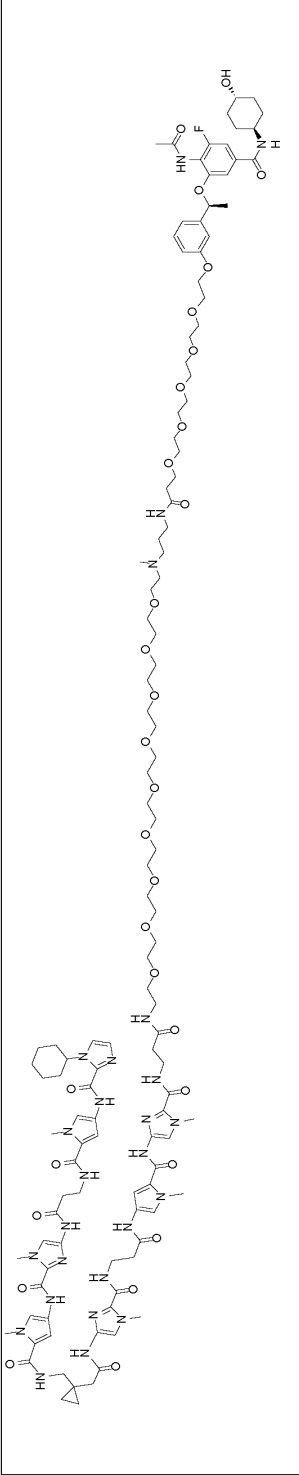
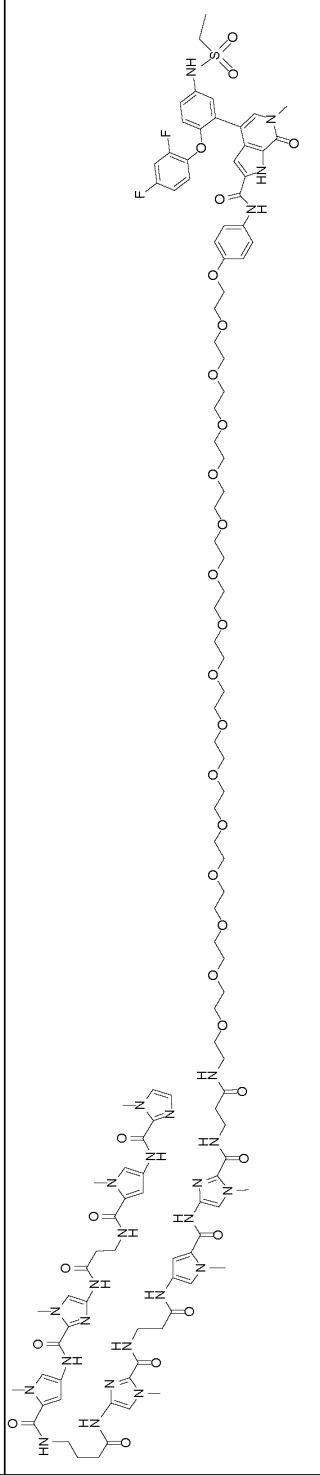
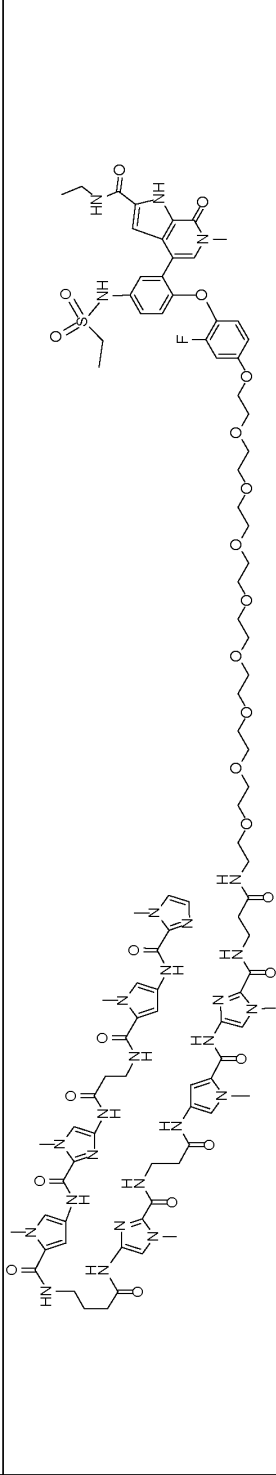
 Chemical structure of compound C-77. It features a complex polycyclic aromatic system with a sulfonamide group (SO₂NH-) and a long, flexible polyether chain (-(OCH₂)₁₂-) attached to the aromatic ring. The structure also includes a pyrazole ring and a carboxylic acid group.	 Chemical structure of compound C-78. It features a complex polycyclic aromatic system with a sulfonamide group (SO₂NH-) and a long, flexible polyether chain (-(OCH₂)₁₂-) attached to the aromatic ring. The structure also includes a pyrazole ring and a carboxylic acid group.	 Chemical structure of compound C-79. It features a complex polycyclic aromatic system with a sulfonamide group (SO₂NH-) and a long, flexible polyether chain (-(OCH₂)₁₂-) attached to the aromatic ring. The structure also includes a pyrazole ring and a carboxylic acid group.
C-77	C-78	C-79

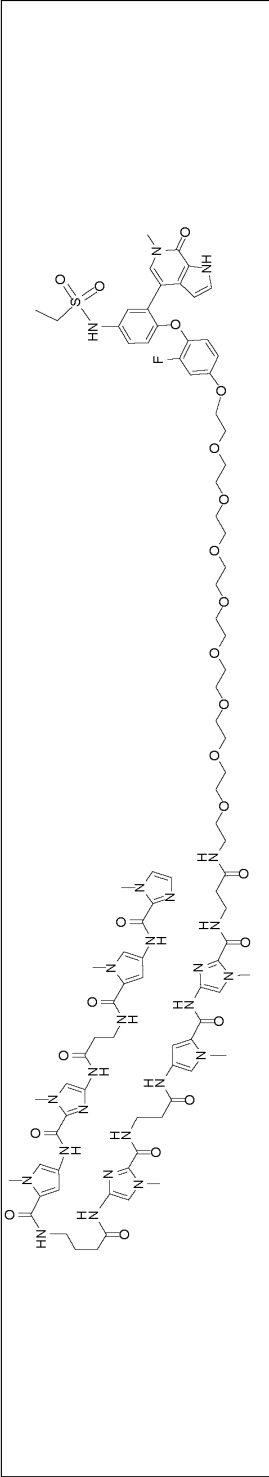
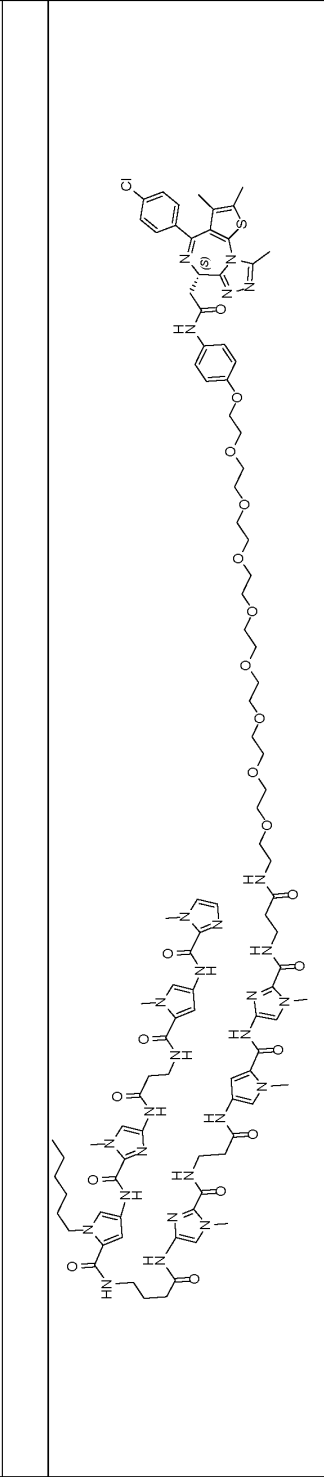
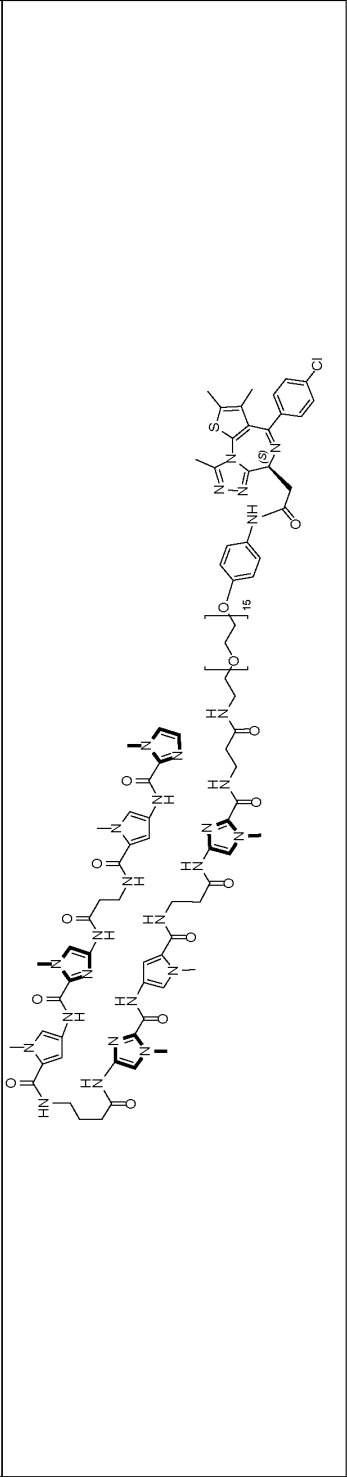


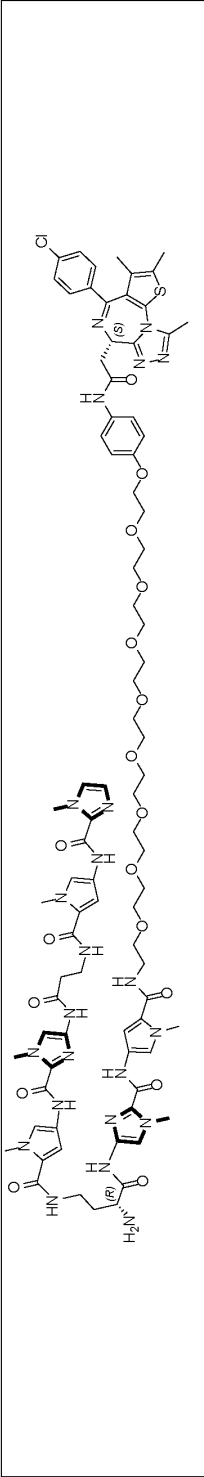
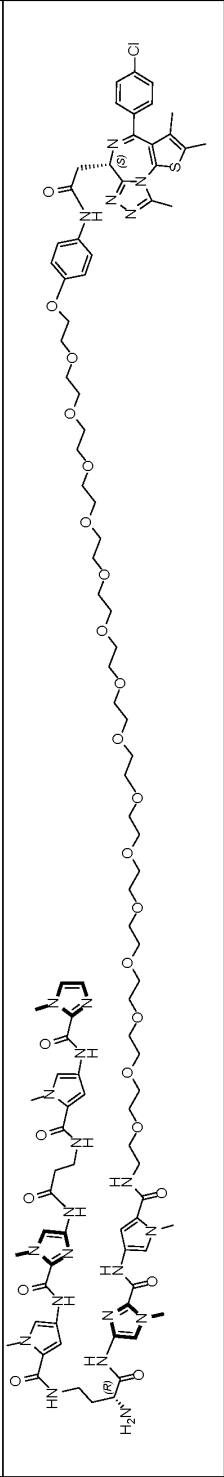
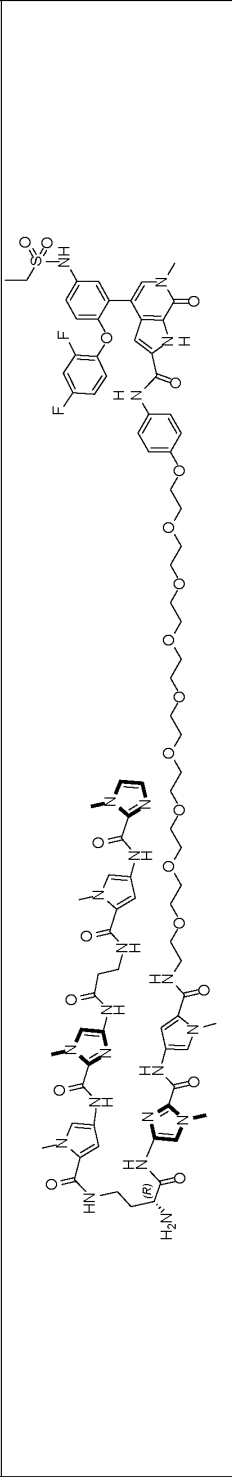
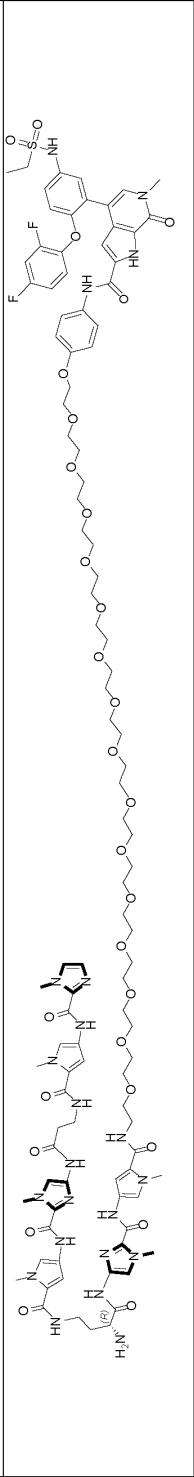
 Chemical structure of compound C-86, featuring a complex polycyclic aromatic system with a sulfonamide group, a fluorine atom, and a long polyether chain.	 Chemical structure of compound C-87, featuring a complex polycyclic aromatic system with a sulfonamide group, a fluorine atom, and a long polyether chain.	 Chemical structure of compound C-88, featuring a complex polycyclic aromatic system with a sulfonamide group, a fluorine atom, and a long polyether chain.
C-86	C-87	C-88

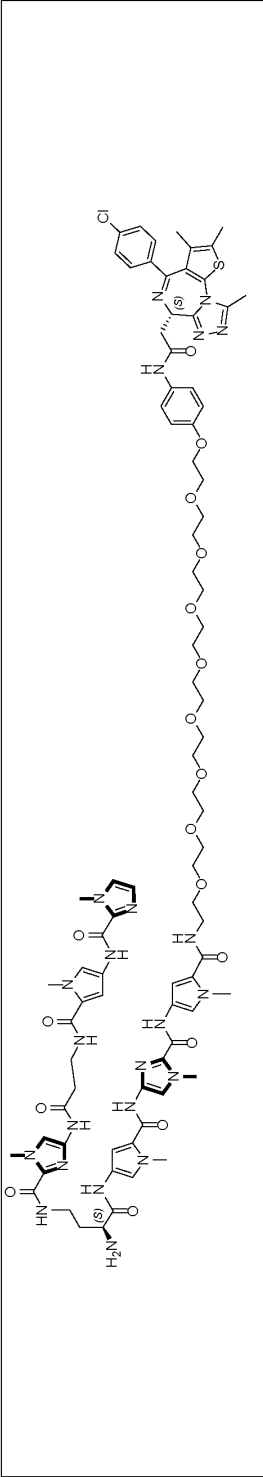
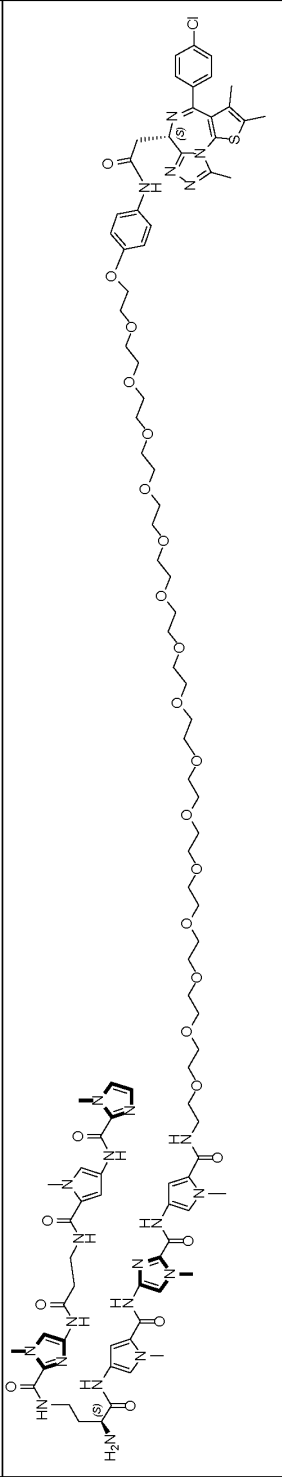
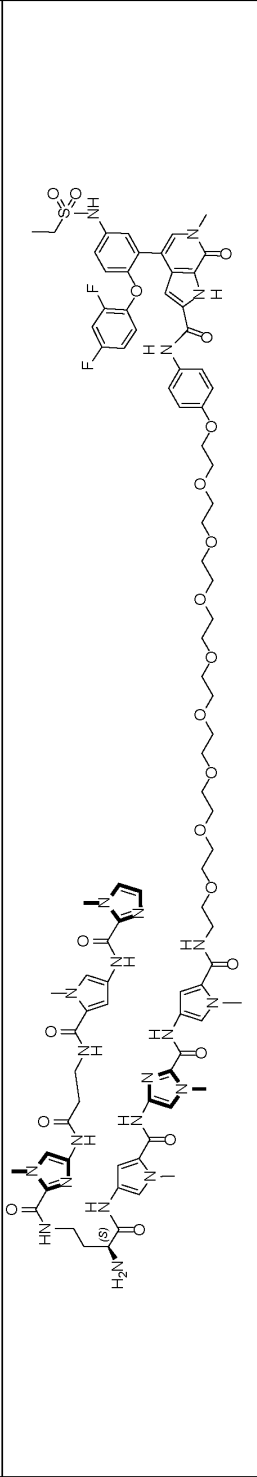
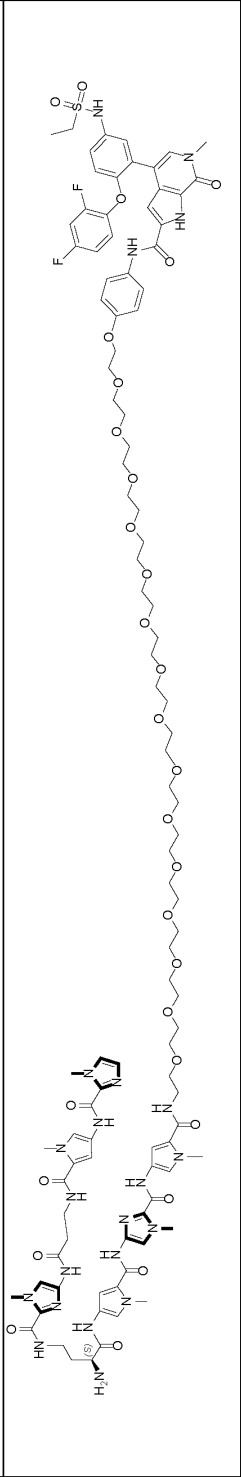
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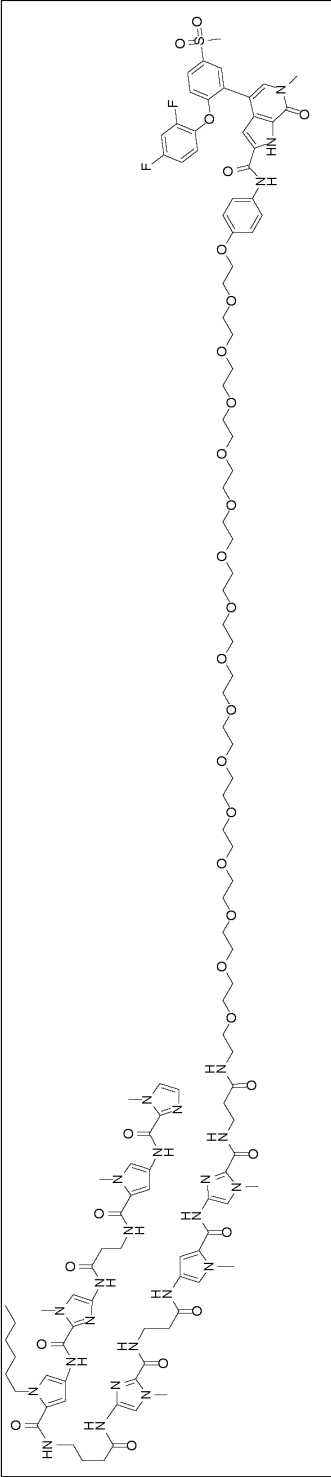
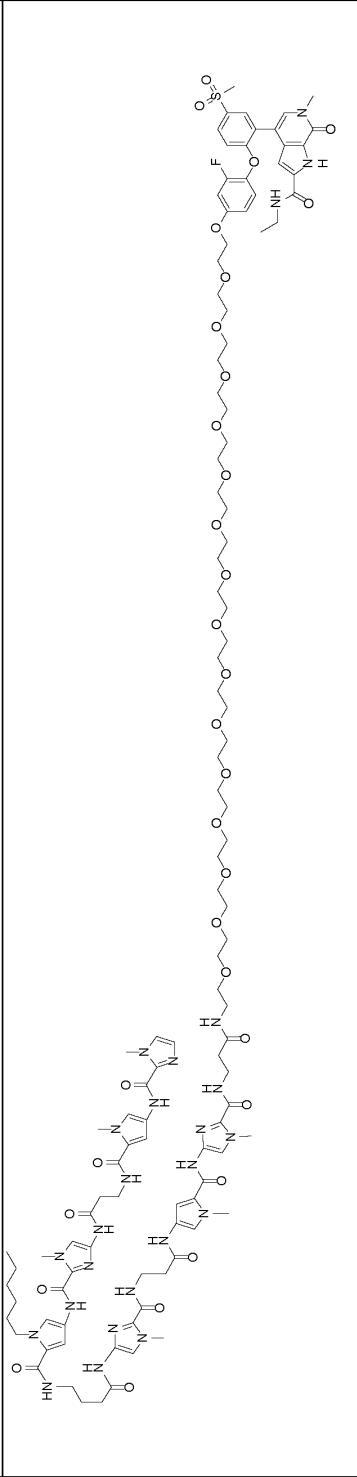
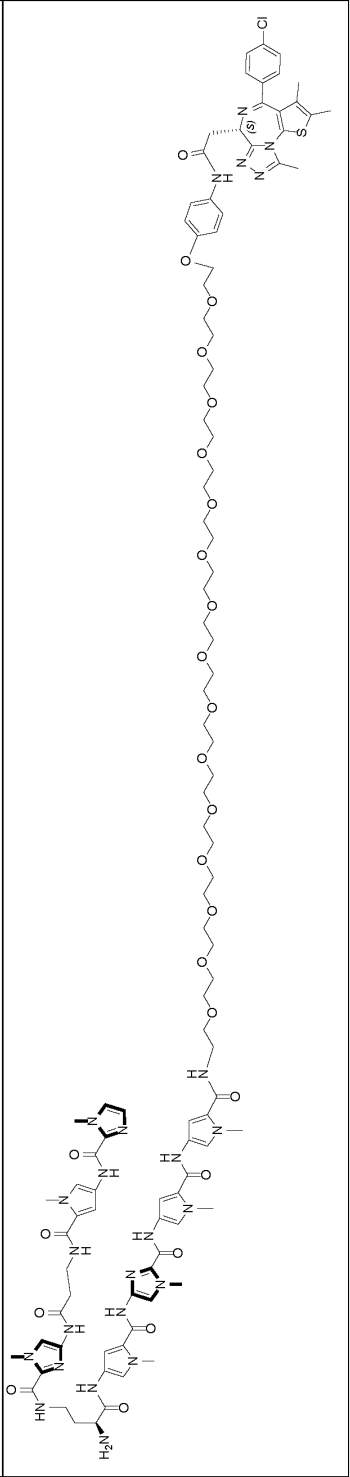
 Chemical structure of compound C-92, featuring a complex polycyclic aromatic system with multiple amide and ether linkages, and a long polyether chain.	 Chemical structure of compound C-93, featuring a complex polycyclic aromatic system with multiple amide and ether linkages, and a long polyether chain.	 Chemical structure of compound C-94, featuring a complex polycyclic aromatic system with multiple amide and ether linkages, and a long polyether chain.
C-92	C-93	C-94

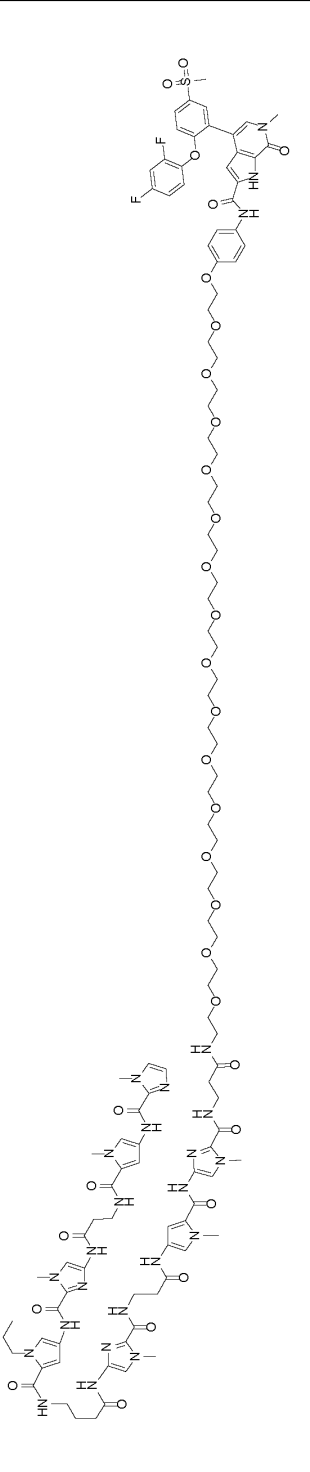
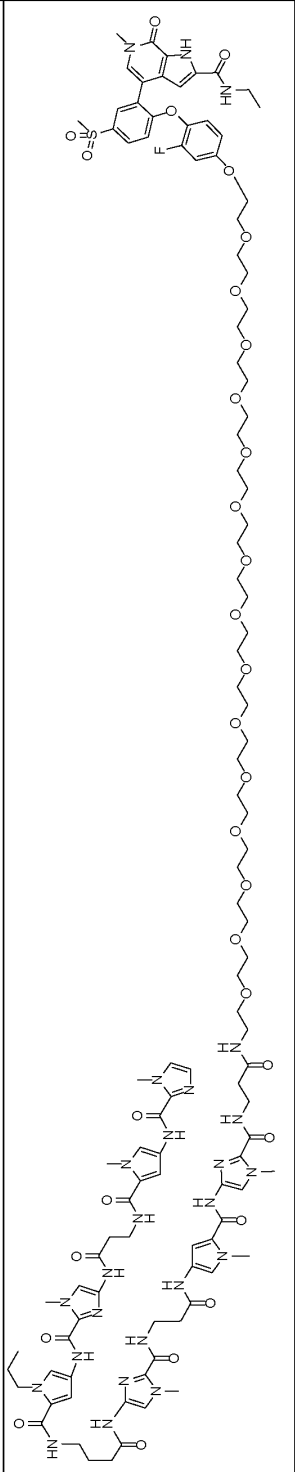
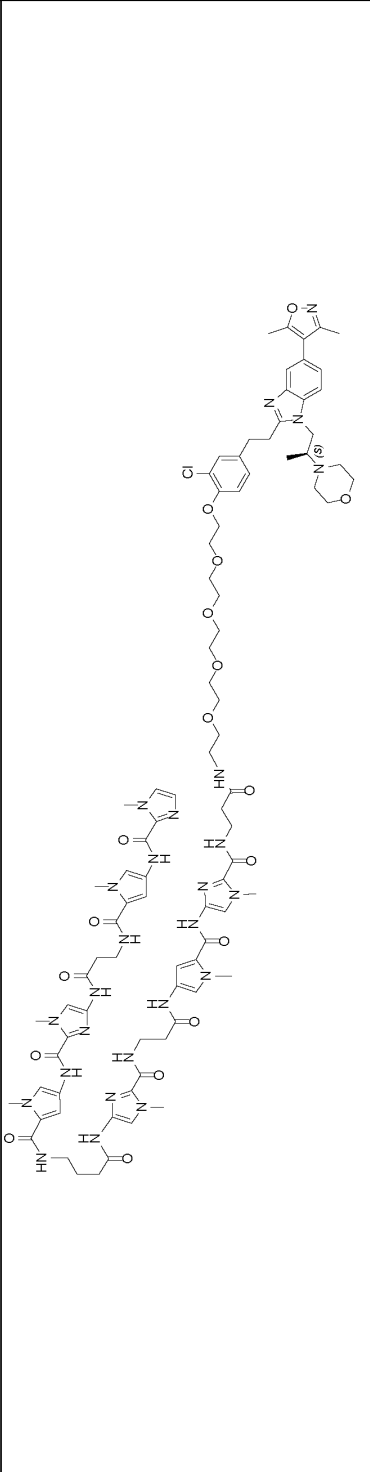
C-95	
C-96	
C-97	

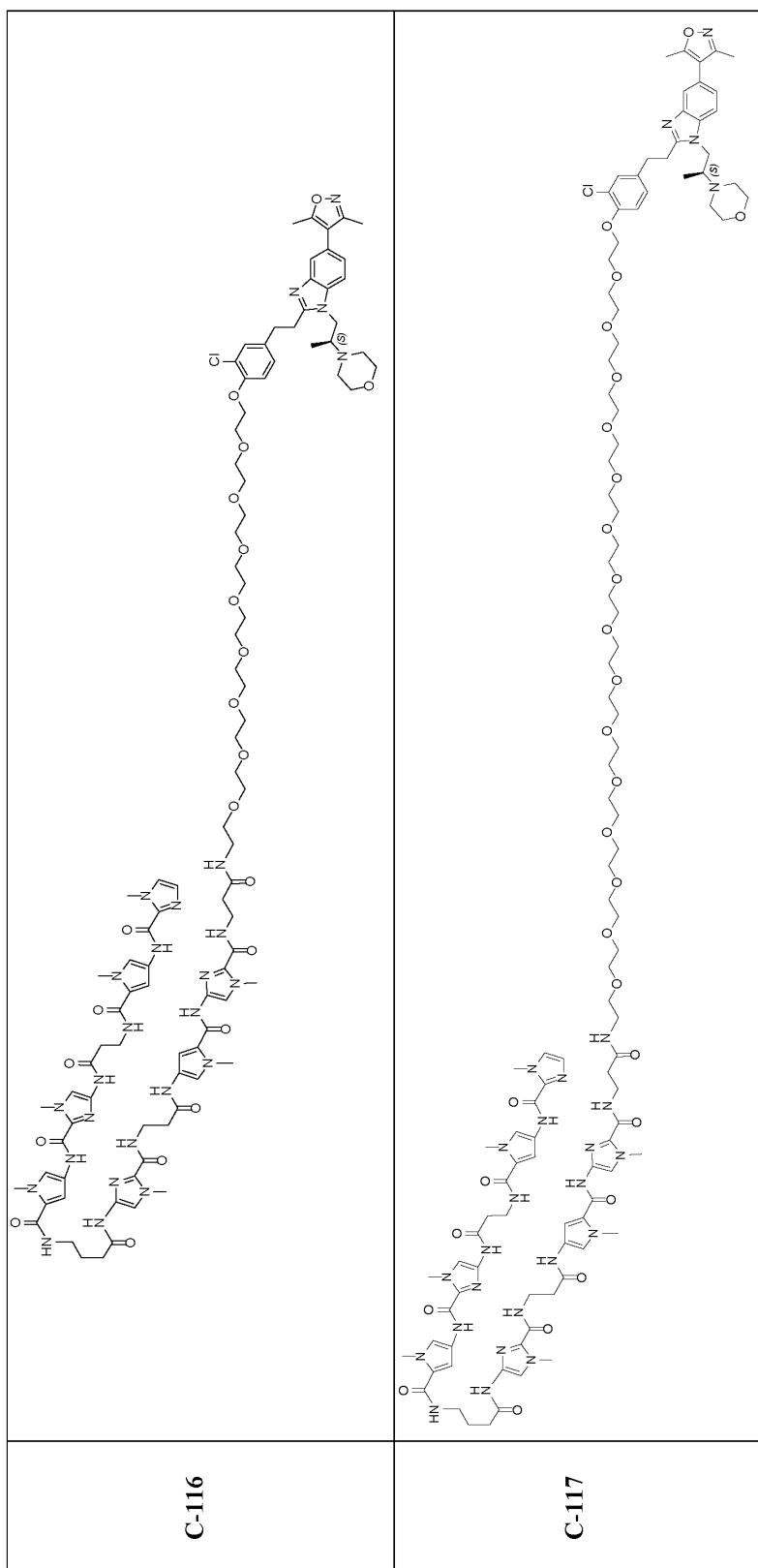
 Chemical structure of compound C-98. It features a central polyether chain with multiple ether linkages. At one end, there is a 4-fluorophenyl group connected to a pyridine ring, which is further substituted with a sulfonamide group. At the other end, the chain is linked to a complex polycyclic aromatic system, including a pyridine ring and a thiazole ring, with various substituents.	 Chemical structure of compound C-100. It features a central polyether chain with multiple ether linkages. At one end, there is a 4-chlorophenyl group connected to a pyridine ring, which is further substituted with a sulfonamide group. At the other end, the chain is linked to a complex polycyclic aromatic system, including a pyridine ring and a thiazole ring, with various substituents.	 Chemical structure of compound C-101. It features a central polyether chain with multiple ether linkages. At one end, there is a 4-chlorophenyl group connected to a pyridine ring, which is further substituted with a sulfonamide group. At the other end, the chain is linked to a complex polycyclic aromatic system, including a pyridine ring and a thiazole ring, with various substituents.
C-98	C-100	C-101

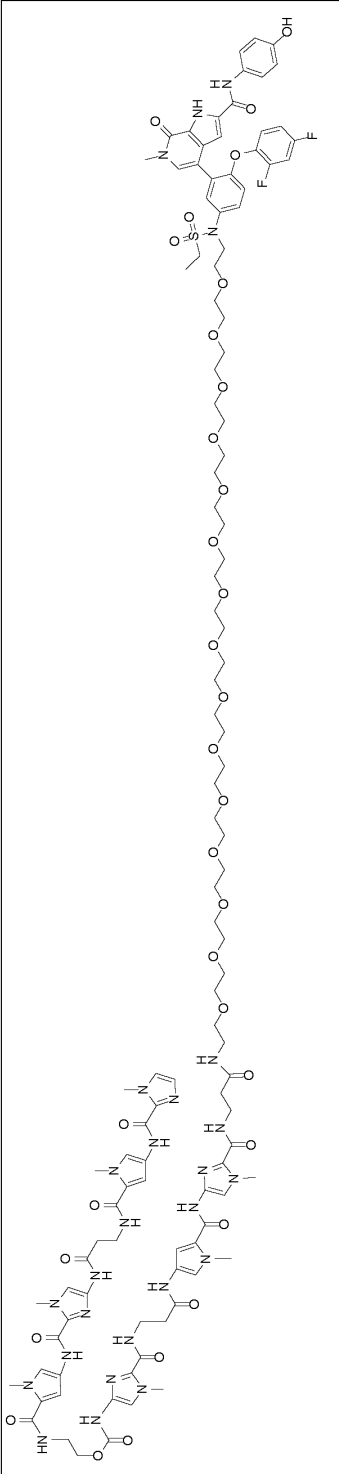
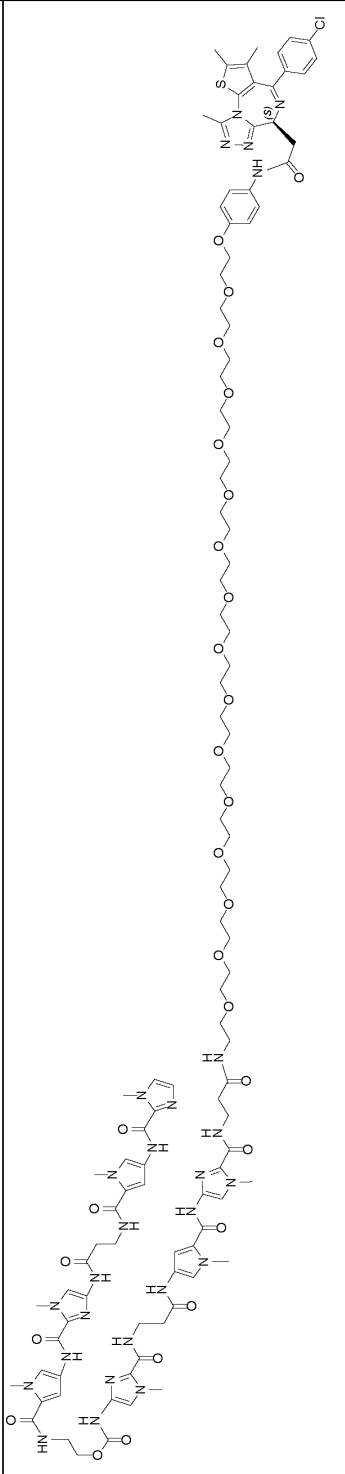
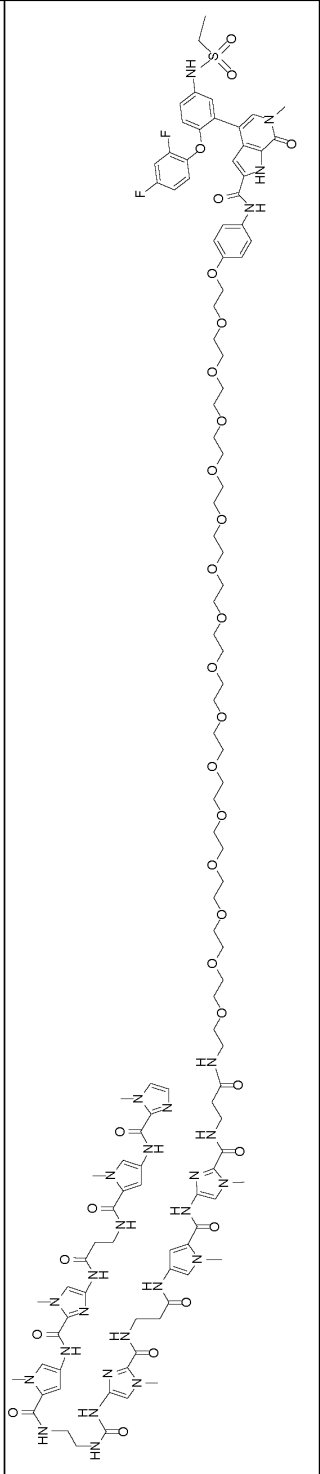
			
C-102	C-103	C-104	C-105

 Chemical structure of C-106: A complex molecule featuring a central pyrazole ring substituted with a 4-chlorophenyl group, a methyl group, and a 1-methyl-1H-pyrazol-5-yl group. This central moiety is linked via an amide bond to a long, flexible polyether chain (1,3-bis(4-phenoxy)propan-2-yl). The other end of the polyether chain is connected to another amide linkage, which is further substituted with a 1-methyl-1H-pyrazol-5-yl group and a 4-methyl-1H-pyrazol-3-yl group.	 Chemical structure of C-107: Similar to C-106, but the central pyrazole ring is substituted with a 4-chlorophenyl group, a methyl group, and a 1-methyl-1H-pyrazol-5-yl group. The polyether chain is linked to a different amide moiety, which includes a 1-methyl-1H-pyrazol-5-yl group and a 4-methyl-1H-pyrazol-3-yl group.	 Chemical structure of C-108: The central pyrazole ring is substituted with a 4-chlorophenyl group, a methyl group, and a 1-methyl-1H-pyrazol-5-yl group. The polyether chain is linked to an amide moiety that includes a 1-methyl-1H-pyrazol-5-yl group and a 4-methyl-1H-pyrazol-3-yl group.	 Chemical structure of C-109: The central pyrazole ring is substituted with a 4-chlorophenyl group, a methyl group, and a 1-methyl-1H-pyrazol-5-yl group. The polyether chain is linked to an amide moiety that includes a 1-methyl-1H-pyrazol-5-yl group and a 4-methyl-1H-pyrazol-3-yl group.
C-106	C-107	C-108	C-109

 Chemical structure of compound C-110. It features a long polyether chain (1,3-bis(2-oxaethyl)propan-1-ol) with a 4-(2,6-difluorophenoxy)phenyl group at one end and a complex polycyclic aromatic system at the other. The polycyclic system includes a pyrazole ring, a pyridine ring, and a benzimidazole-like structure with a sulfonamide group.	 Chemical structure of compound C-111. It features a long polyether chain (1,3-bis(2-oxaethyl)propan-1-ol) with a 4-(2,6-difluorophenoxy)phenyl group at one end and a complex polycyclic aromatic system at the other. The polycyclic system includes a pyrazole ring, a pyridine ring, and a benzimidazole-like structure with a sulfonamide group.	 Chemical structure of compound C-112. It features a long polyether chain (1,3-bis(2-oxaethyl)propan-1-ol) with a 4-(2,6-difluorophenoxy)phenyl group at one end and a complex polycyclic aromatic system at the other. The polycyclic system includes a pyrazole ring, a pyridine ring, and a benzimidazole-like structure with a sulfonamide group.
C-110	C-111	C-112

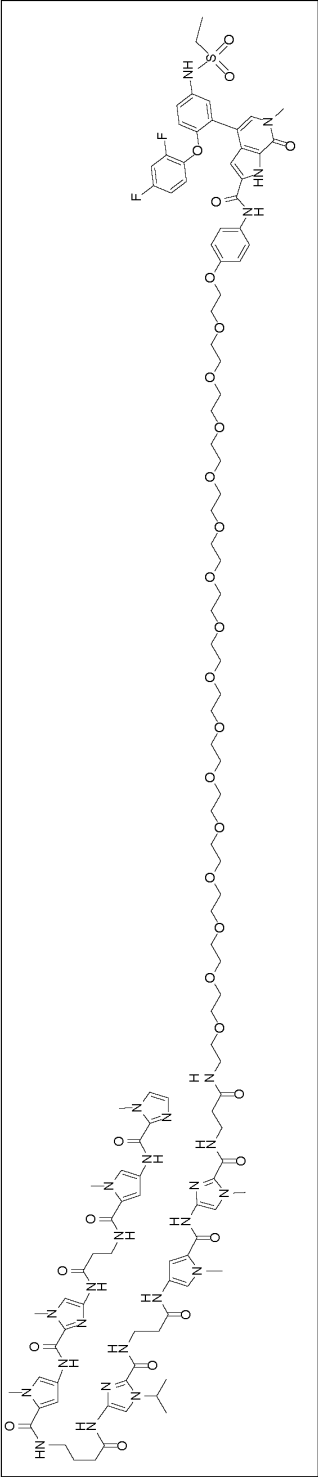
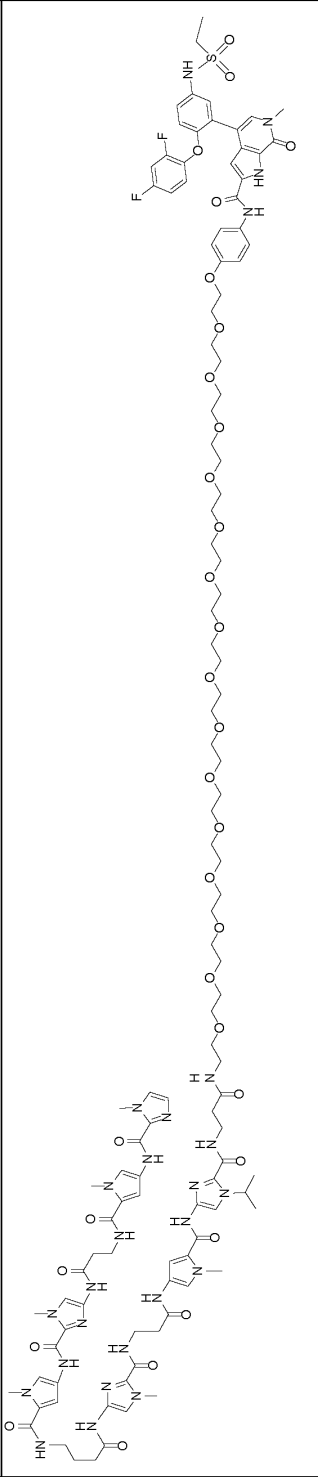
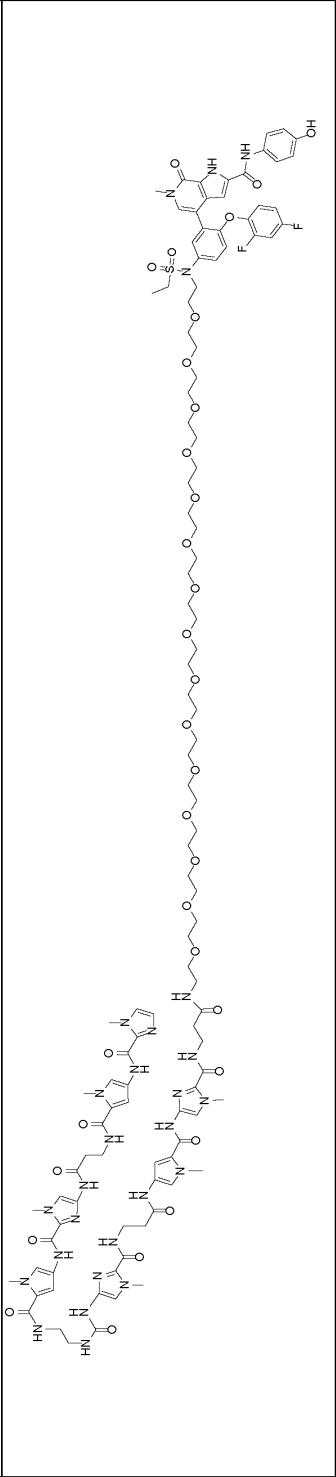
 Chemical structure of compound C-113, featuring a long polyether chain (1,4-bis(2-ethoxyethoxy)benzene derivative) connecting a 4-fluorophenyl group to a complex heterocyclic system. The heterocyclic system includes a pyridine ring, a pyrazole ring, and a sulfonamide group.	 Chemical structure of compound C-114, featuring a long polyether chain (1,4-bis(2-ethoxyethoxy)benzene derivative) connecting a 4-fluorophenyl group to a complex heterocyclic system. The heterocyclic system includes a pyridine ring, a pyrazole ring, and a sulfonamide group.	 Chemical structure of compound C-115, featuring a long polyether chain (1,4-bis(2-ethoxyethoxy)benzene derivative) connecting a 4-chlorophenyl group to a complex heterocyclic system. The heterocyclic system includes a pyridine ring, a pyrazole ring, and a sulfonamide group.
C-113	C-114	C-115

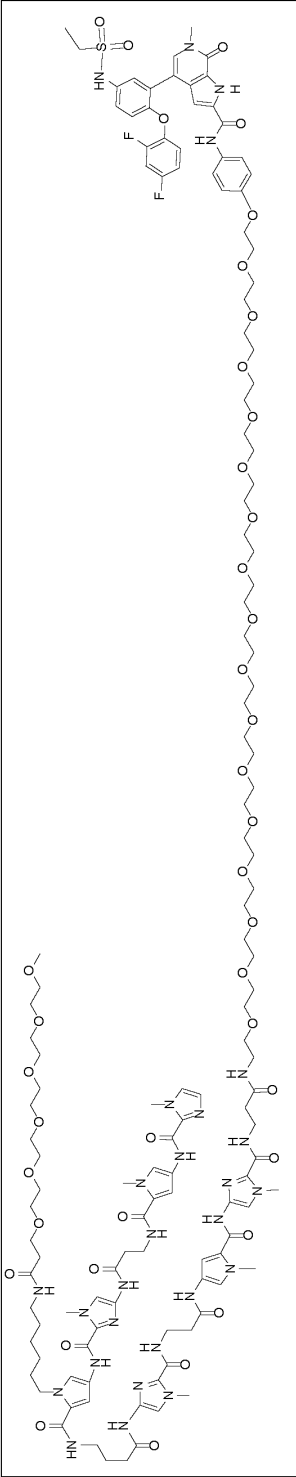
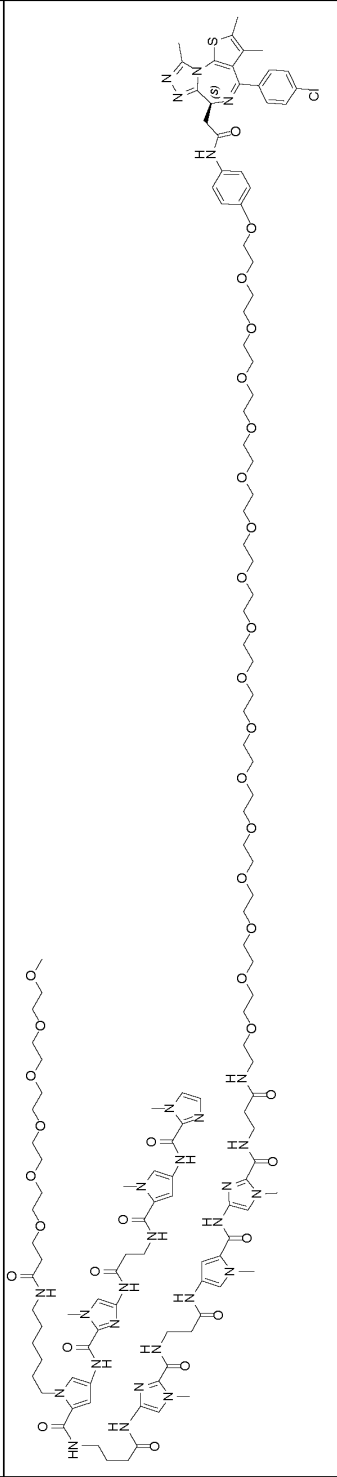
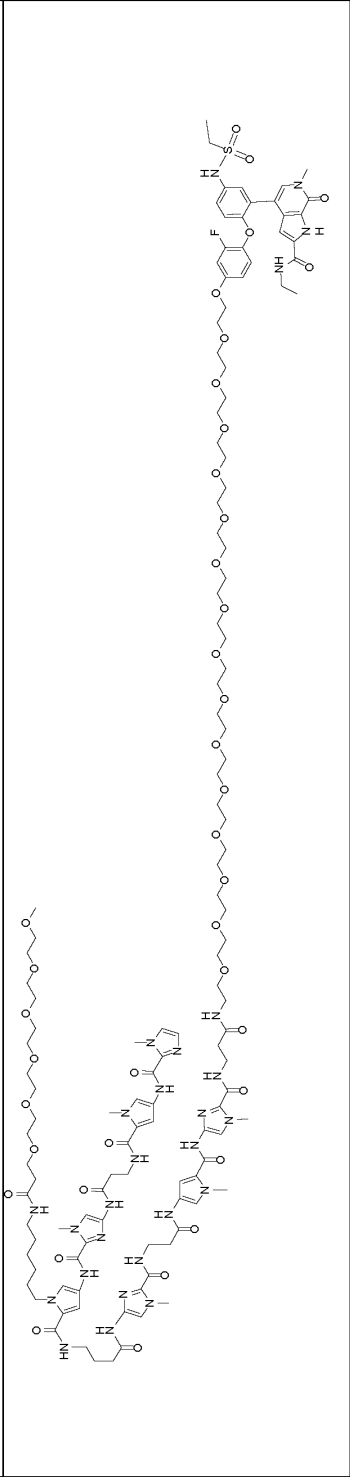


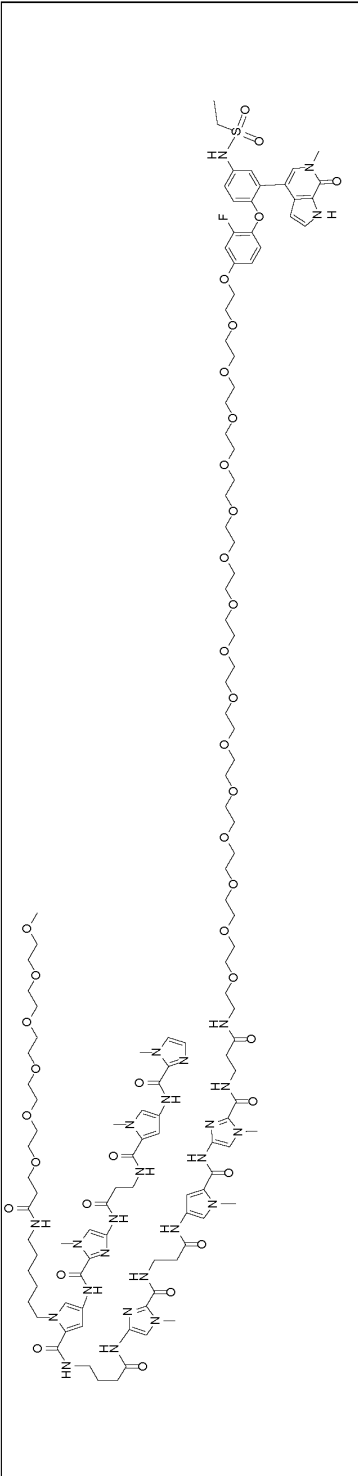
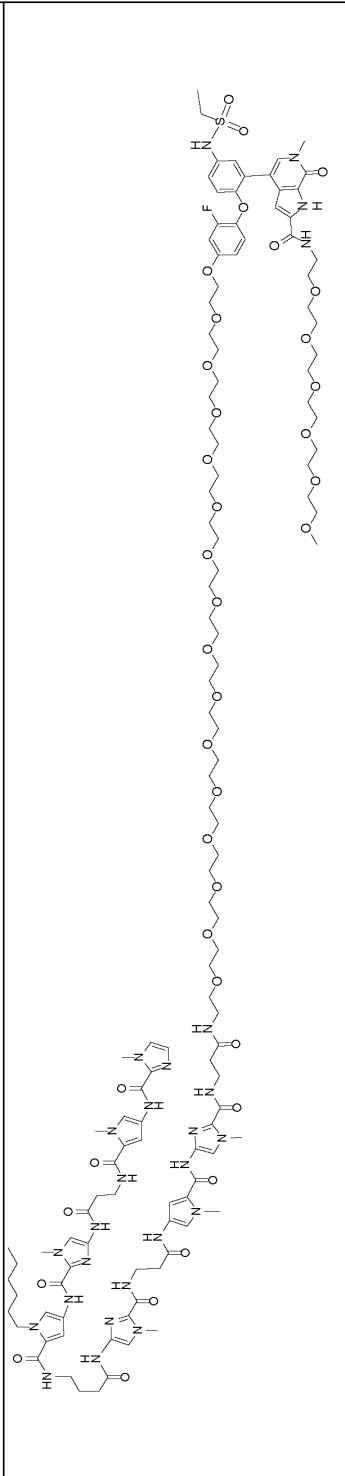
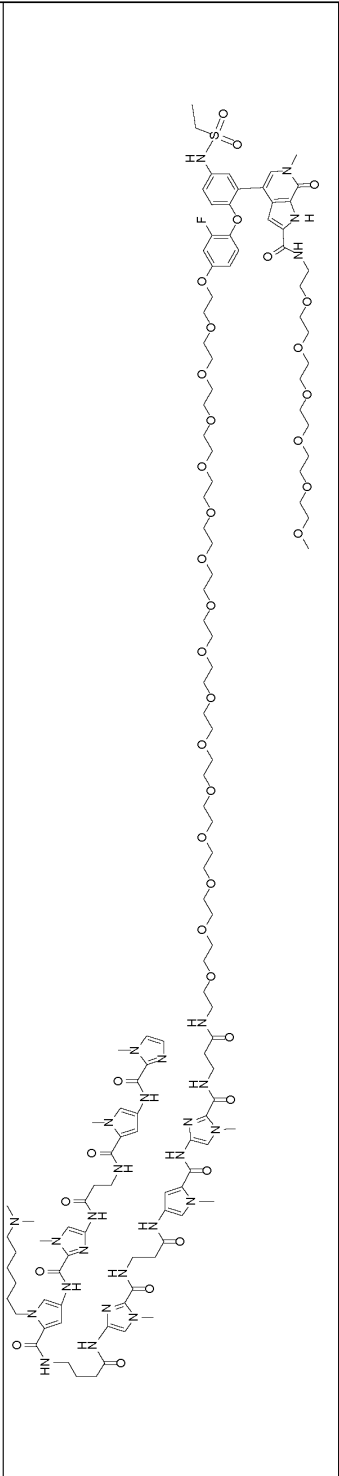
 Chemical structure of C-118: A complex molecule featuring a central pyridine ring substituted with a 4-fluorophenyl group, a 4-hydroxyphenyl group, and a 4-methylphenyl group. The pyridine ring is also substituted with a 4-methylphenyl group and a 4-fluorophenyl group. The molecule includes a long polyether chain (1,3-bis(2-methoxyethoxy)propane) and a 4-methylphenyl group.	 Chemical structure of C-119: A complex molecule featuring a central pyridine ring substituted with a 4-fluorophenyl group, a 4-hydroxyphenyl group, and a 4-methylphenyl group. The pyridine ring is also substituted with a 4-methylphenyl group and a 4-fluorophenyl group. The molecule includes a long polyether chain (1,3-bis(2-methoxyethoxy)propane) and a 4-methylphenyl group.	 Chemical structure of C-120: A complex molecule featuring a central pyridine ring substituted with a 4-fluorophenyl group, a 4-hydroxyphenyl group, and a 4-methylphenyl group. The pyridine ring is also substituted with a 4-methylphenyl group and a 4-fluorophenyl group. The molecule includes a long polyether chain (1,3-bis(2-methoxyethoxy)propane) and a 4-methylphenyl group.
C-118	C-119	C-120

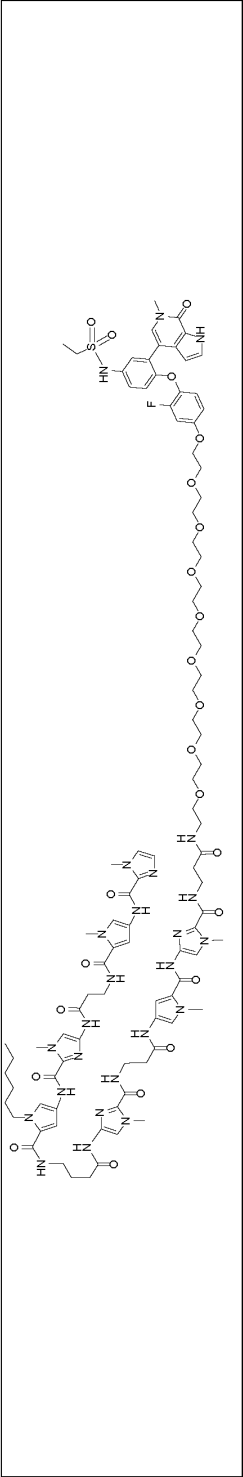
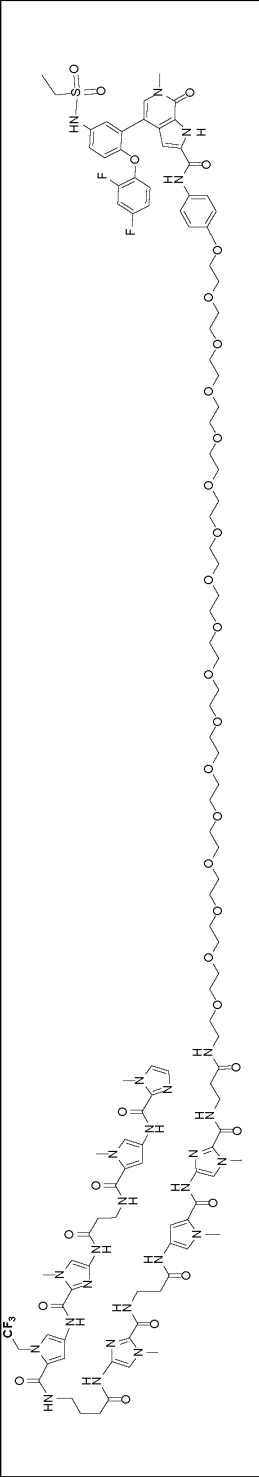
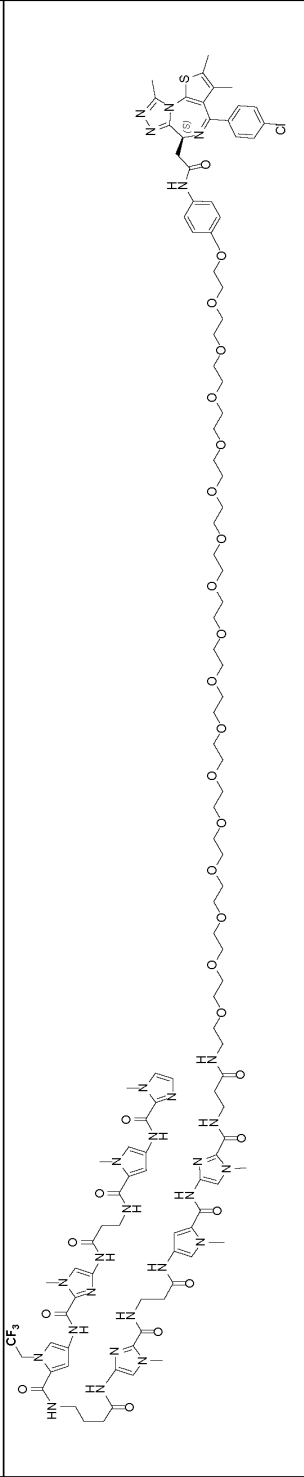
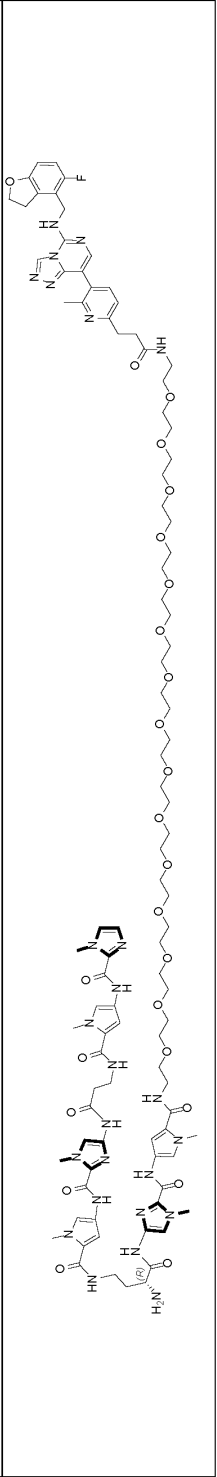
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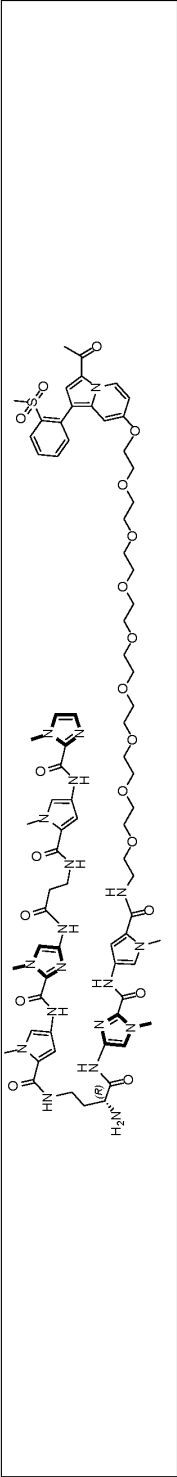
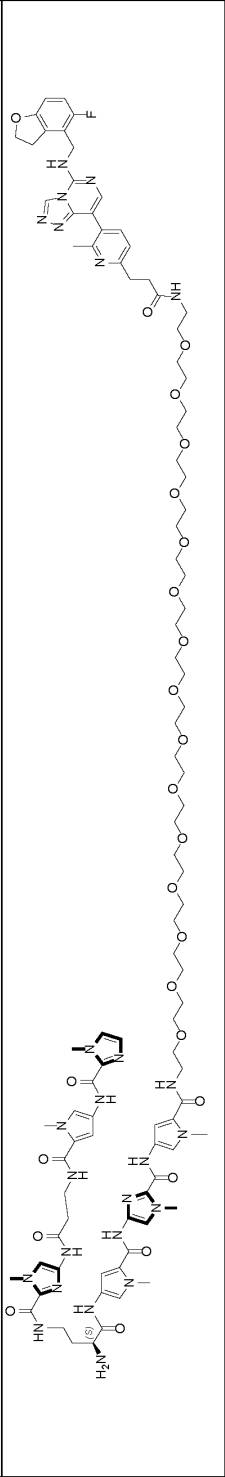
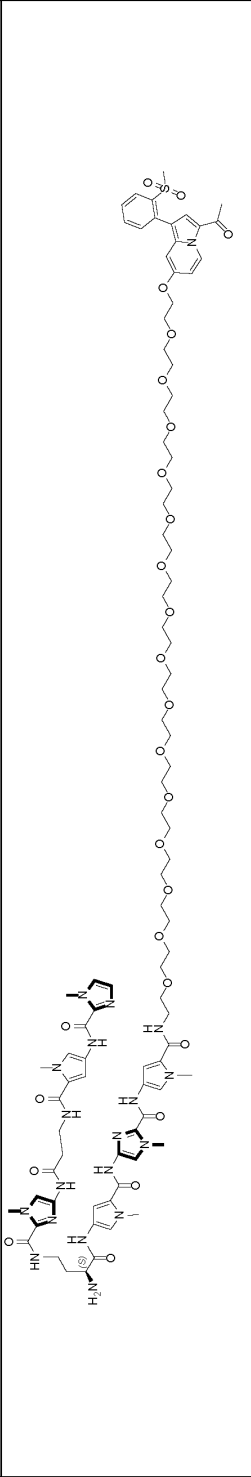
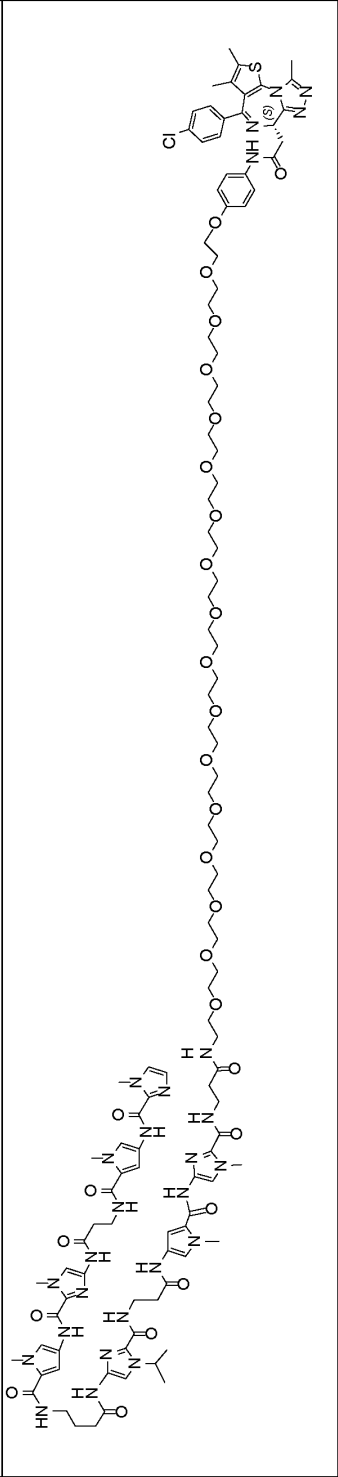
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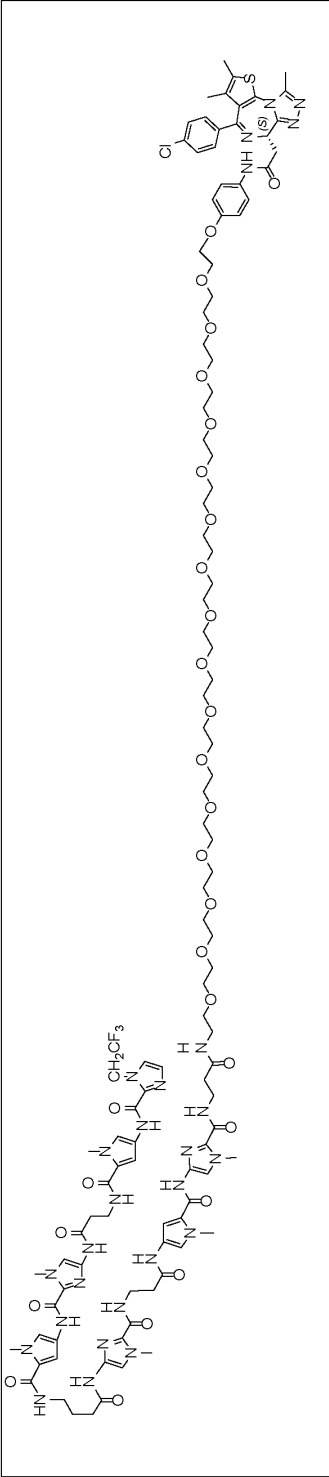
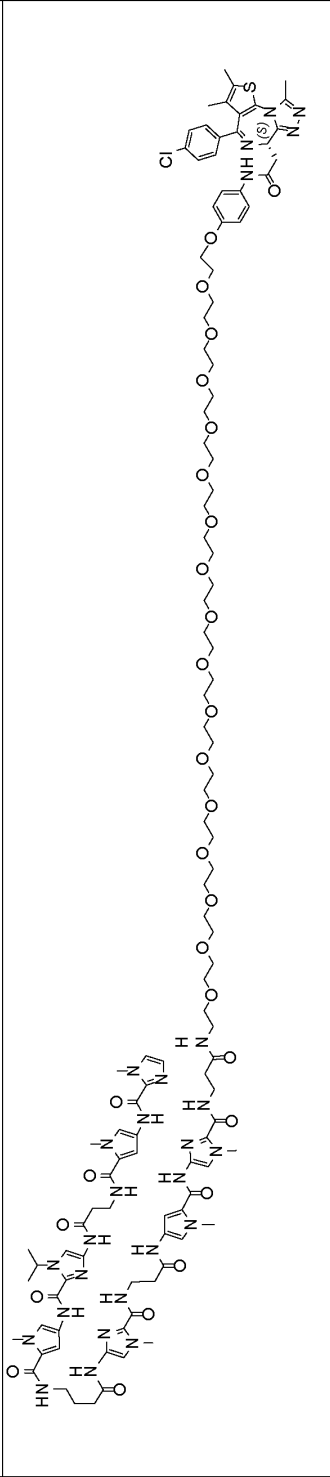
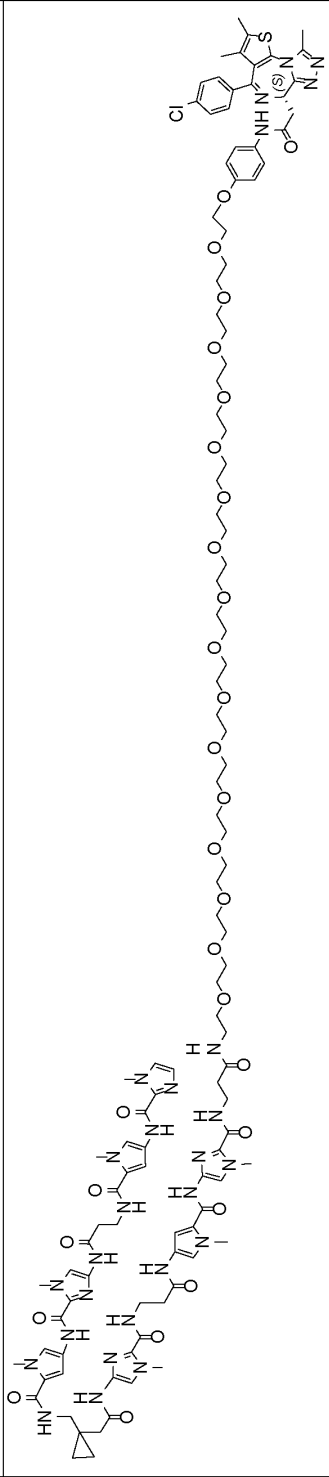
 Chemical structure of C-127: A complex molecule featuring a central pyrazole ring substituted with a 4-(4-fluorophenoxy)phenyl group, a 4-(4-fluorophenoxy)phenyl group, and a 4-(4-fluorophenoxy)phenyl group. The pyrazole ring is also substituted with a 4-(4-fluorophenoxy)phenyl group. The molecule is linked via a long, flexible polyether chain to a complex polycyclic aromatic system, which includes a pyrazole ring, a pyridine ring, and a pyrimidine ring, all substituted with various functional groups including amide, ester, and hydroxyl groups.	 Chemical structure of C-128: A complex molecule featuring a central pyrazole ring substituted with a 4-(4-fluorophenoxy)phenyl group, a 4-(4-fluorophenoxy)phenyl group, and a 4-(4-fluorophenoxy)phenyl group. The pyrazole ring is also substituted with a 4-(4-fluorophenoxy)phenyl group. The molecule is linked via a long, flexible polyether chain to a complex polycyclic aromatic system, which includes a pyrazole ring, a pyridine ring, and a pyrimidine ring, all substituted with various functional groups including amide, ester, and hydroxyl groups.	 Chemical structure of C-129: A complex molecule featuring a central pyrazole ring substituted with a 4-(4-fluorophenoxy)phenyl group, a 4-(4-fluorophenoxy)phenyl group, and a 4-(4-fluorophenoxy)phenyl group. The pyrazole ring is also substituted with a 4-(4-fluorophenoxy)phenyl group. The molecule is linked via a long, flexible polyether chain to a complex polycyclic aromatic system, which includes a pyrazole ring, a pyridine ring, and a pyrimidine ring, all substituted with various functional groups including amide, ester, and hydroxyl groups.
C-127	C-128	C-129

 Chemical structure of compound C-130. It features a central polyether chain (HO(CH₂)₄O)₁₀(CH₂)₄OH. The left end is capped with a 4-(2,6-difluorophenoxy)phenyl group, which is further substituted with a 2-ethylsulfonyl-1H-imidazo[4,5-b]pyridin-5-yl group. The right end is capped with a 4-(2,6-difluorophenoxy)phenyl group, which is further substituted with a 2-ethylsulfonyl-1H-imidazo[4,5-b]pyridin-5-yl group.	 Chemical structure of compound C-131. It features a central polyether chain (HO(CH₂)₄O)₁₀(CH₂)₄OH. The left end is capped with a 4-(2,6-difluorophenoxy)phenyl group, which is further substituted with a 2-ethylsulfonyl-1H-imidazo[4,5-b]pyridin-5-yl group. The right end is capped with a 4-(2,6-difluorophenoxy)phenyl group, which is further substituted with a 2-ethylsulfonyl-1H-imidazo[4,5-b]pyridin-5-yl group.	 Chemical structure of compound C-132. It features a central polyether chain (HO(CH₂)₄O)₁₀(CH₂)₄OH. The left end is capped with a 4-(2,6-difluorophenoxy)phenyl group, which is further substituted with a 2-ethylsulfonyl-1H-imidazo[4,5-b]pyridin-5-yl group. The right end is capped with a 4-(2,6-difluorophenoxy)phenyl group, which is further substituted with a 2-ethylsulfonyl-1H-imidazo[4,5-b]pyridin-5-yl group.
C-130	C-131	C-132

		
C-133	C-134	C-135

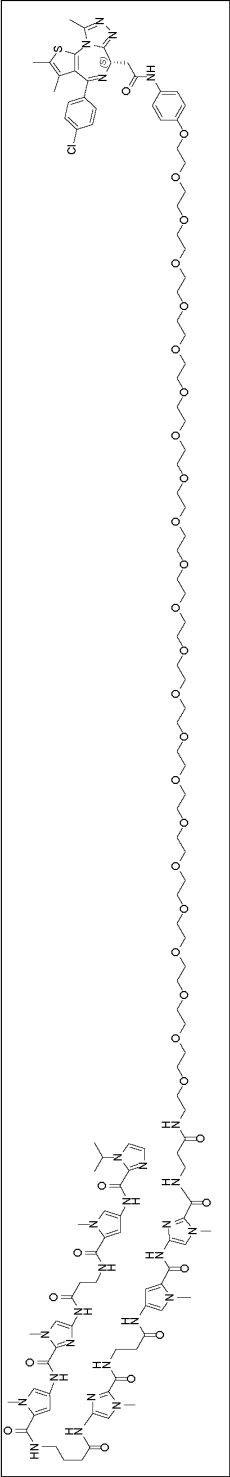
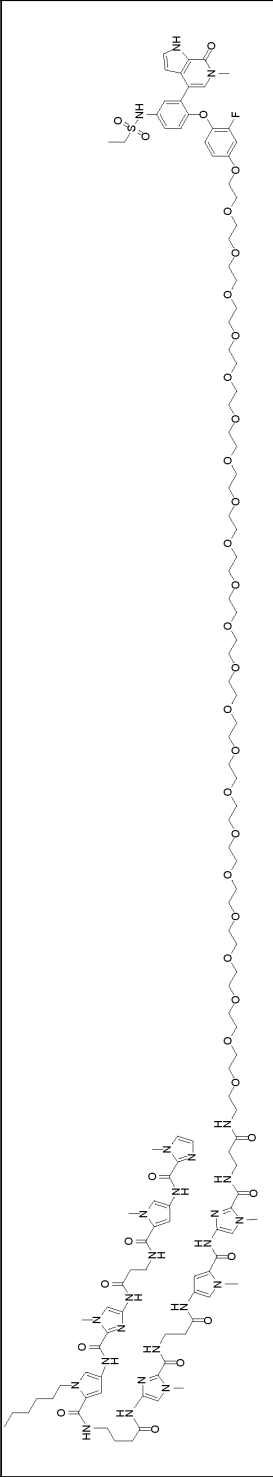
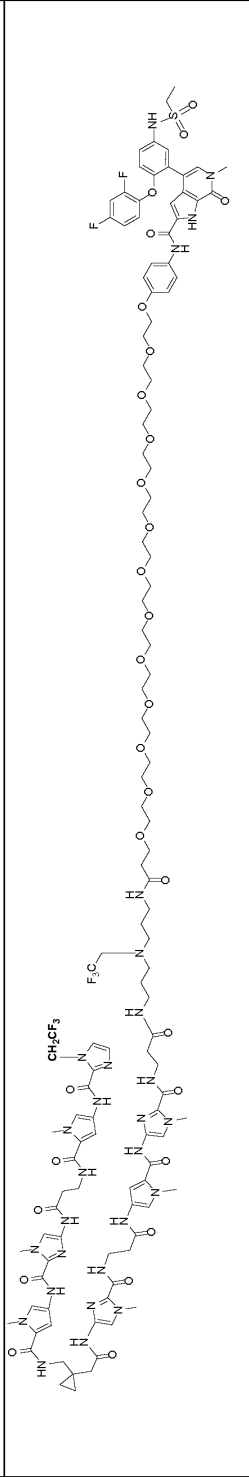
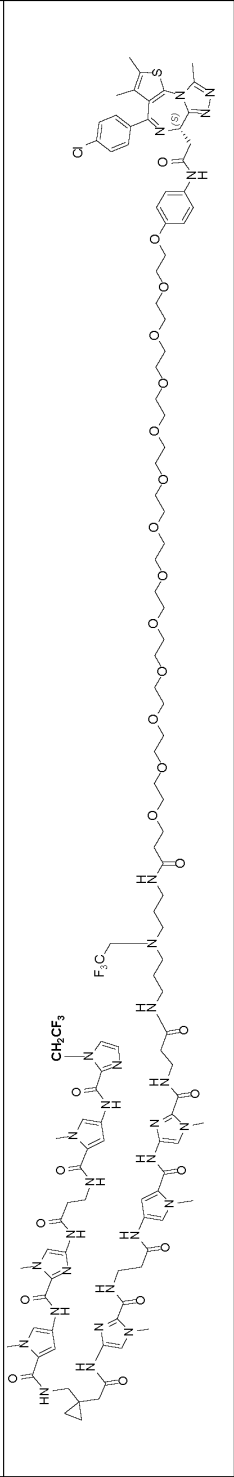
			
C-136	C-137	C-138	C-139

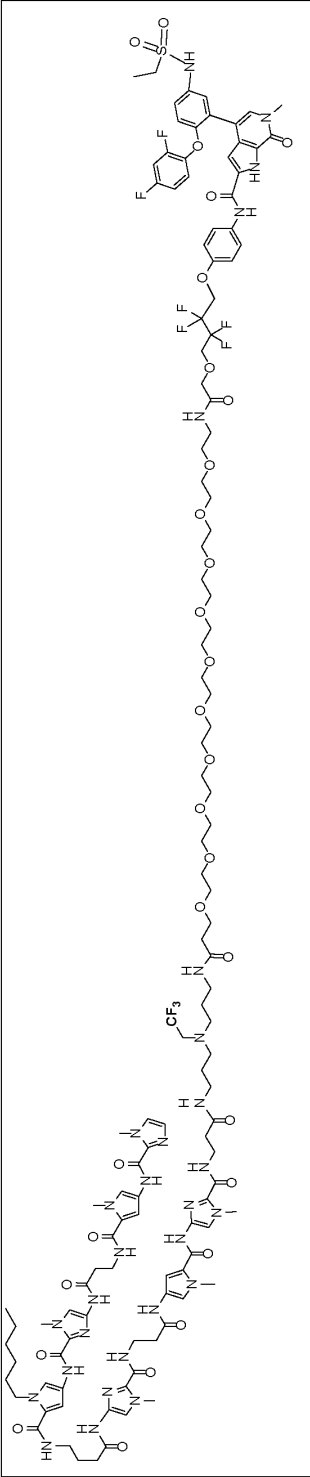
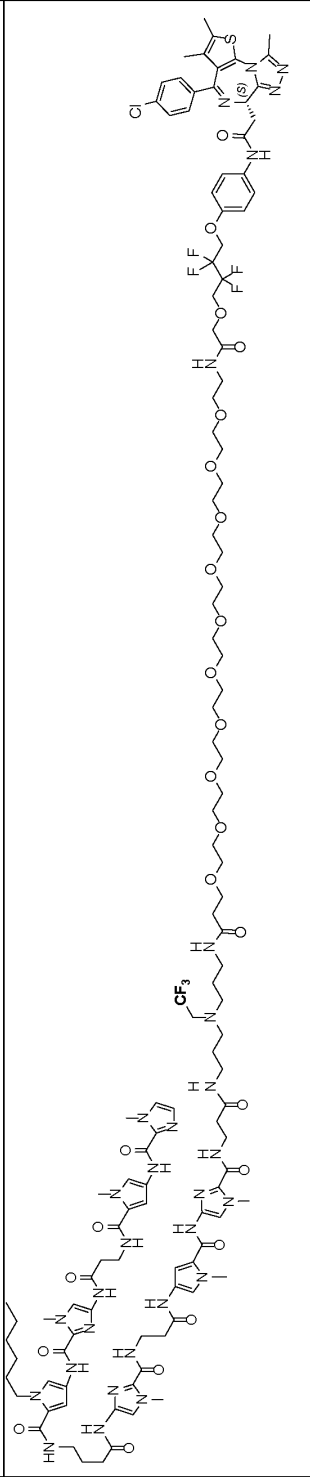
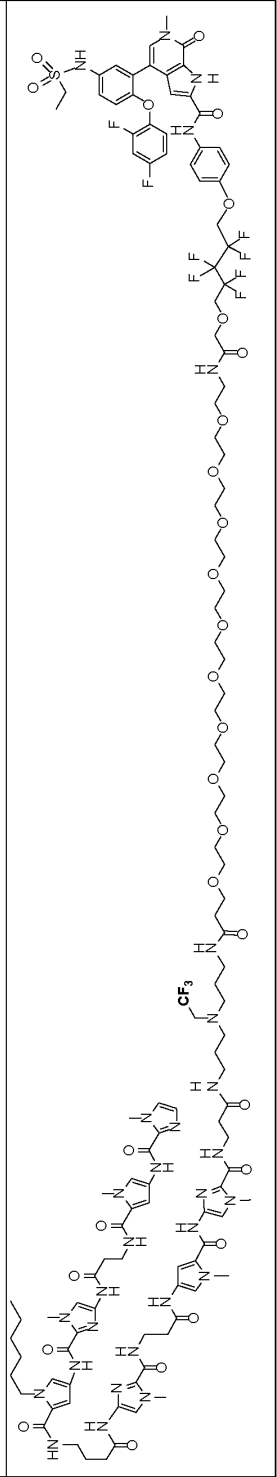
			
C-140	C-141	C-142	C-143

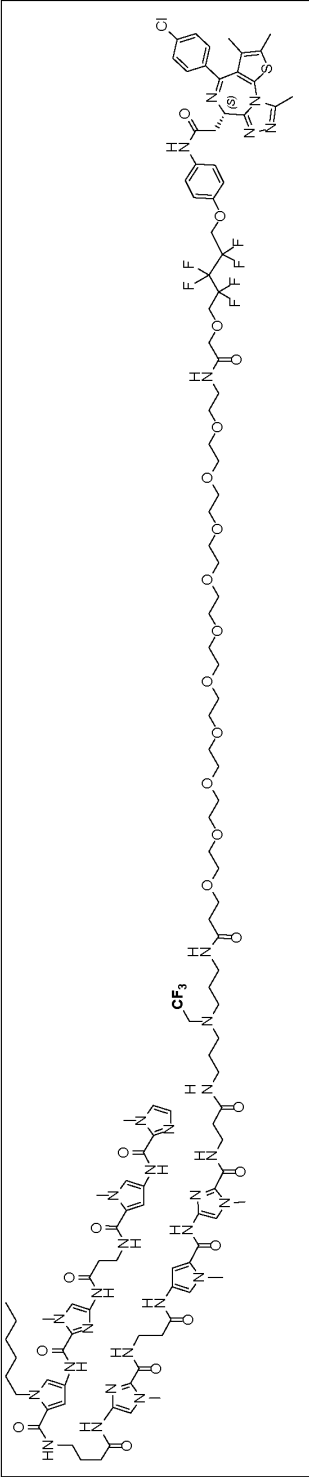
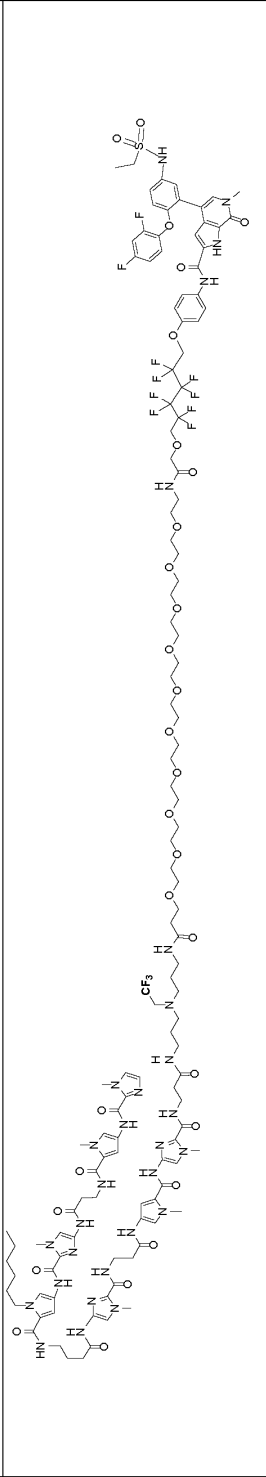
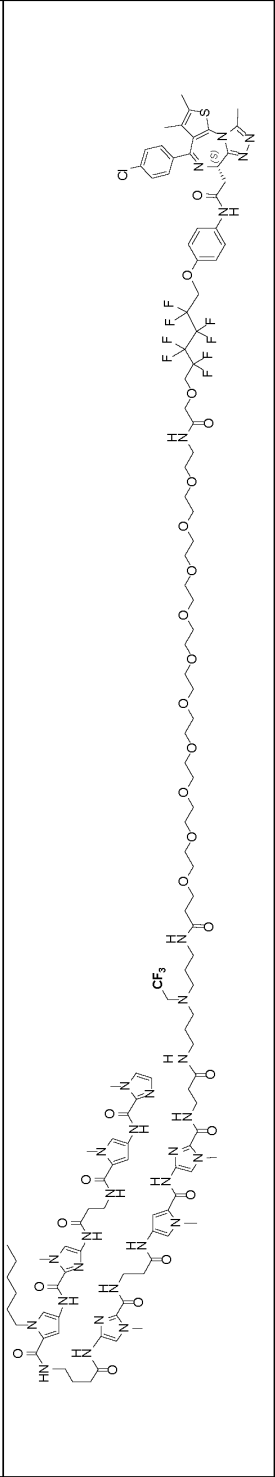
 Chemical structure of compound C-144. It features a long, flexible polyether chain (poly(ethylene glycol) derivative) connecting two complex organic moieties. The left moiety is a macrocyclic-like structure with multiple amide and ester linkages, including a trifluoromethyl group (CH₂CF₃). The right moiety is a substituted benzothiazine derivative with a chlorine atom and a methyl group.	 Chemical structure of compound C-145. It is similar to C-144, featuring a long polyether chain connecting two complex organic moieties. The left moiety is a macrocyclic-like structure with multiple amide and ester linkages. The right moiety is a substituted benzothiazine derivative with a chlorine atom and a methyl group, similar to C-144 but with slight structural variations in the linker and the right-hand moiety.	 Chemical structure of compound C-146. It features a long, flexible polyether chain connecting two complex organic moieties. The left moiety is a macrocyclic-like structure with multiple amide and ester linkages, including a cyclopropyl group. The right moiety is a substituted benzothiazine derivative with a chlorine atom and a methyl group.
C-144	C-145	C-146

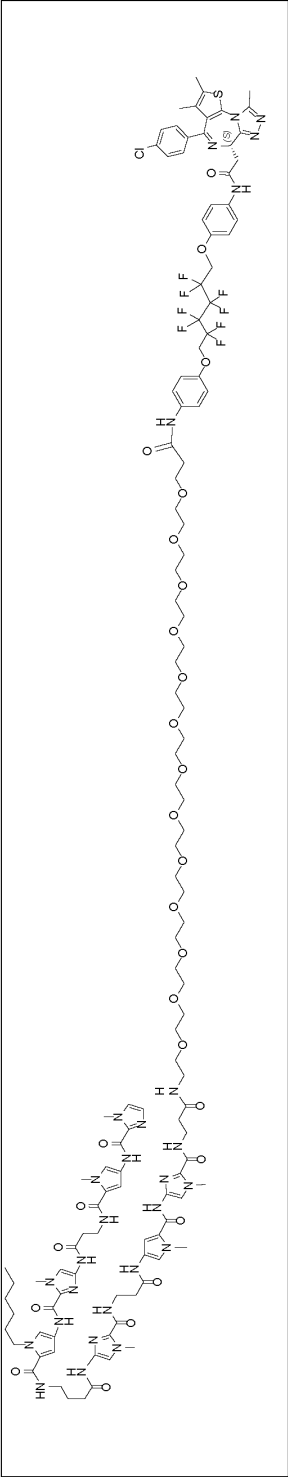
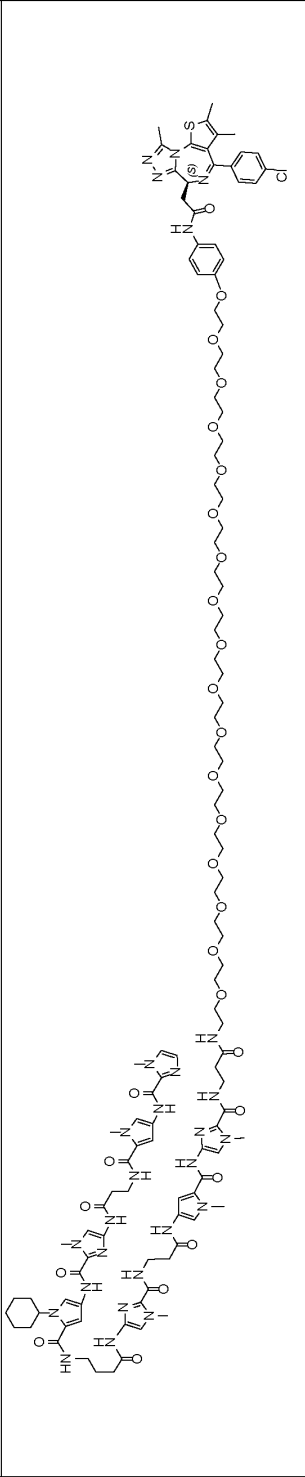
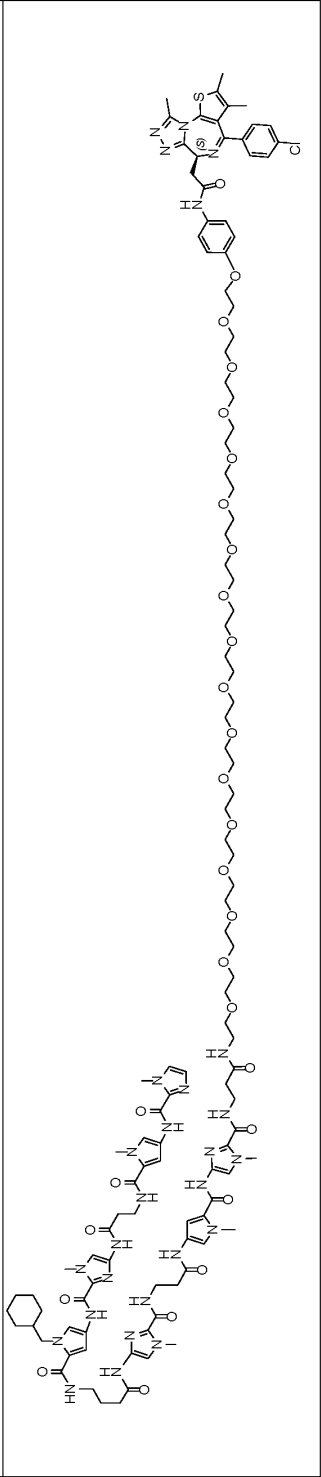


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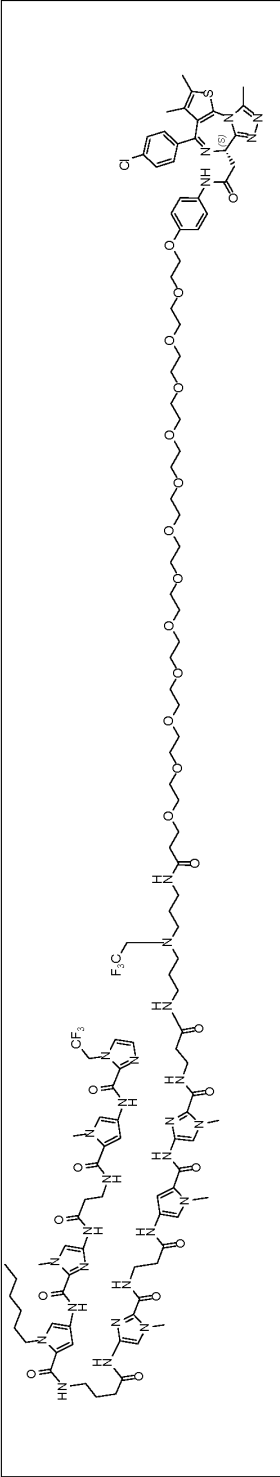
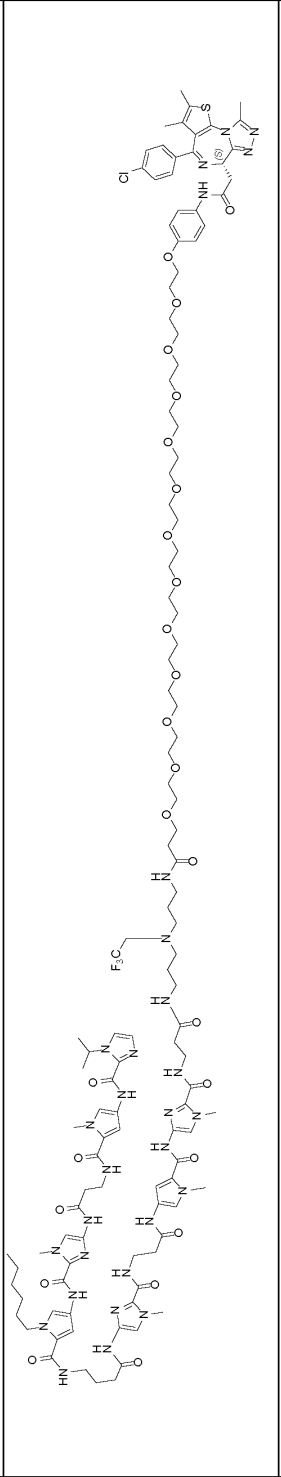
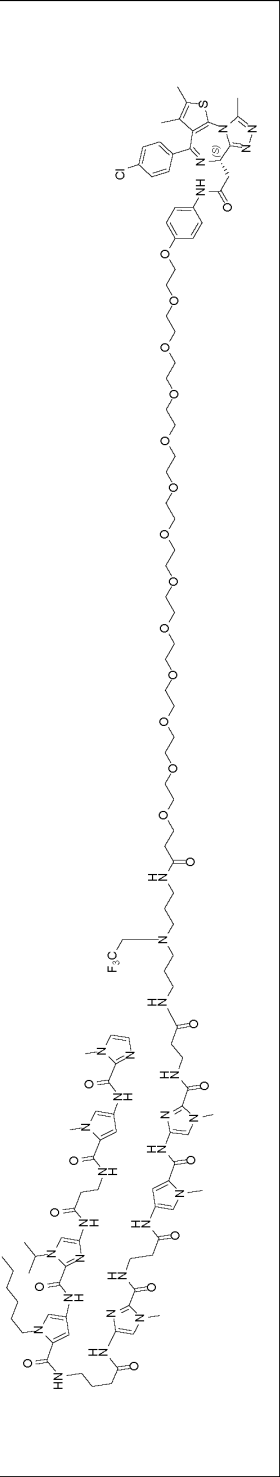
			
C-155	C-156	C-157	C-158

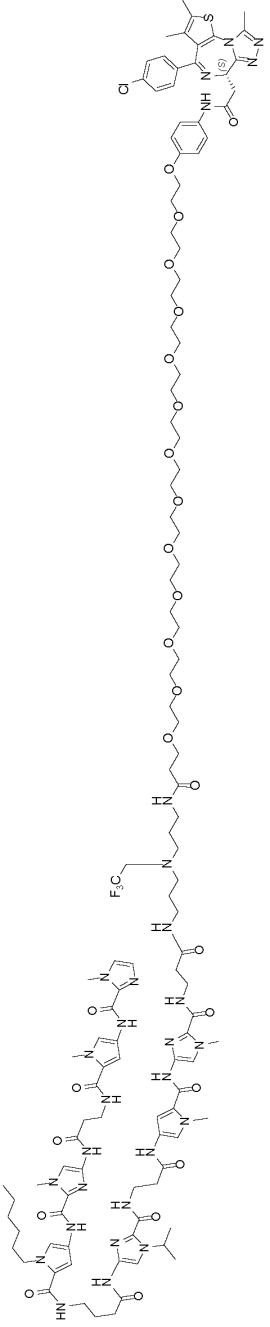
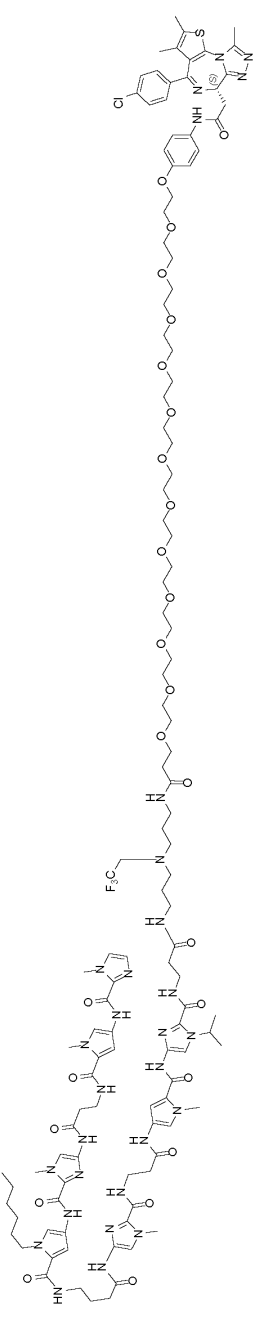
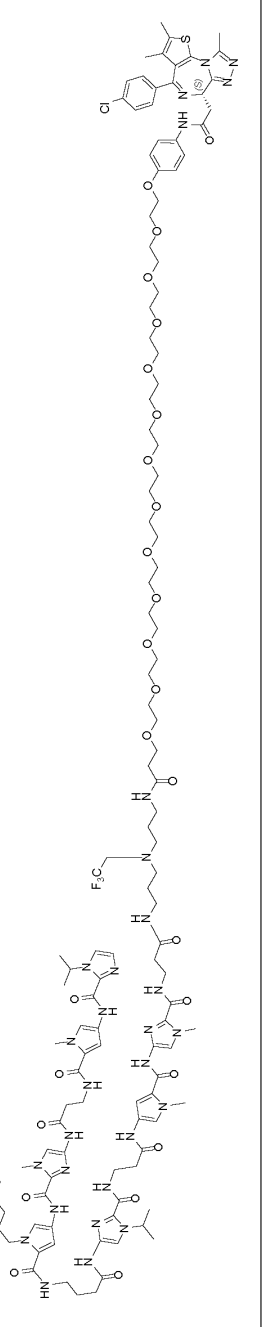
 Chemical structure of C-159: A complex molecule featuring a central pyrazole ring substituted with a 4-fluorophenyl group, a 4-(2,2,2-trifluoroethoxy)phenyl group, and a 4-(2,2,2-trifluoroethyl)phenyl group. The molecule also includes a 4-(2,2,2-trifluoroethyl)phenyl group and a 4-(2,2,2-trifluoroethyl)phenyl group.	 Chemical structure of C-160: A complex molecule featuring a central pyrazole ring substituted with a 4-fluorophenyl group, a 4-(2,2,2-trifluoroethoxy)phenyl group, and a 4-(2,2,2-trifluoroethyl)phenyl group. The molecule also includes a 4-(2,2,2-trifluoroethyl)phenyl group and a 4-(2,2,2-trifluoroethyl)phenyl group.	 Chemical structure of C-161: A complex molecule featuring a central pyrazole ring substituted with a 4-fluorophenyl group, a 4-(2,2,2-trifluoroethoxy)phenyl group, and a 4-(2,2,2-trifluoroethyl)phenyl group. The molecule also includes a 4-(2,2,2-trifluoroethyl)phenyl group and a 4-(2,2,2-trifluoroethyl)phenyl group.
C-159	C-160	C-161

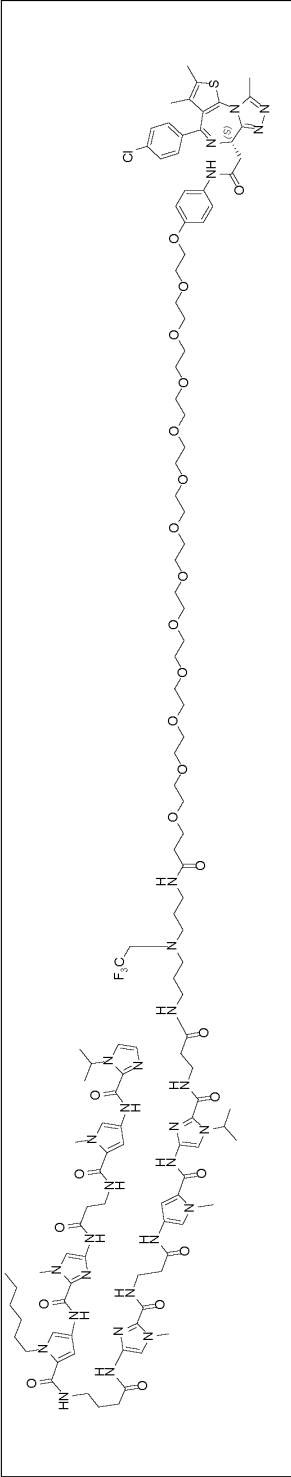
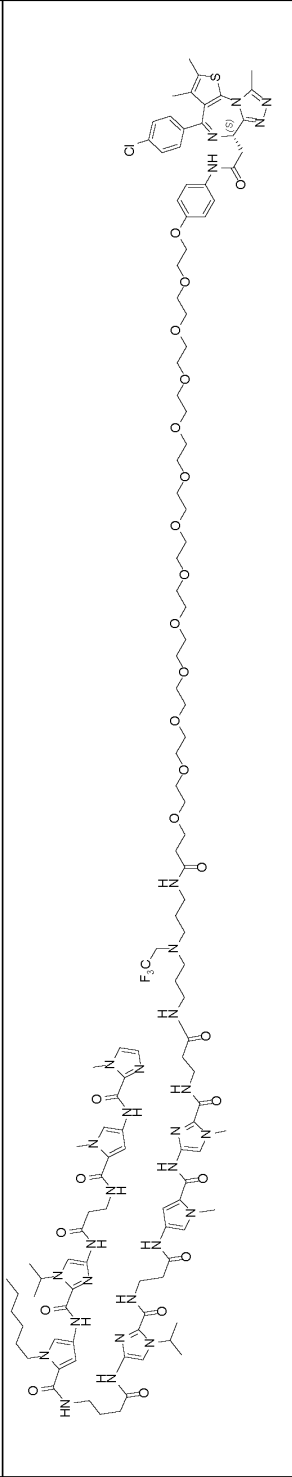
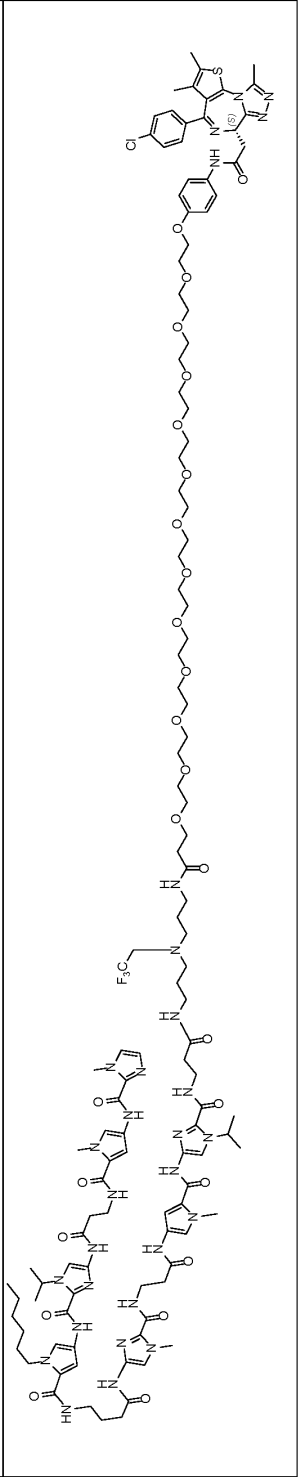
 Chemical structure of compound C-162. It features a central polyether chain with multiple ether linkages. The chain is substituted with a trifluoromethyl group (CF₃) and a complex side chain containing a benzothiazine ring system, a chlorophenyl group, and a sulfonamide moiety.	 Chemical structure of compound C-163. It features a central polyether chain with multiple ether linkages. The chain is substituted with a trifluoromethyl group (CF₃) and a complex side chain containing a benzothiazine ring system, a chlorophenyl group, and a sulfonamide moiety.	 Chemical structure of compound C-164. It features a central polyether chain with multiple ether linkages. The chain is substituted with a trifluoromethyl group (CF₃) and a complex side chain containing a benzothiazine ring system, a chlorophenyl group, and a sulfonamide moiety.
C-162	C-163	C-164

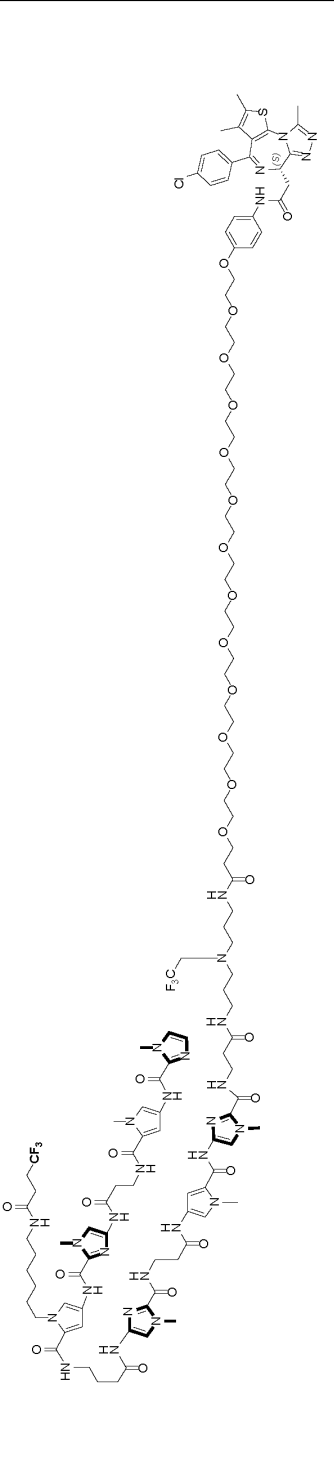
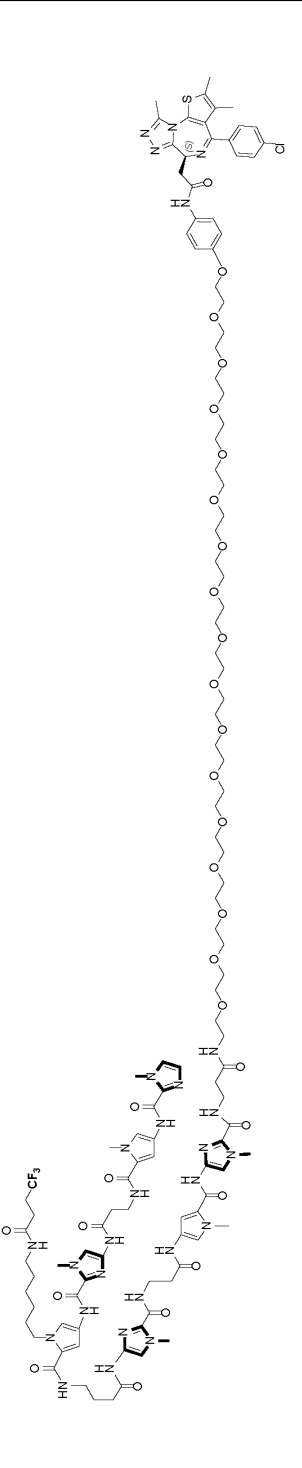
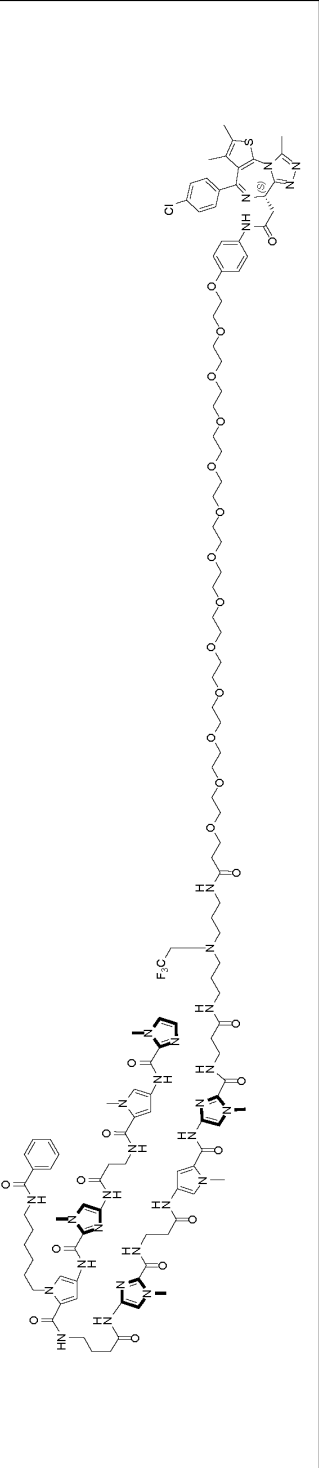
 Chemical structure of C-165: A complex molecule featuring a central pyrazole core substituted with a 4-chlorophenyl group, a 4-(4-chlorophenyl)-1H-pyrazol-5-yl group, and a 4-(4-chlorophenyl)-1H-pyrazol-5-yl group. The molecule is linked via a long, flexible polyether chain to a 4-(4-chlorophenyl)-1H-pyrazol-5-yl group, which is further substituted with a 4-(4-chlorophenyl)-1H-pyrazol-5-yl group.	 Chemical structure of C-166: A complex molecule featuring a central pyrazole core substituted with a 4-chlorophenyl group, a 4-(4-chlorophenyl)-1H-pyrazol-5-yl group, and a 4-(4-chlorophenyl)-1H-pyrazol-5-yl group. The molecule is linked via a long, flexible polyether chain to a 4-(4-chlorophenyl)-1H-pyrazol-5-yl group, which is further substituted with a 4-(4-chlorophenyl)-1H-pyrazol-5-yl group.	 Chemical structure of C-167: A complex molecule featuring a central pyrazole core substituted with a 4-chlorophenyl group, a 4-(4-chlorophenyl)-1H-pyrazol-5-yl group, and a 4-(4-chlorophenyl)-1H-pyrazol-5-yl group. The molecule is linked via a long, flexible polyether chain to a 4-(4-chlorophenyl)-1H-pyrazol-5-yl group, which is further substituted with a 4-(4-chlorophenyl)-1H-pyrazol-5-yl group.
C-165	C-166	C-167

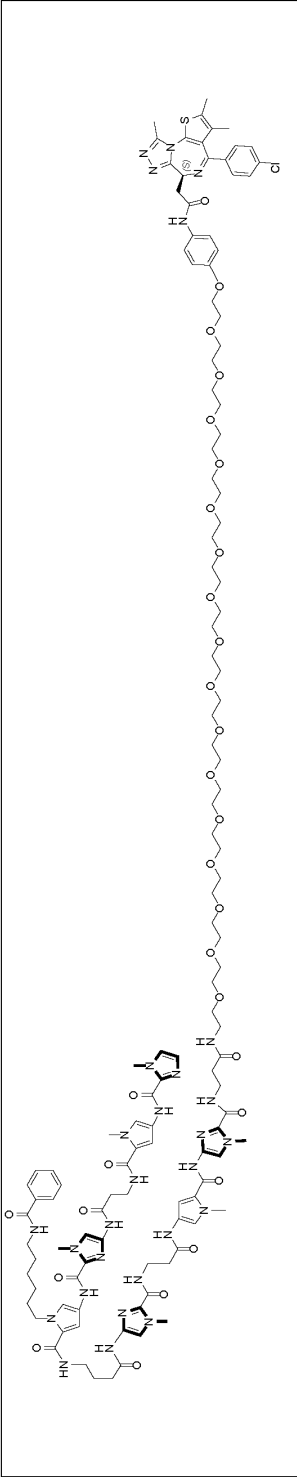
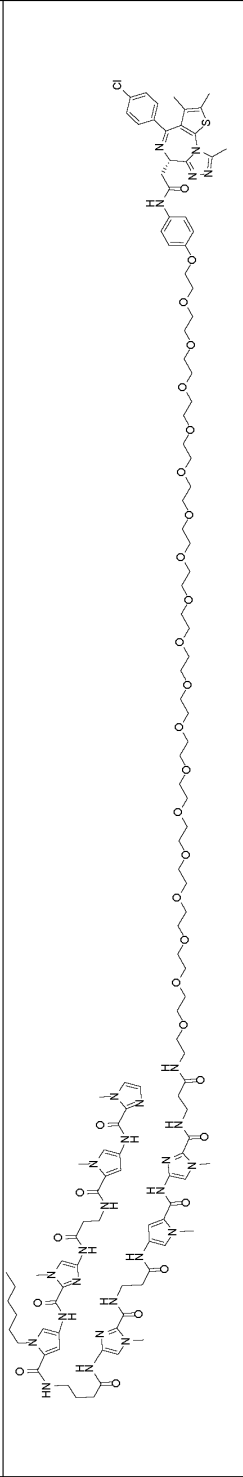
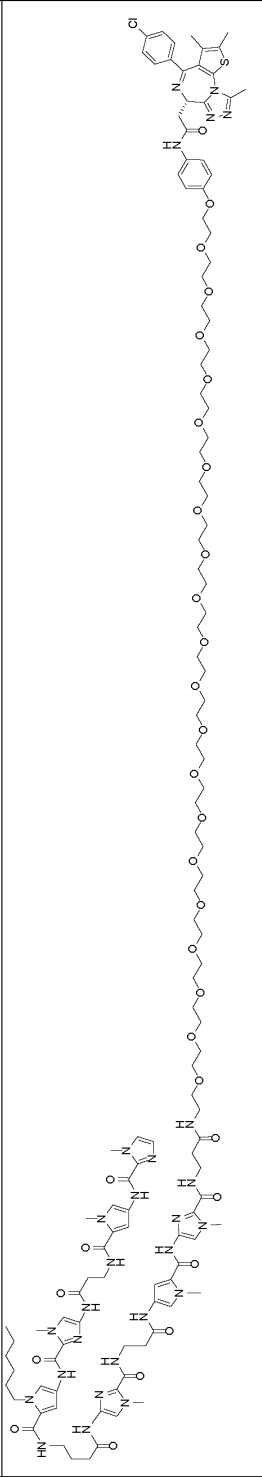
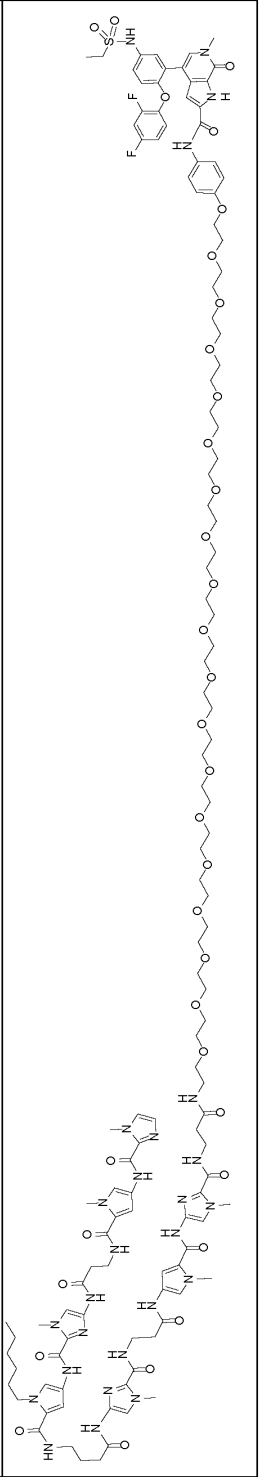
C-168	
C-169	
C-170	

 Chemical structure of C-174: A complex molecule featuring a central core with multiple amide and ester linkages. It includes a long, flexible polyether chain (poly(ethylene glycol) derivative) and a terminal group with a trifluoromethyl (CF₃) substituent. The structure is highly symmetrical and contains several heterocyclic rings, including pyridine and imidazole derivatives.	 Chemical structure of C-175: A complex molecule featuring a central core with multiple amide and ester linkages. It includes a long, flexible polyether chain (poly(ethylene glycol) derivative) and a terminal group with a trifluoromethyl (CF₃) substituent. The structure is highly symmetrical and contains several heterocyclic rings, including pyridine and imidazole derivatives.	 Chemical structure of C-176: A complex molecule featuring a central core with multiple amide and ester linkages. It includes a long, flexible polyether chain (poly(ethylene glycol) derivative) and a terminal group with a trifluoromethyl (CF₃) substituent. The structure is highly symmetrical and contains several heterocyclic rings, including pyridine and imidazole derivatives.
C-174	C-175	C-176

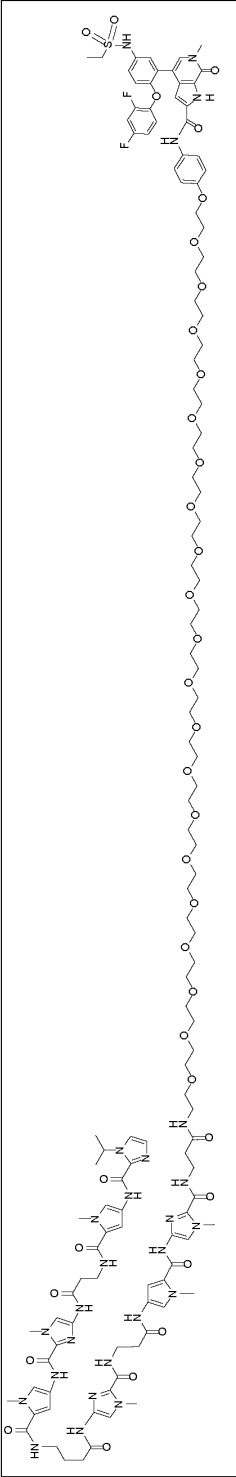
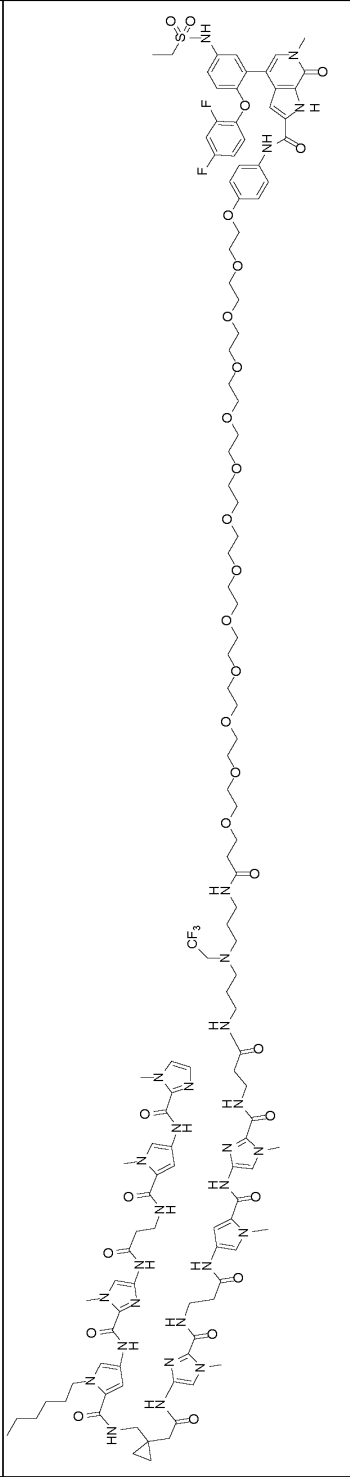
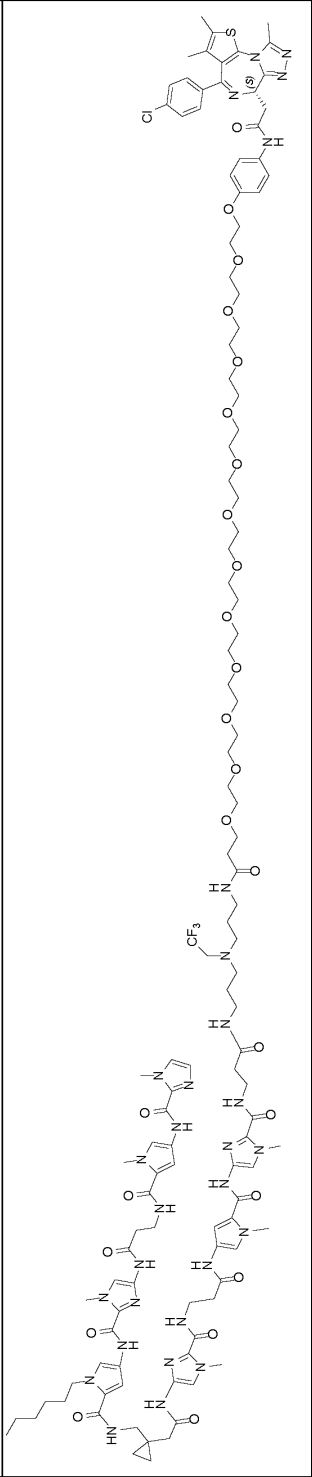
 Chemical structure of compound C-177. It features a complex polycyclic aromatic system with a thiazine ring fused to a benzene ring, which is further fused to a pyridine ring. A chlorine atom is attached to the benzene ring. The structure is linked via an amide bond to a long, flexible polyether chain (poly(ethylene glycol) derivative). This chain is terminated by a trifluoromethyl group (F₃C) and a complex polycyclic aromatic system with a thiazine ring fused to a benzene ring, which is further fused to a pyridine ring. A chlorine atom is attached to the benzene ring.	 Chemical structure of compound C-178. It features a complex polycyclic aromatic system with a thiazine ring fused to a benzene ring, which is further fused to a pyridine ring. A chlorine atom is attached to the benzene ring. The structure is linked via an amide bond to a long, flexible polyether chain (poly(ethylene glycol) derivative). This chain is terminated by a trifluoromethyl group (F₃C) and a complex polycyclic aromatic system with a thiazine ring fused to a benzene ring, which is further fused to a pyridine ring. A chlorine atom is attached to the benzene ring.	 Chemical structure of compound C-179. It features a complex polycyclic aromatic system with a thiazine ring fused to a benzene ring, which is further fused to a pyridine ring. A chlorine atom is attached to the benzene ring. The structure is linked via an amide bond to a long, flexible polyether chain (poly(ethylene glycol) derivative). This chain is terminated by a trifluoromethyl group (F₃C) and a complex polycyclic aromatic system with a thiazine ring fused to a benzene ring, which is further fused to a pyridine ring. A chlorine atom is attached to the benzene ring.
C-177	C-178	C-179

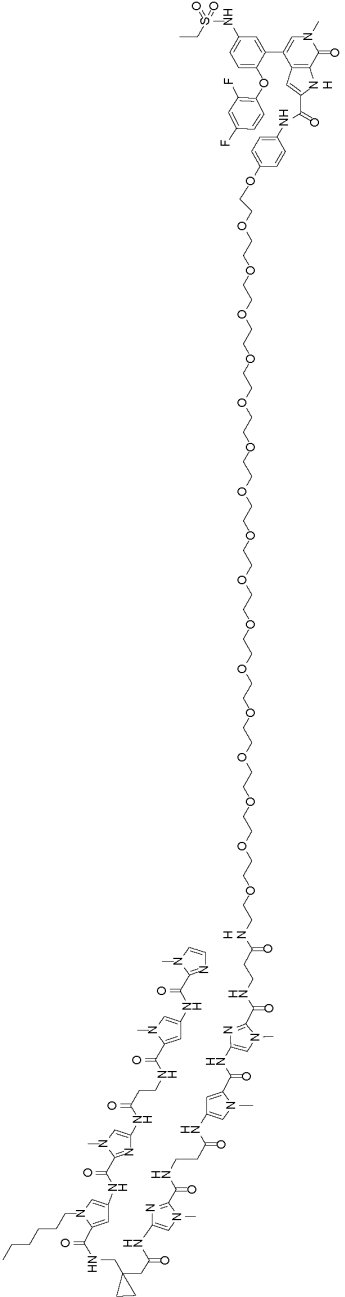
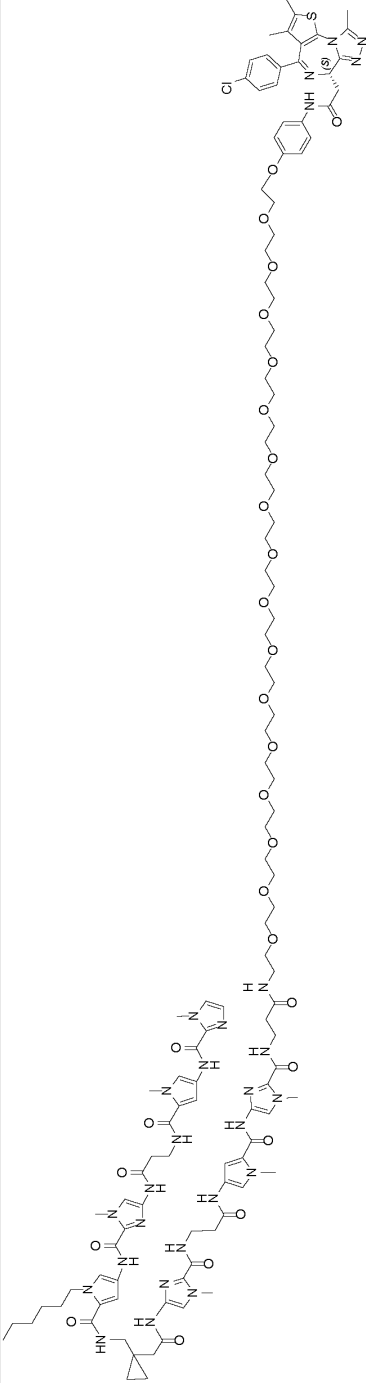
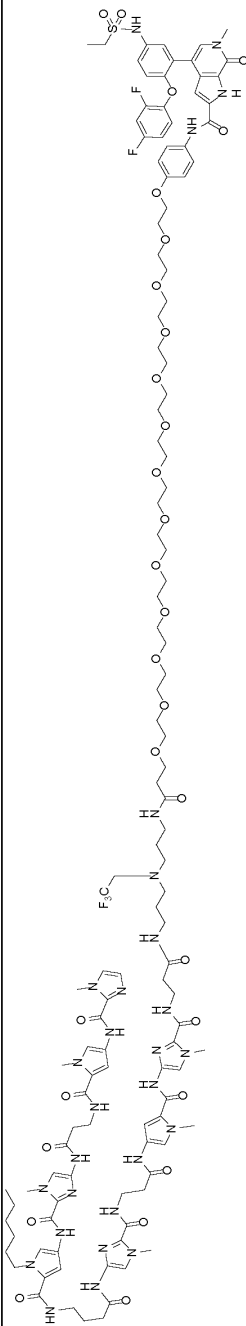
 Chemical structure of compound C-180. It features a complex polycyclic aromatic system with a thiazine ring fused to a pyrazole, which is further fused to a benzene ring. This system is substituted with a chlorine atom and a trifluoromethyl group. The structure is linked via a long, flexible polyether chain to a central amide group. The amide is further substituted with a trifluoromethyl group and a complex polycyclic aromatic system, including a thiazine ring and a pyrazole, which is also fused to a benzene ring. The structure is further substituted with a trifluoromethyl group and a complex polycyclic aromatic system, including a thiazine ring and a pyrazole, which is also fused to a benzene ring.	 Chemical structure of compound C-181. It is identical to C-180, featuring a complex polycyclic aromatic system with a thiazine ring fused to a pyrazole, which is further fused to a benzene ring. This system is substituted with a chlorine atom and a trifluoromethyl group. The structure is linked via a long, flexible polyether chain to a central amide group. The amide is further substituted with a trifluoromethyl group and a complex polycyclic aromatic system, including a thiazine ring and a pyrazole, which is also fused to a benzene ring. The structure is further substituted with a trifluoromethyl group and a complex polycyclic aromatic system, including a thiazine ring and a pyrazole, which is also fused to a benzene ring.	 Chemical structure of compound C-182. It is identical to C-180, featuring a complex polycyclic aromatic system with a thiazine ring fused to a pyrazole, which is further fused to a benzene ring. This system is substituted with a chlorine atom and a trifluoromethyl group. The structure is linked via a long, flexible polyether chain to a central amide group. The amide is further substituted with a trifluoromethyl group and a complex polycyclic aromatic system, including a thiazine ring and a pyrazole, which is also fused to a benzene ring. The structure is further substituted with a trifluoromethyl group and a complex polycyclic aromatic system, including a thiazine ring and a pyrazole, which is also fused to a benzene ring.
C-180	C-181	C-182

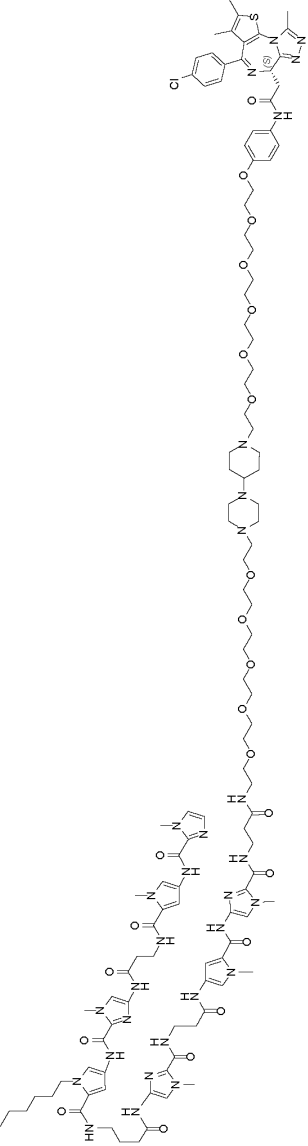
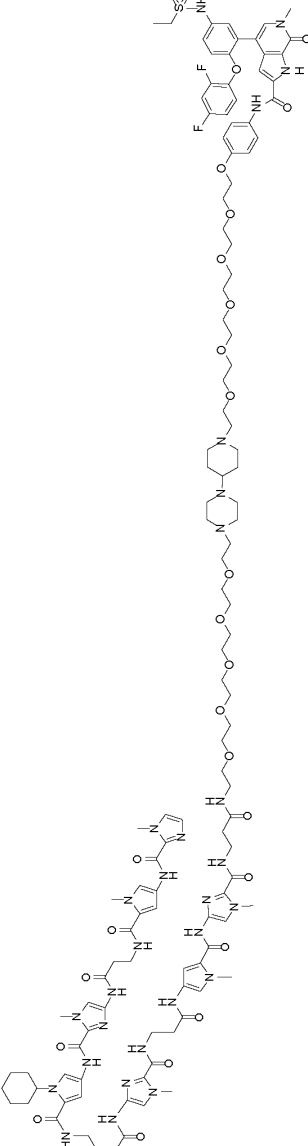
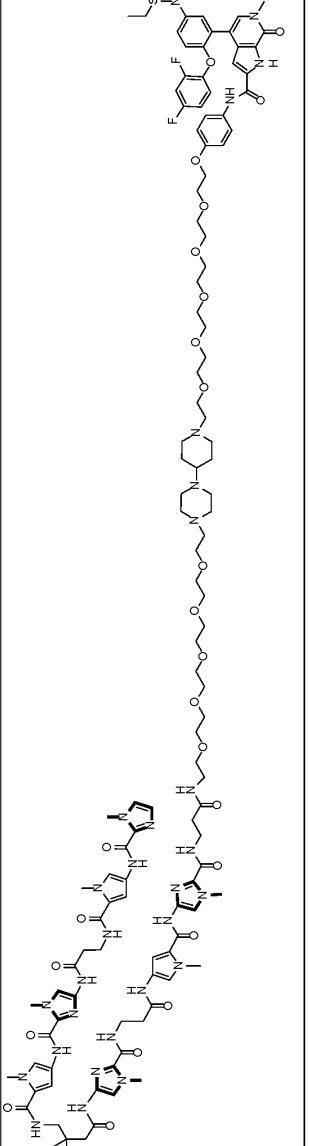
C-186	 Chemical structure of C-186: A complex molecule featuring a central core with multiple amide and ester linkages. It includes a long, flexible polyether chain (poly(ethylene glycol) derivative) and a terminal group with a fluorinated amide. The structure is highly branched and contains several heterocyclic rings, including pyrazoles and a thiazole.
C-187	 Chemical structure of C-187: A complex molecule featuring a central core with multiple amide and ester linkages. It includes a long, flexible polyether chain (poly(ethylene glycol) derivative) and a terminal group with a fluorinated amide. The structure is highly branched and contains several heterocyclic rings, including pyrazoles and a thiazole.
C-188	 Chemical structure of C-188: A complex molecule featuring a central core with multiple amide and ester linkages. It includes a long, flexible polyether chain (poly(ethylene glycol) derivative) and a terminal group with a fluorinated amide. The structure is highly branched and contains several heterocyclic rings, including pyrazoles and a thiazole.

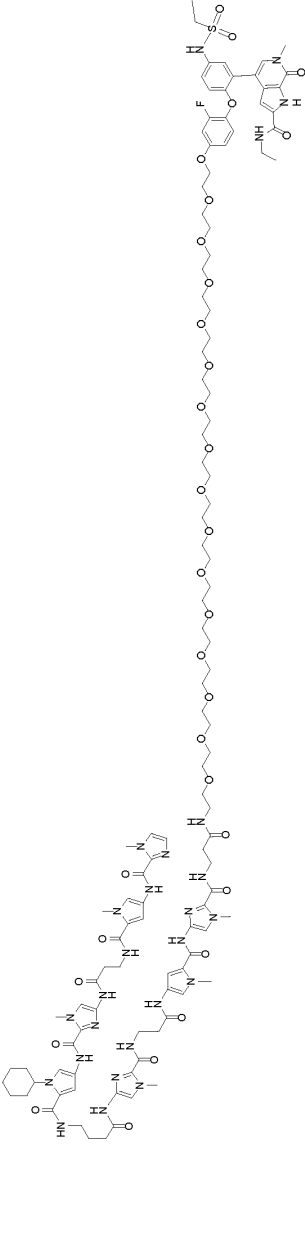
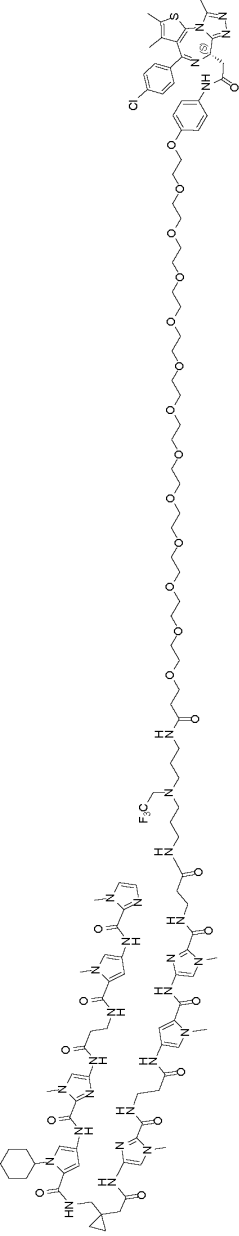
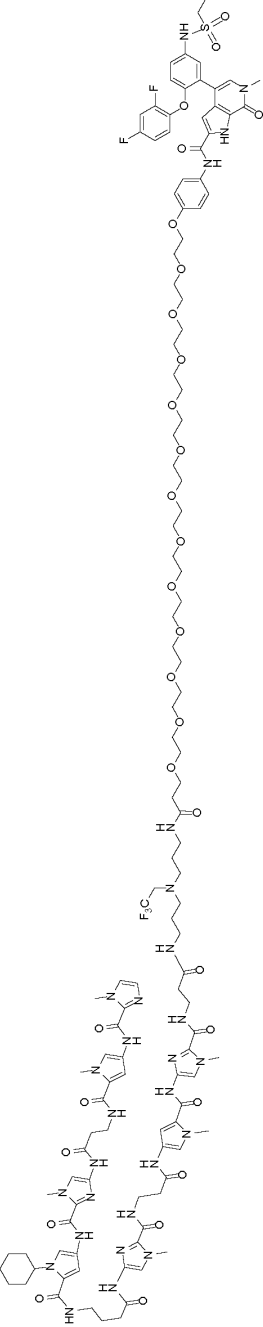
 Chemical structure of compound C-189. It features a 4-chlorophenyl group attached to a 1,2,4-triazole ring. This triazole is linked via a carbonyl group to a long, flexible polyether chain consisting of approximately 15 repeating units of -O-CH2-CH2-O-. The chain terminates in a complex polycyclic aromatic system with multiple amide and carbonyl functional groups.	 Chemical structure of compound C-190. It features a 4-chlorophenyl group attached to a 1,2,4-triazole ring. This triazole is linked via a carbonyl group to a long, flexible polyether chain consisting of approximately 15 repeating units of -O-CH2-CH2-O-. The chain terminates in a complex polycyclic aromatic system with multiple amide and carbonyl functional groups.	 Chemical structure of compound C-191. It features a 4-chlorophenyl group attached to a 1,2,4-triazole ring. This triazole is linked via a carbonyl group to a long, flexible polyether chain consisting of approximately 15 repeating units of -O-CH2-CH2-O-. The chain terminates in a complex polycyclic aromatic system with multiple amide and carbonyl functional groups.	 Chemical structure of compound C-192. It features a 4-chlorophenyl group attached to a 1,2,4-triazole ring. This triazole is linked via a carbonyl group to a long, flexible polyether chain consisting of approximately 15 repeating units of -O-CH2-CH2-O-. The chain terminates in a complex polycyclic aromatic system with multiple amide and carbonyl functional groups.
C-189	C-190	C-191	C-192

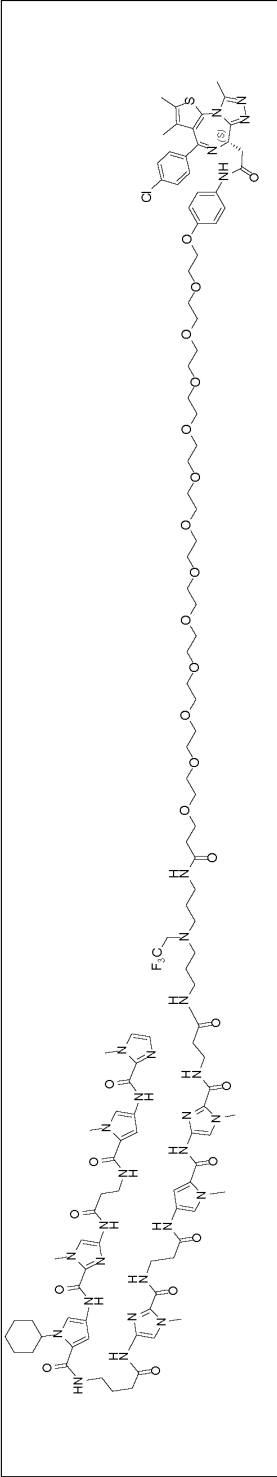
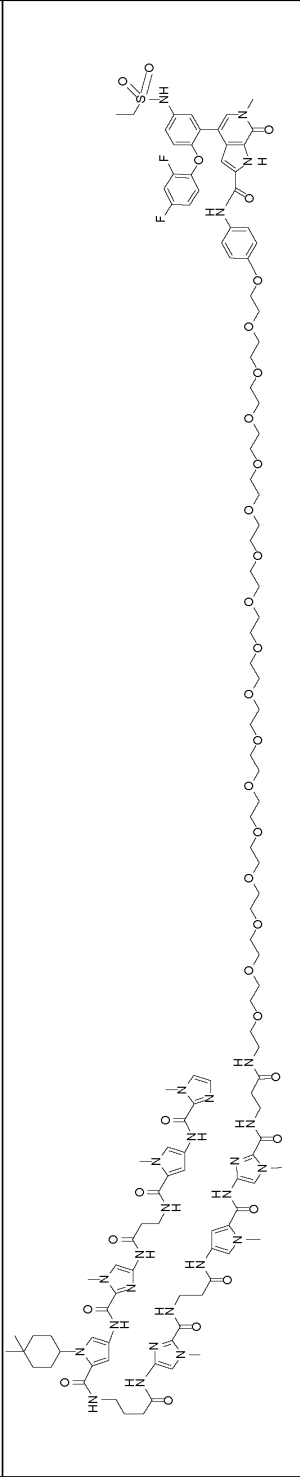
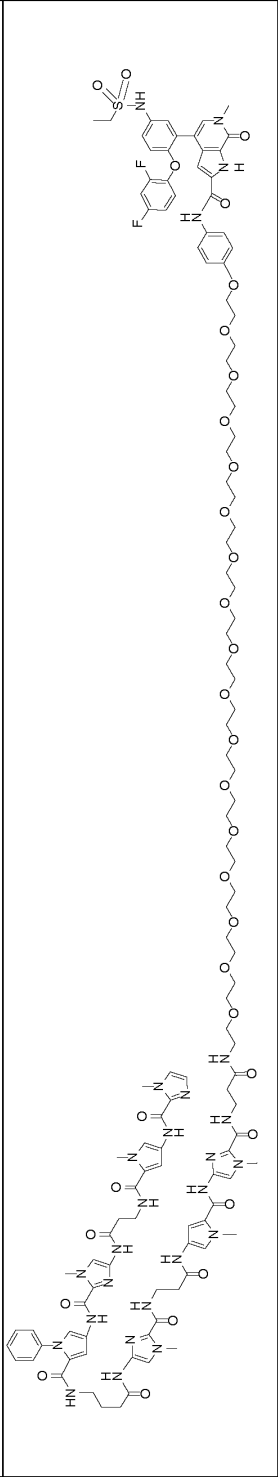
C-193	
C-194	
C-195	
C-196	

 Chemical structure of C-197: A complex molecule featuring a central pyridine ring substituted with a 4-fluorophenyl group, a 4-(4-ethoxyphenoxy)phenyl group, and a 4-(4-ethoxyphenoxy)phenyl group. The molecule is linked via a long, flexible polyether chain to a complex polycyclic aromatic system containing multiple amide and ester linkages.	 Chemical structure of C-198: A complex molecule featuring a central pyridine ring substituted with a 4-fluorophenyl group, a 4-(4-ethoxyphenoxy)phenyl group, and a 4-(4-ethoxyphenoxy)phenyl group. The molecule is linked via a long, flexible polyether chain to a complex polycyclic aromatic system containing multiple amide and ester linkages.	 Chemical structure of C-199: A complex molecule featuring a central pyridine ring substituted with a 4-fluorophenyl group, a 4-(4-ethoxyphenoxy)phenyl group, and a 4-(4-ethoxyphenoxy)phenyl group. The molecule is linked via a long, flexible polyether chain to a complex polycyclic aromatic system containing multiple amide and ester linkages.
C-197	C-198	C-199

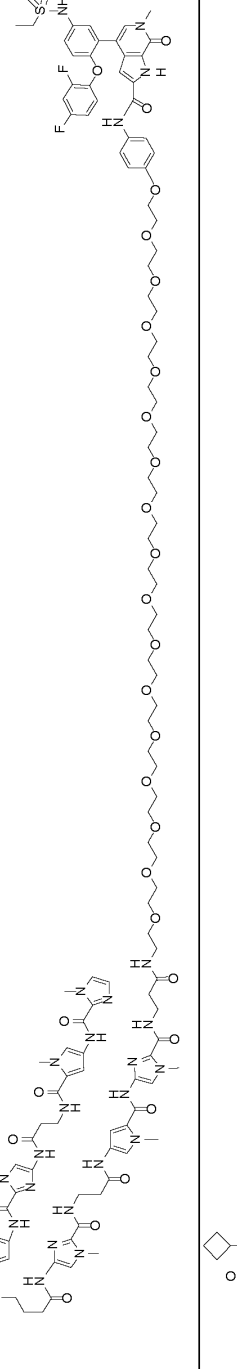
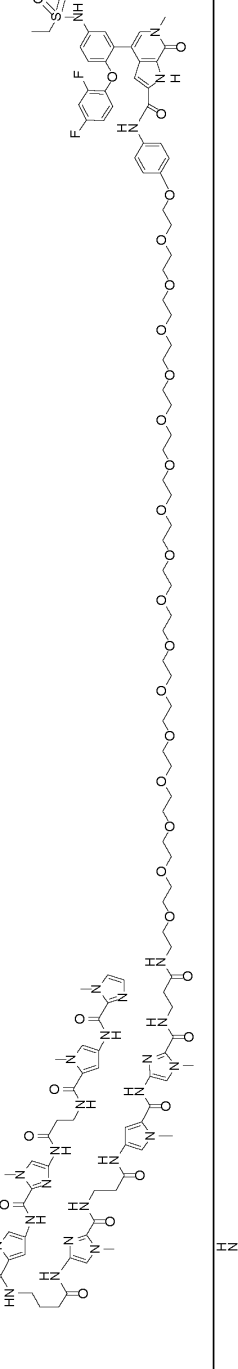
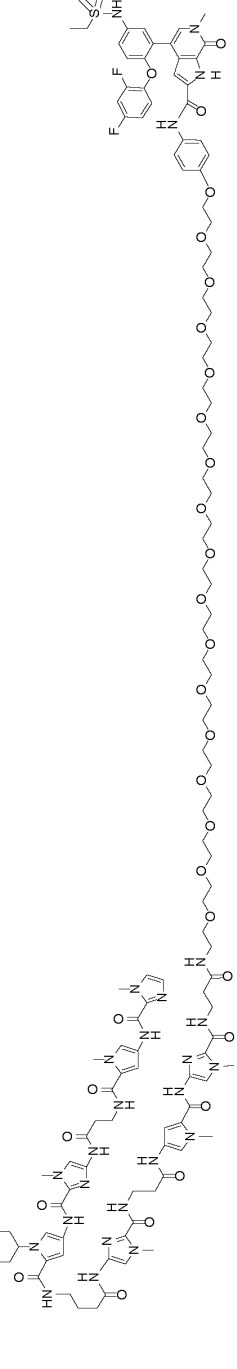
 Chemical structure of compound C-200. It features a long polyether chain (1,3-bis(2-ethanesulfonyl)oxypropane) connecting a 2,6-difluoro-4-(4-methyl-1H-pyridin-2-yl)phenyl group to a complex polycyclic aromatic system. This system includes a 1,2,4-triazole ring, a pyridine ring, and a cyclopropane ring, with various amide and ester linkages.	 Chemical structure of compound C-201. It is similar to C-200 but features a different polycyclic aromatic system at the right end, including a 1,2,4-triazole ring, a pyridine ring, and a cyclopropane ring, with various amide and ester linkages.	 Chemical structure of compound C-202. It is similar to C-200 but features a different polycyclic aromatic system at the right end, including a 1,2,4-triazole ring, a pyridine ring, and a cyclopropane ring, with various amide and ester linkages.
C-200	C-201	C-202

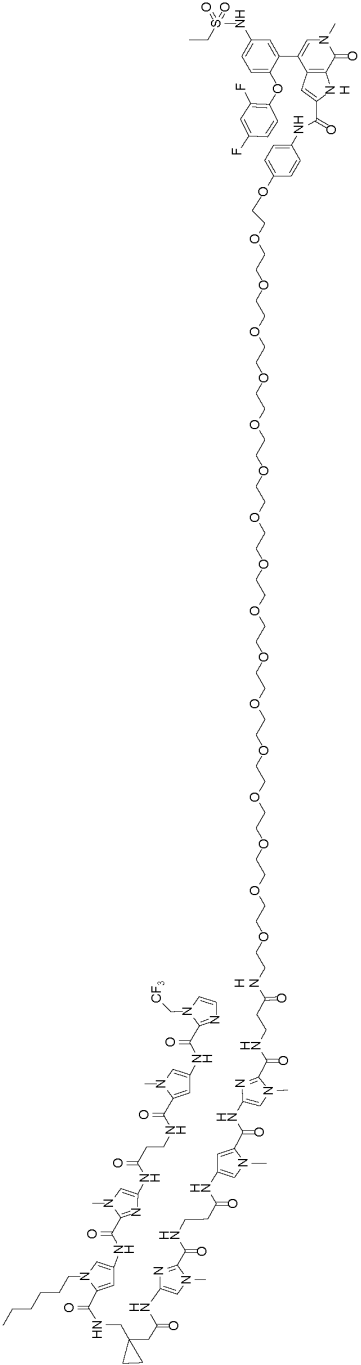
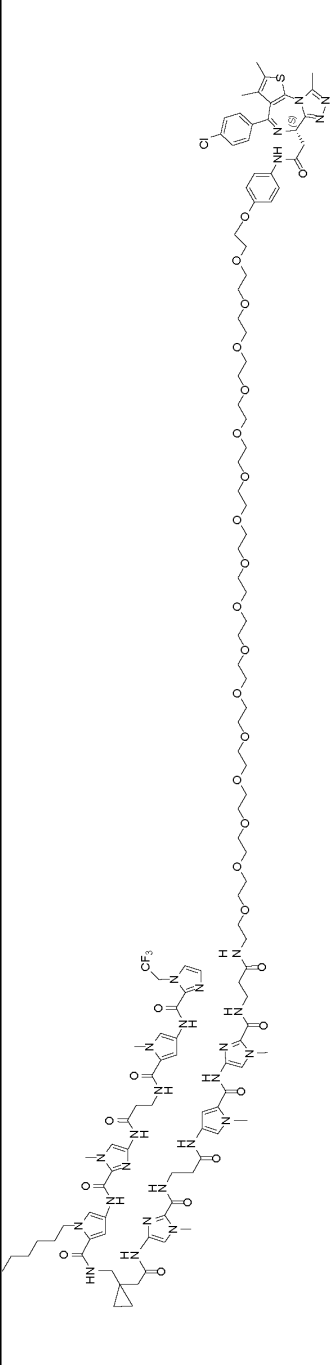
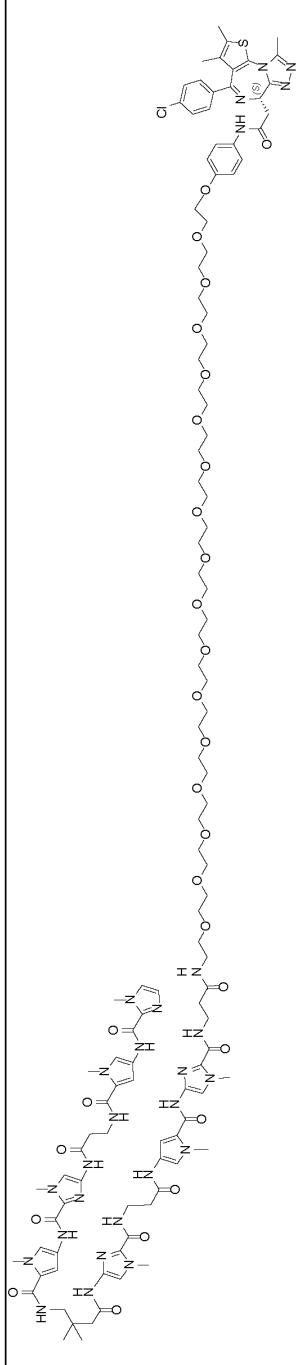
 Chemical structure of C-203: A complex molecule featuring a central piperazine ring connected via a long polyether chain to a thiazine derivative and a pyridine ring. The pyridine ring is substituted with a chlorine atom and a methyl group. The thiazine derivative is substituted with a methyl group and a hydrogen atom.	 Chemical structure of C-204: A complex molecule featuring a central piperazine ring connected via a long polyether chain to a thiazine derivative and a pyridine ring. The pyridine ring is substituted with a methyl group and a hydrogen atom. The thiazine derivative is substituted with a methyl group and a hydrogen atom.	 Chemical structure of C-205: A complex molecule featuring a central piperazine ring connected via a long polyether chain to a thiazine derivative and a pyridine ring. The pyridine ring is substituted with a methyl group and a hydrogen atom. The thiazine derivative is substituted with a methyl group and a hydrogen atom.
C-203	C-204	C-205

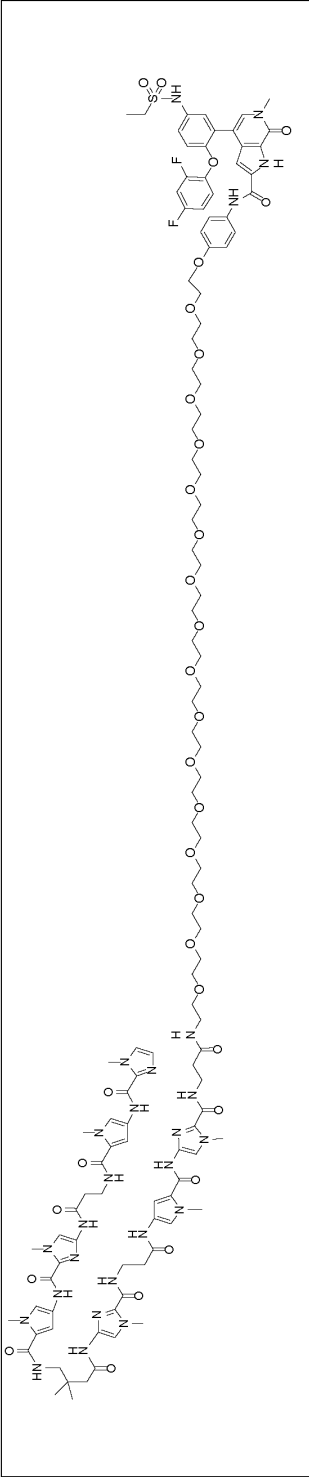
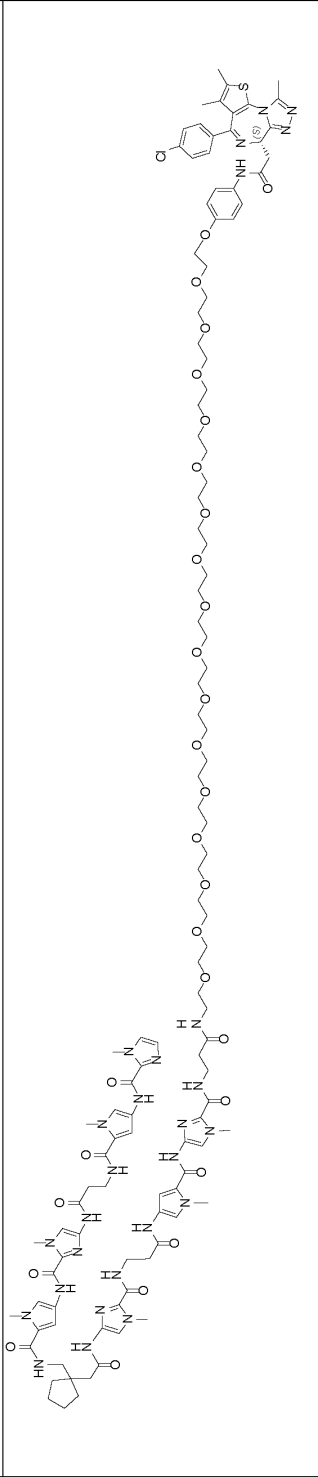
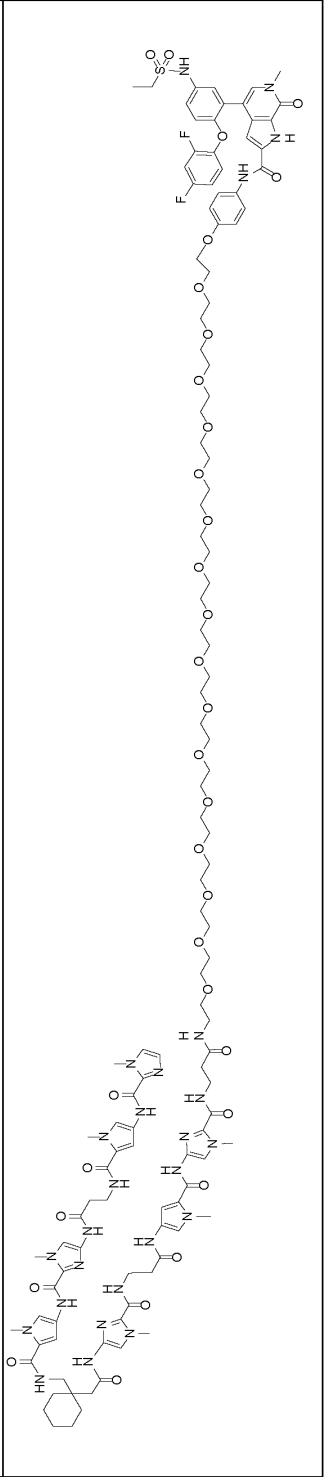
 Chemical structure of C-206: A complex molecule featuring a long polyether chain (10 repeating units of -OCH₂CH₂-) connecting a 4-fluorophenyl group to a 4-(dimethylamino)phenyl group. The 4-(dimethylamino)phenyl group is further substituted with a 4-(dimethylamino)pyridin-2-yl group and a 4-(dimethylamino)pyridin-2-yl group.	 Chemical structure of C-207: A complex molecule featuring a long polyether chain (10 repeating units of -OCH₂CH₂-) connecting a 4-chlorophenyl group to a 4-(dimethylamino)phenyl group. The 4-(dimethylamino)phenyl group is further substituted with a 4-(dimethylamino)pyridin-2-yl group and a 4-(dimethylamino)pyridin-2-yl group.	 Chemical structure of C-208: A complex molecule featuring a long polyether chain (10 repeating units of -OCH₂CH₂-) connecting a 4-fluorophenyl group to a 4-(dimethylamino)phenyl group. The 4-(dimethylamino)phenyl group is further substituted with a 4-(dimethylamino)pyridin-2-yl group and a 4-(dimethylamino)pyridin-2-yl group.
C-206	C-207	C-208

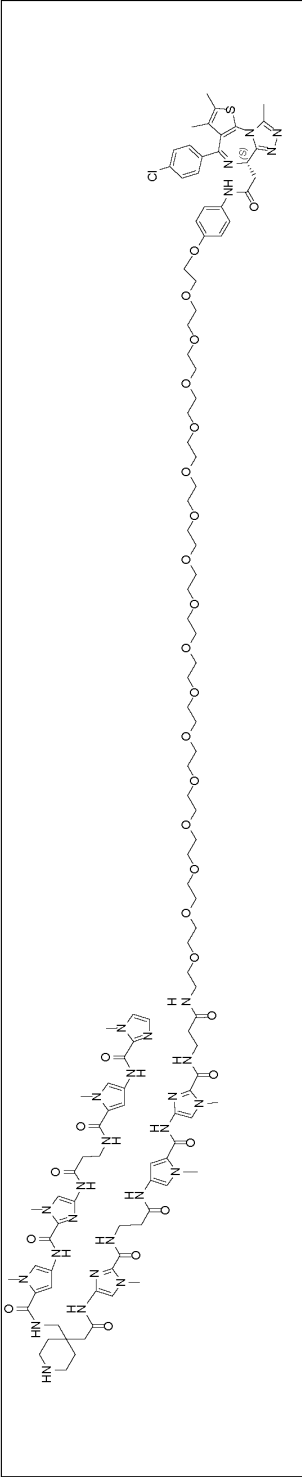
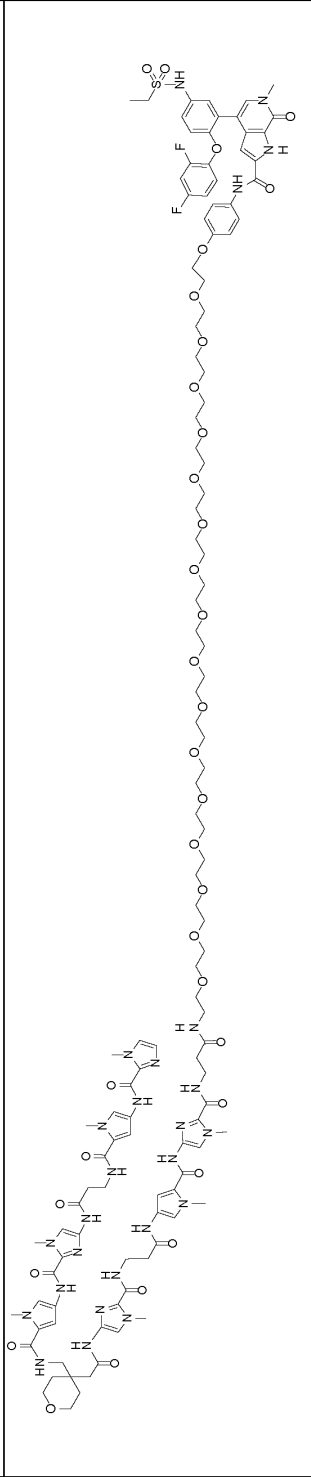
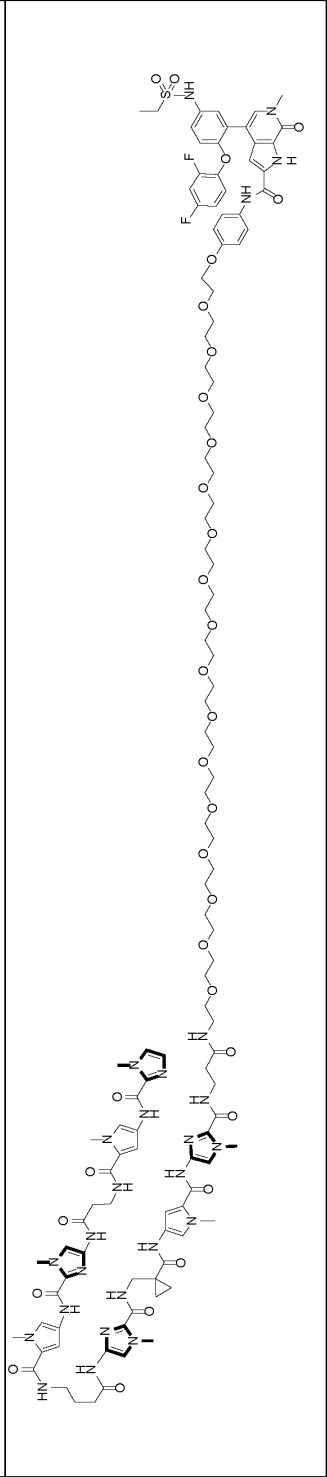
 Chemical structure of C-209: A complex molecule featuring a central core with a thiazole ring, a pyridine ring, and a sulfonamide group. The structure is highly branched and includes a long, flexible polyether chain (poly(ethylene glycol) derivative) attached to the central core. The molecule also contains a cyclohexyl group and a sulfonamide group.	 Chemical structure of C-210: A complex molecule featuring a central core with a thiazole ring, a pyridine ring, and a sulfonamide group. The structure is highly branched and includes a long, flexible polyether chain (poly(ethylene glycol) derivative) attached to the central core. The molecule also contains a cyclohexyl group and a sulfonamide group.	 Chemical structure of C-211: A complex molecule featuring a central core with a thiazole ring, a pyridine ring, and a sulfonamide group. The structure is highly branched and includes a long, flexible polyether chain (poly(ethylene glycol) derivative) attached to the central core. The molecule also contains a cyclohexyl group and a sulfonamide group.
C-209	C-210	C-211

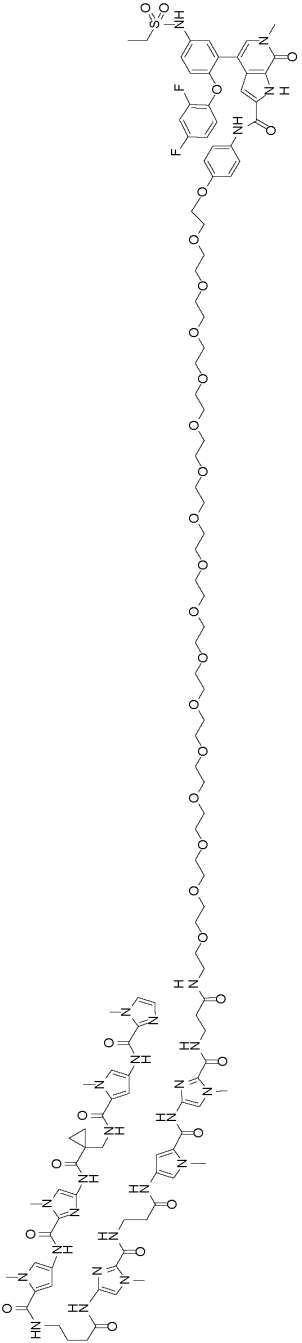
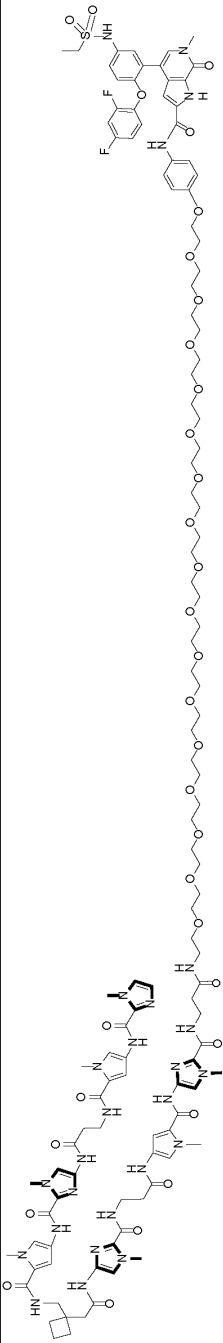
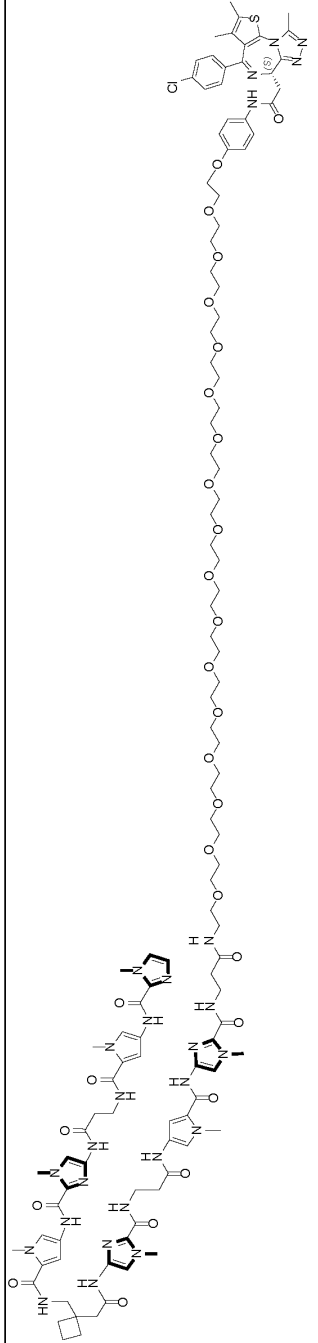
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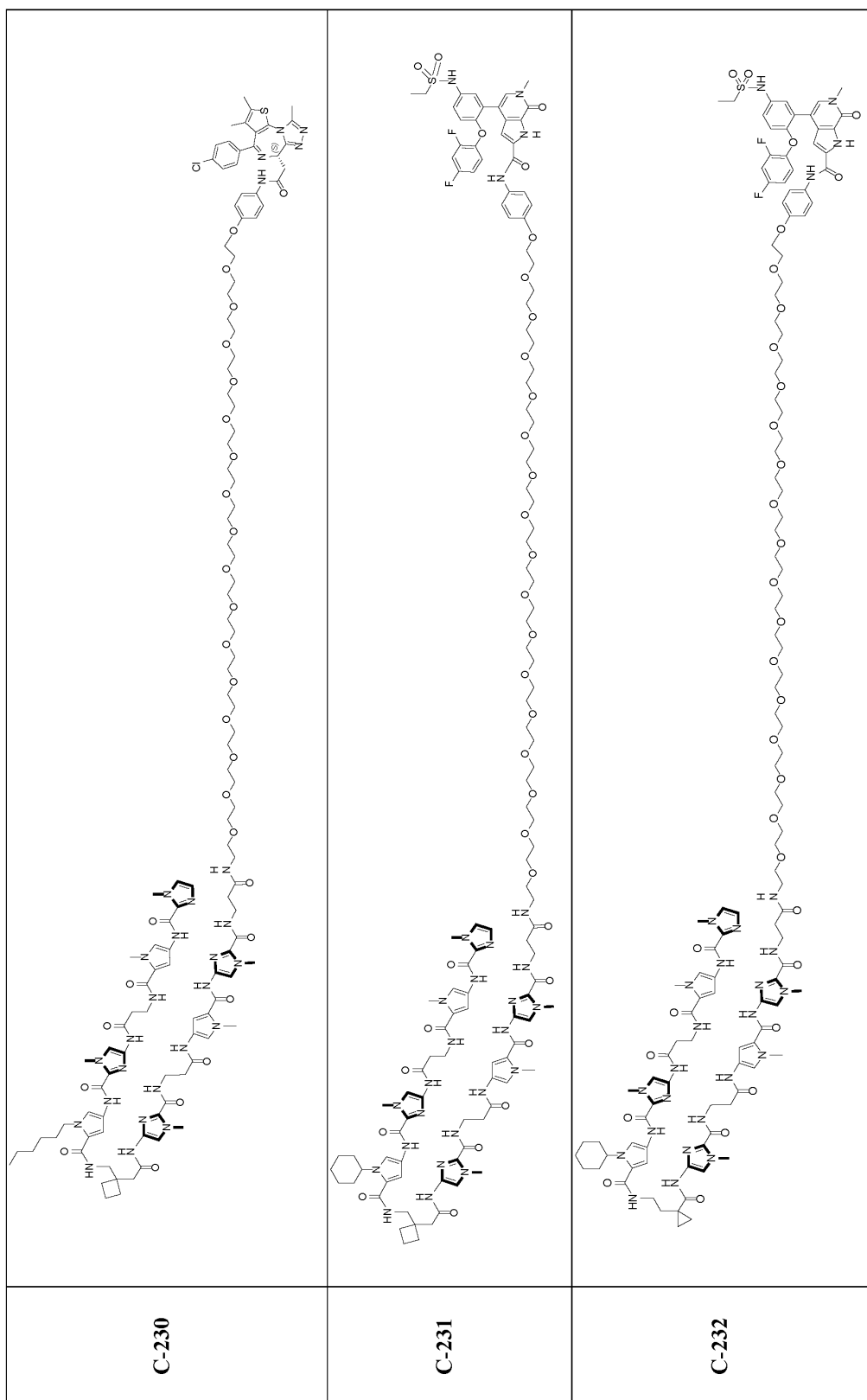
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C-216	
C-217	

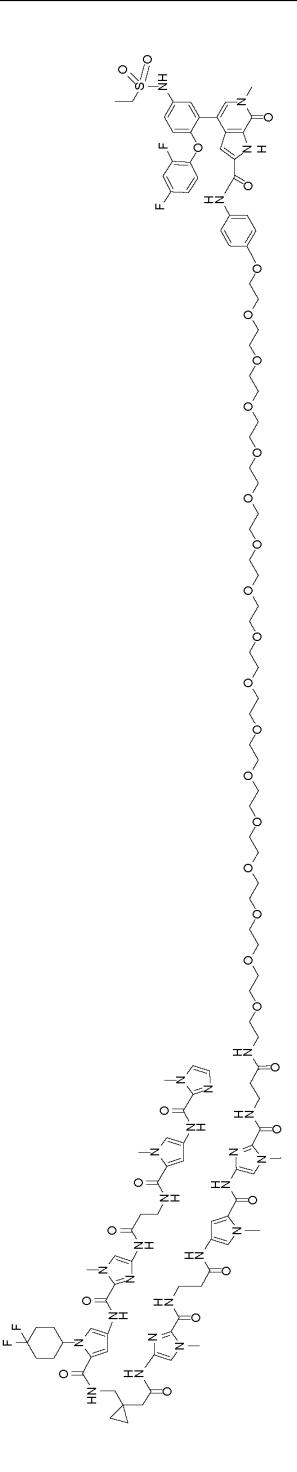
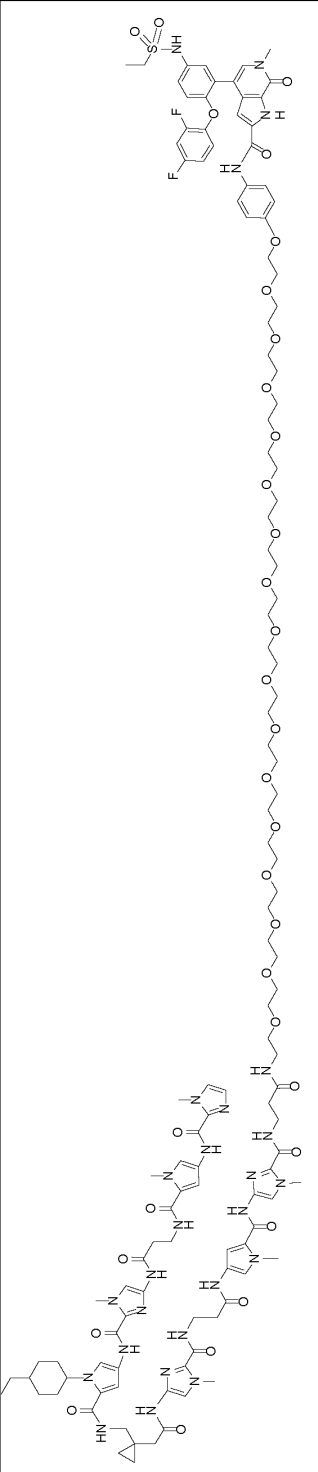
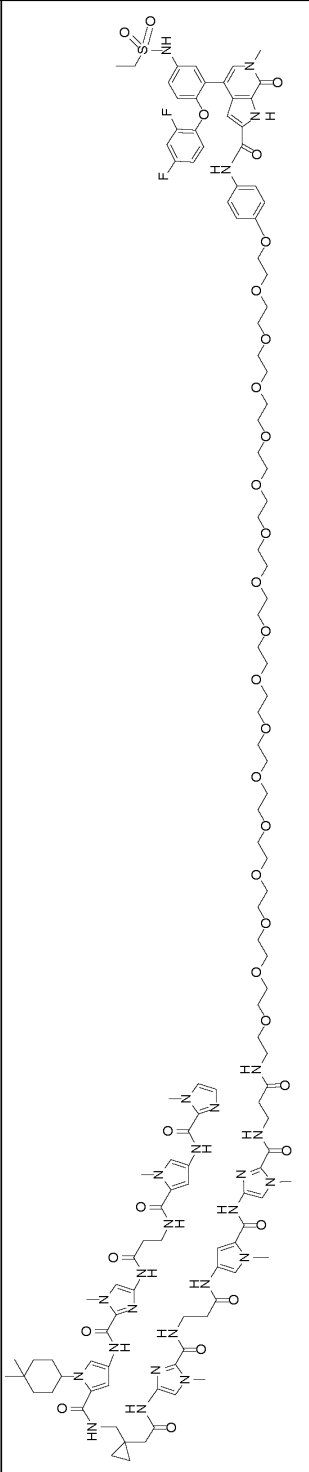
 Chemical structure of compound C-218. It features a complex polycyclic aromatic system with a sulfonamide group (SO₂NH₂) and a fluorine atom. This system is connected via a long, flexible polyether chain (containing 12 oxygen atoms) to a large, multi-ring polycyclic aromatic system. This second system includes a trifluoromethyl group (CF₃) and a cyclopropylmethyl group.	 Chemical structure of compound C-219. It features a complex polycyclic aromatic system with a sulfonamide group (SO₂NH₂) and a fluorine atom. This system is connected via a long, flexible polyether chain (containing 12 oxygen atoms) to a large, multi-ring polycyclic aromatic system. This second system includes a trifluoromethyl group (CF₃) and a cyclopropylmethyl group.	 Chemical structure of compound C-220. It features a complex polycyclic aromatic system with a sulfonamide group (SO₂NH₂) and a fluorine atom. This system is connected via a long, flexible polyether chain (containing 12 oxygen atoms) to a large, multi-ring polycyclic aromatic system. This second system includes a trifluoromethyl group (CF₃) and a cyclopropylmethyl group.
C-218	C-219	C-220

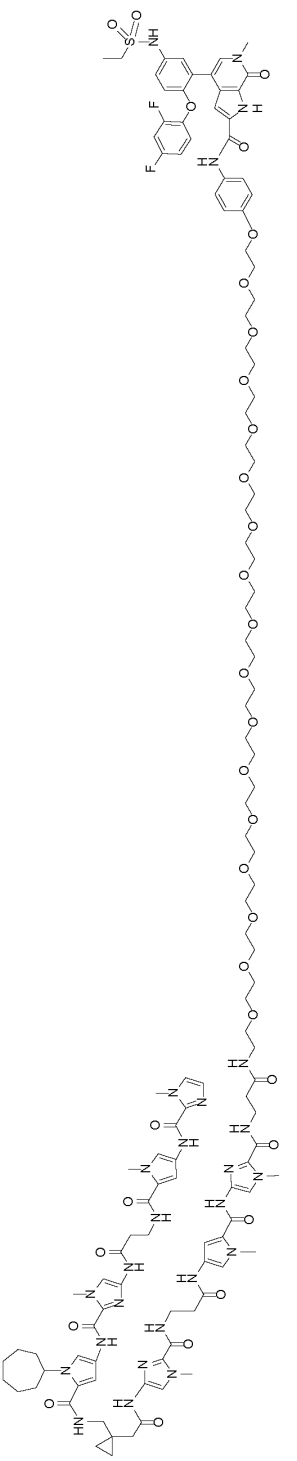
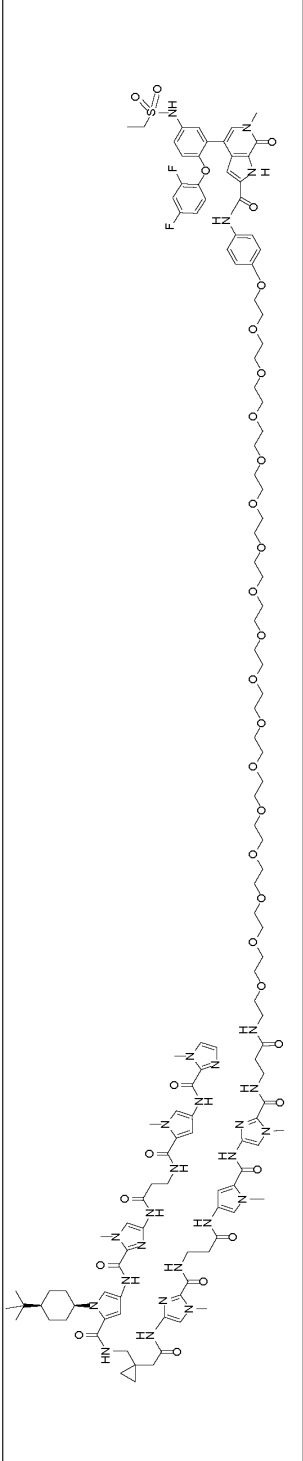
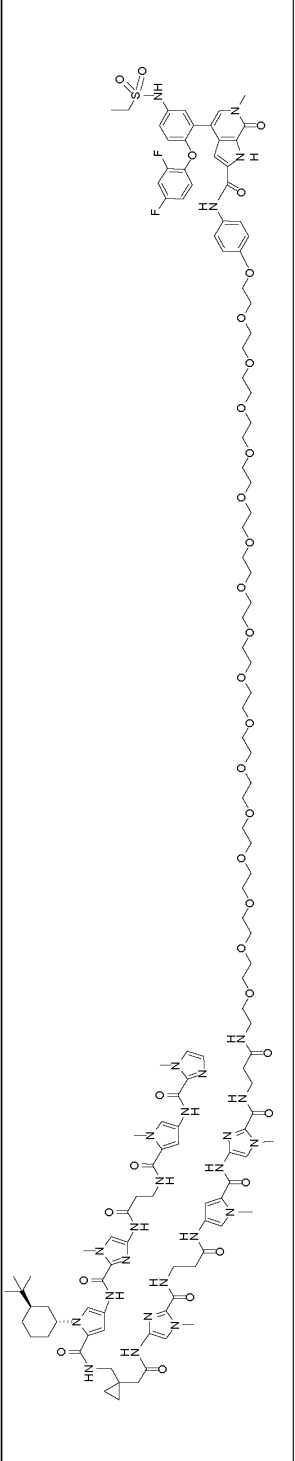
 Chemical structure of compound C-221. It features a long polyether chain (1,3-bis(2-ethoxyethoxy)propane) connecting a substituted benzimidazole moiety to a complex polycyclic amide system. The benzimidazole part has a 2-ethanesulfonylamino group, a fluorine atom, and a 4-fluorophenyl group. The amide system includes a 2,4,6-trimethyl-5-(2,2,3,3-tetramethylbutanamide)pyrimidine-3-carboxamide moiety.	 Chemical structure of compound C-222. It is similar to C-221 but features a different polycyclic amide system at the right end of the polyether chain. This system includes a 2,4,6-trimethyl-5-(2,2,3,3-tetramethylbutanamide)pyrimidine-3-carboxamide moiety and a 4-chlorophenyl group.	 Chemical structure of compound C-223. It is similar to C-221 but features a different polycyclic amide system at the right end of the polyether chain. This system includes a 2,4,6-trimethyl-5-(2,2,3,3-tetramethylbutanamide)pyrimidine-3-carboxamide moiety and a 4-fluorophenyl group.
C-221	C-222	C-223

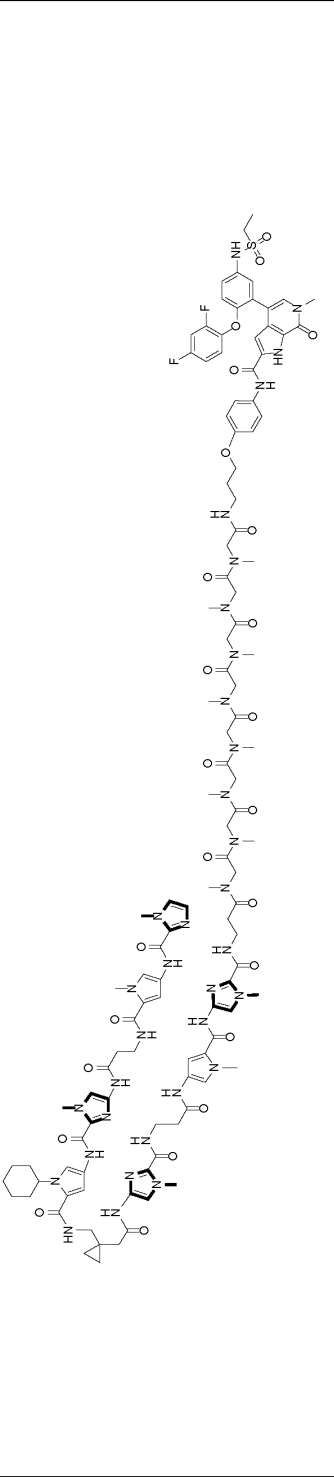
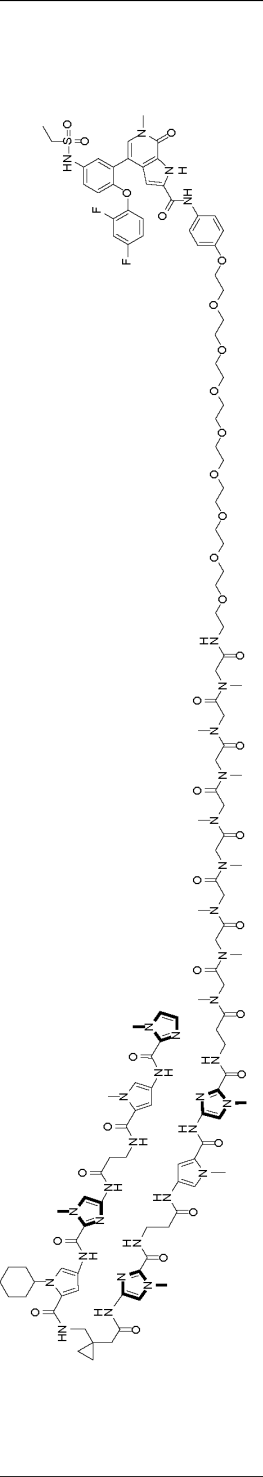
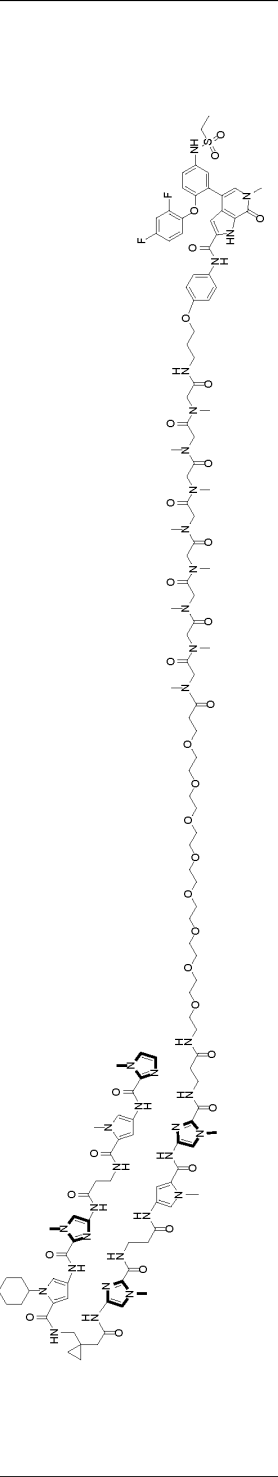
 Chemical structure of compound C-224. It features a 4-chlorophenyl group connected via an amide bond to a 4-((9-oxo-9H-fluoren-2-ylideneamino)oxy)phenyl group. This is linked through a long polyether chain (12 repeating -OCH2CH2O- units) to a 4-((9-oxo-9H-fluoren-2-ylideneamino)oxy)phenyl group. The fluorenyl group is substituted with a 4-((9-oxo-9H-fluoren-2-ylideneamino)oxy)phenyl group and a 4-((9-oxo-9H-fluoren-2-ylideneamino)oxy)phenyl group.	 Chemical structure of compound C-225. It features a 4-((9-oxo-9H-fluoren-2-ylideneamino)oxy)phenyl group connected via an amide bond to a 4-((9-oxo-9H-fluoren-2-ylideneamino)oxy)phenyl group. This is linked through a long polyether chain (12 repeating -OCH2CH2O- units) to a 4-((9-oxo-9H-fluoren-2-ylideneamino)oxy)phenyl group. The fluorenyl group is substituted with a 4-((9-oxo-9H-fluoren-2-ylideneamino)oxy)phenyl group and a 4-((9-oxo-9H-fluoren-2-ylideneamino)oxy)phenyl group.	 Chemical structure of compound C-226. It features a 4-((9-oxo-9H-fluoren-2-ylideneamino)oxy)phenyl group connected via an amide bond to a 4-((9-oxo-9H-fluoren-2-ylideneamino)oxy)phenyl group. This is linked through a long polyether chain (12 repeating -OCH2CH2O- units) to a 4-((9-oxo-9H-fluoren-2-ylideneamino)oxy)phenyl group. The fluorenyl group is substituted with a 4-((9-oxo-9H-fluoren-2-ylideneamino)oxy)phenyl group and a 4-((9-oxo-9H-fluoren-2-ylideneamino)oxy)phenyl group.
C-224	C-225	C-226

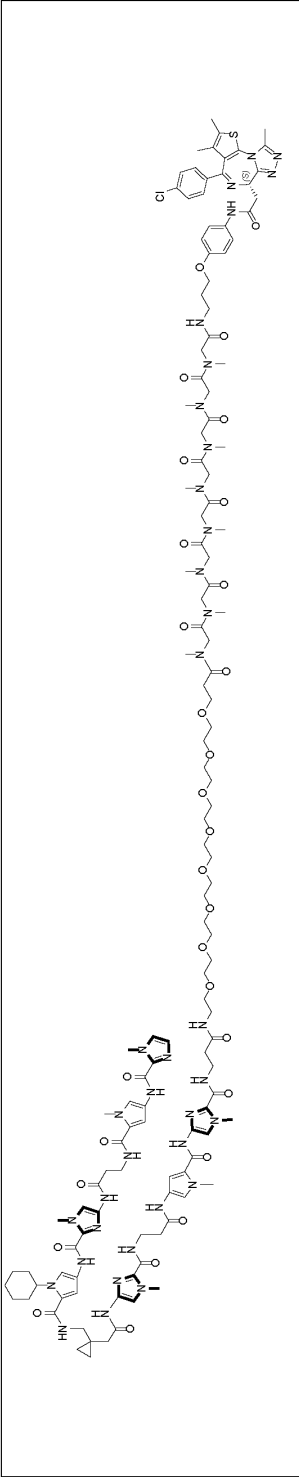
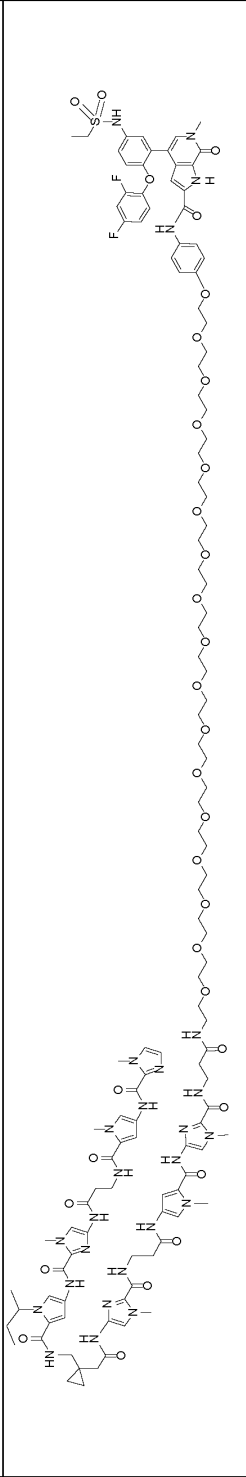
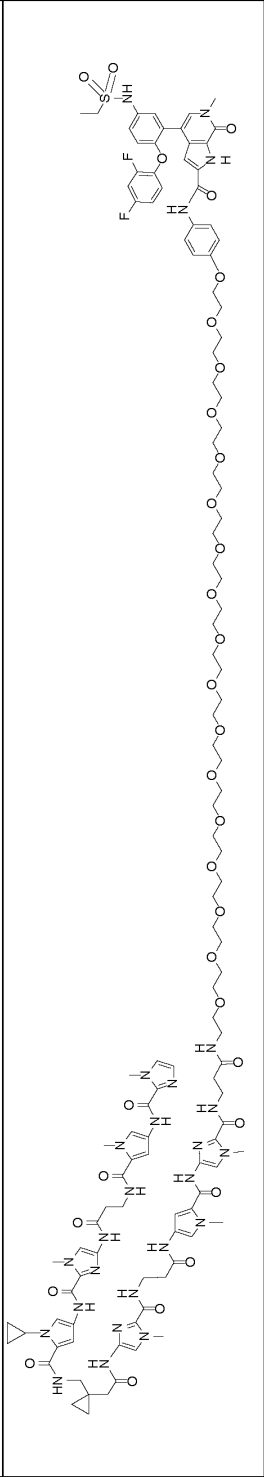
 Chemical structure of C-227: A complex molecule featuring a central core with a fluorinated benzene ring, a pyrazole ring, and a sulfonamide group. This core is linked via a long, flexible polyether chain to a complex polycyclic structure containing multiple amide and imide linkages, and a cyclobutane ring.	C-227
 Chemical structure of C-228: A complex molecule featuring a central core with a fluorinated benzene ring, a pyrazole ring, and a sulfonamide group. This core is linked via a long, flexible polyether chain to a complex polycyclic structure containing multiple amide and imide linkages, and a cyclobutane ring.	C-228
 Chemical structure of C-229: A complex molecule featuring a central core with a fluorinated benzene ring, a pyrazole ring, and a sulfonamide group. This core is linked via a long, flexible polyether chain to a complex polycyclic structure containing multiple amide and imide linkages, and a cyclobutane ring.	C-229

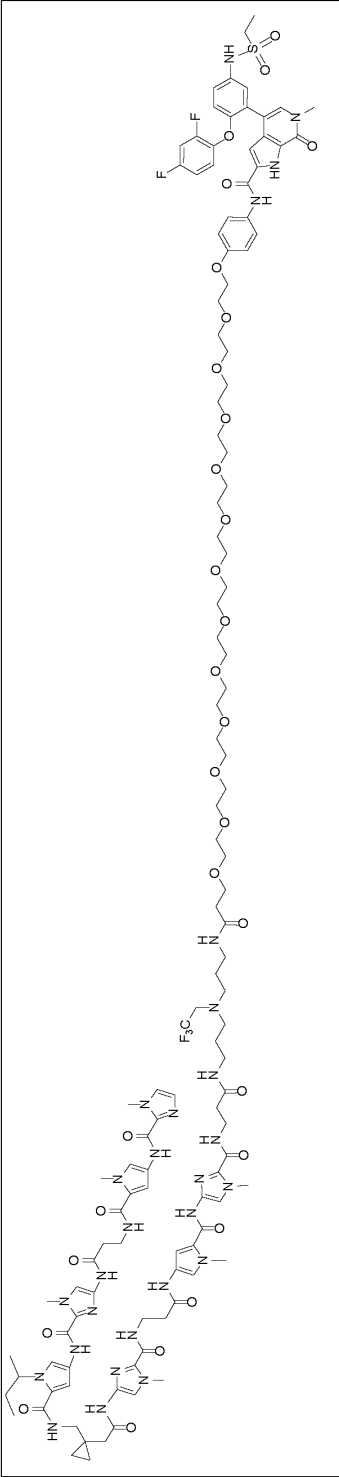
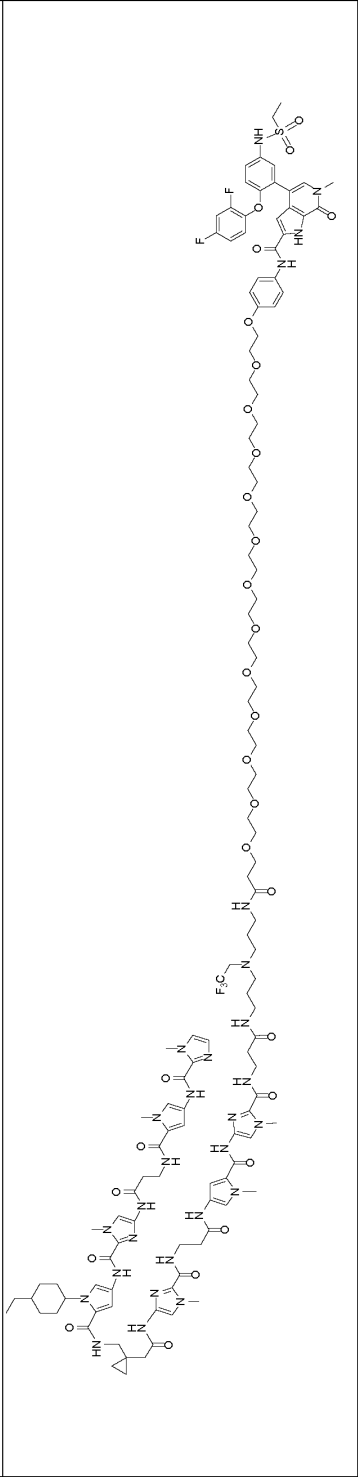
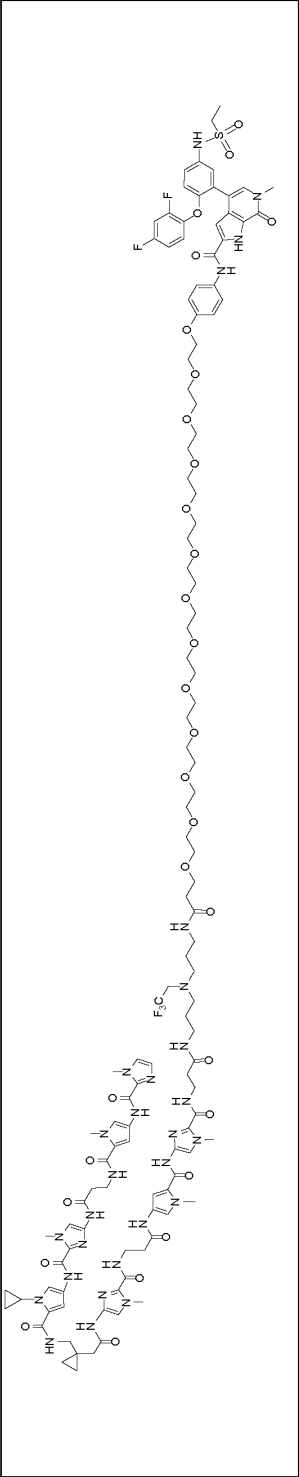


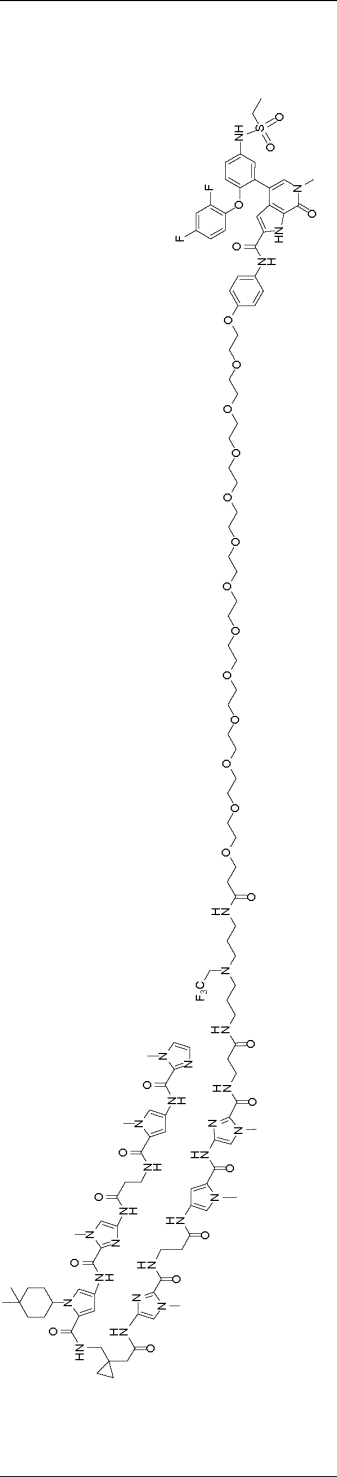
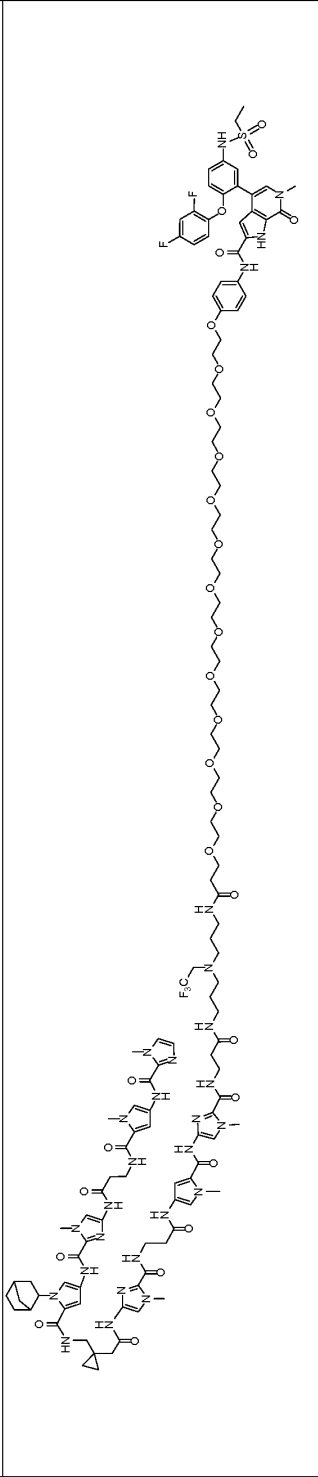
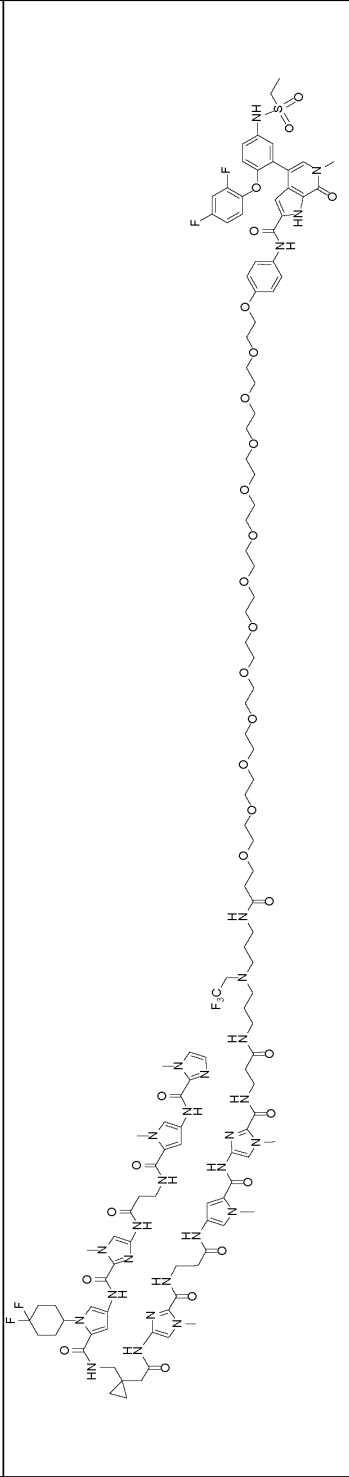
 Chemical structure of compound C-233. It features a complex polycyclic aromatic system with a sulfonamide group (SO₂NH-) and a long, flexible polyether chain (-(OCH₂)₁₀-) attached to the aromatic ring. The structure also includes a fluorinated phenyl group and a pyridine ring.	 Chemical structure of compound C-234. It is similar to C-233 but includes a different substitution pattern on the aromatic ring, featuring a sulfonamide group (SO₂NH-) and a long, flexible polyether chain (-(OCH₂)₁₀-). The structure also includes a fluorinated phenyl group and a pyridine ring.	 Chemical structure of compound C-235. It is similar to C-233 but includes a different substitution pattern on the aromatic ring, featuring a sulfonamide group (SO₂NH-) and a long, flexible polyether chain (-(OCH₂)₁₀-). The structure also includes a fluorinated phenyl group and a pyridine ring.
C-233	C-234	C-235

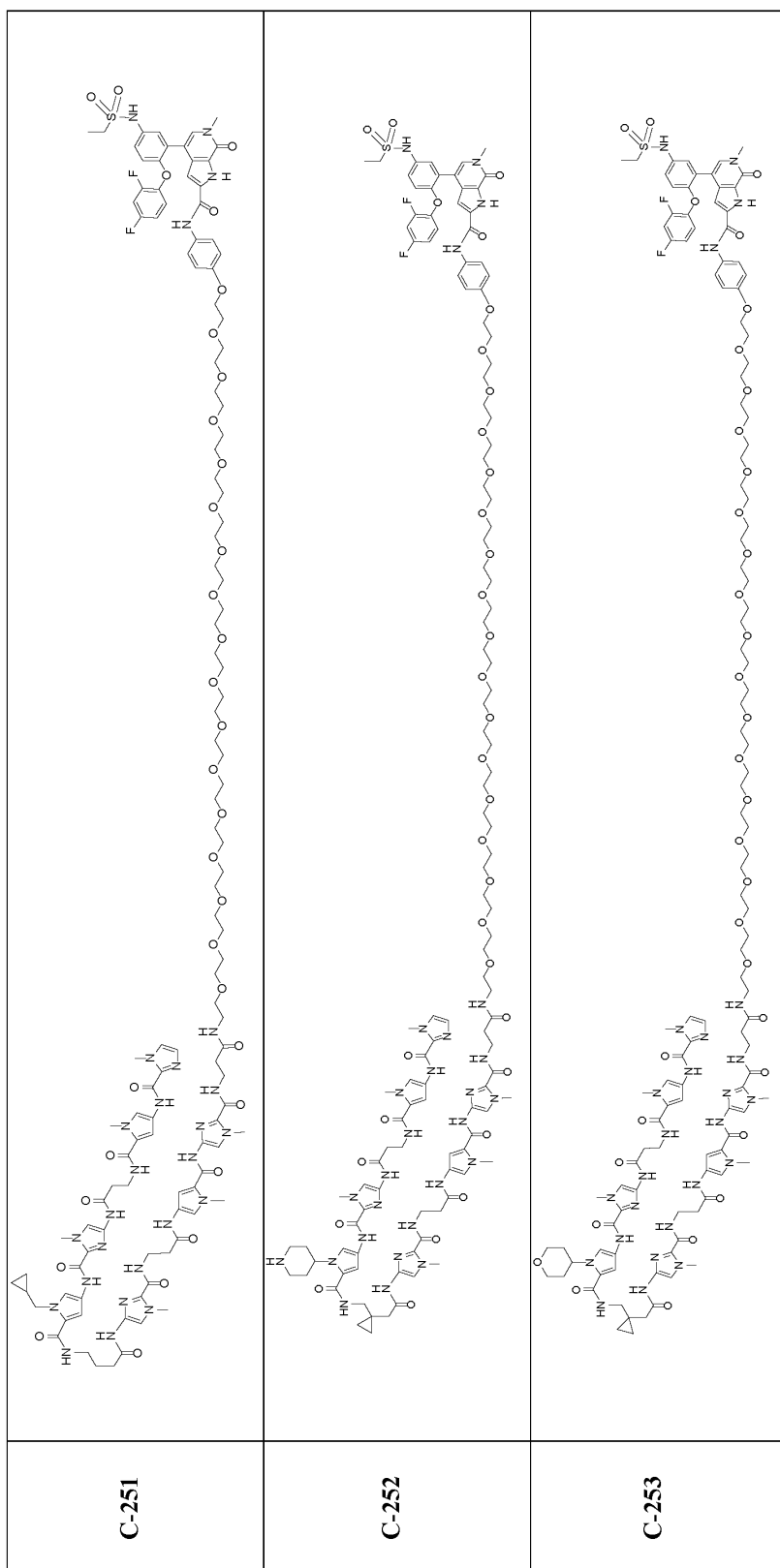
 Chemical structure of C-236: A complex molecule featuring a central pyrazole ring substituted with a 4-(2,2,2-trifluoroethoxy)phenyl group, a 4-(2,2,2-trifluoroethoxy)phenyl group, and a 4-(2,2,2-trifluoroethoxy)phenyl group. The molecule also includes a 4-(2,2,2-trifluoroethoxy)phenyl group and a 4-(2,2,2-trifluoroethoxy)phenyl group.	 Chemical structure of C-237: A complex molecule featuring a central pyrazole ring substituted with a 4-(2,2,2-trifluoroethoxy)phenyl group, a 4-(2,2,2-trifluoroethoxy)phenyl group, and a 4-(2,2,2-trifluoroethoxy)phenyl group. The molecule also includes a 4-(2,2,2-trifluoroethoxy)phenyl group and a 4-(2,2,2-trifluoroethoxy)phenyl group.	 Chemical structure of C-238: A complex molecule featuring a central pyrazole ring substituted with a 4-(2,2,2-trifluoroethoxy)phenyl group, a 4-(2,2,2-trifluoroethoxy)phenyl group, and a 4-(2,2,2-trifluoroethoxy)phenyl group. The molecule also includes a 4-(2,2,2-trifluoroethoxy)phenyl group and a 4-(2,2,2-trifluoroethoxy)phenyl group.
C-236	C-237	C-238

 Chemical structure of compound C-239. It features a central chain of repeating amide units, including a 4-fluorophenyl group, a 4-ethanesulfonylphenyl group, and a 4-(4-fluorophenyl)-2-methyl-1H-imidazole-5-carboxylate group. The chain is terminated by a 4-(4-fluorophenyl)-2-methyl-1H-imidazole-5-carboxylate group and a 4-(4-fluorophenyl)-2-methyl-1H-imidazole-5-carboxylate group.	 Chemical structure of compound C-240. It features a central chain of repeating amide units, including a 4-fluorophenyl group, a 4-ethanesulfonylphenyl group, and a 4-(4-fluorophenyl)-2-methyl-1H-imidazole-5-carboxylate group. The chain is terminated by a 4-(4-fluorophenyl)-2-methyl-1H-imidazole-5-carboxylate group and a 4-(4-fluorophenyl)-2-methyl-1H-imidazole-5-carboxylate group.	 Chemical structure of compound C-241. It features a central chain of repeating amide units, including a 4-fluorophenyl group, a 4-ethanesulfonylphenyl group, and a 4-(4-fluorophenyl)-2-methyl-1H-imidazole-5-carboxylate group. The chain is terminated by a 4-(4-fluorophenyl)-2-methyl-1H-imidazole-5-carboxylate group and a 4-(4-fluorophenyl)-2-methyl-1H-imidazole-5-carboxylate group.
C-239	C-240	C-241

 Chemical structure of C-242: A complex molecule featuring a central polyether chain (poly(2-oxa-1,3-bis(4-oxo-4H-pyrimidin-2-yl)propane)) linked to various functional groups. On the left, there is a cyclohexyl group and a pyrazole ring. On the right, there is a pyrazole ring and a pyridine ring. The molecule also contains a sulfonamide group and a chlorine atom.	 Chemical structure of C-243: A complex molecule featuring a central polyether chain (poly(2-oxa-1,3-bis(4-oxo-4H-pyrimidin-2-yl)propane)) linked to various functional groups. On the left, there is a cyclohexyl group and a pyrazole ring. On the right, there is a pyrazole ring and a pyridine ring. The molecule also contains a sulfonamide group and a chlorine atom.	 Chemical structure of C-244: A complex molecule featuring a central polyether chain (poly(2-oxa-1,3-bis(4-oxo-4H-pyrimidin-2-yl)propane)) linked to various functional groups. On the left, there is a cyclohexyl group and a pyrazole ring. On the right, there is a pyrazole ring and a pyridine ring. The molecule also contains a sulfonamide group and a chlorine atom.
C-242	C-243	C-244

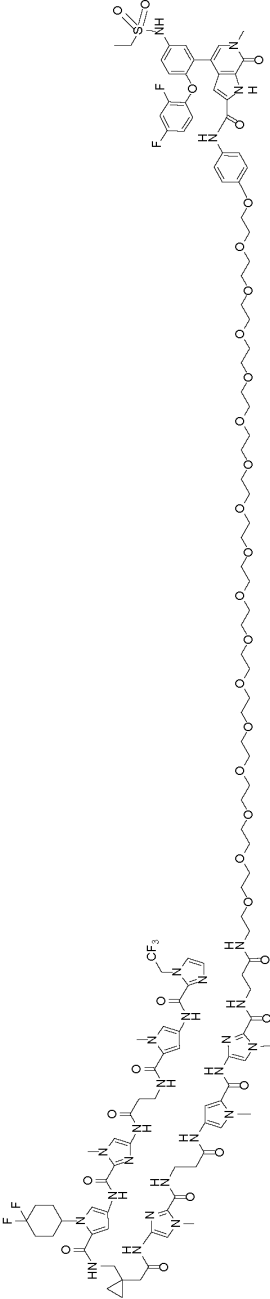
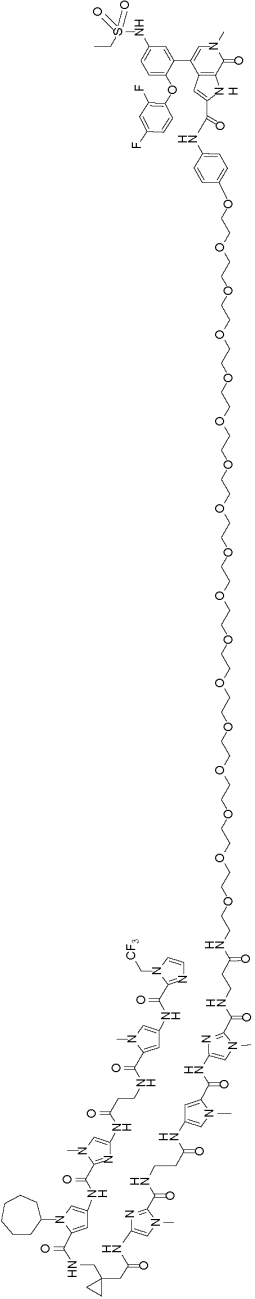
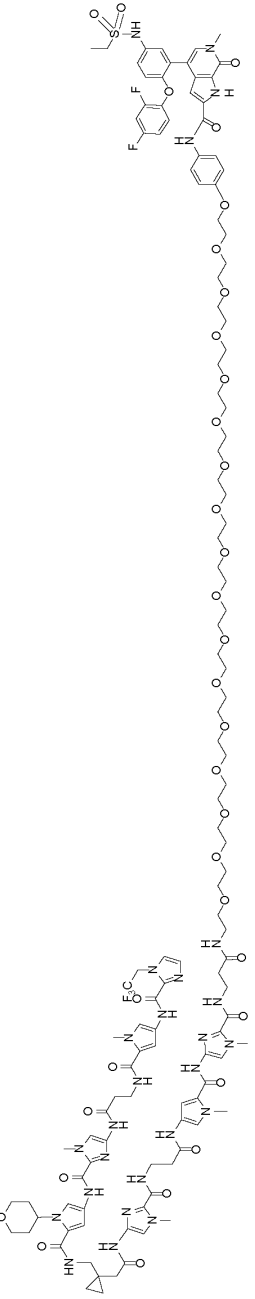
 Chemical structure of compound C-245. It features a complex polycyclic aromatic system with multiple amide and ester linkages. A long, flexible polyether chain is attached to the structure via an amide bond. The molecule also contains a trifluoromethyl group and a sulfonamide moiety.	 Chemical structure of compound C-246. It is similar to C-245 but includes a cyclohexyl group and a different arrangement of the polyether chain. The structure also features a trifluoromethyl group and a sulfonamide moiety.	 Chemical structure of compound C-247. It is similar to C-245 but includes a cyclopropyl group and a different arrangement of the polyether chain. The structure also features a trifluoromethyl group and a sulfonamide moiety.
C-245	C-246	C-247

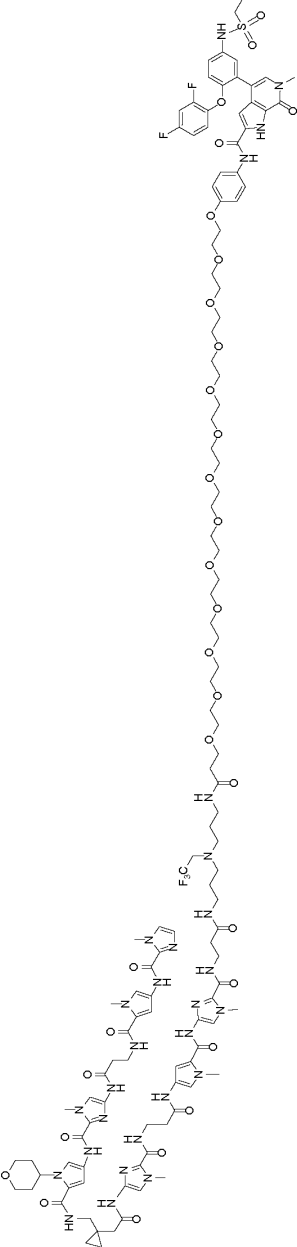
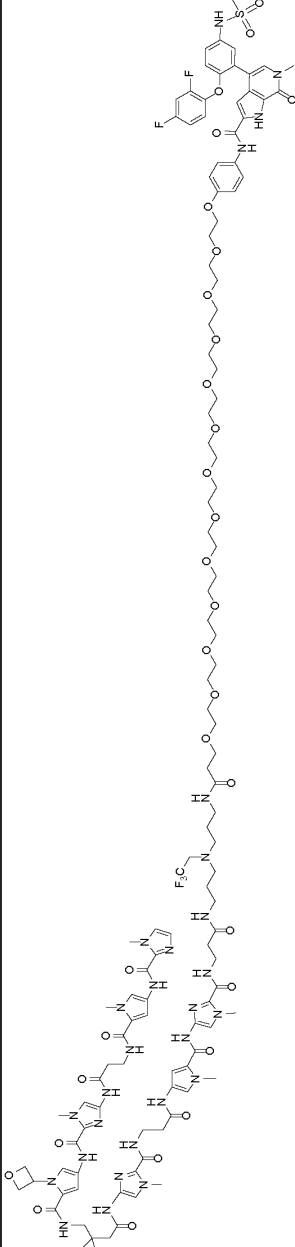
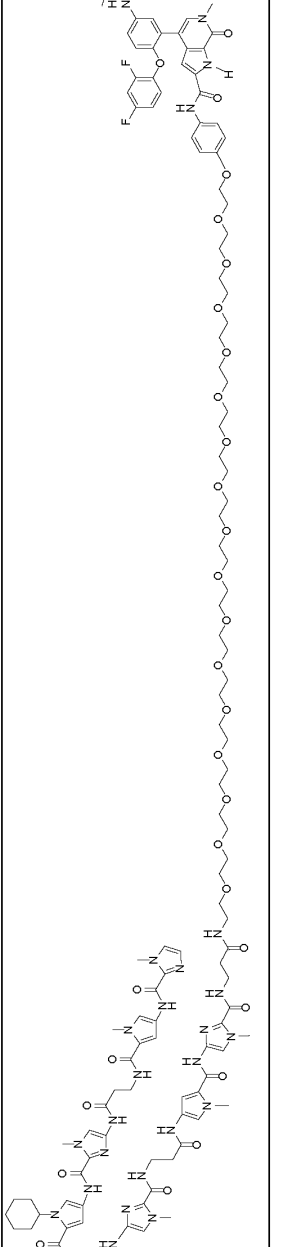
 Chemical structure of compound C-248. It features a complex polycyclic aromatic system with a fluorine substituent, a sulfonamide group, and a long polyether chain. The structure is terminated by a trifluoromethyl group and a cyclopropylmethyl group.	 Chemical structure of compound C-249. It is similar to C-248 but with a different polycyclic aromatic system, featuring a cyclopropylmethyl group and a trifluoromethyl group.	 Chemical structure of compound C-250. It is similar to C-248 but with a different polycyclic aromatic system, featuring a cyclopropylmethyl group and a trifluoromethyl group.
C-248	C-249	C-250

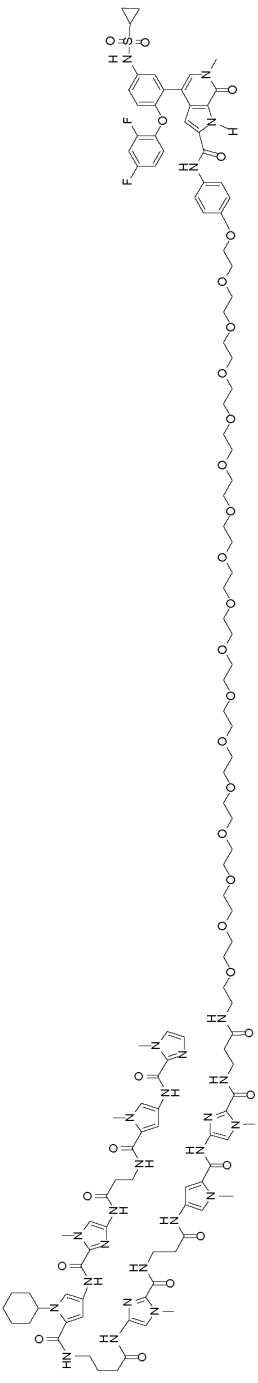
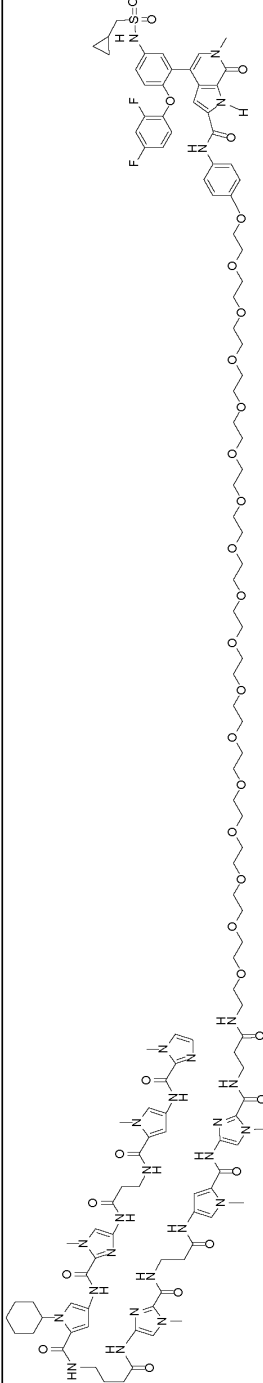
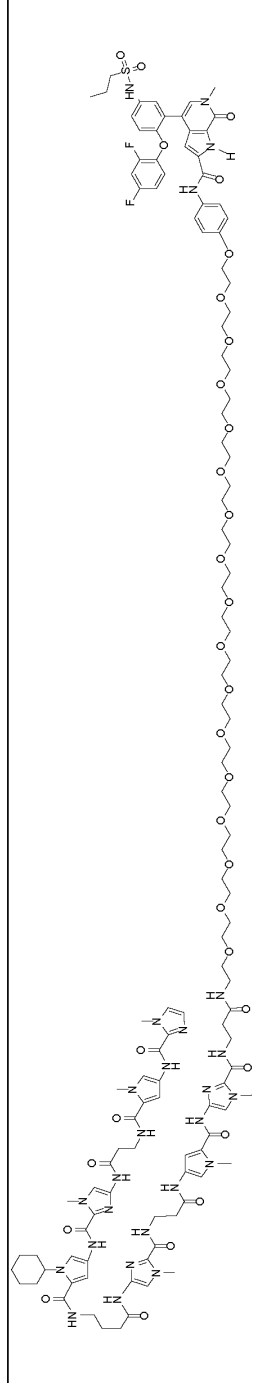


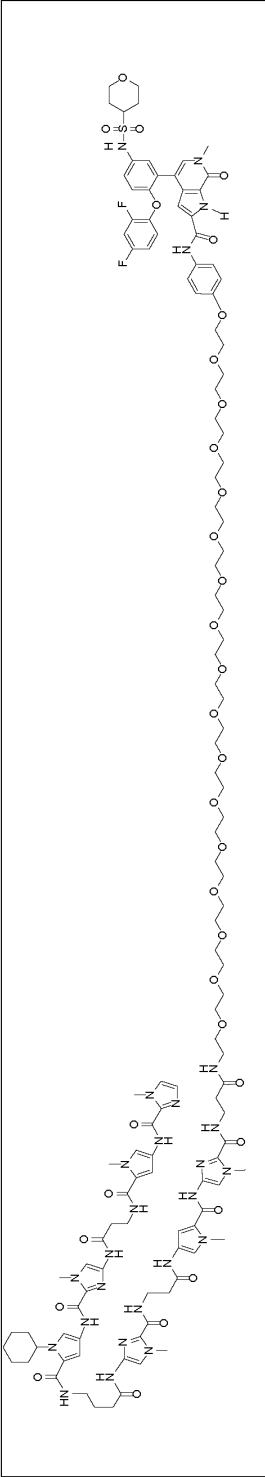
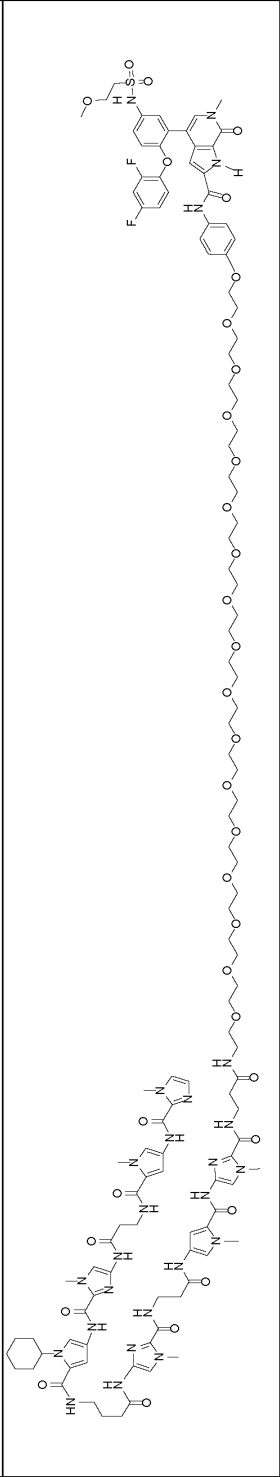
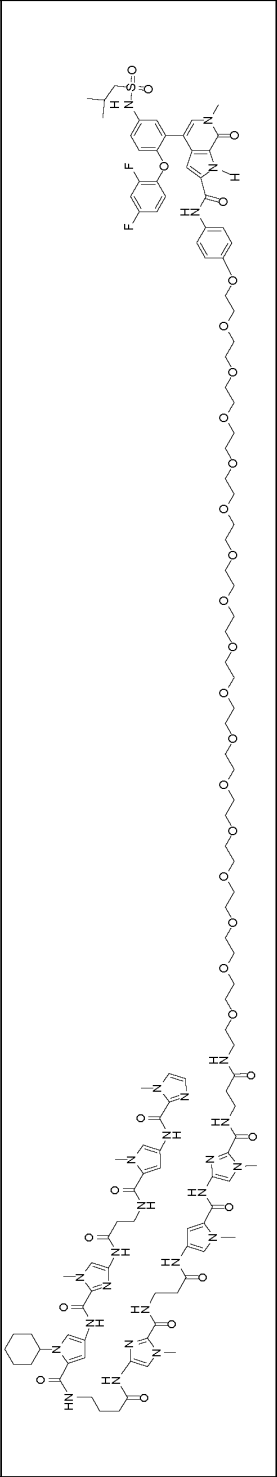
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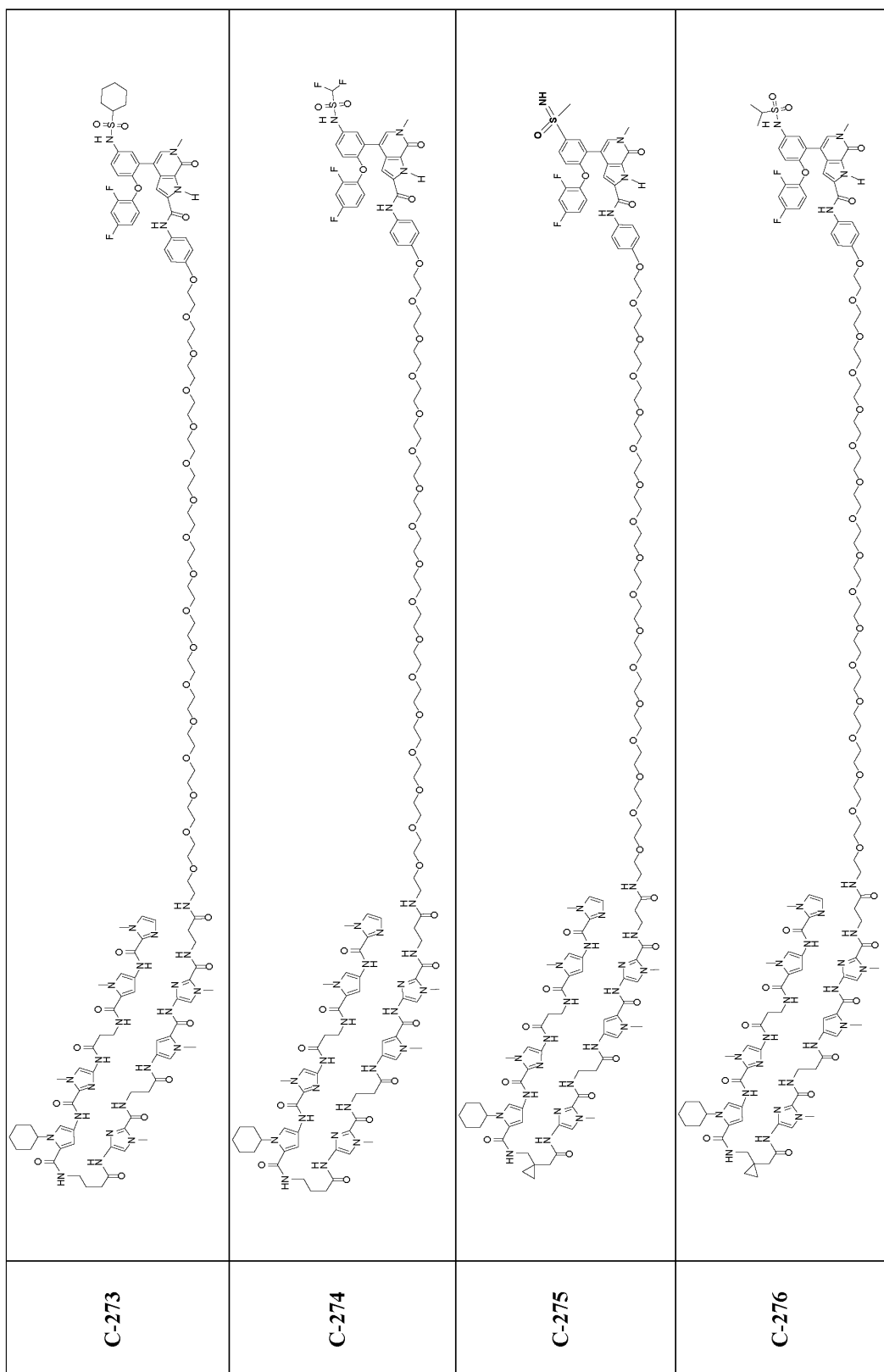
C-258	
C-259	
C-260	

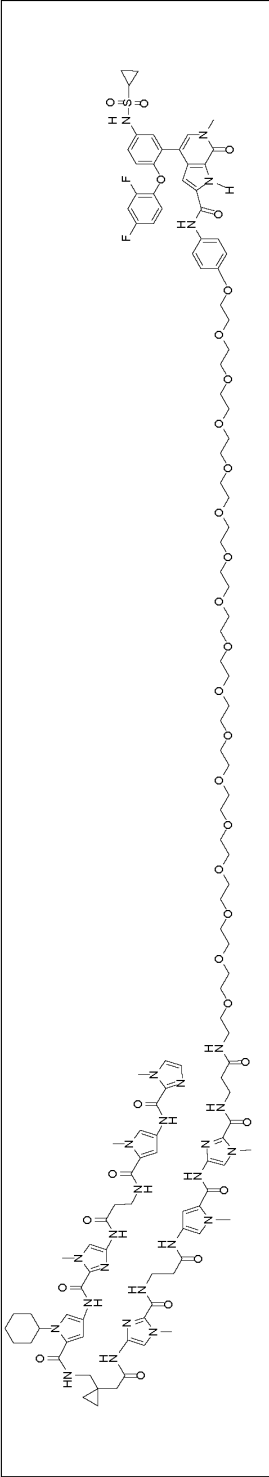
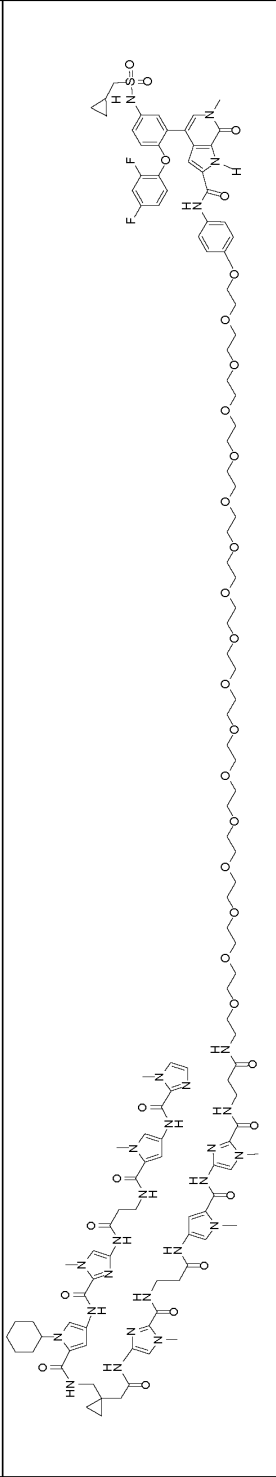
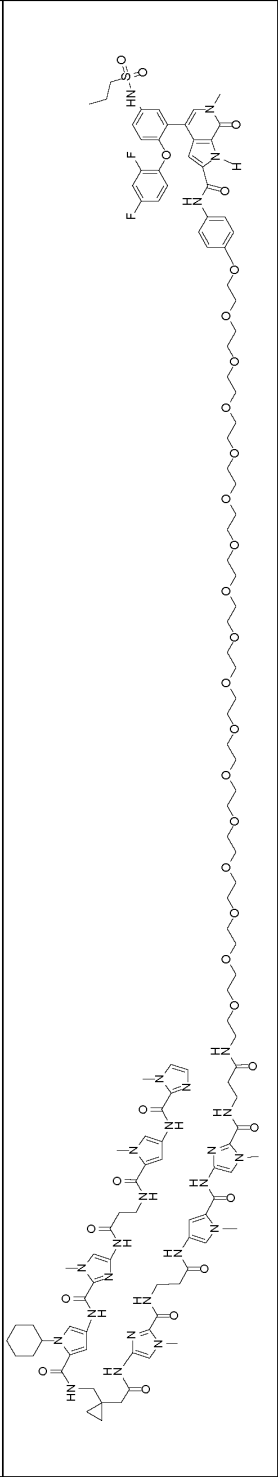
 Chemical structure of C-261: A complex molecule featuring a central pyrazole core substituted with a 4-(2,4-difluorophenoxy)phenyl group, a 4-(2,4-difluorophenoxy)phenyl group, and a 4-(2,4-difluorophenoxy)phenyl group. The molecule also includes a 4-(2,4-difluorophenoxy)phenyl group and a 4-(2,4-difluorophenoxy)phenyl group.	 Chemical structure of C-262: A complex molecule featuring a central pyrazole core substituted with a 4-(2,4-difluorophenoxy)phenyl group, a 4-(2,4-difluorophenoxy)phenyl group, and a 4-(2,4-difluorophenoxy)phenyl group. The molecule also includes a 4-(2,4-difluorophenoxy)phenyl group and a 4-(2,4-difluorophenoxy)phenyl group.	 Chemical structure of C-263: A complex molecule featuring a central pyrazole core substituted with a 4-(2,4-difluorophenoxy)phenyl group, a 4-(2,4-difluorophenoxy)phenyl group, and a 4-(2,4-difluorophenoxy)phenyl group. The molecule also includes a 4-(2,4-difluorophenoxy)phenyl group and a 4-(2,4-difluorophenoxy)phenyl group.
C-261	C-262	C-263

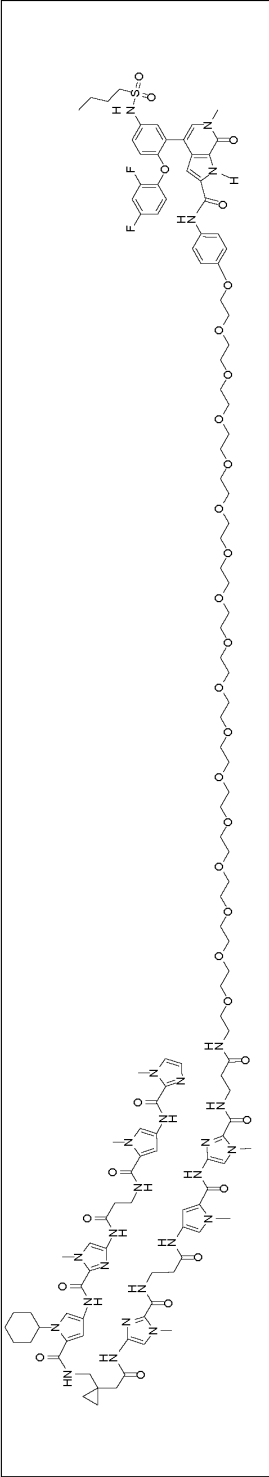
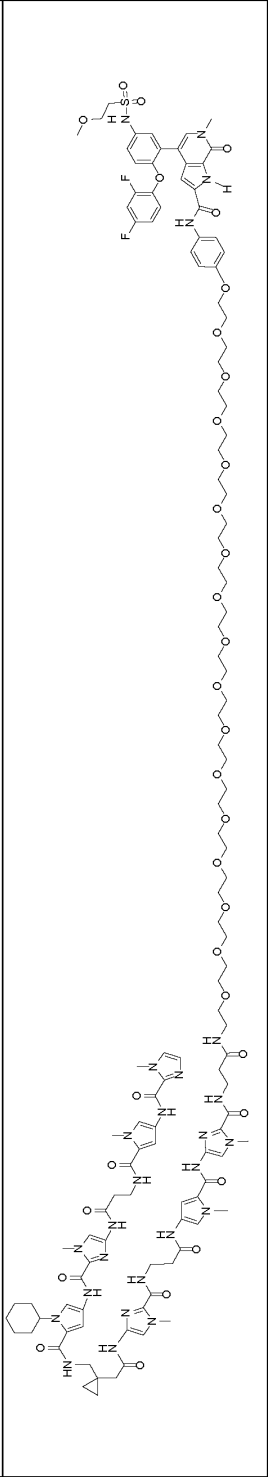
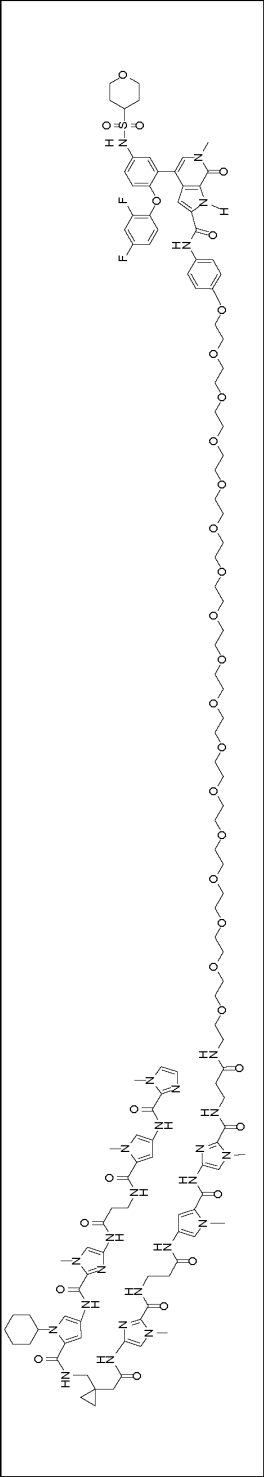
 Chemical structure of compound C-264. It features a complex polycyclic aromatic system with a fluorine substituent, a sulfonamide group, and a long polyether chain. The structure includes a pyridine ring, a pyrazole ring, and a benzimidazole-like core. A long polyether chain (polyoxyethylene) is attached to the structure via an ether linkage. The chain ends in a sulfonamide group. The structure also includes a cyclopropyl group and a morpholine ring.	 Chemical structure of compound C-265. It is similar to C-264 but with a different substitution pattern on the aromatic rings. It features a complex polycyclic aromatic system with a fluorine substituent, a sulfonamide group, and a long polyether chain. The structure includes a pyridine ring, a pyrazole ring, and a benzimidazole-like core. A long polyether chain (polyoxyethylene) is attached to the structure via an ether linkage. The chain ends in a sulfonamide group. The structure also includes a cyclopropyl group and a morpholine ring.	 Chemical structure of compound C-266. It is similar to C-264 but with a different substitution pattern on the aromatic rings. It features a complex polycyclic aromatic system with a fluorine substituent, a sulfonamide group, and a long polyether chain. The structure includes a pyridine ring, a pyrazole ring, and a benzimidazole-like core. A long polyether chain (polyoxyethylene) is attached to the structure via an ether linkage. The chain ends in a sulfonamide group. The structure also includes a cyclopropyl group and a morpholine ring.
C-264	C-265	C-266

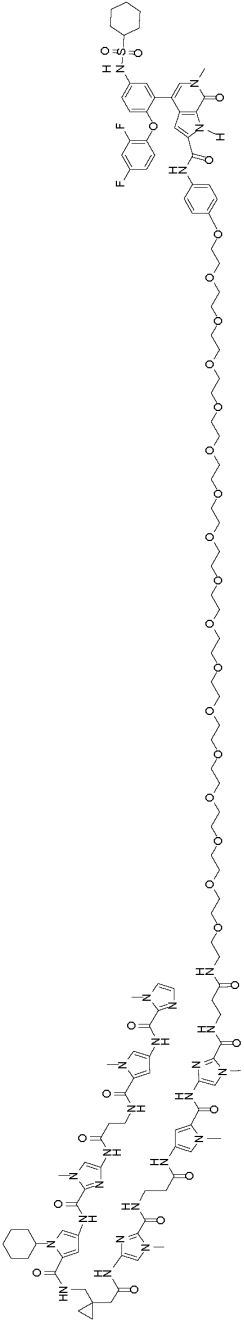
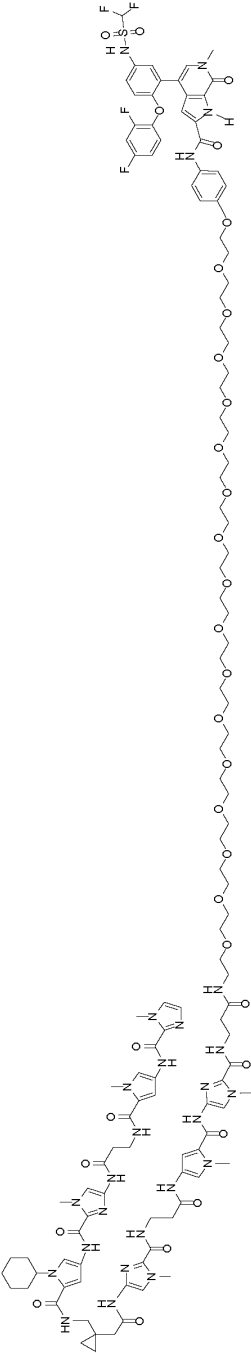
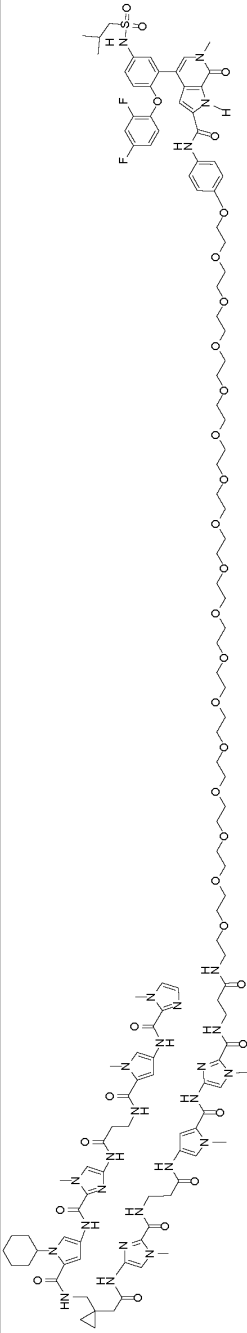
 Chemical structure of compound C-267. It features a central pyrazole ring substituted with a 4-(2,4-difluorophenoxy)phenyl group, a 4-(2,4-difluorophenoxy)phenyl group, and a 4-(2,4-difluorophenoxy)phenyl group. The pyrazole ring is also substituted with a 4-(2,4-difluorophenoxy)phenyl group. The structure includes a long polyether chain (polyoxyethylene) and a terminal sulfonamide group.	C-267
 Chemical structure of compound C-268. It features a central pyrazole ring substituted with a 4-(2,4-difluorophenoxy)phenyl group, a 4-(2,4-difluorophenoxy)phenyl group, and a 4-(2,4-difluorophenoxy)phenyl group. The pyrazole ring is also substituted with a 4-(2,4-difluorophenoxy)phenyl group. The structure includes a long polyether chain (polyoxyethylene) and a terminal sulfonamide group.	C-268
 Chemical structure of compound C-269. It features a central pyrazole ring substituted with a 4-(2,4-difluorophenoxy)phenyl group, a 4-(2,4-difluorophenoxy)phenyl group, and a 4-(2,4-difluorophenoxy)phenyl group. The pyrazole ring is also substituted with a 4-(2,4-difluorophenoxy)phenyl group. The structure includes a long polyether chain (polyoxyethylene) and a terminal sulfonamide group.	C-269

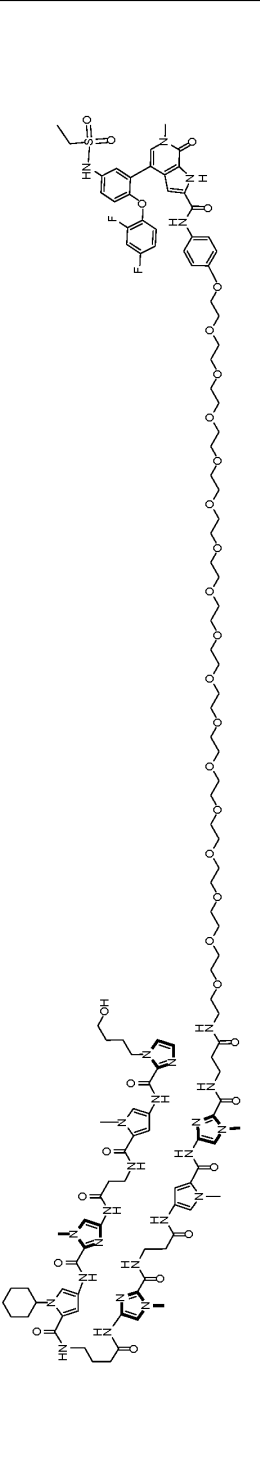
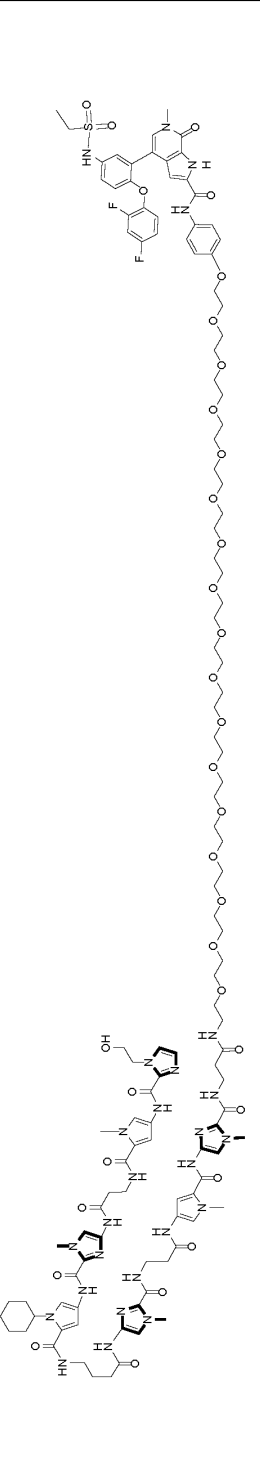
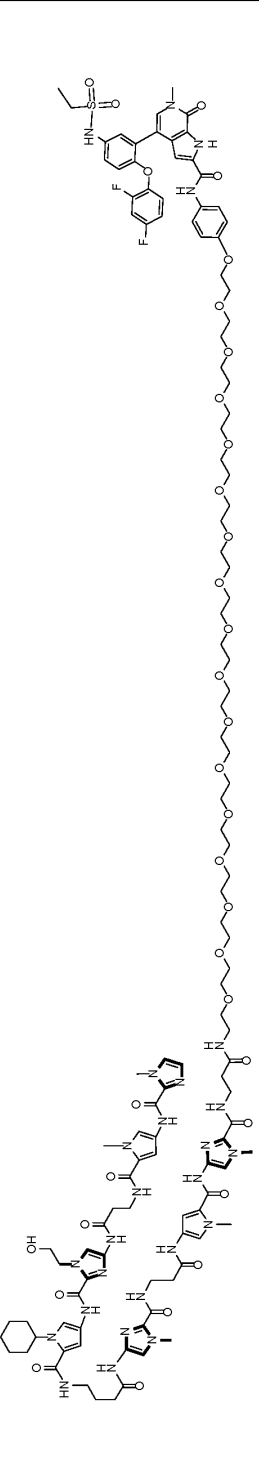
 Chemical structure of compound C-270. It features a central pyrazole ring substituted with a 4-(2,4-difluorophenoxy)phenyl group, a 4-(2,4-difluorophenoxy)phenyl group, and a 4-(2,4-difluorophenoxy)phenyl group. The pyrazole ring is also substituted with a 4-(2,4-difluorophenoxy)phenyl group. The structure includes a long polyether chain (poly(2,2,5-trimethyl-1,3-dioxane-5,7-diyl)) and a sulfonamide group (SO₂NH-). The structure is highly symmetrical and complex.	 Chemical structure of compound C-271. It features a central pyrazole ring substituted with a 4-(2,4-difluorophenoxy)phenyl group, a 4-(2,4-difluorophenoxy)phenyl group, and a 4-(2,4-difluorophenoxy)phenyl group. The pyrazole ring is also substituted with a 4-(2,4-difluorophenoxy)phenyl group. The structure includes a long polyether chain (poly(2,2,5-trimethyl-1,3-dioxane-5,7-diyl)) and a sulfonamide group (SO₂NH-). The structure is highly symmetrical and complex.	 Chemical structure of compound C-272. It features a central pyrazole ring substituted with a 4-(2,4-difluorophenoxy)phenyl group, a 4-(2,4-difluorophenoxy)phenyl group, and a 4-(2,4-difluorophenoxy)phenyl group. The pyrazole ring is also substituted with a 4-(2,4-difluorophenoxy)phenyl group. The structure includes a long polyether chain (poly(2,2,5-trimethyl-1,3-dioxane-5,7-diyl)) and a sulfonamide group (SO₂NH-). The structure is highly symmetrical and complex.
C-270	C-271	C-272

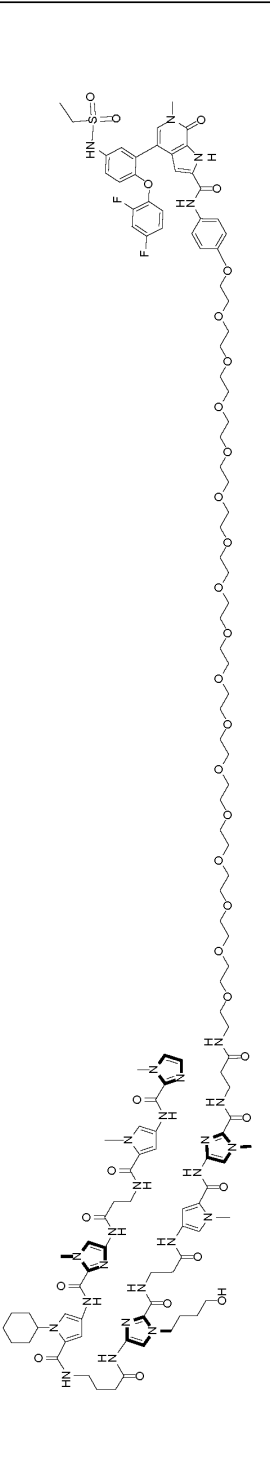
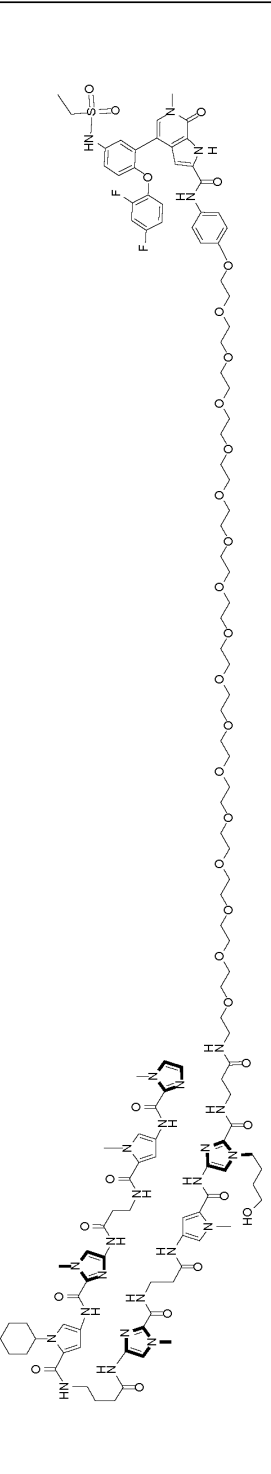
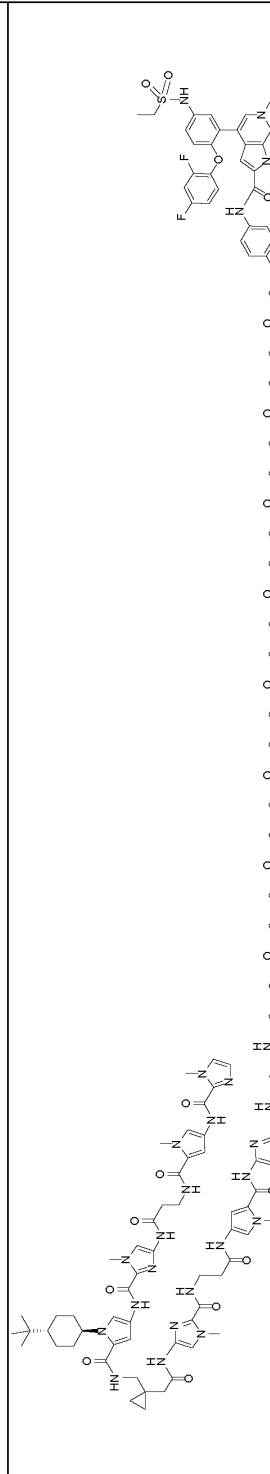


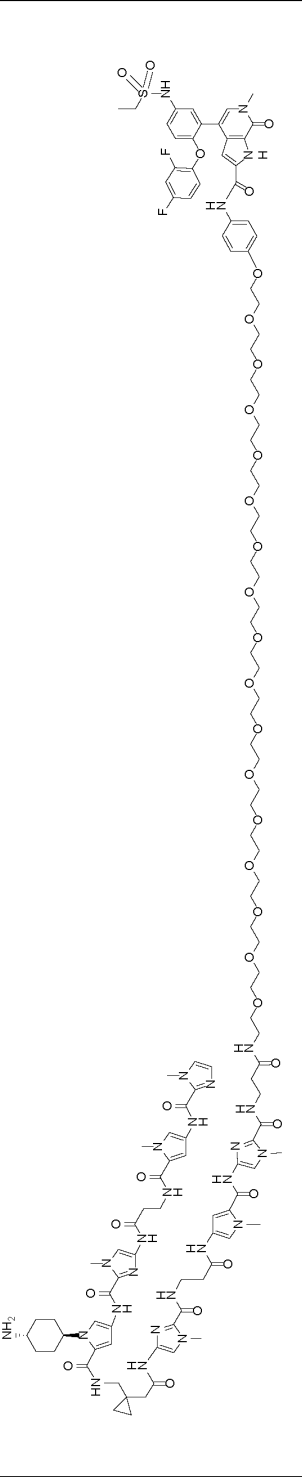
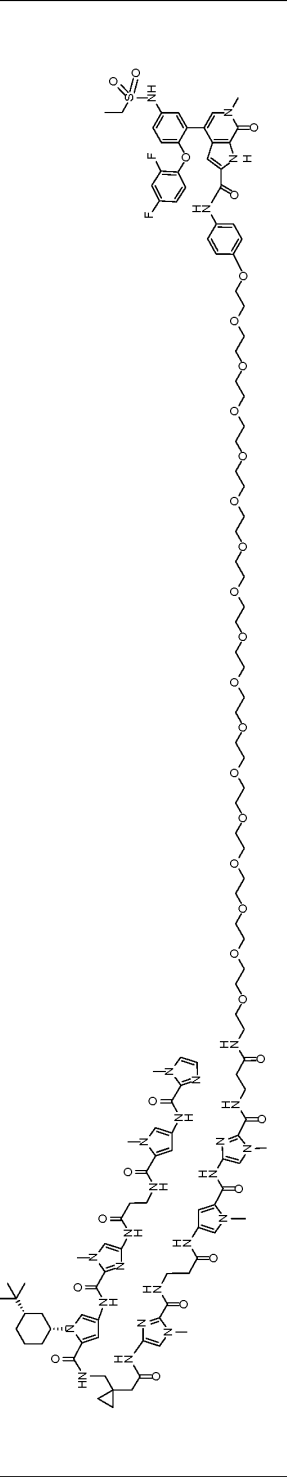
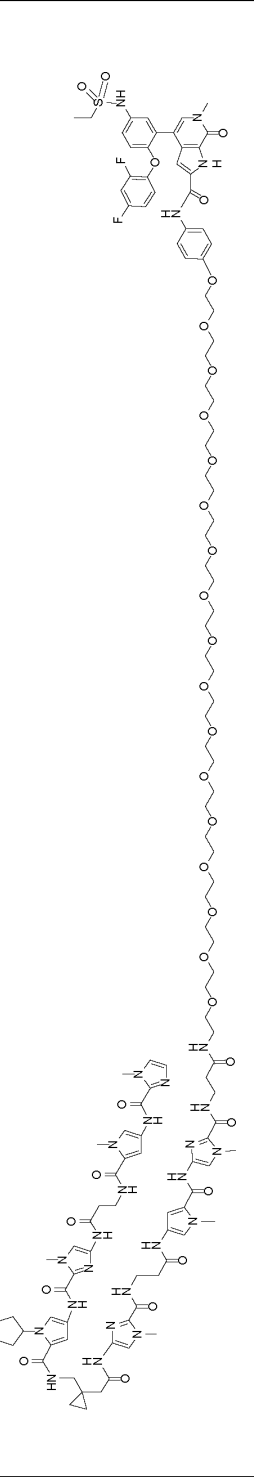
 Chemical structure of compound C-277. It features a complex polycyclic aromatic system with a sulfonamide group (SO₂NH-) and a long, flexible polyether chain (-(OCH₂)₁₂-) attached to the aromatic ring. The structure also includes a cyclopropylmethyl group and a pyridine ring.	 Chemical structure of compound C-278. It is similar to C-277 but features a different aromatic substitution pattern, including a fluorine atom and a different sulfonamide group (SO₂NH-). The polyether chain and other functional groups are also present.	 Chemical structure of compound C-279. It is similar to C-277 but features a different aromatic substitution pattern, including a fluorine atom and a different sulfonamide group (SO₂NH-). The polyether chain and other functional groups are also present.
C-277	C-278	C-279

 Chemical structure of C-280: A complex molecule featuring a central pyrazole core substituted with a 2,4-difluorophenyl group, a 4-(2-ethanesulfonylphenyl) group, and a 4-(2-ethanesulfonylphenyl) group. The molecule is linked via a long, flexible polyether chain to a complex polycyclic aromatic system at the bottom, which includes a cyclohexyl group and a cyclopropyl group.	 Chemical structure of C-281: A complex molecule featuring a central pyrazole core substituted with a 2,4-difluorophenyl group, a 4-(2-ethanesulfonylphenyl) group, and a 4-(2-ethanesulfonylphenyl) group. The molecule is linked via a long, flexible polyether chain to a complex polycyclic aromatic system at the bottom, which includes a cyclohexyl group and a cyclopropyl group.	 Chemical structure of C-282: A complex molecule featuring a central pyrazole core substituted with a 2,4-difluorophenyl group, a 4-(2-ethanesulfonylphenyl) group, and a 4-(2-ethanesulfonylphenyl) group. The molecule is linked via a long, flexible polyether chain to a complex polycyclic aromatic system at the bottom, which includes a cyclohexyl group and a cyclopropyl group.
C-280	C-281	C-282

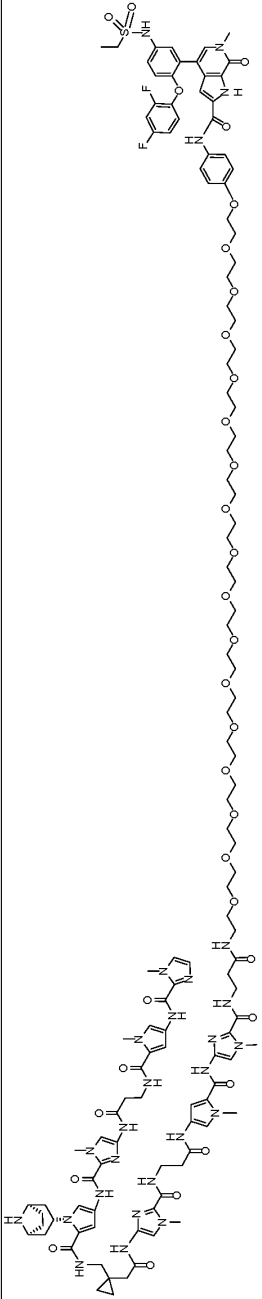
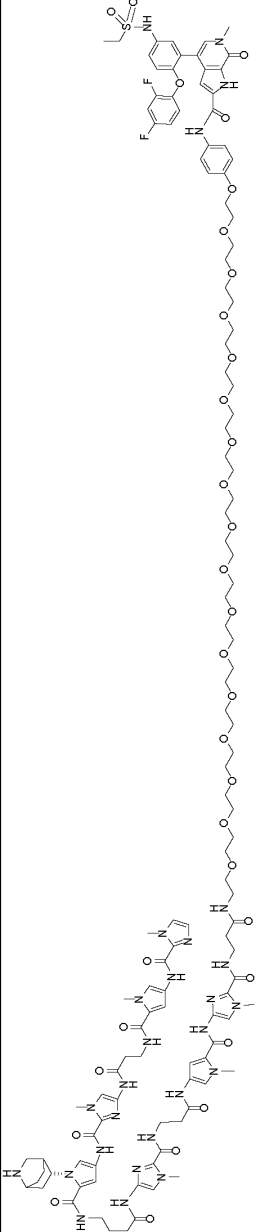
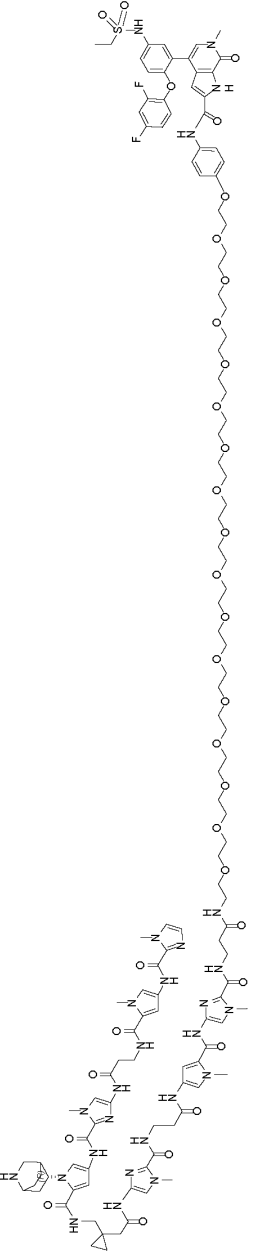
		
C-283	C-284	C-285

 Chemical structure of C-286: A complex molecule featuring a central pyrazole core. It is substituted with a 4-ethanesulfonylphenyl group, a 4-fluorophenyl group, and a 4-(4-ethoxyphenoxy)phenyl group. The pyrazole ring is also substituted with a 4-(4-ethoxyphenoxy)phenyl group and a 4-(4-ethoxyphenoxy)phenyl group. The molecule is linked via a long, flexible polyether chain to a complex polycyclic aromatic system.	 Chemical structure of C-287: A complex molecule featuring a central pyrazole core. It is substituted with a 4-ethanesulfonylphenyl group, a 4-fluorophenyl group, and a 4-(4-ethoxyphenoxy)phenyl group. The pyrazole ring is also substituted with a 4-(4-ethoxyphenoxy)phenyl group and a 4-(4-ethoxyphenoxy)phenyl group. The molecule is linked via a long, flexible polyether chain to a complex polycyclic aromatic system.	 Chemical structure of C-288: A complex molecule featuring a central pyrazole core. It is substituted with a 4-ethanesulfonylphenyl group, a 4-fluorophenyl group, and a 4-(4-ethoxyphenoxy)phenyl group. The pyrazole ring is also substituted with a 4-(4-ethoxyphenoxy)phenyl group and a 4-(4-ethoxyphenoxy)phenyl group. The molecule is linked via a long, flexible polyether chain to a complex polycyclic aromatic system.
C-286	C-287	C-288

 Chemical structure of C-289: A complex molecule featuring a central pyrazole core. It is substituted with a 4-ethanesulfonylphenyl group, a 4-fluorophenyl group, and a 4-(4-ethoxyphenoxy)phenyl group. The pyrazole ring is also substituted with a methyl group and a 4-(4-ethoxyphenoxy)phenyl group. The molecule is linked via a long, flexible polyether chain to a complex polycyclic aromatic system.	 Chemical structure of C-290: A complex molecule featuring a central pyrazole core. It is substituted with a 4-ethanesulfonylphenyl group, a 4-fluorophenyl group, and a 4-(4-ethoxyphenoxy)phenyl group. The pyrazole ring is also substituted with a methyl group and a 4-(4-ethoxyphenoxy)phenyl group. The molecule is linked via a long, flexible polyether chain to a complex polycyclic aromatic system.	 Chemical structure of C-291: A complex molecule featuring a central pyrazole core. It is substituted with a 4-ethanesulfonylphenyl group, a 4-fluorophenyl group, and a 4-(4-ethoxyphenoxy)phenyl group. The pyrazole ring is also substituted with a methyl group and a 4-(4-ethoxyphenoxy)phenyl group. The molecule is linked via a long, flexible polyether chain to a complex polycyclic aromatic system.
C-289	C-290	C-291

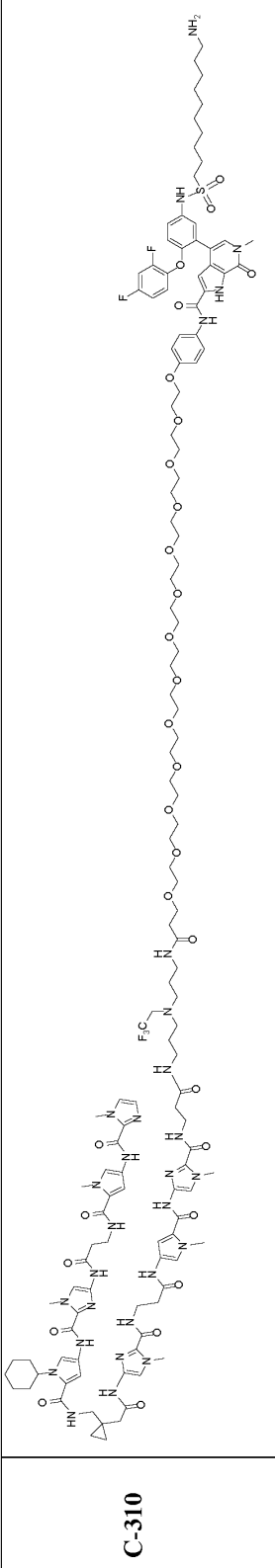
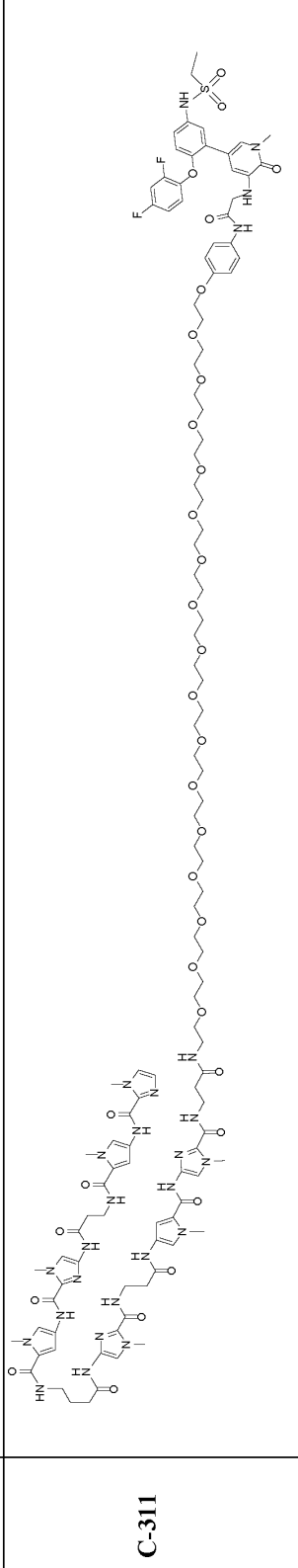
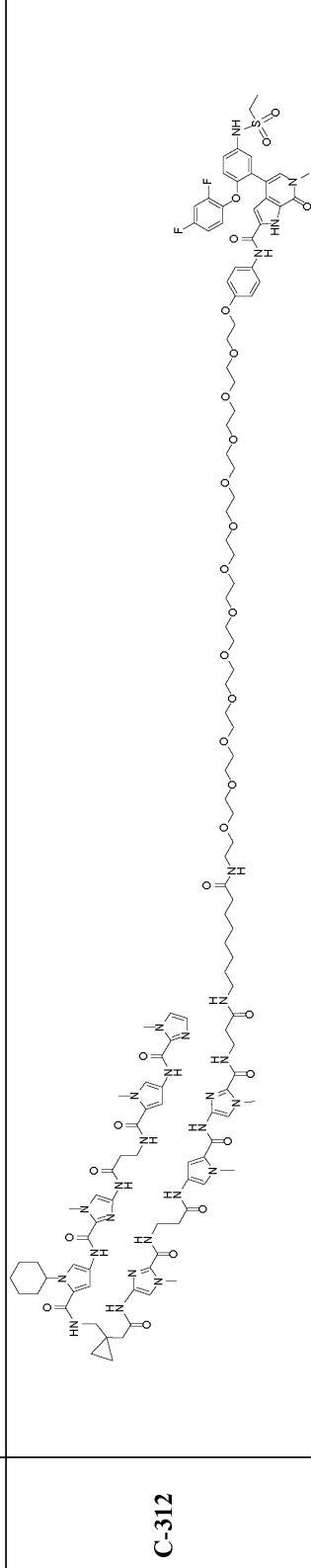
 Chemical structure of C-292: A complex molecule featuring a central pyrazole core substituted with a 4-(2,4-difluorophenoxy)phenyl group, a 4-(2,4-difluorophenoxy)phenyl group, and a 4-(2,4-difluorophenoxy)phenyl group. The molecule is linked via a long, flexible polyether chain to a complex polycyclic aromatic system, which includes a pyrazole ring and a cyclohexyl group.	 Chemical structure of C-293: A complex molecule featuring a central pyrazole core substituted with a 4-(2,4-difluorophenoxy)phenyl group, a 4-(2,4-difluorophenoxy)phenyl group, and a 4-(2,4-difluorophenoxy)phenyl group. The molecule is linked via a long, flexible polyether chain to a complex polycyclic aromatic system, which includes a pyrazole ring and a cyclohexyl group.	 Chemical structure of C-294: A complex molecule featuring a central pyrazole core substituted with a 4-(2,4-difluorophenoxy)phenyl group, a 4-(2,4-difluorophenoxy)phenyl group, and a 4-(2,4-difluorophenoxy)phenyl group. The molecule is linked via a long, flexible polyether chain to a complex polycyclic aromatic system, which includes a pyrazole ring and a cyclohexyl group.
C-292	C-293	C-294

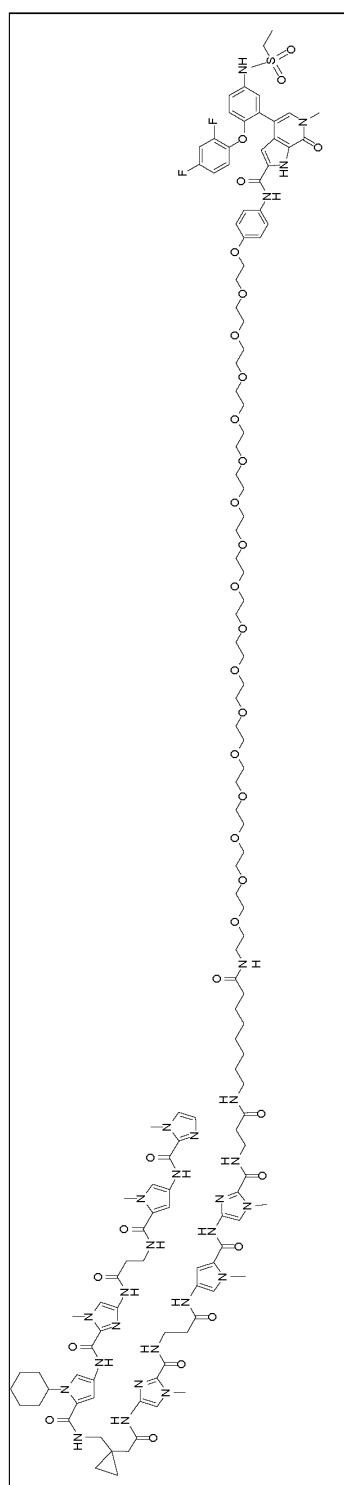
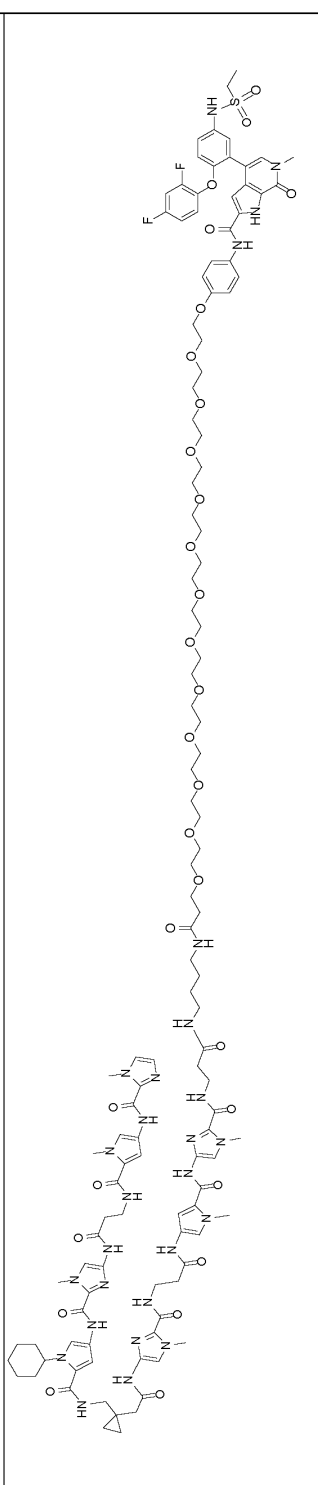
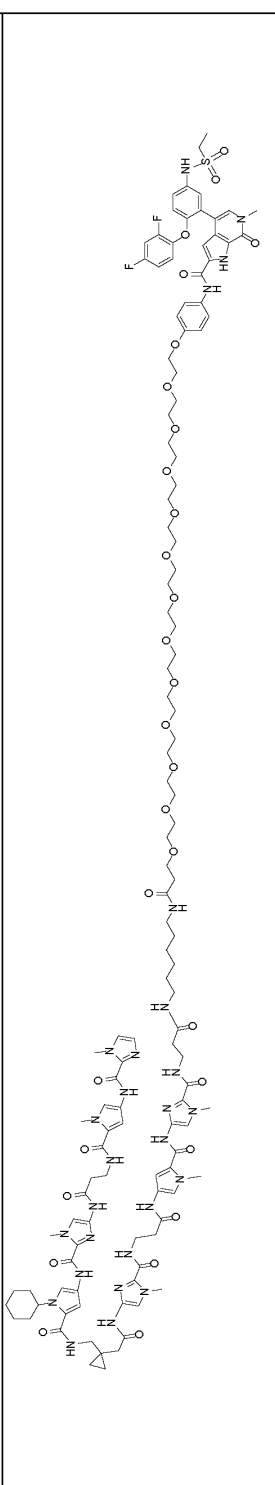


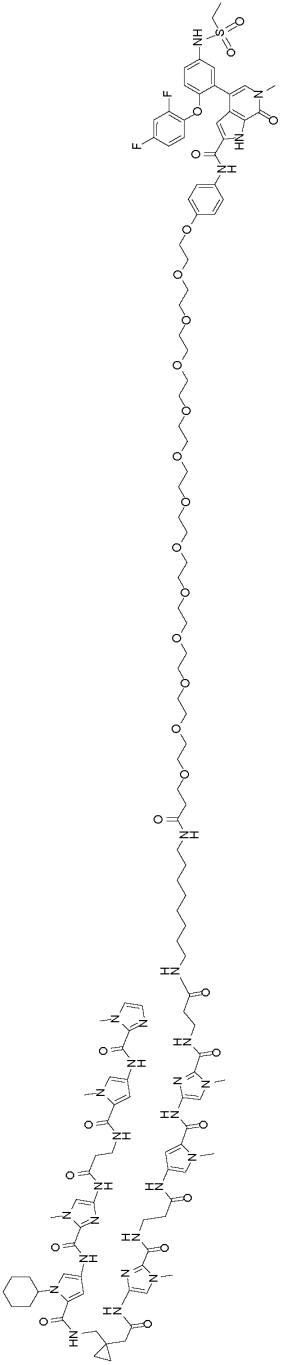
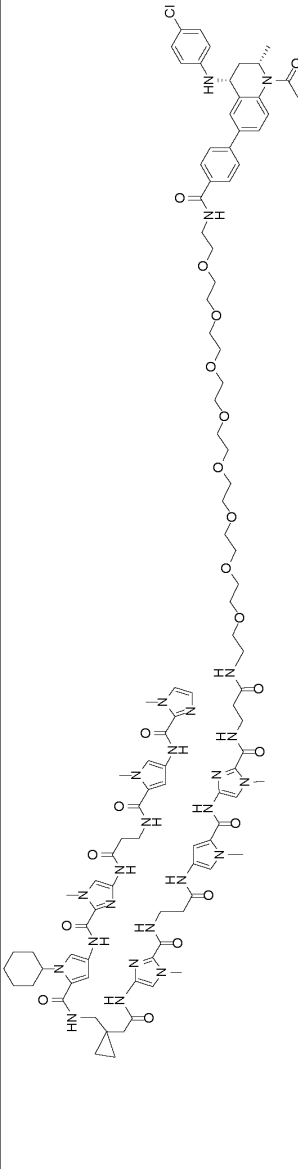
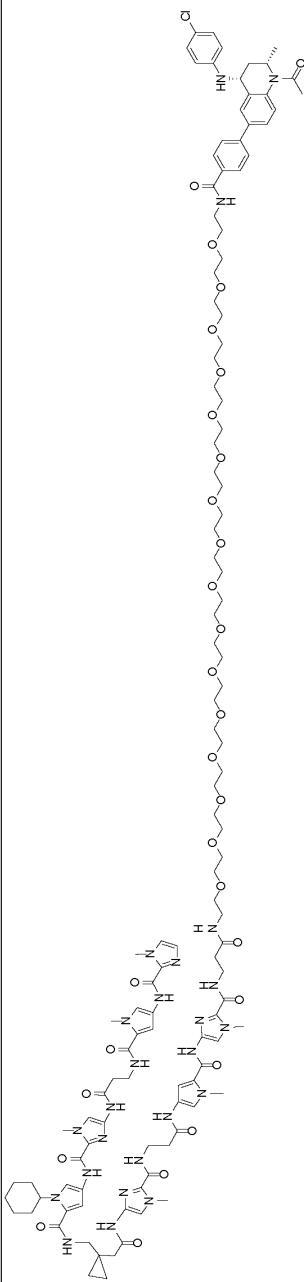
 Chemical structure of C-298: A complex molecule featuring a central pyridine ring substituted with a 2-methyl-4-(2,4-difluorophenoxy)phenyl group, a 2-methyl-4-(2,4-difluorophenoxy)phenyl group, and a 2-methyl-4-(2,4-difluorophenoxy)phenyl group. The molecule is linked via a long, flexible polyether chain to a complex polycyclic aromatic system.	 Chemical structure of C-299: A complex molecule featuring a central pyridine ring substituted with a 2-methyl-4-(2,4-difluorophenoxy)phenyl group, a 2-methyl-4-(2,4-difluorophenoxy)phenyl group, and a 2-methyl-4-(2,4-difluorophenoxy)phenyl group. The molecule is linked via a long, flexible polyether chain to a complex polycyclic aromatic system.	 Chemical structure of C-300: A complex molecule featuring a central pyridine ring substituted with a 2-methyl-4-(2,4-difluorophenoxy)phenyl group, a 2-methyl-4-(2,4-difluorophenoxy)phenyl group, and a 2-methyl-4-(2,4-difluorophenoxy)phenyl group. The molecule is linked via a long, flexible polyether chain to a complex polycyclic aromatic system.
C-298	C-299	C-300

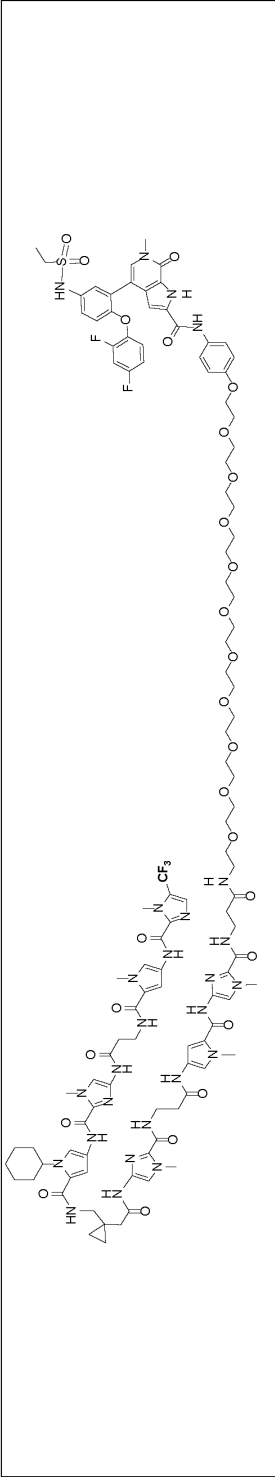
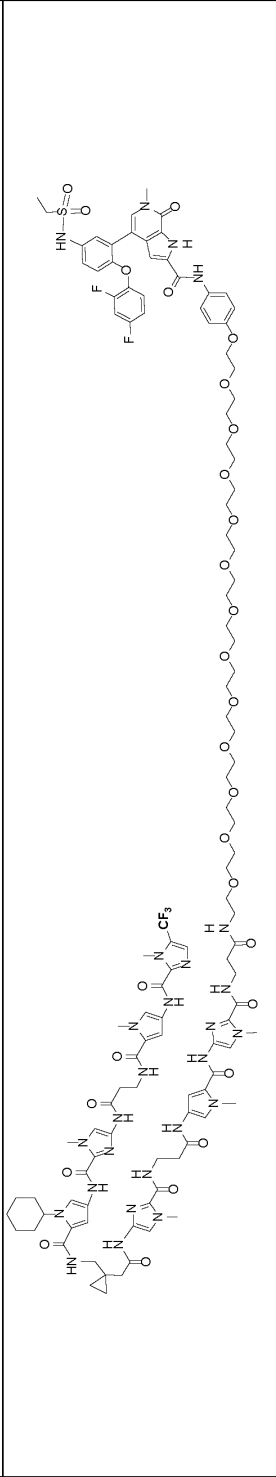
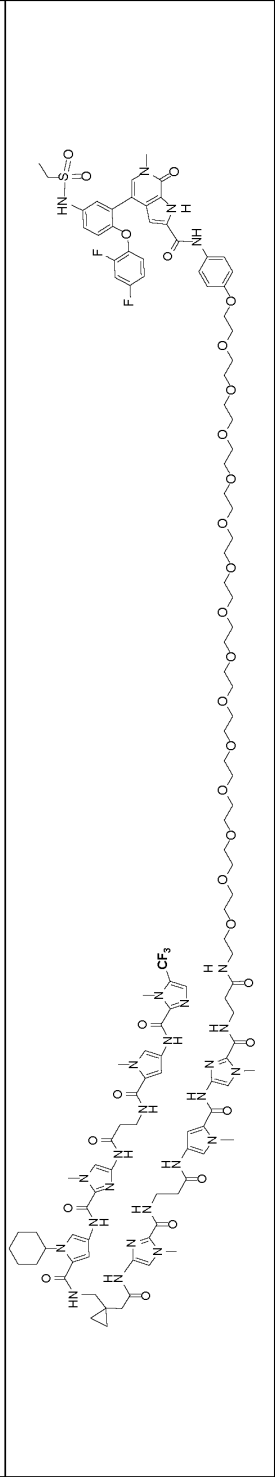
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C-302	
C-303	

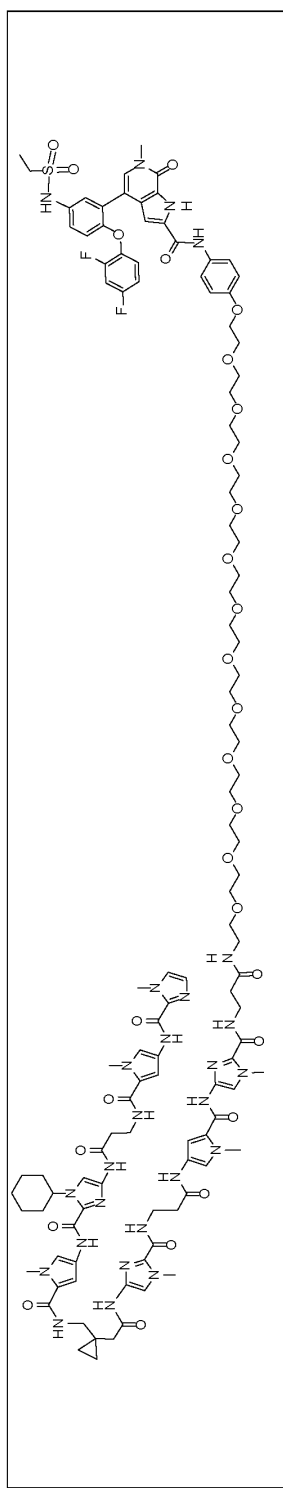
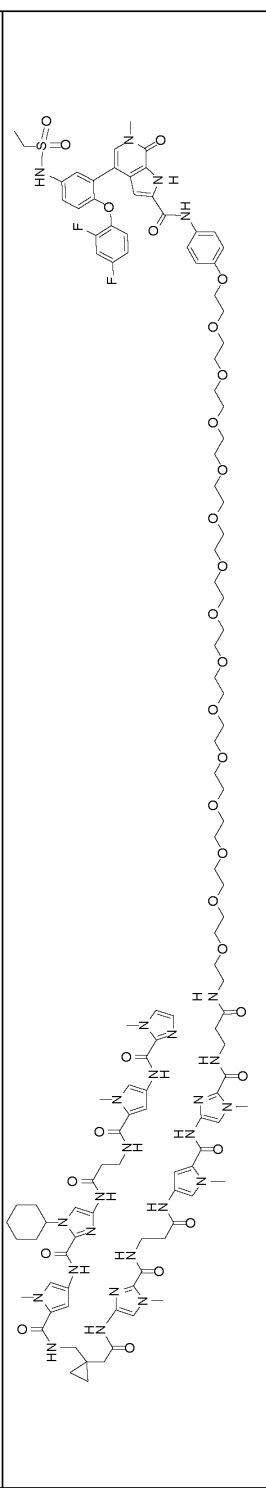
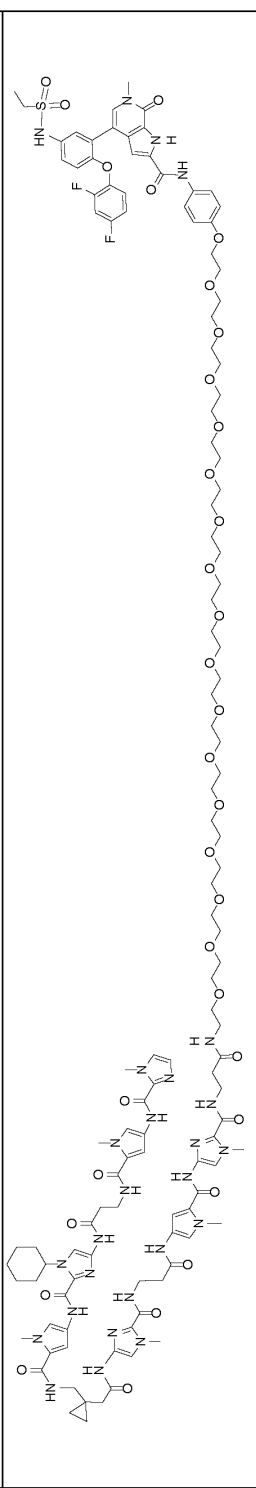
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C-308	
C-309	

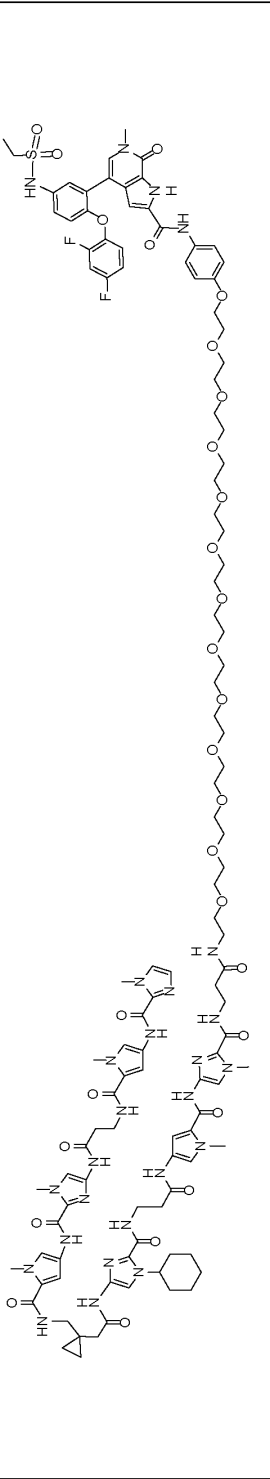
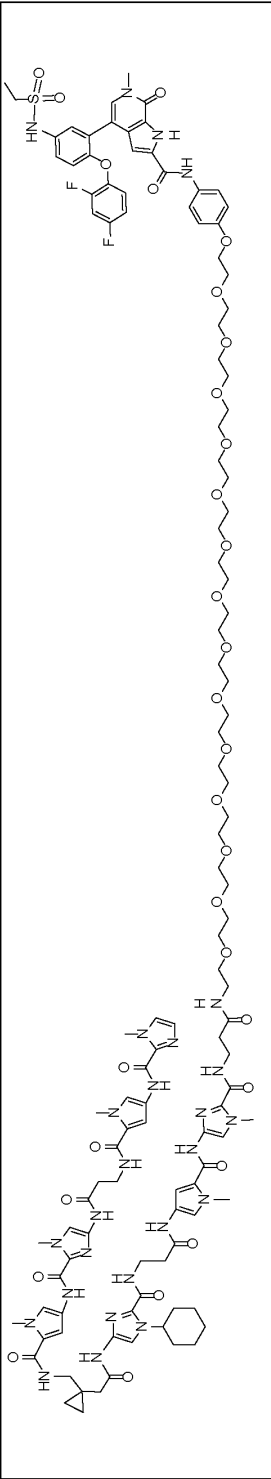
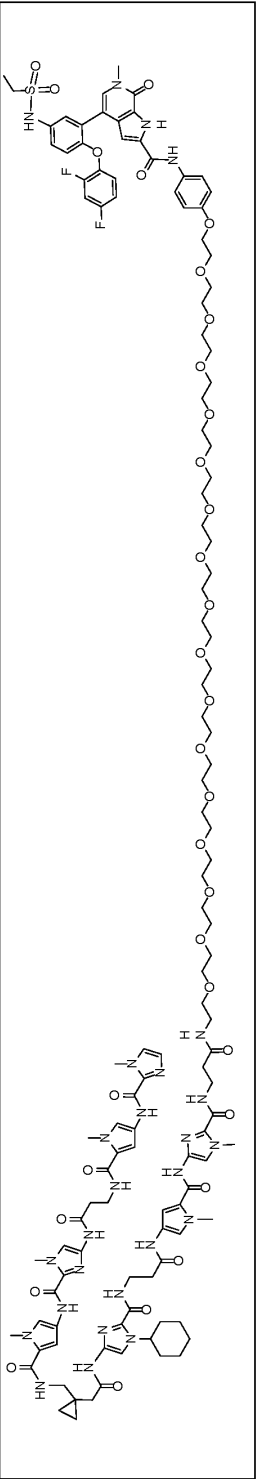
C-310 	C-311 	C-312 
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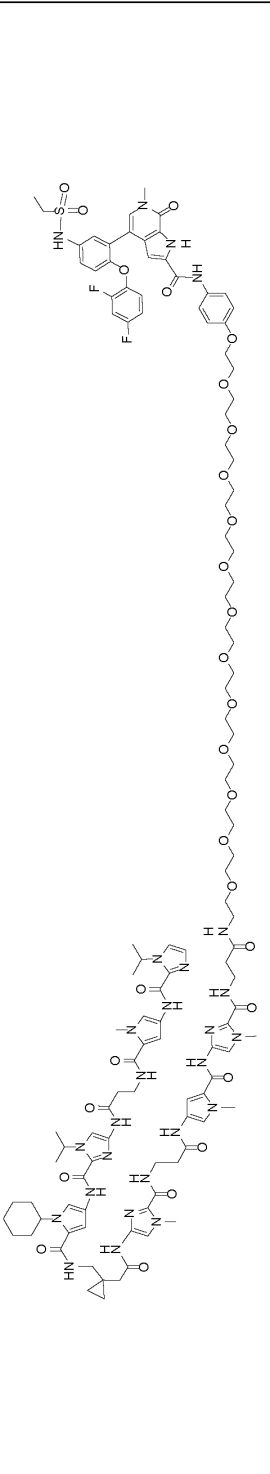
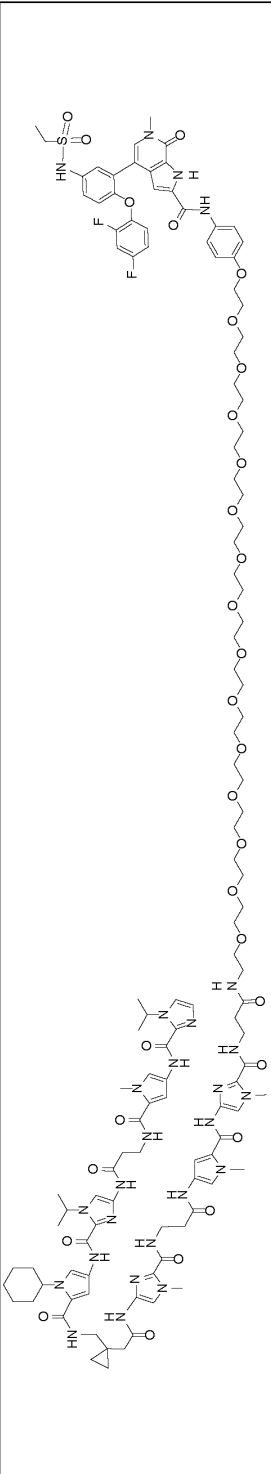
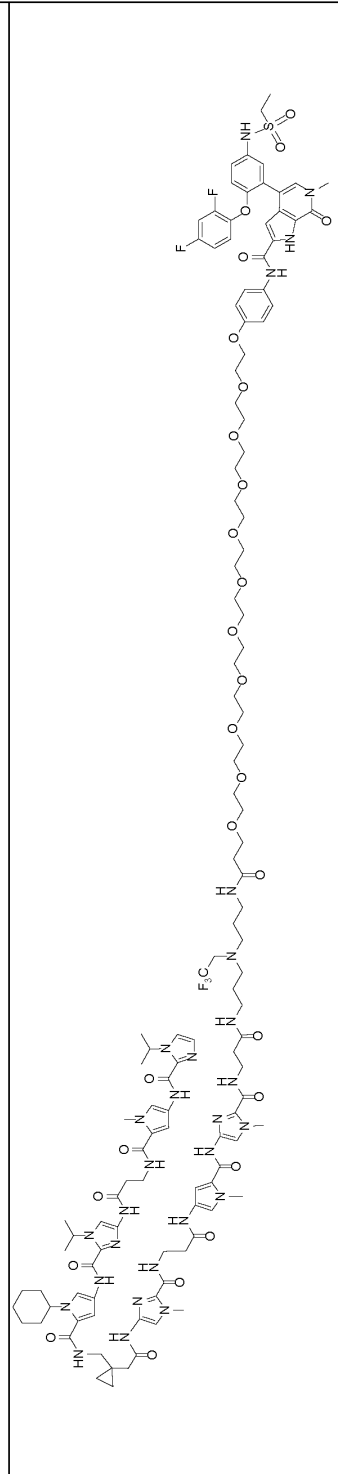
 C-313	 C-314	 C-315
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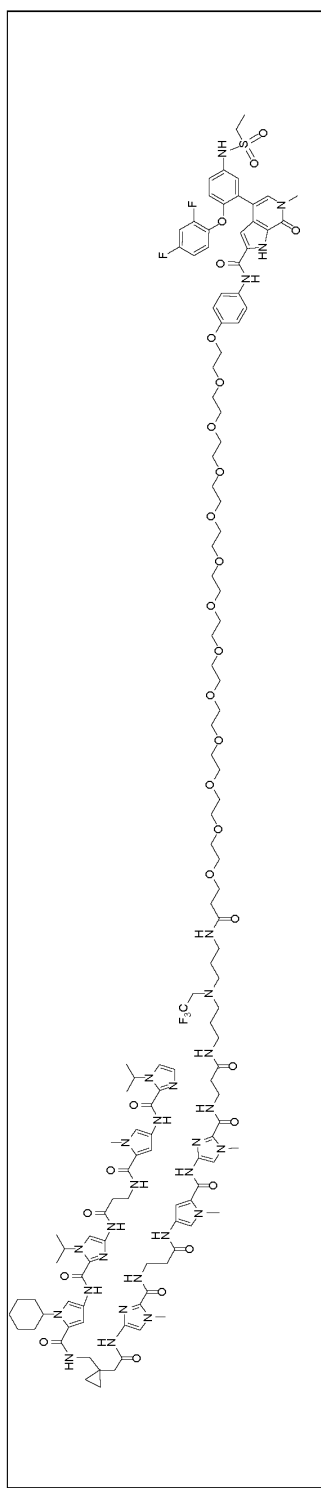
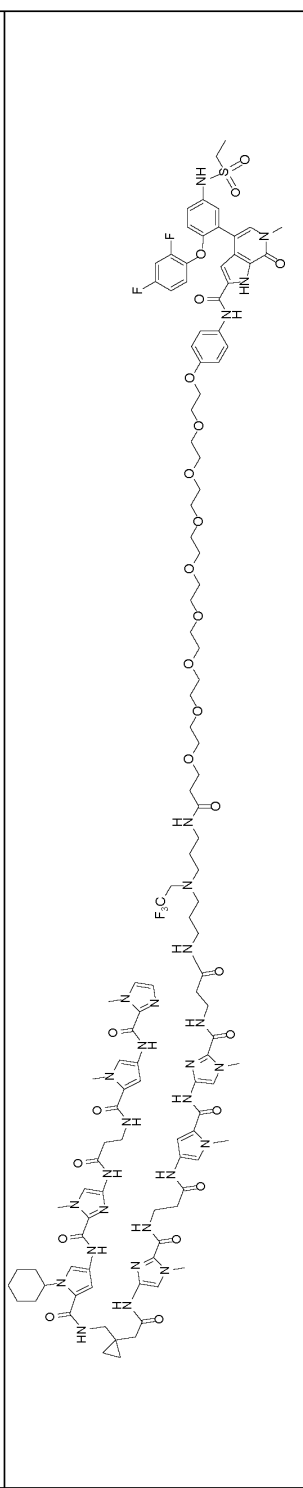
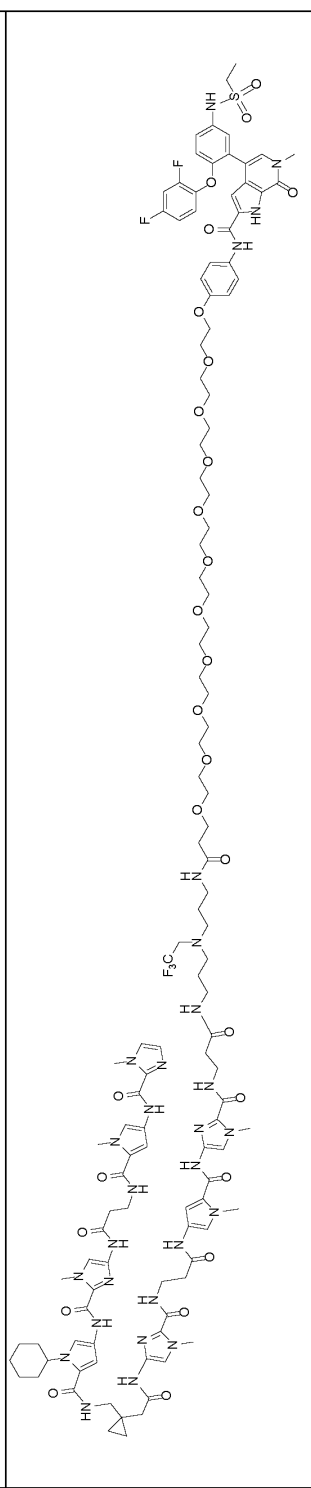
 Chemical structure of C-316: A complex molecule featuring a central polyether chain (a series of 10 oxygen atoms linked by 11 methylene groups) connected to various functional groups. At one end, there is a 4-fluorophenyl group and a 4-methyl-5-sulfamoylphenyl group. At the other end, there is a 4-((4-chlorophenyl)amino)phenyl group. The molecule also contains several amide and ester linkages, and a cyclohexyl group.	 Chemical structure of C-317: A complex molecule featuring a central polyether chain (a series of 10 oxygen atoms linked by 11 methylene groups) connected to various functional groups. At one end, there is a 4-chlorophenyl group and a 4-methyl-5-sulfamoylphenyl group. At the other end, there is a 4-((4-chlorophenyl)amino)phenyl group. The molecule also contains several amide and ester linkages, and a cyclohexyl group.	 Chemical structure of C-318: A complex molecule featuring a central polyether chain (a series of 10 oxygen atoms linked by 11 methylene groups) connected to various functional groups. At one end, there is a 4-chlorophenyl group and a 4-methyl-5-sulfamoylphenyl group. At the other end, there is a 4-((4-chlorophenyl)amino)phenyl group. The molecule also contains several amide and ester linkages, and a cyclohexyl group.
C-316	C-317	C-318

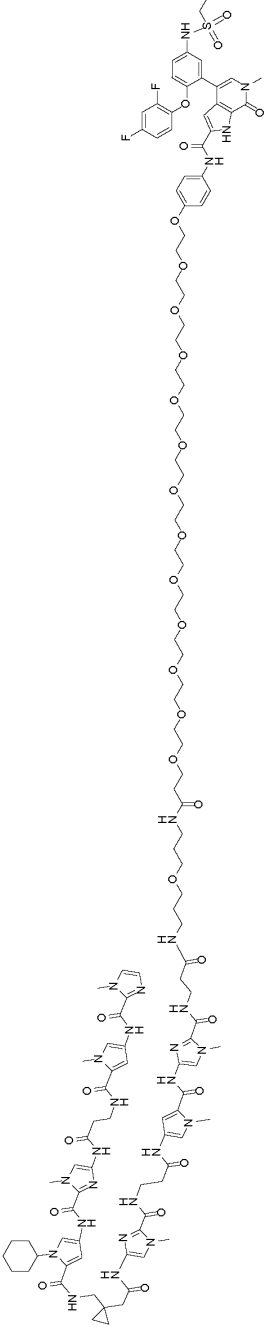
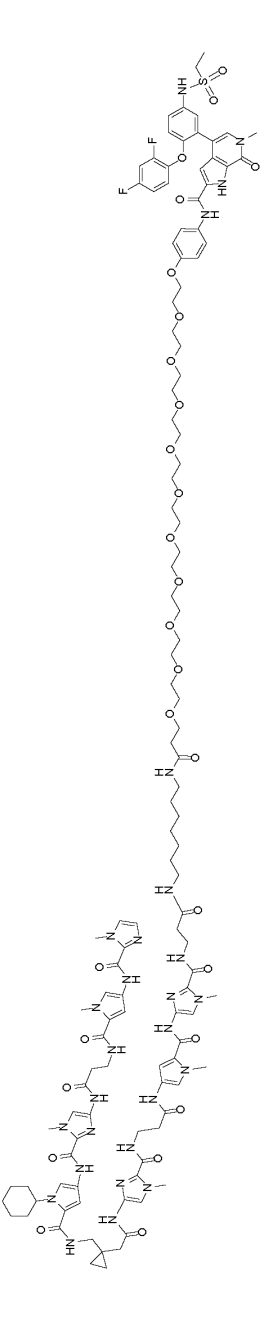
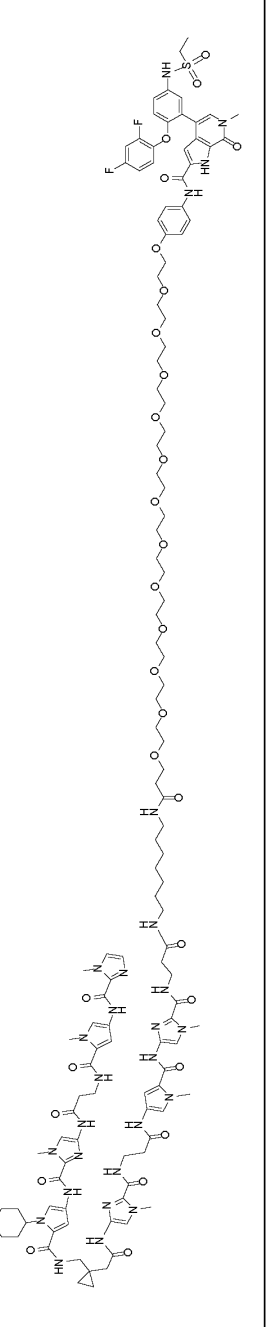
		
C-322	C-323	C-324

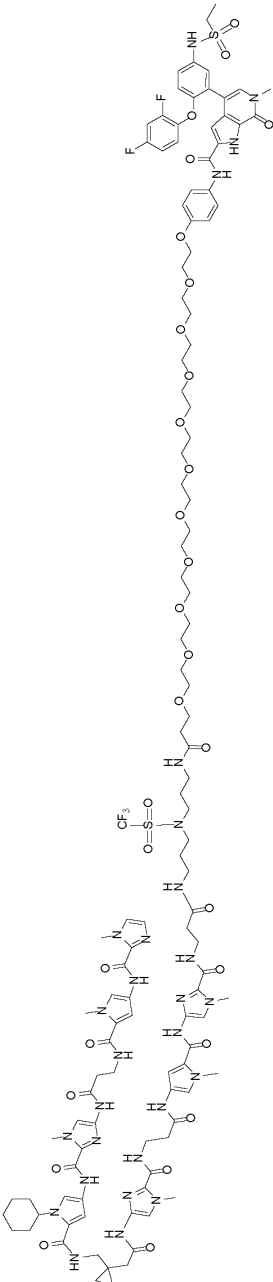
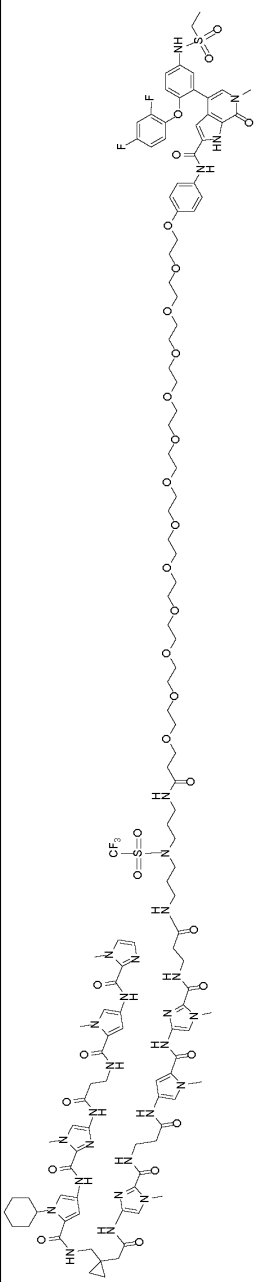
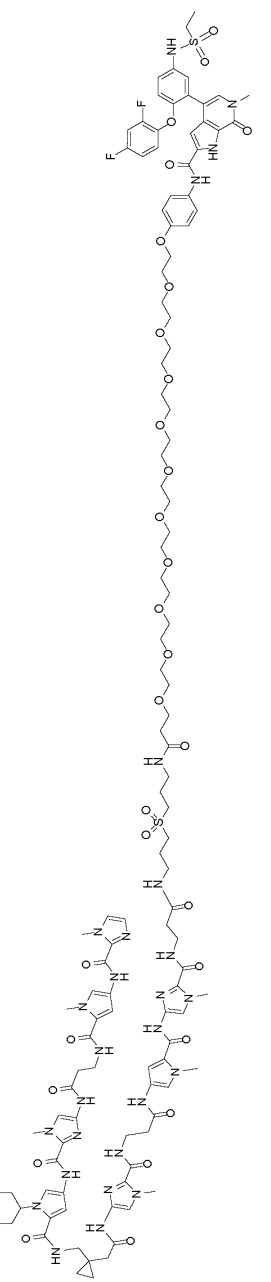
 Chemical structure of C-325: A complex molecule featuring a central pyrazole core. It is substituted with a 4-ethanesulfonylphenyl group, a 4-fluorophenyl group, and a long polyether chain (1,4-bis(2-oxaethyl)benzene). The molecule also contains a 4-((cyclopropylmethyl)amino)-5-oxo-1H-pyrazol-3-yl group and a 4-((cyclopropylmethyl)amino)-5-oxo-1H-pyrazol-3-yl group.	 Chemical structure of C-326: A complex molecule featuring a central pyrazole core. It is substituted with a 4-ethanesulfonylphenyl group, a 4-fluorophenyl group, and a long polyether chain (1,4-bis(2-oxaethyl)benzene). The molecule also contains a 4-((cyclopropylmethyl)amino)-5-oxo-1H-pyrazol-3-yl group and a 4-((cyclopropylmethyl)amino)-5-oxo-1H-pyrazol-3-yl group.	 Chemical structure of C-327: A complex molecule featuring a central pyrazole core. It is substituted with a 4-ethanesulfonylphenyl group, a 4-fluorophenyl group, and a long polyether chain (1,4-bis(2-oxaethyl)benzene). The molecule also contains a 4-((cyclopropylmethyl)amino)-5-oxo-1H-pyrazol-3-yl group and a 4-((cyclopropylmethyl)amino)-5-oxo-1H-pyrazol-3-yl group.
C-325	C-326	C-327

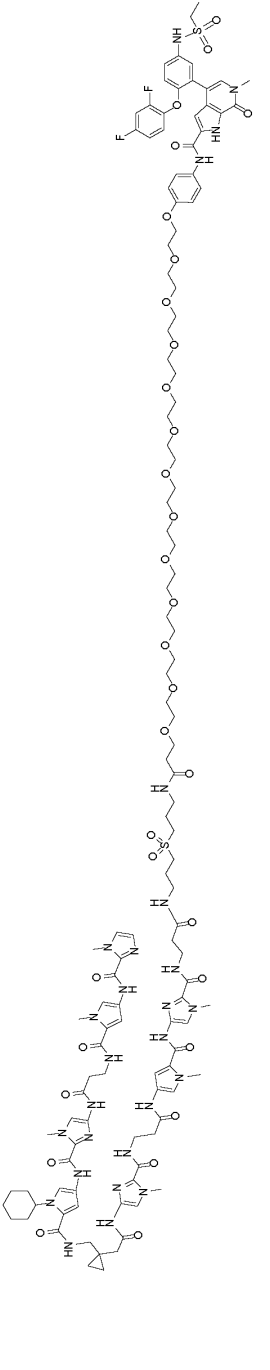
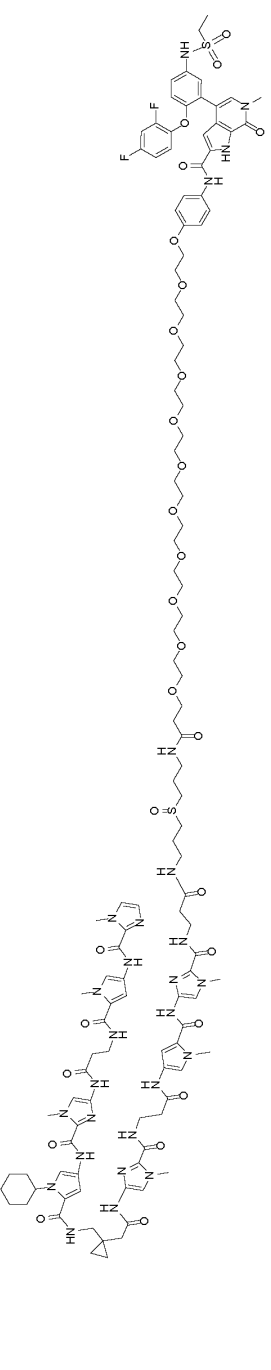
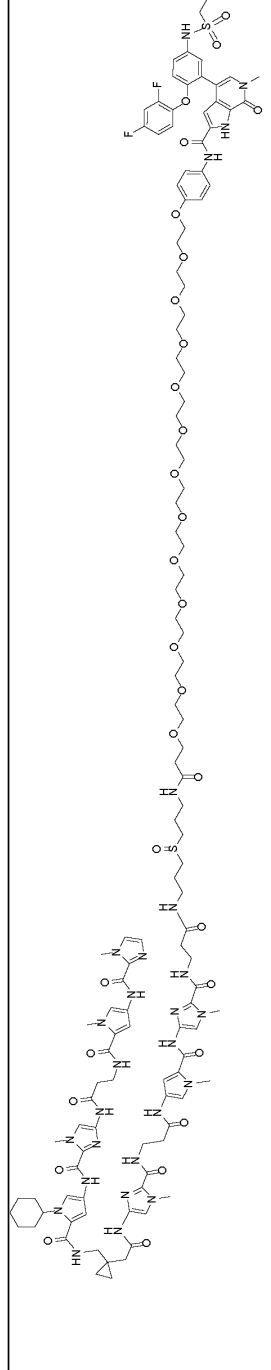
 Chemical structure of compound C-328. It features a central pyrazole ring substituted with a 4-ethanesulfonylphenyl group, a 4-(2,4-difluorophenoxy)phenyl group, and a 4-(2,4-difluorophenyl)phenyl group. The pyrazole ring is also substituted with a 4-(2,4-difluorophenyl)phenyl group. The structure is connected via a long, flexible polyether chain to a complex polycyclic aromatic system.	 Chemical structure of compound C-329. It features a central pyrazole ring substituted with a 4-ethanesulfonylphenyl group, a 4-(2,4-difluorophenoxy)phenyl group, and a 4-(2,4-difluorophenyl)phenyl group. The pyrazole ring is also substituted with a 4-(2,4-difluorophenyl)phenyl group. The structure is connected via a long, flexible polyether chain to a complex polycyclic aromatic system.	 Chemical structure of compound C-330. It features a central pyrazole ring substituted with a 4-ethanesulfonylphenyl group, a 4-(2,4-difluorophenoxy)phenyl group, and a 4-(2,4-difluorophenyl)phenyl group. The pyrazole ring is also substituted with a 4-(2,4-difluorophenyl)phenyl group. The structure is connected via a long, flexible polyether chain to a complex polycyclic aromatic system.
C-328	C-329	C-330

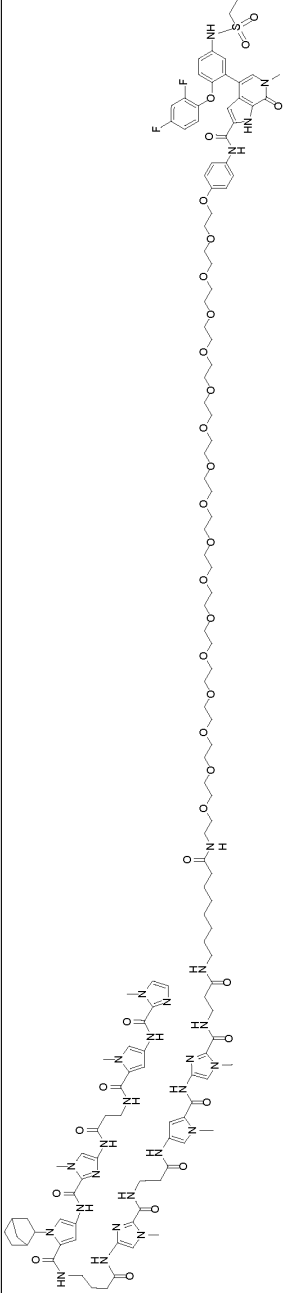
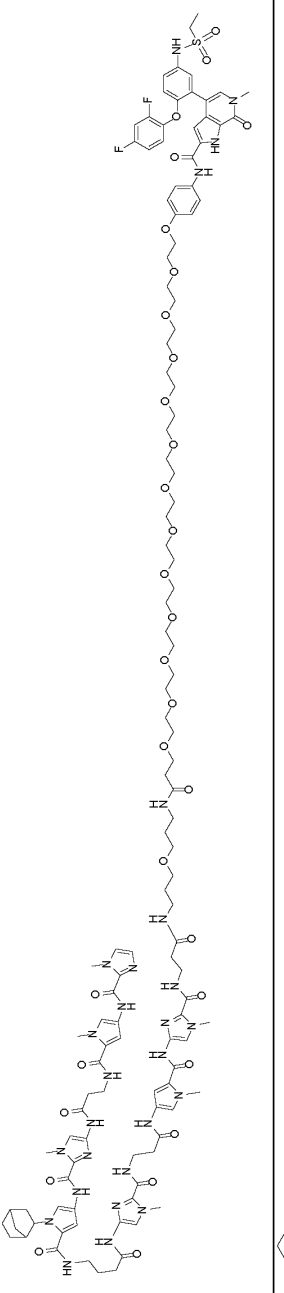
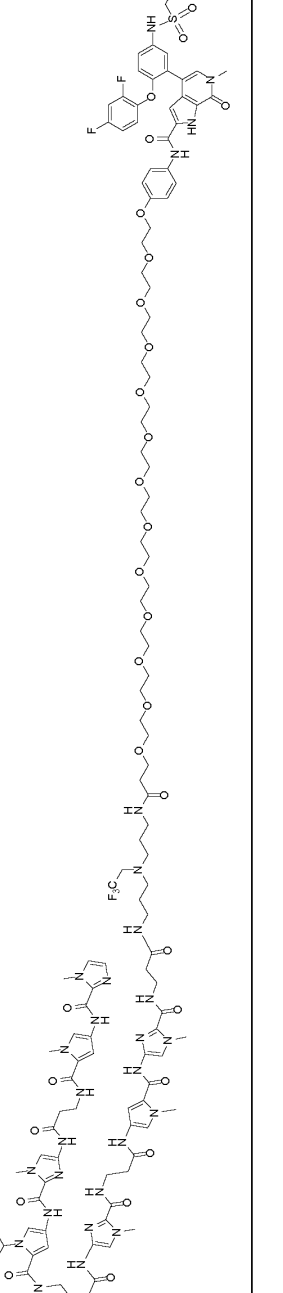
		
C-331	C-332	C-333

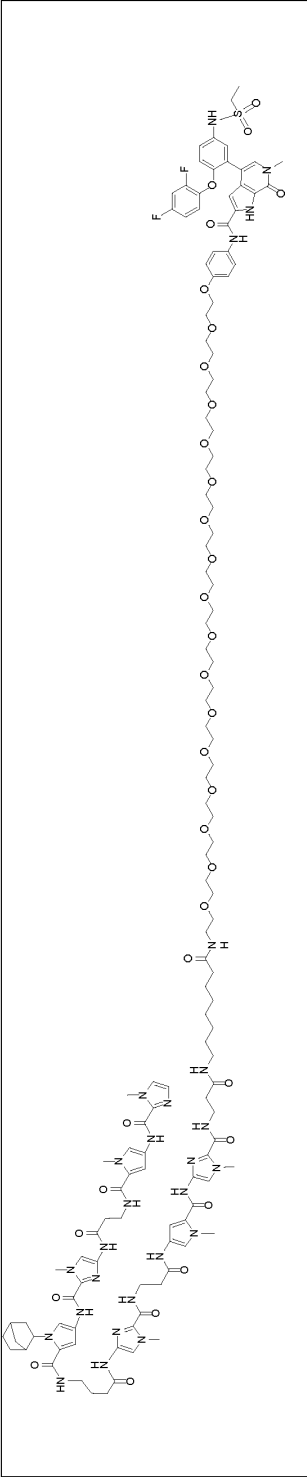
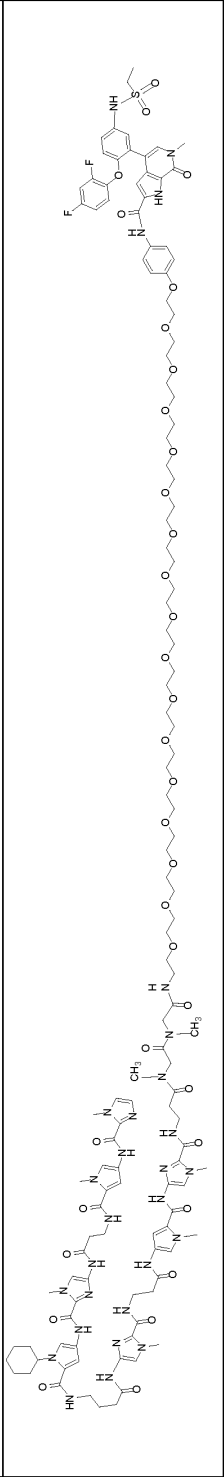
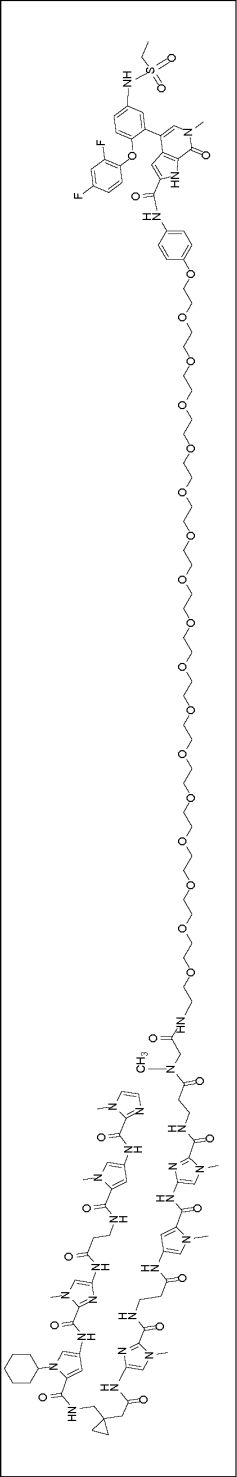
		
C-334	C-335	C-336

 Chemical structure of compound C-340. It features a 4-fluorophenyl group connected via an ether linkage to a pyrazole ring. The pyrazole is substituted with a methyl group and a methylsulfonyl group. A long polyether chain (1,3-bis(2-methoxyethoxy)propane) is attached to the pyrazole ring. The chain terminates in a carboxylic acid group, which is further substituted with a complex side chain containing multiple amide and ester linkages, and a cyclohexyl group.	 Chemical structure of compound C-341. It is similar to C-340, but the side chain at the end of the polyether chain is different, featuring a different arrangement of amide and ester linkages and a cyclohexyl group.	 Chemical structure of compound C-342. It is similar to C-340, but the side chain at the end of the polyether chain is different, featuring a different arrangement of amide and ester linkages and a cyclohexyl group.
C-340	C-341	C-342

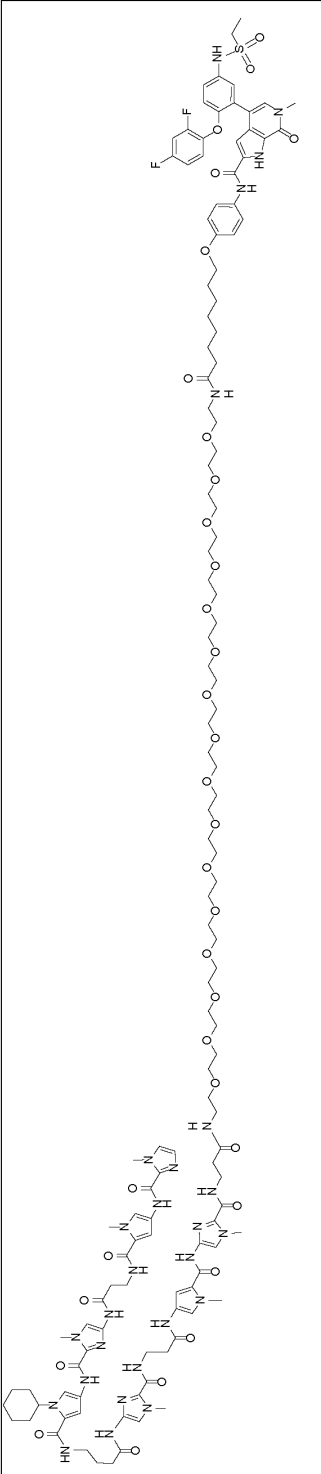
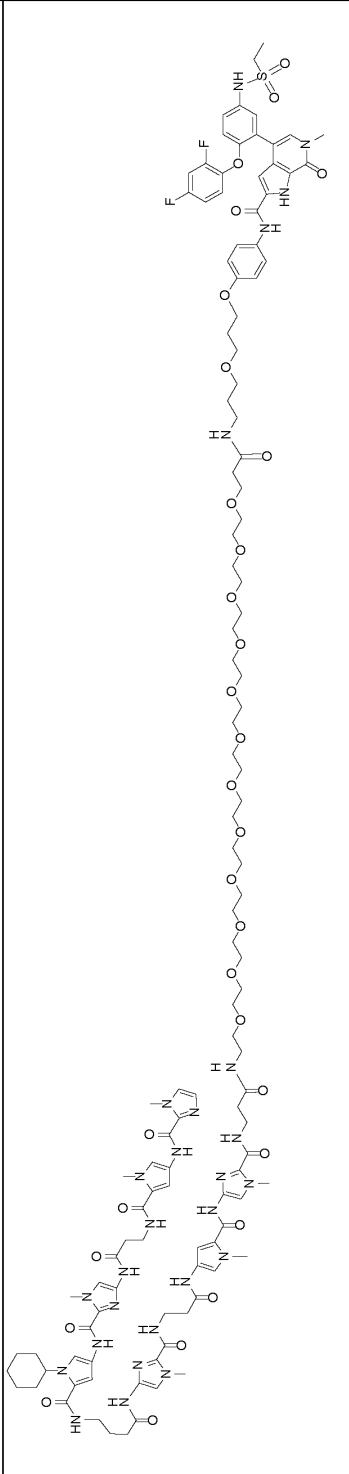
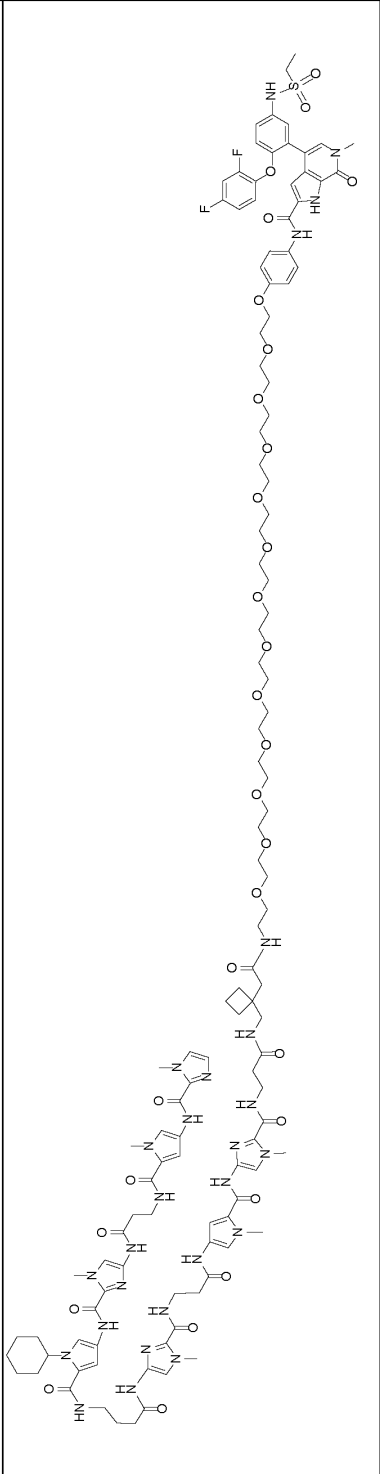
 Chemical structure of compound C-343. It features a complex polycyclic aromatic system with a fluorine substituent and a sulfonamide group. This is linked via an amide bond to a long, flexible polyether chain. The chain terminates in a trifluoromethyl sulfonamide group and a complex polycyclic aromatic system with a cyclohexyl substituent.	 Chemical structure of compound C-344. It is similar to C-343, but the terminal trifluoromethyl sulfonamide group is replaced by a trifluoromethyl sulfonamide group with a different orientation.	 Chemical structure of compound C-345. It is similar to C-343, but the terminal trifluoromethyl sulfonamide group is replaced by a trifluoromethyl sulfonamide group with a different orientation.
C-343	C-344	C-345

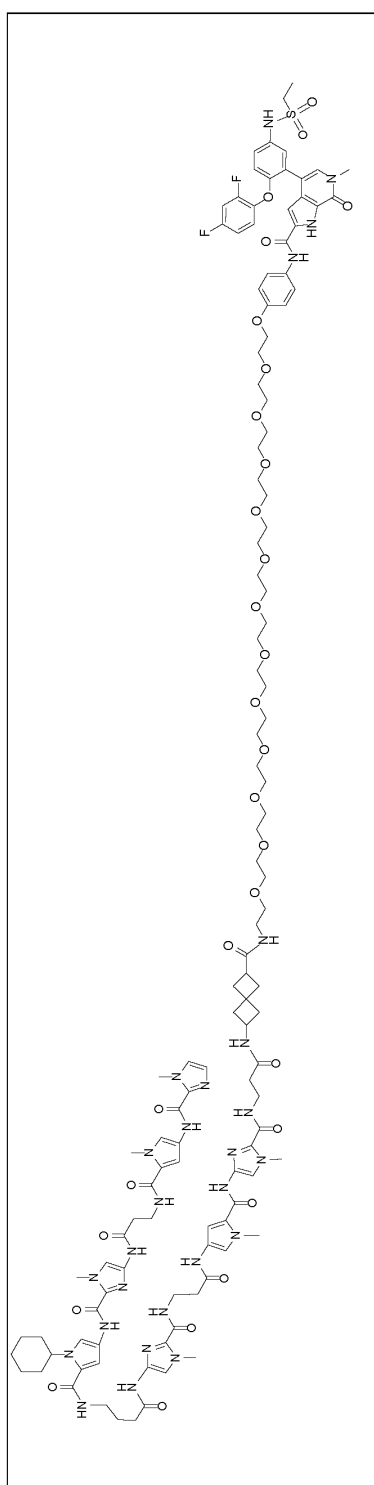
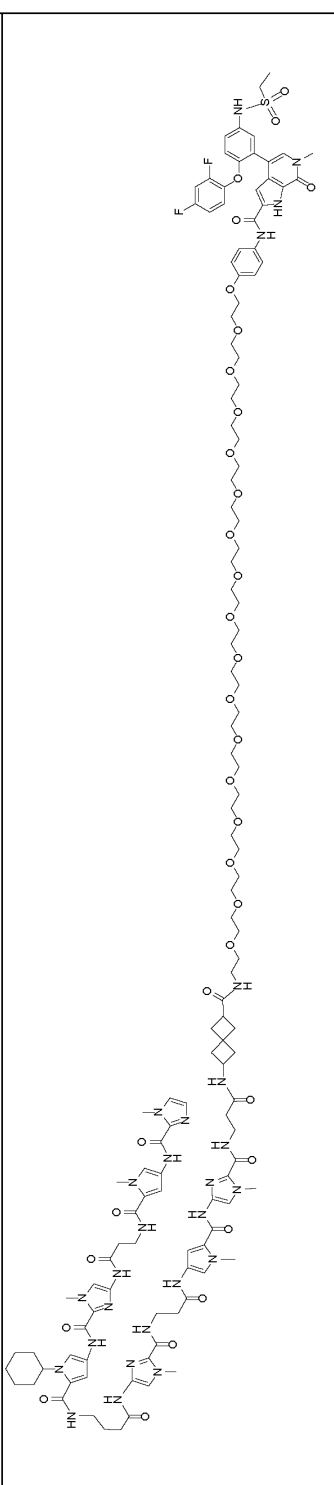
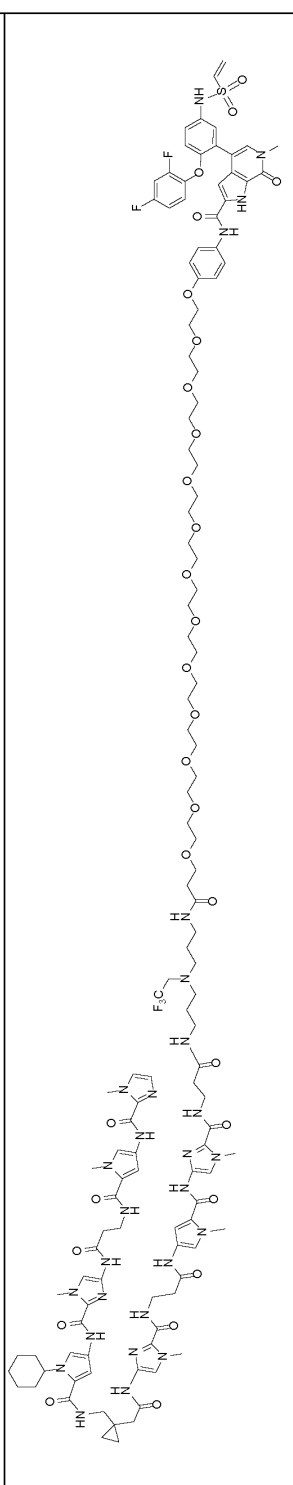
 Chemical structure of compound C-346. It features a complex polycyclic aromatic system with a fluorine substituent, a sulfonamide group, and a long polyether chain. The chain terminates in a sulfonamide group and a complex polycyclic aromatic system with a cyclohexyl substituent.	 Chemical structure of compound C-347. It is similar to C-346 but with a different polycyclic aromatic system at the bottom, featuring a cyclohexyl substituent and a different arrangement of fused rings.	 Chemical structure of compound C-348. It is similar to C-346 but with a different polycyclic aromatic system at the bottom, featuring a cyclohexyl substituent and a different arrangement of fused rings.
C-346	C-347	C-348

 Chemical structure of compound C-349. It features a complex polycyclic aromatic system with a fluorinated phenyl group, a sulfonamide, and a long polyether chain. The chain terminates in a carboxylic acid group, which is linked to a complex polycyclic aromatic system containing a cyclopentadiene ring and a sulfonamide group.	 Chemical structure of compound C-350. It is similar to C-349 but lacks the terminal carboxylic acid group. Instead, it has a long polyether chain that terminates in a carboxylic acid group, which is linked to a complex polycyclic aromatic system containing a cyclopentadiene ring and a sulfonamide group.	 Chemical structure of compound C-351. It is similar to C-349 but lacks the terminal carboxylic acid group. Instead, it has a long polyether chain that terminates in a carboxylic acid group, which is linked to a complex polycyclic aromatic system containing a cyclopentadiene ring and a sulfonamide group.
C-349	C-350	C-351

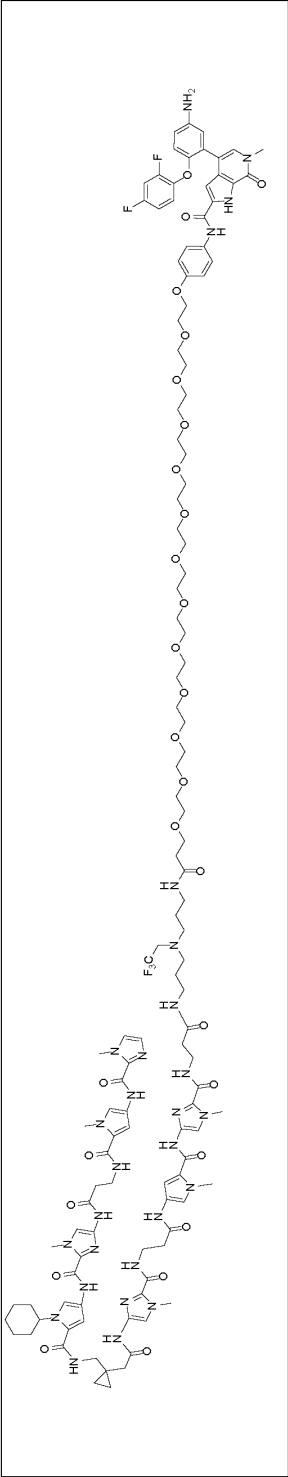
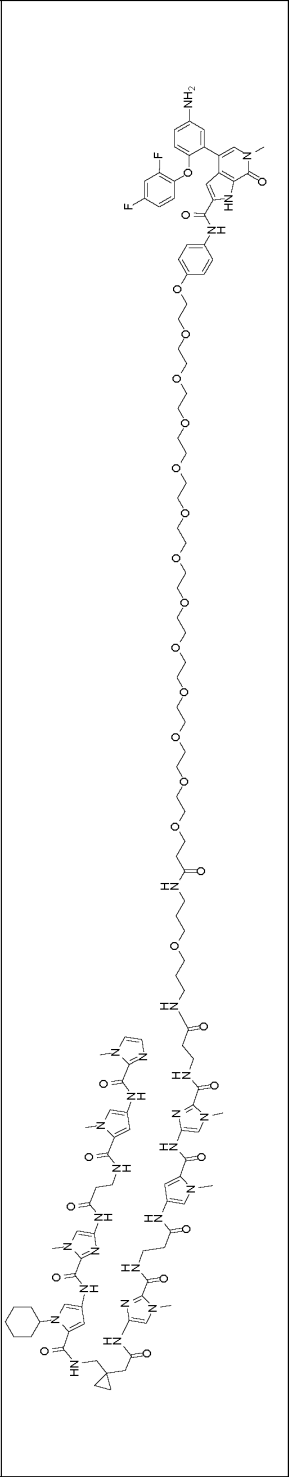
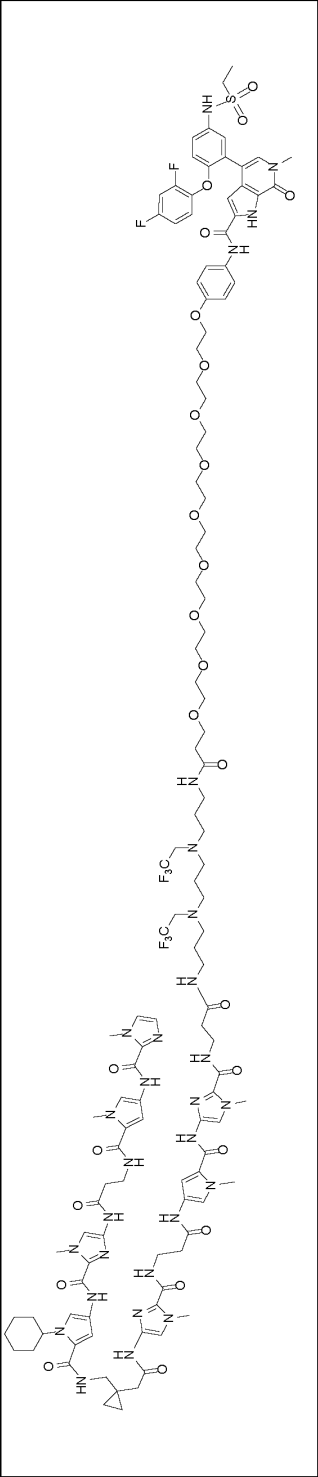
 Chemical structure of C-352: A complex molecule featuring a central pyrazole core substituted with a 4-fluorophenyl group, a 4-methyl-5-oxo-1,2,3,4-tetrahydropyridin-2-yl group, and a 4-methyl-5-oxo-1,2,3,4-tetrahydropyridin-2-yl group. The molecule is linked via a long, flexible polyether chain to a 4-methyl-5-oxo-1,2,3,4-tetrahydropyridin-2-yl group.	C-352
 Chemical structure of C-353: A complex molecule featuring a central pyrazole core substituted with a 4-fluorophenyl group, a 4-methyl-5-oxo-1,2,3,4-tetrahydropyridin-2-yl group, and a 4-methyl-5-oxo-1,2,3,4-tetrahydropyridin-2-yl group. The molecule is linked via a long, flexible polyether chain to a 4-methyl-5-oxo-1,2,3,4-tetrahydropyridin-2-yl group.	C-353
 Chemical structure of C-354: A complex molecule featuring a central pyrazole core substituted with a 4-fluorophenyl group, a 4-methyl-5-oxo-1,2,3,4-tetrahydropyridin-2-yl group, and a 4-methyl-5-oxo-1,2,3,4-tetrahydropyridin-2-yl group. The molecule is linked via a long, flexible polyether chain to a 4-methyl-5-oxo-1,2,3,4-tetrahydropyridin-2-yl group.	C-354

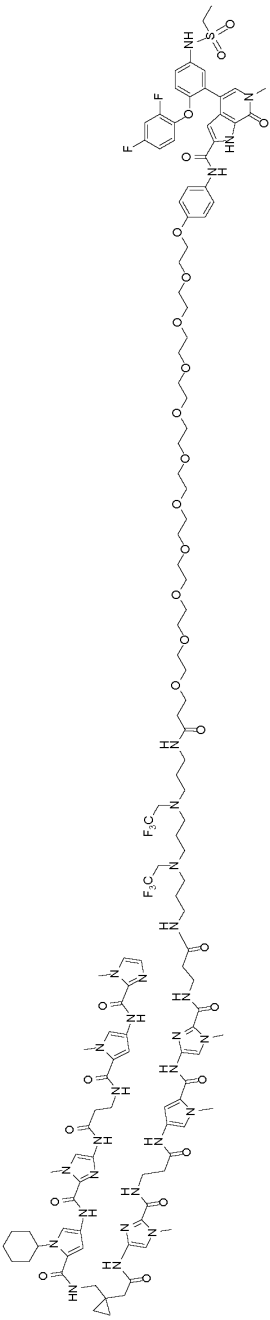
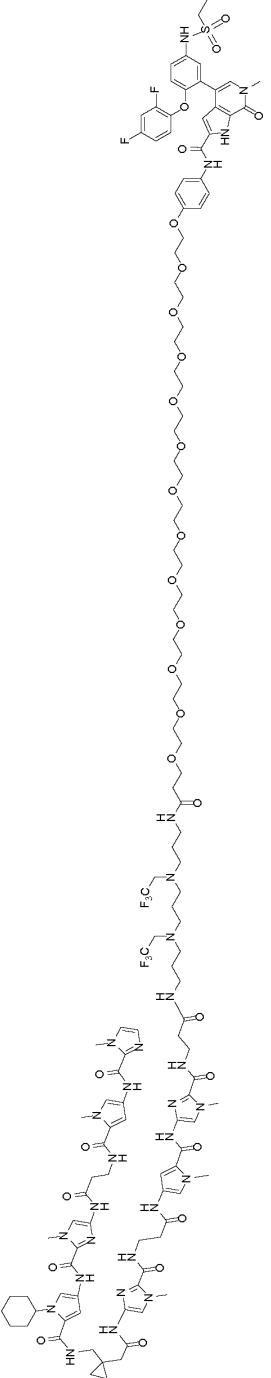
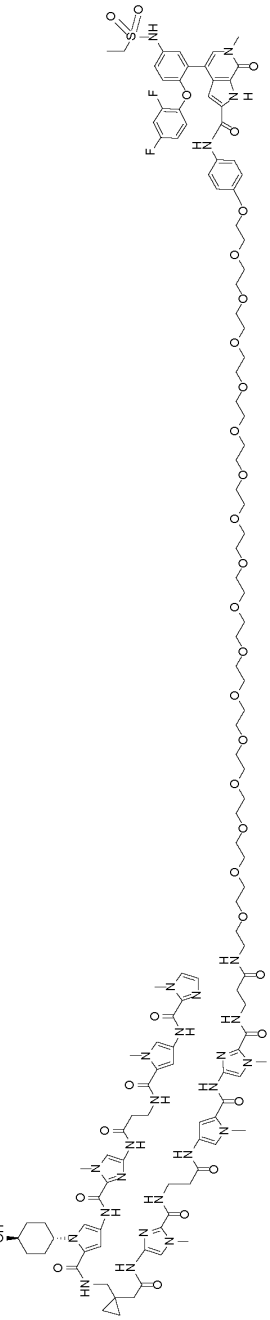
C-355	
C-356	
C-357	

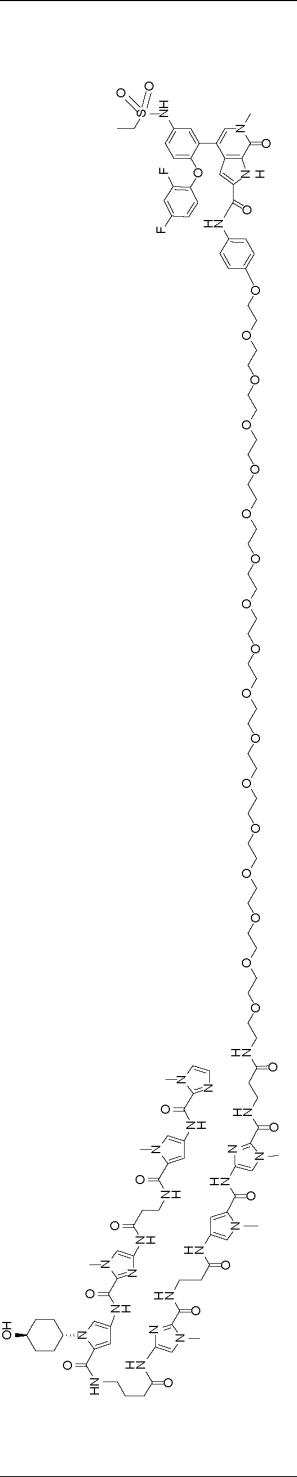
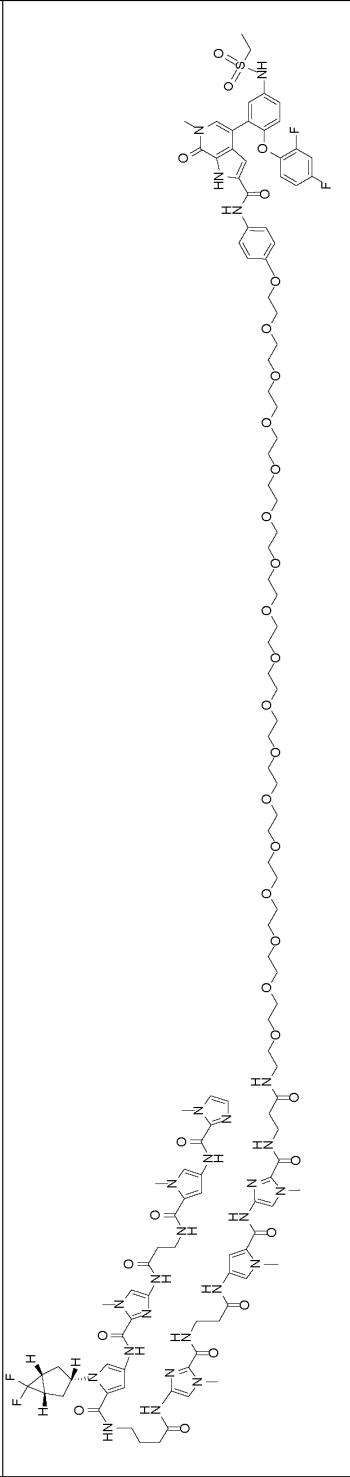
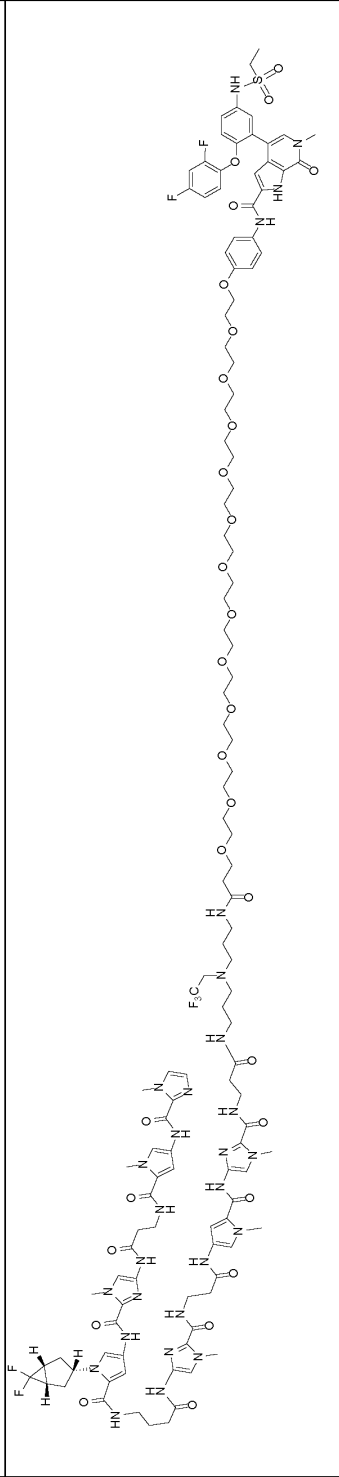
 Chemical structure of compound C-358. It features a complex polycyclic aromatic system with a pyridine ring, a pyrazole ring, and a fluorinated phenyl group. This system is connected via an amide bond to a long, flexible polyether chain consisting of multiple repeating units of -O-CH2-CH2-O-. The chain terminates in a carboxylic acid group.	 Chemical structure of compound C-359. It features a complex polycyclic aromatic system with a pyridine ring, a pyrazole ring, and a fluorinated phenyl group. This system is connected via an amide bond to a long, flexible polyether chain consisting of multiple repeating units of -O-CH2-CH2-O-. The chain terminates in a carboxylic acid group.	 Chemical structure of compound C-360. It features a complex polycyclic aromatic system with a pyridine ring, a pyrazole ring, and a fluorinated phenyl group. This system is connected via an amide bond to a long, flexible polyether chain consisting of multiple repeating units of -O-CH2-CH2-O-. The chain terminates in a carboxylic acid group.
C-358	C-359	C-360

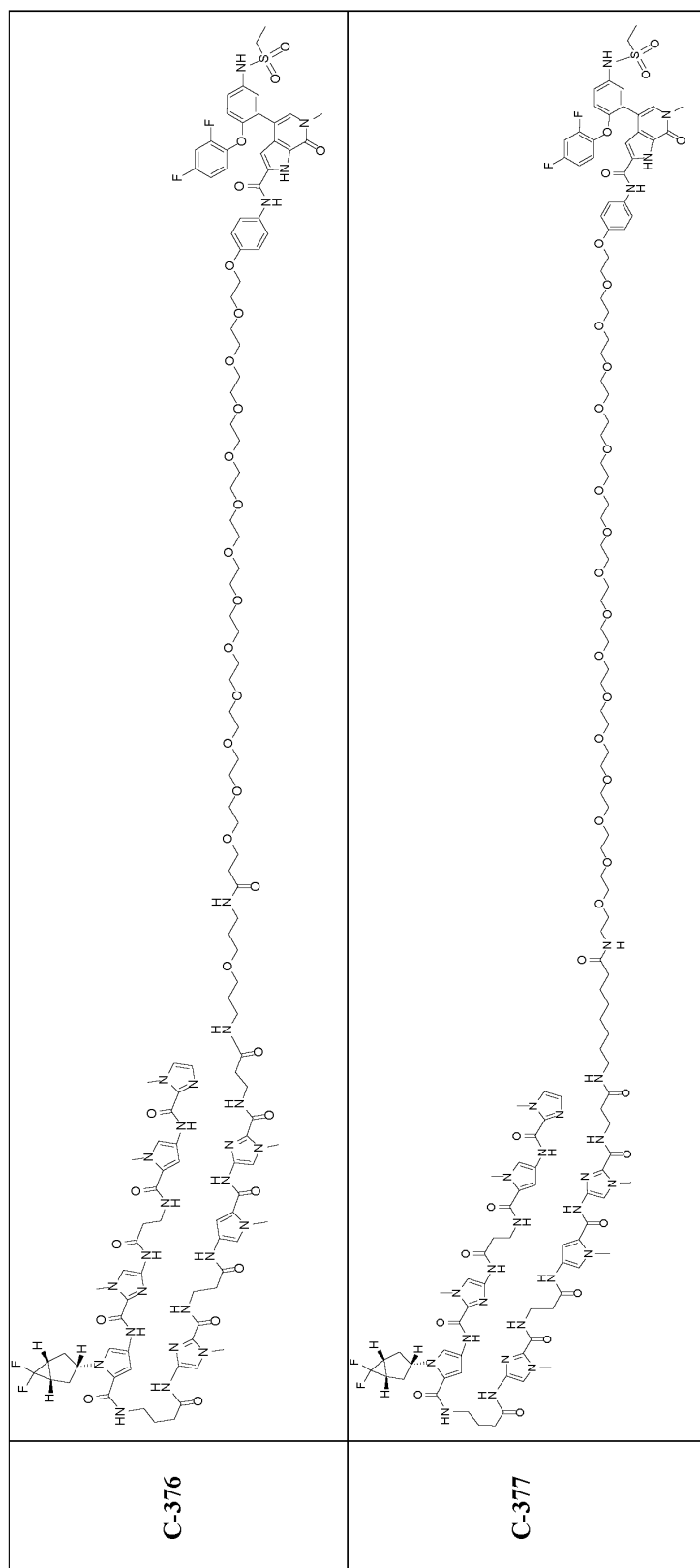
		
C-361	C-362	C-363

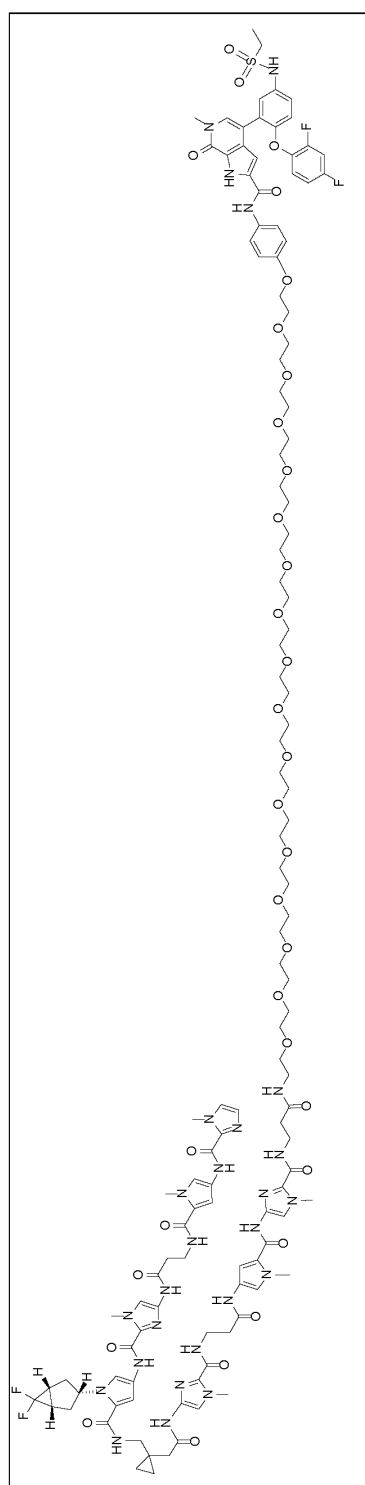
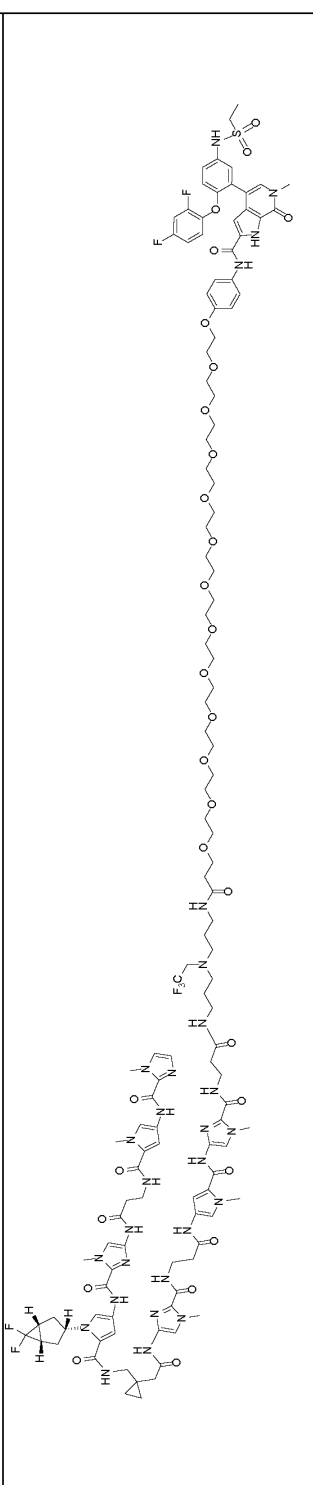
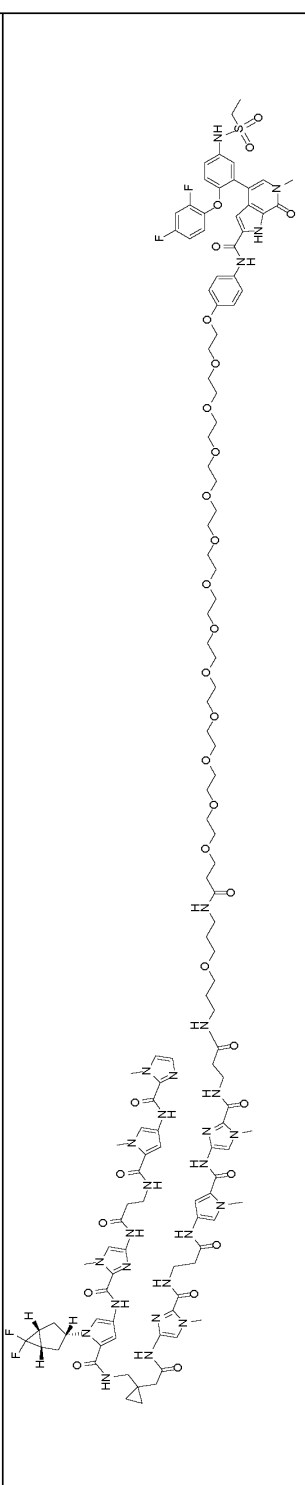


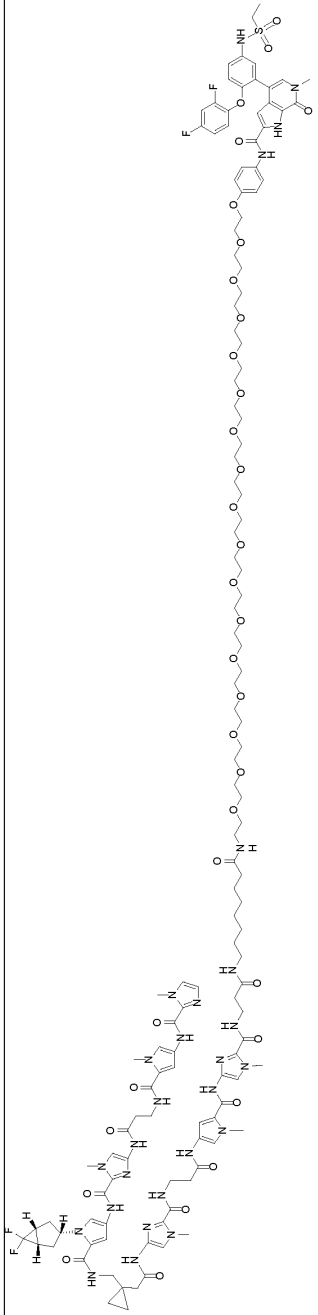
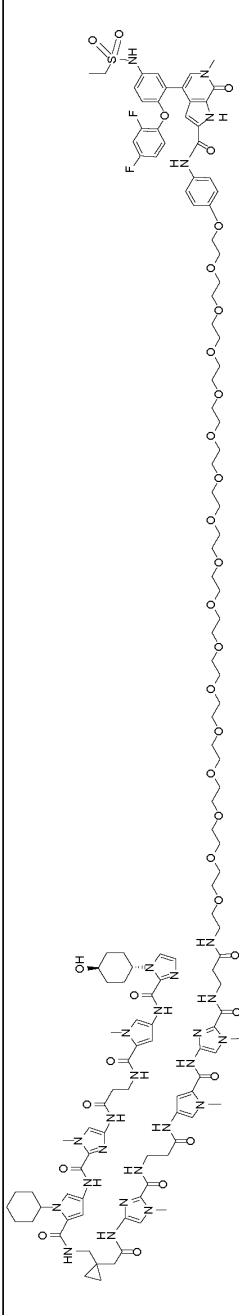
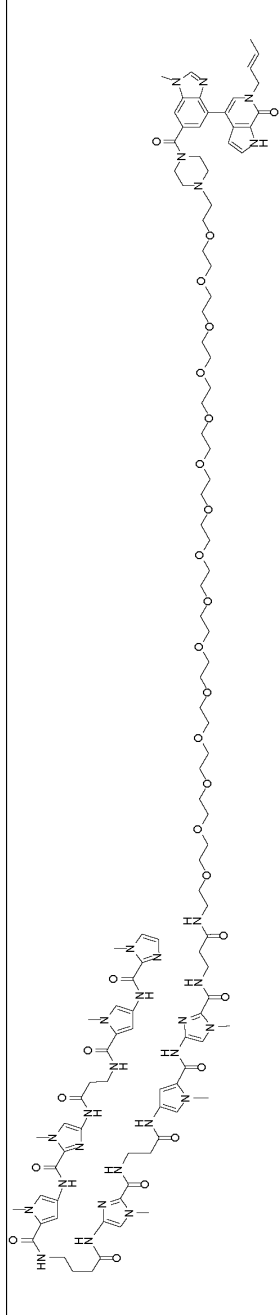
 Chemical structure of C-367: A complex molecule featuring a central pyrazole core substituted with a 4-amino-2-fluorophenyl group, a 4-(4-fluorophenoxy)phenyl group, and a 4-(4-fluorophenoxy)phenyl group. The molecule is linked via a long polyether chain to a 4-(4-fluorophenoxy)phenyl group, which is further connected to a 4-(4-fluorophenoxy)phenyl group. The molecule also contains a 4-(4-fluorophenoxy)phenyl group and a 4-(4-fluorophenoxy)phenyl group.	 Chemical structure of C-368: A complex molecule featuring a central pyrazole core substituted with a 4-amino-2-fluorophenyl group, a 4-(4-fluorophenoxy)phenyl group, and a 4-(4-fluorophenoxy)phenyl group. The molecule is linked via a long polyether chain to a 4-(4-fluorophenoxy)phenyl group, which is further connected to a 4-(4-fluorophenoxy)phenyl group. The molecule also contains a 4-(4-fluorophenoxy)phenyl group and a 4-(4-fluorophenoxy)phenyl group.	 Chemical structure of C-369: A complex molecule featuring a central pyrazole core substituted with a 4-amino-2-fluorophenyl group, a 4-(4-fluorophenoxy)phenyl group, and a 4-(4-fluorophenoxy)phenyl group. The molecule is linked via a long polyether chain to a 4-(4-fluorophenoxy)phenyl group, which is further connected to a 4-(4-fluorophenoxy)phenyl group. The molecule also contains a 4-(4-fluorophenoxy)phenyl group and a 4-(4-fluorophenoxy)phenyl group.
C-367	C-368	C-369

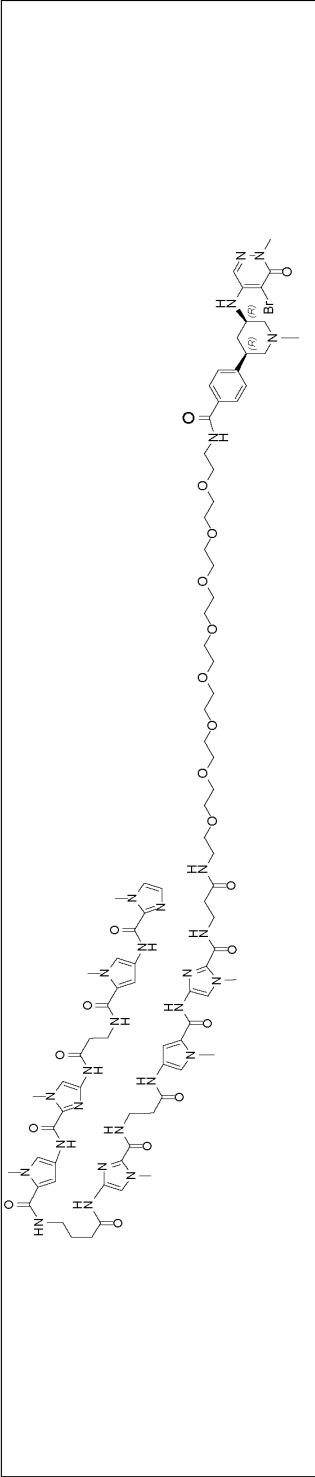
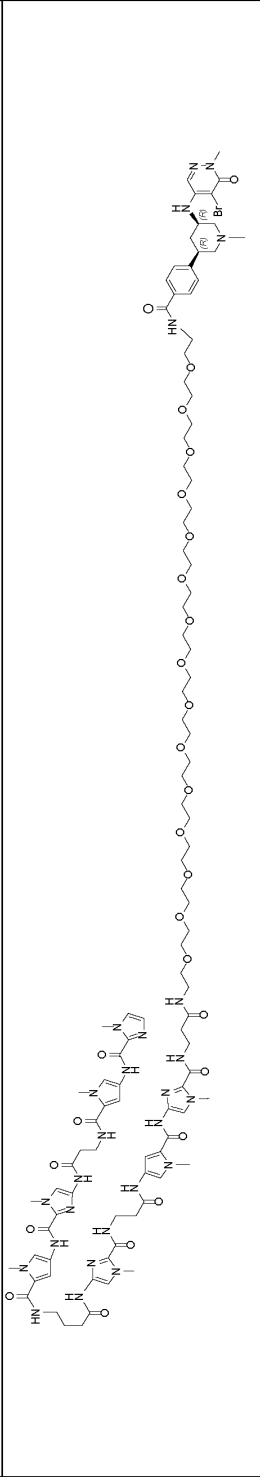
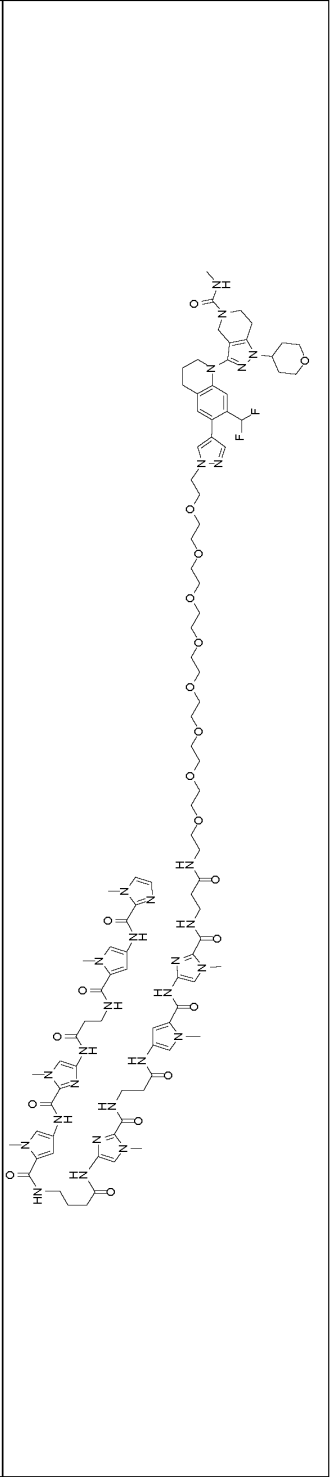
 Chemical structure of compound C-370. It features a complex polycyclic core with multiple amide and ester linkages. A long, flexible polyether chain is attached to the structure. The molecule includes a fluorinated aromatic ring and a sulfonamide group.	 Chemical structure of compound C-371. It is similar to C-370 but features a different polycyclic core and a different arrangement of the polyether chain and aromatic substituents.	 Chemical structure of compound C-372. It is similar to C-370 but features a different polycyclic core and a different arrangement of the polyether chain and aromatic substituents.
C-370	C-371	C-372

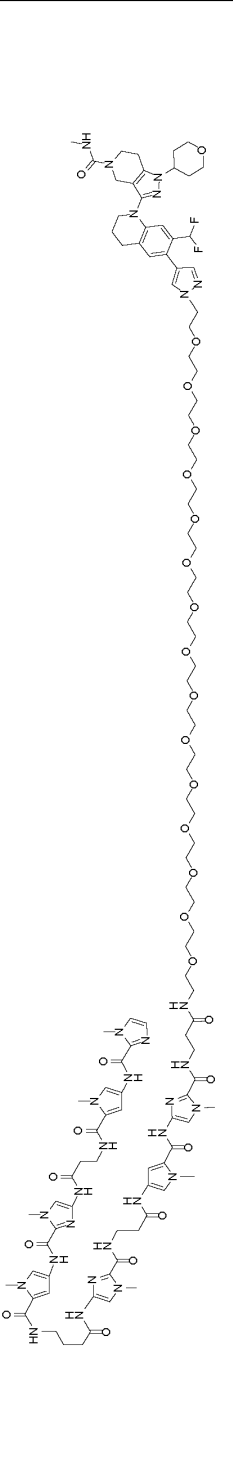
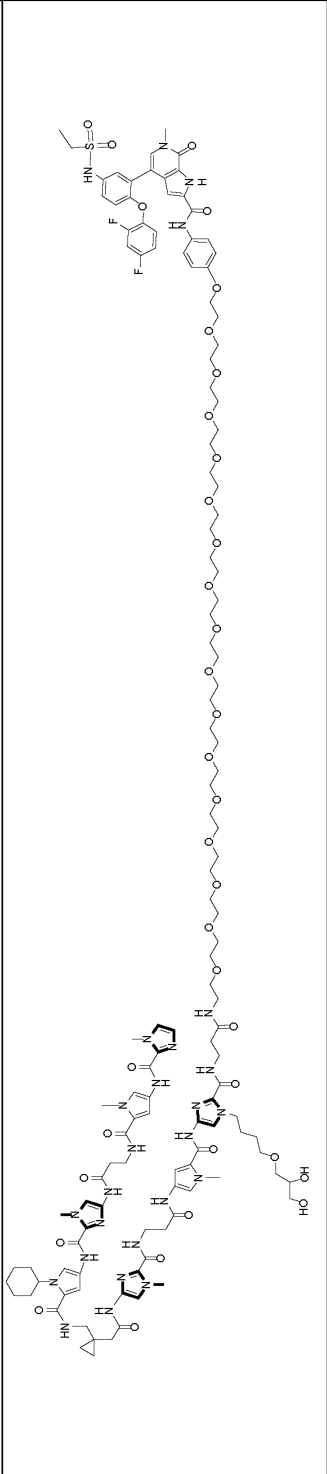
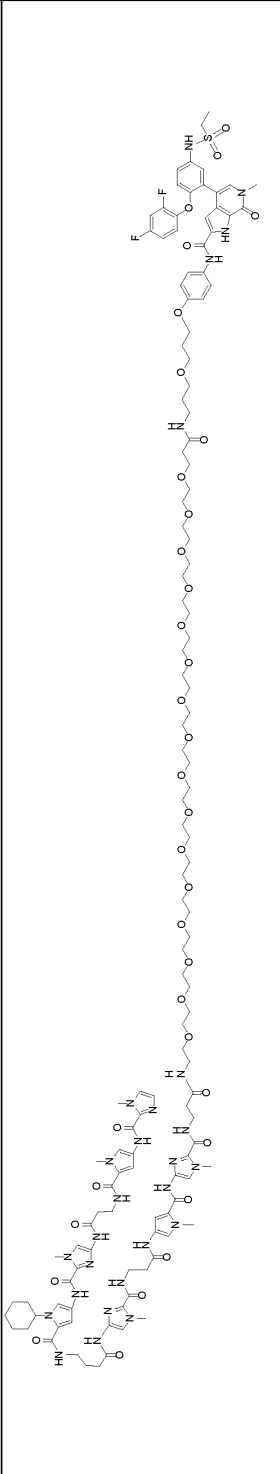
 Chemical structure of C-373: A complex molecule featuring a central pyrazole ring system. The pyrazole is substituted with a 4-fluorophenyl group, a 4-(4-fluorophenoxy)phenyl group, and a 4-(4-fluorophenoxy)phenyl group. The pyrazole is also substituted with a 4-(4-fluorophenoxy)phenyl group. The molecule includes a long, flexible polyether chain (poly(ethylene glycol) derivative) and a sulfonamide group (NH-SO₂-CH₃).	 Chemical structure of C-374: A complex molecule featuring a central pyrazole ring system. The pyrazole is substituted with a 4-fluorophenyl group, a 4-(4-fluorophenoxy)phenyl group, and a 4-(4-fluorophenoxy)phenyl group. The pyrazole is also substituted with a 4-(4-fluorophenoxy)phenyl group. The molecule includes a long, flexible polyether chain (poly(ethylene glycol) derivative) and a sulfonamide group (NH-SO₂-CH₃).	 Chemical structure of C-375: A complex molecule featuring a central pyrazole ring system. The pyrazole is substituted with a 4-fluorophenyl group, a 4-(4-fluorophenoxy)phenyl group, and a 4-(4-fluorophenoxy)phenyl group. The pyrazole is also substituted with a 4-(4-fluorophenoxy)phenyl group. The molecule includes a long, flexible polyether chain (poly(ethylene glycol) derivative) and a sulfonamide group (NH-SO₂-CH₃).
C-373	C-374	C-375

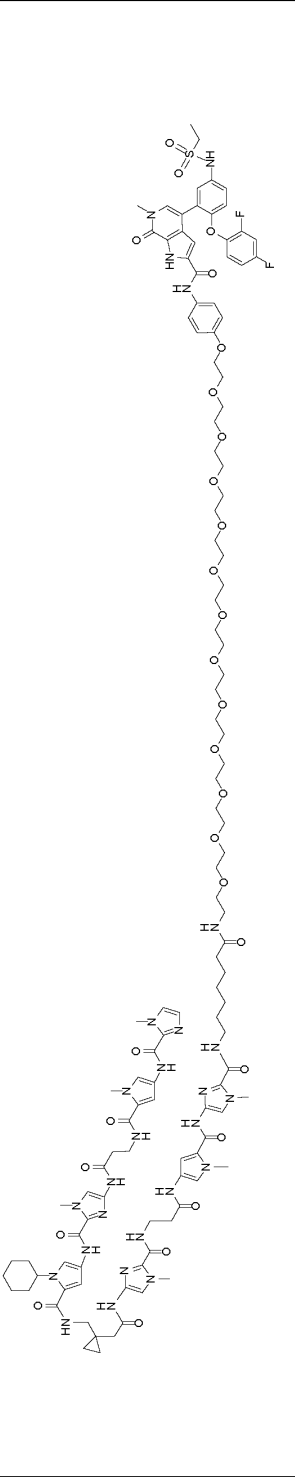
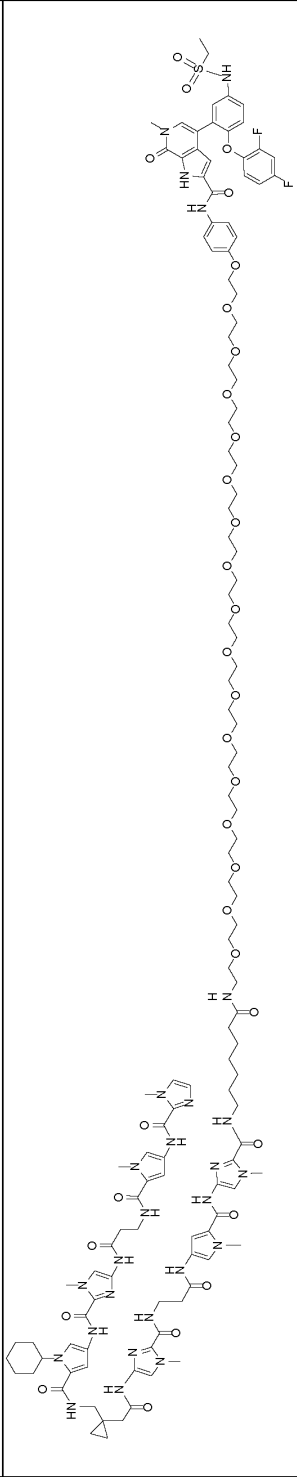
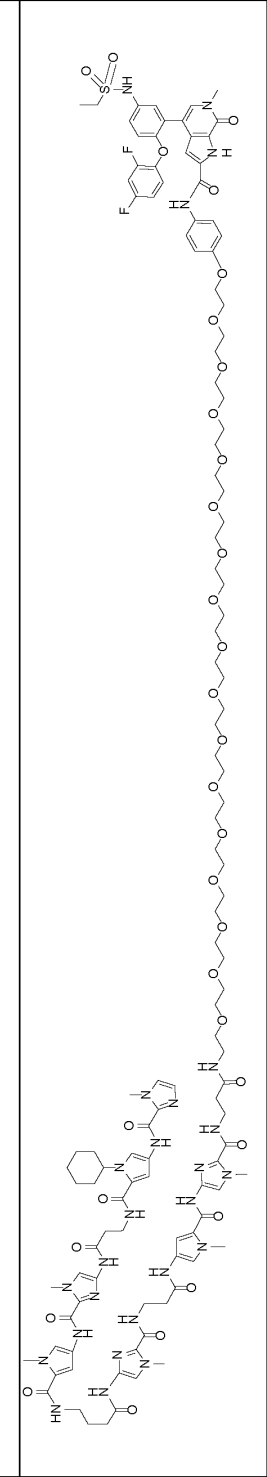


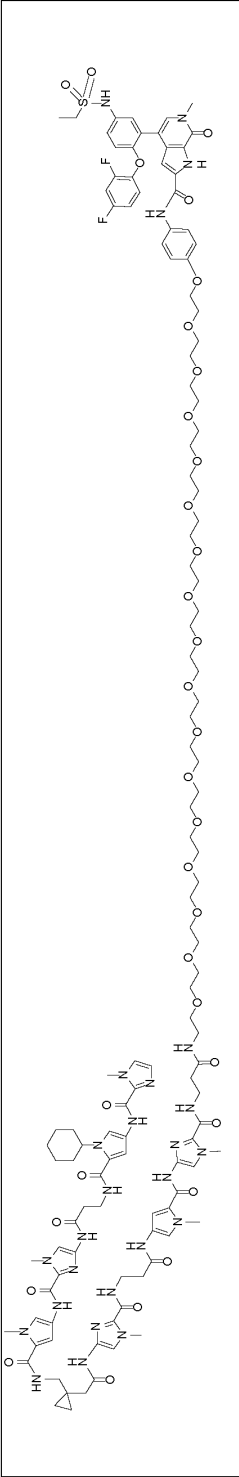
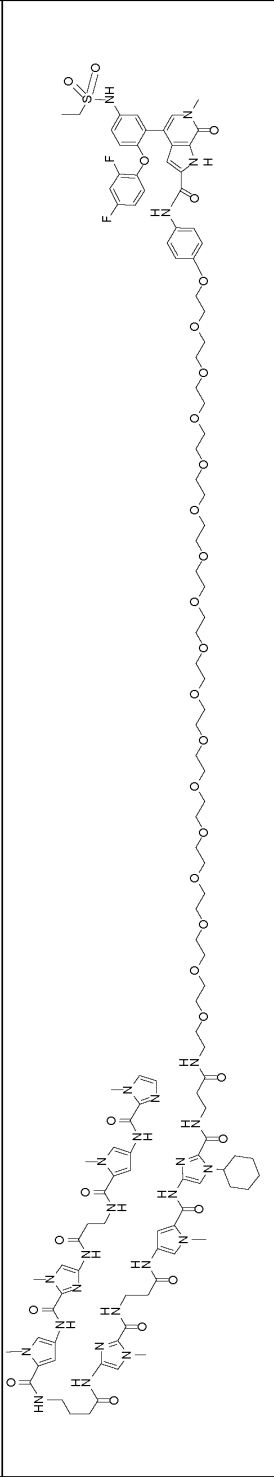
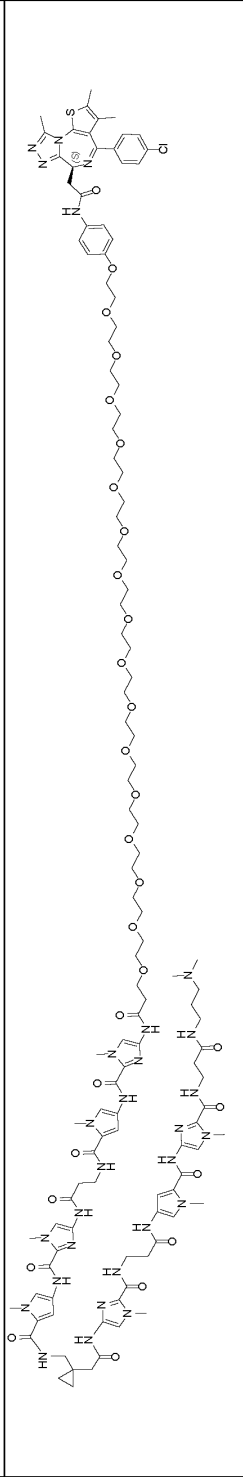
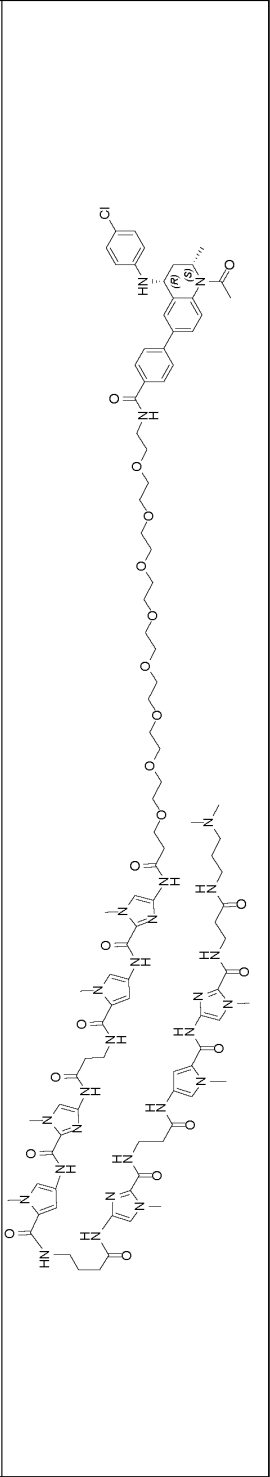
		
C-378	C-379	C-380

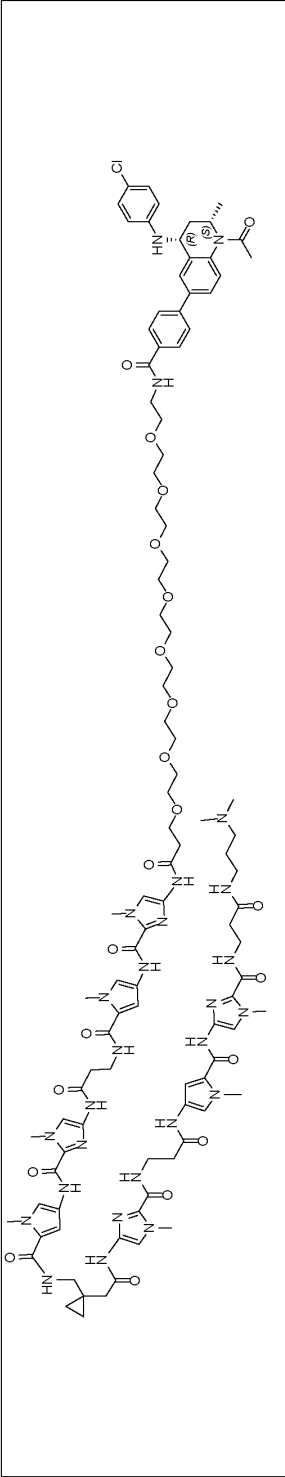
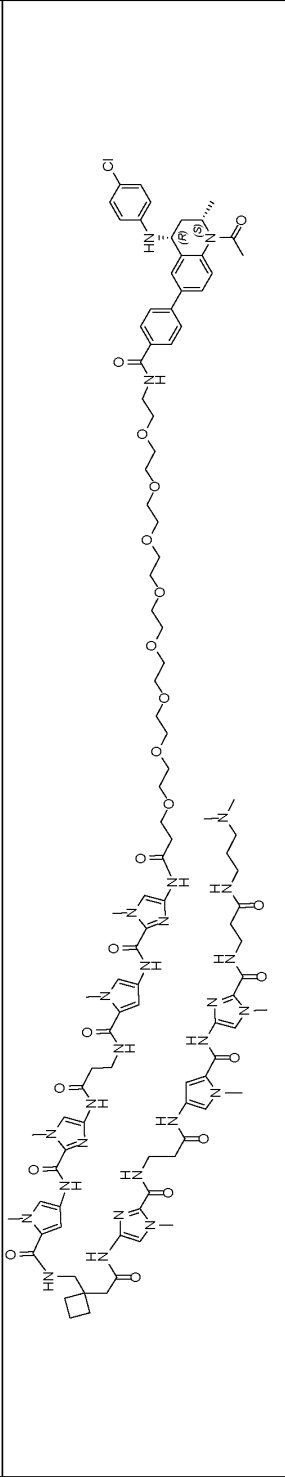
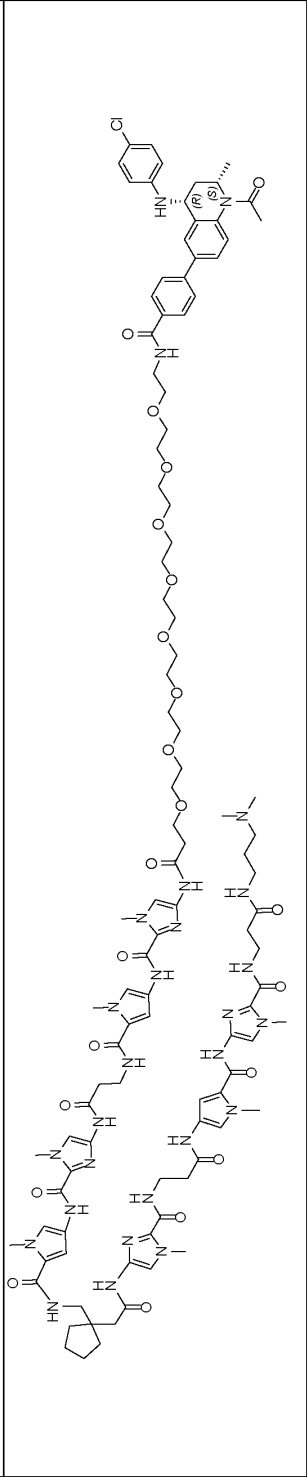
 Chemical structure of compound C-381. It features a complex polycyclic aromatic system with a sulfonamide group, a fluorine atom, and a long polyether chain. The structure is highly branched and includes a cyclopropyl group.	 Chemical structure of compound C-382. It features a complex polycyclic aromatic system with a sulfonamide group, a fluorine atom, and a long polyether chain. The structure is highly branched and includes a cyclopropyl group.	 Chemical structure of compound C-383. It features a complex polycyclic aromatic system with a sulfonamide group, a fluorine atom, and a long polyether chain. The structure is highly branched and includes a cyclopropyl group.
C-381	C-382	C-383

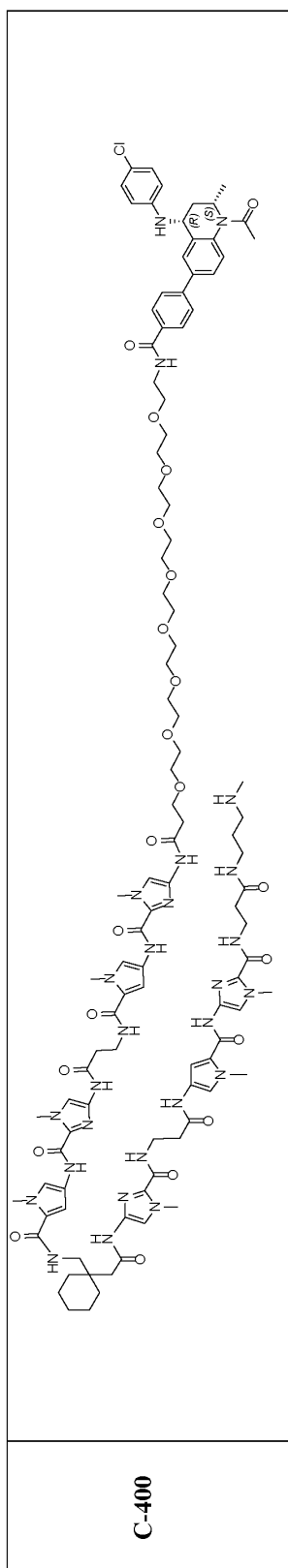
		
C-384	C-385	C-386

 Chemical structure of C-387: A complex molecule featuring a long polyether chain (1,3-bis(2-methoxyethoxy)propane) linked to a pyrazole ring system. The pyrazole is substituted with a fluorine atom and a morpholine ring. The other end of the polyether chain is linked to a pyrazole ring system, which is further substituted with a fluorine atom and a morpholine ring.	 Chemical structure of C-388: A complex molecule featuring a long polyether chain (1,3-bis(2-methoxyethoxy)propane) linked to a pyrazole ring system. The pyrazole is substituted with a fluorine atom and a morpholine ring. The other end of the polyether chain is linked to a pyrazole ring system, which is further substituted with a fluorine atom and a morpholine ring.	 Chemical structure of C-389: A complex molecule featuring a long polyether chain (1,3-bis(2-methoxyethoxy)propane) linked to a pyrazole ring system. The pyrazole is substituted with a fluorine atom and a morpholine ring. The other end of the polyether chain is linked to a pyrazole ring system, which is further substituted with a fluorine atom and a morpholine ring.
C-387	C-388	C-389

 Chemical structure of C-390: A complex molecule featuring a central pyrazole ring system. The pyrazole is substituted with a 4-fluorophenyl group, a 4-(2-fluorophenyl)oxy group, and a 4-(2-fluorophenyl)amino group. The pyrazole is also linked via an amide bond to a long, flexible polyether chain (poly(ethylene glycol) derivative). The polyether chain is terminated by a carboxylic acid group. The pyrazole ring is further substituted with a 4-(2-fluorophenyl)amino group and a 4-(2-fluorophenyl)oxy group.	 Chemical structure of C-391: A complex molecule featuring a central pyrazole ring system. The pyrazole is substituted with a 4-fluorophenyl group, a 4-(2-fluorophenyl)oxy group, and a 4-(2-fluorophenyl)amino group. The pyrazole is also linked via an amide bond to a long, flexible polyether chain (poly(ethylene glycol) derivative). The polyether chain is terminated by a carboxylic acid group. The pyrazole ring is further substituted with a 4-(2-fluorophenyl)amino group and a 4-(2-fluorophenyl)oxy group.	 Chemical structure of C-392: A complex molecule featuring a central pyrazole ring system. The pyrazole is substituted with a 4-fluorophenyl group, a 4-(2-fluorophenyl)oxy group, and a 4-(2-fluorophenyl)amino group. The pyrazole is also linked via an amide bond to a long, flexible polyether chain (poly(ethylene glycol) derivative). The polyether chain is terminated by a carboxylic acid group. The pyrazole ring is further substituted with a 4-(2-fluorophenyl)amino group and a 4-(2-fluorophenyl)oxy group.
C-390	C-391	C-392

			
C-393	C-394	C-395	C-396

 Chemical structure of C-397: A complex molecule featuring a central pyridine ring substituted with a 4-chlorophenyl group, a 4-(4-chlorophenyl)phenyl group, and a 4-(4-chlorophenyl)phenyl group. The pyridine ring is also substituted with a 4-(4-chlorophenyl)phenyl group. The molecule includes a long polyether chain and a dimethylamino group.	 Chemical structure of C-398: A complex molecule featuring a central pyridine ring substituted with a 4-chlorophenyl group, a 4-(4-chlorophenyl)phenyl group, and a 4-(4-chlorophenyl)phenyl group. The pyridine ring is also substituted with a 4-(4-chlorophenyl)phenyl group. The molecule includes a long polyether chain and a dimethylamino group.	 Chemical structure of C-399: A complex molecule featuring a central pyridine ring substituted with a 4-chlorophenyl group, a 4-(4-chlorophenyl)phenyl group, and a 4-(4-chlorophenyl)phenyl group. The pyridine ring is also substituted with a 4-(4-chlorophenyl)phenyl group. The molecule includes a long polyether chain and a dimethylamino group.
C-397	C-398	C-399



Methods of Use

[00530] In another aspect, provided herein is a method of decreasing expression of a gene in a cell, the method comprising contacting the cell with an effective amount of a molecule disclosed herein, or a pharmaceutically acceptable salt thereof.

[00531] In some embodiments, the gene is huntingtin (*HTT*). In some embodiments, the gene is mutant huntingtin.

[00532] In some embodiments, the expression of the gene is at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, or more.

[00533] In another aspect, provided herein is a method of treating Huntington's disease (HD) in a subject in need thereof, the method comprising administering to the subject a molecule described herein, or a pharmaceutically acceptable salt thereof.

[00534] In another aspect, provided herein is a method of treating Huntington's disease-like syndrome

[00535] in a subject in need thereof, the method comprising administering to the subject a molecule described herein, or a pharmaceutically acceptable salt thereof.

[00536] In another aspect, provided herein is a method of treating Juvenile Huntington's disease in a subject in need thereof, the method comprising administering to the subject a molecule described herein, or a pharmaceutically acceptable salt thereof.

[00537] In some embodiments, the method reduces one or more symptoms of Huntington's disease (HD).

[00538] In some embodiments, the one or more symptoms are selected from chorea, cognitive decline, abnormal libido, abnormal eye movement, abnormal sense of smell, aggression, agitation, anxiety, apathy, bradykinesia, bradyphrenia, clumsiness, delusions, depression, difficulty walking, disinhibition, dystonia, gait imbalance, muscle weakness, hallucinations, hostility, hypokinesia, irritability, memory impairment, myoclonus, obsessive-compulsive behavior, poor fine motor coordination, seizure, speech articulation difficulties, staring gaze, weight loss, abnormal cholesterol metabolism, abnormal cerebral white matter, alcoholism, Babinski sign, caudate atrophy, cerebral atrophy, choking, clonus, degeneration of the striatum, excessive daytime sleepiness, impaired visuospatial constructive cognition, inability to walk, insomnia, mutism, oral-pharyngeal dysphagia, rigidity, suicidal ideation, cerebellar atrophy, dementia, gate ataxia, gliosis, hyperreflexia, neuronal loss, or personality changes.

Pharmaceutical Compositions and Administration

[00539] 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.

[00540] 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.

[00541] 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.

[00542] 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.

Definitions

[00543] 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.

[00544] 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.

[00545] 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.

[00546] 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 μM (micromolar),” which is intended to include 1 μM , 3 μM , and everything in between to any number of significant figures (e.g., 1.255 μM , 2.1 μM , 2.9999 μM , etc.).

[00547] The terms below, as used herein, have the following meanings, unless indicated otherwise:

[00548] “oxo” refers to =O.

[00549] “Carboxyl” refers to -COOH.

[00550] “Cyano” refers to -CN.

[00551] “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 “ $\text{C}_1\text{-C}_6$ alkyl” or “ $\text{C}_1\text{-}6$ 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 $\text{C}_1\text{-C}_{10}$ alkyl. In some embodiments, the alkyl is a $\text{C}_1\text{-C}_6$ alkyl. In some embodiments, the alkyl is a $\text{C}_1\text{-C}_5$ alkyl. In some embodiments, the alkyl is a $\text{C}_1\text{-C}_4$ alkyl. In some embodiments, the alkyl is a $\text{C}_1\text{-C}_3$ alkyl. 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.

[00552] “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.

[00553] “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-butenyl, 1,3-butadiynyl and the like. Whenever it appears herein, a numerical range such as “C₂-C₆ alkynyl” or “C₂₋₆alkynyl”, 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.

[00554] “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, -N₃, -CN, -C(O)OH, -C(O)OMe, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, the

alkylene is optionally substituted with halogen, -CN, -OH, or -OMe. In some embodiments, the alkylene is optionally substituted with halogen.

[00555] “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, -N₃, -CN, -C(O)OH, C(O)OMe, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, the alkoxy is optionally substituted with halogen, -CN, -OH, or -OMe. In some embodiments, the alkoxy is optionally substituted with halogen.

[00556] “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, -N₃, -CN, -C(O)OH, C(O)OMe, -CF₃, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, the aryl is optionally substituted with halogen, methyl, ethyl, -CN, -CF₃, -OH, or -OMe. In some embodiments, the aryl is optionally substituted with halogen.

[00557] “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.

[00558] "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.

[00559] "Halo" or "halogen" refers to bromo, chloro, fluoro or iodo. In some embodiments, halogen is fluoro or chloro. In some embodiments, halogen is fluoro.

[00560] 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-dihaloethane, 1,3-dihaloethane, 2,3-dihaloethane, 1,2,3-trihaloethane, 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.

[00561] "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.

[00562] "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.

[00563] "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.

[00564] "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.

[00565] "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, imidazoliny, 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.

[00566] “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, benzofuranyl, benzooxazolyl, benzothiazolyl, benzothiadiazolyl, benzo[b][1,4]dioxepinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothieryl (benzothiophenyl), benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, dibenzofuranyl, 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.

[00567] The term “oligonucleotide sequence” refers to a plurality of nucleic acids having a defined sequence and length (e.g., 2, 3, 4, 5, 6, or even more nucleotides). The term “oligonucleotide repeat sequence” refers to a contiguous expansion of oligonucleotide sequences.

[00568] 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.

[00569] 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.

[00570] The term “linkable unit” refers to methylimidazoles, methylpyrroles, and straight and branched chain aliphatic functionalities (*e.g.*, methylene, ethylene, propylene, butylene, and the like) which optionally contain nitrogen Substituents, and chemical derivatives thereof. The aliphatic functionalities of linkable units can be provided, for example, by condensation of B-alanine or dimethylaminopropylamine during synthesis of the polyamide by methods well known in the art.

[00571] 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.

[00572] 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.

[00573] 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 C₁-C₆ alkyl, C₁-C₆ alkenyl, C₁-C₆ alkynyl, C₁-C₆ heteroalkyl, C₃-C₇ carbocyclyl (optionally substituted with halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, and C₁-C₆ haloalkoxy), C₃-C₇-carbocyclyl-C₁-C₆-alkyl (optionally substituted with halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, and C₁-C₆ 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.

[00574] 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.

[00575] 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.

[00576] 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.

[00577] 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 ^{13}C - or ^{14}C -enriched carbon are within the scope of the present disclosure.

[00578] 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 (^{125}I) or carbon-14 (^{14}C). Isotopic substitution with ^2H , ^{11}C , ^{13}C , ^{14}C , ^{15}C , ^{12}N , ^{13}N , ^{15}N , ^{16}N , ^{16}O , ^{17}O , ^{14}F , ^{15}F , ^{16}F , ^{17}F , ^{18}F , ^{33}S , ^{34}S , ^{35}S , ^{36}S , ^{35}Cl , ^{37}Cl , ^{79}Br , ^{81}Br , and ^{125}I 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.

[00579] 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.

[00580] 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.

[00581] 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.

[00582] 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.

[00583] 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.

[00584] 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.

[00585] 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.

[00586] 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.

[00587] 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.

[00588] 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.

[00589] 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.

[00590] 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.

[00591] 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.

[00592] 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.

[00593] The methods and compositions described herein include the use of amorphous forms as well as crystalline forms (also known as polymorphs). The compounds described herein may be in the form of pharmaceutically acceptable salts. As well, in some embodiments, active metabolites of these compounds having the same type of activity are included in the scope of the present disclosure. In addition, the compounds described herein can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. The solvated forms of the compounds presented herein are also considered to be disclosed herein.

EXAMPLES

[00594] 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 be known to those skilled in the art.

Compound Synthesis

[00595] 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.

[00596] 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 Abbreviations

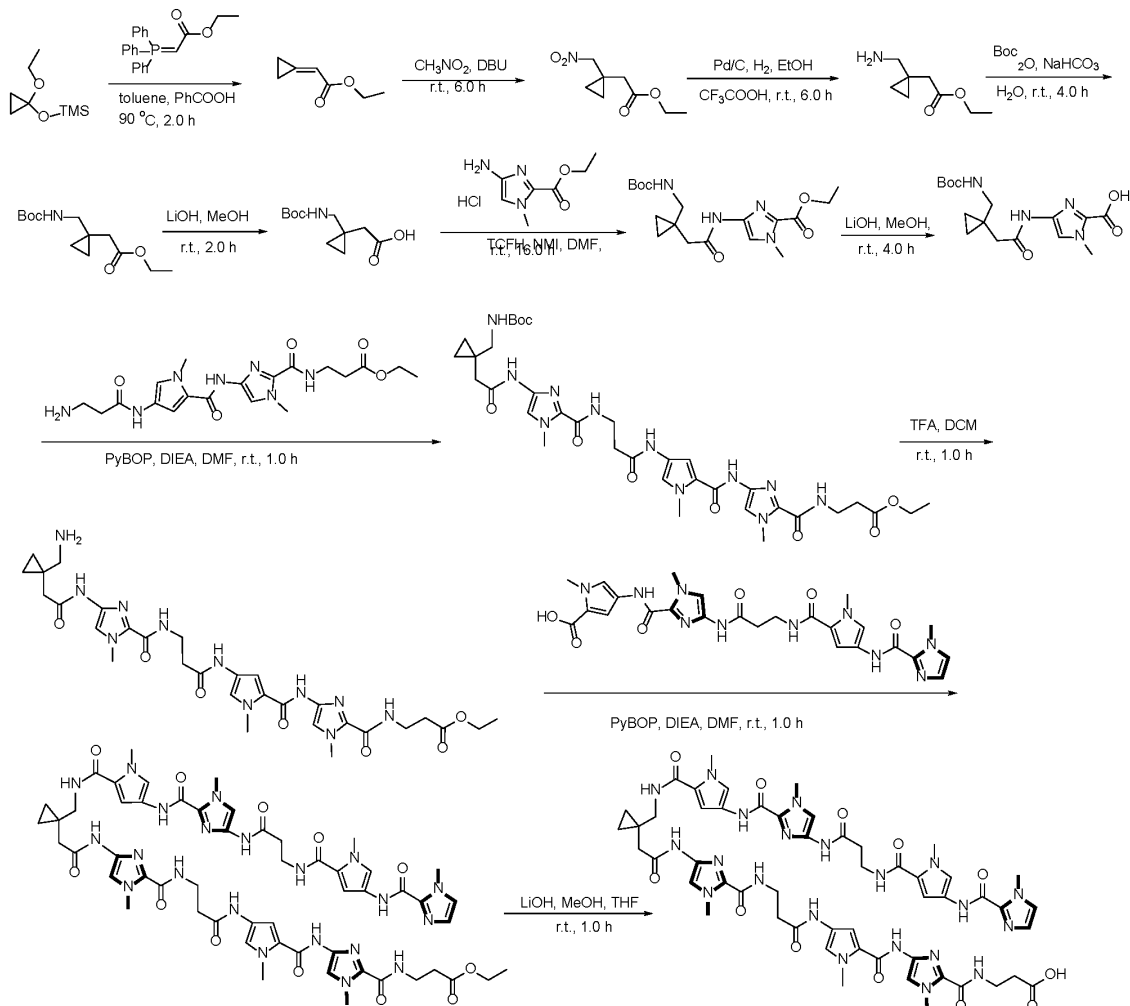
[00597] Ac₂O = acetic anhydride; AcCl = acetyl chloride; AcOH = acetic acid; AIBN = azobisisobutyronitrile; aq. = aqueous; Boc = *tert*-butoxycarbonyl; Bu₃SnH = tributyltin hydride; CD₃OD = deuterated methanol; CDCl₃ = deuterated chloroform; CDI = 1,1'-Carbonyldiimidazole; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; 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; EtOAc = 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; MeI = methyl iodide; 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; NMI = 1-methylimidazole; NMP = N-Methyl-2-pyrrolidone; OAc = acetoxy; 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; TCFH = chloro-N, N, N', N'-tetramethylformamidium hexafluorophosphate; 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 POLYAMIDES

[00598] **Example 1. Synthesis of 3-({1-methyl-4-[1-methyl-4-(3-{{1-methyl-4-(2-{{1-[(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)methyl}cyclopropyl}acetamido)imidazol-2-yl}{formamido}propanamido)pyrrole-2-amido] imidazol-2-yl}{formamido}propanoic acid

[00599] Scheme 1.



[00600] Step 1. To a stirred solution of (1-ethoxycyclopropoxy)trimethylsilane (10.00 g, 57.37 mmol, 1.00 equiv) in toluene (100.00 mL) were added ethyl 2-(triphenyl-lambda5-phosphanylidene)acetate (19.98 g, 57.37 mmol, 1.00 equiv) and benzoic acid (7.00 g, 57.37 mmol, 1.00 equiv) and the reaction mixture was stirred for 2.0 h at 90 °C. The solid was filtered and the filtrate was used directly in the next step without further purification. LC/MS: mass calcd. For $C_7H_{10}O_2$: 126.07, found: 127.10 $[M+H]^+$.

[00601] Step 2. To a solution of crude ethyl 2-cyclopropylideneacetate were added CH_3NO_2 (4.01 mL, 74.83 mmol, 2.36 equiv) and DBU (1.99 mL, 13.32 mmol, 0.42 equiv) at 0 °C and the reaction mixture was stirred for 6.0 h at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with ethyl acetate/petroleum ether (1:8) to afford ethyl 2-[1-(nitromethyl)cyclopropyl]acetate (3.00 g, 50.54%) as a light yellow oil. LC/MS: mass calcd. For $C_8H_{13}NO_4$: 187.08, found: 188.20 $[M+H]^+$.

[00602] Step 3. To a stirred mixture of ethyl 2-[1-(nitromethyl)cyclopropyl]acetate (3.00 g, 16.03 mmol, 1.00 equiv) in EtOH (30.00 mL) was added Pd/C (0.30 g, 10%w/w) and TFA (0.10 mL) at room temperature. The mixture was stirred 6.0 h at room temperature under an atmosphere of hydrogen. The resulting mixture was filtered and the filter cake was washed with EtOH (5x30 mL). The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography and eluted with ethyl acetate/petroleum ether (1:1) to afford the ethyl 2-[1-(aminomethyl)cyclopropyl]acetate (1.50 g, 59.54%) as a light yellow oil. LC/MS: mass calcd. For $C_8H_{15}NO_2$: 157.11, found: 158.15 $[M+H]^+$.

[00603] Step 4. To a stirred mixture of ethyl 2-(1-(aminomethyl)cyclopropyl)acetate (1.50 g, 9.55 mmol, 1.00 equiv) in H_2O (15.00 mL) was added saturated sodium bicarbonate (1.14 M in H_2O , 20.95 mL, 23.88 mmol, 2.50 equiv) and di-tert-butyl dicarbonate (3.13 g, 14.33 mmol, 1.50 equiv) and the mixture was stirred for 4.0 h at room temperature. The reaction mixture was filtered, diluted with water (30 mL), and extracted with EA (3x30 mL). The combined organic layers were washed with water (30 mL), dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. The residue was purified by silica gel column chromatography and eluted with PE/EA (1/1) to afford ethyl 2-(1-(((tert-butoxycarbonyl)amino)methyl)cyclopropyl)acetate (1.23 g, 50.20%) as a light yellow oil. LC/MS: mass calcd. For $C_{13}H_{23}NO_4$: 257.16, found: 258.05 $[M+H]^+$.

[00604] Step 5. To a stirred solution of ethyl 2-(1-(((tert-butoxycarbonyl)amino)methyl)cyclopropyl)acetate (1.23 g, 4.79 mmol, 1.00 equiv) in CH_3OH (20.00 mL) was added LiOH (2 M in H_2O , 11.96 mL, 23.93 mmol, 5.00 equiv) and the mixture was stirred for 2.0 h at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was diluted with water (10 mL) and the mixture was acidified to pH 4~5 with 2 M HCl. The resulting mixture was extracted with EA (3x30 mL) and the combined organic layers were washed with brine (2x30 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford (1-(((tert-butoxycarbonyl)amino)methyl)cyclopropyl)acetic acid (930.00 mg, 84.85%) as a white solid. LCMS: mass calcd. For $C_{11}H_{19}NO_4$: 229.13, found: 252.00 $[M+Na]^+$.

[00605] Step 6. To a stirred mixture of (1-(((tert-butoxycarbonyl)amino)methyl)cyclopropyl)acetic acid (4.20 g, 18.32 mmol, 1.00 equiv) and ethyl 4-amino-1-methylimidazole-2-carboxylate hydrochloride (4.51 g, 21.98 mmol, 1.20 equiv) in DMF (50.00 mL) was added TCFH (6.68 g, 23.82 mmol, 1.30 equiv) and NMI (6.02 g, 73.28 mmol, 4.00 equiv) and the mixture was stirred at room temperature for 16.0 h. The resulting mixture was extracted with EA (3x100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure to afford ethyl 4-[2-(1-(((tert-butoxycarbonyl)amino)methyl)cyclopropyl)acetamido]-1-methylimidazole-2-carboxylate (5.20 g, 74.61%) as a yellow solid. LCMS: mass calcd. For $C_{18}H_{28}N_4O_5$: 380.21, found: 403.10 $[M+Na]^+$.

[00606] Step 7. To the mixture of ethyl 4-[2-(1-(((tert-butoxycarbonyl)amino)methyl)cyclopropyl)acetamido]-1-methylimidazole-2-carboxylate (5.20 g, 13.67 mmol, 1.0 equiv) in MeOH (30.00 mL) was added LiOH (2 M in H_2O , 34.17 mL, 68.34 mmol, 5.00 equiv) and the mixture was stirred at room temperature for 4.0 h. Then the resulting mixture was concentrated

under reduced pressure. The residue was diluted with water (50 mL) and the mixture was acidified to pH 4~5 with 2 M HCl. The precipitated solids were collected by filtration, washed with water (3x20 mL), and dried under vacuum to afford 4-[2-(1-((tert-butoxycarbonyl)amino)methyl)cyclopropyl]acetamido]-1-methylimidazole-2-carboxylic acid (4.60 g, 95.50%) as an off-white solid. LCMS: mass calcd. For $C_{16}H_{24}N_4O_5$: 352.17, found: 353.10 $[M+H]^+$.

[00607] Step 8. To the stirred mixture of 4-[2-(1-((tert-butoxycarbonyl)amino)methyl)cyclopropyl]acetamido]-1-methylimidazole-2-carboxylic acid (1.00 g, 2.84 mmol, 1.00 equiv) and ethyl 3-({4-[4-(3-aminopropanamido)-1-methylpyrrole-2-amido]-1-methylimidazol-2-yl}formamido)propanoate (1.48 g, 3.41 mmol, 1.20 equiv) in DMF (15.00 mL) were added DIEA (0.92 g, 7.10 mmol, 2.05 equiv) and PyBOP (1.92 g, 3.69 mmol, 1.30 equiv) and the mixture was stirred at room temperature for 1.0 h. The resulting mixture was quenched with ice water (50 mL). The precipitated solids were collected by filtration, washed with water (3x30 mL), and concentrated under vacuum to afford ethyl 3-({4-({4-[3-({4-[2-(1-((tert-butoxycarbonyl)amino)methyl)cyclopropyl]acetamido]-1-methylimidazol-2-yl}formamido)propanamido]-1-methylpyrrole-2-amido}-1-methylimidazol-2-yl)formamido)propanoate (1.00 g, 45.89%) as a brown solid. LCMS: mass calcd. For $C_{35}H_{49}N_{11}O_9$: 767.37, found: 768.40 $[M+H]^+$.

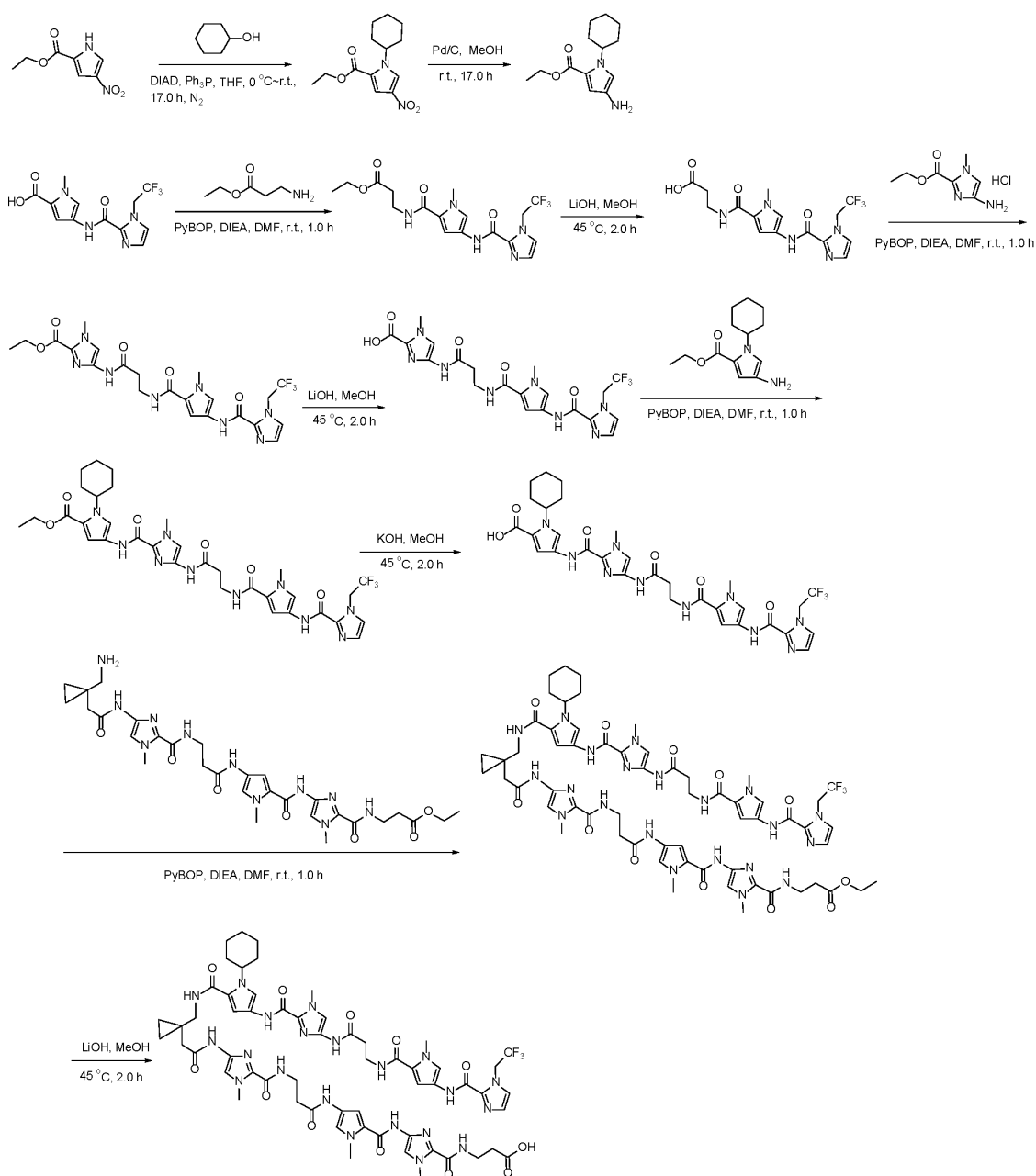
[00608] Step 9. To the stirred solution of ethyl 3-({4-({4-[3-({4-[2-(1-((tert-butoxycarbonyl)amino)methyl)cyclopropyl]acetamido]-1-methylimidazol-2-yl}formamido)propanamido]-1-methylpyrrole-2-amido}-1-methylimidazol-2-yl)formamido)propanoate (1.00 g, 1.32 mmol, 1.00 equiv) in DCM (10.00 mL) was added TFA (2.00 mL) and the resulting mixture was stirred for 1.0 h at room temperature. The mixture was concentrated under vacuum to afford ethyl 3-({4-({4-[3-({4-[2-(1-((aminomethyl)cyclopropyl]acetamido)-1-methylimidazol-2-yl)formamido)propanamido]-1-methylpyrrole-2-amido}-1-methylimidazol-2-yl)formamido)propanoate (1.00 g, crude) as a brown oil. LCMS: mass calcd. For $C_{30}H_{41}N_{11}O_7$: 667.32, found: 668.35 $[M+H]^+$.

[00609] Step 10. To the stirred mixture 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 (0.68 g, 1.20 mmol, 1.00 equiv) and ethyl 3-({4-({4-[3-({4-[2-(1-(aminomethyl)cyclopropyl]acetamido)-1-methylimidazol-2-yl}formamido)propanamido]-1-methylpyrrole-2-amido)-1-methylimidazol-2-yl}formamido)propanoate (0.97 g, 1.45 mmol, 1.20 equiv) in DMF (10.00 mL) was added DIEA (0.78 g, 6.02 mmol, 5.00 equiv) and PyBOP (0.81 g, 1.57 mmol, 1.30 equiv) and the mixture was stirred for 1.0 h at room temperature. The reaction was quenched with ice water (25 mL). The precipitated solids were collected by filtration and the filter cake was washed with H_2O (3x20 mL) and dried under vacuum. This resulted in ethyl 3-({1-methyl-4-[1-methyl-4-(3-({1-methyl-4-(2-({1-({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)methyl)cyclopropyl]acetamido)imidazol-2-yl}formamido)propanamido)pyrrole-2-amido]imidazol-2-yl}formamido)propanoate (1.40 g, 95.72%) as a light brown solid. LCMS: mass calcd. For $C_{53}H_{67}N_{21}O_{12}$: 1213.53, found: 1214.75 $[M+H]^+$.

[00610] Step 11. To the mixture of ethyl 3-({1-methyl-4-[1-methyl-4-(3-({1-methyl-4-(2-({1-({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)methyl}cyclopropyl}acetamido)imidazol-2-yl}formamido}propanamido)pyrrole-2-amido]imidazol-2-yl}formamido)propanoate (1.40 g, 1.15 mmol, 1.00 equiv) in MeOH (6.00 mL) and THF (10.00 mL) was added LiOH (2 M in H₂O, 2.89 mL, 5.77 mmol, 5.00 equiv) and the mixture was stirred for 1.0 h at room temperature. The mixture was concentrated under reduced pressure and then diluted with water (30 mL). The mixture was acidified to pH 4~5 with 2 M HCl and the precipitated solids were collected by filtration, washed with water (3x30 mL), and dried under vacuum. This resulted in 3-({1-methyl-4-[1-methyl-4-(3-({1-methyl-4-(2-({1-({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)methyl}cyclopropyl}acetamido)imidazol-2-yl}formamido}propanamido)pyrrole-2-amido]imidazol-2-yl}formamido)propanoic acid (1.20 g, 87.74%) as a yellow solid. LCMS: mass calcd. For C₅₃H₆₃N₂₁O₁₂: 1185.50, found: 594.00 [M/2+H]⁺.

[00611] Example 2. Synthesis of 3-[(4-{4-[3-({4-[2-(1-{{(1-cyclohexyl-4-{1-methyl-4-[3-({1-methyl-4-[1-(2,2,2-trifluoroethyl)imidazole-2-amido]pyrrol-2-yl}formamido) propanamido]imidazole-2-amido}pyrrol-2-yl}formamido)methyl}cyclopropyl}acetamido]-1-methylimidazol-2-yl}formamido)propanamido]-1-methylpyrrole-2-amido}-1-methylimidazol-2-yl) formamido]propanoic acid

[00612] Scheme 2.



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afford ethyl 1-cyclohexyl-4-nitropyrrole-2-carboxylate (350.00 mg, 24.20%) as a yellow oil. LC/MS: mass calcd. For $C_{13}H_{18}N_2O_4$: 266.13, found: 267.05 [M+H]⁺.

[00614] Step 2. To a solution of ethyl 1-cyclohexyl-4-nitropyrrole-2-carboxylate (170.00 mg, 0.64 mmol, 1.00 equiv) in MeOH (2.00 mL) was added Pd/C (51.00 mg, 30% w/w) and the reaction was stirred for 17.0 h at room temperature under H₂ atmosphere. The mixture was filtrated and the filtrate was concentrated to afford ethyl 4-amino-1-cyclohexylpyrrole-2-carboxylate (150.00 mg, 99.43%) as a yellow oil. LC/MS: mass calcd. For $C_{13}H_{20}N_2O_2$: 236.15, found: 237.05 [M+H]⁺.

[00615] Step 3. To a stirred solution of 1-methyl-4-[1-(2,2,2-trifluoroethyl)imidazole-2-amido]pyrrole-2-carboxylic acid (1.00 g, 3.16 mmol, 1.00 equiv) in DMF (15.00 mL) were added PyBOP (2.47 g, 4.74 mmol, 1.50 equiv), DIEA (1.22 g, 9.48 mmol, 3.00 equiv) and β-alanine ethyl ester (370.44 mg, 3.16 mmol, 1.00 equiv) at 0 °C. The resulting mixture was stirred for 1.0 h at room temperature. The mixture was quenched with ice water (50 mL). The precipitated solids were collected by filtration, washed with H₂O (3x20 mL), and dried under vacuum to afford ethyl 3-({1-methyl-4-[1-(2,2,2-trifluoroethyl)imidazole-2-amido]pyrrol-2-yl}formamido)propanoate (1.20 g, 91.36%) as a yellow solid. LC/MS: mass calcd. For $C_{17}H_{20}F_3N_5O_4$: 415.15, found: 416.15 [M+H]⁺.

[00616] Step 4. To a solution of ethyl 3-({1-methyl-4-[1-(2,2,2-trifluoroethyl)imidazole-2-amido]pyrrol-2-yl}formamido)propanoate (1.20 g, 2.88 mmol, 1.00 equiv) in MeOH (20.00 mL) was added LiOH solution (2M in H₂O, 5.78 mL, 11.52 mmol, 4.00 equiv). The resulting mixture was stirred for 2.0 h at 45 °C. The mixture was then concentrated under vacuum. The residue was dissolved in H₂O (20 mL) and acidified to pH 3~4 with HCl (2 M). The precipitated solids were collected by filtration, washed with H₂O (3x10 mL), and dried under vacuum to afford 3-({1-methyl-4-[1-(2,2,2-trifluoroethyl)imidazole-2-amido]pyrrol-2-yl}formamido)propanoic acid (1.00 g, 89.37%) as a yellow solid. LC/MS: mass calcd. For $C_{15}H_{16}F_3N_5O_4$: 387.12, found: 388.05 [M+H]⁺.

[00617] Step 5. To a stirred solution of 3-({1-methyl-4-[1-(2,2,2-trifluoroethyl)imidazole-2-amido]pyrrol-2-yl}formamido)propanoic acid (1.00 g, 2.58 mmol, 1.00 equiv) in DMF (20.00 mL) was added ethyl 4-amino-1-methylimidazole-2-carboxylate hydrochloride (0.53 g, 2.58 mmol, 1.00 equiv), PyBOP (1.61 g, 3.09 mmol, 1.20 equiv) and DIEA (1.00 g, 7.74 mmol, 3.00 equiv) at 0 °C. The resulting mixture was stirred for 1.0 h at room temperature. The reaction was quenched with ice water (50 mL). The precipitated solids were collected by filtration and the filter cake was washed with H₂O (3x10 mL) and dried under vacuum. To afford ethyl 1-methyl-4-[3-({1-methyl-4-[1-(2,2,2-trifluoroethyl)imidazole-2-amido]pyrrol-2-yl}formamido)propanamido]imidazole-2-carboxylate (1.10 g, 79.12%) as a yellow solid. LC/MS: mass calcd. For $C_{22}H_{25}F_3N_8O_5$: 538.19, found: 539.25 [M+H]⁺.

[00618] Step 6. To a stirred solution of ethyl 1-methyl-4-[3-({1-methyl-4-[1-(2,2,2-trifluoroethyl)imidazole-2-amido]pyrrol-2-yl}formamido)propanamido]imidazole-2-carboxylate (1.00 g, 1.85 mmol, 1.00 equiv) MeOH (20.00 mL) was added LiOH (2M, 3.71 mL, 7.43 mmol, 4.00 equiv) and the reaction mixture was stirred for 2.0 h at 45 °C. The resulting mixture was then concentrated under reduced pressure. The residue was dissolved in H₂O (20 mL) and the mixture was acidified to pH 3~5 with 2 M HCl. The

precipitated solids were collected by filtration, washed with H₂O (3x10 mL), and dried under vacuum to afford 1-methyl-4-[3-({1-methyl-4-[1-(2,2,2-trifluoroethyl)imidazole-2-amido]pyrrol-2-yl}formamido)propanamido]imidazole-2-carboxylic acid (800.00 mg, 84.40%) as a yellow solid. LC/MS: mass calcd. For C₂₀H₂₁F₃N₈O₅: 510.16, found: 511.20 [M+H]⁺.

[00619] Step 7. To a stirred solution of 1-methyl-4-[3-({1-methyl-4-[1-(2,2,2-trifluoroethyl)imidazole-2-amido]pyrrol-2-yl}formamido)propanamido]imidazole-2-carboxylic acid (450.00 mg, 0.88 mmol, 1.00 equiv) in DMF (8.00 mL) was added ethyl 4-amino-1-cyclohexylpyrrole-2-carboxylate (208.23 mg, 0.88 mmol, 1.00 equiv), PyBOP (504.70 mg, 0.97 mmol, 1.10 equiv) and DIEA (341.47 mg, 2.64 mmol, 3.00 equiv) at 0 °C. The resulting mixture was stirred for 1.0 h at room temperature. The reaction was quenched with ice water (15 mL). The precipitated solids were collected by filtration, washed with H₂O (3x5 mL), and dried under vacuum to afford ethyl 1-cyclohexyl-4-{1-methyl-4-[3-({1-methyl-4-[1-(2,2,2-trifluoroethyl)imidazole-2-amido]pyrrol-2-yl}formamido)propanamido]imidazole-2-amido}pyrrole-2-carboxylate (500.00 mg, 77.83%) as a yellow solid. LC/MS: mass calcd. For C₃₃H₃₉F₃N₁₀O₆: 728.30, found: 729.20 [M+H]⁺.

[00620] Step 8. To a stirred solution of ethyl 1-cyclohexyl-4-{1-methyl-4-[3-({1-methyl-4-[1-(2,2,2-trifluoroethyl)imidazole-2-amido]pyrrol-2-yl}formamido)propanamido]imidazole-2-amido}pyrrole-2-carboxylate (500.00 mg, 0.68 mmol, 1.00 equiv) in MeOH (10.00 mL) was added KOH solution (2M in H₂O, 5.15 mL, 10.32 mmol, 15.00 equiv). The resulting mixture was stirred for 2.0 h at 45 °C. Then the mixture was concentrated under reduced pressure. The residue was dissolved in H₂O (5 mL) and the mixture was acidified to pH 3~4 with 2 M HCl. The precipitated solids were collected by filtration, washed with H₂O (3x5 mL), and dried under vacuum to afford 1-cyclohexyl-4-{1-methyl-4-[3-({1-methyl-4-[1-(2,2,2-trifluoroethyl)imidazole-2-amido]pyrrol-2-yl}formamido)propanamido]imidazole-2-amido}pyrrole-2-carboxylic acid (380.00 mg, 79.04%) as a yellow solid. LC/MS: mass calcd. For C₃₁H₃₅F₃N₁₀O₆: 700.27, found: 701.30 [M+H]⁺.

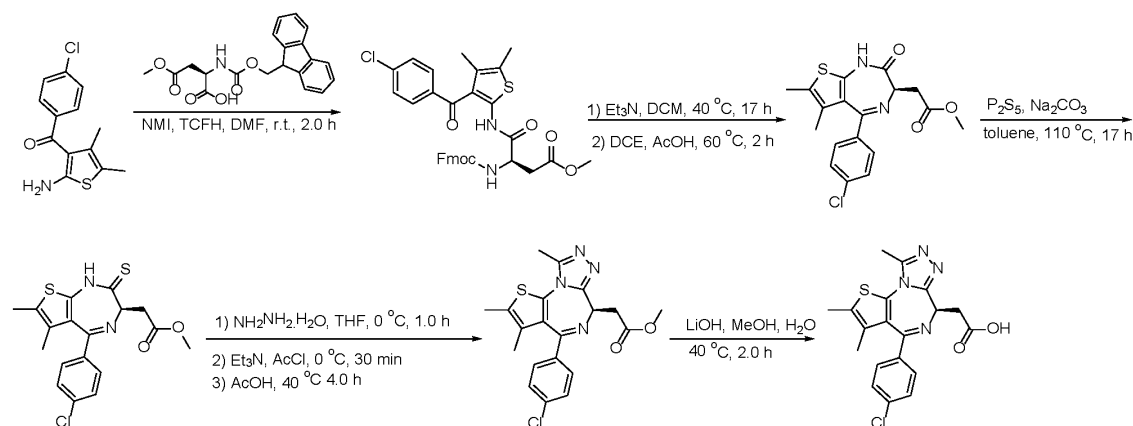
[00621] Step 9. To a stirred solution of 1-cyclohexyl-4-{1-methyl-4-[3-({1-methyl-4-[1-(2,2,2-trifluoroethyl)imidazole-2-amido]pyrrol-2-yl}formamido)propanamido]imidazole-2-amido}pyrrole-2-carboxylic acid (90.00 mg, 0.12 mmol, 1.00 equiv) in DMF (2.00 mL) was added ethyl 3-[(4-{4-[3-({4-[2-(1-{{(tert-butoxycarbonyl)amino}methyl}cyclopropyl)acetamido]-1-methylimidazol-2-yl}formamido)propanamido]-1-methylpyrrole-2-amido}-1-methylimidazol-2-yl)formamido]propanoate (98.63 mg, 0.12 mmol, 1.00 equiv), PyBOP (100.27 mg, 0.19 mmol, 1.50 equiv) and DIEA (49.80 mg, 0.38 mmol, 3.00 equiv) at 0 °C. The resulting mixture was stirred for 1.0 h at room temperature. The reaction was quenched with ice water (5 mL). The precipitated solids were collected by filtration, washed with H₂O (3x2 mL), and dried under vacuum to afford ethyl 3-[(4-{4-[3-({4-[2-(1-{{(1-cyclohexyl-4-{1-methyl-4-[3-({1-methyl-4-[1-(2,2,2-trifluoroethyl)imidazole-2-amido]pyrrol-2-yl}formamido)propanamido]imidazole-2-amido}pyrrol-2-yl)formamido]methyl}cyclopropyl)acetamido]-1-methylimidazol-2-yl}formamido)propanamido]-1-methylpyrrole-2-amido}-1-methylimidazol-2-yl)formamido]propanoate (100.00 mg, 57.65%) as a yellow solid. LC/MS: mass calcd. For C₆₁H₇₄F₃N₂₁O₁₂: 1349.58, found: 676.25 [M/2+H]⁺.

[00622] Step 10. To a stirred solution of ethyl 3-[(4-{4-[3-({4-[2-(1-[(1-cyclohexyl-4-{1-methyl-4-[3-({1-methyl-4-[1-(2,2,2-trifluoroethyl)imidazole-2-amido]pyrrol-2-yl}formamido) propanamido]imidazole-2-amido]pyrrol-2-yl)formamido]methyl}cyclopropyl)acetamido]-1-methylimidazol-2-yl}formamido)propanamido]-1-methylpyrrole-2-amido}-1-methylimidazol-2-yl)formamido]propanoate (120.00 mg, 0.08 mmol, 1.00 equiv) in MeOH (2.00 mL) was added LiOH solution (2M in H₂O, 0.17 mL, 0.35 mmol, 4.00 equiv). The resulting mixture was stirred for 2.0 h at 45 °C. Then the mixture was concentrated under vacuum. The residue was dissolved in H₂O (5 mL) and acidified to pH 3 with HCl (2 M). The precipitated solids were collected by filtration, washed with H₂O (3x10 mL), and dried under vacuum to afford 3-[(4-{4-[3-({4-[2-(1-[(1-cyclohexyl-4-{1-methyl-4-[3-({1-methyl-4-[1-(2,2,2-trifluoroethyl)imidazole-2-amido]pyrrol-2-yl}formamido) propanamido]imidazole-2-amido]pyrrol-2-yl)formamido]methyl}cyclopropyl)acetamido]-1-methylimidazol-2-yl}formamido)propanamido]-1-methylpyrrole-2-amido}-1-methylimidazol-2-yl)formamido]propanoic acid (100.00 mg, 85.10%) as a yellow solid. LC/MS: mass calcd. For C₅₉H₇₀F₃N₂₁O₁₂: 1321.55, found: 1322.35[M+H]⁺.

SYNTHESIS OF TARGETING LIGAND

[00623] Example 3. Synthesis of (R)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-(4-hydroxyphenyl)acetamide

[00624] Scheme 3.



[00625] Step 1. To a stirred solution of (2R)-2-[(9H-fluoren-9-ylmethoxy)carbonyl]amino]-4-methoxy-4-oxobutanoic acid (5.00 g, 13.54 mmol, 1.00 equiv) in DMF (60.00 mL) was added NMI (3.33 g, 40.61 mmol, 3.00 equiv), TCFH (5.70 g, 20.31 mmol, 1.50 equiv) and 3-(4-chlorobenzoyl)-4,5-dimethylthiophen-2-amine (3.96 g, 14.90 mmol, 1.10 equiv) in portions at 0 °C. The resulting mixture was stirred for 2 h at room temperature. The reaction quenched with water/ice (200 mL) and the precipitated solids were collected by filtration, washed with water (3x30 mL), and dried under vacuum. The solid was purified by silica gel column chromatography, eluted with PE/EA (3:1) to afford methyl (3R)-3-[[3-(4-chlorobenzoyl)-4,5-dimethylthiophen-2-yl]carbamoyl]-3-[(9H-fluoren-9-ylmethoxy)carbonyl]amino]propanoate (4.95 g, 56.00%) as a yellow solid. LCMS: mass calcd. For C₃₃H₂₉ClN₂O₆S: 616.14, found: 617.05 [M+H]⁺

[00626] Step 2. To a solution of methyl (3R)-3-amino-3-[[3-(4-chlorobenzoyl)-4,5-dimethylthiophen-2-yl]carbamoyl]propanoate (4.95 g) in DCM was treated with Et₃N followed by AcOH treatment in DCE to give 2.10 g of methyl 2-[(3R)-5-(4-chlorophenyl)-6,7-dimethyl-2-oxo-1H,3H-thieno[2,3-e][1,4]diazepin-3-yl]acetate as a yellow solid (70.00% yield of two steps). LCMS: mass calcd. For C₁₈H₁₇ClN₂O₃S: 376.06, found: 377.15 [M+H]⁺.

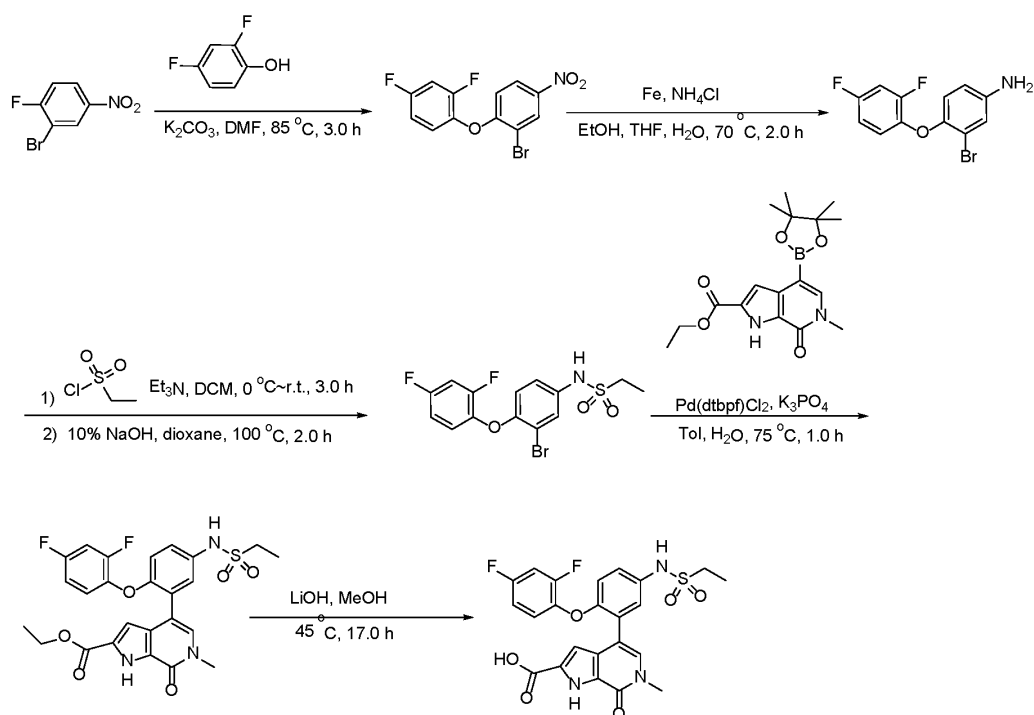
[00627] Step 3. To a solution of methyl 2-[(3R)-5-(4-chlorophenyl)-6,7-dimethyl-2-oxo-1H,3H-thieno[2,3-e][1,4]diazepin-3-yl]acetate (1.10 g, 2.92 mmol, 1.00 equiv) in toluene (25.00 ml) was added P₂S₅ (1.30 g, 0.006 mmol, 2.00 equiv) and Na₂CO₃ (0.62 g, 5.85 mmol, 2.00 equiv). The reaction was stirred at 110 °C for 17 h. The solid was filtered and the filtrate was concentrated. The residue was purified by silica gel column chromatography, eluted with PE: EA = 1:1 to afford methyl 2-[(3R)-5-(4-chlorophenyl)-6,7-dimethyl-2-sulfanylidene-1H,3H-thieno[2,3-e][1,4]diazepin-3-yl]acetate (2 g, crude) as a yellow solid. LCMS: mass calcd. For C₁₈H₁₇ClN₂O₂S₂: 392.04, found: 393.10 [M+H]⁺.

[00628] Step 4. To a solution of methyl 2-[(3R)-5-(4-chlorophenyl)-6,7-dimethyl-2-sulfanylidene-1H,3H-thieno[2,3-e][1,4]diazepin-3-yl]acetate (900.00 mg, 2.29 mmol, 1.00 equiv) in THF (6.00 mL) was added NH₂NH₂·H₂O (344.00 mg, 6.87 mmol, 3.00 equiv) dropwise at 0 °C. The reaction was stirred at 0 °C for 1 h. AcCl (539.41 mg, 6.87 mmol, 3.00 equiv) and Et₃N (695.34 mg, 6.87 mmol, 3.00 equiv) were added and the mixture was stirred at 0 °C for 30 mins. The reaction mixture was then quenched with H₂O (15 mL), extracted with EA (3x15 mL), washed with brine (20 mL), and dried over Na₂SO₄. The solid was filtrated and the filtrate was concentrated to dryness. The crude product was dissolved in AcOH (10.0 mL) and stirred at 40 °C for 4 h. The solvent was removed and the residue was purified by reverse flash chromatography with the following conditions: column, C18 column; mobile phase, MeCN in water (0.05% TFA), 5% to 50% gradient in 40 min; detector, UV 254 nm to afford methyl (R)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetate (400.00 mg, 42.09%) as a yellow solid. LCMS: mass calcd. For C₂₀H₁₉ClN₄O₂S: 414.09, found: 415.10 [M+H]⁺.

[00629] Step 5. A solution of methyl (R)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetate (400.00 mg, 0.96 mmol, 1.00 equiv) in LiOH (2M, 2.00 mL, 4.00 equiv) and MeOH (2.00 mL) was stirred at 40 °C for 2 h. The mixture was acidified with HCl (2M) and concentrated. The residue was dissolved in DMF (2 mL) and purified by reverse phase column with the following conditions: column, C18 column; mobile phase, MeCN in water (0.05% TFA), 5% to 50% gradient in 40 min; detector, UV 254 nm to afford (R)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetic acid (340.00 mg, 87.97% yield) as a white solid. LCMS: mass calcd. For C₁₉H₁₇ClN₄O₂S: 400.09, found: 401.10 [M+H]⁺.

[00630] Example 4. Synthesis of 4-[2-(2,4-difluorophenoxy)-5-ethanesulfonamidophenyl]-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid

[00631] Scheme 4.



[00632] Step 1. A solution of 2,4-difluorophenol (2.66 g, 20.45 mmol, 1.50 equiv) and 2-bromo-1-fluoro-4-nitrobenzene (3.00 g, 13.64 mmol, 1.00 equiv) in DMF (50.00 mL) was stirred at 85 °C for 3.0 h. The reaction was cooled to room temperature and was then diluted with water (150 mL). The precipitate was filtered and the filter cake was washed with water and dried to afford 2-bromo-1-(2,4-difluorophenoxy)-4-nitrobenzene (4.40 g, 98.21%) as light a yellow solid. ¹H NMR (300 MHz, DMSO-*d*₆) δ: 8.56-8.58 (m, 1H), 8.18-8.22 (m, 1H), 7.48-7.63 (m, 2H), 7.22-7.28(m, 1H), 6.99 (d, *J* = 9.0 Hz, 1H).

[00633] Step 2. Iron powder (7.78 g, 139.36 mmol, 10.00 equiv) was added in portions to a stirred solution of 2-bromo-1-(2,4-difluorophenoxy)-4-nitrobenzene (4.40 g, 13.37 mmol, 1.00 equiv) in EtOH (20.00 mL) and THF (20.00 mL), NH₄Cl (7.45 g, 139.36 mmol, 10.00 equiv), and H₂O (20.00 mL) at room temperature. The mixture was heated at 70 °C for 2.0 h. The reaction mixture was cooled to room temperature and was then filtered through a pad of Celite. The filtrate was concentrated under vacuum and the resulting residue was diluted with water (20 mL) and extracted with EA (50 mLx3). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, and concentrated to afford 3-bromo-4-(2,4-difluorophenoxy)aniline (3.77 g, 65.28%) as a brown solid. LC/MS: mass calcd. For C₁₂H₈BrF₂NO: 298.98, found: 299.90, 301.90 [M+H, M+H+2]⁺.

[00634] Step 3. To a mixture of 3-bromo-4-(2,4-difluorophenoxy)aniline (2.51 g, 8.36 mmol, 1.00 equiv) and Et₃N (3.39 g, 33.45 mmol, 4.00 equiv) in DCM (10.00 mL) a solution of ethanesulfonyl chloride (3.23 g, 25.09 mmol, 3.00 equiv) in DCM (10.00 mL) was added dropwise at 0 °C. The reaction mixture was stirred at room temperature for 3.0 h. The reaction was concentrated under vacuum, diluted with water (20 mL), and extracted with EA (20 mLx3). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated under vacuum. The resulting crude was suspended in 1,4-dioxane (30.00

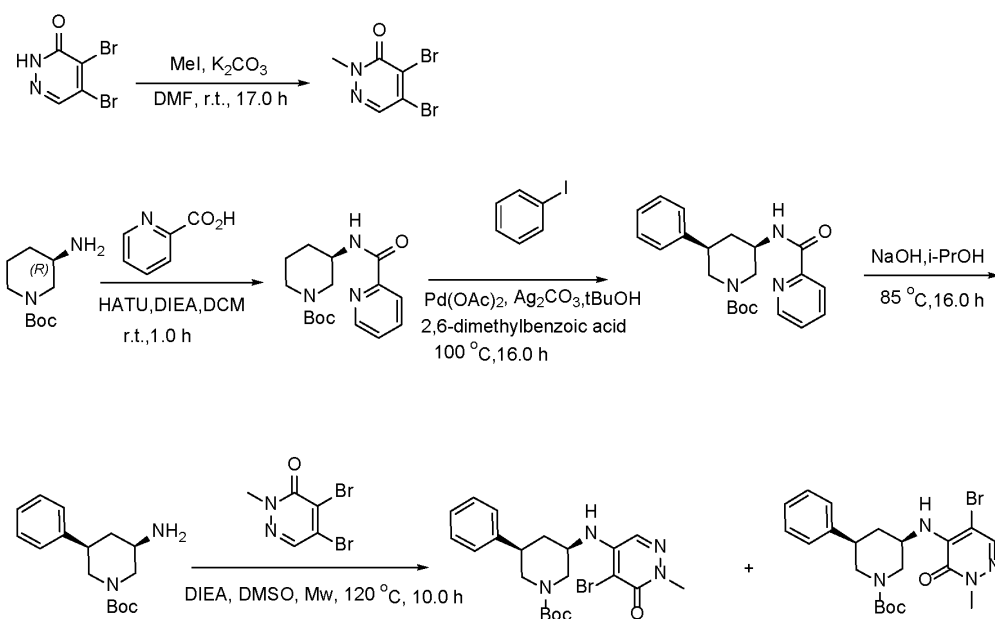
mL) and 10% NaOH (6.00 mL) and the mixture was heated at 100 °C for 2.0 h. The reaction was concentrated under vacuum, diluted with water (20 mL), and extracted with EA (20 mLx3). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated to afford N-[3-bromo-4-(2,4-difluorophenoxy)phenyl]ethanesulfonamide (3.00 g, 92.02% yield) as a brown solid. LC/MS: mass calcd. For C₁₄H₁₂BrF₂NO₃S: 390.97, found: 392.21 [M+H]⁺. ¹H NMR (300 MHz, DMSO-*d*₆) δ: 9.94(s, 1H), 7.46-7.53 (m, 2H), 7.20-7.24 (m, 1H), 7.07-7.15(m, 2H), 6.88-7.04 (m, 1H), 3.09-3.16(m, 2H), 1.21(t, *J* = 7.2 Hz, 3H).

[00635] Step 4. A mixture of N-[3-bromo-4-(2,4-difluorophenoxy)phenyl]ethanesulfonamide (1.00 g, 2.55 mmol, 1.00 equiv) and ethyl 6-methyl-7-oxo-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-*c*]pyridine-2-carboxylate (970.00 mg, 2.80 mmol, 1.10 equiv), Pd(dtbpf)Cl₂ (166.00 mg, 0.25 mmol, 0.10 equiv), and K₃PO₄ (1.10 g, 5.18 mmol, 2.03 equiv) in toluene (8.00 mL) and H₂O (2.00 mL) was stirred for 1.0 h at 75 °C under nitrogen atmosphere. The reaction mixture was cooled to room temperature and was quenched with water (70.00 mL). The mixture was extracted with EA (50 mLx3) and the combined organic layers were washed with water (40 mLx2), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH₂Cl₂/MeOH (15:1) to afford ethyl 4-[2-(2,4-difluorophenoxy)-5-ethanesulfonamidophenyl]-6-methyl-7-oxo-1H-pyrrolo[2,3-*c*]pyridine-2-carboxylate (1.20 g, 88.55%) as a brown solid. LC/MS: mass calcd. For C₂₅H₂₃F₂N₃O₆S: 531.13, found: 532.10 [M+H]⁺.

[00636] Step 5. The procedure was the same as 4-{4-[3-({4-[(2R)-2-[(tert-butoxycarbonyl)amino]-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]-1-methylimidazol-2-yl}formamido)propanamido]-1-methylpyrrole-2-amido}-1-methylimidazole-2-carboxylic acid (Example 3 Step 2). 1.10 g of ethyl 4-[2-(2,4-difluorophenoxy)-5-ethanesulfonamidophenyl]-6-methyl-7-oxo-1H-pyrrolo[2,3-*c*]pyridine-2-carboxylate was used and 1.00 g of the desired product was obtained as a grey solid (95.97% yield). LC/MS: mass calcd. For C₂₃H₁₉F₂N₃O₆S: 503.10, found: 504.10 [M+H]⁺.

[00637] Example 5. Synthesis of tert-butyl (3R,5R)-3-((5-bromo-2-methyl-3-oxo-2,3-dihydropyridazin-4-yl)amino)-5-phenylpiperidine-1-carboxylate

[00638] Scheme 5.



[00639] Step 1. To a solution of 4,5-dibromo-2H-pyridazin-3-one (5.00 g, 19.69 mmol, 1.00 equiv.) in DMF (50.00 mL) was added methyl iodide (8.39 g, 59.08 mmol, 3.00 equiv.) and K_2CO_3 (6.80 g, 49.24 mmol, 2.50 equiv.). The resulting mixture was stirred for 17.0 h at room temperature. The reaction mixture was poured into water (200 mL). The precipitated solids were collected by filtration and washed with water (150.00 mL) and dried to afford 4,5-dibromo-2-methylpyridazin-3-one (3.30 g, 62.54%) as a yellow solid. LC/MS: mass calcd. For $C_5H_4Br_2N_2O$: 265.87, found: 266.85, 268.85 $[M+H, M+H+2]^+$.

[00640] Step 2. To a stirred solution of picolinic acid (10.14 g, 82.38 mmol, 1.10 equiv.) in DCM (100 mL) was added HATU (34.17 g, 89.87 mmol, 1.20 equiv.) and DIEA (10.65 g, 82.38 mmol, 1.10 equiv.). The resulting mixture was stirred at 25 °C for 0.5 h. The tert-butyl (3R)-3-aminopiperidine-1-carboxylate (15.00 g, 74.89 mmol, 1.00 equiv.) and DIEA (19.36 g, 149.79 mmol, 2.00 equiv.) were added in portions and the resulting mixture was stirred at 25 °C for 1.0 h. Then the resulting mixture was concentrated under vacuum and the residue was purified by silica gel column chromatography (30-50% EA/PE) to afford tert-butyl (3R)-3-(pyridine-2-amido)piperidine-1-carboxylate (22.00 g, 96.19%) as a yellow solid. LC/MS: mass calcd. For $C_{16}H_{23}N_3O_3$: 305.17, found: 306.10 $[M+H]^+$.

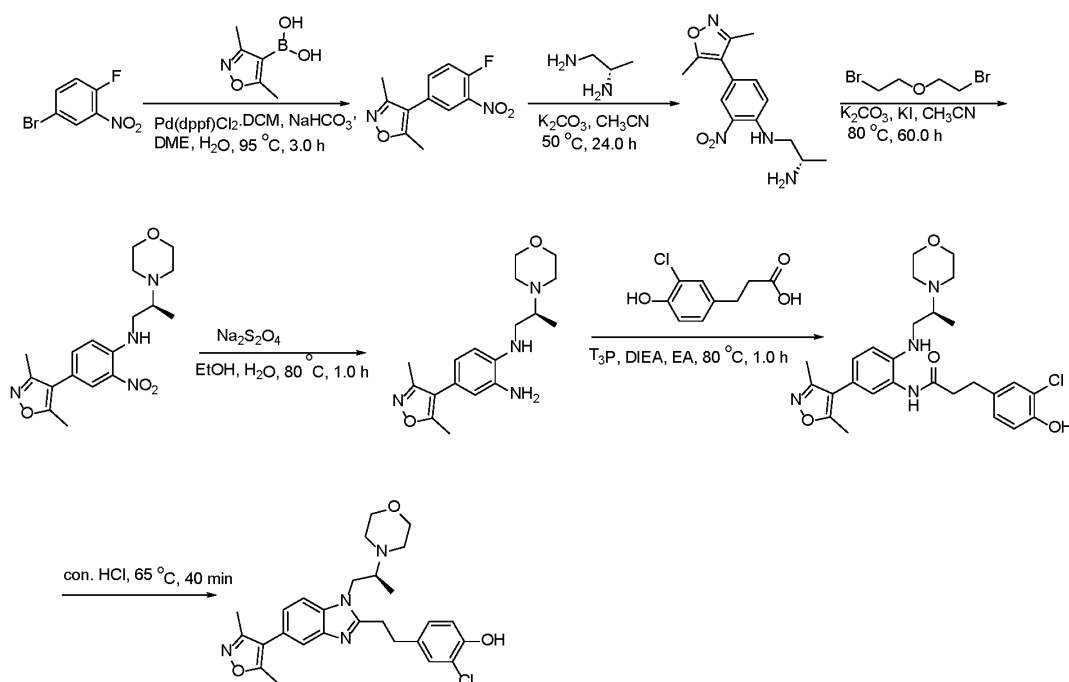
[00641] Step 3. To a stirred solution of tert-butyl (3R)-3-(pyridine-2-amido)piperidine-1-carboxylate (19.00 g, 62.22 mmol, 1.00 equiv.) in 2-methylpropan-2-ol (100 mL) was added iodophenyl (63.47 g, 311.09 mmol, 5.00 equiv.), 2,6-dimethylbenzoic acid (2.34 g, 15.58 mmol, 0.25 equiv.), $Pd(OAc)_2$ (1.40 g, 6.22 mmol, 0.10 equiv.) and Ag_2CO_3 (17.16 g, 62.22 mmol, 1.00 equiv.) and the resulting mixture was stirred at 100 °C for 16.0 h. Then the resulting mixture was concentrated under vacuum and the residue was purified by silica gel column chromatography (30-50% EA/PE) to afford tert-butyl (3R,5R)-3-phenyl-5-(pyridine-2-amido)piperidine-1-carboxylate (10.70 g, 45.08%) as a yellow solid. LC/MS: mass calcd. For $C_{22}H_{27}N_3O_3$: 381.21, found: 326.15 $[M+H-56]^+$.

[00642] Step 4. To a stirred solution of tert-butyl (3R,5R)-3-phenyl-5-(pyridine-2-amido)piperidine-1-carboxylate (10.70 g, 28.05 mmol, 1.00 equiv) in i-PrOH (100 mL) was added NaOH (11.22 g, 280.49 mmol, 10.00 equiv.) and the reaction mixture was stirred for 16.0 h at 85 °C. The reaction was filtered and the filtrate was concentrated. The resulting residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (0.05% NH_4HCO_3), 30% to 50% gradient in 30 min; Detector, UV 254 nm. The fractions were combined and concentrated to afford tert-butyl (3R,5R)-3-amino-5-phenylpiperidine-1-carboxylate (6.50 g, 83.85%) as a white solid. LC/MS: mass calcd. For $\text{C}_{16}\text{H}_{24}\text{N}_2\text{O}_2$: 276.18, found: 277.10 $[\text{M}+\text{H}]^+$.

[00643] Step 5. To a stirred solution of tert-butyl (3R,5R)-3-amino-5-phenylpiperidine-1-carboxylate (6.00 g, 21.71 mmol, 1.00 equiv.) in DMF (50 mL) was added 4,5-dibromo-2-methylpyridazin-3-one (5.82 g, 21.71 mmol, 1.00 equiv.) and DIEA (11.22 g, 86.84 mmol, 4.00 equiv.). The reaction mixture was irradiated with microwave radiation for 10.0 h at 120 °C and then 100.00 mL H_2O was added. The resulting mixture was extracted with EA (100 mLx3), the organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by silica gel column chromatography (30-50% EA/PE) to afford tert-butyl (3R,5R)-3-[(5-bromo-1-methyl-6-oxopyridazin-4-yl)amino]-5-phenylpiperidine-1-carboxylate (5.02 g, 46.83%) as a yellow solid and tert-butyl (3R,5R)-3-[(5-bromo-2-methyl-3-oxo-2,3-dihydropyridazin-4-yl)amino]-5-phenylpiperidine-1-carboxylate (2.00 g, 19.88%) as a yellow solid. LC/MS: mass calcd. For $\text{C}_{21}\text{H}_{27}\text{BrN}_4\text{O}_3$: 462.13, found: 463.10, 465.10 $[\text{M}+\text{H}, \text{M}+\text{H}+2]^+$.

[00644] Example 6. Synthesis of (S)-2-chloro-4-(2-(5-(3,5-dimethylisoxazol-4-yl)-1-(2-morpholinopropyl)-1H-benzo[d]imidazol-2-yl)ethyl)phenol

[00645] Scheme 6.



[00646] Step 1. Into a 500 ml flask was added 4-bromo-1-fluoro-2-nitrobenzene (15.40 g, 70.00 mmol, 1.00 equiv), 3, 5-dimethyl-1,2-oxazol-4-ylboronic acid (9.87 g, 70.001 mmol, 1.00 equiv), NaHCO_3 (11.76 g, 140.00 mmol, 2.00 equiv), $\text{Pd(dppf)Cl}_2 \cdot \text{CH}_2\text{Cl}_2$ (2.86 g, 3.500 mmol, 0.05 equiv), DME (100.00 mL), and H_2O (10.00 mL) and the reaction mixture was stirred at 95 °C for 3.0 h under N_2 atmosphere. The reaction was concentrated and the residue was purified by silica gel column with PE/A (1:1) to yield 4-(4-fluoro-3-nitrophenyl)-3,5-dimethyl-1,2-oxazole (15.7 g, 90.21% yield) as a white solid. LC/MS: mass calcd. For $\text{C}_{11}\text{H}_9\text{FN}_2\text{O}_3$: 236.06, found: 237.10[M+H]⁺.

[00647] Step 2. Into a 500 ml flask was added 4-(4-fluoro-3-nitrophenyl)-3,5-dimethyl-1,2-oxazole (12.70 g, 53.77 mmol, 1.00 equiv), (2S)-propane-1,2-diamine (3.99 g, 53.92 mmol, 1.00 equiv), K_2CO_3 (14.86 g, 107.54 mmol, 2.00 equiv), and CH_3CN (300.00 mL) and the reaction was stirred at 50 °C for 24.0 h. The reaction was filtered and washed with CH_3CN . The filtrate was concentrated and the residue was purified by silica gel column with PE/EA (1:1) to afford (2S)-N1-[4-(3,5-dimethyl-1,2-oxazol-4-yl)-2-nitrophenyl]propane-1,2-diamine (6.10 g, 37.01% yield) as a yellow oil. LC/MS: mass calcd. For $\text{C}_{11}\text{H}_9\text{FN}_2\text{O}_3$: 290.14, found: 291.05[M+H]⁺.

[00648] Step 3. Into a 500 ml flask was added (2S)-N1-[4-(3,5-dimethyl-1,2-oxazol-4-yl)-2-nitrophenyl]propane-1,2-diamine (6.10 g, 21.01 mmol, 1.00 equiv) and CH_3CN (200.00 mL). Then 1-bromo-2-(2-bromoethoxy)ethane (5.36 g, 23.11 mmol, 1.10 equiv), K_2CO_3 (8.71 g, 63.03 mmol, 3.00 equiv), and KI (4.19 g, 25.21 mmol, 1.20 equiv) were added and the reaction mixture was stirred at 80 °C for 60.0 h. The reaction was filtered and the filtrate was concentrated. The residue was purified by silica gel column chromatography with PE/EA (1:1) to afford 4-(3,5-dimethyl-1,2-oxazol-4-yl)-N-[(2S)-2-(morpholin-4-yl)propyl]-2-nitroaniline (6.00 g, 71.31% yield) as a red solid. LC/MS: mass calcd. For $\text{C}_{18}\text{H}_{24}\text{N}_4\text{O}_4$: 360.18, found: 361.10[M+H]⁺.

[00649] Step 4. Into a 500 ml flask was added 4-(3,5-dimethyl-1,2-oxazol-4-yl)-N-[(2S)-2-(morpholin-4-yl)propyl]-2-nitroaniline (3.00 g, 8.32 mmol, 1.00 equiv), EtOH (50.00 mL), H_2O (50.00 mL), and $\text{Na}_2\text{S}_2\text{O}_4$ (7.25 g, 41.62 mmol, 5.00 equiv) and the reaction was stirred at 80 °C for 1.0 h. The reaction was then concentrated under the reduced pressure and the residue was extracted with EA (50 mLx3). The combined organic phase was washed with NaCl (100 mL), dried over anhydrous Na_2SO_4 , and concentrated. The residue (1.70 g, 61.19% yield) was used directly in the next step without further purification. LC/MS: mass calcd. For $\text{C}_{18}\text{H}_{26}\text{N}_4\text{O}_2$: 330.21, found: 331.15[M+H]⁺.

[00650] Step 5. Into a 250 ml flask was added 4-(3,5-dimethyl-1,2-oxazol-4-yl)-N1-[(2S)-2-(morpholin-4-yl)propyl] benzene-1,2-diamine (1.70 g, 5.15 mmol, 1.00 equiv), EA (60.00 mL), 3-(3-chloro-4-hydroxyphenyl) propanoic acid (1.03 g, 5.15 mmol, 1.00 equiv), T_3P (2.46 g, 7.72 mmol, 1.50 equiv), and DIEA (2.66 g, 20.58 mmol, 4.00 equiv) and the reaction mixture was stirred at 80 °C for 1.0 h. Then the reaction mixture was washed with H_2O (20 ml x 3) and the combined organic phase was dried with anhydrous Na_2SO_4 and concentrated. The residue (1.10 g, 27.92% yield) was used directly in the next step without further purification. LC/MS: mass calcd. For $\text{C}_{27}\text{H}_{33}\text{ClN}_4\text{O}_4$: 512.22, found: 513.15 [M+H]⁺.

[00651] Step 6. Into a 100 ml flask was added 3-(3-chloro-4-hydroxyphenyl)-N-[5-(3,5-dimethyl-1,2-oxazol-4-yl)-2-[[[(2S)-2-(morpholin-4-yl)propyl]amino]phenyl]]propanamide (1.10 g, 2.14 mmol, 1.00 equiv) and HCl (20.00 mL) and the reaction mixture was stirred at 65 °C for 40 mins. The reaction was concentrated and the residue was purified by reverse flash chromatography with the following conditions: Column: C18 column; mobile phase: MeCN in water (0.05% NH_4HCO_3), 10% to 50% gradient in 30 min; Detector: UV 254 nm. The fractions were combined and concentrated to afford 2-chloro-4-[2-[5-(3,5-dimethyl-1,2-oxazol-4-yl)-1-[(2S)-2-(morpholin-4-yl)propyl]-1,3-benzodiazol-2-yl]ethyl]phenol (490.00 mg, 46.00% yield) as a white oil. LC/MS: mass calcd. For $\text{C}_{27}\text{H}_{31}\text{ClN}_4\text{O}_3$: 494.21, found: 495.05[M+H]⁺.

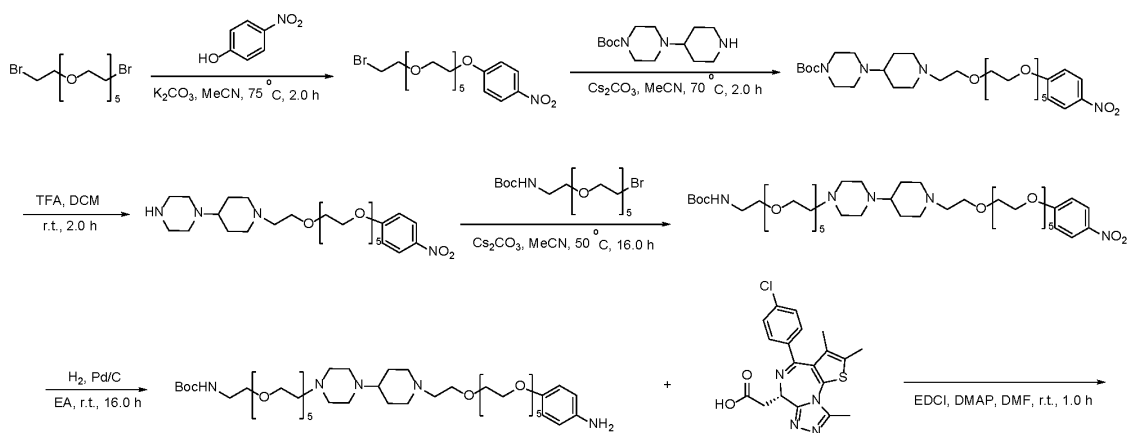
[00652] ^1H NMR (400 MHz, Methanol- d_4) δ : 7.52 - 7.56 (m, 2H), 7.17 - 7.23 (m, 2H), 6.94 (d, J = 8.3 Hz, 1H), 6.81 (d, J = 8.2 Hz, 1H), 4.16 - 4.21 (m, 1H), 3.92 - 3.97 (m, 1H), 3.58 - 3.66 (m, 4H), 3.21 - 3.25 (m, 2H), 3.12 - 3.16 (m, 2H), 2.82 - 2.90 (m, 1H), 2.66 - 2.72 (m, 2H), 2.39 - 2.59 (m, 5H), 2.29 (s, 3H), 0.99 (d, J = 6.7 Hz, 3H).

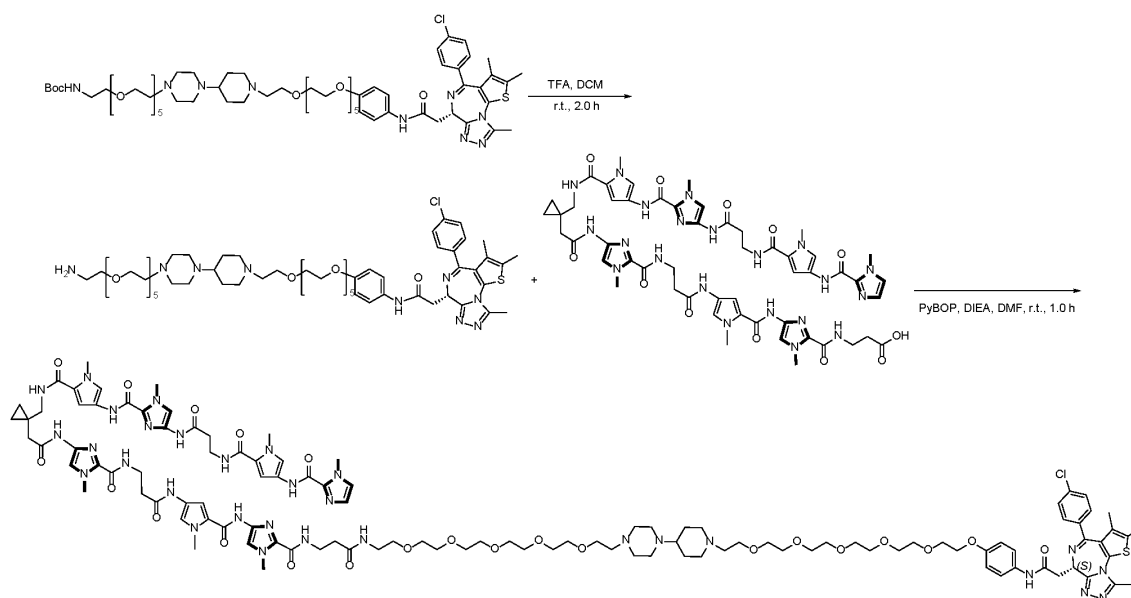
[00653] ^{13}C NMR (75 MHz, MeOD) δ : 165.35, 158.86, 155.96, 151.51, 141.90, 134.59, 132.82, 129.54, 127.68, 123.98, 123.50, 120.25, 118.50, 117.01, 116.32, 110.56, 78.27, 77.83, 77.40, 66.86, 59.47, 32.55, 29.25, 10.79, 10.20, 9.51.

SYNTHESIS OF REPRESENTATIVE COMPOUNDS

[00654] Example 7. Synthesis of Compound C-57

[00655] Scheme 7.





[00656] Step 1. To a stirred mixture of p-nitrophenol (263.00 mg, 1.89 mmol, 1.00 equiv) and 1,17-dibromo-3,6,9,12,15-pentaoxaheptadecane (1.00 g, 2.46 mmol, 1.30 equiv) in CH_3CN (10.00 mL) was added K_2CO_3 (783.87 mg, 5.67 mmol, 3.00 equiv) at room temperature. The resulting mixture was stirred for 2.0 h at 75 °C. The resulting mixture was filtered, the filter cake was washed with MeCN (3x10 mL). The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography, and eluted with PE/EA (1:1) to afford 1-bromo-17-(4-nitrophenoxy)-3,6,9,12,15-pentaoxaheptadecane (500.00 mg, 56.71%) as light yellow oil. LC/MS: mass calcd. For $\text{C}_{18}\text{H}_{28}\text{BrNO}_8$: 465.10, found: 466.00 $[\text{M}+\text{H}]^+$.

[00657] Step 2. To a stirred mixture of 1-bromo-17-(4-nitrophenoxy)-3,6,9,12,15-pentaoxaheptadecane (800.00 mg, 1.72 mmol, 1.00 equiv) and tert-butyl 4-(piperidin-4-yl)piperazine-1-carboxylate (462.15 mg, 1.72 mmol, 1.00 equiv) in CH_3CN (10 mL) was added Cs_2CO_3 (1.12g, 3.43 mmol, 2.00 equiv) at room temperature. The resulting mixture was stirred for 2.0 h at 70 °C. The mixture was filtered and the filter cake was washed with MeCN (3x20 mL). The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography and eluted with PE/EA (1:1) to afford tert-butyl 4-{1-[17-(4-nitrophenoxy)-3,6,9,12,15-pentaoxaheptadecan-1-yl]piperidin-4-yl}piperazine-1-carboxylate (600.00 mg, 53.41%) as a light yellow solid. LC/MS: mass calcd. For $\text{C}_{32}\text{H}_{54}\text{N}_4\text{O}_{18}$: 654.38, found: 655.35 $[\text{M}+\text{H}]^+$.

[00658] Step 3. To a stirred mixture of tert-butyl 4-{1-[17-(4-nitrophenoxy)-3,6,9,12,15-pentaoxaheptadecan-1-yl]piperidin-4-yl}piperazine-1-carboxylate (600.00 mg, 0.92 mmol, 1.00 equiv) in DCM (5.00 mL) was added TFA (1.00 mL) and the resulting mixture was stirred for 1.0 h at room temperature. The resulting mixture was concentrated under reduced pressure to afford 1-{1-[17-(4-nitrophenoxy)-3,6,9,12,15-pentaoxaheptadecan-1-yl]piperidin-4-yl}piperazine (500.00 mg, 98.37%) as a light yellow oil. LC/MS: mass calcd. For $\text{C}_{27}\text{H}_{46}\text{N}_4\text{O}_{18}$: 554.33, found: 555.35 $[\text{M}+\text{H}]^+$.

[00659] Step 4. To a stirred mixture of 1-{1-[17-(4-nitrophenoxy)-3,6,9,12,15-pentaoxaheptadecan-1-yl]piperidin-4-yl}piperazine (470.00 mg, 0.85 mmol, 1.00 equiv) and tert-butyl N-(17-bromo-3,6,9,12,15-pentaoxaheptadecan-1-yl)carbamate (414.17 mg, 0.93 mmol, 1.10 equiv) in CH₃CN (5.00 mL) was added Cs₂CO₃ (690.19 mg, 2.12 mmol, 2.50 equiv) and the resulting mixture was stirred for 16.0 h at 50 °C. The resulting mixture was filtered and the filter cake was washed with MeCN (3x30 mL). The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography, eluted with PE/EA (1:2) to afford tert-butyl N-[17-(4-{1-[17-(4-nitrophenoxy)-3,6,9,12,15-pentaoxaheptadecan-1-yl]piperidin-4-yl}piperazin-1-yl)-3,6,9,12,15-pentaoxaheptadecan-1-yl]carbamate (700.00 mg, 89.98%) as a light yellow oil. LC/MS: mass calcd. For C₄₄H₇₉N₅O₁₅: 917.56, found: 918.60 [M+H]⁺.

[00660] Step 5. To a stirred solution of tert-butyl N-[17-(4-{1-[17-(4-nitrophenoxy)-3,6,9,12,15-pentaoxaheptadecan-1-yl]piperidin-4-yl}piperazin-1-yl)-3,6,9,12,15-pentaoxaheptadecan-1-yl]carbamate (300.00 mg, 0.33 mmol, 1.00 equiv) in EA (10.00 mL) was added Pd/C (0.03 g, 20%w/w) and the resulting mixture was stirred for 16.0 h at room temperature under hydrogen atmosphere. The mixture was filtered and the filter cake was washed with EA (3x10 mL). The filtrate was concentrated under reduced pressure to afford tert-butyl N-[17-(4-{1-[17-(4-aminophenoxy)-3,6,9,12,15-pentaoxaheptadecan-1-yl]piperidin-4-yl}piperazin-1-yl)-3,6,9,12,15-pentaoxaheptadecan-1-yl]carbamate (200.00 mg, 69.44%) as a yellow solid. LC/MS: mass calcd. For C₄₄H₈₁N₅O₁₃: 887.58, found: 888.55 [M+H]⁺.

[00661] Step 6. To a stirred mixture of tert-butyl N-[17-(4-{1-[17-(4-aminophenoxy)-3,6,9,12,15-pentaoxaheptadecan-1-yl]piperidin-4-yl}piperazin-1-yl)-3,6,9,12,15-pentaoxaheptadecan-1-yl]carbamate (90.01 mg, 0.10 mmol, 1.30 equiv) and (S)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetic acid (31.25 mg, 0.08 mmol, 1.00 equiv) in DMF (3.00 mL) was added DMAP (47.62 mg, 0.39 mmol, 5.00 equiv) and EDCI (19.43 mg, 0.10 mmol, 1.30 equiv) and the resulting mixture was stirred for 16.0 h at room temperature. The reaction was quenched with ice water (20 mL). The precipitated solids were collected by filtration and the filter cake was washed with H₂O (3x10 mL) and dried under vacuum. This resulted in tert-butyl (S)-(17-(4-(1-(17-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)phenoxy)-3,6,9,12,15-pentaoxaheptadecyl)piperidin-4-yl)piperazin-1-yl)-3,6,9,12,15-pentaoxaheptadecyl)carbamate (70.00 mg, 70.65%) as a yellow oil. LC/MS: mass calcd. For C₆₃H₉₆ClN₉O₁₄S: 1269.65, found: 1170.50 [M+H]⁺.

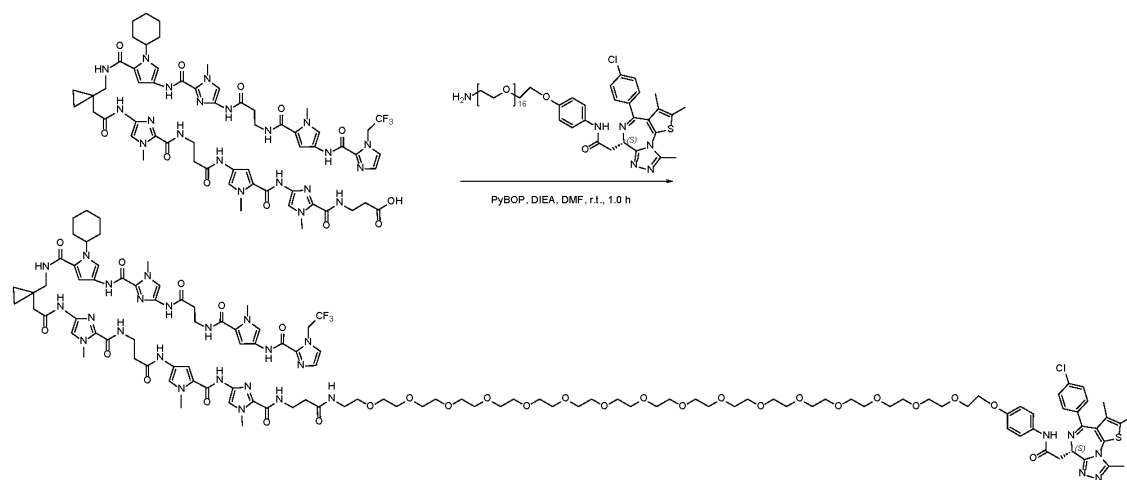
[00662] Step 7. To a stirred solution of tert-butyl (S)-(17-(4-(1-(17-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)phenoxy)-3,6,9,12,15-pentaoxaheptadecyl)piperidin-4-yl)piperazin-1-yl)-3,6,9,12,15-pentaoxaheptadecyl)carbamate (70.00 mg, 0.06 mmol, 1.00 equiv) in DCM (3.00 mL) was added TFA (1.00 mL) and the resulting mixture was stirred for 1.0 h at room temperature. Then the mixture was concentrated under vacuum to afford (S)-N-(4-((17-(4-(4-(17-amino-3,6,9,12,15-pentaoxaheptadecyl)piperazin-1-yl)piperidin-1-yl)-3,6,9,12,15-pentaoxaheptadecyl)oxy)phenyl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-

a[[1,4]diazepin-6-yl)acetamide (70.00 mg, crude) as a yellow oil. LC/MS: mass calcd. For $C_{58}H_{88}ClN_9O_2S$: 1169.60, found: 1170.75 $[M+H]^+$.

[00663] Step 8. To a stirred mixture of (S)-N-(4-((17-(4-(4-(17-amino-3,6,9,12,15-pentaoxaheptadecyl)piperazin-1-yl)piperidin-1-yl)-3,6,9,12,15-pentaoxaheptadecyl) oxy)phenyl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide (70.00 mg, 0.060 mmol, 1.30 equiv) and 3-({1-methyl-4-[1-methyl-4-(3-({1-methyl-4-(2-({1-({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) methyl]cyclopropyl}acetamido)imidazol-2-yl]formamido}propanamido)pyrrole-2-amido]imidazol-2-yl} formamido)propanoic acid (54.55 mg, 0.05 mmol, 1.00 equiv) in DMF (2.00 mL) was added DIEA (29.72 mg, 0.23 mmol, 5.00 equiv) and PyBOP (31.11 mg, 0.06 mmol, 1.30 equiv) and the result mixture was stirred at r.t. for 1.0 h. The mixture was quenched with ice water (10 mL). The precipitated solids were collected by filtration and washed with water (3x10 mL). The crude product was purified by Prep-HPLC with the following conditions: Column: XBridge BEH Shield RP18 Column, 19*250 mm, 5 μ m; Mobile Phase A: Water (10mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 6%B to 36%B in 7 min; Wave Length: 254nm/220nm; RT1(min): 5) to afford (S)-N-(3-((5-((2-((1-(4-(1-(17-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)phenoxy)-3,6,9,12,15-pentaoxaheptadecyl)piperidin-4-yl)piperazin-1-yl)-19-oxo-3,6,9,12,15-pentaoxa-18-azahenicosan-21-yl)carbamoyl)-1-methyl-1H-imidazol-4-yl)carbamoyl)-1-methyl-1H-pyrrol-3-yl)amino)-3-oxopropyl)-1-methyl-4-(2-(1-((1-methyl-4-(1-methyl-4-(3-(1-methyl-4-(1-methyl-1H-imidazole-2-carboxamido)-1H-pyrrole-2-carboxamido)propanamido)-1H-imidazole-2-carboxamido)-1H-pyrrole-2-carboxamido)methyl)cyclopropyl)acetamido)-1H-imidazole-2-carboxamide (8.00 mg,) as a white solid. HRMS: mass calcd. For $C_{111}H_{149}ClN_{30}O_{23}S$: 2337.0821, found: 2338.1048 $[M+H]^+$. HPLC: 99.267% purity

[00664] Example 8. Synthesis of Compound C-58

[00665] Scheme 8.



[00666] To a stirred solution of 3-[(4-{4-[3-({4-[2-(1-{{(1-cyclohexyl-4-{1-methyl-4-[3-({1-methyl-4-[1-(2,2,2-trifluoroethyl)imidazole-2-amido]pyrrol-2-yl}formamido)propanamido]imidazole-2-amido}pyrrol-2-yl)formamido]methyl}cyclopropyl)acetamido]-1-methylimidazol-2-yl}formamido)propanamido]-1-methylpyrrole-2-amido}-1-methylimidazol-2-yl)formamido]propanoic acid (70.00 mg, 0.05 mmol, 1.00 equiv) in DMF (2.00 mL) was added (S)-N-(4-((50-amino-3,6,9,12,15,18,21,24,27,30,33,36,39,42,45,48-hexadecaioxapentacontyl)oxy)phenyl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide (72.20 mg, 0.05 mmol, 1.10 equiv), PyBOP (30.30 mg, 0.05 mmol, 1.10 equiv) and DIEA (20.53 mg, 0.15 mmol, 3.00 equiv) at 0 °C. The resulting mixture was stirred for 1.0 h at room temperature. Then the mixture was quenched with ice water (10 mL). The precipitated solids were collected by filtration, washed with H₂O (3x5 mL), and dried under vacuum. The crude product was purified by Prep-HPLC flash with the following conditions: Column: YMC Triart C18 ExRs Column, 20*250mm, 5µm; Mobile Phase A: Water (10mmol/L NH₄HCO₃), Mobile Phase B: ACN; Flow rate: 25 mL/min mL/min; Gradient: 35% B to 59% B in 12 min, 59%B to 59%B in 13 min; Wave Length: 254nm/220nm nm; RT1(min): 12.42. The fractions were combined and lyophilized to afford (S)-N-(3-((5-((2-((1-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)phenoxy)-52-oxo-3,6,9,12,15,18,21,24,27,30,33,36,39,42,45,48-hexadeca-51-azatetrapentacontan-54-yl)carbamoyl)-1-methyl-1H-imidazol-4-yl)carbamoyl)-1-methyl-1H-pyrrol-3-yl)amino)-3-oxopropyl)-4-(2-(1-((1-cyclohexyl-4-(1-methyl-4-(3-(1-methyl-4-(1-(2,2,2-trifluoroethyl)-1H-imidazole-2-carboxamido)-1H-pyrrole-2-carboxamido)propanamido)-1H-imidazole-2-carboxamido)-1H-pyrrole-2-carboxamido)methyl)cyclopropyl)acetamido)-1-methyl-1H-imidazole-2-carboxamide (24.70 mg, 17.79%) as a white solid. HRMS: mass calcd. C₁₁₈H₁₅₉ClF₃N₂₇O₂₉S: 2542.1158, found: 2543.1193[M+H]⁺. HPLC: 97.004% purity.

[00667] Example 9. General synthesis and purification of the compounds of the disclosure

[00668] Compounds of the disclosure were made by methods similar to Examples 1-8. The compounds were subsequently purified by HRMS methods A or B.

[00669] Method A: Instrument: Waters Acquity I Class UPLC with Xevo G2-XSQ ToF HRMS; Column: ACQUITY UPLC BEH-C18, 2.1 x 50 mm, 2.7 µm; mobile phase A: H₂O (0.1% HCOOH), mobile B, CAN (0.1% HCOOH); Flow rate: 0.4 mL/min; Gradient: 10% B to 95% B in 1.5 min, hold 95% for another 0.5 min, then down to 10% B in 0.3 min, hold 10% B for another 0.7 min; detector: 254nm.

[00670] Method B: Instrument: Waters Acquity I Class UPLC with Xevo G2-XS Q ToF HRMS; Column: ACQUITY UPLC BEH-C18, 2.1 x 50 mm, 2.7 µm; mobile phase A: H₂O (0.1% HCOOH), mobile B, CAN (0.1% HCOOH); Flow rate: 0.4 mL/min; Gradient: 5% B to 40% B in 2.0min, to 95% in another 1.5 min, hold 95% for 1.5 min, then down to 5% B in 0.3 min, hold 5% B for another 0.7 min; detector: 254nm.

[00671] Experimental data for the compounds of the disclosure purified by Method A are provided in Table 4.

Table 4. LCMS analysis of compounds of the disclosure.

Cpd. No.	Calc. Mass	Mass found
C-1	2085.9174	2086.9226
C-2	1923.8713	1924.8776
C-3	1615.6878	1616.6928
C-4	2336.024	2337.0227
C-5	2406.1022	2407.097
C-7	2406.066	2407.0735
C-8	2406.066	2407.0707
C-10	2551.1330	2552.1500
C-11	2553.1486	2554.1422
C-12	2563.133	2564.1409
C-13	2579.164	2580.1748
C-14	2587.114	2588.1284
C-15	2537.117	2560.0986[M+Na] ⁺
C-16	2372.0947	2373.1014
C-17	2105.9218	2106.9261
C-18	2486.1740	2487.1822
C-19	2553.112	2554.1134
C-20	2525.081	1263.5448[M/2+H] ⁺
C-21	2609.1749	2610.1826
C-22	2578.1439	2579.1445
C-23	2455.0391	2456.0465
C-24	2455.0391	2456.0493
C-55	2451.0442	2452.0541
C-56	2474.128	2475.1360
C-57	2337.08	2338.1048
C-58	2542.116	2543.1193
C-59	2537.117	2538.1234
C-60	2448.113	2449.1175
C-61	2450.092	2451.0960
C-62	2474.1285	2475.1494
C-63	2690.2156	1346.1110[M/2+H] ⁺
C-65	2465.0598	2466.0645
C-66	2509.0860	2510.0937
C-67	2577.15	2578.1589
C-68	2625.157	2626.1653
C-69	2589.1486	2590.1557
C-70	2607.1592	2608.1726
C-71	2635.1905	1318.6025[M/2+H] ⁺
C-72	2645.136	2646.1359
C-73	2635.1905	2636.1922
C-74	2607.1592	2608.1750
C-75	2635.1905	2636.1877
C-76	2607.1592	2608.1538
C-77	2593.1436	2594.1425
C-78	2480.0707	2481.0764

C-79	2552.128	2553.1340
C-80	2593.180	2594.1804
C-81	2509.0860	2510.0915
C-82	2589.1486	2590.1509
C-83	2592.1595	2593.1692
C-84	2639.1731	2640.1698
C-85	2646.1313	2647.1285
C-96	2439.0442	2440.0403
C-97	2064.8701	2065.8615
C-98	1993.833	1994.838
C-100	2097.9187	2098.9200
C-101	2336.024	2337.0146
C-102	1777.7339	1778.7456
C-103	2085.9174	2086.9163
C-104	1880.7541	1881.7648
C-105	2188.9376	2189.9359
C-106	1777.7339	1778.7411
C-107	2085.9174	2086.9287
C-108	1880.7541	1881.7619
C-109	2188.9376	2189.9468
C-110	2480.0959	2481.0976
C-111	2414.1053	2415.1071
C-112	2207.9654	2208.9786
C-113	2438.0489	2439.0492
C-114	2370.0791	2373.0673
C-115	1854.8258	1855.8324
C-116	2030.9307	2031.9369
C-117	2339.1142	2340.1233
C-118	2441.0234	2442.0414
C-119	2338.0033	2339.0168
C-120	2440.0394	2441.0594
C-121	2337.0192	2338.0347
C-122	2455.0391	2478.0229[M+Na]
C-123	2454.0551	2455.0563
C-124	2507.0316	2508.0429
C-125	2467.0755	2468.0839
C-126	2467.0755	2468.0980
C-127	2467.0755	2490.0549[M+Na]
C-128	2467.0755	2468.0818
C-129	2440.0394	2441.0450
C-130	2874.3274	2875.3253
C-131	2771.3072	2772.3076
C-132	2764.3106	2765.3084
C-133	2693.2735	2694.2798
C-134	2693.2735	2694.2715
C-135	2736.3157	2737.2969
C-136	2063.9112	2064.9174

C-137	2551.0578	2552.0661
C-138	2448.0376	2449.0367
C-139	2041.9810	2042.9887
C-140	1615.6878	1616.6993
C-141	2041.9810	2042.9897
C-142	1923.8713	1924.8766
C-143	2408.0815	2409.0836
C-144	2448.0376	2449.0361
C-145	2408.0815	2409.0833
C-146	2406.0659	2407.0647
C-147	2096.0268	2096.9963
C-148	2557.0948	2558.1031
C-149	2454.0746	2477.0679[M+Na] ⁺
C-150	2817.3059	2818.3078
C-151	2672.2388	2673.2451
C-152	2775.2590	2776.2608
C-153	2714.2857	2715.2922
C-154	2775.2590	2776.2610
C-155	2672.2388	2673.2431
C-156	2680.2782	2681.2994
C-157	2625.0822	2626.0942
C-158	2522.0620	2523.0759
C-159	2714.1463	2715.1440
C-160	2611.1261	2612.1395
C-161	2764.1431	2765.1395
C-162	2661.1229	2662.1304
C-163	2814.1399	2815.1522
C-164	2711.1197	2712.1167
C-165	2681.1004	2682.1104
C-166	2448.1128	2449.1095
C-167	2462.1285	2463.1327
C-168	2518.1911	2519.1980
C-169	2618.1584	2619.1592
C-170	2498.1372	2499.1372
C-171	2493.1706	2494.1772
C-172	2449.1444	2450.1329
C-174	2566.1246	2567.1303
C-175	2526.1685	2527.1719
C-176	2526.1685	2527.1725
C-177	2526.1685	2527.1797
C-178	2526.1685	2527.1805
C-179	2554.1998	2555.2037
C-180	2554.1998	2555.2125
C-181	2554.1998	2555.1925
C-182	2554.1998	2555.2041
C-183	2637.1981	2638.1906
C-184	2623.1461	2624.1554

C-185	2575.1373	2576.1415
C-186	2637.1617	2638.1559
C-187	2589.1529	2590.1638
C-188	2617.1744	2618.1794
C-189	2569.1656	2570.1706
C-190	2538.1809	2539.1796
C-191	2626.2333	2627.2280
C-192	2641.2011	2642.2053
C-193	2729.2535	2730.2555
C-194	2496.1339	2497.1487
C-195	2584.1864	2585.1887
C-196	2599.1541	2600.1682
C-197	2687.2065	2688.2094
C-198	2627.173	2628.1881
C-199	2524.153	2525.1717
C-200	2579.164	2580.1765
C-201	2476.144	2477.1546
C-202	2601.16	2602.1706
C-203	2381.1447	2382.1619
C-204	2482.1492	2483.1711
C-205	2440.102	2441.1186
C-206	2441.116	2442.1233
C-207	2522.137	2523.1425
C-208	2599.142	2600.1462
C-209	2496.122	2497.1347
C-210	2579.164	2580.1721
C-211	2545.086	2546.0969
C-212	2565.149	2566.1560
C-213	2525.117	2526.1260
C-214	2509.086	2510.1021
C-215	2546.081	2547.0785
C-216	2523.102	2524.1130
C-217	2552.128	2553.1375
C-218	2647.152	2648.1575
C-219	2544.131	2545.1389
C-220	2408.082	2409.0855
C-221	2511.102	2512.1020
C-222	2434.097	2435.1028
C-223	2551.133	2552.1397
C-224	2449.108	2450.1130
C-225	2553.112	2554.1160
C-226	2509.086	2510.0921
C-227	2509.086	1255.5490[M/2+H] ⁺
C-228	2523.102	2524.1054
C-229	2420.082	2421.0900
C-230	2490.160	2491.1452
C-231	2591.164	2592.1666

C-232	2577.1486	2578.1701
C-233	2613.1298	2614.1209
C-234	2605.1799	2606.1988
C-235	2605.1799	2606.1951
C-236	2591.1643	2592.1554
C-237	2633.2112	2634.2316
C-238	2633.2112	2634.2125
C-239	2455.0418	2456.0511
C-240	2793.2358	2794.2451
C-241	2878.2886	1440.1524[M/2+H] ⁺
C-242	2775.2684	1388.6395[M/2+H] ⁺
C-243	2551.1330	2552.1560
C-244	2535.1017	2536.1194
C-245	2599.1418	2600.1445
C-246	2653.1887	2654.1881
C-247	2583.1105	2584.1106
C-248	2653.1887	1327.5917[M/2+H] ⁺
C-249	2637.1574	2638.1575
C-250	2661.1386	2662.1393
C-251	2523.1017	2524.0979
C-252	2578.1439	2579.1461
C-253	2579.1279	2580.1267
C-254	2551.0966	2552.1175
C-255	2549.1173	2550.1190
C-256	2619.1204	2620.1261
C-257	2657.1360	2658.1414
C-258	2603.0891	2604.0943
C-259	2673.1673	2674.1742
C-260	2673.1673	2674.1752
C-261	2681.1172	2682.1223
C-262	2659.1517	2660.1535
C-263	2647.1153	2648.1218
C-264	2627.1367	2628.1358
C-265	2599.1054	1300.5548[M/2+H] ⁺
C-266	2565.1486	2566.1538
C-267	2563.1330	2564.1533
C-268	2577.1486	2578.1510
C-269	2565.1486	2566.1511
C-270	2607.1592	2608.1555
C-271	2581.1436	1291.5732[M/2+H] ⁺
C-272	2579.1643	2580.1730
C-273	2605.1799	2606.1848
C-274	2573.0985	2574.0929
C-275	2547.1381	2548.1437
C-276	2591.1643	2592.1622
C-277	2589.1486	2590.1509
C-278	2603.1643	2604.1616

C-279	2591.1643	2592.1639
C-280	2605.1799	1303.5951[M/2+H] ⁺
C-281	2607.1592	2608.1743
C-282	2633.1749	2634.1789
C-283	2631.1956	2632.2037
C-284	2599.1141	2600.1091
C-285	2605.1799	2606.1816
C-286	2609.1749	2610.1787
C-287	2581.1436	2582.1636
C-288	2581.1436	2582.1584
C-289	2609.1749	2610.1790
C-290	2609.1749	2610.1790
C-291	2633.2112	2634.2088
C-292	2592.1595	2593.1601
C-293	2633.2112	2634.2121
C-294	2563.1330	2564.1376
C-295	2412.0333	2413.0400
C-296	2591.1643	2592.8598
C-297	2578.1439	2579.1451
C-298	2604.1595	2605.1603
C-299	2578.1439	2579.1500
C-300	2604.1595	2605.8588
C-301	2738.2779	2739.2817
C-302	2738.2779	2739.2797
C-303	2738.2779	2739.2746
C-304	2738.2779	2739.2773
C-305	2738.2779	2739.2774
C-306	2696.2309	2697.1269
C-307	2772.247	2773.0904
C-308	2395.106	2396.1116
C-309	2724.2622	2725.085
C-310	2752.2935	2753.2979
C-311	2473.0860	2474.0871
C-312	2542.1591	2543.1615
C-313	2718.264	2719.2721
C-314	2500.1122	2501.109
C-315	2528.1435	2529.1501
C-316	2556.1748	2557.1793
C-317	2063.9562	2064.9563
C-318	2416.1659	2417.1654
C-319	2312.9914	2313.9949
C-320	2401.0438	2402.0505
C-321	2489.0962	2490.1033
C-322	2380.9787	2381.9832
C-323	2469.0312	2470.037
C-324	2557.0836	2558.09
C-325	2401.0438	2402.0482

C-326	2489.0962	2490.1023
C-327	2577.1486	2578.1505
C-328	2401.0438	2402.0491
C-330	2577.1486	2578.1526
C-331	2457.1064	2458.1136
C-332	2545.1588	2546.1636
C-333	2593.1676	2594.1722
C-334	2681.22	2682.2245
C-335	2449.0526	2450.0632
C-336	2537.105	2539.1116
C-337	2533.0795	2534.0838
C-338	2621.1319	2622.1348
C-339	2456.086	2457.0908
C-340	2544.1384	2545.1461
C-341	2454.1067	2455.1123
C-342	2542.1591	2543.1616
C-343	2587.0512	2588.0546
C-344	2675.1037	2676.1129
C-345	2504.053	2505.0571
C-346	2592.1054	2593.107
C-347	2488.0581	2489.0666
C-348	2576.1105	2577.1167
C-350	2530.1228	2531.1277
C-352	2622.1701	2623.1767
C-357	2719.2229	2720.2248
C-359	2518.1228	2519.1288
C-360	2500.1122	2501.1183
C-362	2688.2171	2689.2211
C-364	2716.2484	2717.2533
C-365	2542.1228	2543.1203
C-366	2578.1403	2579.1395
C-367	2533.1642	2534.1717
C-368	2452.1452	2453.1492
C-369	2588.1135	2589.1211
C-372	2593.1436	2594.1410
C-373	2567.1279	2568.1310
C-374	2585.0985	2586.0974
C-375	2633.1073	2634.1075
C-376	2552.0883	2553.0992
C-377	2726.2139	2727.2162
C-384	1955.8179	1956.824
C-385	2264.0014	2264.9958
C-386	2047.9729	2048.9791
C-387	2356.1564	2357.1573
C-388	2709.2273	2710.2322
C-389	2694.2276	2695.2319
C-390	2457.1064	2458.1134

C-391	2633.2112	2634.2164
C-392	2551.133	2552.1397
C-393	2577.1486	2578.1562
C-394	2551.133	2552.1374
C-395	2534.1608	2535.1632
C-396	2097.9729	2098.9788
C-397	2123.9885	2124.9959
C-398	2138.0042	2139.0122
C-399	2152.0198	2153.0205
C-400	2166.0355	2167.0325

BIOLOGICAL EXAMPLES

[00672] Example B-1. Activity

[00673] Fibroblast: a cell type derived from a skin biopsy of a patient. These cells are not altered genetically, so they serve as a primary cell culture model of disease.

[00674] iPSC: induced pluripotent stem cell, a cell type that results as a reprogramming of another cell type (typically skin cells or blood cells) into a more embryonic-like state that enables the development of other cell types to model therapeutic effects of drugs *in vitro*.

[00675] SNP: Single Nucleotide Polymorphism, a variation in a single base pair in a DNA sequence

[00676] Molecular Biology Toolkit:

- qPCR primer probe sets:
 - RNA input normalization was assessed utilizing human glyceraldehyde 3-phosphate dehydrogenase (hGAPDH) TaqMan assay (ThermoFisher cat# 4351370) or Human Cyclophilin (IAPP) TaqMan assay (ThermoFisher cat# 4351372)
 - Total HTT detection was assessed utilizing human Htt TaqMan assay (ThermoFisher cat# 4331182)
 - Allele-specific detection of human HTT expression in HD cells containing the SNP rs362331C/T (Exon 50): for each assay, allele-specific probes to detect the SNP variant contained locked nucleic acid bases to improve allele discrimination, as compared to unmodified DNA probes.
 - 362331-F (331 forward primer)
 - 362331-R (331 reverse primer)
 - 362331-C probe: TCC CTC ATC + C + AC TGT GT
 - 362331-T probe: CTC + A + T + C + T + A + C TGT GT
 - qPCR was performed using Agpath ID one-step reverse transcriptase polymerase chain reaction (RT-PCR) reagent

[00677] Protein measurements were performed via western blots probing with antibody MW1 (polyQ specific) to assess reduction of mtHTT alone. D7F7 (a.a surrounding Pro1218) was used to visualize both wtHTT and mtHTT. Lysates were standardized by DC prior to separation on a 3-8% Tris-acetate gel and transferred via wet transfer method onto nitrocellulose membranes. Blots were probed with the previously

mentioned antibodies and complementary fluorescent secondary antibodies and imaged on the Li-Cor Odyssey® DLx Imaging system.

[00678] Antibody pairing of 2B7 (a.a. 1-17) and MW1 (polyQ specific) will be used to track mtHTT levels while pairing of MAB2166 (a.a. 181-810) and MAB5490 (a.a. 115-129) will be employed to track total full-length HTT.

[00679] Screening of HD molecules methods: GM09197 and/or GM04022 fibroblasts were cultured in T175 flasks incubated at 37 °C and 5% CO₂. Once confluency was reached, the media was removed, the cells were washed with 1X PBS, and cells were dissociated using TrypLE™ Express Enzyme. Media was added to the enzyme and collected into a 15-mL conical tube and centrifuged at 500xg for 5 minutes to pellet the cells. Media and enzyme were aspirated using a serological pipette. Cells were resuspended in fresh media and counted using a Countess 3 Automated Cell Counter. Cells were plated at a density of 15,000 cells/well in a tissue culture-treated polystyrene 96-well dish and incubated at 37 °C and 5% CO₂ overnight. The next day, media was removed using an 8-channel aspirator. 200 µL media/well are added back into the plate. The molecules are formulated to 1 mM and are dispensed using a Multidrop™ Pico 8 Digital Dispenser. After a 48-hour incubation with compounds, media was removed from plates, cells were washed with 1X PBS, and cells were lysed in 40 µL per well guanidinium thiocyanate buffer. RNA was isolated and purified in 382-well glass fiber column plates using chaotropic salts. Human mtHTT, wtHTT, and GAPDH mRNA were measured via RT-PCR using the ThermoFisher QuantStudio™ 7 Flex System in 384-well format. Results of HTT levels were normalized to GAPDH mRNA levels. Normalized HTT mRNA levels were expressed relative to vehicle-treated samples to assess fold change after molecule treatment.

[00680] iPSC-Neuron Duration of Action of HD molecules methods: Fibroblasts isolated from HD patients were reprogrammed into iPSCs expanded in the presence of cytokines and transduced with the Sendai virus, a cytoplasmic RNA vector. These iPSCs expressed stem cell markers and have normal karyotypes and express the pluripotent markers Nanog, Tra-1-60, and SSEA-44. iPSC-derived neuron differentiation methodology followed standard protocols for mixed cortical neuron differentiation resulting in immunohistochemical staining of iPS-Neuron of Tuj1 and Map2. iPSC-neuronal precursor cells were plated at 300,000 cells/well in a PLO/Laminin-521 coated culture-treated polystyrene 96-well dish and incubated at 37 °C and 5% CO₂. The next day, media was changed to allow neuron precursor cells to continue maturation into neurons. Four days later, media was refreshed, and cells were treated with mitotic inhibitor to remove any remaining dividing cells, resulting in a pure neuronal culture. Three days later, media was removed. 200 µL media/well were added back into the plate. The molecules were formulated to 1 mM and dispensed using a Multidrop™ Pico 8 Digital Dispenser. After 96-hour incubation with compounds, media was removed and refreshed and the cells were retreated. After 7 days of compound exposure, media was removed from plates, and cells were lysed in 60 µL of Ambion Lysis buffer. RNA is isolated using PureLink™ RNA isolation kits. cDNA is synthesized with Agilent Superscript II kit. Human mtHTT, wtHTT, and GAPDH mRNA were measured via RT-PCR using the ThermoFisher QuantStudio™ 7 Flex

System in 384-well format. Results of HTT levels were normalized to GAPDH mRNA levels. Normalized HTT mRNA levels were expressed relative to vehicle-treated samples to assess fold change after treatment with the HD compounds.

[00681] $E_{\min}$ for each compound is the lowest %HTT concentration observed within a compound concentration of 0.5nM to 1000 nM. A $\leq 30\%$, B $> 30\%$ to $\leq 50\%$, C $> 50\%$.

[00682] Representative *in vitro* biochemical data is presented in **Table 5**, where IC_{50} is A ≤ 100 nM, B > 100 nM to ≤ 1 μ M, C > 1 μ M.

Table 5. Representative biochemical data in GM09197 and GM04022 fibroblasts.

Cpd. No.	GM 09197 Emin 48 Hr T Allele (%)	GM 04022 Emin 48 hr T Allele (%)	GM09197 IC_{50} 48 hr T Allele (nM)	GM04022 IC_{50} 48 hr T Allele (nM)
C-1	C		C	
C-2	C	C	C	C
C-3	C		C	
C-4	A	B	A	A
C-5	A	B	A	A
C-7		C		C
C-8		C		C
C-10	A	B	A	A
C-11	A	B	A	A
C-12	A	A	A	A
C-13	A	B	A	A
C-14	A	B	A	A
C-15		B		A
C-16	B	B	A	A
C-17	B	C	A	A
C-18	B	B	B	B
C-19		B		A
C-20		B		A
C-21		B		A
C-22	A	A	A	A
C-23	A	C	A	C
C-24	C	C	B	C
C-55	C		C	
C-56	A	B	A	A
C-57	A	A	C	C
C-58		B		A
C-59		C		C
C-60		C		C
C-61		C		C
C-62	A	A	A	A
C-63	C	C	C	C
C-65	A	B	A	A
C-66		A		A

C-67	A	B	A	A
C-68	A	A	A	A
C-69	A	A	A	A
C-70		A		A
C-71		B		A
C-72		B		A
C-73		B		A
C-74		B		A
C-75		B		A
C-76		B		A
C-77	B	B	A	A
C-78	C	C	A	C
C-79		C		C
C-80		C		C
C-81		B		A
C-82		C		A
C-83		B		A
C-84	A	A	A	A
C-85	A	A	C	A
C-96	A	C	A	A
C-97	A	C	A	C
C-98	A	C	A	A
C-100	C		B	
C-101	C		C	
C-102	C		C	
C-103	C		C	
C-104	C		C	
C-105	C		C	
C-106	C		C	
C-107	C		C	
C-108	C		C	
C-109	C		C	
C-110	C	C	C	C
C-111	A	B	A	A
C-112	C		C	
C-113	B	C	A	A
C-114	A	C	A	A
C-118	C		C	
C-119	C		C	
C-120	C		C	
C-121	C		C	
C-122	C	C	C	C
C-123	C		A	
C-124	A	B	A	A
C-125	A	B	A	A
C-126	A	A	A	A
C-127	A	B	A	A

C-128	A	B	A	A
C-129	C		C	
C-130	A	C	A	A
C-131	A	B	B	B
C-132	C	B	C	A
C-133	A	C	B	B
C-134	A	A	A	A
C-135	C	C	C	A
C-136	A	B	A	A
C-137	C	C	A	C
C-138	C	C	C	C
C-140	C	C	C	C
C-142	C		C	
C-143	A	B	A	A
C-144	A	A	A	A
C-145	A	A	A	A
C-146	A	B	A	A
C-147	C	C	C	C
C-148	A	A	A	A
C-149	B	B	A	A
C-150	A	A	A	A
C-151	A	B	A	A
C-152	A	B	A	A
C-153	A	A	A	A
C-154	A	B	A	A
C-155	A	A	A	A
C-156	A	A	A	A
C-157	A	A	A	A
C-158	B	C	A	A
C-159	B	B	A	A
C-160	B	C	C	A
C-161	B	C	A	A
C-162	C	C	A	A
C-163	A	B	A	A
C-164	C	C	A	A
C-165	C	C	C	C
C-166	A	A	A	A
C-167	A	B	A	A
C-168	C	C	C	C
C-169	C	C	C	C
C-170	B	B	A	A
C-171	A	A	A	A
C-172	A	A	A	A
C-175	A	B	A	A
C-177	A	A	A	A
C-178	A	B	A	A
C-179	B	B	A	A

C-180	B	C	A	A
C-181	A	B	A	A
C-182	A	A	A	A
C-183	B	B	A	A
C-184	B	B	A	A
C-185	A	A	A	A
C-186	B	B	A	A
C-188	B	C	A	A
C-189	A	B	A	A
C-190	A	A	A	A
C-191	A	A	A	A
C-192	A	B	A	A
C-193	A	B	A	A
C-198	A	B	A	A
C-199	B	C	A	A
C-200	A	A	A	A
C-201	B	B	A	A
C-202	A	A	A	A
C-203		B		A
C-205		C		A
C-206	A	B	A	A
C-207	A	A	A	A
C-208	A	A	A	A
C-209	A	B	A	A
C-210	A	C	A	A
C-211	A	C	A	C
C-212	A	A	A	A
C-213		C		A
C-214		B		A
C-215	C	C	A	C
C-216	A	C	A	A
C-217		B		A
C-218		A		A
C-219		C		C
C-220		C		C
C-221		C		C
C-222				
C-223		C		C
C-224		C		C
C-225		C		C
C-226		C		C
C-227		C		C
C-228		C		C
C-229		C		C
C-230		C		C
C-231				
C-232				

C-233		C		A
C-234	A		A	
C-235	A	A	A	A
C-236	A		A	
C-237	A		A	
C-238		A		A
C-239		C		C
C-240		C		C
C-243	A		A	
C-244	A		A	
C-245	A		A	
C-246	A		A	
C-247	A		A	
C-248	C		C	
C-249		A		A
C-250		B		A
C-251	A		A	
C-252	A		A	
C-253	A		A	
C-256	A		A	
C-257		A		A
C-259	A		A	
C-260	A		A	
C-262	A		A	
C-264	B		A	
C-267		B		A
C-269		B		A
C-271		B		A
C-272		B		A
C-275		C		A
C-276				
C-277		C		A
C-278				
C-279		C		A
C-280		C		A
C-281				
C-282		C		A
C-283		B		A
C-284		C		A
C-285				
C-286		B		A
C-287		A		A
C-288		B		A
C-289	B		A	
C-290	A		A	
C-291	A		A	
C-292		B		A

C-293		B		A
C-294	A		A	
C-295				
C-296	A	C	A	A
C-297				
C-298	A	B	A	A
C-299	B		A	
C-300	A		A	
C-301	A	A	A	A
C-302	A	A	A	A
C-303	A	A	A	A
C-304	C	C	A	C
C-305	A	B	A	A
C-306	A	B	A	A
C-307	A	A	A	A
C-308	C	C	A	A
C-309	A	B	A	A
C-310	A	B	A	A
C-311	C	C	C	C
C-313	A	A	A	A
C-314	A	A	A	A
C-315	A	A	A	A
C-316	A	B	A	A
C-317	C	C	A	C
C-318	A	B	A	A
C-319	B	C	A	A
C-320	A	C	A	A
C-321	A		A	
C-322	A		A	
C-323	A		A	
C-324	A		A	
C-325	A		A	
C-326	A		A	
C-327	A		A	
C-331	A		A	
C-332	A		A	
C-333	A		A	
C-334	A		A	
C-335	A	B	A	A
C-336	A	B	A	A
C-337	A	B	A	A
C-338	A	A	A	A
C-339	A	B	A	A
C-340	A	A	A	A
C-341	A	C	A	A
C-342	A	B	A	A
C-343	A		A	

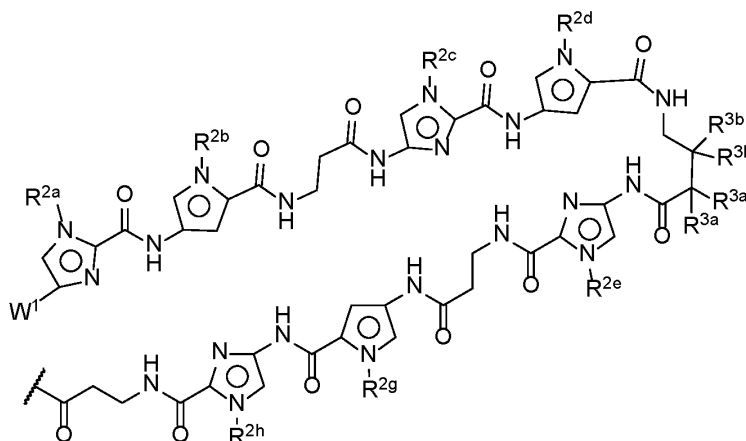
C-344	A		A	
C-345	B	C	A	C
C-346	A	C	A	C
C-347	A	C	A	A
C-348	A	B	A	A

[00683] 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 a first terminus, a second terminus, and an oligomeric backbone moiety, or a pharmaceutically acceptable salt thereof, wherein:
 - a) the first terminus comprises a DNA-binding moiety having the structure of Formula (A-9):



Formula (A-9),

wherein:

W¹ is hydrogen, -C₁-C₆ haloalkyl, or -N=C(N(R^{1e})₂)₂, wherein each R^{1e} is independently hydrogen or optionally substituted 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-C₂₀ alkyl, optionally substituted C₂-C₂₀ alkenyl, optionally substituted C₂-C₂₀ alkynyl, optionally substituted C₁-C₂₀ aminoalkyl, optionally substituted C₁-C₂₀ heteroalkyl, optionally substituted C₂-C₂₀ heteroalkenyl, optionally substituted C₂-C₂₀ heteroalkynyl, optionally substituted C₁-C₂₀ haloalkyl, optionally substituted C₁-C₂₀ hydroxyalkyl, optionally substituted C₃-C₁₀ cycloalkyl, or optionally substituted 3 to 10-membered heterocycloalkyl; each of which is optionally substituted with one or more R^Z;

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

R^{3c} and R^{3d} are each independently hydrogen, alkyl, or PEG;

R^{3e} is alkyl, PEG, cycloalkyl, heterocycloalkyl, or phenyl;

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

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

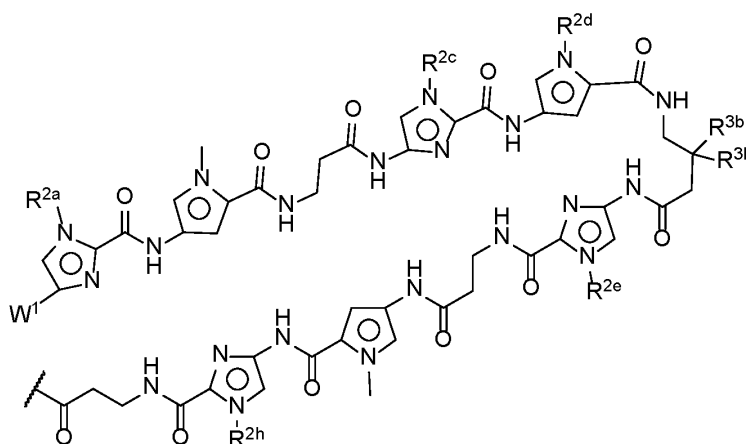
each R^Z is independently halogen, -CN, -OH, -OR^{Za}, -N₃, -NR^{Za}R^{Zb}, -CO(O)R^{Zc}, -C(O)OR^{Zc}, -C(O)NR^{Za}R^{Zb}, -NR^{Za}C(O)R^{Zc}, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₁₀ haloalkyl,

C₁-C₁₀ heteroalkyl, C₃-C₁₀ cycloalkyl, 3 to 10-membered heterocycloalkyl, phenyl, or optionally 5 to 10-membered heteroaryl; wherein

R^{Za} and R^{Zb} are each independently hydrogen, alkyl, haloalkyl, or PEG; and

R^{Zc} is alkyl, haloalkyl, PEG, cycloalkyl, heterocycloalkyl, or phenyl;

- b) the second terminus comprises a protein-binding moiety capable of binding to a regulatory molecule that modulates expression of a gene; and
 - c) the oligomeric backbone links the first terminus and the second terminus.
2. The molecule of claim 1, or a pharmaceutically acceptable salt thereof, wherein each R^{3a} and R^{3b} is independently hydrogen; 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.
 3. The molecule of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein each R^{3a} and each R^{3b} is hydrogen.
 4. The molecule of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein two R^{3a} or together with the atoms to which they are attached form a C₃-C₆ cycloalkyl; and each R^{3b} is hydrogen.
 5. The molecule of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein two R^{3b} together with the atoms to which they are attached form a C₃-C₆ cycloalkyl; and each R^{3a} is hydrogen.
 6. The molecule of any one of claims 1-5, 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 C₁-C₂₀ alkyl, optionally substituted C₂-C₂₀ alkenyl, optionally substituted C₂-C₂₀ alkynyl, optionally substituted C₁-C₂₀ heteroalkyl, optionally substituted C₁-C₂₀ haloalkyl, optionally substituted C₁-C₂₀ hydroxyalkyl, optionally substituted C₃-C₁₀ cycloalkyl, or optionally substituted 3 to 10-membered heterocycloalkyl, each of which is optionally substituted with one or more R^Z.
 7. The molecule of claim 6, 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 C₁-C₁₀ alkyl, optionally substituted C₁-C₁₀ haloalkyl, or optionally substituted C₃-C₈ cycloalkyl.
 8. The molecule of any one of claims 1-5, 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 C₁-C₁₀ alkyl.
 9. The molecule of any one of claims 1-6, 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 C₁-C₁₀ alkyl.
 10. The molecule of claim 9, 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.
 11. The molecule of claim 9, or a pharmaceutically acceptable salt thereof, wherein at least two of R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^{2e}, R^{2g}, or R^{2h} is not methyl.
 12. The molecule of claim 1, wherein the DNA-binding moiety comprises a structure of Formula (I), or a pharmaceutically acceptable salt thereof:



Formula (I),

wherein:

W^1 is hydrogen;

R^{2a} , R^{2c} , R^{2d} , R^{2e} , and R^{2h} are each independently 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} heteroalkyl, optionally substituted C_2 - C_{20} heteroalkenyl, optionally substituted C_2 - C_{20} heteroalkynyl, optionally substituted C_1 - C_{20} haloalkyl, optionally substituted C_1 - C_{20} hydroxyalkyl, optionally substituted C_3 - C_{10} cycloalkyl, or optionally substituted 3 to 10-membered heterocycloalkyl; each of which is optionally substituted with one or more R^Z ;

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

R^{3e} is alkyl, PEG, cycloalkyl, heterocycloalkyl, or phenyl;

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

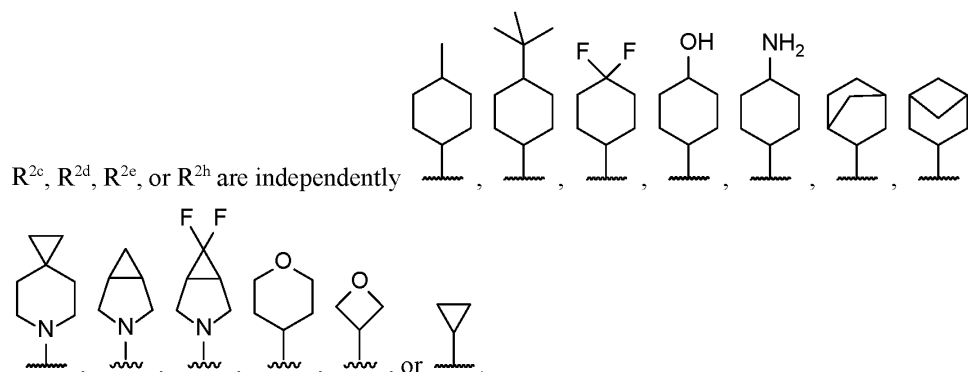
each R^Z is independently halogen, $-CN$, $-OH$, $-OR^{Za}$, $-N_3$, $-NR^{Za}R^{Zb}$, $-CO(O)R^{Zc}$, $-C(O)OR^{Zc}$, $-C(O)NR^{Za}R^{Zb}$, $-NR^{Za}C(O)R^{Zc}$, C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, C_1 - C_{10} haloalkyl, C_1 - C_{10} heteroalkyl, C_3 - C_{10} cycloalkyl, 3 to 10-membered heterocycloalkyl, phenyl, or optionally 5 to 10-membered heteroaryl; wherein

R^{Za} and R^{Zb} are each independently hydrogen, alkyl, haloalkyl, or PEG; and

R^{Zc} is alkyl, haloalkyl, PEG, cycloalkyl, heterocycloalkyl, or phenyl.

13. The molecule of claim 12, or a pharmaceutically acceptable salt thereof, wherein R^{2a} , R^{2c} , R^{2d} , R^{2e} , or R^{2h} are each independently an 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} haloalkyl, optionally substituted C_3 - C_{10} cycloalkyl, or optionally substituted 3 to 10-membered heterocycloalkyl, each of which is optionally substituted with one or more R^Z .

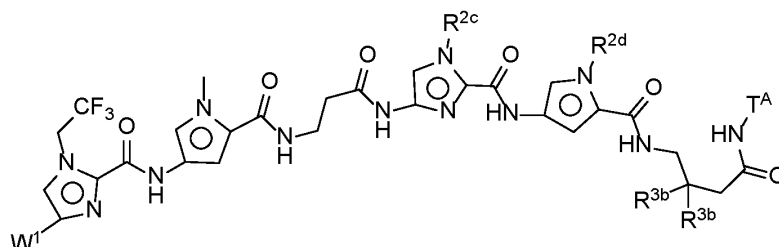
14. The molecule of claim 12, or a pharmaceutically acceptable salt thereof, wherein R^{2a} , R^{2c} , R^{2d} , R^{2e} , or R^{2h} are each independently optionally substituted C_1 - C_{20} alkyl or optionally substituted C_3 - C_{10} cycloalkyl.
15. The molecule of claim 12, or a pharmaceutically acceptable salt thereof, wherein R^{2a} , R^{2c} , R^{2d} , R^{2e} , or R^{2h} are each independently a monocyclic, spirocycloalkyl, or bridged C_3 - C_{10} cycloalkyl.
16. The molecule of claim 12, or a pharmaceutically acceptable salt thereof, wherein one or two of R^{2a} , R^{2c} , R^{2d} , R^{2e} , or R^{2h} are independently an optionally substituted C_3 - C_{10} cycloalkyl or optionally substituted 3 to 10-membered heterocycloalkyl; and the remaining of R^{2a} , R^{2c} , R^{2d} , R^{2e} , or R^{2h} are an optionally substituted C_1 - C_{20} alkyl.
17. The molecule of claim 16, or a pharmaceutically acceptable salt thereof, wherein the remaining of R^{2a} , R^{2c} , R^{2d} , R^{2e} , or R^{2h} are unsubstituted C_1 - C_{10} alkyl.
18. The molecule of any one of claims 12-16, or a pharmaceutically acceptable salt thereof, wherein each R^Z is independently halogen, -CN, -OH, -OR^{Za}, -N₃, -NR^{Za}R^{Zb}, C_1 - C_{10} alkyl, C_1 - C_{10} haloalkyl, or C_3 - C_6 cycloalkyl.
19. The molecule of claim 18, or a pharmaceutically acceptable salt thereof, wherein each R^Z is independently halogen, -OH, -NH₂, or C_1 - C_6 alkyl.
20. The molecule of claim 12, or a pharmaceutically acceptable salt thereof, wherein one or two of R^{2a} ,



21. The molecule of claim 12 or 20, or a pharmaceutically acceptable salt thereof, wherein the remaining of R^{2a} , R^{2c} , R^{2d} , R^{2e} , or R^{2h} are an unsubstituted C_1 - C_{10} alkyl.
22. The molecule of claim 21, or a pharmaceutically acceptable salt thereof, wherein the remaining of R^{2a} , R^{2c} , R^{2d} , R^{2e} , or R^{2h} are independently methyl, ethyl, or isopropyl.
23. The molecule of claim 21, or a pharmaceutically acceptable salt thereof, wherein the remaining of R^{2a} , R^{2c} , R^{2d} , R^{2e} , or R^{2h} are each methyl.
24. The molecule of any one of claims 12-23, or a pharmaceutically acceptable salt thereof, wherein two R^{3b} together with the atom to which they are attached form a C_3 - C_6 cycloalkyl.
25. The molecule of claim 24, or a pharmaceutically acceptable salt thereof, wherein two R^{3b} together with the atoms to which they are attached form a cyclopropyl.
26. The molecule of any one of claims 12-23, or a pharmaceutically acceptable salt thereof, wherein each R^{3b} is hydrogen.

27. A transcription modulator molecule having a first terminus, a second terminus, and an oligomeric backbone moiety, or a pharmaceutically acceptable salt thereof, wherein:

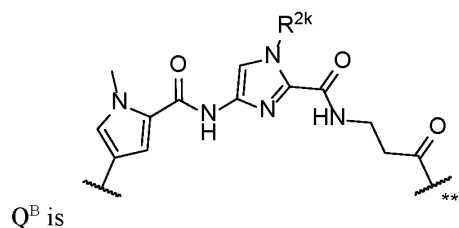
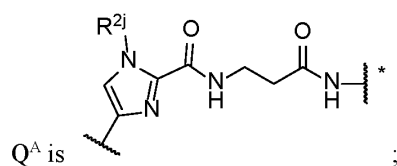
a) the first terminus comprises a DNA-binding moiety having the structure of Formula (II):



Formula (II),

wherein:

T^A is -Q^A-Q^B; wherein



; wherein

R^{2j} is an optionally substituted C₁-C₂₀ alkyl, optionally substituted with one or more R^Z;

R^{2k} is an optionally substituted C₁-C₂₀ alkyl or optionally substituted, C₃-C₁₀ cycloalkyl, each of which is optionally substituted with one or more R^Z;

* is the attachment point of Q^A to Q^B;

** is the attachment point to the oligomeric linker;

W¹ is hydrogen;

R^{2c} and R^{2d} are each independently an optionally substituted C₁-C₂₀ alkyl, optionally substituted, C₃-C₁₀ cycloalkyl, or optionally substituted 3 to 10-membered heterocycloalkyl, each of which is optionally substituted with one or more R^Z;

each R^{3b} is hydrogen or C₁-C₆ alkyl;

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

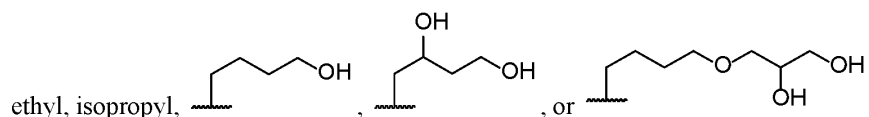
each R^Z is independently halogen, -CN, -OH, -OR^{Za}, -N₃, -NR^{Za}R^{Zb}, -CO(O)R^{Zc}, -C(O)OR^{Zc}, -C(O)NR^{Za}R^{Zb}, -NR^{Za}C(O)R^{Zc}, C₁-C₁₀ alkyl, or C₁-C₁₀ haloalkyl;

or two R^Z together with the atom(s) to which they are attached form a C₃-C₆ cycloalkyl, wherein

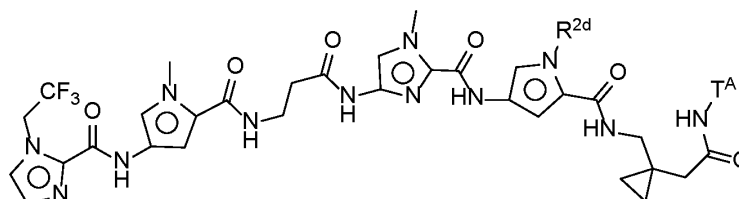
R^{Za} and R^{Zb} are each independently hydrogen, alkyl, haloalkyl, or PEG; and

R^{Zc} is alkyl, haloalkyl, PEG, cycloalkyl, heterocycloalkyl, or phenyl;

- b) the second terminus comprises a protein-binding moiety capable of binding to a regulatory molecule that modulates expression of a gene; and
- c) the oligomeric backbone links the first terminus and the second terminus.
28. The molecule of claim 27, or a pharmaceutically acceptable salt thereof, wherein each R^{3b} is hydrogen.
29. The molecule of claim 27, or a pharmaceutically acceptable salt thereof, wherein two R^{3b} together with the atoms to which they are attached form a C_3 - C_6 cycloalkyl
30. The molecule of claim 29, or a pharmaceutically acceptable salt thereof, wherein two R^{3b} together with the atom to which they are attached form a cyclopropyl.
31. The molecule of any one of claims 27-30, or a pharmaceutically acceptable salt thereof, wherein R^{2c} is an optionally substituted C_1 - C_{20} alkyl, optionally substituted with one or more R^Z , wherein each R^Z is independently halogen, $-OH$, $-OR^{Za}$, $-NR^{Za}R^{Zb}$, or C_1 - C_6 alkyl.
32. The molecule of claim 31, or a pharmaceutically acceptable salt thereof, wherein R^{2c} is methyl,



33. The molecule of claim 32, or a pharmaceutically acceptable salt thereof, wherein R^{2c} is methyl.
34. The molecule of claim 27, wherein the first terminus of Formula (II) has the structure of Formula (IIa), or a pharmaceutically acceptable salt thereof:

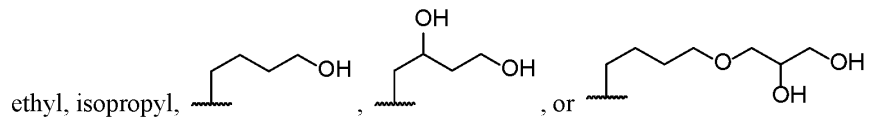


Formula (IIa).

35. The molecule of any one of claims 27-34, or a pharmaceutically acceptable salt thereof, wherein R^{2d} is an optionally substituted C_1 - C_{20} alkyl, optionally substituted with one or more R^Z .
36. The molecule of any one of claims 27-34, or a pharmaceutically acceptable salt thereof, wherein R^{2d} is an optionally substituted C_3 - C_{10} cycloalkyl, optionally substituted with one or more R^Z .
37. The molecule of claim 36, or a pharmaceutically acceptable salt thereof, wherein R^{2d} is an optionally substituted monocyclic, spirocyclic, or bridged C_3 - C_8 cycloalkyl, each of which is optionally substituted with one or more R^Z , wherein each R^Z is independently halogen, $-OH$, $-OR^{Za}$, $-NR^{Za}R^{Zb}$, or C_1 - C_6 alkyl.
38. The molecule of any one of claims 35-37, or a pharmaceutically acceptable salt thereof, wherein each R^Z is independently $-F$, $-OH$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, or $-C(CH_3)_3$.
39. The molecule of any one of claims 27-38, or a pharmaceutically acceptable salt thereof, wherein R^{2j} is an unsubstituted C_1 - C_{10} alkyl.

40. The molecule of any one of claims 27-38, or a pharmaceutically acceptable salt thereof, wherein R^{2j} is an optionally substituted C_1 - C_{20} alkyl.

41. The molecule of claim 39, or a pharmaceutically acceptable salt thereof, wherein R^{2c} is methyl,

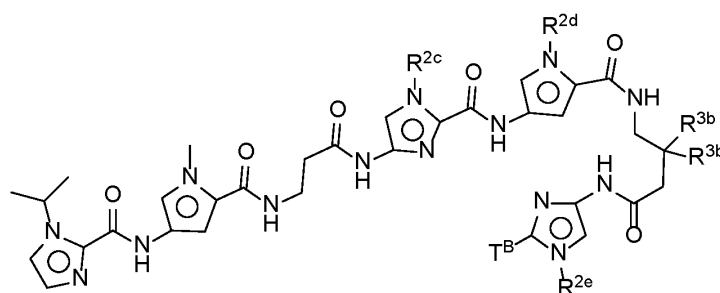


42. The molecule of any one of claims 27-38, or a pharmaceutically acceptable salt thereof, wherein R^{2j} is an unsubstituted C_1 - C_{10} alkyl and R^{2k} is unsubstituted C_1 - C_{10} alkyl.

43. The molecule of claim 42, or a pharmaceutically acceptable salt thereof, wherein R^{2j} is methyl and R^{2k} is methyl.

44. A transcription modulator molecule having a first terminus, a second terminus, and an oligomeric backbone moiety, or a pharmaceutically acceptable salt thereof, wherein:

- a) the first terminus comprises a DNA-binding moiety having the structure of Formula (III):

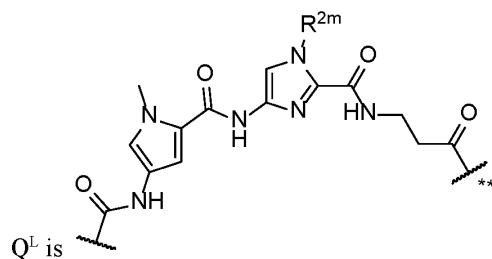


Formula (III),

wherein:

T^B is $-S^1-Q^L$;

S^1 is $-C(O)NH(CH_2)_2-$; wherein



; wherein

R^{2m} is an optionally substituted C_1 - C_{20} alkyl which is optionally substituted with one or more R^Z ;

** is the attachment point to the oligomeric linker;

R^{2c} is an unsubstituted C_1 - C_6 alkyl;

R^{2d} and R^{2e} are each independently an optionally substituted C_1 - C_{20} alkyl, optionally substituted C_3 - C_{10} cycloalkyl, or optionally substituted 3 to 10-membered heterocycloalkyl, each of which is optionally substituted with one or more R^Z ;

each R^{3b} is hydrogen or C_1 - C_6 alkyl;

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

each R^Z is independently halogen, $-CN$, $-OH$, $-OR^{Za}$, $-N_3$, $-NR^{Za}R^{Zb}$, $-CO(O)R^{Zc}$, $-C(O)OR^{Zc}$, $-C(O)NR^{Za}R^{Zb}$, $-NR^{Za}C(O)R^{Zc}$, C_1 - C_{10} alkyl, or C_1 - C_{10} haloalkyl;

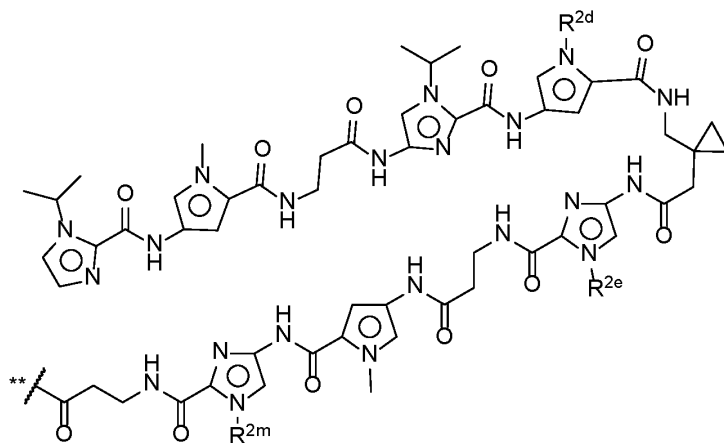
or two R^Z together with the atom(s) to which they are attached form a C_3 - C_6 cycloalkyl, wherein

R^{Za} and R^{Zb} are each independently hydrogen, alkyl, haloalkyl, or PEG; and

R^{Zc} is alkyl, haloalkyl, PEG, cycloalkyl, heterocycloalkyl, or phenyl;

- b) the second terminus comprises a protein-binding moiety capable of binding to a regulatory molecule that modulates expression of a gene; and
- c) the oligomeric backbone links the first terminus and the second terminus.

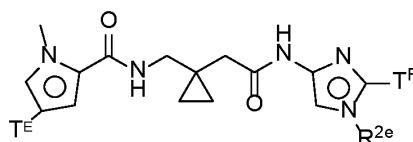
45. The molecule of claim 44, or a pharmaceutically acceptable salt thereof, wherein each R^{3b} is hydrogen.
46. The molecule of claim 44, or a pharmaceutically acceptable salt thereof, wherein two R^{3b} together with the atom to which they are attached form a C_3 - C_6 cycloalkyl.
47. The molecule of claim 46, or a pharmaceutically acceptable salt thereof, wherein two R^{3b} together with the atom to which they are attached form a cyclopropyl.
48. The molecule of any one of claims 44-47, or a pharmaceutically acceptable salt thereof, wherein R^{2c} is methyl, ethyl, or isopropyl.
49. The molecule of claim 44, wherein the first terminus of Formula (III) has the structure of Formula (IIIa), or a pharmaceutically acceptable salt thereof:



Formula (IIIa).

50. The molecule of any one of claims 44-49, or a pharmaceutically acceptable salt thereof, wherein R^{2d} is an optionally substituted C_1 - C_{20} alkyl, optionally substituted with one or more R^Z .
51. The molecule of any one of claims 44-49, or a pharmaceutically acceptable salt thereof, wherein R^{2d} is an optionally substituted C_3 - C_{10} cycloalkyl, optionally substituted with one or more R^Z .
52. The molecule of any one of claims 44-51, or a pharmaceutically acceptable salt thereof, wherein R^{2e} is an optionally substituted C_1 - C_{20} alkyl, optionally substituted with one or more R^Z .

53. The molecule of any one of claims 50-52, or a pharmaceutically acceptable salt thereof, wherein each R^Z is independently halogen, -OH, -OR^{Za}, -NR^{Za}R^{Zb}, or C₁-C₆ alkyl.
54. The molecule of claim 53, or a pharmaceutically acceptable salt thereof, wherein each R^Z is independently -F, -OH, -NH₂, -NHCH₃, -N(CH₃)₂, -CH₃, -CH₂CH₃, -CH(CH₃)₂, or -C(CH₃)₃.
55. The molecule of claim 52, wherein R^{2e} is methyl, ethyl, or isopropyl.
56. The molecule of any one of claims 42-55, or a pharmaceutically acceptable salt thereof, wherein R^{2m} is an unsubstituted C₁-C₆ alkyl.
57. The molecule of claim 56, or a pharmaceutically acceptable salt thereof, wherein R^{2m} is methyl, ethyl, or isopropyl.
58. A transcription modulator molecule having a first terminus, a second terminus, and an oligomeric backbone moiety, or a pharmaceutically acceptable salt thereof, wherein:
- a) the first terminus comprises a DNA-binding moiety having the structure of Formula (V):



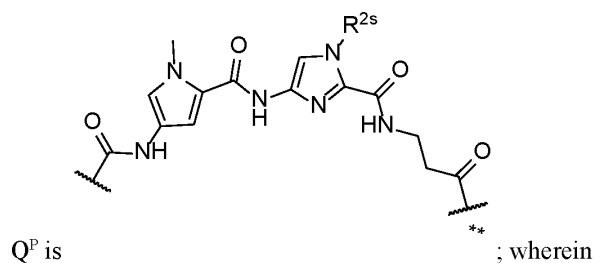
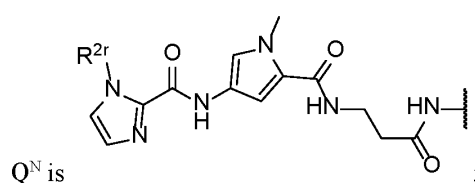
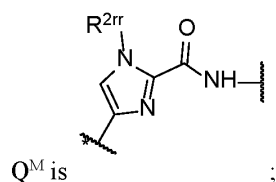
Formula (V),

wherein:

T^E is -Q^M-Q^N;

T^F is -S³-Q^P; wherein

S³ is -C(O)NH(CH₂)₂-;



R^{2r}, R^{2rr}, and R^{2s} are each independently an optionally substituted C₁-C₂₀ alkyl wherein each is optionally substituted with one or more R^Z;

* is the attachment point of Q^M to Q^N ; and

** is the attachment point to the oligomeric linker;

R^{2e} is a C_3 - C_{10} cycloalkyl which is optionally substituted with one or more R^Z ;

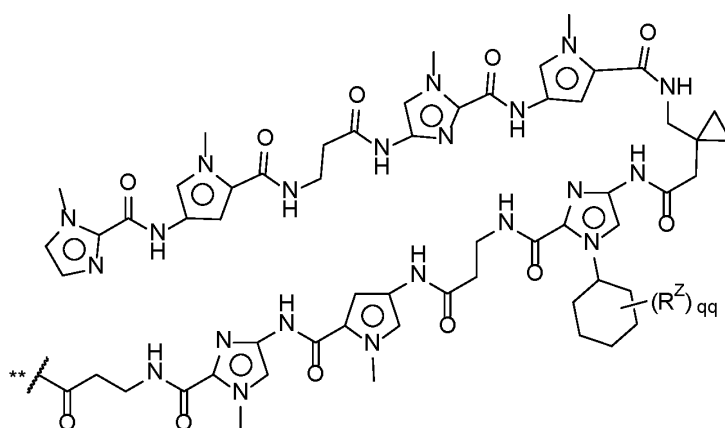
each R^Z is independently halogen, -CN, -OH, -OR^{Za}, -N₃, -NR^{Za}R^{Zb}, -CO(O)R^{Zc}, -C(O)OR^{Zc}, -C(O)NR^{Za}R^{Zb}, -NR^{Za}C(O)R^{Zc}, C_1 - C_{10} alkyl, or C_1 - C_{10} haloalkyl;

or two R^Z together with the atom(s) to which they are attached form a C_3 - C_6 cycloalkyl, wherein

R^{Za} and R^{Zb} are each independently hydrogen, alkyl, haloalkyl, or PEG; and

R^{Zc} is alkyl, haloalkyl, PEG, cycloalkyl, heterocycloalkyl, or phenyl;

- b) the second terminus comprises a protein-binding moiety capable of binding to a regulatory molecule that modulates expression of a gene; and
- c) the oligomeric backbone links the first terminus and the second terminus.
59. The molecule of claim 58, or a pharmaceutically acceptable salt thereof, wherein R^{2r} , R^{2rr} , and R^{2s} are independently an optionally substituted C_1 - C_8 alkyl, each of which is optionally substituted with one or more R^Z ; wherein each R^Z is independently halogen, -OH, -OR^{Za}, or -NR^{Za}R^{Zb}.
60. The molecule of claim 58, or a pharmaceutically acceptable salt thereof, wherein R^{2r} , R^{2rr} , and R^{2s} are independently an unsubstituted C_1 - C_8 alkyl.
61. The molecule of any one of claims 58-60, or a pharmaceutically acceptable salt thereof, wherein R^{2e} is an optionally substituted monocyclic, spirocyclic, or bridge C_3 - C_8 cycloalkyl, each of which is optionally substituted with one or more R^Z .
62. The molecule of claim 61, or a pharmaceutically acceptable salt thereof, wherein R^{2e} is an unsubstituted monocyclic C_6 - C_8 cycloalkyl.
63. The molecule of claim 58, wherein the first terminus comprises the structure of Formula (Va), or a pharmaceutically acceptable salt thereof:



Formula (Va),

wherein:

each R^Z is independently halogen, -CN, -OH, -OR^{Za}, -N₃, -NR^{Za}R^{Zb}, -CO(O)R^{Zc}, -C(O)OR^{Zc}, -C(O)NR^{Za}R^{Zb}, -NR^{Za}C(O)R^{Zc}, C_1 - C_{10} alkyl, C_1 - C_{10} haloalkyl;

or two R^Z together with the atom(s) to which they are attached form a C₃-C₆ cycloalkyl;

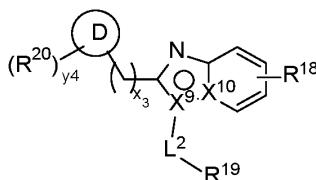
R^{Za} and R^{Zb} are each independently hydrogen, alkyl, haloalkyl, or PEG;

R^{Zc} is alkyl, haloalkyl, PEG, cycloalkyl, heterocycloalkyl, or phenyl; and

qq is 0, 1, or 2.

64. The molecule of claim 63, or a pharmaceutically acceptable salt thereof, wherein each R^Z is independently halogen, -OH, -OR^{Za}, -NR^{Za}R^{Zb}, or C₁-C₆ alkyl.
65. The molecule of claim 64, or a pharmaceutically acceptable salt thereof, wherein each R^Z is independently -F, -OH, -NH₂, -NHCH₃, -N(CH₃)₂, -CH₃, -CH₂CH₃, -CH(CH₃)₂, or -C(CH₃)₃.
66. The molecule of any one of claims 63-65, or a pharmaceutically acceptable salt thereof, wherein qq is 1 or 2.
67. The molecule of claim 63, or a pharmaceutically acceptable salt thereof, wherein qq is 0.
68. The molecule of any one of claims 1-67, or a pharmaceutically acceptable salt thereof, wherein the first terminus is capable of binding the DNA with an affinity of less than 500 nM.
69. The molecule of any one of claims 1-67, or a pharmaceutically acceptable salt thereof, wherein the oligomeric backbone is a linker having a length of less than about 50 Angstroms.
70. The molecule of any one of claims 1-67, or a pharmaceutically acceptable salt thereof, wherein the oligomeric backbone is a linker having a length of about 10 to 60 Angstroms.
71. The molecule of any one of claims 1-67, or a pharmaceutically acceptable salt thereof, wherein the oligomeric backbone comprises a multimer having 2 to 50 spacing moieties, wherein
 - each spacing moiety is independently selected from the group consisting of -((CR^{1b}R^{1b})_x-O)_y-, -((CR^{1b}R^{1b})_x-NR^{1a})_y-, -((CR^{1b}R^{1b})_x-CH=CH-(CR^{1b}R^{1b})_x-O)_y-, optionally substituted C₁-C₁₀ alkyl, optionally substituted C₂-C₁₀ alkenyl, optionally substituted C₂-C₁₀ alkynyl, optionally substituted C₆-C₁₀ arylene, optionally substituted C₃-C₇ cycloalkylene, optionally substituted 5 to 10-membered heteroarylene, optionally substituted 4 to 10-membered heterocycloalkylene, amino acid residue, -O-, -C(O)NR^{1a}-, -NR^{1a}C(O)-, -C(O)-, -NR^{1a}-, -C(O)O-, -S-, -S(O)-, -S(O)₂-, -S(O)₂NR^{1a}-, -NR^{1a}S(O)₂-, and -P(O)OH-, and any combinations thereof; wherein
 - each x is independently 2-4;
 - each y is independently 1-10;
 - each R^{1a} is independently hydrogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ haloalkyl, -S(O)₂-C₁-C₆ alkyl, -S(O)₂-C₁-C₆ haloalkyl, -S(O)₂-C₃-C₆ cycloalkyl, or -S(O)₂N-(C₁-C₆ alkyl)₂; and
 - each R^{1b} is independently hydrogen, halogen, optionally substituted C₁-C₆ alkyl, or optionally substituted C₁-C₆ haloalkyl.
72. The molecule of claim 71, or a pharmaceutically acceptable salt thereof, wherein the oligomeric backbone comprises a multimer having 2 to 50 spacing moieties, wherein each spacing moiety is independently selected from the group consisting of -((CH₂)_x-O)_y-, -((CH₂)_x-NH)_y-, -O-, -C(O)NH-, -NH-, and any combinations thereof.

73. The molecule of claim 71, or a pharmaceutically acceptable salt thereof, wherein the oligomeric backbone comprises a multimer having 2 to 50 spacing moieties selected from $-\text{NHC(O)}((\text{CH}_2)_x-\text{O})_y-$, $-\text{C(O)NH}((\text{CH}_2)_x-\text{O})_y-$.
74. The molecule of any one of claims 1-73, or a pharmaceutically acceptable salt thereof, wherein the second terminus comprises a bromodomain binding moiety.
75. The molecule of any one of claims 1-73, or a pharmaceutically acceptable salt thereof, wherein the second terminus comprises a moiety capable of binding to a bromodomain and extra terminal domain (BET) family member.
76. The molecule of claim 75, or a pharmaceutically acceptable salt thereof, wherein the BET family member is BRD2, BRD3, BRD4, or BRDT.
77. The molecule of any one of claims 1-73, or a pharmaceutically acceptable salt thereof, wherein the second terminus is a moiety capable of binding CBP/p300, PCAF (P300/CBP-Associated Factor), CECR2 (cat eye syndrome chromosome region candidate 2), BRPF (bromodomain and PHD finger-containing protein), ATAD2/ATAD2B (chromatin remodeling proteins), TRIM24 (Tripartite motif-containing 24), BAZ2 (Bromodomain Adjacent to Zinc finger), TAF1 (TBP associated factors), BRD7/9, BPTF (Bromodomain PHD Finger Transcription Factor), SMARCA2/4, or PBRM1.
78. The molecule of claim 77, or a pharmaceutically acceptable salt thereof, wherein the second terminus comprises a moiety capable of binding to a CBP/p300 binding moiety.
79. The molecule of claim 77, or a pharmaceutically acceptable salt thereof, wherein the second terminus a moiety capable of binding to a PCAF (P300/CBP-Associated Factor) moiety.
80. The molecule of any of claims 1-73, wherein the second terminus comprises the structure of Formula (4-A), or a pharmaceutically acceptable salt thereof:



Formula (4-A),

wherein:

Ring D is absent, phenyl, or 5 to 6-membered heteroaryl;

X^9 and X^{10} are each independently C or N, wherein one of X^9 or X^{10} is N;

L^2 is absent, optionally substituted alkylene, $-\text{O}-$, or $-\text{NR}^D-$, wherein R^D is hydrogen or optionally substituted C_1 - C_3 alkyl;

R^{18} is an optionally substituted 5 to 6-membered heteroaryl;

R^{19} is an optionally substituted C_3 - C_8 cycloalkyl or optionally substituted 4 to 7-membered heteroaryl;

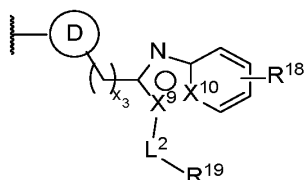
each R^{20} is independently hydrogen, halogen, $-\text{CN}$, $-\text{NO}_2$, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 haloalkyl, or optionally substituted C_1 - C_6 hydroxyalkyl;

x_3 is an integer from 1-3; and

y_4 is an integer from 1-4;

wherein the attachment to the linker is at either R^{19} or at one of R^{20} .

81. The molecule of claim 80, wherein the second terminus comprises the structure of Formula (4-B), or a pharmaceutically acceptable salt thereof:



Formula (4-B),

wherein:

Ring D is absent, optionally substituted phenyl, or optionally substituted 5 to 6-membered heteroaryl;

X^9 and X^{10} are each independently C or N, wherein one of X^9 or X^{10} is N;

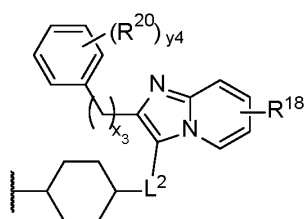
L^2 is absent, optionally substituted alkylene, -O-, or -NR^D-, wherein R^D is hydrogen or optionally substituted C₁-C₃ alkyl;

R^{18} is an optionally substituted 5 to 6-membered heteroaryl;

R^{19} is an optionally substituted C₃-C₈ cycloalkyl or optionally substituted 4 to 7-membered heteroaryl; and

x_3 is an integer from 1-3.

82. The molecule of claim 80, wherein the second terminus comprises the structure of Formula (4-D), or a pharmaceutically acceptable salt thereof:



Formula (4-D),

wherein:

L^2 is an optionally substituted alkylene, -O-, or -NR^D-, wherein R^D is hydrogen or optionally substituted C₁-C₃ alkyl;

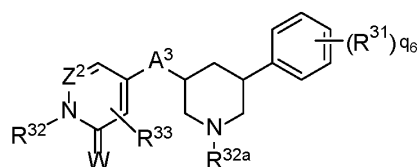
R^{18} is an optionally substituted 5 to 6-membered heteroaryl;

R^{20} is hydrogen, halogen, -CN, -NO₂, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ haloalkyl, or optionally substituted C₁-C₆ hydroxyalkyl;

x_3 is an integer from 1-3; and

y_4 is an integer from 1-4.

83. The molecule of any of claims 1-73, wherein the second terminus comprises the structure of Formula (7-A), or a pharmaceutically acceptable salt thereof:



Formula (7-A),

wherein:

A^3 is -O-, -NH-, or -CH₂-;

Z^2 is CH or N;

W is O or S;

each R^{31} is independently hydrogen, halogen, -OH, -CN, -NO₂, -NH₂, optionally substituted C₁-C₁₀ alkyl, optionally substituted C₁-C₁₀ haloalkyl, optionally substituted C₁-C₁₀ hydroxyalkyl, optionally substituted C₂-C₁₀ alkenyl, optionally substituted C₂-C₁₀ alkynyl, optionally substituted C₃-C₈ cycloalkyl, or optionally substituted 3 to 8-membered heterocycloalkyl;

or two R^{31} together with the atoms to which they are attached join together to form an optionally substituted C₅-C₈ cycloalkyl or optionally substituted 5 to 8-membered heterocycloalkyl;

R^{32} is hydrogen or optionally substituted C₁-C₁₀ alkyl;

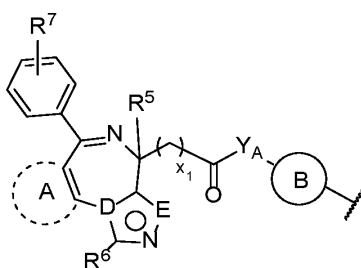
R^{32a} is hydrogen or optionally substituted C₁-C₁₀ alkyl;

R^{33} is hydrogen, halogen, -OH, -CN, -NO₂, -NH₂, optionally substituted C₁-C₁₀ alkyl, optionally substituted C₁-C₁₀ haloalkyl, or optionally substituted C₁-C₁₀ hydroxyalkyl; and

q_6 is 0-4;

wherein Formula (7-A) is attached to the linker is at R^{32a} or at one of R^{31} .

84. The molecule of any one of claims 1-73, wherein the second terminus comprises the structure of Formula (2-A), or a pharmaceutically acceptable salt thereof:



Formula (2-A),

wherein:

Ring A is an optionally substituted aryl or optionally substituted 5 to 6-membered heteroaryl;

Ring B is absent or an optionally substituted 6-membered monocyclic aryl or heteroaryl;

D is C or N;

E is O or N;

Y_A is -NH- or -O-;

R^5 is hydrogen or C₁-C₆ alkyl;

R^6 is selected from hydrogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ haloalkyl, and optionally substituted C₁-C₆ hydroxyalkyl;

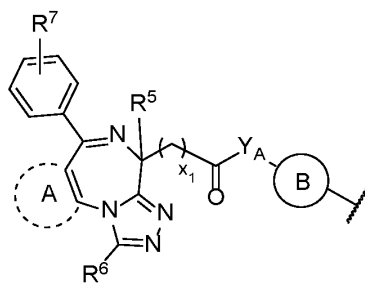
R^7 is selected from hydrogen, halogen, -NO₂, -CN, optionally substituted aryl, optionally substituted C₁-C₂₀ alkyl, optionally substituted C₁-C₂₀ heteroalkyl, optionally substituted C₁-C₆ haloalkyl, and optionally substituted C₁-C₆ hydroxyalkyl;

or R^7 is -NR^{7A}R^{7B}, wherein

R^{7A} and R^{7B} are each independently hydrogen, optionally substituted C₁-C₂₀ alkyl, or optionally substituted C₁-C₂₀ heteroalkyl; and

x_1 is an integer from 1-6.

85. The molecule of claim 84, wherein the second terminus comprises the structure of Formula (2-B), or a pharmaceutically acceptable salt thereof:



Formula (2-B),

wherein:

Ring A is an optionally substituted aryl or optionally substituted 5 to 6-membered heteroaryl;

Ring B is absent or an optionally substituted 6-membered monocyclic aryl or heteroaryl;

Y_A is -NH- or -O-;

R^5 is hydrogen or C₁-C₆ alkyl;

R^6 is selected from hydrogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ haloalkyl, and optionally substituted C₁-C₆ hydroxyalkyl;

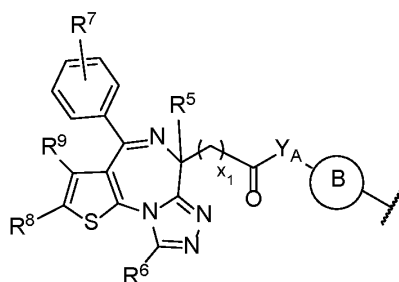
R^7 is selected from hydrogen, halogen, -NO₂, -CN, optionally substituted aryl, optionally substituted C₁-C₂₀ alkyl, optionally substituted C₁-C₂₀ heteroalkyl, optionally substituted C₁-C₆ haloalkyl, and optionally substituted C₁-C₆ hydroxyalkyl;

or R^7 is -NR^{7A}R^{7B}, wherein

R^{7A} and R^{7B} are each independently hydrogen, optionally substituted C₁-C₂₀ alkyl, or optionally substituted C₁-C₂₀ heteroalkyl; and

x_1 is an integer from 1-6.

86. The molecule of claim 84, wherein the second terminus comprises the structure of Formula (2-C), or a pharmaceutically acceptable salt thereof:



Formula (2-C),

wherein:

Ring B is absent or an optionally substituted 6-membered monocyclic aryl or heteroaryl;

Y_A is -NH- or -O-;

R⁵ is hydrogen or C₁-C₆ alkyl;

R⁶ is selected from hydrogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ haloalkyl, and optionally substituted C₁-C₆ hydroxyalkyl;

R⁷ is selected from hydrogen, halogen, -NO₂, -CN, optionally substituted aryl, optionally substituted C₁-C₂₀ alkyl, optionally substituted C₁-C₂₀ heteroalkyl, optionally substituted C₁-C₆ haloalkyl, and optionally substituted C₁-C₆ hydroxyalkyl;

or R⁷ is -NR^{7A}R^{7B}, wherein

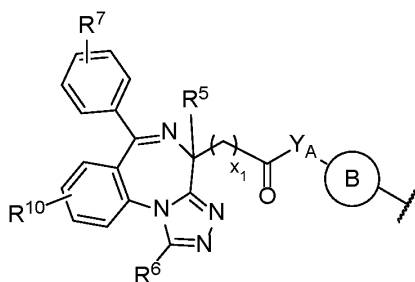
R^{7A} and R^{7B} are each independently hydrogen, optionally substituted C₁-C₂₀ alkyl, or optionally substituted C₁-C₂₀ heteroalkyl;

R⁸ and R⁹ are each independently selected from hydrogen, -C(O)OR^{8a}, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ haloalkyl, or optionally substituted C₁-C₆ hydroxyalkyl; and

R^{8a} is hydrogen, C₁-C₂₀ alkyl, or C₁-C₂₀ heteroalkyl; and

x₁ is an integer from 1-6.

87. The molecule of claim 84, wherein the second terminus of Formula (2-A) has the structure of Formula (2-D), or a pharmaceutically acceptable salt thereof:



Formula (2-D),

wherein:

Ring B is absent or an optionally substituted 6-membered monocyclic aryl or heteroaryl;

Y_A is -NH- or -O-;

R⁵ is hydrogen or C₁-C₆ alkyl;

R^6 is selected from hydrogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 haloalkyl, and optionally substituted C_1 - C_6 hydroxyalkyl;

R^7 is selected from hydrogen, halogen, $-NO_2$, $-CN$, optionally substituted aryl, optionally substituted C_1 - C_{20} alkyl, optionally substituted C_1 - C_{20} heteroalkyl, optionally substituted C_1 - C_6 haloalkyl, and optionally substituted C_1 - C_6 hydroxyalkyl;

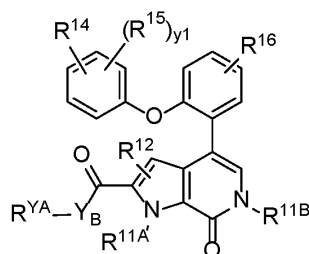
or R^7 is $-NR^{7A}R^{7B}$, wherein

R^{7A} and R^{7B} are each independently hydrogen, optionally substituted C_1 - C_{20} alkyl, or optionally substituted C_1 - C_{20} heteroalkyl;

R^{10} is selected from hydrogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 haloalkyl, or optionally substituted C_1 - C_6 hydroxyalkyl; and

x_1 is an integer from 1-6.

88. The molecule of any of claims 1-73, wherein the second terminus comprises the structure of Formula (3-A), or a pharmaceutically acceptable salt thereof:



Formula (3-A),

wherein:

Y_B is $-CH_2NH-$, $-CH_2O-$, $-NH-$, or $-O-$;

R^{11A} and R^{11B} are each independently hydrogen, or optionally substituted C_1 - C_6 alkyl;

R^{12} is hydrogen, halogen, $-OH$, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 haloalkyl, or optionally substituted C_1 - C_6 hydroxyalkyl;

R^{14} and R^{15} are each independently hydrogen, halogen, $-CN$, $-NO_2$, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 haloalkyl, or optionally substituted C_1 - C_6 hydroxyalkyl;

or R^{14} is $-NR^A R^B$;

R^{16} is optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 alkynyl, optionally substituted C_1 - C_6 hydroxyalkyl, $-S(O)(=NH)R^A$, $-SO_2R^A$, or $-NHSO_2R^A$;

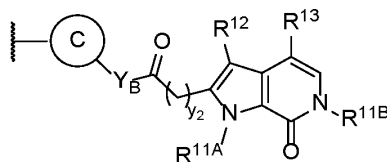
R^{YA} is hydrogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 haloalkyl, or optionally substituted 5-6-membered monocyclic aryl or heteroaryl;

each R^A and R^B is independently hydrogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_1 - C_6 haloalkyl, optionally substituted C_1 - C_6 hydroxyalkyl, optionally substituted C_3 - C_6 cycloalkyl, 4 to 6-membered heterocycloalkyl, or optionally substituted 4 to 6-membered heteroalkyl; and

y_1 is 1-3;

wherein the attachment to the linker is at either R^{14} or at R^{YA} .

89. The molecule of any one of claims 1-73, wherein the second terminus comprises the structure of Formula (3-B), or a pharmaceutically acceptable salt thereof:



Formula (3-B),

wherein:

Ring C is absent, optionally substituted 5 to 6-membered monocyclic aryl or heteroaryl or 4 to 8-membered heterocycle;

Y_B is -NH-, -CH₂NH-, -CH₂O-, or -O-;

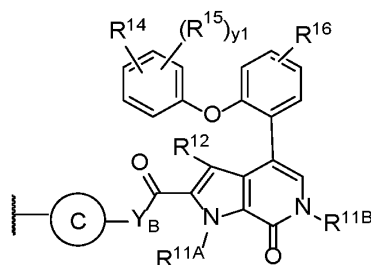
R^{11A} and R^{11B} are each independently hydrogen or optionally substituted C₁-C₆ alkyl;

R^{12} is hydrogen, optionally substituted C₁-C₆ alkyl, C(O) R^A , or C(O)NR^A R^B ; wherein each R^A and R^B is independently hydrogen, optionally substituted C₁-C₆ alkyl, or optionally substituted C₁-C₆ heteroalkyl;

R^{13} is hydrogen, substituted aryl, substituted heteroaryl, or substituted oxydibenzene; and

y_2 is an integer from 0-2.

90. The molecule of claim 88, wherein the second terminus comprises the structure of Formula (3-C), or a pharmaceutically acceptable salt thereof:



Formula (3-C),

wherein:

Ring C is absent, optionally substituted 5 to 6-membered monocyclic aryl or heteroaryl or 4 to 8-membered heterocycle;

Y_B is -CH₂NH-, -CH₂O-, -NH-, or -O-;

R^{12} is hydrogen, halogen, -OH, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ haloalkyl, or optionally substituted C₁-C₆ hydroxyalkyl;

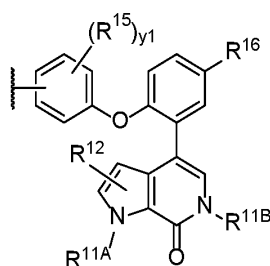
R^{14} and R^{15} are each independently hydrogen, halogen, -CN, -NO₂, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ haloalkyl, or optionally substituted C₁-C₆ hydroxyalkyl; or R^{14} is -NR^A R^B ;

R^{16} is optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 alkynyl, optionally substituted C_1 - C_6 hydroxyalkyl, $-S(O)(=NH)R^A$, $-SO_2R^A$, or $-NHSO_2R^A$;

each R^A and R^B is independently hydrogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_1 - C_6 haloalkyl, optionally substituted C_1 - C_6 hydroxyalkyl, optionally substituted C_3 - C_6 cycloalkyl, or optionally substituted 4 to 6-membered heterocycloalkyl; and

y_1 is an integer from 1-3.

91. The molecule of claim 88, wherein the second terminus comprises the structure of Formula (3-D), or a pharmaceutically acceptable salt thereof:



Formula (3-D),

wherein:

R^{11A} and R^{11B} are each independently hydrogen or optionally substituted C_1 - C_6 alkyl;

R^{12} is hydrogen or an optionally substituted C_1 - C_6 alkyl;

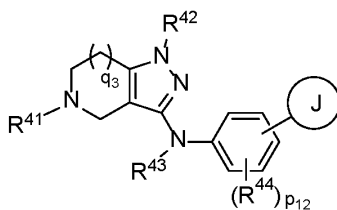
each R^{15} is independently hydrogen, halogen, $-CN$, $-NO_2$, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 haloalkyl, or optionally substituted C_1 - C_6 hydroxyalkyl;

R^{16} is optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 alkynyl, C_1 - C_6 hydroxyalkyl, $-S(O)(=NH)R^A$, $-SO_2R^A$, or $-NHSO_2R^A$;

R^A is hydrogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_1 - C_6 haloalkyl, optionally substituted C_1 - C_6 hydroxyalkyl, optionally substituted C_3 - C_6 cycloalkyl, optionally substituted 4 to 6-membered heterocycloalkyl, or optionally substituted 5 to 6-membered heteroaryl; and

y_1 is an integer from 1-3.

92. The molecule of any one of claims 1-73, wherein the second terminus comprises the structure of Formula (13-A), or a pharmaceutically acceptable salt thereof:



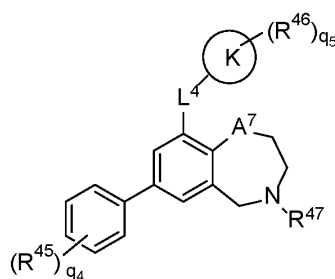
Formula (13-A),

wherein:

Ring J is absent or optionally substituted 5 to 6-membered heteroaryl;

 R^{41} is optionally substituted C_1 - C_6 alkyl, optionally substituted C_3 - C_8 cycloalkyl, $-C(O)R^{41a}$, $-C(O)-$, or $-C(O)NR^{41a}R^{41b}$, wherein R^{41a} and R^{41b} are each independently optionally substituted C_1 - C_{10} alkyl or optionally substituted C_3 - C_8 cycloalkyl; R^{42} is an optionally substituted C_1 - C_{10} alkyl, optionally substituted C_1 - C_{10} haloalkyl, optionally substituted C_3 - C_8 cycloalkyl, or optionally substituted 3 to 8 membered heterocycloalkyl; R^{43} is hydrogen or optionally substituted C_1 - C_{10} alkyl;each R^{44} is independently hydrogen, halogen, $-OH$, $-CN$, $-NO_2$, $-NH_2$, optionally substituted C_1 - C_{10} alkyl, optionally substituted C_1 - C_{10} haloalkyl, C_1 - C_{10} hydroxyalkyl, optionally substituted C_2 - C_{10} alkenyl, optionally substituted C_2 - C_{10} alkynyl, optionally substituted C_3 - C_8 -cycloalkyl, or optionally substituted 3 to 8-membered heterocycloalkyl; or R^{43} and one of R^{44} together with the atoms to which they are attached form an optionally substituted 5 to 8-membered heterocycloalkyl; p_{12} is 1-4; and q_3 is 0 or 1;wherein Formula (13-A) is connected to the linker at Ring J, R^{41} , or R^{42} .

93. The molecule of any one of claims 1-73, wherein the second terminus comprises the structure of Formula (14-A), or a pharmaceutically acceptable salt thereof:



Formula (14-A),

wherein:

Ring K is a 5 to 6-membered heterocycloalkyl;

 A^5 is absent, CH_2 , $-NH-$, or $-O-$; L^4 is alkylene or heteroalkylene;each R^{45} is independently halogen, $-OH$, $-CN$, $-NO_2$, $-NH_2$, optionally substituted C_1 - C_{10} alkyl, optionally substituted C_1 - C_{10} haloalkyl, optionally substituted C_1 - C_{10} heteroalkyl, optionally substituted C_1 - C_{10} hydroxyalkyl, optionally substituted C_2 - C_{10} alkenyl, optionally substituted C_2 - C_{10} alkynyl, optionally substituted C_3 - C_8 -cycloalkyl, or optionally substituted 3 to 8-membered heterocycloalkyl;

each R^{46} is independently hydrogen, halogen, -OH, -CN, -NO₂, -NH₂, optionally substituted C₁-C₁₀ alkyl, optionally substituted C₁-C₁₀ haloalkyl, optionally substituted C₁-C₁₀ hydroxyalkyl, optionally substituted C₂-C₁₀ alkenyl, optionally substituted C₂-C₁₀ alkynyl, optionally substituted C₃-C₈ cycloalkyl, or optionally substituted 3 to 8-membered heterocycloalkyl;

R^{47} is optionally substituted C₁-C₁₀ alkyl, -C(O) R^{47a} , or -C(O)-NR^{47a} R^{47b} , wherein

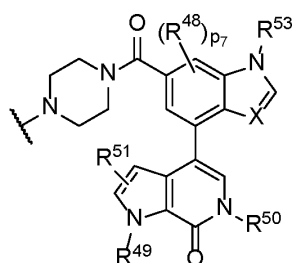
R^{47a} and R^{47b} are each independently optionally substituted C₁-C₁₀ alkyl or optionally substituted C₃-C₈ cycloalkyl;

q_4 is 2-3; and

q_5 is 0-2;

wherein the Formula (14-A) is connected to the linker through Ring K or through one of R^{45} .

94. The molecule of any one of claims 1-73, wherein the second terminus comprises the structure of Formula (15-C), or a pharmaceutically acceptable salt thereof:



Formula (15-C),

wherein:

X is CR⁴⁸ or N;

each R^{48} is hydrogen, halogen, -OH, -CN, -NO₂, -NH₂, C₁-C₁₀ alkyl, C₁-C₁₀ haloalkyl, or C₁-C₁₀ hydroxyalkyl;

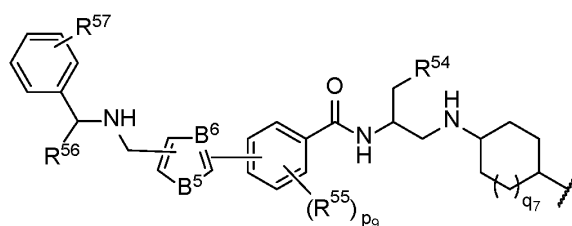
R^{49} and R^{50} are each independently hydrogen, optionally substituted C₁-C₁₀ alkyl, optionally substituted C₁-C₁₀ haloalkyl, optionally substituted C₂-C₁₀ alkenyl, or optionally substituted C₂-C₁₀ alkynyl;

R^{51} is hydrogen, halogen, -OH, -CN, -NO₂, -NH₂, optionally substituted C₁-C₁₀ alkyl, optionally substituted C₁-C₁₀ haloalkyl, optionally substituted C₁-C₁₀ hydroxyalkyl, optionally substituted C₂-C₁₀ alkenyl, or optionally substituted C₂-C₁₀ alkynyl;

R^{53} is hydrogen or optionally substituted C₁-C₁₀ alkyl; and

p_7 is 1-3.

95. The molecule of any one of claims 1-73, wherein the second terminus comprises the structure of Formula (16-A), or a pharmaceutically acceptable salt thereof:



Formula (16-A),

wherein:

B⁵ is -O-, -NH-, or S;

B⁶ is N or CH;

R⁵⁴ is optionally substituted aryl or optionally substituted heteroaryl;

each R⁵⁵ is independently halogen, -OH, -CN, -NO₂, -NH₂, optionally substituted C₁-C₁₀ alkyl, optionally substituted C₁-C₁₀ haloalkyl, optionally substituted C₁-C₁₀ heteroalkyl, or optionally substituted C₁-C₁₀ hydroxyalkyl;

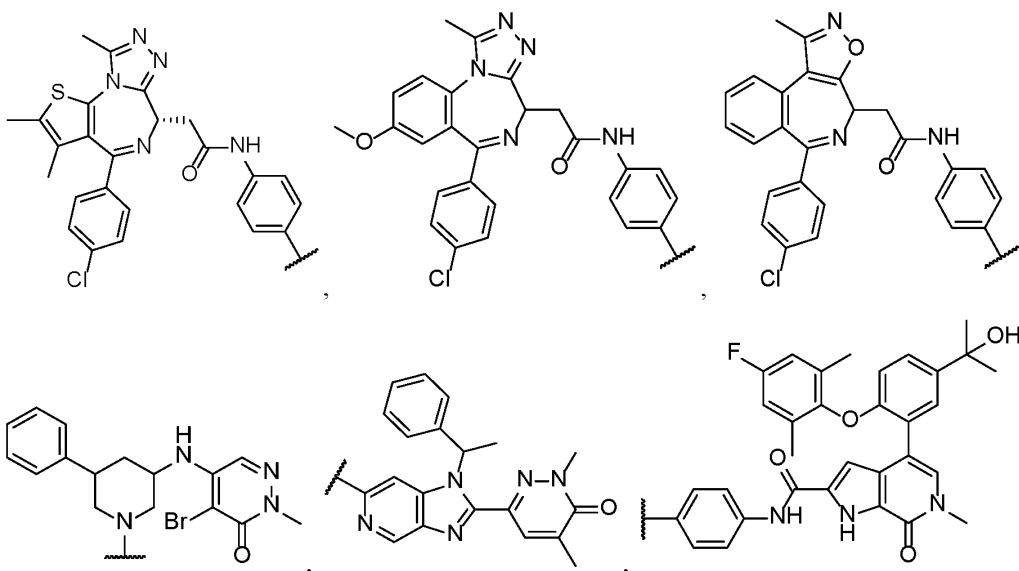
R⁵⁶ is hydrogen, optionally substituted C₁-C₁₀ alkyl, optionally substituted C₁-C₁₀ haloalkyl, or optionally substituted C₁-C₁₀ hydroxyalkyl;

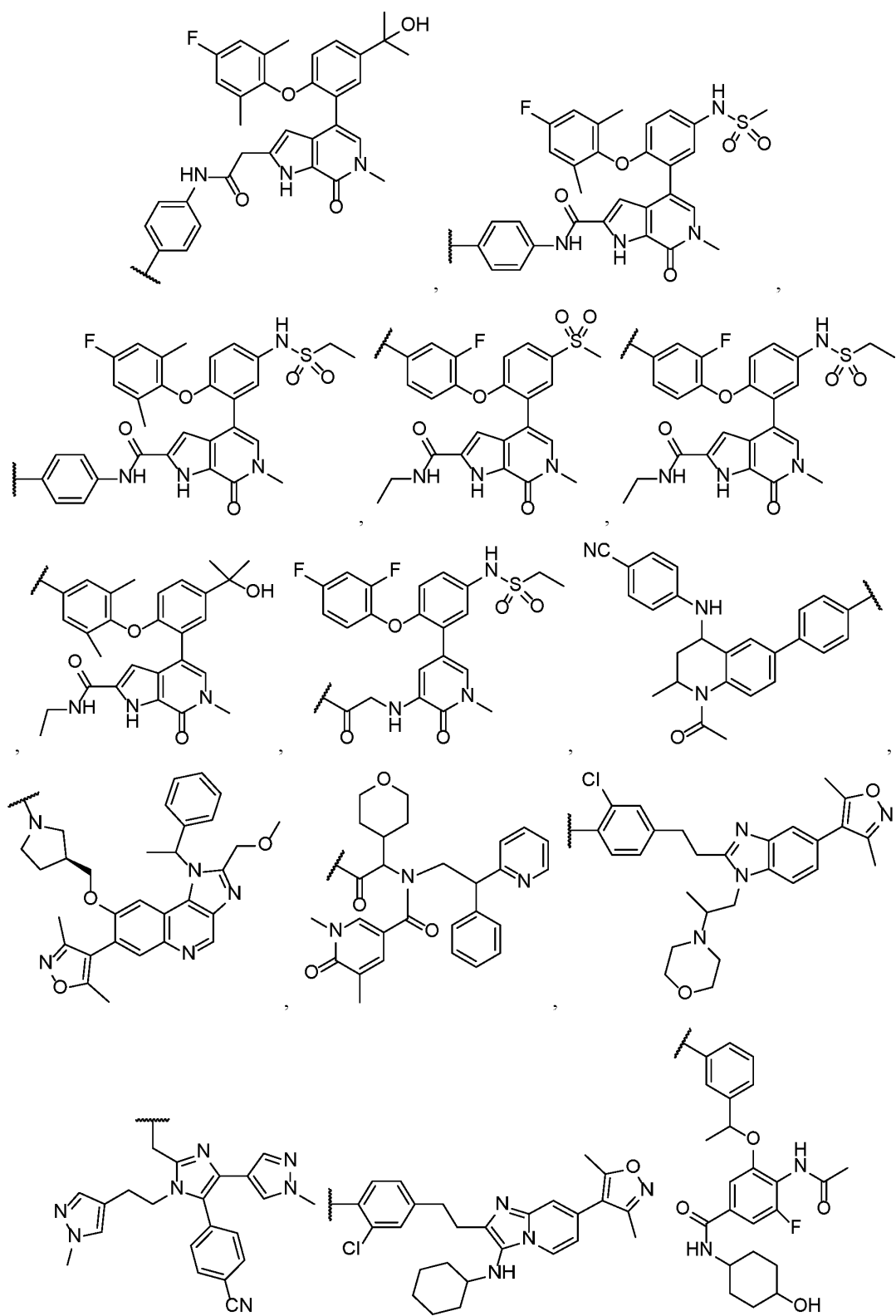
R⁵⁷ is halogen, -OH, -CN, -NO₂, -NH₂, optionally substituted C₁-C₁₀ alkyl, optionally substituted C₁-C₁₀ haloalkyl, or optionally substituted C₁-C₁₀ hydroxyalkyl;

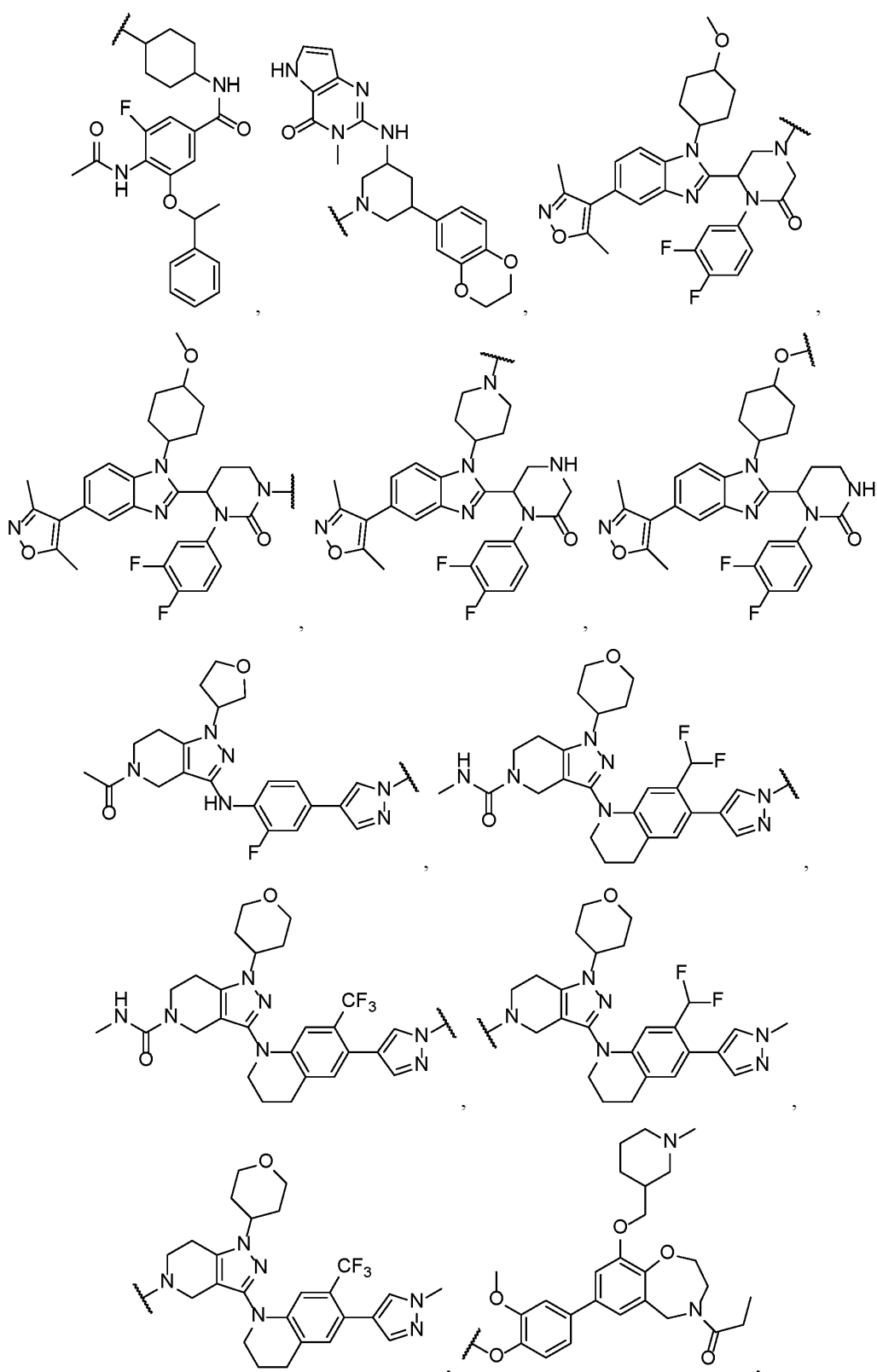
p₉ is 1-3; and

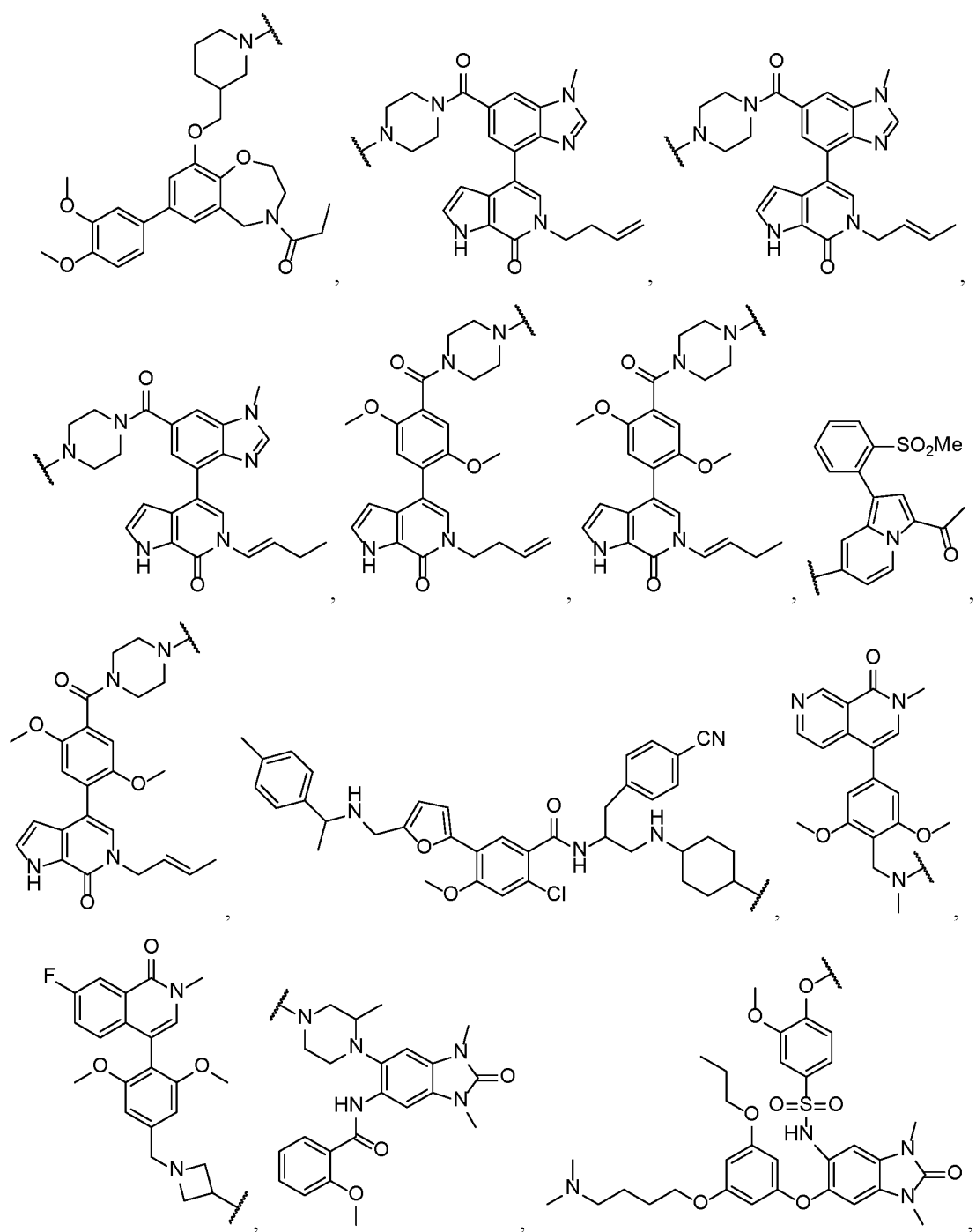
q₇ is 0-2.

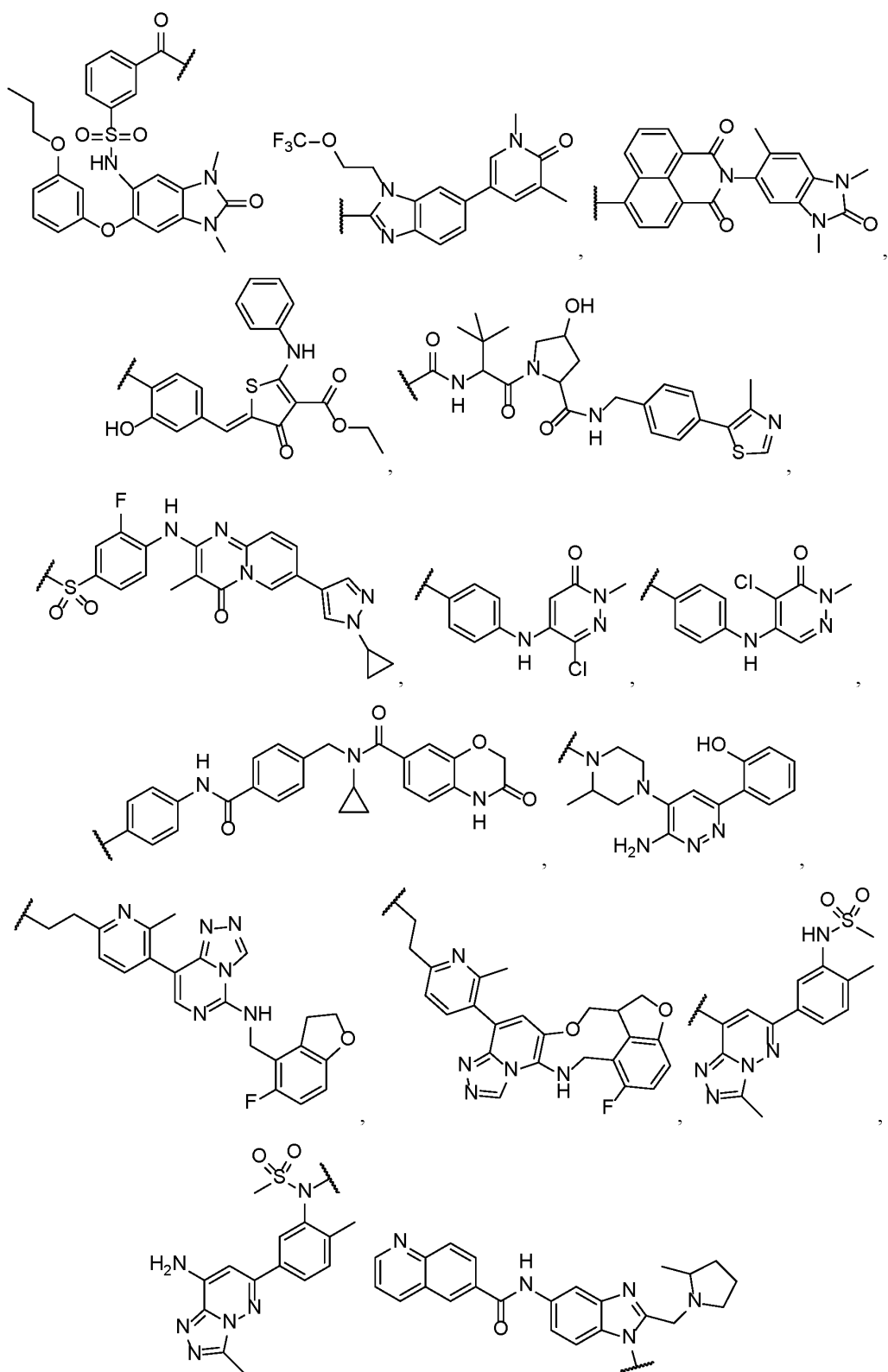
96. The molecule of any of claims 1-73, wherein the second terminus is selected from the group consisting of, or a pharmaceutically acceptable salt thereof:

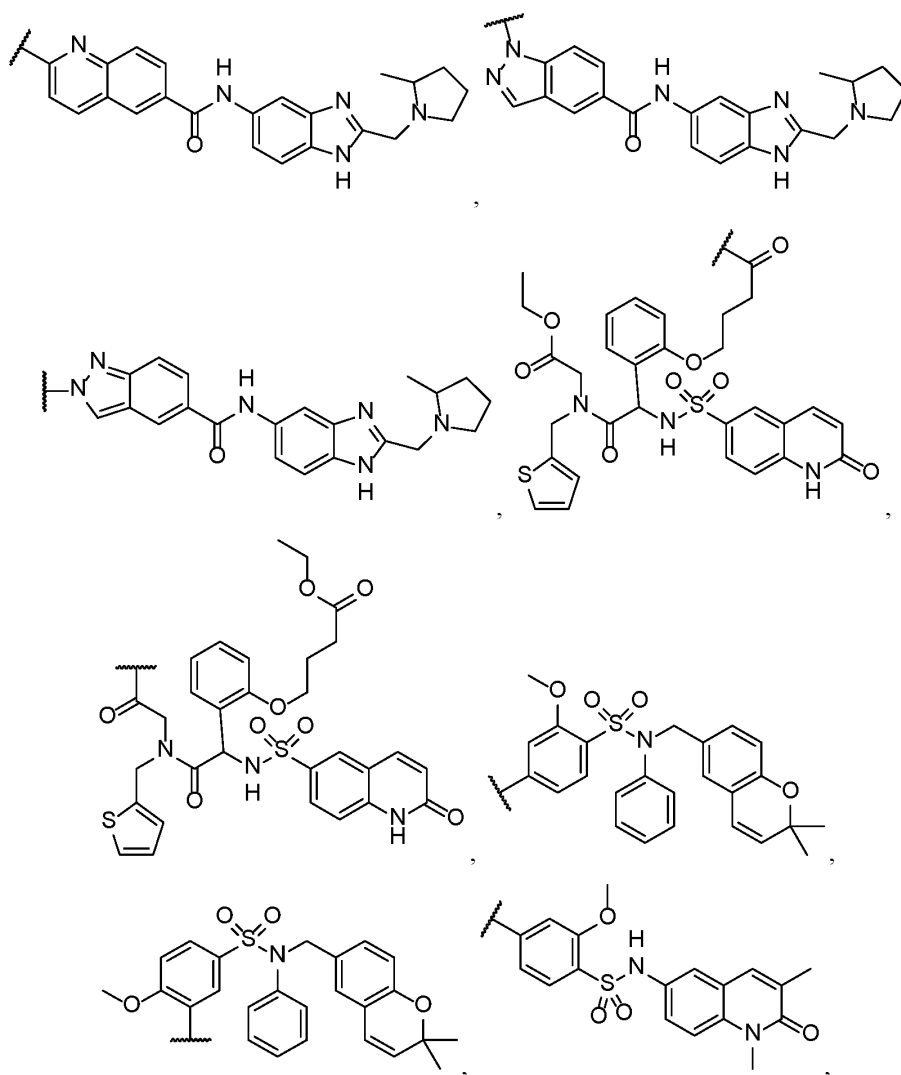


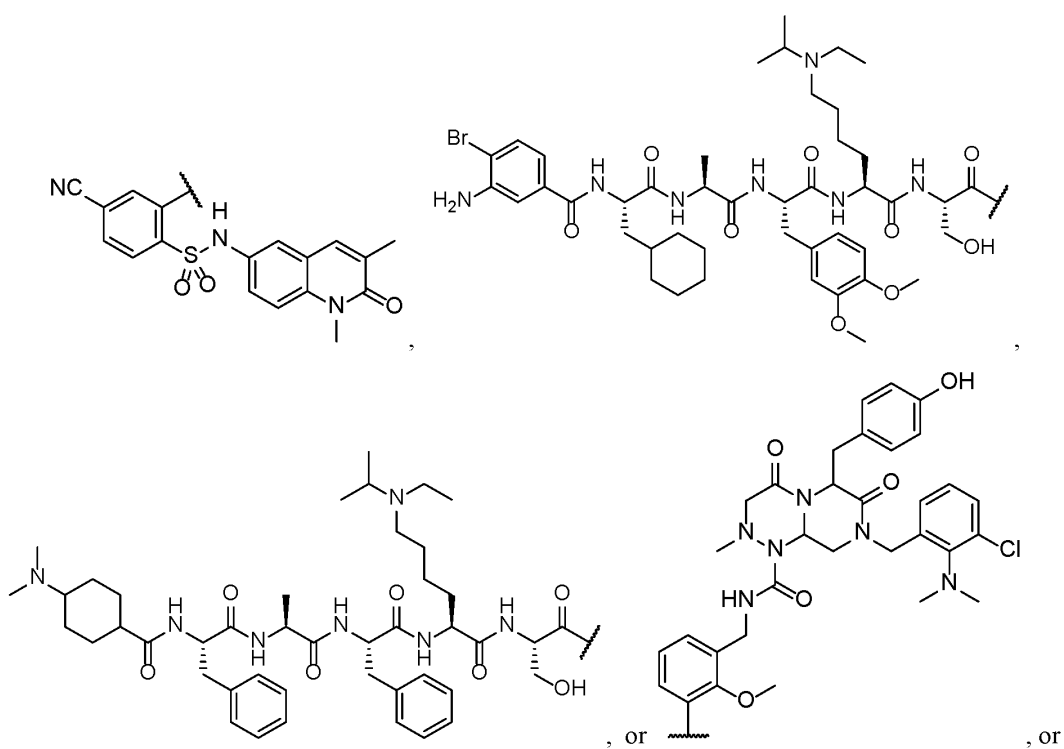






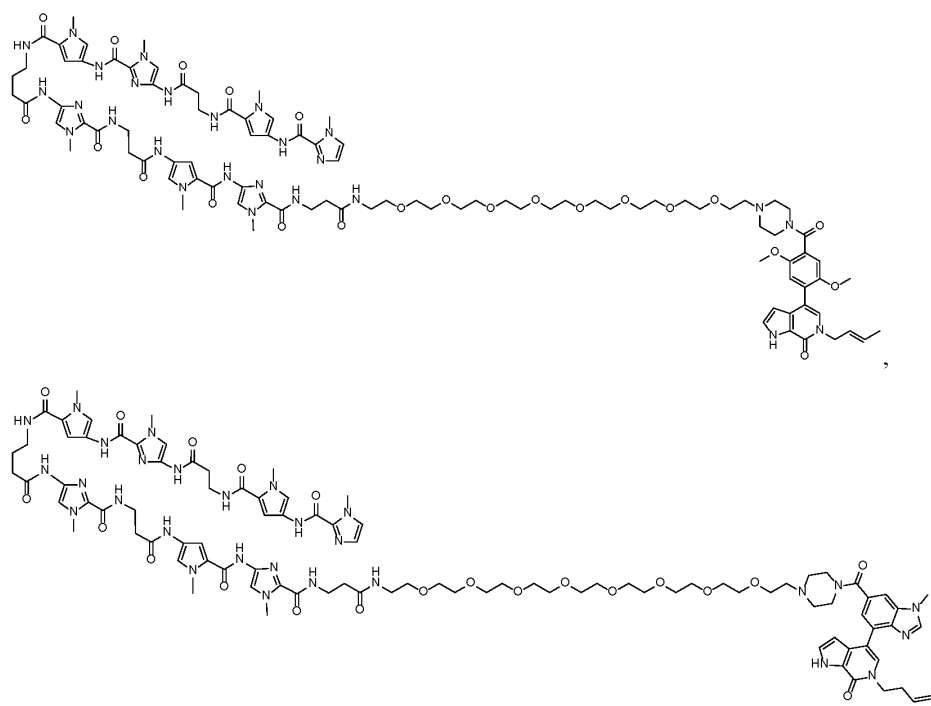


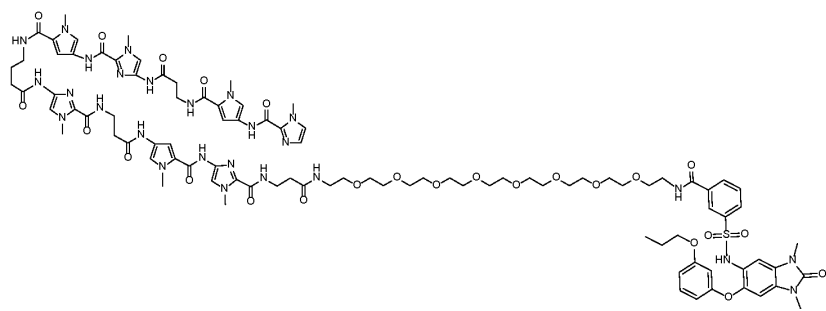
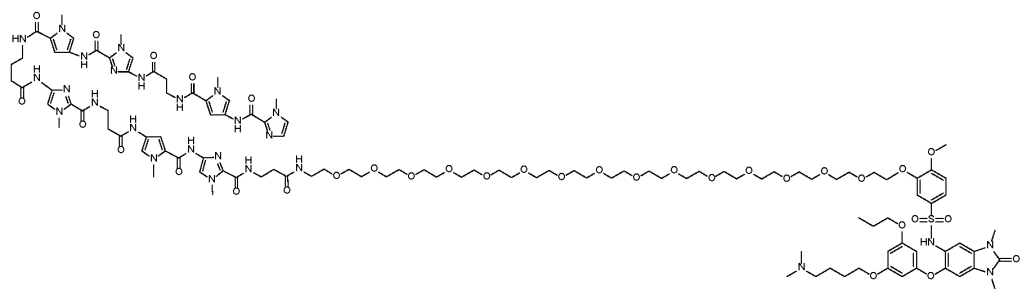
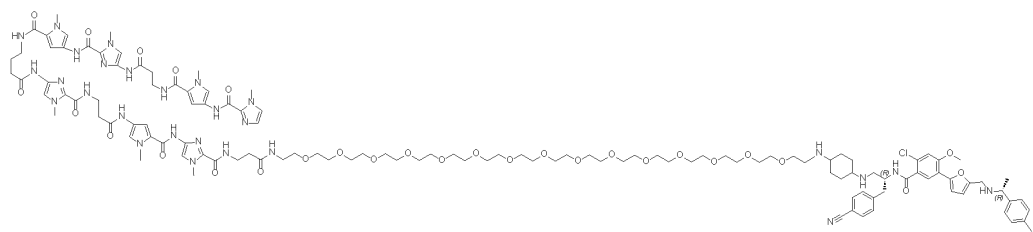
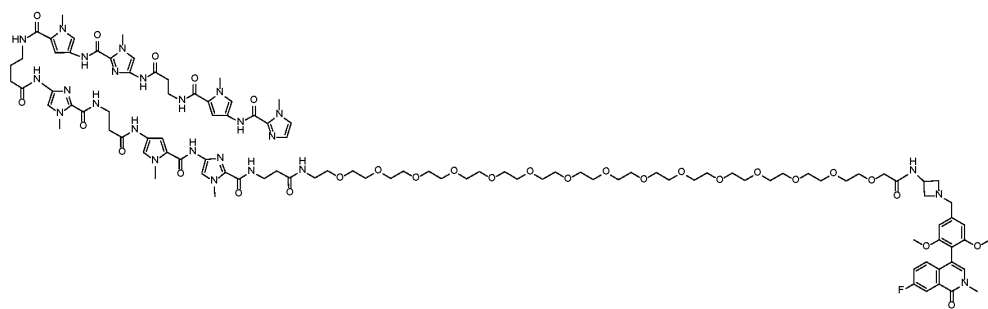
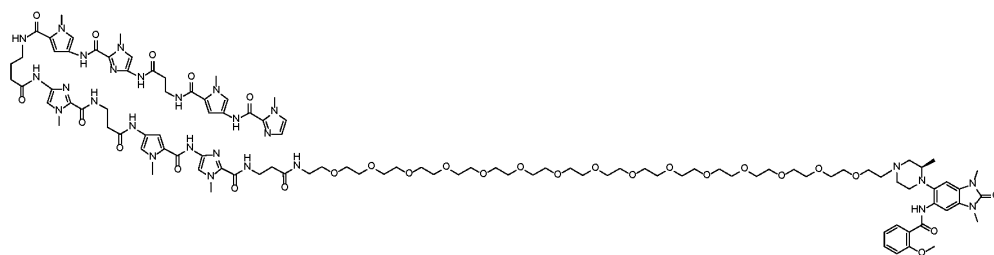


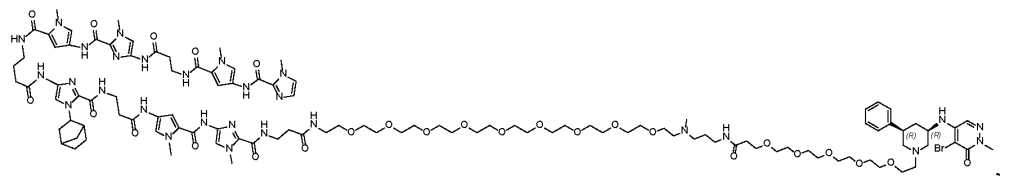
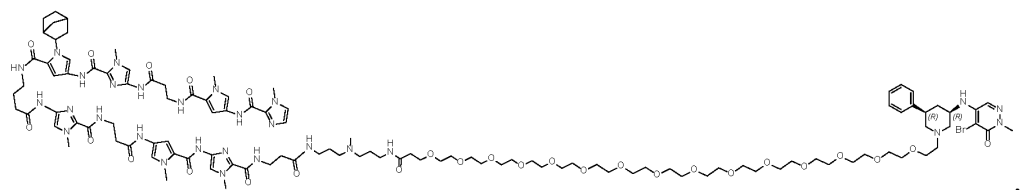
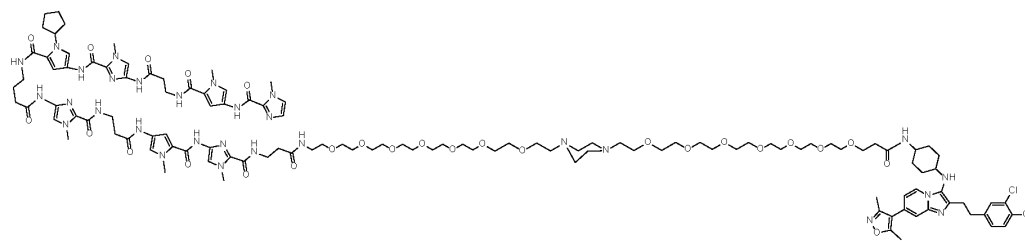
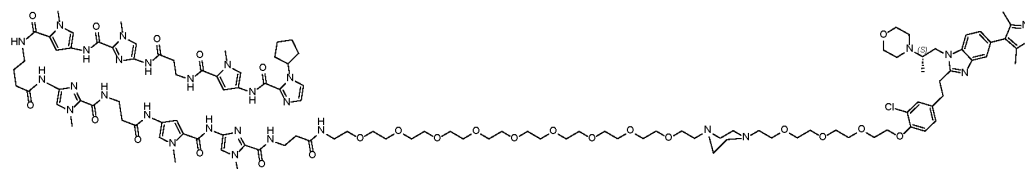
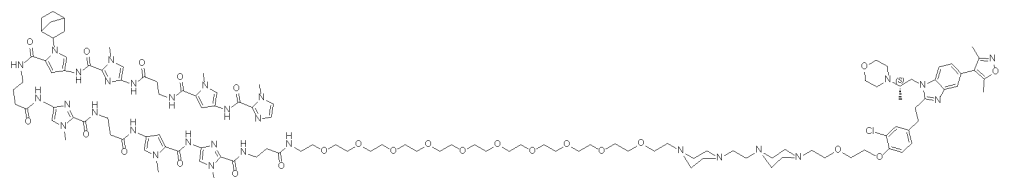
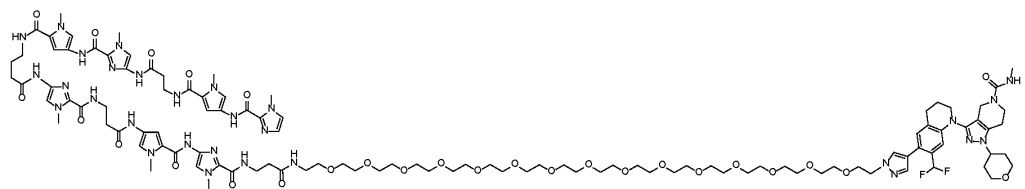
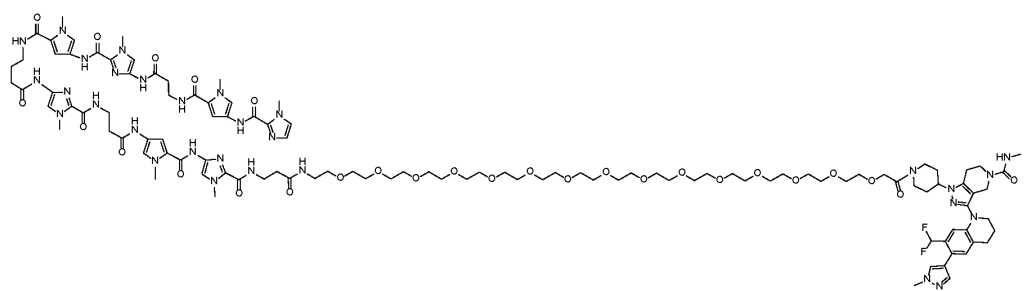


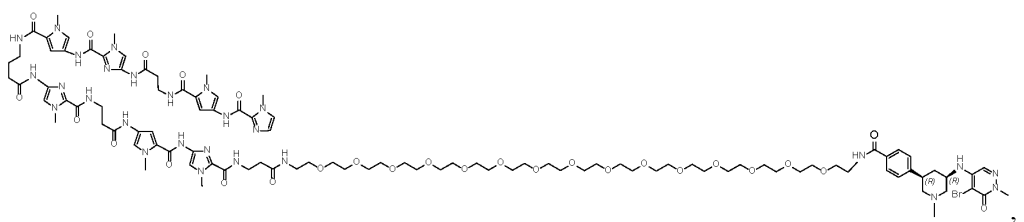
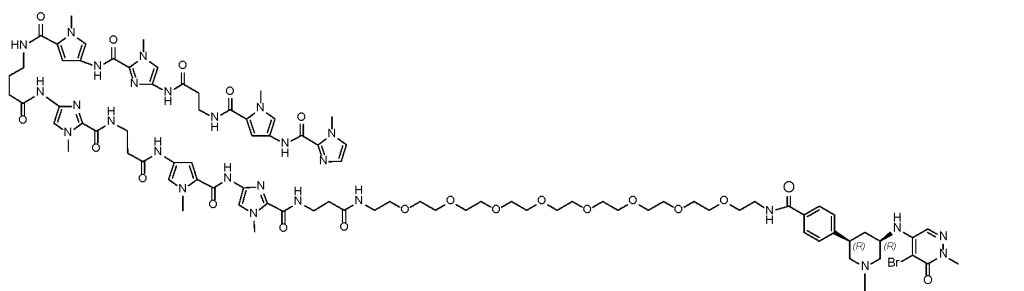
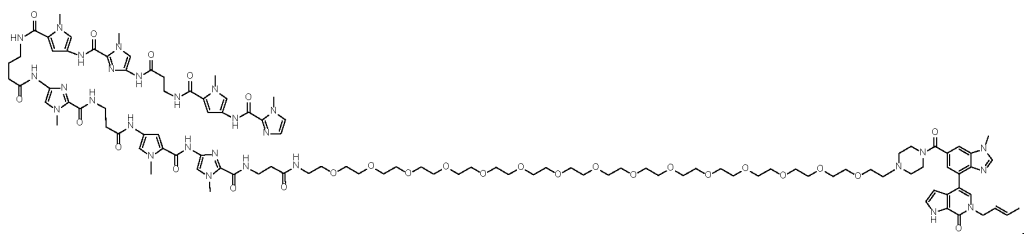
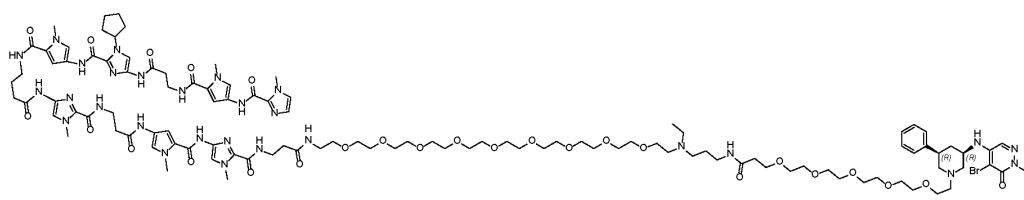
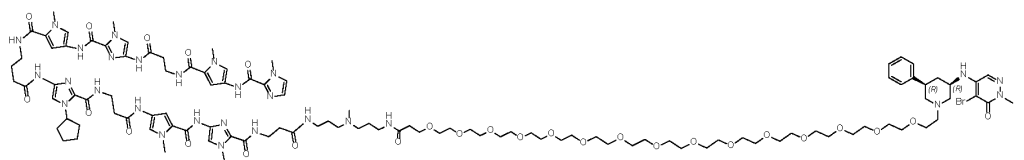
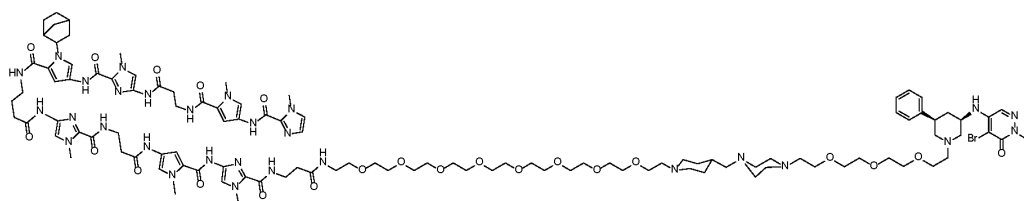
a pharmaceutically acceptable salt thereof.

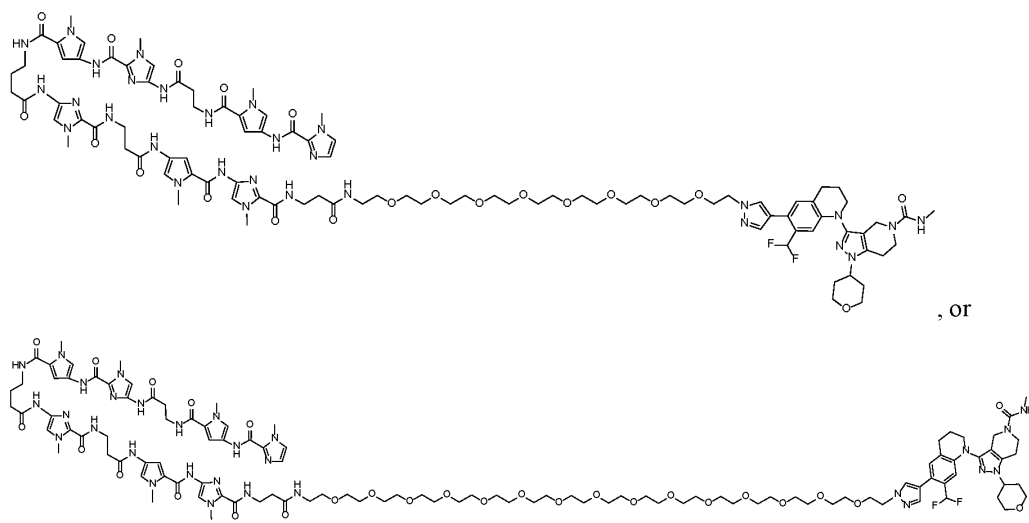
97. A molecule selected from:











or a pharmaceutically acceptable salt thereof.

98. A pharmaceutical composition comprising the molecule of any one of claims 1-97, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient.
99. A method of decreasing expression of a gene in a cell, the method comprising contacting the cell with an effective amount of a molecule of any one of claims 1-97, or a pharmaceutically acceptable salt thereof.
100. The method of claim 99, wherein the gene is *HTT*.
101. A method of treating Huntington's disease (HD) in a subject in need thereof, the method comprising administering to the subject a molecule of any one of claims 1-97, or a pharmaceutically acceptable salt thereof.
102. The method of claim 101, wherein the method reduces one or more symptoms of Huntington's disease.
103. The method of claim 102, wherein the one or more symptoms are selected from chorea, cognitive decline, abnormal libido, abnormal eye movement, abnormal sense of smell, aggression, agitation, anxiety, apathy, bradykinesia, bradyphrenia, clumsiness, delusions, depression, difficulty walking, disinhibition, dystonia, gait imbalance, muscle weakness, hallucinations, hostility, hypokinesia, irritability, memory impairment, myoclonus, obsessive-compulsive behavior, poor fine motor coordination, seizure, speech articulation difficulties, staring gaze, weight loss, abnormal cholesterol metabolism, abnormal cerebral white matter, alcoholism, Babinski sign, caudate atrophy, cerebral atrophy, choking, clonus, degeneration of the striatum, excessive daytime sleepiness, impaired visuospatial constructive cognition, inability to walk, insomnia, mutism, oral-pharyngeal dysphagia, rigidity, suicidal ideation, cerebellar atrophy, dementia, gate ataxia, gliosis, hyperreflexia, neuronal loss, or personality changes.