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(54) **Title:** COMPOUNDS AND METHODS FOR TREATING FRIEDREICH'S ATAXIA

(57) **Abstract:** The present disclosure relates to compounds and methods for modulating the expression of *fxn,* and treating diseases and conditions in which *fxn* plays an active role. The compound can be a transcription modulator molecule having a first terminus, a second terminus, and oligomeric backbone, wherein: a) the first terminus comprises a DNA-binding moiety capable of noncovalently binding to a trinucleotide repeat sequence GAA; b) the second terminus comprises a protein-binding moiety binding to a regulatory molecule that modulates an expression of a gene comprising the nucleotide repeat sequence GAA; and c) the oligomeric backbone comprising a linker between the first terminus and the second terminus.

COMPOUNDS AND METHODS FOR TREATING FRIEDREICH'S ATAXIA

CROSS REFERENCE

[0001] This application claims the benefit of U.S. Application No. 63/297,090, filed January 6, 2022, and U.S. Application No. 63/382,854, filed November 8, 2022 which are hereby incorporated by reference in their 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 *fxn* in a human or animal subject are also provided for the treatment of diseases such as Friedreich's ataxia.

BACKGROUND OF THE DISCLOSURE

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

[0004] Friedreich's ataxia ("FA" or "FRDA") is an autosomal recessive neurodegenerative disorder caused by mutations in the frataxin gene ("*fxn*"), which encodes the protein frataxin ("FXN"), an iron-binding mitochondrial protein involved in electron transport and metabolism. In most subjects with FA, a GAA trinucleotide repeat (from about 66 to over 1000 trinucleotides) is included in the first intron of *fxn*, and this hyperexpansion is responsible for the observed pathology. Hyperexpansion of the GAA repeats results in reduced expression of FXN.

[0005] Friedreich's ataxia is characterized by progressive degradation of the nervous system, particularly sensory neurons. In addition, cardiomyocytes and pancreatic beta cells are susceptible to frataxin depletion. Symptoms usually present by age 18; however, later diagnoses of FA are not uncommon. FA patients develop neurodegeneration of the large sensory neurons and spinocerebellar tracts, as well as cardiomyopathy and diabetes mellitus. Clinical symptoms of FA include ataxia, gait ataxia, muscle weakness, loss of upper body strength, loss of balance, lack of reflexes in lower limbs and tendons, loss of sensation, particularly to vibrations, impairment of position sense, impaired perception of temperature, touch, and pain, hearing and vision impairment, including distorted color vision and involuntary eye movements, irregular foot configuration, including pes cavus and inversion, hearing impairment, dysarthria, dysphagia, impaired breathing, scoliosis, diabetes, intolerance to glucose and carbohydrates, cardiac dysfunctions including hypertrophic cardiomyopathy, arrhythmia, myocardial fibrosis, and cardiac failure. Currently there is no cure for FA, with medical treatments being limited to surgical intervention for the spine and the heart, as well as therapy to assist with balance, coordination, motion, and speech.

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 *fxn*, could modulate the production of *fxn* mRNA that causes Friedreich's ataxia, and thus, reverse the progress of the disease.

[0007] The disclosure provides compounds and methods for recruiting a regulatory molecule into close proximity to *fxn*. The compounds disclosed herein contain: (a) a recruiting moiety that will bind to a regulatory molecule, linked to (b) a DNA binding moiety that will selectively bind to *fxn*. The compounds will counteract the expression of defective *fxn* in the following manner:

(1) The DNA binding moiety will bind selectively the characteristic GAA trinucleotide repeat sequence of *fxn*;

(2) The recruiting moiety, linked to the DNA binding moiety, will thus be held in proximity to *fxn*;

(3) The recruiting moiety, now in proximity to *fxn*, will recruit the regulatory molecule into proximity with the gene; and

(4) The regulatory molecule will modulate expression, and therefore counteract the production of defective *fxn* by direct interaction with the gene.

[0008] The mechanism set forth above will provide an effective treatment for Friedreich's ataxia, which is caused by the expression of defective *fxn* gene. Correction of the expression of the defective *fxn* gene thus represents a promising method for the treatment of Friedreich's ataxia.

[0009] The disclosure provides recruiting moieties that will bind to regulatory molecules. Small molecule inhibitors of regulatory molecules serve as templates for the design of recruiting moieties, since these inhibitors generally act via noncovalent binding to the regulatory molecules.

[0010] The disclosure further provides for DNA binding moieties that will selectively bind to one or more copies of the GAA trinucleotide repeat that is characteristic of the defective *fxn* gene. Selective binding of the DNA binding moiety to *fxn*, made possible due to the high GAA count associated with the defective *fxn* gene, will direct the recruiting moiety into proximity of the gene, and recruit the regulatory molecule into position to up-regulate gene transcription.

[0011] The DNA binding moiety will comprise a polyamide segment that will bind selectively to the target GAA sequence. Polyamides have been designed by Dervan (U.S. Patent Nos. 9,630,950 and 8,524,899) and others that 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 will bind to molecules with three amide units, i.e. triamides. In general, these polyamides will orient in either direction of a DNA sequence, so that the 5'-GAA-3' trinucleotide repeat sequence of *fxn* can be targeted by the polyamides selective either for GAA or for AAG. Furthermore, polyamides that bind to the complementary sequence, in this case, TTC or CTT, will also bind to the trinucleotide repeat sequence of *fxn* and can be employed as well.

[0012] 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 that would be otherwise expected.

[0013] The disclosure, therefore, provides DNA moieties that comprise triamides that are connected by flexible spacers. The spacers alleviate the geometric strain that would otherwise decrease binding affinity of a larger polyamide sequence.

[0014] Disclosed herein are compounds that comprise a polyamide which can bind to one or more copies of the trinucleotide repeat sequence GAA, and can modulate the expression of the defective *fxn* gene. Treatment of a subject with these compounds may counteract the expression of the defective *fxn* gene, and this can reduce the occurrence, severity, and/or frequency of symptoms associated with Friedreich's ataxia. Certain compounds disclosed herein may provide higher binding affinity and/or selectivity than has been observed previously for this class of compound.

[0015] In an aspect disclosed herein are compounds listed in Table 3, or pharmaceutically acceptable salts thereof.

[0016] In another aspect disclosed herein is a pharmaceutical composition comprising a compound disclosed herein or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable excipient.

[0017] In another aspect disclosed herein is a method of modulation of the expression of *fxn* comprising contacting *fxn* with a compound disclosed, or a pharmaceutically acceptable salt thereof.

[0018] In another aspect disclosed herein is a method of treating a disease or condition caused by expression of a defective *fxn* in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof. In some embodiments, the disease is FA.

[0019] Other objects, features, and advantages of the compounds, methods, and compositions described herein will become apparent from the following detailed description. 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

[0020] 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 OF THE DISCLOSURE

[0021] The disclosed herein are compounds (i.e., transcription modulator molecules) that contain DNA binding moieties that can selectively bind to one or more copies of the GAA trinucleotide repeat that is characteristic of the defective *fxn* gene. The compounds also contains moieties that bind to regulatory proteins. The selective binding of the target gene can bring the regulatory protein into proximity to the target gene and thus downregulates transcription of the target gene. The compounds disclosed herein provide higher binding affinity and selectivity than has been observed previously for this class of compounds and can be more effective in treating diseases associated with the defective *fxn* gene.

[0022] The compounds described herein can recruit the regulatory molecule to modulate the expression of the defective *fxn* gene and effectively treat and/or and alleviate the symptoms associated with diseases such as Friedreich ataxia.

Compounds

[0023] The compounds disclosed herein possess useful activity for modulating the transcription of a target gene having one or more GAA repeats (e.g., *fxn*), and may be used in the treatment or prophylaxis of a disease or condition in which the target gene (e.g., *fxn*) plays an active role. Thus, in broad aspect, certain 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. Certain embodiments provide methods for modulating the expression of *fxn*. Other embodiments provide methods for treating a *fxn*-mediated disorder in a patient in need of such treatment, comprising administering to said patient a therapeutically effective amount of a compound or composition according to the present disclosure. Also provided is the use of certain compounds disclosed herein for use in the manufacture of a medicament for the treatment of a disease or condition ameliorated by the modulation of the expression of *fxn*.

[0024] Some embodiments relate to a compound having a first terminus, a second terminus, and oligomeric backbone, wherein: a) the first terminus comprises a DNA-binding moiety capable of noncovalently binding to a nucleotide repeat sequence GAA; b) the second terminus comprises a protein-binding moiety binding to a regulatory molecule that modulates an expression of a gene comprising the nucleotide repeat sequence GAA; and c) the oligomeric backbone comprising a linker between the first terminus and the second terminus. In some embodiments, the second terminus is a Brd4 binding moiety. In some embodiments, the second terminus is not a Brd4 binding moiety.

[0025] In certain embodiments, the compounds have the structure of Formula (I):

$$X\text{-}L\text{-}Y$$

Formula (I),

or a salt thereof, wherein:

X comprises a recruiting moiety is capable of binding to a regulatory moiety within the nucleus;

Y comprises a DNA recognition moiety is capable of noncovalent binding to one or more copies of the trinucleotide repeat sequence GAA; and

L is a linker.

[0026] In some embodiments, the recruiting moiety is capable of noncovalent or covalent binding to a regulatory moiety. In some embodiments, the recruiting moiety is capable of noncovalent binding to a regulatory moiety.

[0027] In certain embodiments, the regulatory molecule is chosen from a bromodomain-containing protein.

[0028] In some embodiments, the first terminus is Y, and the second terminus is X, and the oligomeric backbone is L.

[0029] In certain embodiments, the compounds have the structure of Formula (II):

$$X\text{-}L\text{-}(Y_1\text{-}Y_2\text{-}Y_3)_n\text{-}Y_0$$

Formula (II),

or a salt thereof, wherein:

X comprises a recruiting moiety that is capable of binding to a regulatory molecule within the nucleus;

L is a linker;

Y_1, Y_2, and Y_3 are internal subunits, each of which comprises a moiety chosen from a heterocyclic or heteroaryl ring or a C_1-C_6 straight chain aliphatic segment, and each of which is chemically linked to its two neighbors;

Y_0 is an end subunit which comprises a moiety chosen from a heterocyclic or heteroaryl ring or a straight chain aliphatic segment, which is chemically linked to its single neighbor;

each subunit can noncovalently bind to an individual nucleotide in the GAA repeat sequence;

n is an integer between 1 and 200, inclusive; and

$(Y_1\text{-}Y_2\text{-}Y_3)_n\text{-}Y_0$ combine to form a DNA recognition moiety that is capable of noncovalent binding to one or more copies of the trinucleotide sequence GAA.

[0030] In some embodiments, the compounds of structural Formula (II) comprise a subunit for each individual nucleotide in the GAA repeat sequence.

[0031] In some embodiment, each internal subunit has an amino (-NH-) group and a carboxy (-CO-) group.

[0032] In some embodiments, the compounds of structural Formula (II) comprise amide (-NHCO-) bonds between each pair of internal subunits.

[0033] In some embodiments, the compounds of structural Formula (II) comprise an amide (-NHCO-) bond between L and the left-most internal subunit.

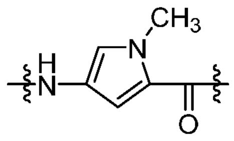
[0034] In some embodiments, the compounds of structural Formula (II) comprise an amide bond between the right-most internal subunit and the end subunit.

[0035] In some embodiments, each subunit comprises a moiety that is independently chosen from a heterocycle and an aliphatic chain.

[0036] In some embodiments, the aliphatic chain is a C_1-C_6 straight chain aliphatic chain. In certain embodiments, the aliphatic chain has structural formula $-(CH_2)_m-$, for m chosen from 1, 2, 3, 4, and 5. In certain embodiments, the aliphatic chain is $-CH_2CH_2-$.

[0037] In some embodiments, the heteroaryl is a monocyclic, bicyclic or polycyclic heteroaryl. In some embodiments, the heteroaryl is a monocyclic heteroaryl. In some embodiments, the heteroaryl is a 5-membered heteroaryl. In some embodiments, each heteroaryl contains a heteroatom independently chosen from N, O, or S. In some embodiments, each heteroaryl is independently chosen from pyrrole, imidazole, thiazole, oxazole, thiophene, and furan.

[0038] In some embodiments, each internal subunit is independently selected from: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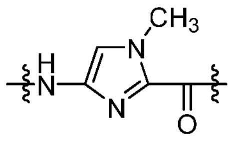
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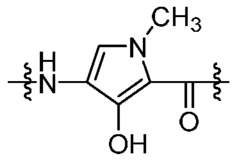
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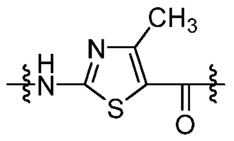
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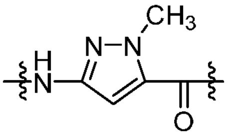
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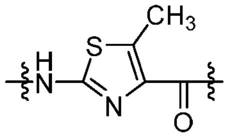
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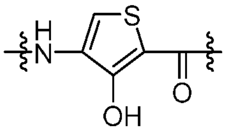
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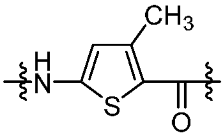
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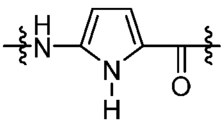
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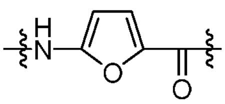
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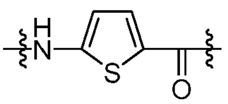
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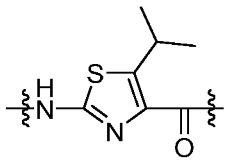
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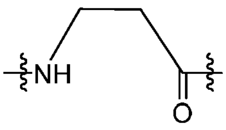
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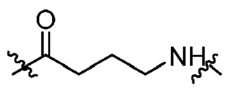
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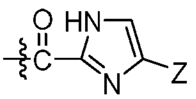
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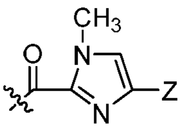
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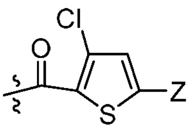
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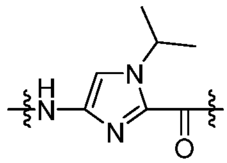
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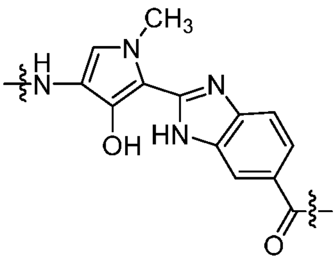
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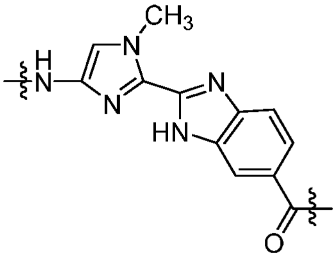
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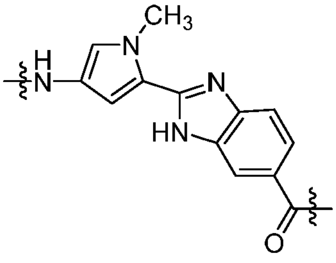
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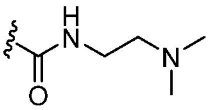
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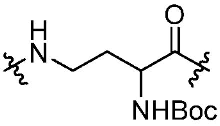
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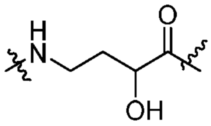
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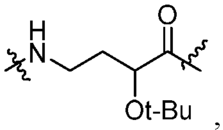
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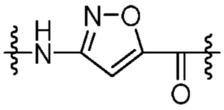
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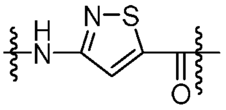
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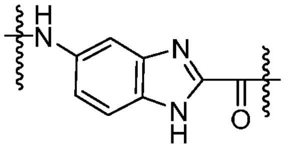

, wherein Z is H, NH_2, $C_{1\text{-}6}$ alkyl, or $C_{1\text{-}6}$ alkylNH_2.

[0039] In some embodiments, n is between 1 and 100, inclusive. In certain embodiments, n is between 1 and 50, inclusive. In certain embodiments, n is between 1 and 20, inclusive. In certain embodiments, n is between 1 and 10, inclusive. In certain embodiments, n is between 1 and 5, inclusive. In certain embodiments, n is an integer between 1 and 3, inclusive. In certain embodiments, n is chosen from 1 and 2. In certain embodiments, n is 1.

[0040] In some embodiments, n is an integer between 1 and 5, inclusive.

[0041] In some embodiments, n is an integer between 1 and 3, inclusive.

[0042] In some embodiments, n is an integer between 1 and 2, inclusive.

[0043] In some embodiments, n is 1.

[0044] In some embodiments, L comprises a C_1-C_6 straight chain aliphatic segment.

[0045] In some embodiments, L comprises $(CH_2OCH_2)_m$; and m is an integer between 1 to 20, inclusive. In some further embodiments, m is an integer between 1 to 10, inclusive. In certain further embodiments, m is an integer between 1 to 5, inclusive.

[0046] In some embodiments, the compounds have the structure of Formula (III):

$$X\text{-}L\text{-}(Y_1\text{-}Y_2\text{-}Y_3)\text{-}(W\text{-}Y_1\text{-}Y_2\text{-}Y_3)_n\text{-}Y_0$$

Formula (III),

or a salt thereof, wherein:

X comprises a recruiting moiety that is capable of binding to a regulatory molecule within the nucleus;

L is a linker;

Y_1, Y_2, and Y_3 are internal subunits, each of which comprises a moiety chosen from a heterocyclic or heteroaryl ring or a C_1-C_6 straight chain aliphatic segment, and each of which is chemically linked to its two neighbors;

Y_0 is an end subunit which comprises a moiety chosen from a heterocyclic ring or a straight chain aliphatic segment, which is chemically linked to its single neighbor;

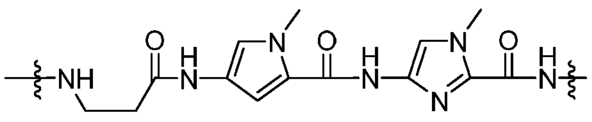
each subunit can noncovalently bind to an individual nucleotide in the GAA repeat sequence;

W is a spacer;

n is an integer between 1 and 200, inclusive; and

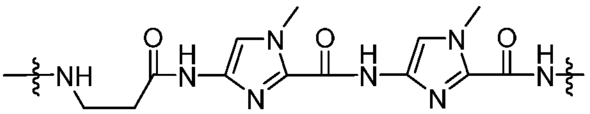
$(Y_1\text{-}Y_2\text{-}Y_3)\text{-}(W\text{-}Y_1\text{-}Y_2\text{-}Y_3)_n\text{-}Y_0$ combine to form a DNA recognition moiety that is capable of noncovalent binding to one or more copies of the trinucleotide repeat sequence GAA.

[0047] In some embodiments, $Y_1\text{-}Y_2\text{-}Y_3$ is:



(“β-Py-Im”).

[0048] In certain embodiments, $Y_1\text{-}Y_2\text{-}Y_3$ is:



(“β-Im-Im”).

[0049] In some embodiments, $Y_1\text{-}Y_2\text{-}Y_3$ is Im-Py-β.

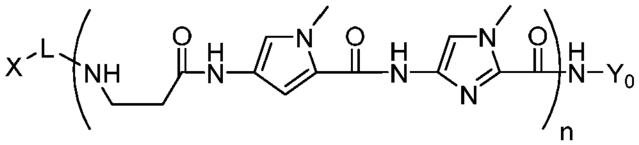
[0050] In some embodiments, $Y_1\text{-}Y_2\text{-}Y_3$ is Im-Im-β.

[0051] In some embodiments, each $Y_1\text{-}Y_2\text{-}Y_3$ is independently chosen from β-Py-Im and β-Im-Im.

[0052] In some embodiments, at most one $Y_1\text{-}Y_2\text{-}Y_3$ is β-Im-Im.

[0053] In some embodiments of the compound of structural Formula (III), n is between 1 and 100, inclusive. In certain embodiments of the compound of structural Formula (III), n is between 1 and 50, inclusive. In certain embodiments of the compound of structural Formula (III), n is between 1 and 20, inclusive. In certain embodiments of the compound of structural Formula (III), n is between 1 and 10, inclusive. In certain embodiments of the compound of structural Formula (III), n is between 1 and 5, inclusive. In certain embodiments of the compound of structural Formula (III), n is chosen from 1 and 2. In certain embodiments of the compound of structural Formula (III), n is 1.

[0054] In some embodiments, the compounds have the structure of Formula (IV):



Formula (IV),

or a salt thereof, wherein:

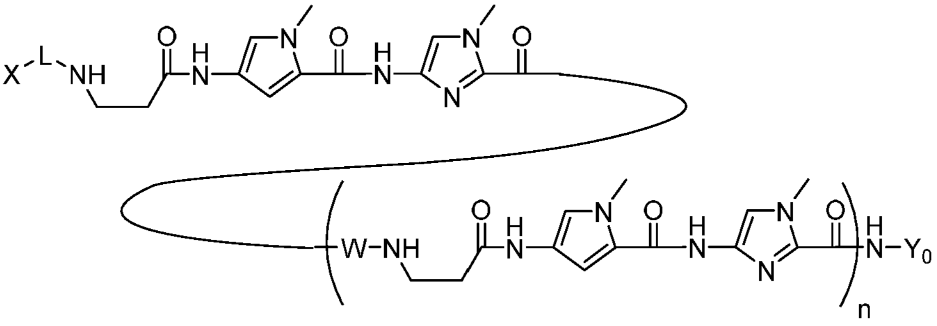
X comprises a recruiting moiety that is capable of binding to a regulatory molecule within the nucleus;

Y_0 is an end subunit which comprises a moiety chosen from a heterocyclic ring or a straight chain aliphatic segment, which is chemically linked to its single neighbor; and

n is an integer between 1 and 200, inclusive.

[0055] In some embodiments of the compound of structural Formula (IV), n is between 1 and 10, inclusive. In certain embodiments of the compound of structural Formula (IV), n is between 1 and 5, inclusive. In certain embodiments of the compound of structural Formula (IV), n is chosen from 1 and 2. In certain embodiments of the compound of structural Formula (IV), n is 1.

[0056] In some embodiments, the compounds have the structure of Formula (V):



Formula (V),

or a salt thereof, wherein:

X comprises a recruiting moiety that is capable of binding to a regulatory molecule within the nucleus; and

W is a spacer;

Y_0 is an end subunit which comprises a moiety chosen from a heterocyclic ring or a straight chain aliphatic segment, which is chemically linked to its single neighbor; and

n is an integer between 1 and 200, inclusive.

[0057] In some embodiments of the compound of structural Formula (V), n is between 1 and 10, inclusive. In certain embodiments of the compound of structural Formula (V), n is between 1 and 5, inclusive. In certain embodiments of the compound of structural Formula (V), n is chosen from 1 and 2. In certain embodiments of the compound of structural Formula (V), n is 1.

[0058] In some embodiments of the compounds of structural Formula (V), wherein: W is $-NHCH_2-(CH_2OCH_2)_p-CH_2CO-$; and p is an integer between 1 and 4, inclusive.

First terminus – DNA binding moiety

[0059] The first terminus interacts and binds with the gene, particularly with the minor grooves of the GAA sequence. In one aspect, the compounds of the present disclosure provide a polyamide sequence for interaction of a single polyamide subunit to each base pair in the GAA repeat sequence. In one aspect, the compounds of the present disclosure provide a turn component (e.g., aliphatic amino acid moiety), in order to enable hairpin binding of the compound to the GAA, in which each nucleotide pair interacts with two subunits of the polyamide.

[0060] In one aspect, the compounds of the present disclosure are more likely to bind to the repeated GAA of *fxn* than to GAA elsewhere in the subject's DNA, due to the high number of GAA repeats associated with *fxn*.

[0061] In one aspect, the compounds of the present disclosure provide more than one copy of the polyamide sequence for noncovalent binding to GAA. In one aspect, the compounds of the present disclosure bind to *fxn* with an affinity that is greater than a corresponding compound that contains a single polyamide sequence.

[0062] In one aspect, the compounds of the present disclosure provide more than one copy of the polyamide sequence for noncovalent binding to the GAA, and the individual polyamide sequences in this compound are linked by a spacer W, as defined above. The spacer W allows this compound to adjust its geometry as needed to alleviate the geometric strain that otherwise affects the noncovalent binding of longer polyamide sequences.

[0063] In certain embodiments, the DNA recognition or binding moiety binds in the minor groove of DNA.

[0064] In certain embodiments, the DNA recognition or binding moiety comprises a polymeric sequence of monomers, wherein each monomer in the polymer selectively binds to a certain DNA base pair.

[0065] In certain embodiments, the DNA recognition or binding moiety comprises a polyamide moiety.

[0066] In certain embodiments, the DNA recognition or binding moiety comprises a polyamide moiety comprising heteroaromatic monomers, wherein each heteroaromatic monomer binds noncovalently to a specific nucleotide, and each heteroaromatic monomer is attached to its neighbor or neighbors via amide bonds.

[0067] In certain embodiments, the DNA recognition moiety binds to a sequence comprising at least 1000 trinucleotide repeats. In certain embodiments, the DNA recognition moiety binds to a sequence comprising at least 500 trinucleotide repeats. In certain embodiments, the DNA recognition moiety binds to a sequence comprising at least 200 trinucleotide repeats. In certain embodiments, the DNA recognition moiety binds to a sequence comprising at least 100 trinucleotide repeats. In certain embodiments, the DNA recognition moiety binds to a sequence comprising at least 50 trinucleotide repeats. In certain embodiments, the DNA recognition moiety binds to a sequence comprising at least 20 trinucleotide repeats.

[0068] The form of the polyamide selected can vary based on the target gene. The first terminus can include a polyamide selected from the group consisting of a linear polyamide, a hairpin polyamide, a H-pin polyamide, an overlapped polyamide, a slipped polyamide, a cyclic polyamide, a tandem polyamide, and an extended polyamide. In some embodiments, the first terminus comprises a linear polyamide. In some embodiments, the first terminus comprises a hairpin polyamide.

[0069] 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 50nM. 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.

[0070] 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.

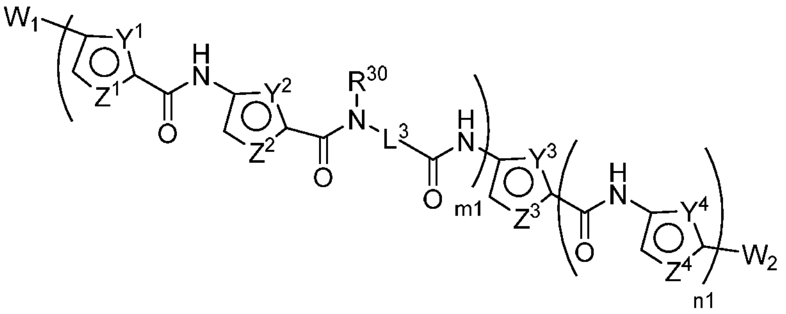
[0071] The binding affinity between the regulatory protein and the ligand on the second terminus can be determined using an assay suitable for the specific protein. The experiment involves measuring the dissociation constant K_d of the ligand for the protein and using either standard protein assay solution conditions or approximate intracellular solution conditions.

[0072] In some embodiments, the first terminus comprises -NH-Q-C(=O)-, wherein Q is an optionally substituted C_{6-10} arylene group, optionally substituted 4-10 membered heterocyclene, optionally substituted 5-10 membered heteroarylene group, or an optionally substituted alkylene group. In some embodiments, Q is an optionally substituted C_{6-10} arylene group or optionally substituted 5-10 membered heteroarylene group. In some embodiments, Q is an optionally substituted 5-10 membered heteroarylene group. In some embodiments, the 5-10 membered heteroarylene group is optionally substituted with 1-4 substituents selected from H, OH, halogen, C_{1-10} alkyl, NO_2, CN, NR'R", C_{1-6} haloalkyl, C_{1-6} alkoxyl, C_{1-6} haloalkoxy, (C_1-C_6 alkoxy) C_1-C_6 alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_7 carbocyclyl, 4-10 membered heterocyclyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, (C_3-C_7 carbocyclyl)C_1-C_6 alkyl, (4-10 membered heterocyclyl)C_1-C_6 alkyl, (C_6-C_{10} aryl)C_1-C_6 alkyl, (C_6-C_{10} aryl)C_1-C_6 alkoxy, (5-10 membered heteroaryl) C_1-C_6 alkyl, (C_3-C_7 carbocyclyl)-amine, (4-10 membered heterocyclyl)amine, (C_6-C_{10} aryl)amine, (5-10 membered heteroaryl)amine, acyl, C-carboxy, O-carboxy, C-amido, N-amido, S-sulfonamido, N-sulfonamido, -SR', C(=O)OH, or C(=O)NR'R"; wherein each R' and R" are independently H, C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_1-C_{10} alkoxyl.

[0073] In some embodiments, the first terminus comprises at least three aromatic carboxamide moieties selected to correspond to the nucleotide repeat sequence GAA and at least one aliphatic amino acid residue chosen from the group consisting of glycine, β-alanine, γ-aminobutyric acid, 2,4-diaminobutyric acid, and 5-aminovaleric acid. In some embodiments, the first terminus comprises at least one β-alanine subunit.

[0074] In some embodiments, the monomer element is independently selected from the group consisting of optionally substituted pyrrole carboxamide monomer, optionally substituted imidazole carboxamide monomer, optionally substituted C-C linked heteromonocyclic/heterobicyclic moiety, and β-alanine.

[0075] In some embodiments, the first terminus comprises a polyamide having the structure of Formula (A-2), or a pharmaceutically acceptable salt thereof:



Formula (A-2),

wherein,

m_1 is 1-4;

n_1 is 0-2;

each Y^1, Y^2, Y^3, and Y^4 is independently CH or N;

each Z^1, Z^2, Z^3, and Z^4 is independently O, S, or NR^{1D};

each L^3 is an optionally substituted C_1-C_6 alkylene, optionally substituted C_3-C_7 cycloalkylene, optionally substituted 3 to 7-membered heterocyclene, or optionally substituted 5 to 6-membered heteroarylene;

each R^{30} is hydrogen or a C_1-C_6 alkyl; or

each R^{30} and L^3 join together with the atom(s) to which they are attached to form a 4- to 7-membered heterocyclic ring;

W_1 is hydrogen, an optionally substituted C_1-C_6 alkyl, $-NR^{1E}-C(=O)-NR^{1E}R^{1F}$, $-C(=O)-NR^{1E}R^{1F}$, or $(AA)_{1-10}$;

W_2 is hydrogen, an optionally substituted C_1-C_6 alkyl, $-C(=O)-NR^{1E}R^{1F}$, or $(AA)_{1-10}$;

each R^{1D} and R^{1E} is independently hydrogen, deuterium, an optionally substituted C_1-C_{50} alkyl, optionally substituted C_1-C_{50} heteroalkyl, or optionally substituted $(PEG)_{1-50}$;

R^{1F} is hydrogen, deuterium, optionally substituted C_1-C_{20} alkyl, C_1-C_{20} heteroalkyl, $(PEG)_{1-20}$, or one or more AA; and

each AA is independently a naturally occurring amino acid.

[0076] In some embodiments, each L^3 is an optionally substituted C_1-C_6 alkylene. In some embodiments, L^3 is a C_2, C_3, C_4, or C_5 alkylene optionally substituted with one or more hydrogen, halogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_3-C_6 cycloalkyl or 4 to 7-membered heterocycloalkyl ring. In some embodiments, L^3 is a C_2 or C_3 alkylene optionally substituted with one or more hydrogen, halogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_3-C_6 cycloalkyl or 4 to 7-membered heterocycloalkyl ring. In some embodiments, L^3 is a C_2 alkylene optionally substituted with one or two hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_3-C_6 cycloalkyl or 4 to 7-membered heterocycloalkyl ring.

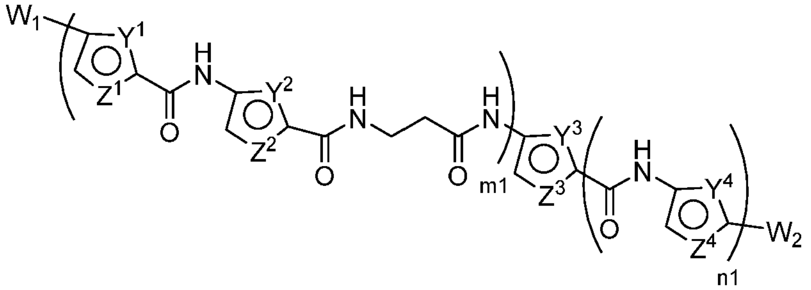
[0077] In some embodiments, each L^3 is independently C_3-C_7 cycloalkylene. In some embodiments, L^3 is a cyclobutylene, cyclopentylene, cyclohexylene, or cycloheptylene ring. In some embodiments, L^3 is cyclobutylene. In some embodiments, L^3 is cyclopentylene. In some embodiments, L^3 is cyclohexylene.

[0078] In some embodiments, each L^3 is 3 to 7-membered heterocyclene. In some embodiments, L^3 is a 4-membered, 5-membered, or 6-membered heterocyclene.

[0079] In some embodiments, each R^{30} is independently hydrogen. In some embodiments, each R^{30} is independently C_1-C_6 alkyl.

[0080] In some embodiments, L^3 and R^{30} join together with the atoms to which they are attached to form a 4- to 7-membered heterocyclic ring. In some embodiments, the ring is a 4-membered heterocyclic ring. In some embodiments, the ring is a 5-membered heterocyclic ring. In some embodiments, the ring is a 6-membebered heterocyclic ring. In some embodiments, the ring is a 7-membered heteroaromatic ring.

[0081] In some embodiments, the first terminus comprises a polyamide having the structure of Formula (A-3), or a pharmaceutically acceptable salt thereof:



Formula (A-3),

wherein,

m_1 is 1-4;

n_1 is 0-2;

each Y^1, Y^2, Y^3, and Y^4 is independently CH or N;

each Z^1, Z^2, Z^3, and Z^4 is independently O, S, or NR^{1D};

W_1 is hydrogen, optionally substituted C_1-C_6 alkyl, $-NR^{1E}-C(=O)-NR^{1E}R^{1F}$, $-C(=O)-NR^{1E}R^{1F}$, or $(AA)_{1-10}$;

W_2 is hydrogen, optionally substituted C_1-C_6 alkyl, $-C(=O)-NR^{1E}R^{1F}$, or $(AA)_{1-10}$;

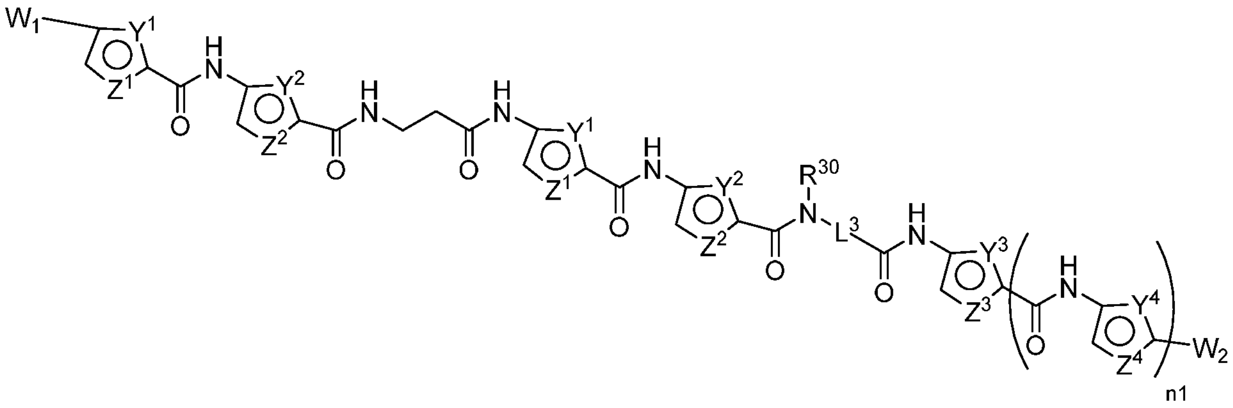
each R^{1D} and R^{1E} is independently hydrogen, deuterium, optionally substituted C_1-C_{50} alkyl, optionally substituted C_1-C_{50} heteroalkyl, or optionally substituted $(PEG)_{1-50}$;

R^{1F} is hydrogen, deuterium, optionally substituted C_1-C_{20} alkyl, optionally substituted C_1-C_{20} heteroalkyl, optionally substituted $(PEG)_{1-20}$, or one or more AA; and

each AA is independently an amino acid residue selected from β-alanine, lysine, and arginine.

[0082] In some embodiments, each L^3 is the same. In some embodiments, each L^3 is different.

[0083] In some embodiments, the first terminus comprises a polyamide having the structure of Formula (A-4), or a pharmaceutically acceptable salt thereof:



Formula (A-4),

wherein,

n_1 is 0-2;

each Y^1, Y^2, Y^3, and Y^4 is independently CH or N;

each Z^1, Z^2, Z^3, and Z^4 is independently O, S, or NR^{1D};

each L^3 is an optionally substituted C_3-C_7 cycloalkylene, optionally substituted 3 to 7-membered heterocyclene, or optionally substituted 5 to 6-membered heteroarylene;

each R^{30} is hydrogen or a C_1-C_6 alkyl; or

each R^{30} and L^3 join together with the atom(s) to which they are attached to form a 4- to 7-membered heterocyclic ring;

W_1 is hydrogen, an optionally substituted C_1-C_6 alkyl, $-NR^{1E}$-C(=O)-$NR^{1E}R^{1F}$, -C(=O)-$NR^{1E}R^{1F}$, or $(AA)_{1\text{-}10}$;

W_2 is hydrogen, an optionally substituted C_1-C_6 alkyl, -C(=O)-$NR^{1E}R^{1F}$, or $(AA)_{1\text{-}10}$;

each R^{1D} and R^{1E} is independently hydrogen, deuterium, an optionally substituted C_1-C_{50} alkyl, optionally substituted C_1-C_{50} heteroalkyl, or optionally substituted $(PEG)_{1\text{-}50}$;

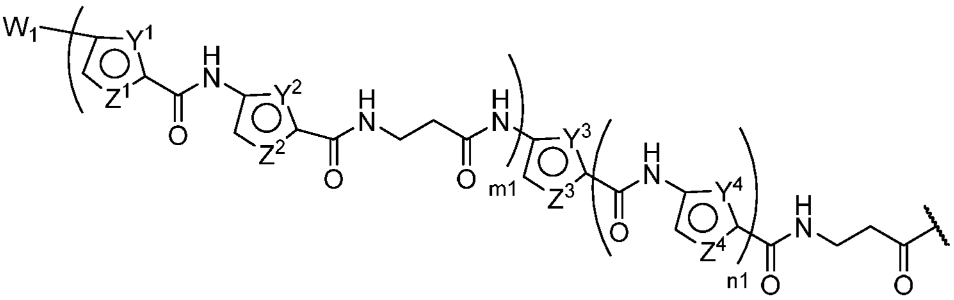
R^{1F} is hydrogen, deuterium, optionally substituted C_1-C_{20} alkyl, C_1-C_{20} heteroalkyl, $(PEG)_{1\text{-}20}$, or one or more AA; and

each AA is independently a naturally occurring amino acid.

[0084] In some embodiments, the linker moiety is connected to the DNA binding moiety (i.e., a polyamide) at W_2. In some embodiments, W_2 is an optionally substituted C_1-C_6 alkyl, -C(=O)-$NR^{1E}R^{1F}$, or $(AA)_{1\text{-}10}$. In some embodiments, W_2 is -C(=O)-$NR^{1E}R^{1F}$. In some embodiments, W_2 is -C(=O)$NHCH_2CH_2C$(=O)-. In some embodiments, W^2 is hydrogen.

[0085] In some embodiments, W^2 is $(AA)_{1\text{-}10}$. **In some embodiments, each AA is independently β-alanine. In some embodiments, AA comprises one β-alanine. In some embodiments, AA comprises two β-alanines.**

[0086] In some embodiments, the first terminus comprises a polyamide having the structure of Formula (A-5), or a pharmaceutically acceptable salt thereof:



Formula (A-5).

[0087] In some embodiments, each R^{1D} and R^{1E} is independently hydrogen, optionally substituted C_1-C_{20} alkyl, optionally substituted C_1-C_{20} heteroalkyl, or optionally substituted $(PEG)_{1-20}$. In some embodiments, each R^{1D} and R^{1E} is independently hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_1-C_{10} heteroalkyl, or optionally substituted $(PEG)_{1-20}$.

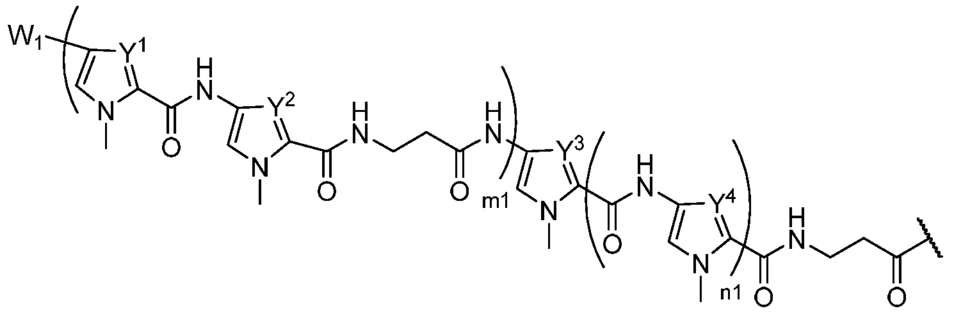
[0088] In some embodiments, each R^{1D} is independently optionally substituted C_1-C_{20} alkyl, optionally substituted C_1-C_{20} heteroalkyl, or optionally substituted $(PEG)_{1-20}$, each of which is optionally substituted with amido, alkyl, alkynyl, azido, amino, halogen, haloalkyl, hydroxy, nitro, oxo (=O), phosphorous hydroxide, or PEG. In some embodiments, each R^{1D} is independently optionally substituted C_1-C_{20}, optionally substituted with -CN, $-NH_2$, $-N_3$, -OH, CF_3, $-OP(=O)(OH)_2$, $-OP(=O)(OCH_3)_2$, $-OP(=O)(OCH_3)(OH)$, or $-OP(=O)_2OH$. In some embodiments, each R^{1D} is independently $(PEG)_{1-50}$. In some embodiments, each R^{1D} is independently $-C(=O)-NR^{2A}R^{2B}$ or $-NR^{2A}R^{2B}$, wherein each R^{2A} and R^{2B} is independently hydrogen, C_1-C_{50} alkyl, or $(PEG)_{1-50}$.

[0089] In some embodiments, each Z^1, Z^2, Z^3, and Z^4 is independently NR^{1D}, wherein R^{1D} is an optionally substituted C_1-C_{20} alkyl or optionally substituted C_1-C_{20} heteroalkyl.

[0090] In some embodiments, each Z^1, Z^2, Z^3, and Z^4 is independently NCH_3.

[0091] In some embodiments, each Z^1, Z^2, Z^3, and Z^4 is independently NH.

[0092] In some embodiments, the first terminus comprises a polyamide having the structure of Formula (A-6), or a pharmaceutically acceptable salt thereof:



Formula (A-6).

[0093] In some embodiments, each Y^1 and Y^3 are N; and each Y^2 and Y^4 are independently CH or N. In some embodiments, each Y^2 and Y^4 is independently CH. In some embodiments, each Y^2 and Y^4 is independently N. In some embodiments, Y^2 is CH and Y^4 is N. In some embodiments, Y^2 is N and Y^4 is CH.

[0094] In some embodiments, each unit m_1 and n_1 are different or the same. In some embodiments, each unit m_1 is different. In some embodiments, each unit m_1 is the same. In some embodiments, each unit n_1 is different. In some embodiments, each unit n_1 is the same.

[0095] In some embodiments, m_1 is 2 or 3; and n_1 is 0 or 1.

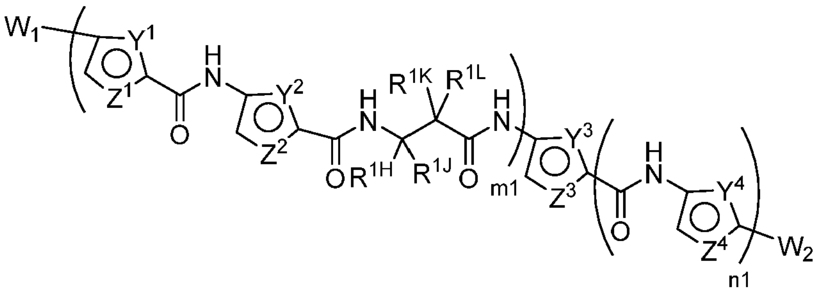
[0096] In some embodiments, m_1 is 2. In some embodiments, m_1 is 1.

[0097] In some embodiments, n_1 is 0. In some embodiments, n_1 is 1.

[0098] In some embodiments, the linker moiety is connected to the DNA binding moiety through W_1. In some embodiments, W_1 is an optionally substituted C_1-C_6 alkyl or -C(=O)-NR^{1E}R^{1F}. In some embodiments, W_1 is -C(=O)-NR^{1E}R^{1F}, wherein R^{1E} is hydrogen; and R^{1F} is hydrogen, optionally substituted C_1-C_{10} alkyl, or optionally substituted (PEG)$_{1-20}$.

[0099] In some embodiments, W_1 is hydrogen.

[00100] In some embodiments, the first terminus comprises a polyamide having the structure of Formula (A-7), or a pharmaceutically acceptable salt thereof:



Formula (A-7),

wherein,

m_1 is 1-4;

n_1 is 0-2;

each Y^1, Y^2, Y^3, and Y^4 is independently CH or N;

each Z^1, Z^2, Z^3, and Z^4 is independently O, S, or NR^{1D};

W_1 is hydrogen, an optionally substituted C_1-C_6 alkyl, -NR^{1E}-C(=O)-NR^{1E}R^{1F}, -C(=O)-NR^{1E}R^{1F}, or (AA)$_{1-10}$;

W_2 is hydrogen, an optionally substituted C_1-C_6 alkyl, -C(=O)-NR^{1E}R^{1F}, or (AA)$_{1-10}$; wherein

each R^{1D} and R^{1E} is independently hydrogen, deuterium, an optionally substituted C_1-C_{50} alkyl, optionally substituted C_1-C_{50} heteroalkyl, or optionally substituted (PEG)$_{1-50}$;

R^{1F} is hydrogen, deuterium, optionally substituted C_1-C_{20} alkyl, C_1-C_{20} heteroalkyl, (PEG)$_{1-20}$, or one or more AA;

each AA is independently a naturally occurring amino acid; and

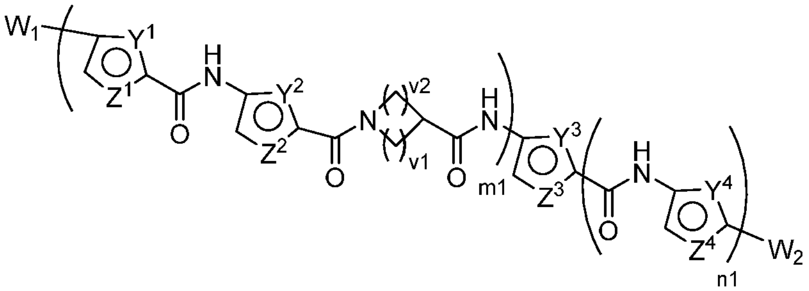
each R^{1H}, R^{1J}, R^{1K}, and R^{1L} is independently hydrogen, deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, or C_1-C_6 hydroxyalkyl; or

R^{1H} and R^{1J} or R^{1L} and R^{1K} combine together with the carbon atom to which they are attached to form C_3-C_6 cycloalkyl or 4 to 7-membered heterocycloalkyl ring.

[00101] In some embodiments, each R^{1H}, R^{1J}, R^{1K}, and R^{1L} is independently hydrogen, halogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, or C_1-C_6 hydroxyalkyl. In some embodiments, each R^{1H}, R^{1J}, R^{1K}, and R^{1L} is independently hydrogen, halogen, or C_1-C_6 alkyl. In some embodiments, each R^{1H}, R^{1J}, R^{1K}, and R^{1L} is independently halogen. In some embodiments, each R^{1H}, R^{1J}, R^{1K}, and R^{1L} is independently C_1-C_6 alkyl. In some embodiments, each R^{1H}, R^{1J}, R^{1K}, and R^{1L} is independently hydrogen.

[00102] In some embodiments, R^{1H} and R^{1J} or R^{1L} and R^{1K} combine together with the atom to which they are attached to form a C_3-C_6 cycloalkyl or 4 to 7-membered heterocycloalkyl ring. In some embodiments, R^{1H} and R^{1J} or R^{1L} and R^{1K} combine together with the atom to which they are attached to form a C_3-C_6 cycloalkyl. In some embodiments, R^{1H} and R^{1J} or R^{1L} and R^{1K} combine together with the atom to which they are attached to form a 4 to 7-membered heterocycloalkyl ring.

[00103] In some embodiments, the first terminus comprises a polyamide having the structure of Formula (A-8), or a pharmaceutically acceptable salt thereof:



Formula (A-8),

wherein,

each v_1 and v_2 are independently 1-3;

m_1 is 1-4;

n_1 is 0-2;

each Y^1, Y^2, Y^3, and Y^4 is independently CH or N;

each Z^1, Z^2, Z^3, and Z^4 is independently O, S, or NR^{1D};

W_1 is hydrogen, an optionally substituted C_1-C_6 alkyl, $-NR^{1E}-C(=O)-NR^{1E}R^{1F}$, $-C(=O)-NR^{1E}R^{1F}$, or $(AA)_{1-10}$;

W_2 is hydrogen, an optionally substituted C_1-C_6 alkyl, $-C(=O)-NR^{1E}R^{1F}$, or $(AA)_{1-10}$; wherein

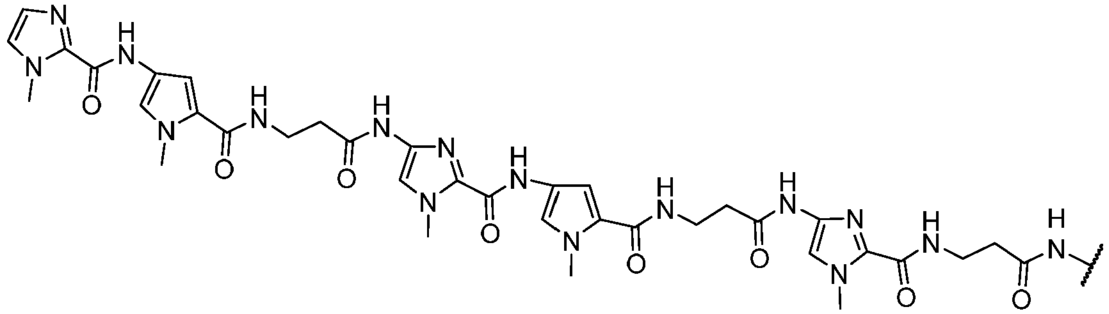
each R^{1D} and R^{1E} is independently hydrogen, deuterium, an optionally substituted C_1-C_{50} alkyl, optionally substituted C_1-C_{50} heteroalkyl, or optionally substituted $(PEG)_{1-50}$;

R^{1F} is hydrogen, deuterium, optionally substituted C_1-C_{20} alkyl, C_1-C_{20} heteroalkyl, $(PEG)_{1-20}$, or one or more AA; and

each AA is independently a naturally occurring amino acid.

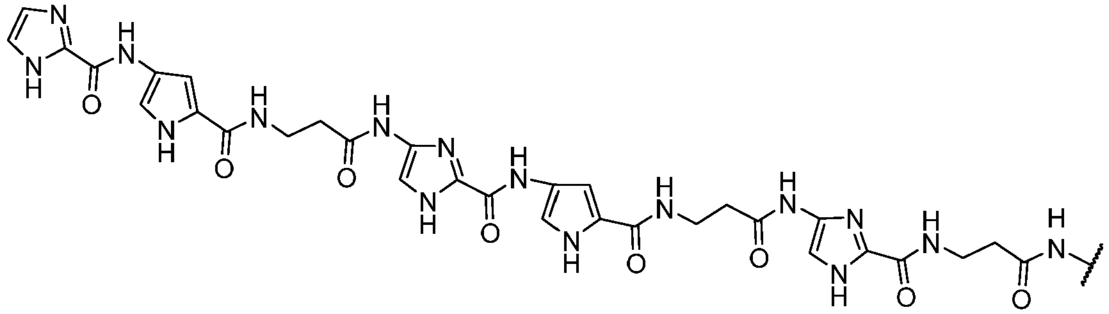
[00104] In some embodiments, each v_1 is independently 1. In some embodiments, each v_1 is independently 2. In some embodiments, each v_1 is independent 3. In some embodiments, each v_2 is independently 1. In some embodiments, each v_2 is independently 2. In some embodiments, each v_2 is independently 3.

[00105] In some embodiments, the first terminus comprises a polyamide having the structure of Formula (A-9), or a pharmaceutically acceptable salt thereof:



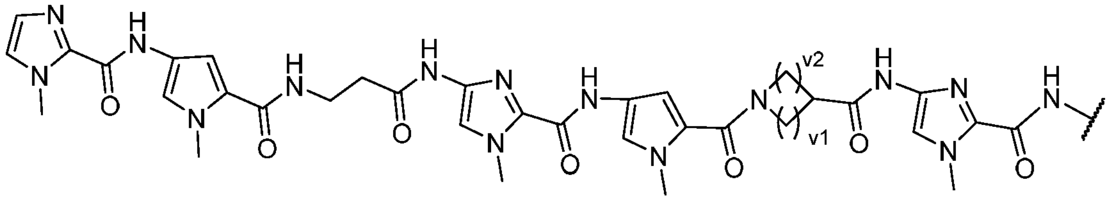
Formula (A-9).

[00106] In some embodiments, the first terminus comprises a polyamide having the structure of Formula (A-10) or a pharmaceutically acceptable salt thereof:



Formula (A-10).

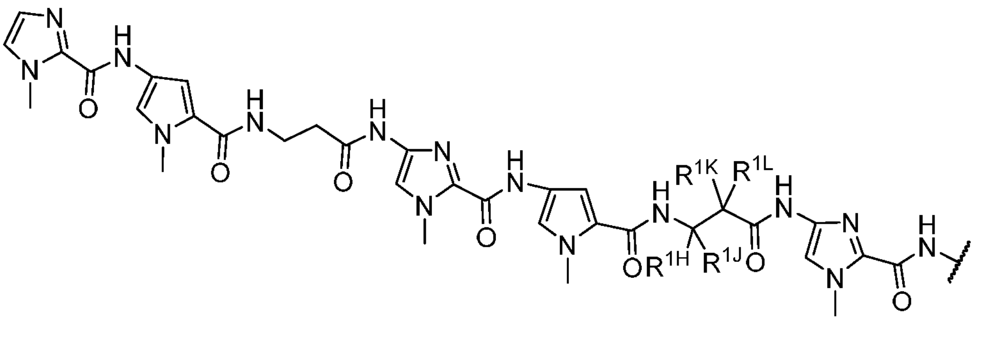
[00107] In some embodiments, the first terminus comprises a polyamide having the structure of Formula (A-11), or a pharmaceutically acceptable salt thereof:



Formula (A-11),

wherein, each v_1 and v_2 are independently 1-3.

[00108] In some embodiments, the first terminus comprises a polyamide having the structure of Formula (A-12), or a pharmaceutically acceptable salt thereof:



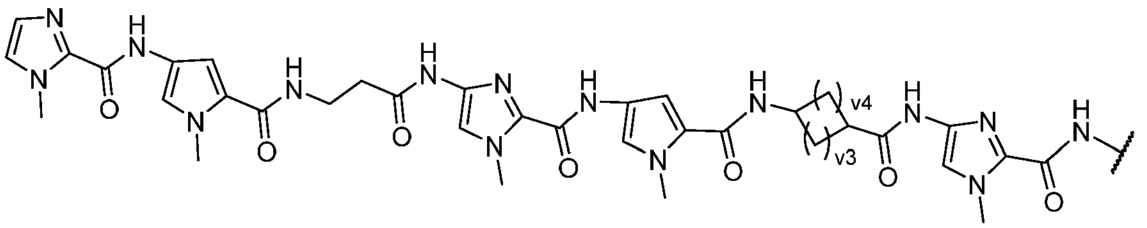
Formula (A-12),

wherein,

each R^{1H}, R^{1J}, R^{1K}, and R^{1L} is independently hydrogen, halogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, or C_1-C_6 hydroxyalkyl; or

R^{1H} and R^{1J} or R^{1L} and R^{1K} combine together with the carbon atom to which they are attached to form a C_3-C_6 cycloalkyl or 4 to 7-membered heterocycloalkyl ring.

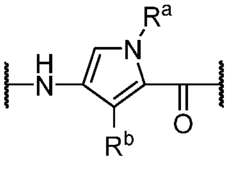
[00109] In some embodiments, the first terminus comprises a polyamide having the structure of Formula (A-13), or a pharmaceutically acceptable salt thereof:



Formula (A-13),

wherein, each v_3 and v_4 are independently 1-3.

[00110] The DNA recognition or binding moiety can include one or more subunits selected from the groups consisting of:



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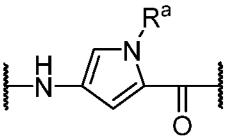
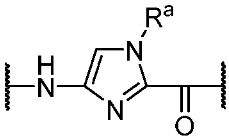


(Py),



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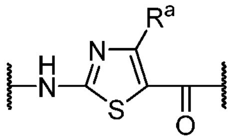

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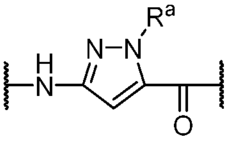

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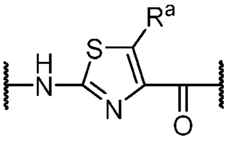

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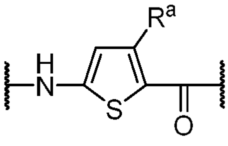

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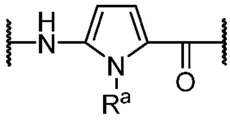

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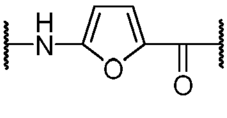

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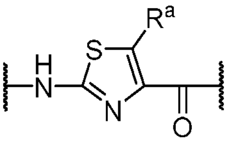

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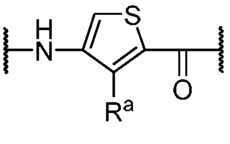

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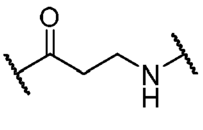

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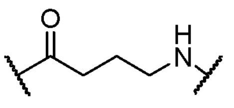

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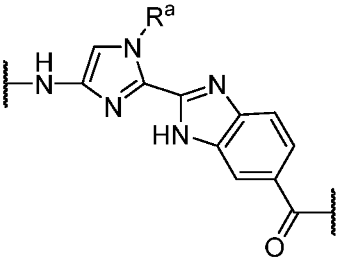

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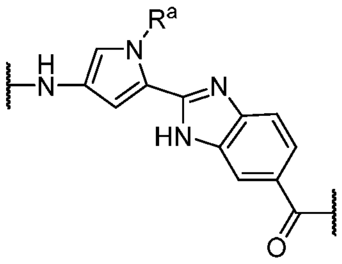

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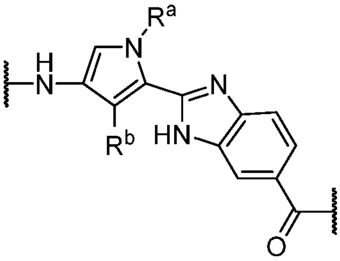
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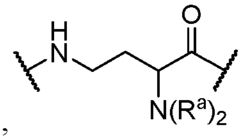
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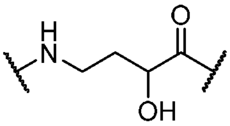
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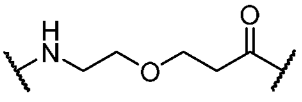
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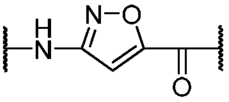
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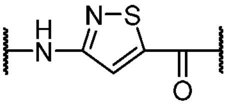
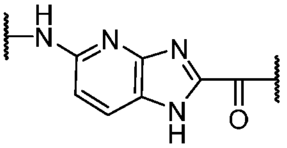
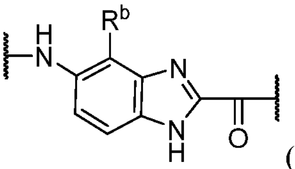

, -NH-benzopyrazinylene-CO-, -NH-phenylene-CO-, -NH-pyridinylene-CO-, -NH-piperidinylene-CO-, -NH-pyrimidinylene-CO-, -NH-anthracenylene-CO-, -NH-quinolinylene-CO-, optionally substituted 5-10 ring heterocycle,

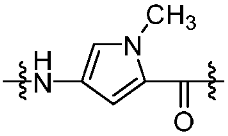

(Ip), and


(Bi), wherein

each R^a is independently H, optionally substituted C_1-C_{20} alkyl, optionally substituted C_1-C_{20} heteroalkyl, optionally substituted C_1-C_{20} haloalkyl, or optionally substituted C_1-C_{20} alkylamino; and

each R^b is independently H, halogen, -OH, optionally substituted C_1-C_{20} alkyl, optionally substituted C_1-C_{20} heteroalkyl, optionally substituted C_1-C_{20} haloalkyl, optionally substituted C_1-C_{20} hydroxyalkyl, or optionally substituted C_1-C_{20} alkylamino.

[00111] The DNA recognition or binding moiety can include one or more subunits selected from the group consisting of: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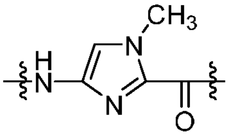
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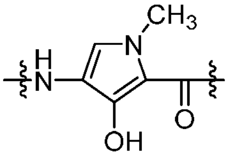
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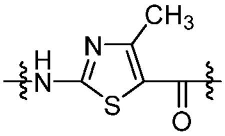
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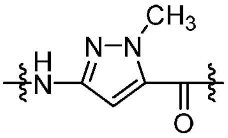
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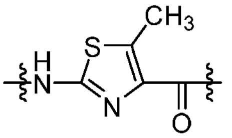
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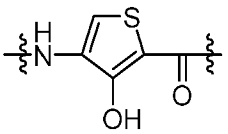
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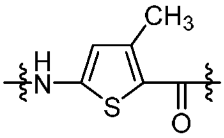
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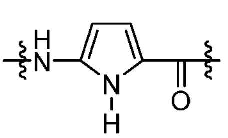
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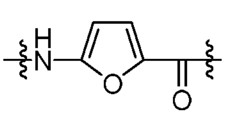
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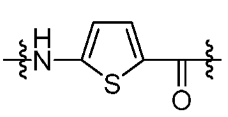
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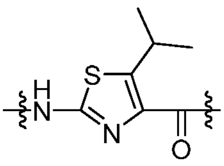
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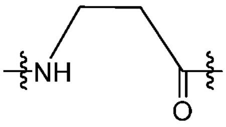
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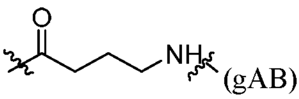
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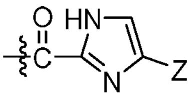
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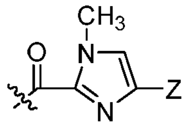
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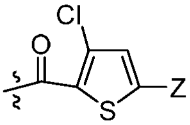
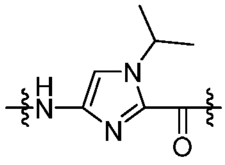
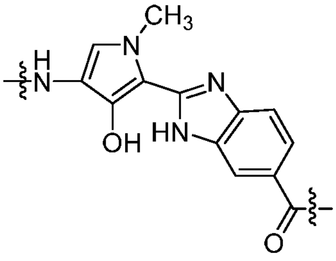
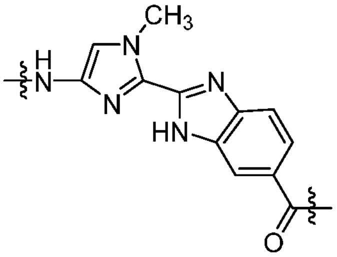
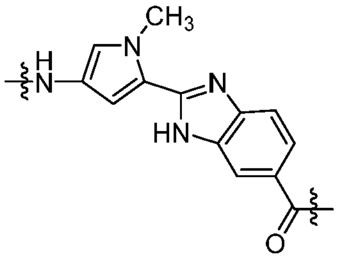
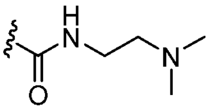
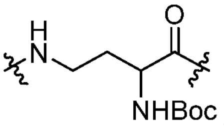
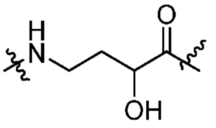
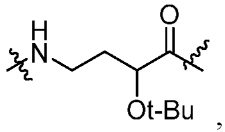
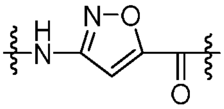
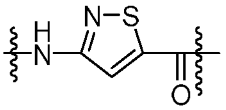
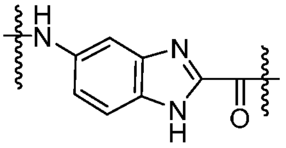
 (CTh),  (iIm),  (HpBi),

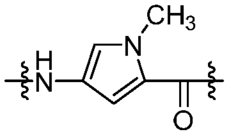
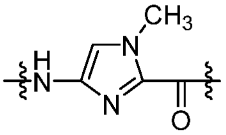
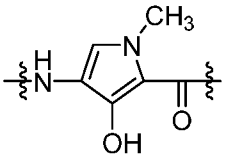
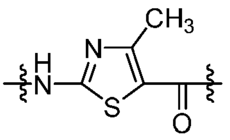
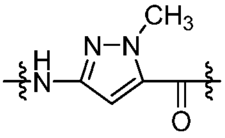
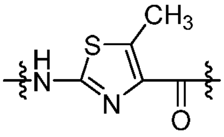
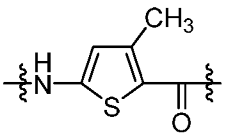
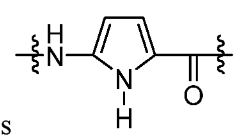
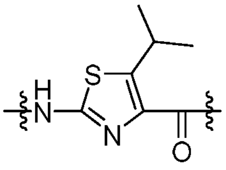
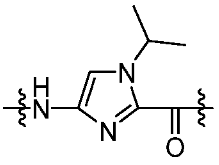
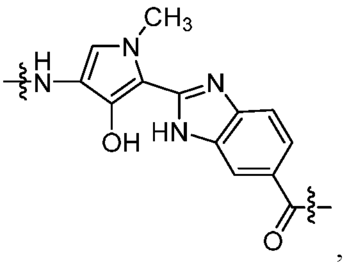
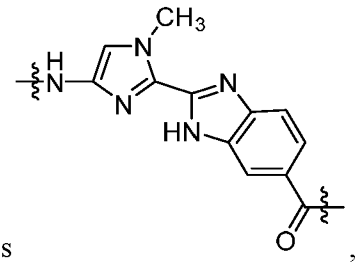
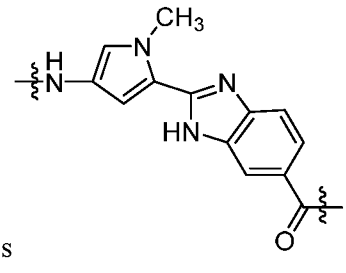
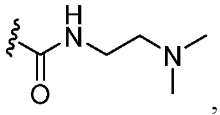
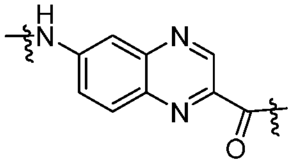
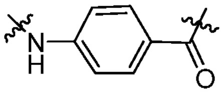
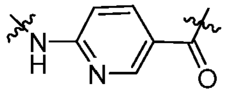
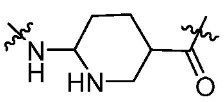
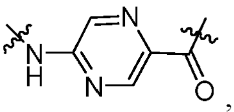
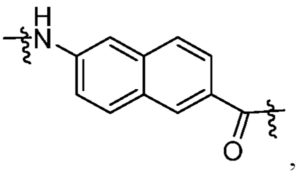
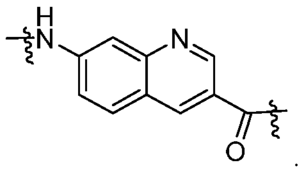
 (ImBi),  (PyBi),  (“Dp”),



, 

, 

, , , -NH-benzopyrazinylene-CO-, -NH-phenylene-CO-, -NH-pyridinylene-CO-, -NH-piperidinylene-CO-, -NH-pyrimidinylene-CO-, -NH-anthracenylene-CO-, -NH-quinolinylene-CO-, and , wherein Z is H, NH_2, C_{1-6} alkyl, or C_{1-6} alkylNH_2.

[00112] In some embodiments, Py is , Im is , Hp is , Th is , Pz is , Nt is , Tn is , Nh is , iNt is , iIm is , HpBi is , ImBi is , PyBi is , Dp is  , -NH-benzopyrazinylene-CO- is  , -NH-phenylene-CO- is  , -NH-pyridinylene-CO- is  , -NH-piperidinylene-CO- is  ,-NH-pyrazinylene-CO- is  , -NH-napthalene-CO- is  , and -NH-quinolinylene-CO- is  .

[00113] In some embodiments, the first terminus comprises one or more subunits selected from the group **consisting of optionally substituted N-methylpyrrole, optionally substituted N-methylimidazole, and β-**alanine.

[00114] The first terminus in the compounds described herein has a high binding affinity to a sequence having multiple repeats of GAA and binds to the target nucleotide repeats preferentially over other nucleotide repeats or nucleotide sequences. In some embodiments, the first terminus has a higher binding affinity to a sequence having multiple repeats of GAA than to a sequence having repeats of CGG. In some embodiments, the first terminus has a higher binding affinity to a sequence having multiple repeats of GAA than to a sequence having repeats of CCG. In some embodiments, the first terminus has a higher binding affinity to a sequence having multiple repeats of GAA than to a sequence having repeats of CCTG. In some embodiments, the first terminus has a higher binding affinity to a sequence having multiple repeats of GAA than to a sequence having repeats of TGGAA. In some embodiments, the first terminus has a higher binding affinity to a sequence having multiple repeats of GAA than to a sequence having repeats of GGGGCC. In some embodiments, the first terminus has a higher binding affinity to a sequence having multiple repeats of GAA than to a sequence having repeats of CAG. In some embodiments, the first terminus has a higher binding affinity to a sequence having multiple repeats of GAA than to a sequence having repeats of CTG.

[00115] Due to the preferential binding between the first terminus and the target nucleotide repeat, the transcription modulation molecules described herein become localized around regions having multiple repeats of GAA. In some embodiments, the local concentration of the first terminus of the molecules described herein is higher near a sequence having multiple repeats of GAA than near a sequence having repeats of CGG. In some embodiments, the local concentration of the first terminus of the molecules described herein is higher near a sequence having multiple repeats of GAA than near a sequence having repeats of CCG. In some embodiments, the local concentration of the first terminus of the molecules described herein is higher near a sequence having multiple repeats of GAA than near a sequence having repeats of CCTG. In some embodiments, the local concentration of the first terminus of the molecules described herein is higher near a sequence having multiple repeats of GAA than near a sequence having repeats of TGGAA. In some embodiments, the local concentration of the first terminus of the molecules described herein is higher near a sequence having multiple repeats of GAA than near a sequence having repeats of GGGGCC. In some embodiments, the local concentration of the first terminus of the molecules described herein is higher near a sequence having multiple repeats of GAA than near a sequence having repeats of CTG. In some embodiments, the local concentration of the first terminus of the molecules described herein is higher near a sequence having multiple repeats of GAA than near a sequence having repeats of CAG.

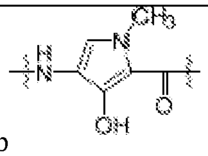
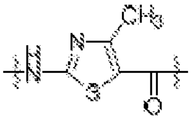
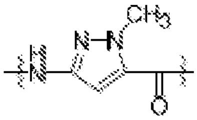
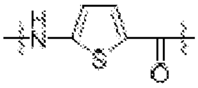
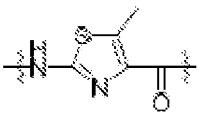
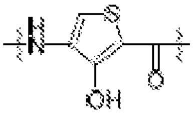
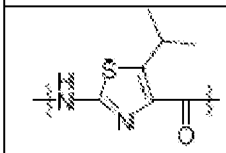
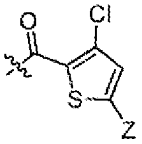
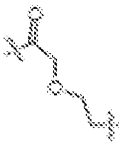
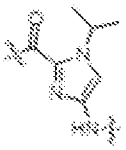
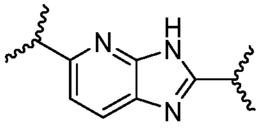
[00116] The first terminus is localized to a sequence having multiple repeats of GAA and binds to the target nucleotide repeats preferentially over other nucleotide repeats. In some embodiments, the sequence has at least 2, 3, 4, 5, 8, 10, 12, 15, 20, 25, 30, 40, 50, 100, 200, 300, 400, or 500 repeats of GAA. In certain embodiments, the sequence comprises at least 1000 nucleotide repeats of GAA. In certain embodiments, the sequence comprises at least 500 nucleotide repeats of GAA. In certain embodiments, the sequence comprises at least 200 nucleotide repeats of GAA. In certain embodiments, the sequence comprises at least 100 nucleotide repeats of GAA. In certain embodiments, the sequence comprises at least 50 nucleotide repeats of GAA. In certain embodiments, the sequence comprises at least 20 nucleotide repeats of GAA.

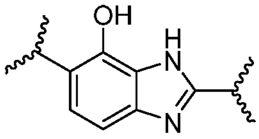
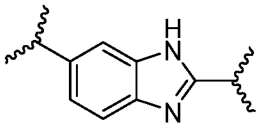
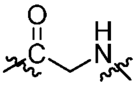
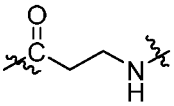
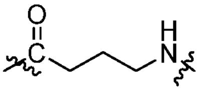
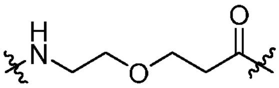
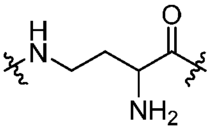
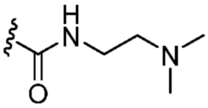
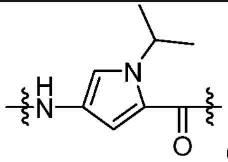
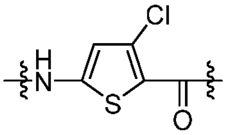
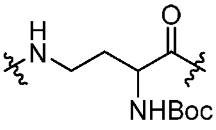
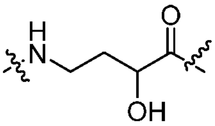
[00117] In one aspect, the compounds of the present disclosure can bind to the repeated GAA of *fxn* than to GAA elsewhere in the subject's DNA.

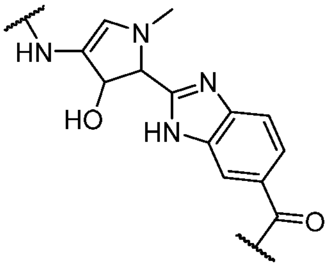
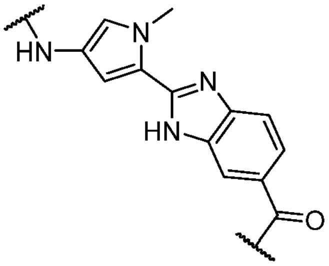
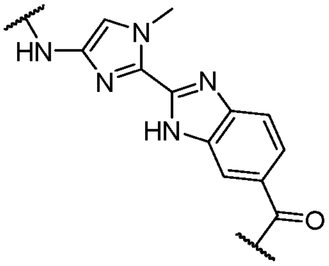
[00118] The polyamide composed of a pre-selected combination of subunits can selectively bind to the DNA in the minor groove. In their hairpin structure, antiparallel side-by-side pairings of two aromatic amino acids bind to DNA sequences, with a polyamide ring packed specifically against each DNA base. N-Methylpyrrole (Py) favors T, A, and C bases, excluding G; N-methylimidazole (Im) is a G-reader; and 3-hydroxyl-N-methylpyrrol (Hp) is specific for thymine base. The nucleotide base pairs can be recognized using different pairings of the amino acid subunits using the paring principle shown in Table 1A and 1B below. For example, an Im/Py pairing reads G·C by symmetry, a Py/Im pairing reads C·G, an Hp/Py pairing can distinguish T·A from A·T, G·C, and C·G, and a Py/Py pairing nonspecifically discriminates both A·T and T·A from G·C and C·G.

[00119] In some embodiments, the first terminus comprises Im corresponding to the nucleotide G; Py or beta corresponding to the nucleotide A; Py corresponding to the nucleotide A, wherein Im is N-alkyl imidazole, Py is N-alkyl pyrrole, and beta is β-alanine. In some embodiments, the first terminus comprises Im/Py to correspond to the nucleotide pair G/C, Py/beta or Py/Py to correspond to the nucleotide pair A/T, and wherein Im is N-alkyl imidazole (e.g., N-methyl imidazole), Py is N-alkyl pyrrole (e.g., N-methyl pyrrole), and beta is β-alanine.

Table 1A. Base paring for single amino acid subunit (Favored (+), disfavored (-)).

Subunit	**G**	**C**	**A**	**T**
Py	-	+	+	+
Im	+	-	-	
 Hp (Hp)	-	-	-	+
 (Th).	-	-	+	+
 (Pz),	-	-	+	+
 (Tp).	-	-	+	+
 (Nt)	+	-	-	-
 (Ht).	-	-	-	+
 (iPTA)	+	-	-	-
 ("CTh");	-	-	-	+
PEG 	-	+	+	+
iIm 	+	-	-	-
 Ip	+	-	-	-

 Hz	-	-	-	+
 Bi	-	-	-	+
 (gly)	-	-	-	-
 (β)	-	-	+	+
 (gAB)	-	-	+ (as a part of the turn)	+ (as a part of the turn)
 (Alx)	-	+	-	-
 (Da)	-	-	+	+
 (Dp)	-	-	+	+
 (iPP)	-	-	+	+
 (CTh)	+	+	-	-
 (Dab)	-	-	+	+
 (gAH)	-	-	+	+

 HpBi	WW* (bind to two nucleotides with same selectivity as Hp-Py)
 PyBi	WW* (bind to two nucleotides with same selectivity as Py-Py)
 ImBi	GW* (bind to two nucleotides with same selectivity as Im-Py)

*The subunit HpBi, ImBi, and PyBi function as a conjugate of two monomer subunits and bind to two nucleotides. The binding property of HpBi, ImBi, and PyBi corresponds to Hp-Py, Im-Py, and Py-Py respectively.

Table 1B. Base pairing for hairpin polyamide.

	G·C	**C·G**	**T·A**	**A·T**
Im/β	+	-	-	-
β/Im	-	+	-	-
Py/ β	-	-	+	+
β/Py	-	-	+	+
β/ β	-	-	+	+
Py/Py	-	-	+	+
Im/Im	-	-	-	-
Im/Py	+	-	-	-
Py/Im	-	+	-	-
Th/Py	-	-	+	-
Py/Th	-	-	-	+
Th/Im	+	-	-	-
Im/Th	-	+	-	-
β/Th	-	-	+	-
Th/β	-	-	-	+

Hp/Py,	-	-	+	-
Py/Hp,	-	-	-	+
Hp/Im	+	-	-	-
Im/Hp	-	+	-	-
Tn/Py	-	-	+	+
Py/Tn,	-	-	+	+
Ht/Py,	-	-	+	+
Py/Ht,	-	-	+	+
Bi/Py,	-	-	+	+
Py/Bi,	-	-	+	+
β/Bi	-	-	+	+
Bi/β	-	-	+	+
Bi/Im,	-	+	-	-
Im/Bi,	+	-	-	-
Tp/Py,	-	-	+	+
Py/Tp,	-	-	+	+
β/Tp	-	-	+	+
Tp/β	-	-	+	+
Tp/Im,	-	+	-	-
Im/Tp	+	-	-	-
Tp/Tp	-	-	+	+
Tp/Tn	-	-	+	+
Tn/Tp	-	-	+	+
Hz/Py,	-	-	+	-
Py/Hz,	-	-	-	+
Ip/Py	+	-	-	-
Py/Ip,	-	+	-	-
Bi/Hz,	-	-	+	+
Hz/Bi,	-	-	+	+
Bi/Bi	-	+	+	+
Th/Py,	-	-	+	+
Py/Th	-	-	+	+
Im/gAB	+	-	-	-
gAB/Im	-	+	-	-
Py/ gAB	+	-	-	-
gAB/Py	-	+	-	-
gAB/ β	-	-	+	+
β/gAB	-	-	+	+
Im/Dp	+	-	-	-
Dp/Im	-	+	-	-
Py/ Dp	-	-	+	+
Dp/Py	-	-	+	+
Dp/β	-	-	+	+
Each of HpBi, ImBi, and PyBi can bind to two nucleotides and have binding properties corresponding to Hp-Py, Im-Py, and Py-Py respectively. HpBi, ImBi, and PyBi can be paired with two monomer subunits or with themselves in a hairpin structure to bind to two nucleotide pairs.				

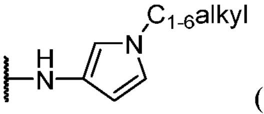
[00120] The monomer subunits of the polyamide can be strung together based on the pairing principles shown in Table 1A and Table 1B. The monomer subunits of the polyamide can be strung together based on the pairing principles shown in Table 1C and Table 1D.

[00121] Table 1C shows an example of the monomer subunits that can bind to the specific nucleotide. The first terminus can include a polyamide described having several monomer subunits stung together, with a **monomer subunit selected from each row. For example, the polyamide can include Im- β-Py that binds to GAA, with Im selected from the first G column, β from the A column, and Py from the second A column.** The polyamide can be any combinations that bind to the subunits of GAA, with a subunit selected from each column in Table 1C, wherein the subunits are strung together following the GAA order.

[00122] In addition, the polyamide can also include a partial or multiple sets of the five subunits, such as 1.5, 2, 2.5, 3, 3.5, or 4 sets of the three subunits. The polyamide can include 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, and 16 monomer subunits. The multiple sets can be joined together by W. In addition to the five subunits or ten subunits, the polyamide can also include 1-4 additional subunits that can link multiple sets of the five subunits.

[00123] The polyamide can include monomer subunits that bind to 2, 3, 4, or 5 nucleotides of GAA. For example, the polyamide can bind to GA, AA, GAA, AAG, AGA, GAAG, AAGA, GAAGA or GAAGAA. The polyamide can include monomer subunits that bind to 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides of GAA repeats. The nucleotides can be joined by W.

[00124] The monomer subunit, when positioned as a terminal unit, does not have an amine, carbonyl, or a carboxylic acid group at the terminal. The amine or carboxylic acid group in the terminal is replaced by a hydrogen. For example, Py, when used as a terminal unit, is understood to have the structure of



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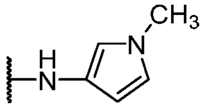
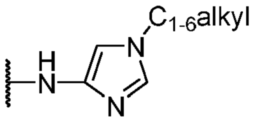


); and Im, when positioned as a terminal unit, is understood to have the structure of



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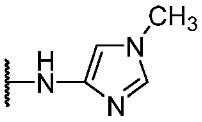
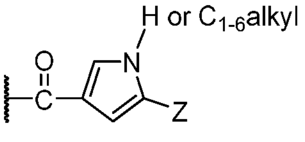


). In addition, when Py or Im is used as a terminal unit, Py and Im can be respectively replaced by PyT



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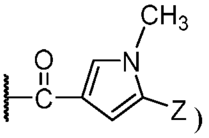
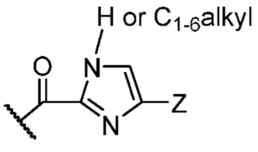


) and ImT



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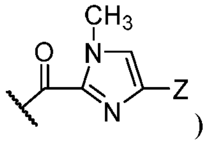


).

[00125] The linear polyamide can have nonlimiting examples including but not limited **β-Py-Im, Im-Py-β-Im-Py-β-Im-Py, Im-Py-β-Im-Py-Py-Im-β, Im-Py-Py-Im-Py-β-Im-β, and any combinations thereof.**

Table 1C. Examples of monomer subunits in a linear polyamide that binds to GAA.

Nucleotide	G	A	A
Subunit that selectively binds to nucleotide	Im or ImT	Py	Py
	iIm or iImT	Th	Th
	PEG	Pz	Pz
	CTh	Tp	Tp
	Nt	PEG	PEG
	iPTA	β	β
	Ip	iPP	iPP
	CTh	Da	Da
		Dp	Dp
		Dab	Dab
		gAH	gAH

[00126] Because the target gene can include multiple repeats of GAA, the subunits can be strung together to bind at least two, three, four, five, six, seven, eight, nine, or ten nucleotides in one or more GAA repeat (e.g., GAAGAAGAAGAA). For example, the polyamide can bind to the GAA repeat by binding to a partial copy, a full copy, or a multiple repeats of GAA such as GA, AA, GAA, AAG, AGA, GAAG, AAGA, GAAGA or GAAGAA. For example, the polyamide can include Im-Py-β-W-Py-β-Py that binds to GAA and its complementary nucleotides on a double strand DNA, in which the Im/Py pair binds to G·C, the Py/β pair binds to A·T, and the β/Py pair binds to G·A. In another example Im-Py-β-Im-W-β-Py-β-Py that binds to GAAG and its complementary nucleotides on a double strand DNA, in which the Im/Py pair binds to the G·C, the Py/β pair binds to A·T, the β/Py pair binds to G·A, and the Im/β pair binds to G·C,. In another example, Im-Py-β-Im-gAB-Im-Py binds to a part of the complementary nucleotides (ACG) on the double strand DNA, in which Im binds to G, Py binds to A, β/Py binds to the A·T, Im/Im binds to G·C.

[00127] Some additional examples of the polyamide include but are not limited to Im-Py-Py-Im-gAB-Py-Im-Im-Py; Im-Py-Py-Im-gAB-Py-Im-Im-PyT; Im-Py-Py-Im-gAB-Py-Im-Im-β; Im-Py-Py-Im-gAB-Py-Im-Im-β-G; Im-β-β-Py-Im-gAB-Py-Im-Im-β; Im-β-Py-Im-gAB-Py-Im-Im-β-G; Im-β-Py-Im-gAB-Py-Im-Im-Py; Im-β-Py-Im-gAB-Py-Im-Im-PyT; Py-Py-Im-β-gAB-Im-Py-Im-Im; Py-Py-Im-β-gAB-Im-Py-Im-ImT; Py-Py-Im-Py-gAB-Im-Py-Im-Im; Py-Py-Im-Py-gAB-Im-Py-Im-ImT; Py-Py-Im-β-gAB-Im-β-Im-Im; Py-Py-Im-β-gAB-Im-β-Im-ImT; Py-Py-Im-Py-gAB-Im-β-Im-Im; Py-Py-Im-Py-gAB-Im-β-Im-ImT; Im-β-Py-gAB-Im-Im-Py; Im-β-Py-gAB-Im-Im-PyT; Im-β-Py-gAB-Im-Im-β; Im-β-Py-gAB-Im-Im-β-G; Im-Py-Py-gAB-Im-Im-β; Im-Py-Py-gAB-Im-Im-β-G; Im-Py-Py-gAB-Im-Im-Py; Im-Py-Py-gAB-Im-Im-PyT; Im-p-Py-gAB-Im-Im-Py; and Im-β-Py-gAB-Im-Im-PyT; wherein G may be hydrogen, alkyl, alkenyl, alkynyl, or -C(=O)-R_B; and R_B may be hydrogen, C_1-C_6 alkyl, C_1-C_6 alkenyl, or C_1-C_6 alkynyl group. In some embodiments, the hairpin polyamide has a structure of Im-Py-β-Im-gAB-Im-Py; Im-Py-β-Im-gAB-Im-Py-β-Im; Py-β-Im-gAB-Im-Py-β-Im; or β-Im-gAB-Im-Py-β-Im.

Second Terminus – Regulatory Binding Moiety

[00128] In some embodiments, the second terminus comprises a protein-binding moiety that is capable of binding to a regulatory molecule that modulates an expression of a gene comprising one or more copies of the trinucleotide repeat sequence GAA.

[00129] In some embodiments, the regulatory molecule is chosen from a nucleosome remodeling factor ("NURF"), a bromodomain PHD finger transcription factor ("BPTF"), a ten-eleven translocation enzyme ("TET"), methylcytosine dioxygenase ("TET1"), a DNA demethylase, a helicase, an acetyltransferase, a **CREB binding protein ("CBP"), a P300, an O-linked β-N-acetylglucosamine-transferase ("OGT"), a P300-** CBP-associated-factor ("PCAF"), histone methyltransferase, histone demethylase, chromodomain, a cyclin-dependent-kinase-9 ("CDK9"), an octamer-binding-transcription-factor ("OCT1"), a histone acetyltransferase ("HAT"), a host-cell-factor-1 ("HCF1"), and a histone deacetylase ("HDAC").

[00130] In some embodiments, the protein-binding moiety binds to the regulatory molecule that is selected from the group consisting of a CBP, a P300, a OGT, a CAF, a CDK9, a NURF, a BPTF, a TET, a TET1, HAT, a HDAC, a HCF1, an OCT1, a P-TEFb, a cyclin-T1, a PRC2, a DNA-demethylase, a helicase, an acetyltransferase, a histone-deacetylase, and a methylated histone lysine protein.

[00131] In some embodiments, the second terminus comprises a moiety that binds to OGT or CBP. In some embodiments, the protein binding moiety is a residue of a compound that binds to OGT or CBP.

[00132] In some embodiments, the second terminus comprises a bromodomain binding moiety. In some embodiments, the bromodomain binding moiety is a BRD2, BRD3, BRD4, or BRDT binding moiety. In some embodiments, the bromodomain binding moiety is a BRD4 binding moiety.

[00133] In some embodiments, the regulatory molecule is a bromodomain-containing protein chosen from BRD2, BRD3, BRD4, and BRDT.

[00134] In some embodiments, the regulatory molecule is BRD4. In certain embodiments, the recruiting moiety is a BRD4 activator.

[00135] In some embodiments, the regulatory molecule modulates the rearrangement of histones.

[00136] In some embodiments, the regulatory molecule modulates the glycosylation, phosphorylation, alkylation, or acylation of histones.

[00137] In some embodiments, the regulatory molecule is a transcription factor.

[00138] In some embodiments, the regulatory molecule is an RNA polymerase.

[00139] In some embodiments, the regulatory molecule is a moiety that regulates the activity of RNA polymerase.

[00140] 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.

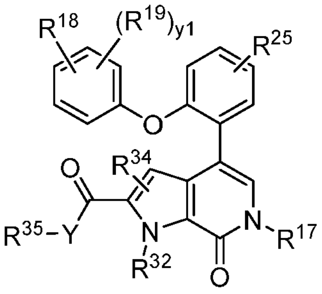
[00141] In certain embodiments, the recruiting moiety binds to the active site of the regulatory molecule. In certain embodiments, the recruiting moiety binds to a regulatory site of the regulatory molecule.

[00142] 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 300 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 is capable of binding the regulatory molecule 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 second terminus is capable of binding the regulatory molecule with an affinity in the range of about 1-600 nM, 10-500 nM, 20-500 nM, 50-400 nM, 100-300 nM, or 50-200 nM.

[00143] In some embodiments, the second terminus is a ligand.

[00144] In some embodiments, the second terminus comprises a pyrrolopyridinone. In some embodiments, the pyrrolopyridinnone is substituted with an optionally substituted oxydibeneze. In some embodiments, the **second terminus comprises an optionally substituted 4-(2-phenoxyphenyl)-6λ^2**-pyrrolo[2,3-c]pyridin-7(1H)-one.

[00145] In some embodiments, the second terminus comprises a compound having the structure of Formula (B), or a pharmaceutically acceptable salt thereof:



Formula (B),

wherein,

Y is -CH_2NH-, CH_2O-, -NH-, or -O-;

R^{17} is hydrogen or C_1-C_6 alkyl;

R^{18} and R^{19} are each independently hydrogen, deuterium, 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^{18} is -NR^AR^B;

R^{25} is an optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_1-C_6 alkenyl, optionally substituted C_1-C_6 alkynyl, optionally substituted C_1-C_6 hydroxyalkyl, -SO_2R^A, or -$NHSO_2R^A$;

R^{32} is hydrogen or an optionally substituted C_1-C_6 alkyl;

R^{34} 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^{35} 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;

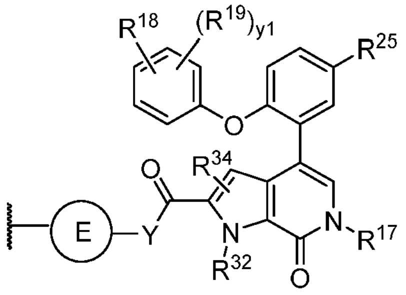
each R^A and R^B is independently hydrogen, deuterium, an optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl; and

y_1 is 1-3; and

wherein attachment to the linker is at either R^{18} or at R^{35}.

[00146] In some embodiments the attachment to the linker is at R^{18}. In some embodiments the attachment to the linker is at R^{35}.

[00147] In some embodiments, the second terminus comprises a compound having the structure of Formula (B-1), or a pharmaceutically acceptable salt thereof:



Formula (B-1),

wherein,

Ring E is absent or an optionally substituted 5-6-membered monocyclic aryl or heteroaryl or optionally substituted 4-8-membered heterocycle;

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

R^{17} is hydrogen or C_1-C_6 alkyl;

R^{18} and R^{19} are each independently hydrogen, deuterium, 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^{18} is $-NR^AR^B$;

R^{25} is an optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_1-C_6 alkenyl, optionally substituted C_1-C_6 alkynyl, optionally substituted C_1-C_6 hydroxyalkyl, -SO_2R^A, or $-NHSO_2R^A$;

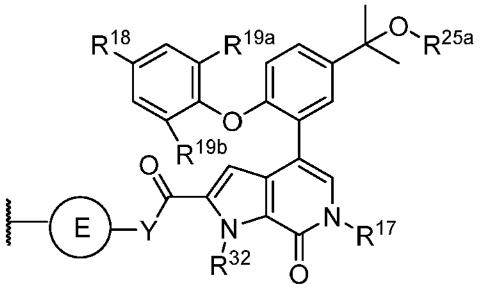
R^{32} is hydrogen or an optionally substituted C_1-C_6 alkyl;

R^{34} 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;

each R^A and R^B is independently hydrogen, deuterium, an optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl; and

y_1 is 1-3.

[00148] In some embodiments, the second terminus comprises a compound having the structure of Formula (B-2), or a pharmaceutically acceptable salt thereof:



Formula (B-2),

wherein,

Ring E is absent or an optionally substituted 5-6-membered monocyclic aryl or heteroaryl or optionally substituted 4-8-membered heterocycle;

Y is -CH_2NH-, CH_2O-, -NH-, or -O-;

R^{17} is hydrogen or C_1-C_6 alkyl;

R^{18} is halogen;

R^{19a} is halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 haloalkyl, or optionally substituted C_1-C_6 hydroxyalkyl;

R^{19b} is hydrogen, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 haloalkyl, or optionally substituted C_1-C_6 hydroxyalkyl;

R^{25a} is hydrogen or an optionally substituted C_1-C_6 alkyl; and

R^{32} is hydrogen or an optionally substituted C_1-C_6 alkyl.

[00149] In some embodiments, Ring E is an optionally substituted 5 or 6-membered monocyclic aryl or heteroaryl, wherein each aryl or heteroaryl is optionally substituted with alkyl, amino, halogen, hydroxy, hydroxyalkyl, or PEG. In some embodiments, Ring E is optionally substituted with one or more R^{33}, wherein each R^{33} is independently selected from deuterium, halogen, hydroxyl, amino, nitro, an optionally substituted C_1-C_{20} alkyl, optionally substituted C_1-C_{20} heteroalkyl, optionally substituted C_1-C_{20} haloalkyl, optionally substituted C_1-C_6 hydroxyalkyl, or optionally substituted $(PEG)_{1-20}$.

[00150] In some embodiments, Ring E is phenyl. In some embodiments, Ring E is a 6-membered heteroaryl. In some embodiments, Ring E is pyridine, pyrazine, or triazine. In some embodiments, Ring E is pyridine. In some embodiments, Ring E is pyrazine. In some embodiments, Ring E is triazine. In some embodiments, Ring E is a 5-membered heteroaryl. In some embodiments, Ring E is a pyrazole. In some embodiments, Ring E is a triazole, pyrrole, imidazole, oxazole, oxadiazole, thiazole, or thiadiazole. In some embodiments, Ring E is a triazole. In some embodiments, Ring E is an imidazole or pyrrole. In some embodiments, an oxazole or oxadiazole. In some embodiments, Ring E is a thiazole or thiadiazole.

[00151] In some embodiments, Ring E is phenyl substituted with one or more -OH, -$(OCH_2CH_2)_m$-OH, or –$(OCH_2CH_2)_m$-O-(C_1-C_6 alkyl). In some embodiments, Ring E is phenyl substituted with one or more -OH. In some embodiments, Ring E is phenyl substituted with -$(OCH_2CH_2)_m$-OH. In some embodiments, Ring E is phenyl substituted with one or more –$(OCH_2CH_2)_m$-O-(C_1-C_6 alkyl).

[00152] In some embodiments, m is 1 to 10. In some embodiments, m is 2 to 10. In some embodiments, m is 3 to 10. In some embodiments, m is 4 to 10. In some embodiments, m is 5 to 10. In some embodiments, m is 6 to 10. In some embodiments, m is 7 to 10. In some embodiments, m is 8 to 10. In some embodiments, m is 9 to 10.

[00153] In some embodiments, m is 1 to 9. In some embodiments, m is 2 to 9. In some embodiments, m is 3 to 9. In some embodiments, m is 4 to 9. In some embodiments, m is 5 to 9. In some embodiments, m is 6 to 9. In some embodiments, m is 7 to 9. In some embodiments, m is 8 to 9.

[00154] In some embodiments, m is 1 to 8. In some embodiments, m is 2 to 8. In some embodiments, m is 3 to 8. In some embodiments, m is 4 to 8. In some embodiments, m is 5 to 8. In some embodiments, m is 6 to 8. In some embodiments, m is 7 to 8.

[00155] In some embodiments, m is 1 to 7. In some embodiments, m is 2 to 7. In some embodiments, m is 3 to 7. In some embodiments, m is 4 to 7. In some embodiments, m is 5 to 7. In some embodiments, m is 6 to 7.

[00156] In some embodiments, m is 1 to 6. In some embodiments, m is 2 to 6. In some embodiments, m is 3 to 6. In some embodiments, m is 4 to 6. In some embodiments, m is 5 to 6.

[00157] In some embodiments, m is 1. In some embodiments, m is 2. In some embodiments, m is 3. In some embodiments, m is 4. In some embodiments, m is 5. In some embodiments, m is 6. In some embodiments, m is 7. In some embodiments, m is 8. In some embodiments, m is 9. In some embodiments, m is 10.

[00158] In some embodiments, Ring E is absent.

[00159] In some embodiments, Y is $-CH_2NH-$ or -NH-. In some embodiments, Y is $-CH_2NH-$. In some embodiments, Y is -NH-. In some embodiments, Y is -O-.

[00160] In some embodiments, R^{17} is hydrogen. In some embodiments, R^{17} is C_1-C_6 alkyl. In some embodiments, R^{17} is methyl, ethyl, propyl. In some embodiments, R^{17} is methyl. In some embodiments, R^{17} is ethyl. In some embodiments, R^{17} is propyl.

[00161] In some embodiments, R^{18} and R^{19} are each independently hydrogen, CN, or NO_2. In some embodiments, R^{18} and R^{19} are each independently halogen or optionally substituted C_1-C_6 alkyl. In some embodiments, R^{18} and R^{19} are each independently bromo, chloro, fluoro, methyl, or ethyl. In some embodiments, R^{18} and R^{19} are each independently fluoro or methyl.

[00162] In some embodiments, R^{18} is halogen. In some embodiments, R^{18} is chloro, bromo, or fluoro. In some embodiments, R^{18} is chloro. In some embodiments, R^{18} is bromo. In some embodiments, R^{18} is fluoro.

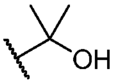
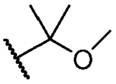
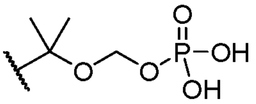
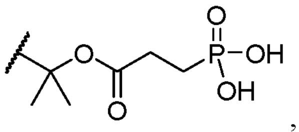
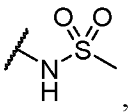
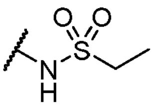
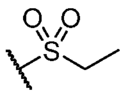
[00163] In some embodiments, R^{19a} is halogen, an optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 haloalkyl. In some embodiments, R^{19a} is halogen or optionally substituted C_1-C_6 alkyl. In some embodiments, R^{19a} is chloro, bromo, fluoro, or methyl. In some embodiments, R^{19a} is fluoro or methyl. In some embodiments, R^{19a} is chloro. In some embodiments, R^{19a} is bromo. In some embodiments, R^{19a} is fluoro. In some embodiments, R^{19a} is methyl.

[00164] In some embodiments, R^{19b} is hydrogen, halogen, or optionally substituted C_1-C_6 alkyl. In some embodiments, R^{19b} is chloro, bromo, fluoro, or methyl. In some embodiments, R^{19b} is chloro. In some embodiments, R^{19b} is bromo. In some embodiments, R^{19b} is fluoro or methyl. In some embodiments, R^{19b} is fluoro. In some embodiments, R^{19b} is methyl. In some embodiments, R^{19b} is hydrogen.

[00165] In some embodiments, R^{25} is an 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.

[00166] In some embodiments, R^{25} is an optionally substituted C_{1-6} alkyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted C_1-C_6 hydroxyalkyl. In some embodiments, R^{25} is C_1-C_6 alkyl or C_1-C_6 heteroalkyl, each of which is optionally substituted with -CN, $-NH_2$, $-N_3$, -OH, CF_3, $-OP(=O)(OH)_2$, or $-O(CH_2)OP(=O)(OH)_2$.

[00167] In some embodiments, R^{25} is $-NHSO_2R^A$, wherein R^A is C_1-C_6 alkyl. In some embodiments, R^{25} is $-NHSO_2Et$. In some embodiments, R^{25} is $-NHSO_2Me$. In some embodiments, R^{25} is $-SO_2R^A$, wherein R^A is C_1-C_6 alkyl. In some embodiments, R^{25} is $-SO_2Et$. In some embodiments, R^{25} is $-SO_2Me$.

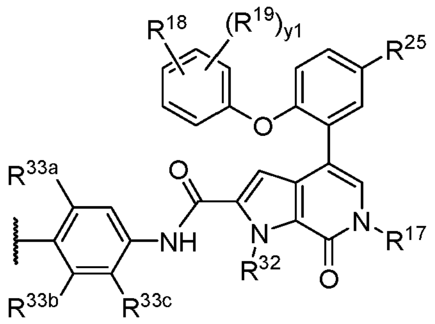
[00168] In some embodiments, R^{25} is , , , , , , , or .

[00169] In some embodiments, R^{25a} is an 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^{25a} is C_1-C_6 alkyl or C_{1-6} heteroalkyl, each of which is optionally substituted with -CN, $-NH_2$, $-N_3$, -OH, CF_3, $-OP(=O)(OH)_2$, $-C(=O)(CH_2)_2P(=O)(OH)_2$, or $-(CH_2)OP(=O)(OH)_2$. In some embodiments, R^{25a} is hydrogen, methyl, ethyl, $-OP(=O)(OH)_2$, or $-(CH_2)OP(=O)(OH)_2$.

[00170] In some embodiments, R^{32} is C_1-C_6 alkyl, optionally substituted with haloalkyl, phosphorous hydroxide. In some embodiments, R^{32} is C_1-C_6 alkyl substituted with $-OP(=O)(OH)_2$. In some embodiments, R^{32} is unsubstituted C_1-C_6 alkyl. In some embodiments, R^{32} is methyl, ethyl, or tert-butyl. In some embodiments, R^{32} is methyl. In some embodiments, R^{32} is ethyl. In some embodiments, R^{32} is tert-butyl. In some embodiments, R^{32} is hydrogen.

[00171] In some embodiments, y_1 is 1. In some embodiments, y_1 is 2. In some embodiments, y_1 is 3.

[00172] In some embodiments, the second terminus comprises a compound having the structure of Formula (B-3), or a pharmaceutically acceptable salt thereof:



Formula (B-3),

wherein,

R^{17} is hydrogen or C_1-C_6 alkyl;

R^{18} and R^{19} are each independently hydrogen, deuterium, halogen, -CN, -NO_2, an optionally substituted -C_1-C_6 alkyl, optionally substituted C_1-C_6 haloalkyl, or optionally substituted C_1-C_6 hydroxyalkyl;

or R^{18} is -NR^AR^B;

R^{25} is an optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_1-C_6 alkenyl, optionally substituted C_1-C_6 alkynyl, optionally substituted C_1-C_6 hydroxyalkyl, -SO_2R^A, or -$NHSO_2R^A$;

R^{32} is hydrogen or an optionally substituted C_1-C_6 alkyl;

each R^{33a}, R^{33b}, and R^{33c} is independently selected from hydrogen, deuterium, halogen, hydroxyl, amino, nitro, an optionally substituted C_1-C_{20} alkyl, optionally substituted C_1-C_{20} heteroalkyl, optionally substituted C_1-C_{20} haloalkyl, optionally substituted C_1-C_6 hydroxyalkyl, or optionally substituted $(PEG)_{1\text{-}20}$;

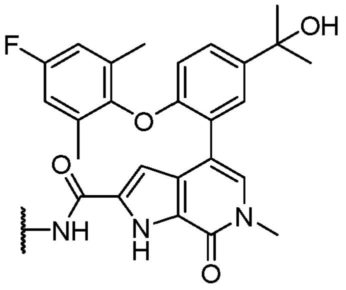
each R^A and R^B is independently hydrogen, deuterium, an optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl; and

y_1 is 1-3.

[00173] In some embodiments, R^{33a}, R^{33b}, and R^{33c} are each independently hydrogen, halogen, hydroxyl, an optionally substituted C_1-C_{20} alkyl, optionally substituted C_1-C_{20} heteroalkyl, or optionally substituted $(PEG)_{1\text{-}20}$. In some embodiments, R^{33a}, R^{33b}, and R^{33c} are each independently hydrogen, halogen, or optionally substituted $(PEG)_{1\text{-}20}$. In some embodiments, R^{33a}, R^{33b}, and R^{33c} are each hydrogen.

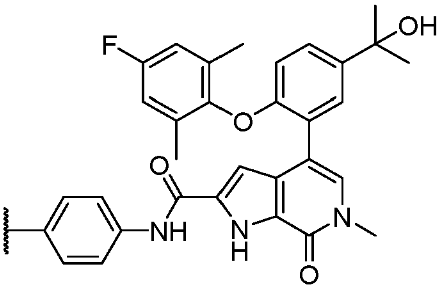
[00174] In some embodiments, R^{33a} is halogen, hydroxyl, an optionally substituted C_1-C_{20} alkyl, optionally substituted C_1-C_{20} heteroalkyl, or optionally substituted $(PEG)_{1\text{-}20}$; and R^{33b} and R^{33c} are each hydrogen. In some embodiments, R^{33a} is an optionally substituted $(PEG)_{1\text{-}20}$; and R^{33b} and R^{33c} are each hydrogen.

[00175] In some embodiments, the second terminus comprises a compound having the structure of Formula (B-4), or a pharmaceutically acceptable salt thereof:



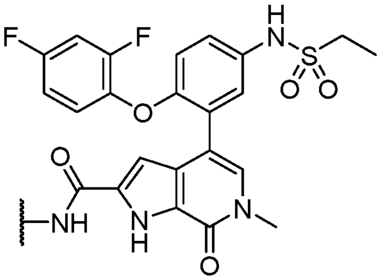
Formula (B-4).

[00176] In some embodiments, the second terminus comprises a compound having the structure of Formula (B-5), or a pharmaceutically acceptable salt thereof:

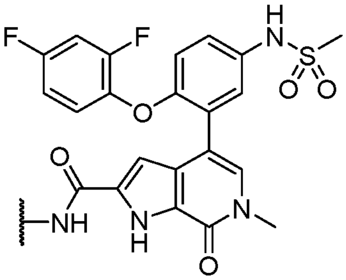


Formula (B-5).

[00177] In some embodiments, the second terminus comprises a compound having the structure of Formula (B-6) or (B-7), or a pharmaceutically acceptable salt thereof:

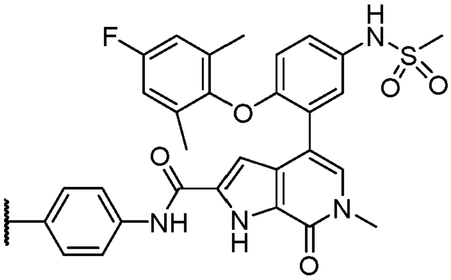


Formula (B-6) or



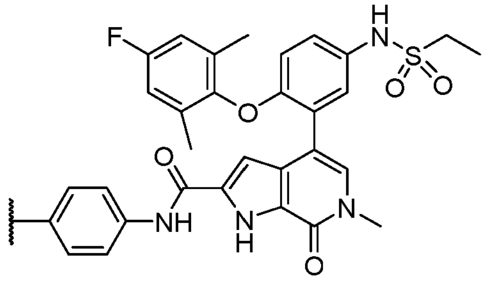
Formula (B-7).

[00178] In some embodiments, the second terminus comprises a compound having the structure of Formula (B-8), or a pharmaceutically acceptable salt thereof:



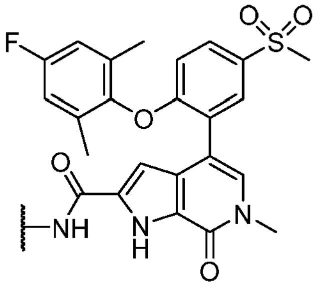
Formula (B-8).

[00179] In some embodiments, the second terminus comprises a compound having the structure of Formula (B-9), or a pharmaceutically acceptable salt thereof:

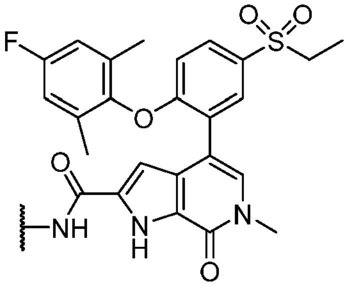


Formula (B-9).

[00180] In some embodiments, the second terminus comprises a compound having the structure of Formula (B-10) or (B-11), or a pharmaceutically acceptable salt thereof:

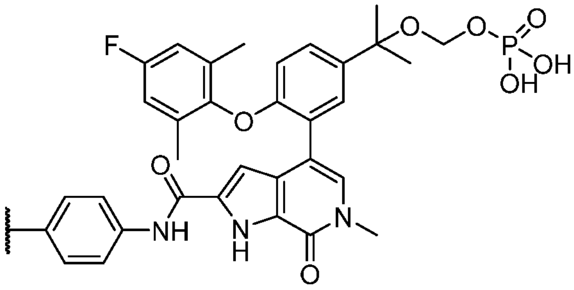


Formula (B-10) or

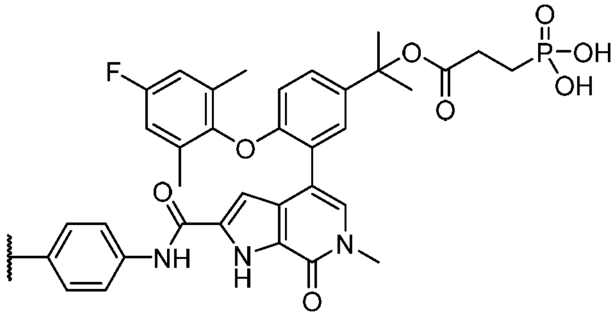


Formula (B-11).

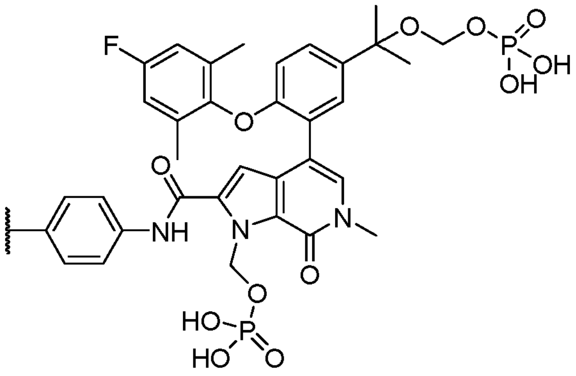
[00181] In some embodiments, the second terminus comprises a compound having the structure of Formula (B-12), (B-13), or (B-14), or a pharmaceutically acceptable salt thereof:



Formula (B-12),

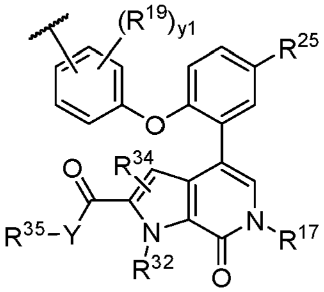


Formula (B-13), or



Formula (B-14).

[00182] In some embodiments, the second terminus comprises a compound having the structure of Formula (B-15), or a pharmaceutically acceptable salt thereof:



Formula (B-15),

wherein,

Y is -CH_2NH-, CH_2O-, -NH-, or -O-;

R^{17} is hydrogen or C_1-C_6 alkyl;

R^{19} are each independently hydrogen, deuterium, 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^{25} is an optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_1-C_6 alkenyl, optionally substituted C_1-C_6 alkynyl, optionally substituted C_1-C_6 hydroxyalkyl, -SO_2R^A, or -$NHSO_2R^A$;

R^{32} is hydrogen or an optionally substituted C_1-C_6 alkyl;

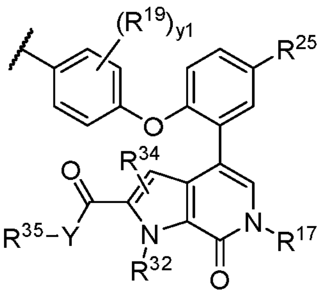
R^{34} is hydrogen, halogen, -OH, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 haloalkyl, or optionally substituted C_1-C_6 hydroxyalkyl;

R^{35} is hydrogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 haloalkyl, or optionally substituted 5-6-membered monocyclic aryl or heteroaryl;

R^A is hydrogen, deuterium, an optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl; and

y_1 is 1-3.

[00183] In some embodiments, the second terminus comprises a compound having the structure of Formula (B-16), or a pharmaceutically acceptable salt thereof:



Formula (B-16),

wherein,

Y is -CH$_2$NH-, CH$_2$O-, -NH-, or -O-;

R^{17} is hydrogen or C$_1$-C$_6$ alkyl;

R^{19} are each independently hydrogen, deuterium, 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^{25} is an optionally substituted C$_1$-C$_6$ alkyl, optionally substituted C$_1$-C$_6$ heteroalkyl, optionally substituted C$_1$-C$_6$ alkenyl, optionally substituted C$_1$-C$_6$ alkynyl, optionally substituted C$_1$-C$_6$ hydroxyalkyl, -SO$_2$R^A, or -NHSO$_2$R^A;

R^{32} is hydrogen or an optionally substituted C$_1$-C$_6$ alkyl;

R^{34} 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^{35} is hydrogen, optionally substituted C$_1$-C$_6$ alkyl, or optionally substituted C$_1$-C$_6$ haloalkyl, or optionally substituted 5-6-membered monocyclic aryl or heteroaryl;

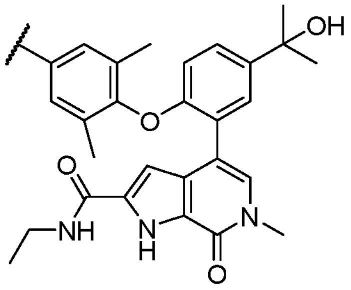
R^A is hydrogen, deuterium, an optionally substituted C$_1$-C$_6$ alkyl, or optionally substituted C$_1$-C$_6$ heteroalkyl; and

y$_1$ is 1-3.

[00184] In some embodiments, R^{34} is hydrogen, halogen, or -OH. In some embodiments, R^{34} is 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^{34} is hydrogen.

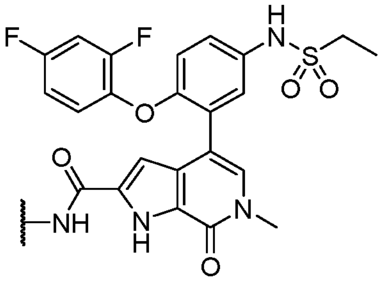
[00185] In some embodiments, R^{35} is optionally substituted C$_1$-C$_6$ alkyl, or optionally substituted C$_1$-C$_6$ haloalkyl. In some embodiments, R^{35} is optionally substituted C$_1$-C$_6$ alkyl. In some embodiments, R^{35} is methyl, ethyl, or iso-propyl. In some embodiments, R^{35} is an optionally substituted 5-6-membered monocyclic aryl or heteroaryl.

[00186] In some embodiments, the second terminus comprises a compound having the structure of Formula (B-17), or a pharmaceutically acceptable salt thereof:



Formula (B-17).

[00187] In some embodiments, the second terminus is selected from:



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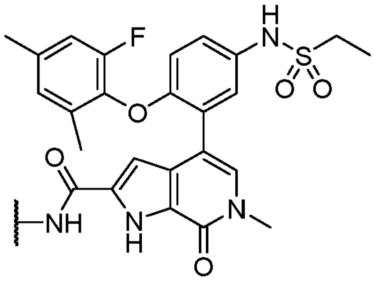

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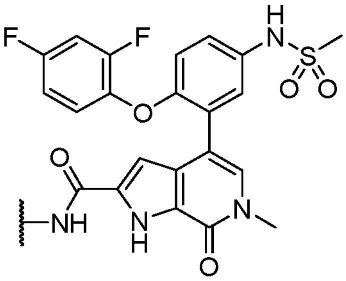

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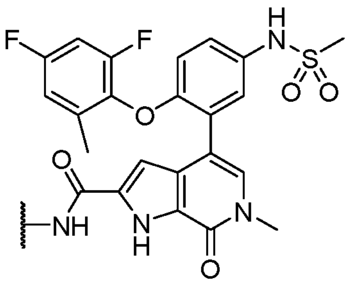

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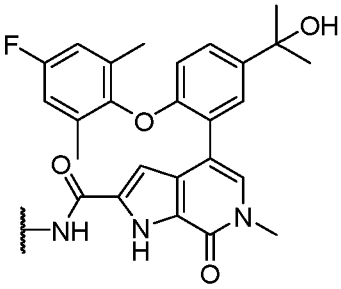

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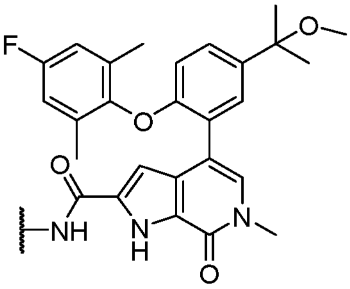

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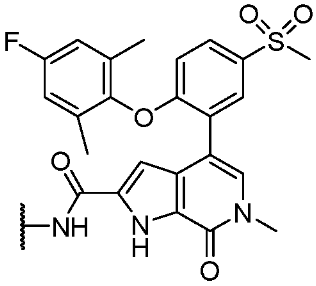

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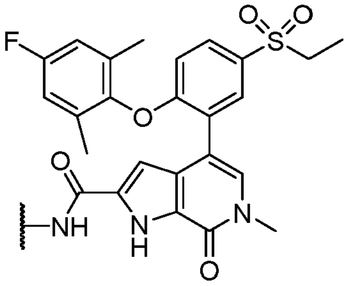

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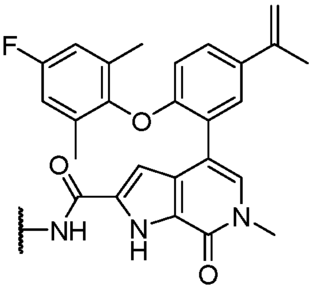

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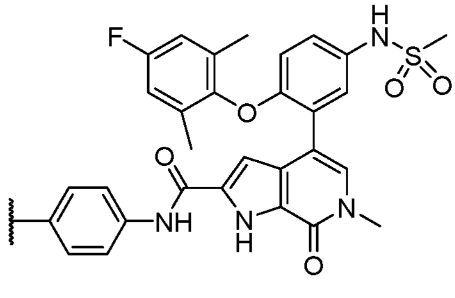

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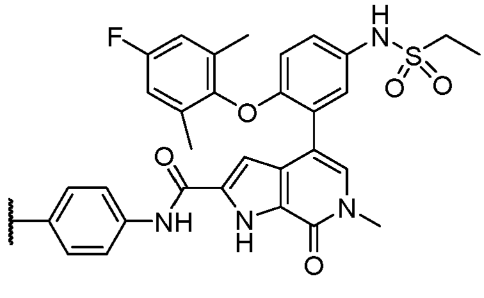

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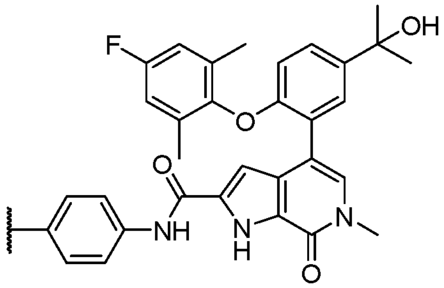
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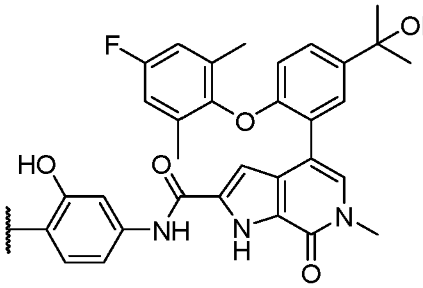
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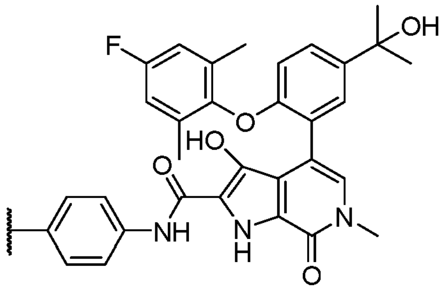
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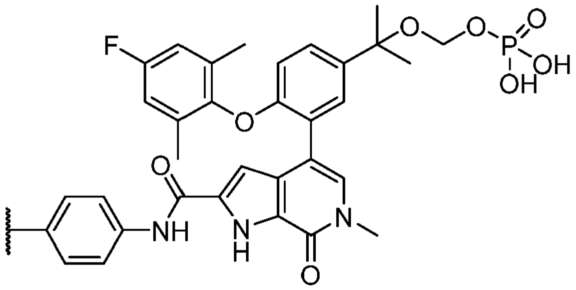
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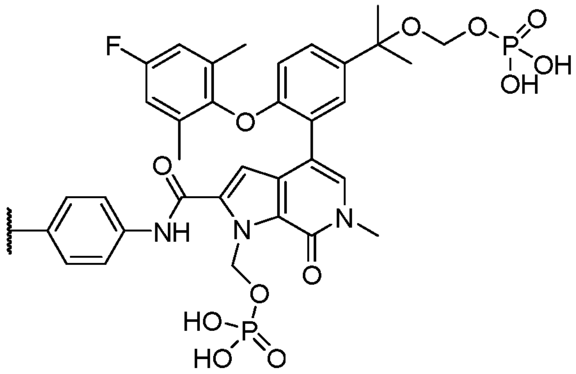
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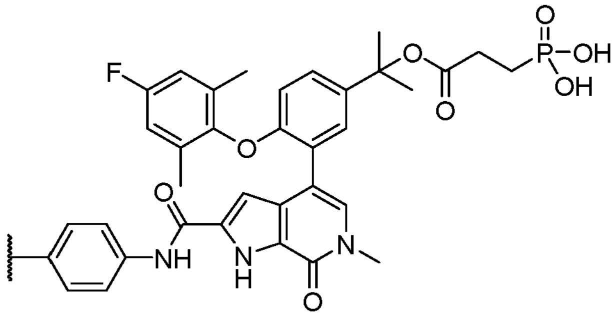
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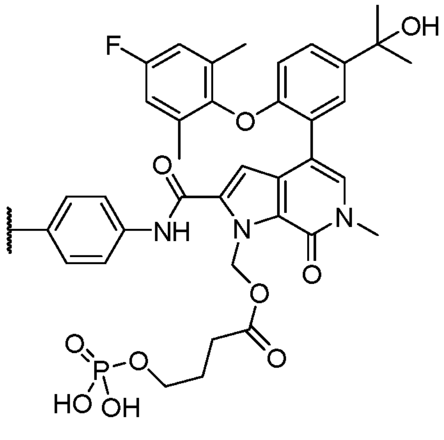
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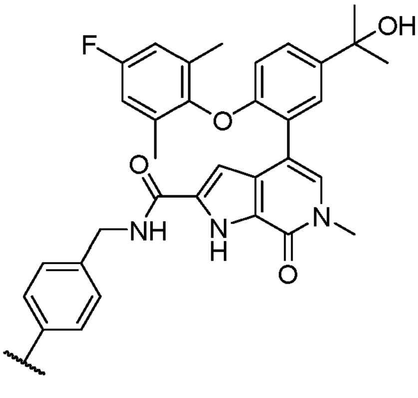
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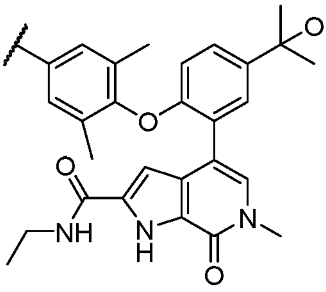
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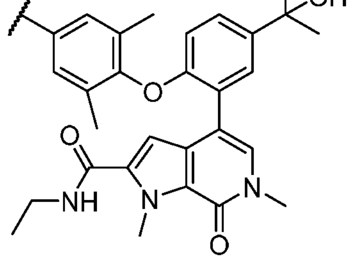

, or a pharmaceutically acceptable salt thereof.

Linker – Oligomeric Backbone

[00188] The oligomeric backbone contains 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.

[00189] 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.

[00190] In some embodiments, the linker comprises between 5 and 50 chain atoms.

[00191] In some embodiments, the linker comprises a multimer having 2 to 50 spacing moieties, wherein the spacing moiety is independently selected from the group consisting of $-((CR^{3a}R^{3b})_x-O)_y-$, $-((CR^{3a}R^{3b})_x-NR^{4a})_y-$, $-((CR^{3a}R^{3b})_x-CH=CH-(CR^{3a}R^{3b})_x-O)_y-$, optionally substituted C_1-C_{12} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_6-C_{10} arylene, optionally substituted C_3-C_7 cycloalkylene, optionally substituted 5- to 10-membered heteroarylene, optionally substituted 4- to 10-membered heterocycloalkylene, amino acid residue, -O-, $-C(=O)NR^{4a}-$, $-NR^{4a}C(=O)-$, $-C(=O)-$, $-NR^1-$, -C(=O)O-, -O-, -S-, -S(=O)-, $-SO_2-$, $-SO_2NR^{4a}-$, $-NR^{4a}SO_2-$, and -P(=O)OH-, and any combinations thereof; wherein

each x is independently 2-4;

each y is independently 1-10;

each R^{3a} and R^{3b} are independently selected from hydrogen, 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, sulfonyl, optionally substituted thioalkoxy, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, and optionally substituted heterocyclyl; and

each R^{4a} is independently a hydrogen or an optionally substituted C_1-C_6 alkyl.

[00192] In some embodiments, the oligomeric backbone comprises $-(T^1-V^1)_a-(T^2-V^2)_b-(T^3-V^3)_c-(T^4-V^4)_d-(T^5-V^5)_e-$, 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 C_1-C_{12} alkylene, optionally substituted alkenylene, optionally substituted alkynylene, $(EA)_w$, $(EDA)_m$, $(PEG)_n$, (modified PEG)$_n$, $(AA)_p$, $-(CR^{2a}OH)_h-$, optionally substituted C_6-C_{10} arylene, optionally substituted C_3-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, wherein

w is an integer from 1 to 20;

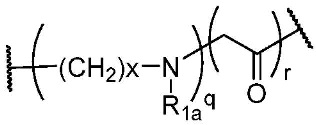
m is an integer from 1 to 20;

n is an integer from 1 to 30;

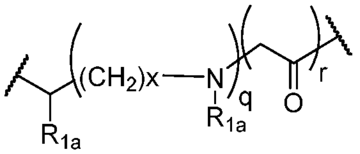
p is an integer from 1 to 20;

h is an integer from 1 to 12;

EA has the following structure



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;

$(PEG)_n$ has the structure of $-(CR^{2a}R^{2b}\text{-}CR^{2a}R^{2b}\text{-}O)_n\text{-}CR^{2a}R^{2b}\text{-}$;

(modified $PEG)_n$ has the structure of replacing at least one $-(CR^{2a}R^{2b}\text{-}CR^{2a}R^{2b}\text{-}O)\text{-}$ in $(PEG)_n$ with $-(CH_2\text{-}CR^{2a}{=}CR^{2a}\text{-}CH_2\text{-}O)\text{-}$ or $-(CR^{2a}R^{2b}\text{-}CR^{2a}R^{2b}\text{-}S)\text{-}$;

AA is an amino acid residue;

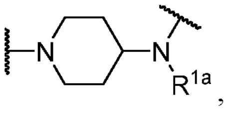
V^1, V^2, V^3, V^4 and V^5 are each independently selected from the group consisting of a bond, CO-, $-NR^{1a}-$, $-CONR^{1a}-$, $-NR^{1a}CO-$, $-CONR^{1a}C_{1\text{-}4}$ alkyl-, $-NR^{1a}CO\text{-}C_{1\text{-}4}$ alkyl-, -C(=O)O-, -OC(=O)-, -O-, -S-, -S(=O)-, $-SO_2-$, $-SO_2NR^{1a}-$, $-NR^{1a}SO_2-$ and -P(=O)OH-;

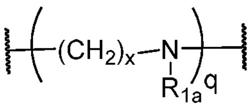
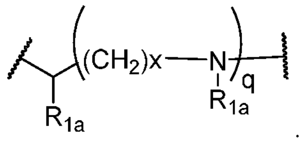
each R^{1a} is independently hydrogen or an optionally substituted $C_{1\text{-}6}$ alkyl; and

each R^{2a} and R^{2b} are independently selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogen, alkoxy, substituted alkoxy, amino, substituted amino, 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.

[00193] 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.

[00194] In some embodiments, n is 3-9. In some embodiments, n is 4-8. In some embodiments, n is 5 or 6.

[00195] In some embodiments, T^1, T^2, T^3, and T^4, and T^5 are each independently selected from $(C_1\text{-}C_{12})$alkyl, substituted $(C_1\text{-}C_{12})$alkyl, $(EA)_w$, $(EDA)_m$, $(PEG)_n$, (modified $PEG)_n$, $(AA)_p$, $-(CR^{2a}OH)_h-$, phenyl, substituted phenyl, piperidin-4-amino (P4A), para-amino-benzyloxycarbonyl (PABC), meta-amino-benzyloxycarbonyl (MABC), para-amino-benzyloxy (PABO), meta-amino-benzyloxy (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 H or $C_1\text{-}C_6$ alkyl.

[00196] In some embodiments, T^1, T^2, T^3, T^4 and T^5 are each independently selected from C_1-C_{12} alkyl, substituted C_1-C_{12} alkyl, $(EA)_w$, $(EDA)_m$, $(PEG)_n$, (modified PEG)$_n$, $(AA)_p$, $-(CR^{2a}OH)_h-$, optionally substituted C_6-C_{10} arylene, 4-10 membered heterocycloalkene, optionally substituted 5-10 membered heteroarylene. In some embodiments, EA has the following structure:  ; and EDA has the following structure:  .

[00197] In some embodiments, x is 2-3 and q is 1-3 for EA and EDA. In some embodiments, R^{1a} is H or C_1-C_6 alkyl.

[00198] In some embodiments, T^4 or T^5 is an optionally substituted C_6-C_{10} arylene.

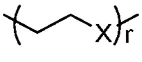
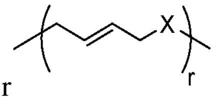
[00199] In some embodiments, T^4 or T^5 is phenylene or substituted phenylene. In some embodiments, T^4 or T^5 is phenylene or phenylene substituted with 1-3 substituents selected from $-C_{1-6}$ alkyl, halogen, OH or amine. In some embodiments, T^4 or T^5 is 5-10 membered heteroarylene or substituted heteroarylene. In some embodiments, T^4 or T^5 is 4-10 membered heterocylcene or substituted heterocyclene. In some embodiments, T^4 or T^5 is heteroarylene or heterocyclene optionally substituted with 1-3 substituents selected from C_1-C_6 alkyl, halogen, OH or amine.

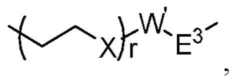
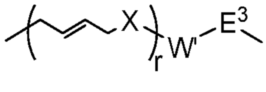
[00200] In some embodiments, T^1, T^2, T^3, T^4 and T^5 and V^1, V^2, V^3, V^4 and V^5 are selected from the following Table 2.

Table 2. Representative linkers.

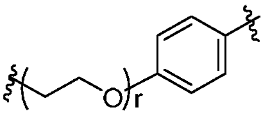
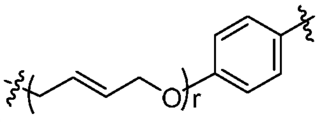
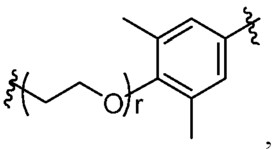
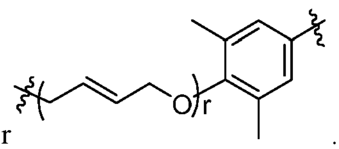
T^1	V^1	T^2	V^2	T^3	V^3	T^4	V^4	T^5	V^5
C_1-C_{12} alkylene	$CONR^{1a}$	$(EA)_w$	CO	$(PEG)_n$	$NR^{1a}CO$	----	----	----	----
C_1-C_{12} alkylene	$CONR^{1a}$	$(EA)_w$	CO	$(PEG)_n$	O	arylene	$NR^{1a}CO$	----	----
C_1-C_{12} alkylene	$CONR^{1a}$	$(EA)_w$	CO	$(PEG)_n$	O	Subst. arylene	$NR^{1a}CO$	----	----
C_1-C_{12} alkylene	$CONR^{1a}$	$(EA)_w$	CO	$(PEG)_n$	O	$NR^{1a}CO$	C_1-C_{12} alkyl	Subst. arylene	$NR^{1a}CO$
C_1-C_{12} alkylene	$CONR^{1a}$	$(EA)_w$	CO	C_1-C_{12} alkyl	$NR^{1a}CO$-C_1-C_4 alkyl	Subst. arylene	NR^{1a}	----	----
C_1-C_{12} alkylene	$CONR^{1a}$	$(EA)_w$	CO	$(PEG)_n$	O	Subst. arylene	---	----	----
$(PEG)_n$	$CONR^{1a}$-C_1-C_4 alkyl	----	----	----	----	----	----	----	---
$(EA)_w$	CO	C_1-C_{12} alkyl	$CONR^{1a}$-C_1-C_4 alkyl	----	----	----	----	----	---
C_1-C_{12}	$CONR^{1a}$	$(EA)_w$	CO	$(PEG)_n$	$NR^{1a}CO$-	----	----	----	----

alkylene					C_1-C_4 alkyl				
$(EA)_w$	CO	$(PEG)_n$	O	phenyl	$NR^{11}CO$-C_{1-4} alkyl	----	----	----	----
C_1-C_{12} alkylene	$CONR^{1a}$	$(PEG)_n$	CO	----	----	----	----	----	---
C_1-C_{12} alkylene	$CONR^{1a}$	$(EA)_w$	CO	Modif $(PEG)_n$	O	arylene	$NR^{1a}CO$	----	----

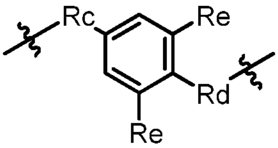
[00201] In some embodiments, the linker comprises  or  ; or any combinations thereof, wherein r is an integer between 1 and 10, preferably between 3 and 7; and X is O, S, or NR^{1a}. In some embodiments, X is O or NR^{1a}. In some embodiments, X is O.

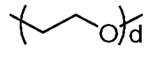
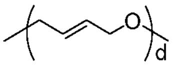
[00202] In some embodiments, the linker comprise a  , or  ; or any combinations thereof; wherein at least one $-(CH_2$-CH_2-$O)$- is replaced with $-((CR^{1a}R^{1b})_x$-$CH=CH$-$(CR^{1a}R^{1b})_x$ $-O)$-, or any combinations thereof; W' is absent, $(CH_2)_{1-5}$, $(CH_2)_{1-5}$-O, $(CH_2)_{1-5}$-$C(=O)NH$-$(CH_2)_{1-5}$-O, $(CH_2)_{1-5}$-$C(=O)NH$-$(CH_2)_{1-5}$, -$(CH_2)_{1-5}$-$NHC(=O)$-$(CH_2)_{1-5}$-O, or -$(CH_2)_{1-5}$-$NHC(=O)$-$(CH_2)_{1-5}$-; E^3 is an optionally substituted C_6-C_{10} arylene group, optionally substituted 4- to10-membered heterocycloalkylene, or optionally substituted 5- to 10-membered heteroarylene; X is O, S, or NH; each R^{1a} and R^{1b} are independently H or C_1-C_6 alkyl; r is an integer between 1 and 10; and x is an integer between 1 and 15. In some embodiments, X is O. In some embodiments, X is NH. In some embodiments, E^3 is a C_6-C_{10} arylene group optionally substituted with 1-3 substituents selected from C_1-C_6 alkyl, halogen, OH or amine.

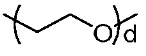
[00203] In some embodiments, E^3 is a phenylene or substituted phenylene.

[00204] In some embodiments, the linker comprise a  ,  ,  , or  .

[00205] In some embodiments, the linker comprises $-X(CH_2)_m(CH_2CH_2O)_n-$, wherein X is -O-, –NH–, or –S–, wherein m is 0 or greater and n is at least 1.

[00206] In some embodiments, the linker comprises  following the second terminus, wherein R_c is selected from a bond, -$N(R^{1a})$-, -O-, and -S-; R_d is selected from -$N(R^{1a})$-, -O-, and -S-; and R_e is independently selected from hydrogen and optionally substituted C_1-C_6 alkyl; and wherein R^{1a} is H or C_1-C_6 alkyl.

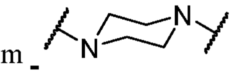
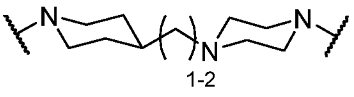
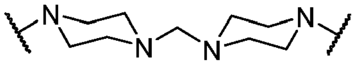
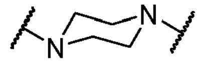
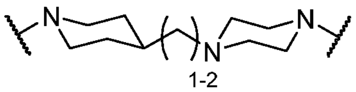
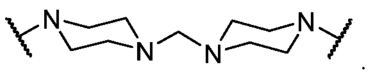
[00207] In some embodiments, the linker comprises one or more structures selected from , , C_1-C_{12} alkyl, arylene, cycloalkylene, heteroarylene, heterocycloalkylene, -O-, -C(=O)NR^{1a}-,-C(=O)-, -NR^{1a}-, -(CH$_2$CH$_2$CH$_2$O)$_y$-, and -(CH$_2$CH$_2$CH$_2$NR^{1a})$_y$-, wherein each d and y are independently 1-10, and each R^{1a} is independently hydrogen or C_1-C_6 alkyl. In some embodiments, d is 4-8.

[00208] In some embodiments, the linker comprises  and each d is independently 3-7. In some embodiments, d is 4-6. In other embodiments, d is between 5-9.

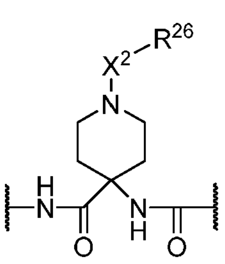
[00209] In some embodiments, the linker comprises –N(R^{1a})(CH$_2$)$_x$N(R^{1b})(CH$_2$)$_x$N–, wherein R^{1a} and R^{1b} are each independently selected from hydrogen or optionally substituted C_1-C_6 alkyl; and each x is independently an integer in the range of 1-6.

[00210] In some embodiments, the linker comprises the linker comprises -(CH$_2$ -C(=O)N(R'')-(CH$_2$)$_q$-N(R')-(CH$_2$)$_q$-N(R'')C(=O)-(CH$_2$)$_x$-C(=O)N(R'')-A^2-, -(CH$_2$)$_x$-C(=O)N(R'')-(CH$_2$ CH$_2$O)$_y$(CH$_2$)$_x$-C(=O)N(R'')-A^2-, -C(=O)N(R'')-(CH$_2$)$_q$-N(R')-(CH$_2$)$_q$-N(R'')C(=O)-(CH$_2$)$_x$-A^2-, -(CH$_2$)$_x$-O-(CH$_2$ CH$_2$O)$_y$-(CH$_2$)$_x$-N(R'')C(=O)-(CH$_2$)$_x$-A^2-, or -N(R'')C(=O)-(CH$_2$)-C(=O)N(R'')-(CH$_2$)$_x$-O(CH$_2$CH$_2$O)$_y$(CH$_2$)$_x$-A^2-; wherein R' is methyl; R'' is hydrogen; each x and y are independently an integer from 1 to 10; each q is independently an integer from 2 to 10; and each A^2 is independently selected from a bond, an optionally substituted C_1-C_{12} alkyl, an optionally substituted C_6-C_{12} arylene, optionally substituted C_3-C_7 cycloalkylene, optionally substituted 5- to 10-membered heteroarylene, and optionally substituted 4- to 10-membered heterocycloalkylene.

[00211] In some embodiments, the linker comprises –(CH$_2$CH$_2$-O)$_{x1}$- or –(CH$_2$CH$_2$-O)$_{x2}$-A^2-(CH$_2$CH$_2$-O)$_{x3}$-, wherein A^2 is an optionally substituted 4- to 10-membered heterocycloalkylene or spirocyclene., and each x_1, x_2, and x_3 is independently an integer from 1-15.

[00212] In some embodiments, A^2 is selected from , , or . In some embodiments, A^2 is . In some embodiments, A^2 is . In some embodiments, A^2 is .

[00213] In some embodiments, A^2 comprises a moiety having the structure:



wherein,

X^2 is absent or -C(=O)-; and

R^{26} is optionally substituted C_1-C_{50} alkyl or optionally substituted C_1-C_{50} heteroalkyl.

[00214] In some embodiments, X^2 is -C(=O)-. In some embodiments, X^2 is absent.

[00215] In some embodiments, R^{26} is C_1-C_{50} alkyl. In some embodiments, R^{26} is C_1-C_{40} alkyl. In some embodiments, R^{26} is C_1-C_{30} alkyl. In some embodiments, R^{26} is C_1-C_{20} alkyl. In some embodiments, R^{26} is C_1-C_{10} alkyl. In some embodiments, R^{26} is C_1-C_{50} heteroalkyl. In some embodiments, R^{26} is C_1-C_{40} heteroalkyl. In some embodiments, R^{26} is C_1-C_{30} heteroalkyl. In some embodiments, R^{26} is C_1-C_{20} heteroalkyl. In some embodiments, R^{26} is C_1-C_{10} heteroalkyl. In some embodiments, the heteroalkyl is polyethylene glycol (PEG).

[00216] In some embodiments, the linker is joined with the first terminus with a group selected from –C(=O)-, -NR^{1a}-, C_1-C_{12} alkyl, -C(=O)NR^{1a}-, and -NR^{1a}C(=O)-; wherein each R^{1a} is independently a hydrogen or optionally substituted C_1-C_{12} alkylene, optionally substituted C_2-C_{10} alkenylene, optionally substituted C_2-C_{10} alkynylene, optionally substituted C_6-C_{10} arylene, optionally substituted C_3-C_7 cycloalkylene, optionally substituted 5- to 10-membered heteroarylene, and optionally substituted 4- to 10-membered heterocycloalkylene.

[00217] In some embodiments, the linker is joined with the first terminus with a group selected from -C(=O)-, -NR^{1a}-, -C(=O)NR^{1a}-, -NR^{1a}C(=O)-, -C(=O)$NR^{1a}C_1$-C_4alkyl-, -NR^{1a}C(=O)-C_1-C_4alkyl-, -C(=O)O-, -OC(=O)-, -O-, -S-, -S(=O)-, -SO_2-, -SO_2NR^{1a}-, -NR^1SO_2-, -P(=O)OH-, -($(CH_2)_x$-O)-, -($(CH_2)_y$-NR^{1a})-, optionally substituted C_1-C_{12} alkylene, optionally substituted C_2-C_{10} alkenylene, optionally substituted C_2-C_{10} alkynylene, optionally substituted C_6-C_{10} arylene, optionally substituted C_3-C_7 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 an optionally substituted C_1-C_6 alkyl.

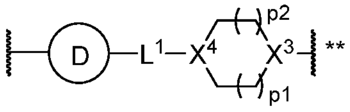
[00218] In some embodiments, the linker is joined with the first terminus with a group selected from -C(=O)-, -NR^{1a}-, $C_{1\text{-}12}$ alkyl, -C(=O)NR^{1a}-, and -NR^{1a}C(=O)-.

[00219] In some embodiments, the linker is joined with the second terminus with a group selected from -C(=O)-, -NR^{1a}-, -C(=O)NR^{1a}-, -NR^{1a}C(=O)-, -C(=O)$NR^{1a}C_1$-C_4 alkyl-, -NR^{1a}C(=O)-C_1-C_4 alkyl-, -C(=O)O-, -OC(=O)-, -O-, -S-, -S(=O)-, -SO_2-, -SO_2NR^{1a}-, -NR^1SO_2-, -P(=O)OH-, -($(CH_2)_x$-O)-, -($(CH_2)_y$-NR^{1a})-, optionally substituted C_1-C_{12} alkylene, optionally substituted C_2-C_{10} alkenylene, optionally substituted C_2-C_{10} alkynylene, optionally substituted C_6-C_{10} arylene, optionally substituted C_3-C_7 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 C_1-C_6 alkyl.

[00220] In some embodiments, the linker is joined with the second terminus with a group selected from -C(=O)-, -NR^{1a}-, -C(=O)NR^{1a}-, -NR^{1a}C(=O)-, -($(CH_2)_x$-O)-, -($(CH_2)_y$-NR^{1a})-, -O-, optionally substituted C_1-C_{12} alkyl, optionally substituted C_6-C_{10} arylene, optionally substituted C_3-C_7 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^1 is independently a hydrogen or optionally substituted C_1-C_6 alkyl.

[00221] In some embodiments, the linker is joined with the second terminus with a group selected from optionally substituted 4- to 10-membered heterocycloalkylene.

[00222] In some embodiments, the linker is joined with the second terminus with a moiety comprising a structure of Formula (C-1), or a pharmaceutically acceptable salt thereof:



Formula (C-1),

wherein,

Ring D is absent or an optionally substituted arylene or optionally substituted heterocycloalkylene;

L^1 is absent or an optionally substituted alkylene, optionally substituted C_2-C_{10} alkenylene, or optionally substituted C_2-C_{10} alkynylene;

each X^3 and X^4 is independently CH or N;

p_1 and p_2 are each independently is 0-3; and

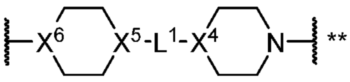
** denotes attachment to the second terminus.

[00223] In some embodiments, Ring D is absent. In some embodiments, Ring D is C_4-C_7 heterocycloalkylene.

[00224] In some embodiments, X^3 is N. In some embodiments, X^3 is CH.

[00225] In some embodiments, X^4 is N. In some embodiments, X^4 is CH.

[00226] In some embodiments, the linker is joined with the second terminus with a moiety comprising a structure of Formula (C-2), or a pharmaceutically acceptable salt thereof:



Formula (C-2),

wherein

L^1 is absent or an optionally substituted alkylene, optionally substituted C_2-C_{10} alkenylene, or optionally substituted C_2-C_{10} alkynylene;

X^4 is independently CH or N;

each X^5 and X^6 is independently N or CH; and

** denotes attachment to the second terminus.

[00227] In some embodiments, each of X^4 and X^5 is independently N or CH; and X^6 is N.

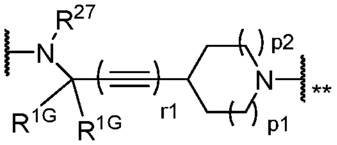
[00228] In some embodiments, L^1 is absent.

[00229] In some embodiments, L^1 is $-(CR^{1G}R^{1G})_x-(\text{alkylene})_2-(CR^{1G}R^{1G})_y-$; wherein x and y are each independently 0 or 1; and each R^{1G} is hydrogen or C_1-C_3 alkyl.

[00230] In some embodiments, L^1 is C_1-C_3 alkylene, C_2-C_4 alkenylene, or C_2-C_4 alkynylene.

[00231] In some embodiments, L^1 is $-CH_2-$, $-CH_2CH_2-$, $-C\equiv C-$, or $-C\equiv C-C\equiv C-$. In some embodiments, L^1 is $-CH_2-$ or $-CH_2CH_2-$. In some embodiments, L^1 is $-C\equiv C-$. In some embodiments, L^1 is $-C\equiv C-C\equiv C-$.

[00232] In some embodiments, the linker is joined with the second terminus with a moiety comprising a structure of Formula (C-3), or a pharmaceutically acceptable salt thereof:



Formula (C-3),

wherein,

p_1 and p_2 are each independently 0-3;

r_1 is 1-3;

R^{27} is an optionally substituted C_1-C_{50} alkyl, optionally substituted C_1-C_{50} heteroalkyl, $-C(=O)(C_1$-C_{50} alkyl), or $-C(=O)(C_1$-C_{50} heteroalkyl), wherein each alkyl and heteroalkyl is optionally substituted

each R^{1G} is independently hydrogen or C_1-C_3 alkyl; and

** denotes attachment to the second terminus.

[00233] In some embodiments, R^{27} is an optionally substituted C_1-C_{50} alkyl or optionally substituted C_1-C_{50} heteroalkyl. In some embodiments, R^{27} is $-C(=O)(C_1$-C_{50} alkyl) or $-C(=O)(C_1$-C_{50} heteroalkyl), wherein each alkyl and heteroalkyl is optionally substituted.

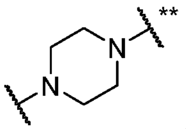
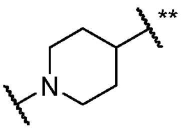
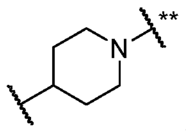
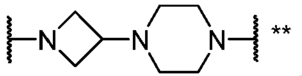
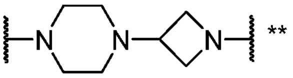
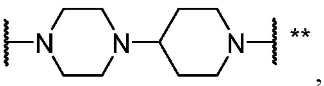
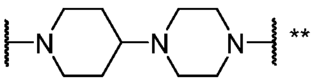
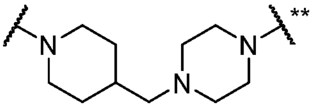
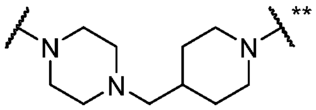
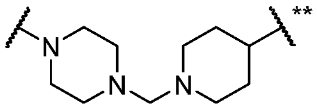
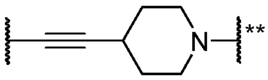
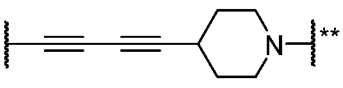
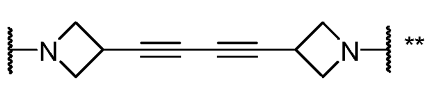
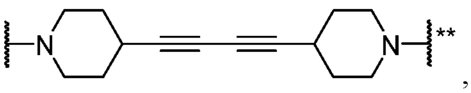
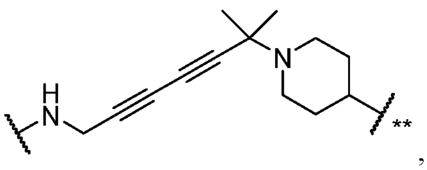
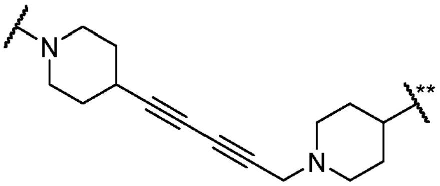
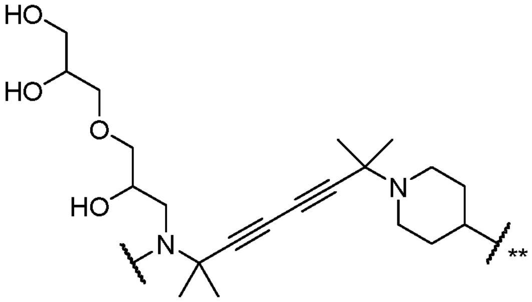
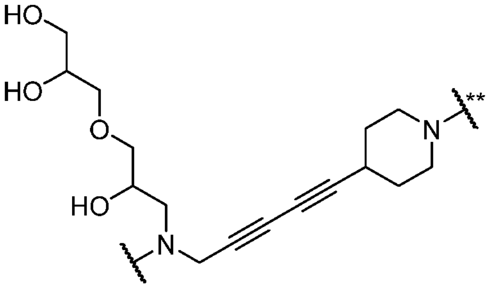
[00234] In some embodiments, R^{27} is C_1-C_{50} alkyl. In some embodiments, R^{27} is C_1-C_{40} alkyl. In some embodiments, R^{27} is C_1-C_{30} alkyl. In some embodiments, R^{27} is C_1-C_{20} alkyl. In some embodiments, R^{27} is C_1-C_{10} alkyl. In some embodiments, R^{27} is C_1-C_{50} heteroalkyl. In some embodiments, R^{27} is C_1-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).

[00235] In some embodiments, each R^{1G} is independently hydrogen. In some embodiments, R^{1G} is independently C_1-C_3 alkyl. In some embodiments, the C_1-C_3 alkyl is methyl, ethyl or propyl. In some embodiments, each R^{1G} is independently methyl.

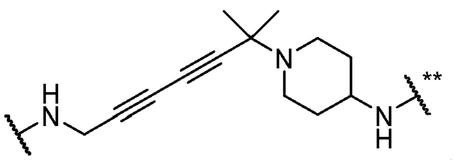
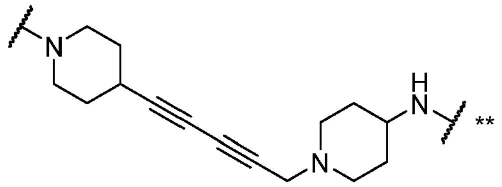
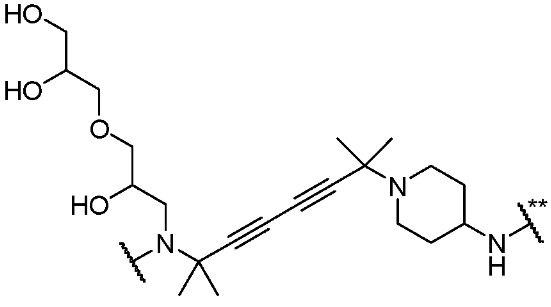
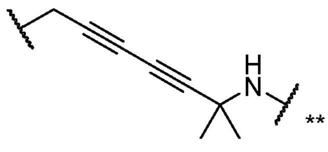
[00236] In some embodiments, p_1 is 0, 1, or 2. In some embodiments, p_1 is 0. In some embodiments, p_1 is 1. In some embodiments, p_1 is 2.

[00237] In some embodiments, r_1 is 1 or 2. In some embodiments, r_1 is 1. In some embodiments, r_1 is 2.

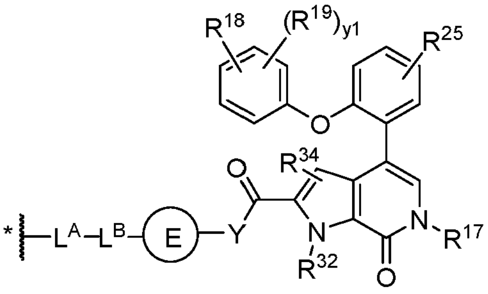
[00238] In some embodiments, the linker is joined with the second terminus with a group selected from:

,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
, and
; wherein ** denotes the connection to the second terminus.

[00239] In some embodiments, the linker is joined with the second terminus with a group selected from:

,
,
, and
; wherein ** denotes the connection to the second terminus.

[00240] In some embodiments, the compound comprises the moiety having the structure of Formula (D-1), or a pharmaceutically acceptable salt thereof:



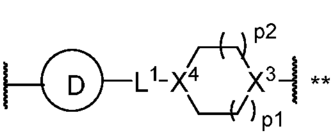
Formula (D-1),

wherein,

Ring E is absent or an optionally substituted 5-6-membered monocyclic aryl or heteroaryl or optionally substituted 4-8 membered heterocycle;

Y is -CH_2NH-, CH_2O-, -NH-, or -O-;

L^A is an optionally substituted alkylene, optionally substituted heteroalkylene, or optionally substituted PEG;

L^B is absent or  , wherein

Ring D is absent or an optionally substituted arylene or optionally substituted heterocycloalkylene;

L^1 is absent or an optionally substituted alkylene, optionally substituted C_2-C_{10} alkenylene, or optionally substituted C_2-C_{10} alkynylene;

each X^3 and X^4 is independently CH or N;

p_1 and p_2 are each independently is 0-3; and

** denotes the point of connection to the ring E or Y;

each X^3 and X^4 is independently CH or N;

R^{17} is hydrogen or C_1-C_6 alkyl;

R^{18} and R^{19} are each independently hydrogen, deuterium, halogen, -CN, -NO_2, an optionally substituted -C_1-C_6 alkyl, optionally substituted C_1-C_6 haloalkyl, or optionally substituted C_1-C_6 hydroxyalkyl;

or R^{18} is -NR^AR^B;

R^{25} is an optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_1-C_6 alkenyl, optionally substituted C_1-C_6 alkynyl, optionally substituted C_1-C_6 hydroxyalkyl, -SO_2R^A, or -$NHSO_2R^A$;

R^{32} is hydrogen or an optionally substituted C_1-C_6 alkyl;

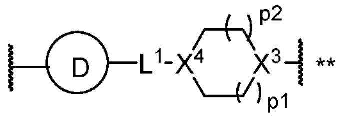
R^{34} is hydrogen, halogen, -OH, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 haloalkyl, or optionally substituted C_1-C_6 hydroxyalkyl;

each R^A and R^B is independently hydrogen, deuterium, an optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl; and

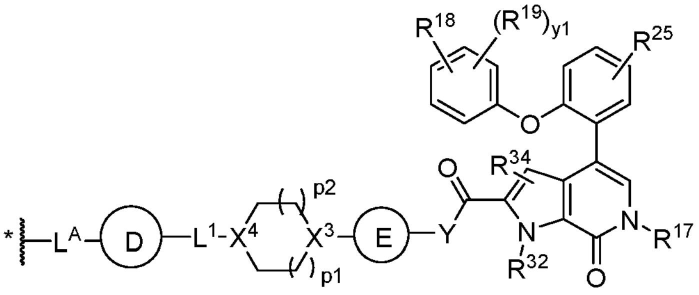
y_1 is 1-3; and

* denotes the attachment to the first terminus.

[00241] In some embodiments, L^B is absent.

[00242] In some embodiments, L^B is .

[00243] In some embodiments, the compound comprises the moiety having the structure of Formula (D-2), or a pharmaceutically acceptable salt thereof:



Formula (D-2),

wherein,

Ring D is absent or an optionally substituted arylene or optionally substituted heterocycloalkylene;

Ring E is absent or an optionally substituted 5-6-membered monocyclic aryl or heteroaryl or optionally substituted 4-8 membered heterocycle;

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

L^A is an optionally substituted alkylene, optionally substituted heteroalkylene, or optionally substituted PEG;

L^1 is absent or an optionally substituted alkylene, optionally substituted C_2-C_{10} alkenylene, or optionally substituted C_2-C_{10} alkynylene;

each X^3 and X^4 is independently CH or N;

R^{17} is hydrogen or C_1-C_6 alkyl;

R^{18} and R^{19} are each independently hydrogen, deuterium, halogen, -CN, $-NO_2$, an optionally substituted -C_1-C_6 alkyl, optionally substituted C_1-C_6 haloalkyl, or optionally substituted C_1-C_6 hydroxyalkyl;

or R^{18} is $-NR^AR^B$;

R^{25} is an optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_1-C_6 alkenyl, optionally substituted C_1-C_6 alkynyl, optionally substituted C_1-C_6 hydroxyalkyl, -SO_2R^A, or $-NHSO_2R^A$;

R^{32} is hydrogen or an optionally substituted C_1-C_6 alkyl;

R^{34} 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;

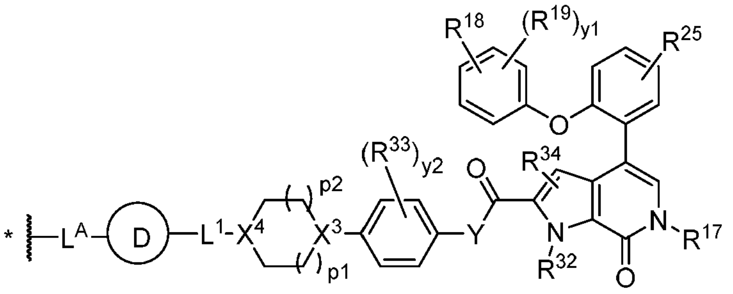
each R^A and R^B is independently hydrogen, deuterium, an optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl;

p_1 and p_2 are each independently is 0-3;

y_1 is 1-3; and

* denotes the attachment to the first terminus.

[00244] In some embodiments, the compound comprises the moiety having the structure of Formula (D-3), or a pharmaceutically acceptable salt thereof:



Formula (D-3),

wherein,

Ring D is absent or an optionally substituted arylene or optionally substituted heterocycloalkylene;

Y is -CH$_2$NH-, CH$_2$O-, -NH-, or -O-;

L^A is an optionally substituted alkylene, optionally substituted heteroalkylene, or optionally substituted PEG;

L^1 is absent or an optionally substituted alkylene, optionally substituted C$_2$-C$_{10}$ alkenylene, or optionally substituted C$_2$-C$_{10}$ alkynylene;

each X^3 and X^4 is independently CH or N;

R^{17} is hydrogen or C$_1$-C$_6$ alkyl;

R^{18} and R^{19} are each independently hydrogen, deuterium, halogen, -CN, -NO$_2$, an optionally substituted -C$_1$-C$_6$ alkyl, optionally substituted C$_1$-C$_6$ haloalkyl, or optionally substituted C$_1$-C$_6$ hydroxyalkyl;

or R^{18} is -NR^{A}R^B;

R^{25} is an optionally substituted C$_1$-C$_6$ alkyl, optionally substituted C$_1$-C$_6$ heteroalkyl, optionally substituted C$_1$-C$_6$ alkenyl, optionally substituted C$_1$-C$_6$ alkynyl, optionally substituted C$_1$-C$_6$ hydroxyalkyl, -SO$_2$R^A, or -NHSO$_2$R^A;

R^{32} is hydrogen or an optionally substituted C$_1$-C$_6$ alkyl;

each R^{33} is independently selected from hydrogen, deuterium, halogen, hydroxyl, amino, nitro, an optionally substituted C$_1$-C$_{20}$ alkyl, optionally substituted C$_1$-C$_{20}$ heteroalkyl, optionally substituted C$_1$-C$_{20}$ haloalkyl, optionally substituted C$_1$-C$_6$ hydroxyalkyl, or optionally substituted (PEG)$_{1\text{-}20}$;

R^{34} 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;

each R^A and R^B is independently hydrogen, deuterium, an optionally substituted C$_1$-C$_6$ alkyl, or optionally substituted C$_1$-C$_6$ heteroalkyl;

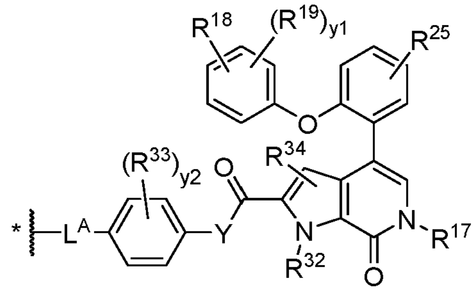
p$_1$ and p$_2$ are each independently is 0-3;

y$_2$ is 1-3;

y$_1$ is 1-3; and

* denotes the attachment to the first terminus.

[00245] In some embodiments, the compound comprises the moiety having the structure of Formula (D-4), or a pharmaceutically acceptable salt thereof:



Formula (D-4),

wherein,

Y is -CH$_2$NH-, CH$_2$O-, -NH-, or -O-;

L^A is an optionally substituted alkylene, optionally substituted heteroalkylene, or optionally substituted PEG;

R^{17} is hydrogen or C$_1$-C$_6$ alkyl;

R^{18} and R^{19} are each independently hydrogen, deuterium, halogen, -CN, -NO$_2$, an optionally substituted -C$_1$-C$_6$ alkyl, optionally substituted C$_1$-C$_6$ haloalkyl, or optionally substituted C$_1$-C$_6$ hydroxyalkyl;

or R^{18} is -NR^{A}R^B;

R^{25} is an optionally substituted C$_1$-C$_6$ alkyl, optionally substituted C$_1$-C$_6$ heteroalkyl, optionally substituted C$_1$-C$_6$ alkenyl, optionally substituted C$_1$-C$_6$ alkynyl, optionally substituted C$_1$-C$_6$ hydroxyalkyl, -SO$_2$R^A, or -NHSO$_2$R^A;

R^{32} is hydrogen or an optionally substituted C$_1$-C$_6$ alkyl;

each R^{33} is independently selected from hydrogen, deuterium, halogen, hydroxyl, amino, nitro, an optionally substituted C$_1$-C$_{20}$ alkyl, optionally substituted C$_1$-C$_{20}$ heteroalkyl, optionally substituted C$_1$-C$_{20}$ haloalkyl, optionally substituted C$_1$-C$_6$ hydroxyalkyl, or optionally substituted (PEG)$_{1\text{-}20}$;

R^{34} 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;

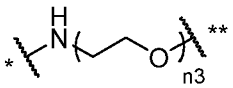
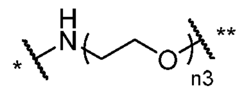
each R^A and R^B is independently hydrogen, deuterium, an optionally substituted C$_1$-C$_6$ alkyl, or optionally substituted C$_1$-C$_6$ heteroalkyl;

y$_2$ is 1-3;

y$_1$ is 1-3; and

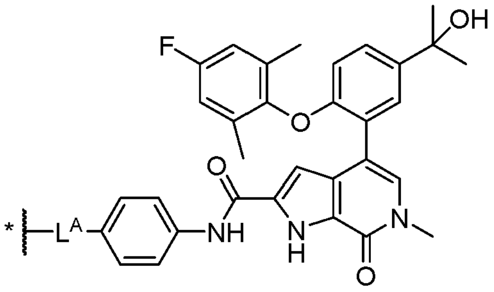
* denotes the attachment to the first terminus.

[00246] In some embodiments, L^A is an optionally substituted C$_1$-C$_{20}$ alkylene or optionally substituted C$_2$-C$_{20}$ heteroalkylene, optionally substituted C$_2$-C$_4$ alkynylene, or optionally substituted PEG$_{1\text{-}20}$, wherein each is optionally substituted with alkyl, amino, cyano, haloalkyl, or oxo (=O).

[00247] In some embodiments, L^A is , wherein n$_3$ is 7, 8, 9, 10, 11, 12, 13, 14, or 15; * denotes the connection to the first terminus; and ** denotes the connection point to the phenyl. In some embodiments, L^A is 

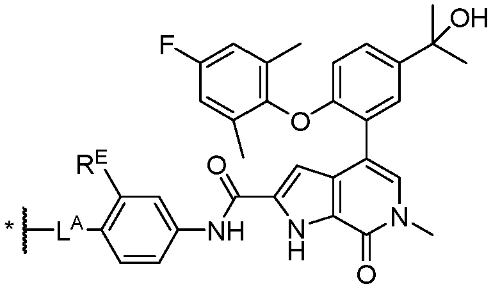
, wherein n_3 is 9, 10, 11, 12, 13, 14, or 15; * denotes the connection to the first terminus; and ** denotes the connection point to the phenyl. In some embodiments, n_3 is 7. In some embodiments, n_3 is 8. In some embodiments, n_3 is 9. In some embodiments, n_3 is 10. In some embodiments, n_3 is 11. In some embodiments, n_3 is 12.

[00248] In some embodiments, the compound comprises the moiety having the structure of Formula (D-5), or a pharmaceutically acceptable salt thereof:



Formula (D-5).

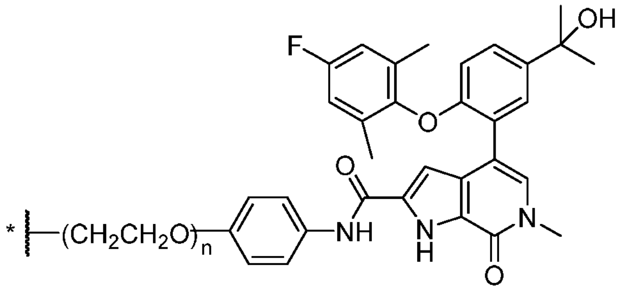
[00249] In some embodiments, the compound comprises the moiety having the structure of Formula (D-6), or a pharmaceutically acceptable salt thereof:



Formula (D-6),

wherein, R^E is -OH, $-(OCH_2CH_2)_m$-OH, or $-(OCH_2CH2)_m$-O(C_1-C_6 alkyl) and m is 1 to 20.

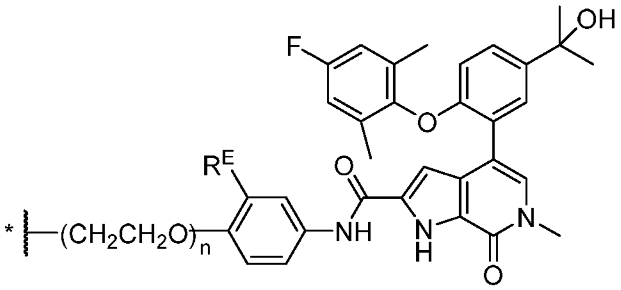
[00250] In some embodiments, the compound comprises the moiety having the structure of Formula (D-7), or a pharmaceutically acceptable salt thereof:



Formula (D-7),

wherein n is 1-20.

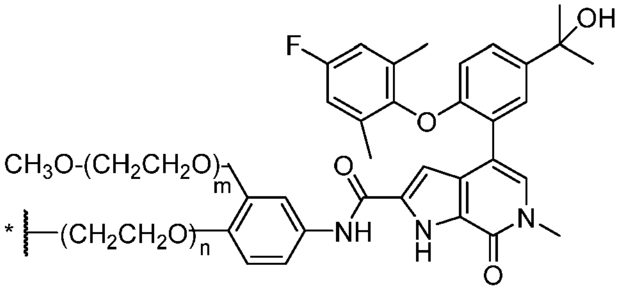
[00251] In some embodiments, the compound comprises the moiety having the structure of Formula (D-8), or a pharmaceutically acceptable salt thereof:



Formula (D-8),

wherein, R^E is -OH, $-(OCH_2CH_2)_m$-OH, or $-(OCH_2CH2)_m$-O(C_1-C_6 alkyl); m is 1 to 20; and n is 1-20.

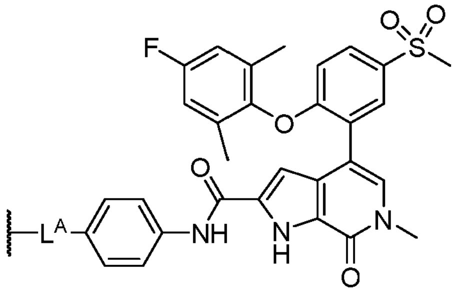
[00252] In some embodiments, the compound comprises the moiety having the structure of Formula (D-9), or a pharmaceutically acceptable salt thereof:



Formula (D-9),

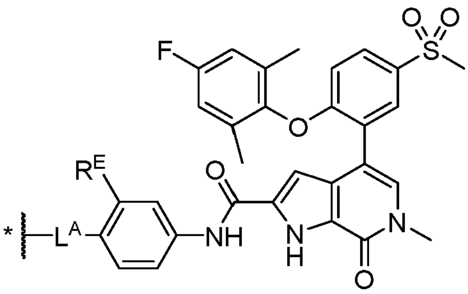
wherein, m is 1-20 and n is 1-20.

[00253] In some embodiments, the compound comprises the moiety having the structure of Formula (D-10), or a pharmaceutically acceptable salt thereof:



Formula (D-10).

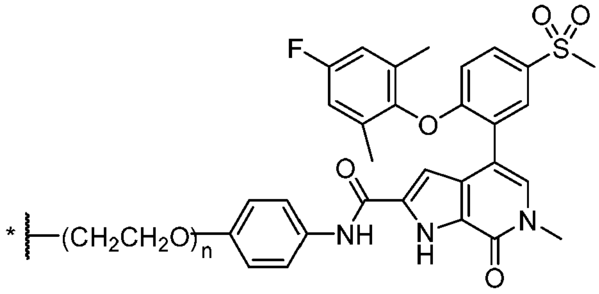
[00254] In some embodiments, the compound comprises the moiety having the structure of Formula (D-11), or a pharmaceutically acceptable salt thereof:



Formula (D-11),

wherein, R^E is -OH, $-(OCH_2CH_2)_m$-OH, or $-(OCH_2CH2)_m$-O(C_1-C_6 alkyl) and m is 1 to 20.

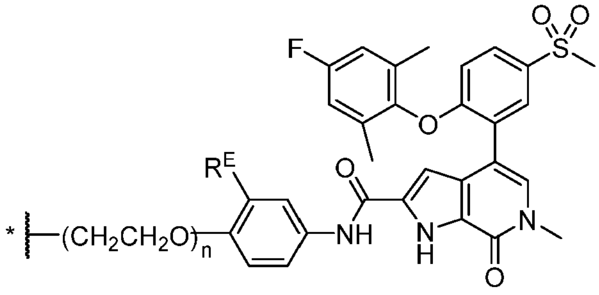
[00255] In some embodiments, the compound comprises the moiety having the structure of Formula (D-12), or a pharmaceutically acceptable salt thereof:



Formula (D-12),

wherein, n is 1-20.

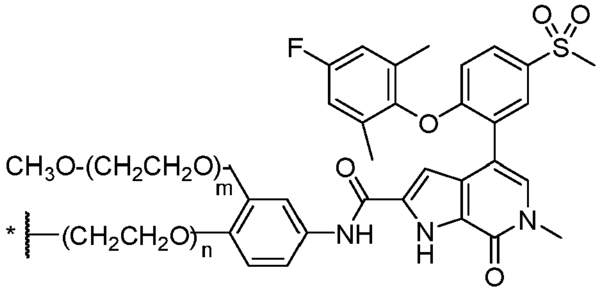
[00256] In some embodiments, the compound comprises the moiety having the structure of Formula (D-13), or a pharmaceutically acceptable salt thereof:



Formula (D-13),

wherein, R^E is -OH, $-(OCH_2CH_2)_m$-OH, or $-(OCH_2CH2)_m-O(C_1-C_6$ alkyl); m is 1 to 20; and n is 1-20.

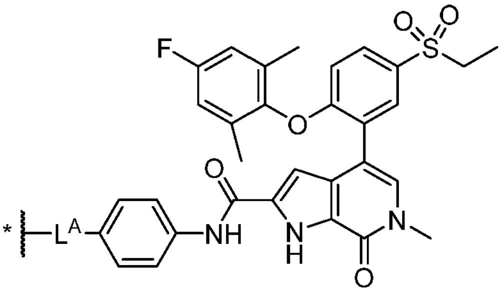
[00257] In some embodiments, the compound comprises the moiety having the structure of Formula (D-14), or a pharmaceutically acceptable salt thereof:



Formula (D-14),

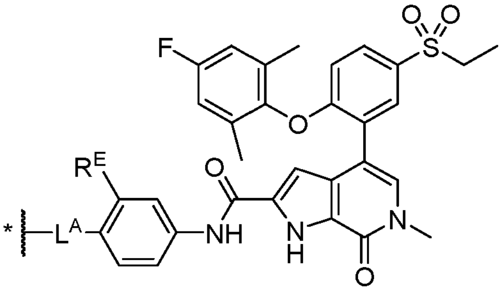
wherein, m is 1 to 20 and n is 1-20.

[00258] In some embodiments, the compound comprises the moiety having the structure of Formula (D-15), or a pharmaceutically acceptable salt thereof:



Formula (D-15).

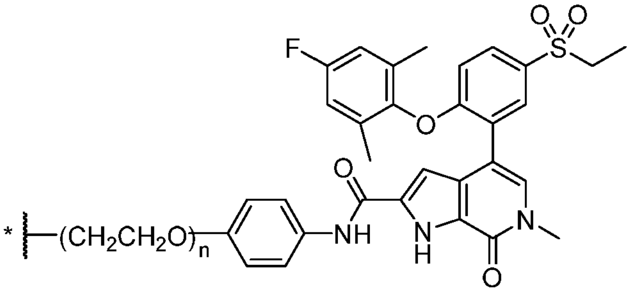
[00259] In some embodiments, the compound comprises the moiety having the structure of Formula (D-16), or a pharmaceutically acceptable salt thereof:



Formula (D-16),

wherein, R^E is -OH, $-(OCH_2CH_2)_m$-OH, or $-(OCH_2CH2)_m$-O(C_1-C_6 alkyl) and m is 1 to 20.

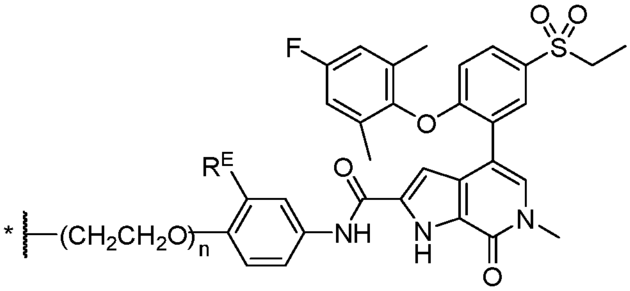
[00260] In some embodiments, the compound comprises the moiety having the structure of Formula (D-17), or a pharmaceutically acceptable salt thereof:



Formula (D-17),

wherein, n is 1-20.

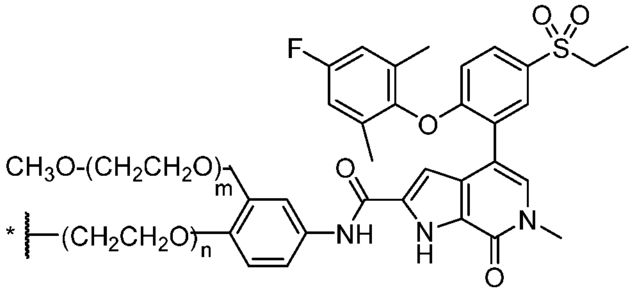
[00261] In some embodiments, the compound comprises the moiety having the structure of Formula (D-18), or a pharmaceutically acceptable salt thereof:



Formula (D-18),

wherein, R^E is -OH, $-(OCH_2CH_2)_m$-OH, or $-(OCH_2CH2)_m$-O(C_1-C_6 alkyl); m is 1 to 20; and n is 1-20.

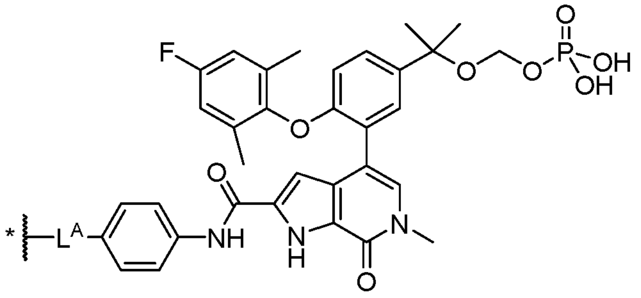
[00262] In some embodiments, the compound comprises the moiety having the structure of Formula (D-19), or a pharmaceutically acceptable salt thereof:



Formula (D-19),

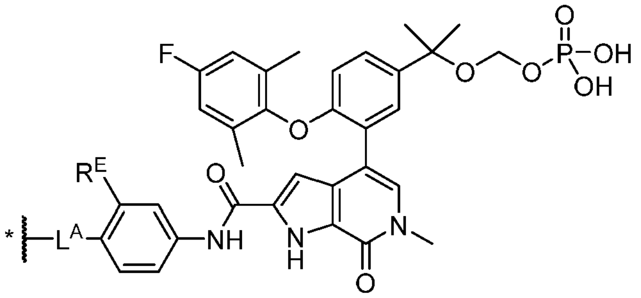
wherein, m is 1 to 20 and n is 1-20.

[00263] In some embodiments, the compound comprises the moiety having the structure of Formula (D-20), or a pharmaceutically acceptable salt thereof:



Formula (D-20).

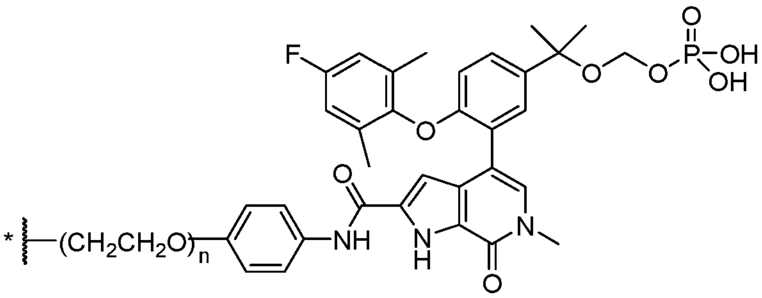
[00264] In some embodiments, the compound comprises the moiety having the structure of Formula (D-21), or a pharmaceutically acceptable salt thereof:



Formula (D-21),

wherein, R^E is -OH, $-(OCH_2CH_2)_m$-OH, or $-(OCH_2CH2)_m$-O(C_1-C_6 alkyl) and m is 1 to 20.

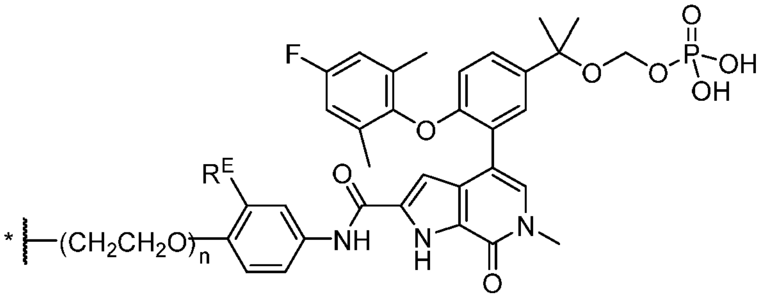
[00265] In some embodiments, the compound comprises the moiety having the structure of Formula (D-22), or a pharmaceutically acceptable salt thereof:



Formula (D-22),

wherein, n is 1-20.

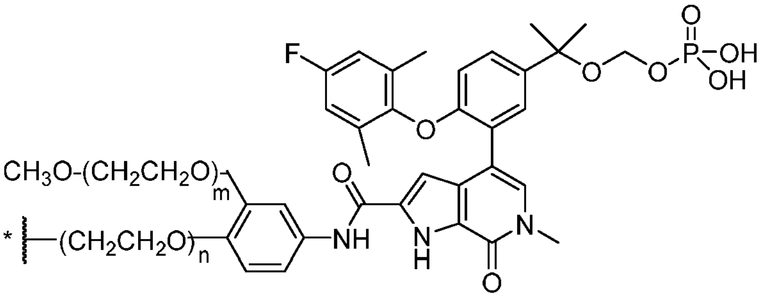
[00266] In some embodiments, the compound comprises the moiety having the structure of Formula (D-23), or a pharmaceutically acceptable salt thereof:



Formula (D-23),

wherein, R^E is -OH, $-(OCH_2CH_2)_m$-OH, or $-(OCH_2CH2)_m$-O(C_1-C_6 alkyl); m is 1 to 20; and n is 1-20.

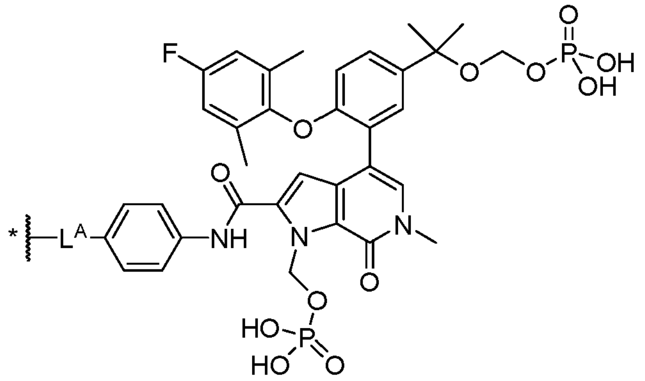
[00267] In some embodiments, the compound comprises the moiety having the structure of Formula (D-24), or a pharmaceutically acceptable salt thereof:



Formula (D-24),

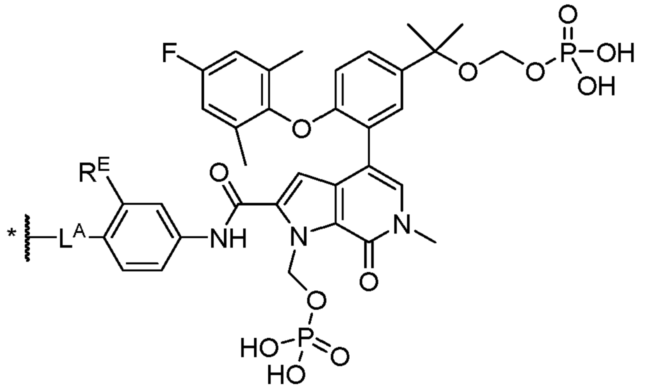
wherein, m is 1 to 20 and n is 1-20.

[00268] In some embodiments, the compound comprises the moiety having the structure of Formula (D-25), or a pharmaceutically acceptable salt thereof:



Formula (D-25).

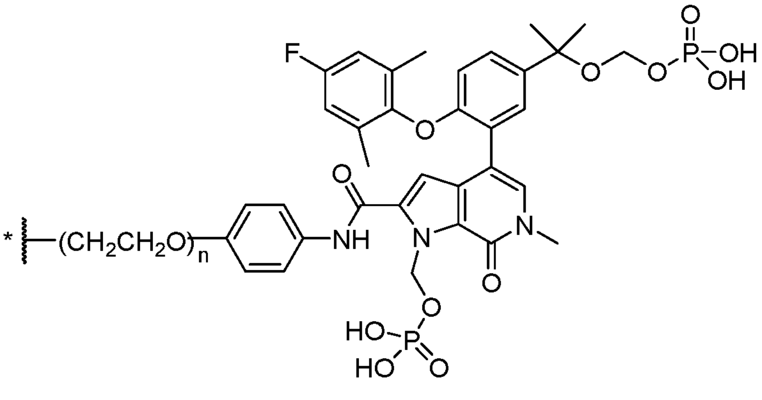
[00269] In some embodiments, the compound comprises the moiety having the structure of Formula (D-26), or a pharmaceutically acceptable salt thereof:



Formula (D-26),

wherein, R^E is -OH, $-(OCH_2CH_2)_m$-OH, or $-(OCH_2CH2)_m$-$O(C_1$-C_6 alkyl) and m is 1 to 20.

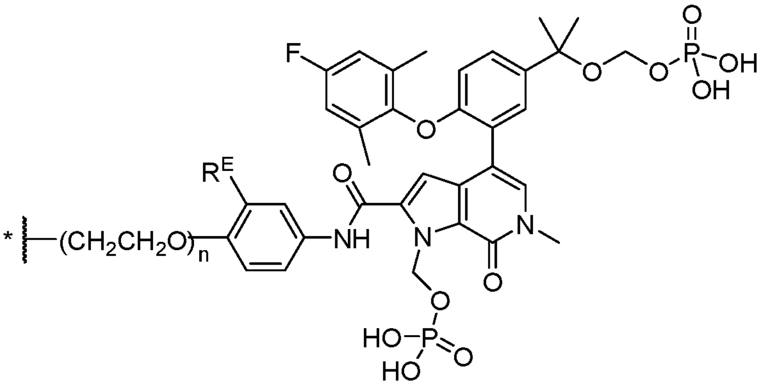
[00270] In some embodiments, the compound comprises the moiety having the structure of Formula (D-27), or a pharmaceutically acceptable salt thereof:



Formula (D-27),

wherein, n is 1-20.

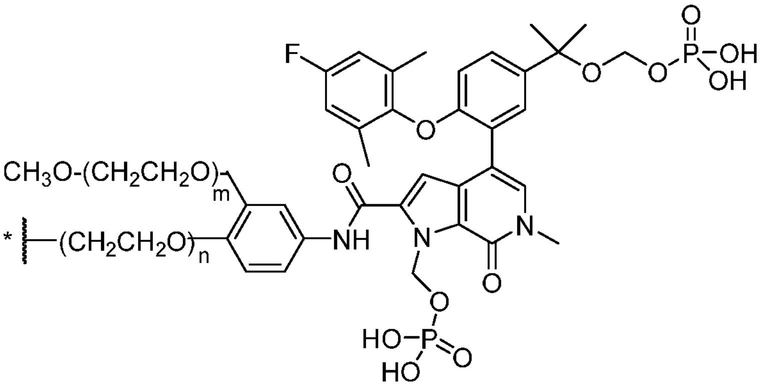
[00271] In some embodiments, the compound comprises the moiety having the structure of Formula (D-28), or a pharmaceutically acceptable salt thereof:



Formula (D-28),

wherein, R^E is -OH, $-(OCH_2CH_2)_m$-OH, or $-(OCH_2CH2)_m-O(C_1-C_6$ alkyl); m is 1 to 20; and n is 1-20.

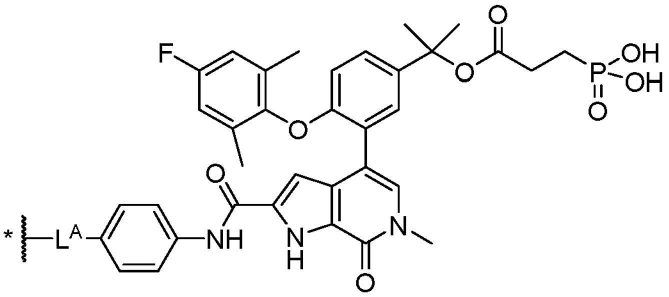
[00272] In some embodiments, the compound comprises the moiety having the structure of Formula (D-29), or a pharmaceutically acceptable salt thereof:



Formula (D-29),

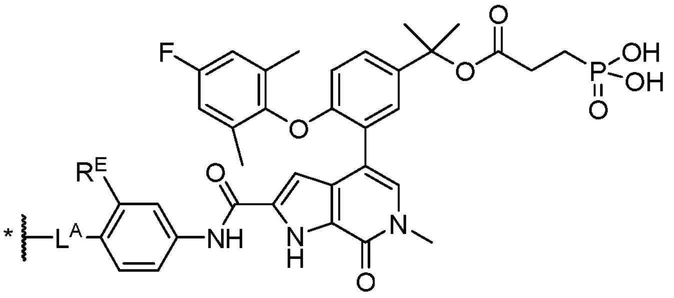
wherein, m is 1 to 20 and n is 1-20.

[00273] In some embodiments, the compound comprises the moiety having the structure of Formula (D-30), or a pharmaceutically acceptable salt thereof:



Formula (D-30).

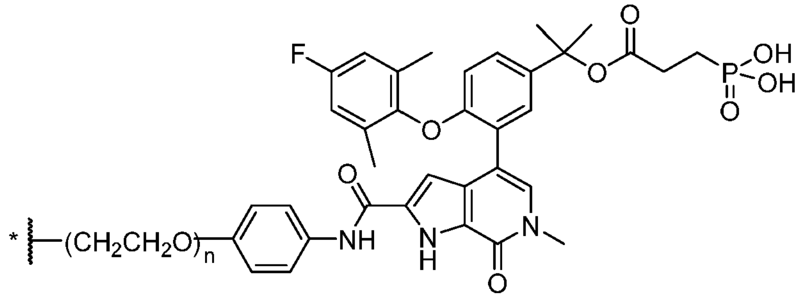
[00274] In some embodiments, the compound comprises the moiety having the structure of Formula (D-31), or a pharmaceutically acceptable salt thereof:



Formula (D-31),

wherein, R^E is -OH, $-(OCH_2CH_2)_m$-OH, or $-(OCH_2CH2)_m-O(C_1-C_6$ alkyl) and m is 1 to 20.

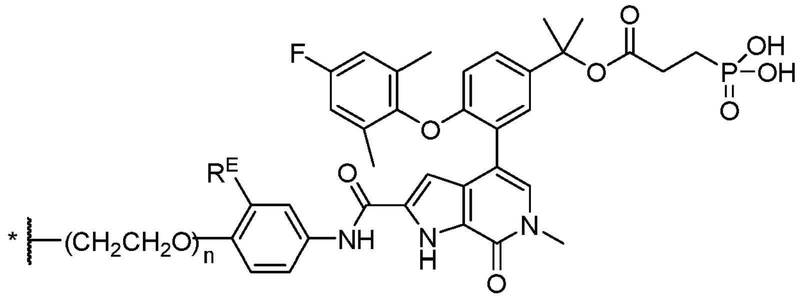
[00275] In some embodiments, the compound comprises the moiety having the structure of Formula (D-32), or a pharmaceutically acceptable salt thereof:



Formula (D-32),

wherein, n is 1-20.

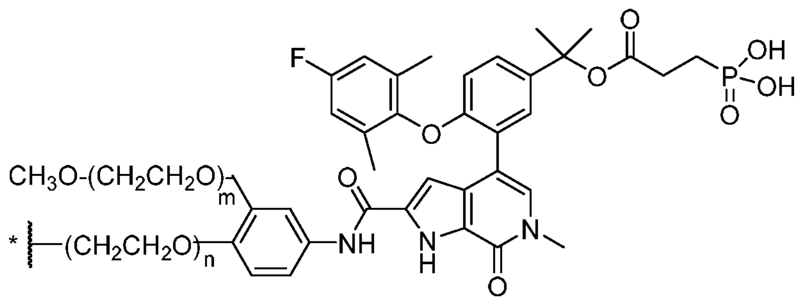
[00276] In some embodiments, the compound comprises the moiety having the structure of Formula (D-33), or a pharmaceutically acceptable salt thereof:



Formula (D-33),

wherein, R^E is -OH, $-(OCH_2CH_2)_m$-OH, or $-(OCH_2CH2)_m-O(C_1-C_6$ alkyl); m is 1 to 20; and n is 1-20.

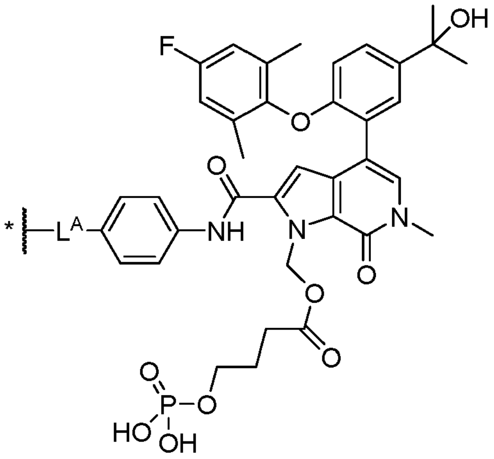
[00277] In some embodiments, the compound comprises the moiety having the structure of Formula (D-34), or a pharmaceutically acceptable salt thereof:



Formula (D-34),

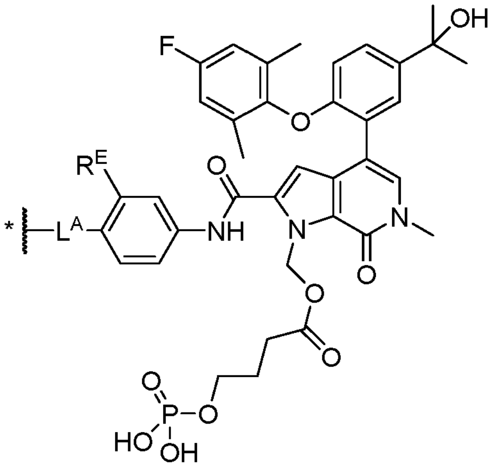
wherein, m is 1 to 20 and n is 1-20.

[00278] In some embodiments, the compound comprises the moiety having the structure of Formula (D-35), or a pharmaceutically acceptable salt thereof:



Formula (D-35).

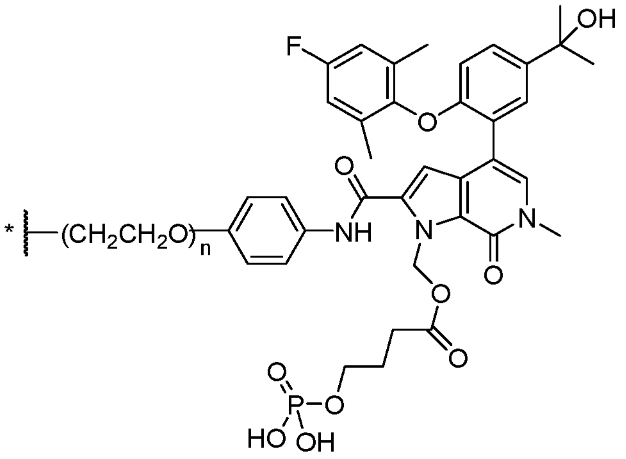
[00279] In some embodiments, the compound comprises the moiety having the structure of Formula (D-36), or a pharmaceutically acceptable salt thereof:



Formula (D-36),

wherein, R^E is -OH, $-(OCH_2CH_2)_m$-OH, or $-(OCH_2CH2)_m$-$O(C_1$-C_6 alkyl) and m is 1 to 20.

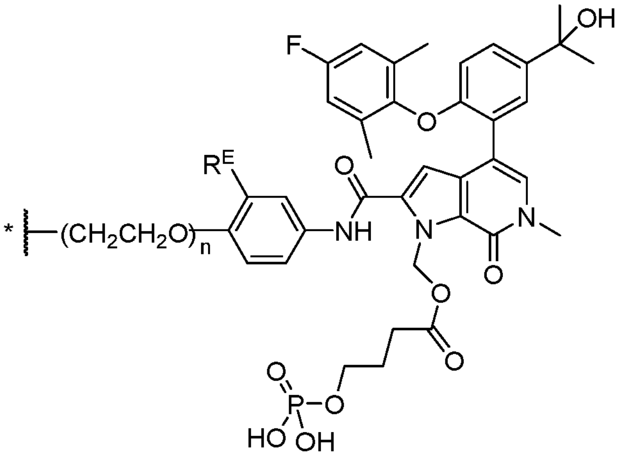
[00280] In some embodiments, the compound comprises the moiety having the structure of Formula (D-37), or a pharmaceutically acceptable salt thereof:



Formula (D-37),

wherein, n is 1-20.

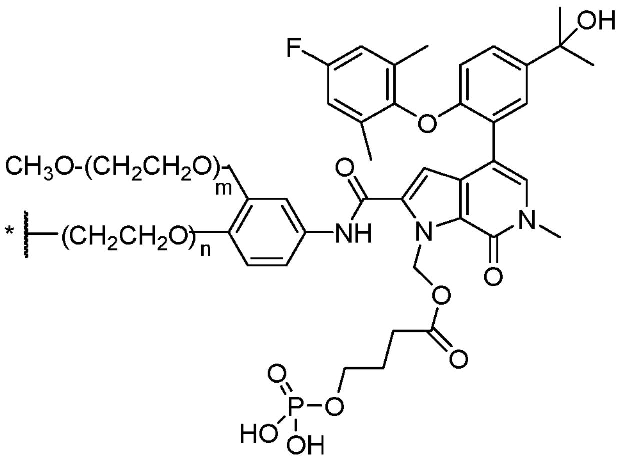
[00281] In some embodiments, the compound comprises the moiety having the structure of Formula (D-38), or a pharmaceutically acceptable salt thereof:



Formula (D-38),

wherein, R^E is -OH, $-(OCH_2CH_2)_m$-OH, or $-(OCH_2CH2)_m$-O(C_1-C_6 alkyl); m is 1 to 20; and n is 1-20.

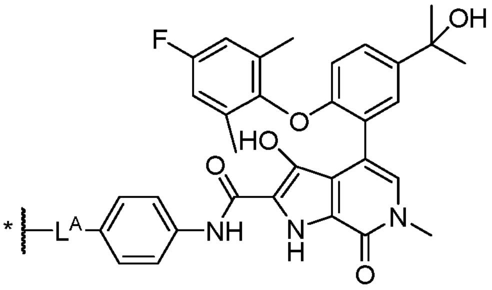
[00282] In some embodiments, the compound comprises the moiety having the structure of Formula (D-39), or a pharmaceutically acceptable salt thereof:



Formula (D-39),

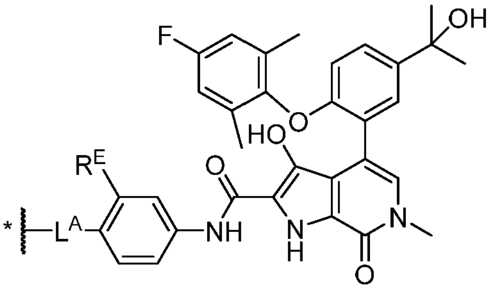
wherein, m is 1 to 20 and n is 1-20.

[00283] In some embodiments, the compound comprises the moiety having the structure of Formula (D-40), or a pharmaceutically acceptable salt thereof:



Formula (D-40).

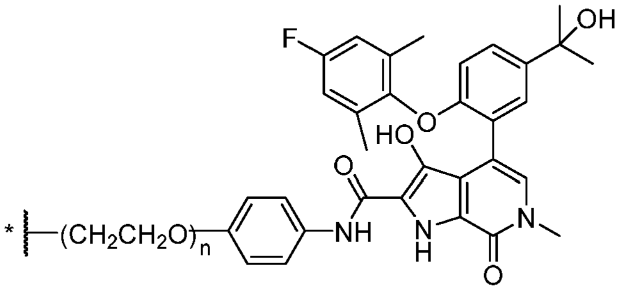
[00284] In some embodiments, the compound comprises the moiety having the structure of Formula (D-41), or a pharmaceutically acceptable salt thereof:



Formula (D-41),

wherein, R^E is -OH, $-(OCH_2CH_2)_m$-OH, or $-(OCH_2CH2)_m-O(C_1-C_6$ alkyl); and m is 1-20.

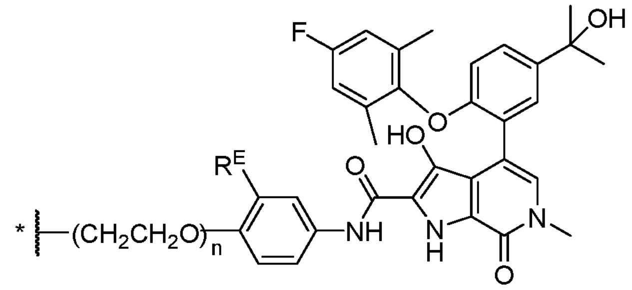
[00285] In some embodiments, the compound comprises the moiety having the structure of Formula (D-42), or a pharmaceutically acceptable salt thereof:



Formula (D-42),

wherein, n is 1-20.

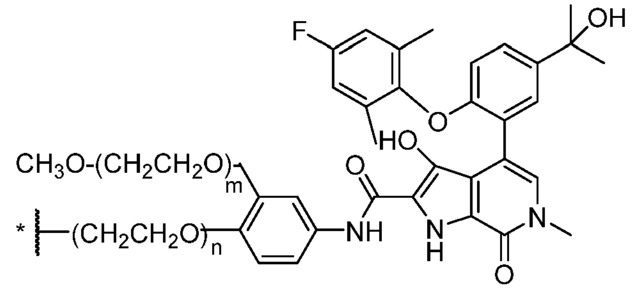
[00286] In some embodiments, the compound comprises the moiety having the structure of Formula (D-43), or a pharmaceutically acceptable salt thereof:



Formula (D-43),

wherein, R^E is -OH, $-(OCH_2CH_2)_m$-OH, or $-(OCH_2CH2)_m$-O(C_1-C_6 alkyl); m is 1 to 20; and n is 1-20.

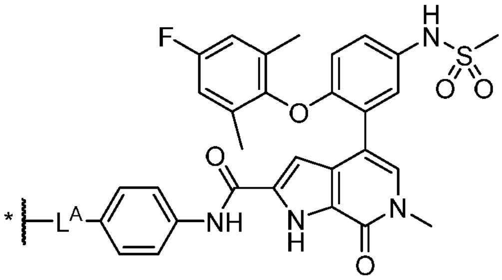
[00287] In some embodiments, the compound comprises the moiety having the structure of Formula (D-44), or a pharmaceutically acceptable salt thereof:



Formula (D-44),

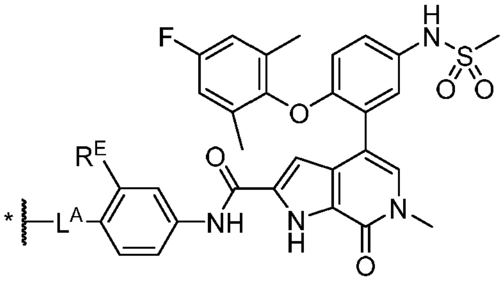
wherein, m is 1 to 20 and n is 1-20.

[00288] In some embodiments, the compound comprises the moiety having the structure of Formula (D-45), or a pharmaceutically acceptable salt thereof:



Formula (D-45).

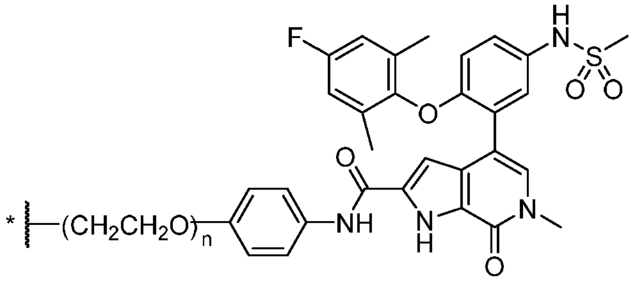
[00289] In some embodiments, the compound comprises the moiety having the structure of Formula (D-46), or a pharmaceutically acceptable salt thereof:



Formula (D-46),

wherein, R^E is -OH, $-(OCH_2CH_2)_m$-OH, or $-(OCH_2CH2)_m$-O(C_1-C_6 alkyl); and m is 1 to 20.

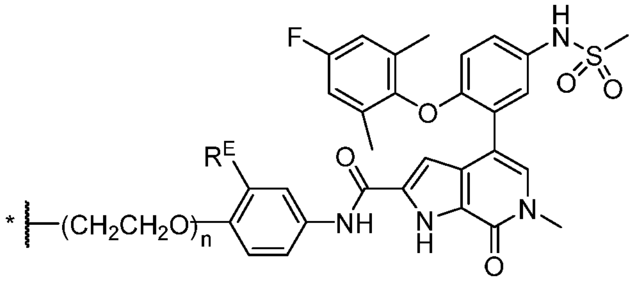
[00290] In some embodiments, the compound comprises the moiety having the structure of Formula (D-47), or a pharmaceutically acceptable salt thereof:



Formula (D-47),

wherein, n is 1-20.

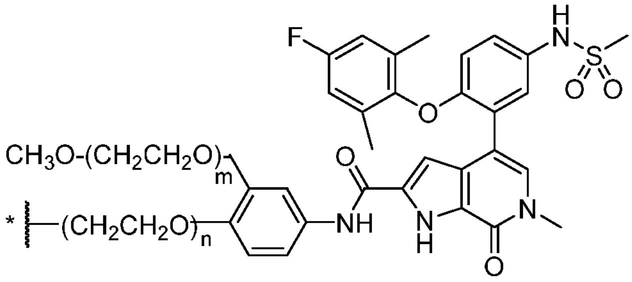
[00291] In some embodiments, the compound comprises the moiety having the structure of Formula (D-48), or a pharmaceutically acceptable salt thereof:



Formula (D-48),

wherein, R^E is -OH, $-(OCH_2CH_2)_m$-OH, or $-(OCH_2CH2)_m-O(C_1-C_6$ alkyl); m is 1 to 20; and n is 1-20.

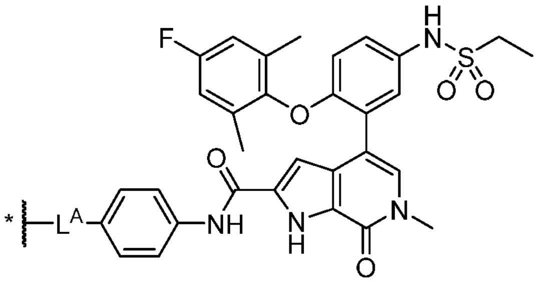
[00292] In some embodiments, the compound comprises the moiety having the structure of Formula (D-49), or a pharmaceutically acceptable salt thereof:



Formula (D-49),

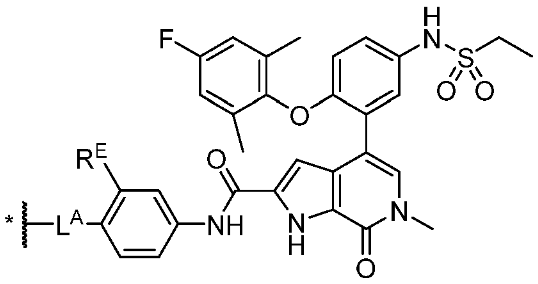
wherein, m is 1 to 20 and n is 1-20.

[00293] In some embodiments, the compound comprises the moiety having the structure of Formula (D-50), or a pharmaceutically acceptable salt thereof:



Formula (D-50).

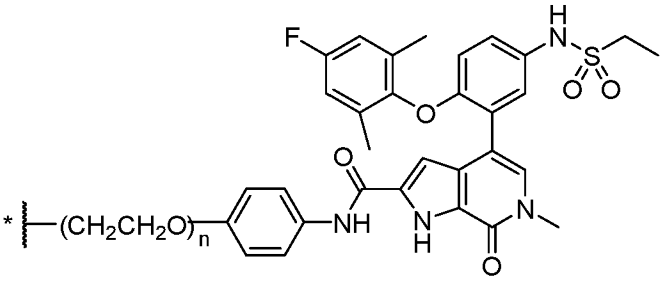
[00294] In some embodiments, the compound comprises the moiety having the structure of Formula (D-51), or a pharmaceutically acceptable salt thereof:



Formula (D-51),

wherein, R^E is -OH, $-(OCH_2CH_2)_m$-OH, or $-(OCH_2CH2)_m$-O(C_1-C_6 alkyl); and m is 1 to 20.

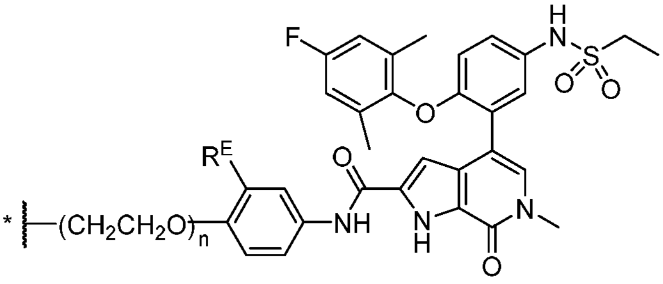
[00295] In some embodiments, the compound comprises the moiety having the structure of Formula (D-52), or a pharmaceutically acceptable salt thereof:



Formula (D-52),

wherein, n is 1-20.

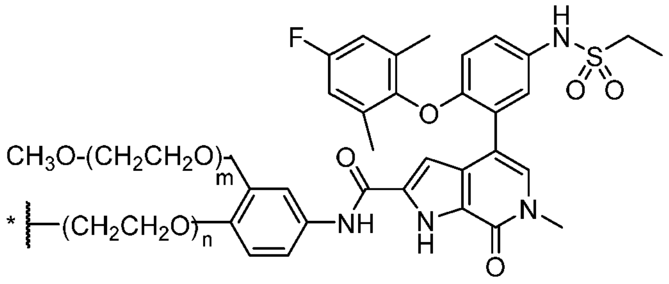
[00296] In some embodiments, the compound comprises the moiety having the structure of Formula (D-53), or a pharmaceutically acceptable salt thereof:



Formula (D-53),

wherein, R^E is -OH, $-(OCH_2CH_2)_m$-OH, or $-(OCH_2CH2)_m$-O(C_1-C_6 alkyl); m is 1 to 20; and n is 1-20.

[00297] In some embodiments, the compound comprises the moiety having the structure of Formula (D-54), or a pharmaceutically acceptable salt thereof:



Formula (D-54),

wherein, m is 1 to 20; and n is 1-20.

[00298] In some embodiments, L^A is an optionally substituted C_2-C_{20} heteroalkylene or optionally substituted PEG_{1-20}, wherein each is optionally substituted with alkyl, amino, cyano, haloalkyl, or oxo (=O). In some embodiments, L^A is C_2-C_{20} heteroalkylene. In some embodiments, L^A is PEG_{1-20}, In some embodiments, L^A is $-NH(CH_2CH_2\text{-}O)_n$- or $-(CH_2CH_2\text{-}O)_n$-, wherein n is 1-20. In some embodiments, L^A is C_2-C_{20} heteroalkylene. In some embodiments, L^A is PEG_{1-20}, In some embodiments, L^A is $-NH(CH_2CH_2\text{-}O)_n$-. In some embodiments, L^A is $-(CH_2CH_2\text{-}O)_n$-.

[00299] In some embodiments, n is 1-15. In some embodiments, n is 7-15. In some embodiments, n is 8-15. In some embodiments, n is 9-15. In some embodiments, n is 7, 8, 9, 10, 11, 12, 13, 14, or 15.

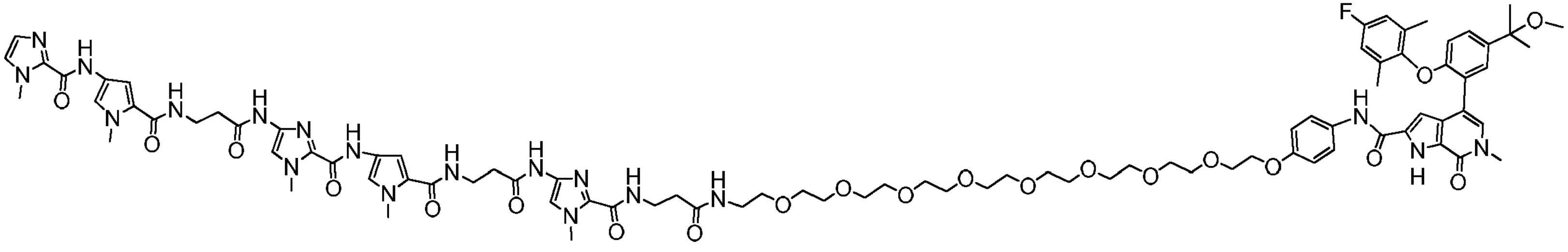
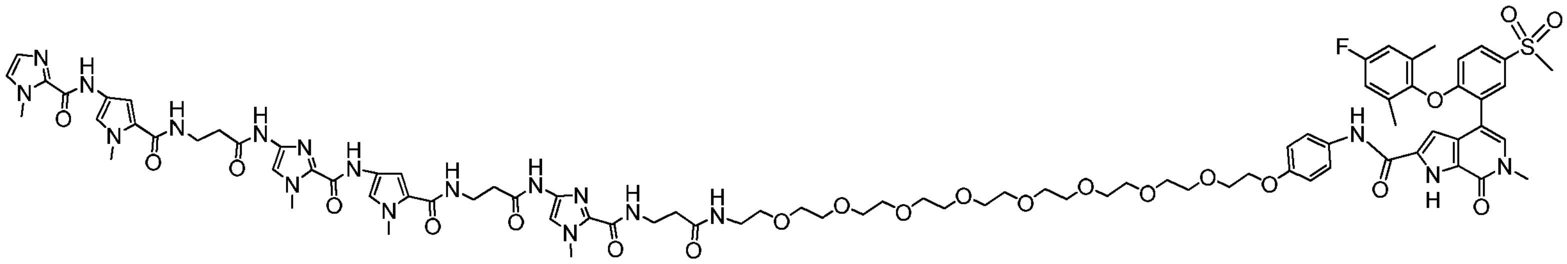
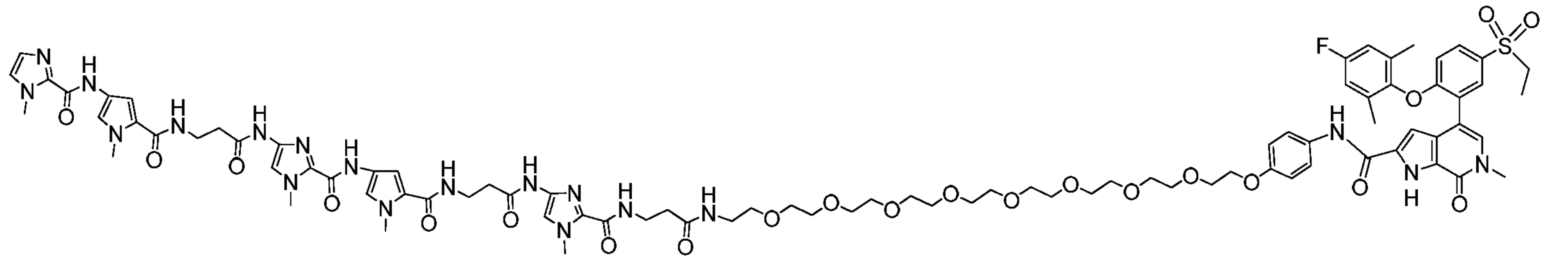
[00300] Also provided are embodiments wherein any embodiment above may be combined with any one or more of these embodiments, provided the combination is not mutually exclusive.

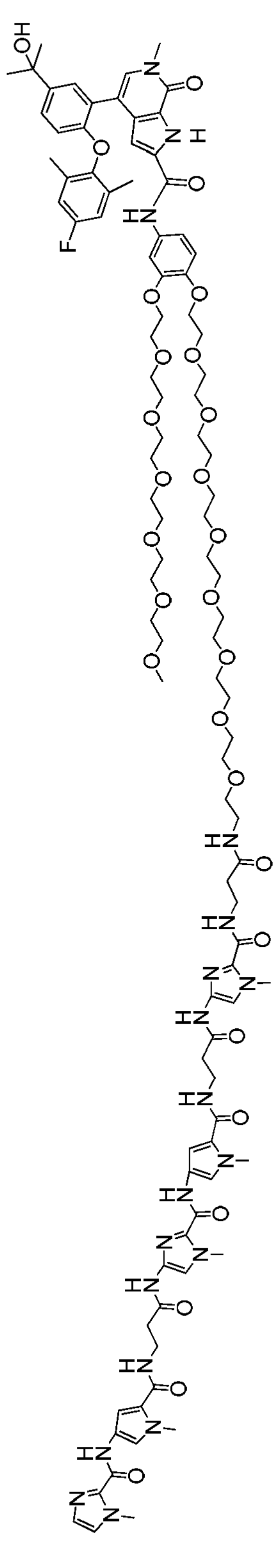
[00301] As used herein, two embodiments are “mutually exclusive” when one is defined to be something which is different than the other. For example, an embodiment wherein two groups combine to form a cycloalkyl is mutually exclusive with an embodiment in which one group is ethyl and the other group is hydrogen. Similarly, an embodiment wherein one group is CH_2 is mutually exclusive with an embodiment wherein the same group is NH.

[00302] In some embodiments, the compound of Formula (I) is a compound selected from Table 3, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound of Formula (I) is a compound selected from Table 3.

[00303] In some embodiments, non-limiting examples of the compounds described herein are presented in Table 3 (next page).

Table 3. Compounds of the disclosure.

Cmpd. No.	**Structure**
1	
2	
3	



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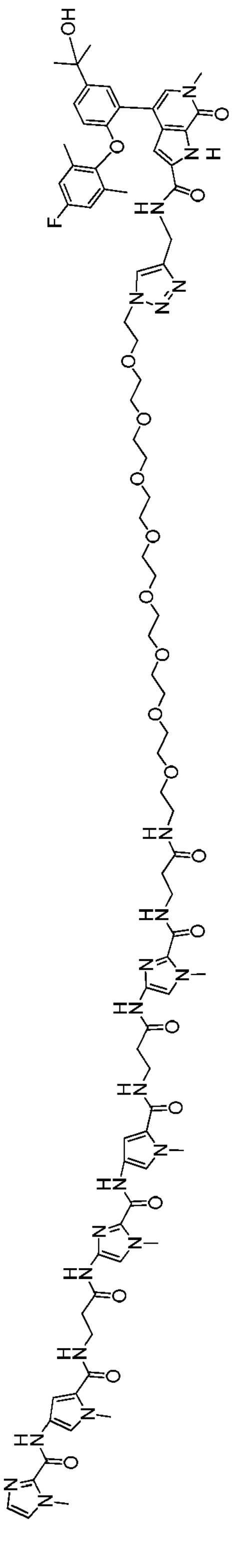

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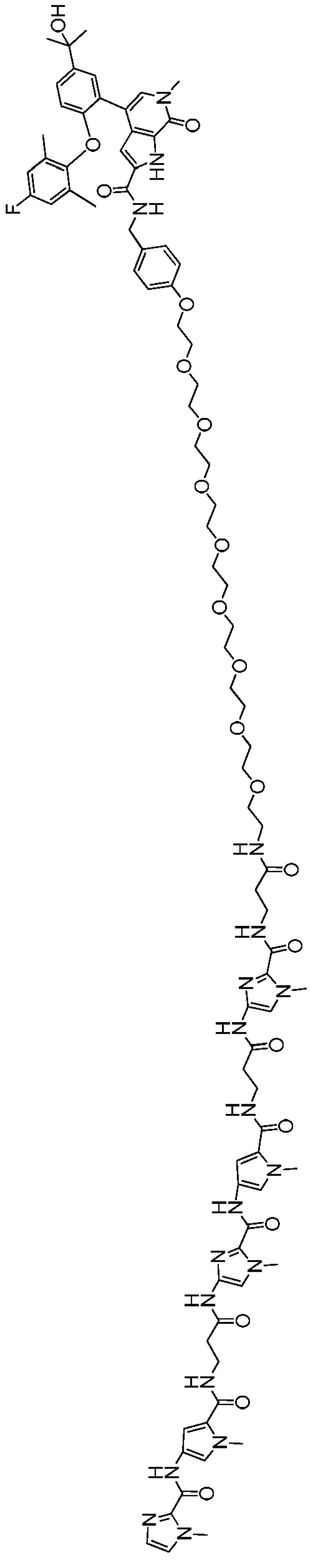

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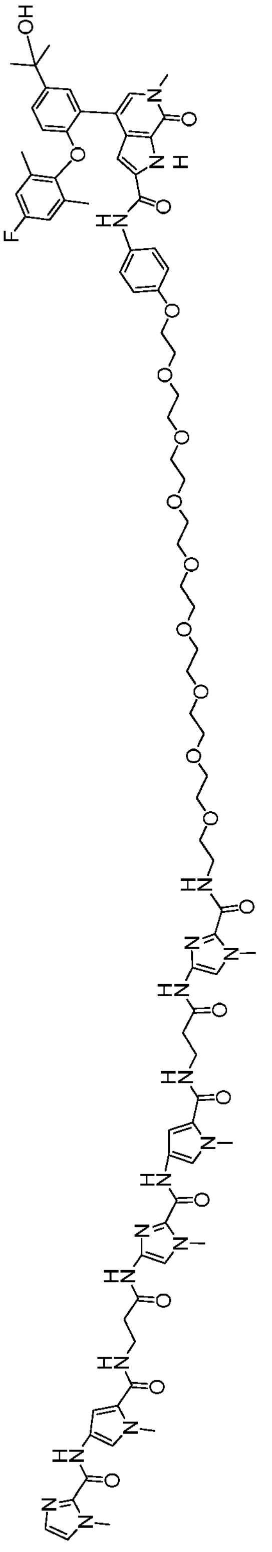

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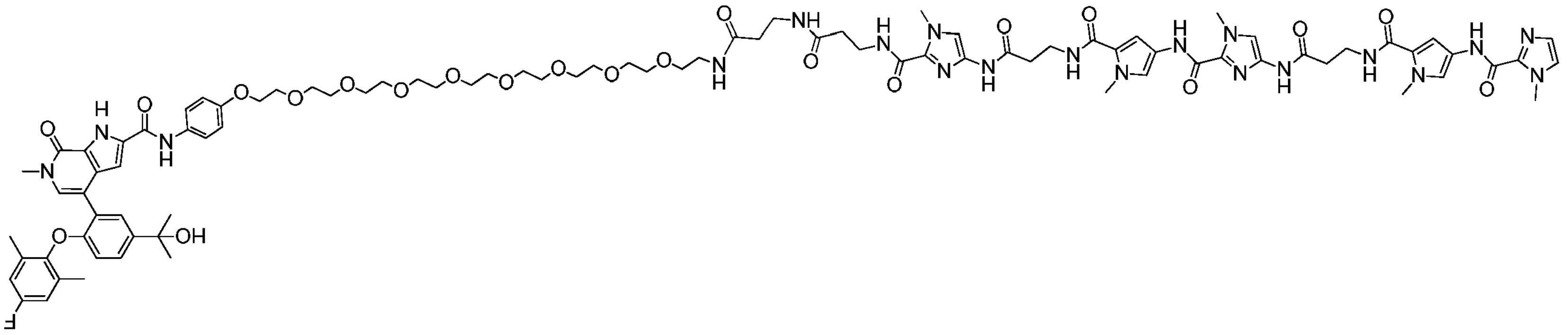

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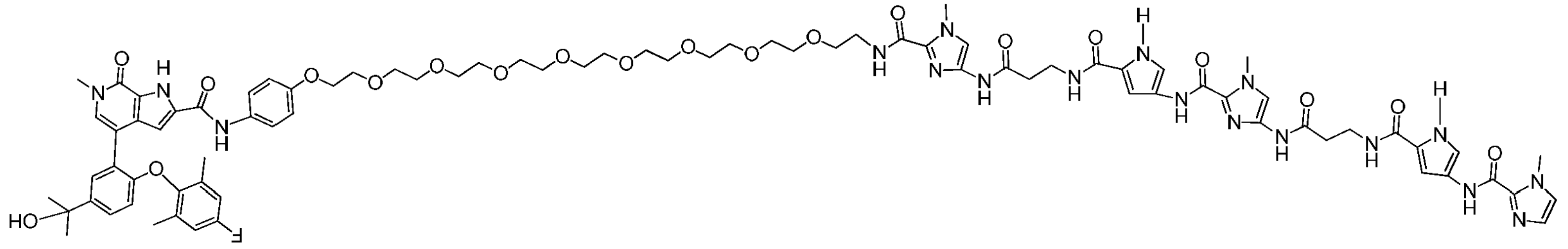

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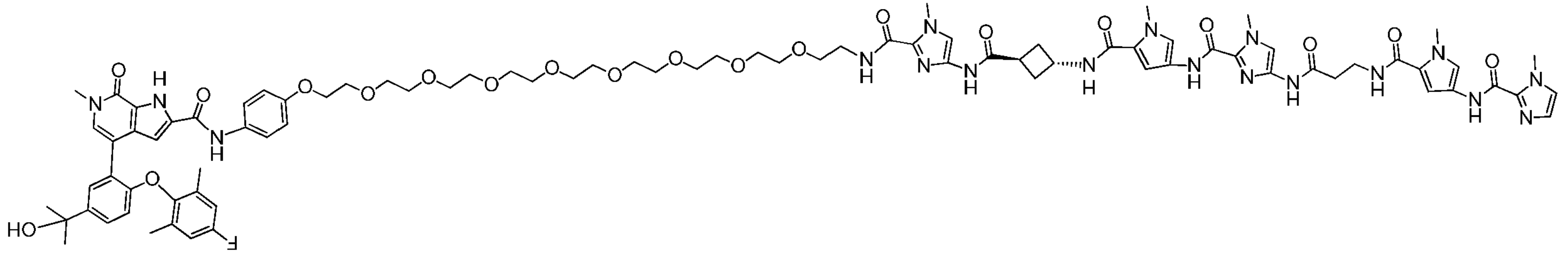

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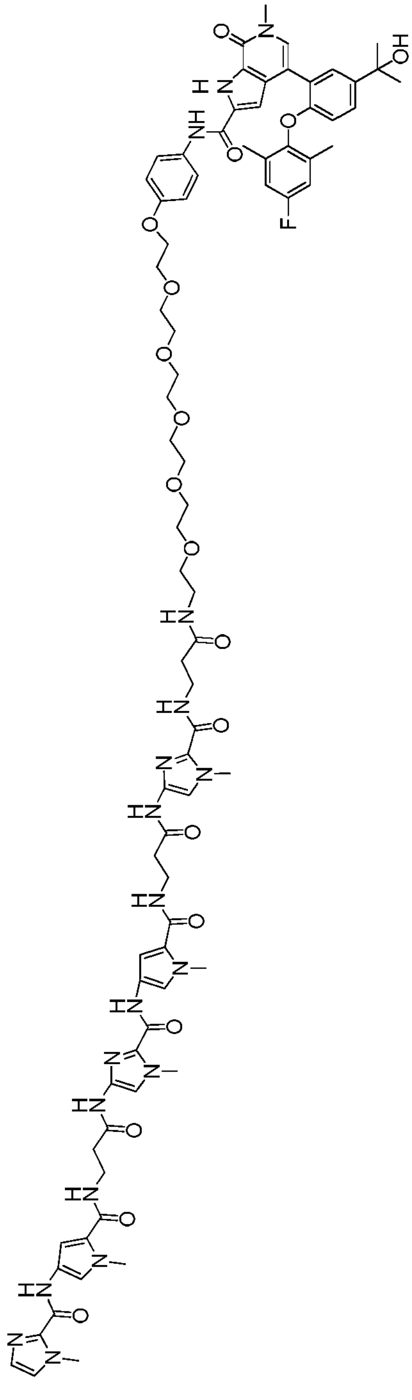

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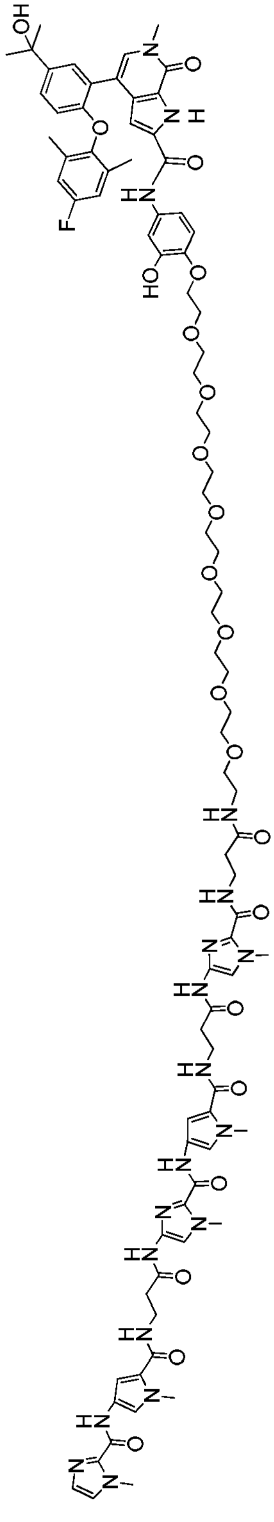

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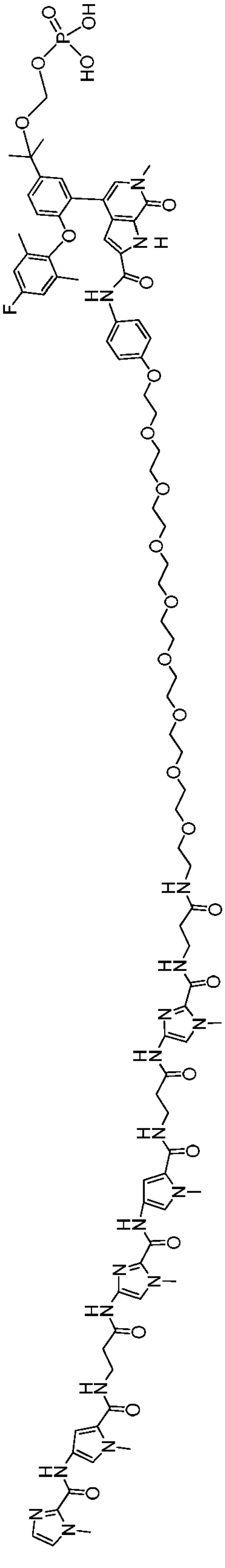

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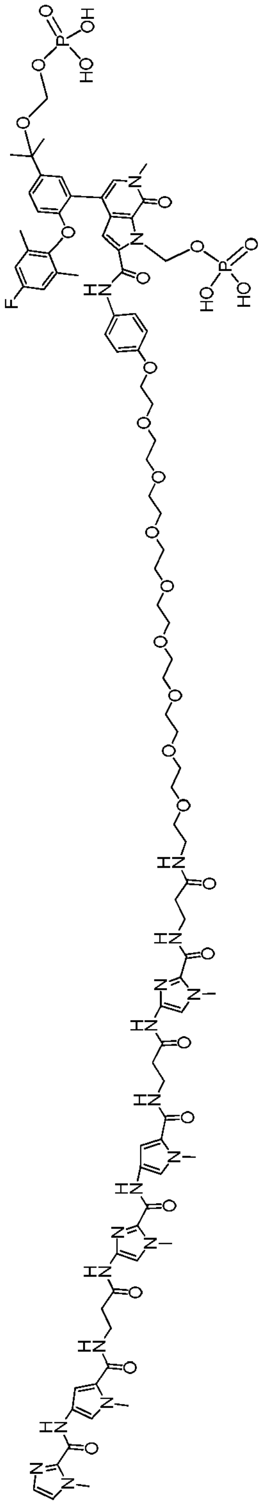

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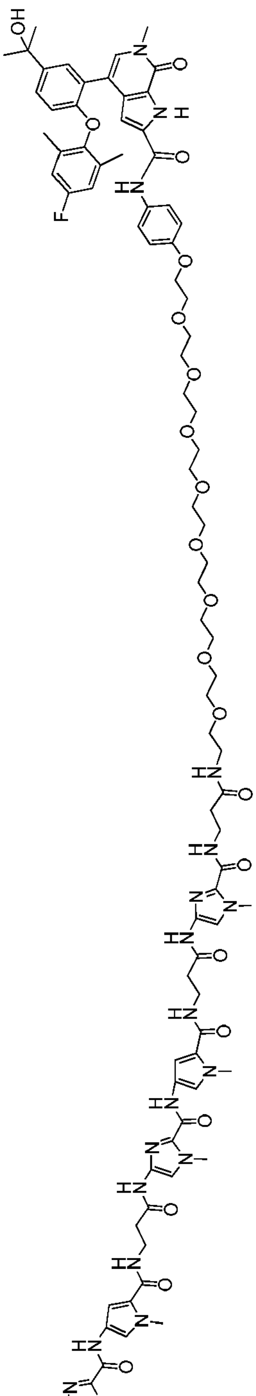

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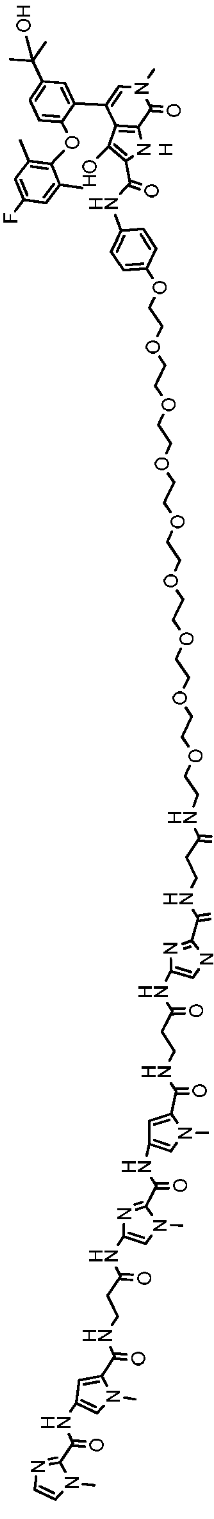

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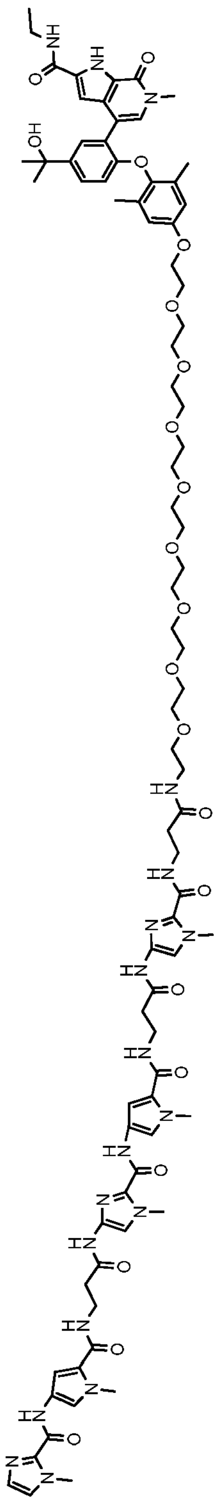

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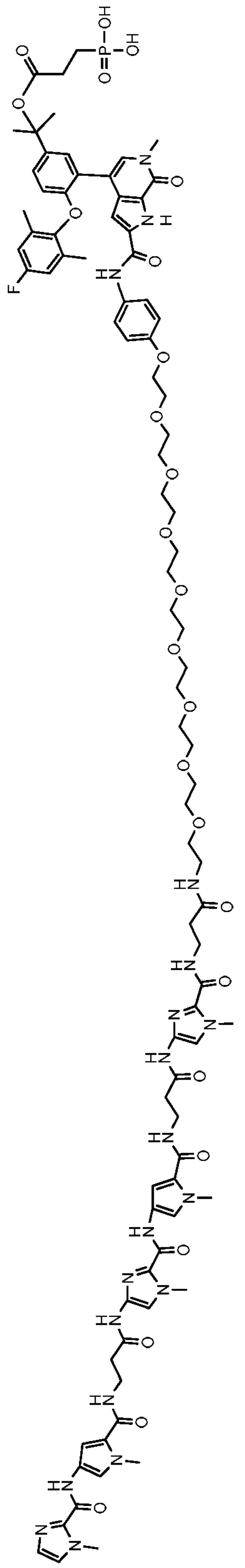

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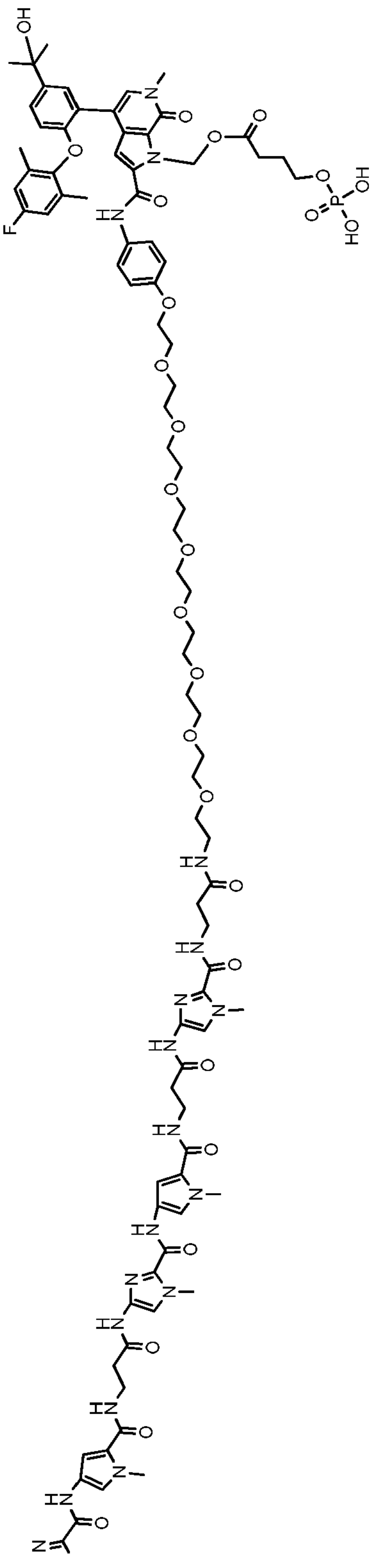

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Further Forms of the Compounds

[00304] In some aspects, a compound disclosed herein possesses one or more stereocenters and each stereocenter exists independently in either the R or S configuration. The compounds presented herein include all diastereomeric, enantiomeric, and epimeric forms as well as the appropriate mixtures thereof. The compounds and methods provided herein include all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the appropriate mixtures thereof. In certain embodiments, compounds described herein are prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds/salts, separating the diastereomers and recovering the optically pure enantiomers. In some embodiments, resolution of enantiomers is carried out using covalent diastereomeric derivatives of the compounds described herein. In another embodiment, diastereomers are separated by separation/resolution techniques based upon differences in solubility. In other embodiments, separation of stereoisomers is performed by chromatography or by the forming diastereomeric salts and separation 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. In one aspect, stereoisomers are obtained by stereoselective synthesis.

[00305] Compounds described herein include isotopically-labeled compounds, which are identical to those recited in the various formulae and structures presented herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into the present compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, sulfur, fluorine, chlorine, and iodine such as, for example, ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{35}S, ^{18}F, ^{36}Cl, and ^{125}I.

[00306] As used herein, the term “isotopic variant” refers to a compound that contains proportions of isotopes at one or more of the atoms that constitute such compound that is greater than natural abundance. For example, an “isotopic variant” of a compound can be radiolabeled, that is, contain one or more radioactive isotopes, or can be labeled with non-radioactive isotopes such as for example, deuterium (^{2}H or D), carbon-13 (^{13}C), nitrogen-15 (^{15}N), or the like. It will be understood that, in a compound where such isotopic substitution is made, the following atoms, where present, may vary, so that for example, any hydrogen may be deuterium, any carbon may be ^{13}C, or any nitrogen may be ^{15}N, and that the presence and placement of such atoms may be determined within the skill of the art.

Methods of Use

[00307] The present disclosure also relates to a method of modulating the transcription of *fxn* comprising the step of contacting *fxn* with a compound as described herein. The cell phenotype, cell proliferation, transcription of *fxn*, production of mRNA from transcription of *fxn*, translation of *fxn*, change in biochemical output produced by the protein coded by *fxn*, or noncovalent binding of the protein coded by *fxn* with a natural binding partner may be monitored. Such methods may be modes of treatment of disease, biological assays, cellular assays, biochemical assays, or the like.

[00308] The compounds described herein can recruit the regulatory molecule to modulate the expression of the defective *fxn* gene and effectively treat and/or and alleviate the symptoms associated with diseases such as Friedreich ataxia.

[00309] Also provided herein is a method of treatment of a disease mediated by transcription of *fxn* comprising the administration of a therapeutically effective amount of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, to a patient in need thereof.

[00310] In some aspects, the present disclosure provides a method of treating or preventing a disease or disorder disclosed herein in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of the present disclosure or a pharmaceutically acceptable salt thereof.

[00311] In some aspects, the present disclosure provides a method of treating a disease or disorder disclosed herein in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of the present disclosure or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the present disclosure.

[00312] In some aspects, the present disclosure provides a method of treating or preventing a disease or disorder disclosed herein in a subject in need thereof, comprising administering to the subject a compound of the present disclosure or a pharmaceutically acceptable salt thereof.

[00313] In some aspects, the present disclosure provides a method of treating a disease or disorder disclosed herein in a subject in need thereof, comprising administering to the subject a compound of the present disclosure or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the present disclosure.

[00314] In some aspects, the present disclosure provides a compound of the present disclosure or a pharmaceutically acceptable salt thereof for use in treating or preventing a disease or disorder disclosed herein.

[00315] In some aspects, the present disclosure provides a compound of the present disclosure or a pharmaceutically acceptable salt thereof for use in treating a disease or disorder disclosed herein.

[00316] In some aspects, the present disclosure provides use of a compound of the present disclosure or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or preventing a disease or disorder disclosed herein.

[00317] In some aspects, the present disclosure provides use of a compound of the present disclosure or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a disease or disorder disclosed herein.

[00318] In some embodiments, the disease or disorder is associated with transcription of *fxn*.

[00319] In some embodiments, the disease is Friedreich's ataxia.

[00320] Also provided is the use of a compound as disclosed herein for the treatment of a disease mediated by transcription of *fxn*.

[00321] Also provided herein is a method of modulation of transcription of *fxn* comprising contacting *fxn* with a compound as disclosed herein, or a pharmaceutically acceptable salt thereof.

[00322] Also provided herein is a method for achieving an effect in a patient comprising the administration of a therapeutically effective amount of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, to a patient, wherein the effect is chosen from improved neural sensation, improved vision, improved balance, improved gait, reduced sensitivity to glucose, and reduced sensitivity to carbohydrates.

[00323] In some embodiments, the compounds described herein can mediate and/or alleviate one or more of muscular atrophy, ataxia, fasciculation, or dementia.

[00324] In some embodiments, the disease or disorder is muscular atrophy.

[00325] In some embodiments, the disease or disorder is ataxia.

[00326] In some embodiments, the disease or disorder is fasciculation.

[00327] In some embodiments, the disease or disorder is dementia.

[00328] Certain compounds of the present disclosure may be effective for treatment of subjects whose genotype has 5 or more repeats of GAA. Certain compounds of the present disclosure may be effective for treatment of subjects whose genotype has 10 or more repeats of GAA. Certain compounds of the present disclosure may be effective for treatment of subjects whose genotype has 20 or more repeats of GAA. Certain compounds of the present disclosure may be effective for treatment of subjects whose genotype has 50 or more repeats of GAA. Certain compounds of the present disclosure may be effective for treatment of subjects whose genotype has 100 or more repeats of GAA. Certain compounds of the present disclosure may be effective for treatment of subjects whose genotype has 200 or more repeats of GAA. Certain compounds of the present disclosure may be effective for treatment of subjects whose genotype has 500 or more repeats of GAA.

[00329] Also provided is a method of modulation of a *fxn*-mediated function in a subject comprising the administration of a therapeutically effective amount of a compound as disclosed herein.

[00330] In certain embodiments, *ex vivo* methods of treatment are provided. *Ex vivo* methods typically include cells, organs, and/or tissues removed from the subject. The cells, organs and/or tissues can, for example, be incubated with the agent under appropriate conditions. The contacted cells, organs, and/or tissues are typically returned to the donor, placed in a recipient, or stored for future use. Thus, the compound is generally in a pharmaceutically acceptable carrier.

[00331] In certain embodiments, administration of the pharmaceutical composition modulates expression of *fxn* within 6 hours of treatment. In certain embodiments, administration of the pharmaceutical composition modulates expression of *fxn* within 24 hours of treatment. In certain embodiments, administration of the pharmaceutical composition modulates expression of *fxn* within 72 hours of treatment.

[00332] In certain embodiments, administration of the pharmaceutical composition causes a 2-fold increase in expression of *fxn*. In certain embodiments, administration of the pharmaceutical composition causes a 5-fold increase in expression of *fxn*. In certain embodiments, administration of the pharmaceutical composition causes a 10-fold increase in expression of *fxn*. In certain embodiments, administration of the pharmaceutical composition causes a 20-fold increase in expression of *fxn*.

[00333] In certain embodiments, administration of the pharmaceutical composition causes a 20% decrease in expression of *fxn*. In certain embodiments, administration of the pharmaceutical composition causes a 50% decrease in expression of *fxn*. In certain embodiments, administration of the pharmaceutical composition causes a 80% decrease in expression of *fxn*. In certain embodiments, administration of the pharmaceutical composition causes a 90% decrease in expression of *fxn*. In certain embodiments, administration of the pharmaceutical composition causes a 95% decrease in expression of *fxn*. In certain embodiments, administration of the pharmaceutical composition causes a 99% decrease in expression of *fxn*.

[00334] In some embodiments, administration of the pharmaceutical composition causes expression of *fxn* to fall within 25% of the level of expression observed for healthy individuals. In some embodiments, administration of the pharmaceutical composition causes expression of *fxn* to fall within 50% of the level of expression observed for healthy individuals. In some embodiments, administration of the pharmaceutical composition causes expression of *fxn* to fall within 75% of the level of expression observed for healthy individuals. In some embodiments, administration of the pharmaceutical composition causes expression of *fxn* to fall within 90% of the level of expression observed for healthy individuals.

Pharmaceutical Compositions and Administration

[00335] Also provided is a method of modulation of a *fxn*-mediated function in a subject comprising the administration of a therapeutically effective amount of a compound as disclosed herein.

[00336] Also provided is a pharmaceutical composition comprising a compound as disclosed herein, together with a pharmaceutically acceptable carrier.

[00337] In certain embodiments, the pharmaceutical composition is formulated for oral administration.

[00338] In certain embodiments, the pharmaceutical composition is formulated for intravenous injection or infusion.

[00339] In certain embodiments, the oral pharmaceutical composition is chosen from a tablet and a capsule.

[00340] In certain embodiments, *ex vivo* methods of treatment are provided. *Ex vivo* methods typically include cells, organs, or tissues removed from the subject. The cells, organs or tissues can, for example, be incubated with the agent under appropriate conditions. The contacted cells, organs, or tissues are typically returned to the donor, placed in a recipient, or stored for future use. Thus, the compound is generally in a pharmaceutically acceptable carrier.

[00341] In certain embodiments, the compound is effective at a concentration less than about 5 μM. In certain embodiments, the compound is effective at a concentration less than about 1 μM. In certain embodiments, the compound is effective at a concentration less than about 400 nM. In certain embodiments, the compound is effective at a concentration less than about 200 nM. In certain embodiments, the compound is effective at a concentration less than about 100 nM. In certain embodiments, the compound is effective at a concentration less than about 50 nM. In certain embodiments, the compound is effective at a concentration less than about 20 nM. In certain embodiments, the compound is effective at a concentration less than about 10 nM.

Combinations and Combinations Treatments

[00342] In certain instances, it may be appropriate to administer at least one of the compounds described herein (or a pharmaceutically acceptable salt thereof) in combination with another therapeutic agent. By way of example only, if one of the side effects experienced by a patient upon receiving one of the compounds herein is hypertension, then it may be appropriate to administer an anti-hypertensive agent in combination with the initial therapeutic agent. Or, by way of example only, the therapeutic effectiveness of one of the compounds described herein may be enhanced by administration of an adjuvant (i.e., by itself the adjuvant may only have minimal therapeutic benefit, but in combination with another therapeutic agent, the overall therapeutic benefit to the patient is enhanced). Or, by way of example only, the benefit of experienced by a patient may be increased by administering one of the compounds described herein with another therapeutic agent (which also includes a therapeutic regimen) that also has therapeutic benefit. By way of example only, in a treatment for diabetes involving administration of one of the compounds described herein, increased therapeutic benefit may result by also providing the patient with another therapeutic agent for diabetes. In any case, regardless of the disease, disorder or condition being treated, the overall benefit experienced by the patient may simply be additive of the two therapeutic agents or the patient may experience a synergistic benefit.

[00343] Specific, non-limiting examples of possible combination therapies include use of certain compounds of the disclosure with an ACE inhibitor.

[00344] In any case, the multiple therapeutic agents (at least one of which is a compound disclosed herein) may be administered in any order or even simultaneously. If simultaneously, the multiple therapeutic agents may be provided in a single, unified form, or in multiple forms (by way of example only, either as a single pill or as two separate pills). One of the therapeutic agents may be given in multiple doses, or both may be given as multiple doses. If not simultaneous, the timing between the multiple doses may be any duration of time ranging from a few minutes to four weeks.

[00345] Thus, in another aspect, certain embodiments provide methods for treating *fxn*-mediated disorders in a human or animal subject in need of such treatment comprising administering to said subject an amount of a compound disclosed herein effective to reduce or prevent said disorder in the subject, in combination with at least one additional agent for the treatment of said disorder that is known in the art. In a related aspect, certain embodiments provide therapeutic compositions comprising at least one compound disclosed herein in combination with one or more additional agents for the treatment of *fxn*-mediated disorders.

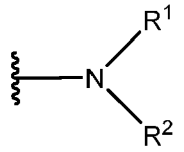
[00346] Besides being useful for human treatment, certain compounds and formulations disclosed herein may also be useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, and the like. More preferred animals include horses, dogs, and cats.

Definitions

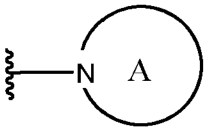
[00347] As used herein, the terms below have the meanings indicated.

[00348] It is to be understood that certain radical naming conventions can include either a mono-radical or a di-radical, depending on the context. For example, where a substituent requires two points of attachment to the rest of the molecule, it is understood that the substituent is a di-radical. For example, a substituent identified as alkyl that requires two points of attachment includes di-radicals such as $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH(CH_3)CH_2-$, and the like. Other radical naming conventions clearly indicate that the radical is a di-radical such as "alkylene," "alkenylene," "arylene", "heteroarylene."

[00349] When two R groups are said to form a ring (e.g., a carbocyclyl, heterocyclyl, aryl, or heteroaryl ring) "together with the atom to which they are attached," it is meant that the collective unit of the atom and the two R groups are the recited ring. The ring is not otherwise limited by the definition of each R group when taken individually. For example, when the following substructure is present:

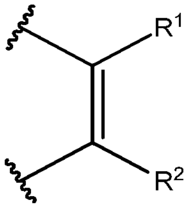


and R^1 and R^2 are defined as selected from the group consisting of hydrogen and alkyl, or R^1 and R^2 together with the nitrogen to which they are attached form a heterocyclyl, it is meant that R^1 and R^2 can be selected from hydrogen or alkyl, or alternatively, the substructure has structure:

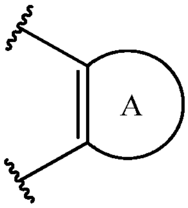


where ring A is a heteroaryl ring containing the depicted nitrogen.

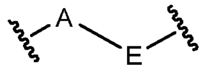
[00350] Similarly, when two "adjacent" R groups are said to form a ring "together with the atom to which they are attached," it is meant that the collective unit of the atoms, intervening bonds, and the two R groups are the recited ring. For example, when the following substructure is present:



and R^1 and R^2 are defined as selected from the group consisting of hydrogen and alkyl, or R^1 and R^2 together with the atoms to which they are attached form an aryl or carbocyclyl, it is meant that R^1 and R^2 can be selected from hydrogen or alkyl, or alternatively, the substructure has structure:



where A is an aryl ring or a carbocyclyl containing the depicted double bond.

[00351] Wherever a substituent is depicted as a di-radical (*i.e.*, has two points of attachment to the rest of the molecule), it is to be understood that the substituent can be attached in any directional configuration unless otherwise indicated. Thus, for example, a substituent depicted as –AE– or  includes the substituent being oriented such that the **A** is attached at the leftmost attachment point of the molecule as well as the case in which **A** is attached at the rightmost attachment point of the molecule.

[00352] 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.).

[00353] The term "about," as used herein, is intended to qualify the numerical values which it modifies, denoting such a value as variable within a margin of error. When no particular margin of error, such as a standard deviation to a mean value given in a chart or table of data, is recited, the term "about" should be understood to mean that range which would encompass the recited value and the range which would be included by rounding up or down to that figure as well, taking into account significant figures.

[00354] 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.

[00355] 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 beta-alanine or dimethylaminopropylamine during synthesis of the polyamide by methods well known in the art.

[00356] The term "linker" refers to a chain of at least 10 contiguous atoms. In certain embodiments, the linker contains no more than 20 non-hydrogen atoms. In certain embodiments, the linker contains no more than 40 non-hydrogen atoms. In certain 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 certain 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 certain 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 certain embodiments, the linker forms a thioester or thioether bond with at least one of the two other groups to which it is attached. In certain embodiments, the linker forms a direct carbon-carbon bond with at least one of the two other groups to which it is attached. In certain embodiments, the linker forms an amine or amide bond with at least one of the two other groups to which it is attached. In certain embodiments, the linker comprises $-(CH_2OCH_2)$- units. In certain embodiments, the linker comprises $-(CH(CH_3)OCH_2)$- units. In certain embodiments, the linker comprises $-(CH_2NR_NCH_2)$ units, for $R_N = C_{1-4}$alkyl. In certain embodiments, the linker comprises an arylene, cycloalkylene, or heterocycloalkylene moiety.

[00357] The term "spacer" refers to a chain of at least 5 contiguous atoms. In certain embodiments, the spacer contains no more than 10 non-hydrogen atoms. In certain embodiments, the spacer contains atoms chosen from C, H, N, O, and S. In certain embodiments, the spacer forms amide bonds with the two other groups to which it is attached. In certain embodiments, the spacer comprises $-(CH_2OCH_2)$- units. In certain embodiments, the spacer comprises $-(CH_2NR_NCH_2)$- units, for $R_N = C_{1-4}$alkyl. In certain embodiments, the spacer contains at least one positive charge at physiological pH.

[00358] The term "turn component" refers to a chain of about 4 to 10 contiguous atoms. In certain embodiments, the turn component contains atoms chosen from C, H, N, O, and S. In certain embodiments, the turn component forms amide bonds with the two other groups to which it is attached. In certain embodiments, the turn component contains at least one positive charge at physiological pH.

[00359] The terms "nucleic acid and "nucleotide" refer to ribonucleotide and deoxyribonucleotide, and analogs thereof, well known in the art.

[00360] 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.

[00361] 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.

[00362] 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.

[00363] The term "acyl," as used herein, alone or in combination, refers to a carbonyl attached to an alkenyl, alkyl, aryl, cycloalkyl, heteroaryl, heterocycle, or any other moiety were the atom attached to the carbonyl is carbon. An "acetyl" group refers to a $-C(=O)CH_3$ group. An "alkylcarbonyl" or "alkanoyl" group refers to an alkyl group attached to the parent molecular moiety through a carbonyl group. Examples of such groups include methylcarbonyl and ethylcarbonyl. Examples of acyl groups include formyl, alkanoyl and aroyl.

[00364] The term "alkenyl," as used herein, alone or in combination, refers to a straight-chain or branched-chain hydrocarbon radical having one or more double bonds and containing from 2 to 20 carbon atoms. In certain embodiments, said alkenyl will comprise from 2 to 6 carbon atoms. The term “alkenylene” refers to a carbon-carbon double bond system attached at two or more positions such as ethenylene [(-CH=CH-),(-C::C-)]. Examples of suitable alkenyl radicals include ethenyl, propenyl, 2-methylpropenyl, 1,4-butadienyl and the like. Unless otherwise specified, the term “alkenyl” may include “alkenylene” groups.

[00365] The term “alkoxy,” as used herein, alone or in combination, refers to an alkyl ether radical, wherein the term alkyl is as defined below. Examples of suitable alkyl ether radicals include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, and the like.

[00366] The term “alkyl,” as used herein, alone or in combination, refers to a straight-chain or branched-chain alkyl radical containing from 1 to 20 carbon atoms. In certain embodiments, said alkyl will comprise from 1 to 10 carbon atoms. In further embodiments, said alkyl will comprise from 1 to 8 carbon atoms. Alkyl groups may be optionally substituted as defined herein. Examples of alkyl radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl, octyl, noyl and the like. The term “alkylene,” as used herein, alone or in combination, refers to a saturated aliphatic group derived from a straight or branched chain saturated hydrocarbon attached at two or more positions, such as methylene ($-CH_2-$). Unless otherwise specified, the term “alkyl” may include “alkylene” groups.

[00367] The term “alkylamino,” as used herein, alone or in combination, refers to an alkyl group attached to the parent molecular moiety through an amino group. Suitable alkylamino groups may be mono- or dialkylated, forming groups such as, for example, N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-ethylmethylamino and the like.

[00368] The term “alkylidene,” as used herein, alone or in combination, refers to an alkenyl group in which one carbon atom of the carbon-carbon double bond belongs to the moiety to which the alkenyl group is attached.

[00369] The term “alkylthio,” as used herein, alone or in combination, refers to an alkyl thioether (R–S–) radical wherein the term alkyl is as defined above and wherein the sulfur may be singly or doubly oxidized. Examples of suitable alkyl thioether radicals include methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, iso-butylthio, sec-butylthio, tert-butylthio, methanesulfonyl, ethanesulfinyl, and the like.

[00370] The term “alkynyl,” as used herein, alone or in combination, refers to a straight-chain or branched chain hydrocarbon radical having one or more triple bonds and containing from 2 to 20 carbon atoms. In certain embodiments, said alkynyl comprises from 2 to 6 carbon atoms. In further embodiments, said alkynyl comprises from 2 to 4 carbon atoms. The term “alkynylene” refers to a carbon-carbon triple bond attached at two positions such as ethynylene (-C:::C-, -C≡C-). Examples of alkynyl radicals include ethynyl, propynyl, hydroxypropynyl, butyn-1-yl, butyn-2-yl, pentyn-1-yl, 3-methylbutyn-1-yl, hexyn-2-yl, and the like. Unless otherwise specified, the term “alkynyl” may include “alkynylene” groups.

[00371] The terms “amido” and “carbamoyl,” as used herein, alone or in combination, refer to an amino group as described below attached to the parent molecular moiety through a carbonyl group, or vice versa. The term “C-amido” as used herein, alone or in combination, refers to a -C(=O)N(RR’) group with R and R’ as defined herein or as defined by the specifically enumerated “R” groups designated. The term “N-amido” as used herein, alone or in combination, refers to a RC(=O)N(R')- group, with R and R' as defined herein or as defined by the specifically enumerated "R" groups designated. The term "acylamino" as used herein, alone or in combination, embraces an acyl group attached to the parent moiety through an amino group. An example of an "acylamino" group is acetylamino ($CH_3C(=O)NH$-).

[00372] The term "amide," as used herein, alone in combination, refers to -C(=O)NRR', wherein R and R' are independently chosen from hydrogen, alkyl, acyl, heteroalkyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl, any of which may themselves be optionally substituted. Additionally, R and R' may combine to form heterocycloalkyl, either of which may be optionally substituted. Amides may be formed by direct condensation of carboxylic acids with amines, or by using acid chlorides. In addition, coupling reagents are known in the art, including carbodiimide-based compounds such as DCC and EDCI.

[00373] The term "amino," as used herein, alone or in combination, refers to -NRR', wherein R and R' are independently chosen from hydrogen, alkyl, acyl, heteroalkyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl, any of which may themselves be optionally substituted. Additionally, R and R' may combine to form heterocycloalkyl, either of which may be optionally substituted.

[00374] The term "aryl," as used herein, alone or in combination, means a carbocyclic aromatic system containing one, two or three rings wherein such polycyclic ring systems are fused together. The term "aryl" embraces aromatic groups such as phenyl, naphthyl, anthracenyl, and phenanthryl. The term "arylene" embraces aromatic groups such as phenylene, naphthylene, anthracenylene, and phenanthrylene.

[00375] The term "arylalkenyl" or "aralkenyl," as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkenyl group.

[00376] The term "arylalkoxy" or "aralkoxy," as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkoxy group.

[00377] The term "arylalkyl" or "aralkyl," as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkyl group.

[00378] The term "arylalkynyl" or "aralkynyl," as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkynyl group.

[00379] The term "arylalkanoyl" or "aralkanoyl" or "aroyl," as used herein, alone or in combination, refers to an acyl radical derived from an aryl-substituted alkanecarboxylic acid such as benzoyl, napthoyl, phenylacetyl, 3-phenylpropionyl (hydrocinnamoyl), 4-phenylbutyryl, (2-naphthyl)acetyl, 4-chlorohydrocinnamoyl, and the like.

[00380] The term aryloxy as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an oxy.

[00381] The terms "benzo" and "benz," as used herein, alone or in combination, refer to the divalent radical C_6H_4= derived from benzene. Examples include benzothiophene and benzimidazole.

[00382] The term "carbamate," as used herein, alone or in combination, refers to an ester of carbamic acid (-NHCOO-) which may be attached to the parent molecular moiety from either the nitrogen or acid end, and which may be optionally substituted as defined herein.

[00383] The term "O-carbamyl" as used herein, alone or in combination, refers to a -OC(O)NRR', group-with R and R' as defined herein.

[00384] The term "N-carbamyl" as used herein, alone or in combination, refers to a ROC(O)NR'- group, with R and R' as defined herein.

[00385] The term "carbonyl," as used herein, when alone includes formyl [-C(=O)H] and in combination is a -C(O)- group.

[00386] The term "carboxyl" or "carboxy," as used herein, refers to -C(=O)OH or the corresponding "carboxylate" anion, such as is in a carboxylic acid salt. An "O-carboxy" group refers to a RC(O)O- group, where R is as defined herein. A "C-carboxy" group refers to a -C(=O)OR groups where R is as defined herein.

[00387] The term "cyano," as used herein, alone or in combination, refers to -CN.

[00388] The term "cycloalkyl," or, alternatively, "carbocycle," as used herein, alone or in combination, refers to a saturated or partially saturated monocyclic, bicyclic or tricyclic alkyl group wherein each cyclic moiety contains from 3 to 12 carbon atom ring members and which may optionally be a benzo fused ring system which is optionally substituted as defined herein. In certain embodiments, said cycloalkyl will comprise from 5 to 7 carbon atoms. Examples of such cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, tetrahydronapthyl, indanyl, octahydronaphthyl, 2,3-dihydro-1H-indenyl, adamantyl and the like. "Bicyclic" and "tricyclic" as used herein are intended to include both fused ring systems, such as decahydronaphthalene, octahydronaphthalene as well as the multicyclic (multicentered) saturated or partially unsaturated type. The latter type of isomer is exemplified in general by, bicyclo[1,1,1]pentane, camphor, adamantane, and bicyclo[3,2,1]octane.

[00389] The term "ester," as used herein, alone or in combination, refers to a carboxy group bridging two moieties linked at carbon atoms.

[00390] The term "ether," as used herein, alone or in combination, refers to an oxy group bridging two moieties linked at carbon atoms.

[00391] The term "halo," or "halogen," as used herein, alone or in combination, refers to fluorine, chlorine, bromine, or iodine.

[00392] The term "haloalkoxy," as used herein, alone or in combination, refers to a haloalkyl group attached to the parent molecular moiety through an oxygen atom.

[00393] The term "haloalkyl," as used herein, alone or in combination, refers to an alkyl radical having the meaning as defined above wherein one or more hydrogens are replaced with a halogen. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. "Haloalkylene" refers to a haloalkyl group attached at two or more positions. Examples include fluoromethylene (-CFH-), difluoromethylene ($-CF_2$ -), chloromethylene (-CHCl-) and the like.

[00394] The term "heteroalkyl," as used herein, alone or in combination, refers to a stable straight or branched chain, or combinations thereof, fully saturated or containing from 1 to 3 degrees of unsaturation, consisting of the stated number of carbon atoms and from one to three heteroatoms chosen from N, O, and S, and wherein the N and S atoms may optionally be oxidized and the N heteroatom may optionally be quaternized. The heteroatom(s) may be placed at any interior position of the heteroalkyl group. Up to two heteroatoms may be consecutive, such as, for example, $-CH_2-NH-OCH_3$.

[00395] The term "heteroaryl," as used herein, alone or in combination, refers to a 3 to 15 membered unsaturated heteromonocyclic ring, or a fused monocyclic, bicyclic, or tricyclic ring system in which at least one of the fused rings is aromatic, which contains at least one atom chosen from N, O, and S. In certain embodiments, said heteroaryl will comprise from 1 to 4 heteroatoms as ring members. In further embodiments, said heteroaryl will comprise from 1 to 2 heteroatoms as ring members. In certain embodiments, said heteroaryl will comprise from 5 to 7 atoms. The term also embraces fused polycyclic groups wherein heterocyclic rings are fused with aryl rings, wherein heteroaryl rings are fused with other heteroaryl rings, wherein heteroaryl rings are fused with heterocycloalkyl rings, or wherein heteroaryl rings are fused with cycloalkyl rings. Examples of heteroaryl groups include pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl, pyranyl, furyl, thienyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, thiadiazolyl, isothiazolyl, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, quinoxalinyl, quinazolinyl, indazolyl, benzotriazolyl, benzodioxolyl, benzopyranyl, benzoxazolyl, benzoxadiazolyl, benzothiazolyl, benzothiadiazolyl, benzofuryl, benzothienyl, chromonyl, coumarinyl, benzopyranyl, tetrahydroquinolinyl, tetrazolopyridazinyl, tetrahydroisoquinolinyl, thienopyridinyl, furopyridinyl, pyrrolopyridinyl and the like. Exemplary tricyclic heterocyclic groups include carbazolyl, benzidolyl, phenanthrolinyl, dibenzofuranyl, acridinyl, phenanthridinyl, xanthenyl and the like.

[00396] The terms “heterocycloalkyl” and, interchangeably, “heterocycle,” as used herein, alone or in combination, each refer to a saturated, partially unsaturated, or fully unsaturated (but nonaromatic) monocyclic, bicyclic, or tricyclic heterocyclic group containing at least one heteroatom as a ring member, wherein each said heteroatom may be independently chosen from nitrogen, oxygen, and sulfur. In certain embodiments, said heterocycloalkyl will comprise from 1 to 4 heteroatoms as ring members. In further embodiments, said heterocycloalkyl will comprise from 1 to 2 heteroatoms as ring members. In certain embodiments, said heterocycloalkyl will comprise from 3 to 8 ring members in each ring. In further embodiments, said heterocycloalkyl will comprise from 3 to 7 ring members in each ring. In yet further embodiments, said heterocycloalkyl will comprise from 5 to 6 ring members in each ring. “Heterocycloalkyl” and “heterocycle” are intended to include sulfones, sulfoxides, N-oxides of tertiary nitrogen ring members, and carbocyclic fused and benzo fused ring systems; additionally, both terms also include systems where a heterocycle ring is fused to an aryl group, as defined herein, or an additional heterocycle group. Examples of heterocycle groups include tetrhydroisoquinoline, aziridinyl, azetidinyl, 1,3-benzodioxolyl, dihydroisoindolyl, dihydroisoquinolinyl, dihydrocinnolinyl, dihydrobenzodioxinyl, dihydro[1,3]oxazolo[4,5-b]pyridinyl, benzothiazolyl, dihydroindolyl, dihy-dropyridinyl, 1,3-dioxanyl, 1,4-dioxanyl, 1,3-dioxolanyl, isoindolinyl, morpholinyl, piperazinyl, pyrrolidinyl, tetrahydropyridinyl, piperidinyl, thiomorpholinyl, and the like. The heterocycle groups may be optionally substituted unless specifically prohibited.

[00397] The term "hydrazinyl" as used herein, alone or in combination, refers to two amino groups joined by a single bond, i.e., -N-N-.

[00398] The term "hydroxy," as used herein, alone or in combination, refers to -OH.

[00399] The term "hydroxyalkyl," as used herein, alone or in combination, refers to a hydroxy group attached to the parent molecular moiety through an alkyl group.

[00400] The term "imino," as used herein, alone or in combination, refers to =N-.

[00401] The term "iminohydroxy," as used herein, alone or in combination, refers to =N(OH) and =N-O-.

[00402] The phrase "in the main chain" refers to the longest contiguous or adjacent chain of carbon atoms starting at the point of attachment of a group to the compounds or molecules of any one of the formulas disclosed herein.

[00403] The term "isocyanato" refers to a -NCO group.

[00404] The term "isothiocyanato" refers to a -NCS group.

[00405] The phrase "linear chain of atoms" refers to the longest straight chain of atoms independently selected from carbon, nitrogen, oxygen and sulfur.

[00406] The term "lower," as used herein, alone or in a combination, where not otherwise specifically defined, means containing from 1 to and including 6 carbon atoms (i.e., C_1-C_6 alkyl).

[00407] The term "lower aryl," as used herein, alone or in combination, means phenyl or naphthyl, either of which may be optionally substituted as provided.

[00408] The term "lower heteroaryl," as used herein, alone or in combination, means either 1) monocyclic heteroaryl comprising five or six ring members, of which between one and four said members may be heteroatoms chosen from N, O, and S, or 2) bicyclic heteroaryl, wherein each of the fused rings comprises five or six ring members, comprising between them one to four heteroatoms chosen from N, O, and S.

[00409] The term "lower cycloalkyl," as used herein, alone or in combination, means a monocyclic cycloalkyl having between three and six ring members (i.e., C_3-C_6 cycloalkyl). Lower cycloalkyls may be unsaturated. Examples of lower cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[00410] The term "lower heterocycloalkyl," as used herein, alone or in combination, means a monocyclic heterocycloalkyl having between three and six ring members, of which between one and four may be heteroatoms chosen from N, O, and S (i.e., C_3-C_6 heterocycloalkyl). Examples of lower heterocycloalkyls include pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, and morpholinyl. Lower heterocycloalkyls may be unsaturated.

[00411] The term “lower amino,” as used herein, alone or in combination, refers to -NRR', wherein R and R' are independently chosen from hydrogen and lower alkyl, either of which may be optionally substituted.

[00412] The term “mercaptyl” as used herein, alone or in combination, refers to an RS- group, where R is as defined herein.

[00413] The term “nitro,” as used herein, alone or in combination, refers to $–NO_2$.

[00414] The terms “oxy” or “oxa,” as used herein, alone or in combination, refer to –O–.

[00415] The term “oxo,” as used herein, alone or in combination, refers to =O.

[00416] The term “perhaloalkoxy” refers to an alkoxy group where all of the hydrogen atoms are replaced by halogen atoms.

[00417] The term “perhaloalkyl” as used herein, alone or in combination, refers to an alkyl group where all of the hydrogen atoms are replaced by halogen atoms.

[00418] The terms “sulfonate,” “sulfonic acid,” and “sulfonic,” as used herein, alone or in combination, refer the $–SO_3H$ group and its anion as the sulfonic acid is used in salt formation.

[00419] The term “sulfanyl,” as used herein, alone or in combination, refers to –S–.

[00420] The term “sulfinyl,” as used herein, alone or in combination, refers to –S(O)–.

[00421] The term “sulfonyl,” as used herein, alone or in combination, refers to $–S(O)_2$-.

[00422] The term “N-sulfonamido” refers to a $RS(=O)_2NR'$- group with R and R’ as defined herein.

[00423] The term “S-sulfonamido” refers to a $-S(=O)_2NRR'$, group, with R and R’ as defined herein.

[00424] The terms “thia” and “thio,” as used herein, alone or in combination, refer to a –S– group or an ether wherein the oxygen is replaced with sulfur. The oxidized derivatives of the thio group, namely sulfinyl and sulfonyl, are included in the definition of thia and thio.

[00425] The term “thiol,” as used herein, alone or in combination, refers to an –SH group.

[00426] The term “thiocarbonyl,” as used herein, when alone includes thioformyl –C(S)H and in combination is a –C(S)– group.

[00427] The term “N-thiocarbamyl” refers to an ROC(S)NR’ group, with R and R’ as defined herein.

[00428] The term “O-thiocarbamyl” refers to a OC(S)NRR’, group with R and R’ as defined herein.

[00429] The term “thiocyanato” refers to a CNS group.

[00430] The term “trihalomethanesulfonamido” refers to a $X_3CS(O)_2NR$ group with X is a halogen and R as defined herein.

[00431] The term “trihalomethanesulfonyl” refers to a $X_3CS(O)_2$ group where X is a halogen.

[00432] The term “trihalomethoxy” refers to a X_3CO group where X is a halogen.

[00433] The term “trisubstituted silyl,” as used herein, alone or in combination, refers to a silicone group substituted at its three free valences with groups as listed herein under the definition of substituted amino. Examples include trimethysilyl, tert-butyldimethylsilyl, triphenylsilyl and the like.

[00434] Any definition herein may be used in combination with any other definition to describe a composite structural group. By convention, the trailing element of any such definition is that which attaches to the parent moiety. For example, the composite group alkylamido would represent an alkyl group attached to the parent molecule through an amido group, and the term alkoxyalkyl would represent an alkoxy group attached to the parent molecule through an alkyl group.

[00435] When a group is defined to be "null," what is meant is that said group is absent.

[00436] The term "optionally substituted" means the anteceding group may be substituted or unsubstituted. When substituted, the substituents of an "optionally substituted" group may include, without limitation, one or more substituents independently selected from the following groups or a particular designated set of groups, alone or in combination: lower alkyl, lower alkenyl, lower alkynyl, lower alkanoyl, lower heteroalkyl, lower heterocycloalkyl, lower haloalkyl, lower haloalkenyl, lower haloalkynyl, lower perhaloalkyl, lower perhaloalkoxy, lower cycloalkyl, phenyl, aryl, aryloxy, lower alkoxy, lower haloalkoxy, oxo, lower acyloxy, carbonyl, carboxyl, lower alkylcarbonyl, lower carboxyester, lower carboxamido, cyano, hydrogen, halogen, hydroxy, amino, lower alkylamino, arylamino, amido, nitro, thiol, lower alkylthio, lower haloalkylthio, lower perhaloalkylthio, arylthio, sulfonate, sulfonic acid, trisubstituted silyl, N_3, SH, SCH_3, $C(O)CH_3$, CO_2CH_3, CO_2H, pyridinyl, thiophene, furanyl, lower carbamate, and lower urea. Where structurally feasible, two substituents may be joined together to form a fused five-, six-, or seven-membered carbocyclic or heterocyclic ring consisting of zero to three heteroatoms, for example forming methylenedioxy or ethylenedioxy. An optionally substituted group may be unsubstituted (e.g., $-CH_2CH_3$), fully substituted (e.g., $-CF_2CF_3$), monosubstituted (e.g., $-CH_2CH_2F$) or substituted at a level anywhere in-between fully substituted and monosubstituted (e.g., $-CH_2CF_3$). Where substituents are recited without qualification as to substitution, both substituted and unsubstituted forms are encompassed. Where a substituent is qualified as "substituted," the substituted form is specifically intended. Additionally, different sets of optional substituents to a particular moiety may be defined as needed; in these cases, the optional substitution will be as defined, often immediately following the phrase, "optionally substituted with".

[00437] As used herein, 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," it is meant that the group is substituted with one or more substituents independently selected from C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, C_1-C_6 heteroalkyl, C_3-C_7 carbocyclyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), C_3-C_7-carbocyclyl-C_1-C_6-alkyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), 3-10 membered heterocyclyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), 3-10 membered heterocyclyl-C_1-C_6-alkyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), aryl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), aryl(C_1-C_6)alkyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), 5-10 membered heteroaryl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6

haloalkyl, and C_1-C_6 haloalkoxy), 5-10 membered heteroaryl(C_1-C_6)alkyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), halo, cyano, hydroxy, C_1-C_6 alkoxy, C_1-C_6 alkoxy(C_1-C_6)alkyl (i.e., ether), aryloxy, sulfhydryl (mercapto), halo(C_1-C_6)alkyl (e.g., $-CF_3$), halo(C_1-C_6)alkoxy (e.g., $-OCF_3$), C_1-C_6 alkylthio, arylthio, amino, amino(C_1-C_6)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.

[00438] The term R or the term R', appearing by itself and without a number designation, unless otherwise defined, refers to a moiety chosen from hydrogen, alkyl, cycloalkyl, heteroalkyl, aryl, heteroaryl and heterocycloalkyl, any of which may be optionally substituted. Such R and R' groups should be understood to be optionally substituted as defined herein. Whether an R group has a number designation or not, every R group, including R, R' and R^n where n=(1, 2, 3, …n), every substituent, and every term should be understood to be independent of every other in terms of selection from a group. Should any variable, substituent, or term (e.g. aryl, heterocycle, R, etc.) occur more than one time in a formula or generic structure, its definition at each occurrence is independent of the definition at every other occurrence. Those of skill in the art will further recognize that certain groups may be attached to a parent molecule or may occupy a position in a chain of elements from either end as written. For example, an unsymmetrical group such as -C(O)N(R)- may be attached to the parent moiety at either the carbon or the nitrogen.

[00439] Asymmetric centers exist in the compounds or molecules disclosed herein. These centers are designated by the symbols "R" or "S," depending on the configuration of substituents around the chiral carbon atom. It should be understood that the disclosure encompasses all stereochemical isomeric forms, including diastereomeric, enantiomeric, and epimeric forms, as well as d-isomers and 1-isomers, and mixtures thereof. Individual stereoisomers of compounds or molecules can be prepared synthetically from commercially available starting materials which contain chiral centers or by preparation of mixtures of enantiomeric products followed by separation such as conversion to a mixture of diastereomers followed by separation or recrystallization, chromatographic techniques, direct separation of enantiomers on chiral chromatographic columns, or any other appropriate method known in the art. Starting compounds or molecules of particular stereochemistry are either commercially available or can be made and resolved by techniques known in the art. Additionally, the compounds or molecules disclosed herein may exist as geometric isomers. The present disclosure includes all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the appropriate mixtures thereof. Additionally, compounds or molecules may exist as tautomers; all tautomeric isomers are provided by this disclosure. Additionally, the compounds or molecules disclosed herein can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms.

[00440] 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.

[00441] The term "disease" as used herein is intended to be generally synonymous, and is used interchangeably with, the terms "disorder," "syndrome," and "condition" (as in medical condition), in that all reflect an abnormal condition of the human or animal body or of one of its parts that impairs normal functioning, is typically manifested by distinguishing signs and symptoms, and causes the human or animal to have a reduced duration or quality of life.

[00442] The term "combination therapy" means the administration of two or more therapeutic agents to treat a therapeutic condition or disorder described in the present disclosure. Such administration encompasses co-administration of these therapeutic agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of active ingredients or in multiple, separate capsules for each active ingredient. In addition, such administration also encompasses use of each type of therapeutic agent in a sequential manner. In either case, the treatment regimen will provide beneficial effects of the drug combination in treating the conditions or disorders described herein.

[00443] The phrase "therapeutically effective" is intended to qualify the amount of active ingredients used in the treatment of a disease or disorder or on the effecting of a clinical endpoint.

[00444] The term "therapeutically acceptable" refers to those compounds or molecules (or salts, prodrugs, tautomers, zwitterionic forms, etc.) which are suitable for use in contact with the tissues of patients without undue toxicity, irritation, and allergic response, are commensurate with a reasonable benefit/risk ratio, and are effective for their intended use.

[00445] As used herein, reference to "treatment" of a patient is intended to include prophylaxis. Treatment may also be preemptive in nature, i.e., it may include prevention of disease. Prevention of a disease may involve complete protection from disease, for example as in the case of prevention of infection with a pathogen, or may involve prevention of disease progression. For example, prevention of a disease may not mean complete foreclosure of any effect related to the diseases at any level, but instead may mean prevention of the symptoms of a disease to a clinically significant or detectable level. Prevention of diseases may also mean prevention of progression of a disease to a later stage of the disease.

[00446] 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.

[00447] The term "prodrug" refers to a compound or molecule that is made more active in vivo. Certain compounds or molecules disclosed herein may also exist as prodrugs, as described in *Hydrolysis in Drug and Prodrug Metabolism : Chemistry, Biochemistry, and Enzymology* (Testa, Bernard and Mayer, Joachim M. Wiley-VHCA, Zurich, Switzerland 2003). Prodrugs of the compounds described herein are structurally modified forms of the compound that readily undergo chemical changes under physiological conditions to provide the compound. Additionally, prodrugs can be converted to the compound by chemical or biochemical methods in an ex vivo environment. For example, prodrugs can be slowly converted to a compound when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent. Prodrugs are often useful because, in some situations, they may be easier to administer than the compound, or parent drug. They may, for instance, be bioavailable by oral administration whereas the parent drug is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. A wide variety of prodrug derivatives are known in the art, such as those that rely on hydrolytic cleavage or oxidative activation of the prodrug. An example, without limitation, of a prodrug would be a compound which is administered as an ester (the "prodrug"), but then is metabolically hydrolyzed to the carboxylic acid, the active entity. Additional examples include peptidyl derivatives of a compound.

[00448] The compounds or molecules disclosed herein can exist as therapeutically acceptable salts. The present disclosure includes compounds or molecules listed above in the form of salts, including acid addition salts. Suitable salts include those formed with both organic and inorganic acids. Such acid addition salts will normally be pharmaceutically acceptable. However, salts of non-pharmaceutically acceptable salts may be of utility in the preparation and purification of the compound or molecule in question. Basic addition salts may also be formed and be pharmaceutically acceptable. For a more complete discussion of the preparation and selection of salts, refer to *Pharmaceutical Salts: Properties, Selection, and Use* (Stahl, P. Heinrich. Wiley-VCHA, Zurich, Switzerland, 2002).

[00449] Basic addition salts can be prepared during the final isolation and purification of the compounds or molecules by reacting a carboxy group with a suitable base such as the hydroxide, carbonate, or bicarbonate of a metal cation or with ammonia or an organic primary, secondary, or tertiary amine. The cations of therapeutically acceptable salts include lithium, sodium, potassium, calcium, magnesium, and aluminum, as well as nontoxic quaternary amine cations such as ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine, tributylamine, pyridine, *N,N*-dimethylaniline, *N*-methylpiperidine, *N*-methylmorpholine, dicyclohexylamine, procaine, dibenzylamine, *N,N*-dibenzylphenethylamine, 1-ephenamine, and *N,N'*-dibenzylethylenediamine. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, and piperazine.

[00450] Other carrier materials and modes of administration known in the pharmaceutical art may also be used. Pharmaceutical compositions of the disclosure may be prepared by any of the well-known techniques of pharmacy, such as effective formulation and administration procedures. Preferred unit dosage formulations are those containing an effective dose, as herein below recited, or an appropriate fraction thereof, of the active ingredient.

[00451] It should be understood that in addition to the ingredients particularly mentioned above, the formulations described above may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

[00452] The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

[00453] The compounds or molecules can be administered in various modes, *e.g.* orally, topically, or by injection. The precise amount of compound administered to a patient will be the responsibility of the attendant physician. The specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diets, time of administration, route of administration, rate of excretion, drug combination, the precise disorder being treated, and the severity of the indication or condition being treated. In addition, the route of administration may vary depending on the condition and its severity. The above considerations concerning effective formulations and administration procedures are well known in the art and are described in standard textbooks.

EXAMPLES

[00454] The following examples are given for the purpose of illustrating various embodiments of the disclosure and are not meant to limit the present disclosure 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 disclosure. Changes therein and other uses which are encompassed within the spirit of the disclosure as defined by the scope of the claims will occur to those skilled in the art.

[00455] While preferred embodiments of the present disclosure 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 disclosure. It should be understood that various alternatives to the embodiments described herein may be employed. It is intended that the following claims define the scope of the disclosure and that methods and structures within the scope of these claims and their equivalents be covered thereby.

Compound Synthesis

[00456] 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.

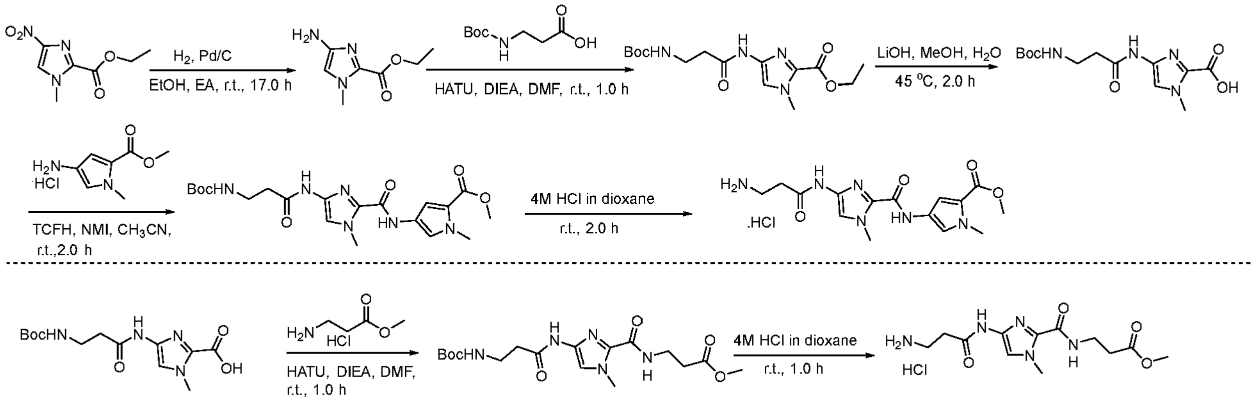
List of Abbreviation

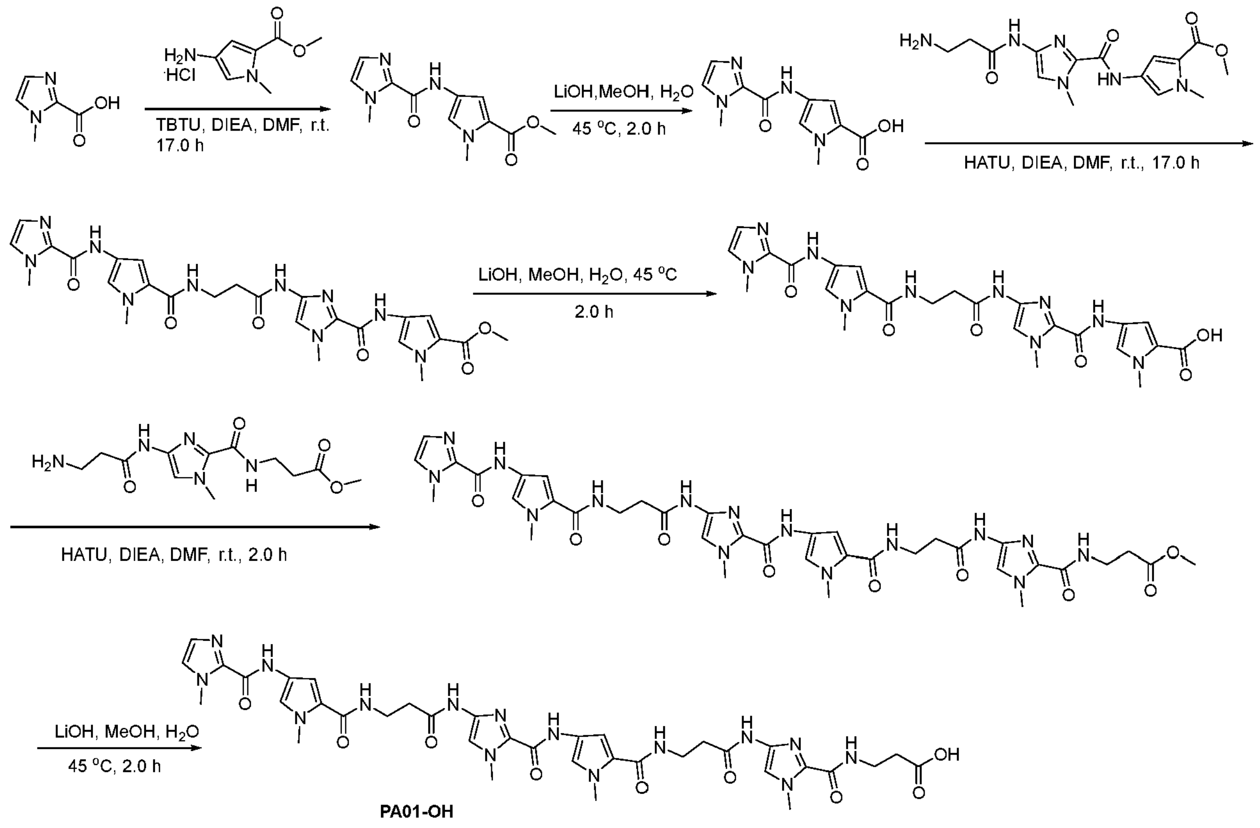
[00457] Ac_2O = acetic anhydride; AcCl = acetyl chloride; AcOH = acetic acid; AIBN = azobisisobutyronitrile; aq. = aqueous; Bu_3SnH = tributyltin hydride; CD_3OD = deuterated methanol; $CDCl_3$ = deuterated chloroform; CDI = 1,1′-Carbonyldiimidazole; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; DCM = dichloromethane; DEAD = diethyl azodicarboxylate; DIBAL-H = di-iso-butyl aluminium hydride; DIEA = DIPEA = N,N-diisopropylethylamine; DMAP = 4-dimethylaminopyridine; DMF = N,Ndimethylformamide; DMSO-d$_6$ = deuterated dimethyl sulfoxide; DMSO = dimethyl sulfoxide; DPPA = diphenylphosphoryl azide; EDC.HCl = EDCI.HCl = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride; Et$_2$O = 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; MeOH = methanol; MP-carbonate resin = macroporous triethylammonium methylpolystyrene carbonate resin; MsCl = mesyl chloride; MTBE = methyl tertiary butyl ether; MW = microwave irradiation ; n-BuLi = n-butyllithium; NaHMDS = Sodium bis(trimethylsilyl)amide; NaOMe = sodium methoxide; NaOtBu = sodium t-butoxide; NBS = N-bromosuccinimide; NCS = N-chlorosuccinimide; NMP = N-Methyl-2-pyrrolidone; Pd(Ph$_3$)$_4$ = tetrakis(triphenylphosphine)palladium(0); Pd$_2$(dba)$_3$ = tris(dibenzylideneacetone)dipalladium(0); PdCl$_2$(PPh$_3$)$_2$ = bis(triphenylphosphine)palladium(II) dichloride; PG = protecting group; prep-HPLC = preparative high-performance liquid chromatography; PyBop = (benzotriazol-1-yloxy)-tripyrrolidinophosphonium hexafluorophosphate; Pyr = pyridine; RT = room temperature; RuPhos = 2-**dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl; sat. = saturated; ss = saturated solution; t-BuOH = tert-**butanol; T3P = Propylphosphonic Anhydride; TBS = TBDMS = *tert*-butyldimethylsilyl; TBSCl = TBDMSCl = *tert*-butyldimethylchlorosilane; TEA = Et$_3$N = triethylamine; TFA = trifluoroacetic acid; TFAA = trifluoroacetic anhydride; THF = tetrahydrofuran; Tol = toluene; TsCl = tosyl chloride; XPhos = 2-**dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl.**

[00458] SYNTHESIS OF REPRESENTATIVE POLYAMIDES

[00459] Example 1. Synthesis of 3-([1-methyl-4-[3-([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)propanamido]imidazol-2-yl]formamido)propanoic acid (PA01-OH)

[00460] Scheme 1.





PA01-OH

[00461] *Step 1: Synthesis of ethyl 4-amino-1-methylimidazole-2-carboxylate*

[00462] To a solution of ethyl 1-methyl-4-nitroimidazole-2-carboxylate (30.00 g, 150.63 mmol, 1.00 equiv) in EtOH (120.00 mL) and EA (120.00 mL) was added Pd/C (8.01 g, 27% w/w). Then the reaction was stirred for 17.0 h at room temperature under H_2 atmosphere. The solid was filtrated out and the filtrate was concentrated to afford ethyl 4-amino-1-methylimidazole-2-carboxylate (22.30 g, 75.20%) as yellow solid. LC/MS: mass calcd. For $C_7H_{11}N_3O_2$: 169.09, found: 170.10 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) **δ: 7.37 (s, 1H), 4.29 - 4.34 (m, 2H), 3.94 (s, 3H), 1.31 (t,** *J* = 7.2 Hz, 3H).

[00463] *Step 2: Synthesis of ethyl 4-[3-[(tert-butoxycarbonyl)amino]propanamido]-1-methylimidazole-2-carboxylate*

[00464] Into a 500 mL flask was added 3-[(tert-butoxycarbonyl) amino]propanoic acid (22.45 g, 118.65 mmol, 0.90 equiv), DMF (180.00 mL). The mixture was cooled to 0 °C, then HATU (75.18 g, 197.71 mmol, 1.50 equiv) and DIEA (51.11 g, 395.43 mmol, 3.00 equiv) were added, the mixture was stirred for 10.0 mins, then ethyl 4-amino-1-methylimidazole-2-carboxylate (22.30 g, 131.81 mmol, 1.00 equiv) was added in portions. The reaction was stirred at room temperature for 1.0 h. The reaction was quenched with ice water (600 mL), and the solution was stirred for 15.0 min. The precipitated solids were collected by filtration and washed with water (3x50 mL) and dried under vacuum. This resulted in ethyl 4-[3-[(tert-butoxycarbonyl)amino] propanamido]-1-methylimidazole-2-carboxylate (34.50 g, 76.90%) as light yellow solid. LC/MS: mass calcd. For $C_{15}H_{24}N_4O_5$: 340.17, found: 341.20 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) **δ: 10.63 (s, 1H), 7.52 (s, 1H), 6.80 (t,** *J* = 5.6 Hz, 1H), 4.23 - 4.28 (m, 2H), 3.90 (s, 3H), 3.15 - 3.20 (m, 2H), 2.42 (t, *J* = 7.2 Hz, 2H), 1.37 (s, 9H), 1.29 (t, *J* = 7.2 Hz, 3H).

[00465] ***Step 3: Synthesis of 4-[3-[(tert-butoxycarbonyl)amino]propanamido]-1-methylimidazole-2-carboxylic acid***

[00466] To a stirred solution of ethyl 4-[3-[(tert-butoxycarbonyl)amino]propanamido]-1 methylimidazole-2-carboxylate (34.50 g, 101.36 mmol, 1.00 equiv) in MeOH (200.00 mL) was added LiOH solution (2M, 202.00 mL, 4.00 equiv) dropwise at room temperature. The resulting mixture was stirred for 2.0 h at 45 °C. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in H_2O (50 mL). The mixture was acidified to pH 3~5 with 2M HCl. The precipitated solids were collected by filtration and washed with H_2O (3x30 mL), dried under vacuum. 4-[3-[(Tert-butoxycarbonyl)amino]propanamido]-1-methylimidazole-2-carboxylic acid (30.00 g, 94.77%) was obtained as white solid. LC/MS: mass calcd. For $C_{13}H_{20}N_4O_5$: 312.14, found: 313.15 $[M+H]^+$. ^{1}**H NMR (300 MHz, DMSO-d6) δ: 10.53 (s, 1H), 7.48 (s, 1H),** 6.79 (t, J = 5.4 Hz, 1H), 3.89 (s, 3H), 3.15 -3.22 (m, 2H), 2.43 (t, J = 7.2 Hz, 2H), 1.37 (s, 9H).

[00467] ***Step 4: Synthesis of methyl 4-(4-[3-[(tert-butoxycarbonyl)amino]propanamido]-1-methylimidazole-2-amido)-1-methylpyrrole-2-carboxylate***

[00468] To a stirred solution of 4-[3-[(tert-butoxycarbonyl)amino]propanamido]-1-methylimidazole-2-carboxylic acid (16.00 g, 51.23 mmol, 1.00 equiv) in CH_3CN (150.00 mL) was added TCFH (21.56 g, 76.84 mmol, 1.50 equiv), NMI (12.62 g, 153.69 mmol, 3.00 equiv) and methyl 4-amino-1-methylpyrrole-2-carboxylate hydrochloride (10.74 g, 56.34 mmol, 1.10 equiv) in portions at 0 °C. The resulting mixture was stirred for 2.0 h at room temperature. The precipitated solids were collected by filtration and washed by CH_3CN (3x20 mL), dried under vacuum. Methyl 4-(4-[3-[(tert-butoxycarbonyl)amino]propanamido]-1-methylimidazole-2-amido)-1-methylpyrrole-2-carboxylate (19.00 g, 82.70%) was obtained as white solid. LC/MS: mass calcd. For $C_{20}H_{28}N_6O_6$: 448.21, found: 449.25 [M+H]+. ^{1}**H NMR (300 MHz, DMSO-d6) δ: 10.24 (s, 1H), 10.11 (s, 1H), 7.52 (s, 1H), 7.33 (s, 1H), 6.99 (s, 1H), 6.82** (t, J = 5.1 Hz, 1H), 3.94 (s, 3H), 3.85 (s, 3H), 3.74 (s, 3H), 3.16 - 3.23 (m, 2H), 2.47 (t, J = 6.9 Hz, 2H), 1.38 (s, 9H).

[00469] ***Step 5: Synthesis of methyl 4-[4-(3-aminopropanamido)-1-methylimidazole-2-amido]-1-methylpyrrole-2-carboxylate hydrochloride***

[00470] A solution of methyl 4-(4-[3-[(tert-butoxycarbonyl)amino]propanamido]-1-methylimidazole-2-amido)-1-methylpyrrole-2-carboxylate (19.00 g, 42.37 mmol, 1.00 equiv) in HCl/1,4-dioxane (4 M, 200.00 mL) was stirred for 2.0 h at room temperature. The resulting mixture was concentrated under vacuum. Methyl 4-[4-(3-aminopropanamido)-1-methylimidazole-2-amido]-1-methylpyrrole-2-carboxylate hydrochloride (19.00 g crude) was obtained as yellow solid. LC/MS: mass calcd. For $C_{15}H_{21}ClN_6O_4$: 348.15, found: 349.05 [M+H]+. ^{1}H NMR (300 MHz, CD_3**OD) δ: 7.37 (s, 2H), 6.91 (s, 1H), 4.03 (s, 3H), 3.88 (s,** 3H), 3.79 (s, 3H), 3.09 (t, J = 6.6 Hz, 2H), 2.64 (t, J = 6.6 Hz, 2H).

[00471] ***Step 6: Synthesis of methyl 3-[(4-[3-[(tert-butoxycarbonyl)amino] propanamido]-1-methylimidazol-2-yl)formamido]propanoate***

[00472] Into a 1000 ml flask was added 4-[3-[(tert-butoxycarbonyl)amino] propanamido]-1-methylimidazole-2-carboxylic acid (11.00 g, 35.22 mmol, 1.00 equiv), DMF (300.00 mL), the mixture was cooled to 0 degrees C, then HATU (20.09 g, 52.83 mmol, 1.50 equiv), DIEA (18.21 g, 140.88 mmol, 4.00 equiv) was added dropwise, the mixture was stirred for 10 mins, methyl 3-aminopropanoate (3.63 g, 35.22 mmol, 1.00 equiv) was added in portions. The reaction was stirred at room temperature for 1.0 h. The reaction mixture was poured into water/ice (600 mL), the solid was filtered out and dried under vacuum. The aqueous phase was extracted by EA (3 x 200 mL), the organic phases were combined and washed by H_2O (1x200 mL) and NaCl (1x200 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column, eluted with pure EA. The fractions were combined and concentrated. Methyl 3-[(4-[3-[(tert-butoxycarbonyl)amino]propanamido]-1- methylimidazol-2-yl)formamido]propanoate (13.00 g, 87.95%) was obtained as yellow solid. LC/MS: mass calcd. For $C_{17}H_{27}N_5O_6$: 397.20, found: 398.20 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) **δ: 10.28 (s, 1H), 7.92 (t,** J = 6.0 Hz, 1H), 7.37 (s, 1H), 6.77 (t, J = 6.0 Hz, 1H), 3.88 (s, 3H), 3.59 (s, 3H), 3.42 - 3.47 (m, 2H), 3.13 - 3.18 (m, 2H), 2.56 (t, J = 6.0 Hz, 2H), 2.42 (t, J = 6.0 Hz, 2H), 1.35 (s, 9H).

[00473] ***Step 7: Synthesis of methyl 3-[[4-(3-aminopropanamido)-1-methylimidazol-2-yl] formamido]propanoate hydrochloride***

[00474] A solution of methyl 3-[(4-[3-[(tert-butoxycarbonyl)amino]propanamido]-1-methylimidazol-2-yl) formamido]propanoate (11.00 g, 27.678 mmol, 1.00 equiv) in HCl/1,4 dioxane (4M, 110.00 mL) was stirred for 1.0 h at room temperature. The resulting mixture was concentrated under vacuum to afford methyl 3-[[4-(3-aminopropanamido)-1-methylimidazol-2-yl]formamido]propanoate hydrochloride (11.00 g, crude) as yellow oil. LC/MS: mass calcd. For $C_{12}H_{19}N_5O_4$: 297.14, found: 298.20 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) **δ: 10.57 (s, 1H), 7.92 (t,** J = 6.0 Hz, 1H), 7.37 (s, 1H), 3.89 (s, 3H), 3.59 (s, 3H), 3.43 - 3.47 (m, 2H), 2.97 - 3.05 (m, 2H), 2.57 - 2.71 (m, 2H), 2.56 (t, J = 6.0 Hz, 2H).

[00475] ***Step 8: Synthesis of methyl 1-methyl-4-(1-methylimidazole-2-amido)pyrrole-2- carboxylate***

[00476] To a stirred solution of 1-methylimidazole-2-carboxylic acid (10.00 g, 79.29 mmol, 7.00 equiv) in DMF (150.00 mL) was added TBTU (38.19 g, 118.94 mmol, 1.50 equiv), methyl 4-amino-1-methylpyrrole-2-carboxylate hydrochloride (16.63 g, 87.24 mmol, 1.10 equiv) and DIEA (30.74 g, 237.88 mmol, 3.00 equiv) in portions at 0 °C. The resulting mixture was stirred for 17.0 h at room temperature. The reaction was poured into water/Ice (450 mL). The precipitated solids were collected by filtration and washed with H_2O (3x50 mL), dried under vacuum. Methyl 1-methyl-4-(1-methylimidazole-2-amido)pyrrole-2-catboxylate (16.50 g, 78.37%) was obtained as white solid. LC/MS: mass calcd. For $C_{12}H_{14}N_4O_3$: 262.11, found: 263.15 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) **δ: 10.54 (s, 1H), 7.54 (s, 1H),** 7.40 (s, 1H), 7.04 (s, 2H), 3.99 (s, 3H), 3.85 (s, 3H), 3.74 (s, 3H).

[00477] ***Step 9: Synthesis of 1-methyl-4-(1-methylimidazole-2-amido)pyrrole-2-carboxylic acid***

[00478] To a stirred solution of methyl 1-methyl-4-(1-methylimidazole-2-amido)pyrrole-2-carboxylate (16.50 g, 62.91 mmol, 1.00 equiv) in MeOH (100.00 mL) was added LiOH solution (2 M, 158.00 mL, 5.00 equiv) dropwise at room temperature. The resulting mixture was stirred for 2.0 h at 45 °C. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in H_2O (50 mL). The mixture was acidified to pH 3~5 with 2M HCl. The precipitated solids were collected by filtration and washed with H_2O (3x30 mL), dried under vacuum. 1-Methyl-4-(1-methylimidazole-2-amido)pyrrole-2-carboxylic acid (12.00 g, 76.84%) was obtained as a white solid. LC/MS: mass calcd. For $C_{11}H_{12}N_4O_3$: 248.09, found: 249.10 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ: 10.52 (s, 1H), 7.48 (s, 1H), 7.41 (s, 1H), 7.06 (s, 1H), 6.99 (s, 1H), 3.99 (s, 3H), 3.82 (s, 3H).

[00479] ***Step 10: Synthesis of methyl 1-methyl-4-[1-methyl-4-(3-[[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido]propanamido)imidazole-2-amido]pyrrole-2-carboxylate***

[00480] To a stirred solution of 1-methyl-4-(1-methylimidazole-2-amido)pyrrole-2-carboxylic acid (9.00 g, 36.255 mmol, 1.00 equiv) in DMF (150.00 mL) was added HATU (20.68 g, 54.38 mmol, 1.50 equiv), DIEA (14.06 g, 108.77 mmol, 3.00 equiv) and methyl 4-[4-(3-aminopropanamido)-1-methylimidazole-2-amido]-1-methylpyrrole-2-carboxylate (13.89 g, 39.872 mmol, 1.10 equiv) in portions at 0 °C. The resulting mixture was stirred for 17.0 h at room temperature. The reaction was poured into water/ice (450 mL) at 0 °C. The precipitated solids were collected by filtration and washed with H2O (3x50 mL), dried under vacuum. Methyl 1-methyl-4-[1-methyl-4-(3-[[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido]propanamido)imidazole-2-amido]pyrrole-2-carboxylate (14.00 g, 63.54%) was obtained as yellow solid. LC/MS: mass calcd. For $C_{26}H_{30}N_{10}O_6$: 578.23, found: 579.10 [M+H]+. ^1H NMR (300 MHz, DMSO-d_6) δ: 10.53 (s, 1H), 10.29 (s, 1H), 10.11 (s, 1H), 8.10 (t, J = 5.4 Hz, 1H), 7.52 (s, 1H), 7.47 (s, 2H), 7.25 (s, 1H), 7.17 (s, 1H), 6.99 (s, 1H), 6.97 (s, 1H), 3.99 (s, 3H), 3.95 (s, 3H), 3.84 (s, 3H), 3.82 (s, 3H), 3.69 (s, 3H), 3.42 - 3.49 (m, 2H), 2.60 (t, J = 7.2 Hz, 2H).

[00481] ***Step 11: Synthesis of 1-methyl-4-[1-methyl-4-(3-[[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido]propanamido)imidazole-2-affordamido] pyrrole-2-carboxylic acid***

[00482] A solution of methyl 1-methyl-4-[1-methyl-4-(3-[[1-methyl-4-(1- methylimidazole-2-amido)pyrrol-2-yl]formamido]propanamido)imidazole-2-amido]pyrrole-2-yl]formamidocarboxylate (14.00 g, 24.20 mmol, 1.00 equiv) in MeOH (70.00 mL) was added LiOH (2M,72.00 mL, 6.00 equiv). The mixture was stirred at 45 °C for 2.0 h. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in H_2O (50 mL). The mixture was acidified to pH 3~5 with 2M HCl. The precipitated solids were collected by filtration and washed with H_2O (3x20 mL), dried under vacuum. 1-methyl-4-[1-methyl-4-(3-[[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido]propanamido)imidazole-2-affordamido] pyrrole-2-carboxylic acid (12.00 g, 81.49%) was obtained as yellow solid. LC/MS: mass calcd. For $C_{25}H_{28}N_{10}O_6$: 564.22, found: 565.15$[M+H]^+$. ^1H NMR (300 MHz, DMSO-d6) δ: 10.72 (s, 1H), 10.32 (s, 1H), 10.08 (s, 1H), 8.14 (t, J = 6.0 Hz, 1H), 7.51 (s, 1H), 7.47 (s, 2H), 7.27 (s, 1H), 7.23 (s, 1H), 6.98 (s, 1H), 6.94 (s, 1H), 4.00 (s, 3H), 3.95 (s, 3H), 3.82 (s, 6H), 3.44 - 3.46 (m, 2H), 2.60 (t, J = 6.6 Hz, 2H).

[00483] ***Step 12: Synthesis of methyl 3-([1-methyl-4-[3-([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)propanamido]imidazol-2-yl]formamido)propanoate***

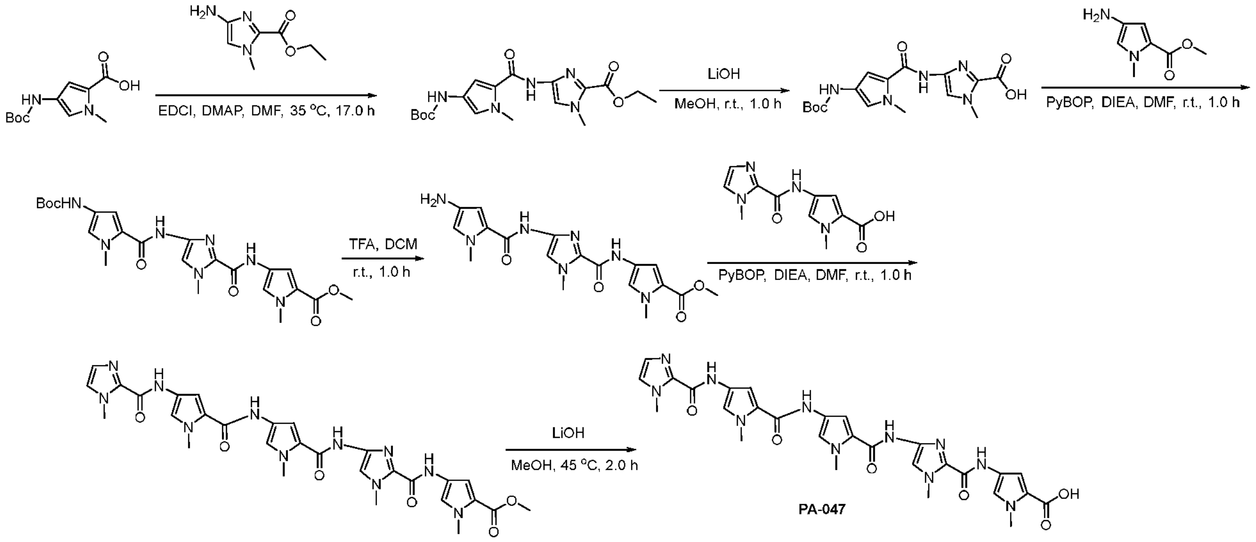
[00484] To a stirred solution of 1-methyl-4-[1-methyl-4-(3-[[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido]propanamido)imidazole-2-amido] pyrrole-2-carboxylic acid (12.00 g, 21.26 mmol, 1.00 equiv) in DMF (100.00 mL) was added HATU (12.12 g, 31.88 mmol, 1.50 equiv), DIEA (8.24 g, 63.77 mmol, 3.00 equiv) and methyl 3-[[4-(3-aminopropanamido)-1-methylimidazol-2-yl]formamido]propanoate (6.95 g, 23.38 mmol, 1.10 equiv) in portions at 0 °C. The resulting mixture was stirred for 2.0 h at room temperature. The reaction was poured into water/ice (300 mL) at 0 ºC. The precipitated solids were collected by filtration and washed with H2O (3x30 mL), dried under vacuum. Methyl 3-([1-methyl-4-[3-([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)propanamido]imidazol-2-yl]formamido)propanoate (13.00 g, 64.77%) was obtained as yellow solid. LC/MS: mass calcd. For $C_{37}H_{45}N_{15}O_9$: 843.35, found: 844.55[M+H]+. **^{1}H NMR (300 MHz, DMSO-d6) δ: 10.41 (s, 1H), 10.37 (s,** 1H), 10.32 (s, 1H), 9.96 (s, 1H), 8.08 (s, 2H), 7.96 (s, 1H), 7.46 (s, 1H), 7.42 (s, 1H), 7.38 (s, 1H), 7.24 (s, 2H), 7.03 (s, 1H), 6.98 (s, 1H), 6.93 (s, 1H), 4.13 (s, 3H), 3.98 (s, 3H), 3.95 (s, 3H), 3.81 (s, 9H), 3.60 (s, 6H), 2.57 - 2.69 (m, 6H).

[00485] ***Step 13: Synthesis of 3-([1-methyl-4-[3-([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)propanamido]imidazol-2-yl]formamido)propanoic acid***

[00486] A solution of methyl 3-([1-methyl-4-[3-([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)propanamido]imidazol-2-yl]formamido)propanoate (10.00 g, 10.59 mmol, 1.00 equiv) in MeOH (60.00 mL) was added 2M LiOH (21.20 mL, 42.40 mmol, 4.00 equiv), the resulting mixture was stirred for 2.0 h at 45 °C. The resulting mixture was concentrated under reduced pressure. The resulting mixture was diluted with water (60 mL). The mixture was acidified to pH 3~5 with 2M HCl. The precipitated solids were collected by filtration and washed with water (3x20 mL). The solid was dried under vacuum. This resulted in 3-([1-methyl-4-[3-([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)propanamido]imidazol-2-yl]formamido)propanoic acid (8.70 g, 84.14%) as a brown solid. LC/MS: mass calcd. For $C_{36}H_{43}N_{15}O_9$: 829.34, found: 830.25[M+H]+. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.46 (s, 1H), 10.39 (s, 1H), 10.31 (s, 1H), 9.93 (s, 1H), 8.05 -8.10 (m, 2H), 7.87 (t, J = 6.0 Hz, 1H), 7.42 - 7.46 (m, 3H), 7.20 - 7.23 (m, 2H), 7.07 (s, 1H), 6.90 - 6.95 (m, 2H), 3.95 (s, 3H), 3.92 (s, 3H), 3.89 (s, 3H), 3.79 (s, 3H), 3.78 (s, 3H), 3.38 - 3.41 (m, 6H), 2.44 - 2.59 (m, 6H).

[00487] **Example 2. Synthesis of 1-methyl-4-(1-methyl-4-{1-methyl-4-[1-methyl-4-(1-methylimidazole-2-amido)pyrrole-2-amido]pyrrole-2-amido}imidazole-2-amido)pyrrole-2-carboxylic acid (PA-047)**

[00488] **Scheme 2.**



PA-047

[00489] ***Step 1: Synthesis of ethyl 4-[4-[(tert-butoxycarbonyl)amino]-1-methylpyrrole- 2-amido]-1-methylimidazole-2-carboxylate***

[00490] To a stirred solution of 4-[(tert-butoxycarbonyl)amino]-1-methylpyrrole-2- carboxylic acid (11.50 g, 47.87 mmol, 1.00 equiv) in DMF (200.00 mL) was added EDCI (22.94 g, 119.66 mmol, 2.50 equiv), ethyl 4-amino-1-methylimidazole- 2-carboxylate (8.10 g, 47.87 mmol, 1.00 equiv) and DMAP (14.62 g, 119.66 mmol, 2.50 equiv) at 0 °C. The resulting mixture was stirred for 17.0 h at 35 °C. After reaction, the reaction was poured into 500 mL ice/water. The precipitated solids were collected by filtration and washed with water (3x50 mL), dried under vacuum. This resulted in ethyl 4-{4-[(tert-butoxycarbonyl)amino]-1-methylpyrrole- 2-amido}-1-methylimidazole-2-carboxylate (16.00 g, 85.48% yield) as light yellow solid. LC/MS: mass calcd. For $C_{18}H_{25}N_5O_5$: 391.19, found: 392.30 $[M+H]^+$.

[00491] ***Step 2: Synthesis of 4-[4-[(tert-butoxycarbonyl)amino]-1-methylpyrrole-2- amido]-1-methylimidazole-2-carboxylic acid***

[00492] The procedure was the same as 4-[3-[(tert-butoxycarbonyl)amino] propanamido]-1-methylimidazole-2-carboxylic acid (Example 1 Step 3), but the reaction temperature was room temperature and the reaction time was 1.0 h. 970.00 mg of ethyl 4-[4-[(tert-butoxycarbonyl)amino]-1-methylpyrrole-2-amido]-1- methylimidazole-2-carboxylate was used, 638.00 mg of 4-[4-[(tert-butoxycarbonyl) amino]-1-methylpyrrole-2-amido]-1-methylimidazole-2-carboxylic acid was obtained as yellow solid (64.36% yield). LC/MS: mass calcd. For $C_{16}H_{21}N_5O_5$: 363.15, found: 364.15 $[M+H]^+$.

[00493] ***Step 3: Synthesis of methyl 4-(4-{4-[(tert-butoxycarbonyl)amino]-1-methylpyrrole-2-amido}-1-methylimidazole-2-amido)-1-methylpyrrole-2-carboxylate***

[00494] 4-{4-[(tert-butoxycarbonyl)amino]-1-methylpyrrole-2-amido}-1-methylimidazole-2-carboxylic acid (6.00 g, 16.51 mmol, 1.00 equiv) was dissolved in DMF (60.00 mL). PyBOP (8.59 g, 16.51 mmol, 1.00 equiv), methyl 4-amino-1-methylpyrrole-2-carboxylate (2.55 g, 16.51 mmol, 1.00 equiv) and DIEA (6.40 g, 49.536 mmol, 3.00 equiv) were added in turn to the solution at 0 °C. The mixture was allowed to warm to room temperature and stirred for 1.0 h. After the reaction was completed, the mixture was added to the ice water (150 mL) dropwise. The solid was generated, filtered out, washed by water (2x15 mL) and dried under vacuum to afford methyl 4-(4-{4-[(tert-butoxycarbonyl)amino]-1-methylpyrrole-2-amido}-1-methylimidazole-2-amido)-1-methylpyrrole-2-carboxylate (7.10 g, 86.08%) as reddish brown solid. LC/MS: mass calcd. for $C_{23}H_{29}N_7O_6$: 499.21, found: 500.15 $[M+H]^+$.

[00495] ***Step 4: Synthesis of methyl 4-[4-(4-amino-1-methylpyrrole- 2-amido)-1-methylimidazole-2-amido]-1-methylpyrrole-2-carboxylate***

[00496] To a stirred solution of methyl 4-(4-{4-[(tert-butoxycarbonyl)amino]-1-methylpyrrole-2-amido}-1-methylimidazole-2-amido)-1-methylpyrrole-2-carboxylate (250.00 mg, 0.500 mmol, 1.00 equiv) in DCM (2.50 mL) was added TFA (0.50 mL) dropwise at room temperature. The resulting mixture was stirred for 1.0 h at room temperature. The resulting mixture was concentrated under vacuum. Methyl 4-[4-(4-amino-1-methylpyrrole-2-amido)-1-methylimidazole-2-amido]-1-methylpyrrole-2-carboxylate (250.00 mg, crude) was obtained as brown-yellow oil. LC/MS: mass calcd. For $C_{18}H_{21}N_7O_4$: 399.17, found: 400.35 $[M+H]^+$.

[00497] ***Step 5: Synthesis of methyl 1-methyl-4-(1-methyl-4-{1- methyl-4-[1-methyl-4-(1-methylimidazole-2-amido)pyrrole-2-amido]pyrrole-2-amido}imidazole-2-amido)pyrrole-2-carboxylate***

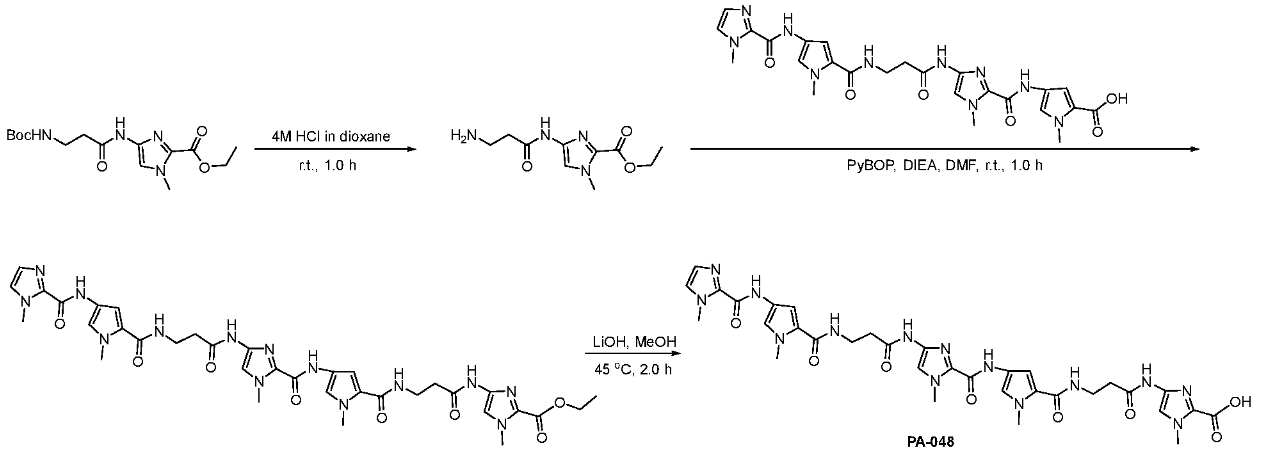
[00498] To a stirred solution of 1-methyl-4-(1-methylimidazole-2-amido)pyrrole-2-carboxylic acid (156.62 mg, 0.63 mmol, 0.90 equiv) in DMF (2.00 mL) was added PyBOP (361.16 mg, 0.69 mmol, 1.00 equiv), methyl 4-[4-(4-amino-1-methylpyrrole-2-amido)-1-methylimidazole-2-amido]-1-methylpyrrole-2-carboxylate (280.00 mg, 0.70 mmol, 1.00 equiv) and DIEA (453.02 mg, 3.51 mmol, 5.00 equiv) in portions at 0 °C. The resulting mixture was stirred for 1.0 h at room temperature. The reaction mixture was purified by reverse phase column directly with the following conditions: column, C18 column; mobile phase, ACN in water (0.05% TFA), 5% to 70% gradient in 50 min; detector, UV 254 nm. The fractions were combined and concentrated. Methyl 1-methyl-4-(1-methyl-4-{1-methyl-4-[1-methyl-4-(1-methylimidazole-2-amido)pyrrole-2-amido]pyrrole-2-amido}imidazole-2-amido)pyrrole-2-carboxylate (240.00 mg, 51.65% yield) was obtained as white solid. LC/MS: mass calcd. For $C_{29}H_{31}N_{11}O_6$: 629.25, found: 630.25 $[M+H]^+$.

[00499] ***Step 6: Synthesis of 1-methyl-4-(1-methyl-4-{1-methyl-4-[1-methyl-4-(1-methylimidazole-2-amido)pyrrole-2-amido]pyrrole-2-amido}imidazole-2-amido)pyrrole-2-carboxylic acid***

[00500] The procedure was the same as 4-[3-[(tert-butoxycarbonyl)amino] propanamido]-1-methylimidazole-2-carboxylic acid (Example 1 Step 3). 240.00 mg of methyl 1-methyl-4-(1-methyl-4-{1-methyl-4-[1-methyl-4-(1-methylimidazole-2-amido)pyrrole-2-amido]pyrrole-2-amido}imidazole-2-amido)pyrrole-2-carboxylate was used, 178.00 mg of 1-methyl-4-(1-methyl-4-{1-methyl-4-[1-methyl-4-(1-methylimidazole-2-amido)pyrrole-2-amido]pyrrole-2-amido}imidazole-2-amido)pyrrole-2-carboxylic acid was obtained as white solid (62.96% yield). LC/MS: mass calcd. For $C_{28}H_{29}N_{11}O_6$: 615.23, found: 616.25 $[M+H]^+$.

[00501] **Example 3. Synthesis of 1-methyl-4-[3-({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)propanamido]imidazole-2-carboxylic acid (PA-048)**

[00502] **Scheme 3.**



PA-048

[00503] ***Step 1: Synthesis of 2-(1-methylimidazol-2-yl)-3H-1,3-benzodiazole-5-carboxylic acid***

[00504] The procedure was the same as (Example 1 Step 7), but the reaction time was 1.0 h. 2.00g of ethyl 4-[3-[(tert-butoxycarbonyl)amino]propanamido]-1-methylimidazole-2-carboxylate was used, 2.00 g crude of ethyl 4-(3-aminopropanamido)-1-methyl-1H- imidazole-2-carboxylate was obtained as off-white solid. LC/MS: mass calcd. For $C_{10}H_{16}N_4O_3$: 240.12, found: 241.10 $[M+H]^+$.

[00505] ***Step 2: Synthesis of ethyl 1-methyl-4-[3-({1-methyl-4-[1-methyl-4-(3-{[1-***

[00506] ***methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-amido]pyrrol-2-yl}formamido)propanamido]imidazole-2-carboxylate***

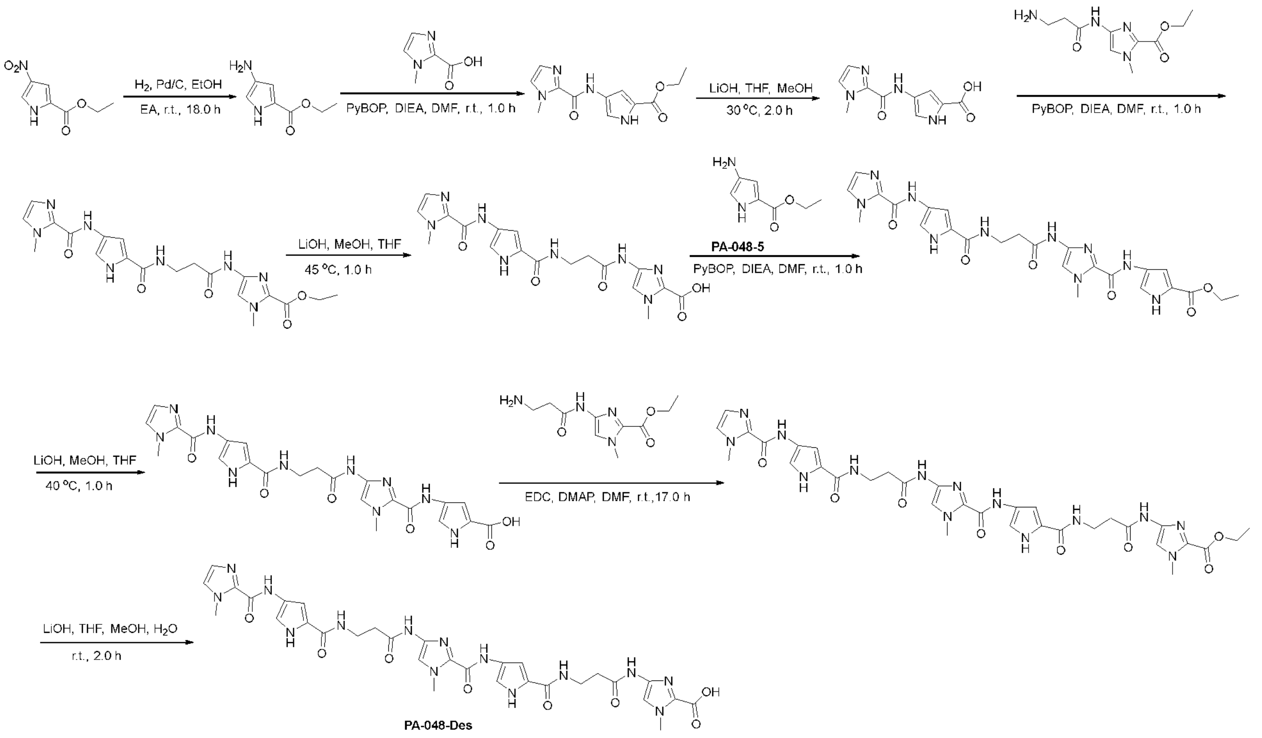
[00507] The procedure was the same as methyl 4-(4-{4-[(tert-butoxycarbonyl)amino]-1- methylpyrrole-2-amido}-1-methylimidazole-2-amido)-1-methylpyrrole-2-carboxylate (Example 2 step 3). 270.00 mg of 1-methyl-4-[1-methyl-4-(3-{[1-methyl-4-(1- methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-amido]pyrrole-2-carboxylic acid was used, 460.00 mg of ethyl 1-methyl-4-[3-({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)propanamido]imidazole-2-carboxylate was obtained as off-white solid (96.45% yield). LC/MS: mass calcd. For $C_{35}H_{42}N_{14}O_8$: 786.33, found: 809.60 $[M+Na]^+$.

[00508] ***Step 3: Synthesis of 1-methyl-4-[3-({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)propanamido]imidazole-2-carboxylic acid***

[00509] The procedure was the same as 4-[3-[(tert-butoxycarbonyl)amino] propanamido]-1-methylimidazole-2-carboxylic acid (Example 1 Step 3). 470.00 mg of ethyl 1-methyl-4-[3-({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)propanamido]imidazole-2-carboxylate was used, 400.00 mg of 1-methyl-4-[3-({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)propanamido]imidazole-2-carboxylic acid was obtained as off-white solid (74.41% yield). LC/MS: mass calcd. For $C_{33}H_{38}N_{14}O_8$:758.30, found:759.55 $[M+H]^+$.

[00510] **Example 4. Synthesis of 1-methyl-4-[3-({4-[1-methyl-4-(3-{[4-(1-methylimidazole-2-amido)-1H-pyrrol-2-yl]formamido}propanamido)imidazole-2-amido]-1H-pyrrol-2-yl}formamido)propanamido]imidazole-2-carboxylic acid (PA-048-Des)**

[00511] **Scheme 4.**



[00512] ***Step 1: Synthesis of ethyl 4-amino-1H-pyrrole-2-carboxylate***

[00513] The procedure was the same as ethyl 4-amino-1-methylimidazole-2- carboxylate (Example 1, step 1), but the reaction time was 18.0 h. 5.00 g of ethyl 4-nitro-1H-pyrrole-2-carboxylate was used, 4.00 g of ethyl 4-amino-1H-pyrrole-2-carboxylate was obtained as brown solid (95.56% yield). LC/MS: mass calcd. For $C_7H_{10}N_2O_2$: 154.07, found: 155.25 $[M+H]^+$.

[00514] ***Step 2: Synthesis of ethyl 4-amino-1H-pyrrole-2-carboxylate***

[00515] Into a 100 mL flask was added 1-methylimidazole-2-carboxylic acid (0.82 g, 6.49 mmol, 1.00 equiv), DMF (20.00 mL), ethyl 4-amino-1H-pyrrole-2-carboxylate (1.00 g, 6.486 mmol, 1.00 equiv), DIEA (3.36 g, 26.01 mmol, 4.01 equiv), the mixture was stirred at room temperature for 5.0 mins, then PyBOP (4.39 g, 8.43 mmol, 1.30 equiv) was added, the reaction was stirred at room temperature for 1.0 h. The reaction was quenched by the addition of water (60 mL) at 0 °C. The resulting mixture was extracted with EtOAc (3x20 mL). The combined organic layers were washed with brine (2x10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with (PE:EA=1:1) to afford ethyl 4-(1-methylimidazole-2-amido)-1H-pyrrole-2-carboxylate (1.50 g, 88.17%) as light green solid. LC/MS: mass calcd. For $C_{12}H_{14}N_4O_3$: 262.11, found: 263.25 $[M+H]^+$.

[00516] ***Step 3: Synthesis of 4-(1-methylimidazole-2-amido)-1H-pyrrole-2-carboxylic acid***

[00517] The procedure was the same as 4-[3-[(tert-butoxycarbonyl)amino] propanamido]-1-methylimidazole-2-carboxylic acid (Example 1 step 9), but the reaction temperature was 30 °C and the reaction solvent was MeOH/THF (2:1). 2.00 g of ethyl 4-(1-methylimidazole-2-amido)-1H-pyrrole-2-carboxylate was used, 2.00 g crude of 4-(1-methylimidazole-2-amido)-1H-pyrrole-2-carboxylic acid was obtained as brown solid. LC/MS: mass calcd. For $C_{10}H_{10}N_4O_3$: 234.08, found: 235.05 $[M+H]^+$.

[00518] ***Step 4: Synthesis of ethyl 1-methyl-4-(3-{[4-(1-methylimidazole-2-amido)-1H- pyrrol-2-yl]formamido}propanamido)imidazole-2-carboxylate***

[00519] The procedure was the same as ethyl 4-amino-1H-pyrrole-2-carboxylate (Example 4 step 2). 1.60 g of 4-(1-methylimidazole-2-amido)- 1H-pyrrole-2-carboxylic acid was used, 1.10 g of ethyl 1-methyl-4- (3-{[4-(1-methylimidazole-2-amido)-1H-pyrrol-2-yl]formamido}propanamido)imidazole-2-carboxylate was obtained as brown solid (35.28% yield). LC/MS: mass calcd. For $C_{20}H_{24}N_8O_5$: 456.19, found: 457.30 $[M+H]^+$.

[00520] ***Step 5: Synthesis of 1-methyl-4-(3-{[4-(1-methylimidazole-2-amido)-1H-pyrrol- 2-yl]formamido}propanamido)imidazole-2-carboxylic acid***

[00521] The procedure was the same as 4-[3-[(tert-butoxycarbonyl)amino] propanamido]-1-methylimidazole-2-carboxylic acid (Example 1 step 9), but the reaction time was 1.0 h and the reaction solvent was MeOH/THF(1:1). 1.10 g of ethyl 1-methyl-4-(3-{[4-(1-methylimidazole-2-amido)-1H-pyrrol-2-yl]formamido}propanamido)imidazole-2-carboxylate was used, 760.00 mg of 1-methyl-4-(3-{[4-(1-methylimidazole-2-amido)-1H-pyrrol-2-yl]formamido}propanamido)imidazole-2-carboxylic acid was obtained as white solid (73.62% yield). LC/MS: mass calcd. For $C_{18}H_{20}N_8O_5$: 428.16, found: 429.15 $[M+H]^+$.

[00522] ***Step 6: Synthesis of ethyl 4-[1-methyl-4-(3-{[4-(1-methylimidazole-2-amido)- 1H-pyrrol-2-yl]formamido}propanamido)imidazole-2-amido]-1H-pyrrole-2-carboxylate***

[00523] The procedure was the same as methyl 4-(4-{4-[(tert-butoxycarbonyl)amino]- 1-methylpyrrole-2-amido}-1-methylimidazole-2-amido)-1-methylpyrrole-2-carboxylate (Example 3 step 2). 760.00 mg of 1-methyl-4-(3-{[4-(1-methylimidazole- 2-amido)-1H-pyrrol-2-yl]formamido}propanamido)imidazole-2-carboxylic acid was used, 1.00 g crude of ethyl 4-[1-methyl-4-(3-{[4-(1-methylimidazole-2-amido)- 1H-pyrrol-2-yl]formamido}propanamido)imidazole-2-amido]-1H-pyrrole-2-carboxylate was obtained as brown solid. LC/MS: mass calcd. For $C_{25}H_{28}N_{10}O_6$: 564.22, found: 565.45 $[M+H]^+$.

[00524] ***Step 7: Synthesis of 4-[1-methyl-4-(3-{[4-(1-methylimidazole-2-amido)-1H- pyrrol-2-yl]formamido}propanamido)imidazole-2-amido]-1H-pyrrole-2-carboxylic acid***

[00525] The procedure was the same as 4-[3-[(tert-butoxycarbonyl)amino] propanamido]-1-methylimidazole-2-carboxylic acid (Example 1 step 3), but the reaction temperature was 40 degrees C and the reaction time was 1.0 h. 1.00 g of ethyl 4-[1-methyl-4-(3-{[4-(1-methylimidazole-2-amido)-1H-pyrrol-2-yl]formamido}propanamido)imidazole-2-amido]-1H-pyrrole-2-carboxylate was used, 930.00 mg crude of 4-[1-methyl-4-(3-{[4-(1-methylimidazole-2-amido)-1H-pyrrol-2-yl]formamido}propanamido)imidazole-2-

amido]-1H-pyrrole-2-carboxylic acid was obtained as brown solid. LC/MS: mass calcd. For $C_{23}H_{24}N_{10}O_6$: 536.19, found: 537.20 $[M+H]^+$.

[00526] ***Step 8: Synthesis of ethyl 1-methyl-4-[3-({4-[1-methyl-4-(3-{[4-(1- methylimidazole-2-amido)-1H-pyrrol-2-yl]formamido}propanamido)imidazole-2-amido]-1H-pyrrol-2-yl}formamido)propanamido]imidazole-2-carboxylate***

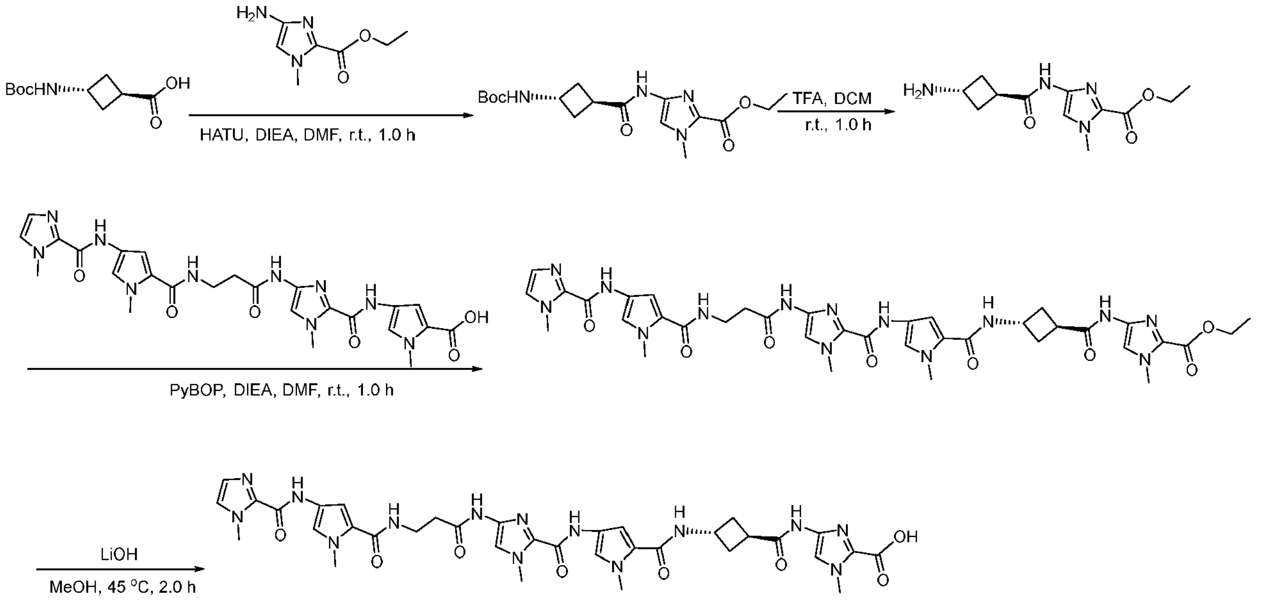
[00527] Into a 100 mL flask was added 4-[1-methyl-4-(3-{[4-(1-methylimidazole-2- amido)-1H-pyrrol-2-yl]formamido}propanamido)imidazole-2-amido]-1H-pyrrole-2-carboxylic acid (650.00 mg, 1.21 mmol, 1.00 equiv), DMF (10.00 mL), ethyl 4-(3-aminopropanamido)-1-methylimidazole-2-carboxylate (292.00 mg, 1.22 mmol, 1.00 equiv), EDCI (1161.00 mg, 6.06 mmol, 5.00 equiv), the mixture was stirred at room temperature for 5.0 mins, then DMAP (740.00 mg, 6.06 mmol, 5.00 equiv) was added, the reaction was stirred at room temperature for 17.0 h. The reaction was poured into ice water (30 mL), The precipitated solids were collected by filtration and washed with water (3x10 mL), dried under vacuum, the crude product was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (0.05% TFA), 10% to 50% gradient in 50 min; detector, UV 254 nm. The fractions were combined and concentrated. This resulted in ethyl 1-methyl-4-[3-({4-[1-methyl-4-(3-{[4-(1-methylimidazole-2-amido)-1H-pyrrol-2-yl]formamido}propanamido)imidazole-2-amido]-1H-pyrrol-2-yl}formamido)propanamido]imidazole-2-carboxylate (320.00 mg, 34.81%) as brown solid. LC/MS: mass calcd. For $C_{33}H_{38}N_{14}O_8$: 758.30, found: 759.55 $[M+H]^+$.

[00528] ***Step 9: Synthesis of 1-methyl-4-[3-({4-[1-methyl-4-(3-{[4-(1-methylimidazole- 2-amido)-1H-pyrrol-2-yl]formamido}propanamido)imidazole-2-amido]-1H-pyrrol-2-yl}formamido)propanamido]imidazole-2-carboxylic acid (PA-048-Des)***

[00529] The procedure was the same as 4-[3-[(tert-butoxycarbonyl)amino] propanamido]-1-methylimidazole-2-carboxylic acid (Example 1 step 3), but the reaction temperature was room temperature. 310.00 mg of ethyl 1-methyl-4-[3-({4-[1-methyl-4-(3-{[4-(1-methylimidazole-2-amido)-1H-pyrrol-2-yl]formamido}propanamido)imidazole-2-amido]-1H-pyrrol-2-yl}formamido)propanamido]imidazole-2-carboxylate was used, 170.00 mg crude of 1-methyl-4-[3-({4-[1-methyl-4-(3-{[4-(1-methylimidazole-2-amido)-1H-pyrrol-2-yl]formamido}propanamido)imidazole-2-amido]-1H-pyrrol-2-yl}formamido)propanamido]imidazole-2-carboxylic acid was obtained as brown solid. LC/MS: mass calcd. For $C_{31}H_{34}N_{14}O_8$: 730.27, found: 731.55 $[M+H]^+$.

[00530] **Example 5. Synthesis of 1-methyl-4-[(1r,3r)-3-{1-methyl-4-[1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-amido]pyrrole-2-amido}cyclobutaneamido]imidazole-2-carboxylic acid (PA-048-P6CB)**

[00531] **Scheme 5.**



PA-048-P6CB

[00532] ***Step 1: Synthesis of ethyl 1-methyl-4-[(1r,3r)-3-[(tert-butoxycarbonyl)amino] cyclobutaneamido]imidazole-2-carboxylate***

[00533] The procedure was the same as methyl 3-[(4-[3-[(tert-butoxycarbonyl)amino] propanamido]-1-methylimidazol-2-yl)formamido]propanoate. 200.00 mg of (1r,3r)-3-[(tert-butoxycarbonyl)amino]cyclobutane-1-carboxylic acid was used, 330.00 mg of ethyl 1-methyl-4-[(1r,3r)-3-[(tert-butoxycarbonyl)amino] cyclobutaneamido]imidazole-2-carboxylate was obtained as orange solid (96.93% yield). LC/MS: mass calcd. For $C_{17}H_{26}N_4O_5$: 366.19, found: 367.25 $[M+H]^+$.

[00534] ***Step 2: Synthesis of ethyl 1-methyl-4-[(1r,3r)-3-aminocyclobutaneamido] imidazole-2-carboxylate***

[00535] The procedure was the same as methyl 4-[4-(4-amino-1-methylpyrrole-2-amido)-1-methylimidazole-2-amido]-1-methylpyrrole-2-carboxylate (Example 2 step 3). 145.00 mg of ethyl 1-methyl-4-[(1r,3r)-3-[(tert-butoxycarbonyl)amino]cyclobutaneamido]imidazole-2-carboxylate was used, 145.00 mg crude of ethyl 1-methyl-4-[(1r,3r)-3-aminocyclobutaneamido]imidazole-2-carboxylate was obtained as yellow oil. LC/MS: mass calcd. For $C_{12}H_{18}N_4O_3$: 266.14, found: 267.10 $[M+H]^+$.

[00536] ***Step 3: Synthesis of ethyl 1-methyl-4-[(1r,3r)-3-{1-methyl-4-[1-methyl-4-(3-{[1- methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-amido]pyrrole-2-amido}cyclobutaneamido]imidazole-2-carboxylate***

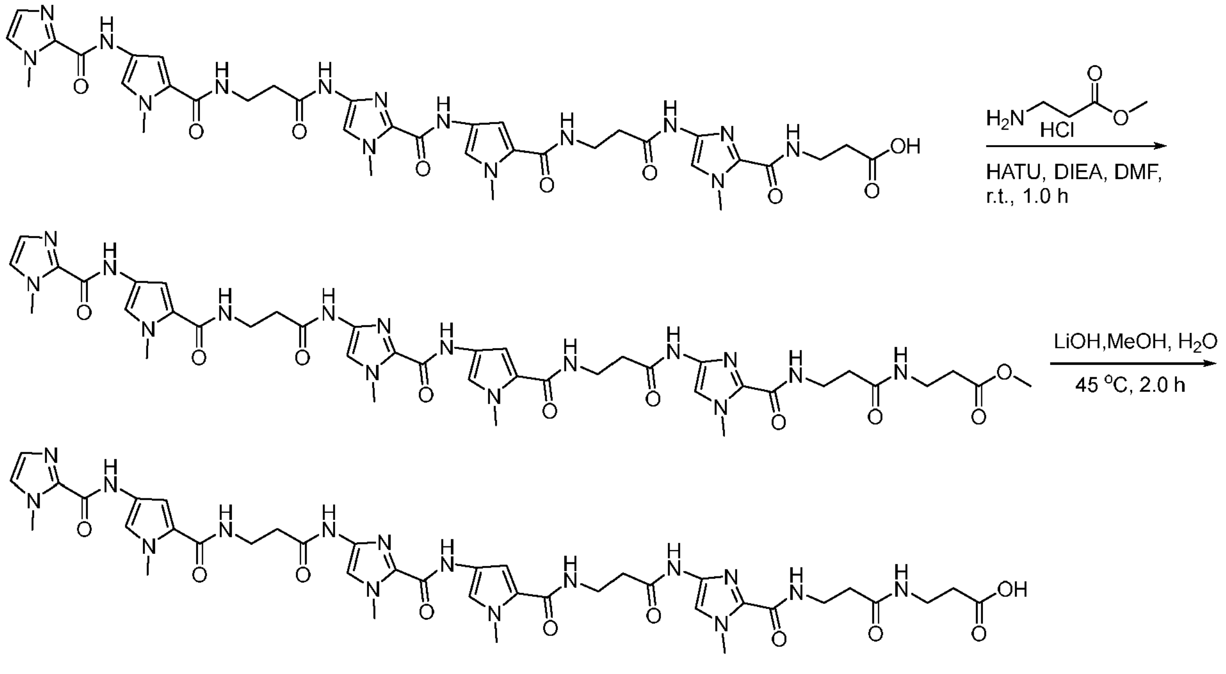
[00537] The procedure was the same as methyl 4-(4-{4-[(tert-butoxycarbonyl)amino]-1-methylpyrrole-2-amido}-1-methylimidazole-2-amido)-1-methylpyrrole-2-carboxylate (Example 2 Step 3). 105.00 mg of ethyl 1-methyl-4-[(1r,3r)-3-aminocyclobutaneamido]imidazole-2-carboxylate was used, 250.00 mg of ethyl 1-methyl-4-[(1r,3r)-3-{1-methyl-4-[1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-amido]pyrrole-2-amido}cyclobutaneamido]imidazole-2-carboxylate was obtained as light yellow solid (78.15% yield). LC/MS: mass calcd. For $C_{37}H_{44}N_{14}O_8$: 812.35, found: 813.50 $[M+H]^+$.

[00538] ***Step 4: Synthesis of 1-methyl-4-[(1r,3r)-3-{1-methyl-4-[1-methyl-4-(3-{[1- methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-amido]pyrrole-2-amido}cyclobutaneamido]imidazole-2-carboxylic acid (PA-048-P6CB)***

[00539] The procedure was the same as 4-[3-[(tert-butoxycarbonyl)amino] propanamido]-1-methylimidazole-2-carboxylic acid (Example 1 Step 3). 250.00 mg of ethyl 1-methyl-4-[(1r,3r)-3-{1-methyl-4-[1-methyl-4-(3-{[1-methyl-4-(1- methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-amido]pyrrole-2-amido}cyclobutaneamido]imidazole-2-carboxylate was used, 210.00 mg of 1-methyl-4-[(1r,3r)-3-{1-methyl-4-[1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-amido]pyrrole-2-amido}cyclobutaneamido]imidazole-2-carboxylic acid was obtained as light yellow solid (87.00% yield). LC/MS: mass calcd. For $C_{35}H_{40}N_{14}O_8$: 784.32, found: 785.40 $[M+H]^+$.

[00540] **Example 6. Synthesis of 3-(3-(1-methyl-4-(3-(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)propanamido)-1H-imidazole-2-carboxamido)propanamido)propanoic acid (PA-001-b)**

[00541] Scheme 6.



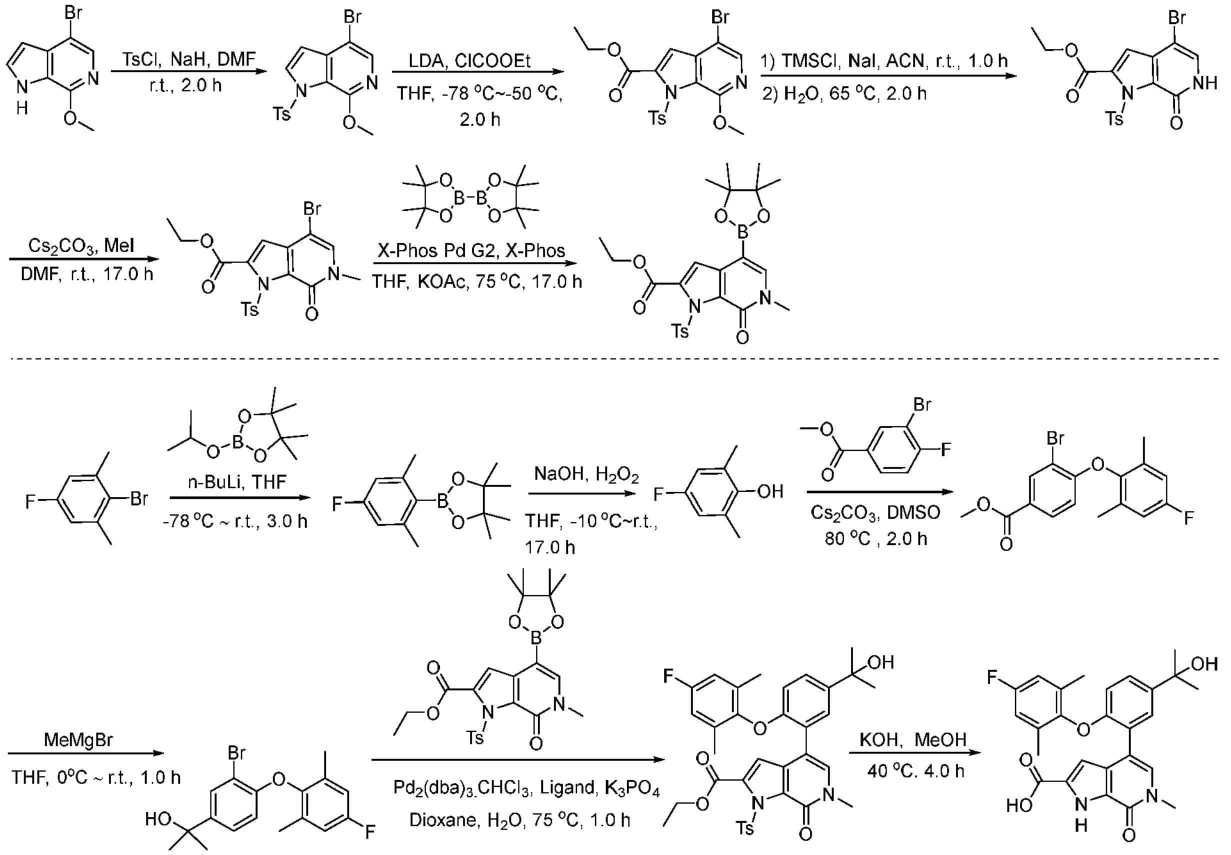
PA-01-b

[00542] Following the similar procedure as reported Example 1, 3-(3-(1-methyl-4-(3-(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)propanamido)-1H-imidazole-2-carboxamido)propanamido)propanoic acid (PA-01-b).

[00543] SYNTHESIS OF REPRESENTATIVE LIGANDS

[00544] **Example 7. Synthesis of 4-[2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl]-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid**

[00545] Scheme 7.



[00546] ***Step 1: Synthesis of 4-bromo-7-methoxy-1-(4-methylbenzenesulfonyl)pyrrolo [2,3-c]pyridine***

[00547] To a solution of 4-bromo-7-methoxy-1H-pyrrolo[2,3-c]pyridine (5.00 g, 22.12 mmol, 1.00 equiv) in DMF (20.00 mL) was added NaH (60%, 796.46 mg, 33.19 mmol, 1.50 equiv) in portions at 0 degrees C. Then the reaction was stirred for 15.0 min followed by addition of TsCl (6.30 g, 33.19 mmol, 1.50 equiv) at 0 °C. The resulting mixture was stirred for additional 2.0 h at room temperature. The mixture was poured into ice and water (60 mL). The solid was filtrated out, washed with H_2O (10 mL) and dried to afford 4-bromo-7-methoxy-1-(4-methylbenzenesulfonyl)pyrrolo[2,3-c] pyridine (7.50 g, 83.98% yield) as white solid. LCMS: mass calcd. For $C_{15}H_{13}BrN_2O_3S$: 379.98, found: 380.95, 382.95 $[M+H, M+2+H]^+$.

[00548] ***Step 2: Synthesis of ethyl 4-bromo-7-methoxy-1-tosyl-1H-pyrrolo[2,3-c]pyridine- 2-carboxylate***

[00549] To a solution of 4-bromo-7-methoxy-1-tosyl-1H-pyrrolo[2,3-c]pyridine (6.30 g, 16.58 mmol, 1.00 equiv) in THF (80.00 mL) was added LDA (2M in THF, 12.50 mL, 24.87 mmol, 1.50 equiv) dropwise at -78 °C and the mixture stirred at -78 °C to -50 °C for 1.0 h, followed by dropwise addition of ClCOOEt (2.69 g, 24.87 mmol, 1.50 equiv). After 2.0 h, the reaction mixture was quenched with saturated NH_4Cl (aq), and the residue was extracted with EA (3x300 mL). The organic phases were combined and dried over Na_2SO_4, filtrated and concentrated. The residue was purified by silica gel column chromatography, eluted with PE/EA=10:1 to afford ethyl 4-bromo-7-methoxy-1-tosyl-1H-pyrrolo[2,3-c]pyridine-2-carboxylate (7.00 g, 90.11% yield) as white solid. LCMS: mass calcd. For $C_{18}H_{17}BrN_2O_5S$: 452.00, found: 453.00, 455.00 $[M+H, M+2+H]^+$.

[00550] ***Step 3: Synthesis of ethyl 4-bromo-7-oxo-1-tosyl-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxylate***

[00551] To a stirred solution of ethyl 4-bromo-7-methoxy-1-tosyl-1H-pyrrolo[2,3-c] pyridine-2-carboxylate (4.00 g, 8.850 mmol, 1.00 equiv) in CH_3CN (80.00 mL) was added TMSCl (1.45 g, 13.28 mmol, 1.50 equiv) and NaI (2.00 g, 13.28 mmol, 1.50 equiv) in portions at room temperature under N_2 atmosphere. The mixture was stirred for 1.0 h at room temperature, then H_2O (238.95 mg, 13.28 mmol, 1.50 equiv) was added dropwise at 65 °C. The mixture was stirred for 2.0 h at 65 °C. The reaction mixture was cooled to room temperature. The precipitate was filtered, washed with water (50 mL), dried over vacuum. Ethyl 4-bromo-7-oxo-1-tosyl-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxylate (4.30 g, crude) was obtained as brown solid. LCMS: mass calcd. For $C_{17}H_{15}BrN_2O_5S$: 437.99, found: 438.95, 440.95 $[M+H, M+2+H]^+$.

[00552] ***Step 4: Synthesis of ethyl 4-bromo-6-methyl-1-(4-methylbenzenesulfonyl)-7- oxopyrrolo[2,3-c]pyridine-2-carboxylate***

[00553] To a solution of ethyl 4-bromo-7-oxo-1-tosyl-6,7-dihydro-1H-pyrrolo[2,3-c] pyridine-2-carboxylate (4.30 g, 9.82 mmol, 1.00 equiv) in DMF (20.00 mL) was added Cs_2CO_3 (3.83 g, 11.78 mmol, 1.20 equiv), MeI (1.67 g, 11.78 mmol, 1.20 equiv) was added dropwise into this reaction. The reaction mixture was stirred for 17.0 h at room temperature under N_2 atmosphere. The mixture was poured into ice water (60 mL). The solid was filtrated out, washed with H_2O (10 mL) and dried to afford ethyl 4-bromo-6-methyl-1-(4-methylbenzenesulfonyl)-7-oxopyrrolo[2,3-c]pyridine-2-carboxylate (4.30 g, crude) as brown solid. LCMS: mass calcd. For $C_{18}H_{17}BrN_2O_5S$: 452.00, found: 453.15, 455.15 $[M+H, M+2+H]^+$.

[00554] ***Step 5: Synthesis of ethyl 6-methyl-1-(4-methylbenzenesulfonyl)-7-oxo-4-(4, 4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolo[2,3-c]pyridine-2-carboxylate***

[00555] To a solution of ethyl 4-bromo-6-methyl-1-(4-methylbenzenesulfonyl)-7- oxopyrrolo[2,3-c]pyridine-2-carboxylate (1.00 g, 2.21 mmol, 1.00 equiv) in THF (30.00 mL) was added bis(pinacolato)diboron (1.12 g, 4.41 mmol, 2.00 equiv), KOAc (650.00 mg, 6.62 mmol, 3.00 equiv), X-Phos Pd G2 (175.00 mg, 0.22 mmol, 0.10 equiv) and X-Phos (106.00 mg, 0.22 mmol, 0.10 equiv) at room temperature under N_2 atmosphere. The resulting mixture was stirred for 17.0 h at 75 °C under N_2 atmosphere. The mixture was concentrated, 40 mL H_2O was added to the residue, then the mixture was extracted with EA (3x40 mL), the organic phases were combined and washed with NaCl solution (40 mL), dried over Na_2SO_4. The solid was filtrated out and the filtrate was concentrated. Ethyl 6-methyl-1-(4-methylbenzenesulfonyl)-7- oxo-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolo[2,3-c]pyridine-2-carboxylate (2.20 g, crude) was obtained as yellow solid. The crude was used for next step directly. LCMS: mass calcd. For $C_{21}H_{25}BN_2O_5S$: 500.18, found: 501.10 $[M+H]^+$.

[00556] ***Step 6: Synthesis of 2-(4-fluoro-2,6-dimethylphenyl)-4,4,5,5-tetramethyl-1,3,2- dioxaborolane***

[00557] A solution of 2-bromo-5-fluoro-1,3-dimethylbenzene (5.00 g, 24.62 mmol, 1.00 equiv) in THF(15.00 mL) was added n-BuLi (2.5 M, 14.77 mL, 36.94 mmol, 1.50 equiv) dropwise at -78 °C under N_2

atmosphere. The mixture was stirred for 3.0 h at -78 °C, then 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6.87 g, 36.94 mmol, 1.50 equiv) was added dropwise at -78 °C. The resulting mixture was warmed to room temperature naturally and stirred for 3.0 h. After reaction, the reaction was quenched with water (20 mL) at 0 °C. The resulting mixture was extracted with EtOAc (3x20 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford 2-(4-fluoro-2,6-dimethylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6.70 g, crude) as a light yellow oil. The crude product was used in the next step directly without further purification. LC/MS: mass calcd. For $C_{14}H_{20}BFO_2$: 250.15, found: 251.30 $[M+1]^+$.

[00558] ***Step 7: Synthesis of 4-fluoro-2,6-dimethylphenol***

[00559] To a stirred solution of 2-(4-fluoro-2,6-dimethylphenyl)-4,4,5,5-tetramethyl-1, 3,2-dioxaborolane (6.70 g, 26.79 mmol, 1.00 equiv) in THF (20.00 mL) were added NaOH (1.61 g, 40.25 mmol, 1.50 equiv) and H_2O_2 (9.99 mL, 428.59 mmol, 16.00 equiv) dropwise at -10 °C under N_2 atmosphere. The resulting mixture was stirred for 17.0 h at room temperature. After reaction, the mixture was acidified to pH=1 with HCl (aq. 2M). The resulting mixture was extracted with EtOAc (3x20 mL). The combined organic layers were washed with saturated $NaHCO_3$ (aq.) (1x10 mL) and saturated $Na_2S_2O_3$(aq.) (1x10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with hexane/EtOAc (12:1) to afford 4-fluoro-2,6-dimethylphenol (2.70 g, 66.88% yield) as white solid. ^{1}HNMR (400 MHz, DMSO) δ: 8.12 (s, 1H), 6.73 (d, J = 9.3 Hz, 2H), 2.16 (s, 6H).

[00560] ***Step 8: Synthesis of methyl 3-bromo-4-(4-fluoro-2,6-dimethylphenoxy)benzoate***

[00561] To a stirred solution of 4-fluoro-2,6-dimethylphenol (2.70 g, 19.26 mmol, 1.00 equiv) and methyl 3-bromo-4-fluorobenzoate (4.94 g, 21.20 mmol, 1.10 equiv) in DMSO (20.00 mL) were added Cs_2CO_3 (9.41 g, 28.90 mmol, 1.50 equiv) at room temperature. The resulting mixture was stirred for 2.0 h at 80 °C. After reaction, the reaction was quenched by the addition of water (30 mL) at room temperature. The resulting mixture was extracted with EtOAc (3x20 mL). The combined organic layers were combined and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with hexane/EtOAc (12:1) to afford methyl 3-bromo-4-(4-fluoro-2,6-dimethylphenoxy)benzoate (6.80 g, 94.95% yield) as white solid. LC/MS: mass calcd. For $C_{16}H_{14}BrFO_3$: 352.01, found: 353.15 $[M+H]^+$.

[00562] ***Step 9: Synthesis of 2-[3-bromo-4-(4-fluoro-2,6-dimethylphenoxy)phenyl]propan- 2-ol***

[00563] To a stirred solution of methyl 3-bromo-4-(4-fluoro-2,6-dimethylphenoxy) benzoate (2.00 g, 5.66 mmol, 1.00 equiv) in THF (10.00 mL) were added bromo (methyl)magnesium (3.00 M in 2-Me-THF, 11.33 mL, 33.98 mmol, 6.00 equiv) at 0 °C under N_2 atmosphere. The resulting mixture was stirred for 1.0 h at 0 °C under N_2 atmosphere. After reaction, the reaction was quenched by the addition of sat. NH_4Cl (aq.) (10 mL) at 0 degrees C. The resulting mixture was extracted with EtOAc (3x10 mL). The combined organic layers were combined and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with hexane/EtOAc

(10:1) to afford 2-[3-bromo-4-(4-fluoro-2,6-dimethyl phenoxy)phenyl]propan-2-ol (1.80 g, 77.40 % yield) as white solid. LC/MS: mass calcd. For $C_{17}H_{18}BrFO_2$: 352.05, found: 335.00 $[M\text{-}OH]^+$.

[00564] ***Step 10: Synthesis of ethyl 4-[2-(4-fluoro-2,6-dimethylphenoxy)-5-(2- hydroxypropan-2-yl)phenyl]-6-methyl-1-(4-methylbenzenesulfonyl)-7-oxopyrrolo[2,3-c]pyridine-2-carboxylate***

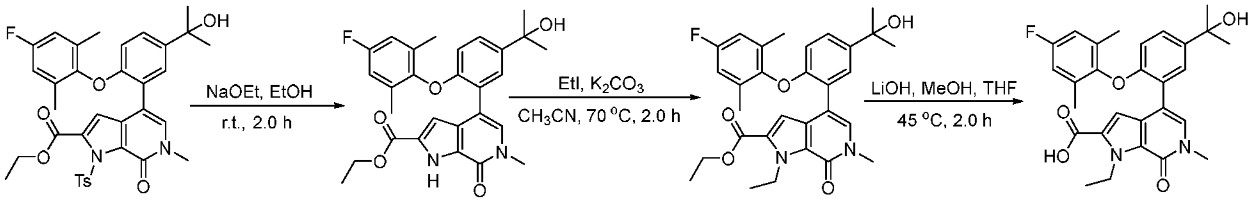
[00565] To a stirred solution of 2-[3-bromo-4-(4-fluoro-2,6-dimethylphenoxy)phenyl] propan-2-ol (500.00 mg, 1.42 mmol, 1.00 equiv) and ethyl 6-methyl-1-(4- methylbenzenesulfonyl)-7-oxo-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolo[2,3-c]pyridine-2-carboxylate (1.42 g, 2.83 mmol, 2.00 equiv) in dioxane (16.00 mL) and H_2O (4.00 mL) were added $Pd_2(dba)_3.CHCl_3$ (129.62 mg, 0.14 mmol, 0.10 equiv), K_3PO_4 (901.39 mg, 4.25 mmol, 3.00 equiv) and 1,3,5,7-tetramethyl-2,4,8-trioxa- 6-phenyl-6-phosphaadamantane (82.00 mg, 0.28 mmol, 0.20 equiv) at room temperature under N_2 atmosphere. The resulting mixture was stirred for 1.0 h at 75 °C under N_2 atmosphere. The reaction was quenched with water at room temperature. The resulting mixture was extracted with EtOAc (3x20 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with hexane/EtOAc (1:1) to afford ethyl 4-[2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl]-6-methyl-1-(4-methylbenzenesulfonyl)-7-oxopyrrolo[2,3-c]pyridine-2-carboxylate (620.00 mg, 48.76% yield) as white solid. LC/MS: mass calcd. For $C_{35}H_{35}FN_2O_7S$: 646.21, found: 647.20 $[M+H]^+$.

[00566] ***Step 11: Synthesis of 4-[2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2 -yl)phenyl]-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid***

[00567] To a stirred solution/mixture of ethyl 4-[2-(4-fluoro-2,6-dimethylphenoxy)-5-(2- hydroxypropan-2-yl)phenyl]-6-methyl-1-(4-methylbenzenesulfonyl)-7-oxopyrrolo[2,3-c]pyridine-2-carboxylate (600.00 mg, 0.93 mmol, 1.00 equiv) in MeOH (15.00 mL) were added KOH (2M, 3.71 mL, 7.42 mmol, 8.00 equiv) at room temperature. The resulting mixture was stirred for 4.0 h at 40 °C. After reaction, the resulting mixture was concentrated under vacuum. Then the residue was dissolved in water (10 mL) and acidified to pH 3 with HCl (2M aq.). The precipitated solids were collected by filtration and washed with water (3x10 mL). The solid was concentrated under vacuum to afford 4-[2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl) phenyl]-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (390.00 mg, 64.26% yield) as white solid. LC/MS: mass calcd. For $C_{26}H_{25}FN_2O_5$: 464.17, found: 465.15 $[M+H]^+$.

[00568] **Example 8. Synthesis of 1-ethyl-4-[2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl]-6-methyl-7-oxopyrrolo[2,3-c]pyridine-2-carboxylic acid**

[00569] **Scheme 8.**



[00570] ***Step 1: Synthesis of ethyl 4-[2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl]-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-carboxylate***

[00571] To a stirred solution of ethyl 4-[2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl]-6-methyl-1-(4-methylbenzenesulfonyl)-7-oxopyrrolo[2,3-c]pyridine-2-carboxylate (3.40 g, 5.26 mmol, 1.00 equiv) in ethyl alcohol (50.00 mL) was added sodium ethoxide (894.40 mg, 13.14 mmol, 2.50 equiv) at room temperature. The resulting mixture was stirred for 2.0 h at room temperature. After reaction, the reaction was poured into citric acid solution (3.32 g, 3.00 equiv, 125 mL). Then the resulting mixture was extracted with EtOAc (3x150 mL). The combined organic layers were washed with water (2x50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was washed with diethyl ether (3x10 mL) to afford ethyl 4-[2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl]-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-carboxylate (2.00 g, 71.78% yield) as white solid. LCMS: mass calcd. For $C_{28}H_{29}FN_2O_5$: 492.21, found: 493.40 $[M+H]^+$.

[00572] ***Step 2: Synthesis of ethyl 1-ethyl-4-[2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl]-6-methyl-7-oxopyrrolo[2,3-c]pyridine-2-carboxylate***

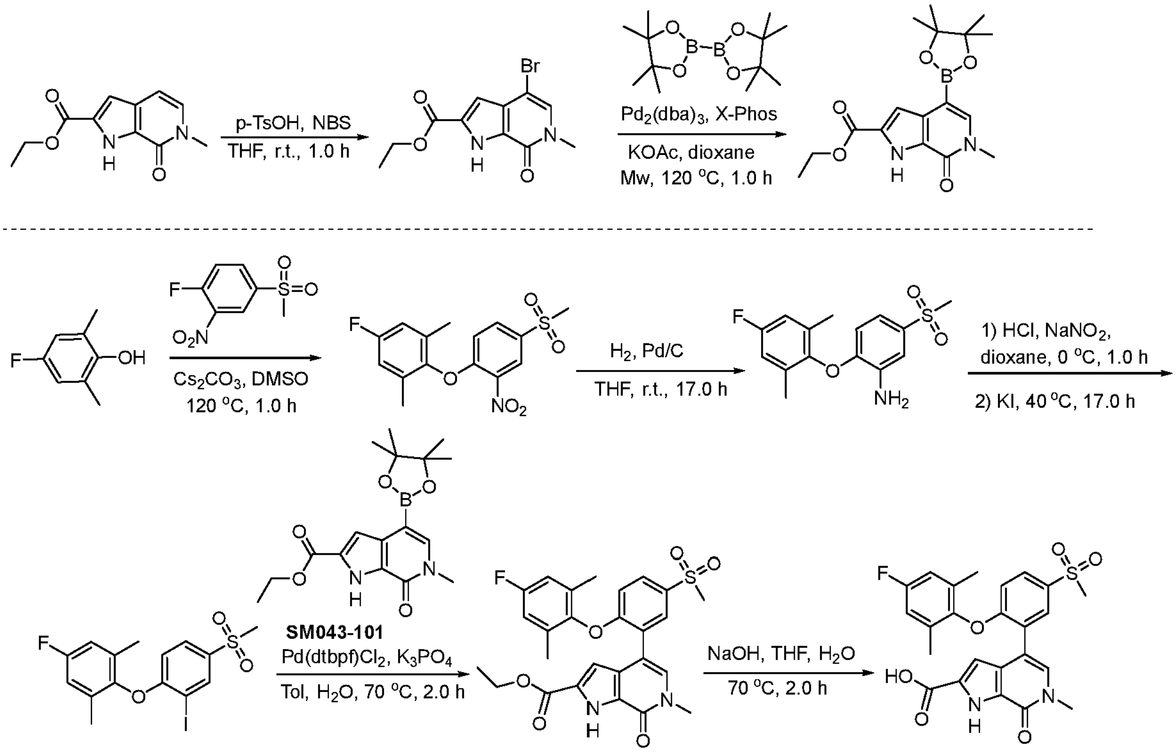
[00573] The procedure was the same as ethyl 1-(5-bromopentyl)-4-[(tert-butoxycarbonyl)amino]pyrrole-2-carboxylate, but the reaction time was 2.0 h. 500.00 mg of ethyl 4-[2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl]-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-carboxylate was used, 500.00 mg of ethyl 1-ethyl-4-[2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl]-6-methyl-7-oxopyrrolo[2,3-c]pyridine-2-carboxylate was obtained as white solid (94.61% yield). LC/MS: mass calcd. For $C_{30}H_{33}FN_2O_5$: 520.24, found: 521.35 $[M+H]^+$.

[00574] ***Step 3: Synthesis of 1-ethyl-4-[2-(4-fluoro-2,6-dimethylphenoxy)- 5-(2-hydroxypropan-2-yl)phenyl]-6-methyl-7-oxopyrrolo[2,3-c]pyridine-2-carboxylic acid***

[00575] The procedure was the same as 4-[3-[(tert-butoxycarbonyl)amino] propanamido]-1-methylimidazole-2-carboxylic acid, but the reaction solvent was MeOH/THF (1:5). 500.00 mg of ethyl 1-ethyl-4-[2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl]-6-methyl-7-oxopyrrolo[2,3-c]pyridine-2-carboxylate was used, 514.00 mg crude of 1-ethyl-4-[2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl]-6-methyl-7-oxopyrrolo[2,3-c]pyridine-2-carboxylic acid was obtained as light yellow solid. LC/MS: mass calcd. For $C_{28}H_{29}FN_2O_5$: 492.21, found: 493.15 $[M+H]^+$.

[00576] **Example 9. Synthesis of 4-[2-(4-fluoro-2,6-dimethylphenoxy)-5-methanesulfonylphenyl]-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid**

[00577] **Scheme 9.**



[00578] ***Step 1: Synthesis of ethyl 4-bromo-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-carboxylate***

[00579] To a stirred solution of ethyl 6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2- carboxylate (10.00 g, 45.41 mmol, 1.00 equiv) in tetrahydrofuran (150.00 mL) was added NBS (8.08 g, 45.41 mmol, 1.00 equiv) and p-TsOH (3.91 g, 22.70 mmol, 0.50 equiv). The resulting mixture was stirred at room temperature for 1.0 h. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography (0-10% MeOH/DCM) to afford ethyl 4-bromo-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-carboxylate (13.00 g, 95.71% yield) as yellow solid. LC/MS: mass calcd. For $C_{11}H_{11}BrN_2O_3$: 298.00, found: 299.00, 301.00 $[M+H, M+2+H]^+$.

[00580] ***Step 2: Synthesis of 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***

[00581] To a stirred solution of ethyl 4-bromo-6-methyl-7-oxo-1H-pyrrolo[2,3-c] pyridine-2-carboxylate (13.00 g, 43.46 mmol, 1.00 equiv) in dioxane (150.00 mL) was added bis(pinacolato)diboron (22.07 g, 86.92 mmol, 2.00 equiv), $Pd_2(dba)_3.CHCl_3$ (4.00 g, 4.36 mmol, 0.10 equiv) and AcOK (8.53 g, 86.92 mmol, 2.00 equiv). The final reaction mixture was irradiated with microwave radiation for 1.0 h at 120 °C. The reaction was proceeded on 1.0 g scale and 13 times were repeated. Then the reaction mixtures were combined and worked up together. 150 mL H_2O was added, the resulting mixture was extracted with EA (3x150 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography (50-70% EA/PE) to afford 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 (10.00 g, 66.47% yield) as yellow solid. LC/MS: mass calcd. For $C_{17}H_{23}BN_2O_5$: 346.17, found: 347.20 $[M+H]^+$.

[00582] ***Step 3: Synthesis of 5-fluoro-2-(4-methanesulfonyl-2-nitrophenoxy)-1,3- dimethylbenzene***

[00583] The procedure was the same as methyl 3-bromo-4-(4-fluoro-2,6-dimethylphenoxy)benzoate, but the reaction temperature was 120 °C and the reaction time was 1.0 h. 2.00 g of 4-fluoro-2,6-dimethylphenol was used, 4.60 g of desired product was obtained as off-white solid (94.05% yield). ^{1}H NMR (300 MHz, DMSO-d6) δ: 8.60 (s, 1H), 8.07 (d, J = 9.0 Hz, 1H), 7.16 (d, J = 9.0 Hz, 2H), 6.88 (d, J = 9.0 Hz, 1H), 3.31 (s, 3H), 2.09 (s, 6H).

[00584] ***Step 4: Synthesis of 2-(2,4-difluorophenoxy)-5-methanesulfonylaniline***

[00585] To a stirred solution of 1-(2,4-difluorophenoxy)-4-methanesulfonyl- 2-nitrobenzene (500.00 mg, 1.52 mmol, 1.00 equiv) in THF (10.00 mL) was added Pd/C (100.00 mg, 20% w/w). The mixture was hydrogenated at room temperature for 17.0 h under H_2 atmosphere using a hydrogen balloon. The resulting mixture was filtered, the filter cake was washed with EA (3x20 mL). The filtrate was concentrated under reduced pressure to afford 2-(2,4-difluorophenoxy)-5-methanesulfonylaniline (450.00 mg, crude) as light yellow oil. The crude product was used in the next step directly without further purification. LC/MS: mass calcd. $C_{15}H_{16}FNO_3S$: 309.08 found: 310.10 $[M+H]^+$.

[00586] ***Step 5: Synthesis of 5-fluoro-2-(2-iodo-4-methanesulfonylphenoxy)-1,3- dimethylbenzene***

[00587] To a stirred solution of 2-(4-fluoro-2,6-dimethylphenoxy)-5-methanesulfonylaniline (500.00 mg, 1.62 mmol, 1.00 equiv) in dioxane (5.00 mL) was added concentrated hydrogen chloride (1.00 mL) dropwise at 0 °C. The resulting mixture was stirred for 10.0 min at 0 °C. To the above mixture was added sodium nitrite (133.81 mg, 1.94 mmol, 1.20 equiv) at 0 °C. The resulting mixture was stirred for additional 1.0 h at 0 °C. To the above mixture was added KI (536.60 mg, 3.23 mmol, 2.00 equiv) at 0 °C. The resulting mixture was stirred for additional 17.0 h at 40 °C. After reaction, the reaction was quenched with water (5 mL) at room temperature. The resulting mixture was extracted with EtOAc (3x10 mL). The combined organic layers were washed with water (1x10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE/EA 5:1) to afford 5-fluoro-2-(2-iodo-4-methanesulfonylphenoxy)-1,3-dimethylbenzene (250.00 mg, 31.65% yield) as light yellow oil. LC/MS: mass calcd. $C_{15}H_{14}FIO_3S$: 419.97, found: 442.95 $[M+Na]^+$.

[00588] ***Step 6: Synthesis of ethyl 4-[2-(4-fluoro-2,6-dimethylphenoxy)-5- methanesulfonylphenyl]-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-carboxylate***

[00589] To a stirred solution of 5-fluoro-2-(2-iodo-4-methanesulfonylphenoxy)-1,3- dimethylbenzene (380.00 mg, 0.90 mmol, 1.00 equiv) in toluene (6.00 mL) and water (1.50 mL) was added 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 (469.56 mg, 1.36 mmol, 1.50 equiv), K_3PO_4 (383.88 mg, 1.81 mmol, 2.00 equiv) and Pd(dtbpf)Cl_2 (58.93 mg, 0.09 mmol, 0.10 equiv) at room temperature under N_2 atmosphere. The resulting mixture was stirred for 2.0 h at 70 °C under N_2 atmosphere. After reaction, the reaction was quenched with water (10 mL) at room temperature. The resulting mixture was extracted with EtOAc (3x10 mL). The combined organic layers were washed with water (1x5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (0~100%) to afford ethyl 4-[2-(4-fluoro-2,6-dimethylphenoxy)-5-methanesulfonylphenyl]-6-methyl-7-oxo-

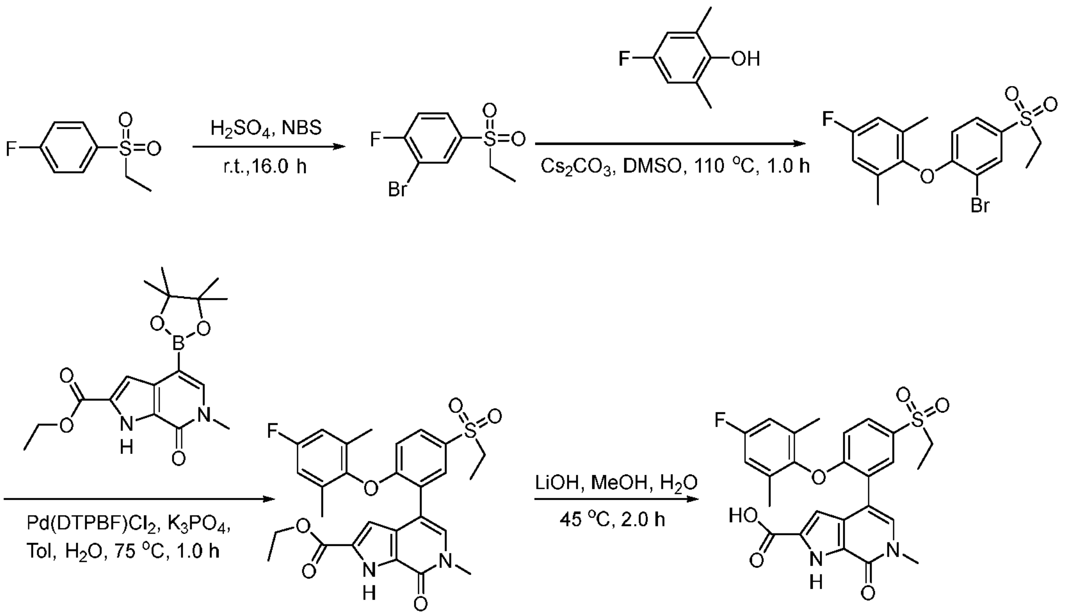
1H-pyrrolo[2,3-c]pyridine-2-carboxylate (250.00 mg, 52.86% yield) as dark yellow solid. LC/MS: mass calcd. $C_{26}H_{25}FN_2O_6S$: 512.14, found: 513.30 $[M+H]^+$.

[00590] ***Step 7: Synthesis of 4-[2-(4-fluoro-2,6-dimethylphenoxy)-5- methanesulfonylphenyl]-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid***

[00591] To a stirred solution of ethyl 4-[2-(4-fluoro-2,6-dimethylphenoxy)-5- methanesulfonylphenyl]-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-carboxylate (240.00 mg, 0.47 mmol, 1.00 equiv) in tetrahydrofuran (1.00 mL) and water (5.00 mL) was added caustic soda (74.91 mg, 1.87 mmol, 4.00 equiv) at room temperature. The resulting mixture was stirred for 2.0 h at 70 °C. After reaction, the resulting mixture was concentrated under reduced pressure. The residue was dissolved in water (5 mL). The mixture was acidified to pH 4 with HCl (aq. 2M). The precipitated solids were collected by filtration and washed with water (3x5 mL), dried under vacuum. This resulted in 4-[2-(4-fluoro-2,6-dimethylphenoxy)-5- methanesulfonylphenyl]- 6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (170.00 mg, 73.44% yield) as light yellow solid. LC/MS: mass calcd. For $C_{24}H_{21}FN_2O_6S$: 484.11, found: 485.10 $[M+H]^+$.

[00592] **Example 10. Synthesis of 4-[5-(ethanesulfonyl)-2-(4-fluoro-2,6-dimethylphenoxy)phenyl]-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid**

[00593] **Scheme 10.**



[00594] ***Step 1: Synthesis of 2-bromo-4-(ethanesulfonyl)-1-fluorobenzene***

[00595] To a stirred solution of fluoresone (1.00 g, 5.31 mmol, 1.00 equiv) in H_2SO_4 (6.00 mL) was added NBS (1.04 g, 5.84 mmol, 1.10 equiv). The resulting mixture was stirred at room temperature for 16.0 h. The resulting mixture was poured into ice water (20 mL). The precipitated solids were collected by filtration, washed with PE (50 mL) and dried to afford 2-bromo-4-(ethanesulfonyl)-1-fluorobenzene (890.00 mg, 62.71% yield) as yellow solid. LC/MS: mass calcd. For $C_8H_8BrFO_2S$: 265.94, 267.05, 268.95[M+H, M+H+2].

[00596] ***Step 2: Synthesis of 2-[2-bromo-4-(ethanesulfonyl)phenoxy]-5-fluoro-1,3- dimethylbenzene***

[00597] The procedure was the same as methyl 3-bromo-4-(4-fluoro-2,6- dimethylphenoxy)benzoate (Example 9 step 2), but the reaction temperature was 110 °C, the reaction time was 1.0 h and the crude product was used for next step without purification. 870.00 mg of 1,3-Dibromo-5-(ethanesulfonyl)- 2-fluorobenzene was used, 950.00 mg of 2-[2-bromo-4-(ethanesulfonyl) phenoxy]-5-fluoro-1,3-dimethylbenzene was obtained as yellow solid (97.56% yield). LC/MS: mass calcd. $C_{16}H_{16}BrFO_3S$: 386.00, found: 387.05, 389.05 $[M+H, M+2+H]^+$.

[00598] ***Step 3: Synthesis of 2-[2-bromo-4-(ethanesulfonyl)phenoxy]-5- fluoro-1,3-dimethylbenzene***

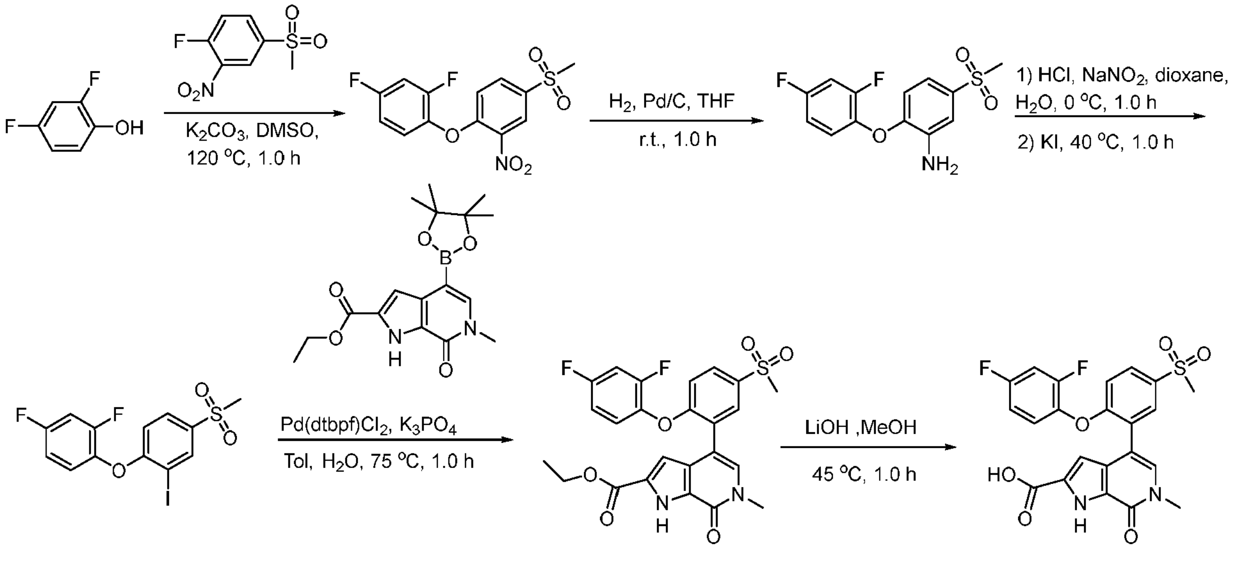
[00599] The procedure was the same as ethyl 4-[2-(4-fluoro-2,6-dimethylphenoxy)- 5-methanesulfonylphenyl]-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-carboxylate (Example 9 step 6), but the reaction temperature was 75 °C and the reaction time was 1.0 h. 950.00 mg of 2-[2-bromo-4-(ethanesulfonyl)phenoxy]-5-fluoro- 1,3-dimethylbenzene was used, 870.00 mg of ethyl 4-[5-(ethanesulfonyl)-2-(4-fluoro-2,6-dimethylphenoxy)phenyl]-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-carboxylate was obtained as yellow solid (67.35% yield). LC/MS: mass calcd. $C_{27}H_{27}FN_2O_6S$: 526.15, found: 527.35 $[M+H]^+$.

[00600] ***Step 4: Synthesis of 4-[5-(ethanesulfonyl)-2-(4-fluoro-2,6-dimethylphenoxy) phenyl]-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid***

[00601] The procedure was the same as 4-[3-[(tert-butoxycarbonyl)amino] propanamido]-1-methylimidazole-2-carboxylic acid. 860.00 mg of ethyl 4-[5-(ethanesulfonyl)-2-(4-fluoro-2,6-dimethylphenoxy)phenyl]-6- methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-carboxylate was used, 590.00 mg of 4-[5-(ethanesulfonyl)-2-(4-fluoro-2,6-dimethylphenoxy)phenyl]-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid was obtained as yellow solid (72.46% yield). LC/MS: mass calcd. $C_{25}H_{23}FN_2O_6S$:498.12, found: 499.25 $[M+H]^+$.

[00602] Example 11. Synthesis of 4-[2-(2,4-difluorophenoxy)-5-methanesulfonylphenyl]-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid

[00603] Scheme 11.



[00604] ***Step 1: Synthesis of 1-(2,4-difluorophenoxy)-4-methanesulfonyl-2-nitrobenzene***

[00605] To a stirred solution of 2,4-difluorophenol (1.78 g, 13.68 mmol, 1.00 equiv) in DMSO (50.00 mL) was added 1-fluoro-4-methanesulfonyl-2-nitrobenzene (3.00 g, 13.682 mmol, 1.00 equiv) and K_2CO_3 (1.89 g, 13.68 mmol, 1.00 equiv). The resulting mixture was stirred at 120 °C for 1.0 h. The reaction mixture was poured into ice-water (120 mL), extracted with EA (3x150 mL). The organic phases were combined and washed with H_2O (100 mL) and NaCl (100 mL), dried over anhydrous Na_2SO_4. The solid was filtered out and the filtrate was concentrated to afford 1-(2,4-difluorophenoxy)-4-methanesulfonyl-2-nitrobenzene (4.20 g, 88.56% yield) as a yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ: **8.61 (s, 1H), 8.15 (d,** J = 8.8 Hz, 1H), 7.55 -7.66 (m, 2H), 7.24 - 7.30 (m, 2H), 3.34 (s, 3H).

[00606] ***Step 2: Synthesis of 2-(2,4-difluorophenoxy)-5-methanesulfonylaniline***

[00607] The procedure was the same as 2-(2,4-difluorophenoxy)-5-methanesulfonylaniline, but the reaction time was 1.0 h. 500.00 mg of 1-(2,4-difluorophenoxy)-4-methanesulfonyl-2-nitrobenzene was used, 420.00 mg of 2-(2,4-difluorophenoxy)-5-methanesulfonylaniline was obtained as colorless oil. LC/MS: mass calcd. For $C_{13}H_{11}F_2NO_3S$: 299.04, found: 300.05 $[M+H]^+$.

[00608] ***Step 3: Synthesis of 1-(2,4-difluorophenoxy)-2-iodo-4-methanesulfonylbenzene***

[00609] The procedure was the same as 5-fluoro-2-(2-iodo-4-methanesulfonylphenoxy)- 1,3-dimethylbenzene, but the reaction time was 1.0 h after KI was added. 420.00 mg of 5-fluoro-2-(2-iodo-4-methanesulfonylphenoxy)-1,3- dimethylbenzene was used, 440.00 mg of 1-(2,4-difluorophenoxy)-2-iodo-4-methanesulfonylbenzene was obtained as yellow solid (78.57% yield). ^1H NMR (400 MHz, DMSO-d_6) δ: 8.38 (s, 1H), 7.86 d, J = 8.4 Hz, 1H), 7.50 - 7.61 (m, 1H), 7.41 - 7.49 (m, 1H), 7.15 - 7.25 (m, 1H), 6.90 (d, J = 8.8 Hz, 1H), 3.26 (s, 3H).

[00610] ***Step 4: Synthesis of ethyl 4-[2-(2,4-difluorophenoxy)-5-methanesulfonylphenyl]- 6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-carboxylate***

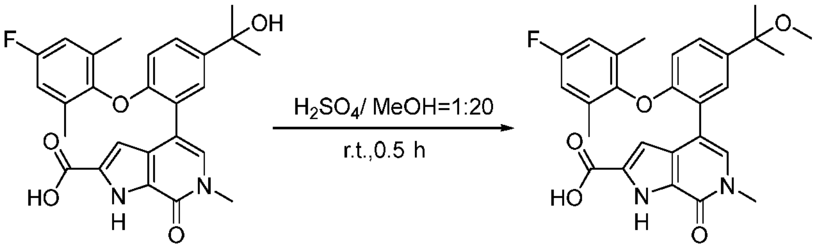
[00611] The procedure was the same as ethyl 4-[2-(4-fluoro-2,6-dimethylphenoxy)-5-methanesulfonylphenyl]-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-carboxylate (Example 9 step 6), but the reaction temperature was 75 °C and reaction time was 1.0 h. 420.00 mg of 1-(2,4-difluorophenoxy)-2-iodo-4-methanesulfonylbenzene was used, 340.00 mg of ethyl 4-[2-(2,4-difluorophenoxy)-5-methanesulfonylphenyl]- 6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-carboxylate was obtained as white solid (62.11% yield). LC/MS: mass calcd. For $C_{24}H_{20}F_2N_2O_6S$: 502.10, found: 503.25 $[M+H]^+$.

[00612] ***Step 5: Synthesis of 4-[2-(2,4-difluorophenoxy)-5-methanesulfonylphenyl]- 6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid***

[00613] The procedure was the same as 4-[3-[(tert-butoxycarbonyl)amino] propanamido]-1-methylimidazole-2-carboxylic acid (Example 1 step 3), but the reaction time was 1.0 h. 320.00 mg of ethyl 4-[2-(2,4-difluorophenoxy)-5- methanesulfonylphenyl]-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-carboxylate was used, 290.00 mg of 4-[2-(2,4-difluorophenoxy)-5-methanesulfonylphenyl]- 6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid was obtained as white solid (92.15% yield). LC/MS: mass calcd. For $C_{22}H_{16}F_2N_2O_6S$: 474.07, found: 475.20 $[M+H]^+$.

[00614] **Example 12. Synthesis of 4-[2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-methoxypropan-2-yl)phenyl]-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid**

[00615] **Scheme 12.**

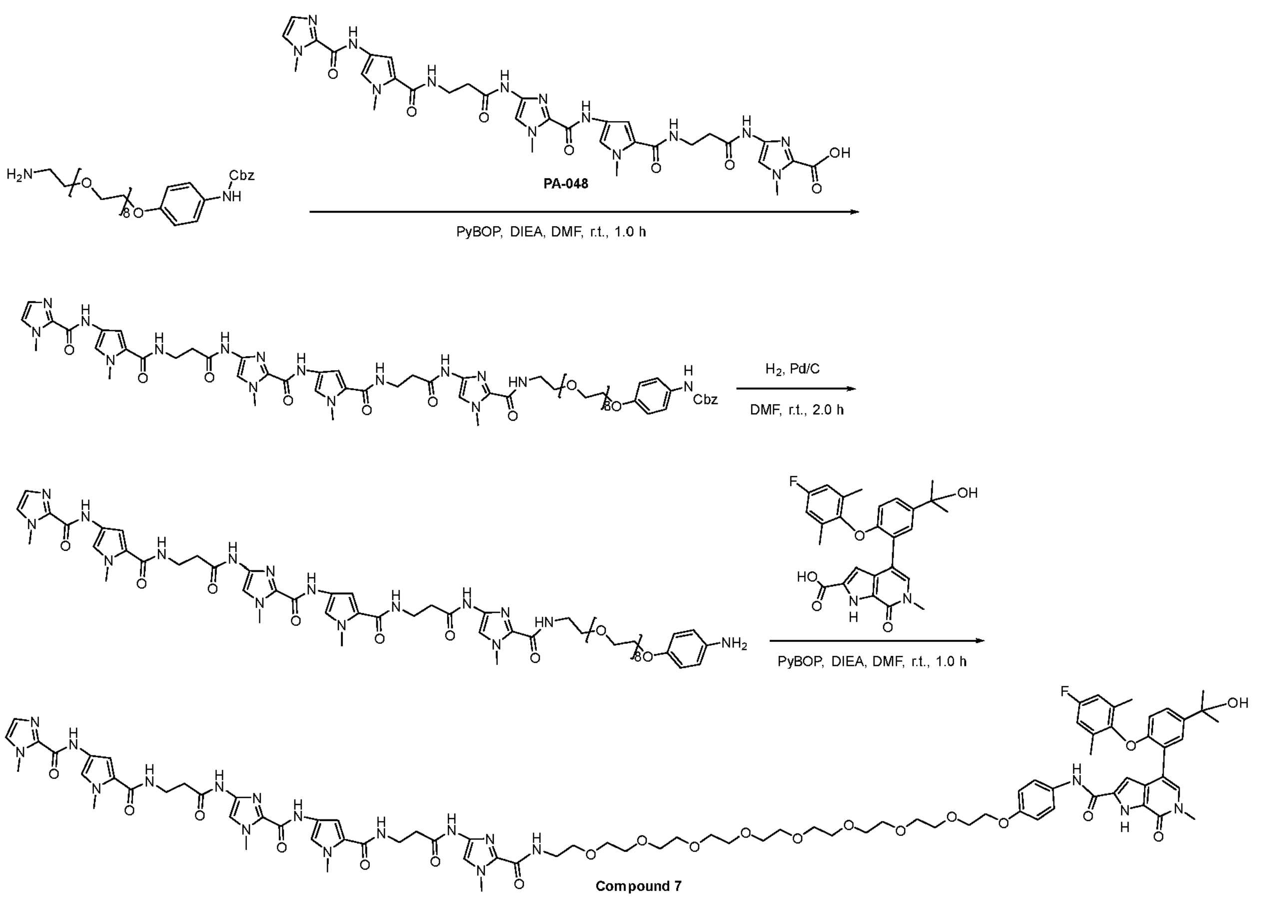


[00616] Into a 25 ml flask was added 4-[2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl]-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (200.00 mg, 0.43 mmol, 1.00 equiv), MeOH (4.00 mL) and H_2SO_4 (0.20 mL). The reaction was stirred at room temperature for 0.5 h. The reaction was adjust to pH=7~8 by $NaHCO_3$ solution, the aqueous layer was extracted with EtOAc (4x10 mL). The combined organic layers were washed with brine (2x10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in 4-[2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-methoxypropan-2-yl)phenyl]-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (220.00 mg, crude) as white solid. LC/MS: mass calcd. For $C_{27}H_{27}FN_2O_5$: 478.19, found: 479.35 $[M+H]^+$.

[00617] **SYNTHESIS OF REPRESENTATIVE COMPOUNDS OF THE DISCLOSURE**

[00618] **Example 13. Synthesis of N-[26-(4-{4-[2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl]-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-amido}phenoxy)-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl]-1-methyl-4-[3-({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)propanamido]imidazole-2-carboxamide (Compound 7)**

[00619] **Scheme 13.**



[00620] ***Step 1: Synthesis of benzyl N-(4-{[26-({1-methyl-4-[3-({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)propanamido]imidazol-2-yl}formamido)-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl]oxy}phenyl)carbamate***

[00621] The procedure was the same as methyl 1-methyl-4-(1-methyl-4-{1-methyl-4-[1-methyl-4-(1-methylimidazole-2-amido)pyrrole-2-amido]pyrrole-2-amido}imidazole-2-amido)pyrrole-2-carboxylate. 150.00 mg of benzyl N-{4-[(26-amino-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl)oxy]phenyl}carbamate was used, 325.00 mg of desired product was obtained as white solid (97.63% yield). LC/MS: mass calcd. for $C_{65}H_{86}N_{16}O_{18}$:1378.63, found: 1379.65 $[M+H]^+$.

[00622] ***Step 2: Synthesis of N-[26-(4-aminophenoxy)-3,6,9,12,15,18,21,24- octaoxahexacosan-1-yl]-1-methyl-4-[3-({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)propanamido]imidazole-2-carboxamide***

[00623] The procedure was the same as 9H-fluoren-9-ylmethyl N-[2-({2-[(5-{[2-({2-[(2-{[26-(4-aminophenoxy)-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl]carbamoyl}ethyl)carbamoyl]-1-methylimidazol-4-yl}carbamoyl)ethyl]carbamoyl}-1-methylpyrrol-3-yl)carbamoyl]-1-methylimidazol-4-yl}carbamoyl)ethyl]carbamate. 380.00 mg of benzyl N-(4-{[26-({1-methyl-4-[3-({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)propanamido]imidazol-2-yl}formamido)-3,6,9,12,15,18,21,24-

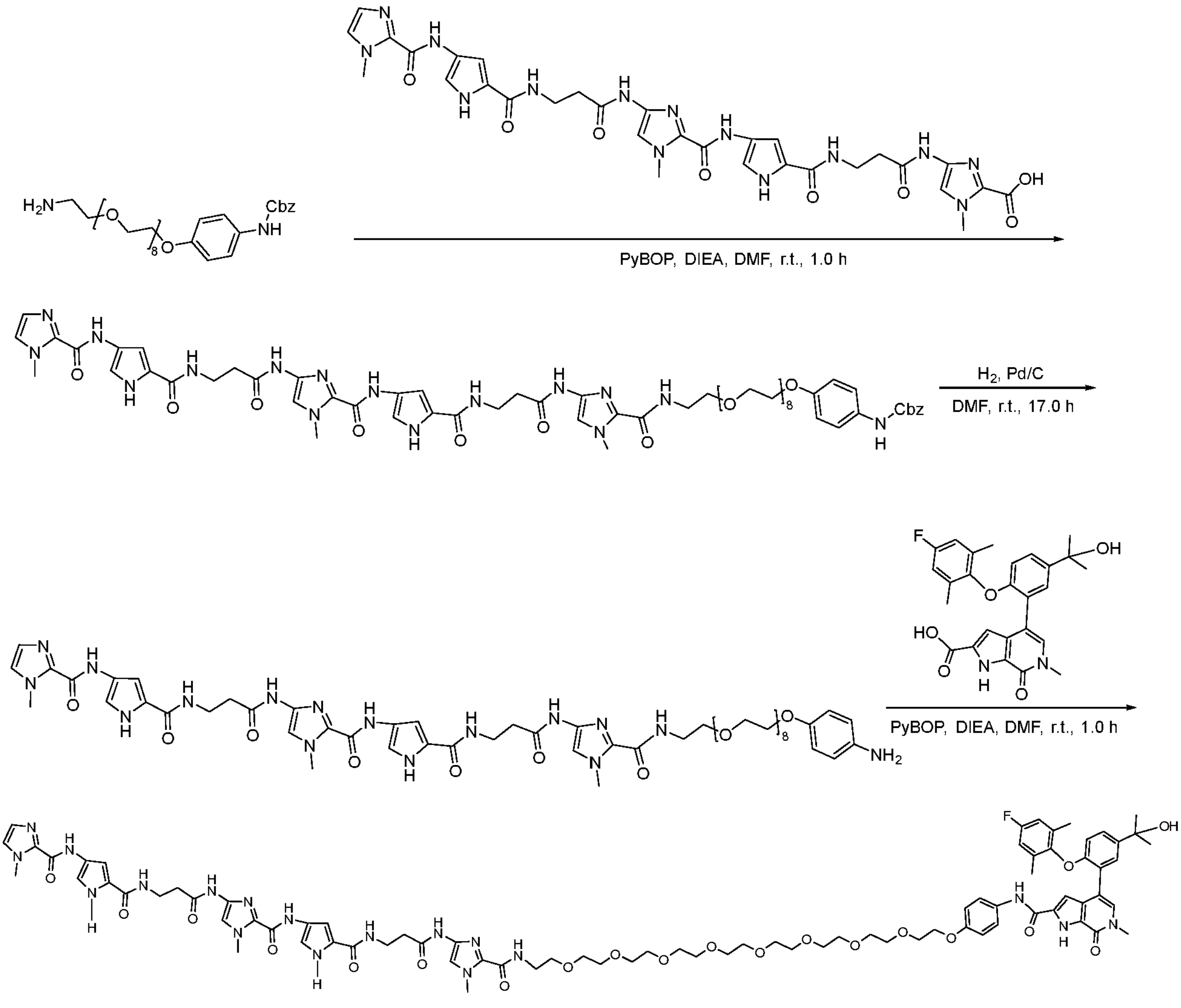
octaoxahexacosan-1-yl]oxy}phenyl)carbamate was used, 350.00 mg crude of desired product was obtained as brown oil. LC/MS: mass calcd. for $C_{57}H_{80}N_{16}O_{16}$: 1244.59, found: 1245.70 $[M+H]^+$.

[00624] ***Step 3: Synthesis of Compound 7***

[00625] The procedure was the same as N-(5-{[2-({2-[(2-{[26-(4-{1-ethyl-4-[2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl]-6-methyl-7-oxopyrrolo[2,3-c]pyridine-2-amido}phenoxy)-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl]carbamoyl}ethyl)carbamoyl]-1-methylimidazol-4-yl}carbamoyl)ethyl]carbamoyl}-1-methylpyrrol-3-yl)-1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-carboxamide (Example 20). 250.00 mg of N-[26-(4-aminophenoxy)-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl]-1-methyl-4-[3-({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)propanamido]imidazole-2-carboxamide was used, 29.90 mg of desired product was obtained as white solid (8.64% yield). HRMS: mass calcd. For $C_{83}H_{103}FN_{18}O_{20}$: 1690.7580, found: 1691.7722 $[M+H]^+$.

[00626] **Example 14. Synthesis of N-[26-(4-{4-[2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl]-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-amido}phenoxy)-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl]-1-methyl-4-[3-({4-[1-methyl-4-(3-{[4-(1-methylimidazole-2-amido)-1H-pyrrol-2-yl]formamido}propanamido)imidazole-2-amido]-1H-pyrrol-2-yl}formamido)propanamido]imidazole-2-carboxamide (Compound 9)**

[00627] **Scheme 14.**



Compound 9

[00628] ***Step 1: Synthesis of benzyl N-(4-{[26-({1-methyl-4-[3-({4-[1-methyl-4-(3-{[4-(1-methylimidazole-2-amido)-1H-pyrrol-2-yl]formamido}propanamido)imidazole-2-amido]-1H-pyrrol-2-yl}formamido)propanamido]imidazol-2-yl}formamido)-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl]oxy}phenyl)carbamate***

[00629] The procedure was the same as methyl 4-(4-{4-[(tert-butoxycarbonyl)amino]-1-methylpyrrole-2-amido}-1-methylimidazole-2-amido)-1-methylpyrrole-2-carboxylate (Example 2 Step 3). 160.00 mg of 1-methyl-4-[3-({4-[1-methyl-4-(3-{[4-(1-methylimidazole-2-amido)-1H-pyrrol-2-yl]formamido}propanamido)imidazole-2-amido]-1H-pyrrol-2-yl}formamido)propanamido]imidazole-2-carboxylic acid was used, 260.00 mg crude of benzyl N-(4-{[26-({1-methyl-4-[3-({4-[1-methyl-4-(3-{[4-(1-methylimidazole-2-amido)-1H-pyrrol-2-yl]formamido}propanamido)imidazole-2-amido]-1H-pyrrol-2-yl}formamido)propanamido]imidazol-2-yl}formamido)-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl]oxy}phenyl)carbamate was obtained as brown solid. LC/MS: mass calcd. for $C_{63}H_{82}N_{16}O_{18}$: 1350.60, found: 676.85 $[M/2+H]^+$.

[00630] ***Step 2: Synthesis of N-[26-(4-aminophenoxy)-3,6,9,12,15,18,21,24- octaoxahexacosan-1-yl]-1-methyl-4-[3-({4-[1-methyl-4-(3-{[4-(1-methylimidazole-2-amido)-1H-pyrrol-2-***

yl]formamido}propanamido)imidazole-2-amido]-1H-pyrrol-2-yl}formamido)propanamido]imidazole-2-carboxamide

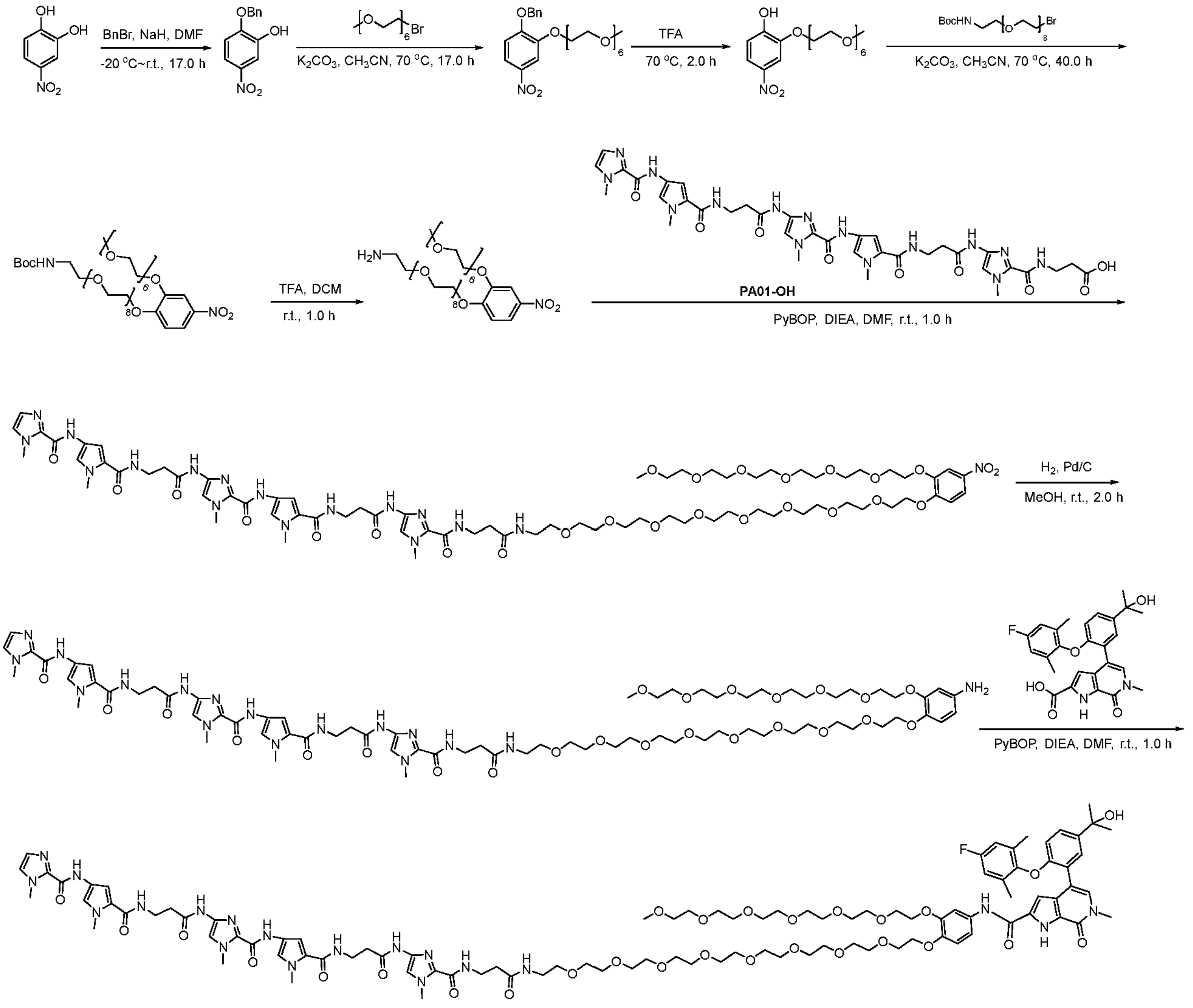
[00631] The procedure was the same as 9H-fluoren-9-ylmethyl N-[2-({2-[(5-{[2-({2-[(2-{[26-(4-aminophenoxy)-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl]carbamoyl}ethyl)carbamoyl]-1-methylimidazol-4-yl}carbamoyl)ethyl]carbamoyl}-1-methylpyrrol-3-yl)carbamoyl]-1-methylimidazol-4-yl}carbamoyl)ethyl]carbamate, but the reaction time was 17.0 h. 250.00 mg of benzyl N-(4-{[26-({1-methyl-4-[3-({4-[1-methyl-4-(3-{[4-(1-methylimidazole-2-amido)-1H-pyrrol-2-yl]formamido}propanamido)imidazole-2-amido]-1H-pyrrol-2-yl}formamido)propanamido]imidazol-2-yl}formamido)-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl]oxy}phenyl)carbamate was used, 170.00 mg crude of desired product was obtained as brown solid. LC/MS: mass calcd. for $C_{55}H_{76}N_{16}O_{16}$: 1216.56, found: 609.80 $[M/2+H]^+$.

[00632] ***Step 3: Synthesis of Compound 9***

[00633] The procedure was the same as N-(5-{[2-({2-[(2-{[26-(4-{1-ethyl-4-[2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl]-6-methyl-7-oxopyrrolo[2,3-c]pyridine-2-amido}phenoxy)-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl]carbamoyl}ethyl)carbamoyl]-1-methylimidazol-4-yl}carbamoyl)ethyl]carbamoyl}-1-methylpyrrol-3-yl)-1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-carboxamide. 160.00 mg of N-[26-(4-aminophenoxy)-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl]-1-methyl-4-[3-({4-[1-methyl-4-(3-{[4-(1-methylimidazole-2-amido)-1H-pyrrol-2-yl]formamido}propanamido)imidazole-2-amido]-1H-pyrrol-2-yl}formamido)propanamido]imidazole-2-carboxamide was used, 30.30 mg of desired product was obtained as white solid (13.71% yield). HRMS: mass calcd. For $C_{81}H_{99}FN_{18}O_{20}$: 1662.7267, found: 1663.7394 $[M+H]^+$.

[00634] **Example 15. Synthesis of N-(5-{[2-({2-[(2-{[26-(4-{4-[2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl]-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-amido}-2-(2,5,8,11,14,17-hexaoxanonadecan-19-yloxy)phenoxy)-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl]carbamoyl}ethyl)carbamoyl]-1-methylimidazol-4-yl}carbamoyl)ethyl]carbamoyl}-1-methylpyrrol-3-yl)-1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-carboxamide (Compound 4)**

[00635] **Scheme 15.**



Compound 4

[00636] ***Step 1: Synthesis of 2-(benzyloxy)-5-nitrophenol***

[00637] To a stirred solution of 4-nitrocatechol (1.00 g, 6.45 mmol, 1.00 equiv) in DMF (10.00 mL) were added NaH (60%, 0.15 g, 6.45 mmol, 1.00 equiv) in portions in 10.0 min at -20 °C. The resulting mixture was stirred for 1.0 h at room temperature. To the above mixture was added benzyl bromide (0.77 mL, 4.51 mmol, 0.70 equiv) in DMF (10.00 mL) dropwise over 30.0 min at -20 °C. The resulting mixture was stirred for additional 17.0 h at room temperature. The reaction mixture was quenched by water and extracted with DCM (3x5 mL). The combined organic layers were combined and concentrated. The residue was purified by silica gel column chromatography, eluted with DCM:MeOH (10:1) to afford 2-(benzyloxy)-5-nitrophenol (0.75 g, 45.54% yield) as yellow oil. LC/MS: mass calcd. For $C_{13}H_{11}NO_4$: 245.06, found: 244.05 $[M-H]^+$.

[00638] ***Step 2: Synthesis of 19-[2-(benzyloxy)-5-nitrophenoxy]-2,5,8,11,14,17- hexaoxanonadecane***

[00639] The procedure was the same as tert-butyl (S)-2-(4-(4-(16-((2-(1H-indol-3-yl)ethyl)amino)hexadecanamido)phenyl)-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 of 2-(benzyloxy)-5-nitrophenol was used, 670.00 mg of 19-[2-(benzyloxy)-5-nitrophenoxy]-2,5,8,11,14,17-hexaoxanonadecane was obtained as light yellow oil (78.45% yield). LC/MS: mass calcd. for $C_{26}H_{37}NO_{10}$: 523.24, found: 541.20 $[M+H_2O]^+$.

[00640] ***Step 3: Synthesis of 2-(2,5,8,11,14,17-hexaoxanonadecan-19-yloxy)-4-nitrophenol***

[00641] 19-[2-(benzyloxy)-5-nitrophenoxy]-2,5,8,11,14,17-hexaoxanonadecane (670.00 mg, 1.280 mmol, 1.00 equiv) was dissolved in TFA (2.00 mL). The resulting mixture was stirred for 2.0 h at 70 degrees C. The resulting mixture was concentrated under reduced pressure to afford 2-(2,5,8,11,14,17-hexaoxanonadecan-19-yloxy)-4-nitrophenol (670.00 mg, crude) as light brown oil. LC/MS: mass calcd. For $C_{19}H_{31}NO_{10}$: 433.19, found: 456.25 $[M+Na]^+$.

[00642] ***Step 4: Synthesis of tert-butyl N-{26-[2-(2,5,8,11,14,17-hexaoxanonadecan-19-yloxy)-4-nitrophenoxy]-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl}carbamate***

[00643] The procedure was the same as tert-butyl (S)-2-(4-(4-(16-((2-(1H-indol-3-yl)ethyl)amino)hexadecanamido)phenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetate, but the reaction time was 40.0 h. 550.00 mg of 2-(2,5,8,11,14,17-hexaoxanonadecan-19-yloxy)-4-nitrophenol was used, 700.00 mg of tert-butyl N-{26-[2-(2,5,8,11,14,17-hexaoxanonadecan-19-yloxy)-4-nitrophenoxy]-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl}carbamate was obtained as light yellow oil (59.38% yield). LC/MS: mass calcd. for $C_{42}H_{76}N_2O_{20}$: 928.49, found: 946.40 $[M+H_2O]^+$.

[00644] ***Step 5: Synthesis of 26-[2-(2,5,8,11,14,17-hexaoxanonadecan-19-yloxy)-4-nitrophenoxy]-3,6,9,12,15,18,21,24-octaoxahexacosan-1-amine***

[00645] The procedure was the same as methyl 4-[4-(4-amino-1-methylpyrrole-2-amido)-1-methylimidazole-2-amido]-1-methylpyrrole-2-carboxylate (Example 2 step 3). 410.00 mg of tert-butyl N-{26-[2-(2,5,8,11,14,17-hexaoxanonadecan-19-yloxy)-4-nitrophenoxy]-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl}carbamate was used, 410.00 mg crude of 26-[2-(2,5,8,11,14,17-hexaoxanonadecan-19-yloxy)-4-nitrophenoxy]-3,6,9,12,15,18,21,24-octaoxahexacosan-1-amine was obtained as brown oil. LC/MS: mass calcd. for $C_{37}H_{68}N_2O_{18}$: 828.44, found: 829.75 $[M+H]^+$.

[00646] ***Step 6: Synthesis of N-[5-({2-[(2-{[2-({26-[2-(2,5,8,11,14,17-hexaoxanonadecan-19-yloxy)-4-nitrophenoxy]-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl}carbamoyl)ethyl]carbamoyl}-1-methylimidazol-4-yl)carbamoyl]ethyl}carbamoyl)-1-methylpyrrol-3-yl]-1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-carboxamide***

[00647] The procedure was the same as methyl 4-(4-{4-[(tert-butoxycarbonyl)amino]-1-methylpyrrole-2-amido}-1-methylimidazole-2-amido)-1-methylpyrrole-2-carboxylate (Example 2 step 3). 360.00 mg of 26-[2-(2,5,8,11,14,17-hexaoxanonadecan-19-yloxy)-4-nitrophenoxy]-3,6,9,12,15,18,21,24-octaoxahexacosan-1-amine was used, 650.00 mg of N-[5-({2-[(2-{[2-({26-[2-(2,5,8,11,14,17-hexaoxanonadecan-19-yloxy)-4-nitrophenoxy]-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl}carbamoyl)ethyl]carbamoyl}-1-methylimidazol-4-yl)carbamoyl]ethyl}carbamoyl)-1-methylpyrrol-3-yl]-1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-carboxamide was obtained as light brown solid (91.22% yield). LC/MS: mass calcd. for $C_{73}H_{109}N_{17}O_{26}$: 1639.77, found: 821.65 $[M/2+H]^+$.

[00648] ***Step 7: Synthesis of N-[5-({2-[(2-{[2-({26-[4-amino-2-(2,5,8,11,14,17-hexaoxanonadecan-19-yloxy)phenoxy]-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl}carbamoyl)ethyl]carbamoyl}-1-***

methylimidazol-4-yl)carbamoyl]ethyl}carbamoyl)-1-methylpyrrol-3-yl]-1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-carboxamide

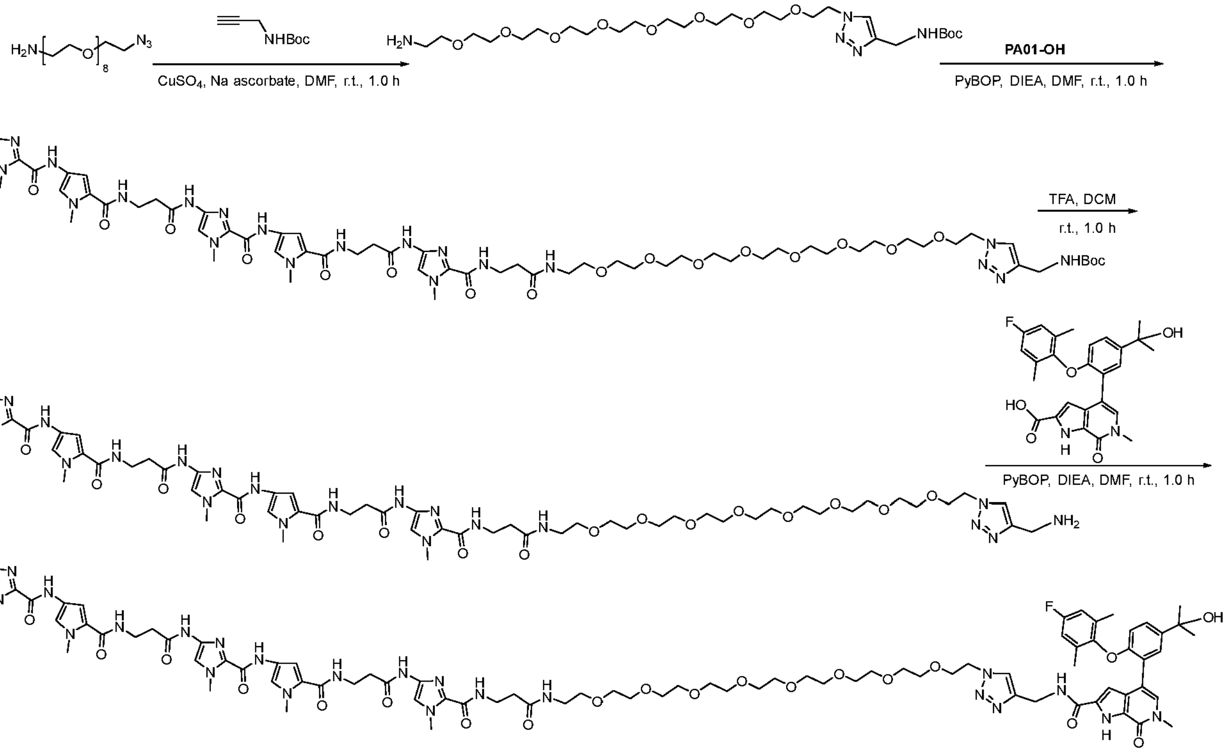
[00649] The procedure was the same as 9H-fluoren-9-ylmethyl N-[2-({2-[(5-{[2-({2-[(2-{[26-(4-aminophenoxy)-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl]carbamoyl}ethyl)carbamoyl]-1-methylimidazol-4-yl}carbamoyl)ethyl]carbamoyl}-1-methylpyrrol-3-yl)carbamoyl]-1-methylimidazol-4-yl}carbamoyl)ethyl]carbamate, but the reaction solvent was MeOH. 720.00 mg of N-[5-({2-[(2-{[2-({26-[2-(2,5,8,11,14,17-hexaoxanonadecan-19-yloxy)-4-nitrophenoxy]-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl}carbamoyl)ethyl]carbamoyl}-1-methylimidazol-4-yl)carbamoyl]ethyl}carbamoyl)-1-methylpyrrol-3-yl]-1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-carboxamide was used, 500.00 mg of N-[5-({2-[(2-{[2-({26-[4-amino-2-(2,5,8,11,14,17-hexaoxanonadecan-19-yloxy)phenoxy]-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl}carbamoyl)ethyl]carbamoyl}-1-methylimidazol-4-yl)carbamoyl]ethyl}carbamoyl)-1-methylpyrrol-3-yl]-1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-carboxamide was obtained as light brown solid (70.74% yield). LC/MS: mass calcd. for $C_{73}H_{111}N_{17}O_{24}$: 1609.79, found: 806.65 $[M/2+H]^+$.

[00650] ***Step 8: Synthesis of Compound 4***

[00651] The procedure was the same as N-(5-{[2-({2-[(2-{[26-(4-{1-ethyl-4-[2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl]-6-methyl-7-oxopyrrolo[2,3-c]pyridine-2-amido}phenoxy)-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl]carbamoyl}ethyl)carbamoyl]-1-methylimidazol-4-yl}carbamoyl)ethyl]carbamoyl}-1-methylpyrrol-3-yl)-1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-carboxamide (Example 20). 300.00 mg of N-[5-({2-[(2-{[2-({26-[4-amino-2-(2,5,8,11,14,17-hexaoxanonadecan-19-yloxy)phenoxy]-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl}carbamoyl)ethyl]carbamoyl}-1-methylimidazol-4-yl)carbamoyl]ethyl}carbamoyl)-1-methylpyrrol-3-yl]-1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-carboxamidewas used, 36.30 mg of N-(5-{[2-({2-[(2-{[26-(4-{4-[2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl]-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-amido}-2-(2,5,8,11,14,17-hexaoxanonadecan-19-yloxy)phenoxy)-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl]carbamoyl}ethyl)carbamoyl]-1-methylimidazol-4-yl}carbamoyl)ethyl]carbamoyl}-1-methylpyrrol-3-yl)-1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-carboxamide was obtained as off-white solid (8.89% yield). HRMS: mass calcd. for $C_{99}H_{134}FN_{19}O_{28}$: 2055.9629, found: 2056.9525 $[M+H]^+$.

[00652] **Example 16. Synthesis of N-{5-[(2-{[2-({2-[(26-{4-[({4-[2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl]-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridin-2-yl}formamido)methyl]-1,2,3-triazol-1-yl}-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl)carbamoyl]ethyl}carbamoyl)-1-methylimidazol-4-yl]carbamoyl}ethyl)carbamoyl]-1-methylpyrrol-3-yl}-1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-carboxamide (Compound 5)**

[00653] Scheme 16.



Compound 5

[00654] ***Step 1: Synthesis of tert-butyl N-{[1-(26-amino-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl)-1,2,3-triazol-4-yl]methyl}carbamate***

[00655] To a stirred solution of tert-butyl N-(prop-2-yn-1-yl)carbamate (318.52 mg, 2.052 mmol, 3.00 equiv) in DMF (6.00 mL) was added $CuSO_4.5H_2O$ (85.41 mg, 0.342 mmol, 0.50 equiv), sodium ascorbate (68.11 mg, 0.342 mmol, 0.50 equiv) and 26-azido-3,6,9,12,15,18,21,24-octaoxahexacosan-1-amine (300.00 mg, 0.684 mmol, 1.00 equiv) in portions at 0 °C. The resulting mixture was stirred for 1.0 h at room temperature. The reaction mixture was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, ACN in water (0.05% TFA), 35% to 45% gradient in 20 min; detector, UV 254 nm. The fractions were combined and concentrated. Tert-butyl N-{[1-(26-amino-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl)-1,2,3-triazol-4-yl]methyl}carbamate (190.00 mg, 46.78%) was obtained as yellow oil. LC/MS: mass calcd. For $C_{26}H_{51}N_5O_{10}$: 593.36, found: 594.55 $[M+H]^+$.

[00656] ***Step 2: Synthesis of tert-butyl N-[(1-{26-[3-({1-methyl-4-[3-({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)propanamido]imidazol-2-yl}formamido)propanamido]-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl}-1,2,3-triazol-4-yl)methyl]carbamate***

[00657] The procedure was the same as methyl 1-methyl-4-(1-methyl-4-{1-methyl-4-[1-methyl-4-(1-methylimidazole-2-amido)pyrrole-2-amido]pyrrole-2-amido}imidazole-2-amido)pyrrole-2-carboxylate. 240.00 mg of 3-({1-methyl-4-[3-({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)propanamido]imidazol-2-yl}formamido)propanoic acid was used, 450.00 mg of tert-butyl N-

[(1-{26-[3-({1-methyl-4-[3-({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)propanamido]imidazol-2-yl}formamido)propanamido]-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl}-1,2,3-triazol-4-yl)methyl]carbamate was obtained as yellow oil (crude). LC/MS: mass calcd. for $C_{62}H_{92}N_{20}O_{18}$: 1404.69, found:1406.00 $[M+H]^+$.

[00658] ***Step 3: Synthesis of N-[5-({2-[(2-{[2-({26-[4-(aminomethyl)-1,2,3-triazol-1-yl]-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl}carbamoyl)ethyl]carbamoyl}-1-methylimidazol-4-yl)carbamoyl]ethyl}carbamoyl)-1-methylpyrrol-3-yl]-1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-carboxamide***

[00659] The procedure was the same as methyl 4-[4-(4-amino-1-methylpyrrole-2-amido)-1-methylimidazole-2-amido]-1-methylpyrrole-2-carboxylate (Example 2 step 4). 200.00 mg of tert-butyl N-[(1-{26-[3-({1-methyl-4-[3-({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)propanamido]imidazol-2-yl}formamido)propanamido]-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl}-1,2,3-triazol-4-yl)methyl]carbamate was used, 200.00 mg crude of N-[5-({2-[(2-{[2-({26-[4-(aminomethyl)-1,2,3-triazol-1-yl]-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl}carbamoyl)ethyl]carbamoyl}-1-methylimidazol-4-yl)carbamoyl]ethyl}carbamoyl)-1-methylpyrrol-3-yl]-1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-carboxamide was obtained as yellow oil. LC/MS: mass calcd. for $C_{57}H_{84}N_{20}O_{16}$: 1304.64, found: 1305.95 $[M+H]^+$.

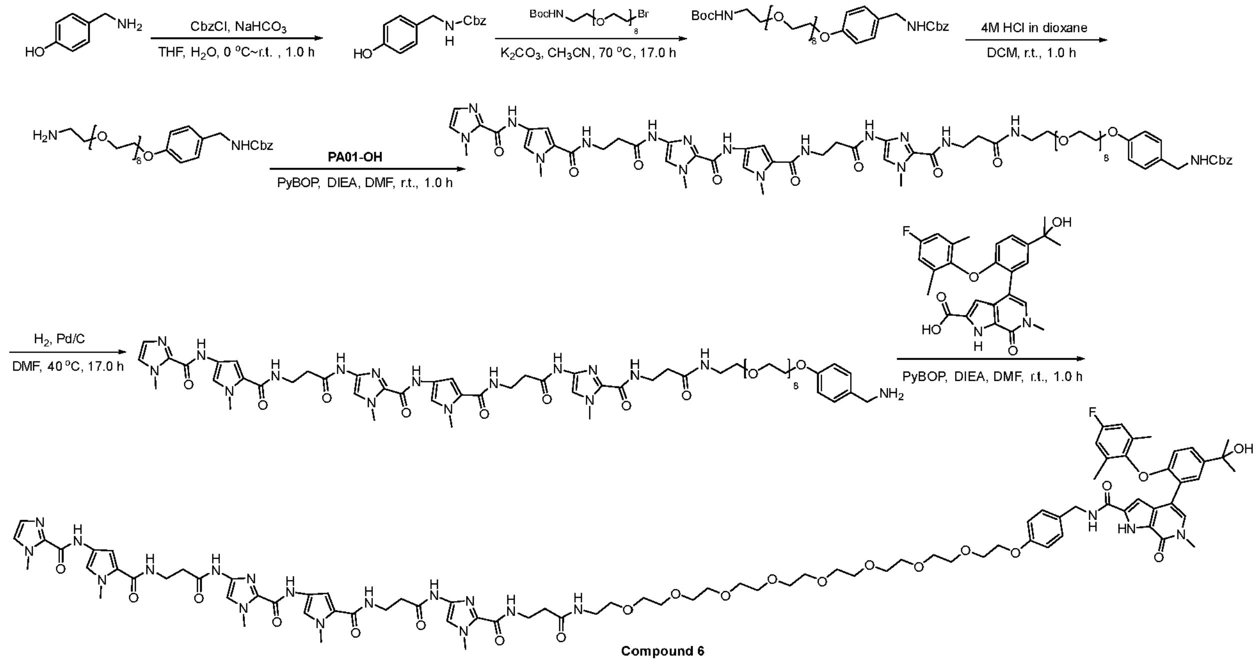
[00660] ***Step 4: Synthesis of Compound 5***

[00661] The procedure was the same as N-(5-{[2-({2-[(2-{[26-(4-{1-ethyl-4-[2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl]-6-methyl-7-oxopyrrolo[2,3-c]pyridine-2-amido}phenoxy)-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl]carbamoyl}ethyl)carbamoyl]-1-methylimidazol-4-yl}carbamoyl)ethyl]carbamoyl}-1-methylpyrrol-3-yl)-1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-carboxamide (Example 20). 180.00 mg of N-[5-({2-[(2-{[2-({26-[4-(aminomethyl)-1,2,3-triazol-1-yl]-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl}carbamoyl)ethyl]carbamoyl}-1-methylimidazol-4-yl)carbamoyl]ethyl}carbamoyl)-1-methylpyrrol-3-yl]-1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-carboxamide was used, 29.80 mg of N-{5-[(2-{[2-({2-[(26-{4-[({4-[2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl]-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridin-2-yl}formamido)methyl]-1,2,3-triazol-1-yl}-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl)carbamoyl]ethyl}carbamoyl)-1-methylimidazol-4-yl]carbamoyl}ethyl)carbamoyl]-1-methylpyrrol-3-yl}-1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-carboxamide was obtained as white solid (12.30% yield). HRMS: mass calcd. for $C_{83}H_{107}FN_{22}O_{20}$: 1750.8016, found: 1751.8142 $[M+H]^+$.

[00662] **Example 17. Synthesis of N-{5-[(2-{[2-({2-[(26-{4-[({4-[2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl]-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridin-2-**

yl}formamido)methyl]phenoxy}-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl)carbamoyl]ethyl}carbamoyl)-1-methylimidazol-4-yl]carbamoyl}ethyl)carbamoyl]-1-methylpyrrol-3-yl}-1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-carboxamide (Compound 6)

[00663] Scheme 17.



[00664] ***Step 1: Synthesis of benzyl N-[(4-hydroxyphenyl)methyl]carbamate***

[00665] Into a 100 mL flask was added 4-(aminomethyl)phenol (500.00 mg, 4.060 mmol, 1.00 equiv), THF (8.00 mL) and H_2O (8.00 mL). The resulting mixture was cooled to 0 °C, $NaHCO_3$ (444.00 mg, 5.285 mmol, 1.30 equiv) was added, benzyl chloroformate (693.00 mg, 4.062 mmol, 1.00 equiv) was added dropwise, stirred at 0 °C for 10.0 mins, then the reaction was stirred at room temperature for 1.0 h. The resulting mixture was extracted with EtOAc (3x20 mL). The combined organic layers were washed with water (1x10 mL), brine (1x10 ml), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure, the residue was triturated with heptane to afford benzyl N-[(4-hydroxyphenyl)methyl]carbamate (680 mg, crude) as off-white solid. LC/MS: mass calcd. For $C_{15}H_{15}NO_3$: 257.11, found: 280.10$[M+Na]^+$.

[00666] ***Step 2: Synthesis of benzyl N-{[4-({26-[(tert-butoxycarbonyl)amino]-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl}oxy)phenyl]methyl}carbamate***

[00667] The procedure was the same as tert-butyl (S)-2-(4-(4-(16-((2-(1H-indol-3-yl)ethyl)amino)hexadecanamido)phenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetate (Example 15 step 2). 300.00 mg of benzyl N-[(4-hydroxyphenyl)methyl]carbamate was used, 720.00 mg of benzyl N-{[4-({26-[(tert-butoxycarbonyl)amino]-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl}oxy)phenyl]methyl}carbamate was obtained as yellow oil (82.02% yield). LC/MS: mass calcd. for $C_{38}H_{60}N_2O_{13}$: 752.41, found: 753.70$[M+H]^+$.

[00668] ***Step 3: Synthesis of benzyl N-({4-[(26-amino-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl)oxy]phenyl}methyl)carbamate***

[00669] The procedure was the same as methyl 4-[4-(3-aminopropanamido)-1- methylimidazole-2-amido]-1-methylpyrrole-2-carboxylate hydrochloride, but the reaction solvent was 4M HCl in dioxane/DCM (1:1) and the reaction time was 1.0 h. 690.00 mg of benzyl N-{[4-({26-[(tert-butoxycarbonyl)amino]-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl}oxy)phenyl]methyl}carbamate was used, 700.00 mg crude of benzyl N-({4-[(26-amino-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl)oxy]phenyl}methyl)carbamate was obtained as yellow oil. LC/MS: mass calcd. for $C_{33}H_{52}N_2O_{11}$: 652.36, found: 653.55[M+H]$^+$.

[00670] ***Step 4: Synthesis of benzyl N-{[4-({26-[3-({1-methyl-4-[3-({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)propanamido]imidazol-2-yl}formamido)propanamido]-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl}oxy)phenyl]methyl}carbamate***

[00671] The procedure was the same as methyl 4-(4-{4-[(tert-butoxycarbonyl)amino]-1-methylpyrrole-2-amido}-1-methylimidazole-2-amido)-1-methylpyrrole-2-carboxylate (Example 2 step 3). 690.00 mg of benzyl N-({4-[(26-amino-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl)oxy]phenyl}methyl)carbamate was used, 1.30 g crude of benzyl N-{[4-({26-[3-({1-methyl-4-[3-({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)propanamido]imidazol-2-yl}formamido)propanamido]-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl}oxy)phenyl]methyl}carbamate was obtained as yellow solid. LC/MS: mass calcd. for $C_{69}H_{93}N_{17}O_{19}$: 1463.68, found: 733.45 [M/2+H]$^+$.

[00672] ***Step 5: Synthesis of N-[5-({2-[(2-{[2-({26-[4-(aminomethyl)phenoxy]-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl}carbamoyl)ethyl]carbamoyl}-1-methylimidazol-4-yl)carbamoyl]ethyl}carbamoyl)-1-methylpyrrol-3-yl]-1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-carboxamide***

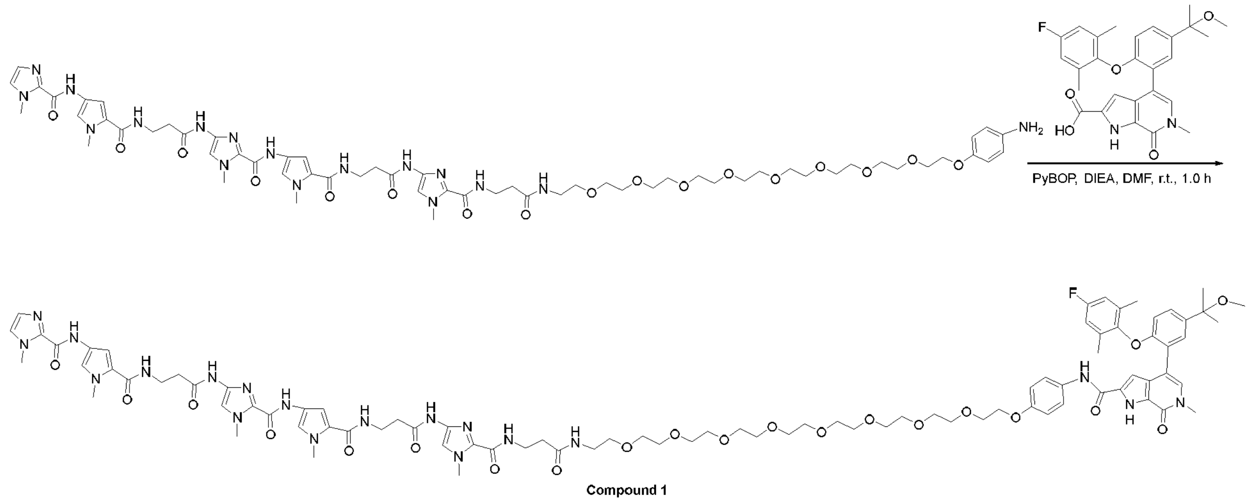
[00673] The procedure was the same as 9H-fluoren-9-ylmethyl N-[2-({2-[(5-{[2-({2-[(2-{[26-(4-aminophenoxy)-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl]carbamoyl}ethyl)carbamoyl]-1-methylimidazol-4-yl}carbamoyl)ethyl]carbamoyl}-1-methylpyrrol-3-yl)carbamoyl]-1-methylimidazol-4-yl}carbamoyl)ethyl]carbamate, but the reaction temperature was 40 °C and the reaction time was 17.0 h. 900.00 mg of benzyl N-{[4-({26-[3-({1-methyl-4-[3-({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)propanamido]imidazol-2-yl}formamido)propanamido]-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl}oxy)phenyl]methyl}carbamate was used, 800.00 mg crude of N-[5-({2-[(2-{[2-({26-[4-(aminomethyl)phenoxy]-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl}carbamoyl)ethyl]carbamoyl}-1-methylimidazol-4-yl)carbamoyl]ethyl}carbamoyl)-1-methylpyrrol-3-yl]-1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-carboxamide was obtained as yellow oil. LC/MS: mass calcd. for $C_{61}H_{87}N_{17}O_{17}$: 1329.65, found: 666.40 [M/2+H]$^+$.

[00674] ***Step 6: Synthesis of Compound 6***

[00675] The procedure was the same as N-(5-{[2-({2-[(2-{[26-(4-{1-ethyl-4-[2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl]-6-methyl-7-oxopyrrolo[2,3-c]pyridine-2-amido}phenoxy)-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl]carbamoyl}ethyl)carbamoyl]-1-methylimidazol-4-yl}carbamoyl)ethyl]carbamoyl}-1-methylpyrrol-3-yl)-1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-carboxamide (Example 20). 200.00 mg of N-[5-({2-[(2-{[2-({26-[4-(aminomethyl)phenoxy]-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl}carbamoyl)ethyl]carbamoyl}-1-methylimidazol-4-yl)carbamoyl]ethyl}carbamoyl)-1-methylpyrrol-3-yl]-1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-carboxamide was used, 25.90 mg of N-{5-[(2-{[2-({2-[(26-{4-[({4-[2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl]-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridin-2-yl}formamido)methyl]phenoxy}-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl)carbamoyl]ethyl}carbamoyl)-1-methylimidazol-4-yl]carbamoyl}ethyl)carbamoyl]-1-methylpyrrol-3-yl}-1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-carboxamide was obtained as white solid (9.39% yield). HRMS: mass calcd. for $C_{87}H_{110}FN_{19}O_{21}$: 1775.8108, found: 1776.8272 $[M+H^+$.

[00676] **Example 18. Synthesis of N-(5-{[2-({2-[(2-{[26-(4-{4-[2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-methoxypropan-2-yl)phenyl]-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-amido}phenoxy)-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl]carbamoyl}ethyl)carbamoyl]-1-methylimidazol-4-yl}carbamoyl)ethyl]carbamoyl}-1-methylpyrrol-3-yl)-1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-carboxamide (Compound 1)**

[00677] **Scheme 18.**



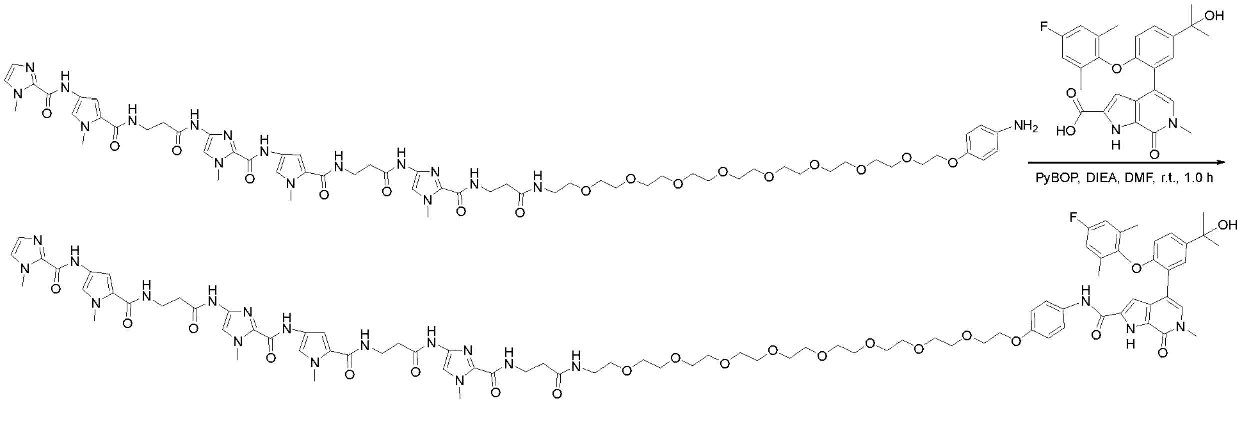
Compound 1

[00678] The procedure was the same as ethyl 4-amino-1H-pyrrole-2-carboxylate (Example 4 step 2), 60.00 mg of 4-[2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-methoxypropan-2-yl)phenyl]-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid was used, 47.40 mg of N-(5-{[2-({2-[(2-{[26-(4-{4-[2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-methoxypropan-2-yl)phenyl]-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-amido}phenoxy)-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl]carbamoyl}ethyl)carbamoyl]-1-methylimidazol-4-yl}carbamoyl)ethyl]carbamoyl}-1-methylpyrrol-3-yl)-1-methyl-4-(3-{[1-methyl-4-(1-

methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-carboxamide was obtained as white solid (20.95% yield). HRMS: mass calcd. for $C_{87}H_{110}FN_{19}O_{21}$: 1775.8108, found: 1776.8225 $[M+H]^+$.

[00679] **Example 19. Synthesis of 4-(2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-N-(4-((1-(1-methyl-4-(3-(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)propanamido)-1H-imidazol-2-yl)-1,5-dioxo-9,12,15,18,21,24,27,30-octaoxa-2,6-diazadotriacontan-32-yl)oxy)phenyl)-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (Compound 15)**

[00680] **Scheme 19.**

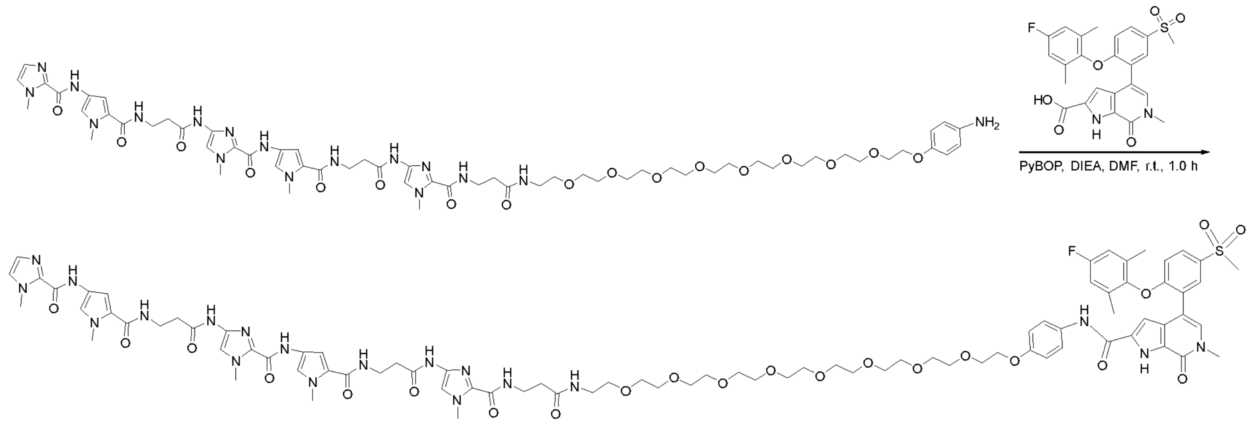


Compound 15

[00681] The procedure was the same as ethyl 4-amino-1H-pyrrole-2-carboxylate (Example 4 step 2). 0.43 g of 4-(2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid was used, 1 g of N-(5-{[2-({2-[(2-{[26-(4-{4-[2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-methoxypropan-2-yl)phenyl]-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-amido}phenoxy)-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl]carbamoyl}ethyl)carbamoyl]-1-methylimidazol-4-yl}carbamoyl)ethyl]carbamoyl}-1-methylpyrrol-3-yl)-1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-carboxamide was obtained as white solid (22.58% yield). HRMS: mass calcd. For $C_{86}H_{108}FN_{19}O_{21}$: 1761.7951, found: 1762.9204 $[M+H]^+$.

[00682] **Example 20. Synthesis of N-(5-{[2-({2-[(2-{[26-(4-{4-[2-(4-fluoro-2,6-dimethylphenoxy)-5-methanesulfonylphenyl]-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-amido}phenoxy)-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl]carbamoyl}ethyl)carbamoyl]-1-methylimidazol-4-yl}carbamoyl)ethyl]carbamoyl}-1-methylpyrrol-3-yl)-1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-carboxamide (Compound 2)**

[00683] **Scheme 20.**

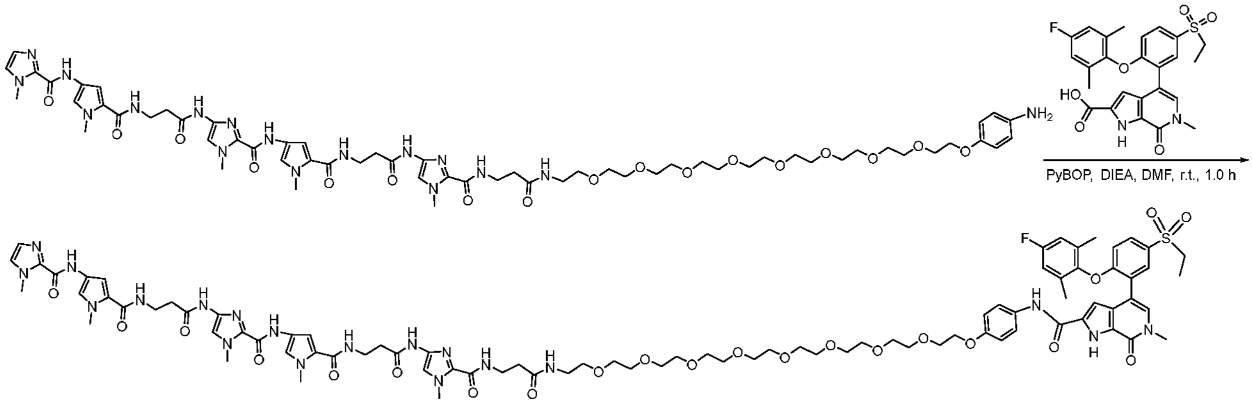


Compound 2

[00684] The procedure was the same as ethyl 4-amino-1H-pyrrole-2-carboxylate (Example 4 Step 2). 150.00 mg of N-(5-{[2-({2-[(2-{[26-(4-aminophenoxy)-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl]carbamoyl}ethyl)carbamoyl]-1-methylimidazol-4-yl}carbamoyl)ethyl]carbamoyl}-1-methylpyrrol-3-yl)-1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-carboxamide was used, 50.50 mg of desired product was obtained as white solid (24.13% yield). HRMS: mass calcd. for $C_{84}H_{104}FN_{19}O_{22}S$: 1781.7308, found: 1782.7370 $[M+H]^+$.

[00685] **Example 21. Synthesis of N-(5-{[2-({2-[(2-{[26-(4-{4-[5-(ethanesulfonyl)-2-(4-fluoro-2,6-dimethylphenoxy)phenyl]-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-amido}phenoxy)-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl]carbamoyl}ethyl)carbamoyl]-1-methylimidazol-4-yl}carbamoyl)ethyl]carbamoyl}-1-methylpyrrol-3-yl)-1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-carboxamide (Compound 3)**

[00686] **Scheme 21.**



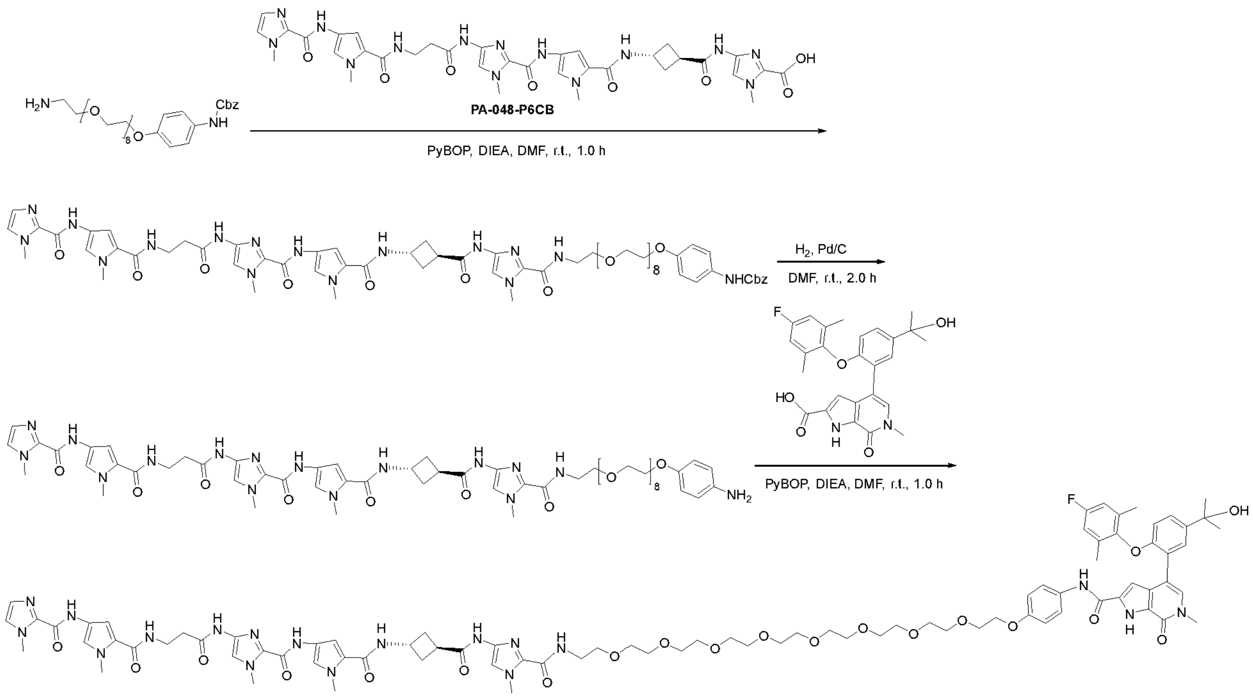
Compound 3

[00687] The procedure was the same as ethyl 4-amino-1H-pyrrole-2-carboxylate (Example 2 step 2). 70.00 mg of 4-[5-(ethanesulfonyl)-2-(4-fluoro-2,6-dimethylphenoxy)phenyl]-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid was used, 6.70 mg of desired product was obtained as white solid (2.48% yield). HRMS: mass calcd. for $C_{85}H_{106}FN_{19}O_{22}S$: 1795.7464, found: 1796.7515 $[M+H]^+$.

[00688] **Example 22. Synthesis of 1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)-N-(1-methyl-5-{[(1r,3r)-3-[(2-{[26-(4-{4-[2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl]-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-**

amido}phenoxy)-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl]carbamoyl}-1-methylimidazol-4-yl)carbamoyl]cyclobutyl]carbamoyl}pyrrol-3-yl)imidazole-2-carboxamide (Compound 8)

[00689] Scheme 22.



Compound 8

[00690] ***Step 1: Synthesis of benzyl N-(4-{[26-({1-methyl-4-[(1r,3r)-3-{1-methyl-4-[1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-amido]pyrrole-2-amido}cyclobutaneamido]imidazol-2-yl}formamido)-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl]oxy}phenyl)carbamate***

[00691] The procedure was the same as ethyl 4-amino-1H-pyrrole-2-carboxylate (Example 4 step 2). 140.00 mg of 1-methyl-4-[(1r,3r)-3-{1-methyl-4-[1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-amido]pyrrole-2-amido}cyclobutaneamido]imidazole-2-carboxylic acid was used, 240.00 mg of desired product was obtained as light yellow solid (95.72% yield). LC/MS: mass calcd. for $C_{67}H_{88}N_{16}O_{18}$: 1404.65, found: 1405.95 $[M+H]^+$.

[00692] ***Step 2: Synthesis of 1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole- 2-amido)pyrrol-2-yl]formamido}propanamido)-N-(1-methyl-5-{[(1r,3r)-3-[(2-{[26-(4-aminophenoxy)-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl]carbamoyl}-1-methylimidazol-4-yl)carbamoyl]cyclobutyl]carbamoyl}pyrrol-3-yl)imidazole-2-carboxamide***

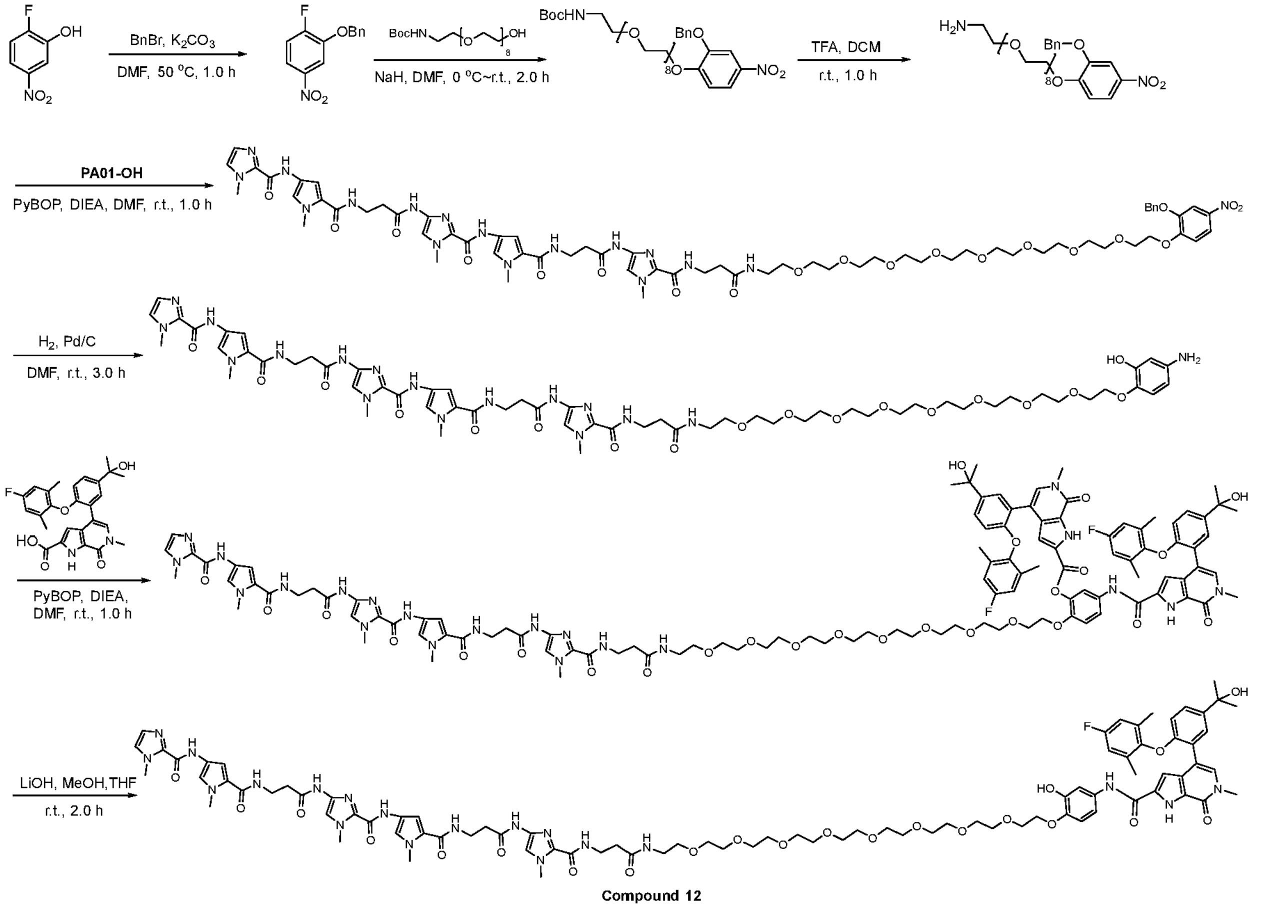
[00693] The procedure was the same as ethyl 4-amino-1-methylimidazole-2- carboxylate (Example 1 step 2), but the reaction time was 2.0 h and solvent was DMF. 240.00 mg of benzyl N-(4-{[26-({1-methyl-4-[(1r,3r)-3-{1-methyl-4-[1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-amido]pyrrole-2-amido}cyclobutaneamido]imidazol-2-yl}formamido)-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl]oxy}phenyl)carbamate was used, 220.00 mg crude of desired product was obtained as yellow oil. LC/MS: mass calcd. for $C_{59}H_{82}N_{16}O_{16}$: 1270.61, found: 636.60 $[M/2+H]^+$.

[00694] *Step 3: Synthesis of Compound 8*

[00695] The procedure was the same as ethyl 4-amino-1H-pyrrole-2-carboxylate (Example 4 step 2). 120.00 mg of 1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)-N-(1-methyl-5-{[(1r,3r)-3-[(2-{[26-(4-aminophenoxy)-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl]carbamoyl}-1-methylimidazol-4-yl)carbamoyl]cyclobutyl]carbamoyl}pyrrol-3-yl)imidazole-2-carboxamide was used, 54.80 mg of desired product was obtained as white solid (32.40% yield). HRMS: mass calcd. For $C_{85}H_{105}FN_{18}O_{20}$: 1716.7737, found: 1717.7781 $[M+H]^+$.

[00696] Example 23. Synthesis of N-(5-{[2-({2-[(2-{[26-(4-{4-[2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl]-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-amido}-2-hydroxyphenoxy)-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl]carbamoyl}ethyl)carbamoyl]-1-methylimidazol-4-yl}carbamoyl)ethyl]carbamoyl}-1-methylpyrrol-3-yl)-1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-carboxamide (Compound 12)

[00697] **Scheme 23.**



[00698] *Step 1: Synthesis of 2-(benzyloxy)-1-fluoro-4-nitrobenzene*

[00699] To a stirred solution of 2-fluoro-5-nitrophenol (1.00 g, 6.365 mmol, 1.00 equiv) in DMF (15.00 mL) was added benzyl bromide (1.63 g, 9.547 mmol, 1.50 equiv) and K_2CO_3 (2.64 g, 19.095 mmol, 3.00 equiv). The resulting mixture was stirred at 50 °C for 1.0 h. The reaction mixture was poured into ice-water

(50 mL), extracted with EA (3x80 mL). The organic phases were combined and washed with H_2O (50 mL) and NaCl (50 mL), dried over anhydrous Na_2SO_4. The solid was filtered out and the filtrate was concentrated. The residue was purified by silica gel column chromatography (0-10% EA/PE) to afford 2-(benzyloxy)-1-fluoro-4-nitrobenzene (1.50 g, 95.32%) as yellow solid.

[00700] ***Step 2: Synthesis of 2-(benzyloxy)-1-fluoro-4-nitrobenzene***

[00701] 2-(benzyloxy)-1-fluoro-4-nitrobenzene (INT-503-201) was synthesized by using NaH (60%1.00 equiv) in DMF as a solvent 0 °C to room temperature and the reaction time was 2.0 h. 100.00 mg of 2-(benzyloxy)-1-fluoro-4-nitrobenzene was used, 290.00 mg of tert-butyl N-{26-[2-(benzyloxy)-4-nitrophenoxy]-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl}carbamate was obtained as yellow oil (96.78% yield). LC/MS: mass calcd. for $C_{36}H_{56}N_2O_{14}$: 740.37, found: 741.50 $[M+H]^+$.

[00702] ***Step 3: Synthesis of 26-[2-(benzyloxy)-4-nitrophenoxy]-3,6,9,12,15,18,21,24-octaoxahexacosan-1-amine***

[00703] The procedure was the same as Example 2 step 4. 240.00 mg of tert-butyl N-{26-[2-(benzyloxy)-4-nitrophenoxy]-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl}carbamate was used, 240.00 mg crude of 26-[2-(benzyloxy)-4-nitrophenoxy]-3,6,9,12,15,18,21,24-octaoxahexacosan-1-amine was obtained as yellow oil. LC/MS: mass calcd. for $C_{31}H_{48}N_2O_{12}$: 640.32, found: 641.55 $[M+H]^+$.

[00704] ***Step 4: Synthesis of N-[5-({2-[(2-{[2-({26-[2-(benzyloxy)-4-nitrophenoxy]-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl}carbamoyl)ethyl]carbamoyl}-1-methylimidazol-4-yl)carbamoyl]ethyl}carbamoyl)-1-methylpyrrol-3-yl]-1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-carboxamide***

[00705] The procedure was the same as Example 2 step 5. 240.00 mg of 26-[2-(benzyloxy)-4-nitrophenoxy]-3,6,9,12,15,18,21,24-octaoxahexacosan-1-amine was used, 500.00 mg of N-[5-({2-[(2-{[2-({26-[2-(benzyloxy)-4-nitrophenoxy]-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl}carbamoyl)ethyl]carbamoyl}-1-methylimidazol-4-yl)carbamoyl]ethyl}carbamoyl)-1-methylpyrrol-3-yl]-1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-carboxamide was obtained as yellow solid (91.90% yield). LC/MS: mass calcd. for $C_{67}H_{89}N_{17}O_{20}$: 1451.64, found: 727.45 $[M/2+H]^+$.

[00706] ***Step 5: Synthesis of N-(5-{[2-({2-[(2-{[26-(4-amino-2-hydroxyphenoxy)-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl]carbamoyl}ethyl)carbamoyl]-1-methylimidazol-4-yl}carbamoyl)ethyl]carbamoyl}-1-methylpyrrol-3-yl)-1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-carboxamide***

[00707] The procedure was the same as ethyl 4-amino-1-methylimidazole-2- carboxylate (Example 1 step 3), but the reaction time was 2.0 h and solvent was DMF. 250.00 mg of N-[5-({2-[(2-{[2-({26-[2-(benzyloxy)-4-nitrophenoxy]-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl}carbamoyl)ethyl]carbamoyl}-1-methylimidazol-4-yl)carbamoyl]ethyl}carbamoyl)-1-methylpyrrol-3-yl]-1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-carboxamide was used, 250.00 mg crude of N-(5-{[2-({2-[(2-{[26-(4-amino-2-hydroxyphenoxy)-3,6,9,12,15,18,21,24-octaoxahexacosan-1-

yl]carbamoyl}ethyl)carbamoyl]-1-methylimidazol-4-yl}carbamoyl)ethyl]carbamoyl}-1-methylpyrrol-3-yl)-1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-carboxamide was obtained as brown oil. LC/MS: mass calcd. for $C_{60}H_{85}N_{17}O_{18}$: 1331.62, found: 667.30 $[M/2+H]^+$.

[00708] ***Step 6. Synthesis of 5-{4-[2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl]-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-amido}-2-({26-[3-({1-methyl-4-[3-({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)propanamido]imidazol-2-yl}formamido)propanamido]-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl}oxy)phenyl 4-[2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl]-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-carboxylate***

[00709] The procedure was the same as ethyl 4-amino-1H-pyrrole-2-carboxylate (Example 4 step 2). 130.00 mg of N-(5-{[2-({2-[(2-{[26-(4-amino-2-hydroxyphenoxy)-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl]carbamoyl}ethyl)carbamoyl]-1-methylimidazol-4-yl}carbamoyl)ethyl]carbamoyl}-1-methylpyrrol-3-yl)-1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-carboxamide was used, 70.00 mg of 5-{4-[2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl]-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-amido}-2-({26-[3-({1-methyl-4-[3-({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)propanamido]imidazol-2-yl}formamido)propanamido]-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl}oxy)phenyl 4-[2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl]-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-carboxylate was obtained as white solid (32.24% yield). LC/MS: mass calcd. For $C_{112}H_{131}F_2N_{21}O_{26}$: 2223.95, found: 1113.45 $[M/2+H]^+$.

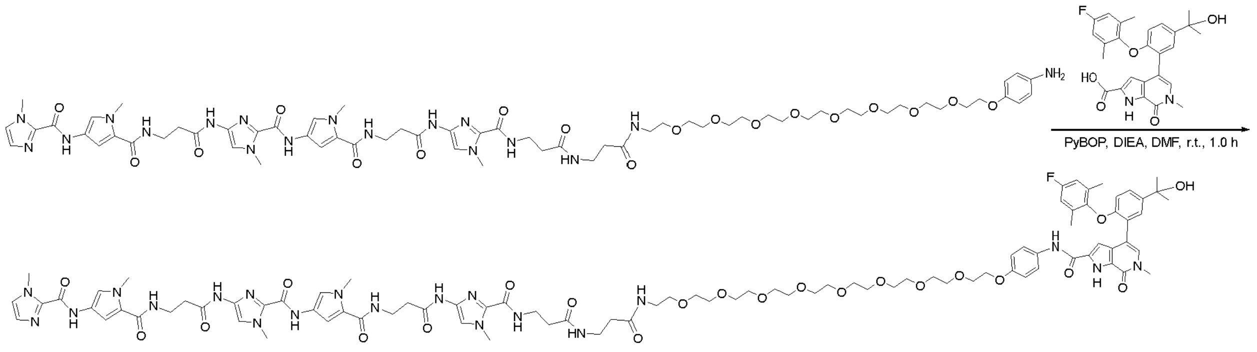
[00710] ***Step 7: Synthesis of Compound 12***

[00711] To a stirred solution of 5-{4-[2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl]-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-amido}-2-({26-[3-({1-methyl-4-[3-({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)propanamido]imidazol-2-yl}formamido)propanamido]-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl}oxy)phenyl 4-[2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl]-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-carboxylate (70.00 mg, 0.031 mmol, 1.00 equiv) in MeOH (2.00 mL) and THF (2.00 mL), LiOH (2M, 0.09 mL, 6.00 equiv) was added and the resulting mixture was stirred for 2.0 h at room temperature. The mixture was concentrated under reduced pressure, the residue was dissolved with 5 mL water, cooled to 0 °C, adjusted PH to 3-5 by 2M HCl. The precipitated solid was collected by filtration and washed with water (2x3 mL) and concentrated under vacuum. The crude was dissolved in DMF, filtered and the filtrate (2.00 mL) was purified by Prep-HPLC **with the following conditions: Column: XBridge Prep Phenyl OBD Column, 19*150 mm, 5μm; Mobile** Phase A: Water(10 mmol/L NH_4HCO_3+0.1%NH3.H_2O), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 28% B to 53% B in 15 min, 53% B; Wave Length: 254 nm; RT1(min): 12.58; Number Of Runs: 0.

The fractions were combined and lyophilized directly to afford N-(5-{[2-({2-[(2-{[26-(4-{4-[2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl]-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-amido}-2-hydroxyphenoxy)-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl]carbamoyl}ethyl)carbamoyl]-1-methylimidazol-4-yl}carbamoyl)ethyl]carbamoyl}-1-methylpyrrol-3-yl)-1-methyl-4-(3-{[1-methyl-4-(1-methylimidazole-2-amido)pyrrol-2-yl]formamido}propanamido)imidazole-2-carboxamide (19.5 mg, 33.43%) as white solid. HRMS: mass calcd. For $C_{86}H_{108}FN_{19}O_{22}$: 1777.7900, found: 1778.7906 $[M+H]^+$.

[00712] **Example 24. Synthesis of 4-(2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-N-(4-((1-(1-methyl-4-(3-(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)propanamido)-1H-imidazol-2-yl)-1,5,9-trioxo-13,16,19,22,25,28,31,34-octaoxa-2,6,10-triazahexatriacontan-36-yl)oxy)phenyl)-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (Compound 10)**

[00713] **Scheme 24.**



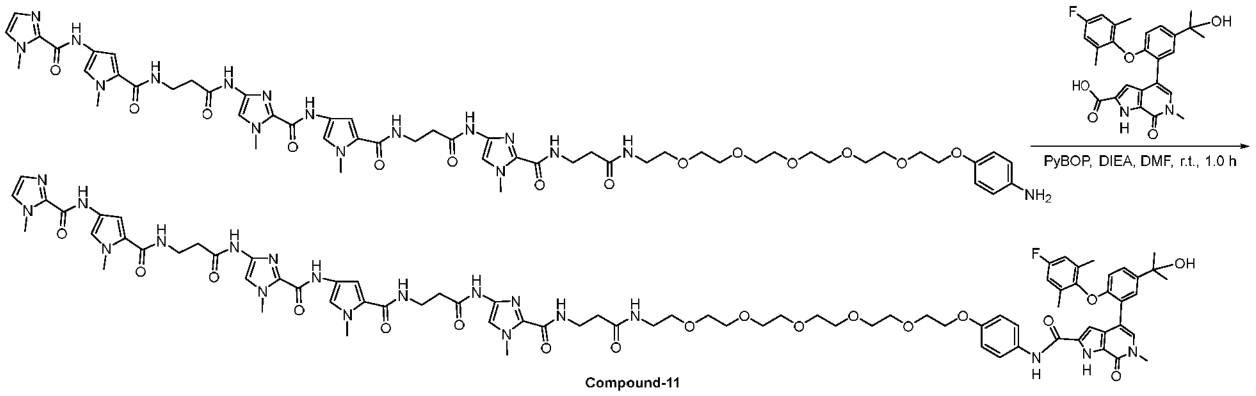
Compound-10

[00714] The procedure was the same as ethyl 4-amino-1H-pyrrole-2-carboxylate (Example 4 step 2). 191.00 mg of 4-(2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid was used, 600 mg of desired product was obtained as white solid. HRMS: mass calcd. for $C_{89}H_{113}FN_{20}O_{22}$: 1832.8322, found:

[00715] 1834.30 $[M+H]^+$.

[00716] **Example 25. Synthesis of 4-((1-(1-methyl-4-(3-(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)propanamido)-1H-imidazol-2-yl)-1,5-dioxo-9,12,15,18,21-pentaoxa-2,6-diazatricosan-23-yl)oxy)phenyl 4-(2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxylate (Compound 11)**

[00717] **Scheme 25.**

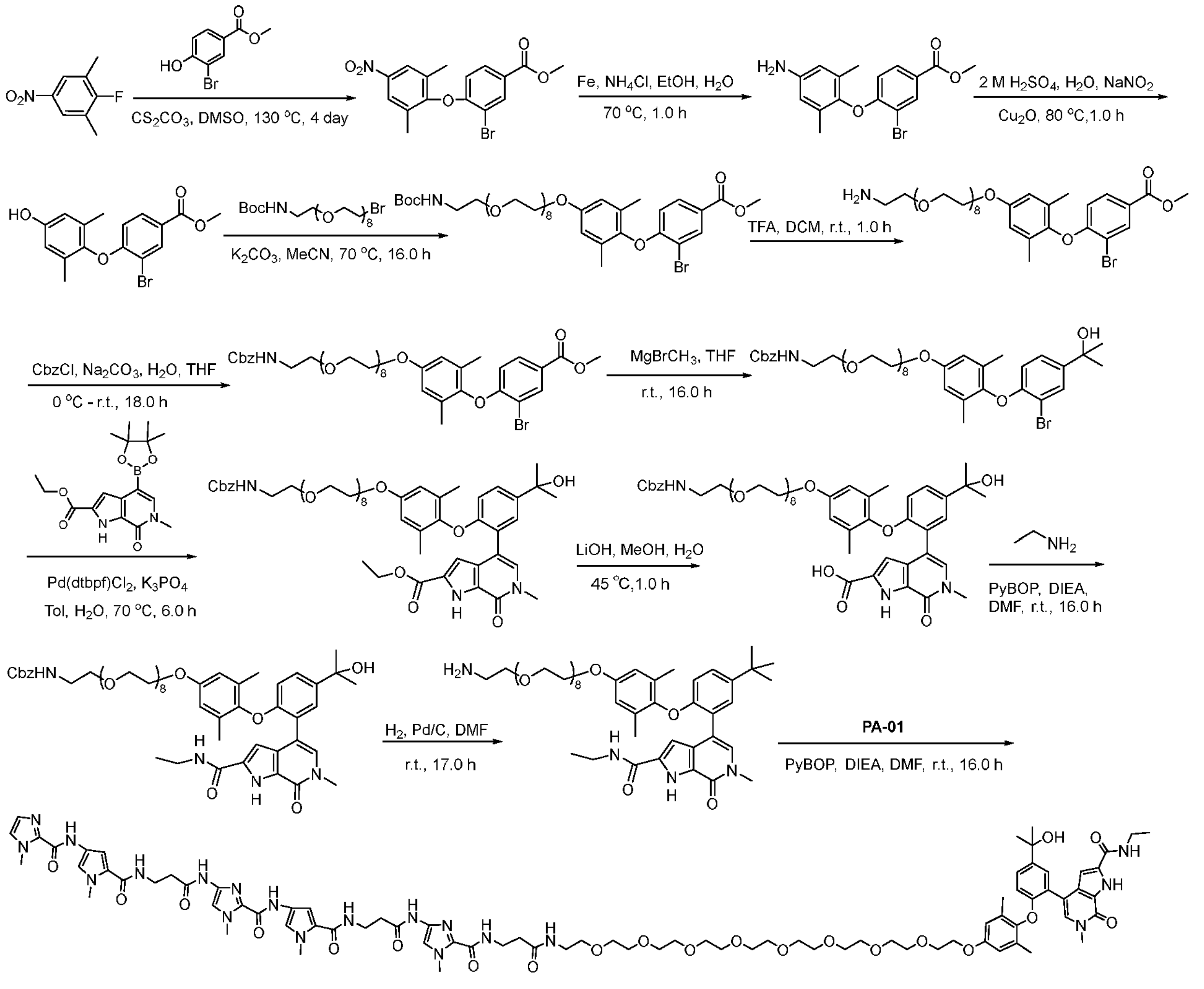


Compound-11

[00718] The procedure was the same as ethyl 4-amino-1H-pyrrole-2-carboxylate (Example 4 step 2). 2.85 g of 4-(2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid DIEA salt was used, 5.5 g of desired product was obtained as white solid. HRMS: mass calcd. for $C_{80}H_{96}FN_{19}O_{18}$: 1630.70, found: 1631.10 $[M+H]^+$.

[00719] **Example 26. Synthesis of 4-(2-(2,6-dimethyl-4-((1-(1-methyl-4-(3-(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)propanamido)-1H-imidazol-2-yl)-1,5-dioxo-9,12,15,18,21,24,27,30-octaoxa-2,6-diazadotriacontan-32-yl)oxy)phenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-N-ethyl-6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (Compound 17)**

[00720] **Scheme 26.**



Compound 17

[00721] ***Step 1: Synthesis of methyl 3-bromo-4-(2,6-dimethyl-4-nitrophenoxy)benzoate***

[00722] To a stirred mixture of 2-fluoro-1,3-dimethyl-5-nitrobenzene (5.80 g, 34.29 mmol, 1.00 equiv) and methyl 3-bromo-4-hydroxybenzoate (8.71 g, 37.717 mmol, 1.1 equiv) in DMSO (30.00 mL) was added Cs_2CO_3 (13.41 g, 41.15 mmol, 1.20 equiv) in portions. The mixture was stirred at 130 °C for 4 days. The resulting mixture was poured into 100 mL H_2O and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (1x 100 mL) and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford methyl 3-bromo-4-(2,6-dimethyl-4-nitrophenoxy)benzoate (1.50 g, 10.36%) as an orange solid. **^{1}H NMR (400 MHz, CDC13) δ: 8.38 (s, 1H),** 8.07(s, 2H), 7.85 (d, J = 8.8Hz, 1H), 6.36 (d, J = 8.4Hz, 1H), 3.93 (s, 3H), 2.24 (s, 6H).

[00723] ***Step 2: Synthesis of methyl 4-(4-amino-2,6-dimethylphenoxy)-3-bromobenzoate***

[00724] To a stirred mixture of methyl 3-bromo-4-(2,6-dimethyl-4-nitrophenoxy)benzoate (1.50 g, 3.95 mmol, 1.00 equiv) in EtOH (20.00 mL) was added NH_4Cl (2.11 g, 39.45 mmol, 10.00 equiv) and H_2O (10.00 mL) at room temperature. The reaction was heated to 70 °C and Fe (2.20 g, 39.45 mmol, 10.00 equiv) was added in portions and the resulting mixture was stirred for 1.0 h at 70 °C. The mixture was filtered, the filter cake was washed with ethanol (3x15 mL) and the filtrate was concentrated under reduced pressure.

The residue was purified by silica gel column chromatography, eluted with PE / EA (2:1) to afford methyl 4-(4-amino-2,6-dimethylphenoxy)-3-bromobenzoate (1.30 g, 88.44%) as a brown solid. LC/MS: mass calcd. For $C_{16}H_{16}BrNO_3$: 349.03, found: 350.00, 352.00 $[M+H, M+H+Na]^+$

[00725] ***Step 3: Synthesis of 3-bromo-4-(4-hydroxy-2,6-dimethylphenoxy)benzoate***

[00726] Methyl 4-(4-amino-2,6-dimethylphenoxy)-3-bromobenzoate (1.30 g, 3.71 mmol, 1.00 equiv) was dissolved in a cooled solution of H_2O (10.00 mL) and 2 M H_2SO_4 (5.00 mL) and $NaNO_2$ (0.26 g, 3.71 mmol, 1.00 equiv) was added. The mixture was stirred for 10 minutes and then Cu_2O (0.27 g, 1.86 mmol, 0.50 equiv) was added in batches and the mixture was stirred at 80 °C for 1.0 h. The mixture was then extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (1x30 mL), dried over anhydrous Na_2SO_4 and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (3:1) to afford methyl 3-bromo-4-(4-hydroxy-2,6-dimethylphenoxy)benzoate (0.60 g, 41.42%) as an orange solid. LC/MS: mass calcd. For $C_{16}H_{15}BrO_4$: 350.02, found: 349.00, 351.00 $[M-H, M-H+2]^-$

[00727] ***Step 4: Synthesis of methyl 3-bromo-4-[4-({26-[(tert-butoxycarbonyl)amino]-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl}oxy)-2,6-dimethylphenoxy]benzoate***

[00728] To a mixture of methyl 3-bromo-4-(4-hydroxy-2,6-dimethylphenoxy)benzoate (600.00 mg, 1.71 mmol, 1.00 equiv) and tert-butyl N-(26-bromo-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl)carbamate (984.96 mg, 1.71 mmol, 1.00 equiv) in ACN (10.00 mL) was added K_2CO_3 (708.35 mg, 5.12 mmol, 3.00 equiv) in portions and the resulting mixture was stirred at 70 °C for 16.0 h. The mixture was then filtered, the filter cake was washed with MeCN (3x10 mL) and the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (0.1% TFA), 10% to 50% gradient in 10 min; detector, UV 254 nm. The fraction were combined and concentrated to afford methyl 3-bromo-4-[4-({26-[(tert-butoxycarbonyl)amino]-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl}oxy)-2,6-dimethylphenoxy]benzoate (750.00 mg, 52.88%) as a yellow oil. LC/MS: mass calcd. For $C_{39}H_{60}BrNO_{14}$: 845.32, found: 846.30, 848.30 $[M+H, M+H+2]^+$

[00729] ***Step 5: Synthesis of methyl 4-{4-[(26-amino-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl)oxy]-2,6-dimethylphenoxy}-3-bromobenzoate***

[00730] To a solution of methyl 3-bromo-4-[4-({26-[(tert-butoxycarbonyl)amino]-3,6,9,12,15,18, 21,24-octaoxahexacosan-1-yl}oxy)-2,6-dimethylphenoxy]benzoate (750.00 mg, 0.89 mmol, 1.00 equiv) in DCM (10.00 mL) was added TFA (2.00 mL) at room temperature and the mixture was stirred for 1.0 h. The resulting mixture was concentrated under reduced pressure to afford methyl 4-{4-[(26-amino-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl)oxy]-2,6-dimethylphenoxy}-3-bromobenzoate (750.00 mg, crude) as a yellow oil. LC/MS: mass calcd. For $C_{34}H_{52}BrNO_{12}$: 745.27, found: 746.25, 478.25 $[M+H, M+H+2]^+$.

[00731] ***Step 6: Synthesis of methyl 4-{4-[(26-{[(benzyloxy)carbonyl]amino}-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl)oxy]-2,6-dimethylphenoxy}-3-bromobenzoate***

[00732] Cbz-Cl (319.85 mg, 1.87 mmol, 2.00 equiv) was added via syringe into a mixture of methyl 4-{4-[(26-amino-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl)oxy]-2,6-dimethylphenoxy}-3-bromobenzoate (750.00 mg, 0.94 mmol, 1.00 equiv) and Na_2CO_3 (149.04 mg, 1.41 mmol, 1.50 equiv) in H_2O (10.00 mL) and THF (3.00 mL) at 0 °C. The resulting mixture was stirred at room temperature for 18.0 h and was then extracted with CH_2Cl_2 (3 x 30mL). The combined organic layers were washed with brine (1x30 mL), dried over anhydrous Na_2SO_4 and the filtrate was concentrated under reduced pressure to afford methyl 4-{4-[(26-{[(benzyloxy)carbonyl]amino}-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl)oxy]-2,6-dimethylphenoxy}-3-bromobenzoate (680.00 mg, 75.76%) as a yellow liquid. LC/MS: mass calcd. For $C_{42}H_{58}BrNO_{14}$: 879.30, found: 880.30, 882.30 $[M+H, M+H+2]^+$.

[00733] ***Step 7: Synthesis of benzyl N-(26-{4-[2-bromo-4-(2-hydroxypropan-2-yl)phenoxy]-3,5-dimethylphenoxy}-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl)carbamate***

[00734] To a stirred solution of methyl 4-{4-[(26-{[(benzyloxy)carbonyl]amino}-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl)oxy]-2,6-dimethylphenoxy}-3-bromobenzoate (680.00 mg, 0.77 mmol, 1.00 equiv) in THF (10.00 mL) was added MeMgBr (1.0 M, 7.72 mL, 7.72 mmol, 10.00 equiv) dropwise at 0 °C under nitrogen for 10 min. The mixture is then allowed to warm to room temperature and was stirred for 16.0 h. The resulting mixture was diluted with water (10 mL) at 0 °C and extracted with EA (3x15 mL). The combined organic layers were washed with brine (1x20 mL), dried over anhydrous Na_2SO_4, and the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (10 mmol/L NH_4HCO_3), 10% to 50% gradient in 10 min; detector, UV 254 nm. The fraction were combined and concentrated to afford benzyl N-(26-{4-[2-bromo-4-(2-hydroxypropan-2-yl)phenoxy]-3,5-dimethylphenoxy}-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl)carbamate (450.00 mg, 59.56%) as yellow oil._LC/MS: mass calcd. For $C_{43}H_{62}BrNO_{13}$: 879.34, found: 878.20 , 880.20$[M-H, M-H+2]^-$.

[00735] ***Step 8: Synthesis of ethyl 4-(2-{4-[(26-{[(benzyloxy)carbonyl]amino}-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl)oxy]-2,6-dimethylphenoxy}-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-carboxylate***

[00736] To a stirred mixture of benzyl N-(26-{4-[2-bromo-4-(2-hydroxypropan-2-yl)phenoxy]-3,5-dimethylphenoxy}-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl)carbamate (450.00 mg, 0.51 mmol, 1.00 equiv), ethyl 6-methyl-7-oxo-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxylate, (230.00 mg, 0.66 mmol, 1.30 equiv) and Pd(dtbpf)Cl_2 (33.30 mg, 0.05 mmol, 0.10 equiv) in toluene (10.00 mL) was added K_3PO_4 (325.31 mg, 1.53 mmol, 3.00 equiv) in H_2O (1.00 mL) dropwise at room temperature. The mixture was stirred at 70 °C for 6.0 h. The resulting mixture was filtered, the filter cake was washed with EtOAc (3x10 mL), and the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (10 mmol/L NH_4HCO_3), 10% to 50% gradient in 10 min; detector, UV 254 nm. The fraction were combined and concentrated to afford ethyl 4-(2-{4-[(26-{[(benzyloxy)carbonyl]amino}-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl)oxy]-2,6-dimethylphenoxy}-5-

(2-hydroxypropan-2-yl)phenyl)-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-carboxylate (200.00 mg, 34.54%) as a yellow oil. LC/MS: mass calcd. For $C_{54}H_{73}N_3O_{16}$: 1019.50, found: 1020.35 $[M+H]^+$.

[00737] ***Step 9: Synthesis of 4-(2-{4-[(26-{[(benzyloxy)carbonyl]amino}-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl)oxy]-2,6-dimethylphenoxy}-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid***

[00738] To a stirred solution of ethyl 4-(2-{4-[(26-{[(benzyloxy)carbonyl]amino}-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl)oxy]-2,6-dimethylphenoxy}-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-carboxylate (320.00 mg, 0.31 mmol, 1.00 equiv) in MeOH (10.00 mL) was added LiOH (37.56 mg, 1.57 mmol, 5.00 equiv) in water (3.00 mL). The mixture was stirred at 45 °C for 1.0 h. The mixture was then acidified to pH 4 with HCl (2 M). The precipitated solids were collected by filtration and washed with anhydrous ether (3x10 mL) to afford 4-(2-{4-[(26-{[(benzyloxy)carbonyl]amino}-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl)oxy]-2,6-dimethylphenoxy}-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (150.00 mg, 65.55%) as a yellow soild. LC/MS: mass calcd. For : $C_{52}H_{69}N_3O_{16}$: 991.47, found: 992.50 $[M+H]^+$.

[00739] ***Step 10: Synthesis of benzyl N-[26-(4-{2-[2-(ethylcarbamoyl)-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridin-4-yl]-4-(2-hydroxypropan-2-yl)phenoxy}-3,5-dimethylphenoxy)-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl]carbamate***

[00740] To a stirred mixture of 4-(2-{4-[(26-{[(benzyloxy)carbonyl]amino}-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl)oxy]-2,6-dimethylphenoxy}-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (150.00 mg, 0.15 mmol, 1.00 equiv), ethylamine (6.82 mg, 0.15 mmol, 1.00 equiv) and PyBOP (118.02 mg, 0.23 mmol, 1.50 equiv) in DMF (6.00 mL) were added DIEA (48.85 mg, 0.38 mmol, 2.50 equiv) dropwise. The mixture was stirred at room temperature for 16.0 h. The resulting mixture was filtered and purified by reverse flash chromatography (column, C18 silica gel; mobile phase, MeCN in water (0.1% TFA), 10% to 50% gradient in 10 min; detector, UV 254 nm). The fraction were combined and concentrated to afford benzyl N-[26-(4-{2-[2-(ethylcarbamoyl)-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridin-4-yl]-4-(2-hydroxypropan-2-yl)phenoxy}-3,5-dimethylphenoxy)-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl]carbamate (100.00 mg, 59.06%) as a yellow oil. LC/MS: mass calcd. For $C_{54}H_{74}N_4O_{15}$: 1018.52, found: 1019.40 $[M+H]^+$.

[00741] ***Step 11: Synthesis of 4-(2-{4-[2-(2-aminoethoxy)ethoxy]-2,6-dimethylphenoxy}-5-(2-hydroxypropan-2-yl)phenyl)-N-ethyl-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-carboxamide***

[00742] To a stirred mixture of benzyl N-[26-(4-{2-[2-(ethylcarbamoyl)-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridin-4-yl]-4-(2-hydroxypropan-2-yl)phenoxy}-3,5-dimethylphenoxy)-3,6,9,12,15,18,21,24-octaoxahexacosan-1-yl]carbamate (100.00 mg, 0.10 mmol, 1.00 equiv) in DMF (10.00 mL) was added Pd/C (20.00 mg, 20% w/w) in portions at room temperature. The mixture was stirred under H_2 for 17.0 h. The resulting mixture was filtered, the filter cake was washed with MeOH (3x10mL), and concentrated. The resulting residue was lyophilized to afford 4-(2-{4-[2-(2-aminoethoxy)ethoxy]-2,6-dimethylphenoxy}-5-(2-

hydroxypropan-2-yl)phenyl)-N-ethyl-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (80.00 mg, 120.18%) as a a yellow solid. LC/MS: mass calcd. For $C_{46}H_{68}N_4O_{13}$: 884.48, found: 885.40[M+H]$^+$.

[00743] ***Step 12: Synthesis of Compound 17***

[00744] To a stirred mixture of 4-(2-{4-[2-(2-aminoethoxy)ethoxy]-2,6-dimethylphenoxy}-5-(2-hydroxypropan-2-yl)phenyl)-N-ethyl-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (80.00 mg, 0.14 mmol, 1.00 equiv), 3-({1-methyl-4-[3-({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)propanamido]imidazol-2-yl} formamido)propanoic acid, (PA-01, Example 1) (115.12 mg, 0.14 mmol, 1.00 equiv) and PyBOP (108.29 mg, 0.21 mmol, 1.50 equiv) in DMF (2.00 mL) was added DIEA (44.82 mg, 0.35 mmol, 2.50 equiv) dropwise. The mixture was stirred at r.t. for 16.0 h. The mixture was then filtered and purified by Prep-HPLC (Column: XBridge Shield RP18 OBD Column, 19*250 mm, 10µm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3 + 0.1%$NH_3.H_2O$), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 20% B to 45% B in 15 min, 45% B; Wave Length: 254 nm; RT1(min): 14. The fractions were combined and lyophilized to afford the title compound (Compound 17) (16.1 mg, 6.61%) as a white solid._HRMS: mass calcd. For $C_{82}H_{109}N_{19}O_{21}$: 1695.8045, found: 1696.8142 [M+H]$^+$. HPLC: 96.625% purity.

[00745] **Example 27. General synthesis and purification of the compounds of the disclosure**

[00746] Compounds of the disclosure were made by methods similar to Examples 1-26. The compounds were subsequently purified by HRMS methods A or B.

[00747] 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: H_2O (0.1% HCOOH), mobile B, CAN (0.1% HCOOH); Flow rate:0.4mL/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.

[00748] 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, 2.7µm; mobile phase A: H_2O (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.

[00749] 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.

Cmpd. No.	Observed [M+H]+ from TOF-HRMS [m/z]
1	1776.8225
2	1782.7370
3	1796.7515
4	2056.9525
5	1751.8142

Cmpd. No.	Observed [M+H]+ from TOF-HRMS [m/z]
6	1776.8272
7	1691.7722
8	1717.7781
9	1663.7394
10	1834.30
11	1631.10
12	1778.7906
15	1762.8062
17	1696.8142
18	1898.7955
19	1958.8153

BIOLOGICAL EXAMPLES

[00750] **Example B1: EC_{50} Assay**

[00751] Cell culture: Cells were cultured in RPMI1640 medium + 15% FBS. Cells were maintained at a density between 2 x 10^6/mL and 1 x 0^6/mL. Cells were centrifuged, resuspended in fresh medium, counted and plated at 150,000 cells per well in 100 µL in a non-coated, flat bottom tissue culture plate.

[00752] Compound treatment: 10 mM stock solution of FA GeneTAC was diluted 1:10 in DMSO followed by a 1:100 dilution in growth medium. Working solution was then further diluted to 10X desired final concentration of 150 nM. Compound was then diluted at a 1:3 ratio into growth medium containing 0.01% DMSO. 5-point, 3-fold dose response curve was generated. 11 µL of 10X compound was added to wells containing 100 µL cell suspension of GM15850. 11 µL growth medium containing 0.01% DMSO was added to all wells not treated with FA GeneTAC. Cells were allowed to incubate for 48 hrs prior to cell lysis using guanidine isothiocyanate solution.

[00753] RNA isolation: Total RNA was isolated and purified in 384-well column filter plates using chaotropic salt.

[00754] qRT-PCR: qRT-PCR reactions were assembled using AgPath-ID reagents (Thermo Fisher) using 6uL mastermix and 4 µL RNA. qRT-PCR TaqMan primer probe sets against human FXN (Assay ID Hs01075496_m1) and human GAPDH (Assay ID Hs00266705_g1) were used to measure the intended targets. qRT-PCR was run on the ThermoFisher QuantStudio 6 PRO instrument using the manufacturer's recommended cycling conditions.

[00755] Data analysis: qPCR data was analyzed using Thermo Fisher Design and Analysis software. Data was exported to Excel and hFXN expression was normalized to hGAPDH expression

[00756] Representative *in vitro* biochemical data is presented in Table 5. A < 100 nM; B is 100 nM to 500 nM; C > 500 nM.

Table 5. *In vitro* potency data.

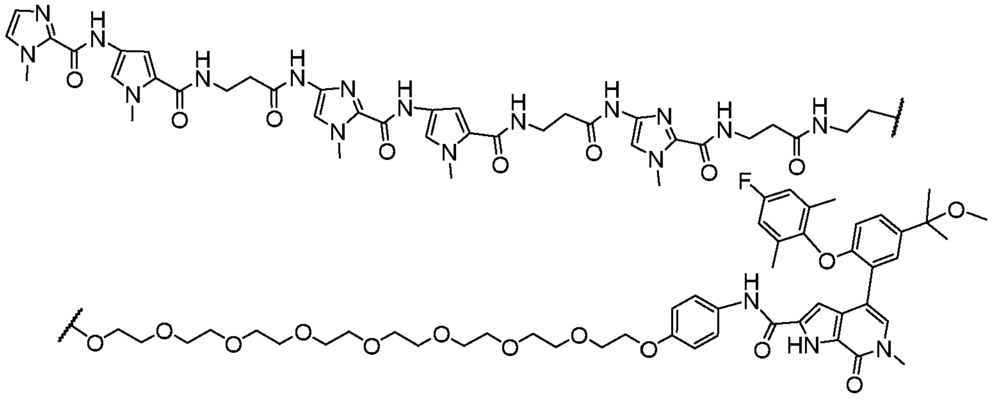
Cmpd. No.	EC_{50} WT (nM, 48 hr)
1	A
2	A
3	A
4	A
5	A
6	A
7	A
8	A
9	A
10	A
11	A
12	A
15	A
17	A

[00757] While preferred embodiments of the present disclosure 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 disclosure. It should be understood that various alternatives to the embodiments of the disclosure described herein may be employed in practicing the disclosure. It is intended that the following claims define the scope of the disclosure and that methods and structures within the scope of these claims and their equivalents be covered thereby.

CLAIMS

WHAT IS CLAIMED IS:

1. A compound selected from:



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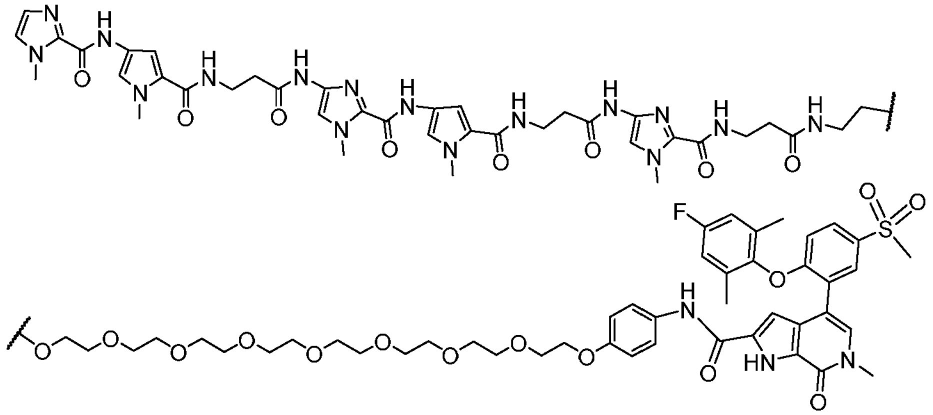

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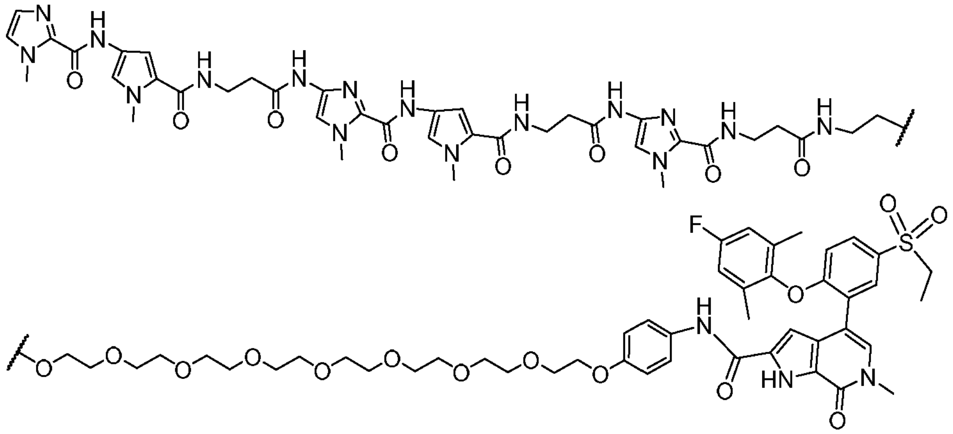

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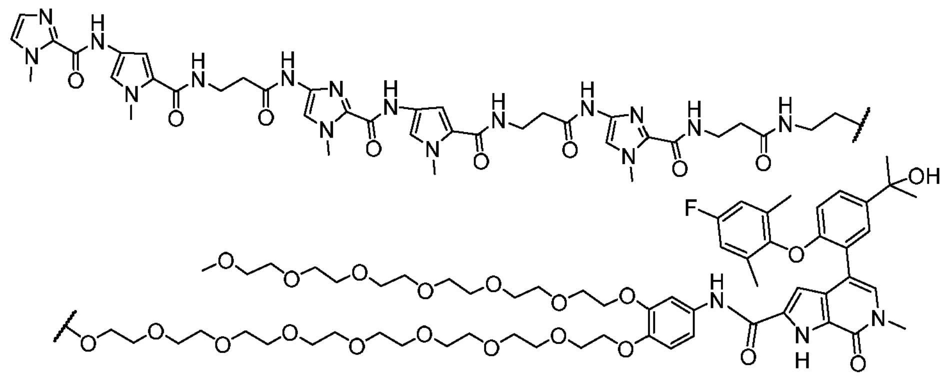

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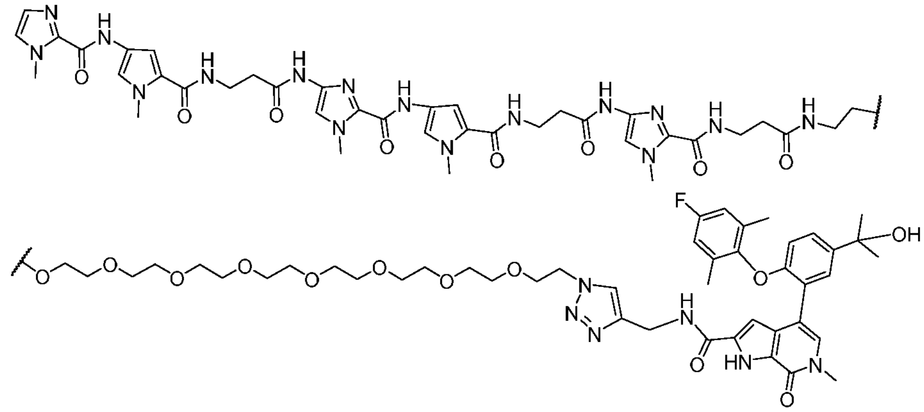

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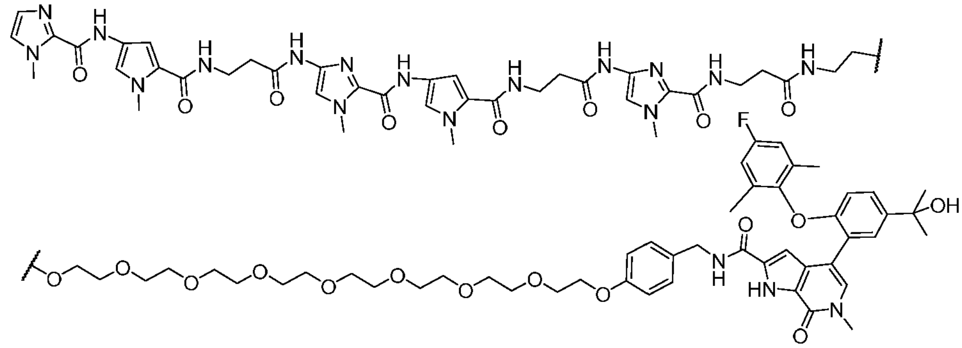

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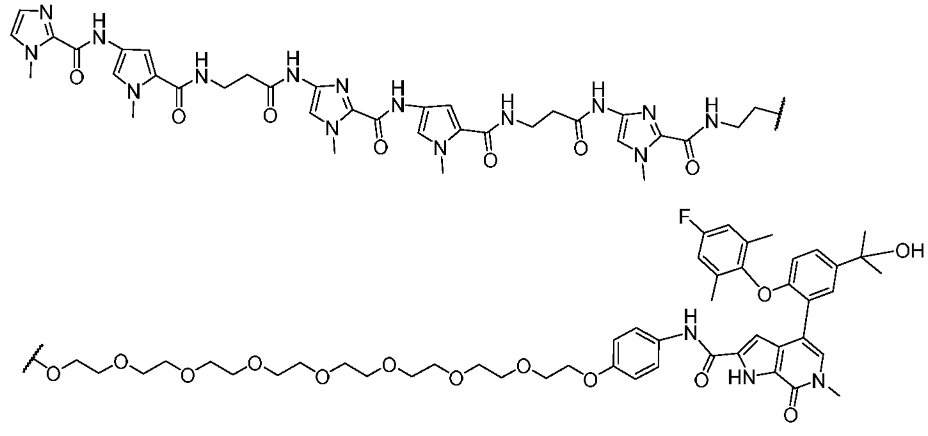

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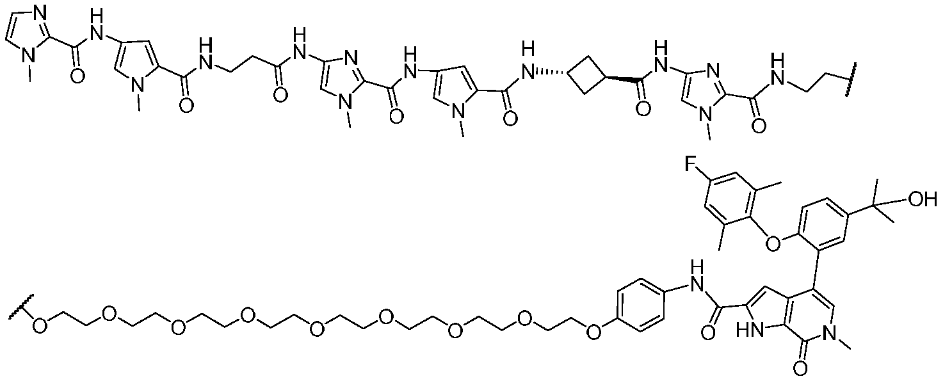

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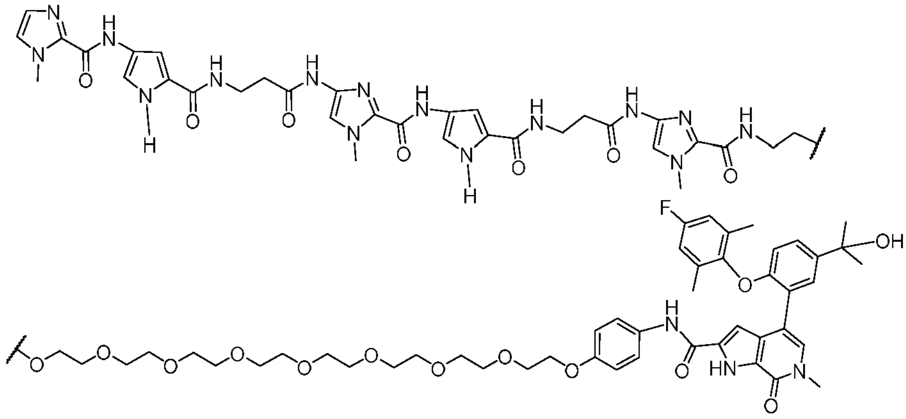

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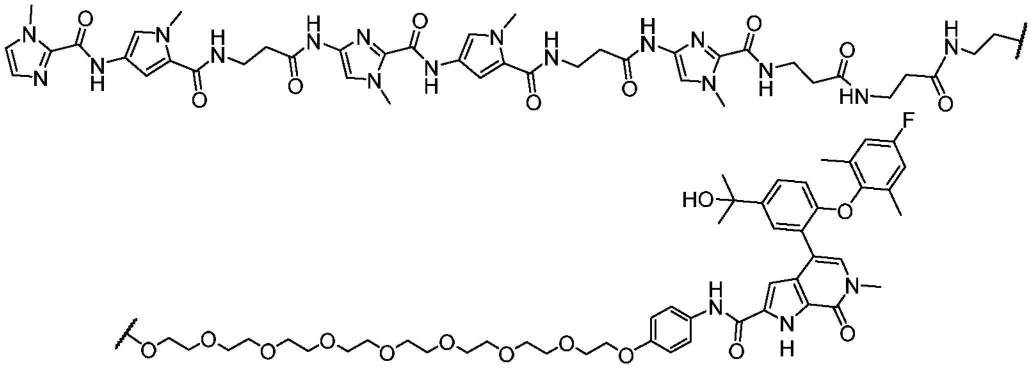

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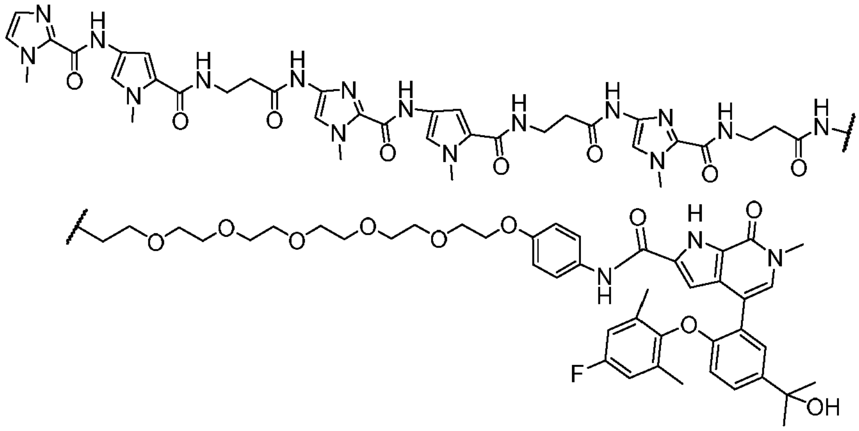

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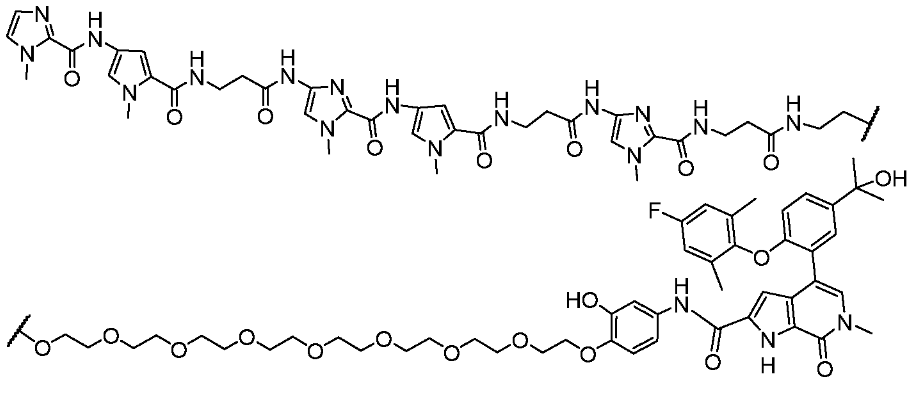

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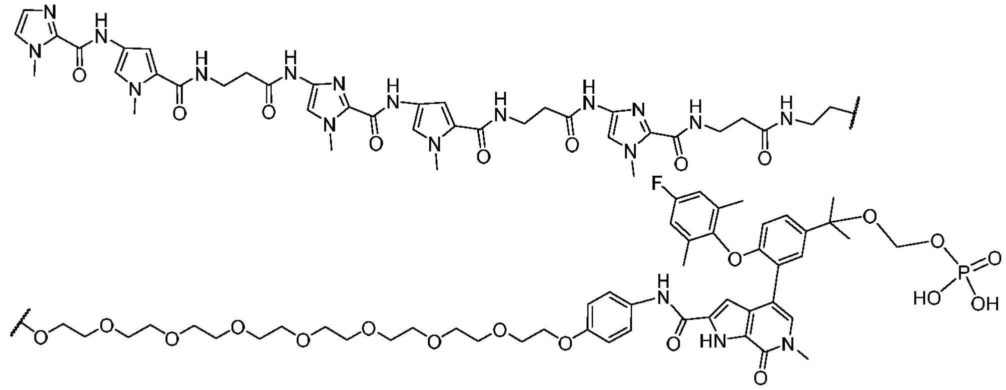

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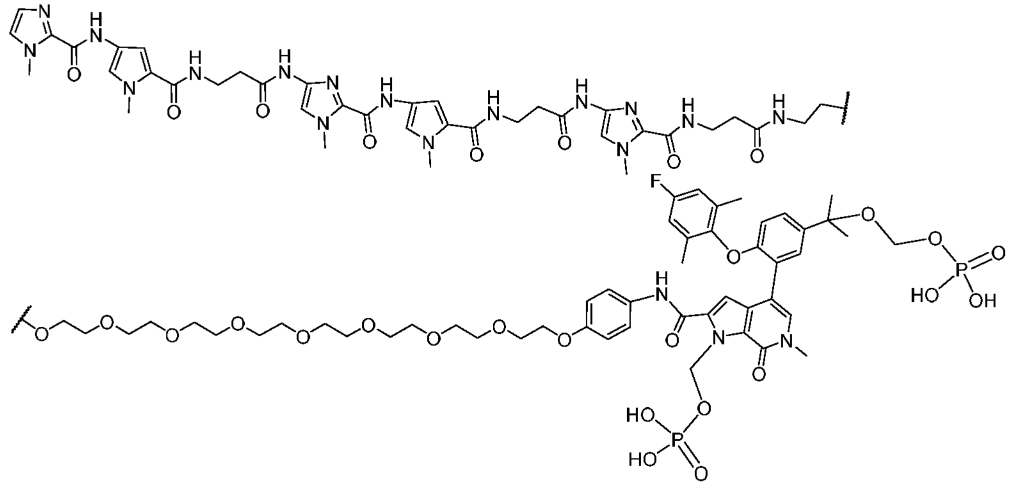

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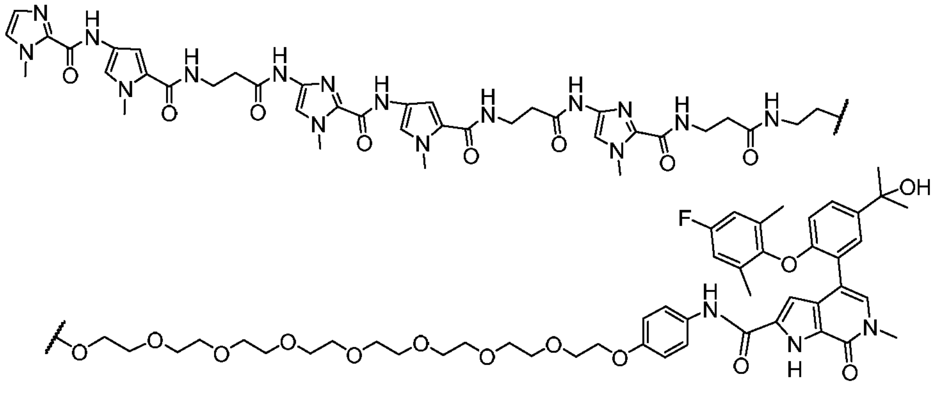

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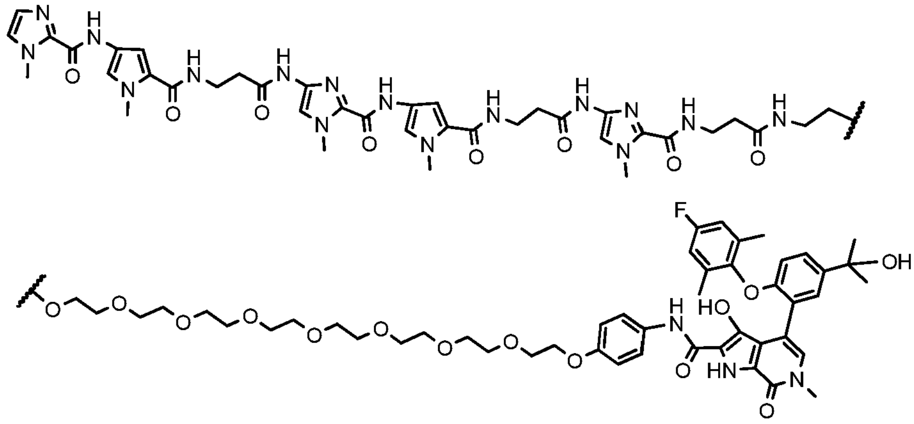

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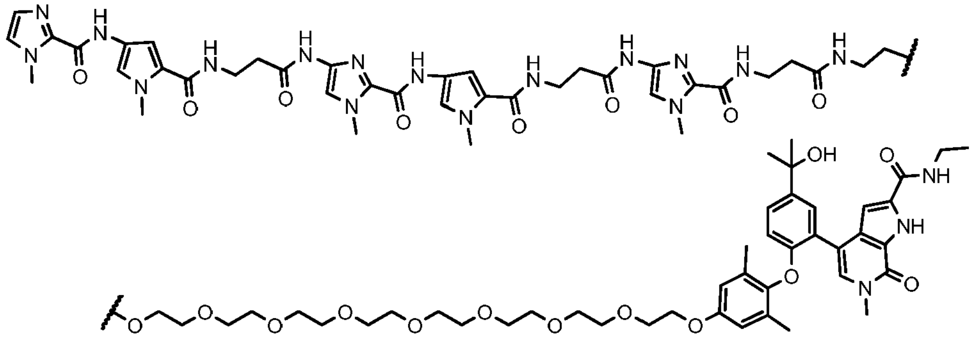

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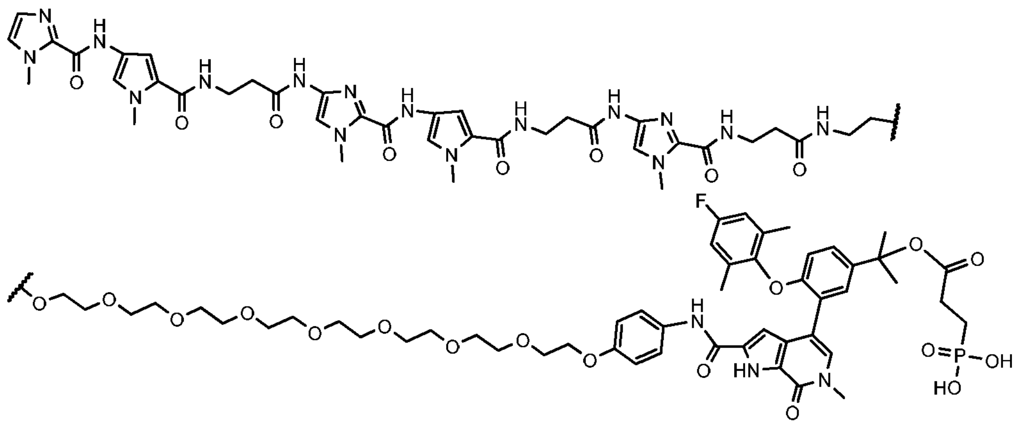

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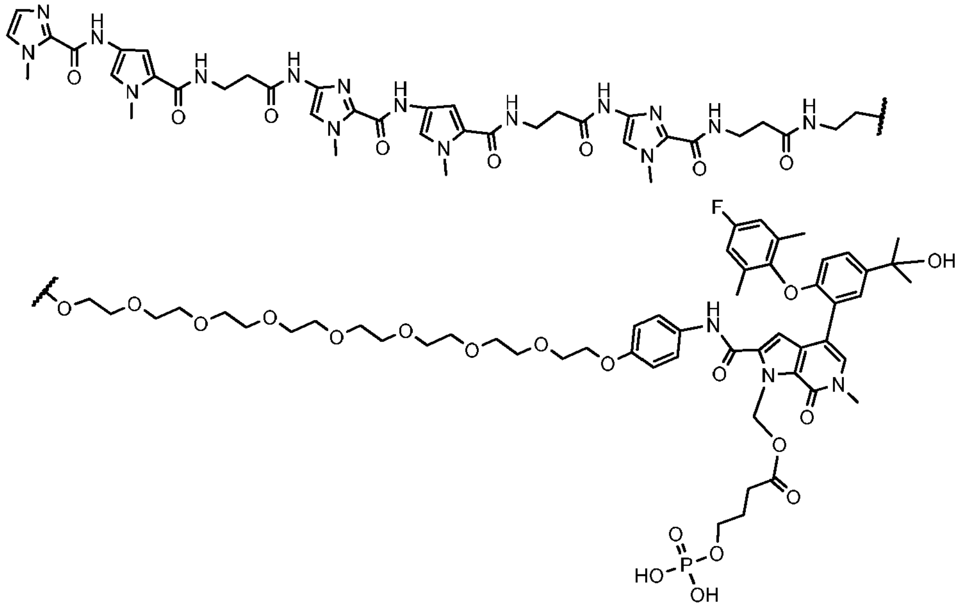
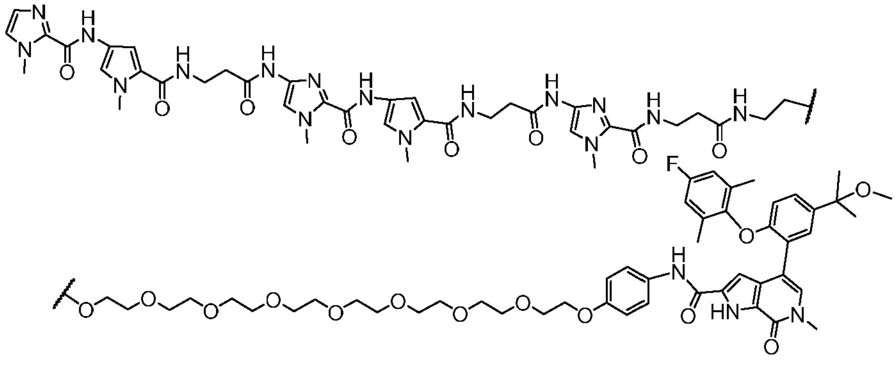


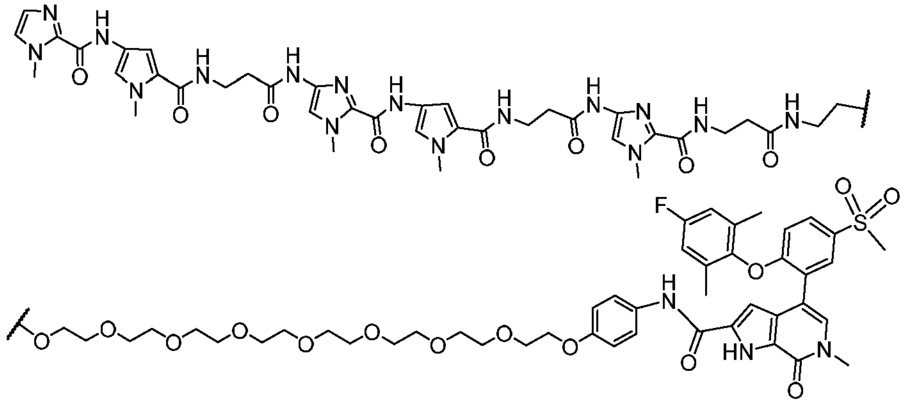
19, or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein the compound is:



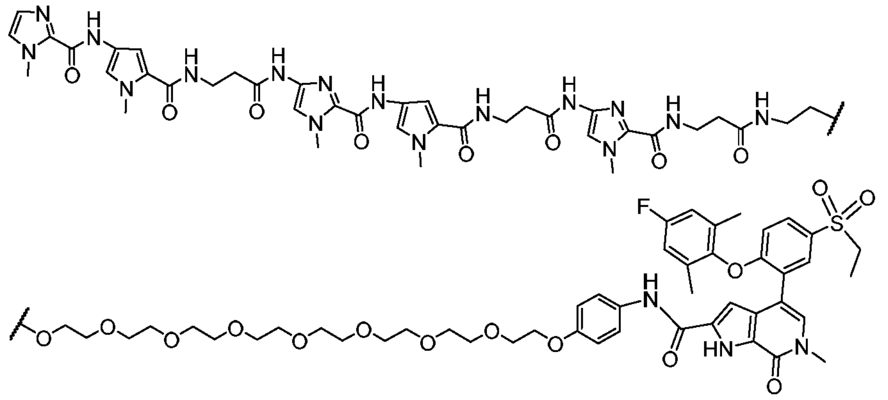
1, or a pharmaceutically acceptable salt thereof.

3. The compound of claim 1, wherein the compound is:



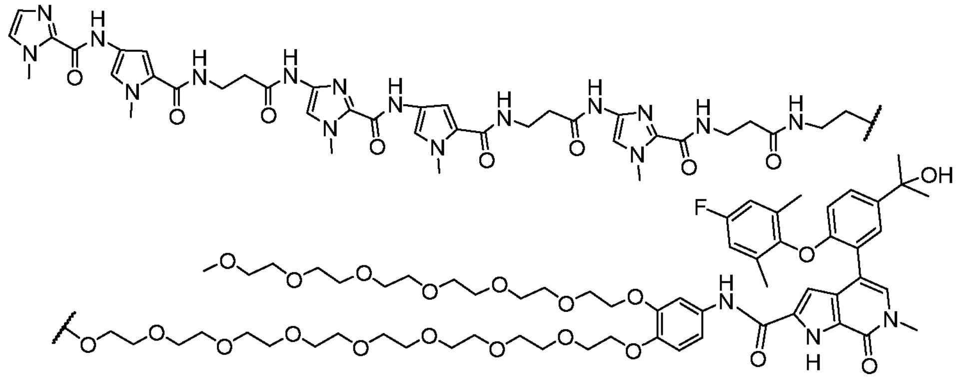
2, or a pharmaceutically acceptable salt thereof.

4. The compound of claim 1, wherein the compound is:



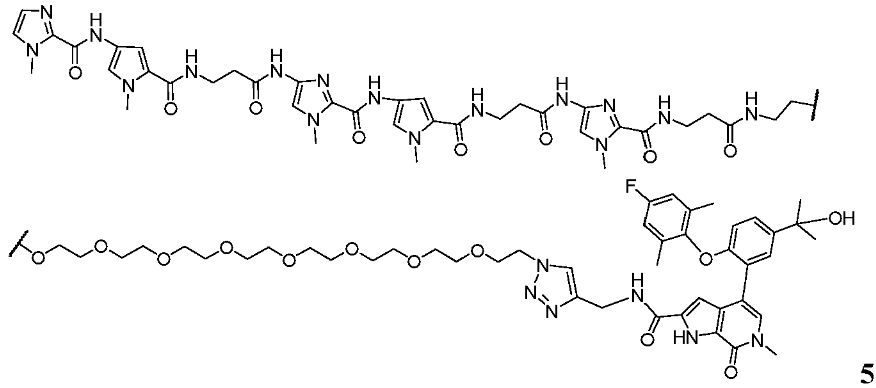
3, or a pharmaceutically acceptable salt thereof.

5. The compound of claim 1, wherein the compound is:



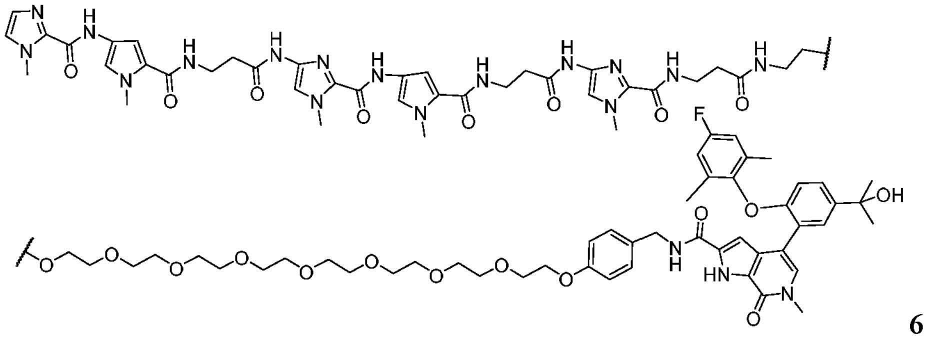
4, or a pharmaceutically acceptable salt thereof.

6. The compound of claim 1, wherein the compound is:



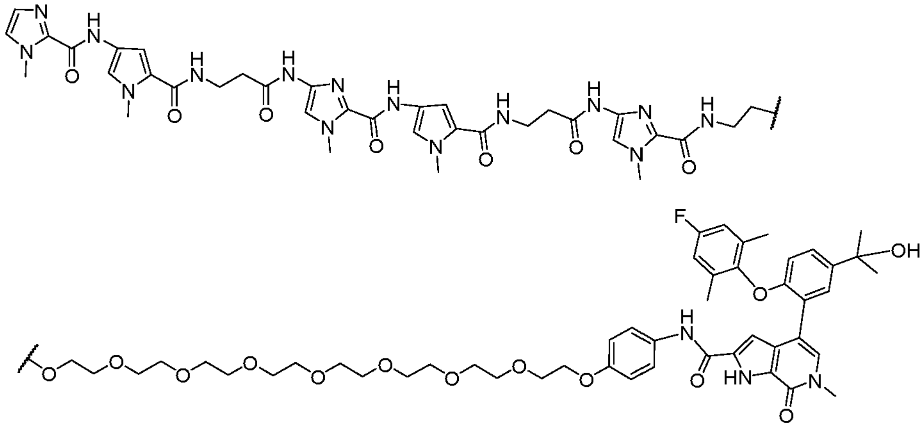
5, or a pharmaceutically acceptable salt thereof.

7. The compound of claim 1, wherein the compound is:



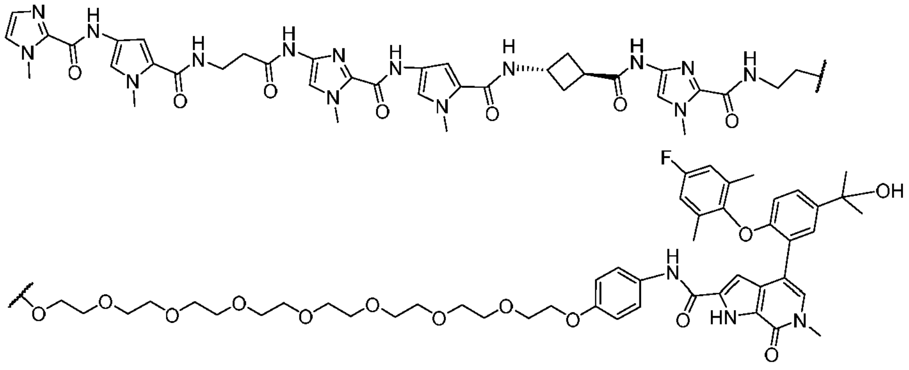
6, or a pharmaceutically acceptable salt thereof.

8. The compound of claim 1, wherein the compound is:



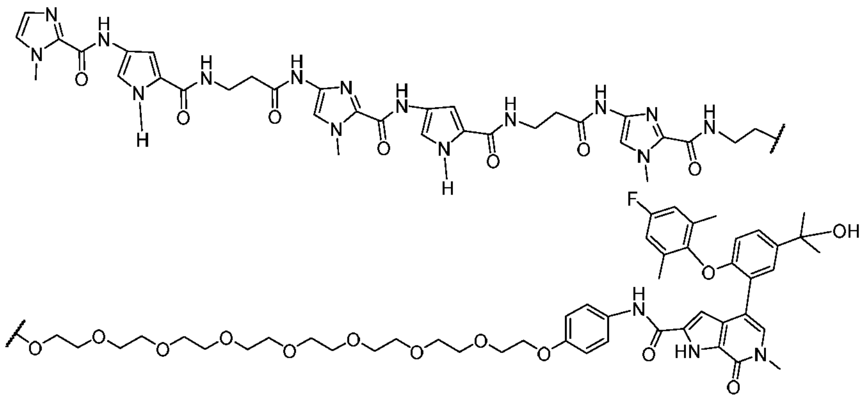
7, or a pharmaceutically acceptable salt thereof.

9. The compound of claim 1, wherein the compound is:



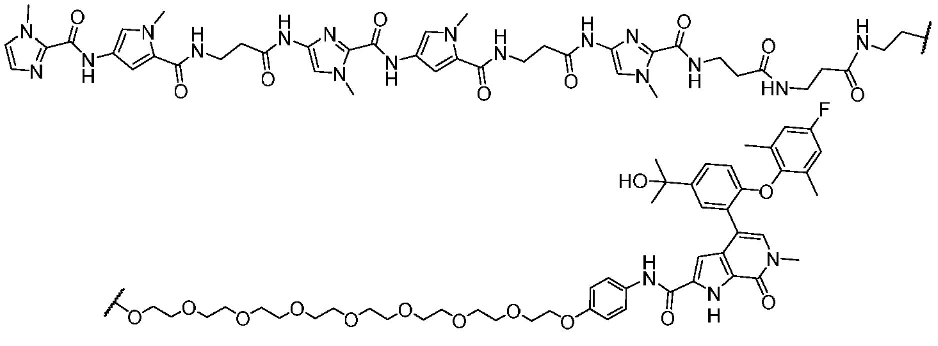
8, or a pharmaceutically acceptable salt thereof.

10. The compound of claim 1, wherein the compound is



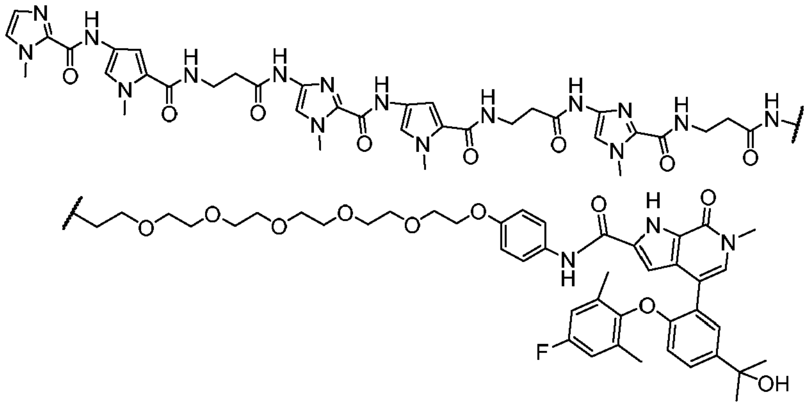
9, or a pharmaceutically acceptable salt thereof.

11. The compound of claim 1, wherein the compound is



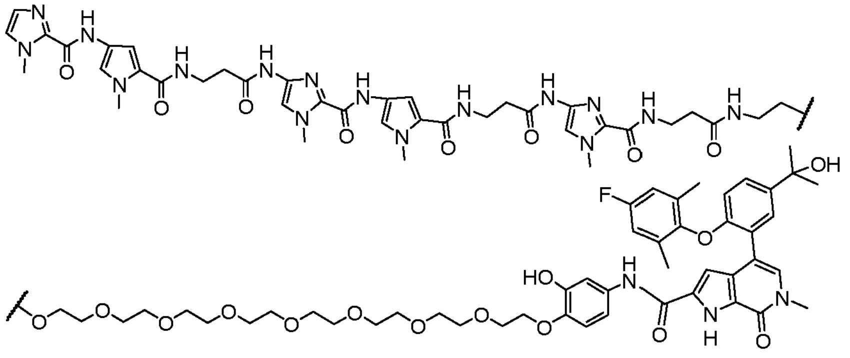
10, or a pharmaceutically acceptable salt thereof.

12. The compound of claim 1, wherein the compound is



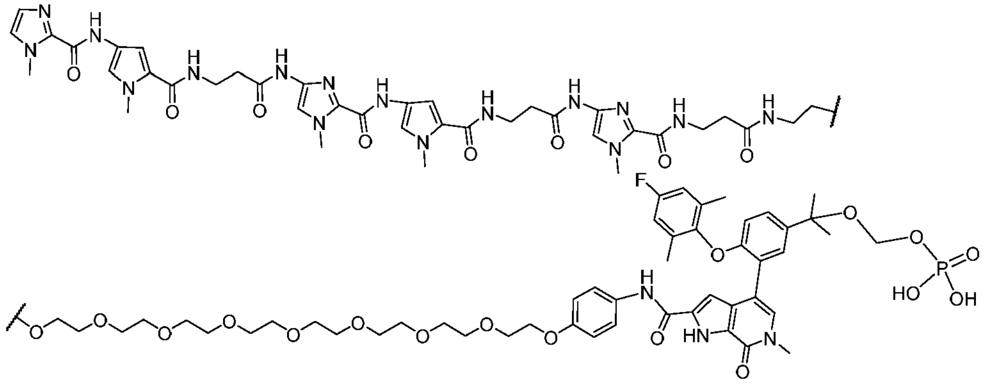
11, or a pharmaceutically acceptable salt thereof.

13. The compound of claim 1, wherein the compound is



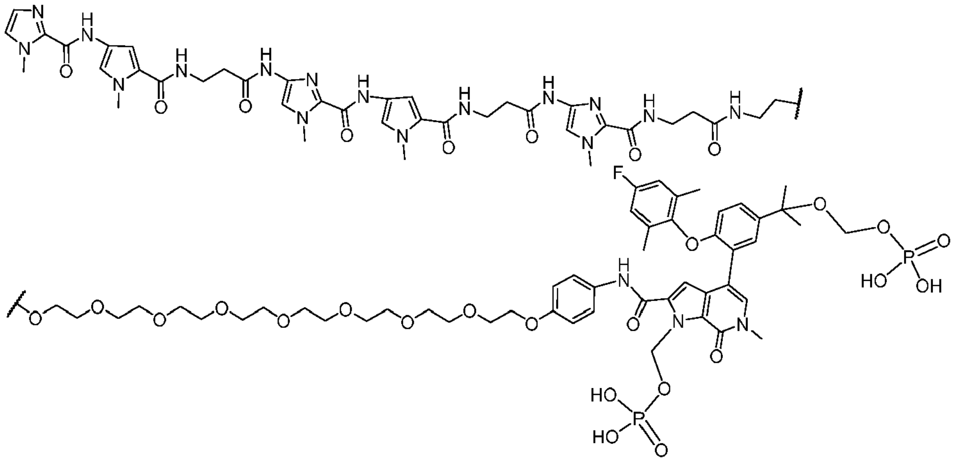
12, or a pharmaceutically acceptable salt thereof.

14. The compound of claim 1, wherein the compound is



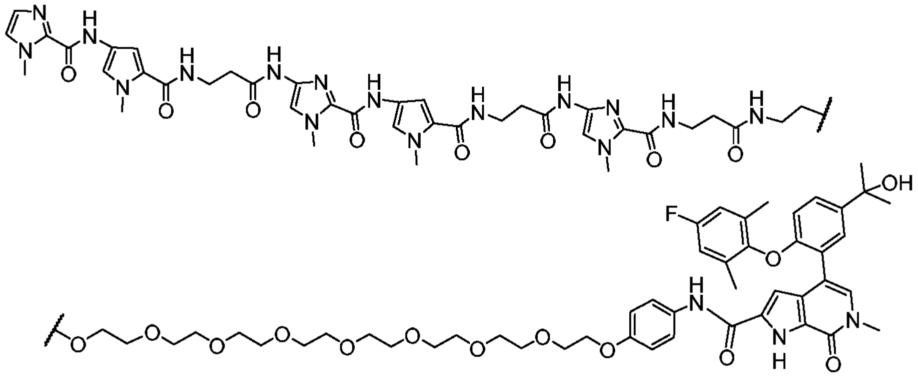
13, or a pharmaceutically acceptable salt thereof.

15. The compound of claim 1, wherein the compound is



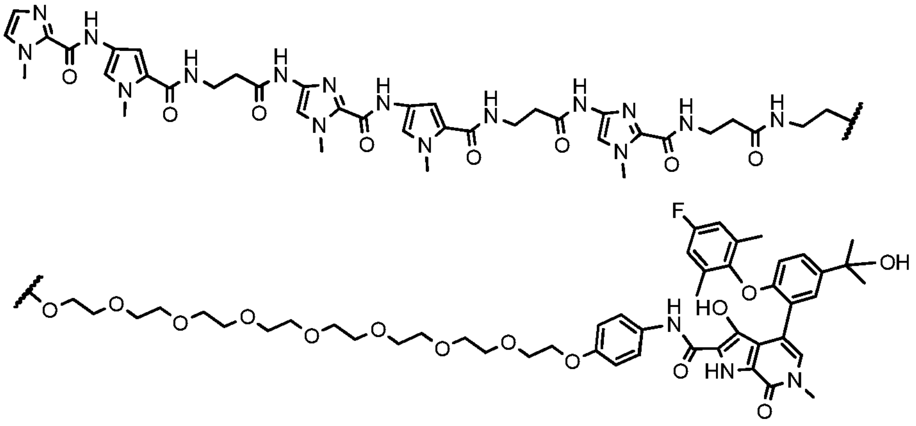
14, or a pharmaceutically acceptable salt thereof.

16. The compound of claim 1, wherein the compound is



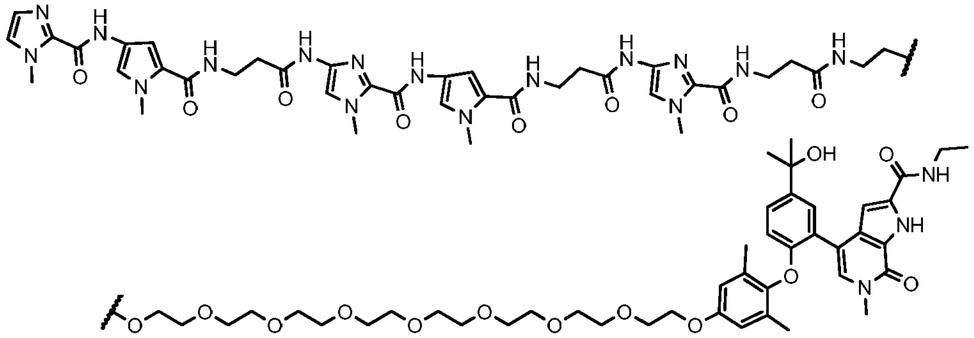
15, or a pharmaceutically acceptable salt thereof.

17. The compound of claim 1, wherein the compound is:



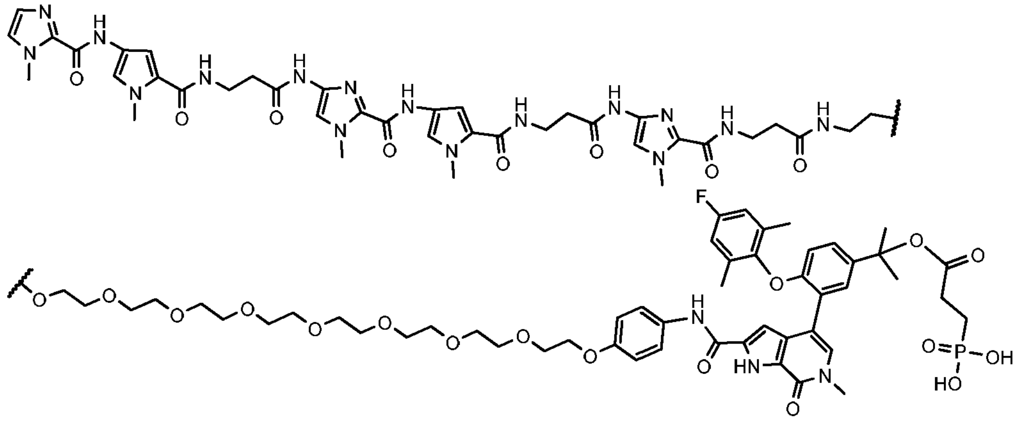
16, or a pharmaceutically acceptable salt thereof.

18. The compound of claim 1, wherein the compound is:



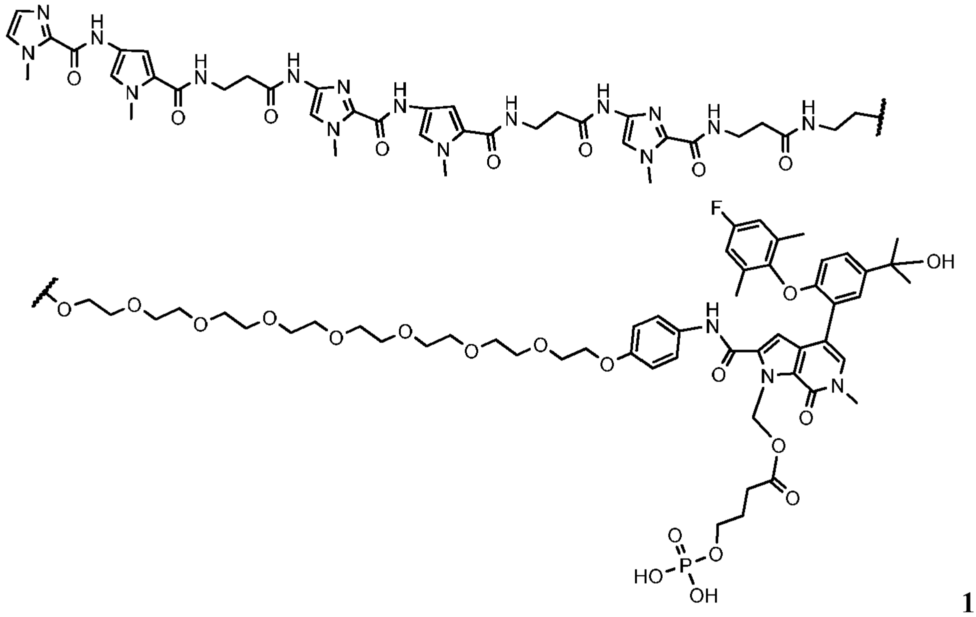
17, or a pharmaceutically acceptable salt thereof.

19. The compound of claim 1, wherein the compound is:



18, or a pharmaceutically acceptable salt thereof.

20. The compound of claim 1, wherein the compound is:



19, or a pharmaceutically acceptable salt thereof.

21. A pharmaceutical composition comprising a compound of any one of claims 1-20, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient.

22. A method of modulation of the expression of *fxn* comprising contacting *fxn* with a compound of any one of claims 1-20, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 21.

23. A method of treatment of a disease or condition caused by expression of a defective *fxn* in a patient in need thereof, comprising administering to the patient a compound of any one of claims 1-20, or a pharmaceutically acceptable salt thereof, or a pharmaceutical compositin of claim 21.

24. The method of claim 23, wherein the disease is Friedreich's ataxia (FA).

25. A method of treating Freidreich's ataxia (FA) in a patient in need thereof, comprising administering to the patient a compound of any one of claims 1-20, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 21.

26. The method of claim 25, wherein the method comprises alleviating one or more of muscular atrophy, ataxia, fasciculation, or dementia.