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(54) Title: LUNG LOCALIZED INHIBITORS OF ALPHA(V)BETA 6

(57) Abstract: Described herein are compounds, compositions, and methods of their use treatment of a lung disease.

LUNG LOCALIZED INHIBITORS OF ALPHA(V)BETA6

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Application Serial No. 62/002,621, filed May 23, 2014, which is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

[0002] Idiopathic pulmonary fibrosis (IPF) is a progressively fibrotic interstitial lung disease that is associated with a median survival of 2-3 years from initial diagnosis. To date, there is no treatment approved for IPF in the United States. Transforming growth factor (TGF)-beta has a central role in driving many of the pathological processes that characterize pulmonary fibrosis. Inhibition of the integrin alpha(v)beta6, a key activator of TGF-beta in lung, is an attractive therapeutic strategy, as it may be possible to inhibit TGF-beta at sites of alpha(v)beta6 up-regulation without affecting other homeostatic roles of TGF-beta.

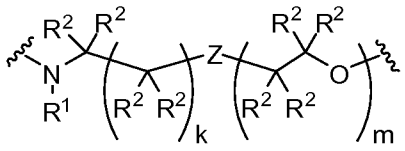
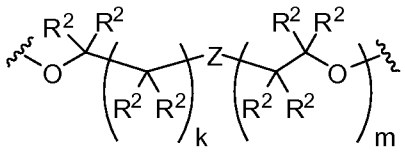
SUMMARY OF THE INVENTION

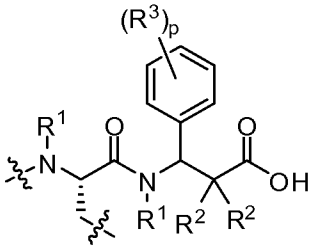
[0003] In one aspect, provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, metabolite, deuteride, N-oxide, tautomer, stereoisomer, or isomer thereof, having the structure:

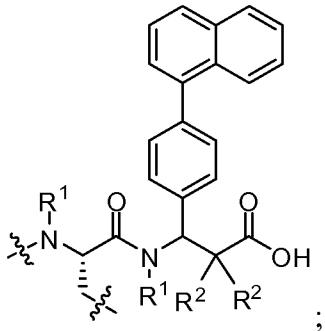
$$Y^1-L^1-B^1-J^1-A^1-X-A^2-J^2-B^2-L^2-Y^2$$

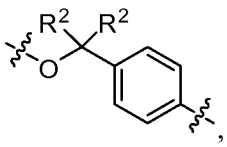
Formula (I);

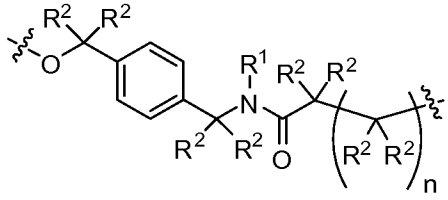
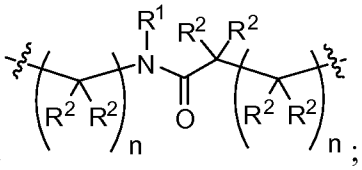
wherein:

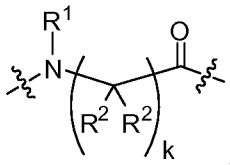
A^1 and A^2 are independently selected from:  and ;

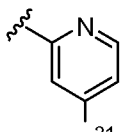
B^1 and B^2 are independently selected from:  and

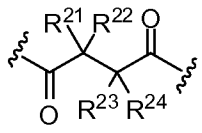
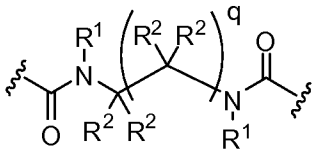
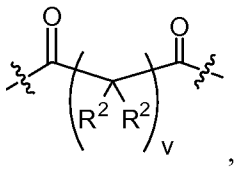
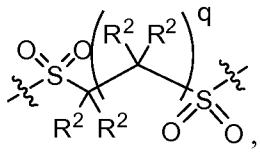
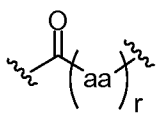
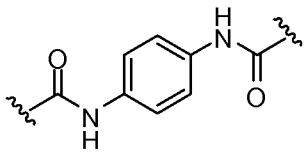
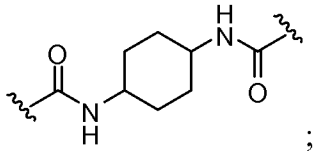
;

J^1 and J^2 are independently selected from a bond, ,

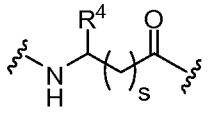
, and ;

L^1 and L^2 are independently selected from: ;

Y^1 and Y^2 are independently selected from: ;

X is alkylene, -C(O)-, , , , , , , or ;

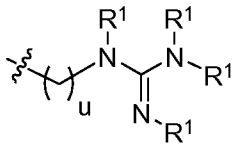
Z is O or CR^2R^2;

aa is ;

each R^1 is independently selected from H, alkyl, haloalkyl, arylalkyl, and heteroarylalkyl;

each R^2 is independently selected from H, halo, -CN, $-SR^1$, alkyl, cycloalkyl, haloalkyl, $-OR^1$, and $-R^4$;

each R^3 is independently selected from halo, alkyl, -CN, haloalkyl, $-OR^1$, and $-NR^1R^1$;

each R^4 is independently selected from $-CO_2R^1$, -(alkylene)-(CO_2R^1), hydroxyalkyl, -(alkylene)($S(O)_t$)(alkyl), -(alkylene)(NR^5R^5), and ;

each R^5 is independently selected from H, alkyl, haloalkyl, arylalkyl, heteroarylalkyl, aryl, and heteroaryl;

R^{21}, R^{22}, R^{23}, and R^{24} are independently selected from H, halo, -CN, $-SR^1$, alkyl, cycloalkyl, haloalkyl, $-NR^1R^1$, and $-OR^1$;

each R^{31} is independently selected from H and alkyl;

each k is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

each m is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

each n is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

each p is independently selected from 0, 1, 2, 3, and 4;

q is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

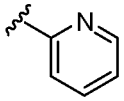
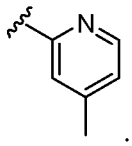
r is 3, 4, 5, 6, or 7;

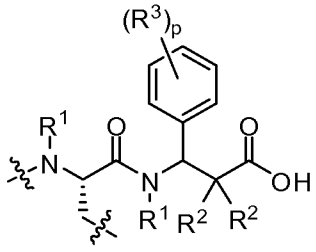
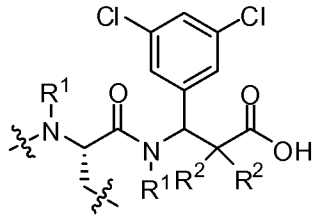
each s is independently selected from 0, 1, 2, 3, and 4;

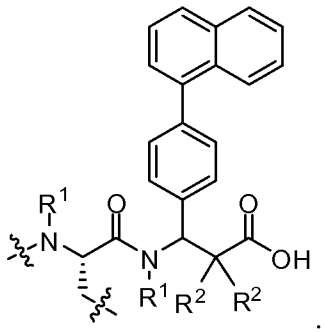
each t is independently selected from 0, 1, and 2;

each u is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10; and

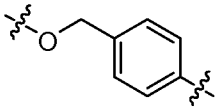
v is selected from 3, 4, 5, 6, 7, 8, 9, and 10.

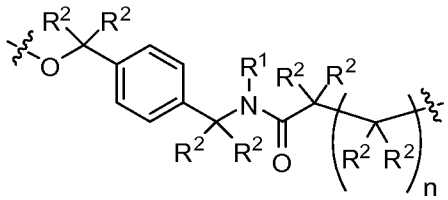
[0004] In some embodiments described above or below of a compound of Formula (I), Y^1 and Y^2 are the same. In some embodiments described above or below of a compound of Formula (I), Y^1 and Y^2 are both . In some embodiments described above or below of a compound of Formula (I), Y^1 and Y^2 are both .

[0005] In some embodiments described above or below of a compound of Formula (I), B^1 and B^2 are the same. In some embodiments described above or below of a compound of Formula (I), B^1 and B^2 are both . In some embodiments described above or below of a compound of Formula (I), B^1 and B^2 are both . In some embodiments described above or below of a compound of Formula (I), B^1 and B^2 are both

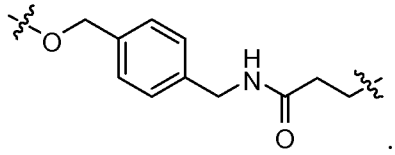


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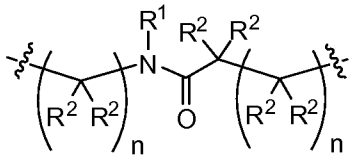
[0006] In some embodiments described above or below of a compound of Formula (I), J^1 and J^2 are the same. In some embodiments described above or below of a compound of Formula (I), J^1 and J^2 are both . In some embodiments described above or below of a



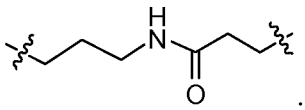
compound of Formula (I), J^1 and J^2 are both . In some embodiments described above or below of a compound of Formula (I), J^1 and J^2 are both



. In some embodiments described above or below of a compound of Formula (I), J^1 and J^2 are both

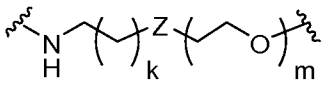


. In some embodiments described above or below of a compound of Formula (I), J^1 and J^2 are both

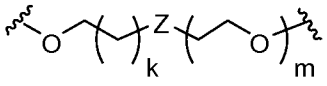


. In some embodiments described above or below of a compound of Formula (I), J^1 and J^2 are both a bond.

[0007] In some embodiments described above or below of a compound of Formula (I), A^1 and A^2 are the same. In some embodiments described above or below of a compound of Formula (I), A^1 and A^2 are not the same. In some embodiments described above or below of a compound of Formula (I), A^1 and A^2 are both



. In some embodiments described above or below of a compound of Formula (I), A^1 and A^2 are both



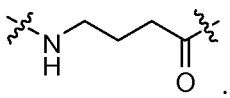
.

[0008] In some embodiments described above or below of a compound of Formula (I), Z is O.

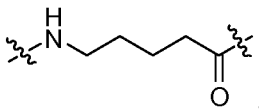
[0009] In some embodiments described above or below of a compound of Formula (I), k is 1.

[0010] In some embodiments described above or below of a compound of Formula (I), each m is independently 0, 1, 2, or 3.

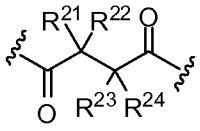
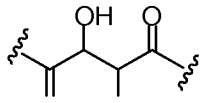
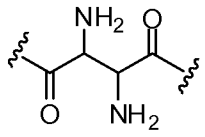
[0011] In some embodiments described above or below of a compound of Formula (I), L^1 and L^2 are the same. In some embodiments described above or below of a compound of Formula (I), L^1 and L^2 are both

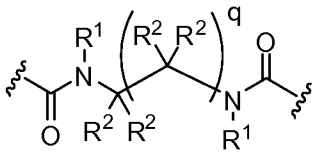
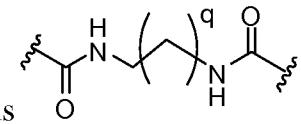
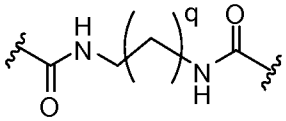
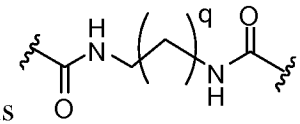


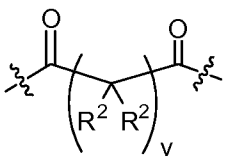
. In certain embodiments described above or below of a compound of Formula (I), L^1 and L^2 are both

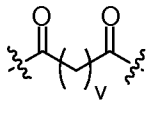
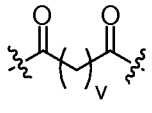


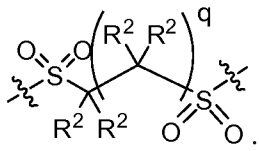
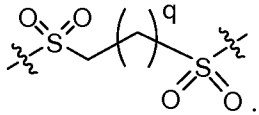
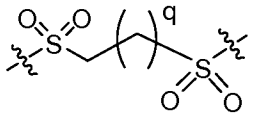
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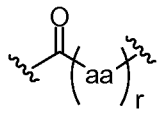
[0012] In some embodiments described above or below of a compound of Formula (I), X is . In some embodiments described above or below of a compound of Formula (I), R^{21} and R^{23} are the same and R^{22} and R^{24} are the same. In some embodiments described above or below of a compound of Formula (I), X is . In some embodiments described above or below of a compound of Formula (I), X is . In some embodiments described above or below of a compound of Formula (I), R^{21} and R^{22} are the same. In some embodiments described above or below of a compound of Formula (I), R^{23} and R^{24} are the same. In some embodiments described above or below of a compound of Formula (I), R^{21}, R^{22}, R^{23}, and R^{24} are the same.

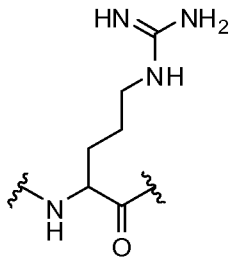
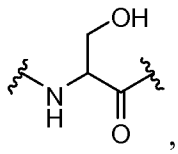
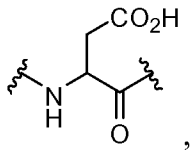
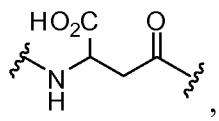
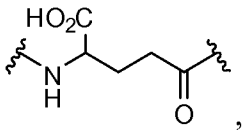
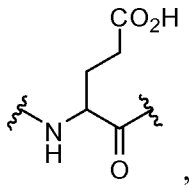
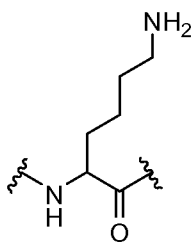
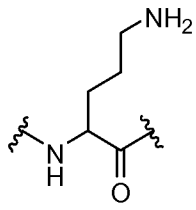
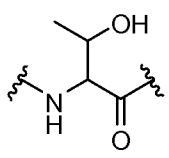
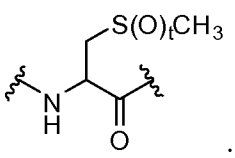
[0013] In some embodiments described above or below of a compound of Formula (I), X is . In certain embodiments described above or below of a compound of Formula (I), X is . In some embodiments described above or below of a compound of Formula (I), X is  and q is 3. In some embodiments described above or below of a compound of Formula (I), X is  and q is 5.

[0014] In some embodiments described above or below of a compound of Formula (I), X is . In certain embodiments described above or below of a compound of Formula

(I), X is . In certain embodiments described above or below of a compound of Formula (I), X is  and v is 4.

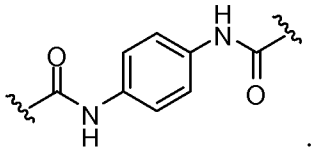
[0015] In some embodiments described above or below of a compound of Formula (I), X is . In certain embodiments described above or below of a compound of Formula (I), X is . In certain embodiments described above or below of a compound of Formula (I), X is  and q is 3.

[0016] In some embodiments described above or below of a compound of Formula (I), X is . In certain embodiments described above or below of a compound of Formula (I), aa is selected from:

, , , , , , , , , and .

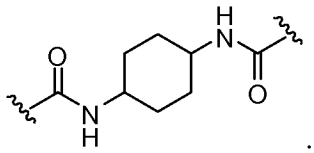
[0017] In some embodiments described above or below of a compound of Formula (I), r is 4, 5, or 6.

[0018] In some embodiments described above or below of a compound of Formula (I), X is



.

[0019] In some embodiments described above or below of a compound of Formula (I), X is

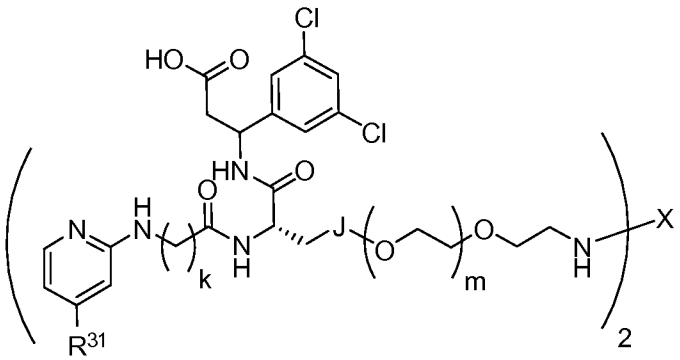


.

[0020] In some embodiments described above or below of a compound of Formula (I), X is alkylene. In some embodiments described above or below of a compound of Formula (I), X is -CH_2CH_2-. In some embodiments described above or below of a compound of Formula (I), X is -$CH_2CH_2CH_2$-.

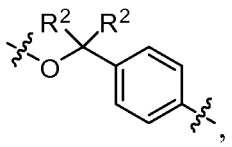
[0021] In some embodiments described above or below of a compound of Formula (I), X is -C(O)-.

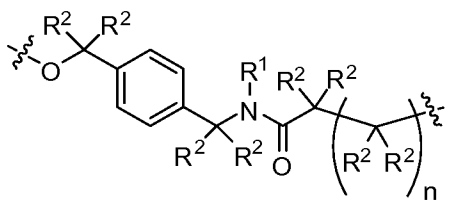
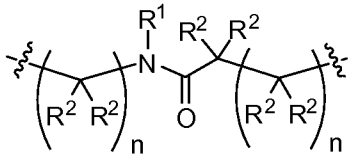
[0022] In another embodiment, provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, metabolite, deuteride, N-oxide, tautomer, stereoisomer, or isomer thereof, having the structure of Formula (Ia):

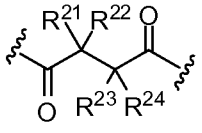
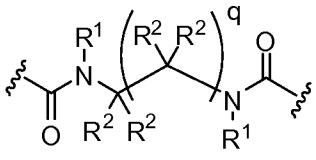
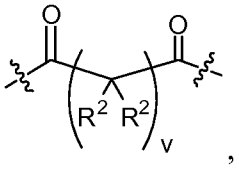
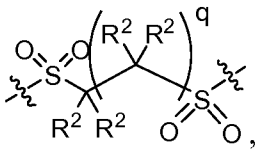
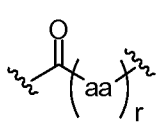
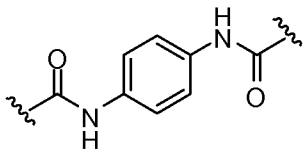
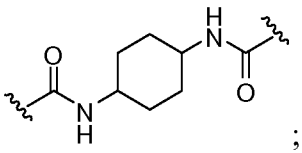


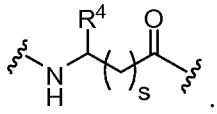
Formula (Ia);

wherein:

each J is independently selected from a bond, ,

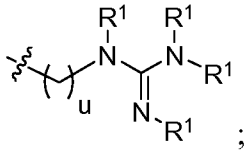
, and ;

X is alkylene, -C(O)-, , , , , , , or ;

aa is ;

each R^1 is independently selected from H and alkyl;

each R^2 is independently selected from H, halo, -CN, -SR^1, alkyl, cycloalkyl, haloalkyl, -OR^1, and -R^4;

each R^4 is independently selected from -CO_2R^1, -(alkylene)-(CO_2R^1), hydroxyalkyl, -(alkylene)($S(O)_t$)(alkyl), -(alkylene)(NR^5R^5), and ;

each R^5 is independently selected from H, alkyl, haloalkyl, arylalkyl, heteroarylalkyl, aryl, and heteroaryl;

R^{21}, R^{22}, R^{23}, and R^{24} are independently selected from H, halo, -CN, -SR^1, alkyl, cycloalkyl, haloalkyl, -NR^1R^1, and -OR^1;

each R^{31} is independently selected from H and alkyl;

each k is independently selected from 3, 4, and 5;

each m is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

each n is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

q is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

r is 3, 4, 5, 6, or 7;

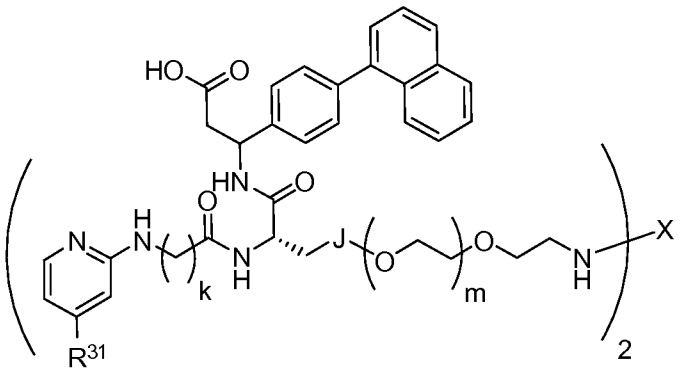
each s is independently selected from 0, 1, 2, 3, and 4;

each t is independently selected from 0, 1, and 2;

each u is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10; and

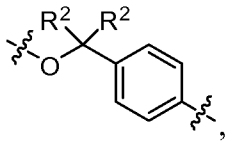
v is selected from 3, 4, 5, 6, 7, 8, 9, and 10.

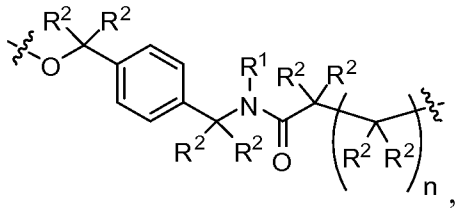
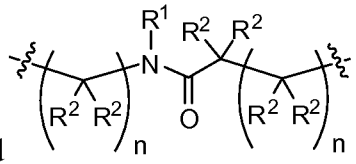
[0023] In another embodiment, provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, metabolite, deuteride, N-oxide, tautomer, stereoisomer, or isomer thereof, having the structure of Formula (Ib):

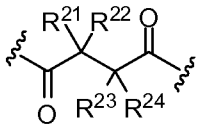
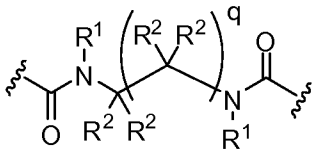
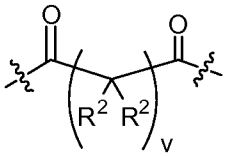


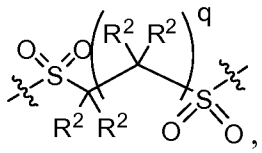
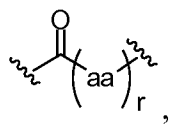
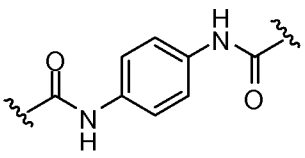
Formula (Ib);

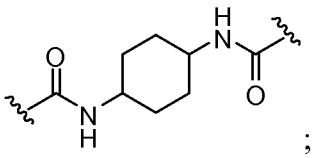
wherein:

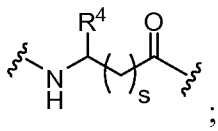
each J is independently selected from a bond, ,

 , and  ;

X is alkylene, -C(O)-,  ,  ,  ,

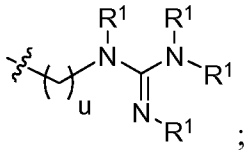
 ,  ,  , or

 ;

aa is  ;

each R^1 is independently selected from H and alkyl;

each R^2 is independently selected from H, halo, -CN, -SR^1, alkyl, cycloalkyl, haloalkyl, -OR^1, and -R^4;

each R^4 is independently selected from -CO_2R^1, -(alkylene)-(CO_2R^1), hydroxyalkyl, -(alkylene)($S(O)_t$)(alkyl), -(alkylene)(NR^5R^5), and ;

each R^5 is independently selected from H, alkyl, haloalkyl, arylalkyl, heteroarylalkyl, aryl, and heteroaryl;

R^{21}, R^{22}, R^{23}, and R^{24} are independently selected from H, halo, -CN, -SR^1, alkyl, cycloalkyl, haloalkyl, -NR^1R^1, and -OR^1;

each R^{31} is independently selected from H and alkyl;

each k is independently selected from 3, 4, and 5;

each m is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

each n is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

q is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

r is 3, 4, 5, 6, or 7;

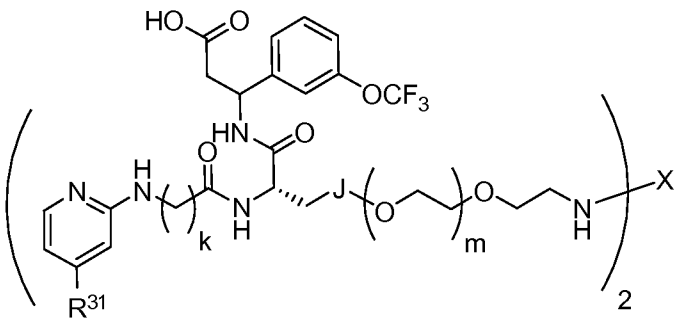
each s is independently selected from 0, 1, 2, 3, and 4;

each t is independently selected from 0, 1, and 2;

each u is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10; and

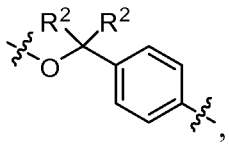
v is selected from 3, 4, 5, 6, 7, 8, 9, and 10.

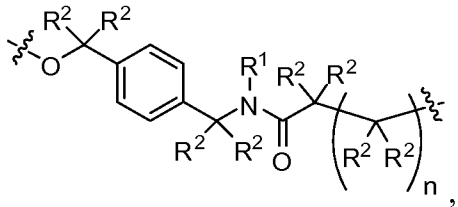
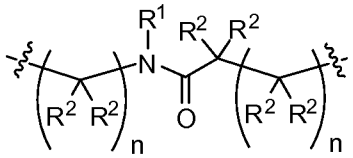
[0024] In another embodiment, provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, metabolite, deuteride, N-oxide, tautomer, stereoisomer, or isomer thereof, having the structure of Formula (Ic):

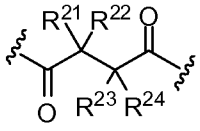
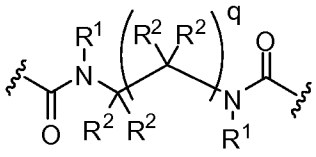
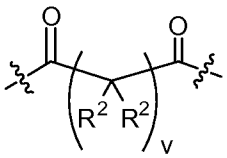


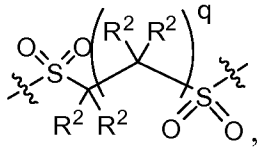
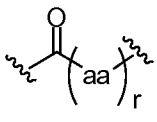
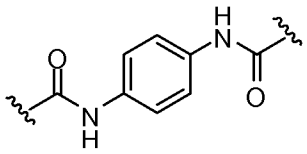
Formula (Ic);

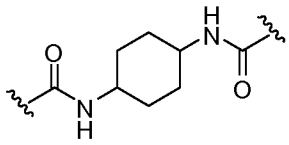
wherein:

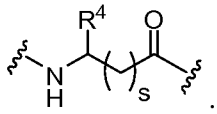
each J is independently selected from a bond, ,

, and ;

X is alkylene, -C(O)-, , , ,

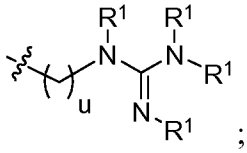
, , , or

;

aa is ;

each R^1 is independently selected from H and alkyl;

each R^2 is independently selected from H, halo, -CN, -SR^1, alkyl, cycloalkyl, haloalkyl, -OR^1, and -R^4;

each R^4 is independently selected from -CO_2R^1, -(alkylene)-(CO_2R^1), hydroxyalkyl, -(alkylene)($S(O)_t$)(alkyl), -(alkylene)(NR^5R^5), and ;

each R^5 is independently selected from H, alkyl, haloalkyl, arylalkyl, heteroarylalkyl, aryl, and heteroaryl;

R^{21}, R^{22}, R^{23}, and R^{24} are independently selected from H, halo, -CN, -SR^1, alkyl, cycloalkyl, haloalkyl, -NR^1R^1, and -OR^1;

each R^{31} is independently selected from H and alkyl;

each k is independently selected from 3, 4, and 5;

each m is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

each n is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

q is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

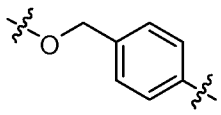
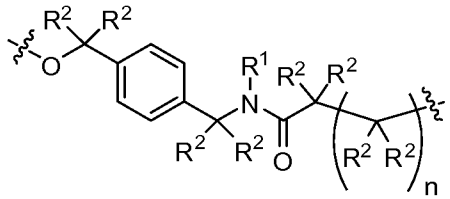
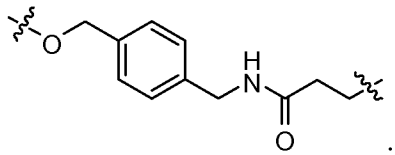
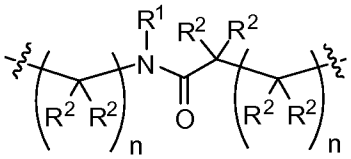
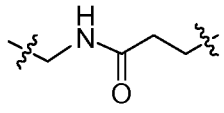
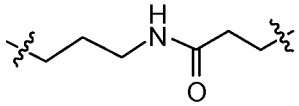
r is 3, 4, 5, 6, or 7;

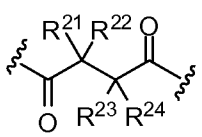
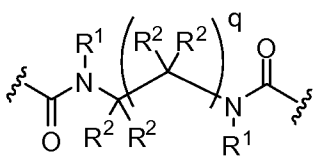
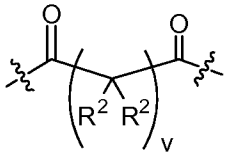
each s is independently selected from 0, 1, 2, 3, and 4;

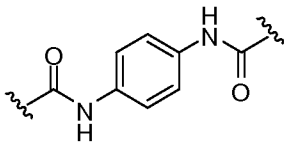
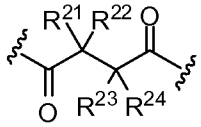
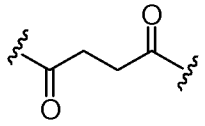
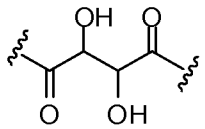
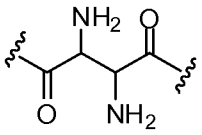
each t is independently selected from 0, 1, and 2;

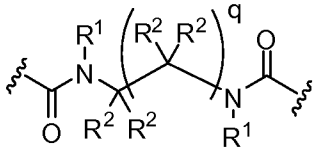
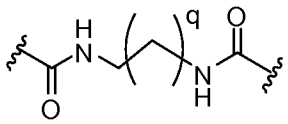
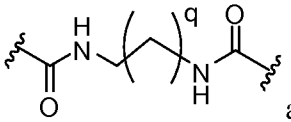
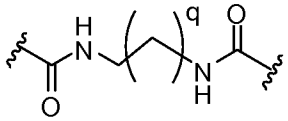
each u is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10; and

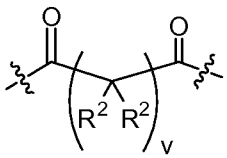
v is selected from 3, 4, 5, 6, 7, 8, 9, and 10.

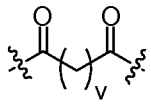
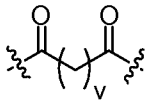
[0025] In some embodiments described above or below of a compound of Formula (Ia), (Ib), or (Ic), each J is . In some embodiments described above or below of a compound of Formula (Ia), (Ib), or (Ic), each J is . In some embodiments described above or below of a compound of Formula (Ia), (Ib), or (Ic), each J is . In some embodiments described above or below of a compound of Formula (Ia), (Ib), or (Ic), J^1 and J^2 are both . In some embodiments described above or below of a compound of Formula (Ia), (Ib), or (Ic), each J is . In some embodiments described above or below of a compound of Formula (Ia), (Ib), or (Ic), each J is . In some embodiments described above or below of a compound of Formula (Ia), (Ib), or (Ic), each J is a bond.

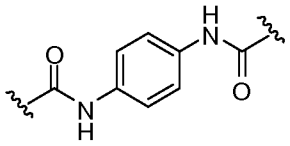
[0026] In some embodiments described above or below of a compound of Formula (Ia), (Ib), or (Ic), X is -C(O)-, , , , or


. In some embodiments described above or below of a compound of Formula (Ia), (Ib), or (Ic), X is 
. In some embodiments described above or below of a compound of Formula (Ia), (Ib), or (Ic), X is 
. In some embodiments described above or below of a compound of Formula (Ia), (Ib), or (Ic), X is 
. In some embodiments described above or below of a compound of Formula (Ia), (Ib), or (Ic), X is 
.

[0027] In some embodiments described above or below of a compound of Formula (Ia), (Ib), or (Ic), X is 
. In certain embodiments described above or below of a compound of Formula (Ia), (Ib), or (Ic), X is 
. In some embodiments described above or below of a compound of Formula (Ia), (Ib), or (Ic), X is 
and q is 3. In some embodiments described above or below of a compound of Formula (Ia), (Ib), or (Ic), X is 
and q is 5.

[0028] In some embodiments described above or below of a compound of Formula (Ia), (Ib), or (Ic), X is 
. In certain embodiments described above or below of a compound of

Formula (Ia), (Ib), or (Ic), X is . In certain embodiments described above or below of a compound of Formula (Ia), (Ib), or (Ic), X is  and v is 4.

[0029] In some embodiments described above or below of a compound of Formula (Ia), (Ib), or (Ic), X is .

[0030] In some embodiments described above or below of a compound of Formula (Ia), (Ib), or (Ic), each m is independently 0, 1, 2, or 3. In some embodiments described above or below of a compound of Formula (Ia), (Ib), or (Ic), each m is 1. In some embodiments described above or below of a compound of Formula (Ia), (Ib), or (Ic), each m is 2. In some embodiments described above or below of a compound of Formula (Ia), (Ib), or (Ic), each m is 3.

[0031] In some embodiments described above or below of a compound of Formula (Ia), (Ib), or (Ic), each R^{31} is H. In some embodiments described above or below of a compound of Formula (Ia), (Ib), or (Ic), each R^{31} is alkyl. In some embodiments described above or below of a compound of Formula (Ia), (Ib), or (Ic), each R^{31} is methyl. In some embodiments described above or below of a compound of Formula (Ia), (Ib), or (Ic), each R^{31} is ethyl.

[0032] In some embodiments described above or below of a compound of Formula (Ia), (Ib), or (Ic), each k is 3. In some embodiments described above or below of a compound of Formula (Ia), (Ib), or (Ic), each k is 4.

[0033] Also provided herein is a pharmaceutical composition comprising a compound of Formula (I), (Ia), (Ib), or (Ic) as described above and below, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, metabolite, N-oxide, tautomer, stereoisomer, or isomer thereof, and a pharmaceutically acceptable excipient.

[0034] Further provided herein is a method of treating a lung disease, the method comprising administering a composition comprising a compound of Formula (I), (Ia), (Ib), or (Ic) as described above and below.

[0035] Further provided herein is a method to treat idiopathic pulmonary fibrosis in a mammal, the method comprising administering to the mammal a composition comprising a compound of Formula (I), (Ia), (Ib), or (Ic) as described above and below.

[0036] Further provided herein is the use of a compound of Formula (I), (Ia), (Ib), or (Ic), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, in the manufacture of a medicament for treating a lung disease. Further provided herein is the use of a compound of

Formula (I), (Ia), (Ib), or (Ic), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, in the manufacture of a medicament for treating idiopathic pulmonary fibrosis.

INCORPORATION BY REFERENCE

[0037] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

DETAILED DESCRIPTION OF THE INVENTION

[0038] Idiopathic pulmonary fibrosis (IPF) represents the most common cause of death from progressive lung disease.

[0039] Transforming growth factor (TGF)-beta has a central role in driving many of the pathological processes that characterize pulmonary fibrosis. In animal models, TGF-β, a pleitropic cytokine, is increased prior to collagen synthesis. Furthermore, in lungs of individuals with pulmonary fibrosis, immunohistochemical staining reveals increased TGF-β, most notably in areas of regeneration and remodeling. TGF-β exists in 3 isoforms in mammals, and a growing body of evidence suggests that one of these, TGF-β1, is a key pro-fibrotic agent. Its activity is characterized by the promotion of extracellular matrix production, fibroblast to myofibroblast differentiation, and inhibition of autophagy in fibroblasts. These insights have made TGF-β1 an important ongoing therapeutic target in IPF.

[0040] The integrin alpha(v)beta6 is a major TGF-beta activator in the lung. Alpha(v)beta6 is overexpressed in human lung fibrosis within pneumocytes lining the alveolar ducts and alveoli. Therefore, inhibition of alpha(v)beta6-mediated TGF-beta activation is a plausible strategy to treat lung fibrosis. Partial inhibition of αvβ6 integrin, a key activator or TGF-β1, has been shown to prevent bleomycin-induced pulmonary fibrosis without exacerbating inflammation in mice.

[0041] Disclosed herein are dimeric compounds useful for the treatment of lung diseases including idiopathic pulmonary fibrosis (IPF). The compounds disclosed herein are integrin alpha(v)beta6 blockers that demonstrate improved potency and/or PK properties. Also disclosed herein are compositions comprising such compounds, and methods of their use for the inhibition of integrin alpha(v)beta6 and the treatment of IPF.

Definitions

[0042] In the following description, certain specific details are set forth in order to provide a thorough understanding of various embodiments. However, one skilled in the art will understand that the invention may be practiced without these details. In other instances, well-known structures have not been shown or described in detail to avoid unnecessarily

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

[0043] Reference throughout this specification to "one embodiment" or "an embodiment" means that a particular feature, structure or characteristic described in connection with the embodiment is included in at least one embodiment. Thus, the appearances of the phrases "in one embodiment" or "in an embodiment" in various places throughout this specification are not necessarily all referring to the same embodiment. Furthermore, the particular features, structures, or characteristics may be combined in any suitable manner in one or more embodiments. Also, as used in this specification and the appended claims, the singular forms "a", "an", and "the" include plural referents unless the content clearly dictates otherwise. It should also be noted that the term "or" is generally employed in its sense including "and/or" unless the content clearly dictates otherwise.

[0044] The terms below, as used herein, have the following meanings, unless indicated otherwise:

[0045] "Amino" refers to the $-NH_2$ radical.

[0046] "Cyano" or "nitrile" refers to the -CN radical.

[0047] "Hydroxy" or "hydroxyl" refers to the -OH radical.

[0048] "Nitro" refers to the $-NO_2$ radical.

[0049] "Oxo" refers to the =O substituent.

[0050] "Oxime" refers to the =N-OH substituent.

[0051] "Thioxo" refers to the =S substituent.

[0052] "Alkyl" refers to a straight or branched hydrocarbon chain radical, has from one to thirty carbon atoms, and is attached to the rest of the molecule by a single bond. Alkyls comprising any number of carbon atoms from 1 to 30 are included. An alkyl comprising up to 30 carbon atoms is referred to as a C_1-C_{30} alkyl, likewise, for example, an alkyl comprising up to 12 carbon atoms is a C_1-C_{12} alkyl. Alkyls (and other moieties defined herein) comprising other numbers of carbon atoms are represented similarly. Alkyl groups include, but are not limited to, C_1-C_{30} alkyl, C_1-C_{20} alkyl, C_1-C_{15} alkyl, C_1-C_{10} alkyl, C_1-C_8 alkyl, C_1-C_6 alkyl, C_1-C_4 alkyl, C_1-C_3 alkyl, C_1-C_2 alkyl, C_2-C_8 alkyl, C_3-C_8 alkyl and C_4-C_8 alkyl. Representative alkyl groups include, but are not limited to, methyl, ethyl, *n*-propyl, 1-methylethyl (*iso*-propyl), *n*-butyl, *i*-butyl, *s*-butyl, *n*-pentyl, 1,1-dimethylethyl (*t*-butyl), 3-methylhexyl, 2-methylhexyl, vinyl, allyl,

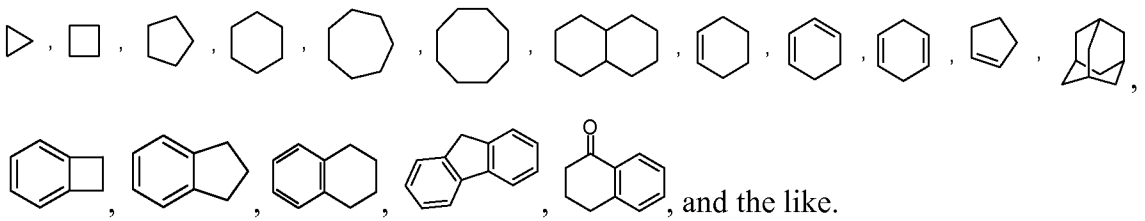
propynyl, and the like. Alkyl comprising unsaturations include alkenyl and alkynyl groups. Unless stated otherwise specifically in the specification, an alkyl group may be optionally substituted as described below.

[0053] "Alkylene" or "alkylene chain" refers to a straight or branched divalent hydrocarbon chain, as described for alkyl above. Unless stated otherwise specifically in the specification, an alkylene group may be optionally substituted as described below.

[0054] "Alkoxy" refers to a radical of the formula $-OR_a$ where R_a is an alkyl radical as defined. Unless stated otherwise specifically in the specification, an alkoxy group may be optionally substituted as described below.

[0055] "Aryl" refers to a radical derived from a hydrocarbon ring system comprising hydrogen, 6 to 30 carbon atoms and at least one aromatic ring. The aryl radical may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused or bridged ring systems. Aryl radicals include, but are not limited to, aryl radicals derived from the hydrocarbon ring systems of aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, fluoranthene, fluorene, *as*-indacene, *s*-indacene, indane, indene, naphthalene, phenalene, phenanthrene, pleiadene, pyrene, and triphenylene. Unless stated otherwise specifically in the specification, the term "aryl" or the prefix "ar-" (such as in "aralkyl") is meant to include aryl radicals that are optionally substituted.

[0056] "Cycloalkyl" or "carbocycle" refers to a stable, non-aromatic, monocyclic or polycyclic carbocyclic ring, which may include fused or bridged ring systems, which is saturated or unsaturated. Representative cycloalkyls or carbocycles include, but are not limited to, cycloalkyls having from three to fifteen carbon atoms, from three to ten carbon atoms, from three to eight carbon atoms, from three to six carbon atoms, from three to five carbon atoms, or three to four carbon atoms. Monocyclic cycloalkyls or carbocycles include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic cycloalkyls or carbocycles include, for example, adamantyl, norbornyl, decalinyl, bicyclo[3.3.0]octane, bicyclo[4.3.0]nonane, cis-decalin, trans-decalin, bicyclo[2.1.1]hexane, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, bicyclo[3.2.2]nonane, and bicyclo[3.3.2]decane, and 7,7-dimethyl-bicyclo[2.2.1]heptanyl. Unless otherwise stated specifically in the specification, a cycloalkyl or carbocycle group may be optionally substituted. Illustrative examples of cycloalkyl groups include, but are not limited to, the following moieties:



and the like.

[0057] "Fused" refers to any ring structure described herein which is fused to an existing ring structure. When the fused ring is a heterocyclyl ring or a heteroaryl ring, any carbon atom on the existing ring structure which becomes part of the fused heterocyclyl ring or the fused heteroaryl ring may be replaced with a nitrogen atom.

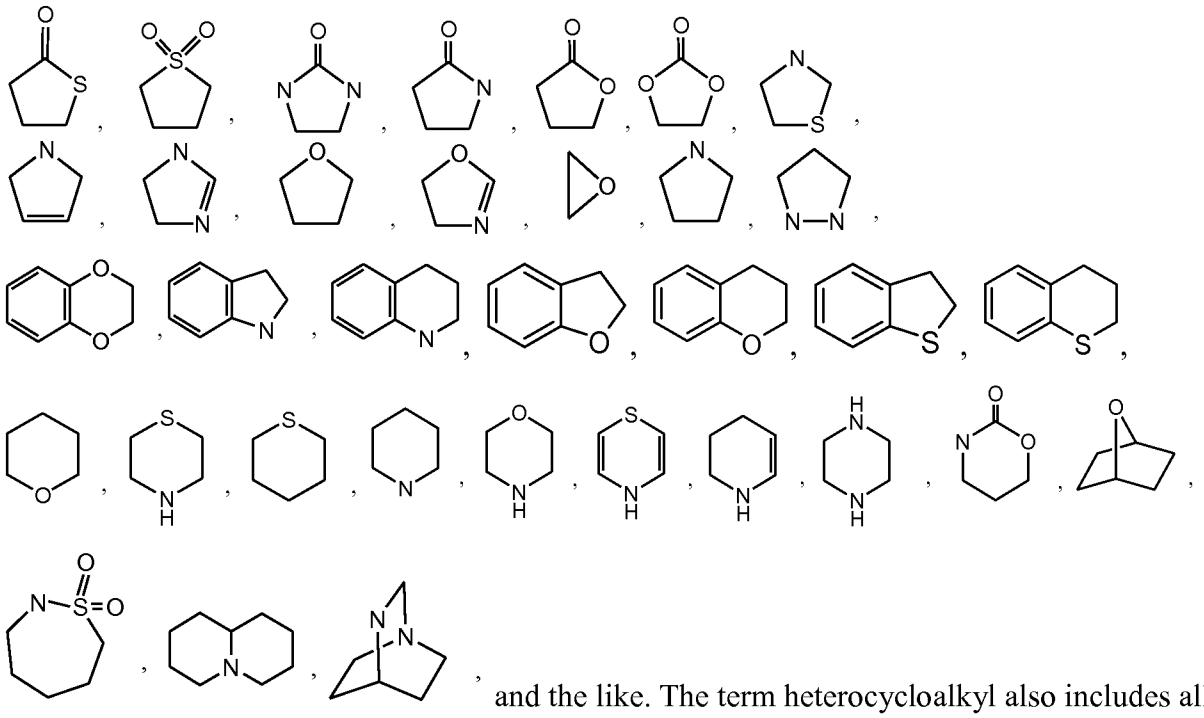
[0058] "Halo" or "halogen" refers to bromo, chloro, fluoro or iodo.

[0059] "Haloalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, *e.g.*, trifluoromethyl, difluoromethyl, fluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,2-difluoroethyl, 3-bromo-2-fluoropropyl, 1,2-dibromoethyl, and the like. Unless stated otherwise specifically in the specification, a haloalkyl group may be optionally substituted.

[0060] "Haloalkoxy" similarly refers to a radical of the formula $-OR_a$ where R_a is a haloalkyl radical as defined. Unless stated otherwise specifically in the specification, a haloalkoxy group may be optionally substituted as described below.

[0061] "Heterocycloalkyl" or "heterocyclyl" or "heterocyclic ring" or "heterocycle" refers to a stable 3- to 24-membered non-aromatic ring radical comprising 2 to 23 carbon atoms and from one to 8 heteroatoms selected from the group consisting of nitrogen, oxygen, phosphorous and sulfur. Unless stated otherwise specifically in the specification, the heterocyclyl radical may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heterocyclyl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized; and the heterocyclyl radical may be partially or fully saturated. Examples of such heterocyclyl radicals include, but are not limited to, azetidinyl, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, 1,1-dioxo-thiomorpholinyl, 12-crown-4, 15-crown-5, 18-crown-6, 21-crown-7, aza-18-crown-6, diaza-18-crown-6, aza-21-crown-7, and diaza-21-crown-7. Unless stated otherwise specifically in the specification, a heterocyclyl group may be optionally

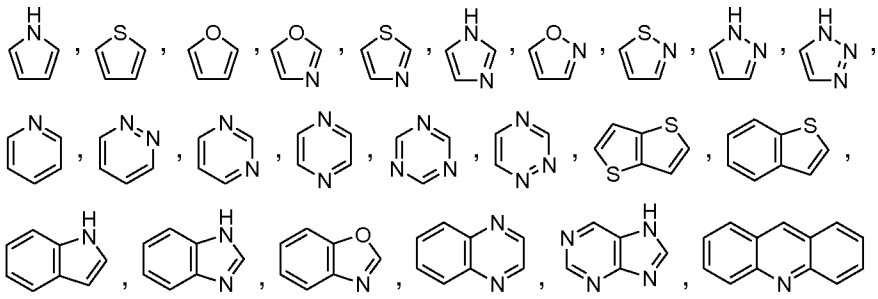
substituted. Illustrative examples of heterocycloalkyl groups, also referred to as non-aromatic heterocycles, include:



and the like. The term heterocycloalkyl also includes all ring forms of the carbohydrates, including but not limited to the monosaccharides, the disaccharides and the oligosaccharides. Unless otherwise noted, heterocycloalkyls have from 2 to 10 carbons in the ring. It is understood that when referring to the number of carbon atoms in a heterocycloalkyl, the number of carbon atoms in the heterocycloalkyl is not the same as the total number of atoms (including the heteroatoms) that make up the heterocycloalkyl (i.e. skeletal atoms of the heterocycloalkyl ring). Unless stated otherwise specifically in the specification, a heterocycloalkyl group may be optionally substituted.

[0062] The term "heteroaryl" as used herein, alone or in combination, refers to optionally substituted aromatic monoradicals containing from about five to about twenty skeletal ring atoms, where one or more of the ring atoms is a heteroatom independently selected from among oxygen, nitrogen, sulfur, phosphorous, silicon, selenium and tin but not limited to these atoms and with the proviso that the ring of said group does not contain two adjacent O or S atoms. In embodiments in which two or more heteroatoms are present in the ring, the two or more heteroatoms can be the same as each another, or some or all of the two or more heteroatoms can each be different from the others. The term heteroaryl includes optionally substituted fused and non-fused heteroaryl radicals having at least one heteroatom. The term heteroaryl also includes fused and non-fused heteroaryls having from five to about twelve skeletal ring atoms, as well as those having from five to about ten skeletal ring atoms. Bonding to a heteroaryl group can be via a carbon atom or a heteroatom. Thus, as a non-limiting example, an imidiazole group may be

attached to a parent molecule via any of its carbon atoms (imidazol-2-yl, imidazol-4-yl or imidazol-5-yl), or its nitrogen atoms (imidazol-1-yl or imidazol-3-yl). Likewise, a heteroaryl group may be further substituted via any or all of its carbon atoms, and/or any or all of its heteroatoms. A fused heteroaryl radical may contain from two to four fused rings where the ring of attachment is a heteroaromatic ring and the other individual rings may be alicyclic, heterocyclic, aromatic, heteroaromatic or any combination thereof. A non-limiting example of a single ring heteroaryl group includes pyridyl; fused ring heteroaryl groups include benzimidazolyl, quinolinyl, acridinyl; and a non-fused bi-heteroaryl group includes bipyridinyl. Further examples of heteroaryls include, without limitation, furanyl, thienyl, oxazolyl, acridinyl, azepinyl, phenazinyl, benzimidazolyl, benzindolyl,benzofuranyl, benzofuranonyl,benzoxazolyl, benzothiazolyl, benzothiadiazolyl, benzothiophenyl, benzoxadiazolyl, benzodioxolyl, benzo[*b*][1,4]dioxepinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzotriazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzothienyl (benzothiophenyl), benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, dibenzofuranyl, dibenzothiophenyl, furanonyl, imidazolyl, indolyl, isoxazolyl, isoquinolinyl, indolizinyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, indolizinyl, isothiazolyl, isoindolyloxadiazolyl, indazolyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxiranyl, 1-oxidopyridinyl, 1-oxidopyrimidinyl, 1-oxidopyrazinyl, 1-oxidopyridazinyl, 1-phenyl-1*H*-pyrrolyl, phenothiazinyl, phenoxazinyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrrolyl, pyrazinyl, pyrazolyl, purinyl, phthalazinyl, pteridinyl, quinolinyl, quinazolinyl, quinoxalinyl, quinuclidinyl,triazolyl, tetrazolyl, thiazolyl, triazinyl, thiadiazolyl, tetrahydroquinolinyl, thiazolyl, and thiophenyl and the like, and their oxides, such as for example pyridyl-N-oxide. Illustrative examples of heteroaryl groups include the following moieties:

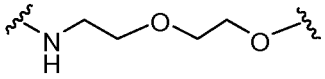
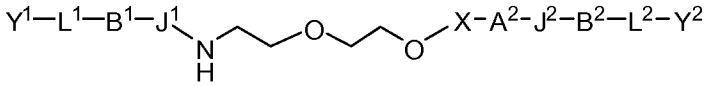
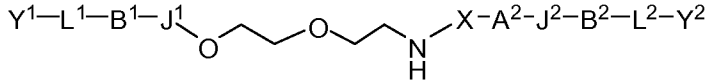


and the like.

[0063] All the above groups may be either substituted or unsubstituted. The term "substituted" as used herein means any of the above groups (*e.g.* alkyl, alkylene, alkoxy, aryl, cycloalkyl, haloalkyl, heterocyclyl and/or heteroaryl) may be further functionalized wherein at least one hydrogen atom is replaced by a bond to a non-hydrogen atom substituent. Unless stated specifically in the specification, a substituted group may include one or more substituents selected from: oxo, amino, $-CO_2H$, nitrile, nitro, hydroxyl, thiooxy, alkyl, alkylene, alkoxy,

aryl, cycloalkyl, heterocyclyl, heteroaryl, dialkylamines, arylamines, alkylarylamines, diarylamines, trialkylammonium ($-N^+R_3$), N-oxides, imides, and enamines; a silicon atom in groups such as trialkylsilyl groups, dialkylarylsilyl groups, alkyldiarylsilyl groups, triarylsilyl groups, perfluoroalkyl or perfluoroalkoxy, for example, trifluoromethyl or trifluoromethoxy. "Substituted" also means any of the above groups in which one or more hydrogen atoms are replaced by a higher-order bond (*e.g.*, a double- or triple-bond) to a heteroatom such as oxygen in oxo, carbonyl, carboxyl, and ester groups; and nitrogen in groups such as imines, oximes, hydrazones, and nitriles. For example, "substituted" includes any of the above groups in which one or more hydrogen atoms are replaced
with $-NH_2$, $-NR_gC(=O)NR_gR_h$, $-NR_gC(=O)OR_h$, $-NR_gSO_2R_h$, $-OC(=O)NR_gR_h$, $-OR_g$, $-SR_g$, $-SOR_g$, $-SO_2R_g$, $-OSO_2R_g$, $-SO_2OR_g$, $=NSO_2R_g$, and $-SO_2NR_gR_h$. In the foregoing, R_g and R_h are the same or different and independently hydrogen, alkyl, alkoxy, alkylamino, thioalkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocyclyl, *N*-heterocyclyl, heterocyclylalkyl, heteroaryl, *N*-heteroaryl and/or heteroarylalkyl. In addition, each of the foregoing substituents may also be optionally substituted with one or more of the above substituents. Furthermore, any of the above groups may be substituted to include one or more internal oxygen, sulfur, or nitrogen atoms. For example, an alkyl group may be substituted with one or more internal oxygen atoms to form an ether or polyether group. Similarily, an alkyl group may be substituted with one or more internal sulfur atoms to form a thioether, disulfide, etc.

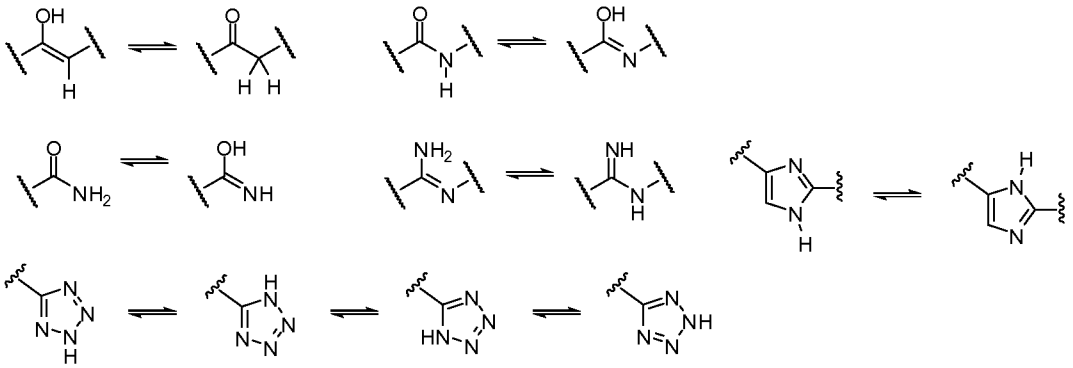
[0064] The term "optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, "optionally substituted alkyl" means either "alkyl" or "substituted alkyl" as defined above. Further, an optionally substituted group may be un-substituted (e.g., $-CH_2CH_3$), fully substituted (e.g., $-CF_2CF_3$), mono-substituted (e.g., $-CH_2CH_2F$) or substituted at a level anywhere in-between fully substituted and mono-substituted (e.g., $-CH_2CHF_2$, $-CH_2CF_3$, $-CF_2CH_3$, $-CFHCHF_2$, etc). It will be understood by those skilled in the art with respect to any group containing one or more substituents that such groups are not intended to introduce any substitution or substitution patterns (e.g., substituted alkyl includes optionally substituted cycloalkyl groups, which in turn are defined as including optionally substituted alkyl groups, potentially ad infinitum) that are sterically impractical and/or synthetically non-feasible. Thus, any substituents described should generally be understood as having a maximum molecular weight of about 1,000 daltons, and more typically, up to about 500 daltons.

[0065] The label  in a compound fragment denotes the attachment point to the remainder of the compound. Compound fragments containg two can be attached to the remainder of the compound in either orientation. For example, when A^1 is , the compound of Formula (I) can be  or .

[0066] An "effective amount" or "therapeutically effective amount" refers to an amount of a compound administered to a mammalian subject, either as a single dose or as part of a series of doses, which is effective to produce a desired therapeutic effect.

[0067] "Treatment" of an individual (e.g. a mammal, such as a human) or a cell is any type of intervention used in an attempt to alter the natural course of the individual or cell. In some embodiments, treatment includes administration of a pharmaceutical composition, subsequent to the initiation of a pathologic event or contact with an etiologic agent and includes stabilization of the condition (e.g., condition does not worsen) or alleviation of the condition. In other embodiments, treatment also includes prophylactic treatment (e.g., administration of a composition described herein when an individual is suspected to be suffering from a bacterial infection).

[0068] A "tautomer" refers to a proton shift from one atom of a molecule to another atom of the same molecule. The compounds presented herein may exist as tautomers. Tautomers are compounds that are interconvertible by migration of a hydrogen atom, accompanied by a switch of a single bond and adjacent double bond. In bonding arrangements where tautomerization is possible, a chemical equilibrium of the tautomers will exist. All tautomeric forms of the compounds disclosed herein are contemplated. The exact ratio of the tautomers depends on several factors, including temperature, solvent, and pH. Some examples of tautomeric interconversions include:



[0069] A "metabolite" of a compound disclosed herein is a derivative of that compound that is formed when the compound is metabolized. The term "active metabolite" refers to a biologically active derivative of a compound that is formed when the compound is metabolized. The term "metabolized," as used herein, refers to the sum of the processes (including, but not limited to, hydrolysis reactions and reactions catalyzed by enzymes, such as, oxidation reactions) by which a particular substance is changed by an organism. Thus, enzymes may produce specific structural alterations to a compound. For example, cytochrome P450 catalyzes a variety of oxidative and reductive reactions while uridine diphosphate glucuronyl transferases catalyze the transfer of an activated glucuronic-acid molecule to aromatic alcohols, aliphatic alcohols, carboxylic acids, amines and free sulfhydryl groups. Further information on metabolism may be obtained from The Pharmacological Basis of Therapeutics, 9th Edition, McGraw-Hill (1996). Metabolites of the compounds disclosed herein can be identified either by administration of compounds to a host and analysis of tissue samples from the host, or by incubation of compounds with hepatic cells *in vitro* and analysis of the resulting compounds. Both methods are well known in the art. In some embodiments, metabolites of a compound are formed by oxidative processes and correspond to the corresponding hydroxy-containing compound. In some embodiments, a compound is metabolized to pharmacologically active metabolites.

Compounds

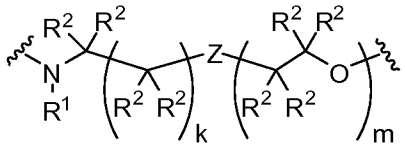
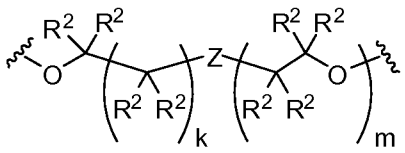
[0070] Described herein are compounds for the treatment of a lung disease. Further described herein are compounds for the treatment of idiopathic pulmonary fibrosis.

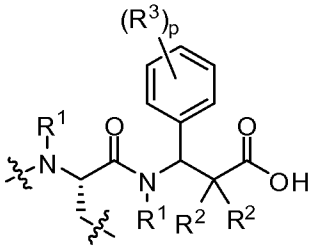
[0071] In one aspect, provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, metabolite, deuteride, N-oxide, tautomer, stereoisomer, or isomer thereof, having the structure:

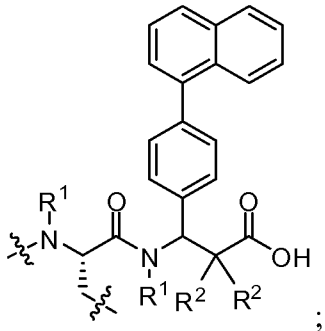
$$Y^1-L^1-B^1-J^1-A^1-X-A^2-J^2-B^2-L^2-Y^2$$

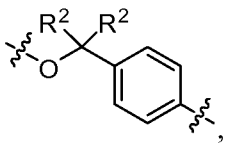
Formula (I);

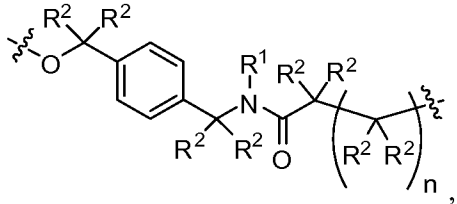
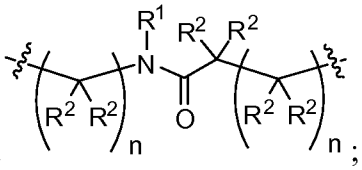
wherein:

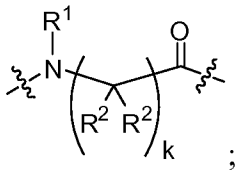
A^1 and A^2 are independently selected from:  and ;

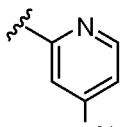
B^1 and B^2 are independently selected from:  and

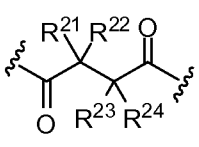
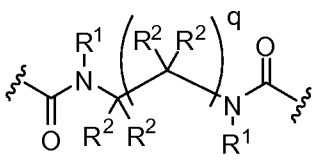
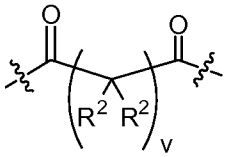
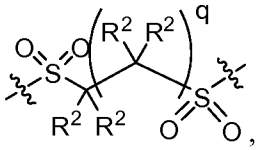
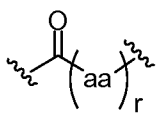
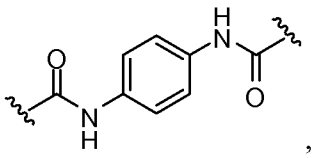
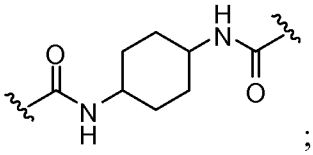
;

J^1 and J^2 are independently selected from a bond, ,

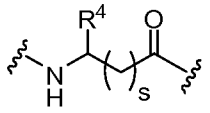
, and ;

L^1 and L^2 are independently selected from: ;

Y^1 and Y^2 are independently selected from: ;

X is alkylene, -C(O)-  ,  ,  ,  ,  ,  , or  ;

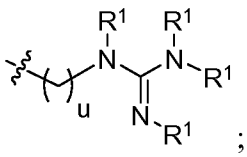
Z is O or CR^2R^2;

aa is  ;

each R^1 is independently selected from H, alkyl, haloalkyl, arylalkyl, and heteroarylalkyl;

each R^2 is independently selected from H, halo, -CN, $-SR^1$, alkyl, cycloalkyl, haloalkyl, $-OR^1$, and $-R^4$;

each R^3 is independently selected from halo, alkyl, -CN, haloalkyl, $-OR^1$, and $-NR^1R^1$;

each R^4 is independently selected from $-CO_2R^1$, -(alkylene)-(CO_2R^1), hydroxyalkyl, -(alkylene)($S(O)_t$)(alkyl), -(alkylene)(NR^5R^5), and  ;

each R^5 is independently selected from H, alkyl, haloalkyl, arylalkyl, heteroarylalkyl, aryl, and heteroaryl;

R^{21}, R^{22}, R^{23}, and R^{24} are independently selected from H, halo, -CN, $-SR^1$, alkyl, cycloalkyl, haloalkyl, $-NR^1R^1$, and $-OR^1$;

each R^{31} is independently selected from H and alkyl;

each k is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

each m is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

each n is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

each p is independently selected from 0, 1, 2, 3, and 4;

q is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

r is 3, 4, 5, 6, or 7;

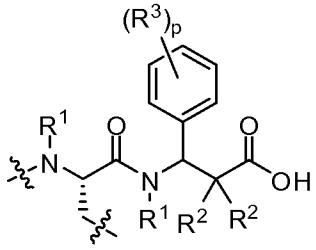
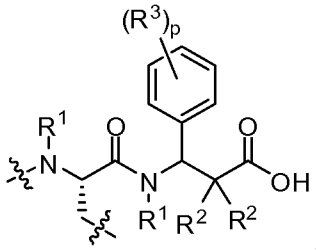
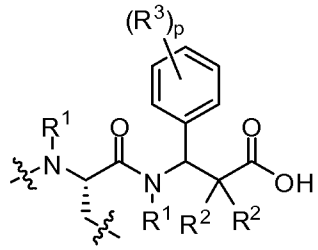
each s is independently selected from 0, 1, 2, 3, and 4;

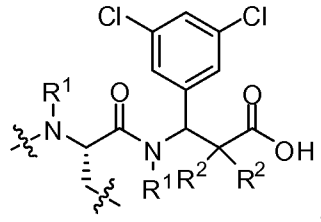
each t is independently selected from 0, 1, and 2;

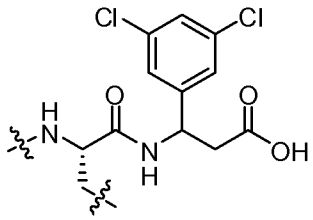
each u is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10; and

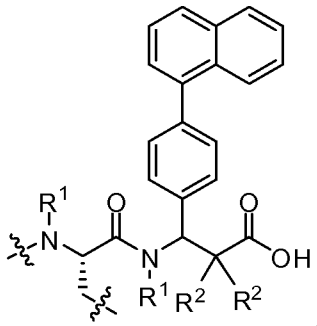
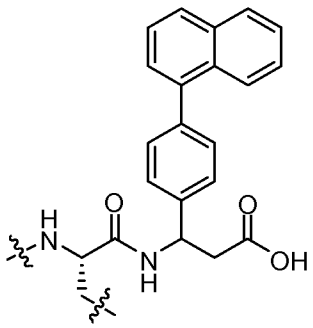
v is selected from 3, 4, 5, 6, 7, 8, 9, and 10.

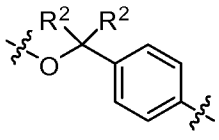
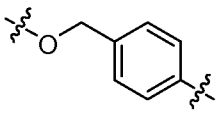
[0072] In some embodiments described above or below of a compound of Formula (I), Y^1 and Y^2 are the same. In some embodiments described above or below of a compound of Formula (I), Y^1 and Y^2 are the same and R^{31} is H. In some embodiments described above or below of a compound of Formula (I), Y^1 and Y^2 are the same and R^{31} is alkyl. In some embodiments described above or below of a compound of Formula (I), Y^1 and Y^2 are the same and R^{31} is -CH_3. In some embodiments described above or below of a compound of Formula (I), Y^1 and Y^2 are the same and R^{31} is -CH_2CH_3.

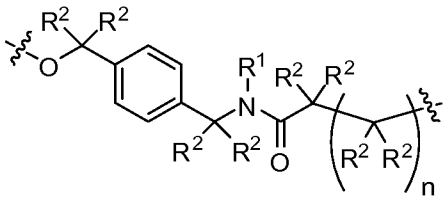
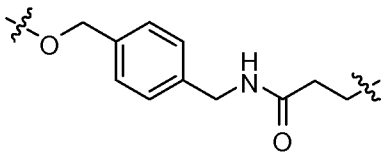
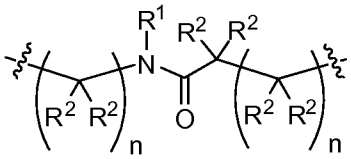
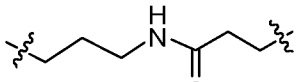
[0073] In some embodiments described above or below of a compound of Formula (I), B^1 and B^2 are the same. In some embodiments described above or below of a compound of Formula (I), B^1 and B^2 are both . In certain embodiments described above or below of a compound of Formula (I), p is 0. In certain embodiments described above or below of a compound of Formula (I), p is 1. In certain embodiments described above or below of a compound of Formula (I), p is 2. In some embodiments described above or below of a compound of Formula (I), B^1 and B^2 are both ; p is 2 and each R^3 is halo. In some embodiments described above or below of a compound of Formula (I), B^1 and B^2 are both ; p is 2 and each R^3 is chloro. In some embodiments described

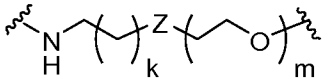
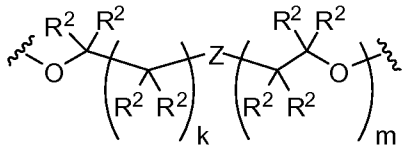
above or below of a compound of Formula (I), B^1 and B^2 are both . In some embodiments described above or below of a compound of Formula (I), B^1 and B^2 are both

.

[0074] In some embodiments described above or below of a compound of Formula (I), B^1 and B^2 are both . In some embodiments described above or below of a compound of Formula (I), B^1 and B^2 are both .

[0075] In some embodiments described above or below of a compound of Formula (I), J^1 and J^2 are the same. In some embodiments described above or below of a compound of Formula (I), J^1 and J^2 are both . In some embodiments described above or below of a compound of Formula (I), J^1 and J^2 are both . In some embodiments described above or below of a compound of Formula (I), J^1 and J^2 are both

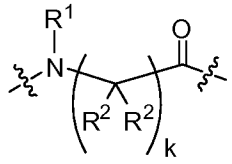
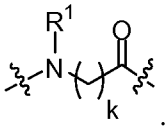
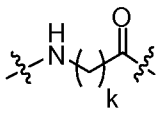
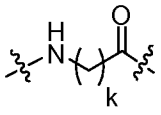
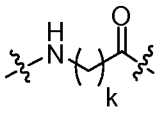
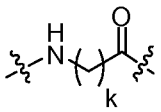
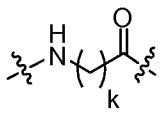

. In some embodiments described above or below of a compound of Formula (I), J^1 and J^2 are both 
. In some embodiments described above or below of a compound of Formula (I), J^1 and J^2 are both 
. In some embodiments described above or below of a compound of Formula (I), J^1 and J^2 are both 
. In some embodiments described above or below of a compound of Formula (I), J^1 and J^2 are both a bond.

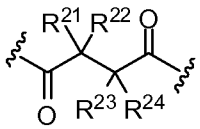
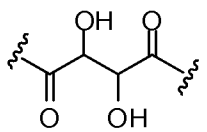
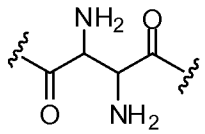
[0076] In some embodiments described above or below of a compound of Formula (I), A^1 and A^2 are the same. In some embodiments described above or below of a compound of Formula (I), A^1 and A^2 are both 
. In some embodiments described above or below of a compound of Formula (I), A^1 and A^2 are both 
.

[0077] In some embodiments described above or below of a compound of Formula (I), Z is O. In certain embodiments described above or below of a compound of Formula (I), each k is independently 1, 2, or 3. In certain embodiments described above or below of a compound of Formula (I), each k is 1. In certain embodiments described above or below of a compound of Formula (I), each m is independently 0, 1, 2, or 3. In certain embodiments described above or below of a compound of Formula (I), each m is 0. In certain embodiments described above or below of a compound of Formula (I), each m is 1. In certain embodiments described above or below of a compound of Formula (I), each m is 2. In certain embodiments described above or below of a compound of Formula (I), each m is 3.

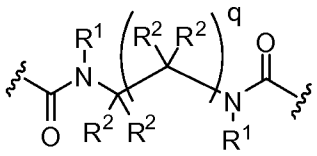
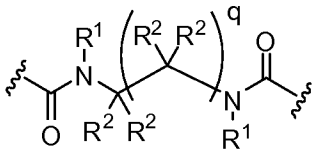
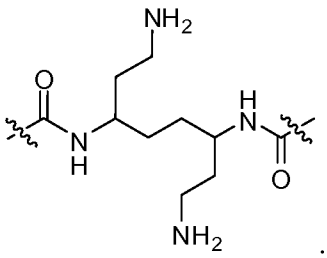
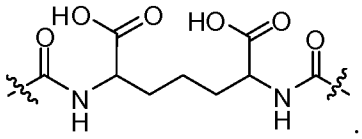
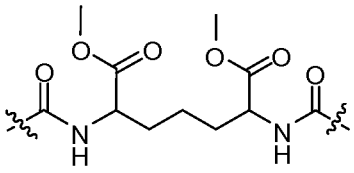
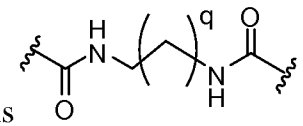
[0078] In some embodiments described above or below of a compound of Formula (I), Z is CR^2R^2. In some embodiments described above or below of a compound of Formula (I), Z is CH_2.

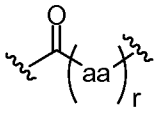
[0079] In some embodiments described above or below of a compound of Formula (I), L^1 and L^2 are the same.

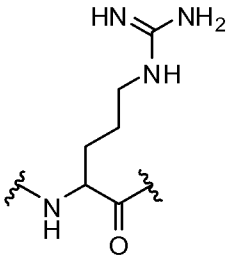
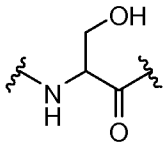
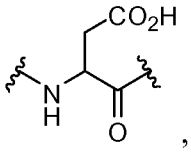
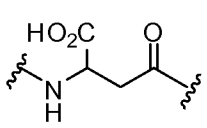
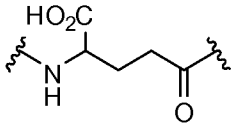
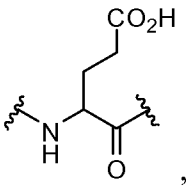
[0080] In some embodiments described above or below of a compound of Formula (I), L^1 and L^2 are both . In some embodiments described above or below of a compound of Formula (I), L^1 and L^2 are both . In some embodiments described above or below of a compound of Formula (I), L^1 and L^2 are both . In some embodiments described above or below of a compound of Formula (I), L^1 and L^2 are both  and k is 2. In some embodiments described above or below of a compound of Formula (I), L^1 and L^2 are both  and k is 3. In some embodiments described above or below of a compound of Formula (I), L^1 and L^2 are both  and k is 4. In some embodiments described above or below of a compound of Formula (I), L^1 and L^2 are both  and k is 5.

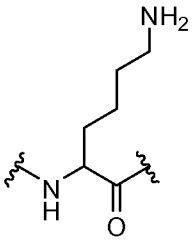
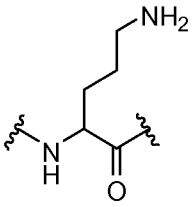
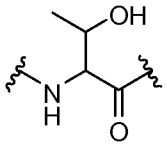
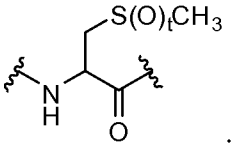
[0081] In some embodiments described above or below of a compound of Formula (I), X is . In some embodiments described above or below of a compound of Formula (I), R^{21} and R^{23} are the same and R^{22} and R^{24} are the same. In certain embodiments described above or below of a compound of Formula (I), X is . In certain embodiments described above or below of a compound of Formula (I), X is . In some embodiments

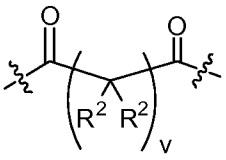
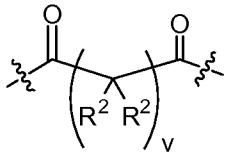
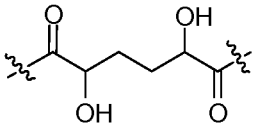
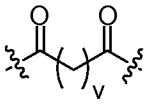
described above or below of a compound of Formula (I), R^{21} and R^{22} are the same. In some embodiments described above or below of a compound of Formula (I), R^{23} and R^{24} are the same. In some embodiments described above or below of a compound of Formula (I), R^{21}, R^{22}, R^{23}, and R^{24} are the same.

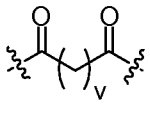
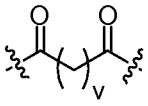
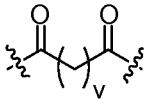
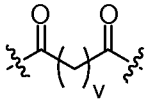
[0082] In some embodiments described above or below of a compound of Formula (I), X is . In some embodiments described above or below of a compound of Formula (I), X is ; each R^2 is independently selected from H, alkyl, -OH, -CO_2H, - CO_2alkyl, and -(alkylene)(NH_2); and q is 1, 2, 3, 4, 5, or 6. In certain embodiments described above or below of a compound of Formula (I), X is . In certain embodiments described above or below of a compound of Formula (I), X is . In certain embodiments described above or below of a compound of Formula (I), X is . In certain embodiments described above or below of a compound of Formula (I), X is . In certain embodiments described above or below of a compound of Formula (I), q is 1, 2, 3, 4, 5, or 6. In certain embodiments described above or below of a compound of Formula (I), q is 1. In certain embodiments described above or below of a compound of Formula (I), q is 2. In certain embodiments described above or below of a compound of Formula (I), q is 3. In certain embodiments described above or below of a compound of Formula (I), q is 4. In certain embodiments described above or below of a compound of Formula (I), q is 5. In certain embodiments described above or below of a compound of Formula (I), q is 6.

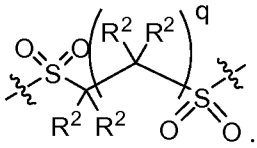
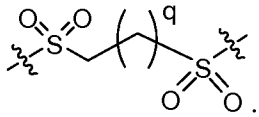
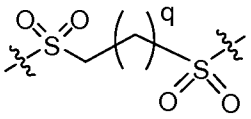
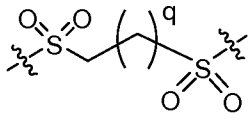
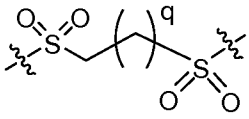
[0083] In some embodiments described above or below of a compound of Formula (I), X is . In certain embodiments described above or below of a compound of Formula (I), aa is selected from:

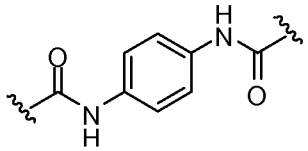
, , , , , ,

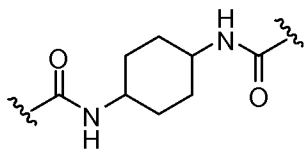
, , , and . In some embodiments described above or below of a compound of Formula (I), r is 4, 5, or 6.

[0084] In some embodiments described above or below of a compound of Formula (I), X is . In some embodiments described above or below of a compound of Formula (I), X is  and each R^2 is independently selected from H, alkyl, -OH, -CO_2H, -CO_2alkyl, and -(alkylene)(NH_2). In certain embodiments described above or below of a compound of Formula (I), X is . In certain embodiments described above or below of a compound of Formula (I), X is . In certain embodiments described above

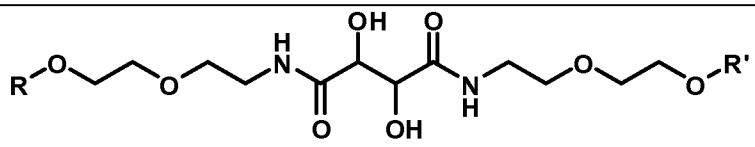
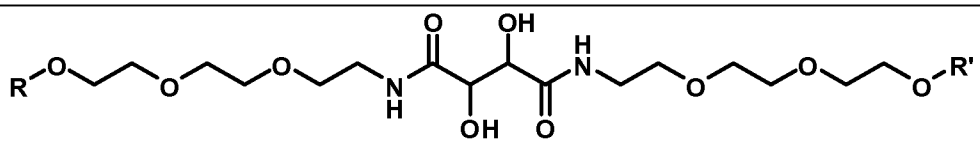
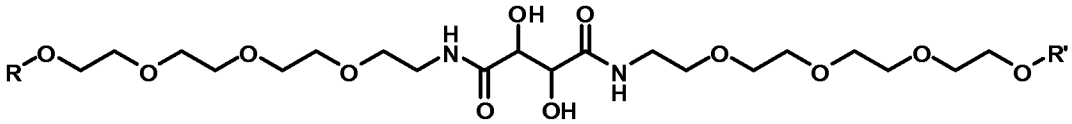
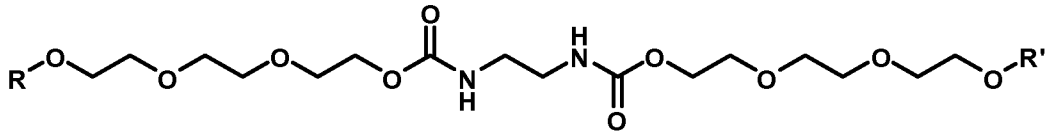
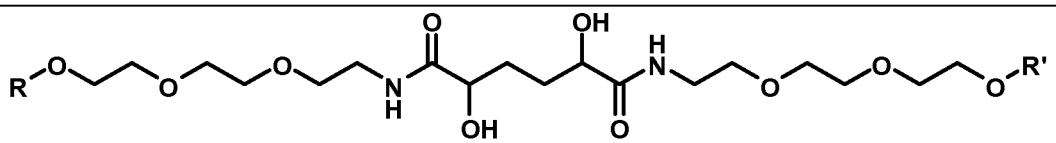
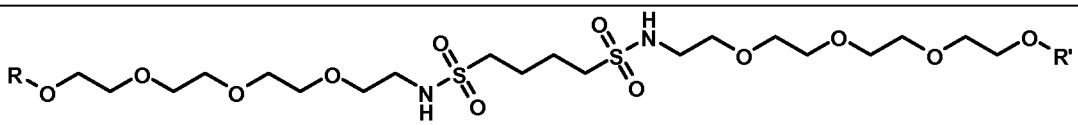
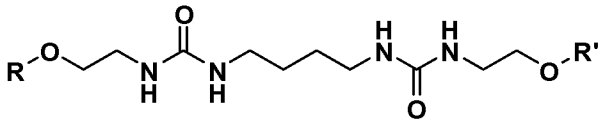
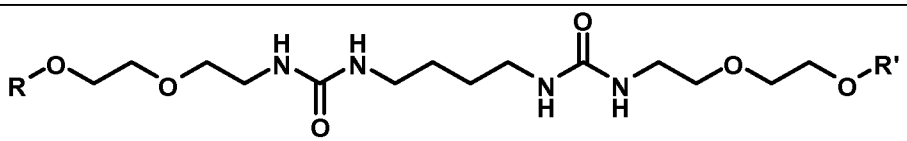
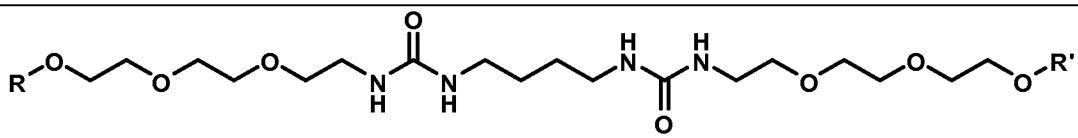
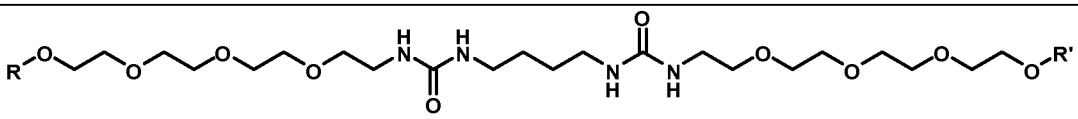
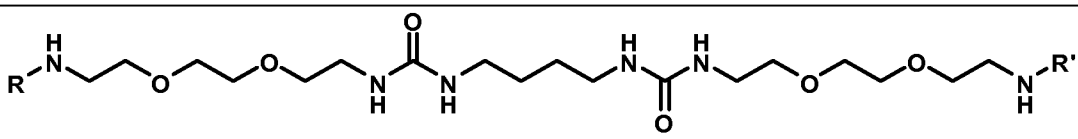
or below of a compound of Formula (I), X is  and v is 3. In certain embodiments described above or below of a compound of Formula (I), X is  and v is 4. In certain embodiments described above or below of a compound of Formula (I), X is  and v is 5. In certain embodiments described above or below of a compound of Formula (I), X is  and v is 6.

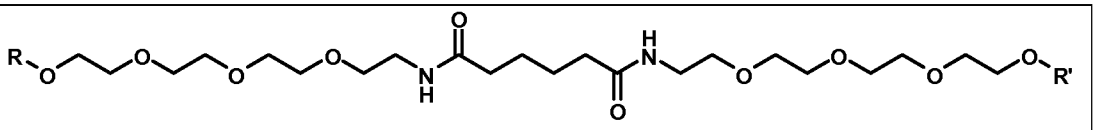
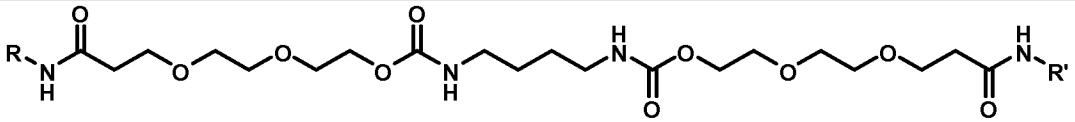
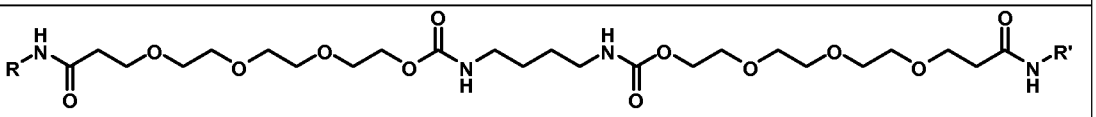
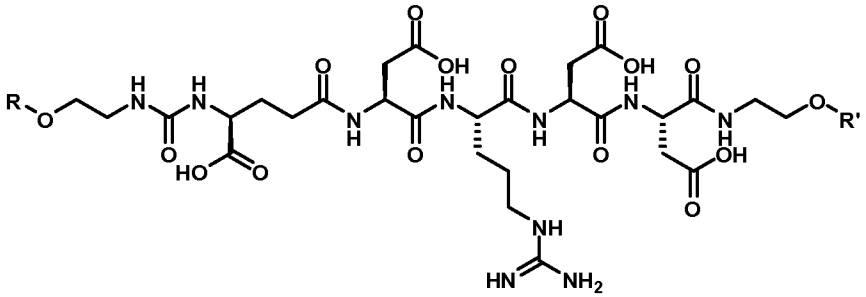
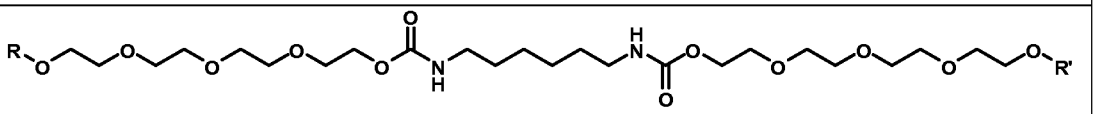
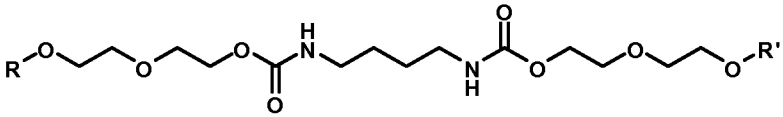
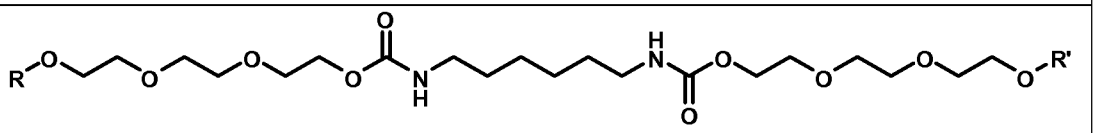
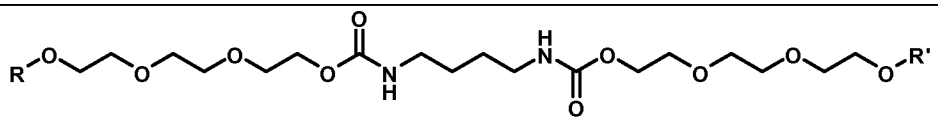
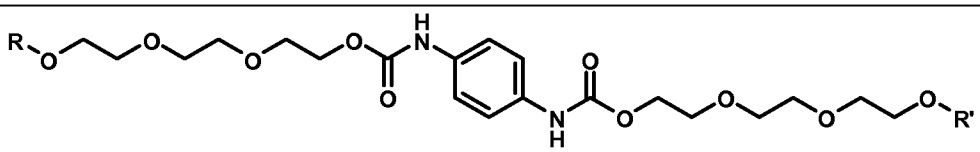
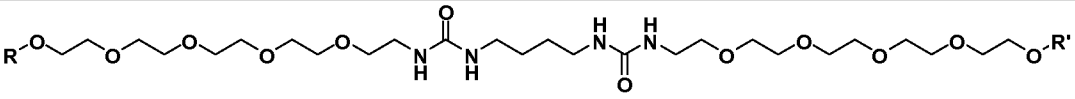
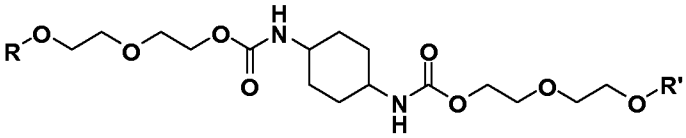
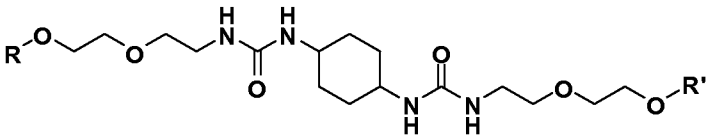
[0085] In some embodiments described above or below of a compound of Formula (I), X is . In certain embodiments described above or below of a compound of Formula (I), X is . In certain embodiments described above or below of a compound of Formula (I), X is  and q is 2. In certain embodiments described above or below of a compound of Formula (I), X is  and q is 3. In certain embodiments described above or below of a compound of Formula (I), X is  and q is 4.

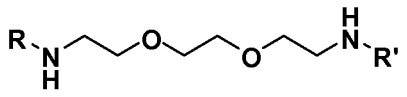
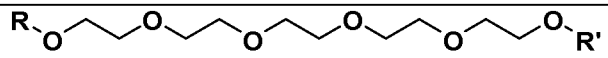
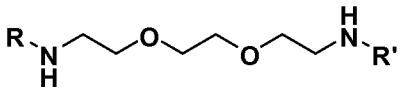
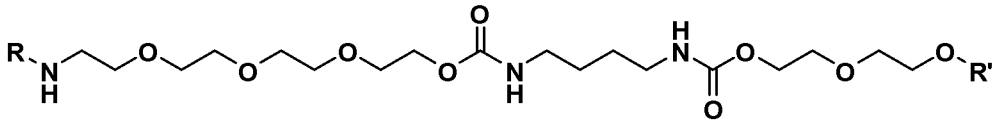
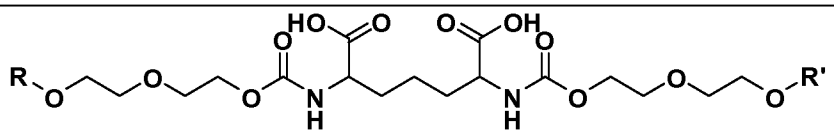
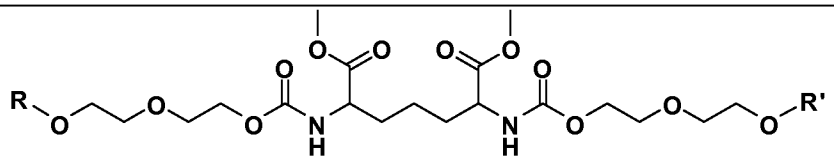
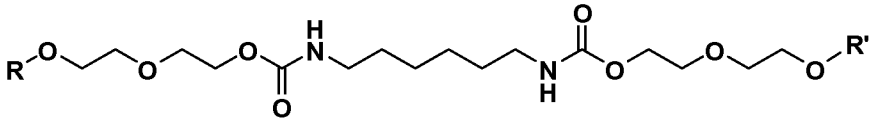
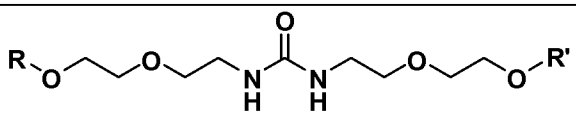
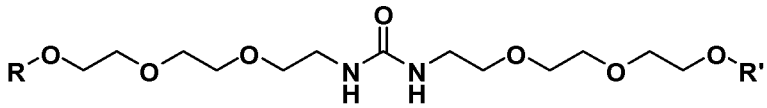
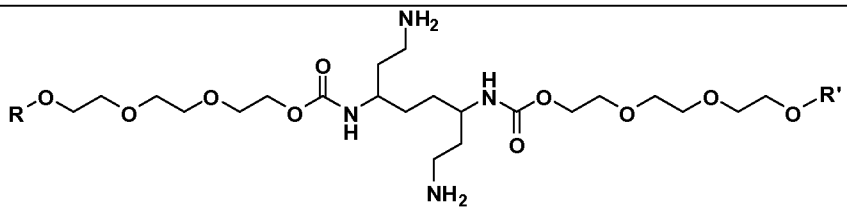
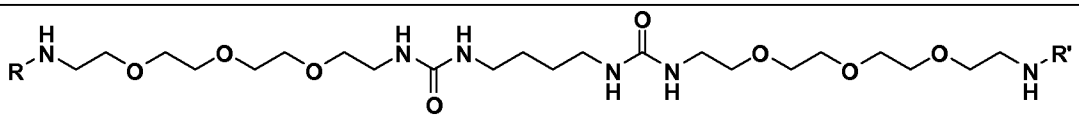
[0086] In some embodiments described above or below of a compound of Formula (I), X is .

[0087] In some embodiments described above or below of a compound of Formula (I), X is .

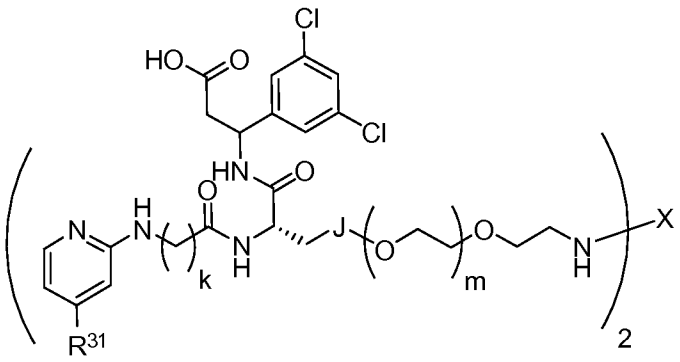
[0088] In some embodiments are compounds of Formula (I), wherein A^1-X-A^2 is a linker with the structure shown in the table below and R is -J^1-B^1-L^1-Y^1 and R' is -J^2-B^2-L^2-Y^2 wherein J^1, J^2, B^1, B^2, L^1, L^2, Y^1, and Y^2 are described above:

Linker #	A^1-X-A^2
1	
2	
3	
4	
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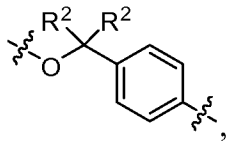
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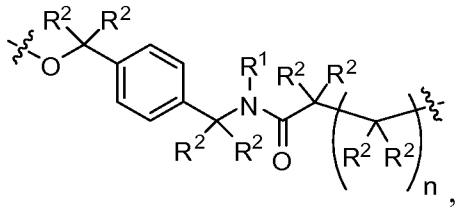
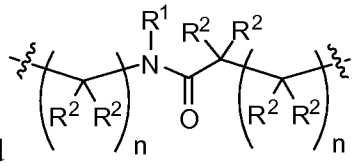
[0089] In another embodiment, provided herein is a compound of Formula (Ia), or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, metabolite, deuteride, N-oxide, tautomer, stereoisomer, or isomer thereof, having the structure:

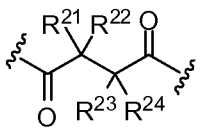
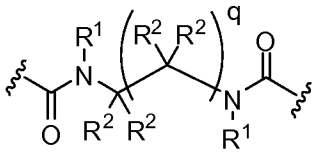
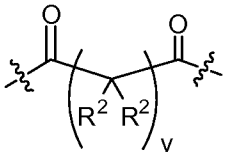


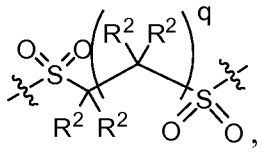
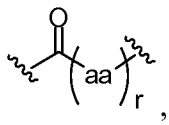
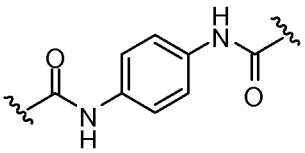
Formula (Ia);

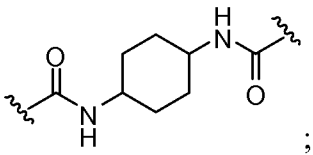
wherein:

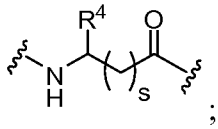
each J is independently selected from a bond, ,

, and ;

X is alkylene, -C(O)-, , , ,

, , , or

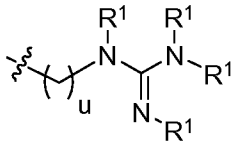
;

aa is ;

each R^1 is independently selected from H and alkyl;

each R^2 is independently selected from H, halo, -CN, -SR^1, alkyl, cycloalkyl, haloalkyl, -OR^1, and -R^4;

each R^4 is independently selected from $-CO_2R^1$, -(alkylene)-(CO_2R^1), hydroxyalkyl,



-(alkylene)($S(O)_t$)(alkyl), -(alkylene)(NR^5R^5), and ;

each R^5 is independently selected from H, alkyl, haloalkyl, arylalkyl, heteroarylalkyl, aryl, and heteroaryl;

R^{21}, R^{22}, R^{23}, and R^{24} are independently selected from H, halo, -CN, $-SR^1$, alkyl, cycloalkyl, haloalkyl, $-NR^1R^1$, and $-OR^1$;

each R^{31} is independently selected from H and alkyl;

each k is independently selected from 3, 4, and 5;

each m is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

each n is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

q is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

r is 3, 4, 5, 6, or 7;

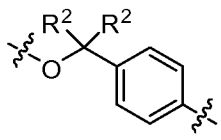
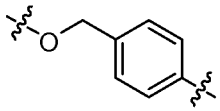
each s is independently selected from 0, 1, 2, 3, and 4;

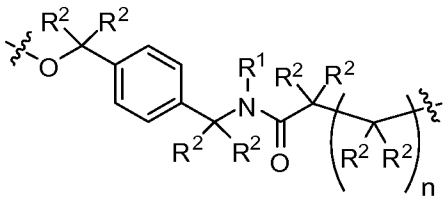
each t is independently selected from 0, 1, and 2;

each u is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10; and

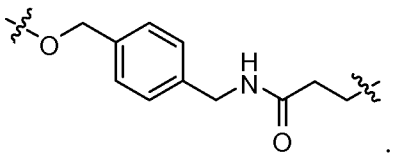
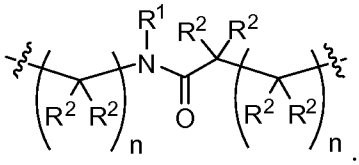
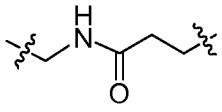
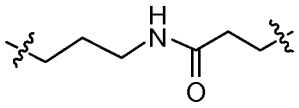
v is selected from 3, 4, 5, 6, 7, 8, 9, and 10.

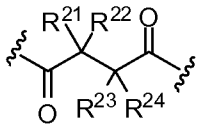
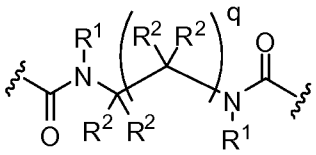
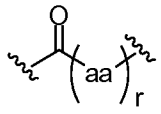
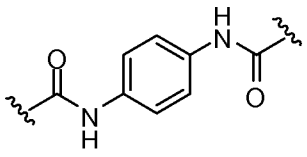
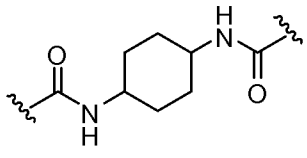
[0090] In some embodiments is a compound of Formula (Ia) wherein each R^{31} is H. In some embodiments is a compound of Formula (Ia) wherein each R^{31} is alkyl. In some embodiments is a compound of Formula (Ia) wherein each R^{31} is methyl. In some embodiments is a compound of Formula (Ia) wherein each R^{31} is ethyl.

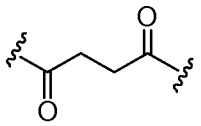
[0091] In some embodiments is a compound of Formula (Ia) wherein each J is the same. In some embodiments is a compound of Formula (Ia) wherein each J is . In some embodiments is a compound of Formula (Ia) wherein each J is . In some embodiments is a compound of Formula (Ia) wherein each J is

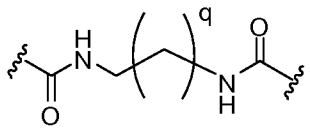
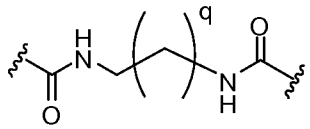
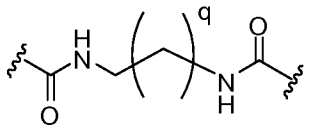
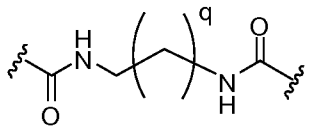
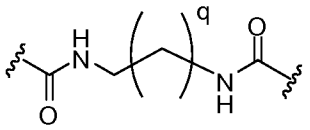
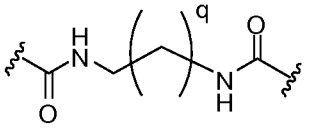
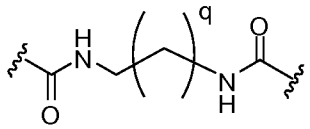


. In some embodiments is a compound of Formula (Ia)

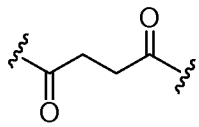
wherein each J is  . In some embodiments is a compound of Formula (Ia) wherein each J is  . In some embodiments is a compound of Formula (Ia) wherein each J is  . In some embodiments is a compound of Formula (Ia) wherein each J is  . In some embodiments is a compound of Formula (Ia) wherein each J is a bond.

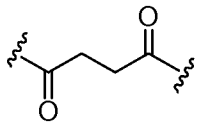
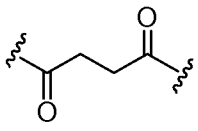
[0092] In some embodiments is a compound of Formula (Ia) wherein X is  . In some embodiments is a compound of Formula (Ia) wherein X is  . In some embodiments is a compound of Formula (Ia) wherein X is  . In some embodiments is a compound of Formula (Ia) wherein X is  . In some embodiments is a compound of Formula (Ia) wherein X is  . In some embodiments is a compound of Formula (Ia) wherein X is alkylene. In some embodiments is a compound of Formula (Ia) wherein X is -C(O)-.

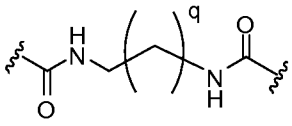
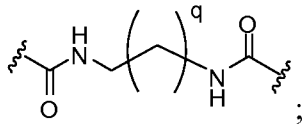
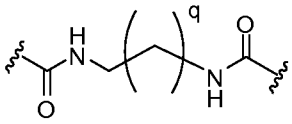
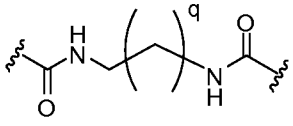
[0093] In some embodiments is a compound of Formula (Ia) wherein X is  .

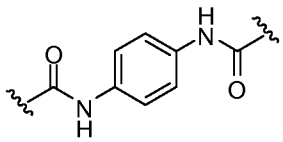
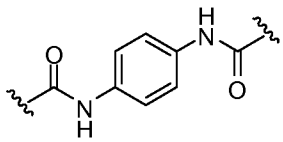
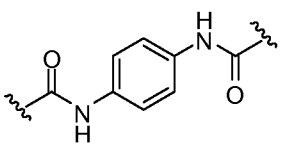
[0094] In some embodiments is a compound of Formula (Ia) wherein X is  and q is 1. In some embodiments is a compound of Formula (Ia) wherein X is  and q is 2. In some embodiments is a compound of Formula (Ia) wherein X is  and q is 3. In some embodiments is a compound of Formula (Ia) wherein X is  and q is 4. In some embodiments is a compound of Formula (Ia) wherein X is  and q is 5. In some embodiments is a compound of Formula (Ia) wherein X is  and q is 6. In some embodiments is a compound of Formula (Ia) wherein X is  and q is 7.

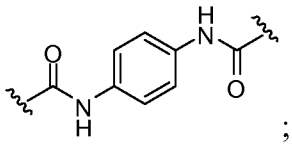
[0095] In some embodiments is a compound of Formula (Ia) wherein m is 0. In some embodiments is a compound of Formula (Ia) wherein m is 1. In some embodiments is a compound of Formula (Ia) wherein m is 2. In some embodiments is a compound of Formula (Ia) wherein m is 3. In some embodiments is a compound of Formula (Ia) wherein m is 4. In some embodiments is a compound of Formula (Ia) wherein m is 5. In some embodiments is a compound of Formula (Ia) wherein m is 6. In some embodiments is a compound of Formula (Ia) wherein m is 7.

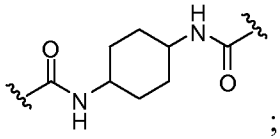
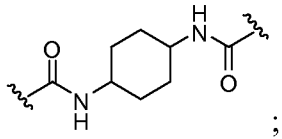
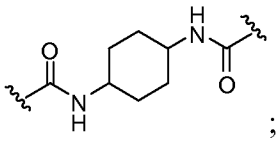
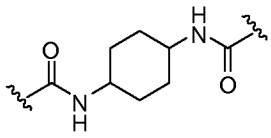
[0096] In some embodiments is a compound of Formula (Ia) wherein X is ; and each m is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10. In some embodiments is

a compound of Formula (Ia) wherein X is  ; and each m is independently selected from 0, 1, 2, 3, 4, 5, and 6. In some embodiments is a compound of Formula (Ia) wherein X is  ; and each m is independently selected from 1, 2, 3, 4, and 5.

[0097] In some embodiments is a compound of Formula (Ia) wherein X is  ; q is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; and each m is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10. In some embodiments is a compound of Formula (Ia) wherein X is  ; q is 1, 2, 3, 4, 5, and each m is independently selected from 0, 1, 2, 3, 4, 5, and 6. In some embodiments is a compound of Formula (Ia) wherein X is  ; q is 3, 4, or 5; and each m is independently selected from 1, 2, 3, 4, and 5. In some embodiments is a compound of Formula (Ia) wherein X is  ; q is 3, 4, or 5; and each m is independently selected from 1, 2, 3, 4, and 5.

[0098] In some embodiments is a compound of Formula (Ia) wherein X is  ; and each m is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10. In some embodiments is a compound of Formula (Ia) wherein X is  ; and each m is independently selected from 0, 1, 2, 3, 4, 5, and 6. In some embodiments is a compound of Formula (Ia) wherein X is  ; and each m is independently

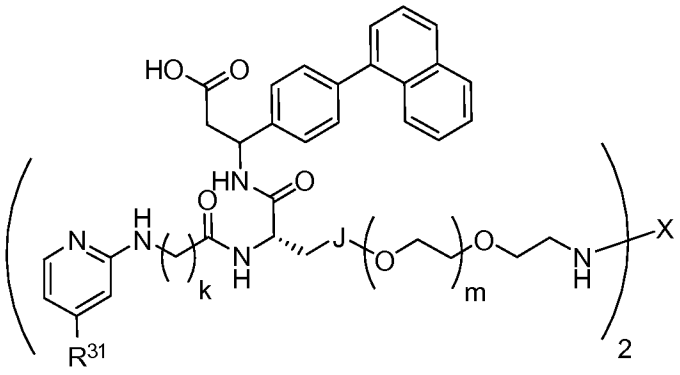
selected from 1, 2, 3, 4, and 5. In some embodiments is a compound of Formula (Ia) wherein X is  ; and each m is independently selected from 1, 2, 3, 4, and 5.

[0099] In some embodiments is a compound of Formula (Ia) wherein X is  ; and each m is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10. In some embodiments is a compound of Formula (Ia) wherein X is  ; and each m is independently selected from 0, 1, 2, 3, 4, 5, and 6. In some embodiments is a compound of Formula (Ia) wherein X is  ; and each m is independently selected from 1, 2, 3, 4, and 5. In some embodiments is a compound of Formula (Ia) wherein X is  ; and each m is independently selected from 1, 2, 3, 4, and 5.

[00100] In some embodiments is a compound of Formula (Ia) wherein X is alkylene; and each m is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10. In some embodiments is a compound of Formula (Ia) wherein X is alkylene; and each m is independently selected from 0, 1, 2, 3, 4, 5, and 6. In some embodiments is a compound of Formula (Ia) wherein X is alkylene; and each m is independently selected from 1, 2, 3, 4, and 5. In some embodiments is a compound of Formula (Ia) wherein X is alkylene; and each m is independently selected from 1, 2, 3, 4, and 5.

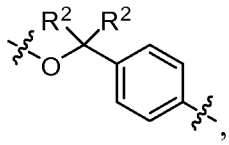
[00101] In some embodiments is a compound of Formula (Ia) wherein X is -C(O)-; and each m is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10. In some embodiments is a compound of Formula (Ia) wherein X is -C(O)-; and each m is independently selected from 0, 1, 2, 3, 4, 5, and 6. In some embodiments is a compound of Formula (Ia) wherein X is -C(O)-; and each m is independently selected from 1, 2, 3, 4, and 5. In some embodiments is a compound of Formula (Ia) wherein X is -C(O)-; and each m is independently selected from 1, 2, 3, 4, and 5.

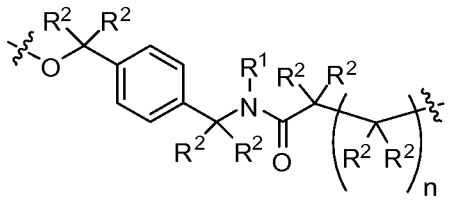
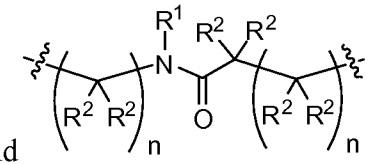
[00102] In another embodiment, provided herein is a compound of Formula (Ib), or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, metabolite, deuteride, N-oxide, tautomer, stereoisomer, or isomer thereof, having the structure:

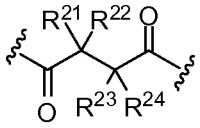
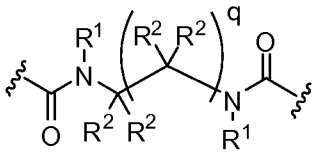
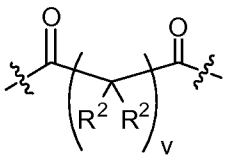


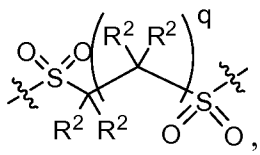
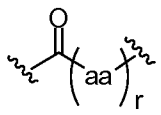
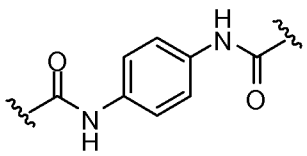
Formula (Ib);

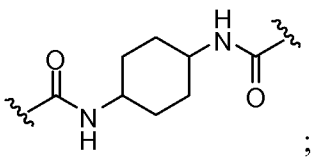
wherein:

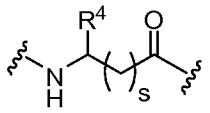
each J is independently selected from a bond, ,

 , and  ;

X is alkylene, -C(O)-,  ,  ,  ,

 ,  ,  , or

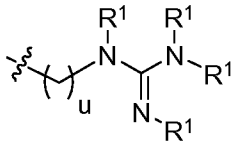
 ;

aa is  ;

each R^1 is independently selected from H and alkyl;

each R^2 is independently selected from H, halo, -CN, -SR^1, alkyl, cycloalkyl, haloalkyl, -OR^1, and -R^4;

each R^4 is independently selected from $-CO_2R^1$, -(alkylene)-(CO_2R^1), hydroxyalkyl,



-(alkylene)($S(O)_t$)(alkyl), -(alkylene)(NR^5R^5), and ;

each R^5 is independently selected from H, alkyl, haloalkyl, arylalkyl, heteroarylalkyl, aryl, and heteroaryl;

R^{21}, R^{22}, R^{23}, and R^{24} are independently selected from H, halo, -CN, $-SR^1$, alkyl, cycloalkyl, haloalkyl, $-NR^1R^1$, and $-OR^1$;

each R^{31} is independently selected from H and alkyl;

each k is independently selected from 3, 4, and 5;

each m is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

each n is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

q is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

r is 3, 4, 5, 6, or 7;

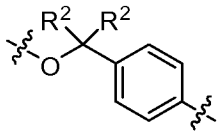
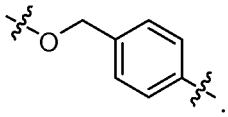
each s is independently selected from 0, 1, 2, 3, and 4;

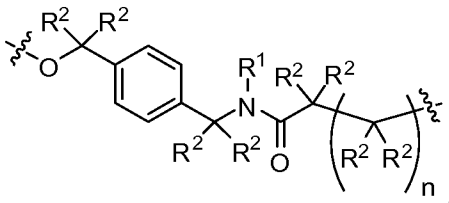
each t is independently selected from 0, 1, and 2;

each u is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10; and

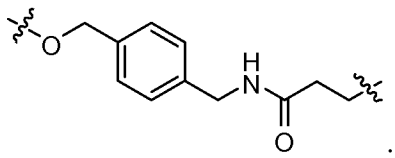
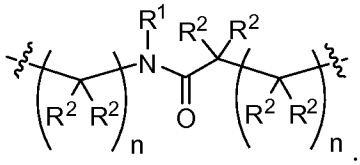
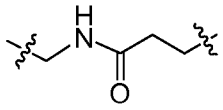
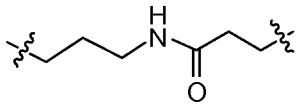
v is selected from 3, 4, 5, 6, 7, 8, 9, and 10.

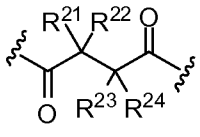
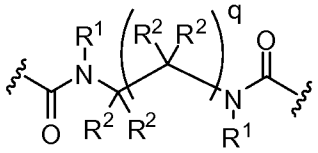
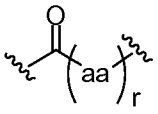
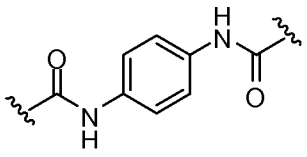
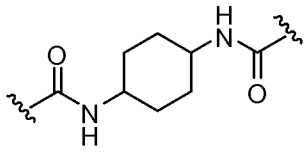
[00103] In some embodiments is a compound of Formula (Ib) wherein each R^{31} is H. In some embodiments is a compound of Formula (Ib) wherein each R^{31} is alkyl. In some embodiments is a compound of Formula (Ib) wherein each R^{31} is methyl. In some embodiments is a compound of Formula (Ib) wherein each R^{31} is ethyl.

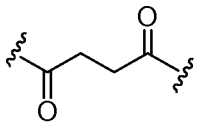
[00104] In some embodiments is a compound of Formula (Ib) wherein each J is the same. In some embodiments is a compound of Formula (Ib) wherein each J is . In some embodiments is a compound of Formula (Ib) wherein each J is . In some embodiments is a compound of Formula (Ib) wherein each J is

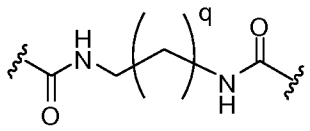
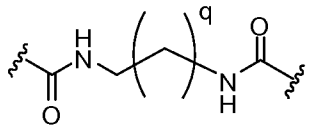
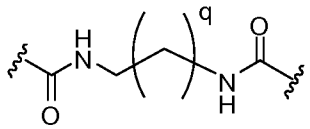
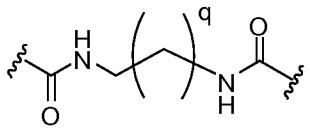
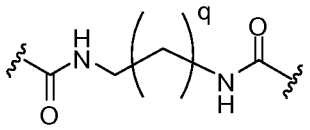
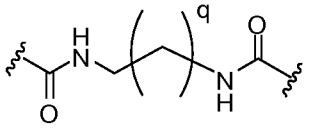
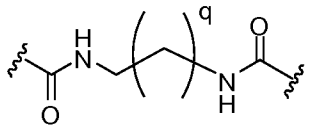


. In some embodiments is a compound of Formula (Ib)

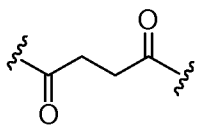
wherein each J is . In some embodiments is a compound of Formula (Ib) wherein each J is . In some embodiments is a compound of Formula (Ib) wherein each J is . In some embodiments is a compound of Formula (Ib) wherein each J is . In some embodiments is a compound of Formula (Ib) wherein each J is a bond.

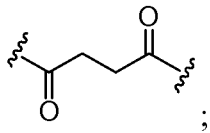
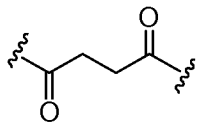
[00105] In some embodiments is a compound of Formula (Ib) wherein X is . In some embodiments is a compound of Formula (Ib) wherein X is . In some embodiments is a compound of Formula (Ib) wherein X is . In some embodiments is a compound of Formula (Ib) wherein X is . In some embodiments is a compound of Formula (Ib) wherein X is . In some embodiments is a compound of Formula (Ib) wherein X is alkylene. In some embodiments is a compound of Formula (Ib) wherein X is -C(O)-.

[00106] In some embodiments is a compound of Formula (Ib) wherein X is .

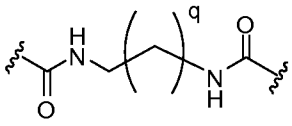
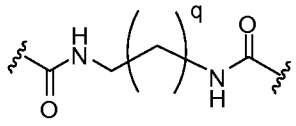
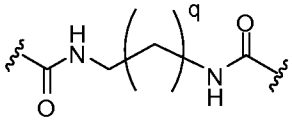
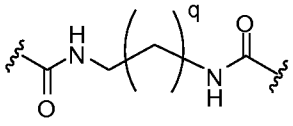
[00107] In some embodiments is a compound of Formula (Ib) wherein X is  and q is 1. In some embodiments is a compound of Formula (Ib) wherein X is  and q is 2. In some embodiments is a compound of Formula (Ib) wherein X is  and q is 3. In some embodiments is a compound of Formula (Ib) wherein X is  and q is 4. In some embodiments is a compound of Formula (Ib) wherein X is  and q is 5. In some embodiments is a compound of Formula (Ib) wherein X is  and q is 6. In some embodiments is a compound of Formula (Ib) wherein X is  and q is 7.

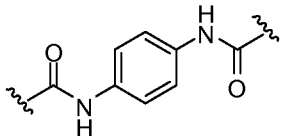
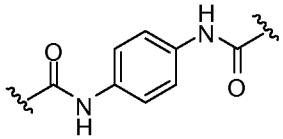
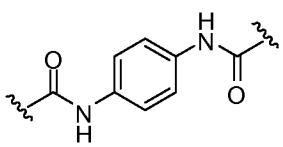
[00108] In some embodiments is a compound of Formula (Ib) wherein m is 0. In some embodiments is a compound of Formula (Ib) wherein m is 1. In some embodiments is a compound of Formula (Ib) wherein m is 2. In some embodiments is a compound of Formula (Ib) wherein m is 3. In some embodiments is a compound of Formula (Ib) wherein m is 4. In some embodiments is a compound of Formula (Ib) wherein m is 5. In some embodiments is a compound of Formula (Ib) wherein m is 6. In some embodiments is a compound of Formula (Ib) wherein m is 7.

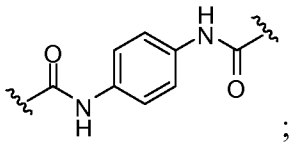
[00109] In some embodiments is a compound of Formula (Ib) wherein X is ; and each m is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10. In some

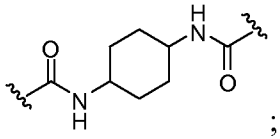
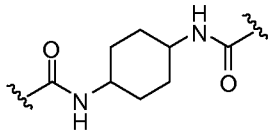
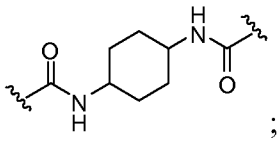
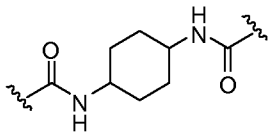
embodiments is a compound of Formula (Ib) wherein X is  ; and each m is independently selected from 0, 1, 2, 3, 4, 5, and 6. In some embodiments is a compound of Formula (Ib) wherein X is  ; and each m is independently selected from 1, 2, 3, 4, and 5.

[00110]

[00111] In some embodiments is a compound of Formula (Ib) wherein X is  ; q is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; and each m is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10. In some embodiments is a compound of Formula (Ib) wherein X is  ; q is 1, 2, 3, 4, 5, and each m is independently selected from 0, 1, 2, 3, 4, 5, and 6. In some embodiments is a compound of Formula (Ib) wherein X is  ; q is 3, 4, or 5; and each m is independently selected from 1, 2, 3, 4, and 5. In some embodiments is a compound of Formula (Ib) wherein X is  ; q is 3, 4, or 5; and each m is independently selected from 1, 2, 3, 4, and 5.

[00112] In some embodiments is a compound of Formula (Ib) wherein X is  ; and each m is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10. In some embodiments is a compound of Formula (Ib) wherein X is  ; and each m is independently selected from 0, 1, 2, 3, 4, 5, and 6. In some embodiments is a compound of Formula (Ib) wherein X is  ; and each m is independently

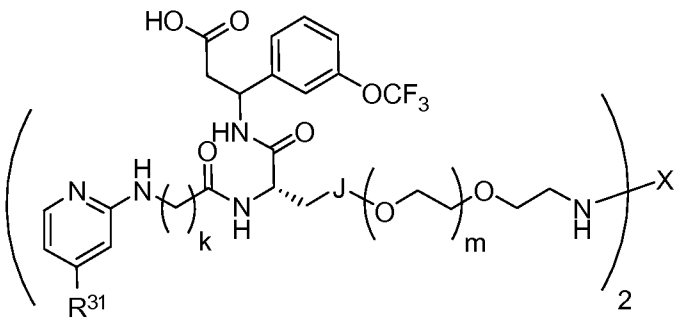
selected from 1, 2, 3, 4, and 5. In some embodiments is a compound of Formula (Ib) wherein X is  ; and each m is independently selected from 1, 2, 3, 4, and 5.

[00113] In some embodiments is a compound of Formula (Ib) wherein X is  ; and each m is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10. In some embodiments is a compound of Formula (Ib) wherein X is  ; and each m is independently selected from 0, 1, 2, 3, 4, 5, and 6. In some embodiments is a compound of Formula (Ib) wherein X is  ; and each m is independently selected from 1, 2, 3, 4, and 5. In some embodiments is a compound of Formula (Ib) wherein X is  ; and each m is independently selected from 1, 2, 3, 4, and 5.

[00114] In some embodiments is a compound of Formula (Ib) wherein X is alkylene; and each m is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10. In some embodiments is a compound of Formula (Ib) wherein X is alkylene; and each m is independently selected from 0, 1, 2, 3, 4, 5, and 6. In some embodiments is a compound of Formula (Ib) wherein X is alkylene; and each m is independently selected from 1, 2, 3, 4, and 5. In some embodiments is a compound of Formula (Ib) wherein X is alkylene; and each m is independently selected from 1, 2, 3, 4, and 5.

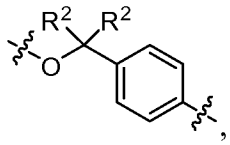
[00115] In some embodiments is a compound of Formula (Ib) wherein X is -C(O)-; and each m is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10. In some embodiments is a compound of Formula (Ib) wherein X is -C(O)-; and each m is independently selected from 0, 1, 2, 3, 4, 5, and 6. In some embodiments is a compound of Formula (Ib) wherein X is -C(O)-; and each m is independently selected from 1, 2, 3, 4, and 5. In some embodiments is a compound of Formula (Ib) wherein X is -C(O)-; and each m is independently selected from 1, 2, 3, 4, and 5.

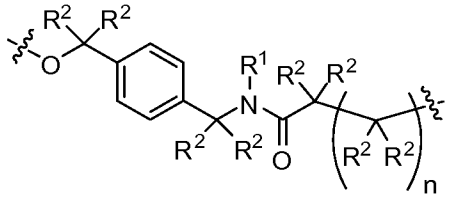
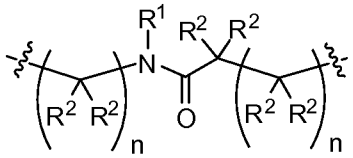
[00116] In another embodiment, provided herein is a compound of Formula (Ic), or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, metabolite, deuteride, N-oxide, tautomer, stereoisomer, or isomer thereof, having the structure:

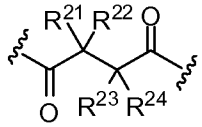
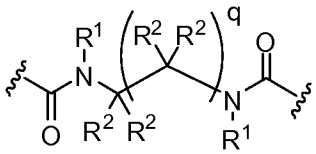
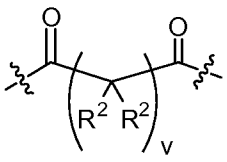


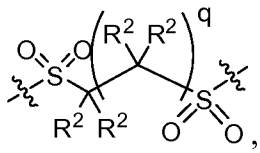
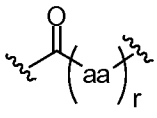
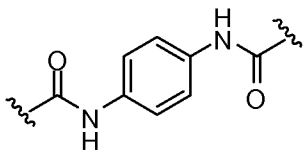
Formula (Ic);

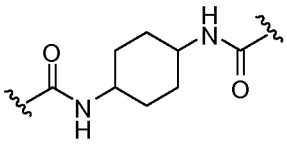
wherein:

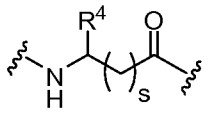
each J is independently selected from a bond, ,

, and ;

X is alkylene, -C(O)-, , , ,

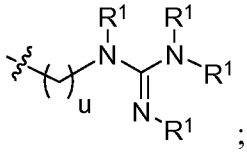
, , , or

;

aa is ;

each R^1 is independently selected from H and alkyl;

each R^2 is independently selected from H, halo, -CN, -SR^1, alkyl, cycloalkyl, haloalkyl, -OR^1, and -R^4;

each R^4 is independently selected from -CO_2R^1, -(alkylene)-(CO_2R^1), hydroxyalkyl, -(alkylene)($S(O)_t$)(alkyl), -(alkylene)(NR^5R^5), and ;

each R^5 is independently selected from H, alkyl, haloalkyl, arylalkyl, heteroarylalkyl, aryl, and heteroaryl;

R^{21}, R^{22}, R^{23}, and R^{24} are independently selected from H, halo, -CN, -SR^1, alkyl, cycloalkyl, haloalkyl, -NR^1R^1, and -OR^1;

each R^{31} is independently selected from H and alkyl;

each k is independently selected from 3, 4, and 5;

each m is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

each n is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

q is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

r is 3, 4, 5, 6, or 7;

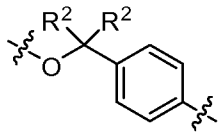
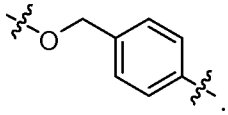
each s is independently selected from 0, 1, 2, 3, and 4;

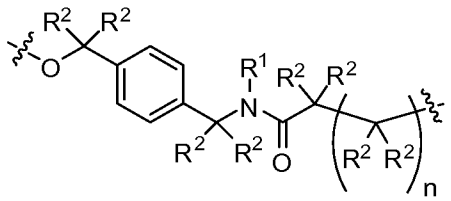
each t is independently selected from 0, 1, and 2;

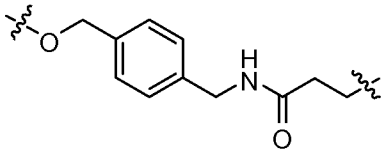
each u is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10; and

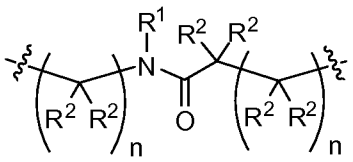
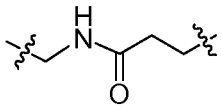
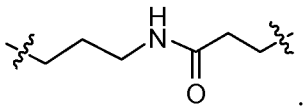
v is selected from 3, 4, 5, 6, 7, 8, 9, and 10.

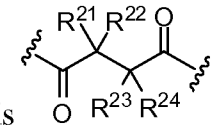
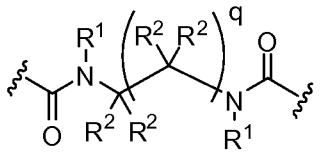
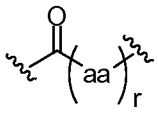
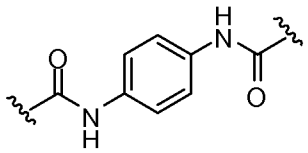
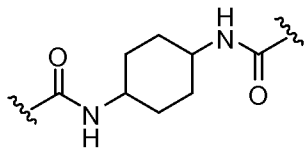
[00117] In some embodiments is a compound of Formula (Ic) wherein each R^{31} is H. In some embodiments is a compound of Formula (Ic) wherein each R^{31} is alkyl. In some embodiments is a compound of Formula (Ic) wherein each R^{31} is methyl. In some embodiments is a compound of Formula (Ic) wherein each R^{31} is ethyl.

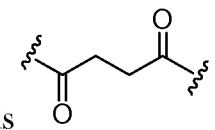
[00118] In some embodiments is a compound of Formula (Ic) wherein each J is the same. In some embodiments is a compound of Formula (Ic) wherein each J is . In some embodiments is a compound of Formula (Ic) wherein each J is . In some embodiments is a compound of Formula (Ic) wherein each J is



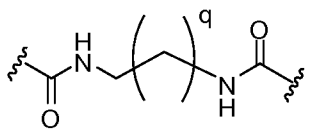
. In some embodiments is a compound of Formula (Ic) wherein each J is . In some embodiments is a compound of

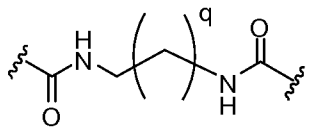
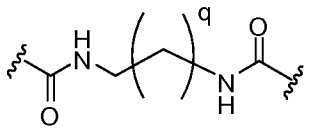
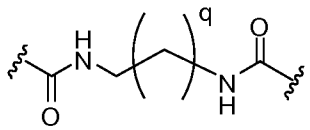
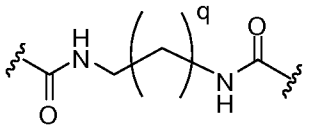
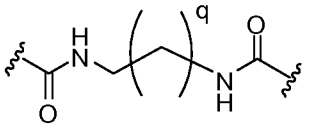
Formula (Ic) wherein each J is . In some embodiments is a compound of Formula (Ic) wherein each J is . In some embodiments is a compound of Formula (Ic) wherein each J is . In some embodiments is a compound of Formula (Ic) wherein each J is a bond.

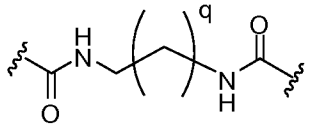
[00119] In some embodiments is a compound of Formula (Ic) wherein X is . In some embodiments is a compound of Formula (Ic) wherein X is . In some embodiments is a compound of Formula (Ic) wherein X is . In some embodiments is a compound of Formula (Ic) wherein X is . In some embodiments is a compound of Formula (Ic) wherein X is . In some embodiments is a compound of Formula (Ic) wherein X is alkylene. In some embodiments is a compound of Formula (Ic) wherein X is -C(O)-.

[00120] In some embodiments is a compound of Formula (Ic) wherein X is .

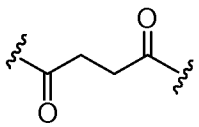
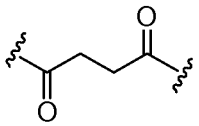
[00121] In some embodiments is a compound of Formula (Ic) wherein X is

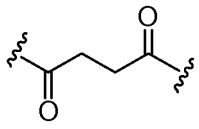
 and q is 1. In some embodiments is a compound of Formula (Ic)

wherein X is  and q is 2. In some embodiments is a compound of Formula (Ic) wherein X is  and q is 3. In some embodiments is a compound of Formula (Ic) wherein X is  and q is 4. In some embodiments is a compound of Formula (Ic) wherein X is  and q is 5. In some embodiments is a compound of Formula (Ic) wherein X is  and q is 6. In some embodiments is a compound of Formula (Ic) wherein X is

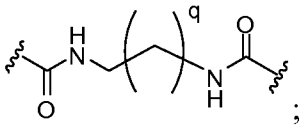
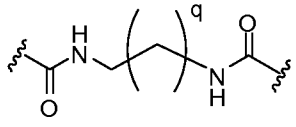
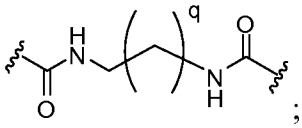
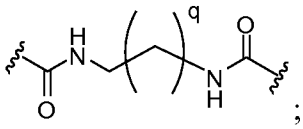
 and q is 7.

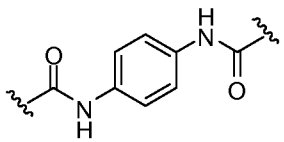
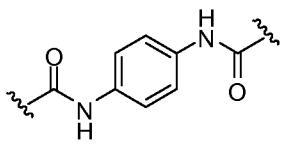
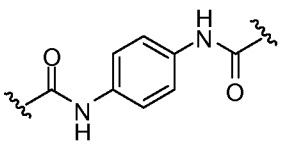
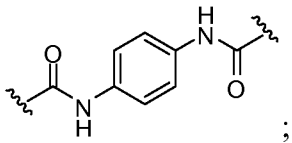
[00122] In some embodiments is a compound of Formula (Ic) wherein m is 0. In some embodiments is a compound of Formula (Ic) wherein m is 1. In some embodiments is a compound of Formula (Ic) wherein m is 2. In some embodiments is a compound of Formula (Ic) wherein m is 3. In some embodiments is a compound of Formula (Ic) wherein m is 4. In some embodiments is a compound of Formula (Ic) wherein m is 5. In some embodiments is a compound of Formula (Ic) wherein m is 6. In some embodiments is a compound of Formula (Ic) wherein m is 7.

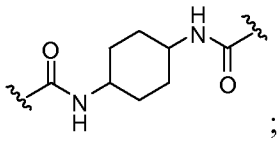
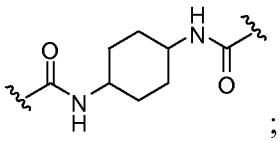
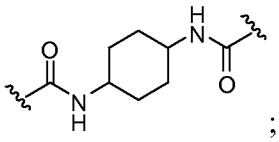
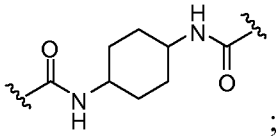
[00123] In some embodiments is a compound of Formula (Ic) wherein X is ; and each m is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10. In some embodiments is a compound of Formula (Ic) wherein X is ; and each m is independently selected from 0, 1, 2, 3, 4, 5, and 6. In some embodiments is a compound of

Formula (Ic) wherein X is  ; and each m is independently selected from 1, 2, 3, 4, and 5.

[00124]

[00125] In some embodiments is a compound of Formula (Ic) wherein X is  ; q is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; and each m is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10. In some embodiments is a compound of Formula (Ic) wherein X is  ; q is 1, 2, 3, 4, 5, and each m is independently selected from 0, 1, 2, 3, 4, 5, and 6. In some embodiments is a compound of Formula (Ic) wherein X is  ; q is 3, 4, or 5; and each m is independently selected from 1, 2, 3, 4, and 5. In some embodiments is a compound of Formula (Ic) wherein X is  ; q is 3, 4, or 5; and each m is independently selected from 1, 2, 3, 4, and 5.

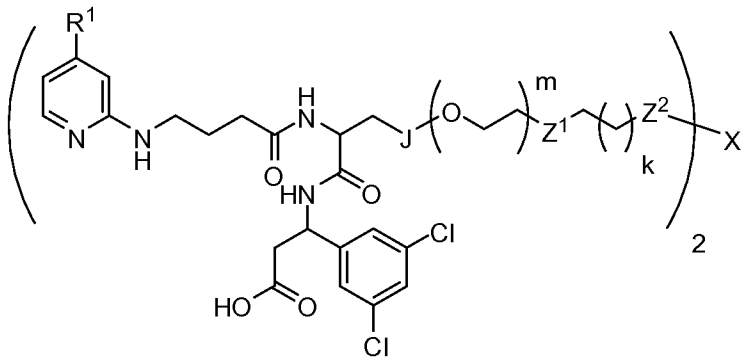
[00126] In some embodiments is a compound of Formula (Ic) wherein X is  ; and each m is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10. In some embodiments is a compound of Formula (Ic) wherein X is  ; and each m is independently selected from 0, 1, 2, 3, 4, 5, and 6. In some embodiments is a compound of Formula (Ic) wherein X is  ; and each m is independently selected from 1, 2, 3, 4, and 5. In some embodiments is a compound of Formula (Ic) wherein X is  ; and each m is independently selected from 1, 2, 3, 4, and 5.

[00127] In some embodiments is a compound of Formula (Ic) wherein X is  ; and each m is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10. In some embodiments is a compound of Formula (Ic) wherein X is  ; and each m is independently selected from 0, 1, 2, 3, 4, 5, and 6. In some embodiments is a compound of Formula (Ic) wherein X is  ; and each m is independently selected from 1, 2, 3, 4, and 5. In some embodiments is a compound of Formula (Ic) wherein X is  ; and each m is independently selected from 1, 2, 3, 4, and 5.

[00128] In some embodiments is a compound of Formula (Ic) wherein X is alkylene; and each m is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10. In some embodiments is a compound of Formula (Ic) wherein X is alkylene; and each m is independently selected from 0, 1, 2, 3, 4, 5, and 6. In some embodiments is a compound of Formula (Ic) wherein X is alkylene; and each m is independently selected from 1, 2, 3, 4, and 5. In some embodiments is a compound of Formula (Ic) wherein X is alkylene; and each m is independently selected from 1, 2, 3, 4, and 5.

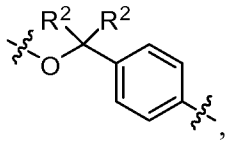
[00129] In some embodiments is a compound of Formula (Ic) wherein X is -C(O)-; and each m is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10. In some embodiments is a compound of Formula (Ic) wherein X is -C(O)-; and each m is independently selected from 0, 1, 2, 3, 4, 5, and 6. In some embodiments is a compound of Formula (Ic) wherein X is -C(O)-; and each m is independently selected from 1, 2, 3, 4, and 5. In some embodiments is a compound of Formula (Ic) wherein X is -C(O)-; and each m is independently selected from 1, 2, 3, 4, and 5.

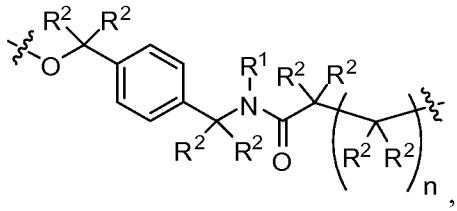
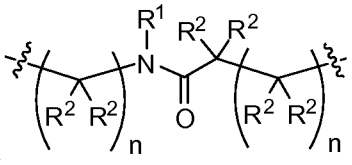
[00130] In another embodiment, provided herein is a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, metabolite, deuteride, N-oxide, tautomer, stereoisomer, or isomer thereof, having the structure:

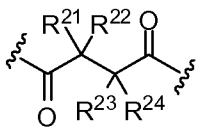
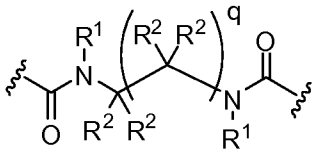
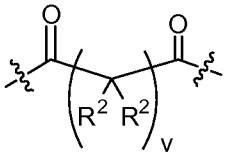


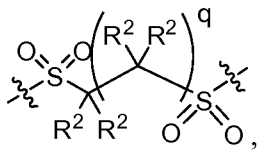
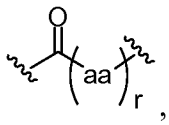
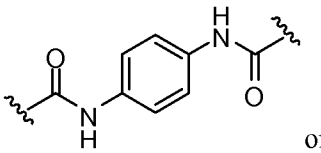
Formula (II);

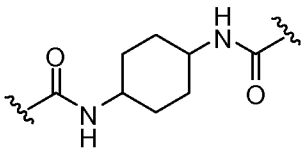
wherein:

each J is independently selected from a bond, ,

, and ;

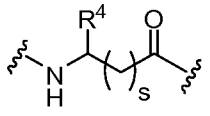
X is alkylene, -C(O)-, , , ,

, ,  or

;

Z^1 is O or CR^2R^2;

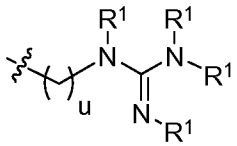
Z^2 is O or NH;

aa is ;

each R^1 is independently selected from H and alkyl;

each R^2 is independently selected from H, halo, -CN, -SR^1, alkyl, cycloalkyl, haloalkyl, -OR^1, and -R^4;

each R^4 is independently selected from alkyl, $-CO_2R^1$, -(alkylene)-(CO_2R^1), hydroxyalkyl,



-(alkylene)($S(O)_t$)(alkyl), -(alkylene)(NR^5R^5), and ;

each R^5 is independently selected from H, alkyl, haloalkyl, arylalkyl, heteroarylalkyl, aryl, and heteroaryl;

R^{21}, R^{22}, R^{23}, and R^{24} are independently selected from H, halo, -CN, $-SR^1$, alkyl, cycloalkyl, haloalkyl, $-NR^1R^1$, and $-OR^1$;

each k is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

each m is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

each n is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

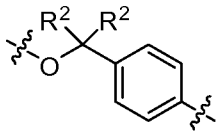
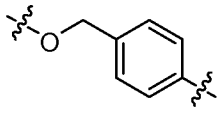
q is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

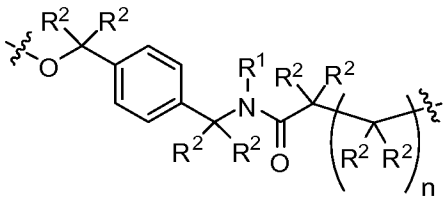
r is 3, 4, 5, 6, or 7;

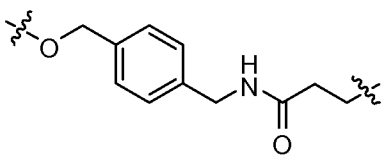
each s is independently selected from 0, 1, 2, 3, and 4;

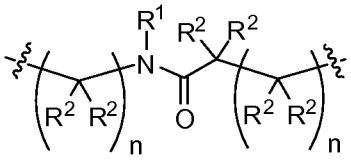
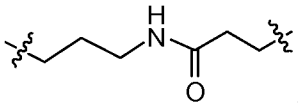
each t is independently selected from 0, 1, and 2; and

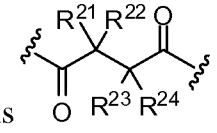
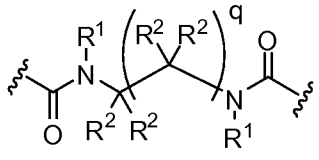
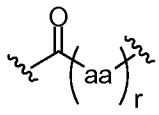
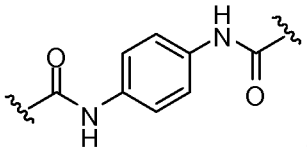
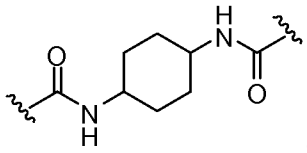
each u is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10.

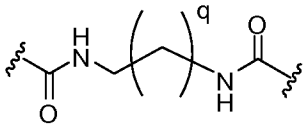
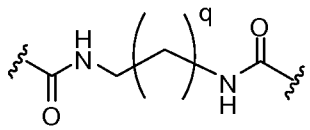
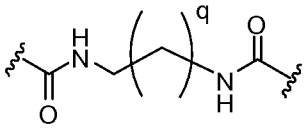
[00131] In some embodiments is a compound of Formula (II) wherein each J is the same. In some embodiments is a compound of Formula (II) wherein each J is . In some embodiments is a compound of Formula (II) wherein each J is . In some embodiments is a compound of Formula (II) wherein each J is

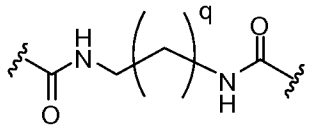
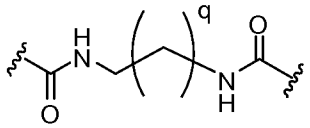
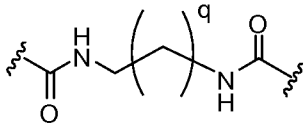


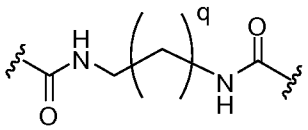
. In some embodiments is a compound of Formula (II) wherein each J is . In some embodiments is a compound of

Formula (II) wherein each J is . In some embodiments is a compound of Formula (II) wherein each J is . In some embodiments is a compound of Formula (II) wherein each J is a bond.

[00132] In some embodiments is a compound of Formula (II) wherein X is . In some embodiments is a compound of Formula (II) wherein X is . In some embodiments is a compound of Formula (II) wherein X is . In some embodiments is a compound of Formula (II) wherein X is . In some embodiments is a compound of Formula (II) wherein X is . In some embodiments is a compound of Formula (II) wherein X is alkylene. In some embodiments is a compound of Formula (II) wherein X is -C(O)-.

[00133] In some embodiments is a compound of Formula (II) wherein X is  and q is 1. In some embodiments is a compound of Formula (II) wherein X is  and q is 2. In some embodiments is a compound of Formula (II) wherein X is  and q is 3. In some embodiments is a

compound of Formula (II) wherein X is  and q is 4. In some embodiments is a compound of Formula (II) wherein X is  and q is 5. In some embodiments is a compound of Formula (II) wherein X is  and q is 6. In some embodiments is a compound of Formula (II) wherein X is

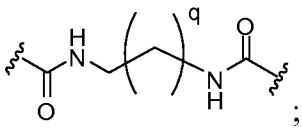
 and q is 7.

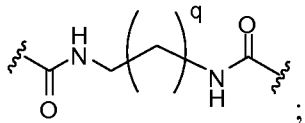
[00134] In some embodiments is a compound of Formula (II) wherein Z^1 is O; and Z^2 is O. In some embodiments is a compound of Formula (II) wherein Z^1 is O; and Z^2 is NH. In some embodiments is a compound of Formula (II) wherein Z^1 is CH_2; and Z^2 is O. In some embodiments is a compound of Formula (II) wherein Z^1 is CH_2; and Z^2 is NH.

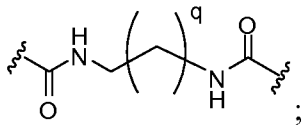
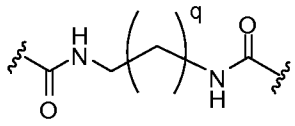
[00135] In some embodiments is a compound of Formula (II) wherein k is 1. In some embodiments is a compound of Formula (II) wherein k is 2. In some embodiments is a compound of Formula (II) wherein k is 3. In some embodiments is a compound of Formula (II) wherein k is 4. In some embodiments is a compound of Formula (II) wherein k is 5.

[00136] In some embodiments is a compound of Formula (II) wherein m is 0. In some embodiments is a compound of Formula (II) wherein m is 1. In some embodiments is a compound of Formula (II) wherein m is 2. In some embodiments is a compound of Formula (II) wherein m is 3. In some embodiments is a compound of Formula (II) wherein m is 4. In some embodiments is a compound of Formula (II) wherein m is 5. In some embodiments is a compound of Formula (II) wherein m is 6. In some embodiments is a compound of Formula (II) wherein m is 7.

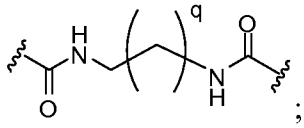
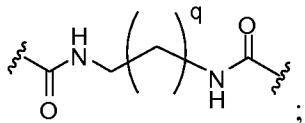
[00137] In some embodiments is a compound of Formula (II) wherein X is

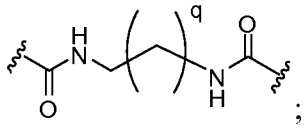
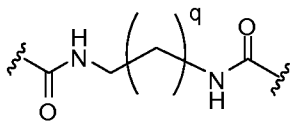
 ; q is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; Z^1 is O; Z^2 is O; each m is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10; and each k is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10. In some embodiments is a compound of Formula

(II) wherein X is  ; q is 1, 2, 3, 4, 5, or 6; Z^1 is O; Z^2 is O; each m is independently selected from 0, 1, 2, 3, 4, 5, and 6; and each k is independently selected from 1, 2, 3, 4, and 5. In some embodiments is a compound of Formula (II) wherein X is

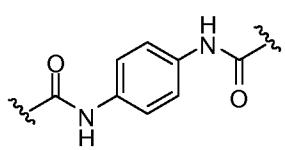
 ; q is 3, 4, or 5; Z^1 is O; Z^2 is O; each m is independently selected from 1, 2, 3, 4, and 5; and each k is independently selected from 1, 2, and 3. In some embodiments is a compound of Formula (II) wherein X is  ; q is 3, 4, or 5; Z^1 is O; Z^2 is O; each m is independently selected from 1, 2, 3, 4, and 5; and each k is 1.

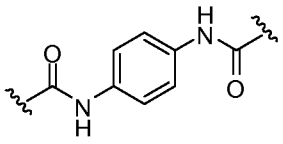
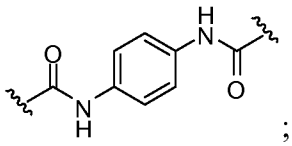
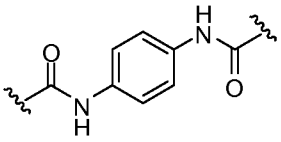
[00138] In some embodiments is a compound of Formula (II) wherein X is

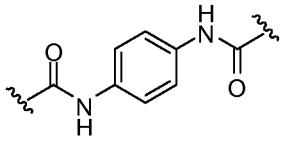
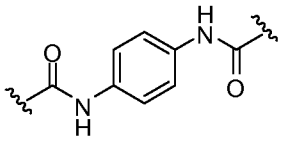
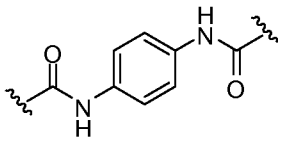
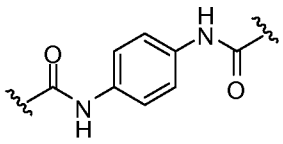
 ; q is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; Z^1 is O; Z^2 is NH; each m is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10; and each k is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10. In some embodiments is a compound of Formula (II) wherein X is  ; q is 1, 2, 3, 4, 5, or 6; Z^1 is O; Z^2 is NH; each m is independently selected from 0, 1, 2, 3, 4, 5, and 6; and each k is independently selected from 1, 2, 3, 4, and 5. In some embodiments is a compound of Formula (II) wherein X is

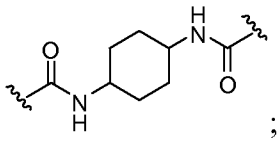
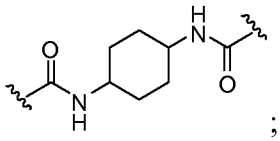
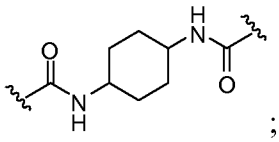
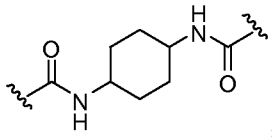
 ; q is 3, 4, or 5; Z^1 is O; Z^2 is NH; each m is independently selected from 1, 2, 3, 4, and 5; and each k is independently selected from 1, 2, and 3. In some embodiments is a compound of Formula (II) wherein X is  ; q is 3, 4, or 5; Z^1 is O; Z^2 is NH; each m is independently selected from 1, 2, 3, 4, and 5; and each k is 1.

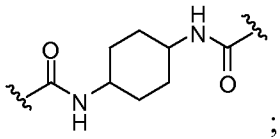
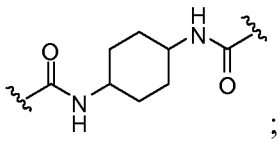
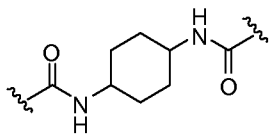
[00139] In some embodiments is a compound of Formula (II) wherein X is

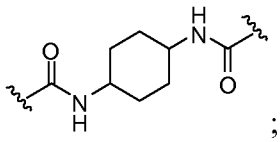
 ; Z^1 is O; Z^2 is O; each m is independently selected from 0, 1, 2, 3, 4, 5, 6,

7, 8, 9, and 10; and each k is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10. In some embodiments is a compound of Formula (II) wherein X is  ; Z^1 is O; Z^2 is O; each m is independently selected from 0, 1, 2, 3, 4, 5, and 6; and each k is independently selected from 1, 2, 3, 4, and 5. In some embodiments is a compound of Formula (II) wherein X is  ; Z^1 is O; Z^2 is O; each m is independently selected from 1, 2, 3, 4, and 5; and each k is independently selected from 1, 2, and 3. In some embodiments is a compound of Formula (II) wherein X is  ; Z^1 is O; Z^2 is O; each m is independently selected from 1, 2, 3, 4, and 5; and each k is 1.

[00140] In some embodiments is a compound of Formula (II) wherein X is  ; Z^1 is O; Z^2 is NH; each m is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10; and each k is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10. In some embodiments is a compound of Formula (II) wherein X is  ; Z^1 is O; Z^2 is NH; each m is independently selected from 0, 1, 2, 3, 4, 5, and 6; and each k is independently selected from 1, 2, 3, 4, and 5. In some embodiments is a compound of Formula (II) wherein X is  ; Z^1 is O; Z^2 is NH; each m is independently selected from 1, 2, 3, 4, and 5; and each k is independently selected from 1, 2, and 3. In some embodiments is a compound of Formula (II) wherein X is  ; Z^1 is O; Z^2 is NH; each m is independently selected from 1, 2, 3, 4, and 5; and each k is 1.

[00141] In some embodiments is a compound of Formula (II) wherein X is ; Z^1 is O; Z^2 is O; each m is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10; and each k is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10. In some embodiments is a compound of Formula (II) wherein X is ; Z^1 is O; Z^2 is O; each m is independently selected from 0, 1, 2, 3, 4, 5, and 6; and each k is independently selected from 1, 2, 3, 4, and 5. In some embodiments is a compound of Formula (II) wherein X is ; Z^1 is O; Z^2 is O; each m is independently selected from 1, 2, 3, 4, and 5; and each k is independently selected from 1, 2, and 3. In some embodiments is a compound of Formula (II) wherein X is ; Z^1 is O; Z^2 is O; each m is independently selected from 1, 2, 3, 4, and 5; and each k is 1.

[00142] In some embodiments is a compound of Formula (II) wherein X is ; Z^1 is O; Z^2 is NH; each m is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10; and each k is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10. In some embodiments is a compound of Formula (II) wherein X is ; Z^1 is O; Z^2 is NH; each m is independently selected from 0, 1, 2, 3, 4, 5, and 6; and each k is independently selected from 1, 2, 3, 4, and 5. In some embodiments is a compound of Formula (II) wherein X is ; Z^1 is O; Z^2 is NH; each m is independently selected from 1, 2, 3, 4, and 5; and each k is independently selected from 1, 2, and 3. In some

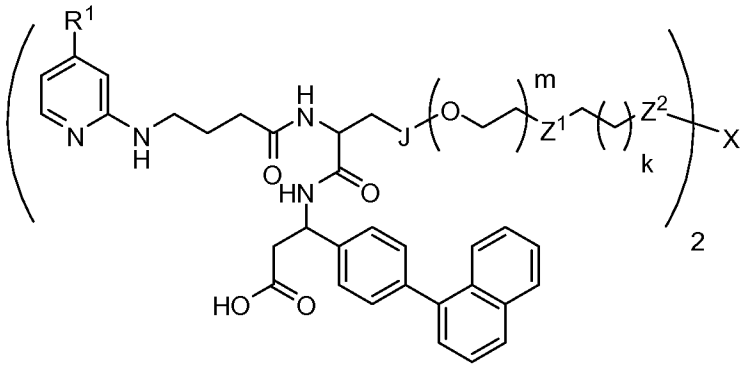
embodiments is a compound of Formula (II) wherein X is  ; Z^1 is O; Z^2 is NH; each m is independently selected from 1, 2, 3, 4, and 5; and each k is 1.

[00143] In some embodiments is a compound of Formula (II) wherein X is alkylene; Z^1 is O; Z^2 is O; each m is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10; and each k is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10. In some embodiments is a compound of Formula (II) wherein X is alkylene; Z^1 is O; Z^2 is O; each m is independently selected from 0, 1, 2, 3, 4, 5, and 6; and each k is independently selected from 1, 2, 3, 4, and 5. In some embodiments is a compound of Formula (II) wherein X is alkylene; Z^1 is O; Z^2 is O; each m is independently selected from 1, 2, 3, 4, and 5; and each k is independently selected from 1, 2, and 3. In some embodiments is a compound of Formula (II) wherein X is alkylene; Z^1 is O; Z^2 is O; each m is independently selected from 1, 2, 3, 4, and 5; and each k is 1.

[00144] In some embodiments is a compound of Formula (II) wherein X is alkylene; Z^1 is O; Z^2 is NH; each m is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10; and each k is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10. In some embodiments is a compound of Formula (II) wherein X is alkylene; Z^1 is O; Z^2 is NH; each m is independently selected from 0, 1, 2, 3, 4, 5, and 6; and each k is independently selected from 1, 2, 3, 4, and 5. In some embodiments is a compound of Formula (II) wherein X is alkylene; Z^1 is O; Z^2 is NH; each m is independently selected from 1, 2, 3, 4, and 5; and each k is independently selected from 1, 2, and 3. In some embodiments is a compound of Formula (II) wherein X is alkylene; Z^1 is O; Z^2 is NH; each m is independently selected from 1, 2, 3, 4, and 5; and each k is 1.

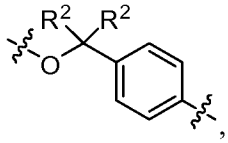
[00145] In some embodiments is a compound of Formula (II) wherein X is -C(O)-; Z^1 is O; Z^2 is NH; each m is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10; and each k is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10. In some embodiments is a compound of Formula (II) wherein X is -C(O)-; Z^1 is O; Z^2 is NH; each m is independently selected from 0, 1, 2, 3, 4, 5, and 6; and each k is independently selected from 1, 2, 3, 4, and 5. In some embodiments is a compound of Formula (II) wherein X is -C(O)-; Z^1 is O; Z^2 is NH; each m is independently selected from 1, 2, 3, 4, and 5; and each k is independently selected from 1, 2, and 3. In some embodiments is a compound of Formula (II) wherein X is -C(O)-; Z^1 is O; Z^2 is NH; each m is independently selected from 1, 2, 3, 4, and 5; and each k is 1.

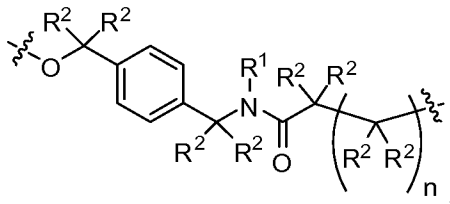
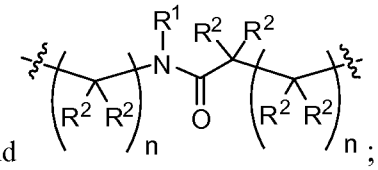
[00146] In another embodiment, provided herein is a compound of Formula (IIa), or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, metabolite, deuteride, N-oxide, tautomer, stereoisomer, or isomer thereof, having the structure:

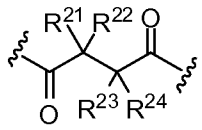
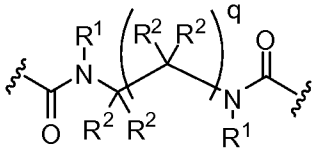
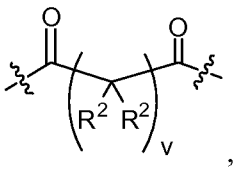


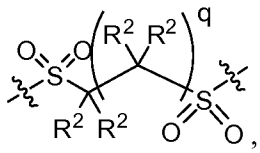
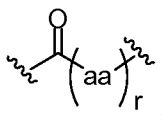
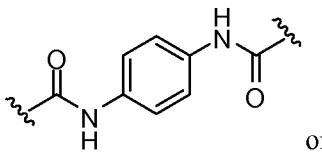
Formula (IIa);

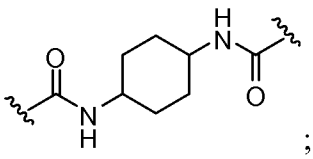
wherein:

each J is independently selected from a bond, ,

 and ;

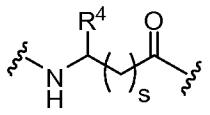
X is alkylene, -C(O)-, , , ,

, ,  or

;

Z^1 is O or CR^2R^2;

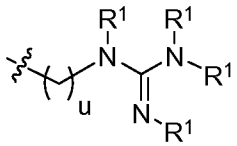
Z^2 is O or NH;

aa is ;

each R^1 is independently selected from H and alkyl;

each R^2 is independently selected from H, halo, -CN, -SR^1, alkyl, cycloalkyl, haloalkyl, -OR^1, and -R^4;

each R^4 is independently selected from alkyl, $-CO_2R^1$, -(alkylene)-(CO_2R^1), hydroxyalkyl,



-(alkylene)$(S(O)_t)$(alkyl), -(alkylene)(NR^5R^5), and ;

each R^5 is independently selected from H, alkyl, haloalkyl, arylalkyl, heteroarylalkyl, aryl, and heteroaryl;

R^{21}, R^{22}, R^{23}, and R^{24} are independently selected from H, halo, -CN, $-SR^1$, alkyl, cycloalkyl, haloalkyl, $-NR^1R^1$, and $-OR^1$;

each k is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

each m is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

each n is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

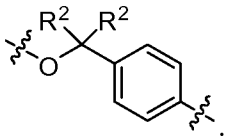
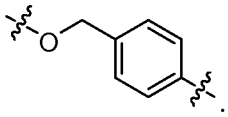
q is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

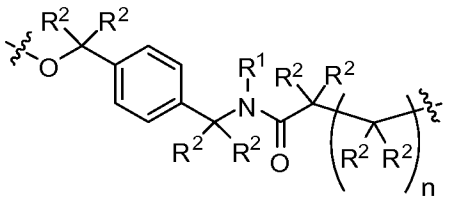
r is 3, 4, 5, 6, or 7;

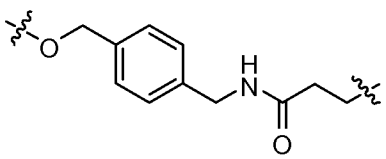
each s is independently selected from 0, 1, 2, 3, and 4;

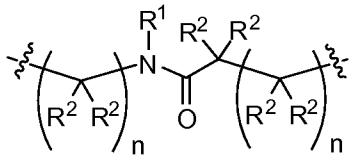
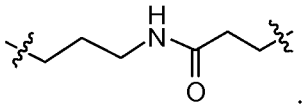
each t is independently selected from 0, 1, and 2; and

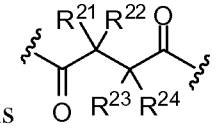
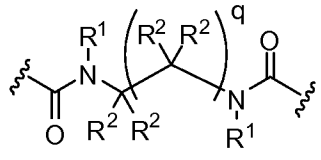
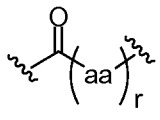
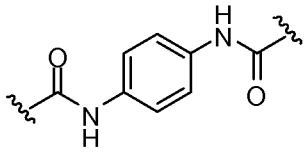
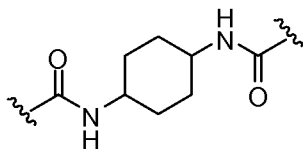
each u is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10.

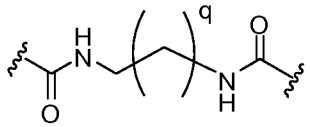
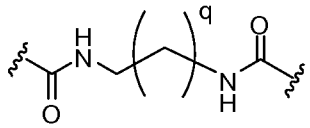
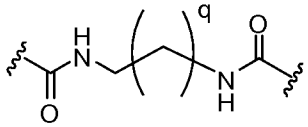
[00147] In some embodiments is a compound of Formula (IIa) wherein each J is the same. In some embodiments is a compound of Formula (IIa) wherein each J is . In some embodiments is a compound of Formula (IIa) wherein each J is . In some embodiments is a compound of Formula (IIa) wherein each J is

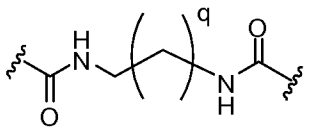
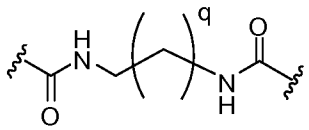
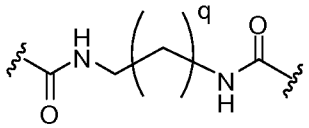
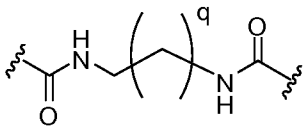


. In some embodiments is a compound of Formula (IIa) wherein each J is . In some embodiments is a compound of

Formula (IIa) wherein each J is . In some embodiments is a compound of Formula (IIa) wherein each J is . In some embodiments is a compound of Formula (IIa) wherein each J is a bond.

[00148] In some embodiments is a compound of Formula (IIa) wherein X is . In some embodiments is a compound of Formula (IIa) wherein X is . In some embodiments is a compound of Formula (IIa) wherein X is . In some embodiments is a compound of Formula (IIa) wherein X is . In some embodiments is a compound of Formula (IIa) wherein X is . In some embodiments is a compound of Formula (IIa) wherein X is alkylene. In some embodiments is a compound of Formula (IIa) wherein X is -C(O)-.

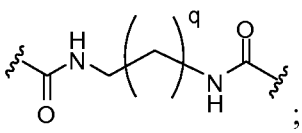
[00149] In some embodiments is a compound of Formula (IIa) wherein X is  and q is 1. In some embodiments is a compound of Formula (IIa) wherein X is  and q is 2. In some embodiments is a compound of Formula (IIa) wherein X is  and q is 3. In some embodiments is a

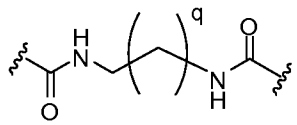
compound of Formula (IIa) wherein X is  and q is 4. In some embodiments is a compound of Formula (IIa) wherein X is  and q is 5. In some embodiments is a compound of Formula (IIa) wherein X is  and q is 6. In some embodiments is a compound of Formula (IIa) wherein X is  and q is 7.

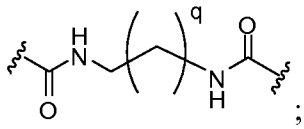
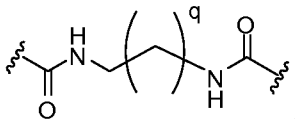
[00150] In some embodiments is a compound of Formula (IIa) wherein Z^1 is O; and Z^2 is O. In some embodiments is a compound of Formula (IIa) wherein Z^1 is O; and Z^2 is NH. In some embodiments is a compound of Formula (IIa) wherein Z^1 is CH_2; and Z^2 is O. In some embodiments is a compound of Formula (IIa) wherein Z^1 is CH_2; and Z^2 is NH.

[00151] In some embodiments is a compound of Formula (IIa) wherein k is 1. In some embodiments is a compound of Formula (IIa) wherein k is 2. In some embodiments is a compound of Formula (IIa) wherein k is 3. In some embodiments is a compound of Formula (IIa) wherein k is 4. In some embodiments is a compound of Formula (IIa) wherein k is 5.

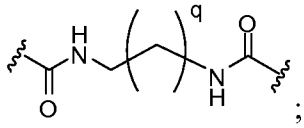
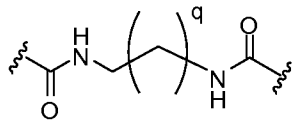
[00152] In some embodiments is a compound of Formula (IIa) wherein m is 0. In some embodiments is a compound of Formula (IIa) wherein m is 1. In some embodiments is a compound of Formula (IIa) wherein m is 2. In some embodiments is a compound of Formula (IIa) wherein m is 3. In some embodiments is a compound of Formula (IIa) wherein m is 4. In some embodiments is a compound of Formula (IIa) wherein m is 5. In some embodiments is a compound of Formula (IIa) wherein m is 6. In some embodiments is a compound of Formula (IIa) wherein m is 7.

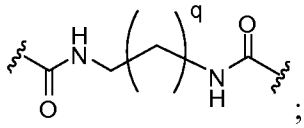
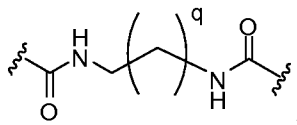
[00153] In some embodiments is a compound of Formula (IIa) wherein X is ; q is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; Z^1 is O; Z^2 is O; each m is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10; and each k is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10. In some embodiments is a compound of Formula

(IIa) wherein X is  ; q is 1, 2, 3, 4, 5, or 6; Z^1 is O; Z^2 is O; each m is independently selected from 0, 1, 2, 3, 4, 5, and 6; and each k is independently selected from 1, 2, 3, 4, and 5. In some embodiments is a compound of Formula (IIa) wherein X is

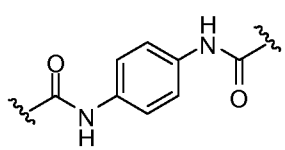
 ; q is 3, 4, or 5; Z^1 is O; Z^2 is O; each m is independently selected from 1, 2, 3, 4, and 5; and each k is independently selected from 1, 2, and 3. In some embodiments is a compound of Formula (IIa) wherein X is  ; q is 3, 4, or 5; Z^1 is O; Z^2 is O; each m is independently selected from 1, 2, 3, 4, and 5; and each k is 1.

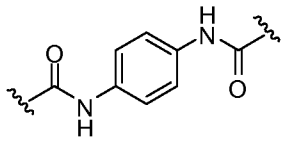
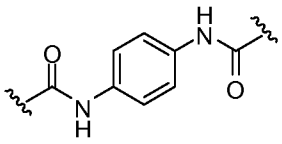
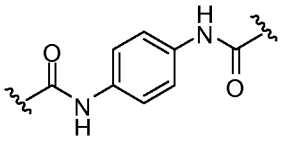
[00154] In some embodiments is a compound of Formula (IIa) wherein X is

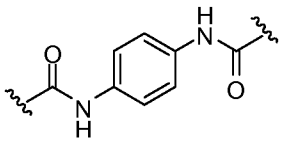
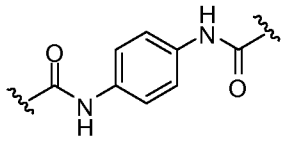
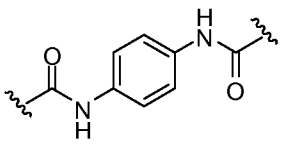
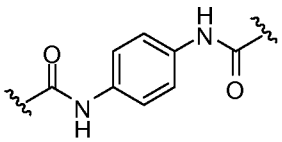
 ; q is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; Z^1 is O; Z^2 is NH; each m is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10; and each k is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10. In some embodiments is a compound of Formula (IIa) wherein X is  ; q is 1, 2, 3, 4, 5, or 6; Z^1 is O; Z^2 is NH; each m is independently selected from 0, 1, 2, 3, 4, 5, and 6; and each k is independently selected from 1, 2, 3, 4, and 5. In some embodiments is a compound of Formula (IIa) wherein X is

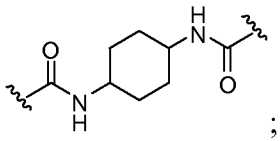
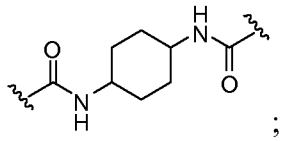
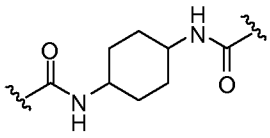
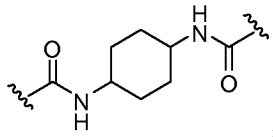
 ; q is 3, 4, or 5; Z^1 is O; Z^2 is NH; each m is independently selected from 1, 2, 3, 4, and 5; and each k is independently selected from 1, 2, and 3. In some embodiments is a compound of Formula (IIa) wherein X is  ; q is 3, 4, or 5; Z^1 is O; Z^2 is NH; each m is independently selected from 1, 2, 3, 4, and 5; and each k is 1.

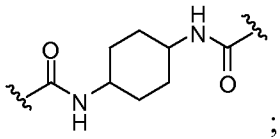
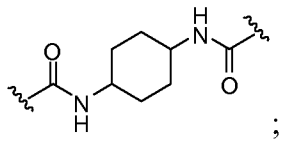
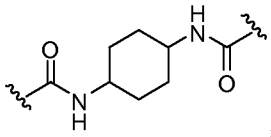
[00155] In some embodiments is a compound of Formula (IIa) wherein X is

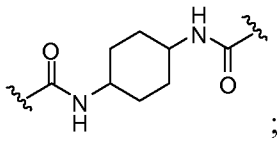
 ; Z^1 is O; Z^2 is O; each m is independently selected from 0, 1, 2, 3, 4, 5, 6,

7, 8, 9, and 10; and each k is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10. In some embodiments is a compound of Formula (IIa) wherein X is  ; Z^1 is O; Z^2 is O; each m is independently selected from 0, 1, 2, 3, 4, 5, and 6; and each k is independently selected from 1, 2, 3, 4, and 5. In some embodiments is a compound of Formula (IIa) wherein X is  ; Z^1 is O; Z^2 is O; each m is independently selected from 1, 2, 3, 4, and 5; and each k is independently selected from 1, 2, and 3. In some embodiments is a compound of Formula (IIa) wherein X is  ; Z^1 is O; Z^2 is O; each m is independently selected from 1, 2, 3, 4, and 5; and each k is 1.

[00156] In some embodiments is a compound of Formula (IIa) wherein X is  ; Z^1 is O; Z^2 is NH; each m is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10; and each k is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10. In some embodiments is a compound of Formula (IIa) wherein X is  ; Z^1 is O; Z^2 is NH; each m is independently selected from 0, 1, 2, 3, 4, 5, and 6; and each k is independently selected from 1, 2, 3, 4, and 5. In some embodiments is a compound of Formula (IIa) wherein X is  ; Z^1 is O; Z^2 is NH; each m is independently selected from 1, 2, 3, 4, and 5; and each k is independently selected from 1, 2, and 3. In some embodiments is a compound of Formula (IIa) wherein X is  ; Z^1 is O; Z^2 is NH; each m is independently selected from 1, 2, 3, 4, and 5; and each k is 1.

[00157] In some embodiments is a compound of Formula (IIa) wherein X is ; Z^1 is O; Z^2 is O; each m is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10; and each k is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10. In some embodiments is a compound of Formula (IIa) wherein X is ; Z^1 is O; Z^2 is O; each m is independently selected from 0, 1, 2, 3, 4, 5, and 6; and each k is independently selected from 1, 2, 3, 4, and 5. In some embodiments is a compound of Formula (IIa) wherein X is ; Z^1 is O; Z^2 is O; each m is independently selected from 1, 2, 3, 4, and 5; and each k is independently selected from 1, 2, and 3. In some embodiments is a compound of Formula (IIa) wherein X is ; Z^1 is O; Z^2 is O; each m is independently selected from 1, 2, 3, 4, and 5; and each k is 1.

[00158] In some embodiments is a compound of Formula (IIa) wherein X is ; Z^1 is O; Z^2 is NH; each m is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10; and each k is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10. In some embodiments is a compound of Formula (IIa) wherein X is ; Z^1 is O; Z^2 is NH; each m is independently selected from 0, 1, 2, 3, 4, 5, and 6; and each k is independently selected from 1, 2, 3, 4, and 5. In some embodiments is a compound of Formula (IIa) wherein X is ; Z^1 is O; Z^2 is NH; each m is independently selected from 1, 2, 3, 4, and 5; and each k is independently selected from 1, 2, and 3. In some

embodiments is a compound of Formula (IIa) wherein X is  ; Z^1 is O; Z^2 is NH; each m is independently selected from 1, 2, 3, 4, and 5; and each k is 1.

[00159] In some embodiments is a compound of Formula (IIa) wherein X is alkylene; Z^1 is O; Z^2 is O; each m is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10; and each k is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10. In some embodiments is a compound of Formula (IIa) wherein X is alkylene; Z^1 is O; Z^2 is O; each m is independently selected from 0, 1, 2, 3, 4, 5, and 6; and each k is independently selected from 1, 2, 3, 4, and 5. In some embodiments is a compound of Formula (IIa) wherein X is alkylene; Z^1 is O; Z^2 is O; each m is independently selected from 1, 2, 3, 4, and 5; and each k is independently selected from 1, 2, and 3. In some embodiments is a compound of Formula (IIa) wherein X is alkylene; Z^1 is O; Z^2 is O; each m is independently selected from 1, 2, 3, 4, and 5; and each k is 1.

[00160] In some embodiments is a compound of Formula (IIa) wherein X is alkylene; Z^1 is O; Z^2 is NH; each m is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10; and each k is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10. In some embodiments is a compound of Formula (IIa) wherein X is alkylene; Z^1 is O; Z^2 is NH; each m is independently selected from 0, 1, 2, 3, 4, 5, and 6; and each k is independently selected from 1, 2, 3, 4, and 5. In some embodiments is a compound of Formula (IIa) wherein X is alkylene; Z^1 is O; Z^2 is NH; each m is independently selected from 1, 2, 3, 4, and 5; and each k is independently selected from 1, 2, and 3. In some embodiments is a compound of Formula (IIa) wherein X is alkylene; Z^1 is O; Z^2 is NH; each m is independently selected from 1, 2, 3, 4, and 5; and each k is 1.

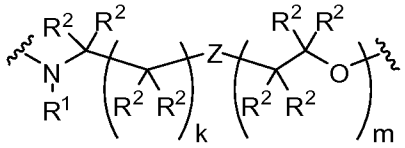
[00161] In some embodiments is a compound of Formula (IIa) wherein X is -C(O)-; Z^1 is O; Z^2 is NH; each m is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10; and each k is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10. In some embodiments is a compound of Formula (IIa) wherein X is -C(O)-; Z^1 is O; Z^2 is NH; each m is independently selected from 0, 1, 2, 3, 4, 5, and 6; and each k is independently selected from 1, 2, 3, 4, and 5. In some embodiments is a compound of Formula (IIa) wherein X is -C(O)-; Z^1 is O; Z^2 is NH; each m is independently selected from 1, 2, 3, 4, and 5; and each k is independently selected from 1, 2, and 3. In some embodiments is a compound of Formula (IIa) wherein X is -C(O)-; Z^1 is O; Z^2 is NH; each m is independently selected from 1, 2, 3, 4, and 5; and each k is 1.

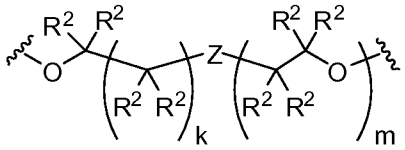
[00162] In another aspect, provided herein is a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, metabolite, deuteride, N-oxide, tautomer, stereoisomer, or isomer thereof, having the structure:

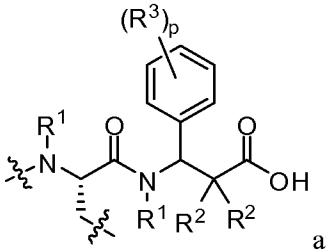
$Y^1-L^1-B^1-J^1-A^1-X-A^2-J^2-B^2-L^2-Y^2$

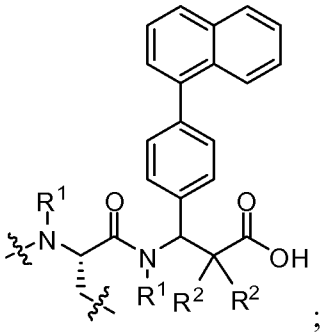
Formula (III);

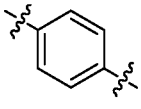
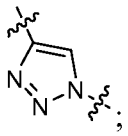
wherein:

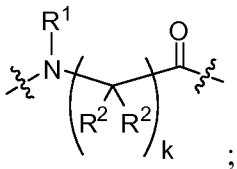
A^1 and A^2 are independently selected from:  and

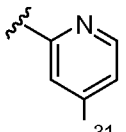
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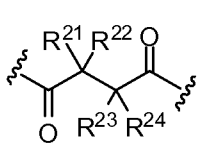
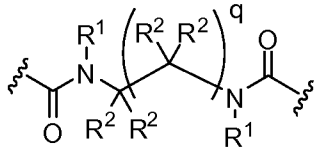
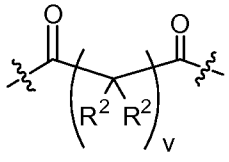
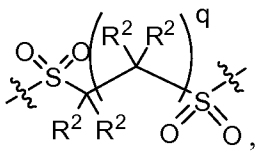
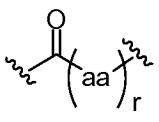
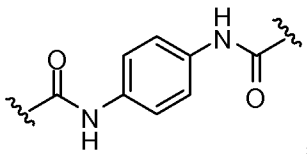
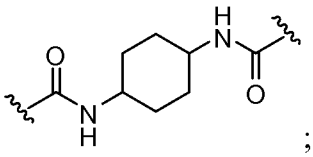
B^1 and B^2 are independently selected from:  and

;

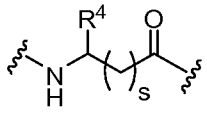
J^1 and J^2 are independently selected from , and ;

L^1 and L^2 are independently selected from: ;

Y^1 and Y^2 are independently selected from: ;

X is alkylene, -C(O)-, -C(O)C(O)-, , , , , , , or ;

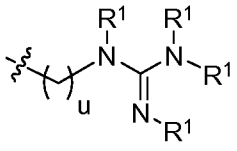
Z is O or CR^2R^2;

aa is ;

each R^1 is independently selected from H, alkyl, haloalkyl, arylalkyl, and heteroarylalkyl;

each R^2 is independently selected from H, halo, -CN, $-SR^1$, alkyl, cycloalkyl, haloalkyl, $-OR^1$, and $-R^4$;

each R^3 is independently selected from halo, alkyl, -CN, haloalkyl, $-OR^1$, and $-NR^1R^1$;

each R^4 is independently selected from $-CO_2R^1$, -(alkylene)-(CO_2R^1), hydroxyalkyl, -(alkylene)($S(O)_t$)(alkyl), -(alkylene)(NR^5R^5), and ;

each R^5 is independently selected from H, alkyl, haloalkyl, arylalkyl, heteroarylalkyl, aryl, and heteroaryl;

R^{21}, R^{22}, R^{23}, and R^{24} are independently selected from H, halo, -CN, $-SR^1$, alkyl, cycloalkyl, haloalkyl, $-NR^1R^1$, and $-OR^1$;

each R^{31} is independently selected from H and alkyl;

each k is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

each m is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

each p is independently selected from 0, 1, 2, 3, and 4;

q is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

r is 3, 4, 5, 6, or 7;

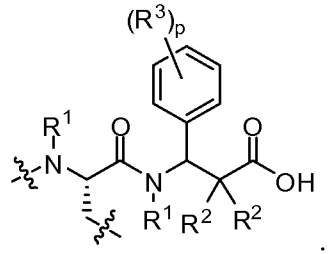
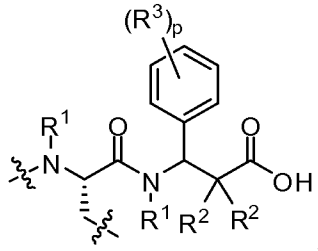
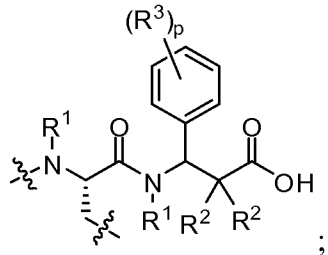
each s is independently selected from 0, 1, 2, 3, and 4;

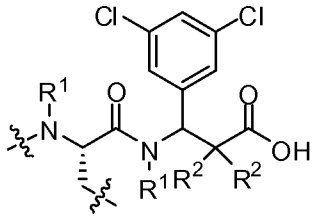
each t is independently selected from 0, 1, and 2;

each u is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10; and

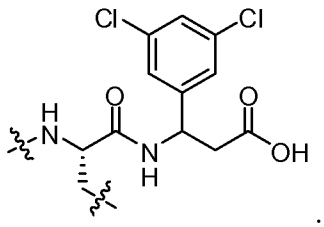
v is selected from 3, 4, 5, 6, 7, 8, 9, and 10.

[00163] In some embodiments described above or below of a compound of Formula (III), Y^1 and Y^2 are the same. In some embodiments described above or below of a compound of Formula (III), Y^1 and Y^2 are the same and R^{31} is H. In some embodiments described above or below of a compound of Formula (III), Y^1 and Y^2 are the same and R^{31} is alkyl. In some embodiments described above or below of a compound of Formula (III), Y^1 and Y^2 are the same and R^{31} is $-CH_3$. In some embodiments described above or below of a compound of Formula (III), Y^1 and Y^2 are the same and R^{31} is $-CH_2CH_3$.

[00164] In some embodiments described above or below of a compound of Formula (III), B^1 and B^2 are the same. In some embodiments described above or below of a compound of Formula (III), B^1 and B^2 are both . In certain embodiments described above or below of a compound of Formula (III), p is 0. In certain embodiments described above or below of a compound of Formula (III), p is 1. In certain embodiments described above or below of a compound of Formula (III), p is 2. In some embodiments described above or below of a compound of Formula (III), B^1 and B^2 are both ; p is 2 and each R^3 is halo. In some embodiments described above or below of a compound of Formula (III), B^1 and B^2 are both ; p is 2 and each R^3 is chloro. In some embodiments described above or below of a compound of Formula (III), B^1 and B^2 are both

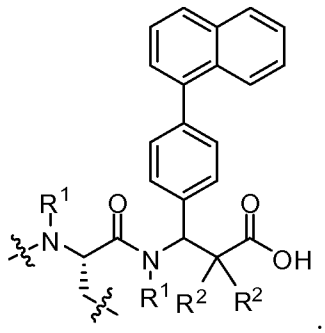


. In some embodiments described above or below of a compound of Formula (III), B^1 and B^2 are both

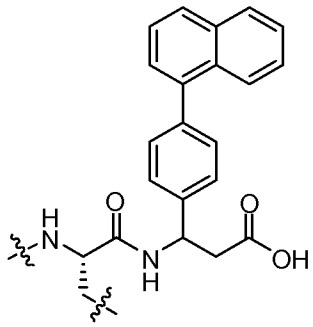


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[00165] In some embodiments described above or below of a compound of Formula (III), B^1 and B^2 are both

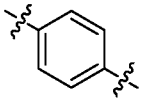


. In some embodiments described above or below of a compound of Formula (III), B^1 and B^2 are both

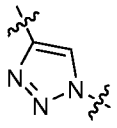


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[00166] In some embodiments described above or below of a compound of Formula (III), J^1 and J^2 are the same. In some embodiments described above or below of a compound of Formula (III), J^1 and J^2 are both

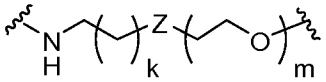


. In some embodiments described above or below of a compound of Formula (III), J^1 and J^2 are both



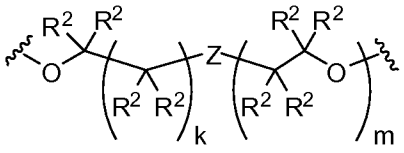
.

[00167] In some embodiments described above or below of a compound of Formula (III), A^1 and A^2 are the same. In some embodiments described above or below of a compound of Formula (III), A^1 and A^2 are both



. In some embodiments described

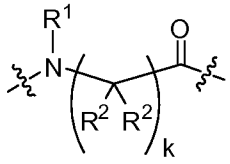
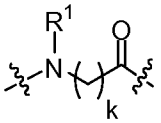
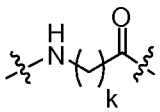
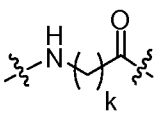
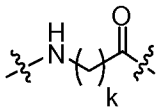
above or below of a compound of Formula (III), A^1 and A^2 are both

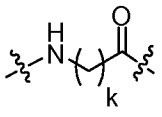
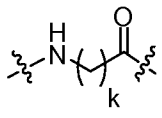


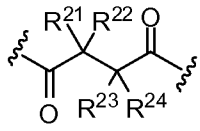
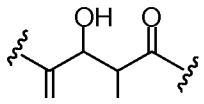
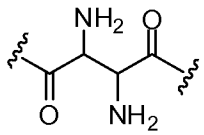
[00168] In some embodiments described above or below of a compound of Formula (III), Z is O. In certain embodiments described above or below of a compound of Formula (III), each k is independently 1, 2, or 3. In certain embodiments described above or below of a compound of Formula (III), each k is 1. In certain embodiments described above or below of a compound of Formula (III), each m is independently 0, 1, 2, or 3. In certain embodiments described above or below of a compound of Formula (III), each m is 0. In certain embodiments described above or below of a compound of Formula (III), each m is 1. In certain embodiments described above or below of a compound of Formula (III), each m is 2. In certain embodiments described above or below of a compound of Formula (III), each m is 3.

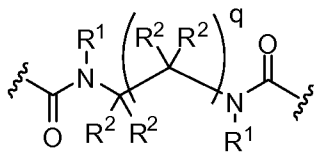
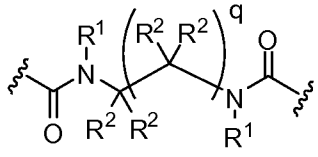
[00169] In some embodiments described above or below of a compound of Formula (III), Z is CR^2R^2. In some embodiments described above or below of a compound of Formula (III), Z is CH_2.

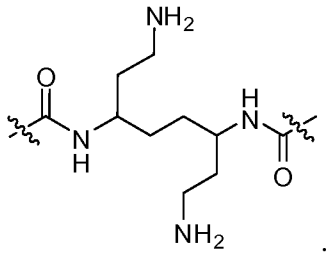
[00170] In some embodiments described above or below of a compound of Formula (III), L^1 and L^2 are the same.

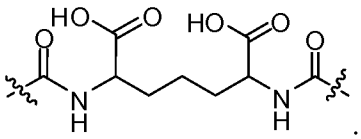
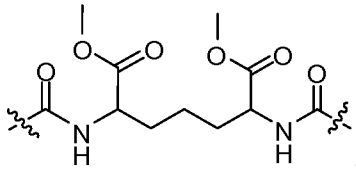
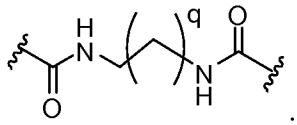
[00171] In some embodiments described above or below of a compound of Formula (III), L^1 and L^2 are both . In some embodiments described above or below of a compound of Formula (III), L^1 and L^2 are both . In some embodiments described above or below of a compound of Formula (III), L^1 and L^2 are both . In some embodiments described above or below of a compound of Formula (III), L^1 and L^2 are both  and k is 2. In some embodiments described above or below of a compound of Formula (III), L^1 and L^2 are both  and k is 3. In some embodiments described above

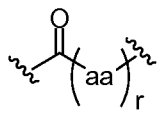
or below of a compound of Formula (III), L^1 and L^2 are both  and k is 4. In some embodiments described above or below of a compound of Formula (III), L^1 and L^2 are both  and k is 5.

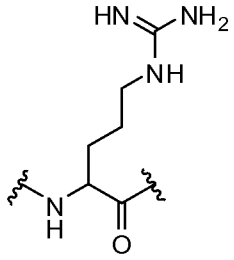
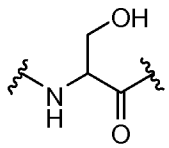
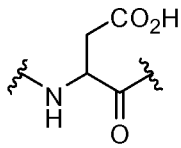
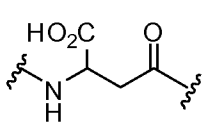
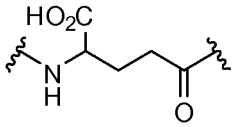
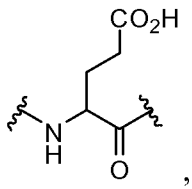
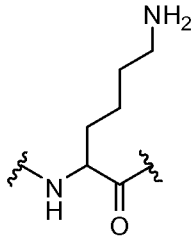
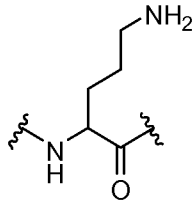
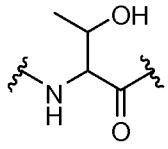
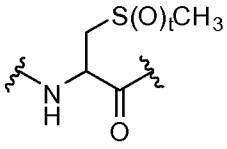
[00172] In some embodiments described above or below of a compound of Formula (III), X is . In some embodiments described above or below of a compound of Formula (III), R^{21} and R^{23} are the same and R^{22} and R^{24} are the same. In certain embodiments described above or below of a compound of Formula (III), X is . In certain embodiments described above or below of a compound of Formula (III), X is . In some embodiments described above or below of a compound of Formula (III), R^{21} and R^{22} are the same. In some embodiments described above or below of a compound of Formula (III), R^{23} and R^{24} are the same. In some embodiments described above or below of a compound of Formula (III), R^{21}, R^{22}, R^{23}, and R^{24} are the same.

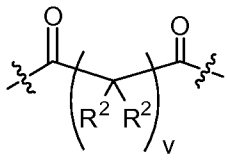
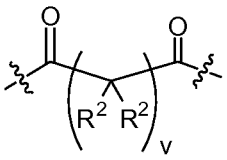
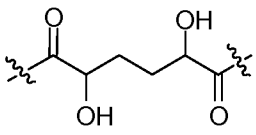
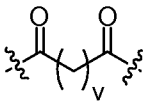
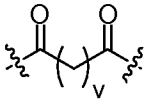
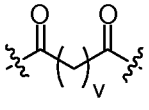
[00173] In some embodiments described above or below of a compound of Formula (III), X is . In some embodiments described above or below of a compound of Formula (III), X is ; each R^2 is independently selected from H, alkyl, -OH, $-CO_2H$, $-CO_2$alkyl, and -(alkylene)(NH_2); and q is 1, 2, 3, 4, 5, or 6. In certain embodiments described above or below of a compound of Formula (III), X is

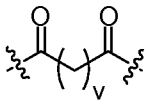
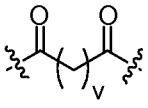


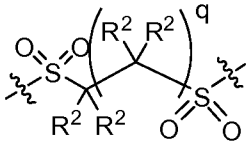
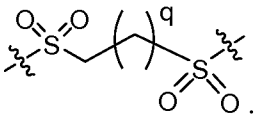
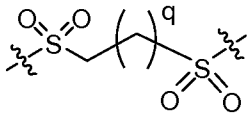
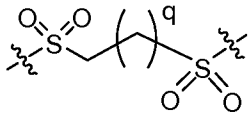
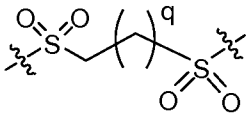
. In certain embodiments described above or below of a compound of Formula (III), X is . In certain embodiments described above or below of a compound of Formula (III), X is . In certain embodiments described above or below of a compound of Formula (III), X is . In certain embodiments described above or below of a compound of Formula (III), q is 1, 2, 3, 4, 5, or 6. In certain embodiments described above or below of a compound of Formula (III), q is 1. In certain embodiments described above or below of a compound of Formula (III), q is 2. In certain embodiments described above or below of a compound of Formula (III), q is 3. In certain embodiments described above or below of a compound of Formula (III), q is 4. In certain embodiments described above or below of a compound of Formula (III), q is 5. In certain embodiments described above or below of a compound of Formula (III), q is 6.

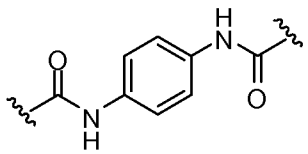
[00174] In some embodiments described above or below of a compound of Formula (III), X is . In certain embodiments described above or below of a compound of Formula (III), aa is selected from:

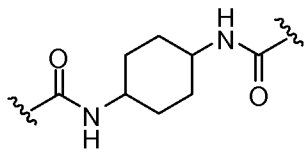









, and . In some embodiments described above or below of a compound of Formula (III), r is 4, 5, or 6.

[00175] In some embodiments described above or below of a compound of Formula (III), X is . In some embodiments described above or below of a compound of Formula (III), X is  and each R^2 is independently selected from H, alkyl, -OH, $-CO_2H$, $-CO_2$alkyl, and -(alkylene)(NH_2). In certain embodiments described above or below of a compound of Formula (III), X is . In certain embodiments described above or below of a compound of Formula (III), X is . In certain embodiments described above or below of a compound of Formula (III), X is  and v is 3. In certain embodiments described above or below of a compound of Formula (III), X is  and v is 4. In certain embodiments described above or below of a compound of Formula (III), X is

 and v is 5. In certain embodiments described above or below of a compound of Formula (III), X is  and v is 6.

[00176] In some embodiments described above or below of a compound of Formula (III), X is . In certain embodiments described above or below of a compound of Formula (III), X is . In certain embodiments described above or below of a compound of Formula (III), X is  and q is 2. In certain embodiments described above or below of a compound of Formula (III), X is  and q is 3. In certain embodiments described above or below of a compound of Formula (III), X is  and q is 4.

[00177] In some embodiments described above or below of a compound of Formula (III), X is .

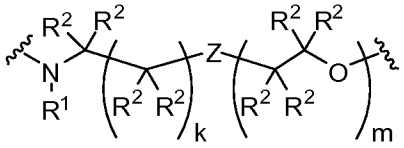
[00178] In some embodiments described above or below of a compound of Formula (III), X is .

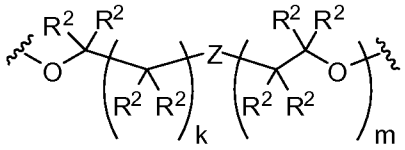
[00179] In another aspect, provided herein is a compound of Formula (IV), or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, metabolite, deuteride, N-oxide, tautomer, stereoisomer, or isomer thereof, having the structure:

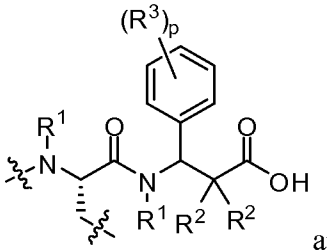
$$Y^1-L^1-B^1-J^1-A^1-X-A^2-J^2-B^2-L^2-Y^2$$

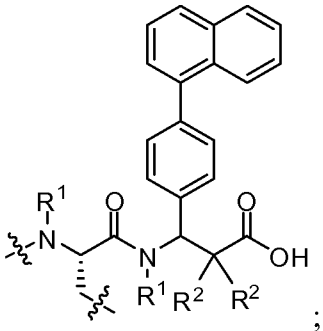
Formula (IV);

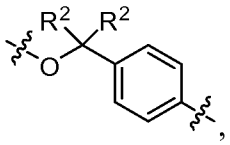
wherein:

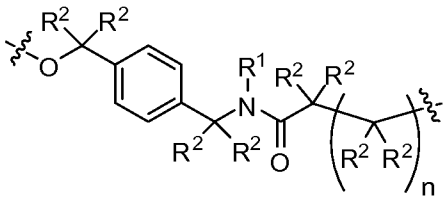
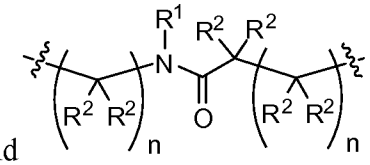
A^1 and A^2 are independently selected from:  and

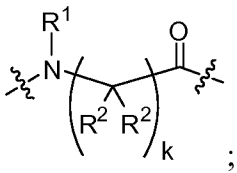
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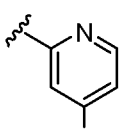
B^1 and B^2 are independently selected from:  and

;

J^1 and J^2 are independently selected from a bond, ,

 , and ;

L^1 and L^2 are independently selected from: ;

Y^1 and Y^2 are independently selected from: ;

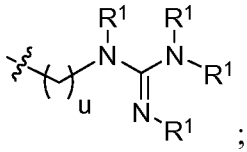
X is -C(O)C(O)-;

Z is O or CR^2R^2;

each R^1 is independently selected from H, alkyl, haloalkyl, arylalkyl, and heteroarylalkyl;

each R^2 is independently selected from H, halo, -CN, -SR^1, alkyl, cycloalkyl, haloalkyl, -OR^1, and -R^4;

each R^3 is independently selected from halo, alkyl, -CN, haloalkyl, -OR^1, and -NR^1R^1;

each R^4 is independently selected from -CO_2R^1, -(alkylene)-(CO_2R^1), hydroxyalkyl, -(alkylene)($S(O)_t$)(alkyl), -(alkylene)(NR^5R^5), and  ;

each R^5 is independently selected from H, alkyl, haloalkyl, arylalkyl, heteroarylalkyl, aryl, and heteroaryl;

R^{21}, R^{22}, R^{23}, and R^{24} are independently selected from H, halo, -CN, -SR^1, alkyl, cycloalkyl, haloalkyl, -NR^1R^1, and -OR^1;

each R^{31} is independently selected from H and alkyl;

each k is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

each m is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

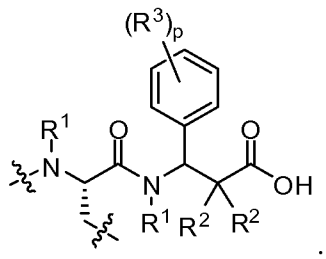
each n is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

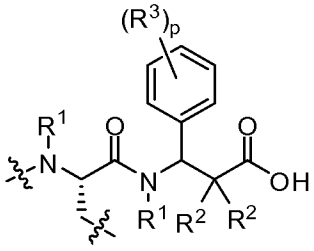
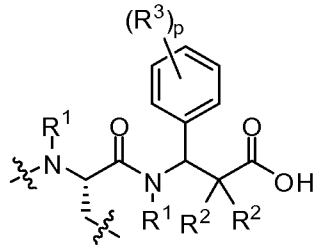
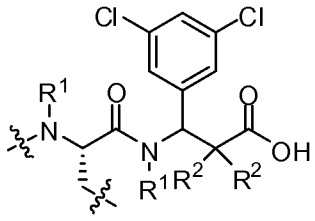
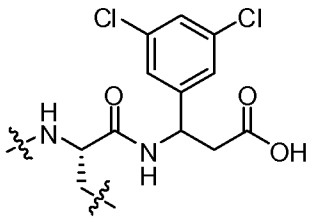
each p is independently selected from 0, 1, 2, 3, and 4;

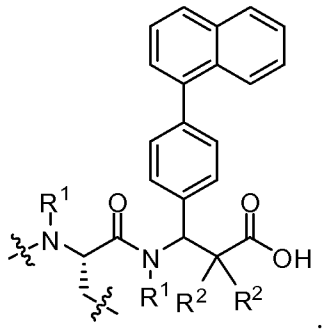
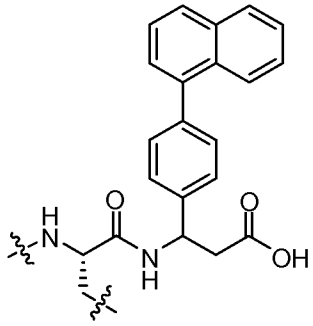
each t is independently selected from 0, 1, and 2; and

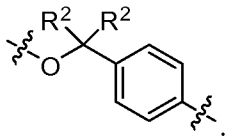
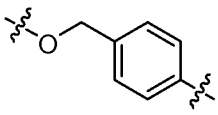
each u is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10.

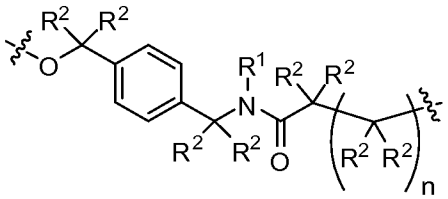
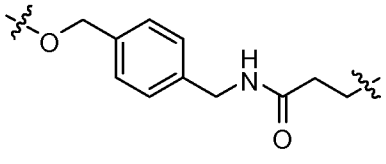
[00180] In some embodiments described above or below of a compound of Formula (IV), Y^1 and Y^2 are the same. In some embodiments described above or below of a compound of Formula (IV), Y^1 and Y^2 are the same and R^{31} is H. In some embodiments described above or below of a compound of Formula (IV), Y^1 and Y^2 are the same and R^{31} is alkyl. In some embodiments described above or below of a compound of Formula (IV), Y^1 and Y^2 are the same and R^{31} is -CH_3. In some embodiments described above or below of a compound of Formula (IV), Y^1 and Y^2 are the same and R^{31} is -CH_2CH_3.

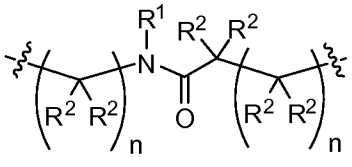
[00181] In some embodiments described above or below of a compound of Formula (IV), B^1 and B^2 are the same. In some embodiments described above or below of a compound of Formula (IV), B^1 and B^2 are both  . In certain embodiments described

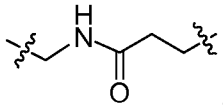
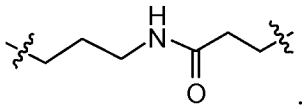
above or below of a compound of Formula (IV), p is 0. In certain embodiments described above or below of a compound of Formula (IV), p is 1. In certain embodiments described above or below of a compound of Formula (IV), p is 2. In some embodiments described above or below of a compound of Formula (IV), B^1 and B^2 are both ; p is 2 and each R^3 is halo. In some embodiments described above or below of a compound of Formula (IV), B^1 and B^2 are both ; p is 2 and each R^3 is chloro. In some embodiments described above or below of a compound of Formula (IV), B^1 and B^2 are both . In some embodiments described above or below of a compound of Formula (IV), B^1 and B^2 are both .

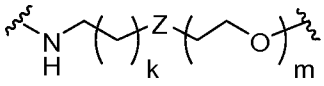
[00182] In some embodiments described above or below of a compound of Formula (IV), B^1 and B^2 are both . In some embodiments described above or below of a compound of Formula (IV), B^1 and B^2 are both .

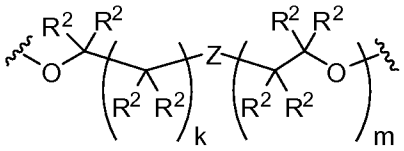
[00183] In some embodiments described above or below of a compound of Formula (I), J^1 and J^2 are the same. In some embodiments described above or below of a compound of Formula (I), J^1 and J^2 are both . In some embodiments described above or below of a compound of Formula (I), J^1 and J^2 are both . In some embodiments described above or below of a compound of Formula (I), J^1 and J^2 are both

. In some embodiments described above or below of a compound of Formula (I), J^1 and J^2 are both . In some embodiments described above or below of a compound of Formula (I), J^1 and J^2 are both

. In some embodiments described above or below of a compound of

Formula (I), J^1 and J^2 are both . In some embodiments described above or below of a compound of Formula (I), J^1 and J^2 are both . In some embodiments described above or below of a compound of Formula (I), J^1 and J^2 are both a bond.

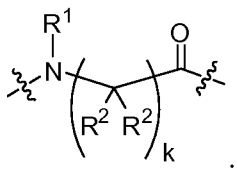
[00184] In some embodiments described above or below of a compound of Formula (IV), A^1 and A^2 are the same. In some embodiments described above or below of a compound of Formula (IV), A^1 and A^2 are both . In some embodiments described above or below of a compound of Formula (IV), A^1 and A^2 are both

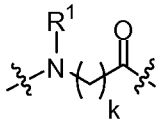
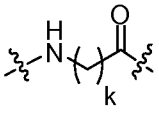
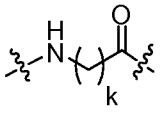
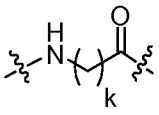
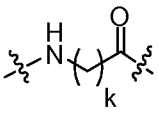
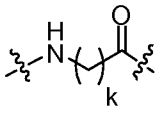
.

[00185] In some embodiments described above or below of a compound of Formula (IV), Z is O. In certain embodiments described above or below of a compound of Formula (IV), each k is independently 1, 2, or 3. In certain embodiments described above or below of a compound of Formula (IV), each k is 1. In certain embodiments described above or below of a compound of Formula (IV), each m is independently 0, 1, 2, or 3. In certain embodiments described above or below of a compound of Formula (IV), each m is 0. In certain embodiments described above or below of a compound of Formula (IV), each m is 1. In certain embodiments described above or below of a compound of Formula (IV), each m is 2. In certain embodiments described above or below of a compound of Formula (IV), each m is 3.

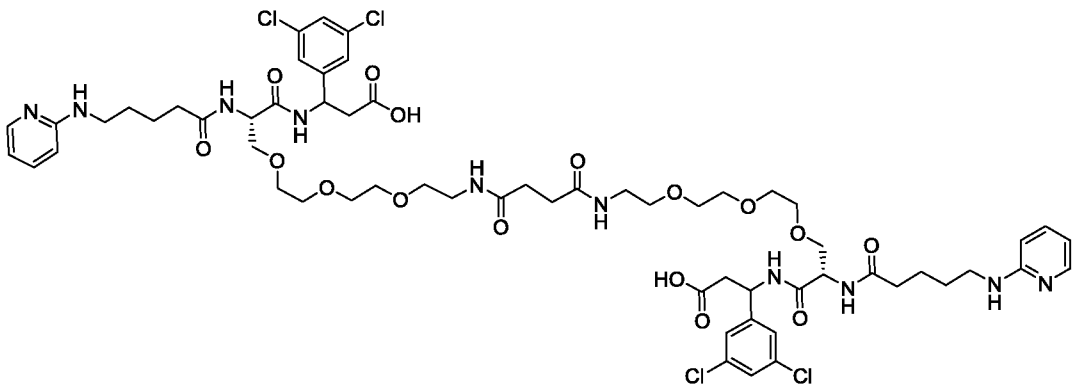
[00186] In some embodiments described above or below of a compound of Formula (IV), Z is CR^2R^2. In some embodiments described above or below of a compound of Formula (IV), Z is CH_2.

[00187] In some embodiments described above or below of a compound of Formula (IV), L^1 and L^2 are the same.

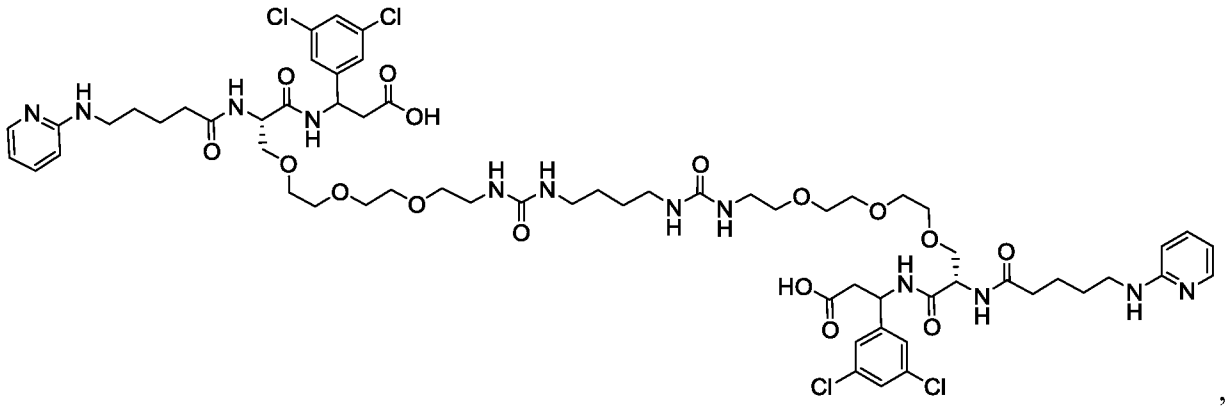
[00188] In some embodiments described above or below of a compound of Formula (IV), L^1 and L^2 are both . In some embodiments described above or below of a

compound of Formula (IV), L^1 and L^2 are both . In some embodiments described above or below of a compound of Formula (IV), L^1 and L^2 are both . In some embodiments described above or below of a compound of Formula (IV), L^1 and L^2 are both  and k is 2. In some embodiments described above or below of a compound of Formula (IV), L^1 and L^2 are both  and k is 3. In some embodiments described above or below of a compound of Formula (IV), L^1 and L^2 are both  and k is 4. In some embodiments described above or below of a compound of Formula (IV), L^1 and L^2 are both  and k is 5.

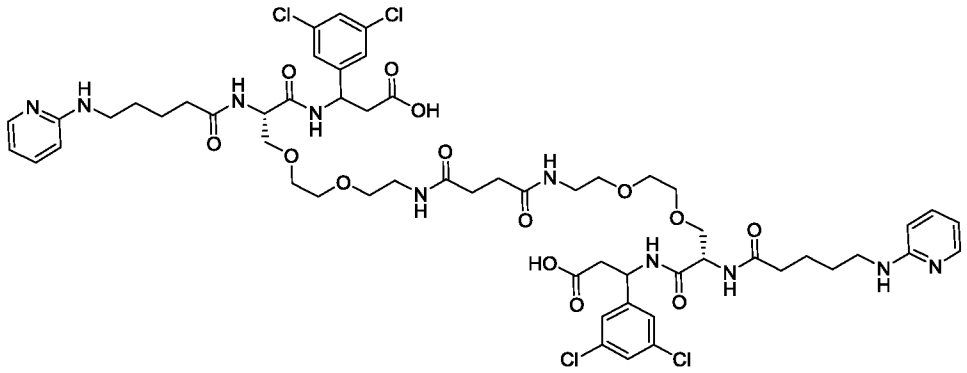
[00189] In some embodiments, provided herein are compounds, or pharmaceutically acceptable salts, solvates, polymorphs, prodrugs, metabolites, N-oxides, tautomers, stereoisomers, or isomers thereof, selected from:



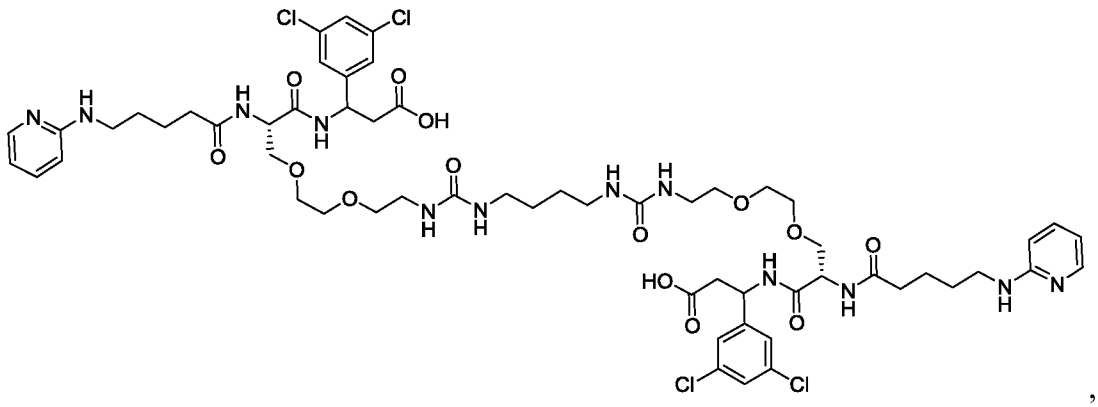
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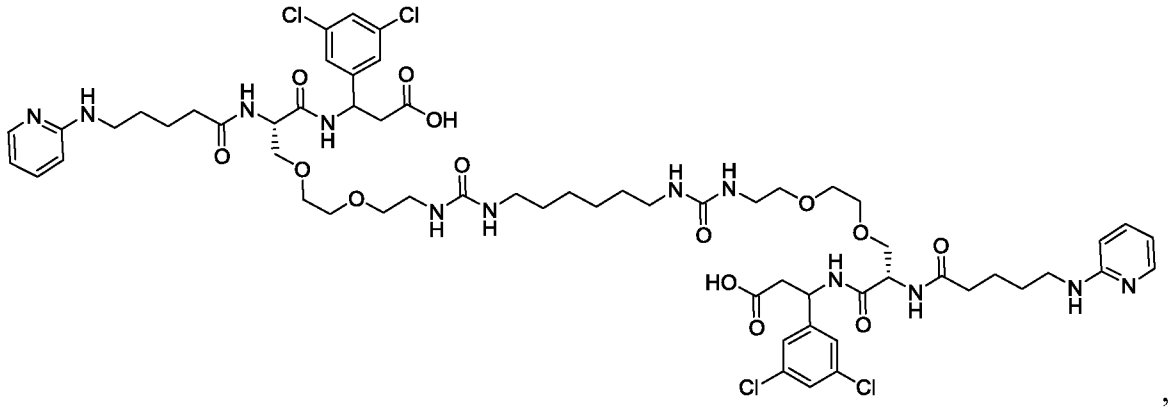
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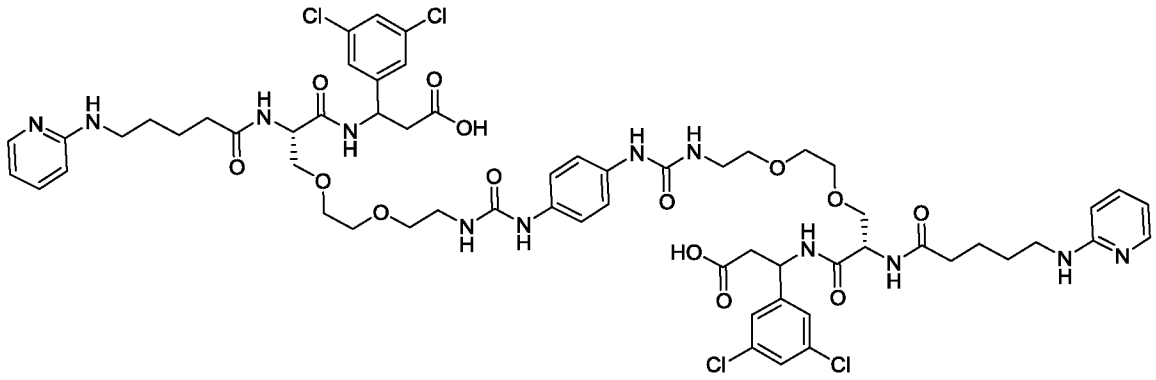
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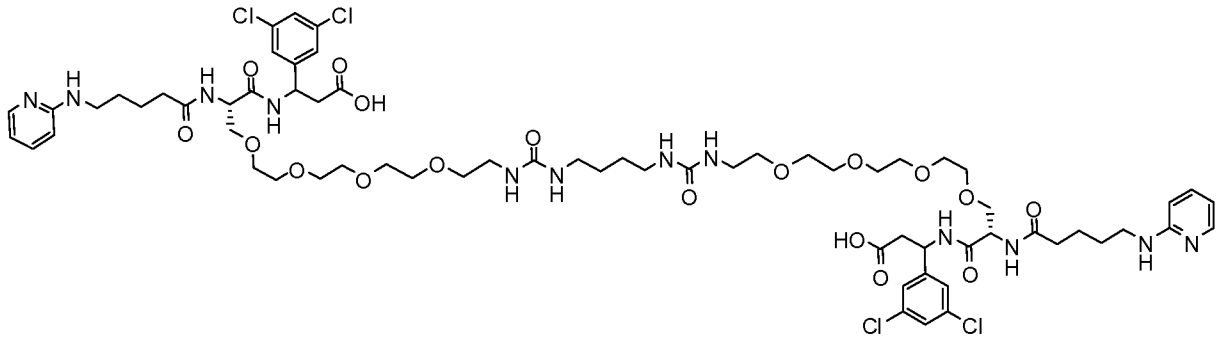
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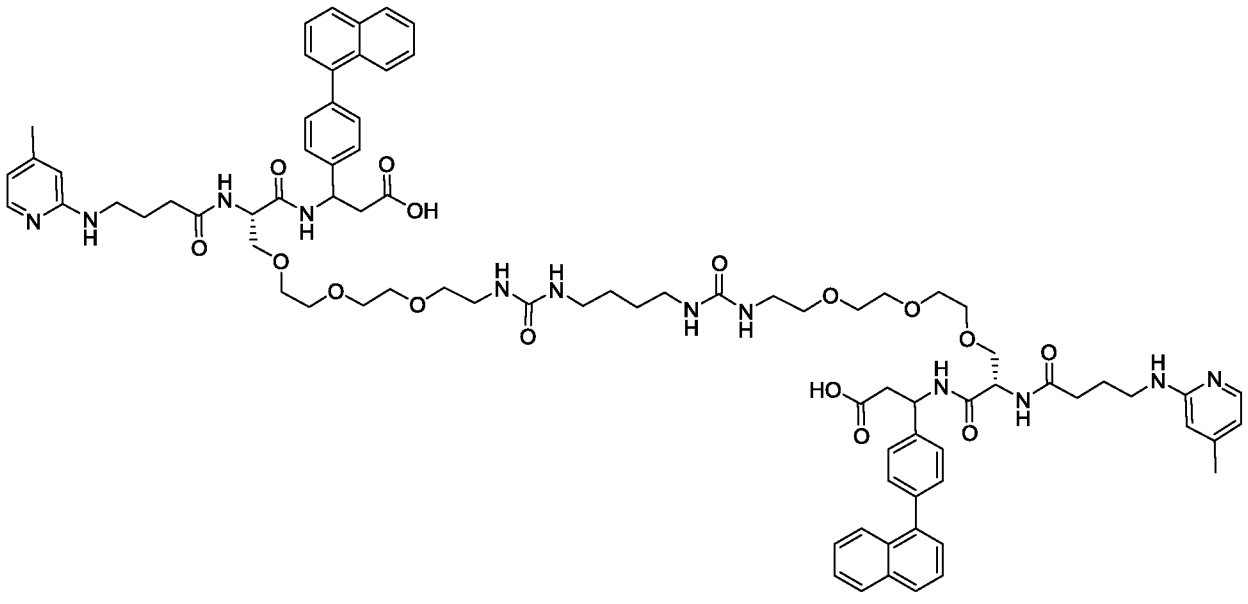
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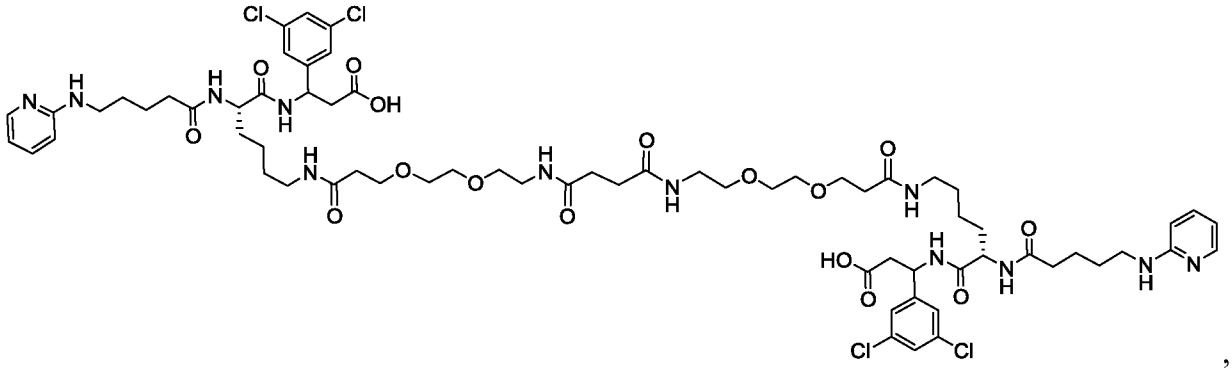
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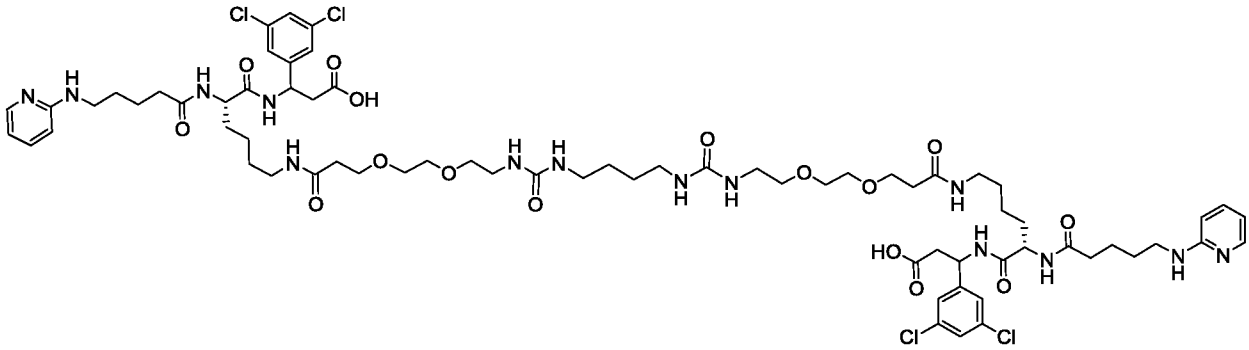
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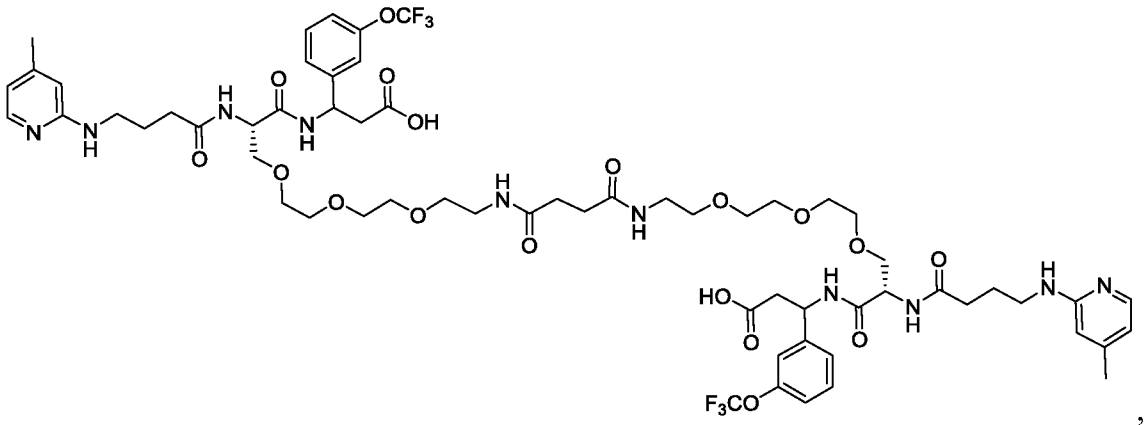


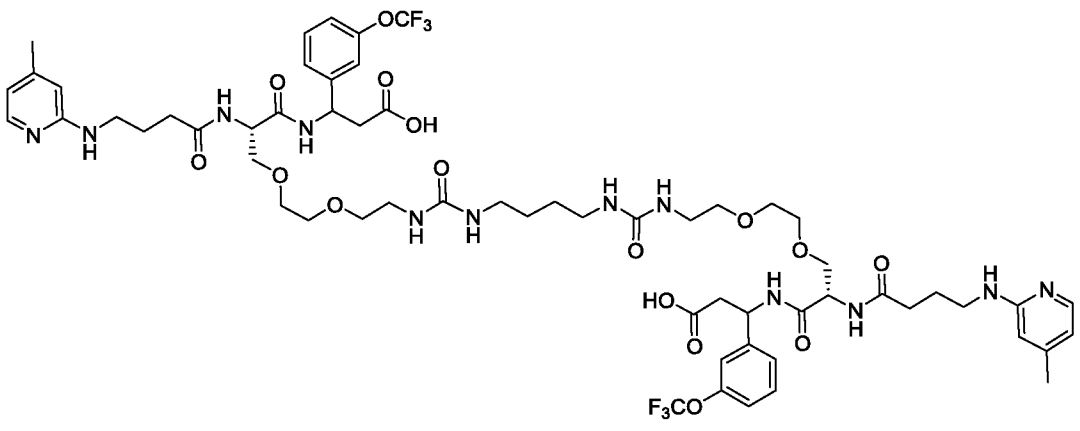
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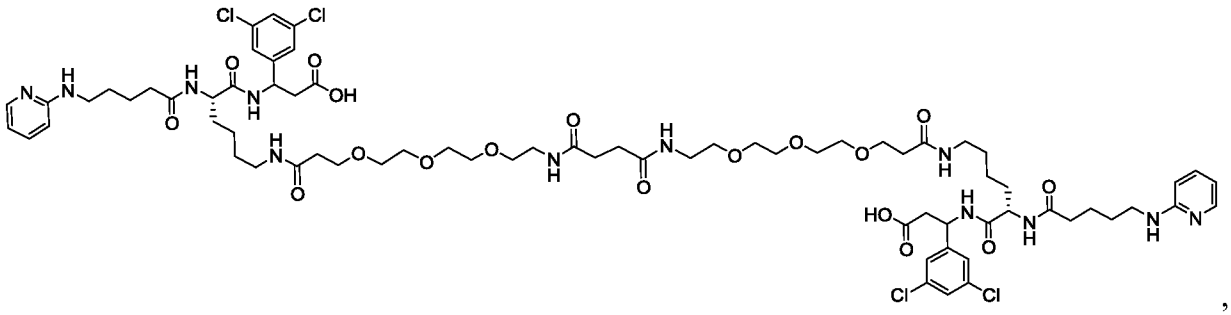


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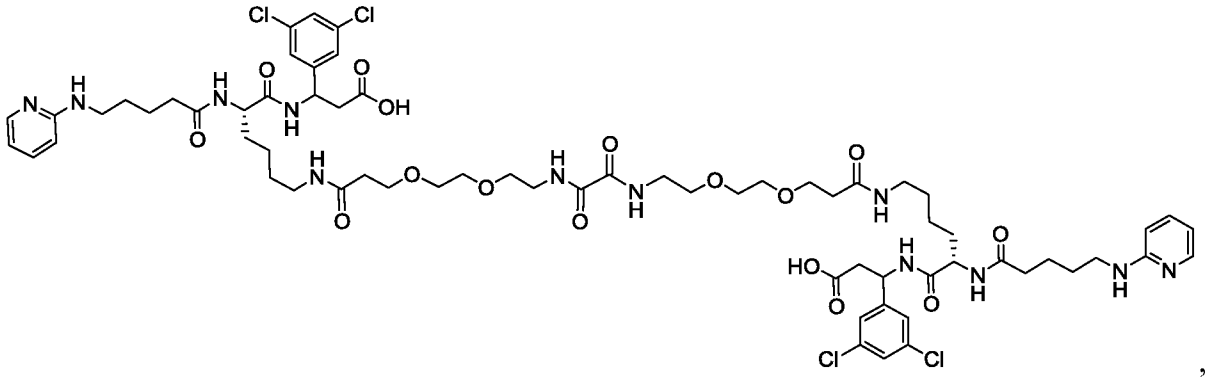
[00190] In some embodiments, provided herein are compounds, or pharmaceutically acceptable salts, solvates, polymorphs, prodrugs, metabolites, N-oxides, tautomers, stereoisomers, or isomers thereof, selected from:



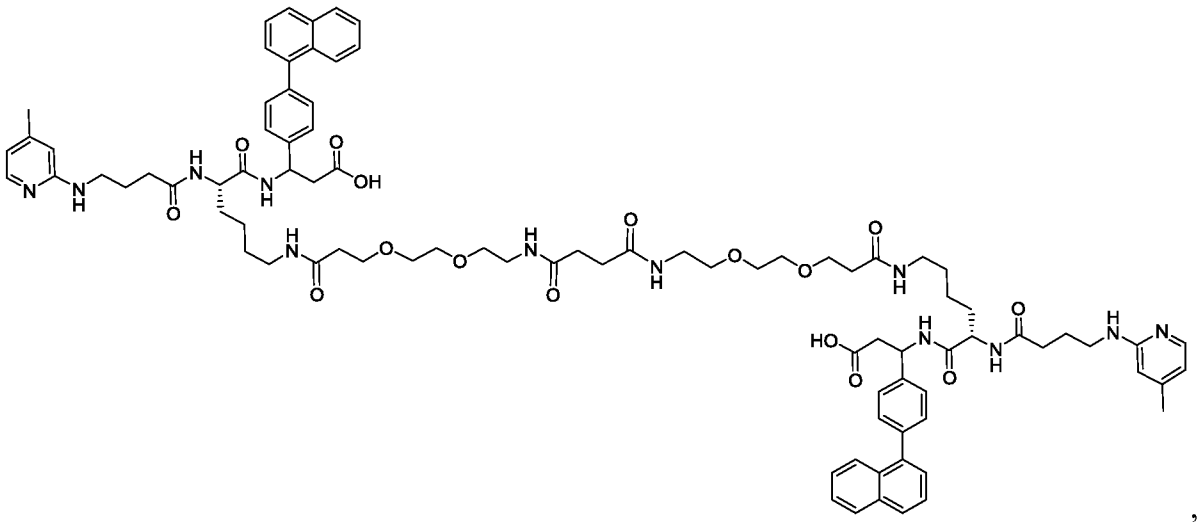




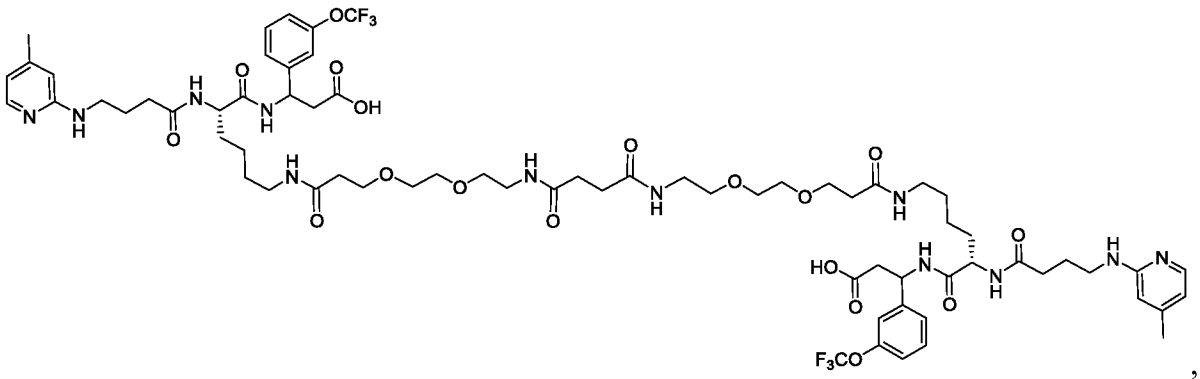
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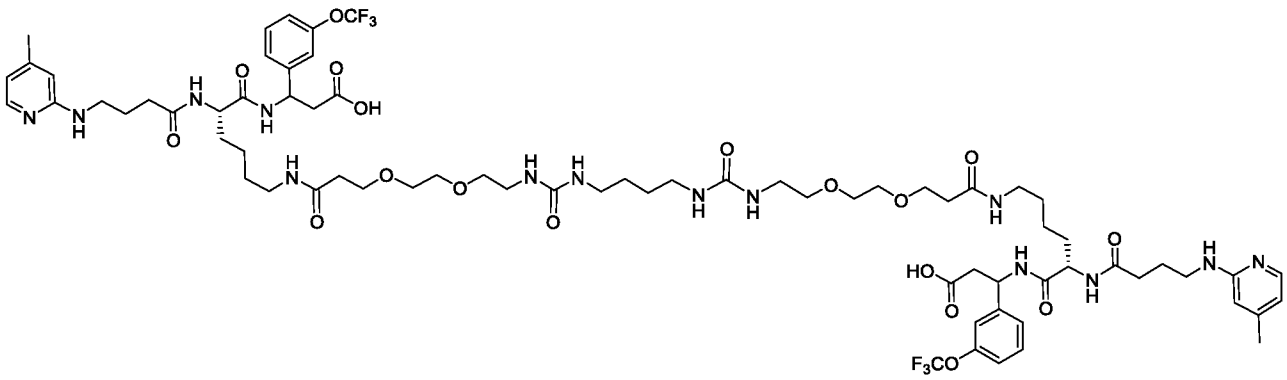
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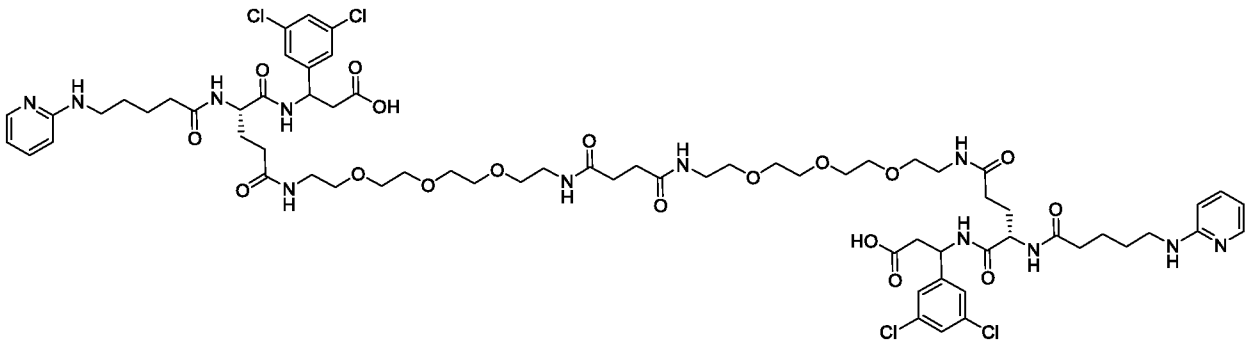
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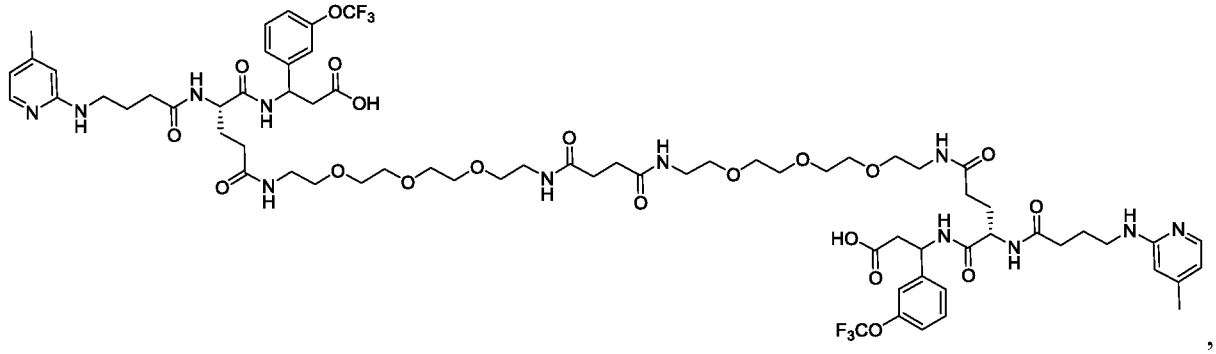


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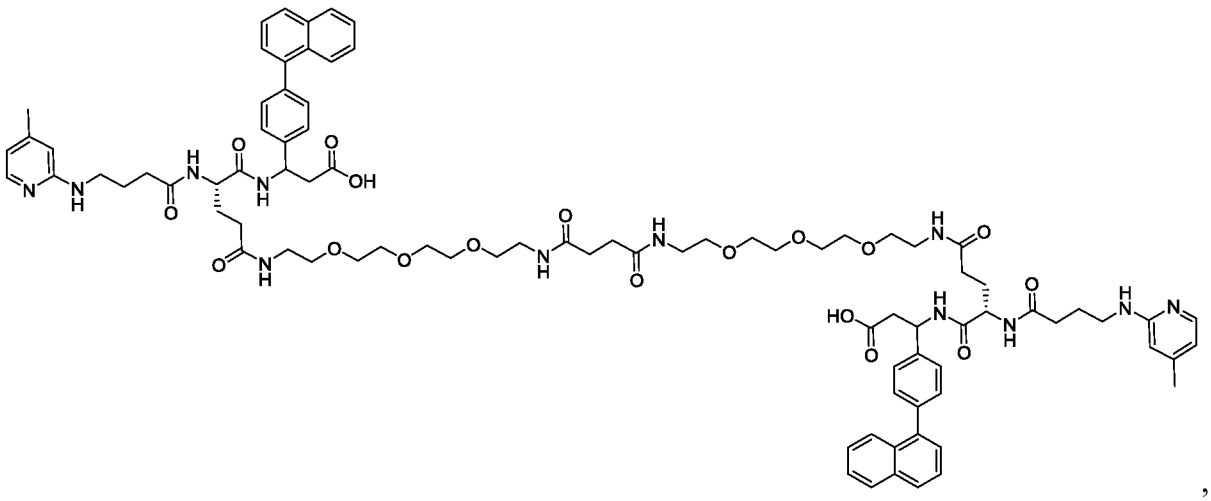
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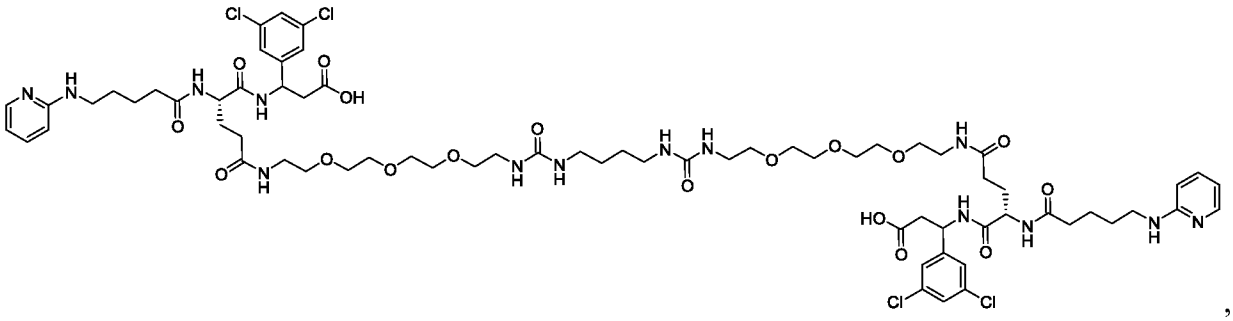


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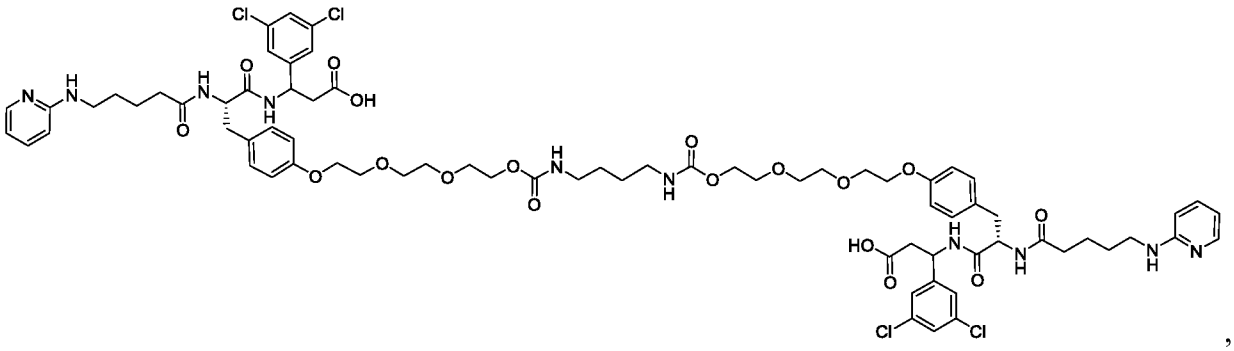
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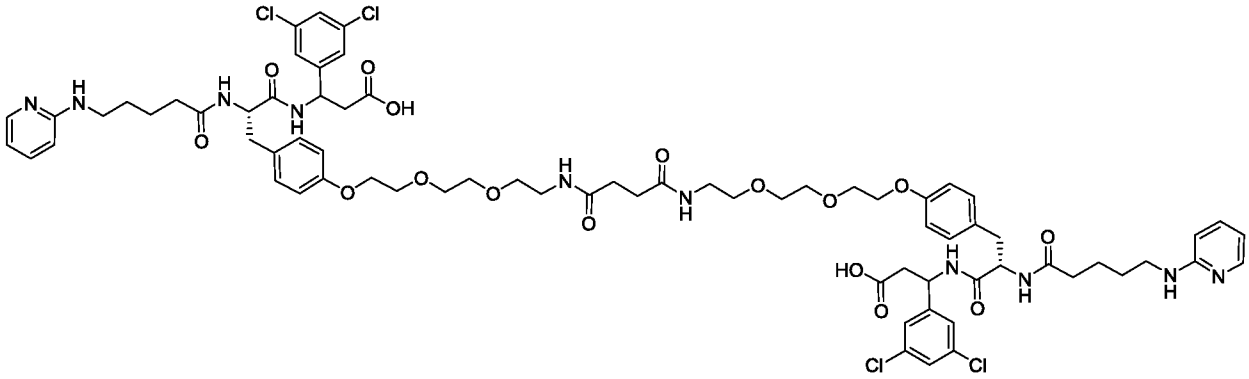
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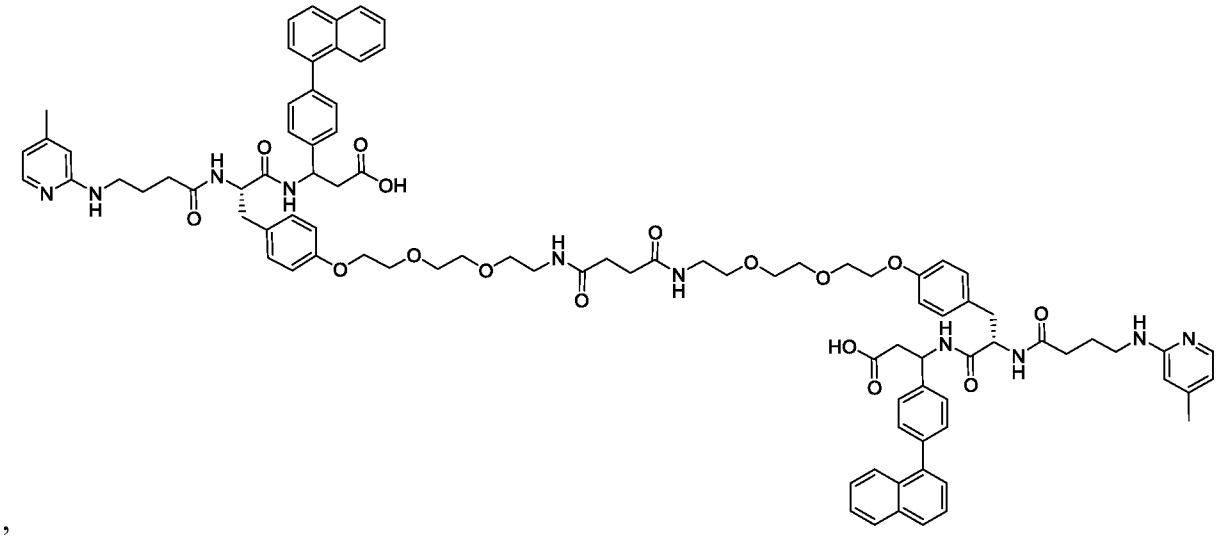


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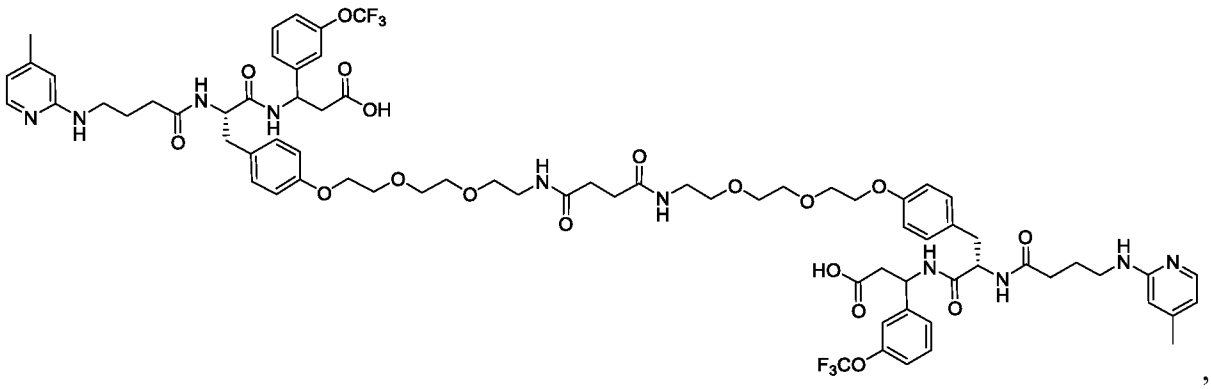


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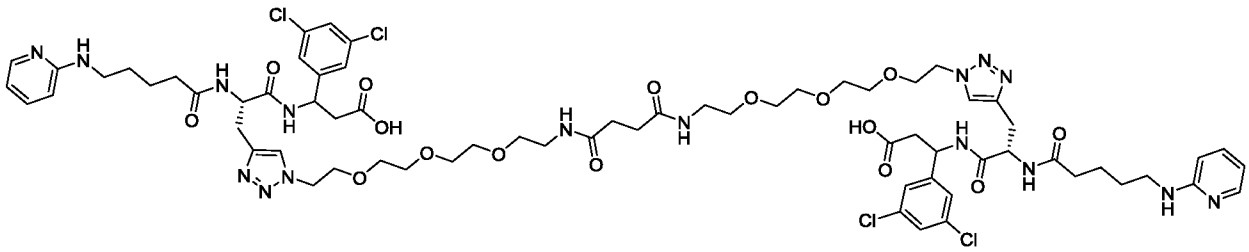




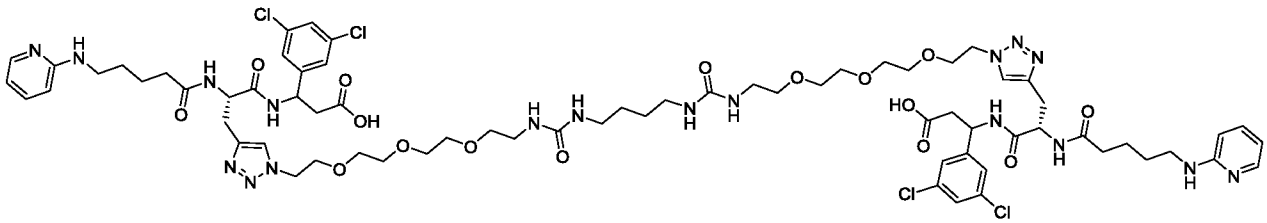
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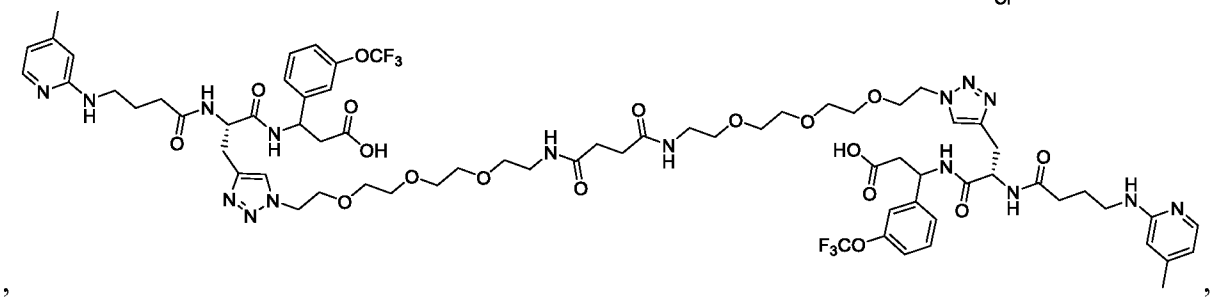


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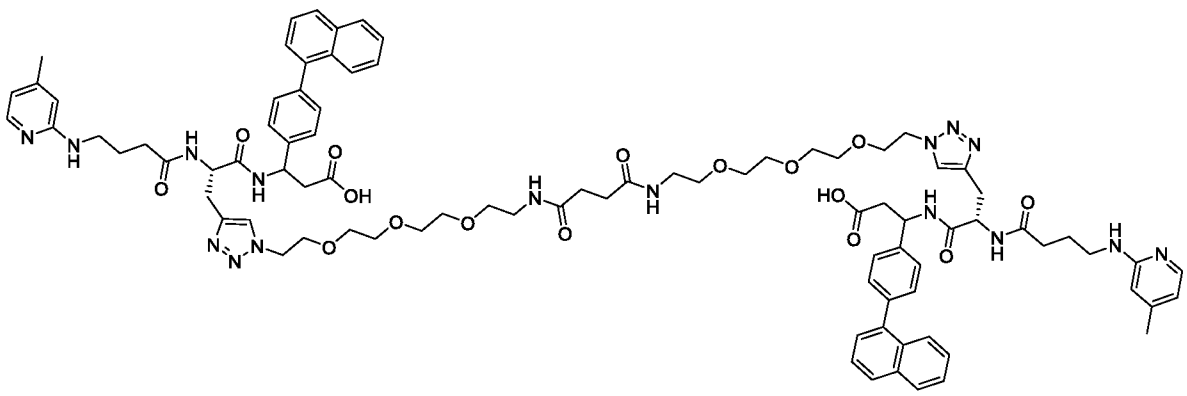
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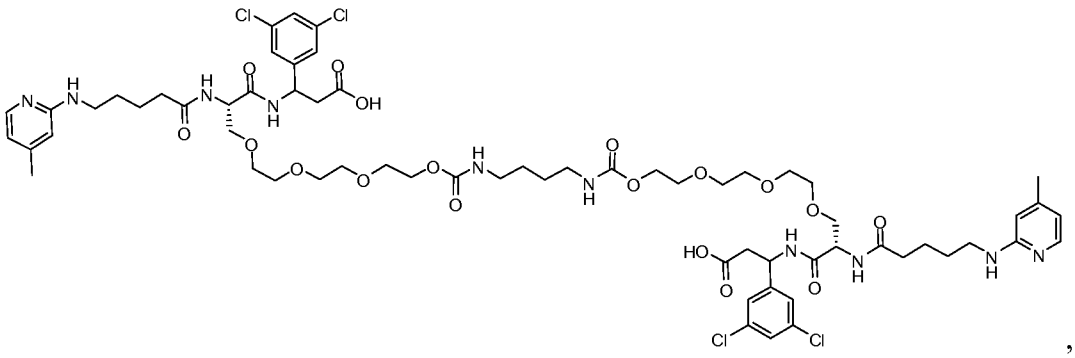
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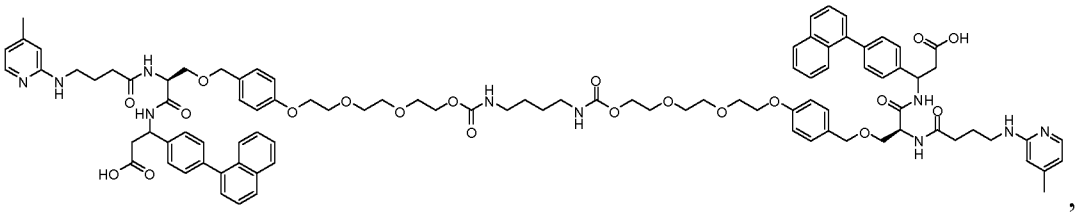
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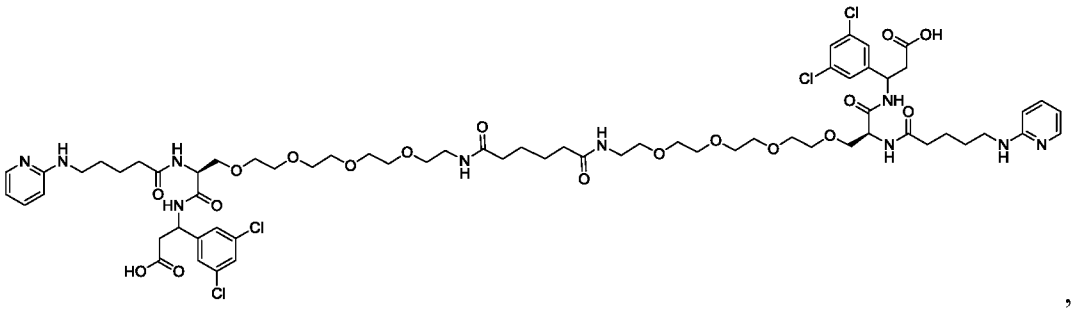
[00191] In some embodiments, provided herein are compounds, or pharmaceutically acceptable salts, solvates, polymorphs, prodrugs, metabolites, N-oxides, tautomers, stereoisomers, or isomers thereof, selected from:



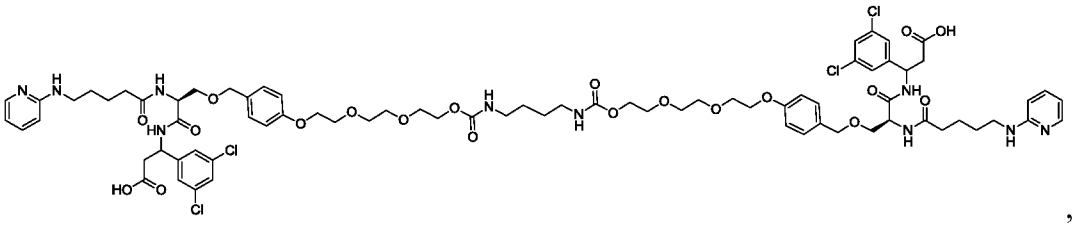
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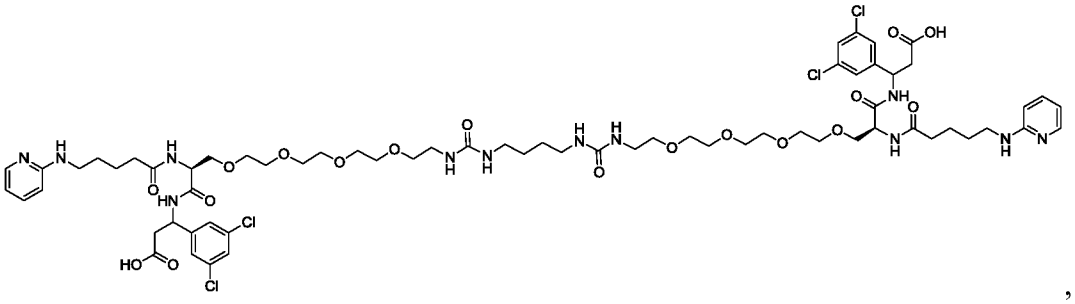
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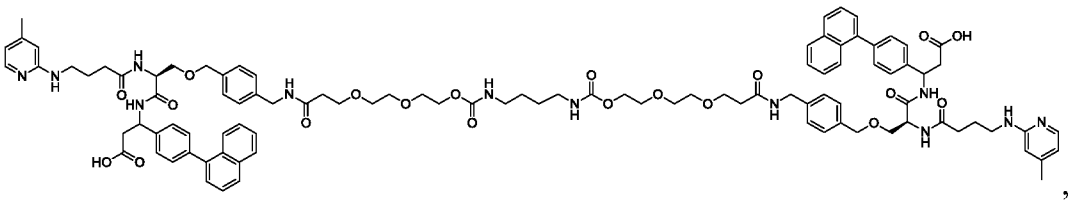
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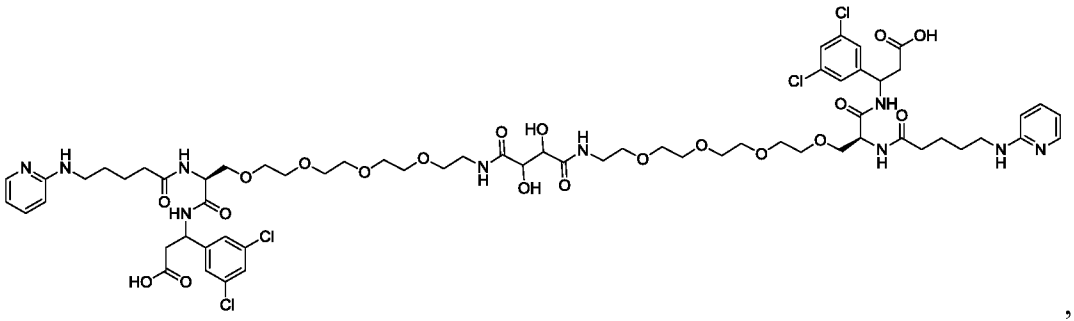
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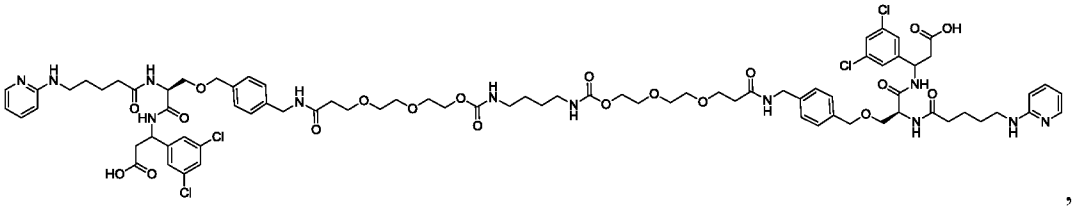
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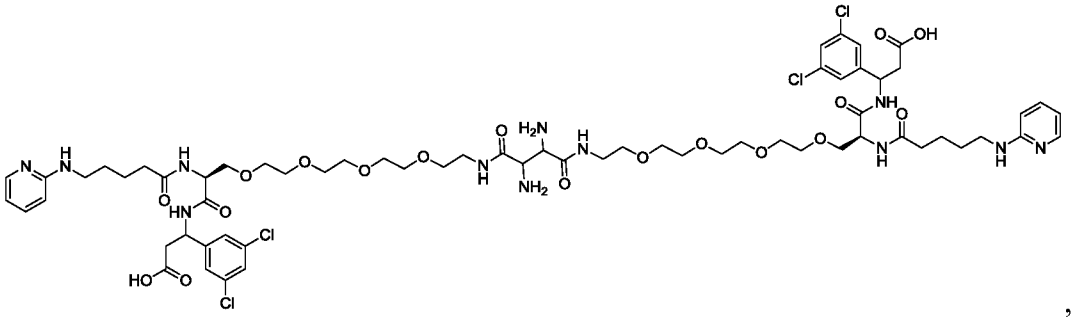
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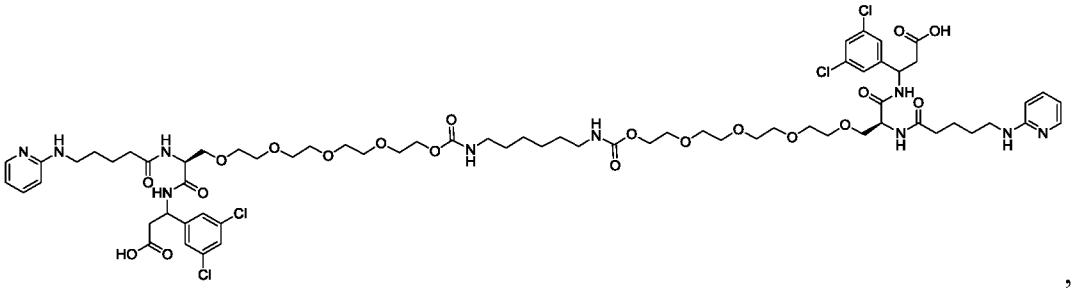
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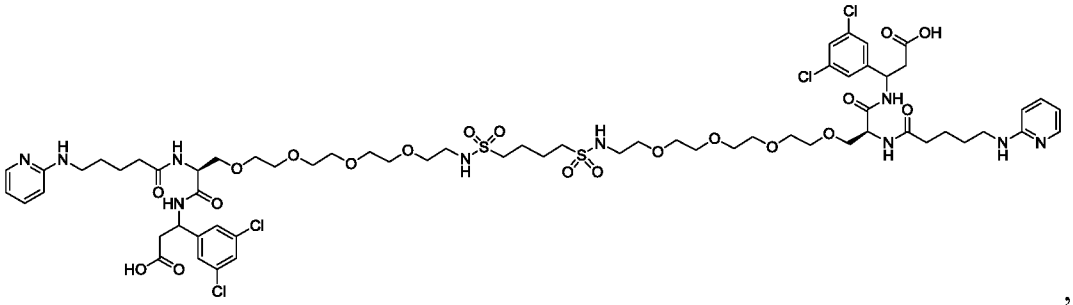
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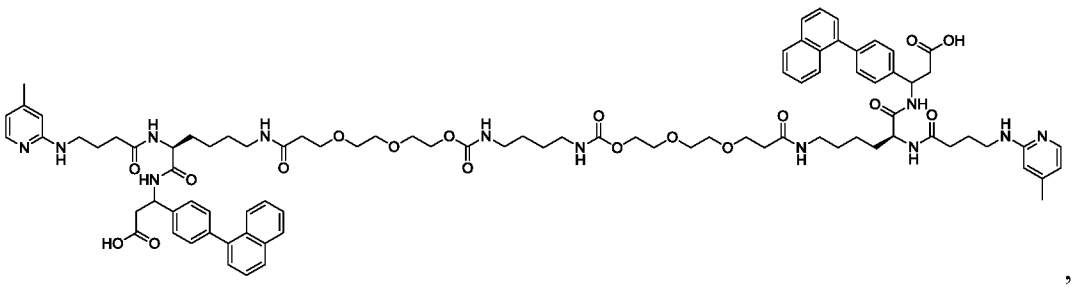
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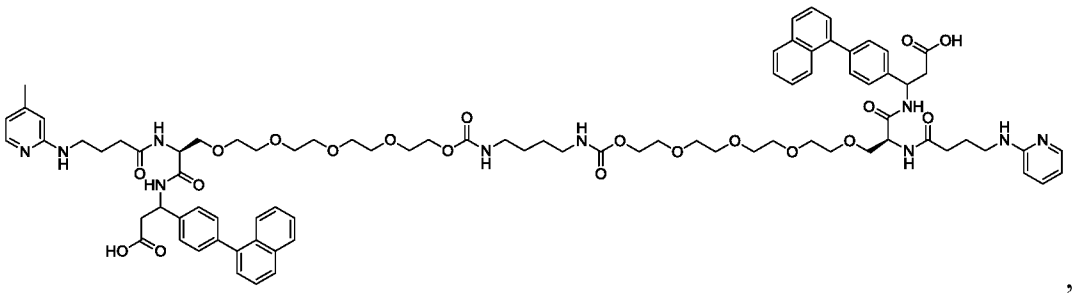
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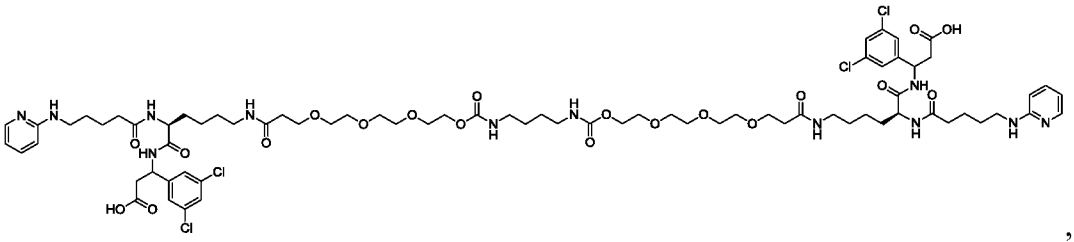
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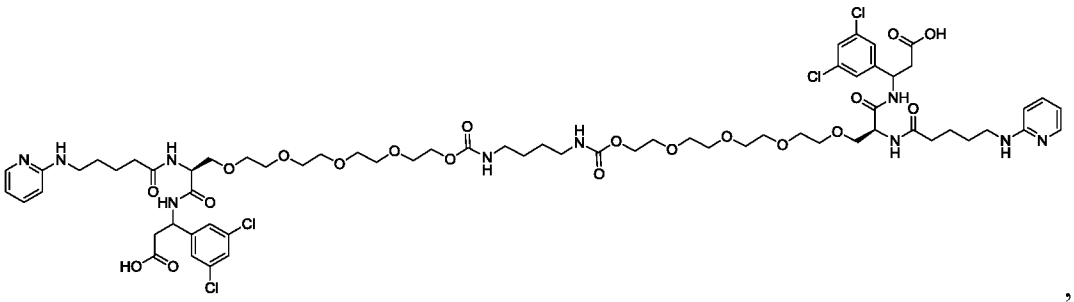
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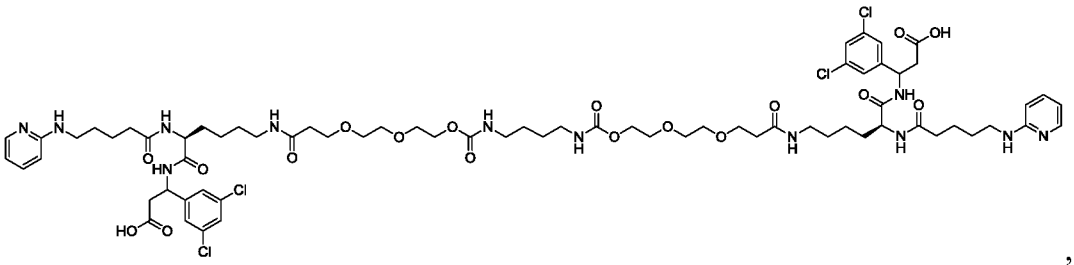
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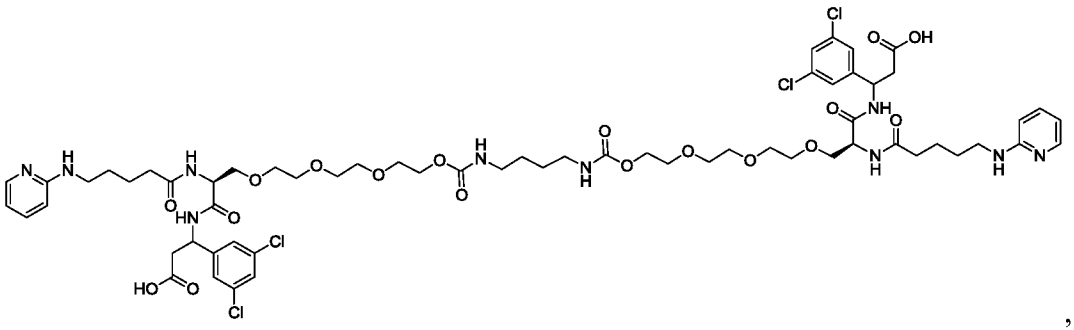
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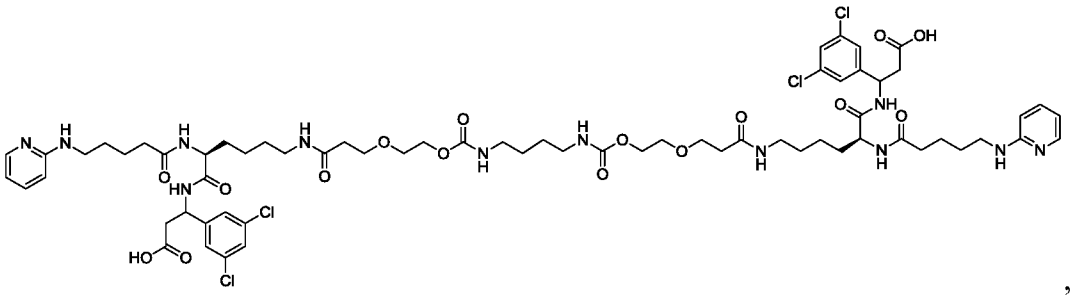
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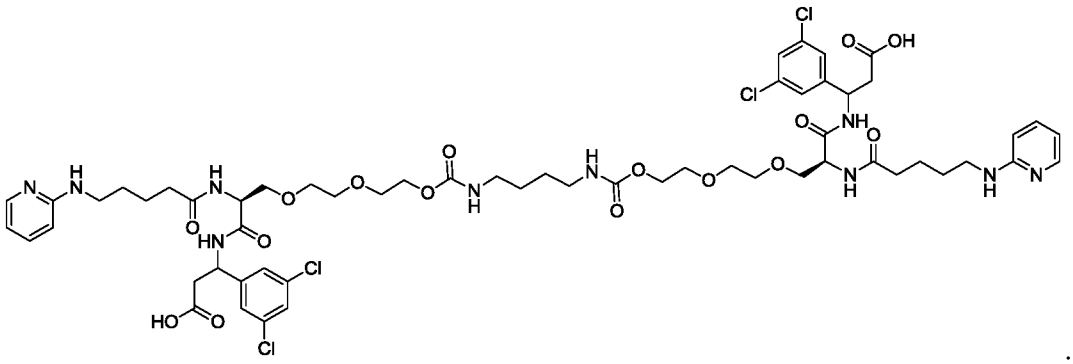
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Preparation of Compounds

[00192] Described herein are compounds of Formula (I), (Ia), (Ib), (Ic), (II), (IIa), (III), or (IV) that treat a lung disease, and processes for their preparation. Also described herein are pharmaceutically acceptable salts, pharmaceutically acceptable solvates, pharmaceutically active metabolites, and pharmaceutically acceptable prodrugs of such compounds. Pharmaceutical compositions comprising at least one such compound or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, pharmaceutically active metabolite or pharmaceutically acceptable prodrug of such compound, and a pharmaceutically acceptable excipient are also provided.

[00193] Also described herein are compounds of Formula (I), (Ia), (Ib), (Ic), (II), (IIa), (III), or (IV) that treat idiopathic pulmonary fibrosis, and processes for their preparation. Also described herein are pharmaceutically acceptable salts, pharmaceutically acceptable solvates, pharmaceutically active metabolites, and pharmaceutically acceptable prodrugs of such compounds. Pharmaceutical compositions comprising at least one such compound or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, pharmaceutically active metabolite or pharmaceutically acceptable prodrug of such compound, and a pharmaceutically acceptable excipient are also provided.

[00194] Compounds of Formula (I), (Ia), (Ib), (Ic), (II), (IIa), (III), or (IV) may be synthesized using standard synthetic reactions known to those of skill in the art or using methods known in the art. The reactions can be employed in a linear sequence to provide the compounds or they

may be used to synthesize fragments which are subsequently joined by the methods known in the art.

[00195] The starting material used for the synthesis of the compounds described herein may be synthesized or can be obtained from commercial sources, such as, but not limited to, Aldrich Chemical Co. (Milwaukee, Wisconsin), Bachem (Torrance, California), or Sigma Chemical Co. (St. Louis, Mo.). The compounds described herein, and other related compounds having different substituents can be synthesized using techniques and materials known to those of skill in the art, such as described, for example, in March, ADVANCED ORGANIC CHEMISTRY 4th Ed., (Wiley 1992); Carey and Sundberg, ADVANCED ORGANIC CHEMISTRY 4th Ed., Vols. A and B (Plenum 2000, 2001); Green and Wuts, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS 3rd Ed., (Wiley 1999); Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-17 (John Wiley and Sons, 1991); Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplementals (Elsevier Science Publishers, 1989); Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991); and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989); (all of which are incorporated by reference in their entirety). Other methods for the synthesis of compounds described herein may be found in International Patent Publication No. WO 01/01982901, Arnold *et al. Bioorganic & Medicinal Chemistry Letters* 10 (2000) 2167-2170; Burchat *et al. Bioorganic & Medicinal Chemistry Letters* 12 (2002) 1687-1690. General methods for the preparation of compound as disclosed herein may be derived from known reactions in the field, and the reactions may be modified by the use of appropriate reagents and conditions, as would be recognized by the skilled person, for the introduction of the various moieties found in the formulae as provided herein.

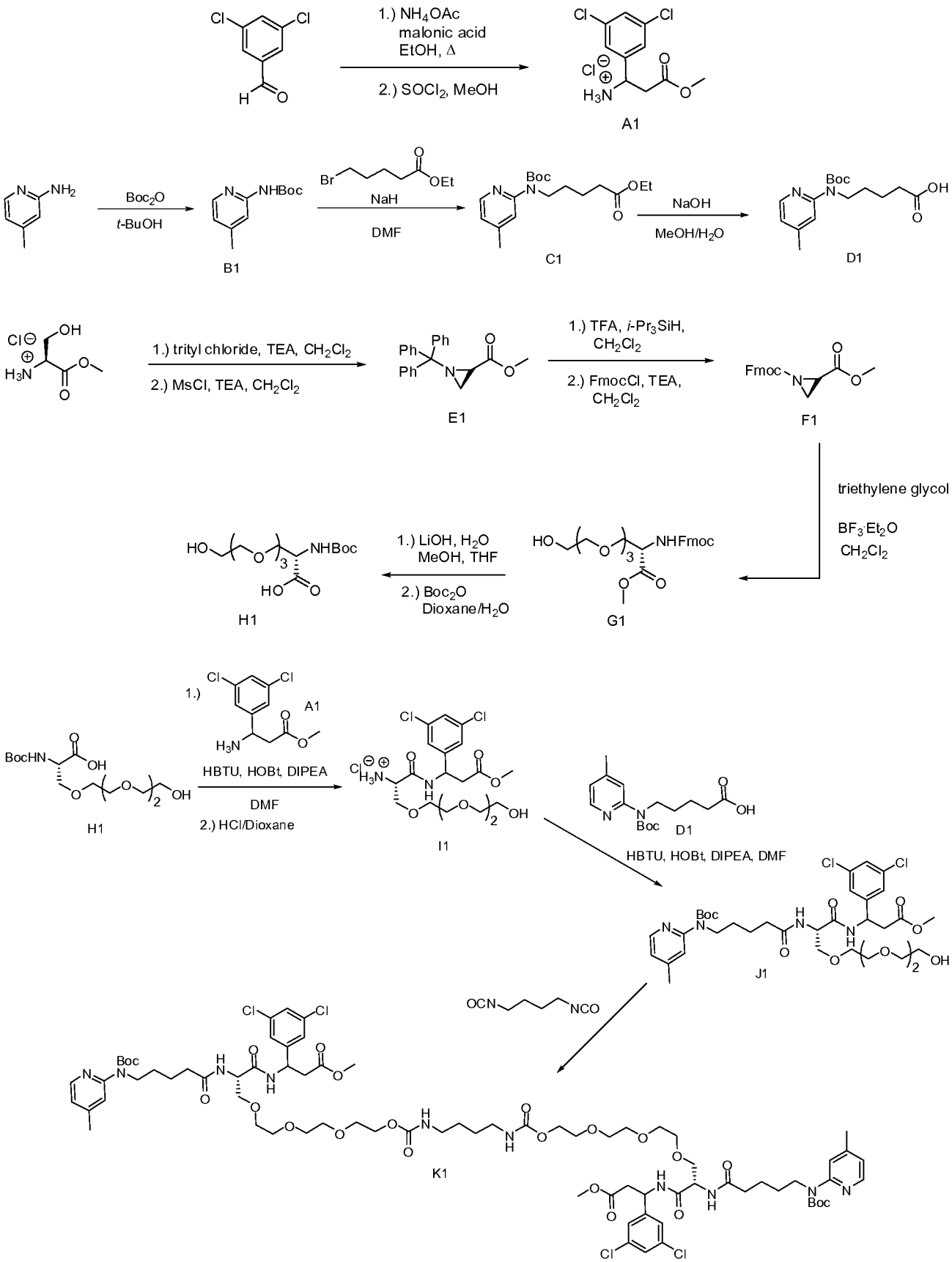
[00196] The products of the reactions may be isolated and purified, if desired, using conventional techniques, including, but not limited to, filtration, distillation, crystallization, chromatography and the like. Such materials may be characterized using conventional means, including physical constants and spectral data.

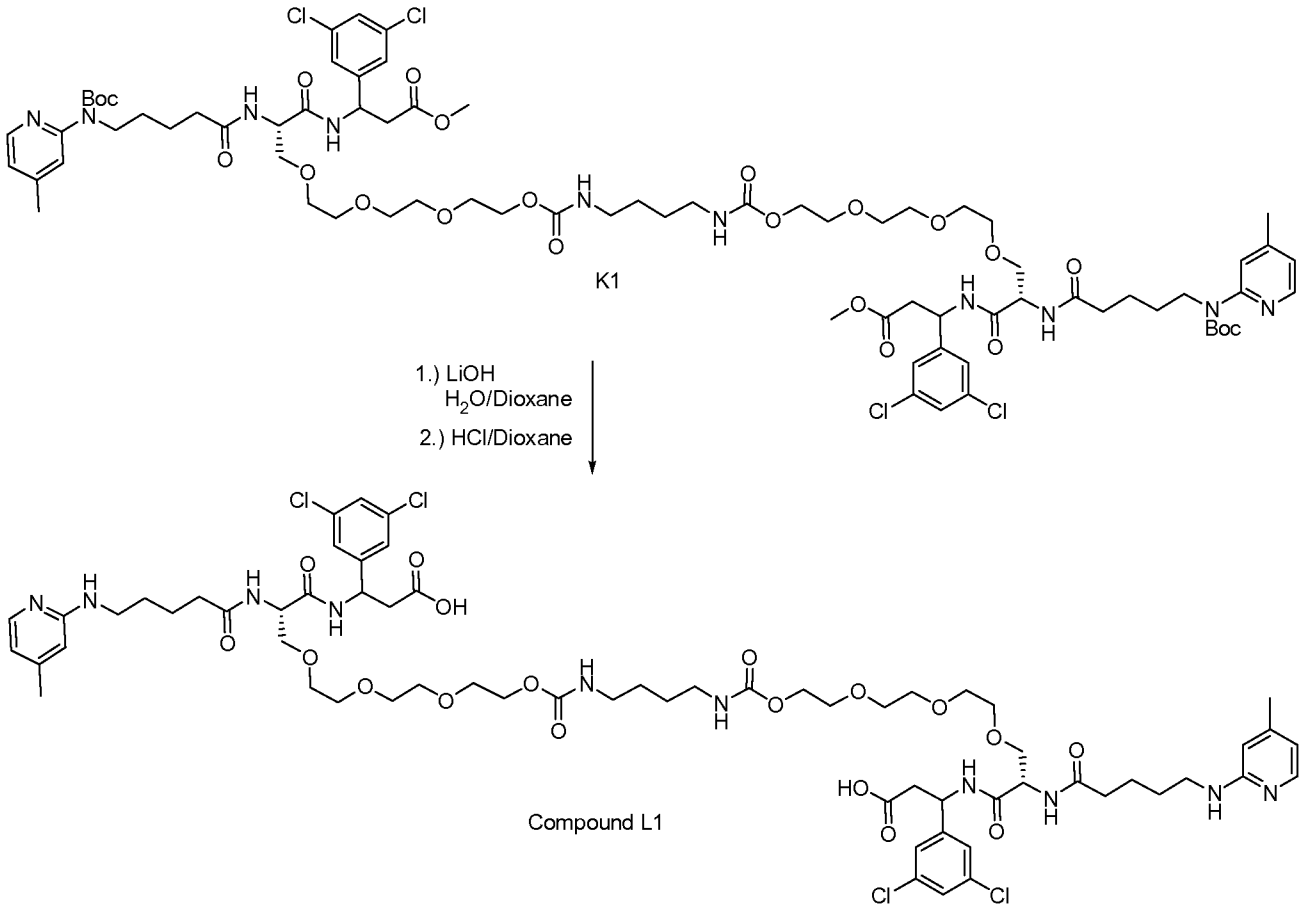
[00197] Compounds described herein may be prepared as a single isomer or a mixture of isomers.

[00198] The starting materials and intermediates for the compounds of this invention may be prepared by the application or adaptation of the methods described below, their obvious chemical equivalents, or, for example, as described in literature such as The Science of Synthesis, Volumes 1-8. Editors E. M. Carreira et al. Thieme publishers (2001-2008). Details of reagent and reaction options are also available by structure and reaction searches using commercial computer search engines such as SciFinder or Reaxys.

[00199] A representative compound of Formula (I) can be prepared as depicted in Scheme 1.

Scheme 1





Further Forms of Compounds Disclosed Herein

Isomers

[00200] Furthermore, in some embodiments, the compounds described herein exist as geometric isomers. In some embodiments, the compounds described herein possess one or more double bonds. The compounds presented herein include all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the corresponding mixtures thereof. In some situations, compounds exist as tautomers. The compounds described herein include all possible tautomers within the formulas described herein. In some situations, the compounds described herein possess one or more chiral centers and each center exists in the R configuration, or S confirguration. The compounds described herein include all diastereomeric, enantiomeric, and epimeric forms as well as the corresponding mixtures thereof. In additional embodiments of the compounds and methods provided herein, mixtures of enantiomers and/or diastereoisomers, resulting from a single preparative step, combination, or interconversion are useful for the applications described herein. In some embodiments, the 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, separating the

diastereomers and recovering the optically pure enantiomers. In some embodiments, dissociable complexes are preferred (e.g., crystalline diastereomeric salts). In some embodiments, the diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and are separated by taking advantage of these dissimilarities. In some embodiments, the diastereomers are separated by chiral chromatography, or preferably, by separation/resolution techniques based upon differences in solubility. In some embodiments, the optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that would not result in racemization.

Labeled compounds

[00201] In some embodiments, the compounds described herein exist in their isotopically-labeled forms. In certain embodiments, the compounds described herein exist as partially or fully deuterated forms. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such isotopically-labeled compounds. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such isotopically-labeled compounds as pharmaceutical compositions. Thus, in some embodiments, the compounds disclosed herein include isotopically-labeled compounds, which are identical to those recited 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 compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine and chloride, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, $^{18}0$, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively. Compounds described herein, and the metabolites, pharmaceutically acceptable salts, esters, prodrugs, solvate, hydrates or derivatives thereof which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labeled compounds, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i. e., ^{3}H and carbon-14, i. e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavy isotopes such as deuterium, *i.e.*, ^{2}H, produces certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements. In some embodiments, the isotopically labeled compounds, pharmaceutically acceptable salt, ester, prodrug, solvate, hydrate or derivative thereof is prepared by any suitable method.

[00202] In some embodiments, the compounds described herein are labeled by other means, including, but not limited to, the use of chromophores or fluorescent moieties, bioluminescent labels, or chemiluminescent labels.

Pharmaceutically acceptable salts

[00203] In some embodiments, the compounds described herein exist as their pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts as pharmaceutical compositions.

[00204] In some embodiments, the compounds described herein possess acidic or basic groups and therefore react with any of a number of inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt. In some embodiments, these salts are prepared *in situ* during the final isolation and purification of the compounds of the invention, or by separately reacting a purified compound in its free form with a suitable acid or base, and isolating the salt thus formed.

[00205] Examples of pharmaceutically acceptable salts include those salts prepared by reaction of the compounds described herein with a mineral, organic acid or inorganic base, such salts including, acetate, acrylate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, bisulfite, bromide, butyrate, butyn-1,4-dioate, camphorate, camphorsulfonate, caproate, caprylate, chlorobenzoate, chloride, citrate, cyclopentanepropionate, decanoate, digluconate, dihydrogenphosphate, dinitrobenzoate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptanoate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hexyne-1,6-dioate, hydroxybenzoate, γ-hydroxybutyrate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, iodide, isobutyrate, lactate, maleate, malonate, methanesulfonate, mandelate metaphosphate, methanesulfonate, methoxybenzoate, methylbenzoate, monohydrogenphosphate, 1-napthalenesulfonate, 2-napthalenesulfonate, nicotinate, nitrate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, pyrosulfate, pyrophosphate, propiolate, phthalate, phenylacetate, phenylbutyrate, propanesulfonate, salicylate, succinate, sulfate, sulfite, succinate, suberate, sebacate, sulfonate, tartrate, thiocyanate, tosylate undeconate and xylenesulfonate.

[00206] Further, the compounds described herein can be prepared as pharmaceutically acceptable salts formed by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid, including, but not limited to, inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid metaphosphoric

acid, and the like; and organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, p-toluenesulfonic acid, tartaric acid, trifluoroacetic acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, arylsulfonic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 2-naphthalenesulfonic acid, 4-methylbicyclo-[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid and muconic acid. In some embodiments, other acids, such as oxalic, while not in themselves pharmaceutically acceptable, are employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

[00207] In some embodiments, those compounds described herein which comprise a free acid group react with a suitable base, such as the hydroxide, carbonate, bicarbonate, sulfate, of a pharmaceutically acceptable metal cation, with ammonia, or with a pharmaceutically acceptable organic primary, secondary, tertiary, or quaternary amine. Representative salts include the alkali or alkaline earth salts, like lithium, sodium, potassium, calcium, and magnesium, and aluminum salts and the like. Illustrative examples of bases include sodium hydroxide, potassium hydroxide, choline hydroxide, sodium carbonate, $N^+(C_{1-4}$ alkyl$)_4$, and the like.

[00208] Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like. It should be understood that the compounds described herein also include the quaternization of any basic nitrogen-containing groups they contain. In some embodiments, water or oil-soluble or dispersible products are obtained by such quaternization.

Solvates

[00209] In some embodiments, the compounds described herein exist as solvates. The invention provides for methods of treating diseases by administering such solvates. The invention further provides for methods of treating diseases by administering such solvates as pharmaceutical compositions.

[00210] Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and, in some embodiments, are formed during the process of crystallization with pharmaceutically acceptable solvents such as water, ethanol, and the like. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. Solvates of the compounds

described herein can be conveniently prepared or formed during the processes described herein. By way of example only, hydrates of the compounds described herein can be conveniently prepared by recrystallization from an aqueous/organic solvent mixture, using organic solvents including, but not limited to, dioxane, tetrahydrofuran or methanol. In addition, the compounds provided herein can exist in unsolvated as well as solvated forms. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the compounds and methods provided herein.

Polymorphs

[00211] In some embodiments, the compounds described herein exist as polymorphs. The invention provides for methods of treating diseases by administering such polymorphs. The invention further provides for methods of treating diseases by administering such polymorphs as pharmaceutical compositions.

[00212] Thus, the compounds described herein include all their crystalline forms, known as polymorphs. Polymorphs include the different crystal packing arrangements of the same elemental composition of a compound. In certain instances, polymorphs have different X-ray diffraction patterns, infrared spectra, melting points, density, hardness, crystal shape, optical and electrical properties, stability, and solubility. In certain instances, various factors such as the recrystallization solvent, rate of crystallization, and storage temperature cause a single crystal form to dominate.

Prodrugs

[00213] In some embodiments, the compounds described herein exist in prodrug form. The invention provides for methods of treating diseases by administering such prodrugs. The invention further provides for methods of treating diseases by administering such prodrugs as pharmaceutical compositions.

[00214] Prodrugs are generally drug precursors that, following administration to an individual and subsequent absorption, are converted to an active, or a more active species via some process, such as conversion by a metabolic pathway. Some prodrugs have a chemical group present on the prodrug that renders it less active and/or confers solubility or some other property to the drug. Once the chemical group has been cleaved and/or modified from the prodrug the active drug is generated. Prodrugs are often useful because, in some situations, they are easier to administer than the parent drug. They are, for instance, bioavailable by oral administration whereas the parent is not. In certain insatnces, the prodrug also has improved solubility in pharmaceutical compositions over the parent drug. An example, without limitation, of a prodrug would be a compound as described herein which is administered as an ester (the "prodrug") to

facilitate transmittal across a cell membrane where water solubility is detrimental to mobility but which then is metabolically hydrolyzed to the carboxylic acid, the active entity, once inside the cell where water-solubility is beneficial. A further example of a prodrug might be a short peptide (polyamino acid) bonded to an acid group where the peptide is metabolized to reveal the active moiety. (See for example Bundgaard, "Design and Application of Prodrugs" in *A Textbook of Drug Design and Development*, Krosgaard-Larsen and Bundgaard, Ed., 1991, Chapter 5, 113-191, which is incorporated herein by reference).

[00215] In some embodiments, prodrugs are designed as reversible drug derivatives, for use as modifiers to enhance drug transport to site-specific tissues. The design of prodrugs to date has been to increase the effective water solubility of the therapeutic compound for targeting to regions where water is the principal solvent.

[00216] Additionally, prodrug derivatives of compounds described herein can be prepared by methods described herein are otherwise known in the art (for further details see Saulnier *et al.*, *Bioorganic and Medicinal Chemistry Letters*, **1994**, *4*, 1985). By way of example only, appropriate prodrugs can be prepared by reacting a non-derivatized compound with a suitable carbamylating agent, such as, but not limited to, 1,1-acyloxyalkylcarbanochloridate, *para*-nitrophenyl carbonate, or the like. Prodrug forms of the herein described compounds, wherein the prodrug is metabolized *in vivo* to produce a derivative as set forth herein are included within the scope of the claims. Indeed, some of the herein-described compounds are prodrugs for another derivative or active compound.

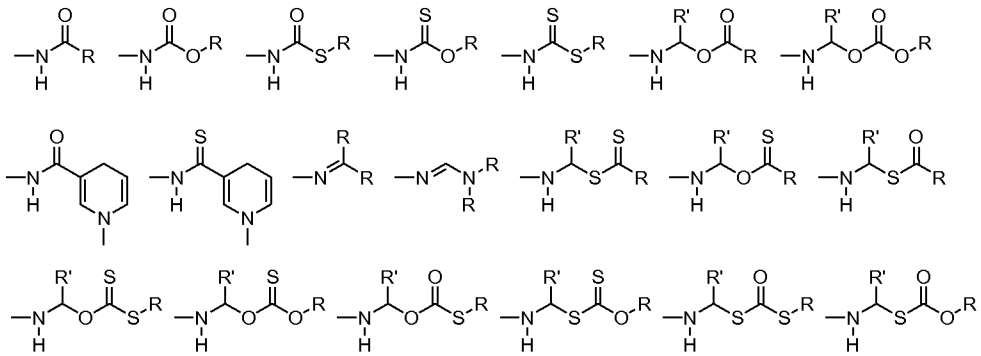
[00217] In some embodiments, prodrugs include compounds wherein an amino acid residue, or a polypeptide chain of two or more (e. g., two, three or four) amino acid residues is covalently joined through an amide or ester bond to a free amino, hydroxy or carboxylic acid group of compounds of the present invention. The amino acid residues include but are not limited to the 20 naturally occurring amino acids and also includes 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, norvaline, beta-alanine, gamma-aminobutyric acid, cirtulline, homocysteine, homoserine, ornithine and methionine sulfone. In other embodiments, prodrugs include compounds wherein a nucleic acid residue, or an oligonucleotide of two or more (e. g., two, three or four) nucleic acid residues is covalently joined to a compound of the present invention.

[00218] Pharmaceutically acceptable prodrugs of the compounds described herein also include, but are not limited to, esters, carbonates, thiocarbonates, N-acyl derivatives, N-acyloxyalkyl derivatives, quaternary derivatives of tertiary amines, N-Mannich bases, Schiff bases, amino acid conjugates, phosphate esters, metal salts and sulfonate esters. Compounds having free

amino, amido, hydroxy or carboxylic groups can be converted into prodrugs. For instance, free carboxyl groups can be derivatized as amides or alkyl esters. In certain instances, all of these prodrug moieties incorporate groups including but not limited to ether, amine and carboxylic acid functionalities.

[00219] Hydroxy prodrugs include esters, such as though not limited to, acyloxyalkyl (e.g. acyloxymethyl, acyloxyethyl) esters, alkoxycarbonyloxyalkyl esters, alkyl esters, aryl esters, phosphate esters, sulfonate esters, sulfate esters and disulfide containing esters; ethers, amides, carbamates, hemisuccinates, dimethylaminoacetates and phosphoryloxymethyloxycarbonyls, as outlined in *Advanced Drug Delivery Reviews* **1996**, *19*, 115.

[00220] Amine derived prodrugs include, but are not limited to the following groups and combinations of groups:



as well as sulfonamides and phosphonamides.

[00221] In certain instances, sites on any aromatic ring portions are susceptible to various metabolic reactions, therefore incorporation of appropriate substituents on the aromatic ring structures, can reduce, minimize or eliminate this metabolic pathway.

Metabolites

[00222] In some embodiments, compounds of Formula (I), (Ia), (Ib), (Ic), (II), (IIa), (III), or (IV) are susceptible to various metabolic reactions. Therefore, in some embodiments, incorporation of appropriate substituents into the structure will reduce, minimize, or eliminate a metabolic pathway. In specific embodiments, the appropriate substituent to decrease or eliminate the susceptibility of an aromatic ring to metabolic reactions is, by way of example only, a halogen, or an alkyl group.

[00223] In additional or further embodiments, the compounds of Formula (I), (Ia), (Ib), (Ic), (II), (IIa), (III), or (IV) described herein are metabolized upon administration to an organism in need to produce a metabolite that is then used to produce a desired effect, including a desired therapeutic effect.

Pharmaceutical Compositions/Formulations

[00224] In another aspect, provided herein are pharmaceutical composition comprising a compound of Formula (I), (Ia), (Ib), (Ic), (II), (IIa), (III), or (IV) as described herein, or a pharmaceutically acceptable salt, polymorph, solvate, prodrug, metabolite, deuteride, N-oxide, stereoisomer, or isomer thereof, and a pharmaceutically acceptable excipient.

[00225] In some embodiments, the compounds described herein are formulated into pharmaceutical compositions. Pharmaceutical compositions are formulated in a conventional manner using one or more pharmaceutically acceptable inactive ingredients that facilitate processing of the active compounds into preparations that can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. A summary of pharmaceutical compositions described herein can be found, for example, in Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins1999), herein incorporated by reference for such disclosure.

[00226] Provided herein are pharmaceutical compositions that include a compound of Formula (I), (Ia), (Ib), (Ic), (II), (IIa), (III), or (IV) and at least one pharmaceutically acceptable inactive ingredient. In some embodiments, the compounds described herein are administered as pharmaceutical compositions in which a compound of Formula (I), (Ia), (Ib), (Ic), (II), (IIa), (III), or (IV) is mixed with other active ingredients, as in combination therapy. In other embodiments, the pharmaceutical compositions include other medicinal or pharmaceutical agents, carriers, adjuvants, preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure, and/or buffers. In yet other embodiments, the pharmaceutical compositions include other therapeutically valuable substances.

[00227] A pharmaceutical composition, as used herein, refers to a mixture of a compound of Formula (I), (Ia), (Ib), (Ic), (II), (IIa), (III), or (IV) with other chemical components (i.e. pharmaceutically acceptable inactive ingredients), such as carriers, excipients, binders, filling agents, suspending agents, flavoring agents, sweetening agents, disintegrating agents, dispersing agents, surfactants, lubricants, colorants, diluents, solubilizers, moistening agents, plasticizers, stabilizers, penetration enhancers, wetting agents, anti-foaming agents, antioxidants, preservatives, or one or more combination thereof. The pharmaceutical composition facilitates administration of the compound to an organism. In practicing the methods of treatment or use provided herein, therapeutically effective amounts of compounds described herein are

administered in a pharmaceutical composition to a mammal having a disease, disorder, or condition to be treated. In some embodiments, the mammal is a human. A therapeutically effective amount can vary widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. The compounds can be used singly or in combination with one or more therapeutic agents as components of mixtures.

[00228] Described herein is a pharmaceutical composition comprising a compound of Formula (I), (Ia), (Ib), (Ic), (II), (IIa), (III), or (IV), and a pharmaceutically acceptable excipient, where the compound is in a formulation suitable for delivery by inhalation. The inhalational route of administration provides the advantage that the inhaled drug can directly target the lung. An inhalational pharmaceutical delivery system is one that is suitable for respiratory therapy by delivery of an active agent to mucosal linings of the bronchi. This invention can utilize a system that depends on the power of a compressed gas to expel an active agent from a container. An aerosol or pressurized package can be employed for this purpose.

[00229] As used herein, the term "aerosol" is used in its conventional sense as referring to very fine liquid or solid particles carries by a propellant gas under pressure to a site of therapeutic application. When a pharmaceutical aerosol is employed in the context of the present disclosure, the aerosol contains an active agent, which can be dissolved, suspended, or emulsified in a mixture of a fluid carrier and a propellant. The aerosol can be in the form of a solution, suspension, emulsion, powder, or semi-solid preparation. Aerosols employed in the present invention are intended for administration as fine, solid particles or as liquid mists via the respiratory tract of a patient. Various types of propellants known to one of skill in the art can be utilized. Suitable propellants include, but are not limited to, hydrocarbons or other suitable gas. In the case of the pressurized aerosol, the dosage unit may be determined by providing a value to deliver a metered amount.

[00230] In some embodiments a compound of Formula (I), (Ia), (Ib), (Ic), (II), (IIa), (III), or (IV) is formulated for delivery with a nebulizer, which is an instrument that generates very fine liquid particles of substantially uniform size in a gas. For example, a liquid containing an active agent is dispersed as droplets. The small droplets can be carried by a current of air through an outlet tube of the nebulizer. The resulting mist penetrates into the respiratory tract of the patient.

[00231] In some embodiments, a powder composition containing a compound of Formula (I), (Ia), (Ib), (Ic), (II), (IIa), (III), or (IV), with or without a lubricant, carrier, or propellant, can be administered to a mammal in need of therapy. This embodiment of the invention can be carried out with a conventional device for administering a powder pharmaceutical composition by

inhalation. For example, a powder mixture of the compound and a suitable powder base such as lactose or starch may be presented in unit dosage form in for example capsular or cartridges, e.g. gelatin, or blister packs, from which the powder may be administered with the aid of an inhaler.

[00232] Pharmaceutical compositions including a compound of Formula (I), (Ia), (Ib), (Ic), (II), (IIa), (III), or (IV) are manufactured in a conventional manner, such as, by way of example only, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or compression processes.

[00233] The pharmaceutical compositions will include at least one compound of Formula (I), (Ia), (Ib), (Ic), (II), (IIa), (III), or (IV) as an active ingredient in free-acid or free-base form, or in a pharmaceutically acceptable salt form. In addition, the methods and pharmaceutical compositions described herein include the use of *N*-oxides (if appropriate), crystalline forms, amorphous phases, as well as active metabolites of these compounds having the same type of activity. In some embodiments, compounds described herein exist in unsolvated form or in solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. The solvated forms of the compounds presented herein are also considered to be disclosed herein.

[00234] Any conventional carrier or excipient may be used in the pharmaceutical compositions of the embodiments. The choice of a particular carrier or excipient, or combinations of carriers or excipients, will depend on the mode of administration being used to treat a particular patient or type of medical condition or disease state.

Combination Treatment

[00235] The compounds according to Formula (I), (Ia), (Ib), (Ic), (II), (IIa), (III), or (IV) may be used in combination with one or more additional antibiotic agents, recombinant human DNase, hypertonic saline, anti-inflammatory agents and bronchodilators.

[00236] The antibiotic agent may be selected from an aminoglycoside, ansamycin, carbacephem, carbapenem, cephalosporin, glycopeptide, lincosamide, lipopeptide, macrolide, monobactam, nitrofurans, penicillin, polypeptide, quinolone, sulfonamide, or tetracycline antibiotic. Examples of antibiotic agents include, but are not limited to, Aminoglycoside derivatives like amikacin, gentamicin, kanamycin, neomycin, netilmicin, tobramicin, paromomycin; Ansamycin derivatives like geldanamycin, herbimycin; Carbacephem derivatives like loracarbef, Carbapenem derivatives like ertapenem, doripenem, imipenem, meropenem; Cephalosporin derivatives like cefadroxil, cefazolin, cefalotin, cefalexin, cefaclor, cefamandole, cefoxitin, cefprozil, cefuroxime, cefixime, cefdinir, cefditoren, cefoperazone, cefotaxime, cefpodoxime, ceftazidime, ceftibuten, ceftizoxime, ceftriaxone, cefepime, ceftobiprole;

Glycopeptide derivatives like teicoplanin, vancomycin, telavancin; Lincosamides like clindamycin, lincomycin; Lipopeptide derivatives like daptomycin; Macrolide derivatives like azithromycin, clarithromycin, dirithromycin, erythromycin, roxithromycin, troleandomycin; telithreomycin, spectinomycin; Monobactam derivatives like aztreonam; Nitrofuran derivatives like furazolidone, nitrofurantoin; Penicillin derivatives like amoxicillin, ampicillin, azlocillin, carbinicillin, cloxacillin, dicloxacillin, flucloxacillin, mezlocillin, methicillin, nafcillin, oxacillin, penicillin G, penicillin V, piperacillin, temocillin, ticarcillin; Penicillin combinations like amoxicillin/clavulanate, ampicillin/sulbactam, piperacillin/tazobactam, ticarcillin/clavulanate; Polypeptide derivatives like bacitracin, colistin, polymyxin B; Quinolone derivatives like ciprofloxacin, enoxacin, gatifloxacin, levofloxacin, lomefloxacin, moxifloxacin, nalidixic acid, norfloxacin, ofloxacin, trovafloxacin, grepafloxacin, sparfloxacin, temafloxacin; Sulfonamide derivatives like mafenide, sulfonamidochrysoidine, sulfacetamide, sulfadiazine, silver sulfadiazine, sulfamethoxazole, sulfanilimide, sulfasalazine, sulfisoxazole, trimethoprim, trimethoprim/sulfamethoxazole; Tetracyclin derivatives like demeclocycline, doxycycline, minocycline, oxytetracycline, tetracycline; Derivatives against mycobacteria like clofazimine, dapsone, capreomycin, cycloserine, ethambutol, ethioamide, isoniazid, pyrazinamide, rifampin, refampicin, rifabutin, rifapentine, streptomycin; or other antibiotic agents like arsphenamine, chloramphenicol, fosfomycin, fusidic acid, linezolid, metronidazole, mupirocin, platensimycin, quinupristin/dalfopristin, rifaximin, thiampheniol, tigecycline, tinidazole.

[00237] Examples of bronchodilator agents include, but are not limited to, β_2-adrenergic receptor agonists such as albuterol, levalbuterol, pirbuterol, epinephrine, ephedrine, terbutaline, salmeterol, clenbuterol, formoterol, bambuterol, and indacaterol.

[00238] Anti-inflammatory agents include, but are not limited to, NSAIDS and glucocorticoids. Non-limiting examples of NSAIDS include aspirin, diflunisal, salsalate, ibuprofen, dexibuprofen, naproxen, fenoprofen, ketoprofen, dexketoprofen, flurbiprofen, oxaprozin, loxoprofen, indomethacin, tolmetin, sulindac, etodolac, ketorolac, nabumetone, diclofenac, piroxicam, meloxicam, tenoxicam, droxicam, lornoxicam, isoxicam, mefenamic acid, meclofenamic acid, flufenamic acid, tolfenamic acid, celecoxib, parecoxib, etoricoxib, lumiracoxib, and firocoxib. Glucocorticoids include, but are not limited to, hydrocortisone, cortisone, prednisone, prednisolone, methylprednisolone, dexamethasone, betamethasone, triamcinolone, beclometasone, or fludrocortisone.

Administration of Pharmaceutical Composition

[00239] Described herein are pharmaceutical compositions comprising a compound of Formula (I), (Ia), (Ib), (Ic), (II), (IIa), (III), or (IV) and a pharmaceutically acceptable excipient, where the

compound is in a formulation suitable for administration by inhalation, e.g., inhalation into the lungs.

[00240] Further described herein are pharmaceutical compositions comprising a compound of Formula (I), (Ia), (Ib), (Ic), (II), (IIa), (III), or (IV) utilized for administration wherein absorption is limited such that the compound is rendered substantially impermeable or substantially systemically non-bioavailable by means of increasing the molecular weight of the compound. In some embodiments, the compound of Formula (I), (Ia), (Ib), (Ic), (II), (IIa), (III), or (IV) may be rendered substantially impermeable or substantially systemically non-bioavailable by means of increasing the polar surface area.

[00241] For therapeutic use in lung diseases, local delivery to the lung can be carried out. Delivery by inhalation or insufflating aerosols provides high level concentrations of drug compared to the concentration absorbed systemically. Compositions highly selective or localized in the lung act substantially in the lung without exposure to other tissues or organs. In this way, any systemic effects can be minimized. In addition, administration by inhalation can provide for smaller doses delivered locally to the specific cells in the lung which are most in need of treatment. By delivering smaller doses, any adverse side effects are eliminated or substantially reduced. By delivering directly to the cells which are most in need of treatment, the effect of the treatment will be realized more quickly.

[00242] The compound of Formula (I), (Ia), (Ib), (Ic), (II), (IIa), (III), or (IV) may be administered to the subject by means of a pharmaceutical delivery system for the inhalation route. The compounds may be formulated in a form suitable for administration by inhalation. The pharmaceutical delivery system is one that is suitable for respiratory therapy by administration via inhalation of a compound of any one of Formula (I), (Ia), (Ib), (Ic), (II), (IIa), (III), or (IV) thereof to the lung.

[00243] In certain embodiments, the pharmaceutical compositions are suitable for inhaled administration. Suitable pharmaceutical compositions for inhaled administration will typically be in the form of an aerosol or a powder. Such compositions are generally administered using well-known delivery devices, such as a nebulizer inhaler, a metered-dose inhaler (MDI), a dry powder inhaler (DPI) or a similar delivery device. When a pharmaceutical aerosol is employed in this invention, the aerosol contains the therapeutically active compound, which can be dissolved, suspended, or emulsified in a mixture of a fluid carrier and a propellant. The aerosol can be in the form of a solution, suspension, emulsion, powder, or semi-solid preparation. Aerosols employed in the present embodiments are intended for administration as fine, solid particles or as liquid mists via the respiratory tract of a patient. Various types of propellants

known to one of skill in the art can be utilized. Examples of suitable propellants include, but are not limited to, hydrocarbons or other suitable gas. In the case of the pressurized aerosol, the dosage unit may be determined by providing a value to deliver a metered amount.

[00244] In certain embodiments, the pharmaceutical composition comprising a compound of Formula (I), (Ia), (Ib), (Ic), (II), (IIa), (III), or (IV) is administered by inhalation using a nebulizer inhaler. Such nebulizer devices typically produce a stream of high velocity air that causes the pharmaceutical composition comprising the active agent to spray as a mist that is carried into the patient's respiratory tract. Accordingly, when formulated for use in a nebulizer inhaler, the active agent is typically dissolved in a suitable carrier to form a solution. Alternatively, the active agent can be micronized and combined with a suitable carrier to form a suspension of micronized particles of respirable size.

[00245] In certain embodiments, the pharmaceutical composition comprising a compound of Formula (I), (Ia), (Ib), (Ic), (II), (IIa), (III), or (IV) is administered by inhalation using a dry powder inhaler. Such dry powder inhalers typically administer the active agent as a free-flowing powder that is dispersed in a patient's air-stream during inspiration. In order to achieve a free-flowing powder, the active agent is typically formulated with a suitable excipient such as lactose or starch.

[00246] In certain embodiments, the pharmaceutical composition comprising a compound of Formula (I), (Ia), (Ib), (Ic), (II), (IIa), (III), or (IV) is administered by inhalation using a metered-dose inhaler. Such metered-dose inhalers typically discharge a measured amount of the active agent or a pharmaceutically acceptable salt thereof using compressed propellant gas. Accordingly, pharmaceutical compositions administered using a metered-dose inhaler can comprise a solution or suspension of the active agent in a liquefied propellant.

Methods

[00247] Provided herein is a method to treat a lung disease in a mammal, the method comprising administering to the mammal a composition comprising a compound of Formula (I), (Ia), (Ib), (Ic), (II), (IIa), (III), or (IV) or as described above and below.

[00248] Also provided herein is a method to treat idiopathic pulmonary fibrosis in a mammal, the method comprising administering to the mammal a composition comprising a compound of Formula (I), (Ia), (Ib), (Ic), (II), (IIa), (III), or (IV) or as described above and below.

[00249] Also provided herein is the use of a compound of Formula (I), (Ia), (Ib), (Ic), (II), (IIa), (III), or (IV), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, in the manufacture of a medicament for treating a lung disease. Further provided herein is the use of a compound of Formula (I), (Ia), (Ib), (Ic), (II), (IIa), (III), or (IV), or a pharmaceutically

acceptable salt, solvate, or prodrug thereof, in the manufacture of a medicament for treating idiopathic pulmonary fibrosis.

EXAMPLES

List of abbreviations

[00250] As used above, and throughout the description of the invention, the following abbreviations, unless otherwise indicated, shall be understood to have the following meanings:

ACN	acetonitrile
Bn	benzyl
BOC or Boc	*tert*-butyl carbamate
BOP	benzotriazol-1-yl-oxytris (dimethylamino) phosphonium
t-Bu	tert-butyl
Cbz	benzyl carbamate
Cy	Cyclohexyl
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane (CH_2Cl_2)
DIC	1,3-diisopropylcarbodiimide
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DIEA	diisopropylethylamine
DMAP	4-(N,N-dimethylamino)pyridine
DMP reagent	Dess-Martin Periodinane reagent
DMF	dimethylformamide
DMA	N,N-Dimethylacetamide
DME	1,2-Dimethoxy-ethane
DMSO	dimethylsulfoxide
Dppf	1,1'-Bis(diphenylphosphino)ferrocene
EDCI	1-ethyl-3-(3-dimethylaminopropyl) carbodiimide HCl
eq	equivalent(s)
Et	ethyl
Et_2O	diethyl ether
EtOH	ethanol
EtOAc	ethyl acetate

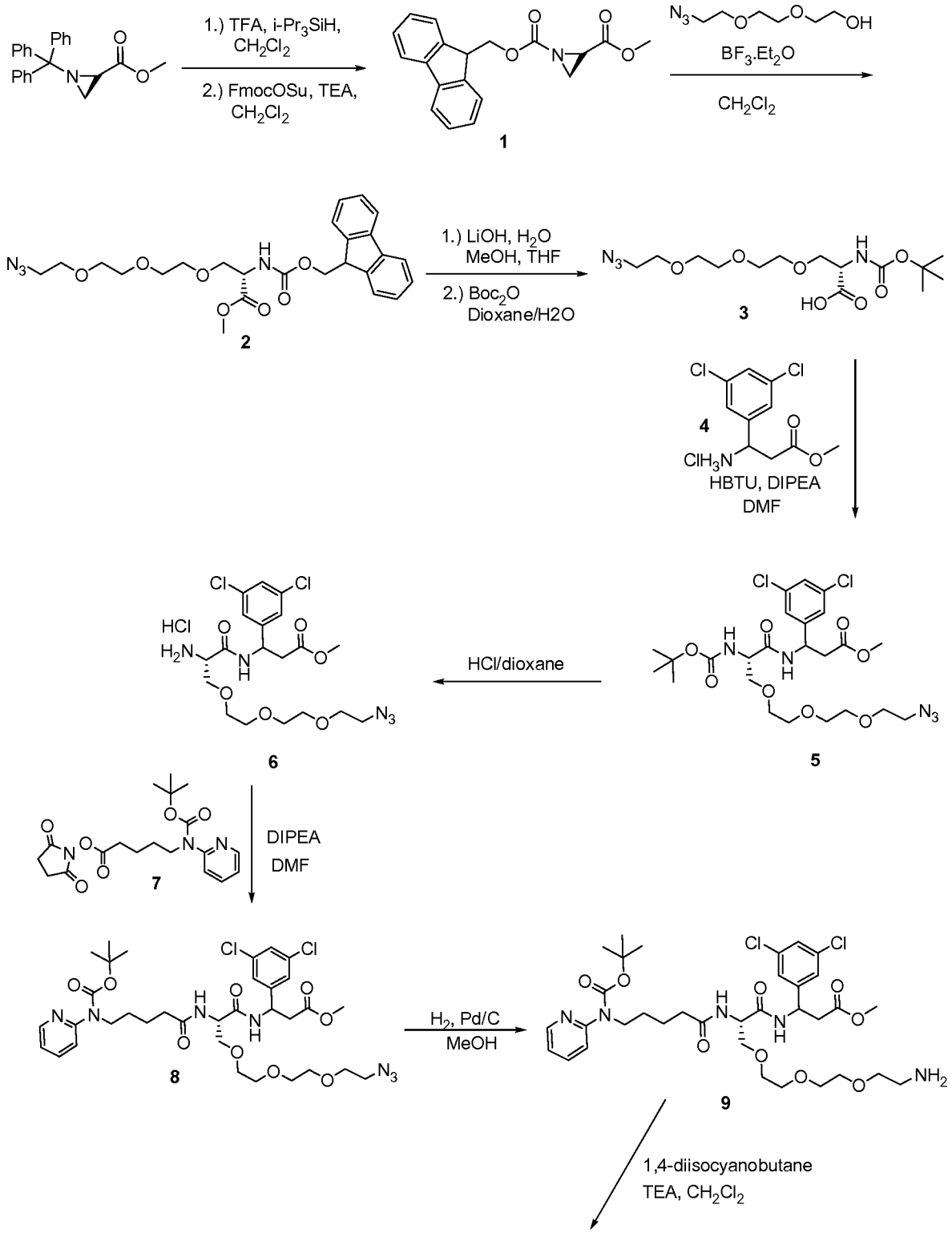
HOAt	1-hydroxy-7-azabenzotriazole
HOBT	1-hydroxybenztriazole
HOSu	N-hydroxysuccinamide
HPLC	high performance liquid chromatography
LAH	lithium aluminum anhydride
Me	methyl
MeI	methyliodide
MeOH	methanol
MOMCl	methoxymethylchloride
MOM	methoxymethyl
MS	mass spectroscopy
NMP	*N*-methyl-pyrrolidin-2-one
NMR	nuclear magnetic resonance
PyBOP	benzotriazole-1-yl-oxytris-pyrrolidino-phosphonium Hexafluorophosphate
SPHOS	2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl
TBD	1,5,7-triazabicyclo[4.4.0]-dec-5-ene
RP-HPLC	reverse phase-high pressure liquid chromatography
TBS	*tert*-butyldimethylsilyl
TBSCl	*tert*-butyldimethylsilyl chloride
TBTU	O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium
TEOC	2-Trimethylsilylethyl Carbamate
TFA	trifluoroacetic acid
Tf_2O	trifluoromethanesulfonic anhydride
TMG	1,1,3,3-Tetramethylguanidine
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
XPHOS	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

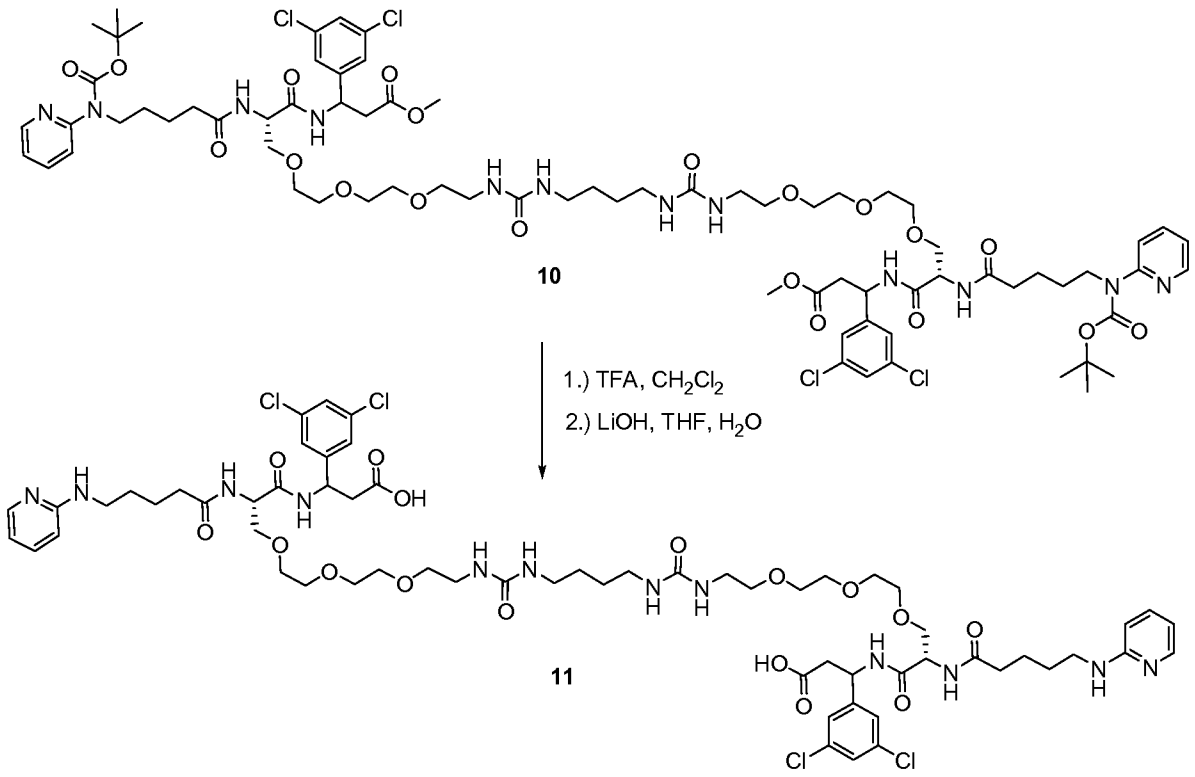
General Examples for the Preparation of Compounds of the Invention

[00251] The starting materials and intermediates for the compounds of this invention may be prepared by the application or adaptation of the methods described below, their obvious chemical equivalents, or, for example, as described in literature such as The Science of

Synthesis, Volumes 1-8. Editors E. M. Carreira et al. Thieme publishers (2001-2008). Details of reagent and reaction options are also available by structure and reaction searches using commercial computer search engines such as Scifinder or Reaxys. LC/MS Method A is a low mass spec method – scanning up to 1 kDa; LC/MS Method B is a high mass spec method – scanning up to 2.2 kDa.

Example 1: Synthesis of Compound 11





[00252] A solution of *N*-trityl-2-carboxymethyl-aziridine (1.00 g, 2.91 mmol) and triisopropylsilane (920 mg, 5.83 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 °C in an ice bath and TFA (2 mL) was added dropwise. The solution was stirred for 2 hours and the reaction progress was monitored by TLC. Upon completion of the reaction, the solvent was removed *in vacuo* affording a white solid and an orange oil. Hexanes (10 mL) was added and gently warmed to dissolve all of the solid, resulting in two liquid phases. The top phase was decanted and more hexanes (10 mL) was added. The heating/decanting process was repeated. The resulting orange oil was dried *in vacuo*. The crude oil was dissolved in CH_2Cl_2 (10 mL), cooled to 0 °C in an ice bath and FmocOSu (980 mg, 2.91 mmol) was added. To this solution was added TEA (590 mg, 5.82 mmol) and the reaction mixture was stirred for 5 hours at room temperature. TLC analysis of the reaction mixture confirmed the presence of the desired product. The reaction was quenched with sat. NH_4Cl (1 mL), diluted with water (10 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over $NaSO_4$, filtered and the filtrate was evaporated *in vacuo* to afford an orange oil. The mixture was purified by column chromatography (hexanes:ethyl acetate) to afford **1** as a tacky white solid (652 mg, 69%). ^1H NMR (400 MHz, $CDCl_3$) δ 2.49 (dd, J = 1.2, 5.6 Hz, 1H), 2.65 (dd, J = 1.2, 3.2 Hz, 1H), 3.13 (dd, J = 3.2, 5.6 Hz, 1H), 3.76 (s, 3H), 4.29 (t, J = 7.2 Hz, 1H) 4.39 (m, 1H), 4.51 (m, 1H), 7.33 (t, J = 7.2 Hz, 2H), 7.44 (t, J = 7.2 Hz, 2H), 7.62 (d, J = 8.4 Hz, 2H), 7.80 (d, J = 7.6 Hz, 2H).

[00253] To a solution of **1** (2.00 g, 6.19 mmol) and N_3-PEG_3-OH (2.71 g, 15.48 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added $BF_3{\cdot}OEt_2$ (10 drops). The resulting solution was allowed to stir at room temperature for 48 hours and the reaction progress was monitored by TLC. The reaction was quenched with sat. NH_4Cl (1 mL), diluted with water (20 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with brine (3 x 30 mL), dried over $NaSO_4$, filtered and the filtrate was evaporated to afford a light yellow oil. The mixture was purified by column chromatography (hexanes:ethyl acetate) to afford **2** as a viscous clear oil (1.92 g, 62%). ^1H NMR (400 MHz, $CDCl_3$) δ 3.38 (t, J = 5.2 Hz, 2H), 3.60-3.78 (m, 12H), 3.80 (s, 3H), 4.01 (m, 1H), 4.29 (t, J = 7.2 Hz, 1H) 4.37-4.54 (m, 3H), 5.89 (d, br, J = 8.8 Hz, 1H), 7.35 (t, J = 7.6 Hz, 2H), 7.43 (t, J = 7.6 Hz, 2H), 7.65 (t, J = 7.2 Hz, 2H), 7.79 (d, J = 7.2 Hz, 2H).

[00254] Fmoc-Ser(PEG_3-N_3)-OMe (1.92 g, 3.84 mmol) was dissolved in dioxane (8 mL) and methanol (8 mL), and 1M LiOH (16 mL) was added to the solution at 0 °C with vigorous stirring. The reaction was stirred at room temperature and monitored by LC/MS until full hydrolysis of both the Fmoc and methyl ester was observed (method A: t = 2.44 min, *m/z* = 263 $[M+H]^+$). Upon completion of the reaction, the solvents were removed *in vacuo* producing a white solid and pale yellow oil. The residue was dissolved in water (15 mL) and Et_2O (30 mL). The aqueous layer was collected, washed with Et_2O (10 mL) and the pH of the solution was adjusted to 8 using 3M HCl. A solution of *t*-Boc anhydride (912 mg, 4.22 mmol) in dioxane (15 mL) was added at room temperature and the resulting mixture was stirred overnight. Reaction completion was confirmed by LC/MS (method A: t = 3.46 min, *m/z* = 263 $[M\text{-}Boc+H]^+$, 385 $[M+Na]^+$) and the organic solvent was evaporated using a stream of N_2. The aqueous layer was basified to pH 12 using 1M NaOH, washed with Et_2O (2 x 20 mL) and carefully acidified to pH 5.5 with 3M HCl (aq). The water was removed by lyophilization to afford a clear oil and white solid. To the crude mixture was added CH_2Cl_2 (20 mL) to dissolve the oil and any insoluble salt was removed by filtration. Concentration of the filtrate *in vacuo* afforded **3** as a viscous clear oil (945 mg, 68%); ^1H NMR (400 MHz, $CDCl_3$) δ 1.45 (s, 9H), 3.43 (t, J = 5.2 Hz, 2H), 3.64-3.70 (m, 12 H), 4.10 (m, 1H), 5.90 (s, br, 1H); LC/MS (method A): 3.46 min, *m/z* = 263 $[M\text{-}Boc+H]^+$.

[00255] To a solution of **4** (400 mg, 1.42 mmol), **3** (616 mg, 1.70 mmol), HBTU (645 mg, 1.70 mmol) and HOBt (27 mg, 0.17 mmol) in DMF (4 mL) was added DIPEA (430 mg, 3.40 mmol), dropwise at 0 °C. The resulting solution was stirred at room temperature for 2 hours and the reaction was monitored by TLC. Upon completion of the reaction, water (50 mL) and CH_2Cl_2 (30 mL) were added. The organic layer was collected and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with brine (3 x 40 mL), dried

over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The crude was purified by column chromatrography (hexanes:ethyl acetate) to afford **5** (488 mg, 58%) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 1.47 (s, 9H), 2.31 (m, 2H), 2.82-2.90 (m, 2H), 3.40 (m, 2H), 3.42-3.55 (m, 1H), 3.54-3.75 (m, 14H), 3.78-3.88 (m, 1H), 4.30 (m, 1H), 5.37 (m, 1H), 5.54-5.70 (m, 1H), 7.22 (m, 1H), 7.24-7.27 (m, 2H); LC/MS (method A): t = 4.21 min, *m/z* = 614 $[M+Na]^+$, 492 $[M\text{-}Boc+H]^+$.

[00256] To a solution of **5** (450 mg, 0.76 mmol) in dioxane (2 mL) was added 4M HCl/dioxane (5 mL), dropwise. The reaction mixture was stirred at room temperature overnight. The resulting solution was then concentrated *in vacuo* affording a pale yellow oil. The oil was triturated with ether to afford **6** (334 mg, 84%) as a tacky white solid, which was used in the subsequent step without further purification.

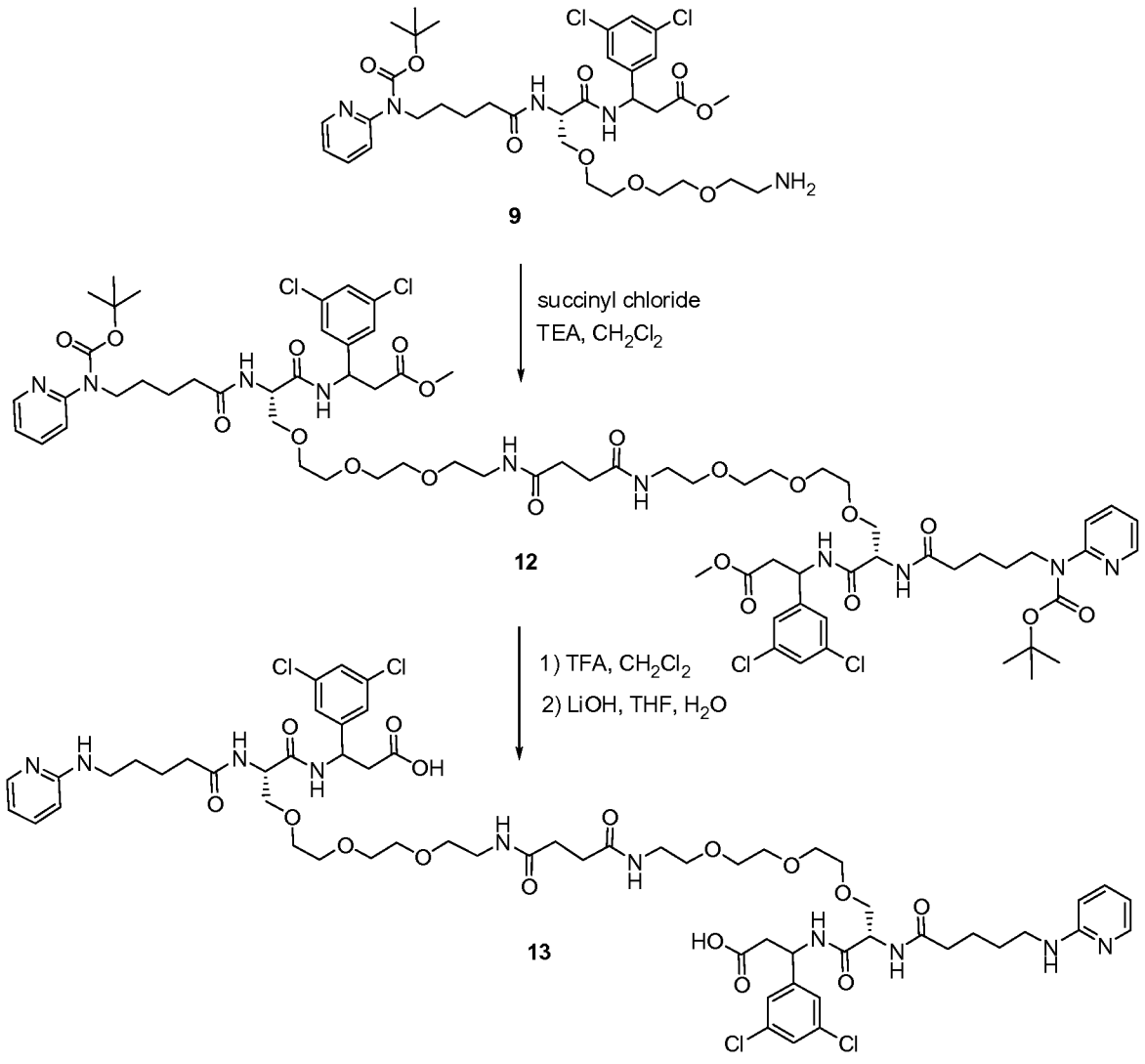
[00257] To a solution of **6** (250 mg, 0.47 mmol) and **7** (223 mg, 0.57 mmol) in DMF (3 mL) was added DIPEA (145 mg, 1.14 mmol), dropwise. The resulting solution was stirred at room temperature for 5 hours and the reaction progress was monitored by TLC. Upon completion of the reaction, water (30 mL) and CH_2Cl_2 (30 mL) were added. The organic layer was collected and the aqueous layer was extracted with CH_2Cl_2 (2 x 40 mL). The combined organic layers were washed with brine (3 x 40 mL), dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The crude residue was purified by column chromatrography (CH_2Cl_2:MeOH) to afford **8** (244 mg, 68%) as a clear oil. ^1H NMR (400 MHz, $CDCl_3$) δ 1.52 (s, 9H), 1.69 (m, 4H), 2.31 (m, 2H), 2.85 (m, 2H), 3.38 (q, J = 5.2 Hz, 2H), 3.42-3.55 (m, 1H), 3.60-3.75 (m, 13H), 3.86 (m, 2H), 4.57 (m, 1H), 5.35 (m, 1H), 7.03 (m, 1H), 7.22-7.27 (m, 3H), 7.54-7.76 (m, 3H), 8.39 (m, 1H); LC/MS (method A): t = 4.11 min, *m/z* = 768 $[M+H]^+$, 678 $[M+\text{-}Boc+H]^+$.

[00258] To a solution of **8** (230 mg, 0.30 mmol) in MeOH (5 mL) was added Pd/C (50 mg). The reaction vessel was purged with H_2 gas and the mixture was stirred under H_2 for 20 minutes, during which time the reaction progress was monitored by TLC. Upon disappearance of the starting material, the reaction vessel was purged with N_2 and MeOH (8 mL) was added. The Pd/C was removed by filtration and the filtrate was concentrated in vacuo to afford **9** (209 mg, 94%) as a clear oil. LC/MS (method A): t = 3.34 min, *m/z* = 742 $[M+H]^+$, 764 $[M+Na]^+$.

[00259] To a solution of **9** (100 mg, 0.135 mmol) and TEA (41 mg, 0.41 mmol) in CH_2Cl_2 (3.0 mL) was added a solution of 1,4-diisocyanobutane (6.6 mg, 0.061 mmol) in CH_2Cl_2 (1.0 mL), dropwise at room temperature. The resulting solution was stirred at room temperature overnight. The solvent was evaporated and the crude material **10** was used directly for the next step. LC/MS (method B): t = 3.96 min, 1625 $[M+H]^+$, 1525 $[M\text{-}Boc+H]^+$.

[00260] To a solution of crude **10** (99 mg, 0.061 mmol) in dioxane (1 mL) was added 4M HCl/dioxane (2 mL), dropwise. The reaction mixture was stirred at room temperature and the reaction progress was monitored by LC/MS (method B: t = 3.47, 1425 $[M+H]^+$). Upon completion of the reaction, the solvent was evaporated and the resulting oil was dissolved in dioxane (2 mL). To this solution was added 2M LiOH (2 mL), and the reaction mixture was stirred at room temperature. Upon completion of the reaction, the solution was neutralized with 3M HCl and the dioxane was evaporated by a N_2 stream. MeCN (2 mL) was added to afford a pale yellow solution. Purification by preparatory HPLC (0.05% TFA, water/MeCN) afforded **11** (16 mg) as the TFA salt. ^{1}H NMR (400 MHz, CD_3OD) δ 1.48 (m, 4H), 1.69-1.79 (m, 8H), 2.39 (m, 4H), 2.88 (m, 4H), 3.12 (m, 4H), 3.29 (m, 4H), 3.39 (t, J = 6.8 Hz, 2H), 3.52 (q, J = 5.2 Hz, 4H), 3.59-3.78 (m, 22H), 4.55 (t, J = 5.2 Hz, 2H), 5.29 (t, J = 6.4 Hz, 2H), 6.87 (m, 2H), 7.03 (t, J = 8.4 Hz, 2H), 7.34 (m, 2H), 7.36 (m, 4H), 7.80 (d, J = 8.4 Hz, 2H), 7.86 (m, 2H); LC/MS (method B): t = 3.31 min, *m/z* = 1397 $[M+H]^+$, 699 $[M+2H]^{2+}$.

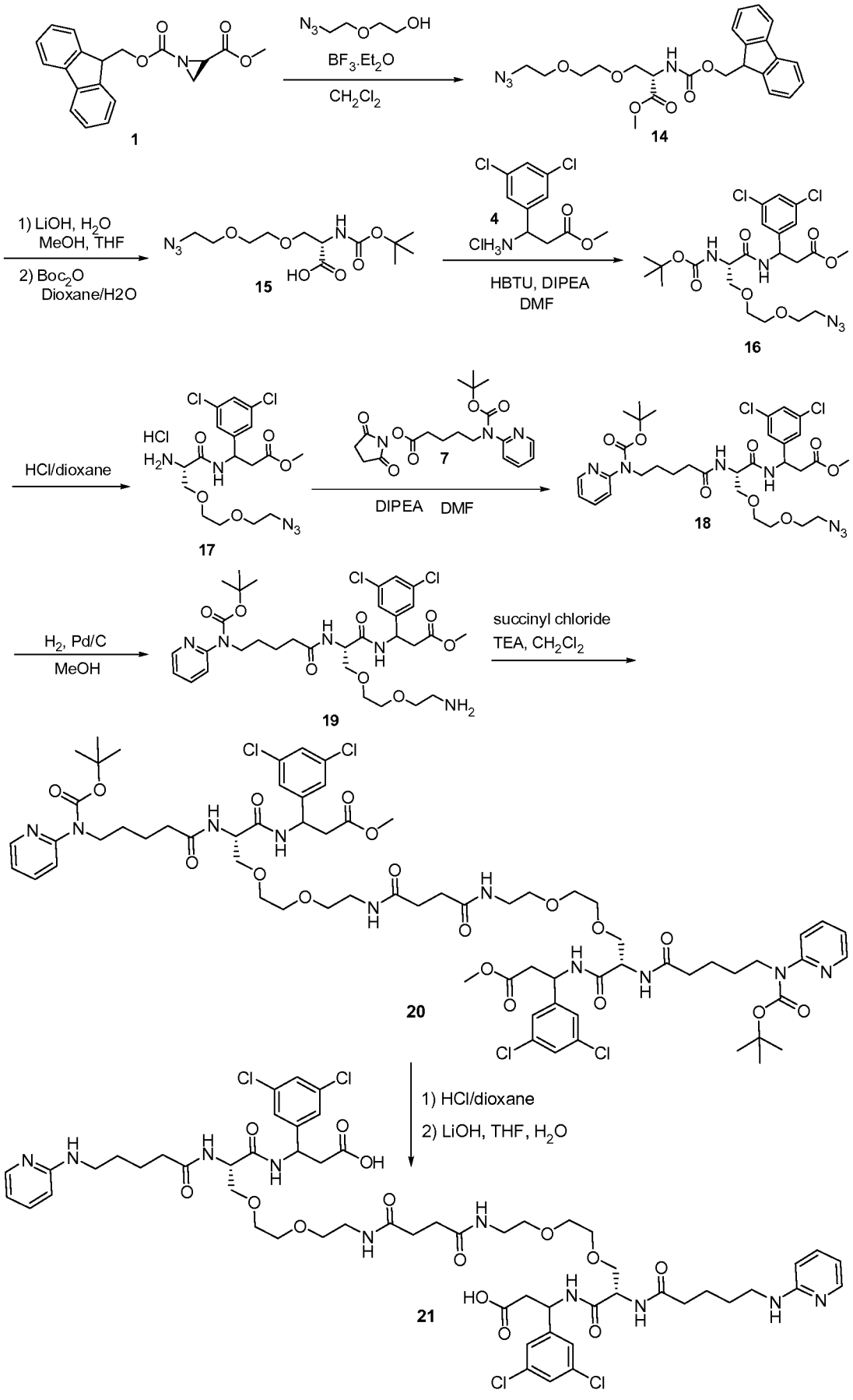
Example 2: Synthesis of Compound 13



[00261] A solution of **9** (100 mg, 0.135 mmol) and TEA (68 mg, 0.68 mmol) in CH_2Cl_2 (3.0 mL) was cooled to -20 °C in a dry ice/acetone bath. To this was added a solution of succinyl chloride (9.4 mg, 0.061 mmol) in CH_2Cl_2 (1.0 mL), dropwise. The resulting solution was stirred at room temperature overnight. The solvent was evaporated and the crude material **12** was used directly for the next step. LC/MS (method B): t = 4.09 min, 1468 $[M\text{-}Boc+H]^+$, 1368 $[M\text{-}2Boc+H]^+$.

[00262] To a solution of crude **12** (95 mg, 0.061 mmol) in dioxane (1 mL) was added 4M HCl/dioxane (2 mL), dropwise. The reaction mixture was stirred at room temperature and the reaction progress was monitored by LC/MS (method B: t = 3.46, 1367 $[M+H]^+$). Upon completion of the reaction, the solvent was evaporated and the resulting oil was dissolved in dioxane (2 mL). To this solution was added 2M LiOH (2 mL), and the reaction mixture was stirred at room temperature. Upon completion of the reaction, the solution was neutralized with 3M HCl and the dioxane was evaporated by a N_2 stream. MeCN (2 mL) was added to afford an orange solution. Purification by preparatory HPLC (0.05% TFA, water/MeCN) afforded **13** (22 mg) as the TFA salt. ^1H NMR (400 MHz, CD_3OD) δ 1.64-1.80 (m, 8H), 2.39 (m, J = 6.8 Hz, 4H), 2.50 (s, 4H), 2.86 (m, 4H), 3.36 (m, 4H), 3.53 (q, J = 5.2 Hz, 4H), 3.60-3.78 (m, 18 H), 4.56 (q, J = 5.2 Hz, 2H), 5.29 (t, J = 7.2 Hz, 2H), 6.88 (m, 2H), 7.03 (t, J = 8.8 Hz, 2H), 7.32 (m, 2H), 7.36 (m, 4H), 7.80 (m, 2H), 7.87 (m, 2H); LC/MS (method B): t = 3.34 min, *m/z* = 1339 $[M+H]^+$, 670 $[M+2H]^{2+}$.

Example 3: Synthesis of Compound 21



[00263] To a solution of **1** (1.00 g, 3.10 mmol) and N_3-PEG_2-OH (1.22 g, 9.29 mmol) in CH_2Cl_2 (8 mL) at 0 °C was added $BF_3{\cdot}OEt_2$ (7 drops). The resulting solution was allowed to stir at room temperature for 48 hours and the reaction progress was monitored by TLC. The reaction was quenched with sat. NH_4Cl (1 mL), diluted with water (10 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were washed with brine (3 x 20 mL), dried over $NaSO_4$, filtered and the filtrate was evaporated to afford a light yellow oil. The mixture was purified by column chromatography (hexanes:ethyl acetate) to afford **14** as a viscous clear oil (1.13 g, 80%). ^1H NMR (400 MHz, $CDCl_3$) δ 3.38 (m, 2H), 3.54-3.88 (m, 8H), 3.74 (s, 3H), 4.09 (m, 1H), 4.29 (m, 1H) 4.37-4.54 (m, 3H), 5.90 (d, br, J = 8.4 Hz, 1H), 7.36 (t, J = 7.6 Hz, 2H), 7.45 (t, J = 7.6 Hz, 2H), 7.65 (t, J = 7.2 Hz, 2H), 7.80 (d, J = 7.2 Hz, 2H).

[00264] Compound **14** (1.13 g, 2.49 mmol) was dissolved in dioxane (5 mL) and methanol (5 mL), and 1M LiOH (10 mL) was added to the solution at 0 °C with vigorous stirring. The reaction was stirred at room temperature and monitored by LC/MS until full hydrolysis of both the Fmoc and methyl ester was observed (method A: t = 2.28 min, *m/z* = 219 $[M+H]^+$). Upon completion of the reaction, the solvents were removed *in vacuo* producing a white solid and pale yellow oil. The residue was dissolved in water (10 mL) and Et_2O (20 mL). The aqueous layer was collected, washed with Et_2O (10 mL) and the pH of the solution was adjusted to 8 using 3M HCl. A solution of *t*-Boc anhydride (650 mg, 2.98 mmol) in dioxane (8 mL) was added at room temperature and the resulting mixture was stirred overnight. Reaction completion was confirmed by LC/MS (method A: t = 3.46 min, *m/z* = 263 $[M\text{-}Boc+H]^+$, 385 $[M+Na]^+$) and the organic solvent was evaporated using a stream of N_2. The aqueous layer was basified to pH 12 using 1M NaOH, washed with Et_2O (2 x 20 mL) and carefully acidified to pH 5.5 with 3 M HCl (aq). The water was removed by lyophilization to afford a clear oil and white solid. To the crude mixture was added CH_2Cl_2 (20 mL) to dissolve the oil and any insoluble salt was removed by filtration. Concentration of the filtrate *in vacuo* afforded **15** as a viscous clear oil (490 mg, 62%). ^1H NMR (400 MHz, $CDCl_3$) δ 1.45 (s, 9H), 3.44 (t, J = 4.8 Hz, 2H), 3.62-3.71 (m, 8 H), 4.14 (m, 1H), 4.69 (s, br, 1H), 5.81 (s, br, 1H); LC/MS (method A): t = 3.43 min, *m/z* = 219 $[M\text{-}Boc+H]^+$.

[00265] To a solution of **4** (310 mg, 1.10 mmol), **15** (420 mg, 1.32 mmol), HBTU (500 mg, 1.32 mmol) and HOBt (21 mg, 0.13 mmol) in DMF was added DIPEA (335 mg, 2.64 mmol), dropwise at 0 °C. The resulting solution was stirred at room temperature for 2 hours and the reaction was monitored by TLC. Upon completion of the reaction, water (30 mL) and CH_2Cl_2 (40 mL) were added. The organic layer was collected and the aqueous layer was extracted with CH_2Cl_2 (2 x 40 mL). The combined organic layers were washed with brine (3 x 50 mL), dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The crude was purified by

column chromatrography (hexanes:ethyl acetate) to afford **16** (385 mg, 64%) as a white solid. LC/MS (method A): t = 4.17 min, *m/z* = 570 $[M+Na]^+$, 448 $[M-Boc+H]^+$.

[00266] To a solution of **16** (380 mg, 0.69 mmol) in dioxane (2 mL) was added 4M HCl/dioxane (4 mL), dropwise. The reaction mixture was stirred at room temperature overnight. The resulting solution was then concentrated *in vacuo* affording a pale yellow oil. The oil was triturated with ether to afford **17** (294 mg, 88%) as a white solid, which was used in the subsequent step without further purification.

[00267] To a solution of **17** (290 mg, 0.60 mmol) and **7** (305 mg, 0.78 mmol) in DMF (3 mL) was added DIPEA (190 mg, 1.51 mmol), dropwise. The resulting solution was stirred at room temperature for 5 hours and the reaction progress was monitored by TLC. Upon completion of the reaction, water (40 mL) and CH_2Cl_2 (30 mL) were added. The organic layer was collected and the aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layers were washed with brine (3 x 40 mL), dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The crude residue was purified by column chromatrography (CH_2Cl_2:MeOH) to afford **18** (267 mg, 62%) as a clear oil. ^1H NMR (400 MHz, $CDCl_3$) δ 1.48 (s, 9H), 1.69 (m, 4H), 2.29 (m, 2H), 2.84 (m, 2H), 3.38 (m, 2H), 3.45 (m, 1H), 3.59-3.88 (m, 11H), 4.55 (m, 1H), 5.37 (m, 1H), 7.03 (m, 1H), 7.20 (s, 1H), 7.27 (s, 2H), 7.54-7.76 (m, 3H), 8.40 (s, br, 1H); LC/MS (method A): t = 3.97 min, *m/z* = 624 $[M-Boc+H]^+$, 746 $[M+Na]^+$.

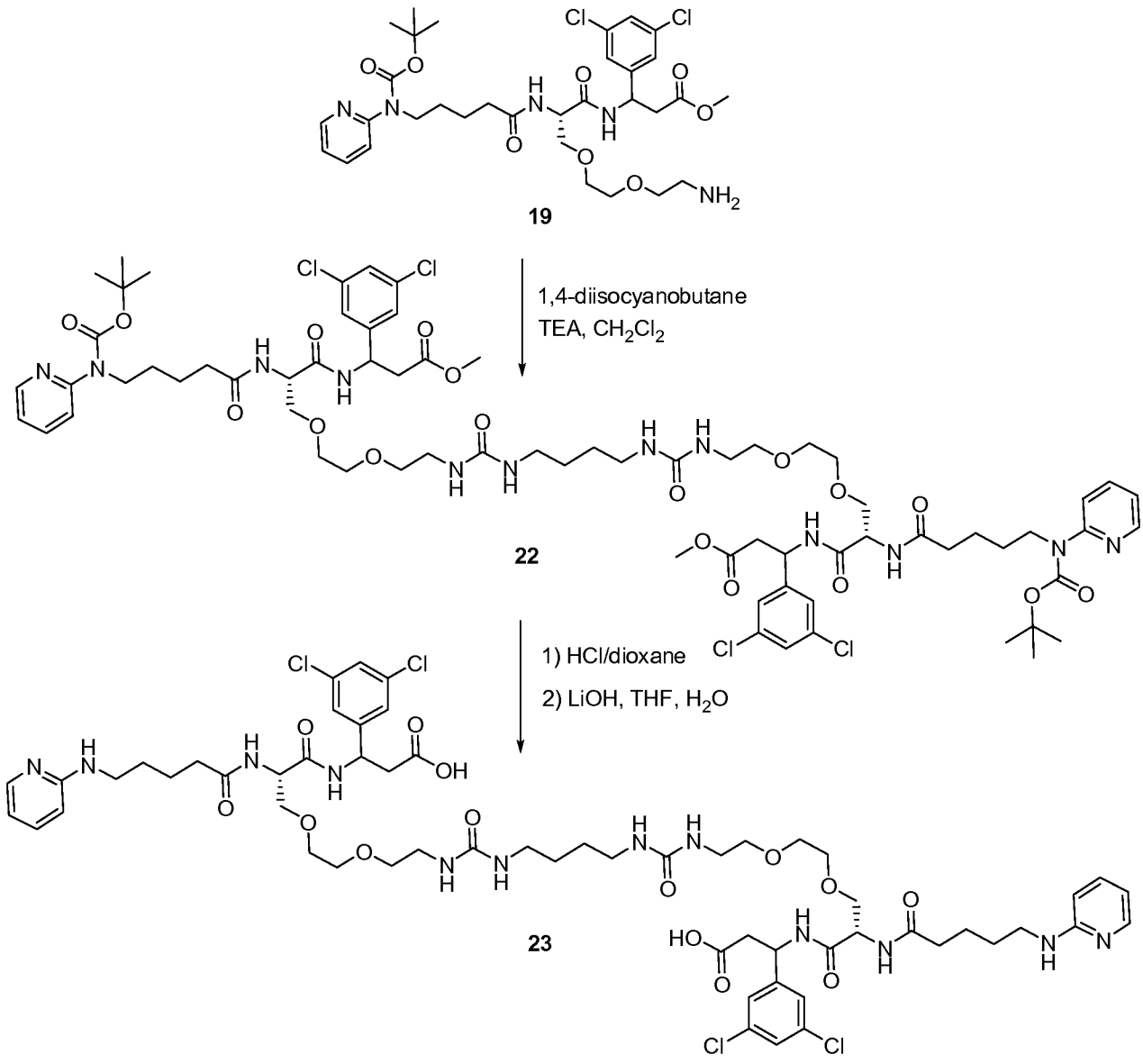
[00268] To a solution of **18** (260 mg, 0.36 mmol) in MeOH (5 mL) was added Pd/C (50 mg). The reaction vessel was purged with H_2 gas and the mixture was stirred under H_2 for 20 minutes, during which time the reaction progress was monitored by TLC. Upon disappearance of the starting material, the reaction vessel was purged with N_2 and MeOH (10 mL) was added. The Pd/C was removed by filtration and the filtrate was concentrated in vacuo to afford **19** (206 mg, 82%) as a clear oil. LC/MS (method A): t = 3.32 min, *m/z* = 598 $[M-Boc+H]^+$, 698 $[M+H]^+$.

[00269] A solution of **19** (30 mg, 0.043 mmol) and TEA (22 mg, 0.22 mmol) in CH_2Cl_2 (1.5 mL) was cooled to -20 °C in a dry ice/acetone bath. To the reaction mixture was added a solution of succinyl chloride (3.0 mg, 0.019 mmol) in CH_2Cl_2 (0.5 mL), dropwise. The resulting solution was stirred at room temperature overnight. The solvent was evaporated and the crude material **20** was used directly for the next step. LC/MS (method B): t = 4.39 min, *m/z* = 1479 $[M+H]^+$, 1379 $[M-Boc+H]^+$.

[00270] To a solution of crude **20** (28 mg, 0.019 mmol) in dioxane (0.3 mL) was added 4M HCl/dioxane (1 mL), dropwise. The reaction mixture was stirred at room temperature and the reaction progress was monitored by LC/MS (Method B: t = 3.60; *m/z* = 1279 $[M+H]^+$). Upon completion of the reaction, the solvent was evaporated and the resulting oil was dissolved in

dioxane (1 mL). To this solution was added 2M LiOH (1 mL), and the reaction mixture was stirred at room temperature. Upon completion of the reaction, the solution was neutralized with 3M HCl and the dioxane was evaporated by a N_2 stream. MeCN (1 mL) was added to afford an orange solution. Purification by preparatory HPLC (0.05% TFA, water/MeCN) afforded **21** (3.6 mg) as the TFA salt. LC/MS (method B): t = 3.21 min, *m/z* = 1251 $[M+H]^+$, 626 $[M+2H]^{2+}$.

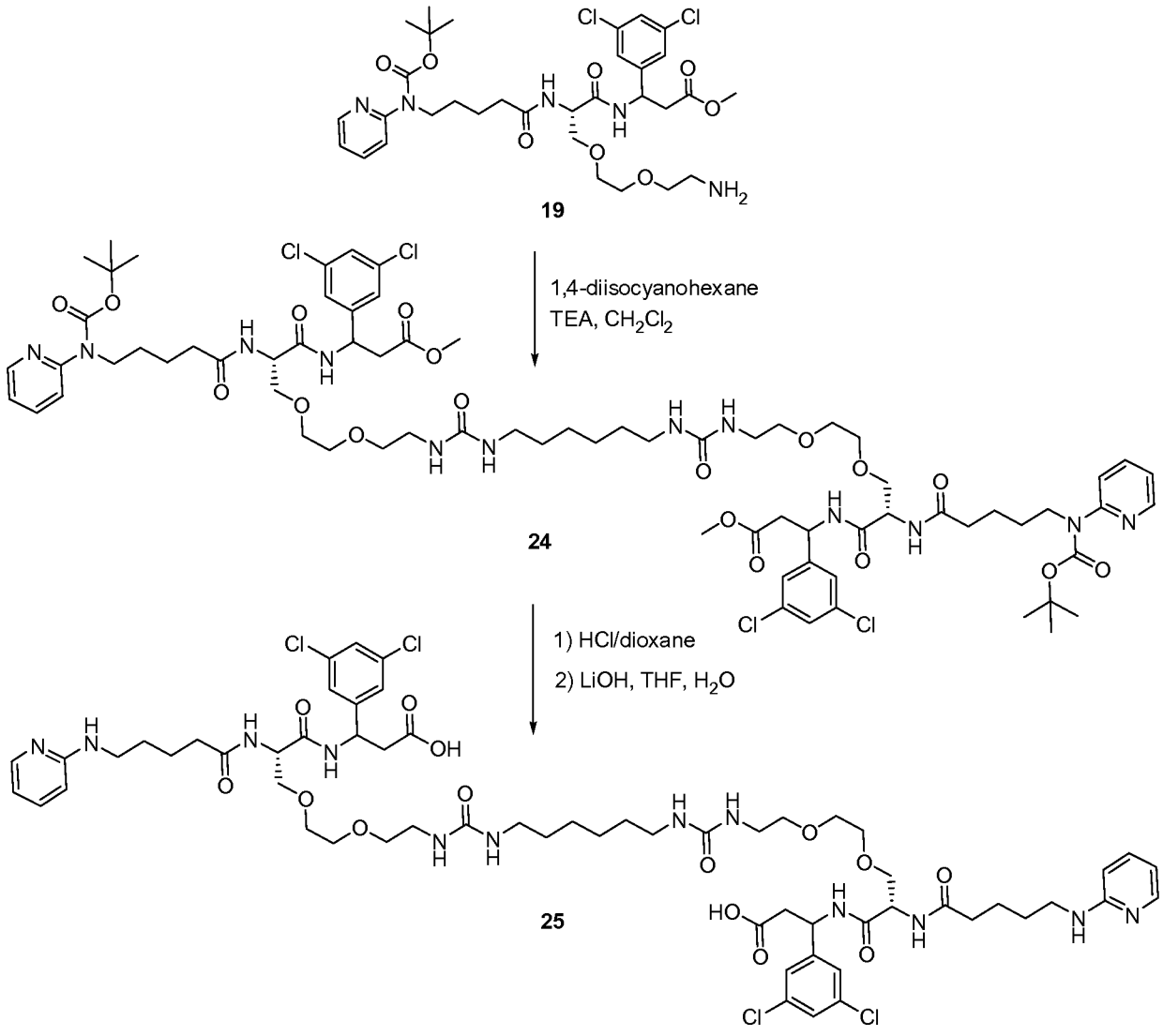
Example 4: Synthesis of Compound 23



[00271] To a solution of **9** (110 mg, 0.158 mmol) and TEA (48 mg, 0.47 mmol) in CH_2Cl_2 (3.0 mL) was added a solution of 1,4-diisocyanobutane (7.7 mg, 0.071 mmol) in CH_2Cl_2 (1.0 mL), dropwise at room temperature. The resulting solution was stirred at room temperature overnight. The solvent was evaporated and the crude material **22** was used directly for the next step. LC/MS (method B): t = 4.30 min, *m/z* = 1537 $[M+H]^+$, 1437 $[M\text{-}Boc+H]^+$.

[00272] To a solution of crude **22** (109 mg, 0.071 mmol) in dioxane (1.5 mL) was added 4M HCl/dioxane (2.5 mL), dropwise. The reaction mixture was stirred at room temperature and the reaction progress was monitored by LC/MS (Method B: t = 3.46; *m/z* = 1337 $[M+H]^+$). Upon completion of the reaction, the solvent was evaporated and the resulting oil was dissolved in dioxane (3 mL). To this solution was added 2M LiOH (3 mL), and the reaction mixture was stirred at room temperature. Upon completion of the reaction, the solution was neutralized with 3M HCl and the dioxane was evaporated by a N_2 stream. MeCN (2 mL) was added to afford a pale yellow solution. Purification by preparatory HPLC (0.05% TFA, water/MeCN) and subsequent lyophilization afforded **23** (16 mg) as the TFA salt. ^1H NMR (400 MHz, CD_3OD) δ 1.48 (m, 4H), 1.68-1.81 (m, 8H), 2.39 (m, 4H), 2.87 (m, 4H), 3.13 (m, 4H), 3.28 (m, 4H), 3.37 (m, 2H), 3.48-3.80 (m, 16H), 4.57 (q, J = 5.2 Hz, 2H), 5.29 (t, J = 6.4 Hz, 2H), 6.88 (m, 2H), 7.04 (t, J = 8.8 Hz, 2H), 7.32 (m, 2H), 7.36 (m, 4H), 7.81 (m, 2H), 7.88 (m, 2H); LC/MS (method B): t = 3.23 min, *m/z* = 1309 $[M+H]^+$, 655 $[M+2H]^{2+}$.

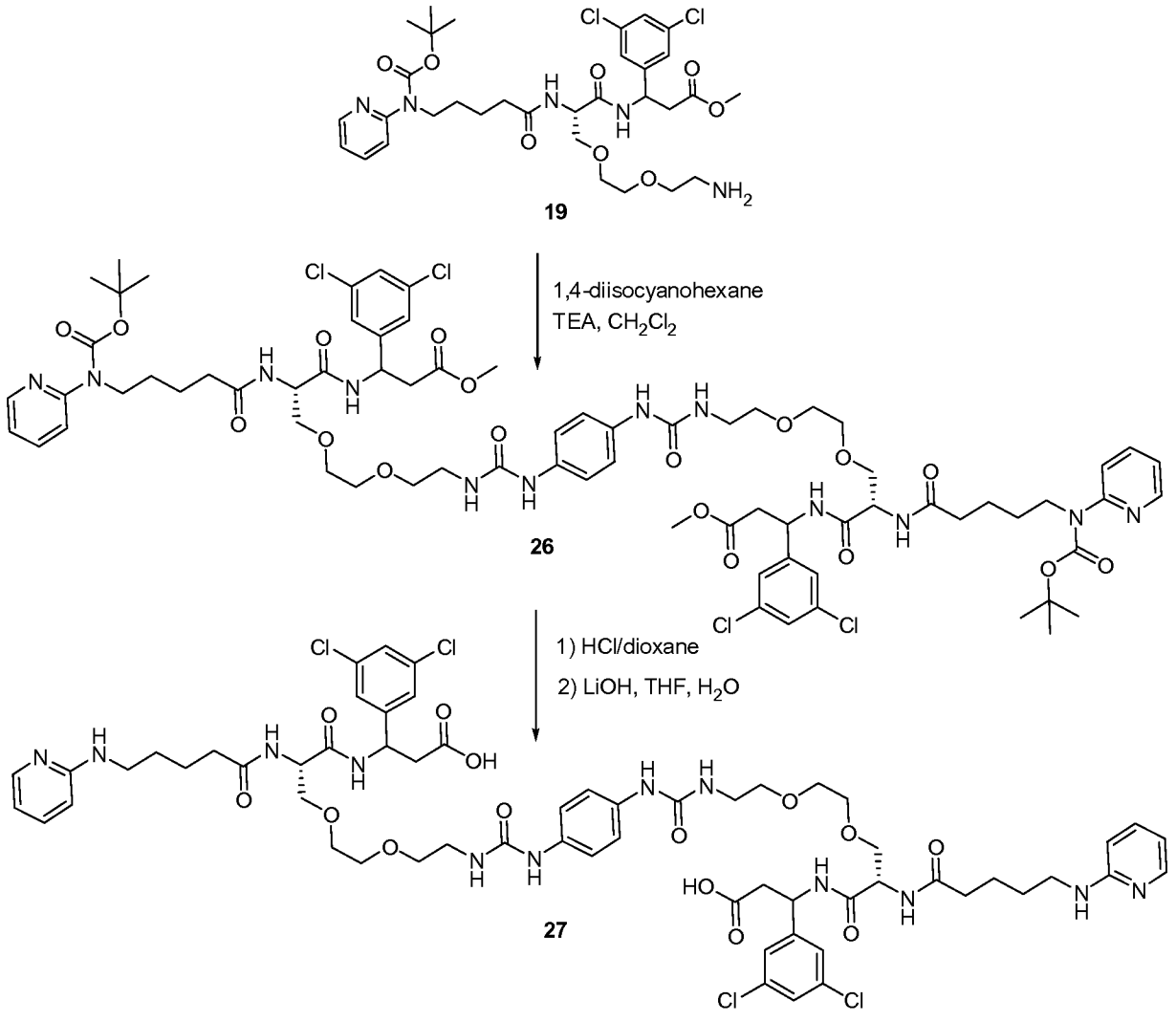
Example 5: Synthesis of Compound 25



[00273] To a solution of **9** (30 mg, 0.043 mmol) and TEA (13 mg, 0.13 mmol) in CH_2Cl_2 (1.5 mL) was added a solution of 1,6-diisocyanohexane (3.2 mg, 0.019 mmol) in CH_2Cl_2 (0.5 mL), dropwise at room temperature. The resulting solution was stirred at room temperature overnight. The solvent was evaporated and the crude material **24** was used directly for the next step. LC/MS (method B): t = 4.44 min, *m/z* = 1565 $[M+H]^+$, 1465 $[M\text{-}Boc+H]^+$.

[00274] To a solution of crude **24** (30 mg, 0.019 mmol) in dioxane (0.3 mL) was added 4M HCl/dioxane (1 mL), dropwise. The reaction mixture was stirred at room temperature and the reaction progress was monitored by LC/MS (Method B: t = 3.32; *m/z* = 1365 $[M+H]^+$). Upon completion of the reaction, the solvent was evaporated and the resulting oil was dissolved in dioxane (1 mL). To this solution was added 2M LiOH (1 mL), and the reaction mixture was stirred at room temperature. Upon completion of the reaction, the solution was neutralized with 3M HCl and the dioxane was evaporated by a N_2 stream. MeCN (1 mL) was added to afford a pale yellow solution. Purification by preparatory HPLC (0.05% TFA, water/MeCN) afforded **25** (3.2 mg) as the TFA salt. LC/MS (method B): t = 3.28 min, *m/z* = 1337 $[M+H]^+$, 669 $[M+2H]^{2+}$.

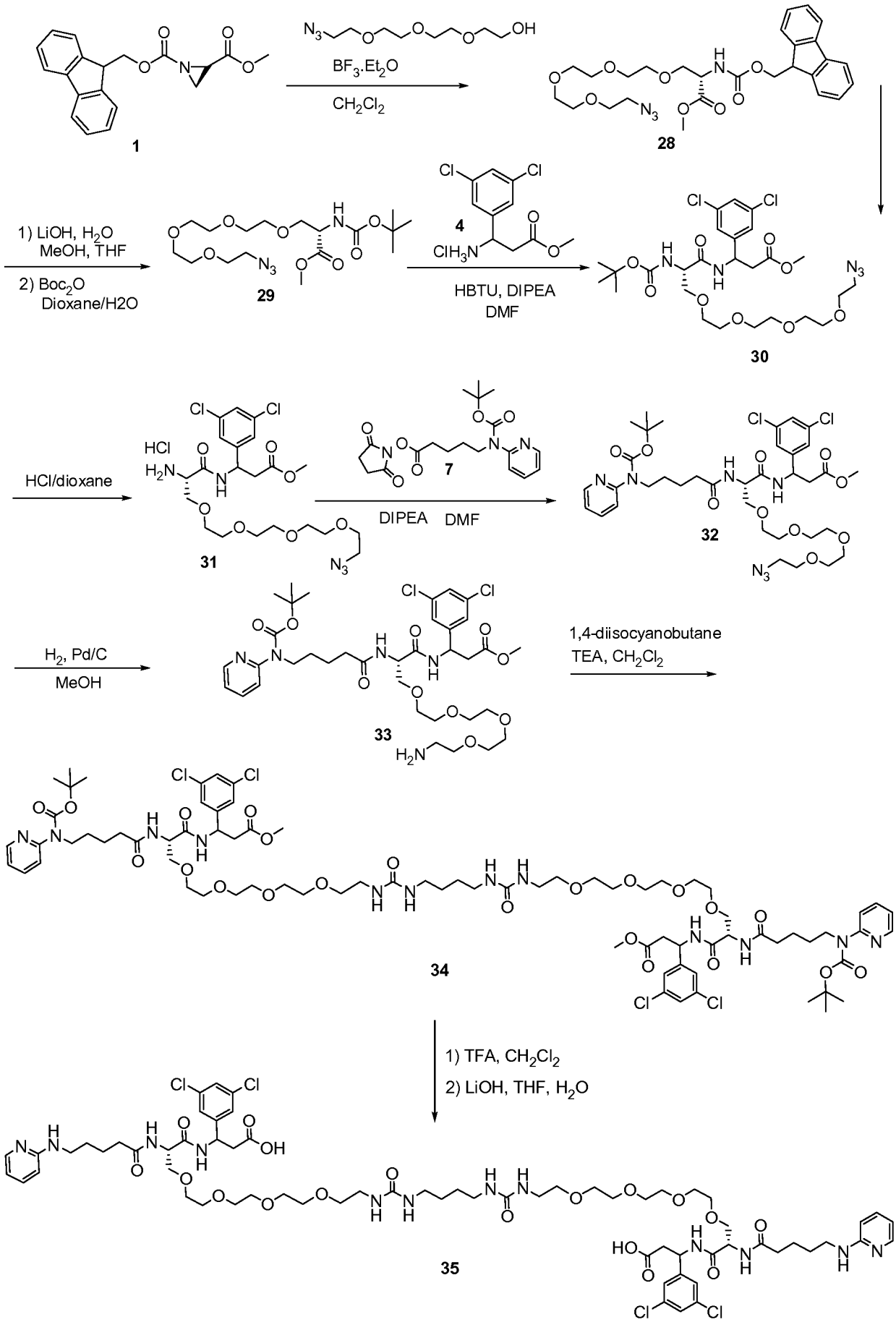
Example 6: Synthesis of Compound 27



[00275] To a solution of **9** (30 mg, 0.043 mmol) and TEA (13 mg, 0.13 mmol) in CH_2Cl_2 (1.5 mL) was added a solution of 1,4-phenylene diisocyante (3.2 mg, 0.019 mmol) in CH_2Cl_2 (0.5 mL), dropwise at room temperature. The resulting solution was stirred at room temperature overnight. The solvent was evaporated and the crude material **26** was used directly for the next step. LC/MS (method B): t = 4.31 min, *m/z* = 1457 $[M\text{-}Boc+H]^+$, 679 $[M\text{-}2Boc+2H]^{2+}$.

[00276] To a solution of crude **26** (29 mg, 0.019 mmol) in dioxane (0.3 mL) was added 4M HCl/dioxane (1 mL), dropwise. The reaction mixture was stirred at room temperature and the reaction progress was monitored by LC/MS (method B: t = 3.42; *m/z* = 1357 $[M+H]^+$) Upon completion of the reaction, the solvent was evaporated and the resulting oil was dissolved in dioxane (1 mL). To this solution was added 2M LiOH (1 mL), and the reaction mixture was stirred at room temperature. Upon completion of the reaction, the solution was neutralized with 3M HCl and the dioxane was evaporated by a N_2 stream. MeCN (1 mL) was added to afford a pale yellow solution. Purification by preparatory HPLC (0.05% TFA, water/MeCN) afforded **27** (2.6 mg) as the TFA salt. LC/MS (method B): t = 3.23 min, *m/z* = 1329 $[M+H]^+$.

Example 7: Synthesis of Compound 35



[00277] To a solution of **1** (1.00 g, 3.09 mmol) and N_3-PEG_3-OH (2.03 g, 9.29 mmol) in CH_2Cl_2 (8 mL) at 0 °C was added $BF_3{\cdot}OEt_2$ (7 drops). The resulting solution was allowed to stir at room temperature for 48 hours and the reaction progress was monitored by TLC. The reaction was quenched with sat. NH_4Cl (1 mL), diluted with water (10 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were washed with brine (3 x 20 mL), dried over $NaSO_4$, filtered and the filtrate was evaporated to afford a light yellow oil. The mixture was purified by column chromatography (hexanes:ethyl acetate) to afford **28** as a viscous clear oil (1.22 g, 73%). ^1H NMR (400 MHz, $CDCl_3$) δ 3.38 (t, J = 5.2 Hz, 2H), 3.58-3.76 (m, 16H), 3.78 (s, 3H), 4.00 (dd, J = 3.6, 9.6 Hz, 1H), 4.27 (t, J = 7.2 Hz, 1H) 4.39 (dd, J = 7.2, 10.4 Hz, 1H), 4.49 (m, 1H), 5.97 (d, br, J = 8.8 Hz, 1H), 7.35 (t, J = 7.6 Hz, 2H), 7.43 (t, J = 7.6 Hz, 2H), 7.65 (t, J = 7.2 Hz, 2H), 7.79 (d, J = 7.2 Hz, 2H).

[00278] Compound **28** (1.22 g, 2.24 mmol) was dissolved in dioxane (5 mL) and methanol (5 mL), and 1M LiOH (10 mL) was added to the solution at 0 °C with vigorous stirring. The reaction was stirred at room temperature and monitored by LC/MS until full hydrolysis of both the Fmoc and methyl ester was observed. Upon completion of the reaction, the solvents were removed *in vacuo* producing a white solid and pale yellow oil. The residue was dissolved in water (10 mL) and Et_2O (20 mL). The aqueous layer was collected, washed with Et_2O (10 mL) and the pH of the solution was adjusted to 8 using 3M HCl. A solution of *t*-Boc anhydride (585 mg, 2.69 mmol) in dioxane (8mL) was added at room temperature and the resulting mixture was stirred overnight. Reaction completion was confirmed by LC/MS (3.46 min, *m/z* = 307 $[M\text{-}Boc+H]^+$, 429 $[M+Na]^+$) and the organic solvent was evaporated using a stream of N_2. The aqueous layer was basified to pH 12 using 1M NaOH, washed with Et_2O (2 x 20 mL), and carefully acidified to pH 5.5 with 3M HCl (aq). The water was removed by lyophilization to afford a clear oil and white solid. To the crude mixture was added CH_2Cl_2 (20 mL) to dissolve the oil and any insoluble salt was removed by filtration. Concentration of the filtrate *in vacuo* afforded **29** as a viscous clear oil (673 mg, 74%). ^1H NMR (400 MHz, $CDCl_3$) δ 1.48 (s, 9H), 3.43 (t, J = 5.2 Hz, 2H), 3.60-3.78 (m, 16 H), 4.16 (m, 1H), 5.87 (s, br, 1H); LC/MS (method A): t = 3.45 min, *m/z* = 307 $[M\text{-}Boc+H]^+$, 429 $[M+Na]^+$.

[00279] To a solution of **4** (300 mg, 1.06 mmol), **29** (520 mg, 1.28 mmol), HBTU (488 mg, 1.28 mmol) and HOBt (21 mg, 0.13 mmol) in DMF was added DIPEA (322 mg, 2.56 mmol), dropwise at 0 °C. The resulting solution was stirred at room temperature for 2 hours and the reaction was monitored by TLC. Upon completion of the reaction, water (40 mL) and CH_2Cl_2 (30 mL) were added. The organic layer was collected and the aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layers were washed with brine (3 x 40 mL), dried

over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The crude was purified by column chromatrography (hexanes:ethyl acetate) to afford **30** (288 mg, 47%) as a white solid. LC/MS (method A): t = 4.25 min, *m/z* = 658 $[M+Na]^+$, 536 $[M-Boc+H]^+$.

[00280] To a solution of **30** (268 mg, 0.42 mmol) in dioxane (1 mL) was added 4M HCl/dioxane (3 mL), dropwise. The reaction mixture was stirred at room temperature overnight. The resulting solution was then concentrated *in vacuo* affording a pale yellow oil. The oil was triturated with ether to afford **31** (199 mg, 84%) as a tacky white solid, which was used in the subsequent step without further purification.

[00281] To a solution of **31** (186 mg, 0.33 mmol) and **7** (155 mg, 0.39 mmol) in DMF (2 mL) was added DIPEA (100 mg, 0.78 mmol), dropwise. The resulting solution was stirred at room temperature for 5 hours and the reaction progress was monitored by TLC. Upon completion of the reaction, water (25 mL) and CH_2Cl_2 (30 mL) were added. The organic layer was collected and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine (3 x 30 mL), dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The crude residue was purified by column chromatrography (CH_2Cl_2:MeOH) to afford **32** (156 mg, 59%) as a clear oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.52 (s, 9H), 1.69 (m, 4H), 2.31 (m, 2H), 2.88 (m, 2H), 3.38 (m, 2H), 3.45 (m, 1H), 3.59-3.82 (m, 16H), 4.55 (m, 1H), 5.38 (m, 1H), 7.04 (m, 1H), 7.20 (s, 1H), 7.27 (s, 2H), 7.52-7.80 (m, 3H) 8.40 (m, 1H); LC/MS (method A): t = 3.87 min, *m/z* = 834 $[M+Na]^+$, 712 $[M-Boc+H]^+$.

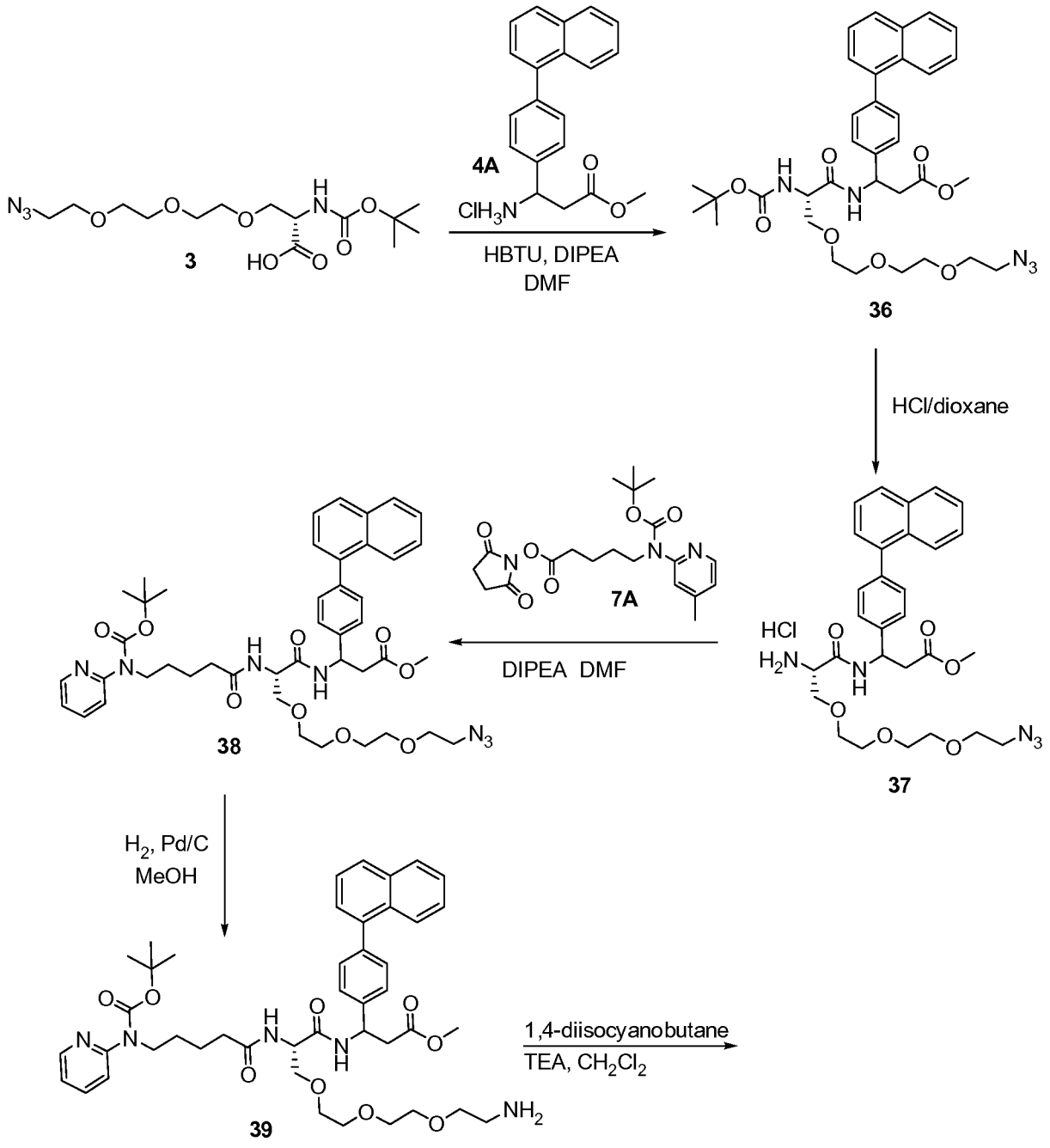
[00282] To a solution of **32** (144 mg, 0.18 mmol) in MeOH (5 mL) was added Pd/C (35 mg). The reaction vessel was purged with H_2 gas and the mixture was stirred under H_2 for 20 minutes, during which time the reaction progress was monitored by TLC. Upon disappearance of the starting material, the reaction vessel was purged with N_2 and MeOH (8 mL) was added. The Pd/C was removed by filtration and the filtrate was concentrated in vacuo to afford **33** (122 mg, 87%) as a clear oil. LC/MS (method A): t = 3.35 min, *m/z* = 786 $[M+H]^+$, 686 $[M-Boc+H]^+$.

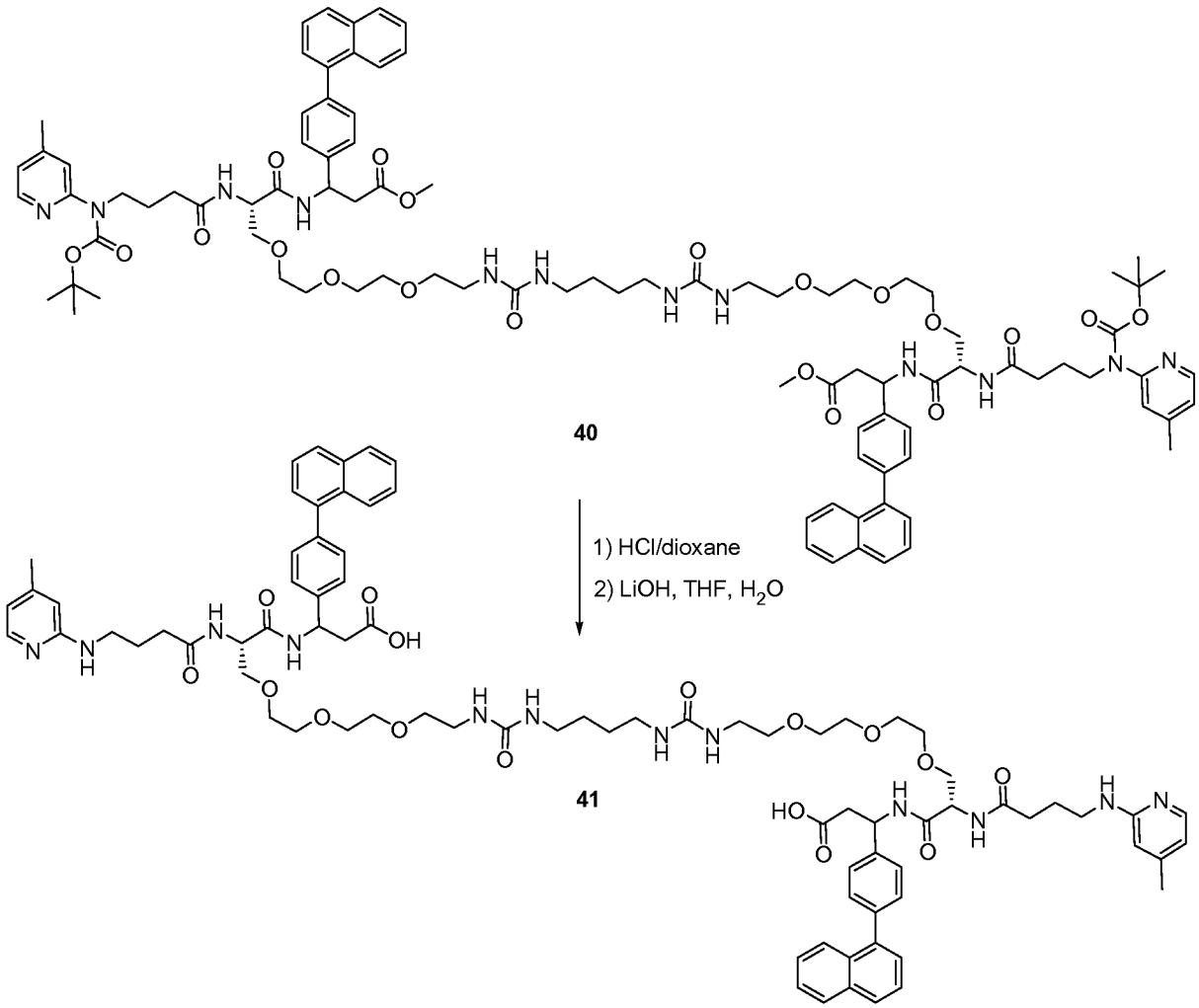
[00283] To a solution of **33**(115 mg, 0.147 mmol) and TEA (44 mg, 0.44 mmol) in CH_2Cl_2 (3.0 mL) was added a solution of 1,4-diisocyanobutane (7.2 mg, 0.066 mmol) in CH_2Cl_2 (1.0 mL), dropwise at room temperature. The resulting solution was stirred at room temperature overnight. The solvent was evaporated and the crude material **34** was used directly for the next step. LCMS (method B): t = 4.27 min, *m/z* = 1713 $[M+H]^+$, 1613 $[M-Boc+H]^+$.

[00284] To a solution of crude **34** (113 mg, 0.066 mmol) in dioxane (1 mL) was added 4M HCl/dioxane (2 mL), dropwise. The reaction mixture was stirred at room temperature and the reaction progress was monitored by LC/MS (method B: t = 3.42; *m/z* = 1513 $[M+H]^+$). Upon completion of the reaction, the solvent was evaporated and the resulting oil was dissolved in

dioxane (2 mL). To this solution was added 2M LiOH (2 mL), and the reaction mixture was stirred at room temperature. Upon completion of the reaction, the solution was neutralized with 3M HCl and the dioxane was evaporated by a N_2 stream. MeCN (2 mL) was added to afford a pale yellow solution. Purification by preparatory HPLC (0.05% TFA, water/MeCN) afforded **35** (14 mg) as the TFA salt. ^{1}H NMR (400 MHz, CD_3OD) δ 1.46 (m, 4H), 1.66-1.79 (m, 8H), 2.40 (m, 4H), 2.87 (m, 4H), 3.13 (m, 4H), 3.29 (m, 4H), 3.37 (t, J = 6.4 Hz, 2H), 3.52 (m, 4H), 3.60-3.79 (m, 28H), 4.56 (q, J = 5.2 Hz, 2H), 5.30 (t, J = 6.8 Hz, 2H), 6.88 (m, 2H), 7.04 (t, J = 8.8 Hz, 2H), 7.32 (m, 2H), 7.37 (m, 4H), 7.81 (m, 2H), 7.88 (m, 2H); LC/MS (method B): t = 3.25 min, *m/z* = 1485 $[M+H]^+$, 743 $[M+2H]^{2+}$.

Example 8: Synthesis of Compound 41





[00285] A solution of **4A** (300 mg, 0.83 mmol), **3** (340 mg, 0.99 mmol), HBTU (375 mg, 0.99 mmol) and HOBt (16 mg, 0.10 mmol) in DMF (4 mL) was added DIPEA (250 mg, 2.00 mmol), dropwise at 0 °C. The resulting solution was stirred at room temperature for 2 hours and the reaction progress was monitored by TLC. Upon completion of the reaction, water (40 mL) and CH_2Cl_2 (30 mL) were added. The organic layer was collected and the aqueous layer was extracted with CH_2Cl_2 (2 x 40 mL). The combined organic layers were washed with brine (3 x 30 mL), dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The crude residue was purified by column chromatrography (hexanes:ethyl acetate) to afford **36** (358 mg, 67%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (s, 9H), 2.97 (m, 2H), 3.48 (m, 2H), 3.66-3.82 (m, 14H), 4.37 (s, br, 1H), 5.55 (m, 1H), 5.74 (s, br, 1H), 7.47 (m, 8H), 7.89 (m, 3H); LC/MS (method A): t = 4.65 min, *m/z* = 672 $[M+Na]^+$, 550 $[M-Boc+H]^+$.

[00286] To a solution of **36** (345 mg, 0.53 mmol) in dioxane (1 mL) was added 4M HCl/dioxane (3 mL), dropwise. The reaction mixture was stirred at room temperature overnight. The resulting solution was then concentrated *in vacuo*, affording a pale yellow oil. The oil was triturated with ether to afford **37** (276 mg, 89%) as a sticky white solid. LC/MS (method A): t = 3.63 min, *m/z* = 550 $[M+H]^+$, 572 $[M+Na]^+$.

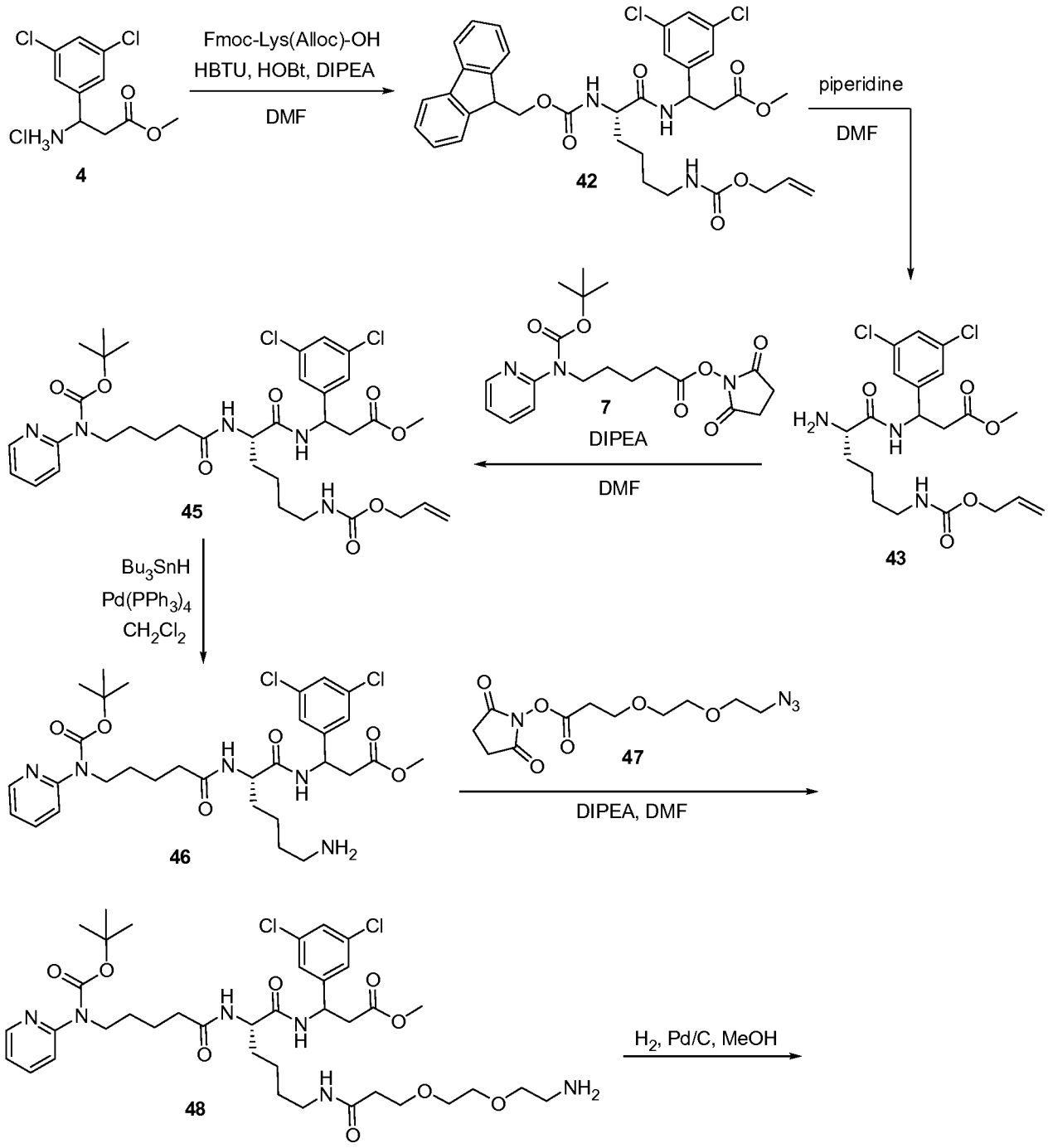
[00287] To a solution of **37** (260 mg, 0.32 mmol) and **7A** (148 mg, 0.38 mmol) in DMF (2 mL) was added DIPEA (95 mg, 0.76 mmol), dropwise. The resulting solution was stirred at room temperature for 5 hours and the reaction progress was monitored by TLC. Upon completion of the reaction, water (30 mL) and CH_2Cl_2 (30 mL) were added. The organic layer was collected and the aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layers were washed with brine (3 x 30 mL), dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The crude product was purified by column chromatrography (CH_2Cl_2:MeOH) to afford **38** (187 mg, 71%) as a clear oil. LC/MS (method B): t = 4.14 min, *m/z* = 826 $[M+H]^+$, 726 $[M\text{-}Boc+H]^+$.

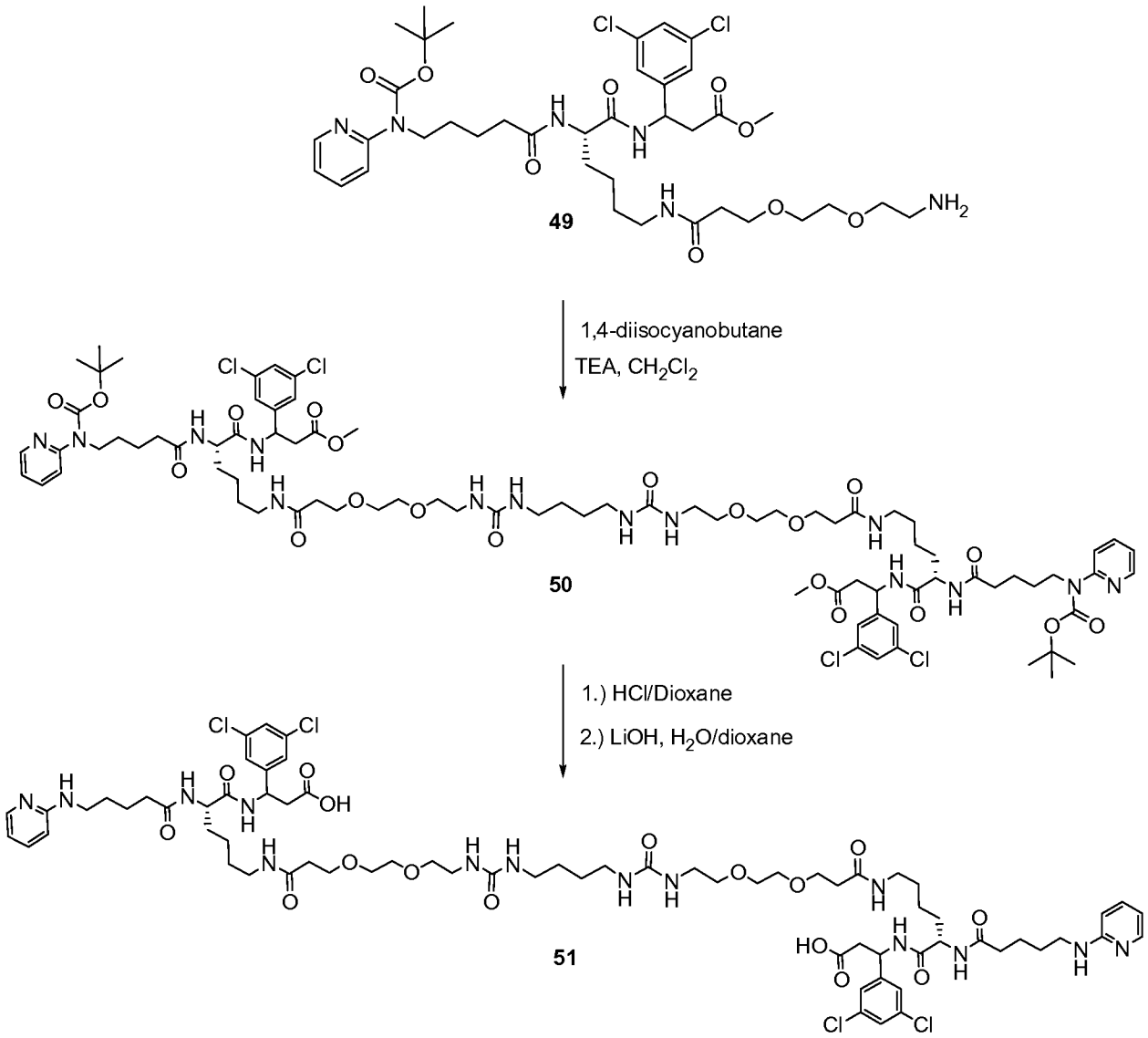
[00288] To a solution of **38** (150 mg, 0.18 mmol) in MeOH (4 mL) was added Pd/C (60 mg). The reaction vessel was purged with H_2 gas and the mixture was stirred under H_2 for 20 minutes, during which time the reaction progress was monitored by TLC. Upon disappearance of the starting material, the reaction vessel was purged with N_2 and MeOH (8 mL) was added. The Pd/C was removed by filtration and the filtrate was concentrated *in vacuo* to afford **39** (132 mg, 91%) as a clear oil. LC/MS (method B): t = 3.48 min, *m/z* = 800 $[M+H]^+$, 700 $[M\text{-}Boc+H]^+$.

[00289] To a solution of **39** (120 mg, 0.15 mmol) and TEA (45 mg, 0.45 mmol) in CH_2Cl_2 (2 mL) was added a solution of 1,4-diisocyanobutane (9.5 mg, 0.067 mmol) in CH_2Cl_2 (1 mL), dropwise at room temperature. The resulting solution was stirred at room temperature overnight. The solvent was evaporated and the crude material **40** was used directly for the next step. LC/MS (method B): t = 4.45 min, *m/z* = 1761 $[M+Na]^+$, 1641 $[M\text{-}Boc+H]^+$.

[00290] To a solution of crude **40** (118 mg, 0.067 mmol) in dioxane (0.5 mL) was added 4M HCl/dioxane (1.5 mL), dropwise. The reaction mixture was stirred at room temperature and the reaction progress was monitored by LC/MS (method B: t = 3.77, 1540 $[M+H]^+$). Upon completion of the reaction, the solvent was evaporated and the resulting oil was dissolved in dioxane (2 mL). To this solution was added 2M LiOH (2 mL), and the reaction mixture was stirred at room temperature. Upon completion of the reaction, the solution was neutralized with 3M HCl and the dioxane was evaporated by a N_2 stream. MeCN (3 mL) was added to afford pale yellow solution. Purification by preparatory HPLC (0.05% TFA, water/MeCN) afforded **41** (11 mg) as the TFA salt. ^1H NMR (400 MHz, CD_3OD) δ 1.46 (m, 4H), 1.98 (m, 4H), 2.32 (d, J = 9.2 Hz, 6H), 2.48 (m, 4H), 2.98 (m, 4H), 3.09 (m, 4H), 3.26 (m, 4H), 3.47 (m, 4H), 3.54-3.72 (m, 16H), 3.81 (m, 4H), 4.61 (q, J = 5.2 Hz, 2H), 5.50 (m, 2H), 6.65 (m, 2H), 6.80 (m, 2H), 7.35 (m, 2H), 7.41 (m, 6H), 7.42-7.52 (m, 8H), 7.64 (dd, J = 6.8, 17.2 Hz, 2H), 7.79 (t, J = 7.6 Hz, 2H), 7.88 (d, J = 8.0 Hz, 2H), 7.93 (d, J = 8.0 Hz, 2H); LC/MS (method B): t = 3.66 min, *m/z* = 1512 $[M+H]^+$, 756 $[M+2H]^{2+}$.

Example 9: Synthesis of Compound 51





[00291] To a solution of **4** (2.00 g, 7.09 mmol), Fmoc-Lys(Alloc)-OH (3.53 g, 7.82 mmol), HBTU (2.96 g, 7.08 mmol) and HOBt (112 mg, 0.71 mmol) in DMF (10 mL) was added DIPEA (1.58 g, 15.6 mmol), dropwise at 0 °C. The resulting solution was stirred at room temperature for 2 hours and the reaction progress was monitored by TLC. Upon completion of the reaction, water (40 mL) and CH_2Cl_2 (30 mL) were added. The organic layer was collected and the aqueous layer was extracted with CH_2Cl_2 (3 x 40 mL). The combined organic layers were washed with brine (3 x 50 mL), dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The crude residue was purified by column chromatrography (hexanes:ethyl acetate) to afford **42** (3.66 g, 76%) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 1.41 (m, 2H), 1.57 (m, 2H), 1.68-179 (m, 3H), 1.90 (m, 1H), 2.83 (m, 2H), 3.21 (m, 2H), 3.62 (d, 3H)), 4.24 (q, J = 7.6 Hz, 2H), 4.42 (m, 2H), 4.57 (m, 2H), 4.78-4.96 (m, 1H), 5.21 (d, J = 10.4 Hz, 2H), 5.32 (m, 2H), 5.61 (t, J = 9.6 Hz, 1H), 5.91 (m, 1H), 7.24 (m, 3H), 7.32 (m, 2H), 7.41 (t, J = 7.6 Hz, 2H), 7.51 (m, 1H), 7.61 (t, J = 7.6 Hz, 2H), 7.78 (d, J = 7.6 Hz, 2H).

[00292] To a solution of **42** (3.65 g, 5.36 mmol) in DMF (5 mL) was added a 20% solution of piperidine in DMF (5 mL), dropwise. The reaction mixture was stirred at room temperature and the reaction progress was monitored by TLC. Upon completion of the reaction as evidenced by the disappearance of the starting material, the reaction mixture was concentrated *in vacuo* and the resulting residue was partitioned beween 0.1 N HCl (20 mL) and ether (30 mL). The aqueous layer was collected, washed with ether (3 x 20) and lyophilized to afford crude **43** (1.82 g, 74%) as a yellow oil.

[00293] Crude **43** (1.80 g, 3.92 mmol) and **7** (1.84 g, 4.71 mmol) were dissolved in DMF (10 mL) and DIPEA (1.19 g, 9.42 mmol) was added dropwise. The resulting solution was stirred at room temperature overnight. Upon completion of the reaction, water (50 mL) and CH_2Cl_2 (40 mL) were added. The organic layer was collected and the aqueous layer was extracted with CH_2Cl_2 (2 x 40 mL). The combined organic layers were washed with brine (3 x 50 mL), dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The crude residue was purified by column chromatrography (CH_2Cl_2:MeOH) to afford **45** (2.14 g, 71%) as a clear oil. LC/MS (method A): t = 4.02 min, *m/z* = 758 $[M+Na]^+$, 636 $[M\text{-}Boc+H]^+$.

[00294] To a solution of **45** (400 mg, 0.54 mmol) and $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) in CH_2Cl_2 (5 mL) was added Bu_3SnH (320 mg, 1.08 mmol), dropwise at 0 °C. The mixture was allowed to stir while warming to room temperature, during which time the reaction progress was monitored by TLC. Upon completion of the reaction, the mixture was concentrated *in vacuo* and the crude residue was partitioned between 0.1 N HCl (10 mL) and hexanes (10 mL). The organic layer was removed and the resulting aqueous layer was washed with hexanes (2 x 10 mL) and ether (2 x 10 mL) before being lyophilized to afford crude **46** (270 mg, 76%) as yellow oil. LC/MS (method A): t = 3.40 min, *m/z* = 652 $[M+H]^+$, 552 $[M\text{-}Boc+H]^+$.

[00295] To a solution of crude **46** (250 mg, 0.39 mmol) and **47** (142 mg, 0.48 mmol) in DMF (2 mL) was added DIPEA (120 mg, 0.96 mmol) dropwise. The resulting solution was stirred at room temperature overnight. Upon completion of the reaction, water (20 mL) and CH_2Cl_2 (30 mL) were added. The organic layer was collected and the aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layers were washed with brine (3 x 30 mL), dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The crude residue was purified by column chromatrography (CH_2Cl_2:MeOH) to afford **48** (212 mg, 66%) as a clear oil. LC/MS (method A): t = 3.86 min, *m/z* = 859 $[M+Na]^+$, 737 $[M\text{-}Boc+H]^+$.

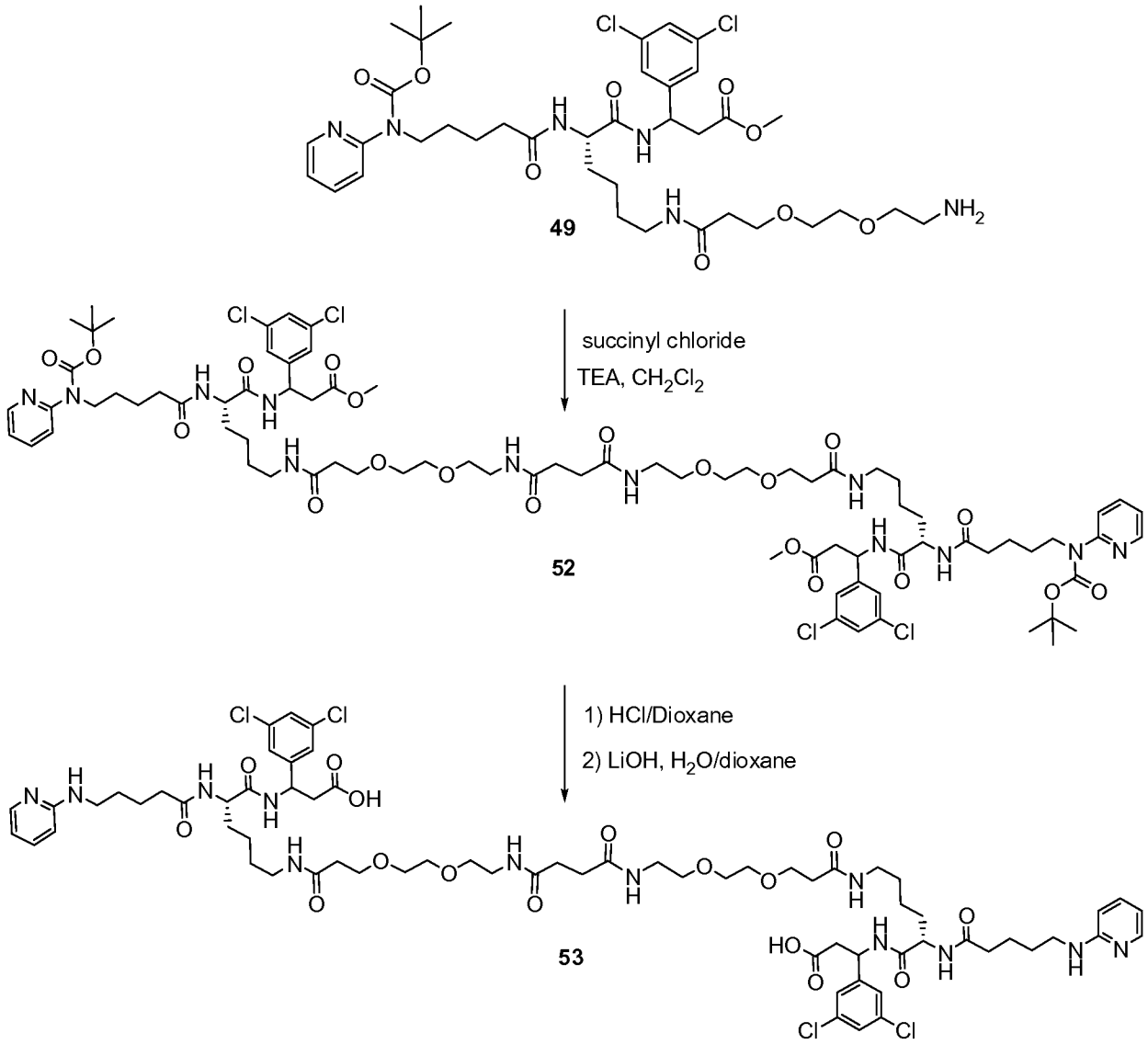
[00296] To a solution of **48** (200 mg, 0.24 mmol) in MeOH (8 mL) was added Pd/C (40 mg). The reaction vessel was purged with H_2 gas and the mixture was stirred under H_2 for 20 minutes, during which time the reaction progress was monitored by TLC. Upon disappearance of the

starting material, the reaction vessel was purged with N_2 and MeOH (10 mL) was added. The Pd/C was removed by filtration and the filtrate was concentrated *in vacuo* to afford **49** (182 mg, 94%) as a clear oil. LC/MS (method A): t = 3.27 min, *m/z* = 811 $[M+H]^+$, 711 $[M-Boc+H]^+$.

[00297] To a solution of **49** (90 mg, 0.11 mmol) and TEA (44 mg, 0.44 mmol) in CH_2Cl_2 (3 mL) was added a solution of 1,4-diisocyanobutane (7.0 mg, 0.050 mmol) in CH_2Cl_2 (0.5 mL), dropwise at room temperature. The resulting solution was stirred at room temperature overnight. The solvent was evaporated and the crude material **50** was used directly for the next step. LC/MS (method B): t = 4.18 min, *m/z* = 1665 $[M+H]^+$, 782 $[M+2H]^{2+}$.

[00298] To a solution of crude **50** (83 mg, 0.50 mmol) in dioxane (0.5 mL) was added 4M HCl/dioxane (1.0 mL), dropwise. The reaction mixture was stirred at room temperature and the reaction progress was monitored by LC/MS (method B: t = 3.38; *m/z* = 1564 $[M+H]^+$). Upon completion of the reaction, the solvent was evaporated and the resulting oil was dissolved in dioxane (1 mL). To this solution was added 2M LiOH (2 mL), and the reaction mixture was stirred at room temperature. Upon completion of the reaction, the solution was neutralized with 3M HCl and the dioxane was evaporated by a N_2 stream. MeCN (2 mL) was added to afford a pale yellow solution. Purification by preparatory HPLC (0.05% TFA, water/MeCN) afforded **51** (18 mg) as the TFA salt. ^1H NMR (400 MHz, CD_3OD) δ 1.46 (m, 4H), 1.62-1.94 (m, 8H), 2.30 (m, 2H), 2.53 (m, 2H), 2.74 (m, 4H), 3.10 (m, 4H), 3.30 (m, 4H), 3.30 (q, J = 6.8 Hz, 2H), 3.52 (q, 4H), 3.55-3.68 (m, 16H), 3.68-3.76 (m, 4H), 3.92 (m, 2H), 4.56 (t, J = 5.2 Hz, 2H), 5.29 (m, 2H), 6.68 (m, 2H), 6.82 (t, J = 8.0 Hz, 2H), 7.26 (m, 2H), 7.36 (m, 4H), 7.74-7.82 (m, 4H); LC/MS (method B): t = 3.21 min, *m/z* = 1535 $[M+H]^+$, 768 $[M+2H]^{2+}$.

Example 10: Synthesis of Compound 53

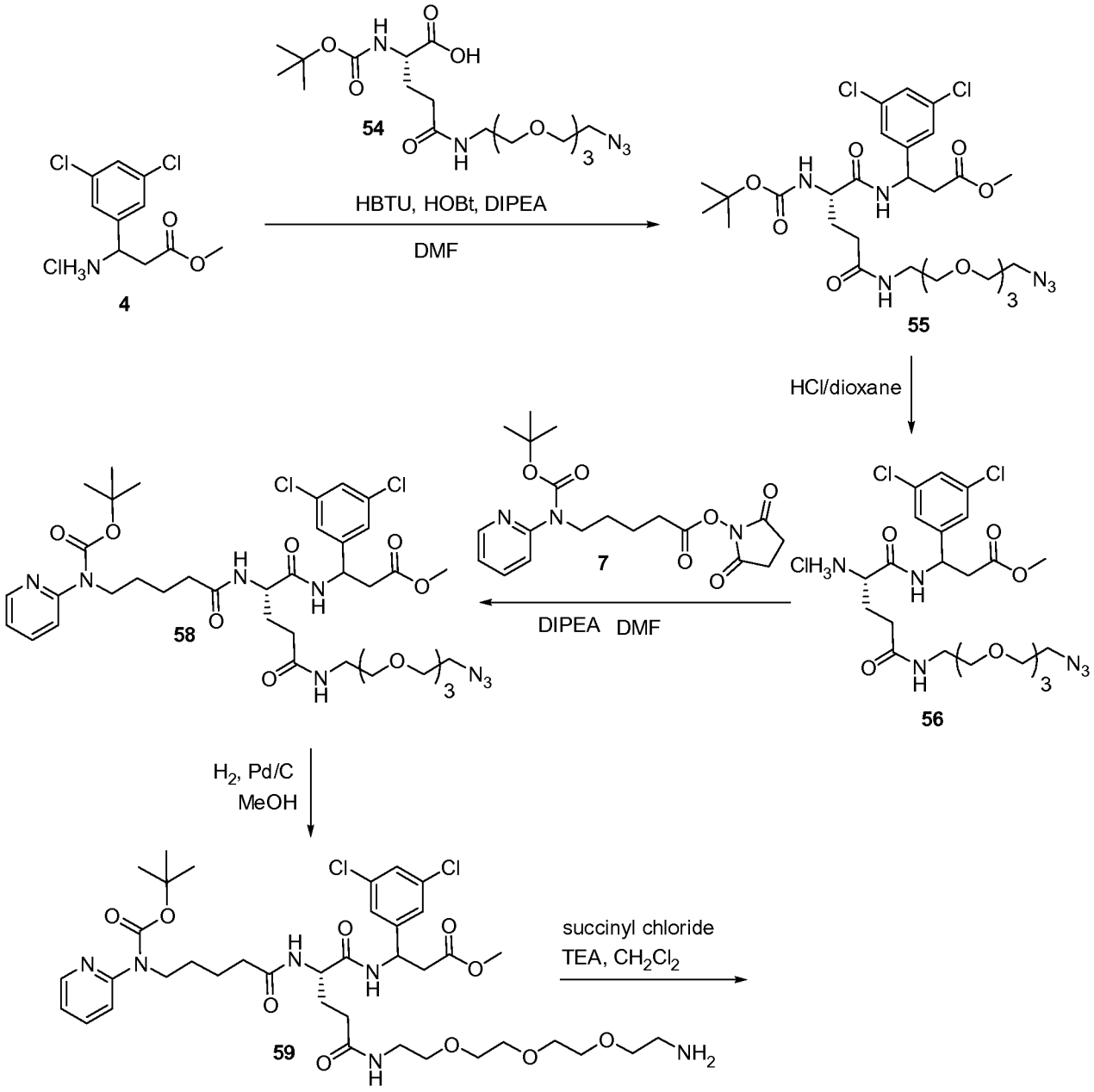


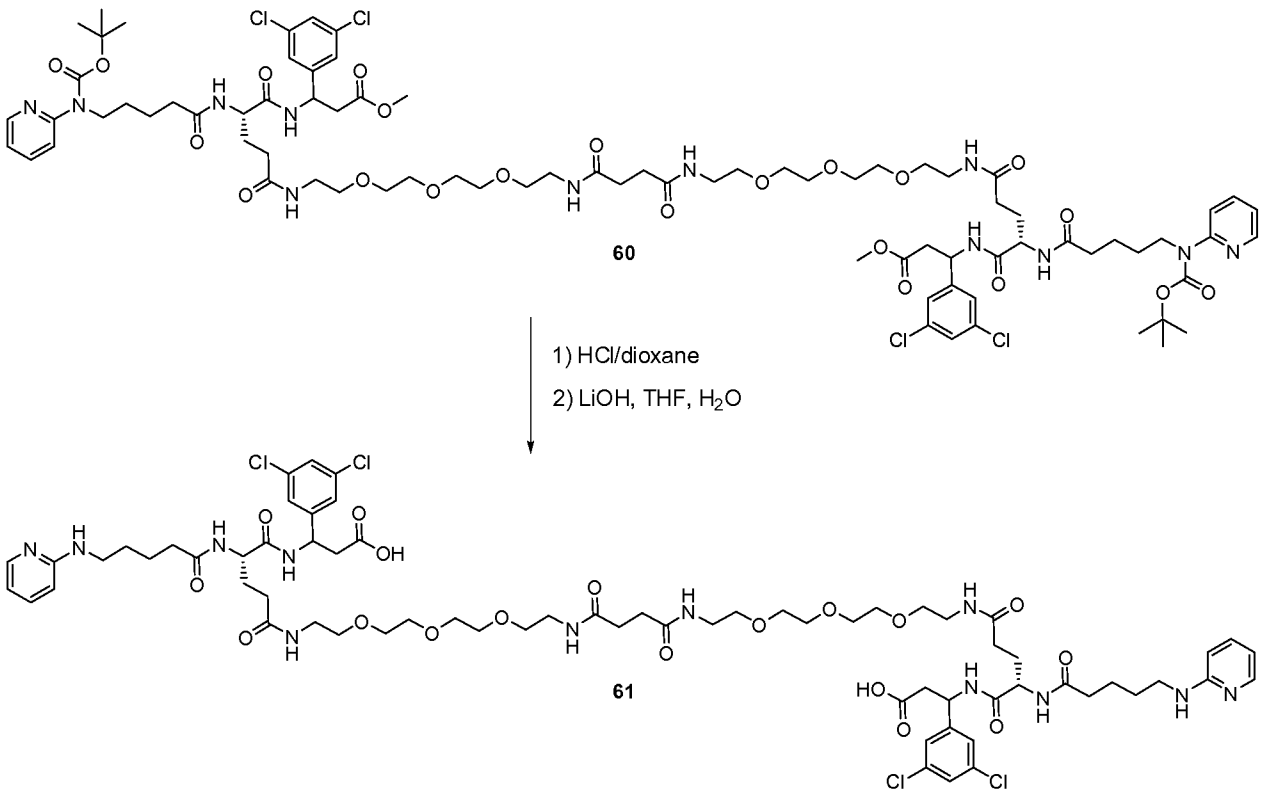
[00299] A solution of **49** (90 mg, 0.11 mmol) and TEA (56 mg, 0.55 mmol) in CH_2Cl_2 (3 mL) was cooled to -20 °C in a dry ice/acetone bath. To this mixture was added a solution of succinyl chloride (7.6 mg, 0.05 mmol) in CH_2Cl_2 (0.5 mL), dropwise. The resulting solution was stirred at room temperature overnight. The solvent was evaporated and the crude material **52** was used directly for the next step. LC/MS (method B): t = 4.20 min, *m/z* = 1605 $[M+H]^+$, 753 $[M+2H]^{2+}$.

[00300] To a solution of crude **52** (80 mg, 0.050 mmol) in dioxane (0.5 mL) was added 4M HCl/dioxane (1.0 mL), dropwise. The reaction mixture was stirred at room temperature and the reaction progress was monitored by LC/MS (method B: t = 3.42; *m/z* = 1505 $[M+H]^+$). Upon completion of the reaction, the solvent was evaporated and the resulting oil was dissolved in dioxane (1 mL). To this solution was added 2M LiOH (2 mL), and the reaction mixture was stirred at room temperature. Upon completion of the reaction, the solution was neutralized with 3M HCl and the dioxane was evaporated by a N_2 stream. MeCN (2 mL) was added to afford an

orange solution. Purification by preparatory HPLC (0.05% TFA, water/MeCN) afforded **53** (22 mg) as the TFA salt. ^{1}H NMR (400 MHz, CD_3OD) δ 1.28-1.48 (m, 4H), 1.53 (m, 4H), 1.63-1.71 (m, 10H), 2.35 (m, 4H), 2.46 (m, 4H), 2.52 (m, 2H), 2.74 (m, 4H), 2.86 (m, 4H), 3.12-3.24 (m, 6H), 3.52 (m, 2H), 3.52 (q, 4H), 3.54 (q, J = 5.4 Hz, 2H), 3.55-3.68 (m, 8H), 3.76 (m, 4H), 4.32 (m, 2H), 5.26 (q, J = 5.2 Hz, 2H), 6.88 (q, J = 6.8 Hz, 2H), 7.03 (dd, J = 9.2, 24.0 Hz, 2H), 7.25-7.38 (m, 6H), 7.70-7.86 (m, 4H); LC/MS (method B): t = 3.22 min, *m/z* = 1477 $[M+H]^+$, 739 $[M+2H]^{2+}$.

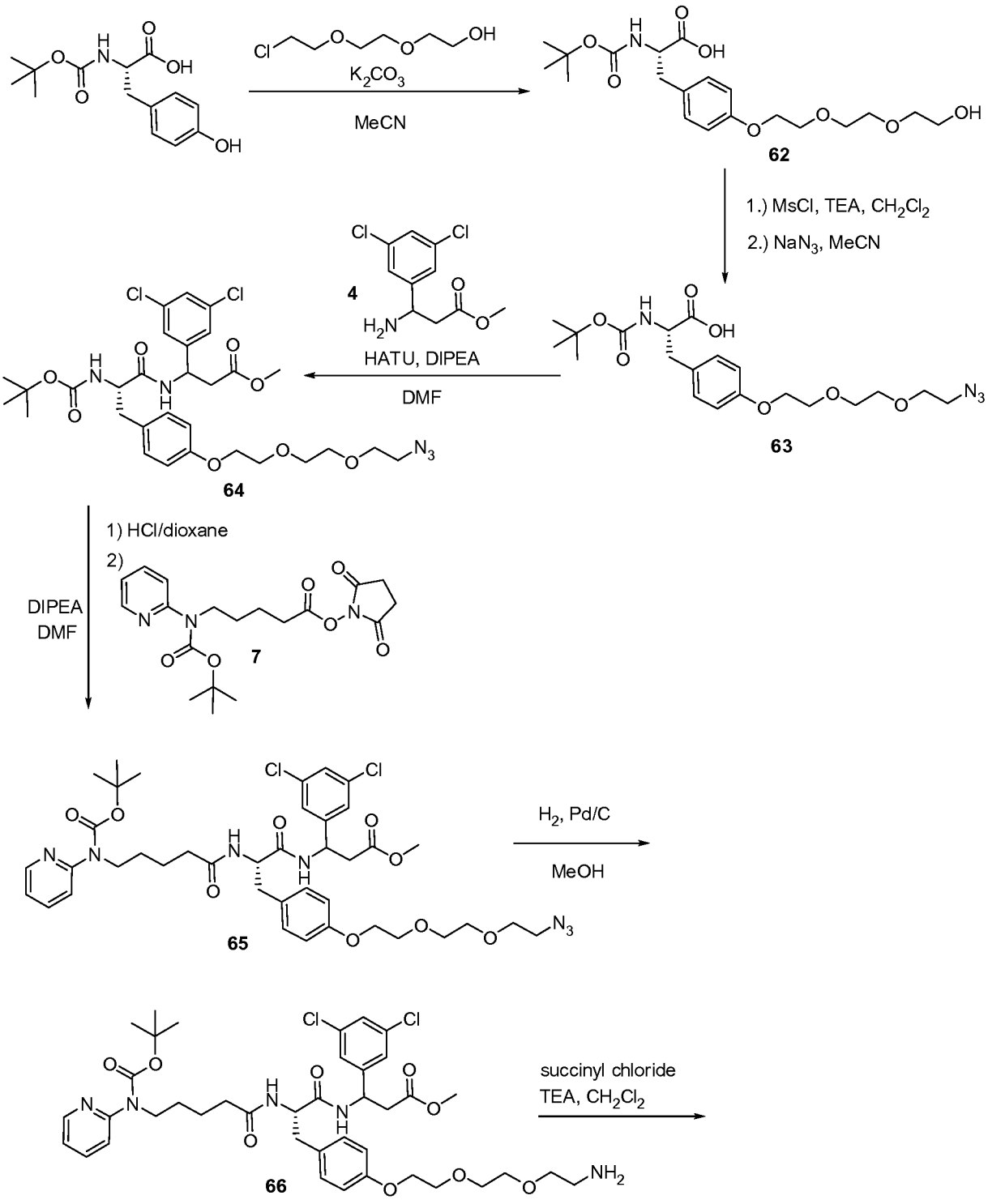
Example 11: Synthesis of Compound 61

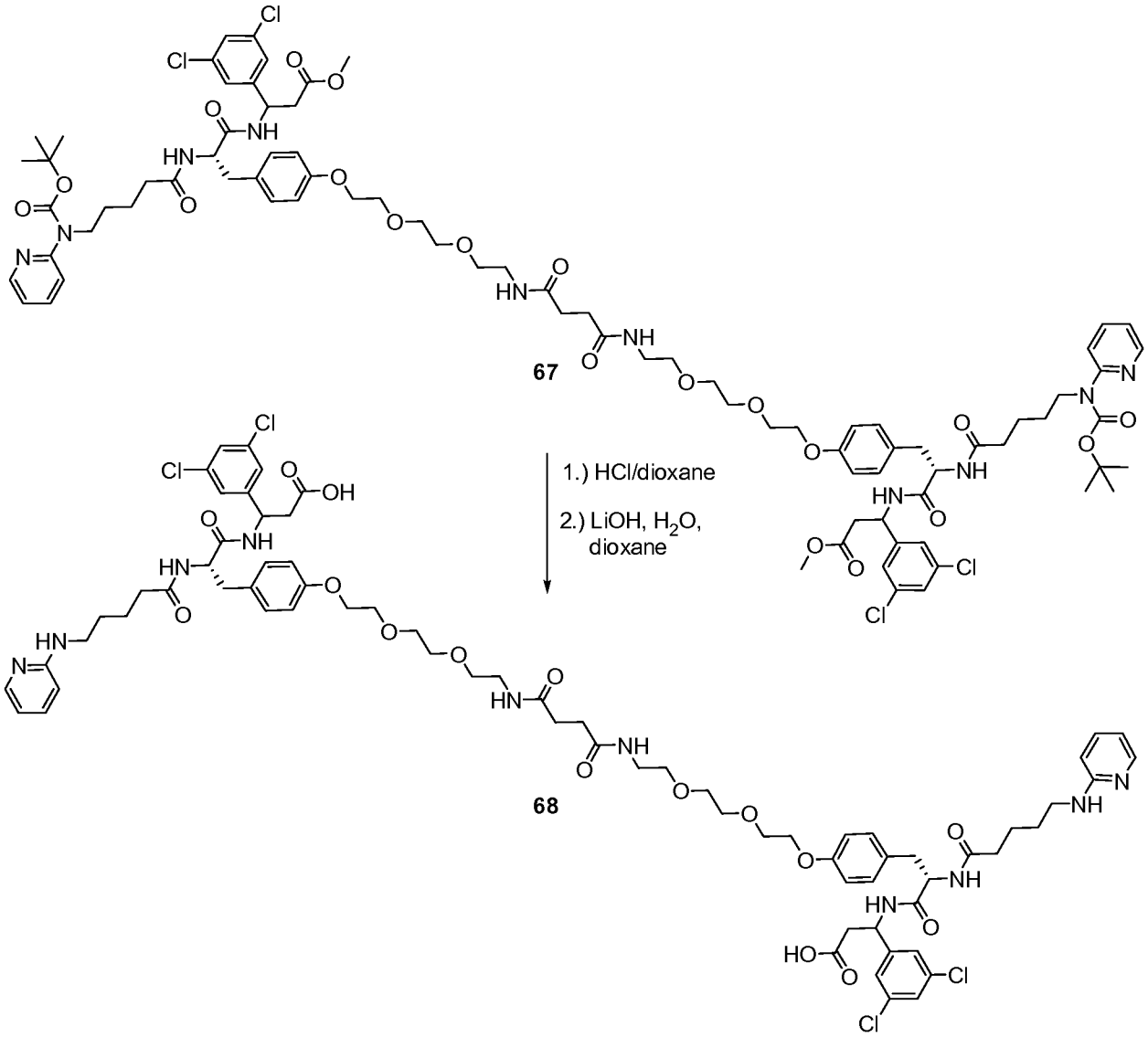




[00301] A representative compound of Formula (Ic), Compound **61**, is prepared as depicted above.

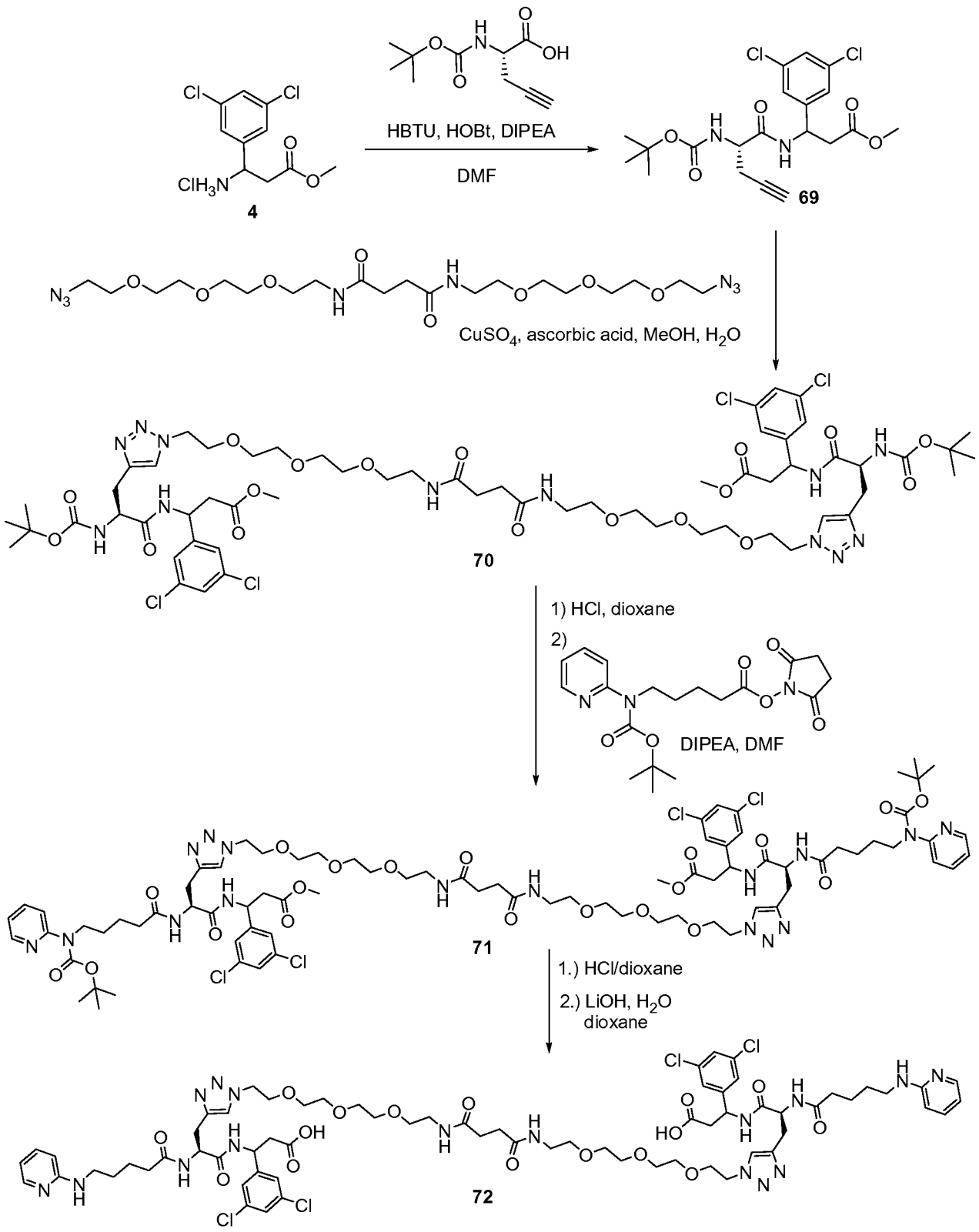
Example 12: Synthesis of Compound 68





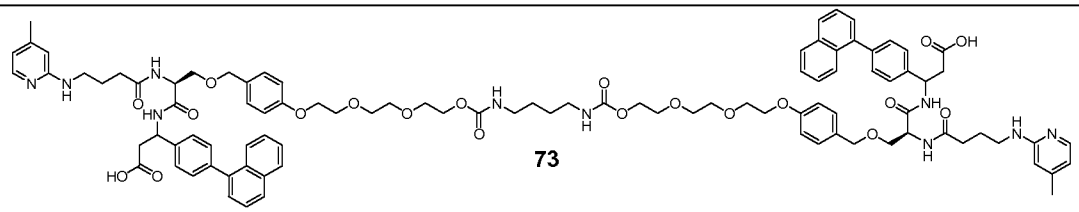
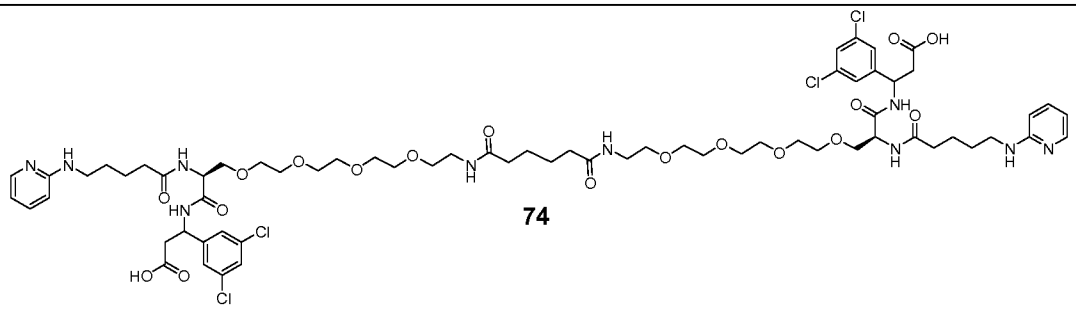
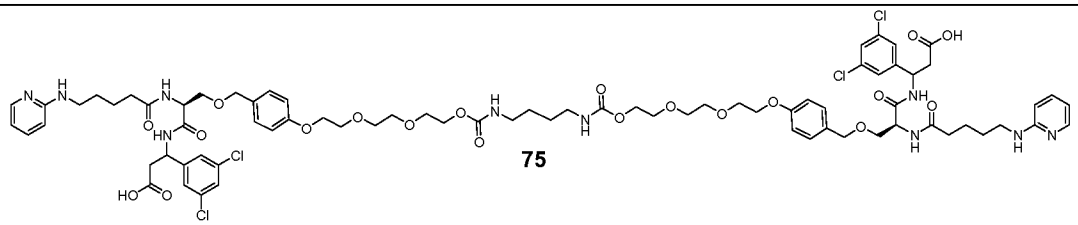
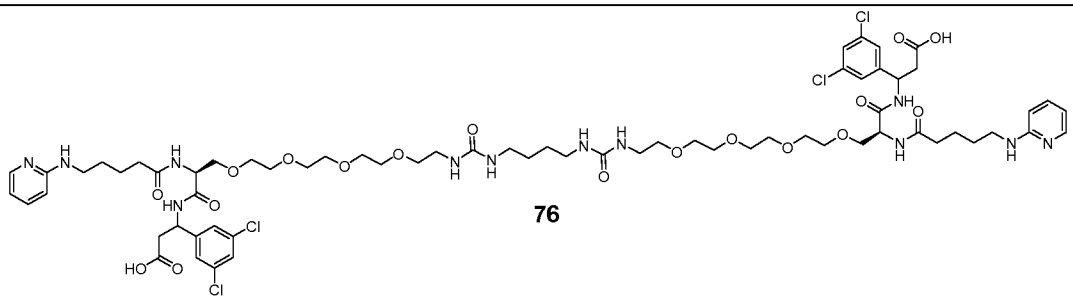
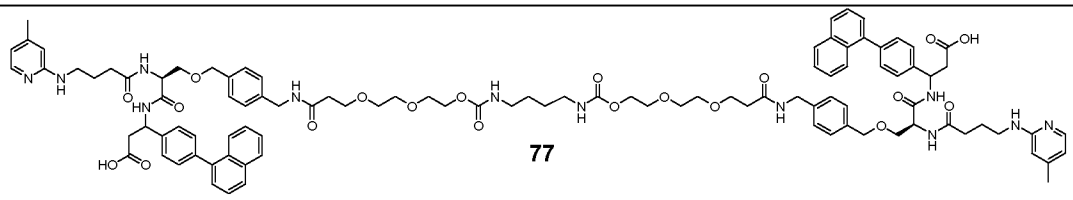
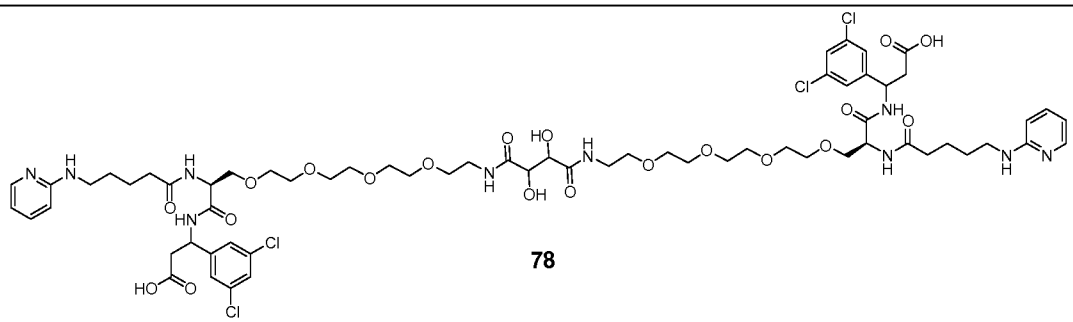
[00302] A representative compound of Formula (III), Compound **68**, is prepared as depicted above.

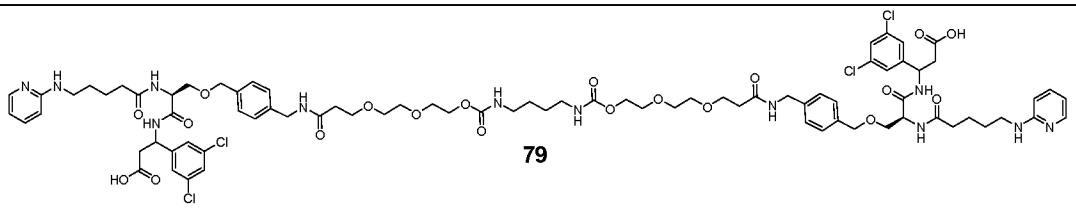
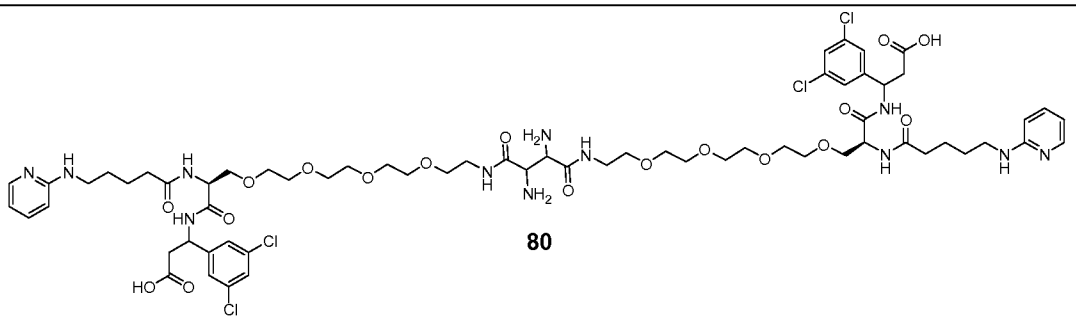
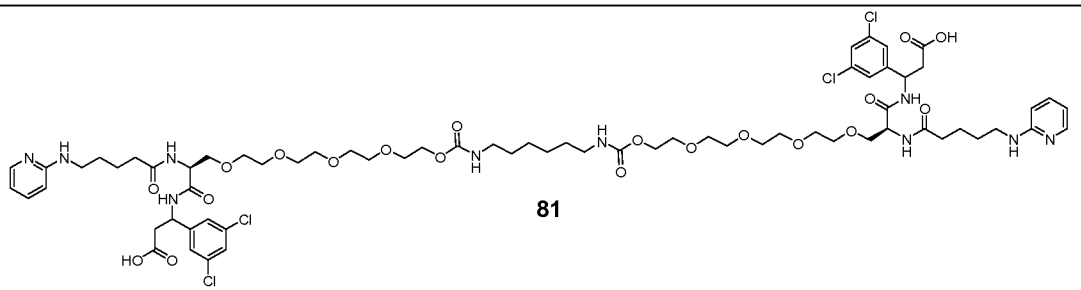
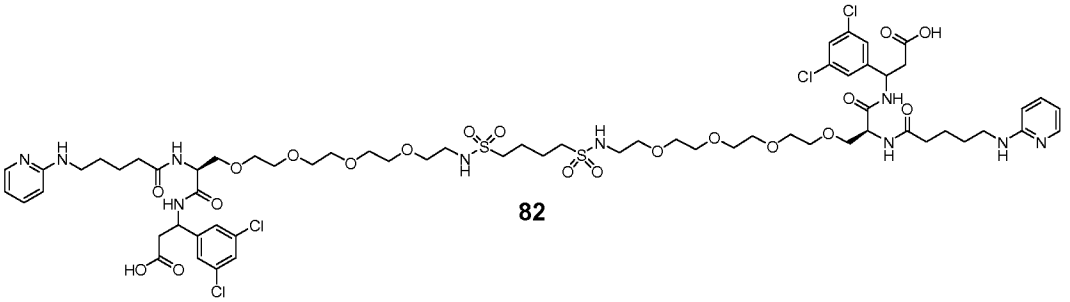
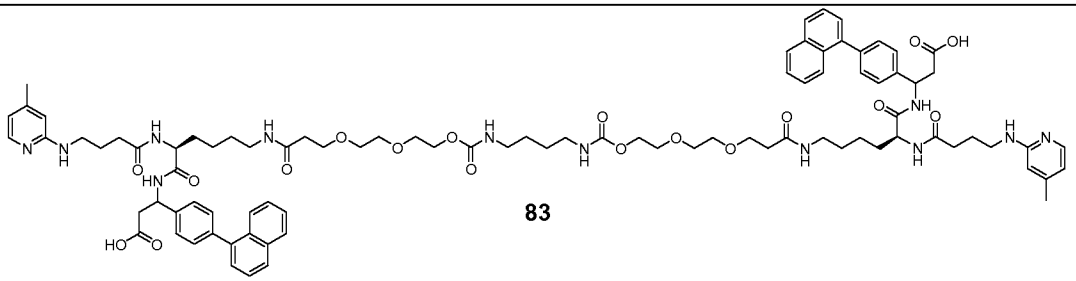
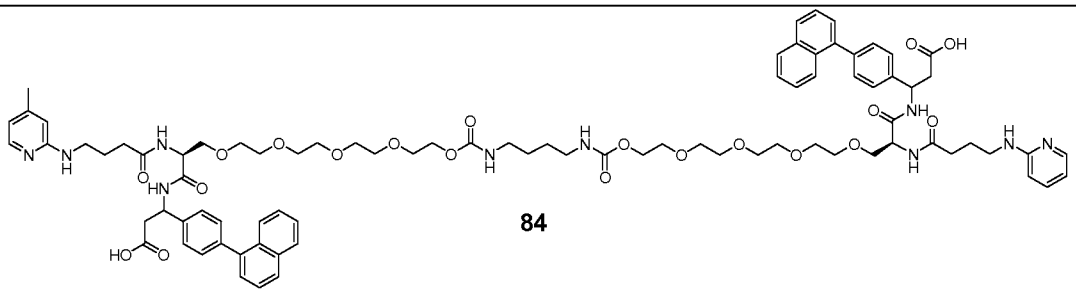
Example 13: Synthesis of Compound 72

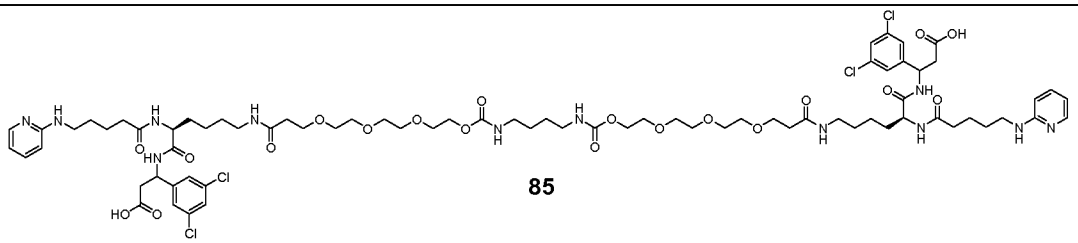
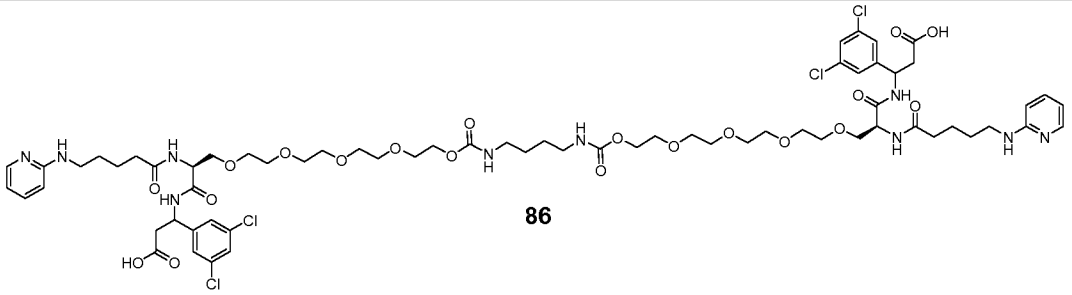
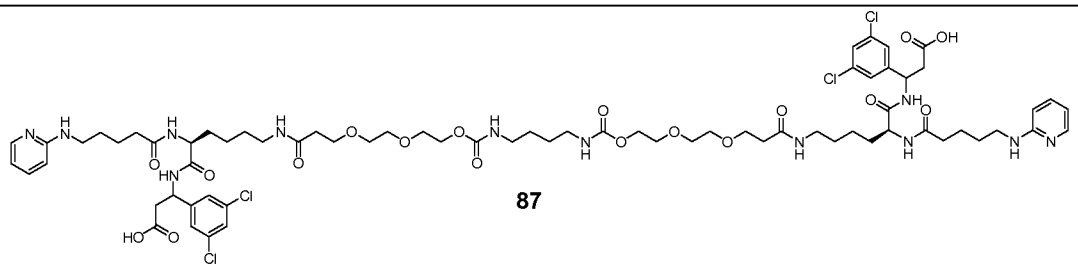
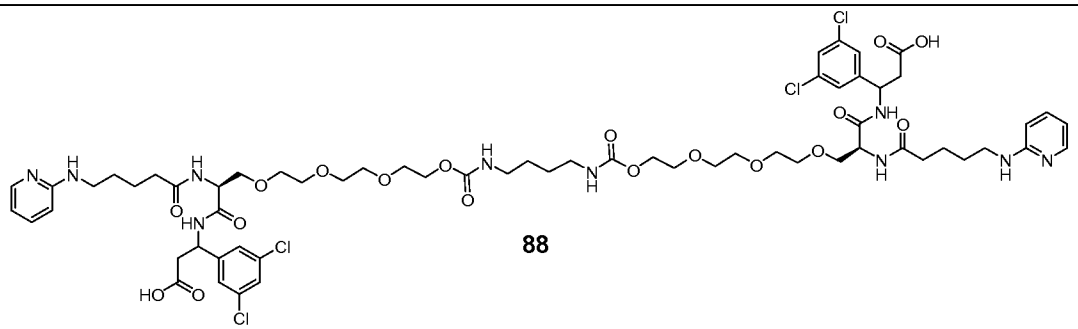
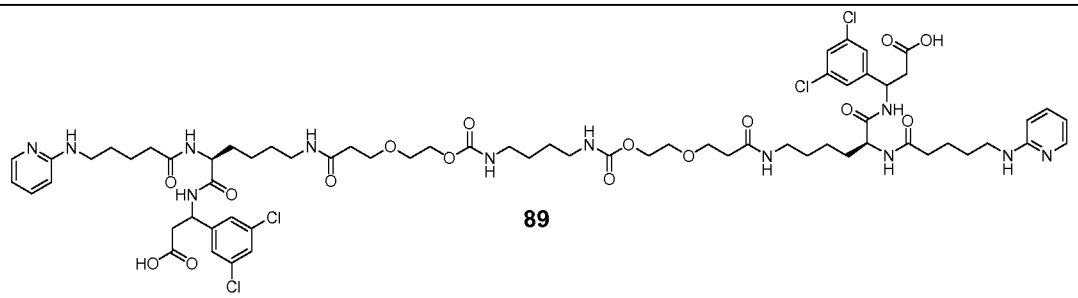
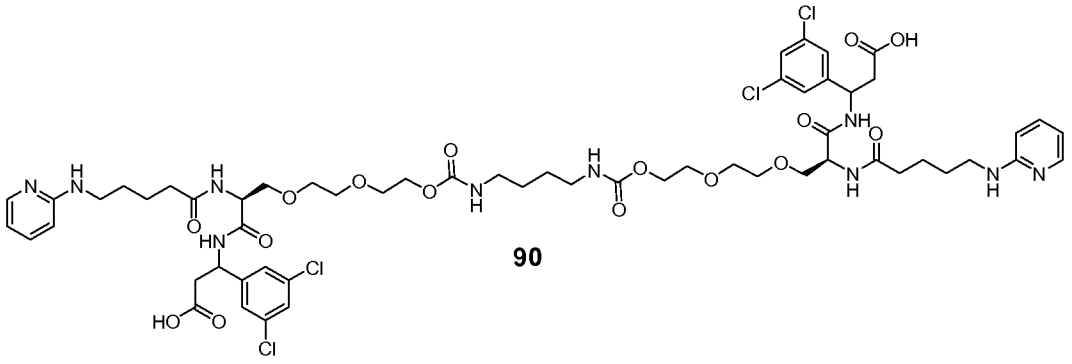


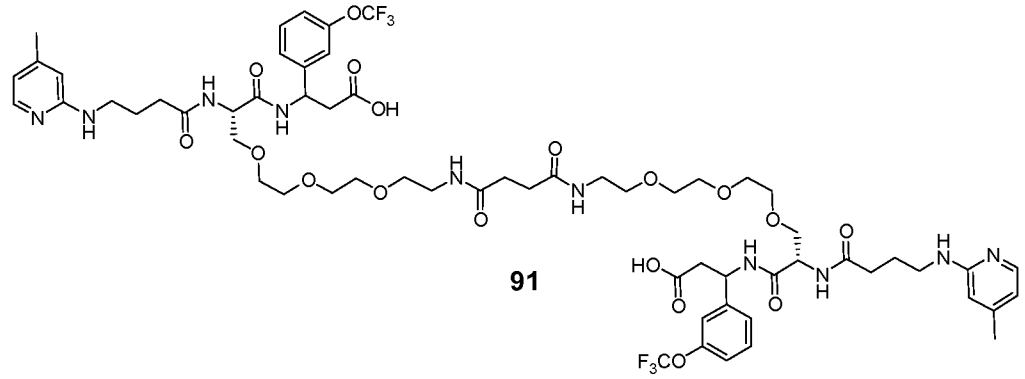
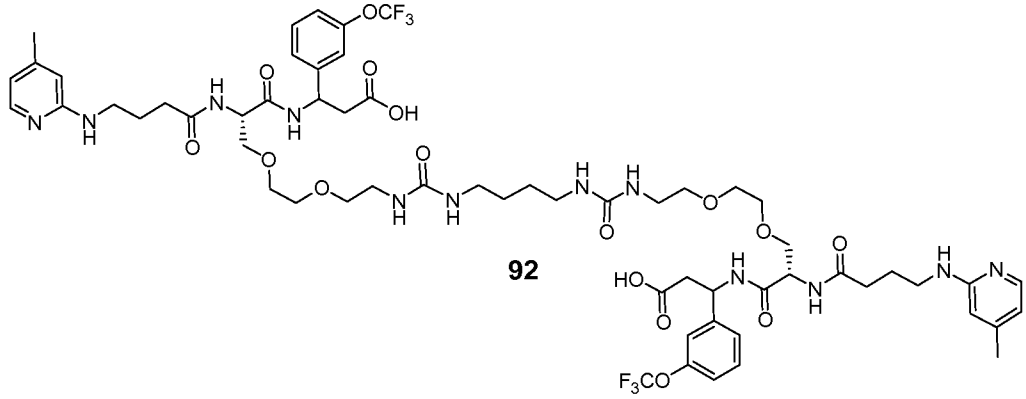
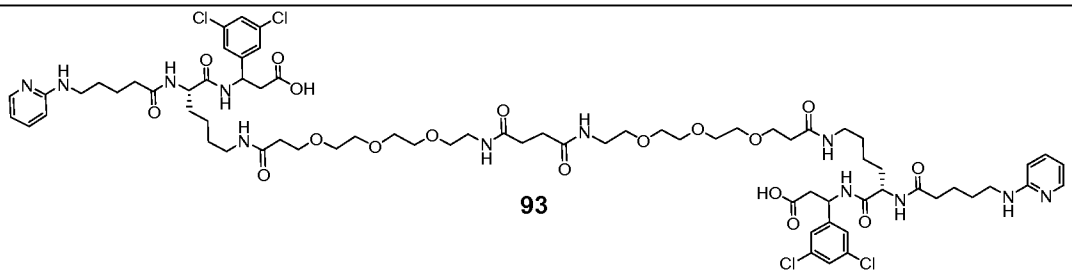
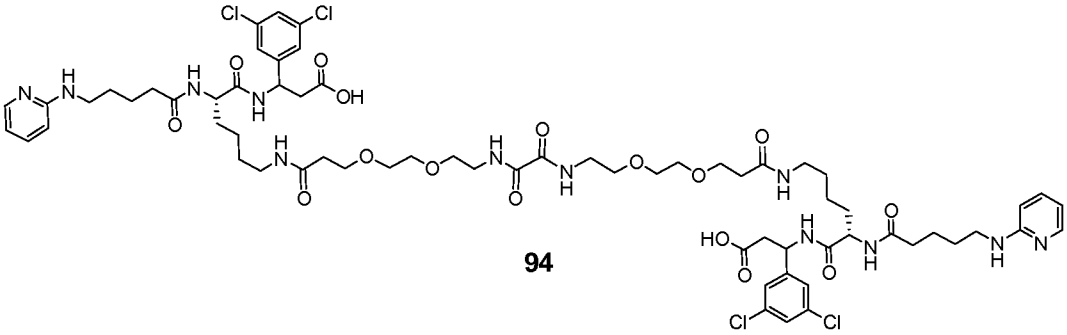
[00303] A representative compound of Formula (III), Compound **72**, is prepared as depicted above.

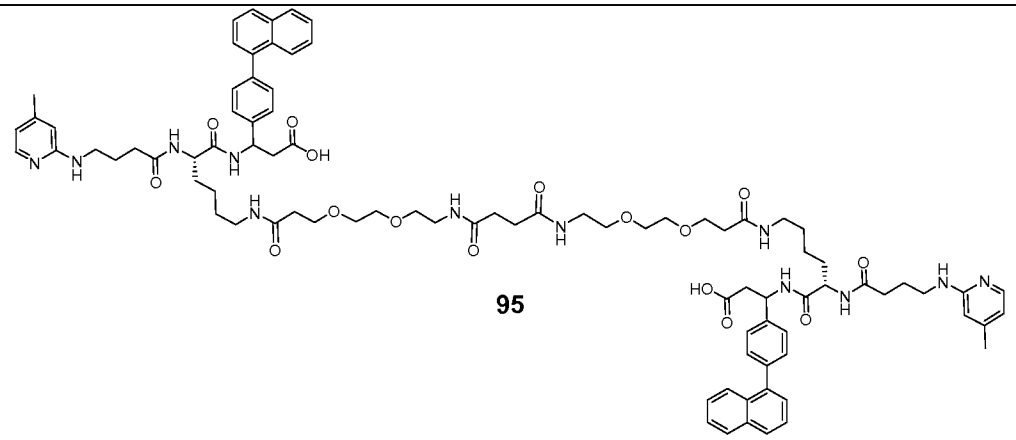
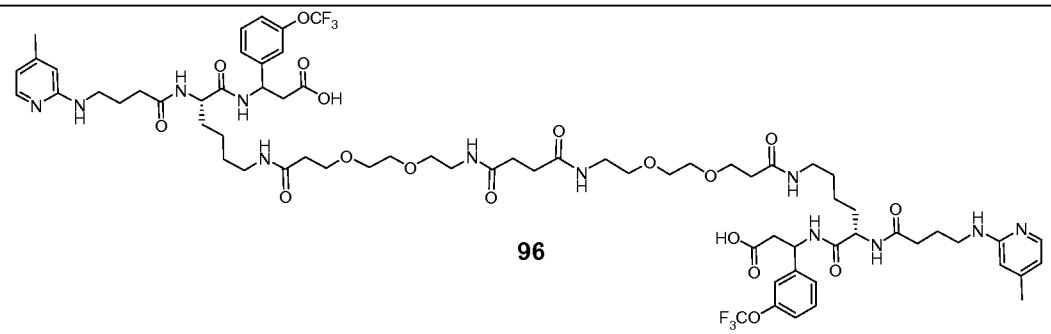
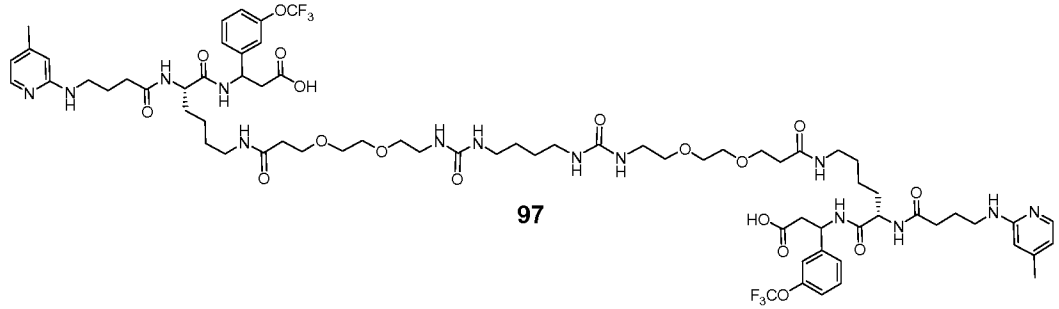
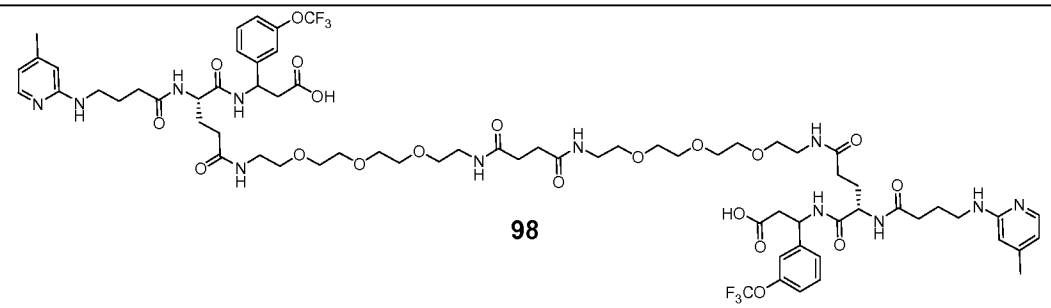
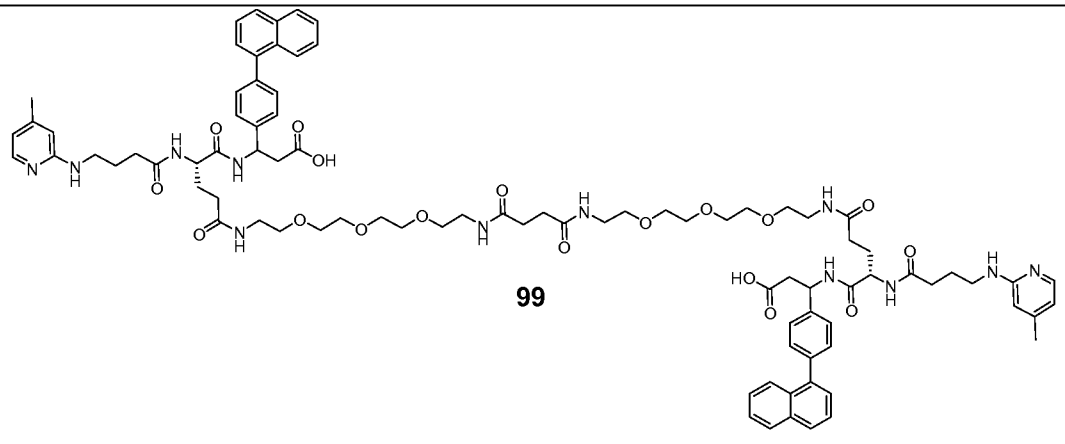
[00304] Examples 14-47 (Compounds **73-106**) may be prepared using analogous procedures as outlined in the Examples above:

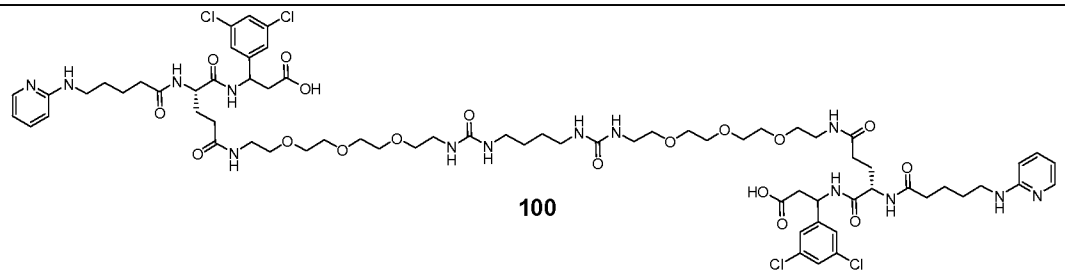
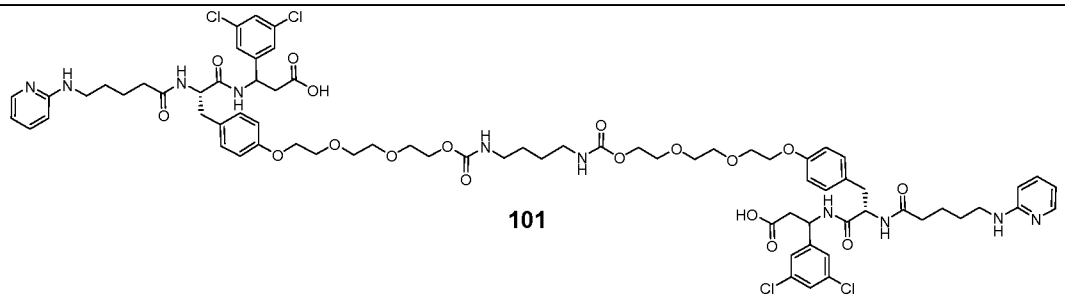
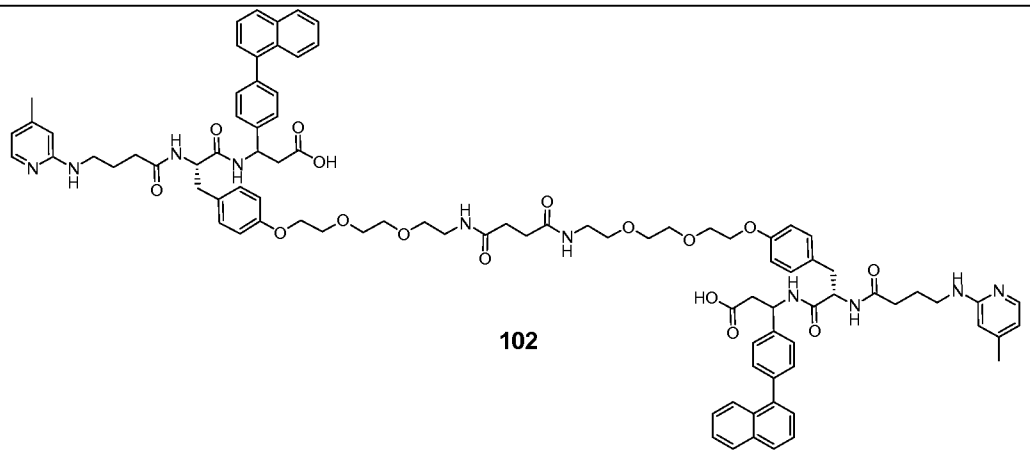
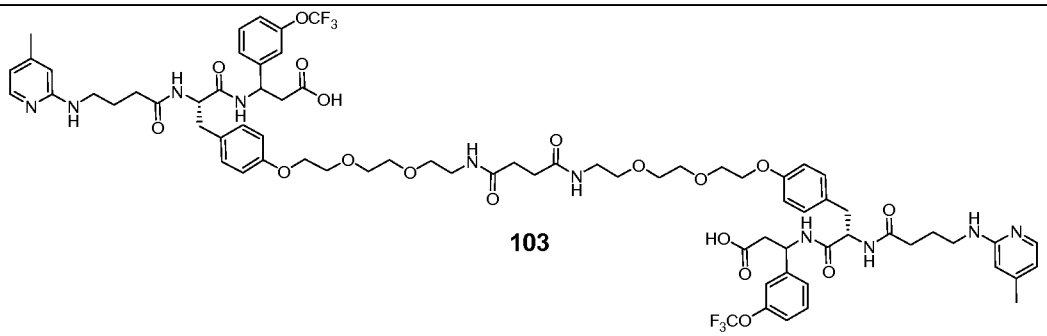
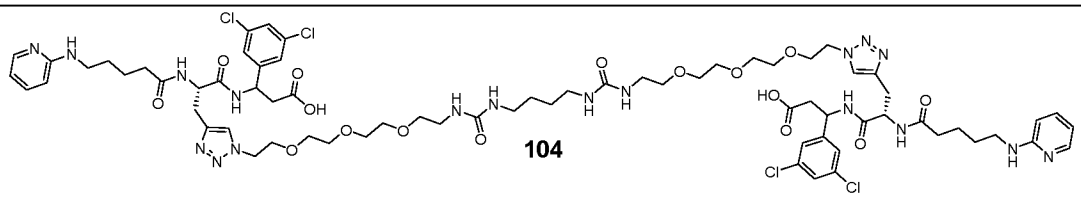
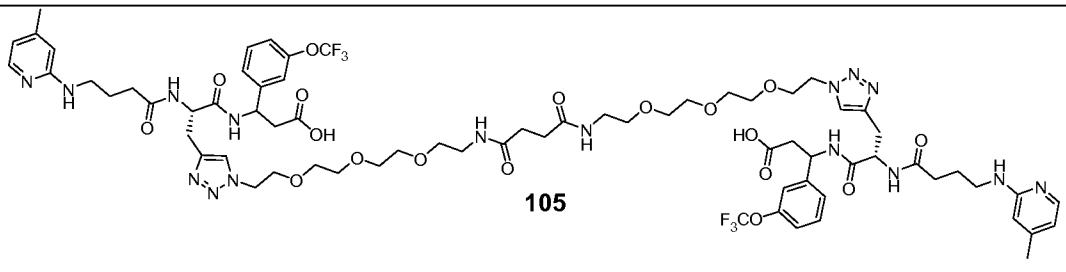
Example	Structure
14	 73
15	 74
16	 75
17	 76
18	 77
19	 78

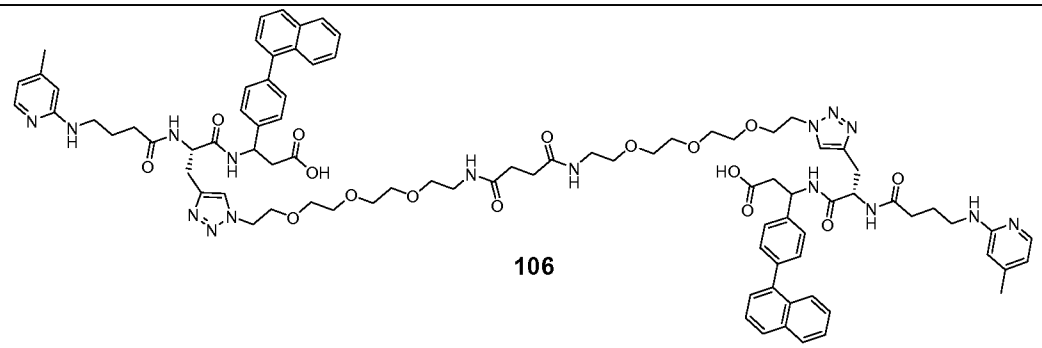
20	 **79**
21	 **80**
22	 **81**
23	 **82**
24	 **83**
25	 **84**

26	 **85**
27	 **86**
28	 **87**
29	 **88**
30	 **89**
31	 **90**

32	 **91**
33	 **92**
34	 **93**
35	 **94**

36	 **95**
37	 **96**
38	 **97**
39	 **98**
40	 **99**

41	 100
42	 101
43	 102
44	 103
45	 104
46	 105

47	 106

Example 48: Integrin-Ligand Competition Assays

[00305] Integrins were diluted to 1-5 μg/ml in TBS and adsorbed onto high binding 96 well plates for 16 h at 4 °C. After blocking for 2 h with 1% BSA in TBS at 37 C, biotinylated ligand (fibronectin, vitronectin or fibrinogen) was diluted in TBS containing 0.1% BSA and allowed to bind for 3 h at 37 °C. Unbound ligand was removed by washing with TBS. Serially diluted inhibitors in TBS containing 0.1% BSA were added in parallel with biotinylated fibronectin, vitronectin, or fibrinogen. After a 3-h incubation at 37 °C and washing with TBS, bound ligand was detected using a streptavidin-horseradish peroxidase conjugate. Following incubation with HRP substrate for 5 minutes, absorbance at 450 nm was used to quantify bound ligand.

[00306] Table 1 below shows biological activity (IC_{50}) for compounds described herein. The IC_{50} activity is graded as: ++ = <100 nM; + = 100 nM to 1 μM.

Table 1

Cmpd #	Activity
11	++
13	++
51	+
53	+

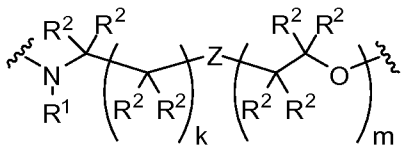
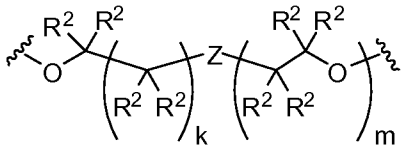
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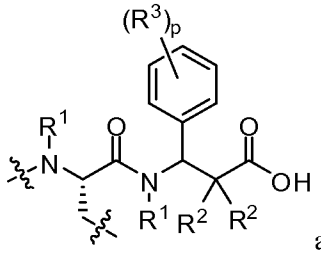
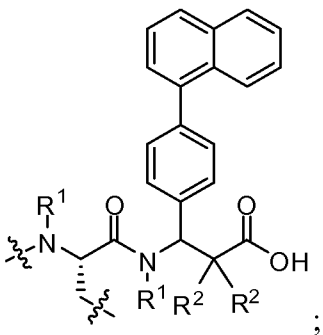
1. A compound of Formula (I), a pharmaceutically acceptable salt, solvate, polymorph, prodrug, metabolite, deuteride, N-oxide, tautomer, stereoisomer, or isomer thereof, having the structure:

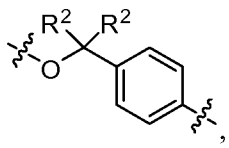
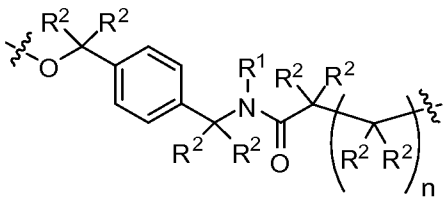
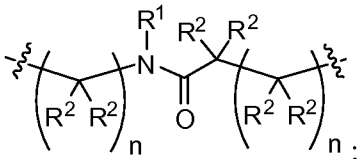
$$Y^1-L^1-B^1-J^1-A^1-X-A^2-J^2-B^2-L^2-Y^2$$

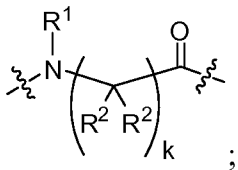
Formula (I);

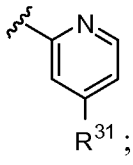
wherein:

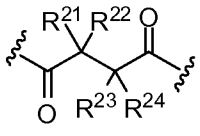
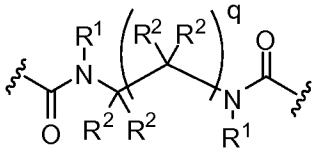
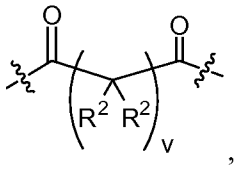
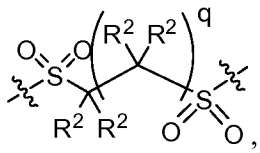
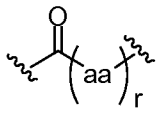
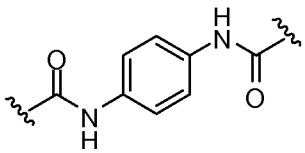
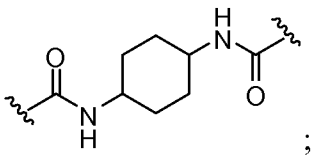
A^1 and A^2 are independently selected from:  and ;

B^1 and B^2 are independently selected from:  and ;

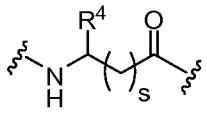
J^1 and J^2 are independently selected from a bond, , , and ;

L^1 and L^2 are independently selected from:  ;

Y^1 and Y^2 are independently selected from:  ;

X is alkylene, -C(O)-,  ,  ,  ,  ,  ,  , or  ;

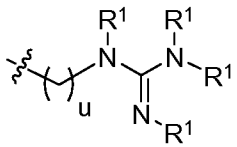
Z is O or CR^2R^2;

aa is  ;

each R^1 is independently selected from H, alkyl, haloalkyl, arylalkyl, and heteroarylalkyl;

each R^2 is independently selected from H, halo, -CN, $-SR^1$, alkyl, cycloalkyl, haloalkyl, $-OR^1$, and $-R^4$;

each R^3 is independently selected from halo, alkyl, -CN, haloalkyl, $-OR^1$, and $-NR^1R^1$;

each R^4 is independently selected from $-CO_2R^1$, -(alkylene)-(CO_2R^1), hydroxyalkyl, -(alkylene)($S(O)_tR^1$)(alkyl), -(alkylene)(NR^5R^5), and  ;

each R^5 is independently selected from H, alkyl, haloalkyl, arylalkyl, heteroarylalkyl, aryl, and heteroaryl;

R^{21}, R^{22}, R^{23}, and R^{24} are independently selected from H, halo, -CN, $-SR^1$, alkyl, cycloalkyl, haloalkyl, $-NR^1R^1$, and $-OR^1$;

each R^{31} is independently selected from H and alkyl;

each k is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

each m is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

each n is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

each p is independently selected from 0, 1, 2, 3, and 4;

q is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

r is 3, 4, 5, 6, or 7;

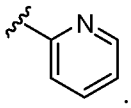
each s is independently selected from 0, 1, 2, 3, and 4;

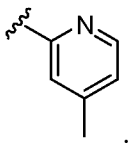
each t is independently selected from 0, 1, and 2;

each u is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10; and

v is selected from 3, 4, 5, 6, 7, 8, 9, and 10.

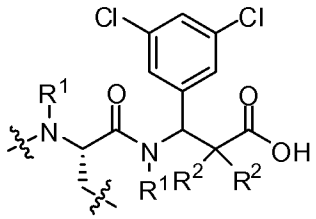
2. The compound of claim 1 wherein Y^1 and Y^2 are the same.

3. The compound of claim 2 wherein Y^1 and Y^2 are both .

4. The compound of claim 2 wherein Y^1 and Y^2 are both .

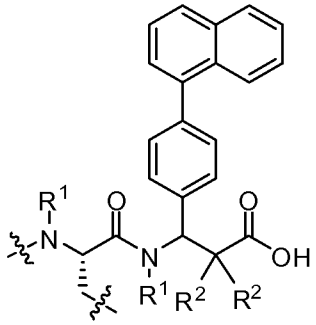
5. The compound of any one of claims 1-4 wherein B^1 and B^2 are the same.

6. The compound of any one of claims 1-5 wherein B^1 and B^2 are both



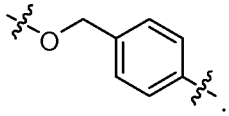
.

7. The compound of any one of claims 1-5 wherein B^1 and B^2 are both

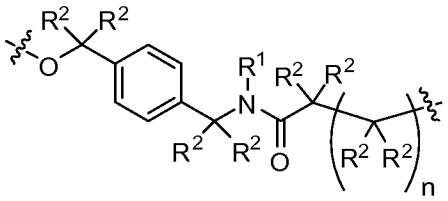


.

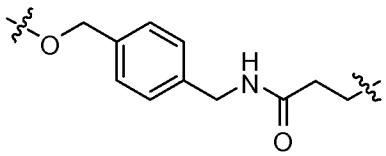
8. The compound of any one of claims 1-7 wherein J^1 and J^2 are the same.

9. The compound of any one of claims 1-8 wherein J^1 and J^2 are both .

10. The compound of any one of claims 1-8 wherein J^1 and J^2 are both

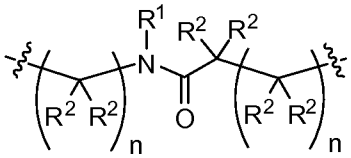


.

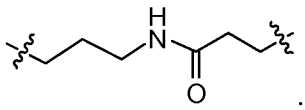


11. The compound of claim 10 wherein J^1 and J^2 are both .

12. The compound of any one of claims 1-8 wherein J^1 and J^2 are both



.

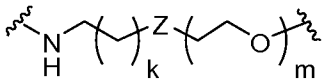


13. The compound of claim 12 wherein J^1 and J^2 are both .

14. The compound of any one of claims 1-8 wherein J^1 and J^2 are both a bond.

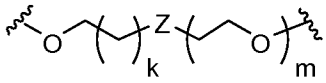
15. The compound of any one of claims 1-14 wherein A^1 and A^2 are the same.

16. The compound of any one of claims 1-15 wherein A^1 and A^2 are both



.

17. The compound of any one of claims 1-15 wherein A^1 and A^2 are both



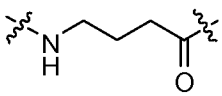
.

18. The compound of any one of claims 1-17 wherein Z is O.

19. The compound of any one of claims 1-18 wherein k is 1.

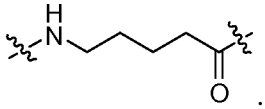
20. The compound of any one of claims 1-19 wherein each m is independently 0, 1, 2, or 3.

21. The compound of any one of claims 1-20 wherein L^1 and L^2 are the same.

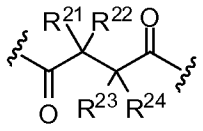


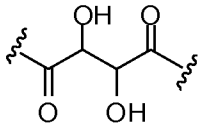
22. The compound of any one of claims 1-21 wherein L^1 and L^2 are both .

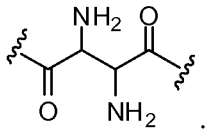
23. The compound of any one of claims 1-21 wherein L^1 and L^2 are both

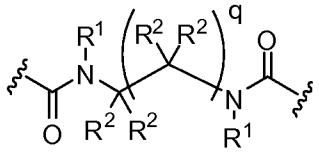


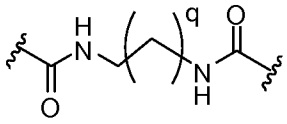
.

24. The compound of any one of claims 1-23 wherein X is .

25. The compound of claim 24 wherein X is .

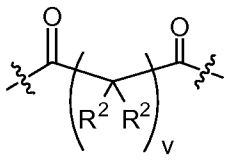
26. The compound of claim 24 wherein X is .

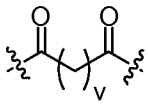
27. The compound of any one of claims 1-23 wherein X is .

28. The compound of claim 27 wherein X is .

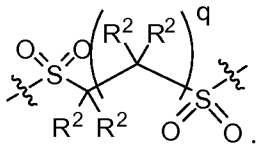
29. The compound of claim 28 wherein q is 3.

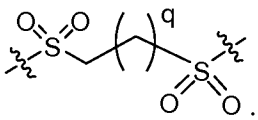
30. The compound of claim 28 wherein q is 5.

31. The compound of any one of claims 1-23 wherein X is .

32. The compound of claim 31 wherein X is .

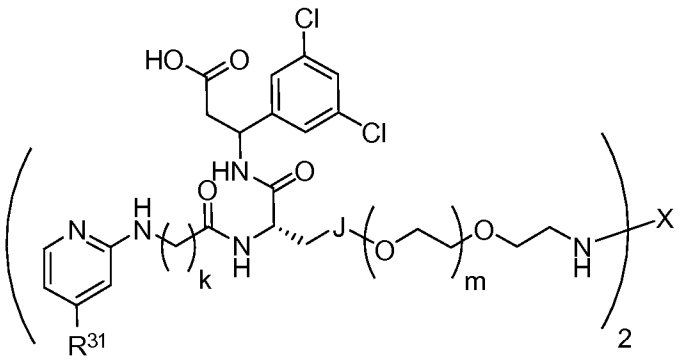
33. The compound of claim 32 wherein v is 4.

34. The compound of any one of claims 1-23 wherein X is .

35. The compound of claim 34 wherein X is .

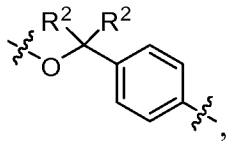
36. The compound of claim 35 wherein q is 3.

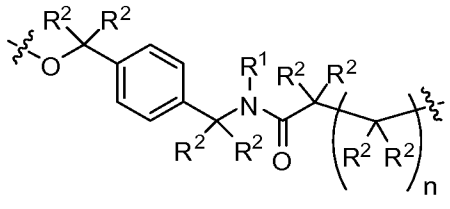
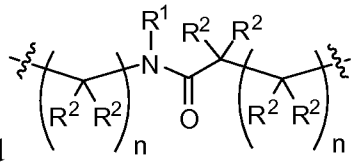
37. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, metabolite, deuteride, N-oxide, tautomer, stereoisomer, or isomer thereof, having the structure of Formula (Ia):

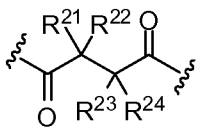
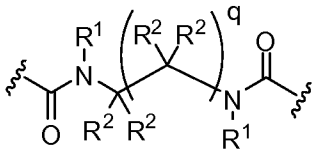
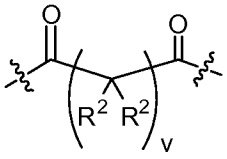


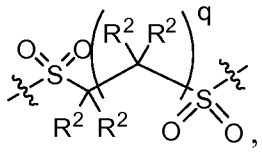
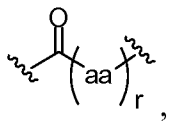
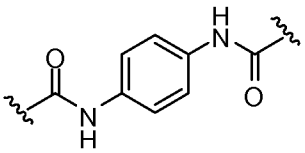
Formula (Ia);

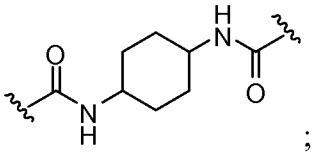
wherein:

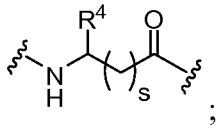
each J is independently selected from a bond, ,

, and ;

X is alkylene, -C(O)-, , , ,

, , , or

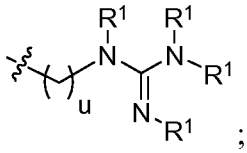
;

aa is ;

each R^1 is independently selected from H and alkyl;

each R^2 is independently selected from H, halo, -CN, -SR^1, alkyl, cycloalkyl, haloalkyl, -OR^1, and -R^4;

each R^4 is independently selected from $-CO_2R^1$, -(alkylene)-(CO_2R^1), hydroxyalkyl,



-(alkylene)$(S(O)_t)$(alkyl), -(alkylene)(NR^5R^5), and ;

each R^5 is independently selected from H, alkyl, haloalkyl, arylalkyl, heteroarylalkyl, aryl, and heteroaryl;

R^{21}, R^{22}, R^{23}, and R^{24} are independently selected from H, halo, -CN, $-SR^1$, alkyl, cycloalkyl, haloalkyl, $-NR^1R^1$, and $-OR^1$;

each R^{31} is independently selected from H and alkyl;

each k is independently selected from 3, 4, and 5;

each m is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

each n is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

q is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

r is 3, 4, 5, 6, or 7;

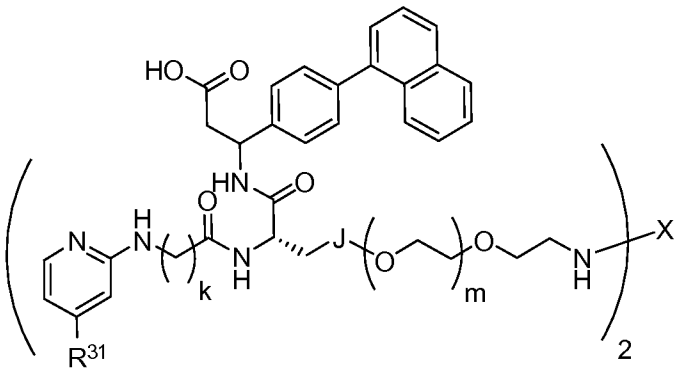
each s is independently selected from 0, 1, 2, 3, and 4;

each t is independently selected from 0, 1, and 2; and

each u is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10; and

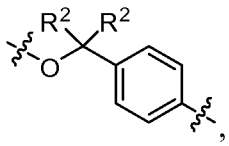
v is selected from 3, 4, 5, 6, 7, 8, 9, and 10.

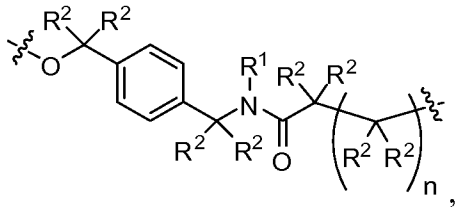
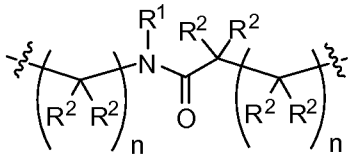
38. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, metabolite, deuteride, N-oxide, tautomer, stereoisomer, or isomer thereof, having the structure of Formula (Ib):

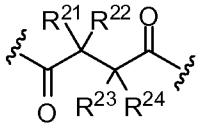
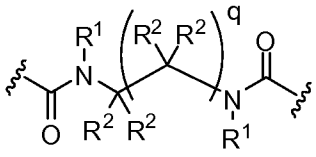
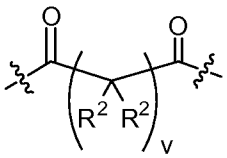


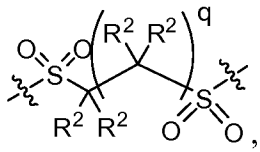
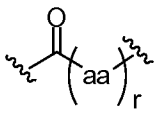
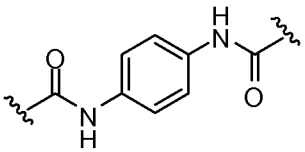
Formula (Ib);

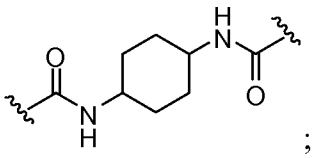
wherein:

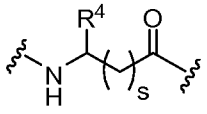
each J is independently selected from a bond, ,

, and ;

X is alkylene, -C(O)-, , , ,

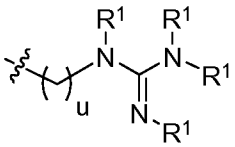
, , , or

;

aa is ;

each R^1 is independently selected from H and alkyl;

each R^2 is independently selected from H, halo, -CN, -SR^1, alkyl, cycloalkyl, haloalkyl, -OR^1, and -R^4;

each R^4 is independently selected from -CO_2R^1, -(alkylene)-(CO_2R^1), hydroxyalkyl, -(alkylene)($S(O)_tR^1$), -(alkylene)(NR^5R^5), and ;

each R^5 is independently selected from H, alkyl, haloalkyl, arylalkyl, heteroarylalkyl, aryl, and heteroaryl;

R^{21}, R^{22}, R^{23}, and R^{24} are independently selected from H, halo, -CN, -SR^1, alkyl, cycloalkyl, haloalkyl, -NR^1R^1, and -OR^1;

each R^{31} is independently selected from H and alkyl;

each k is independently selected from 3, 4, and 5;

each m is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

each n is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

q is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

r is 3, 4, 5, 6, or 7;

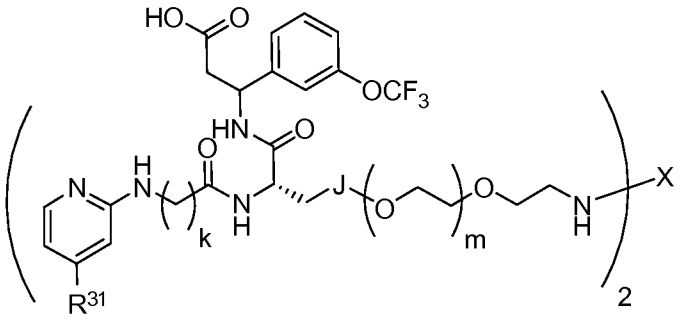
each s is independently selected from 0, 1, 2, 3, and 4;

each t is independently selected from 0, 1, and 2;

each u is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10; and

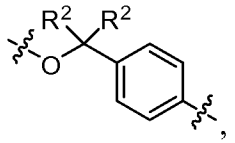
v is selected from 3, 4, 5, 6, 7, 8, 9, and 10.

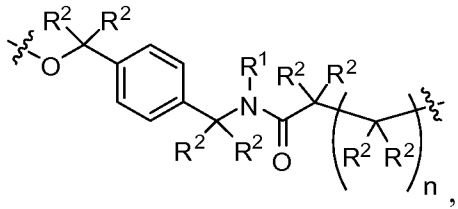
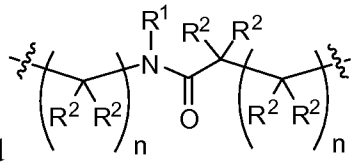
39. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, metabolite, deuteride, N-oxide, tautomer, stereoisomer, or isomer thereof, having the structure of Formula (Ic):

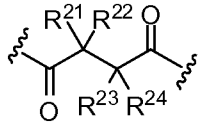
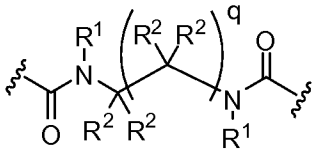
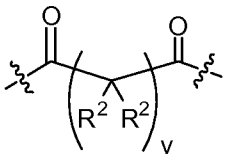
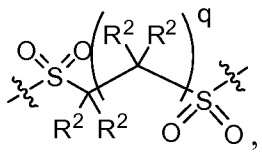
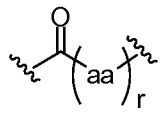
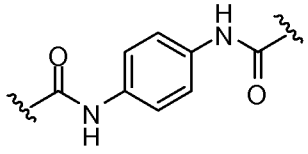
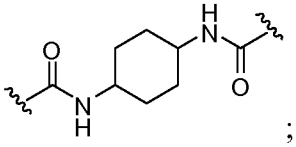


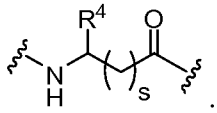
Formula (Ic);

wherein:

each J is independently selected from a bond, ,

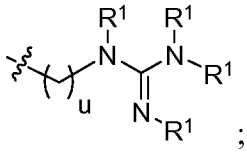
, and ;

X is alkylene, -C(O)-, , , , , , , or ;

aa is  ;

each R^1 is independently selected from H and alkyl;

each R^2 is independently selected from H, halo, -CN, -SR^1, alkyl, cycloalkyl, haloalkyl, -OR^1, and -R^4;

each R^4 is independently selected from -CO_2R^1, -(alkylene)-(CO_2R^1), hydroxyalkyl, -(alkylene)($S(O)_t$)(alkyl), -(alkylene)(NR^5R^5), and  ;

each R^5 is independently selected from H, alkyl, haloalkyl, arylalkyl, heteroarylalkyl, aryl, and heteroaryl;

R^{21}, R^{22}, R^{23}, and R^{24} are independently selected from H, halo, -CN, -SR^1, alkyl, cycloalkyl, haloalkyl, -NR^1R^1, and -OR^1;

each R^{31} is independently selected from H and alkyl;

each k is independently selected from 3, 4, and 5;

each m is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

each n is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

q is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

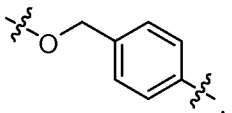
r is 3, 4, 5, 6, or 7;

each s is independently selected from 0, 1, 2, 3, and 4;

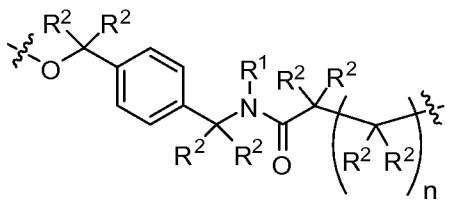
each t is independently selected from 0, 1, and 2;

each u is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10; and

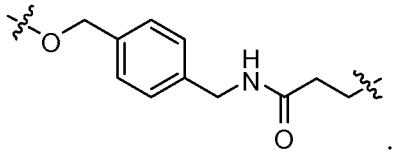
v is selected from 3, 4, 5, 6, 7, 8, 9, and 10.

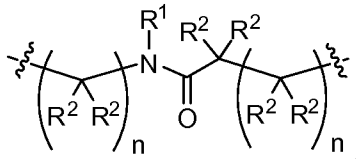
40. The compound of any one of claims 37-39 wherein each J is .

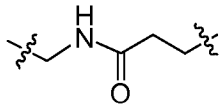
41. The compound of any one of claims 37-39 wherein each J is

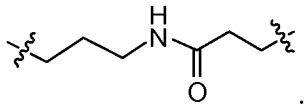


.

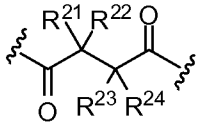
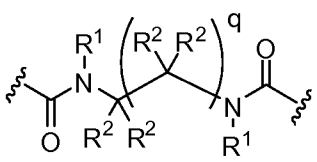
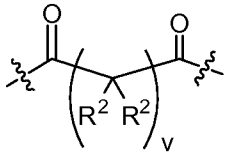
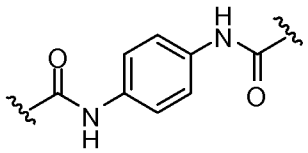
42. The compound of claim 41 wherein each J is .

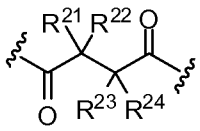
43. The compound of any one of claims 37-39 wherein each J is .

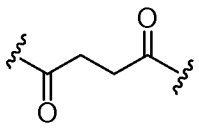
44. The compound of claim 43 wherein each J is .

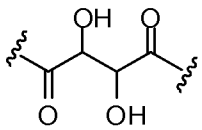
45. The compound of claim 43 wherein each J is .

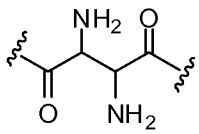
46. The compound of any one of claims 37-39 wherein each J is a bond.

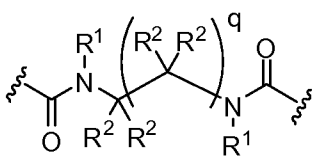
47. The compound of any one of claims 37-46 wherein X is -C(O)-, , , , or .

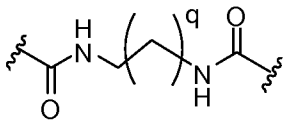
48. The compound of any one of claims 37-46 wherein X is .

49. The compound of claim 48 wherein X is .

50. The compound of claim 48 wherein X is .

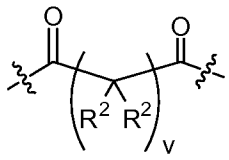
51. The compound of claim 48 wherein X is .

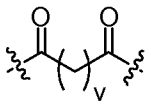
52. The compound of any one of claims 37-46 wherein X is .

53. The compound of claim 52 wherein X is  .

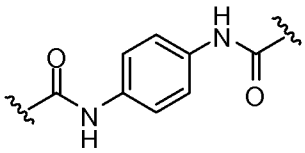
54. The compound of claim 53 wherein q is 3.

55. The compound of claim 53 wherein q is 5.

56. The compound of any one of claims 37-46 wherein X is  .

57. The compound of claim 56 wherein X is  .

58. The compound of claim 57 wherein v is 4.

59. The compound of any one of claims 37-46 wherein X is  .

60. The compound of any one of claims 37-59 wherein each m is independently 0, 1, 2, or 3.

61. The compound of any one of claims 37-59 wherein each m is 1.

62. The compound of any one of claims 37-59 wherein each m is 2.

63. The compound of any one of claims 37-59 wherein each m is 3.

64. The compound of any one of claims 37-63 wherein each R^{31} is H.

65. The compound of any one of claims 37-63 wherein each R^{31} is alkyl.

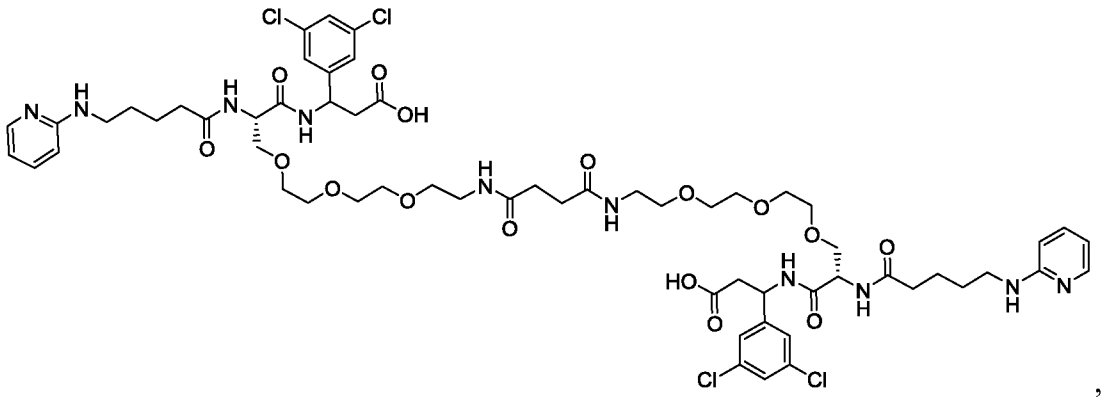
66. The compound of any one of claims 37-63 wherein each R^{31} is methyl.

67. The compound of any one of claims 37-63 wherein each R^{31} is ethyl.

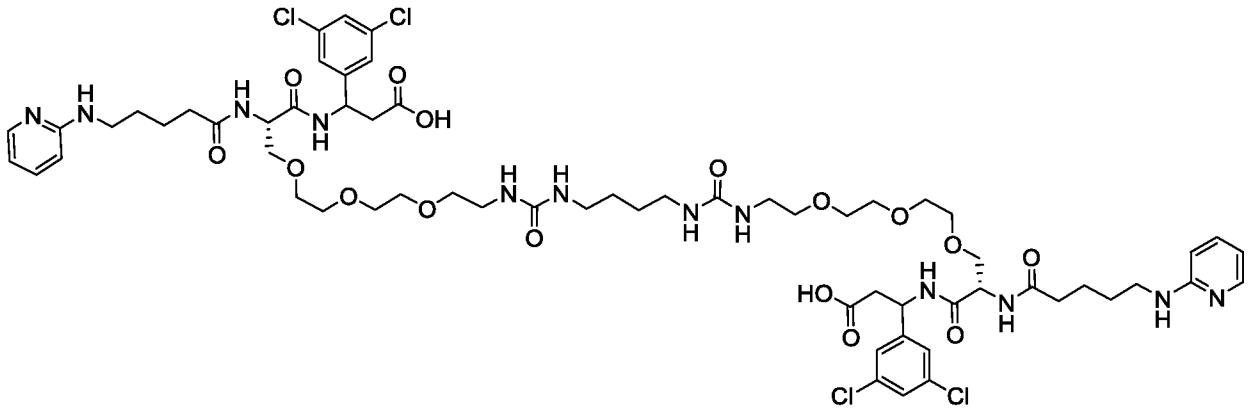
68. The compound of any one of claims 37-67 wherein each k is 3.

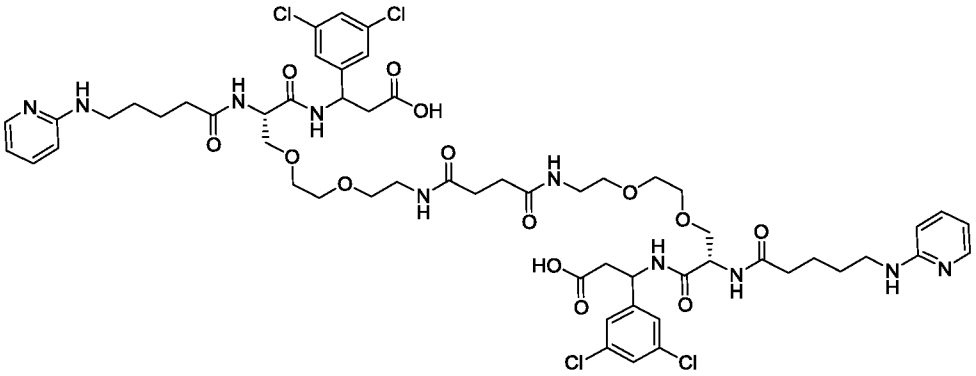
69. The compound of any one of claims 37-67 wherein each k is 4.

70. The compound of claim 1 wherein the compound is selected from:



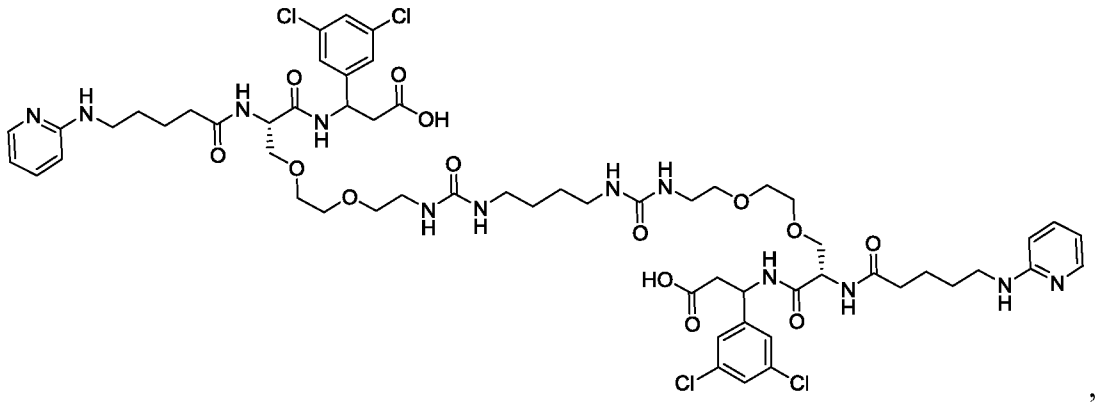
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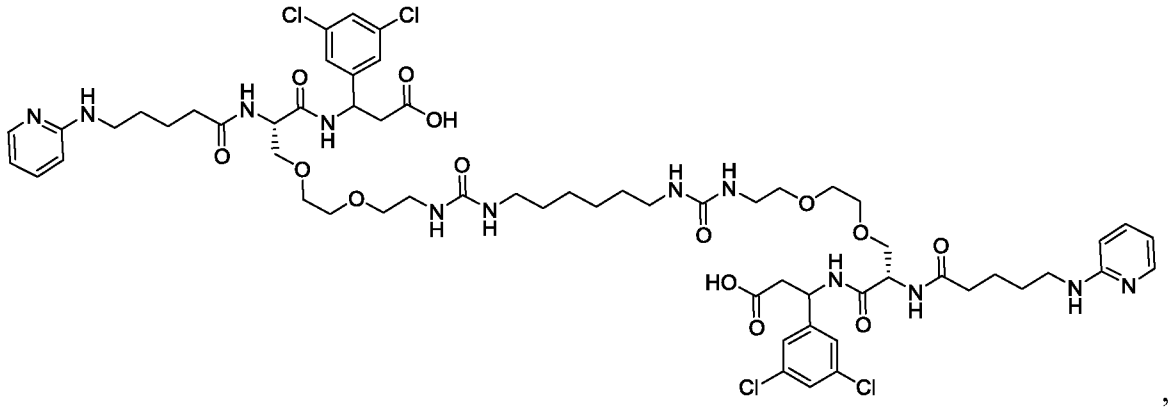


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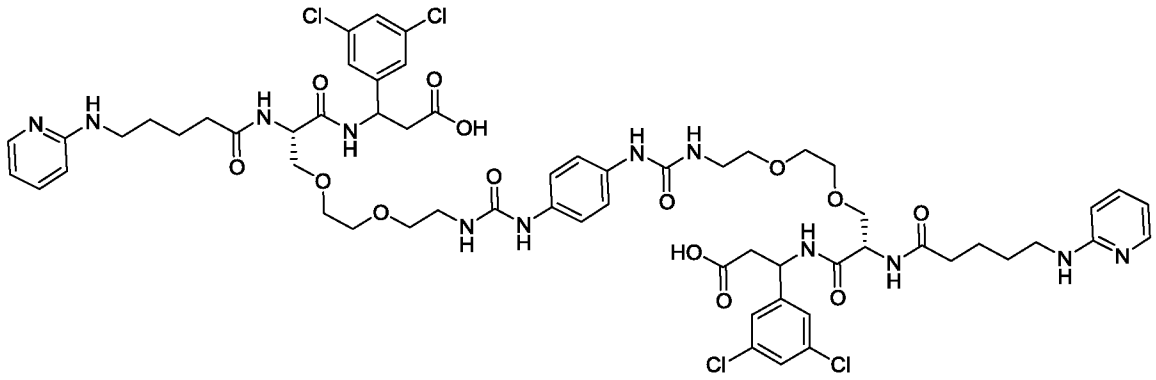
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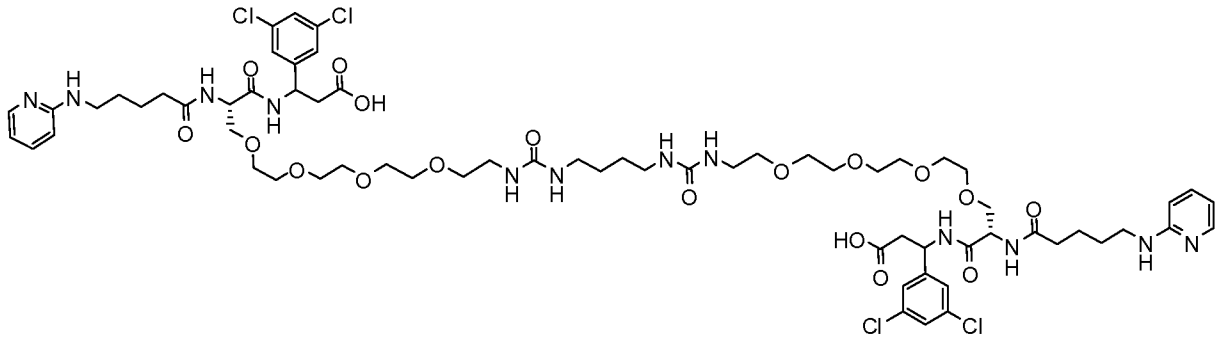
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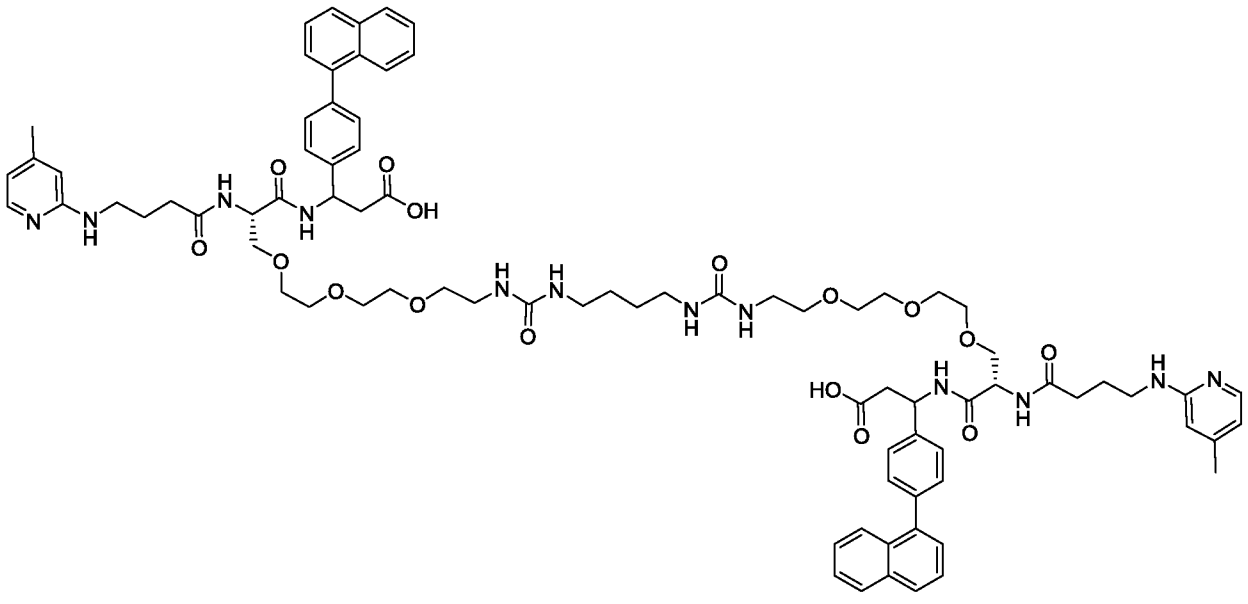
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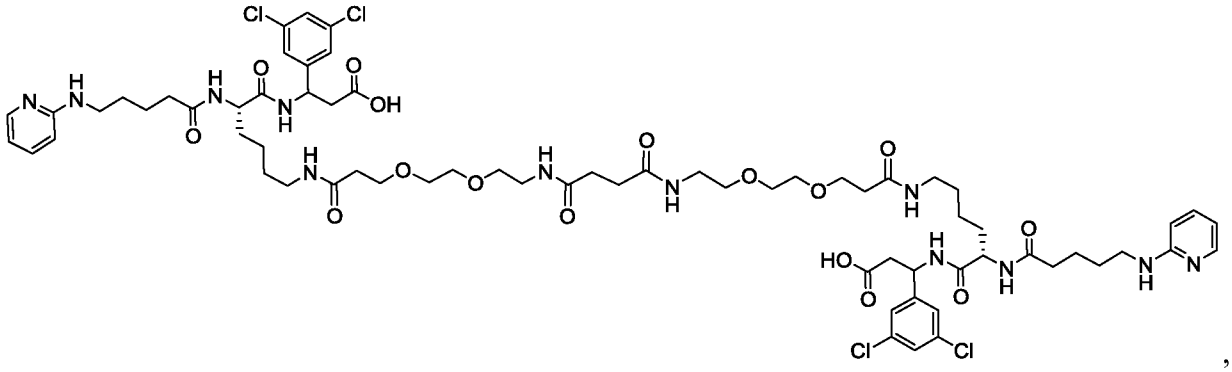
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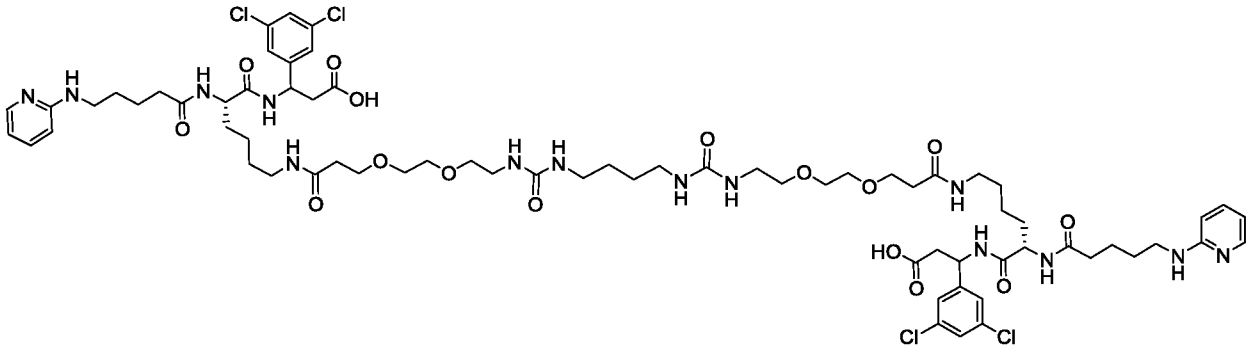
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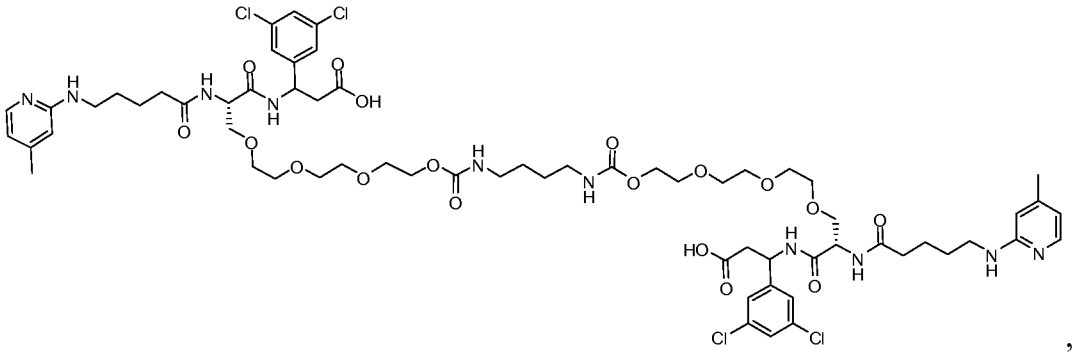


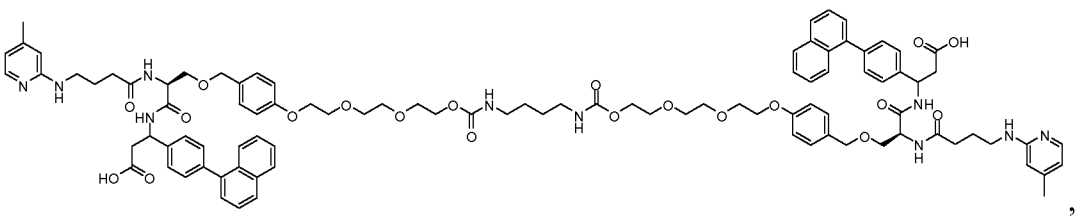
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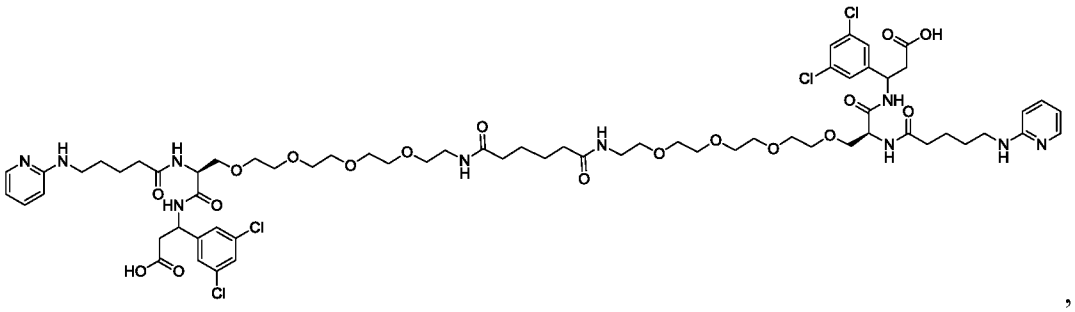


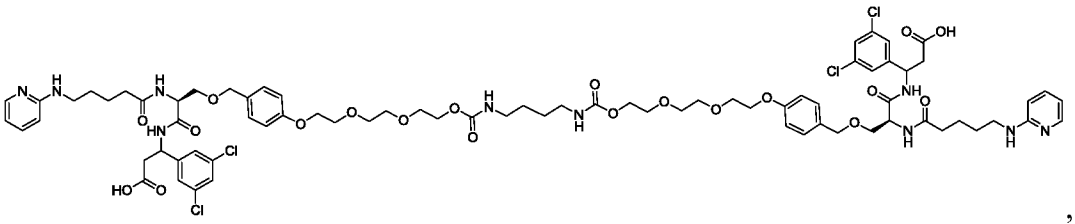
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71. The compound of claim 1 wherein the compound is selected from:

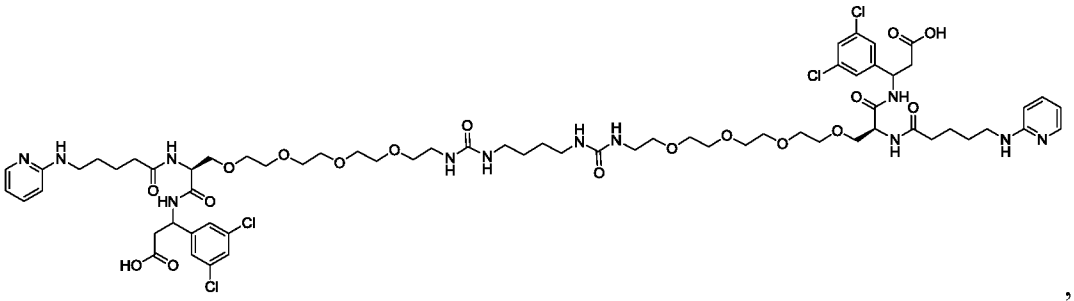




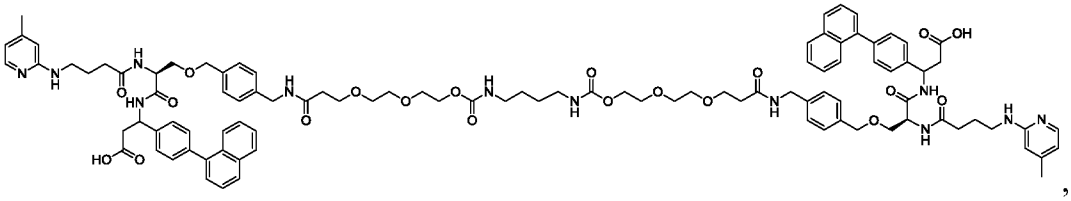




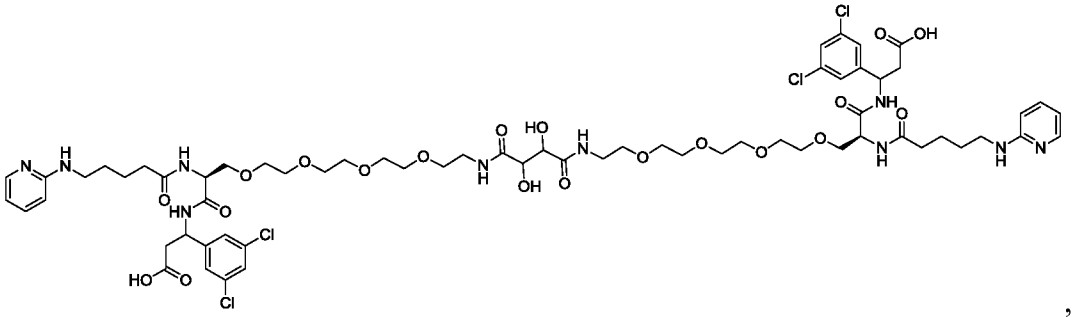
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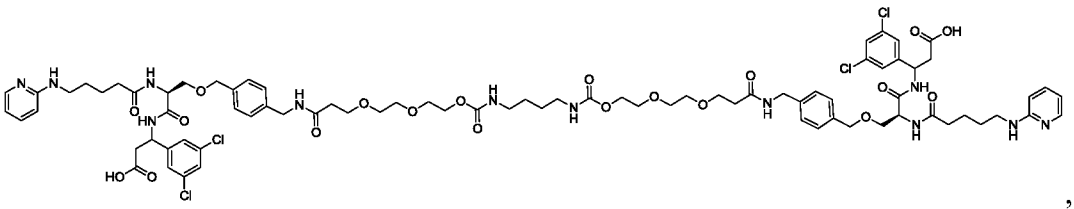
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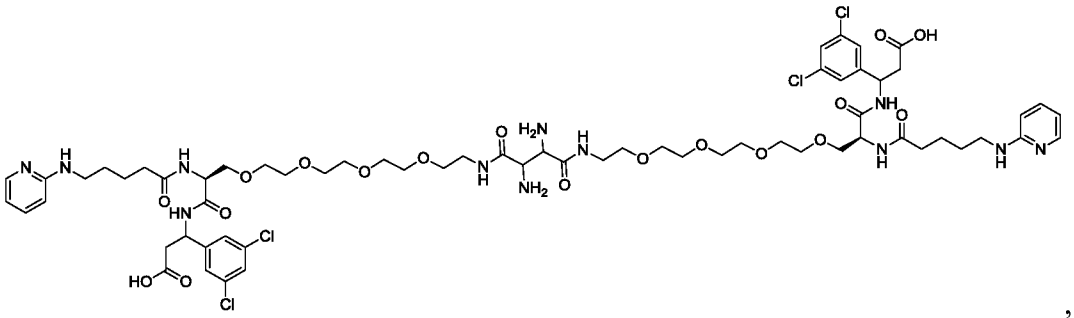
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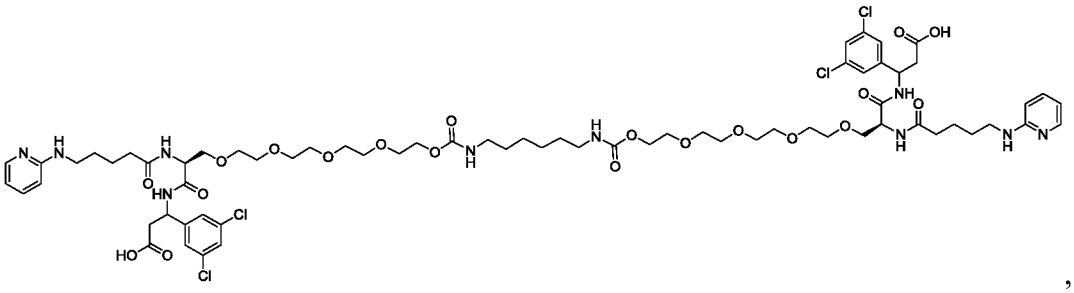
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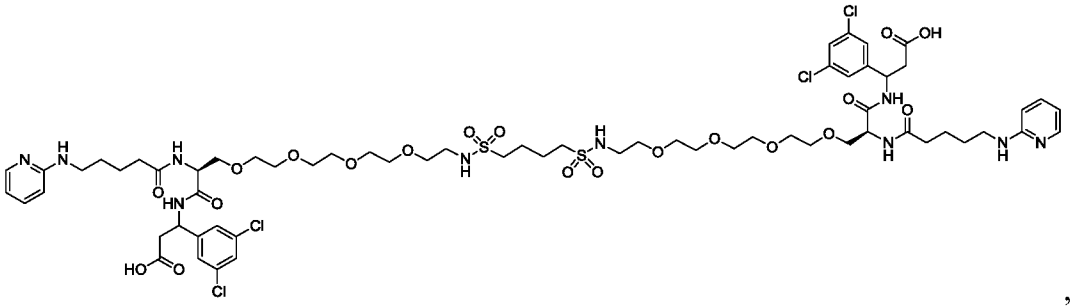
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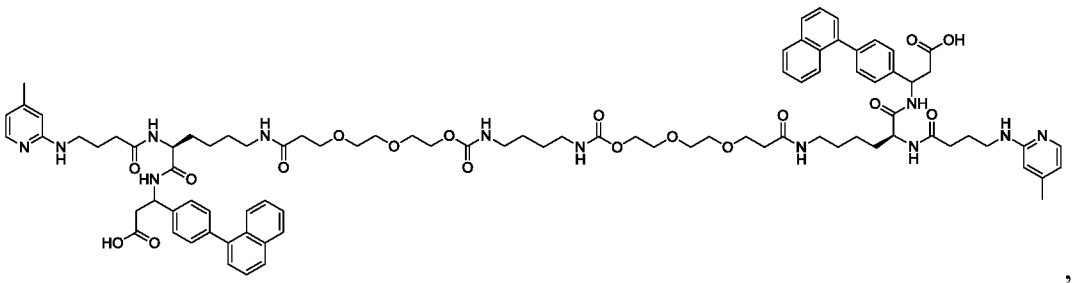
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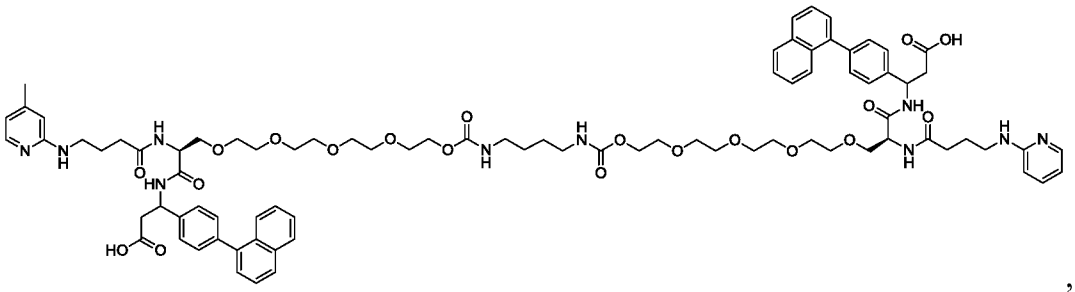
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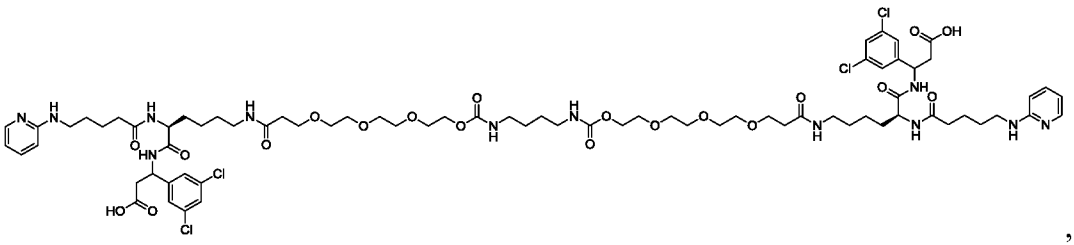
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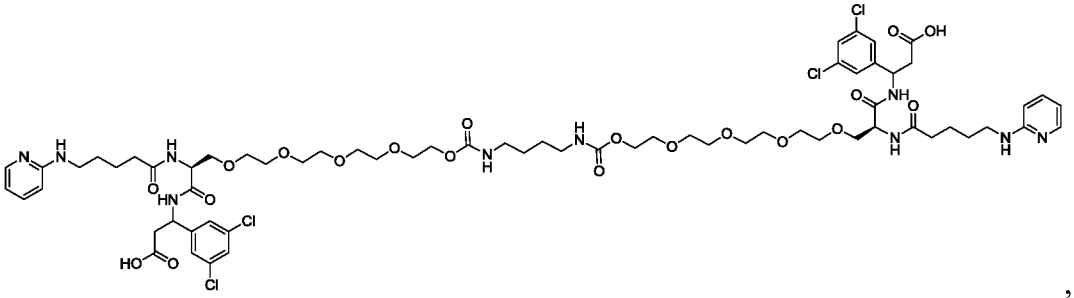
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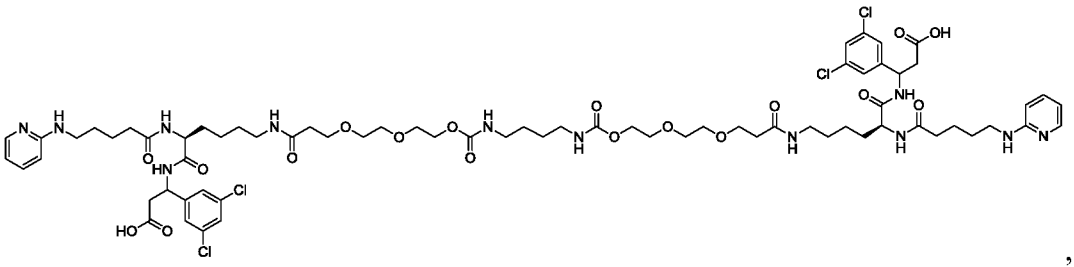
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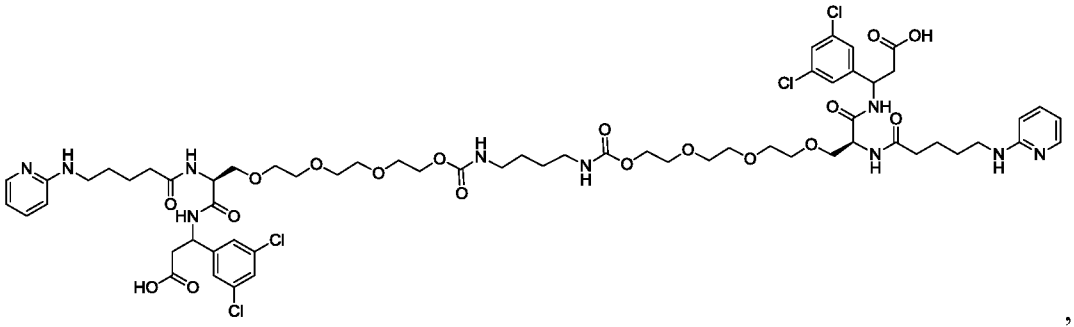
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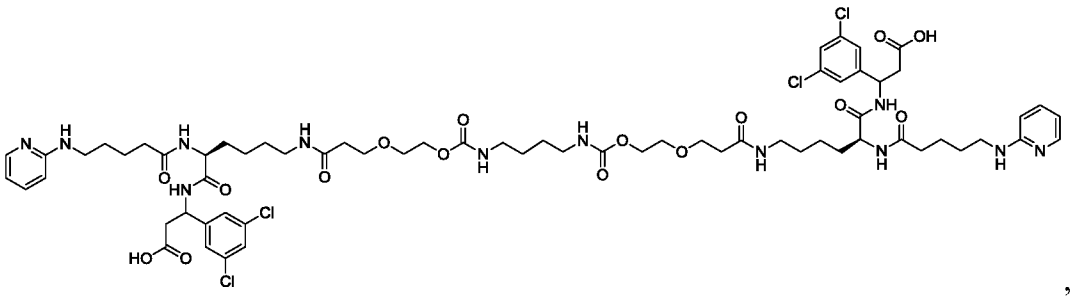
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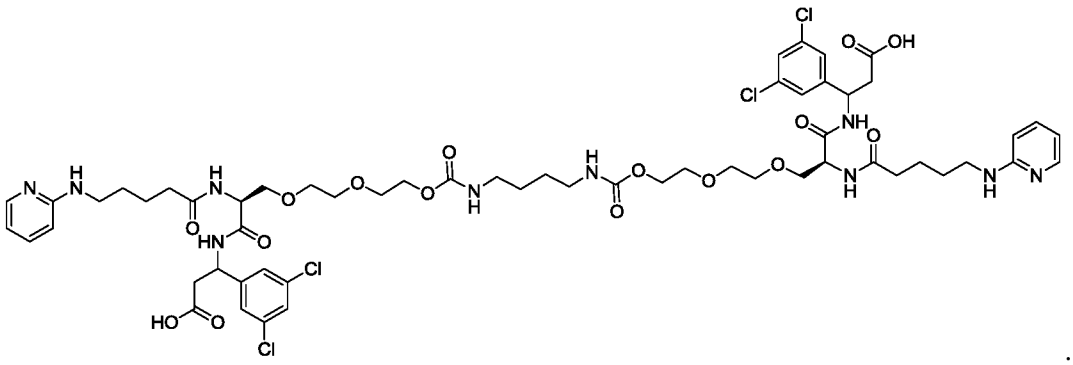
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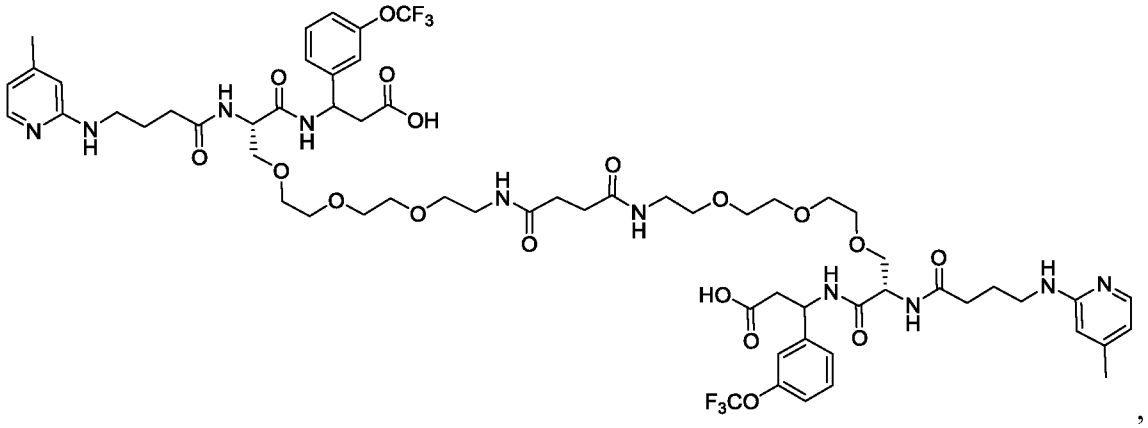


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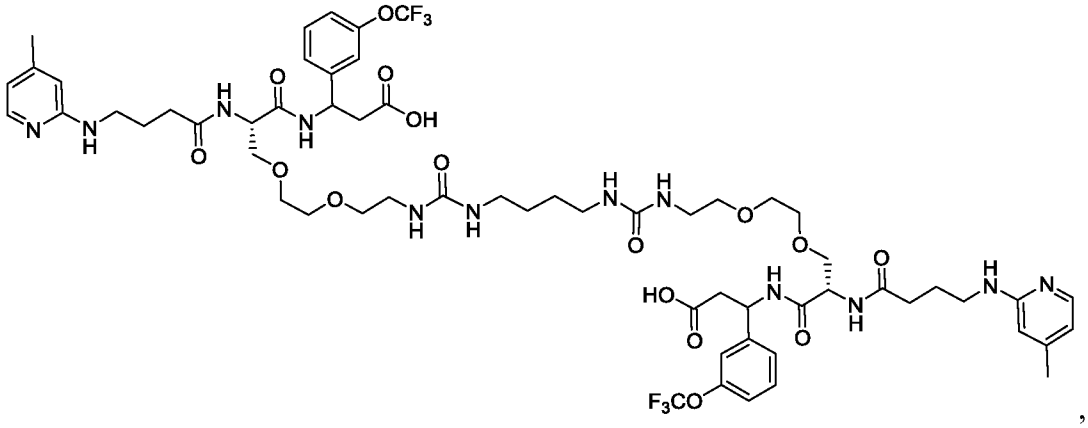


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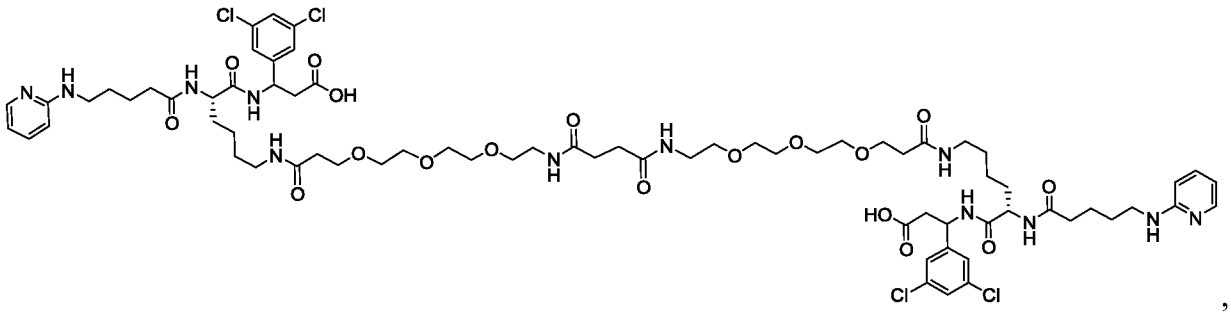
72. A compound, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, metabolite, deuteride, N-oxide, tautomer, stereoisomer, or isomer thereof, wherein the compound is selected from:



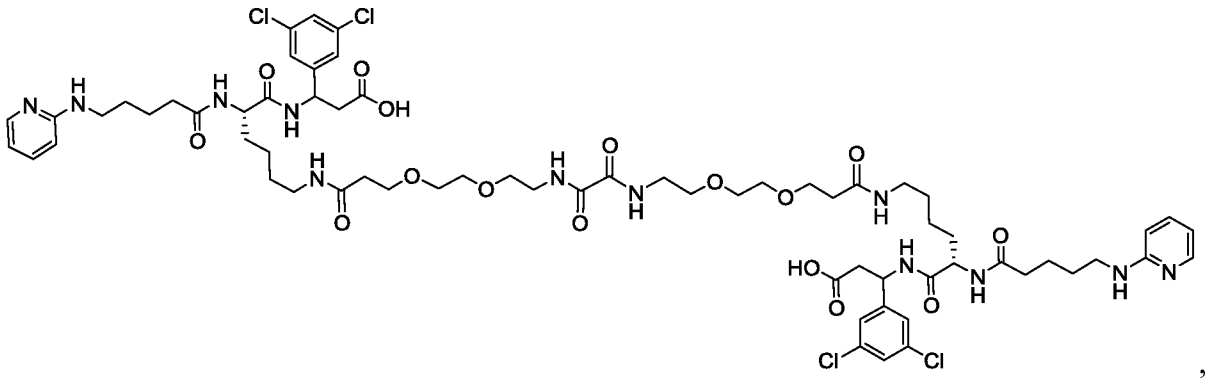
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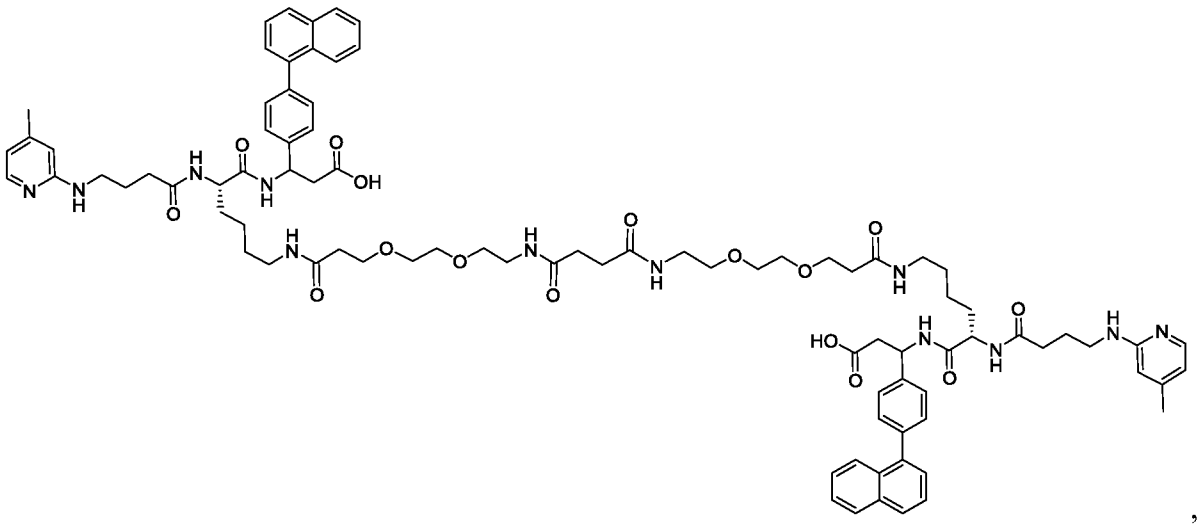
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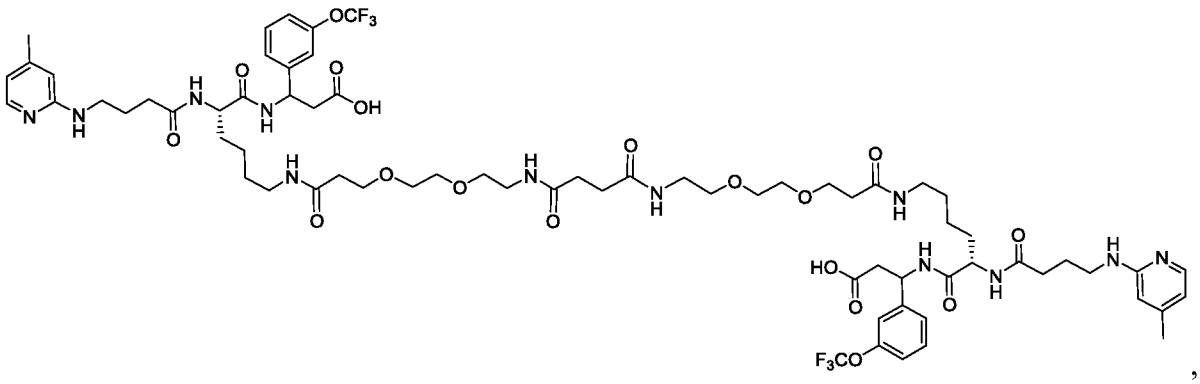
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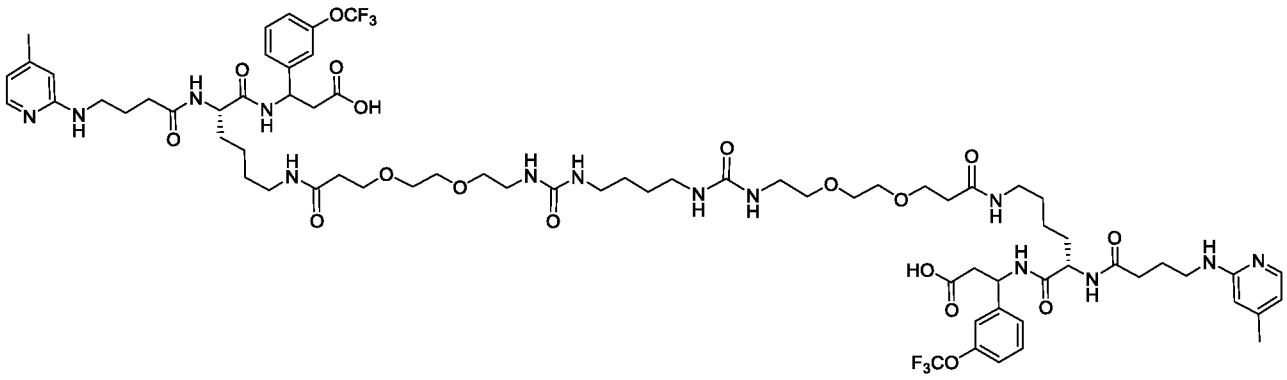
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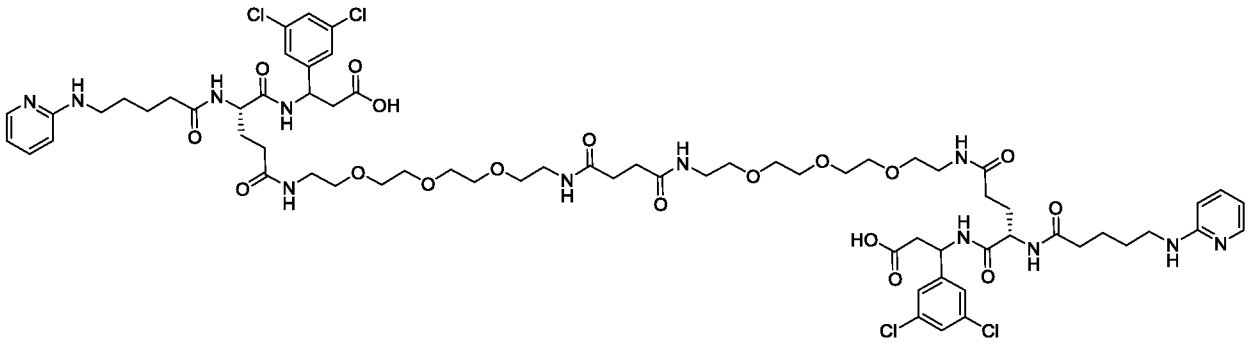
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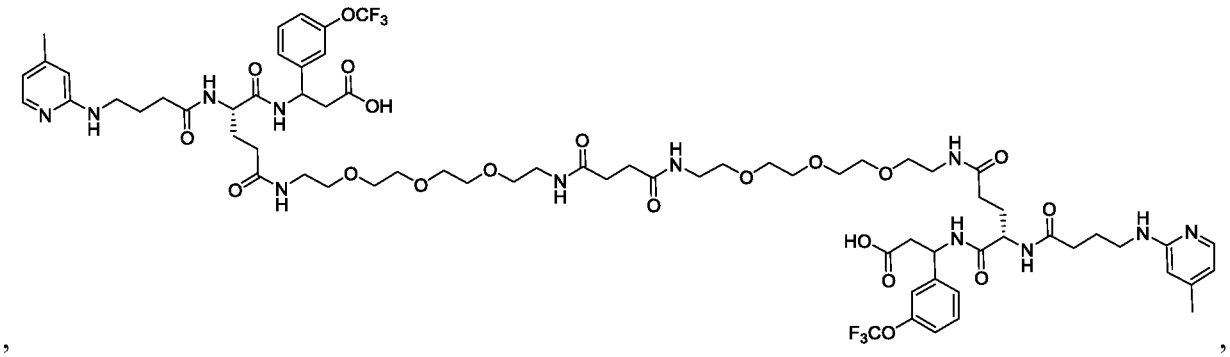


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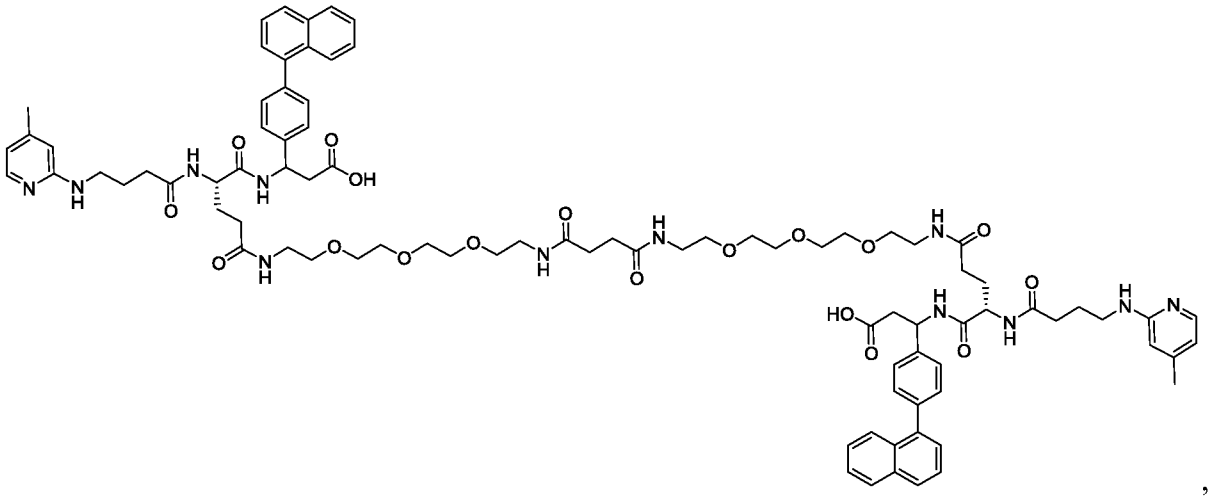


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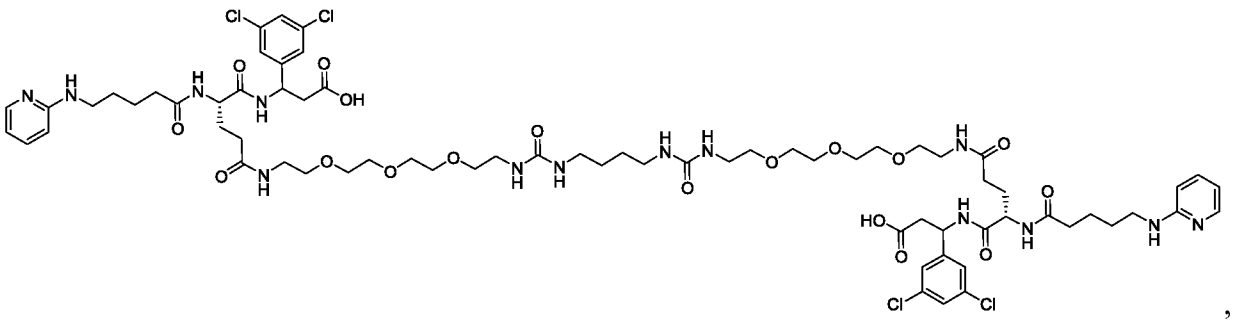




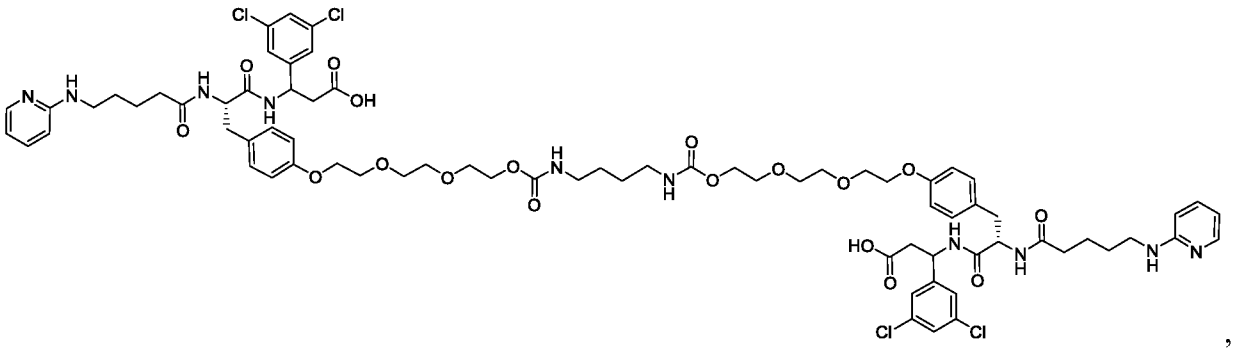
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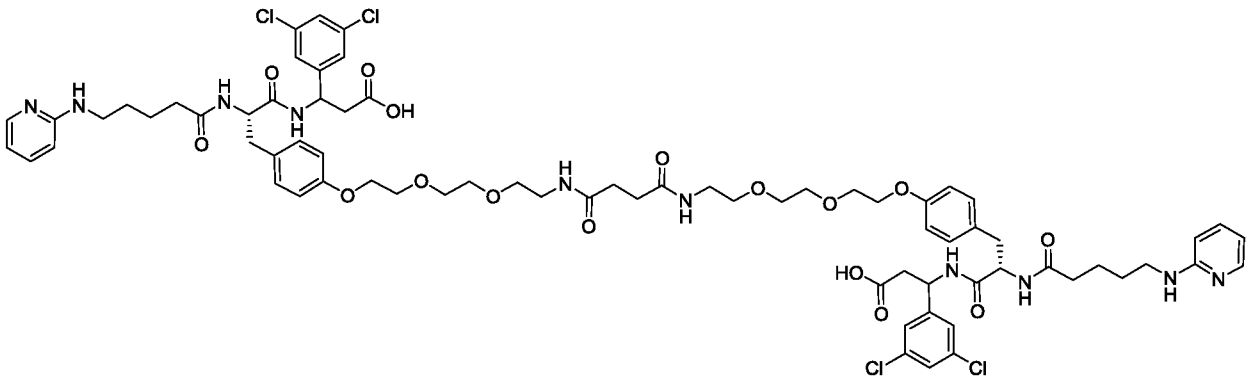
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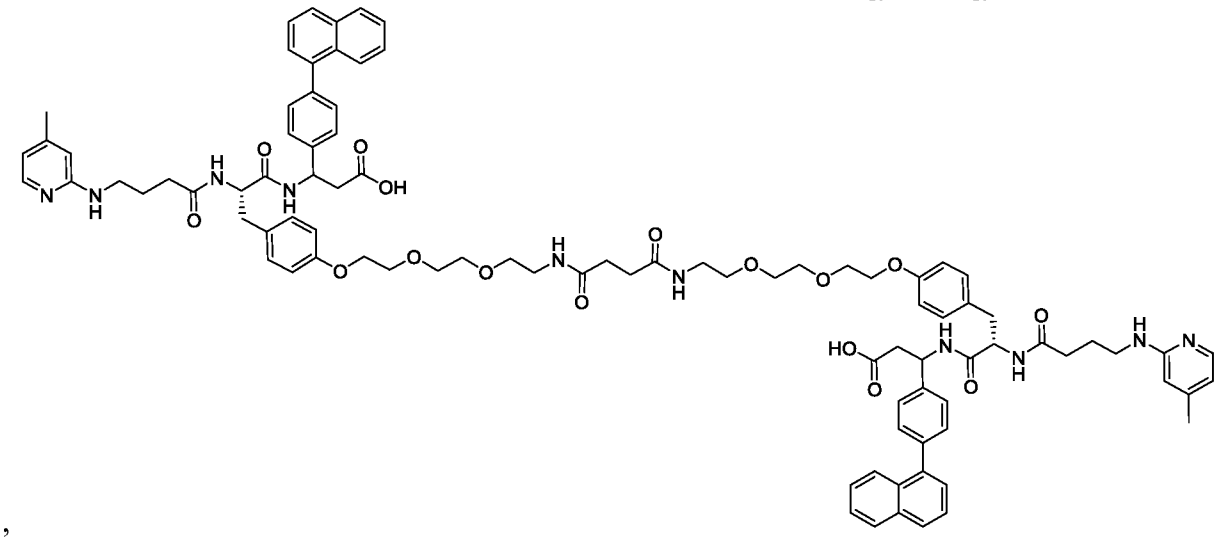


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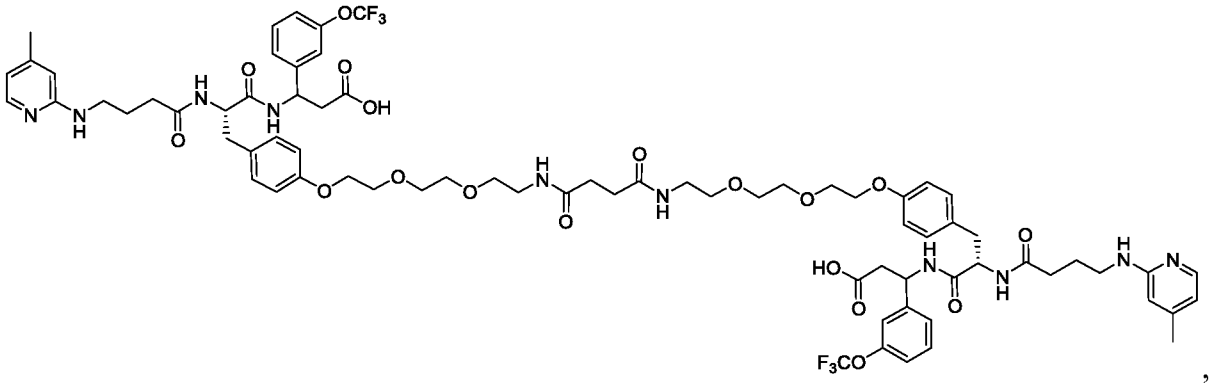
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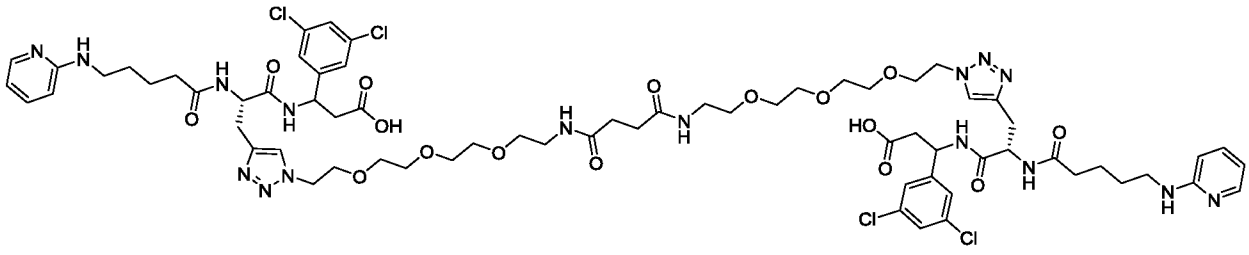


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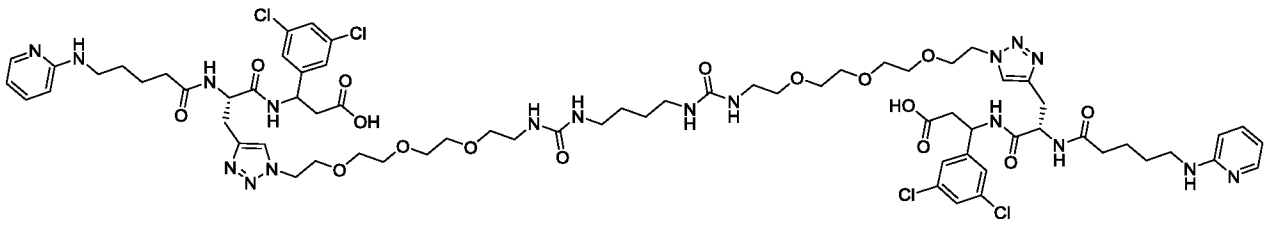
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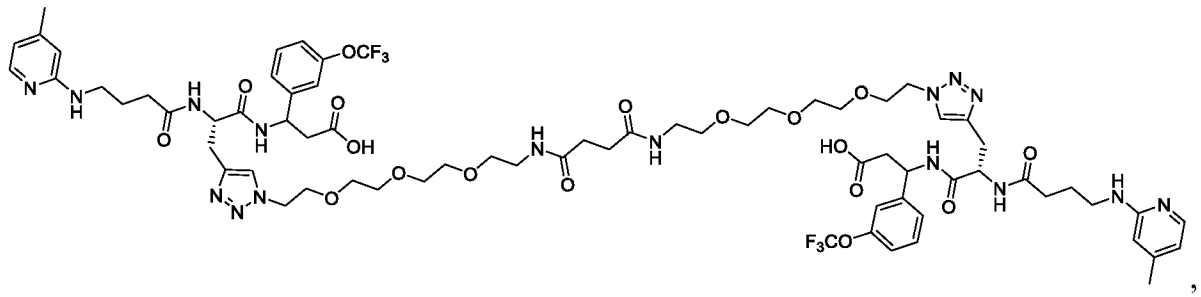


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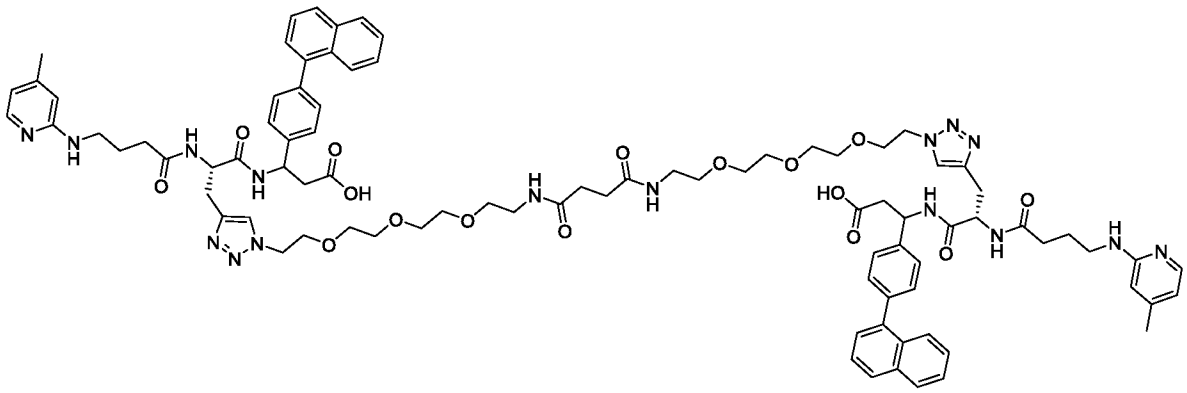


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and

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73. A pharmaceutical composition comprising a compound of any one of claims 1-72 or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, metabolite, deuteride, N-oxide, tautomer, stereoisomer, or isomer thereof, and a pharmaceutically acceptable excipient.

74. A method of treating a lung disease in a mammal, the method comprising administering to the mammal a composition comprising a compound of any one of claims 1-72.

75. The method of claim 74 wherein the lung disease is idiopathic pulmonary fibrosis.