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(54) **COMPOSITIONS AND METHODS FOR TREATING EZH2-MEDIATED CANCER**

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(57) **ABSTRACT**

Methods for designing bivalent compounds which selectively degrade/disrupt EZH2 and compositions and methods of using such degraders/disruptors to treat EZH2-mediated cancer are provided.

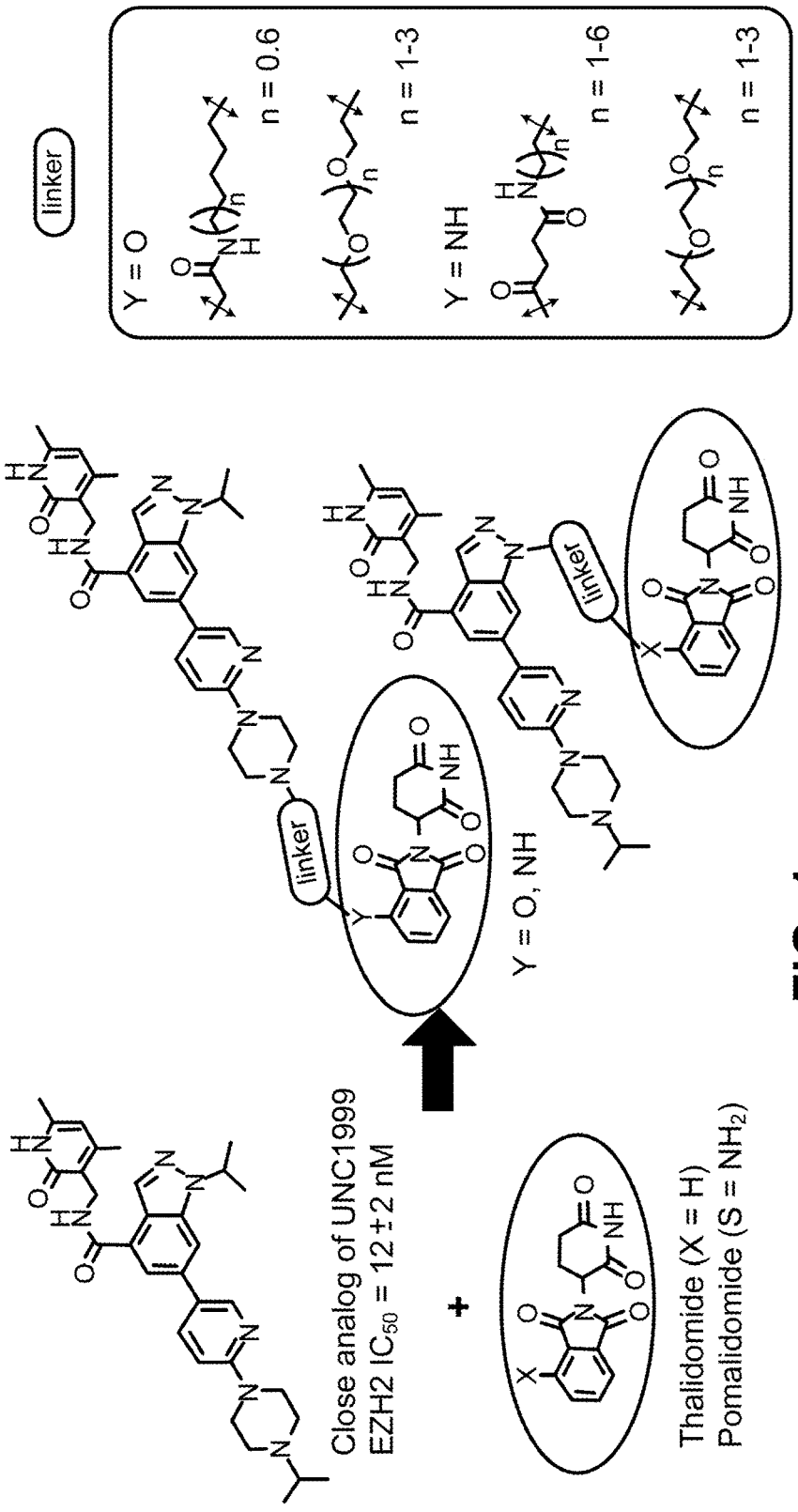

linker
Y = O
n = 0.6
n = 1-3
Y = NH
n = 1-6
n = 1-3
Close analog of UNC1999
EZH2 IC50 = 12 ± 2 nM
+
Thalidomide (X = H)
Pomalidomide (S = NH2)
Y = O, NH

FIG. 1

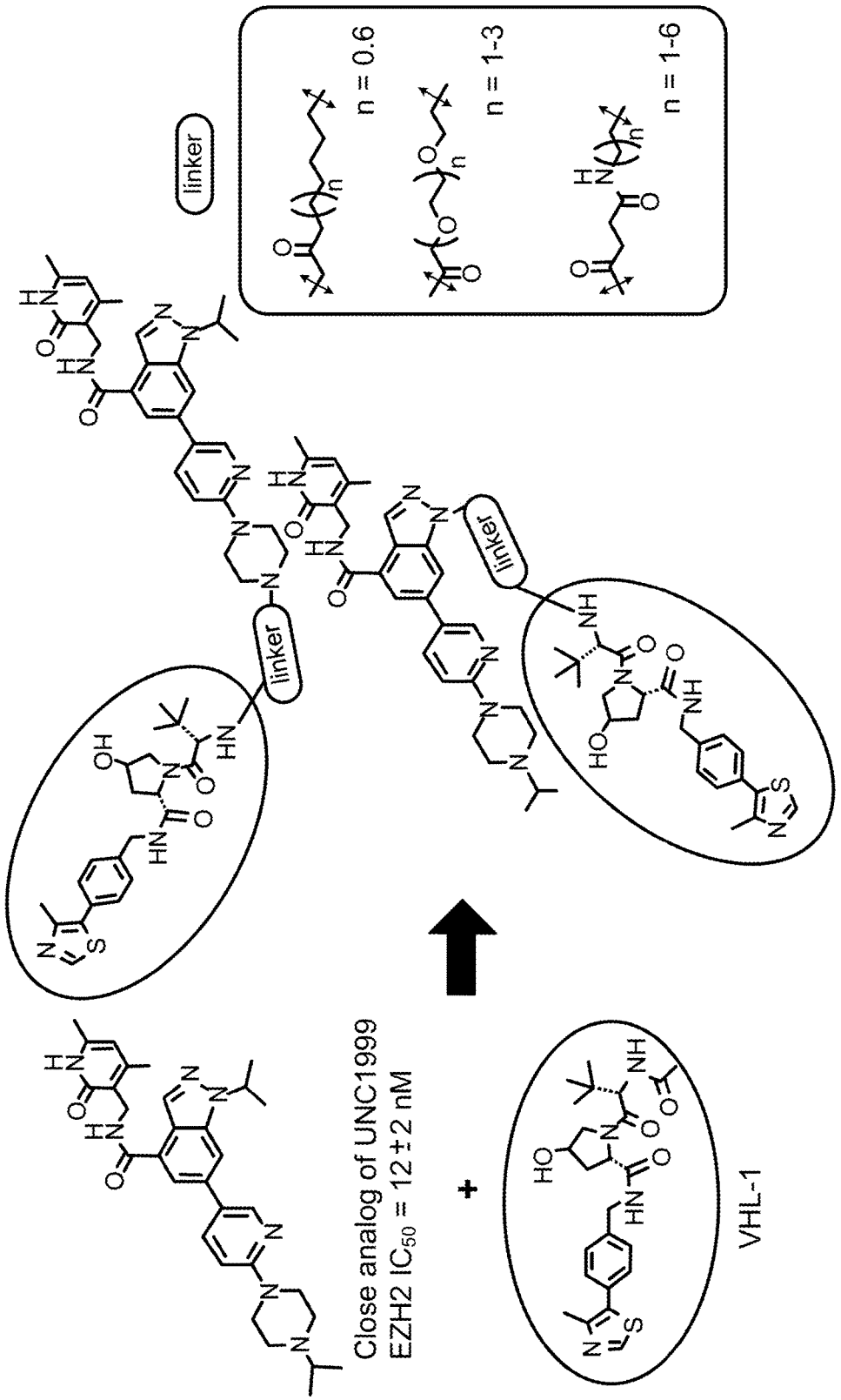

Close analog of UNC1999
EZH2 IC50 = 12 ± 2 nM
+
VHL-1
linker
linker
linker
n = 0.6
n = 1-3
n = 1-6

FIG. 2

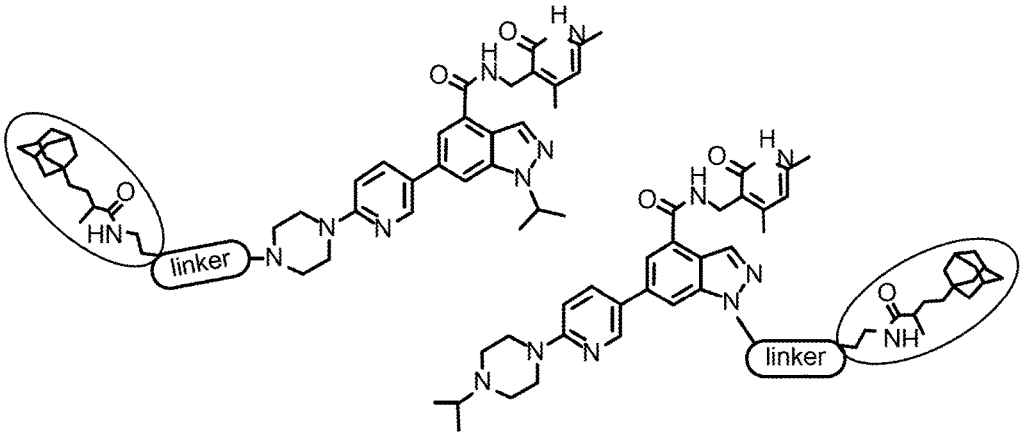


FIG. 3

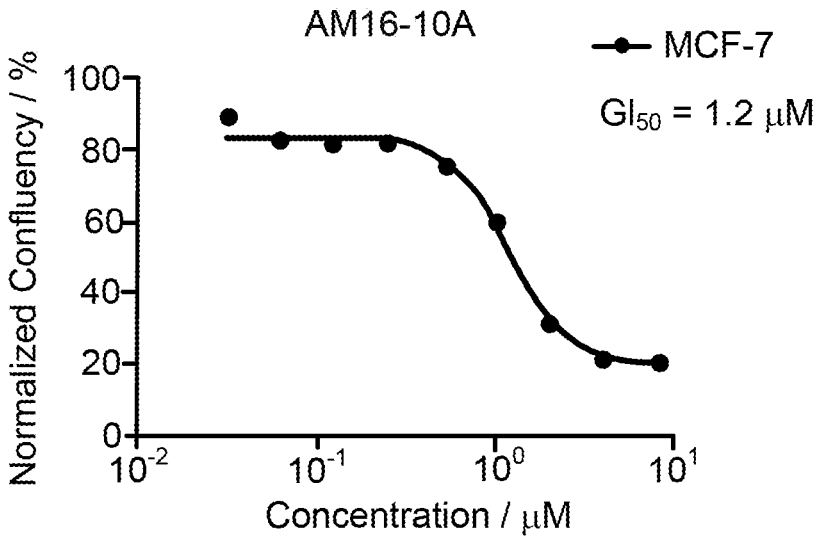

AM16-10A
MCF-7
GI_{50} = 1.2 μM
Normalized Confluency / %
100
80
60
40
20
0
10^{-2}
10^{-1}
10^{0}
10^{1}
Concentration / μM

FIG. 4

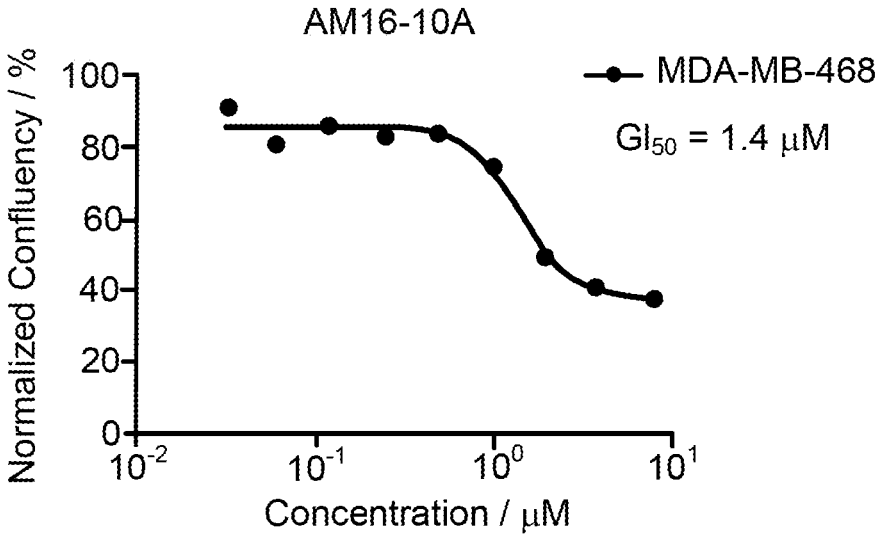

AM16-10A
MDA-MB-468
GI_{50} = 1.4 μM
Normalized Confluency / %
100
80
60
40
20
0
10^{-2}
10^{-1}
10^{0}
10^{1}
Concentration / μM

FIG. 5

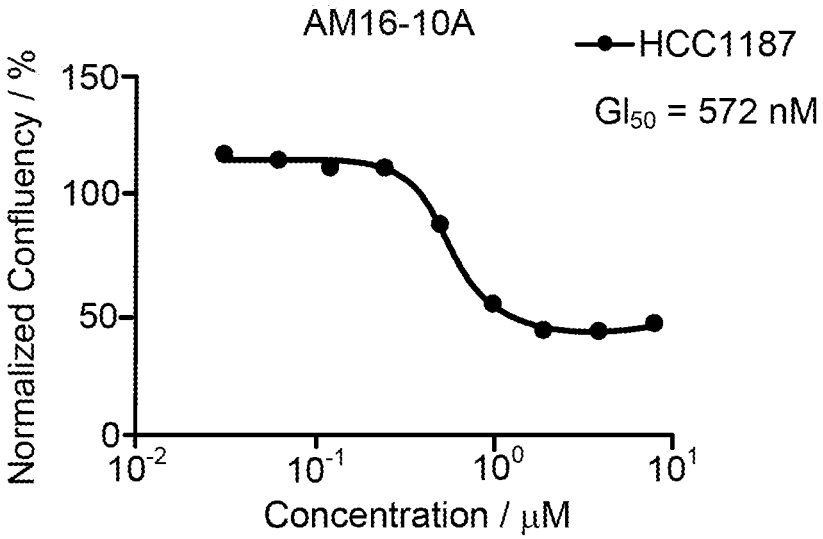

AM16-10A
HCC1187
GI_{50} = 572 nM
Normalized Confluency / %
150
100
50
0
10^{-2}
10^{-1}
10^{0}
10^{1}
Concentration / μM

FIG. 6

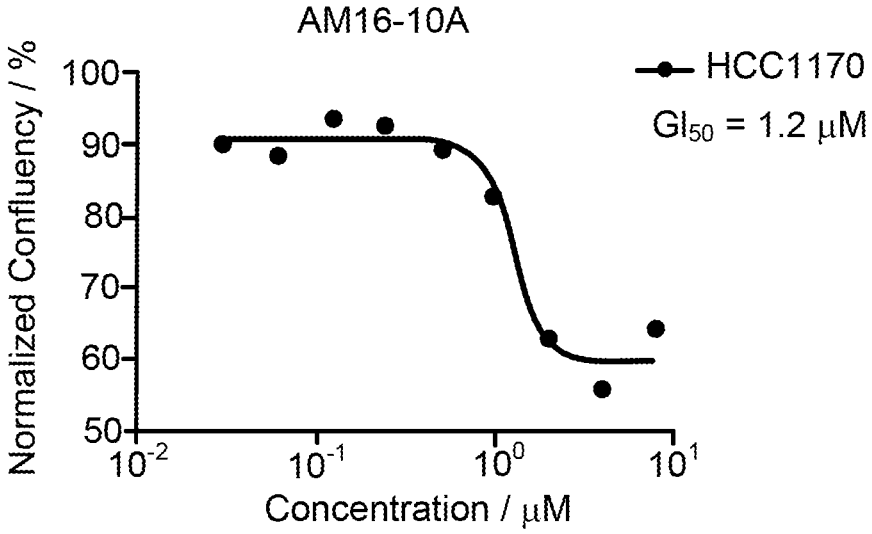

AM16-10A
HCC1170
GI_{50} = 1.2 μM
Normalized Confluency / %
100
90
80
70
60
50
10^{-2}
10^{-1}
10^{0}
10^{1}
Concentration / μM

FIG. 7

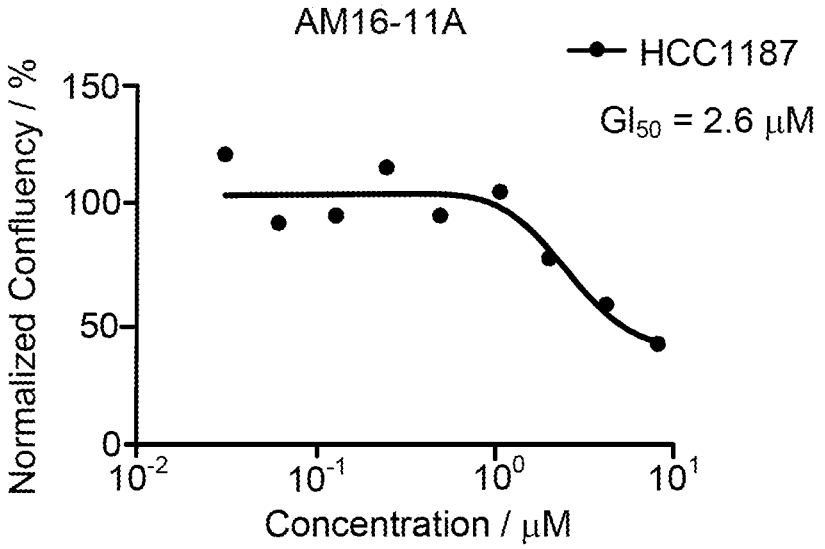

AM16-11A
HCC1187
GI_{50} = 2.6 μM
Normalized Confluency / %
150
100
50
0
10^{-2}
10^{-1}
10^{0}
10^{1}
Concentration / μM

FIG. 8

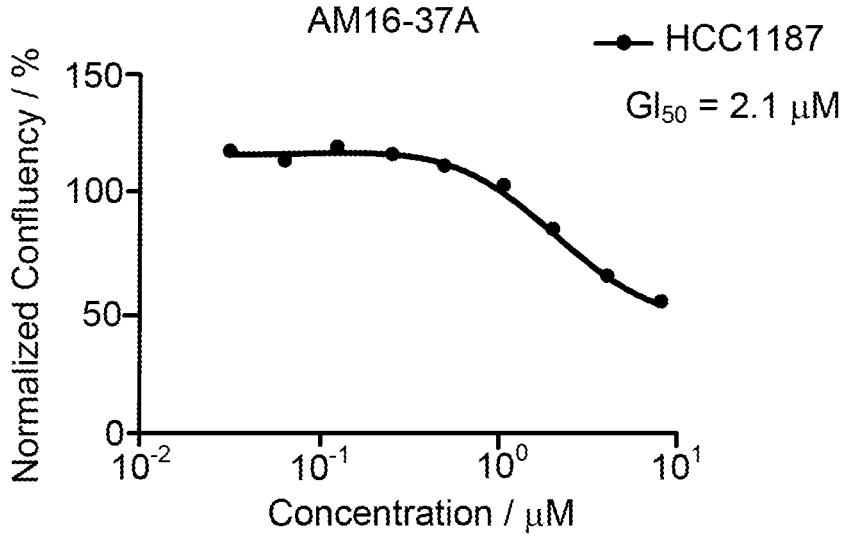

AM16-37A
HCC1187
GI_{50} = 2.1 μM
Normalized Confluency / %
150
100
50
0
10^{-2}
10^{-1}
10^{0}
10^{1}
Concentration / μM

FIG. 9

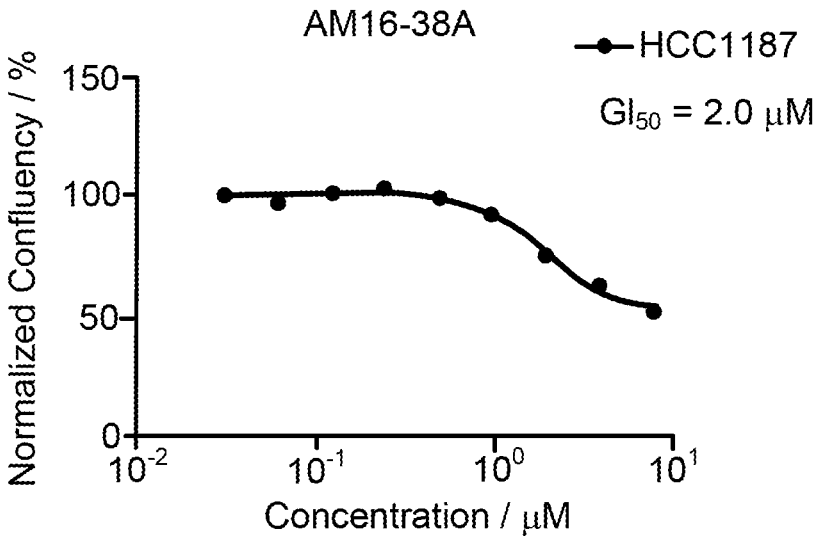

AM16-38A
HCC1187
GI_{50} = 2.0 μM
Normalized Confluency / %
150
100
50
0
10^{-2}
10^{-1}
10^{0}
10^{1}
Concentration / μM

FIG. 10

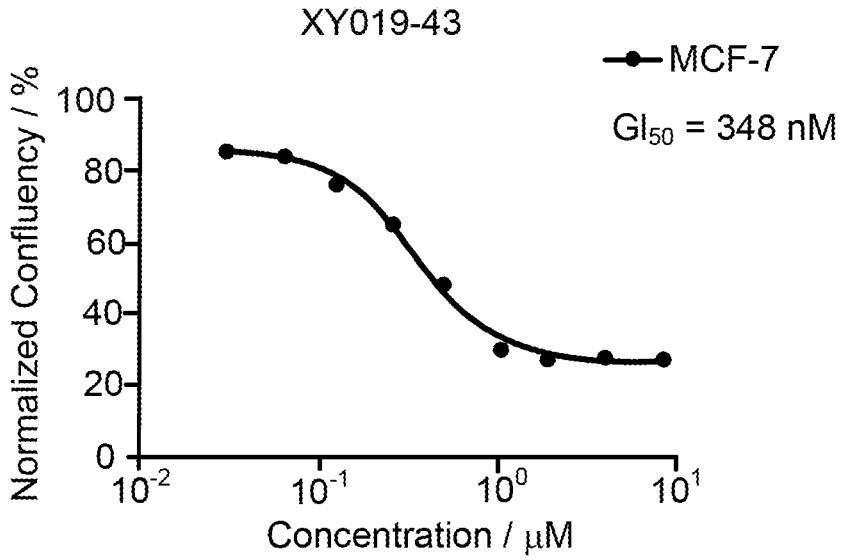

XY019-43
MCF-7
GI_{50} = 348 nM
Normalized Confluency / %
100
80
60
40
20
0
10^{-2}
10^{-1}
10^{0}
10^{1}
Concentration / μM

FIG. 11

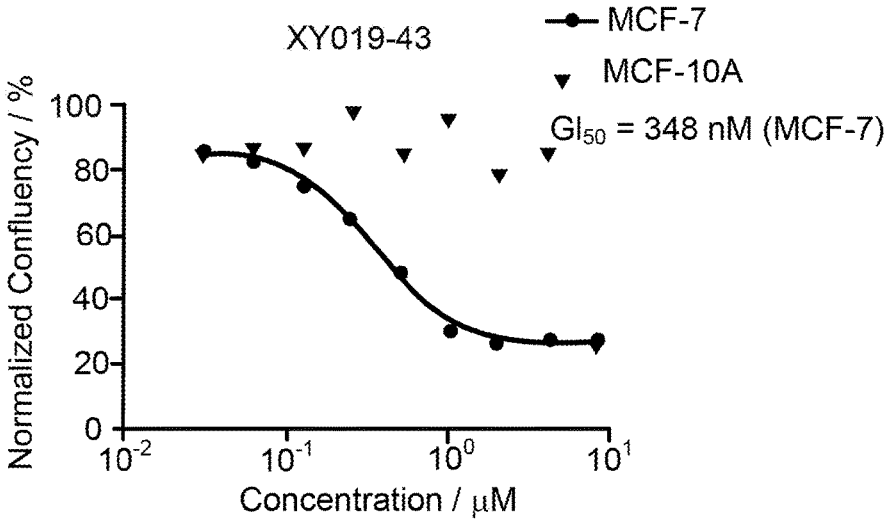

XY019-43
MCF-7
MCF-10A
GI50 = 348 nM (MCF-7)
Normalized Confluency / %
100
80
60
40
20
0
10-2
10-1
100
101
Concentration / μM

FIG. 12

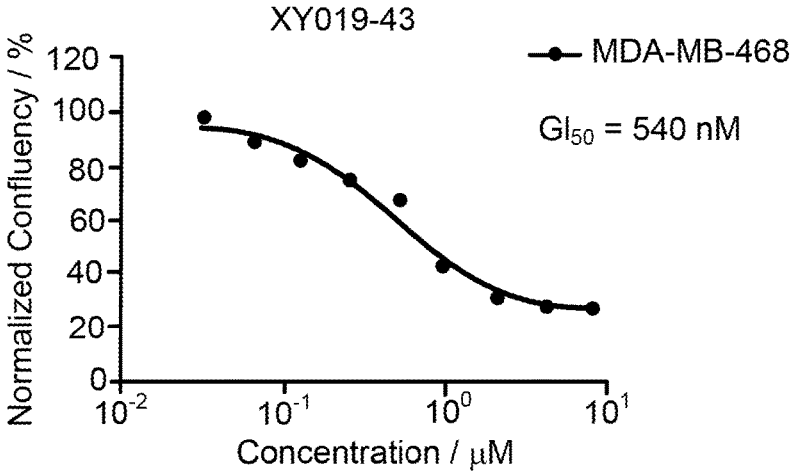

XY019-43
MDA-MB-468
GI50 = 540 nM
Normalized Confluency / %
120
100
80
60
40
20
0
10-2
10-1
100
101
Concentration / μM

FIG. 13

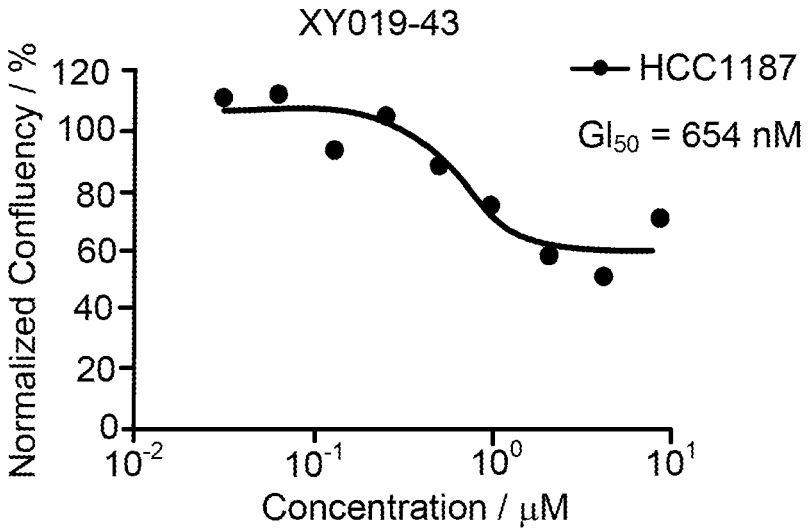

XY019-43
HCC1187
GI_{50} = 654 nM
Normalized Confluency / %
120
100
80
60
40
20
0
10^{-2}
10^{-1}
10^{0}
10^{1}
Concentration / μM

FIG. 14

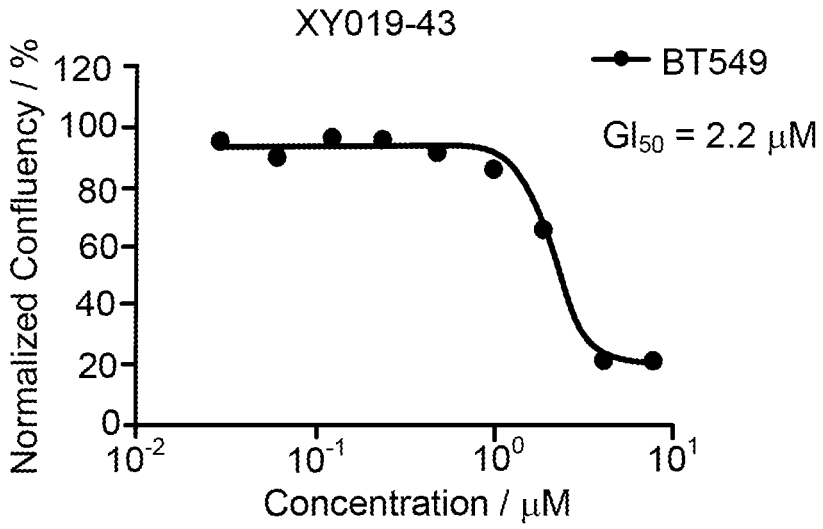

XY019-43
BT549
GI_{50} = 2.2 μM
Normalized Confluency / %
120
100
80
60
40
20
0
10^{-2}
10^{-1}
10^{0}
10^{1}
Concentration / μM

FIG. 15

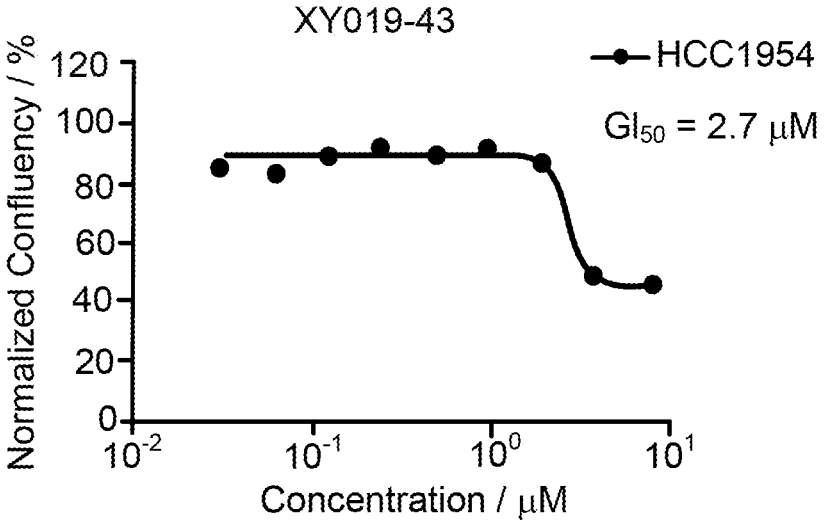

XY019-43
HCC1954
GI_{50} = 2.7 μM
Normalized Confluency / %
120
100
80
60
40
20
0
10^{-2}
10^{-1}
10^{0}
10^{1}
Concentration / μM

FIG. 16

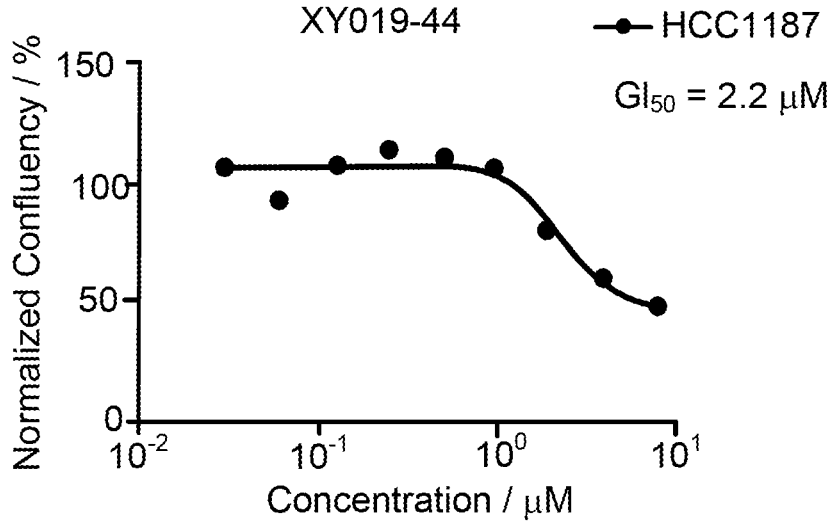

XY019-44
HCC1187
GI_{50} = 2.2 μM
Normalized Confluency / %
150
100
50
0
10^{-2}
10^{-1}
10^{0}
10^{1}
Concentration / μM

FIG. 17

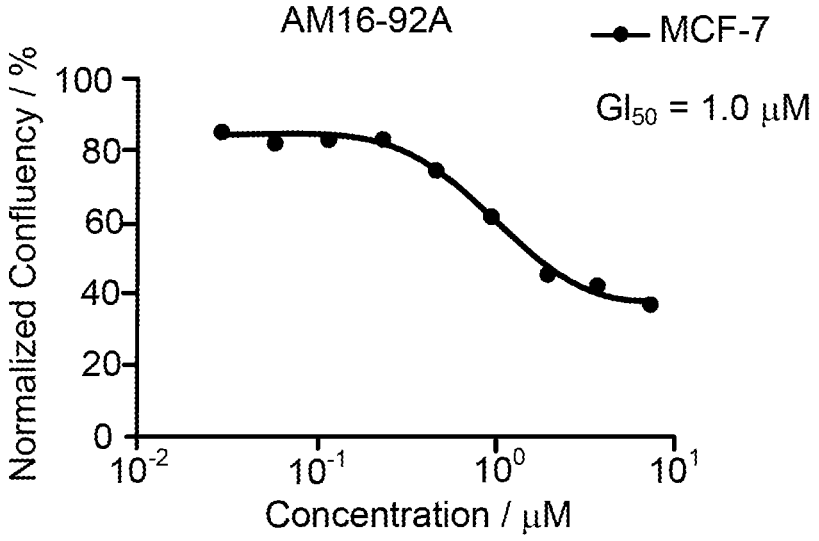

AM16-92A
MCF-7
GI50 = 1.0 μM
Normalized Confluency / %
100
80
60
40
20
0
10-2
10-1
100
101
Concentration / μM

FIG. 18

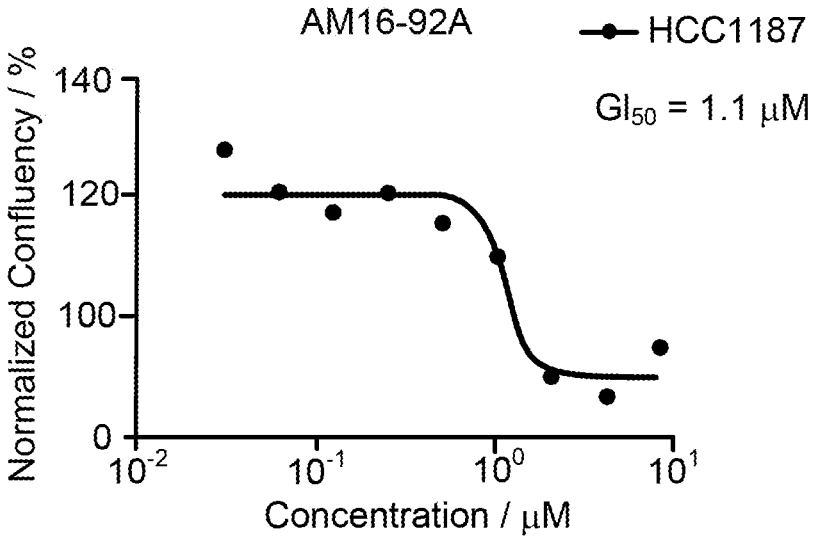

AM16-92A
HCC1187
GI50 = 1.1 μM
Normalized Confluency / %
140
120
100
0
10-2
10-1
100
101
Concentration / μM

FIG. 19

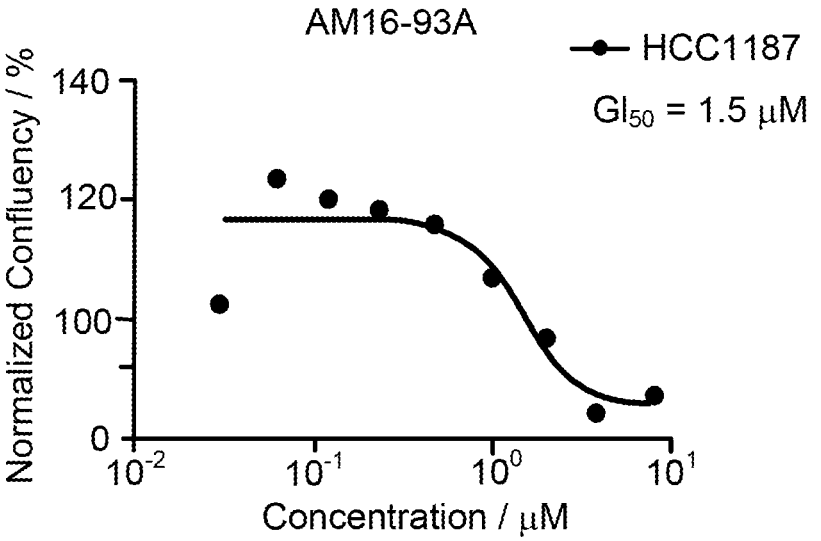

AM16-93A
HCC1187
GI_{50} = 1.5 μM
Normalized Confluency / %
140
120
100
0
10^{-2}
10^{-1}
10^{0}
10^{1}
Concentration / μM

FIG. 20

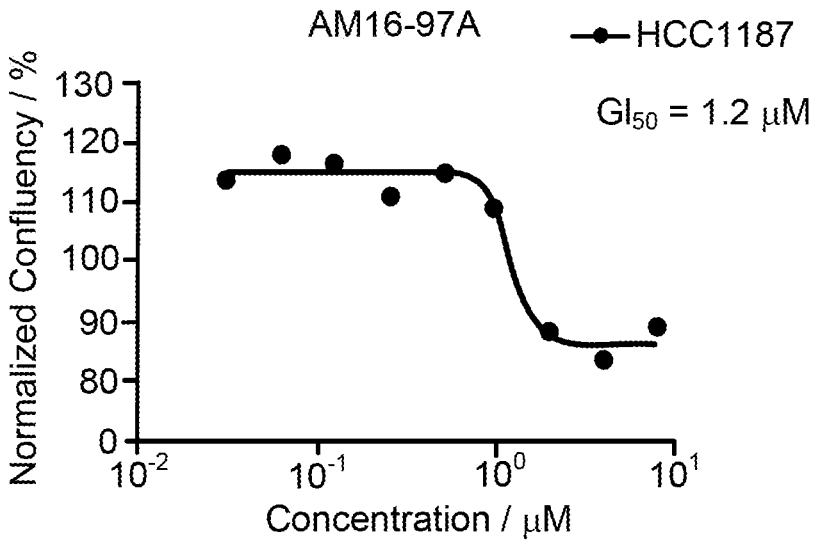

AM16-97A
HCC1187
GI_{50} = 1.2 μM
Normalized Confluency / %
130
120
110
100
90
80
0
10^{-2}
10^{-1}
10^{0}
10^{1}
Concentration / μM

FIG. 21

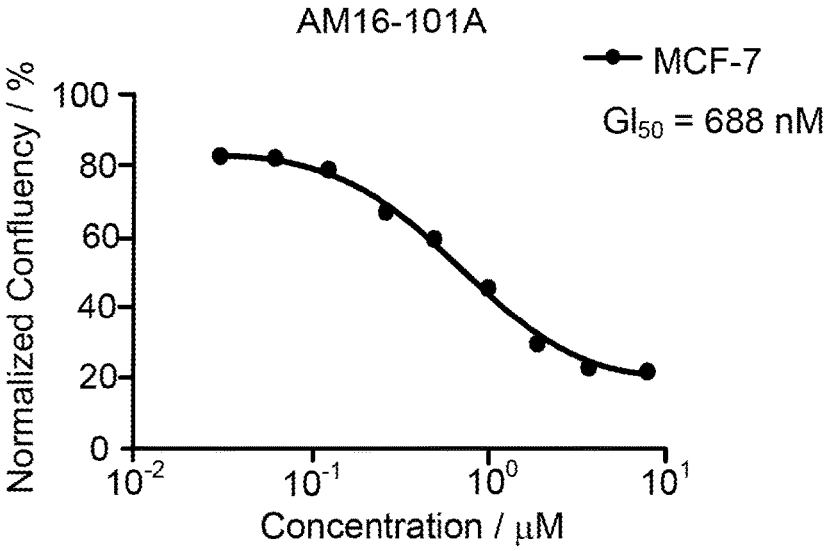

AM16-101A
MCF-7
GI50 = 688 nM
Normalized Confluency / %
100
80
60
40
20
0
10-2
10-1
100
101
Concentration / μM

FIG. 22

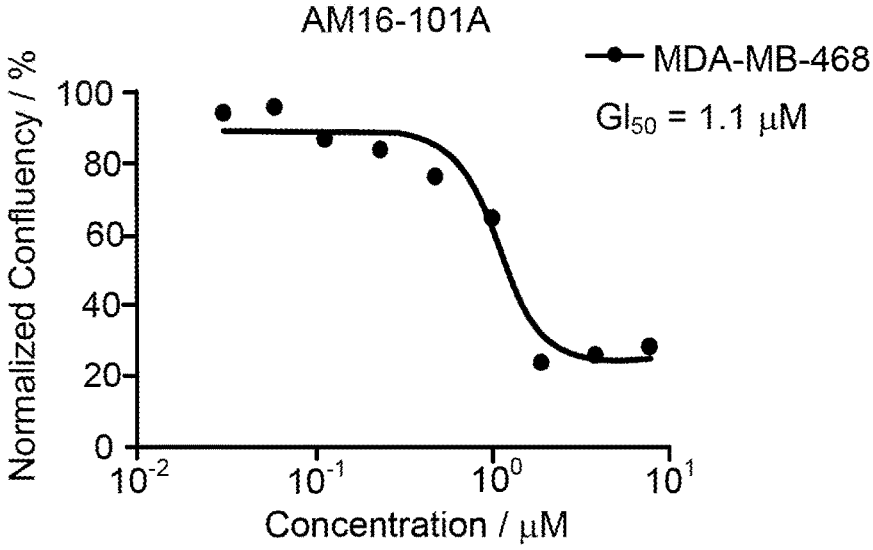

AM16-101A
MDA-MB-468
GI50 = 1.1 μM
Normalized Confluency / %
100
80
60
40
20
0
10-2
10-1
100
101
Concentration / μM

FIG. 23

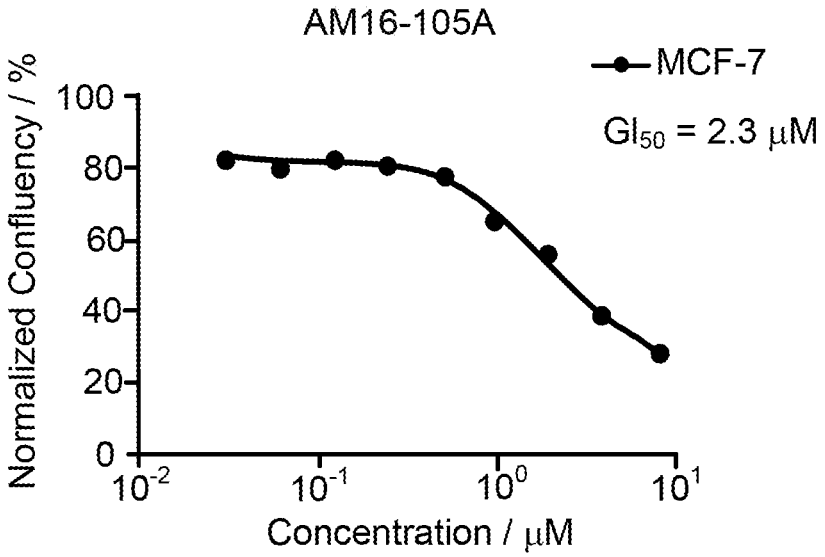

AM16-105A
MCF-7
GI_{50} = 2.3 μM
Normalized Confluency / %
100
80
60
40
20
0
10^{-2}
10^{-1}
10^{0}
10^{1}
Concentration / μM

FIG. 24

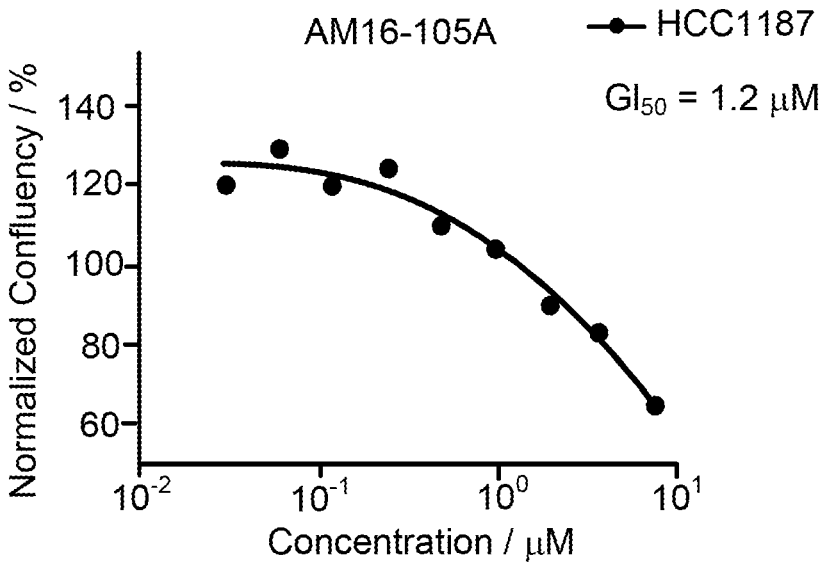

AM16-105A
HCC1187
GI_{50} = 1.2 μM
Normalized Confluency / %
140
120
100
80
60
10^{-2}
10^{-1}
10^{0}
10^{1}
Concentration / μM

FIG. 25

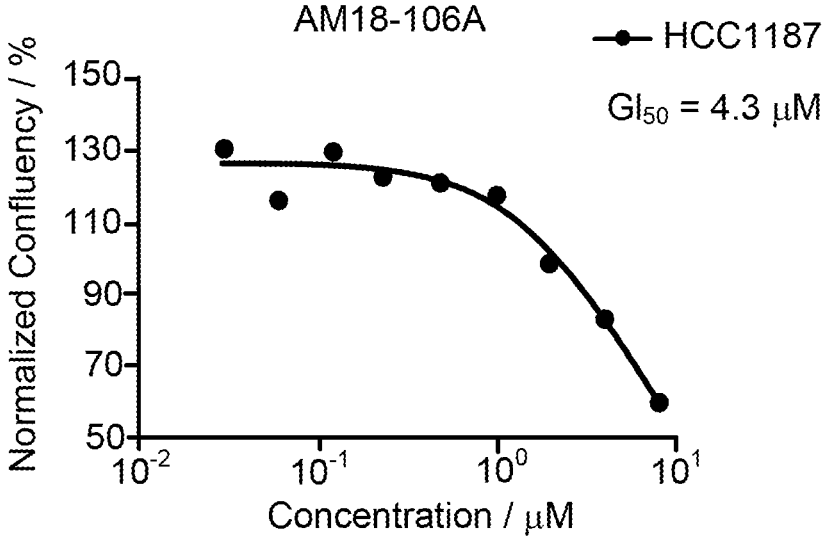

AM18-106A
HCC1187
GI50 = 4.3 μM
Normalized Confluency / %
150
130
110
90
70
50
10-2
10-1
100
101
Concentration / μM

FIG. 26

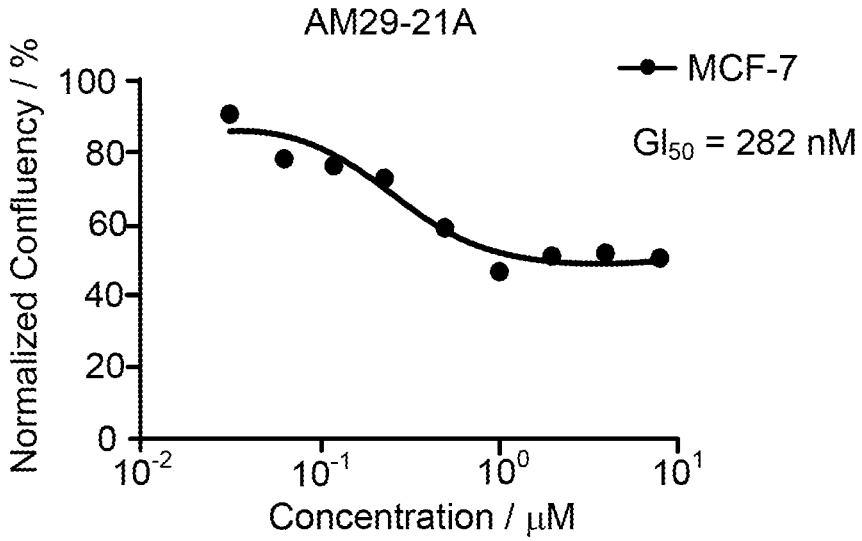

AM29-21A
MCF-7
GI50 = 282 nM
Normalized Confluency / %
100
80
60
40
20
0
10-2
10-1
100
101
Concentration / μM

FIG. 27

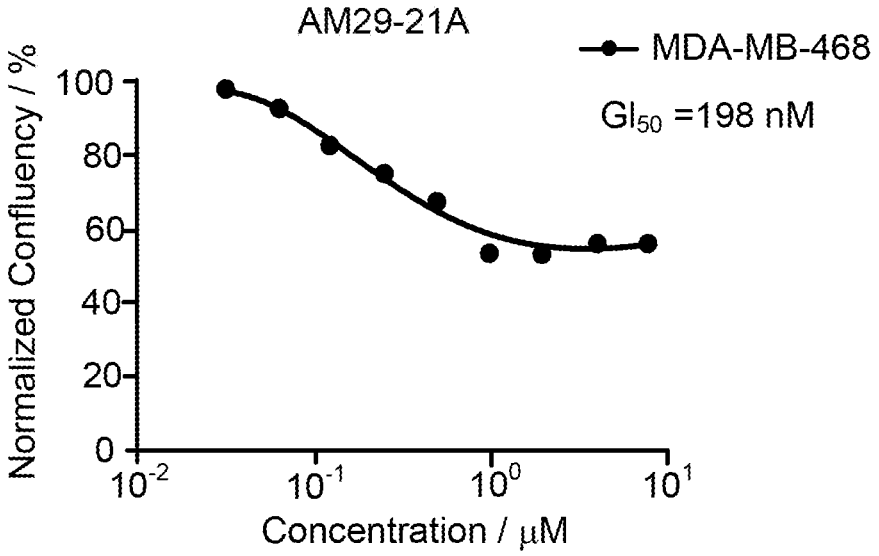

AM29-21A
MDA-MB-468
GI_{50} =198 nM
Normalized Confluency / %
100
80
60
40
20
0
10^{-2}
10^{-1}
10^{0}
10^{1}
Concentration / μM

FIG. 28

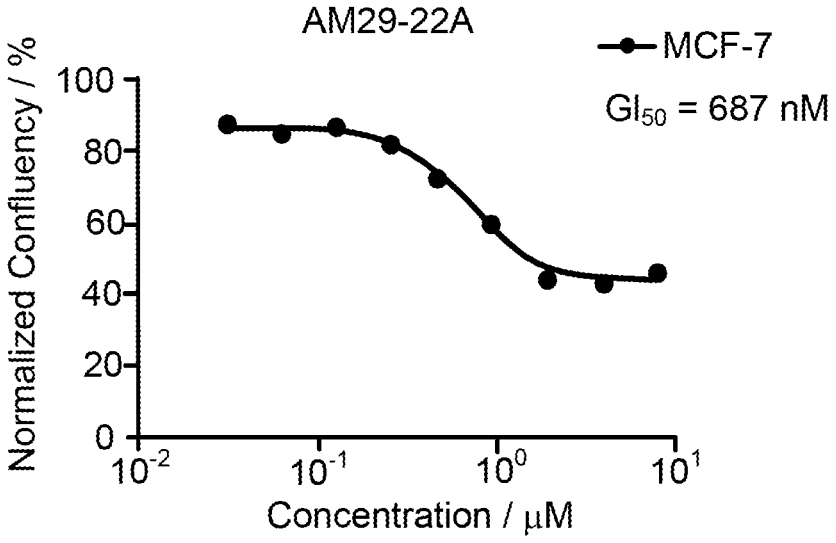

AM29-22A
MCF-7
GI_{50} = 687 nM
Normalized Confluency / %
100
80
60
40
20
0
10^{-2}
10^{-1}
10^{0}
10^{1}
Concentration / μM

FIG. 29

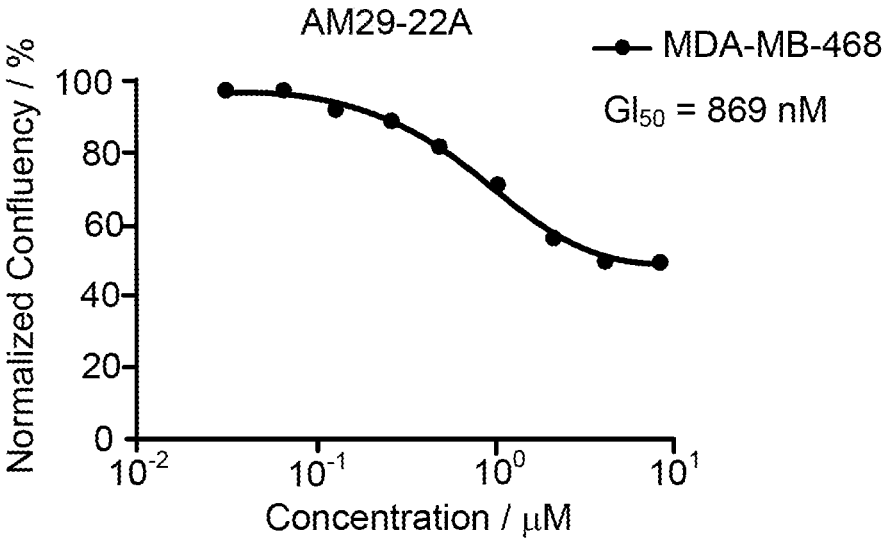

AM29-22A
MDA-MB-468
GI50 = 869 nM
Normalized Confluency / %
100
80
60
40
20
0
10-2
10-1
100
101
Concentration / μM

FIG. 30

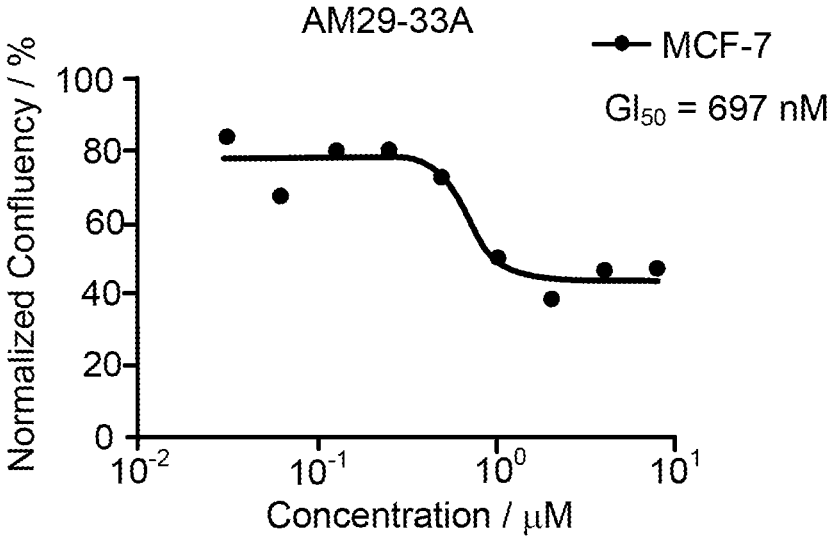

AM29-33A
MCF-7
GI50 = 697 nM
Normalized Confluency / %
100
80
60
40
20
0
10-2
10-1
100
101
Concentration / μM

FIG. 31

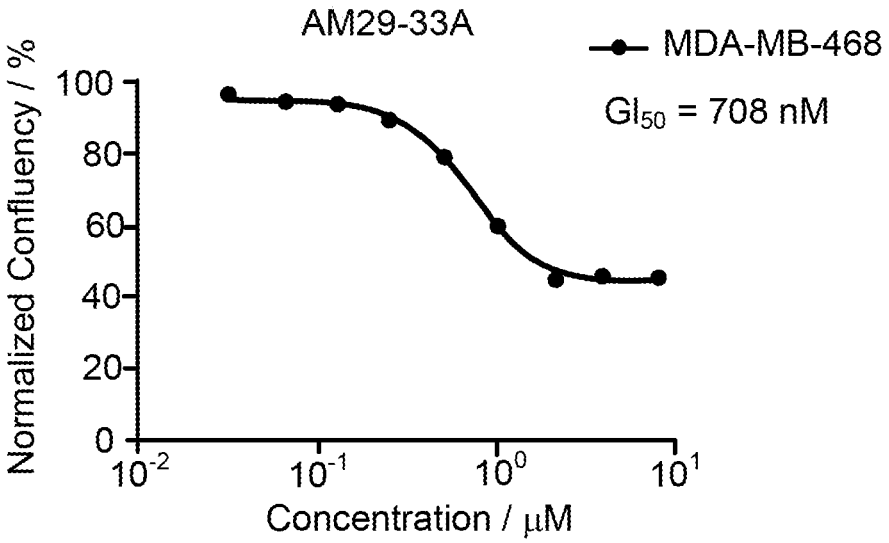

AM29-33A
MDA-MB-468
GI_{50} = 708 nM
Normalized Confluency / %
100
80
60
40
20
0
10^{-2}
10^{-1}
10^{0}
10^{1}
Concentration / μM

FIG. 32

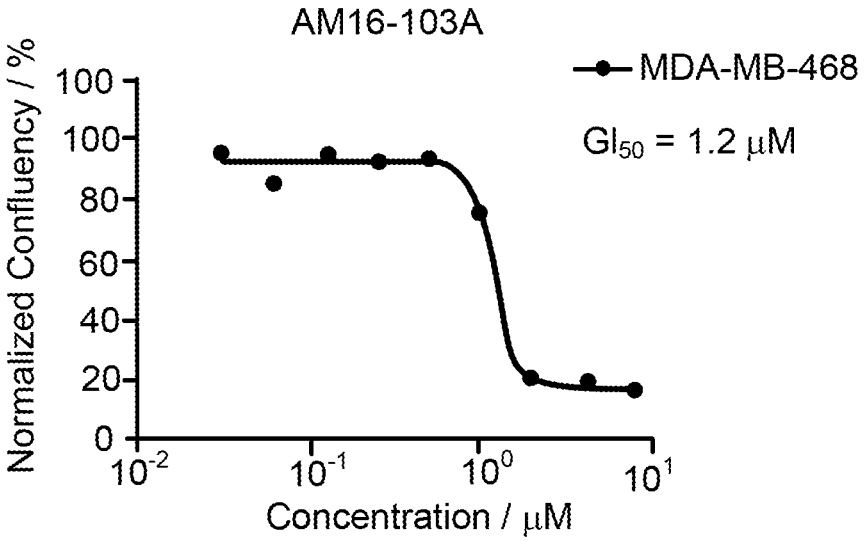

AM16-103A
MDA-MB-468
GI_{50} = 1.2 μM
Normalized Confluency / %
100
100
80
60
40
20
0
10^{-2}
10^{-1}
10^{0}
10^{1}
Concentration / μM

FIG. 33

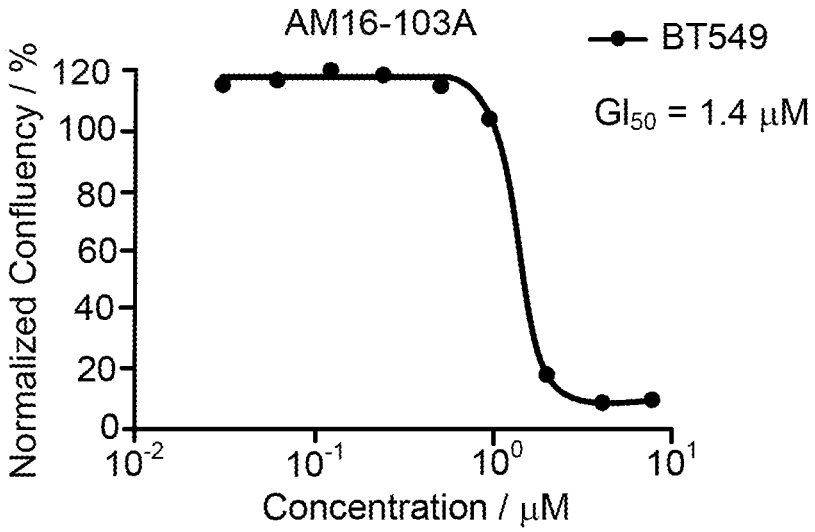

AM16-103A
BT549
GI_{50} = 1.4 μM
Normalized Confluency / %
120
100
80
60
40
20
0
10^{-2}
10^{-1}
10^{0}
10^{1}
Concentration / μM

FIG. 34

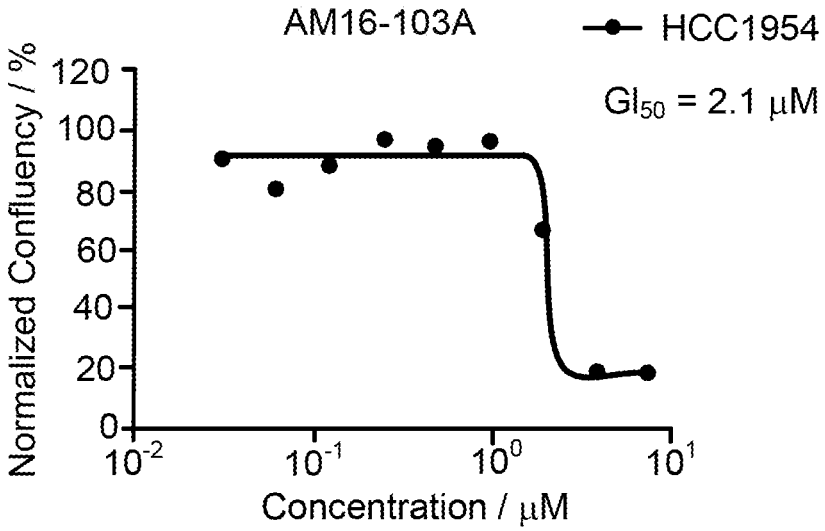

AM16-103A
HCC1954
GI_{50} = 2.1 μM
Normalized Confluency / %
120
100
80
60
40
20
0
10^{-2}
10^{-1}
10^{0}
10^{1}
Concentration / μM

FIG. 35

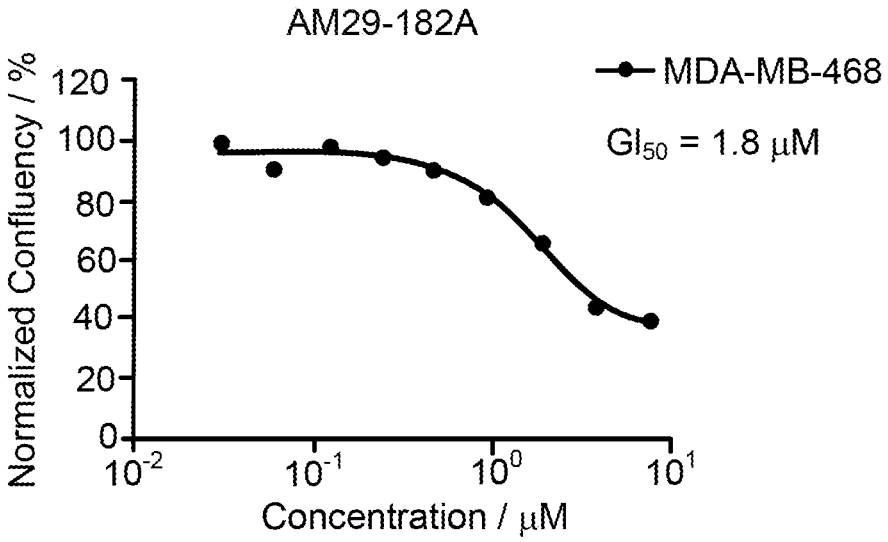

AM29-182A
MDA-MB-468
GI_{50} = 1.8 μM
Normalized Confluency / %
120
100
80
60
40
20
0
10^{-2}
10^{-1}
10^{0}
10^{1}
Concentration / μM

FIG. 36

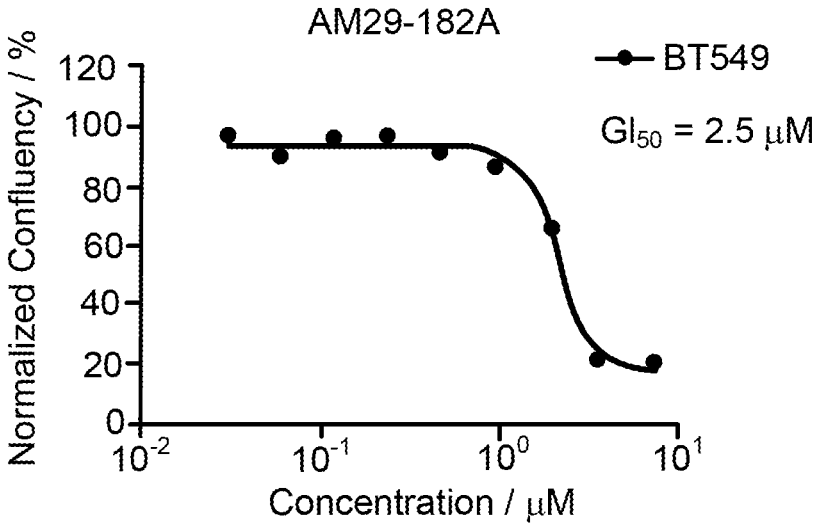

AM29-182A
BT549
GI_{50} = 2.5 μM
Normalized Confluency / %
120
100
80
60
40
20
0
10^{-2}
10^{-1}
10^{0}
10^{1}
Concentration / μM

FIG. 37

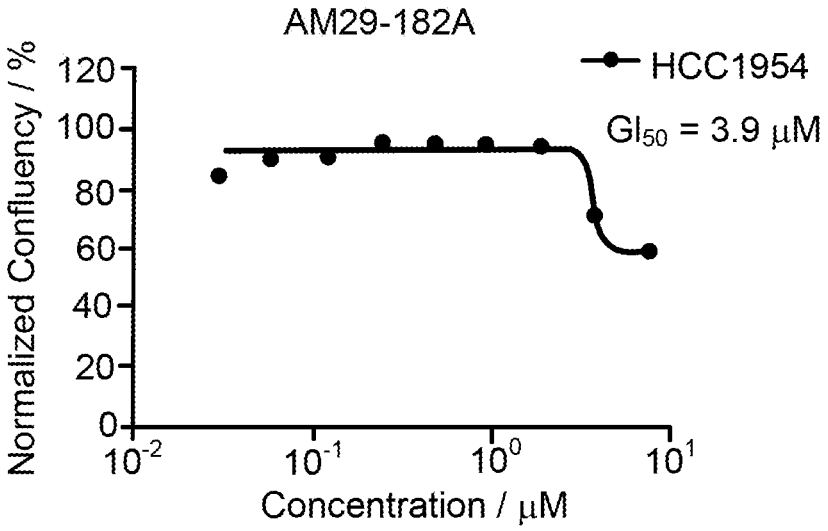

AM29-182A
HCC1954
GI_{50} = 3.9 μM
Normalized Confluency / %
120
100
80
60
40
20
0
10^{-2}
10^{-1}
10^{0}
10^{1}
Concentration / μM

FIG. 38

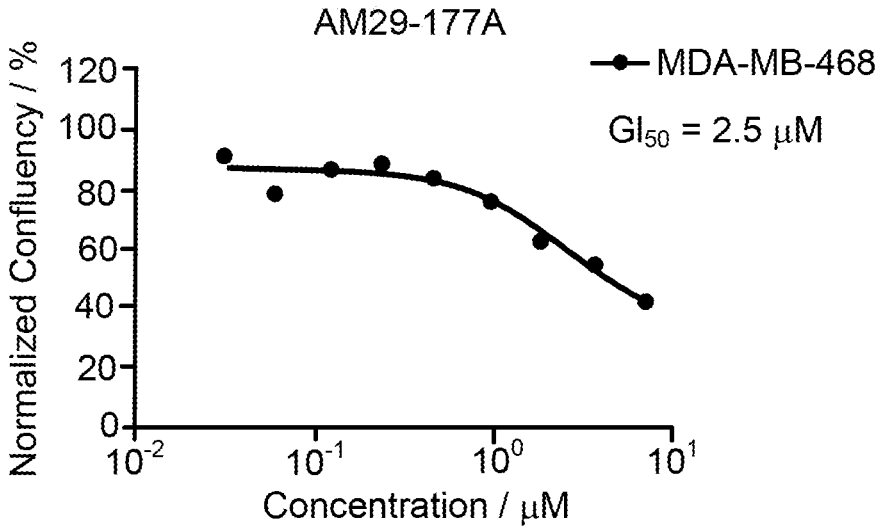

AM29-177A
MDA-MB-468
GI_{50} = 2.5 μM
Normalized Confluency / %
120
100
80
60
40
20
0
10^{-2}
10^{-1}
10^{0}
10^{1}
Concentration / μM

FIG. 39

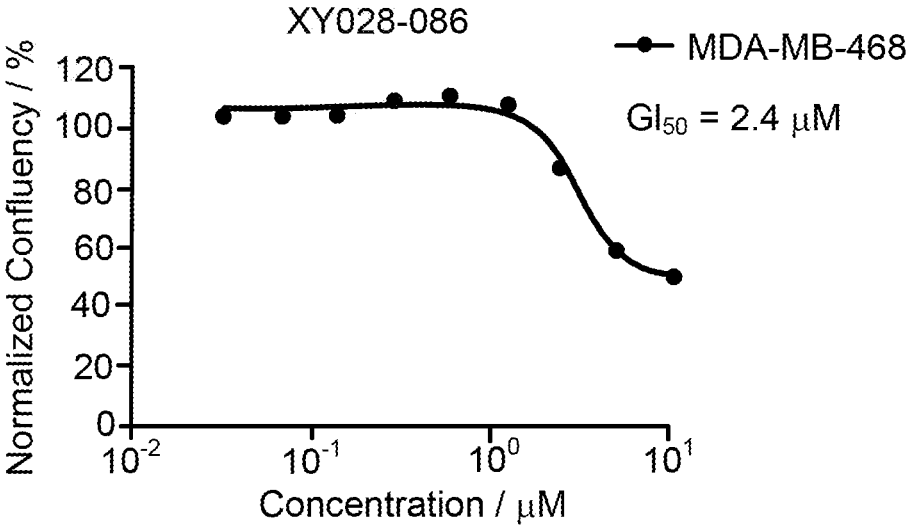

XY028-086
MDA-MB-468
GI50 = 2.4 μM
Normalized Confluency / %
120
100
80
60
40
20
0
10-2
10-1
100
101
Concentration / μM

FIG. 40

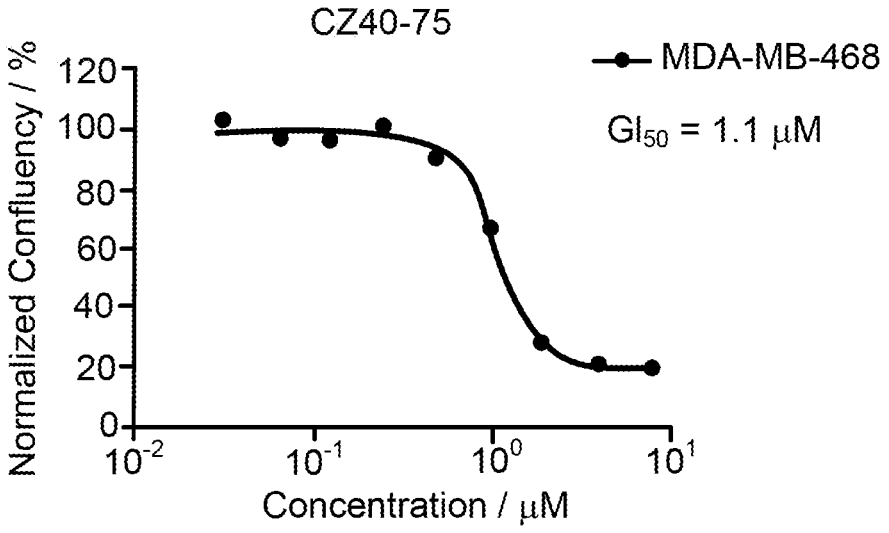

CZ40-75
MDA-MB-468
GI50 = 1.1 μM
Normalized Confluency / %
120
100
80
60
40
20
0
10-2
10-1
100
101
Concentration / μM

FIG. 41

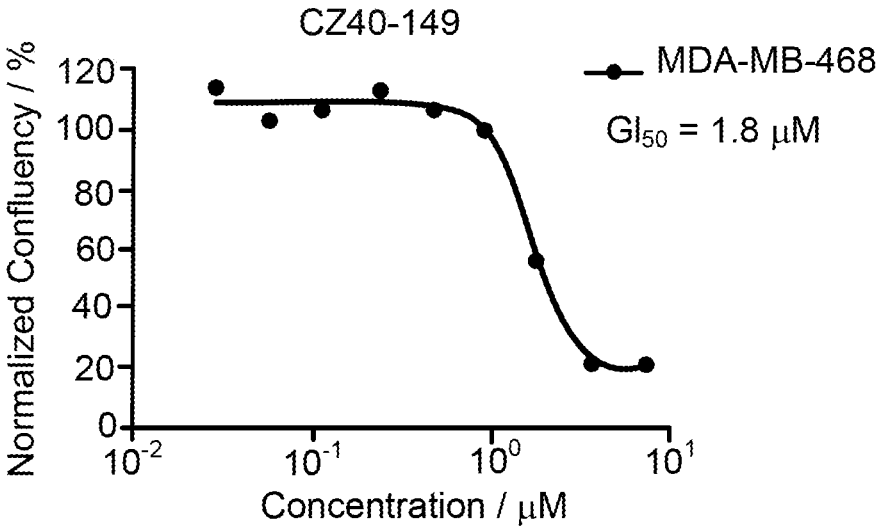

CZ40-149
MDA-MB-468
GI_{50} = 1.8 μM
Normalized Confluency / %
120
100
80
60
40
20
0
10^{-2}
10^{-1}
10^{0}
10^{1}
Concentration / μM

FIG. 42

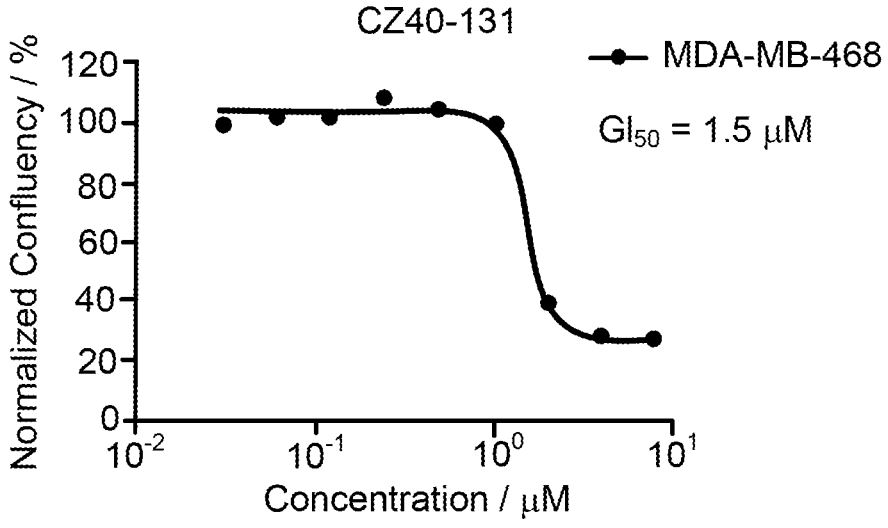

CZ40-131
MDA-MB-468
GI_{50} = 1.5 μM
Normalized Confluency / %
120
100
80
60
40
20
0
10^{-2}
10^{-1}
10^{0}
10^{1}
Concentration / μM

FIG. 43

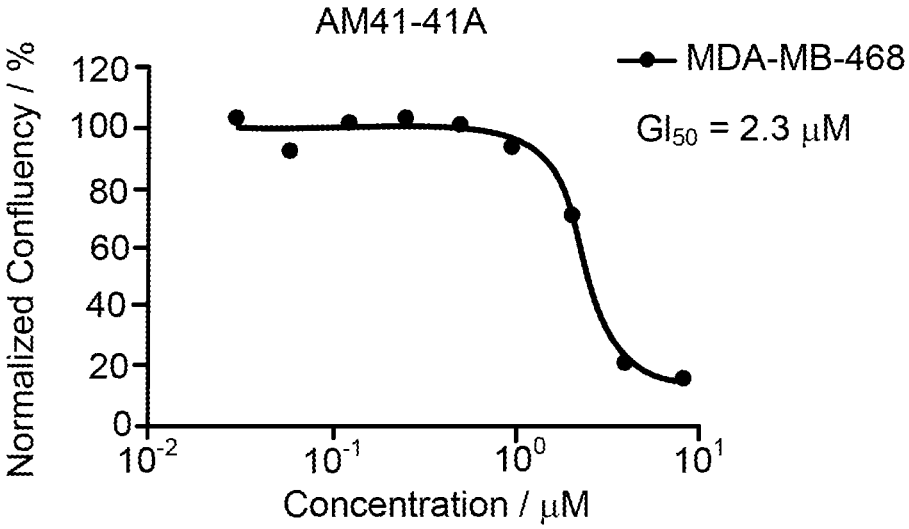

AM41-41A
MDA-MB-468
GI_{50} = 2.3 μM
Normalized Confluency / %
120
100
80
60
40
20
0
10^{-2}
10^{-1}
10^{0}
10^{1}
Concentration / μM

FIG. 44

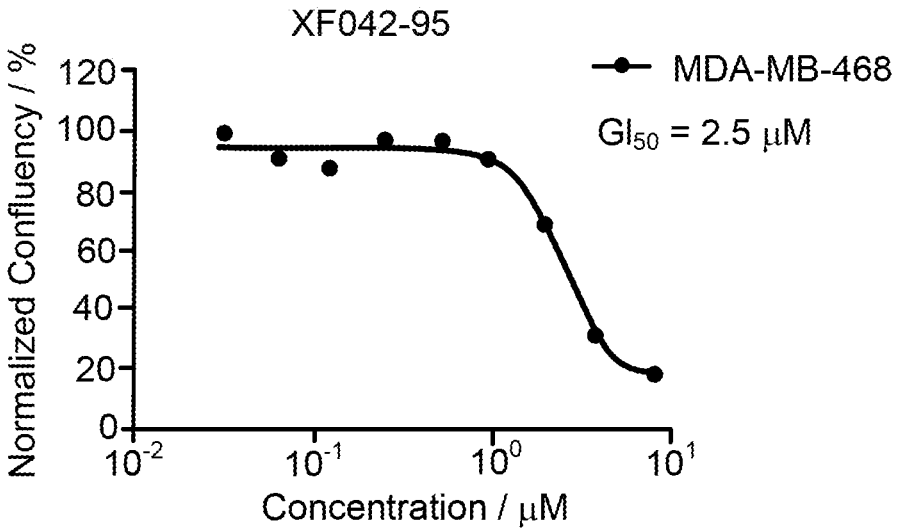

XF042-95
MDA-MB-468
GI_{50} = 2.5 μM
Normalized Confluency / %
120
100
80
60
40
20
0
10^{-2}
10^{-1}
10^{0}
10^{1}
Concentration / μM

FIG. 45

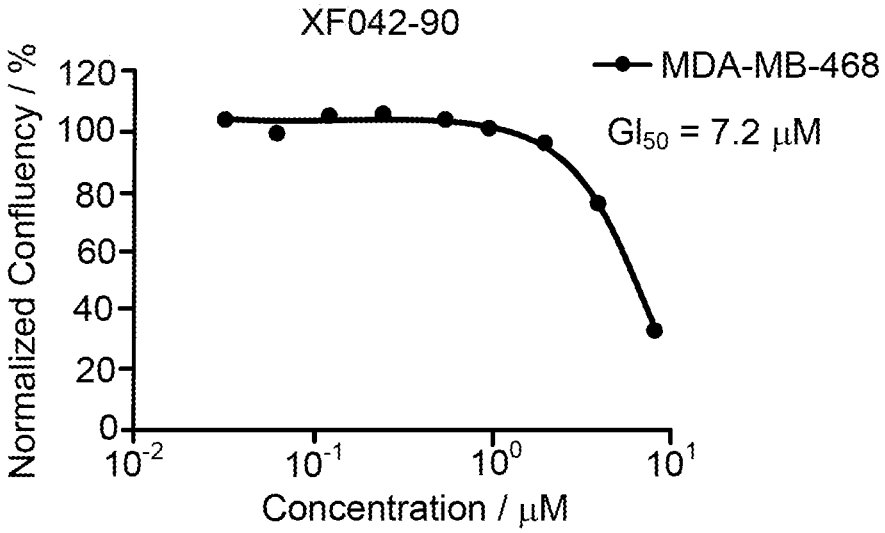

XF042-90
MDA-MB-468
GI_{50} = 7.2 μM
Normalized Confluency / %
120
100
80
60
40
20
0
10^{-2}
10^{-1}
10^{0}
10^{1}
Concentration / μM

FIG. 46

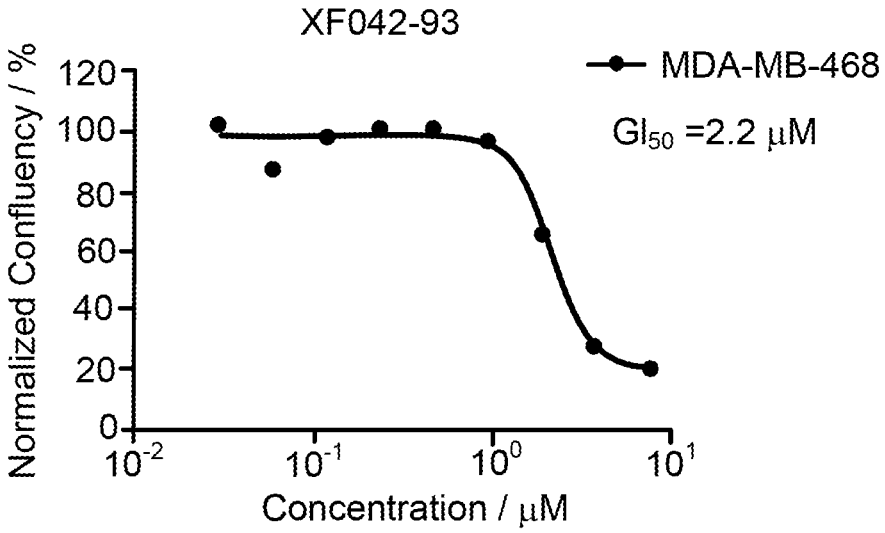

XF042-93
MDA-MB-468
GI_{50} =2.2 μM
Normalized Confluency / %
120
100
80
60
40
20
0
10^{-2}
10^{-1}
10^{0}
10^{1}
Concentration / μM

FIG. 47

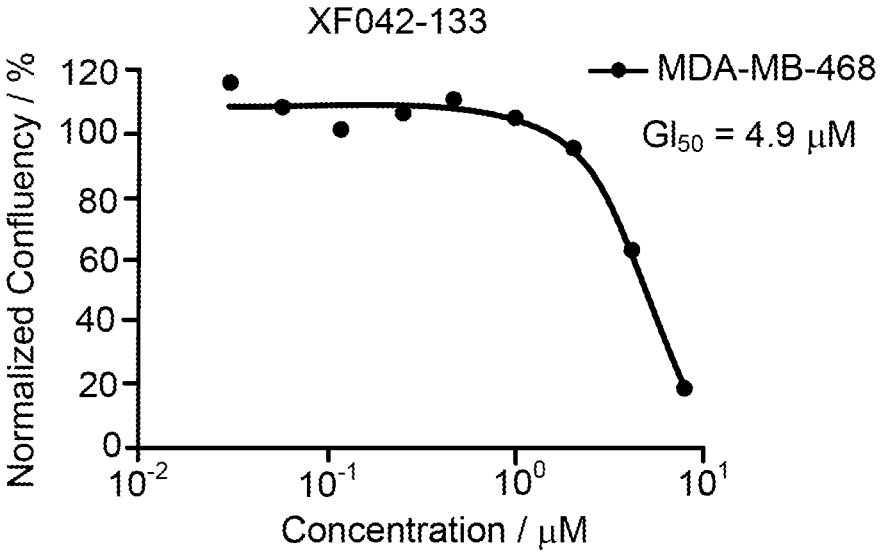

XF042-133
MDA-MB-468
GI_{50} = 4.9 μM
Normalized Confluency / %
120
100
80
60
40
20
0
10^{-2}
10^{-1}
10^{0}
10^{1}
Concentration / μM

FIG. 48

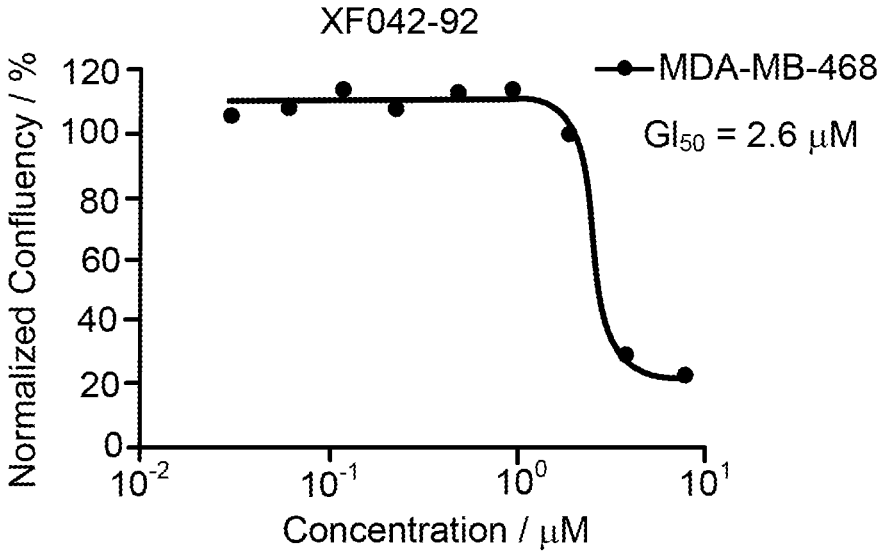

XF042-92
MDA-MB-468
GI_{50} = 2.6 μM
Normalized Confluency / %
120
100
80
60
40
20
0
10^{-2}
10^{-1}
10^{0}
10^{1}
Concentration / μM

FIG. 49

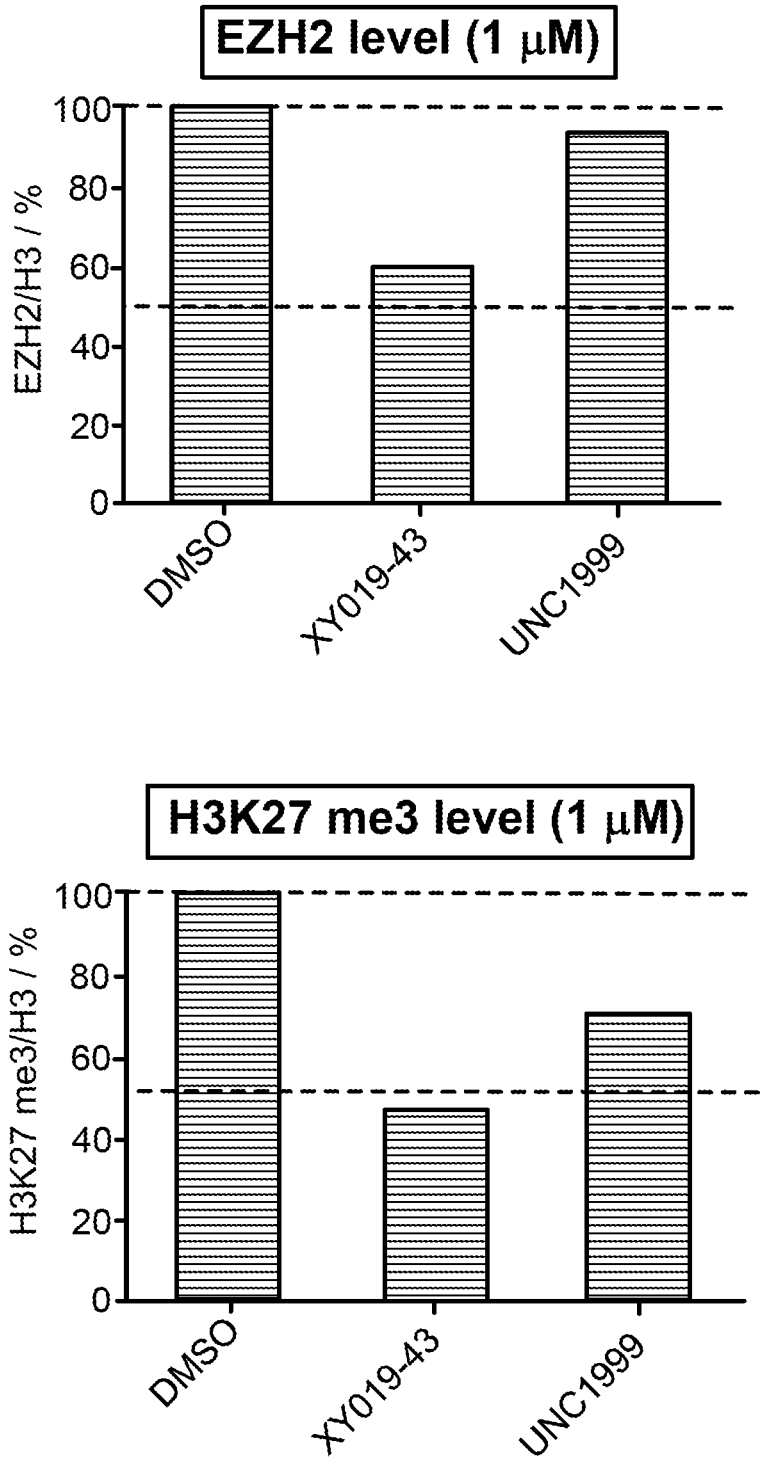
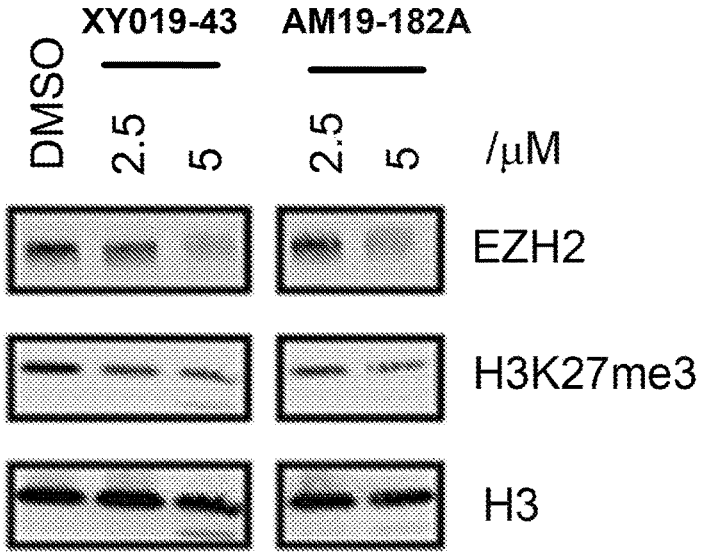
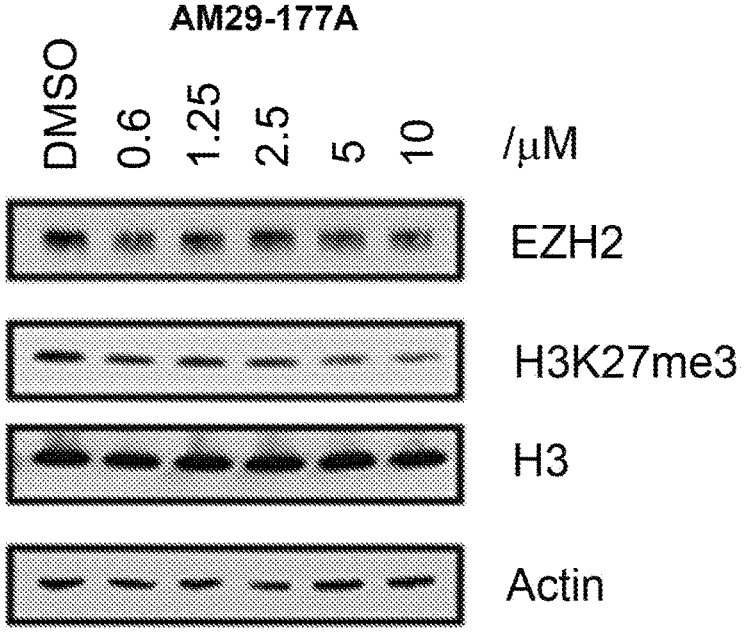

EZH2 level (1 μM)
EZH2/H3 / %
100
80
60
40
20
0
DMSO
XY019-43
UNC1999
H3K27 me3 level (1 μM)
H3K27 me3/H3 / %
100
80
60
40
20
0
DMSO
XY019-43
UNC1999

FIG. 50



MDA-MB-468, 2 days

FIG. 51



MDA-MB-468, 2 days

FIG. 52

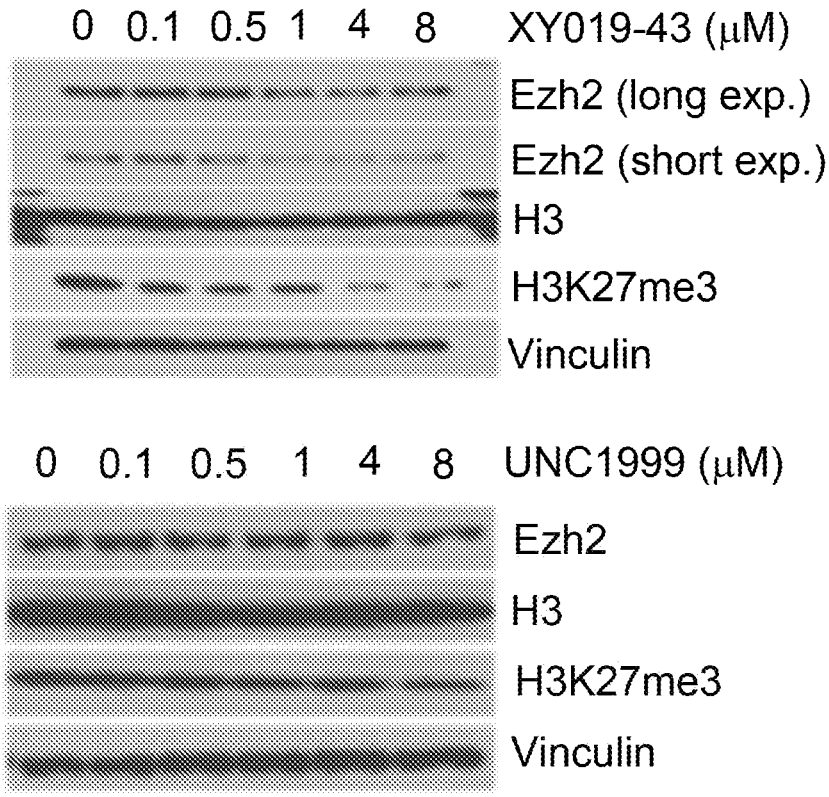

0 0.1 0.5 1 4 8 XY019-43 (μM)
Ezh2 (long exp.)
Ezh2 (short exp.)
H3
H3K27me3
Vinculin
0 0.1 0.5 1 4 8 UNC1999 (μM)
Ezh2
H3
H3K27me3
Vinculin

FIG. 53

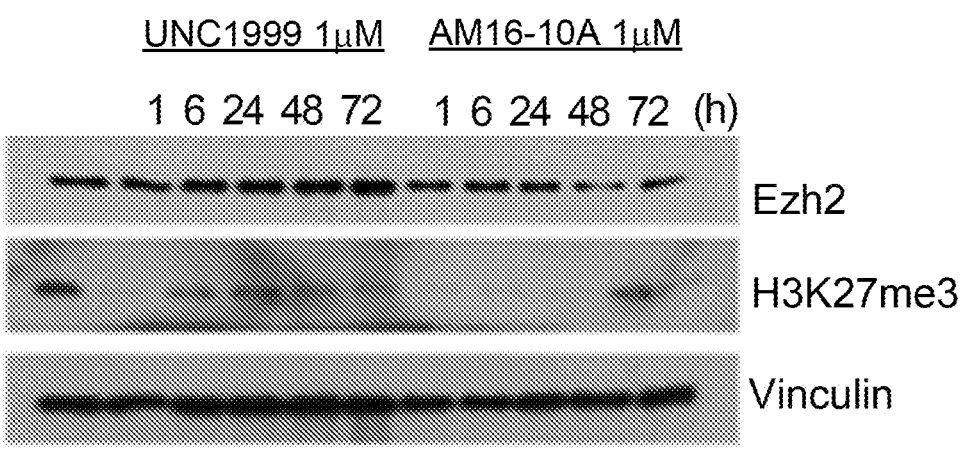

HCC1187
UNC1999 1μM
AM16-10A 1μM
1 6 24 48 72 1 6 24 48 72 (h)
Ezh2
H3K27me3
Vinculin

FIG. 54

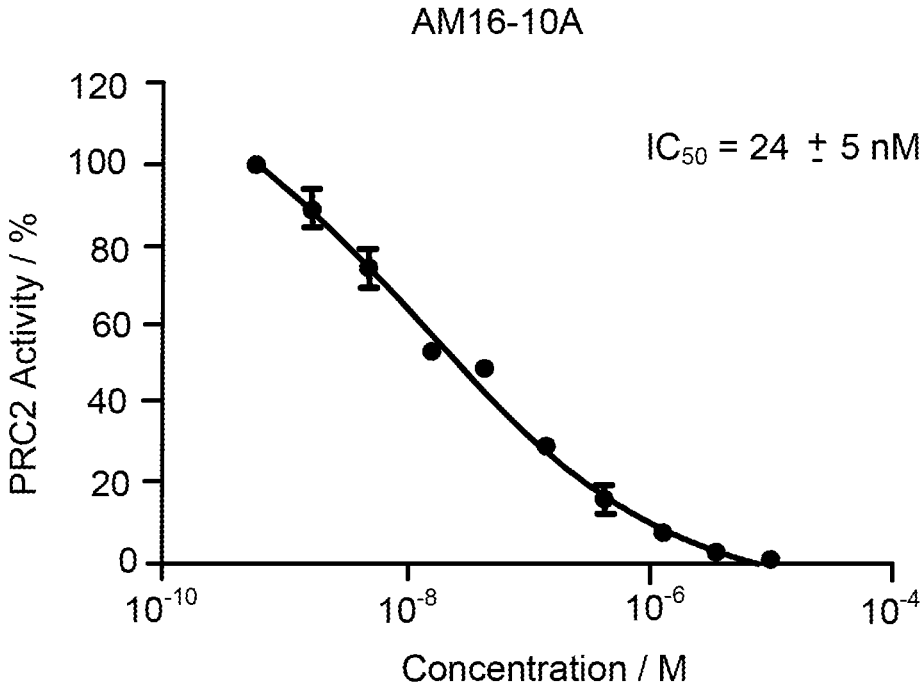

AM16-10A
120
100
80
60
40
20
0
PRC2 Activity / %
IC50 = 24 ± 5 nM
10-10
10-8
10-6
10-4
Concentration / M

FIG. 55

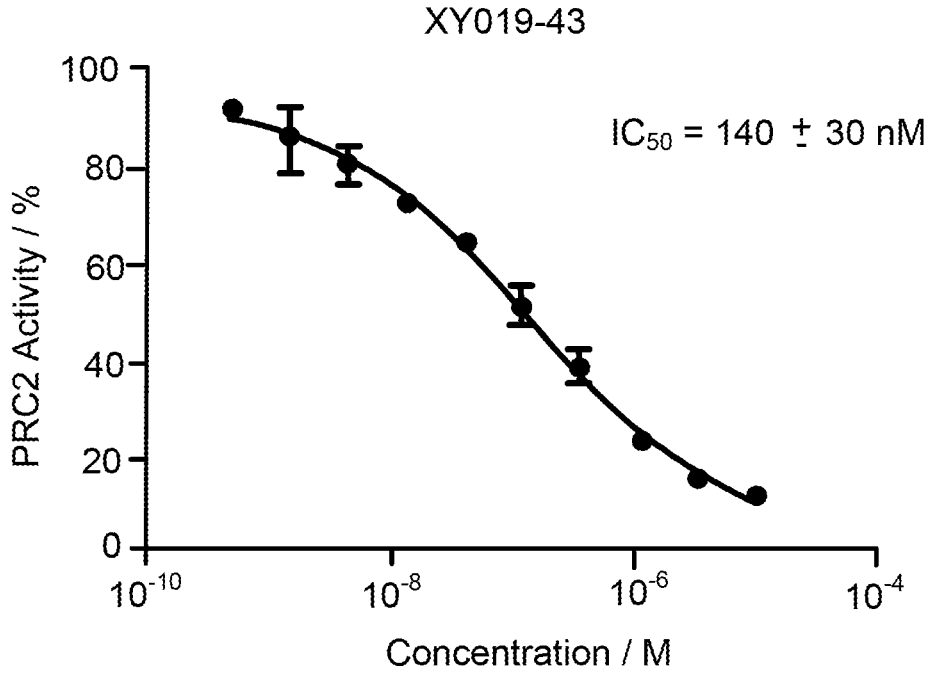

XY019-43
100
80
60
40
20
0
PRC2 Activity / %
IC50 = 140 ± 30 nM
10-10
10-8
10-6
10-4
Concentration / M

FIG. 56

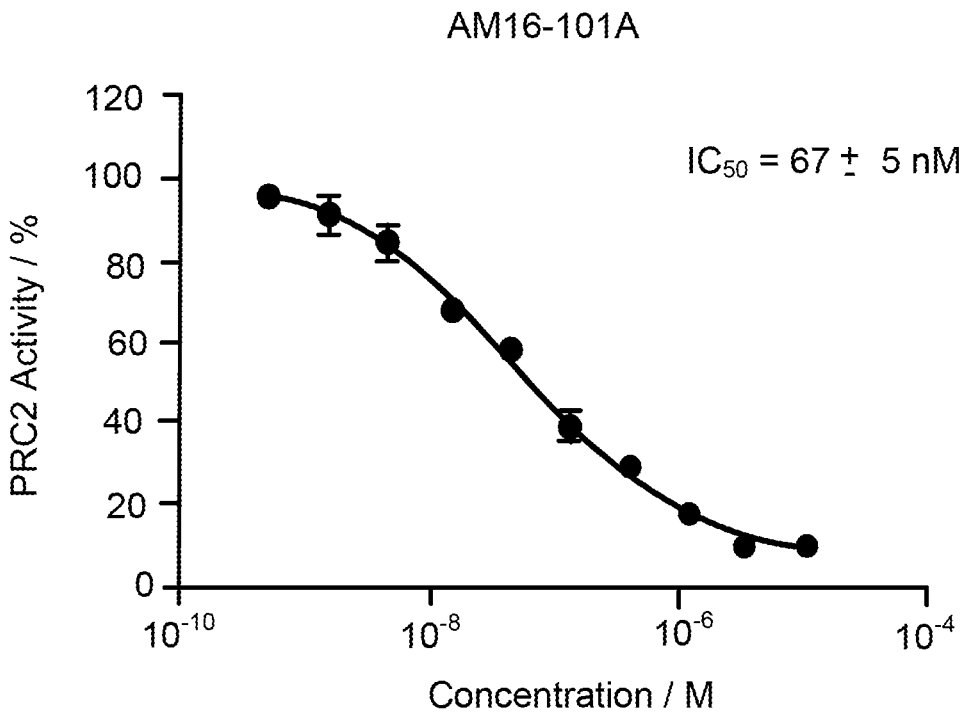

AM16-101A
IC50 = 67 ± 5 nM
PRC2 Activity / %
120
100
80
60
40
20
0
10-10
10-8
10-6
10-4
Concentration / M

FIG. 57

COMPOSITIONS AND METHODS FOR TREATING EZH2-MEDIATED CANCER

TECHNICAL FIELD

[0001] This disclosure relates to compositions and methods for administering one or more bivalent compounds which selectively degrade/disrupt enhancer of zeste homologue 2 (EZH2) to a subject for the treatment of EZH2-mediated cancer, and to methods for designing such degraders/disruptors.

BACKGROUND OF THE INVENTION

[0002] EZH2 (enhancer of zeste homolog 2) is the main catalytic subunit of the polycomb repressive complex 2 (PRC2) that catalyzes methylation of histone H3 lysine 27 (H3K27) (Cao et al., 2002; Czermin et al., 2002; Kuzmichev et al., 2002; Muller et al., 2002). The trimethylation of H3K27 (H3K27me3) is a transcriptionally repressive epigenetic mark that regulates gene expression, differentiation, and development. Dysregulation of EZH2, other PRC2 components (e.g., EED and SUZ12), and/or H3K27 trimethylation have been associated with a number of cancers. For example, EZH2 is overexpressed in a broad spectrum of cancers, including prostate cancer, breast cancer, myeloma, and lymphoma. High EZH2 expression correlates with poor prognosis (Bachmann et al., 2006; Bodor et al., 2011; Bracken et al., 2003; Kim and Roberts, 2016; Kleer et al., 2003; Morin et al., 2010; Sauvageau and Sauvageau, 2010; Varambally et al., 2002). Hyper-trimethylation of H3K27 catalyzed by PRC2 drives tumorigenesis and progression of cancers including diffused large B cell lymphoma (DLBCL) and malignant rhabdoid tumor (MRT) (Majer et al., 2012; McCabe et al., 2012a; Sneeringer et al., 2010). Thus, pharmacological inhibition of EZH2 has been pursued as a targeted therapy for treating these cancers. In fact, EZH2 inhibitors, which effectively inhibit the methyltransferase activity of EZH2, display robust antiproliferative activity in DLBCL and MRT cellular and animal models (Kaniskan et al., 2017; Wang et al., 2015; Xu et al., 2015). A number of EZH2 inhibitors including UNC1999, an orally bioavailable inhibitor developed by the inventors of the present application, have been reported (Bradley et al., 2014; Brooun et al., 2016; Campbell et al., 2015; Gao et al., 2016; Garapaty-Rao et al., 2013; Gehling et al., 2015; Kaniskan et al., 2017; Knutson et al., 2013; Knutson et al., 2012; Konze et al., 2013; Kung et al., 2016; McCabe et al., 2012b; Qi et al., 2012; Song et al., 2016; Verma et al., 2012; Yang et al., 2016). Among them, EPZ-6438, GSK126, CPI-1205, and PF-06821497 have entered Phase I/II clinical trials for the treatment of several subtypes of lymphoma and MRT.

[0003] Breast cancer (BC) has the highest incidence rate (43.3/100,000) and is one of the leading causes of cancer death among women (14.9%) in North America (Stewart and Wild, 2014). Triple-negative breast cancer (TNBC), a subtype of BC that lacks estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), represents ~12-20% of all BCs. TNBC has poor prognosis, high recurrence, and a low survival rate (Lin et al., 2012). Currently, there are no effective therapies for treating a substantial portion of TNBC patients, highlighting an unmet medical need (Gluz et al., 2009).

[0004] Overexpression of EZH2 has been identified as a major driver for breast cancer development and progression (Bachmann et al., 2006; Bracken et al., 2003; Chang et al., 2011; Holm et al., 2012; Fujii et al., 2011; Gonzalez et al., 2014; Kleer et al., 2003; Mahara et al., 2016). It has been shown that EZH2 downregulates the tumor and metastasis suppressor RKIP (Raf-1 kinase inhibitor protein) (Ren et al., 2012), tumor suppressor KLF2 (Kruppel-like factor) (Taniguchi et al., 2012), forkhead box transcription factor FOXC1 (Du et al., 2012), and tumor suppressor RUNX3 (Runt-related transcription factor 3) (Fujii et al., 2008). Knockdown of EZH2 via RNA interference blocks proliferation of breast cancer cells (Fujii et al., 2008; Gonzalez et al., 2008). However, current EZH2 inhibitors, which do not affect EZH2 protein levels, are ineffective at inhibiting growth of breast cancer cells with EZH2 overexpression even though they effectively inhibit the enzymatic activity of EZH2. Therefore, overexpression of EZH2, but not the catalytic activity of EZH2/PRC2, is critical for breast cancer progression.

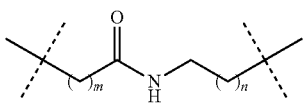
SUMMARY

[0005] The present disclosure relates generally to bivalent compounds which selectively degrade/disrupt EZH2 ("EZH2 degraders/disruptors"), and to methods for the treatment of EZH2-mediated cancers, which include, but are not limited to, cancers that overexpress EZH2 relative to wild-type tissues of the same species and tissue types, with the EZH2 degraders/disruptors. Without wishing to be bound by theory, because the EZH2 degraders/disruptors disclosed herein have dual functions (enzyme inhibition plus protein degradation/disruption), the bivalent compounds disclosed/claimed here can be significantly more effective therapeutic agents than current EZH2 inhibitors, which inhibit the enzymatic activity of EZH2 but do not affect EZH2 protein levels. The present disclosure further provides methods for identifying EZH2 degraders/disruptors as described herein.

[0006] More specifically, the document provides a bivalent compound including an EZH2 ligand conjugated to a degradation/disruption tag. The EZH2 ligand can be an EZH2 inhibitor. The EZH2 ligand can, for example, include UNC1999, EPZ005687, EPZ-6438, GSK126, EI1, CPI-1205, GSK343, CPI-360, EPZ011989, N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-isopropyl-6-(6-(4-isopropylpiperazin-1-yl)pyridin-3-yl)-1H-indazole-4-carboxamide ("compound 24") (see, e.g., Yang et al., 2016), 3-chloro-4-(2-cyano-3-(pyridazin-4-yl)phenoxy)-N-(2,2,6,6-tetramethylpiperidin-4-yl)benzamide ("compound 3") (see, e.g., Garapaty-Rao et al., 2013), 5,8-dichloro-2-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-7-(3,5-dimethylisoxazol-4-yl)-3,4-dihydroisoquinolin-1(2H)-one ("compound 31") (see, e.g., Kung et al., 2016), ZLD1039, PF-06821497, and JQEZ5, and analogs thereof. The degradation/disruption tag can bind to a ubiquitin ligase (e.g., an E3 ligase such as a cereblon E3 ligase or a VHL E3 ligase) and/or mimic EZH2 protein misfolding. The degradation/disruption tag can include a bulky and/or hydrophobic group. The degradation/disruption tag can, for example, include adamantane, 1-((4,4,5,5,5-pentafluoropentyl)sulfinyl)nonane, pomalidomide, thalidomide, lenalidomide, VHL-1, and analogs thereof.

[0007] In any of the above-described bivalent compounds, an EZH2 ligand can be conjugated to a degradation/disruption tag through a linker. The linker can, for example, include an acyclic or cyclic saturated or unsaturated carbon, ethylene glycol, amide, amino, ether, or carbonyl containing group. The linker can, for example, include one or more of Formulas I-XIV:

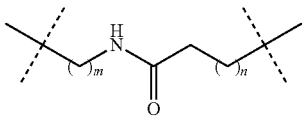
Formula I



m = 0-15
n = 0-15

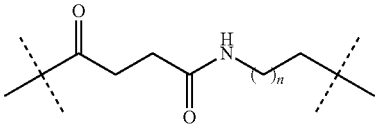
-continued

Formula II



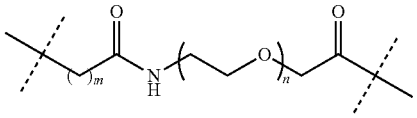
m = 0-15
n = 0-15

Formula III



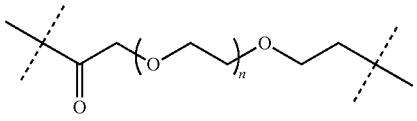
n = 0-15

Formula IV



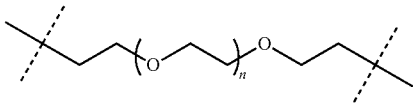
m = 0-15
n = 0-15

Formula V



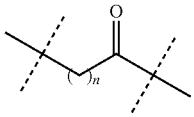
n = 0-15

Formula VI



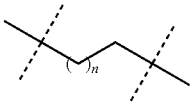
n = 0-15

Formula VII



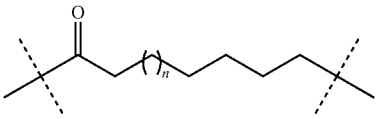
n = 0-15

Formula VIII



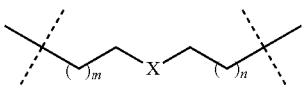
n = 0-15

Formula IX



n = 0-15

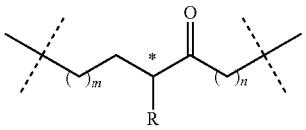
Formula X



X = O, NR
R = H, C_{1-6} alkyl
m = 0-15
n = 0-15

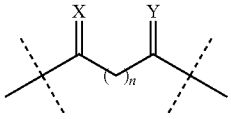
-continued

Formula XI



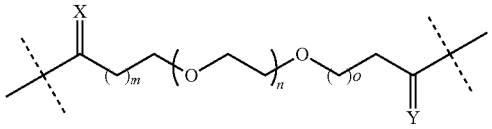
R = H, C_{1-6} alkyl
m = 0-15
n = 0-15
* R, S and racemic

Formula XII



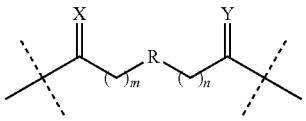
X = O or H_2
Y = O or H_2
n = 0-15

Formula XIII



X = O or H_2
Y = O or H_2
m = 0-15
n = 0-6
o = 0-15

Formula XIV

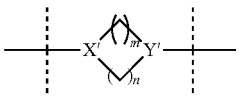


X = O or H_2
Y = O or H_2
m = 0-15
n = 0-15

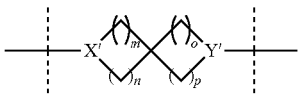
R is independently —CH_2—; —CF_2—; —CH(C_{1-3}) alkyl)—; —C(C_{1-3}) alkyl)(C_{1-3} alkyl)—; —CH═CH—; —C(C_{1-3}) alkyl)═C(C_{1-3})alkyl)—; —C≡C—; —O—; —NH—; —N(C_{1-3} alkyl)—; —C(O)NH—; —C(O) N(C_{1-3} alkyl)—;

3-13 membered rings, fused rings, bridged rings, or spiro rings with or without heteroatoms (—NH—, —N(C_{1-3} alkyl)—, O).

A few examples of R group:

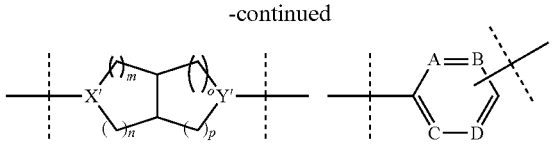


X′ = N or CH
Y′ = N or CH
m = 0-5
n = 0-5



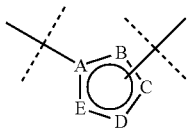
X′ = N or CH
Y′ = N or CH
m = 0-5
n = 0-5
0 = 0-5
p = 0-5

-continued



X′ = N or CH
Y′ = N or CH
m = 0-5
n = 0-5
0 = 0-5
p = 0-5

A = CH, C(C_{1-3} alkyl), or N
B = CH, C(C_{1-3} alkyl), or N
C = CH, C(C_{1-3} alkyl), or N
D = CH, C(C_{1-3} alkyl), or N



A = C, CH, C(C_{1-3} alkyl), N, NH, N(C_{1-3} alkyl), O, S
B = C, CH, C(C_{1-3} alkyl), N, NH, N(C_{1-3} alkyl), O, S
C = C, CH, C(C_{1-3} alkyl), N, NH, N(C_{1-3} alkyl), O, S
D = C, CH, C(C_{1-3} alkyl), N,NH, N(C_{1-3} alkyl), O, S

[0008] Any of the above-described bivalent compounds can include, for example, AM16-10A, AM16-11A, AM16-37A, AM16-38A, XY019-43, XY019-44, XY019-079, XY019-080, AM16-91A, AM16-92A, AM16-93A, AM16-97A, AM16-100A, AM16-101A, AM16-102A, AM16-105A, AM16-106A, XY012-120, AM29-21A, AM29-22A, AM29-32A, AM29-33A, AM16-103A, AM29-182A, AM29-55A, AM29-151A, AM29-152A, AM29-137A, AM29-153A, AM29-138A, AM29-154A, AM29-139A, AM29-155A, AM29-170A, AM29-156A, AM29-171A, AM29-157A, AM29-172A, AM29-173A, AM16-79A, AM29-177A, AM29-141A, AM29-178A, AM29-142A, AM29-179A, AM29-143A, AM29-180A, AM29-144A, AM29-145A, AM29-181A, AM41-16A, AM41-17A, AM41-18A, XY012-157, XF034-164A, XF034-165A, XF034-166A, XF034-167A, XF034-168A, XY019-041, XF034-169A, XF034-170A, XF034-171A, CZ40-10, CZ40-09, CZ40-11, XY019-077, XY019-083, XY019-084, XF034-172A, XF034-173A, XF034-174A, XF034-175A, XF034-176A, XF034-177A, YS36-48, YS36-49, YS36-50, YS36-51, YS36-52, YS36-53, YS36-54, YS36-55, YS36-56, YS36-57, YS36-58, YS36-59, XY028-086, CZ40-72, CZ40-73, CZ40-75, CZ40-149, CZ40-74, CZ40-131, AM41-36A, AM41-37A, AM41-39A, AM41-41A, AM41-38A, AM41-40A, XF042-84, XF042-85, XF042-95, XF042-132, XF042-86, XF042-94, XF042-89, XF042-90, XF042-93, XF042-133, XF042-91, and XF042-92.

[0009] Another aspect of the document is a bivalent compound, which can include, for example, AM16-10A, AM16-11A, AM16-37A, AM16-38A, XY019-43, XY019-44, XY019-079, XY019-080, AM16-91A, AM16-92A, AM16-93A, AM16-97A, AM16-100A, AM16-101A, AM16-102A, AM16-105A, AM16-106A, XY012-120, AM29-21A, AM29-22A, AM29-32A, AM29-33A, AM16-103A, AM29-182A, AM29-55A, AM29-151A, AM29-152A, AM29-137A, AM29-153A, AM29-138A, AM29-154A, AM29-139A, AM29-155A, AM29-170A, AM29-156A, AM29-171A, AM29-157A, AM29-172A, AM29-173A, AM16-79A, AM29-177A, AM29-141A, AM29-178A, AM29-142A, AM29-179A, AM29-143A, AM29-180A, AM29-144A, AM29-145A, AM29-181A, AM41-16A, AM41-17A, AM41-18A, XY012-157, XF034-164A, XF034-165A, XF034-166A, XF034-167A, XF034-168A, XY019-041, XF034-169A, XF034-170A, XF034-171A, CZ40-10, CZ40-09, CZ40-11, XY019-077, XY019-083, XY019-084, XF034-172A, XF034-173A, XF034-174A, XF034-175A, XF034-176A, XF034-177A, YS36-48, YS36-49, YS36-50, YS36-51, YS36-52, YS36-53, YS36-54, YS36-55, YS36-56, YS36-57, YS36-58, YS36-59, XY028-086, CZ40-72, CZ40-73, CZ40-75, CZ40-149, CZ40-74, CZ40-131, AM41-36A, AM41-37A, AM41-39A, AM41-41A, AM41-38A, AM41-40A, XF042-84, XF042-85, XF042-95, XF042-132, XF042-86, XF042-94, XF042-89, XF042-90, XF042-93, XF042-133, XF042-91, and XF042-92.

[0010] Also provided by the document is a method of treating an EZH2-mediated cancer, which includes administering to a subject in a subject in need thereof with an EZH2-mediated cancer bivalent compound including an EZH2 ligand conjugated to a degradation/disruption tag. The EZH2-mediated cancer can overexpress EZH2 relative to a wild-type tissue of the same species and tissue type. The EZH2-mediated cancer can express hyper-trimethylated H3K27. The bivalent compound can include, for example, AM16-10A, AM16-11A, AM16-37A, AM16-38A, XY019-43, XY019-44, XY019-079, XY019-080, AM16-91A, AM16-92A, AM16-93A, AM16-97A, AM16-100A, AM16-101A, AM16-102A, AM16-105A, AM16-106A, XY012-120, AM29-21A, AM29-22A, AM29-32A, AM29-33A, AM16-103A, AM29-182A, AM29-55A, AM29-151A, AM29-152A, AM29-137A, AM29-153A, AM29-138A, AM29-154A, AM29-139A, AM29-155A, AM29-170A, AM29-156A, AM29-171A, AM29-157A, AM29-172A, AM29-173A, AM16-79A, AM29-177A, AM29-141A, AM29-178A, AM29-142A, AM29-179A, AM29-143A, AM29-180A, AM29-144A, AM29-145A, AM29-181A, AM41-16A, AM41-17A, AM41-18A, XY012-157, XF034-164A, XF034-165A, XF034-166A, XF034-167A, XF034-168A, XY019-041, XF034-169A, XF034-170A, XF034-171A, CZ40-10, CZ40-09, CZ40-11, XY019-077, XY019-083, XY019-084, XF034-172A, XF034-173A, XF034-174A, XF034-175A, XF034-176A, XF034-177A, YS36-48, YS36-49, YS36-50, YS36-51, YS36-52, YS36-53, YS36-54, YS36-55, YS36-56, YS36-57, YS36-58, YS36-59, XY028-086, CZ40-72, CZ40-73, CZ40-75, CZ40-149, CZ40-74, CZ40-131, AM41-36A, AM41-37A, AM41-39A, AM41-41A, AM41-38A, AM41-40A, XF042-84, XF042-85, XF042-95, XF042-132, XF042-86, XF042-94, XF042-89, XF042-90, XF042-93, XF042-133, XF042-91, and XF042-92.

[0011] In any of the above-described methods, the bivalent compound can be administered to the subject orally, parenterally, intradermally, subcutaneously, topically, or rectally.

[0012] Any of the above-described methods can further include treating the subject with one or more additional therapeutic regimens for treating cancer. The additional therapeutic regimens for treating cancer can include, for example, surgery, chemotherapy, radiation therapy (e.g., ionizing radiation or ultraviolet light), hormone therapy, or immunotherapy (e.g., antibody therapy). For example, one or more bivalent compounds can be administered to the subject in conjunction with an effective amount of at least one established chemotherapeutic agent (e.g., actinomycin D, cyclophosphamide, doxorubicin, etoposide, and/or paclitaxel).

[0013] In any of the above-described methods, the EZH2-mediated cancer can include breast cancer (e.g., triple-negative breast cancer), glioblastoma, prostate cancer, uterine cancer, ovarian cancer, pancreatic cancer, melanoma, renal cell carcinoma, bladder cancer, colorectal cancer, lymphoma, leukemia, malignant rhabdoid tumor, and oropharyngeal cancer.

[0014] In any of the above-described methods, the EZH2-mediated cancer can include a relapsed cancer.

[0015] In any of the above-described methods, the EZH2-mediated cancer can be (known, predicted, or determined to be) refractory to one or more previous treatments (e.g., surgery, chemotherapy, radiation therapy, hormone therapy, or immunotherapy).

[0016] Moreover, the document additionally provides identifying a bivalent compound which mediates degradation/disruption of EZH2, the method including:

[0017] providing a bivalent test compound including an EZH2 ligand conjugated to a degradation/disruption tag;

[0018] contacting the bivalent test compound with a cell including a ubiquitin ligase and EZH2;

[0019] determining whether EZH2 levels decrease in the cell; and

[0020] identifying the bivalent test compound as a bivalent compound which mediates reduction of EZH2 if EZH2 levels decrease in the cell. The cell can be a cancer cell (e.g., an EZH2-mediated cancer cell).

[0021] As used herein, the terms "about" and "approximately" are defined as being within plus or minus 10% of a given value or state, preferably within plus or minus 5% of said value or state.

[0022] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Methods and materials are described herein for use in the present invention; other, suitable methods and materials known in the art can also be used. The materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, sequences, database entries, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control.

[0023] Other features and advantages of the invention will be apparent from the following detailed description and figures, and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0024] FIG. **1** depicts exemplary structures of bivalent compounds as described in the instant disclosure. Thalidomide/pomalidomide-based EZH2 degraders/disruptors and exemplary linkers 1-4.

[0025] FIG. **2** depicts exemplary structures of VHL-1-based EZH2 degraders/disruptors and exemplary linkers 5-7.

[0026] FIG. **3** depicts exemplary structures of adamantane-based EZH2 degraders/disruptors.

[0027] FIG. **4** is a graph depicting the GI_{50} for AM16-10A for MCF-7 cells.

[0028] FIG. **5** is a graph depicting the GI_{50} for AM16-10A for MDA-MB-468 cells.

[0029] FIG. **6** is a graph depicting the GI_{50} for AM16-10A for HCC1187 cells.

[0030] FIG. **7** is a graph depicting the GI_{50} for AM16-10A for HCC1170 cells.

[0031] FIG. **8** is a graph depicting the GI_{50} for AM16-11A for HCC1187 cells.

[0032] FIG. **9** is a graph depicting the GI_{50} for AM16-37A for HCC1187 cells.

[0033] FIG. **10** is a graph depicting the GI_{50} for AM16-38A for HCC1187 cells.

[0034] FIG. **11** is a graph depicting the GI_{50} for XY019-43 for MCF-7 cells.

[0035] FIG. **12** is a graph depicting the GI_{50} for XY019-43 for MCF-7 and MCF-10A (control) cells.

[0036] FIG. **13** is a graph depicting the GI_{50} for XY019-43 for MDA-MB-468 cells.

[0037] FIG. **14** is a graph depicting the GI_{50} for XY019-43 for HCC1187 cells.

[0038] FIG. **15** is a graph depicting the GI_{50} for XY019-43 for BT549 cells.

[0039] FIG. **16** is a graph depicting the GI_{50} for XY019-43 for HCC1954 cells.

[0040] FIG. **17** is a graph depicting the GI_{50} for XY019-44 for HCC1187 cells.

[0041] FIG. **18** is a graph depicting the GI_{50} for AM16-92A for MCF-7 cells.

[0042] FIG. **19** is a graph depicting the GI_{50} for AM16-92A for HCC1187 cells.

[0043] FIG. **20** is a graph depicting the GI_{50} for AM16-93A for HCC1187 cells.

[0044] FIG. **21** is a graph depicting the GI_{50} for AM16-97A for HCC1187 cells.

[0045] FIG. **22** is a graph depicting the GI_{50} for AM16-101A for MCF-7 cells.

[0046] FIG. **23** is a graph depicting the GI_{50} for AM16-101A for MDA-MB-468 cells.

[0047] FIG. **24** is a graph depicting the GI_{50} for AM16-105A for MCF-7 cells.

[0048] FIG. **25** is a graph depicting the GI_{50} for AM16-105A for HCC1187 cells.

[0049] FIG. **26** is a graph depicting the GI_{50} for AM16-106A for HCC1187 cells.

[0050] FIG. **27** is a graph depicting the GI_{50} for AM29-21A for MCF-7 cells.

[0051] FIG. **28** is a graph depicting the GI_{50} for AM29-21A for MDA-MB-468 cells.

[0052] FIG. **29** is a graph depicting the GI_{50} for AM29-22A for MCF-7 cells.

[0053] FIG. **30** is a graph depicting the GI_{50} for AM29-22A for MDA-MB-468 cells.

[0054] FIG. **31** is a graph depicting the GI_{50} for AM29-33A for MCF-7 cells.

[0055] FIG. **32** is a graph depicting the GI_{50} for AM29-33A for MDA-MB-468 cells.

[0056] FIG. **33** is a graph depicting the GI_{50} for AM16-103A for MDA-MB-468 cells.

[0057] FIG. **34** is a graph depicting the GI_{50} for AM16-103A for BT549 cells.

[0058] FIG. **35** is a graph depicting the GI_{50} for AM16-103A for HCC1954 cells.

[0059] FIG. **36** is a graph depicting the GI_{50} for AM29-182A for MDA-MB-468 cells.

[0060] FIG. **37** is a graph depicting the GI_{50} for AM29-182A for BT549 cells.

[0061] FIG. **38** is a graph depicting the GI_{50} for AM29-182A for HCC1954 cells.

[0062] FIG. **39** is a graph depicting the GI_{50} for AM29-177A for MDA-MB-468 cells.

[0063] FIG. **40** is a graph depicting the GI_{50} for XY028-086 for MDA-MB-468 cells. FIG. **41** is a graph depicting the GI_{50} for CZ40-75 for MDA-MB-468 cells.

[0064] FIG. **42** is a graph depicting the GI_{50} for CZ40-149 for MDA-MB-468 cells.

[0065] FIG. **43** is a graph depicting the GI_{50} for CZ40-131 for MDA-MB-468 cells.

[0066] FIG. **44** is a graph depicting the GI_{50} for AM41-41A for MDA-MB-468 cells.

[0067] FIG. **45** is a graph depicting the GI_{50} for XF042-95 for MDA-MB-468 cells.

[0068] FIG. **46** is a graph depicting the GI_{50} for XF042-90 for MDA-MB-468 cells.

[0069] FIG. **47** is a graph depicting the GI_{50} for XF042-93 for MDA-MB-468 cells.

[0070] FIG. **48** is a graph depicting the GI_{50} for XF042-133 for MDA-MB-468 cells.

[0071] FIG. **49** is a graph depicting the GI_{50} for XF042-92 for MDA-MB-468 cells.

[0072] FIG. **50** is a graph depicting Western blot results showing EZH2 (2-day treatment) and H3K27me3 (1-day treatment) levels in MCF-7 cells treated with 1 μM AM16-10A, UNC1999 (negative control), or DMSO.

[0073] FIG. **51** is a Western blot showing EZH2 and H3K27me3 levels in MDA-MB-468 cells treated for 2 days with 2.5 or 5 μM XY019-43, AM29-182A, or DMSO.

[0074] FIG. **52** is a Western blot showing EZH2 and H3K27me3 levels in MDA-MB-468 cells treated for 2 days with various concentrations of AM29-177A or DMSO.

[0075] FIG. **53** is a Western blot showing EZH2 and H3K27me3 levels in MDA-MB-468 cells treated for 1 day with various concentrations of XY019-43, UNC1999 (negative control), or DMSO.

[0076] FIG. **54** is a Western blot showing EZH2 and H3K27me3 levels in HCC1187 cells treated for various times (h) with 1 μM AM16-100A, UNC1999 (negative control), or DMSO.

[0077] FIG. **55** is a graph depicting the in vitro IC_{50} of AM16-10A for PRC2-EZH2.

[0078] FIG. **56** is a graph depicting the in vitro IC_{50} of XY019-43 for PRC2-EZH2.

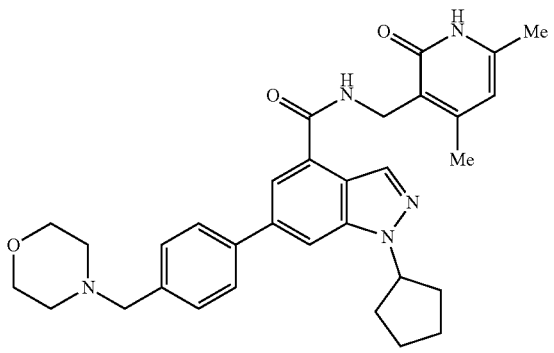
[0079] FIG. **57** is a graph depicting the in vitro IC_{50} of AM16-101A for PRC2-EZH2.

DETAILED DESCRIPTION

[0080] The present disclosure is based, in part, on the discovery that novel bivalent compounds which selectively degrade/disrupt EZH2 ("EZH2 degraders/disruptors") are useful in the treatment of EZH2-mediated cancers, including but not limited to TNBC. As discussed in the following examples, this disclosure provides specific examples of novel EZH2 degraders/disruptors. The effect of exemplary degraders/disruptors on the proliferation of different tumor cell lines was examined. The effect of exemplary degraders/disruptors on EZH2 and H3K27me3 protein levels and the enzymatic activity of the PRC2-EZH2 complex were also evaluated. This novel therapeutic approach can be beneficial, particularly since the standard of care for TNBC is primarily chemotherapy and radiation. In addition, without wishing to be bound by theory, because the EZH2 degraders/disruptors disclosed herein have dual functions (enzyme inhibition plus protein degradation/disruption), they can be significantly more effective than current EZH2 inhibitors, which inhibit the enzymatic activity of EZH2 but do not affect EZH2 protein levels, for treating other EZH2-mediated cancers.

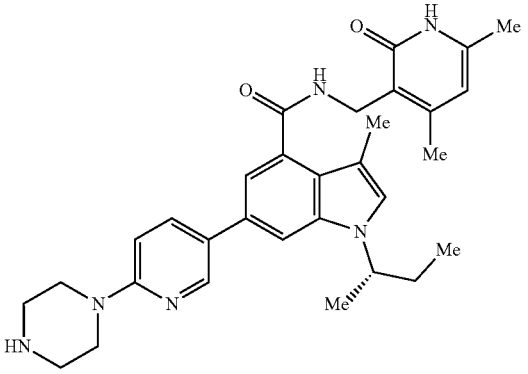
[0081] A number of selective EZH2 inhibitors, including UNC1999, EPZ005687, EPZ-6438, GSK126, EI1, CPI-1205, GSK343, CPI-360, EPZ011989, compound 24, compound 3, compound 31, ZLD1039, PF-06821497, and JQEZ5 have been discovered (Bradley et al., 2014; Broun et al., 2016; Campbell et al., 2015; Gao et al., 2016; Garapaty-Rao et al., 2013; Gehling et al., 2015; Kaniskan et al., 2017; Knutson et al., 2013; Knutson et al., 2012; Konze et al., 2013; Kung et al., 2016; McCabe et al., 2012b; Qi et al., 2012; Song et al., 2016; Verma et al., 2012; Yang et al., 2016). Some of these inhibitors (e.g., EPZ-6438, GSK126, CPI-1205, and PF-06821497) have been in clinical trials for treating diffused large B cell lymphoma (DLBCL), follicular lymphoma (FL), and malignant rhabdoid tumor (MRT). However, these inhibitors have exhibited very limited success in treating breast cancers and prostate cancers mainly because these compounds only inhibit the methyltransferase activity of EZH2, but do not change EZH2 protein levels. Representative examples of selective EZH2 inhibitors are provided below.

(1)



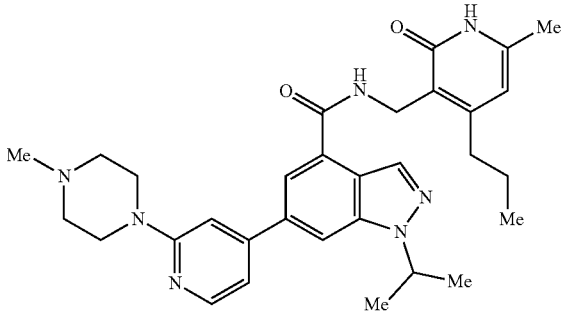
EPZ005687

(2)



GSK126

(3)



GSK343

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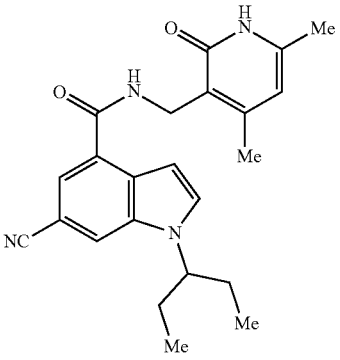
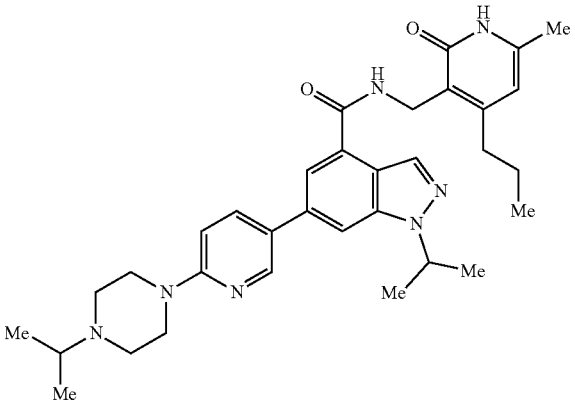
(4)



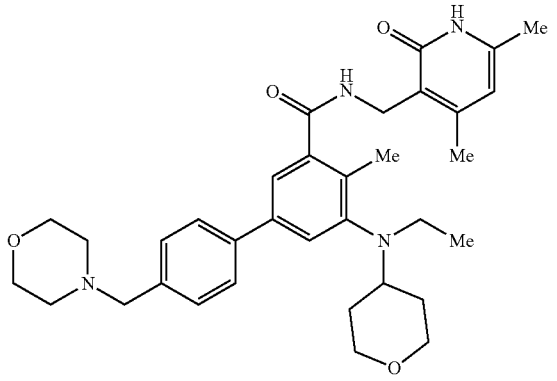
EI1

(5)



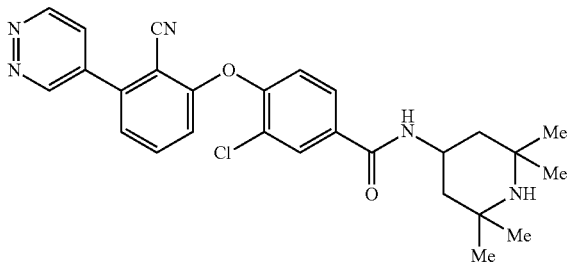
UNC1999

(6)



EPZ-6438 (E7438)

7



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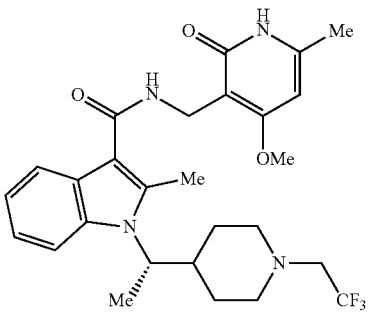
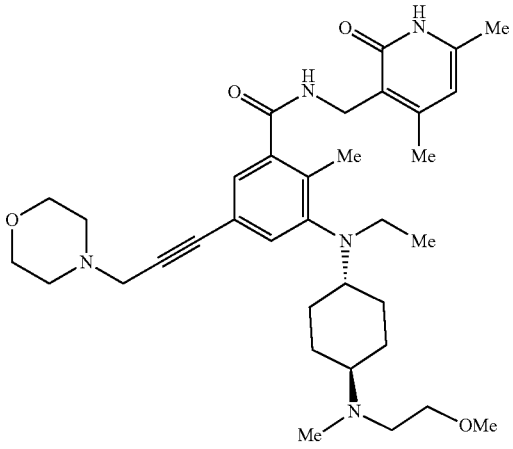
(8)



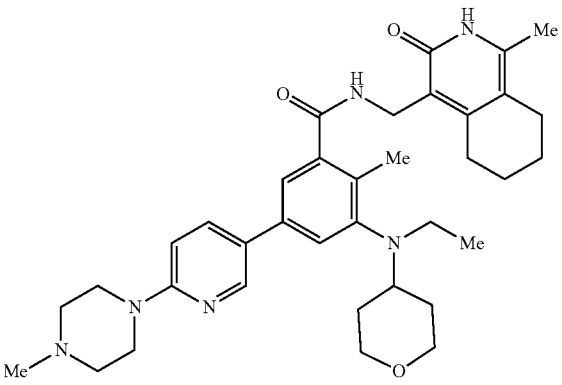
CPI-1205

(9)



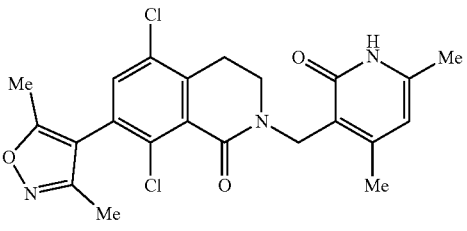
EPZ011989

(10)



ZLD1039

11



Representative Small-Molecule EZH2 Inhibitors

[0082] As described earlier, known EZH2 inhibitors (Bradley et al., 2014; Brooun et al., 2016; Campbell et al., 2015; Gao et al., 2016; Garapaty-Rao et al., 2013; Gehling et al., 2015; Kaniskan et al., 2017; Knutson et al., 2013; Knutson et al., 2012; Konze et al., 2013; Kung et al., 2016; McCabe et al., 2012b; Qi et al., 2012; Song et al., 2016; Verma et al., 2012; Yang et al., 2016) inhibit the catalytic activity of the PRC2-EZH2, but do not change EZH2 protein levels. Here, a different approach was taken: an EZH2 ligand or targeting moiety (e.g., an EZH2 inhibitor such as UNC1999 or compound 24) was linked with a ubiquitin ligase (e.g., an E3 ligase)-binding moiety (e.g., thalidomide or VHL-1) or a hydrophobic group (e.g., adamantane) to generate bivalent compounds. These bivalent inhibitors (EZH2 degraders/disruptors) recruit the ubiquitination machinery to EZH2, leading to selective degradation of EZH2 via the ubiquitin-proteasome pathway, and/or mimic EZH2 protein misfolding and subsequent degradation at the proteasome or loss of function. Therefore, these degraders/disruptors can be effective therapeutic agents for treating breast cancers (including TNBC), prostate cancers, and other cancers while current EZH2 inhibitors are ineffective. In addition, these EZH2 degraders/disruptors can be more effective than EZH2 inhibitors for the treatment of those EZH2-mediated cancers where EZH2 inhibitors are effective, including, e.g., DLBCB, FL, and MRT.

[0083] Accordingly, in some aspects, the present disclosure provides bivalent compounds, referred to herein as "EZH2 degraders/disruptors", comprising an enhancer of zeste homologue 2 (EZH2) ligand (or targeting moiety) conjugated to a degradation/disruption tag. Linkage of the EZH2 ligand to the degradation/disruption tag can be direct, or indirect via a linker.

[0084] As used herein, the term "enhancer of zeste homologue 2 ligand" or "EZH2 ligand" refers to compound that associates and/or binds to EZH2. The EZH2 ligand can be, e.g., a small-molecule compound (i.e., a molecule of molecular weight less than about 1.5 kilodaltons (kDa)), a peptide, or an antibody or fragment thereof which is capable of binding to EZH2 and/or interfering with the methyltransferase enzymatic activity of EZH2.

[0085] The EZH2 ligand can be an EZH2 inhibitor, which is capable of interfering with the methyltransferase enzymatic activity of EZH2. As used herein, an "inhibitor" refers to an agent that restrains, retards, or otherwise causes inhibition of a physiological, chemical or enzymatic action or function. An inhibitor may cause at least 5% decrease in enzyme activity. An inhibitor may also refer to a drug, compound or agent that prevents or reduces the expression, transcription or translation of a gene or protein. An inhibitor may reduce or prevent the function of a protein, for instance by binding to and/or activating/inactivating another protein or receptor. In some aspects, the EZH2 inhibitors of the present disclosure include, for example, UNC1999, EPZ005687, EPZ-6438, GSK126, EI1, CPI-1205, GSK343, CPI-360, EPZ011989, compound 24, compound 3, compound 31, ZLD1039, PF-06821497, JQEZ5, and analogs thereof.

[0086] As used herein, the term "degradation/disruption tag" refers to a moiety, which associates with/binds to a ubiquitin ligase for recruitment of the corresponding ubiquitination machinery to the EHZ2/PRC2 complex, or mimics EZH2 protein misfolding and subsequent degradation at the proteasome or loss of function. One or more degradation/disruption tags can be introduced to the solvent-exposed portion of an EZH2 ligand to create EZH2 degraders/disruptors. Exemplary structures of EZH2 degraders/disruptors containing such tags are illustrated in FIGS. **1-3**.

[0087] For example, a docking model of UNC1999 and its close analogs in PRC2 crystal structures (Brooun et al., 2016; Jiao and Liu, 2015; Justin et al., 2016) shows that two regions of UNC1999 and its analogs are solvent-exposed, thus presenting suitable handles to introduce a degradation/disruption tag without interfering with the inhibitors' ability to bind to EZH2. These regions are the piperazine portion (marked in red in FIGS. **1-3**) and isopropyl group (marked in blue in FIGS. **1-3**). Structure-activity relationship (SAR) studies showed that modifying these two portions resulted in negligible effects on the molecule's potency towards EZH2 (Konze et al., 2013; Yang et al., 2016).

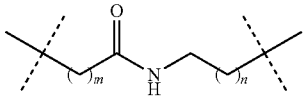
[0088] In some aspects, the degradation/disruption tags of the present disclosure include, for example, immunomodulatory drugs (e.g., thalidomide, pomalidomide, and lenalidomide), VHL-1, bulky hydrophobic groups (e.g., adamantane and 1-((4,4,5,5,5-pentafluoropentyl)sulfinyl)nonane), and their analogs. Immunomodulatory drugs such as thalidomide and pomalidomide (structures shown in FIG. **1**) bind cereblon (CRBN or $CRL4^{CRBN}$), a component of a cullin-RING ubiquitin ligase (CRL) complex (Bondeson et al., 2015; Chamberlain et al., 2014; Fischer et al., 2014; Ito et al., 2010; Winter et al., 2015). VHL-1 (structure shown in FIG. **2**), a hydroxyproline-containing ligand, binds van Hippel-Lindau protein (VHL or $CRL2^{VHL}$), a component of another CRL complex (Bondeson et al., 2015; Buckley et al., 2012a; Buckley et al., 2012b; Galdeano et al., 2014; Zengerle et al., 2015). Bulky hydrophobic groups (e.g., adamantane) mimic protein misfolding, leading to the degradation of the target protein by proteasome (Buckley and Crews, 2014).

[0089] As used herein, a "linker" is a bond, molecule or group of molecules that binds (i.e., bridges) two separate entities to one another. A Linker can provide for optimal spacing of the two entities. The term "linker" in some aspects refers to any agent or molecule that bridges the EZH2 ligand to the degradation/disruption tag. One of ordinary skill in the art recognizes that sites on the EZH2 ligand and/or the degradation/disruption tag, which are not necessary for the function of the bivalent compound of the present disclosures, are ideal sites for attaching a linker, provided that the linker, once attached to the conjugate of the present disclosures, does not interfere with the function of the bivalent compound, i.e., the ability to target EZH2 and recruit a ubiquitin ligase or mimic protein misfolding. The length of the linker can be adjusted to minimize the molecu-

lar weight of the degrader/disruptor, avoid any steric interference of EZH2 with the E3 ligase, and/or enhance mimicry of EZH2 protein misfolding by the hydrophobic tag at the same time.

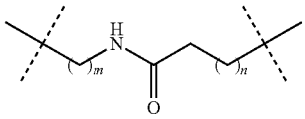
[0090] Exemplary linkers include, but are not limited to, the linkers of Formulas I-XIV below:

Formula I



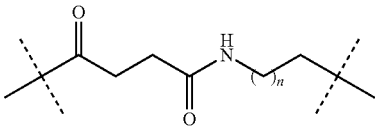
m = 0-15
n = 0-15

Formula II



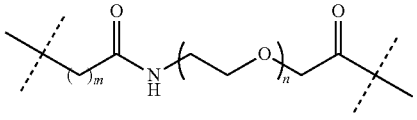
m = 0-15
n = 0-15

Formula III



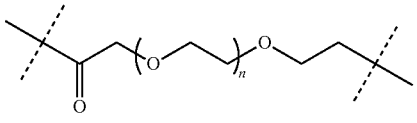
n = 0-15

Formula IV



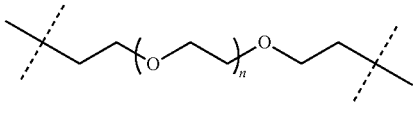
m = 0-15
n = 0-15

Formula V



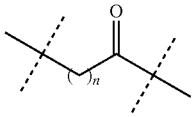
n = 0-15

Formula VI



n = 0-15

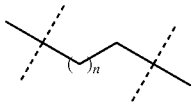
Formula VII



n = 0-15

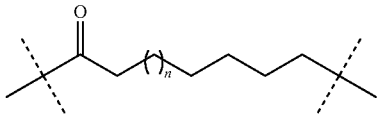
-continued

Formula VIII



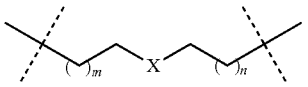
n = 0-15

Formula IX



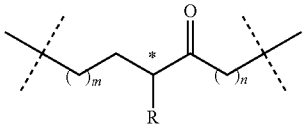
n = 0-15

Formula X



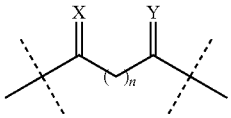
X = O, NR
R = H, C_{1-6} alkyl
m = 0-15
n = 0-15

Formula XI



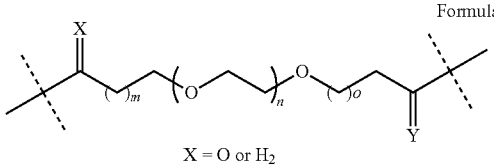
R = H, C_{1-6} alkyl
m = 0-15
n = 0-15
* R, S and racemic

Formula XII



X = O or H_2
Y = O or H_2
n = 0-15

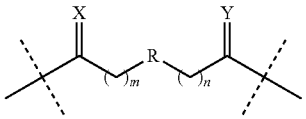
Formula XIII



X = O or H_2
Y = O or H_2
m = 0-15
n = 0-6
o = 0-15

-continued

Formula XIV

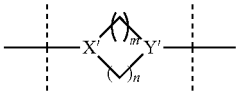


X = O or H_2
Y = O or H_2
m = 0-15
n = 0-15

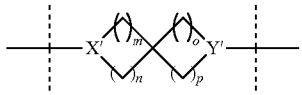
R is independently —CH_2— ; —CF_2— ; —$CH(C_{1-3}$ alkyl)— ; —$C(C_{1-3}$ alkyl)(C_{1-3} alkyl)— ; —CH═CH— ; —$C(C_{1-3}$ alkyl)═$C(C_{1-3}$alkyl)— ; —C≡C— ; —O— ; —NH— ; —$N(C_{1-3}$ alkyl)— ; —C(O)NH— ; —C(O) $N(C_{1-3}$ alkyl)— ;

3-13 membered rings, fused rings, bridged rings, or spiro rings with or without heteroatoms (—NH— , —$N(C_{1-3}$ alkyl)— , O).

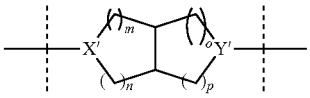
A few examples of R group:



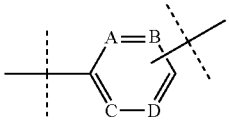
X′ = N or CH
Y′ = N or CH
m = 0-5
n = 0-5



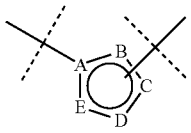
X′ = N or CH
Y′ = N or CH
m = 0-5
n = 0-5
0 = 0-5
p = 0-5



X′ = N or CH
Y′ = N or CH
m = 0-5
n = 0-5
0 = 0-5
p = 0-5



A = CH, $C(C_{1-3}$ alkyl), or N
B = CH, $C(C_{1-3}$ alkyl), or N
C = CH, $C(C_{1-3}$ alkyl), or N
D = CH, $C(C_{1-3}$ alkyl), or N



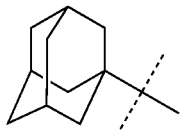
A = C, CH, $C(C_{1-3}$ alkyl), N, NH, $N(C_{1-3}$ alkyl), O, S
B = C, CH, $C(C_{1-3}$ alkyl), N, NH, $N(C_{1-3}$ alkyl), O, S
C = C, CH, $C(C_{1-3}$ alkyl), N, NH, $N(C_{1-3}$ alkyl), O, S
D = C, CH, $C(C_{1-3}$ alkyl), N,NH, $N(C_{1-3}$ alkyl), O, S

[0091] In some aspects, the EZH2 degraders/disruptors have the form "X-linker-Y", as shown below:

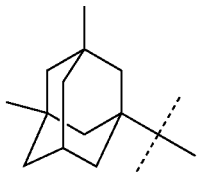
wherein X comprises a degradation/disruption tag (e.g., adamantane) and Y comprises an EZH2 ligand (e.g., an EZH2 inhibitor). Exemplary degradation/disruption tags (X) and exemplary EZH2 ligands (Y) are described above and are also illustrated below:

X includes but is not limited to

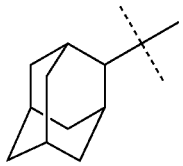
I



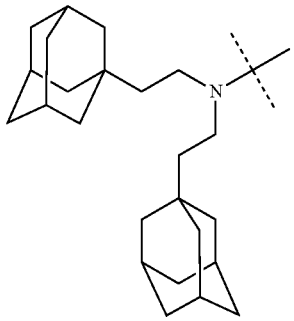
II



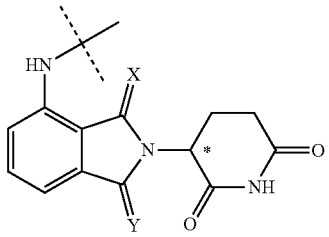
III



IV

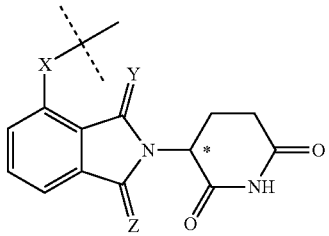


V



X = O or H_2
Y = O or H_2
* R, S and racemic

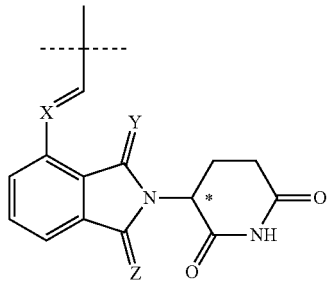
VI



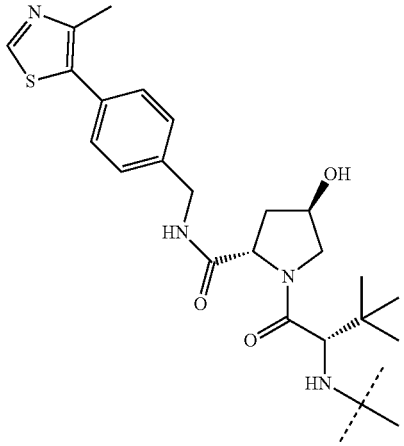
X = O, C_{1-6} alkyl
Y = O or H_2
Z = O or H_2
* R, S and racemic

-continued

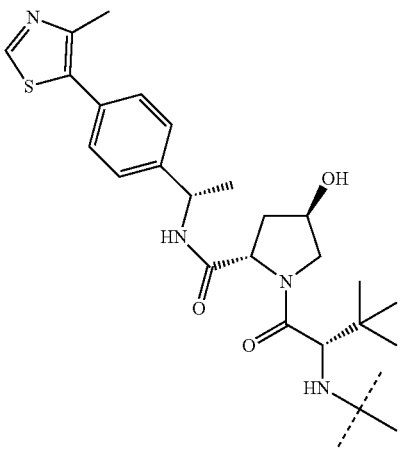
VII



X = C_{1-6} alkyl
Y = O or H_2
Z = O or H_2
* R, S and racemic



VIII



IX

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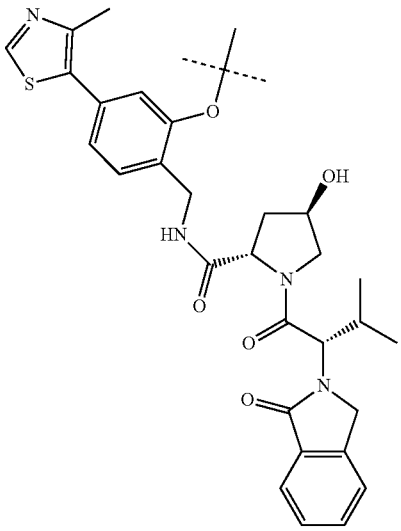
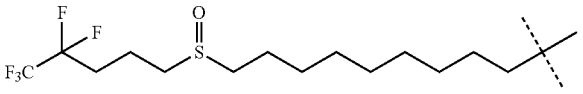
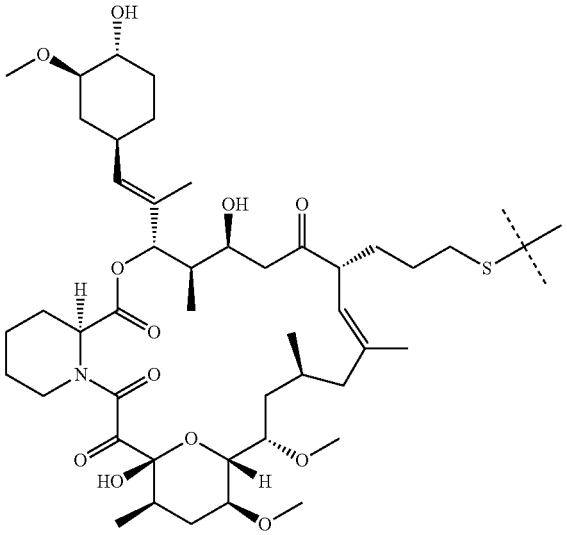
X



XI

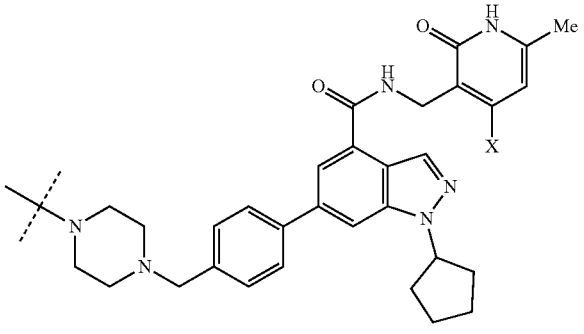


XII



Y includes but is not limited to

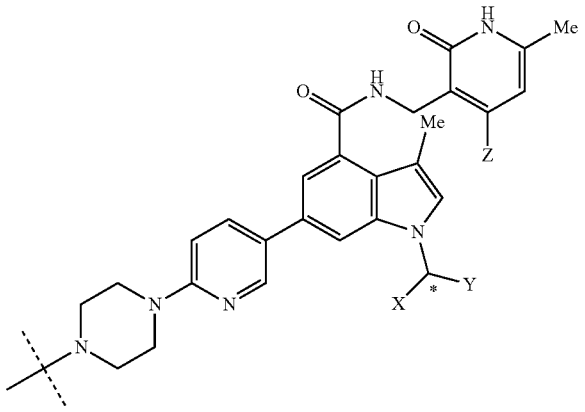
I



X = C_{1-6} alkyl, MeO——

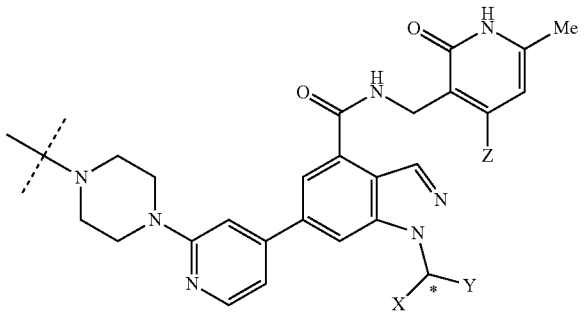
-continued

II



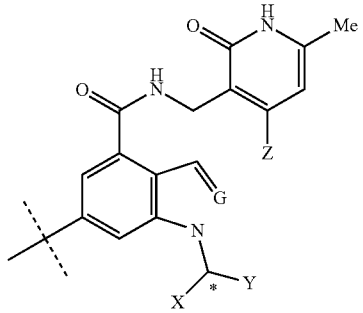
X = H, C_{1-6} alkyl
Y = H, C_{1-6} alkyl
Z = C_{1-6} alkyl, MeO——
* R, S and racemic

III



X = H, C_{1-6} alkyl
Y = H, C_{1-6} alkyl
Z = C_{1-6} alkyl, MeO——
* R, S and racemic

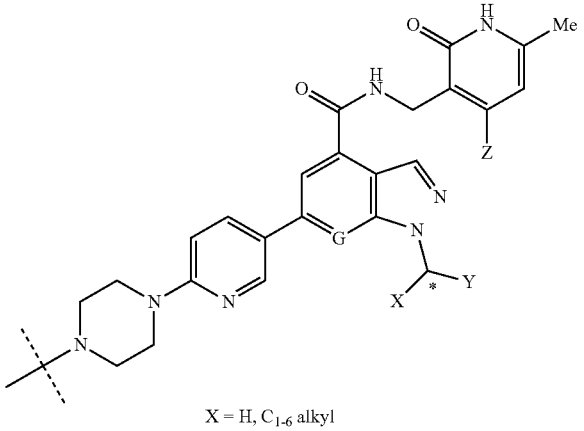
IV



X = H, C_{1-6} alkyl
Y = H, C_{1-6} alkyl
Z = C_{1-6} alkyl, MeO——
G = CH or N
* R, S and racemic

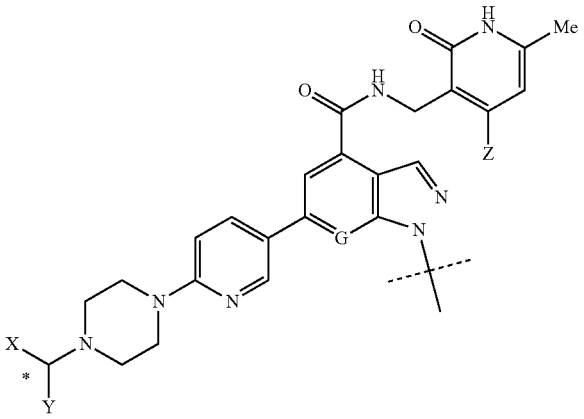
-continued

V



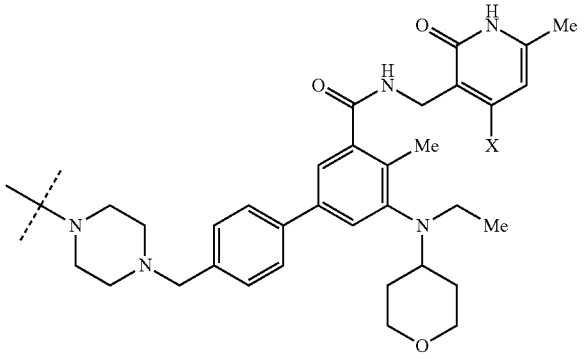
X = H, C_{1-6} alkyl
Y = H, C_{1-6} alkyl
Z = C_{1-6} alkyl, MeO——
G = CH or N
* R, S and racemic

VI



X = H, C_{1-6} alkyl
Y = H, C_{1-6} alkyl
Z = C_{1-6} alkyl, MeO——
G = CH or N
* R, S and racemic

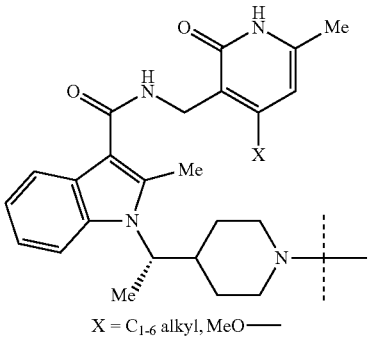
VII



X = C_{1-6} alkyl, MeO——

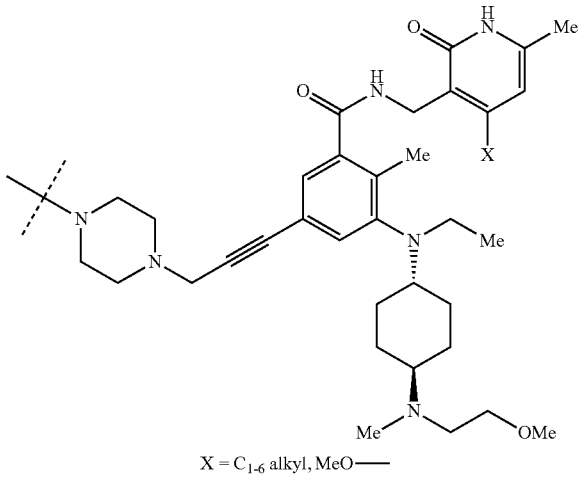
-continued

VIII



$X = C_{1\text{-}6}$ alkyl, MeO—

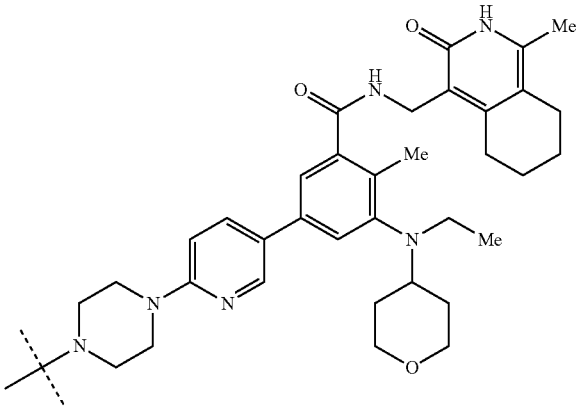
IX



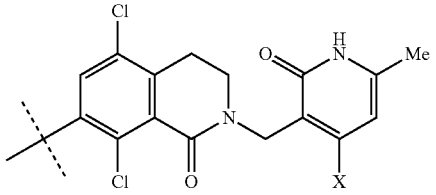
$X = C_{1\text{-}6}$ alkyl, MeO—

-continued

X



XI



$X = C_{1\text{-}6}$ alkyl, MeO—

[0092] Novel EZH2 degraders/disruptors developed using the principles and methods described herein are shown in Table 1. Additional EZH2 degraders/disruptors can also be developed using the principles and methods disclosed herein. For example, other linkers, other degradation/disruptor tags, and/or other EZH2 ligands can be synthesized and tested. Some exemplary compounds are shown in the Figures following Table 1.

TABLE 1

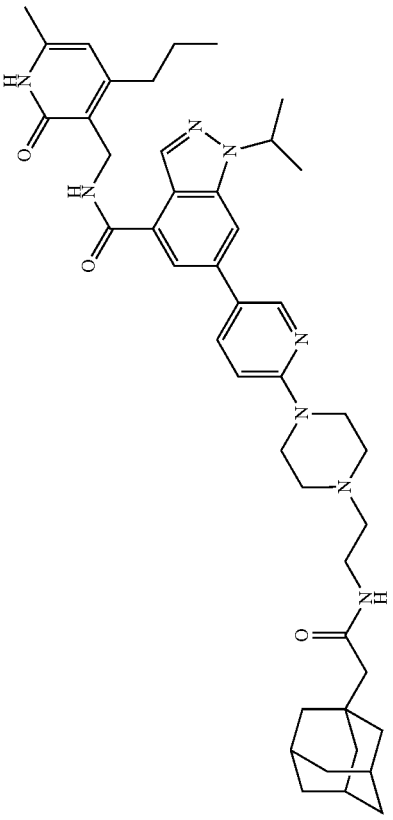
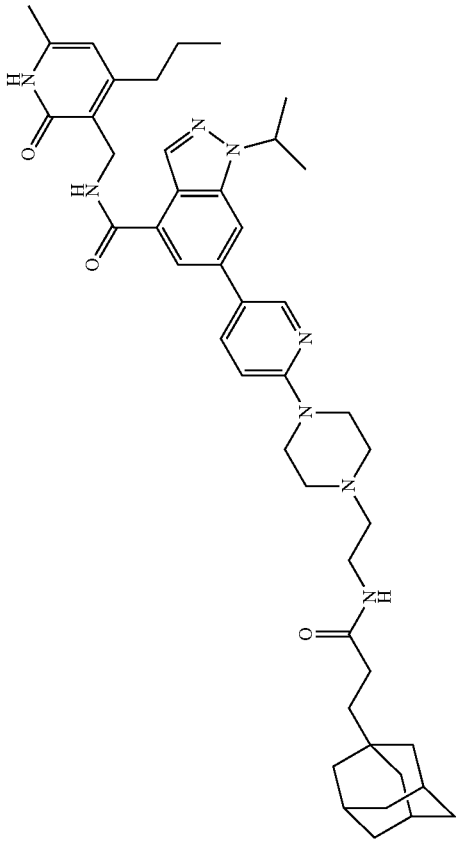
	Structure	Chemical Name
AM16-10A		6-(6-(4-(2-(2-((3r,5r,7r)-adamantan-1-yl)acetamido)ethyl)piperazin-1-yl)pyridin-3-yl)-1-isopropyl-N-((6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl)-1H-indazole-4-carboxamide
AM16-11A		6-(6-(4-(2-(3-((1r,3s)-adamantan-1-yl)propanamido)ethyl)piperazin-1-yl)pyridin-3-yl)-1-isopropyl-N-((6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl)-1H-indazole-4-carboxamide

TABLE 1-continued

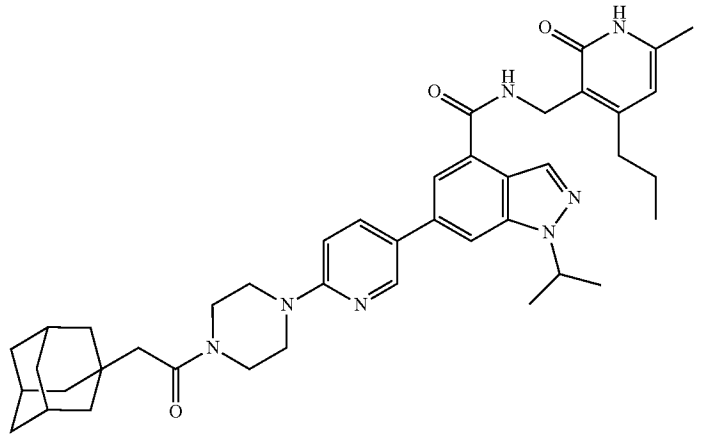
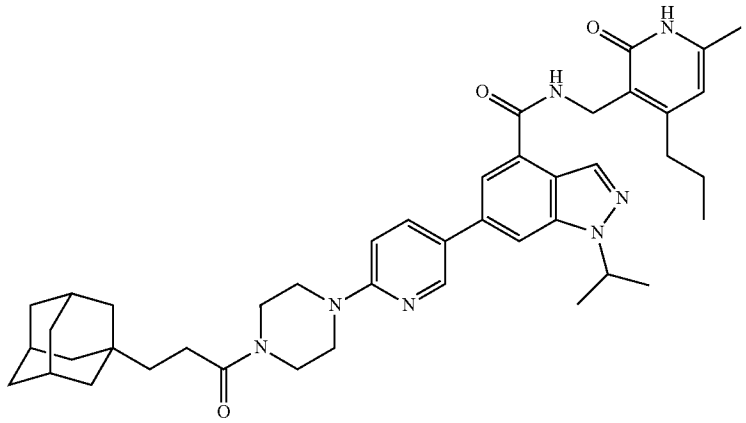
	Structure	Chemical Name
AM16-37A		6-(6-(4-(2-((1s,3s)-adamantan-1-yl)acetyl)piperazin-1-yl)pyridin-3-yl)-1-isopropyl-N-((6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl)-1H-indazole-4-carboxamide
AM16-38A		6-(6-(4-(3-((3r,5r,7r)-adamantan-1-yl)propanoyl)piperazin-1-yl)pyridin-3-yl)-1-isopropyl-N-((6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl)-1H-indazole-4-carboxamide

TABLE 1-continued

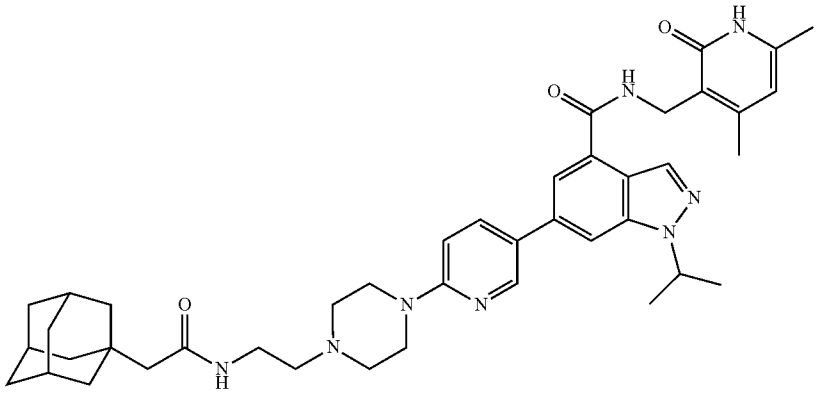
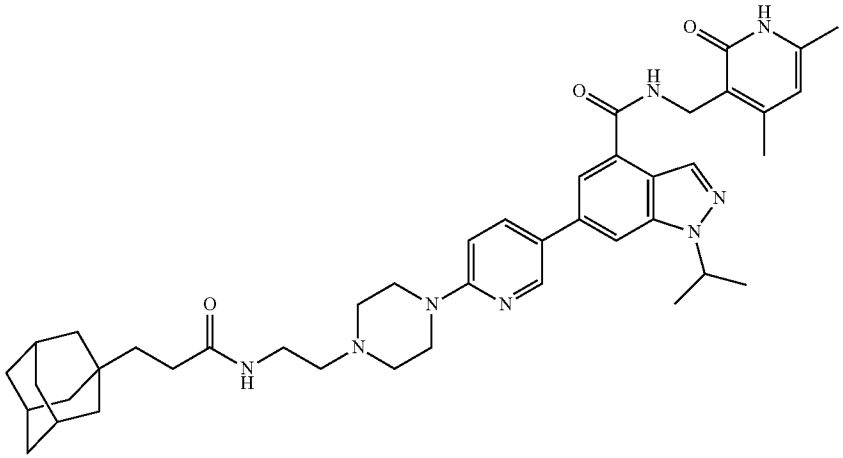
	Structure	Chemical Name
XY019-43		6-(6-(4-(2-(2-((3r,5r,7r)-adamantan-1-yl)acetamido)ethyl)piperazin-1-yl)pyridin-3-yl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-isopropyl-1H-indazole-4-carboxamide
XY019-44		6-(6-(4-(2-(3-((3r,5r,7r)-adamantan-1-yl)propanamido)ethyl)piperazin-1-yl)pyridin-3-yl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-isopropyl-1H-indazole-4-carboxamide

TABLE 1-continued

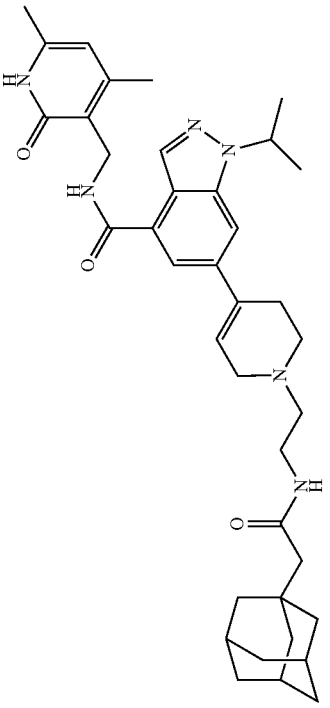
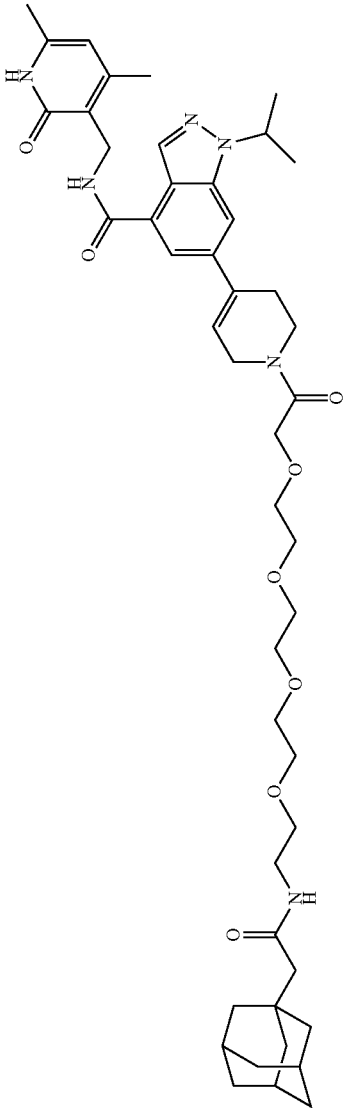
	Structure	Chemical Name
XY019-079		6-(1-(2-(2-((3r,5r,7r)-adamantan-1-yl)acetamido)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-isopropyl-1H-indazole-4-carboxamide
XY019-080		6-(1-(1-((3r,5r,7r)-adamantan-1-yl)-2-oxo-6,9,12,15-tetraoxa-3-azaheptadecan-17-oyl)-1,2,3,6-tetrahydropyridin-4-yl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-isopropyl-1H-indazole-4-carboxamide

TABLE 1-continued

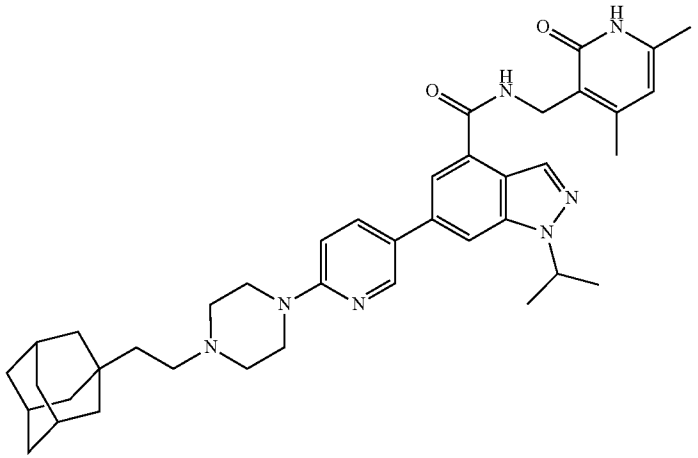
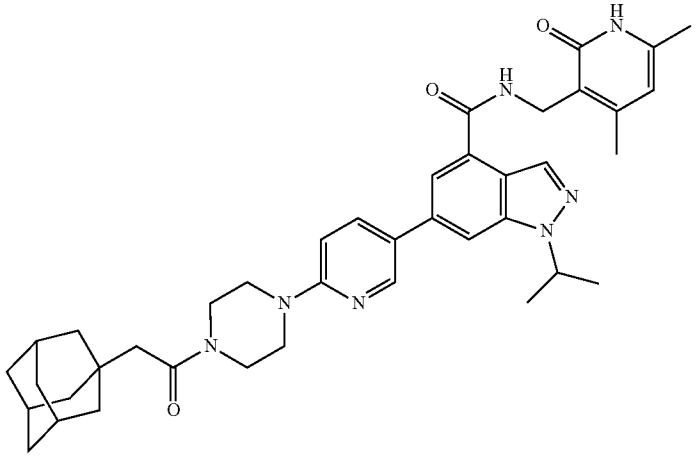
	Structure	Chemical Name
AM16-91A		6-(6-(4-(2-((1s,3s)-adamantan-1-yl)ethyl)piperazin-1-yl)pyridin-3-yl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-isopropyl-1H-indazole-4-carboxamide
AM16-92A		6-(6-(4-(2-((1s,3s)-adamantan-1-yl)acetyl)piperazin-1-yl)pyridin-3-yl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-isopropyl-1H-indazole-4-carboxamide

TABLE 1-continued

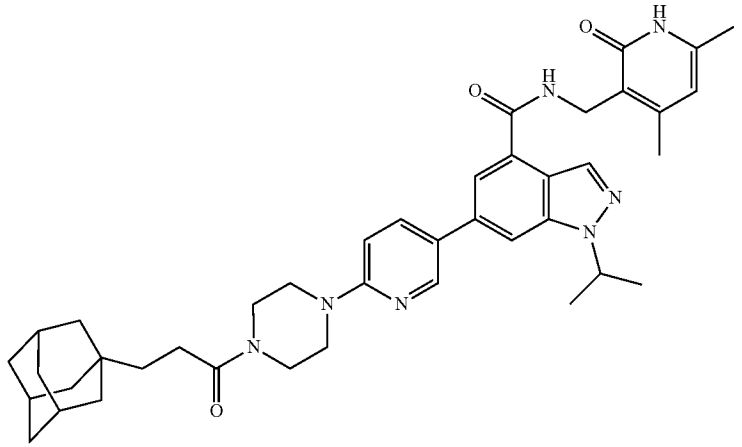
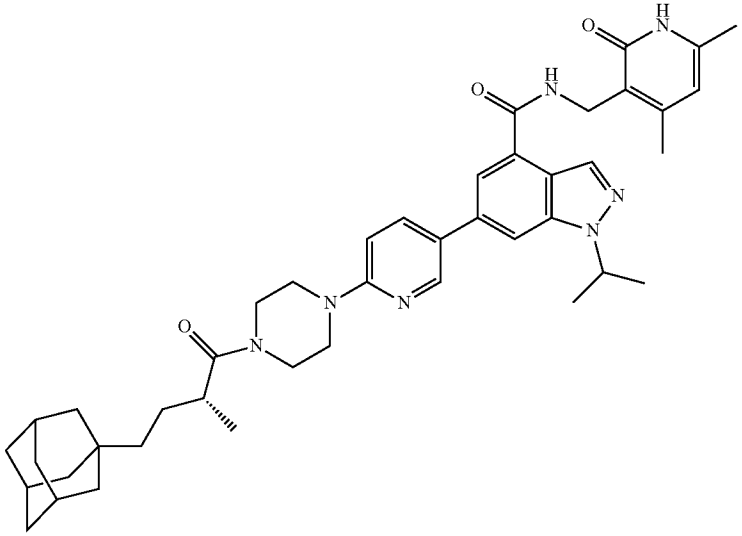
	Structure	Chemical Name
AM16-93A		6-(6-(4-(3-((1r,3s)-adamantan-1-yl)propanoyl)piperazin-1-yl)pyridin-3-yl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-isopropyl-1H-indazole-4-carboxamide
AM16-97A		6-(6-(4-((2R)-4-((1r,3S)-adamantan-1-yl)-2-methylbutanoyl)piperazin-1-yl)pyridin-3-yl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-isopropyl-1H-indazole-4-carboxamide

TABLE 1-continued

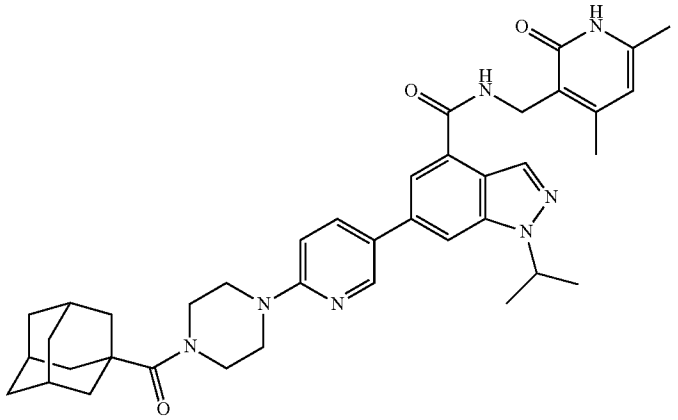
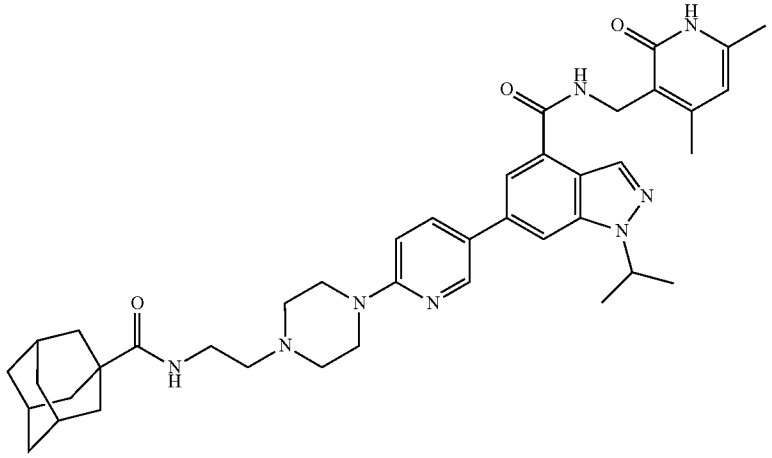
	Structure	Chemical Name
AM16-100A		6-(6-(4-((3r,5r,7r)-adamantane-1-carbonyl)piperazin-1-yl)pyridin-3-yl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-isopropyl-1H-indazole-4-carboxamide
AM16-101A		6-(6-(4-(2-((1s,3s)-adamantane-1-carboxamido)ethyl)piperazin-1-yl)pyridin-3-yl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-isopropyl-1H-indazole-4-carboxamide

TABLE 1-continued

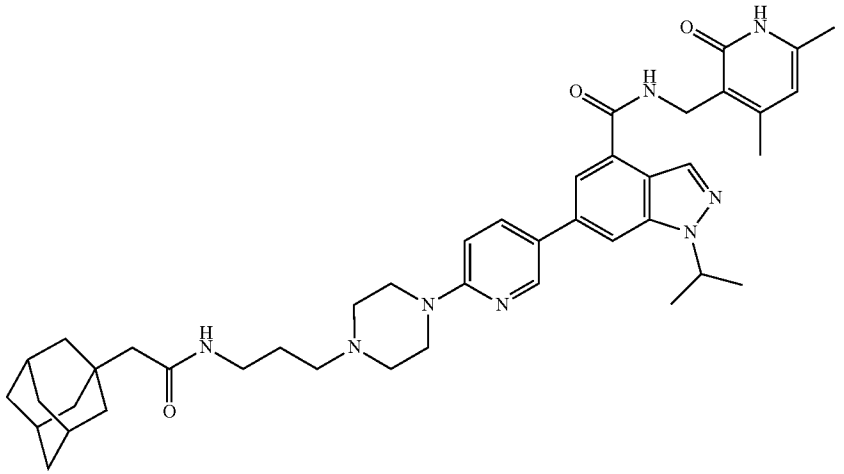
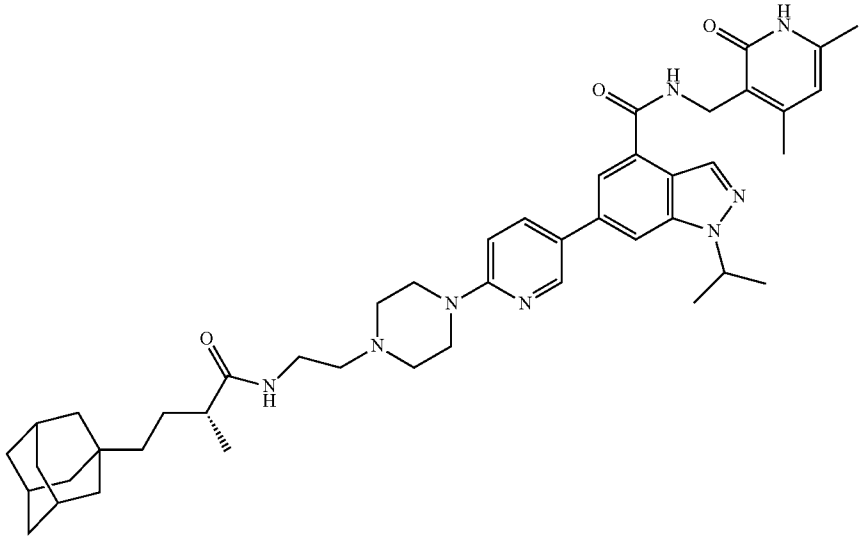
	Structure	Chemical Name
AM16-102A		6-(6-(4-(3-(2-((1s,3s)-adamantan-1-yl)acetamido)propyl)piperazin-1-yl)pyridin-3-yl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-isopropyl-1H-indazole-4-carboxamide
AM16-105A		6-(6-(4-(2-((2R)-4-((1r,3S)-adamantan-1-yl)-2-methylbutanamido)ethyl)piperazin-1-yl)pyridin-3-yl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-isopropyl-1H-indazole-4-carboxamide

TABLE 1-continued

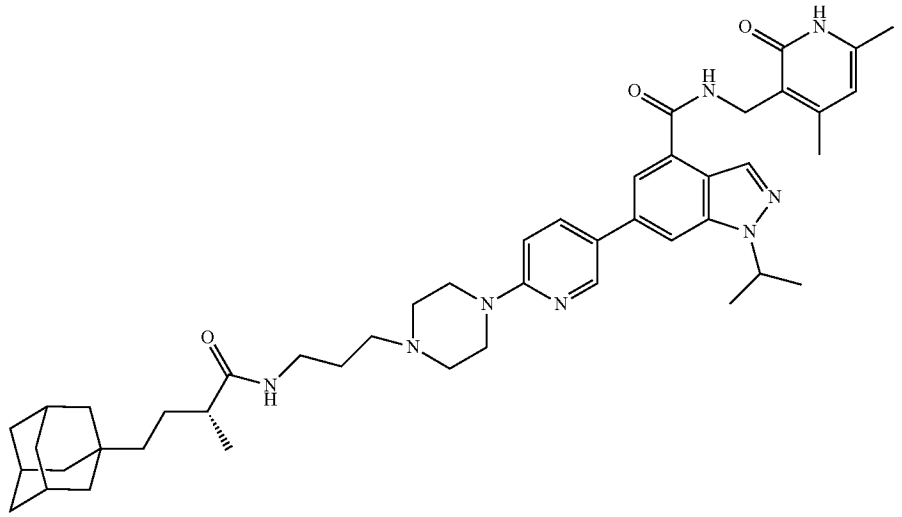
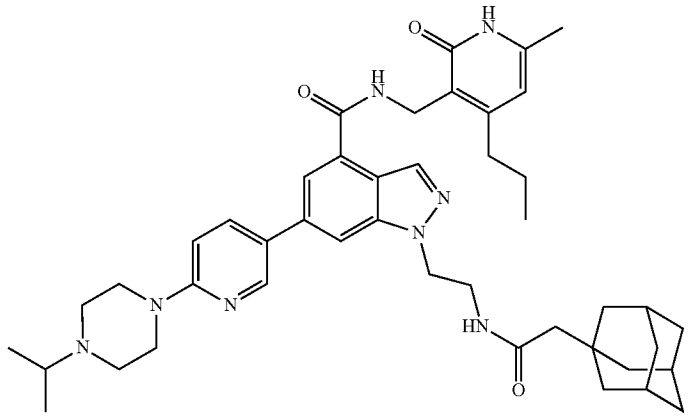
	Structure	Chemical Name
AM16-106A		6-(6-(4-(3-((R)-4-((3R,5R,7R)-adamantan-1-yl)-2-methylbutanamido)propyl)piperazin-1-yl)pyridin-3-yl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-isopropyl-1H-indazole-4-carboxamide
XY012-120		1-(2-(2-((1s,3s)-adamantan-1-yl)acetamido)ethyl)-6-(6-(4-isopropylpiperazin-1-yl)pyridin-3-yl)-N-((6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl)-1H-indazole-4-carboxamide

TABLE 1-continued

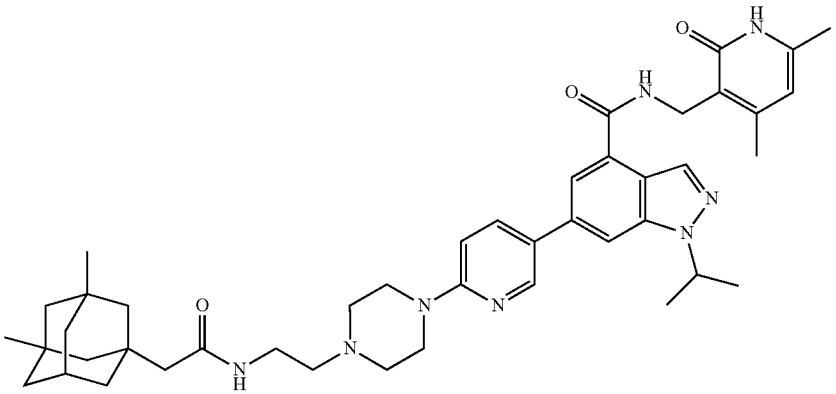
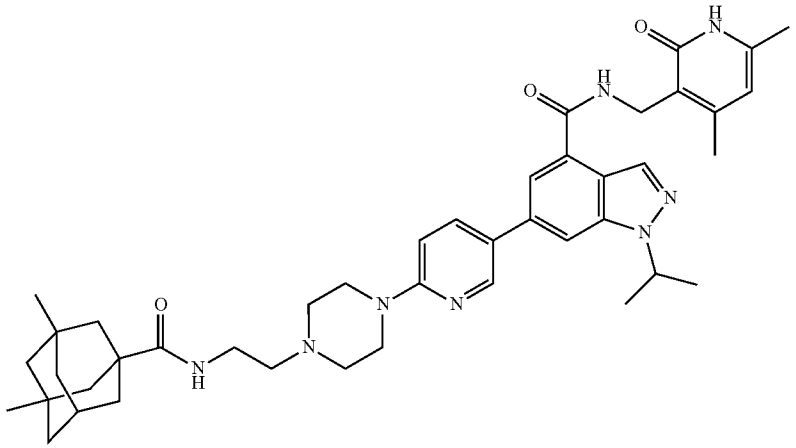
	Structure	Chemical Name
AM29-21A		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-(6-(4-(2-(2-((1r,3R,5S,7r)-3,5-dimethyladamantan-1-yl)acetamido)ethyl)piperazin-1-yl)pyridin-3-yl)-1-isopropyl-1H-indazole-4-carboxamide
AM29-22A		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-(6-(4-(2-((1R,3S)-3,5-dimethyladamantane-1-carboxamido)ethyl)piperazin-1-yl)pyridin-3-yl)-1-isopropyl-1H-indazole-4-carboxamide

TABLE 1-continued

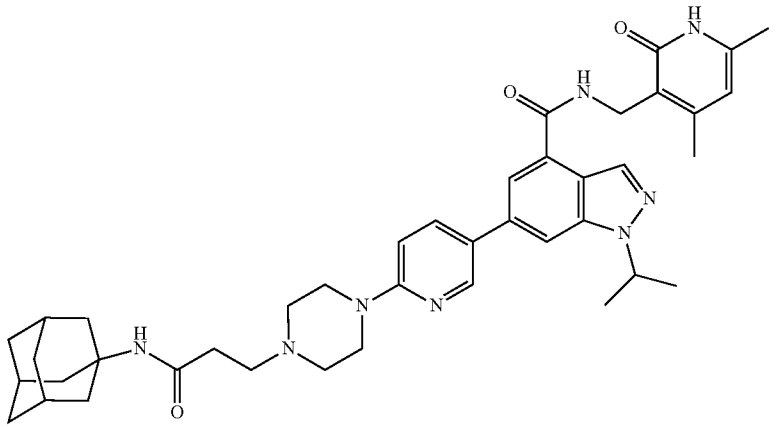
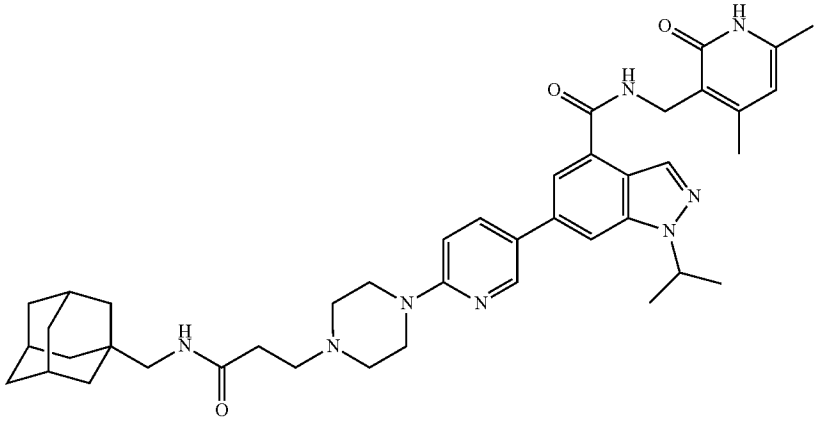
	Structure	Chemical Name
AM29-32A		6-(6-(4-(3-(((1s,3s)-adamantan-1-yl)amino)-3-oxopropyl)piperazin-1-yl)pyridin-3-yl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-isopropyl-1H-indazole-4-carboxamide
AM29-33A		6-(6-(4-(3-((((3r,5r,7r)-adamantan-1-yl)methyl)amino)-3-oxopropyl)piperazin-1-yl)pyridin-3-yl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-isopropyl-1H-indazole-4-carboxamide

TABLE 1-continued

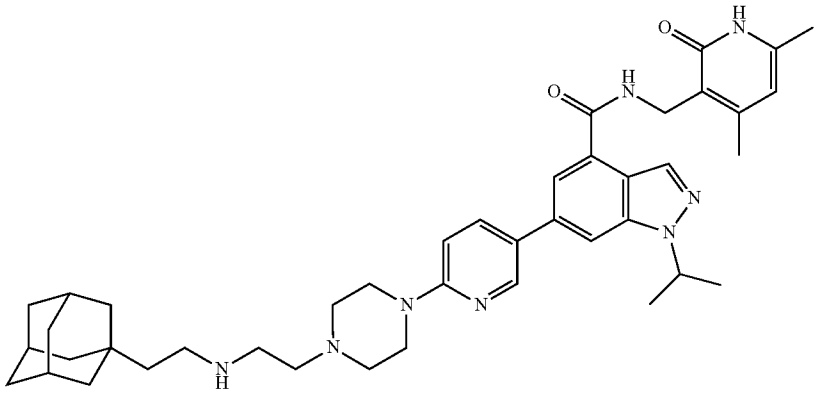
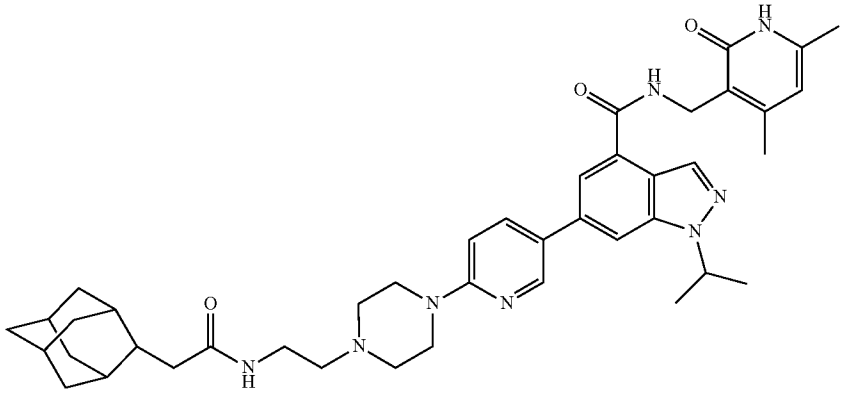
	Structure	Chemical Name
AM16-103A		6-(6-(4-(2-((3r,5r,7r)-adamantan-1-yl)ethyl)amino)ethyl)piperazin-1-yl)pyridin-3-yl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-isopropyl-1H-indazole-4-carboxamide
AM29-182A		6-(6-(4-(2-(2-((1r,3r,5r,7r)-adamantan-2-yl)acetamido)ethyl)piperazin-1-yl)pyridin-3-yl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-isopropyl-1H-indazole-4-carboxamide

TABLE 1-continued

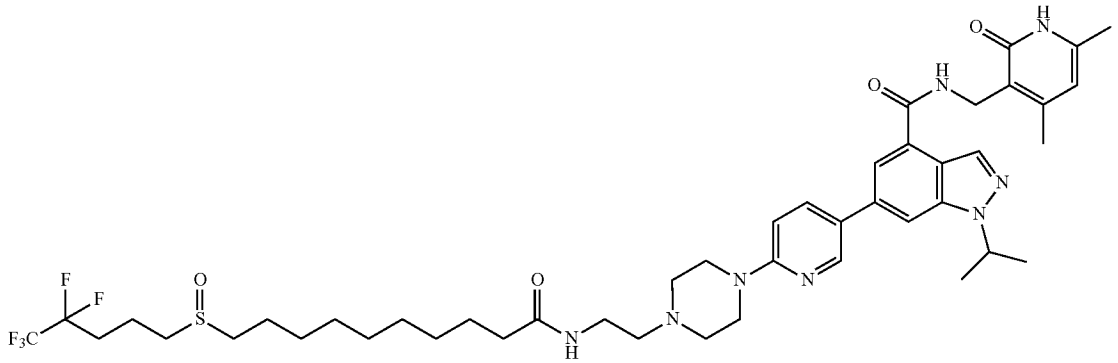
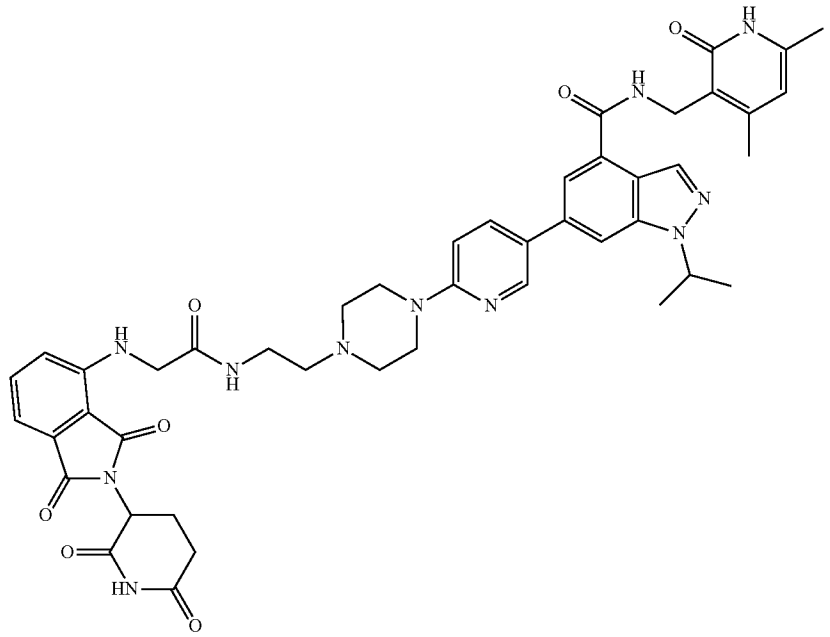
	Structure	Chemical Name
AM29-55A		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-isopropyl-6-(6-(4-(2-(10-((4,4,5,5,5-pentafluoropentyl)sulfinyl)decanamido)ethyl)piperazin-1-yl)pyridin-3-yl)-1H-indazole-4-carboxamide
AM29-151A		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-(6-(4-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)acetamido)ethyl)piperazin-1-yl)pyridin-3-yl)-1-isopropyl-1H-indazole-4-carboxamide

TABLE 1-continued

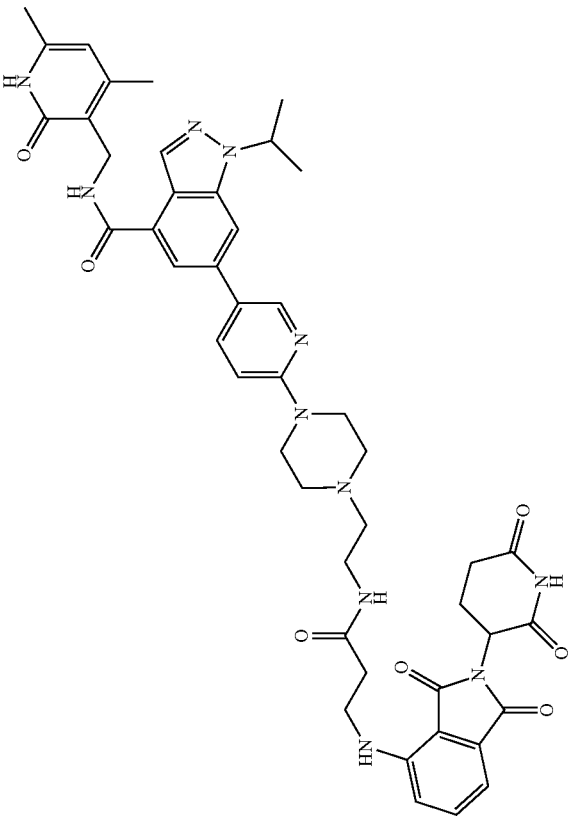
	Structure	Chemical Name
AM29-152A		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-(6-(4-(2-(3-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propanamido)ethyl)piperazin-1-yl)pyridin-3-yl)-1-isopropyl-1H-indazole-4-carboxamide

TABLE 1-continued

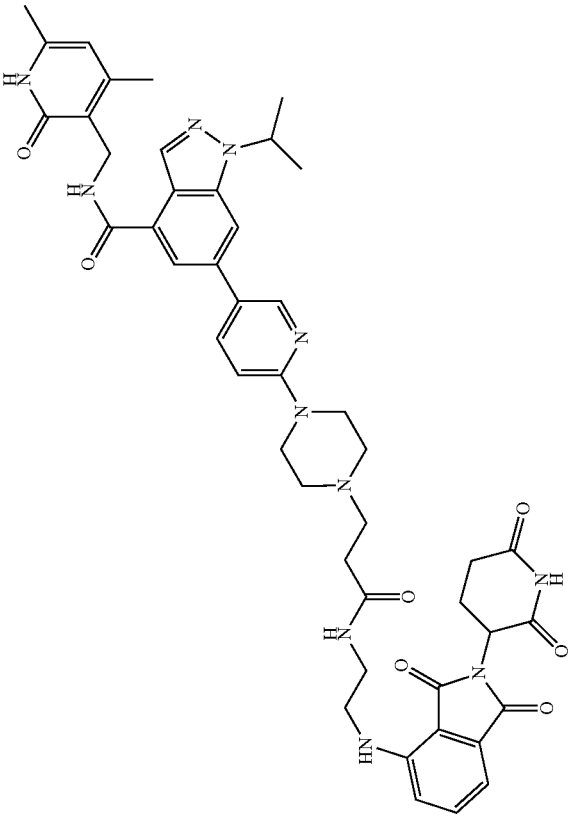
	Structure	Chemical Name
AM29-137A		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-(6-(4-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethyl)amino)-3-oxopropyl)piperazin-1-yl)pyridin-3-yl)-1-isopropyl-1H-indazole-4-carboxamide

TABLE 1-continued

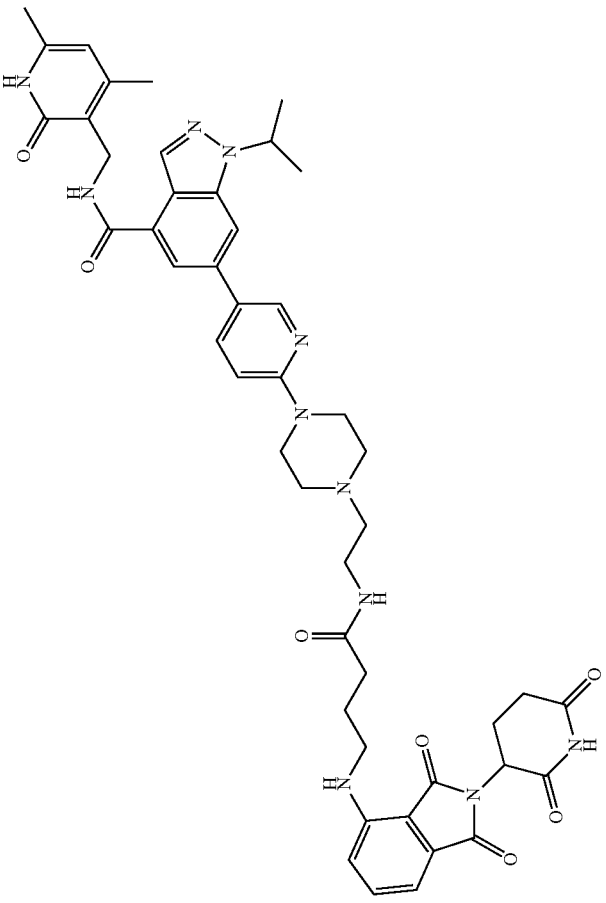
	Structure	Chemical Name
AM29-153A		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-(6-(4-(2-(4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)butanamido)ethyl)piperazin-1-yl)pyridin-3-yl)-1-isopropyl-1H-indazole-4-carboxamide

TABLE 1-continued

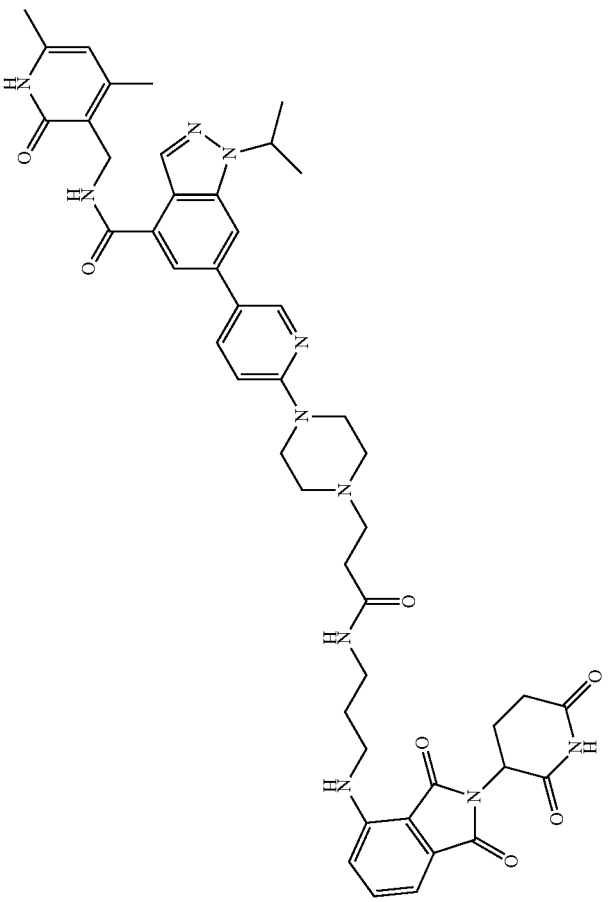
	Structure	Chemical Name
AM29-138A		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-(6-(4-(3-((3-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propyl)amino)-3-oxopropyl)piperazin-1-yl)pyridin-3-yl)-1-isopropyl-1H-indazole-4-carboxamide

TABLE 1-continued

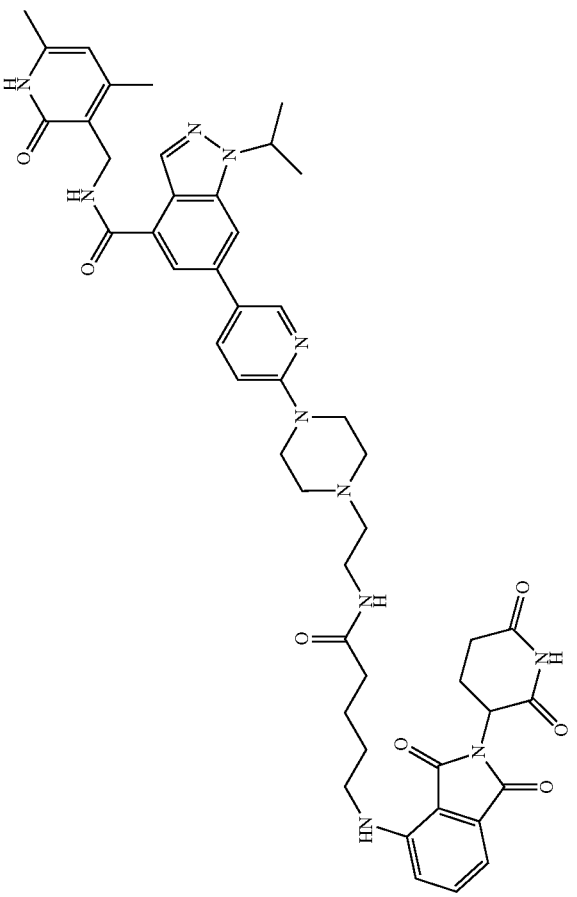
	Structure	Chemical Name
AM29-154A		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-(6-(4-(2-(5-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)pentanamido)ethyl)piperazin-1-yl)pyridin-3-yl)-1-isopropyl-1H-indazole-4-carboxamide

TABLE 1-continued

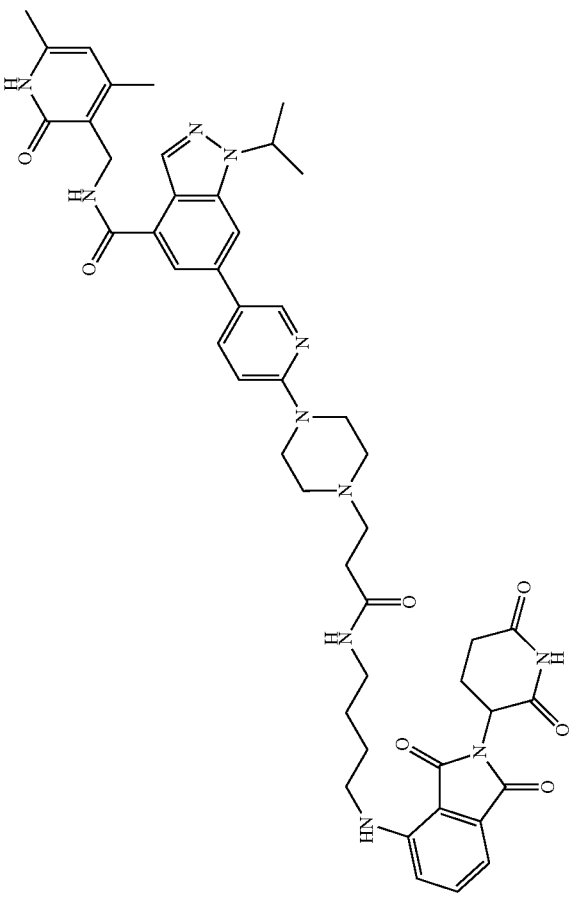
	Structure	Chemical Name
AM29-139A		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-(6-(4-(3-((4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)butyl)amino)-3-oxopropyl)piperazin-1-yl)pyridin-3-yl)-1-isopropyl-1H-indazole-4-carboxamide

TABLE 1-continued

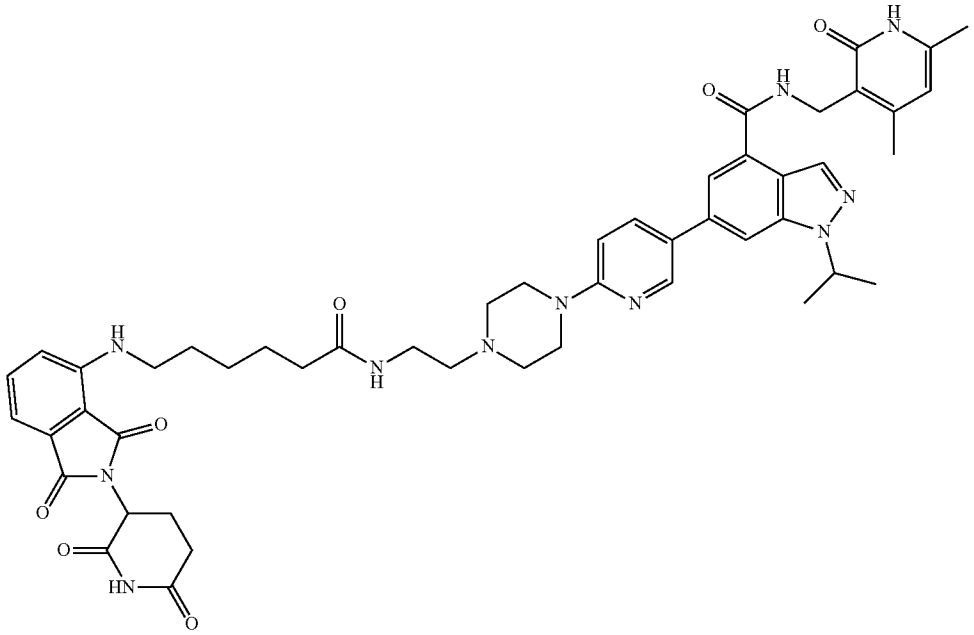
	Structure	Chemical Name
AM29-155A		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-(6-(4-(2-(6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)hexanamido)ethyl)piperazin-1-yl)pyridin-3-yl)-1-isopropyl-1H-indazole-4-carboxamide

TABLE 1-continued

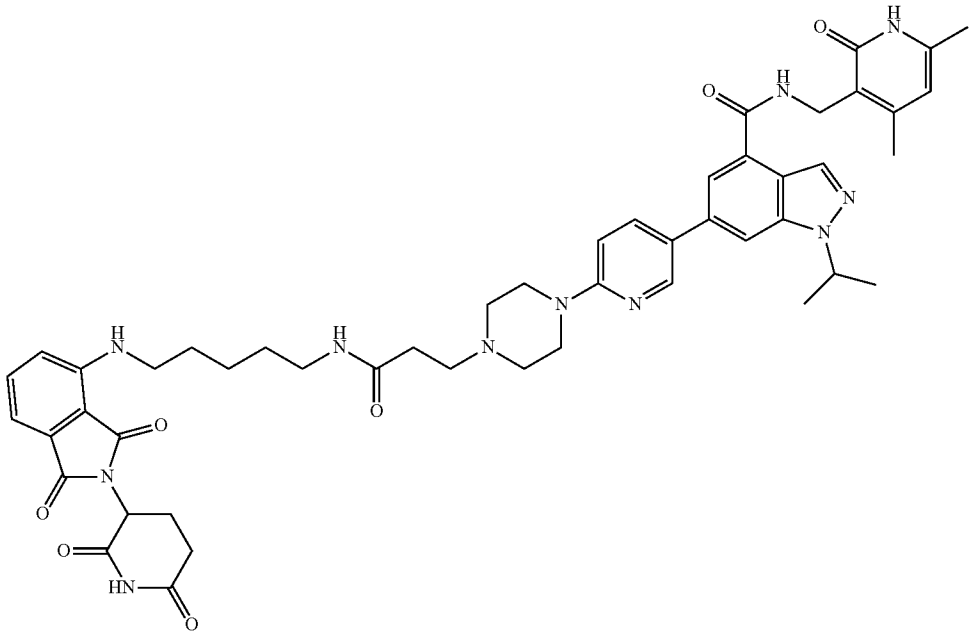
	Structure	Chemical Name
AM29-170A		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-(6-(4-(3-(5-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)pentyl)amino)-3-oxopropyl)piperazin-1-yl)pyridin-3-yl)-1-isopropyl-1H-indazole-4-carboxamide

TABLE 1-continued

	Structure	Chemical Name
AM29-156A		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-(6-(4-(2-(7-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)heptanamido)ethyl)piperazin-1-yl)pyridin-3-yl)-1-isopropyl-1H-indazole-4-carboxamide

TABLE 1-continued

	Structure	Chemical Name
AM29-171A		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-(6-(4-(3-((6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)hexyl)amino)-3-oxopropyl)piperazin-1-yl)pyridin-3-yl)-1-isopropyl-1H-indazole-4-carboxamide

TABLE 1-continued

	Structure	Chemical Name
AM29-157A		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-(6-(4-(2-(8-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)octanamido)ethyl)piperazin-1-yl)pyridin-3-yl)-1-isopropyl-1H-indazole-4-carboxamide

TABLE 1-continued

	Structure	Chemical Name
AM29-172A		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-(6-(4-(3-((7-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)heptyl)amino)-3-oxopropyl)piperazin-1-yl)pyridin-3-yl)-1-isopropyl-1H-indazole-4-carboxamide

TABLE 1-continued

	Structure	Chemical Name
AM29-173A		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-(6-(4-(3-((8-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)octyl)amino)-3-oxopropyl)piperazin-1-yl)pyridin-3-yl)-1-isopropyl-1H-indazole-4-carboxamide

TABLE 1-continued

	Structure	Chemical Name
AM16-79A		6-(6-(4-(1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-12-oxo-3,6,9-trioxa-13-azapentadecan-15-yl)piperazin-1-yl)pyridin-3-yl)-1-isopropyl-N-((6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl)-1H-indazole-4-carboxamide

TABLE 1-continued

	Structure	Chemical Name
AM29-177A		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-(6-(4-(2-(3-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)propanamido)ethyl)piperazin-1-yl)pyridin-3-yl)-1-isopropyl-1H-indazole-4-carboxamide

TABLE 1-continued

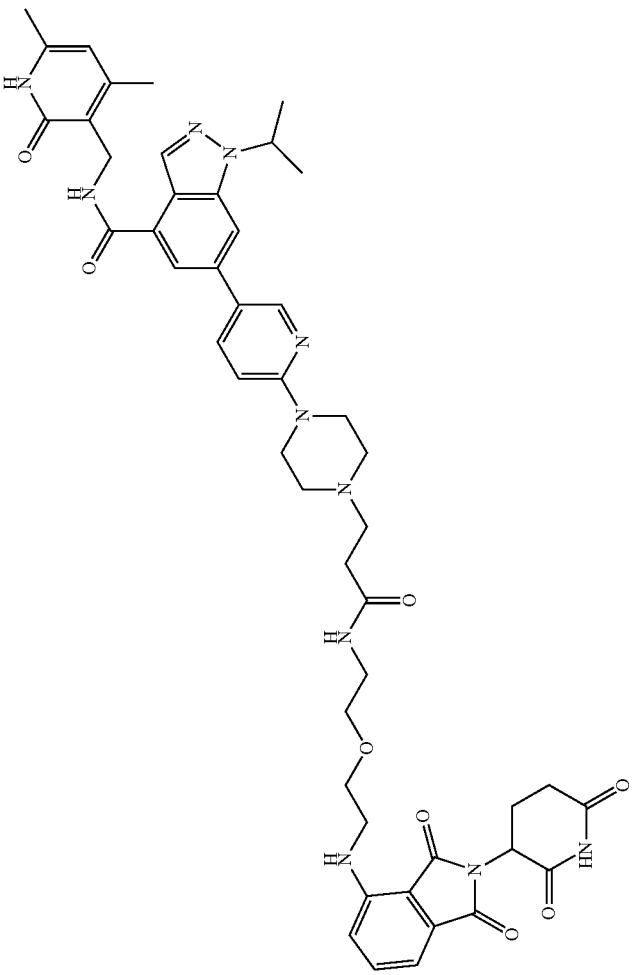
	Structure	Chemical Name
AM29-141A		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-(6-(4-(3-((2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethyl)amino)-3-oxopropyl)piperazin-1-yl)pyridin-3-yl)-1-isopropyl-1H-indazole-4-carboxamide

TABLE 1-continued

	Structure	Chemical Name
AM29-178A		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-(6-(4-(2-(3-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)propanamido)ethyl)piperazin-1-yl)pyridin-3-yl)-1-isopropyl-1H-indazole-4-carboxamide

TABLE 1-continued

	Structure	Chemical Name
AM29-142A		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-(6-(4-(3-((2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethyl)amino)-3-oxopropyl)piperazin-1-yl)pyridin-3-yl)-1-isopropyl-1H-indazole-4-carboxamide

TABLE 1-continued

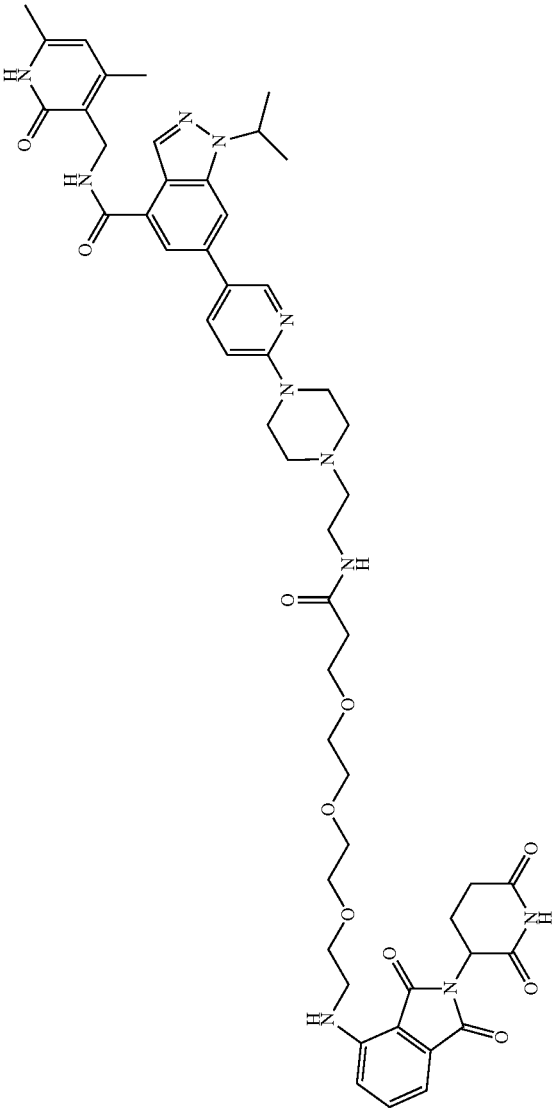
	Structure	Chemical Name
AM29-179A		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-(6-(4-(1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-12-oxo-3,6,9-trioxa-13-azapentadecan-15-yl)piperazin-1-yl)pyridin-3-yl)-1-isopropyl-1H-indazole-4-carboxamide

TABLE 1-continued

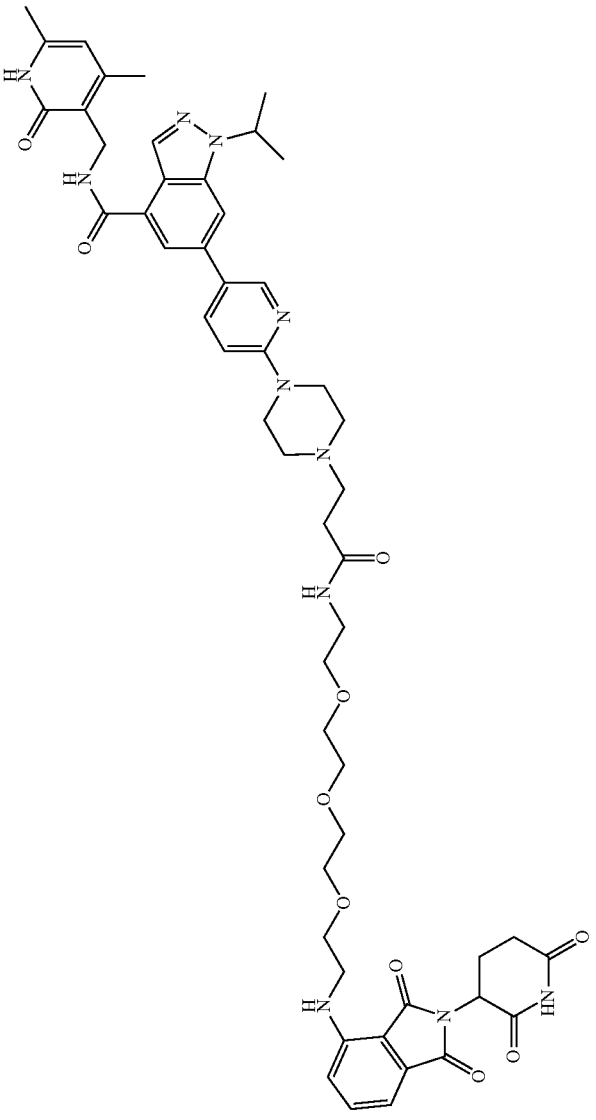
	Structure	Chemical Name
AM29-143A		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-(6-(4-(1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-13-oxo-3,6,9-trioxa-12-azapentadecan-15-yl)piperazin-1-yl)pyridin-3-yl)-1-isopropyl-1H-indazole-4-carboxamide

TABLE 1-continued

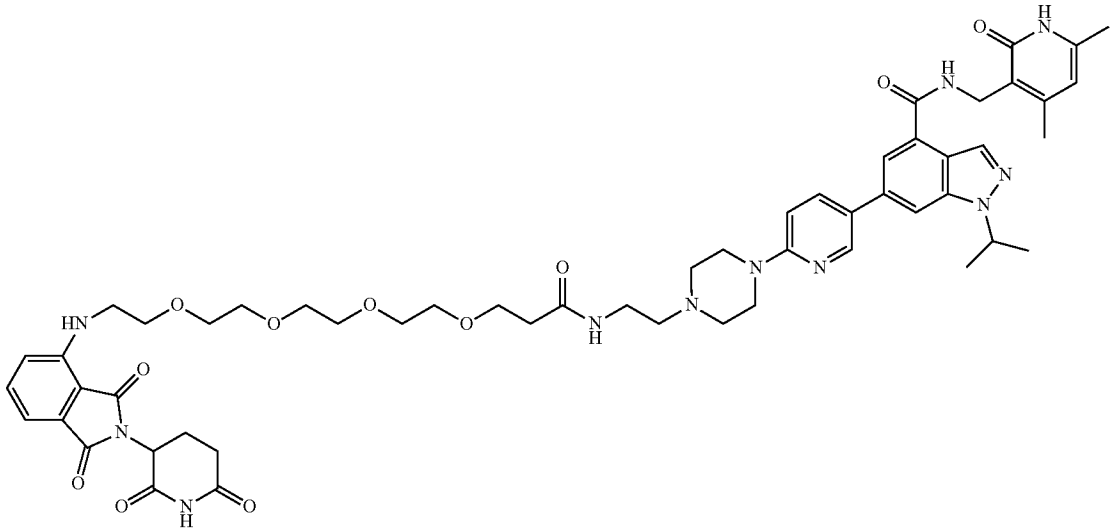
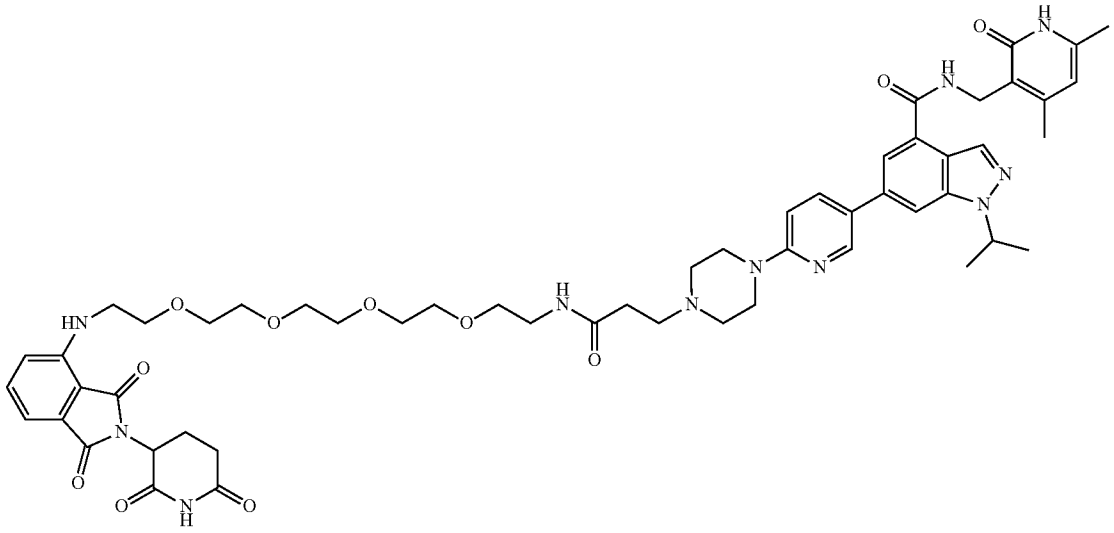
	Structure	Chemical Name
AM29-180A		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-(6-(4-(1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-15-oxo-3,6,9,12-tetraoxa-16-azaoctadecan-18-yl)piperazin-1-yl)pyridin-3-yl)-1-isopropyl-1H-indazole-4-carboxamide
AM29-144A		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-(6-(4-(1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-16-oxo-3,6,9,12-tetraoxa-15-azaoctadecan-18-yl)piperazin-1-yl)pyridin-3-yl)-1-isopropyl-1H-indazole-4-carboxamide

TABLE 1-continued

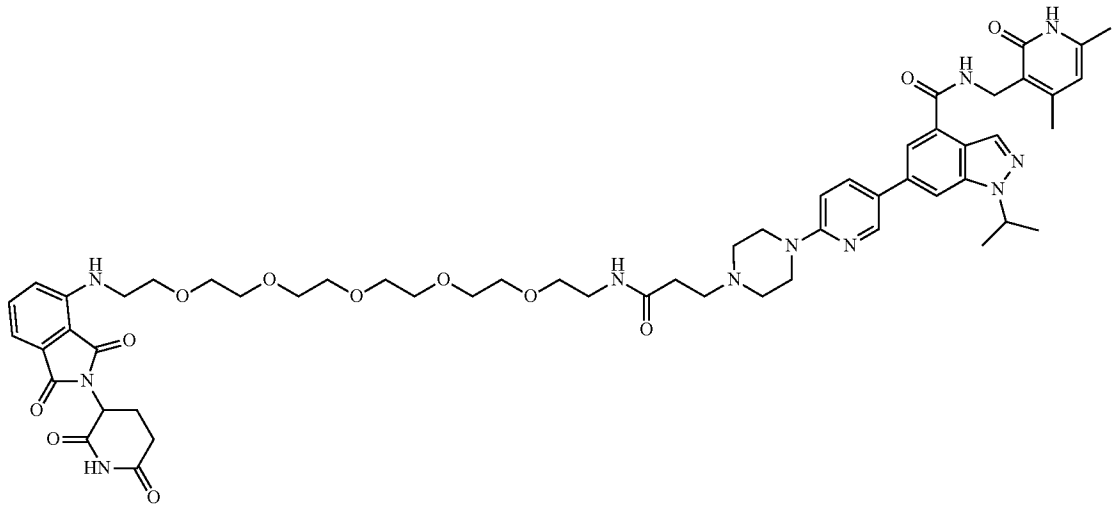
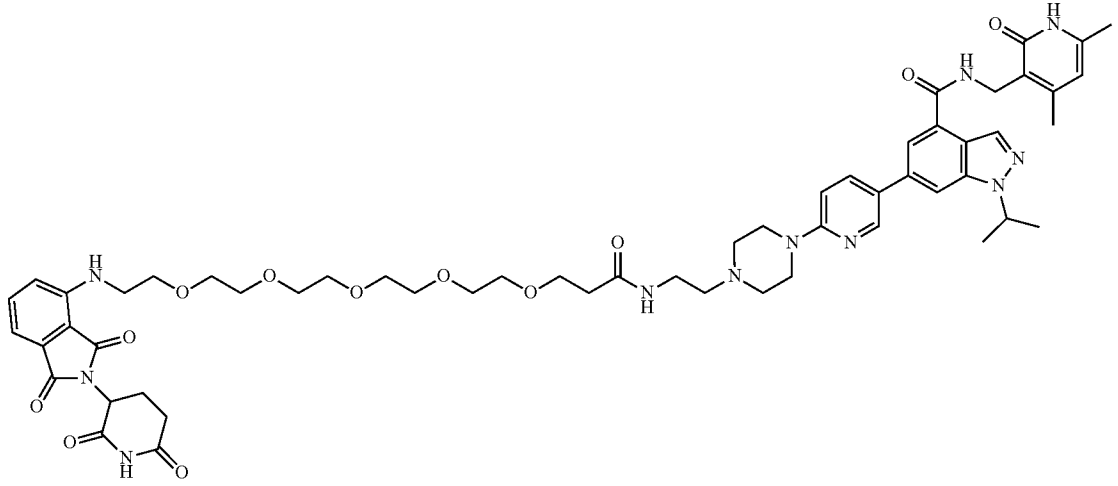
	Structure	Chemical Name
AM29-145A		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-(6-(4-(1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-19-oxo-3,6,9,12,15-pentaoxa-18-azahenicosan-21-yl)piperazin-1-yl)pyridin-3-yl)-1-isopropyl-1H-indazole-4-carboxamide
AM29-181A		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-(6-(4-(1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-18-oxo-3,6,9,12,15-pentaoxa-19-azahenicosan-21-yl)piperazin-1-yl)pyridin-3-yl)-1-isopropyl-1H-indazole-4-carboxamide

TABLE 1-continued

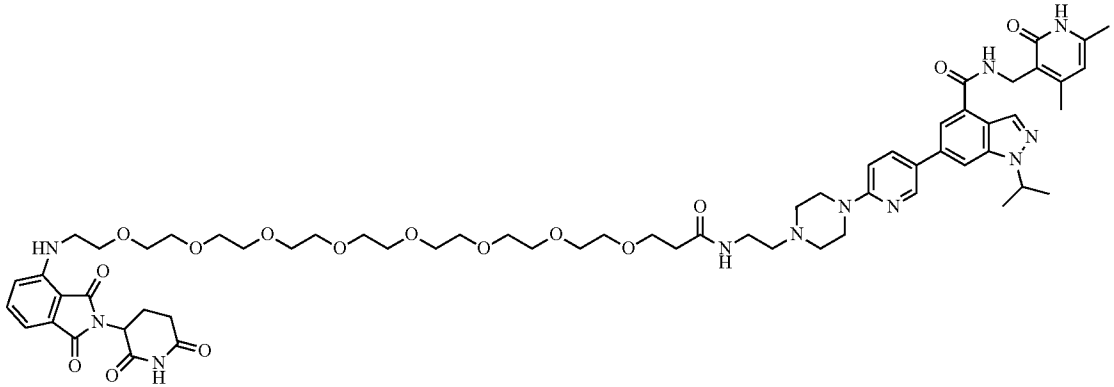
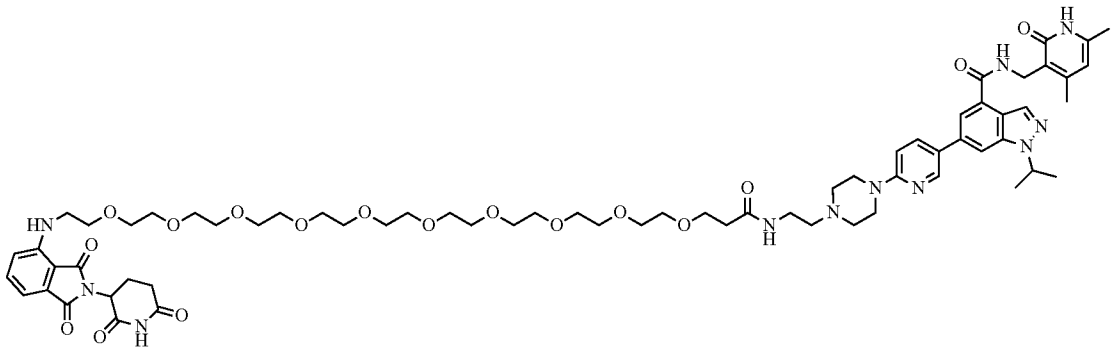
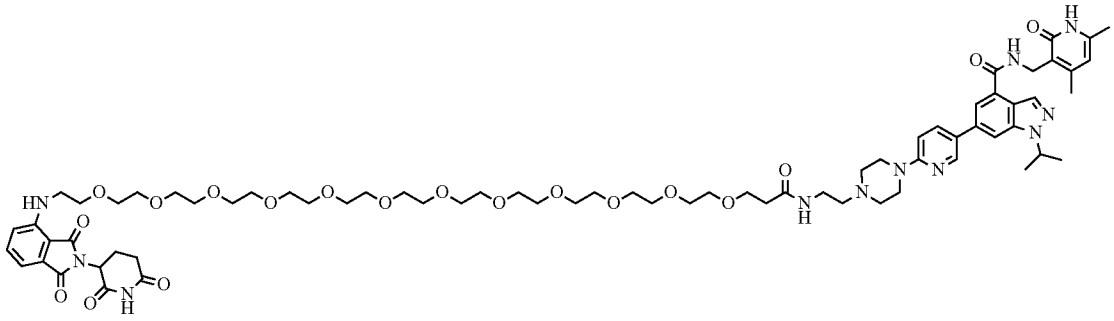
	Structure	Chemical Name
AM41-16A		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-(6-(4-(1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-27-oxo-3,6,9,12,15,18,21,24-octaoxa-28-azatriacontan-30-yl)piperazin-1-yl)pyridin-3-yl)-1-isopropyl-1H-indazole-4-carboxamide
AM41-17A		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-(6-(4-(1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-33-oxo-3,6,9,12,15,18,21,24,27,30-decaoxa-34-azahexatriacontan-36-yl)piperazin-1-yl)pyridin-3-yl)-1-isopropyl-1H-indazole-4-carboxamide
AM41-18A		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-(6-(4-(1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-39-oxo-3,6,9,12,15,18,21,24,27,30,33,36-dodecaoxa-40-azadotetracontan-42-yl)piperazin-1-yl)pyridin-3-yl)-1-isopropyl-1H-indazole-4-carboxamide

TABLE 1-continued

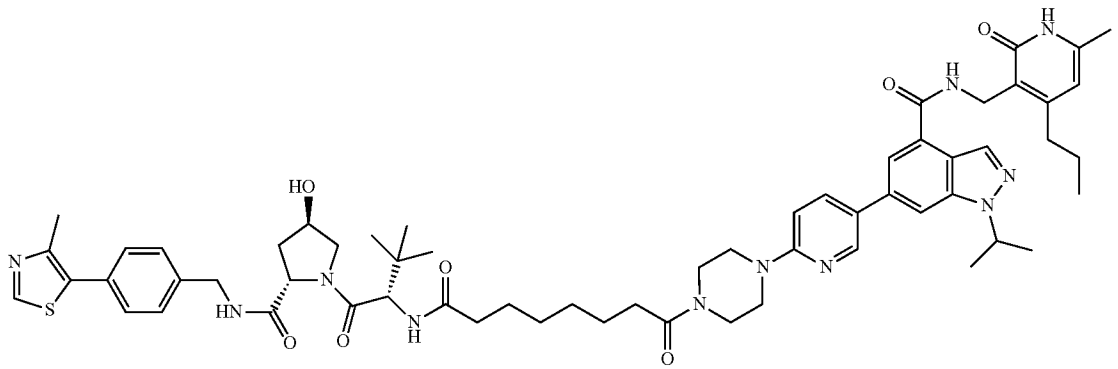
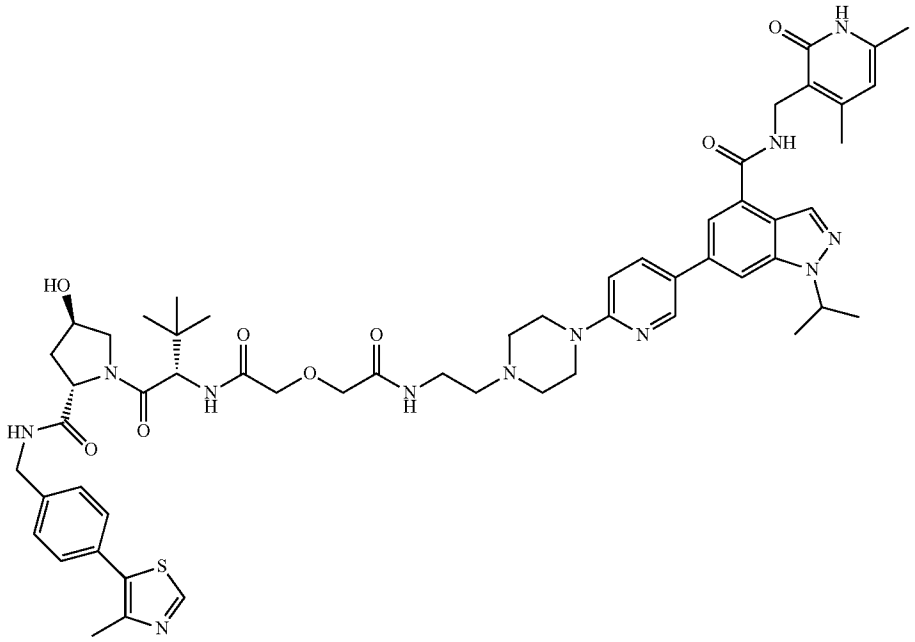
	Structure	Chemical Name
XY012-157		6-(6-(4-(8-(((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-8-oxooctanoyl)piperazin-1-yl)pyridin-3-yl)-1-isopropyl-N-((6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl)-1H-indazole-4-carboxamide
XF034-164A		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-(6-(4-(2-(2-(2-(((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-2-oxoethoxy)acetamido)ethyl)piperazin-1-yl)pyridin-3-yl)-1-isopropyl-1H-indazole-4-carboxamide

TABLE 1-continued

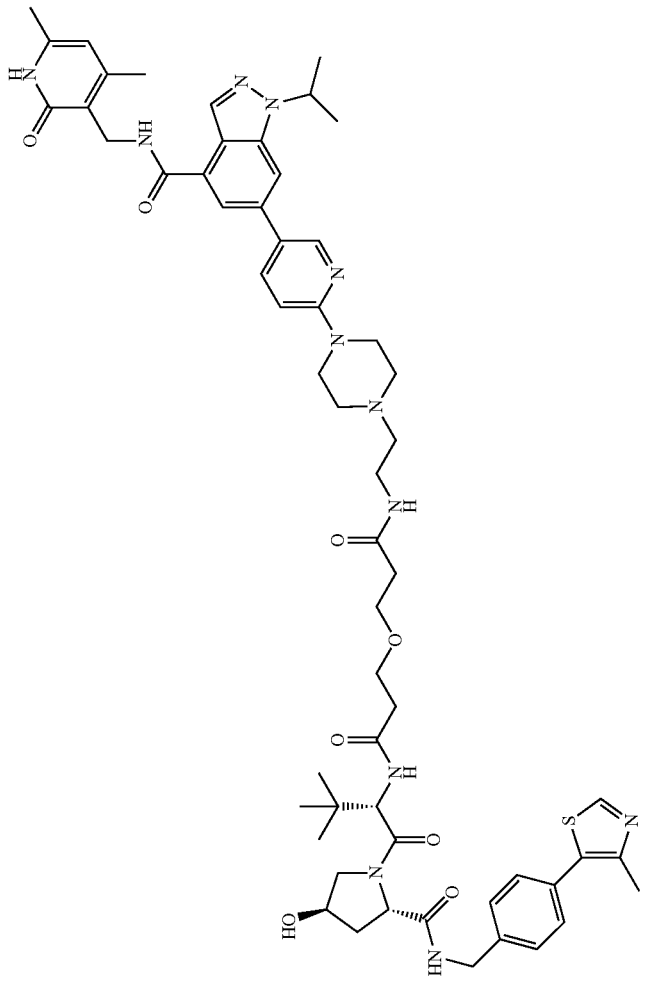
	Structure	Chemical Name
XF034-165A		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-(6-(4-(2-(3-(3-(((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-3-oxopropoxy)propanamido)ethyl)piperazin-1-yl)pyridin-3-yl)-1-isopropyl-1H-indazole-4-carboxamide

TABLE 1-continued

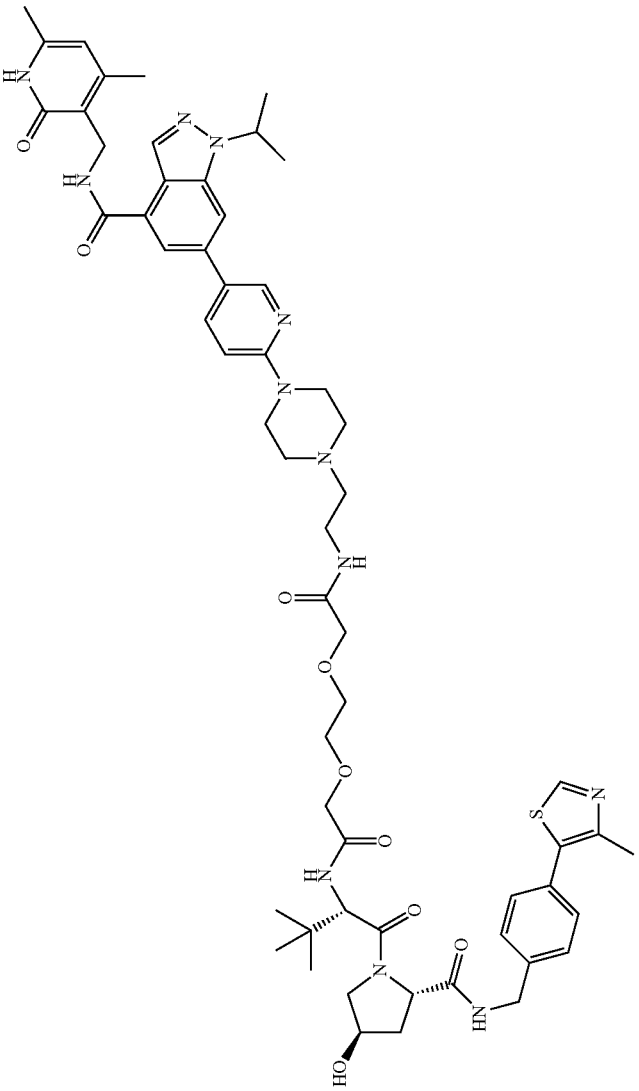
	Structure	Chemical Name
XF034-166A		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-(6-(4-((S)-13-(2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-14,14-dimethyl-4,11-dioxo-6,9-dioxa-3,12-diazapentadecyl)piperazin-1-yl)pyridin-3-yl)-1-isopropyl-1H-indazole-4-carboxamide

TABLE 1-continued

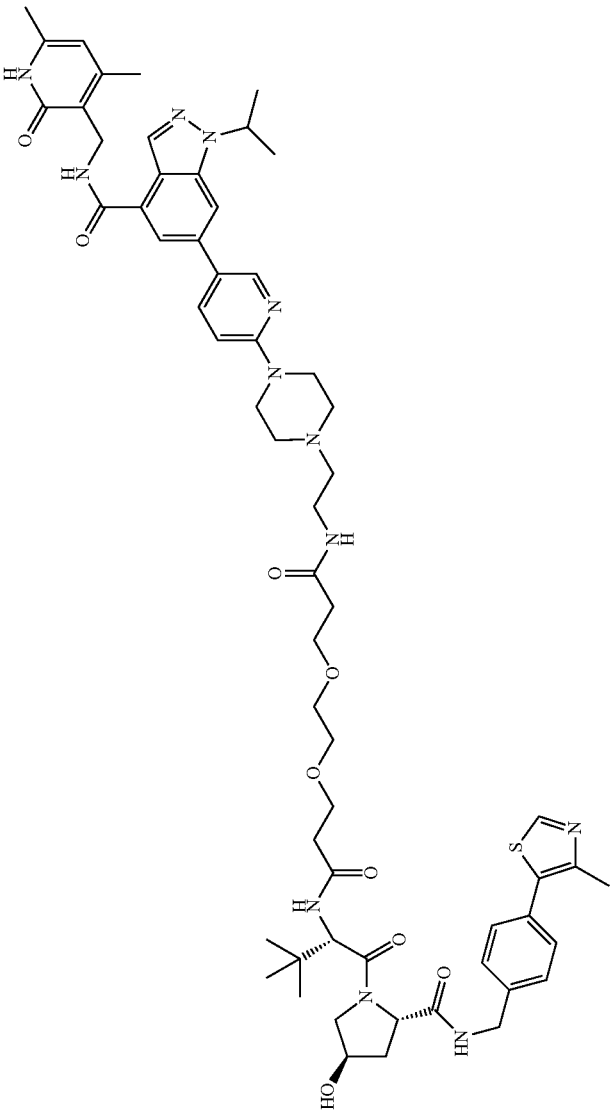
	Structure	Chemical Name
XF034-167A		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-(6-(4-((S)-15-(2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-16,16-dimethyl-4,13-dioxo-7,10-dioxa-3,14-diazaheptadecyl)piperazin-1-yl)pyridin-3-yl)-1-isopropyl-1H-indazole-4-carboxamide

TABLE 1-continued

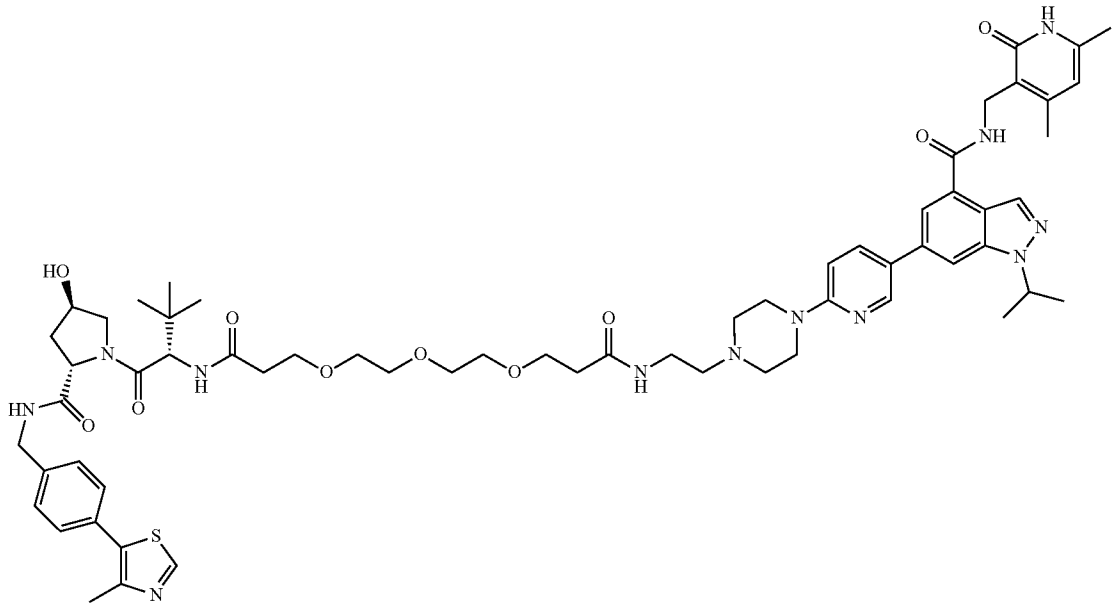
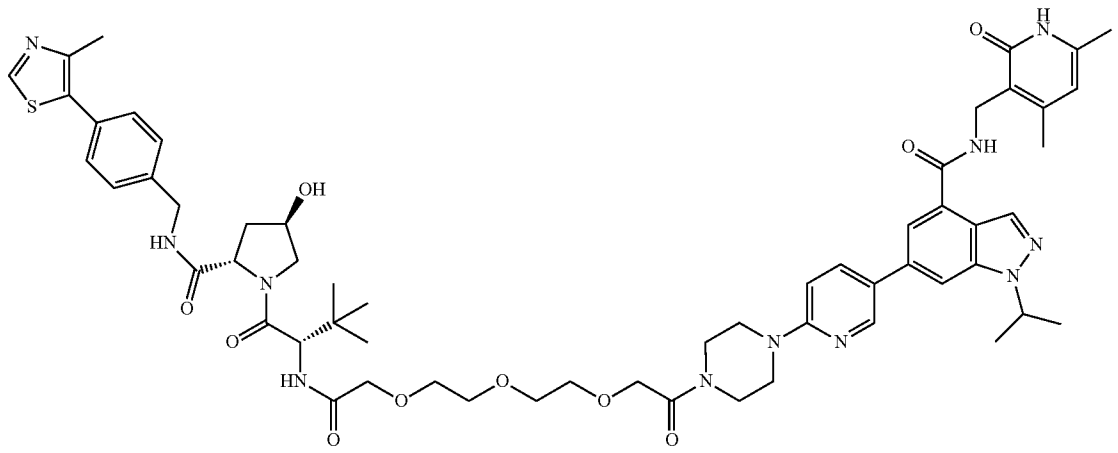
	Structure	Chemical Name
XF034-168A		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-(6-(4-((S)-18-(2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-19,19-dimethyl-4,16-dioxo-7,10,13-trioxa-3,17-diazaicosyl)piperazin-1-yl)pyridin-3-yl)-1-isopropyl-1H-indazole-4-carboxamide
XY019-041		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-(6-(4-((S)-13-(2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-14,14-dimethyl-11-oxo-3,6,9-trioxa-12-azapentadecanoyl)piperazin-1-yl)pyridin-3-yl)-1-isopropyl-1H-indazole-4-carboxamide

TABLE 1-continued

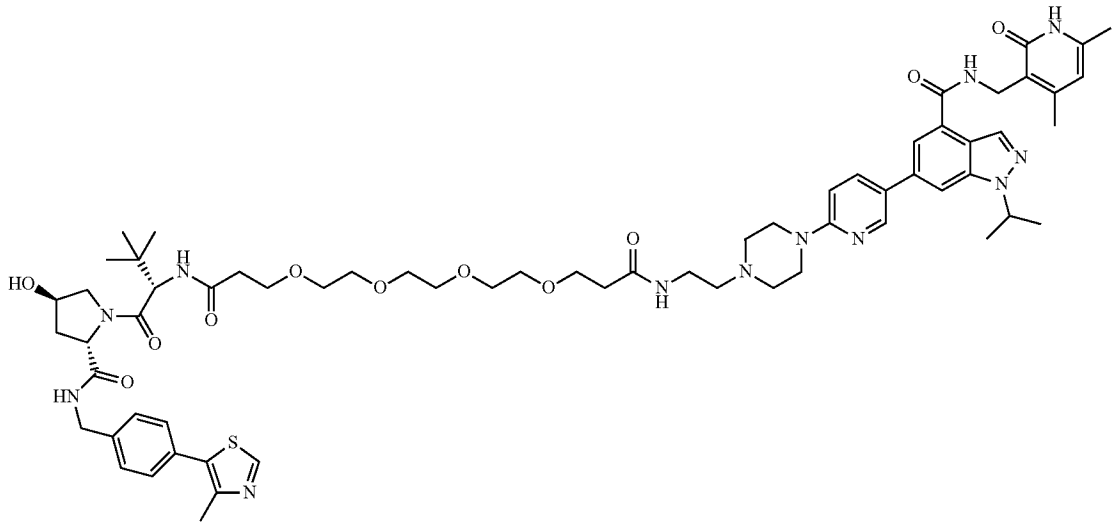
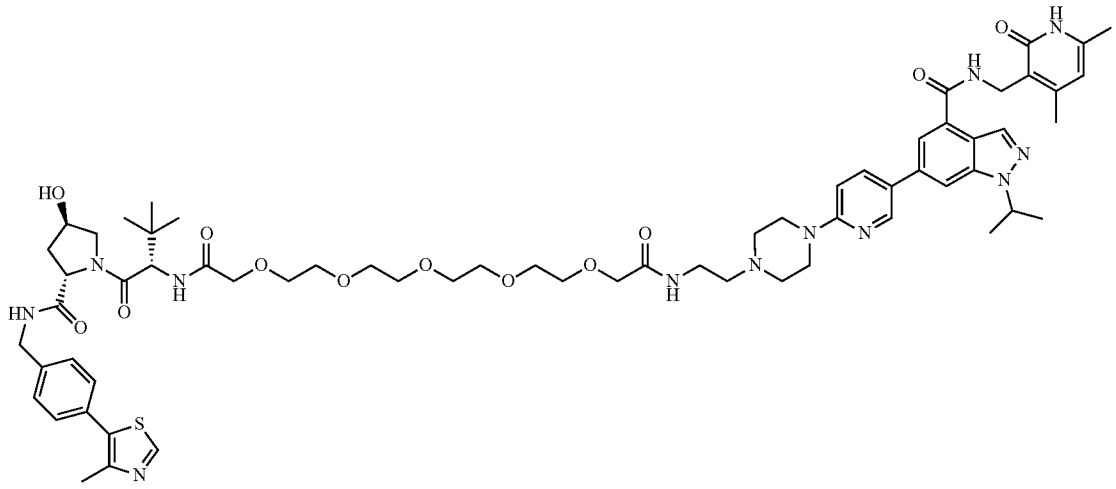
	Structure	Chemical Name
XF034-169A		N^1-(2-(4-(5-(4-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-1-isopropyl-1H-indazol-6-yl)pyridin-2-yl)piperazin-1-yl)ethyl)-N16-((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-4,7,10,13-tetraoxahexadecanediamide
XF034-170A		N^1-(2-(4-(5-(4-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-1-isopropyl-1H-indazol-6-yl)pyridin-2-yl)piperazin-1-yl)ethyl)-N^{17}-((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-3,6,9,12,15-pentaoxaheptadecanediamide

TABLE 1-continued

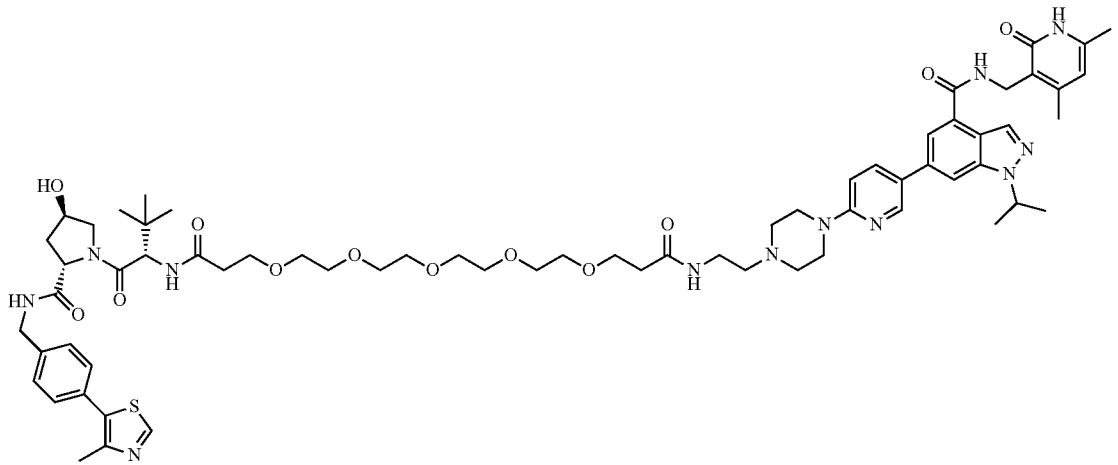
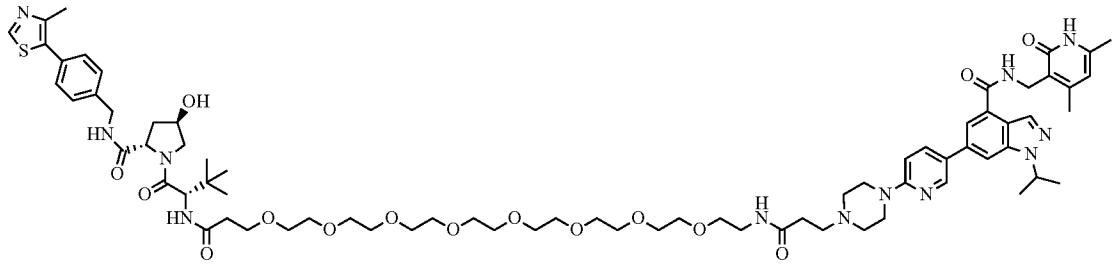
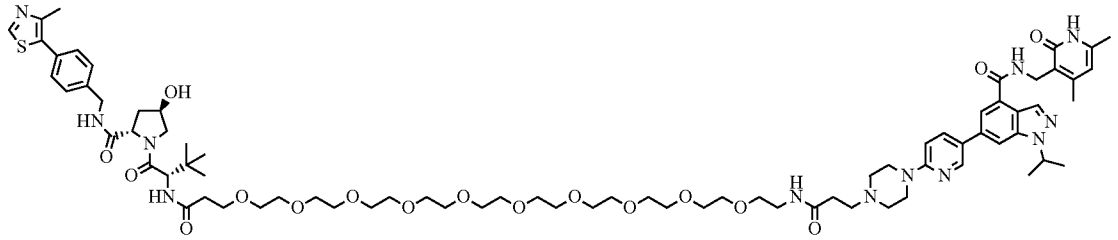
	Structure	Chemical Name
XF034-171A		N^1-(2-(4-(5-(4-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-1-isopropyl-1H-indazol-6-yl)pyridin-2-yl)piperazin-1-yl)ethyl)-N^{19}-((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-4,7,10,13,16-pentaoxanonadecanediamide
CZ40-10		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-(6-(4-((S)-33-(2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-34,34-dimethyl-3,31-dioxo-7,10,13,16,19,22,25,28-octaoxa-4,32-diazapentatriacontyl)piperazin-1-yl)pyridin-3-yl)-1-isopropyl-1H-indazole-4-carboxamide
CZ40-09		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-(6-(4-((S)-39-(2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-40,40-dimethyl-3,37-dioxo-7,10,13,16,19,22,25,28,31,34-decaoxa-4,38-diazahentetracontyl)piperazin-1-yl)pyridin-3-yl)-1-isopropyl-1H-indazole-4-carboxamide

TABLE 1-continued

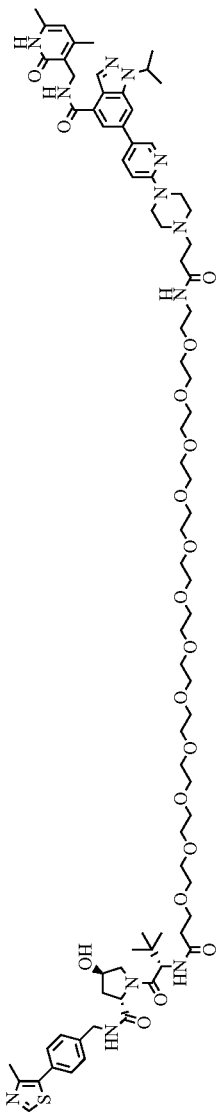
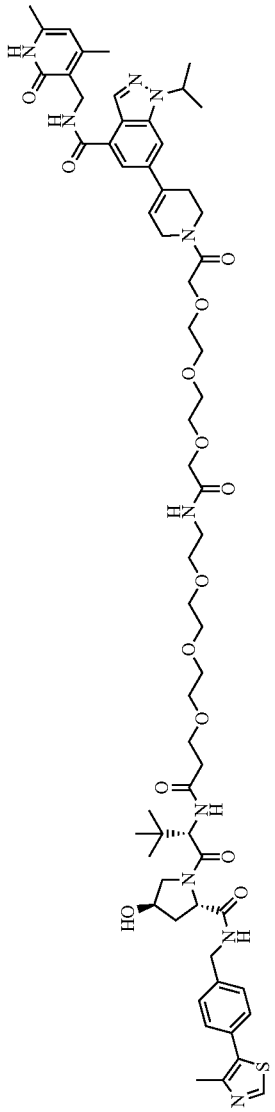
	Structure	Chemical Name
CZ40-11		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-(6-(4-((S)-45-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-46,46-dimethyl-3,43-dioxo-7,10,13,16,19,22,25,28,31,34,37,40-dodecaoxa-4,44-diazaheptatetracontyl)piperazin-1-yl)pyridin-3-yl)-1-isopropyl-1H-indazole-4-carboxamide
XY019-077		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-(1-((S)-13-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-14,14-dimethyl-11-oxo-3,6,9-trioxa-12-azapentadecanoyl)-1,2,3,6-tetrahydropyridin-4-yl)-1-isopropyl-1H-indazole-4-carboxamide
XY019-083		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-(1-((S)-26-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-27,27-dimethyl-11,24-dioxo-3,6,9,15,18,21-hexaoxa-12,25-diazaoctacosanoyl)-1,2,3,6-tetrahydropyridin-4-yl)-1-isopropyl-1H-indazole-4-carboxamide

TABLE 1-continued

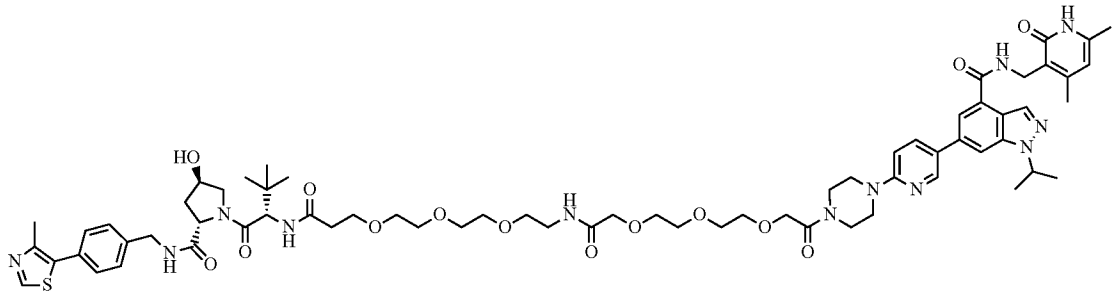
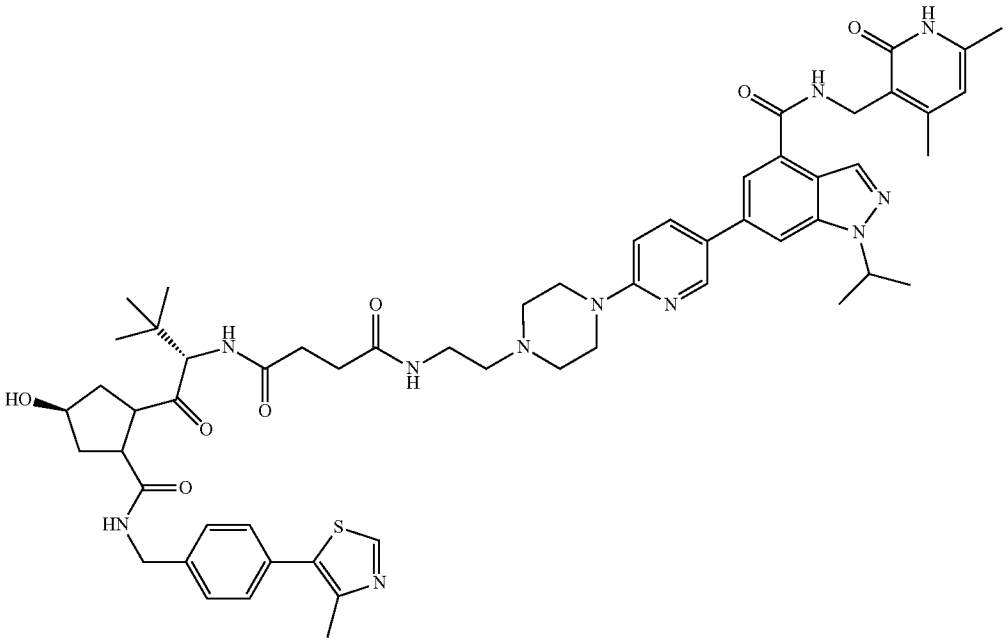
	Structure	Chemical Name
XY019-084		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-(6-(4-((S)-26-(2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-27,27-dimethyl-11,24-dioxo-3,6,9,15,18,21-hexaoxa-12,25-diazaoctacoctacosanoyl)piperazin-1-yl)pyridin-3-yl)-1-isopropyl-1H-indazole-4-carboxamide
XF034-172A		N^1-(2-(4-(5-(4-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-1-isopropyl-1H-indazol-6-yl)pyridin-2-yl)piperazin-1-yl)ethyl)-N^4-((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)succinamide

TABLE 1-continued

	Structure	Chemical Name
XF034-173A		N^1-(2-(4-(5-(4-((((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-1-isopropyl-1H-indazol-6-yl)pyridin-2-yl)piperazin-1-yl)ethyl)-N^5-((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)glutaramide

TABLE 1-continued

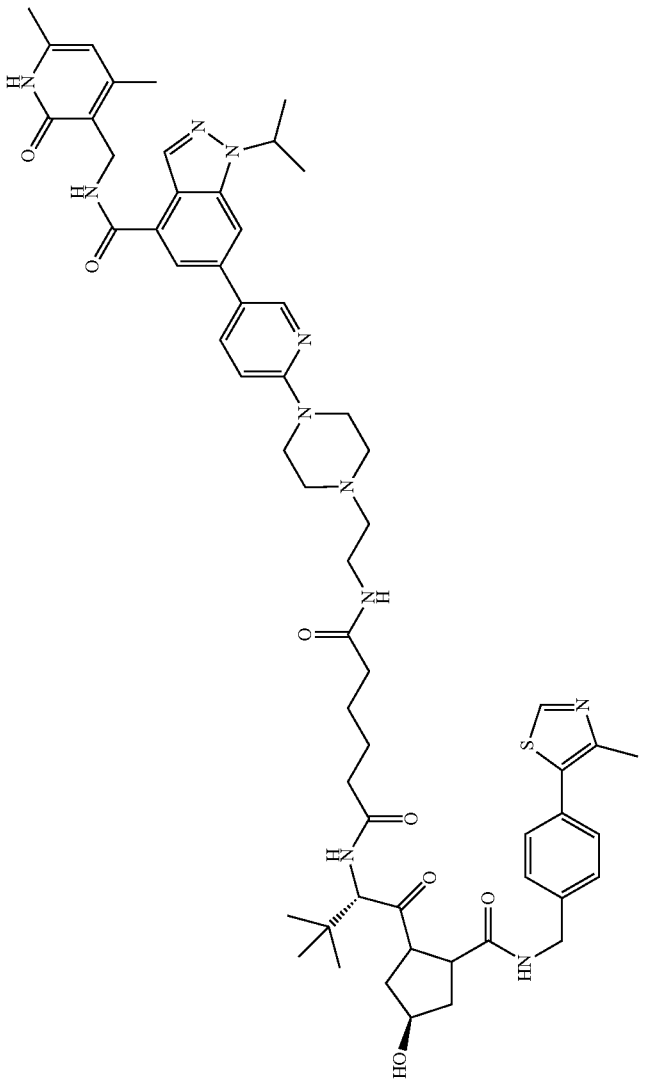
	Structure	Chemical Name
XF034-174A		N^1-(2-(4-(5-(4-((((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-1-isopropyl-1H-indazol-6-yl)pyridin-2-yl)piperazin-1-yl)ethyl)-N^6-((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)adipamide

TABLE 1-continued

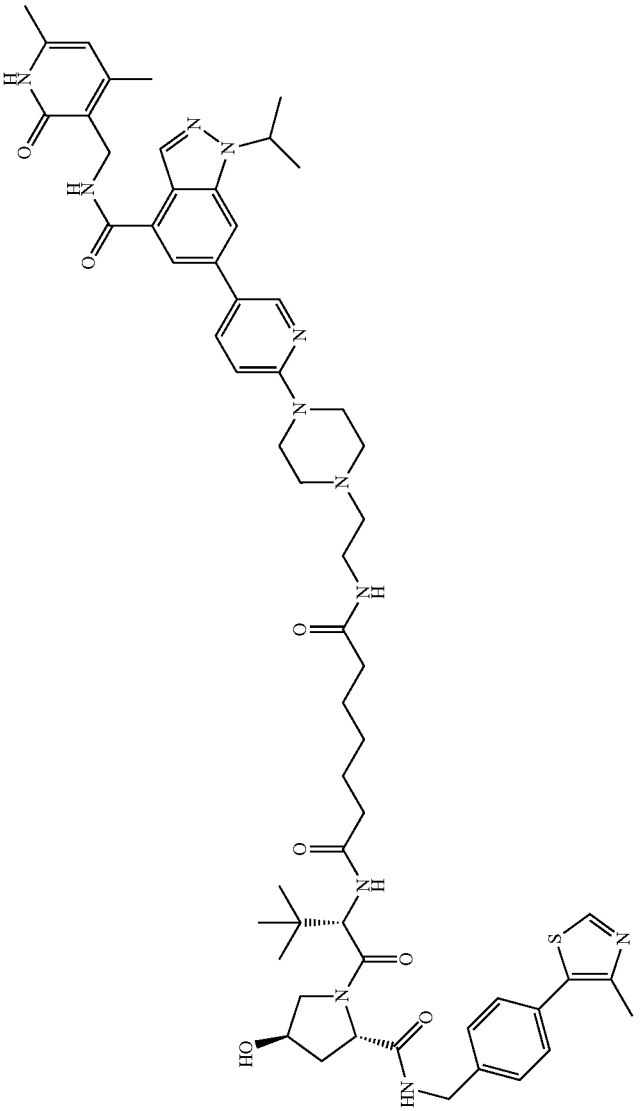
	Structure	Chemical Name
XF034-175A		N^1-(2-(4-(5-(4-((((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-1-isopropyl-1H-indazol-6-yl)pyridin-2-yl)piperazin-1-yl)ethyl)-N^7-((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)heptanediamide

TABLE 1-continued

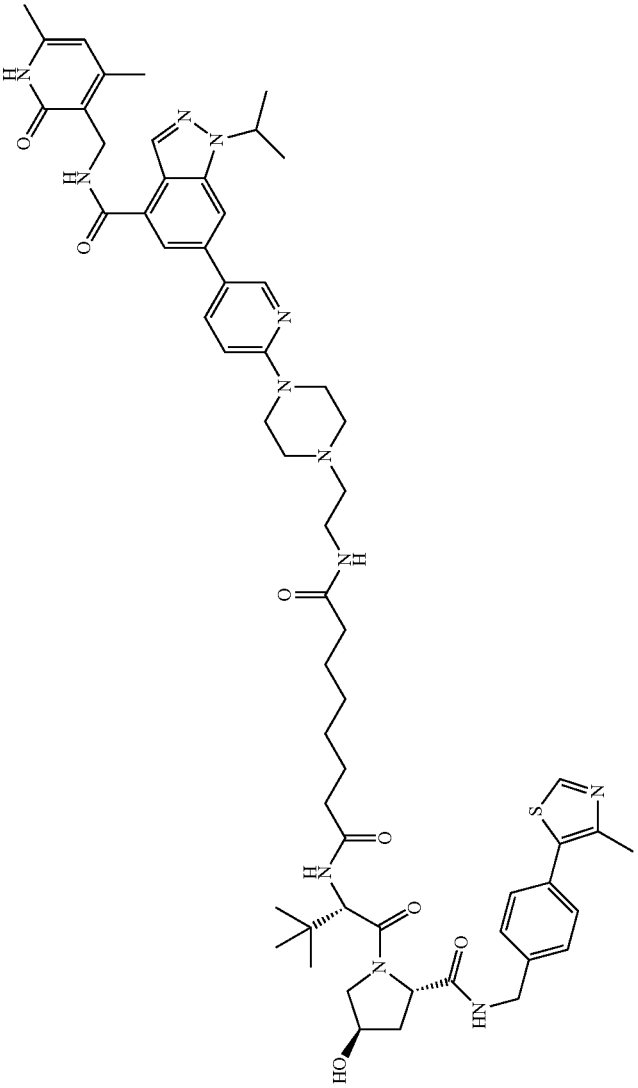
	Structure	Chemical Name
XF034-176A		N^1-(2-(4-(5-(4-((((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-1-isopropyl-1H-indazol-6-yl)pyridin-2-yl)piperazin-1-yl)ethyl)-N^8-((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)octanediamide

TABLE 1-continued

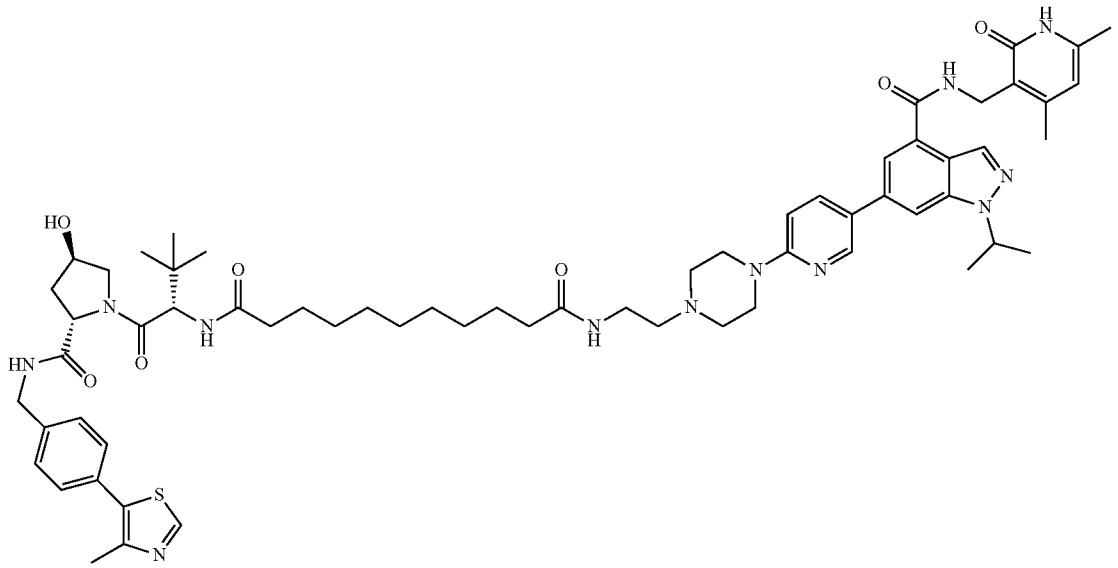
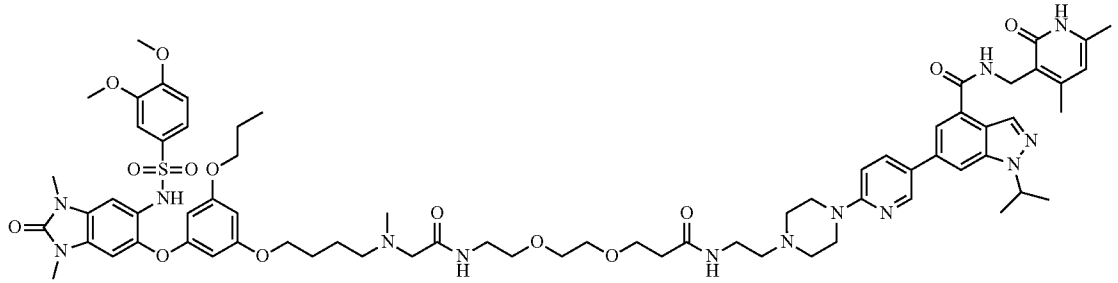
	Structure	Chemical Name
XF034-177A		N^1-(2-(4-(5-(4-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-1-isopropyl-1H-indazol-6-yl)pyridin-2-yl)piperazin-1-yl)ethyl)-N^{11}-((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)undecanediamide
YS36-48		6-(6-(4-(20-(3-((6-((3,4-dimethoxyphenyl)sulfonamido)-1,3-dimethyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)oxy)-5-propoxyphenoxy)-16-methyl-4,14-dioxo-7,10-dioxa-3,13,16-triazaicosyl)piperazin-1-yl)pyridin-3-yl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-isopropyl-1H-indazole-4-carboxamide

TABLE 1-continued

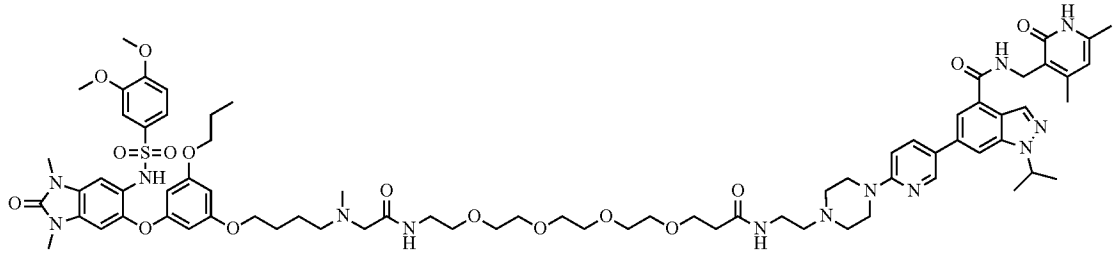
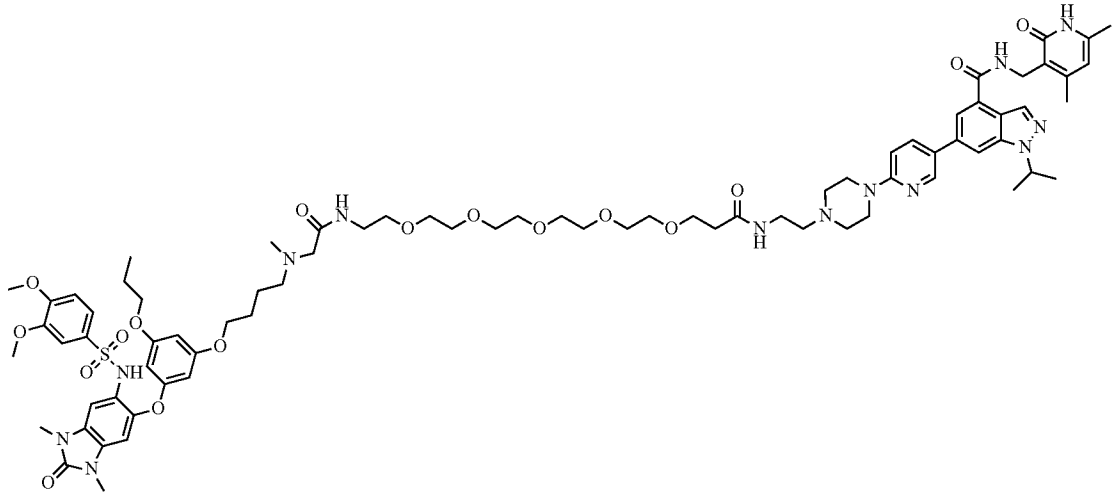
	Structure	Chemical Name
YS36-49		6-(6-(4-(26-(3-((6-((3,4-dimethoxyphenyl)sulfonamido)-1,3-dimethyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)oxy)-5-propoxyphenoxy)-22-methyl-4,20-dioxo-7,10,13,16-tetraoxa-3,19,22-triazahexacosyl)piperazin-1-yl)pyridin-3-yl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-isopropyl-1H-indazole-4-carboxamide
YS36-50		6-(6-(4-(29-(3-((6-((3,4-dimethoxyphenyl)sulfonamido)-1,3-dimethyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)oxy)-5-propoxyphenoxy)-25-methyl-4,23-dioxo-7,10,13,16,19-pentaoxa-3,22,25-triazanonacosybpiperazin-1-yl)pyridin-3-yl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-isopropyl-1H-indazole-4-carboxamide

TABLE 1-continued

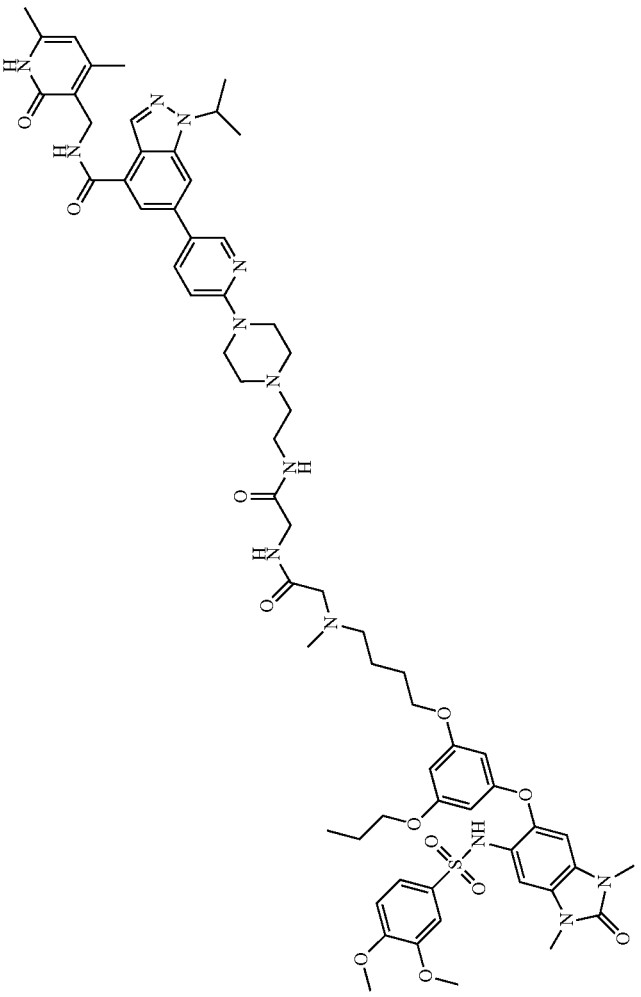
	Structure	Chemical Name
YS36-51		6-(6-(4-(2-(2-(2-((4-(3-((6-((3,4-dimethoxyphenyl)sulfonamido)-1,3-dimethyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)oxy)-5-propoxyphenoxy)butyl)(methyl)amino)acetamido)acetamido)ethyl)piperazin-1-yl)pyridin-3-yl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-isopropyl-1H-indazole-4-carboxamide

TABLE 1-continued

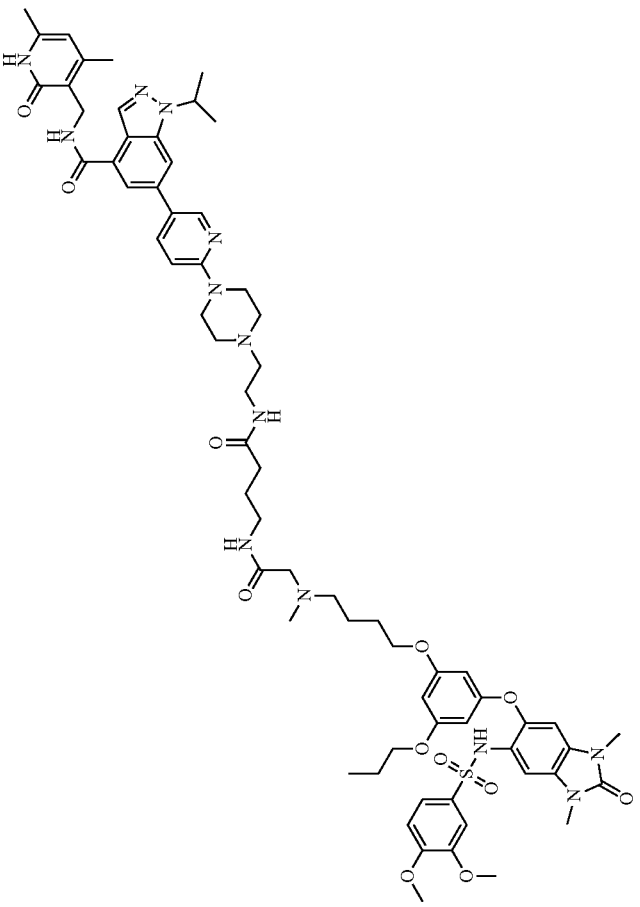
	Structure	Chemical Name
YS36-52		6-(6-(4-(2-(4-(2-((4-(3-((6-((3,4-dimethoxyphenyl)sulfonamido)-1,3-dimethyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)oxy)-5-propoxyphenoxy)butyl)(methyl)amino)acetamido)butanamido)ethyl)piperazin-1-yl)pyridin-3-yl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-isopropyl-1H-indazole-4-carboxamide

TABLE 1-continued

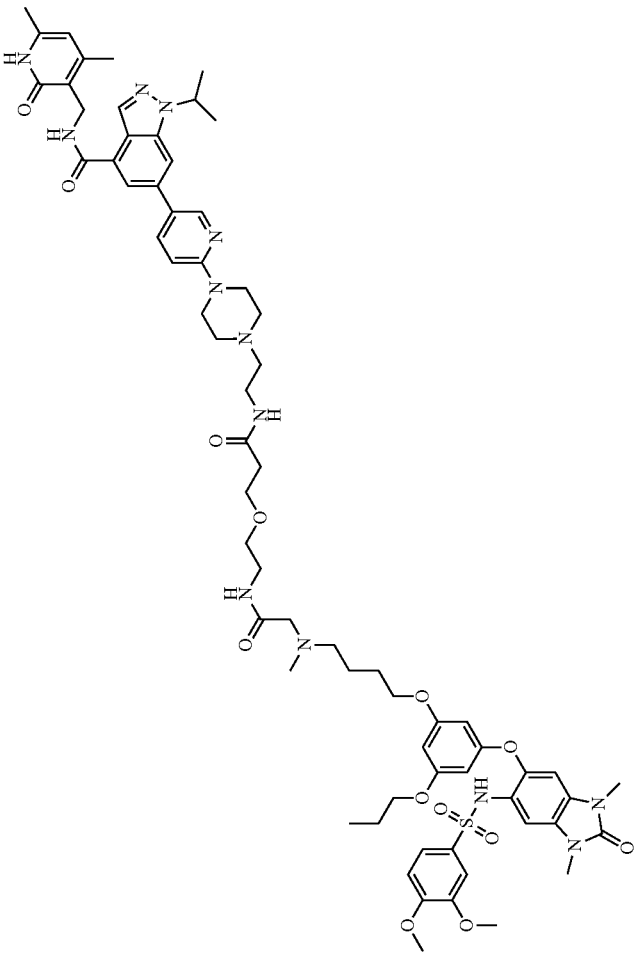
	Structure	Chemical Name
YS36-53		6-(6-(4-(17-(3-((6-((3,4-dimethoxyphenyl)sulfonamido)-1,3-dimethyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)oxy)-5-propoxyphenoxy)-13-methyl-4,11-dioxo-7-oxa-3,10,13-triazaheptadecyl)piperazin-1-yl)pyridin-3-yl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-isopropyl-1H-indazole-4-carboxamide

TABLE 1-continued

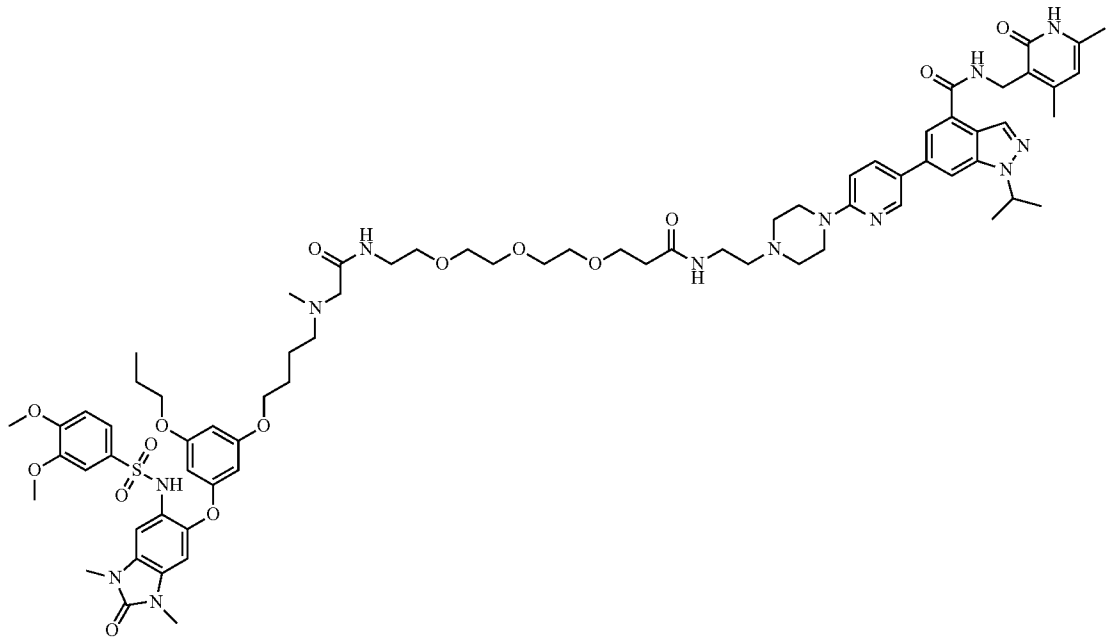
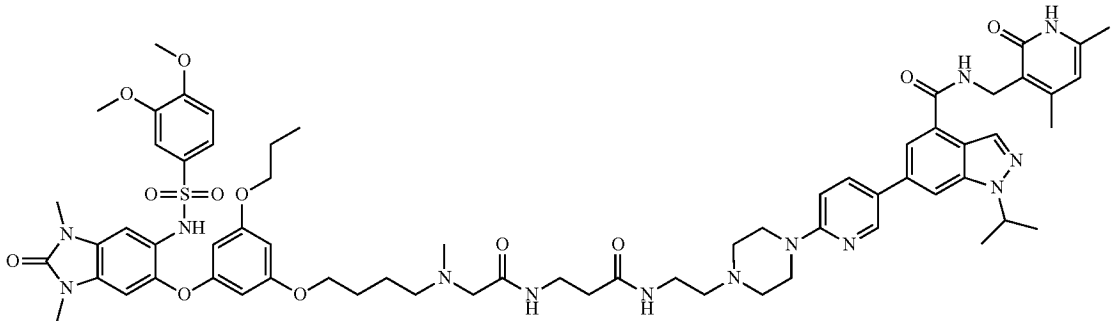
	Structure	Chemical Name
YS36-54		6-(6-(4-(23-(3-((6-((3,4-dimethoxyphenyl)sulfonamido)-1,3-dimethyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)oxy)-5-propoxyphenoxy)-19-methyl-4,17-dioxo-7,10,13-trioxa-3,16,19-triazatricosyl)piperazin-1-yl)pyridin-3-yl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-isopropyl-1H-indazole-4-carboxamide
YS36-55		6-(6-(4-(2-(3-(2-((4-(3-((6-((3,4-dimethoxyphenyl)sulfonamido)-1,3-dimethyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)oxy)-5-propoxyphenoxy)butyl)(methyl)amino)acetamido)propanamido)ethyl)piperazin-1-yl)pyridin-3-yl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-isopropyl-1H-indazole-4-carboxamide

TABLE 1-continued

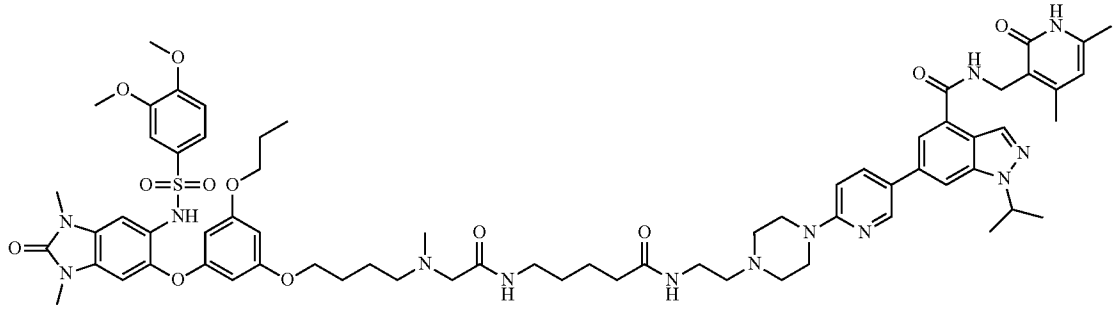
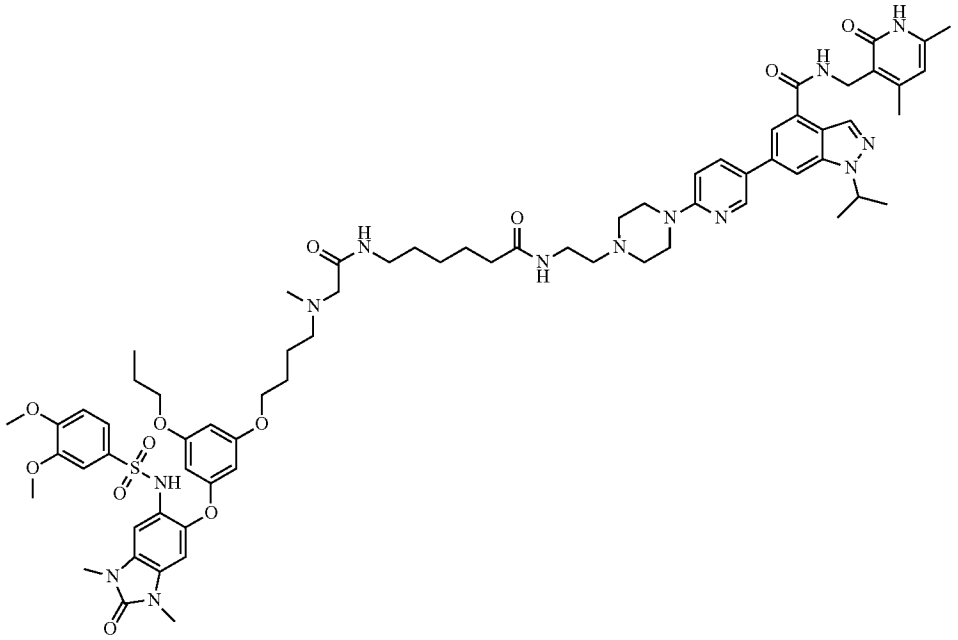
	Structure	Chemical Name
YS36-56		6-(6-(4-(2-(5-(2-((4-(3-((6-((3,4-dimethoxyphenyl)sulfonamido)-1,3-dimethyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)oxy)-5-propoxyphenoxy)butyl)(methyl)amino)acetamido)pentanamido)ethyl)piperazin-1-yl)pyridin-3-yl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-isopropyl-1H-indazole-4-carboxamide
YS36-57		6-(6-(4-(2-(6-(2-((4-(3-((6-((3,4-dimethoxyphenyl)sulfonamido)-1,3-dimethyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)oxy)-5-propoxyphenoxy)butyl)(methyl)amino)acetamido)hexanamido)ethyl)piperazin-1-yl)pyridin-3-yl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-isopropyl-1H-indazole-4-carboxamide

TABLE 1-continued

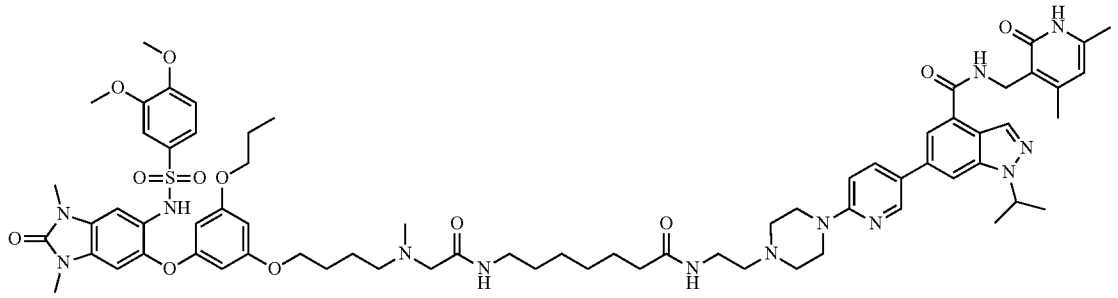
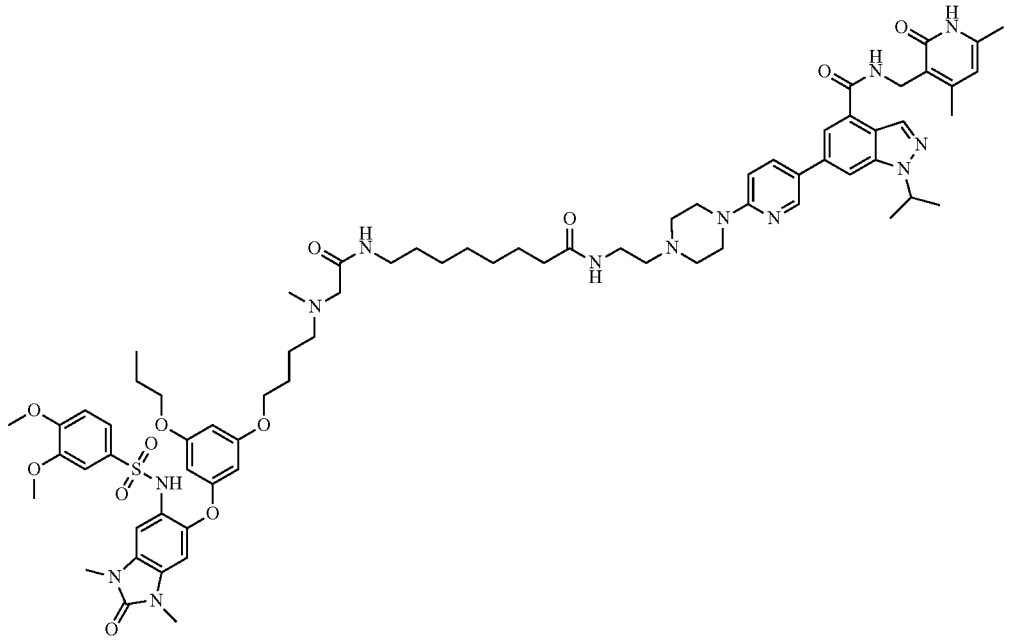
	Structure	Chemical Name
YS36-58		6-(6-(4-(2-(7-(2-((4-(3-((6-((3,4-dimethoxyphenyl)sulfonamido)-1,3-dimethyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)oxy)-5-propoxyphenoxy)butyl)(methyl)amino)acetamido)heptanamido)ethyl)piperazin-1-yl)pyridin-3-yl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-isopropyl-1H-indazole-4-carboxamide
YS36-59		6-(6-(4-(2-(8-(2-((4-(3-((6-((3,4-dimethoxyphenyl)sulfonamido)-1,3-dimethyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)oxy)-5-propoxyphenoxy)butyl)(methyl)amino)acetamido)octanamido)ethyl)piperazin-1-yl)pyridin-3-yl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-isopropyl-1H-indazole-4-carboxamide

TABLE 1-continued

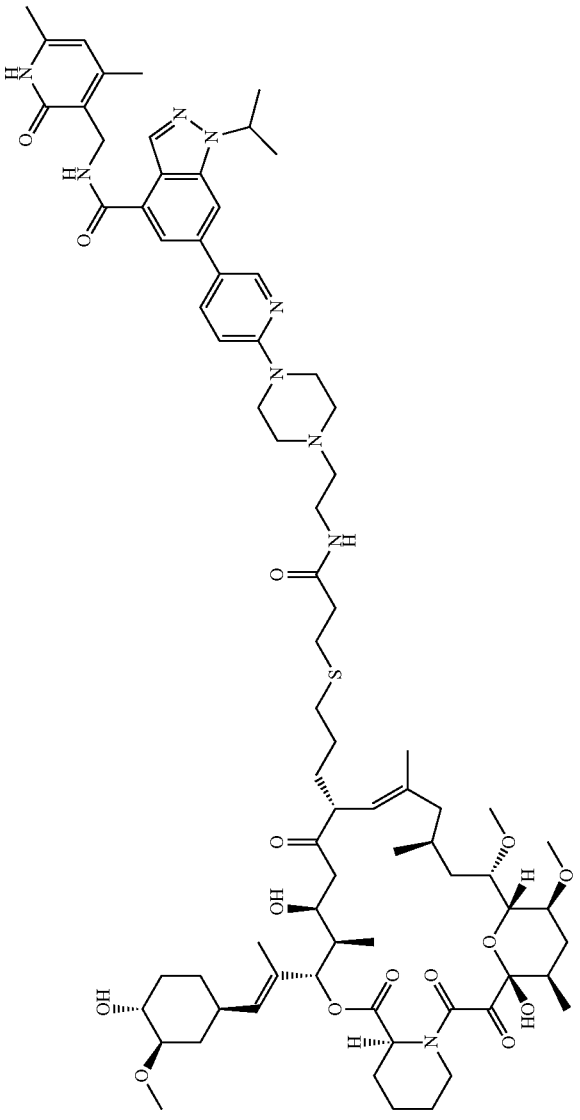
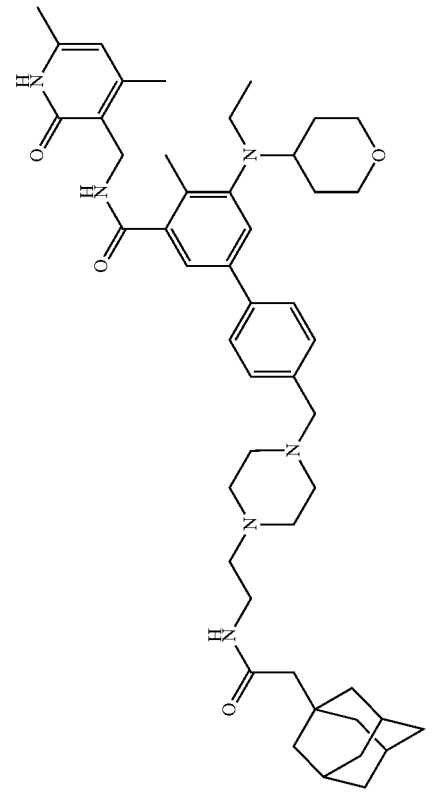
	Structure	Chemical Name
XY028-086		FK506 adduct with N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-isopropyl-6-(6-(4-(2-(3-mercaptopropanamido)ethyl)piperazin-1-yl)pyridin-3-yl)-1H-indazole-4-carboxamide
CZ40-72		4'-((4-(2-(2-((3r,5r,7r)-adamantan-1-yl)acetamido)ethyl)piperazin-1-yl)methyl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-4-methyl-[1,1'-biphenyl]-3-carboxamide

TABLE 1-continued

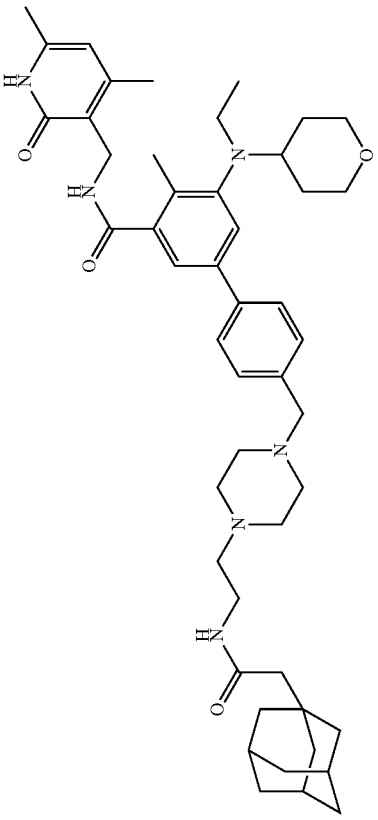
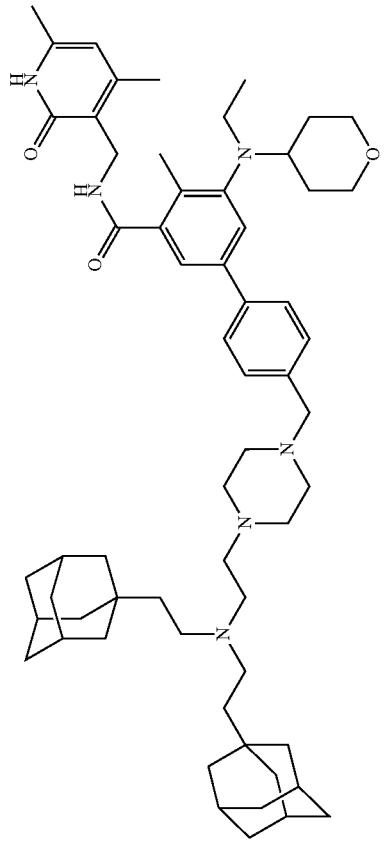
	Structure	Chemical Name
CZ40-73		4'-((4-(2-(2-((1R,3S,5r,7r)-adamantan-2-yl)acetamido)ethyl)piperazin-1-yl)methyl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(ethyl((tetrahydro-2H-pyran-4-yl)amino)-4-methyl-[1,1'-biphenyl]-3-carboxamide
CZ40-75		4'-((4-(2-((2-((1s,3S)-adamantan-1-yl)ethyl)(2-(3R,5R,7R)-adamantan-1-yl)ethyl)amino)ethyl)piperazin-1-yl)methyl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(ethyl((tetrahydro-2H-pyran-4-yl)amino)-4-methyl-[1,1'-biphenyl]-3-carboxamide

TABLE 1-continued

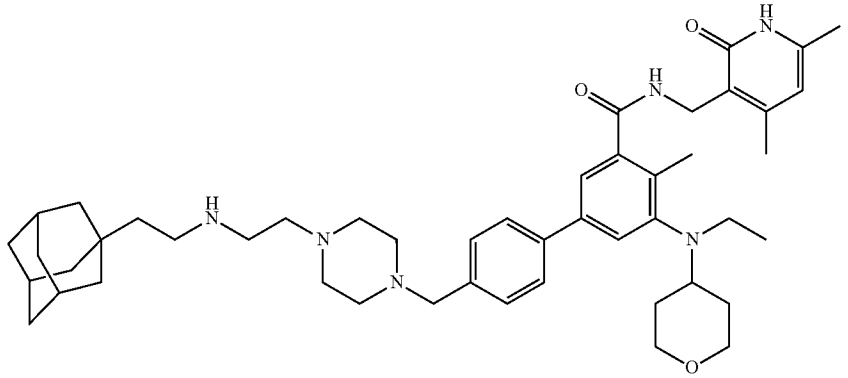
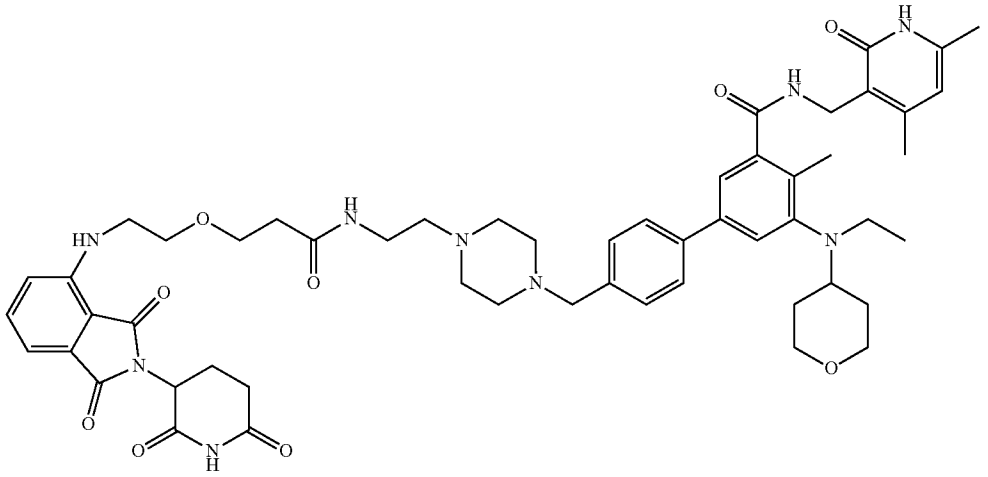
	Structure	Chemical Name
CZ40-149		4'-((4-(2-((2-((1s,3s)-adamantan-1-yl)ethyl)amino)ethyl)piperazin-1-yl)methyl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-4-methyl-[1,1'-biphenyl]-3-carboxamide
CZ40-74		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-4'-((4-(2-(3-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)propanamido)ethyl)piperazin-1-yl)methyl)-5-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-4-methyl-[1,1'-biphenyl]-3-carboxamide

TABLE 1-continued

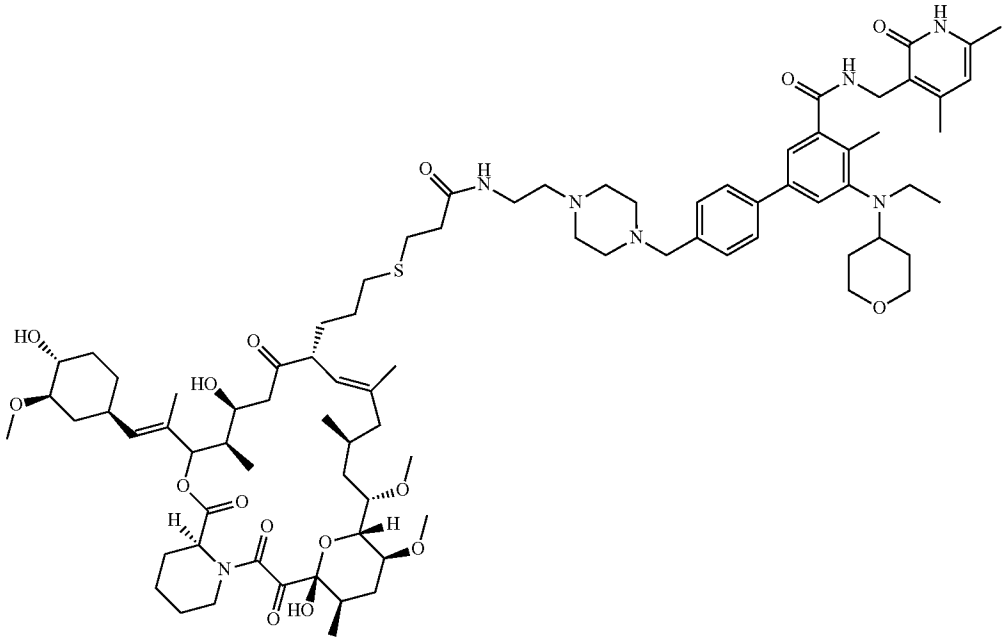
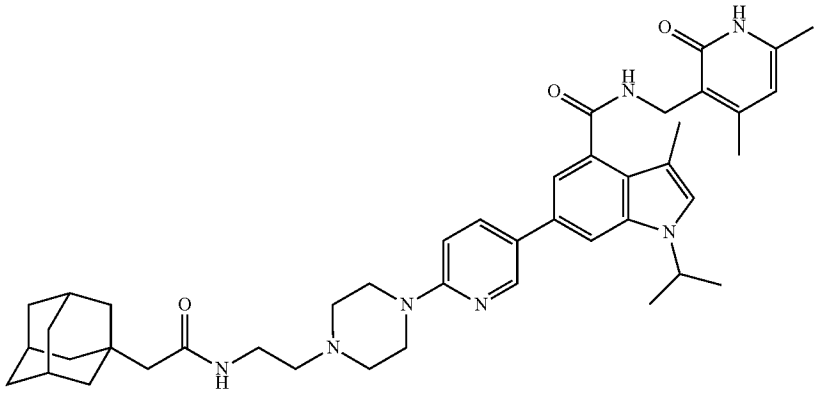
	Structure	Chemical Name
CZ40-131		FK506 adduct with N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(ethyl(tetrahydro-2H-pyran-4-3,1)amino)-4'-((4-(2-(3-mercaptopropanamido)ethyl)piperazin-1-yl)methyl)-4-methyl-[1,1'-biphenyl]-3-carboxamide
AM41-36A		6-(6-(4-(2-(2-((3r,5r,7r)-adamantan-1-yl)acetamido)ethyl)piperazin-1-yl)pyridin-3-yl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-isopropyl-3-methyl-1H-indole-4-carboxamide

TABLE 1-continued

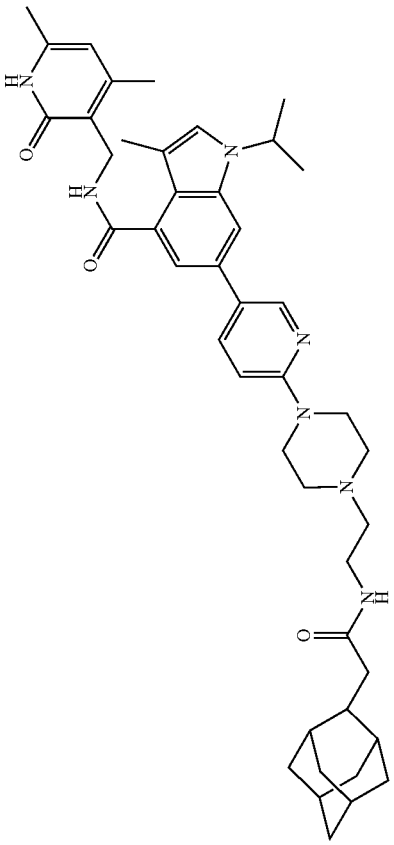
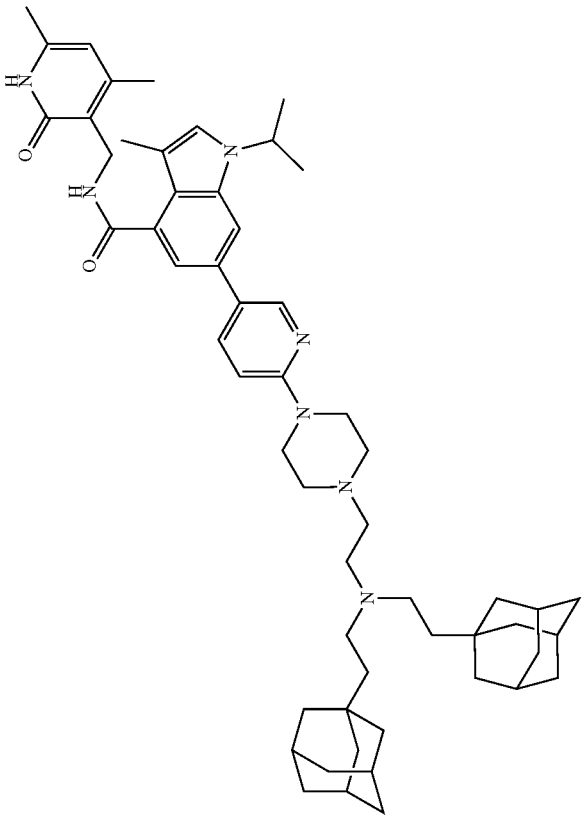
	Structure	Chemical Name
AM41-37A		6-(6-(4-(2-(2-((1r,3r,5r,7r)-adamantan-2-yl)acetamido)ethyl)piperazin-1-yl)pyridin-3-yl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-isopropyl-3-methyl-1H-indole-4-carboxamide
AM41-39A		6-(6-(4-(2-(bis(2-((3R,5R,7R)-adamantan-1-yl)ethyl)amino)ethyl)piperazin-1-yl)pyridin-3-yl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-isopropyl-3-methyl-1H-indole-4-carboxamide

TABLE 1-continued

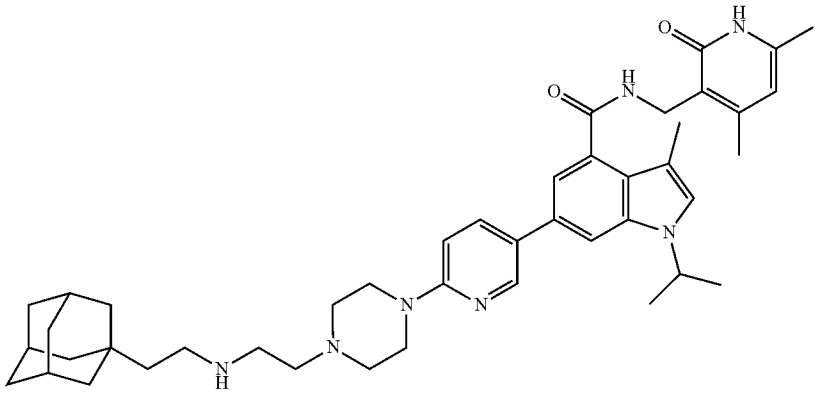
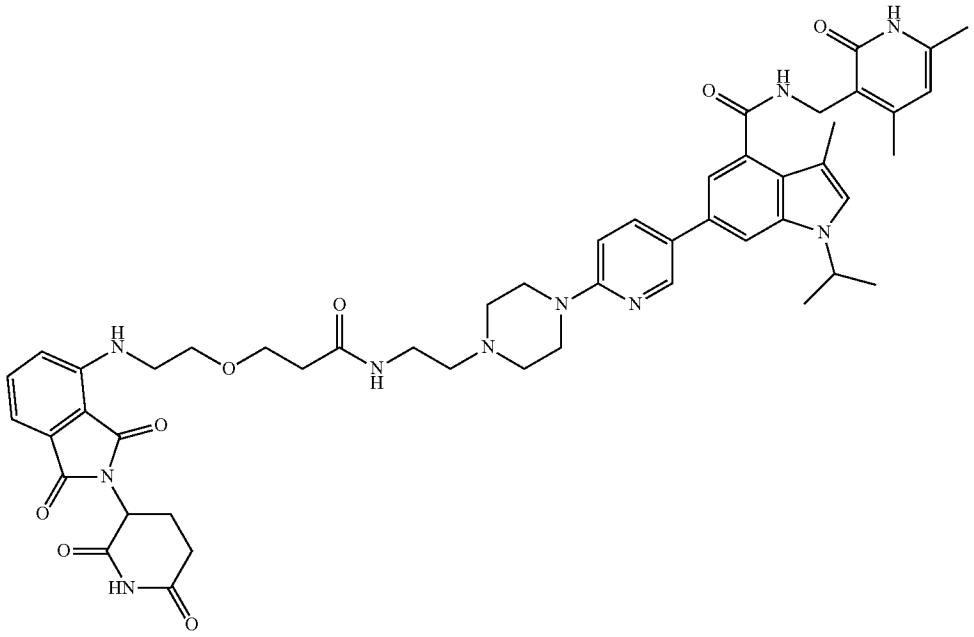
	Structure	Chemical Name
AM41-41A		6-(6-(4-(2-((2-((3r,5r,7r)-adamantan-1-yl)ethyl)amino)ethyl)piperazin-1-yl)pyridin-3-yl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-isopropyl-3-methyl-1H-indole-4-carboxamide
AM41-38A		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-(6-(4-(2-(3-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)propanamido)ethyl)piperazin-1-yl)pyridin-3-yl)-1-isopropyl-3-methyl-1H-indole-4-carboxamide

TABLE 1-continued

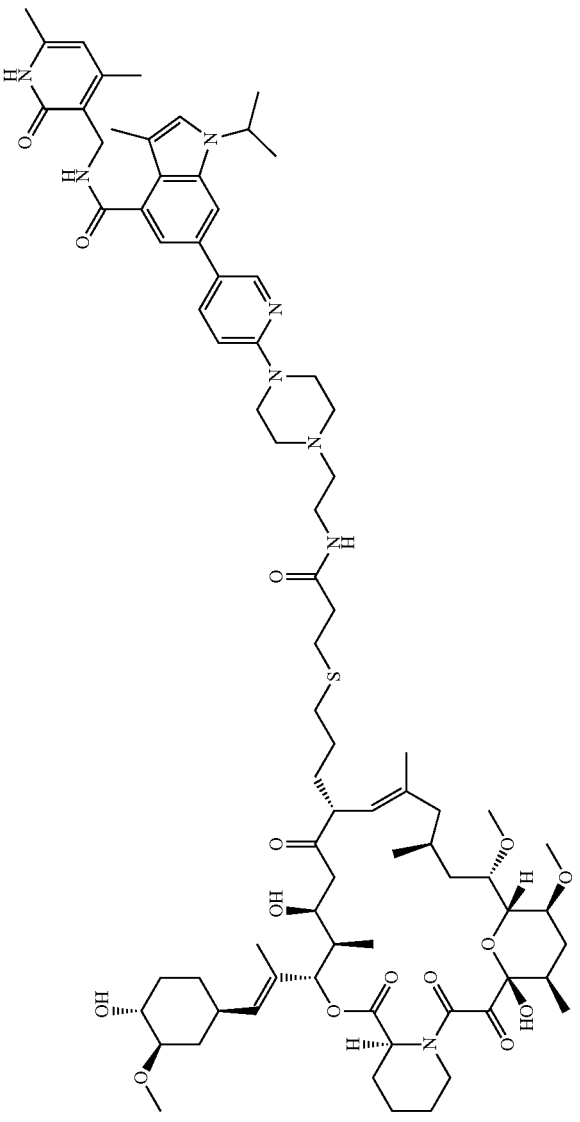
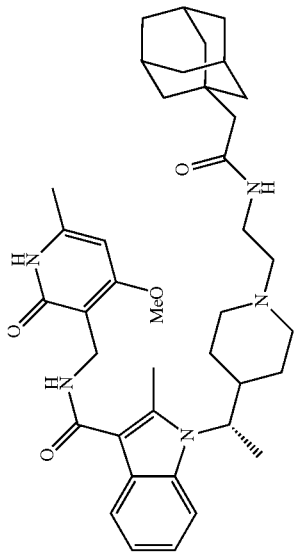
	Structure	Chemical Name
AM41-40A		FK506 adduct with N-((4,6-dimethyl-2-oxo-1,2-dihhydropyridin-3-yl)methyl-1-isopropyl-6-(6-(4-(2-(3-mercaptopropanamido)ethyl)piperazin-1-yl)pyridin-3-yl)-3-methyl-1H-indole-4-carboxamide
XF042-84		1-((S)-1-(1-(2-(4-((3S,5S,7S)-adamantan-1-yl)acetamido)ethyl)piperidin-4-yl)ethyl)-N-((4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-1H-indole-3-carboxamide

TABLE 1-continued

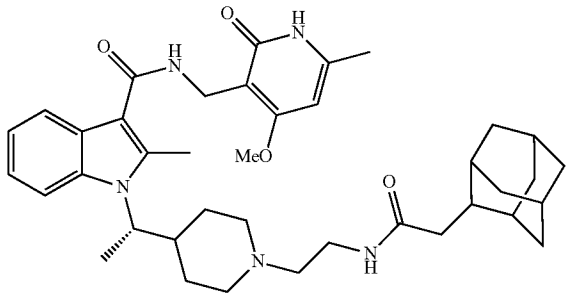
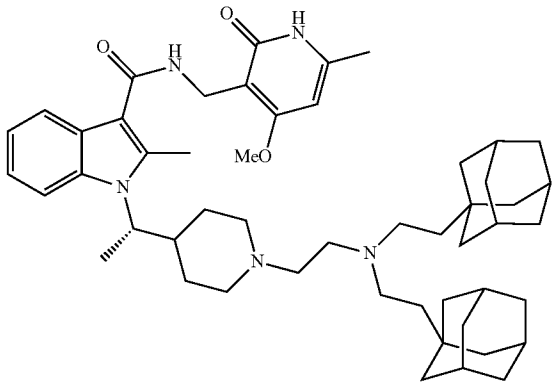
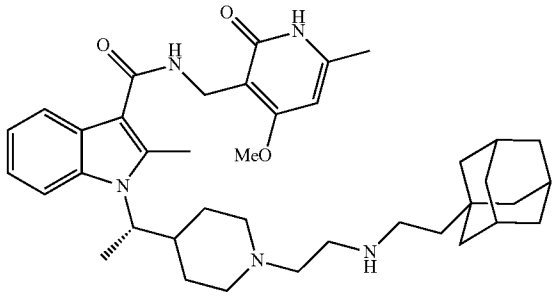
	Structure	Chemical Name
XF042-85		1-((S)-1-(1-(2-(2-((1R,3S,5S,7S)-adamantan-2-yl)acetamido)ethyl)piperidin-4-yl)ethyl)-N-((4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-1H-indole-3-carboxamide
XF042-95		1-((S)-1-(1-(2-(bis(2-((3S,5S,7S)-adamantan-1-yl)ethyl)amino)ethyl)piperidin-4-yl)ethyl)-N-((4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-1H-indole-3-carboxamide
XF042-132		1-((S)-1-(1-(2-((2-((3S,5S,7S)-adamantan-1-yl)ethyl)amino)ethyl)piperidin-4-yl)ethyl)-N-((4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-1H-indole-3-carboxamide

TABLE 1-continued

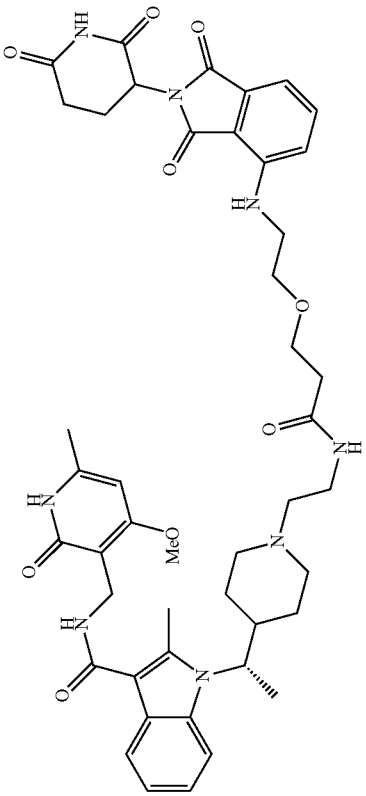
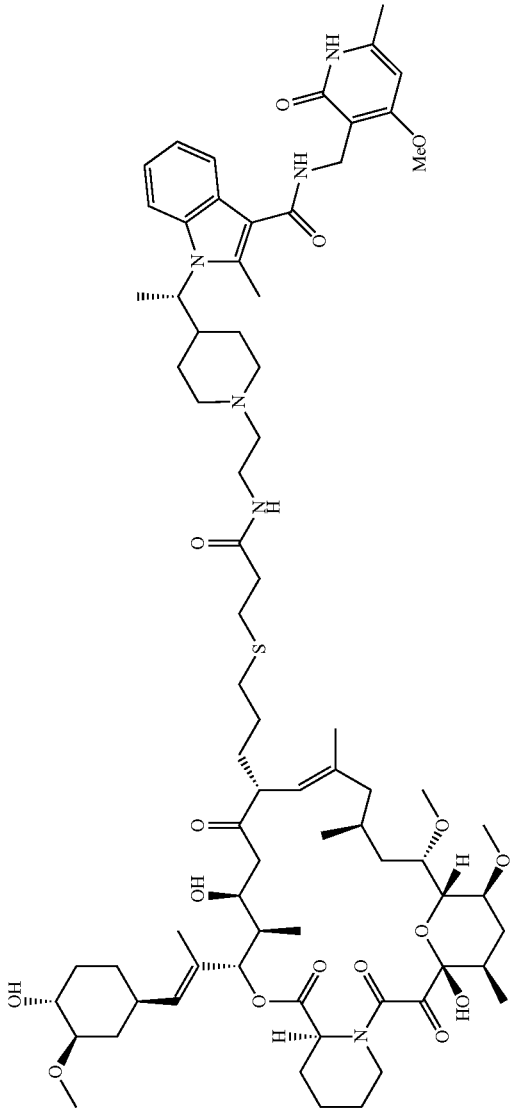
	Structure	Chemical Name
XF042-86		1-((1S)-1-(1-(2-(3-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)propanamido)ethyl)piperidin-4-yl)ethyl)-N-((4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-1H-indole-3-carboxamide
XF042-94		FK506 adduct with (S)-1-(1-(2-(3-mercaptopropanamido)ethyl)piperidin-4-yl)ethyl)-N-((4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-1H-indole-3-carboxamide

TABLE 1-continued

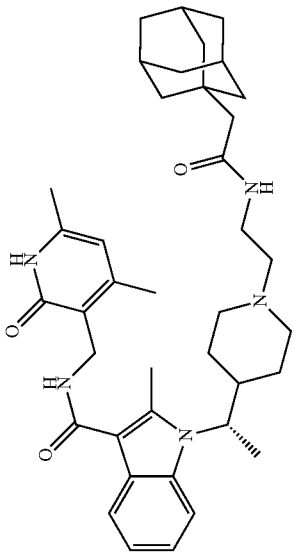
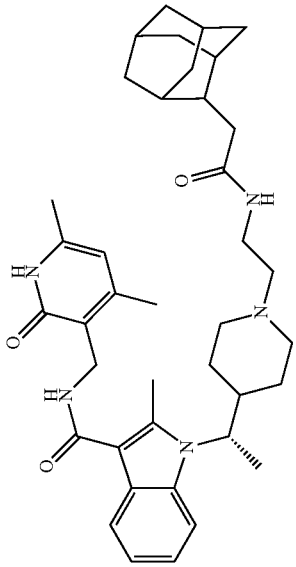
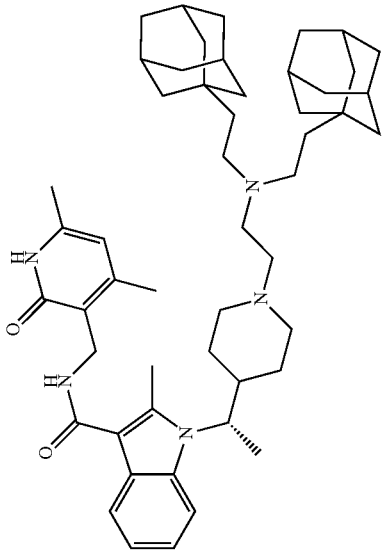
	Structure	Chemical Name
XF042-89		1-((S)-1-(1-(2-((3S,5S,7S)-adamantan-1-yl)acetamido)ethyl)piperidin-4-yl)ethyl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-1H-indole-3-carboxamide
XF042-90		1-((S)-1-(1-(2-((1R,3S,5S,7S)-adamantan-2-yl)acetamido)ethyl)piperidin-4-yl)ethyl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-1H-indole-3-carboxamide
XF042-93		1-((S)-1-(1-(2-(bis(2-((3S,5S,7S)-adamantan-1-yl)ethyl)amino)ethyl)piperidin-4-yl)ethyl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-1H-indole-3-carboxamide

TABLE 1-continued

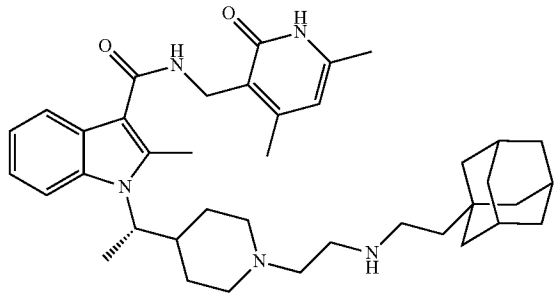
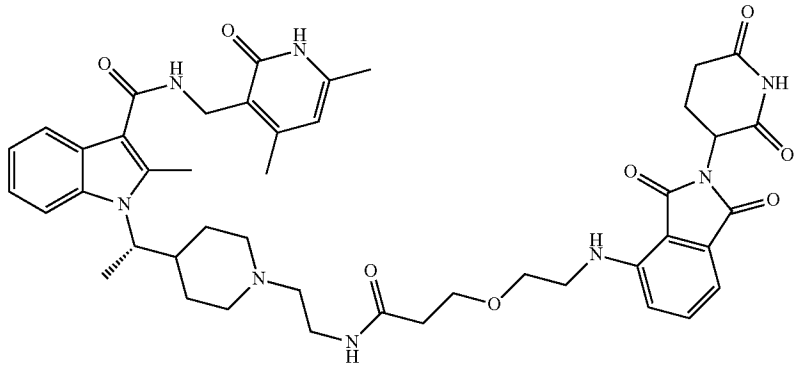
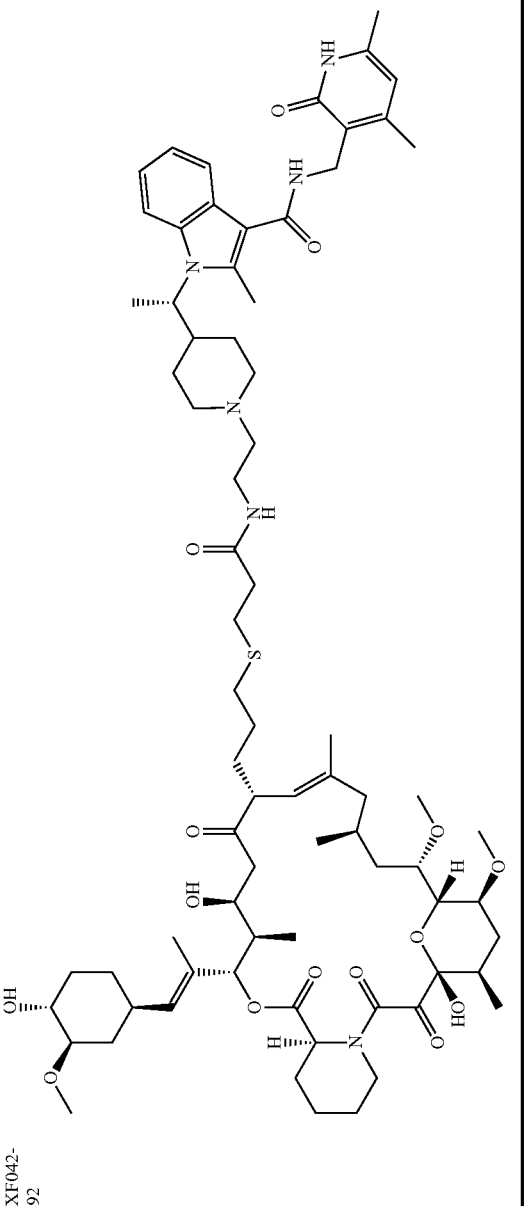
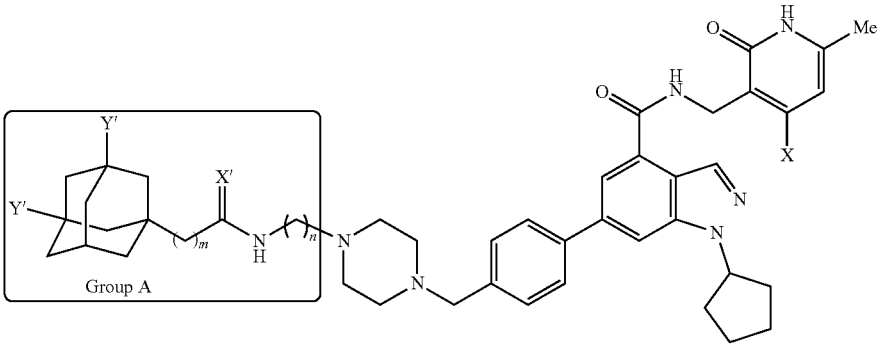
	Structure	Chemical Name
XF042-133		1-((S)-1-(1-(2-((2-((3S,5S,7S)-adamantan-1-yl)ethyl)amino)ethyl)piperidin-4-ybethyl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-1H-indole-3-carboxamide
XF042-91		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(1S)-1-(1-(2-(3-(2-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)propanamido)ethyl)piperidin-4-yl)ethyl)-2-methyl-1H-indole-3-carboxamide

TABLE 1-continued

	Structure	Chemical Name
XF042-92		FK506 adduct with (S)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(1-(2-(3-mercaptopropanamido)ethyl)piperidin-4-yl)ethyl)-2-methyl-1H-indole-3-carboxamide

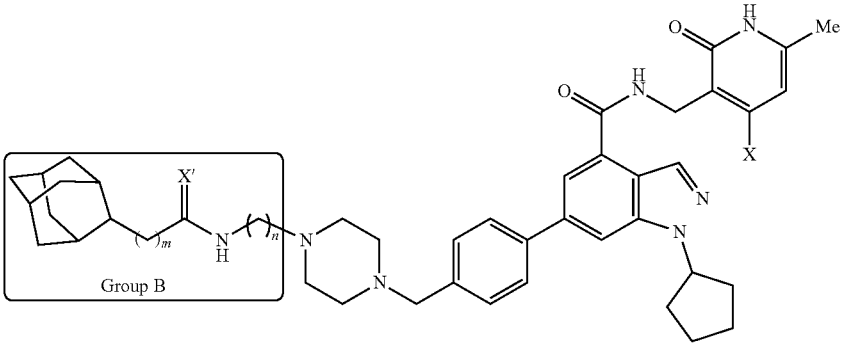
Additional Exemplary Compounds (I)

[0093]



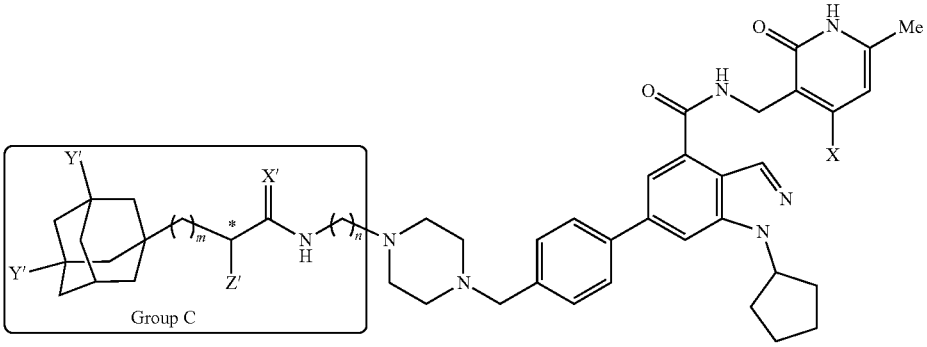
X = C_{1-6} alkyl, MeO-

In Group A:
X′ = O or H_2
Y′ = H, C_{1-6} alkyl
m = 0-15
n = 2-15



X = C_{1-6} alkyl, MeO-

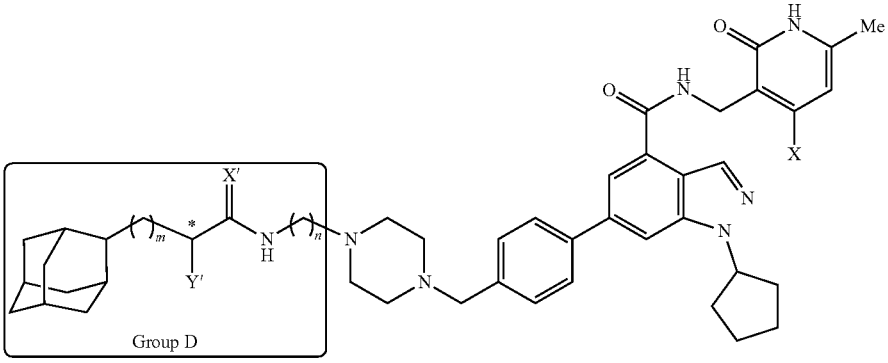
In Group B:
X′ = O or H_2
m = 0-15
n = 2-15



X = C_{1-6} alkyl, MeO-

In Group C:
X′ = O or H_2
Y′ = H, C_{1-6} alkyl
Z′ = C_{1-6} alkyl
m = 0-15
n = 2-15
* R, S and racemic

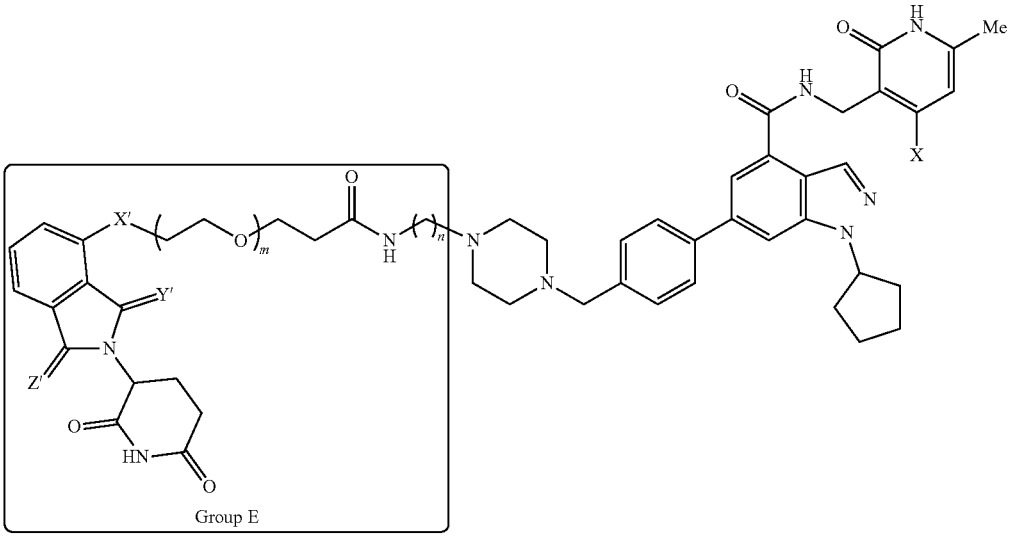
-continued



Group D

X = C_{1-6} alkyl, MeO-

In Group D:
X′ = O or H_2
Y′ = C_{1-6} alkyl
m = 0-15
n = 2-15
* R, S and racemic

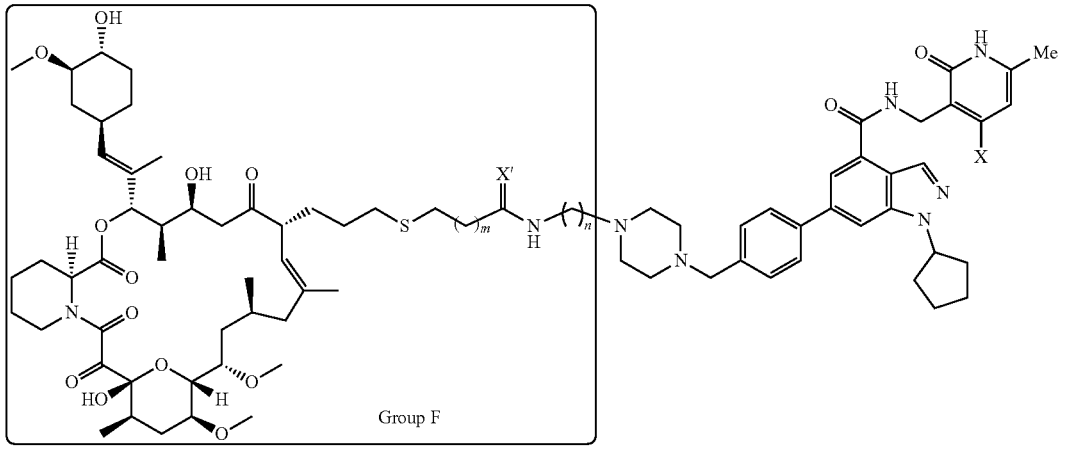


Group E

X = C_{1-6} alkyl, MeO-

In Group E:
X′ = NH, O or C_{1-6} alkyl
Y′ = O or H_2
Z′ = O or H_2
m = 0-15
n = 2-15
* R, S and racemic

-continued



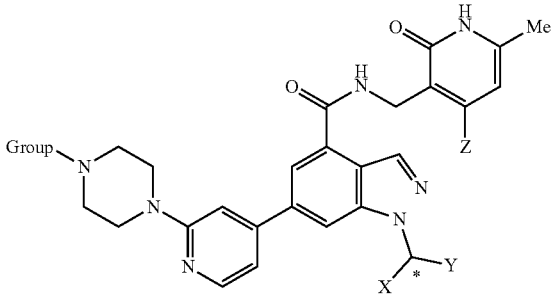
X = C_{1-6} alkyl, MeO-

In Group F:
X′ = O or H_2
m = 0-15
n = 2-15

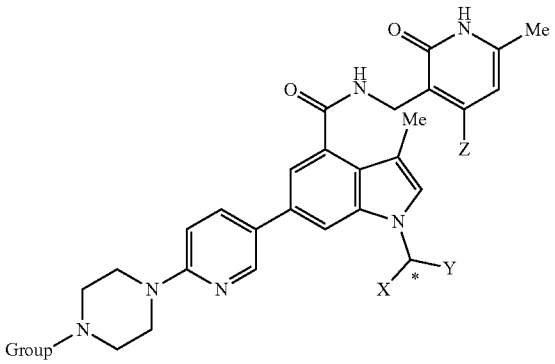
Additional Exemplary Compounds (II)

[0094] Group=Group A,B,C,D,E, or F which appeared in the figure "Additional exemplary compounds (I)"Each structure below represents the combination of variants of inhibitor and variants of each Group (as illustrated in the figure "Additional exemplary compounds (I)"and in the current figure "Additional exemplary compounds (II)")

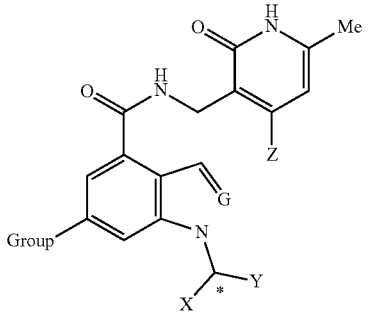
-continued



X = H, C_{1-6} alkyl
Y = H, C_{1-6} alkyl
Z = C_{1-6} alkyl, MeO-
* R, S and racemic

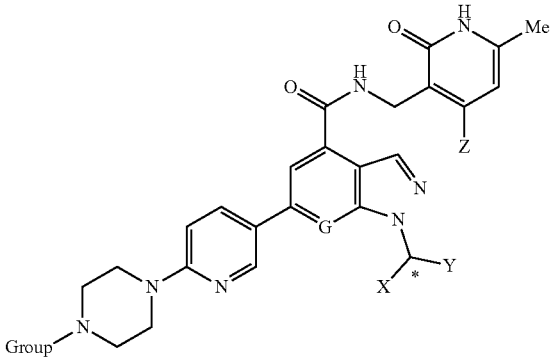


X = H, C_{1-6} alkyl
Y = H, C_{1-6} alkyl
Z = C_{1-6} alkyl, MeO-
* R, S and racemic

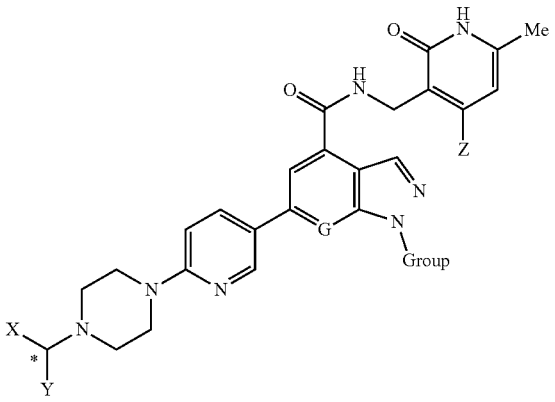


X = H, C_{1-6} alkyl
Y = H, C_{1-6} alkyl
Z = C_{1-6} alkyl, MeO-
G = CH or N
* R, S and racemic

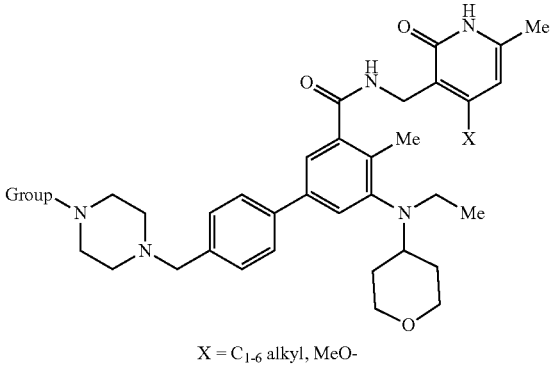
-continued



X = H, C_{1-6} alkyl
Y = H, C_{1-6} alkyl
Z = C_{1-6} alkyl, MeO-
G = CH or N
* R, S and racemic



X = H, C_{1-6} alkyl
Y = H, C_{1-6} alkyl
Z = C_{1-6} alkyl, MeO-
G = CH or N
* R, S and racemic



X = C_{1-6} alkyl, MeO-

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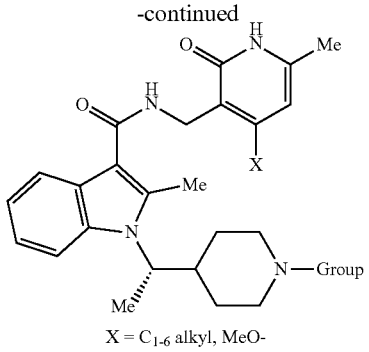
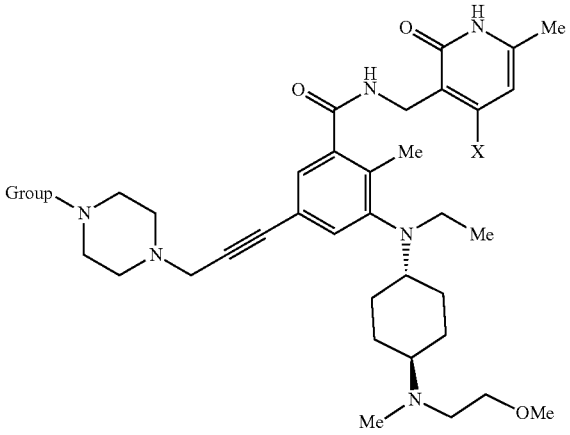
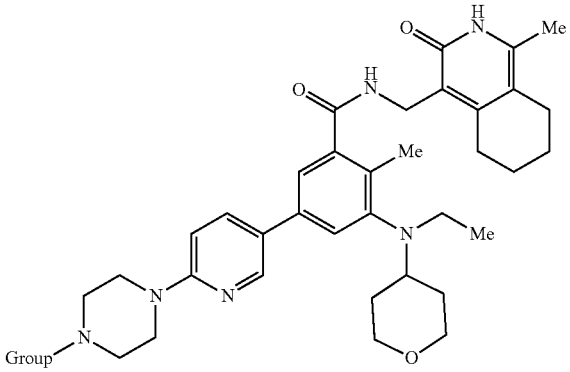
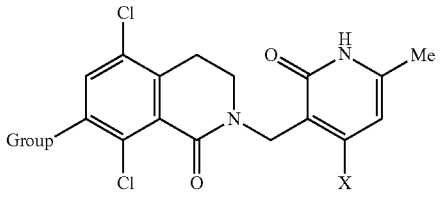


X = C_{1-6} alkyl, MeO-



X = C_{1-6} alkyl, MeO-





X = C_{1-6} alkyl, MeO-

[0095] The inhibitory activity of EZH2 degraders/disruptors can be assessed by EZH2 biochemical assays known in the art (Konze et al., 2013; Yang et al., 2016); see, e.g., Example 115. Their binding affinity to EZH2 can be assessed using standard biophysical assays known in the art (e.g., ITC, SPR). Cellular assays (e.g., as depicted in Examples 113 and 114) can be used to assess the compounds' ability to induce EZH2 degradation/disruption, reduce the H3K27me3 mark, and/or inhibit cancer cell

proliferation. Assays suitable for use in any or all of these steps are known in the art, and include, e.g., Western blotting and MTT. Suitable cell lines for use in any or all of these steps are known in the art and include, e.g., HCC70, HCC1170, HCC1187, MDA-MB-468, MDA-MB-231, MCF-7, BT549, HCC1954, HeLa S3, HEK 293, U2OS, and HFF cells.

[0096] By way of non-limiting example, detailed synthesis protocols are shown in the Examples below for specific exemplary EZH2 degraders/disruptors.

[0097] In certain aspects, the compositions and methods described herein include the manufacture and use of pharmaceutical compositions and medicaments that include compounds identified by a method described herein as active ingredients. Also included are the pharmaceutical compositions themselves.

[0098] In some instances, the compositions disclosed herein can include other compounds, drugs, and/or agents used for the treatment of cancer. For example, in some instances, therapeutic compositions disclosed herein can be combined with one or more (e.g., one, two, three, four, five, or less than ten) compounds.

[0099] In some instances, the compositions disclosed herein can include EZH2 degraders/disruptors such as AM16-10A, XY019-43, AM29-182A, AM19-177A, AM16-103A, CZ40-75, CZ40-149, AM41-41A, XF042-95, XF042-93, XF042-133, XY028-086, CZ40-131, and XF042-92.

[0100] An EZH2 degrader/disruptor can selectively affect EZH2-mediated cancer cells (e.g., TNBC cells) compared to WT, normal or non-tumor cells (i.e., a degrader/disruptor able to kill or inhibit the growth of EZH2-mediated cancer cells while also having a relatively low ability to lyse or inhibit the growth of WT, normal or non-tumor cells), e.g., possess a GI_{50} for one or more EZH2-mediated cancer cells more than 1.5-fold lower, more than 2-fold lower, more than 2.5-fold lower, more than 3-fold lower, more than 4-fold lower, more than 5-fold lower, more than 6-fold lower, more than 7-fold lower, more than 8-fold lower, more than 9-fold lower, more than 10-fold lower, more than 15-fold lower, or more than 20-fold lower than its GI_{50} for one or more WT, normal or non-tumor cells, e.g., WT, normal or non-tumor cells of the same species and tissue type as the EZH2-mediated cancer cells.

[0101] One or more of the EZH2 degraders/disruptors disclosed herein can be formulated for use as or in pharmaceutical compositions. Such compositions can be formulated or adapted for administration to a subject via any route, e.g., any route approved by the Food and Drug Administration (FDA). Exemplary methods are described in the FDA Data Standards Manual (DSM) (available at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/DataStandardsManualmonographs). The pharmaceutical compositions may be formulated for oral, parenteral, or transdermal delivery. The compound of the invention may also be combined with other pharmaceutical agents.

[0102] The pharmaceutical compositions disclosed herein can be administered, e.g., orally, parenterally, by inhalation spray or nebulizer, topically, rectally, nasally, buccally, vaginally, via an implanted reservoir, by injection (e.g., intravenously, intra-arterially, subdermally, intraperitoneally, intramuscularly, and/or subcutaneously), in an ophthalmic preparation, or via transmucosal administration. Suitable dosages may range from about 0.001 to about 100 mg/kg of body weight, or according to the requirements of the particular drug. The pharmaceutical compositions of this invention can contain any conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. In some cases, the pH of the formulation can be adjusted with pharmaceutically acceptable acids, bases, or buffers to enhance the stability of the formulated compound or its delivery form. The term "parenteral" as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intraarticular, intra-arterial, intrasynovial, intrasternal, intrathecal, intralesional, and intracranial injection or infusion techniques. Alternatively or in addition, the present invention may be administered according to any of the methods as described in the FDA DSM.

[0103] Pharmaceutical compositions typically include a pharmaceutically acceptable carrier. The term "pharmaceutically acceptable carrier or adjuvant" refers to a carrier or adjuvant that may be administered to a patient, together with a compound of this invention, and which does not destroy the pharmacological activity thereof and is nontoxic when administered in doses sufficient to deliver a therapeutic amount of the compound. As used herein the language "pharmaceutically acceptable carrier" includes saline, solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration.

[0104] As used herein, the phrase "pharmaceutically acceptable" refers to molecular entities and compositions that are generally believed to be physiologically tolerable and do not typically produce an allergic or similar untoward reaction, such as gastric upset, dizziness and the like, when administered to a human. As used herein, the term "pharmaceutically acceptable derivative" means any pharmaceutically acceptable salt, solvate or prodrug, e.g., ester, of an atovaquone-related compound described herein, which upon administration to the recipient is capable of providing (directly or indirectly) a compound described herein, or an active metabolite or residue thereof. Such derivatives are recognizable to those skilled in the art, without undue experimentation. Nevertheless, reference is made to the teaching of Burger's Medicinal Chemistry and Drug Discovery, 5th Edition, Vol 1: Principles and Practice, which is incorporated herein by reference to the extent of teaching such derivatives. Pharmaceutically acceptable derivatives include salts, solvates, esters, carbamates, and/or phosphate esters.

[0105] In some cases, the pH of the formulation may be adjusted with pharmaceutically acceptable acids, bases or buffers to enhance the stability of the formulated compound or its delivery form. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intra-articular, intraarterial, intrasynovial, intrastemal, intrathecal, intralesional and intracranial injection or infusion techniques.

[0106] Pharmaceutical compositions are typically formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, e.g., intravenous, intradermal, subcutaneous, oral (e.g., inhalation), transdermal (topical), transmucosal, and rectal administration.

[0107] As used herein, the EZH2 degraders/disruptors disclosed herein are defined to include pharmaceutically acceptable derivatives or prodrugs thereof. A "pharmaceu-

tically acceptable derivative or prodrug" means any pharmaceutically acceptable salt, ester, salt of an ester, or other derivative of a compound or agent disclosed herein which, upon administration to a recipient, is capable of providing (directly or indirectly) a compound of this invention. Particularly favored derivatives and prodrugs are those that increase the bioavailability of the compounds disclosed herein when such compounds are administered to a mammal (e.g., by allowing an orally administered compound to be more readily absorbed into the blood) or which enhance delivery of the parent compound to a biological compartment (e.g., the brain or lymphatic system) relative to the parent species. Preferred prodrugs include derivatives where a group that enhances aqueous solubility or active transport through the gut membrane is appended to the structure of formulae described herein.

[0108] The EZH2 degraders/disruptors disclosed herein include pure enantiomers, mixtures of enantiomers, pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixtures of diastereoisomeric racemates and the meso-form and pharmaceutically acceptable salts, solvent complexes, morphological forms, or deuterated derivative thereof.

[0109] In some instances, pharmaceutical compositions can include an effective amount of one or more EZH2 degraders/disruptors. The terms "effective amount" and "effective to treat," as used herein, refer to an amount or a concentration of one or more compounds or a pharmaceutical composition described herein utilized for a period of time (including acute or chronic administration and periodic or continuous administration) that is effective within the context of its administration for causing an intended effect or physiological outcome (e.g., treatment or prevention of cell growth, cell proliferation, or cancer).

[0110] In some aspects, the present disclosure provides methods for using a composition comprising an EZH2 degrader/disruptor, including pharmaceutical compositions (indicated below as 'X') disclosed herein in the following methods:

[0111] Substance X for use as a medicament in the treatment of one or more diseases or conditions disclosed herein (e.g., neurodegenerative disease, referred to in the following examples as 'Y'). Use of substance X for the manufacture of a medicament for the treatment of Y; and substance X for use in the treatment of Y.

[0112] In some instances, therapeutic compositions disclosed herein can be formulated for sale in the US, import into the US, and/or export from the US.

[0113] The pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

[0114] The methods herein contemplate administration of an effective amount of compound or compound composition to achieve the desired or stated effect. Typically, the pharmaceutical compositions of this invention will be administered from about 1 to about 6 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. A typical preparation will contain from about 5% to about 95% active compound (w/w). Alternatively, such preparations can contain from about 20% to about 80% active compound.

[0115] In some aspects, an effective dose of an EZH2 degrader/disruptor can include, but is not limited to, e.g., about 0.00001, 0.0001, 0.001, 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.1, 0.15, 0.2, 0.25, 0.3, 0.35, 0.4, 0.45, 0.5, 0.55, 0.6, 0.65, 0.7, 0.75, 0.8, 0.85, 0.9, 0.95, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 2500, 5000, or 10000 mg/kg/day.

[0116] Pharmaceutical compositions of this invention can include one or more EZH2 degraders/disruptors and any pharmaceutically acceptable carrier and/or vehicle. In some instances, pharmaceuticals can further include one or more additional therapeutic agents in amounts effective for achieving a modulation of disease or disease symptoms. Such additional therapeutic agents may include conventional chemotherapeutic agents known in the art. When co-administered, EZH2 degraders/disruptors disclosed herein can operate in conjunction with conventional chemotherapeutic agents to produce mechanistically additive or synergistic therapeutic effects.

[0117] When the compositions of this invention comprise a combination of a compound of the formulae described herein and one or more additional therapeutic or prophylactic agents, both the compound and the additional agent should be present at dosage levels of between about 1 to 100%, and more preferably between about 5 to 95% of the dosage normally administered in a monotherapy regimen. The additional agents may be administered separately, as part of a multiple dose regimen, from the compounds of this invention. Alternatively, those agents may be part of a single dosage form, mixed together with the compounds of this invention in a single composition.

[0118] Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, self-emulsifying drug delivery systems (SEDDS) such as d-α-tocopherol polyethylene glycol 1000 succinate, surfactants used in pharmaceutical dosage forms such as Tween®s or other similar polymeric delivery matrices, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat. Cyclodextrins such as α-, β-, and γ-cyclodextrin, may also be advantageously used to enhance delivery of compounds of the formulae described herein.

[0119] Pharmaceutical compositions can be in the form of a solution or powder for injection. Such compositions may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween® 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed

oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, or carboxymethyl cellulose or similar dispersing agents which are commonly used in the formulation of pharmaceutically acceptable dosage forms such as emulsions and or suspensions. Other commonly used surfactants such as Tween®s, Spann's, and/or other similar emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

[0120] Pharmaceutical compositions can be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, emulsions and aqueous suspensions, dispersions and solutions. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions and/or emulsions are administered orally, the active ingredient may be suspended or dissolved in an oily phase is combined with emulsifying and/or suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

[0121] The pharmaceutical compositions of this invention may also be administered in the form of suppositories for rectal administration. These compositions can be prepared by mixing a compound of this invention with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the active components. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

[0122] Alternatively or in addition, pharmaceutical compositions can be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

[0123] Pharmaceutically acceptable salts of the EZH2 degraders/disruptors of this disclosure include, e.g., those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acid salts include acetate, adipate, benzoate, benzenesulfonate, butyrate, citrate, digluconate, dodecylsulfate, formate, fumarate, glycolate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, lactate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, palmoate, phosphate, picrate, pivalate, propionate, salicylate, succinate, sulfate, tartrate, tosylate, trifluoromethylsulfonate, and undecanoate. Salts derived from appropriate bases include, e.g., alkali metal (e.g., sodium), alkaline earth metal (e.g., magnesium), ammonium and N-(alkyl)$^{4+}$ salts. The invention also envisions the quaternization of any basic nitrogen-containing groups of the degraders disclosed herein. Water or oil-soluble or dispersible products can be obtained by such quaternization.

[0124] The methods described herein include methods for the treatment of disorders associated with EZH2-mediated cancer, the methods include administering a therapeutically effective amount of an EZH2 degrader/disruptor as described herein, to a subject (e.g., a mammalian subject, e.g., a human subject) who is in need of, or who has been determined to be in need of, such treatment.

[0125] In some instances, methods can include selection of a human subject who has or had a condition or disease. In some instances, suitable subjects include, for example, subjects who have or had a condition or disease but that resolved the disease or an aspect thereof, present reduced symptoms of disease (e.g., relative to other subjects (e.g., the majority of subjects) with the same condition or disease), and/or that survive for extended periods of time with the condition or disease (e.g., relative to other subjects (e.g., the majority of subjects) with the same condition or disease), e.g., in an asymptomatic state (e.g., relative to other subjects (e.g., the majority of subjects) with the same condition or disease).

[0126] The terms "treat", "treating," or "treatment," as used herein, refer to partially or completely alleviating, inhibiting, ameliorating, and/or relieving the disease or condition from which the subject is suffering. This means any manner in which one or more of the symptoms of a disease or disorder (e.g., cancer) are ameliorated or otherwise beneficially altered. As used herein, amelioration of the symptoms of a particular disorder (e.g., cancer) refers to any lessening, whether permanent or temporary, lasting or transient that can be attributed to or associated with treatment by the compositions and methods of the present invention. In some aspects, treatment can promote or result in, for example, a decrease in the number of tumor cells (e.g., in a subject) relative to the number of tumor cells prior to treatment; a decrease in the viability (e.g., the average/mean viability) of tumor cells (e.g., in a subject) relative to the viability of tumor cells prior to treatment; and/or reductions in one or more symptoms associated with one or more tumors in a subject relative to the subject's symptoms prior to treatment.

[0127] As used herein, the term "treating cancer" means causing a partial or complete decrease in the rate of growth of a tumor, and/or in the size of the tumor and/or in the rate of local or distant tumor metastasis, and/or the overall tumor burden in a subject, and/or any decrease in tumor survival, in the presence of a degrader/disruptor (e.g., an EZH2 degrader/disruptor) described herein.

[0128] As used herein, the term "preventing a disease" (e.g., preventing cancer) in a subject means for example, to stop the development of one or more symptoms of a disease in a subject before they occur or are detectable, e.g., by the patient or the patient's doctor. Preferably, the disease (e.g., cancer) does not develop at all, i.e., no symptoms of the disease are detectable. However, it can also result in delaying or slowing of the development of one or more symptoms of the disease. Alternatively, or in addition, it can result in the decreasing of the severity of one or more subsequently developed symptoms.

[0129] Exemplary EZH2-mediated cancers that can be treated with EZH2 degraders/disruptors include, for example, INI1-negative tumors, lymphoma (including diffuse large B-cell lymphoma (DLBCL), follicular lymphoma

(FL), and non-Hodgkin's lymphoma (NHL)), malignant rhabdoid tumor, multiple myeloma, relapsed/refractory synovial sarcoma, breast cancers (including TNBC), prostate cancers, other solid tumors, acute lymphoblastic leukemia, acute myeloid leukemia, adrenocortical carcinoma, AIDS-related cancers, anal cancer, astrocytoma, childhood cerebellar cancer, basal cell carcinoma, skin cancer (non-melanoma), bile duct cancer, bladder cancer, bone cancer, osteosarcoma/malignant fibrous histiocytoma, brain stem glioma, brain tumor, cerebellar astrocytoma, cerebral astrocytoma/malignant glioma, ependymoma, medulloblastoma, supratentorial primitive neuroectodermal tumors, visual pathway and hypothalamic glioma, bronchial adenomas/carcinoids, Burkitt's lymphoma, carcinoid tumors, central nervous system lymphoma, cervical cancer, chronic lymphocytic leukemia, chronic myelogenous leukemia, chronic myeloproliferative disorder, colon cancer, colorectal cancer, cutaneous T-cell lymphoma, endometrial cancer, esophageal cancer, melanoma, retinoblastoma, gallbladder cancer, gastrointestinal carcinoid tumors, germ cell tumors, hairy cell leukemia, head and neck cancer, hepatocellular (liver) cancer, Hodgkin's lymphoma, hypopharyngeal cancer, islet cell carcinoma, Kaposi's sarcoma, kidney (renal cell) cancer, laryngeal cancer, lip and oral cavity cancer, lung cancer (small cell and non-small cell), Merkel cell carcinoma, mesothelioma, multiple endocrine neoplasia syndrome, multiple myeloma/plasma cell neoplasm mycosis fungoides, myelodysplastic syndrome, myeloid leukemia, myeloproliferative disorders, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, oropharyngeal cancer, ovarian cancer, pancreatic cancer, parathyroid cancer, penile cancer, neuroectodermal tumors, pituitary tumors, pleuropulmonary blastoma, rectal cancer, rhabdomyosarcoma, salivary gland cancer, Ewing sarcoma, soft tissue sarcoma, uterine sarcoma, Sezary syndrome, small intestine cancer, squamous cell carcinoma, squamous neck cancer, stomach (gastric) cancer, testicular cancer, thymoma, thymic carcinoma, thyroid cancer, transitional cell cancer, trophoblastic tumors, urethral cancer, uterine cancer, vaginal cancer, vulvar cancer, Waldenstrom's macroglobulinemia, and Wilms' tumor.

[0130] The terms "prevent," "preventing," and "prevention," as used herein, shall refer to a decrease in the occurrence of a disease or decrease in the risk of acquiring a disease or its associated symptoms in a subject. The prevention may be complete, e.g., the total absence of disease or pathological cells in a subject. The prevention may also be partial, such that the occurrence of the disease or pathological cells in a subject is less than that which would have occurred without the present invention.

[0131] The term "subject," as used herein, refers to any animal. In some instances, the subject is a mammal. In some instances, the term "subject," as used herein, refers to a human (e.g., a man, a woman, or a child).

[0132] In some instances, subject selection can include obtaining a sample from a subject (e.g., a candidate subject) and testing the sample for an indication that the subject is suitable for selection. In some instances, the subject can be confirmed or identified, e.g. by a health care professional, as having had or having a condition or disease. In some instances, exhibition of a positive immune response towards a condition or disease can be made from patient records, family history, and/or detecting an indication of a positive immune response. In some instances multiple parties can be included in subject selection. For example, a first party can obtain a sample from a candidate subject and a second party can test the sample. In some instances, subjects can be selected and/or referred by a medical practitioner (e.g., a general practitioner). In some instances, subject selection can include obtaining a sample from a selected subject and storing the sample and/or using the in the methods disclosed herein. Samples can include, for example, cells or populations of cells.

[0133] In general, methods include selecting a subject and administering to the subject an effective amount of one or more of the EZH2 degraders/disruptors described herein, e.g., in or as a pharmaceutical composition, and optionally repeating administration as required for the prophylaxis or treatment of cancer and can be administered, e.g., orally, intravenously or topically.

[0134] Specific dosage and treatment regimens for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health status, sex, diet, time of administration, rate of excretion, drug combination, the severity and course of the disease, condition or symptoms, the patient's disposition to the disease, condition or symptoms, and the judgment of the treating physician.

[0135] In some instances, treatments methods can include a single administration, multiple administrations, and repeating administration as required for the prophylaxis or treatment of the disease or condition from which the subject is suffering (e.g., an EZH2-mediated cancer, e.g., breast cancers including TNBC). In some instances treatment methods can include assessing a level of disease in the subject prior to treatment, during treatment, and/or after treatment. In some instances, treatment can continue until a decrease in the level of disease in the subject is detected.

[0136] The terms "administer," "administering," or "administration," as used herein refers to implanting, absorbing, ingesting, injecting, or inhaling, the inventive drug, regardless of form. In some instances, one or more of the compounds disclosed herein can be administered to a subject topically (e.g., nasally) and/or orally. For example, the methods herein include administration of an effective amount of compound or compound composition to achieve the desired or stated effect. Specific dosage and treatment regimens for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health status, sex, diet, time of administration, rate of excretion, drug combination, the severity and course of the disease, condition or symptoms, the patient's disposition to the disease, condition or symptoms, and the judgment of the treating physician. Following administration, the subject can be evaluated to detect, assess, or determine their level of disease. In some instances, treatment can continue until a change (e.g., reduction) in the level of disease in the subject is detected.

[0137] Upon improvement of a patient's condition (e.g., a change (e.g., decrease) in the level of disease in the subject), a maintenance dose of a compound, composition or combination of this invention may be administered, if necessary. Subsequently, the dosage or frequency of administration, or both, may be reduced, as a function of the symptoms, to a

level at which the improved condition is retained. Patients may, however, require intermittent treatment on a long-term basis upon any recurrence of disease symptoms.

[0138] An effective amount can be administered in one or more administrations, applications or dosages. A therapeutically effective amount of a therapeutic compound (i.e., an effective dosage) depends on the therapeutic compounds selected. The compositions can be administered one from one or more times per day to one or more times per week; including once every other day. The skilled artisan will appreciate that certain factors may influence the dosage and timing required to effectively treat a subject, including but not limited to the severity of the disease or disorder, previous treatments, the general health and/or age of the subject, and other diseases present.

[0139] Moreover, treatment of a subject with a therapeutically effective amount of the therapeutic compounds described herein can include a single treatment or a series of treatments. For example, effective amounts can be administered at least once. Upon improvement of a patient's condition, a maintenance dose of a compound, composition or combination of this invention may be administered, if necessary. Subsequently, the dosage or frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition is retained. Patients may, however, require intermittent treatment on a long-term basis upon any recurrence of disease symptoms.

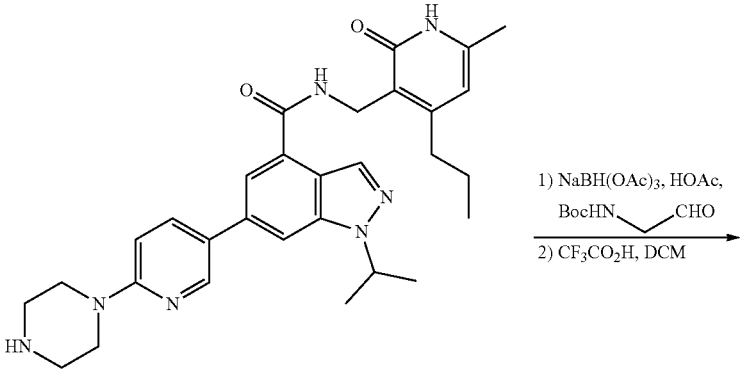
Examples

[0140] Methods

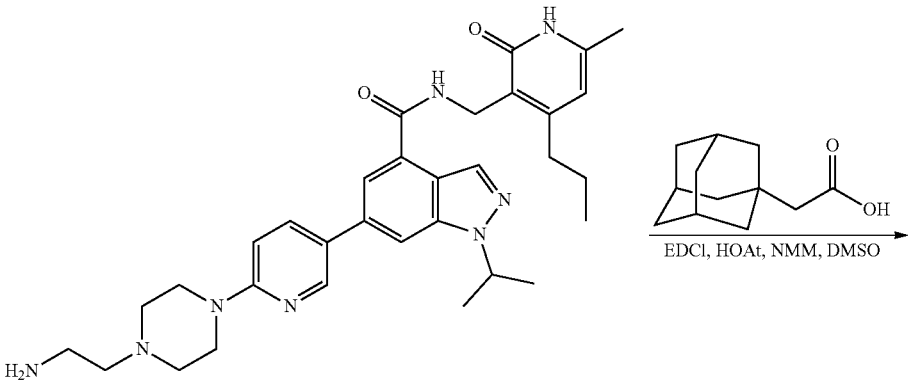
[0141] HPLC: HPLC spectra for all compounds were acquired using an Agilent™ 1200 Series system with DAD detector. Chromatography was performed on a 2.1×150 mm Zorbax™ 300SB-C18 5 μm column with water containing 0.1% formic acid as solvent A and acetonitrile containing 0.1% formic acid as solvent B at a flow rate of 0.4 ml/min. The gradient program was as follows: 1% B (0-1 min), 1-99% B (1-4 min), and 99% B (4-8 min). High-resolution mass spectra (HRMS) data were acquired in positive ion mode using an Agilent™ G1969A API-TOF with an electrospray ionization (ESI) source. Nuclear Magnetic Resonance (NMR) spectra were acquired on a Bruker® DRX-600 spectrometer with 600 MHz for proton (^{1}H NMR) and 150 MHz for carbon (13C NMR); chemical shifts are reported in (6). Preparative HPLC was performed on Agilent™ Prep 1200 series with UV detector set to 254 nm. Samples were injected onto a Phenomenex™ LUNA® 75×30 mm, 5 μm, C18 column at room temperature. The flow rate was 40 ml/min. A linear gradient was used with 10% (or 50%) of MeOH (A) in H_2O (with 0.1% TFA) (B) to 100% of MeOH (A). HPLC was used to establish the purity of target compounds. All final compounds had >95% purity using the HPLC methods described above.

Example 1: Synthesis of AM16-10A

[0142]

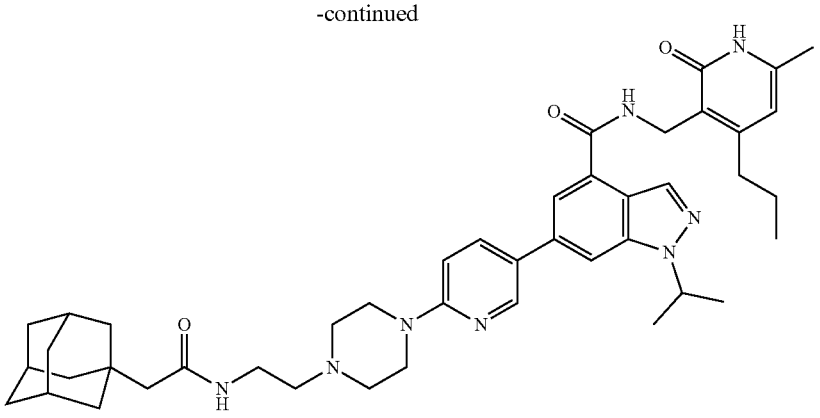


Intermediate 1



Intermediate 2

-continued



AM16-10A

[0143] Intermediate 1 (385 mg, 0.60 mmol) and N-Boc-2-aminoacetaldehyde (191 mg, 1.2 mmol, Sigma®, #472654) were dissolved in DMF (5.0 mL) and acetic acid (0.5 mL). To the solution was added sodium triacetoxyborohydride (254 mg, 1.2 mmol) at 0° C. After being stirred overnight at room temperature, the mixture was filtered and purified by reverse-phase ISCO™ (10%-100% methanol/0.1% TFA in H_2O) to afford compound tert-butyl (2-(4-(5-(1-isopropyl-4-(((6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-1H-indazol-6-yl)pyridin-2-yl)piperazin-1-yl)ethyl)carbamate 2,2,2-trifluoroacetate. The obtained intermediate was dissolved in DCM (30 mL) and treated with trifluoroacetic acid (5.0 mL) at room temperature. After being stirred overnight at room temperature, the mixture was concentrated and purified by reverse-phase ISCO™ to afford intermediate 2 (302 mg, 73% over 2 steps). Intermediate 2 (100 mg, 0.15 mmol), HOAt (1-hydroxy-7-azabenzo-triazole) (31 mg, 0.23 mmol) and 1-adamantaneacetic acid (35 mg, 0.18 mmol, Sigma®, #127272) were dissolved in DMSO (2.0 mL). To the solution were added NMM (66 μL, 0.60 mmol), and EDCI (43 mg, 0.23 mmol) successively at room temperature. After being stirred overnight at room temperature, the mixture was concentrated under vacuum and purified by preparative HPLC (10%-100% methanol/0.1% TFA in H_2O) to afford AM16-10A as white solid in TFA salt form (75 mg, 58%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.47 (s, 1H), 8.37 (s, 1H), 7.85 (d, J=7.8 Hz, 1H), 7.60 (brs, 4H), 6.75 (d, J=8.3 Hz, 1H), 6.38 (s, 1H), 4.95-4.84 (m, 1H), 4.67 (s, 2H), 4.28-3.54 (m, 7H), 3.50-2.97 (m, 6H), 2.88 (t, J=7.3 Hz, 2H), 2.40 (s, 3H), 1.92 (brs, 5H), 1.65-1.51 (m, 20H), 1.03 (t, J=7.2 Hz, 3H).

Example 2: Synthesis of AM16-11A

[0144] AM16-11A was synthesized according to the procedures for preparing AM16-10A from intermediate 2 (92 mg, 0.13 mmol), HOAt (27 mg, 0.20 mmol), 3-(1-adamantyl)propanoic acid (33 mg, 0.16 mmol, Matrix Scientific™, #038155), NMM (57 μL, 0.52 mmol), EDCI (39 mg, 0.20 mmol), and DMSO (2.0 mL). AM16-11A was obtained as white solid in TFA salt form (58 mg, 51%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.57-8.49 (m, 1H), 8.37 (s, 1H), 8.08 (d, J=8.8 Hz, 1H), 7.94 (s, 1H), 7.76 (s, 1H), 7.06 (d, J=8.8 Hz, 1H), 6.17 (s, 1H), 5.12-5.05 (m, 1H), 4.60 (s, 2H), 4.25-3.60 (m, 6H), 3.60-3.33 (m, 6H), 2.77-2.69 (m, 2H), 2.27 (s, 3H), 2.23-2.16 (m, 2H), 1.93 (brs, 2H), 1.77-1.71 (m, 3H), 1.68-1.58 (m, 6H), 1.58-1.53 (m, 6H), 1.49 (brs, 6H), 1.41-1.32 (m, 2H), 1.02 (t, J=7.3 Hz, 3H).

Example 3: Synthesis of AM16-37A

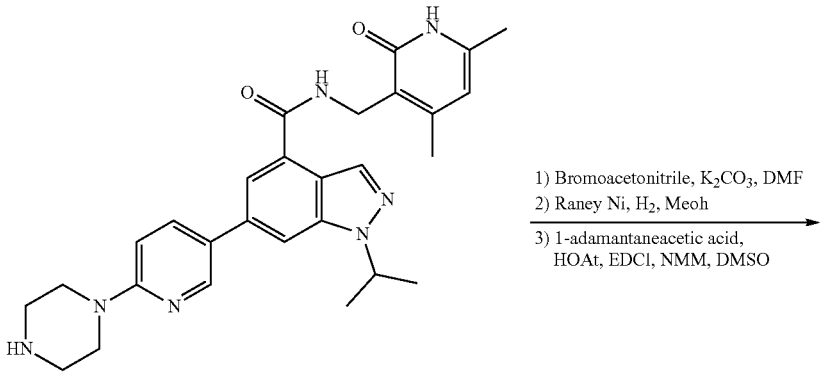
[0145] AM16-37A was synthesized according to the procedures for preparing AM16-10A from intermediate 1 (100 mg, 0.16 mmol), HOAt (33 mg, 0.24 mmol), 1-adamantaneacetic acid (38 mg, 0.19 mmol), NMM (71 μL, 0.64 mmol), EDCI (46 mg, 0.24 mmol), and DMSO (2.0 mL). AM16-37A was obtained as yellow solid (73 mg, 65%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.51 (s, 1H), 8.38 (s, 1H), 7.94-7.78 (m, 2H), 7.69 (s, 1H), 7.60 (s, 1H), 6.77 (d, J=8.7 Hz, 1H), 6.09 (brs, 1H), 4.96-4.82 (m, 1H), 4.65 (s, 2H), 3.81 (brs, 2H), 3.70 (s, 2H), 3.58 (brs, 2H), 3.47 (s, 2H), 2.77 (t, J=7.4 Hz, 2H), 2.27 (brs, 3H), 2.21 (s, 2H), 2.00-1.90 (m, 2H), 1.68-1.53 (m, 23H), 1.01 (t, J=7.2 Hz, 3H).

Example 4: Synthesis of AM16-38A

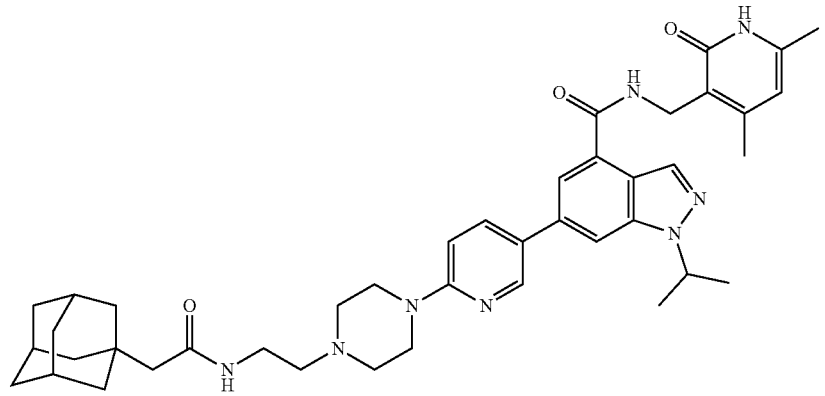
[0146] AM16-38A was synthesized according to the procedures for preparing AM16-10A from intermediate 1 (100 mg, 0.16 mmol), HOAt (33 mg, 0.24 mmol), 1-adamantaneacetic acid (38 mg, 0.19 mmol), NMM (71 μL, 0.64 mmol), EDCI (46 mg, 0.24 mmol), and DMSO (2.0 mL). AM16-38A was obtained as brown solid (69 mg, 60%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.51 (s, 1H), 8.38 (s, 1H), 7.92-7.80 (m, 2H), 7.70 (s, 1H), 7.59 (s, 1H), 6.75 (d, J=8.6 Hz, 1H), 6.05 (s, 1H), 4.94-4.83 (m, 1H), 4.65 (s, 2H), 3.77 (brs, 2H), 3.71 (brs, 2H), 3.63 (brs, 2H), 3.56 (brs, 2H), 2.75 (t, J=7.4 Hz, 2H), 2.37-2.31 (m, 2H), 2.25 (s, 3H), 1.95 (d, J=17.0 Hz, 2H), 1.70 (t, J=12.9 Hz, 4H), 1.64-1.57 (m, 12H), 1.49 (s, 5H), 1.00 (t, J=7.3 Hz, 3H).

Example 5: Synthesis of the XY019-43

[0147]



Intermediate 3



XY019-43

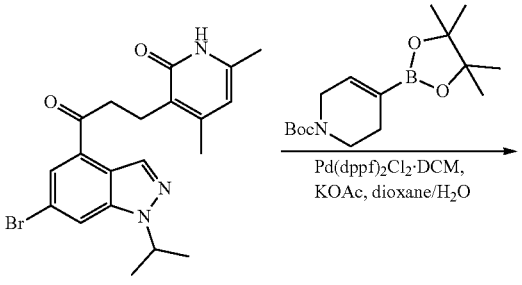
[0148] Intermediate 3 (80 mg, 0.16 mmol) was dissolved in DMF (10 mL). To the solution were added bromoacetonitrile (21 mg, 0.18 mmol) and potassium carbonate (66 mg, 0.48 mmol). After being stirred overnight at room temperature, the reaction mixture was filtered and concentrated. The residue was dissolved in methanol (30 mL) and ammonia solution (5.0 mL, 7 M in methanol). To the solution was added Raney® nickel (50 mg). The contents were purged and kept under hydrogen (balloon pressure) overnight before being filtered and concentrated under vacuum. Half of the residue was dissolved in DMSO (3.0 mL). To the solution were added NMM (24 mg, 0.24 mmol), 1-adamantaneacetic acid (19 mg, 0.10 mmol), HOAt (16 mg, 0.12 mmol), and EDCI (23 mg, 0.12 mmol). The mixture was allowed to stir at room temperature overnight. The progress of the reaction was monitored by LC-MS. The crude product was filtered and purified by preparative HPLC to yield XY019-43 as solid in TFA salt form (10 mg, 17%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.58 (d, J=2.4 Hz, 1H), 8.36 (s, 1H), 8.12 (dd, J=2.5, 8.9 Hz, 1H), 7.95 (s, 1H), 7.77 (s, 1H), 7.09 (d, J=8.9 Hz, 1H), 6.16 (s, 1H), 5.09 (p, J=6.6 Hz, 1H), 4.58 (s, 2H), 3.62 (t, J=6.1 Hz, 2H), 3.53 (brs, 8H), 3.34 (t, J=6.1 Hz, 2H), 2.43 (s, 3H), 2.26 (s, 3H), 2.00 (s, 2H), 1.96 (s, 3H), 1.76 (d, J=12.4 Hz, 3H), 1.71-1.61 (m, 9H), 1.57 (d, J=6.6 Hz, 6H). HRMS (m/z) for $C_{42}H_{55}N_8O_3^+$ $[M+H]^+$: calculated 719.4392, found 719.4396.

Example 6: Synthesis of XY019-44

[0149] XY019-44 (12 mg, 21%) was synthesized according to the procedures for preparing XY019-43. ^{1}H NMR (600 MHz, CD_3OD) δ 8.58 (s, 1H), 8.37 (s, 1H), 8.13 (dd, J=2.5, 8.9 Hz, 1H), 7.95 (s, 1H), 7.78 (s, 1H), 7.10 (d, J=8.9 Hz, 1H), 6.17 (s, 1H), 5.09 (p, J=6.7 Hz, 1H), 4.58 (s, 2H), 3.61 (t, J=5.9 Hz, 2H), 3.48 (brs, 8H), 3.35 (t, J=5.9 Hz, 2H), 2.44 (s, 3H), 2.26 (s, 3H), 2.24-2.20 (m, 2H), 1.95 (s, 2H), 1.75 (d, J=12.4 Hz, 3H), 1.66 (d, J=12.0 Hz, 3H), 1.57 (d, J=6.5 Hz, 6H), 1.51 (s, 6H), 1.44-1.35 (m, 3H). HRMS (m/z) for $C_{43}H_{57}N_8O_3^+$ $[M+H]^+$: calculated 733.4548, found 733.4544.

Example 7: Synthesis of XY019-079

[0150]



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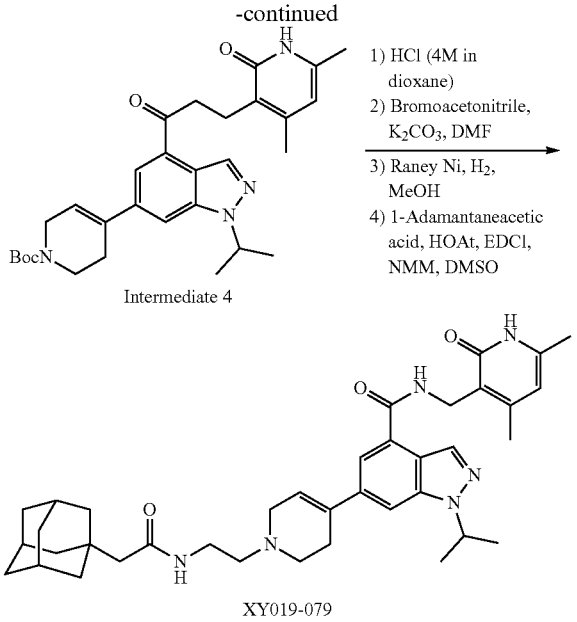
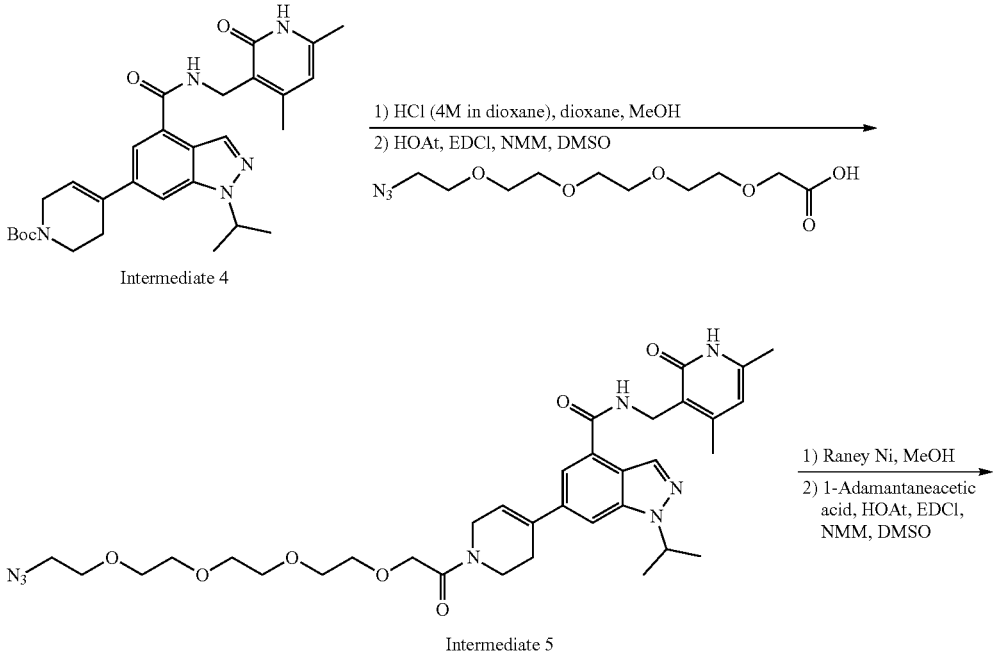


[0151] 6-Bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-isopropyl-1H-indazole-4-carboxamide (294 mg, 0.707 mmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (262 mg, 0.85 mmol) and KOAc (207 mg, 2.1 mmol) were dissolved in 1,4-dioxane (30 mL) and water (5.0 mL) in a flask. To the solution was added $Pd(dppf)Cl_2$. DCM (30 mg, 10% wt) under argon atmosphere at room temperature. The mixture was heated at 80° C. overnight before being cooled to room temperature. The crude intermediate was filtered and purified by flash column chromatography (0-100% MeOH in DCM) to yield intermediate 4 (320 mg, 87%). MS (m/z) $[M+H]^+$: 520.2. To the solution of intermediate 4 (60 mg, 0.12 mmol) in dioxane (5.0 mL), and methanol (5.0 mL) was added hydrogen chloride (1.0 mL, 4 M in dioxane) dropwise. The resulting solution was stirred at room temperature for 2 h before being concentrated under vacuum. The resulting residue was dissolved in DMF (10 mL). To the solution were added potassium carbonate (100 mg, 0.69 mmol) and bromoacetonitrile (30 mg, 0.25 mmol). After being stirred overnight at room temperature, the reaction mixture was filtered and concentrated. The crude intermediate obtained was dissolved in methanol (30 mL) and ammonia in methanol (7 M, 5.0 mL). To the solution was added Raney® nickel (20% wt) in catalytic amount. The reaction mixture was purged and stirred under hydrogen (balloon pressure) overnight. The reaction was monitored via LC-MS. Upon completion, the reaction mixture was filtered and concentrated under vacuum. The crude intermediate obtained was dissolved in DMSO (3.0 mL). To the solution were added NMM (35 mg, 0.35 mmol), 1-adamantaneacetic acid (27 mg, 0.14 mmol), HOAt (24 mg, 0.17 mmol), and EDCI (33 mg, 0.17 mmol). The mixture was allowed to stir at room temperature overnight. The progress of the reaction was monitored by LC-MS. The crude product was filtered and purified by preparative HPLC to yield XY019-079 as solid (15 mg, 20%). ^1H NMR (600 MHz, CD_3OD) δ 8.34 (s, 1H), 7.82 (s, 1H), 7.70 (s, 1H), 6.35 (s, 1H), 6.18 (s, 1H), 5.05 (p, J=6.7 Hz, 1H), 4.56 (s, 2H), 4.29-4.17 (m, 1H), 4.00-3.88 (m, 2H), 3.71-3.61 (m, 2H), 3.47-3.38 (m, 3H), 3.08-3.00 (m, 2H), 2.43 (s, 3H), 2.26 (s, 3H), 2.00 (s, 2H), 1.99-1.90 (m, 3H), 1.75 (t, J=7.7 Hz, 3H), 1.70-1.59 (m, 9H), 1.55 (d, J=6.7 Hz, 6H). HRMS (m/z) for $C_{38}H_{51}N_6O_3^+$ $[M+H]^+$: calculated 639.4017, found 639.4028.

Example 8: Synthesis of XY019-080

[0152]



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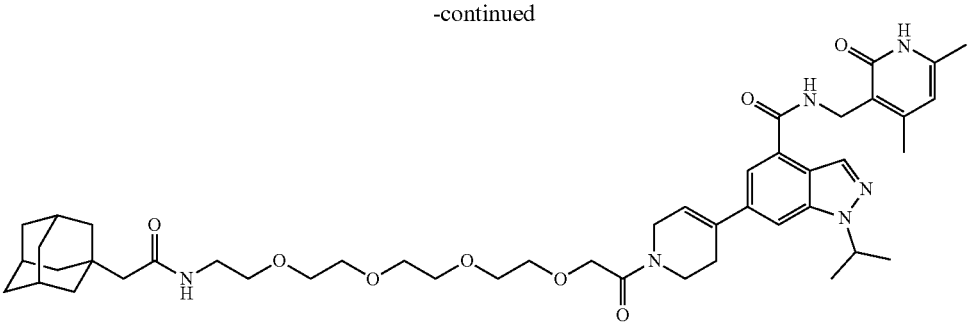
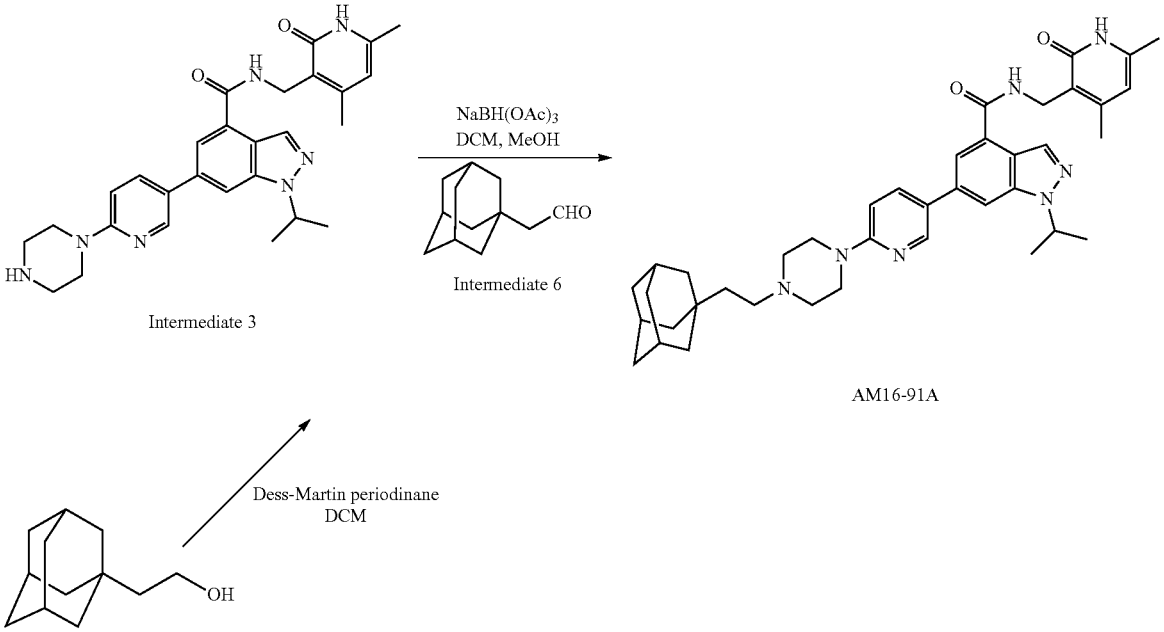


XY019-080

[0153] To the solution of intermediate 4 (60 mg, 0.12 mmol) in dioxane (5.0 mL), and methanol (5.0 mL) was added hydrogen chloride (1.0 mL, 4 M in dioxane) dropwise. The mixture was stirred at room temperature for 2 h before being concentrated under vacuum. The resulting residue was dissolved in DMSO (3.0 mL). To the solution were added NMM (70 mg, 0.70 mmol), 14-azido-3,6,9,12-tetraoxatetradecanoic acid (38 mg, 0.14 mmol), HOAt (24 mg, 0.17 mmol), and EDCI (33 mg, 0.17 mmol). The mixture was stirred overnight at room temperature. The progress of the reaction was monitored by LC-MS. The crude intermediate was filtered and purified by preparative HPLC to yield intermediate 5 (37 mg, 47%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.32 (d, J=2.1 Hz, 1H), 7.75 (s, 1H), 7.69 (s, 1H), 6.33 (d, J=14.0 Hz, 1H), 6.18 (s, 1H), 5.04 (p, J=6.6 Hz, 1H), 4.56 (s, 2H), 4.33 (d, J=19.0 Hz, 2H), 4.25 (d, J=8.7 Hz, 2H), 3.85 (t, J=5.7 Hz, 1H), 3.78 (t, J=5.6 Hz, 1H), 3.73-3.53 (m, 16H), 2.77 (s, 1H), 2.68 (s, 1H), 2.43 (s, 3H), 2.26 (s, 3H), 1.55 (d, J=6.6 Hz, 6H). MS (m/z) $[M+H]^+$: 679.3. Intermediate 5 (37 mg, 0.05 mmol) was dissolved in methanol (30 mL) and ammonia solution (5.0 mL, 7 M in methanol). To the solution was added Raney® nickel (20% wt) in catalytic amount. The reaction mixture was purged and stirred under hydrogen (balloon pressure) overnight. The reaction was monitored via LC-MS. Upon completion, the reaction mixture was filtered and concentrated under vacuum. The resulting residue was dissolved in DMSO (3.0 mL). To the solution were added NMM (15 mg, 0.15 mmol), 1-adamantaneacetic acid (12 mg, 0.06 mmol), HOAt (10 mg, 0.08 mmol), and EDCI (14 mg, 0.08 mmol). The reaction mixture was stirred at room temperature overnight. The progress of the reaction was monitored by LC-MS. The crude product was filtered and purified by preparative HPLC to yield XY019-080 as solid (4.5 mg, 20%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.32 (s, 1H), 7.74 (s, 1H), 7.69 (d, J=4.7 Hz, 1H), 6.33 (d, J=12.4 Hz, 1H), 6.16 (s, 1H), 5.04 (p, J=6.6 Hz, 1H), 4.57 (s, 2H), 4.34 (d, J=20.5 Hz, 2H), 4.25 (s, 2H), 3.86 (t, J=5.7 Hz, 1H), 3.77 (t, J=5.6 Hz, 1H), 3.73-3.45 (m, 12H), 2.77 (s, 1H), 2.68 (s, 1H), 2.42 (s, 3H), 2.26 (s, 3H), 2.02 (s, 1H), 1.95 (s, 1H), 1.92-1.85 (m, 4H), 1.80-1.56 (m, 15H), 1.55 (d, J=7.1 Hz, 6H). HRMS (m/z) for $C_{46}H_{65}N_6O_8^+$ $[M+H]^+$: calculated 829.4858, found 829.4855.

Example 9: Synthesis of AM16-91A

[0154]



[0155] 1-Adamantaneethanol (1.0 gram, 5.6 mmol, Sigma®, #188115) was dissolved in DCM (15 mL). To the solution was added Dess-Martin periodinane (5.0 mL) at 0° C. After being stirred overnight at room temperature, the mixture was purified by ISCO™ to afford intermediate 6 (780 mg, 79%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.86 (t, J=3.2 Hz, 1H), 2.12 (d, J=3.2 Hz, 2H), 1.98 (brs, 3H), 1.67-1.64 (m, 12H). Intermediate 3 (100 mg, 0.16 mmol) and intermediate 6 (35 mg, 0.20 mmol) were dissolved in DCM (3.0 mL), and methanol (3.0 mL). To the solution was added sodium triacetoxyborohydride (55 mg, 0.26 mmol) at 0° C. After being stirred overnight at room temperature, the mixture was filtered and purified by preparative HPLC to afford AM16-91A as yellow solid in TFA salt form (99 mg, 80%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.53 (brs, 1H), 8.37 (s, 1H), 8.12-8.02 (m, 1H), 7.93 (s, 1H), 7.76 (s, 1H), 7.03 (d, J=8.7 Hz, 1H), 6.14 (s, 1H), 5.11-5.03 (m, 1H), 4.57 (s, 2H), 4.49 (brs, 2H), 3.69 (brs, 2H), 3.34-3.03 (m, 6H), 2.42 (s, 3H), 2.24 (s, 3H), 1.96 (brs, 3H), 1.79-1.73 (m, 3H), 1.70-1.65 (m, 3H), 1.59-1.54 (m, 14H).

Example 10: Synthesis of AM16-92A

[0156] AM16-92A was synthesized according to the procedures for preparing AM16-10A from intermediate 3 (100 mg, 0.16 mmol), HOAt (33 mg, 0.24 mmol), 1-adamantaneacetic acid (38 mg, 0.20 mmol), NMM (71 μL, 0.64 mmol), EDCI (46 mg, 0.24 mmol), and DMSO (2.0 mL). AM16-92A was obtained as white solid in TFA salt form (77 mg, 61%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.45-8.32 (m, 3H), 8.02 (s, 1H), 7.78 (s, 1H), 7.36-7.28 (m, 1H), 6.15 (s, 1H), 5.15-5.05 (m, 1H), 4.58 (s, 2H), 3.92-3.88 (m, 2H), 3.86-3.83 (m, 2H), 3.80-3.76 (m, 4H), 2.44 (s, 3H), 2.28 (s, 2H), 2.26 (s, 3H), 1.99-1.96 (m, 3H), 1.73-1.67 (m, 12H), 1.58 (s, 3H), 1.57 (s, 3H).

Example 11: Synthesis of AM16-93A

[0157] AM16-93A was synthesized according to the procedures for preparing AM16-10A from intermediate 3 (100 mg, 0.16 mmol), HOAt (33 mg, 0.24 mmol), 3-(1-adamantyl)propanoic acid (42 mg, 0.20 mmol), NMM (71 μL, 0.64 mmol), EDCI (46 mg, 0.24 mmol), and DMSO (2.0 mL). AM16-93A was obtained green solid in TFA salt form (85 mg, 66%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.43-8.36 (m, 2H), 8.34-8.28 (m, 1H), 8.01 (s, 1H), 7.77 (s, 1H), 7.30-7.21 (m, 1H), 6.15 (s, 1H), 5.14-5.04 (m, 1H), 4.58 (s, 2H), 3.81 (brs, 6H), 3.76-3.70 (m, 2H), 2.45-2.38 (m, 5H), 2.25 (s, 3H), 1.99-1.94 (m, 3H), 1.73-1.69 (m, 3H), 1.60-1.54 (m, 12H), 1.49 (s, 3H), 1.41-1.37 (m, 2H).

Example 12: Synthesis of AM16-97A

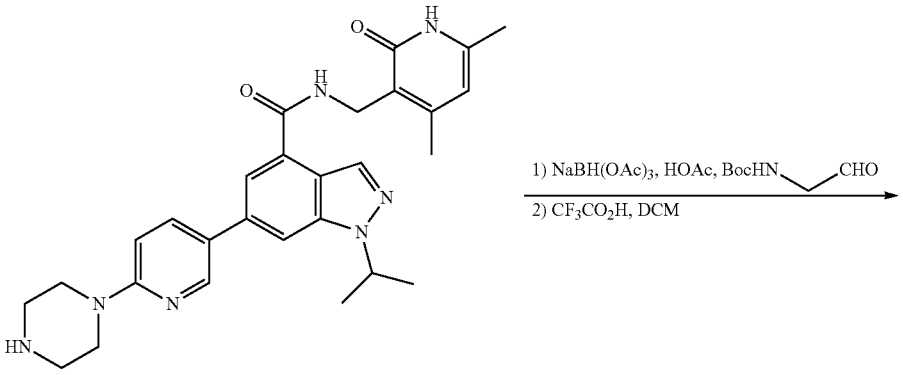
[0158] AM16-97A was synthesized according to the procedures for preparing AM16-10A from intermediate 3 (67 mg, 0.11 mmol), HOAt (23 mg, 0.17 mmol), (2R)-4-((1r,3S)-adamantan-1-yl)-2-methylbutanoic acid (25 mg, 0.11 mmol), NMM (49 μL, 0.44 mmol), EDCI (33 mg, 0.17 mmol), and DMSO (2.0 mL). (2R)-4-((1r,3S)-Adamantan-1-yl)-2-methylbutanoic acid was synthesized according to the procedures reported previously(Neklesa et al., 2011). AM16-97A was obtained as brown solid in TFA salt form (58 mg, 63%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.43 (brs, 1H), 8.37 (s, 1H), 8.23 (brs, 1H), 7.98 (s, 1H), 7.77 (s, 1H), 7.17 (brs, 1H), 6.13 (s, 1H), 5.13-5.03 (m, 1H), 4.57 (s, 2H), 3.89-3.79 (m, 4H), 3.76 (brs, 2H), 3.70 (brs, 2H), 2.84-2.74 (m, 1H), 2.43 (s, 3H), 2.25 (s, 3H), 1.92 (brs, 3H), 1.77-1.70 (m, 3H), 1.67-1.63 (m, 3H), 1.59-1.54 (m, 6H), 1.50 (brs, 6H), 1.46-1.29 (m, 2H), 1.13 (d, J=6.6 Hz, 3H), 1.10-0.98 (m, 2H).

Example 13: Synthesis of AM16-100A

[0159] AM16-100A was synthesized according to the procedures for preparing AM16-10A from intermediate 3 (75 mg, 0.12 mmol), HOAt (25 mg, 0.18 mmol), 1-adamantanecarboxylic acid (27 mg, 0.15 mmol, Sigma®, #106399), NMM (53 μL, 0.48 mmol), EDCI (35 mg, 0.18 mmol), and DMSO (1.5 mL). AM16-100A was obtained as brown solid in TFA salt form (92 mg, 99%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.44-8.30 (m, 3H), 8.02 (s, 1H), 7.77 (s, 1H), 7.32 (d, J=9.3 Hz, 1H), 6.16 (s, 1H), 5.13-5.04 (m, 1H), 4.58 (s, 2H), 4.00-3.94 (m, 4H), 3.79-3.73 (m, 4H), 2.43 (s, 3H), 2.26 (s, 3H), 2.06-1.79 (m, 15H), 1.58 (s, 3H), 1.57 (s, 3H).

Example 14: Synthesis of AM16-101A

[0160]



Intermediate 3

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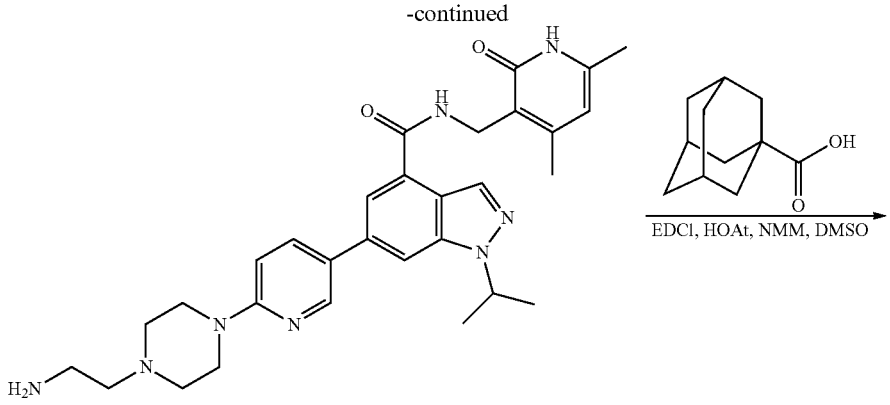
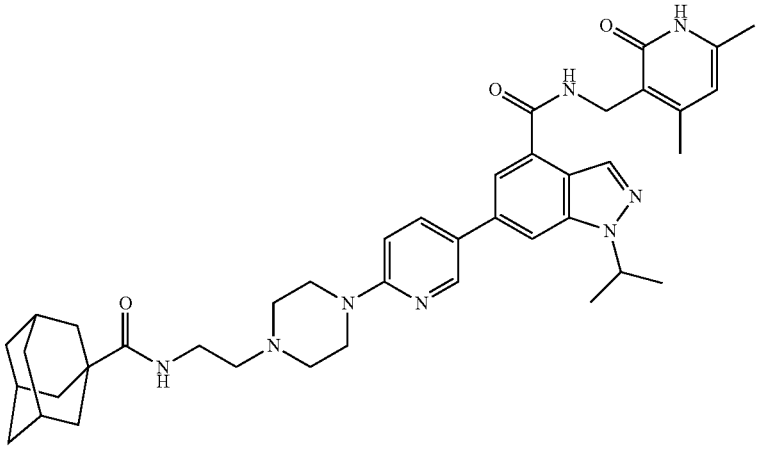


Intermediate 7

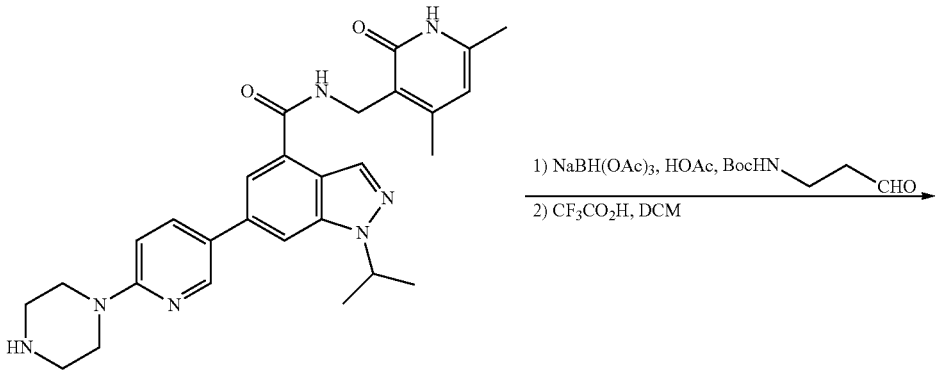


AM16-101A

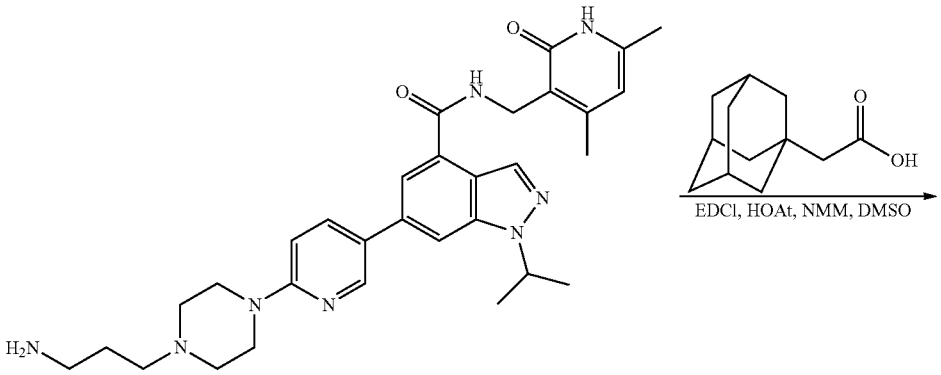
[0161] Intermediate 3 (963 mg, 1.6 mmol) and N-Boc-2-aminoacetaldehyde (750 mg, 4.7 mmol) were dissolved in DCM (10 mL), and methanol (10 mL). To the solution was added sodium triacetoxyborohydride (1.3 gram, 6.3 mmol) at 0° C. After being stirred overnight at room temperature, the mixture was purified by reverse-phase ISCO™ (10%-100% methanol/0.1% TFA in H_2O) to afford compound tert-butyl (2-(4-(5-(4-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-1-isopropyl-1H-indazol-6-yl)pyridin-2-yl)piperazin-1-yl)ethyl)carbamate (1.1 gram). The obtained intermediate was dissolved in DCM (30 mL) and treated with trifluoroacetic acid (5.0 mL) at room temperature. After being stirred overnight at room temperature, the mixture was purified by reverse-phase ISCO™ to afford intermediate 7 (750 mg, 72% over 2 steps). AM16-101A was synthesized according to the procedures for preparing AM16-10A from intermediate 7 (75 mg, 0.11 mmol), HOAt (23 mg, 0.17 mmol), 1-adamantanecarboxylic acid (25 mg, 0.14 mmol), NMM (51 μL, 0.46 mmol), EDCI (33 mg, 0.17 mmol), and DMSO (1.5 mL). AM16-101A was obtained as off-white solid in TFA salt form (80 mg, 86%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.55 (brs, 1H), 8.37 (s, 1H), 8.14 (d, J=8.9 Hz, 1H), 7.96 (s, 1H), 7.77 (s, 1H), 7.11 (d, J=8.9 Hz, 1H), 6.18 (s, 1H), 5.13-5.04 (m, 1H), 4.58 (s, 2H), 4.34-3.40 (m, 10H), 3.39-3.34 (m, 2H), 2.44 (s, 3H), 2.26 (s, 3H), 2.03 (brs, 3H), 1.88 (s, 6H), 1.80 (d, J=12.3 Hz, 3H), 1.74 (d, J=12.0 Hz, 3H), 1.58 (s, 3H), 1.57 (s, 3H).

Example 15: Synthesis of AM16-102A

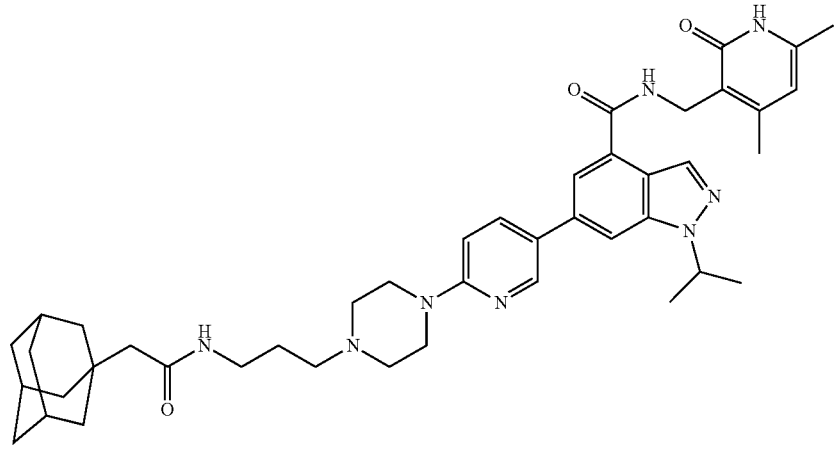
[0162]



Intermediate 3



Intermediate 8



AM16-102A

[0163] Intermediate 3 (250 mg, 0.41 mmol) and tert-butyl (3-oxopropyl)carbamate (106 mg, 0.61 mmol, AstaTech, #71690) were dissolved in DCM (2.0 mL), and methanol (2.0 mL). To the solution was added sodium triacetoxyborohydride (261 mg, 1.2 mmol) at 0° C. After being stirred overnight at room temperature, the mixture was purified by reverse-phase ISCO™ (10%-100% methanol/0.1% TFA in H_2O) to afford compound tert-butyl (2-(4-(5-(4-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-1-isopropyl-1H-indazol-6-yl)pyridin-2-yl)piperazin-1-yl) ethyl)carbamate. The obtained intermediate was dissolved in DCM (10 mL) and treated with trifluoroacetic acid (1.7 mL) at room temperature. After being stirred overnight at room temperature, the mixture was purified by reverse-phase ISCO™ to afford intermediate 8 (233 mg, 85% over 2 steps). AM16-102A was synthesized according to the procedures for preparing AM16-10A from intermediate 8 (116 mg, 0.17 mmol), HOAt (35 mg, 0.26 mmol), 1-adamantaneacetic acid

(41 mg, 0.21 mmol), NMM (75 μL, 0.68 mmol), EDCI (50 mg, 0.26 mmol), and DMSO (1.5 mL). AM16-102A was obtained as white solid in TFA salt form (101 mg, 70%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.55-8.46 (m, 1H), 8.37 (s, 1H), 8.16 (dd, J=8.9, 1.7 Hz, 1H), 7.96 (s, 1H), 7.76 (s, 1H), 7.13 (d, J=9.1 Hz, 1H), 6.20 (s, 1H), 5.14-5.02 (m, 1H), 4.58 (s, 2H), 3.87-3.31 (m, 8H), 3.27-3.22 (m, 2H), 2.43 (s, 3H), 2.26 (s, 3H), 2.07-1.99 (m, 2H), 1.98-1.86 (m, 5H), 1.78-1.60 (m, 14H), 1.57 (s, 3H), 1.56 (s, 3H).

Example 16: Synthesis of AM16-105A

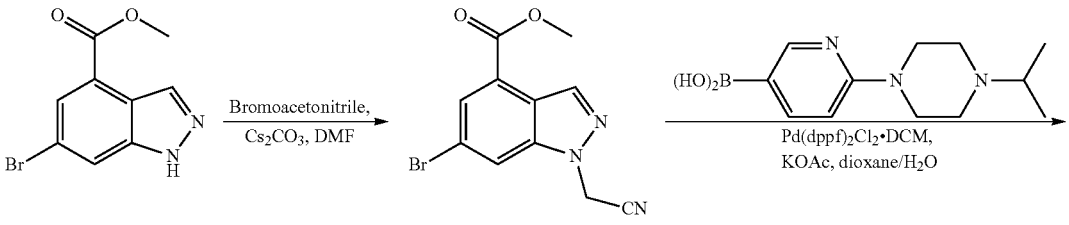
[0164] AM16-105A was synthesized according to the procedures for preparing AM16-10A from intermediate 7 (100 mg, 0.15 mmol), HOAt (31 mg, 0.23 mmol), (2R)-4-((1r, 3S)-adamantan-1-yl)-2-methylbutanoic acid (36 mg, 0.15 mmol), NMM (66 μL, 0.60 mmol), EDCI (44 mg, 0.23 mmol), and DMSO (1.5 mL). AM16-105A was obtained as white solid in TFA salt form (102 mg, 77%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.55 (d, J=1.8 Hz, 1H), 8.37 (s, 1H), 8.11 (dd, J=8.9, 2.0 Hz, 1H), 7.95 (s, 1H), 7.77 (s, 1H), 7.08 (d, J=8.9 Hz, 1H), 6.17 (s, 1H), 5.13-5.04 (m, 1H), 4.58 (s, 2H), 4.21-3.53 (m, 8H), 3.36 (t, J=6.3 Hz, 2H), 2.43 (s, 3H), 2.30-2.20 (m, 4H), 1.92 (s, 3H), 1.69 (dd, J=51.3, 11.9 Hz, 8H), 1.58 (s, 3H), 1.56 (s, 3H), 1.49 (s, 7H), 1.41-1.31 (m, 1H), 1.13 (d, J=6.8 Hz, 3H), 1.08 (td, J=13.0, 4.1 Hz, 1H), 0.98 (td, J=13.0, 4.3 Hz, 1H).

Example 17: Synthesis of AM16-106A

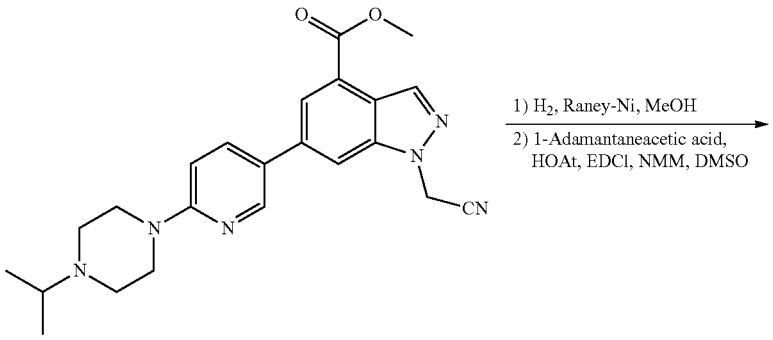
[0165] AM16-106A was synthesized according to the procedures for preparing AM16-10A from intermediate 8 (100 mg, 0.15 mmol), HOAt (31 mg, 0.23 mmol), (2R)-4-((1r, 3S)-adamantan-1-yl)-2-methylbutanoic acid (36 mg, 0.15 mmol), NMM (66 μL, 0.60 mmol), EDCI (44 mg, 0.23 mmol), and DMSO (1.5 mL). AM16-106A was obtained as solid in TFA salt form (101 mg, 76%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.53 (s, 1H), 8.37 (s, 1H), 8.12 (dd, J=8.9, 2.0 Hz, 1H), 7.94 (s, 1H), 7.76 (s, 1H), 7.09 (d, J=9.0 Hz, 1H), 6.18 (s, 1H), 5.13-5.03 (m, 1H), 4.58 (s, 2H), 4.41-3.34 (m, 8H), 3.23 (t, J=7.5 Hz, 2H), 2.43 (s, 3H), 2.26 (s, 3H), 2.24-2.17 (m, 1H), 2.08-1.97 (m, 2H), 1.91 (brs, 3H), 1.78-1.58 (m, 8H), 1.57 (s, 3H), 1.56 (s, 3H), 1.48 (s, 7H), 1.39-1.30 (m, 1H), 1.13 (d, J=6.8 Hz, 3H), 1.07 (td, J=12.9, 4.0 Hz, 1H), 0.97 (td, J=13.0, 4.3 Hz, 1H).

Example 18: Synthesis of XY012-120

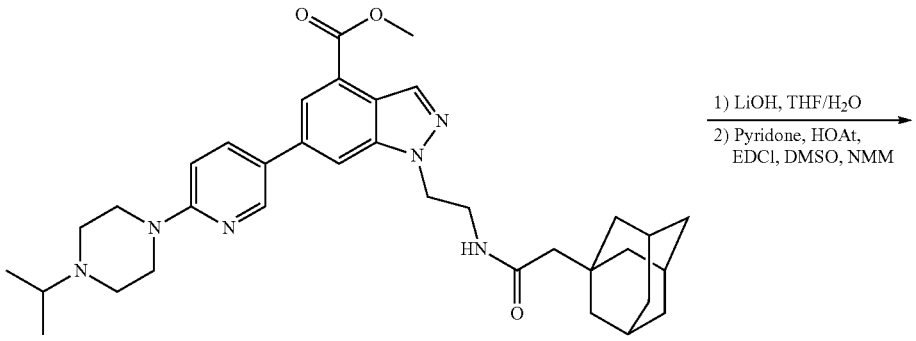
[0166]



Intermediate 9

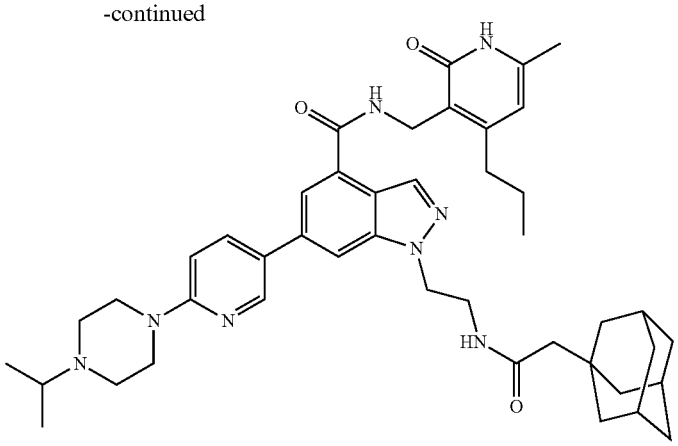


Intermediate 10



Intermediate 11

-continued



XY012-120

[0167] To the solution of methyl 6-bromo-1H-indazole-4-carboxylate (1.0 g, 3.9 mmol) in acetonitrile (100 mL) were added Cs_2CO_3 (2.6 g, 7.8 mmol) and bromoacetonitrile (0.71 g, 5.9 mmol) successively. And the reaction mixture was stirred at 60° C. for 30 min. Upon completion, the mixture was filtered, concentrated and purified by flash column chromatography (0-20% ethyl acetate in hexane) to yield intermediate 9 (0.24 g, 21%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.11 (s, 1H), 7.88 (s, 1H), 5.32 (s, 2H), 4.04 (s, 3H). MS (m/z) $[M+H]^+$: 293.9/295.9. Intermediate 9 (100 mg, 0.34 mmol), (6-(4-isopropylpiperazin-1-yl)pyridin-3-yl)boronic acid (94 mg, 0.37 mmol), and potassium acetate (100 mg, 1.0 mmol) were dissolved in 1,4-dioxane (30 mL) and water (5.0 mL). To the resulting solution was added Pd(dppf)Cl_2.DCM (20 mg, 20% wt) under argon atmosphere at room temperature. The mixture was heated at 80° C. overnight. After being cooled to room temperature, the mixture was purified by flash column chromatography (0-15% MeOH in DCM) to yield intermediate 10 (130 mg, 91%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.49-8.45 (m, 2H), 8.09-8.05 (m, 2H), 7.91 (dt, J=2.9, 8.9 Hz, 1H), 6.92 (dd, J=3.2, 8.8 Hz, 1H), 5.67 (s, 2H), 4.02 (s, 3H), 3.75 (t, J=5.2 Hz, 4H), 3.16-3.07 (m, 1H), 3.01 (t, J=5.0 Hz, 4H), 1.26 (dd, J=3.0, 6.5 Hz, 6H). MS (m/z) $[M+H]^+$: 419.2. To the solution of intermediate 10 (110 mg, 0.26 mmol) in methanol (30 mL) was added Raney® nickel (20% wt) in catalytic amount. The reaction mixture was purged and stirred under hydrogen (balloon pressure) overnight. The reaction was monitored via LC-MS. Upon completion, the reaction mixture was filtered and concentrated under vacuum. Half of the resulting residue was dissolved in DMSO (3.0 mL). To the solution were added NMM (40 mg, 0.39 mmol), 1-adamantaneacetic acid (28 mg, 0.14 mmol), HOAt (27 mg, 0.20 mmol), and EDCI (38 mg, 0.20 mmol). The mixture was stirred at room temperature overnight. The progress of the reaction was monitored by LC-MS. The crude intermediate was filtered and purified by preparative HPLC to yield intermediate 11 as solid (17 mg, 21%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.56 (d, J=2.6 Hz, 1H), 8.46 (d, J=2.2 Hz, 1H), 8.13 (dd, J=2.6, 8.9 Hz, 1H), 8.10 (s, 1H), 8.05 (s, 1H), 7.16 (d, J=8.9 Hz, 1H), 4.70-4.56 (m, 6H), 4.02 (s, 3H), 3.76 (t, J=5.9 Hz, 4H), 3.67-3.57 (m, 3H), 1.74 (s, 2H), 1.68 (s, 3H), 1.59-1.52 (m, 3H), 1.45-1.37 (m, 9H), 1.31 (s, 6H). MS (m/z) $[M+H]^+$: 599.3. To the solution of intermediate 11 (17 mg, 0.03 mmol) in THF/H_2O (8.0 mL/2.0 mL) was added LiOH (4.0 mg, 0.17 mmol). And the resulting mixture was stirred overnight at room temperature. The disappearance of starting material was confirmed by TLC. The reaction mixture was then concentrated under vacuum and the resulting residue was dissolved in DMSO (2.0 mL). To the solution were added 3-(aminomethyl)-4,6-dimethylpyridin-2(1H)-one (7.0 mg, 0.032 mmol), NMM (9.0 mg, 0.085 mmol), HOAt (6.0 mg, 0.043 mmol), and EDCI (8.0 mg, 0.043 mmol). The mixture was allowed to stir overnight at room temperature. The progress of the reaction was monitored by LC-MS. The crude product was filtered and purified by preparative HPLC to yield XY012-120 as solid in TFA salt form (12 mg, 57%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.55 (d, J=2.4 Hz, 1H), 8.40 (s, 1H), 8.21 (dd, J=2.5, 9.0 Hz, 1H), 7.96 (s, 1H), 7.79 (d, J=1.3 Hz, 1H), 7.21 (d, J=9.1 Hz, 1H), 6.22 (s, 1H), 4.65-4.54 (m, 4H), 3.74 (t, J=5.9 Hz, 2H), 3.63 (p, J=6.6 Hz, 1H), 3.38 (brs, 8H), 2.78-2.73 (m, 2H), 2.28 (s, 3H), 1.72 (s, 2H), 1.68-1.62 (m, 5H), 1.53-1.49 (m, 3H), 1.43 (d, J=6.6 Hz, 6H), 1.40-1.34 (m, 3H), 1.30-1.26 (m, 6H), 1.02 (t, J=7.3 Hz, 3H). HRMS (m/z) for $C_{44}H_{59}N_8O_3^+$ $[M+H]^+$: calculated 747.4705, found 747.4704.

Example 19: Synthesis of AM29-21A

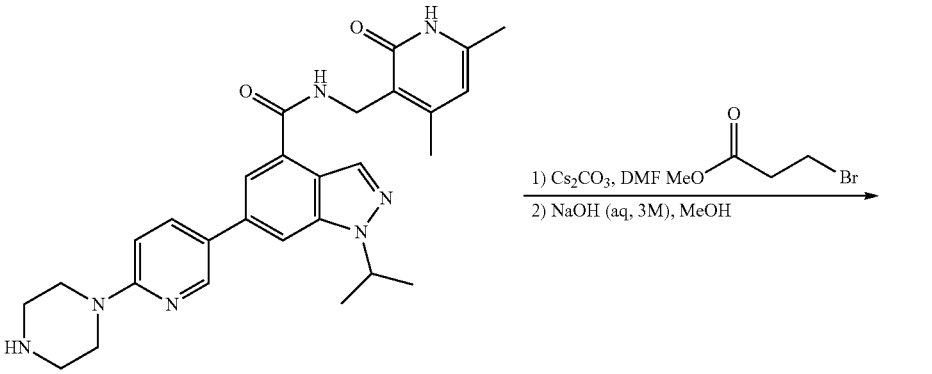
[0168] AM29-21A was synthesized according to the procedures for preparing AM16-10A from intermediate 5 (80 mg, 0.09 mmol), HOAt (19 mg, 0.14 mmol), 3,5-dimethyl-adamantane-1-acetic acid (25 mg, 0.11 mmol, Sigma®, #679976), NMM (40 μL, 0.36 mmol), EDCI (27 mg, 0.14 mmol), and DMSO (1.0 mL). AM29-21A was obtained as off-white solid in TFA salt form (58 mg, 74%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.50 (d, J=2.3 Hz, 1H), 8.37 (s, 1H), 8.19 (dd, J=9.1, 2.4 Hz, 1H), 7.96 (s, 1H), 7.76 (s, 1H), 7.16 (d, J=9.1 Hz, 1H), 6.22 (s, 1H), 5.13-5.04 (m, 1H), 4.58 (s, 2H), 3.98 (brs, 4H), 3.64 (t, J=6.0 Hz, 2H), 3.58 (brs, 4H), 3.38 (t, J=6.0 Hz, 2H), 2.44 (s, 3H), 2.28 (s, 3H), 2.08-1.96 (m, 3H), 1.57 (s, 3H), 1.56 (s, 3H), 1.45 (d, J=1.9 Hz, 2H), 1.36-1.17 (m, 9H), 1.16-1.11 (m, 1H), 1.07 (d, J=12.3 Hz, 1H), 0.80 (s, 6H).

Example 20: Synthesis of AM29-22A

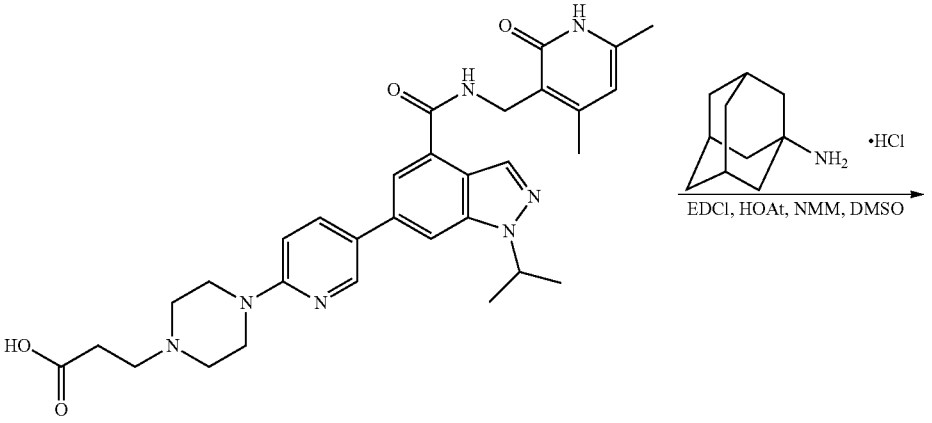
[0169] AM29-22A was synthesized according to the procedures for preparing AM16-10A from intermediate 5 (80 mg, 0.09 mmol), HOAt (19 mg, 0.14 mmol), 3,5-dimethyladamantane-1-carboxylic acid (23 mg, 0.11 mmol, Sigma®, #679984), NMM (40 μL, 0.36 mmol), EDCI (27 mg, 0.14 mmol), and DMSO (1.0 mL). AM29-22A was obtained as off-white solid in TFA salt form (67 mg, 87%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.49 (d, J=2.3 Hz, 1H), 8.37 (s, 1H), 8.18 (dd, J=9.1, 2.4 Hz, 1H), 7.96 (s, 1H), 7.76 (s, 1H), 7.15 (d, J=9.1 Hz, 1H), 6.22 (s, 1H), 5.10-5.03 (m, 1H), 4.58 (s, 2H), 3.98 (brs, 4H), 3.64 (t, J=5.9 Hz, 2H), 3.56 (brs, 4H), 3.37 (t, J=5.9 Hz, 2H), 2.44 (s, 3H), 2.27 (s, 3H), 2.15-2.06 (m, 1H), 1.70 (d, J=2.0 Hz, 2H), 1.56 (d, J=6.6 Hz, 6H), 1.48 (dd, J=37.2, 12.5 Hz, 4H), 1.39-1.35 (m, 3H), 1.22-1.12 (m, 2H), 0.85 (s, 6H).

Example 21: Synthesis of AM29-32A

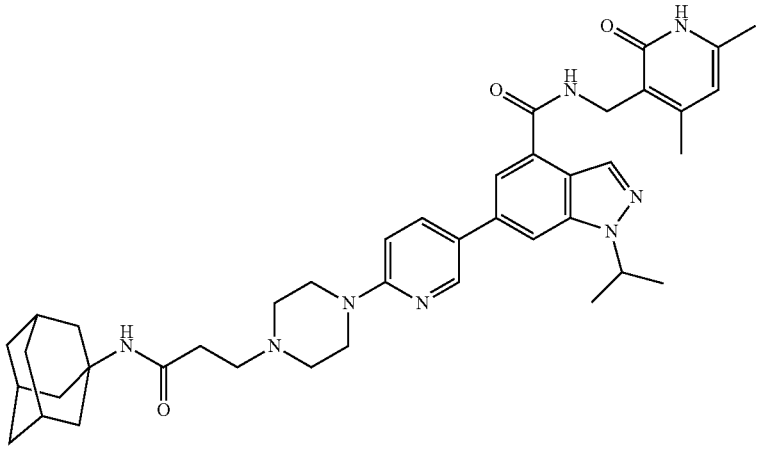
[0170]



Intermediate 3



Intermediate 12



AM29-32A

[0171] Intermediate 3 (100 mg, 0.16 mmol) and methyl 3-bromopropionate (41 mg, 0.25 mmol, Sigma®, #679984) were dissolved in DMF (1.0 mL). To the solution was added cesium carbonate (105 mg, 0.32 mmol) at room temperature. After being stirred overnight at room temperature, to the mixture were added sodium hydroxide solution (0.5 mL, 3M), and methanol (2.0 mL). After being stirred for additional 2 h at room temperature, the mixture was concentrated under vacuum and purified by preparative HPLC to afford intermediate 12 as a TFA salt (110 mg, 99%). AM29-32A was synthesized according to the procedures for preparing AM16-10A from intermediate 12 (55 mg, 0.08 mmol), HOAt (17 mg, 0.12 mmol), amantadine hydrochloride (19 mg, 0.10 mmol, Sigma®, #A1260), NMM (35 μL, 0.32 mmol), EDCI (23 mg, 0.12 mmol), and DMSO (1.0 mL). AM29-32A was obtained as off-white solid in TFA salt form (18 mg, 27%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.55 (d, J=2.3 Hz, 1H), 8.38 (s, 1H), 8.25 (dd, J=9.0, 2.4 Hz, 1H), 8.00 (s, 1H), 7.79 (s, 1H), 7.22 (d, J=9.1 Hz, 1H), 6.25 (s, 1H), 5.15-5.06 (m, 1H), 4.60 (s, 2H), 4.20-3.80 (m, 4H), 3.66-3.44 (m, 6H), 2.73 (t, J=6.8 Hz, 2H), 2.46 (s, 3H), 2.29 (s, 3H), 2.10-1.97 (m, 9H), 1.76-1.68 (m, 6H), 1.58 (s, 3H), 1.57 (s, 3H).

Example 22: Synthesis of AM29-33A

[0172] AM29-33A was synthesized according to the procedures for preparing AM16-10A from intermediate 12 (55 mg, 0.08 mmol), HOAt (17 mg, 0.12 mmol), 1-adamantanemethylamine (16 mg, 0.10 mmol, Acros Organics, #177420010), NMM (35 μL, 0.32 mmol), EDCI (23 mg, 0.12 mmol), and DMSO (1.0 mL). AM29-33A was obtained as off-white solid in TFA salt form (60 mg, 90%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.52 (s, 1H), 8.38 (s, 1H), 8.21 (dd, J=8.8, 1.7 Hz, 1H), 7.98 (s, 1H), 7.77 (s, 1H), 7.18 (d, J=8.8 Hz, 1H), 6.23 (s, 1H), 5.15-5.02 (m, 1H), 4.59 (s, 2H), 3.98 (brs, 4H), 3.62-3.44 (m, 6H), 2.91 (s, 2H), 2.85 (t, J=6.6 Hz, 2H), 2.45 (s, 3H), 2.28 (s, 3H), 1.96 (brs, 3H), 1.75 (d, J=11.9 Hz, 3H), 1.66 (d, J=11.8 Hz, 3H), 1.59-1.55 (m, 6H), 1.52 (brs, 6H).

Example 23: Synthesis of AM16-103A

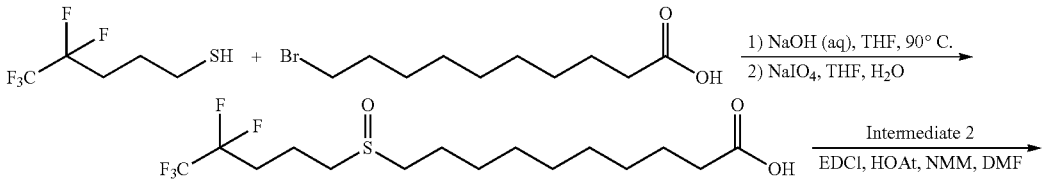
[0173] Intermediate 7 (60 mg, 0.09 mmol) and intermediate 6 (48 mg, 0.27 mmol) were dissolved in DCM (1.5 mL), and methanol (1.5 mL). To the solution was added sodium triacetoxyborohydride (77 mg, 0.36 mmol) at 0° C. After being stirred overnight at room temperature, the mixture was purified by preparative HPLC to afford AM16-103A as yellow solid in TFA salt form (59 mg, 80%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.44 (d, J=2.3 Hz, 1H), 8.38 (s, 1H), 8.34 (dd, J=9.3, 2.3 Hz, 1H), 8.02 (s, 1H), 7.78 (d, J=0.9 Hz, 1H), 7.34 (d, J=9.3 Hz, 1H), 6.17 (s, 1H), 5.15-5.05 (m, 1H), 4.58 (s, 2H), 3.90-3.82 (m, 4H), 3.35 (t, J=6.1 Hz, 2H), 3.14-3.09 (m, 2H), 3.05-2.96 (m, 6H), 2.44 (s, 3H), 2.26 (s, 3H), 1.99 (brs, 3H), 1.79 (d, J=12.3 Hz, 3H), 1.70 (d, J=11.7 Hz, 3H), 1.61-1.57 (m, 12H), 1.53-1.47 (m, 2H).

Example 24: Synthesis of AM29-182A

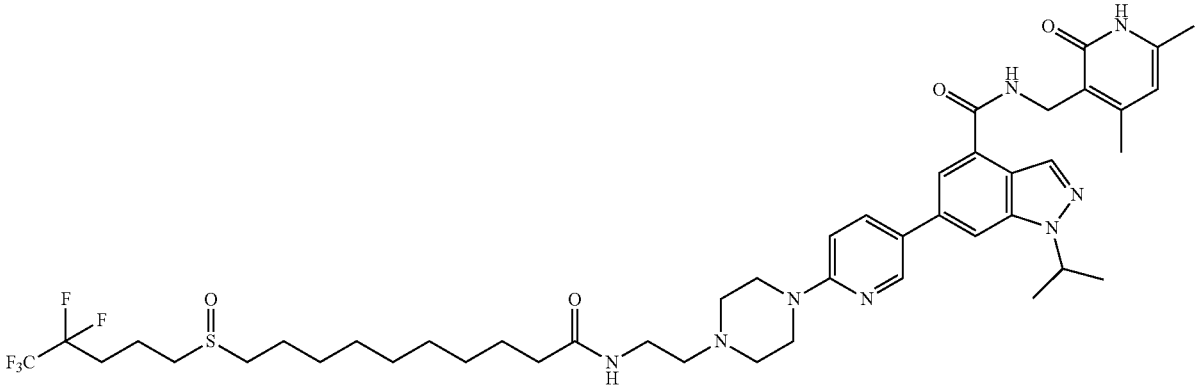
[0174] AM29-182A was synthesized according to the procedures for preparing XY019-43 from intermediate 7 (30 mg, 0.05 mmol), HOAt (9 mg, 0.07 mmol), 2-(adamantan-2-yl)acetic acid (11 mg, 0.06 mmol), NMM (20 μL, 0.18 mmol), EDCI (14 mg, 0.07 mmol), and DMSO (1.0 mL). AM29-182 was obtained as white solid in TFA salt form (27 mg, 72%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.57 (d, J=2.4 Hz, 1H), 8.37 (s, 1H), 8.20 (dd, J=9.0, 2.5 Hz, 1H), 7.98 (s, 1H), 7.79 (s, 1H), 7.17 (d, J=9.0 Hz, 1H), 6.21 (s, 1H), 5.13-5.05 (m, 1H), 4.59 (s, 2H), 3.98 (brs, 4H), 3.63 (t, J=6.0 Hz, 2H), 3.55 (brs, 4H), 3.36 (t, J=5.8 Hz, 2H), 2.45 (s, 3H), 2.44 (d, J=7.6 Hz, 2H), 2.28 (s, 3H), 2.24 (t, J=7.6 Hz, 1H), 1.98-1.93 (m, 2H), 1.92-1.85 (m, 3H), 1.85-1.79 (m, 3H), 1.78 (brs, 2H), 1.69 (brs, 2H), 1.61 (brs, 2H), 1.58 (s, 3H), 1.57 (s, 3H).

Example 25: Synthesis of AM29-55A

[0175]



Intermediate 13

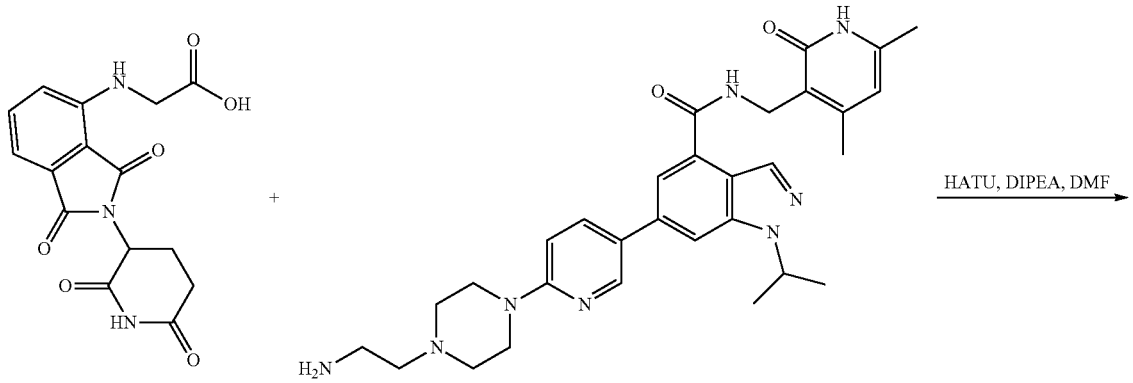


AM29-55A

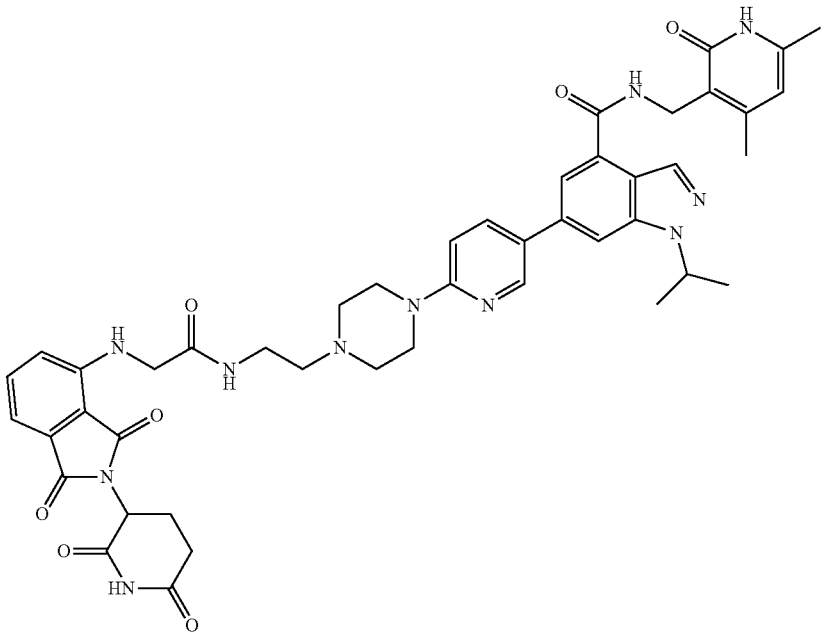
[0176] To the solution of 4,4,5,5,5-pentafluoropentane-1-thiol (1.3 g, 6.8 mmol) and 10-bromodecanoic acid (1.4 g, 5.7 mmol) in THF (10 mL) was added sodium hydroxide aqueous solution (18%, 20 mL) dropwise. The reaction mixture was stirred at 90° C. for 4 hours. Upon completion, the pH value of reaction mixture was adjust to <6 using hydrochloric acid solution. After extraction with DCM, the organic layer was concentrated under vacuum. The residue was dissolved in THF (10 mL) and water (10 mL). To the resulting solution was added sodium periodate (0.5 g, 2.5 mmol) in portions at 0° C. After being stirred overnight at room temperature, the pH value of reaction mixture was adjusted to <5 using hydrochloric acid solution. After extraction with DCM and concentration under vacuum, crude intermediate 13 was obtained and used for the next step without further purification. AM29-55A was synthesized according to the procedures for preparing AM16-10A from intermediate 2 (60 mg, 0.08 mmol), HOAt (17 mg, 0.12 mmol), intermediate 13 (31 mg, 0.08 mmol), NMM (44 μL, 0.40 mmol), EDCI (23 mg, 0.12 mmol) and DMF (1.0 mL). AM29-55A was obtained as yellow solid in TFA salt form (22 mg, 27%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.57 (d, J=2.4 Hz, 1H), 8.37 (s, 1H), 8.16 (dd, J=9.0, 2.4 Hz, 1H), 7.96 (s, 1H), 7.78 (s, 1H), 7.13 (d, J=9.0 Hz, 1H), 6.19 (s, 1H), 5.14-5.04 (m, 1H), 4.59 (s, 2H), 3.97 (brs, 3H), 3.63 (t, J=5.9 Hz, 2H), 3.55 (brs, 3H), 3.36 (t, J=5.9 Hz, 2H), 2.94-2.87 (m, 1H), 2.86-2.75 (m, 3H), 2.45 (s, 3H), 2.39-2.28 (m, 2H), 2.27 (s, 3H), 2.12-2.01 (m, 2H), 1.82-1.71 (m, 2H), 1.69-1.60 (m, 2H), 1.58 (s, 3H), 1.57 (s, 3H), 1.54-1.22 (m, 14H).

Example 26: Synthesis of AM29-151A

[0177]



Intermediate 7



AM29-151A

[0178] Intermediate 7 (10 mg, 0.02 mmol), HATU (1-[Bis (dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate) (11 mg, 0.03 mmol) and (2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl) glycine (6 mg, 0.02 mmol) were dissolved in DMF (1.0 mL). To the solution were added DIPEA (11 μL, 0.06 mmol) at room temperature. After being stirred overnight at room temperature, the mixture was purified by preparative HPLC (10%-100% methanol/0.1% TFA in H_2O) to afford AM29-151A as yellow solid in TFA salt form (11 mg, 73%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.58 (s, 1H), 8.36 (s, 1H), 8.09 (d, J=8.6 Hz, 1H), 7.94 (s, 1H), 7.77 (s, 1H), 7.60 (t, J=7.7 Hz, 1H), 7.15 (d, J=7.0 Hz, 1H), 7.05 (d, J=8.8 Hz, 1H), 6.95 (d, J=8.4 Hz, 1H), 6.15 (s, 1H), 5.15-5.00 (m, 2H), 4.58 (s, 2H), 4.08 (s, 2H), 3.99-3.33 (m, 10H), 3.15-2.79 (m, 2H), 2.77-2.64 (m, 2H), 2.43 (s, 3H), 2.25 (s, 3H), 2.14-2.04 (m, 1H), 1.58 (s, 3H), 1.57 (s, 3H), 1.29 (brs, 1H).

Example 27: Synthesis of AM29-152A

[0179] AM29-152A was synthesized according to the procedures for preparing AM29-151A from intermediate 7 (10 mg, 0.02 mmol), HATU (11 mg, 0.03 mmol), 3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propanoic acid (6 mg, 0.02 mmol), DIPEA (11 μL, 0.06 mmol), and DMF (1.0 mL). AM29-152A was obtained as yellow solid in TFA salt form (9.6 mg, 65%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.58 (s, 1H), 8.37 (s, 1H), 8.08 (d, J=8.7 Hz, 1H), 7.96 (s, 1H), 7.78 (s, 1H), 7.59 (t, J=7.7 Hz, 1H), 7.15 (d, J=8.4 Hz, 1H), 7.06 (dd, J=16.8, 7.9 Hz, 2H), 6.16 (s, 1H), 5.14-5.06 (m, 1H), 5.03-4.94 (m, 1H), 4.59 (s, 2H), 4.24-3.34 (m, 12H), 2.85-2.53 (m, 6H), 2.44 (s, 3H), 2.26 (s, 3H), 2.11-1.99 (m, 1H), 1.59 (s, 3H), 1.58 (s, 3H), 1.29 (brs, 1H).

Example 28: Synthesis of AM29-137A

[0180] AM29-137A was synthesized according to the procedures for preparing AM29-151A from intermediate 12 (10 mg, 0.02 mmol), HATU (11 mg, 0.03 mmol), 4-((2-aminoethyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (8 mg, 0.02 mmol), DIPEA (11 μL, 0.06 mmol), and DMF (1.0 mL). AM29-137A was obtained as yellow solid in TFA salt form (11 mg, 75%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.56 (s, 1H), 8.38 (s, 1H), 8.11-8.03 (m, 1H), 7.94 (s, 1H), 7.77 (s, 1H), 7.57 (t, J=7.8 Hz, 1H), 7.12 (d, J=8.5 Hz, 1H), 7.08 (d, J=7.0 Hz, 1H), 7.03 (d, J=8.9 Hz, 1H), 6.15 (s, 1H), 5.14-5.07 (m, 1H), 5.06-4.99 (m, 1H), 4.58 (s, 2H), 4.35-3.39 (m, 13H), 2.87-2.75 (m, 3H), 2.74-2.65 (m, 2H), 2.43 (s, 3H), 2.25 (s, 3H), 2.14-2.04 (m, 1H), 1.58 (s, 3H), 1.57 (s, 3H), 1.45-1.23 (m, 1H).

Example 29: Synthesis of AM29-153A

[0181] AM29-153A was synthesized according to the procedures for preparing AM29-151A from intermediate 7 (10 mg, 0.02 mmol), HATU (11 mg, 0.03 mmol), 4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)butanoic acid (6 mg, 0.02 mmol), DIPEA (11 μL, 0.06 mmol), and DMF (1.0 mL). AM29-153A was obtained as yellow solid in TFA salt form (11 mg, 78%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.58 (d, J=2.1 Hz, 1H), 8.37 (s, 1H), 8.12 (dd, J=8.9, 2.3 Hz, 1H), 7.96 (s, 1H), 7.78 (s, 1H), 7.60-7.48 (m, 1H), 7.11-7.06 (m, 2H), 7.06-7.02 (m, 1H), 6.17 (s, 1H), 5.14-5.01 (m, 2H), 4.58 (s, 2H), 3.87-3.36 (m, 12H), 2.87-2.80 (m, 1H), 2.77-2.65 (m, 3H), 2.44 (s, 3H), 2.41-2.34 (m, 2H), 2.26 (s, 3H), 2.11-2.07 (m, 1H), 2.04-1.96 (m, 2H), 1.63-1.52 (m, 6H), 1.37-1.16 (m, 1H).

Example 30: Synthesis of AM29-138A

[0182] AM29-138A was synthesized according to the procedures for preparing AM29-151A from intermediate 12 (10 mg, 0.02 mmol), HATU (11 mg, 0.03 mmol), 4-((3-aminopropyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (8 mg, 0.02 mmol), DIPEA (11 μL, 0.06 mmol), and DMF (1.0 mL). AM29-138A was obtained as yellow solid in TFA salt form (14 mg, 96%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.55 (s, 1H), 8.37 (s, 1H), 8.10 (d, J=8.8 Hz, 1H), 7.94 (s, 1H), 7.77 (s, 1H), 7.54 (t, J=7.7 Hz, 1H), 7.14-6.97 (m, 3H), 6.16 (s, 1H), 5.13-5.01 (m, 2H), 4.58 (s, 2H), 4.28-3.34 (m, 13H), 2.90-2.75 (m, 3H), 2.75-2.63 (m, 2H), 2.43 (s, 3H), 2.25 (s, 3H), 2.13-2.05 (m, 1H), 1.90-1.79 (m, 2H), 1.57 (s, 3H), 1.56 (s, 3H), 1.29 (brs, 1H).

Example 31: Synthesis of AM29-154A

[0183] AM29-154A was synthesized according to the procedures for preparing AM29-151A from intermediate 7 (10 mg, 0.02 mmol), HATU (11 mg, 0.03 mmol), 5-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)pentanoic acid (7 mg, 0.02 mmol), DIPEA (11 μL, 0.06 mmol), and DMF (1.0 mL). AM29-154A was obtained as yellow solid in TFA salt form (12 mg, 82%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.57 (s, 1H), 8.37 (s, 1H), 8.07 (dd, J=8.7, 2.1 Hz, 1H), 7.94 (s, 1H), 7.77 (s, 1H), 7.57-7.49 (m, 1H), 7.18-6.95 (m, 3H), 6.14 (s, 1H), 5.14-5.05 (m, 1H), 5.04-4.99 (m, 1H), 4.58 (s, 2H), 4.39-3.32 (m, 13H), 2.86-2.75 (m, 1H), 2.73-2.52 (m, 2H), 2.43 (s, 3H), 2.34 (t, J=7.1 Hz, 2H), 2.25 (s, 3H), 2.15-2.02 (m, 1H), 1.81-1.73 (m, 2H), 1.73-1.64 (m, 2H), 1.58 (s, 3H), 1.57 (s, 3H), 1.29 (brs, 1H).

Example 32: Synthesis of AM29-139A

[0184] AM29-139A was synthesized according to the procedures for preparing AM29-151A from intermediate 12 (10 mg, 0.02 mmol), HATU (11 mg, 0.03 mmol), 4-((4-aminobutyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (8 mg, 0.02 mmol), DIPEA (11 μL, 0.06 mmol), and DMF (1.0 mL). AM29-139A was obtained as yellow solid in TFA salt form (9.8 mg, 66%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.57 (s, 1H), 8.37 (s, 1H), 8.13-8.04 (m, 1H), 7.94 (s, 1H), 7.77 (s, 1H), 7.54 (t, J=7.8 Hz, 1H), 7.23-6.91 (m, 3H), 6.15 (s, 1H), 5.13-5.06 (m, 1H), 5.06-5.00 (m, 1H), 4.58 (s, 2H), 4.44-3.34 (m, 11H), 3.29-3.22 (m, 2H), 2.90-2.61 (m, 5H), 2.43 (s, 3H), 2.25 (s, 3H), 2.12-2.03 (m, 1H), 1.75-1.61 (m, 4H), 1.58 (s, 3H), 1.57 (s, 3H), 1.29 (brs, 1H).

Example 33: Synthesis of AM29-155A

[0185] AM29-155A was synthesized according to the procedures for preparing AM29-151A from intermediate 7 (10 mg, 0.02 mmol), HATU (11 mg, 0.03 mmol), 6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino) hexanoic acid (7 mg, 0.02 mmol), DIPEA (11 μL, 0.06 mmol), and DMF (1.0 mL). AM29-155A was obtained as yellow solid in TFA salt form (12 mg, 76%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.57 (s, 1H), 8.37 (s, 1H), 8.16-8.06 (m, 1H), 7.95 (s, 1H), 7.78 (s, 1H), 7.57-7.48 (m, 1H), 7.08 (d, J=8.9 Hz, 1H), 7.02 (dd, J=13.8, 7.8 Hz, 2H), 6.17 (s, 1H), 5.14-5.06 (m, 1H), 5.06-4.99 (m, 1H), 4.58 (s, 2H), 4.21-3.32 (m, 13H), 2.88-2.77 (m, 1H), 2.76-2.62 (m, 2H), 2.44 (s, 3H), 2.30 (t, J=7.2 Hz, 2H), 2.26 (s, 3H), 2.14-2.05 (m, 1H), 1.75-1.63 (m, 4H), 1.58 (s, 3H), 1.57 (s, 3H), 1.51-1.40 (m, 2H), 1.36-1.19 (m, 1H).

Example 34: Synthesis of AM29-170A

[0186] AM29-170A was synthesized according to the procedures for preparing AM29-151A from intermediate 12 (20

mg, 0.02 mmol), HATU (22 mg, 0.06 mmol), 4-((5-aminopentyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (17 mg, 0.04 mmol), DIPEA (20 μL, 0.12 mmol), and DMF (1.0 mL). AM29-170A was obtained as yellow solid in TFA salt form (20 mg, 64%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.50 (s, 1H), 8.38 (s, 1H), 8.14 (d, J=6.6 Hz, 1H), 7.95 (s, 1H), 7.76 (s, 1H), 7.58-7.44 (m, 1H), 7.18-7.05 (m, 1H), 7.05-6.91 (m, 2H), 6.20 (s, 1H), 5.15-5.00 (m, 2H), 4.58 (s, 2H), 4.35-3.33 (m, 11H), 3.28-3.08 (m, 3H), 2.90-2.61 (m, 5H), 2.43 (s, 3H), 2.26 (s, 3H), 2.14-2.02 (m, 1H), 1.65 (s, 3H), 1.57-1.49 (m, 6H), 1.44 (s, 2H), 1.37-1.23 (m, 1H).

Example 35: Synthesis of AM29-156A

[0187] AM29-156A was synthesized according to the procedures for preparing AM29-151A from intermediate 7 (10 mg, 0.02 mmol), HATU (11 mg, 0.03 mmol), 7-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)heptanoic acid (7 mg, 0.02 mmol), DIPEA (11 μL, 0.06 mmol), and DMF (1.0 mL). AM29-156A was obtained as yellow solid in TFA salt form (13 mg, 83%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.57 (d, J=2.4 Hz, 1H), 8.37 (s, 1H), 8.16-8.07 (m, 1H), 7.95 (s, 1H), 7.78 (s, 1H), 7.55-7.51 (m, 1H), 7.13-7.07 (m, 1H), 7.04-7.00 (m, 2H), 6.18 (s, 1H), 5.10-5.00 (m, 2H), 4.58 (s, 2H), 4.31-3.40 (m, 11H), 3.04 (t, J=2.8 Hz, 1H), 2.91 (t, J=2.7 Hz, 1H), 2.89-2.78 (m, 2H), 2.78-2.63 (m, 4H), 2.44 (t, J=2.6 Hz, 3H), 2.26 (s, 3H), 2.11-2.07 (m, 1H), 1.69-1.66 (m, 3H), 1.60-1.51 (m, 6H), 1.44-1.40 (m, 4H), 1.29 (brs, 1H).

Example 36: Synthesis of AM29-171A

[0188] AM29-171A was synthesized according to the procedures for preparing AM29-151A from intermediate 12 (20 mg, 0.02 mmol), HATU (22 mg, 0.06 mmol), 4-((6-aminohexyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (17 mg, 0.04 mmol), DIPEA (20 μL, 0.12 mmol), and DMF (1.0 mL). AM29-171A was obtained as yellow solid in TFA salt form (20 mg, 66%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.49 (s, 1H), 8.37 (s, 1H), 8.14 (d, J=8.2 Hz, 1H), 7.94 (s, 1H), 7.75 (s, 1H), 7.49 (t, J=7.7 Hz, 1H), 7.10 (d, J=9.0 Hz, 1H), 6.96 (d, J=7.7 Hz, 2H), 6.19 (s, 1H), 5.10-5.00 (m, 2H), 4.58 (s, 2H), 4.33-3.70 (m, 4H), 3.66-3.34 (m, 6H), 3.25 (t, J=6.5 Hz, 2H), 3.20 (t, J=6.7 Hz, 2H), 2.88-2.76 (m, 3H), 2.75-2.62 (m, 2H), 2.43 (s, 3H), 2.26 (s, 3H), 2.12-2.02 (m, 1H), 1.65-1.59 (m, 2H), 1.56 (s, 3H), 1.55 (s, 3H), 1.54-1.48 (m, 2H), 1.47-1.32 (m, 4H).

Example 37: Synthesis of AM29-157A

[0189] AM29-157A was synthesized according to the procedures for preparing AM29-151A from intermediate 7 (10 mg, 0.02 mmol), HATU (11 mg, 0.03 mmol), 8-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)octanoic acid (8 mg, 0.02 mmol), DIPEA (11 μL, 0.06 mmol), and DMF (1.0 mL). AM29-157A was obtained as yellow solid in TFA salt form (11 mg, 67%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.58 (d, J=2.3 Hz, 1H), 8.37 (s, 1H), 8.11-8.02 (m, 1H), 7.94 (s, 1H), 7.77 (s, 1H), 7.57-7.46 (m, 1H), 7.21-6.94 (m, 3H), 6.14 (s, 1H), 5.13-5.01 (m, 2H), 4.58 (s, 2H), 4.36-3.32 (m, 12H), 3.07-2.78 (m, 2H), 2.76-2.65 (m, 2H), 2.48-2.35 (m, 3H), 2.30-2.19 (m, 5H), 2.12-2.05 (m, 1H), 1.75-1.60 (m, 4H), 1.60-1.51 (m, 6H), 1.41 (dd, J=19.6, 8.1 Hz, 7H).

Example 38: Synthesis of AM29-172A

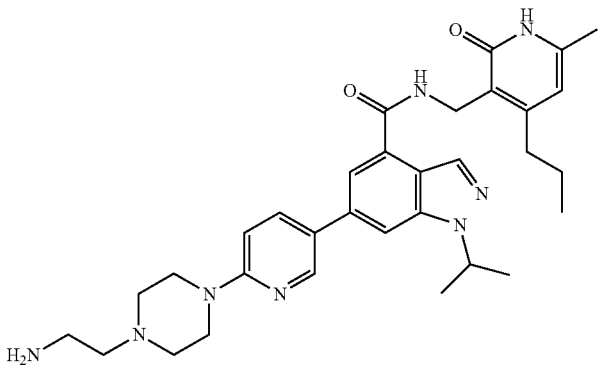
[0190] AM29-172A was synthesized according to the procedures for preparing AM29-151A from intermediate 12 (20 mg, 0.02 mmol), HATU (22 mg, 0.06 mmol), 4-((7-aminoheptyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (18 mg, 0.04 mmol), DIPEA (20 μL, 0.12 mmol), and DMF (1.0 mL). AM29-172A was obtained as yellow solid in TFA salt form (23 mg, 73%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.50 (s, 1H), 8.38 (s, 1H), 8.13 (d, J=7.9 Hz, 1H), 7.94 (s, 1H), 7.75 (s, 1H), 7.49 (t, J=7.7 Hz, 1H), 7.09 (d, J=8.9 Hz, 1H), 6.96 (d, J=7.6 Hz, 2H), 6.19 (s, 1H), 5.11-5.00 (m, 2H), 4.58 (s, 2H), 3.98 (brs, 3H), 3.59-3.36 (m, 6H), 3.35 (s, 1H), 3.25 (t, J=6.6 Hz, 2H), 3.20 (t, J=6.8 Hz, 2H), 2.88-2.76 (m, 3H), 2.75-2.62 (m, 2H), 2.43 (s, 3H), 2.26 (s, 3H), 2.13-2.03 (m, 1H), 1.65-1.59 (m, 2H), 1.57 (s, 3H), 1.56 (s, 3H), 1.53-1.47 (m, 2H), 1.44-1.29 (m, 6H).

Example 39: Synthesis of AM29-173A

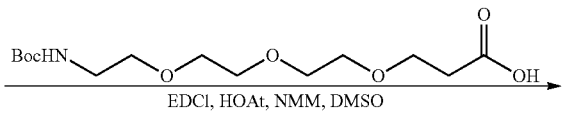
[0191] AM29-173A was synthesized according to the procedures for preparing AM29-151A from intermediate 12 (20 mg, 0.02 mmol), HATU (22 mg, 0.06 mmol), 4-((8-aminooctyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (18 mg, 0.04 mmol), DIPEA (20 μL, 0.12 mmol), and DMF (1.0 mL). AM29-173A was obtained as yellow solid in TFA salt form (26 mg, 82%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.53 (d, J=2.3 Hz, 1H), 8.38 (s, 1H), 8.13 (dd, J=8.9, 2.4 Hz, 1H), 7.95 (s, 1H), 7.77 (s, 1H), 7.54-7.45 (m, 1H), 7.10 (d, J=9.0 Hz, 1H), 6.99 (d, J=7.8 Hz, 2H), 6.19 (s, 1H), 5.13-5.07 (m, 1H), 5.06-5.00 (m, 1H), 4.58 (s, 2H), 4.21-3.73 (m, 3H), 3.61-3.39 (m, 6H), 3.27 (t, J=6.9 Hz, 2H), 3.20 (t, J=7.1 Hz, 2H), 2.89-2.64 (m, 5H), 2.44 (s, 3H), 2.26 (s, 3H), 2.12-2.05 (m, 1H), 1.67-1.59 (m, 2H), 1.57 (s, 3H), 1.56 (s, 3H), 1.54-1.47 (m, 2H), 1.45-1.21 (m, 9H).

Example 40: Synthesis of AM16-79A

[0192]



Intermediate 2



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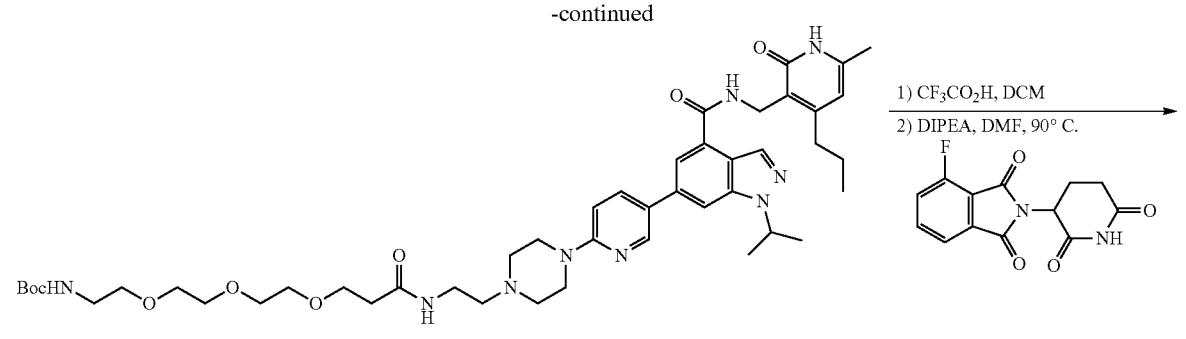
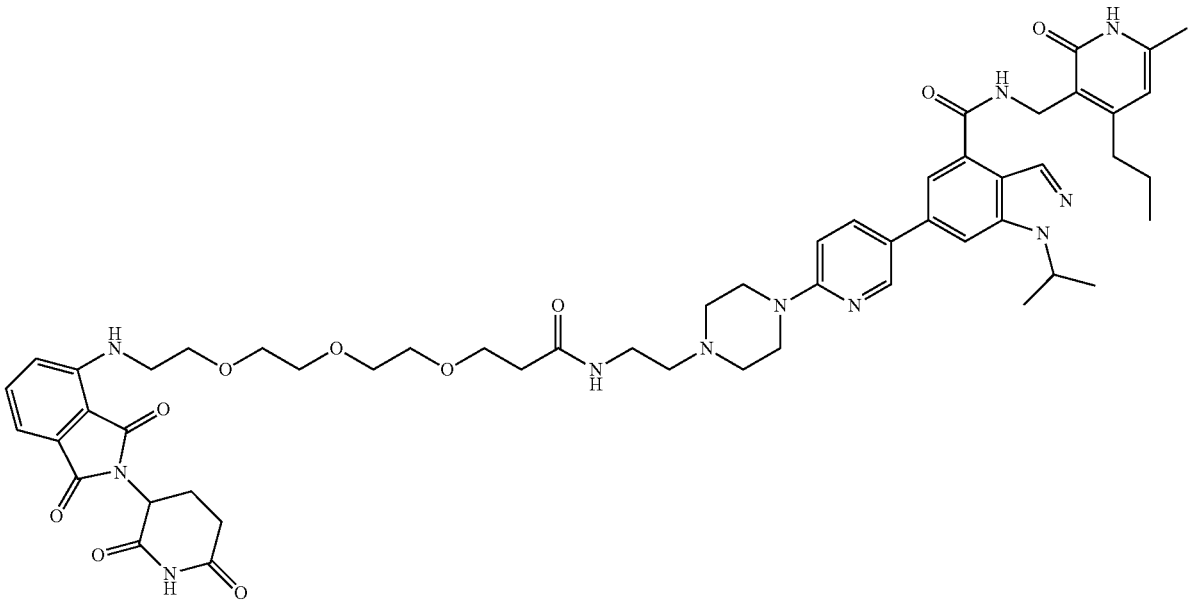


Intermediate 14



AM16-79A

[0193] Intermediate 14 was synthesized according to the procedures for preparing AM16-10A from intermediate 2 (110 mg, 0.16 mmol), HOAt (33 mg, 0.24 mmol), 2,2-dimethyl-4-oxo-3,8,11,14-tetraoxa-5-azaheptadecan-17-oic acid (62 mg, 0.19 mmol, Broadpharm, BP-21656), NMM (71 μL, 0.64 mmol), EDCI (46 mg, 0.24 mmol), and DMSO (2.0 mL). Intermediate 14 was dissolved in DCM (2.0 mL) and to the solution was added trifluoroacetic acid (0.5 mL) at room temperature. After being stirred for 1 h at room temperature, the mixture was concentrated, basified with sodium bicarbonate solution and extracted with DCM. Organic phase was concentrated under vacuum and purified by ISCO™ silica gel column (0-20% MeOH in DCM) to afford compound 6-(6-(4-(1-amino-12-oxo-3,6,9-trioxa-13-azapentadecan-15-yl)piperazin-1-yl)pyridin-3-yl)-1-isopropyl-N-((6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl)-1H-indazole-4-carboxamide. This compound was dissolved in anhydrous DMF (2.0 mL). To the resulting solution was added DIPEA (56 μL, 0.32 mmol). After being stirred overnight at 90° C., the mixture was concentrated under vacuum and purified by preparative HPLC to afford AM16-79A as yellow solid in TFA salt form (30 mg, 16% over 3 steps). ^{1}H NMR (600 MHz, CD_3OD) δ 8.59-8.47 (m, 1H), 8.38 (s, 1H), 8.37-8.20 (m, 1H), 8.19-8.10 (m, 1H), 8.06-7.86 (m, 1H), 7.79-7.72 (m, 1H), 7.48-7.38 (m, 1H), 7.29-7.13 (m, 1H), 7.01-6.86 (m, 1H), 6.24 (s, 1H), 5.16-5.01 (m, 2H), 4.62 (s, 2H), 4.28-3.35 (m, 26H), 2.98-2.56 (m, 5H), 2.55-2.41 (m, 2H), 2.29 (s, 3H), 2.13-2.00 (m, 1H), 1.70-1.60 (m, 2H), 1.58 (d, J=6.4 Hz, 6H), 1.03 (t, J=7.2 Hz, 3H).

Example 41: Synthesis of AM29-177A

[0194] AM29-177A was synthesized according to the procedures for preparing AM29-151A from intermediate 7 (20 mg, 0.03 mmol), HATU (23 mg, 0.06 mmol), 3-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)propanoic acid (14 mg, 0.04 mmol), DIPEA (21 μL, 0.12 mmol), and DMF (1.0 mL). AM29-177A was obtained as yellow solid in TFA salt form (30 mg, 95%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.49 (s, 1H), 8.38 (s, 1H), 8.09 (d, J=8.8 Hz, 1H), 7.94 (s, 1H), 7.75 (s, 1H), 7.50 (t, J=7.7 Hz, 1H), 7.12-7.02 (m, 2H), 6.98 (d, J=6.9 Hz, 1H), 6.19 (s, 1H), 5.15-5.05 (m, 1H), 5.05-5.00 (m, 1H), 4.59 (s, 2H), 4.23-3.39 (m, 16H), 3.35 (s, 2H), 2.89-2.77 (m, 1H), 2.76-2.61 (m, 2H), 2.58-2.48 (m, 2H), 2.44 (s, 3H), 2.26 (s, 3H), 2.13-2.05 (m, 1H), 1.58 (s, 3H), 1.57 (s, 3H).

Example 42: Synthesis of AM29-141A

[0195] AM29-141A was synthesized according to the procedures for preparing AM29-151A from intermediate 12 (10 mg, 0.02 mmol), HATU (11 mg, 0.03 mmol), 4-((2-(2-aminoethoxy) ethyl)amino)-2-(2,6-dioxopiperidin-3-yl) isoindoline-1,3-dione (8 mg, 0.02 mmol), DIPEA (11 μL, 0.06 mmol), and DMF (1.0 mL). AM29-141A was obtained as yellow liquid in TFA salt form (4.8 mg, 32%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.56 (d, J=2.3 Hz, 1H), 8.37 (s, 1H), 8.02 (dd, J=8.8, 2.5 Hz, 1H), 7.92 (s, 1H), 7.76 (s, 1H), 7.59-7.51 (m, 1H), 7.10-7.03 (m, 2H), 6.98 (d, J=8.8 Hz, 1H), 6.14 (s, 1H), 5.11-5.04 (m, 2H), 4.58 (s, 2H), 4.07-3.37 (m, 20H), 2.86-2.81 (m, 1H), 2.74-2.70 (m, 2H), 2.44 (s, 3H), 2.25 (s, 3H), 2.14-2.09 (m, 1H), 1.59 (s, 3H), 1.58 (s, 3H).

Example 43: Synthesis of AM29-178A

[0196] AM29-178A was synthesized according to the procedures for preparing AM29-151A from intermediate 7 (20 mg, 0.03 mmol), HATU (23 mg, 0.06 mmol), 3-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino) ethoxy)ethoxy)propanoic acid (16 mg, 0.04 mmol), DIPEA (21 μL, 0.12 mmol), and DMF (1.0 mL). AM29-178A was obtained as yellow solid in TFA salt form (27 mg, 85%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.49 (s, 1H), 8.38 (s, 1H), 8.10 (d, J=9.0 Hz, 1H), 7.93 (s, 1H), 7.74 (s, 1H), 7.46 (t, J=7.8 Hz, 1H), 7.07 (d, J=9.0 Hz, 1H), 7.01 (d, J=8.5 Hz, 1H), 6.93 (d, J=7.0 Hz, 1H), 6.20 (s, 1H), 5.12-5.05 (m, 1H), 5.04-4.99 (m, 1H), 4.59 (s, 2H), 4.27-3.32 (m, 22H), 2.89-2.77 (m, 1H), 2.76-2.59 (m, 2H), 2.51 (t, J=5.5 Hz, 2H), 2.44 (s, 3H), 2.27 (s, 3H), 2.11-2.03 (m, 1H), 1.58 (s, 3H), 1.57 (s, 3H).

Example 44: Synthesis of AM29-142A

[0197] AM29-142A was synthesized according to the procedures for preparing AM29-151A from intermediate 12 (10 mg, 0.02 mmol), HATU (11 mg, 0.03 mmol), 4-((2-(2-(2-aminoethoxy) ethoxy)ethyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (8 mg, 0.02 mmol), DIPEA (11 μL, 0.06 mmol), and DMF (1.0 mL). AM29-142A was obtained as brown liquid in TFA salt form (4 mg, 25%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.58 (d, J=1.8 Hz, 1H), 8.37 (s, 1H), 8.05 (dd, J=8.7, 2.0 Hz, 1H), 7.93 (s, 1H), 7.77 (s, 1H), 7.56-7.51 (m, 1H), 7.10-7.06 (m, 1H), 7.05-7.00 (m, 2H), 6.14 (s, 1H), 5.11-5.03 (m, 2H), 4.58 (s, 2H), 3.79-3.40 (m, 23H), 2.87-2.80 (m, 1H), 2.77-2.72 (m, 3H), 2.43 (s, 3H), 2.25 (s, 3H), 2.12-2.06 (m, 1H), 1.58 (s, 3H), 1.57 (s, 3H).

Example 45: Synthesis of AM29-179A

[0198] AM29-179A was synthesized according to the procedures for preparing AM29-151A from intermediate 7 (20 mg, 0.03 mmol), HATU (23 mg, 0.06 mmol), 3-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl) amino)ethoxy)ethoxy)ethoxy)propanoic acid (18 mg, 0.04 mmol), DIPEA (21 μL, 0.12 mmol), and DMF (1.0 mL). AM29-179A was obtained as yellow solid in TFA salt form (26 mg, 78%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.50 (s, 1H), 8.38 (s, 1H), 8.13 (d, J=9.0 Hz, 1H), 7.94 (s, 1H), 7.75 (s, 1H), 7.46-7.39 (m, 1H), 7.12 (d, J=9.0 Hz, 1H), 6.98 (d, J=8.5 Hz, 1H), 6.93 (d, J=7.1 Hz, 1H), 6.22 (s, 1H), 5.11-5.06 (m, 1H), 5.06-5.00 (m, 1H), 4.59 (s, 2H), 3.97-3.37 (m, 26H), 2.88-2.78 (m, 1H), 2.77-2.61 (m, 2H), 2.50 (t, J=5.6 Hz, 2H), 2.45 (s, 3H), 2.27 (s, 3H), 2.13-2.02 (m, 1H), 1.58 (s, 3H), 1.57 (s, 3H).

Example 46: Synthesis of AM29-143A

[0199] AM29-143A was synthesized according to the procedures for preparing AM29-151A from intermediate 12 (10 mg, 0.02 mmol), HATU (11 mg, 0.03 mmol), 4-((2-(2-(2-(2-aminoethoxy) ethoxy)ethoxy)ethyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (9 mg, 0.02 mmol), DIPEA (11 μL, 0.06 mmol), and DMF (1.0 mL). AM29-143A was obtained as brown liquid in TFA salt form (11 mg, 67%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.57 (d, J=2.3 Hz, 1H), 8.37 (s, 1H), 8.05 (dd, J=8.8, 2.4 Hz, 1H), 7.93 (s, 1H), 7.76 (s, 1H), 7.51 (dd, J=8.4, 7.3 Hz, 1H), 7.06 (d, J=8.6 Hz, 1H), 7.01 (dd, J=7.9, 3.4 Hz, 2H), 6.14 (s, 1H), 5.12-5.02 (m, 2H), 4.58 (s, 2H), 3.97-3.31 (m, 26H), 2.89-2.80 (m, 1H), 2.79-2.64 (m, 4H), 2.43 (s, 3H), 2.25 (s, 3H), 2.13-2.06 (m, 1H), 1.58 (s, 3H), 1.57 (s, 3H).

Example 47: Synthesis of AM29-180A

[0200] AM29-180A was synthesized according to the procedures for preparing AM29-151A from intermediate 7 (20 mg, 0.03 mmol), HATU (23 mg, 0.06 mmol), 1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6, 9,12-tetraoxapentadecan-15-oic acid (20 mg, 0.04 mmol), DIPEA (21 μL, 0.12 mmol), and DMF (1.0 mL). AM29-180A was obtained as yellow solid in TFA salt form (31 mg, 90%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.51 (s, 1H), 8.38 (s, 1H), 8.15 (d, J=9.0 Hz, 1H), 7.95 (s, 1H), 7.76 (s, 1H), 7.44 (t, J=7.8 Hz, 1H), 7.14 (d, J=9.0 Hz, 1H), 6.98 (d, J=8.5 Hz, 1H), 6.93 (d, J=7.0 Hz, 1H), 6.22 (s, 1H), 5.11-5.05 (m, 1H), 5.04-4.99 (m, 1H), 4.59 (s, 2H), 4.04-3.38 (m, 30H), 2.89-2.78 (m, 1H), 2.75-2.60 (m, 2H), 2.53-2.47 (m, 2H), 2.45 (s, 3H), 2.27 (s, 3H), 2.11-2.02 (m, 1H), 1.57 (s, 3H), 1.56 (s, 3H).

Example 48: Synthesis of AM29-144A

[0201] AM29-144A was synthesized according to the procedures for preparing AM29-151A from intermediate 12 (10 mg, 0.02 mmol), HATU (11 mg, 0.03 mmol), 4-((14-amino-3,6,9,12-tetraoxatetradecyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (10 mg, 0.02 mmol), DIPEA (11 μL, 0.06 mmol), and DMF (1.0 mL). AM29-144A was obtained as yellow solid in TFA salt form (9 mg, 53%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.55 (d, J=2.0 Hz, 1H), 8.37 (s, 1H), 8.09 (dd, J=8.9, 2.1 Hz, 1H), 7.94 (s, 1H), 7.77 (s, 1H), 7.58-7.45 (m, 1H), 7.16-7.02 (m, 2H), 7.01-6.93 (m, 1H), 6.16 (s, 1H), 5.13-5.06 (m, 1H), 5.06-5.01 (m, 1H), 4.58 (s, 2H), 4.18-3.36 (m, 30H), 2.79-2.76 (m, 1H), 2.75-2.63 (m, 2H), 2.44 (s, 3H), 2.36 (t, J=8.1 Hz, 1H), 2.26 (s, 3H), 2.13-2.07 (m, 1H), 2.06-1.97 (m, 1H), 1.58 (s, 3H), 1.57 (s, 3H).

Example 49: Synthesis of AM29-145A

[0202] AM29-145A was synthesized according to the procedures for preparing AM29-151A from intermediate 12 (10 mg, 0.02 mmol), HATU (11 mg, 0.03 mmol), 4-((17-amino-3,6,9,12,15-pentaoxaheptadecyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (11 mg, 0.02 mmol), DIPEA (11 μL, 0.06 mmol), and DMF (1.0 mL). AM29-145A was obtained as yellow liquid in TFA salt form (12 mg, 70%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.58 (d, J=2.4 Hz, 1H), 8.37 (s, 1H), 8.05 (dd, J=8.8, 2.5 Hz, 1H), 7.93 (s, 1H), 7.77 (d, J=0.9 Hz, 1H), 7.50 (dd, J=8.4, 7.3 Hz, 1H), 7.04 (dd, J=8.7, 6.5 Hz, 2H), 7.00 (d, J=7.1 Hz, 1H), 6.15 (s, 1H), 5.12-5.06 (m, 1H), 5.04 (dd, J=12.8, 5.5 Hz, 1H), 4.58 (s, 2H), 4.00-3.31 (m, 34H), 2.90-2.77 (m, 3H), 2.76-2.64 (m, 2H), 2.44 (s, 3H), 2.25 (s, 3H), 2.12-2.04 (m, 1H), 1.58 (s, 3H), 1.57 (s, 3H).

Example 50: Synthesis of AM29-181A

[0203] AM29-181A was synthesized according to the procedures for preparing AM29-151A from intermediate 7 (20 mg, 0.03 mmol), HATU (23 mg, 0.06 mmol), 1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12,15-pentaoxaoctadecan-18-oic acid (21 mg, 0.04 mmol), DIPEA (21 μL, 0.12 mmol), and DMF (1.0 mL). AM29-181A was obtained as yellow solid in TFA salt form (9 mg, 25%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.53 (s, 1H), 8.38 (d, J=2.7 Hz, 1H), 8.24-8.15 (m, 1H), 7.97 (s, 1H), 7.77 (s, 1H), 7.51-7.41 (m, 1H), 7.18 (dd, J=8.8, 3.0 Hz, 1H), 6.99 (dd, J=8.4, 3.3 Hz, 1H), 6.94 (dd, J=6.8, 3.5 Hz, 1H), 6.23 (s, 1H), 5.14-5.05 (m, 1H), 5.05-4.99 (m, 1H), 4.59 (s, 2H), 4.25-3.37 (m, 34H), 2.88-2.78 (m, 1H), 2.76-2.60 (m, 2H), 2.50 (d, J=3.3 Hz, 2H), 2.45 (d, J=3.1 Hz, 3H), 2.27 (d, J=2.8 Hz, 3H), 2.11-2.04 (m, 1H), 1.57 (s, 6H).

Example 51: Synthesis of AM41-16A

[0204] AM41-16A was synthesized according to the procedures for preparing AM29-151A from intermediate 7 (18 mg, 0.03 mmol), HATU (21 mg, 0.05 mmol), 1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12,15,18,21,24-octaoxaheptacosan-27-oic acid (19 mg, 0.03 mmol), DIPEA (19 μL, 0.11 mmol), and DMF (1.0 mL). AM41-16A was obtained as yellow liquid in TFA salt form (31 mg, 86%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.58 (d, J=2.4 Hz, 1H), 8.37 (s, 1H), 8.14 (dd, J=9.0, 2.4 Hz, 1H), 7.96 (s, 1H), 7.78 (s, 1H), 7.51-7.45 (m, 1H), 7.13 (d, J=9.0 Hz, 1H), 7.02 (d, J=8.6 Hz, 1H), 6.98 (d, J=7.0 Hz, 1H), 6.18 (s, 1H), 5.15-5.05 (m, 1H), 5.02 (dd, J=12.6, 5.5 Hz, 1H), 4.59 (s, 2H), 3.94-3.37 (m, 46H), 2.90-2.79 (m, 1H), 2.76-2.62 (m, 2H), 2.52 (t, J=5.6 Hz, 2H), 2.44 (s, 3H), 2.26 (s, 3H), 2.12-2.05 (m, 1H), 1.58 (s, 3H), 1.57 (s, 3H).

Example 52: Synthesis of AM41-17A

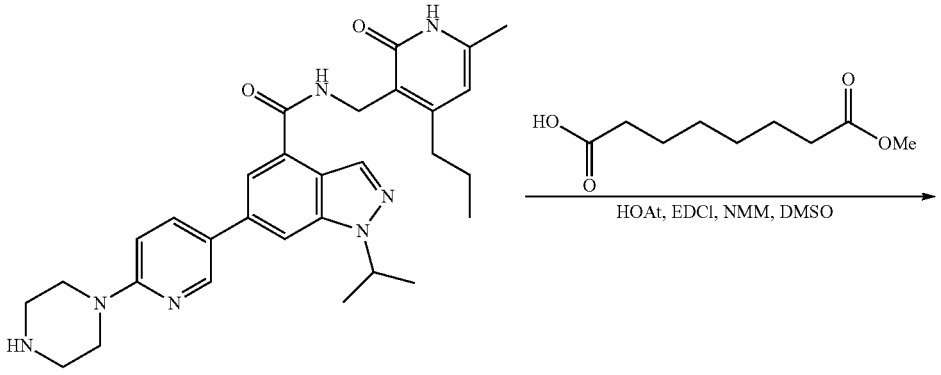
[0205] AM41-17A was synthesized according to the procedures for preparing AM29-151A from intermediate 7 (18 mg, 0.03 mmol), HATU (18 mg, 0.05 mmol), 1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12,15,18,21,24,27,30-decaoxatritriacontan-33-oic acid (19 mg, 0.02 mmol), DIPEA (17 μL, 0.10 mmol), and DMF (1.0 mL). AM41-17A was obtained as yellow liquid in TFA salt form (27 mg, 79%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.57 (d, J=2.3 Hz, 1H), 8.38 (s, 1H), 8.21 (dd, J=9.0, 2.2 Hz, 1H), 7.99 (s, 1H), 7.79 (s, 1H), 7.49 (dd, J=8.3, 7.4 Hz, 1H), 7.20 (d, J=9.0 Hz, 1H), 7.02 (d, J=8.6 Hz, 1H), 6.99 (d, J=7.0 Hz, 1H), 6.21 (s, 1H), 5.14-5.06 (m, 1H), 5.05-5.00 (m, 1H), 4.59 (s, 2H), 4.23-3.37 (m, 54H), 2.89-2.79 (m, 1H), 2.76-2.62 (m, 2H), 2.52 (t, J=5.7 Hz, 2H), 2.45 (s, 3H), 2.27 (s, 3H), 2.13-2.05 (m, 1H), 1.58 (s, 3H), 1.57 (s, 3H).

Example 53: Synthesis of AM41-18A

[0206] AM41-18A was synthesized according to the procedures for preparing AM29-151A from intermediate 7 (18 mg, 0.03 mmol), HATU (14 mg, 0.04 mmol), 1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12,15,18,21,24,27,30,33,36-dodecaoxanonatriacontan-39-oic acid (16 mg, 0.02 mmol), DIPEA (13 μL, 0.07 mmol), and DMF (1.0 mL). AM41-18A was obtained as yellow liquid in TFA salt form (18 mg, 66%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.60 (d, J=2.4 Hz, 1H), 8.38 (s, 1H), 8.20 (dd, J=9.0, 2.4 Hz, 1H), 7.99 (s, 1H), 7.80 (d, J=0.9 Hz, 1H), 7.51 (dd, J=8.4, 7.2 Hz, 1H), 7.18 (d, J=9.0 Hz, 1H), 7.04 (d, J=8.6 Hz, 1H), 7.01 (d, J=7.1 Hz, 1H), 6.19 (s, 1H), 5.13-5.07 (m, 1H), 5.03 (dd, J=12.8, 5.5 Hz, 1H), 4.59 (s, 2H), 4.27-3.32 (m, 62H), 2.89-2.79 (m, 1H), 2.77-2.64 (m, 2H), 2.52 (t, J=5.7 Hz, 2H), 2.45 (s, 3H), 2.27 (s, 3H), 2.13-2.05 (m, 1H), 1.58 (s, 3H), 1.57 (s, 3H).

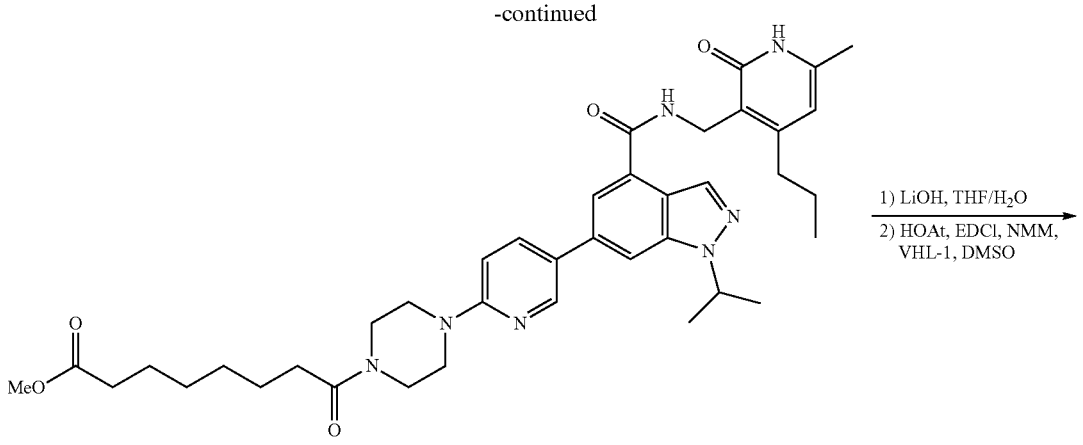
Example 54: Synthesis of XY012-157

[0207]

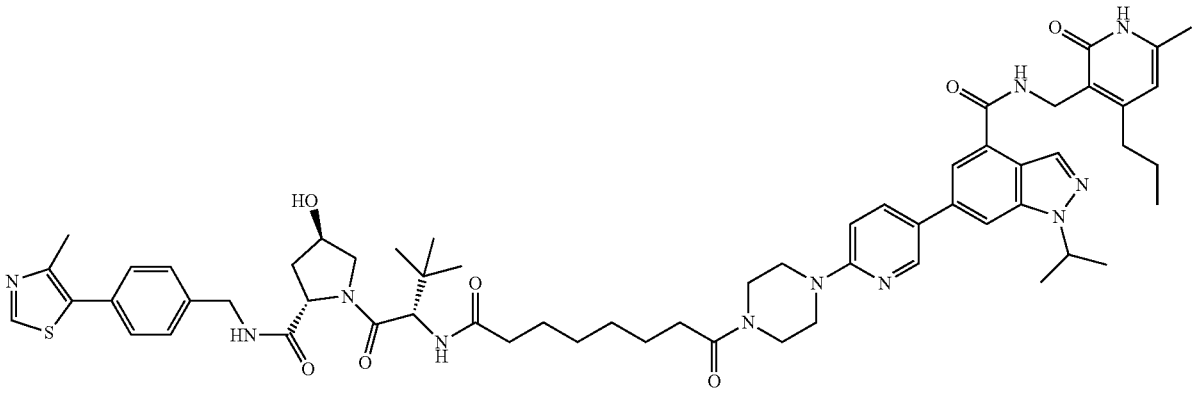


Intermediate 1

-continued



Intermediate 15

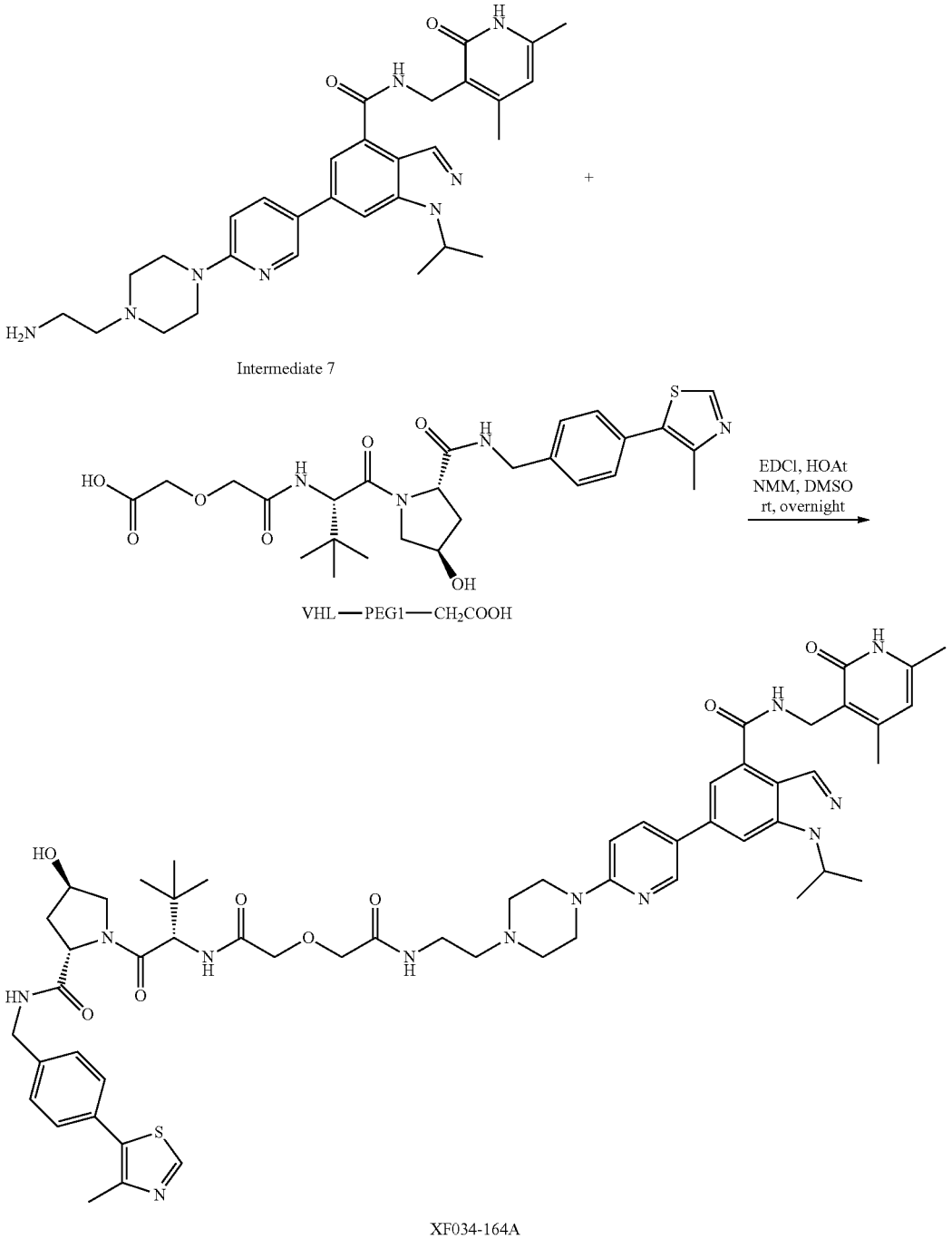


XY012-157

[0208] To the solution of intermediate 1 (45 mg, 0.09 mmol) in DMSO (2.0 mL) were added NMM (26 mg, 0.26 mmol), 8-methoxy-8-oxooctanoic acid (19 mg, 0.10 mmol), HOAt (17 mg, 0.13 mmol), and EDCI (25 mg, 0.13 mmol). The mixture was allowed to stir at room temperature overnight. The progress of the reaction was monitored by LC-MS. Upon completion, the mixture was concentrated under vacuum and purified by preparative HPLC to afford intermediate 15 (35 mg, 58%) as solid. MS (m/z) $[M+H]^+$: 698.3. To the stirring solution of intermediate 15 (35 mg, 0.05 mmol) in THF/H_2O (10 mL/5.0 mL) was added lithium hydroxide (6.0 mg, 0.22 mmol) and the resulting mixture was stirred overnight at room temperature. The progress of the reaction was monitored by LC-MS. Upon completion, the reaction mixture was concentrated under vacuum and the resulting residue was dissolved in DMSO (2.0 mL). To the solution were added NMM (23 mg, 0.23 mmol), VHL-1 (35 mg, 0.08 mmol), HOAt (10 mg, 0.08 mmol), and EDCI (14 mg, 0.08 mmol). The mixture was allowed to stir at room temperature overnight. The progress of the reaction was monitored by LC-MS. Upon completion, the mixture was concentrated under vacuum and purified by preparative HPLC to afford XY012-157 (11 mg, 20%) as solid. ^1H NMR (600 MHz, CD_3OD) δ 8.99 (s, 1H), 8.49 (dd, J=9.5, 2.2 Hz, 1H), 8.39 (d, J=2.3 Hz, 2H), 8.07 (s, 1H), 7.78 (s, 1H), 7.47 (d, J=1.8 Hz, 1H), 7.46 (d, J=3.7 Hz, 2H), 7.41 (d, J=8.2 Hz, 2H), 6.18 (s, 1H), 5.11 (dt, J=13.2, 6.6 Hz, 1H), 4.64 (s, 1H), 4.60 (s, 2H), 4.58-4.47 (m, 3H), 4.36 (d, 1H), 3.91 (d, J=11.0 Hz, 1H), 3.88-3.77 (m, 9H), 2.77-2.74 (m, 2H), 2.50-2.43 (m, 5H), 2.35-2.18 (m, 6H), 2.11-2.04 (m, 1H), 1.70-1.60 (m, 6H), 1.58 (d, J=6.6 Hz, 6H), 1.44-1.35 (m, 4H), 1.05-0.99 (m, 12H). MS (m/z) $[M+H]^+$: 1096.2.

Example 55: Synthesis of XF034-164A

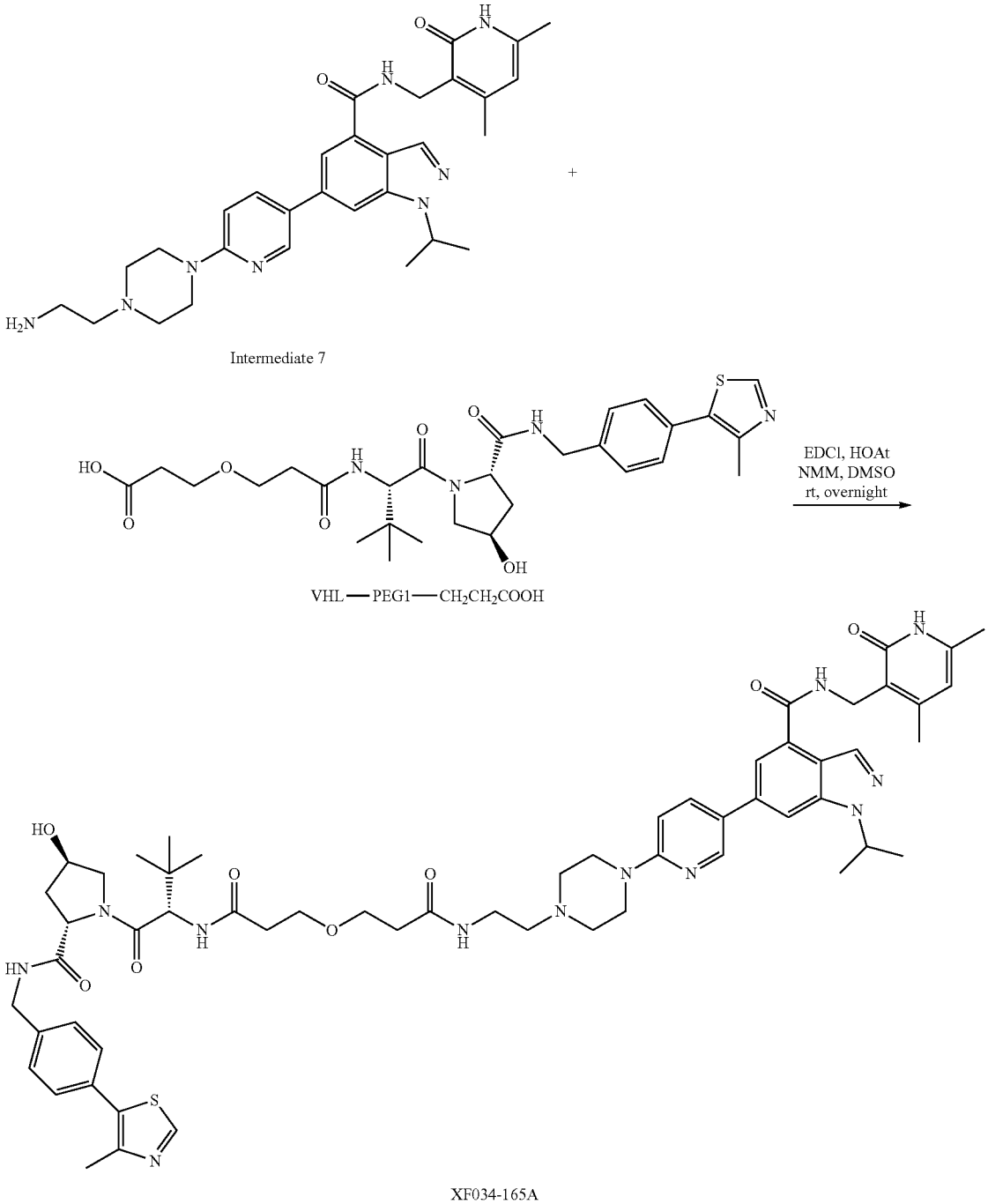
[0209]



[0210] Intermediate 7 (10 mg, 0.02 mmol), HOAt (3.7 mg, 0.03 mmol), and VHL-PEG1-CH_2COOH (10 mg, 0.02 mmol) were dissolved in DMSO (1.0 mL). To the solution were added NMM (5.3 μL, 0.06 mmol), and EDCI (4.3 mg, 0.03 mmol) successively at room temperature. After being stirred overnight at room temperature, the mixture was purified by preparative HPLC (10%-100% methanol/0.1% TFA in H_2O) to afford XF034-164A as white solid in TFA salt form (14 mg, 72%). ^1H NMR (600 MHz, CD_3OD) δ 9.00 (s, 1H), 8.56 (d, J=2.6 Hz, 1H), 8.37 (s, 1H), 8.17 (dd, J=9.3, 2.5 Hz, 1H), 7.96 (s, 1H), 7.78 (s, 1H), 7.46-7.38 (m, 4H), 7.15 (d, J=9.2 Hz, 1H), 6.21 (s, 1H), 5.11-5.06 (m, 1H), 4.71 (s, 1H), 4.62-4.53 (m, 4H), 4.53-4.43 (m, 2H), 4.43-4.33 (m, 2H), 4.23-4.10 (m, 5H), 3.90 (d, J=11.1 Hz, 2H), 3.84-3.79 (m, 2H), 3.76-3.68 (m, 2H), 3.64-3.49 (m, 3H), 3.42 (t, J=5.7 Hz, 2H), 2.47-2.42 (m, 6H), 2.29-2.21 (m, 4H), 2.13-2.05 (m, 1H), 1.57 (d, J=6.5 Hz, 6H), 1.06 (s, 9H).

Example 56: Synthesis of XF034-165A

[0211]

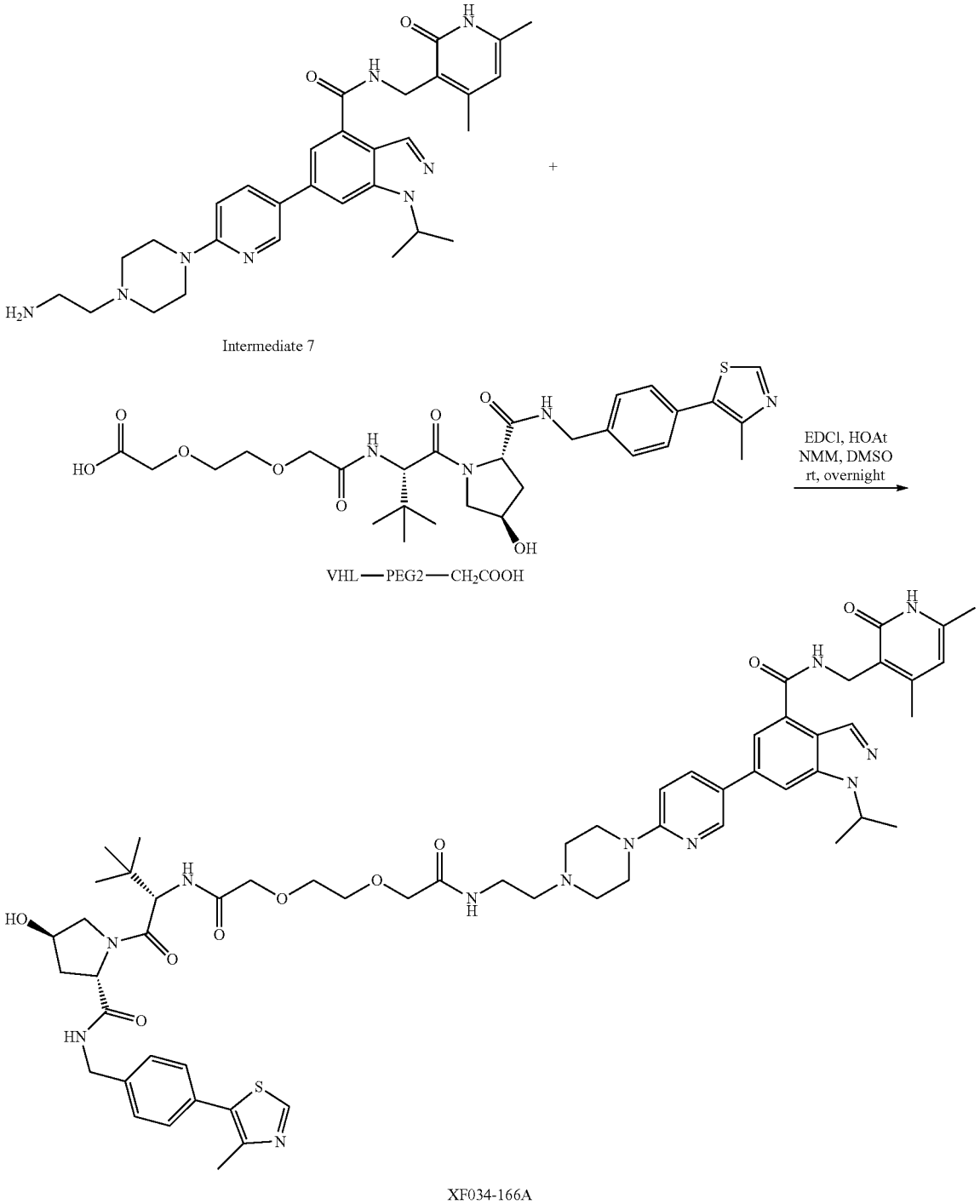


XF034-165A

[0212] XF034-165A was synthesized according to the procedures for preparing XF034-164A from intermediate 7 (10 mg, 0.02 mmol), HOAt (3.7 mg, 0.03 mmol), VHL-PEG1-CH_2CH_2COOH (10.6 mg, 0.02 mmol), NMM (5.3 μL, 0.06 mmol), EDCI (4.3 mg, 0.03 mmol), and DMSO (1.0 mL). XF034-165A was obtained as white solid in TFA salt form (20 mg, 98%). ^1H NMR (600 MHz, CD_3OD) δ 9.04 (s, 1H), 8.55 (d, J=2.4 Hz, 1H), 8.37 (s, 1H), 8.20 (dd, J=8.8, 2.5 Hz, 1H), 7.97 (s, 1H), 7.78 (s, 1H), 7.46-7.39 (m, 4H), 7.19 (d, J=9.1 Hz, 1H), 6.22 (s, 1H), 5.12-5.05 (m, 1H), 4.64 (s, 1H), 4.58 (s, 4H), 4.53-4.49 (m, 2H), 4.38 (d, J=15.3 Hz, 2H), 3.90 (d, J=10.9 Hz, 2H), 3.81 (dd, J=10.9, 3.7 Hz, 2H), 3.75-3.69 (m, 4H), 3.65 (t, J=5.2 Hz, 4H), 3.57 (s, 2H), 3.38 (t, J=5.7 Hz, 2H), 2.62-2.42 (m, 10H), 2.27 (s, 4H), 2.12-2.03 (m, 1H), 1.57 (d, J=6.5 Hz, 6H), 1.03 (d, J=10.3 Hz, 9H).

Example 57: Synthesis of XF034-166A

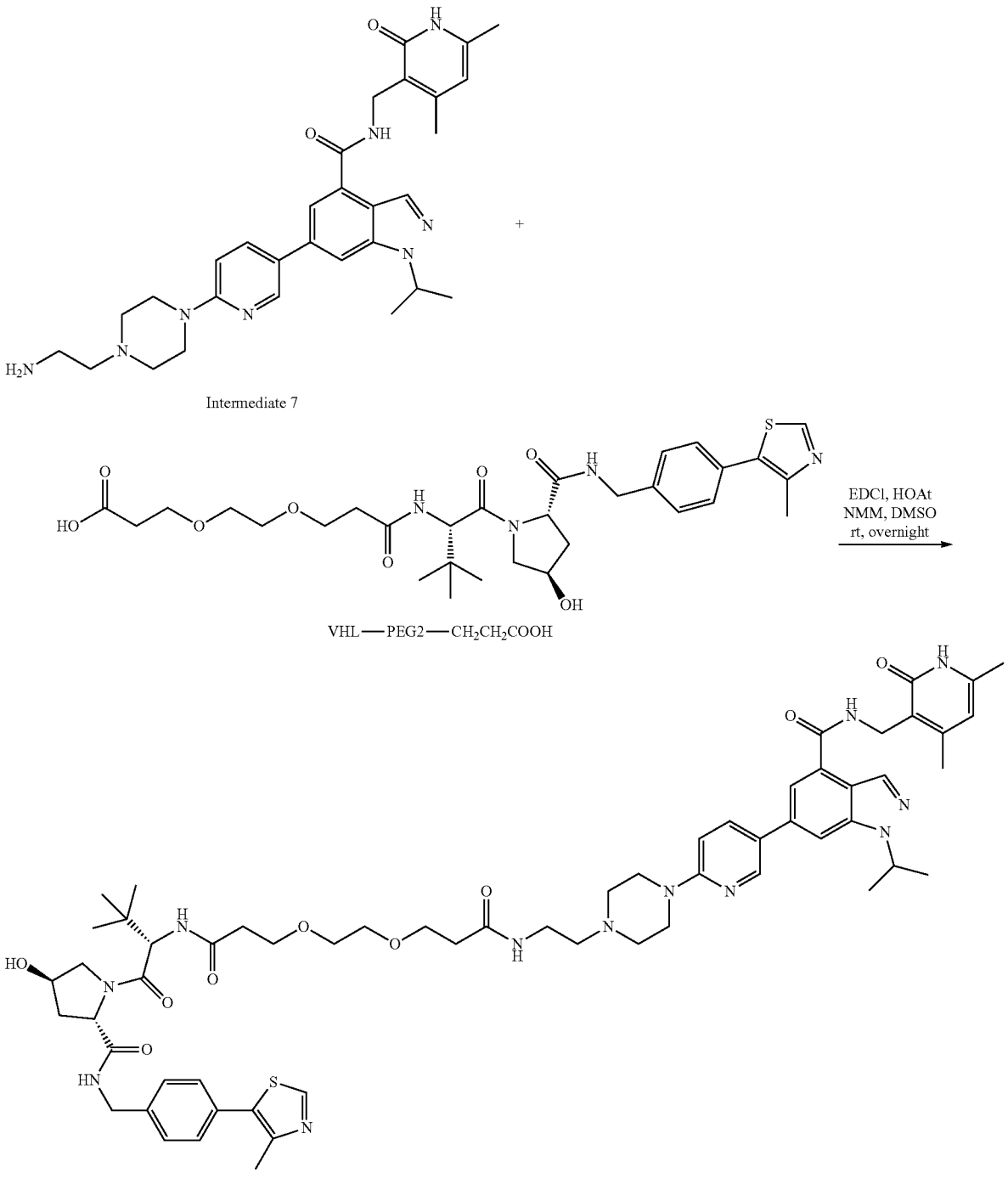
[0213]



[0214] XF034-166A was synthesized according to the procedures for preparing XF034-164A from intermediate 7 (10 mg, 0.02 mmol), HOAt (3.7 mg, 0.03 mmol), VHL-PEG2-CH_2COOH (10.9 mg, 0.02 mmol), NMM (5.3 μL, 0.06 mmol), EDCI (4.3 mg, 0.03 mmol), and DMSO (1.0 mL). XF034-166A was obtained as white solid in TFA salt form (16 mg, 77%). ^1H NMR (600 MHz, CD_3OD) δ 9.02 (s, 1H), 8.55 (d, J=2.6 Hz, 1H), 8.37 (s, 1H), 8.17 (dd, J=9.1, 2.5 Hz, 1H), 7.96 (s, 1H), 7.81-7.75 (m, 1H), 7.73 (d, J=9.3 Hz, 1H), 7.48-7.41 (m, 3H), 7.15 (d, J=9.0 Hz, 1H), 6.21 (s, 1H), 5.08 (p, J=6.7 Hz, 1H), 4.71 (s, 1H), 4.58 (d, J=7.2 Hz, 3H), 4.51 (s, 1H), 4.49-4.40 (m, 2H), 4.21-3.48 (m, 19H), 3.46-3.35 (m, 2H), 2.45 (d, J=9.4 Hz, 6H), 2.27 (s, 4H), 2.12-2.05 (m, 1H), 1.57 (d, J=6.6 Hz, 7H), 1.05 (s, 9H).

Example 58: Synthesis of XF034-167A

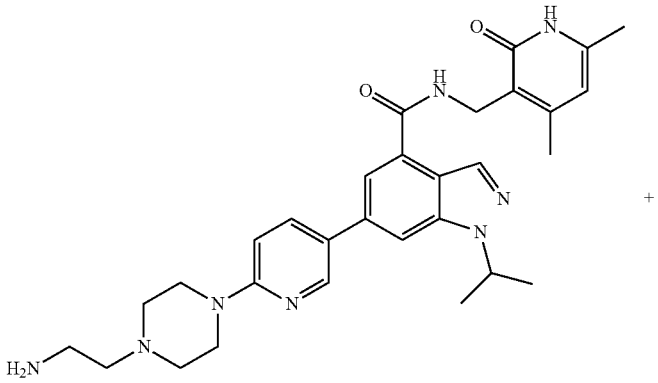
[0215]



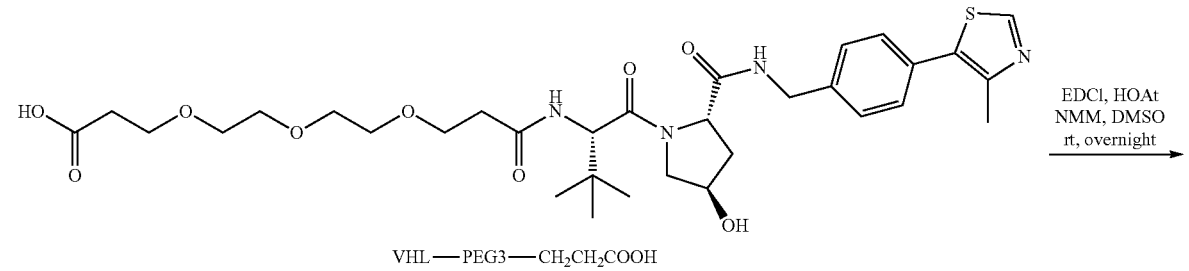
[0216] XF034-167A was synthesized according to the procedures for preparing XF034-164A from intermediate 7 (10 mg, 0.02 mmol), HOAt (3.7 mg, 0.03 mmol), VHL-PEG2-CH_2CH_2COOH (11.4 mg, 0.02 mmol), NMM (5.3 μL, 0.06 mmol), EDCI (4.3 mg, 0.03 mmol), and DMSO (1.0 mL). XF034-167A was obtained as white solid in TFA salt form (16 mg, 74%). ^1H NMR (600 MHz, CD_3OD) δ 8.96 (s, 1H), 8.58 (s, 1H), 8.37 (s, 1H), 8.14 (dt, J=8.9, 1.4 Hz, 1H), 7.99-7.93 (m, 1H), 7.78 (q, J=1.5 Hz, 1H), 7.48-7.40 (m, 4H), 7.13 (d, J=9.0 Hz, 1H), 6.17 (s, 1H), 5.08 (t, J=6.7 Hz, 1H), 4.64 (d, J=7.6 Hz, 1H), 4.60-4.44 (m, 5H), 4.35 (d, J=15.5 Hz, 1H), 3.88 (d, J=10.7 Hz, 2H), 3.82-3.51 (m, 18H), 3.37 (t, J=5.6 Hz, 2H), 2.56 (q, J=5.8 Hz, 2H), 2.53-2.48 (m, 2H), 2.45 (ddd, J=11.8, 2.8, 1.1 Hz, 6H), 2.29-2.19 (m, 4H), 2.07 (ddd, J=13.4, 9.2, 4.6 Hz, 1H), 1.57 (d, J=7.1 Hz, 6H), 1.03-1.00 (m, 9H).

Example 59: Synthesis of XF034-168A

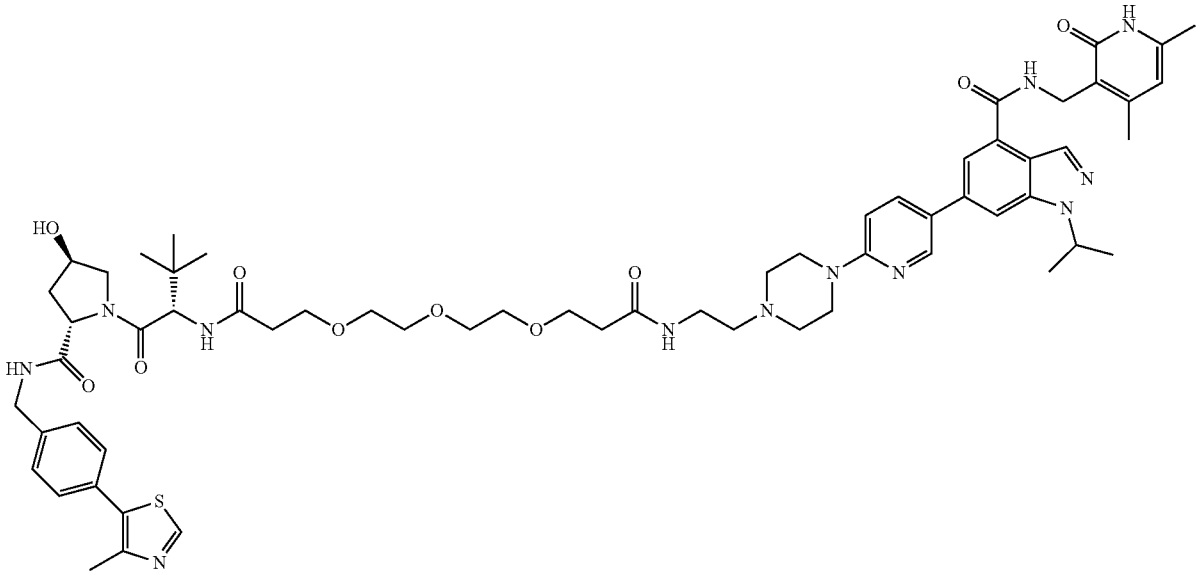
[0217]



Intermediate 7



VHL—PEG3—CH_2CH_2COOH

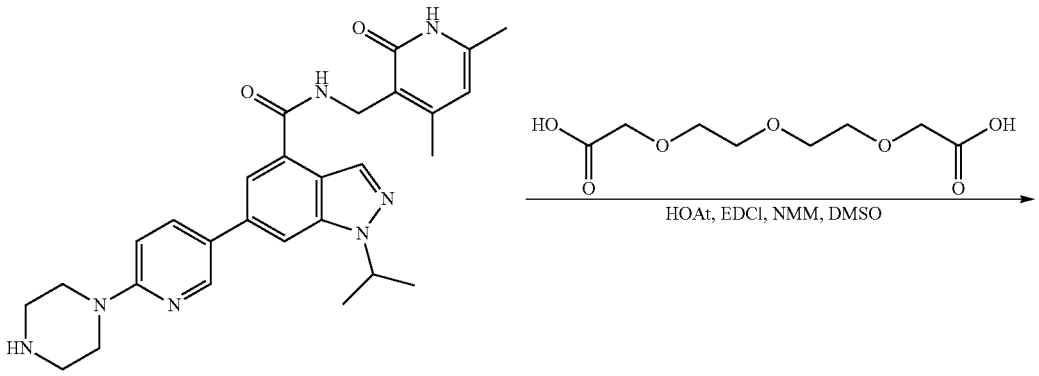


XF034-168A

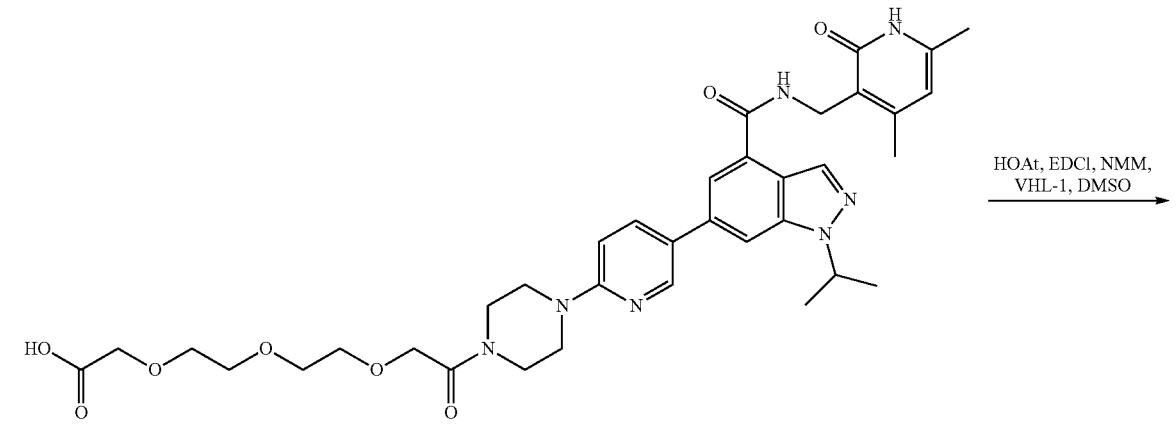
[0218] XF034-168A was synthesized according to the procedures for preparing XF034-164A from intermediate 7 (10 mg, 0.02 mmol), HOAt (3.7 mg, 0.03 mmol), VHL-PEG3-CH_2CH_2COOH (12.2 mg, 0.02 mmol), NMM (5.3 μL, 0.05 mmol), EDCI (4.3 mg, 0.03 mmol), and DMSO (1.0 mL). XF034-168A was obtained as white solid in TFA salt form (13 mg, 58%). ^1H NMR (600 MHz, CD_3OD) δ 8.96 (s, 1H), 8.58 (d, J=2.5 Hz, 1H), 8.37 (s, 1H), 8.14 (dd, J=9.1, 2.6 Hz, 1H), 7.95 (s, 1H), 7.82-7.74 (m, 1H), 7.43 (ddd, J=32.4, 21.2, 7.9 Hz, 4H), 7.13 (d, J=8.9 Hz, 1H), 6.17 (s, 1H), 5.11-5.02 (m, 1H), 4.64 (d, J=7.9 Hz, 1H), 4.60-4.46 (m, 5H), 4.36 (d, J=15.6 Hz, 1H), 3.88 (d, J=10.5 Hz, 2H), 3.83-3.49 (m, 22H), 3.37 (t, J=5.7 Hz, 2H), 2.62-2.40 (m, 10H), 2.28-2.17 (m, 4H), 2.10-2.03 (m, 1H), 1.57 (d, J=6.5 Hz, 6H), 1.03 (d, J=6.9 Hz, 9H).

Example 60: Synthesis of XY019-041

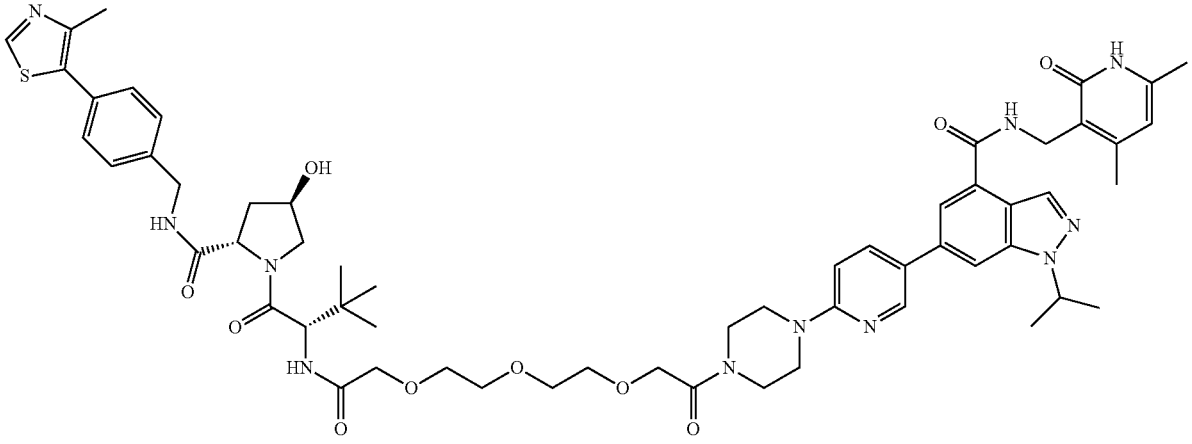
[0219]



Intermediate 3



Intermediate 16



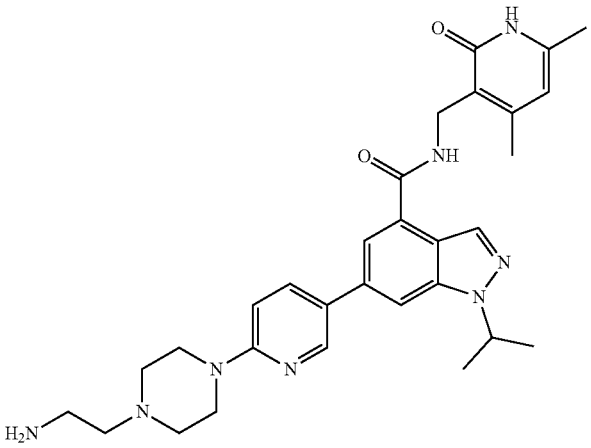
XY019-041

[0220] To the solution of intermediate 3 (80 mg, 0.16 mmol) in DMSO (5.0 mL) were added NMM (48 mg, 0.48 mmol), 2,2'-((oxybis(ethane-2,1-diyl))bis(oxy))diacetic acid (76 mg, 0.24 mmol), HOAt (33 mg, 0.24 mmol), and EDCI (46 mg, 0.24 mmol). The mixture was allowed to stir at room temperature overnight. The progress of the reaction was monitored by LC-MS. Upon completion, the mixture was concentrated under vacuum and purified by preparative HPLC to afford intermediate 16 (76 mg, 67%). MS (m/z) $[M+H]^+$: 704.3. To the solution of intermediate 16 (50 mg, 0.07 mmol) in DMSO (2.0 mL) were added NMM (21 mg, 0.21 mmol), VHL-1 (40 mg, 0.09 mmol), HOAt (15 mg, 0.11 mmol), and EDCI (20 mg, 0.11 mmol). The resulting mixture was allowed to stir at room temperature overnight. The progress of the reaction was monitored by LC-MS. Upon completion, the mixture was concentrated under

vacuum and purified by preparative HPLC to afford XY019-041 (40 mg, 50%) as solid. ^{1}H NMR (600 MHz, CD_3OD) δ 9.08 (s, 1H), 8.48 (dd, J=9.5, 1.8 Hz, 1H), 8.39 (s, 1H), 8.35 (s, 1H), 8.07 (s, 1H), 7.79 (s, 1H), 7.50-7.38 (m, 5H), 6.21 (s, 1H), 5.15-5.06 (m, 1H), 4.66 (s, 1H), 4.57 (d, J=12.7 Hz, 2H), 4.56-4.44 (m, 2H), 4.38-4.23 (m, 2H), 4.04 (d, J=15.8 Hz, 1H), 3.94 (d, J=15.7 Hz, 1H), 3.91-3.60 (m, 20H), 2.48 (s, 3H), 2.44 (s, 3H), 2.30-2.19 (m, 4H), 2.10-2.04 (m, 1H), 1.57 (d, 6H), 1.04 (s, 9H). MS (m/z) $[M+H]^+$: 1116.1.

Example 61: Synthesis of XF034-169A

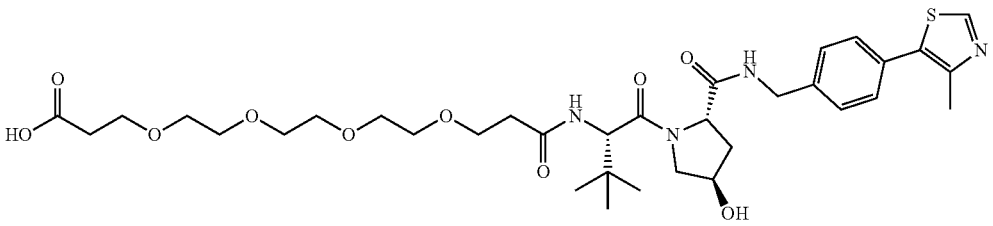
[0221]



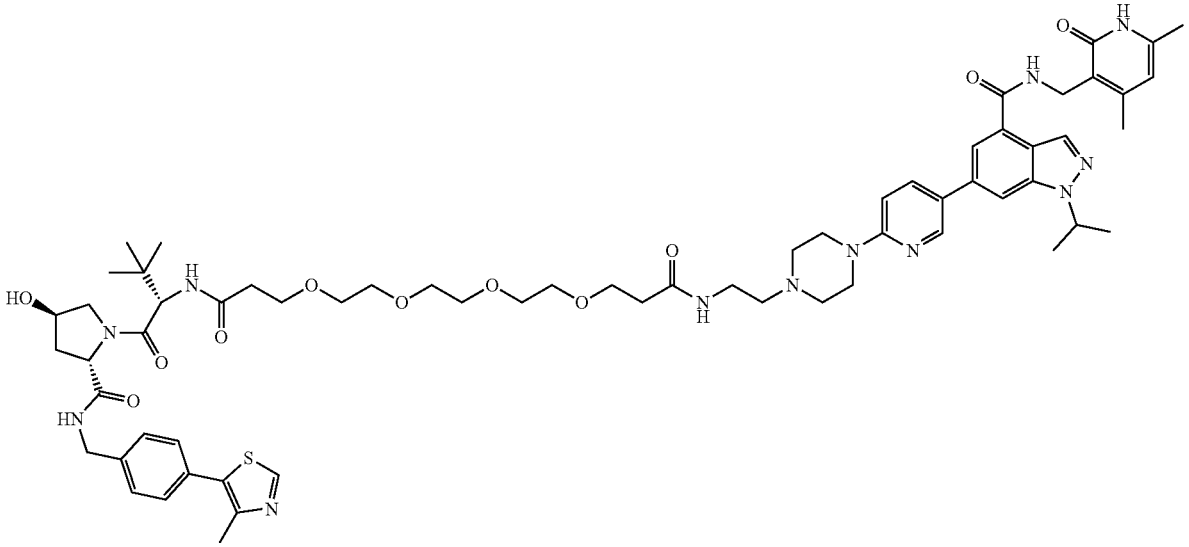
Intermediate 7

+

EDCI, HOAt
NMM, DMSO
rt, overnight



VHL-PEG4—CH_2CH_2COOH

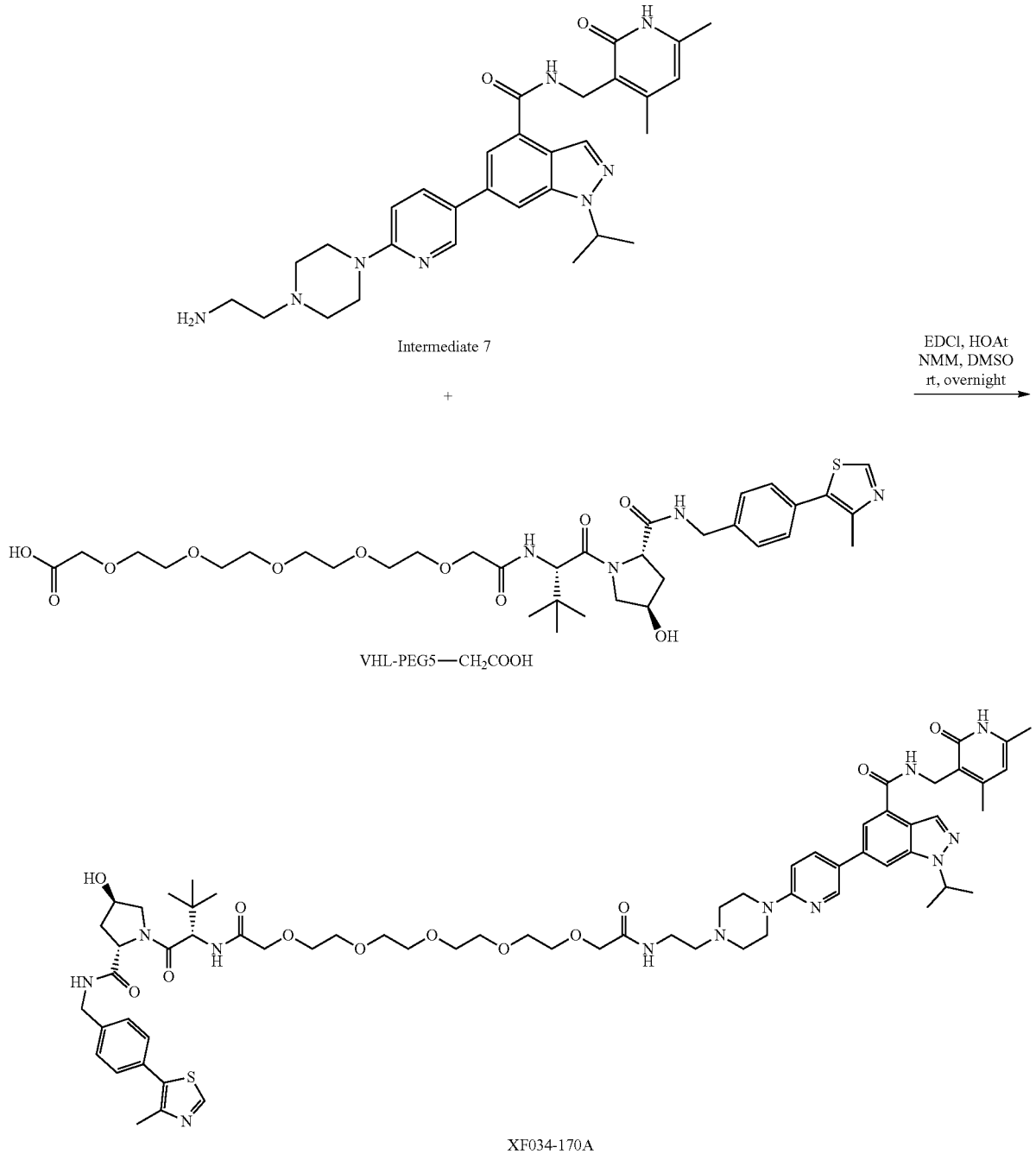


XF034-169A

[0222] XF034-169A was synthesized according to the procedures for preparing XF034-164A from intermediate 7 (10 mg, 0.02 mmol), HOAt (3.7 mg, 0.03 mmol), VHL-PEG4-CH_2CH_2COOH (13 mg, 0.02 mmol), NMM (5.3 μL, 0.06 mmol), EDCI (4.3 mg, 0.03 mmol), and DMSO (1.0 mL). XF034-169A was obtained as white solid in TFA salt form (20 mg, 90%). ^1H NMR (600 MHz, CD_3OD) δ 9.07 (s, 1H), 8.57 (d, J=2.5 Hz, 1H), 8.37 (s, 1H), 8.22 (dd, J=9.0, 2.5 Hz, 1H), 7.98 (s, 1H), 7.79 (s, 1H), 7.44 (ddd, J=33.1, 20.3, 7.9 Hz, 4H), 7.20 (d, J=9.0 Hz, 1H), 6.22 (s, 1H), 5.17-5.07 (m, 1H), 4.66-4.45 (m, 6H), 4.36 (d, J=15.5 Hz, 1H), 3.88 (d, J=10.8 Hz, 2H), 3.83-3.50 (m, 25H), 3.39 (t, J=5.7 Hz, 2H), 2.60-2.42 (m, 10H), 2.27 (s, 4H), 2.25-2.19 (m, 1H), 2.07 (td, J=12.5, 10.8, 4.4 Hz, 1H), 1.57 (d, J=6.6 Hz, 6H), 1.02 (s, 9H).

Example 62: Synthesis of XF034-170A

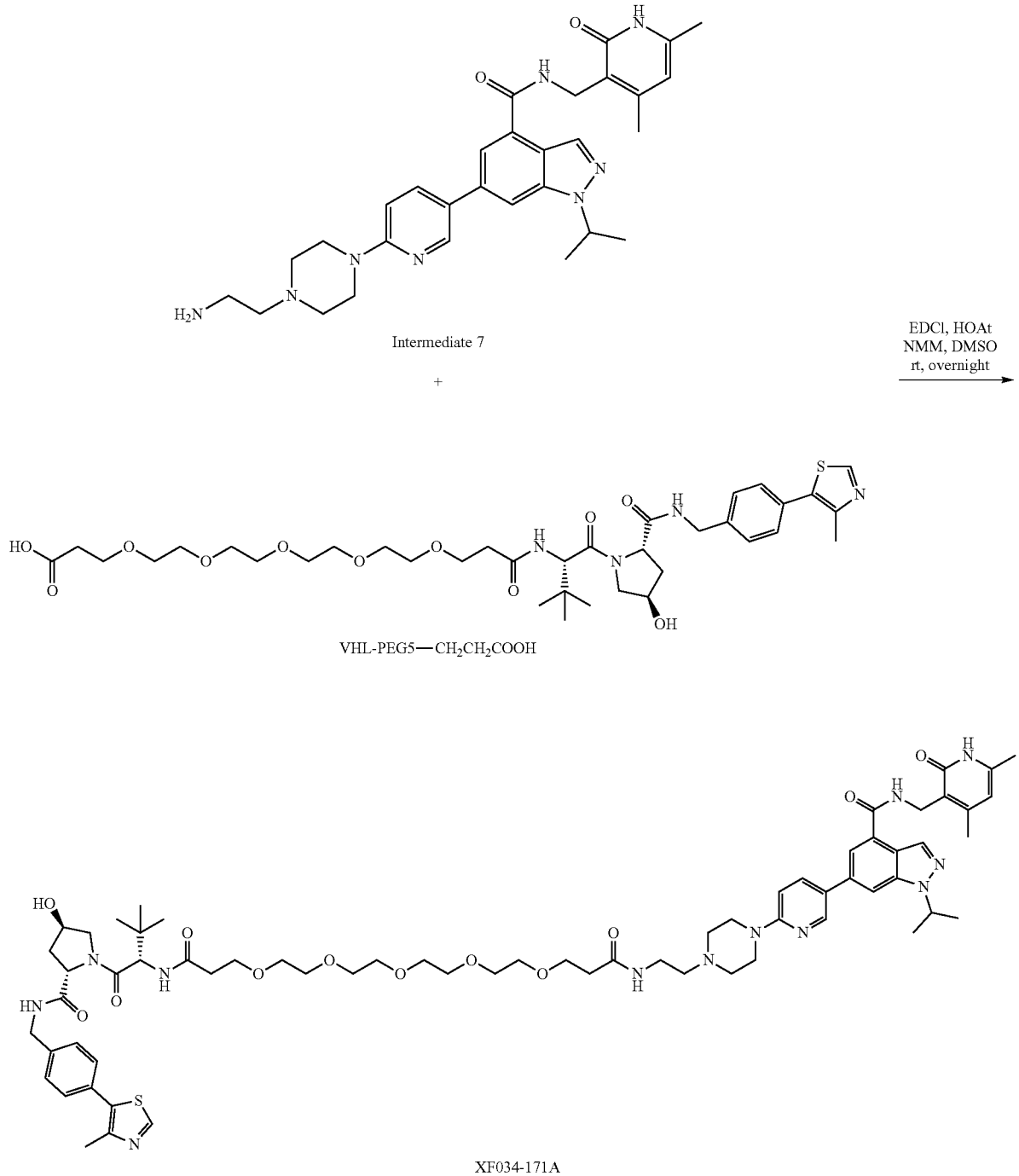
[0223]



[0224] XF034-170A was synthesized according to the procedures for preparing XF034-164A from intermediate 7 (10 mg, 0.02 mmol), HOAt (3.7 mg, 0.03 mmol), VHL-PEG5-CH_2COOH (13 mg, 0.02 mmol), NMM (5.3 μL, 0.06 mmol), EDCI (4.3 mg, 0.03 mmol), and DMSO (1.0 mL). XF034-170A was obtained as white solid in TFA salt form (17 mg, 76%). ^1H NMR (600 MHz, CD_3OD) δ 9.04 (s, 1H), 8.56 (s, 1H), 8.37 (s, 1H), 8.20 (d, J=9.1 Hz, 1H), 7.98 (s, 1H), 7.78 (s, 1H), 7.50-7.35 (m, 4H), 7.18 (d, J=9.1 Hz, 1H), 6.22 (s, 1H), 5.08 (s, 1H), 4.58 (t, J=46.0 Hz, 6H), 4.37 (d, J=15.6 Hz, 1H), 4.18-3.50 (m, 32H), 3.42 (s, 2H), 2.53-2.35 (m, 6H), 2.25 (d, J=22.7 Hz, 4H), 2.08 (s, 1H), 1.57 (d, J=6.8 Hz, 6H), 1.03 (d, J=15.1 Hz, 9H).

Example 63: Synthesis of XF034-171A

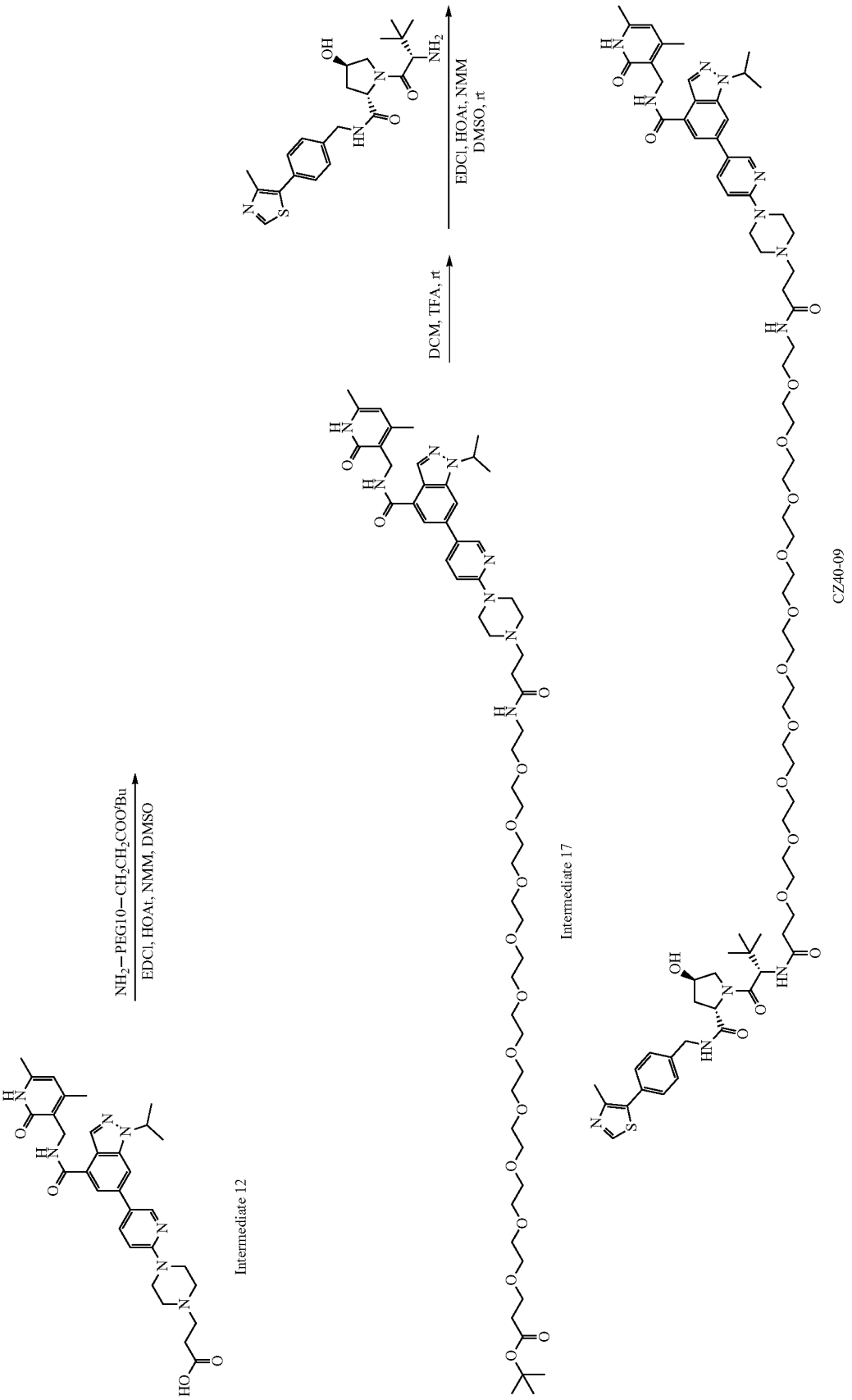
[0225]



[0226] CZ40-10 was synthesized according to the procedures for preparing CZ40-09 by reaction with NH_2-PEG8-$CH_2CH_2COO^tBu$. ^1H NMR (600 MHz, CD_3OD) δ 9.07 (s, 1H), 8.52 (d, J=2.5 Hz, 1H), 8.37 (s, 1H), 8.20 (dd, J=9.0, 2.5 Hz, 1H), 7.97 (s, 1H), 7.77 (d, J=1.3 Hz, 1H), 7.46 (d, J=8.1 Hz, 2H), 7.40-7.38 (m, 2H), 7.17 (d, J=9.1 Hz, 1H), 6.19 (s, 1H), 5.09-5.05 (m, 1H), 4.64 (s, 1H), 4.58-4.49 (m, 5H), 4.35 (d, J=15.5 Hz, 1H), 3.88 (d, J=11.0 Hz, 2H), 3.79 (dd, J=10.9, 3.9 Hz, 2H), 3.69 (qdd, J=9.7, 6.9, 5.1 Hz, 4H), 3.63-3.53 (m, 36H), 3.40 (t, J=5.3 Hz, 2H), 2.83 (t, J=6.8 Hz, 2H), 2.56 (ddd, J=15.0, 7.5, 5.2 Hz, 1H), 2.48-2.44 (m, 4H), 2.42 (s, 3H), 2.25-2.20 (m, 4H), 2.07 (ddd, J=13.3, 9.2, 4.5 Hz, 1H), 1.55 (d, J=6.6 Hz, 6H), 1.03 (s, 9H).ESI m/z=1407.73 $[M+H]^+$.

Example 65: Synthesis of CZ40-09

[0227]


NH2—PEG10—CH2CH2COOtBu
EDCI, HOAt, NMM, DMSO
DCM, TFA, rt
EDCI, HOAt, NMM
DMSO, rt
Intermediate 12
Intermediate 17
CZ40-09

[0228] To the solution of NH_2-PEG10-$CH_2CH_2COO^tBu$ (58 mg, 0.10 mmol) and intermediate 12 (69 mg, 0.12 mmol) in DMSO (1.0 mL) were added HOAt (21 mg, 0.15 mmol), EDCI (29 mg, 0.15 mmol), and NMM (44 μL, 0.40 mmol) at room temperature. After being stirred overnight, the reaction mixture was purified by prepared HPLC to give intermediate 17 (110 mg, 99%) as yellow oil.

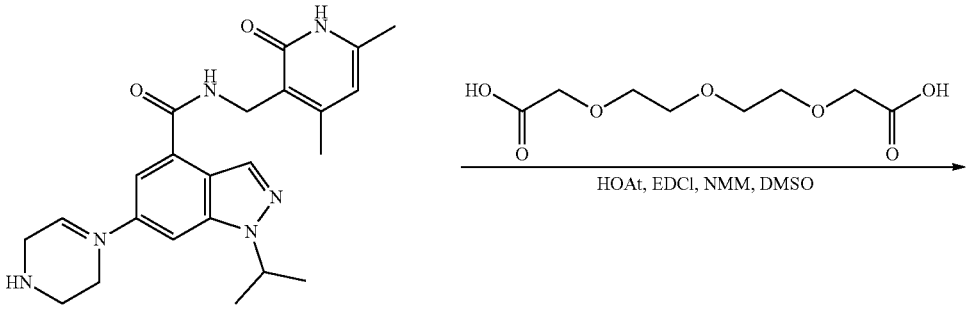
[0229] Intermediate 17 (110 mg, 0.10 mmol) was dissolved in dichloromethane (2.0 mL) and treated with trifluoroacetic acid (2.0 mL) at room temperature for 2 h. The mixture was concentrated and dried. The residue was dissolved in DMSO (1.0 mL). (2S,4R)-1-((S)-2-amino-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl) benzyl)pyrrolidine-2-carboxamide (43 mg, 0.10 mmol), HOAt (21 mg, 0.15 mmol), EDCI (29 mg, 0.15 mmol), and NMM (88 μL, 0.80 mmol) were added to the solution subsequently at room temperature. After being stirred overnight, the reaction mixture was purified by prepared HPLC to afford CZ40-09 (120 mg, 80%) as white solid in TFA salt form. ^1H NMR (600 MHz, CD_3OD) δ 8.98 (s, 1H), 8.54 (d, J=2.5 Hz, 1H), 8.37 (s, 1H), 8.14 (dd, J=9.0, 2.5 Hz, 1H), 7.95 (s, 1H), 7.77 (d, J=1.3 Hz, 1H), 7.46 (d, J=8.1 Hz, 2H), 7.40-7.38 (m, 2H), 7.11 (d, J=9.1 Hz, 1H), 6.16 (s, 1H), 5.09-5.05 (m, 1H), 4.64 (s, 1H), 4.58-4.49 (m, 5H), 4.34 (d, J=15.5 Hz, 1H), 3.88 (d, J=11.0 Hz, 2H), 3.79 (dd, J=10.9, 3.9 Hz, 2H), 3.69 (qdd, J=9.7, 6.9, 5.1 Hz, 4H), 3.63-3.53 (m, 44H), 3.41 (t, J=5.3 Hz, 2H), 2.82 (t, J=6.8 Hz, 2H), 2.56 (ddd, J=15.0, 7.5, 5.2 Hz, 1H), 2.48-2.44 (m, 4H), 2.41 (s, 3H), 2.24-2.18 (m, 4H), 2.07 (ddd, J=13.3, 9.2, 4.5 Hz, 1H), 1.56 (d, J=6.6 Hz, 6H), 1.03 (s, 9H). ESI m/z=1496.85 $[M+H]^+$.

Example 66: Synthesis of CZ40-11

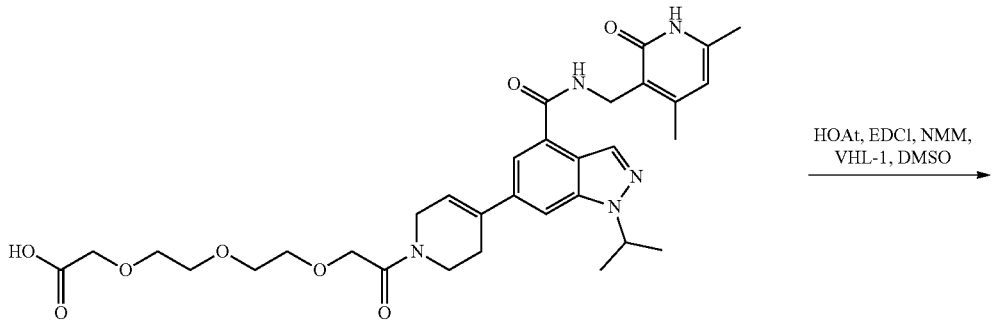
[0230] CZ40-11 was synthesized according to the procedures for preparing CZ40-09 by reaction with NH_2-PEG12-$CH_2CH_2COO^tBu$. ^1H NMR (600 MHz, CD_3OD) δ 9.01 (s, 1H), 8.54 (d, J=2.5 Hz, 1H), 8.37 (s, 1H), 8.17 (dd, J=9.0, 2.5 Hz, 1H), 7.97 (s, 1H), 7.77 (d, J=1.3 Hz, 1H), 7.46 (d, J=8.1 Hz, 2H), 7.40-7.38 (m, 2H), 7.15 (d, J=9.1 Hz, 1H), 6.17 (s, 1H), 5.09-5.05 (m, 1H), 4.64 (s, 1H), 4.58-4.49 (m, 5H), 4.35 (d, J=15.5 Hz, 1H), 3.88 (d, J=11.0 Hz, 2H), 3.79 (dd, J=10.9, 3.9 Hz, 2H), 3.69 (qdd, J=9.7, 6.9, 5.1 Hz, 4H), 3.63-3.53 (m, 52H), 3.40 (t, J=5.3 Hz, 2H), 2.82 (t, J=6.8 Hz, 2H), 2.56 (ddd, J=15.0, 7.5, 5.2 Hz, 1H), 2.48-2.43 (m, 4H), 2.42 (s, 3H), 2.25-2.20 (m, 4H), 2.07 (ddd, J=13.3, 9.2, 4.5 Hz, 1H), 1.55 (d, J=6.6 Hz, 6H), 1.02 (s, 9H).ESI m/z=1583.83 $[M+H]^+$.

Example 67: Synthesis of XY019-077

[0231]

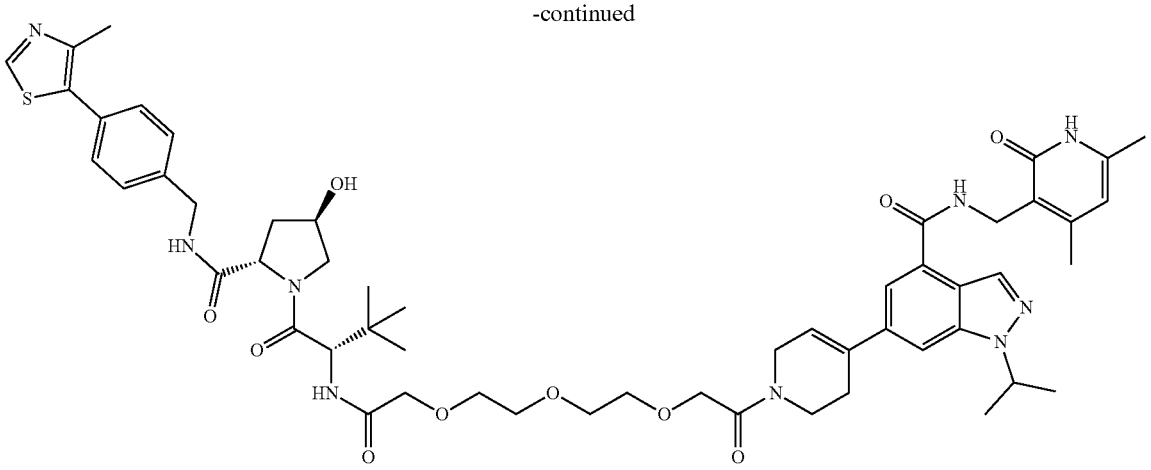


Intermediate 18



Intermediate 19

-continued

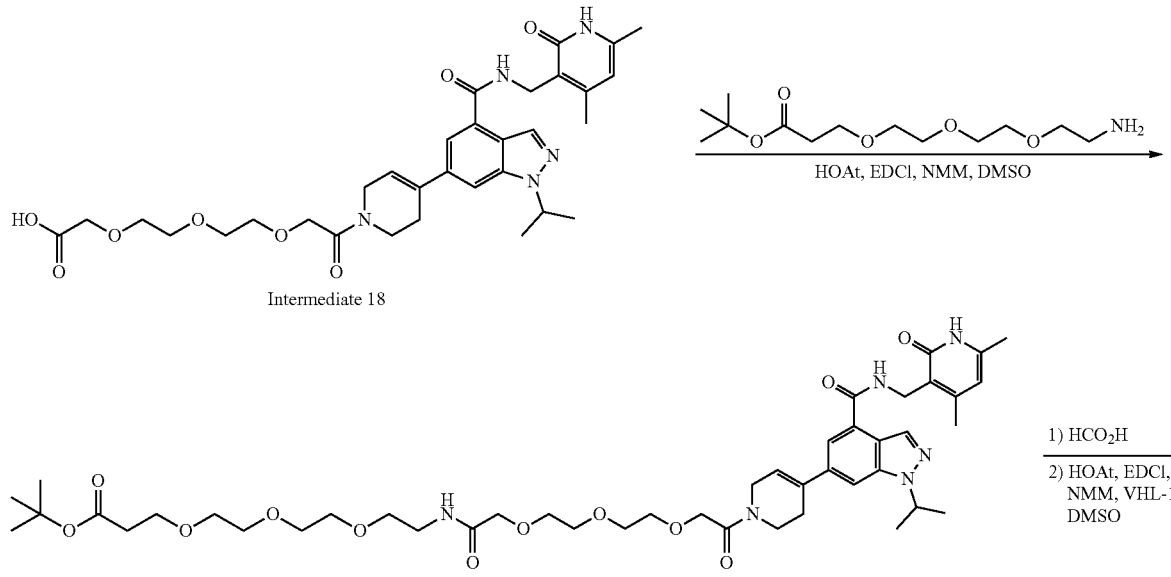


XY019-077

[0232] XY019-077 (20 mg, 43%) was synthesized according to the procedures for preparing XY019-041 from intermediate 18. ^{1}H NMR (600 MHz, CD_3OD) δ 8.99 (s, 1H), 8.32 (s, 1H), 7.73 (s, 1H), 7.67 (d, J=6.3 Hz, 1H), 7.43 (d, J=7.3 Hz, 2H), 7.39 (d, J=8.0 Hz, 2H), 6.29 (d, J=21.0 Hz, 1H), 6.19 (s, 1H), 5.02 (dt, J=13.2, 6.5 Hz, 1H), 4.68 (s, 1H), 4.58-4.46 (m, 5H), 4.40-4.25 (m, 3H), 4.21 (s, 2H), 4.06-3.92 (m, 2H), 3.85 (d, J=11.4 Hz, 1H), 3.81-3.63 (m, 11H), 2.74-2.59 (m, 2H), 2.46 (s, 3H), 2.42 (s, 3H), 2.29-2.17 (m, 4H), 2.11-2.03 (m, 1H), 1.53 (d, J=6.6 Hz, 6H), 1.02 (s, 9H). MS (m/z) $[M+H]^+$: 1036.2.

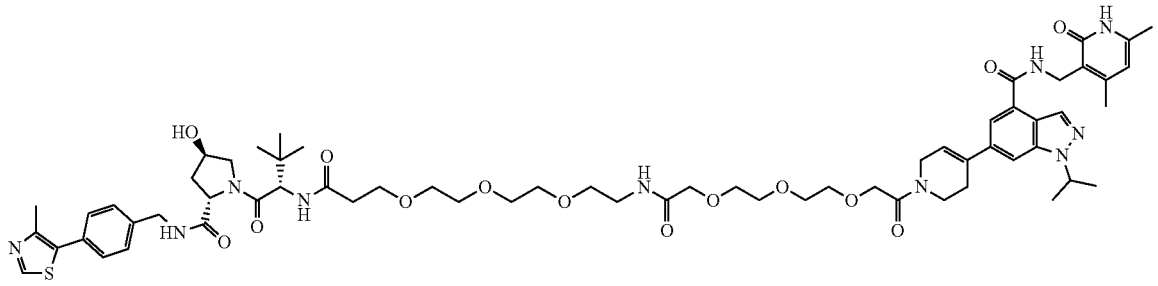
Example 68: Synthesis of XY019-083

[0233]



Intermediate 18

Intermediate 19



XY019-083

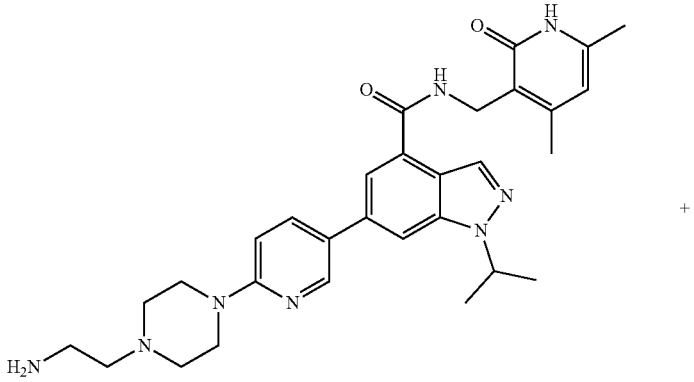
[0234] To the solution of intermediate 20 (22 mg, 0.03 mmol) in DMSO (3.0 mL) were added NMM (10 mg, 0.09 mmol), tert-butyl 3-(2-(2-(2-aminoethoxy)ethoxy)ethoxy) propanoate (13 mg, 0.04 mmol), HOAt (6.4 mg, 0.05 mmol), and EDCI (46 mg, 0.05 mmol). The mixture was allowed to stir at room temperature overnight. The progress of the reaction was monitored by LC-MS. Upon completion, the mixture was concentrated under vacuum and purified by preparative HPLC to afford intermediate 21 (21 mg, 70%). The solution of intermediate 21 (21 mg, 0.02 mmol) in formic acid (5.0 mL) was stirred overnight at room temperature. The progress of the reaction was monitored by LC-MS. Upon completion, the reaction was concentrated under vacuum and the resulting residue was dissolved in DMSO (2.0 mL). To the resulting solution were added VHL-1 (13 mg, 0.03 mmol), NMM (14 mg, 0.14 mmol), HOAt (4.6 mg, 0.03 mmol), and EDCI (6.5 mg, 0.03 mmol). The reaction mixture was allowed to stir at room temperature overnight. The progress of the reaction was monitored by LC-MS. Upon completion, the mixture was concentrated under vacuum and purified by preparative HPLC to afford XY019-083 (4.5 mg, 16%) as solid. ^{1}H NMR (600 MHz, CD_3OD) δ 8.90 (s, 1H), 8.32 (s, 1H), 7.74 (s, 1H), 7.68 (s, 1H), 7.45 (d, J=8.1 Hz, 2H), 7.39 (d, J=8.0 Hz, 2H), 6.32 (d, J=21.1 Hz, 1H), 6.13 (s, 1H), 5.06-4.99 (m, 1H), 4.64 (d, J=8.9 Hz, 1H), 4.58-4.45 (m, 5H), 4.40-4.30 (m, 2H), 4.24 (s, 1H), 4.00-3.94 (m, 2H), 3.90-3.83 (m, 2H), 3.82-3.36 (m, 25H), 2.93-2.85 (m, 2H), 2.71 (d, J=45.0 Hz, 2H), 2.59-2.50 (m, 1H), 2.46 (s, 3H), 2.41 (s, 3H), 2.26-2.17 (m, 4H), 2.07 (d, J=8.8 Hz, 1H), 1.54 (d, J=6.5 Hz, 6H), 1.02 (s, 9H). MS (m/z) $[M+H]^+$: 1240.2.

Example 69: Synthesis of XY019-084

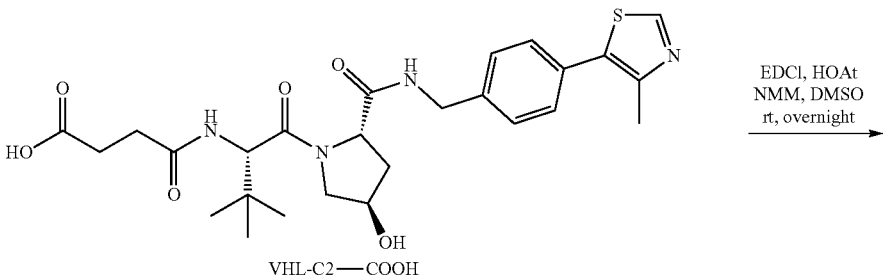
[0235] XY019-084 (20 mg, 49%) was synthesized according to the procedures for preparing XY019-083 from intermediate 16. ^{1}H NMR (600 MHz, CD_3OD) δ 9.07 (s, 1H), 8.50 (d, J=9.4 Hz, 1H), 8.39 (s, 2H), 8.08 (s, 1H), 7.80 (s, 1H), 7.49 (d, J=9.5 Hz, 1H), 7.46 (d, J=8.0 Hz, 2H), 7.41 (d, J=8.0 Hz, 2H), 6.19 (s, 1H), 5.11 (dt, J=13.0, 6.5 Hz, 1H), 4.63 (s, 1H), 4.61-4.44 (m, 5H), 4.36 (s, 1H), 4.34 (s, 2H), 4.00 (s, 2H), 3.87 (M, 9H), 3.78 (dd, J=10.9, 3.5 Hz, 1H), 3.75-3.65 (m, 10H), 3.63-3.55 (m, 9H), 3.53 (t, J=5.5 Hz, 2H), 3.40 (t, J=5.3 Hz, 2H), 2.59-2.52 (m, 1H), 2.48 (s, 3H), 2.44 (s, 3H), 2.26 (s, 3H), 2.25-2.17 (m, 1H), 2.09-2.03 (m, 1H), 1.58 (d, J=6.6 Hz, 6H), 1.03 (s, 9H). HRMS (m/z) for $C_{67}H_{91}N_{12}O_{14}S^+$ $[M+H]^+$: calculated 1319.6493, found 1319.6483.

Example 70: Synthesis of XF034-172A

[0236]

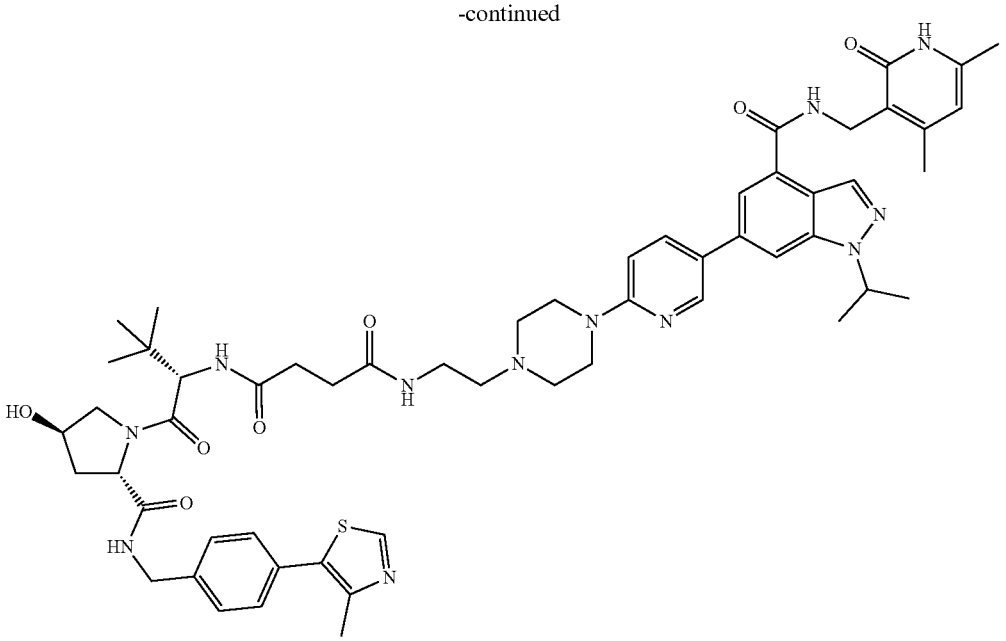


Intermediate 7



VHL-C2—COOH

-continued

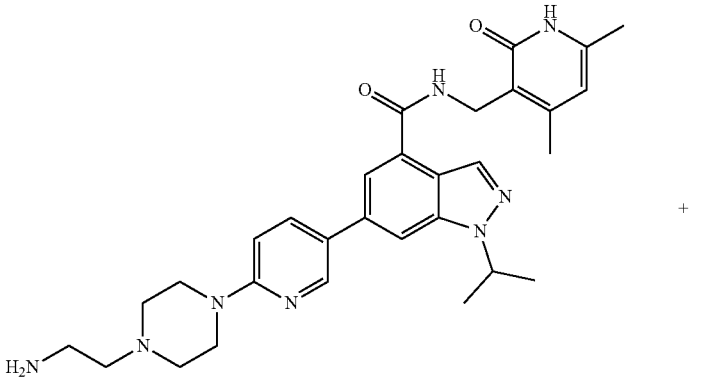


XF034-172A

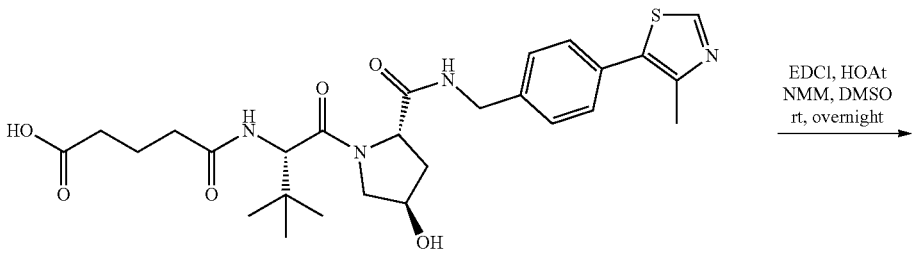
[0237] XF034-172A was synthesized according to the procedures for preparing XF034-164A from intermediate 7 (10 mg, 0.02 mmol), HOAt (3.7 mg, 0.03 mmol), VHL-C2-COOH (9.8 mg, 0.02 mmol), NMM (5.3 μL, 0.06 mmol), EDCI (4.3 mg, 0.03 mmol), and DMSO (1.0 mL). XF034-172A was obtained as white solid in TFA salt form (10 mg, 51%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.98 (s, 1H), 8.58 (d, J=2.6 Hz, 1H), 8.37 (s, 1H), 8.15 (dd, J=9.2, 2.5 Hz, 1H), 7.95 (s, 1H), 7.77 (s, 1H), 7.49-7.36 (m, 5H), 7.14 (d, J=8.9 Hz, 2H), 6.19 (s, 1H), 5.08 (p, J=6.7 Hz, 1H), 4.61-4.49 (m, 5H), 4.45 (s, 1H), 4.35 (d, J=15.5 Hz, 1H), 3.81-3.51 (m, 10H), 3.39 (t, J=5.5 Hz, 2H), 2.68 (q, J=10.8, 8.5 Hz, 2H), 2.49-2.43 (m, 8H), 2.26 (s, 4H), 2.09-2.04 (m, 1H), 1.57 (d, J=6.5 Hz, 6H), 1.02 (s, 9H).

Example 71: Synthesis of XF034-173A

[0238]

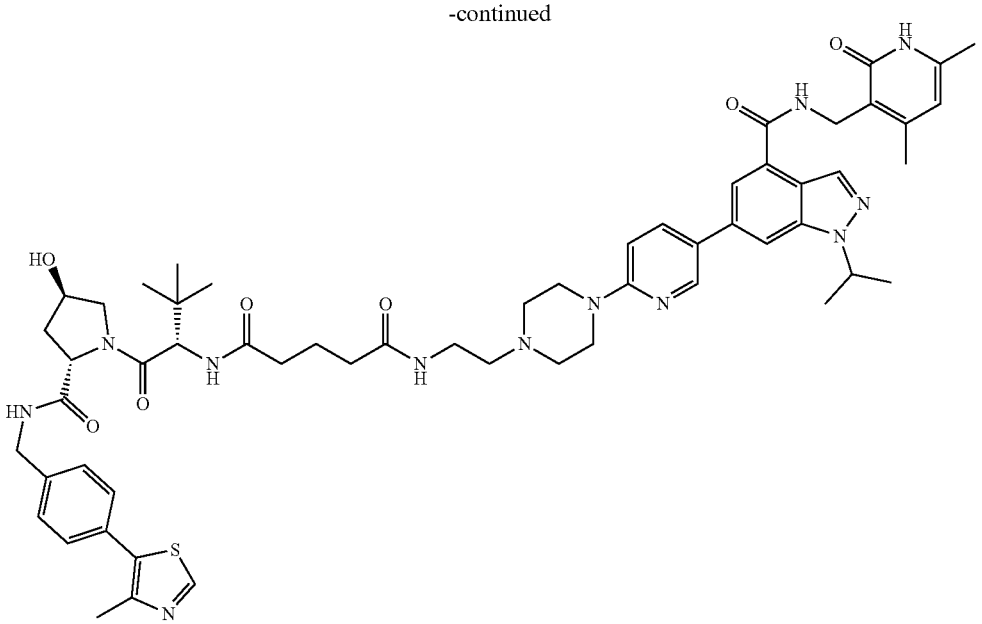


Intermediate 7



VHL-C3—COOH

-continued

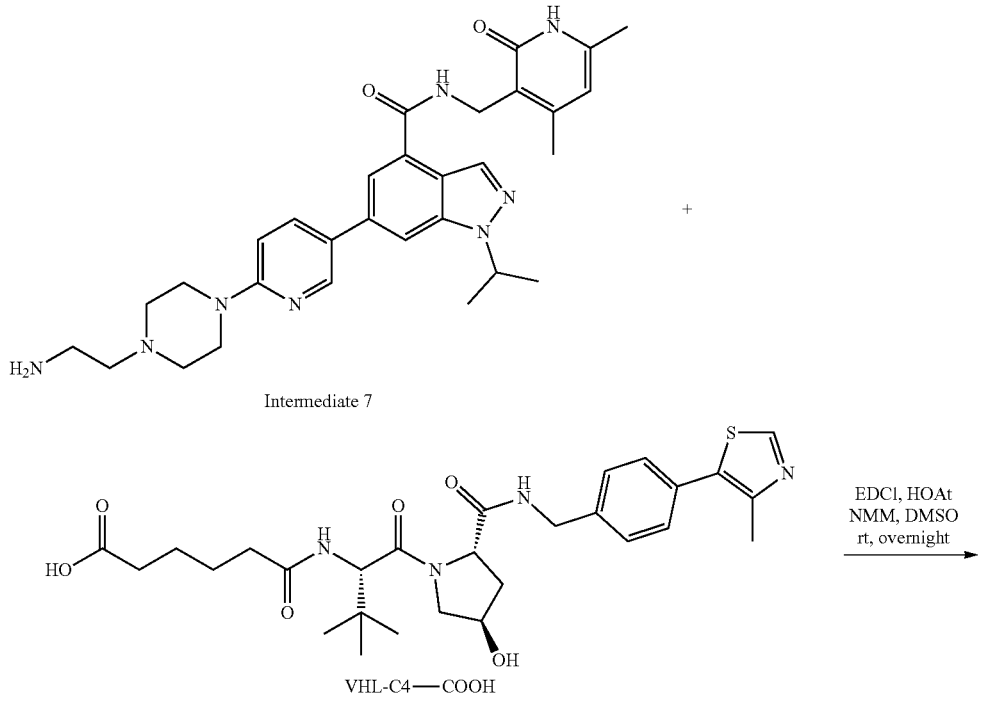


XF034-173A

[0239] XF034-173A was synthesized according to the procedures for preparing XF034-164A from intermediate 7 (10 mg, 0.02 mmol), HOAt (3.7 mg, 0.03 mmol), VHL-C3-COOH (10 mg, 0.02 mmol), NMM (5.3 μL, 0.06 mmol), EDCI (4.3 mg, 0.03 mmol), and DMSO (1.0 mL). XF034-173A was obtained as white solid in TFA salt form (14 mg, 70%). ^{1}H NMR (600 MHz, CD_3OD) δ 9.00 (s, 1H), 8.56 (d, J=2.6 Hz, 1H), 8.37 (s, 1H), 8.16 (dd, J=9.2, 2.5 Hz, 1H), 7.96 (s, 1H), 7.77 (s, 1H), 7.51-7.36 (m, 4H), 7.15 (d, J=9.0 Hz, 1H), 6.20 (s, 1H), 5.15-5.06 (m, 1H), 4.60-4.48 (m, 6H), 4.36 (d, J=15.4 Hz, 1H), 3.92 (d, J=11.1 Hz, 2H), 3.81 (dd, J=11.0, 3.9 Hz, 2H), 3.76-3.43 (m, 8H), 3.37 (t, J=5.8 Hz, 2H), 2.45 (d, J=9.0 Hz, 6H), 2.39-2.19 (m, 8H), 2.09 (td, J=13.3, 11.3, 4.7 Hz, 1H), 1.98-1.89 (m, 2H), 1.57 (d, J=6.6 Hz, 6H), 1.05 (s, 9H).

Example 72: Synthesis of XF034-174A

[0240]



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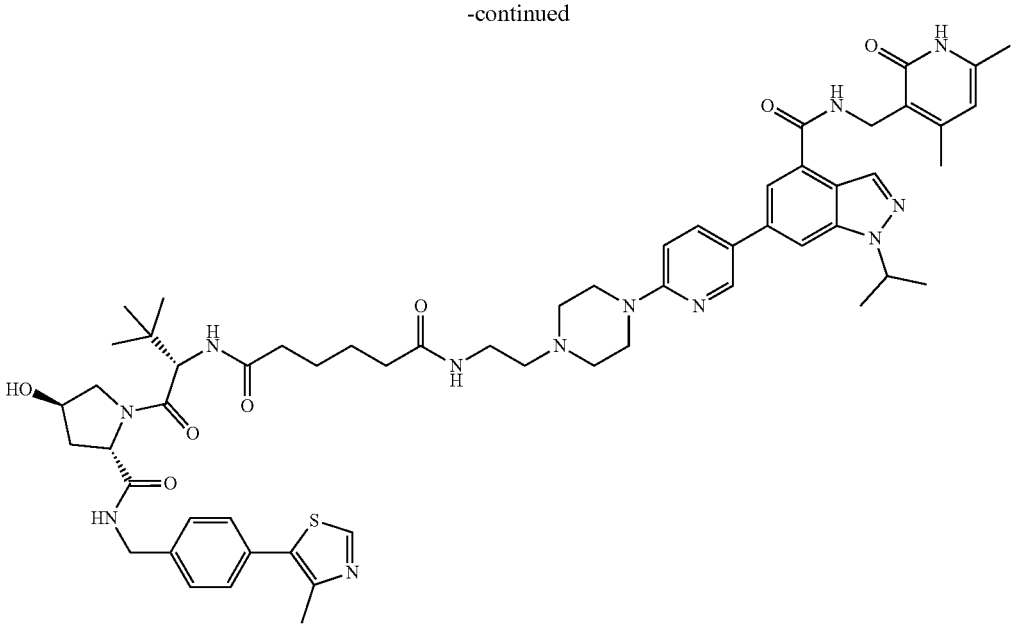
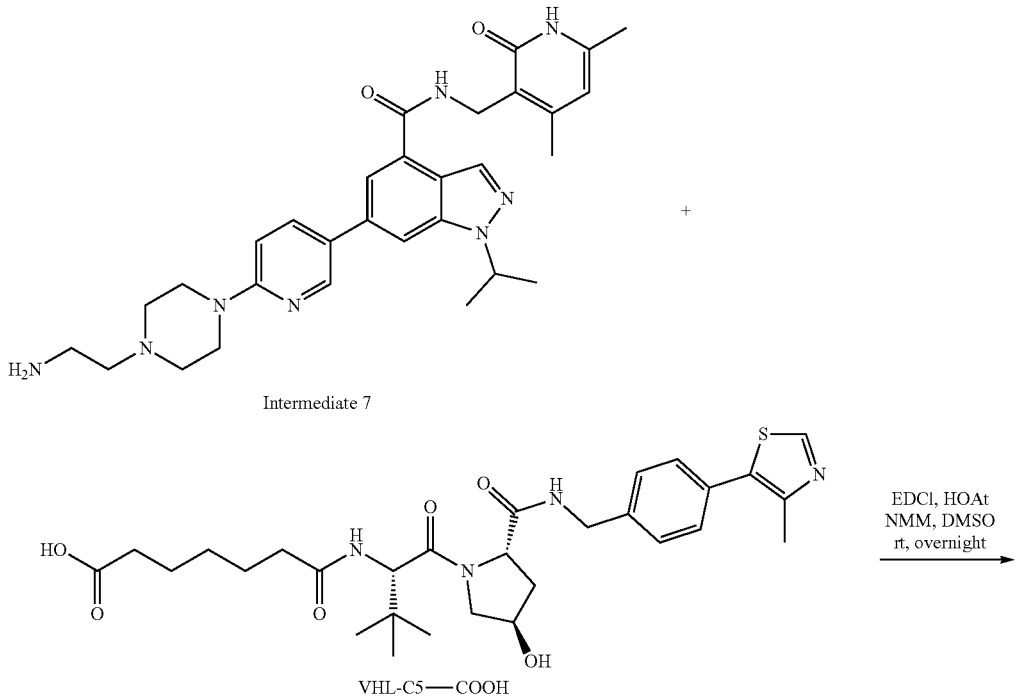


XF034-174A

[0241] XF034-174A was synthesized according to the procedures for preparing XF034-164A from intermediate 7 (10 mg, 0.02 mmol), HOAt (3.7 mg, 0.03 mmol), VHL-C4-COOH (11 mg, 0.02 mmol), NMM (5.3 μL, 0.06 mmol), EDCI (4.3 mg, 0.03 mmol), and DMSO (1.0 mL). XF034-174A was obtained as white solid in TFA salt form (14 mg, 72%). ^{1}H NMR (600 MHz, CD_3OD) δ 9.04 (s, 1H), 8.62-8.51 (m, 1H), 8.37 (d, J=3.3 Hz, 1H), 8.24-8.16 (m, 1H), 7.97 (d, J=3.6 Hz, 1H), 7.78 (d, J=3.4 Hz, 1H), 7.50-7.40 (m, 4H), 7.17 (dd, J=9.1, 3.5 Hz, 1H), 6.21 (s, 1H), 5.12-5.06 (m, 1H), 4.62-4.50 (m, 6H), 4.39-4.35 (m, 1H), 4.13-3.44 (m, 12H), 3.37 (t, J=5.7 Hz, 2H), 2.45 (dd, J=14.5, 3.5 Hz, 6H), 2.34-2.19 (m, 8H), 2.08 (td, J=9.6, 5.1 Hz, 1H), 1.67-1.61 (m, 4H), 1.57 (dd, J=6.7, 3.3 Hz, 6H), 1.03 (d, J=3.5 Hz, 9H).

Example 73: Synthesis of XF034-175A

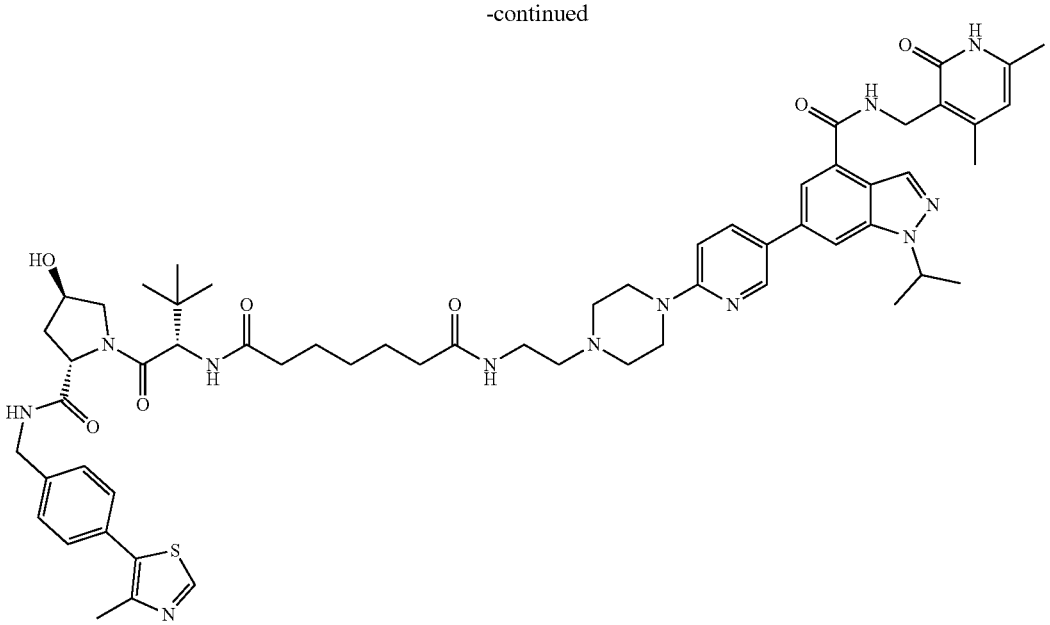
[0242]



Intermediate 7

VHL-C5—COOH

-continued

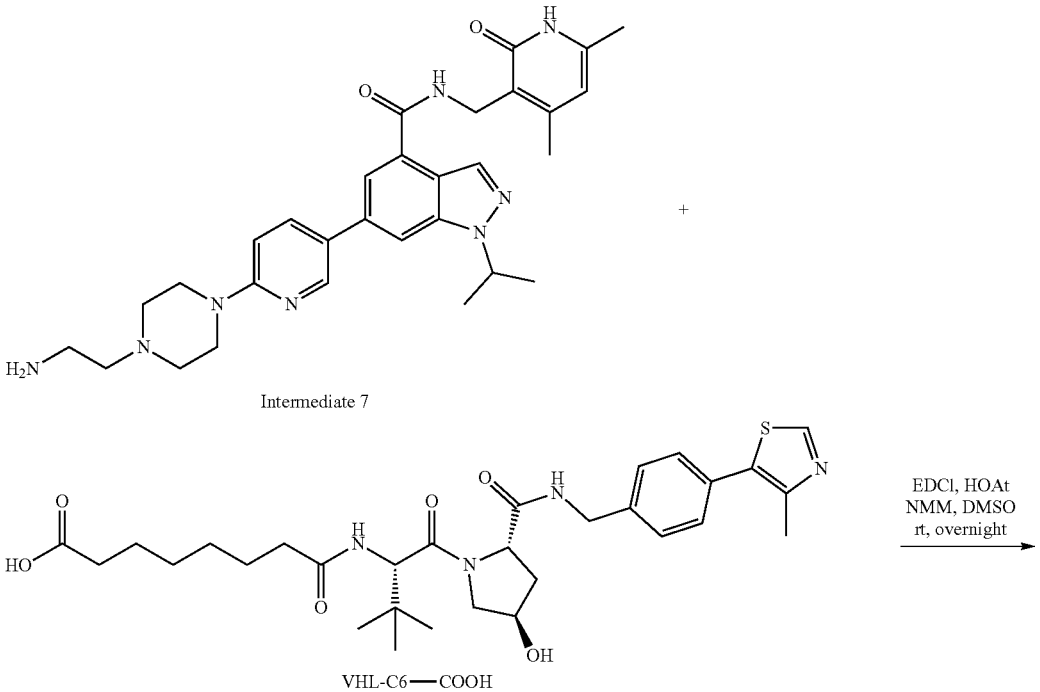


XF034-175A

[0243] XF034-175A was synthesized according to the procedures for preparing XF034-164A from intermediate 7 (10 mg, 0.02 mmol), HOAt (3.7 mg, 0.03 mmol), VHL-C5-COOH (11 mg, 0.02 mmol), NMM (5.3 μL, 0.06 mmol), EDCI (4.3 mg, 0.03 mmol), and DMSO (1.0 mL). XF034-175A was obtained as white solid in TFA salt form (17 mg, 83%). ^{1}H NMR (600 MHz, CD_3OD) δ 9.00 (s, 1H), 8.57 (d, J=2.6 Hz, 1H), 8.37 (s, 1H), 8.20-8.11 (m, 1H), 7.96 (s, 1H), 7.78 (s, 1H), 7.54-7.33 (m, 4H), 7.15 (d, J=9.0 Hz, 1H), 6.20 (s, 1H), 5.08 (p, J=6.7 Hz, 1H), 4.63 (s, 1H), 4.62-4.45 (m, 5H), 4.36 (d, J=15.4 Hz, 1H), 4.14-3.40 (m, 12H), 3.36 (t, J=6.0 Hz, 2H), 2.46 (d, J=16.3 Hz, 6H), 2.33-2.17 (m, 8H), 2.08 (td, J=12.7, 10.9, 4.4 Hz, 1H), 1.61 (dd, J=42.7, 7.3 Hz, 10H), 1.37 (q, J=7.8 Hz, 2H), 1.03 (s, 9H).

Example 74: Synthesis of XF034-176A

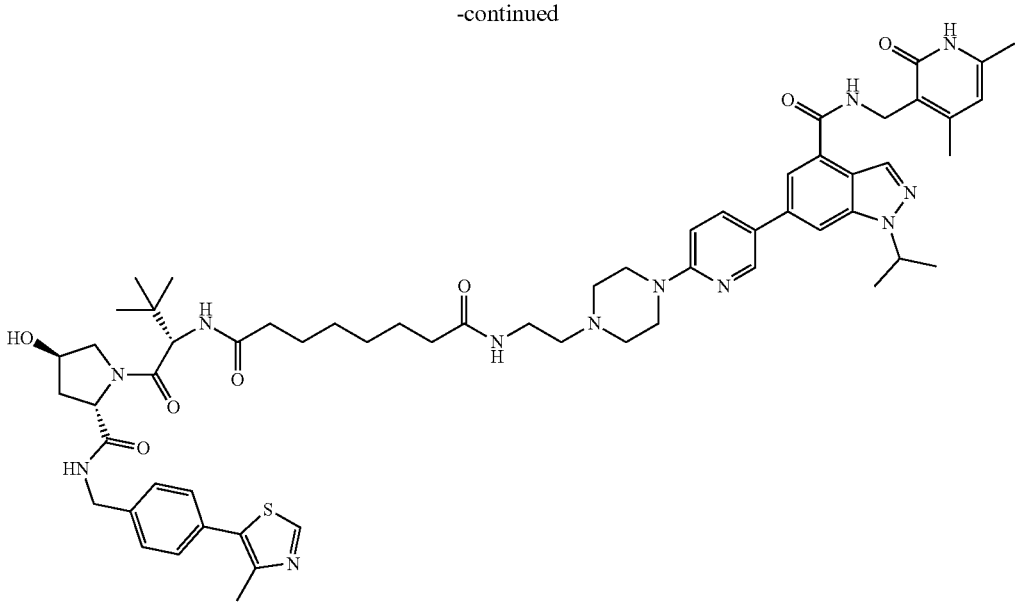
[0244]



Intermediate 7

VHL-C6—COOH

-continued

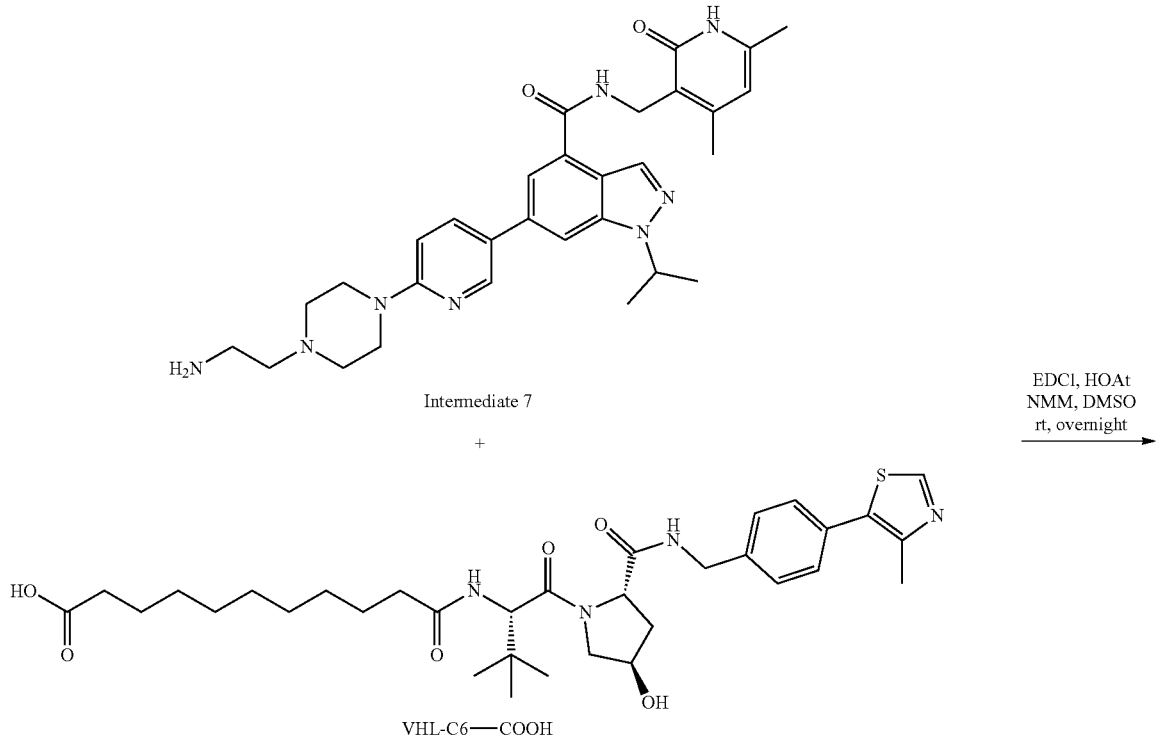


XF034-176A

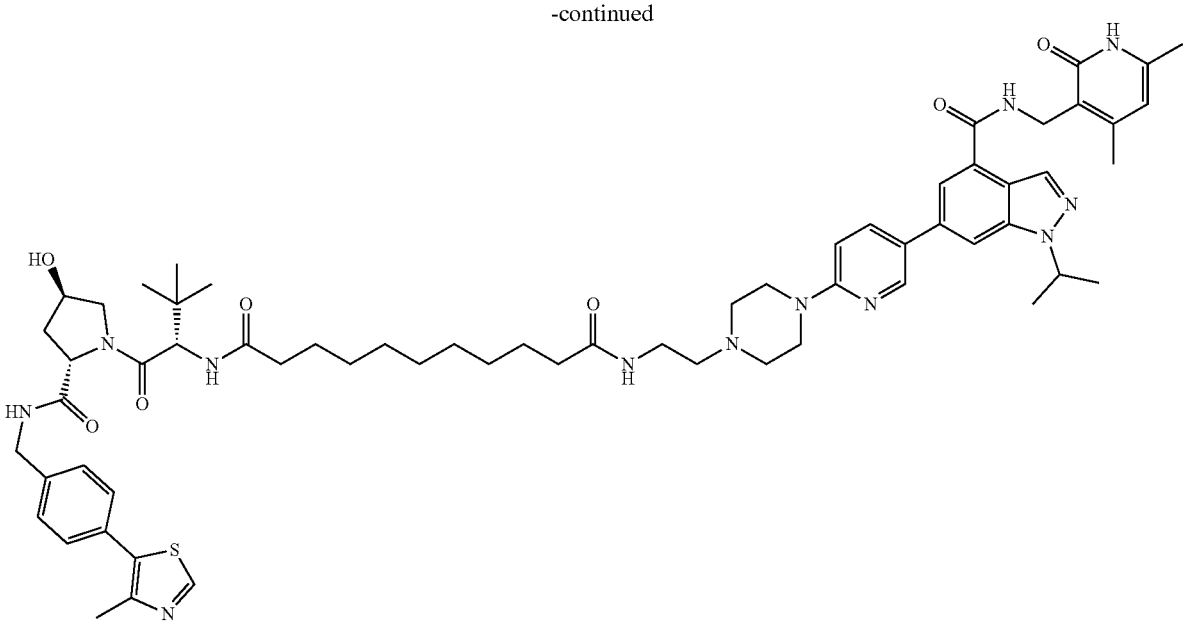
[0245] XF034-176A was synthesized according to the procedures for preparing XF034-164A from intermediate 7 (10 mg, 0.02 mmol), HOAt (3.7 mg, 0.03 mmol), VHL-C6-COOH (11 mg, 0.02 mmol), NMM (5.3 μL, 0.06 mmol), EDCI (4.3 mg, 0.03 mmol), and DMSO (1.0 mL). XF034-176A was obtained as white solid in TFA salt form (12 mg, 61%). ^{1}H NMR (600 MHz, CD_3OD) δ 9.03 (s, 1H), 8.58 (d, J=2.6 Hz, 1H), 8.37 (s, 1H), 8.19-8.11 (m, 1H), 7.97 (s, 1H), 7.78 (s, 1H), 7.54-7.27 (m, 4H), 7.15 (d, J=8.9 Hz, 1H), 6.19 (s, 1H), 5.09 (q, J=6.6 Hz, 1H), 4.63 (s, 1H), 4.62-4.46 (m, 5H), 4.36 (d, J=15.4 Hz, 1H), 4.15-3.44 (m, 12H), 3.35 (t, J=6.0 Hz, 2H), 2.46 (d, J=16.8 Hz, 6H), 2.25 (d, J=10.1 Hz, 8H), 2.11-2.03 (m, 1H), 1.65-1.52 (m, 10H), 1.35 (s, 4H), 1.03 (s, 9H).

Example 75: Synthesis of XF034-177A

[0246]



-continued

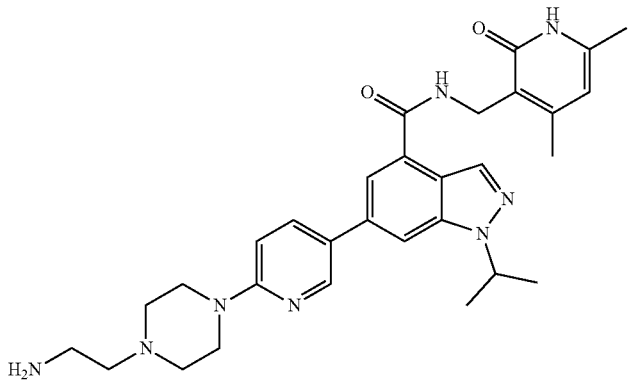


XF034-177A

[0247] XF034-177A was synthesized according to the procedures for preparing XF034-164A from intermediate 7 (10 mg, 0.02 mmol), HOAt (3.7 mg, 0.03 mmol), VHL-C9-COOH (12 mg, 0.02 mmol), NMM (5.3 μL, 0.06 mmol), EDCI (4.3 mg, 0.03 mmol), and DMSO (1.0 mL). XF034-177A was obtained as white solid in TFA salt form (9 mg, 41%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.99 (s, 1H), 8.59 (d, J=2.5 Hz, 1H), 8.37 (s, 1H), 8.16 (d, J=8.8 Hz, 1H), 7.96 (s, 1H), 7.79 (s, 1H), 7.60-7.22 (m, 4H), 7.14 (d, J=8.9 Hz, 1H), 6.19 (s, 1H), 5.08 (q, J=6.6 Hz, 1H), 4.63 (s, 1H), 4.60-4.44 (m, 5H), 4.35 (d, J=15.4 Hz, 1H), 3.99-3.43 (m, 12H), 3.35 (d, J=6.1 Hz, 2H), 2.46 (d, J=18.4 Hz, 6H), 2.33-2.16 (m, 8H), 2.08 (td, J=13.2, 11.1, 4.4 Hz, 1H), 1.66-1.52 (m, 10H), 1.32 (s, 10H), 1.03 (s, 9H).

Example 76: Synthesis of YS36-48

[0248]



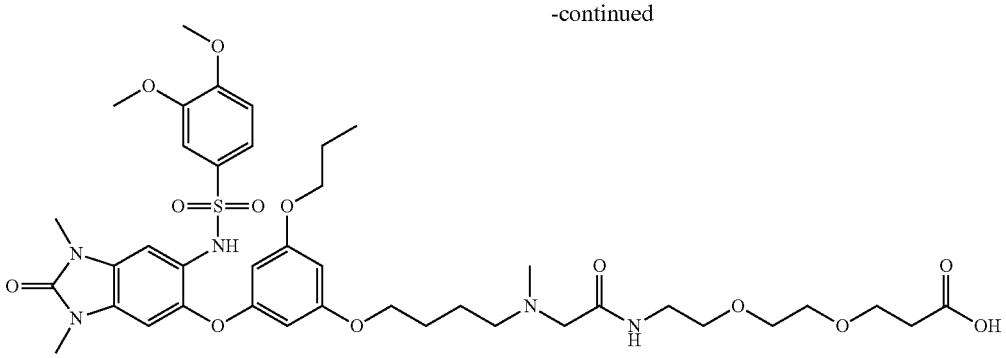
Intermediate 7

+

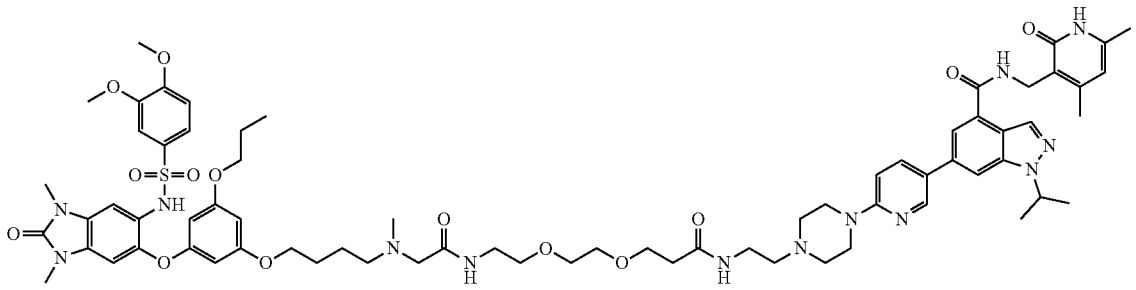
EDCI, HOAt, NMM

DMSO, rt

-continued



Intermediate 22

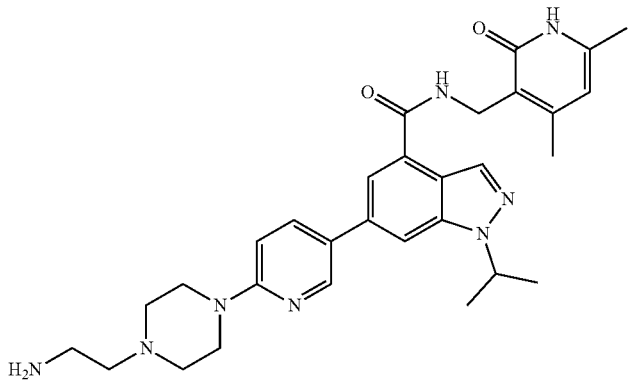


YS36-48

[0249] Intermediate 22 (10 mg, 0.01 mmol), HOAt (4.3 mg, 0.03 mmol), and intermediate 7 (10 mg, 0.01 mmol) were dissolved in DMSO (1.0 mL). To the solution were added NMM (14 μL, 0.13 mmol), and EDCI (6.1 mg, 0.03 mmol) successively at room temperature. After being stirred overnight at room temperature, the mixture was purified by preparative HPLC (10%-100% methanol/0.1% TFA in H_2O) to afford YS36-48 as white solid in TFA salt form (10 mg, 62%). ^1H NMR (600 MHz, CD_3OD) δ 8.59 (d, J=2.5 Hz, 1H), 8.36 (s, 1H), 8.11 (dd, J=9.0, 2.5 Hz, 1H), 7.94 (s, 1H), 7.78 (s, 1H), 7.33 (s, 1H), 7.20 (dd, J=8.4, 2.1 Hz, 1H), 7.15 (d, J=2.1 Hz, 1H), 7.09 (d, J=8.9 Hz, 1H), 6.78 (d, J=8.5 Hz, 1H), 6.61 (s, 1H), 6.14 (d, J=16.1 Hz, 2H), 5.76 (d, J=2.4 Hz, 1H), 5.61 (d, J=2.4 Hz, 1H), 5.08 (p, J=6.5 Hz, 1H), 4.58 (s, 2H), 3.98 (bs, 8H), 3.84 (t, J=5.9 Hz, 2H), 3.79 (s, 3H), 3.75 (q, J=6.3 Hz, 4H), 3.65 (t, J=5.8 Hz, 2H), 3.60-3.59 (m, 9H), 3.54 (t, J=5.4 Hz, 4H), 3.43-3.40 (m, 5H), 3.36 (t, J=5.8 Hz, 2H), 3.24 (s, 3H), 2.94 (s, 3H), 2.51 (t, J=6.1 Hz, 2H), 2.43 (s, 3H), 2.25 (s, 3H), 1.90 (q, J=8.0 Hz, 2H), 1.80 (q, J=7.1, 6.7 Hz, 2H), 1.74 (p, J=6.9 Hz, 2H), 1.57 (d, J=6.6 Hz, 6H), 1.00 (t, J=7.4 Hz, 3H).

Example 77: Synthesis of YS36-49

[0250]



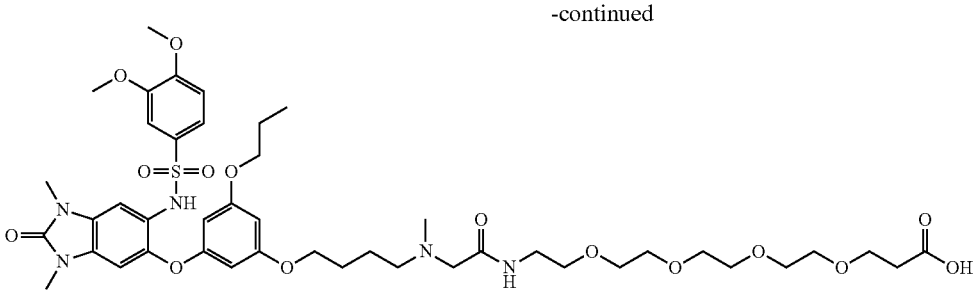
Intermediate 7

+

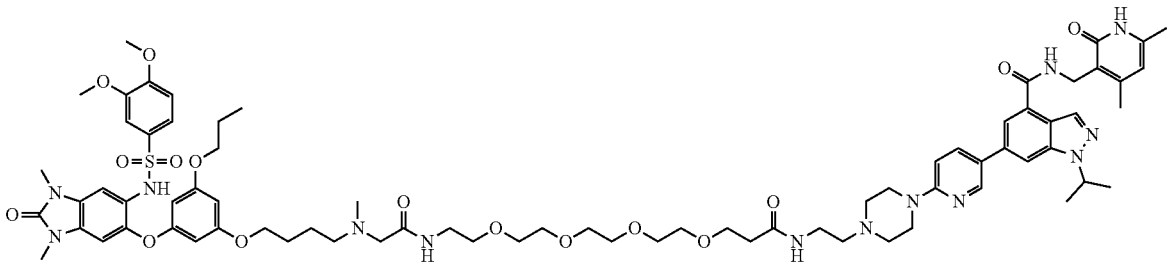
EDCI, HOAt, NMM

DMSO, rt

-continued



Intermediate 23

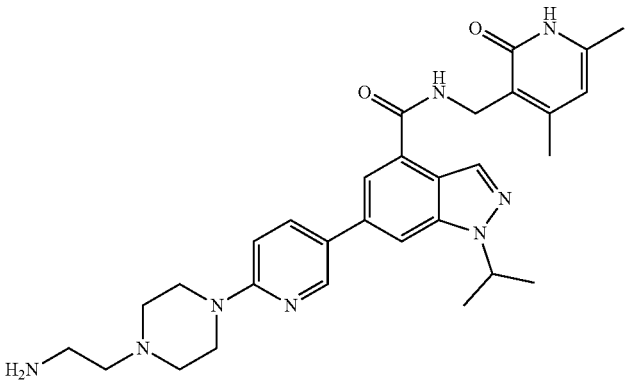


YS36-49

[0251] YS36-49 was synthesized according to the procedures for preparing YS36-48 from intermediate 23 (10 mg, 0.01 mmol), HOAt (4.3 mg, 0.03 mmol), intermediate 7 (10 mg, 0.01 mmol), NMM (14 μL, 0.13 mmol), EDCI (6.1 mg, 0.03 mmol), and DMSO (1.0 mL). YS36-49 was obtained as white solid in TFA salt form (11 mg, 65%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.58 (d, J=2.5 Hz, 1H), 8.36 (s, 1H), 8.17 (dd, J=9.0, 2.5 Hz, 1H), 7.97 (s, 1H), 7.78 (d, J=1.3 Hz, 1H), 7.33 (s, 1H), 7.24-7.09 (m, 3H), 6.78 (d, J=8.5 Hz, 1H), 6.61 (s, 1H), 6.19 (s, 1H), 6.13 (d, J=2.4 Hz, 1H), 5.75 (d, J=2.4 Hz, 1H), 5.61 (d, J=2.2 Hz, 1H), 5.08 (p, J=6.7 Hz, 1H), 4.58 (s, 2H), 3.98 (s, 8H), 3.84 (t, J=5.8 Hz, 2H), 3.80 (d, J=1.0 Hz, 3H), 3.76 (q, J=5.9 Hz, 4H), 3.65 (d, J=5.9 Hz, 2H), 3.63-3.48 (m, 21H), 3.43-3.35 (m, 7H), 3.24 (d, J=1.1 Hz, 3H), 2.94 (s, 3H), 2.51 (t, J=5.9 Hz, 2H), 2.44 (s, 3H), 2.26 (s, 3H), 1.93-1.89 (m, 2H), 1.81 (dt, J=14.2, 6.7 Hz, 2H), 1.75-1.71 (m, 2H), 1.57 (d, J=6.6 Hz, 6H), 1.00 (t, J=7.4 Hz, 3H).

Example 78: Synthesis of YS36-50

[0252]

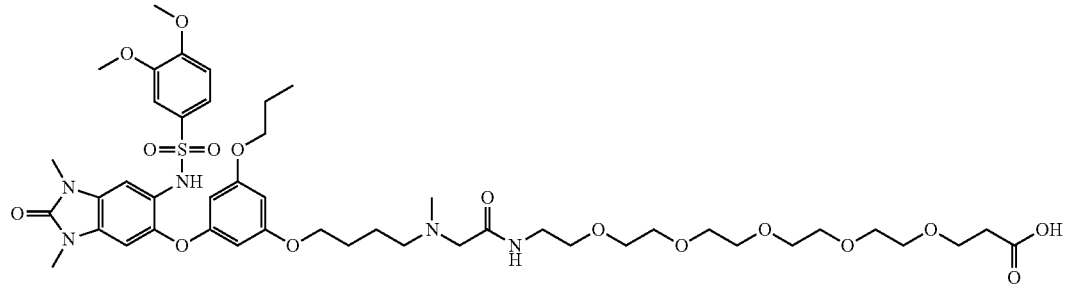


Intermediate 7

+

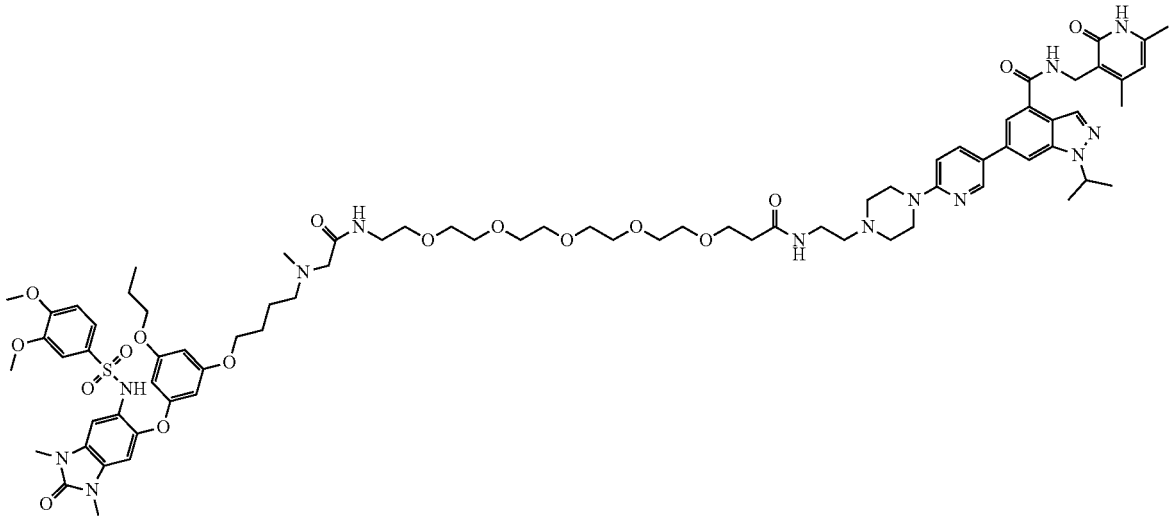
EDCI, HOAt, NMM

DMSO, rt



Intermediate 24

-continued

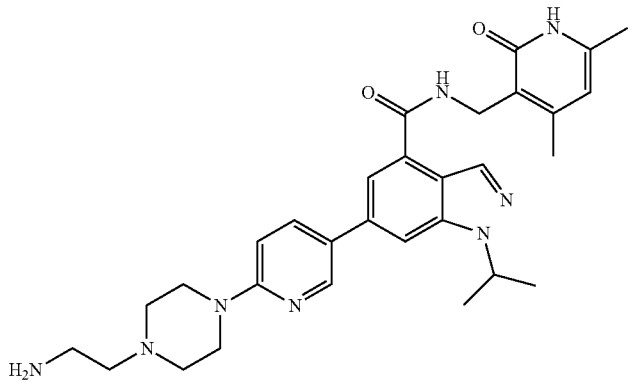


YS36-50

[0253] YS36-50 was synthesized according to the procedures for preparing YS36-48 from intermediate 24 (10 mg, 0.01 mmol), HOAt (4.3 mg, 0.03 mmol), intermediate 7 (10 mg, 0.01 mmol), NMM (14 μL, 0.13 mmol), EDCI (6.1 mg, 0.03 mmol), and DMSO (1.0 mL). YS36-50 was obtained as white solid in TFA salt form (8 mg, 46%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.59 (d, J=2.5 Hz, 1H), 8.36 (s, 1H), 8.13 (dd, J=8.9, 2.6 Hz, 1H), 7.96 (s, 1H), 7.78 (d, J=1.4 Hz, 1H), 7.33 (s, 1H), 7.22-7.07 (m, 3H), 6.78 (d, J=8.5 Hz, 1H), 6.61 (s, 1H), 6.17 (s, 1H), 6.14 (s, 1H), 5.76 (s, 1H), 5.61 (s, 1H), 5.08 (p, J=6.5 Hz, 1H), 4.57 (s, 2H), 4.10-3.87 (m, 8H), 3.84 (t, J=5.8 Hz, 2H), 3.80 (s, 3H), 3.77-3.75 (m, 4H), 3.66 (d, J=5.7 Hz, 2H), 3.62-3.47 (m, 25H), 3.39 (d, J=22.5 Hz, 7H), 3.24 (s, 3H), 2.94 (s, 3H), 2.51 (t, J=5.9 Hz, 2H), 2.43 (s, 3H), 2.26 (s, 3H), 1.93-1.89 (m, 2H), 1.82-1.78 (m, 2H), 1.74 (d, J=7.1 Hz, 2H), 1.57 (d, J=6.6 Hz, 6H), 1.00 (t, J=7.4 Hz, 3H).

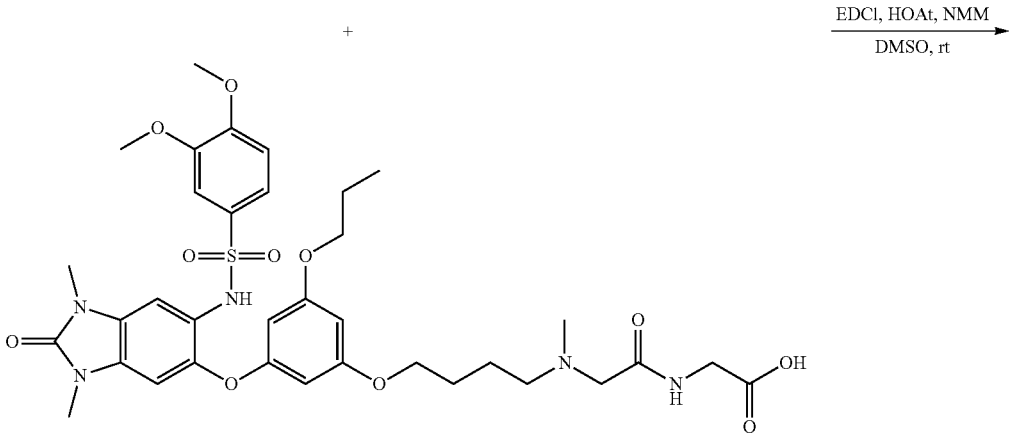
Example 79: Synthesis of YS36-51

[0254]

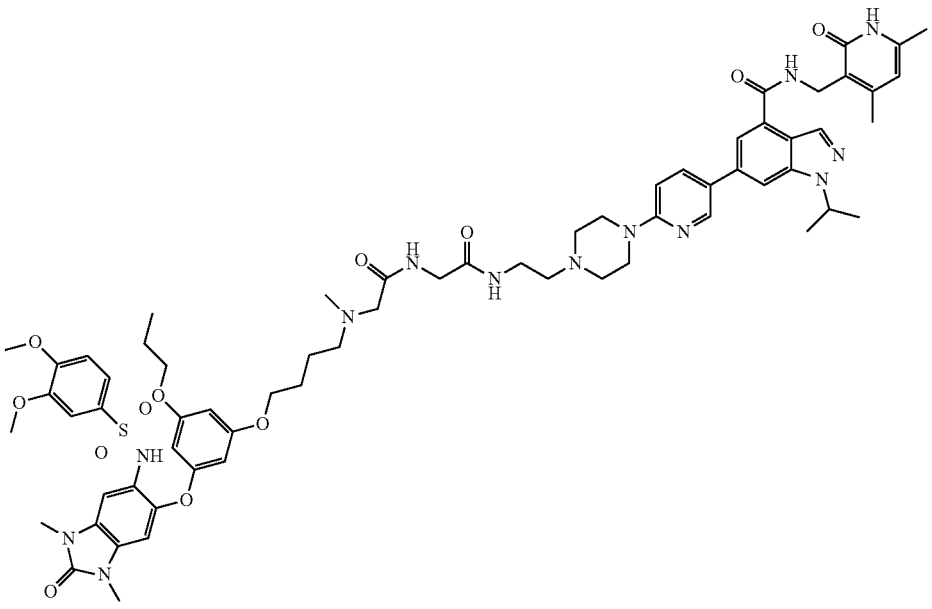


Intermediate 7

-continued



Intermediate 25

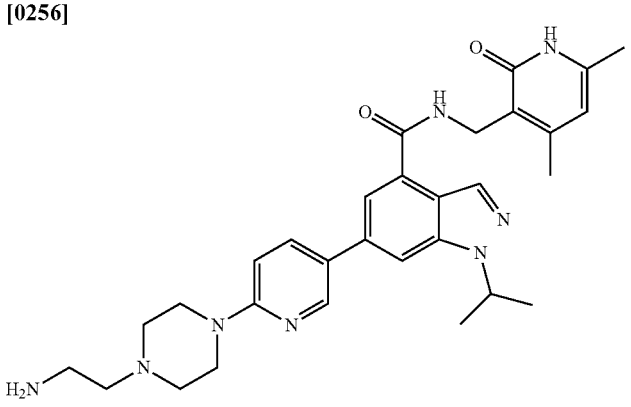


YS36-51

[0255] YS36-51 was synthesized according to the procedures for preparing YS36-48 from intermediate 25 (10 mg, 0.01 mmol), HOAt (4.3 mg, 0.03 mmol), intermediate 7 (10 mg, 0.01 mmol), NMM (14 μL, 0.13 mmol), EDCI (6.1 mg, 0.03 mmol), and DMSO (1.0 mL). YS36-51 was obtained as white solid in TFA salt form (9 mg, 60%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.56 (d, J=2.5 Hz, 1H), 8.36 (s, 1H), 8.12 (dd, J=8.9, 2.5 Hz, 1H), 7.94 (s, 1H), 7.77 (d, J=1.3 Hz, 1H), 7.31 (s, 1H), 7.23-7.00 (m, 3H), 6.77 (d, J=8.5 Hz, 1H), 6.60 (s, 1H), 6.21-6.08 (m, 2H), 5.74 (t, J=2.1 Hz, 1H), 5.63 (t, J=2.2 Hz, 1H), 5.08 (p, J=6.7 Hz, 1H), 4.58 (s, 2H), 4.06 (bs, 8H), 3.98 (s, 2H), 3.86 (t, J=5.9 Hz, 2H), 3.79 (s, 3H), 3.74 (t, J=6.5 Hz, 2H), 3.68 (t, J=6.0 Hz, 2H), 3.60 (s, 3H), 3.53 (bs, 4H), 3.38 (d, J=5.5 Hz, 5H), 3.23 (s, 3H), 2.97 (s, 3H), 2.44 (s, 3H), 2.25 (s, 3H), 1.93 (q, J=8.2, 7.4 Hz, 2H), 1.81 (p, J=6.3 Hz, 2H), 1.71 (q, J=7.0 Hz, 2H), 1.57 (d, J=6.6 Hz, 6H), 0.98 (t, J=7.4 Hz, 3H).

Example 80: Synthesis of YS36-52

[0256]

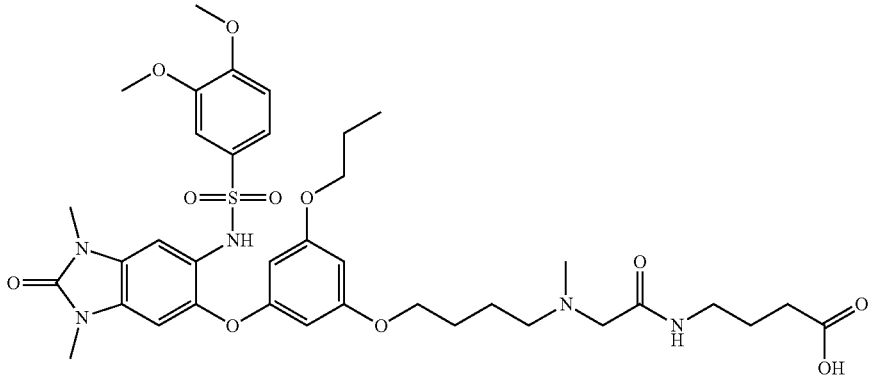


Intermediate 7

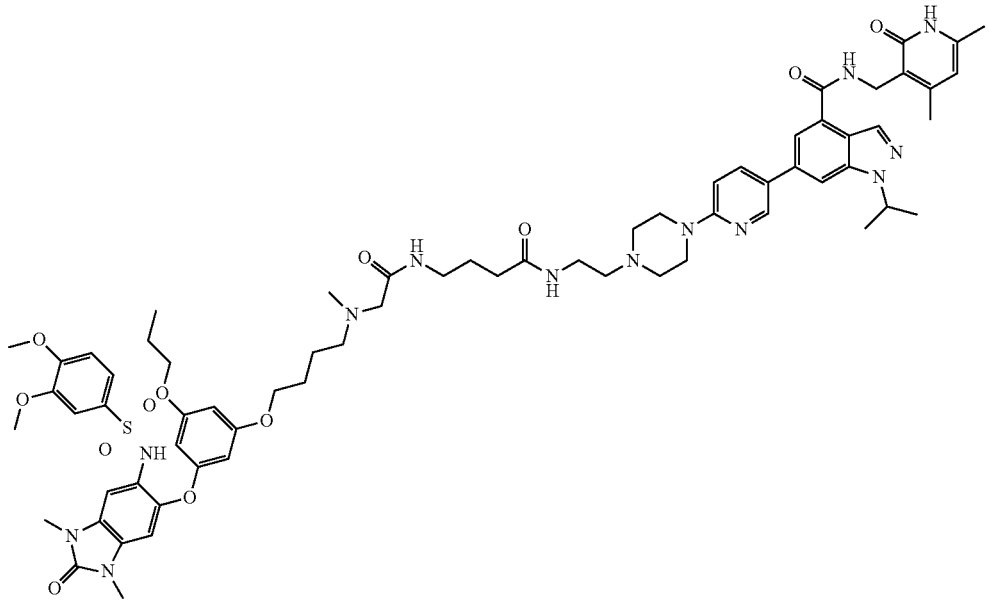
\+

EDCl, HOAt, NMM

DMSO, rt



Intermediate 26



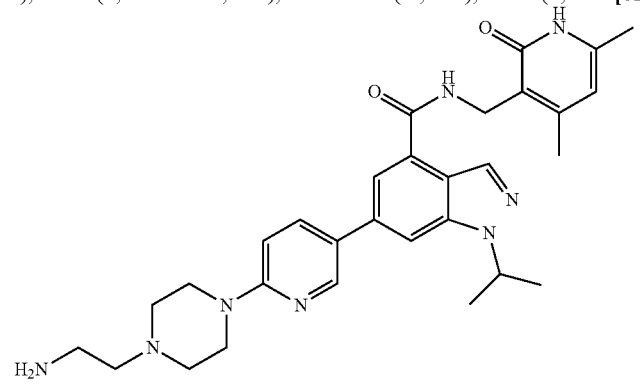
YS36-52

[0257] YS36-52 was synthesized according to the procedures for preparing YS36-48 from intermediate 26 (10 mg, 0.01 mmol), HOAt (4.3 mg, 0.03 mmol), intermediate 7 (10 mg, 0.01 mmol), NMM (14 μL, 0.13 mmol), EDCI (6.1 mg, 0.03 mmol), and DMSO (1.0 mL). YS36-52 was obtained as white solid in TFA salt form (13 mg, 85%). ^{1}H NMR (600

MHz, CD_3OD) δ 8.56 (d, J=2.5 Hz, 1H), 8.37 (s, 1H), 8.18 (dd, J=9.0, 2.6 Hz, 1H), 7.97 (s, 1H), 7.78 (d, J=1.4 Hz, 1H), 7.32 (d, J=2.8 Hz, 1H), 7.26-7.09 (m, 3H), 6.77 (d, J=8.6 Hz, 1H), 6.61 (s, 1H), 6.21 (s, 1H), 6.13 (q, J=2.0 Hz, 1H), 5.75 (t, J=2.1 Hz, 1H), 5.66-5.56 (m, 1H), 5.09 (p, J=6.7 Hz, 1H), 4.58 (s, 2H), 3.96 (s, 8H), 3.85 (t, J=5.8 Hz, 2H), 3.80 (s, 3H), 3.75 (d, J=6.5 Hz, 2H), 3.60-3.62 (m, 9H), 3.38 (d, J=19.0 Hz, 5H), 3.27 (d, J=6.2 Hz, 2H), 3.24 (s, 3H), 2.95 (s, 3H), 2.45 (s, 3H), 2.28 (d, J=16.8 Hz, 5H), 1.94-1.90 (m, 2H), 1.86-1.80 (m, 4H), 1.73 (d, J=7.2 Hz, 2H), 1.57 (d, J=6.6 Hz, 6H), 1.00 (d, J=7.5 Hz, 3H).

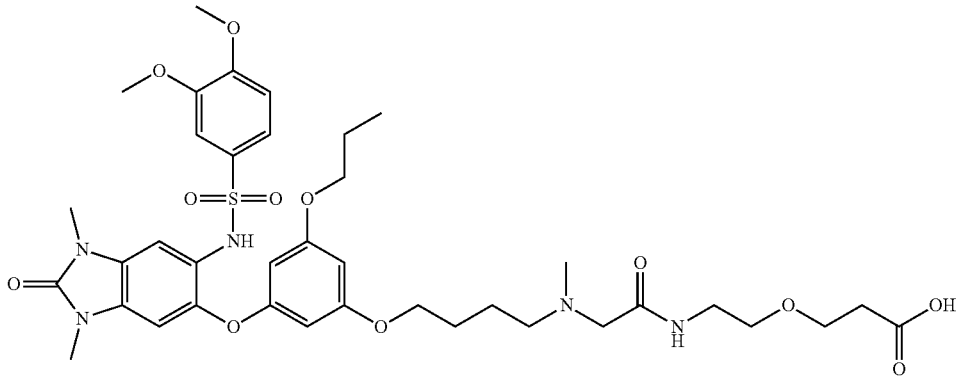
Example 81: Synthesis of YS36-53

[0258]



Intermediate 7

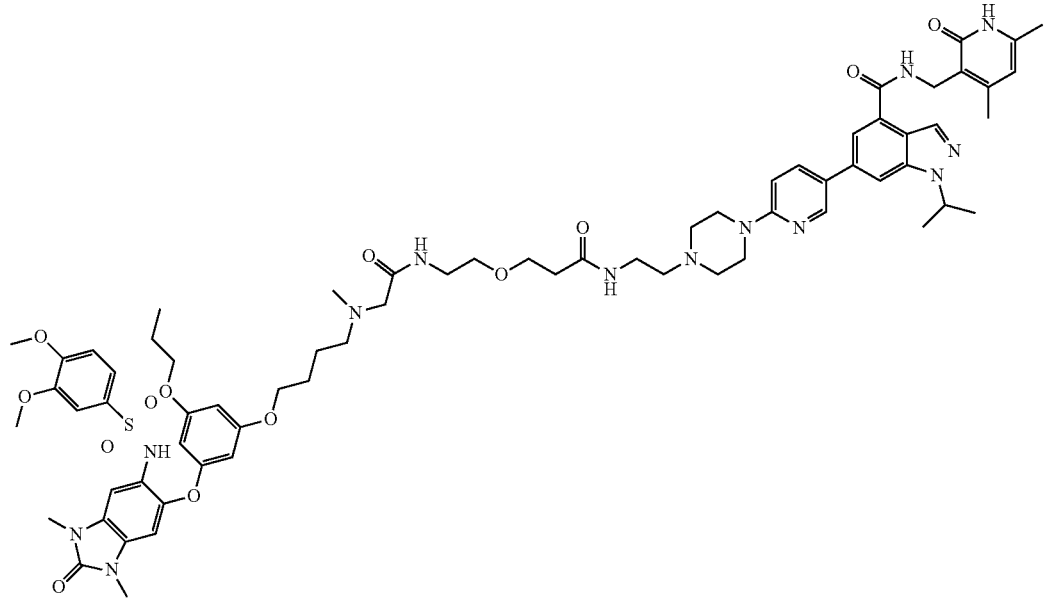
\+



Intermediate 27

EDCl, HOAt, NMM

DMSO, rt

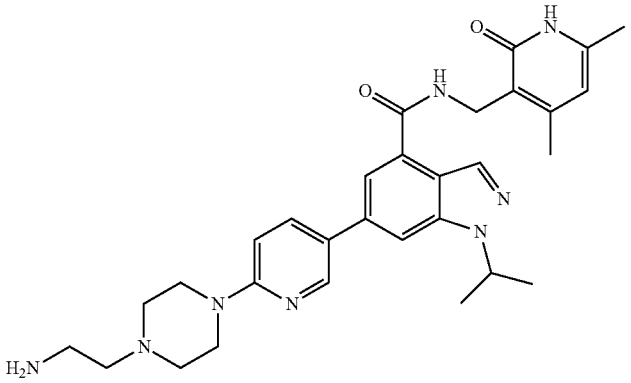


YS36-53

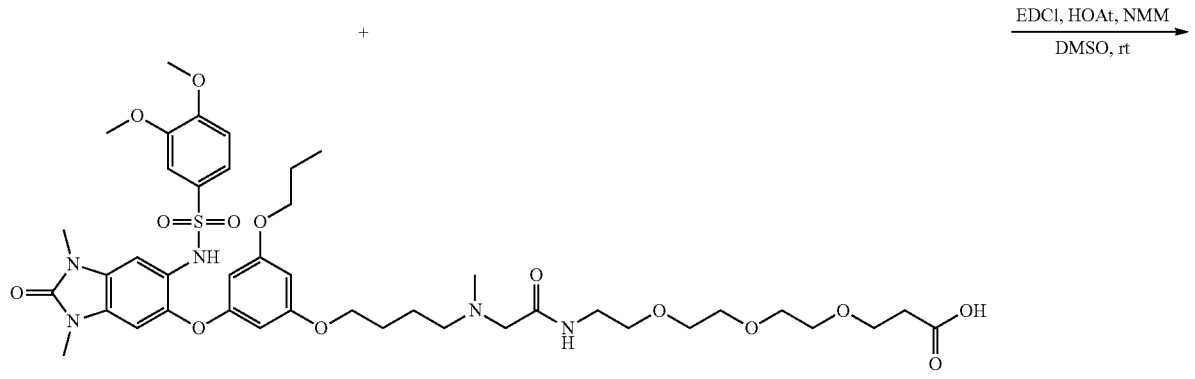
[0259] YS36-53 was synthesized according to the procedures for preparing YS36-48 from intermediate 27 (10 mg, 0.01 mmol), HOAt (4.3 mg, 0.03 mmol), intermediate 7 (10 mg, 0.01 mmol), NMM (14 μL, 0.13 mmol), EDCI (6.1 mg, 0.03 mmol), and DMSO (1.0 mL). YS36-53 was obtained as white solid in TFA salt form (15 mg, 96%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.57 (d, J=2.5 Hz, 1H), 8.37 (s, 1H), 8.19 (dd, J=9.0, 2.5 Hz, 1H), 7.97 (s, 1H), 7.79 (d, J=1.4 Hz, 1H), 7.32 (s, 1H), 7.21-7.09 (m, 3H), 6.78 (d, J=8.5 Hz, 1H), 6.61 (s, 1H), 6.22 (s, 1H), 6.13 (t, J=2.2 Hz, 1H), 5.75 (t, J=2.1 Hz, 1H), 5.62 (t, J=2.1 Hz, 1H), 5.10-5.07 (m, 1H), 4.58 (s, 2H), 3.98 (bs, 8H), 3.85 (t, J=5.9 Hz, 2H), 3.80 (s, 3H), 3.76 (d, J=6.5 Hz, 2H), 3.72 (d, J=6.1 Hz, 2H), 3.64 (d, J=5.9 Hz, 2H), 3.60 (s, 3H), 3.53 (t, J=5.5 Hz, 6H), 3.43 (d, J=5.6 Hz, 2H), 3.40 (s, 3H), 3.37 (d, J=5.8 Hz, 2H), 3.24 (s, 3H), 2.95 (s, 3H), 2.51 (d, J=6.1 Hz, 2H), 2.45 (s, 3H), 2.27 (s, 3H), 1.94-1.90 (m, 2H), 1.83-1.79 (m, 2H), 1.73 (q, J=7.0 Hz, 2H), 1.57 (d, J=6.6 Hz, 6H), 1.00 (t, J=7.4 Hz, 3H).

Example 82: Synthesis of YS36-54

[0260]

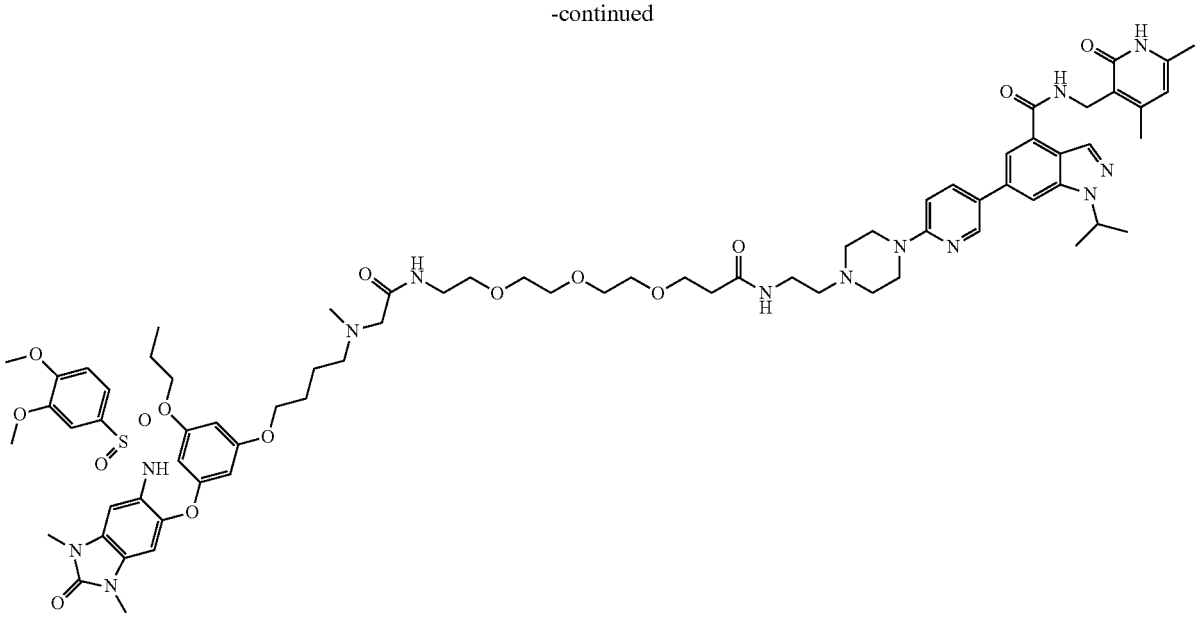


Intermediate 7



Intermediate 28

-continued

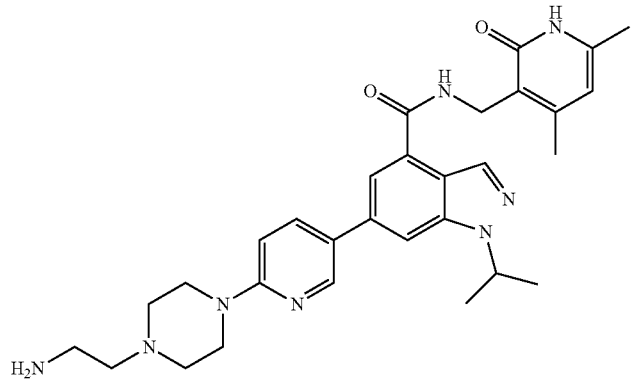


YS36-54

[0261] YS36-54 was synthesized according to the procedures for preparing YS36-48 from intermediate 28 (10 mg, 0.01 mmol), HOAt (4.3 mg, 0.03 mmol), intermediate 7 (10 mg, 0.01 mmol), NMM (14 μL, 0.13 mmol), EDCI (6.1 mg, 0.03 mmol), and DMSO (1.0 mL). YS36-54 was obtained as white solid in TFA salt form (10 mg, 60%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.59 (d, J=2.5 Hz, 1H), 8.36 (s, 1H), 8.10 (dd, J=8.9, 2.6 Hz, 1H), 7.94 (s, 1H), 7.77 (d, J=1.3 Hz, 1H), 7.33 (s, 1H), 7.26-7.07 (m, 3H), 6.78 (d, J=8.5 Hz, 1H), 6.61 (s, 1H), 6.22-6.04 (m, 2H), 5.76 (t, J=2.1 Hz, 1H), 5.61 (t, J=2.1 Hz, 1H), 5.12-5.06 (m, 1H), 4.57 (s, 2H), 3.91 (m, 8H), 3.84 (t, J=5.9 Hz, 2H), 3.79 (s, 3H), 3.77-3.74 (m, 4H), 3.65 (t, J=5.8 Hz, 2H), 3.62-3.47 (m, 17H), 3.40 (d, J=5.4 Hz, 5H), 3.37 (t, J=5.8 Hz, 2H), 3.23 (s, 3H), 2.94 (s, 3H), 2.51 (t, J=6.0 Hz, 2H), 2.43 (s, 3H), 2.25 (s, 3H), 1.91-1.87 (m, 2H), 1.81-1.76 (m, 2H), 1.74-1.71 (m, 2H), 1.57 (d, J=6.6 Hz, 6H), 1.00 (t, J=7.4 Hz, 3H).

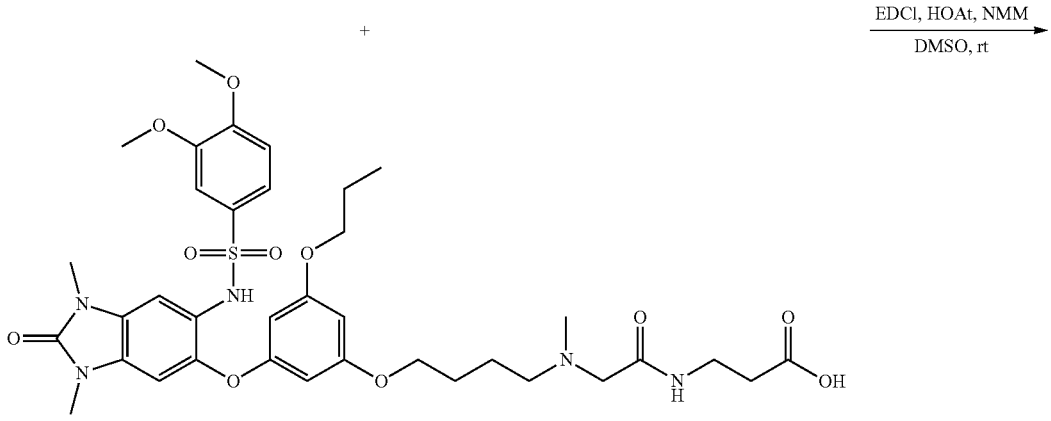
Example 83: Synthesis of YS36-55

[0262]

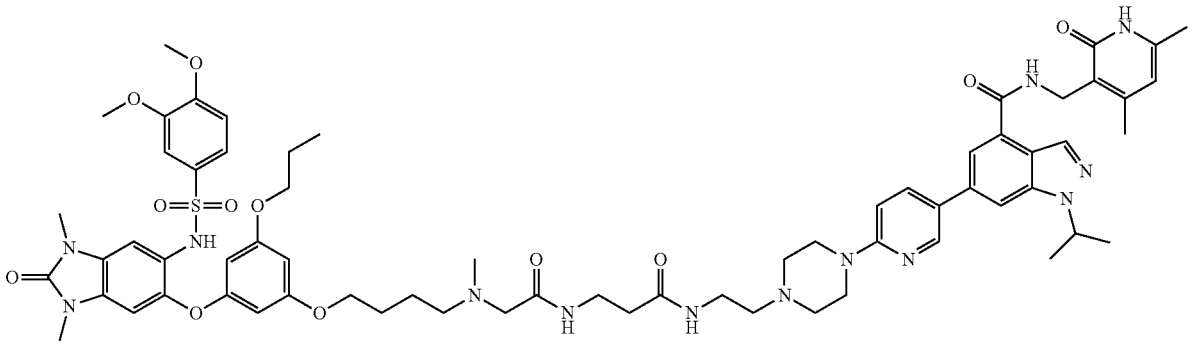


Intermediate 7

-continued



Intermediate 29

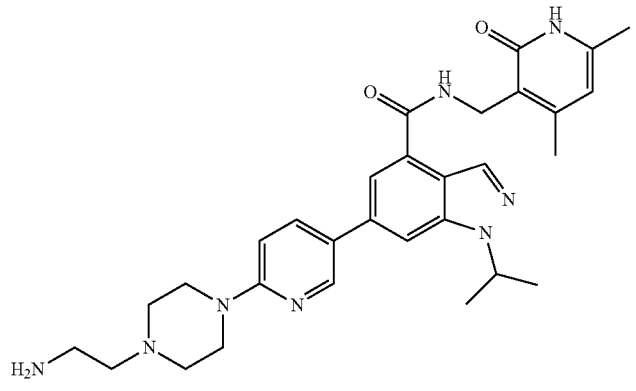


YS36-55

[0263] YS36-55 was synthesized according to the procedures for preparing YS36-48 from intermediate 29 (10 mg, 0.01 mmol), HOAt (4.3 mg, 0.03 mmol), intermediate 7 (10 mg, 0.01 mmol), NMM (14 μL, 0.13 mmol), EDCI (6.1 mg, 0.03 mmol), and DMSO (1.0 mL). YS36-55 was obtained as white solid in TFA salt form (9 mg, 59%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.57 (d, J=2.5 Hz, 1H), 8.37 (s, 1H), 8.13 (dd, J=9.0, 2.5 Hz, 1H), 7.95 (s, 1H), 7.78 (s, 1H), 7.32 (s, 1H), 7.20 (dd, J=8.5, 2.2 Hz, 1H), 7.15 (d, J=2.2 Hz, 1H), 7.10 (d, J=8.9 Hz, 1H), 6.78 (d, J=8.5 Hz, 1H), 6.61 (s, 1H), 6.18 (s, 1H), 6.14 (t, J=2.2 Hz, 1H), 5.75 (t, J=2.1 Hz, 1H), 5.63 (t, J=2.2 Hz, 1H), 5.09 (p, J=6.6 Hz, 1H), 4.58 (s, 2H), 3.99 (bs, 8H), 3.86 (t, J=5.9 Hz, 2H), 3.80 (s, 3H), 3.76 (t, J=6.5 Hz, 2H), 3.61-3.63 (m, 5H), 3.53-3.55 (m, 4H), 3.39 (s, 3H), 3.35 (t, J=5.9 Hz, 2H), 3.26 (s, 2H), 3.24 (s, 3H), 2.95 (s, 3H), 2.49 (t, J=6.7 Hz, 2H), 2.44 (s, 3H), 2.26 (s, 3H), 1.91 (dd, J=16.1, 8.0 Hz, 2H), 1.82 (q, J=7.3, 6.7 Hz, 2H), 1.72 (p, J=7.1 Hz, 2H), 1.57 (d, J=6.7 Hz, 6H), 1.00 (t, J=7.4 Hz, 3H).

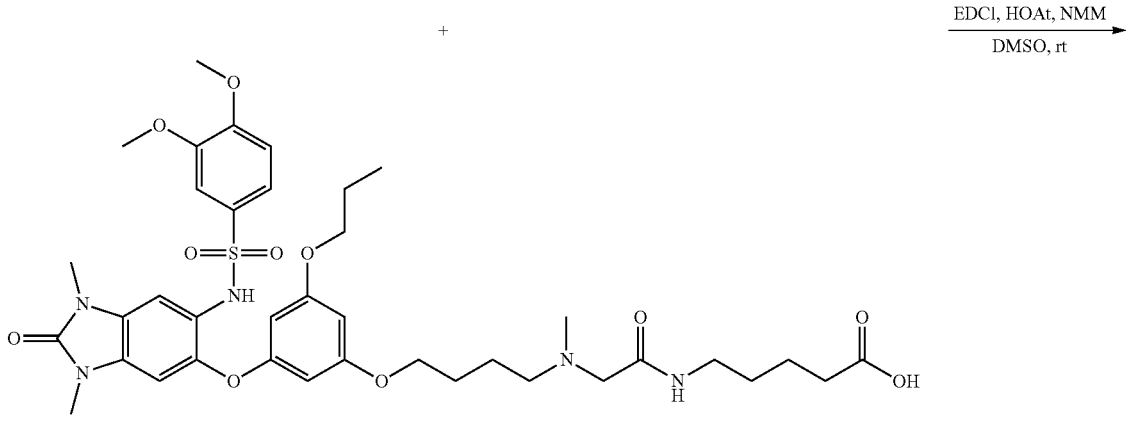
Example 84: Synthesis of YS36-56

[0264]

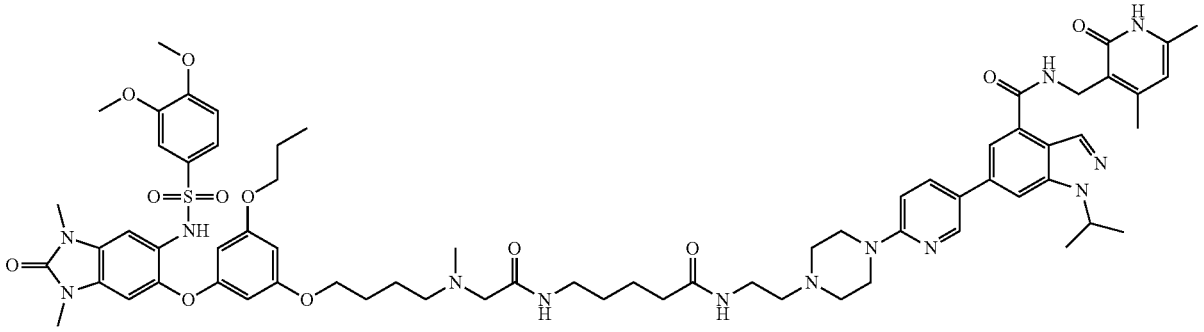


Intermediate 7

-continued



Intermediate 30

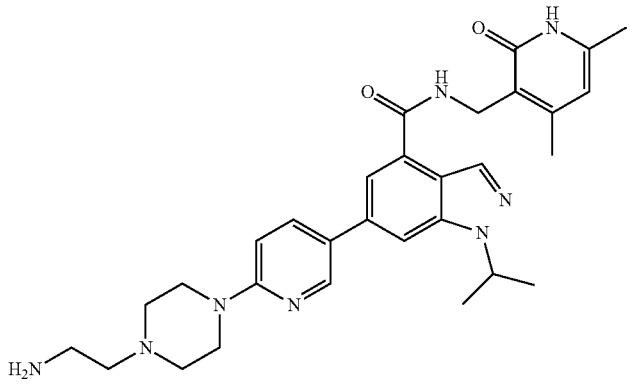


YS36-56

[0265] YS36-56 was synthesized according to the procedures for preparing YS36-48 from intermediate 30 (10 mg, 0.01 mmol), HOAt (4.3 mg, 0.03 mmol), intermediate 7 (10 mg, 0.01 mmol), NMM (14 μL, 0.13 mmol), EDCI (6.1 mg, 0.03 mmol), and DMSO (1.0 mL). YS36-56 was obtained as white solid in TFA salt form (9 mg, 58%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.58 (d, J=2.6 Hz, 1H), 8.36 (s, 1H), 8.14 (dd, J=8.9, 2.6 Hz, 1H), 7.96 (s, 1H), 7.78 (d,J=1.3 Hz, 1H), 7.33 (s, 1H), 7.20 (dd, J=8.4, 2.2 Hz, 1H), 7.15 (d, J=2.3 Hz, 1H), 7.12 (d, J=8.9 Hz, 1H), 6.78-6.77 (m, 1H), 6.61 (s, 1H), 6.18 (s, 1H), 6.14 (t, J=2.2 Hz, 1H), 5.77-5.75 (m, 1H), 5.64-5.60 (m, 1H), 5.09 (p, J=6.6 Hz, 1H), 4.58 (s, 2H), 3.91 (bs, 8H), 3.86 (d, J=5.8 Hz, 2H), 3.80 (s, 3H), 3.76 (t, J=6.5 Hz, 2H), 3.61-3.63 (m, 5H), 3.53 (bs, 4H), 3.40 (s, 3H), 3.35 (d, J=6.0 Hz, 2H), 3.26 (s, 2H), 3.24 (s, 3H), 2.95-2.92 (m, 3H), 2.44 (s, 3H), 2.26 (d, J=4.4 Hz, 5H), 1.91 (q, J=8.0 Hz, 2H), 1.82 (d, J=7.0 Hz, 2H), 1.73 (h, J=7.1 Hz, 2H), 1.63 (p, J=7.3 Hz, 2H), 1.57 (dd, J=7.5, 4.8 Hz, 8H), 1.02-0.97 (m, 3H).

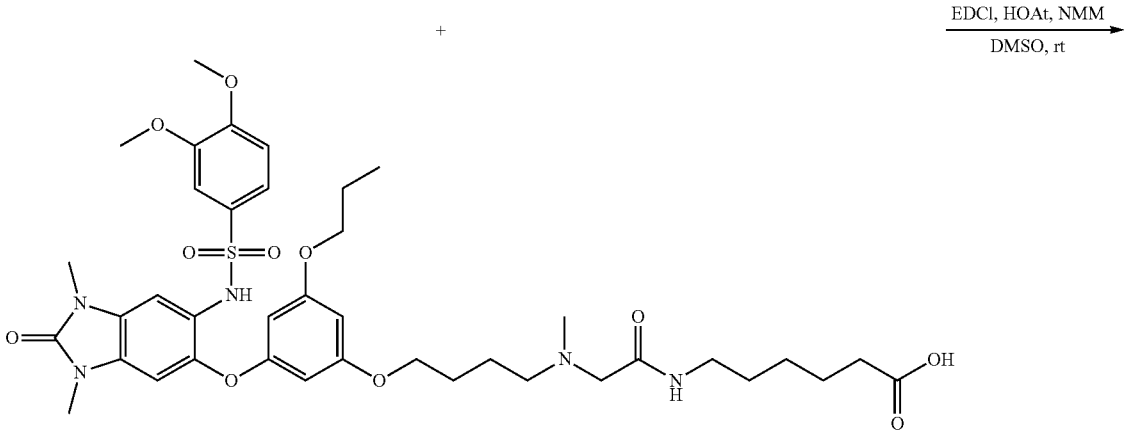
Example 85: Synthesis of YS36-57

[0266]

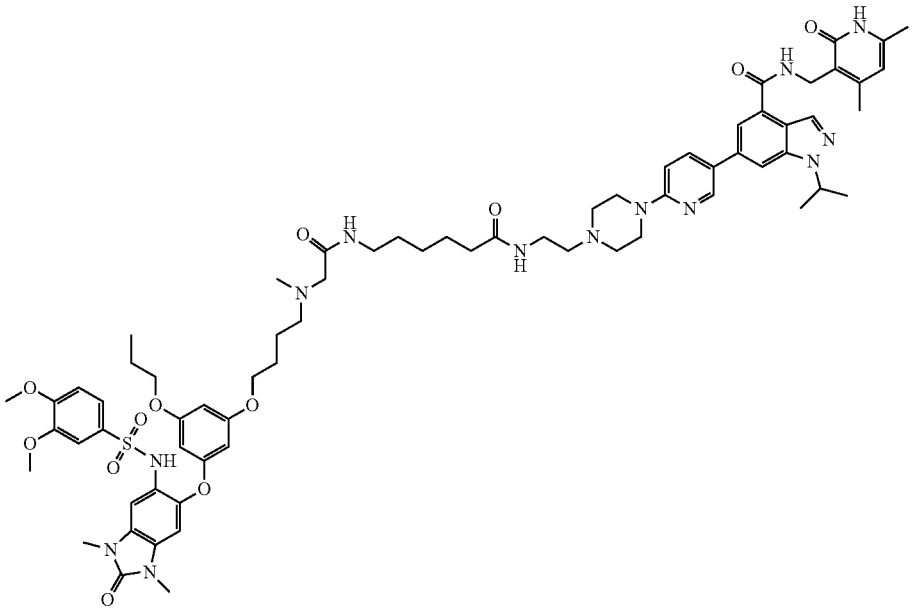


Intermediate 7

-continued



Intermediate 31

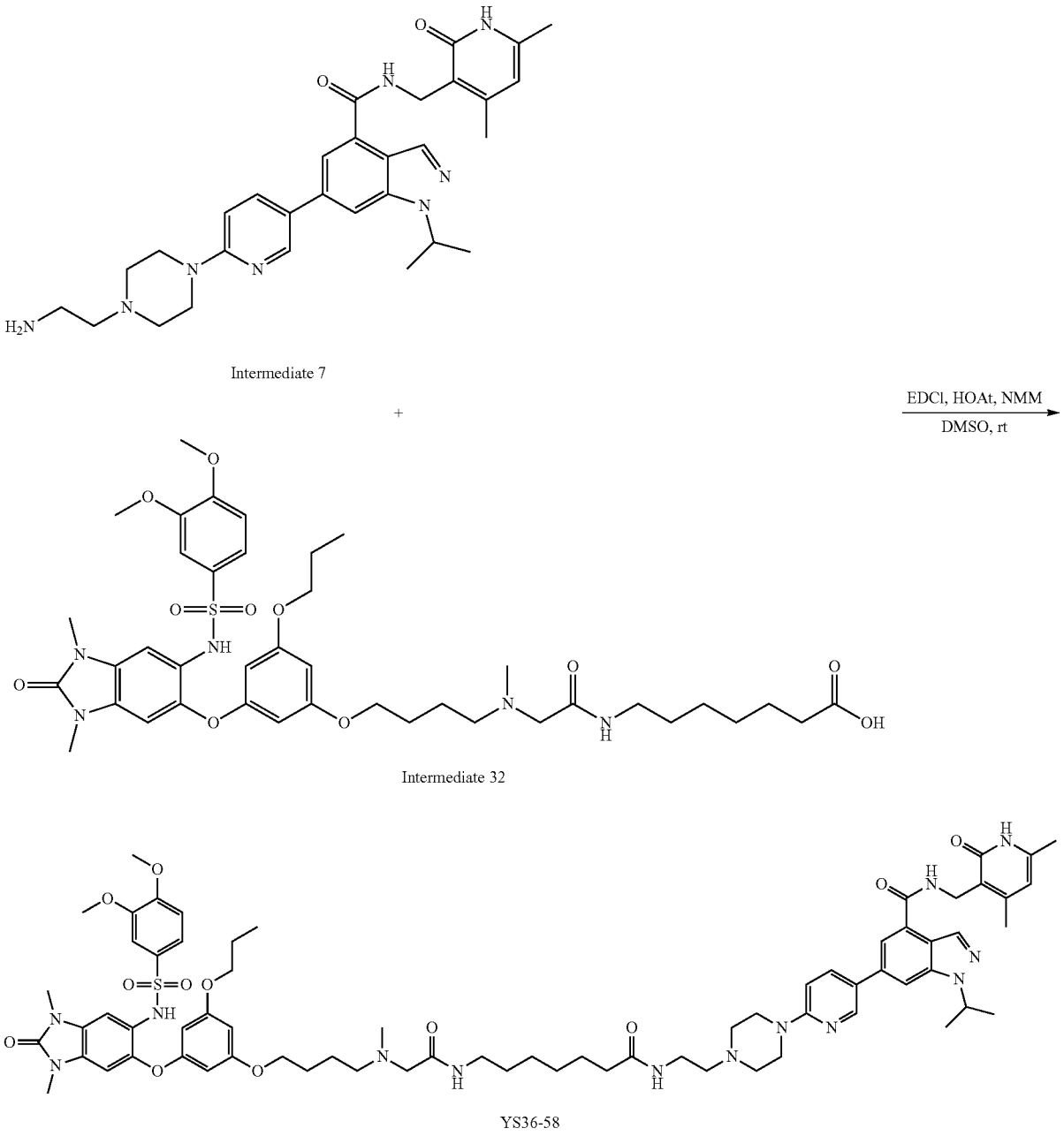


YS36-57

[0267] YS36-57 was synthesized according to the procedures for preparing YS36-48 from intermediate 31 (10 mg, 0.01 mmol), HOAt (4.3 mg, 0.03 mmol), intermediate 7 (10 mg, 0.01 mmol), NMM (14 μL, 0.13 mmol), EDCI (6.1 mg, 0.03 mmol), and DMSO (1.0 mL). YS36-57 was obtained as white solid in TFA salt form (9 mg, 58%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.58 (d, J=2.5 Hz, 1H), 8.36 (s, 1H), 8.15 (dd, J=9.0, 2.5 Hz, 1H), 7.96 (s, 1H), 7.78 (d, J=1.2 Hz, 1H), 7.33 (s, 1H), 7.22-7.09 (m, 3H), 6.78 (d, J=8.5 Hz, 1H), 6.61 (s, 1H), 6.18 (s, 1H), 6.14 (t, J=2.2 Hz, 1H), 5.76 (t, J=2.1 Hz, 1H), 5.60 (t, J=2.1 Hz, 1H), 5.09 (p, J=6.6 Hz, 1H), 4.58 (s, 2H), 3.91 (bs, 8H), 3.84 (d, J=5.9 Hz, 2H), 3.80 (s, 3H), 3.77 (t, J=6.5 Hz, 2H), 3.61-3.63 (m, 5H), 3.53 (bs, 4H), 3.41 (s, 3H), 3.35 (t, J=5.9 Hz, 2H), 3.24 (s, 5H), 2.94 (s, 3H), 2.44 (s, 3H), 2.26 (s, 3H), 2.23 (t, J=7.7 Hz, 2H), 1.91 (q, J=8.3 Hz, 2H), 1.81 (q, J=7.2, 6.6 Hz, 2H), 1.74 (h, J=7.1 Hz, 2H), 1.61 (t, J=7.7 Hz, 2H), 1.57 (d, J=6.6 Hz, 6H), 1.52 (d, J=7.7 Hz, 2H), 1.35 (q, J=8.1 Hz, 2H), 1.00 (t, J=7.4 Hz, 3H).

Example 86: Synthesis of YS36-58

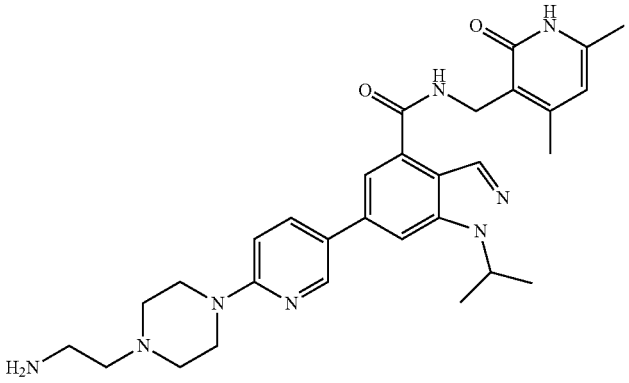
[0268]



[0269] YS36-58 was synthesized according to the procedures for preparing YS36-48 from intermediate 32 (10 mg, 0.01 mmol), HOAt (4.3 mg, 0.03 mmol), intermediate 7 (10 mg, 0.01 mmol), NMM (14 μL, 0.13 mmol), EDCI (6.1 mg, 0.03 mmol), and DMSO (1.0 mL). YS36-58 was obtained as white solid in TFA salt form (11 mg, 70%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.61 (d, J=2.5 Hz, 1H), 8.35 (s, 1H), 8.11-8.08 (m, 1H), 7.94 (s, 1H), 7.77 (s, 1H), 7.34 (s, 1H), 7.21 (dd, J=8.5, 2.1 Hz, 1H), 7.16 (d, J=2.2 Hz, 1H), 7.07 (s, 1H), 6.79 (d, J=8.5 Hz, 1H), 6.61 (s, 1H), 6.14 (s, 2H), 5.79 (t, J=2.1 Hz, 1H), 5.59 (t, J=2.2 Hz, 1H), 5.09-5.07 (m, 1H), 4.57 (s, 2H), 3.98 (bs, 8H), 3.85 (t, J=5.9 Hz, 2H), 3.80 (s, 3H), 3.77 (t, J=6.5 Hz, 2H), 3.61-3.63 (m, 5H), 3.53 (bs, 4H), 3.41 (s, 3H), 3.34 (s, 2H), 3.19 (s, 5H), 2.93 (s, 3H), 2.44 (s, 2H), 2.25-2.21 (m, 5H), 1.94-1.90 (m, 3H), 1.81 (t, J=7.2 Hz, 2H), 1.74 (d, J=7.1 Hz, 2H), 1.57 (d, J=6.6 Hz, 8H), 1.51 (d, J=7.0 Hz, 2H), 1.34-1.31 (m, 4H), 1.01 (t, J=7.4 Hz, 3H).

Example 87: Synthesis of YS36-59

[0270]

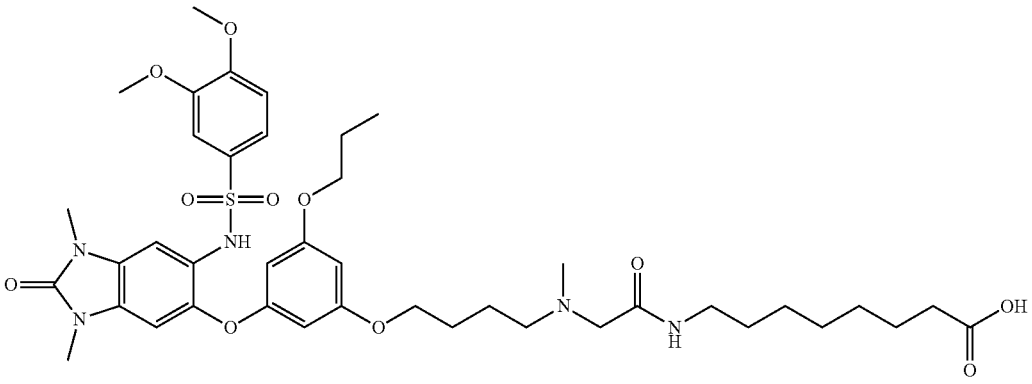


Intermediate 7

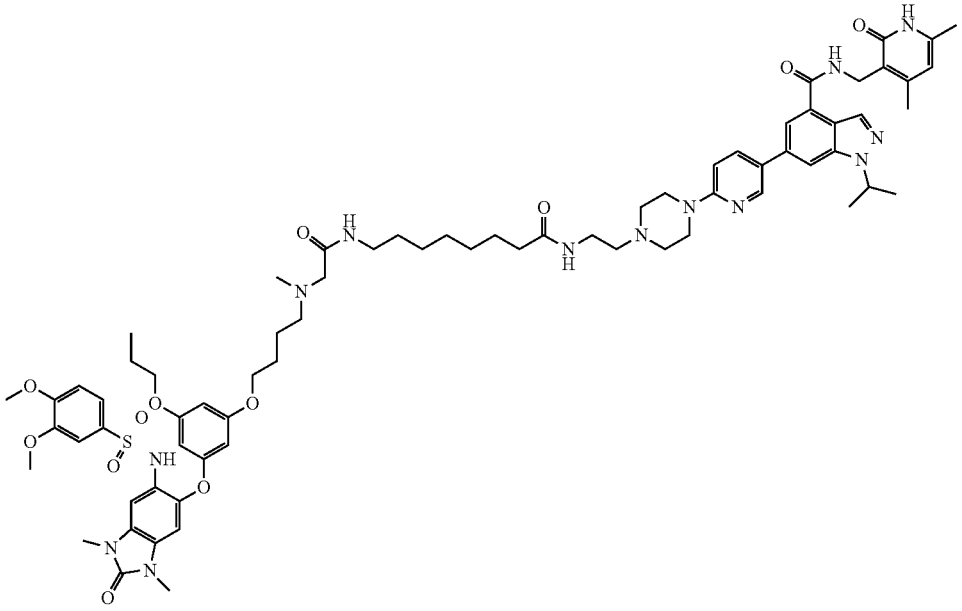
+

EDCl, HOAt, NMM

DMSO, rt



Intermediate 33

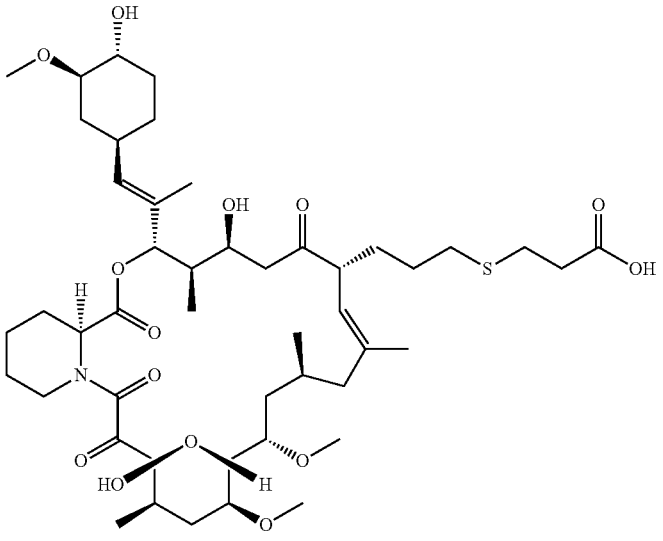


YS36-59

[0271] YS36-59 was synthesized according to the procedures for preparing YS36-48 from intermediate 33 (10 mg, 0.01 mmol), HOAt (4.3 mg, 0.03 mmol), intermediate 7 (10 mg, 0.01 mmol), NMM (14 μL, 0.13 mmol), EDCI (6.1 mg, 0.03 mmol), and DMSO (1.0 mL). YS36-59 was obtained as white solid in TFA salt form (12 mg, 76%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.59 (d, J=2.5 Hz, 1H), 8.36 (s, 1H), 8.13 (dd, J=8.9, 2.6 Hz, 1H), 7.95 (s, 1H), 7.78 (d, J=1.3 Hz, 1H), 7.34 (s, 1H), 7.23-7.08 (m, 3H), 6.78 (d, J=8.5 Hz, 1H), 6.61 (s, 1H), 6.19-6.13 (m, 2H), 5.77 (t, J=2.1 Hz, 1H), 5.59 (t, J=2.2 Hz, 1H), 5.11-5.06 (m, 1H), 4.58 (s, 2H), 3.90 (bs, 8H), 3.85 (t, J=5.9 Hz, 2H), 3.80 (s, 3H), 3.77 (t, J=6.5 Hz, 2H), 3.62-3.63 (m, 5H), 3.53 (m, 4H), 3.41 (s, 3H), 3.35 (t, J=5.9 Hz, 2H), 3.24 (s, 5H), 2.93 (s, 3H), 2.44 (s, 3H), 2.27-2.20 (m, 5H), 1.92 (p, J=7.7 Hz, 2H), 1.81 (p, J=6.2 Hz, 2H), 1.73 (p, J=7.0 Hz, 2H), 1.57 (d, J=6.6 Hz, 8H), 1.49 (d, J=7.0 Hz, 2H), 1.34-1.29 (m, 6H), 1.01 (t, J=7.4 Hz, 3H).

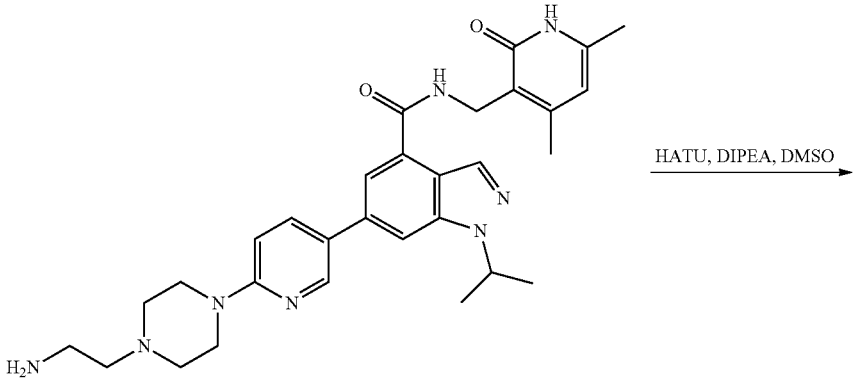
Example 88: Synthesis of XY028-086

[0272]



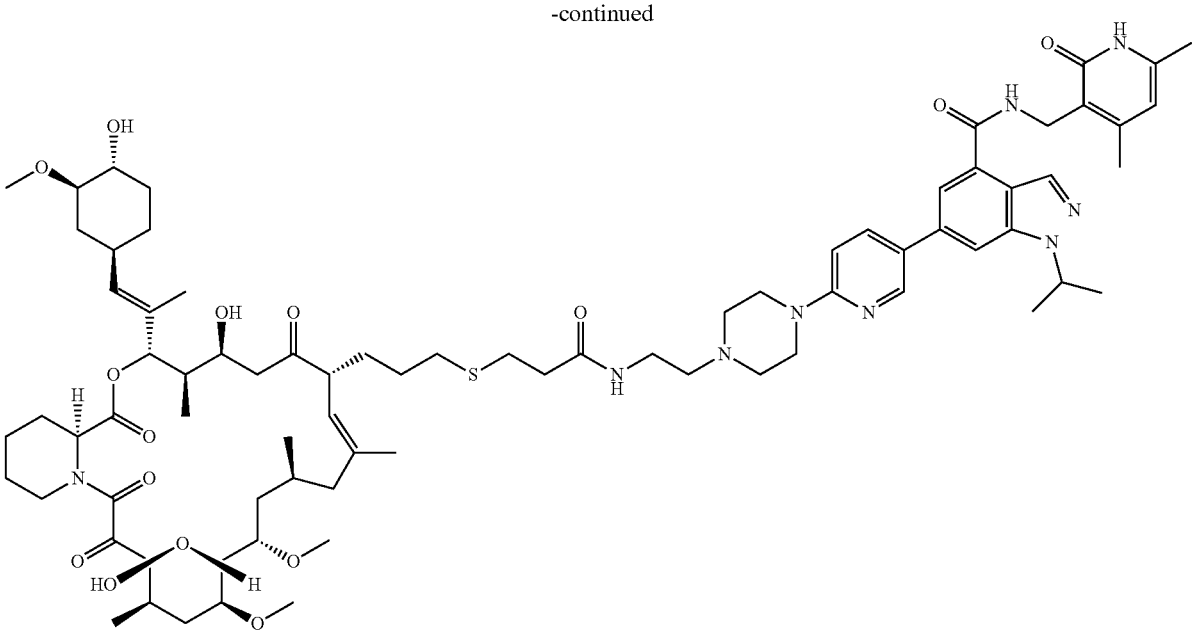
Intermediate 34

+



Intermediate 7

-continued

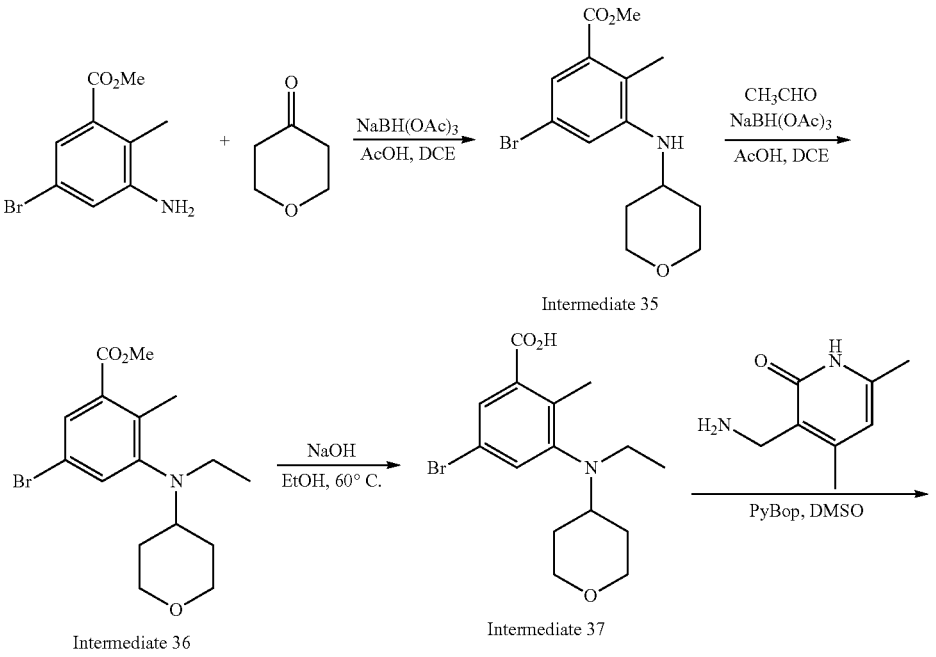


XY028-086

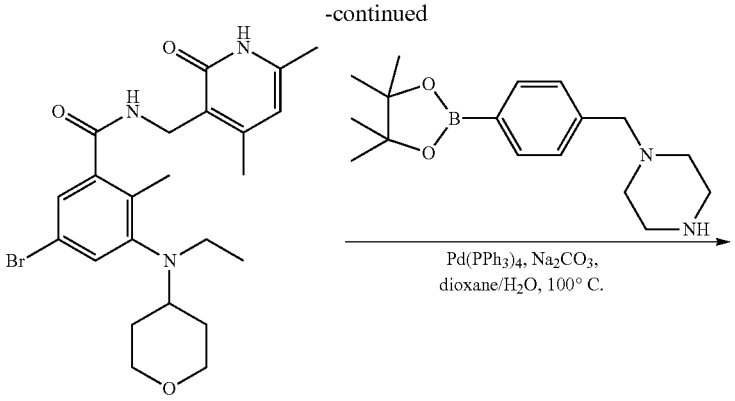
[0273] Intermediate 34 (20 mg, 0.02 mmol), intermediate 7 (15 mg, 0.02 mmol) and DIPEA (16 μL, 0.09 mmol) were dissolved in DMSO (1.0 mL). To the solution were added HATU (17 mg, 0.04 mmol) at room temperature. After being stirred overnight at room temperature, the mixture was purified by preparative HPLC (10%-100% methanol/0.1% TFA in H_2O) to afford XY028-086 as white solid in TFA salt form. ^1H NMR (600 MHz, CD_3OD) δ 8.58 (s, 1H), 8.38 (s, 1H), 8.22-8.13 (m, 1H), 7.98 (s, 1H), 7.80 (s, 1H), 7.18 (t, J=10.2 Hz, 1H), 6.21 (s, 1H), 5.28-5.20 (m, 1H), 5.18 (d, J=8.1 Hz, 1H), 5.14-5.02 (m, 2H), 4.59 (s, 2H), 4.32 (d, J=12.8 Hz, 1H), 4.21-3.83 (m, 4H), 3.80-3.46 (m, 10H), 3.45-3.33 (m, 10H), 3.07-2.66 (m, 5H), 2.62-2.50 (m, 4H), 2.45 (s, 3H), 2.37-2.24 (m, 5H), 2.21-0.70 (m, 51H).

Example 89: Synthesis of CZ40-72

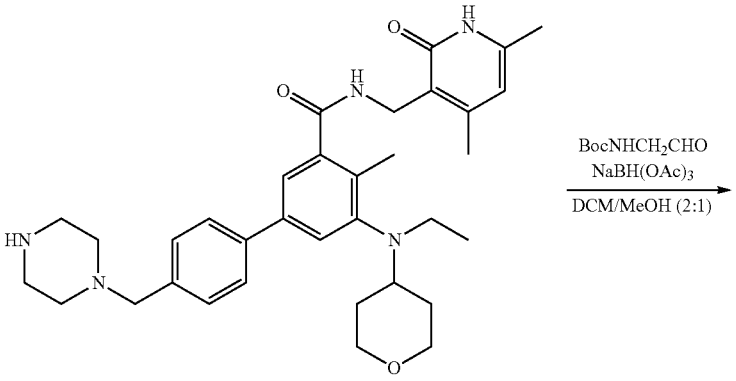
[0274]



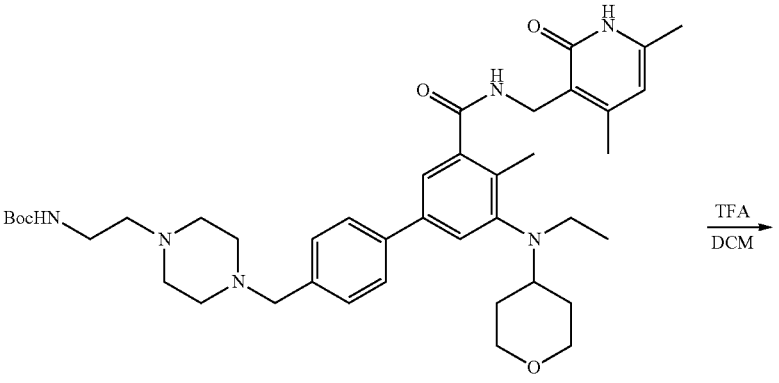
-continued



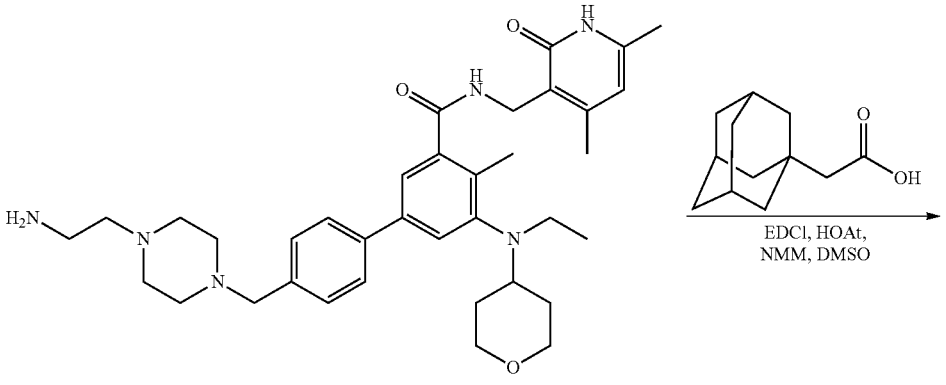
Intermediate 38



Intermediate 39

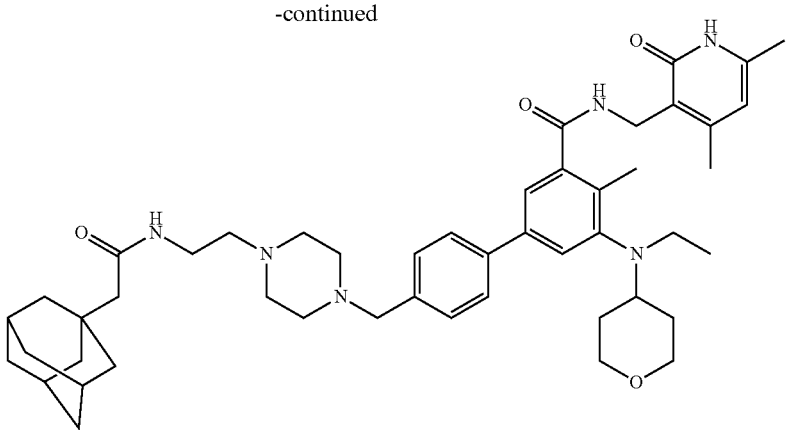


Intermediate 40



Intermediate 41

-continued



CZ40-72

[0275] Intermediate 39 was synthesized from methyl 3-amino-5-bromo-2-methylbenzoate according to the Patent WO2012142504.

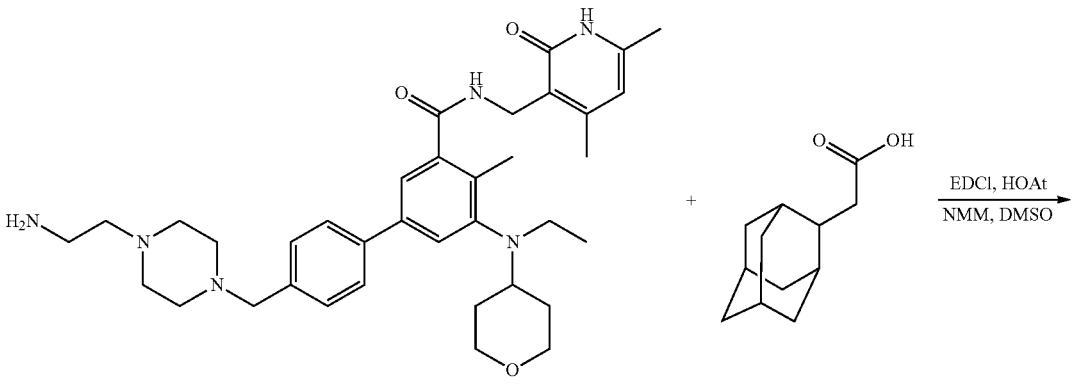
[0276] Intermediate 39 (228 mg, 0.40 mmol) and N-Boc-2-aminoacetaldehyde (96 mg, 0.60 mmol) were dissolved in DCM (4.0 mL), and methanol (2.0 mL). To the solution was added sodium triacetoxyborohydride (254 mg, 1.2 mmol) at 0° C. After being stirred overnight at room temperature, the mixture was quenched with water and extracted with DCM (10 mL for 3 times), dried and purified by ISCO™ (DCM/MeOH=20:1 to 10:1) to afford intermediate 40 (85 mg, 30%) as white solid.

[0277] Intermediate 40 (85 mg, 0.12 mmol) was dissolved in DCM (1.0 mL) and treated with trifluoroacetic acid (1.0 mL) at room temperature for 2 h. The mixture was concentrated and dried to give the crude intermediate 41 in TFA salt form. This product was used directly in the next step without further purification.

[0278] Intermediate 41 (14 mg, 0.02 mmol) was dissolved in DMSO (1.0 mL). 1-Adamantaneacetic acid (4 mg, 0.02 mmol), HOAt (4 mg, 0.03 mmol), EDCI (6 mg, 0.03 mmol), and NMM (11 μL, 0.09 mmol) were added to the solution subsequently at room temperature. After being stirred overnight, the reaction mixture was purified by prepared HPLC to afford CZ40-72 (11 mg, 75%) as white solid in TFA salt form. ^{1}H NMR (600 MHz, CD_3OD) δ 7.86 (s, 1H), 7.77 (d, J=7.9 Hz, 2H), 7.70 (s, 1H), 7.56 (d, J=7.9 Hz, 2H), 6.14 (s, 1H), 4.50 (s, 2H), 4.12 (s, 2H), 3.99 (d, J=11.5 Hz, 2H), 3.70 (s, 2H), 3.46 (t, J=6.2 Hz, 2H), 3.38 (t, J=11.8 Hz, 2H), 3.24-3.14 (m, 9H), 3.01 (t, J=6.1 Hz, 2H), 2.43 (s, 3H), 2.40 (s, 3H), 2.25 (s, 3H), 1.94 (s, 2H), 1.93 (brs, 4H), 1.74-1.72 (m, 3H), 1.67-1.60 (m, 12H), 1.03 (t, J=7.0 Hz, 3H). ESI m/z=791.51 $[M+H]^+$.

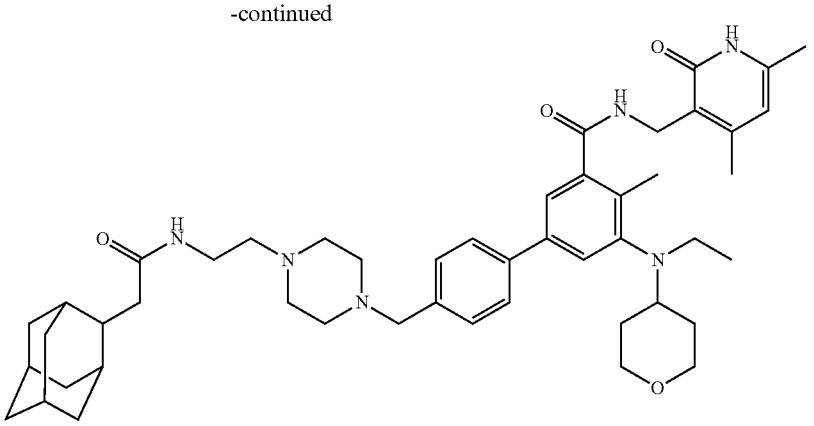
Example 90: Synthesis of CZ40-73

[0279]



Intermediate 41

-continued

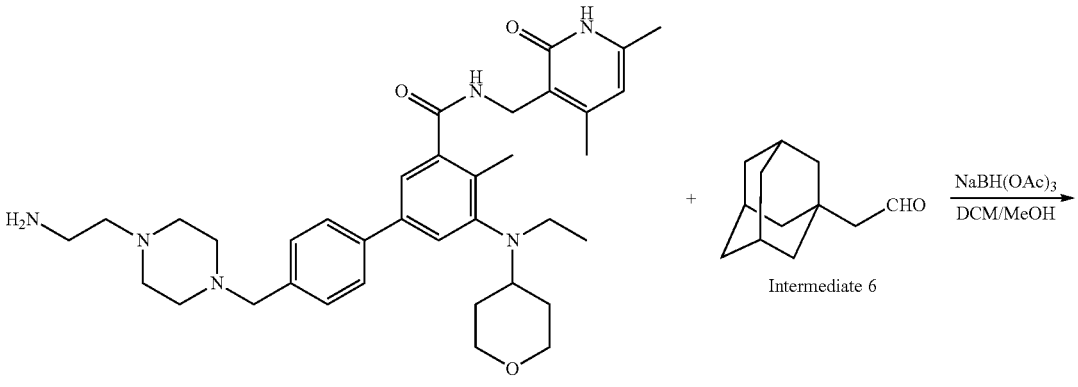


CZ40-73

[0280] Intermediate 41 (14 mg, 0.02 mmol) was dissolved in DMSO (1.0 mL). 2-Adamantaneacetic acid (4 mg, 0.02 mmol), HOAt (4 mg, 0.03 mmol), EDCI (6 mg, 0.03 mmol), and NMM (11 μL, 0.09 mmol) were added to the solution subsequently at room temperature. After being stirred overnight, the reaction mixture was purified by prepared HPLC to afford CZ40-73 (10 mg, 68%) as white solid in TFA salt form. ^{1}H NMR (600 MHz, CD_3OD) δ 7.86 (s, 1H), 7.77 (d, J=7.9 Hz, 2H), 7.70 (s, 1H), 7.57 (d, J=8.2 Hz, 2H), 6.14 (s, 1H), 4.50 (s, 2H), 4.13 (s, 2H), 3.99 (d, J=11.6 Hz, 2H), 3.69 (s, 2H), 3.46 (t, J=6.1 Hz, 2H), 3.38 (t, J=11.8 Hz, 2H), 3.23-3.15 (m, 9H), 3.01 (t, J=6.1 Hz, 2H), 2.43 (s, 3H), 2.39 (s, 3H), 2.37 (d, J=7.8 Hz, 2H), 2.25 (s, 3H), 2.20 (t, J=8.2 Hz, 1H), 1.93 (d, J=13.1 Hz, 2H), 1.86 (d, J=12.6 Hz, 4H), 1.81-1.73 (m, 8H), 1.66 (s, 2H), 1.56 (d, J=12.8 Hz, 2H), 1.02 (t, J=7.0 Hz, 3H). ESI m/z=791.51 $[M+H]^+$.

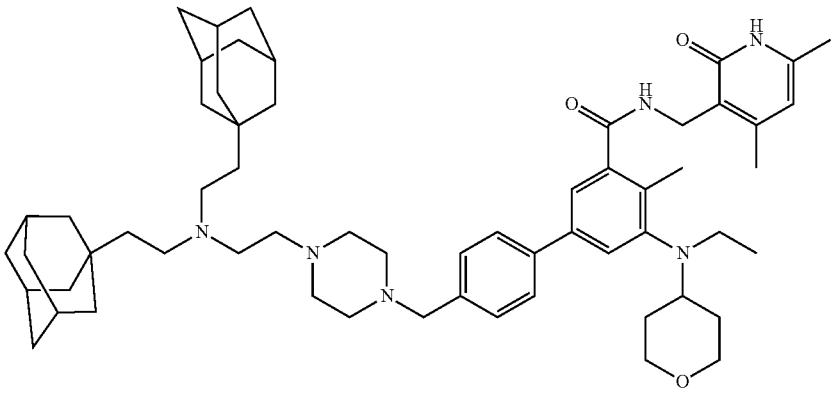
Example 91: Synthesis of CZ40-75

[0281]



Intermediate 41

Intermediate 6

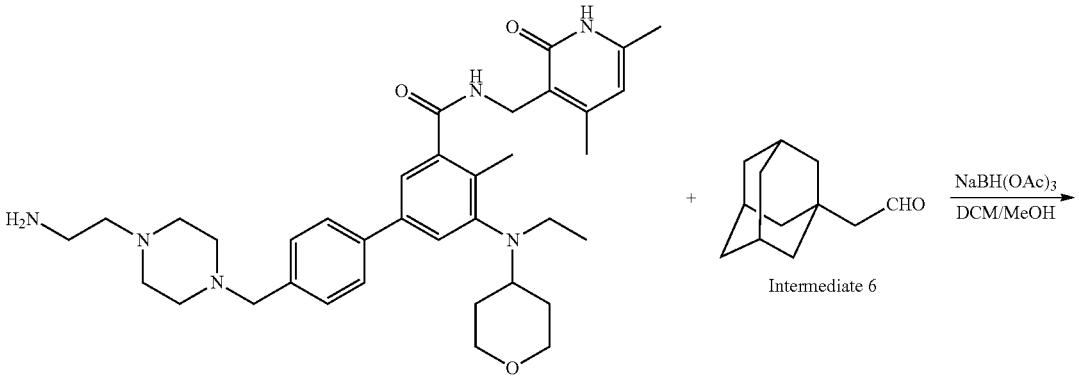


CZ40-75

[0282] Intermediate 41 (14 mg, 0.02 mmol) and intermediate 6 (12 mg, 0.06 mmol) were dissolved in DCM (4.0 mL), and methanol (2.0 mL). To the solution was added sodium triacetoxyborohydride (13 mg, 0.06 mmol) at 0° C. After being stirred overnight at room temperature, the mixture was quenched with water and extracted with DCM (10 mL for 3 times), dried and purified by prepared HPLC to afford CZ40-75 (12 mg, 77%) as white solid in TFA salt form. ^{1}H NMR (600 MHz, CD_3OD) δ 7.57 (d, J=8.4 Hz, 2H), 7.46 (d, J=1.9 Hz, 1H), 7.40 (d, J=8.4 Hz, 2H), 7.32 (d, J=1.9 Hz, 1H), 6.13 (s, 1H), 4.49 (s, 2H), 3.95-3.89 (m, 2H), 3.74 (s, 2H), 3.37 (dd, J=11.7, 2.1 Hz, 2H), 3.27-3.09 (m, 9H), 2.72-2.66 (m, 10H), 2.39 (s, 3H), 2.32 (s, 3H), 2.25 (s 3H), 1.99-1.94 (m, 4H), 1.75 (d, J=12.4 Hz, 6H), 1.70-1.58 (m, 10H), 1.56 (d, J=2.8 Hz, 14H), 1.47-1.41 (m, 4H), 0.90 (t, J=7.0 Hz, 3H).

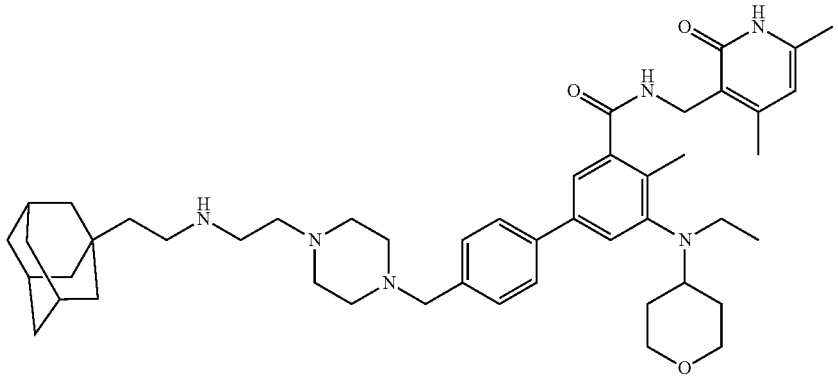
Example 92: Synthesis of CZ40-149

[0283]



Intermediate 41

Intermediate 6

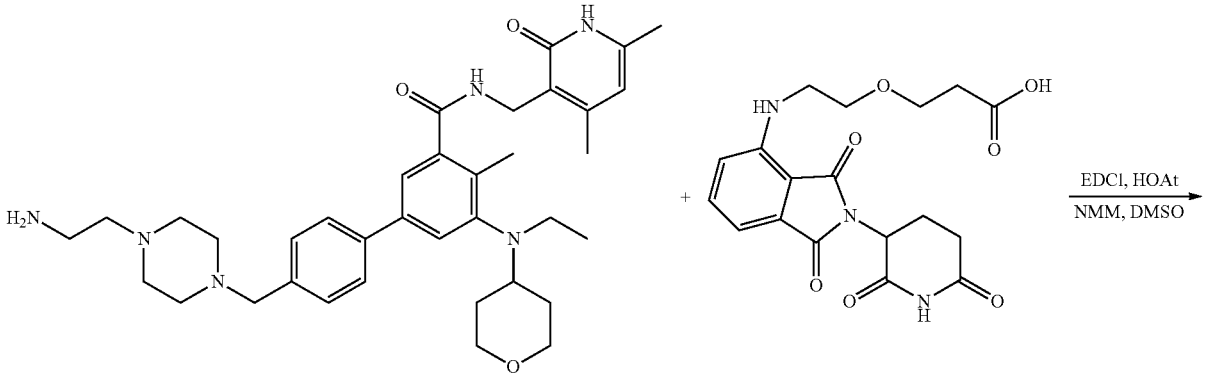


CZ40-149

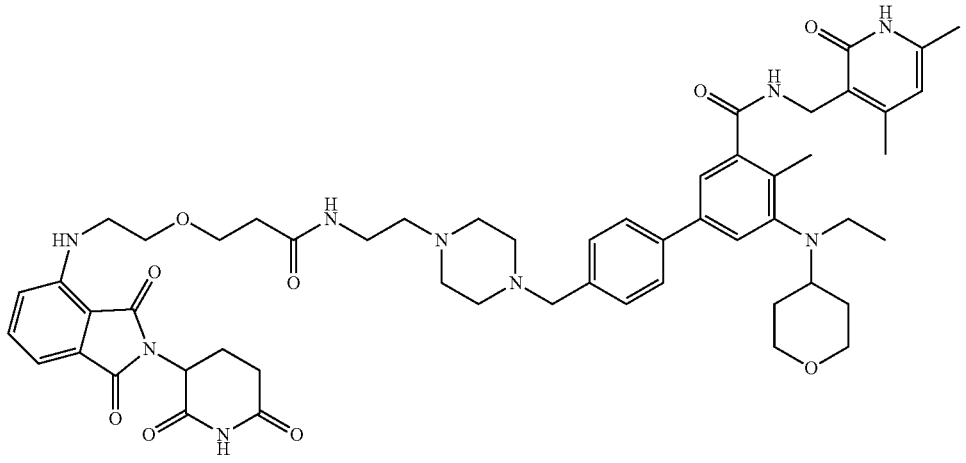
[0284] Intermediate 41 (14 mg, 0.02 mmol) and intermediate 6 (4 mg, 0.02 mmol) were dissolved in DCM (2.0 mL), and methanol (1.0 mL). To the solution was added sodium triacetoxyborohydride (13 mg, 0.06 mmol) at room temperature. After being stirred overnight at room temperature, the mixture was quenched with water and extracted with DCM (10 mL for 3 times), dried and purified by prepared HPLC to afford CZ40-149 (8 mg, 51%) as white solid in TFA salt form. ^{1}H NMR (600 MHz, CD_3OD) δ 7.56 (d, J=7.9 Hz, 2H), 7.45 (d, J=1.7 Hz, 1H), 7.41 (d, J=7.9 Hz, 2H), 7.32 (d, J=1.8 Hz, 1H), 6.12 (s, 1H), 5.12 (s, 1H), 4.49 (s, 2H), 3.92 (d, J=11.6 Hz, 2H), 3.66 (s, 2H), 3.40-3.33 (m, 3H), 3.13 (ddt, J=23.6, 11.7, 5.4 Hz, 5H), 3.07-3.02 (m, 2H), 2.68-2.54 (m, 8H), 2.39 (s, 3H), 2.32 (s, 3H), 2.24 (s, 3H), 1.96 (s, 2H), 1.76 (d, J=12.2 Hz, 4H), 1.71-1.61 (m, 5H), 1.56 (d, J=2.8 Hz, 6H), 1.47-1.42 (m, 2H), 1.28 (s, 2H), 0.90 (t, J=7.0 Hz, 3H).

Example 93: Synthesis of CZ40-74

[0285]



Intermediate 41

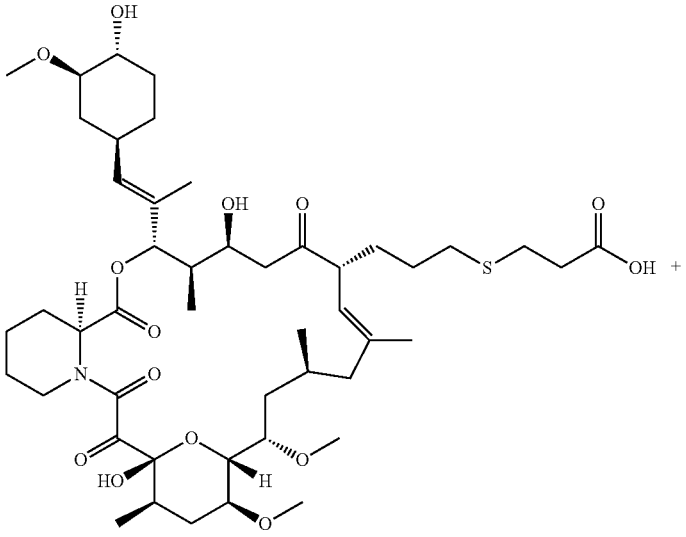


CZ40-74

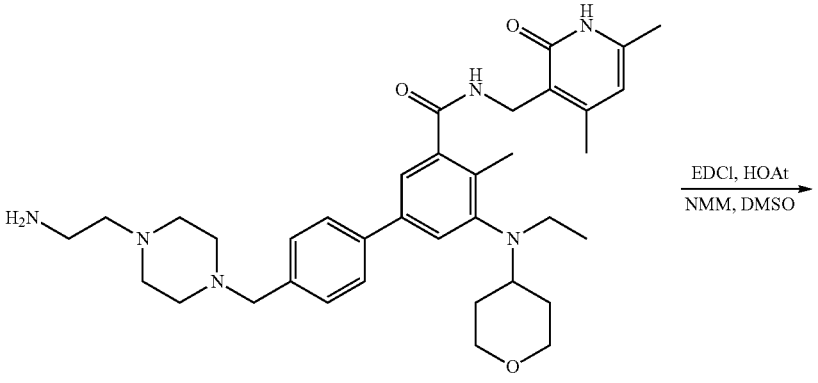
[0286] Intermediate 41 (14 mg, 0.02 mmol) was dissolved in DMSO (1.0 mL). 3-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)propanoic acid (8 mg, 0.02 mmol), HOAt (4 mg, 0.03 mmol), EDCI (6 mg, 0.03 mmol), and NMM (11 μL, 0.09 mmol) were added to the solution subsequently at room temperature. After being stirred overnight, the reaction mixture was purified by prepared HPLC to afford CZ40-74 (5 mg, 28%) as yellow solid in TFA salt form. ^{1}H NMR (600 MHz, CD_3OD) δ 7.68-7.67 (m, 3H), 7.55-7.51 (m, 2H), 7.47 (d, J=8.0 Hz, 2H), 7.08 (d, J=8.4 Hz, 1H), 7.03 (d, J=7.2 Hz, 1H), 6.12 (s, 1H), 5.08-5.00 (m, 1H), 4.50 (s, 2H), 3.94 (brs, 6H), 3.76 (t, J=5.4 Hz, 2H), 3.68 (t, J=5.4 Hz, 2H), 3.48 (t, J=5.0 Hz, 2H), 3.44-3.33 (m, 6H), 3.09 (s, 4H), 2.93 (s, 6H), 2.83 (ddd, J=17.7, 14.0, 5.3 Hz, 2H), 2.76-2.63 (m, 2H), 2.50-2.43 (m, 2H), 2.39 (d, J=4.0 Hz, 6H), 2.24 (s, 3H), 2.11-2.07 (m, 1H), 1.74 (s, 2H), 0.97 (s, 3H). ESI m/z=986.50 $[M+H]^+$.

Example 94: Synthesis of CZ40-131

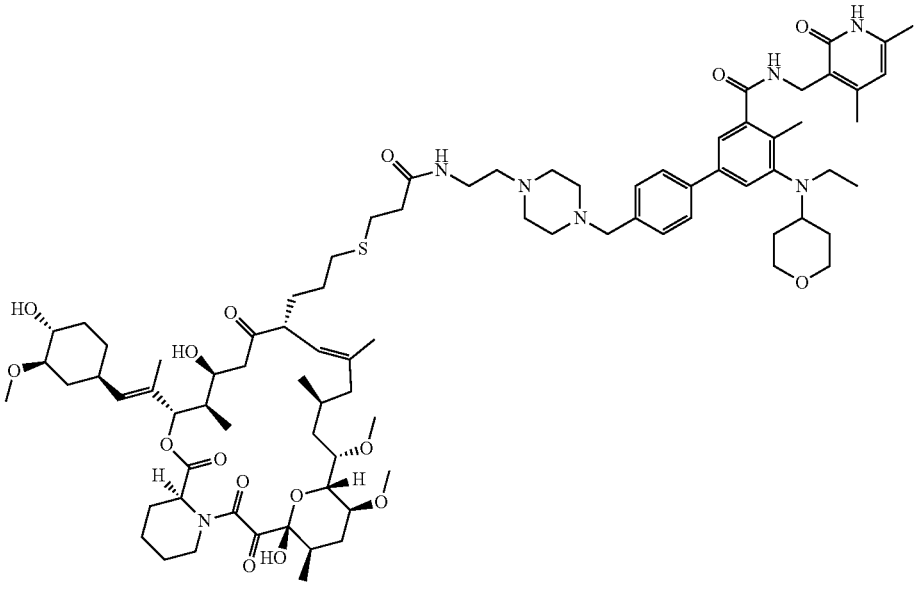
[0287]



Intermediate 34



Intermediate 41

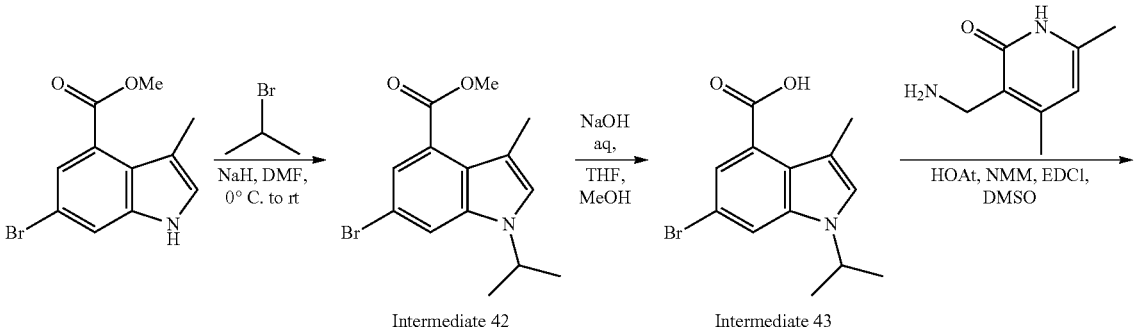


CZ40-131

[0288] Intermediate 41 (14 mg, 0.02 mmol) was dissolved in DMSO (1.0 mL). Intermediate 34 (16 mg, 0.02 mmol), HOAt (4 mg, 0.03 mmol), EDCI (6 mg, 0.03 mmol), and NMM (11 μL, 0.09 mmol) were added to the solution subsequently at room temperature. After being stirred overnight, the reaction mixture was purified by prepared HPLC to afford CZ40-31 (14 mg, 47%) as white solid in TFA salt form. ^{1}H NMR (600 MHz, CD_3OD) δ 7.90 (s, 1H), 7.78 (d, J=7.9 Hz, 2H), 7.74 (s, 1H), 7.58 (dd, J=8.3, 3.2 Hz, 2H), 6.15 (s, 1H), 5.28-4.97 (m, 3H), 4.65 (s, 1H), 4.51 (s, 2H), 4.33 (d, J=13.4 Hz, 1H), 4.14 (d, J=8.4 Hz, 2H), 4.03-3.97 (m, 4H), 3.74 (dd, J=9.7, 2.9 Hz, 2H), 3.69-3.67 (m, 1H), 3.61 (dt, J=11.9, 5.6 Hz, 1H), 3.51 (q, J=6.0 Hz, 4H), 3.40-3.32 (m, 12H), 3.20 (brs, 4H), 3.10 (q, J=6.2 Hz, 2H), 3.06-2.92 (m, 2H), 2.82 (dd, J=14.4, 5.2 Hz, 1H), 2.80-2.69 (m, 2H), 2.57-2.45 (m, 4H), 2.44 (s, 3H), 2.40 (s, 3H), 2.37-2.28 (m, 3H), 2.25 (s, 3H), 2.21-1.17 (m, 34H), 1.14-1.01 (m, 4H), 0.98-0.84 (m, 12H). ESI m/z=1506.87 $[M+H]^+$.

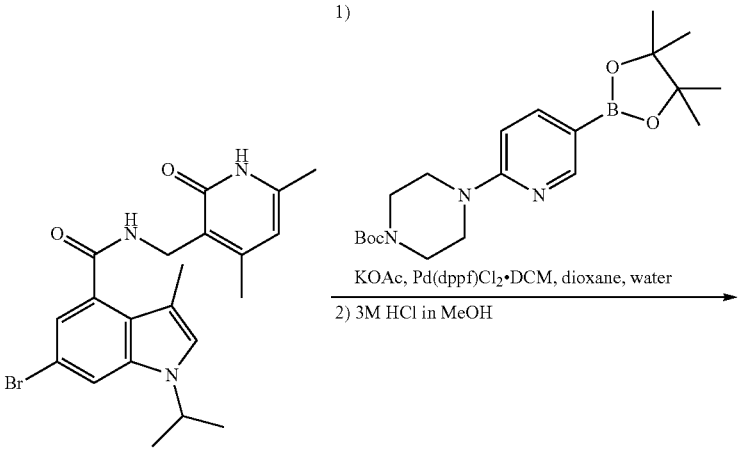
Example 95: Synthesis of AM41-36A

[0289]

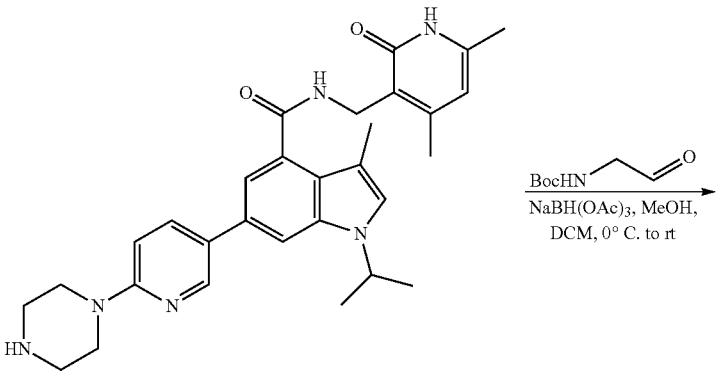


Intermediate 42

Intermediate 43

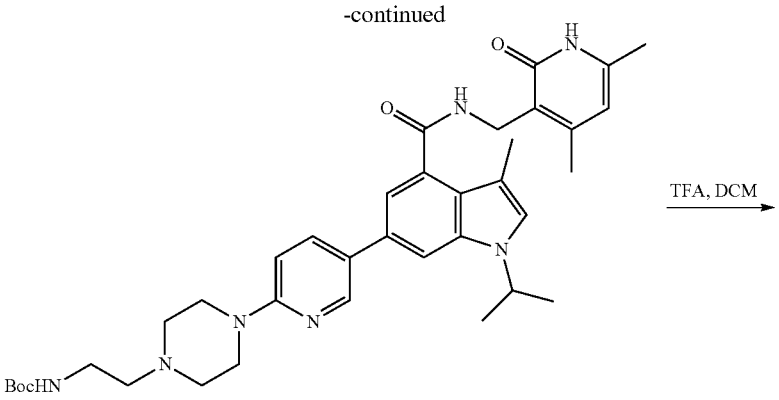


Intermediate 44

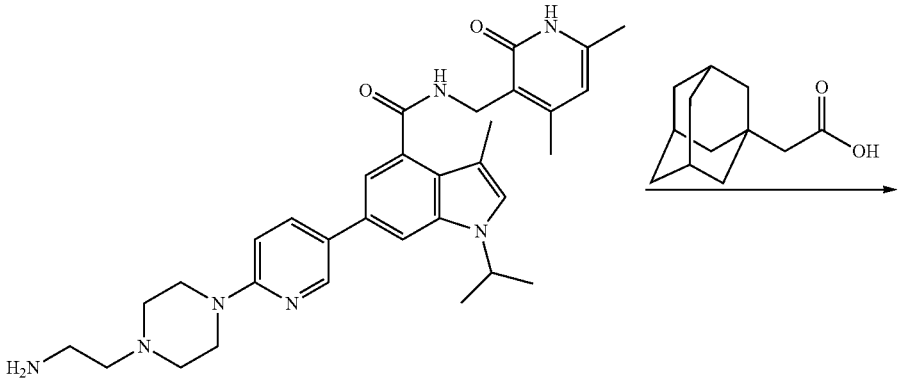


Intermediate 45

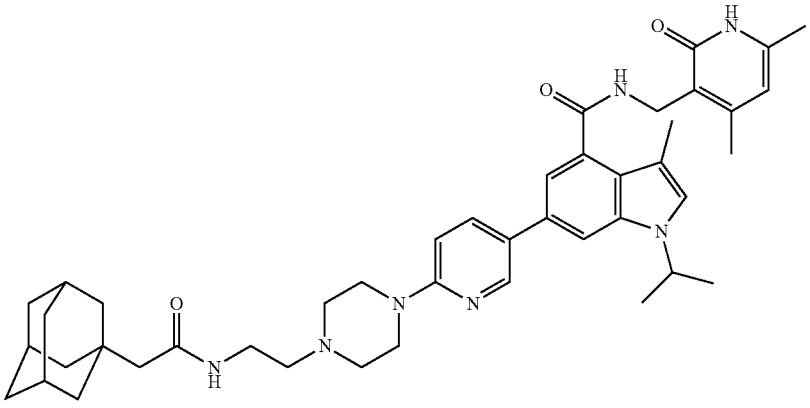
-continued



Intermediate 46



Intermediate 47



AM41-36A

[0290] Intermediate 47 (20 mg, 0.03 mmol), HOAt (6 mg, 0.05 mmol), 1-adamantaneacetic acid (7 mg, 0.04 mmol), and EDCI (9 mg, 0.05 mmol) were dissolved in DMSO (1.0 mL). To the solution was added NMM (14 μL, 0.12 mmol) at room temperature. After being stirred overnight at room temperature, the mixture was purified by preparative HPLC (10%-100% methanol/0.1% TFA in H_2O) to afford AM41-36A as off-white solid in TFA salt form (25 mg, 100%). ^1H NMR (600 MHz, CD_3OD) 8.44 (d, J=2.3 Hz, 1H), 8.30 (dd, J=9.1, 2.4 Hz, 1H), 7.74 (d, J=1.0 Hz, 1H), 7.34-7.29 (m, 2H), 7.27 (s, 1H), 6.22 (s, 1H), 4.86-4.80 (m, 1H), 4.57 (s, 2H), 3.98 (s, 4H), 3.61 (dd, J=18.9, 12.9 Hz, 6H), 3.37-3.35 (m, 2H), 2.45 (s, 3H), 2.28 (s, 3H), 2.22 (s, 3H), 2.01 (s, 2H), 1.97 (brs, 3H), 1.79-1.72 (m, 3H), 1.71-1.64 (m, 9H), 1.50 (s, 3H), 1.49 (s, 3H).

Example 96: Synthesis of AM41-37A

[0291] AM41-37A was synthesized according to the procedures for preparing AM41-36A from AM41-35A (20 mg, 0.03 mmol), HOAt (6 mg, 0.05 mmol), 2-(adamantan-2-yl) acetic acid (7 mg, 0.04 mmol), EDCI (9 mg, 0.05 mmol), NMM (14 μL, 0.12 mmol), and DMSO (1.0 mL). AM41-37A was obtained as off-white solid in TFA salt form (21 mg, 83%). ^1H NMR (600 MHz, CD_3OD) δ 8.43 (d, J=2.3 Hz, 1H), 8.29 (dd, J=9.1, 2.4 Hz, 1H), 7.74 (d, J=1.3 Hz, 1H), 7.33-7.25 (m, 3H), 6.21 (s, 1H), 4.86-4.78 (m, 1H), 4.57 (s, 2H), 3.98 (brs, 4H), 3.62 (t, J=5.9 Hz, 2H), 3.56 (brs, 4H), 3.38-3.33 (m, 2H), 2.46-2.40 (m, 5H), 2.27 (s, 3H), 2.26-2.23 (m, 1H), 2.22 (s, 3H), 1.98-1.92 (m, 2H), 1.92-1.

85 (m, 3H), 1.84-1.74 (m, 5H), 1.69 (brs, 2H), 1.61 (brs, 1H), 1.59 (brs, 1H), 1.50 (s, 3H), 1.49 (s, 3H).

Example 97: Synthesis of AM41-39A

[0292] AM41-39A was synthesized according to the procedures for preparing AM16-103A from AM41-35A (20 mg, 0.03 mmol), intermediate 6 (16 mg, 0.09 mmol), sodium triacetoxyborohydride (26 mg, 0.12 mmol), DCM (0.5 mL), and methanol (0.5 mL). AM41-39A was obtained as white solid (6 mg, 24%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.44 (d, J=2.5 Hz, 1H), 7.92 (dd, J=8.9, 2.5 Hz, 1H), 7.64 (d, J=1.3 Hz, 1H), 7.27 (d, J=1.1 Hz, 1H), 7.20 (s, 1H), 6.91 (d, J=8.8 Hz, 1H), 6.12 (s, 1H), 4.82-4.76 (m, 1H), 4.56 (s, 2H), 3.64-3.52 (m, 4H), 3.30-3.27 (m, 2H), 3.25-3.19 (m, 4H), 2.75 (t, J=5.7 Hz, 2H), 2.70-2.60 (m, 4H), 2.43 (s, 3H), 2.24 (s, 3H), 2.22 (s, 3H), 1.98 (brs, 7H), 1.81-1.75 (m, 6H), 1.72-1.68 (m, 6H), 1.60-1.58 (m, 11H), 1.50 (s, 3H), 1.49 (s, 3H), 1.48-1.44 (m, 4H).

Example 98: Synthesis of AM41-41A

[0293] AM41-41A was synthesized according to the procedures for preparing AM16-103A from AM41-35A (20 mg, 0.03 mmol), intermediate 6 (5 mg, 0.03 mmol), sodium triacetoxyborohydride (26 mg, 0.12 mmol), DCM (0.5 mL), and methanol (0.5 mL). AM41-41A was obtained as white solid (10 mg, 46%). ^{1}H NMR (600 MHz, MeOD) δ 8.42 (d, J=2.2 Hz, 1H), 7.92 (dd, J=8.9, 2.4 Hz, 1H), 7.63 (s, 1H), 7.27 (s, 1H), 7.20 (s, 1H), 6.92 (d, J=8.9 Hz, 1H), 6.13 (s, 1H), 4.83-4.75 (m, 1H), 4.56 (s, 2H), 3.62-3.54 (m, 4H), 3.19 (t, J=5.7 Hz, 2H), 3.12-3.03 (m, 2H), 2.70 (t, J=5.7 Hz, 2H), 2.67-2.59 (m, 4H), 2.43 (s, 3H), 2.24 (s, 3H), 2.21 (s, 3H), 1.98 (brs, 5H), 1.78 (d, J=12.1 Hz, 2H), 1.70 (d, J=11.7 Hz, 2H), 1.58 (s, 6H), 1.50 (s, 3H), 1.49 (s, 3H), 1.40-1.34 (m, 2H).

Example 99: Synthesis of AM41-38A

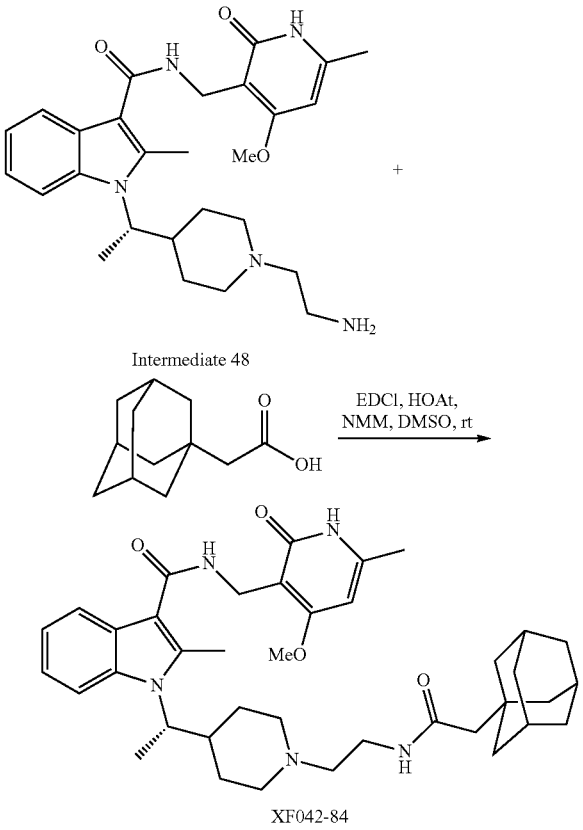
[0294] AM41-38A was synthesized according to the procedures for preparing AM29-151A from AM41-35A (20 mg, 0.03 mmol), HATU (23 mg, 0.06 mmol), 3-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino) ethoxy)propanoic acid (14 mg, 0.04 mmol), DIPEA (21 μL, 0.12 mmol), and DMF (1.0 mL). AM41-38A was obtained as yellow solid in TFA salt form (16 mg, 51%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.38 (d, J=2.1 Hz, 1H), 8.20 (dd, J=9.1, 2.2 Hz, 1H), 7.72 (s, 1H), 7.51 (dd, J=8.4, 7.2 Hz, 1H), 7.30 (d, J=1.0 Hz, 1H), 7.27 (s, 1H), 7.20 (d, J=9.2 Hz, 1H), 7.07 (d, J=8.6 Hz, 1H), 6.98 (d, J=7.0 Hz, 1H), 6.21 (s, 1H), 5.04 (dd, J=12.7, 5.5 Hz, 1H), 4.86-4.80 (m, 1H), 4.57 (s, 2H), 3.92 (brs, 4H), 3.80 (t, J=5.7 Hz, 2H), 3.71 (t, J=4.9 Hz, 2H), 3.65-3.41 (m, 9H), 3.37-3.31 (m, 2H), 2.88-2.77 (m, 1H), 2.75-2.61 (m, 2H), 2.53 (t, J=5.6 Hz, 2H), 2.45 (s, 3H), 2.27 (s, 3H), 2.22 (s, 3H), 2.11-2.04 (m, 1H), 1.51 (s, 3H), 1.49 (s, 3H).

Example 100: Synthesis of AM41-40A

[0295] AM41-40A was synthesized according to the procedures for preparing XY028-086. AM41-40A was obtained as off-white solid in TFA salt form (15 mg, 44%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.48 (dd, J=6.7, 2.2 Hz, 1H), 8.17 (td, J=8.7, 2.3 Hz, 1H), 7.73-7.66 (m, 1H), 7.31 (d, J=0.8 Hz, 1H), 7.25 (s, 1H), 7.23-7.16 (m, 1H), 6.17 (s, 1H), 5.24 (dd, J=27.8, 4.2 Hz, 1H), 5.17 (d, J=8.9 Hz, 1H), 5.10-4.97 (m, 1H), 4.82 (dd, J=13.6, 6.9 Hz, 1H), 4.61 (d, J=54.1 Hz, 3H), 4.32 (d, J=11.0 Hz, 1H), 4.21-3.79 (m, 5H), 3.70-3.48 (m, 10H), 3.41-3.35 (m, 10H), 3.09-2.69 (m, 6H), 2.55 (dt, J=10.4, 6.6 Hz, 4H), 2.45 (s, 3H), 2.38-2.27 (m, 2H), 2.26 (s, 3H), 2.21 (s, 3H), 2.10 (ddd, J=30.0, 21.7, 14.0 Hz, 4H), 1.86 (ddd, J=23.7, 15.8, 9.8 Hz, 4H), 1.75 (s, 3H), 1.66 (d, J=9.6 Hz, 3H), 1.62-1.56 (m, 5H), 1.50 (s, 3H), 1.50 (s, 3H), 1.49 (s, 3H), 1.49 (s, 3H), 1.40-1.27 (m, 4H), 1.23-1.15 (m, 1H), 1.10-1.04 (m, 1H), 0.95-0.87 (m, 10H).

Example 101: Synthesis of XF042-84

[0296]

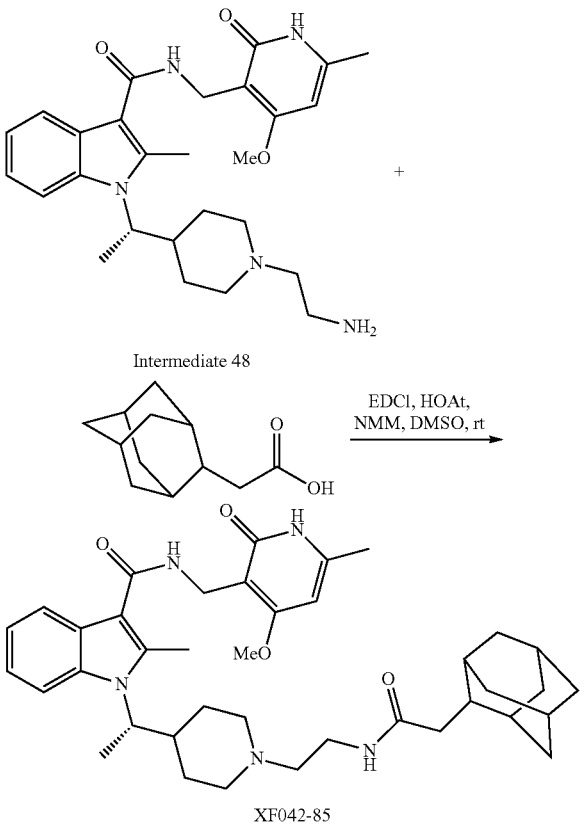


XF042-84

[0297] Intermediate 48 was synthesized according to the procedures published in J. Med. Chem. 2016, 59, 9928-9941. Intermediate 48 (20 mg, 0.04 mmol), HOAt (8.6 mg, 0.06 mmol), and 1-adamantaneacetic acid (8.1 mg, 0.04 mmol) were dissolved in DMSO (1.0 mL). To the solution were added NMM (14 μL, 0.13 mmol), and EDCI (12 mg, 0.06 mmol) successively at room temperature. After being stirred overnight at room temperature, the mixture was purified by preparative HPLC (10%-100% methanol/0.1% TFA in H_2O) to afford XF042-84 as white solid in TFA salt form (28 mg, 98%). H[1] NMR (600 MHz, CD_3OD) δ 7.77-7.73 (m, 1H), 7.66-7.59 (m, 1H), 7.16 (pd, J=7.2, 1.4 Hz, 2H), 6.70 (s, 1H), 4.57 (s, 2H), 4.27 (dq, J=14.0, 7.1 Hz, 1H), 4.06 (s, 3H), 3.77 (d, J=12.4 Hz, 1H), 3.51 (t, J=6.1 Hz, 2H), 3.46 (d, J=12.7 Hz, 1H), 3.18 (dp, J=25.1, 6.9, 6.4 Hz, 2H), 3.09-3.02 (m, 1H), 2.79-2.73 (m, 1H), 2.69-2.60 (m, 4H), 2.46 (s, 3H), 2.31 (d, J=14.4 Hz, 1H), 1.94 (d, J=13.8 Hz, 5H), 1.73 (d, J=12.3 Hz, 4H), 1.68-1.58 (m, 12H), 1.45-1.36 (m, 1H), 1.06 (d, J=14.4 Hz, 1H).

Example 102: Synthesis of XF042-85

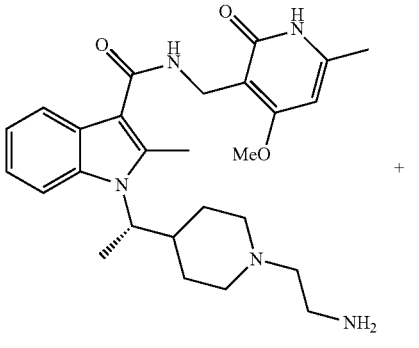
[0298]



[0299] XF042-85 was synthesized according to the procedures for preparing XF042-84 from intermediate 48 (20 mg, 0.04 mmol), HOAt (8.6 mg, 0.06 mmol), 2-adamantaneacetic acid (8.1 mg, 0.04 mmol), NMM (14 μL, 0.13 mmol), EDCI (12 mg, 0.06 mmol), and DMSO (1.0 mL). XF042-85 was obtained as white solid in TFA salt form (24 mg, 85%). ^{1}H NMR (600 MHz, CD_3OD) δ 7.74 (d, J=7.4 Hz, 1H), 7.62 (d, J=7.7 Hz, 1H), 7.14 (p, J=6.9 Hz, 2H), 6.55 (s, 1H), 4.57 (s, 2H), 4.25 (t, J=8.8 Hz, 1H), 4.02 (d, J=1.9 Hz, 3H), 3.76 (d, J=12.3 Hz, 1H), 3.52 (t, J=5.9 Hz, 2H), 3.44 (d, J=12.5 Hz, 1H), 3.22-3.12 (m, 2H), 3.05 (t, J=12.9 Hz, 1H), 2.77-2.70 (m, 1H), 2.68-2.60 (m, 4H), 2.43-2.35 (m, 5H), 2.30 (d, J=14.3 Hz, 1H), 2.19 (s, 1H), 1.93-1.83 (m, 5H), 1.77 (d, J=18.3 Hz, 5H), 1.73-1.62 (m, 6H), 1.55 (d, J=13.0 Hz, 2H), 1.39 (q, J=13.8 Hz, 1H), 1.05 (d, J=14.5 Hz, 1H).

Example 103: Synthesis of XF042-95

[0300]



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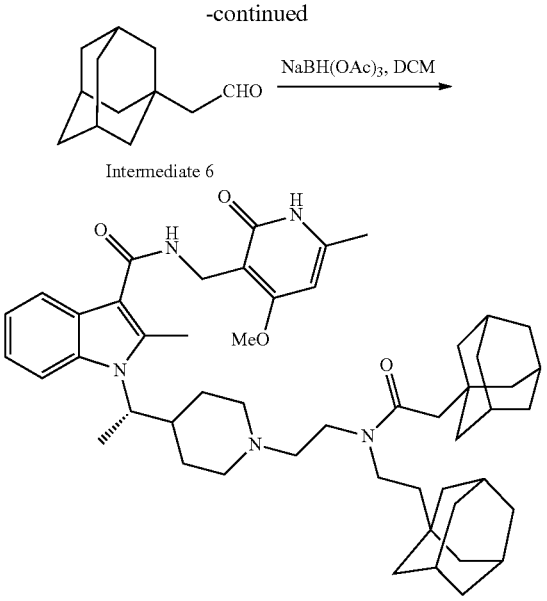
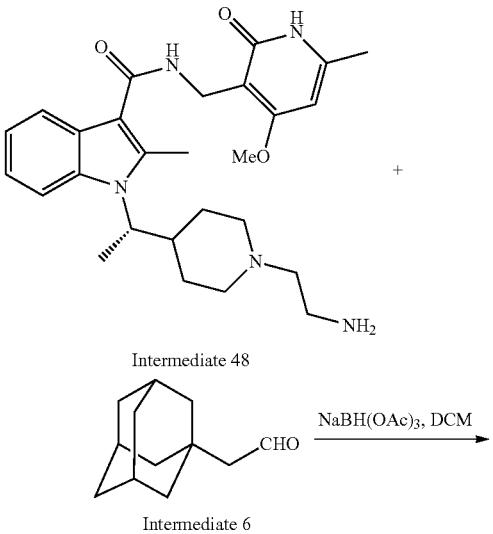


[0301] Intermediate 48 (25 mg, 0.05 mmol) and intermediate 6 (28 mg, 0.16 mmol) were dissolved in DCM (2 mL). To the solution was added the sodium triacetoxyborohydride (34 mg, 0.02 mmol) at 0° C. After being stirred overnight at room temperature, the mixture was evaporated and purified by ISCO™ to afford XF042-95 as white solid (8.9 mg, 27%). ^{1}H NMR (600 MHz, CD_3OD) δ 7.71 (d, J=8.0 Hz, 1H), 7.58 (d, J=8.3 Hz, 1H), 7.09 (d, J=8.6 Hz, 2H), 6.31 (s, 1H), 4.53 (s, 2H), 4.17 (s, 1H), 3.97 (d, J=2.3 Hz, 3H), 3.09 (s, 4H), 2.80 (d, J=11.7 Hz, 1H), 2.67 (s, 1H), 2.60 (s, 3H), 2.33 (s, 3H), 2.18 (d, J=11.5 Hz, 1H), 2.07 (s, 1H), 1.97 (s, 6H), 1.86 (d, J=11.2 Hz, 1H), 1.80-1.49 (m, 31H), 1.39 (d, J=9.1 Hz, 5H), 1.29 (s, 1H), 1.12 (s, 1H), 0.89 (d, J=13.5 Hz, 1H).

Example 104: Synthesis of XF042-132

[0302]



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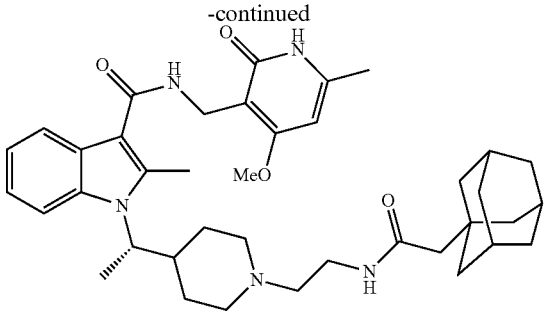
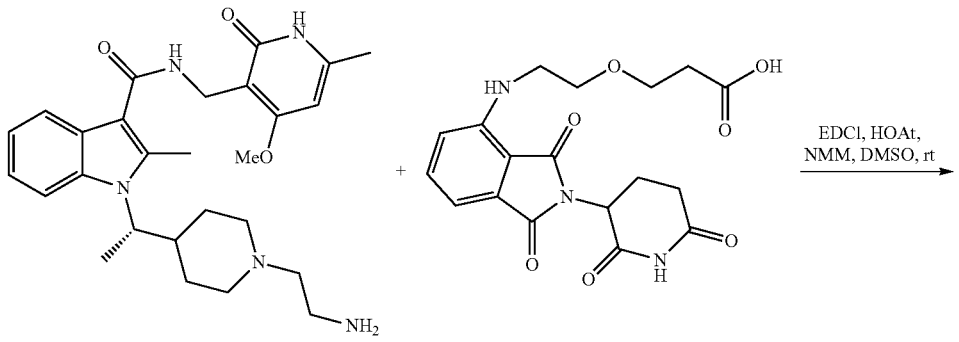


XF042-132

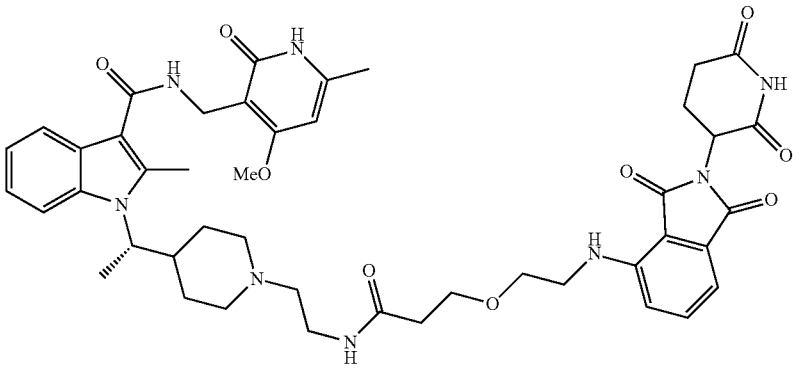
[0303] XF042-132 was synthesized according to the procedures for preparing XF042-95 from intermediate 48 (15 mg, 0.03 mmol) and intermediate 6 (5.8 mg, 0.03 mmol). XF042-132 was obtained as white solid (8.2 mg, 98%). ^{1}H NMR (600 MHz, CD_3OD) δ 7.70 (d, J=7.8 Hz, 1H), 7.57 (d, J=8.0 Hz, 1H), 7.10 (dt, J=18.5, 7.3 Hz, 2H), 6.33 (s, 1H), 4.52 (s, 2H), 4.18 (dq, J=13.9, 7.1 Hz, 1H), 3.98 (d, J=3.8 Hz, 3H), 3.06 (s, 2H), 3.05-2.97 (m, 3H), 2.74 (d, J=15.4 Hz, 1H), 2.60 (s, 3H), 2.55 (dq, J=13.0, 7.1, 6.0 Hz, 2H), 2.34 (s, 3H), 2.30 (d, J=10.6 Hz, 1H), 2.16-2.09 (m, 1H), 2.04 (d, J=13.1 Hz, 1H), 1.96 (s, 2H), 1.93 (s, 1H), 1.84-1.74 (m, 3H), 1.68 (d, J=12.3 Hz, 2H), 1.64-1.50 (m, 10H), 1.46-1.40 (m, 3H), 1.28 (s, 3H), 1.16-1.08 (m, 1H), 0.86 (s, 1H).

Example 105: Synthesis of XF042-86

[0304]



Intermediate 48

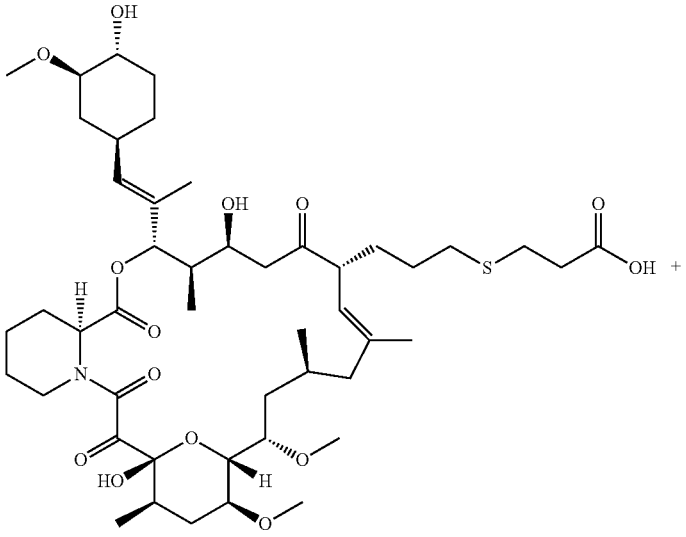


XF042-86

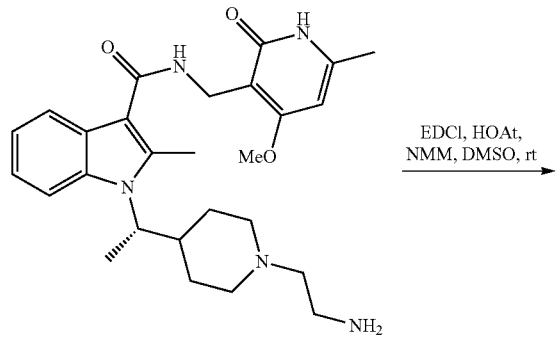
[0305] XF042-86 was synthesized according to the procedures for preparing XF042-84 from intermediate 48 (20 mg, 0.04 mmol), HOAt (8.6 mg, 0.06 mmol), 3-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino) ethoxy)propanoic acid (16.2 mg, 0.04 mmol), NMM (14 μL, 0.13 mmol), EDCI (12 mg, 0.06 mmol), and DMSO (1.0 mL). XF042-86 was obtained as yellow solid in TFA salt form (29 mg, 82%). ^{1}H NMR (600 MHz, CD_3OD) δ 7.73 (d, J=7.3 Hz, 1H), 7.58 (t, J=8.4 Hz, 1H), 7.55-7.41 (m, 1H), 7.19-7.10 (m, 2H), 7.08-6.93 (m, 2H), 6.66 (s, 1H), 5.02 (tdd, J=17.0, 10.6, 5.5 Hz, 1H), 4.57 (d, J=4.7 Hz, 2H), 4.22 (q, J=7.8 Hz, 1H), 4.04 (s, 3H), 3.74 (td, J=6.2, 2.6 Hz, 2H), 3.70-3.65 (m, 2H), 3.65-3.61 (m, 2H), 3.48 (tt, J=11.3, 6.2 Hz, 2H), 3.40 (t, J=5.1 Hz, 2H), 3.11 (ddq, J=25.8, 14.0, 7.0, 6.3 Hz, 2H), 2.98 (d, J=13.5 Hz, 1H), 2.85-2.78 (m, 1H), 2.71-2.63 (m, 3H), 2.60-2.54 (m, 4H), 2.46 (d, J=19.0 Hz, 5H), 2.23 (t, J=16.1 Hz, 1H), 2.07 (d, J=13.8 Hz, 1H), 1.60 (dd, J=14.2, 6.9 Hz, 4H), 1.32 (q, J=13.5 Hz, 1H), 0.97 (t, J=13.7 Hz, 1H).

Example 106: Synthesis of XF042-94

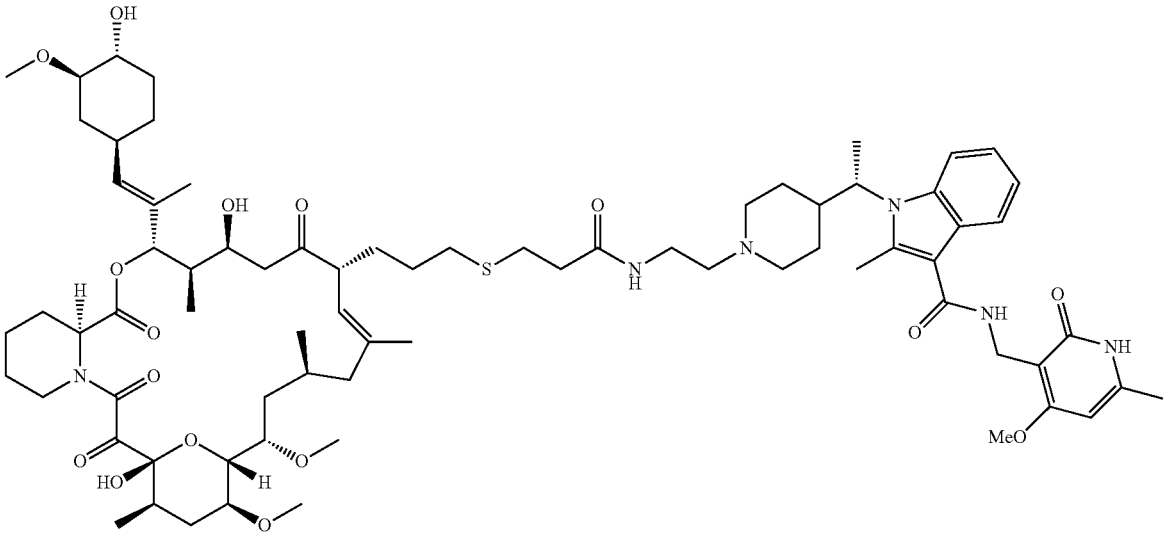
[0306]



Intermediate 34



Intermediate 48

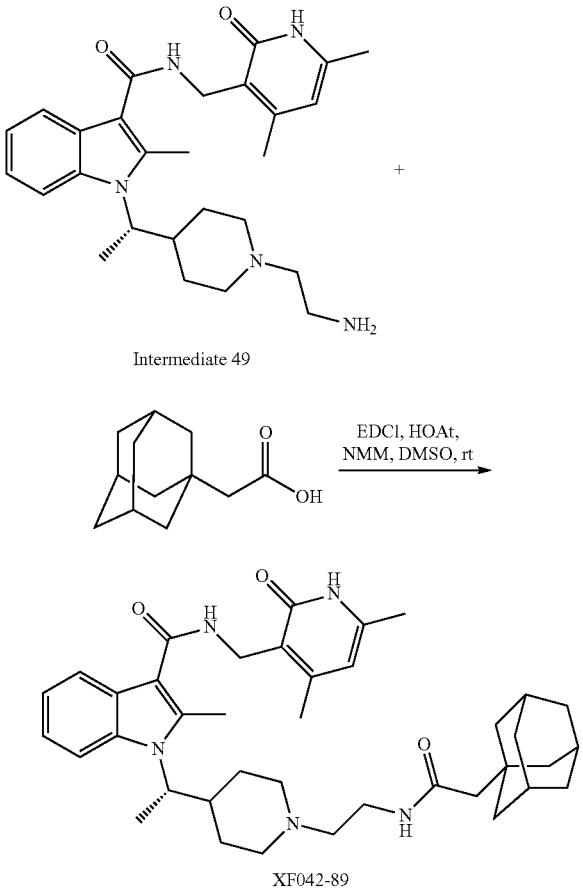


XF042-94

[0307] XF042-94 was synthesized according to the procedures for preparing XF042-84 from intermediate 48 (10 mg, 0.02 mmol), HOAt (4.1 mg, 0.03 mmol), intermediate 34 (19 mg, 0.02 mmol), NMM (6.5 μL, 0.06 mmol), EDCI (5.8 mg, 0.03 mmol), and DMSO (1.0 mL). XF042-94 was obtained as white solid in TFA salt form (22 mg, 81%). ^{1}H NMR (600 MHz, CD_3OD) δ 7.74 (d, J=7.5 Hz, 1H), 7.62 (d, J=7.8 Hz, 1H), 7.17-7.09 (m, 2H), 6.53 (s, 1H), 5.28-5.13 (m, 2H), 4.97 (ddtt, J=9.8, 6.2, 2.5, 1.2 Hz, 1H), 4.67-4.63 (m, 1H), 4.57 (s, 2H), 4.43-4.25 (m, 2H), 4.01-4.03 (m, 4H), 3.80 (d, J=12.3 Hz, 1H), 3.75-3.13 (m, 21H), 3.13-2.85 (m, 3H), 2.85-2.24 (m, 16H), 2.23-1.16 (m, 35H), 1.10-0.60 (m, 11H).

Example 107: Synthesis of XF042-89

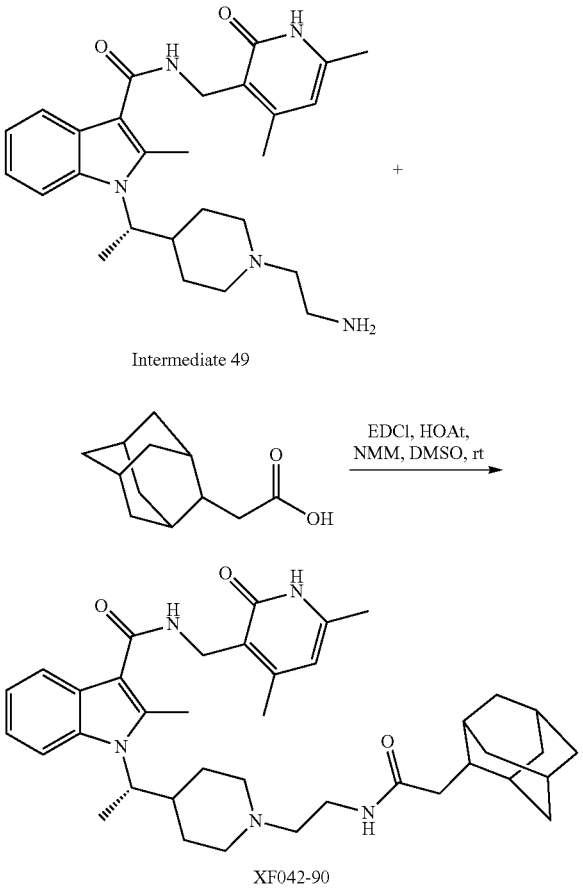
[0308]



[0309] XF042-89 was synthesized according to the procedures for preparing XF042-84 from intermediate 49 (21 mg, 0.05 mmol), HOAt (8.7 mg, 0.07 mmol), 1-adamantaneacetic acid (8.7 mg, 0.05 mmol), NMM (15 μL, 0.14 mmol), EDCI (14 mg, 0.07 mmol), and DMSO (1.0 mL). XF042-89 was obtained as white solid in TFA salt form (20 mg, 71%). ^{1}H NMR (600 MHz, CD_3OD) δ 7.77-7.72 (m, 1H), 7.61 (d, J=8.0 Hz, 1H), 7.19-7.07 (m, 2H), 6.22 (s, 1H), 4.55 (d, J=3.0 Hz, 2H), 4.25 (dq, J=13.7, 7.0 Hz, 1H), 3.77 (d, J=12.4 Hz, 1H), 3.53-3.49 (m, 2H), 3.45 (d, J=12.6 Hz, 1H), 3.23-3.13 (m, 2H), 3.10-3.01 (m, 1H), 2.75 (dd, J=9.2, 4.2 Hz, 1H), 2.61 (s, 4H), 2.44 (s, 3H), 2.28 (s, 4H), 1.94 (d, J=14.4 Hz, 5H), 1.75-1.60 (m, 16H), 1.38 (d, J=13.4 Hz, 1H), 1.07 (d, J=14.6 Hz, 1H).

Example 108: Synthesis of XF042-90

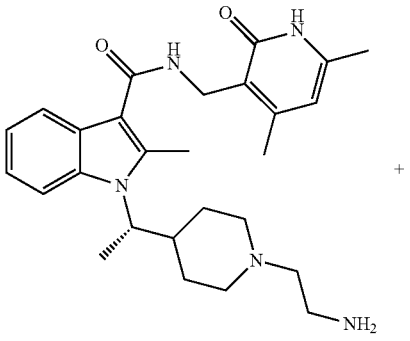
[0310]



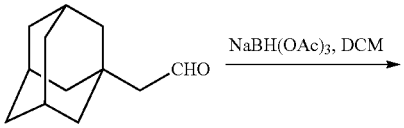
[0311] XF042-90 was synthesized according to the procedures for preparing XF042-84 from intermediate 2 (21 mg, 0.05 mmol), HOAt (8.7 mg, 0.07 mmol), 2-adamantaneacetic acid (8.7 mg, 0.05 mmol), NMM (15 μL, 0.14 mmol), EDCI (13.5 mg, 0.07 mmol), and DMSO (1.0 mL). XF042-90 was obtained as white solid in TFA salt form (24 mg, 83%). ^{1}H NMR (600 MHz, CD_3OD) δ 7.74 (d, J=7.7 Hz, 1H), 7.61 (d, J=8.2 Hz, 1H), 7.18-7.09 (m, 2H), 6.26 (s, 1H), 4.55 (d, J=2.4 Hz, 2H), 4.25 (dq, J=14.0, 7.1 Hz, 1H), 3.76 (d, J=12.4 Hz, 1H), 3.51 (t, J=5.8 Hz, 2H), 3.44 (d, J=12.5 Hz, 1H), 3.23-3.10 (m, 2H), 3.05 (t, J=12.6 Hz, 1H), 2.78-2.71 (m, 1H), 2.67-2.62 (m, 1H), 2.61 (s, 3H), 2.45 (s, 3H), 2.38 (d, J=7.6 Hz, 2H), 2.29 (s, 4H), 2.19 (s, 1H), 1.91 (d, J=13.0 Hz, 2H), 1.89-1.83 (m, 3H), 1.80-1.74 (m, 5H), 1.71-1.60 (m, 6H), 1.56 (d, J=12.8 Hz, 2H), 1.37 (q, J=13.5 Hz, 1H), 1.07 (d, J=14.6 Hz, 1H).

Example 109: Synthesis of XF042-93

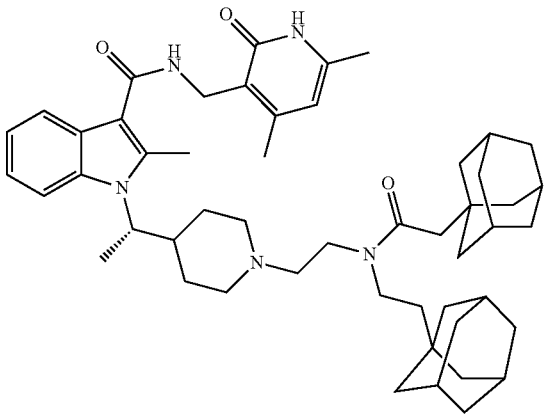
[0312]



Intermediate 49



Intermediate 6

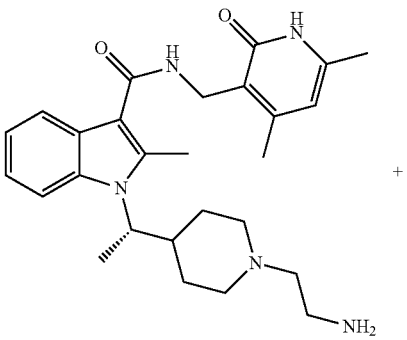


XF042-93

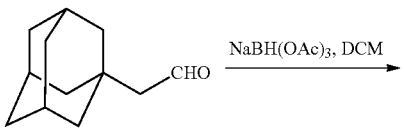
[0313] XF042-93 was synthesized according to the procedures for preparing XF042-95 from intermediate 49 (29 mg, 0.06 mmol) and intermediate 6 (33 mg, 0.19 mmol). XF042-93 was obtained as white solid (10 mg, 26%). ^{1}H NMR (600 MHz, CD_3OD) δ 7.72 (d, J=7.6 Hz, 1H), 7.58 (d, J=8.0 Hz, 1H), 7.14-7.07 (m, 2H), 6.13 (s, 1H), 4.53 (s, 2H), 4.17 (dt, J=13.6, 6.9 Hz, 1H), 3.09 (d, J=11.6 Hz, 4H), 2.79 (d, J=11.7 Hz, 1H), 2.67-2.52 (m, 5H), 2.42 (s, 3H), 2.38-2.28 (m, 1H), 2.25 (s, 3H), 2.18 (t, J=11.8 Hz, 1H), 2.08 (d, J=12.8 Hz, 1H), 1.96 (s, 6H), 1.85 (t, J=11.6 Hz, 1H), 1.76 (d, J=12.4 Hz, 6H), 1.72-1.49 (m, 21H), 1.48-1.21 (m, 8H), 1.13 (tt, J=14.2, 7.2 Hz, 1H), 0.89 (dd, J=13.9, 8.7 Hz, 1H).

Example 110: Synthesis of XF042-133

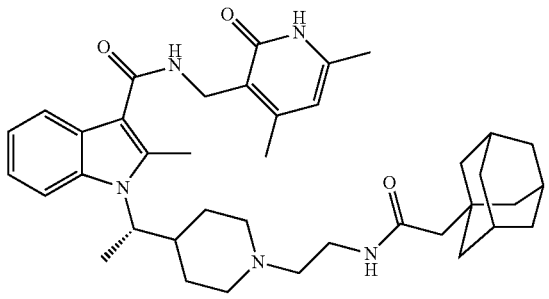
[0314]



Intermediate 49



Intermediate 6

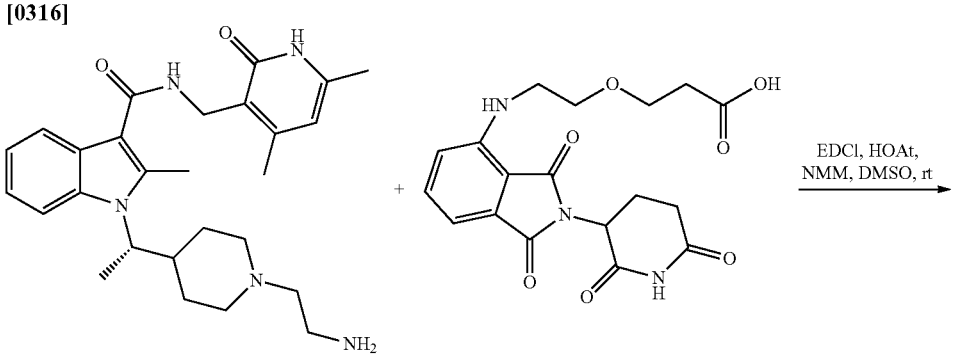


XF042-133

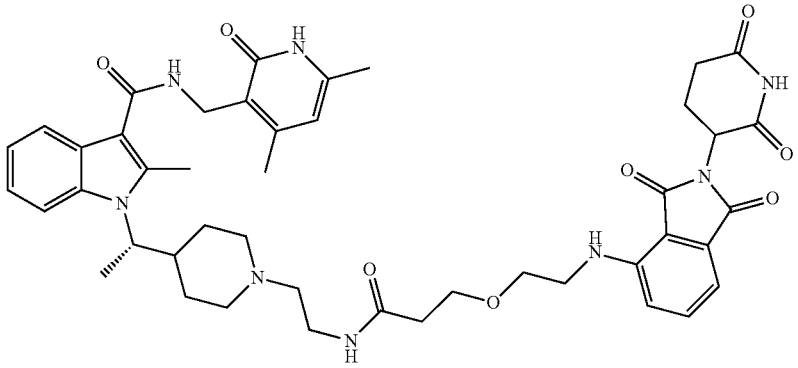
[0315] XF042-133 was synthesized according to the procedures for preparing XF042-95 from intermediate 49 (15 mg, 0.03 mmol) and intermediate 6 (5.8 mg, 0.03 mmol). XF042-133 was obtained as white solid (16.3 mg, 87%). ^{1}H NMR (600 MHz, CD_3OD) δ 7.70 (d, J=7.8 Hz, 1H), 7.58 (d, J=8.1 Hz, 1H), 7.10 (dt, J=21.6, 7.4 Hz, 2H), 6.17 (s, 1H), 4.55 (s, 2H), 4.19 (dq, J=13.9, 7.1 Hz, 1H), 3.64 (d, J=11.8 Hz, 1H), 3.19 (dt, J=21.5, 7.1 Hz, 3H), 3.07-3.00 (m, 2H), 2.89 (d, J=11.4 Hz, 1H), 2.78 (d, J=22.0 Hz, 2H), 2.59 (s, 3H), 2.42 (s, 3H), 2.37 (h, J=8.6, 7.7 Hz, 2H), 2.26 (s, 3H), 2.02 (d, J=75.9 Hz, 5H), 1.76 (d, J=12.4 Hz, 3H), 1.70-1.50 (m, 11H), 1.48-1.39 (m, 3H), 1.38-1.17 (m, 4H), 0.91-0.88 (m, 1H).

Example 111: Synthesis of XF042-91

[0316]



Intermediate 49

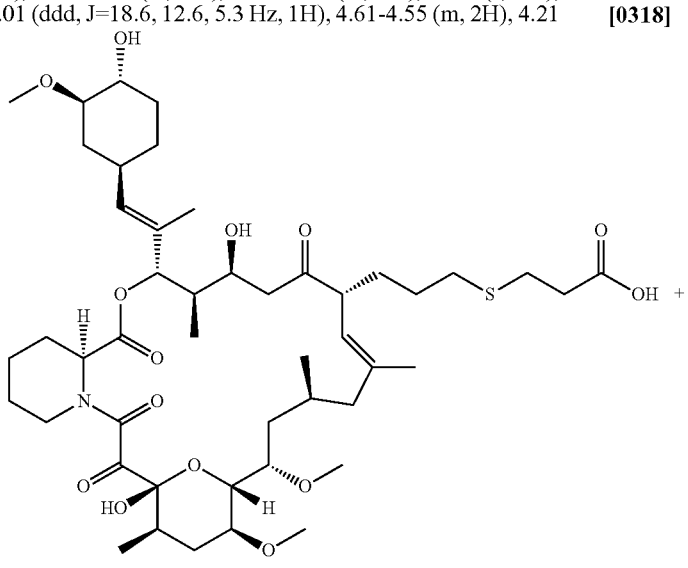


XF042-91

[0317] XF042-91 was synthesized according to the procedures for preparing XF042-84 from intermediate 49 (21 mg, 0.05 mmol), HOAt (9.2 mg, 0.07 mmol), 3-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino) ethoxy)propanoic acid (18 mg, 0.05 mmol), NMM (15 μL, 0.14 mmol), EDCI (14 mg, 0.06 mmol), and DMSO (1.0 mL). XF042-91 was obtained as yellow solid in TFA salt form (33 mg, 89%). ^{1}H NMR (600 MHz, CD_3OD) δ 7.74 (s, 1H), 7.56 (t, J=6.6 Hz, 1H), 7.49 (ddd, J=10.4, 8.4, 7.0 Hz, 1H), 7.18-7.09 (m, 2H), 7.04-6.95 (m, 2H), 6.34 (s, 1H), 5.01 (ddd, J=18.6, 12.6, 5.3 Hz, 1H), 4.61-4.55 (m, 2H), 4.21 (dt, J=11.4, 6.2 Hz, 1H), 3.74 (t, J=5.6 Hz, 2H), 3.68 (d, J=13.4 Hz, 1H), 3.62 (t, J=5.1 Hz, 2H), 3.48 (dq, J=11.2, 5.5 Hz, 2H), 3.44 (d, J=5.6 Hz, 1H), 3.40 (t, J=5.0 Hz, 3H), 3.35 (d, J=12.1 Hz, 2H), 3.17-3.06 (m, 2H), 2.98 (d, J=12.9 Hz, 1H), 2.87-2.78 (m, 1H), 2.74-2.67 (m, 3H), 2.59 (d, J=4.4 Hz, 3H), 2.51-2.44 (m, 3H), 2.31 (s, 3H), 2.23 (t, J=16.6 Hz, 1H), 2.10-2.04 (m, 1H), 1.60 (dd, J=14.9, 6.9 Hz, 4H), 1.31 (s, 1H), 0.98 (t, J=13.8 Hz, 1H).

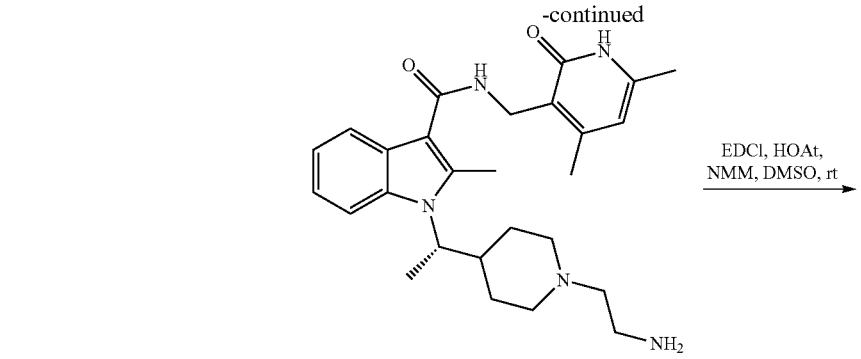
Example 112: Synthesis of XF042-92

[0318]

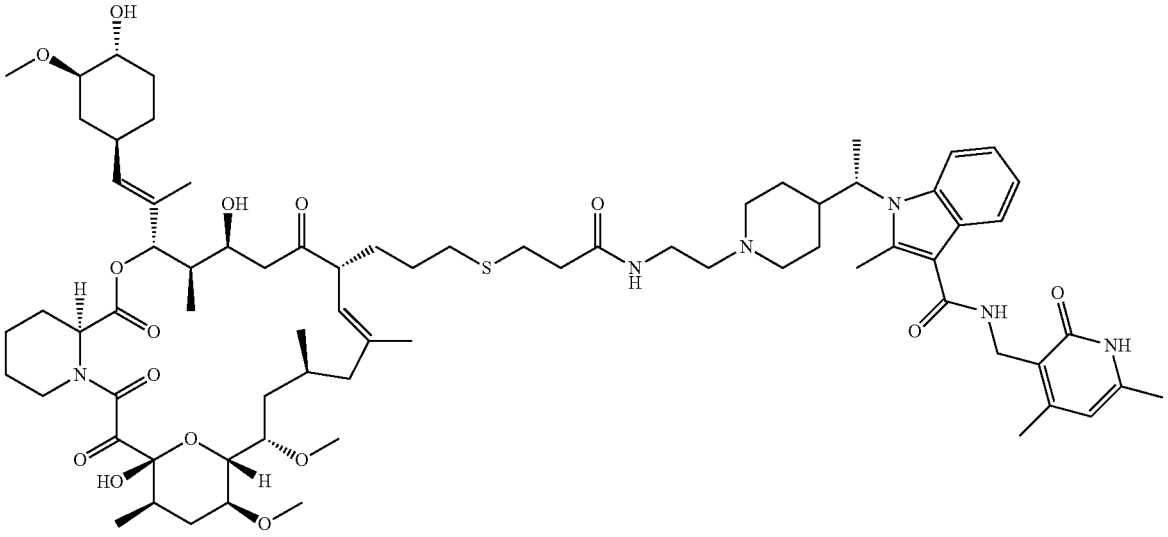


Intermediate 34

-continued



Intermediate 49



XF042-92

[0319] XF042-92 was synthesized according to the procedures for preparing XF042-84 from intermediate 49 (11 mg, 0.02 mmol), HOAt (4.5 mg, 0.03 mmol), intermediate 34 (21 mg, 0.02 mmol), NMM (7.2 μL, 0.07 mmol), EDCI (6.3 mg, 0.03 mmol), and DMSO (1.0 mL). XF042-92 was obtained as white solid in TFA salt form (19 mg, 60%). ^{1}H NMR (600 MHz, CD_3OD) δ 7.75 (s, 1H), 7.62 (d, J=7.9 Hz, 1H), 7.16-7.07 (m, 2H), 6.25 (s, 1H), 5.30-5.16 (m, 2H), 4.96 (ddtt, J=11.1, 7.4, 2.5, 1.2 Hz, 1H), 4.65 (t, J=3.7 Hz, 1H), 4.56 (s, 2H), 4.35-4.21 (m, 1H), 4.06-3.94 (m, 1H), 3.85-2.85 (m, 25H), 2.85-2.58 (m, 7H), 2.57-1.97 (m, 18H), 1.95-0.72 (m, 41H).

Example 113: Proliferation Assays

[0320] 1-3×10^3 cells were seeded in 96-well plates in duplicates and treated at the indicated compound concentrations. Cells were monitored using the IncuCyte live cell imaging system (Essen BioScience™, Ann Arbor, Mich.) which was placed in a cell culture incubator operated at 37° C. and 5% CO_2. Cell confluence was determined using calculations derived from phase-contrast images. The concentration for 50% of maximal inhibition of cell proliferation (GI_{50}) values were determined by fitting to a standard four-parameter logistic using GraphPad PrismR v5. Results are provided in Tables 2 and 3. Graphs depicting the GI_{50s} of select EZH2 degraders/disruptors described here for various cancer cell lines are shown in FIGS. **4-49**.

TABLE 2

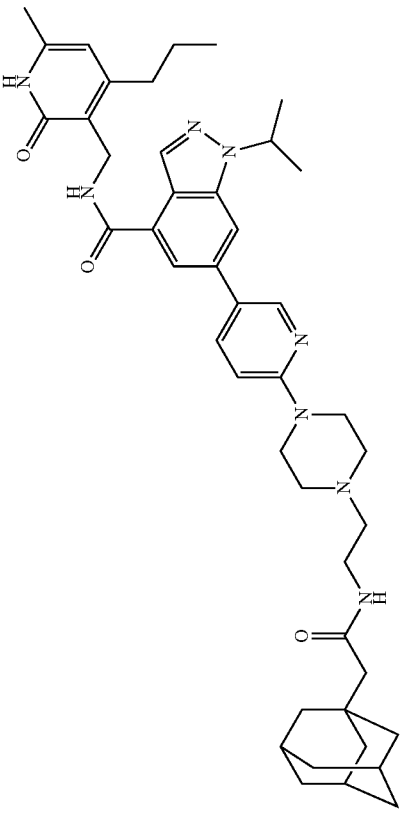
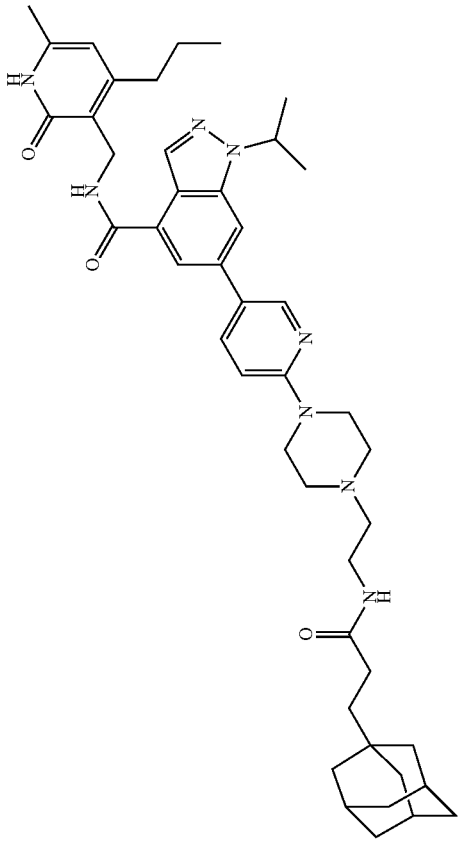
Cmpd #	Structure	GI_{50} (μM) MCF-7	GI_{50} (μM) MDA-MB-468	GI_{50} (μM) HCC1187	GI_{50} (μM) HCC1170
AM16-10A		1.2	1.4	0.57	1.2
AM16-11A		N/A	N/A	2.6	N/A

TABLE 2-continued

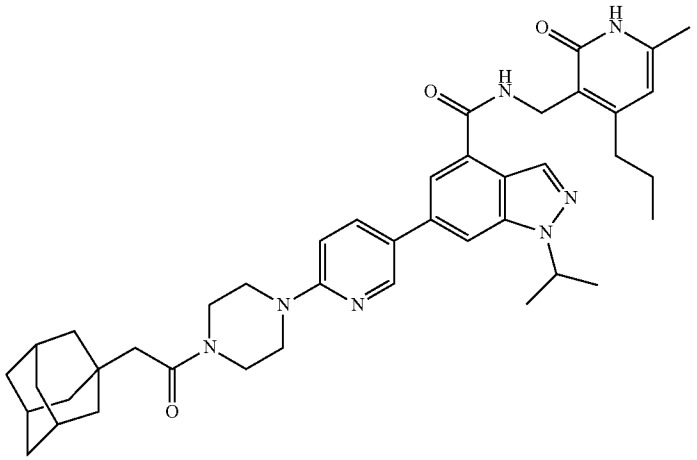
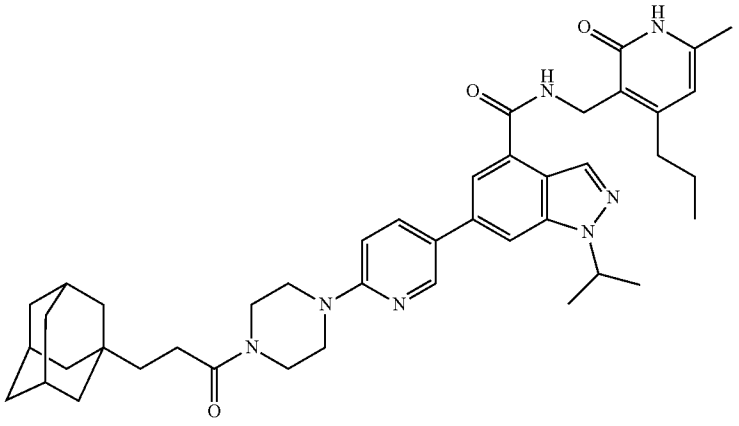
Cmpd #	Structure	GI_{50} (μM) MCF-7	GI_{50} (μM) MDA-MB-468	GI_{50} (μM) HCC1187	GI_{50} (μM) HCC1170
AM16-37A		N/A	N/A	2.1	N/A
AM16-38A		N/A	N/A	2.0	N/A

TABLE 2-continued

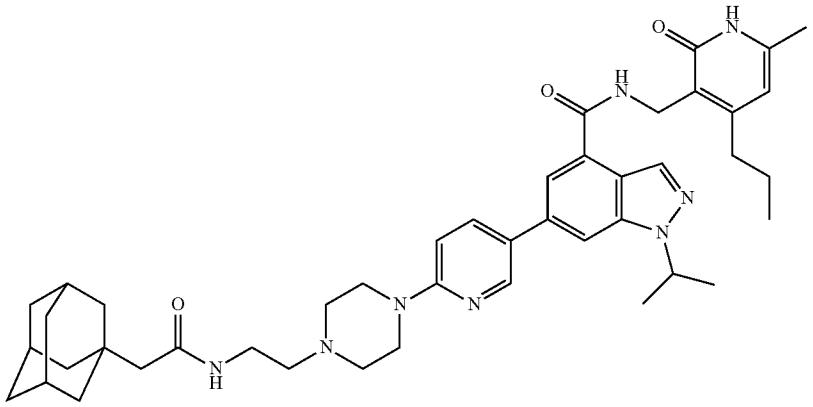
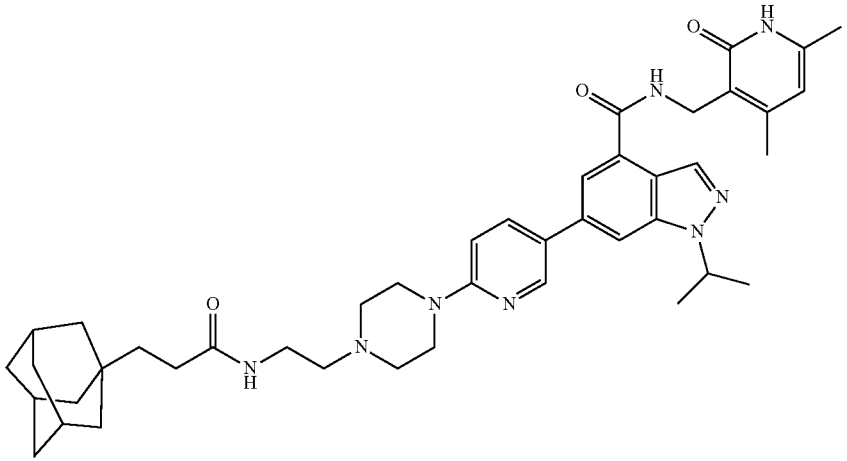
Cmpd #	Structure	GI_{50} (μM) MCF-7	GI_{50} (μM) MDA-MB-468	GI_{50} (μM) HCC1187	GI_{50} (μM) HCC1170
XY019-43		0.35	0.54	0.65	N/A
XY019-44		N/A	N/A	2.2	N/A

TABLE 2-continued

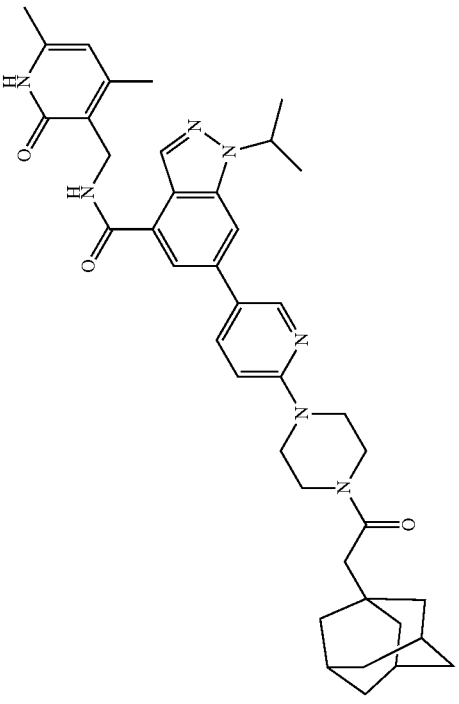
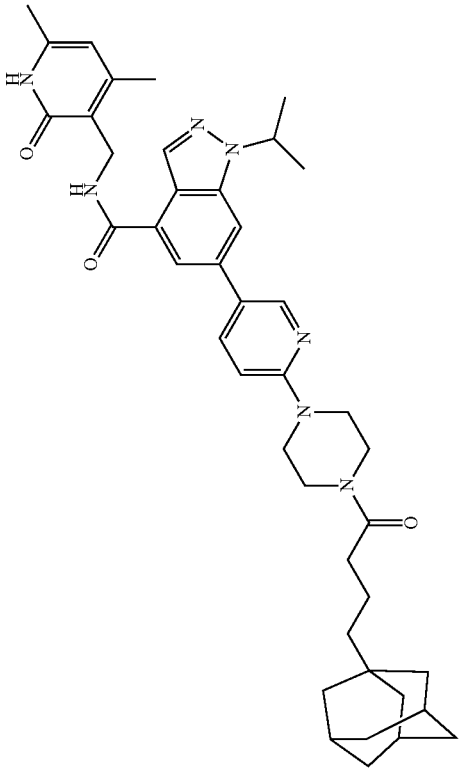
Cmpd #	Structure	GI_{50} (μM) MCF-7	GI_{50} (μM) MDA-MB-468	GI_{50} (μM) HCC1187	GI_{50} (μM) HCC1170
AM16-92A		1.0	N/A	1.1	N/A
AM16-93A		N/A	N/A	1.5	N/A

TABLE 2-continued

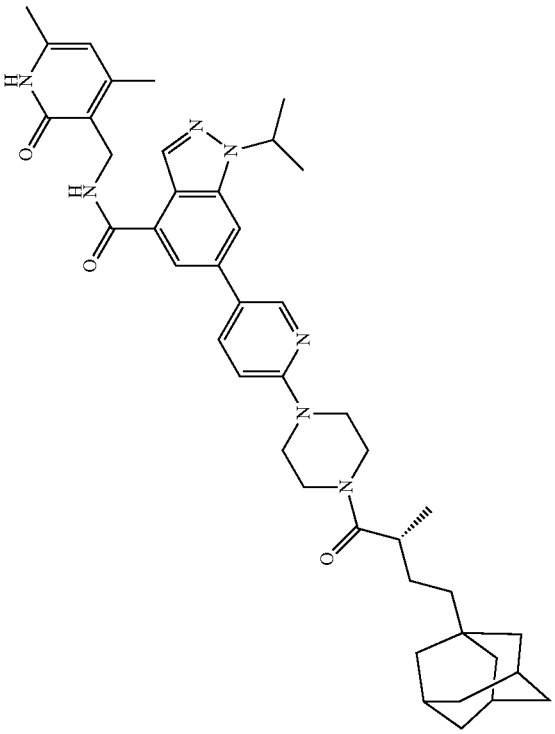
Cmpd #	Structure	GI_{50} (μM) MCF-7	GI_{50} (μM) MDA-MB-468	GI_{50} (μM) HCC1187	GI_{50} (μM) HCC1170
AM16-97A		N/A	N/A	1.2	N/A

TABLE 2-continued

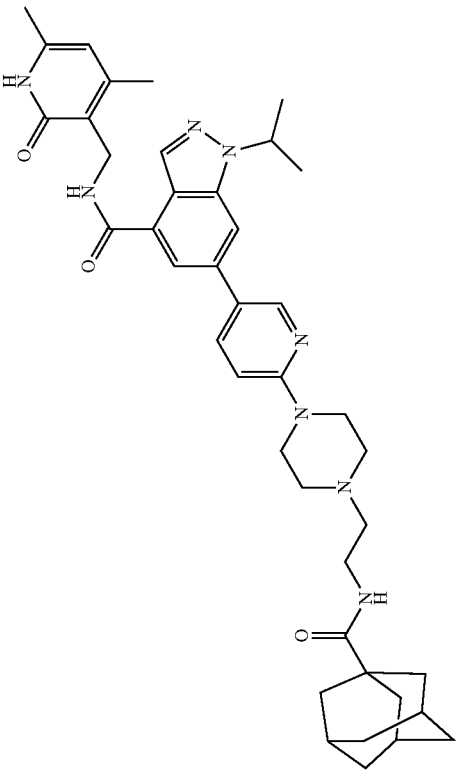
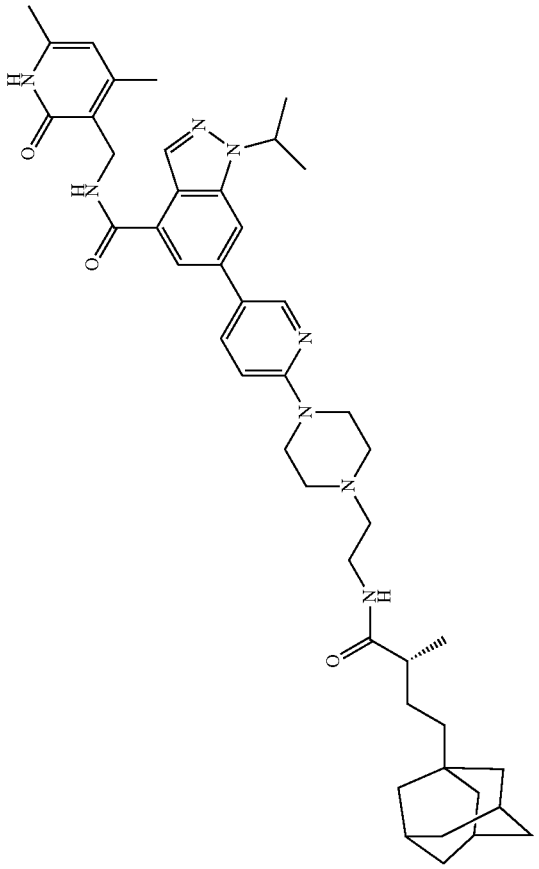
Cmpd #	Structure	GI_{50} (μM) MCF-7	GI_{50} (μM) MDA-MB-468	GI_{50} (μM) HCC1187	GI_{50} (μM) HCC1170
AM16-101A		0.69	1.1	N/A	N/A
AM16-105A		2.3	N/A	1.2	N/A

TABLE 2-continued

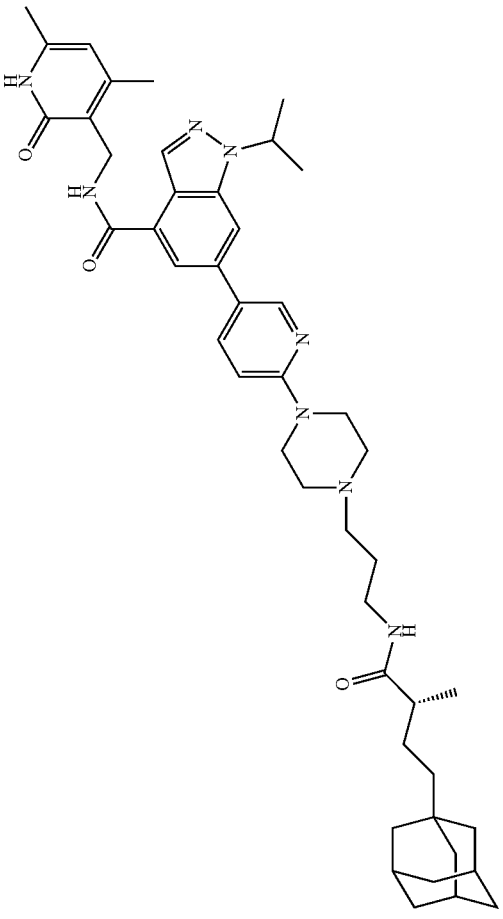
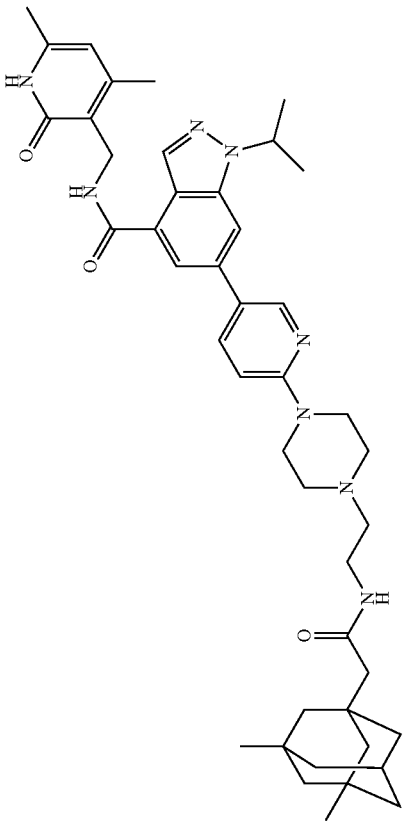
Cmpd #	Structure	GI_{50} (μM) MCF-7	GI_{50} (μM) MDA-MB-468	GI_{50} (μM) HCC1187	GI_{50} (μM) HCC1170
AM16-106A		N/A	N/A	4.3	N/A
AM29-21A		0.28	0.20	N/A	N/A

TABLE 2-continued

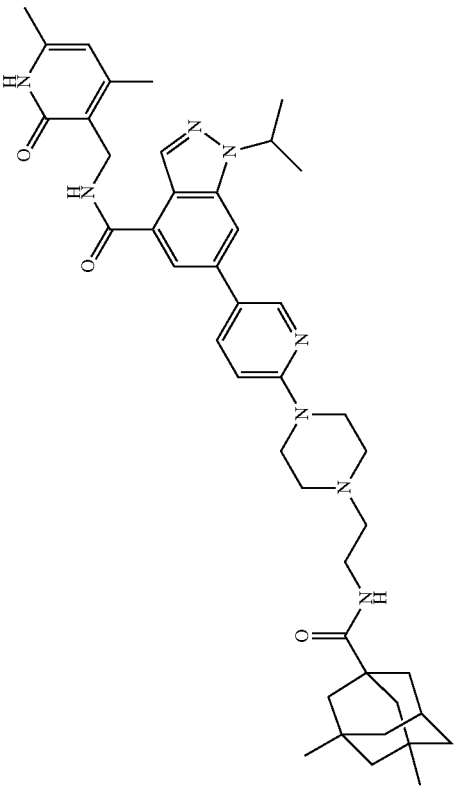
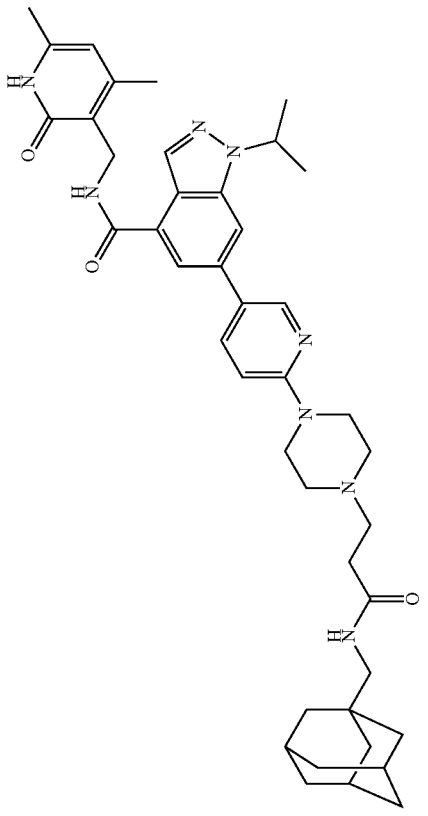
Cmpd #	Structure	GI_{50} (μM) MCF-7	GI_{50} (μM) MDA-MB-468	GI_{50} (μM) HCC1187	GI_{50} (μM) HCC1170
AM29-22A		0.69	0.87	N/A	N/A
AM29-33A		0.70	0.71	N/A	N/A

TABLE 2-continued

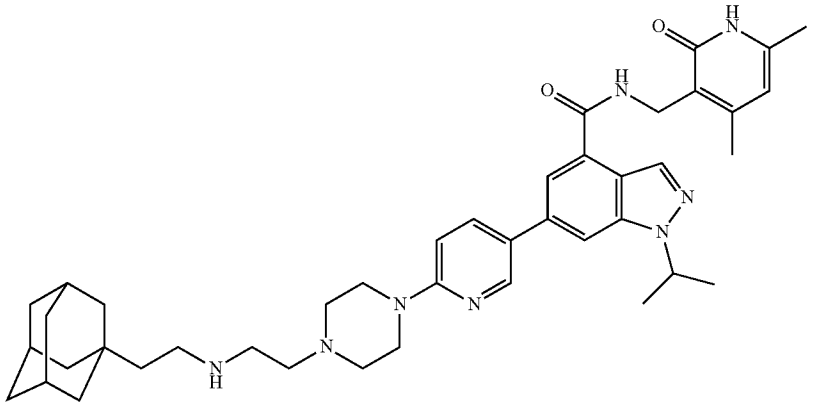
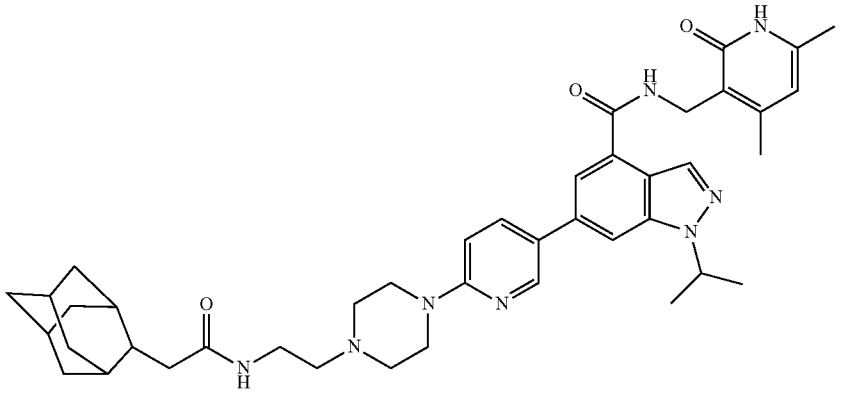
Cmpd #	Structure	GI_{50} (μM) MCF-7	GI_{50} (μM) MDA-MB-468	GI_{50} (μM) HCC1187	GI_{50} (μM) HCC1170
AM16-103A		N/A	1.2	N/A	N/A
AM29-182A		N/A	1.8	N/A	N/A

TABLE 2-continued

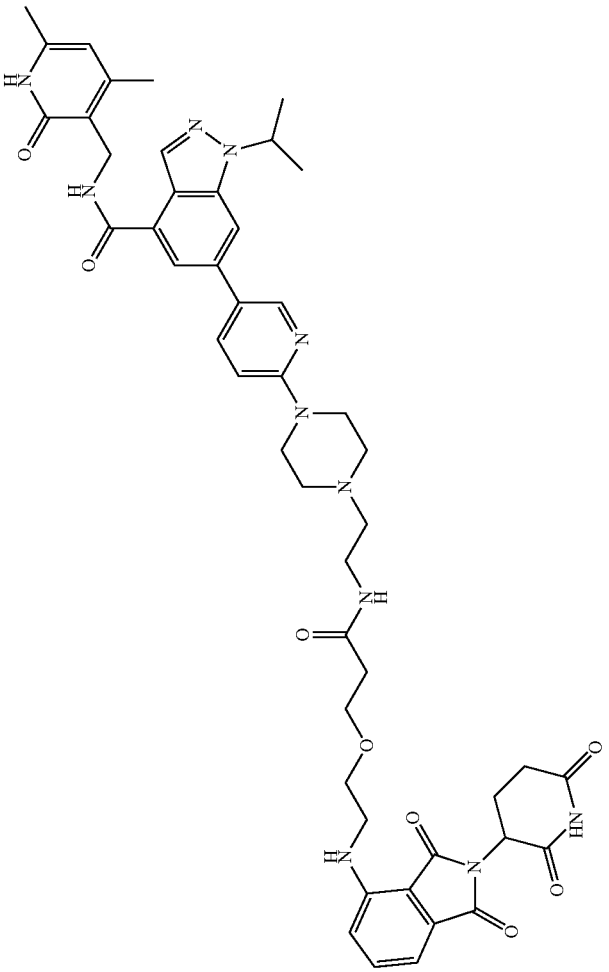
Cmpd #	Structure	GI_{50} (μM) MCF-7	GI_{50} (μM) MDA-MB-468	GI_{50} (μM) HCC1187	GI_{50} (μM) HCC1170
AM29-177A		N/A	2.5	N/A	N/A

TABLE 2-continued

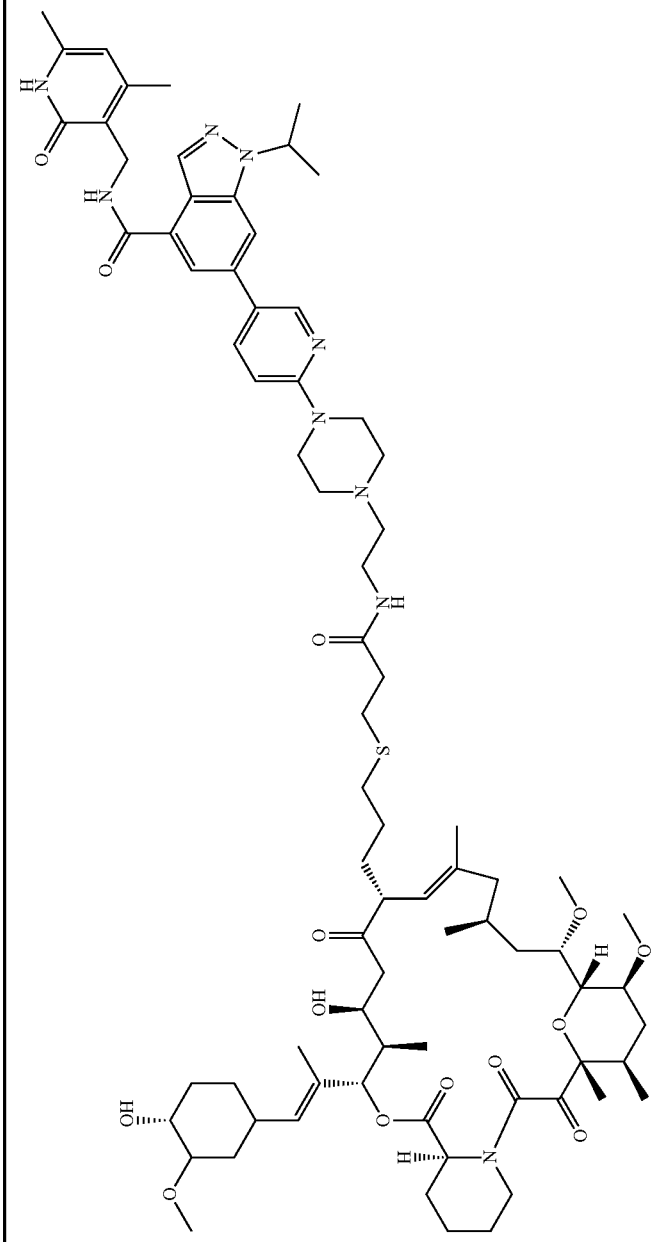
Cmpd #	Structure	GI_{50} (μM) MCF-7	GI_{50} (μM) MDA-MB-468	GI_{50} (μM) HCC1187	GI_{50} (μM) HCC1170
XY028-086		N/A	2.4	N/A	N/A

TABLE 2-continued

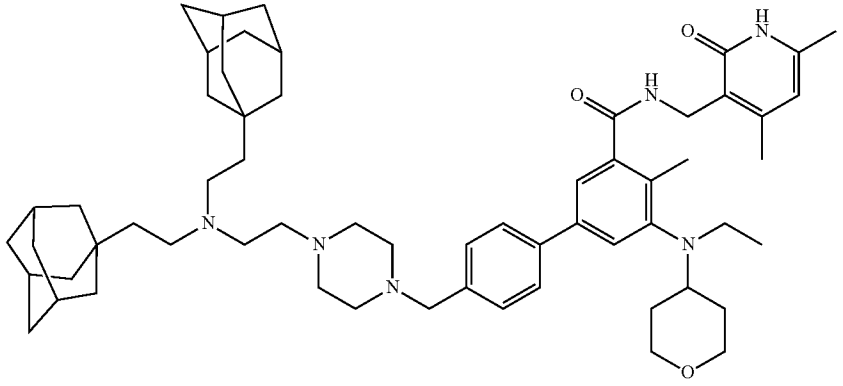
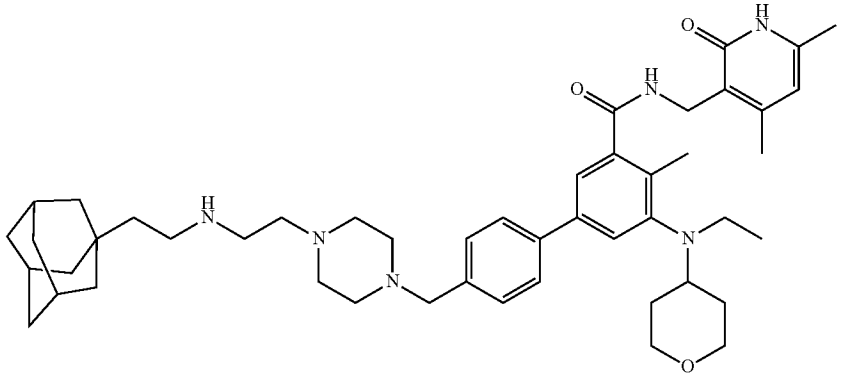
Cmpd #	Structure	GI_{50} (μM) MCF-7	GI_{50} (μM) MDA-MB-468	GI_{50} (μM) HCC1187	GI_{50} (μM) HCC1170
CZ40-75		N/A	1.1	N/A	N/A
CZ40-149		N/A	1.8	N/A	N/A

TABLE 2-continued

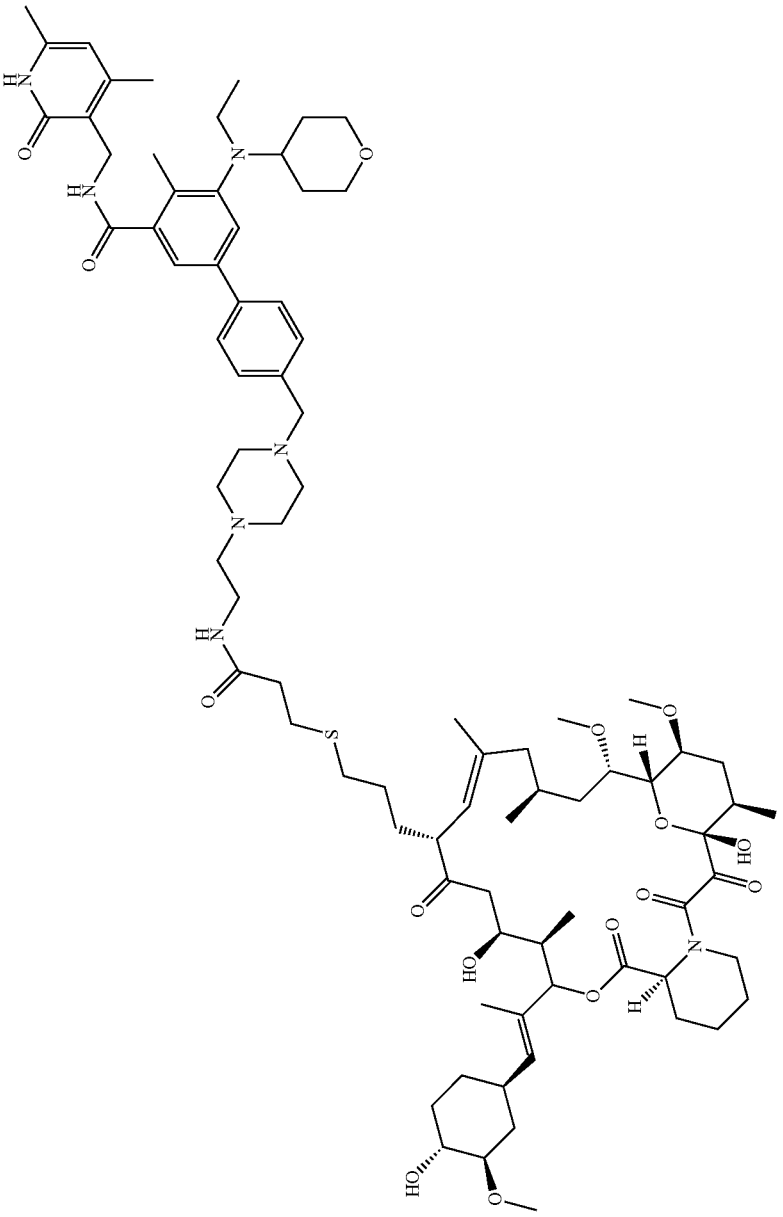
Cmpd #	Structure	GI_{50} (μM) MCF-7	GI_{50} (μM) MDA-MB-468	GI_{50} (μM) HCC1187	GI_{50} (μM) HCC1170
CZ40-131		N/A	1.5	N/A	N/A

TABLE 2-continued

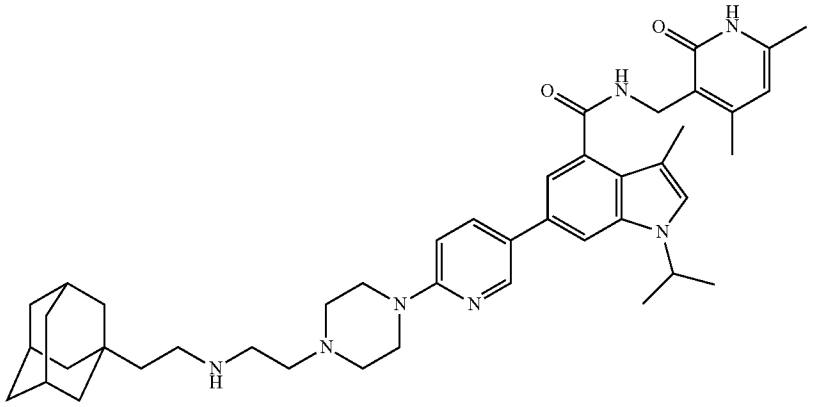
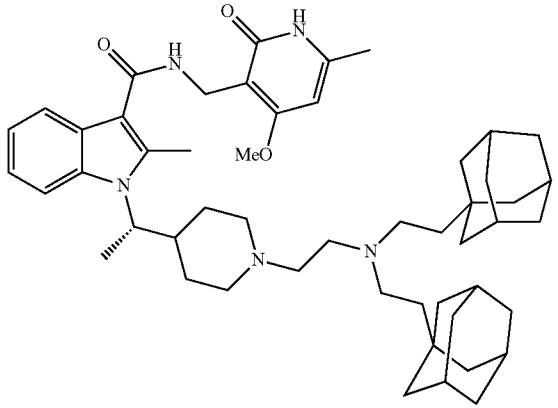
Cmpd #	Structure	GI_{50} (μM) MCF-7	GI_{50} (μM) MDA-MB-468	GI_{50} (μM) HCC1187	GI_{50} (μM) HCC1170
AM41-41A		N/A	2.3	N/A	N/A
XF042-95		N/A	2.5	N/A	N/A

TABLE 2-continued

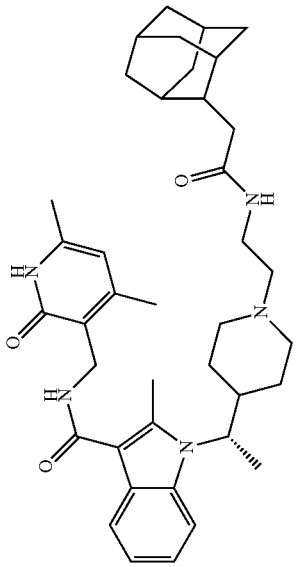
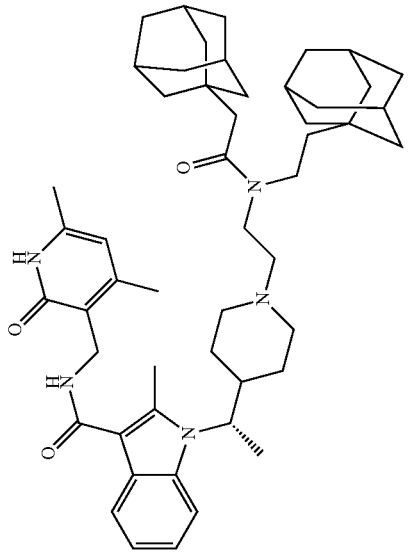
Cmpd #	Structure	GI_{50} (μM) MCF-7	GI_{50} (μM) MDA-MB-468	GI_{50} (μM) HCC1187	GI_{50} (μM) HCC1170
XF042-90		N/A	7.2	N/A	N/A
XF042-93		N/A	2.2	N/A	N/A

TABLE 2-continued

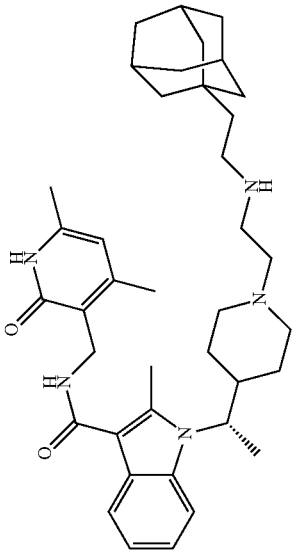
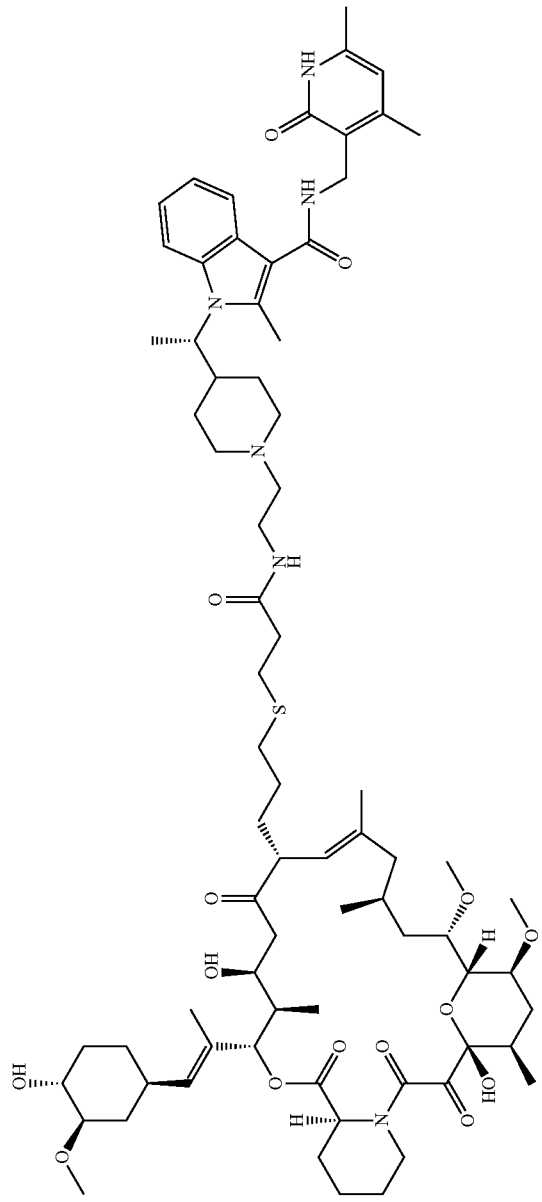
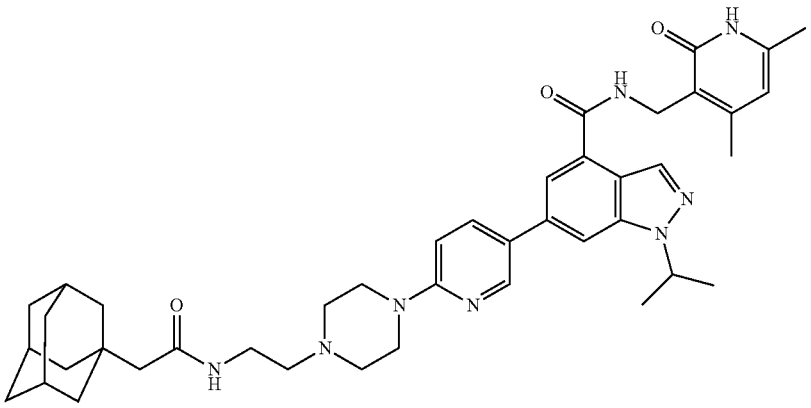
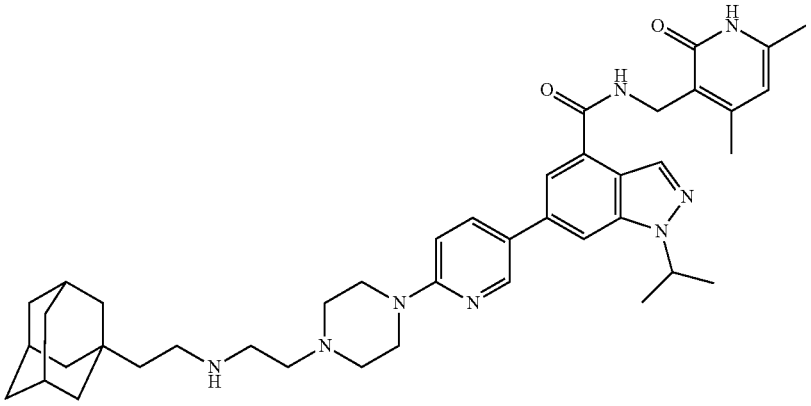
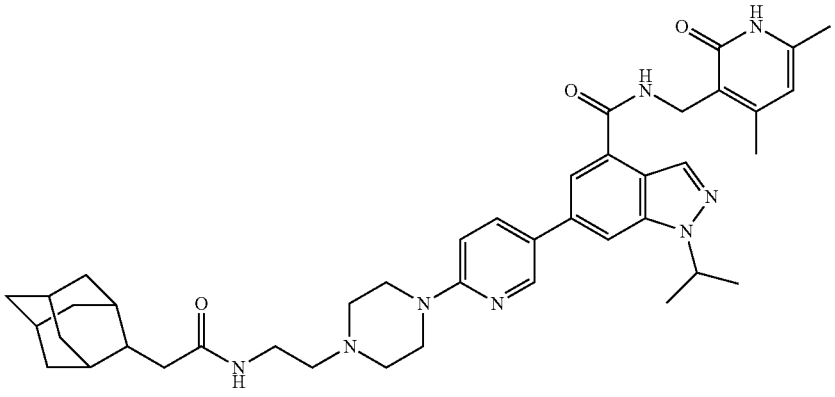
Cmpd #	Structure	GI_{50} (μM) MCF-7	GI_{50} (μM) MDA-MB-468	GI_{50} (μM) HCC1187	GI_{50} (μM) HCC1170
XF042-133		N/A	4.9	N/A	N/A
XF042-92		N/A	2.6	N/A	N/A

TABLE 3

Cmpd #	Structure	GI_{50} (μM) BT549	GI_{50} (μM) HCC1954
XY019-43		2.2	2.7
AM16-103A		1.4	2.1
AM29-182A		2.5	3.9

Example 114: Western Blot Assays

[0321] Approximately 1×10^4 cells were plated into 6-well plates and treated with compound at indicated concentration and for the indicated time. Protein lysates were prepared using Laemmli buffer and the concentration of protein lysates were determined using Bradford assay. An average of 10-20 μg of protein per sample were analyzed on a 4-20% tris-glycine polyacrylamide gel or a NuPAGE™ 4-12% Bis-Tris protein gel. EZH2 (Cell Signaling® #5246), H3K27me3 (Millipore™ #07-449), Vinculin (Sigma® #V9131), H3 (Cell Signaling® #4499S) or 1-actin (Sigma® #A4700) primary antibodies were used according to the manufacturer's instructions.

[0322] Cellular EZH2 and H3K27me3 levels in MCF-7 cells treated with XY019-43 or UNC1999 (negative control) at 1 μM are shown in FIG. **50**. Cellular EZH2 and H3K27me3 levels in MDA-MB-468 cells treated with XY019-43, AM19-182A, AM29-177, or UNC1999 (negative control) at various concentrations for various time points are shown in FIGS. **51-53**. In addition, cellular EZH2

and H3K27me3 levels in HCC1187 cells treated with 1 μM AM16-10A or UNC1999 (negative control) for various time points are shown in FIG. **54**.

Example 115: Biochemical Assays

[0323] Methyltransferase activity assays were performed by monitoring the incorporation of tritiumlabeled methyl group from S-adenosylmethionine (^{3}H-SAM) to biotinylated peptide substrates using Scintillation Proximity Assay (SPA) for EZH2/PRC2 5-component complex. Compounds were dissolved in DMSO to a stock concentration of 10 mM. Compounds were tested in a 10-dose IC_{50} mode with 3-fold serial dilution, in duplicate, at 10 μM. Reactions were carried out at 1 μM SAM and 5 μM Histone H3. Results for AM16-10A, XY019-43 and AM16-101A are shown in FIGS. **55-57**.

Other Embodiments

[0324] It is to be understood that while the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

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What is claimed is:

1. A bivalent compound comprising an enhancer of zeste homologue 2 (EZH2) ligand conjugated to a degradation/disruption tag.

2. The bivalent compound of claim **1**, wherein the EZH2 ligand is an EZH2 inhibitor.

3. The bivalent compound of claim **2**, wherein the EZH2 ligand is selected from the group consisting of UNC1999, EPZ005687, EPZ-6438, GSK126, EI1, CPI-1205, GSK343, CPI-360, EPZ011989, compound 24, compound 3, compound 31, ZLD1039, PF-06821497, JQEZ5, and analogs thereof.

4. The bivalent compound of any one of claims **1** to **3**, wherein the degradation/disruption tag is selected from the group consisting of adamantane, 1-((4,4,5,5,5-pentafluoropentyl)sulfinyl)nonane, pomalidomide, thalidomide, lenalidomide, VHL-1, and analogs thereof.

5. The bivalent compound of any one of claims **1** to **4**, wherein the degradation/disruption tag binds to a ubiquitin ligase or mimics EZH2 protein misfolding.

6. The bivalent compound of claim **5**, wherein the ubiquitin ligase is an E3 ligase.

7. The bivalent compound of claim **6**, wherein the E3 ligase is selected from the group consisting of cereblon E3 ligase and VHL E3 ligase.

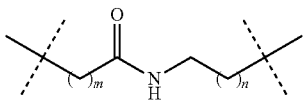
8. The bivalent compound of claim **5**, wherein the degradation/disruption tag that mimics EZH2 protein misfolding comprises a hydrophobic group.

9. The bivalent compound of any one of claims **1**-**8**, wherein the EZH2 ligand is conjugated to the degradation/disruption tag through a linker.

10. The bivalent compound of claim **9**, wherein the linker comprises an acyclic or cyclic saturated or unsaturated carbon, ethylene glycol, amide, amino, ether, or carbonyl containing group.

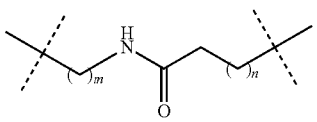
11. The bivalent compound of claim **9** or **10**, wherein the linker is selected from the group consisting of:

Formula I



m = 0-15
n = 0-15

Formula II



m = 0-15
n = 0-15

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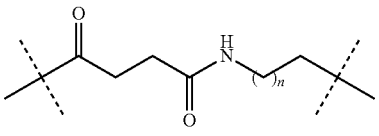
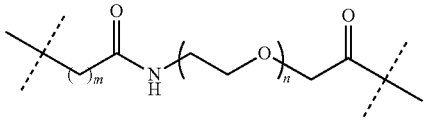
Formula III



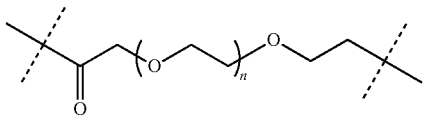
n = 0-15

Formula IV



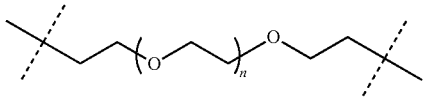
m = 0-15
n = 0-15

Formula V



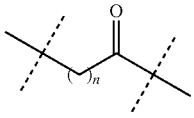
n = 0-15

Formula VI



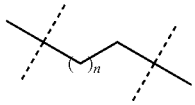
n = 0-15

Formula VII



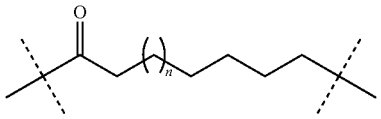
n = 0-15

Formula VIII



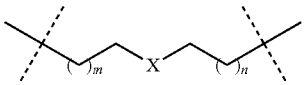
n = 0-15

Formula IX



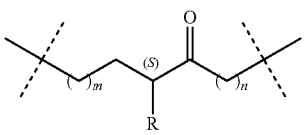
n= 0-15

Formula X



X = O, NR
R = H, C_{1-6}alkyl
m = 0-15
n = 0-15

Formula XI



(S)

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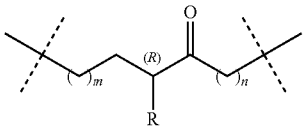
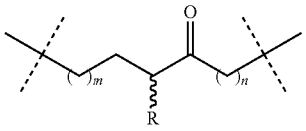
Formula XI



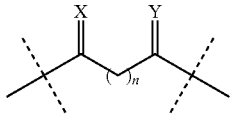
(R)

Formula XI



R = H, C_{1-6}alkyl
m = 0-15
n = 0-15
Racemic

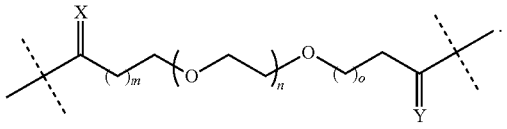
Formula XII



and

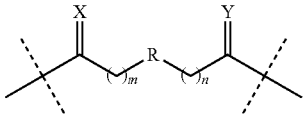
X = O or H_2
Y = O or H_2
n = 0-15

Formula XIII



X = O or H_2
Y = O or H_2
m = 0-15
n = 0-6
o = 0-15

12. The bivalent compound of claim **9** or **10**, wherein the linker is:

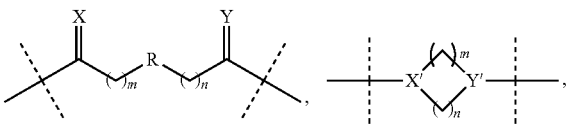


wherein R is independently —CH_2—; —CF_2—; —CH(C_{1-3} alkyl)-; —C(C_{1-3} alkyl)(C_{1-3} alkyl)-; —CH═CH—; —C(C_{1-3} alkyl)═C(C_{1-3} alkyl)-; —C≡C—; —O—; —NH—; —N(C_{1-3} alkyl)-; —C(O)NH—; —C(O)N(C_{1-3} alkyl)-; or a 3-13 membered ring, a fused ring, a bridged ring, or a spiro ring with or without one or more heteroatoms selected from the group consisting of —NH—, —N(C_{1-3} alkyl)-, and —O—;

X and Y are independently O or H_2; and

m and n are independently 0-15.

13. The bivalent compound of claim **12**, wherein R is selected from the group consisting of:



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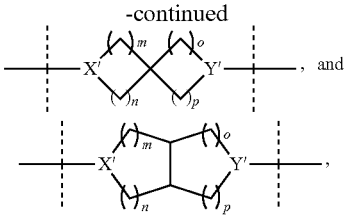
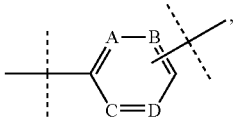
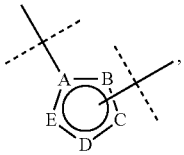


wherein X' and Y' are independently N or CH, and m, n, o, and p are independently 0-5;
or the group consisting of:



wherein A, B, C, and D are independently CH, C(C_{1-3} alkyl), or N, and



wherein A, B, C, D, and E are independently CH, C(C_{1-3} alkyl), N, NH, N(C_{1-3} alkyl), O, or S.

14. The bivalent compound of any of claims **1-13**, wherein the bivalent compound is selected from the group consisting of AM16-10A, AM16-11A, AM16-37A, AM16-38A, XY019-43, XY019-44, XY019-079, XY019-080, AM16-91A, AM16-92A, AM16-93A, AM16-97A, AM16-100A, AM16-101A, AM16-102A, AM16-105A, AM16-106A, XY012-120, AM29-21A, AM29-22A, AM29-32A, AM29-33A, AM16-103A, AM29-182A, AM29-55A, AM29-151A, AM29-152A, AM29-137A, AM29-153A, AM29-138A, AM29-154A, AM29-139A, AM29-155A, AM29-170A, AM29-156A, AM29-171A, AM29-157A, AM29-172A, AM29-173A, AM16-79A, AM29-177A, AM29-141A, AM29-178A, AM29-142A, AM29-179A, AM29-143A, AM29-180A, AM29-144A, AM29-145A, AM29-181A, AM41-16A, AM41-17A, AM41-18A, XY012-157, XF034-164A, XF034-165A, XF034-166A, XF034-167A, XF034-168A, XY019-041, XF034-169A, XF034-170A, XF034-171A, CZ40-10, CZ40-09, CZ40-11, XY019-077, XY019-083, XY019-084, XF034-172A, XF034-173A, XF034-174A, XF034-175A, XF034-176A, XF034-177A, YS36-48, YS36-49, YS36-50, YS36-51, YS36-52, YS36-53, YS36-54, YS36-55, YS36-56, YS36-57, YS36-58, YS36-59, XY028-086, CZ40-72, CZ40-73, CZ40-75, CZ40-149, CZ40-74, CZ40-131, AM41-36A, AM41-37A, AM41-39A, AM41-41A, AM41-38A, AM41-40A, XF042-84, XF042-85, XF042-95, XF042-132, XF042-86, XF042-94, XF042-89, XF042-90, XF042-93, XF042-133, XF042-91, and XF042-92.

15. A bivalent compound selected from the group consisting of AM16-10A, AM16-11A, AM16-37A, AM16-38A, XY019-43, XY019-44, XY019-079, XY019-080, AM16-91A, AM16-92A, AM16-93A, AM16-97A, AM16-100A, AM16-101A, AM16-102A, AM16-105A, AM16-106A, XY012-120, AM29-21A, AM29-22A, AM29-32A, AM29-33A, AM16-103A, AM29-182A, AM29-55A, AM29-151A, AM29-152A, AM29-137A, AM29-153A, AM29-138A, AM29-154A, AM29-139A, AM29-155A, AM29-170A, AM29-156A, AM29-171A, AM29-157A, AM29-172A, AM29-173A, AM16-79A, AM29-177A, AM29-141A, AM29-178A, AM29-142A, AM29-179A, AM29-143A, AM29-180A, AM29-144A, AM29-145A, AM29-181A, AM41-16A, AM41-17A, AM41-18A, XY012-157, XF034-164A, XF034-165A, XF034-166A, XF034-167A, XF034-168A, XY019-041, XF034-169A, XF034-170A, XF034-171A, CZ40-10, CZ40-09, CZ40-11, XY019-077, XY019-083, XY019-084, XF034-172A, XF034-173A, XF034-174A, XF034-175A, XF034-176A, XF034-177A, YS36-48, YS36-49, YS36-50, YS36-51, YS36-52, YS36-53, YS36-54, YS36-55, YS36-56, YS36-57, YS36-58, YS36-59, XY028-086, CZ40-72, CZ40-73, CZ40-75, CZ40-149, CZ40-74, CZ40-131, AM41-36A, AM41-37A, AM41-39A, AM41-41A, AM41-38A, AM41-40A, XF042-84, XF042-85, XF042-95, XF042-132, XF042-86, XF042-94, XF042-89, XF042-90, XF042-93, XF042-133, XF042-91, and XF042-92.

16. A method of treating an enhancer of zeste homologue 2 (EZH2)-mediated cancer, comprising administering to a subject in a subject in need thereof with an EZH2-mediated cancer a bivalent compound comprising an enhancer of zeste homologue 2 (EZH2) ligand conjugated to a degradation/disruption tag.

17. The method of claim **16**, wherein the EZH2-mediated cancer overexpresses EZH2 relative to a wild-type tissue of the same species and tissue type.

18. The method of claim **16** or **17**, wherein the EZH2-mediated cancer comprises hyper-trimethylated H3K27.

19. The method of any of claims **16-18**, wherein the at least one bivalent compound is selected from the group consisting of AM16-10A, AM16-11A, AM16-37A, AM16-38A, XY019-43, XY019-44, XY019-079, XY019-080, AM16-91A, AM16-92A, AM16-93A, AM16-97A, AM16-100A, AM16-101A, AM16-102A, AM16-105A, AM16-106A, XY012-120, AM29-21A, AM29-22A, AM29-32A, AM29-33A, AM16-103A, AM29-182A, AM29-55A, AM29-151A, AM29-152A, AM29-137A, AM29-153A, AM29-138A, AM29-154A, AM29-139A, AM29-155A, AM29-170A, AM29-156A, AM29-171A, AM29-157A, AM29-172A, AM29-173A, AM16-79A, AM29-177A, AM29-141A, AM29-178A, AM29-142A, AM29-179A, AM29-143A, AM29-180A, AM29-144A, AM29-145A, AM29-181A, AM41-16A, AM41-17A, AM41-18A, XY012-157, XF034-164A, XF034-165A, XF034-166A, XF034-167A, XF034-168A, XY019-041, XF034-169A, XF034-170A, XF034-171A, CZ40-10, CZ40-09, CZ40-11, XY019-077, XY019-083, XY019-084, XF034-172A, XF034-173A, XF034-174A, XF034-175A, XF034-176A, XF034-177A, YS36-48, YS36-49, YS36-50, YS36-51, YS36-52, YS36-53, YS36-54, YS36-55, YS36-56, YS36-57, YS36-58, YS36-59, XY028-086, CZ40-72, CZ40-73, CZ40-75, CZ40-149, CZ40-74, CZ40-131, AM41-36A, AM41-37A, AM41-39A, AM41-41A, AM41-38A, AM41-40A, XF042-84, XF042-85, XF042-95, XF042-132, XF042-86, XF042-94, XF042-89, XF042-90, XF042-93, XF042-133, XF042-91, and XF042-92.

20. The method of any of claims **16-19**, wherein the at least one bivalent compound is administered orally, parenterally, intradermally, subcutaneously, topically, or rectally.

21. The method of any of claims **16-20**, further comprising treating the subject with one or more additional therapeutic regimens for treating cancer.

22. The method of claim **21**, wherein the one or more additional therapeutic regimens are selected from the group consisting of surgery, chemotherapy, radiation therapy, hormone therapy, and immunotherapy.

23. The method of any of claims **16-22**, wherein the EZH2-mediated cancer is selected from the group consisting of breast cancer, glioblastoma, prostate cancer, uterine cancer, ovarian cancer, pancreatic cancer, melanoma, renal cell carcinoma, bladder cancer, colorectal cancer, lymphoma, leukemia, malignant rhabdoid tumor, and oropharyngeal cancer.

24. The method of claim **23**, wherein the breast cancer is triple-negative breast cancer (TNBC).

25. The method of any of claims **16-24**, wherein the EZH2-mediated cancer is a relapsed cancer.

26. The method of any of claims **16-25**, wherein the EZH2-mediated cancer was refractory to one or more previous treatments.

27. A method for identifying a bivalent compound which mediates degradation/disruption of EZH2, the method comprising:

providing a bivalent test compound comprising an EZH2 ligand conjugated to a degradation/disruption tag;

contacting the bivalent test compound with a cell comprising a ubiquitin ligase and EZH2;

determining whether EZH2 levels decrease in the cell; and

identifying the bivalent test compound as a bivalent compound which mediates reduction of EZH2 if EZH2 levels decrease in the cell.

28. The method of claim **27**, wherein the cell is a cancer cell.

29. The method of claim **28**, wherein the cancer cell is an EZH2-mediated cancer cell.

* * * * *