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(54) Titre : COMPOSES DE DEGRADATION/PERTURBATION DE LA PROTEINE TYROSINE KINASE 6 (PTK6) ET METHODES D'UTILISATION

(54) Title: PROTEIN TYROSINE KINASE 6 (PTK6) DEGRADATION / DISRUPTION COMPOUNDS AND METHODS OF USE

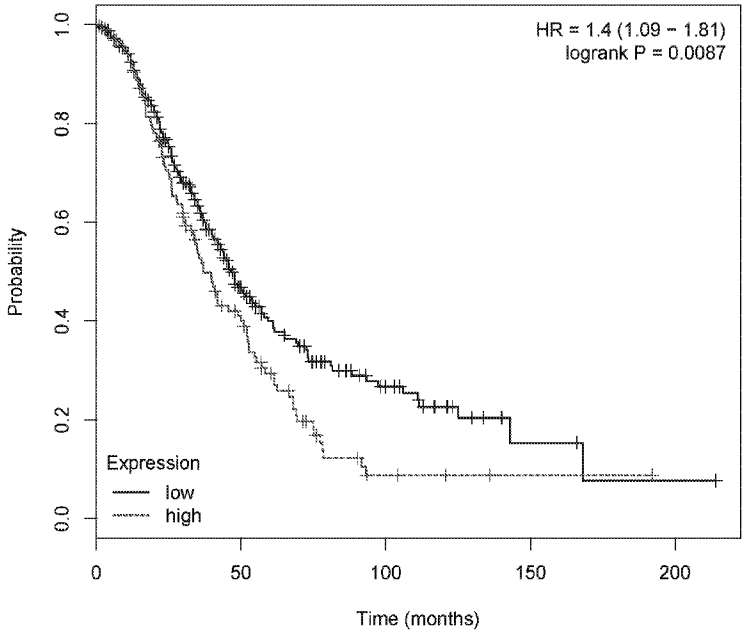

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FIG. 1

(57) Abrégé/Abstract:
Disclosed herein are protein tyrosine kinase 6 (PTK6) degradation / disruption compounds including a PTK6 ligand, a degradation / disruption tag, and a linker, and methods of using such compounds in the treatment of PTK6-mediated diseases.

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(54) Title: PROTEIN TYROSINE KINASE 6 (PTK6) DEGRADATION / DISRUPTION COMPOUNDS AND METHODS OF USE

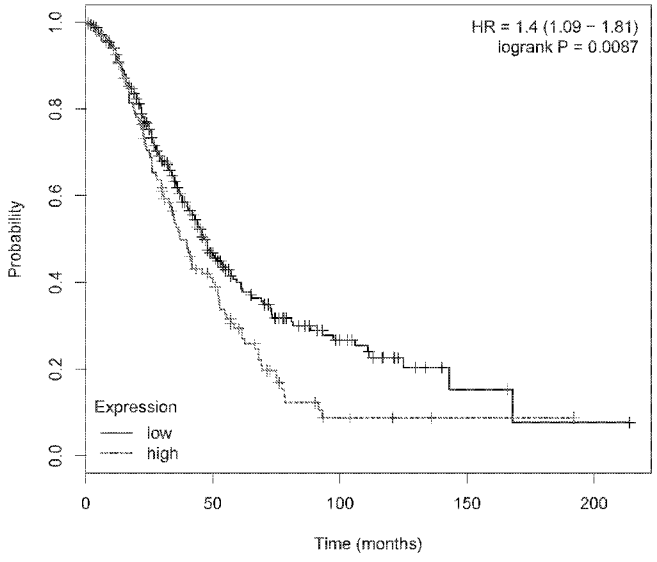

FIG. 1

(57) Abstract: Disclosed herein are protein tyrosine kinase 6 (PTK6) degradation / disruption compounds including a PTK6 ligand, a degradation / disruption tag, and a linker, and methods of using such compounds in the treatment of PTK6-mediated diseases.

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[Continued on next page]

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CECI EST LE TOME 1 DE 2
CONTENANT LES PAGES 1 À 227

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CONTAINING PAGES 1 TO 227

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PROTEIN TYROSINE KINASE 6 (PTK6) DEGRADATION / DISRUPTION COMPOUNDS AND METHODS OF USE

CROSS-REFERENCE TO RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application Serial No. 62/694,118, filed July 5, 2018. The entire contents of the foregoing are incorporated by reference.

TECHNICAL FIELD

This disclosure relates to bivalent compounds (e.g., bi-functional small molecule compounds) which degrade and/or disrupt the protein tyrosine kinase 6 (PTK6, also known as breast tumor kinase or Brk) compositions comprising one or more of the bivalent compounds, and to methods of use thereof for the treatment of PTK6-mediated disease in a subject in need thereof. The disclosure also relates to methods for designing such bivalent compounds.

BACKGROUND OF THE INVENTION

PTK6, a member of a distinct family of non-receptor tyrosine kinases distantly related to Src kinases, is expressed in breast cancers and multiple other cancer types (Brauer and Tyner, 2010; Derry et al., 2003; Mitchell et al., 1994; Ostrander et al., 2010; Schmandt et al., 2006). PTK6 promotes oncogenic phenotypes including enhanced proliferation, enhanced anoikis resistance, regulation of autophagy, epithelial-mesenchymal transition, and migration/invasion, via kinase activity-dependent and/or independent mechanisms (Brauer and Tyner, 2010; Castro and Lange, 2010; Harvey and Crompton, 2003; Harvey et al., 2009; Ito et al., 2016; Ostrander et al., 2010; Park et al., 2015; Zheng et al., 2013). Unlike the distantly related src kinases, PTK6 lacks a myristylation sequence. Therefore, PTK6 exhibits a broader range of cellular localization that could impact its activities; PTK6 protein has been detected in the nucleus, cytosol, and membranes of cells (Derry et al., 2003).

PTK6 has a role in multiple cancer types, including prostate, pancreatic, bladder, ovarian, liver and cervical cancers. Specifically, down regulation of PTK6 expression (via siRNA/shRNA) in pancreatic and liver cancer cells were reported to impair their viability (Chen et al., 2016; Ono

et al., 2014). In addition to its roles in cancer cell survival regulation, PTK6 promotes epithelial-mesenchymal transition (EMT), a developmental process often coopted by cancer cells to promote invasion/migration, chemotherapy resistance and metastases. We showed that PTK6 promotes EMT of triple negative breast cancer cells and enhances their capacity for invasion and metastases by regulating the stability of Snail, a transcription factor (Ito et al., 2016). shRNA-mediated downregulation of PTK6 expression inhibited 3D growth, migration and metastasis of triple negative breast cancer cells (Ito et al., 2016).

Reduction of PTK6 protein levels is unlikely to have major side effects on the host/patient. Genetically engineered PTK6 knockout mice are viable, reach maturity and reproduce normally. The only phenotype observed thus far is the hyperproliferation of cells in the small intestine, consistent with a role for PTK6 in enterocyte differentiation (Haegebarth et al., 2006). Crossing of these PTK6-/- mice with ErbB2 (Her2) transgenic mice that develop mammary gland tumors resulted in decreased lung metastases, again supporting a critical role for PTK6 protein in cancer metastases (Peng et al., 2015).

A few PTK6 inhibitors are known, including compound 21d (Zeng et al., 2011), compound 4f (Mahmoud et al., 2014), compound 1 (Yamamoto, 2016), XMU-MP-2 (Jiang et al., 2017), and compound 3s (Cardenas et al., 2018). Compound 21d was recently validated (Ito et al., 2017; Ito et al., 2016). Compound 21d treatment phenocopied the effects of PTK6 shRNA with respect to EMT regulation of TNBC cells. However, with respect to 3D growth, treatment with compound 21d did not consistently phenocopy the effects of shRNA for all cell lines evaluated. Indeed, kinase-independent oncogenic activities of PTK6 have been reported (Harvey and Crompton, 2003) and may account for these discrepancies and may limit the generalized utility of kinase inhibition as a therapeutic strategy. PTK6 degraders that reduce PTK6 protein levels would therefore more consistently phenocopy the effects of PTK6 knockdown via RNA interference and overcome kinase-independent activities of PTK6.

SUMMARY OF THE INVENTION

Unlike PTK6 inhibitors, which inhibit the kinase activity of PTK6, the PTK6 degradation / disruption compounds ("PTK6 degraders") disclosed herein bind and induce degradation of PTK6, thus eliminating any scaffolding functions of PTK6 in addition to the kinase activity of

PTK6. The PTK6 degraders disclosed herein are bivalent compounds, including a PTK6 ligand conjugated to a degradation / disruption tag via a linker.

The PTK6 degraders disclosed herein offer a novel mechanism for treating PTK6-mediated diseases. In particular, the present PTK6 degraders have the ability to target PTK6 for degradation, as opposed to merely inhibit the kinase activity of PTK6.

In an aspect, this disclosure provides a method of treating PTK6-mediated diseases, the method including administering one or more PTK6 degraders to a subject who has an PTK6-mediated disease, the PTK6 degraders being bivalent compounds including a PTK6 ligand conjugated to a degradation/disruption tag via a linker. The PTK6-mediated disease can be a disease resulting from PTK6 expression. The PTK6-mediated disease can have elevated PTK6 expression relative to a wild-type tissue of the same species and tissue type. Non-limiting examples of PTK6-mediated diseases include breast cancer, ovarian cancer, prostate cancer, colon cancer, pancreatic cancer, bladder cancer, liver cancer, and cervical cancer.

The PTK6-mediated cancer can include, e.g., a relapsed cancer. The PTK6-mediated cancer can, e.g., be refractory to one or more previous treatments.

The present disclosure relates generally to bivalent compounds (e.g., bi-functional small molecule compounds) which degrade and/or disrupt PTK6, and to methods for the treatment of PTK6-mediated cancer (i.e., a cancer which depends on PTK6 protein; or cancer having elevated levels of PTK6, or PTK6 activity relative to a wild-type tissue of the same species and tissue type). Because the PTK6 degraders/disruptors have dual functions (kinase-activity inhibition plus protein degradation/disruption), the bivalent compounds of the present disclosure can be significantly more effective therapeutic agents than current PTK6 inhibitors, which inhibit the kinase activity of PTK6, but do not affect PTK6 protein levels. The present disclosure further provides methods for identifying PTK6 degraders/disruptors as described herein.

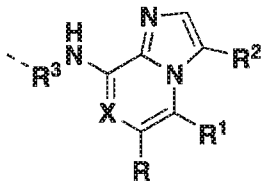
More specifically, the present disclosure provides a bivalent compound including an PTK6 ligand conjugated to a degradation/disruption tag via a linker.

In some aspects, the PTK6 degraders/disruptors have the form "**PI-Linker-EL**", as shown below:

wherein **PI** (a ligand for a "protein of interest," i.e., the protein to be degraded) comprises an PTK6 ligand (e.g., an PTK6 kinase inhibitor), and **EL** (e.g., a ligand for an E3 ligase) comprises a degradation/disruption tag (e.g., E3 ligase ligand). Exemplary PTK6 ligands (**PI**), exemplary degradation/disruption tags (**EL**), and exemplary linkers (**Linker**) are illustrated below:

PTK6 Ligands

PTK6 Ligands include but are not limited to:



FORMULA 1

Wherein

R is selected from H, halo, or unsubstituted or optionally substituted C_{1-8} alkyl, C_1-C_8 haloalkyl, C_1-C_8 hydroxyalkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} heterocyclyl, C_1-C_8 alkyleneOR^4, C_1-C_8 alkyleneSR^5, C_1-C_8 alkylene NR^{6}R^7, C_2-C_8 alkenyl, C_2-C_8 alkynyl, OR^4, SR^5, and NR^{6}R^7;

R^1 is selected from H, C_{1-8} alkyl, C_1-C_8 hydroxyalkyl, C_1-C_8 alkoxyalkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} heterocyclyl, OR^8, SR^9, and NR^{10}R^{11};

R^2 is selected from C_6-C_{10} aryl or C_5-C_{10} heteroaryl. R^2 is unsubstituted or optionally substituted with one or more of groups selected from halo, =O, =S, CN, NO_2, C_{1-8} alkyl, C_1-C_8 haloalkyl, C_1-C_8 hydroxyalkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} heterocyclyl, C_1-C_8 alkyleneOR^{12}, C_1-C_8 alkyleneSR^{13}, C_1-C_8 alkylene NR^{14}R^{15}, C_2-C_8 alkenyl, C_2-C_8 alkynyl, OR^{12}, SR^{13}, and NR^{14}R^{15};

R^3 is selected from C_6-C_{10} aryl or C_5-C_{10} heteroaryl. R^3 is unsubstituted or substituted with one or more of groups selected from C_1-C_8 alkyl, C_1-C_8 haloalkyl, C_1-C_8 hydroxyalkyl, C_1-C_8 alkoxyalkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} heterocyclyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, halo, CN, NO_2, =O, =S, R^{16}, OR^{16}, SR^{17}, SO_2R^{18}, NR^{19}R^{20}, C(O)R^{16}, C(O)OR^{16}, C(S)OR^{16}, C(O)NR^{19}R^{20},

C(S) $NR^{19}R^{20}$, $NR^{19}C(O)R^{16}$, $NR^{19}C(O)OR^{16}$, $NR^{19}S(O)R^{16}$, $NR^{19}S(O)OR^{16}$, $S(O)R^{16}$, $S(O)OR^{16}$, and $S(O)ONR^{19}R^{20}$;

R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} are independently selected from H, C_1-C_8 alkyl, C_1-C_8 haloalkyl, C_1-C_8 hydroxyalkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} heterocyclyl, $C(O)C_1$-C_8 alkyl, $C(O)C_1$-C_8 haloalkyl, $C(O)C_1$-C_8 hydroxyalkyl, $C(O)C_3$-C_{10} cycloalkyl, and $C(O)C_3$-C_{10} heterocyclyl, or
R^6 and R^7; R^{10} and R^{11}; R^{14} and R^{15} together with the nitrogen atom to which they connected can independently form 3-10 membered heterocyclyl rings;

R^{16}, R^{17}, and R^{18} are independently selected from H, C_1-C_8 alkyl, C_1-C_8 haloalkyl, C_1-C_8 alkoxyalkyl, C_1-C_8 hydroxyalkyl, C_3-C_8 cycloalkyl, C_3-C_7 heterocycloalkyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, $C(O)C_1$-C_8 alkyl, $C(O)C_1$-C_8 haloalkyl, $C(O)C_1$-C_8 hydroxyalkyl, $C(O)C_1$-C_8 alkoxyalkyl, $C(O)C_3$-C_{10} cycloalkyl, $C(O)C_3$-C_{10} heterocyclyl, $C(O)C_6$-C_{10} aryl, $C(O)C_5$-C_{10} heteroaryl, C_1-C_8 alkyleneC_3-C_{10} cycloalkyl, C_1-C_8 alkyleneC_3-C_{10} heterocycloalkyl, C_1-C_8 alkyleneC_6-C_{10} aryl, C_1-C_8 alkylene, and C_5-C_{10} heteroaryl;

R^{19} and R^{20} are independently selected from H, C_1-C_8 alkyl, C_1-C_8 haloalkyl, C_1-C_8 alkoxyalkyl, C_1-C_8 hydroxyalkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} heterocycloalkyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, $C(O)C_1$-C_8 alkyl, $C(O)C_1$-C_8 haloalkyl, $C(O)C_1$-C_8 hydroxyalkyl, $C(O)C_1$-C_8 alkoxyalkyl, $C(O)C_3$-C_{10} cycloalkyl, $C(O)C_3$-C_{10} heterocycloalkyl, $C(O)C_6$-C_{10} aryl, $C(O)C_5$-C_{10} heteroaryl, $C(O)OC_1$-C_8 alkyl, $C(O)OC_1$-C_8 haloalkyl, $C(O)OC_1$-C_8 hydroxyalkyl, $C(O)OC_1$-C_8 alkoxyalkyl, $C(O)OC_3$-C_{10} cycloalkyl, $C(O)OC_3$-C_{10} heterocyclyl, $C(O)OC_6$-C_{10} aryl, $C(O)OC_5$-C_{10} heteroaryl, $C(O)NC_1$-C_8 alkyl, $C(O)NC_1$-C_8 haloalkyl, $C(O)NC_1$-C_8 hydroxyalkyl, $C(O)NC_1$-C_8 alkoxyalkyl, $C(O)NC_3$-C_{10} cycloalkyl, $C(O)NC_3$-C_{10} heterocyclyl, $C(O)NC_6$-C_{10} aryl, $C(O)NC_5$-C_{10} heteroaryl, SO_2C_1-C_8 alkyl, SO_2C_1-C_8 haloalkyl, SO_2C_1-C_8 hydroxyalkyl, SO_2C_1-C_8 alkoxyalkyl, SO_2C_3-C_{10} cycloalkyl, SO_2C_3-C_{10} heterocyclyl, SO_2C_6-C_{10} aryl, SO_2C_5-C_{10} heteroaryl, C_1-C_8 alkyleneC_3-C_{10} cycloalkyl, C_1-C_8 alkyleneC_3-C_{10} heterocycloalkyl, C_1-C_8 alkyleneC_6-C_{10} aryl, C_1-C_8 alkyleneC_5-C_{10} heteroaryl, or
R^{19} and R^{20} together with the nitrogen atom to which they connected can independently form 3-10 membered heterocyclyl rings; and

X is selected from CH or N.

In some aspects of Formula 1, R is selected from H, halogen, optionally substituted C_{1-3} alkyl, and optionally substituted C_{1-3} alkoxy.

In some aspects of Formula 1, R is selected from H, F, CH_3, CH_2F, CHF_2, CF_3, CH_2CH_3, CH_2CF_3, i-Pr, c-Pr, OCH_3, OCH_2F, $OCHF_2$, OCF_3, OCH_2CH_3, OCH_2CF_3, Oi-Pr, and Oc-Pr.

In some aspects of Formula 1, R is selected from CH_3, CF_3, CH_2CH_3, CH_2CF_3, and c-Pr.

In some aspects of Formula 1, R is selected from CH_3, and c-Pr.

In some aspects of Formula 1, R is c-Pr.

In some aspects of Formula 1, R^1 is selected from H, halogen, optionally substituted C_{1-3} alkyl, and optionally substituted C_{1-3} alkoxy.

In some aspects of Formula 1, R^1 is selected from H, F, CH_3, CH_2F, CHF_2, CF_3, CH_2CH_3, CH_2CF_3, i-Pr, c-Pr, OCH_3, OCH_2F, $OCHF_2$, OCF_3, OCH_2CH_3, OCH_2CF_3, Oi-Pr, and Oc-Pr.

In some aspects of Formula 1, R^1 is selected from H, F, CH_3, and CF_3.

In some aspects of Formula 1, R^1 is H.

In some aspects of Formula 1, R^2 is selected from phenyl and 5-6 membered heteroaryl, which are optionally substituted with one or more of groups selected from halogen, optionally substituted C_{1-3} alkyl, and optionally substituted C_{1-3} alkoxy.

In some aspects of Formula 1, R^2 is 5-6 membered heteroaryl, which are optionally substituted with one or more of groups selected from halogen, optionally substituted C_{1-3} alkyl, and optionally substituted C_{1-3} alkoxy.

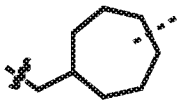
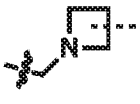
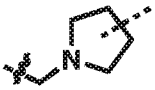
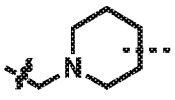
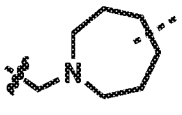
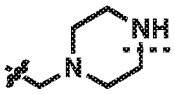
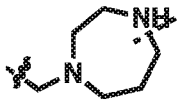
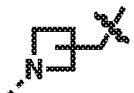
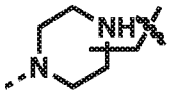
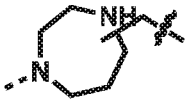
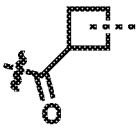
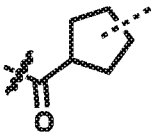
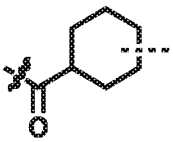
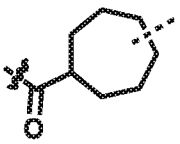
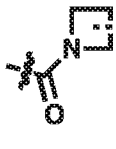
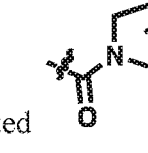
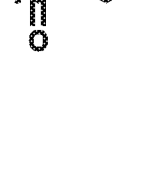
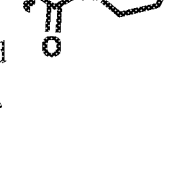
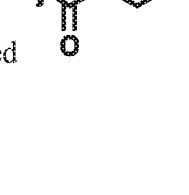
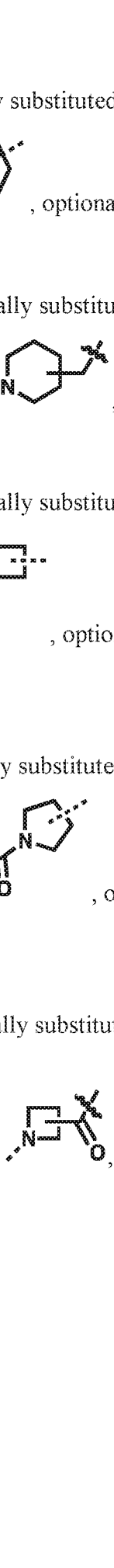
In some aspects of Formula 1, R^2 is selected from phenyl, , and .

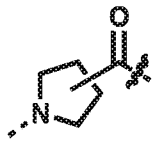
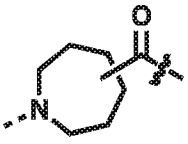
In some aspects of Formula 1, R^2 is .

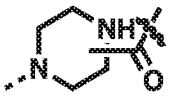
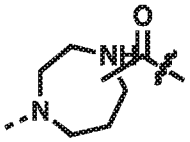
In some aspects of Formula 1, R^3 is selected from phenyl, and 5-6 membered heteroaryl, which are optionally substituted with one or more of groups selected from halogen, optionally

substituted C_{1-8} alkyl, and optionally substituted C_{1-8} alkoxy, optionally substituted C_{1-8} alkylene, optionally substituted 3-8 membered carbocyclyl, optionally substituted 4-8 membered heterocyclyl, optionally substituted aryl, optionally substituted 5-6 membered heteroaryl, -CO-, -C(O)-(C_{1-8} alkylene)-, -C(O)-NH(C_{1-8} alkylene)-, -C(O)-N(C_{1-8} alkylene)(C_{1-8} alkylene)-, -C(O)-(3-8 membered carbocyclyl)-, -C(O)-(4-8 membered heterocyclyl)-, -C(O)-(5-6 membered heteroaryl)-, -NH(C_{1-8} alkylene)-, -N(C_{1-8} alkylene)(C_{1-8} alkylene)-, - CH_2-(3-8 membered carbocyclyl)-, - CH_2-(4-8 membered heterocyclyl)-, and -CH_2-(5-6 membered heteroaryl)-.

In some aspects of Formula 1, R^3 is selected from phenyl, and 5-6 membered heteroaryl, which are optionally substituted with one or more of groups selected from F, Cl, CH_3, CF_3, OCH_3, OCF_3, CH_2CH_3, CH_2CF_3, OCH_2CH_3, OCH_2CF_3, i-Pr, c-Pr, i-PrO, c-PrO, -CO-, optionally substituted , optionally substituted , optionally substituted

 , optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted , optionally substituted , optionally substituted , optionally substituted  , optionally substituted  , optionally substituted , optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted , optionally substituted , optionally substituted , optionally substituted , optionally substituted , optionally substituted , optionally substituted  , optionally substituted

 , optionally substituted , optionally substituted  ,

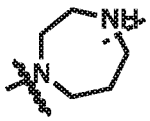
optionally substituted  , and optionally substituted  .

In some aspects of Formula 1, R^3 is selected from phenyl, thiophene, thiazole, isothiazole, pyrolyl, pyrazolyl, imidazolyl, pyridinyl, pyrimidinyl, and pyrazinyl, which are optionally substituted with one or more of groups selected from F, Cl, CH_3, CF_3, OCH_3, OCF_3, CH_2CH_3, CH_2CF_3, OCH_2CH_3, OCH_2CF_3, i-Pr, c-Pr, i-PrO, c-PrO, -CO-, optionally substituted ,

optionally substituted , optionally substituted , optionally substituted

, optionally substituted , optionally substituted , optionally

substituted , optionally substituted , optionally substituted ,

optionally substituted , optionally substituted  , optionally substituted

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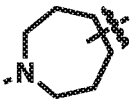
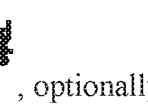
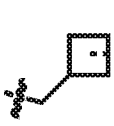
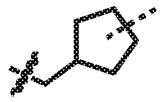
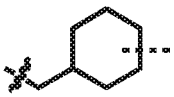
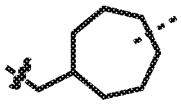
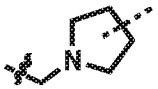
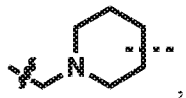
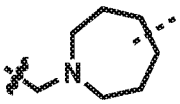
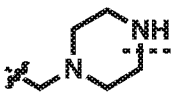
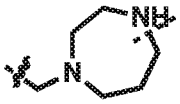
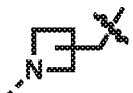
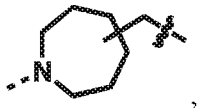
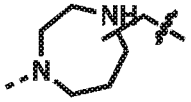
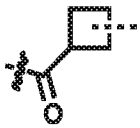
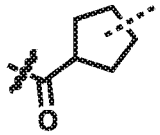
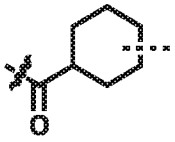
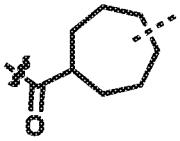
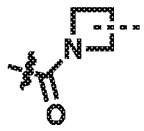
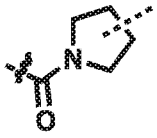
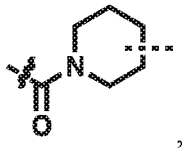
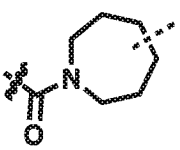
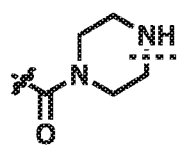
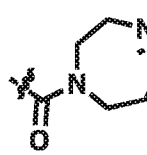
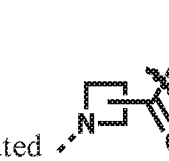
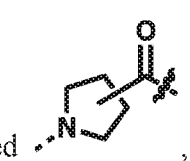
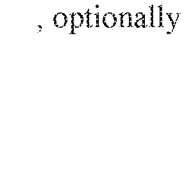
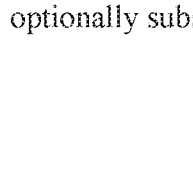
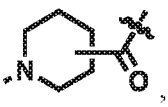
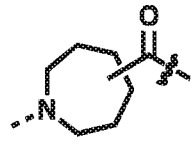
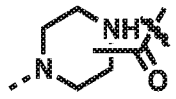
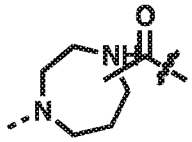
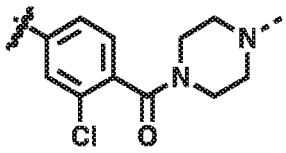
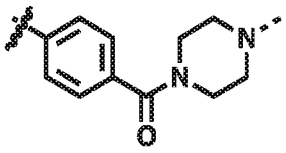
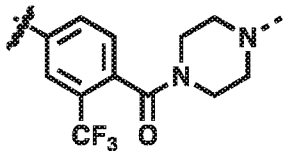
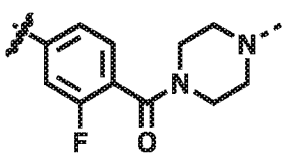
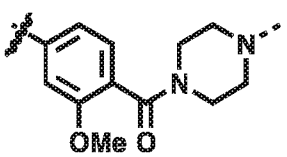
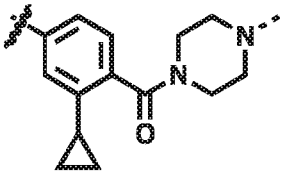
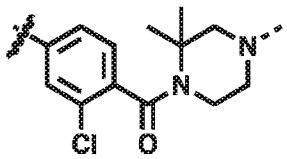
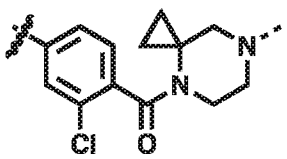
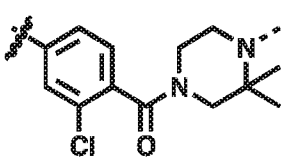
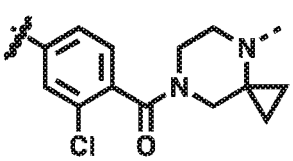
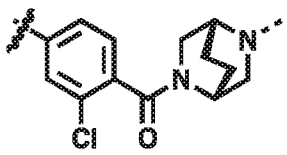
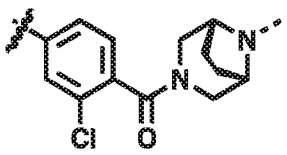
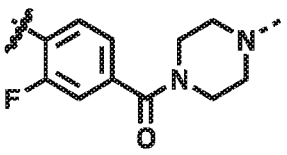
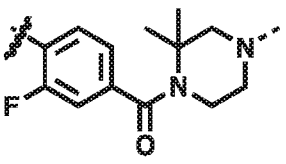
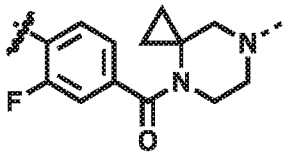
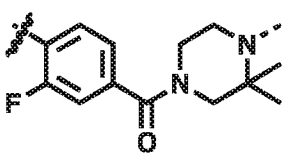
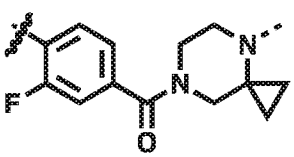
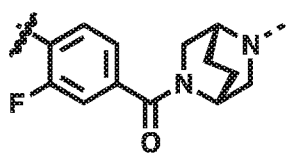
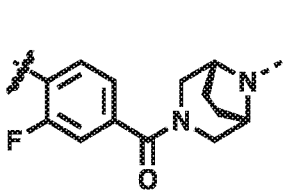
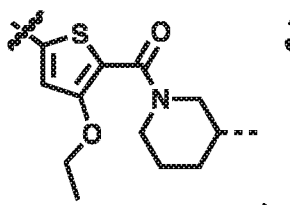
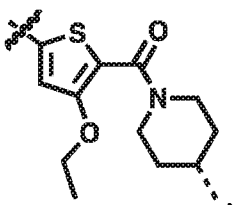
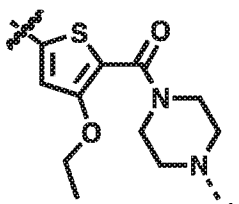
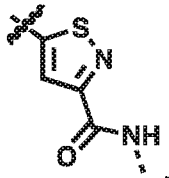
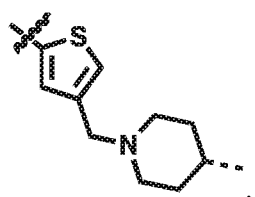
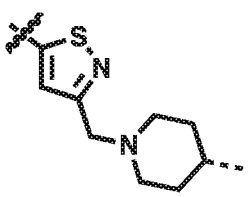
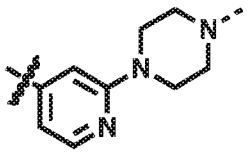
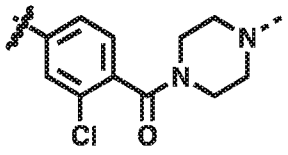
substituted  , optionally substituted  , optionally substituted ,

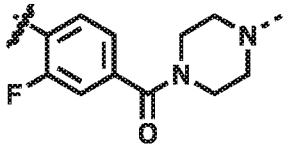
optionally substituted , optionally substituted  , optionally substituted

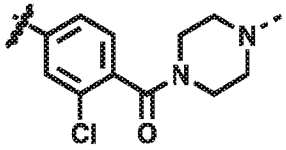
 , optionally substituted  , optionally substituted  ,
optionally substituted , optionally substituted  , optionally substituted
 , optionally substituted  , optionally substituted  ,
optionally substituted  , optionally substituted  , optionally substituted
, optionally substituted , optionally substituted  ,
optionally substituted , optionally substituted  , optionally substituted
, optionally substituted  , optionally substituted  , optionally
substituted  , optionally substituted  , optionally substituted
 , optionally substituted  , optionally substituted  , optionally
substituted  , optionally substituted  , optionally substituted
 , optionally substituted  , optionally substituted  , optionally
substituted  , optionally substituted  , optionally substituted
, optionally substituted , optionally substituted , optionally

substituted  , optionally substituted  , optionally substituted  , and optionally substituted  .

In some aspects of Formula 1, R^3 is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  .

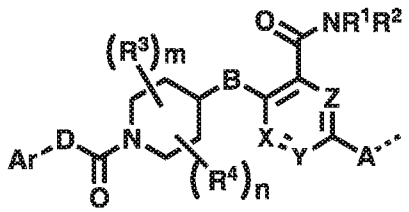
In some aspects of Formula 1, R^3 is selected from  , and



In some aspects of Formula 1, R^3 is  .

In some aspects of Formula 1, X is N.

PTK6 Ligands also include but are not limited to:



FORMULA 2

Wherein

X, Y and Z are independently selected from null, CR^5, and N, wherein

R^5 is selected from hydrogen, halogen, or optionally substituted C_{1-3} alkyl;

A is selected from null or $-R^6-R^7-$, wherein

R^6 and R^7 are independently selected from null, NR^8, O, S, C(O), $C(O)NR^8$, $NR^8C(O)$, $NR^8C(O)NR^9$, $OC(O)NR^9$, $NR^8C(O)O$, S(O), $S(O)NR^8$, $NR^8S(O)$, $NR^8S(O)NR^9$, $OS(O)NR^9$, $NR^8S(O)O$, $S(O)_2$, $S(O)_2NR^8$, $NR^8S(O)_2$, $NR^8S(O)_2NR^9$, $OS(O)_2NR^9$, $NR^8S(O)_2O$, optionally substituted C_1-C_8 alkylene, optionally substituted C_2-C_8 alkenylene, optionally substituted C_2-C_8 alkynylene, optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10

membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, wherein

R^8 and R^9 are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted 3-10 membered carbocyclylC_1-C_8alkyl, optionally substituted 4-10 membered heterocyclylC_1-C_8alkyl, optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^8 and R^9 together with the atom to which they are connected form a 4-20 membered heterocyclyl ring;

B and D are independently selected from $CR^{10}R^{11}$, NR^{10}, O, SO, or SO_2, wherein

R^{10} and R^{11} are independently selected from hydrogen, halogen, hydroxy, cyano, nitro, and optionally substituted C_1-C_3 alkyl, or

R^{10} and R^{11} together with the atom to which they are connected form a 3-6 membered carbocyclyl rings or 4-6 membered heterocyclyl ring;

R^1 and R^2 are independently selected from hydrogen, and optionally substituted C_1-C_3 alkyl, or R^1 and R^2 together with the atom to which they are connected form a 4-6 membered heterocyclyl ring;

R^3 and R^4, at each occurrence, are independently selected from hydrogen, fluoro, hydroxyl, cyano, amino, nitro, optionally substituted C_1-C_3 alkyl, optionally substituted C_1-C_3 alkoxy, and optionally substituted C_1-C_3 alkylamino.

m and n are independently selected from 0, 1, 2, 3, and 4.

Ar is selected from aryl, and heteroaryl, which are optionally substituted with one or more substituents independently selected from hydrogen, halogen, oxo, CN, NO_2, OR^{12}, SR^{12}, $NR^{12}R^{13}$, $OCOR^{12}$, OCO_2R^{12}, $OCON(R^{12})R^{13}$, COR^{12}, CO_2R^{12}, $CON(R^{12})R^{13}$, SOR^{12}, SO_2R^{12},

$SO_2N(R^{12})R^{13}$, $NR^{14}CO_2R^{12}$, $NR^{14}COR^{12}$, $NR^{14}C(O)N(R^{12})R^{13}$, $NR^{14}SOR^{12}$, $NR^{14}SO_2R^{12}$, $NR^{14}SO_2N(R^{12})R^{13}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted 4-10 membered heterocyclylC_1-C_8alkyl, optionally substituted 3-10 membered carbocyclylC_1-C_8alkyl, optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, wherein

R^{12}, R^{13}, and R^{14} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted 3-10 membered carbocyclylC_1-C_8alkyl, optionally substituted 4-10 membered heterocyclylC_1-C_8alkyl, optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^{12} and R^{13}, R^{12} and R^{14} together with the atom to which they are connected form a 4-20 membered heterocyclyl ring;

In some aspects of Formula 2, X, Y and Z are independently selected from CH, CF, and N.

In some aspects of Formula 2, X is N; Y and Z are independently selected from CH, CF, and N.

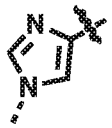
In some aspects of Formula 2, X is N; Y and Z are CH.

In some aspects of Formula 2, A is null or selected from optionally substituted 3-8 membered carbocyclyl, optionally substituted 4-8 membered heterocyclyl, optionally substituted 6 membered aryl, optionally substituted 5-6 membered heteroaryl, fused rings, bridged rings, and spiro rings.

In some aspects of Formula 2, A is null, phenyl, 4-8 membered heterocyclyl, and 5-6 membered heteroaryl, which are optionally substituted by F, OH, CN, NO_2, NH_2, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 alkoxy, optionally substituted 3-10

membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl.

In some aspects of Formula 2, A is null, phenyl, 4-8 membered heterocyclyl, and 5-6 membered heteroaryl, which are optionally substituted by F, OH, CN, NO_2, NH_2, CH_3, CF_3, i-Pr, and c-Pr.

In some aspects of Formula 2, A is  .

In some aspects of Formula 2, B and D are independently selected from CH_2, CHOH, $CHCH_3$, $C(CH_3)_2$, , CHF, CF_2, O, NH, and NCH_3.

In some aspects of Formula 2, B is O.

In some aspects of Formula 2, D is CH_2.

In some aspects of Formula 2, R^1 and R^2 are independently selected from H, and optionally substituted C_1-C_3 alkyl, with the proviso that at least one of R^1 and R^2 is H.

In some aspects of Formula 2, R^1 and R^2 are independently selected from H, and CH_3, with the proviso that at least one of R^1 and R^2 is H.

In some aspects of Formula 2, R^1 and R^2 are H.

In some aspects of Formula 2, R^3 and R^4, at each occurrence, are independently selected from H, F, OH, CN, NH_2, NO_2, CH_3, CH_2F, CHF_2, CF_3, i-Pr, and c-Pr.

In some aspects of Formula 2, R^3 and R^4, at each occurrence, are independently selected from H, and F.

In some aspects of Formula 2, m and n are independently selected from 0, 1, and 2.

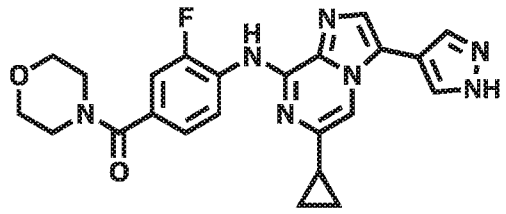
In some aspects of Formula 2, m and n are 1.

In some aspects of Formula 2, Ar is selected from aryl, and heteroaryl, which are optionally substituted with one or more substituents independently selected from H, F, =O, CN, NO_2, CH_3, OCH_3, CH_2F, CHF_2, CF_3, OCH_2F, $OCHF_2$, OCF_3, i-Pr, and c-Pr.

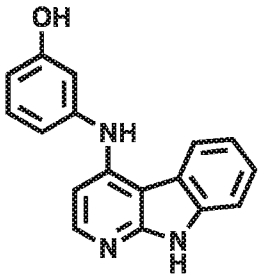
In some aspects of Formula 2, Ar is phenyl, which is optionally substituted with one or more substituents independently selected from H, F, =O, CN, NO_2, CH_3, OCH_3, CH_2F, CHF_2, CF_3, OCH_2F, $OCHF_2$, OCF_3, i-Pr, and c-Pr.

In some aspects of Formula 2, Ar is 4-OCF_3 substituted phenyl.

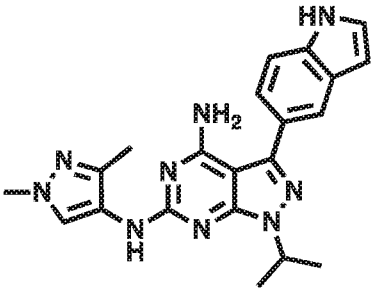
In some aspects, the PTK6 ligand may be a derivative of following compounds:



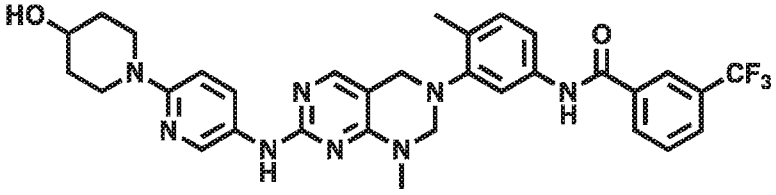
Compound 21d



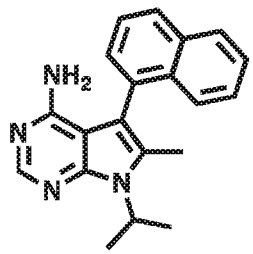
Compound 4f



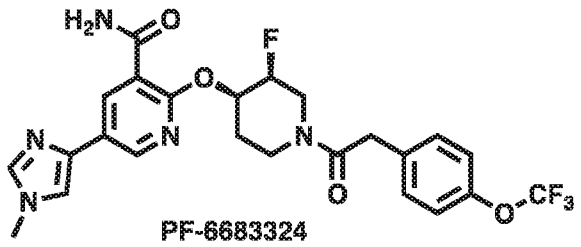
Compound 1



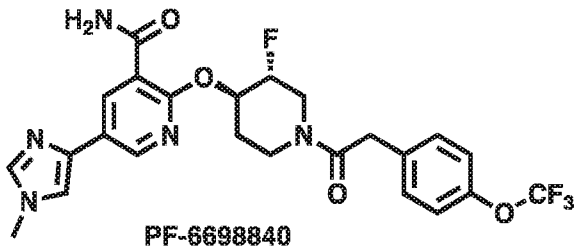
XMU-MP-2



Compound 3s

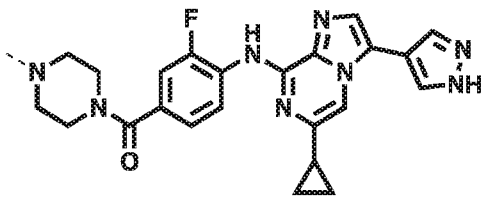


PF-6683324

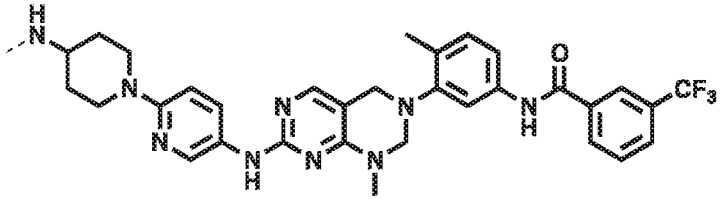


PF-6698840

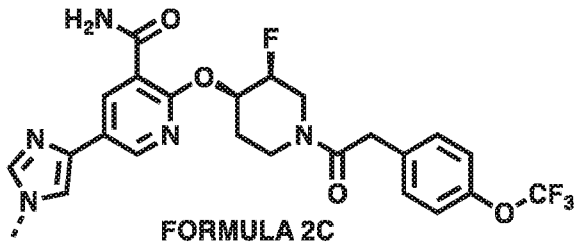
In some aspects, the PTK6 ligand can be, e.g.:



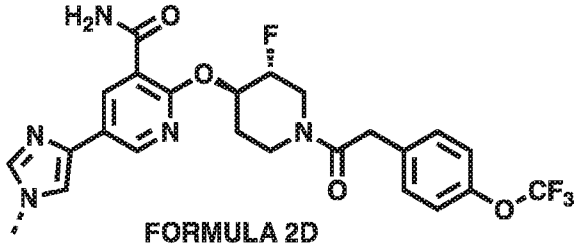
FORMULA 2A



FORMULA 2B



FORMULA 2C

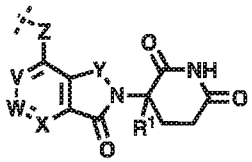


FORMULA 2D

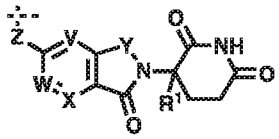
The PTK6 ligand can be bound to PTK6 and/or PTK6 mutant proteins.

Degradation / Disruption Tags

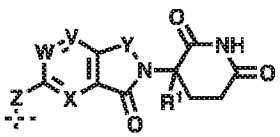
Degradation / Disruption Tags (**EL**) include but are not limited to:



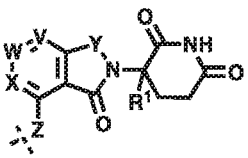
FORMULA 3A



FORMULA 3B



FORMULA 3C



FORMULA 3D,

wherein

V, W, and X are independently selected from CR^2 and N;

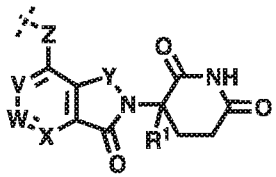
Y is selected from CO, CR^3R^4, and N=N;

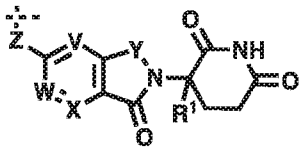
Z is selected from null, CO, CR^5R^6, NR^5, O, optionally substituted C_1-C_{10} alkylene, optionally substituted C_1-C_{10} alkenylene, optionally substituted C_1-C_{10} alkynylene, optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted C_3-C_{13} fused cycloalkyl, optionally substituted C_3-C_{13} fused heterocyclyl, optionally substituted C_3-C_{13} bridged cycloalkyl, optionally substituted C_3-C_{13} bridged heterocyclyl, optionally substituted C_3-C_{13} spiro cycloalkyl, optionally substituted C_3-C_{13} spiro heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl; preferly, Z is selected from null, CH_2, CH=CH, C≡C, NH and O;

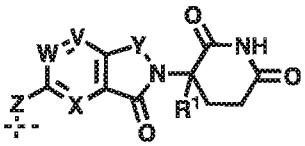
R^1, and R^2 are independently selected from hydrogen, halogen, cyano, nitro, optionally substituted C_1-C_6 alkyl, optionally substituted 3 to 6 membered carbocyclyl, and optionally substituted 4 to 6 membered heterocyclyl;

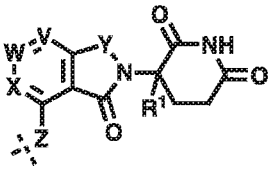
R^3, and R^4 are independently selected from hydrogen, halogen, cyano, nitro, optionally substituted C_1-C_6 alkyl, optionally substituted 3 to 6 membered carbocyclyl, and optionally substituted 4 to 6 membered heterocyclyl; or R^3 and R^4 together with the atom to which they are connected form a 3-6 membered carbocyclyl, or 4-6 membered heterocyclyl; and

R^5 and R^6 are independently selected from null, hydrogen, halogen, oxo, hydroxyl, amino, cyano, nitro, optionally substituted C_1-C_6 alkyl, optionally substituted 3 to 6 membered carbocyclyl, and optionally substituted 4 to 6 membered heterocyclyl; or R^5 and R^6 together with the atom to which they are connected form a 3-6 membered carbocyclyl, or 4-6 membered heterocyclyl.


FORMULA 3A


FORMULA 3B


FORMULA 3C


FORMULA 3D

wherein

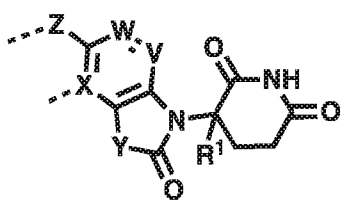
V, W, and X are independently CR^2 or N,

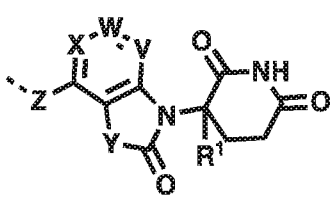
Y is CO or CH_2,

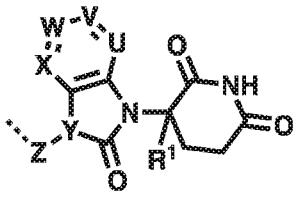
Z is CH_2, NH, or O,

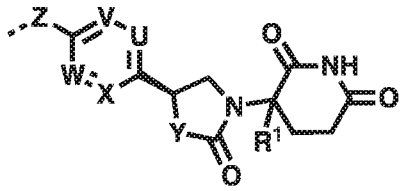
R^1 is hydrogen, methyl, or fluoro, and

R^2 is hydrogen, halogen, or C_1-C_5 alkyl;

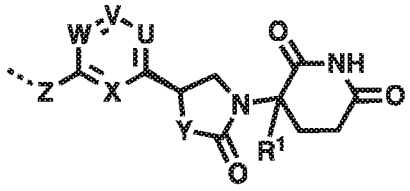

FORMULA 3E


FORMULA 3F


FORMULA 3G



FORMULA 3H



FORMULA 3I

wherein

U, V, W, and X are independently selected from CR^2 and N;

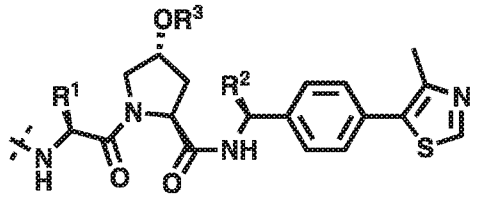
Y is selected from CR^3R^4, NR^3 and O; preferly, Y is selected from CH_2, NH, NCH_3 and O;

Z is selected from null, CO, CR^5R^6, NR^5, O, optionally substituted C_1-C_{10} alkylene, optionally substituted C_1-C_{10} alkenylene, optionally substituted C_1-C_{10} alkynylene, optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted C_3-C_{13} fused cycloalkyl, optionally substituted C_3-C_{13} fused heterocyclyl, optionally substituted C_3-C_{13} bridged cycloalkyl, optionally substituted C_3-C_{13} bridged heterocyclyl, optionally substituted C_3-C_{13} spiro cycloalkyl, optionally substituted C_3-C_{13} spiro heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl; preferly, Z is selected from null, CH_2, CH=CH, C≡C, NH and O;

R^1, and R^2 are independently selected from hydrogen, halogen, cyano, nitro, optionally substituted C_1-C_6 alkyl, optionally substituted 3 to 6 membered carbocyclyl, and optionally substituted 4 to 6 membered heterocyclyl;

R^3, and R^4 are independently selected from hydrogen, halogen, cyano, nitro, optionally substituted C_1-C_6 alkyl, optionally substituted 3 to 6 membered carbocyclyl, and optionally substituted 4 to 6 membered heterocyclyl; or R^3 and R^4 together with the atom to which they are connected form a 3-6 membered carbocyclyl, or 4-6 membered heterocyclyl; and

R^5 and R^6 are independently selected from null, hydrogen, halogen, oxo, hydroxyl, amino, cyano, nitro, optionally substituted C_1-C_6 alkyl, optionally substituted 3 to 6 membered carbocyclyl, and optionally substituted 4 to 6 membered heterocyclyl; or R^5 and R^6 together with the atom to which they are connected form a 3-6 membered carbocyclyl, or 4-6 membered heterocyclyl.

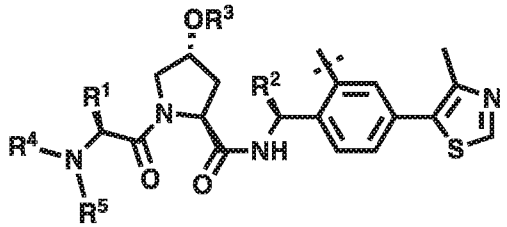


FORMULA 4A

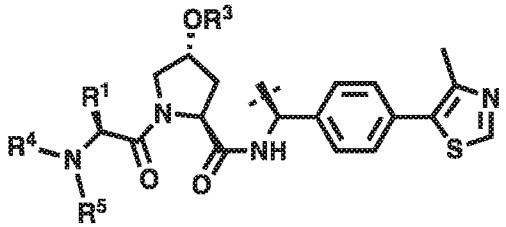
wherein

R^1 and R^2 are independently hydrogen, C_1-C_8 alkyl, C_1-C_8 alkoxyalkyl, C_1-C_8 haloalkyl, C_1-C_8 hydroxyalkyl, C_1-C_8 aminoalkyl, C_1-C_8 alkylaminoalkyl, C_3-C_7 cycloalkyl, C_3-C_7 heterocyclyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl;

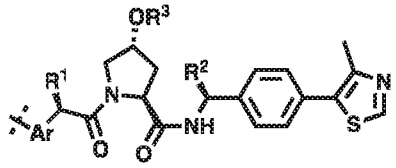
R^3 is H, $C(O)C_1$-C_8 alkyl, $C(O)C_1$-C_8 alkoxyalkyl, $C(O)C_1$-C_8 haloalkyl, $C(O)C_1$-C_8 hydroxyalkyl, $C(O)C_1$-C_8 aminoalkyl, $C(O)C_1$-C_8 alkylaminoalkyl, $C(O)C_3$-C_7 cycloalkyl, $C(O)C_3$-C_7 heterocyclyl, $C(O)C_2$-C_8 alkenyl, $C(O)C_2$-C_8 alkynyl, $C(O)OC_1$-C_8 alkoxyalkyl, $C(O)OC_1$-C_8 haloalkyl, $C(O)OC_1$-C_8 hydroxyalkyl, $C(O)OC_1$-C_8 aminoalkyl, $C(O)OC_1$-C_8 alkylaminoalkyl, $C(O)OC_3$-C_7 cycloalkyl, $C(O)OC_3$-C_7 heterocyclyl, $C(O)OC_2$-C_8 alkenyl, $C(O)OC_2$-C_8 alkynyl, $C(O)NC_1$-C_8 alkoxyalkyl, $C(O)NC_1$-C_8 haloalkyl, $C(O)NC_1$-C_8 hydroxyalkyl, $C(O)NC_1$-C_8 aminoalkyl, $C(O)NC_1$-C_8 alkylaminoalkyl, $C(O)NC_3$-C_7 cycloalkyl, $C(O)NC_3$-C_7 heterocyclyl, $C(O)NC_2$-C_8 alkenyl, $C(O)NC_2$-C_8 alkynyl, $P(O)(OH)_2$, $P(O)(OC_1$-C_8 $alkyl)_2$, or $P(O)(OC_1$-C_8 $aryl)_2$,



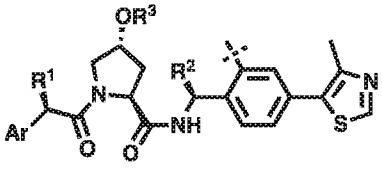
FORMULA 4B



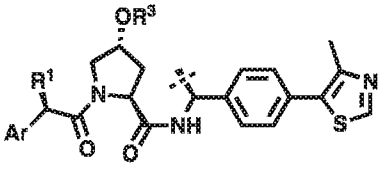
FORMULA 4C



FORMULA 4D



FORMULA 4E



FORMULA 4F

wherein

R^1 and R^2 are independently selected from hydrogen, halogen, OH, NH_2, CN, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-C_8 hydroxyalkyl, optionally substituted C_1-C_8 aminoalkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_7 cycloalkyl, optionally substituted 3-7 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, and optionally substituted C_2-C_8 alkynyl; (preferably, R^1 is selected from iso-propyl or tert-butyl; and R^2 is selected from hydrogen or methyl);.

R^3 is hydrogen, optionally substituted C(O)C_1-C_8 alkyl, optionally substituted C(O)C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C(O)C_1-C_8 haloalkyl, optionally substituted C(O)C_1-C_8 hydroxyalkyl, optionally substituted C(O)C_1-C_8 aminoalkyl, optionally substituted C(O)C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C(O)C_3-C_7 cycloalkyl, optionally substituted C(O)(3-7 membered heterocyclyl), optionally substituted C(O)C_2-C_8 alkenyl, optionally substituted C(O)C_2-C_8 alkynyl, optionally substituted C(O)OC_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C(O)OC_1-C_8 haloalkyl, optionally substituted C(O)OC_1-C_8 hydroxyalkyl, optionally substituted C(O)OC_1-C_8 aminoalkyl, optionally substituted C(O)OC_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C(O)OC_3-C_7 cycloalkyl, optionally substituted C(O)O(3-7 membered heterocyclyl), optionally substituted C(O)OC_2-C_8 alkenyl, optionally substituted C(O)OC_2-C_8 alkynyl, optionally substituted C(O)NC_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C(O)NC_1-C_8 haloalkyl, optionally substituted C(O)NC_1-C_8 hydroxyalkyl, optionally substituted C(O)NC_1-C_8 aminoalkyl, optionally substituted C(O)NC_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C(O)NC_3-C_7 cycloalkyl, optionally substituted C(O)N(3-7 membered heterocyclyl), optionally substituted C(O)NC_2-C_8 alkenyl, optionally substituted C(O)NC_2-C_8 alkynyl, optionally substituted P(O)$(OH)_2$, optionally substituted P(O)$(OC_1$-C_8 alkyl$)_2$, and optionally substituted P(O)$(OC_1$-C_8 aryl$)_2$; and

R^4 and R^5 are independently selected from hydrogen, COR^6, CO_2R^6, $CONR^6R^7$, SOR^6, SO_2R^6, $SO_2NR^6R^7$, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, wherein

R^6 and R^7 are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl,

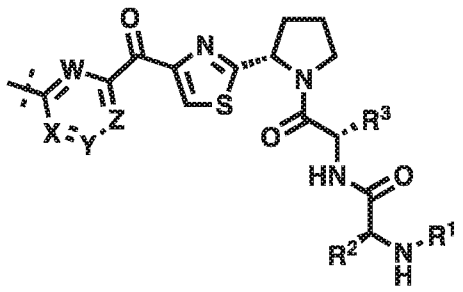
optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^4 and R^5; R^6 and R^7 together with the atom to which they are connected form a 4-8 membered cycloalkyl or heterocyclyl ring;

Ar is selected from aryl and heteroaryl, each of which is optionally substituted with one or more substituents independently selected from F, Cl, CN, NO_2, OR^8, NR^8R^9, COR^8, CO_2R^8, $CONR^8R^9$, SOR^8, SO_2R^8, $SO_2NR^9R^{10}$, NR^9COR^{10}, $NR^8C(O)NR^9R^{10}$, NR^9SOR^{10}, $NR^9SO_2R^{10}$, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 alkoxyalkyl, optionally substituted C_1-C_6 haloalkyl, optionally substituted C_1-C_6 hydroxyalkyl, optionally substituted C_1-C_6alkylaminoC_1-C_6alkyl, optionally substituted C_3-C_7 cycloalkyl, optionally substituted 3-7 membered heterocyclyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted aryl, and optionally substituted C_4-C_5 heteroaryl, wherein

R^8, R^9, and R^{10} are independently selected from null, hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted C_3-C_7 cycloalkyl, optionally substituted 3-7 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^8 and R^9; R^9 and R^{10} together with the atom to which they are connected form a 4-8 membered cycloalkyl or heterocyclyl ring.

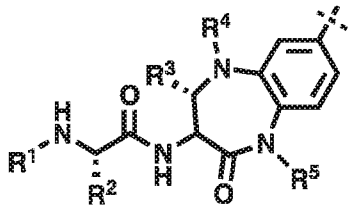


FORMULA 5A

wherein

R^1, R^2, R^3, and R^4 are independently hydrogen, C_1-C_8 alkyl, C_1-C_8 alkoxyalkyl, C_1-C_8 haloalkyl, C_1-C_8 hydroxyalkyl, C_3-C_7 cycloalkyl, C_3-C_7 heterocyclyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl, and V, W, X, and Z are independently CR^4 or N.

And



FORMULA 5B,

wherein

R^1, R^2, and R^3 are independently selected from hydrogen, halogene, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-C_8 hydroxyalkyl, optionally substituted C_3-C_7 cycloalkyl, optionally substituted 3-7 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, and optionally substituted C_2-C_8 alkynyl;

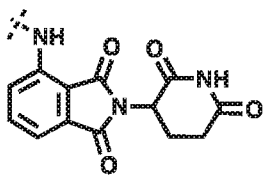
R^4 and R^5 are independently selected from hydrogen, COR^6, CO_2R^6, $CONR^6R^7$, SOR^6, SO_2R^6, $SO_2NR^6R^7$, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted aryl-C_1-C_8alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, wherein

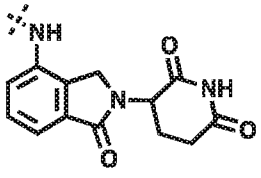
R^6 and R^7 are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^6 and R^7 together with the atom to which they are connected form a 4-8 membered cycloalkyl or heterocyclyl ring.

In some aspects, the degradation/disruption tag can be, for example, pomalidomide (Fischer et al., 2014), thalidomide (Fischer et al., 2014), lenalidomide (Fischer et al., 2014), VH032 (Galdeano et al., 2014; Maniaci et al., 2017), adamantine (Xie et al., 2014), 1-((4,4,5,5,5-pentafluoropentyl)sulfinyl)nonane (E.Wakeling, 1995), nutlin-3a (Vassilev et al., 2004), RG7112 (Vu et al., 2013), RG7338, AMG 232 (Sun et al., 2014), AA-115 (Aguilar et al., 2017), bestatin (Hiroyuki Suda et al., 1976), MV1 (Varfolomeev et al., 2007), LCL161 (Weisberg et al., 2010), FK506 (Liu et al., 1991) rapamycin (Fan et al., 2017; Rodrik-Outmezguine et al., 2016) and/or analogs thereof.

In some aspects, the degradation/disruption tag can be, e.g., one of the following structures:


FORMULA 6A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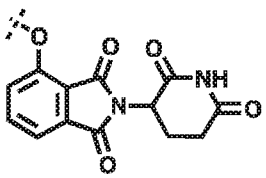
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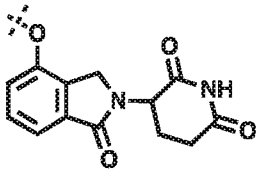
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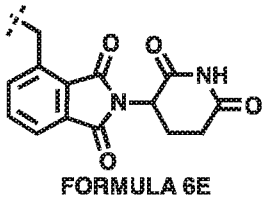
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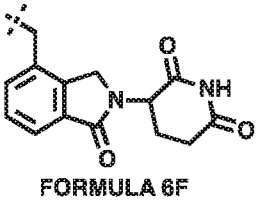
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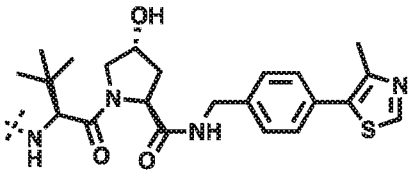
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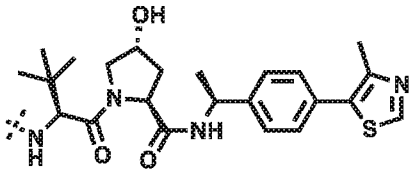
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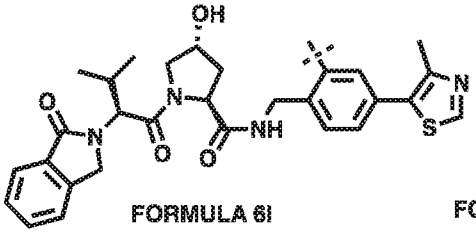
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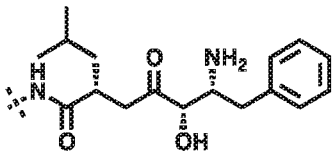
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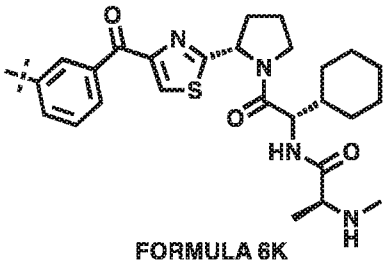
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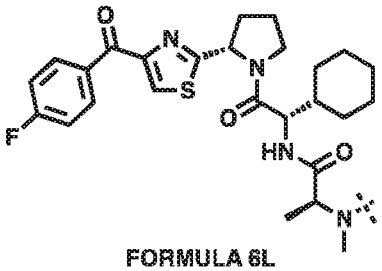
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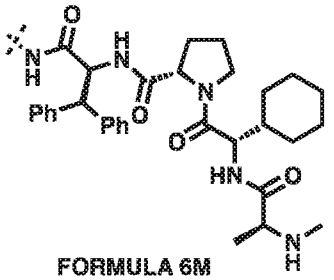
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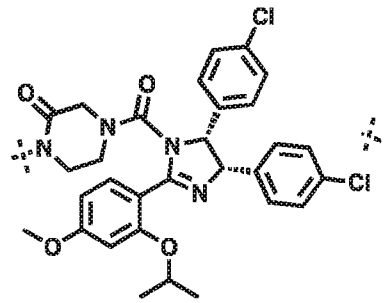
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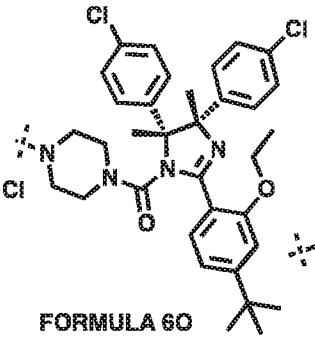
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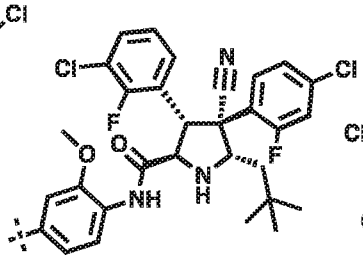
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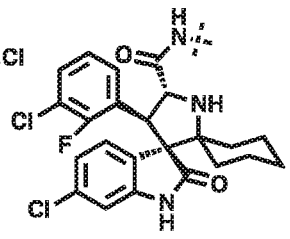
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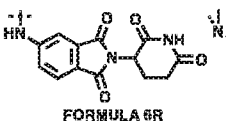
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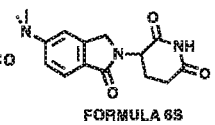
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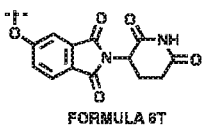
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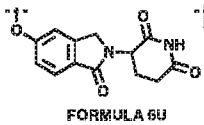
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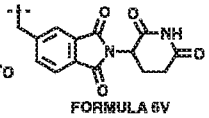
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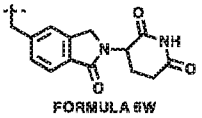
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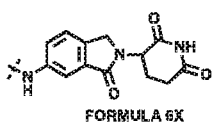
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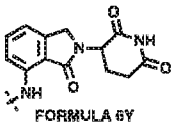
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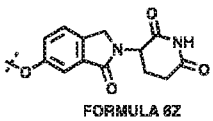
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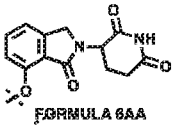
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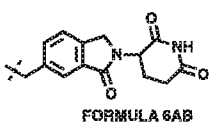
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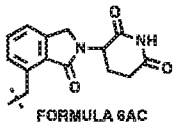
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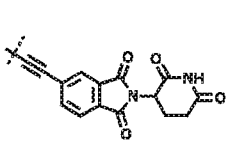
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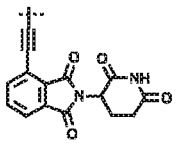
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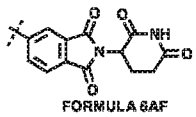
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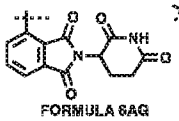
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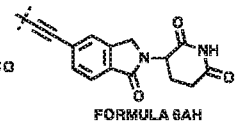
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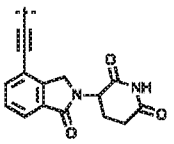
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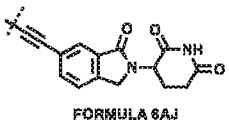
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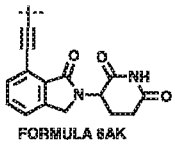
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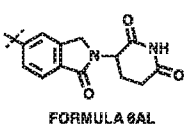
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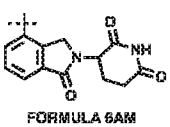
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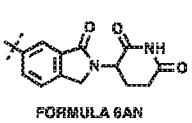
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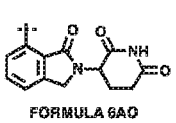
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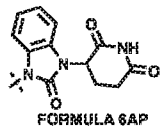
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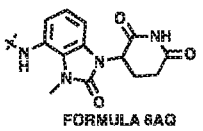
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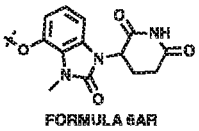
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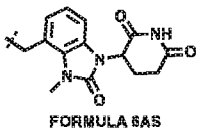
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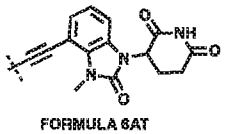
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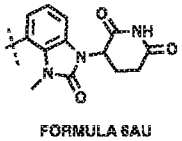
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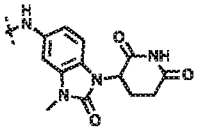
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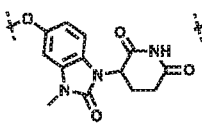
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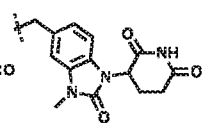
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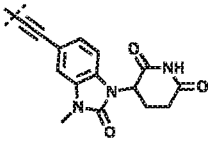
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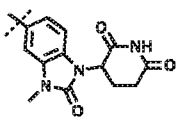
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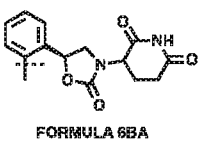
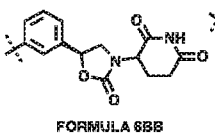

FORMULA 6BA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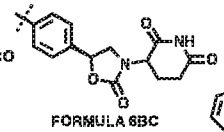
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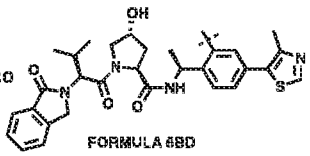
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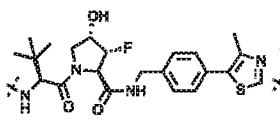
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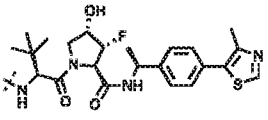
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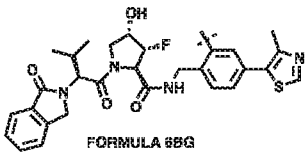
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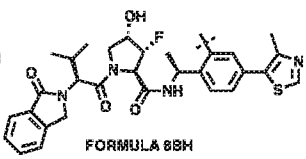
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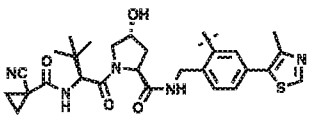
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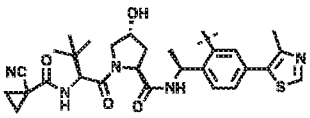
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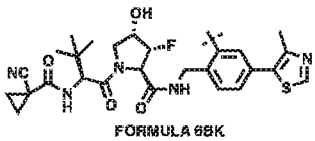
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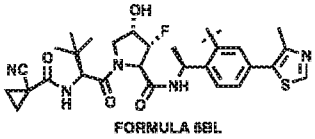
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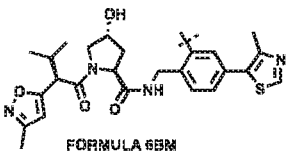
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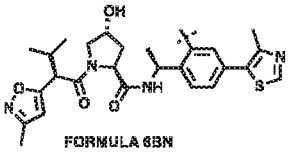
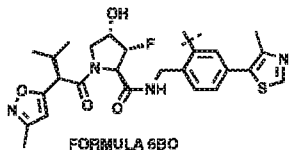
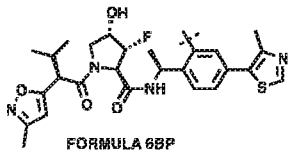

FORMULA 6BN


FORMULA 6BO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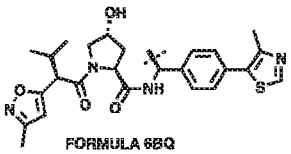
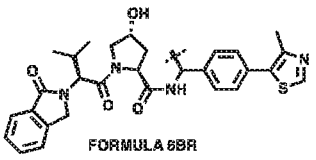

FORMULA 6BQ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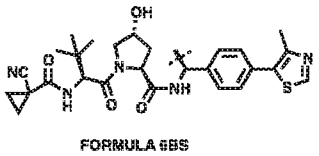
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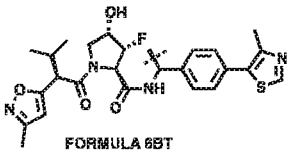
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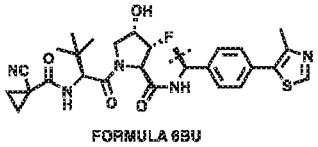
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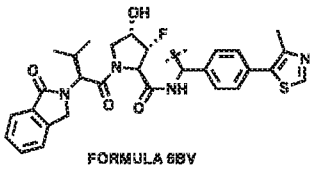
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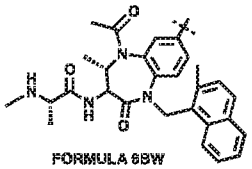
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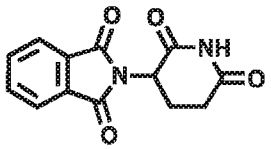
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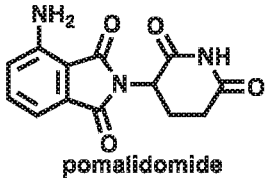
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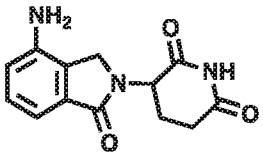
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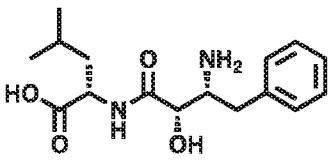
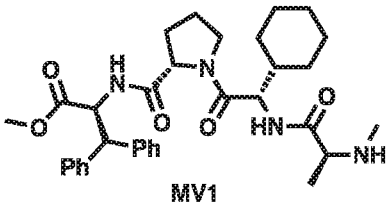

bestatin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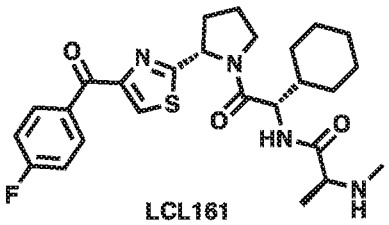
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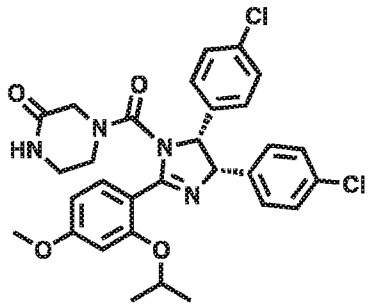
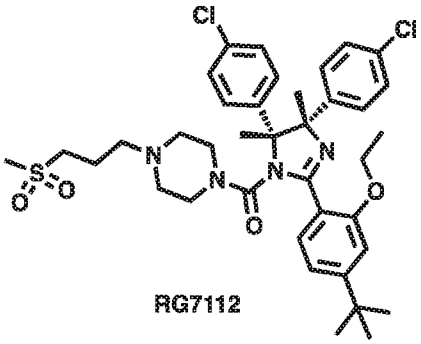

nutlin-3a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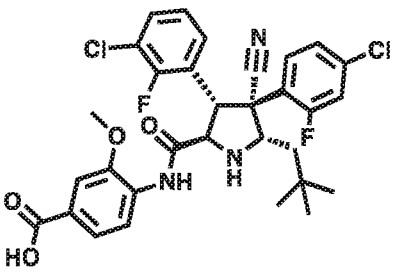
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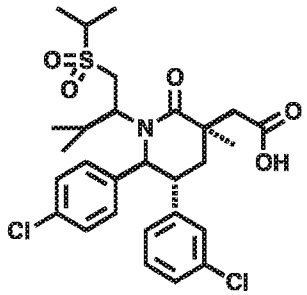
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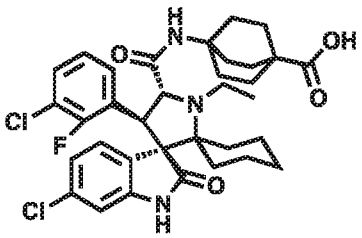
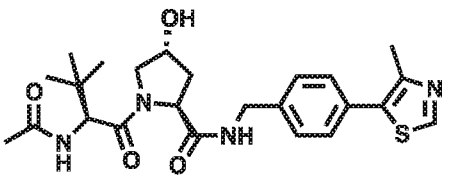
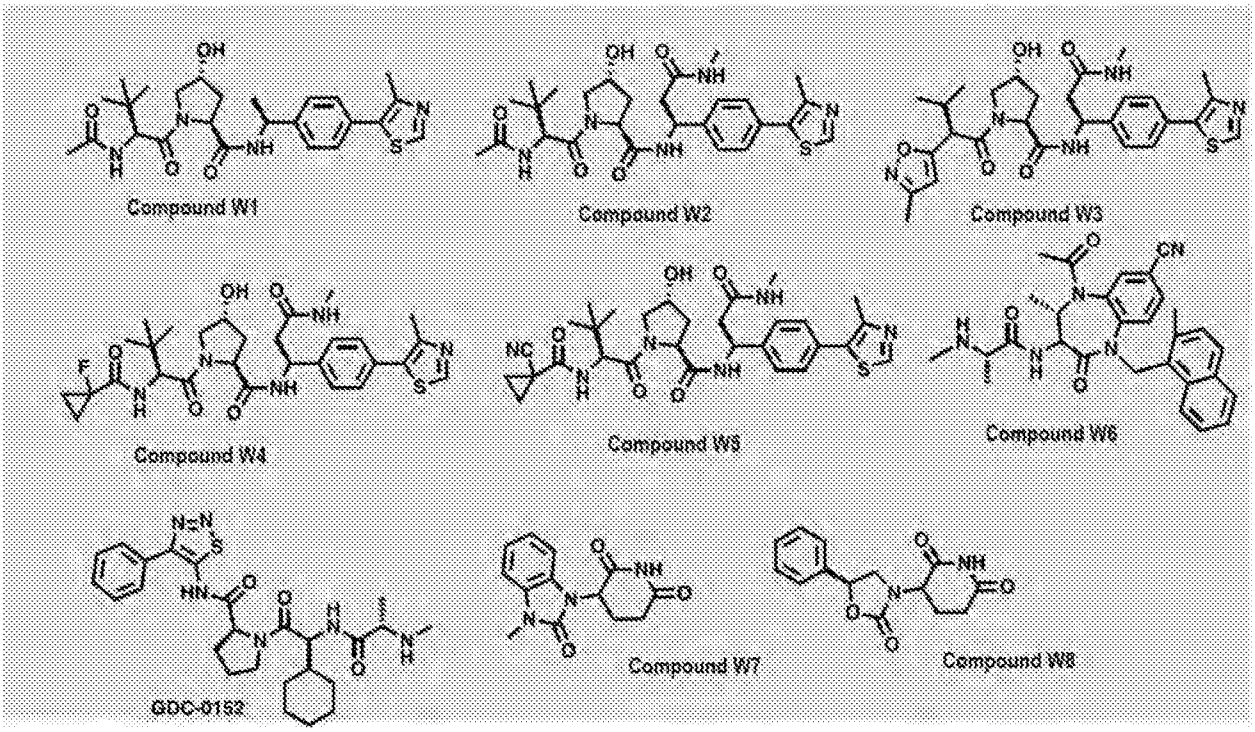

AA-115


VH032

5

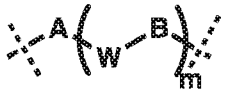


In some aspects, the degradation/disruption tag can bind to a ubiquitin ligase (e.g., an E3 ligase such as a cereblon E3 ligase, a VHL E3 ligase, a MDM2 ligase, a TRIM21 ligase, a TRIM24 ligase, a KEAP1 ligase and/or an IAP ligase) and/or serve as a hydrophobic group or a tag group that leads to PTK6 protein misfolding.

Linkers

In all of the above-described compounds, the PTK6 ligand is conjugated to the degradation/disruption tag through a linker. The linker can include, for example, acyclic or cyclic saturated or unsaturated carbon, ethylene glycol, amide, amino, ether, urea, carbamate, aromatic, heteroaromatic, heterocyclic and/or carbonyl containing groups with different lengths.

In some aspects, the linker can be a moiety of:



FORMULA 7

wherein

A, W and B, at each occurrence, are independently selected from null, or bivalent moiety selected from $R^{'}$-$R^{''}$, $R^{'}COR^{''}$, $R^{'}CO_2R^{''}$, $R^{'}C(O)N(R^{1})R^{''}$, $R^{'}C(S)N(R^{1})R^{''}$, $R^{'}OR^{''}$, $R^{'}OC(O)R^{''}$, $R^{'}OC(O)OR^{''}$, $R^{'}OCON(R^{1})R^{''}$, $R^{'}SR^{''}$, $R^{'}SOR^{''}$, $R^{'}SO_2R^{''}$, $R^{'}SO_2N(R^{1})R^{''}$, $R^{'}N(R^{1})R^{''}$, $R^{'}NR^{1}COR^{''}$, $R^{'}NR^{1}C(O)OR^{''}$, $R^{'}NR^{1}CON(R^{2})R^{''}$, $R^{'}NR^{1}C(S)R^{''}$, $R^{'}NR^{1}S(O)R^{''}$, $R^{'}NR^{1}S(O)_2R^{''}$, and $R^{'}NR^{1}S(O)_2N(R^{2})R^{''}$, wherein

$R^{'}$ and $R^{''}$ are independently selected from null, optionally substituted R^{r}-(C_1-C_8 alkyl), or a moiety comprising of optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 hydroxyalkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-C_8 alkylene, optionally substituted C_2-C_8 alkenylene, optionally substituted C_2-C_8 alkynylene, optionally substituted C_1-C_8 hydroxyalkylene, optionally substituted C_1-C_8alkoxyC_1-C_8alkylene, optionally substituted C_1-C_8alkylaminoC_1-C_8alkylene, optionally substituted C_1-C_8 haloalkylene, optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted C_3-C_{13} fused cycloalkyl, optionally substituted C_3-C_{13} fused heterocyclyl, optionally substituted C_3-C_{13} bridged cycloalkyl, optionally substituted C_3-C_{13} bridged heterocyclyl, optionally substituted C_3-C_{13} spiro cycloalkyl, optionally substituted C_3-C_{13} spiro heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

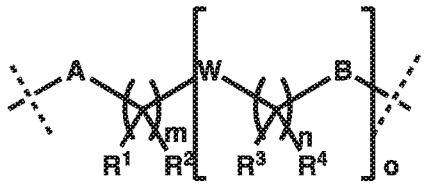
R^{r} is selected from optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted C_3-C_{13} fused cycloalkyl, optionally substituted C_3-C_{13} fused heterocyclyl, optionally substituted C_3-C_{13} bridged cycloalkyl, optionally substituted C_3-C_{13} bridged heterocyclyl, optionally substituted C_3-C_{13} spiro cycloalkyl, optionally substituted C_3-C_{13} spiro heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^{1} and R^{2} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxyalkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-C_8

hydroxyalkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

R' and R'', R^1 and R^2, R' and R^1, R' and R^2, R'' and R^1, R'' and R^2 together with the atom to which they are connected form a 3-20 membered cycloalkyl or 4-20 membered heterocyclyl ring; and

m is 0 to 15.



FORMULA 7A,

wherein

R^1, R^2, R^3 and R^4, at each occurrence, are independently selected from hydrogen, halogen, hydroxyl, amino, cyano, nitro, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8 alkoxyalkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-C_8 hydroxyalkyl, optionally substituted C_1-C_8 alkylamino, and optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-10 membered carbocyclyl, optionally substituted 3-8 membered cycloalkoxy, optionally substituted 3-10 membered carbocyclylamino, optionally substituted 4-8 membered membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^1 and R^2, R^3 and R^4 together with the atom to which they are connected form a 3-20 membered cycloalkyl or 4-20 membered heterocyclyl ring;

A, W and B, at each occurrence, are independently selected from null, or bivalent moiety selected from R'-R'', R'COR'', R'CO_2R'', R'C(O)N(R^5)R'', R'C(S)N(R^5)R'', R'OR'', R'OC(O)R'', R'OC(O)OR'', R'OCONR^{5}R'', R'SR'', R'SOR'', R'SO_2R'', R'SO_2N(R^5)R'', R'N(R^5)R'', R'NR^{5}COR'', R'NR^{5}C(O)OR'', R'NR^{5}CON(R^6)R'', R'NR^{5}C(S)R'', R'NR^{5}S(O)R'', R'NR^{5}S(O)$_2$R'', and R'NR^{5}S(O)$_2$N(R^6)R'', wherein

$R^{'}$ and $R^{''}$ are independently selected from null, optionally substituted R^{r}-(C_1-C_8 alkyl), or a moiety comprising of optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 hydroxyalkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-C_8 alkylene, optionally substituted C_2-C_8 alkenylene, optionally substituted C_2-C_8 alkynylene, optionally substituted C_1-C_8 hydroxyalkylene, optionally substituted C_1-C_8alkoxyC_1-C_8alkylene, optionally substituted C_1-C_8alkylaminoC_1-C_8alkylene, optionally substituted C_1-C_8 haloalkylene, optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted C_3-C_{13} fused cycloalkyl, optionally substituted C_3-C_{13} fused heterocyclyl, optionally substituted C_3-C_{13} bridged cycloalkyl, optionally substituted C_3-C_{13} bridged heterocyclyl, optionally substituted C_3-C_{13} spiro cycloalkyl, optionally substituted C_3-C_{13} spiro heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^{r} is selected from optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted C_3-C_{13} fused cycloalkyl, optionally substituted C_3-C_{13} fused heterocyclyl, optionally substituted C_3-C_{13} bridged cycloalkyl, optionally substituted C_3-C_{13} bridged heterocyclyl, optionally substituted C_3-C_{13} spiro cycloalkyl, optionally substituted C_3-C_{13} spiro heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

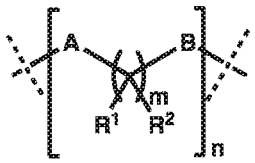
R^5 and R^6 are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxyalkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-C_8 hydroxyalkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

$R^{'}$ and $R^{''}$, R^5 and R^6, $R^{'}$ and R^5, $R^{'}$ and R^6, $R^{''}$ and R^5, $R^{''}$ and R^6 together with the atom to which they are connected form a 3-20 membered cycloalkyl or 4-20 membered heterocyclyl ring;

m is 0 to 15;

n, at each occurrence, is 0 to 15; and

o is 0 to 15.



FORMULA 7B,

wherein

R^1 and R^2, at each occurrence, are independently selected from hydrogen, halogen, hydroxyl, amino, cyano, nitro, and optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8 alkoxy C_1-C_8 alkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-C_8 hydroxyalkyl, optionally substituted C_1-C_8 alkylamino, C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted 3-10 membered carbocyclyl, optionally substituted 3-8 membered cycloalkoxy, optionally substituted 3-10 membered carbocyclylamino, optionally substituted 4-10 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^1 and R^2 together with the atom to which they are connected form a 3-20 membered cycloalkyl or 4-20 membered heterocyclyl ring;

A and B, at each occurrence, are independently selected from null, or bivalent moiety selected from R'-R'', $R'COR''$, $R'CO_2R''$, $R'C(O)NR^3R''$, $R'C(S)NR^3R''$, $R'OR''$, $R'OC(O)R''$, $R'OC(O)OR''$, $R'OCON(R^3)R''$, $R'SR''$, $R'SOR''$, $R'SO_2R''$, $R'SO_2N(R^3)R''$, $R'N(R^3)R''$, $R'NR^3COR''$, $R'NR^3C(O)OR''$, $R'NR^3CON(R^4)R'$, $R'NR^3C(S)R''$, $R'NR^3S(O)R''$, $R'NR^3S(O)_2R''$, and $R'NR^3S(O)_2N(R^4)R''$, wherein

R' and R'' are independently selected from null, optionally substituted R^r-(C_1-C_8 alkyl), or a moiety comprising of optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 hydroxyalkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-C_8 alkylene, optionally substituted C_2-C_8 alkenylene, optionally substituted C_2-C_8 alkynylene, optionally substituted C_1-C_8 hydroxyalkylene, optionally substituted C_1-C_8alkoxyC_1-C_8alkylene, optionally substituted C_1-C_8alkylaminoC_1-C_8alkylene, optionally substituted C_1-C_8 haloalkylene, optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted C_3-C_{13} fused cycloalkyl, optionally substituted C_3-C_{13} fused heterocyclyl, optionally

substituted C_3-C_{13} bridged cycloalkyl, optionally substituted C_3-C_{13} bridged heterocyclyl, optionally substituted C_3-C_{13} spiro cycloalkyl, optionally substituted C_3-C_{13} spiro heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

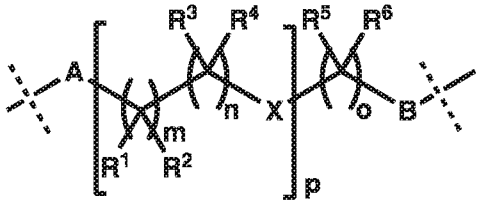
R^r is selected from optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted C_3-C_{13} fused cycloalkyl, optionally substituted C_3-C_{13} fused heterocyclyl, optionally substituted C_3-C_{13} bridged cycloalkyl, optionally substituted C_3-C_{13} bridged heterocyclyl, optionally substituted C_3-C_{13} spiro cycloalkyl, optionally substituted C_3-C_{13} spiro heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^3 and R^4 are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxyalkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-C_8 hydroxyalkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

$R^{'}$ and $R^{''}$, R^3 and R^4, $R^{'}$ and R^3, $R^{'}$ and R^4, $R^{''}$ and R^3, $R^{''}$ and R^4 together with the atom to which they are connected form a 3-20 membered cycloalkyl or 4-20 membered heterocyclyl ring;

m, at each occurrence, is 0 to 15; and

n is 0 to 15.



FORMULA 7C,

wherein

X is selected from O, NH, and NR^7;

R^1, R^2, R^3, R^4, R^5, and R^6, at each occurrence, are independently selected from hydrogen, halogen, hydroxyl, amino, cyano, nitro, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8 alkoxy C_1-C_8 alkyl, optionally substituted C_1-C_8 haloalkyl,

optionally substituted C_1-C_8 hydroxyalkyl, optionally substituted C_1-C_8 alkylamino, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-10 membered carbocyclyl, optionally substituted 3-8 membered cycloalkoxy, optionally substituted 4-10 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

A and B are independently selected from null, or bivalent moiety selected from $R^{'}$-$R^{''}$, $R^{'}COR^{''}$, $R^{'}CO_2R^{''}$, $R^{'}C(O)N(R^8)R^{''}$, $R^{'}C(S)N(R^8)R^{''}$, $R^{'}OR^{''}$, $R^{'}OC(O)R^{''}$, $R^{'}OC(O)OR^{''}$, $R^{'}OCON(R^8)R^{''}$, $R^{'}SR^{''}$, $R^{'}SOR^{''}$, $R^{'}SO_2R^{''}$, $R^{'}SO_2N(R^8)R^{''}$, $R^{'}N(R^8)R^{''}$, $R^{'}NR^8COR^{''}$, $R^{'}NR^8C(O)OR^{''}$, $R^{'}NR^8CON(R^9)R^{''}$, $R^{'}NR^8C(S)R^{''}$, $R^{'}NR^8S(O)R^{''}$, $R^{'}NR^8S(O)_2R^{''}$, and $R^{'}NR^8S(O)_2N(R^9)R^{''}$, wherein

$R^{'}$ and $R^{''}$ are independently selected from null, optionally substituted R^r-(C_1-C_8 alkyl), or a moiety comprising of optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 hydroxyalkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-C_8 alkylene, optionally substituted C_2-C_8 alkenylene, optionally substituted C_2-C_8 alkynylene, optionally substituted C_1-C_8 hydroxyalkylene, optionally substituted C_1-C_8alkoxyC_1-C_8alkylene, optionally substituted C_1-C_8alkylaminoC_1-C_8alkylene, optionally substituted C_1-C_8 haloalkylene, optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted C_3-C_{13} fused cycloalkyl, optionally substituted C_3-C_{13} fused heterocyclyl, optionally substituted C_3-C_{13} bridged cycloalkyl, optionally substituted C_3-C_{13} bridged heterocyclyl, optionally substituted C_3-C_{13} spiro cycloalkyl, optionally substituted C_3-C_{13} spiro heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^r is selected from optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted C_3-C_{13} fused cycloalkyl, optionally substituted C_3-C_{13} fused heterocyclyl, optionally substituted C_3-C_{13} bridged cycloalkyl, optionally substituted C_3-C_{13} bridged heterocyclyl, optionally substituted C_3-C_{13} spiro cycloalkyl, optionally substituted C_3-C_{13} spiro heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^7, R^8 and R^9 are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxyalkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-

C_8 hydroxyalkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

$R^{'}$ and $R^{''}$, R^8 and R^9, $R^{'}$ and R^8, $R^{'}$ and R^9, $R^{''}$ and R^8, $R^{''}$ and R^9 together with the atom to which they are connected form a 3-20 membered cycloalkyl or 4-20 membered heterocyclyl ring;

m, at each occurrence, is 0 to 15;

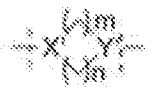
n, at each occurrence, is 0 to 15;

o is 0 to 15; and

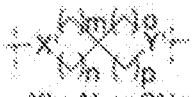
p is 0 to 15.

In some aspects of Formulae 7, 7A, 7B, and 7C, the linker moiety comprises a ring selected from the group consisting of a 3 to 13 membered ring, a 3 to 13 membered fused ring, a 3 to 13 membered bridged ring, and a 3 to13 membered spiro ring.

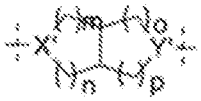
In some aspects of Formulae 7, 7A, 7B, and 7C, the linker moiety comprises a ring selected from the group consisting of Formula C1, C2, C3, C4 and C5:



Formula C1,

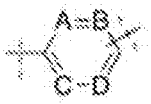


Formula C2,



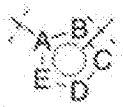
X' = N or CH
Y' = N or CH
m = 0-5
n = 0-5
o = 0-5
p = 0-5

Formula C3,



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

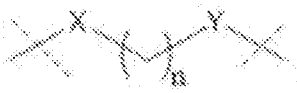
Formula C4, and



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
E = C, CH, C(C1-3 alkyl), N, NH, N(C1-3alkyl), O, S

Formula C5.

In some aspects, the linker can also be a moiety of:

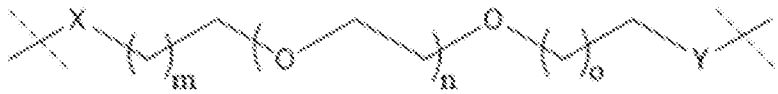


Formula A,

wherein X is C=O or CH_2,

Y is C=O or CH_2, and

n is 0-15;



Formula B,

wherein X is C=O or CH_2,

Y is C=O or CH_2,

m is 0-15,

n is 0-6, and

o is 0-15; or

Formula C,

wherein

X is C=O or CH_2,

Y is C=O or CH_2,

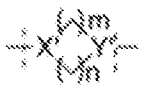
R is $-CH_2-$, $-CF_2-$, $-CH(C_{1-3}$ alkyl)–, $-C(C_{1-3}$ alkyl)$(C_{1-3}$ alkyl)–, –CH=CH–, $-C(C_{1-3}$ alkyl)$=C(C_{1-3}$ alkyl)–, –C=C–, –O–, –NH–, $-N(C_{1-3}$ alkyl)–, $-C(O)NH-$, $-C(O)N(C_{1-3}$ alkyl)–, a 3-13 membered ring, a 3-13 membered fused ring, a 3-13 membered bridged ring, and/or a 3-13 membered spiro ring,

m is 0-15, and

n is 0-15.

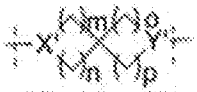
In some aspects of Formula C, R is a 3-13 membered ring, a 3-13 membered fused ring, a 3-13 membered bridged ring, and/or a 3-13 membered spiro ring, one or more of which can contain one or more heteroatoms.

In some aspects of Formula C, R has a structure of:



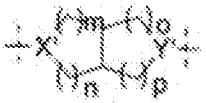
X' = N or CH
Y' = N or CH
m = 0-5
n = 0-5

Formula C1,



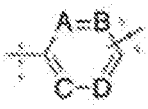
X' = N or CH
Y' = N or CH
m = 0-5
n = 0-5
o = 0-5
p = 0-5

Formula C2,



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

Formula C3,



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

Formula C4, or

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
E = C, CH, C(C1-3 alkyl), N, NH, N(C1-3alkyl), O, S

Formula C5.

In some aspects, the bivalent compound is a compound selected from the following compounds, as identified in Table 1 below: YX39-86, YX39-89, YX39-90, YX39-91, YX39-92, YX39-93, YX39-94, YX39-96, YX39-97, YX39-98, YX39-99, YX39-100, YX39-101, YX39-102, YX39-103, YX39-104, YX39-105, YX39-106, YX39-107, YX39-127, YX39-128, YX39-129, YX44-158, YX44-172, YX44-184, YX49-7-2, YX49-8, YX49-9, YX49-10, YX49-11, YX49-24, YX49-99, YX49-100, YX49-101, YX49-102, YX59-122, YX69-5, YX69-157, YX69-158, YX69-159, YX69-182, YX69-183, YX69-184, YX79-3, YX79-4, YX79-5, YX79-6, YX79-

10, YX79-11, YX79-12, YX79-13, YX79-14, YX79-15, YX79-16, YX79-17, YX79-18, YX79-19, YX79-20, YX79-21, YX79-22, YX79-23, YX79-24, YX79-25, YX79-29, YX79-30, YX79-34, YX79-35, YX79-36, YX79-37, YX79-38, YX79-39, YX79-40, YX79-41, YX79-42, YX79-43, YX79-56, YX79-57, YX79-58, YX79-59, YX79-60, YX79-61, YX79-62, YX79-63, YX79-64, YX79-65, YX79-66, YX79-67, YX79-68, YX79-69, YX79-70, YX79-86, YX79-87, YX79-88, YX79-89, YX79-90, YX79-91, YX79-92, YX79-93, YX79-94, YX79-95, YX79-967, YX79-97, YX79-131, YX79-132, YX79-133, YX79-134, YX79-135, YX79-136, YX79-137, YX79-138, YX79-139, YX79-140, YX79-141, YX79-142, YX79-143, YX79-144, YX79-145, YX79-146, YX79-147, YX79-148, YX79-149, YX79-150, YX79-151, YX79-152, YX79-153, YX79-154, YX79-155, YX79-156. YX79-157, YX79-158, YX79-159, YX79-160, YX79-161, YX79-162, YX79-164, YX79-165, JH077-29, JH077-30, JH077-31, JH077-32, JH077-33, JH077-34, JH077-35, JH077-35, JH077-36, JH077-37, JH077-38, JH077-39, JH077-40, JH077-41, JH077-47, JH077-48, JH077-49, JH077-51, JH077-52, JH077-53, JH077-54, JH077-55, JH077-56, JH077-57, JH077-58, JH077-65, JH077-66, JH077-67, JH077-68, JH077-69, JH077-70, JH077-71, JH077-72, JH077-73, JH077-74, JH077-75, JH077-76, JH077-76, JH077-77, JH077-78, JH077-79, JH077-80, JH077-81, JH077-82, JH077-83, JH077-84, JH077-85, JH077-86, JH077-87, JH077-88, JH077-89, JH077-90, JH077-91, JH077-92, JH077-93 examples 190-280, or analogs thereof.

In some aspects, this disclosure provides a method of treating PTK6-mediated cancers, the method including administering to a subject in need thereof one or more bivalent compounds including a PTK6 ligand conjugated to a degradation/disruption tag via a linker. The PTK6-mediated cancer can be a cancer resulting from (aberrant) PTK6 activation. The PTK6-mediated cancer can have elevated PTK6 expression relative to a wild-type tissue of the same species and tissue type. Non-limiting examples of PTK6-mediated diseases include breast cancer, ovarian cancer, prostate cancer, colon cancer, pancreatic cancer, bladder cancer, liver cancer, and cervical cancer.

The PTK6-mediated cancer can be a relapsed cancer. The PTK6-mediated cancer can have been refractory to one or more previous treatments by different therapies.

In any of the above-described methods, the bivalent compounds can be YX39-86, YX39-89, YX39-90, YX39-91, YX39-92, YX39-93, YX39-94, YX39-96, YX39-97, YX39-98, YX39-99, YX39-100, YX39-101, YX39-102, YX39-103, YX39-104, YX39-105, YX39-106, YX39-107,

YX39-127, YX39-128, YX39-129, YX44-158, YX44-172, YX44-184, YX49-7-2, YX49-8, YX49-9, YX49-10, YX49-11, YX49-24, YX49-99, YX49-100, YX49-101, YX49-102, YX59-122, YX69-5, YX69-157, YX69-158, YX69-159, YX69-182, YX69-183, YX69-184, YX79-3, YX79-4, YX79-5, YX79-6, YX79-10, YX79-11, YX79-12, YX79-13, YX79-14, YX79-15, YX79-16, YX79-17, YX79-18, YX79-19, YX79-20, YX79-21, YX79-22, YX79-23, YX79-24, YX79-25, YX79-29, YX79-30, YX79-34, YX79-35, YX79-36, YX79-37, YX79-38, YX79-39, YX79-40, YX79-41, YX79-42, YX79-43, YX79-56, YX79-57, YX79-58, YX79-59, YX79-60, YX79-61, YX79-62, YX79-63, YX79-64, YX79-65, YX79-66, YX79-67, YX79-68, YX79-69, YX79-70, YX79-86, YX79-87, YX79-88, YX79-89, YX79-90, YX79-91, YX79-92, YX79-93, YX79-94, YX79-95, YX79-967, YX79-97, YX79-131, YX79-132, YX79-133, YX79-134, YX79-135, YX79-136, YX79-137, YX79-138, YX79-139, YX79-140, YX79-141, YX79-142, YX79-143, YX79-144, YX79-145, YX79-146, YX79-147, YX79-148, YX79-149, YX79-150, YX79-151, YX79-152, YX79-153, YX79-154, YX79-155, YX79-156. YX79-157, YX79-158, YX79-159, YX79-160, YX79-161, YX79-162, YX79-164, YX79-165, JH077-29, JH077-30, JH077-31, JH077-32, JH077-33, JH077-34, JH077-35, JH077-35, JH077-36, JH077-37, JH077-38, JH077-39, JH077-40, JH077-41, JH077-47, JH077-48, JH077-49, JH077-51, JH077-52, JH077-53, JH077-54, JH077-55, JH077-56, JH077-57, JH077-58, JH077-65, JH077-66, JH077-67, JH077-68, JH077-69, JH077-70, JH077-71, JH077-72, JH077-73, JH077-74, JH077-75, JH077-76, JH077-76, JH077-77, JH077-78, JH077-79, JH077-80, JH077-81, JH077-82, JH077-83, JH077-84, JH077-85, JH077-86, JH077-87, JH077-88, JH077-89, JH077-90, JH077-91, JH077-92, JH077-93 examples 190-280, or analogs thereof.

In some aspects of the methods described herein, the bivalent compounds can be administered, e.g., orally, parenterally, intradermally, subcutaneously, topically, and/or rectally.

Any of the above-described methods can further include treating a subject with one or more additional therapeutic regimens for treating cancer. The one or more additional therapeutic regimens for treating cancer can be, e.g., one or more of surgery, chemotherapy, radiation therapy, hormone therapy, or immunotherapy.

This disclosure additionally provides a method for identifying a bivalent compound which mediates degradation/disruption of PTK6, the method including providing a heterobifunctional test compound including a PTK6 ligand conjugated to a degradation/disruption tag via a linker,

contacting the heterobifunctional test compound with a cell (e.g., a cancer cell such as a PTK6-mediated cancer cell) including a ubiquitin ligase and PTK6.

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. The terms "bivalent" and "bi-functional" are used interchangeably herein. 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.

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

Figure 1. Kaplan-Meier curves showing prognostic significance of high PTK6 transcript expression based on analysis using KMPlot.com. Higher expression of PTK6 is associated with poorer survival for patients with ovarian cancer, stage 2/3.

Figures 2 – 5. Effects of exemplary compounds on reducing PTK6 protein levels in breast cancer cells. Triple negative MDA-MB231 cells were treated for 24 hours with 500 nM, 2uM or 2.5uM of test compound and lysed. Proteins were resolved by SDS/PAGE and immunblotted with antibody to PTK6 (Santa Cruz, Cell Signaling) or GAPDH loading control (Cell Signaling).

Figure 6a. PTK6 degraders, but not kinase activity inhibitor suppress viability in 3D cultures. MDA-MB231 triple negative breast cancer cells were seeded into 3D Matrigel cultures (4x10^3 cells/well) and treated with indicated PTK6 degraders, negative control compounds or PTK6 kinase activity inhibitor at 1uM for 5 days with re-feeding of compound after 3 days in culture. Viability was assessed using 3D Cell Titer glo (Promega). **Figure 6b.** Expression of PTK6 in cells treated with PTK6 degraders, negative control compounds or PTK6 kinase activity inhibitor was assessed after 24 hour treatment in monolayer cultures with 1uM of compound. Cells were lysed and proteins were resolved and probed with anti-PTK6 antibody (Cell Signaling)

Figure 7a. PTK6 degrader treatment suppresses growth of ER+ breast cancer cells. ER+ breast cancer cells (MCF-7) were treated with indicated concentrations of top candidate degraders, negative control compounds or PTK6 kinase activity inhibitor for 24 hours, lysed and proteins were resolved by SDS-PAGE. PTK6 expression was interrogated by Western analysis. **Figure 7b.** MCF-7 cells were seeded into 3D Matrigel cultures and treated with indicated PTK6 degraders or PTK6 kinase inhibitor for 4 days. Viability was quantified using 3-D Cell Titer glo (Promega).

Figure 8. Treatment with PTK6 degraders, but not kinase activity inhibitor, suppress viability of chemotherapy-resistant ovarian cancer cells (CP70). Cells were seeded into 3D Matrigel cultures and treated with compounds (2uM) for 6 days. Viability was assessed using 3D Cell Titre glo assay (Promega)

Figure 9. PTK6 degrader suppresses PTK6 expression in a proteasome-dependent manner. MDA-MB231 cells (left) or OV2008 cells (right) were pre-treated with DMSO or MG-132 (10uM) for two hours, then treated for an additional 4 hours with DMSO or PTK6 degrader at the indicated concentrations.

Figure 10. PTK6 kinase activity inhibitor pre-treatment prevents PTK6 degrader-dependent suppression of PTK6 expression. MDA-MB231 cells in monolayer cultures were pre-treated with DMSO or PTK6 kinase activity inhibitor (5uM), then treated for an additional 24 hours with PTK6 degrader, YX39-105. Cells were lysed and expression of PTK6 was assessed by Western analysis.

Figure 11. PTK6 degraders suppress PTK6 expression in endocrine therapy-resistant ER+ breast cancer cells (MCF/EDR). MCF7EDR cells in monolayer cultures were treated with PTK6 degraders for 24 hours at the indicated concentrations. Cells were lysed and expression of PTK6 was assessed.

Figure 12a. PTK6 degraders, but not kinase activity inhibitor, suppress viability in 3D cultures. Expression of PTK6 in cells treated with PTK6 degraders, negative control compounds or PTK6 kinase activity inhibitor was assessed after 24 hour treatment in monolayer cultures with 1uM of compound. Cells were lysed and proteins were resolved and probed with anti-PTK6 antibody (Cell Signaling). **Figure 12b.** MDA-MB231 triple negative breast cancer cells were seeded into 3D Matrigel cultures (4x10^3 cells/well) and treated with indicated PTK6 degraders, negative control compounds or PTK6 kinase activity inhibitor at 1uM for 6 days with re-feeding of compound after 3 days in culture. Viability was assessed using 3D Cell Titer glo (Promega).

Figure 13. PTK6 degraders suppress PTK6 expression. MDA-MB231 cells were treated with compounds (500nM or 1uM) for 24 hours in monolayer cultures. Cells were lysed and lysates were probed with anti-PTK6 antibody.

DETAILED DESCRIPTION

The present disclosure is based in part, on the discovery that novel heterobifunctional small molecules which degrade PTK6 and/or PTK6 mutant are useful in the treatment of PTK6-mediated diseases, particularly breast cancer, ovarian cancer, prostate cancer, colon cancer, pancreatic cancer, bladder cancer, liver cancer and cervical cancer.

Successful strategies for selective degradation/disruption of the target protein induced by a bifunctional small molecule include recruiting an E3 ubiquitin ligase and mimicking protein misfolding with a hydrophobic tag (Buckley and Crews, 2014). The bifunctional molecules have three moieties: one E3-binder moiety that binds an E3 ubiquitin ligase; one targeted protein-binder moiety that binds the protein target of interest; and a linker moiety that connects the E3-binder and the targeted protein-binder moieties (Buckley and Crews, 2014). The induced proximity leads to selective ubiquitination of the target followed by its degradation at the proteasome. Several types of high affinity small-molecule E3 ligase ligands have been identified/developed. They include (1) immunomodulatory drugs (IMiDs) such as thalidomide and pomalidomide, which bind cereblon (CRBN or CRL4CRBN), 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); (2) VHL-1, a hydroxyproline-containing ligand, which binds van Hippel-Lindau protein (VHL or CRL2VHL), 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); (3) compound 7, which selectively binds KEAP1, a component of a CRL3 complex(Davies et al., 2016); (4) AMG232, which selectively binds MDM2, a heterodimeric RING E3 ligase(Sun et al., 2014); and (5) LCL161, which selectively binds IAP, a homodimeric RING E3 ligase (Ohoka et al., 2017; Okuhira et al., 2011; Shibata et al., 2017). The technology has been applied to degradation of several protein targets (Bondeson et al., 2015; Buckley et al., 2015; Lai et al., 2016; Lu et al., 2015; Winter et al., 2015; Zengerle et al., 2015), but not to degradation of PTK6 or PTK6 mutant proteins. In addition, a hydrophobic tagging approach, which utilizes a bulky and hydrophobic adamantyl group, has been developed to mimic protein misfolding, leading to the degradation of

the target protein by proteasome (Buckley and Crews, 2014). This approach has been applied to selective degradation of the pseudokinase Her3 (Xie et al., 2014), but not to degradation of PTK6 or PTK6 mutant proteins.

As discussed in the following examples, this disclosure provides specific examples of novel PTK6 degraders/disruptors, and examines the effect of exemplary degraders/disruptors in inhibiting/disrupting PTK6 function, reducing PTK6 protein levels, and inhibiting cancer cell proliferation. The results indicate that these novel small molecules can be beneficial in treating human disease, especially breast cancer, ovarian cancer, prostate cancer, colon cancer, pancreatic cancer, bladder cancer, liver cancer and cervical cancer.

A number of selective small-molecule PTK6 kinase inhibitors, such as compound 21d (Zeng et al., 2011), compound 4f (Mahmoud et al., 2014), compound 1 (Yamamoto, 2016), XMU-MP-2 (Jiang et al., 2017), and compound 3s (Cardenas et al., 2018), have been reported.

Currently available small molecules targeting PTK6 focus on inhibition of the kinase activity of PTK6. In the present disclosure, a different approach is taken: to develop compounds that directly and selectively target not only the kinase activity of PTK6, but also its protein level. Strategies for inducing protein degradation include recruiting E3 ubiquitin ligases, mimicking protein misfolding with hydrophobic tags, and inhibiting chaperones. For example, a thalidomide-JQ1 bivalent compound has been used to hijack the cereblon E3 ligase, inducing highly selective BET protein degradation *in vitro* and *in vivo* and resulting in a demonstrated delay in leukemia progression in mice (Winter et al., 2015). Similarly, BET protein degradation has also been induced via another E3 ligase, VHL (Zengerle et al., 2015). Partial degradation of Her3 has been induced using an adamantane-modified compound (Xie et al., 2014). Such an approach, based on the use of bivalent small molecule compounds, permits more flexible regulation of protein levels *in vitro* and *in vivo* compared with techniques such as gene knockout or shRNA (short hairpin RNA) knockdown. Unlike gene knockout or shRNA knockdown, a small molecule approach further provides an opportunity to study dose and time dependency in a disease model through varying the concentrations and frequencies of administration of the relevant small molecule.

This disclosure includes all stereoisomers, geometric isomers, tautomers and isotopes of the structures depicted and compounds named herein. This disclosure also includes compounds

described herein, regardless of how they are prepared, e.g., synthetically, through biological process (e.g., metabolism or enzyme conversion), or a combination thereof.

This disclosure includes pharmaceutically acceptable salts of the structures depicted and compounds named herein.

One or more constituent atoms of the compounds presented herein can be replaced or substituted with isotopes of the atoms in natural or non-natural abundance. In some embodiments, the compound includes at least one deuterium atom. In some embodiments, the compound includes two or more deuterium atoms. In some embodiments, the compound includes 1-2, 1-3, 1-4, 1-5, or 1-6 deuterium atoms. In some embodiments, all of the hydrogen atoms in a compound can be replaced or substituted by deuterium atoms. In some embodiments, the compound includes at least one fluorine atom. In some embodiments, the compound includes two or more fluorine atoms. In some embodiments, the compound includes 1-2, 1-3, 1-4, 1-5, or 1-6 fluorine atoms. In some embodiments, all of the hydrogen atoms in a compound can be replaced or substituted by fluorine atoms.

Degraders

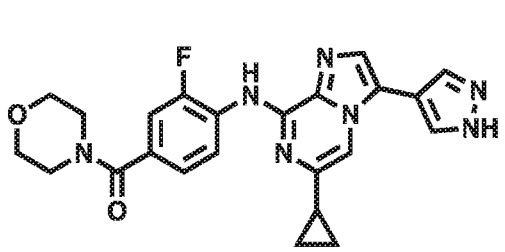
In some aspects, the present disclosure provides bivalent compounds, also referred to herein as degraders, comprising an PTK6 ligand (or targeting moiety) conjugated to a degradation tag. Linkage of the PTK6 ligand to the degradation tag can be direct, or indirect via a linker.

As used herein, the terms "Protein tyrosine kinase 6 ligand", "breast tumor kinase ligand", "PTK6 ligand", "Brk ligand", or "PTK6 targeting moiety" are to be construed broadly, and encompass a wide variety of molecules ranging from small molecules to large proteins that associate with or bind to PTK6. The PTK6 ligand or targeting moiety can be, for example, a small molecule compound (i.e., a molecule of molecular weight less than about 1.5 kilodaltons (kDa)), a peptide or polypeptide, nucleic acid or oligonucleotide, carbohydrate such as oligosaccharides, or an antibody or fragment thereof.

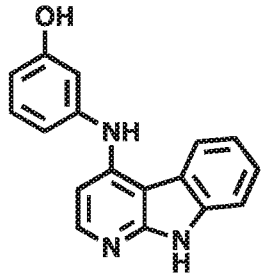
The PTK6 ligand or targeting moiety can be a PTK6 kinase inhibitor (e.g., compound 21d (Zeng et al., 2011), compound 4f (Mahmoud et al., 2014), compound 1 (Yamamoto, 2016), XMU-MP-2 (Jiang et al., 2017), and compound 3s (Cardenas et al., 2018), and analogs thereof), which is capable of inhibiting the kinase activity of PTK6. As used herein, a "PTK6 kinase inhibitor" refers to an agent that restrains, retards, or otherwise causes inhibition of a physiological, chemical

or enzymatic action or function and causes a decrease in binding of at least 5%. An inhibitor can also or alternately refer to a drug, compound, or agent that prevents or reduces the expression, transcription, or translation of a gene or protein. An inhibitor can reduce or prevent the function of a protein, e.g., by binding to or activating/inactivating another protein or receptor.

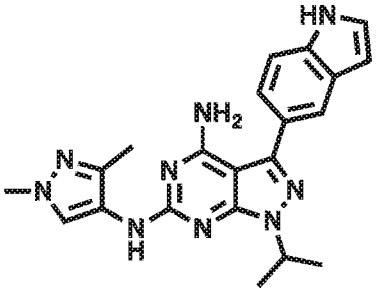
Exemplary PTK6 ligands include, but are not limited to, the compounds listed below:



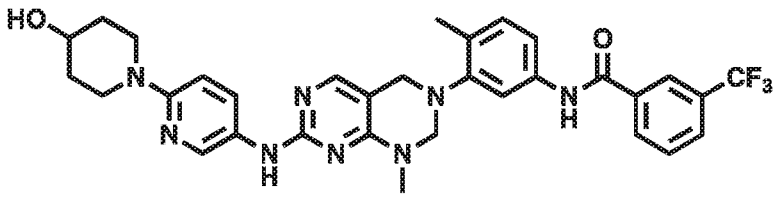
Compound 21d



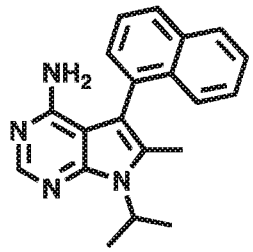
Compound 4f



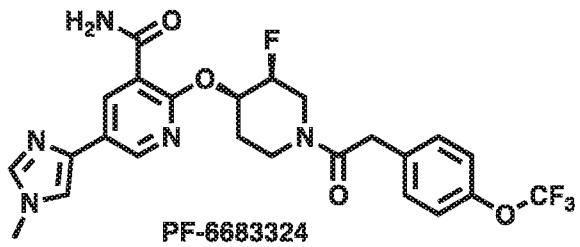
Compound 1



XMU-MP-2



Compound 3s



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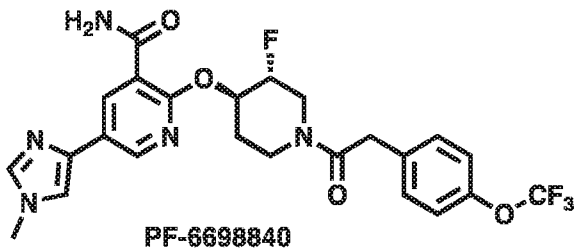

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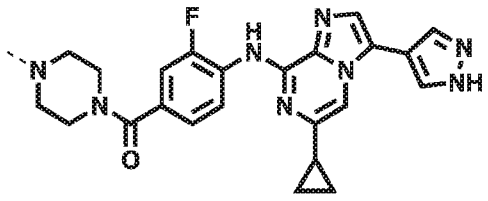
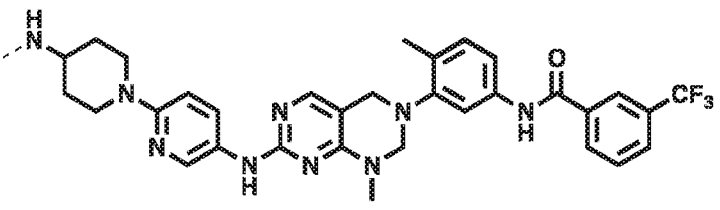
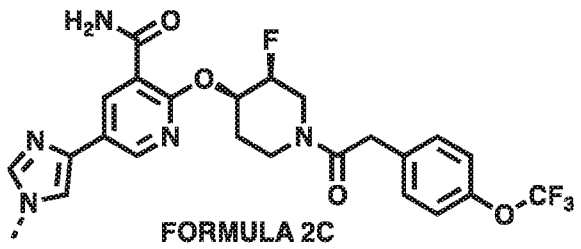


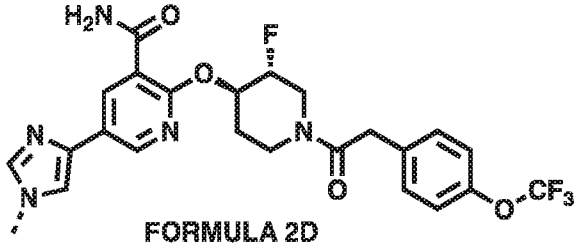
FORMULA 2A



FORMULA 2B



FORMULA 2C



FORMULA 2D

As used herein, the term "degradation/disruption tag" refers to a compound, which associates with or binds to an ubiquitin ligase for recruitment of the corresponding ubiquitination machinery to PTK6 or induces PTK6 protein misfolding and subsequent degradation at the proteasome or loss of function.

In some aspects, the degradation/disruption tags of the present disclosure include, e.g., pomalidomide (Fischer et al., 2014), thalidomide (Fischer et al., 2014), lenalidomide (Fischer et al., 2014), VH032 (Galdeano et al., 2014; Maniaci et al., 2017), adamantine (Xie et al., 2014), 1-((4,4,5,5,5-pentafluoropentyl)sulfinyl)nonane (E.Wakeling, 1995), nutlin-3a (Vassilev et al., 2004), RG7112 (Vu et al., 2013), RG7338, AMG 232 (Sun et al., 2014), AA-115 (Aguilar et al., 2017), bestatin (Hiroyuki Suda et al., 1976), MV1 (Varfolomeev et al., 2007), LCL161 (Weisberg et al., 2010), FK506 (Liu et al., 1991) rapamycin (Fan et al., 2017; Rodrik-Outmezguine et al., 2016), and/or analogs thereof.

As used herein, a "linker" is a bond, molecule, or group of molecules that binds two separate entities to one another. Linkers provide for optimal spacing of the two entities. The term "linker" in some aspects refers to any agent or molecule that bridges the PTK6 ligand to the degradation/disruption tag. One of ordinary skill in the art recognizes that sites on the PTK6 ligand or the degradation/disruption tag, which are not necessary for the function of the degraders of the present disclosure, 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 PTK6 ligand, i.e., its ability to bind PTK6, or the function of the degradation/disruption tag, i.e., its ability to recruit a ubiquitin ligase.

The length of the linker of the bivalent compound can be adjusted to minimize the molecular weight of the disruptors/degraders and avoid the clash of the PTK6 ligand or targeting moiety with the ubiquitin ligase or induce PTK6 misfolding by the hydrophobic tag at the same time.

In some aspects, the degradation/disruption tags of the present disclosure include, for example, pomalidomide (Fischer et al., 2014), thalidomide (Fischer et al., 2014), lenalidomide (Fischer et al., 2014), VH032 (Galdeano et al., 2014; Maniaci et al., 2017), adamantine (Xie et al., 2014), 1-((4,4,5,5,5-pentafluoropentyl)sulfinyl)nonane (E.Wakeling, 1995), nutlin-3a (Vassilev et al., 2004), RG7112 (Vu et al., 2013), RG7338, AMG 232 (Sun et al., 2014), AA-115 (Aguilar et al., 2017), bestatin (Hiroyuki Suda et al., 1976), MV1 (Varfolomeev et al., 2007), LCL161 (Weisberg et al., 2010), FK506 (Liu et al., 1991) rapamycin (Fan et al., 2017; Rodrik-Outmezguine et al., 2016), and analogs thereof. The degradation/disruption tags can be attached to each portion of interest in the structure of a PTK6 ligand or targeting moiety (e.g., compound 21d (Zeng et al., 2011), compound 4f (Mahmoud et al., 2014), compound 1 (Yamamoto, 2016), XMU-MP-2 (Jiang et al., 2017), and compound 3s (Cardenas et al., 2018), and analogs thereof) with linkers of different types and lengths in order to generate effective bivalent compounds. In particular, attaching pomalidomide or VHL-1 to either portion of the molecule can recruit the cereblon E3 ligase or VHL E3 ligase to PTK6.

The bivalent compounds disclosed herein can selectively affect PTK6-mediated disease cells compared to WT (wild type) cells (i.e., an PTK6 degrader/disruptor able to kill or inhibit the growth of an PTK6-mediated disease cell while also having a relatively low ability to lyse or inhibit the growth of a WT cell), e.g., possess a GI_{50} for one or more PTK6-mediated disease 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 cells, e.g., WT cells of the same species and tissue type as the PTK6-mediated disease cells.

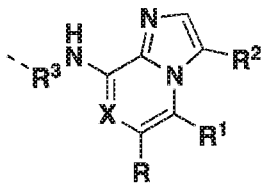
Additional bivalent compounds (i.e., PTK6 degraders/disruptors) can be developed using the principles and methods disclosed herein. For example, other linkers, degradation/disruption tags, and PTK6 binding/inhibiting moieties (not limited to compound 21d (Zeng et al., 2011), compound 4f (Mahmoud et al., 2014), compound 1 (Yamamoto, 2016), XMU-MP-2 (Jiang et al., 2017), and compound 3s (Cardenas et al., 2018), and analogs thereof) can be synthesized and tested.

In some aspects, the PTK6 degraders/disruptors have the form "**PI-Linker-EL**", as shown below:

wherein **PI** (a ligand for a "protein of interest," i.e., the protein to be degraded) comprises an PTK6 ligand (e.g., an PTK6 kinase inhibitor), and **EL** (e.g., a ligand for an E3 ligase) comprises a degradation/disruption tag (e.g., E3 ligase ligand). Exemplary PTK6 ligands (**PI**), exemplary degradation/disruption tags (**EL**), and exemplary linkers (**Linker**) are illustrated below:

PTK6 Ligands

PTK6 Ligands include but are not limited to:



FORMULA 1

Wherein

R is selected from H, halo, or unsubstituted or optionally substituted C_{1-8} alkyl, C_1-C_8 haloalkyl, C_1-C_8 hydroxyalkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} heterocyclyl, C_1-C_8 alkyleneOR^4, C_1-C_8 alkyleneSR^5, C_1-C_8 alkylene NR^{6}R^7, C_2-C_8 alkenyl, C_2-C_8 alkynyl, OR^4, SR^5, NR^{6}R^7,

R^1 is selected from H, C_{1-8} alkyl, C_1-C_8 hydroxyalkyl, C_1-C_8 alkoxyalkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} heterocyclyl, OR^8, SR^9, NR^{10}R^{11},

R^2 is selected from C_6-C_{10} aryl or C_5-C_{10} heteroaryl. R^2 is unsubstituted or optionally substituted with one or more of groups selected from halo, =O, =S, CN, NO_2, C_{1-8} alkyl, C_1-C_8 haloalkyl, C_1-C_8 hydroxyalkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} heterocyclyl, C_1-C_8 alkyleneOR^{12}, C_1-C_8 alkyleneSR^{13}, C_1-C_8 alkylene NR^{14}R^{15}, C_2-C_8 alkenyl, C_2-C_8 alkynyl, OR^{12}, SR^{13}, NR^{14}R^{15},

R^3 is selected from C_6-C_{10} aryl or C_5-C_{10} heteroaryl. R^3 is unsubstituted or substituted with one or more of groups selected from C_1-C_8 alkyl, C_1-C_8 haloalkyl, C_1-C_8 hydroxyalkyl, C_1-C_8 alkoxyalkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} heterocyclyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, halo, CN, NO_2, =O, =S, R^{16}, OR^{16}, SR^{17}, SO_2R^{18}, NR^{19}R^{20}, C(O)R^{16}, C(O)OR^{16}, C(S)OR^{16}, C(O)NR^{19}R^{20},

C(S) $NR^{19}R^{20}$, $NR^{19}C(O)R^{16}$, $NR^{19}C(O)OR^{16}$, $NR^{19}S(O)R^{16}$, $NR^{19}S(O)OR^{16}$, $S(O)R^{16}$, $S(O)OR^{16}$, and $S(O)ONR^{19}R^{20}$,

R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} are independently selected from H, C_1-C_8 alkyl, C_1-C_8 haloalkyl, C_1-C_8 hydroxyalkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} heterocyclyl, $C(O)C_1$-C_8 alkyl, $C(O)C_1$-C_8 haloalkyl, $C(O)C_1$-C_8 hydroxyalkyl, $C(O)C_3$-C_{10} cycloalkyl, and $C(O)C_3$-C_{10} heterocyclyl, or
R^6 and R^7; R^{10} and R^{11}; R^{14} and R^{15} together with the nitrogen atom to which they connected can independently form 3-10 membered heterocyclyl rings,

R^{16}, R^{17}, and R^{18} are independently selected from H, C_1-C_8 alkyl, C_1-C_8 haloalkyl, C_1-C_8 alkoxyalkyl, C_1-C_8 hydroxyalkyl, C_3-C_8 cycloalkyl, C_3-C_7 heterocycloalkyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, $C(O)C_1$-C_8 alkyl, $C(O)C_1$-C_8 haloalkyl, $C(O)C_1$-C_8 hydroxyalkyl, $C(O)C_1$-C_8 alkoxyalkyl, $C(O)C_3$-C_{10} cycloalkyl, $C(O)C_3$-C_{10} heterocyclyl, $C(O)C_6$-C_{10} aryl, $C(O)C_5$-C_{10} heteroaryl, C_1-C_8 alkyleneC_3-C_{10} cycloalkyl, C_1-C_8 alkyleneC_3-C_{10} heterocycloalkyl, C_1-C_8 alkyleneC_6-C_{10} aryl, C_1-C_8 alkylene, or C_5-C_{10} heteroaryl,

R^{19} and R^{20} are independently selected from H, C_1-C_8 alkyl, C_1-C_8 haloalkyl, C_1-C_8 alkoxyalkyl, C_1-C_8 hydroxyalkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} heterocycloalkyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, $C(O)C_1$-C_8 alkyl, $C(O)C_1$-C_8 haloalkyl, $C(O)C_1$-C_8 hydroxyalkyl, $C(O)C_1$-C_8 alkoxyalkyl, $C(O)C_3$-C_{10} cycloalkyl, $C(O)C_3$-C_{10} heterocycloalkyl, $C(O)C_6$-C_{10} aryl, $C(O)C_5$-C_{10} heteroaryl, $C(O)OC_1$-C_8 alkyl, $C(O)OC_1$-C_8 haloalkyl, $C(O)OC_1$-C_8 hydroxyalkyl, $C(O)OC_1$-C_8 alkoxyalkyl, $C(O)OC_3$-C_{10} cycloalkyl, $C(O)OC_3$-C_{10} heterocyclyl, $C(O)OC_6$-C_{10} aryl, $C(O)OC_5$-C_{10} heteroaryl, $C(O)NC_1$-C_8 alkyl, $C(O)NC_1$-C_8 haloalkyl, $C(O)NC_1$-C_8 hydroxyalkyl, $C(O)NC_1$-C_8 alkoxyalkyl, $C(O)NC_3$-C_{10} cycloalkyl, $C(O)NC_3$-C_{10} heterocyclyl, $C(O)NC_6$-C_{10} aryl, $C(O)NC_5$-C_{10} heteroaryl, SO_2C_1-C_8 alkyl, SO_2C_1-C_8 haloalkyl, SO_2C_1-C_8 hydroxyalkyl, SO_2C_1-C_8 alkoxyalkyl, SO_2C_3-C_{10} cycloalkyl, SO_2C_3-C_{10} heterocyclyl, SO_2C_6-C_{10} aryl, SO_2C_5-C_{10} heteroaryl, C_1-C_8 alkyleneC_3-C_{10} cycloalkyl, C_1-C_8 alkyleneC_3-C_{10} heterocycloalkyl, C_1-C_8 alkyleneC_6-C_{10} aryl, C_1-C_8 alkyleneC_5-C_{10} heteroaryl, or
R^{19} and R^{20} together with the nitrogen atom to which they connected can independently form 3-10 membered heterocyclyl rings, and

X is selected from CH or N.

In some aspects of Formula 1, R is selected from H, halogen, optionally substituted C_{1-3} alkyl, and optionally substituted C_{1-3} alkoxy.

In some aspects of Formula 1, R is selected from H, F, CH_3, CH_2F, CHF_2, CF_3, CH_2CH_3, CH_2CF_3, i-Pr, c-Pr, OCH_3, OCH_2F, $OCHF_2$, OCF_3, OCH_2CH_3, OCH_2CF_3, Oi-Pr, and Oc-Pr.

In some aspects of Formula 1, R is selected from CH_3, CF_3, CH_2CH_3, CH_2CF_3, and c-Pr.

In some aspects of Formula 1, R is selected from CH_3, and c-Pr.

In some aspects of Formula 1, R is c-Pr.

In some aspects of Formula 1, R^1 is selected from H, halogen, optionally substituted C_{1-3} alkyl, and optionally substituted C_{1-3} alkoxy.

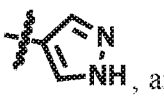
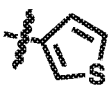
In some aspects of Formula 1, R^1 is selected from H, F, CH_3, CH_2F, CHF_2, CF_3, CH_2CH_3, CH_2CF_3, i-Pr, c-Pr, OCH_3, OCH_2F, $OCHF_2$, OCF_3, OCH_2CH_3, OCH_2CF_3, Oi-Pr, and Oc-Pr.

In some aspects of Formula 1, R^1 is selected from H, F, CH_3, and CF_3.

In some aspects of Formula 1, R^1 is H.

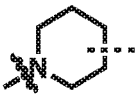
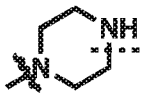
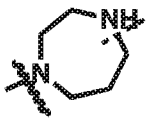
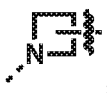
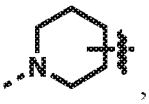
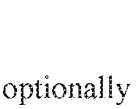
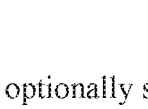
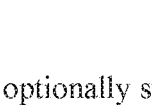
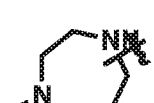
In some aspects of Formula 1, R^2 is selected from phenyl and 5-6 membered heteroaryl, which are optionally substituted with one or more of groups selected from halogen, optionally substituted C_{1-3} alkyl, and optionally substituted C_{1-3} alkoxy.

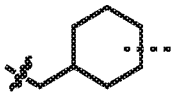
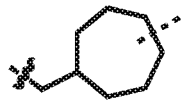
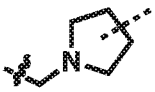
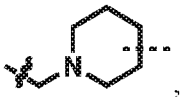
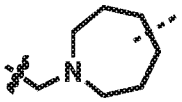
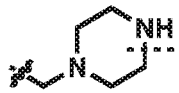
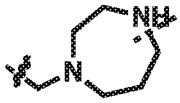
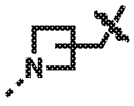
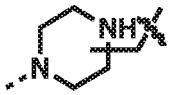
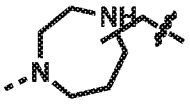
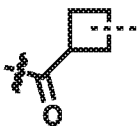
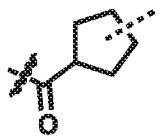
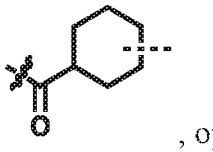
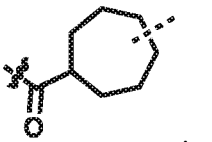
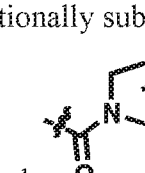
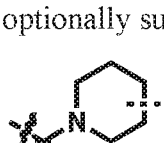
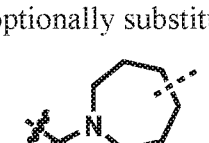
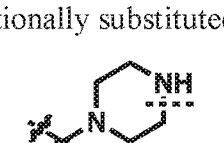
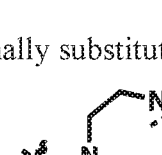
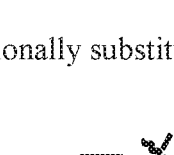
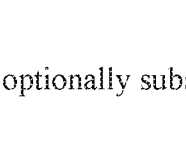
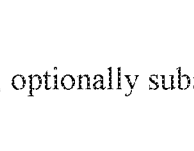
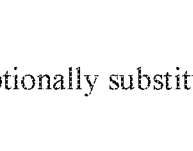
In some aspects of Formula 1, R^2 is 5-6 membered heteroaryl, which are optionally substituted with one or more of groups selected from halogen, optionally substituted C_{1-3} alkyl, and optionally substituted C_{1-3} alkoxy.

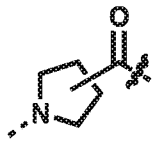
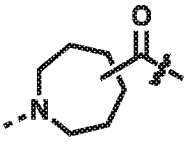
In some aspects of Formula 1, R^2 is selected from phenyl,  , and  .

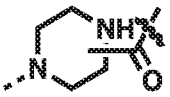
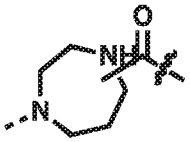
In some aspects of Formula 1, R^2 is .

In some aspects of Formula 1, R^3 is selected from phenyl, and 5-6 membered heteroaryl, which are optionally substituted with one or more of groups selected from halogen, optionally substituted C_{1-8} alkyl, and optionally substituted C_{1-8} alkoxy, optionally substituted C_{1-8} alkylene, optionally substituted 3-8 membered carbocyclyl, optionally substituted 4-8 membered heterocyclyl, optionally substituted aryl, optionally substituted 5-6 membered heteroaryl, -CO-, -C(O)-(C_{1-8} alkylene)-, -C(O)-NH(C_{1-8} alkylene)-, -C(O)-N(C_{1-8} alkylene)(C_{1-8} alkylene)-, -C(O)-(3-8 membered carbocyclyl)-, -C(O)-(4-8 membered heterocyclyl)-, -C(O)-(5-6 membered heteroaryl)-, -NH(C_{1-8} alkylene)-, -N(C_{1-8} alkylene)(C_{1-8} alkylene)-, - CH_2-(3-8 membered carbocyclyl)-, - CH_2-(4-8 membered heterocyclyl)-, and -CH_2-(5-6 membered heteroaryl)-.

In some aspects of Formula 1, R^3 is selected from phenyl, and 5-6 membered heteroaryl, which are optionally substituted with one or more of groups selected from F, Cl, CH_3, CF_3, OCH_3, OCF_3, CH_2CH_3, CH_2CF_3, OCH_2CH_3, OCH_2CF_3, i-Pr, c-Pr, i-PrO, c-PrO, -CO-, optionally substituted , optionally substituted , optionally substituted , optionally substituted , optionally substituted , optionally substituted , optionally substituted , optionally substituted  , optionally substituted , optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted , optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted .

substituted , optionally substituted  , optionally substituted  , optionally substituted , optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted , optionally substituted , optionally substituted , optionally substituted  , optionally substituted  , optionally substituted , optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted , optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted , optionally substituted , optionally substituted

 , optionally substituted , optionally substituted  ,

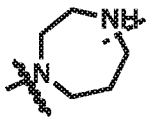
optionally substituted  , and optionally substituted  .

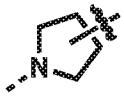
In some aspects of Formula 1, R^3 is selected from phenyl, thiophene, thiazole, isothiazole, pyrolyl, pyrazolyl, imidazolyl, pyridinyl, pyrimidinyl, and pyrazinyl, which are optionally substituted with one or more of groups selected from F, Cl, CH_3, CF_3, OCH_3, OCF_3, CH_2CH_3, CH_2CF_3, OCH_2CH_3, OCH_2CF_3, i-Pr, c-Pr, i-PrO, c-PrO, -CO-, optionally substituted ,

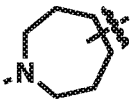
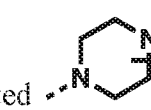
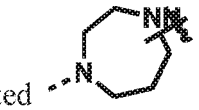
optionally substituted , optionally substituted , optionally substituted

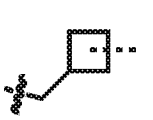
, optionally substituted , optionally substituted , optionally

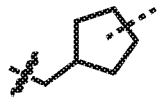
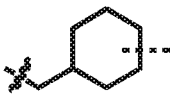
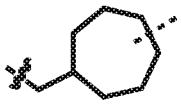
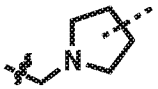
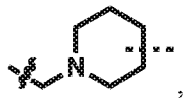
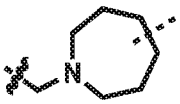
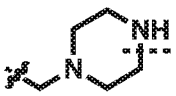
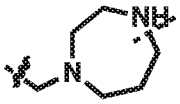
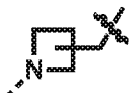
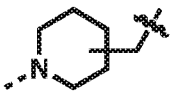
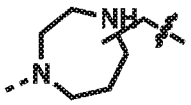
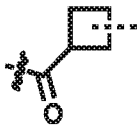
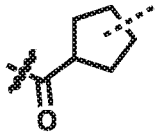
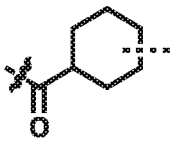
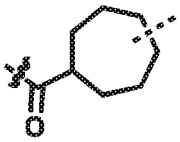
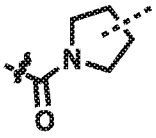
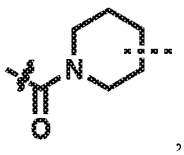
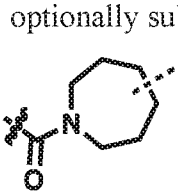
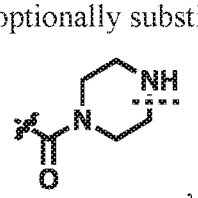
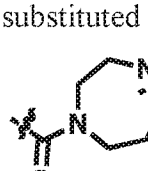
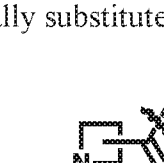
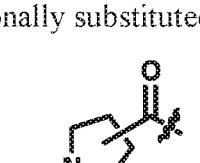
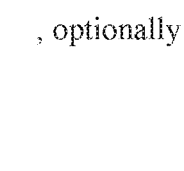
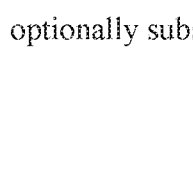
substituted , optionally substituted , optionally substituted ,

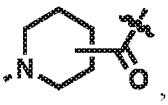
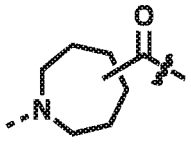
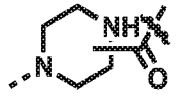
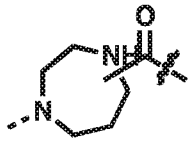
optionally substituted , optionally substituted  , optionally substituted

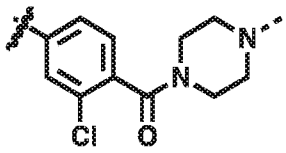
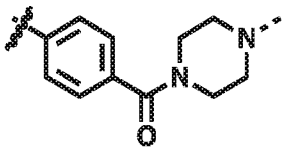
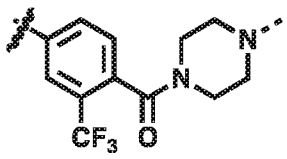
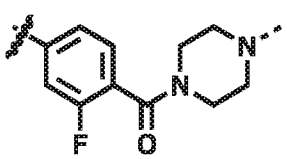
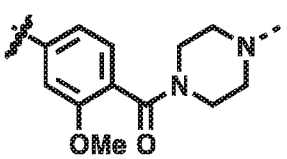
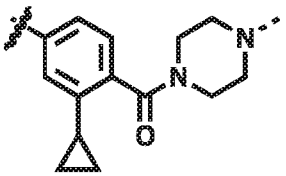
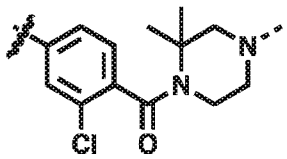
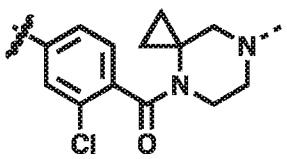
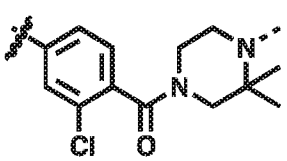
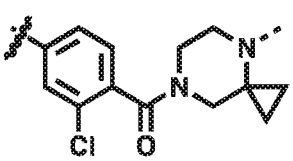
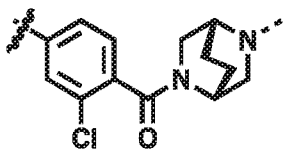
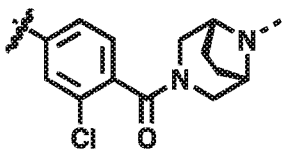
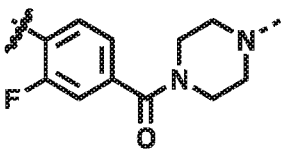
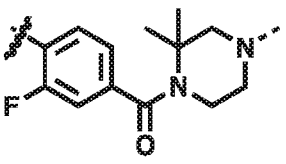
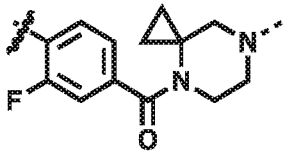
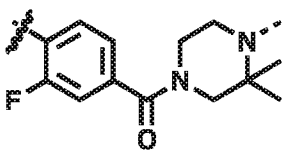
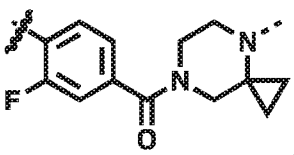
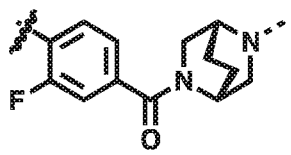
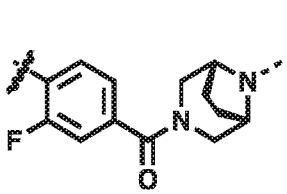
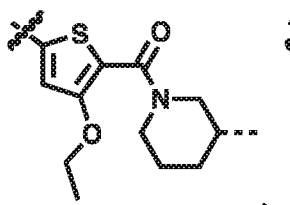
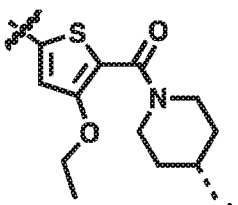
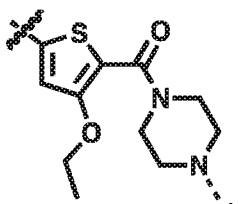
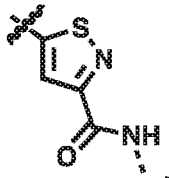
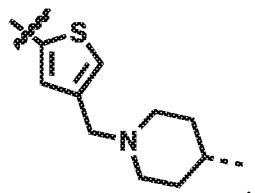
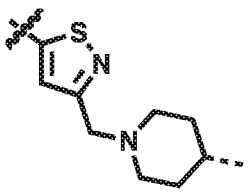
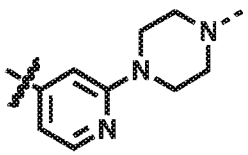
, optionally substituted  , optionally substituted , optionally

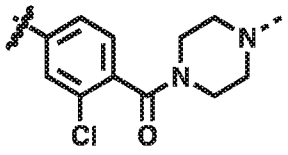
substituted  , optionally substituted  , optionally substituted  ,

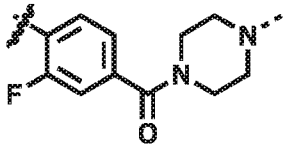
optionally substituted , optionally substituted  , optionally substituted

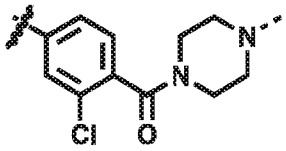
 , optionally substituted  , optionally substituted  ,
optionally substituted , optionally substituted  , optionally substituted
 , optionally substituted  , optionally substituted  ,
optionally substituted  , optionally substituted  , optionally substituted
, optionally substituted  , optionally substituted ,
optionally substituted , optionally substituted  , optionally substituted
, optionally substituted  , optionally substituted  , optionally
substituted  , optionally substituted  , optionally substituted
, optionally substituted  , optionally substituted  , optionally
substituted  , optionally substituted  , optionally substituted
 , optionally substituted  , optionally substituted  , optionally
substituted  , optionally substituted  , optionally substituted
, optionally substituted , optionally substituted , optionally

substituted  , optionally substituted  , optionally substituted  , and optionally substituted  .

In some aspects of Formula 1, R^3 is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  .

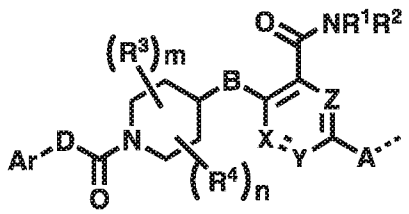
In some aspects of Formula 1, R^3 is selected from  , and



In some aspects of Formula 1, R^3 is  .

In some aspects of Formula 1, X is N.

PTK6 Ligands could also be:



FORMULA 2

Wherein

X, Y and Z are independently selected from null, CR^5, and N, wherein

R^5 is selected from hydrogen, halogen, or optionally substituted C_{1-3} alkyl;

A is selected from null or $-R^6-R^7-$, wherein

R^6 and R^7 are independently selected from null, NR^8, O, S, C(O), $C(O)NR^8$, $NR^8C(O)$, $NR^8C(O)NR^9$, $OC(O)NR^9$, $NR^8C(O)O$, S(O), $S(O)NR^8$, $NR^8S(O)$, $NR^8S(O)NR^9$, $OS(O)NR^9$, $NR^8S(O)O$, $S(O)_2$, $S(O)_2NR^8$, $NR^8S(O)_2$, $NR^8S(O)_2NR^9$, $OS(O)_2NR^9$, $NR^8S(O)_2O$, optionally substituted C_1-C_8 alkylene, optionally substituted C_2-C_8 alkenylene, optionally substituted C_2-C_8

alkynylene, optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, wherein

R^8 and R^9 are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted 3-10 membered carbocyclylC_1-C_8alkyl, optionally substituted 4-10 membered heterocyclylC_1-C_8alkyl, optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^8 and R^9 together with the atom to which they are connected form a 4-20 membered heterocyclyl ring;

B and D are independently selected from $CR^{10}R^{11}$, NR^{10}, O, SO, or SO_2, wherein

R^{10} and R^{11} are independently selected from hydrogen, halogen, hydroxy, cyano, nitro, and optionally substituted C_1-C_3 alkyl, or

R^{10} and R^{11} together with the atom to which they are connected form a 3-6 membered carbocyclyl rings or 4-6 membered heterocyclyl ring;

R^1 and R^2 are independently selected from hydrogen, and optionally substituted C_1-C_3 alkyl, or R^1 and R^2 together with the atom to which they are connected form a 4-6 membered heterocyclyl ring;

R^3 and R^4, at each occurrence, are independently selected from hydrogen, fluoro, hydroxyl, cyano, amino, nitro, optionally substituted C_1-C_3 alkyl, optionally substituted C_1-C_3 alkoxy, and optionally substituted C_1-C_3 alkylamino.

m and n are independently selected from 0, 1, 2, 3, and 4.

Ar is selected from aryl, and heteroaryl, which are optionally substituted with one or more substituents independently selected from hydrogen, halogen, oxo, CN, NO_2, OR^{12}, SR^{12},

$NR^{12}R^{13}$, $OCOR^{12}$, OCO_2R^{12}, $OCON(R^{12})R^{13}$, COR^{12}, CO_2R^{12}, $CON(R^{12})R^{13}$, SOR^{12}, SO_2R^{12}, $SO_2N(R^{12})R^{13}$, $NR^{14}CO_2R^{12}$, $NR^{14}COR^{12}$, $NR^{14}C(O)N(R^{12})R^{13}$, $NR^{14}SOR^{12}$, $NR^{14}SO_2R^{12}$, $NR^{14}SO_2N(R^{12})R^{13}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted 4-10 membered heterocyclylC_1-C_8alkyl, optionally substituted 3-10 membered carbocyclylC_1-C_8alkyl, optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, wherein

R^{12}, R^{13}, and R^{14} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted 3-10 membered carbocyclylC_1-C_8alkyl, optionally substituted 4-10 membered heterocyclylC_1-C_8alkyl, optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^{12} and R^{13}, R^{12} and R^{14} together with the atom to which they are connected form a 4-20 membered heterocyclyl ring;

In some aspects of Formula 2, X, Y and Z are independently selected from CH, CF, and N.

In some aspects of Formula 2, X is N; Y and Z are independently selected from CH, CF, and N.

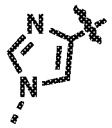
In some aspects of Formula 2, X is N; Y and Z are CH.

In some aspects of Formula 2, A is null or selected from optionally substituted 3-8 membered carbocyclyl, optionally substituted 4-8 membered heterocyclyl, optionally substituted 6 membered aryl, optionally substituted 5-6 membered heteroaryl, fused rings, bridged rings, and spiro rings.

In some aspects of Formula 2, A is null, phenyl, 4-8 membered heterocyclyl, and 5-6 membered heteroaryl, which are optionally substituted by F, OH, CN, NO_2, NH_2, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 alkoxy, optionally substituted 3-10

membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl.

In some aspects of Formula 2, A is null, phenyl, 4-8 membered heterocyclyl, and 5-6 membered heteroaryl, which are optionally substituted by F, OH, CN, NO_2, NH_2, CH_3, CF_3, i-Pr, and c-Pr.

In some aspects of Formula 2, A is  .

In some aspects of Formula 2, B and D are independently selected from CH_2, CHOH, $CHCH_3$, $C(CH_3)_2$, , CHF, CF_2, O, NH, and NCH_3.

In some aspects of Formula 2, B is O.

In some aspects of Formula 2, D is CH_2.

In some aspects of Formula 2, R^1 and R^2 are independently selected from H, and optionally substituted C_1-C_3 alkyl, with the proviso that at least one of R^1 and R^2 is H.

In some aspects of Formula 2, R^1 and R^2 are independently selected from H, and CH_3, with the proviso that at least one of R^1 and R^2 is H.

In some aspects of Formula 2, R^1 and R^2 are H.

In some aspects of Formula 2, R^3 and R^4, at each occurrence, are independently selected from H, F, OH, CN, NH_2, NO_2, CH_3, CF_3, i-Pr, and c-Pr.

In some aspects of Formula 2, R^3 and R^4, at each occurrence, are independently selected from H, and F.

In some aspects of Formula 2, m and n are independently selected from 0, 1, and 2.

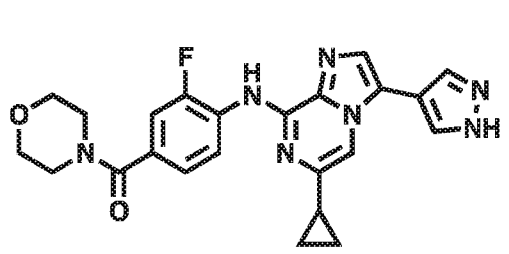
In some aspects of Formula 2, m and n are 1.

In some aspects of Formula 2, Ar is selected from aryl, and heteroaryl, which are optionally substituted with one or more substituents independently selected from H, F, =O, CN, NO_2, CH_3, OCH_3, CH_2F, CHF_2, CF_3, OCH_2F, $OCHF_2$, OCF_3, i-Pr, and c-Pr.

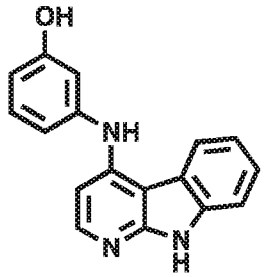
In some aspects of Formula 2, Ar is phenyl, which is optionally substituted with one or more substituents independently selected from H, F, =O, CN, NO_2, CH_3, OCH_3, CH_2F, CHF_2, CF_3, OCH_2F, $OCHF_2$, OCF_3, i-Pr, and c-Pr.

In some aspects of Formula 2, Ar is 4-OCF_3 substituted phenyl.

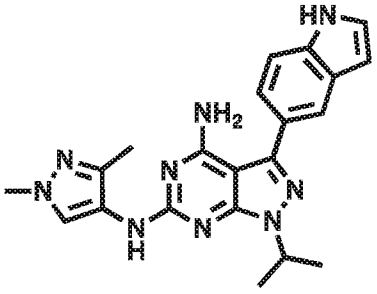
In some aspects, the PTK6 ligand can be derivatives of following compounds:



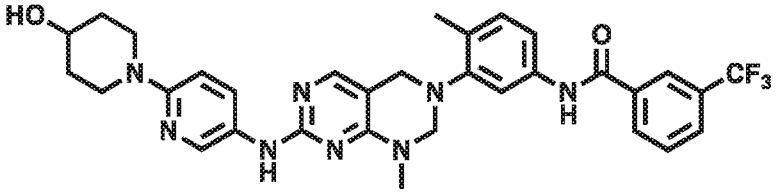
Compound 21d



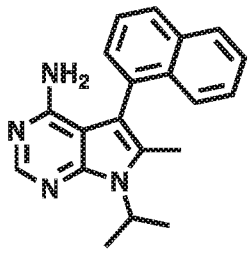
Compound 4f



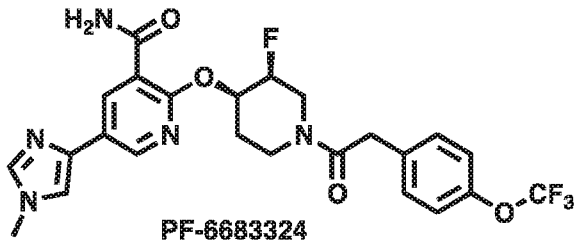
Compound 1



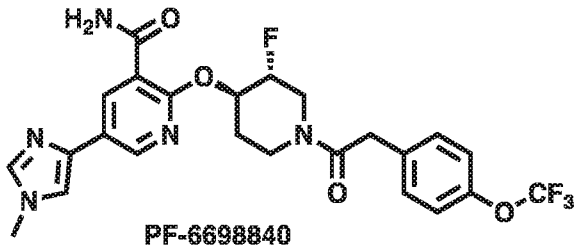
XMU-MP-2



Compound 3s

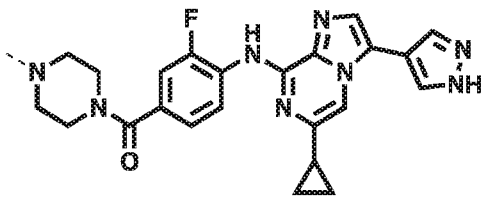


PF-6683324

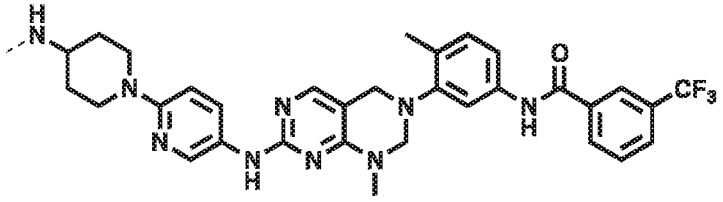


PF-6698840

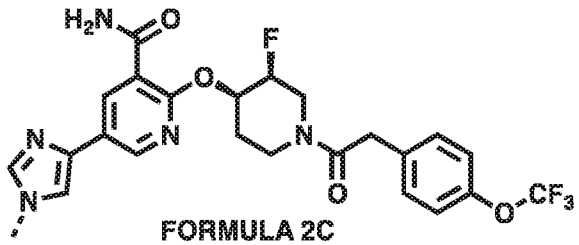
In some aspects, the PTK6 ligand can be, e.g.:



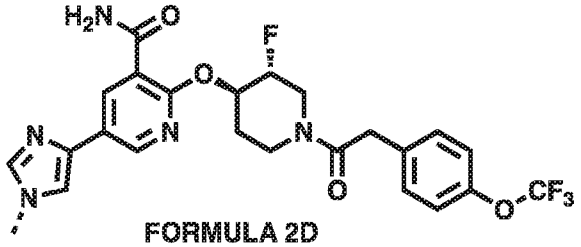
FORMULA 2A



FORMULA 2B



FORMULA 2C

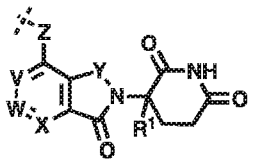


FORMULA 2D

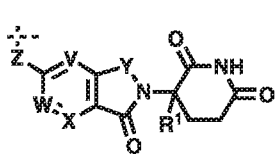
The PTK6 ligand can be bound to PTK6 and/or PTK6 mutant proteins.

Degradation / Disruption Tags

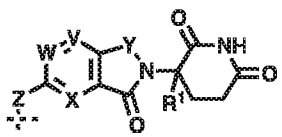
Degradation / Disruption Tags (**EL**) include but are not limited to:



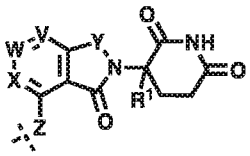
FORMULA 3A



FORMULA 3B



FORMULA 3C



FORMULA 3D,

wherein

V, W, and X are independently selected from CR^2 and N;

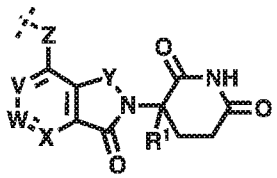
Y is selected from CO, CR^3R^4, and N=N;

Z is selected from null, CO, CR^5R^6, NR^5, O, optionally substituted C_1-C_{10} alkylene, optionally substituted C_1-C_{10} alkenylene, optionally substituted C_1-C_{10} alkynylene, optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted C_3-C_{13} fused cycloalkyl, optionally substituted C_3-C_{13} fused heterocyclyl, optionally substituted C_3-C_{13} bridged cycloalkyl, optionally substituted C_3-C_{13} bridged heterocyclyl, optionally substituted C_3-C_{13} spiro cycloalkyl, optionally substituted C_3-C_{13} spiro heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl; preferly, Z is selected from null, CH_2, CH=CH, C≡C, NH and O;

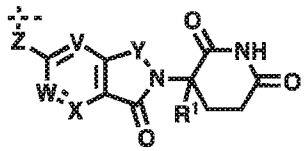
R^1, and R^2 are independently selected from hydrogen, halogen, cyano, nitro, optionally substituted C_1-C_6 alkyl, optionally substituted 3 to 6 membered carbocyclyl, and optionally substituted 4 to 6 membered heterocyclyl;

R^3, and R^4 are independently selected from hydrogen, halogen, cyano, nitro, optionally substituted C_1-C_6 alkyl, optionally substituted 3 to 6 membered carbocyclyl, and optionally substituted 4 to 6 membered heterocyclyl; or R^3 and R^4 together with the atom to which they are connected form a 3-6 membered carbocyclyl, or 4-6 membered heterocyclyl; and

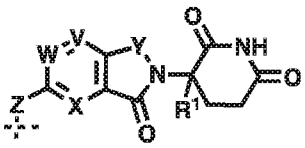
R^5 and R^6 are independently selected from null, hydrogen, halogen, oxo, hydroxyl, amino, cyano, nitro, optionally substituted C_1-C_6 alkyl, optionally substituted 3 to 6 membered carbocyclyl, and optionally substituted 4 to 6 membered heterocyclyl; or R^5 and R^6 together with the atom to which they are connected form a 3-6 membered carbocyclyl, or 4-6 membered heterocyclyl.



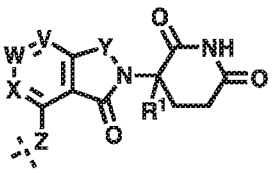
FORMULA 3A



FORMULA 3B



FORMULA 3C



FORMULA 3D

wherein

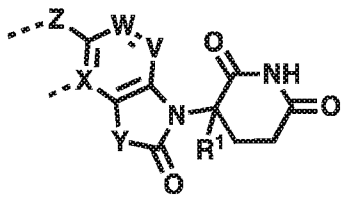
V, W, and X are independently CR^2 or N,

Y is CO or CH_2,

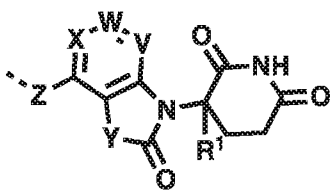
Z is CH_2, NH, or O,

R^1 is hydrogen, methyl, or fluoro, and

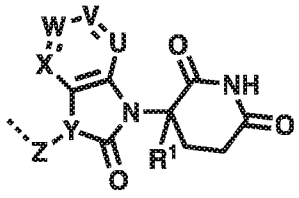
R^2 is hydrogen, halogen, or C_1-C_5 alkyl;



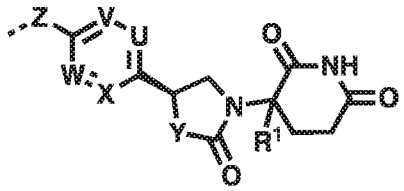
FORMULA 3E



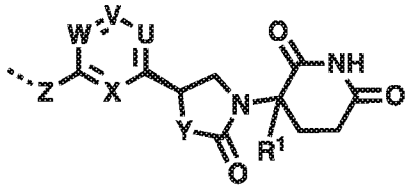
FORMULA 3F



FORMULA 3G



FORMULA 3H



FORMULA 3I

wherein

U, V, W, and X are independently selected from CR^2 and N;

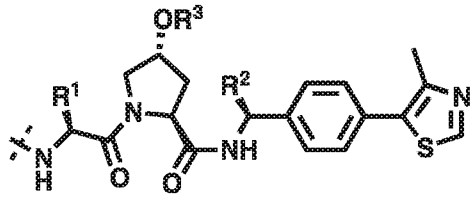
Y is selected from CR^3R^4, NR^3 and O; preferably, Y is selected from CH_2, NH, NCH_3 and O;

Z is selected from null, CO, CR^5R^6, NR^5, O, optionally substituted C_1-C_{10} alkylene, optionally substituted C_1-C_{10} alkenylene, optionally substituted C_1-C_{10} alkynylene, optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted C_3-C_{13} fused cycloalkyl, optionally substituted C_3-C_{13} fused heterocyclyl, optionally substituted C_3-C_{13} bridged cycloalkyl, optionally substituted C_3-C_{13} bridged heterocyclyl, optionally substituted C_3-C_{13} spiro cycloalkyl, optionally substituted C_3-C_{13} spiro heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl; preferly, Z is selected from null, CH_2, CH=CH, C≡C, NH and O;

R^1, and R^2 are independently selected from hydrogen, halogen, cyano, nitro, optionally substituted C_1-C_6 alkyl, optionally substituted 3 to 6 membered carbocyclyl, and optionally substituted 4 to 6 membered heterocyclyl;

R^3, and R^4 are independently selected from hydrogen, halogen, cyano, nitro, optionally substituted C_1-C_6 alkyl, optionally substituted 3 to 6 membered carbocyclyl, and optionally substituted 4 to 6 membered heterocyclyl; or R^3 and R^4 together with the atom to which they are connected form a 3-6 membered carbocyclyl, or 4-6 membered heterocyclyl; and

R^5 and R^6 are independently selected from null, hydrogen, halogen, oxo, hydroxyl, amino, cyano, nitro, optionally substituted C_1-C_6 alkyl, optionally substituted 3 to 6 membered carbocyclyl, and optionally substituted 4 to 6 membered heterocyclyl; or R^5 and R^6 together with the atom to which they are connected form a 3-6 membered carbocyclyl, or 4-6 membered heterocyclyl.

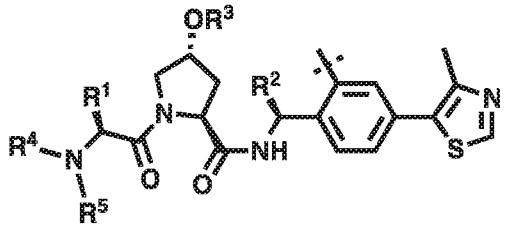


FORMULA 4A

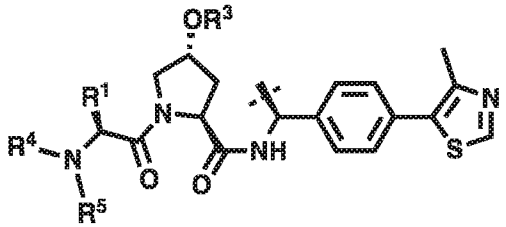
wherein

R^1 and R^2 are independently hydrogen, C_1-C_8 alkyl, C_1-C_8 alkoxyalkyl, C_1-C_8 haloalkyl, C_1-C_8 hydroxyalkyl, C_1-C_8 aminoalkyl, C_1-C_8 alkylaminoalkyl, C_3-C_7 cycloalkyl, C_3-C_7 heterocyclyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl;

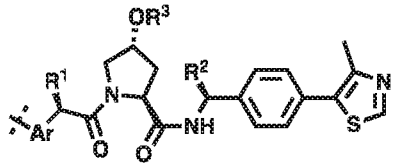
R^3 is H, $C(O)C_1$-C_8 alkyl, $C(O)C_1$-C_8 alkoxyalkyl, $C(O)C_1$-C_8 haloalkyl, $C(O)C_1$-C_8 hydroxyalkyl, $C(O)C_1$-C_8 aminoalkyl, $C(O)C_1$-C_8 alkylaminoalkyl, $C(O)C_3$-C_7 cycloalkyl, $C(O)C_3$-C_7 heterocyclyl, $C(O)C_2$-C_8 alkenyl, $C(O)C_2$-C_8 alkynyl, $C(O)OC_1$-C_8 alkoxyalkyl, $C(O)OC_1$-C_8 haloalkyl, $C(O)OC_1$-C_8 hydroxyalkyl, $C(O)OC_1$-C_8 aminoalkyl, $C(O)OC_1$-C_8 alkylaminoalkyl, $C(O)OC_3$-C_7 cycloalkyl, $C(O)OC_3$-C_7 heterocyclyl, $C(O)OC_2$-C_8 alkenyl, $C(O)OC_2$-C_8 alkynyl, $C(O)NC_1$-C_8 alkoxyalkyl, $C(O)NC_1$-C_8 haloalkyl, $C(O)NC_1$-C_8 hydroxyalkyl, $C(O)NC_1$-C_8 aminoalkyl, $C(O)NC_1$-C_8 alkylaminoalkyl, $C(O)NC_3$-C_7 cycloalkyl, $C(O)NC_3$-C_7 heterocyclyl, $C(O)NC_2$-C_8 alkenyl, $C(O)NC_2$-C_8 alkynyl, $P(O)(OH)_2$, $P(O)(OC_1$-C_8 $alkyl)_2$, or $P(O)(OC_1$-C_8 $aryl)_2$.



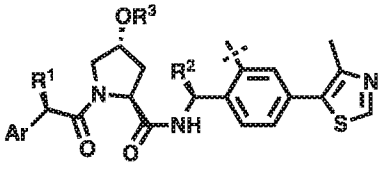
FORMULA 4B



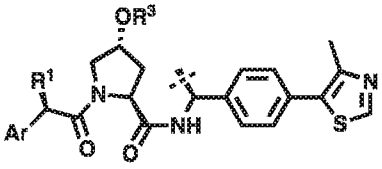
FORMULA 4C



FORMULA 4D



FORMULA 4E



FORMULA 4F

wherein

R^1 and R^2 are independently selected from hydrogen, halogen, OH, NH_2, CN, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-C_8 hydroxyalkyl, optionally substituted C_1-C_8 aminoalkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_7 cycloalkyl, optionally substituted 3-7 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, and optionally substituted C_2-C_8 alkynyl; (preferably, R^1 is selected from iso-propyl or tert-butyl; and R^2 is selected from hydrogen or methyl);.

R^3 is hydrogen, optionally substituted C(O)C_1-C_8 alkyl, optionally substituted C(O)C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C(O)C_1-C_8 haloalkyl, optionally substituted C(O)C_1-C_8 hydroxyalkyl, optionally substituted C(O)C_1-C_8 aminoalkyl, optionally substituted C(O)C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C(O)C_3-C_7 cycloalkyl, optionally substituted C(O)(3-7 membered heterocyclyl), optionally substituted C(O)C_2-C_8 alkenyl, optionally substituted C(O)C_2-C_8 alkynyl, optionally substituted C(O)OC_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C(O)OC_1-C_8 haloalkyl, optionally substituted C(O)OC_1-C_8 hydroxyalkyl, optionally substituted C(O)OC_1-C_8 aminoalkyl, optionally substituted C(O)OC_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C(O)OC_3-C_7 cycloalkyl, optionally substituted C(O)O(3-7 membered heterocyclyl), optionally substituted C(O)OC_2-C_8 alkenyl, optionally substituted C(O)OC_2-C_8 alkynyl, optionally substituted C(O)NC_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C(O)NC_1-C_8 haloalkyl, optionally substituted C(O)NC_1-C_8 hydroxyalkyl, optionally substituted C(O)NC_1-C_8 aminoalkyl, optionally substituted C(O)NC_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C(O)NC_3-C_7 cycloalkyl, optionally substituted C(O)N(3-7 membered heterocyclyl), optionally substituted C(O)NC_2-C_8 alkenyl, optionally substituted C(O)NC_2-C_8 alkynyl, optionally substituted P(O)$(OH)_2$, optionally substituted P(O)$(OC_1$-C_8 alkyl$)_2$, and optionally substituted P(O)$(OC_1$-C_8 aryl$)_2$; and

R^4 and R^5 are independently selected from hydrogen, COR^6, CO_2R^6, $CONR^6R^7$, SOR^6, SO_2R^6, $SO_2NR^6R^7$, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, wherein

R^6 and R^7 are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl,

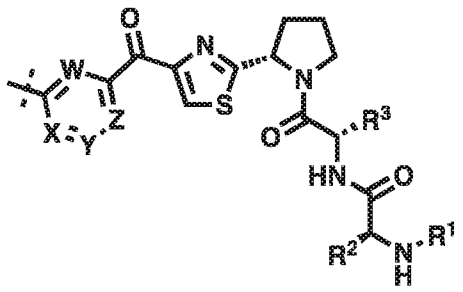
optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^4 and R^5; R^6 and R^7 together with the atom to which they are connected form a 4-8 membered cycloalkyl or heterocyclyl ring;

Ar is selected from aryl and heteroaryl, each of which is optionally substituted with one or more substituents independently selected from F, Cl, CN, NO_2, OR^8, NR^8R^9, COR^8, CO_2R^8, $CONR^8R^9$, SOR^8, SO_2R^8, $SO_2NR^9R^{10}$, NR^9COR^{10}, $NR^8C(O)NR^9R^{10}$, NR^9SOR^{10}, $NR^9SO_2R^{10}$, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 alkoxyalkyl, optionally substituted C_1-C_6 haloalkyl, optionally substituted C_1-C_6 hydroxyalkyl, optionally substituted C_1-C_6alkylaminoC_1-C_6alkyl, optionally substituted C_3-C_7 cycloalkyl, optionally substituted 3-7 membered heterocyclyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted aryl, and optionally substituted C_4-C_5 heteroaryl, wherein

R^8, R^9, and R^{10} are independently selected from null, hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted C_3-C_7 cycloalkyl, optionally substituted 3-7 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^8 and R^9; R^9 and R^{10} together with the atom to which they are connected form a 4-8 membered cycloalkyl or heterocyclyl ring.



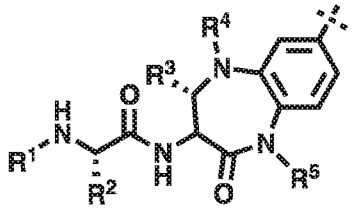
FORMULA 5A

wherein

R^1, R^2, R^3, and R^4 are independently hydrogen, C_1-C_8 alkyl, C_1-C_8 alkoxyalkyl, C_1-C_8 haloalkyl, C_1-C_8 hydroxyalkyl, C_3-C_7 cycloalkyl, C_3-C_7 heterocyclyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl, and

V, W, X, and Z are independently CR^4 or N.

And



FORMULA 5B,

wherein

R^1, R^2, and R^3 are independently selected from hydrogen, halogene, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-C_8 hydroxyalkyl, optionally substituted C_3-C_7 cycloalkyl, optionally substituted 3-7 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, and optionally substituted C_2-C_8 alkynyl;

R^4 and R^5 are independently selected from hydrogen, COR^6, CO_2R^6, $CONR^6R^7$, SOR^6, SO_2R^6, $SO_2NR^6R^7$, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted aryl-C_1-C_8alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, wherein

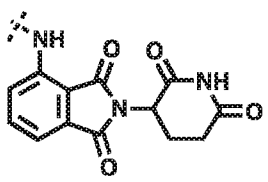
R^6 and R^7 are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or

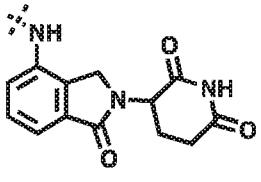
R^6 and R^7 together with the atom to which they are connected form a 4-8 membered cycloalkyl or heterocyclyl ring.

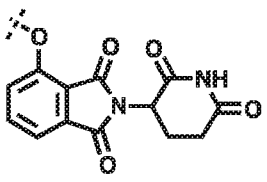
In some aspects, the degradation/disruption tag can be, for example, pomalidomide (Fischer et al., 2014), thalidomide (Fischer et al., 2014), lenalidomide (Fischer et al., 2014), VH032 (Galdeano et al., 2014; Maniaci et al., 2017), adamantine (Xie et al., 2014), 1-((4,4,5,5,5-pentafluoropentyl)sulfinyl)nonane (E.Wakeling, 1995), nutlin-3a (Vassilev et al., 2004), RG7112

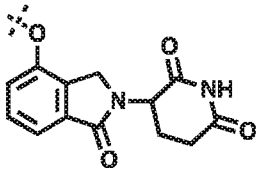
(Vu et al., 2013), RG7338, AMG 232 (Sun et al., 2014), AA-115 (Aguilar et al., 2017), bestatin (Hiroyuki Suda et al., 1976), MV1 (Varfolomeev et al., 2007), LCL161 (Weisberg et al., 2010), FK506 (Liu et al., 1991) rapamycin (Fan et al., 2017; Rodrik-Outmezguine et al., 2016), and/or analogs thereof.

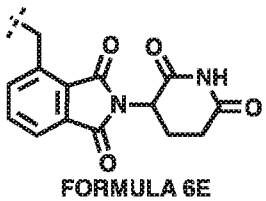
In some aspects, the degradation/disruption tag can be, e.g., one of the following structures:

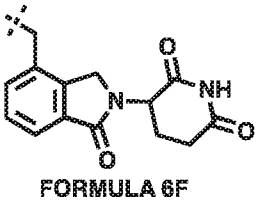

FORMULA 6A

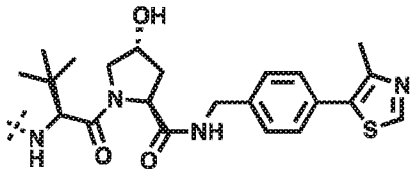

FORMULA 6B

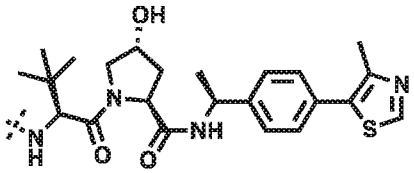

FORMULA 6C

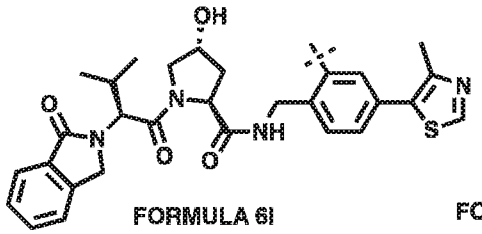

FORMULA 6D

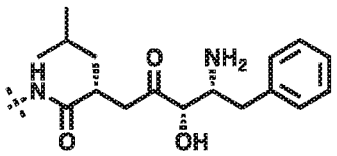

FORMULA 6E

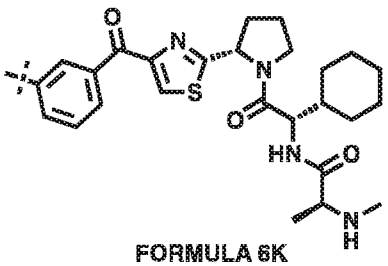

FORMULA 6F

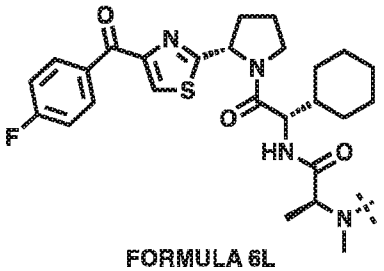

FORMULA 6G

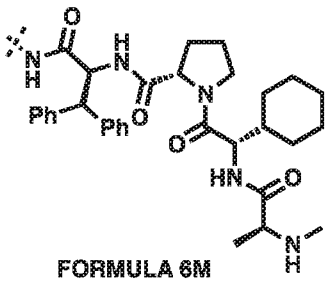

FORMULA 6H

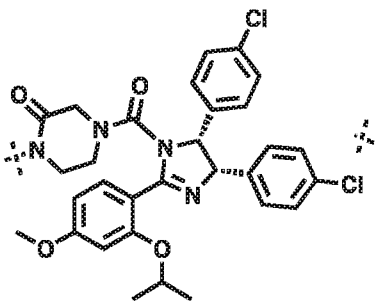

FORMULA 6I


FORMULA 6J


FORMULA 6K


FORMULA 6L


FORMULA 6M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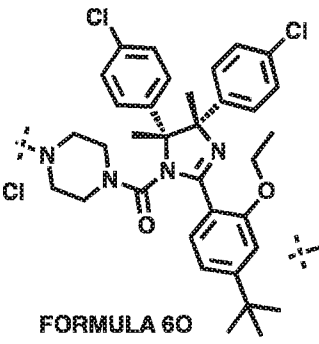
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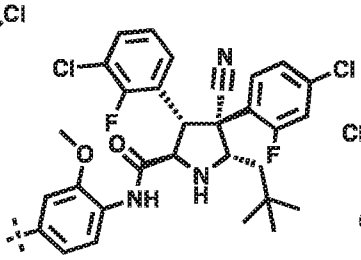
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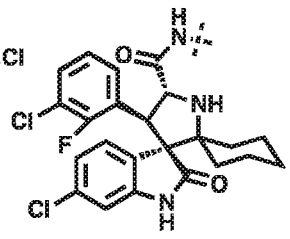
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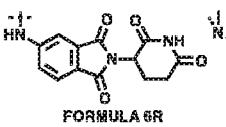
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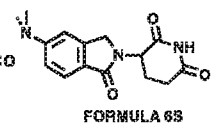
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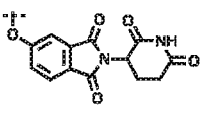
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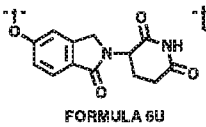
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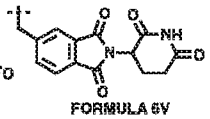
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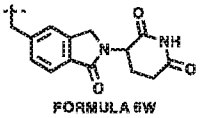
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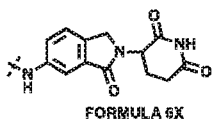
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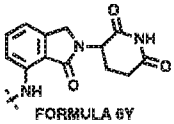
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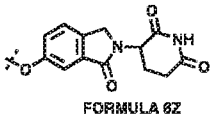
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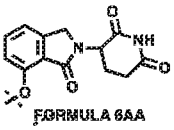
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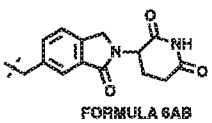
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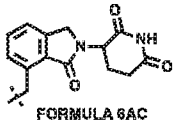
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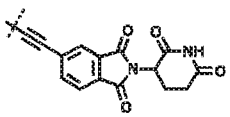
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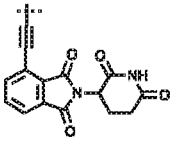
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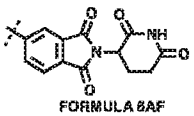
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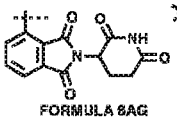
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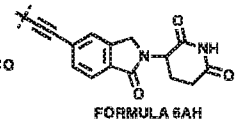
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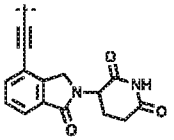
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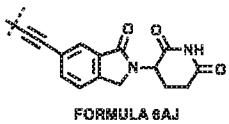
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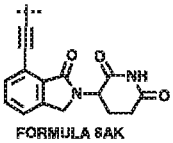
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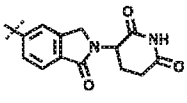
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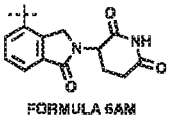
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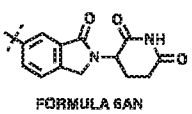
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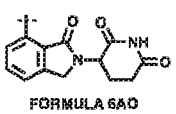
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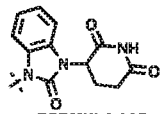
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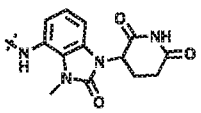
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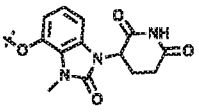
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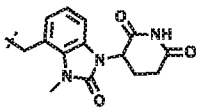
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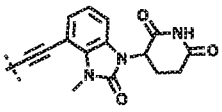
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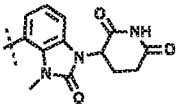
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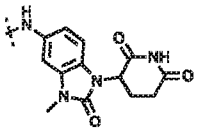
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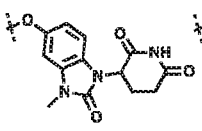
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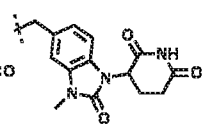
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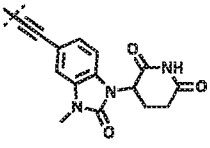
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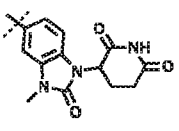
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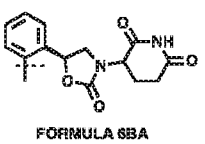
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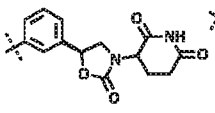
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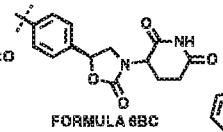
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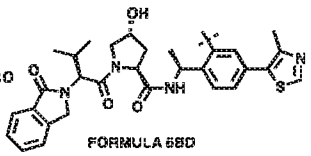
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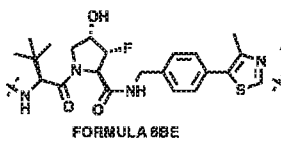
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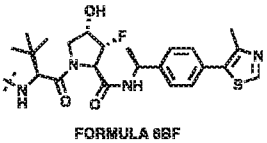
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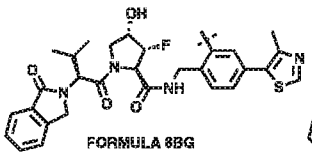
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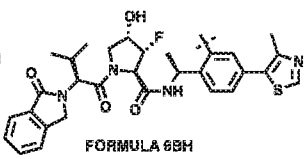
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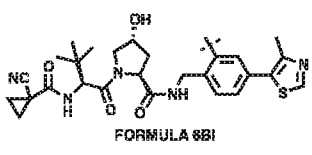
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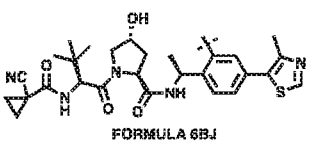
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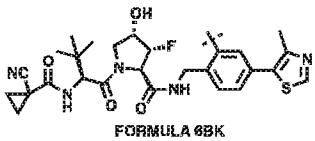
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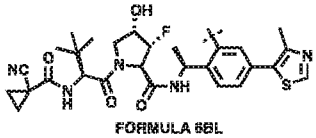
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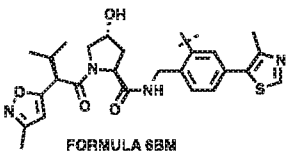
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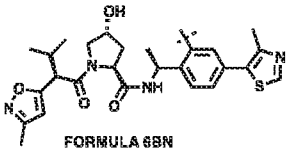
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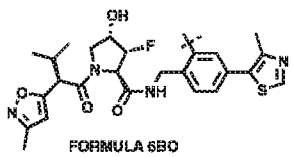
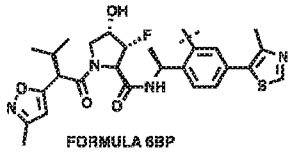

FORMULA 6BO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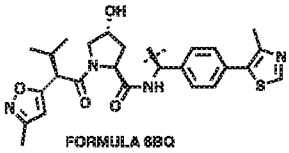
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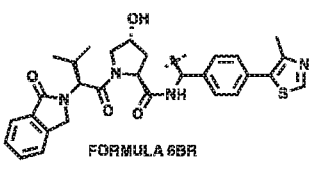
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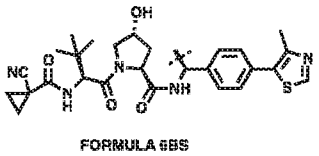
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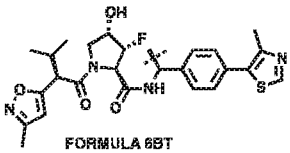
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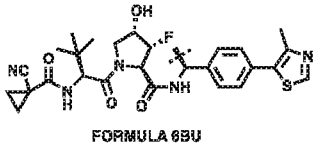
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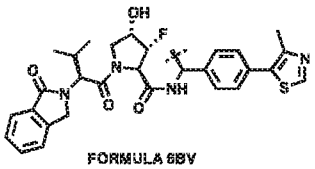
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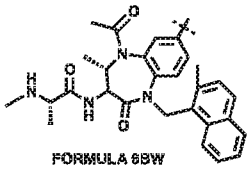
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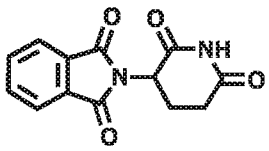
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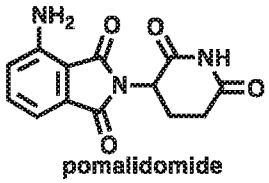
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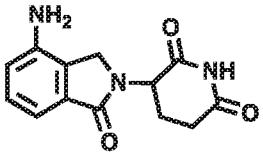
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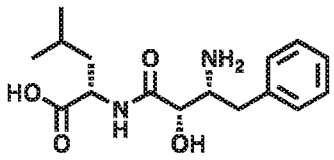
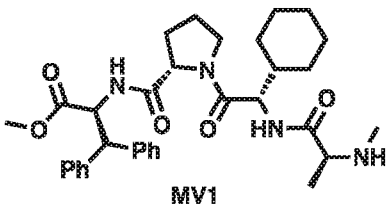

bestatin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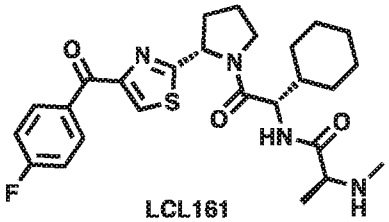
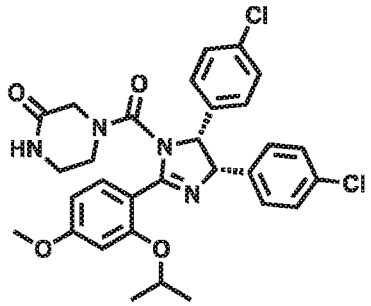
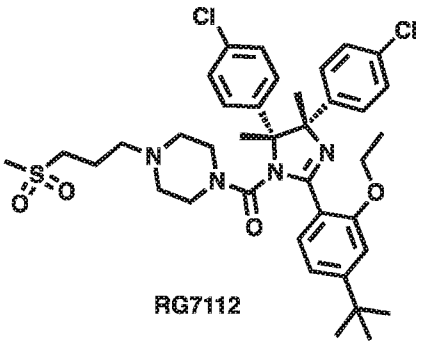

LCL161


nutlin-3a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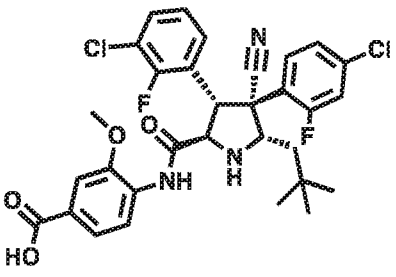
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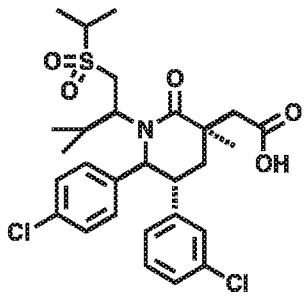
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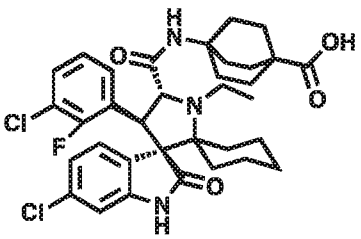
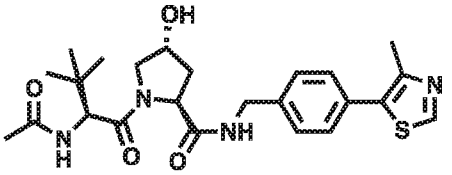
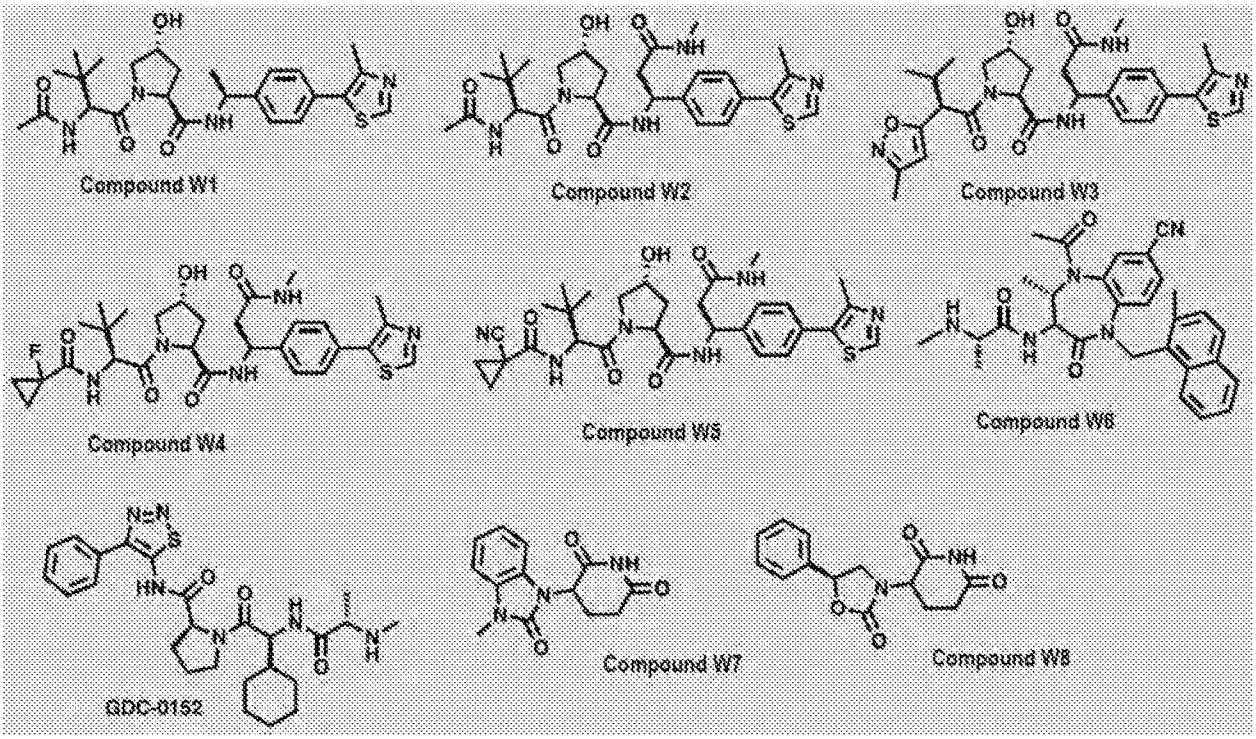

AA-115


VH032

5

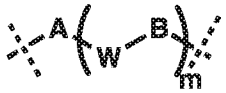


In some aspects, the degradation/disruption tag can bind to a ubiquitin ligase (e.g., an E3 ligase such as a cereblon E3 ligase, a VHL E3 ligase, a MDM2 ligase, a TRIM21 ligase, a TRIM24 ligase, a KEAP1 E3 ligase and/or an IAP ligase) and/or serve as a hydrophobic group or a tag that leads to PTK6 protein misfolding.

Linkers

In all of the above-described compounds, the PTK6 ligand is conjugated to the degradation/disruption tag through a linker. The linker can include, for example, acyclic or cyclic saturated or unsaturated carbon, ethylene glycol, amide, amino, ether, urea, carbamate, aromatic, heteroaromatic, heterocyclic and/or carbonyl containing groups with different lengths.

In some aspects, the linker can be a moiety of:



FORMULA 7

wherein

A, W and B, at each occurrence, are independently selected from null, or bivalent moiety selected from R'-R'', R'COR'', R'CO_2R'', R'C(O)N(R^1)R'', R'C(S)N(R^1)R'', R'OR'', R'OC(O)R'', R'OC(O)OR'', R'OCON(R^1)R'', R'SR'', R'SOR'', R'SO_2R'', R'SO_2N(R^1)R'', R'N(R^1)R'', R'NR^1COR'', R'NR^1C(O)OR'', R'NR^1CON(R^2)R'', R'NR^1C(S)R'', R'NR^1S(O)R'', R'NR^1S(O)$_2$R'', and R'NR^1S(O)$_2$N(R^2)R'', wherein

R' and R'' are independently selected from null, optionally substituted R^r-(C_1-C_8 alkyl), or a moiety comprising of optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 hydroxyalkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-C_8 alkylene, optionally substituted C_2-C_8 alkenylene, optionally substituted C_2-C_8 alkynylene, optionally substituted C_1-C_8 hydroxyalkylene, optionally substituted C_1-C_8alkoxyC_1-C_8alkylene, optionally substituted C_1-C_8alkylaminoC_1-C_8alkylene, optionally substituted C_1-C_8 haloalkylene, optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted C_3-C_{13} fused cycloalkyl, optionally substituted C_3-C_{13} fused heterocyclyl, optionally substituted C_3-C_{13} bridged cycloalkyl, optionally substituted C_3-C_{13} bridged heterocyclyl, optionally substituted C_3-C_{13} spiro cycloalkyl, optionally substituted C_3-C_{13} spiro heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

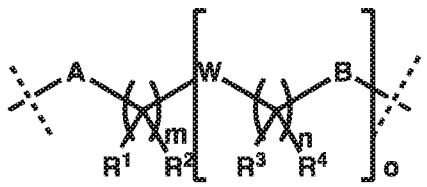
R^r is selected from optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted C_3-C_{13} fused cycloalkyl, optionally substituted C_3-C_{13} fused heterocyclyl, optionally substituted C_3-C_{13} bridged cycloalkyl, optionally substituted C_3-C_{13} bridged heterocyclyl, optionally substituted C_3-C_{13} spiro cycloalkyl, optionally substituted C_3-C_{13} spiro heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^1 and R^2 are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted

C_1-C_8 alkoxyalkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-C_8 hydroxyalkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

R' and R'', R^1 and R^2, R' and R^1, R' and R^2, R'' and R^1, R'' and R^2 together with the atom to which they are connected form a 3-20 membered cycloalkyl or 4-20 membered heterocyclyl ring; and

m is 0 to 15.



FORMULA 7A,

wherein

R^1, R^2, R^3 and R^4, at each occurrence, are independently selected from hydrogen, halogen, hydroxyl, amino, cyano, nitro, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8 alkoxyalkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-C_8 hydroxyalkyl, optionally substituted C_1-C_8 alkylamino, and optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-10 membered carbocyclyl, optionally substituted 3-8 membered cycloalkoxy, optionally substituted 3-10 membered carbocyclylamino, optionally substituted 4-8 membered membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^1 and R^2, R^3 and R^4 together with the atom to which they are connected form a 3-20 membered cycloalkyl or 4-20 membered heterocyclyl ring;

A, W and B, at each occurrence, are independently selected from null, or bivalent moiety selected from R'-R'', R'COR'', R'CO_2R'', R'C(O)N(R^5)R'', R'C(S)N(R^5)R'', R'OR'', R'OC(O)R'', R'OC(O)OR'', R'OCONR^{5}R'', R'SR'', R'SOR'', R'SO_2R'', R'SO_2N(R^5)R'', R'N(R^5)R'',

$R^{'}NR^5COR^{''}$, $R^{'}NR^5C(O)OR^{''}$, $R^{'}NR^5CON(R^6)R^{''}$, $R^{'}NR^5C(S)R^{''}$, $R^{'}NR^5S(O)R^{''}$, $R^{'}NR^5S(O)_2R^{''}$, and $R^{'}NR^5S(O)_2N(R^6)R^{''}$, wherein

$R^{'}$ and $R^{''}$ are independently selected from null, optionally substituted R^r-(C_1-C_8 alkyl), or a moiety comprising of optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 hydroxyalkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-C_8 alkylene, optionally substituted C_2-C_8 alkenylene, optionally substituted C_2-C_8 alkynylene, optionally substituted C_1-C_8 hydroxyalkylene, optionally substituted C_1-C_8alkoxyC_1-C_8alkylene, optionally substituted C_1-C_8alkylaminoC_1-C_8alkylene, optionally substituted C_1-C_8 haloalkylene, optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted C_3-C_{13} fused cycloalkyl, optionally substituted C_3-C_{13} fused heterocyclyl, optionally substituted C_3-C_{13} bridged cycloalkyl, optionally substituted C_3-C_{13} bridged heterocyclyl, optionally substituted C_3-C_{13} spiro cycloalkyl, optionally substituted C_3-C_{13} spiro heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^r is selected from optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted C_3-C_{13} fused cycloalkyl, optionally substituted C_3-C_{13} fused heterocyclyl, optionally substituted C_3-C_{13} bridged cycloalkyl, optionally substituted C_3-C_{13} bridged heterocyclyl, optionally substituted C_3-C_{13} spiro cycloalkyl, optionally substituted C_3-C_{13} spiro heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

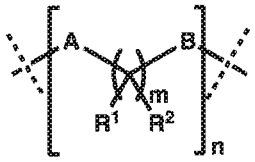
R^5 and R^6 are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxyalkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-C_8 hydroxyalkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

$R^{'}$ and $R^{''}$, R^5 and R^6, $R^{'}$ and R^5, $R^{'}$ and R^6, $R^{''}$ and R^5, $R^{''}$ and R^6 together with the atom to which they are connected form a 3-20 membered cycloalkyl or 4-20 membered heterocyclyl ring;

m is 0 to 15;

n, at each occurrence, is 0 to 15; and

o is 0 to 15.



FORMULA 7B,

wherein

R^1 and R^2, at each occurrence, are independently selected from hydrogen, halogen, hydroxyl, amino, cyano, nitro, and optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8 alkoxy C_1-C_8 alkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-C_8 hydroxyalkyl, optionally substituted C_1-C_8 alkylamino, C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted 3-10 membered carbocyclyl, optionally substituted 3-8 membered cycloalkoxy, optionally substituted 3-10 membered carbocyclylamino, optionally substituted 4-10 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^1 and R^2 together with the atom to which they are connected form a 3-20 membered cycloalkyl or 4-20 membered heterocyclyl ring;

A and B, at each occurrence, are independently selected from null, or bivalent moiety selected from R'-R'', $R'COR''$, $R'CO_2R''$, $R'C(O)NR^3R''$, $R'C(S)NR^3R''$, $R'OR''$, $R'OC(O)R''$, $R'OC(O)OR''$, $R'OCON(R^3)R''$, $R'SR''$, $R'SOR''$, $R'SO_2R''$, $R'SO_2N(R^3)R''$, $R'N(R^3)R''$, $R'NR^3COR''$, $R'NR^3C(O)OR''$, $R'NR^3CON(R^4)R'$, $R'NR^3C(S)R''$, $R'NR^3S(O)R''$, $R'NR^3S(O)_2R''$, and $R'NR^3S(O)_2N(R^4)R''$, wherein

R' and R'' are independently selected from null, optionally substituted R^r-(C_1-C_8 alkyl), or a moiety comprising of optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 hydroxyalkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-C_8 alkylene, optionally substituted C_2-C_8 alkenylene, optionally substituted C_2-C_8 alkynylene, optionally substituted C_1-C_8 hydroxyalkylene, optionally substituted C_1-C_8alkoxyC_1-C_8alkylene, optionally substituted C_1-C_8alkylaminoC_1-C_8alkylene, optionally substituted C_1-C_8 haloalkylene, optionally substituted 3-

10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted C_3-C_{13} fused cycloalkyl, optionally substituted C_3-C_{13} fused heterocyclyl, optionally substituted C_3-C_{13} bridged cycloalkyl, optionally substituted C_3-C_{13} bridged heterocyclyl, optionally substituted C_3-C_{13} spiro cycloalkyl, optionally substituted C_3-C_{13} spiro heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

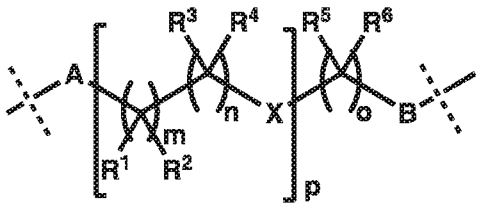
R^f is selected from optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted C_3-C_{13} fused cycloalkyl, optionally substituted C_3-C_{13} fused heterocyclyl, optionally substituted C_3-C_{13} bridged cycloalkyl, optionally substituted C_3-C_{13} bridged heterocyclyl, optionally substituted C_3-C_{13} spiro cycloalkyl, optionally substituted C_3-C_{13} spiro heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^3 and R^4 are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxyalkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-C_8 hydroxyalkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

$R^{'}$ and $R^{''}$, R^3 and R^4, $R^{'}$ and R^3, $R^{'}$ and R^4, $R^{''}$ and R^3, $R^{''}$ and R^4 together with the atom to which they are connected form a 3-20 membered cycloalkyl or 4-20 membered heterocyclyl ring;

m, at each occurrence, is 0 to 15; and

n is 0 to 15.



FORMULA 7C,

wherein

X is selected from O, NH, and NR^7;

R^1, R^2, R^3, R^4, R^5, and R^6, at each occurrence, are independently selected from hydrogen, halogen, hydroxyl, amino, cyano, nitro, optionally substituted C_1-C_8 alkyl, optionally substituted

C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8 alkoxy C_1-C_8 alkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-C_8 hydroxyalkyl, optionally substituted C_1-C_8 alkylamino, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-10 membered carbocyclyl, optionally substituted 3-8 membered cycloalkoxy, optionally substituted 4-10 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

A and B are independently selected from null, or bivalent moiety selected from $R^{'}$-$R^{''}$, $R^{'}COR^{''}$, $R^{'}CO_2R^{''}$, $R^{'}C(O)N(R^8)R^{''}$, $R^{'}C(S)N(R^8)R^{''}$, $R^{'}OR^{''}$, $R^{'}OC(O)R^{''}$, $R^{'}OC(O)OR^{''}$, $R^{'}OCON(R^8)R^{''}$, $R^{'}SR^{''}$, $R^{'}SOR^{''}$, $R^{'}SO_2R^{''}$, $R^{'}SO_2N(R^8)R^{''}$, $R^{'}N(R^8)R^{''}$, $R^{'}NR^8COR^{''}$, $R^{'}NR^8C(O)OR^{''}$, $R^{'}NR^8CON(R^9)R^{''}$, $R^{'}NR^8C(S)R^{''}$, $R^{'}NR^8S(O)R^{''}$, $R^{'}NR^8S(O)_2R^{''}$, and $R^{'}NR^8S(O)_2N(R^9)R^{''}$, wherein

$R^{'}$ and $R^{''}$ are independently selected from null, optionally substituted R^r-(C_1-C_8 alkyl), or a moiety comprising of optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 hydroxyalkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-C_8 alkylene, optionally substituted C_2-C_8 alkenylene, optionally substituted C_2-C_8 alkynylene, optionally substituted C_1-C_8 hydroxyalkylene, optionally substituted C_1-C_8alkoxyC_1-C_8alkylene, optionally substituted C_1-C_8alkylaminoC_1-C_8alkylene, optionally substituted C_1-C_8 haloalkylene, optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted C_3-C_{13} fused cycloalkyl, optionally substituted C_3-C_{13} fused heterocyclyl, optionally substituted C_3-C_{13} bridged cycloalkyl, optionally substituted C_3-C_{13} bridged heterocyclyl, optionally substituted C_3-C_{13} spiro cycloalkyl, optionally substituted C_3-C_{13} spiro heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^r is selected from optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted C_3-C_{13} fused cycloalkyl, optionally substituted C_3-C_{13} fused heterocyclyl, optionally substituted C_3-C_{13} bridged cycloalkyl, optionally substituted C_3-C_{13} bridged heterocyclyl, optionally substituted C_3-C_{13} spiro cycloalkyl, optionally substituted C_3-C_{13} spiro heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^7, R^8 and R^9 are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxyalkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-C_8 hydroxyalkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

$R^{'}$ and $R^{''}$, R^8 and R^9, $R^{'}$ and R^8, $R^{'}$ and R^9, $R^{''}$ and R^8, $R^{''}$ and R^9 together with the atom to which they are connected form a 3-20 membered cycloalkyl or 4-20 membered heterocyclyl ring;

m, at each occurrence, is 0 to 15;

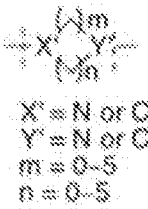
n, at each occurrence, is 0 to 15;

o is 0 to 15; and

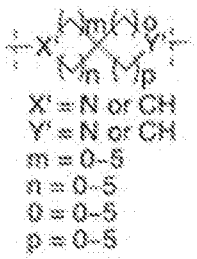
p is 0 to 15.

In some aspects of Formulae 7, 7A, 7B, and 7C, the linker moiety comprises a ring selected from the group consisting of a 3 to 13 membered ring, a 3 to 13 membered fused ring, a 3 to 13 membered bridged ring, and a 3 to13 membered spiro ring.

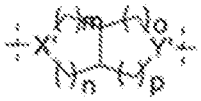
In some aspects of Formulae 7, 7A, 7B, and 7C, the linker moiety comprises a ring selected from the group consisting of Formula C1, C2, C3, C4 and C5:



Formula C1,

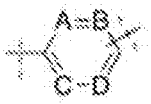


Formula C2,



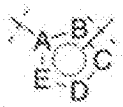
X' = N or CH
Y' = N or CH
m = 0-5
n = 0-5
o = 0-5
p = 0-5

Formula C3,



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

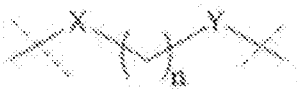
Formula C4, and



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
E = C, CH, C(C1-3 alkyl), N, NH, N(C1-3alkyl), O, S

Formula C5.

In some aspects, the linker can also be a moiety of:

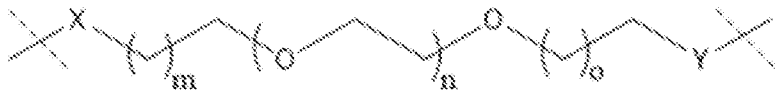


Formula A,

wherein X is C=O or CH_2,

Y is C=O or CH_2, and

n is 0-15;



Formula B,

wherein X is C=O or CH_2,

Y is C=O or CH_2,

m is 0-15,

n is 0-6, and

o is 0-15; or

Formula C,

wherein

X is C=O or CH_2,

Y is C=O or CH_2,

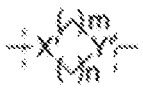
R is $-CH_2-$, $-CF_2-$, $-CH(C_{1-3}$ alkyl)–, $-C(C_{1-3}$ alkyl)(C_{1-3} alkyl)–, –CH=CH–, $-C(C_{1-3}$ alkyl)=C(C_{1-3} alkyl)–, –C=C–, –O–, –NH–, $-N(C_{1-3}$ alkyl)–, $-C(O)NH-$, $-C(O)N(C_{1-3}$ alkyl)–, a 3-13 membered ring, a 3-13 membered fused ring, a 3-13 membered bridged ring, and/or a 3-13 membered spiro ring,

m is 0-15, and

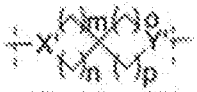
n is 0-15.

In some aspects of Formula C, R is a 3-13 membered ring, a 3-13 membered fused ring, a 3-13 membered bridged ring, and/or a 3-13 membered spiro ring, one or more of which can contain one or more heteroatoms.

In some aspects of Formula C, R has a structure of:

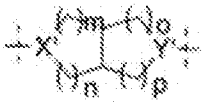


Formula C1,



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

Formula C2,



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

Formula C3,

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

Formula C4, or

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
E = C, CH, C(C1-3 alkyl), N, NH, N(C1-3alkyl), O, S

Formula C5.

Synthesis and Testing of Bivalent Compounds

The binding affinity of novel synthesized bivalent compounds (i.e., PTK6 degraders/disruptors) can be assessed using standard biophysical assays known in the art (e.g., isothermal titration calorimetry (ITC), surface plasmon resonance (SPR)). Cellular assays can then be used to assess the bivalent compound's ability to induce PTK6 degradation and inhibit cancer cell proliferation. Besides evaluating a bivalent compound's induced changes in the protein expression of PTK6 or PTK6 mutant proteins, enzymatic activity can also be assessed. Assays

suitable for use in any or all of these steps are known in the art, and include, e.g., Western blotting, quantitative mass spectrometry (MS) analysis, flow cytometry, enzymatic inhibition, ITC, SPR, cell growth inhibition and xenograft and PDX models. Suitable cell lines for use in any or all of these steps are known in the art and include, cancer cell lines: 1) Breast (MDA-MB231, MCF7, UACC893, HCC1954, T47D, BT474, ZR751); 2) Ovarian (DOV-13, HeyC2, OV2008, OvCAR5); 3) Pancreatic (PANC-1, BxP3, Capan1, Hs766T, MIAPaCa2); 4) Prostate (PC-3, DU145). Suitable mouse models for use in any or all of these steps are known in the art and include, patient-derived xenograft models of triple negative breast cancer.

By way of non-limiting example, detailed synthesis protocols are described in the Examples for specific exemplary PTK6 degraders/disruptors.

Pharmaceutically acceptable isotopic variations of the compounds disclosed herein are contemplated and can be synthesized using conventional methods known in the art or methods corresponding to those described in the Examples (substituting appropriate reagents with appropriate isotopic variations of those reagents). Specifically, an isotopic variation is a compound in which at least one atom is replaced by an atom having the same atomic number, but an atomic mass different from the atomic mass usually found in nature. Useful isotopes are known in the art and include, for example, isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, and chlorine. Exemplary isotopes thus include, e.g., ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{17}O, ^{18}O, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl.

Isotopic variations (e.g., isotopic variations containing ^{2}H) can provide therapeutic advantages resulting from greater metabolic stability, e.g., increased *in vivo* half-life or reduced dosage requirements. In addition, certain isotopic variations (particularly those containing a radioactive isotope) can be used in drug or substrate tissue distribution studies. The radioactive isotopes tritium (^{3}H) and carbon-14 (^{14}C) are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

Pharmaceutically acceptable solvates of the compounds disclosed herein are contemplated. A solvate can be generated, e.g., by substituting a solvent used to crystallize a compound disclosed herein with an isotopic variation (e.g., D_2O in place of H_2O, d_6-acetone in place of acetone, or d_6-DMSO in place of DMSO).

Pharmaceutically acceptable fluorinated variations of the compounds disclosed herein are contemplated and can be synthesized using conventional methods known in the art or methods

corresponding to those described in the Examples (substituting appropriate reagents with appropriate fluorinated variations of those reagents). Specifically, a fluorinated variation is a compound in which at least one hydrogen atom is replaced by a fluoro atom. Fluorinated variations can provide therapeutic advantages resulting from greater metabolic stability, e.g., increased *in vivo* half-life or reduced dosage requirements.

Pharmaceutically acceptable prodrugs of the compounds disclosed herein are contemplated and can be synthesized using conventional methods known in the art or methods corresponding to those described in the Examples (e.g., converting hydroxyl groups or carboxylic acid groups to ester groups). As used herein, a "prodrug" refers to a compound that can be converted via some chemical or physiological process (e.g., enzymatic processes and metabolic hydrolysis) to a therapeutic agent. Thus, the term "prodrug" also refers to a precursor of a biologically active compound that is pharmaceutically acceptable. A prodrug may be inactive when administered to a subject, i.e. an ester, but is converted *in vivo* to an active compound, for example, by hydrolysis to the free carboxylic acid or free hydroxyl. The prodrug compound often offers advantages of solubility, tissue compatibility or delayed release in an organism. The term "prodrug" is also meant to include any covalently bonded carriers, which release the active compound *in vivo* when such prodrug is administered to a subject. Prodrugs of an active compound may be prepared by modifying functional groups present in the active compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent active compound. Prodrugs include compounds wherein a hydroxy, amino or mercapto group is bonded to any group that, when the prodrug of the active compound is administered to a subject, cleaves to form a free hydroxy, free amino or free mercapto group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of an alcohol or acetamide, formamide and benzamide derivatives of an amine functional group in the active compound and the like.

Characterization of Exemplary PTK6 Degraders/Disruptors

Specific exemplary PTK6 degraders/disruptors were characterized in triple negative MDA-231 breast cancer cells cells (Examples 83-85, Figs. 2-5). Bifunctional compounds YX39-101, YX39-102, YX39-103, YX39-104, YX39-105, YX39-106, and YX39-107 in particular were found to be effective in reducing PTK6 protein levels in MDA-231 cells at 500 nM (Fig. 3). In addition, YX69-159, YX79-10, YX79-11, YX79-12, YX79-15, YX79-36, YX79-37, YX79-40,

YX79-41, YX79-42, YX79-59, and YX79-65 were also found to potently suppress PTK6 expression in MDA-MB231 cells at 500nM (Fig 4, 5).

Treatment of cells in 3D Matrigel culture assays often give better insight into the activity of compounds in in vivo (mouse) biological models than standard (2D) monolayer culture systems. Treatment of triple negative or ER+ breast cancer cells with PTK6 degraders that reduced PTK6 protein levels suppressed viability and invasive branching of triple negative MDA-MB231 breast cancer cells in 3D cultures (Figs. 6, 7). Using 3D Cell Titer Glo (Promega), the effect of PTK6 degrader treatment on cell viability was quantified; treatment with PTK6 degraders significantly impaired viability in a concentration-dependent manner, comparable to the effects observed with the PTK6 shRNA vectors (Fig. 6, 7). At comparable concentrations, a PTK6 kinase inhibitor (P21d) had only a modest effect on viability of cells in 3D cell culture (Fig. 6, 7), thus supporting kinase-independent functions of PTK6 that regulate growth of some PTK6+ tumors that would be better targeted with PTK6 degraders. Similarly, treatment with top PTK6 degraders, but not PTK6 kinase activity inhibitor suppressed viability of 3D cultures of CP70 cells, a platinum chemotherapy-resistant ovarian cancer cell line (Fig 8).

Mechanistically, suppression of PTK6 expression observed with degrader treatment is dependent on proteasome activity. Pre-treatment of cells with the proteasome inhibitor MG-132, prevents downregulation of PTK6 expression (Fig 9). In addition, pre-treatment with the PTK6 kinase activity inhibitor that binds to the same binding site(s) as the PTK6 degraders rescues PTK6 protein levels in the degrader-treated cells (Fig 10).

PTk6 degraders suppress PTK6 expression in cell lines that are resistant to current standard of care therapies. Degraders downregulate expression in ER+ breast cancer cells that are resistant to estrogen deprivation (Fig 11), highlighting the potential utility of PTK6 degraders to target therapy resistant disease.

Definition of Terms

"Alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation. An alkyl may comprise one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, or sixteen carbon

atoms. In certain embodiments, an alkyl comprises one to fifteen carbon atoms (*e.g.*, C_1-C_{15} alkyl). In certain embodiments, an alkyl comprises one to thirteen carbon atoms (*e.g.*, C_1-C_{13} alkyl). In certain embodiments, an alkyl comprises one to eight carbon atoms (*e.g.*, C_1-C_8 alkyl). In other embodiments, an alkyl comprises five to fifteen carbon atoms (*e.g.*, C_5-C_{15} alkyl). In other embodiments, an alkyl comprises five to eight carbon atoms (*e.g.*, C_5-C_8 alkyl). The alkyl is attached to the rest of the molecule by a single bond, for example, methyl (Me), ethyl (Et), *n*-propyl, 1-methylethyl (*iso*-propyl), *n*-butyl, *n*-pentyl, 1,1-dimethylethyl (*t*-butyl), pentyl, 3-methylhexyl, 2-methylhexyl, and the like.

"Alkenyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one double bond. An alkenyl may comprise two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, or sixteen carbon atoms. In certain embodiments, an alkenyl comprises two to twelve carbon atoms (*e.g.*, C_2-C_{12} alkenyl). In certain embodiments, an alkenyl comprises two to eight carbon atoms (*e.g.*, C_2-C_8 alkenyl). In certain embodiments, an alkenyl comprises two to six carbon atoms (*e.g.*, C_2-C_6 alkenyl). In other embodiments, an alkenyl comprises two to four carbon atoms (*e.g.*, C_2-C_4 alkenyl). The alkenyl is attached to the rest of the molecule by a single bond, for example, ethenyl (*i.e.*, vinyl), prop-1-enyl (*i.e.*, allyl), but-1-enyl, pent-1-enyl, penta-1,4-dienyl, and the like.

The term "allyl," as used herein, means a $-CH_2CH{=}CH_2$ group.

As used herein, the term "alkynyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one triple bond. An alkynyl may comprise two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, or sixteen carbon atoms. In certain embodiments, an alkynyl comprises two to twelve carbon atoms (*e.g.*, C_2-C_{12} alkynyl). In certain embodiments, an alkynyl comprises two to eight carbon atoms (*e.g.*, C_2-C_8 alkynyl). In other embodiments, an alkynyl has two to six carbon atoms (*e.g.*, C_2-C_6 alkynyl). In other embodiments, an alkynyl has two to four carbon atoms (*e.g.*, C_2-C_4 alkynyl). The alkynyl is attached to the rest of the molecule by a single bond. Examples of such groups include, but are not limited to, ethynyl, propynyl, 1-butynyl, 2-butynyl, 1-pentynyl, 2-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, and the like.

The term " alkoxy", as used herein, means an alkyl group as defined herein witch is attached to the rest of the molecule via an oxygen atom. Examples of such groups include, but are not

limited to, methoxy, ethoxy, n-propyloxy, iso-propyloxy, n-butoxy, iso-butoxy, tert-butoxy, pentyloxy, hexyloxy, and the like.

The term "aryl", as used herein, " refers to a radical derived from an aromatic monocyclic or multicyclic hydrocarbon ring system by removing a hydrogen atom from a ring carbon atom. The aromatic monocyclic or multicyclic hydrocarbon ring system contains only hydrogen and carbon atoms. An aryl may comprise from six to eighteen carbon atoms, where at least one of the rings in the ring system is fully unsaturated, *i.e.*, it contains a cyclic, delocalized (4n+2) π–electron system in accordance with the Hückel theory. In certain embodiments, an aryl comprises six to fourteen carbon atoms (C_6-C_{14} aryl). In certain embodiments, an aryl comprises six to ten carbon atoms (C_6-C_{10} aryl). Examples of such groups include, but are not limited to, phenyl, fluorenyl and naphthyl. The terms "Ph" and "phenyl," as used herein, mean a -C_6H_5 group.

The term "heteroaryl", refers to a radical derived from a 3- to 18-membered aromatic ring radical that comprises two to seventeen carbon atoms and from one to six heteroatoms selected from nitrogen, oxygen and sulfur. As used herein, the heteroaryl radical may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, wherein at least one of the rings in the ring system is fully unsaturated, *i.e.*, it contains a cyclic, delocalized (4n+2) π–electron system in accordance with the Hückel theory. Heteroaryl includes fused or bridged ring systems. In certain embodiments, a heteroaryl refers to a radical derived from a 3- to 10-membered aromatic ring radical (3-10 membered heteroaryl). In certain embodiments, a heteroaryl refers to a radical derived from 5- to 7-membered aromatic ring (5-7 membered heteroaryl). Heteroaryl includes fused or bridged ring systems. The heteroatom(s) in the heteroaryl radical is optionally oxidized. One or more nitrogen atoms, if present, are optionally quaternized. The heteroaryl is attached to the rest of the molecule through any atom of the ring(s). Examples of such groups include, but not limited to, pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl,pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, furopyridinyl, and the like. In certain embodiments, an heteroaryl is attached to the rest of the molecule via a ring carbon atom. In certain embodiments, an heteroaryl is attached to the rest of the molecule via a nitrogen atom (N-attached) or a carbon atom (C-attached). For instance, a group

derived from pyrrole may be pyrrol-1-yl (N-attached) or pyrrol-3-yl (C-attached). Further, a group derived from imidazole may be imidazol-1-yl (N-attached) or imidazol-3-yl (C-attached).

The term "heterocyclyl", as used herein, means a non-aromatic, monocyclic, bicyclic, tricyclic, or tetracyclic radical having a total of from 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13 atoms in its ring system, and containing from 3 to 12 carbon atoms and from 1 to 4 heteroatoms each independently selected from O, S and N, and with the proviso that the ring of said group does not contain two adjacent O atoms or two adjacent S atoms. A heterocyclyl group may include fused, bridged or spirocyclic ring systems. In certain embodiments, a heterocyclyl group comprises 3 to 10 ring atoms (3-10 membered heterocyclyl). In certain embodiments, a heterocyclyl group comprises 3 to 8 ring atoms (3-8 membered heterocyclyl). In certain embodiments, a heterocyclyl group comprises 4 to 8 ring atoms (4-8 membered heterocyclyl). In certain embodiments, a heterocyclyl group comprises 3 to 6 ring atoms (3-6 membered heterocyclyl). A heterocyclyl group may contain an oxo substituent at any available atom that will result in a stable compound. For example, such a group may contain an oxo atom at an available carbon or nitrogen atom. Such a group may contain more than one oxo substituent if chemically feasible. In addition, it is to be understood that when such a heterocyclyl group contains a sulfur atom, said sulfur atom may be oxidized with one or two oxygen atoms to afford either a sulfoxide or sulfone. An example of a 4 membered heterocyclyl group is azetidinyl (derived from azetidine). An example of a 5 membered cycloheteroalkyl group is pyrrolidinyl. An example of a 6 membered cycloheteroalkyl group is piperidinyl. An example of a 9 membered cycloheteroalkyl group is indolinyl. An example of a 10 membered cycloheteroalkyl group is 4H-quinolizinyl. Further examples of such heterocyclyl groups include, but are not limited to, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidino, morpholino, thiomorpholino, thioxanyl, piperazinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranyl, 4*H*-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, 3*H*-indolyl, quinolizinyl, 3-oxopiperazinyl, 4-methylpiperazinyl, 4-ethylpiperazinyl, and 1-oxo-2,8,diazaspiro[4.5]dec-8-yl. A heteroaryl group may be attached to the rest of molecular via a

carbon atom (C-attached) or a nitrogen atom (N-attached). For instance, a group derived from piperazine may be piperazin-1-yl (N-attached) or piperazin-2-yl (C-attached).

The term " cycloalkyl" means a saturated, monocyclic, bicyclic, tricyclic, or tetracyclic radical having a total of from 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13 carbon atoms in its ring system. A cycloalkyl may be fused, bridged or spirocyclic. In certain embodiments, a cycloalkyl comprises 3 to 8 carbon ring atoms (C_3-C_8 cycloalkyl). In certain embodiments, a cycloalkyl comprises 3 to 6 carbon ring atoms (C_3-C_6 cycloalkyl). Examples of such groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cycloheptyl, adamantyl, and the like.

The term “cycloalkylene” is a bidentate radical obtained by removing a hydrogen atom from a cycloalkyl ring as defined above. Examples of such groups include, but are not limited to, cyclopropylene, cyclobutylene, cyclopentylene, cyclopentenylene, cyclohexylene, cycloheptylene, and the like.

The term "spirocyclic" as used herein has its conventional meaning, that is, any ring system containing two or more rings wherein two of the rings have one ring carbon in common. Each ring of the spirocyclic ring system, as herein defined, independently comprises 3 to 20 ring atoms. Preferably, they have 3 to 10 ring atoms. Non-limiting examples of a spirocyclic system include spiro[3.3]heptane, spiro[3.4]octane, and spiro[4.5]decane.

The term cyano" refers to a -C≡N group.

An "aldehyde" group refers to a –C(O)H group.

An "alkoxy" group refers to both an –O-alkyl, as defined herein.

An "alkoxycarbonyl" refers to a -C(O)-alkoxy, as defined herein.

An "alkylaminoalkyl" group refers to an -alkyl-NR-alkyl group, as defined herein.

An "alkylsulfonyl" group refer to a -SO_2alkyl, as defined herein.

An "amino" group refers to an optionally substituted -NH_2.

An "aminoalkyl" group refers to an –alky-amino group, as defined herein.

An "aminocarbonyl" refers to a -C(O)-amino, as defined herein.

An "arylalkyl" group refers to -alkylaryl, where alkyl and aryl are defined herein.

An "aryloxy" group refers to both an –O-aryl and an –O-heteroaryl group, as defined herein.

An "aryloxycarbonyl" refers to -C(O)-aryloxy, as defined herein.

An "arylsulfonyl" group refers to a -SO_2aryl, as defined herein.

A "carbonyl" group refers to a -C(O)- group, as defined herein.

A "carboxylic acid" group refers to a –C(O)OH group.

A "cycloalkoxy" refers to a –O-cycloalkyl group, as defined herein.

A "halo" or "halogen" group refers to fluorine, chlorine, bromine or iodine.

A "haloalkyl" group refers to an alkyl group substituted with one or more halogen atoms.

A "hydroxy" group refers to an -OH group.

A "nitro" group refers to a -NO_2 group.

An "oxo" group refers to the =O substituent.

A "trihalomethyl" group refers to a methyl substituted with three halogen atoms.

The term "substituted," means that the specified group or moiety bears one or more substituents independently selected from C_1-C_4 alkyl, aryl, heteroaryl, aryl-C_1-C_4 alkyl-, heteroaryl-C_1-C_4 alkyl-, C_1-C_4 haloalkyl, -OC_1-C_4 alkyl, -OC_1-C_4 alkylphenyl, -C_1-C_4 alkyl-OH, -OC_1-C_4 haloalkyl, halo, -OH, -NH_2, -C_1-C_4 alkyl-NH_2, -N(C_1-C_4 alkyl)(C_1-C_4 alkyl), -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_4 alkylphenyl), -NH(C_1-C_4 alkylphenyl), cyano, nitro, oxo, -CO_2H, -C(O)OC_1-C_4 alkyl, -CON(C_1-C_4 alkyl)(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -$CONH_2$, -NHC(O)(C_1-C_4 alkyl), -NHC(O)(phenyl), -N(C_1-C_4 alkyl)C(O)(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)C(O)(phenyl), -C(O)C_1-C_4 alkyl, -C(O)C_1-C_4 alkylphenyl, -C(O)C_1-C_4 haloalkyl, -OC(O)C_1-C_4 alkyl, -SO_2(C_1-C_4 alkyl), -SO_2(phenyl), -SO_2(C_1-C_4 haloalkyl), -SO_2NH_2, -SO_2NH(C_1-C_4 alkyl), -SO_2NH(phenyl), -NHSO_2(C_1-C_4 alkyl), -NHSO_2(phenyl), and -NHSO_2(C_1-C_4 haloalkyl).

The term "null" means the absence of an atom or moiety, and there is a bond between adjacent atoms in the structure.

The term "optionally substituted" means that the specified group may be either unsubstituted or substituted by one or more substituents as defined herein. It is to be understood that in the compounds of the present invention when a group is said to be "unsubstituted," or is "substituted" with fewer groups than would fill the valencies of all the atoms in the compound, the remaining valencies on such a group are filled by hydrogen. For example, if a C_6 aryl group, also called "phenyl" herein, is substituted with one additional substituent, one of ordinary skill in the art would understand that such a group has 4 open positions left on carbon atoms of the C_6 aryl ring (6 initial positions, minus one at which the remainder of the compound of the present invention

is attached to and an additional substituent, remaining 4 positions open). In such cases, the remaining 4 carbon atoms are each bound to one hydrogen atom to fill their valencies. Similarly, if a C_6 aryl group in the present compounds is said to be "disubstituted," one of ordinary skill in the art would understand it to mean that the C_6 aryl has 3 carbon atoms remaining that are unsubstituted. Those three unsubstituted carbon atoms are each bound to one hydrogen atom to fill their valencies.

As used herein, the same symbol in a different FORMULA may have a different definition, for example, the definition of R1 in FORMULA 1 is as defined with respect to FORMULA 1 and the definition of R1 in FORMULA 6 is as defined with respect to FORMULA 6.

As used herein, when m (or n or o or p) is defined by a range, for example, "m is 0 to 15" or "m = 0-3" mean that m is an integer from 0 to 15 (i.e. m is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15) or m is an integer from 0 to 3(i.e. m is 0, 1,2, or 3) or is any integer in the defined range.

"Pharmaceutically acceptable salt" includes both acid and base addition salts. A pharmaceutically acceptable salt of any one of the bivalent compounds described herein is intended to encompass any and all pharmaceutically suitable salt forms. Preferred pharmaceutically acceptable salts of the compounds described herein are pharmaceutically acceptable acid addition salts and pharmaceutically acceptable base addition salts.

"Pharmaceutically acceptable acid addition salt" refers to those salts which retain the biological effectiveness and properties of the free bases, which are not biologically or otherwise undesirable, and which are formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, hydroiodic acid, hydrofluoric acid, phosphorous acid, and the like. Also included are salts that are formed with organic acids such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, alkanedioic acids, aromatic acids, aliphatic and. aromatic sulfonic acids, etc. and include, for example, acetic acid, trifluoroacetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like. Exemplary salts thus include sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, nitrates, phosphates, monohydrogenphosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, trifluoroacetates,

propionates, caprylates, isobutyrates, oxalates, malonates, succinate suberates, sebacates, fumarates, maleates, mandelates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, phthalates, benzenesulfonates, toluenesulfonates, phenylacetates, citrates, lactates, malates, tartrates, methanesulfonates, and the like. Also contemplated are salts of amino acids, such as arginates, gluconates, and galacturonates (see, for example, Berge S.M. et al., "Pharmaceutical Salts," *Journal of Pharmaceutical Science,* 66:1-19 (1997), which is hereby incorporated by reference in its entirety). Acid addition salts of basic compounds may be prepared by contacting the free base forms with a sufficient amount of the desired acid to produce the salt according to methods and techniques with which a skilled artisan is familiar.

"Pharmaceutically acceptable base addition salt" refers to those salts that retain the biological effectiveness and properties of the free acids, which are not biologically or otherwise undesirable. These salts are prepared from addition of an inorganic base or an organic base to the free acid. Pharmaceutically acceptable base addition salts may be formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Salts derived from inorganic bases include, but are not limited to, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, for example, isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, diethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, *N,N*-dibenzylethylenediamine, chloroprocaine, hydrabamine, choline, betaine, ethylenediamine, ethylenedianiline, *N*-methylglucamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, *N*-ethylpiperidine, polyamine resins and the like. See Berge et al., *supra*.

As used herein, the same symbol in a different FORMULA may have a different definition, for example, the definition of R^1 in FORMULA 1 is different from that in FORMULA 6.

As used herein, when m(or n or o or p) is definited as, for example, “m is 0 to 15” or “m = 0-5” mean m is m is an integer from 0 to 15 (or 0 to 5).

Pharmaceutical Compositions

In some aspects, the compositions and methods described herein include the manufacture and use of pharmaceutical compositions and medicaments that include one or more bivalent compounds as disclosed herein. Also included are the pharmaceutical compositions themselves.

In some aspects, the compositions disclosed herein can include other compounds, drugs, or agents used for the treatment of cancer. For example, in some instances, pharmaceutical compositions disclosed herein can be combined with one or more (e.g., one, two, three, four, five, or less than ten) compounds. Such additional compounds can include, e.g., conventional chemotherapeutic agents known in the art. When co-administered, PTK6 degraders/disruptors disclosed herein can operate in conjunction with conventional chemotherapeutic agents to produce mechanistically additive or synergistic therapeutic effects.

In some aspects, the pH of the compositions disclosed herein can be adjusted with pharmaceutically acceptable acids, bases, or buffers to enhance the stability of the PTK6 degraders/disruptor or its delivery form.

Pharmaceutical compositions typically include a pharmaceutically acceptable carrier, adjuvant, or vehicle. 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. A pharmaceutically acceptable carrier, adjuvant, or vehicle is a composition that can be administered to a patient, together with a compound of the 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. Exemplary conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles include saline, solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration.

In particular, pharmaceutically acceptable carriers, adjuvants, and vehicles that can 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 Tweens 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.

As used herein, the PTK6 degraders/disruptors disclosed herein are defined to include pharmaceutically acceptable derivatives or prodrugs thereof. A "pharmaceutically acceptable derivative" means any pharmaceutically acceptable salt, solvate, or prodrug, e.g., carbamate, ester, phosphate 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 described herein, or an active metabolite or residue thereof. 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. 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.

The PTK6 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 derivatives thereof.

In particular, pharmaceutically acceptable salts of the PTK6 degraders/disruptors disclosed herein 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 PTK6 degraders/disruptors disclosed herein. Water or oil-soluble or dispersible products can be obtained by such quaternization.

In some aspects, the pharmaceutical compositions disclosed herein can include an effective amount of one or more PTK6 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). In some aspects, pharmaceutical compositions can further include one or more additional compounds, drugs, or agents used for the treatment of cancer (e.g., conventional chemotherapeutic agents) in amounts effective for causing an intended effect or physiological outcome (e.g., treatment or prevention of cell growth, cell proliferation, or cancer).

In some aspects, the pharmaceutical compositions disclosed herein can be formulated for sale in the United States, import into the United States, or export from the United States.

Administration of Pharmaceutical Compositions

The pharmaceutical compositions disclosed herein 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). In particular, the pharmaceutical compositions can be formulated for and administered via oral, parenteral, or transdermal delivery. The term "parenteral" as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intraperitoneal, intra-articular, intra-arterial,

intrasynovial, intrasternal, intrathecal, intralesional, and intracranial injection or infusion techniques.

For example, the pharmaceutical compositions disclosed herein can be administered, e.g., topically, rectally, nasally (e.g., by inhalation spray or nebulizer), buccally, vaginally, subdermally (e.g., by injection or via an implanted reservoir), or ophthalmically.

For example, pharmaceutical compositions of this invention 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 or emulsions are administered orally, the active ingredient may be suspended or dissolved in an oily phase is combined with emulsifying or suspending agents. If desired, certain sweetening, flavoring, or coloring agents can be added.

For example, the pharmaceutical compositions of this invention can 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.

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

For example, the pharmaceutical compositions of this invention can be administered by injection (e.g., as a solution or powder). Such compositions can 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, e.g., 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 can 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, e.g., olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions can 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 Tweens, Spans, or other similar emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms can also be used for the purposes of formulation.

In some aspects, an effective dose of a pharmaceutical composition of this invention 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, or according to the requirements of the particular pharmaceutical composition.

When the pharmaceutical compositions disclosed herein include a combination of a compound of the formulae described herein (e.g., an PTK6 degraders/disruptors) and one or more additional compounds (e.g., one or more additional compounds, drugs, or agents used for the treatment of cancer or any other condition or disease, including conditions or diseases known to be associated with or caused by cancer), both the compound and the additional compound 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 can be administered separately, as part of a multiple dose regimen, from the compounds of this invention. Alternatively, those agents can be part of a single dosage form, mixed together with the compounds of this invention in a single composition.

In some aspects, the pharmaceutical compositions disclosed herein can be included in a container, pack, or dispenser together with instructions for administration.

Methods of Treatment

The methods disclosed herein contemplate administration of an effective amount of a compound or composition to achieve the desired or stated effect. Typically, the compounds or compositions of the invention will be administered from about 1 to about 6 times per day or, alternately or in addition, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that can 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.

In some aspects, the present disclosure provides methods for using a composition comprising a PTK6 degrader/disruptor, including pharmaceutical compositions (indicated below as 'X') disclosed herein in the following methods:

Substance X for use as a medicament in the treatment of one or more diseases or conditions disclosed herein (e.g., cancer, 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.

In some aspects, the methods disclosed include the administration of a therapeutically effective amount of one or more of the compounds or compositions 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. In some aspects, the methods disclosed include selecting a subject and administering to the subject an effective amount of one or more of the compounds or compositions described herein, and optionally repeating administration as required for the prevention or treatment of cancer.

In some aspects, 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 aspects, 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 aspects, 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), 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). In some aspects, exhibition of a positive immune response towards a condition or disease can be made from patient records, family history, or detecting an indication of a positive immune response. In some aspects, 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 aspects, subjects can be selected or referred by a medical practitioner (e.g., a general practitioner). In some aspects, subject selection can include obtaining a sample from a selected subject and storing the sample or using the in the methods disclosed herein. Samples can include, e.g., cells or populations of cells.

In some aspects, methods of treatment can include a single administration, multiple administrations, and repeating administration of one or more compounds disclosed herein as required for the prevention or treatment of the disease or condition from which the subject is suffering (e.g., an PTK6-mediated disease). In some aspects, methods of treatment can include assessing a level of disease in the subject prior to treatment, during treatment, or after treatment. In some aspects, treatment can continue until a decrease in the level of disease in the subject is detected.

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).

The terms "administer," "administering," or "administration," as used herein, refer to implanting, ingesting, injecting, inhaling, or otherwise absorbing a compound or composition, regardless of form. For example, the methods disclosed herein include administration of an effective amount of a compound or composition to achieve the desired or stated effect.

The terms "treat", "treating," or "treatment," as used herein, refer to partially or completely alleviating, inhibiting, ameliorating, 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 embodiments, 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; a decrease in the rate of growth of tumor cells; a decrease in the rate of local or distant tumor metastasis; 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.

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 PTK6 degrader/disruptor) described herein.

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, occurs later than, or develops more slowly than that which would have occurred without the present invention. Exemplary PTK6-mediated diseases that can be treated with PTK6 degraders/disruptors include, for example, breast cancer, ovarian cancer, prostate cancer, colon cancer, pancreatic cancer, bladder cancer, liver cancer and cervical cancer.

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.

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.

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. Moreover, treatment of a subject with a therapeutically effective amount of the compounds or compositions described herein can include a single treatment or a series of treatments. For example, effective amounts can be administered at least once. The compositions can be administered 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 can 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 or age of the subject, and other diseases present.

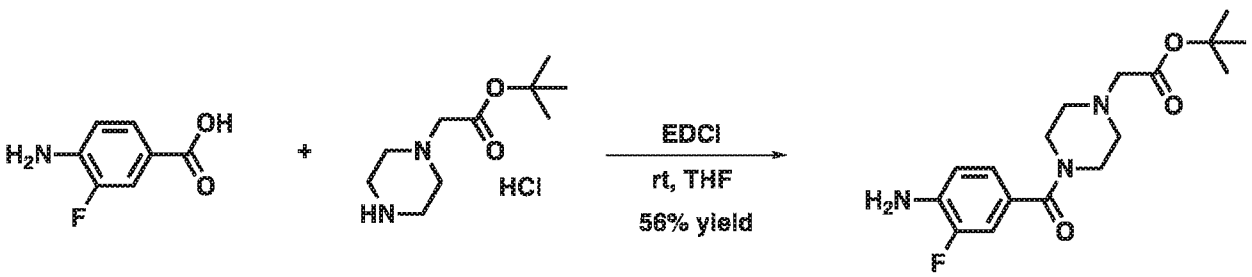
Following administration, the subject can be evaluated to detect, assess, or determine their level of disease. In some instances, treatment can continue until a change (e.g., reduction) in the level of disease in the subject is detected. Upon improvement of a patient's condition (e.g., a change (e.g., decrease) in the level of disease in the subject), a maintenance dose of a compound, or composition disclosed herein can be administered, if necessary. Subsequently, the dosage or frequency of administration, or both, can be reduced, e.g., 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.

The present disclosure is also described and demonstrated by way of the following examples. However, the use of these and other examples anywhere in the specification is illustrative only and in no way limits the scope and meaning of the invention or of any exemplified term. Likewise, the invention is not limited to any particular preferred embodiment or aspect described herein. Indeed, many modifications and variations may be apparent to those skilled in the art upon reading this specification, and such variations can be made without departing from the invention in spirit or in scope. The invention is therefore to be limited only by the terms of the appended claims along with the full scope of equivalents to which those claims are entitled.

EXAMPLES

Procedures for the synthesis of intermediates for PTK6 PROTACs

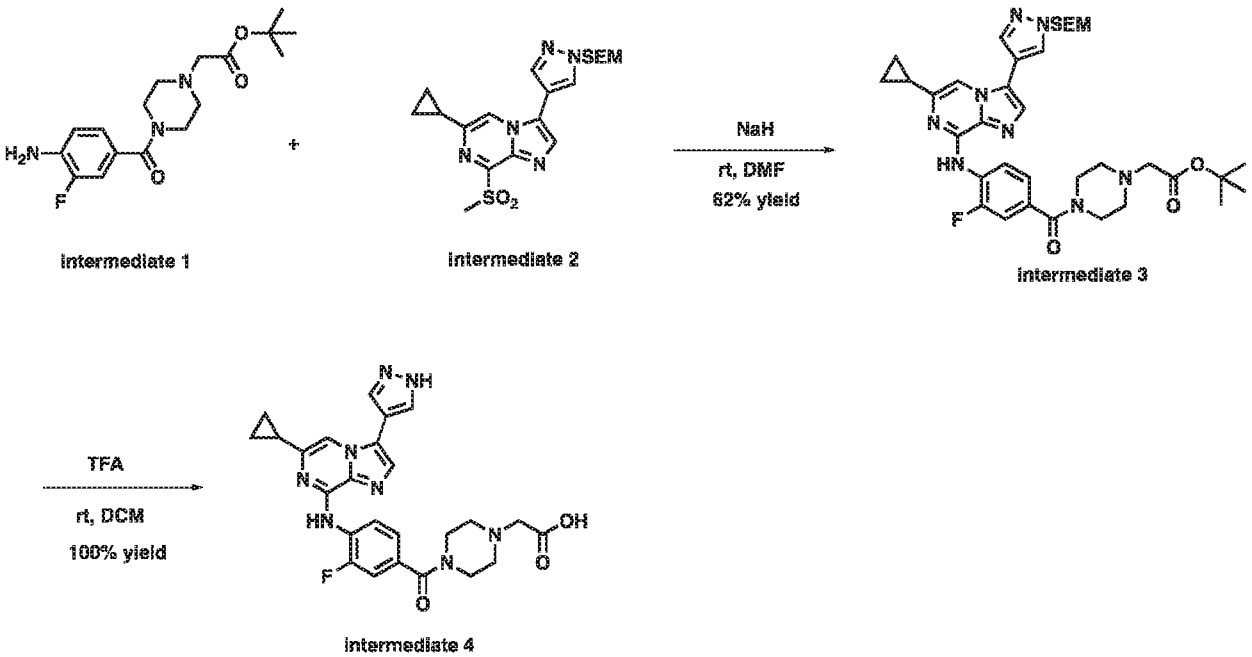
Scheme 1. Synthesis of intermediate 1



intermediate 1

Intermediate 1: ***tert*-Butyl 2-(4-(4-amino-3-fluorobenzoyl)piperazin-1-yl)acetate.** To a mixture of 4-amino-3-fluorobenzoic acid (613 mg, 3.9 mmol) and *tert*-butyl 2-(piperazin-1-yl)acetate hydrochloride (908 mg, 3.3 mmol) in THF (20 mL) were added DIEA (2.3 mL, 13.2 mmol) and EDCI (762 mg, 4.0 mmol). The resulting solution was stirred at room temperature ("rt"). After being stirred for 12 hours ("h"), the reaction was quenched with water. After concentration under reduced pressure, the resulting residue was purified by reverse-phase chromatography to yield the title compound (740 mg, 56% yield) as brown oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.13 (dd, J = 11.4, 1.5 Hz, 1H), 7.07 (d, J = 8.1 Hz, 1H), 6.77 (t, J = 8.5 Hz, 1H), 3.95 (s, 2H), 3.68 (br, 4H), 2.62 (br, 4H), 1.48 (s, 9H).

Scheme 2. Synthesis of intermediate 4



intermediate 1

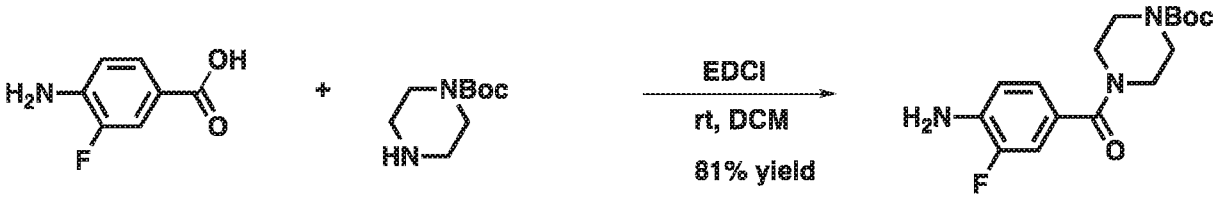
intermediate 2

intermediate 3

intermediate 4

Intermediate 4: 2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetic acid. To a solution of intermediate **1** (298 mg, 0.88 mmol) and intermediate **2** (Zeng et al., 2011) (170 mg, 0.39 mmol) in DMF (6 mL) was added NaH (39 mg, 0.98 mmol). The reaction solution was stirred at rt for 3 h before being quench with water. After concentration under reduced pressure, the resulting residue was purified by reverse-phase chromatography to yield intermediate **3** (160 mg, 59% yield) as brown oil. Intermediate **3** (160 mg, 0.23 mmol) was dissolved in DCM/TFA (2:1, 3mL). The resulting solution was stirred at rt for 1 h before being concentrated under reduced pressure to yield the title compound (170 mg, 0.23 mmol) as brown oil. ^{1}H NMR (600 MHz, CD_3OD) δ 8.45 (q, J = 7.8 Hz, 1H), 8.18 (s, 2H), 8.06 (s, 1H), 8.01 (s, 1H), 7.43 (dd, J = 11.1, 1.5 Hz, 1H), 7.38 (dd, J = 8.5, 1.3 Hz, 1H), 4.21 (s, 2H), 3.98 (br, 4H), 3.55 (br, 4H), 2.19 – 2.08 (m, 1H), 1.06 – 0.91 (m, 4H).

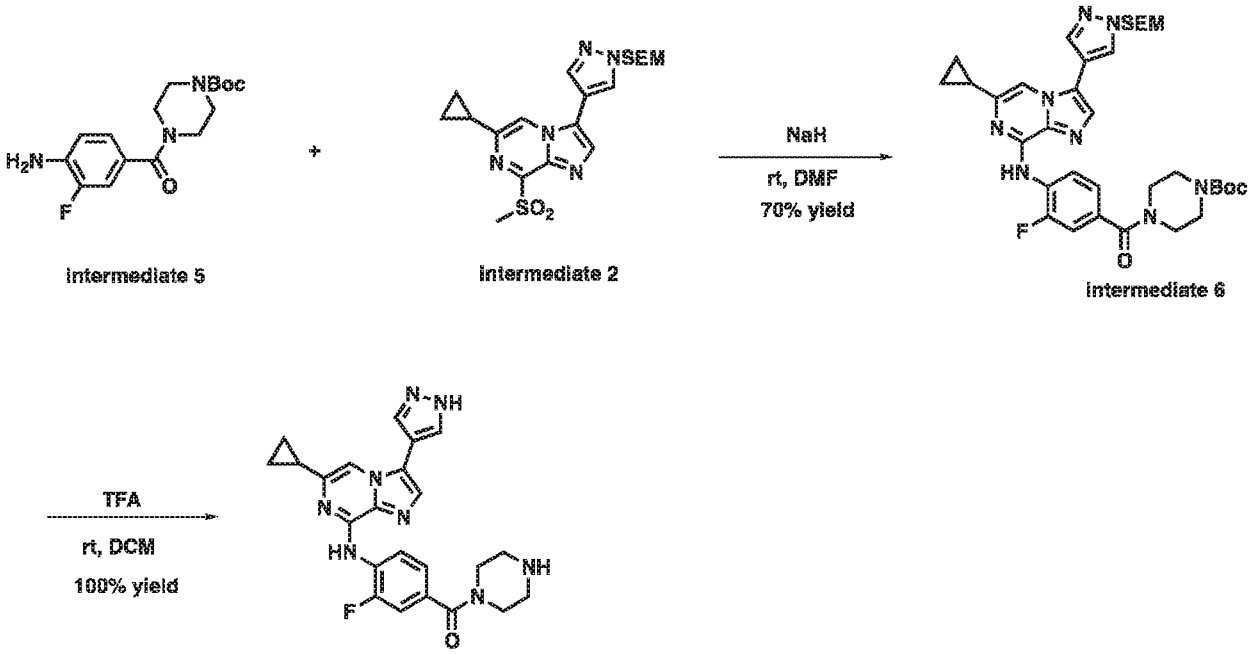
Scheme 3. Synthesis of intermediate 5



intermediate 5

Intermediate 5: *tert*-Butyl 4-(4-amino-3-fluorobenzoyl)piperazine-1-carboxylate. To a mixture of 4-amino-3-fluorobenzoic acid (182 mg, 1.1 mmol) and *tert*-butyl piperazine-1-carboxylate (228 mg, 1.2 mmol) in DCM (5 mL) were added DIEA (0.26 mL, 1.5 mmol) and EDCI (236 mg, 1.2 mmol). The resulting solution was stirred at rt for 12 h before being quenched with water. After concentration under reduced pressure, the resulting residue was purified by reverse-phase chromatography to yield the title compound (306 mg, 81% yield) as white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.13 (d, J = 11.3 Hz, 1H), 7.06 (d, J = 8.0 Hz, 1H), 6.78 (t, J = 8.4 Hz, 1H), 3.99 (s, 2H), 3.60 (br, 4H), 3.47 (br, 4H), 1.49 (s, 9H).

Scheme 4. Synthesis of intermediate 7

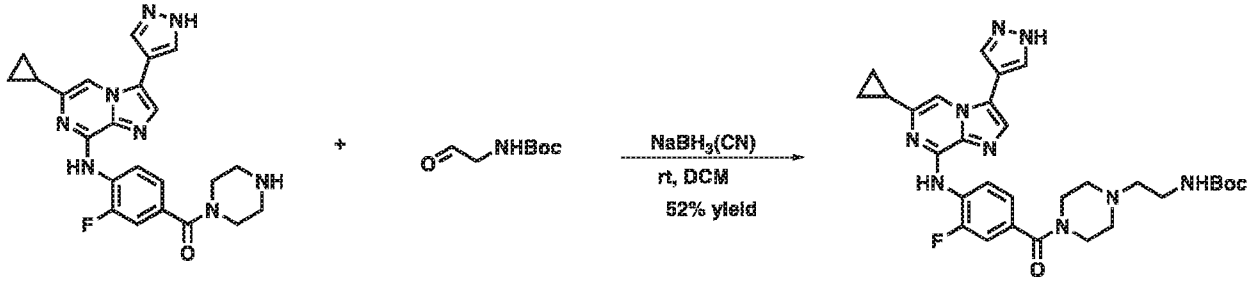


intermediate 5 intermediate 2 intermediate 6

intermediate 7

Intermediate 7: (4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorophenyl)(piperazin-1-yl)methanone. Intermediate 7 was synthesized according to the procedures for the preparation of intermediate **4** as brown oil. ^{1}H NMR (600 MHz, CD_3OD) δ 8.47 (t, *J* = 8.1 Hz, 1H), 8.17 (s, 2H), 8.03 (s, 1H), 8.01 (s, 1H), 7.43 (dd, *J* = 11.2, 1.6 Hz, 1H), 7.38 (dd, *J* = 8.4, 1.5 Hz, 1H), 3.92 (s, 4H), 3.45 – 3.26 (m, 4H), 2.19 – 2.07 (m, 1H), 1.09 – 0.92 (m, 4H).

Scheme 5. Synthesis of intermediate 8

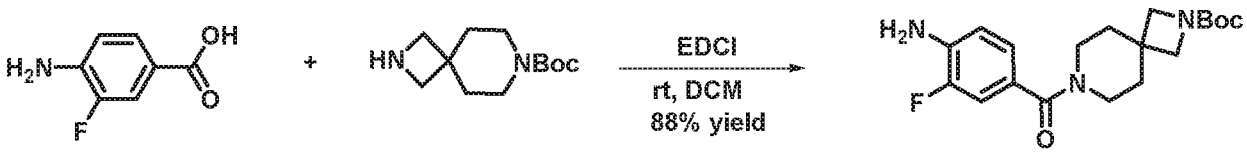


intermediate 7 intermediate 8

Intermediate 8: *tert*-Butyl (2-(4-(4-((6-cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)ethyl)carbamate. To a solution of intermediate 7 (10 mg, 0.018 mmol) and *tert*-butyl (2-oxoethyl)carbamate (4.3 mg 0.027 mmol)

in DCM (1 mL) was added sodium cyanoborohydride (5.9 mg, 0.1 mmol). After being stirred at rt for 12 h, the solution was concentrated under reduced pressure. The resulting residue was purified by HPLC to yield the title compound (5.5 mg, 52%) as brown oil. ^{1}H NMR (600 MHz, CD_3OD) δ 8.76 (t, J = 8.2 Hz, 1H), 8.15 (s, 2H), 7.98 (s, 1H), 7.84 (s, 1H), 7.47 (dd, J = 11.2, 1.7 Hz, 1H), 7.41 (dd, J = 9.3, 7.9 Hz, 1H), 3.86 – 3.39 (m, 12H), 2.18 – 2.08 (m, 1H), 1.49 (s, 9H), 1.11 – 1.02 (m, 2H), 1.02 – 0.91 (m, 2H).

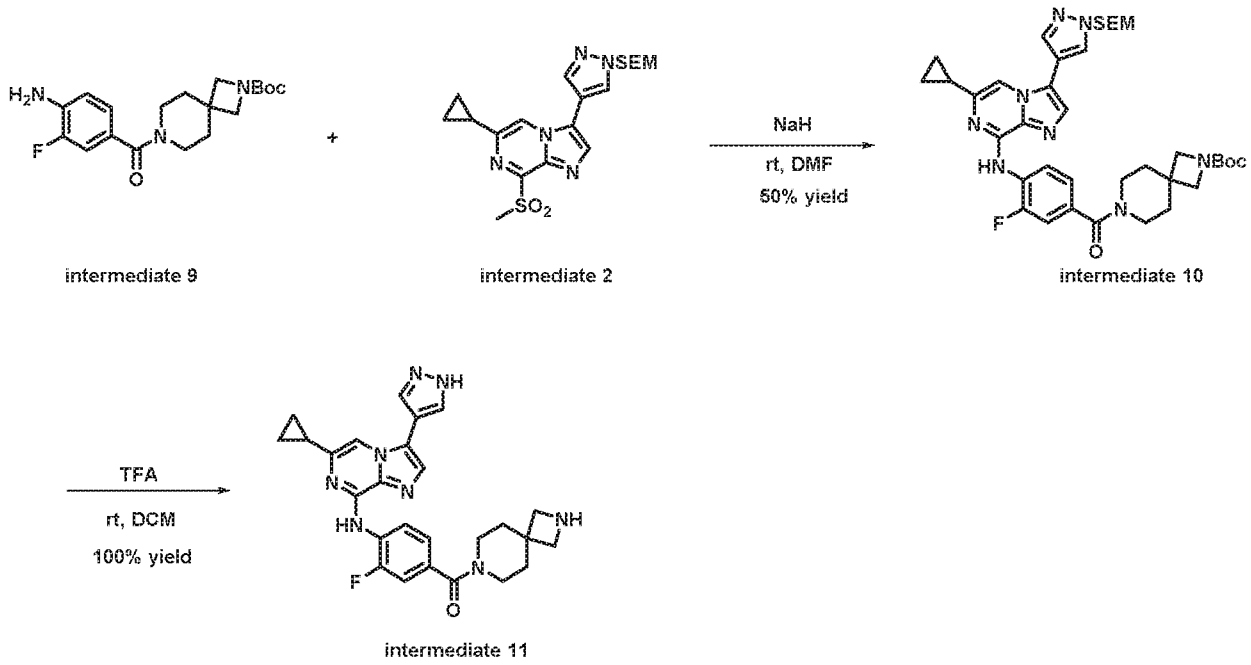
Scheme 6. Synthesis of intermediate 9



intermediate 9

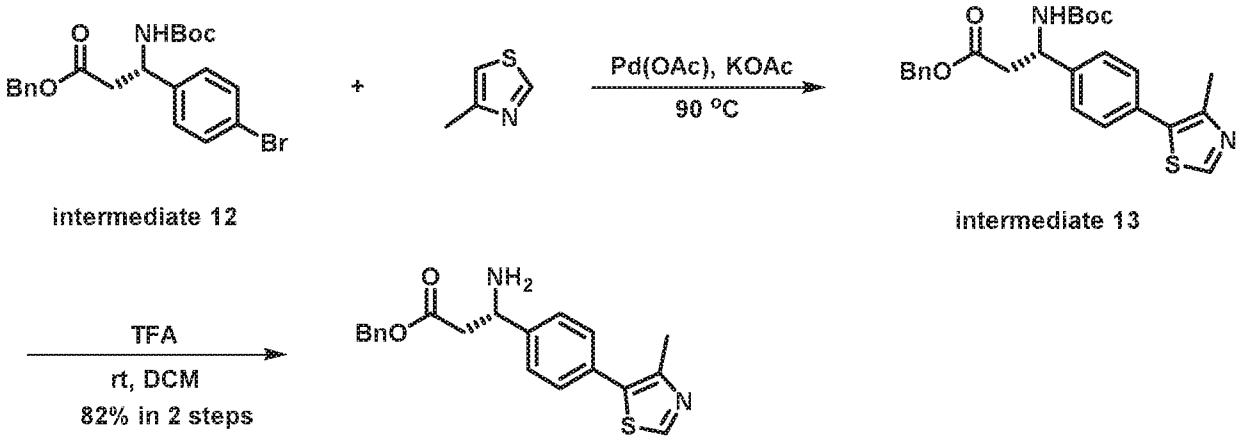
Intermediate 9: *tert*-Butyl 7-(4-amino-3-fluorobenzoyl)-2,7-diazaspiro[3.5]nonane-2-carboxylate. Intermediate **9** was synthesized according to the procedure for the preparation of Intermediate **5** as a white solid. ^{1}H NMR (500 MHz, CD_3OD) δ 7.09 (dd, J = 11.7, 1.7 Hz, 1H), 7.03 (dd, J = 8.2, 1.6 Hz, 1H), 6.85 (t, J = 8.5 Hz, 1H), 3.72 (br, 4H), 3.58 (br, 4H), 1.81 (br, 4H), 1.46 (s, 9H).

Scheme 7. Synthesis of intermediate 11



Intermediate 11: (4-((6-Cyclopropyl-3-(1H-pyrazol-4-yl)imidazo[1,2-a]pyrazin-8-yl)amino)-3-fluorophenyl)(2,7-diazaspiro[3.5]nonan-7-yl)methanone. Intermediate **11** was synthesized according to the procedures for the preparation of intermediate **4**. ^{1}H NMR (600 MHz, CD_3OD) δ 8.47 (t, J = 8.0 Hz, 1H), 8.18 (s, 2H), 8.03 (s, 1H), 8.01 (s, 1H), 7.36 (d, J = 11.1 Hz, 1H), 7.31 (d, J = 8.3 Hz, 1H), 3.96 (br, 4H), 3.80 – 3.44 (m, 4H), 2.20 – 2.09 (m, 1H), 1.95 (br, 4H), 1.06 – 0.94 (m, 4H).

Scheme 8. Synthesis of intermediate 14



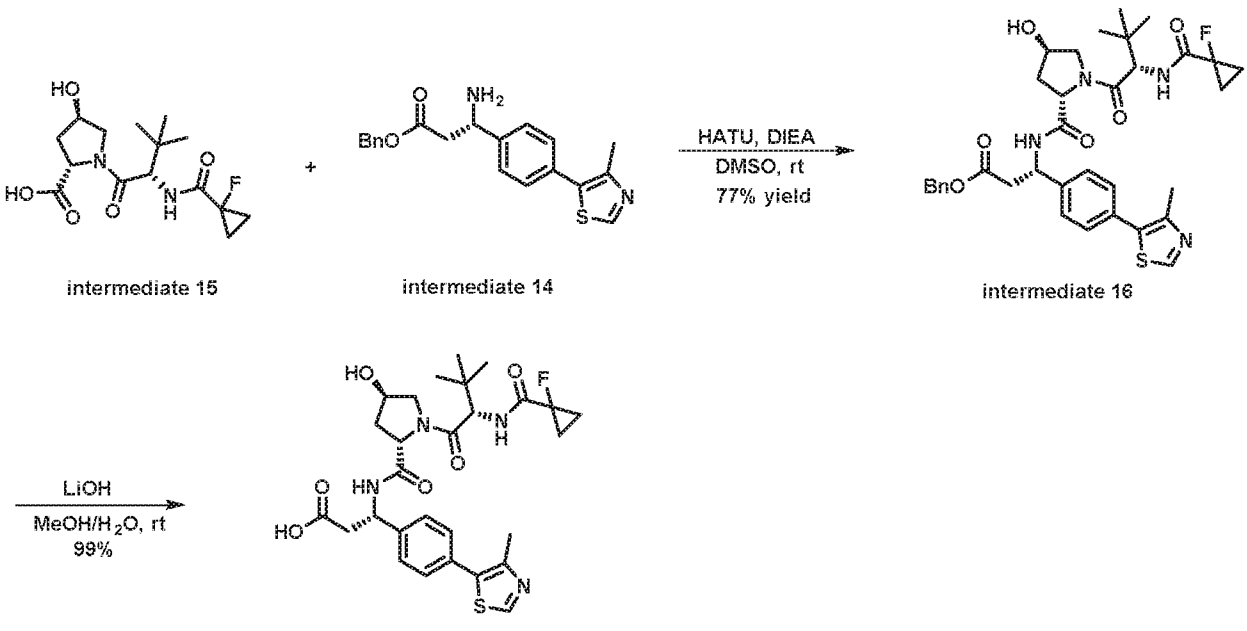
intermediate 12 intermediate 13

intermediate 14

Intermediate 14: Benzyl (S)-3-amino-3-(4-(4-methylthiazol-5-yl)phenyl)propanoate

Intermediated 14 was synthesized from a commercial available intermediate **12,** in 2 steps 82% yield, according to a known procedure(Han et al., 2019).

Scheme 9. Synthesis of intermediate 17

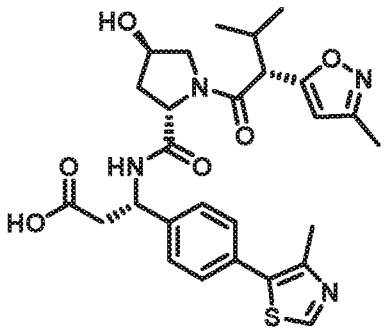


intermediate 15 intermediate 14 intermediate 16

intermediate 17

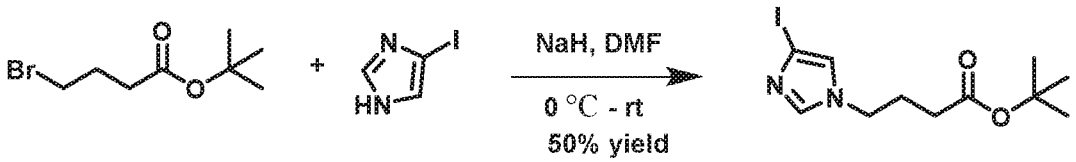
Intermediate 17: (S)-3-((2S,4R)-1-((S)-2-(1-Fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)-3-(4-(4-methylthiazol-5-

yl)phenyl)propanoic acid. Intermediate 17 was synthesized according to a known procedure (Han et al., 2019). ^{1}H NMR (600 MHz, CD_3OD) δ 9.31 (s, 1H), 7.52 (d, J = 8.2 Hz, 1H), 7.49 – 7.44 (m, 2H), 5.42 – 5.27 (m, 1H), 4.77 – 4.69 (m, 1H), 4.62 – 4.37 (m, 2H), 3.97 – 3.81 (m, 1H), 3.78 – 3.72 (m, 1H), 3.05 – 2.97 (m, 1H), 2.94 – 2.83 (m, 1H), 2.51 (s, 3H), 2.30 – 2.14 (m, 1H), 2.13 – 1.90 (m, 1H), 1.41 – 1.22 (m, 3H), 1.11 (s, 3H), 1.05 (s, 6H).



Intermediate 18: (S)-3-((2S,4R)-4-Hydroxy-1-((R)-3-methyl-2-(3-methylisoxazol-5-yl)butanoyl)pyrrolidine-2-carboxamido)-3-(4-(4-methylthiazol-5-yl)phenyl)propanoic acid. Intermediate **18** was synthesized according to the procedures for the preparation of Intermediate **17**. δ 9.22 – 9.08 (m, 1H), 7.62 – 7.39 (m, 4H), 6.29 – 6.13 (m, 1H), 5.47 – 5.31 (m, 1H), 4.63 – 4.34 (m, 2H), 3.93 – 3.84 (m, 1H), 3.76 (dd, J = 29.5, 10.4 Hz, 1H), 3.69 – 3.57 (m, 1H), 3.08 – 2.83 (m, 2H), 2.53 (s, 3H), 2.47 – 2.36 (m, 1H), 2.30 – 2.23 (m, 3H), 2.23 – 2.13 (m, 1H), 2.03 – 1.94 (m, 1H), 1.11 – 1.02 (m, 3H), 0.93 – 0.86 (m, 3H).

Scheme 10. Synthesis of intermediate 19

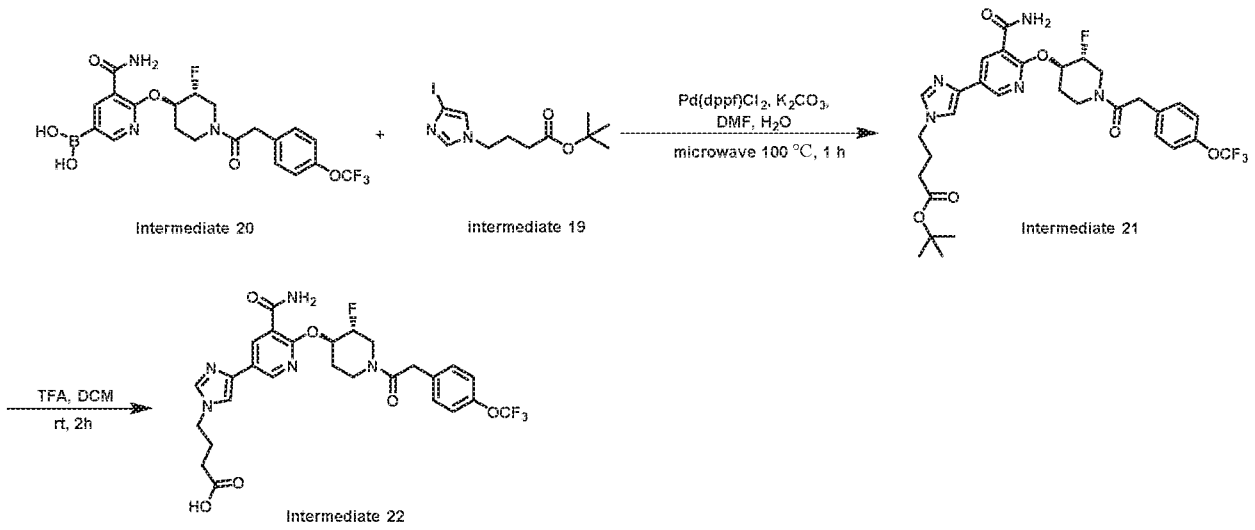


intermediate 19

Intermediate 19: *tert*-Butyl 4-(4-iodo-1H-imidazol-1-yl)butanoate. To a solution of 4-iodo-1H-imidazole (1.5 g, 7.73 mmol) in DMF (10 mL) at 0 °C, was added NaH (0.93 g, 23.19 mmol). After being stirred at 0 °C for 0.5 h, *tert*-butyl 4-bromobutanoate (3.45 g, 15.46 mmol) was added. The mixture was allowed to warm up to rt and stirred for 16 h, before water (100 mL) was poured into the reaction mixture at 0 °C, and extracted with EtOAc (3×100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The resulting residue was purified by

reverse-phase column to provide title compound (1.3 g, 50% yield) as yellow oil. ^{1}H NMR (600 MHz, CD_3OD) δ 8.12 (d, J = 1.4 Hz, 1H), 7.46 (d, J = 1.4 Hz, 1H), 4.14 (t, J = 7.1 Hz, 2H), 2.26 (t, J = 7.2 Hz, 2H), 2.06 (p, J = 7.1 Hz, 2H), 1.44 (s, 9H).

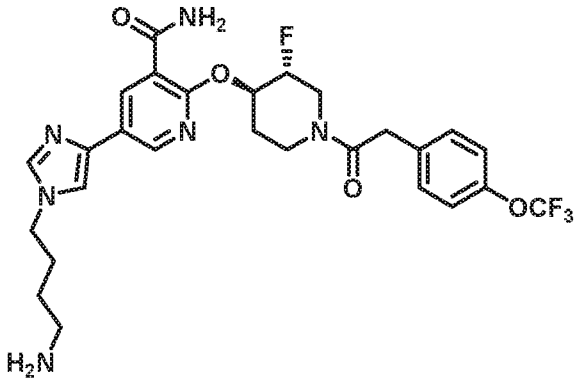
Scheme 11. Synthesis of intermediate 22



Intermediate 20 intermediate 19 Intermediate 21

Intermediate 22

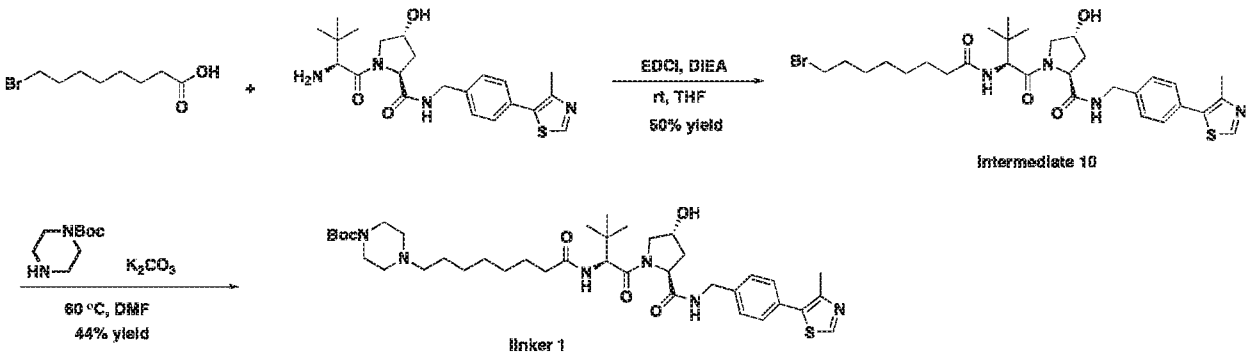
Intermediate 22: 4-(4-(5-Carbamoyl-6-(((3R,4R)-3-fluoro-1-(2-(4-(trifluoromethoxy)phenyl)acetyl)piperidin-4-yl)oxy)pyridin-3-yl)-1H-imidazol-1-yl)butanoic acid. To a solution of intermediate **20** (1.0 g, 2.06 mmol) in DMF (5 mL) and H_2O (1 mL), were added intermediate **19** (0.76 g, 2.27 mmol), K_2CO_3 (1.14 g, 8.24 mmol), and $Pd(dppf)Cl_2$ (151 mg, 0.21 mmol). The reaction mixture was purged with nitrogen for 5 min before being irradiated by microwave at 100 °C for 1 h. The solvent was evaporated and purified by reverse-phase column to provide intermediate **21** (0.7 g, 52%) as yellow solid. ^{1}H NMR (800 MHz, CD_3OD) δ 9.03 (s, 1H), 8.66 (dd, J = 6.5, 2.6 Hz, 1H), 8.57 (dd, J = 8.5, 2.6 Hz, 1H), 8.07 (d, J = 3.2 Hz, 1H), 7.37 (d, J = 8.0 Hz, 2H), 7.29 – 7.19 (m, 2H), 5.70 – 5.61 (m, 1H), 4.32 (t, J = 7.3 Hz, 2H), 4.14 – 4.00 (m, 1H), 3.95 – 3.85 (m, 3H), 3.83 – 3.77 (m, 2H), 3.63 – 3.58 (m, 1H), 2.39 (t, J = 7.1 Hz, 2H), 2.21 (p, J = 7.1 Hz, 3H), 1.96 – 1.76 (m, 1H), 1.44 (s, 9H). To a solution of intermediate **21** (0.7 g, 1.08 mmol) in DCM (2 mL), was added TFA (2 mL). After being stirred at rt for 2 h, the solvent was evaporated to yield the title compound (0.7 g, 92% yield) as yellow solid, which was used in the next step without further purification.



Intermediate 23: 5-(1-(4-Aminobutyl)-1H-imidazol-4-yl)-2-(((3R,4R)-3-fluoro-1-(2-(4-(trifluoromethoxy)phenyl)acetyl)piperidin-4-yl)oxy)nicotinamide Intermediate **23** was synthesized according to the procedures for the preparation of intermediate **22**.

Procedures for the synthesis of Linkers

Scheme 12. Synthesis of linker 1

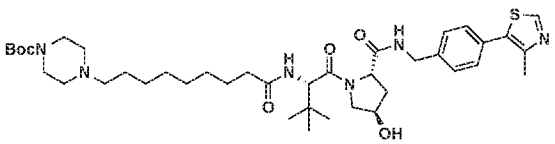


Intermediate 10: **(2*S*,4*R*)-1-((*S*)-2-(8-Bromooctanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide** To a mixture of 8-bromooctanoic acid (24 mg, 0.11 mmol) and VHL-1 (48 mg, 0.11 mmol) in THF (1 mL) were added DIEA (0.05 mL, 0.29 mmol) and EDCI (23.5 mg, 0.12 mmol). After being stirred at rt for 12 h, the reaction was concentrated under reduced pressure. The resulting residue was purified by HPLC to obtain the title compound (32 mg, 50% yield) as brown oil. ^{1}H NMR (600 MHz, CD3OD) δ 9.01 (s, 1H), 7.49 (d, J = 6.8 Hz, 2H), 7.45 (d, J = 8.1 Hz, 2H), 4.66 (s, 1H), 4.63 – 4.48 (m, 3H), 4.38 (dd, J = 15.3, 6.8 Hz, 1H), 3.93 (d, J = 11.1 Hz, 1H), 3.83 (dd, J = 10.9, 3.9 Hz, 1H), 3.60 –

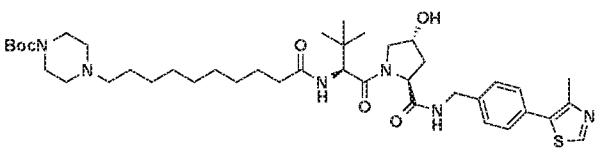
3.54 (m, 2H), 2.51 (s, 3H), 2.38 – 2.16 (m, 3H), 2.17 – 2.04 (m, 1H), 1.80 – 1.73 (m, 2H), 1.64 (dt, *J* = 13.5, 7.1 Hz, 2H), 1.51 – 1.43 (m, 2H), 1.42 – 1.33 (m, 4H), 1.06 (s, 9H).

Linker 1: *tert*-Butyl 4-(8-(((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-8-oxooctyl)piperazine-1-carboxylate To a solution of intermediate **10** (28 mg, 0.043 mmol) and *tert*-butyl piperazine-1-carboxylate (17 mg, 0.092 mmol) in DMF (1 mL) was added K_2CO_3 (14 mg, 0.1 mmol). After being heated at 60 °C for 4 h, the reaction mixture was cooled to rt. The insoluble materials were filtered off. And the filtrate was concentrated under reduced pressure. The resulting residue was purified by HPLC to obtain the title compound (30 mg, 44% yield) as brown oil. ^{1}H NMR (600 MHz, CD_3OD) δ 9.20 (s, 1H), 7.51 (d, *J* = 8.1 Hz, 2H), 7.46 (d, *J* = 8.1 Hz, 2H), 4.66 (s, 1H), 4.61 – 4.49 (m, 3H), 4.40 (d, *J* = 15.6 Hz, 1H), 4.23 (d, *J* = 13.1 Hz, 2H), 3.93 (d, *J* = 11.0 Hz, 1H), 3.83 (dd, *J* = 10.9, 3.8 Hz, 1H), 3.60 – 3.51 (m, 2H), 3.28 – 3.10 (m, 4H), 3.02 (t, *J* = 11.1 Hz, 2H), 2.53 (s, 3H), 2.37 – 2.21 (m, 3H), 2.14 – 2.06 (m, 1H), 1.82 – 1.71 (m, 2H), 1.68 – 1.57 (m, 2H), 1.49 (s, 9H), 1.45 – 1.33 (m, 6H), 1.06 (s, 9H).

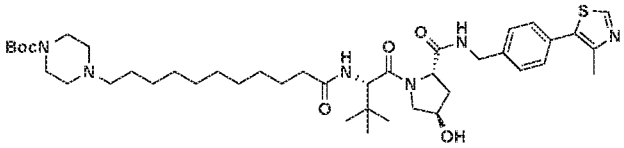
Linker **2**, linker **3**, linker **4** and linker **5** were synthesized according to the procedure for the preparation of linker **1**



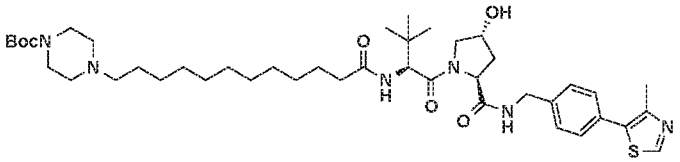
Linker 2: *tert*-Butyl 4-(9-(((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-9-oxononyl)piperazine-1-carboxylate. White solid 67% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 9.15 (s, 1H), 7.51 (d, *J* = 7.9 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 4.66 (s, 1H), 4.63 – 4.49 (m, 3H), 4.40 (d, *J* = 15.5 Hz, 1H), 4.23 (d, *J* = 12.9 Hz, 2H), 3.93 (d, *J* = 11.0 Hz, 1H), 3.83 (dd, *J* = 10.9, 3.6 Hz, 1H), 3.63 – 3.51 (m, 2H), 3.29 – 3.08 (m, 4H), 3.02 (t, *J* = 10.5 Hz, 2H), 2.53 (s, 3H), 2.37 – 2.21 (m, 3H), 2.17 – 2.04 (m, 1H), 1.82 – 1.72 (m, 2H), 1.70 – 1.56 (m, 2H), 1.49 (s, 9H), 1.46 – 1.31 (m, 8H), 1.05 (s, 9H).



Linker 3: *tert*-Butyl 4-(10-(((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-10-oxodecyl)piperazine-1-carboxylate. White solid 60% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 9.14 (s, 1H), 7.51 (d, *J* = 8.1 Hz, 2H), 7.45 (d, *J* = 7.6 Hz, 2H), 4.66 (s, 1H), 4.63 – 4.50 (m, 3H), 4.39 (d, *J* = 15.5 Hz, 1H), 4.23 (d, *J* = 13.1 Hz, 2H), 3.93 (d, *J* = 11.0 Hz, 1H), 3.83 (dd, *J* = 10.9, 3.9 Hz, 1H), 3.68 – 3.48 (m, 2H), 3.28 – 3.10 (m, 4H), 3.02 (t, *J* = 10.6 Hz, 2H), 2.53 (s, 3H), 2.41 – 2.18 (m, 3H), 2.17 – 2.04 (m, 1H), 1.82 – 1.70 (m, 2H), 1.70 – 1.58 (m, 2H), 1.49 (s, 9H), 1.44 – 1.28 (m, 10H), 1.06 (s, 9H).

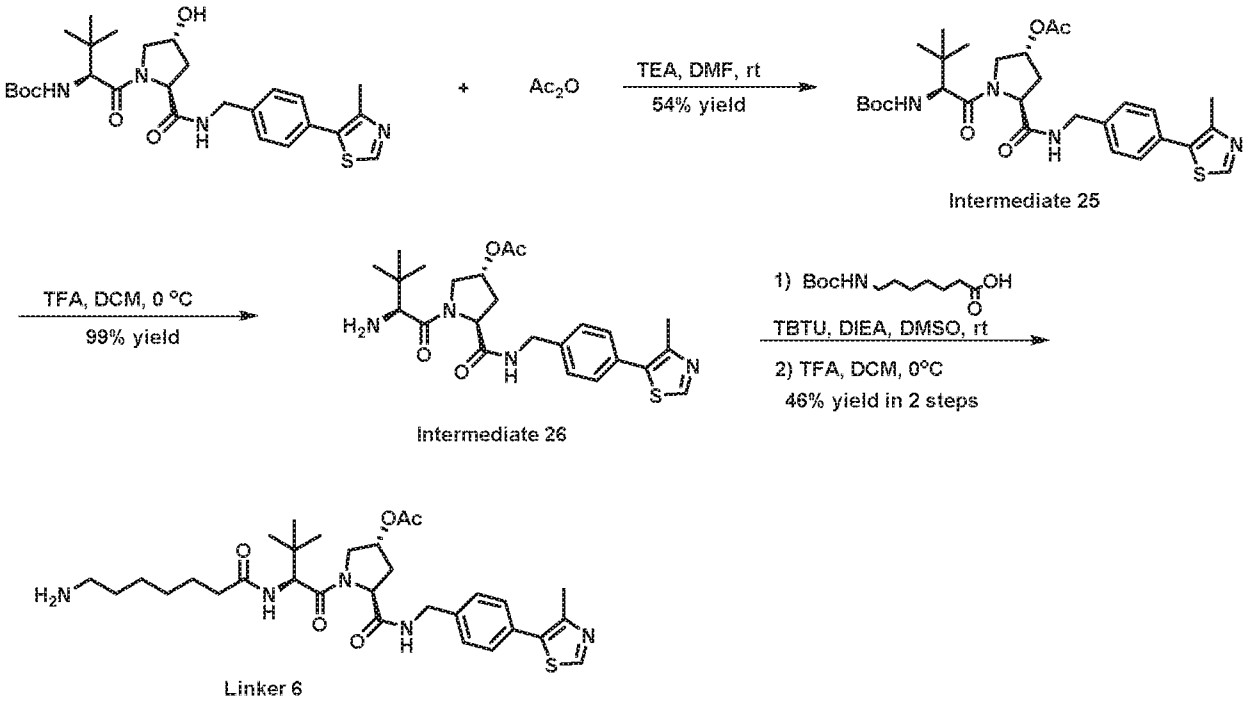


Linker 4: *tert*-Butyl 4-(11-(((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-11-oxoundecyl)piperazine-1-carboxylate. White solid 62% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 9.17 (s, 1H), 7.51 (d, *J* = 7.5 Hz, 2H), 7.46 (d, *J* = 7.8 Hz, 2H), 4.66 (s, 1H), 4.63 – 4.49 (m, 3H), 4.39 (d, *J* = 15.4 Hz, 1H), 4.23 (d, *J* = 12.6 Hz, 2H), 3.93 (d, *J* = 10.8 Hz, 1H), 3.87 – 3.78 (m, 1H), 3.72 – 3.45 (m, 2H), 3.28 – 3.11 (m, 4H), 3.06 – 2.97 (m, 2H), 2.53 (s, 3H), 2.36 – 2.19 (m, 3H), 2.15 – 2.04 (m, 1H), 1.85 – 1.71 (m, 2H), 1.72 – 1.56 (m, 2H), 1.49 (s, 9H), 1.45 – 1.26 (m, 12H), 1.04 (s, 9H).



Linker 5: *tert*-Butyl 4-(12-(((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-12-oxododecyl)piperazine-1-carboxylate. White solid 56% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 9.16 (s, 1H), 7.51 (t, *J* = 6.6 Hz, 2H), 7.46 (d, *J* = 8.1 Hz, 2H), 4.66 (s, 1H), 4.62 – 4.49 (m, 3H), 4.38 (d, *J* = 9.7 Hz, 1H), 4.23 (d, *J* = 13.2 Hz, 2H), 3.93 (d, *J* = 11.0 Hz, 1H), 3.83 (dd, *J* = 10.9, 3.7 Hz, 1H), 3.71 – 3.46 (m, 2H), 3.28 – 3.08 (m, 4H), 3.09 – 2.90 (m, 2H), 2.53 (s, 3H), 2.39 – 2.18 (m, 3H), 2.15 – 2.02 (m, 1H), 1.76 (s, 2H), 1.71 – 1.55 (m, 2H), 1.49 (s, 9H), 1.44 – 1.27 (m, 14H), 1.04 (s, 9H).

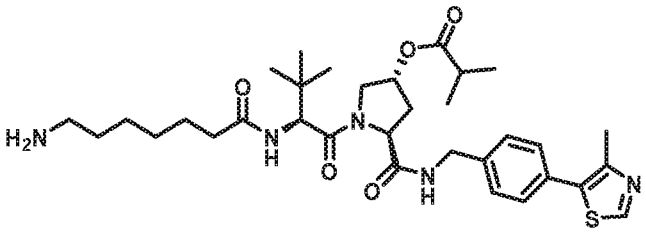
Scheme 13. Synthesis of linker 6



Intermediate 26: (3R,5S)-1-((S)-2-Amino-3,3-dimethylbutanoyl)-5-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-3-yl acetate. To a solution of Boc protected VHL-1 (600 mg, 1.1 mmol) in DCM (6 mL), were added Ac_2O (0.2 mL, 2.1 mmol) and TEA (0.32 mL, 2.3 mmol). The solution was stirred at rt for 3 d, before being quenched with water, and extracted with DCM (3×5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The resulting residue was purified by reverse-phase column to yield intermediate **25** as white oil (340 mg, 54% yield). Intermediate 25 was dissolved in DCM and TFA (7:2, 9 mL) in ice-water bath. The resulting solution was stirred at 0 °C for 30 min, before being concentrated to yield the title compound as oil (556 mg, 99% yield).

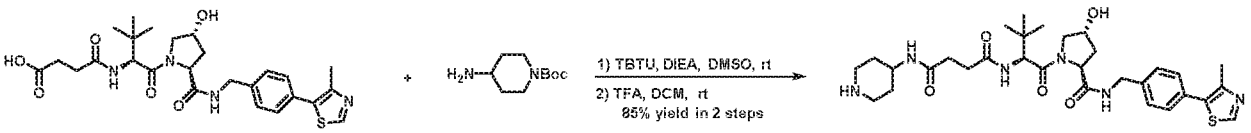
Linker 6: (3R,5S)-1-((S)-2-(7-Aminoheptanamido)-3,3-dimethylbutanoyl)-5-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-3-yl acetate. To a solution of Intermediate **26** (29 mg. 0.05 mmol) in DMSO (0.5 mL), were added the Boc protected amino acid (12 mg, 0.05 mmol), TBTU (17 mg, 0.05 mmol) and DIEA (0.1 mL, 0.57 mmol). The solution was stirred at rt for 1 h. After being quenched with MeOH, the reaction was diluted with DCM (2 mL) and TFA (0.5 mL). The resulting solution was stirred at 0 °C for 30 min before being concentrated. The resulting residue was purified by prep-HPLC to yield the title compound (17 mg, 49% yield). ^{1}H NMR (600 MHz, CD_3OD) δ 9.21 (s, 1H), 7.53 – 7.45 (m, 4H), 5.44 – 5.36 (m, 1H), 4.62 – 4.50

(m, 3H), 4.40 (d, J = 15.5 Hz, 1H), 4.19 (d, J = 11.8 Hz, 1H), 3.94 (dd, J = 11.7, 4.0 Hz, 1H), 2.93 (t, J = 7.6 Hz, 2H), 2.53 (s, 3H), 2.42 (dd, J = 13.9, 7.6 Hz, 1H), 2.38 – 2.23 (m, 3H), 2.07 (s, 3H), 1.73 – 1.60 (m, 4H), 1.50 – 1.36 (m, 4H), 1.06 (s, 10H).



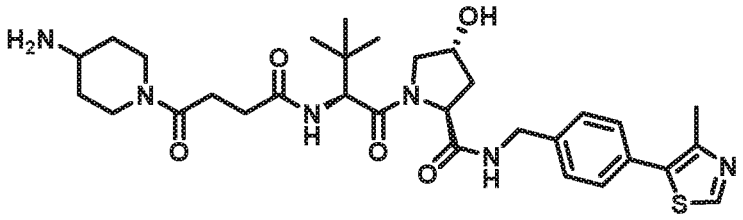
Linker 7: (3R,5S)-1-((S)-2-(7-Aminoheptanamido)-3,3-dimethylbutanoyl)-5-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-3-yl isobutyrate. Linker 7 was synthesized according to the procedures for the preparation of linker **6** with 57% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 9.31 (s, 1H), 7.50 (dd, J = 26.4, 8.1 Hz, 4H), 5.42 – 5.35 (m, 1H), 4.61 – 4.54 (m, 3H), 4.41 (d, J = 15.6 Hz, 1H), 4.16 (d, J = 11.8 Hz, 1H), 3.95 (dd, J = 11.7, 3.9 Hz, 1H), 2.93 (t, J = 7.6 Hz, 2H), 2.58 – 2.53 (m, 4H), 2.44 – 2.38 (m, 1H), 2.37 – 2.23 (m, 3H), 1.73 – 1.60 (m, 4H), 1.47 – 1.34 (m, 4H), 1.16 (d, J = 7.0 Hz, 6H), 1.06 (s, 9H).

Scheme 14. Synthesis of linker 8



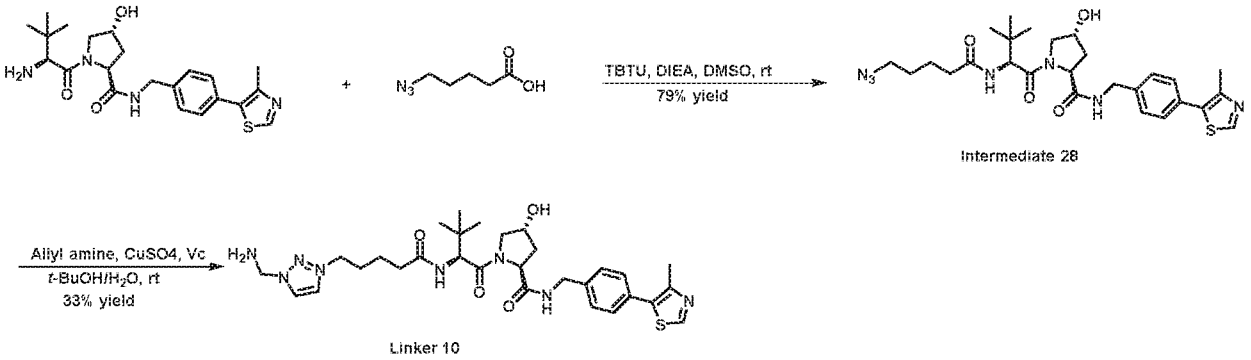
Intermediate 27 Linker 8

Linker 8: (2*S*,4*R*)-1-((*S*)-2-(4-(4-Aminopiperidin-1-yl)-4-oxobutanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. Linker **8** was synthesized according to the procedures for the preparation of linker **6** with 86% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 9.14 (s, 1H), 7.51 (d, J = 8.3 Hz, 2H), 7.49 – 7.42 (m, 2H), 4.65 – 4.50 (m, 4H), 4.39 (d, J = 15.5 Hz, 1H), 3.98 – 3.86 (m, 2H), 3.81 (dd, J = 11.0, 3.9 Hz, 1H), 3.47 – 3.37 (m, 2H), 3.11 (td, J = 12.9, 3.0 Hz, 2H), 2.64 (dd, J = 14.9, 7.5 Hz, 1H), 2.58 – 2.45 (m, 6H), 2.29 – 2.20 (m, 1H), 2.10 (ddd, J = 13.2, 9.0, 4.4 Hz, 3H), 1.78 – 1.65 (m, 2H), 1.05 (s, 9H).



Linker 9: (2S,4R)-1-((S)-2-(4-(4-Aminopiperidin-1-yl)-4-oxobutanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. Linker **9** was synthesized according to the procedures for the preparation of linker **6** in 73% yield. δ 9.28 (s, 1H), 7.51 (dd, *J* = 10.2, 5.7 Hz, 2H), 7.46 (d, *J* = 8.2 Hz, 2H), 4.68 – 4.49 (m, 5H), 4.41 (dd, *J* = 15.6, 2.1 Hz, 1H), 4.10 (d, *J* = 13.8 Hz, 1H), 3.91 (d, *J* = 11.0 Hz, 1H), 3.81 (dd, *J* = 11.0, 3.8 Hz, 1H), 3.39 (t, *J* = 11.5 Hz, 1H), 3.18 (t, *J* = 13.3 Hz, 1H), 2.79 – 2.60 (m, 4H), 2.60 – 2.49 (m, 4H), 2.26 (dd, *J* = 13.1, 7.7 Hz, 1H), 2.17 – 2.00 (m, 3H), 1.61 (dt, *J* = 12.1, 8.1 Hz, 1H), 1.55 – 1.41 (m, 1H), 1.05 (s, 9H).

Scheme 15. Synthesis of linker 10

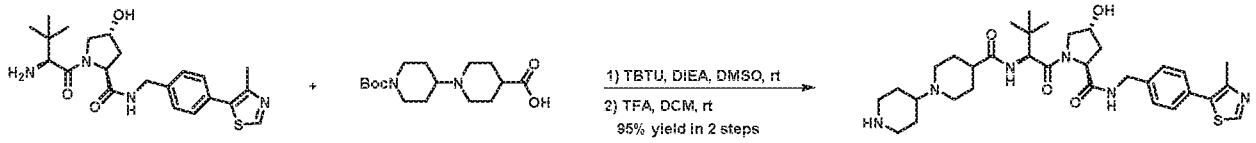


Intermediate 28: (2S,4R)-1-((S)-2-(5-Azidopentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. Intermediate 28 was synthesized according to the procedures for the preparation of linker **6** in 79% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.88 (s, 1H), 7.50 – 7.38 (m, 4H), 4.66 (s, 1H), 4.62 (t, *J* = 8.3 Hz, 1H), 4.59 – 4.50 (m, 2H), 4.38 (d, *J* = 15.5 Hz, 1H), 3.93 (d, *J* = 11.1 Hz, 1H), 3.82 (dd, *J* = 10.9, 3.9 Hz, 1H), 3.31 (t, *J* = 6.7 Hz, 2H), 2.49 (s, 3H), 2.41 – 2.20 (m, 4H), 2.14 – 2.07 (m, 1H), 1.77 – 1.56 (m, 4H), 1.06 (s, 9H).

Linker 10: (2S,4R)-1-((S)-2-(5-(1-(Aminomethyl)-1H-1,2,3l4-triazol-3-yl)pentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. Intermediate **28** (35 mg, 0.06 mmol) was dissolved in *t*-BuOH and water (5:1, 0.5 mL), followed by allyl amine (3.4 mg, 0.06 mmol), $CuSO_4$ (20 mg, 0.08 mmol) and Vc (1 mg,

0.004 mmol). The mixture was stirred at room temperature. After 24 h, the solvent concentrated, the resulted residue was purified by prep-HPLC to yield the title compound (15 mg, 33% yield). ^{1}H NMR (500 MHz, CD_3OD) δ 9.13 (s, 1H), 8.06 (s, 1H), 7.48 (dd, J = 24.2, 8.2 Hz, 4H), 4.64 (s, 1H), 4.60 – 4.51 (m, 3H), 4.47 (t, J = 6.9 Hz, 2H), 4.40 (d, J = 15.5 Hz, 1H), 4.26 (s, 2H), 3.92 (d, J = 11.0 Hz, 1H), 3.83 (dd, J = 10.9, 3.9 Hz, 1H), 2.52 (s, 3H), 2.40 – 2.30 (m, 2H), 2.28 – 2.21 (m, 1H), 2.16 – 2.07 (m, 1H), 1.98 – 1.90 (m, 2H), 1.66 – 1.56 (m, 2H), 1.05 (s, 9H).

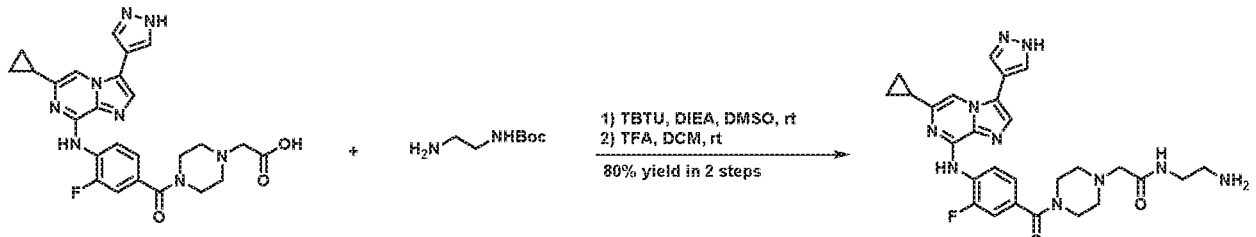
Scheme 16. Synthesis of linker 11



Intermediate 29 Linker 11

Linker 11: Linker **11** was synthesized according to the procedures for the preparation of linker **6** in 95% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 9.28 (s, 1H), 7.51 (d, J = 8.1 Hz, 2H), 7.44 (d, J = 8.1 Hz, 2H), 4.70 – 4.50 (m, 4H), 4.39 (d, J = 15.6 Hz, 1H), 3.92 (d, J = 10.1 Hz, 1H), 3.82 (dd, J = 10.9, 3.6 Hz, 1H), 3.74 – 3.53 (m, 5H), 3.14 (t, J = 12.2 Hz, 4H), 2.79 – 2.65 (m, 1H), 2.52 (s, 3H), 2.40 (d, J = 12.7 Hz, 2H), 2.31 – 2.22 (m, 1H), 2.20 – 1.93 (m, 8H), 1.06 (s, 9H).

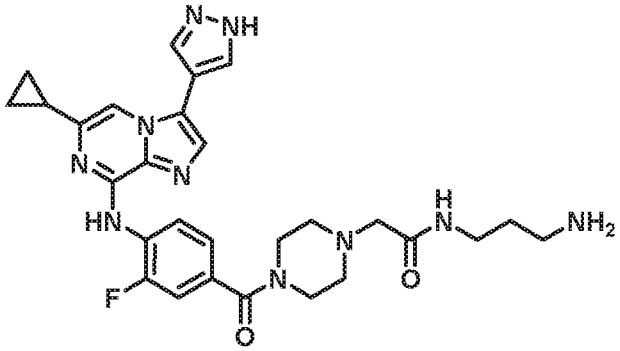
Scheme 17. Synthesis of linker 12



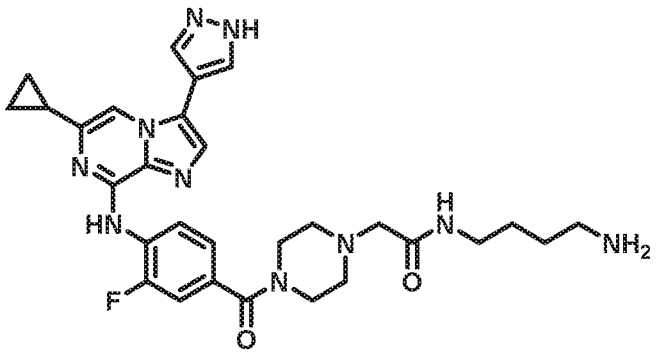
Intermediate 4 Linker 12

Linker 12: *N*-(2-Aminoethyl)-2-(4-(4-((6-cyclopropyl-3-(1H-pyrazol-4-yl)imidazo[1,2-a]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamide. Linker **12** was synthesized according to the procedures for the preparation of linker **6** in 80% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 9.28 (s, 1H), 7.51 (d, J = 8.1 Hz, 2H), 7.44 (d, J = 8.1 Hz, 2H), 4.70 – 4.50 (m, 4H), 4.39 (d, J = 15.6 Hz, 1H), 3.92 (d, J = 10.1 Hz, 1H), 3.82 (dd, J = 10.9, 3.6 Hz, 1H), 3.74 – 3.53 (m, 5H), 3.14 (t, J = 12.2 Hz, 4H), 2.79 – 2.65 (m, 1H), 2.52 (s, 3H), 2.40 (d, J = 12.7 Hz, 2H), 2.31 – 2.22 (m, 1H), 2.20 – 1.93 (m, 8H), 1.06 (s, 9H).

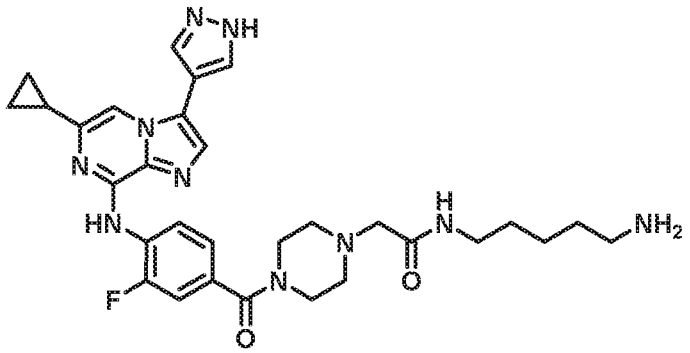
Linkers **13 – 23** were synthesized according to the procedures for the preparation of Linker **12**.



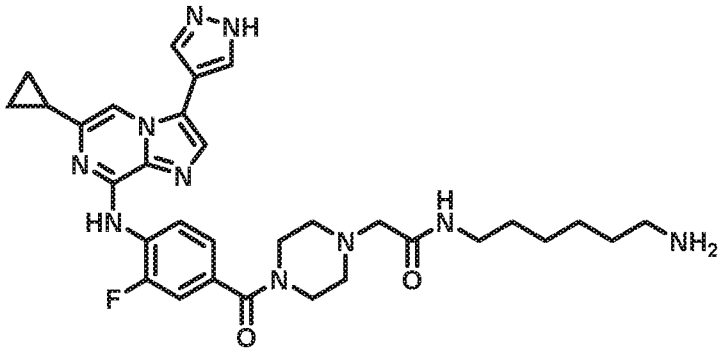
Linker 13: *N*-(3-Aminopropyl)-2-(4-(4-((6-cyclopropyl-3-(1H-pyrazol-4-yl)imidazo[1,2-a]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamide. 82% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.60 (t, *J* = 8.2 Hz, 1H), 8.14 (s, 2H), 7.95 (s, 1H), 7.90 (s, 1H), 7.43 (dd, *J* = 11.2, 1.6 Hz, 1H), 7.39 (d, *J* = 8.5 Hz, 1H), 4.12 – 3.85 (m, 6H), 3.49 (br, 4H), 3.40 (t, *J* = 6.7 Hz, 2H), 3.01 (t, *J* = 7.4 Hz, 2H), 2.21 – 2.04 (m, 1H), 1.97 – 1.84 (m, 2H), 1.07 – 0.92 (m, 4H).



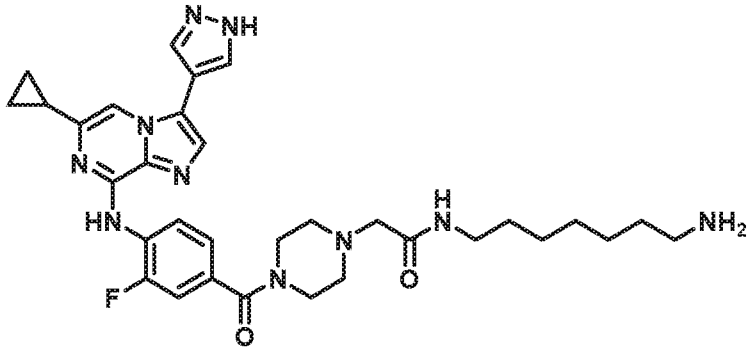
Linker 14: *N*-(4-Aminobutyl)-2-(4-(4-((6-cyclopropyl-3-(1H-pyrazol-4-yl)imidazo[1,2-a]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamide. 86% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.73 (t, *J* = 8.1 Hz, 1H), 8.14 (s, 2H), 7.90 (s, 1H), 7.77 (s, 1H), 7.42 (d, *J* = 11.3 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 3.96 (br, 6H), 3.41 (br, 4H), 2.97 (t, *J* = 7.3 Hz, 2H), 2.14 – 2.03 (m, 1H), 1.79 – 1.58 (m, 4H), 1.07 – 1.00 (m, 2H), 1.00 – 0.89 (m, 2H).



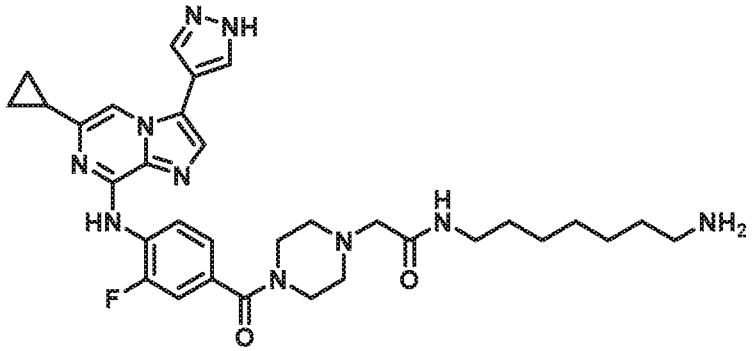
Linker 15: *N*-(5-Aminopentyl)-2-(4-(4-((6-cyclopropyl-3-(1H-pyrazol-4-yl)imidazo[1,2-a]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamide. 80% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.66 (t, *J* = 8.2 Hz, 1H), 8.14 (s, 2H), 7.94 (s, 1H), 7.85 (s, 1H), 7.44 (dd, *J* = 11.3, 1.8 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 1H), 4.21 – 3.77 (m, 6H), 3.48 (br, 4H), 3.30 (t, *J* = 7.1 Hz, 2H), 2.95 (t, *J* = 7.6 Hz, 2H), 2.15 – 2.04 (m, 1H), 1.79 – 1.66 (m, 2H), 1.66 – 1.55 (m, 2H), 1.51 – 1.41 (m, 2H), 1.09 – 0.92 (m, 4H).



Linker 16: *N*-(6-Aminohexyl)-2-(4-(4-((6-cyclopropyl-3-(1H-pyrazol-4-yl)imidazo[1,2-a]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamide. 79% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.73 (t, *J* = 8.2 Hz, 1H), 8.12 (s, 2H), 7.90 (s, 1H), 7.76 (s, 1H), 7.46 – 7.40 (m, 1H), 7.38 (d, *J* = 8.5 Hz, 1H), 4.13 – 3.86 (m, 6H), 3.43 (br, 4H), 3.29 (t, *J* = 7.1 Hz, 2H), 2.94 (t, *J* = 7.5 Hz, 2H), 2.14 – 2.04 (m, 1H), 1.74 – 1.64 (m, 2H), 1.64 – 1.54 (m, 2H), 1.49 – 1.39 (m, 4H), 1.07 – 1.00 (m, 2H), 1.00 – 0.92 (m, 2H).

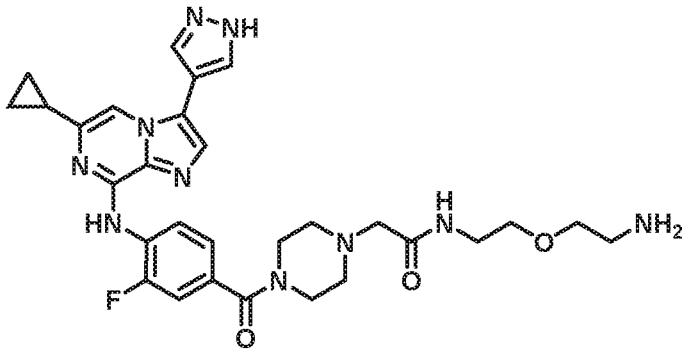


Linker 17: *N*-(7-Aminoheptyl)-2-(4-(4-((6-cyclopropyl-3-(1H-pyrazol-4-yl)imidazo[1,2-a]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamide. 83% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.74 (t, *J* = 8.2 Hz, 1H), 8.12 (s, 2H), 7.91 (s, 1H), 7.76 (s, 1H), 7.43 (dd, *J* = 11.3, 1.7 Hz, 1H), 7.38 (d, *J* = 8.5 Hz, 1H), 4.05 – 3.86 (m, 6H), 3.43 (br, 4H), 3.28 (t, *J* = 7.2 Hz, 2H), 3.00 – 2.86 (m, 2H), 2.21 – 2.00 (m, 1H), 1.73 – 1.63 (m, 2H), 1.63 – 1.53 (m, 2H), 1.47 – 1.33 (m, 6H), 1.07 – 0.99 (m, 2H), 0.99 – 0.91 (m, 2H).

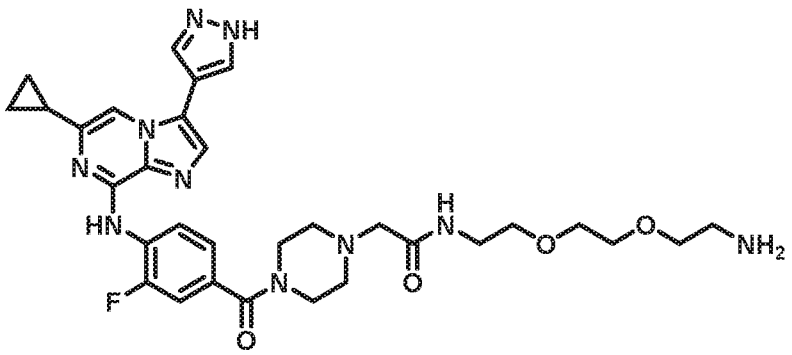


Linker 18: *N*-(7-Aminoheptyl)-2-(4-(4-((6-cyclopropyl-3-(1H-pyrazol-4-yl)imidazo[1,2-a]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamide. 83% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.74 (t, *J* = 8.2 Hz, 1H), 8.12 (s, 2H), 7.91 (s, 1H), 7.76 (s, 1H), 7.43 (dd, *J* = 11.3, 1.7 Hz, 1H), 7.38 (d, *J* = 8.5 Hz, 1H), 4.05 – 3.86 (m, 6H), 3.43 (br, 4H), 3.28 (t, *J* = 7.2 Hz,

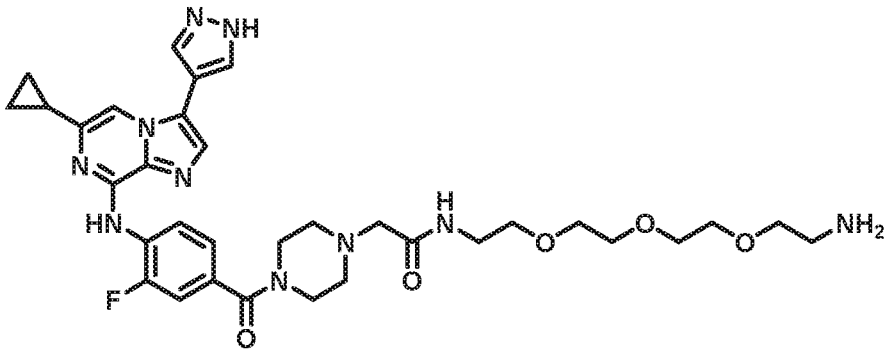
2H), 3.00 – 2.86 (m, 2H), 2.21 – 2.00 (m, 1H), 1.73 – 1.63 (m, 2H), 1.63 – 1.53 (m, 2H), 1.47 – 1.33 (m, 6H), 1.07 – 0.99 (m, 2H), 0.99 – 0.91 (m, 2H).



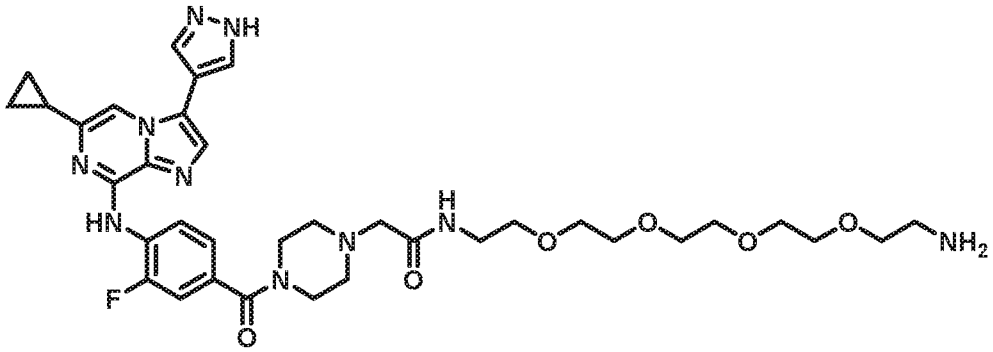
Linker 19: *N*-(2-(2-Aminoethoxy)ethyl)-2-(4-(4-((6-cyclopropyl-3-(1H-pyrazol-4-yl)imidazo[1,2-a]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamide. 82% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.65 (t, *J* = 8.2 Hz, 1H), 8.16 (s, 2H), 7.98 (s, 1H), 7.92 (s, 1H), 7.46 (dd, *J* = 11.3, 1.6 Hz, 1H), 7.41 (d, *J* = 8.5 Hz, 1H), 4.13 – 3.89 (m, 6H), 3.76 – 3.68 (m, 2H), 3.63 (t, *J* = 5.4 Hz, 2H), 3.56 – 3.44 (m, 6H), 3.18 – 3.12 (m, 2H), 2.18 – 2.09 (m, 1H), 1.09 – 1.02 (m, 2H), 1.01 – 0.96 (m, 2H).



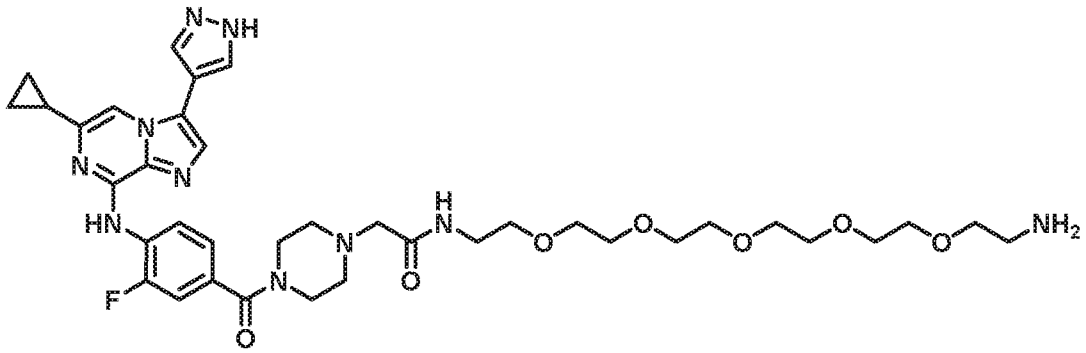
Linker 20: *N*-(2-(2-(2-Aminoethoxy)ethoxy)ethyl)-2-(4-(4-((6-cyclopropyl-3-(1H-pyrazol-4-yl)imidazo[1,2-a]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamide. 85% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.75 (t, *J* = 8.2 Hz, 1H), 8.12 (s, 2H), 7.91 (s, 1H), 7.76 (s, 1H), 7.43 (dd, *J* = 11.3, 1.7 Hz, 1H), 7.39 (d, *J* = 8.5 Hz, 1H), 4.04 – 3.86 (m, 6H), 3.77 – 3.71 (m, 2H), 3.69 (s, 4H), 3.62 (t, *J* = 5.6 Hz, 2H), 3.49 (t, *J* = 5.5 Hz, 2H), 3.40 (br, 4H), 3.20 – 3.11 (m, 2H), 2.16 – 2.04 (m, 1H), 1.06 – 1.01 (m, 2H), 1.00 – 0.91 (m, 2H).



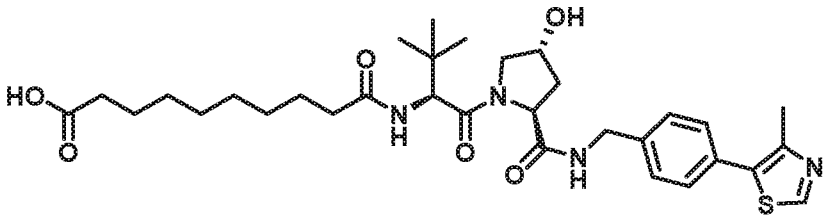
Linker 21: ***N*-(2-(2-(2-(2-Aminoethoxy)ethoxy)ethoxy)ethyl)-2-(4-(4-((6-cyclopropyl-3-(1H-pyrazol-4-yl)imidazo[1,2-a]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamide.** 84% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.66 (t, *J* = 8.2 Hz, 1H), 8.16 (s, 2H), 7.99 (s, 1H), 7.93 (s, 1H), 7.46 (d, *J* = 12.7 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 1H), 4.09 – 3.95 (m, 6H), 3.78 – 3.64 (m, 12H), 3.64 – 3.58 (m, 2H), 3.52 – 3.45 (m, 4H), 3.19 – 3.12 (m, 2H), 2.15 (t, *J* = 6.3 Hz, 1H), 1.13 – 0.93 (m, 4H).



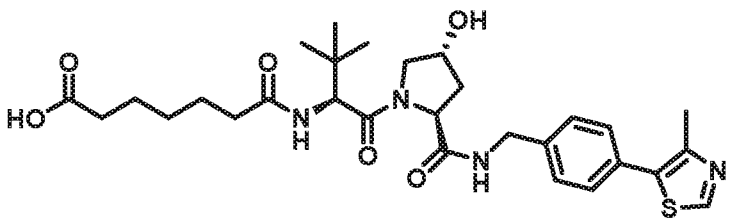
Linker 22: ***N*-(14-Amino-3,6,9,12-tetraoxatetradecyl)-2-(4-(4-((6-cyclopropyl-3-(1H-pyrazol-4-yl)imidazo[1,2-a]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamide.** 81% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.66 (t, *J* = 8.2 Hz, 1H), 8.15 (s, 2H), 7.97 (s, 1H), 7.89 (s, 1H), 7.45 (dd, *J* = 11.3, 1.7 Hz, 1H), 7.41 (d, *J* = 8.4 Hz, 1H), 4.14 – 3.88 (m, 6H), 3.78 – 3.72 (m, 2H), 3.72 – 3.64 (m, 12H), 3.61 (t, *J* = 5.4 Hz, 2H), 3.53 – 3.42 (m, 6H), 3.20 – 3.12 (m, 2H), 2.17 – 2.08 (m, 1H), 1.08 – 1.01 (m, 2H), 1.01 – 0.93 (m, 2H).



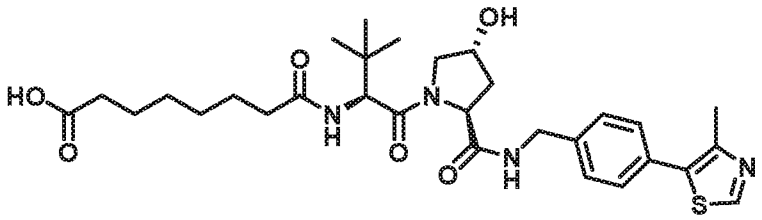
Linker 23: *N*-(17-Amino-3,6,9,12,15-pentaoxaheptadecyl)-2-(4-(4-((6-cyclopropyl-3-(1H-pyrazol-4-yl)imidazo[1,2-a]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamide. 78% yield. ^{1}H NMR (500 MHz, CD3OD) δ 8.66 (t, *J* = 8.2 Hz, 1H), 8.15 (s, 2H), 7.97 (s, 1H), 7.89 (s, 1H), 7.45 (dd, *J* = 11.2, 1.7 Hz, 1H), 7.41 (d, *J* = 8.5 Hz, 1H), 4.12 – 3.94 (m, 6H), 3.77 – 3.73 (m, 2H), 3.73 – 3.65 (m, 16H), 3.62 – 3.60 (m, 2H), 3.52 – 3.44 (m, 6H), 3.18 – 3.10 (m, 2H), 2.19 – 2.07 (m, 1H), 1.08 – 0.92 (m, 4H).



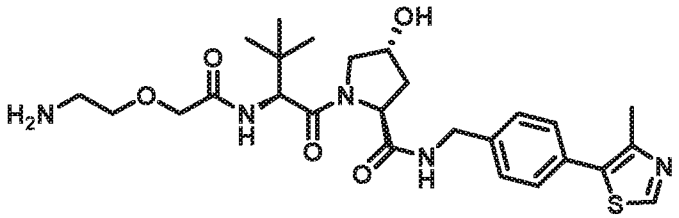
Linker 24: 10-(((S)-1-((2S,4R)-4-Hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-10-oxodecanoic acid Linker **24** was synthesized in a reportd method (Galdeano et al., 2014; Maniaci et al., 2017).



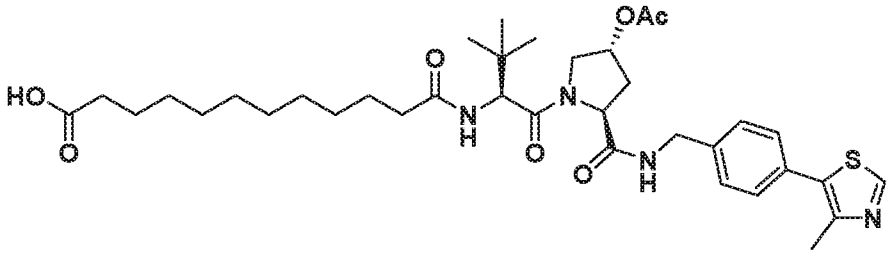
Linker 25: 7-(((S)-1-((2S,4R)-4-Hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-7-oxoheptanoic acid Linker **25** was synthesized in a reportd method (Galdeano et al., 2014; Maniaci et al., 2017).



Linker 26: 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-oxooctanoic acid Linker **24** was synthesized in a reportd method (Galdeano et al., 2014; Maniaci et al., 2017).

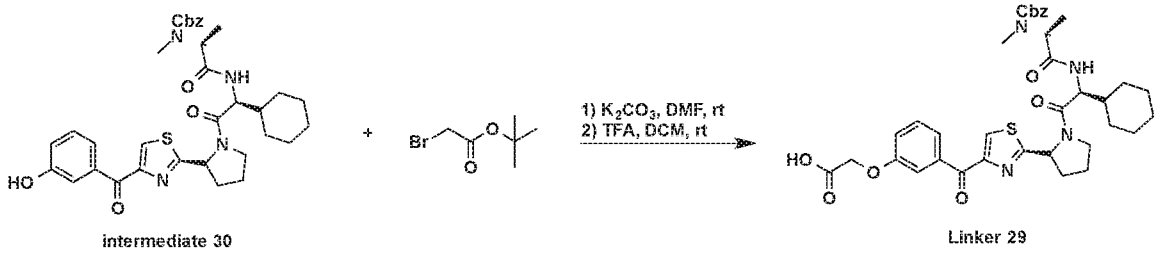


Linker 27: (2S,4R)-1-((S)-2-(2-(2-Aminoethoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide Linker **26** was synthesized in a reportd method (Galdeano et al., 2014; Maniaci et al., 2017).



Linker 28: 12-(((S)-1-((2S,4R)-4-acetoxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-12-oxododecanoic acid Linker **28** was synthesized in the same procedure as linker **6.**

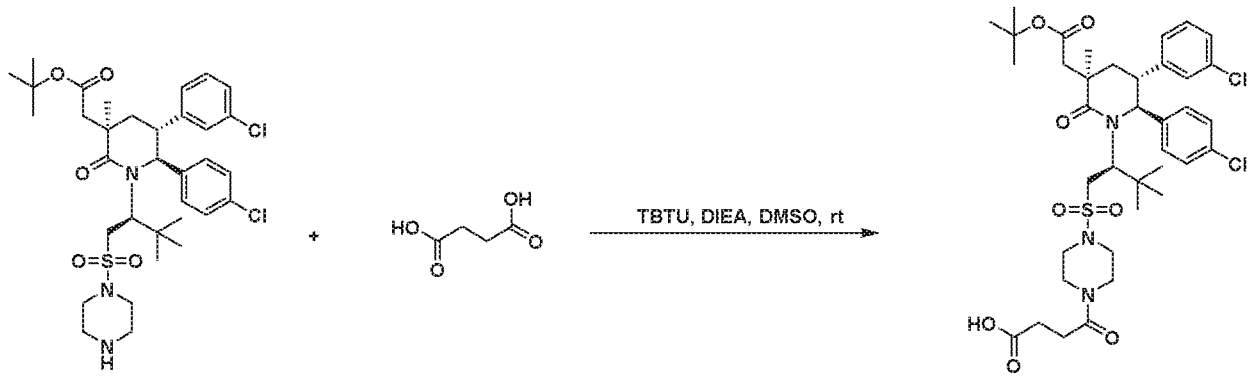
Scheme 18. Synthesis of linker 29



intermediate 30 Linker 29

Linker 29: 2-(3-(2-((*R*)-1-((*S*)-2-((*S*)-2-(((Benzyloxy)carbonyl)(methyl)amino)propanamido)-2-cyclohexylacetyl)pyrrolidin-2-yl)thiazole-4-carbonyl)phenoxy)acetic acid. The title compound can be synthesized according to the following procedures: To a solution of intermediate **30** (1 equive.) in DMF, will be added K_2CO_3 (1.5 equiv.), followed by *tert*-butyl 2-bromoacetate (1.5 equiv.). After being stirred at rt for 12 h, the mixture will be filtered. And the filtrate will be collected and concentrated. The resulting residue will be purified by HPLC. The purified compound will be dissolved in DCM and TFA (1:1). After being stirred at rt for 1 h, the solvent will be removed to yield the title compound.

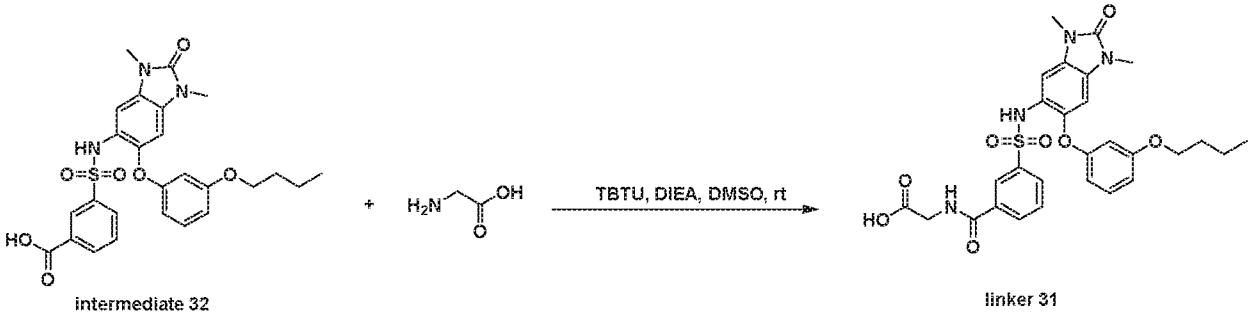
Scheme 19. Synthesis of linker 30



intermediate 31 linker 30

Linker 30: 4-(4-(((S)-2-((3R,5R,6S)-3-(2-(*tert*-Butoxy)-2-oxoethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-1-yl)-3,3-dimethylbutyl)sulfonyl)piperazin-1-yl)-4-oxobutanoic acid. The title compound can be synthesized according to the following procedures: To a solution of intermediate **31** (1 equiv.) in DMSO, will be added succinic acid (5 equiv.), followed by TBTU (1.1 equiv.) and DIEA (1.5 equiv.). After being stirred at rt for 1 h, the mixture will be concentrated. The resulting residue will be purified by HPLC to yield the title compound.

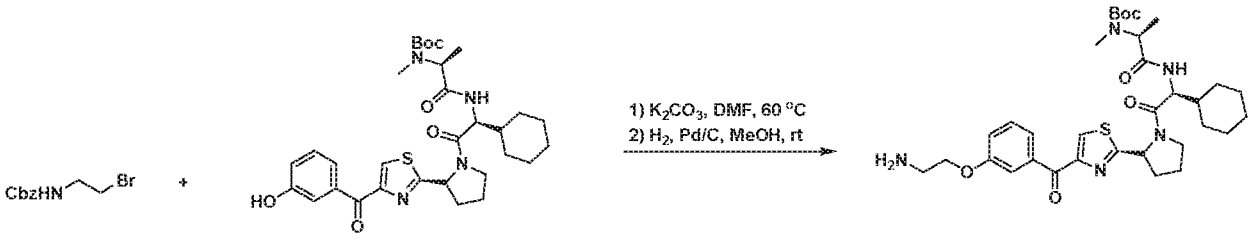
Scheme 20. Synthesis of linker 31



intermediate 32 linker 31

Linker 31: (3-(*N*-(6-(3-Butoxyphenoxy)-1,3-dimethyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)sulfamoyl)benzoyl)glycine. The title compound can be synthesized according to the following procedures: To a solution of intermediate **32** (1 equiv.) in DMSO will be added glycine (1.1 equiv.), followed by TBTU (1.1 equiv.) and DIEA (1.5 equiv.). After being stirred at rt for 1 h, the mixture will be concentrated. The resulted residue will be purified by HPLC to yield the title compound.

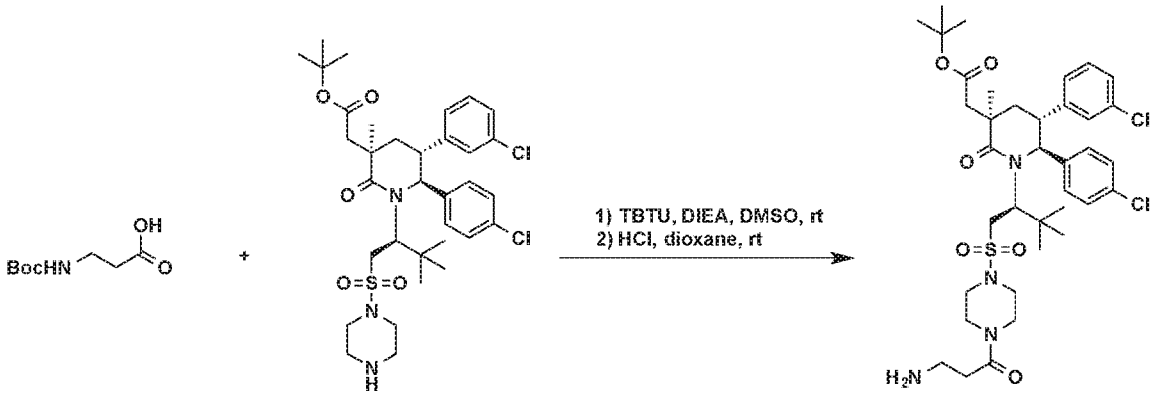
Scheme 21. Synthesis of linker 32



intermediate 33 intermediate 34 linker 32

Linker 32: *tert*-Butyl ((S)-1-(((S)-2-((R)-2-(4-(3-(2-aminoethoxy)benzoyl)thiazol-2-yl)pyrrolidin-1-yl)-1-cyclohexyl-2-oxoethyl)amino)-1-oxopropan-2-yl)(methyl)carbamate. The title compound can be synthesized according to the following procedures: To a mixture of intermediate 33 (1.2 equiv.) and intermediate 34 (1 equiv.) in DMF, will be added K_2CO_3 (1.5 equiv.). After being heated at 60 °C for 12 h, the mixture will be filtered. The filtrate will be collected and concentrated. The resulting residue will be purified by HPLC. The purified compound will be dissolved in MeOH, followed by Pd/C (0.1 equiv.). After being stirred at rt for 2 h under H_2 atmosphere, the mixture will be filtered. The filtrate will be collected and concentrated to yield the title compound.

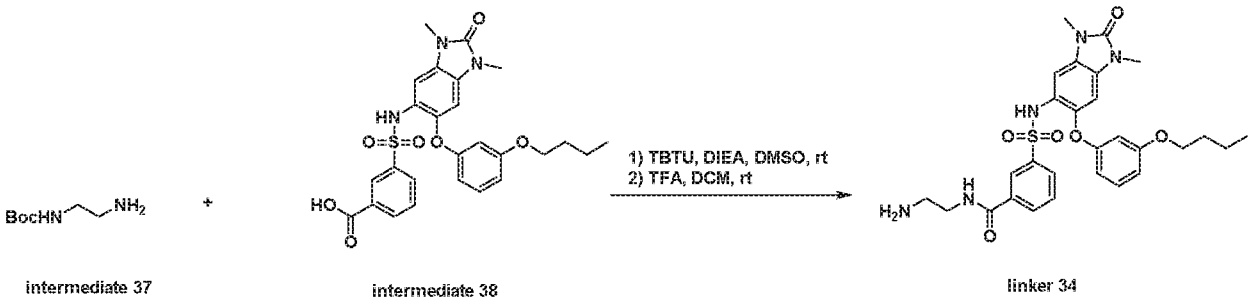
Scheme 22. Synthesis of linker 33



intermediate 35 intermediate 36 linker 33

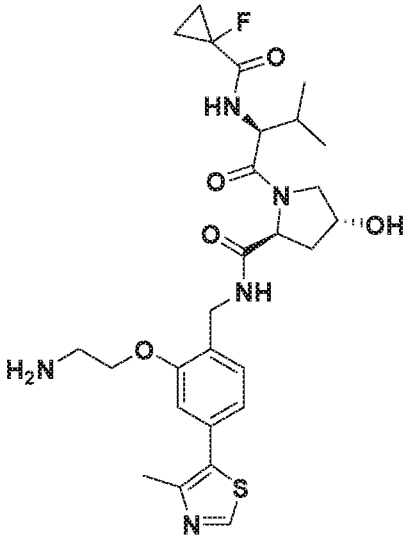
Linker 33: *tert*-Butyl 2-((3*R*,5*R*,6*S*)-1-((*S*)-1-((4-(3-aminopropanoyl)piperazin-1-yl)sulfonyl)-3,3-dimethylbutan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetate. The title compound can be synthesized according to the following procedures: To a mixture of intermediate **35** (1 equiv.) and intermediate **36** (1.1 equiv.) in DMSO, will be added TBTU (1.1 equiv.) and DIEA (1.5 equiv.). After being stirred at rt for 1 h, the solution will be concentrated. The resulting residue will be diluted with HCl in dioxane (4 N). The resulting mixture will be stirred at rt for 2 h, before being concentrated. The resulting residue will be purified by HPLC to yield the title compound.

Scheme 23. Synthesis of linker 34



intermediate 37 intermediate 38 linker 34

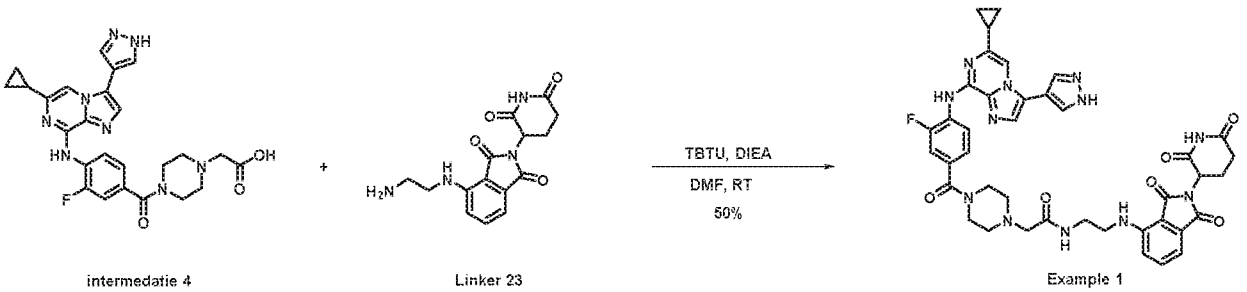
Linker 34: *N*-(2-Aminoethyl)-3-(N-(6-(3-butoxyphenoxy)-1,3-dimethyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)sulfamoyl)benzamide. Linker **34** will be synthesized according to the procedures for the synthesis of linker **33**.



Linker 35: (2S,4R)-*N*-(2-(2-Aminoethoxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((1-fluorocyclopropane-1-carbonyl)-L-valyl)-4-hydroxypyrrolidine-2-carboxamide. Linker **35** will be synthesized using a known method (Farnaby et al., 2019).

Procedures for the synthesis of Examples

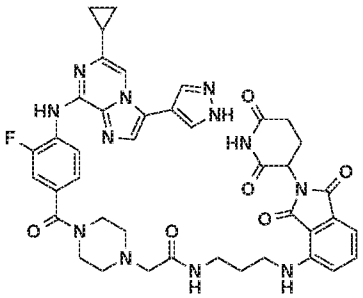
Scheme 24. Synthesis of Example 1



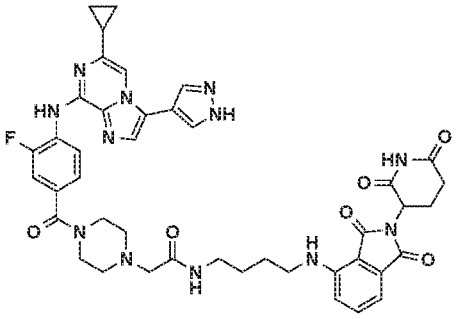
intermedatie 4 Linker 23 Example 1

Example 1: 2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-*N*-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethyl)acetamide. To a solution of intermediate **4** (7 mg, 0.011 mmol) and linker **6** (5 mg, 0.012 mmol) in DMF (0.5 mL) were added DIEA (17 μL, 0.1 mmol) and TBTU (6 mg, 0.02 mmol). After being stirred at rt for 12 h, the mixture was purified by HPLC to yield the title compound (6 mg, 50% yield) as brown oil. ^{1}H NMR (600 MHz, CD_3OD) δ 8.82 (t, *J* = 8.2 Hz, 1H), 8.13 (s, 2H), 7.93 (s, 1H), 7.75 (s, 1H), 7.64 – 7.55 (m, 1H), 7.40 (dd, *J* = 26.8, 9.8 Hz, 2H), 7.17 (d, *J* = 8.6 Hz, 1H), 7.09 (d, *J* = 7.0 Hz, 1H), 5.04 (dd, *J* = 12.8, 5.3 Hz, 1H), 4.14 – 3.71 (m, 6H), 3.66 – 3.46 (m, 4H), 3.27 – 3.12 (m, 2H), 2.84 (dd, *J* = 25.0, 11.5 Hz, 1H), 2.81 – 2.63 (m, 2H), 2.18 – 2.01 (m, 2H), 1.11 – 1.02 (m, 2H), 1.01 – 0.90 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{40}H_{40}FN_{12}O_6^+$, 803.3172; found 803.3190.

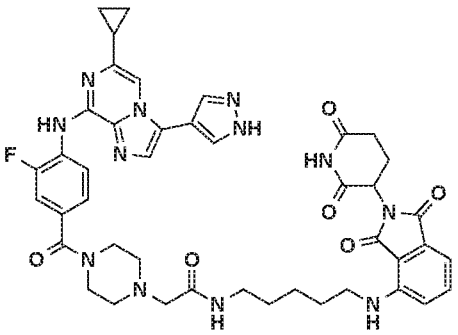
Example compounds **2 – 22, 37 – 45, 63, 64, 102 – 107, and 130 – 134** were synthesized according to the procedure for the preparation of example compound **1**.



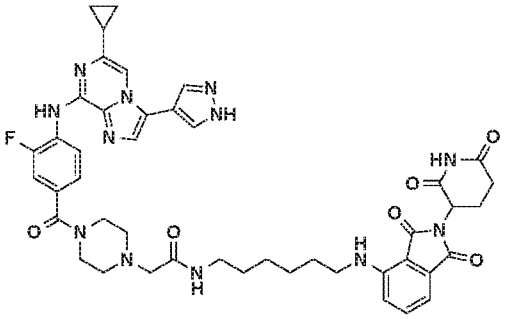
Example 2: 2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-*N*-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propyl)acetamide. 55% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 8.77 (t, *J* = 8.1 Hz, 1H), 8.11 (s, 2H), 7.92 (s, 1H), 7.80 (s, 1H), 7.56 (t, *J* = 7.7 Hz, 1H), 7.40 (dd, *J* = 27.8, 9.8 Hz, 2H), 7.06 (t, *J* = 8.7 Hz, 2H), 5.08 (dd, *J* = 12.7, 5.2 Hz, 1H), 3.96 (br, 6H), 3.53 – 3.36 (m, 6H), 2.91 – 2.53 (m, 3H), 2.22 – 2.00 (m, 2H), 2.00 – 1.82 (m, 2H), 1.12 – 1.01 (m, 2H), 1.00 – 0.92 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{41}H_{42}FN_{12}O_6^+$, 817.3329; found 817.3310.



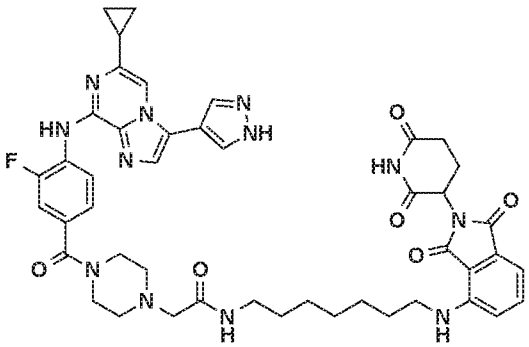
Example 3: 2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-*N*-(4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)butyl)acetamide. 48% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 8.80 (t, *J* = 8.2 Hz, 1H), 8.14 (s, 2H), 7.94 (s, 1H), 7.78 (s, 1H), 7.57 (dd, *J* = 13.9, 6.5 Hz, 1H), 7.44 (d, *J* = 11.1 Hz, 1H), 7.40 (d, *J* = 8.5 Hz, 1H), 7.11 – 7.02 (m, 2H), 5.07 (dd, *J* = 12.8, 5.4 Hz, 1H), 3.95 (br, 6H), 3.45 – 3.34 (m, 6H), 2.92 – 2.82 (m, 2H), 2.80 – 2.66 (m, 2H), 2.17 – 2.05 (m, 3H), 1.78 – 1.61 (m, 4H), 1.08 – 1.02 (m, 2H), 0.99 – 0.91 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{42}H_{44}FN_{12}O_6^+$, 831.3485; found 831.3502.



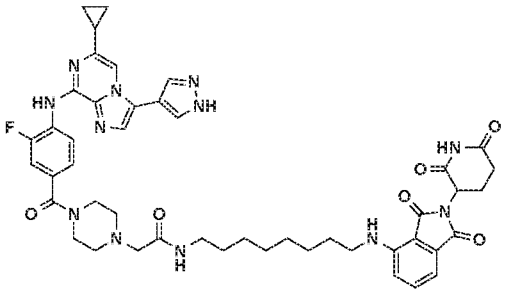
Example 4: 2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-*N*-(5-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)pentyl)acetamide. 60% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 8.82 (t, *J* = 8.2 Hz, 1H), 8.13 (s, 2H), 7.93 (s, 1H), 7.74 (s, 1H), 7.59 – 7.53 (m, 1H), 7.44 (d, *J* = 12.5 Hz, 1H), 7.40 (d, *J* = 8.5 Hz, 1H), 7.10 – 7.03 (m, 2H), 5.09 (dd, *J* = 12.6, 5.5 Hz, 2H), 3.80 (br, 6H), 3.43 – 3.35 (m, 4H), 2.94 – 2.81 (m, 2H), 2.81 – 2.65 (m, 3H), 2.18 – 2.04 (m, 2H), 1.79 – 1.67 (m, 2H), 1.68 – 1.56 (m, 2H), 1.56 – 1.43 (m, 2H), 1.05 (dd, *J* = 7.4, 3.0 Hz, 2H), 0.97 – 0.90 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{43}H_{46}FN_{12}O_6^+$, 845.3642; found 845.3620.



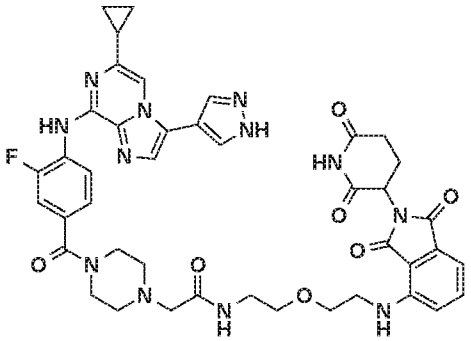
Example 5: 2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-*N*-(6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)hexyl)acetamide. 50% yield. ^{1}H NMR (600 MHz, CD_3OD δ 8.76 (t, *J* = 8.1 Hz, 1H), 8.08 (s, 2H), 7.89 (s, 1H), 7.80 (s, 1H), 7.56 – 7.51 (m, 1H), 7.44 – 7.33 (m, 2H), 7.08 – 6.96 (m, 2H), 5.04 (dd, *J* = 12.5, 4.9 Hz, 2H), 4.09 – 3.77 (m, 6H), 3.41 (br, 4H), 3.30 – 3.22 (m, 2H), 2.93 – 2.70 (m, 5H), 2.16 – 2.05 (m, 2H), 1.76 – 1.67 (m, 2H), 1.63 – 1.54 (m, 2H), 1.53 – 1.38 (m, 4H), 1.08 – 1.00 (m, 2H), 1.00 – 0.91 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{44}H_{48}FN_{12}O_6^+$, 859.3798; found 859.3810.



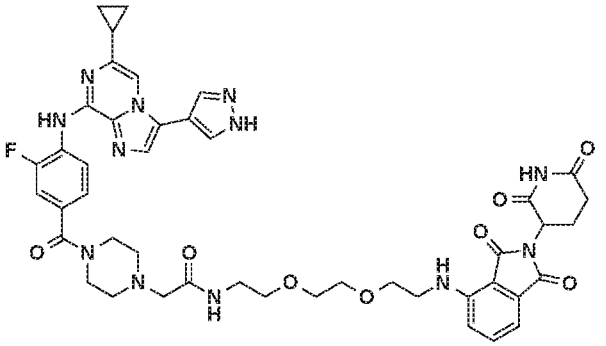
Example 6: 2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-*N*-(7-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)heptyl)acetamide. 49% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 8.81 (t, *J* = 8.2 Hz, 1H), 8.09 (s, 2H), 7.88 (s, 1H), 7.72 (s, 1H), 7.56 – 7.50 (m, 1H), 7.44 – 7.34 (m, 2H), 7.08 – 6.96 (m, 2H), 5.10 – 4.96 (m, 1H), 4.13 – 3.68 (m, 6H), 3.41 (br, 4H), 3.30 – 3.22 (m, 2H), 2.92 – 2.81 (m, 2H), 2.81 – 2.67 (m, 3H), 2.17 – 2.04 (m, 2H), 1.75 – 1.64 (m, 2H), 1.61 – 1.50 (m, 2H), 1.50 – 1.34 (m, 6H), 1.07 – 0.99 (m, 2H), 0.99 – 0.91 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{45}H_{50}FN_{12}O_6^+$, 873.3955; found 873.3543.



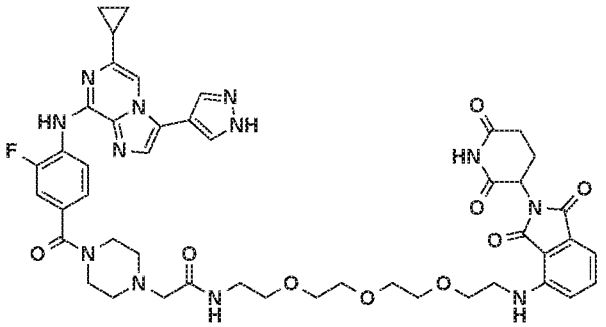
Example 7: 2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-*N*-(8-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)octyl)acetamide. 51% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 8.79 (t, *J* = 8.2 Hz, 1H), 8.14 (s, 2H), 7.93 (s, 1H), 7.78 (s, 1H), 7.55 – 7.48 (m, 1H), 7.48 – 7.33 (m, 2H), 7.09 – 6.97 (m, 2H), 5.13 – 5.01 (m, 1H), 4.07 – 3.77 (m, 6H), 3.42 (br, 4H), 3.30 – 3.18 (m, 2H), 2.94 – 2.82 (m, 2H), 2.82 – 2.64 (m, 3H), 2.17 – 2.03 (m, 2H), 1.74 – 1.61 (m, 2H), 1.62 – 1.50 (m, 2H), 1.50 – 1.27 (m, 8H), 1.09 – 1.00 (m, 2H), 0.97 – 0.91 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{46}H_{52}FN_{12}O_6^+$, 887.4111; found 887.4119.



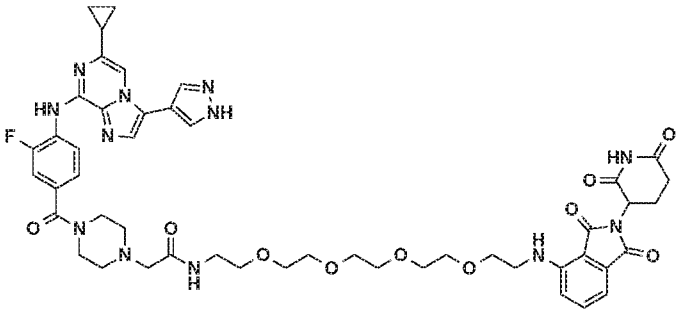
Example 8: 2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-*N*-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethyl)acetamide. 65% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 8.80 (t, *J* = 8.3 Hz, 1H), 8.10 (s, 2H), 7.90 (s, 1H), 7.74 (s, 1H), 7.55 (d, *J* = 7.4 Hz, 1H), 7.37 (dd, *J* = 23.0, 9.9 Hz, 2H), 7.11 – 7.00 (m, 2H), 5.09 (dd, *J* = 12.8, 5.5 Hz, 1H), 4.03 – 3.80 (m, 6H), 3.80 – 3.70 (m, 2H), 3.70 – 3.58 (m, 2H), 3.58 – 3.41 (m, 6H), 2.93 – 2.83 (m, 1H), 2.82 – 2.68 (m, 3H), 2.56 – 2.35 (m, 1H), 2.19 – 2.13 (m, 1H), 2.11 – 2.05 (m, 1H), 1.10 – 1.00 (m, 2H), 0.97 – 0.89 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{42}H_{44}FN_{12}O_7^+$, 847.3434; found 847.3455.



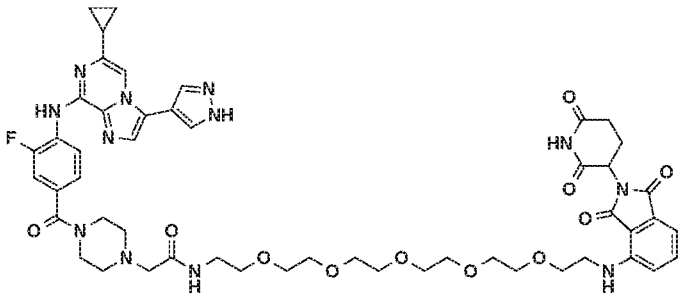
Example 9: 2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-*N*-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethyl)acetamide. 62% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 8.80 (t, J = 8.1 Hz, 1H), 7.97 (s, 2H), 7.73 (s, 1H), 7.61 (s, 1H), 7.50 (dd, J = 8.4, 7.2 Hz, 1H), 7.29 (t, J = 10.1 Hz, 2H), 7.06 – 7.02 (m, 1H), 6.98 (d, J = 8.5 Hz, 1H), 4.98 (dd, J = 12.4, 5.4 Hz, 1H), 3.86 – 3.70 (m, 6H), 3.67 (d, J = 4.6 Hz, 4H), 3.61 (t, J = 5.2 Hz, 2H), 3.52 – 3.39 (m, 6H), 3.07 – 2.86 (m, 4H), 2.87 – 2.68 (m, 3H), 2.19 – 2.09 (m, 1H), 2.05 – 1.97 (m, 1H), 1.07 – 1.00 (m, 2H), 0.99 – 0.90 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{44}H_{48}FN_{12}O_8^+$, 891.3697; found 891.3682.



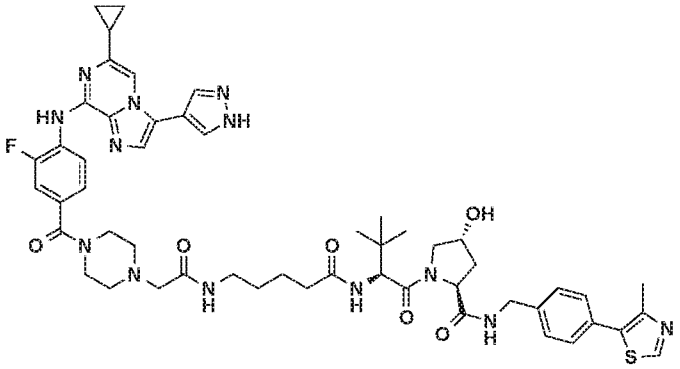
Example 10: 2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-*N*-(2-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethoxy)ethyl)acetamide. 59% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 8.82 (t, J = 8.2 Hz, 1H), 7.98 (s, 2H), 7.75 (s, 1H), 7.60 (s, 1H), 7.56 – 7.47 (m, 1H), 7.31 (t, J = 9.5 Hz, 2H), 7.09 – 6.90 (m, 2H), 5.02 – 4.96 (m, 1H), 3.86 – 3.70 (m, 6H), 3.67 – 3.61 (m, 8H), 3.50 – 3.30 (m, 8H), 3.09 – 2.89 (m, 4H), 2.87 – 2.68 (m, 3H), 2.16 – 2.05 (m, 1H), 2.04 – 1.97 (m, 1H), 1.07 – 0.98 (m, 2H), 0.96 – 0.91 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{46}H_{52}FN_{12}O_9^+$, 835.3959; found 935.3966.



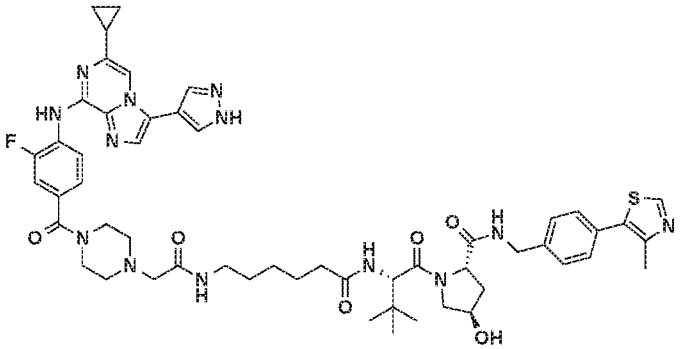
Example 11: 2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-*N*-(17-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12,15-pentaoxaheptadecyl)acetamide. 51% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 8.80 (t, *J* = 8.2 Hz, 1H), 8.03 (s, 2H), 7.82 (s, 1H), 7.69 (s, 1H), 7.54 – 7.46 (m, 1H), 7.41 – 7.30 (m, 2H), 7.06 – 6.97 (m, 2H), 5.02 (dd, *J* = 12.6, 5.4 Hz, 1H), 4.04 – 3.79 (m, 6H), 3.72 (dd, *J* = 14.2, 9.0 Hz, 2H), 3.71 – 3.60 (m, 14H), 3.58 (t, *J* = 5.2 Hz, 2H), 3.46 (ddd, *J* = 15.6, 12.3, 7.9 Hz, 4H), 3.33 (br, 2H), 2.88 – 2.67 (m, 3H), 2.19 – 2.08 (m, 1H), 2.08 – 1.98 (m, 1H), 1.09 – 1.00 (m, 2H), 1.00 – 0.90 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{48}H_{56}FN_{12}O_{10}^+$, 979.4221; found 979.4241.



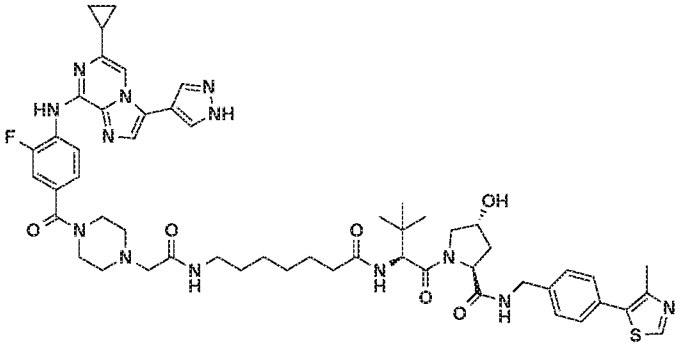
Example 12: 2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-*N*-(17-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12,15-pentaoxaheptadecyl)acetamide. 56% yield. ^{1}H NMR (600 MHz, CD_3OD δ 8.81 (t, *J* = 8.2 Hz, 1H), 8.01 (s, 2H), 7.80 (s, 1H), 7.66 (s, 1H), 7.53 – 7.47 (m, 1H), 7.40 – 7.28 (m, 2H), 7.02 (dd, *J* = 22.3, 7.8 Hz, 2H), 5.06 – 4.95 (m, 1H), 3.92 (br, 4H), 3.83 – 3.53 (m, 22H), 3.52 – 3.36 (m, 4H), 3.26 (br, 4H), 2.89 – 2.66 (m, 3H), 2.18 – 2.06 (m, 1H), 2.08 – 1.96 (m, 1H), 1.09 – 0.98 (m, 2H), 0.99 – 0.88 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{50}H_{60}FN_{12}O_{11}^+$, 1023.4483; found 1023.4509



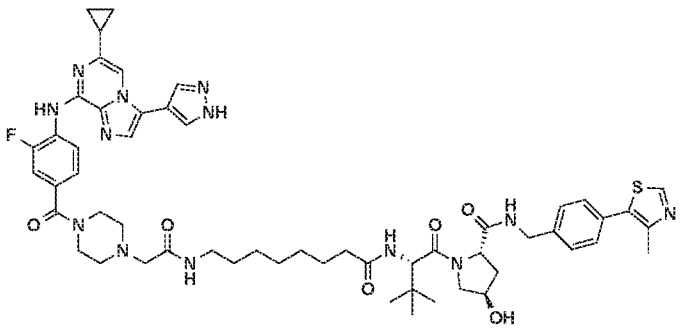
Example 13: (2*S*,4*R*)-1-((*S*)-2-(5-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamido)pentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. 60% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 8.94 (s, 1H), 8.74 (t, *J* = 8.0 Hz, 1H), 8.15 (s, 2H), 7.97 (s, 1H), 7.85 (s, 1H), 7.52 – 7.35 (m, 6H), 4.65 (s, 1H), 4.61 – 4.32 (m, 4H), 4.12 – 3.87 (m, 7H), 3.82 (dd, *J* = 10.9, 3.7 Hz, 1H), 3.48 (br, 4H), 3.31 – 3.21 (m, 2H), 2.48 (s, 3H), 2.40 – 2.18 (m, 3H), 2.16 – 2.03 (m, 2H), 1.74 – 1.49 (m, 4H), 1.08 – 1.00 (m, 11H), 1.01 – 0.92 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{52}H_{63}FN_{13}O_6S^+$, 1016.4724; found 1016.4701.



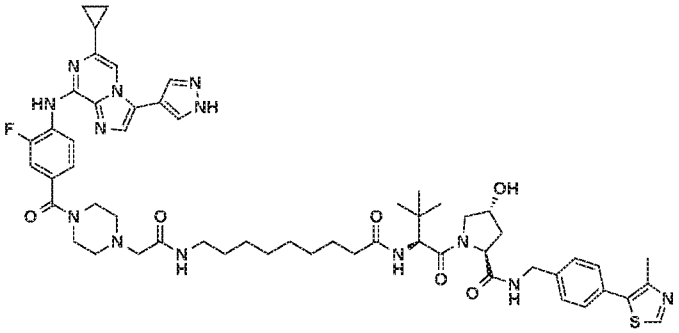
Example 14: (2*S*,4*R*)-1-((*S*)-2-(6-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamido)hexanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. 70% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 8.96 (s, 1H), 8.73 (t, *J* = 8.1 Hz, 1H), 8.15 (s, 2H), 7.98 (s, 1H), 7.86 (s, 1H), 7.54 – 7.34 (m, 6H), 4.65 (s, 1H), 4.64 – 4.43 (m, 3H), 4.42 – 4.35 (m, 1H), 4.15 – 3.86 (m, 7H), 3.83 (dd, *J* = 10.9, 3.4 Hz, 1H), 3.47 (br, 4H), 3.29 (t, *J* = 6.9 Hz, 2H), 2.49 (s, 3H), 2.37 – 2.19 (m, 3H), 2.19 – 2.00 (m, 2H), 1.75 – 1.48 (m, 4H), 1.46 – 1.32 (m, 2H), 1.10 – 1.00 (m, 11H), 1.00 – 0.91 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{53}H_{65}FN_{13}O_6S^+$, 1030.4880; found 1030.4855.



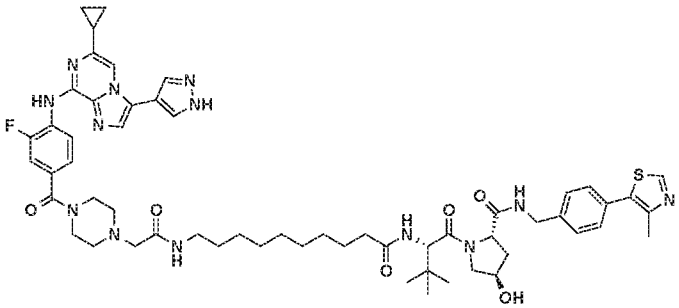
Example 15: (2*S*,4*R*)-1-((*S*)-2-(7-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamido)heptanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. 55% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 9.00 (s, 1H), 8.70 (t, *J* = 8.2 Hz, 1H), 8.14 (s, 2H), 8.01 (s, 1H), 7.89 (s, 1H), 7.51 – 7.39 (m, 6H), 4.66 (s, 1H), 4.63 – 4.48 (m, 3H), 4.39 (d, *J* = 15.6 Hz, 1H), 4.06 – 3.86 (m, 7H), 3.83 (dd, *J* = 10.9, 3.8 Hz, 1H), 3.47 (br, 4H), 3.30 – 3.23 (m, 2H), 2.49 (s, 3H), 2.36 – 2.18 (m, 3H), 2.12 (dddd, *J* = 17.4, 13.2, 8.6, 4.6 Hz, 2H), 1.72 – 1.49 (m, 4H), 1.43 – 1.32 (m, 4H), 1.10 – 1.01 (m, 11H), 1.00 – 0.93 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{54}H_{67}FN_{13}O_6S^+$, 1044.5037; found 1044.5020.



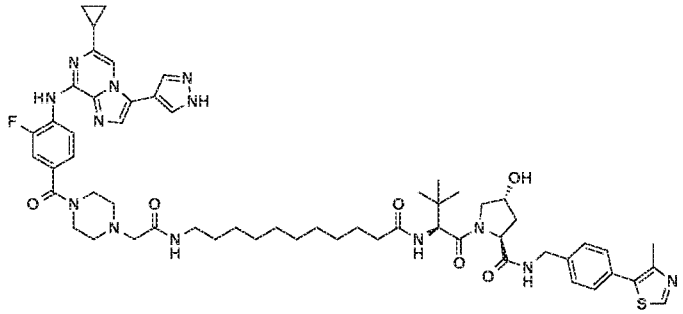
Example 16: (2*S*,4*R*)-1-((*S*)-2-(8-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamido)octanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. 65% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 8.97 (s, 1H), 8.73 (t, *J* = 8.2 Hz, 1H), 8.15(s, 2H), 7.98 (s, 1H), 7.87 (s, 1H), 7.50 – 7.37 (m, 6H), 4.66 (s, 1H), 4.62 – 4.49 (m, 3H), 4.39 (d, *J* = 15.4 Hz, 1H), 3.97 (br, 6H), 3.92 (d, *J* = 11.0 Hz, 1H), 3.83 (dd, *J* = 10.9, 3.9 Hz, 1H), 3.47 (br, 4H), 3.28 (t, *J* = 7.0 Hz, 2H), 2.49 (s, 3H), 2.35 – 2.18 (m, 3H), 2.18 – 2.03 (m, 2H), 1.68 – 1.51 (m, 4H), 1.37 (br, 6H), 1.10 – 1.00 (m, 11H), 0.99 – 0.94 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{55}H_{69}FN_{13}O_6S^+$, 1058.5192; found 1058.5211.



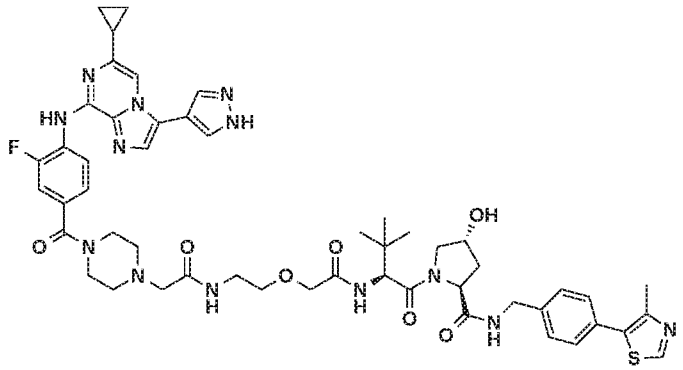
Example 17: (2*S*,4*R*)-1-((*S*)-2-(9-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamido)nonanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. 54% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 8.91 (s, 1H), 8.80 (t, *J* = 8.2 Hz, 1H), 8.14 (s, 2H), 7.94 (s, 1H), 7.77 (s, 1H), 7.53 – 7.32 (m, 6H), 4.66 (s, 1H), 4.63 – 4.46 (m, 3H), 4.38 (d, *J* = 15.5 Hz, 1H), 4.11 – 3.87 (m, 7H), 3.83 (dd, *J* = 11.0, 3.4 Hz, 1H), 3.43 (br, 4H), 3.27 (t, *J* = 6.8 Hz, 1H), 2.49 (s, 3H), 2.37 – 2.16 (m, 3H), 2.17 – 1.95 (m, 2H), 1.68 – 1.50 (m, 4H), 1.45 – 1.26 (m, 8H), 1.09 – 1.00 (m, 11H), 0.99 – 0.91 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{56}H_{71}FN_{13}O_6S^+$, 1072.5350; found 1072.5380.



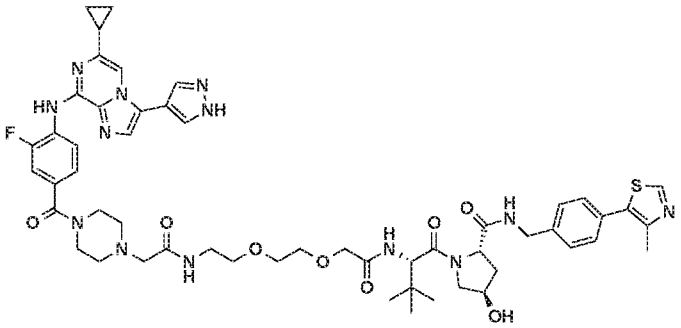
Example 18: (2*S*,4*R*)-1-((*S*)-2-(10-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamido)decanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. 56% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 8.87 (s, 1H), 8.83 (t, *J* = 8.2 Hz, 1H), 8.09 (s, 2H), 7.88 (d, *J* = 16.1 Hz, 1H), 7.71 (s, 1H), 7.50 – 7.34 (m, 6H), 4.65 (s, 1H), 4.62 – 4.42 (m, 3H), 4.37 (d, *J* = 15.5 Hz, 1H), 4.02 – 3.78 (m, 8H), 3.34 – 3.32 (m, 4H), 3.27 (t, *J* = 7.1 Hz, 2H), 2.50 (s, 3H), 2.35 – 2.19 (m, 3H), 2.14 – 2.00 (m, 2H), 1.70 – 1.38 (m, 4H), 1.40 – 1.23 (m, 10H), 1.08 – 0.99 (m, 11H), 0.99 – 0.88 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{57}H_{73}FN_{13}O_6S^+$, 1086.5506; found 1086.5530.



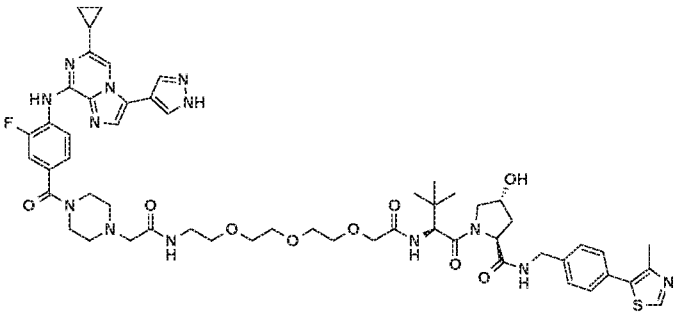
Example 19: (2*S*,4*R*)-1-((*S*)-2-(11-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamido)undecanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. 59% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 8.89 (s, 1H), 8.78 (t, *J* = 8.2 Hz, 1H), 8.09 (s, 2H), 7.90 (s, 1H), 7.76 (s, 1H), 7.49 – 7.34 (m, 6H), 4.66 (s, 1H), 4.61 – 4.46 (m, 3H), 4.36 (dd, *J* = 15.2, 8.7 Hz, 1H), 4.12 – 3.86 (m, 7H), 3.82 (dd, *J* = 10.9, 3.8 Hz, 1H), 3.42 (br, 4H), 3.28 – 3.20 (m, 2H), 2.50 (s, 3H), 2.40 – 2.18 (m, 3H), 2.17 – 2.03 (m, 2H), 1.68 – 1.49 (m, 4H), 1.41 – 1.21 (m, 12H), 1.12 – 1.00 (m, 11H), 1.00 – 0.90 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{58}H_{75}FN_{13}O_6S^+$, 1100.5663; found 1100.5639.



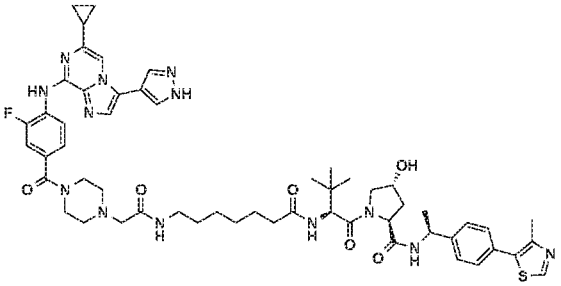
Example 20: (2*S*,4*R*)-1-((*S*)-2-(2-(2-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamido)ethoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. 67% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 8.93 (s, 1H), 8.67 (t, *J* = 8.1 Hz, 1H), 8.16 (s, 2H), 7.98 (s, 1H), 7.90 (s, 1H), 7.52 – 7.30 (m, 6H), 4.76 (s, 1H), 4.61 – 4.42 (m, 3H), 4.31 (d, *J* = 15.3 Hz, 1H), 4.18 – 3.88 (m, 9H), 3.87 – 3.67 (m, 2H), 3.67 – 3.56 (m, 2H), 3.57 – 3.40 (m, 5H), 2.45 (s, 3H), 2.34 – 2.21 (m, 1H), 2.19 – 2.02 (m, 2H), 1.11 – 1.01 (m, 11H), 1.00 – 0.94 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{51}H_{61}FN_{13}O_7S^+$, 1018.4516; found 1018.4501.



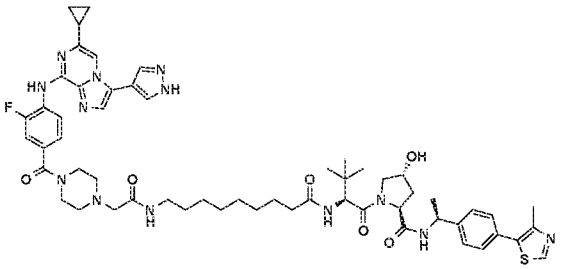
Example 21: (2*S*,4*R*)-1-((*S*)-2-(*tert*-Butyl)-14-(4-(4-((6-cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-4,13-dioxo-6,9-dioxa-3,12-diazatetradecanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. 65% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 8.94 (s, 1H), 8.70 (t, *J* = 8.1 Hz, 1H), 8.16 (s, 2H), 7.97 (s, 1H), 7.88 (s, 1H), 7.51 – 7.34 (m, 6H), 4.82 (s, 1H), 4.59 – 4.47 (m, 3H), 4.46 – 4.38 (m, 1H), 4.19 – 3.81 (m, 10H), 3.79 – 3.53 (m, 8H), 3.47 (br, 4H), 2.49 (s, 3H), 2.39 – 2.27 (m, 1H), 2.18 – 2.07 (m, 2H), 1.14 – 1.01 (m, 11H), 1.01 – 0.91 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{53}H_{65}FN_{13}O_8S^+$, 1062.4778; found 1062.4790.



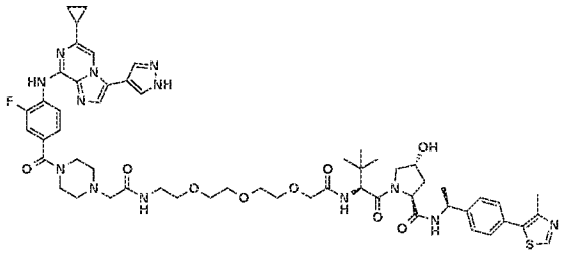
Example 22: (2*S*,4*R*)-1-((*S*)-2-(*tert*-Butyl)-17-(4-(4-((6-cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-4,16-dioxo-6,9,12-trioxa-3,15-diazaheptadecanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. 70% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 8.93 (s, 1H), 8.77 (t, *J* = 8.1 Hz, 1H), 8.15 (s, 2H), 7.95 (s, 1H), 7.83 (s, 1H), 7.54 – 7.30 (m, 6H), 4.64 (s, 1H), 4.63 – 4.48 (m, 3H), 4.38 (d, *J* = 15.5 Hz, 1H), 4.15 – 3.88 (m, 7H), 3.82 (d, *J* = 7.2 Hz, 1H), 3.80 – 3.71 (m, 2H), 3.71 – 3.56 (m, 10H), 3.48 (br, 4H), 2.65 – 2.55 (m, 1H), 2.53 (m, 4H), 2.32 – 2.23 (m, 1H), 2.18 – 2.00 (m, 2H), 1.13 – 1.02 (m, 11H), 1.00 – 0.91 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{55}H_{69}FN_{13}O_9S^+$, 1106.5040; found 1106.5018.



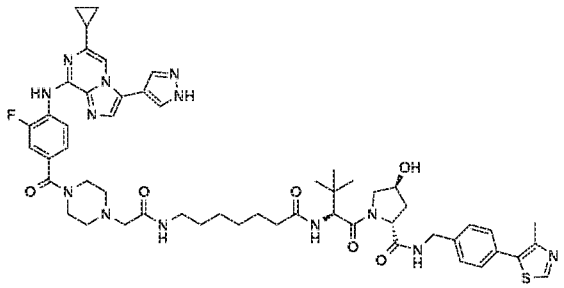
Example 37: (2*S*,4*R*)-1-((*S*)-2-(7-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamido)heptanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide. 65% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 9.10 (s, 1H), 8.64 (t, *J* = 8.2 Hz, 1H), 8.18 (s, 2H), 8.03 (s, 1H), 7.99 (s, 1H), 7.52 – 7.27 (m, 6H), 5.02 (q, *J* = 7.0 Hz, 1H), 4.65 (s, 1H), 4.59 (dd, *J* = 14.1, 5.7 Hz, 1H), 4.45 (s, 1H), 4.05 – 4.01 (m, 6H), 3.90 (d, *J* = 11.0 Hz, 1H), 3.77 (dd, *J* = 11.0, 3.9 Hz, 1H), 3.57 – 3.38 (m, 4H), 3.28 (t, *J* = 7.0 Hz, 2H), 2.51 (s, 3H), 2.40 – 2.25 (m, 2H), 2.25 – 2.13 (m, 2H), 2.01 – 1.92 (m, 1H), 1.69 – 1.55 (m, 4H), 1.52 (d, *J* = 7.0 Hz, 3H), 1.44 – 1.33 (m, 4H), 1.12 – 1.03 (m, 11H), 1.03 – 0.97 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{55}H_{69}FN_{13}O_6S^+$, 1058.5193; found 1058.5165.



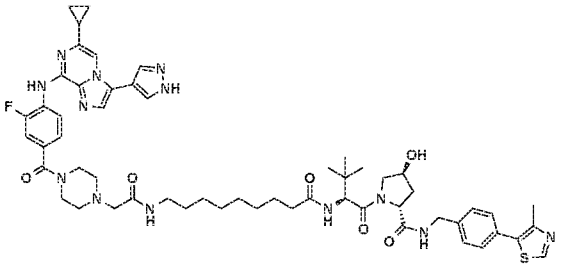
Example 38: (2*S*,4*R*)-1-((*S*)-2-(9-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamido)nonanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide. 67% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 9.01 (s, 1H), 8.72 (t, *J* = 8.2 Hz, 1H), 8.16 (s, 2H), 8.00 (s, 1H), 7.90 (s, 1H), 7.53 – 7.34 (m, 6H), 5.02 (q, *J* = 6.8 Hz, 1H), 4.65 (s, 1H), 4.62 – 4.54 (m, 1H), 4.47 – 4.42 (m, 1H), 4.20 – 3.82 (m, 7H), 3.77 (dd, *J* = 11.1, 3.9 Hz, 1H), 3.58 – 3.38 (m, 4H), 3.28 (t, *J* = 7.0 Hz, 2H), 2.51 (s, 3H), 2.37 – 2.19 (m, 3H), 2.18 – 2.11 (m, 1H), 2.01 – 1.93 (m, 1H), 1.61 (dd, *J* = 18.7, 6.8 Hz, 4H), 1.52 (d, *J* = 7.0 Hz, 3H), 1.39 – 1.34 (m, 8H), 1.10 – 1.01 (m, 11H), 1.01 – 0.95 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{57}H_{73}FN_{13}O_6S^+$, 1086.5506; found 1086.5545.



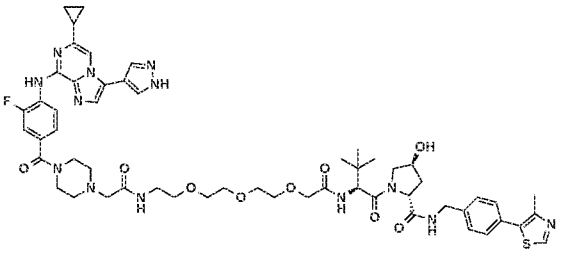
Example 39: (2*S*,4*R*)-1-((*S*)-2-(*tert*-Butyl)-17-(4-(4-((6-cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-4,16-dioxo-6,9,12-trioxa-3,15-diazaheptadecanoyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide. 50% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 9.14 (s, 1H), 8.62 (t, *J* = 8.2 Hz, 1H), 8.19 (s, 2H), 8.05 (s, 1H), 8.03 (s, 1H), 7.52 – 7.40 (m, 6H), 5.02 (q, *J* = 6.9 Hz, 1H), 4.71 (s, 1H), 4.62 – 4.56 (m, 1H), 4.47 (s, 1H), 4.14 – 4.08 (m, 2H), 4.04 (s, 2H), 3.88 (d, *J* = 11.2 Hz, 1H), 3.80 – 3.74 (m, 4H), 3.73 – 3.65 (m, 8H), 3.61 (t, *J* = 5.2 Hz, 2H), 3.58 – 3.40 (m, 7H), 2.51 (s, 3H), 2.29 – 2.22 (m, 1H), 2.20 – 2.13 (m, 1H), 2.01 – 1.93 (m, 1H), 1.53 (d, *J* = 7.0 Hz, 3H), 1.09 – 1.05 (m, 11H), 1.03 – 0.97 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{56}H_{71}FN_{13}O_9S^+$, 1120.5179; found 1120.5148.



Example 40: (2*R*,4*S*)-1-((*S*)-2-(7-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamido)heptanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. 62% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.95 (s, 1H), 8.72 (t, *J* = 8.2 Hz, 1H), 8.15 (s, 2H), 7.97 (s, 1H), 7.86 (s, 1H), 7.50 – 7.37 (m, 6H), 4.59 (t, *J* = 7.4 Hz, 1H), 4.55 – 4.45 (m, 3H), 4.40 (d, *J* = 15.6 Hz, 1H), 4.10 – 3.85 (m, 7H), 3.74 (d, *J* = 10.7 Hz, 1H), 3.55 – 3.42 (m, 4H), 3.26 – 3.17 (m, 2H), 2.51 (s, 3H), 2.35 – 2.20 (m, 2H), 2.20 – 2.04 (m, 3H), 1.59 – 1.42 (m, 4H), 1.34 – 1.23 (m, 4H), 1.15 – 1.02 (m, 11H), 1.01 – 0.93 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{54}H_{67}FN_{13}O_6S^+$, 1044.5037; found 1044.5058.

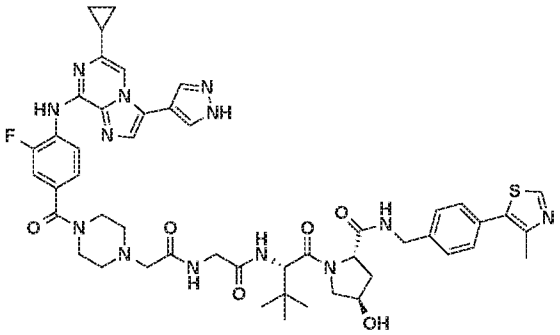


Example 41: (2*R*,4*S*)-1-((*S*)-2-(9-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamido)nonanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. 67% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.96 (s, 1H), 8.72 (t, *J* = 8.2 Hz, 1H), 8.15 (s, 2H), 7.97 (s, 1H), 7.86 (s, 1H), 7.50 – 7.36 (m, 6H), 4.64 – 4.56 (m, 1H), 4.56 – 4.44 (m, 3H), 4.38 (d, *J* = 15.6 Hz, 1H), 4.14 – 3.85 (m, 7H), 3.78 – 3.72 (m, 1H), 3.57 – 3.41 (m, 4H), 3.27 – 3.20 (m, 2H), 2.51 (s, 3H), 2.36 – 2.00 (m, 5H), 1.57 – 1.19 (m, 12H), 1.15 – 1.03 (m, 11H), 1.02 – 0.93 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{56}H_{71}FN_{13}O_6S^+$, 1072.5350; found 1072.5359.

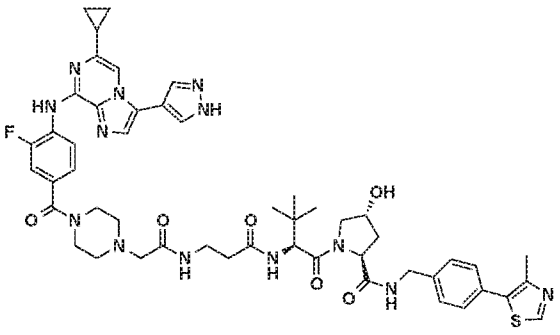


Example 42: (2*R*,4*S*)-1-((*S*)-2-(*tert*-Butyl)-17-(4-(4-((6-cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-4,16-dioxo-6,9,12-trioxa-3,15-diazaheptadecanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. 54% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 9.01 (s, 1H), 8.63 (t, *J* = 8.2 Hz, 1H), 8.17 (s, 2H), 8.01 (s, 1H), 7.96 (s, 1H), 7.51 – 7.32 (m, 6H), 4.68 – 4.63 (m, 1H), 4.60 – 4.47 (m, 3H), 4.37 (d, *J* = 15.6 Hz, 1H), 4.09 – 3.84 (m, 8H), 3.80 (d, *J* = 10.9 Hz, 1H), 3.71 – 3.54 (m, 11H), 3.54 – 3.40 (m, 6H), 2.50 (s, 3H), 2.34 – 2.25 (m, 1H), 2.19 – 2.10 (m, 2H), 1.13

– 1.03 (m, 11H), 1.03 – 0.94 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{55}H_{69}FN_{13}O_9S^+$, 1106.5040; found 1106.5017.

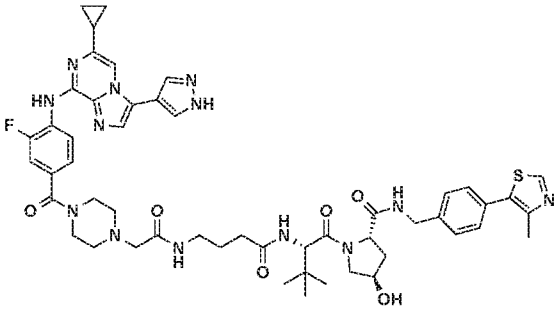


Example 43: (2*S*,4*R*)-1-((*S*)-2-(2-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamido)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. 57% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 9.06 (s, 1H), 8.65 (t, *J* = 8.2 Hz, 1H), 8.16 (s, 2H), 8.01 (s, 1H), 7.96 (s, 1H), 7.55 – 7.37 (m, 6H), 4.67 (s, 1H), 4.61 – 4.47 (m, 3H), 4.38 (d, *J* = 15.5 Hz, 1H), 4.14 – 3.92 (m, 8H), 3.92 – 3.79 (m, 2H), 3.50 (br, 4H), 2.50 (s, 3H), 2.30 – 2.20 (m, 1H), 2.20 – 2.04 (m, 2H), 1.06 (s, 9H), 1.05 – 1.02 (m, 2H), 1.02 – 0.96 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{49}H_{57}FN_{13}O_6S^+$, 974.4254; found 974.4266.

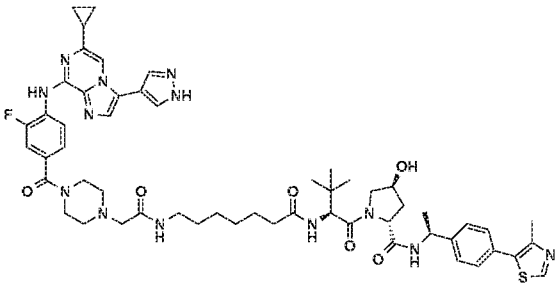


Example 44: (2*S*,4*R*)-1-((*S*)-2-(3-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamido)propanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. 53% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.97 (s, 1H), 8.66 (t, *J* = 8.2 Hz, 1H), 8.16 (s, 2H), 7.99 (s, 1H), 7.92 (s, 1H), 7.53 – 7.33 (m, 6H), 4.64 (s, 1H), 4.62 – 4.47 (m, 3H), 4.42 (d, *J* = 15.5 Hz, 1H), 3.97 (dd, *J* = 12.8, 8.7 Hz, 6H), 3.83 (dd, *J* = 10.9, 3.7 Hz, 1H), 3.63 –

3.55 (m, 1H), 3.52 – 3.42 (m, 4H), 2.72 – 2.57 (m, 2H), 2.54 – 2.44 (m, 5H), 2.32 – 2.22 (m, 1H), 2.21 – 2.08 (m, 2H), 1.12 – 1.02 (m, 11H), 1.02 – 0.95 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{50}H_{59}FN_{13}O_6S^+$, 988.4411; found 988.4432.

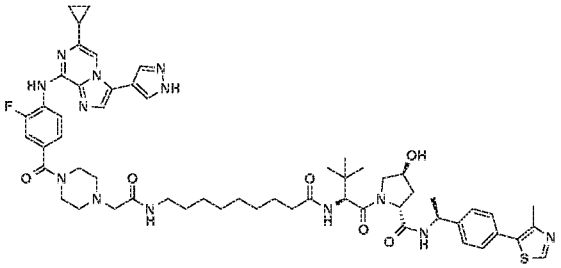


Example 45: (2*S*,4*R*)-1-((*S*)-2-(4-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamido)butanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. 51% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.95 (s, 1H), 8.75 – 8.64 (m, 1H), 8.15 (s, 2H), 7.97 (s, 1H), 7.87 (s, 1H), 7.52 – 7.33 (m, 6H), 4.64 (s, 1H), 4.62 – 4.48 (m, 3H), 4.40 (d, *J* = 15.4 Hz, 1H), 4.12 – 3.89 (m, 7H), 3.83 (dd, *J* = 10.9, 3.8 Hz, 1H), 3.64 – 3.36 (m, 4H), 2.48 (s, 3H), 2.42 – 2.30 (m, 2H), 2.30 – 2.21 (m, 1H), 2.19 – 2.06 (m, 2H), 1.97 – 1.77 (m, 2H), 1.14 – 1.02 (m, 11H), 1.02 – 0.93 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{51}H_{61}FN_{13}O_6S^+$, 1002.4567; found 1002.4578.

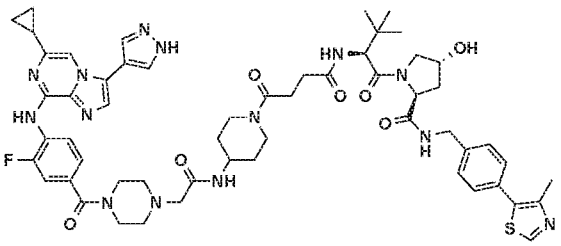


Example 63: (2*R*,4*S*)-1-((*S*)-2-(7-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamido)heptanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide. 59% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.98 (s, 1H), 8.70 (t, *J* = 8.2 Hz, 1H), 8.15 (s, 2H), 7.98 (s, 1H), 7.89 (s, 1H), 7.55 – 7.37 (m, 6H), 5.03 (q, *J* = 6.7 Hz, 1H), 4.61 – 4.51

(m, 2H), 4.51 – 4.44 (m, 1H), 4.08 – 3.87 (m, 6H), 3.71 (d, *J* = 10.9 Hz, 1H), 3.55 – 3.42 (m, 4H), 3.30 – 3.16 (m, 3H), 2.52 (s, 3H), 2.35 – 2.27 (m, 1H), 2.27 – 2.18 (m, 2H), 2.18 – 2.09 (m, 2H), 1.65 – 1.50 (m, 4H), 1.48 (d, *J* = 7.0 Hz, 3H), 1.39 – 1.27 (m, 4H), 1.15 – 1.02 (m, 11H), 1.02 – 0.92 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{55}H_{69}FN_{13}O_6S^+$, 1058.5193; found 1058.5165.



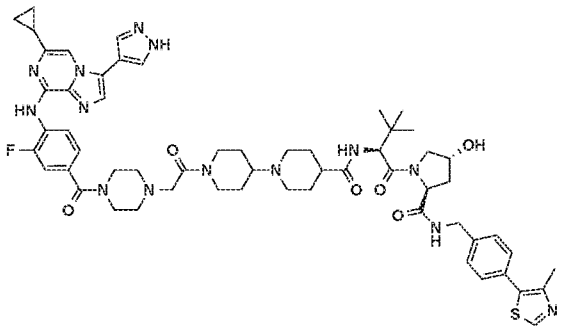
Example 64: (2*R*,4*S*)-1-((*S*)-2-(9-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamido)nonanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide. 61% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.96 (s, 1H), 8.73 (t, *J* = 8.2 Hz, 1H), 8.15 (s, 2H), 7.97 (s, 1H), 7.86 (s, 1H), 7.56 – 7.32 (m, 6H), 5.03 (q, *J* = 6.8 Hz, 1H), 4.60 – 4.55 (m, 1H), 4.53 (s, 1H), 4.50 – 4.45 (m, 1H), 4.10 – 3.85 (m, 6H), 3.76 – 3.67 (m, 1H), 3.56 – 3.40 (m, 4H), 3.30 – 3.21 (m, 3H), 2.51 (s, 3H), 2.35 – 2.26 (m, 1H), 2.26 – 2.17 (m, 2H), 2.17 – 2.08 (m, 2H), 1.65 – 1.50 (m, 4H), 1.47 (d, *J* = 7.0 Hz, 3H), 1.37 – 1.28 (m, 8H), 1.11 – 1.03 (m, 11H), 1.00 – 0.94 (m, 2H).HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{57}H_{73}FN_{13}O_6S^+$, 1086.5506; found 1086.5545.



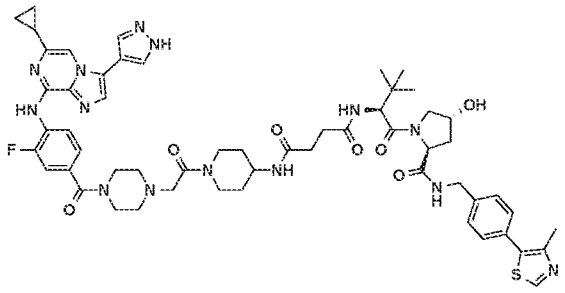
Example 102: (2*S*,4*R*)-1-((*S*)-2-(4-(4-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamido)piperidin-1-yl)-4-oxobutanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-

yl)benzyl)pyrrolidine-2-carboxamide. 70% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.97 (s, 1H), 8.71 (t, *J* = 8.2 Hz, 1H), 8.14 (s, 2H), 7.96 (s, 1H), 7.85 (s, 1H), 7.54 – 7.29 (m, 6H), 4.64 – 4.48 (m, 4H), 4.44 – 4.35 (m, 2H), 4.10 – 3.93 (m, 6H), 3.90 (d, *J* = 10.6 Hz, 1H), 3.81 (dd, *J* = 11.0, 3.8 Hz, 1H), 3.57 – 3.42 (m, 4H), 3.28 – 3.20 (m, 1H), 2.87 (t, *J* = 12.2 Hz, 1H), 2.79 – 2.52 (m, 4H), 2.50 (s, 3H), 2.29 – 2.19 (m, 1H), 2.17 – 2.06 (m, 2H), 2.04 – 1.89 (m, 2H), 1.58 – 1.34 (m, 2H), 1.11 – 1.01 (m, 11H), 1.01 – 0.94 (m, 2H).

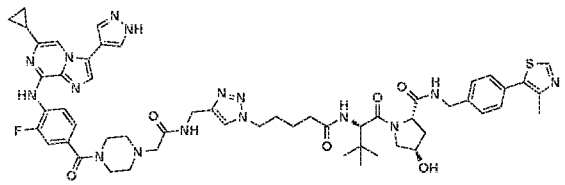
HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{56}H_{68}FN_{14}O_7S^+$, 1099.5095; found 1099.5107.



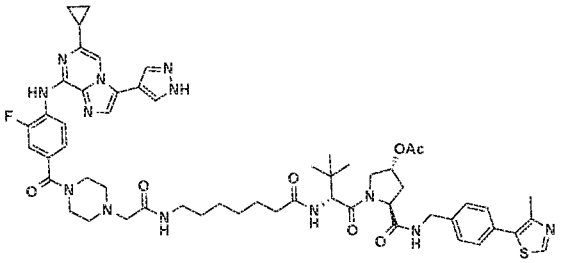
Example 103: 1'-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetyl)-*N*-((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-[1,4'-bipiperidine]-4-carboxamide. 66% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 9.00 (s, 1H), 8.69 (t, *J* = 8.2 Hz, 1H), 8.16 (s, 2H), 7.99 (s, 1H), 7.90 (s, 1H), 7.52 – 7.39 (m, 6H), 4.73 (d, *J* = 12.8 Hz, 1H), 4.65 (d, *J* = 8.8 Hz, 1H), 4.61 – 4.50 (m, 3H), 4.46 (d, *J* = 16.2 Hz, 1H), 4.41 – 4.32 (m, 2H), 4.14 – 3.94 (m, 2H), 3.90 – 3.88 (m, 1H), 3.83 (dd, *J* = 10.9, 3.7 Hz, 1H), 3.69 – 3.61 (m, 2H), 3.59 – 3.41 (m, 4H), 3.22 (t, *J* = 12.4 Hz, 1H), 3.11 – 3.06 (m, 1H), 2.79 (t, *J* = 12.4 Hz, 1H), 2.74 – 2.65 (m, 1H), 2.50 (s, 3H), 2.31 – 2.18 (m, 3H), 2.18 – 2.06 (m, 4H), 2.06 – 1.93 (m, 2H), 1.91 – 1.78 (m, 1H), 1.76 – 1.62 (m, 1H), 1.11 – 1.01 (m, 11H), 1.01 – 0.94 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{56}H_{68}FN_{14}O_7S^+$, 1099.5095; found 1099.5088.



Example 104: N^1-(1-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetyl)piperidin-4-yl)-N^4-((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)succinamide. 60% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 9.00 (s, 1H), 8.70 (t, *J* = 8.2 Hz, 1H), 8.16 (s, 2H), 7.99 (s, 1H), 7.89 (s, 1H), 7.52 – 7.39 (m, 6H), 4.63 (s, 1H), 4.60 – 4.49 (m, 3H), 4.44 – 4.30 (m, 5H), 4.27 – 3.76 (m, 7H), 3.76 – 3.63 (m, 2H), 3.65 – 3.36 (m, 4H), 3.23 (t, *J* = 12.9 Hz, 1H), 2.98 (t, *J* = 12.1 Hz, 1H), 2.66 – 2.59 (m, 1H), 2.57 – 2.52 (m, 1H), 2.52 – 2.47 (m, 6H), 2.29 – 2.20 (m, 1H), 2.17 – 2.06 (m, 2H), 2.03 – 1.89 (m, 2H), 1.57 – 1.28 (m, 4H), 1.09 – 1.01 (m, 11H), 1.01 – 0.93 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{56}H_{72}FN_{14}O_6S^+$, 1111.5499; found 1111.5483.

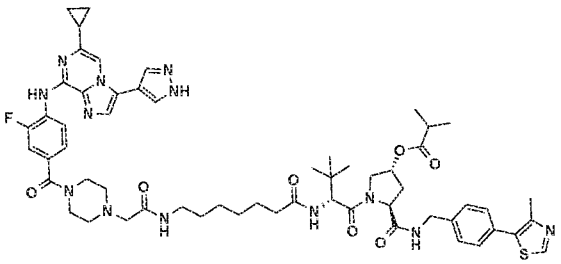


Example 105: (2*S*,4*R*)-1-((*R*)-2-(5-(4-((2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamido)methyl)-1*H*-1,2,3-triazol-1-yl)pentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. 71% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 8.97 (s, 1H), 8.69 (t, *J* = 8.2 Hz, 1H), 8.16 (s, 2H), 7.98 (s, 1H), 7.95 (s, 1H), 7.88 (s, 1H), 7.51 – 7.35 (m, 6H), 4.63 (s, 1H), 4.60 – 4.56 (m, 1H), 4.56 – 4.49 (m, 4H), 4.44 – 4.36 (m, 3H), 4.10 – 3.85 (m, 7H), 3.82 (dd, *J* = 10.9, 3.8 Hz, 1H), 3.57 – 3.40 (m, 4H), 2.49 (s, 3H), 2.37 – 2.28 (m, 2H), 2.28 – 2.22 (m, 1H), 2.17 – 2.06 (m, 2H), 1.96 – 1.87 (m, 2H), 1.66 – 1.55 (m, 2H), 1.07 – 1.00 (m, 11H), 1.00 – 0.94 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{55}H_{66}FN_{16}O_6S^+$, 1097.5050; found 1097.5059.

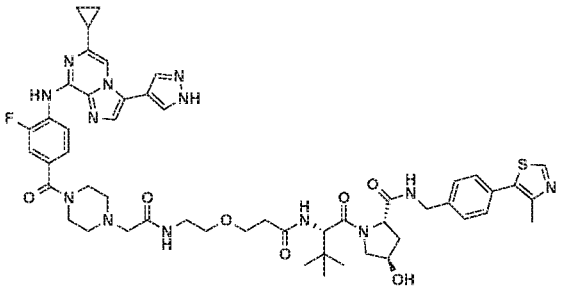


Example 106: (3*R*,5*S*)-1-((*R*)-2-(7-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamido)heptanamido)-3,3-dimethylbutanoyl)-5-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-3-yl acetate.

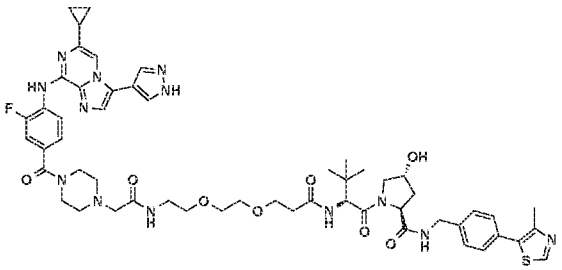
64% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 8.95 (s, 1H), 8.72 (t, *J* = 8.2 Hz, 1H), 8.15 (s, 2H), 7.96 (s, 1H), 7.85 (s, 1H), 7.53 – 7.30 (m, 6H), 5.40 – 5.34 (m, 1H), 4.60 – 4.49 (m, 3H), 4.39 (d, *J* = 15.4 Hz, 1H), 4.19 (d, *J* = 11.8 Hz, 1H), 4.14 – 3.77 (m, 7H), 3.55 – 3.39 (m, 4H), 3.28 (t, *J* = 7.0 Hz, 2H), 2.49 (s, 3H), 2.44 – 2.37 (m, 1H), 2.37 – 2.22 (m, 3H), 2.16 – 2.10 (m, 1H), 2.06 (s, 3H), 1.69 – 1.60 (m, 2H), 1.60 – 1.51 (m, 2H), 1.44 – 1.33 (m, 4H), 1.10 – 1.00 (m, 11H), 0.99 – 0.94 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{55}H_{69}FN_{13}O_7S^+$, 1086.5142; found 1086.5154.



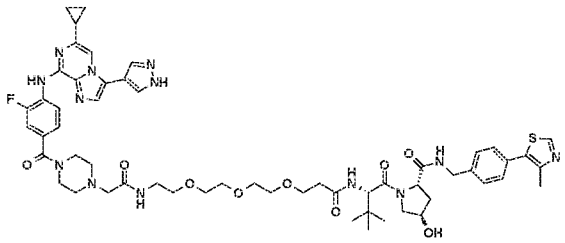
Example 107: (3*R*,5*S*)-1-((*R*)-2-(7-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamido)heptanamido)-3,3-dimethylbutanoyl)-5-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-3-yl isobutyrate. 68% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 8.99 (s, 1H), 8.68 (t, *J* = 8.2 Hz, 1H), 8.16 (s, 2H), 7.98 (s, 1H), 7.89 (s, 1H), 7.50 – 7.36 (m, 6H), 5.41 – 5.35 (m, 1H), 4.63 – 4.51 (m, 3H), 4.39 (d, *J* = 15.5 Hz, 1H), 4.16 (d, *J* = 11.8 Hz, 1H), 4.11 – 3.81 (m, 7H), 3.42 (d, *J* = 61.1 Hz, 4H), 3.27 (t, *J* = 7.0 Hz, 2H), 2.59 – 2.52 (m, 1H), 2.49 (s, 3H), 2.43 – 2.36 (m, 1H), 2.36 – 2.20 (m, 3H), 2.17 – 2.08 (m, 1H), 1.68 – 1.50 (m, 4H), 1.44 – 1.30 (m, 4H), 1.15 (d, *J* = 7.0 Hz, 6H), 1.08 – 1.02 (m, 11H), 1.01 – 0.94 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{57}H_{73}FN_{13}O_7S^+$, 1114.5455; found 1114.5437.



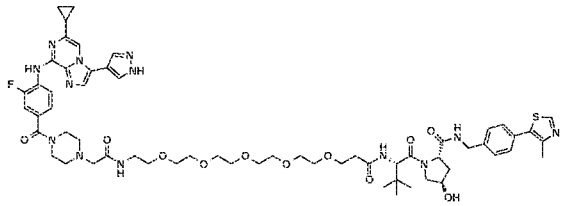
Example 130: (2*S*,4*R*)-1-((*S*)-2-(3-(2-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamido)ethoxy)propanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. 60% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 8.92 (s, 1H), 8.70 (t, *J* = 8.1 Hz, 1H), 8.15 (s, 2H), 7.96 (d, *J* = 1.3 Hz, 1H), 7.86 (s, 1H), 7.49 – 7.36 (m, 6H), 4.68 (s, 1H), 4.61 – 4.50 (m, 2H), 4.50 – 4.41 (m, 2H), 4.13 – 3.81 (m, 8H), 3.75 (t, *J* = 5.7 Hz, 2H), 3.66 – 3.54 (m, 2H), 3.54 – 3.41 (m, 6H), 2.60 – 2.51 (m, 2H), 2.46 (s, 3H), 2.33 – 2.24 (m, 1H), 2.18 – 2.06 (m, 2H), 1.11 – 1.01 (m, 11H), 1.01 – 0.94 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{52}H_{63}FN_{13}O_7S^+$, 1032.4673; found 1032.4677.



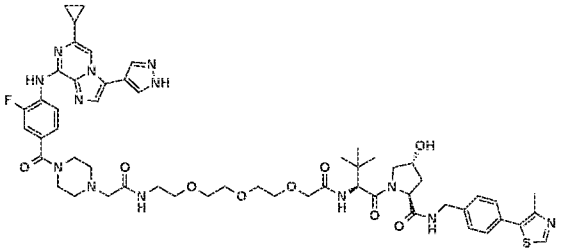
Example 131: (2*S*,4*R*)-1-((*S*)-14-(*tert*-Butyl)-1-(4-(4-((6-cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-2,12-dioxo-6,9-dioxa-3,13-diazapentadecan-15-oyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. 62% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 8.94 (s, 1H), 8.71 (t, *J* = 8.2 Hz, 1H), 8.16 (s, 2H), 7.97 (s, 1H), 7.87 (s, 1H), 7.49 – 7.37 (m, 6H), 4.68 (s, 1H), 4.60 – 4.55 (m, 1H), 4.55 – 4.48 (m, 2H), 4.41 (d, *J* = 15.4 Hz, 1H), 4.10 – 3.81 (m, 8H), 3.79 – 3.73 (m, 2H), 3.66 – 3.62 (m, 4H), 3.59 (t, *J* = 5.3 Hz, 2H), 3.52 – 3.43 (m, 6H), 2.64 – 2.56 (m, 1H), 2.56 – 2.49 (m, 1H), 2.47 (s, 3H), 2.30 – 2.22 (m, 1H), 2.17 – 2.03 (m, 2H), 1.08 – 1.03 (m, 11H), 1.00 – 0.95 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{54}H_{67}FN_{13}O_8S^+$, 1076.4935; found 1076.4931.



Example 132: (2*S*,4*R*)-1-((*S*)-17-(*tert*-butyl)-1-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-2,15-dioxo-6,9,12-trioxa-3,16-diazaoctadecan-18-oyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. 61% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 8.96 (s, 1H), 8.70 (t, *J* = 8.2 Hz, 1H), 8.16 (s, 2H), 7.98 (s, 1H), 7.88 (s, 1H), 7.51 – 7.37 (m, 6H), 4.67 (s, 1H), 4.58 (t, *J* = 8.4 Hz, 1H), 4.55 – 4.50 (m, 2H), 4.39 (d, *J* = 15.5 Hz, 1H), 4.10 – 3.85 (m, 7H), 3.82 (dd, *J* = 11.0, 3.8 Hz, 1H), 3.80 – 3.72 (m, 2H), 3.66 – 3.62 (m, 8H), 3.59 (t, *J* = 5.3 Hz, 2H), 3.55 – 3.43 (m, 6H), 2.65 – 2.56 (m, 1H), 2.56 – 2.50 (m, 1H), 2.48 (s, 3H), 2.30 – 2.22 (m, 1H), 2.17 – 2.06 (m, 2H), 1.08 – 1.02 (m, 11H), 0.97 (dm, *J* = 8.0, 2.4 Hz, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{56}H_{71}FN_{13}O_9S^+$, 1120.5197; found 1120.5190.

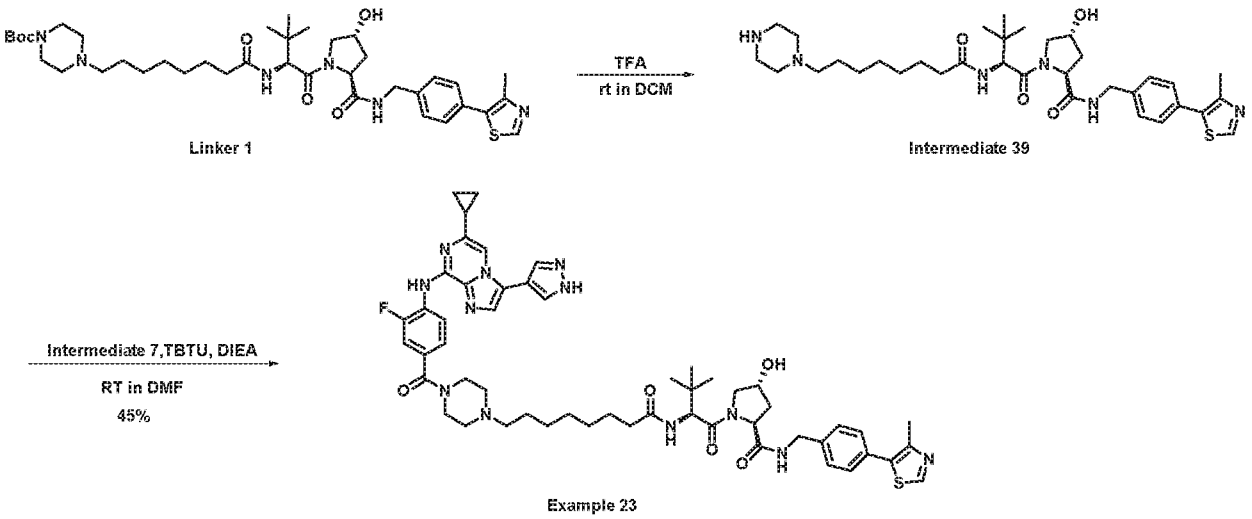


Example 133: (2*S*,4*R*)-1-((*S*)-23-(*tert*-Butyl)-1-(4-(4-((6-cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-2,21-dioxo-6,9,12,15,18-pentaoxa-3,22-diazatetracosan-24-oyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. 60% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 8.98 (s, 1H), 8.70 (t, *J* = 8.2 Hz, 1H), 8.16 (s, 2H), 7.99 (s, 1H), 7.89 (s, 1H), 7.52 – 7.32 (m, 6H), 4.67 (s, 1H), 4.58 (t, *J* = 8.4 Hz, 1H), 4.56 – 4.50 (m, 2H), 4.38 (d, *J* = 15.5 Hz, 1H), 4.09 – 3.84 (m, 7H), 3.82 (dd, *J* = 10.9, 3.8 Hz, 1H), 3.74 (ddd, *J* = 13.1, 8.9, 4.7 Hz, 3H), 3.65 – 3.63 (m, 16H), 3.60 (t, *J* = 5.3 Hz, 2H), 3.52 – 3.46 (m, 6H), 2.63 – 2.57 (m, 1H), 2.53 – 2.47 (m, 4H), 2.28 – 2.22 (m, 1H), 2.19 – 2.06 (m, 2H), 1.07 – 1.03 (m, 11H), 1.00 – 0.96 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{60}H_{79}FN_{13}O_{11}S^+$, 1208.5721; found 1208.5744.



Example 134: (2*S*,4*R*)-1-((*S*)-2-(*tert*-Butyl)-17-(4-(4-((6-cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-4,16-dioxo-6,9,12-trioxa-3,15-diazaheptadecanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. 51% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 9.02 (s, 1H), 8.64 (t, *J* = 8.2 Hz, 1H), 8.17 (s, 2H), 8.01 (s, 1H), 7.96 (s, 1H), 7.44 (ddd, *J* = 16.4, 12.1, 7.9 Hz, 6H), 4.72 (s, 1H), 4.62 – 4.49 (m, 3H), 4.40 (d, *J* = 15.5 Hz, 1H), 4.15 – 3.95 (m, 6H), 3.91 (d, *J* = 11.0 Hz, 1H), 3.85 – 3.81 (m, 1H), 3.77 – 3.73 (m, 2H), 3.73 – 3.69 (m, 2H), 3.69 – 3.66 (m, 2H), 3.66 – 3.62 (m, 2H), 3.58 (t, *J* = 5.0 Hz, 2H), 3.55 – 3.40 (m, 6H), 2.50 (s, 3H), 2.32 – 2.23 (m, 1H), 2.12 (ddd, *J* = 22.6, 10.6, 4.4 Hz, 2H), 1.11 – 1.02 (m, 11H), 1.01 – 0.94 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{55}H_{69}FN_{13}O_9S^+$, 1106.5040; found 1106.5049.

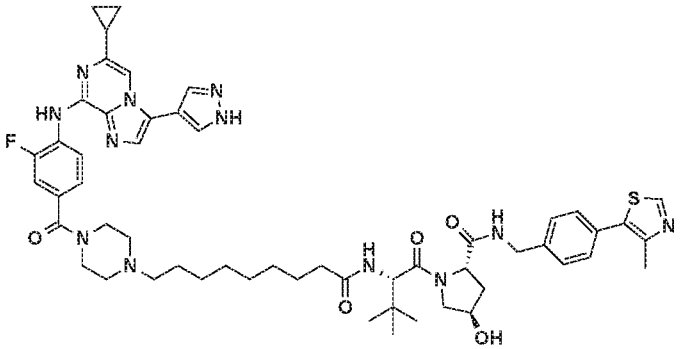
Scheme 25. Synthesis of example 23



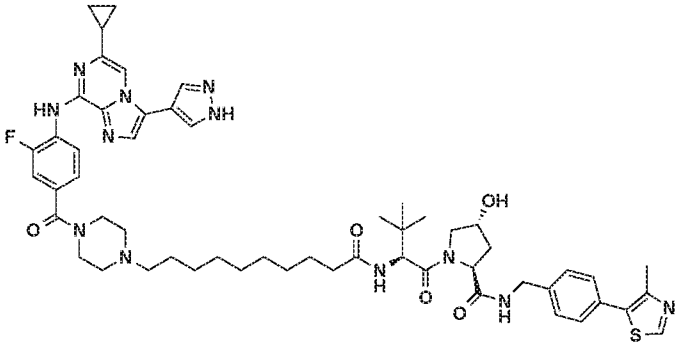
Example 23: (2*S*,4*R*)-1-((*S*)-2-(8-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)octanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. A solution of linker **1** (14mg, 0.019 mmol) in DCM/TFA (2:1, 1 mL) was stirred at rt for 2 h. After concentration under

reduced pressure, the resulting crude intermediate **11** was obtained without further purification. To a solution of intermediate **11** and intermediate 7 (5.2 mg, 0.014 mmol) in DMF (1 mL) were added DIEA (17 μL, 0.1 mmol) and TBTU (7 mg, 0.02 mmol). After being stirred at rt for 12 h, the mixture was purified by HPLC to yield the title compound (6 mg, 45% yield) as brown oil. ^{1}H NMR (600 MHz, CD_3OD) δ 8.97 (s, 1H), 8.72 (t, J = 8.1 Hz, 1H), 8.16 (s, 2H), 7.99 (s, 1H), 7.88 (s, 1H), 7.52 – 7.38 (m, 6H), 4.67 (s, 1H), 4.61 – 4.48 (m, 3H), 4.39 (d, J = 15.4 Hz, 1H), 3.93 (d, J = 10.9 Hz, 1H), 3.83 (d, J = 7.6 Hz, 1H), 3.73 – 3.39 (m, 6H), 3.26 – 3.11 (m, 4H), 2.50 (s, 3H), 2.38 – 2.20 (m, 3H), 2.20 – 2.05 (m, 2H), 1.83 – 1.73 (m, 2H), 1.73 – 1.58 (m, 2H), 1.50 – 1.34 (m, 6H), 1.11 – 0.93 (m, 13H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{53}H_{66}FN_{12}O_5S^+$, 1001.4978; found 1001.4999.

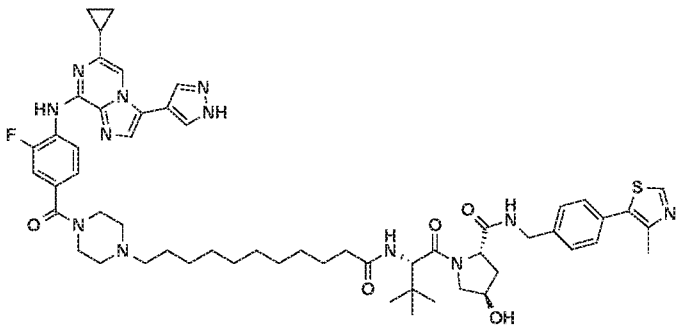
Example compounds **24** – **27** were synthesized according to the procedures for the preparation of example compound **23**.



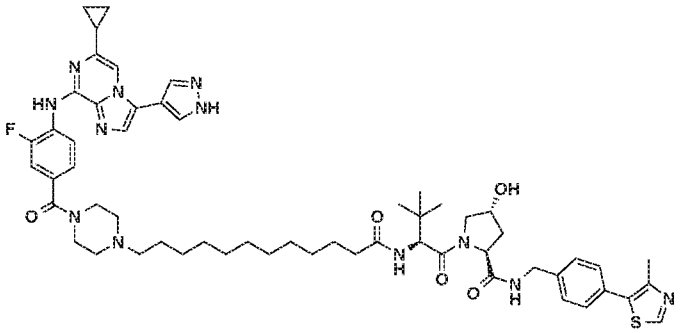
Example 24: (2*S*,4*R*)-1-((*S*)-2-(9-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)nonanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. 58% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 8.98 (s, 1H), 8.72 (t, J = 8.2 Hz, 1H), 8.15 (s, 2H), 7.98 (s, 1H), 7.88 (s, 1H), 7.52 – 7.38 (m, 6H), 4.67 (s, 1H), 4.64 – 4.50 (m, 3H), 4.39 (d, J = 15.5 Hz, 1H), 3.92 (d, J = 11.0 Hz, 1H), 3.83 (dd, J = 10.9, 3.8 Hz, 1H), 3.73 – 3.40 (m, 6H), 3.27 – 3.13 (m, 4H), 2.50 (s, 3H), 2.37 – 2.20 (m, 3H), 2.17 – 2.07 (m, 2H), 1.83 – 1.73 (m, 2H), 1.71 – 1.59 (m, 2H), 1.50 – 1.35 (m, 8H), 1.04 (d, J = 13.8 Hz, 11H), 1.00 – 0.92 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{54}H_{68}FN_{12}O_5S^+$, 1015.5135; found 1015.5110.



Example 25: (2*S*,4*R*)-1-((*S*)-2-(10-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)decanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. 67% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 8.95 (s, 1H), 8.77 (t, *J* = 8.2 Hz, 1H), 8.16 (s, 2H), 7.98 (s, 1H), 7.83 (s, 1H), 7.52 – 7.34 (m, 6H), 4.66 (s, 1H), 4.62 – 4.48 (m, 3H), 4.38 (d, *J* = 15.5 Hz, 1H), 3.92 (d, *J* = 11.0 Hz, 1H), 3.83 (dd, *J* = 10.9, 3.9 Hz, 1H), 3.74 – 3.38 (m, 6H), 3.25 – 3.12 (m, 4H), 2.49 (s, 3H), 2.37 – 2.18 (m, 3H), 2.18 – 2.04 (m, 2H), 1.85 – 1.72 (m, 2H), 1.69 – 1.54 (m, 2H), 1.48 – 1.30 (m, 10H), 1.11 – 0.87 (m, 13H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{55}H_{70}FN_{12}O_5S^+$, 1029.5291; found 1029.5270.

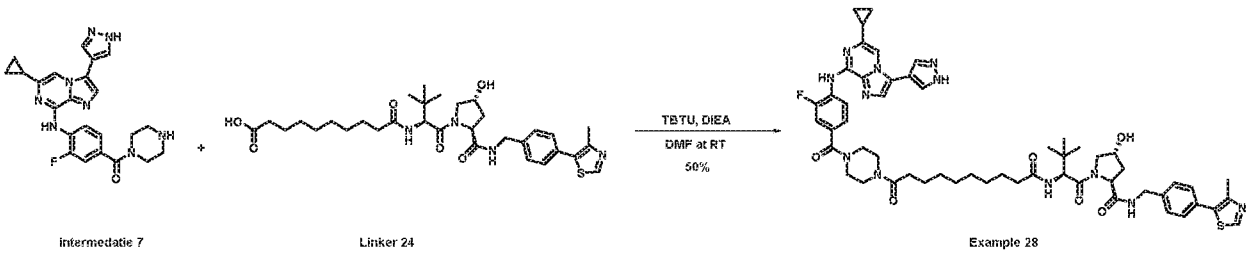


Example 26: (2*S*,4*R*)-1-((*S*)-2-(11-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)undecanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. 63% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 8.95 (s, 1H), 8.77 (t, *J* = 8.2 Hz, 1H), 8.15 (s, 2H), 7.97 (s, 1H), 7.83 (s, 1H), 7.51 – 7.39 (m, 6H), 4.69 – 4.64 (m, 1H), 4.61 – 4.49 (m, 3H), 4.38 (dd, *J* = 15.3, 4.8 Hz, 1H), 3.92 (d, *J* = 11.1 Hz, 1H), 3.83 (dd, *J* = 10.9, 3.9 Hz, 1H), 3.76 – 3.37 (m, 6H), 3.28 – 3.06 (m, 4H), 2.50 (s, 3H), 2.38 – 2.20 (m, 3H), 2.20 – 2.05 (m, 2H), 1.87 – 1.72 (m, 2H), 1.71 – 1.54 (m, 2H), 1.48 – 1.28 (m, 12H), 1.09 – 0.93 (m, 13H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{56}H_{72}FN_{12}O_5S^+$, 1043.5448; found 1043.5440.



Example 27: (2*S*,4*R*)-1-((*S*)-2-(12-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)dodecanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. 62% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 8.94 (s, 1H), 8.77 (t, *J* = 8.2 Hz, 1H), 8.15 (s, 2H), 7.96 (s, 1H), 7.81 (s, 1H), 7.50 – 7.38 (m, 6H), 4.67 (s, 1H), 4.63 – 4.50 (m, 3H), 4.42 – 4.33 (m, 1H), 3.92 (d, *J* = 11.0 Hz, 1H), 3.83 (dd, *J* = 10.9, 3.9 Hz, 1H), 3.75 – 3.39 (m, 6H), 3.27 – 3.10 (m, 4H), 2.49 (s, 3H), 2.38 – 2.17 (m, 3H), 2.17 – 2.05 (m, 2H), 1.87 – 1.73 (m, 2H), 1.69 – 1.54 (m, 2H), 1.47 – 1.27 (m, 14H), 1.13 – 0.89 (m, 13H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{57}H_{74}FN_{12}O_5S^+$, 1057.5604; found 1057.5630.

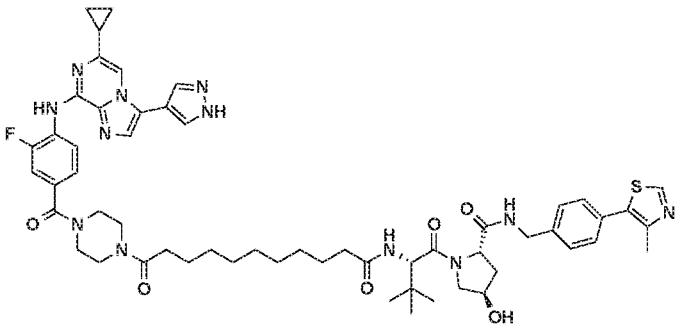
Scheme 26. Synthesis of example 28



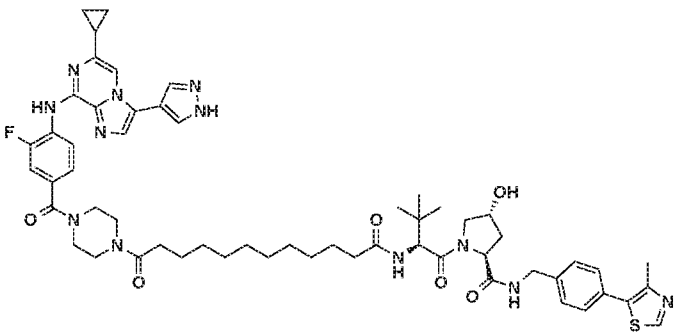
Example 28: (2*S*,4*R*)-1-((*S*)-2-(10-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-10-oxodecanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. To a solution of intermediate 7 (12 mg, 0.021 mmol) and linker 7 (11 mg, 0.018mmol) in DMF (0.5 mL) were added DIEA (17 μL, 0.1 mmol) and TBTU (6 mg, 0.02 mmol). After being stirred at rt for 12 h, the mixture was purified by HPLC to yield the title compound

(11 mg, 59%) as brown oil. ^{1}H NMR (600 MHz, CD_3OD) δ 9.10 (s, 1H), 8.57 (t, J = 8.1 Hz, 1H), 8.19 (s, 2H), 8.08 – 8.01 (m, 2H), 7.55 – 7.35 (m, 6H), 4.66 (s, 1H), 4.63 – 4.48 (m, 3H), 4.38 (dd, J = 15.2, 6.4 Hz, 1H), 3.93 (d, J = 11.0 Hz, 1H), 3.82 (dd, J = 10.9, 3.8 Hz, 1H), 3.63 (br, 8H), 2.50 (s, 3H), 2.45 (s, 2H), 2.36 – 2.20 (m, 3H), 2.20 – 2.14 (m, 1H), 2.10 (ddd, J = 11.2, 8.1, 3.4 Hz, 1H), 1.63 (br, 4H), 1.35 (br, J = 12.8 Hz, 8H), 1.10 – 0.96 (m, 13H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{55}H_{68}FN_{12}O_6S^+$, 1043.5084; found 1043.5103.

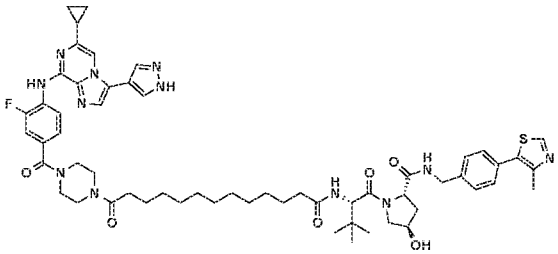
Example compounds **29, 30, 32 – 36, 46 – 62** and **65 – 74** were synthesized according to the procedures for the preparation of example **28** compound.



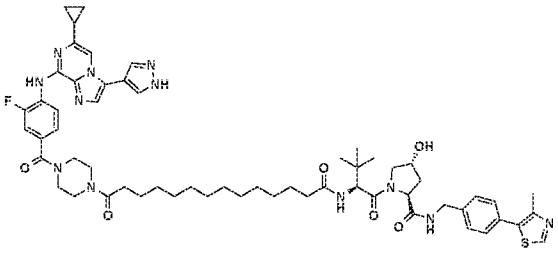
Example 29: (2*S*,4*R*)-1-((*S*)-2-(11-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-11-oxoundecanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. 60% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 9.12 (s, 1H), 8.56 (t, J = 8.1 Hz, 1H), 8.20 (s, 2H), 8.07 (s, 2H), 7.55 – 7.33 (m, 6H), 4.66 (s, 1H), 4.63 – 4.48 (m, 3H), 4.38 (d, J = 15.3 Hz, 1H), 3.93 (d, J = 10.9 Hz, 1H), 3.82 (dd, J = 10.9, 3.7 Hz, 1H), 3.78 – 3.47 (m, 8H), 2.53 (s, 3H), 2.49 – 2.38 (m, 2H), 2.35 – 2.21 (m, 3H), 2.21 – 2.14 (m, 1H), 2.14 – 2.06 (m, 1H), 1.63 (d, J = 6.2 Hz, 4H), 1.35 (br, 10H), 1.12 – 0.96 (m, 13H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{56}H_{70}FN_{12}O_6S^+$, 1057.5241; found 1057.5269.



Example 30: (2*S*,4*R*)-1-((*S*)-2-(12-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-12-oxododecanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. 69% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 9.04 (s, 1H), 8.60 (t, *J* = 8.0 Hz, 1H), 8.18 (s, 2H), 8.02 (s, 1H), 7.98 (s, 1H), 7.54 – 7.32 (m, 6H), 4.66 (s, 1H), 4.63 – 4.49 (m, 3H), 4.38 (d, *J* = 15.5 Hz, 1H), 3.92 (d, *J* = 10.9 Hz, 1H), 3.87 – 3.45 (m, 9H), 2.50 (s, 3H), 2.45 (br, 2H), 2.38 – 2.20 (m, 3H), 2.19 – 2.01 (m, 2H), 1.62 (br, 4H), 1.34 (br, 12H), 1.12 – 0.89 (m, 13H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{57}H_{72}FN_{12}O_6S^+$, 1071.5397; found 1071.5420.\

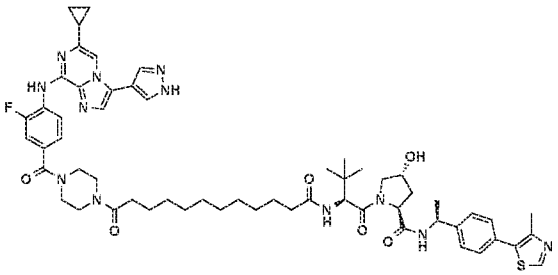


Example 32: (2*S*,4*R*)-1-((*S*)-2-(13-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-13-oxotridecanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. 65% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 8.99 (s, 1H), 8.65 (t, *J* = 8.0 Hz, 1H), 8.17 (s, 2H), 8.00 (s, 1H), 7.92 (s, 1H), 7.52 – 7.35 (m, 6H), 4.65 (s, 1H), 4.61 – 4.49 (m, 3H), 4.37 (d, *J* = 15.5 Hz, 1H), 3.92 (d, *J* = 10.8 Hz, 1H), 3.86 – 3.50 (m, 9H), 2.50 (s, 3H), 2.48 – 2.41 (m, 2H), 2.37 – 2.19 (m, 3H), 2.18 – 2.05 (m, 2H), 1.70 – 1.53 (m, 4H), 1.43 – 1.24 (m, 14H), 1.12 – 1.01 (m, 11H), 1.01 – 0.96 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{58}H_{74}FN_{12}O_6S^+$, 1085.5554; found 1085.5529.

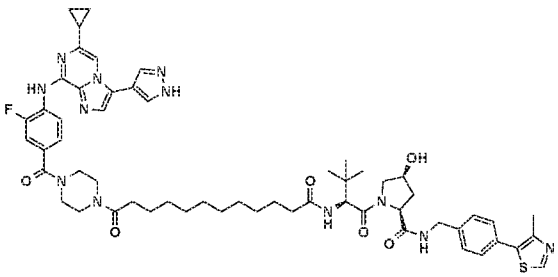


**Example 33: (2*S*,4*R*)-1-((*S*)-2-(14-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-14-oxotetradecanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-

carboxamide. 61% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 9.01 (s, 1H), 8.64 (t, *J* = 7.9 Hz, 1H), 8.17 (s, 2H), 8.01 (s, 1H), 7.95 (s, 1H), 7.52 – 7.34 (m, 6H), 4.65 (s, 1H), 4.62 – 4.48 (m, 3H), 4.37 (d, *J* = 15.5 Hz, 1H), 3.92 (d, *J* = 10.9 Hz, 1H), 3.86 – 3.52 (m, 9H), 2.50 (s, 3H), 2.48 – 2.41 (m, 2H), 2.36 – 2.20 (m, 3H), 2.18 – 2.06 (m, 2H), 1.72 – 1.55 (m, 4H), 1.45 – 1.24 (m, 16H), 1.10 – 1.02 (m, 11H), 1.02 – 0.96 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{59}H_{76}FN_{12}O_6S^+$, 1099.5710; found 1099.5709.

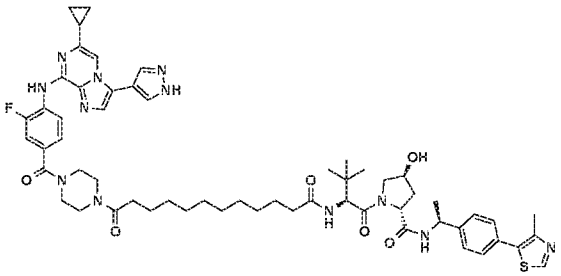


Example 34: (2*S*,4*R*)-1-((*S*)-2-(12-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-12-oxododecanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide. 63% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 9.04 (s, 1H), 8.61 (t, *J* = 6.5 Hz, 1H), 8.18 (s, 2H), 8.02 (s, 1H), 7.97 (s, 1H), 7.50 – 7.35 (m, 6H), 5.02 (q, *J* = 6.5 Hz, 1H), 4.65 (s, 1H), 4.59 (t, *J* = 8.3 Hz, 1H), 4.45 (s, 1H), 3.90 (d, *J* = 11.0 Hz, 1H), 3.86 – 3.50 (m, 9H), 2.51 (s, 3H), 2.49 – 2.41 (m, 2H), 2.37 – 2.18 (m, 3H), 2.18 – 2.11 (m, 1H), 2.00 – 1.92 (m, 1H), 1.72 – 1.56 (m, 5H), 1.52 (d, *J* = 6.9 Hz, 3H), 1.44 – 1.28 (m, 12H), 1.11 – 1.02 (m, 11H), 1.02 – 0.96 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{58}H_{74}FN_{12}O_6S^+$, 1085.5554; found 1085.5550.

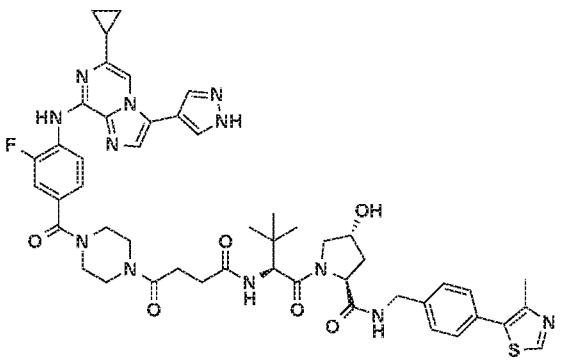


**Example 35: (2*S*,4*S*)-1-((*S*)-2-(12-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-12-oxododecanamido)-3,3-

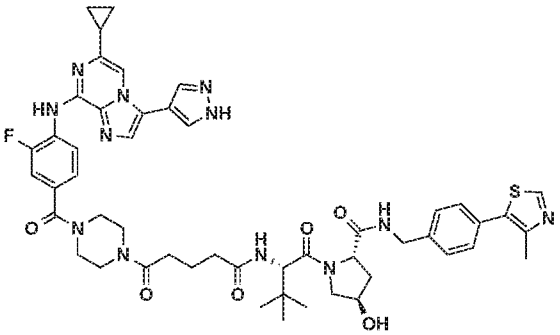
dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. 70% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 9.13 (s, 1H), 8.55 (t, *J* = 8.1 Hz, 1H), 8.20 (s, 2H), 8.06 (s, 1H), 7.52 – 7.36 (m, 6H), 4.61 – 4.49 (m, 3H), 4.41 (s, 2H), 4.07 (dd, *J* = 10.5, 5.1 Hz, 1H), 3.88 – 3.50 (m, 9H), 2.51 (s, 3H), 2.48 – 2.39 (m, 3H), 2.34 – 2.22 (m, 2H), 2.20 – 2.13 (m, 1H), 2.01 – 1.96 (m, 1H), 1.70 – 1.52 (m, 4H), 1.44 – 1.29 (m, 12H), 1.10 – 0.97 (m, 13H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{57}H_{72}FN_{12}O_6S^+$, 1071.5397; found 1071.5388.



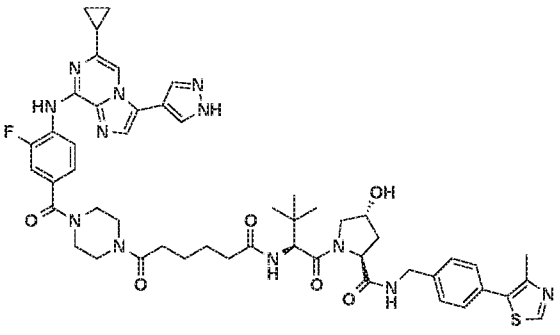
Example 36: (2*R*,4*S*)-1-((*S*)-2-(12-(4-(4-(((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-12-oxododecanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide. 69% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.91 (s, 1H), 8.73 (t, *J* = 8.2 Hz, 1H), 8.13 (s, 2H), 7.91 (s, 1H), 7.77 (s, 1H), 7.52 (d, *J* = 8.2 Hz, 2H), 7.45 (d, *J* = 8.2 Hz, 2H), 7.43 – 7.38 (m, 1H), 7.35 (d, *J* = 8.7 Hz, 1H), 5.12 – 4.98 (m, 1H), 4.61 – 4.54 (m, 1H), 4.52 – 4.42 (m, 2H), 3.97 (dd, *J* = 10.7, 4.9 Hz, 1H), 3.84 – 3.51 (m, 9H), 2.50 (s, 3H), 2.48 – 2.39 (m, 2H), 2.34 – 2.27 (m, 1H), 2.27 – 2.17 (m, 2H), 2.16 – 2.04 (m, 2H), 1.70 – 1.51 (m, 4H), 1.47 (d, *J* = 7.0 Hz, 3H), 1.31 (d, *J* = 23.5 Hz, 14H), 1.13 – 1.01 (m, 11H), 0.95 (dt, *J* = 6.8, 3.9 Hz, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{58}H_{74}FN_{12}O_6S^+$, 1085.5554; found 1085.5561.



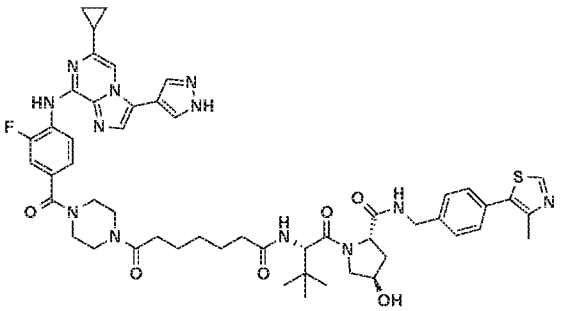
Example 46: (2*S*,4*R*)-1-((*S*)-2-(4-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-4-oxobutanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. 63% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 9.03 (s, 1H), 8.59 (t, *J* = 8.1 Hz, 1H), 8.17 (s, 2H), 8.03 – 7.95 (m, 2H), 7.57 – 7.35 (m, 6H), 4.62 (s, 1H), 4.61 – 4.49 (m, 3H), 4.39 (d, *J* = 15.5 Hz, 1H), 3.91 (d, *J* = 10.9 Hz, 1H), 3.82 (dd, *J* = 10.9, 3.7 Hz, 1H), 3.68 (s, 8H), 2.81 – 2.56 (m, 4H), 2.50 (s, 3H), 2.31 – 2.20 (m, 1H), 2.20 – 2.06 (m, 2H), 1.06 (s, 11H), 1.02 – 0.95 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{49}H_{56}FN_{12}O_6S^+$, 959.4145; found 959.4130.



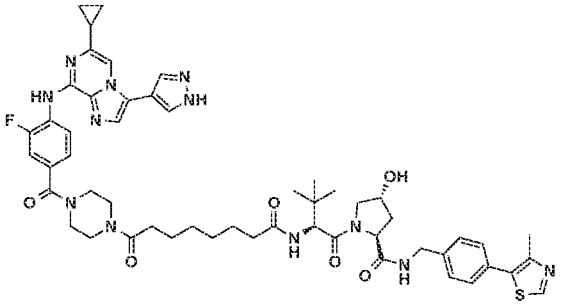
Example: 47: (2*S*,4*R*)-1-((*S*)-2-(5-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-5-oxopentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. 69% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.97 (s, 1H), 8.63 (s, 1H), 8.16 (s, 2H), 7.99 (s, 1H), 7.93 (s, 1H), 7.52 – 7.33 (m, 6H), 4.64 (s, 1H), 4.63 – 4.47 (m, 3H), 4.37 (d, *J* = 15.5 Hz, 1H), 4.03 – 3.89 (m, 1H), 3.82 (d, *J* = 8.3 Hz, 2H), 3.80 – 3.54 (m, 8H), 2.55 – 2.42 (m, 5H), 2.37 (t, *J* = 7.0 Hz, 2H), 2.30 – 2.18 (m, 1H), 2.19 – 2.07 (m, 2H), 2.00 – 1.89 (m, 2H), 1.13 – 1.03 (m, 11H), 1.03 – 0.94 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{50}H_{58}FN_{12}O_6S^+$, 973.4302; found 973.4335



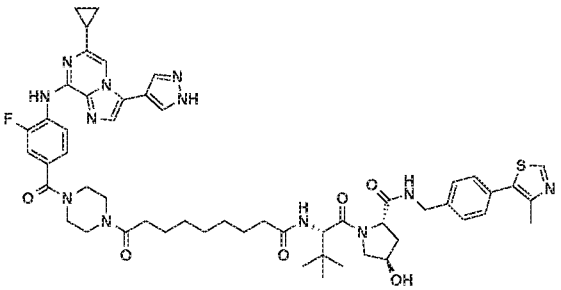
Example 48: (2*S*,4*R*)-1-((*S*)-2-(6-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-6-oxohexanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. 68% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.98 (s, 1H), 8.64 (t, *J* = 8.1 Hz, 1H), 8.17 (s, 2H), 8.00 (s, 1H), 7.93 (s, 1H), 7.53 – 7.34 (m, 6H), 4.66 (s, 1H), 4.62 – 4.49 (m, 3H), 4.38 (d, *J* = 15.5 Hz, 1H), 3.93 (d, *J* = 11.2 Hz, 1H), 3.87 – 3.80 (m, 1H), 3.78 – 3.54 (m, 8H), 2.56 – 2.41 (m, 5H), 2.41 – 2.29 (m, 2H), 2.28 – 2.20 (m, 1H), 2.19 – 2.07 (m, 2H), 1.80 – 1.54 (m, 4H), 1.12 – 1.02 (m, 11H), 1.02 – 0.94 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{51}H_{60}FN_{12}O_6S^+$, 987.4458; found 987.4440.



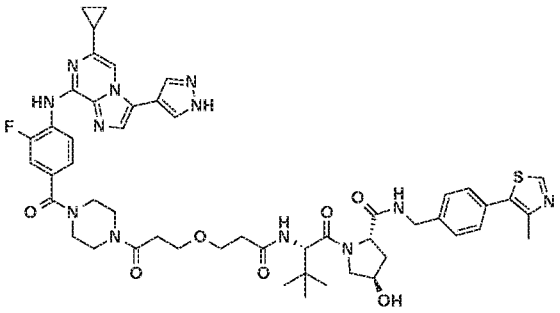
Example 49: (2*S*,4*R*)-1-((*S*)-2-(7-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-7-oxoheptanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. 61% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 9.98 – 9.35 (m, 1H), 9.00 (s, 1H), 8.61 (t, *J* = 8.2 Hz, 1H), 8.16 (s, 2H), 7.99 (s, 1H), 7.94 (s, 1H), 7.42 (td, *J* = 26.5, 8.6 Hz, 6H), 4.66 (s, 1H), 4.63 – 4.48 (m, 3H), 4.37 (d, *J* = 15.5 Hz, 1H), 3.93 (d, *J* = 11.0 Hz, 1H), 3.82 (dd, *J* = 10.9, 3.7 Hz, 1H), 3.79 – 3.50 (m, 8H), 2.59 – 2.39 (m, 5H), 2.39 – 2.19 (m, 3H), 2.13 (ddd, *J* = 13.4, 8.2, 3.7 Hz, 2H), 1.66 (d, *J* = 6.6 Hz, 4H), 1.52 – 1.32 (m, 2H), 1.12 – 1.02 (m, 11H), 1.02 – 0.91 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{52}H_{62}FN_{12}O_6S^+$, 1001.4615; found 1001.4601.



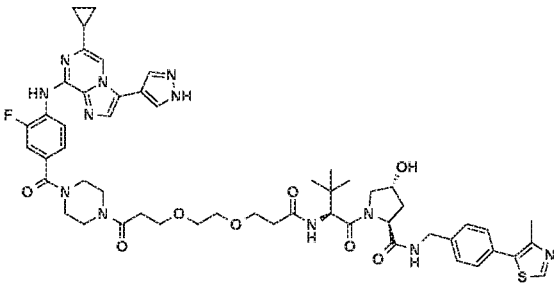
Example 50: (2*S*,4*R*)-1-((*S*)-2-(8-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-8-oxooctanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. 55% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 9.01 (s, 1H), 8.61 (t, *J* = 8.2 Hz, 1H), 8.17 (s, 2H), 7.99 (s, 1H), 7.95 (s, 1H), 7.55 – 7.33 (m, 6H), 4.66 (s, 1H), 4.56 (dt, *J* = 23.6, 8.2 Hz, 3H), 4.38 (d, *J* = 15.5 Hz, 1H), 3.93 (d, *J* = 11.0 Hz, 1H), 3.82 (dd, *J* = 10.9, 3.7 Hz, 1H), 3.78 – 3.53 (m, 8H), 2.50 (s, 3H), 2.49 – 2.41 (m, 2H), 2.38 – 2.20 (m, 3H), 2.20 – 2.06 (m, 2H), 1.70 – 1.55 (m, 4H), 1.40 (d, *J* = 3.4 Hz, 4H), 1.10 – 1.02 (m, 11H), 1.02 – 0.95 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{53}H_{64}FN_{12}O_6S^+$, 1015.4771; found 1015.4788.



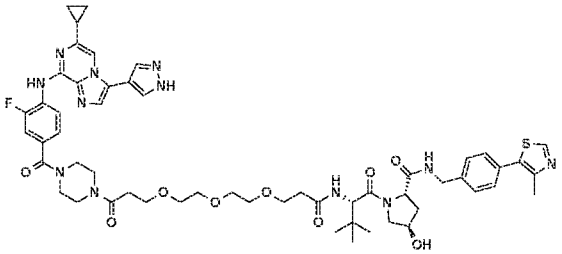
Example 51: (2*S*,4*R*)-1-((*S*)-2-(9-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-9-oxononanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. 59% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.93 (s, 1H), 8.69 (t, *J* = 8.2 Hz, 1H), 8.14 (s, 2H), 7.94 (s, 1H), 7.84 (s, 1H), 7.53 – 7.33 (m, 6H), 4.70 – 4.48 (m, 4H), 4.38 (d, *J* = 15.5 Hz, 1H), 3.93 (d, *J* = 11.0 Hz, 1H), 3.82 (dd, *J* = 10.9, 3.8 Hz, 1H), 3.79 – 3.51 (m, 8H), 2.52 – 2.41 (m, 5H), 2.36 – 2.27 (m, 2H), 2.27 – 2.18 (m, 1H), 2.15 – 2.08 (m, 2H), 1.71 – 1.58 (m, 4H), 1.47 – 1.30 (m, 6H), 1.14 – 0.91 (m, 13H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{54}H_{66}FN_{12}O_6S^+$, 1029.4928; found 1029.4943.



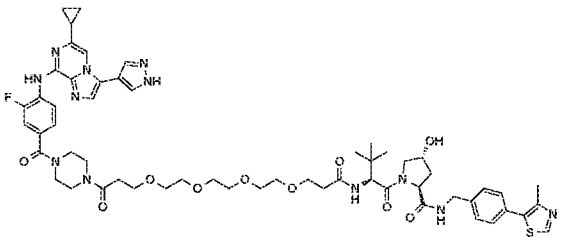
Example: 52 (2*S*,4*R*)-1-((*S*)-2-(3-(3-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-3-oxopropoxy)propanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. 66% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.94 (s, 1H), 8.62 (t, *J* = 8.2 Hz, 1H), 8.17 (s, 2H), 7.98 (s, 1H), 7.92 (s, 1H), 7.48 – 7.31 (m, 6H), 4.70 (s, 1H), 4.65 – 4.42 (m, 3H), 4.36 (d, *J* = 15.3 Hz, 1H), 3.91 (d, *J* = 10.5 Hz, 1H), 3.86 – 3.54 (m, 13H), 2.83 – 2.66 (m, 2H), 2.59 – 2.49 (m, 2H), 2.46 (s, 3H), 2.31 – 2.20 (m, 1H), 2.12 (ddd, *J* = 19.8, 10.8, 6.1 Hz, 2H), 1.13 – 0.91 (m, 13H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{51}H_{60}FN_{12}O_7S^+$, 1003.4407; found 1003.4427.



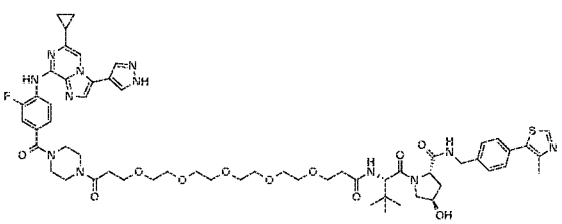
Example 53: (2*S*,4*R*)-1-((*S*)-2-(3-(2-(3-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-3-oxopropoxy)ethoxy)propanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. 64% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 9.01 (s, 1H), 8.59 (t, *J* = 8.2 Hz, 1H), 8.17 (s, 2H), 8.00 (s, 1H), 7.98 (s, 1H), 7.51 – 7.33 (m, 6H), 4.68 (s, 1H), 4.63 – 4.48 (m, 3H), 4.37 (d, *J* = 15.5 Hz, 1H), 3.90 (d, *J* = 10.9 Hz, 1H), 3.84 – 3.56 (m, 17H), 2.79 – 2.69 (m, 2H), 2.62 – 2.42 (m, 5H), 2.29 – 2.19 (m, 1H), 2.20 – 2.05 (m, 2H), 1.12 – 0.94 (m, 15H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{53}H_{64}FN_{12}O_8S^+$, 1047.4669; found 1047.4671.



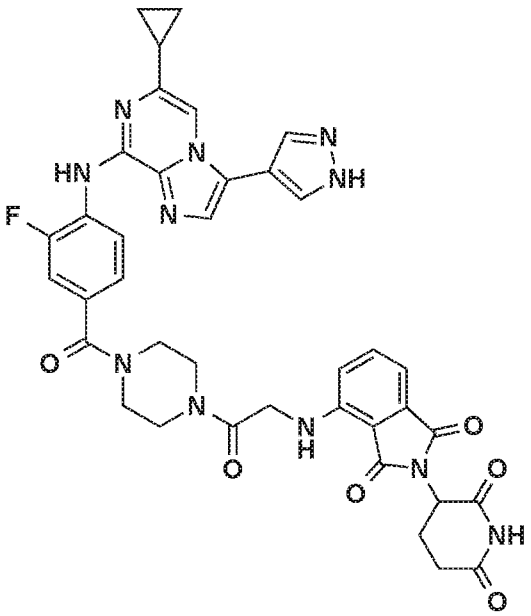
Example 54: (2*S*,4*R*)-1-((*S*)-2-(*tert*-Butyl)-16-(4-(4-((6-cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-4,16-dioxo-7,10,13-trioxa-3-azahexadecanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. 56% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 9.04 (s, 1H), 8.57 (t, *J* = 5.9 Hz, 1H), 8.18 (s, 2H), 8.02 (s, 1H), 8.00 (s, 1H), 7.52 – 7.30 (m, 6H), 4.67 (s, 1H), 4.64 – 4.48 (m, 3H), 4.37 (d, *J* = 15.5 Hz, 1H), 3.91 (d, *J* = 11.0 Hz, 1H), 3.88 – 3.46 (m, 21H), 2.71 (s, 2H), 2.65 – 2.44 (m, 5H), 2.30 – 2.20 (m, 1H), 2.20 – 2.04 (m, 2H), 1.13 – 0.93 (m, 13H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{55}H_{68}FN_{12}O_9S^+$, 1091.4931; found 1091.4933.



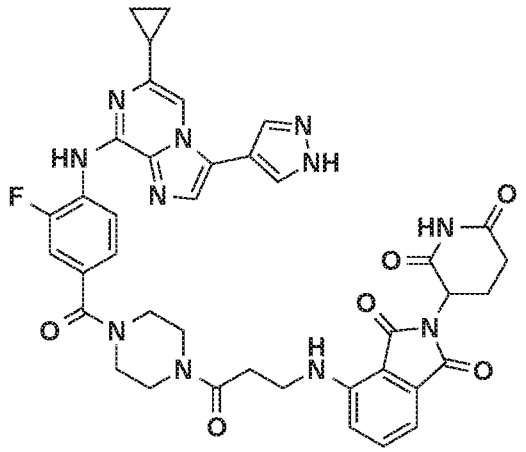
Example 55: (2*S*,4*R*)-1-((*S*)-2-(*tert*-Butyl)-19-(4-(4-((6-cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-4,19-dioxo-7,10,13,16-tetraoxa-3-azanonadecanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. 63% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 9.03 (s, 1H), 8.59 (t, *J* = 8.1 Hz, 1H), 8.18 (s, 2H), 8.02 (s, 1H), 7.99 (s, 1H), 7.59 – 7.34 (m, 6H), 4.66 (s, 1H), 4.63 – 4.49 (m, 3H), 4.37 (d, *J* = 15.5 Hz, 1H), 3.90 (d, *J* = 11.0 Hz, 1H), 3.87 – 3.49 (m, 25H), 2.70 (d, *J* = 19.9 Hz, 2H), 2.67 – 2.42 (m, 5H), 2.23 (dd, *J* = 13.0, 7.6 Hz, 1H), 2.20 – 2.04 (m, 2H), 1.15 – 0.90 (m, 13H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{57}H_{72}FN_{12}O_{10}S^+$, 1135.5194; found 1135.5208.



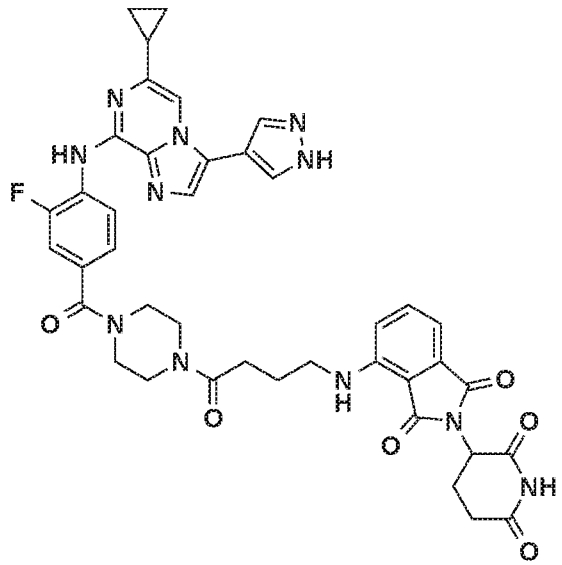
Example 56: (2*S*,4*R*)-1-((*S*)-2-(*tert*-Butyl)-22-(4-(4-((6-cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-4,22-dioxo-7,10,13,16,19-pentaoxa-3-azadocosanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. 51% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.95 (s, 1H), 8.66 (t, *J* = 8.2 Hz, 1H), 8.15 (s, 2H), 7.96 (s, 1H), 7.88 (s, 1H), 7.52 – 7.34 (m, 6H), 4.66 (s, 1H), 4.63 – 4.49 (m, 3H), 4.36 (d, *J* = 15.5 Hz, 1H), 3.90 (d, *J* = 10.9 Hz, 1H), 3.85 – 3.50 (m, 29H), 2.72 (s, 2H), 2.63 – 2.54 (m, 1H), 2.53 – 2.43 (m, 4H), 2.30 – 2.18 (m, 1H), 2.11 (m, 2H), 1.13 – 0.93 (m, 13H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{59}H_{76}FN_{12}O_{11}S^+$, 1179.5456; found 1179.5440.



Example 57: 4-((2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-2-oxoethyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione. 70% yield. ^{1}H NMR (500 MHz, Acetone) δ 8.81 (t, *J* = 8.4 Hz, 1H), 8.21 (s, 2H), 8.07 – 7.97 (m, 1H), 7.79 (d, *J* = 8.8 Hz, 1H), 7.67 – 7.59 (m, 1H), 7.50 – 7.40 (m, 2H), 7.11 (d, *J* = 7.3 Hz, 2H), 5.12 (dd, *J* = 12.6, 5.4 Hz, 1H), 4.35 (s, 2H), 3.80 (s, 8H), 3.06 – 2.93 (m, 1H), 2.88 – 2.76 (m, 2H), 2.28 – 2.20 (m, 1H), 2.19 – 2.14 (m, 2H), 1.13 – 1.05 (m, 2H), 1.00 – 0.92 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{38}H_{35}FN_{11}O_6S^+$, 760.2750; found 760.2755.

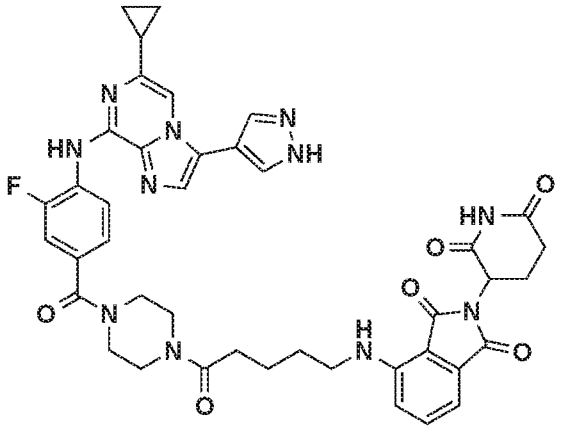


Example 58: 4-((3-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-3-oxopropyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione. 72% yield. ^{1}H NMR (500 MHz, Acetone) δ 8.67 – 8.57 (m, 1H), 8.09 (s, 1H), 7.94 – 7.86 (m, 2H), 7.70 (d, *J* = 3.8 Hz, 1H), 7.50 (dd, *J* = 8.4, 7.2 Hz, 1H), 7.34 – 7.25 (m, 2H), 7.07 (d, *J* = 8.6 Hz, 1H), 6.96 (d, *J* = 7.0 Hz, 1H), 4.97 (dd, *J* = 12.7, 5.5 Hz, 1H), 3.67 – 3.52 (m, 10H), 2.90 – 2.79 (m, 1H), 2.75 (s, 2H), 2.72 – 2.61 (m, 2H), 2.16 – 2.06 (m, 1H), 2.06 – 2.01 (m, 1H), 1.01 – 0.91 (m, 2H), 0.88 – 0.78 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{39}H_{37}FN_{11}O_6S^+$, 774.2907; found 774.2901

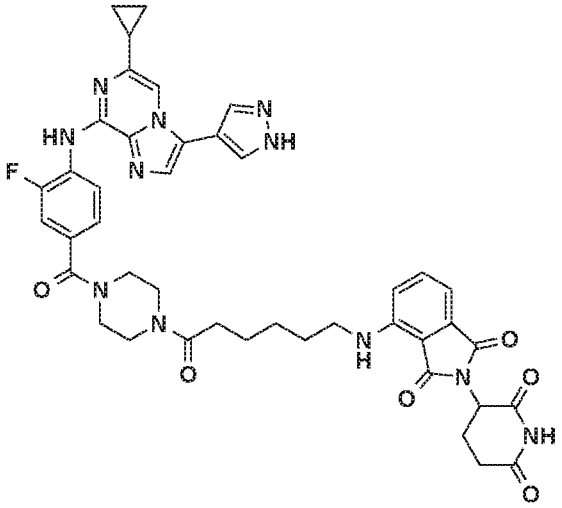


Example 59: 4-((4-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-4-oxobutyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione. 60% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.73 (t, *J* = 8.1 Hz, 1H), 8.01

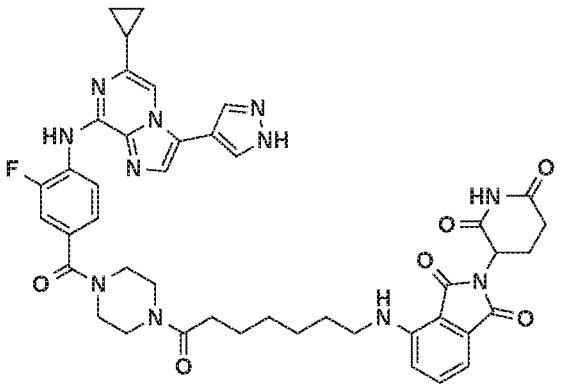
(s, 2H), 7.80 (s, 1H), 7.72 (s, 1H), 7.59 – 7.50 (m, 1H), 7.33 (t, J = 4.9 Hz, 2H), 7.12 – 7.00 (m, 2H), 4.99 (dd, J = 12.0, 5.5 Hz, 1H), 3.65 (d, J = 30.6 Hz, 8H), 3.42 (t, J = 6.7 Hz, 2H), 2.87 – 2.70 (m, 3H), 2.60 – 2.51 (m, 2H), 2.16 – 2.08 (m, 1H), 2.08 – 1.97 (m, 3H), 1.10 – 1.01 (m, 2H), 1.01 – 0.93 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{40}H_{39}FN_{11}O_6S^+$, 788.3063; found 788.3089.



Example 60: 4-((5-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-5-oxopentyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione. 69% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.77 (t, J = 8.3 Hz, 1H), 7.96 (s, 2H), 7.74 (s, 1H), 7.64 (s, 1H), 7.55 – 7.47 (m, 1H), 7.31 (t, J = 8.3 Hz, 2H), 7.07 (d, J = 7.1 Hz, 1H), 6.98 (d, J = 8.6 Hz, 1H), 4.96 (dd, J = 11.0, 6.5 Hz, 1H), 3.77 – 3.50 (m, 8H), 3.39 – 3.34 (m, 2H), 2.85 – 2.70 (m, 3H), 2.53 – 2.42 (m, 2H), 2.18 – 2.04 (m, 1H), 2.05 – 1.92 (m, 1H), 1.85 – 1.67 (m, 4H), 1.10 – 1.03 (m, 2H), 1.00 – 0.91 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{41}H_{41}FN_{11}O_6S^+$, 802.3220; found 802.3249.

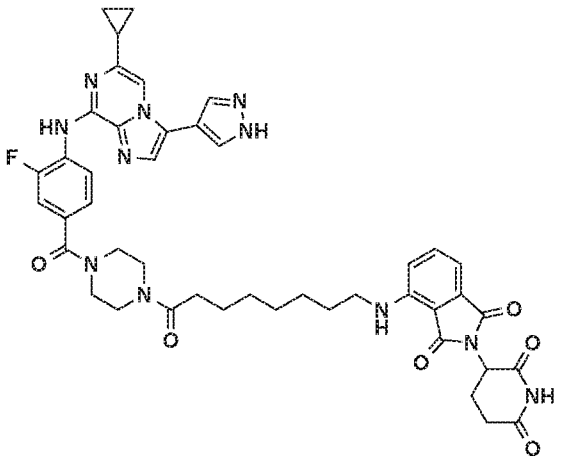


Example 61: 4-((6-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-6-oxohexyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione. 65% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.71 (t, *J* = 8.2 Hz, 1H), 8.00 (s, 2H), 7.78 (s, 1H), 7.71 (s, 1H), 7.56 – 7.49 (m, 1H), 7.32 (t, *J* = 9.6 Hz, 2H), 7.05 (d, *J* = 7.1 Hz, 1H), 6.97 (d, *J* = 8.6 Hz, 1H), 4.97 (dd, *J* = 12.0, 5.5 Hz, 1H), 3.78 – 3.55 (m, 8H), 3.34 – 3.29 (m, 2H), 2.85 – 2.69 (m, 3H), 2.51 – 2.40 (m, 2H), 2.18 – 2.07 (m, 1H), 2.06 – 1.97 (m, 1H), 1.77 – 1.64 (m, 4H), 1.55 – 1.44 (m, 2H), 1.08 – 1.02 (m, 2H), 0.99 – 0.93 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{42}H_{43}FN_{11}O_6S^+$, 816.3375; found 816.3390.

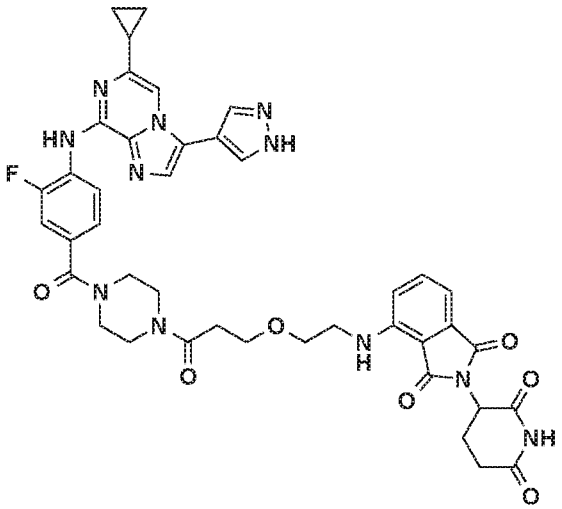


Example 62: 4-((7-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-7-oxoheptyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione. 68% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.67 (t, *J* = 8.1 Hz, 1H), 8.06 (s, 2H), 7.86 (s, 1H), 7.81 (s, 1H), 7.56 – 7.48 (m, 1H), 7.39 – 7.29 (m, 2H), 7.04 (d, *J* = 7.0 Hz, 1H), 6.99 (d, *J* = 8.5 Hz, 1H), 5.01 (dd, *J* = 12.3, 5.4 Hz, 1H), 3.85 – 3.44 (m, 8H), 2.85 – 2.68 (m,

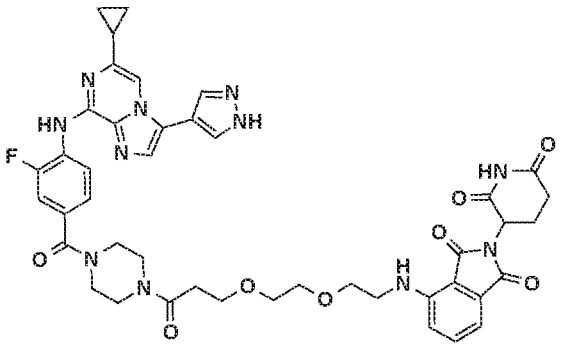
3H), 2.44 (s, 2H), 2.17 – 2.01 (m, 2H), 1.75 – 1.61 (m, 4H), 1.54 – 1.39 (m, 4H), 1.10 – 1.01 (m, 2H), 1.00 – 0.93 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{43}H_{45}FN_{11}O_6S^+$, 830.3533; found 830.3549.



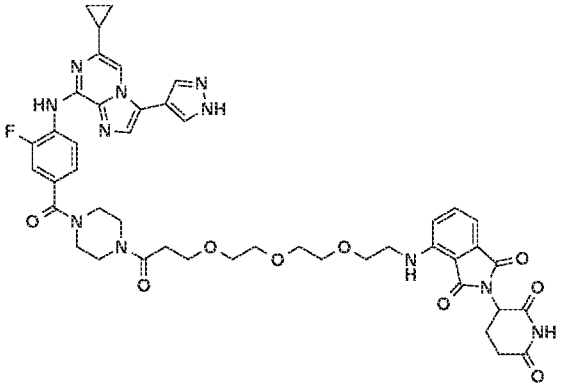
Example 65: 4-((8-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-8-oxooctyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione. 62% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.75 (t, *J* = 8.3 Hz, 1H), 8.01 (s, 2H), 7.79 (s, 1H), 7.69 (s, 1H), 7.56 – 7.44 (m, 1H), 7.40 – 7.25 (m, 2H), 7.09 – 7.00 (m, 1H), 6.97 (d, *J* = 8.6 Hz, 1H), 4.99 (dd, *J* = 12.2, 5.3 Hz, 1H), 3.82 – 3.49 (m, 8H), 3.31 – 3.27 (m, 2H), 2.86 – 2.69 (m, 3H), 2.46 – 2.36 (m, 2H), 2.19 – 2.08 (m, 1H), 2.06 – 1.98 (m, 1H), 1.78 – 1.53 (m, 4H), 1.52 – 1.33 (m, 6H), 1.10 – 1.00 (m, 2H), 1.00 – 0.92 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{44}H_{47}FN_{11}O_6S^+$, 844.3689; found 844.3671.



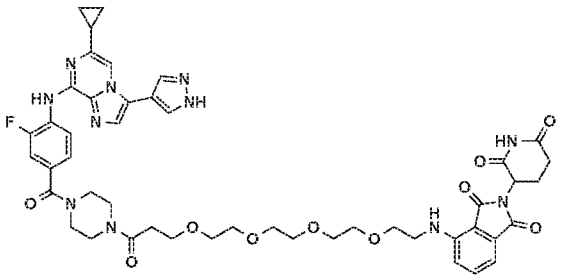
Example 66: 4-((2-(3-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-3-oxopropoxy)ethyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione. 69% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.71 (t, *J* = 7.6 Hz, 1H), 7.98 (s, 2H), 7.76 (s, 1H), 7.67 (s, 1H), 7.58 – 7.48 (m, 1H), 7.35 – 7.17 (m, 2H), 7.07 (d, *J* = 7.0 Hz, 1H), 6.99 (d, *J* = 8.5 Hz, 1H), 4.96 (dd, *J* = 11.9, 5.2 Hz, 1H), 3.83 (t, *J* = 5.8 Hz, 2H), 3.80 – 3.54 (m, 10H), 3.48 (t, *J* = 4.9 Hz, 2H), 2.85 – 2.65 (m, 5H), 2.14 – 2.05 (m, 1H), 2.05 – 1.95 (m, 1H), 1.09 – 1.01 (m, 2H), 0.99 – 0.91 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{41}H_{41}FN_{11}O_7S^+$, 818.3169; found 818.3178.



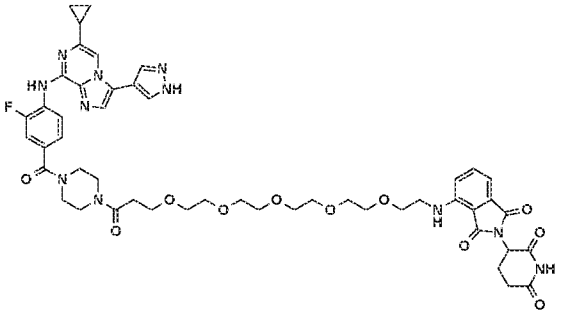
Example 67: 4-((2-(2-(3-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-3-oxopropoxy)ethoxy)ethyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione. 65% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.69 (t, *J* = 8.3 Hz, 1H), 8.00 (s, 2H), 7.77 (s, 1H), 7.70 (s, 1H), 7.55 – 7.37 (m, 1H), 7.28 (t, *J* = 8.3 Hz, 2H), 7.10 – 6.84 (m, 2H), 4.96 (dd, *J* = 12.2, 5.4 Hz, 1H), 3.79 (t, *J* = 6.0 Hz, 2H), 3.77 – 3.51 (m, 14H), 3.51 – 3.40 (m, 2H), 2.85 – 2.60 (m, 5H), 2.16 – 2.06 (m, 1H), 2.06 – 1.96 (m, 1H), 1.09 – 1.00 (m, 2H), 0.99 – 0.90 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{43}H_{45}FN_{11}O_8S^+$, 862.3431; found 862.3453.



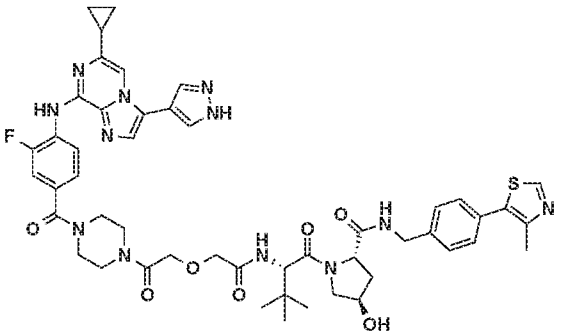
Example 68: 4-((2-(2-(2-(3-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-3-oxopropoxy)ethoxy)ethoxy)ethyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione. 60% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.66 (t, *J* = 8.2 Hz, 1H), 8.01 (s, 2H), 7.79 (s, 1H), 7.74 (s, 1H), 7.53 – 7.45 (m, 1H), 7.31 (t, *J* = 10.1 Hz, 2H), 6.99 (dd, *J* = 21.6, 6.9 Hz, 2H), 4.97 (dd, *J* = 12.3, 5.5 Hz, 1H), 3.78 (t, *J* = 6.1 Hz, 2H), 3.75 – 3.54 (m, 18H), 3.51 – 3.42 (m, 2H), 2.86 – 2.58 (m, 5H), 2.17 – 2.07 (m, 1H), 2.07 – 1.97 (m, 1H), 1.07 – 1.01 (m, 2H), 0.98 – 0.91 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{45}H_{49}FN_{11}O_9S^+$, 906.3693; found 906.3688.



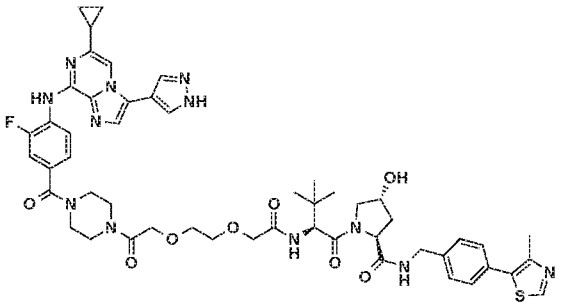
Example 69: 4-((15-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-15-oxo-3,6,9,12-tetraoxapentadecyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione. 59% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.65 (t, *J* = 8.1 Hz, 1H), 8.03 (s, 2H), 7.82 (s, 1H), 7.77 (s, 1H), 7.54 – 7.42 (m, 1H), 7.34 (t, *J* = 5.0 Hz, 2H), 7.00 (dd, *J* = 17.7, 7.8 Hz, 2H), 4.98 (dd, *J* = 12.4, 5.4 Hz, 1H), 3.78 (t, *J* = 6.1 Hz, 2H), 3.76 – 3.54 (m, 22H), 3.51 – 3.42 (m, 2H), 2.88 – 2.59 (m, 5H), 2.16 – 2.07 (m, 1H), 2.08 – 2.00 (m, 1H), 1.08 – 1.01 (m, 2H), 1.01 – 0.92 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{47}H_{53}FN_{11}O_{10}S^+$, 950.3955; found 950.3944.



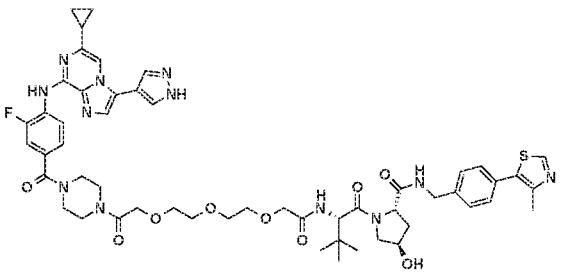
Example 70: 4-((18-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-18-oxo-3,6,9,12,15-pentaoxaoctadecyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione. 63% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.66 (t, *J* = 8.3 Hz, 1H), 7.99 (s, 2H), 7.77 (s, 1H), 7.73 (s, 1H), 7.54 – 7.45 (m, 1H), 7.42 – 7.23 (m, 2H), 7.04 (d, *J* = 7.1 Hz, 1H), 6.97 (d, *J* = 8.6 Hz, 1H), 4.96 (dd, *J* = 11.9, 5.6 Hz, 1H), 3.88 – 3.52 (m, 30H), 3.52 – 3.44 (m, 2H), 2.90 – 2.61 (m, 5H), 2.12 (dd, *J* = 8.9, 5.2 Hz, 1H), 2.07 – 1.95 (m, 1H), 1.11 – 1.00 (m, 2H), 1.00 – 0.90 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{49}H_{57}FN_{11}O_{11}S^+$, 994.4218; found 994.4230.



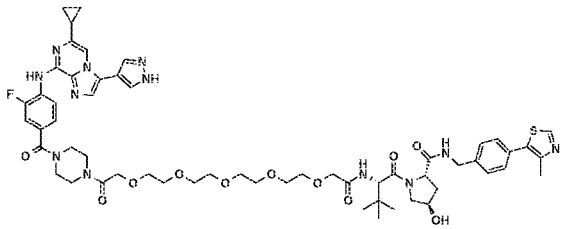
Example 71: (2*S*,4*R*)-1-((*S*)-2-(2-(2-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-2-oxoethoxy)ethoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. 60% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.98 (s, 1H), 8.60 (t, *J* = 8.2 Hz, 1H), 8.16 (s, 2H), 7.97 (s, 1H), 7.92 (s, 1H), 7.53 – 7.20 (m, 6H), 4.71 (s, 1H), 4.64 – 4.35 (m, 6H), 4.20 (d, *J* = 15.1 Hz, 1H), 4.11 (d, *J* = 15.1 Hz, 1H), 3.91 (d, *J* = 10.9 Hz, 1H), 3.83 (dd, *J* = 11.0, 3.7 Hz, 1H), 3.80 – 3.50 (m, 8H), 2.49 (s, 3H), 2.29 – 2.21 (m, 1H), 2.18 – 2.07 (m, 2H), 1.08 (s, 9H), 1.06 – 1.01 (m, 2H), 1.01 – 0.93 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{49}H_{56}FN_{12}O_7S^+$, 975.4094; found 975.4086.



Example 72: (2*S*,4*R*)-1-((*S*)-2-(2-(2-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-2-oxoethoxy)ethoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. 66% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.98 (s, 1H), 8.59 (t, *J* = 8.2 Hz, 1H), 8.16 (s, 2H), 7.98 (s, 1H), 7.94 (s, 1H), 7.40 (ddd, *J* = 37.7, 18.3, 8.2 Hz, 6H), 4.73 (s, 1H), 4.65 – 4.42 (m, 3H), 4.41 – 4.30 (m, 3H), 4.13 – 4.03 (m, 2H), 3.93 – 3.49 (m, 14H), 2.48 (s, 3H), 2.30 – 2.19 (m, 1H), 2.19 – 2.05 (m, 2H), 1.15 – 0.91 (m, 13H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{51}H_{60}FN_{12}O_8S^+$, 1019.4356; found 1019.4377.

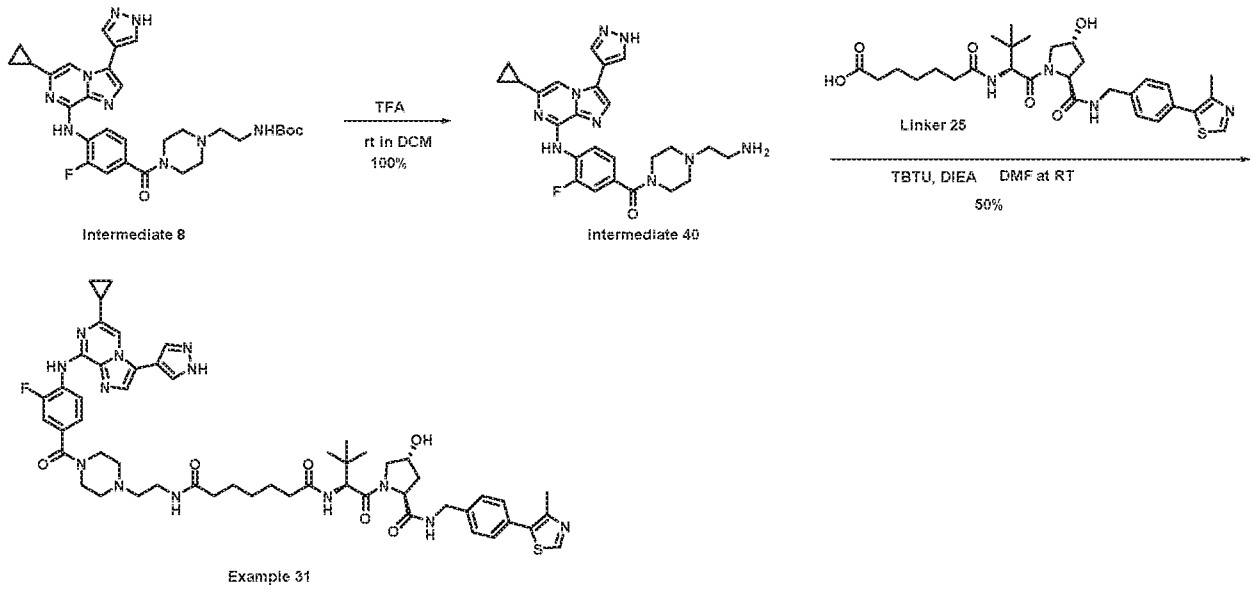


Example 73: (2*S*,4*R*)-1-((*S*)-2-(*tert*-Butyl)-14-(4-(4-((6-cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-4,14-dioxo-6,9,12-trioxa-3-azatetradecanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. 67% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 9.03 (s, 1H), 8.58 (t, *J* = 8.2 Hz, 1H), 8.17 (s, 2H), 8.01 (s, 1H), 7.98 (s, 1H), 7.55 – 7.23 (m, 6H), 4.72 (s, 1H), 4.65 – 4.48 (m, 3H), 4.42 – 4.23 (m, 3H), 4.11 – 3.95 (m, 2H), 3.92 – 3.49 (m, 18H), 2.50 (s, 3H), 2.30 – 2.20 (m, 1H), 2.20 – 2.05 (m, 2H), 1.12 – 0.94 (m, 13H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{53}H_{64}FN_{12}O_9S^+$, 1063.4618; found 1063.4632.



Example 74: (2*S*,4*R*)-1-((*S*)-2-(*tert*-Butyl)-20-(4-(4-((6-cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-4,20-dioxo-6,9,12,15,18-pentaoxa-3-azaicosanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. 56% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 9.11 (s, 1H), 8.55 (t, *J* = 8.0 Hz, 1H), 8.18 (s, 2H), 8.03 (s, 2H), 7.56 – 7.32 (m, 6H), 4.71 (s, 1H), 4.64 – 4.49 (m, 3H), 4.37 (d, *J* = 15.6 Hz, 1H), 4.31 (s, 2H), 4.07 (d, *J* = 4.1 Hz, 2H), 3.94 – 3.48 (m, 26H), 2.51 (s, 3H), 2.29 – 2.20 (m, 1H), 2.20 – 2.06 (m, 2H), 1.13 – 0.93 (m, 13H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{57}H_{72}FN_{12}O_{11}S^+$, 1151.5143; found 1151.5117.

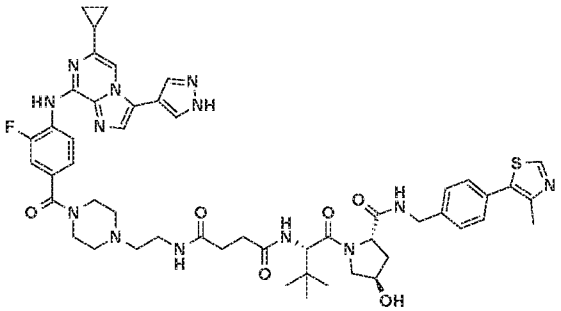
Scheme 27. Synthesis of example 31



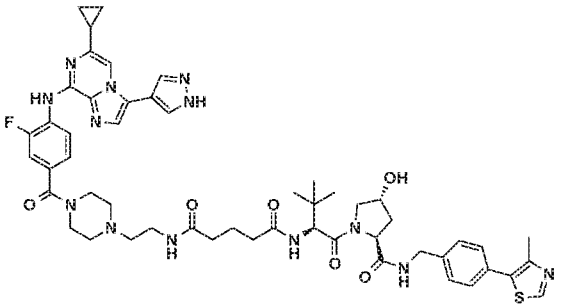
Example 31: N^1-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)ethyl)-N^7-((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)heptanediamide. A solution of intermediate **8** in DCM/TFA (2:1, 1 mL) was stirred at rt. After 2 h, the solvent was removed under reduced pressure to obtain intermediate **9** as brown oil. To a

solution of intermediate **9** (5 mg, 0.009 mmol) and linker **8** (5 mg, 0.008mmol) in DMF (0.5 mL) were added DIEA (17 μL, 0.1 mmol) and TBTU (4 mg, 0.01 mmol). After being stirred at rt for 12 h, the mixture was purified by HPLC to yield the title compound (7 mg, 75%) as the brown oil. ^{1}H NMR (600 MHz, CD_3OD) δ 8.98 – 8.91 (m, 1H), 8.74 (t, J = 8.2 Hz, 1H), 8.15 (s, 2H), 7.98 (s, 1H), 7.86 (s, 1H), 7.52 – 7.37 (m, 6H), 4.66 (s, 1H), 4.64 – 4.50 (m, 3H), 4.38 (d, J = 15.4 Hz, 1H), 3.92 (d, J = 11.0 Hz, 1H), 3.83 (dd, J = 10.9, 3.8 Hz, 1H), 3.77 – 3.34 (m, 12H), 2.50 (s, 3H), 2.42 – 2.21 (m, 5H), 2.21 – 2.05 (m, 2H), 1.71 – 1.58 (m, 4H), 1.43 – 1.33 (m, 2H), 1.12 – 0.86 (m, 13H). HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{54}H_{67}FN_{13}O_6S^+$, 1044.5037; found 1044.5060.

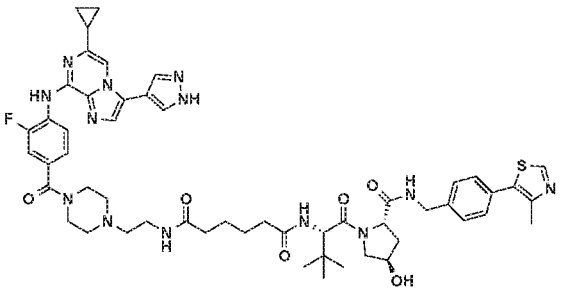
Example compounds **75 – 101** were synthesized according to the procedures for the preparation of example compound **28.**



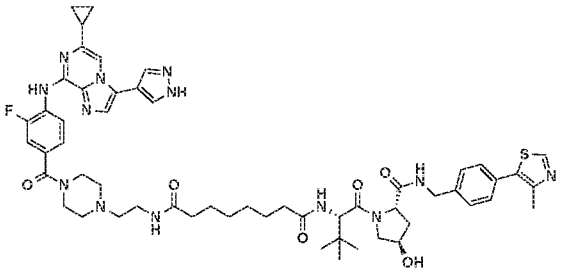
Example 75: N^1-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)ethyl)-N^4-((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)succinamide. 70% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.98 (s, 1H), 8.68 (t, J = 8.2 Hz, 1H), 8.15 (s, 2H), 7.98 (s, 1H), 7.90 (s, 1H), 7.53 – 7.36 (m, 6H), 4.63 – 4.49 (m, 4H), 4.38 (d, J = 15.5 Hz, 1H), 3.87 – 3.77 (m, 2H), 3.77 – 3.42 (m, 10H), 3.38 (t, J = 4.8 Hz, 2H), 2.72 – 2.66 (m, 2H), 2.53 – 2.46 (m, 5H), 2.30 – 2.21 (m, 1H), 2.17 – 2.06 (m, 2H), 1.13 – 1.00 (m, 11H), 1.00 – 0.95 (m, 2H). HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{51}H_{61}FN_{13}O_6S^+$, 1002.4567; found 1002.4587.



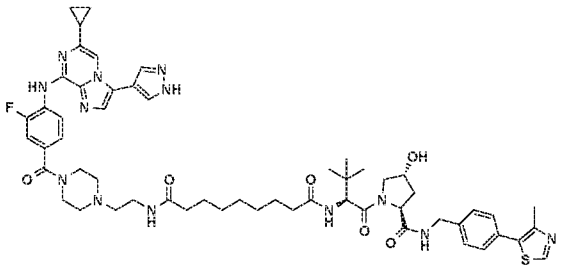
Example 76: N^1-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)ethyl)-N^5-((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)glutaramide. 73% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.96 (s, 1H), 8.69 (t, *J* = 8.2 Hz, 1H), 8.15 (s, 2H), 7.97 (s, 1H), 7.87 (s, 1H), 7.55 – 7.34 (m, 6H), 4.63 (s, 1H), 4.62 – 4.50 (m, 3H), 4.39 (d, *J* = 15.5 Hz, 1H), 3.94 (d, *J* = 11.0 Hz, 1H), 3.83 (dd, *J* = 11.0, 3.8 Hz, 1H), 3.71 – 3.41 (m, 10H), 3.37 (t, *J* = 5.8 Hz, 2H), 2.48 (s, 3H), 2.43 – 2.22 (m, 5H), 2.17 – 2.08 (m, 2H), 2.00 – 1.91 (m, 2H), 1.10 – 1.02 (m, 11H), 1.00 – 0.95 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{52}H_{63}FN_{13}O_6S^+$, 1016.4724; found 1016.4739.



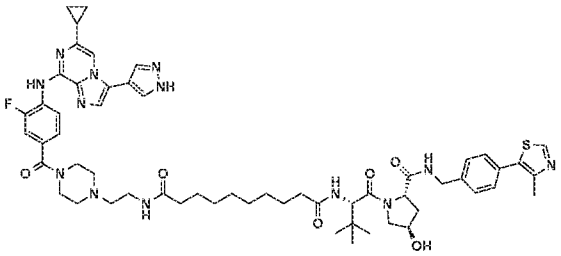
Example 77: N^1-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)ethyl)-N^6-((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)adipamide. 55% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.97 (s, 1H), 8.70 (t, *J* = 8.2 Hz, 1H), 8.15 (s, 2H), 7.97 (s, 1H), 7.88 (s, 1H), 7.53 – 7.29 (m, 6H), 4.64 (s, 1H), 4.63 – 4.49 (m, 3H), 4.39 (d, *J* = 15.4 Hz, 1H), 3.92 (d, *J* = 11.1 Hz, 1H), 3.83 (dd, *J* = 11.0, 3.8 Hz, 1H), 3.72 – 3.40 (m, 10H), 3.37 (t, *J* = 5.9 Hz, 2H), 2.49 (s, 3H), 2.38 – 2.19 (m, 5H), 2.18 – 2.06 (m, 2H), 1.74 – 1.57 (m, 4H), 1.11 – 1.01 (m, 11H), 1.01 – 0.92 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{53}H_{65}FN_{13}O_6S^+$, 1030.4880; found 1030.4897.



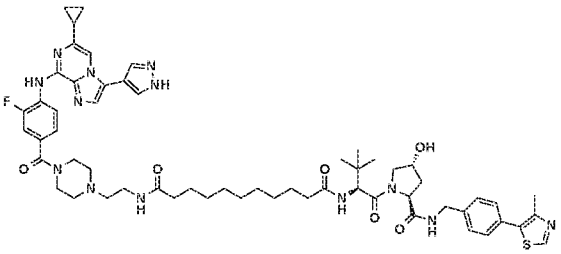
Example 78: N^1-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)ethyl)-N^8-((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)octanediamide. 73% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.99 (s, 1H), 8.69 (t, *J* = 8.2 Hz, 1H), 8.15 (s, 2H), 7.98 (s, 1H), 7.90 (s, 1H), 7.59 – 7.25 (m, 6H), 4.65 (s, 1H), 4.63 – 4.49 (m, 3H), 4.38 (d, *J* = 15.5 Hz, 1H), 3.92 (d, *J* = 11.0 Hz, 1H), 3.83 (dd, *J* = 10.9, 3.8 Hz, 1H), 3.71 – 3.40 (m, 10H), 3.39 – 3.35 (m, 2H), 2.49 (s, 3H), 2.38 – 2.19 (m, 5H), 2.19 – 2.05 (m, 2H), 1.76 – 1.56 (m, 4H), 1.47 – 1.31 (m, 4H), 1.11 – 1.01 (m, 11H), 1.01 – 0.93 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{55}H_{69}FN_{13}O_6S^+$, 1058.5193; found 1058.5177.



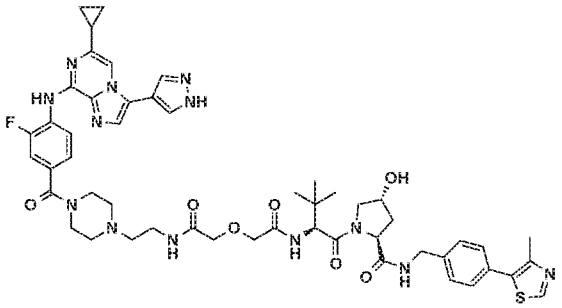
Example 79: N^1-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)ethyl)-N^9-((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)nonanediamide. 69% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.95 (s, 1H), 8.73 (t, *J* = 8.2 Hz, 1H), 8.14 (s, 2H), 7.96 (s, 1H), 7.84 (s, 1H), 7.53 – 7.33 (m, 6H), 4.65 (s, 1H), 4.62 – 4.49 (m, 3H), 4.38 (d, *J* = 15.5 Hz, 1H), 3.92 (d, *J* = 11.1 Hz, 1H), 3.82 (dd, *J* = 10.9, 3.9 Hz, 1H), 3.73 – 3.40 (m, 10H), 3.37 – 3.35 (m, 2H), 2.49 (s, 3H), 2.35 – 2.18 (m, 5H), 2.16 – 2.05 (m, 2H), 1.69 – 1.55 (m, 4H), 1.36 (s, 6H), 1.12 – 1.00 (m, 11H), 1.00 – 0.92 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{56}H_{71}FN_{13}O_6S^+$, 1072.5350; found 1072.5371.



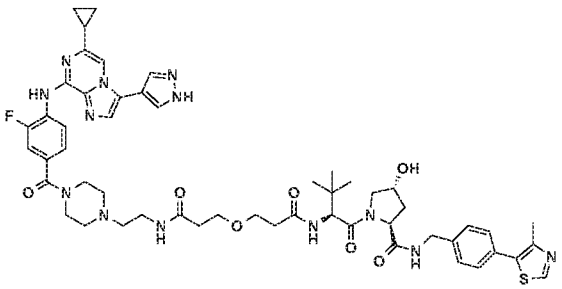
Example 80: N^1-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)ethyl)-N^{10}-((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)decanediamide. 63% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 9.01 (s, 1H), 8.68 (t, *J* = 8.2 Hz, 1H), 8.16 (s, 2H), 7.99 (s, 1H), 7.91 (s, 1H), 7.61 – 7.30 (m, 6H), 4.66 (s, 1H), 4.62 – 4.49 (m, 3H), 4.38 (d, *J* = 15.5 Hz, 1H), 3.92 (d, *J* = 11.0 Hz, 1H), 3.82 (dd, *J* = 10.9, 3.8 Hz, 1H), 3.68 – 3.39 (m, 10H), 3.39 – 3.35 (m, 2H), 2.50 (s, 3H), 2.37 – 2.19 (m, 5H), 2.19 – 2.06 (m, 2H), 1.71 – 1.54 (m, 4H), 1.42 – 1.27 (m, 8H), 1.11 – 1.02 (m, 11H), 1.02 – 0.95 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{57}H_{73}FN_{13}O_6S^+$, 1086.5506; found 1086.5519.



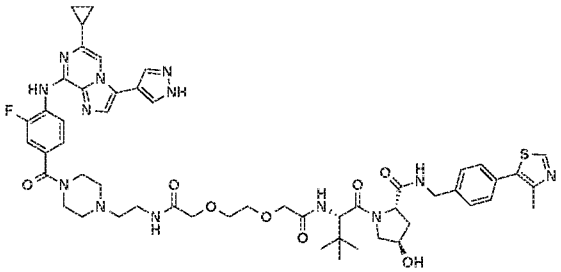
Example 81: N^1-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)ethyl)-N^{11}-((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)undecanediamide. 67% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 9.00 (s, 1H), 8.69 (t, *J* = 8.2 Hz, 1H), 8.16 (s, 2H), 7.99 (s, 1H), 7.90 (s, 1H), 7.53 – 7.31 (m, 6H), 4.65 (s, 1H), 4.61 – 4.50 (m, 3H), 4.38 (d, *J* = 15.5 Hz, 1H), 3.92 (d, *J* = 11.0 Hz, 1H), 3.82 (dd, *J* = 10.9, 3.9 Hz, 1H), 3.69 – 3.39 (m, 10H), 3.38 – 3.34 (m, 2H), 2.50 (s, 3H), 2.36 – 2.19 (m, 5H), 2.19 – 2.06 (m, 2H), 1.73 – 1.54 (m, 4H), 1.44 – 1.24 (m, 10H), 1.11 – 0.95 (m, 13H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{58}H_{75}FN_{13}O_6S^+$, 1100.5663; found 1100.5655.



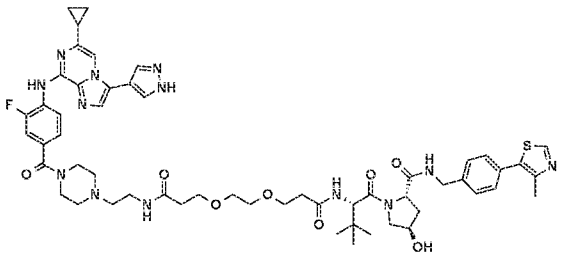
Example 82: (2*S*,4*R*)-1-((*S*)-2-(2-(2-((2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)ethyl)amino)-2-oxoethoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. 66% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.98 (s, 1H), 8.66 (t, *J* = 8.2 Hz, 1H), 8.15 (s, 2H), 7.98 (s, 1H), 7.91 (s, 1H), 7.56 – 7.32 (m, 6H), 4.73 (s, 1H), 4.63 – 4.44 (m, 3H), 4.39 (d, *J* = 15.5 Hz, 1H), 4.25 – 4.09 (m, 4H), 3.92 (d, *J* = 11.0 Hz, 1H), 3.84 (dd, *J* = 11.0, 3.7 Hz, 1H), 3.76 – 3.37 (m, 12H), 2.48 (s, 3H), 2.31 – 2.23 (m, 1H), 2.18 – 2.05 (m, 2H), 1.11 – 1.02 (m, 11H), 1.01 – 0.95 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{51}H_{61}FN_{13}O_7S^+$, 1018.4516; found 1018.4516.



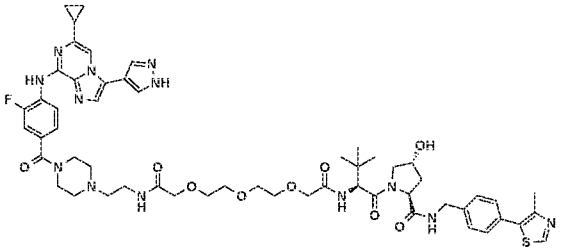
Example 83: (2*S*,4*R*)-1-((*S*)-2-(3-(3-((2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)ethyl)amino)-3-oxopropoxy)propanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. 68% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.98 (s, 1H), 8.66 (t, *J* = 8.2 Hz, 1H), 8.16 (s, 2H), 7.99 (s, 1H), 7.92 (s, 1H), 7.53 – 7.34 (m, 6H), 4.66 (s, 1H), 4.63 – 4.48 (m, 3H), 4.40 (d, *J* = 15.4 Hz, 1H), 3.91 (d, *J* = 11.1 Hz, 1H), 3.83 (dd, *J* = 11.0, 3.8 Hz, 1H), 3.74 (dd, *J* = 13.5, 5.9 Hz, 4H), 3.69 – 3.35 (m, 12H), 2.61 – 2.50 (m, 4H), 2.48 (s, 3H), 2.31 – 2.20 (m, 1H), 2.18 – 2.06 (m, 2H), 1.10 – 1.01 (m, 11H), 1.01 – 0.94 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{53}H_{65}FN_{13}O_7S^+$, 1046.4829; found 1046.4813.



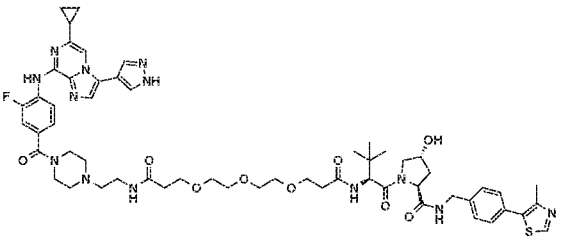
Example 84: (2*S*,4*R*)-1-((*S*)-2-(*tert*-Butyl)-14-(4-(4-((6-cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-4,11-dioxo-6,9-dioxa-3,12-diazatetradecanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. 61% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.98 (s, 1H), 8.67 (t, *J* = 8.2 Hz, 1H), 8.16 (s, 2H), 7.99 (s, 1H), 7.91 (s, 1H), 7.52 – 7.33 (m, 6H), 4.72 (s, 1H), 4.61 – 4.55 (m, 1H), 4.55 – 4.51 (m, 1H), 4.46 (s, 2H), 4.16 (d, *J* = 15.6 Hz, 1H), 4.12 – 4.05 (m, 3H), 3.91 (d, *J* = 11.1 Hz, 1H), 3.84 (dd, *J* = 11.1, 3.6 Hz, 1H), 3.82 – 3.72 (m, 14H), 3.69 (t, *J* = 5.6 Hz, 2H), 3.40 (dd, *J* = 11.0, 5.3 Hz, 2H), 2.49 (s, 3H), 2.34 – 2.24 (m, 1H), 2.21 – 2.03 (m, 2H), 1.13 – 1.01 (m, 13H), 1.01 – 0.94 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{53}H_{65}FN_{13}O_8S^+$, 1062.4778; found 1062.4753.



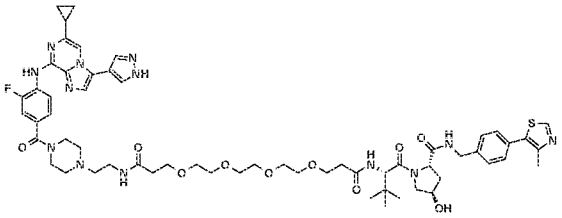
Example 85: (2*S*,4*R*)-1-((*S*)-2-(*tert*-Butyl)-16-(4-(4-((6-cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-4,13-dioxo-7,10-dioxa-3,14-diazahexadecanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. 61% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.99 (s, 1H), 8.66 (t, *J* = 8.2 Hz, 1H), 8.16 (s, 2H), 7.98 (s, 1H), 7.91 (s, 1H), 7.57 – 7.34 (m, 6H), 4.67 (s, 1H), 4.63 – 4.49 (m, 3H), 4.39 (d, *J* = 15.5 Hz, 1H), 3.91 (d, *J* = 10.1 Hz, 1H), 3.88 – 3.70 (m, 7H), 3.70 – 3.42 (m, 12H), 3.42 – 3.36 (m, 2H), 2.65 – 2.44 (m, 7H), 2.30 – 2.20 (m, 1H), 2.20 – 2.06 (m, 2H), 1.13 – 0.90 (m, 13H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{55}H_{69}FN_{13}O_8S^+$, 1090.5091; found 1090.5083.



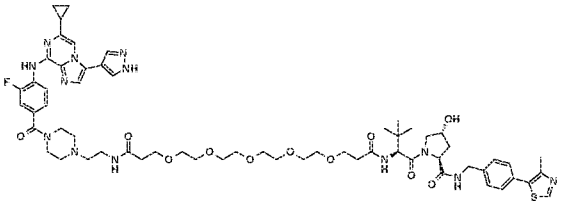
Example 86: (2*S*,4*R*)-1-((*S*)-2-(*tert*-Butyl)-17-(4-(4-((6-cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-4,14-dioxo-6,9,12-trioxa-3,15-diazaheptadecanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. 67% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.99 (s, 1H), 8.66 (t, *J* = 8.2 Hz, 1H), 8.16 (s, 2H), 7.99 (s, 1H), 7.92 (s, 1H), 7.54 – 7.38 (m, 6H), 4.69 (s, 1H), 4.61 – 4.50 (m, 3H), 4.39 (d, *J* = 15.5 Hz, 1H), 4.18 – 4.10 (m, 2H), 4.09 – 3.99 (m, 2H), 3.90 (d, *J* = 11.0 Hz, 1H), 3.86 – 3.80 (m, 1H), 3.80 – 3.44 (m, 18H), 3.40 (t, *J* = 5.6 Hz, 2H), 2.49 (s, 3H), 2.26 (dd, *J* = 13.1, 7.6 Hz, 1H), 2.19 – 2.04 (m, 2H), 1.18 – 1.00 (m, 11H), 1.01 – 0.94 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{55}H_{69}FN_{13}O_9S^+$, 1106.5040; found 1106.5071.



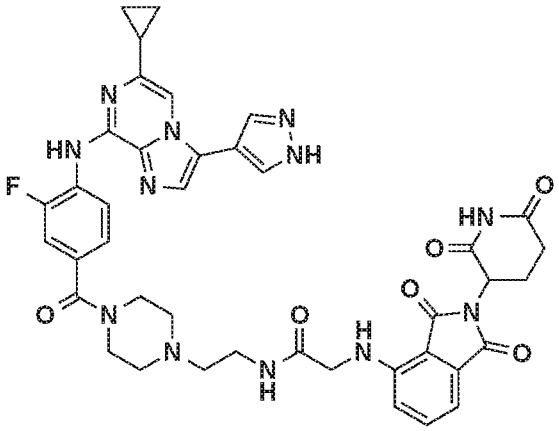
Example 87: (2*S*,4*R*)-1-((*S*)-2-(*tert*-Butyl)-19-(4-(4-((6-cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-4,16-dioxo-7,10,13-trioxa-3,17-diazanonadecanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. 64% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 9.07 (s, 1H), 8.61 (t, *J* = 8.2 Hz, 1H), 8.18 (s, 2H), 8.03 (s, 1H), 8.00 (s, 1H), 7.54 – 7.28 (m, 6H), 4.66 (s, 1H), 4.63 – 4.49 (m, 3H), 4.39 (d, *J* = 15.5 Hz, 1H), 3.91 (d, *J* = 11.0 Hz, 1H), 3.82 (dd, *J* = 11.0, 3.8 Hz, 1H), 3.80 – 3.70 (m, 6H), 3.70 – 3.42 (m, 16H), 3.41 – 3.36 (m, 2H), 2.65 – 2.44 (m, 7H), 2.29 – 2.21 (m, 1H), 2.20 – 2.06 (m, 2H), 1.10 – 1.02 (m, 11H), 1.02 – 0.96 (m, 1H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{57}H_{73}FN_{13}O_9S^+$, 1134.5353; found 1134.5370.



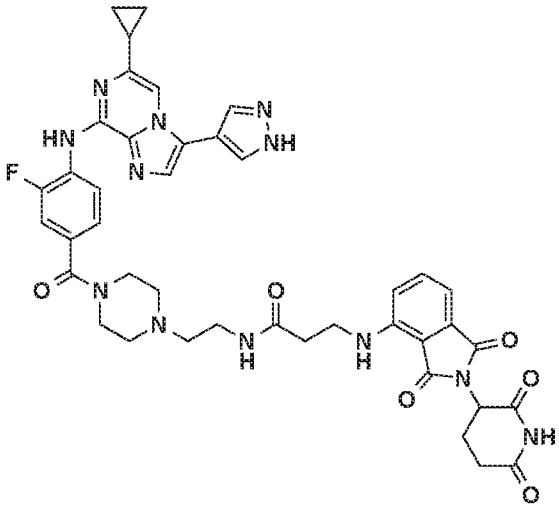
Example 88: N^1-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)ethyl)-N^{16}-((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-4,7,10,13-tetraoxahexadecanediamide. 60% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 9.03 (s, 1H), 8.65 (t, *J* = 8.2 Hz, 1H), 8.17 (s, 2H), 8.01 (s, 1H), 7.96 (s, 1H), 7.52 – 7.39 (m, 6H), 4.66 (s, 1H), 4.62 – 4.49 (m, 3H), 4.38 (d, *J* = 15.5 Hz, 1H), 3.91 (d, *J* = 11.0 Hz, 1H), 3.82 (dd, *J* = 11.0, 3.8 Hz, 1H), 3.80 – 3.69 (m, 6H), 3.69 – 3.42 (m, 20H), 3.42 – 3.36 (m, 2H), 2.65 – 2.43 (m, 7H), 2.29 – 2.19 (m, 1H), 2.19 – 2.06 (m, 2H), 1.11 – 1.01 (m, 11H), 1.01 – 0.94 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{59}H_{77}FN_{13}O_{10}S^+$, 1178.5616; found 1178.5627.



Example 89: N^1-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)ethyl)-N^{19}-((*S*)-1-((2*S*,4*R*)-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. 62% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 9.06 (s, 1H), 8.63 (t, *J* = 8.2 Hz, 1H), 8.17 (s, 2H), 8.02 (s, 1H), 7.98 (s, 1H), 7.61 – 7.34 (m, 6H), 4.66 (s, 1H), 4.62 – 4.49 (m, 3H), 4.38 (d, *J* = 15.5 Hz, 1H), 3.91 (d, *J* = 10.8 Hz, 1H), 3.85 – 3.71 (m, 7H), 3.70 – 3.41 (m, 24H), 3.41 – 3.37 (m, 2H), 2.63 – 2.46 (m, 7H), 2.29 – 2.20 (m, 1H), 2.20 – 2.07 (m, 2H), 1.14 – 0.95 (m, 13H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{61}H_{81}FN_{13}O_{11}S^+$, 1222.5878; found 1222.5899.

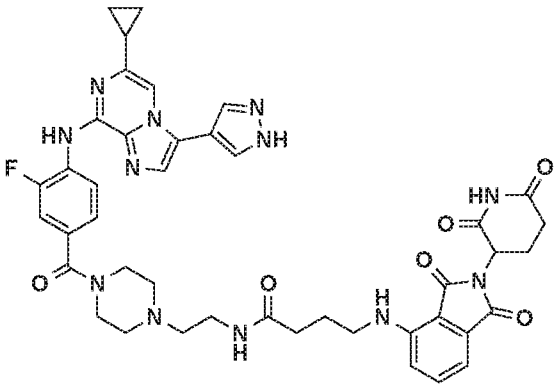


Example 90: *N*-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)ethyl)-2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)acetamide. 70% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.78 (t, *J* = 8.2 Hz, 1H), 7.98 (s, 2H), 7.77 (s, 1H), 7.67 (s, 1H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.36 (m, 2H), 7.14 (d, *J* = 7.1 Hz, 1H), 6.88 (d, *J* = 8.5 Hz, 1H), 5.00 (dd, *J* = 12.0, 5.6 Hz, 1H), 4.14 – 3.78 (m, 6H), 3.65 (t, *J* = 5.5 Hz, 2H), 3.49 – 3.35 (m, 4H), 3.32 – 3.29 (m, 2H), 2.86 – 2.70 (m, 3H), 2.17 – 2.08 (m, 1H), 2.06 – 1.97 (m, 1H), 1.08 – 1.00 (m, 2H), 0.99 – 0.91 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{40}H_{40}FN_{12}O_6S^+$, 803.3172; found 803.3178.

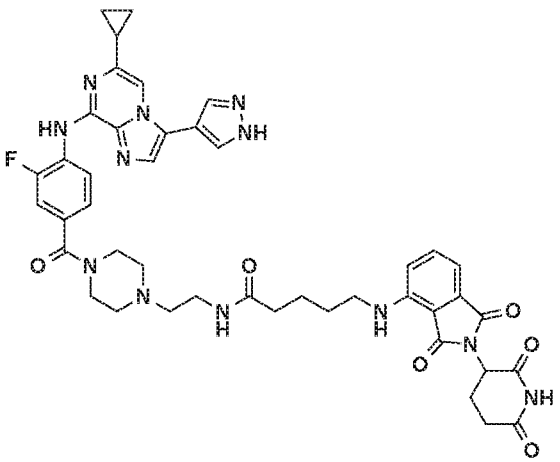


Example 91: *N*-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)ethyl)-3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propenamide. 71% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.69 (t, *J* = 8.1 Hz, 1H), 7.99 (s, 2H), 7.79 (s, 1H), 7.74 (s, 1H), 7.57 – 7.50 (m, 1H), 7.41 – 7.29 (m, 2H), 7.06 (dd, *J* = 17.8, 7.8 Hz, 2H), 4.98 (dd, *J* = 12.3, 5.6 Hz, 1H), 4.20 – 3.70 (m, 4H), 3.70 – 3.54

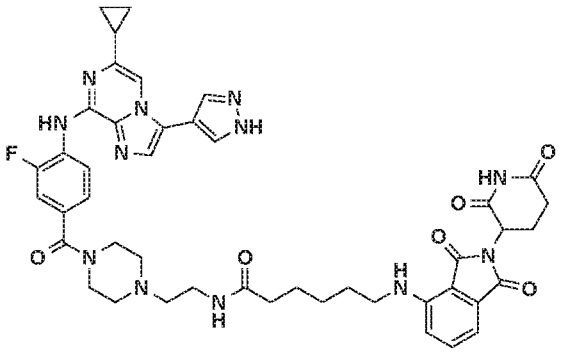
(m, 4H), 3.53 – 3.37 (m, 4H), 3.28 (t, *J* = 5.6 Hz, 2H), 2.89 – 2.67 (m, 3H), 2.64 – 2.53 (m, 2H), 2.18 – 2.08 (m, 1H), 2.07 – 1.97 (m, 1H), 1.08 – 0.99 (m, 2H), 1.00 – 0.90 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{41}H_{42}FN_{12}O_6S^+$, 817.3329; found 817.3311.



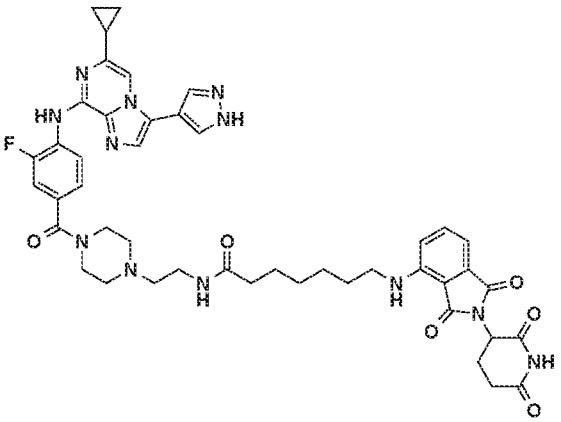
Example 92: *N*-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)ethyl)-4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)butanamide. 73% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.73 (t, *J* = 8.1 Hz, 1H), 7.99 (s, 2H), 7.77 (s, 1H), 7.71 (s, 1H), 7.56 – 7.47 (m, 1H), 7.35 (dd, *J* = 13.2, 10.5 Hz, 2H), 7.05 (d, *J* = 7.1 Hz, 1H), 7.00 (d, *J* = 8.6 Hz, 1H), 4.98 (dd, *J* = 12.2, 5.6 Hz, 1H), 4.19 – 3.62 (m, 4H), 3.56 (t, *J* = 5.6 Hz, 2H), 3.49 – 3.34 (m, 4H), 3.28 (t, *J* = 5.6 Hz, 2H), 2.85 – 2.68 (m, 3H), 2.37 (t, *J* = 7.0 Hz, 2H), 2.17 – 2.08 (m, 1H), 2.07 – 1.95 (m, 3H), 1.09 – 1.02 (m, 2H), 0.99 – 0.91 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{42}H_{44}FN_{12}O_6S^+$, 831.3485; found 831.3499.



Example 93: *N*-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)ethyl)-5-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)pentanamide. 69% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.69 (t, *J* = 8.1 Hz, 1H), 8.00 (s, 2H), 7.79 (s, 1H), 7.75 (s, 1H), 7.54 – 7.46 (m, 1H), 7.41 – 7.30 (m, 2H), 7.04 (d, *J* = 7.1 Hz, 1H), 6.96 (d, *J* = 8.6 Hz, 1H), 4.97 (dd, *J* = 12.2, 5.7 Hz, 1H), 4.19 – 3.68 (m, 4H), 3.59 (t, *J* = 5.5 Hz, 2H), 3.52 – 3.36 (m, 4H), 3.32 – 3.23 (m, 2H), 2.87 – 2.68 (m, 3H), 2.30 (t, *J* = 7.1 Hz, 2H), 2.18 – 2.06 (m, 1H), 2.06 – 1.97 (m, 1H), 1.72 (ddd, *J* = 20.9, 12.7, 7.6 Hz, 4H), 1.09 – 1.01 (m, 2H), 1.01 – 0.92 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{43}H_{46}FN_{12}O_6S^+$, 845.3642; found 845.3655.

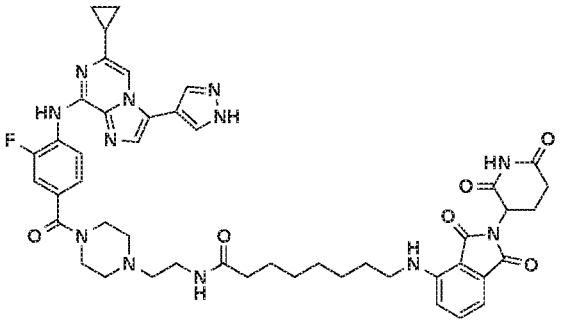


Example 94: *N*-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)ethyl)-6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)hexanamide. 64% yield. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{44}H_{48}FN_{12}O_6S^+$, 859.3798; found 859.3811.

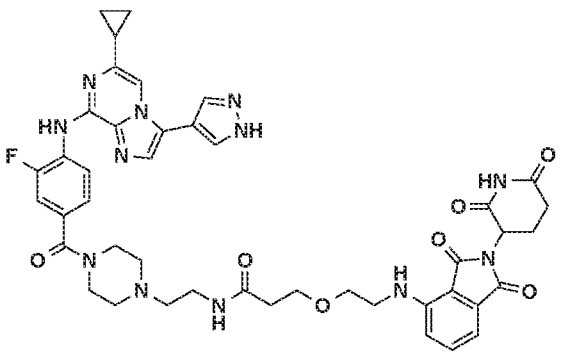


Example 95: *N*-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)ethyl)-7-((2-(2,6-dioxopiperidin-3-yl)-1,3-

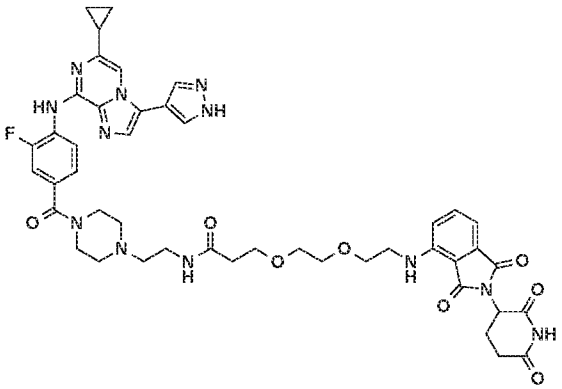
dioxoisoindolin-4-yl)amino)heptanamide. 70% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.73 (t, *J* = 8.1 Hz, 1H), 7.98 (s, 2H), 7.77 (s, 1H), 7.71 (s, 1H), 7.50 (dd, *J* = 8.5, 7.2 Hz, 1H), 7.43 – 7.30 (m, 2H), 7.04 (d, *J* = 7.1 Hz, 1H), 6.94 (d, *J* = 8.6 Hz, 1H), 4.97 (dd, *J* = 12.1, 5.6 Hz, 1H), 4.17 – 3.69 (m, 4H), 3.59 (t, *J* = 5.7 Hz, 2H), 3.51 – 3.37 (m, 4H), 3.32 – 3.26 (m, 4H), 2.90 – 2.69 (m, 3H), 2.24 (t, *J* = 7.6 Hz, 2H), 2.17 – 2.09 (m, 1H), 2.05 – 1.98 (m, 1H), 1.73 – 1.57 (m, 4H), 1.50 – 1.33 (m, 4H), 1.08 – 1.01 (m, 2H), 0.99 – 0.92 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{45}H_{50}FN_{12}O_6S^+$, 873.3955; found 873.3928.



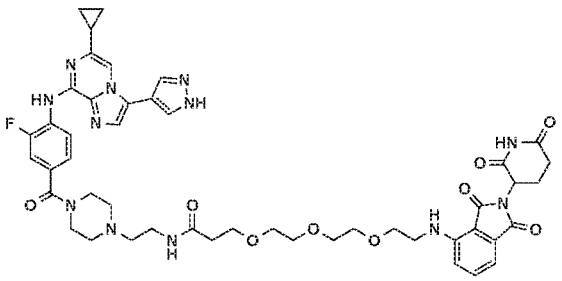
Example 96: *N*-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)ethyl)-8-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)octanamide. 71% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.67 (t, *J* = 8.1 Hz, 1H), 8.01 (s, 2H), 7.80 (s, 1H), 7.76 (s, 1H), 7.54 – 7.46 (m, 1H), 7.41 – 7.31 (m, 2H), 7.04 (t, *J* = 7.9 Hz, 1H), 6.93 (d, *J* = 8.6 Hz, 1H), 4.97 (dd, *J* = 12.1, 5.6 Hz, 1H), 4.17 – 3.66 (m, 4H), 3.59 (t, *J* = 5.6 Hz, 2H), 3.54 – 3.37 (m, 4H), 3.33 – 3.21 (m, 4H), 2.86 – 2.68 (m, 3H), 2.22 (t, *J* = 7.6 Hz, 2H), 2.17 – 2.07 (m, 1H), 2.08 – 1.96 (m, 1H), 1.73 – 1.52 (m, 4H), 1.49 – 1.29 (m, 6H), 1.09 – 1.00 (m, 2H), 1.01 – 0.90 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{46}H_{52}FN_{12}O_6S^+$, 887.4111; found 887.4114.



Example 97: *N*-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)ethyl)-3-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)propenamide. 73% yield. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{43}H_{46}FN_{12}O_7S^+$, 861.3591; found 861.3588.

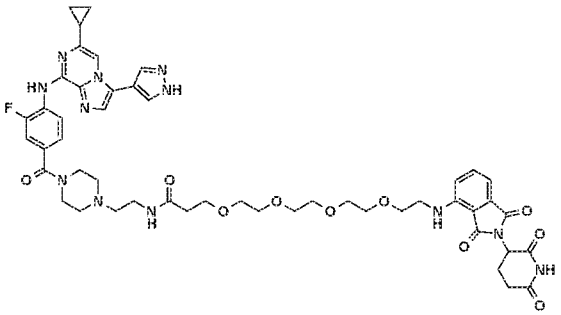


Example 98: *N*-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)ethyl)-3-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)propenamide. 70% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.75 (t, *J* = 8.2 Hz, 1H), 7.98 (s, 2H), 7.76 (s, 1H), 7.67 (s, 1H), 7.54 – 7.46 (m, 1H), 7.41 – 7.25 (m, 2H), 7.05 (d, *J* = 7.0 Hz, 1H), 6.98 (d, *J* = 8.6 Hz, 1H), 4.99 (dd, *J* = 12.3, 5.6 Hz, 1H), 4.21 – 3.83 (m, 4H), 3.77 (t, *J* = 5.8 Hz, 2H), 3.72 (t, *J* = 5.1 Hz, 2H), 3.65 (s, 4H), 3.61 – 3.52 (m, 2H), 3.52 – 3.36 (m, 6H), 3.31 – 3.23 (m, 2H), 2.90 – 2.70 (m, 3H), 2.50 (t, *J* = 5.8 Hz, 2H), 2.18 – 2.09 (m, 1H), 2.01 (ddd, *J* = 12.9, 8.3, 4.2 Hz, 1H), 1.06 – 1.00 (m, 2H), 1.00 – 0.90 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{45}H_{50}FN_{12}O_8S^+$, 905.3853; found 905.3829.

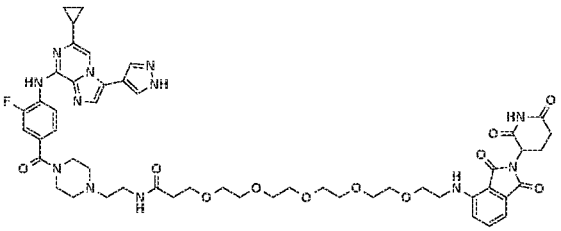


Example 99: *N*-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)ethyl)-3-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethoxy)propenamide. 68% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.72 (t, *J* = 8.1 Hz, 1H), 7.96 (s, 2H), 7.74 (s, 1H), 7.66 (d, *J* = 12.2 Hz, 1H),

7.49 (dd, J = 8.4, 7.2 Hz, 1H), 7.34 (dd, J = 17.0, 5.7 Hz, 2H), 7.05 (d, J = 7.1 Hz, 1H), 6.97 (t, J = 8.8 Hz, 1H), 4.97 (dd, J = 12.3, 5.6 Hz, 1H), 4.12 – 3.80 (m, 4H), 3.79 – 3.69 (m, 4H), 3.69 – 3.53 (m, 10H), 3.53 – 3.35 (m, 6H), 3.31 – 3.27 (m, 2H), 2.85 – 2.69 (m, 3H), 2.48 (t, J = 5.8 Hz, 2H), 2.17 – 2.09 (m, 1H), 2.02 – 1.95 (m, 1H), 1.05 – 0.99 (m, 2H), 0.98 – 0.92 (m, 2H). HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{47}H_{54}FN_{12}O_9S^+$, 949.4115; found 949.4133.



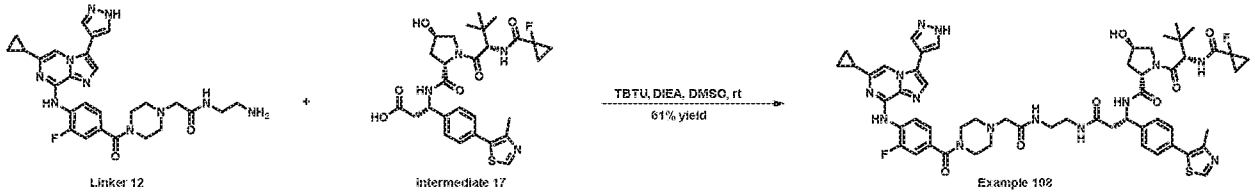
Example 100: *N*-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)ethyl)-1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12-tetraoxapentadecan-15-amide. 66% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.71 (t, J = 8.1 Hz, 1H), 7.99 (s, 2H), 7.78 (s, 1H), 7.72 (s, 1H), 7.54 – 7.44 (m, 1H), 7.36 (dd, J = 17.1, 5.9 Hz, 2H), 7.04 (d, J = 7.1 Hz, 1H), 6.98 (d, J = 8.6 Hz, 1H), 4.98 (dd, J = 12.4, 5.6 Hz, 1H), 4.15 – 3.80 (m, 4H), 3.80 – 3.70 (m, 4H), 3.70 – 3.53 (m, 14H), 3.52 – 3.36 (m, 6H), 3.32 – 3.29 (m, 2H), 2.87 – 2.68 (m, 3H), 2.49 (t, J = 5.8 Hz, 2H), 2.19 – 2.08 (m, 1H), 2.08 – 1.97 (m, 1H), 1.09 – 0.99 (m, 2H), 1.00 – 0.90 (m, 2H). HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{49}H_{58}FN_{12}O_{10}S^+$, 993.4377; found 993.4369.



Example 101: *N*-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)ethyl)-1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12,15-pentaoxaoctadecan-18-amide. 72% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.74 (t, J = 8.1 Hz, 1H), 7.97 (s, 2H), 7.73 (s, 1H), 7.66 (s, 1H), 7.52 – 7.47 (m, 1H), 7.39 – 7.29 (m, 2H), 7.05 (d, J = 7.1 Hz, 1H), 6.98 (d, J = 8.6 Hz, 1H), 4.96 (dd, J = 12.2,

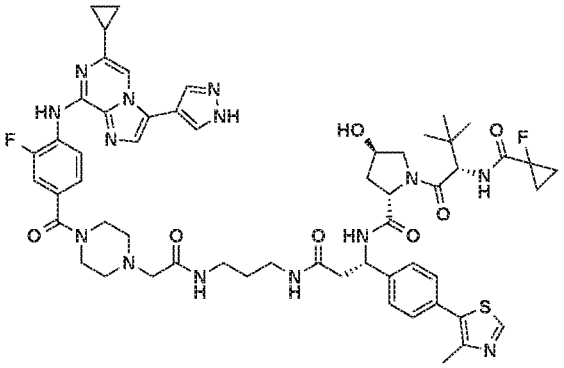
5.6 Hz, 1H), 4.13 – 3.77 (m, 4H), 3.79 – 3.69 (m, 4H), 3.69 – 3.54 (m, 18H), 3.52 – 3.35 (m, 6H), 3.32 – 3.28 (m, 2H), 2.86 – 2.68 (m, 3H), 2.49 (t, J = 5.8 Hz, 2H), 2.13 (dd, J = 9.6, 5.9 Hz, 1H), 2.04 – 1.92 (m, 1H), 1.07 – 1.00 (m, 2H), 1.00 – 0.92 (m, 2H). HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{51}H_{62}FN_{12}O_{11}S^+$, 1037.4640; found 1037.4655.

Scheme 28. Synthesis of example 108

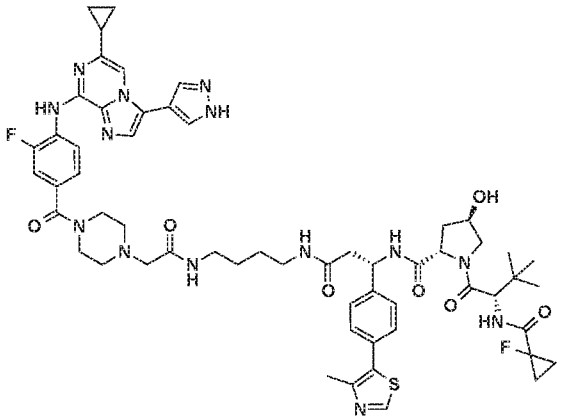


Example 108: (2*S*,4*R*)-*N*-((*S*)-3-((2-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamido)ethyl)amino)-1-(4-(4-methylthiazol-5-yl)phenyl)-3-oxopropyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide. Example **108** was synthesized according to the procedures for the preparation of example **1**. 61% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.99 – 8.92 (m, 1H), 8.75 – 8.65 (m, 1H), 8.16 (s, 2H), 7.97 (s, 1H), 7.91 (s, 1H), 7.55 – 7.36 (m, 6H), 5.43 – 5.29 (m, 1H), 4.77 – 4.66 (m, 1H), 4.64 – 4.55 (m, 1H), 4.53 – 4.45 (m, 1H), 4.10 – 3.91 (m, 6H), 3.87 (d, J = 11.2 Hz, 1H), 3.78 (dd, J = 11.1, 3.5 Hz, 1H), 3.57 – 3.40 (m, 6H), 3.32 – 3.26 (m, 2H), 2.88 – 2.70 (m, 2H), 2.49 (s, 3H), 2.25 (dd, J = 13.1, 7.6 Hz, 1H), 2.17 – 2.07 (m, 1H), 1.97 (ddd, J = 13.5, 9.5, 4.4 Hz, 1H), 1.44 – 1.27 (m, 4H), 1.12 (s, 3H), 1.10 – 1.02 (m, 9H), 0.99 – 0.94 (m, 2H). HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{55}H_{65}F_2N_{14}O_7S^+$, 1103.4844; found 1103.4856.

Example compounds **109 – 129** were synthesized according to the procedures for the preparation of example compound **108**.

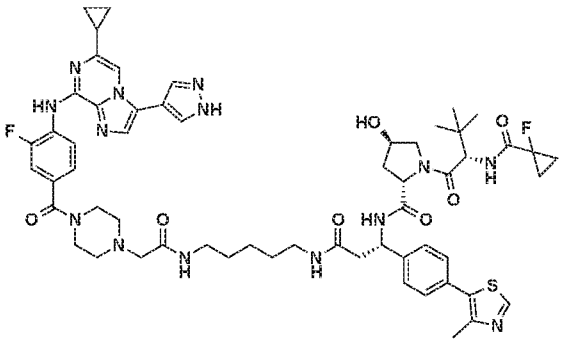


Example 109: (2*S*,4*R*)-*N*-((*S*)-3-((3-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamido)propyl)amino)-1-(4-(4-methylthiazol-5-yl)phenyl)-3-oxopropyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide. 68% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.96 (s, 1H), 8.75 – 8.63 (m, 1H), 8.15 (s, 2H), 7.98 (s, 1H), 7.89 (s, 1H), 7.54 – 7.36 (m, 6H), 5.41 – 5.29 (m, 1H), 4.75 (d, *J* = 9.1 Hz, 1H), 4.66 – 4.53 (m, 1H), 4.47 (s, 1H), 4.13 – 3.89 (m, 6H), 3.85 (d, *J* = 11.2 Hz, 1H), 3.78 (dd, *J* = 11.1, 3.6 Hz, 1H), 3.55 – 3.41 (m, 4H), 3.27 – 3.09 (m, 4H), 2.93 – 2.84 (m, 1H), 2.82 – 2.70 (m, 1H), 2.49 (s, 3H), 2.30 – 2.17 (m, 1H), 2.17 – 2.05 (m, 1H), 2.02 – 1.91 (m, 1H), 1.71 – 1.55 (m, 2H), 1.45 – 1.25 (m, 4H), 1.12 (s, 2H), 1.10 – 1.00 (m, 9H), 0.97 (dd, *J* = 8.1, 2.4 Hz, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{56}H_{67}F_2N_{14}O_7S^+$, 1117.5000; found 1117.4977.

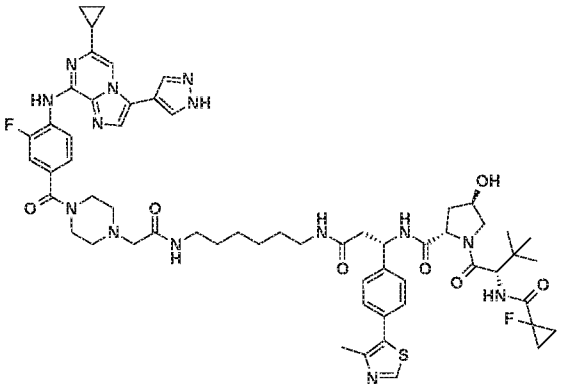


Example 110: (2*S*,4*R*)-*N*-((*S*)-3-((4-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamido)butyl)amino)-1-(4-(4-methylthiazol-5-yl)phenyl)-3-oxopropyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide. 63% yield. ^{1}H NMR (600 MHz,

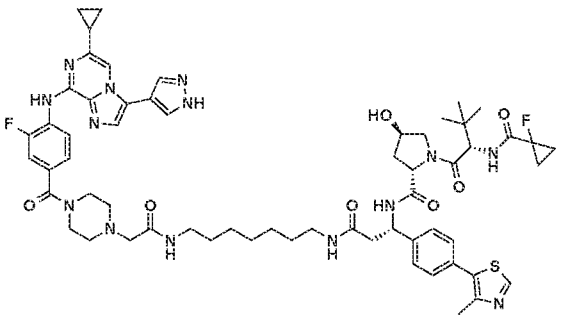
CD_3OD) δ 8.99 – 8.86 (m, 1H), 8.76 – 8.65 (m, 1H), 8.15 (s, 2H), 8.00 – 7.93 (m, 1H), 7.85 (s, 1H), 7.52 – 7.36 (m, 6H), 5.40 – 5.21 (m, 1H), 4.78 – 4.71 (m, 1H), 4.66 – 4.53 (m, 2H), 4.51 – 4.37 (m, 1H), 4.16 – 3.87 (m, 6H), 3.85 (d, J = 11.3 Hz, 1H), 3.80 – 3.73 (m, 1H), 3.58 – 3.37 (m, 4H), 3.29 – 3.18 (m, 2H), 3.18 – 3.09 (m, 2H), 2.89 – 2.66 (m, 2H), 2.49 (s, 3H), 2.28 – 2.18 (m, 1H), 2.16 – 2.05 (m, 1H), 2.02 – 1.90 (m, 1H), 1.55 – 1.25 (m, 8H), 1.13 (s, 3H), 1.10 – 1.01 (m, 8H), 0.99 – 0.93 (m, 2H). HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{57}H_{69}F_2N_{14}O_7S^+$, 1131.5157; found 1131.5131.



Example 111: (2*S*,4*R*)-*N*-((*S*)-3-((5-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamido)pentyl)amino)-1-(4-(4-methylthiazol-5-yl)phenyl)-3-oxopropyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide. 59% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 8.92 (s, 1H), 8.72 (t, J = 8.3 Hz, 1H), 8.15 (s, 2H), 7.95 (s, 1H), 7.84 (s, 1H), 7.53 – 7.36 (m, 6H), 5.42 – 5.23 (m, 1H), 4.75 (d, J = 9.2 Hz, 1H), 4.67 – 4.53 (m, 2H), 4.52 – 4.42 (m, 1H), 4.17 – 3.89 (m, 6H), 3.86 (d, J = 11.1 Hz, 1H), 3.80 – 3.73 (m, 1H), 3.58 – 3.38 (m, 4H), 3.28 – 3.04 (m, 4H), 2.89 – 2.66 (m, 2H), 2.48 (s, 3H), 2.28 – 2.17 (m, 1H), 2.15 – 2.06 (m, 1H), 2.04 – 1.91 (m, 1H), 1.57 – 1.19 (m, 10H), 1.13 (s, 3H), 1.10 – 1.00 (m, 8H), 1.00 – 0.93 (m, 2H). HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{58}H_{71}F_2N_{14}O_7S^+$, 1145.5313; found 1145.5335.

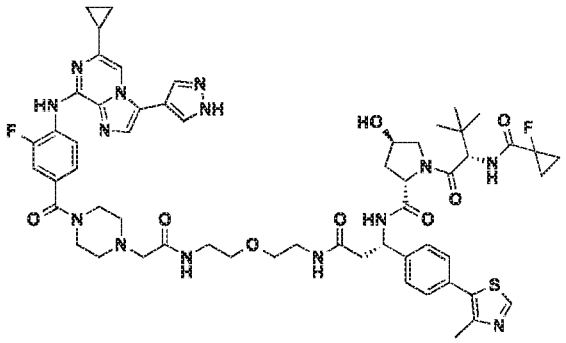


Example 112: (2*S*,4*R*)-*N*-((*S*)-3-((6-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamido)hexyl)amino)-1-(4-(4-methylthiazol-5-yl)phenyl)-3-oxopropyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide. 70% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 8.93 (s, 1H), 8.76 – 8.70 (m, 1H), 8.15 (s, 2H), 7.96 (d, *J* = 1.6 Hz, 1H), 7.84 (s, 1H), 7.52 – 7.37 (m, 6H), 5.38 – 5.24 (m, 1H), 4.76 (d, *J* = 8.9 Hz, 1H), 4.66 – 4.53 (m, 2H), 4.51 – 4.38 (m, 1H), 4.15 – 3.88 (m, 6H), 3.85 (d, *J* = 11.2 Hz, 1H), 3.78 (dd, *J* = 11.1, 3.6 Hz, 1H), 3.57 – 3.39 (m, 4H), 3.27 – 3.04 (m, 4H), 2.91 – 2.67 (m, 2H), 2.49 (d, *J* = 2.2 Hz, 3H), 2.28 – 2.17 (m, 1H), 2.17 – 2.06 (m, 1H), 2.05 – 1.94 (m, 1H), 1.57 – 1.16 (m, 12H), 1.13 (s, 2H), 1.10 – 1.01 (m, 9H), 0.98 – 0.93 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{59}H_{73}F_2N_{14}O_7S^+$, 1159.5470; found 1159.5439.

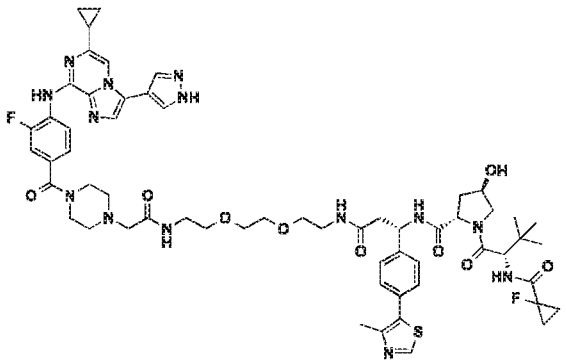


Example 113: (2*S*,4*R*)-*N*-((*S*)-3-((7-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamido)heptyl)amino)-1-(4-(4-methylthiazol-5-yl)phenyl)-3-oxopropyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide. 60% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 8.96 – 8.88 (m, 1H), 8.79 – 8.69 (m, 1H), 8.15 (s, 2H), 7.96 (s, 1H), 7.82 (s, 1H), 7.52 – 7.31 (m, 6H), 5.41 – 5.22 (m, 1H), 4.76 (d, *J* = 9.1 Hz, 1H), 4.67 – 4.52 (m, 2H), 4.48 (d, *J* =

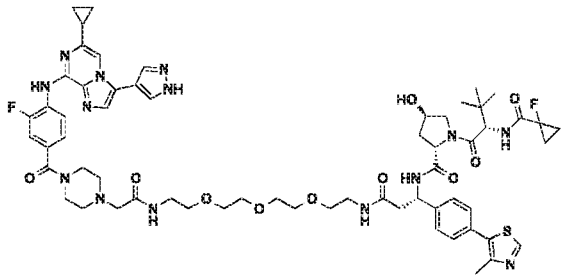
13.4 Hz, 1H), 4.16 – 3.88 (m, 6H), 3.85 (d, J = 11.1 Hz, 1H), 3.82 – 3.71 (m, 1H), 3.57 – 3.38 (m, 4H), 3.29 – 3.00 (m, 4H), 2.88 – 2.66 (m, 2H), 2.49 (s, 3H), 2.28 – 2.17 (m, 1H), 2.17 – 2.06 (m, 1H), 2.02 – 1.91 (m, 1H), 1.56 – 1.15 (m, 14H), 1.13 (s, 2H), 1.09 – 1.01 (m, 9H), 0.99 – 0.93 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{60}H_{75}F_2N_{14}O_7S^+$, 1173.5626; found 1173.5644.



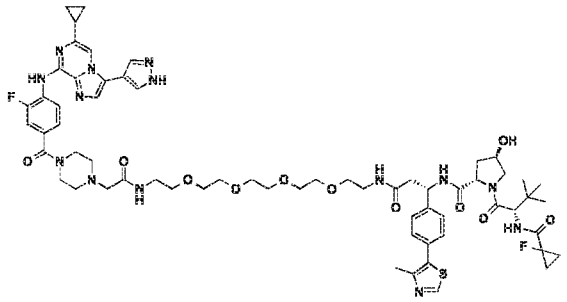
Example 114: (2*S*,4*R*)-*N*-((*S*)-3-((2-(2-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamido)ethoxy)ethyl)amino)-1-(4-(4-methylthiazol-5-yl)phenyl)-3-oxopropyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide. 66% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 8.93 – 8.87 (m, 1H), 8.77 – 8.66 (m, 1H), 8.16 (s, 2H), 7.97 (s, 1H), 7.85 (d, J = 2.8 Hz, 1H), 7.53 – 7.35 (m, 6H), 5.43 – 5.33 (m, 1H), 4.76 (d, J = 9.0 Hz, 1H), 4.65 – 4.56 (m, 2H), 4.52 – 4.45 (m, 1H), 4.12 – 3.89 (m, 6H), 3.87 (d, J = 11.3 Hz, 1H), 3.78 (dd, J = 11.1, 3.6 Hz, 1H), 3.62 – 3.36 (m, 12H), 2.93 – 2.82 (m, 1H), 2.82 – 2.72 (m, 1H), 2.48 (s, 3H), 2.30 – 2.20 (m, 1H), 2.17 – 2.08 (m, 1H), 2.02 – 1.94 (m, 1H), 1.46 – 1.26 (m, 4H), 1.14 (s, 2H), 1.09 – 1.02 (m, 9H), 0.99 – 0.94 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{57}H_{69}F_2N_{14}O_8S^+$, 1147.5106; found 1147.5124.



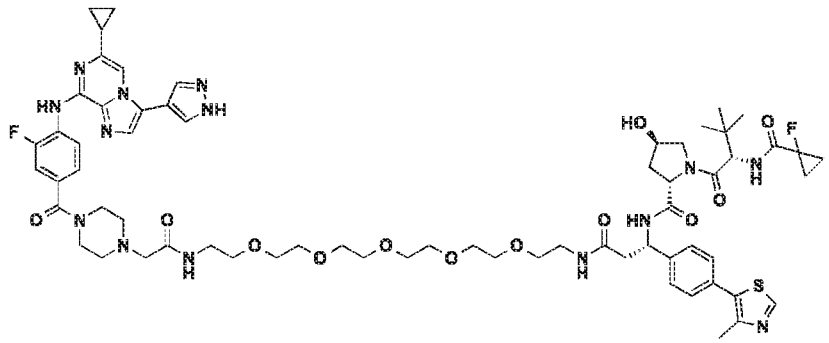
Example 115: (2*S*,4*R*)-*N*-((*S*)-1-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-15-(4-(4-methylthiazol-5-yl)phenyl)-2,13-dioxo-6,9-dioxa-3,12-diazapentadecan-15-yl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide. 65% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 8.91 – 8.88 (m, 1H), 8.76 – 8.68 (m, 1H), 8.15 (s, 2H), 7.96 (s, 1H), 7.84 (s, 1H), 7.53 – 7.37 (m, 6H), 5.45 – 5.32 (m, 1H), 4.75 (d, *J* = 9.0 Hz, 1H), 4.63 – 4.54 (m, 2H), 4.51 – 4.42 (m, 1H), 4.12 – 3.88 (m, 6H), 3.85 (d, *J* = 11.2 Hz, 1H), 3.78 (dd, *J* = 10.9, 3.5 Hz, 1H), 3.65 – 3.54 (m, 7H), 3.54 – 3.39 (m, 9H), 2.91 – 2.70 (m, 2H), 2.48 (s, 3H), 2.28 – 2.18 (m, 1H), 2.16 – 2.06 (m, 1H), 2.03 – 1.93 (m, 1H), 1.42 – 1.26 (m, 4H), 1.13 (s, 2H), 1.10 – 1.01 (m, 9H), 0.99 – 0.92 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{59}H_{73}F_2N_{14}O_9S^+$, 1191.5368; found 1191.5355.



Example 116: (2*S*,4*R*)-*N*-((*S*)-1-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-18-(4-(4-methylthiazol-5-yl)phenyl)-2,16-dioxo-6,9,12-trioxa-3,15-diazaoctadecan-18-yl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide. 63% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 8.94 (s, 1H), 8.68 (t, *J* = 8.1 Hz, 1H), 8.17 (s, 2H), 7.99 (s, 1H), 7.91 (s, 1H), 7.48 – 7.38 (m, 6H), 5.41 – 5.31 (m, 1H), 4.76 (d, *J* = 8.7 Hz, 1H), 4.62 – 4.48 (m, 2H), 4.47 – 4.38 (m, 1H), 4.12 – 3.88 (m, 6H), 3.85 (d, *J* = 11.2 Hz, 1H), 3.80 – 3.72 (m, 1H), 3.69 – 3.54 (m, 11H), 3.54 – 3.39 (m, 9H), 2.90 – 2.70 (m, 2H), 2.49 (s, 3H), 2.29 – 2.18 (m, 1H), 2.18 – 2.07 (m, 1H), 2.01 – 1.94 (m, 1H), 1.43 – 1.27 (m, 6H), 1.15 – 1.11 (m, 2H), 1.10 – 1.02 (m, 9H), 0.99 – 0.95 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{61}H_{77}F_2N_{14}O_{10}S^+$, 1235.5630; found 1235.5641.

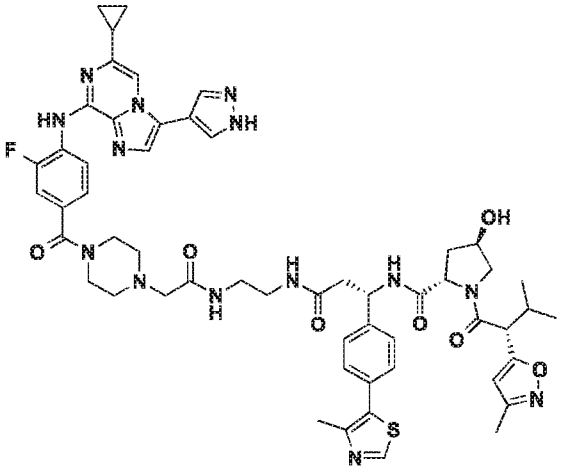


Example 117: (2*S*,4*R*)-*N*-((*S*)-1-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-21-(4-(4-methylthiazol-5-yl)phenyl)-2,19-dioxo-6,9,12,15-tetraoxa-3,18-diazahenicosan-21-yl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide. 61% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 8.91 (s, 1H), 8.77 – 8.71 (m, 1H), 8.15 (s, 2H), 7.96 (s, 1H), 7.83 (s, 1H), 7.48 – 7.38 (m, 6H), 5.40 – 5.30 (m, 1H), 4.76 (d, J = 9.0 Hz, 1H), 4.63 – 4.49 (m, 2H), 4.47 – 4.38 (m, 1H), 4.13 – 3.88 (m, 6H), 3.85 (d, J = 11.2 Hz, 1H), 3.78 (dd, J = 11.2, 3.8 Hz, 1H), 3.68 – 3.52 (m, 16H), 3.52 – 3.38 (m, 8H), 2.90 – 2.68 (m, 2H), 2.49 (s, 3H), 2.30 – 2.20 (m, 1H), 2.18 – 2.07 (m, 1H), 2.06 – 1.91 (m, 1H), 1.44 – 1.25 (m, 4H), 1.13 (s, 2H), 1.10 – 1.01 (m, 9H), 0.99 – 0.93 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{63}H_{81}F_2N_{14}O_{11}S^+$, 1279.5893; found 1279.5870.

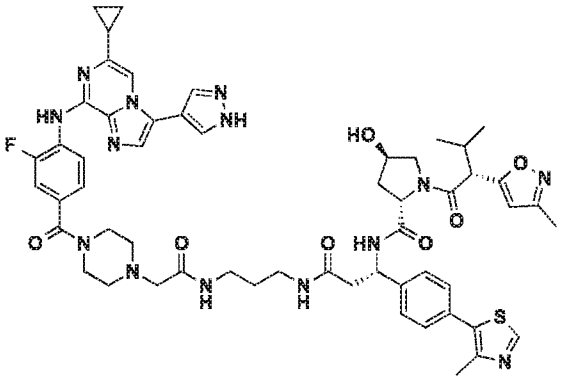


Example 118: (2*S*,4*R*)-*N*-((*S*)-1-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-24-(4-(4-methylthiazol-5-yl)phenyl)-2,22-dioxo-6,9,12,15,18-pentaoxa-3,21-diazatetracosan-24-yl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide. 60% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 8.93 (s, 1H), 8.76 – 8.67 (m, 1H), 8.15 (s, 2H), 7.97 (s, 1H), 7.85 (s, 1H), 7.49 – 7.38 (m, 6H), 5.42 – 5.30 (m, 1H), 4.76 (d, J = 9.2 Hz, 1H), 4.66 – 4.48 (m, 2H), 4.48 – 4.39 (m, 1H), 4.14 – 3.89 (m, 6H), 3.85 (d, J = 11.3 Hz, 1H), 3.81

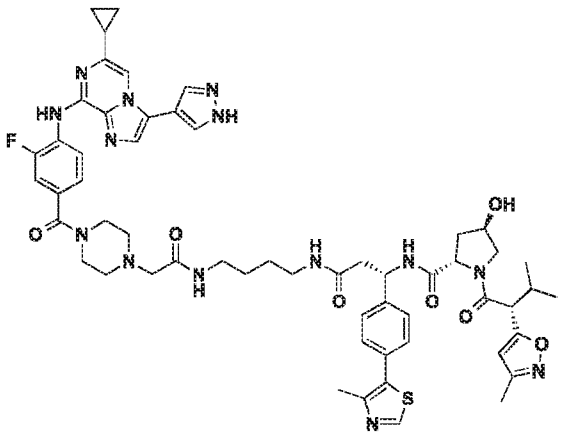
– 3.72 (m, 1H), 3.67 – 3.52 (m, 22H), 3.52 – 3.36 (m, 6H), 2.90 – 2.69 (m, 2H), 2.49 (s, 3H), 2.28 – 2.19 (m, 1H), 2.15 – 2.07 (m, 1H), 2.06 – 1.93 (m, 1H), 1.35 (ddt, *J* = 19.9, 15.9, 6.4 Hz, 4H), 1.13 (s, 2H), 1.10 – 1.01 (m, 9H), 0.98 – 0.93 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{65}H_{85}F_2N_{14}O_{12}S^+$, 1323.6155; found 1323.6170.



Example 119: (2*S*,4*R*)-*N*-((*S*)-3-((2-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamido)ethyl)amino)-1-(4-(4-methylthiazol-5-yl)phenyl)-3-oxopropyl)-4-hydroxy-1-((*R*)-3-methyl-2-(3-methylisoxazol-5-yl)butanoyl)pyrrolidine-2-carboxamide. 68% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.93 (s, 1H), 8.74 – 8.59 (m, 1H), 8.15 (s, 2H), 7.94 (s, 1H), 7.86 (s, 1H), 7.48 – 7.36 (m, 6H), 6.28 (s, 1H), 5.40 – 5.24 (m, 1H), 4.62 – 4.57 (m, 1H), 4.56 – 4.51 (m, 1H), 4.47 (s, 1H), 4.16 – 3.91 (m, 5H), 3.89 – 3.77 (m, 2H), 3.72 – 3.64 (m, 1H), 3.64 – 3.41 (m, 6H), 3.19 – 3.05 (m, 1H), 2.84 – 2.61 (m, 2H), 2.46 (s, 3H), 2.27 (s, 3H), 2.15 – 2.05 (m, 1H), 2.00 – 1.89 (m, 1H), 1.12 – 1.05 (m, 3H), 1.05 – 0.90 (m, 4H), 0.90 – 0.84 (m, 3H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{54}H_{62}FN_{14}O_7S^+$, 1069.4625; found 1069.4635.

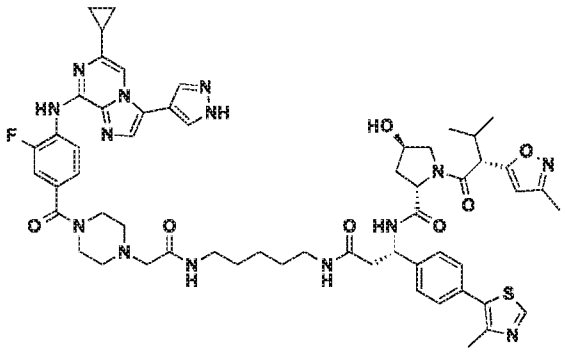


Example 120: (2*S*,4*R*)-*N*-((*S*)-3-((3-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamido)propyl)amino)-1-(4-(4-methylthiazol-5-yl)phenyl)-3-oxopropyl)-4-hydroxy-1-((*R*)-3-methyl-2-(3-methylisoxazol-5-yl)butanoyl)pyrrolidine-2-carboxamide. 60% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 8.99 – 8.93 (m, 1H), 8.72 – 8.66 (m, 1H), 8.16 (s, 2H), 7.99 (d, *J* = 2.7 Hz, 1H), 7.91 (s, 1H), 7.53 – 7.36 (m, 6H), 6.26 (d, *J* = 10.3 Hz, 1H), 5.40 – 5.27 (m, 1H), 4.62 – 4.49 (m, 1H), 4.45 (s, 1H), 4.10 – 3.61 (m, 9H), 3.57 – 3.40 (m, 4H), 3.27 – 3.13 (m, 4H), 2.91 – 2.71 (m, 2H), 2.49 (d, *J* = 5.3 Hz, 3H), 2.46 – 2.36 (m, 1H), 2.31 – 2.23 (m, 3H), 2.17 – 2.10 (m, 1H), 2.02 – 1.91 (m, 1H), 1.73 – 1.61 (m, 2H), 1.12 – 1.02 (m, 5H), 1.00 – 0.95 (m, 2H), 0.91 – 0.85 (m, 3H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{55}H_{64}FN_{14}O_7S^+$, 1083.4782; found 1083.4781.

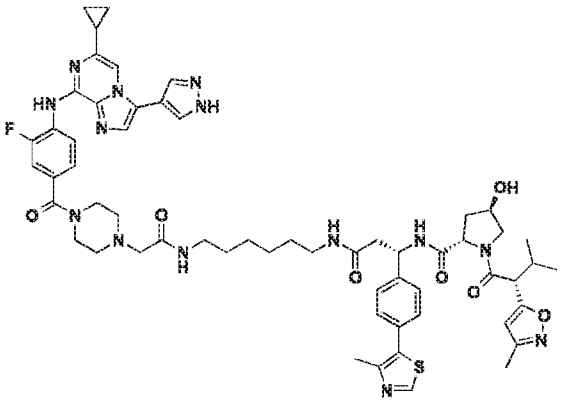


Example 121: (2*S*,4*R*)-*N*-((*S*)-3-((4-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamido)butyl)amino)-1-(4-(4-methylthiazol-5-yl)phenyl)-3-oxopropyl)-4-hydroxy-1-((*R*)-3-methyl-2-(3-methylisoxazol-5-yl)butanoyl)pyrrolidine-2-carboxamide. 59% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 8.91 (d, *J* = 16.4 Hz, 1H), 8.78 – 8.68 (m, 1H), 8.15 (s, 2H), 7.97 – 7.92 (m, 1H), 7.83 (s, 1H), 7.49 – 7.34

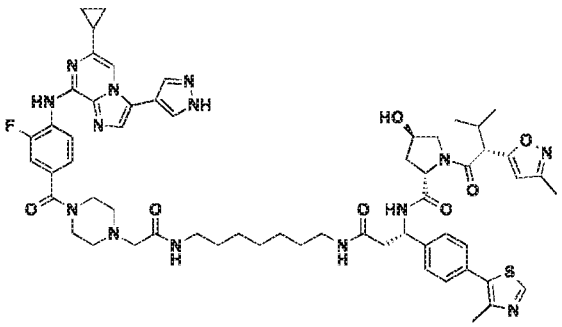
(m, 6H), 6.25 (d, J = 12.4 Hz, 1H), 5.39 – 5.25 (m, 1H), 4.61 – 4.48 (m, 1H), 4.45 (s, 1H), 4.18 – 3.57 (m, 9H), 3.57 – 3.40 (m, 4H), 3.28 – 3.07 (m, 4H), 2.87 – 2.65 (m, 2H), 2.47 (d, J = 11.2 Hz, 3H), 2.46 – 2.38 (m, 1H), 2.26 (d, J = 16.8 Hz, 3H), 2.15 – 2.08 (m, 1H), 2.01 – 1.94 (m, 1H), 1.56 – 1.42 (m, 4H), 1.12 – 0.99 (m, 5H), 0.99 – 0.92 (m, 2H), 0.88 (dd, J = 13.1, 6.7 Hz, 3H). HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{56}H_{66}FN_{14}O_7S^+$, 1097.4938; found 1097.4928.



Example 122: (2*S*,4*R*)-*N*-((*S*)-3-((5-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamido)pentyl)amino)-1-(4-(4-methylthiazol-5-yl)phenyl)-3-oxopropyl)-4-hydroxy-1-((*R*)-3-methyl-2-(3-methylisoxazol-5-yl)butanoyl)pyrrolidine-2-carboxamide. 70% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 8.92 – 8.86 (m, 1H), 8.78 – 8.69 (m, 1H), 8.15 (s, 2H), 7.94 (d, J = 3.4 Hz, 1H), 7.82 (s, 1H), 7.50 – 7.34 (m, 6H), 6.26 (d, J = 27.8 Hz, 1H), 5.37 – 5.27 (m, 1H), 4.60 – 4.48 (m, 1H), 4.46 (s, 1H), 4.09 – 3.56 (m, 9H), 3.55 – 3.41 (m, 4H), 3.28 – 3.02 (m, 4H), 2.87 – 2.65 (m, 2H), 2.47 (d, J = 10.7 Hz, 3H), 2.45 – 2.38 (m, 1H), 2.26 (d, J = 11.4 Hz, 3H), 2.18 – 2.09 (m, 1H), 2.02 – 1.93 (m, 1H), 1.61 – 1.23 (m, 6H), 1.10 – 1.06 (m, 3H), 1.05 – 0.99 (m, 2H), 0.99 – 0.92 (m, 2H), 0.91 – 0.85 (m, 3H). HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{57}H_{68}FN_{14}O_7S^+$, 1111.5095; found 1111.5078.

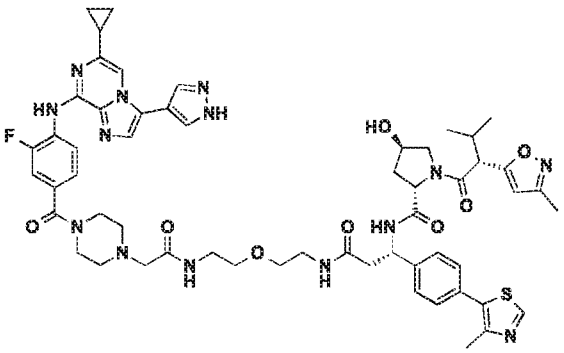


Example 123: (2*S*,4*R*)-*N*-((*S*)-3-((6-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamido)hexyl)amino)-1-(4-(4-methylthiazol-5-yl)phenyl)-3-oxopropyl)-4-hydroxy-1-((*R*)-3-methyl-2-(3-methylisoxazol-5-yl)butanoyl)pyrrolidine-2-carboxamide. 73% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 8.95 – 8.86 (m, 1H), 8.78 – 8.69 (m, 1H), 8.14 (s, 2H), 7.94 (d, *J* = 2.2 Hz, 1H), 7.80 (s, 1H), 7.49 – 7.37 (m, 6H), 6.25 (d, *J* = 21.7 Hz, 1H), 5.38 – 5.25 (m, 1H), 4.62 – 4.48 (m, 1H), 4.46 (s, 1H), 4.11 – 3.56 (m, 9H), 3.55 – 3.38 (m, 4H), 3.24 (dd, *J* = 16.7, 9.9 Hz, 2H), 3.18 – 3.06 (m, 2H), 2.91 – 2.68 (m, 2H), 2.52 – 2.46 (m, 3H), 2.46 – 2.36 (m, 1H), 2.30 – 2.23 (m, 3H), 2.21 – 2.06 (m, 1H), 2.01 – 1.92 (m, 1H), 1.52 – 1.45 (m, 2H), 1.45 – 1.35 (m, 2H), 1.35 – 1.28 (m, 2H), 1.28 – 1.18 (m, 2H), 1.11 – 1.00 (m, 5H), 0.99 – 0.92 (m, 2H), 0.92 – 0.85 (m, 3H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{58}H_{70}FN_{14}O_7S^+$, 1125.5251; found 1125.5270.

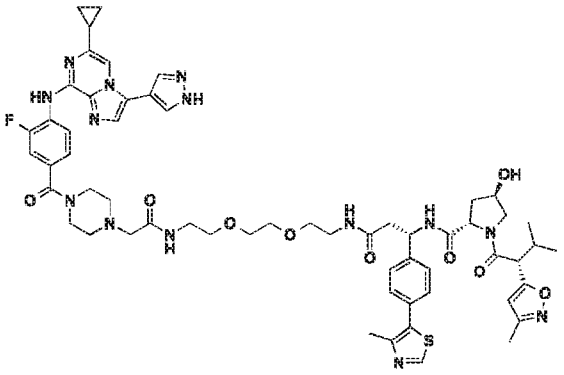


Example 124: (2*S*,4*R*)-*N*-((*S*)-3-((7-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamido)heptyl)amino)-1-(4-(4-methylthiazol-5-yl)phenyl)-3-oxopropyl)-4-hydroxy-1-((*R*)-3-methyl-2-(3-methylisoxazol-5-yl)butanoyl)pyrrolidine-2-carboxamide. 63% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 8.97 – 8.86 (m, 1H), 8.77 – 8.66 (m, 1H), 8.15 (s, 2H), 7.97 (d, *J* = 3.1 Hz, 1H), 7.86 (s, 1H), 7.51 – 7.36 (m, 6H), 6.26 (d, *J* = 24.9 Hz, 1H), 5.38 – 5.27 (m, 1H), 4.60 – 4.48 (m, 1H), 4.46 (s, 1H), 4.13 – 3.57

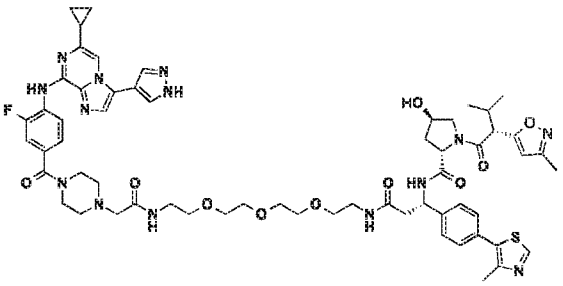
(m, 9H), 3.57 – 3.40 (m, 4H), 3.27 – 3.18 (m, 2H), 3.18 – 3.04 (m, 2H), 2.88 – 2.68 (m, 2H), 2.49 (d, J = 9.4 Hz, 3H), 2.46 – 2.34 (m, 1H), 2.26 (d, J = 12.3 Hz, 3H), 2.22 – 2.09 (m, 1H), 2.02 – 1.91 (m, 1H), 1.55 – 1.44 (m, 2H), 1.44 – 1.34 (m, 2H), 1.34 – 1.25 (m, 4H), 1.25 – 1.16 (m, 2H), 1.10 – 1.01 (m, 5H), 0.99 – 0.93 (m, 2H), 0.93 – 0.85 (m, 3H). HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{59}H_{72}FN_{14}O_7S^+$, 1139.5408; found 1139.5411.



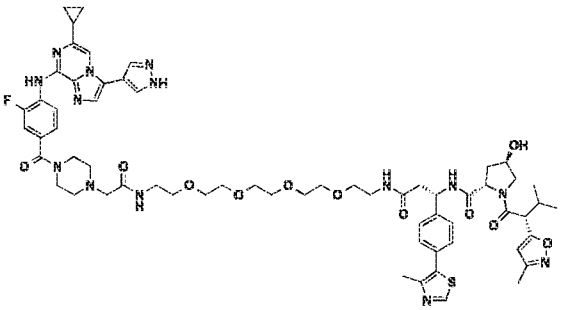
Example 125: (2*S*,4*R*)-*N*-((*S*)-3-((2-(2-(2-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamido)ethoxy)ethyl)amino)-1-(4-(4-methylthiazol-5-yl)phenyl)-3-oxopropyl)-4-hydroxy-1-((*R*)-3-methyl-2-(3-methylisoxazol-5-yl)butanoyl)pyrrolidine-2-carboxamide. 65% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 8.89 – 8.81 (m, 1H), 8.78 – 8.66 (m, 1H), 8.15 (d, J = 1.9 Hz, 2H), 7.95 (d, J = 3.1 Hz, 1H), 7.82 (s, 1H), 7.50 – 7.32 (m, 6H), 6.26 (d, J = 31.5 Hz, 1H), 5.40 – 5.28 (m, 1H), 4.62 – 4.49 (m, 1H), 4.47 (s, 1H), 4.12 – 3.67 (m, 9H), 3.67 – 3.38 (m, 12H), 2.92 – 2.70 (m, 2H), 2.48 – 2.37 (m, 4H), 2.29 – 2.23 (m, 3H), 2.15 – 2.06 (m, 1H), 2.03 – 1.94 (m, 1H), 1.11 – 0.99 (m, 5H), 0.99 – 0.92 (m, 2H), 0.89 (dd, J = 20.6, 6.7 Hz, 3H). HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{56}H_{66}FN_{14}O_8S^+$, 1113.4887; found 1113.4899.



Example 126: (2*S*,4*R*)-*N*-((*S*)-1-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-15-(4-(4-methylthiazol-5-yl)phenyl)-2,13-dioxo-6,9-dioxa-3,12-diazapentadecan-15-yl)-4-hydroxy-1-((*R*)-3-methyl-2-(3-methylisoxazol-5-yl)butanoyl)pyrrolidine-2-carboxamide. 60% yield. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{58}H_{70}FN_{14}O_9S^+$, 1157.5149; found 1157.5177.

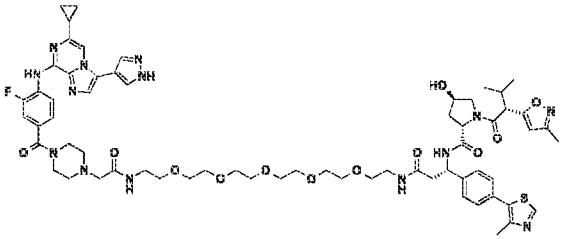


Example 127: (2*S*,4*R*)-*N*-((*S*)-1-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-18-(4-(4-methylthiazol-5-yl)phenyl)-2,16-dioxo-6,9,12-trioxa-3,15-diazaoctadecan-18-yl)-4-hydroxy-1-((*R*)-3-methyl-2-(3-methylisoxazol-5-yl)butanoyl)pyrrolidine-2-carboxamide. 63% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 8.89 (d, *J* = 15.4 Hz, 1H), 8.75 – 8.65 (m, 1H), 8.15 (s, 2H), 7.96 (d, *J* = 2.5 Hz, 1H), 7.85 (s, 1H), 7.52 – 7.34 (m, 6H), 6.32 – 6.21 (m, 1H), 5.41 – 5.30 (m, 1H), 4.61 – 4.48 (m, 1H), 4.46 (s, 1H), 4.12 – 3.68 (m, 9H), 3.68 – 3.54 (m, 8H), 3.54 – 3.41 (m, 8H), 2.90 – 2.71 (m, 2H), 2.53 – 2.45 (m, 3H), 2.45 – 2.37 (m, 1H), 2.31 – 2.22 (m, 3H), 2.16 – 2.09 (m, 1H), 2.02 – 1.94 (m, 1H), 1.12 – 0.99 (m, 5H), 0.99 – 0.93 (m, 2H), 0.93 – 0.84 (m, 3H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{60}H_{74}FN_{14}O_{10}S^+$, 1201.5412; found 1201.5431.



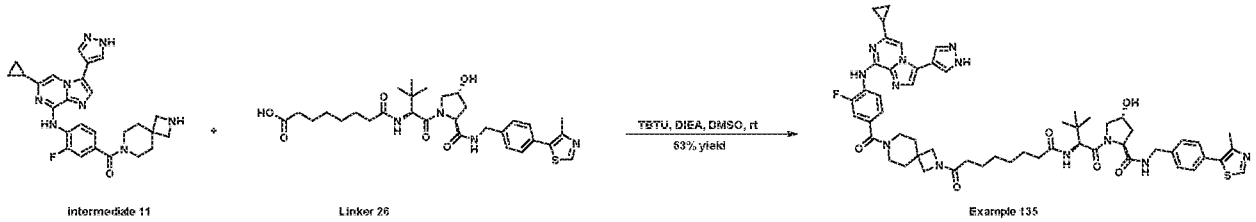
Example 128: (2*S*,4*R*)-*N*-((*S*)-1-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-21-(4-(4-methylthiazol-5-yl)phenyl)-2,19-dioxo-6,9,12,15-tetraoxa-3,18-diazahenicosan-21-yl)-4-hydroxy-1-((*R*)-3-methyl-2-(3-

methylisoxazol-5-yl)butanoyl)pyrrolidine-2-carboxamide. 60% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 8.95 – 8.88 (m, 1H), 8.76 – 8.65 (m, 1H), 8.16 (s, 2H), 7.97 (d, *J* = 4.0 Hz, 1H), 7.87 (s, 1H), 7.52 – 7.31 (m, 6H), 6.25 (d, *J* = 22.2 Hz, 1H), 5.40 – 5.27 (m, 1H), 4.60 – 4.48 (m, 1H), 4.46 (s, 1H), 4.11 – 3.69 (m, 9H), 3.68 – 3.55 (m, 12H), 3.55 – 3.43 (m, 8H), 2.90 – 2.72 (m, 2H), 2.54 – 2.45 (m, 3H), 2.45 – 2.35 (m, 1H), 2.33 – 2.22 (m, 3H), 2.18 – 2.09 (m, 1H), 2.03 – 1.90 (m, 1H), 1.15 – 1.00 (m, 5H), 1.00 – 0.92 (m, 2H), 0.92 – 0.84 (m, 3H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{62}H_{78}FN_{14}O_{11}S^+$, 1245.5674; found 1245.5677.



Example 129: (2*S*,4*R*)-*N*-((*S*)-1-(4-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-24-(4-(4-methylthiazol-5-yl)phenyl)-2,22-dioxo-6,9,12,15,18-pentaoxa-3,21-diazatetracosan-24-yl)-4-hydroxy-1-((*R*)-3-methyl-2-(3-methylisoxazol-5-yl)butanoyl)pyrrolidine-2-carboxamide. 67% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 8.94 – 8.87 (m, 1H), 8.77 – 8.68 (m, 1H), 8.16 (s, 2H), 7.96 (d, *J* = 3.3 Hz, 1H), 7.85 (d, *J* = 2.1 Hz, 1H), 7.51 – 7.34 (m, 6H), 6.26 (d, *J* = 22.2 Hz, 1H), 5.39 – 5.27 (m, 1H), 4.60 – 4.48 (m, 1H), 4.46 (s, 1H), 4.12 – 3.68 (m, 9H), 3.68 – 3.53 (m, 16H), 3.53 – 3.41 (m, 8H), 2.92 – 2.70 (m, 2H), 2.52 – 2.46 (m, 3H), 2.46 – 2.35 (m, 1H), 2.31 – 2.23 (m, 3H), 2.23 – 2.09 (m, 1H), 2.03 – 1.92 (m, 1H), 1.12 – 1.00 (m, 5H), 1.00 – 0.93 (m, 2H), 0.93 – 0.84 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{64}H_{82}FN_{14}O_{12}S^+$, 1289.5636; found 1289.5661.

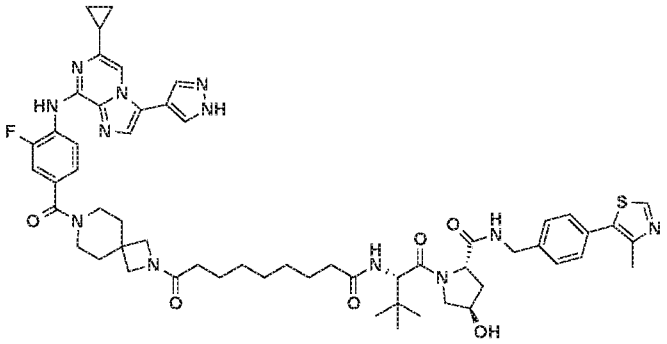
Scheme 29. Synthesis of example 135



Example 135: (2*S*,4*R*)-1-((*S*)-2-(8-(7-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)-2,7-diazaspiro[3.5]nonan-2-yl)-8-oxooctanamido)-

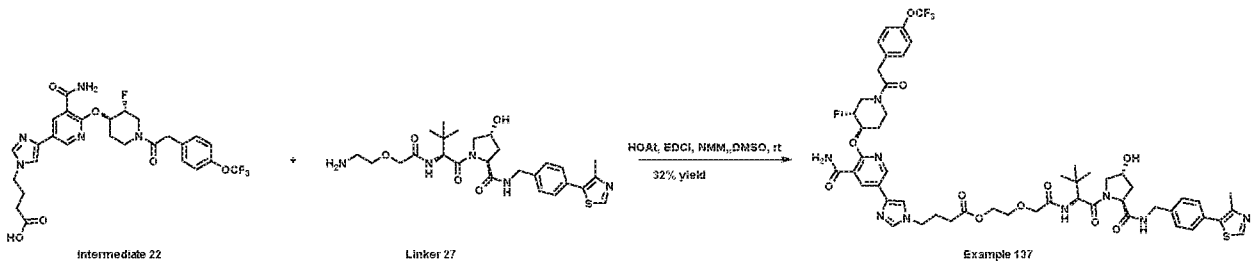
3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. Example **135** was synthesized according to the procedures for the preparation of example **1**. 63% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 9.03 (s, 1H), 8.58 (t, *J* = 8.1 Hz, 1H), 8.18 (s, 2H), 8.02 (s, 1H), 7.98 (s, 1H), 7.49 (d, *J* = 8.1 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 11.3 Hz, 1H), 7.34 (d, *J* = 8.4 Hz, 1H), 4.66 (s, 1H), 4.63 – 4.49 (m, 3H), 4.38 (d, *J* = 15.5 Hz, 1H), 4.06 – 3.96 (m, 2H), 3.92 (d, *J* = 10.9 Hz, 1H), 3.82 (dd, *J* = 10.9, 3.8 Hz, 1H), 3.80 – 3.67 (m, 4H), 3.62 – 3.42 (m, 2H), 2.50 (s, 3H), 2.36 – 2.20 (m, 3H), 2.20 – 2.13 (m, 3H), 2.13 – 2.07 (m, 1H), 1.97 – 1.75 (m, 4H), 1.69 – 1.57 (m, 4H), 1.43 – 1.33 (m, 4H), 1.11 – 1.03 (m, 11H), 1.01 – 0.97 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{56}H_{67}FN_{12}O_6S^+$, 1055.5084; found 1055.5099.

Example compound **136** was synthesized according to the procedures for the preparation of example compound **135**.



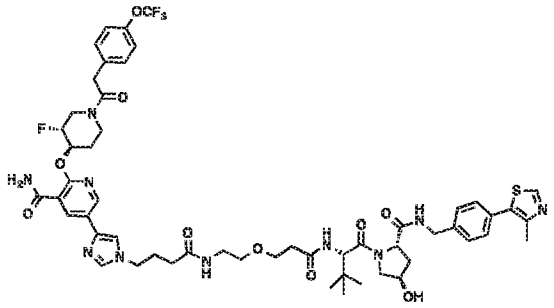
Example 136: (2*S*,4*R*)-1-((*S*)-2-(9-(7-(4-((6-Cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)-2,7-diazaspiro[3.5]nonan-2-yl)-9-oxononanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide. 66% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 9.00 (s, 1H), 8.61 (t, *J* = 8.2 Hz, 1H), 8.17 (s, 2H), 8.01 (s, 1H), 7.96 (s, 1H), 7.49 (d, *J* = 8.2 Hz, 2H), 7.44 (d, *J* = 8.3 Hz, 2H), 7.39 (dd, *J* = 11.2, 1.8 Hz, 1H), 7.34 (d, *J* = 9.7 Hz, 1H), 4.66 (s, 1H), 4.61 – 4.50 (m, 3H), 4.38 (d, *J* = 15.5 Hz, 1H), 4.05 – 3.96 (m, 2H), 3.92 (d, *J* = 11.2 Hz, 1H), 3.82 (dd, *J* = 10.9, 3.9 Hz, 1H), 3.80 – 3.63 (m, 4H), 3.62 – 3.43 (m, 2H), 2.50 (s, 3H), 2.35 – 2.21 (m, 3H), 2.20 – 2.12 (m, 3H), 2.12 – 2.07 (m, 1H), 1.97 – 1.75 (m, 4H), 1.68 – 1.57 (m, 4H), 1.41 – 1.31 (m, 6H), 1.09 – 1.04 (m, 11H), 1.01 – 0.96 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{57}H_{67}FN_{12}O_6S^+$, 1055.5084; found 1055.5099.

Scheme 30. Synthesis of Example 137

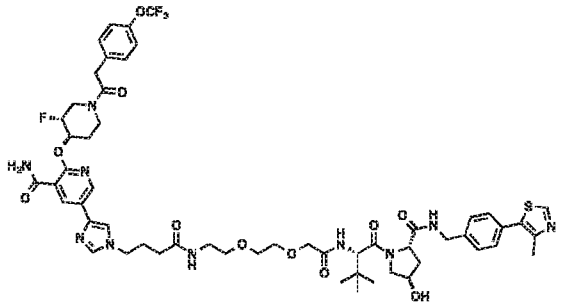


Example 137: 2-(((3*R*,4*R*)-3-Fluoro-1-(2-(4-(trifluoromethoxy)phenyl)acetyl)piperidin-4-yl)oxy)-5-(1-(4-((2-(2-(((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-2-oxoethoxy)ethyl)amino)-4-oxobutyl)-1*H*-imidazol-4-yl)nicotinamide. To a solution of intermediate **22** (10 mg, 0.017 mmol) and linker **27** (9 mg, 0.017 mmol) in DMSO (0.5 mL), were added NMM (10 μL, 0.085 mmol), EDCI (5 mg, 0.026 mmol), and HOAt (3.5 mg, 0.026 mmol). After being stirred at rt for 12 h, the mixture was concentrated and purified by HPLC to yield the title compound (6 mg, 32% yield) as the brown oil. ^{1}H NMR (600 MHz, CD_3OD) δ 9.01 (s, 1H), 8.90 (s, 1H), 8.65 (s, 1H), 8.57 (s, 1H), 8.04 (s, 1H), 7.43 (d, J = 8.3 Hz, 2H), 7.40 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 7.9 Hz, 2H), 7.25 (d, J = 8.2 Hz, 2H), 5.69 – 5.59 (m, 1H), 4.83 – 4.76 (m, 1H), 4.71 (s, 1H), 4.59 – 4.53 (m, 1H), 4.52 – 4.46 (m, 2H), 4.38 (d, J = 15.5 Hz, 1H), 4.30 (t, J = 7.0 Hz, 2H), 4.07 (d, J = 15.2 Hz, 1H), 4.04 – 3.97 (m, 2H), 3.92 – 3.86 (m, 3H), 3.83 – 3.76 (m, 3H), 3.68 – 3.56 (m, 3H), 3.46 – 3.34 (m, 2H), 2.46 (s, 3H), 2.34 (t, J = 7.0 Hz, 2H), 2.29 – 2.17 (m, 4H), 2.13 – 2.04 (m, 1H), 1.91 – 1.75 (m, 1H), 1.03 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{53}H_{63}F_4N_{10}O_{10}S^+$, 1107.4380; found 1107.4449.

Example compounds **138 – 189** were synthesized according to the procedures for the preparation of example compound **137.**

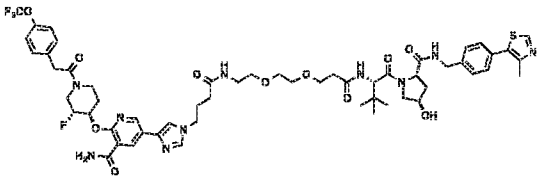


Example 138: 2-(((3*R*,4*R*)-3-Fluoro-1-(2-(4-(trifluoromethoxy)phenyl)acetyl)piperidin-4-yl)oxy)-5-(1-(4-((2-(3-(((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-3-oxopropoxy)ethyl)amino)-4-oxobutyl)-1*H*-imidazol-4-yl)nicotinamide. 40% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 9.03 (s, 1H), 8.91 (s, 1H), 8.71 – 8.63 (m, 1H), 8.58 (dd, *J* = 4.9, 2.5 Hz, 1H), 8.05 (t, *J* = 1.6 Hz, 1H), 7.44 (d, *J* = 8.3 Hz, 2H), 7.41 – 7.39 (m, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.2 Hz, 2H), 5.70 – 5.58 (m, 1H), 4.57 (dd, *J* = 9.1, 7.6 Hz, 2H), 4.52 – 4.47 (m, 2H), 4.38 (d, *J* = 15.5 Hz, 1H), 4.31 (t, *J* = 7.0 Hz, 2H), 4.18 – 3.98 (m, 1H), 3.94 – 3.84 (m, 3H), 3.83 – 3.76 (m, 3H), 3.75 – 3.68 (m, 3H), 3.64 – 3.56 (td, *J* = 12.1, 11.6, 4.4 Hz, 1H), 3.52 (t, *J* = 5.4 Hz, 2H), 3.38 – 3.33 (m, 2H), 2.59 – 2.50 (m, 2H), 2.46 (s, 3H), 2.32 (t, *J* = 7.4 Hz, 2H), 2.28 – 2.17 (m, 4H), 2.09 (ddd, *J* = 13.3, 9.2, 4.5 Hz, 1H), 1.92 – 1.75 (m, 1H), 1.03 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{54}H_{65}F_4N_{10}O_{10}S^+$, 1121.4536; found 1121.4535.

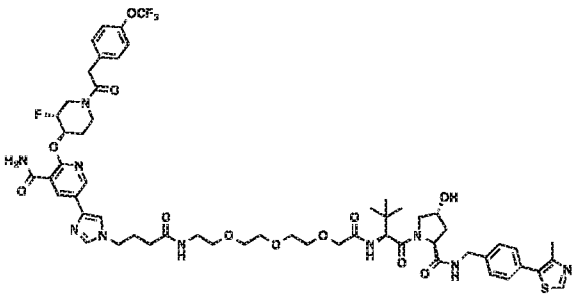


Example 139: 2-(((3*R*,4*R*)-3-Fluoro-1-(2-(4-(trifluoromethoxy)phenyl)acetyl)piperidin-4-yl)oxy)-5-(1-((*S*)-3-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-2,2-dimethyl-5,14-dioxo-7,10-dioxa-4,13-diazaheptadecan-17-yl)-1*H*-imidazol-4-yl)nicotinamide. 33% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 9.01 (s, 1H), 8.90 (s, 1H), 8.65 (s, 1H), 8.58 (s, 1H), 8.04 (s, 1H), 7.43 (d, *J* = 11.3 Hz, 2H), 7.40 (d, *J* = 8.1 Hz, 2H), 7.37 (d, *J* = 8.1 Hz, 2H), 7.25 (d, *J* = 8.1 Hz, 2H), 5.68 – 5.59 (m,

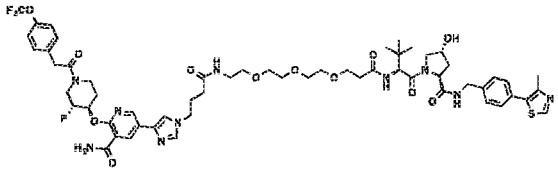
1H), 4.83 – 4.78 (m, 1H), 4.75 (d, J = 8.1 Hz, 1H), 4.55 (t, J = 8.5 Hz, 1H), 4.52 – 4.46 (m, 2H), 4.39 (d, J = 15.5 Hz, 1H), 4.28 (t, J = 7.0 Hz, 2H), 4.16 – 4.08 (m, 1H), 4.06 – 3.98 (m, 2H), 3.88 (t, J = 5.7 Hz, 3H), 3.84 – 3.77 (m, 3H), 3.73 – 3.69 (m, 3H), 3.66 – 3.60 (m, 3H), 3.58 – 3.54 (m, 2H), 3.49 – 3.43 (m, 1H), 2.46 (s, 3H), 2.33 (dt, J = 14.7, 7.1 Hz, 2H), 2.29 – 2.23 (m, 2H), 2.20 (t, J = 7.1 Hz, 2H), 2.13 – 2.04 (m, 1H), 1.91 – 1.77 (m, 1H), 1.04 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{55}H_{67}F_4N_{10}O_{11}S^+$, 1151.4642; found 1151.4634.



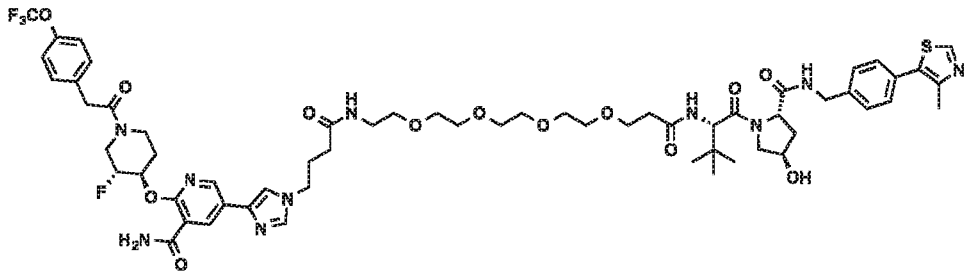
Example 140: 2-(((3*R*,4*R*)-3-Fluoro-1-(2-(4-(trifluoromethoxy)phenyl)acetyl)piperidin-4-yl)oxy)-5-(1-((*S*)-3-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-2,2-dimethyl-5,15-dioxo-8,11-dioxa-4,14-diazaoctadecan-18-yl)-1*H*-imidazol-4-yl)nicotinamide. 41% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 9.06 (s, 1H), 8.93 (s, 1H), 8.67 (dd, J = 4.7, 2.6 Hz, 1H), 8.60 – 8.54 (m, 1H), 8.08 (s, 1H), 7.46 (d, J = 8.0 Hz, 2H), 7.41 (d, J = 8.1 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 8.2 Hz, 2H), 5.69 – 5.61 (m, 1H), 4.83 – 4.77 (m, 1H), 4.65 (s, 1H), 4.56 (t, J = 8.4 Hz, 1H), 4.53 – 4.48 (m, 2H), 4.37 (d, J = 15.4 Hz, 1H), 4.31 (t, J = 6.9 Hz, 2H), 4.16 – 3.99 (m, 1H), 3.94 – 3.84 (m, 3H), 3.84 – 3.76 (m, 3H), 3.75 – 3.69 (m, 2H), 3.65 – 3.57 (m, 5H), 3.53 (t, J = 5.3 Hz, 2H), 3.34 (t, J = 5.4 Hz, 2H), 2.61 – 2.52 (m, 1H), 2.50 – 2.44 (d, J = 3.8 Hz, 4H), 2.31 (t, J = 6.9 Hz, 2H), 2.23 (p, J = 7.2 Hz, 4H), 2.08 (ddd, J = 13.3, 9.4, 4.5 Hz, 1H), 1.91 – 1.75 (m, 1H), 1.03 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{56}H_{69}F_4N_{10}O_{11}S^+$, 1165.4799; found 1165.4808.



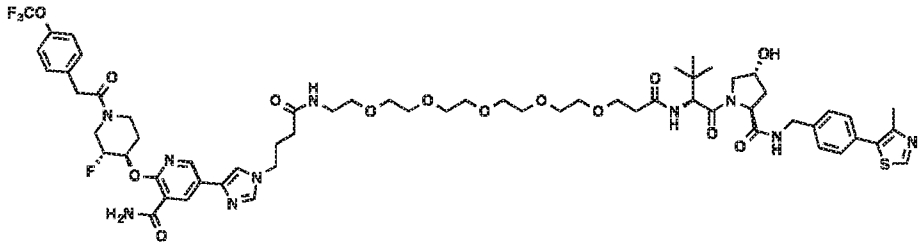
Example 141: 2-(((3*R*,4*R*)-3-Fluoro-1-(2-(4-(trifluoromethoxy)phenyl)acetyl)piperidin-4-yl)oxy)-5-(1-((*S*)-3-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-2,2-dimethyl-5,17-dioxo-7,10,13-trioxa-4,16-diazaicosan-20-yl)-1*H*-imidazol-4-yl)nicotinamide. 31% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 9.07 (s, 1H), 8.96 (s, 1H), 8.67 (dd, *J* = 4.8, 2.7 Hz, 1H), 8.59 (dd, *J* = 6.0, 2.6 Hz, 1H), 8.08 (s, 1H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.42 (d, *J* = 8.1 Hz, 2H), 7.37 (d, *J* = 8.1 Hz, 2H), 7.24 (d, *J* = 8.1 Hz, 2H), 5.69 – 5.60 (s, 1H), 4.83 – 4.77 (m, 1H), 4.69 (s, 1H), 4.59 – 4.55 (m, 1H), 4.54 – 4.48 (m, 2H), 4.37 (d, *J* = 15.5 Hz, 1H), 4.31 (t, *J* = 6.9 Hz, 2H), 4.16 – 4.06 (m, 1H), 4.04 – 3.98 (m, 2H), 3.92 – 3.84 (m, 3H), 3.80 (dd, *J* = 11.1, 3.9 Hz, 3H), 3.72 – 3.64 (m, 7H), 3.62 (q, *J* = 5.1, 4.6 Hz, 2H), 3.55 – 3.48 (m, 2H), 3.37 – 3.32 (m, 2H), 2.48 (s, 3H), 2.29 (d, *J* = 6.6 Hz, 2H), 2.27 – 2.18 (m, 4H), 2.13 – 2.04 (m, 1H), 1.92 – 1.76 (m, 1H), 1.04 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{57}H_{71}F_4N_{10}O_{12}S^+$, 1195.4904; found 1195.4888.



Example 142: 2-(((3*R*,4*R*)-3-Fluoro-1-(2-(4-(trifluoromethoxy)phenyl)acetyl)piperidin-4-yl)oxy)-5-(1-((*S*)-3-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-2,2-dimethyl-5,18-dioxo-8,11,14-trioxa-4,17-diazahenicosan-21-yl)-1*H*-imidazol-4-yl)nicotinamide. 35% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.97 (s, 1H), 8.89 (d, *J* = 4.9 Hz, 1H), 8.66 (q, *J* = 4.3, 3.8 Hz, 1H), 8.60 – 8.54 (m, 1H), 8.04 (s, 1H), 7.45 (td, *J* = 7.9, 6.9, 3.1 Hz, 2H), 7.40 (dt, *J* = 6.2, 1.9 Hz, 2H), 7.36 (dd, *J* = 7.9, 4.8 Hz, 2H), 7.24 (d, *J* = 7.9 Hz, 2H), 5.64 (brs, 1H), 4.60 – 4.52 (m, 2H), 4.51 – 4.46 (m, 2H), 4.40 – 4.34 (m, 1H), 4.32 – 4.27 (m, 2H), 4.19 – 3.97 (m, 1H), 3.92 – 3.82 (m, 3H), 3.81 – 3.76 (m, 3H), 3.74 – 3.66 (m, 3H), 3.65 – 3.55 (m, 9H), 3.52 (q, *J* = 5.1 Hz, 2H), 3.38 – 3.33 (m, 2H), 2.59 – 2.50 (m, 1H), 2.49 – 2.42 (m, 4H), 2.30 (p, *J* = 5.6, 5.2 Hz, 2H), 2.27 – 2.17 (m, 4H), 2.09 (ddd, *J* = 13.3, 9.0, 4.5 Hz, 1H), 1.91 – 1.73 (d, *J* = 41.5 Hz, 1H), 1.03 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{58}H_{73}F_4N_{10}O_{12}S^+$, 1209.5061; found 1209.5067.

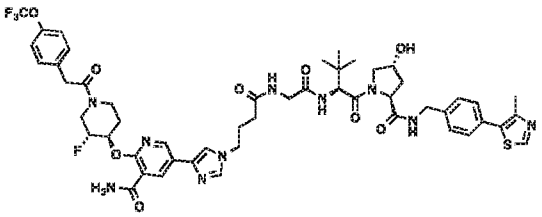


Example 143: 2-(((3*R*,4*R*)-3-Fluoro-1-(2-(4-(trifluoromethoxy)phenyl)acetyl)piperidin-4-yl)oxy)-5-(1-((*S*)-3-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-2,2-dimethyl-5,18-dioxo-8,11,14-trioxa-4,17-diazahenicosan-21-yl)-1*H*-imidazol-4-yl)nicotinamide. 45% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 9.07 (d, *J* = 3.5 Hz, 1H), 8.96 (d, *J* = 3.5 Hz, 1H), 8.67 (q, *J* = 3.3 Hz, 1H), 8.59 (dt, *J* = 6.3, 3.0 Hz, 1H), 8.09 (d, *J* = 3.8 Hz, 1H), 7.46 (dd, *J* = 8.2, 3.4 Hz, 2H), 7.43 – 7.39 (m, 2H), 7.37 (dd, *J* = 8.5, 3.3 Hz, 2H), 7.24 (d, *J* = 8.1 Hz, 2H), 5.65 (brs, 1H), 4.60 – 4.53 (m, 2H), 4.52 – 4.47 (m, 2H), 4.40 – 4.29 (m, 3H), 4.17 – 3.98 (m, 1H), 3.91 – 3.85 (m, 3H), 3.83 – 3.76 (m, 3H), 3.75 – 3.66 (m, 3H), 3.64 – 3.56 (m, 14H), 3.53 (td, *J* = 5.4, 3.5 Hz, 3H), 2.60 – 2.51 (m, 1H), 2.49 – 2.42 (m, 4H), 2.34 – 2.29 (m, 2H), 2.28 – 2.17 (m, 4H), 2.12 – 2.05 (m, 1H), 1.92 – 1.76 (m, 1H), 1.03 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{60}H_{77}F_4N_{10}O_{13}S^+$, 1253.5323; found 1253.5312.

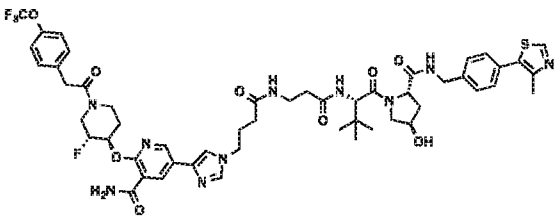


Example 144: 2-(((3*R*,4*R*)-3-Fluoro-1-(2-(4-(trifluoromethoxy)phenyl)acetyl)piperidin-4-yl)oxy)-5-(1-((*S*)-3-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-2,2-dimethyl-5,24-dioxo-8,11,14,17,20-pentaoxa-4,23-diazaheptacosan-27-yl)-1*H*-imidazol-4-yl)nicotinamide. 34% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 9.07 (s, 1H), 8.93 (s, 1H), 8.67 (s, 1H), 8.60 (d, *J* = 5.9 Hz, 1H), 8.09 (s, 1H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 8.1 Hz, 2H), 7.25 (d, *J* = 8.1 Hz, 2H), 5.70 – 5.60 (m, 1H), 4.83 – 4.77 (m, 2H), 4.65 (s, 1H), 4.57 (dd, *J* = 16.9, 8.6 Hz, 1H), 4.53 – 4.47 (m, 1H), 4.40 – 4.30 (m, 3H), 4.17 – 4.00 (s, 1H), 3.93 – 3.84 (m, 3H), 3.83 – 3.77 (m,

3H), 3.75 – 3.67 (m, 3H), 3.65 – 3.56 (m, 16H), 3.53 (t, *J* = 5.3 Hz, 2H), 3.34 (t, *J* = 5.4 Hz, 2H), 2.60 – 2.53 (m, 1H), 2.51 – 2.43 (m, 4H), 2.32 (t, *J* = 6.9 Hz, 2H), 2.29 – 2.17 (m, 4H), 2.12 – 2.02 (m, 1H), 1.91 – 1.75 (m, 1H), 1.03 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{62}H_{81}F_4N_{10}O_{14}S^+$, 1297.5585; found 1297.5596.

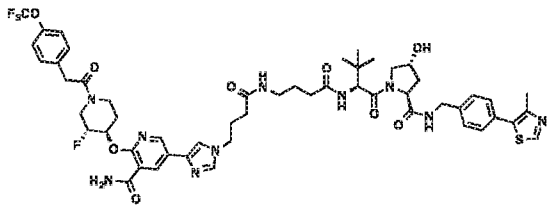


Example 145: 2-(((3*R*,4*R*)-3-fluoro-1-(2-(4-(trifluoromethoxy)phenyl)acetyl)piperidin-4-yl)oxy)-5-(1-(4-((2-(((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-2-oxoethyl)amino)-4-oxobutyl)-1*H*-imidazol-4-yl)nicotinamide 39% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 9.10 (s, 1H), 8.93 (s, 1H), 8.66 (t, *J* = 3.4 Hz, 1H), 8.58 (dd, *J* = 4.7, 2.7 Hz, 1H), 8.11 (s, 1H), 7.45 (dt, *J* = 8.2, 3.0 Hz, 2H), 7.41 – 7.35 (m, 4H), 7.24 (d, *J* = 7.8 Hz, 2H), 5.64 (brs, 1H), 4.66 – 4.62 (m, 1H), 4.59 – 4.52 (m, 2H), 4.50 (d, *J* = 4.2 Hz, 2H), 4.39 – 4.32 (m, 3H), 4.20 – 3.98 (m, 1H), 3.94 – 3.84 (m, 5H), 3.83 – 3.75 (m, 3H), 3.71 – 3.54 (m, 1H), 2.52 – 2.42 (m, 3H), 2.40 – 2.34 (m, 2H), 2.32 – 2.17 (m, 4H), 2.09 (ddd, *J* = 13.3, 9.0, 4.4 Hz, 1H), 1.93 – 1.73 (m, 1H), 1.04 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{51}H_{59}F_4N_{10}O_9S^+$, 1063.4118; found 1063.4128.

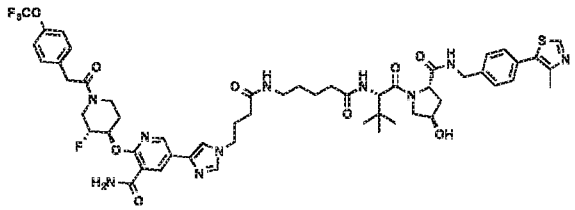


Example 146 2-(((3*R*,4*R*)-3-Fluoro-1-(2-(4-(trifluoromethoxy)phenyl)acetyl)piperidin-4-yl)oxy)-5-(1-(4-((3-(((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-3-oxopropyl)amino)-4-oxobutyl)-1*H*-imidazol-4-yl)nicotinamide. 37% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 8.97 (s, 1H), 8.89 (s, 1H), 8.66 (s, 1H), 8.57 (s, 1H), 8.05 (s, 1H), 7.44 (d, *J* = 7.5 Hz, 2H), 7.41 – 7.34 (m, 4H), 7.25 (d, *J* = 8.2 Hz, 2H), 5.69 – 5.59 (m, 1H), 4.60 (s, 1H), 4.56 –

4.54 (m, 1H), 4.52 (d, J = 6.4 Hz, 1H), 4.51 – 4.48 (m, 1H), 4.37 (d, J = 15.6 Hz, 1H), 4.29 (t, J = 7.0 Hz, 2H), 4.15 – 3.99 (m, 1H), 3.94 (d, J = 11.1 Hz, 1H), 3.90 – 3.86 (m, 2H), 3.83 – 3.76 (m 3H), 3.65 – 3.56 (m, 1H), 3.48 – 3.42 (m, 1H), 3.42 – 3.35 (m, 1H), 2.60 – 2.43 (m, 5H), 2.29 – 2.25 (m, 3H), 2.24 – 2.17 (m, 4H), 2.11 – 2.05 (m, 1H), 1.91 – 1.76 (m, 1H), 1.03 (s, 9H). HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{52}H_{61}F_4N_{10}O_9S^+$, 1077.4274; found 1077.4290.

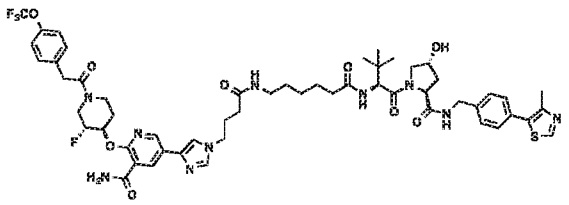


Example 147: 2-(((3*R*,4*R*)-3-Fluoro-1-(2-(4-(trifluoromethoxy)phenyl)acetyl)piperidin-4-yl)oxy)-5-(1-(4-((4-(((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-4-oxobutyl)amino)-4-oxobutyl)-1*H*-imidazol-4-yl)nicotinamide. 41% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 9.09 (s, 1H), 8.96 (s, 1H), 8.66 (dd, J = 4.6, 2.6 Hz, 1H), 8.57 (dd, J = 6.0, 2.6 Hz, 1H), 8.09 (s, 1H), 7.46 (d, J = 8.0 Hz, 2H), 7.41 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 8.1 Hz, 2H), 7.24 (d, J = 8.1 Hz, 2H), 5.69 – 5.60 (m, 1H), 4.82 – 4.73 (m, 1H), 4.62 (s, 1H), 4.57 (d, J = 8.4 Hz, 1H), 4.55 (d, J = 7.1 Hz, 1H), 4.52 – 4.48 (m, 1H), 4.36 (d, J = 15.5 Hz, 1H), 4.33 (t, J = 7.1 Hz, 2H), 4.18 – 3.99 (m, 1H), 3.94 – 3.87 (m, 3H), 3.85 – 3.76 (m, 3H), 3.64 – 3.57 (m, 1H), 3.18 (t, J = 6.9 Hz, 2H), 2.47 (s, 3H), 2.31 (q, J = 7.3 Hz, 3H), 2.29 – 2.19 (m, 5H), 2.09 (ddd, J = 13.4, 9.3, 4.6 Hz, 1H), 1.92 – 1.79 (m, 1H), 1.76 (p, J = 7.2 Hz, 2H), 1.04 (s, 9H). HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{53}H_{63}F_4N_{10}O_9S^+$, 1091.4431; found 1091.4445.

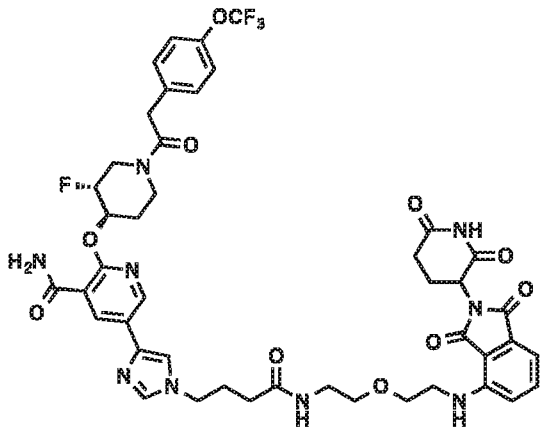


Example 148: 2-(((3*R*,4*R*)-3-Fluoro-1-(2-(4-(trifluoromethoxy)phenyl)acetyl)piperidin-4-yl)oxy)-5-(1-(4-((5-(((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-5-

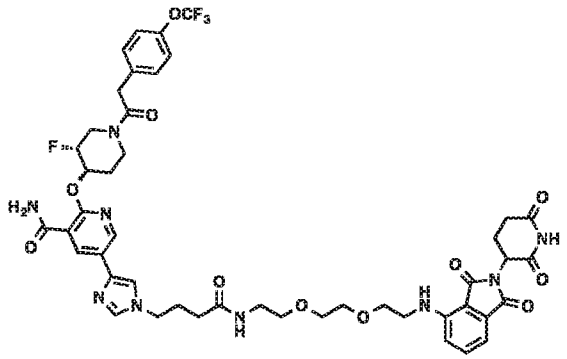
oxopentyl)amino)-4-oxobutyl)-1*H*-imidazol-4-yl)nicotinamide 33% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 9.04 (s, 1H), 8.90 (s, 1H), 8.67 (s, 1H), 8.59 (s, 1H), 8.07 (s, 1H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.40 (d, *J* = 8.2 Hz, 2H), 7.37 (d, *J* = 7.9 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 5.68 – 5.61 (m, 1H), 4.62 (s, 1H), 4.56 (d, *J* = 8.4 Hz, 1H), 4.55 – 4.53 (m, 1H), 4.52 – 4.48 (m, 2H), 4.36 (d, *J* = 15.5 Hz, 1H), 4.32 (t, *J* = 7.0 Hz, 3H), 3.92 – 3.86 (m, 4H), 3.83 – 3.76 (m, 3H), 3.66 – 3.57 (m, 1H), 3.21 – 3.09 (m, 3H), 2.48 – 2.45 (m, 5H), 2.32 – 2.27 (m, 4H), 2.26 – 2.19 (m, 3H), 1.91 – 1.76 (m, 1H), 1.64 – 1.57 (m, 1H), 1.53 – 1.46 (m, 1H), 1.03 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{54}H_{65}F_4N_{10}O_9S^+$, 1105.4587; found 1105.4638.



Example 149: 2-(((3*R*,4*R*)-3-Fluoro-1-(2-(4-(trifluoromethoxy)phenyl)acetyl)piperidin-4-yl)oxy)-5-(1-(4-((6-(((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-6-oxohexyl)amino)-4-oxobutyl)-1*H*-imidazol-4-yl)nicotinamide. 39% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 9.03 (s, 1H), 8.90 (s, 1H), 8.66 (s, 1H), 8.58 (d, *J* = 5.8 Hz, 1H), 8.06 (s, 1H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 8.2 Hz, 2H), 5.69 – 5.60 (m, 1H), 4.64 – 4.62 (m, 1H), 4.59 – 4.53 (m, 1H), 4.52 – 4.48 (m, 1H), 4.39 – 4.33 (m, 1H), 4.32 – 4.26 (m, 3H), 3.92 – 3.87 (m, 4H), 3.83 – 3.77 (m, 3H), 3.66 – 3.62 (m, 1H), 3.43 – 3.41 (m, 1H), 3.21 – 3.18 (m, 1H), 3.14 (t, *J* = 7.1 Hz, 3H), 2.48– 2.45 (m, 4H), 2.29 (d, *J* = 7.0 Hz, 4H), 2.25 – 2.19 (m, 4H), 2.11 – 2.06 (m, 1H), 1.62 – 1.57 (m, 1H), 1.51 – 1.47 (m, 1H), 1.36 – 1.30 (m, 2H), 1.03 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{55}H_{67}F_4N_{10}O_9S^+$, 1119.4744; found 1119.4838.

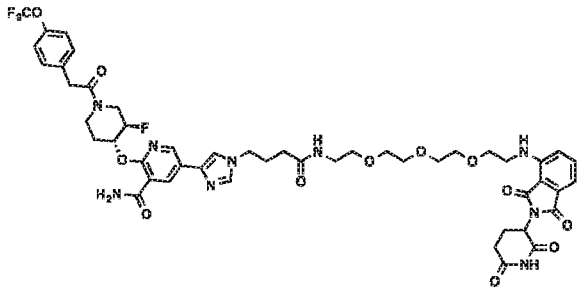


Example 150: 5-(1-(4-((2-(2-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethyl)amino)-4-oxobutyl)-1*H*-imidazol-4-yl)-2-(((3*R*,4*R*)-3-fluoro-1-(2-(4-(trifluoromethoxy)phenyl)acetyl)piperidin-4-yl)oxy)nicotinamide. 33% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 8.81 (s, 1H), 8.60 (s, 1H), 8.52 (s, 1H), 7.92 (s, 1H), 7.50 (s, 1H), 7.38 (d, *J* = 7.7 Hz, 2H), 7.25 (d, *J* = 8.2 Hz, 2H), 7.03 (d, *J* = 8.4 Hz, 1H), 6.99 (d, *J* = 7.8 Hz, 1H), 5.67 – 5.57 (m, 1H), 5.04 (dd, *J* = 12.8, 5.4 Hz, 1H), 4.23 (t, *J* = 7.0 Hz, 2H), 3.89 (d, *J* = 5.5 Hz, 2H), 3.84 – 3.77 (m, 2H), 3.72 (t, *J* = 5.2 Hz, 3H), ,3.61 (t, *J* = 5.2 Hz, 3H), 3.50 – 3.46 (m, 2H), 3.44 – 3.37 (m, 2H), 2.89 – 2.81 (m, 1H), 2.76 – 2.70 (m, 1H), 2.68 – 2.64 (m, 1H), 2.29 (t, *J* = 6.8 Hz, 2H), 2.22 – 2.17 (m, 2H), 2.12 – 2.06 (m, 1H), 1.92 – 1.84 (m, 1H), 1.83 – 1.75 (m, 1H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{44}H_{46}F_4N_9O_{10}^+$, 936.3298; found 936.3292.

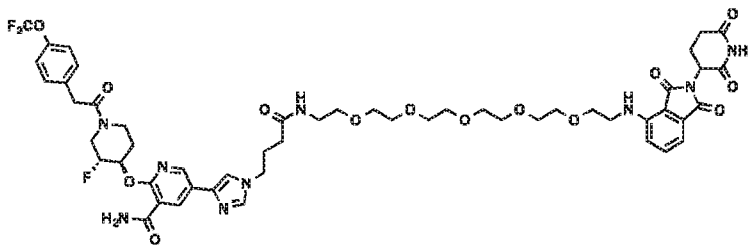


Example 151: 5-(1-(4-((2-(2-(2-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethyl)amino)-4-oxobutyl)-1*H*-imidazol-4-yl)-2-(((3*R*,4*R*)-3-fluoro-1-(2-(4-(trifluoromethoxy)phenyl)acetyl)piperidin-4-yl)oxy)nicotinamide. 37% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 9.01 (s, 1H), 8.59 (dd, *J* = 5.1, 2.6 Hz, 1H), 8.52 (dd, *J* = 6.0, 2.6 Hz, 1H), 8.01 (s, 1H), 7.54 – 7.45 (m, 1H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 8.1 Hz, 2H), 7.06 –

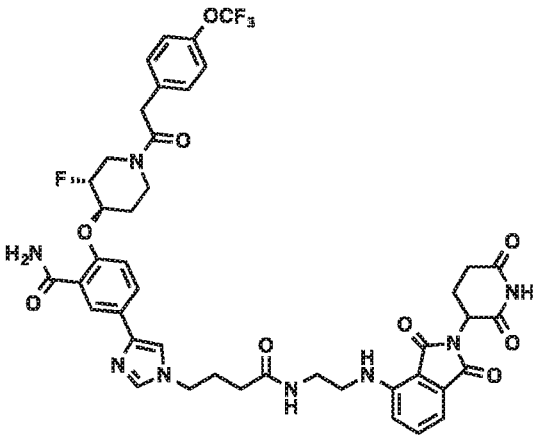
6.88 (m, 1H), 5.68 – 5.57 (m, 1H), 5.04 (dd, J = 12.8, 5.4 Hz, 1H), 4.27 (t, J = 6.6 Hz, 2H), 4.19 – 3.99 (m, 1H), 3.94 – 3.85 (m, 2H), 3.84 – 3.76 (m, 2H), 3.72 (t, J = 5.0 Hz, 2H), 3.69 (dd, J = 6.3, 2.7 Hz, 2H), 3.66 (dd, J = 6.2, 2.8 Hz, 2H), 3.63 – 3.58 (m, 1H), 3.57 (t, J = 5.3 Hz, 2H), 3.45 (t, J = 5.3 Hz, 2H), 3.35 (td, J = 5.2, 2.3 Hz, 2H), 2.85 (ddd, J = 18.7, 13.9, 5.4 Hz, 1H), 2.74 (dt, J = 17.4, 3.2 Hz, 1H), 2.67 (qd, J = 13.2, 4.6 Hz, 1H), 2.31 – 2.18 (m, 5H), 2.12 – 2.05 (m, 1H), 1.92 – 1.76 (m, 1H). HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{46}H_{50}F_4N_9O_{11}^+$, 980.3560; found 980.3641.



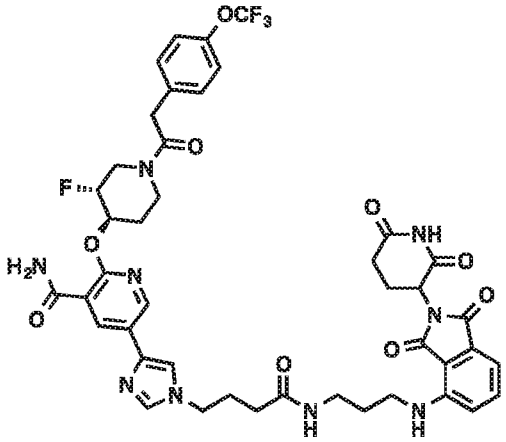
Example 152: 5-(1-(1-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-13-oxo-3,6,9-trioxa-12-azahexadecan-16-yl)-1*H*-imidazol-4-yl)-2-(((3*R*,4*R*)-3-fluoro-1-(2-(4-(trifluoromethoxy)phenyl)acetyl)piperidin-4-yl)oxy)nicotinamide. 36% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 8.99 (s, 1H), 8.60 (dd, J = 5.6, 2.6 Hz, 1H), 8.55 – 8.50 (m, 1H), 8.00 (s, 1H), 7.59 – 7.44 (m, 1H), 7.37 (d, J = 8.1 Hz, 2H), 7.25 (d, J = 8.1 Hz, 2H), 7.12 – 6.87 (m, 2H), 5.67 – 5.57 (m, 1H), 5.05 (dd, J = 12.7, 5.5 Hz, 1H), 4.83 – 4.78 (m, 1H), 4.27 (t, J = 6.7 Hz, 2H), 4.19 – 4.00 (m, 1H), 3.94 – 3.85 (m, 2H), 3.84 – 3.75 (m, 2H), 3.73 – 3.65 (m, 10H), 3.63 – 3.58 (m, 2H), 3.52 (t, J = 5.2 Hz, 2H), 3.45 – 3.40 (m, 2H), 2.87 (ddd, J = 18.8, 14.0, 5.4 Hz, 1H), 2.77 – 2.71 (m, 1H), 2.71 – 2.61 (m, 1H), 2.30 – 2.26 (m, 2H), 2.25 – 2.19 (m, 3H), 2.14 – 2.07 (m, 1H), 1.92 – 1.75 (m, 1H). HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{48}H_{54}F_4N_9O_{12}^+$, 1024.3823; found 1024.3845.



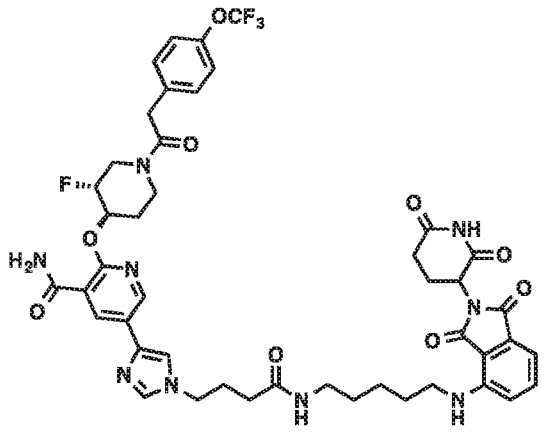
Example 153: 5-(1-(1-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-19-oxo-3,6,9,12,15-pentaoxa-18-azadocosan-22-yl)-1*H*-imidazol-4-yl)-2-(((3*R*,4*R*)-3-fluoro-1-(2-(4-(trifluoromethoxy)phenyl)acetyl)piperidin-4-yl)oxy)nicotinamide. 34% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 9.02 (s, 1H), 8.63 (dd, *J* = 4.0, 2.5 Hz, 1H), 8.56 (dd, *J* = 4.9, 2.6 Hz, 1H), 8.04 (s, 1H), 7.51 (dd, *J* = 8.6, 7.1 Hz, 1H), 7.40 – 7.33 (m, 2H), 7.24 (d, *J* = 8.2 Hz, 2H), 7.04 (d, *J* = 8.6 Hz, 1H), 7.01 (d, *J* = 7.1 Hz, 1H), 5.68 – 5.57 (m, 1H), 5.03 (dd, *J* = 12.8, 5.4 Hz, 1H), 4.30 (t, *J* = 6.9 Hz, 2H), 4.20 – 3.98 (m, 1H), 3.93 – 3.84 (m, 2H), 3.83 – 3.75 (m, 2H), 3.71 (t, *J* = 5.2 Hz, 2H), 3.67 – 3.64 (m, 4H), 3.63 – 3.59 (m, 5H), 3.58 – 3.55 (m, 6H), 3.53 (t, *J* = 5.3 Hz, 2H), 3.46 (t, *J* = 5.1 Hz, 2H), 3.34 (t, *J* = 5.3 Hz, 2H), 2.85 (ddd, *J* = 17.7, 14.0, 5.3 Hz, 1H), 2.77 – 2.71 (m, 1H), 2.70 – 2.62 (m, 1H), 2.29 (t, *J* = 6.4 Hz, 2H), 2.23 (t, *J* = 6.6 Hz, 3H), 2.10 (ddt, *J* = 13.1, 5.5, 2.7 Hz, 1H), 1.95 – 1.84 (m, 1H), 1.83 – 1.74 (m, 1H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{52}H_{62}F_4N_9O_{14}^+$, 1112.4347; found 1112.4816.



Example 154: 5-(1-(4-((2-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethyl)amino)-4-oxobutyl)-1*H*-imidazol-4-yl)-2-(((3*R*,4*R*)-3-fluoro-1-(2-(4-(trifluoromethoxy)phenyl)acetyl)piperidin-4-yl)oxy)benzamide. 40% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.85 (s, 1H), 8.63 (dd, *J* = 4.8, 2.5 Hz, 1H), 8.55 (dd, *J* = 4.8, 2.5 Hz, 1H), 7.95 (s, 1H), 7.59 – 7.50 (m, 1H), 7.41 – 7.33 (m, 2H), 7.24 (d, *J* = 8.2 Hz, 2H), 7.10 (d, *J* = 8.6 Hz, 1H), 7.02 (d, *J* = 7.1 Hz, 1H), 5.69 – 5.58 (m, 1H), 5.01 (dd, *J* = 12.4, 5.4 Hz, 1H), 4.23 (t, *J* = 7.1 Hz, 2H), 4.16 – 3.98 (m, 1H), 3.94 – 3.85 (m, 3H), 3.83 – 3.73 (m, 2H), 3.65 – 3.57 (m, 1H), 3.48 – 3.43 (m, 4H), 2.81 (ddd, *J* = 18.0, 14.2, 5.4 Hz, 1H), 2.73 – 2.70 (m, 1H), 2.68 – 2.61 (m, 1H), 2.29 (t, *J* = 7.0 Hz, 2H), 2.21 – 2.16 (m, 2H), 2.12 – 2.04 (m, 1H), 1.93 – 1.74 (m, 1H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{42}H_{42}F_4N_9O_9^+$, 892.3036; found 892.3066.

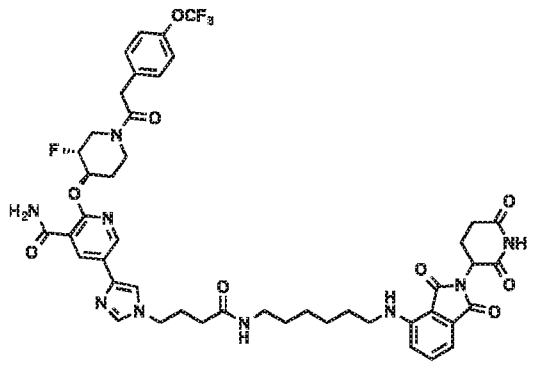


Example 155: 5-(1-(4-((3-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propyl)amino)-4-oxobutyl)-1*H*-imidazol-4-yl)-2-(((3*R*,4*R*)-3-fluoro-1-(2-(4-(trifluoromethoxy)phenyl)acetyl)piperidin-4-yl)oxy)nicotinamide 33% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 9.00 (s, 1H), 8.75 – 8.62 (m, 1H), 8.60 – 8.52 (m, 1H), 8.04 (s, 1H), 7.53 (t, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 7.9 Hz, 2H), 7.25 (d, *J* = 8.1 Hz, 2H), 7.07 – 6.96 (m, 2H), 5.68 – 5.57 (m, 1H), 5.05 (dd, *J* = 12.7, 5.5 Hz, 1H), 4.30 (t, *J* = 7.1 Hz, 2H), 4.16 – 3.99 (m, 1H), 3.94 – 3.84 (m, 3H), 3.82 – 3.72 (m, 2H), 3.63 – 3.57 (m, 1H), 3.37 – 3.34 (m, 2H), 2.85 (ddd, *J* = 18.1, 13.9, 5.3 Hz, 1H), 2.79 – 2.63 (m, 2H), 2.32 (t, *J* = 7.1 Hz, 2H), 2.22 (q, *J* = 7.2 Hz, 3H), 2.13 – 2.06 (m, 1H), 1.95 – 1.85 (m, 1H), 1.82 (t, *J* = 6.5 Hz, 3H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{43}H_{44}F_4N_9O_9^+$, 906.3193; found 906.3197.

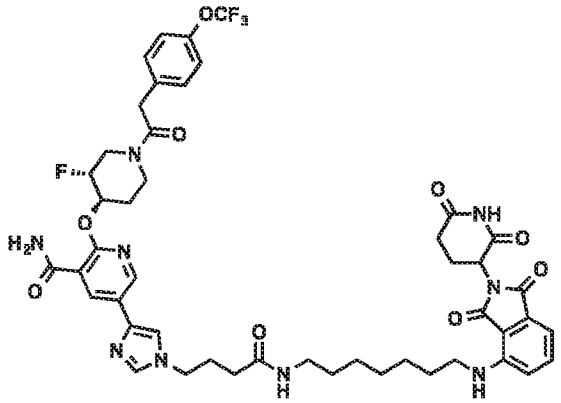


Example 157: 5-(1-(4-((5-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)pentyl)amino)-4-oxobutyl)-1*H*-imidazol-4-yl)-2-(((3*R*,4*R*)-3-fluoro-1-(2-(4-(trifluoromethoxy)phenyl)acetyl)piperidin-4-yl)oxy)nicotinamide. 37% yield. ^{1}H NMR (600

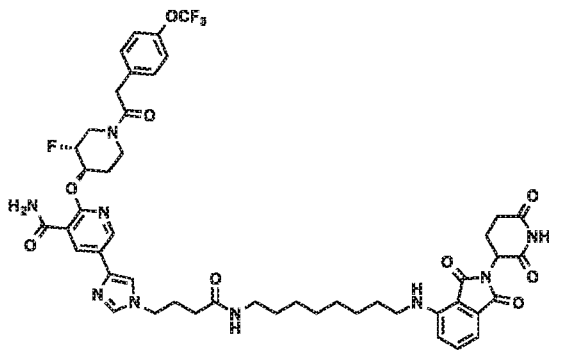
MHz, CD_3OD) δ 9.02 (s, 1H), 8.65 (dd, J = 4.4, 2.6 Hz, 1H), 8.57 (dd, J = 6.5, 2.6 Hz, 1H), 8.03 (s, 1H), 7.61 – 7.48 (m, 1H), 7.37 (d, J = 8.2 Hz, 2H), 7.24 (d, J = 8.1 Hz, 2H), 7.03 (d, J = 8.6 Hz, 1H), 7.00 (d, J = 7.1 Hz, 1H), 5.69 – 5.60 (m, 1H), 5.04 (dd, J = 12.8, 5.5 Hz, 1H), 4.83 – 4.76 (m, 1H), 4.28 (t, J = 7.1 Hz, 2H), 4.17 – 3.98 (m, 1H), 3.93 – 3.84 (m, 3H), 3.83 – 3.70 (m, 2H), 3.63 – 3.56 (m, 1H), 3.18 (t, J = 6.9 Hz, 2H), 2.93 – 2.79 (m, 1H), 2.76 – 2.71 (m, 1H), 2.71 – 2.64 (m, 1H), 2.29 (t, J = 7.0 Hz, 2H), 2.22 (q, J = 6.9 Hz, 3H), 2.13 – 2.04 (m, 1H), 1.92 – 1.75 (m, 1H), 1.69 – 1.63 (m, 2H), 1.57 – 1.51 (m, 2H), 1.47 – 1.40 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{45}H_{48}F_4N_9O_9^+$, 934.3506; found 934.3521.



Example 158: 5-(1-(4-((6-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)hexyl)amino)-4-oxobutyl)-1*H*-imidazol-4-yl)-2-(((3*R*,4*R*)-3-fluoro-1-(2-(4-(trifluoromethoxy)phenyl)acetyl)piperidin-4-yl)oxy)nicotinamide. 36% yield. ^1H NMR (600 MHz, CD_3OD) δ 8.98 (s, 1H), 8.65 (d, J = 3.7 Hz, 1H), 8.58 (d, J = 6.3 Hz, 1H), 8.03 (s, 1H), 7.54 (dd, J = 8.6, 7.1 Hz, 1H), 7.37 (d, J = 8.3 Hz, 2H), 7.24 (d, J = 8.2 Hz, 2H), 7.03 (d, J = 4.2 Hz, 1H), 7.02 (d, J = 2.6 Hz, 1H), 5.69 – 5.60 (m, 1H), 5.05 (dd, J = 12.9, 5.4 Hz, 1H), 4.82 –4.78 (m, 1H), 4.30 (t, J = 7.0 Hz, 2H), 4.17 – 3.98 (m, 1H), 3.94 – 3.84 (m, 3H), 3.83 – 3.73 (m, 2H), 3.62 – 3.56 (m, 1H), 3.15 (t, J = 7.0 Hz, 2H), 2.93 – 2.81 (m, 1H), 2.79 – 2.64 (m, 2H), 2.29 (t, J = 7.1 Hz, 2H), 2.25 – 2.17 (m, 3H), 2.13 – 2.07 (m, 1H), 1.92 – 1.76 (m, 1H), 1.65 (t, J = 7.5 Hz, 2H), 1.50 (t, J = 7.3 Hz, 2H), 1.46 – 1.40 (m, 2H), 1.39 – 1.35 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{46}H_{50}F_4N_9O_9^+$, 948.3662; found 948.3695.

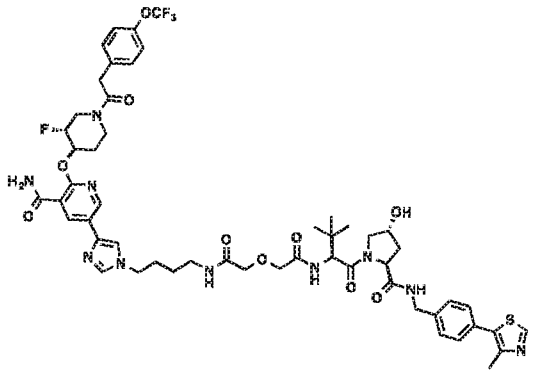


Example 159: 5-(1-(4-((7-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)heptyl)amino)-4-oxobutyl)-1*H*-imidazol-4-yl)-2-(((3*R*,4*R*)-3-fluoro-1-(2-(4-(trifluoromethoxy)phenyl)acetyl)piperidin-4-yl)oxy)nicotinamide.34% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 9.00 (s, 1H), 8.65 (d, *J* = 3.7 Hz, 1H), 8.60 – 8.53 (m, 1H), 8.04 (s, 1H), 7.54 (dd, *J* = 8.6, 7.1 Hz, 1H), 7.37 (d, *J* = 8.2 Hz, 2H), 7.24 (d, *J* = 8.2 Hz, 2H), 7.03 (d, *J* = 5.1 Hz, 1H), 7.01 (d, *J* = 3.5 Hz, 1H), 5.69 – 5.60 (m, 1H), 5.05 (dd, *J* = 12.8, 5.5 Hz, 1H), 4.30 (t, *J* = 7.0 Hz, 2H), 4.18 – 3.95 (m, 1H), 3.95 – 3.84 (m, 3H), 3.83 – 3.73 (m, 2H), 3.62 – 3.55 (m, 1H), 3.13 (t, *J* = 7.0 Hz, 2H), 2.91 – 2.80 (m, 1H), 2.77 – 2.64 (m, 2H), 2.29 (t, *J* = 6.9 Hz, 2H), 2.23 (q, *J* = 7.1 Hz, 3H), 2.13 – 2.06 (m, 1H), 1.95 – 1.75 (m, 1H), 1.69 – 1.58 (m, 2H), 1.50 – 1.45 (m, 2H), 1.44 – 1.39 (m, 2H), 1.38 – 1.28 (s, 5H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{47}H_{52}F_4N_9O_9^+$, 962.3819; found 962.3863.

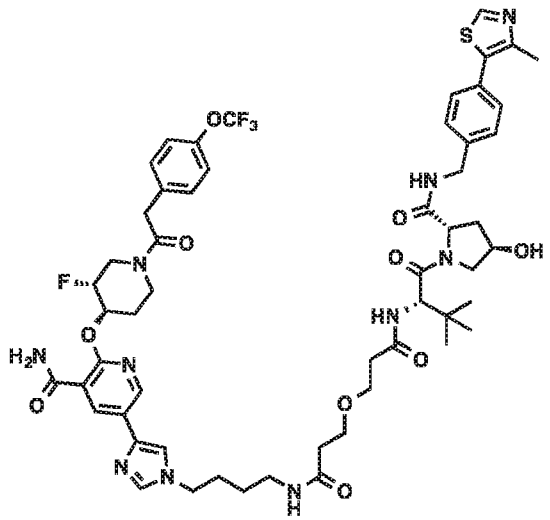


Example 160: 5-(1-(4-((8-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)octyl)amino)-4-oxobutyl)-1*H*-imidazol-4-yl)-2-(((3*R*,4*R*)-3-fluoro-1-(2-(4-(trifluoromethoxy)phenyl)acetyl)piperidin-4-yl)oxy)nicotinamide. 38% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 9.05 (s, 1H), 8.65 (dd, *J* = 4.6, 2.6 Hz, 1H), 8.57 (dd, *J* = 6.2, 2.5 Hz, 1H), 8.06 (s, 1H), 7.53 (dd, *J* = 9.1, 6.8 Hz, 1H), 7.37 (d, *J* = 8.1 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.02 (d,

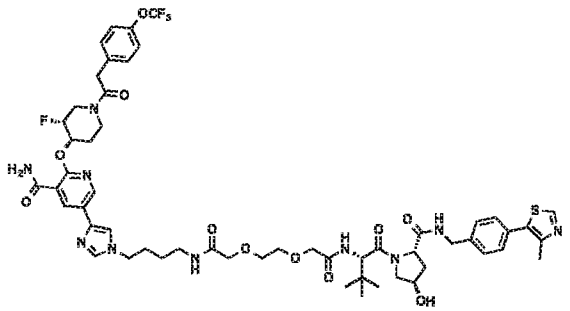
J = 7.7 Hz, 2H), 5.71 – 5.60 (m, 1H), 5.08 – 4.97 (m, 2H), 4.31 (t, J = 7.0 Hz, 2H), 4.17 – 3.99 (m, 1H), 3.92 – 3.84 (m, 3H), 3.83 – 3.74 (m, 2H), 3.62 – 3.49 (m, 1H), 3.13 (t, J = 7.1 Hz, 2H), 2.90 – 2.80 (m, 1H), 2.77 – 2.64 (m, 2H), 2.35 – 2.27 (m, 2H), 2.26 – 2.18 (m, 3H), 2.13 – 2.08 (m, 1H), 1.98 – 1.84 (m, 1H), 1.68 – 1.61 (m, 3H), 1.52 – 1.38 (m, 4H), 1.37 – 1.31 (m, 5H). HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{48}H_{54}F_4N_9O_9^+$, 976.3975; found 976.4135.



Example 161: 2-(((3*R*,4*R*)-3-Fluoro-1-(2-(4-(trifluoromethoxy)phenyl)acetyl)piperidin-4-yl)oxy)-5-(1-(4-(2-(2-(((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-2-oxoethoxy)acetamido)butyl)-1*H*-imidazol-4-yl)nicotinamide.35% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 9.09 (s, 1H), 9.01 (s, 1H), 8.66 (dd, J = 4.8, 2.5 Hz, 1H), 8.57 (dd, J = 6.1, 2.6 Hz, 1H), 8.09 (d, J = 2.0 Hz, 1H), 7.46 (d, J = 8.3 Hz, 2H), 7.41 (d, J = 8.2 Hz, 2H), 7.39 – 7.34 (m, 2H), 7.24 (d, J = 8.0 Hz, 2H), 5.64 (brs, 1H), 4.83 – 4.76 (m, 1H), 4.71 (d, J = 6.9 Hz, 1H), 4.61 – 4.55 (m, 1H), 4.54 – 4.47 (m, 2H), 4.38 – 4.34 (m, 1H), 4.35 – 4.27 (m, 2H), 4.16 – 4.11 (m, 3H), 4.10 – 4.05 (m, 2H), 3.93 – 3.85 (m, 3H), 3.84 – 3.75 (m, 3H), 3.66 – 3.55 (m, 1H), 3.36 – 3.31 (m, 2H), 2.48 (s, 3H), 2.31 – 2.16 (m, 2H), 2.12 – 2.05 (m, 1H), 2.02 – 1.93 (m, 2H), 1.91 – 1.76 (m, 1H), 1.62 (p, J = 7.0 Hz, 2H), 1.04 (s, 9H). HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{53}H_{63}F_4N_{10}O_{10}S^+$, 1107.4380; found 1107.4389.

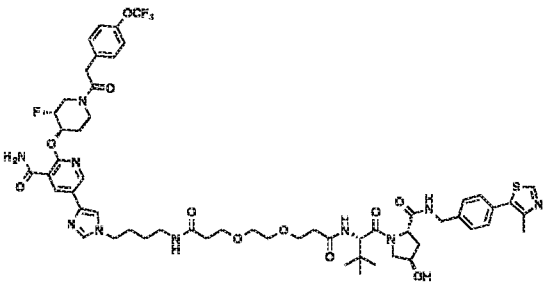


Example 162: 2-(((3*R*,4*R*)-3-Fluoro-1-(2-(4-(trifluoromethoxy)phenyl)acetyl)piperidin-4-yl)oxy)-5-(1-(4-(3-(3-(((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-3-oxopropoxy)propanamido)butyl)-1*H*-imidazol-4-yl)nicotinamide. 31% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 9.07 (s, 1H), 8.94 (s, 1H), 8.66 (dd, *J* = 4.7, 2.6 Hz, 1H), 8.58 (dd, *J* = 6.0, 2.6 Hz, 1H), 8.09 (s, 1H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.41 (d, *J* = 8.2 Hz, 2H), 7.37 (d, *J* = 7.8 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 5.69 – 5.61 (m, 1H), 4.84 – 4.75 (m, 1H), 4.64 (s, 1H), 4.60 – 4.54 (m, 1H), 4.54 – 4.48 (m, 2H), 4.36 (d, *J* = 15.5 Hz, 1H), 4.31 (t, *J* = 7.3 Hz, 2H), 4.22 – 3.94 (m, 1H), 3.93 – 3.84 (m, 3H), 3.83 – 3.75 (m, 3H), 3.74 – 3.64 (ddq, *J* = 18.5, 10.1, 4.9, 4.4 Hz, 5H), 3.62 – 3.56 (m, 1H), 3.28 – 3.20 (h, *J* = 6.7 Hz, 2H), 2.57 – 2.49 (m, 1H), 2.47 (s, 3H), 2.45 – 2.41 (m, 2H), 2.29 – 2.17 (m, 2H), 2.11 – 2.05 (m, 1H), 1.94 (q, *J* = 7.5 Hz, 2H), 1.91 – 1.76 (m, 1H), 1.57 (p, *J* = 7.1 Hz, 2H), 1.03 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{55}H_{67}F_4N_{10}O_{10}S^+$, 1135.4693; found 1135.4730.

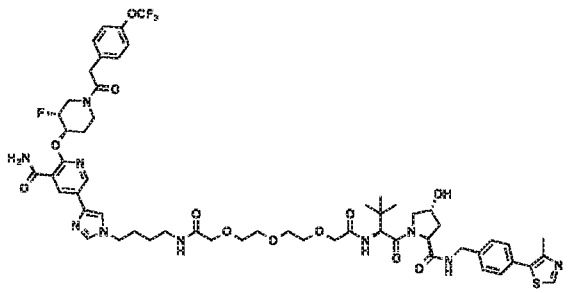


Example 163: 2-(((3*R*,4*R*)-3-Fluoro-1-(2-(4-(trifluoromethoxy)phenyl)acetyl)piperidin-4-yl)oxy)-5-(1-((*S*)-3-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-

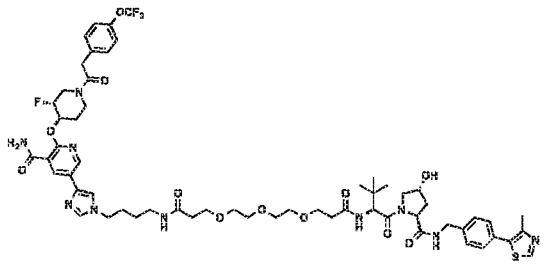
yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-2,2-dimethyl-5,12-dioxo-7,10-dioxa-4,13-diazaheptadecan-17-yl)-1*H*-imidazol-4-yl)nicotinamide. 39% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 9.06 (s, 1H), 8.92 (s, 1H), 8.65 (dd, *J* = 4.8, 2.7 Hz, 1H), 8.57 (dd, *J* = 5.9, 2.6 Hz, 1H), 8.08 (s, 1H), 7.45 – 7.39 (m, 4H), 7.38 – 7.36 (m, 2H), 7.25 (d, *J* = 8.1 Hz, 2H), 5.68 – 5.59 (m, 1H), 4.83 – 4.76 (m, 1H), 4.73 – 4.66 (m, 1H), 4.57 (t, *J* = 8.5 Hz, 1H), 4.52 – 4.46 (m, 1H), 4.45 – 4.38 (m, 2H), 4.34 – 4.27 (m, 2H), 4.15 – 4.07 (m, 2H), 4.07 – 3.97 (m, 4H), 3.93 – 3.83 (m, 3H), 3.82 – 3.77 (m, 3H), 3.76 – 3.69 (m, 5H), 3.64 – 3.54 (m, 1H), 2.47 (s, 3H), 2.26 (dd, *J* = 13.2, 7.6 Hz, 1H), 2.22 – 2.12 (m, 1H), 2.08 (ddd, *J* = 13.4, 9.4, 4.3 Hz, 1H), 2.00 – 1.91 (m, 2H), 1.90 – 1.75 (m, 1H), 1.66 – 1.53 (m, 2H), 1.02 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{55}H_{67}F_4N_{10}O_{11}S^+$, 1151.4642; found 1151.4645.



Example 164: 2-(((3*R*,4*R*)-3-Fluoro-1-(2-(4-(trifluoromethoxy)phenyl)acetyl)piperidin-4-yl)oxy)-5-(1-((*S*)-3-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-2,2-dimethyl-5,14-dioxo-8,11-dioxa-4,15-diazanonadecan-19-yl)-1*H*-imidazol-4-yl)nicotinamide. 38% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 9.07 (s, 1H), 8.96 (s, 1H), 8.67 (dd, *J* = 4.7, 2.6 Hz, 1H), 8.59 (dd, *J* = 6.1, 2.6 Hz, 1H), 8.09 (d, *J* = 2.0 Hz, 1H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 8.2 Hz, 2H), 7.38 – 7.35 (m, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 5.69 – 5.60 (m, 1H), 4.83 – 4.77 (m, 1H), 4.64 (s, 1H), 4.60 – 4.52 (m, 1H), 4.52 – 4.47 (m, 2H), 4.36 (d, *J* = 15.5 Hz, 1H), 4.31 (t, *J* = 7.3 Hz, 2H), 4.15 – 3.99 (m, 1H), 3.93 – 3.84 (m, 3H), 3.80 (dd, *J* = 11.0, 4.0 Hz, 3H), 3.75 – 3.64 (m, 5H), 3.61 – 3.51 (m, 5H), 3.26 (t, *J* = 6.8 Hz, 2H), 2.57 – 2.51 (m, 1H), 2.47 (s, 4H), 2.44 – 2.39 (m, 2H), 2.28 – 2.17 (m, 1H), 2.08 (ddd, *J* = 13.4, 9.3, 4.4 Hz, 1H), 1.97 (p, *J* = 7.5 Hz, 2H), 1.84 (d, *J* = 49.2 Hz, 1H), 1.57 (p, *J* = 7.0 Hz, 2H), 1.03 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{57}H_{71}F_4N_{10}O_{11}S^+$, 1179.4955; found 1179.5066.

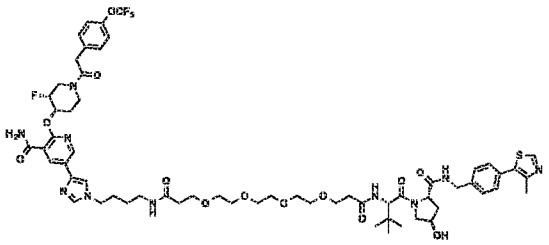


Example 165: 2-(((3*R*,4*R*)-3-Fluoro-1-(2-(4-(trifluoromethoxy)phenyl)acetyl)piperidin-4-yl)oxy)-5-(1-((*S*)-3-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-2,2-dimethyl-5,15-dioxo-7,10,13-trioxa-4,16-diazaicosan-20-yl)-1*H*-imidazol-4-yl)nicotinamide. 30% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 9.07 (s, 1H), 8.95 (s, 1H), 8.66 (dd, *J* = 4.7, 2.6 Hz, 1H), 8.58 (dd, *J* = 6.1, 2.6 Hz, 1H), 8.09 (d, *J* = 2.1 Hz, 1H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.39 – 7.35 (m, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 5.64 (brs, 1H), 4.82 – 4.73 (m, 1H), 4.70 (s, 1H), 4.60 – 4.54 (m, 2H), 4.53 – 4.47 (m, 2H), 4.36 (d, *J* = 15.5 Hz, 1H), 4.33 – 4.27 (m, 2H), 4.11 – 3.98 (m, 3H), 3.98 – 3.91 (m, 2H), 3.91 – 3.84 (m, 3H), 3.83 – 3.76 (m, 3H), 3.75 – 3.65 (m, 9H), 3.30 – 3.28 (m, 1H), 2.47 (s, 3H), 2.29 – 2.17 (m, 2H), 2.09 (ddd, *J* = 13.4, 9.4, 4.4 Hz, 1H), 1.95 (p, *J* = 7.4 Hz, 2H), 1.90 – 1.76 (m, 1H), 1.58 (p, *J* = 7.2 Hz, 2H), 1.03 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{57}H_{71}F_4N_{10}O_{12}S^+$, 1195.4904; found 1195.5010.

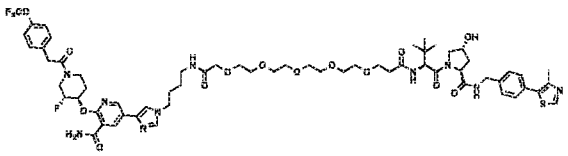


Example 166: 2-(((3*R*,4*R*)-3-Fluoro-1-(2-(4-(trifluoromethoxy)phenyl)acetyl)piperidin-4-yl)oxy)-5-(1-((*S*)-3-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-2,2-dimethyl-5,17-dioxo-8,11,14-trioxa-4,18-diazadocosan-22-yl)-1*H*-imidazol-4-yl)nicotinamide. 30% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 9.05 (s, 1H), 8.91 (s, 1H), 8.67 (dd, *J* = 4.7, 2.5 Hz, 1H), 8.59 (dd, *J* = 6.0, 2.6 Hz, 1H), 8.09 (t, *J* = 1.9 Hz, 1H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.40 (d, *J* = 8.1 Hz, 2H), 7.39 – 7.34 (m, 2H), 7.24 (d, *J* = 8.5 Hz, 2H), 5.65 (brs, 1H), 4.85 – 4.76 (m, 1H), 4.64 (s, 1H), 4.60 – 4.54 (m, 1H), 4.52 – 4.47 (m, 1H), 4.36 (d, *J* = 15.5 Hz, 1H), 4.31 (t, *J* = 7.3 Hz, 2H), 4.15 – 3.99 (m, 1H), 3.93 – 3.83

(m, 3H), 3.80 (dd, J = 11.0, 4.0 Hz, 2H), 3.70 (dt, J = 13.7, 6.0 Hz, 4H), 3.63 – 3.51 (m, 8H), 3.35 (s, 4H), 3.27 (t, J = 6.7 Hz, 2H), 2.56 (ddd, J = 15.0, 7.3, 5.3 Hz, 1H), 2.47 (s, 3H), 2.42 (t, J = 6.0 Hz, 2H), 2.29 – 2.18 (m, 2H), 2.08 (ddd, J = 13.3, 9.3, 4.5 Hz, 1H), 1.97 (p, J = 7.4 Hz, 2H), 1.91 – 1.76 (m, 1H), 1.57 (p, J = 7.0 Hz, 2H), 1.03 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{59}H_{75}F_4N_{10}O_{12}S^+$, 1223.5217; found 1223.5263.

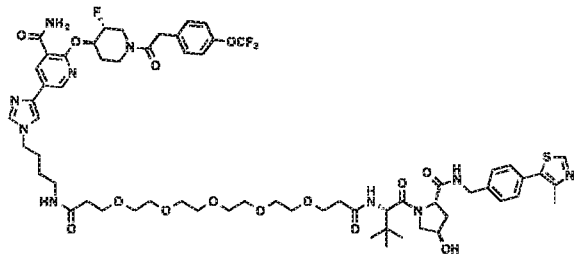


Example 167: N^1-(4-(4-(5-Carbamoyl-6-(((3*R*,4*R*)-3-fluoro-1-(2-(4-(trifluoromethoxy)phenyl)acetyl)piperidin-4-yl)oxy)pyridin-3-yl)-1*H*-imidazol-1-yl)butyl)-N^{16}-((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-4,7,10,13-tetraoxahexadecanediamide. 31% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 9.06 (s, 1H), 8.91 (s, 1H), 8.67 (dd, J = 4.6, 2.5 Hz, 1H), 8.59 (dd, J = 6.2, 2.6 Hz, 1H), 8.10 (d, J = 2.1 Hz, 1H), 7.46 (d, J = 8.1 Hz, 2H), 7.41 (d, J = 8.2 Hz, 2H), 7.38 – 7.34 (m, 2H), 7.27 – 7.20 (m, 2H), 5.75 – 5.58 (m, 1H), 4.84 – 4.75 (m, 1H), 4.64 (s, 1H), 4.60 – 4.54 (m, 1H), 4.53 – 4.47 (m, 1H), 4.36 (d, J = 15.5 Hz, 1H), 4.32 (t, J = 7.3 Hz, 2H), 4.17 – 3.97 (m, 1H), 3.94 – 3.84 (m, 3H), 3.80 (dd, J = 11.0, 3.9 Hz, 2H), 3.75 – 3.66 (m, 5H), 3.65 – 3.52 (m, 13H), 3.35 (s, 2H), 3.27 (t, J = 6.7 Hz, 2H), 2.59 – 2.52 (m, 1H), 2.47 (s, 3H), 2.42 (t, J = 6.0 Hz, 2H), 2.32 – 2.18 (m, 2H), 2.08 (ddd, J = 13.3, 9.2, 4.4 Hz, 1H), 1.97 (p, J = 7.4 Hz, 2H), 1.91 – 1.76 (m, 1H), 1.58 (p, J = 6.9 Hz, 2H), 1.03 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{61}H_{79}F_4N_{10}O_{13}S^+$, 1267.5479; found 1267.5484.

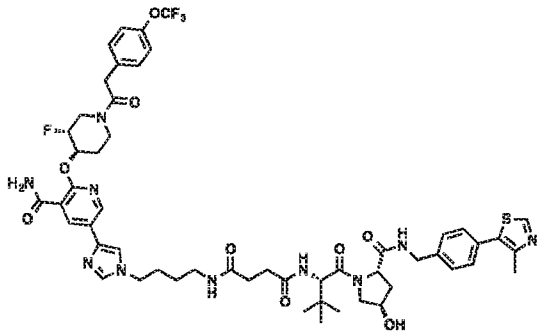


Example 168: N^1-(4-(4-(5-Carbamoyl-6-(((3*R*,4*R*)-3-fluoro-1-(2-(4-(trifluoromethoxy)phenyl)acetyl)piperidin-4-yl)oxy)pyridin-3-yl)-1*H*-imidazol-1-yl)butyl)-N^{18}-((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-3,6,9,12,15-pentaoxaoctadecanediamide. 31% yield. ^{1}H

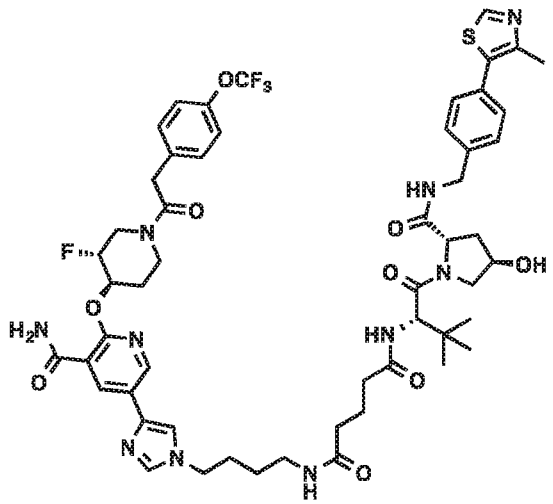
NMR (600 MHz, CD_3OD) δ 9.09 (s, 1H), 8.95 (s, 1H), 8.67 (dd, *J* = 4.7, 2.6 Hz, 1H), 8.59 (dd, *J* = 5.8, 2.6 Hz, 2H), 8.10 (s, 1H), 7.46 (d, *J* = 8.1 Hz, 3H), 7.44 – 7.40 (m, 4H), 7.37 (d, *J* = 8.0 Hz, 4H), 7.24 (d, *J* = 8.1 Hz, 4H), 5.69 – 5.61 (m, 1H), 4.84 – 4.76 (m, 1H), 4.69 (s, 1H), 4.59 – 4.56 (m, 1H), 4.55 (d, *J* = 5.4 Hz, 1H), 4.53 – 4.48 (m, 2H), 4.36 (d, *J* = 15.6 Hz, 1H), 4.32 (t, *J* = 7.3 Hz, 2H), 4.09 – 4.00 (m, 3H), 3.97 (s, 2H), 3.91 – 3.84 (m, 3H), 3.83 – 3.76 (m, 3H), 3.71 – 3.67 (m, 5H), 3.66 – 3.62 (m, 10H), 3.61 – 3.57 (m, 5H), 2.48 (s, 3H), 2.36 – 2.16 (m, 2H), 2.08 (ddd, *J* = 13.2, 9.3, 4.3 Hz, 1H), 1.97 (p, *J* = 7.4 Hz, 2H), 1.91 – 1.76 (m, 1H), 1.61 (q, *J* = 7.5 Hz, 2H), 1.04 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{62}H_{81}F_4N_{10}O_{14}S^+$, 1297.5585; found 1297.5586.



Example 169: N^1-(4-(4-(5-Carbamoyl-6-(((3*R*,4*R*)-3-fluoro-1-(2-(4-(trifluoromethoxy)phenyl)acetyl)piperidin-4-yl)oxy)pyridin-3-yl)-1*H*-imidazol-1-yl)butyl)-N^{19}-((*S*)-1-((2*S*,4*R*)-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. 33% yield. ^1H NMR (600 MHz, CD_3OD) δ 9.08 (s, 1H), 8.94 (s, 1H), 8.68 (dd, *J* = 4.5, 2.5 Hz, 1H), 8.60 (dd, *J* = 6.3, 2.6 Hz, 1H), 8.11 (t, *J* = 1.8 Hz, 1H), 7.47 (d, *J* = 8.1 Hz, 2H), 7.41 (d, *J* = 8.2 Hz, 2H), 7.37 (dd, *J* = 8.6, 1.9 Hz, 2H), 7.28 – 7.15 (m, 2H), 5.70 – 5.61 (m, 1H), 4.83 – 4.75 (m, 1H), 4.65 (s, 1H), 4.60 – 4.54 (m, 1H), 4.53 – 4.48 (m, 1H), 4.36 (d, *J* = 15.5 Hz, 1H), 4.32 (t, *J* = 7.3 Hz, 2H), 4.18 – 3.97 (m, 1H), 3.94 – 3.83 (m, 3H), 3.80 (dd, *J* = 11.0, 3.8 Hz, 3H), 3.74 – 3.66 (m, 5H), 3.61 – 3.58 (m, 8H), 3.57 – 3.54 (m, 9H), 3.28 (t, *J* = 6.7 Hz, 2H), 2.56 (ddd, *J* = 14.9, 7.4, 5.1 Hz, 1H), 2.47 (s, 4H), 2.42 (t, *J* = 5.9 Hz, 2H), 2.29 – 2.18 (m, 2H), 2.08 (ddd, *J* = 13.3, 9.2, 4.5 Hz, 1H), 1.98 (p, *J* = 7.4 Hz, 2H), 1.91 – 1.76 (m, 1H), 1.58 (p, *J* = 6.9 Hz, 2H), 1.03 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{63}H_{83}F_4N_{10}O_{14}S^+$, 1311.5742; found 1311.5700.

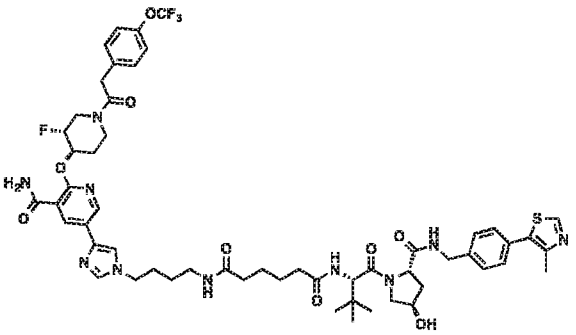


Example 170: N^1-(4-(4-(5-Carbamoyl-6-(((3*R*,4*R*)-3-fluoro-1-(2-(4-(trifluoromethoxy)phenyl)acetyl)piperidin-4-yl)oxy)pyridin-3-yl)-1*H*-imidazol-1-yl)butyl)-N^4-((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)succinamide. 37% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 9.07 (s, 1H), 8.91 (s, 1H), 8.67 (dd, *J* = 4.7, 2.6 Hz, 1H), 8.59 (dd, *J* = 6.3, 2.5 Hz, 1H), 8.12 (d, *J* = 2.9 Hz, 1H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.40 (d, *J* = 8.1 Hz, 2H), 7.38 – 7.35 (m, 2H), 7.24 (d, *J* = 8.1 Hz, 2H), 5.69 – 5.60 (m, 1H), 4.82 – 4.72 (m, 1H), 4.59 (s, 1H), 4.57 – 4.53 (m, 1H), 4.52 – 4.46 (m, 1H), 4.36 (d, *J* = 15.5 Hz, 1H), 4.31 (t, *J* = 7.3 Hz, 2H), 4.21 – 3.96 (m, 1H), 3.94 – 3.83 (m, 4H), 3.82 – 3.74 (m, 3H), 3.66 – 3.55 (m, 1H), 3.24 (t, *J* = 6.8 Hz, 2H), 2.66 – 2.59 (m, 1H), 2.56 – 2.50 (m, 1H), 2.49 – 2.45 (m, 5H), 2.31 – 2.17 (m, 2H), 2.07 (ddd, *J* = 13.3, 9.2, 4.4 Hz, 1H), 1.96 (p, *J* = 7.5 Hz, 2H), 1.90 – 1.74 (m, 1H), 1.56 (p, *J* = 7.1 Hz, 2H), 1.01 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{53}H_{63}F_4N_{10}O_9S^+$, 1091.4431; found 1091.4437.

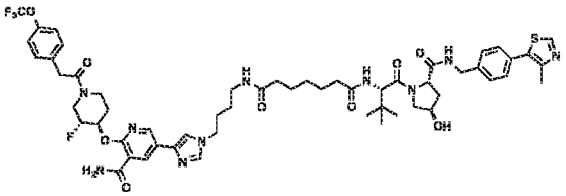


Example 171: N^1-(4-(4-(5-Carbamoyl-6-(((3*R*,4*R*)-3-fluoro-1-(2-(4-(trifluoromethoxy)phenyl)acetyl)piperidin-4-yl)oxy)pyridin-3-yl)-1*H*-imidazol-1-yl)butyl)-N^5-((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)glutaramide. 35% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 9.09

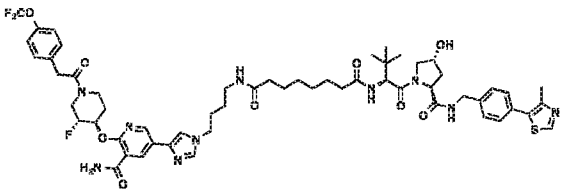
(s, 1H), 8.96 (s, 1H), 8.67 (dd, J = 4.7, 2.6 Hz, 1H), 8.58 (dd, J = 6.2, 2.6 Hz, 1H), 8.09 (d, J = 2.3 Hz, 1H), 7.46 (d, J = 8.1 Hz, 2H), 7.41 (d, J = 8.1 Hz, 2H), 7.38 – 7.33 (m, 2H), 7.24 (d, J = 8.1 Hz, 2H), 5.69 – 5.60 (m, 1H), 4.83 – 4.76 (m, 1H), 4.61 (s, 1H), 4.59 – 4.55 (m, 1H), 4.55 – 4.52 (m, 1H), 4.51 – 4.48 (m, 1H), 4.36 (d, J = 15.5 Hz, 1H), 4.31 (t, J = 7.3 Hz, 2H), 4.16 – 3.97 (m, 1H), 3.92 (d, J = 10.8 Hz, 1H), 3.90 – 3.87 (d, J = 9.3 Hz, 2H), 3.84 – 3.76 (m, 2H), 3.65 – 3.55 (m, 1H), 3.24 (t, J = 6.9 Hz, 2H), 2.47 (s, 3H), 2.38 – 2.25 (m, 3H), 2.25 – 2.18 (m, 3H), 2.16 (s, 2H), 2.08 (ddd, J = 13.3, 9.2, 4.4 Hz, 1H), 1.99 – 1.92 (m, 2H), 1.91 – 1.85 (m, 2H), 1.57 (p, J = 7.1 Hz, 2H), 1.03 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{54}H_{65}F_4N_{10}O_9S^+$, 1105.4587; found 1105.4619.



Example 172: N^1-(4-(4-(5-Carbamoyl-6-(((3*R*,4*R*)-3-fluoro-1-(2-(4-(trifluoromethoxy)phenyl)acetyl)piperidin-4-yl)oxy)pyridin-3-yl)-1*H*-imidazol-1-yl)butyl)-N^6-((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)adipamide. 39% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 9.10 (s, 1H), 8.97 (s, 1H), 8.67 (dd, J = 4.6, 2.5 Hz, 1H), 8.58 (dd, J = 6.2, 2.6 Hz, 1H), 8.10 (t, J = 1.9 Hz, 1H), 7.47 (d, J = 8.0 Hz, 2H), 7.41 (d, J = 8.1 Hz, 2H), 7.38 – 7.35 (m, 2H), 7.24 (d, J = 8.1 Hz, 2H), 5.69 – 5.60 (m, 1H), 4.83 – 4.76 (m, 1H), 4.62 (s, 1H), 4.60 – 4.54 (m, 1H), 4.53 (d, J = 15.8 Hz, 1H), 4.51 – 4.48 (m, 1H), 4.36 (d, J = 15.5 Hz, 1H), 4.32 (t, J = 7.2 Hz, 2H), 4.19 – 3.96 (m, 1H), 3.93 – 3.83 (m, 3H), 3.80 (dd, J = 11.1, 4.1 Hz, 3H), 3.64 – 3.54 (m, 1H), 3.24 (t, J = 6.8 Hz, 2H), 2.47 (s, 3H), 2.37 – 2.24 (m, 3H), 2.23 – 2.18 (m, 3H), 2.08 (ddd, J = 13.3, 9.1, 4.4 Hz, 1H), 1.96 (p, J = 7.3 Hz, 2H), 1.91 – 1.76 (m, 1H), 1.67 – 1.59 (m, 4H), 1.56 (q, J = 7.5 Hz, 2H), 1.03 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{55}H_{67}F_4N_{10}O_9S^+$, 1119.4744; found 1119.4723.

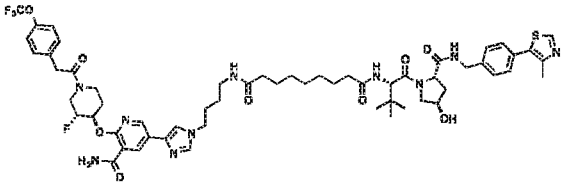


Example 173: N^1-(4-(4-(5-Carbamoyl-6-(((3*R*,4*R*)-3-fluoro-1-(2-(4-(trifluoromethoxy)phenyl)acetyl)piperidin-4-yl)oxy)pyridin-3-yl)-1*H*-imidazol-1-yl)butyl)-N^7-((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)heptanediamide. 30% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 9.10 (s, 1H), 9.02 (s, 1H), 8.67 (dd, *J* = 4.7, 2.6 Hz, 1H), 8.58 (dd, *J* = 6.3, 2.6 Hz, 1H), 8.10 (d, *J* = 1.9 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.42 (d, *J* = 8.2 Hz, 2H), 7.39 – 7.34 (m, 2H), 7.29 – 7.16 (m, 2H), 5.69 – 5.60 (m, 1H), 4.83 – 4.75 (m, 1H), 4.63 (s, 1H), 4.59 – 4.56 (m, 1H), 4.53 (d, *J* = 16.2 Hz, 1H), 4.51 – 4.48 (m, 1H), 4.36 (d, *J* = 15.5 Hz, 1H), 4.32 (t, *J* = 7.1 Hz, 2H), 4.17 – 3.97 (m, 1H), 3.93 – 3.83 (m, 3H), 3.80 (dd, *J* = 11.0, 4.0 Hz, 3H), 3.66 – 3.55 (m, 1H), 3.23 (t, *J* = 7.0 Hz, 2H), 2.48 (s, 3H), 2.33 – 2.25 (m, 1H), 2.26 – 2.20 (m, 3H), 2.18 (t, *J* = 7.5 Hz, 2H), 2.08 (ddd, *J* = 13.4, 9.2, 4.5 Hz, 1H), 1.96 (p, *J* = 7.3 Hz, 2H), 1.91 – 1.76 (m, 1H), 1.66 – 1.53 (m, 6H), 1.33 (p, *J* = 7.7 Hz, 2H), 1.03 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{56}H_{69}F_4N_{10}O_9S^+$, 1133.4900; found 1133.4889.

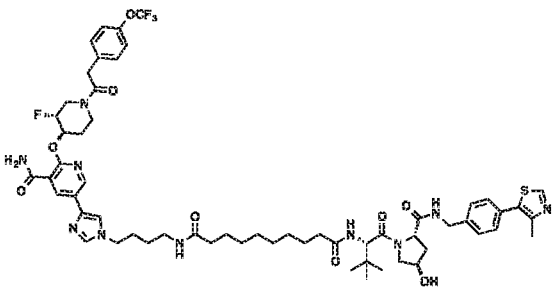


Example 174: N^1-(4-(4-(5-Carbamoyl-6-(((3*R*,4*R*)-3-fluoro-1-(2-(4-(trifluoromethoxy)phenyl)acetyl)piperidin-4-yl)oxy)pyridin-3-yl)-1*H*-imidazol-1-yl)butyl)-N^8-((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)octanediamide. 38% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 9.05 (s, 1H), 8.91 (s, 1H), 8.67 (dd, *J* = 4.6, 2.6 Hz, 1H), 8.58 (dd, *J* = 6.2, 2.6 Hz, 1H), 8.08 (d, *J* = 1.8 Hz, 1H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 8.2 Hz, 2H), 7.38 – 7.34 (m, 2H), 7.29 – 7.20 (m, 2H), 5.78 – 5.57 (m, 1H), 4.83 – 4.76 (d, *J* = 17.3 Hz, 1H), 4.63 (s, 1H), 4.60 – 4.55 (m, 1H), 4.53 (d, *J* = 15.5 Hz, 1H), 4.51 – 4.48 (m, 1H), 4.36 (d, *J* = 15.5 Hz, 1H), 4.31 (t, *J* = 7.3 Hz, 2H), 4.19 – 3.95 (m, 1H), 3.94 – 3.84 (m, 3H), 3.80 (dd, *J* = 11.0, 4.0 Hz, 3H), 3.66 – 3.55 (m, 1H), 3.24 (t, *J* = 7.0 Hz, 2H), 2.47 (s, 3H), 2.31 – 2.27 (m, 1H), 2.26 – 2.19 (m, 3H), 2.17 (t,

J = 7.5 Hz, 2H), 2.08 (ddd, *J* = 13.2, 9.2, 4.5 Hz, 1H), 1.95 (p, *J* = 7.3 Hz, 2H), 1.91 – 1.76 (m, 1H), 1.64 – 1.52 (m, 6H), 1.43 – 1.23 (m, 4H), 1.03 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{57}H_{71}F_4N_{10}O_9S^+$, 1147.5057; found 1147.5161.

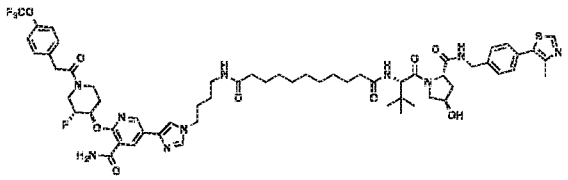


Example 175: N^1-(4-(4-(5-Carbamoyl-6-(((3*R*,4*R*)-3-fluoro-1-(2-(4-(trifluoromethoxy)phenyl)acetyl)piperidin-4-yl)oxy)pyridin-3-yl)-1*H*-imidazol-1-yl)butyl)-N^9-((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)nonanediamide. 37% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 9.12 (s, 1H), 9.05 (s, 1H), 8.69 (dd, *J* = 4.6, 2.6 Hz, 1H), 8.60 (dd, *J* = 6.3, 2.6 Hz, 1H), 8.11 (d, *J* = 2.0 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 8.2 Hz, 2H), 7.40 – 7.35 (m, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 5.71 – 5.62 (m, 1H), 4.85 – 4.77 (m, 1H), 4.65 (s, 1H), 4.61 – 4.57 (m, 1H), 4.55 (d, *J* = 15.5 Hz, 1H), 4.52 – 4.50 (m, 1H), 4.38 (d, *J* = 15.5 Hz, 1H), 4.34 (t, *J* = 7.2 Hz, 2H), 4.20 – 4.00 (m, 1H), 3.96 – 3.85 (m, 3H), 3.82 (dd, *J* = 11.0, 4.0 Hz, 2H), 3.66 – 3.58 (m, 1H), 3.25 (t, *J* = 6.9 Hz, 2H), 2.50 (s, 3H), 2.30 (dq, *J* = 15.3, 7.6 Hz, 2H), 2.24 (dd, *J* = 13.6, 7.4 Hz, 2H), 2.20 – 2.16 (m, 4H), 2.10 (ddd, *J* = 13.3, 9.2, 4.5 Hz, 1H), 1.97 (p, *J* = 7.3 Hz, 2H), 1.93 – 1.78 (m, 1H), 1.67 – 1.51 (m, 6H), 1.38 – 1.26 (m, 5H), 1.05 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{58}H_{73}F_4N_{10}O_9S^+$, 1161.5213; found 1161.5303.

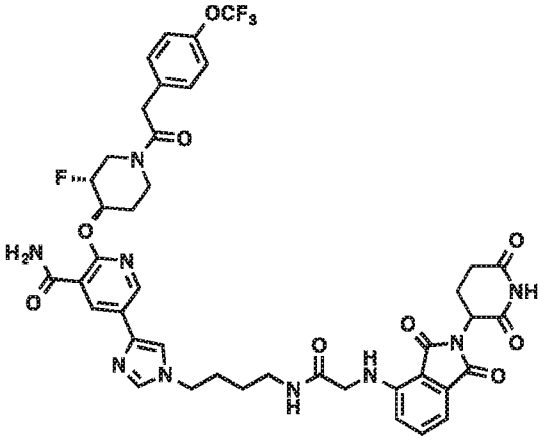


Example 176: N^1-(4-(4-(5-Carbamoyl-6-(((3*R*,4*R*)-3-fluoro-1-(2-(4-(trifluoromethoxy)phenyl)acetyl)piperidin-4-yl)oxy)pyridin-3-yl)-1*H*-imidazol-1-yl)butyl)-N^{10}-((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-

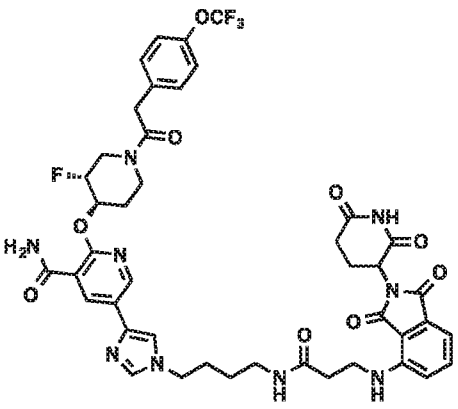
yl)-3,3-dimethyl-1-oxobutan-2-yl)decanediamide. 30% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 9.07 (s, 1H), 8.92 (s, 1H), 8.67 (dd, *J* = 4.6, 2.6 Hz, 1H), 8.58 (dd, *J* = 6.2, 2.6 Hz, 1H), 8.09 (t, *J* = 2.0 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 8.2 Hz, 2H), 7.39 – 7.35 (m, 2H), 7.24 (d, *J* = 8.1 Hz, 2H), 5.69 – 5.60 (m, 1H), 4.83 – 4.76 (m, 1H), 4.64 (s, 1H), 4.59 – 4.55 (m, 1H), 4.55 – 4.52 (s, 1H), 4.51 – 4.48 (m, 1H), 4.36 (d, *J* = 15.5 Hz, 1H), 4.32 (t, *J* = 7.3 Hz, 2H), 4.21 – 3.96 (m, 1H), 3.95 – 3.84 (m, 3H), 3.80 (dd, *J* = 11.0, 4.1 Hz, 3H), 3.68 – 3.56 (m, 1H), 3.24 (t, *J* = 6.9 Hz, 2H), 2.47 (s, 3H), 2.28 (dq, *J* = 15.6, 7.8 Hz, 2H), 2.22 (dd, *J* = 13.4, 7.1 Hz, 2H), 2.17 (t, *J* = 7.5 Hz, 2H), 2.08 (ddd, *J* = 13.3, 9.1, 4.5 Hz, 1H), 1.96 (p, *J* = 7.4 Hz, 2H), 1.91 – 1.76 (m, 1H), 1.64 – 1.52 (m, 6H), 1.34 – 1.25 (m, 8H), 1.03 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{59}H_{75}F_4N_{10}O_9S^+$, 1175.5370; found 1175.5453.



Example 177: N^1-(4-(4-(5-Carbamoyl-6-(((3*R*,4*R*)-3-fluoro-1-(2-(4-(trifluoromethoxy)phenyl)acetyl)piperidin-4-yl)oxy)pyridin-3-yl)-1*H*-imidazol-1-yl)butyl)-N^{11}-((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)undecanediamide. 31% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 9.02 (s, 1H), 8.90 (s, 1H), 8.67 (dd, *J* = 4.6, 2.6 Hz, 1H), 8.58 (dd, *J* = 6.3, 2.6 Hz, 1H), 8.07 (t, *J* = 1.9 Hz, 1H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.41 (d, *J* = 8.2 Hz, 2H), 7.39 – 7.34 (m, 2H), 7.24 (d, *J* = 8.5 Hz, 2H), 5.69 – 5.60 (m, 1H), 4.83 – 4.75 (m, 1H), 4.63 (s, 1H), 4.60 – 4.55 (m, 1H), 4.54 – 4.51 (m, 1H), 4.51 – 4.47 (m, 1H), 4.35 (d, *J* = 15.5 Hz, 1H), 4.31 (t, *J* = 7.3 Hz, 2H), 4.16 – 3.99 (m, 1H), 3.94 – 3.84 (m, 3H), 3.83 – 3.76 (m, 3H), 3.65 – 3.56 (m, 1H), 3.24 (t, *J* = 6.9 Hz, 2H), 2.47 (s, 3H), 2.28 (td, *J* = 15.3, 14.9, 7.7 Hz, 2H), 2.23 – 2.19 (m, 2H), 2.17 (t, *J* = 7.5 Hz, 2H), 2.08 (ddd, *J* = 13.3, 9.1, 4.5 Hz, 1H), 1.95 (p, *J* = 7.4 Hz, 2H), 1.91 – 1.76 (m, 1H), 1.57 (q, *J* = 7.4 Hz, 6H), 1.35 – 1.22 (m, 10H), 1.03 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{60}H_{77}F_4N_{10}O_9S^+$, 1189.5526; found 1189.5613.



Example 178: 5-(1-(4-(2-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)acetamido)butyl)-1*H*-imidazol-4-yl)-2-(((3*R*,4*R*)-3-fluoro-1-(2-(4-(trifluoromethoxy)phenyl)acetyl)piperidin-4-yl)oxy)nicotinamide. 35% yield. ^{1}H NMR (600 MHz, CD_3OD) δ 9.05 (s, 1H), 8.62 (dd, *J* = 5.2, 2.6 Hz, 1H), 8.55 (dd, *J* = 6.5, 2.6 Hz, 1H), 8.00 (d, *J* = 1.8 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 1H), 7.37 (dd, *J* = 8.5, 2.0 Hz, 2H), 7.25 (d, *J* = 8.1 Hz, 2H), 7.05 (d, *J* = 7.1 Hz, 1H), 6.86 (d, *J* = 8.5 Hz, 1H), 5.69 – 5.60 (m, 1H), 5.05 (dd, *J* = 12.9, 5.5 Hz, 1H), 4.28 (t, *J* = 7.3 Hz, 2H), 4.17 – 4.02 (m, 1H), 4.00 (s, 2H), 3.94 – 3.84 (m, 3H), 3.84 – 3.72 (m, 2H), 3.64 – 3.58 (m, 1H), 2.85 (ddd, *J* = 17.7, 14.0, 5.3 Hz, 1H), 2.77 – 2.72 (m, 1H), 2.72 – 2.65 (m, 1H), 2.31 – 2.17 (m, 1H), 2.10 (ddt, *J* = 12.3, 6.9, 3.9 Hz, 1H), 1.90 (p, *J* = 7.4 Hz, 3H), 1.84 – 1.77 (m, 1H), 1.57 (p, *J* = 7.0 Hz, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{42}H_{42}F_4N_9O_9^+$, 892.3036; found 892.4059.



Example 179: 5-(1-(4-(3-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propanamido)butyl)-1*H*-imidazol-4-yl)-2-(((3*R*,4*R*)-3-fluoro-1-(2-(4-

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME 1 DE 2
CONTENANT LES PAGES 1 À 227

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JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME 1 OF 2
CONTAINING PAGES 1 TO 227

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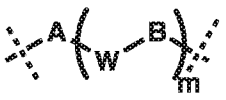
NOM DU FICHIER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

CLAIMS

What is claimed is:

1. A bivalent compound comprising a protein tyrosine kinase 6 (PTK6) ligand conjugated to a degradation/disruption tag through a linker, said linker selected from the group consisting of:

(a) 

FORMULA 7

wherein

A, W and B, at each occurrence, are independently selected from null, or bivalent moiety selected from R'-R'', R'COR'', R'CO_2R'', R'C(O)N(R^1)R'', R'C(S)N(R^1)R'', R'OR'', R'OC(O)R'', R'OC(O)OR'', R'OCON(R^1)R'', R'SR'', R'SOR'', R'SO_2R'', R'SO_2N(R^1)R'', R'N(R^1)R'', R'NR^1COR'', R'NR^1C(O)OR'', R'NR^1CON(R^2)R'', R'NR^1C(S)R'', R'NR^1S(O)R'', R'NR^1S(O)$_2$R'', and R'NR^1S(O)$_2$N(R^2)R'', wherein

R' and R'' are independently selected from null, optionally substituted R^r-(C_1-C_8 alkyl), or a moiety comprising of optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 hydroxyalkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-C_8 alkylene, optionally substituted C_2-C_8 alkenylene, optionally substituted C_2-C_8 alkynylene, optionally substituted C_1-C_8 hydroxyalkylene, optionally substituted C_1-C_8alkoxyC_1-C_8alkylene, optionally substituted C_1-C_8alkylaminoC_1-C_8alkylene, optionally substituted C_1-C_8 haloalkylene, optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted C_3-C_{13} fused cycloalkyl, optionally substituted C_3-C_{13} fused heterocyclyl, optionally substituted C_3-C_{13} bridged cycloalkyl, optionally substituted C_3-C_{13} bridged heterocyclyl,

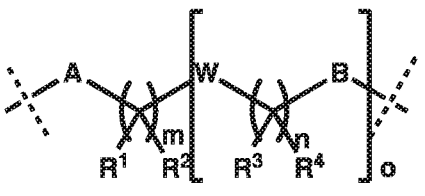
optionally substituted C_3-C_{13} spiro cycloalkyl, optionally substituted C_3-C_{13} spiro heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^r is selected from optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted C_3-C_{13} fused cycloalkyl, optionally substituted C_3-C_{13} fused heterocyclyl, optionally substituted C_3-C_{13} bridged cycloalkyl, optionally substituted C_3-C_{13} bridged heterocyclyl, optionally substituted C_3-C_{13} spiro cycloalkyl, optionally substituted C_3-C_{13} spiro heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^1 and R^2 are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxyalkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-C_8 hydroxyalkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

$R^{'}$ and $R^{''}$, R^1 and R^2, $R^{'}$ and R^1, $R^{'}$ and R^2, $R^{''}$ and R^1, $R^{''}$ and R^2 together with the atom to which they are connected form a 3-20 membered cycloalkyl or 4-20 membered heterocyclyl ring; and

m is 0 to 15;

(b) 

FORMULA 7A,

wherein

R^1, R^2, R^3 and R^4, at each occurrence, are independently selected from hydrogen, halogen, hydroxyl, amino, cyano, nitro, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8 alkoxyalkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-C_8 hydroxyalkyl, optionally substituted C_1-C_8 alkylamino, and optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-10 membered carbocyclyl,

optionally substituted 3-8 membered cycloalkoxy, optionally substituted 3-10 membered carbocyclylamino, optionally substituted 4-8 membered membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^1 and R^2, R^3 and R^4 together with the atom to which they are connected form a 3-20 membered cycloalkyl or 4-20 membered heterocyclyl ring;

A, W and B, at each occurrence, are independently selected from null, or bivalent moiety selected from R'-R'', $R'COR''$, $R'CO_2R''$, $R'C(O)N(R^5)R''$, $R'C(S)N(R^5)R''$, $R'OR''$, $R'OC(O)R''$, $R'OC(O)OR''$, $R'OCONR^5R''$, $R'SR''$, $R'SOR''$, $R'SO_2R''$, $R'SO_2N(R^5)R''$, $R'N(R^5)R''$, $R'NR^5COR''$, $R'NR^5C(O)OR''$, $R'NR^5CON(R^6)R''$, $R'NR^5C(S)R''$, $R'NR^5S(O)R''$, $R'NR^5S(O)_2R''$, and $R'NR^5S(O)_2N(R^6)R''$, wherein

R' and R'' are independently selected from null, optionally substituted R^r-(C_1-C_8 alkyl), or a moiety comprising of optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 hydroxyalkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-C_8 alkylene, optionally substituted C_2-C_8 alkenylene, optionally substituted C_2-C_8 alkynylene, optionally substituted C_1-C_8 hydroxyalkylene, optionally substituted C_1-C_8alkoxyC_1-C_8alkylene, optionally substituted C_1-C_8alkylaminoC_1-C_8alkylene, optionally substituted C_1-C_8 haloalkylene, optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted C_3-C_{13} fused cycloalkyl, optionally substituted C_3-C_{13} fused heterocyclyl, optionally substituted C_3-C_{13} bridged cycloalkyl, optionally substituted C_3-C_{13} bridged heterocyclyl, optionally substituted C_3-C_{13} spiro cycloalkyl, optionally substituted C_3-C_{13} spiro heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^r is selected from optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted C_3-C_{13} fused cycloalkyl, optionally substituted C_3-C_{13} fused heterocyclyl, optionally substituted C_3-C_{13} bridged cycloalkyl, optionally substituted C_3-C_{13} bridged heterocyclyl, optionally substituted C_3-C_{13} spiro cycloalkyl, optionally substituted C_3-C_{13} spiro heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^5 and R^6 are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted

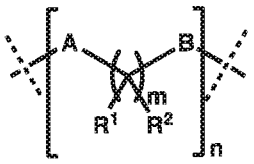
C_1-C_8 alkoxyalkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-C_8 hydroxyalkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

$R^{'}$ and $R^{''}$, R^5 and R^6, $R^{'}$ and R^5, $R^{'}$ and R^6, $R^{''}$ and R^5, $R^{''}$ and R^6 together with the atom to which they are connected form a 3-20 membered cycloalkyl or 4-20 membered heterocyclyl ring;

m is 0 to 15;

n, at each occurrence, is 0 to 15; and

o is 0 to 15;

(c) 

FORMULA 7B,

wherein

R^1 and R^2, at each occurrence, are independently selected from hydrogen, halogen, hydroxyl, amino, cyano, nitro, and optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8 alkoxy C_1-C_8 alkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-C_8 hydroxyalkyl, optionally substituted C_1-C_8 alkylamino, C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted 3-10 membered carbocyclyl, optionally substituted 3-8 membered cycloalkoxy, optionally substituted 3-10 membered carbocyclylamino, optionally substituted 4-10 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^1 and R^2 together with the atom to which they are connected form a 3-20 membered cycloalkyl or 4-20 membered heterocyclyl ring;

A and B, at each occurrence, are independently selected from null, or bivalent moiety selected from $R^{'}$-$R^{''}$, $R^{'}COR^{''}$, $R^{'}CO_2R^{''}$, $R^{'}C(O)NR^3R^{''}$, $R^{'}C(S)NR^3R^{''}$, $R^{'}OR^{''}$, $R^{'}OC(O)R^{''}$, $R^{'}OC(O)OR^{''}$, $R^{'}OCON(R^3)R^{''}$, $R^{'}SR^{''}$, $R^{'}SOR^{''}$, $R^{'}SO_2R^{''}$, $R^{'}SO_2N(R^3)R^{''}$, $R^{'}N(R^3)R^{''}$, $R^{'}NR^3COR^{''}$, $R^{'}NR^3C(O)OR^{''}$, $R^{'}NR^3CON(R^4)R^{'}$, $R^{'}NR^3C(S)R^{''}$, $R^{'}NR^3S(O)R^{''}$, $R^{'}NR^3S(O)_2R^{''}$, and $R^{'}NR^3S(O)_2N(R^4)R^{''}$, wherein

$R^{'}$ and $R^{''}$ are independently selected from null, optionally substituted R^{r}-(C_1-C_8 alkyl), or a moiety comprising of optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 hydroxyalkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-C_8 alkylene, optionally substituted C_2-C_8 alkenylene, optionally substituted C_2-C_8 alkynylene, optionally substituted C_1-C_8 hydroxyalkylene, optionally substituted C_1-C_8alkoxyC_1-C_8alkylene, optionally substituted C_1-C_8alkylaminoC_1-C_8alkylene, optionally substituted C_1-C_8 haloalkylene, optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted C_3-C_{13} fused cycloalkyl, optionally substituted C_3-C_{13} fused heterocyclyl, optionally substituted C_3-C_{13} bridged cycloalkyl, optionally substituted C_3-C_{13} bridged heterocyclyl, optionally substituted C_3-C_{13} spiro cycloalkyl, optionally substituted C_3-C_{13} spiro heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

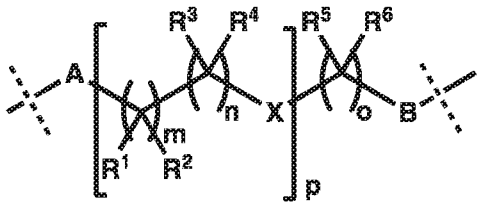
R^{r} is selected from optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted C_3-C_{13} fused cycloalkyl, optionally substituted C_3-C_{13} fused heterocyclyl, optionally substituted C_3-C_{13} bridged cycloalkyl, optionally substituted C_3-C_{13} bridged heterocyclyl, optionally substituted C_3-C_{13} spiro cycloalkyl, optionally substituted C_3-C_{13} spiro heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^3 and R^4 are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxyalkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-C_8 hydroxyalkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

$R^{'}$ and $R^{''}$, R^3 and R^4, $R^{'}$ and R^3, $R^{'}$ and R^4, $R^{''}$ and R^3, $R^{''}$ and R^4 together with the atom to which they are connected form a 3-20 membered cycloalkyl or 4-20 membered heterocyclyl ring;

m, at each occurrence, is 0 to 15; and

n is 0 to 15;



(d)

FORMULA 7C,

wherein

X is selected from O, NH, and NR^7;

R^1, R^2, R^3, R^4, R^5, and R^6, at each occurrence, are independently selected from hydrogen, halogen, hydroxyl, amino, cyano, nitro, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8 alkoxy C_1-C_8 alkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-C_8 hydroxyalkyl, optionally substituted C_1-C_8 alkylamino, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-10 membered carbocyclyl, optionally substituted 3-8 membered cycloalkoxy, optionally substituted 4-10 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

A and B are independently selected from null, or bivalent moiety selected from $R^{'}$-$R^{''}$, $R^{'}COR^{''}$, $R^{'}CO_2R^{''}$, $R^{'}C(O)N(R^8)R^{''}$, $R^{'}C(S)N(R^8)R^{''}$, $R^{'}OR^{''}$, $R^{'}OC(O)R^{''}$, $R^{'}OC(O)OR^{''}$, $R^{'}OCON(R^8)R^{''}$, $R^{'}SR^{''}$, $R^{'}SOR^{''}$, $R^{'}SO_2R^{''}$, $R^{'}SO_2N(R^8)R^{''}$, $R^{'}N(R^8)R^{''}$, $R^{'}NR^8COR^{''}$, $R^{'}NR^8C(O)OR^{''}$, $R^{'}NR^8CON(R^9)R^{''}$, $R^{'}NR^8C(S)R^{''}$, $R^{'}NR^8S(O)R^{''}$, $R^{'}NR^8S(O)_2R^{''}$, and $R^{'}NR^8S(O)_2N(R^9)R^{''}$, wherein

$R^{'}$ and $R^{''}$ are independently selected from null, optionally substituted R^{r}-(C_1-C_8 alkyl), or a moiety comprising of optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 hydroxyalkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-C_8 alkylene, optionally substituted C_2-C_8 alkenylene, optionally substituted C_2-C_8 alkynylene, optionally substituted C_1-C_8 hydroxyalkylene, optionally substituted C_1-C_8alkoxyC_1-C_8alkylene, optionally substituted C_1-C_8alkylaminoC_1-C_8alkylene, optionally substituted C_1-C_8 haloalkylene, optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted C_3-C_{13} fused cycloalkyl, optionally substituted C_3-C_{13} fused heterocyclyl, optionally substituted C_3-C_{13} bridged cycloalkyl, optionally substituted C_3-C_{13} bridged heterocyclyl,

optionally substituted C_3-C_{13} spiro cycloalkyl, optionally substituted C_3-C_{13} spiro heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^r is selected from optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted C_3-C_{13} fused cycloalkyl, optionally substituted C_3-C_{13} fused heterocyclyl, optionally substituted C_3-C_{13} bridged cycloalkyl, optionally substituted C_3-C_{13} bridged heterocyclyl, optionally substituted C_3-C_{13} spiro cycloalkyl, optionally substituted C_3-C_{13} spiro heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^7, R^8 and R^9 are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxyalkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-C_8 hydroxyalkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

$R^{'}$ and $R^{''}$, R^8 and R^9, $R^{'}$ and R^8, $R^{'}$ and R^9, $R^{''}$ and R^8, $R^{''}$ and R^9 together with the atom to which they are connected form a 3-20 membered cycloalkyl or 4-20 membered heterocyclyl ring;

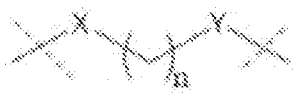
m, at each occurrence, is 0 to 15;

n, at each occurrence, is 0 to 15;

o is 0 to 15; and

p is 0 to 15;

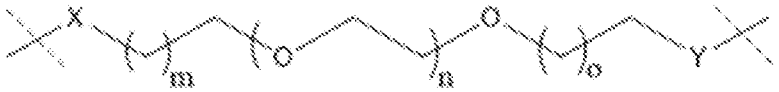
(e) the linker comprises a ring selected from the group consisting of a 3 to 13 membered ring, a 3 to 13 membered fused ring, a 3 to 13 membered bridged ring, and a 3 to13 membered spiro ring;

(f)  Formula A,

wherein X is C=O or CH_2,

Y is C=O or CH_2, and

n is 0-15;



(g) Formula B,

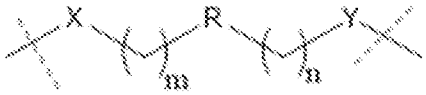
wherein X is C=O or CH_2,

Y is C=O or CH_2,

m is 0-15,

n is 0-6, and

o is 0-15; or



(h) Formula C,

wherein

X is C=O or CH_2,

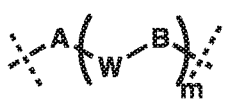
Y is C=O or CH_2,

R is $–CH_2–$, $–CF_2–$, $–CH(C_{1-3}$ alkyl$)–$, $–C(C_{1-3}$ alkyl$)(C_{1-3}$ alkyl$)–$, $–CH=CH–$, $–C(C_{1-3}$ alkyl$)=C(C_{1-3}$ alkyl$)–$, $–C\equiv C–$, $–O–$, $–NH–$, $–N(C_{1-3}$ alkyl$)–$, $–C(O)NH–$, $–C(O)N(C_{1-3}$ alkyl$)–$, a 3-13 membered ring, a 3-13 membered fused ring, a 3-13 membered bridged ring, and/or a 3-13 membered spiro ring,

m is 0-15, and

n is 0-15.

2. The bivalent compound of claim 1, wherein the linker comprises:



FORMULA 7

wherein

A, W and B, at each occurrence, are independently selected from null, or bivalent moiety selected from R'-R'', $R'COR''$, $R'CO_2R''$, $R'C(O)N(R^1)R''$, $R'C(S)N(R^1)R''$, $R'OR''$, $R'OC(O)R''$, $R'OC(O)OR''$, $R'OCON(R^1)R''$, $R'SR''$, $R'SOR''$, $R'SO_2R''$, $R'SO_2N(R^1)R''$, $R'N(R^1)R''$, $R'NR^1COR''$, $R'NR^1C(O)OR''$, $R'NR^1CON(R^2)R''$, $R'NR^1C(S)R''$, $R'NR^1S(O)R''$, $R'NR^1S(O)_2R''$, and $R'NR^1S(O)_2N(R^2)R''$, wherein

R' and R'' are independently selected from null, optionally substituted R^r-(C_1-C_8 alkyl), or a moiety comprising of optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 hydroxyalkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-C_8 alkylene, optionally substituted C_2-C_8 alkenylene, optionally substituted C_2-C_8 alkynylene, optionally substituted C_1-C_8 hydroxyalkylene, optionally substituted C_1-C_8alkoxyC_1-C_8alkylene, optionally substituted C_1-C_8alkylaminoC_1-C_8alkylene, optionally substituted C_1-C_8 haloalkylene, optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted C_3-C_{13} fused cycloalkyl, optionally substituted C_3-C_{13} fused heterocyclyl, optionally substituted C_3-C_{13} bridged cycloalkyl, optionally substituted C_3-C_{13} bridged heterocyclyl, optionally substituted C_3-C_{13} spiro cycloalkyl, optionally substituted C_3-C_{13} spiro heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

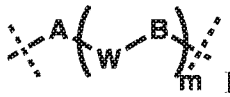
R^r is selected from optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted C_3-C_{13} fused cycloalkyl, optionally substituted C_3-C_{13} fused heterocyclyl, optionally substituted C_3-C_{13} bridged cycloalkyl, optionally substituted C_3-C_{13} bridged heterocyclyl, optionally substituted C_3-C_{13} spiro cycloalkyl, optionally substituted C_3-C_{13} spiro heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^1 and R^2 are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxyalkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-C_8 hydroxyalkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

R' and R'', R^1 and R^2, R' and R^1, R' and R^2, R'' and R^1, R'' and R^2 together with the atom to which they are connected form a 3-20 membered cycloalkyl or 4-20 membered heterocyclyl ring; and

m is 0 to 15.

3. The bivalent compound of claim 1 or 2, wherein the linker comprises:



FORMULA 7, wherein

A is R'C(O)NR''R^1, wherein R' and R" are each optionally substituted C_1-C_8 alkylene;

W is R'OR", wherein R' and R" are each null;

B is optionally substituted C_1-C_8 alkylene;

R^1 is hydrogen; and

m is 2 to 5.

4. The bivalent compound of claim 3, wherein

A is R'C(O)NR''R^1, wherein R' and R" are each –CH_2CH_2-;

W is –O-;

B is –CH_2CH_2-;

R^1 is hydrogen; and

m is 2 to 5.

5. The bivalent compound of claim 3, wherein

A is R'C(O)NR''R^1, wherein R' and R" are each –CH_2CH_2-;

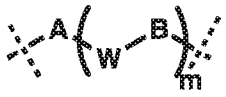
W is –O-;

B is –CH_2CH_2-;

R^1 is hydrogen; and

m is 4 or 5.

6. The bivalent compound of claim 1 or 2, wherein the linker comprises:

 FORMULA 7, wherein

A is R'C(O)R'', wherein R' is optionally substituted 4-10 membered heterocyclyl and R" is optionally substituted C_1-C_8 alkylene;

W is R'OR", wherein R' and R" are each null;

B is optionally substituted C_1-C_8 alkylene; and

m is 2 to 9.

7. The bivalent compound of claim 6, wherein

A is R'C(O)R'', wherein R' is piperazine and R" is $-CH_2CH_2-$;

W is –O-;

B is $-CH_2CH_2-$;

R^1 is hydrogen; and

m is 2 to 7 or 9.

8. The bivalent compound of claim 6, wherein

A is R'C(O)R'', wherein R' is piperazine and R" is $-CH_2CH_2-$;

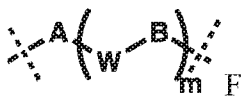
W is –O-;

B is $-CH_2CH_2-$;

R^1 is hydrogen; and

m is 4-6, 8 or 9.

9. The bivalent compound of claim 1 or 2, wherein the linker comprises:

 FORMULA 7, wherein

A is R'C(O)R'', wherein R' is optionally substituted 4-10 membered heterocyclyl and R" is optionally substituted C_1-C_8 alkylene;

W is R'OR", wherein R' is null and R" is optionally substituted C_1-C_8 alkylene;

B is R'C(O)R", wherein R' is null or optionally substituted C_1-C_8 alkylene; and

m is 1.

10. The bivalent compound of claim 9, wherein

A is R'C(O)NR''R^1, wherein R' is piperazine and R" is –CH_2-;

W is –OCH_2-;

B is –C(O)-; and

m is 1.

11. The bivalent compound of claim 9, wherein

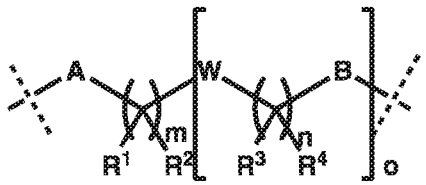
A is R'C(O)NR''R^1, wherein R' is piperazine and R" is –CH_2-;

W is –OCH_2CH_2O-;

B is –$CH_2C(O)$-; and

m is 1.

12. The bivalent compound of claim 1, wherein the linker comprises:



FORMULA 7A,

wherein

R^1, R^2, R^3 and R^4, at each occurrence, are independently selected from hydrogen, halogen, hydroxyl, amino, cyano, nitro, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8 alkoxyalkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-C_8 hydroxyalkyl, optionally substituted C_1-C_8 alkylamino, and optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-10 membered carbocyclyl, optionally substituted 3-8 membered cycloalkoxy, optionally substituted 3-10 membered carbocyclylamino, optionally substituted 4-8 membered membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^1 and R^2, R^3 and R^4 together with the atom to which they are connected form a 3-20 membered cycloalkyl or 4-20 membered heterocyclyl ring;

A, W and B, at each occurrence, are independently selected from null, or bivalent moiety selected from R'-R'', $R'COR''$, $R'CO_2R''$, $R'C(O)N(R^5)R''$, $R'C(S)N(R^5)R''$, $R'OR''$, $R'OC(O)R''$, $R'OC(O)OR''$, $R'OCONR^5R''$, $R'SR''$, $R'SOR''$, $R'SO_2R''$, $R'SO_2N(R^5)R''$, $R'N(R^5)R''$, $R'NR^5COR''$, $R'NR^5C(O)OR''$, $R'NR^5CON(R^6)R''$, $R'NR^5C(S)R''$, $R'NR^5S(O)R''$, $R'NR^5S(O)_2R''$, and $R'NR^5S(O)_2N(R^6)R''$, wherein

R' and R'' are independently selected from null, optionally substituted R^r-(C_1-C_8 alkyl), or a moiety comprising of optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 hydroxyalkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-C_8 alkylene, optionally substituted C_2-C_8 alkenylene, optionally substituted C_2-C_8 alkynylene, optionally substituted C_1-C_8 hydroxyalkylene, optionally substituted C_1-C_8alkoxyC_1-C_8alkylene, optionally substituted C_1-C_8alkylaminoC_1-C_8alkylene, optionally substituted C_1-C_8 haloalkylene, optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted C_3-C_{13} fused cycloalkyl, optionally substituted C_3-C_{13} fused heterocyclyl, optionally substituted C_3-C_{13} bridged cycloalkyl, optionally substituted C_3-C_{13} bridged heterocyclyl, optionally substituted C_3-C_{13} spiro cycloalkyl, optionally substituted C_3-C_{13} spiro heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^r is selected from optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted C_3-C_{13} fused cycloalkyl, optionally substituted C_3-C_{13} fused heterocyclyl, optionally substituted C_3-C_{13} bridged cycloalkyl, optionally substituted C_3-C_{13} bridged heterocyclyl, optionally substituted C_3-C_{13} spiro cycloalkyl, optionally substituted C_3-C_{13} spiro heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^5 and R^6 are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxyalkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-C_8 hydroxyalkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

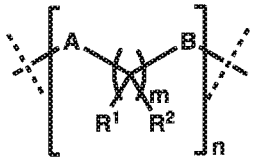
R' and R'', R5 and R6, R' and R5, R' and R6, R'' and R5, R'' and R6 together with the atom to which they are connected form a 3-20 membered cycloalkyl or 4-20 membered heterocyclyl ring;

m is 0 to 15;

n, at each occurrence, is 0 to 15; and

o is 0 to 15.

13. The bivalent compound of claim 1, wherein the linker comprises:



FORMULA 7B,

wherein

R1 and R2, at each occurrence, are independently selected from hydrogen, halogen, hydroxyl, amino, cyano, nitro, and optionally substituted C1-C8 alkyl, optionally substituted C1-C8 alkoxy, optionally substituted C1-C8 alkoxy C1-C8 alkyl, optionally substituted C1-C8 haloalkyl, optionally substituted C1-C8 hydroxyalkyl, optionally substituted C1-C8 alkylamino, C1-C8alkylaminoC1-C8alkyl, optionally substituted 3-10 membered carbocyclyl, optionally substituted 3-8 membered cycloalkoxy, optionally substituted 3-10 membered carbocyclylamino, optionally substituted 4-10 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R1 and R2 together with the atom to which they are connected form a 3-20 membered cycloalkyl or 4-20 membered heterocyclyl ring;

A and B, at each occurrence, are independently selected from null, or bivalent moiety selected from R'-R'', R'COR'', R'CO2R'', R'C(O)NR3R'', R'C(S)NR3R'', R'OR'', R'OC(O)R'', R'OC(O)OR'', R'OCON(R3)R'', R'SR'', R'SOR'', R'SO2R'', R'SO2N(R3)R'', R'N(R3)R'', R'NR3COR'', R'NR3C(O)OR'', R'NR3CON(R4)R', R'NR3C(S)R'', R'NR3S(O)R'', R'NR3S(O)2R'', and R'NR3S(O)2N(R4)R'', wherein

R' and R'' are independently selected from null, optionally substituted R^r-(C_1-C_8 alkyl), or a moiety comprising of optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 hydroxyalkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-C_8 alkylene, optionally substituted C_2-C_8 alkenylene, optionally substituted C_2-C_8 alkynylene, optionally substituted C_1-C_8 hydroxyalkylene, optionally substituted C_1-C_8alkoxyC_1-C_8alkylene, optionally substituted C_1-C_8alkylaminoC_1-C_8alkylene, optionally substituted C_1-C_8 haloalkylene, optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted C_3-C_{13} fused cycloalkyl, optionally substituted C_3-C_{13} fused heterocyclyl, optionally substituted C_3-C_{13} bridged cycloalkyl, optionally substituted C_3-C_{13} bridged heterocyclyl, optionally substituted C_3-C_{13} spiro cycloalkyl, optionally substituted C_3-C_{13} spiro heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^r is selected from optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted C_3-C_{13} fused cycloalkyl, optionally substituted C_3-C_{13} fused heterocyclyl, optionally substituted C_3-C_{13} bridged cycloalkyl, optionally substituted C_3-C_{13} bridged heterocyclyl, optionally substituted C_3-C_{13} spiro cycloalkyl, optionally substituted C_3-C_{13} spiro heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

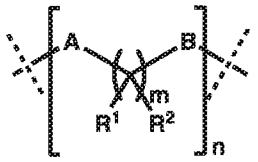
R^3 and R^4 are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxyalkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-C_8 hydroxyalkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

R' and R'', R^3 and R^4, R' and R^3, R' and R^4, R'' and R^3, R'' and R^4 together with the atom to which they are connected form a 3-20 membered cycloalkyl or 4-20 membered heterocyclyl ring;

m, at each occurrence, is 0 to 15; and

n is 0 to 15.

14. The bivalent compound of claim 1, wherein the linker comprises:



FORMULA 7B,

wherein

R^1 and R^2, at each occurrence, are independently selected from hydrogen, halogen, hydroxyl, amino, cyano, nitro, and optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8 alkoxy C_1-C_8 alkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-C_8 hydroxyalkyl, optionally substituted C_1-C_8 alkylamino, C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted 3-10 membered carbocyclyl, optionally substituted 3-8 membered cycloalkoxy, optionally substituted 3-10 membered carbocyclylamino, optionally substituted 4-10 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^1 and R^2 together with the atom to which they are connected form a 3-20 membered cycloalkyl or 4-20 membered heterocyclyl ring;

A and B, at each occurrence, are independently selected from null, or bivalent moiety selected from R'-R'', $R'COR''$, $R'CO_2R''$, $R'C(O)NR^3R''$, $R'C(S)NR^3R''$, $R'OR''$, $R'OC(O)R''$, $R'OC(O)OR''$, $R'OCON(R^3)R''$, $R'SR''$, $R'SOR''$, $R'SO_2R''$, $R'SO_2N(R^3)R''$, $R'N(R^3)R''$, $R'NR^3COR''$, $R'NR^3C(O)OR''$, $R'NR^3CON(R^4)R'$, $R'NR^3C(S)R''$, $R'NR^3S(O)R''$, $R'NR^3S(O)_2R''$, and $R'NR^3S(O)_2N(R^4)R''$, wherein

R' and R'' are independently selected from null, optionally substituted R^r-(C_1-C_8 alkyl), or a moiety comprising of optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 hydroxyalkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-C_8 alkylene, optionally substituted C_2-C_8 alkenylene, optionally substituted C_2-C_8 alkynylene, optionally substituted C_1-C_8 hydroxyalkylene, optionally substituted C_1-C_8alkoxyC_1-C_8alkylene, optionally substituted C_1-C_8alkylaminoC_1-C_8alkylene, optionally substituted C_1-C_8 haloalkylene, optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally

substituted C_3-C_{13} fused cycloalkyl, optionally substituted C_3-C_{13} fused heterocyclyl, optionally substituted C_3-C_{13} bridged cycloalkyl, optionally substituted C_3-C_{13} bridged heterocyclyl, optionally substituted C_3-C_{13} spiro cycloalkyl, optionally substituted C_3-C_{13} spiro heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^r is selected from optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted C_3-C_{13} fused cycloalkyl, optionally substituted C_3-C_{13} fused heterocyclyl, optionally substituted C_3-C_{13} bridged cycloalkyl, optionally substituted C_3-C_{13} bridged heterocyclyl, optionally substituted C_3-C_{13} spiro cycloalkyl, optionally substituted C_3-C_{13} spiro heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

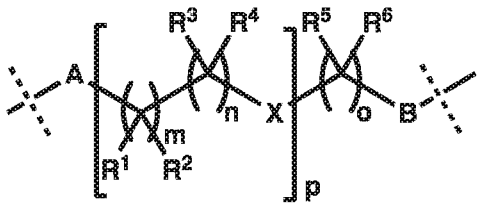
R^3 and R^4 are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxyalkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-C_8 hydroxyalkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

$R^{'}$ and $R^{''}$, R^3 and R^4, $R^{'}$ and R^3, $R^{'}$ and R^4, $R^{''}$ and R^3, $R^{''}$ and R^4 together with the atom to which they are connected form a 3-20 membered cycloalkyl or 4-20 membered heterocyclyl ring;

m, at each occurrence, is 0 to 15; and

n is 0 to 15.

15. The bivalent compound of claim 14, wherein the linker comprises:



FORMULA 7C,

wherein

R^5 and R^6 are at each occurrence, hydrogen;

A is R'C(O)NR''R^1 or R'NR^1C(O)R", wherein R' is optionally substituted C_1-C_8 alkylene and R" is null;

B is R'C(O)R'', wherein both R' and R''are null, or B is null;

R^1 is hydrogen; and

o is 6 to 10; and

p is 0.

16. The bivalent compound of claim 15, wherein

R^5 and R^6 are at each occurrence, hydrogen;

A is R'C(O)NR''R^1 or R'NR^1C(O)R", wherein R' is $-CH_2CH_2CH_2-$ and R" is null;

B is –C(O)-;

R^1 is hydrogen; and

o is 7 to 10; and

p is 0.

17. The bivalent compound of claim 15, wherein

R^5 and R^6 are at each occurrence, hydrogen;

A is R'C(O)NR''R^1 or R'NR^1C(O)R", wherein R' is $-CH_2CH_2-$ and R" is null;

B is –C(O)-;

R^1 is hydrogen; and

o is 6 to 10; and

p is 0.

18. The bivalent compound of claim 15, wherein

R^5 and R^6 are at each occurrence, hydrogen;

A is R'C(O)NR''R^1, wherein R' is $-CH_2CH_2-$ and R" is null;

B is –C(O)-;

R^1 is hydrogen; and

o is 6, 9 or 10; and

p is 0.

19. The bivalent compound of claim 15, wherein

R^5 and R^6 are at each occurrence, hydrogen;

A is R'NR^1C(O)R", wherein R' is $-CH_2CH_2-$ and R" is null;

B is –C(O)-;

R^1 is hydrogen; and

o is 6 to 10; and

p is 0.

20. The bivalent compound of claim 15, wherein

R^5 and R^6 are at each occurrence, hydrogen;

A is R'C(O)NR''R^1, wherein R' is $-CH_2CH_2CH_2-$ and R" is null;

B is null;

R^1 is hydrogen; and

o is 7 or 8; and

p is 0.

21. The bivalent compound of claim 15, wherein

R^5 and R^6 are at each occurrence, hydrogen;

A is R'C(O)NR''R^1, wherein R' is $-CH_2CH_2-$ and R" is null;

B is null;

R^1 is hydrogen; and

o is 6 to 8; and

p is 0.

22. The bivalent compound of claim 15, wherein

R^5 and R^6 are at each occurrence, hydrogen;

A is R'C(O)NR''R^1, wherein R' is $-CH_2CH_2-$ and R" is null;

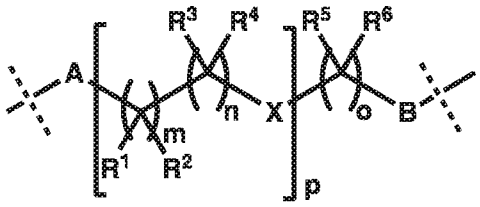
B is null;

R^1 is hydrogen; and

o is 8; and

p is 0.

23. The bivalent compound of claim 14, wherein the linker comprises:



FORMULA 7C, wherein

R^5 and R^6 are at each occurrence, hydrogen;

A is R'C(O)R'', wherein R' is optionally substituted 4-10 membered heterocyclyl and R" is optionally substituted C_1-C_8 alkylene;

B is R'C(O)R'', wherein R' and R'' are each null;

o is 4 to 12; and

p is 0.

24. The bivalent compound of claim 23, wherein

A is R'C(O)R'', wherein R' is piperazine and R" is $-CH_2CH_2-$;

W is –O-;

B is –C(O)-;

o is 4 to 11; and

p is 0.

25. The bivalent compound of claim 23, wherein

A is R'C(O)R'', wherein R' is piperazine and R" is $-CH_2CH_2-$;

W is –O-;

B is –C(O)-;

o is 9 to 12; and

p is 0.

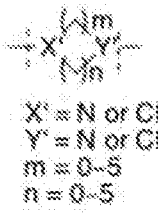
26. The bivalent compound of any one of claims 1, 2, 12, 13 or 14, wherein A and B, at each occurrence, are independently selected from null, CO, NH, NH-CO, CO-NH,

CH_2-NH-CO, CH_2-CO-NH, NH-CO-CH_2, CO-NH-CH_2, CH_2-NH-CH_2-CO-NH, CH_2-NH-CH_2-NH-CO, -CO-NH, CO-NH- CH_2-NH-CH_2 and CH_2-NH-CH_2.

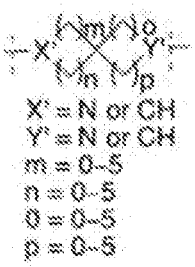
27. The bivalent compound of any one of claims 1, 2, 12, 13 or 14, wherein o is 0 to 5.

28. The bivalent compound of any one of claims 1, 2, 12, 13 or 14, wherein the linker comprises one or more rings selected from the group consisting of a 3 to 13 membered ring, a 3 to 13 membered fused ring, a 3 to 13 membered bridged ring, and a 3 to13 membered spiro ring.

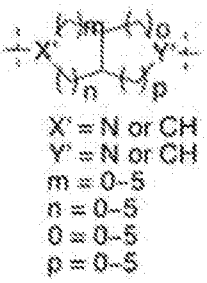
29. The bivalent compound of any one of claims 1, 2, 12, 13 or 14, wherein the linker comprises one or more rings selected from the group consisting of:

(a) 

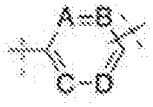
FORMULA C1,

(b) 

FORMULA C2,

(c) 

FORMULA C3,



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

(d) FORMULA C4, and

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
E = C, CH, C(C1-3 alkyl), N, NH, N(C1-3alkyl), O, S

(e) FORMULA C5.

30. The bivalent compound of claim 1, wherein the linker comprises:

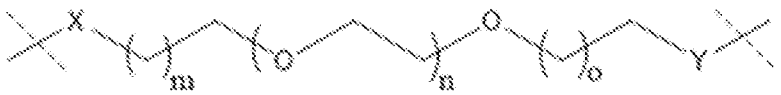
FORMULA A, wherein

X is C=O or CH_2,

Y is C=O or CH_2, and

n is 0-15.

31. The bivalent compound of claim 1, wherein the linker comprises:



FORMULA B, wherein

X is C=O or CH_2,

Y is C=O or CH_2,

m is 0-15,

n is 0-6, and

o is 0-15.

32. The bivalent compound of claim 1, wherein the linker comprises:

FORMULA C wherein

X is C=O or CH_2,

Y is C=O or CH_2,

R is $–CH_2–$, $–CF_2–$, $–CH(C_{1-3}$ 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$)–$, a 3-13 membered ring, a 3-13 membered fused ring, a 3-13 membered bridged ring, and/or a 3-13 membered spiro ring,

m is 0-15, and

n is 0-15.

33. The bivalent compound of claim 1, wherein the linker comprises:

FORMULA C wherein

X is C=O,

Y is C=O,

R is –NH–,

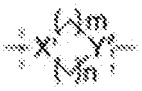
m is 0, and

n is 0-15.

34. The bivalent compound of claim 1, subpart (h), or claim 32, wherein

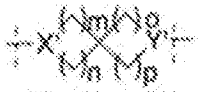
R is a 3-13 membered ring, a 3-13 membered fused ring, a 3-13 membered bridged ring, and/or a 3-13 membered spiro ring, one or more of which can contain one or more heteroatoms.

35. The bivalent compound of claim 1, subpart (h), or claim 32, wherein R has a structure of



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

(a) FORMULA C1,

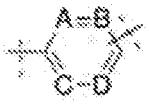


X' = N or CH
Y' = N or CH
m = 0-5
n = 0-5
o = 0-5
p = 0-5

(b) FORMULA C2,

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

(c) FORMULA C3,



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

(d) FORMULA C4, or

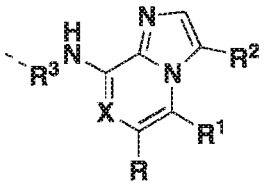
A = C, CH, C(C_{1-3} alkyl), N, NH, N(C_{1-3} alkyl), O, S
B = C, CH, C(C_{1-3} alkyl), N, NH, N(C_{1-3} alkyl), O, S
C = C, CH, C(C_{1-3} alkyl), N, NH, N(C_{1-3} alkyl), O, S
D = C, CH, C(C_{1-3} alkyl), N, NH, N(C_{1-3} alkyl), O, S
E = C, CH, C(C1-3 alkyl), N, NH, N(C1-3alkyl), O, S

(e) FORMULA C5.

36. The bivalent compound of any one of claims 1 to 35, wherein the linker is covalently bonded to the PTK6 ligand.

37. The bivalent compound of claim 36, wherein the covalent bond is an amide bond or an amino bond.

38. The bivalent compound of any one of claims 1 – 37, wherein the PTK6 ligand is selected from the group consisting of:



FORMULA 1

wherein

R is selected from H, halo, or unsubstituted or optionally substituted C_{1-8} alkyl, C_1-C_8 haloalkyl, C_1-C_8 hydroxyalkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} heterocyclyl, C_1-C_8 alkyleneOR^4, C_1-C_8 alkyleneSR^5, C_1-C_8 alkylene NR^{6}R^7, C_2-C_8 alkenyl, C_2-C_8 alkynyl, OR^4, SR^5, NR^{6}R^7;

R^1 is selected from H, C_{1-8} alkyl, C_1-C_8 hydroxyalkyl, C_1-C_8 alkoxyalkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} heterocyclyl, OR^8, SR^9, NR^{10}R^{11};

R^2 is selected from C_6-C_{10} aryl or C_5-C_{10} heteroaryl. R^2 is unsubstituted or optionally substituted with one or more of groups selected from halo, =O, =S, CN, NO_2, C_{1-8} alkyl, C_1-C_8 haloalkyl, C_1-C_8 hydroxyalkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} heterocyclyl, C_1-C_8 alkyleneOR^{12}, C_1-C_8 alkyleneSR^{13}, C_1-C_8 alkylene NR^{14}R^{15}, C_2-C_8 alkenyl, C_2-C_8 alkynyl, OR^{12}, SR^{13}, NR^{14}R^{15};

R^3 is selected from C_6-C_{10} aryl or C_5-C_{10} heteroaryl. R^3 is unsubstituted or substituted with one or more of groups selected from C_1-C_8 alkyl, C_1-C_8 haloalkyl, C_1-C_8 hydroxyalkyl, C_1-C_8 alkoxyalkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} heterocyclyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, halo, CN, NO_2, =O, =S, R^{16}, OR^{16}, SR^{17}, SO_2R^{18}, NR^{19}R^{20}, C(O)R^{16}, C(O)OR^{16}, C(S)OR^{16}, C(O)NR^{19}R^{20}, C(S) NR^{19}R^{20}, NR^{19}C(O)R^{16}, NR^{19}C(O)OR^{16}, NR^{19}S(O)R^{16}, NR^{19}S(O)OR^{16}, S(O)R^{16}, S(O)OR^{16}, and S(O)ONR^{19}R^{20};

R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} are independently selected from H, C_1-C_8 alkyl, C_1-C_8 haloalkyl, C_1-C_8 hydroxyalkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} heterocyclyl, $C(O)C_1$-C_8 alkyl, $C(O)C_1$-C_8 haloalkyl, $C(O)C_1$-C_8 hydroxyalkyl, $C(O)C_3$-C_{10} cycloalkyl, and $C(O)C_3$-C_{10} heterocyclyl, or R^6 and R^7; R^{10} and R^{11}; R^{14} and R^{15} together with the nitrogen atom to which they connected can independently form 3-10 membered heterocyclyl rings;

R^{16}, R^{17}, and R^{18} are independently selected from H, C_1-C_8 alkyl, C_1-C_8 haloalkyl, C_1-C_8 alkoxyalkyl, C_1-C_8 hydroxyalkyl, C_3-C_8 cycloalkyl, C_3-C_7 heterocycloalkyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, $C(O)C_1$-C_8 alkyl, $C(O)C_1$-C_8 haloalkyl, $C(O)C_1$-C_8 hydroxyalkyl, $C(O)C_1$-C_8 alkoxyalkyl, $C(O)C_3$-C_{10} cycloalkyl, $C(O)C_3$-C_{10} heterocyclyl, $C(O)C_6$-C_{10} aryl, $C(O)C_5$-C_{10} heteroaryl, C_1-C_8 alkyleneC_3-C_{10} cycloalkyl, C_1-C_8 alkyleneC_3-C_{10} heterocycloalkyl, C_1-C_8 alkyleneC_6-C_{10} aryl, C_1-C_8 alkylene, or C_5-C_{10} heteroaryl;

R^{19} and R^{20} are independently selected from H, C_1-C_8 alkyl, C_1-C_8 haloalkyl, C_1-C_8 alkoxyalkyl, C_1-C_8 hydroxyalkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} heterocycloalkyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, $C(O)C_1$-C_8 alkyl, $C(O)C_1$-C_8 haloalkyl, $C(O)C_1$-C_8 hydroxyalkyl, $C(O)C_1$-C_8 alkoxyalkyl, $C(O)C_3$-C_{10} cycloalkyl, $C(O)C_3$-C_{10} heterocycloalkyl, $C(O)C_6$-C_{10} aryl, $C(O)C_5$-C_{10} heteroaryl, $C(O)OC_1$-C_8 alkyl, $C(O)OC_1$-C_8 haloalkyl, $C(O)OC_1$-C_8 hydroxyalkyl, $C(O)OC_1$-C_8 alkoxyalkyl, $C(O)OC_3$-C_{10} cycloalkyl, $C(O)OC_3$-C_{10} heterocyclyl, $C(O)OC_6$-C_{10} aryl, $C(O)OC_5$-C_{10} heteroaryl, $C(O)NC_1$-C_8 alkyl, $C(O)NC_1$-C_8 haloalkyl, $C(O)NC_1$-C_8 hydroxyalkyl, $C(O)NC_1$-C_8 alkoxyalkyl, $C(O)NC_3$-C_{10} cycloalkyl, $C(O)NC_3$-C_{10} heterocyclyl, $C(O)NC_6$-C_{10} aryl, $C(O)NC_5$-C_{10} heteroaryl, SO_2C_1-C_8 alkyl, SO_2C_1-C_8 haloalkyl, SO_2C_1-C_8 hydroxyalkyl, SO_2C_1-C_8 alkoxyalkyl, SO_2C_3-C_{10} cycloalkyl, SO_2C_3-C_{10} heterocyclyl, SO_2C_6-C_{10} aryl, SO_2C_5-C_{10} heteroaryl, C_1-C_8 alkyleneC_3-C_{10} cycloalkyl, C_1-C_8 alkyleneC_3-C_{10} heterocycloalkyl, C_1-C_8 alkyleneC_6-C_{10} aryl, C_1-C_8 alkyleneC_5-C_{10} heteroaryl, or R^{19} and R^{20} together with the nitrogen atom to which they connected can independently form 3-10 membered heterocyclyl rings; and

X is selected from CH or N.

39. The bivalent compound of claim 38, wherein R is selected from H, halogen, optionally substituted C_{1-3} alkyl, and optionally substituted C_{1-3} alkoxy.

40. The bivalent compound of claim 38, wherein R is selected from H, F, CH_3, CH_2F, CHF_2, CF_3, CH_2CH_3, CH_2CF_3, i-Pr, c-Pr, OCH_3, OCH_2F, $OCHF_2$, OCF_3, OCH_2CH3, $OCH2CF_3$, Oi-Pr and Oc-Pr.

41. The bivalent compound of claim 38, wherein R is selected from CH_3, CF_3, CH_2CH_3, CH_2CF_3 and c-Pr.

42. The bivalent compound of claim 38, wherein R is selected from CH_3 and c-Pr.

43. The bivalent compound of claim 38, wherein R is c-Pr.

44. The bivalent compound of claim 38, wherein R^1 is selected from H, halogen, optionally substituted C_{1-3} alkyl, and optionally substituted C_{1-3} alkoxy.

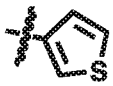
45. The bivalent compound of claim 38, wherein , R^1 is selected from H, F, CH_3, CH_2F, CHF_2, CF_3, CH_2CH_3, CH_2CF_3, i-Pr, c-Pr, OCH_3, OCH_2F, $OCHF_2$, OCF_3, OCH_2CH_3, OCH_2CF_3, Oi-Pr, and Oc-Pr.

46. The bivalent compound of claim 38, wherein R^1 is selected from H, F, CH_3, and CF_3.

47. The bivalent compound of claim 38, wherein R^1 is H.

48. The bivalent compound of claim 38, wherein R^2 is selected from phenyl and 5-6 membered heteroaryl, which are optionally substituted with one or more of groups selected from halogen, optionally substituted C_{1-3} alkyl, and optionally substituted C_{1-3} alkoxy.

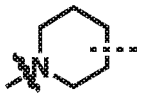
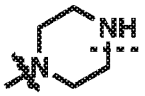
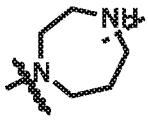
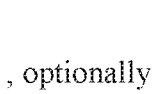
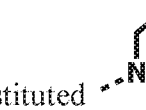
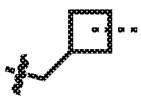
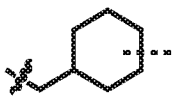
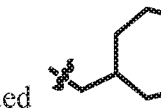
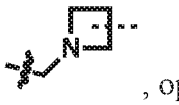
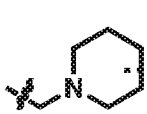
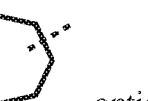
49. The bivalent compound of claim 38, wherein R^2 is 5-6 membered heteroaryl, which are optionally substituted with one or more of groups selected from halogen, optionally substituted C_{1-3} alkyl, and optionally substituted C_{1-3} alkoxy.

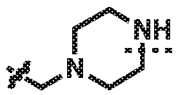
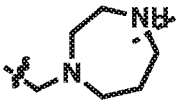
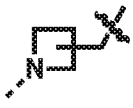
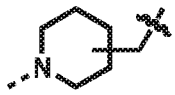
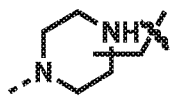
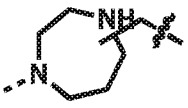
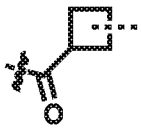
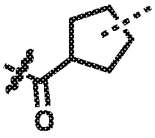
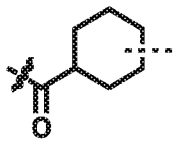
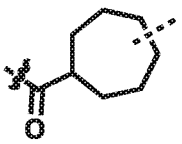
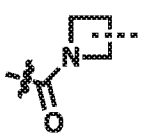
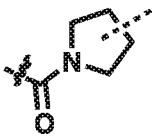
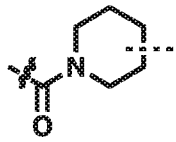
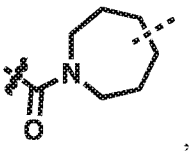
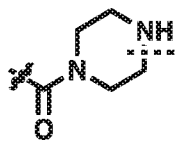
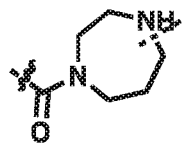
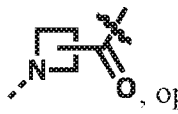
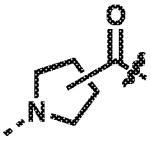
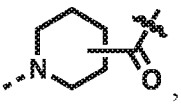
50. The bivalent compound of claim 38, wherein R^2 is selected from phenyl, , and  .

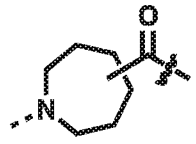
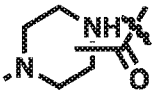
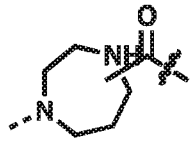
51. The bivalent compound of claim 38, wherein R^2 is .

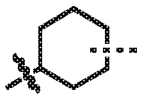
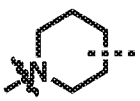
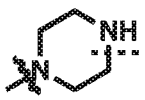
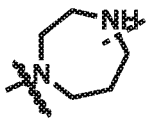
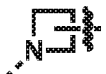
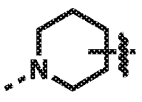
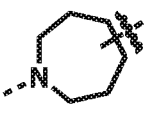
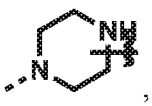
52. The bivalent compound of claim 38, wherein R^3 is selected from phenyl, and 5-6 membered heteroaryl, which are optionally substituted with one or more of groups selected from halogen, optionally substituted C_{1-8} alkyl, and optionally substituted C_{1-8} alkoxy, optionally substituted C_{1-8} alkylene, optionally substituted 3-8 membered carbocyclyl, optionally substituted 4-8 membered heterocyclyl, optionally substituted aryl, optionally substituted 5-6 membered heteroaryl, -CO-, -C(O)-(C_{1-8} alkylene)-, -C(O)-NH(C_{1-8} alkylene)-, -C(O)-N(C_{1-8} alkylene)(C_{1-8} alkylene)-, -C(O)-(3-8 membered carbocyclyl)-, -C(O)-(4-8 membered heterocyclyl)-, -C(O)-(5-6 membered heteroaryl)-, -NH(C_{1-8} alkylene)-, -N(C_{1-8} alkylene)(C_{1-8} alkylene)-, -CH_2-(3-8 membered carbocyclyl)-, -CH_2-(4-8 membered heterocyclyl)-, and -CH_2-(5-6 membered heteroaryl)-.

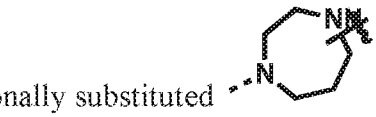
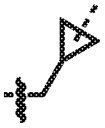
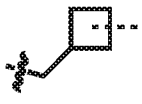
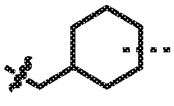
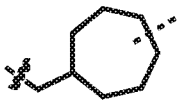
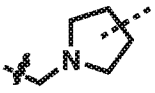
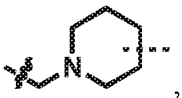
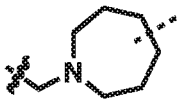
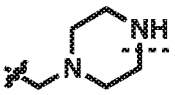
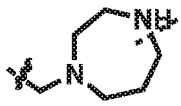
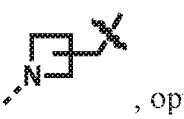
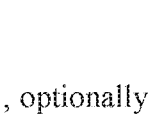
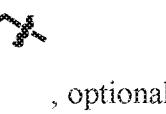
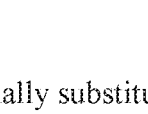
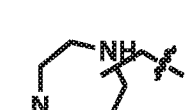
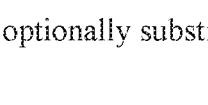
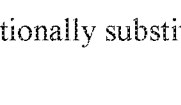
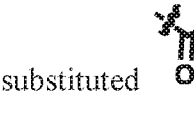
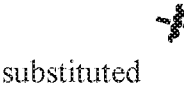
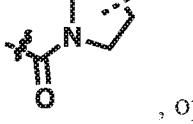
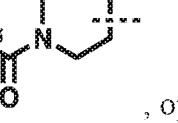
53. The bivalent compound of claim 38, wherein R^3 is selected from phenyl, and 5-6 membered heteroaryl, which are optionally substituted with one or more of groups

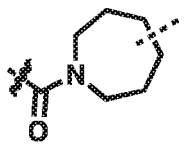
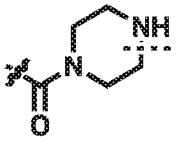
selected from F, Cl, CH_3, CF_3, OCH_3, OCF_3, CH_2CH_3, CH_2CF_3, OCH_2CH_3, OCH_2CF_3, i-Pr, c-Pr, i-PrO, c-PrO, -CO-, optionally substituted , optionally substituted , optionally substituted , optionally substituted , optionally substituted , optionally substituted , optionally substituted , optionally substituted  , optionally substituted , optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted , optionally substituted , optionally substituted  , optionally substituted , optionally substituted  , optionally substituted , optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted , optionally substituted  , optionally substituted  , optionally substituted , optionally substituted , optionally substituted , optionally substituted , optionally

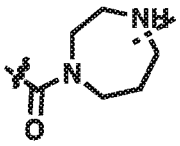
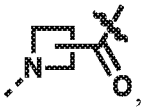
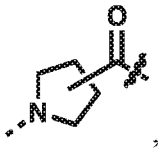
substituted  , optionally substituted  , optionally substituted  , optionally substituted , optionally substituted  , optionally substituted , optionally substituted  , optionally substituted  , optionally substituted , optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted  ,

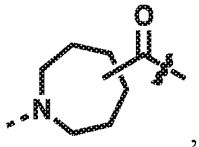
optionally substituted  , optionally substituted  , and optionally substituted  .

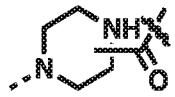
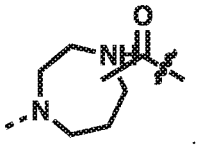
54. The bivalent compound of claim 38, wherein R^3 is selected from phenyl, thiophene, thiazole, isothiazole, pyrolyl, pyrazolyl, imidazolyl, pyridinyl, pyrimidinyl, and pyrazinyl, which are optionally substituted with one or more of groups selected from F, Cl, CH_3, CF_3, OCH_3, OCF_3, CH_2CH_3, CH_2CF_3, OCH_2CH_3, OCH_2CF_3, i-Pr, c-Pr, i-PrO, c-PrO, -CO-, optionally substituted , optionally substituted , optionally substituted , optionally substituted  , optionally substituted , optionally substituted , optionally substituted , optionally substituted  , optionally substituted , optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted , optionally substituted  , optionally substituted  , optionally substituted  ,

optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted , optionally substituted  , optionally substituted  , optionally substituted , optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted , optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted , optionally substituted , optionally substituted , optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted , optionally substituted , optionally substituted , optionally substituted , optionally substituted

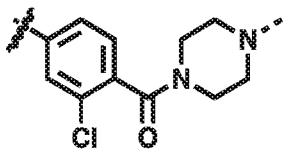
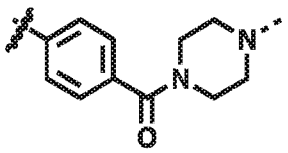
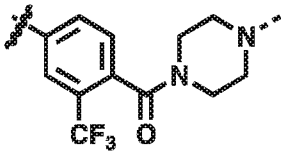
 , optionally substituted  , optionally substituted

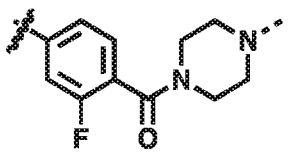
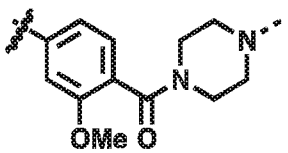
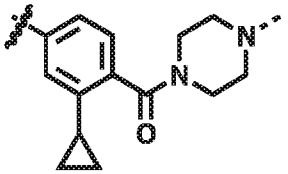
 , optionally substituted  , optionally substituted  ,

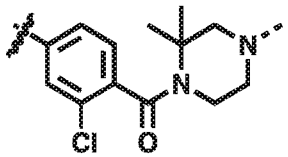
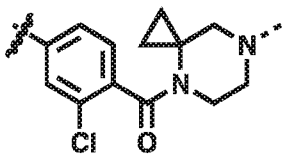
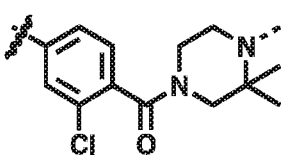
optionally substituted , optionally substituted  ,

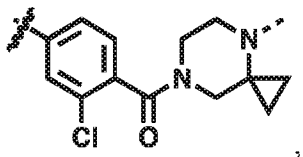
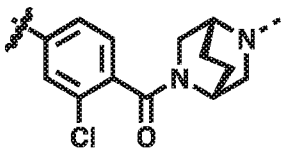
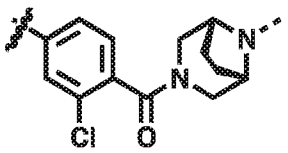
optionally substituted  , and optionally substituted  .

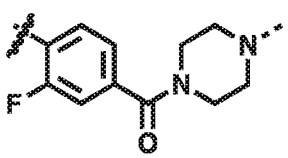
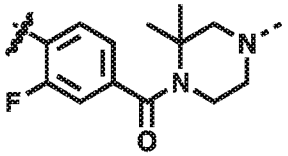
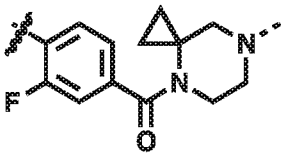
55. The bivalent compound of claim 38, wherein R^3 is selected from

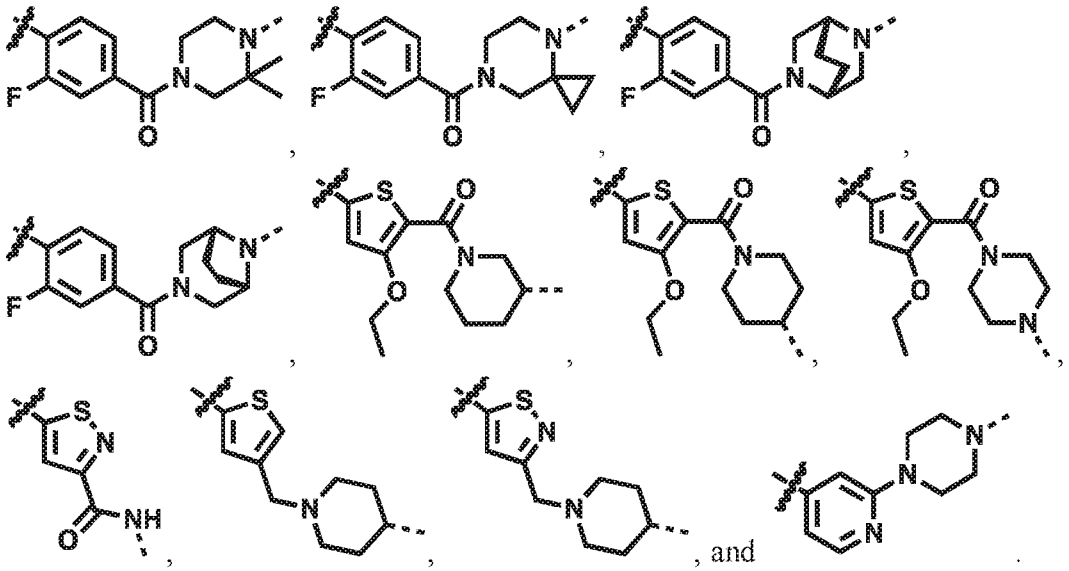
 ,  ,  ,

 ,  ,  ,

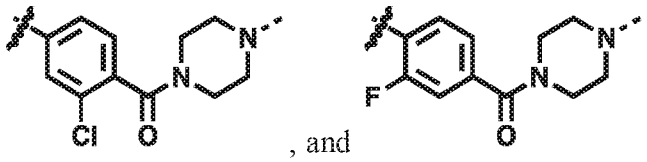
 ,  ,  ,

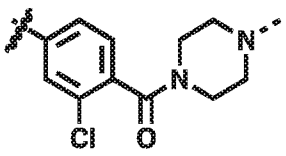
 ,  ,  ,

 ,  ,  ,



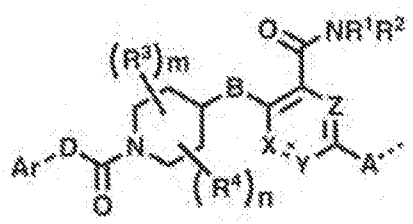
56. The bivalent compound of claim 38, wherein R^3 is selected from



57. The bivalent compound of claim 38, wherein R^3 is  .

58. The bivalent compound of claim 38, wherein X is N.

59. The bivalent compound of any one of claims 1 – 37, wherein the PTK6 ligand is selected from the group consisting of:



FORMULA 2

wherein

X, Y and Z are independently selected from null, CR^5, and N, wherein

R^5 is selected from hydrogen, halogen, or optionally substituted C_{1-3} alkyl;

A is selected from null or $-R^6-R^7-$, wherein

R^6 and R^7 are independently selected from null, NR^8, O, S, C(O), $C(O)NR^8$, $NR^8C(O)$, $NR^8C(O)NR^9$, $OC(O)NR^9$, $NR^8C(O)O$, S(O), $S(O)NR^8$, $NR^8S(O)$, $NR^8S(O)NR^9$, $OS(O)NR^9$, $NR^8S(O)O$, $S(O)_2$, $S(O)_2NR^8$, $NR^8S(O)_2$, $NR^8S(O)_2NR^9$, $OS(O)_2NR^9$, $NR^8S(O)_2O$, optionally substituted C_1-C_8 alkylene, optionally substituted C_2-C_8 alkenylene, optionally substituted C_2-C_8 alkynylene, optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, wherein

R^8 and R^9 are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted 3-10 membered carbocyclylC_1-C_8alkyl, optionally substituted 4-10 membered heterocyclylC_1-C_8alkyl, optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or R^8 and R^9 together with the atom to which they are connected form a 4-20 membered heterocyclyl ring;

B and D are independently selected from $CR^{10}R^{11}$, NR^{10}, O, SO, or SO_2, wherein R^{10} and R^{11} are independently selected from hydrogen, halogen, hydroxy, cyano, nitro, and optionally substituted C_1-C_3 alkyl, or R^{10} and R^{11} together with the atom to which they are connected form a 3-6 membered carbocyclyl rings or 4-6 membered heterocyclyl ring;

R^1 and R^2 are independently selected from hydrogen, and optionally substituted C_1-C_3 alkyl, or R^1 and R^2 together with the atom to which they are connected form a 4-6 membered heterocyclyl ring;

R^3 and R^4, at each occurrence, are independently selected from hydrogen, fluoro, hydroxyl, cyano, amino, nitro, optionally substituted C_1-C_3 alkyl, optionally substituted C_1-C_3 alkoxy, and optionally substituted C_1-C_3 alkylamino;

m and n are independently selected from 0, 1, 2, 3, and 4; and

Ar is selected from aryl, and heteroaryl, which are optionally substituted with one or more substituents independently selected from hydrogen, halogen, oxo, CN, NO_2, OR^{12}, SR^{12}, $NR^{12}R^{13}$, $OCOR^{12}$, OCO_2R^{12}, $OCON(R^{12})R^{13}$, COR^{12}, CO_2R^{12}, $CON(R^{12})R^{13}$, SOR^{12}, SO_2R^{12}, $SO_2N(R^{12})R^{13}$, $NR^{14}CO_2R^{12}$, $NR^{14}COR^{12}$, $NR^{14}C(O)N(R^{12})R^{13}$, $NR^{14}SOR^{12}$, $NR^{14}SO_2R^{12}$, $NR^{14}SO_2N(R^{12})R^{13}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted 4-10 membered heterocyclylC_1-C_8alkyl, optionally substituted 3-10 membered carbocyclylC_1-C_8alkyl, optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, wherein R^{12}, R^{13}, and R^{14} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted 3-10 membered carbocyclylC_1-C_8alkyl, optionally substituted 4-10 membered heterocyclylC_1-C_8alkyl, optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or R^{12} and R^{13}, R^{12} and R^{14} together with the atom to which they are connected form a 4-20 membered heterocyclyl ring.

60. The bivalent compound of claim 59, wherein X, Y and Z are independently selected from CH, CF, and N.

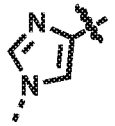
61. The bivalent compound of claim 59, wherein X is N; and Y and Z are independently selected from CH, CF, and N.

62. The bivalent compound of claim 59, wherein X is N; and Y and Z are CH.

63. The bivalent compound of claim 59, wherein A is null or selected from optionally substituted 3-8 membered carbocyclyl, optionally substituted 4-8 membered heterocyclyl, optionally substituted 6 membered aryl, optionally substituted 5-6 membered heteroaryl, fused rings, bridged rings, and spiro rings.

64. The bivalent compound of claim 59, wherein A is null, phenyl, 4-8 membered heterocyclyl, and 5-6 membered heteroaryl, which are optionally substituted by F, OH, CN, NO_2, NH_2, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 alkoxy, optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl.

65. The bivalent compound of claim 59, wherein A is null, phenyl, 4-8 membered heterocyclyl, and 5-6 membered heteroaryl, which are optionally substituted by F, OH, CN, NO_2, NH_2, CH_3, CF_3, i-Pr, and c-Pr.

66. The bivalent compound of claim 59, wherein A is  .

67. The bivalent compound of claim 59, wherein B and D are independently selected from CH_2, CHOH, $CHCH_3$, $C(CH_3)_2$, , CHF, CF_2, O, NH, and NCH_3.

68. The bivalent compound of claim 59, wherein B is O.

69. The bivalent compound of claim 59, wherein D is CH_2.

70. The bivalent compound of claim 59, wherein R^1 and R^2 are independently selected from H, and optionally substituted C_1-C_3 alkyl, with the proviso that at least one of R^1 and R^2 is H.

71. The bivalent compound of claim 59, wherein R^1 and R^2 are independently selected from H, and CH_3, with the proviso that at least one of R^1 and R^2 is H.

72. The bivalent compound of claim 59, wherein R^1 and R^2 are H.

73. The bivalent compound of claim 59, wherein R^3 and R^4, at each occurrence, are independently selected from H, F, OH, CN, NH_2, NO_2, CH_3, CF_3, i-Pr, and c-Pr.

74. The bivalent compound of claim 59, wherein R^3 and R^4, at each occurrence, are independently selected from H, and F.

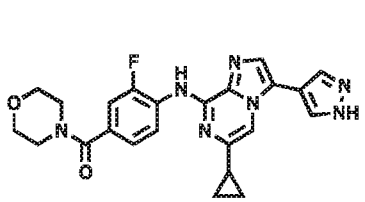
75. The bivalent compound of claim 59, wherein m and n are independently selected from 0, 1, and 2.

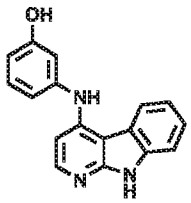
76. The bivalent compound of claim 59, wherein m and n are 1.

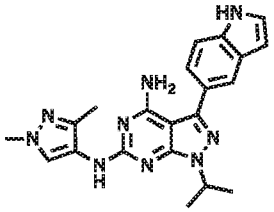
77. The bivalent compound of claim 59, wherein Ar is selected from aryl, and heteroaryl, which are optionally substituted with one or more substituents independently selected from H, F, =O, CN, NO_2, CH_3, OCH_3, CH_2F, CHF_2, CF_3, OCH_2F, $OCHF_2$, OCF_3, i-Pr, and c-Pr.

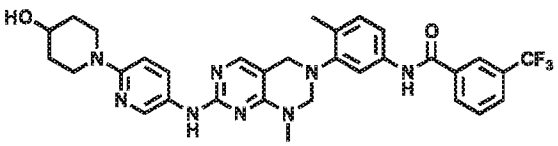
78. The bivalent compound of claim 59, wherein Ar is 4-OCF_3 substituted phenyl.

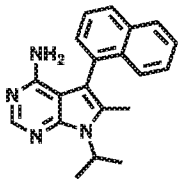
79. The bivalent compound of any one of claims 1 – 37, wherein the PTK6 ligand is selected from the group consisting of:

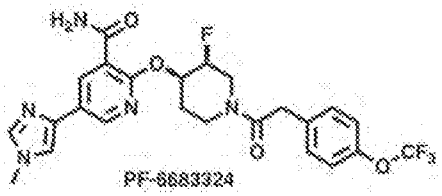

Compound 21d

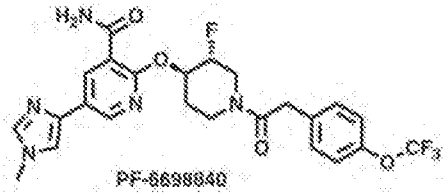

Compound 4f


Compound 1


XMU-MP-2

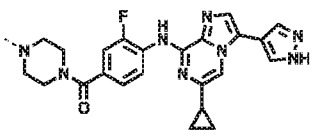

Compound 3s

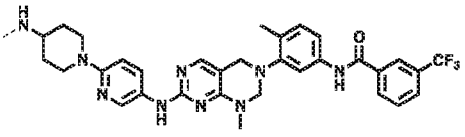

PF-6683324

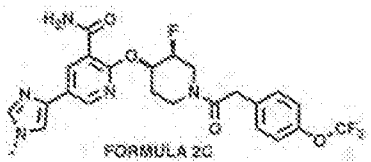

PF-6699840

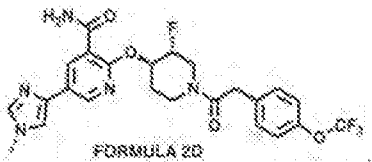
and derivatives thereof.

80. The bivalent compound of any one of claims 1 – 37, wherein the PTK6 ligand is selected from the group consisting of:

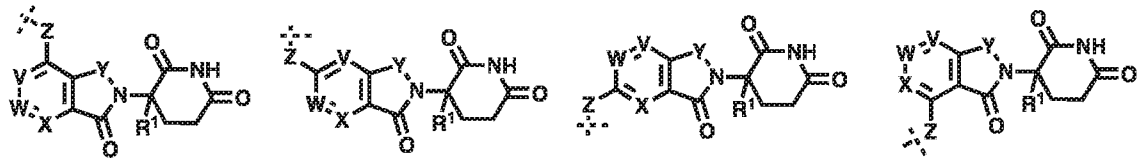

FORMULA 2A


FORMULA 2B


FORMULA 2C


FORMULA 2D

81. The bivalent compound of any one of claims 1 – 80, wherein the degradation/disruption tag is selected from the group consisting of:



FORMULA 3A FORMULA 3B FORMULA 3C FORMULA 3D,

wherein

V, W, and X are independently selected from CR^2 and N;

Y is selected from CO, CR^3R^4, and N=N;

Z is selected from null, CO, CR^5R^6, NR^5, O, optionally substituted C_1-C_{10} alkylene, optionally substituted C_1-C_{10} alkenylene, optionally substituted C_1-C_{10} alkynylene, optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted C_3-C_{13} fused cycloalkyl, optionally substituted C_3-C_{13} fused heterocyclyl, optionally substituted C_3-C_{13} bridged cycloalkyl, optionally substituted C_3-C_{13} bridged heterocyclyl, optionally substituted C_3-C_{13} spiro cycloalkyl, optionally substituted C_3-C_{13} spiro heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl; preferly, Z is selected from null, CH_2, CH=CH, C≡C, NH and O;

R^1, and R^2 are independently selected from hydrogen, halogen, cyano, nitro, optionally substituted C_1-C_6 alkyl, optionally substituted 3 to 6 membered carbocyclyl, and optionally substituted 4 to 6 membered heterocyclyl;

R^3, and R^4 are independently selected from hydrogen, halogen, cyano, nitro, optionally substituted C_1-C_6 alkyl, optionally substituted 3 to 6 membered carbocyclyl, and optionally substituted 4 to 6 membered heterocyclyl; or R^3 and R^4 together with the atom to which they are connected form a 3-6 membered carbocyclyl, or 4-6 membered heterocyclyl; and

R^5 and R^6 are independently selected from null, hydrogen, halogen, oxo, hydroxyl, amino, cyano, nitro, optionally substituted C_1-C_6 alkyl, optionally substituted 3 to 6 membered carbocyclyl, and optionally substituted 4 to 6 membered heterocyclyl; or R^5

and R^6 together with the atom to which they are connected form a 3-6 membered carbocyclyl, or 4-6 membered heterocyclyl.

82. The bivalent compound of claim 81, wherein

V, W, and X are independently CR^2 or N,

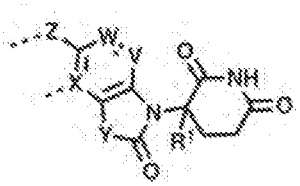
Y is CO or CH_2,

Z is CH_2, NH, or O,

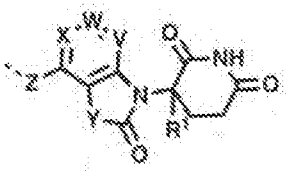
R^1 is hydrogen, methyl, or fluoro, and

R^2 is hydrogen, halogen, or C_1-C_5 alkyl.

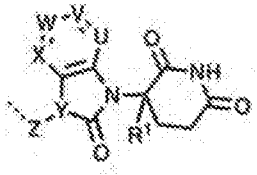
83. The bivalent compound of any one of claims 1 – 80, wherein the degradation/disruption tag is selected from the group consisting of:



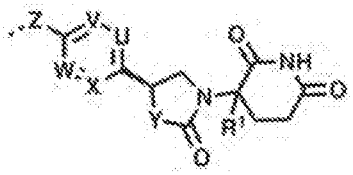
FORMULA 3E



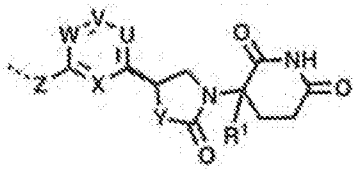
FORMULA 3F



FORMULA 3G



FORMULA 3H



FORMULA 3I

wherein

U, V, W, and X are independently selected from CR^2 and N;

Y is selected from CR^3R^4, NR^3 and O; optionally, Y is selected from CH_2, NH, NCH_3 and O;

Z is selected from null, CO, CR^5R^6, NR^5, O, optionally substituted C_1-C_{10} alkylene, optionally substituted C_1-C_{10} alkenylene, optionally substituted C_1-C_{10} alkynylene, optionally

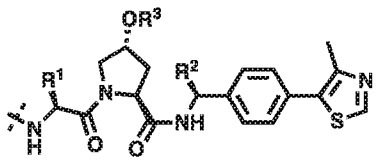
substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted C_3-C_{13} fused cycloalkyl, optionally substituted C_3-C_{13} fused heterocyclyl, optionally substituted C_3-C_{13} bridged cycloalkyl, optionally substituted C_3-C_{13} bridged heterocyclyl, optionally substituted C_3-C_{13} spiro cycloalkyl, optionally substituted C_3-C_{13} spiro heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl; preferly, Z is selected from null, CH_2, CH=CH, C≡C, NH and O;

R^1, and R^2 are independently selected from hydrogen, halogen, cyano, nitro, optionally substituted C_1-C_6 alkyl, optionally substituted 3 to 6 membered carbocyclyl, and optionally substituted 4 to 6 membered heterocyclyl;

R^3, and R^4 are independently selected from hydrogen, halogen, cyano, nitro, optionally substituted C_1-C_6 alkyl, optionally substituted 3 to 6 membered carbocyclyl, and optionally substituted 4 to 6 membered heterocyclyl; or R^3 and R^4 together with the atom to which they are connected form a 3-6 membered carbocyclyl, or 4-6 membered heterocyclyl; and

R^5 and R^6 are independently selected from null, hydrogen, halogen, oxo, hydroxyl, amino, cyano, nitro, optionally substituted C_1-C_6 alkyl, optionally substituted 3 to 6 membered carbocyclyl, and optionally substituted 4 to 6 membered heterocyclyl; or R^5 and R^6 together with the atom to which they are connected form a 3-6 membered carbocyclyl, or 4-6 membered heterocyclyl.

84. The bivalent compound of any one of claims 1 – 80, wherein the degradation/disruption tag is selected from the group consisting of:



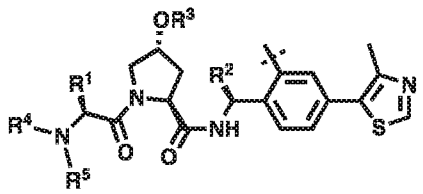
FORMULA 4A

wherein

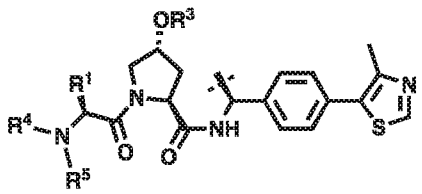
R^1 and R^2 are independently hydrogen, C_1-C_8 alkyl, C_1-C_8 alkoxyalkyl, C_1-C_8 haloalkyl, C_1-C_8 hydroxyalkyl, C_1-C_8 aminoalkyl, C_1-C_8 alkylaminoalkyl, C_3-C_7 cycloalkyl, C_3-C_7 heterocyclyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl;

R^3 is H, $C(O)C_1$-C_8 alkyl, $C(O)C_1$-C_8 alkoxyalkyl, $C(O)C_1$-C_8 haloalkyl, $C(O)C_1$-C_8 hydroxyalkyl, $C(O)C_1$-C_8 aminoalkyl, $C(O)C_1$-C_8 alkylaminoalkyl, $C(O)C_3$-C_7 cycloalkyl, $C(O)C_3$-C_7 heterocyclyl, $C(O)C_2$-C_8 alkenyl, $C(O)C_2$-C_8 alkynyl, $C(O)OC_1$-C_8 alkoxyalkyl, $C(O)OC_1$-C_8 haloalkyl, $C(O)OC_1$-C_8 hydroxyalkyl, $C(O)OC_1$-C_8 aminoalkyl, $C(O)OC_1$-C_8 alkylaminoalkyl, $C(O)OC_3$-C_7 cycloalkyl, $C(O)OC_3$-C_7 heterocyclyl, $C(O)OC_2$-C_8 alkenyl, $C(O)OC_2$-C_8 alkynyl, $C(O)NC_1$-C_8 alkoxyalkyl, $C(O)NC_1$-C_8 haloalkyl, $C(O)NC_1$-C_8 hydroxyalkyl, $C(O)NC_1$-C_8 aminoalkyl, $C(O)NC_1$-C_8 alkylaminoalkyl, $C(O)NC_3$-C_7 cycloalkyl, $C(O)NC_3$-C_7 heterocyclyl, $C(O)NC_2$-C_8 alkenyl, $C(O)NC_2$-C_8 alkynyl, $P(O)(OH)_2$, $P(O)(OC_1$-C_8 alkyl$)_2$, or $P(O)(OC_1$-C_8 aryl$)_2$.

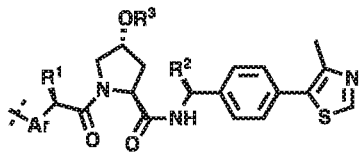
85. The bivalent compound of any one of claims 1 – 80, wherein the degradation/disruption tag is selected from the group consisting of:



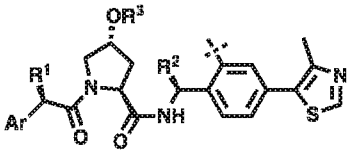
FORMULA 4B



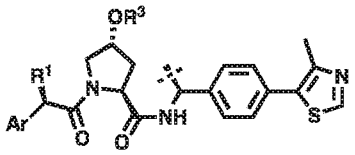
FORMULA 4C



FORMULA 4D



FORMULA 4E



FORMULA 4F

wherein

R^1 and R^2 are independently selected from hydrogen, halogen, OH, NH_2, CN, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-C_8 hydroxyalkyl, optionally substituted C_1-C_8 aminoalkyl, optionally substituted C_1-C_8alkylaminoC_1-

C_8alkyl, optionally substituted C_3-C_7 cycloalkyl, optionally substituted 3-7 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, and optionally substituted C_2-C_8 alkynyl; (preferably, R^1 is selected from iso-propyl or tert-butyl; and R^2 is selected from hydrogen or methyl);

R^3 is hydrogen, optionally substituted C(O)C_1-C_8 alkyl, optionally substituted C(O)C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C(O)C_1-C_8 haloalkyl, optionally substituted C(O)C_1-C_8 hydroxyalkyl, optionally substituted C(O)C_1-C_8 aminoalkyl, optionally substituted C(O)C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C(O)C_3-C_7 cycloalkyl, optionally substituted C(O)(3-7 membered heterocyclyl), optionally substituted C(O)C_2-C_8 alkenyl, optionally substituted C(O)C_2-C_8 alkynyl, optionally substituted C(O)OC_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C(O)OC_1-C_8 haloalkyl, optionally substituted C(O)OC_1-C_8 hydroxyalkyl, optionally substituted C(O)OC_1-C_8 aminoalkyl, optionally substituted C(O)OC_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C(O)OC_3-C_7 cycloalkyl, optionally substituted C(O)O(3-7 membered heterocyclyl), optionally substituted C(O)OC_2-C_8 alkenyl, optionally substituted C(O)OC_2-C_8 alkynyl, optionally substituted C(O)NC_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C(O)NC_1-C_8 haloalkyl, optionally substituted C(O)NC_1-C_8 hydroxyalkyl, optionally substituted C(O)NC_1-C_8 aminoalkyl, optionally substituted C(O)NC_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C(O)NC_3-C_7 cycloalkyl, optionally substituted C(O)N(3-7 membered heterocyclyl), optionally substituted C(O)NC_2-C_8 alkenyl, optionally substituted C(O)NC_2-C_8 alkynyl, optionally substituted P(O)$(OH)_2$, optionally substituted P(O)$(OC_1$-C_8 alkyl$)_2$, and optionally substituted P(O)$(OC_1$-C_8 aryl$)_2$; and

R^4 and R^5 are independently selected from hydrogen, COR^6, CO_2R^6, $CONR^6R^7$, SOR^6, SO_2R^6, $SO_2NR^6R^7$, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, wherein

R^6 and R^7 are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or

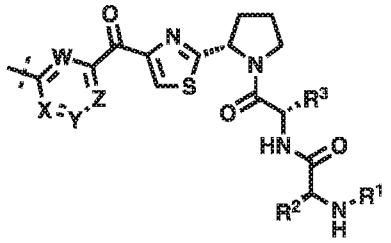
R^4 and R^5; R^6 and R^7 together with the atom to which they are connected form a 4-8 membered cycloalkyl or heterocyclyl ring;

Ar is selected from aryl and heteroaryl, each of which is optionally substituted with one or more substituents independently selected from F, Cl, CN, NO_2, OR^8, NR^8R^9, COR^8, CO_2R^8, $CONR^8R^9$, SOR^8, SO_2R^8, $SO_2NR^9R^{10}$, NR^9COR^{10}, $NR^8C(O)NR^9R^{10}$, NR^9SOR^{10}, $NR^9SO_2R^{10}$, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 alkoxyalkyl, optionally substituted C_1-C_6 haloalkyl, optionally substituted C_1-C_6 hydroxyalkyl, optionally substituted C_1-C_6alkylaminoC_1-C_6alkyl, optionally substituted C_3-C_7 cycloalkyl, optionally substituted 3-7 membered heterocyclyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted aryl, and optionally substituted C_4-C_5 heteroaryl, wherein

R^8, R^9, and R^{10} are independently selected from null, hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted C_3-C_7 cycloalkyl, optionally substituted 3-7 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^8 and R^9; R^9 and R^{10} together with the atom to which they are connected form a 4-8 membered cycloalkyl or heterocyclyl ring.

86. The bivalent compound of any one of claims 1 – 80, wherein the degradation/disruption tag is selected from the group consisting of:

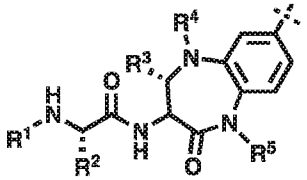


FORMULA 5A

wherein

R^1, R^2, R^3, and R^4 are independently hydrogen, C_1-C_8 alkyl, C_1-C_8 alkoxyalkyl, C_1-C_8 haloalkyl, C_1-C_8 hydroxyalkyl, C_3-C_7 cycloalkyl, C_3-C_7 heterocyclyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl, and V, W, X, and Z are independently CR^4 or N.

87. The bivalent compound of any one of claims 1 – 80, wherein the degradation/disruption tag is selected from the group consisting of:



FORMULA 5B,

wherein

R^1, R^2, and R^3 are independently selected from hydrogen, halogene, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-C_8 hydroxyalkyl, optionally substituted C_3-C_7 cycloalkyl, optionally substituted 3-7 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, and optionally substituted C_2-C_8 alkynyl;

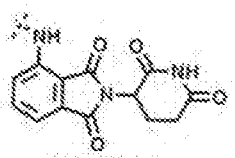
R^4 and R^5 are independently selected from hydrogen, COR^6, CO_2R^6, $CONR^6R^7$, SOR^6, SO_2R^6, $SO_2NR^6R^7$, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted aryl-C_1-

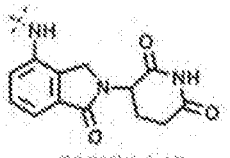
C_8alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, wherein

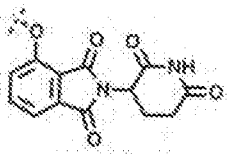
R^6 and R^7 are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or

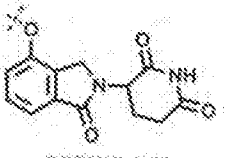
R^6 and R^7 together with the atom to which they are connected form a 4-8 membered cycloalkyl or heterocyclyl ring.

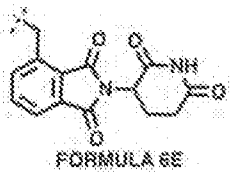
88. The bivalent compound of any one of claims 1 – 63, wherein the degradation/disruption tag is selected from the group consisting of:

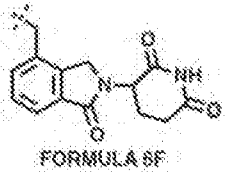

FORMULA 6A

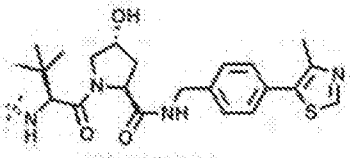

FORMULA 6B

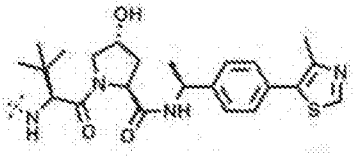

FORMULA 6C

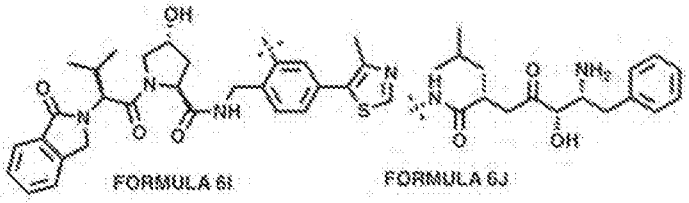

FORMULA 6D

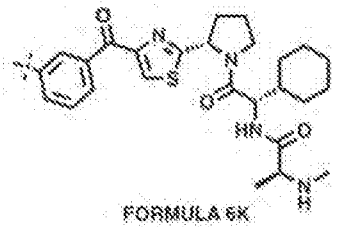

FORMULA 6E

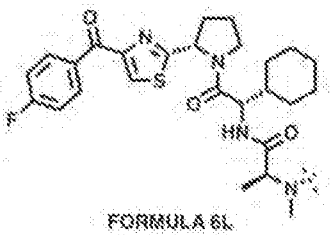

FORMULA 6F

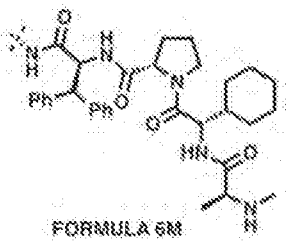

FORMULA 6G

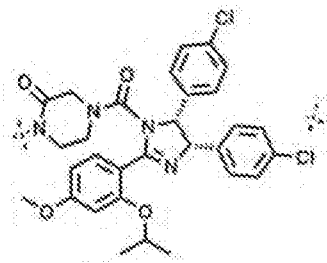

FORMULA 6H

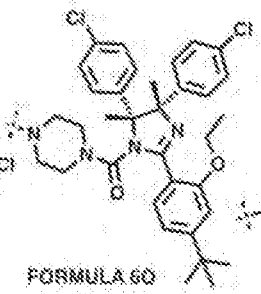

FORMULA 6I FORMULA 6J

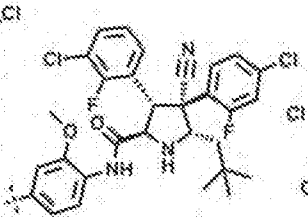

FORMULA 6K

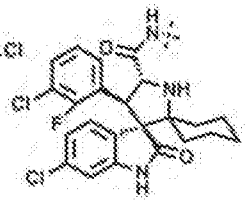

FORMULA 6L


FORMULA 6M

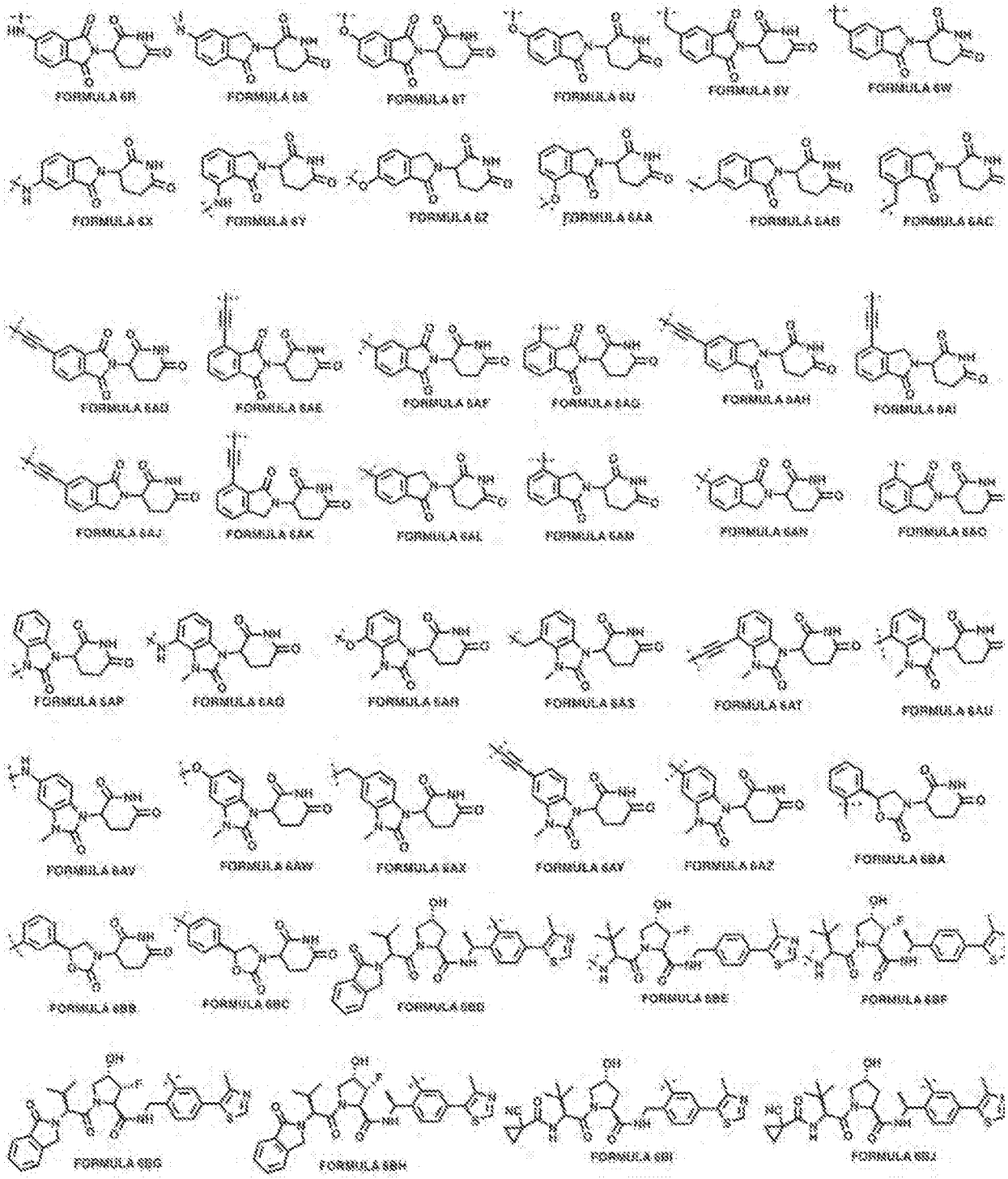

FORMULA 6N


FORMULA 6O


FORMULA 6P


FORMULA 6Q

5


FORMULA 6R
FORMULA 6S
FORMULA 6T
FORMULA 6U
FORMULA 6V
FORMULA 6W
FORMULA 6X
FORMULA 6Y
FORMULA 6Z
FORMULA 6AA
FORMULA 6AB
FORMULA 6AC
FORMULA 6AD
FORMULA 6AE
FORMULA 6AF
FORMULA 6AG
FORMULA 6AH
FORMULA 6AI
FORMULA 6AJ
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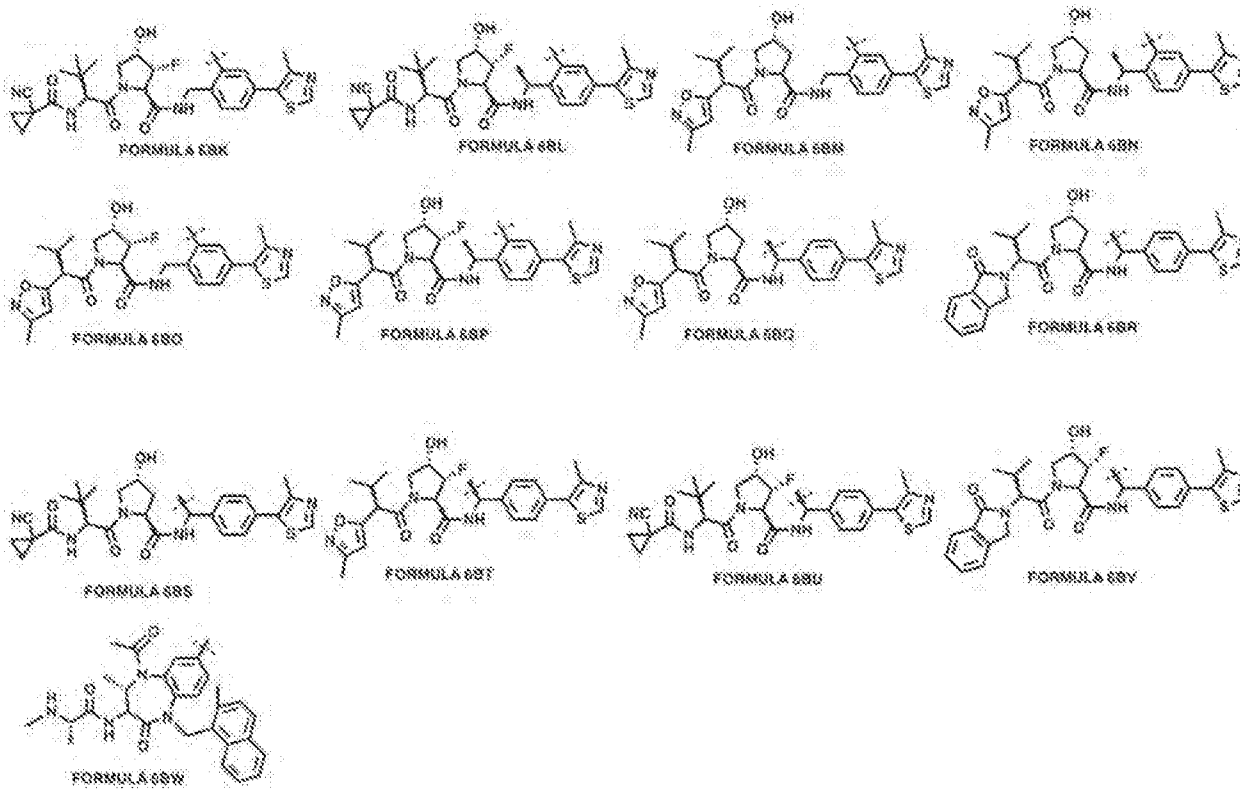
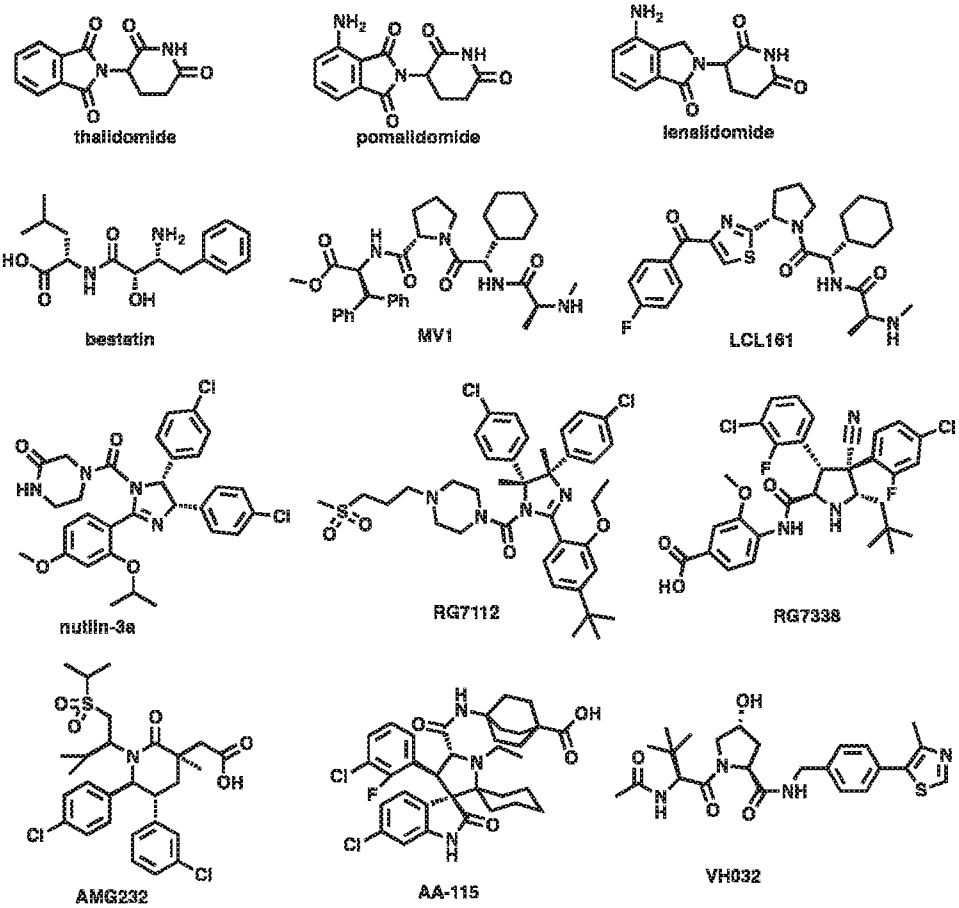
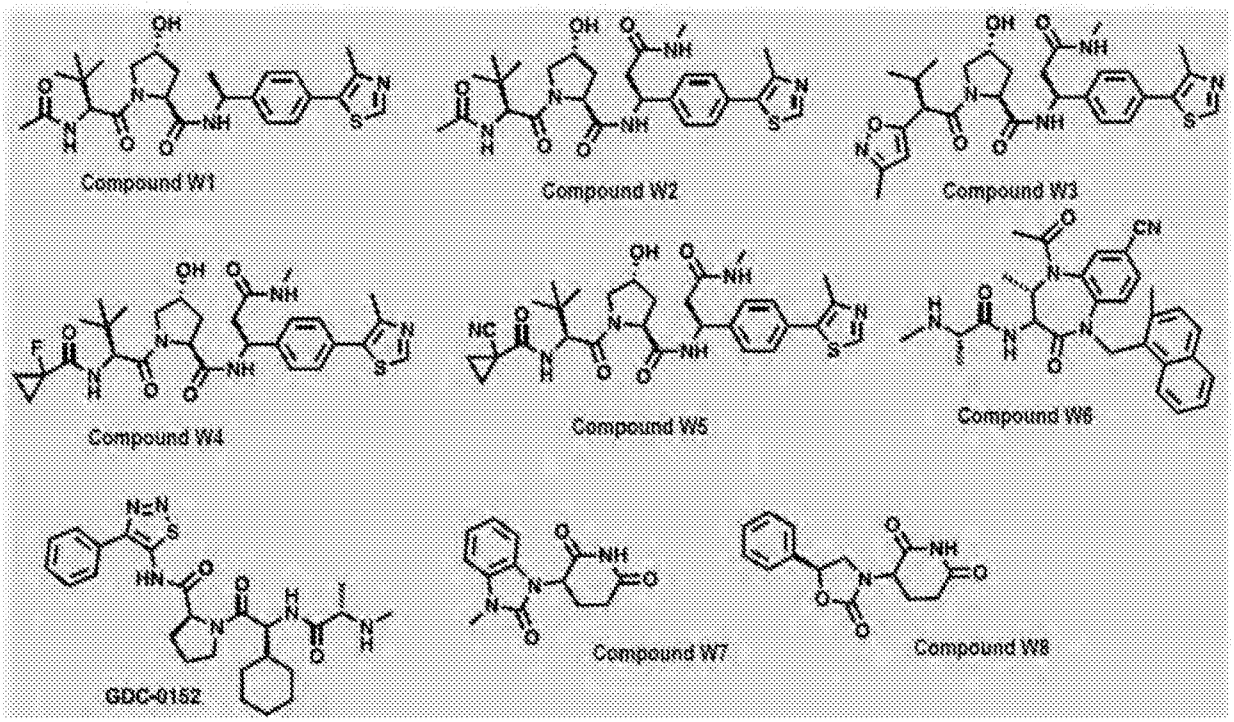
FORMULA 6BH
FORMULA 6BI
FORMULA 6BJ


FORMULA 6BK
FORMULA 6BL
FORMULA 6BM
FORMULA 6BN
FORMULA 6BO
FORMULA 6BP
FORMULA 6BQ
FORMULA 6BR
FORMULA 6BS
FORMULA 6BT
FORMULA 6BU
FORMULA 6BV
FORMULA 6BW


thalidomide
pomalidomide
lenalidomide
bestatin
MV1
LCL161
nutlin-3a
RG7112
RG7338
AMG232
AA-115
VH032



89. The bivalent compound of any one of claims 1 – 80, wherein the degradation/disruption tag binds to a ubiquitin ligase and/or serves as a hydrophobic group that leads to PTK6 protein misfolding.

90. The bivalent compound of claim 89, wherein the ubiquitin ligase is an E3 ligase.

91. The bivalent compound of claim 90, wherein the E3 ligase is selected from the group consisting of a cereblon E3 ligase, a VHL E3 ligase, a MDM2 ligase, a TRIM24 ligase, a TRIM21 ligase, a KEAP1 ligase and an IAP ligase.

92. A bivalent compound selected from the group consisting of:
YX39-86, YX39-89, YX39-90, YX39-91, YX39-92, YX39-93, YX39-94, YX39-96, YX39-97, YX39-98, YX39-99, YX39-100, YX39-101, YX39-102, YX39-103, YX39-104, YX39-105, YX39-106, YX39-107, YX39-127, YX39-128, YX39-129, YX44-158, YX44-172, YX44-184, YX49-7-2, YX49-8, YX49-9, YX49-10, YX49-11, YX49-24,

YX49-99, YX49-100, YX49-101, YX49-102, YX59-122, YX69-5, YX69-157, YX69-158, YX69-159, YX69-182, YX69-183, YX69-184, YX79-3, YX79-4, YX79-5, YX79-6, YX79-10, YX79-11, YX79-12, YX79-13, YX79-14, YX79-15, YX79-16, YX79-17, YX79-18, YX79-19, YX79-20, YX79-21, YX79-22, YX79-23, YX79-24, YX79-25, YX79-29, YX79-30, YX79-34, YX79-35, YX79-36, YX79-37, YX79-38, YX79-39, YX79-40, YX79-41, YX79-42, YX79-43, YX79-56, YX79-57, YX79-58, YX79-59, YX79-60, YX79-61, YX79-62, YX79-63, YX79-64, YX79-65, YX79-66, YX79-67, YX79-68, YX79-69, YX79-70, YX79-86, YX79-87, YX79-88, YX79-89, YX79-90, YX79-91, YX79-92, YX79-93, YX79-94, YX79-95, YX79-967, YX79-97, YX79-131, YX79-132, YX79-133, YX79-134, YX79-135, YX79-136, YX79-137, YX79-138, YX79-139, YX79-140, YX79-141, YX79-142, YX79-143, YX79-144, YX79-145, YX79-146, YX79-147, YX79-148, YX79-149, YX79-150, YX79-151, YX79-152, YX79-153, YX79-154, YX79-155, YX79-156. YX79-157, YX79-158, YX79-159, YX79-160, YX79-161, YX79-162, YX79-164, YX79-165, JH077-29, JH077-30, JH077-31, JH077-32, JH077-33, JH077-34, JH077-35, JH077-35, JH077-36, JH077-37, JH077-38, JH077-39, JH077-40, JH077-41, JH077-47, JH077-48, JH077-49, JH077-51, JH077-52, JH077-53, JH077-54, JH077-55, JH077-56, JH077-57, JH077-58, JH077-65, JH077-66, JH077-67, JH077-68, JH077-69, JH077-70, JH077-71, JH077-72, JH077-73, JH077-74, JH077-75, JH077-76, JH077-76, JH077-77, JH077-78, JH077-79, JH077-80, JH077-81, JH077-82, JH077-83, JH077-84, JH077-85, JH077-86, JH077-87, JH077-88, JH077-89, JH077-90, JH077-91, JH077-92, JH077-93 and analogs thereof.

93. A bivalent compound selected from the group consisting of:

YX39-86, YX39-89, YX39-90, YX39-91, YX39-92, YX39-93, YX39-94, YX39-96, YX39-97, YX39-98, YX39-99, YX39-100, YX39-101, YX39-102, YX39-103, YX39-104, YX39-105, YX39-106, YX39-107, YX39-127, YX39-128, YX39-129, YX44-158, YX44-172, YX44-184, YX49-7-2, YX49-8, YX49-9, YX49-10, YX49-11, YX49-24, YX49-99, YX49-100, YX49-101, YX49-102, YX59-122, YX69-5, YX69-157, YX69-158, YX69-159, YX69-182, YX69-183, YX69-184, YX79-3, YX79-4, YX79-5, YX79-6, YX79-10, YX79-11, YX79-12, YX79-13, YX79-14, YX79-15, YX79-16, YX79-17, YX79-18, YX79-19, YX79-20, YX79-21, YX79-22, YX79-23, YX79-24, YX79-25, YX79-29, YX79-30, YX79-34, YX79-35, YX79-36, YX79-37,

YX79-38, YX79-39, YX79-40, YX79-41, YX79-42, YX79-43, YX79-56, YX79-57, YX79-58, YX79-59, YX79-60, YX79-61, YX79-62, YX79-63, YX79-64, YX79-65, YX79-66, YX79-67, YX79-68, YX79-69, YX79-70, YX79-86, YX79-87, YX79-88, YX79-89, YX79-90, YX79-91, YX79-92, YX79-93, YX79-94, YX79-95, YX79-967, YX79-97, YX79-131, YX79-132, YX79-133, YX79-134, YX79-135, YX79-136, YX79-137, YX79-138, YX79-139, YX79-140, YX79-141, YX79-142, YX79-143, YX79-144, YX79-145, YX79-146, YX79-147, YX79-148, YX79-149, YX79-150, YX79-151, YX79-152, YX79-153, YX79-154, YX79-155, YX79-156. YX79-157, YX79-158, YX79-159, YX79-160, YX79-161, YX79-162, YX79-164, YX79-165, JH077-29, JH077-30, JH077-31, JH077-32, JH077-33, JH077-34, JH077-35, JH077-35, JH077-36, JH077-37, JH077-38, JH077-39, JH077-40, JH077-41, JH077-47, JH077-48, JH077-49, JH077-51, JH077-52, JH077-53, JH077-54, JH077-55, JH077-56, JH077-57, JH077-58, JH077-65, JH077-66, JH077-67, JH077-68, JH077-69, JH077-70, JH077-71, JH077-72, JH077-73, JH077-74, JH077-75, JH077-76, JH077-76, JH077-77, JH077-78, JH077-79, JH077-80, JH077-81, JH077-82, JH077-83, JH077-84, JH077-85, JH077-86, JH077-87, JH077-88, JH077-89, JH077-90, JH077-91, JH077-92, JH077-93 and analogs thereof.

94. A bivalent compound selected from the group consisting of compounds 190 – 280 of Table 1.

95. A bivalent compound selected from the group consisting of YX39-101, YX39-102, YX39-103, YX39-104, YX39-105, YX39-106, YX39-107, YX-49-24, YX49-99, YX49-100, YX49-101, YX49-102, YX69-157, YX69-158, YX69-159, YX79-10, YX79-11, YX79-12, YX79-15, YX79-36, YX79-37, YX79-40, YX79-42, YX79-59 and YX-79-65.

96. (2S,4R)-1-((S)-2-(5-(2-(4-(4-((6-cyclopropyl-3-(1H-pyrazol-4-yl)imidazo[1,2-a]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamido)pentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (YX39-101).

97. (2S,4R)-1-((S)-2-(6-(2-(4-(4-((6-cyclopropyl-3-(1H-pyrazol-4-yl)imidazo[1,2-a]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamido)hexanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (YX39-102).

98. (2S,4R)-1-((S)-2-(7-(2-(4-(4-((6-cyclopropyl-3-(1H-pyrazol-4-yl)imidazo[1,2-a]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamido)heptanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (YX39-103).

99. (2S,4R)-1-((S)-2-(8-(2-(4-(4-((6-cyclopropyl-3-(1H-pyrazol-4-yl)imidazo[1,2-a]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamido)octanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (YX39-104).

100. (2S,4R)-1-((S)-2-(9-(2-(4-(4-((6-cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamido)nonanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (YX39-105).

101. (2S,4R)-1-((S)-2-(10-(2-(4-(4-((6-cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamido)decanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (YX39-106).

102. (2S,4R)-1-((S)-2-(11-(2-(4-(4-((6-cyclopropyl-3-(1H-pyrazol-4-yl)imidazo[1,2-a]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamido)undecanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (YX39-107).

103. (2S,4R)-1-((S)-2-(12-(4-(4-((6-cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-12-oxododecanamido)-3,3-

dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (YX49-24).

104. (2*S*,4*R*)-1-((*S*)-2-(12-(4-(4-((6-cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-12-oxododecanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (YX49-99).

105. (2*S*,4*R*)-1-((*S*)-2-(13-(4-(4-((6-cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-13-oxotridecanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (YX49-100).

106. (2*S*,4*R*)-1-((*S*)-2-(14-(4-(4-((6-cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-14-oxotetradecanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (YX49-101).

107. (2*S*,4*R*)-1-((*S*)-2-(*tert*-butyl)-17-(4-(4-((6-cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-4,16-dioxo-6,9,12-trioxa-3,15-diazaheptadecanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (YX49-102).

108. (2*S*,4*R*)-1-((*S*)-2-(7-(2-(4-(4-((6-cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamido)heptanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (YX69-157).

109. (2*S*,4*R*)-1-((*S*)-2-(9-(2-(4-(4-((6-cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)acetamido)nonanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (YX69-158).

110. (2S,4R)-1-((S)-2-(tert-butyl)-17-(4-(4-((6-cyclopropyl-3-(1H-pyrazol-4-yl)imidazo[1,2-a]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-4,16-dioxo-6,9,12-trioxa-3,15-diazaheptadecanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (YX69-159).

111. (2S,4R)-1-((S)-2-(5-(4-(4-((6-cyclopropyl-3-(1H-pyrazol-4-yl)imidazo[1,2-a]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-5-oxopentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (YX79-10).

112. (2*S*,4*R*)-1-((*S*)-2-(6-(4-(4-((6-cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-6-oxohexanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (YX79-11).

113. (2*S*,4*R*)-1-((*S*)-2-(7-(4-(4-((6-cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-7-oxoheptanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (YX79-12).

114. (2*S*,4*R*)-1-((*S*)-2-(3-(3-(4-(4-((6-cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-3-oxopropoxy)propanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (YX79-15).

115. 4-((2-(2-(3-(4-(4-((6-cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-3-oxopropoxy)ethoxy)ethyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (YX79-36).

116. 4-((2-(2-(2-(3-(4-(4-((6-cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-3-oxopropoxy)ethoxy)ethoxy)ethyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (YX79-37).

117. (2*S*,4*R*)-1-((*S*)-2-(2-(2-(4-(4-((6-cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-2-oxoethoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (YX79-40).

118. (2*S*,4*R*)-1-((*S*)-2-(*tert*-butyl)-14-(4-(4-((6-cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-4,14-dioxo-6,9,12-trioxa-3-azatetradecanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (YX79-42).

119. N^1-(2-(4-(4-((6-cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)ethyl)-N^8-((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)octanediamide (YX79-59).

120. (2*S*,4*R*)-1-((*S*)-2-(*tert*-butyl)-14-(4-(4-((6-cyclopropyl-3-(1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)-3-fluorobenzoyl)piperazin-1-yl)-4,11-dioxo-6,9-dioxa-3,12-diazatetradecanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (YX79-65).

121. A method of treating a protein tyrosine kinase 6 (PTK6)-mediated disease, comprising administering to a subject with a PTK6-mediated disease, a bivalent compound comprising a PTK6 ligand conjugated to a degradation/disruption tag through a linker.

122. The method of claim 121, wherein the PTK6-mediated disease results from PTK6 expression or mutation.

123. The method of claim 121 or 122, wherein a tissue from the subject has elevated PTK6 function relative to a wild-type tissue of the same species and tissue type.

124. The method of any one of claims 121-123, wherein the bivalent compound is selected from the group consisting of YX39-101, YX39-102, YX39-103, YX39-104, YX39-105, YX39-106, YX39-107, YX-49-24, YX49-99, YX49-100, YX49-101, YX49-102, YX69-157, YX69-158, YX69-159, YX79-10, YX79-11, YX79-12, YX79-15, YX79-36, YX79-37, YX79-40, YX79-42, YX79-59 and YX-79-65.

125. The method of any one of claims 121-124, wherein the bivalent compound is administered to the subject orally, parenterally, intradermally, subcutaneously, topically, or rectally.

126. The method of any one of claims 121-125, further comprising treating the subject with an additional therapeutic regimen for treating cancer.

127. The method of claim 126, wherein the additional therapeutic regimen is selected from the group consisting of surgery, chemotherapy, radiation therapy, hormone therapy, and immunotherapy.

128. The method of any one of claims 121-127, wherein the PKT6-mediated disease is selected from the group consisting of leukemia, lymphoma, ovarian cancer, stomach cancer, cervical cancer, uterine cancer, gastric cancer, head neck squamous cell carcinoma (HNSCC), colorectal cancer (CRC), lung cancer, pancreatic cancer, bladder cancer, breast cancer, and neuroblastoma.

129. The method of any one of claims 121-128, wherein the PTK6-mediated disease is a relapsed cancer.

130. The method of any one of claims 121-129, wherein the PTK6-mediated disease is refractory to one or more previous treatments.

131. A method for identifying a bivalent compound which mediates degradation/disruption of PKT6, the method comprising:

providing a heterobifunctional test compound comprising a PKT6 ligand conjugated to a degradation/disruption tag through a linker;

contacting the heterobifunctional test compound with a cell comprising a ubiquitin ligase and PKT6;

determining whether PKT6 levels decrease in the cell; and

identifying the heterobifunctional test compound as a bivalent compound which mediates degradation/reduction of PKT6 levels decrease in the cell.

132. The method of claim 131, wherein the cell is a cancer cell.

133. The method of claim 132, wherein the cancer cell is a PKT6-mediated cancer cell.

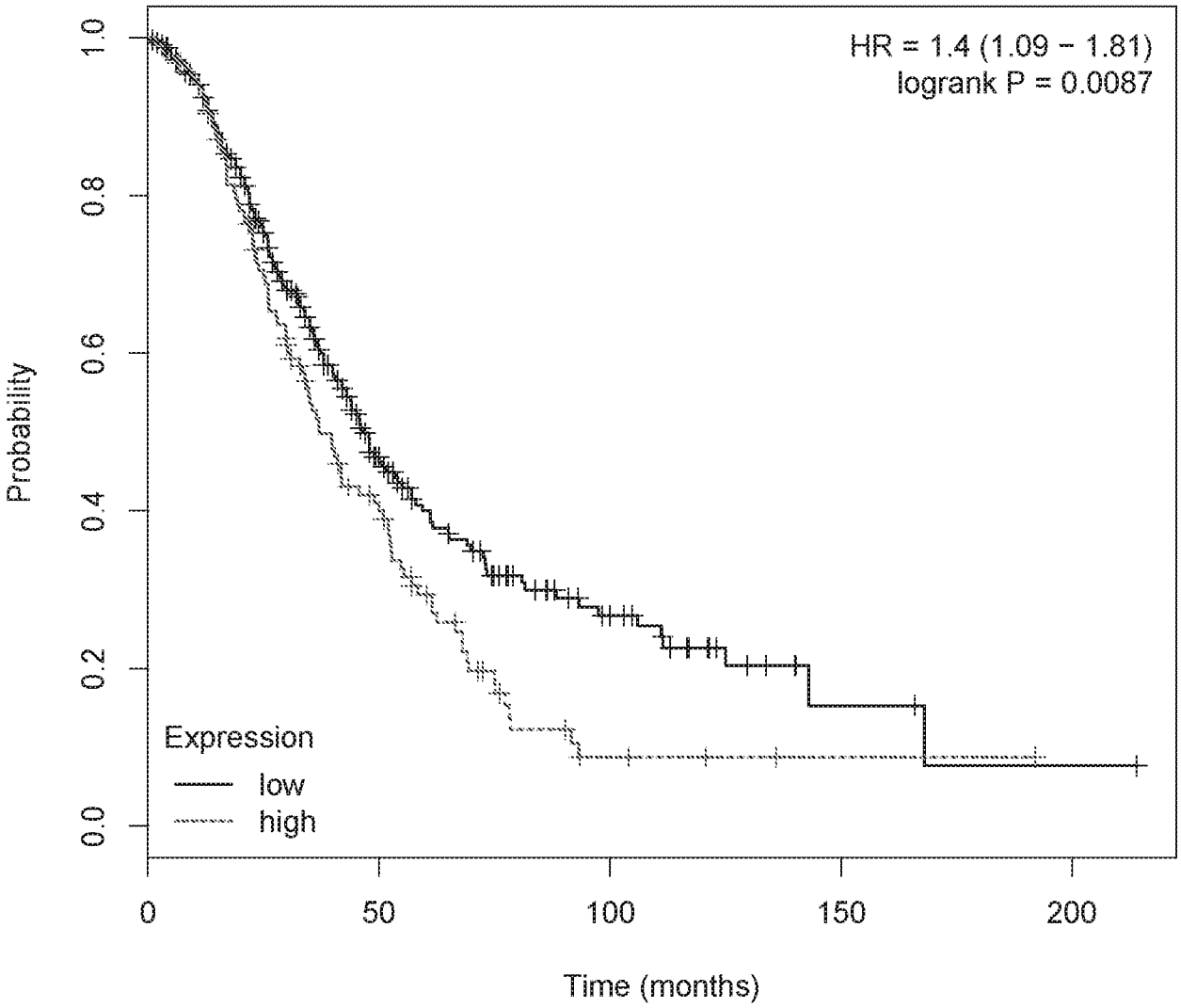


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FIG. 1

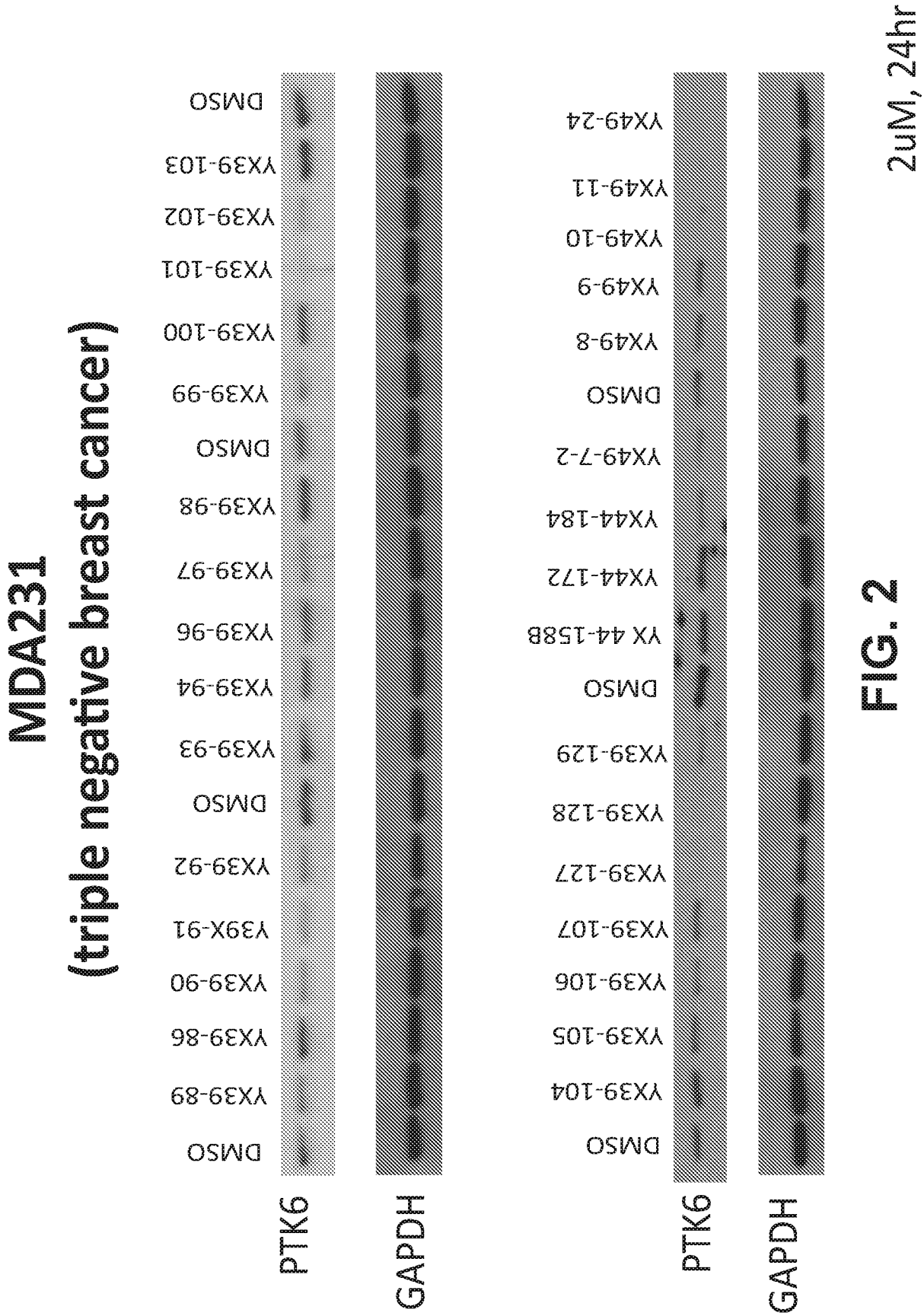

MDA231
(triple negative breast cancer)
2uM, 24hr
PTK6
GAPDH
DMSO
YX39-89
YX39-86
YX39-90
Y39X-91
YX39-92
DMSO
YX39-93
YX39-94
YX39-96
YX39-97
YX39-98
DMSO
YX39-99
YX39-100
YX39-101
YX39-102
YX39-103
DMSO
YX39-104
YX39-105
YX39-106
YX39-107
YX39-127
YX39-128
YX39-129
DMSO
YX 44-158B
YX44-172
YX44-184
YX49-7-2
DMSO
YX49-8
YX49-9
YX49-10
YX49-11
YX49-24

FIG. 2

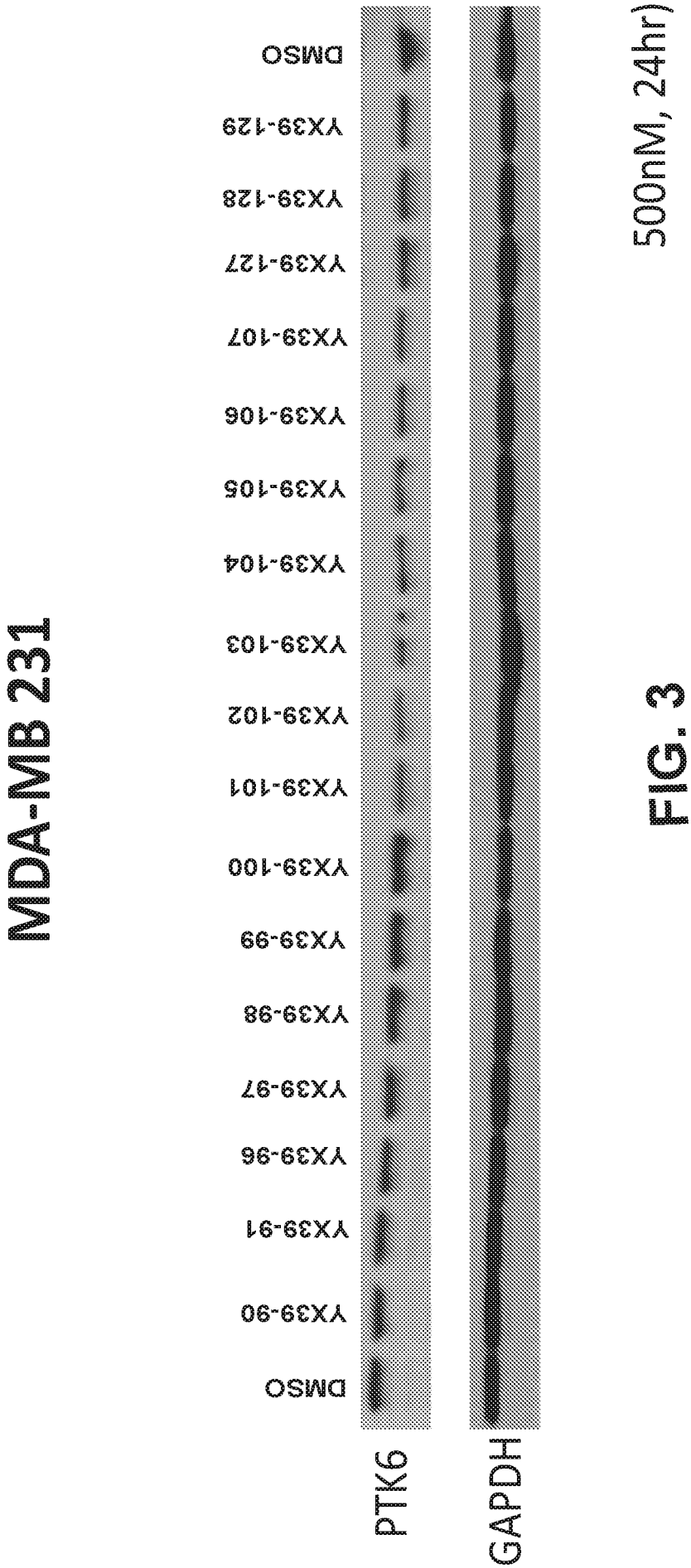
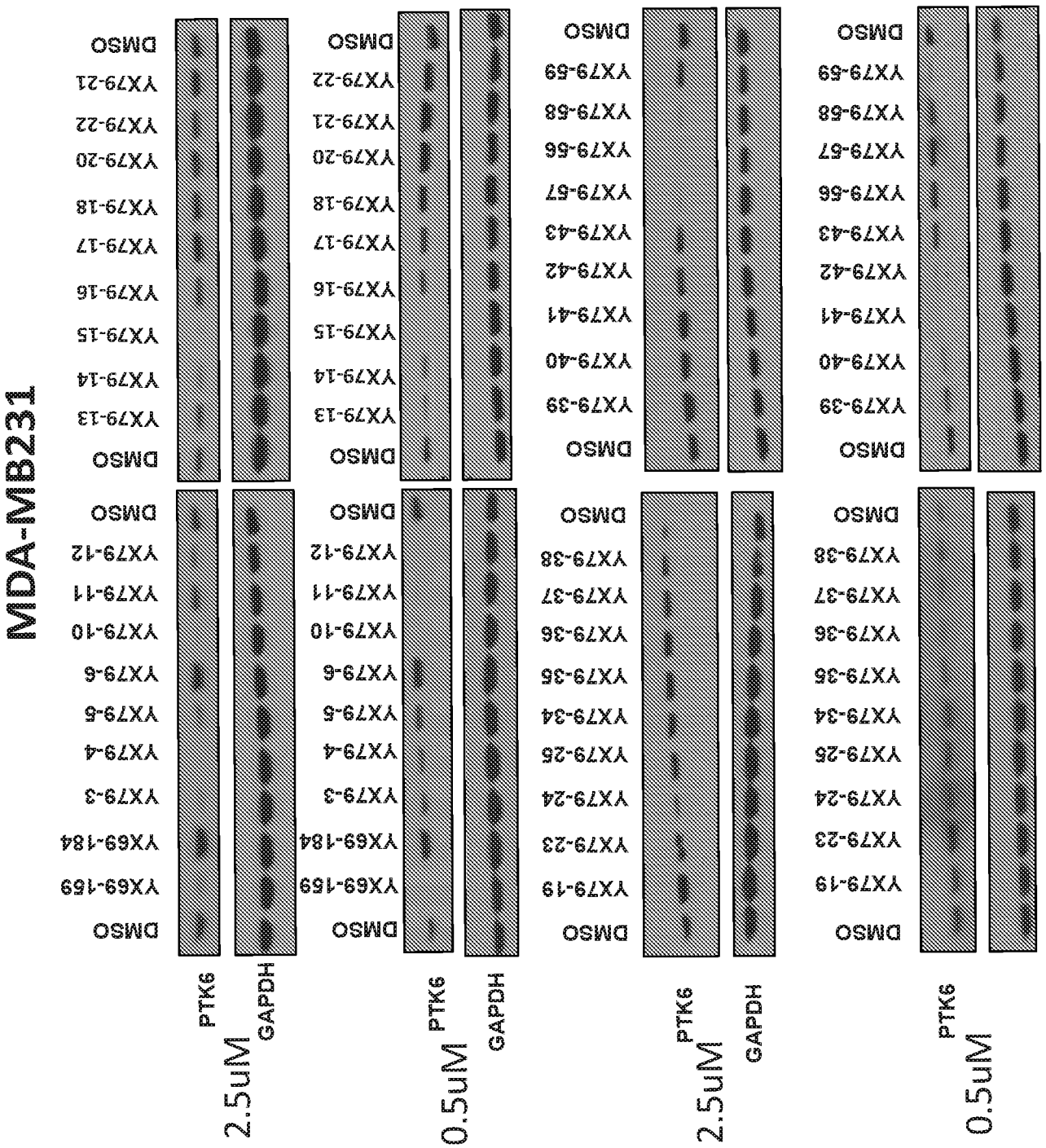

MDA-MB 231
DMSO
YX39-90
YX39-91
YX39-96
YX39-97
YX39-98
YX39-99
YX39-100
YX39-101
YX39-102
YX39-103
YX39-104
YX39-105
YX39-106
YX39-107
YX39-127
YX39-128
YX39-129
DMSO
PTK6
GAPDH
500nM, 24hr)

FIG. 3

FIG. 4


MDA-MB231
PTK6
GAPDH
2.5uM
0.5uM
DMSO
YX69-159
YX69-184
YX79-3
YX79-4
YX79-5
YX79-6
YX79-10
YX79-11
YX79-12
YX79-13
YX79-14
YX79-15
YX79-16
YX79-17
YX79-18
YX79-20
YX79-21
YX79-22
YX79-23
YX79-24
YX79-25
YX79-34
YX79-35
YX79-36
YX79-37
YX79-38
YX79-39
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YX79-57
YX79-58
YX79-59

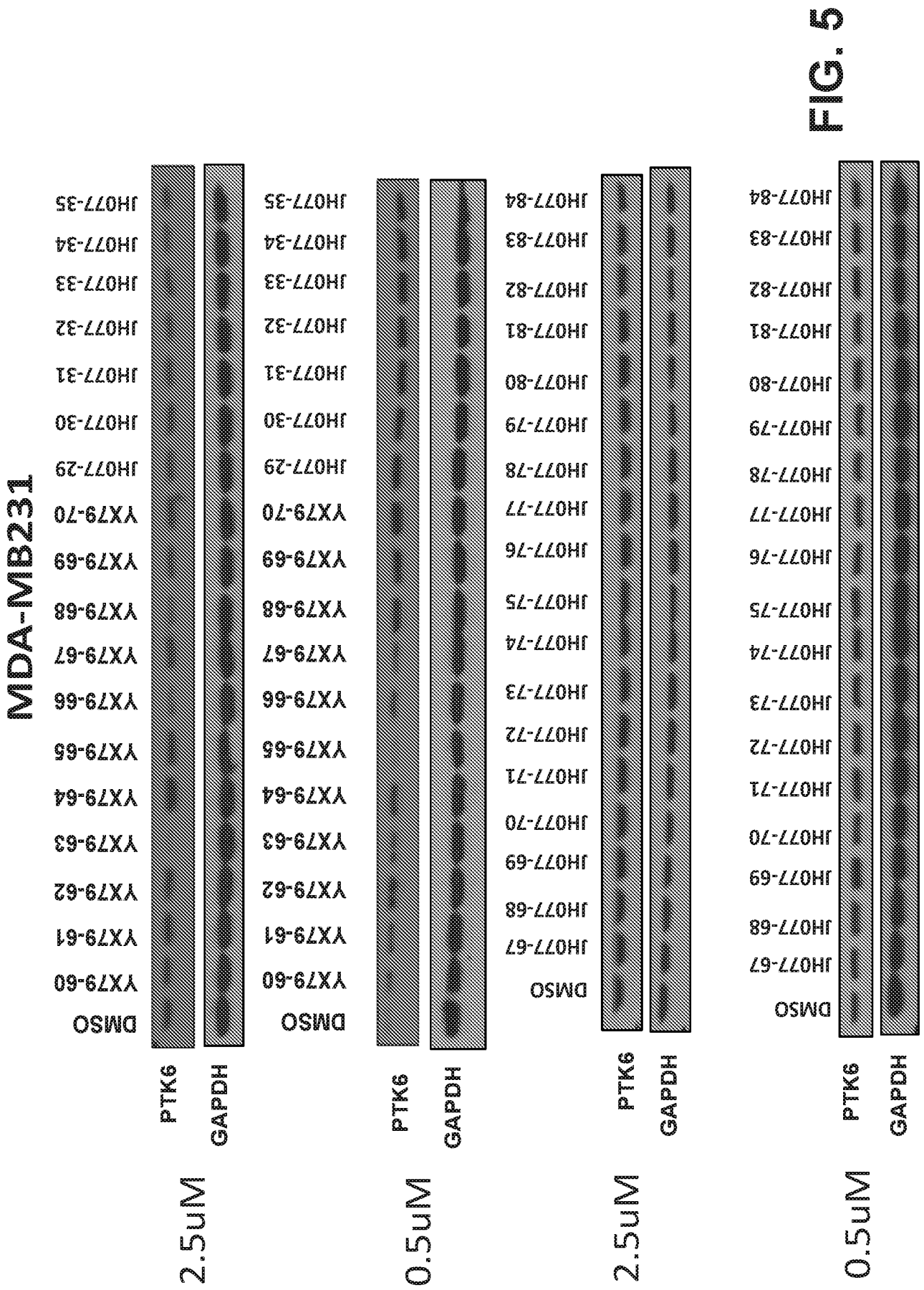
MDA-MB231
2.5uM
0.5uM
2.5uM
0.5uM
PTK6
GAPDH
DMSO
JH077-67
JH077-68
JH077-69
JH077-70
JH077-71
JH077-72
JH077-73
JH077-74
JH077-75
JH077-76
JH077-77
JH077-78
JH077-79
JH077-80
JH077-81
JH077-82
JH077-83
JH077-84
YX79-60
YX79-61
YX79-62
YX79-63
YX79-64
YX79-65
YX79-66
YX79-67
YX79-68
YX79-69
YX79-70
JH077-29
JH077-30
JH077-31
JH077-32
JH077-33
JH077-34
JH077-35

FIG. 5

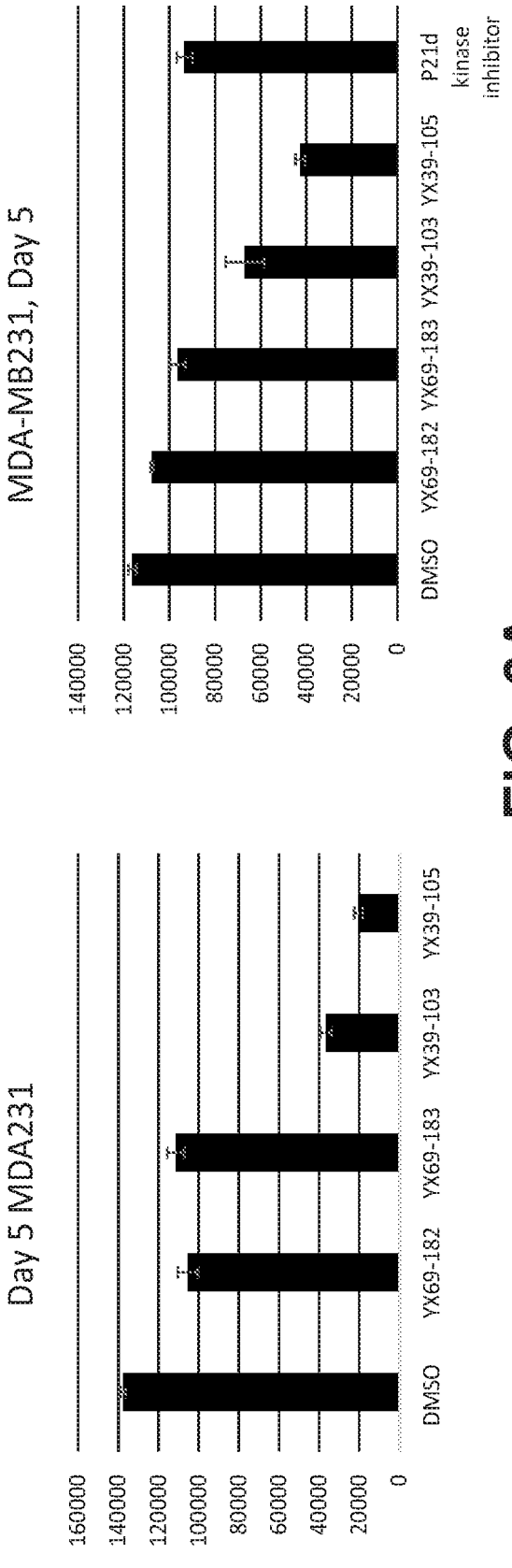
MDA-MB231, Day 5
140000
120000
100000
80000
60000
40000
20000
0
DMSO
YX69-182
YX69-183
YX39-103
YX39-105
P21d kinase inhibitor
Day 5 MDA231
160000
140000
120000
100000
80000
60000
40000
20000
0
DMSO
YX69-182
YX69-183
YX39-103
YX39-105

FIG. 6A

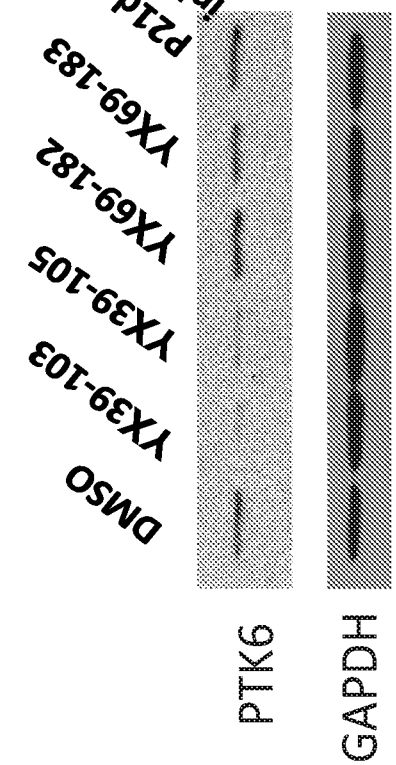
DMSO
YX39-103
YX39-105
YX69-182
YX69-183
P21d (kinase inhibitor)
PTK6
GAPDH

FIG. 6B

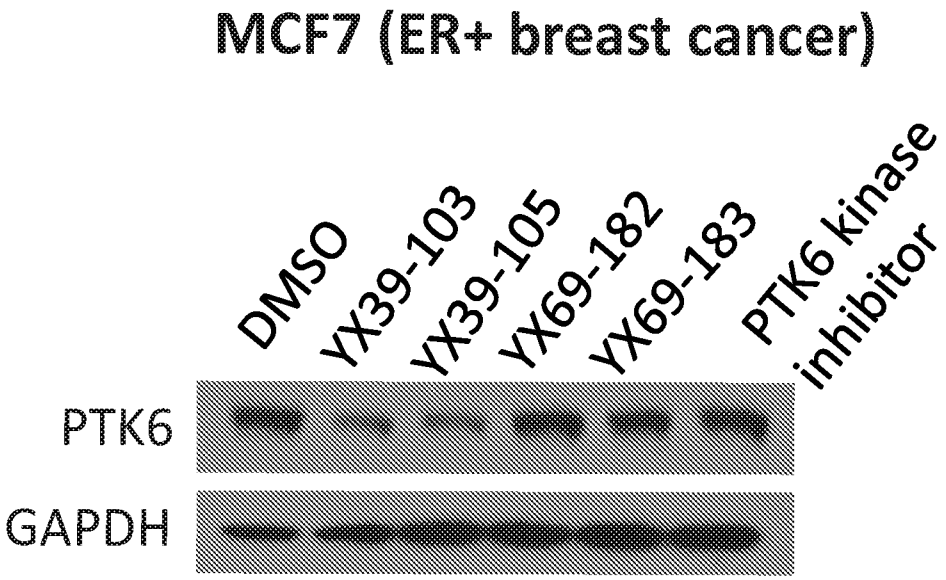
MCF7 (ER+ breast cancer)
DMSO
YX39-103
YX39-105
YX69-182
YX69-183
PTK6 kinase inhibitor
PTK6
GAPDH

FIG. 7A

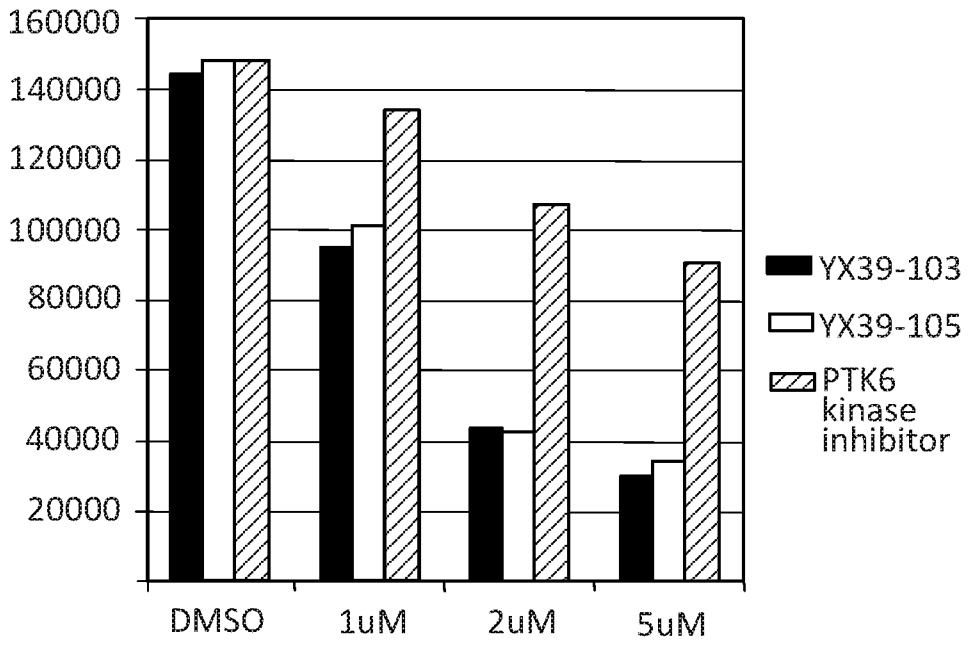
160000
140000
120000
100000
80000
60000
40000
20000
DMSO
1uM
2uM
5uM
YX39-103
YX39-105
PTK6 kinase inhibitor

FIG. 7B

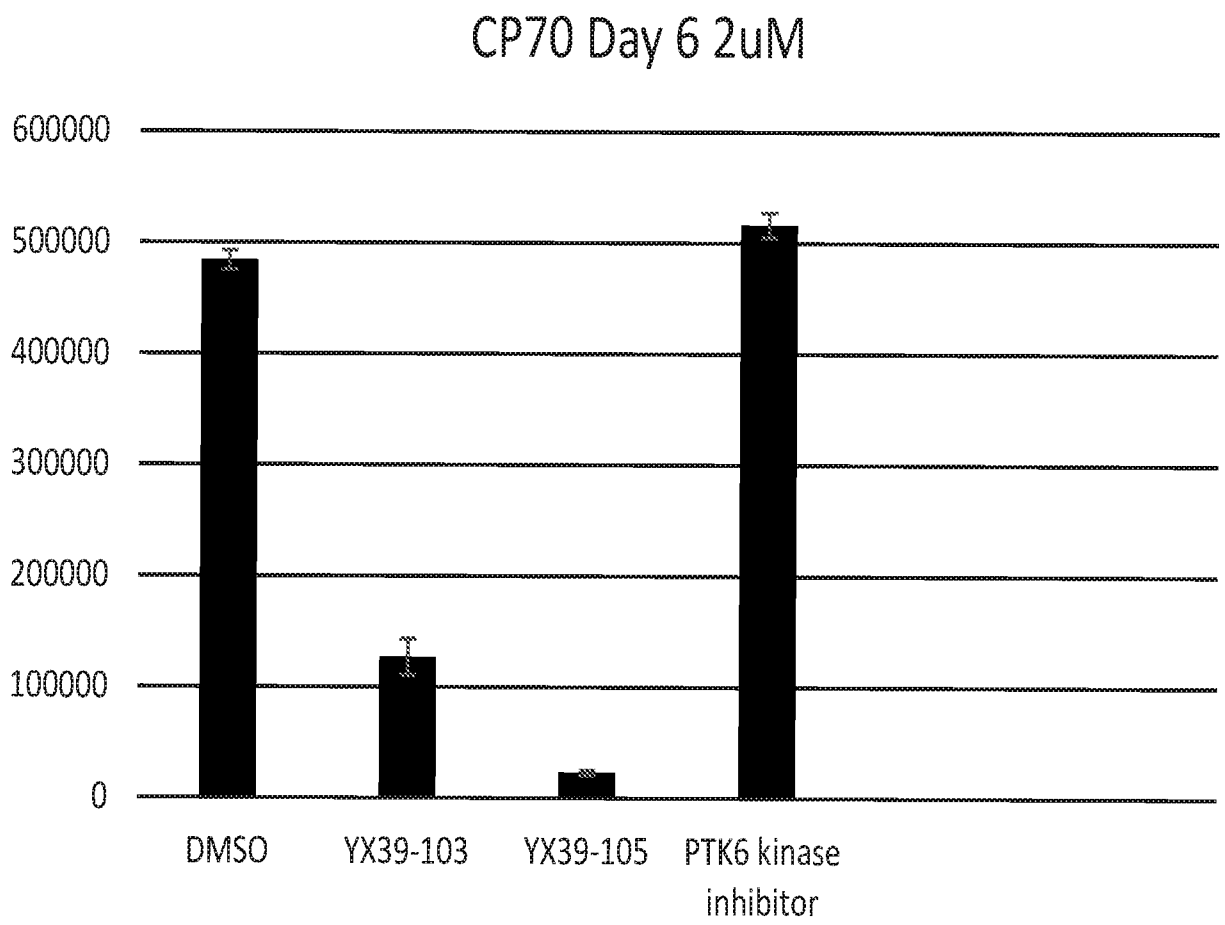
CP70 Day 6 2uM
600000
500000
400000
300000
200000
100000
0
DMSO
YX39-103
YX39-105
PTK6 kinase inhibitor

FIG. 8

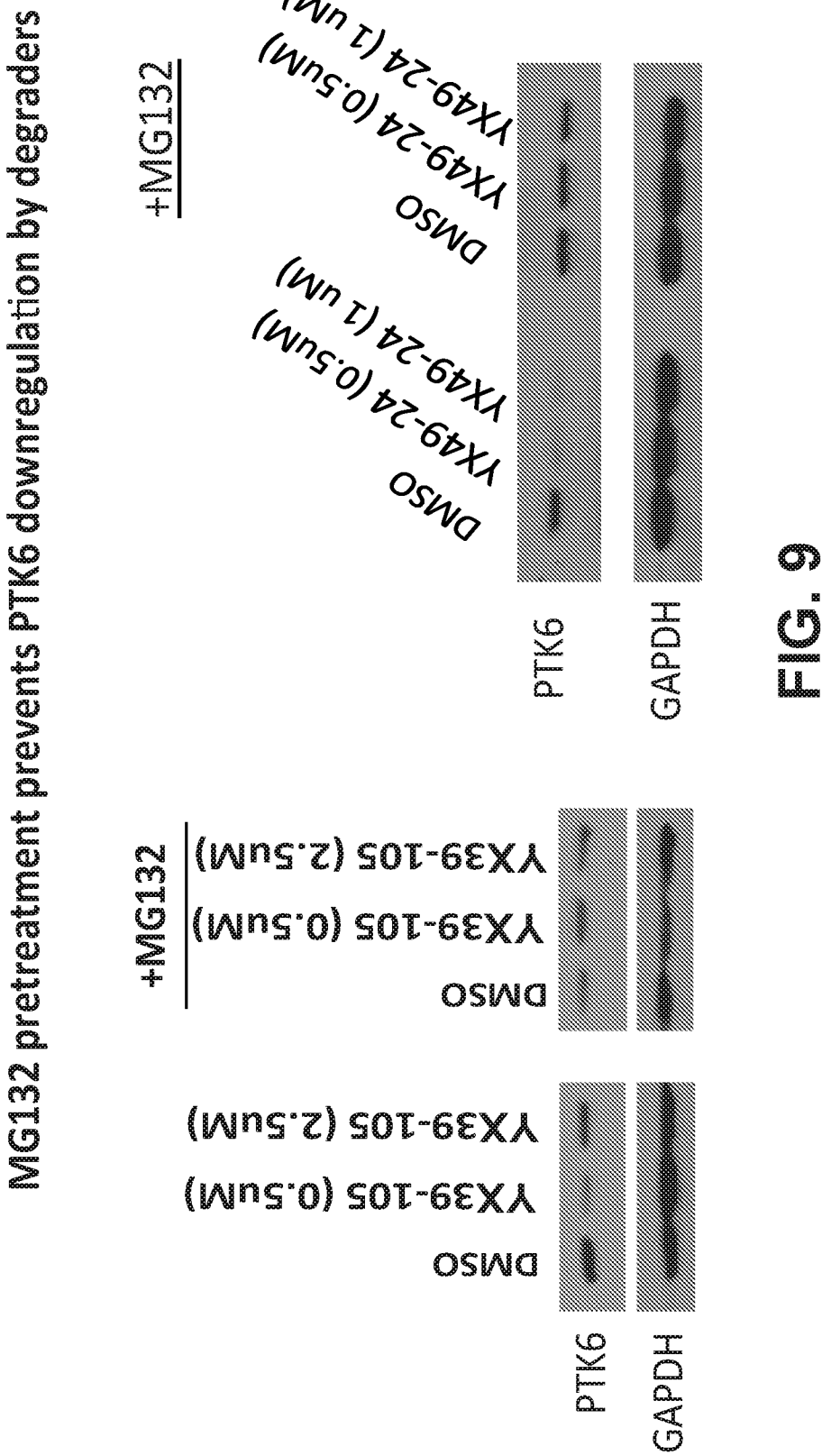
MG132 pretreatment prevents PTK6 downregulation by degraders
PTK6
GAPDH
DMSO
YX39-105 (0.5uM)
YX39-105 (2.5uM)
+MG132
DMSO
YX39-105 (0.5uM)
YX39-105 (2.5uM)
PTK6
GAPDH
DMSO
YX49-24 (0.5uM)
YX49-24 (1 uM)
+MG132
DMSO
YX49-24 (0.5uM)
YX49-24 (1 uM)

FIG. 9

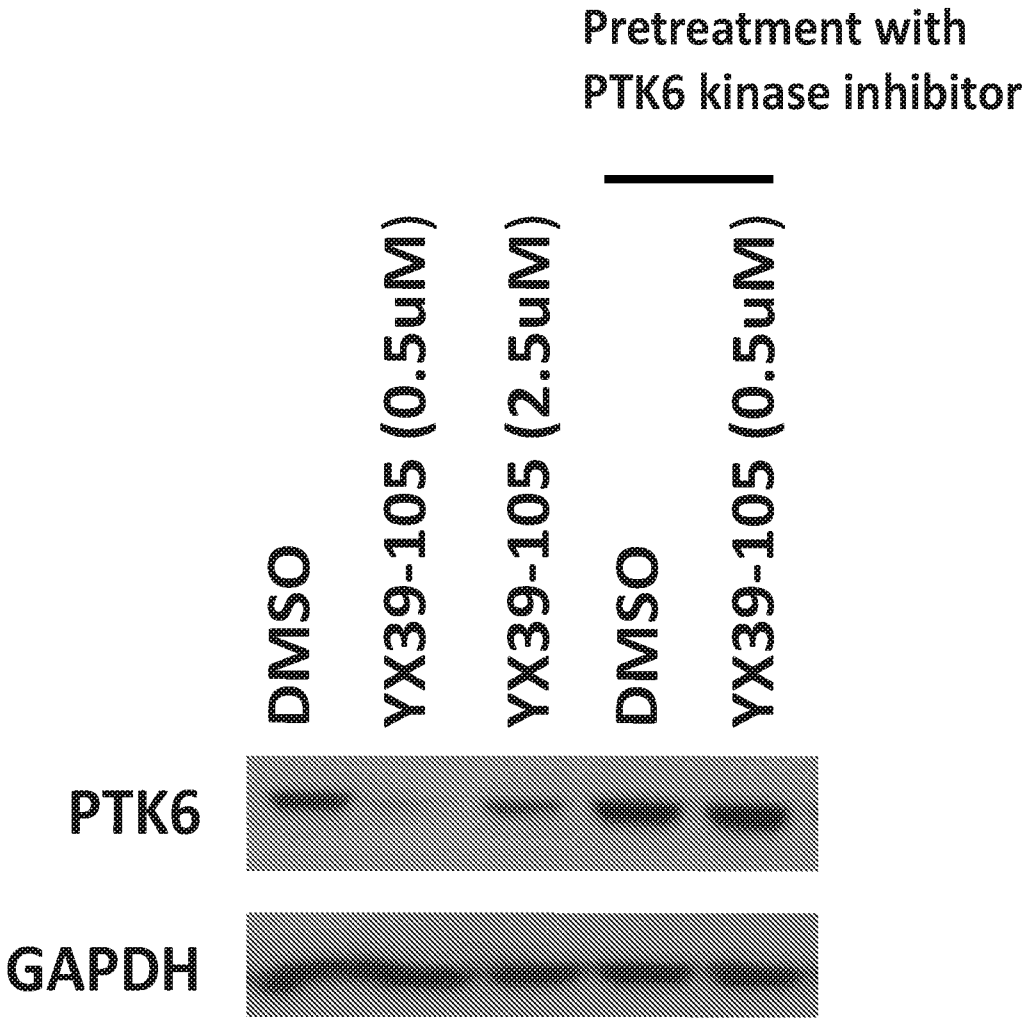
Pretreatment with
PTK6 kinase inhibitor
DMSO
YX39-105 (0.5uM)
YX39-105 (2.5uM)
DMSO
YX39-105 (0.5uM)
PTK6
GAPDH

FIG. 10

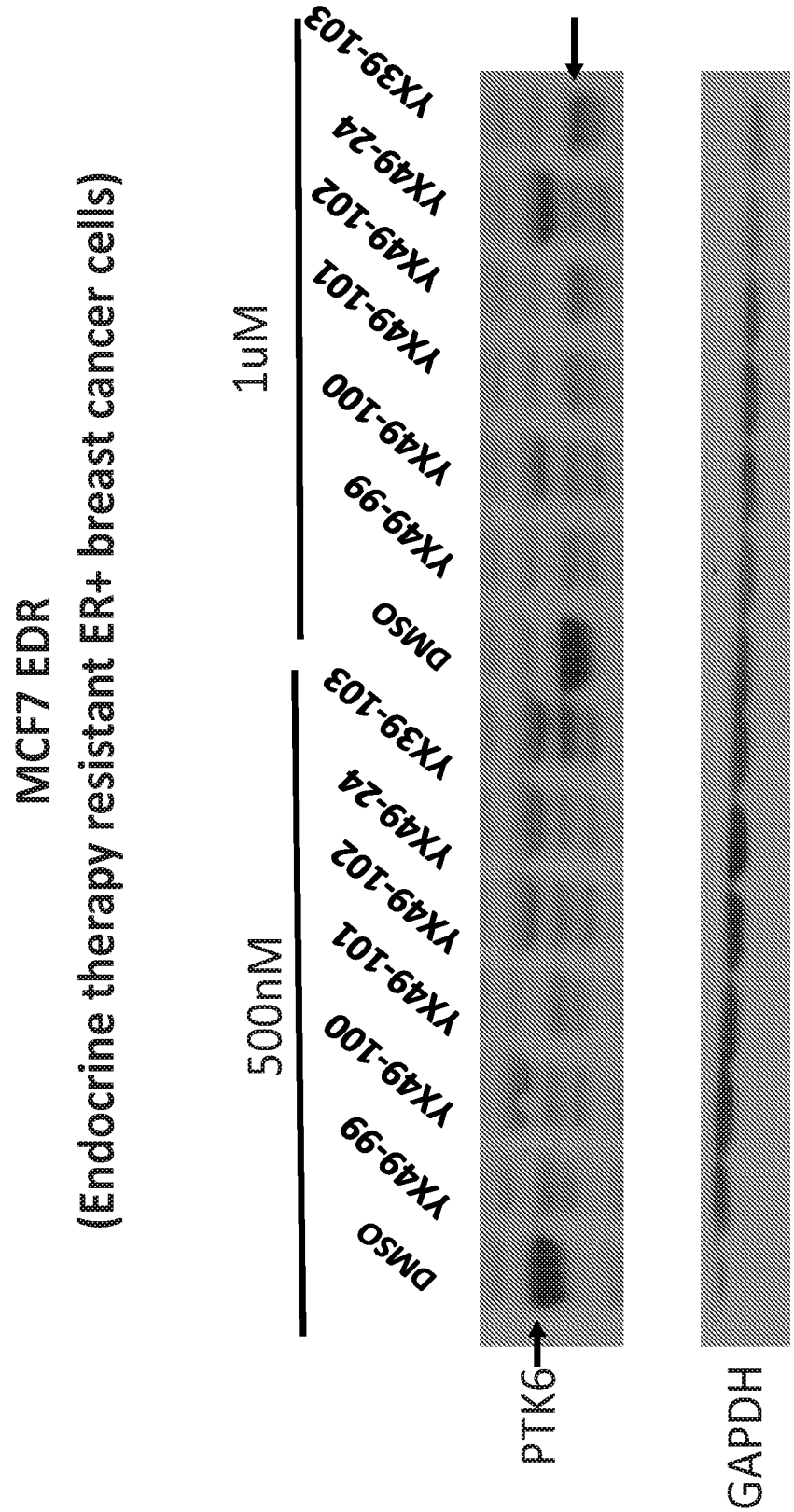
MCF7 EDR
(Endocrine therapy resistant ER+ breast cancer cells)
1uM
500nM
DMSO
YX49-99
YX49-100
YX49-101
YX49-102
YX49-24
YX39-103
PTK6
GAPDH

FIG. 11

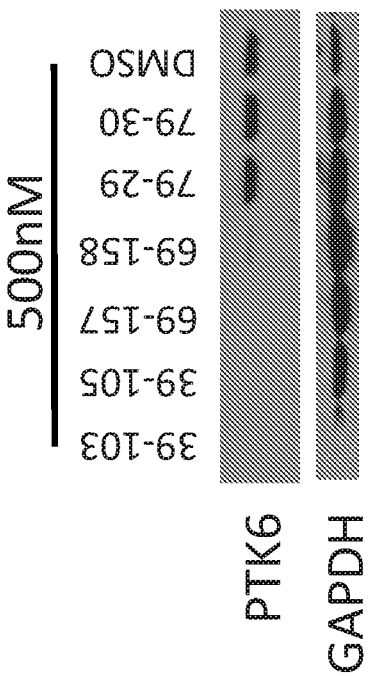

FIG. 12A

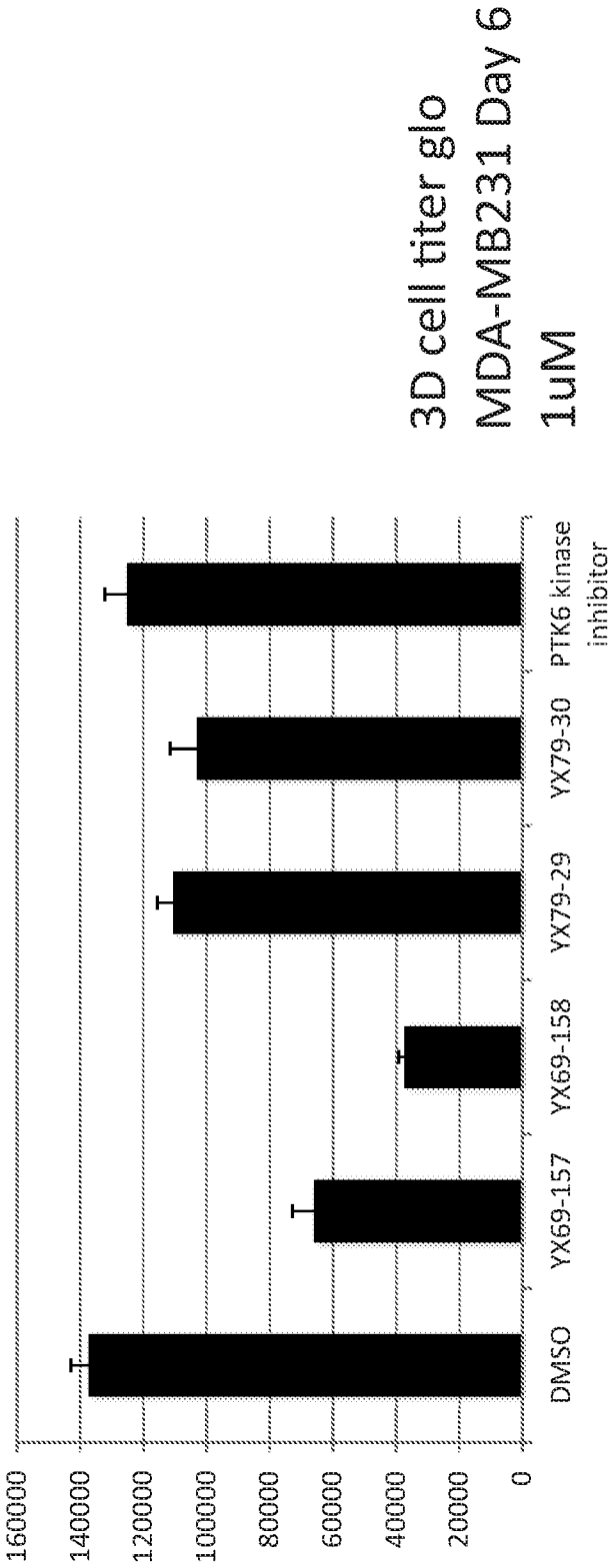

FIG. 12B

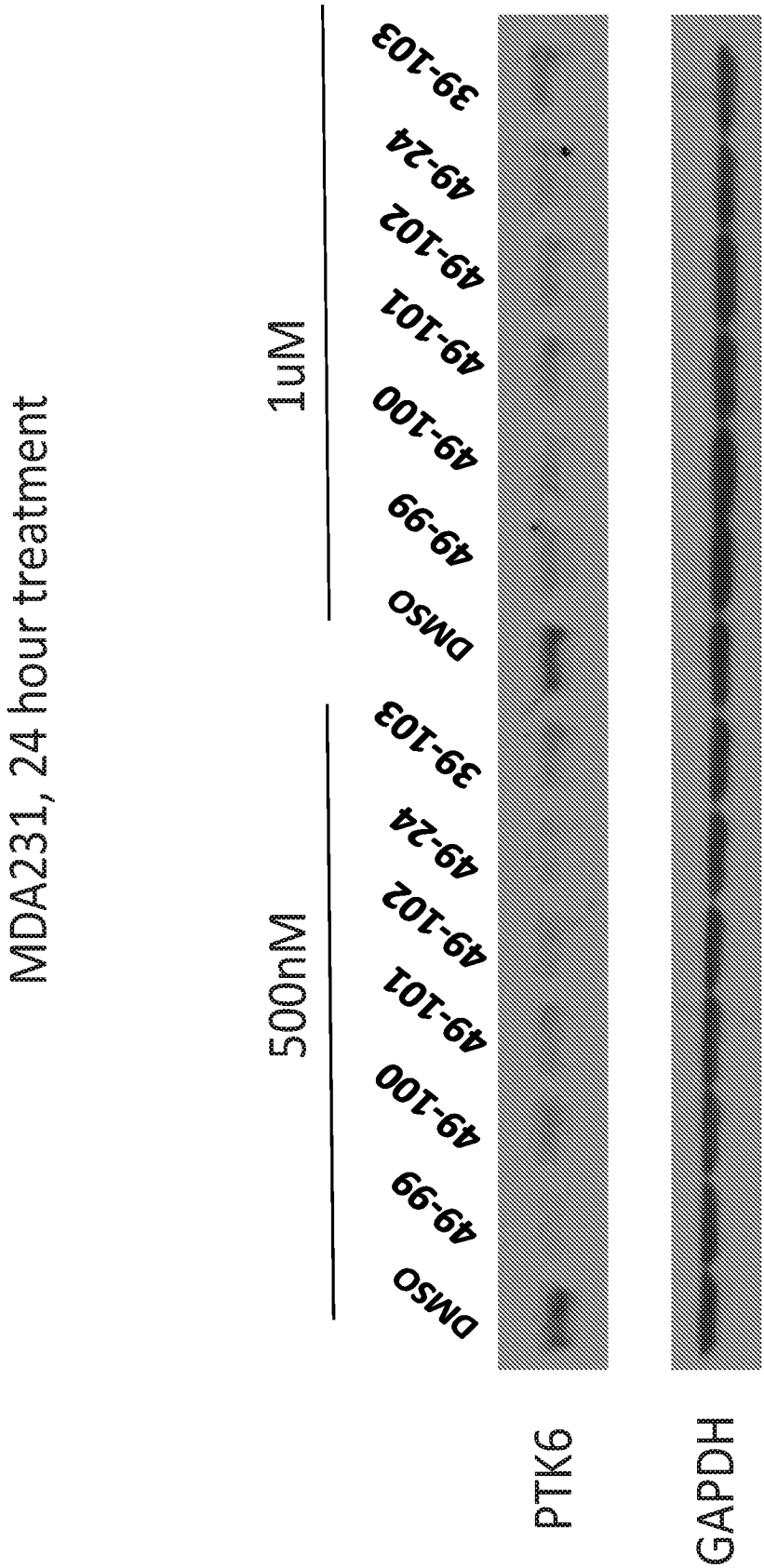
MDA231, 24 hour treatment
500nM
1uM
DMSO
49-99
49-100
49-101
49-102
49-24
49-103
PTK6
GAPDH

FIG. 13

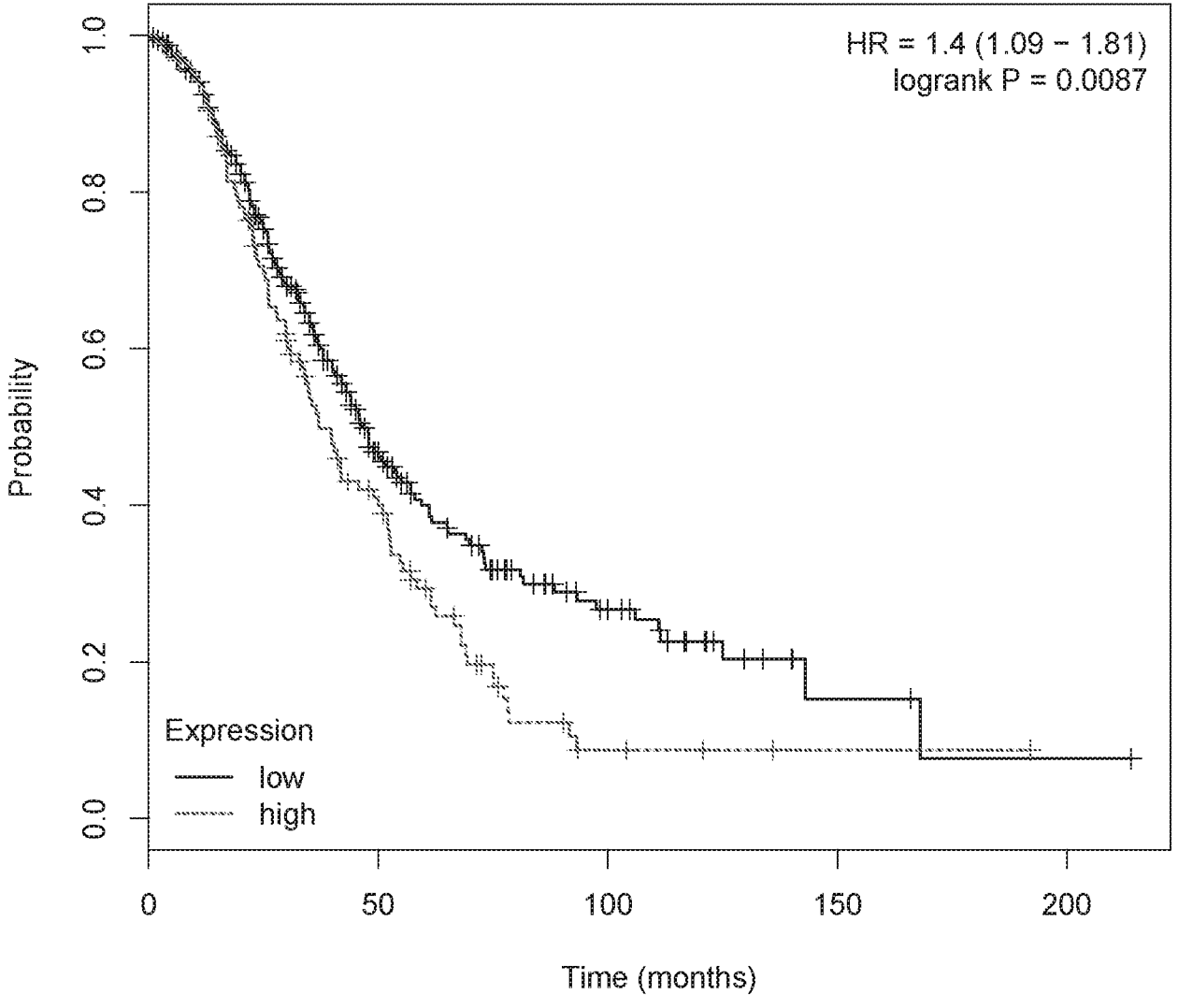

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FIG. 1