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(54) Title: SERINE THREONINE KINASE (AKT) DEGRADATION / DISRUPTION COMPOUNDS AND METHODS OF USE

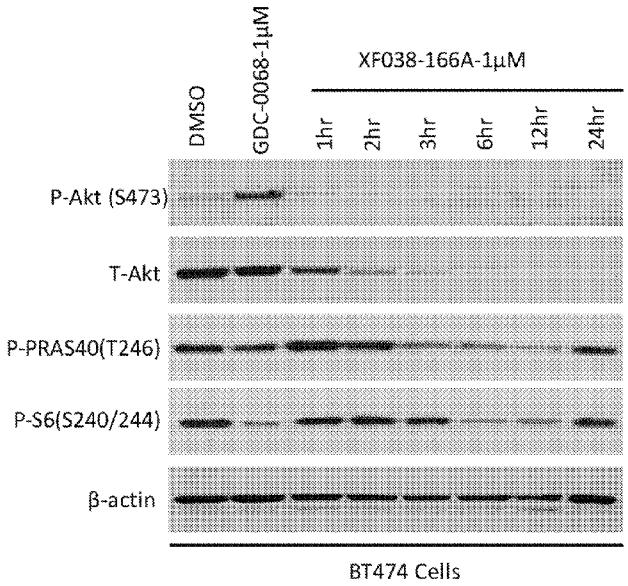


FIG. 2

(57) Abstract: Disclosed herein are serine threonine kinase (AKT) degradation / disruption compounds including an AKT ligand, a degradation / disruption tag, and a linker, and methods of using such compounds in the treatment of AKT-mediated diseases.

WO 2019/173516 A1

[Continued on next page]

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SERINE THREONINE KINASE (AKT) DEGRADATION / DISRUPTION COMPOUNDS AND METHODS OF USE

CROSS-REFERENCE TO RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application No 62/639,240 filed March 6, 2018. The entire contents of the foregoing are incorporated herein by reference.

TECHNICAL FIELD

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

BACKGROUND OF THE INVENTION

Significant efforts have been spent attempting to develop small molecule inhibitors of the kinase activity of the serine threonine kinase AKT (also known as protein kinase B or PKB) because over-activation of AKT is frequently associated with many human malignancies, including colon cancer, ovarian cancer, brain cancer, lung cancer, pancreatic cancer, breast cancer, prostate cancer, and gastric carcinomas. In addition to cancer, aberrant AKT activation has been associated with a variety of other severe human diseases, including developmental and overgrowth syndromes, cardiovascular disease, diabetes, inflammatory and autoimmune disorders, and neurological disorders (Manning and Toker, 2017). AKT is encoded by three closely related genes (AKT1 (PKB-α), AKT2 (PKB-β), and AKT3 (PKB-γ)) and is the central node of the PI3K–AKT–mTOR signaling pathway. The AKT signaling pathway can be aberrantly activated by multiple mechanisms in cancers, including, e.g., loss of the tumor suppressor PTEN; activating mutations in AKT, the p110α subunit of PI3K, and/or the PIK3CA gene; and/or increased receptor tyrosine kinase signaling.

However, traditional catalytic inhibition of AKT has not been an optimal solution for treating AKT overexpression. For example, although ATP-competitive inhibitors like GDC0068 (Blake et al., 2012) function as pan-AKT inhibitors, they also stabilize AKT in its active conformation, resulting in AKT hyperphosphorylation. Moreover, AKT has functions in addition to the (catalytic) activity targeted by small molecule inhibitors. AKT's kinase-independent functions promote cancer cell survival in a pleckstrin homology (PH)-domain

dependent manner. Studies have shown that the enzymatic inhibitor GDC0068 alone was not very effective in a colon cancer xenograft with RAS/RAF activation albeit with PIK3CA mutation. Similarly, GDC0068 also failed to result in significant objective tumor shrinkage in a phase I clinical trial (Saura et al., 2017).

Unlike traditional enzyme inhibitors, which only inhibit the catalytic activity of the target enzyme, the AKT degradation / disruption compounds ("AKT degraders") disclosed herein bind and induce degradation of AKT, thus eliminating any scaffolding functions of AKT in addition to eliminating its enzymatic activity. The AKT degraders disclosed herein are bivalent compounds, including an AKT ligand conjugated to a degradation / disruption tag via a linker.

The AKT degraders disclosed herein offer a novel mechanism for treating AKT-mediated diseases. In particular, the ability of the AKT degraders to target AKT for degradation, as opposed to merely inhibiting AKT's catalytic activity, is expected to overcome resistance, regardless of whether specific drugs were used in a prior treatment and regardless of whether the resistance is caused by gene mutation, amplification, or otherwise.

In an aspect, this disclosure provides a method of treating AKT-mediated diseases, the method including administering one or more AKT degraders to a subject who has an AKT-mediated disease, the AKT degraders being bivalent compounds including an AKT ligand conjugated to a degradation/disruption tag via a linker. The AKT-mediated disease can be a disease resulting from AKT activation. The AKT-mediated disease can have elevated AKT enzymatic activity relative to a wild-type tissue of the same species and tissue type. Non-limiting examples of AKT-mediated diseases include inflammatory, hyperproliferative cardiovascular, neurodegenerative, gynecological, and dermatological diseases and disorders.

In an aspect, the AKT degraders of the present disclosure can be employed for the treatment of hyperproliferative disorders, including cancers angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma, myxoma, rhabdomyoma, fibroma, lipoma, teratoma, squamous cell carcinoma, undifferentiated small cell carcinoma, undifferentiated large cell carcinoma, adenocarcinoma, alveolar carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma, non-small cell lung cancer, small cell lung cancer, leiomyosarcoma, stomach carcinoma, ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, neurofibroma, tubular adenoma, villous adenoma, hamartoma, kidney cancer, Wilm's tumor, nephroblastoma, leukemia, bladder cancer, urethra cancer, transitional cell carcinoma, prostate cancer, seminoma, embryonal carcinoma, teratocarcinoma,

choriocarcinoma, interstitial cell carcinoma, fibroadenoma, adenomatoid tumors, hepatoma, hepatocellular carcinoma, cholangiocarcinoma, hepatoblastoma, hepatocellular adenoma, osteogenic sarcoma, osteosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma, reticulum cell sarcoma, multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma, osteocartilaginous exostoses, benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma, giant cell tumors, osteoma, granuloma, xanthoma, osteitis deformans, meningioma, meningiosarcoma, gliomatosis, astrocytoma, medulloblastoma, glioma, ependymoma, germinoma, pinealoma, glioblastoma multiforme, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors, spinal cord neurofibroma, endometrial carcinoma, cervical carcinoma, pre-tumor cervical dysplasia, ovarian carcinoma, serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma, granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, intraepithelial carcinoma, melanoma, clear cell carcinoma, botryoid sarcoma, embryonal fallopian tubes carcinoma, acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, myelodysplastic syndrome, Hodgkin's disease, non-Hodgkin's lymphoma, advanced melanoma, malignant melanoma, basal cell carcinoma, moles dysplastic nevi, angioma, dermatofibroma, keloids, psoriasis, neuroblastoma, metastatic breast cancer, colon cancer, oral cancer, hairy cell leukemia, head and neck cancer, refractory metastatic disease; Kaposi's sarcoma, Bannayan-Zonana syndrome, Cowden disease and Lhermitte-Duclos disease.

The compounds and methods of this disclosure can be also used to treat diseases and conditions such as rheumatoid arthritis, osteoarthritis, Crohn's disease, angiofibroma, retinal vascularization, diabetic retinopathy, age-related macular degeneration, macular degeneration, multiple sclerosis, obesity, Alzheimer's disease, restenosis, autoimmune diseases, allergy, asthma, endometriosis, atherosclerosis, vein graft stenosis, peri-anastomatic prosthetic graft stenosis, prostate hyperplasia, chronic obstructive pulmonary disease, psoriasis, inhibition of neurological damage due to tissue repair, scar tissue formation, multiple sclerosis, inflammatory bowel disease, infections, particularly bacterial, viral, retroviral or parasitic infections, pulmonary disease, neoplasm, Parkinson's disease, transplant rejection, and septic shock.

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

SUMMARY OF THE INVENTION

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

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

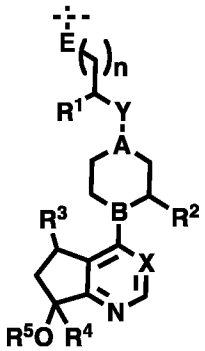
In some aspects, the AKT degraders/disruptors have the form "**PI-Linker-EL**", as shown below:



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

AKT Ligands

AKT Ligands include but are not limited to:



FORMULA 1

wherein

A, B, and X are independently N, CH, or CR^6,

Y is CH_2, CO, SO, SO_2, CR^7R^8, $CONR^7$, or SO_2NR^7,

E is NH, NR^9, O, C_1-C_8 alkyl, C_1-C_8 alkoxy, C_1-C_8 alkoxyalkyl, C_1-C_8 haloalkyl, C_1-C_8 hydroxyalkyl, C_3-C_8 cycloalkyl, C_3-C_7 heterocyclyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, OR^9, SR^9, NR^9R^{10}, CN, NO_2, $(CR^9R^{10})mNR^{11}R^{12}$, $(CR^9R^{10})mC(O)R^{11}$, $(N\ R^9R^{10})mNR^{11}R^{12}$, $(NR^9R^{10})mC(O)R^{11}$, COR^9, CO_2R^9, $CONR^9R^{10}$, NR^9COR^{10}, NR^9SOR^{10}, $NR^9SO_2R^{10}$, SOR^9, SO_2R^9, $SO_2NR^9R^{10}$, $(CR^9R^{10})m$-aryl, or $(CR^9R^{10})m$-heteroaryl,

R^1 is H, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkoxy, C_1-C_8 alkoxyalkyl, aryl, C_1-C_8 alkylaryl, haloaryl, arylalkyl, heteroaryl, or heteroarylalkyl,

R^2, R^3, R^4, and R^6 are independently hydrogen, halogen, amino, C_1-C_8 alkylamino, arylamino, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkoxy, or C_1-C_8 alkoxyalkyl,

R^5, R^7, and R^8 are independently H, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, or C_1-C_8 alkoxyalkyl,

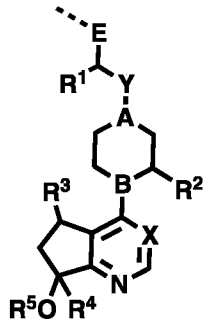
R^9, R^{10}, R^{11}, and R^{12} are independently H, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkoxy, C_2-C_8 alkenyl, C_2-C_8 alkynyl, arylalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, or heteroarylalkyl,

R^9 and R^{10}, R^{11} and R^{12} can independently form 4-8 membered alkyl or heterocyclyl rings,

m = 0-8,

and

n = 0-8; and



FORMULA 2

wherein

A, B and X are independently selected from N and CR^6, wherein

R^6 is independently selected from hydrogen, halogen, cyano, nitro, hydroxyl, amino, 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 amino, optionally substituted C_1-C_8 alkylamino, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-

10 membered carbocyclyl, and optionally substituted 4-10 membered heterocyclyl;

Y is selected from CR^7R^8, CO, SO, SO_2, $CONR^7$, and SO_2NR^7, wherein

R^7 and R^8 is independently selected from hydrogen, halogen, 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 alkylamino, optionally substituted C_1-C_8 alkylamino C_1-C_8 alkyl, optionally substituted 3 to 10 membered carbocyclyl, and optionally substituted 4-10 membered heterocyclyl, or

R^7 and R^8 together with the atom to which they are connected form an optionally substituted 3-10 membered carbocyclyl or an optionally substituted 4-10 membered heterocyclyl ring;

E is connected to the "linker" moiety of the bivalent compound, and is selected from null, R'-R'' R'OR'', R'SR'', R'NR^9R'', R'OC(O)R'', R'OC(O)OR'', R'$OCONR^9$R'', R'C(O)R'', R'C(O)OR'', R'$CONR^9$R'', R'S(O)R'', R'$S(O)_2$R'', R'SO_2NR^9R'', R'NR^{10}C(O)OR'', R'NR^{10}C(O)R'', R'NR^{10}C(O)NR^9R'', R'NR^{10}S(O)R'', R'$NR^{10}S(O)_2$R'', and R'$NR^{10}S(O)_2NR^9$R'', wherein

R' and R'' are independently selected from null, 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 haloalkylene, 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 alkylene)O(C_1-C_8 alkylene), optionally substituted (C_1-C_8 alkylene)N(C_1-C_8 alkylene), optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted C_3-C_{13} fused carbocyclyl, optionally substituted C_3-C_{13} fused heterocyclyl, optionally substituted C_3-C_{13} bridged carbocyclyl, optionally substituted C_3-C_{13} bridged heterocyclyl, optionally substituted C_3-C_{13} spiro carbocyclyl, optionally substituted C_3-C_{13} spiro heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^9 and R^{10} 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 carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

R' and R'', R9 and R10, R' and R9, R' and R10, R'' and R9, R'' and R10 together with the atom to which they are connected form a 4-20 membered heterocyclyl ring;

R1 is selected from hydrogen, halogen, and optionally substituted C1-C8 alkyl, optionally substituted C2-C8 alkenyl, optionally substituted C2-C8 alkynyl, optionally substituted C1-C8 alkoxy, optionally substituted C1-C8 alkoxy C1-C8 alkyl, optionally substituted C1-C8 alkylamino, optionally substituted C1-C8 alkylamino C1-C8 alkyl, optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

R2, R3 and R4 are independently selected from hydrogen, halogen, cyano, nitro, hydroxyl, optionally substituted C1-C8 alkyl, optionally substituted C2-C8 alkenyl, optionally substituted C2-C8 alkynyl, optionally substituted C1-C8 alkoxy, optionally substituted aryloxy, optionally substituted C1-C8 alkoxyC1-C8 alkyl, optionally substituted amino, optionally substituted C1-C8 alkylamino, optionally substituted C1-C8 alkylaminoC1-C8 alkyl, optionally substituted arylamino, optionally substituted 3-10 membered carbocyclyl, and optionally substituted 4-10 membered heterocyclyl;

R5 is selected from hydrogen, optionally substituted C1-C8 alkyl, optionally substituted C2-C8 alkenyl, optionally substituted C2-C8 alkynyl, optionally substituted C1-C8 alkoxyC1-C8 alkyl, optionally substituted C1-C8 alkylaminoC1-C8 alkyl, optionally substituted 3-10 membered carbocyclyl, and optionally substituted 4-10 membered heterocyclyl; and

In one embodiment, A is selected from N, CH and CNH_2.

In another embodiment, A is N.

In one embodiment, B and X are independently selected from N and CH.

In another embodiment, B is N.

In another embodiment, X is N.

In another embodiment, Y is selected from CH_2, CO, CONH and NHCO.

In another embodiment, Y is CO.

In another embodiment, E is selected from null, O, N, optionally substituted C1-C8 alkylene, optionally substituted (C1-C8 alkylene)O, optionally substituted (C1-C8 alkylene)N, optionally substituted 3-10 membered carbocyclylene, optionally substituted (3-10 membered carbocyclylene)O, optionally substituted (3-10 membered carbocyclylene)N, optionally substituted 4-10 membered heterocyclylene, optionally substituted (4-10 membered heterocyclylene)O, optionally substituted (4-10 membered heterocyclylene)N,

optionally substituted aryl, and optionally substituted heteroaryl.

In another embodiment, R^1 is selected from optionally substituted aryl and optionally substituted heteroaryl.

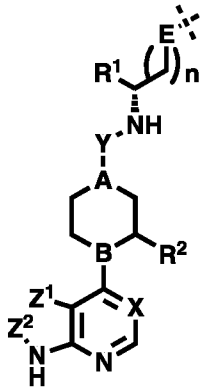
In another embodiment, R^1 is selected from optionally substituted phenyl.

In another embodiment, R^1 is 4-chlorophenyl.

In another embodiment, R^2, R^3, R^4 and R^5 are independently selected from H, F, Cl, CN, NO_2, CH_3, CF_3, iPr, and cPr.

In another embodiment, R^2, R^4 and R^5 are H.

In another embodiment, R^3 is CH_3.



FORMULA 3

wherein

A, B, and X are independently N or CR^3,

Y is CH_2, CO, SO, SO_2, CR^4R^5, $CONR^4$, or SO_2NR^4,

E is NH, NR^6, O, C_1-C_8 alkyl, C_1-C_8 alkoxy, C_1-C_8 alkoxyalkyl, C_1-C_8 haloalkyl, C_1-C_8 hydroxyalkyl, C_3-C_8 cycloalkyl, C_3-C_8 heterocyclyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, OR^6, SR^6, NR^6R^7, CN, NO_2, $(CR^6R^7)mNR^8R^9$, $(CR^6R^7)mC(O)R^8$, $(N\ R^6R^7)mNR^8R^9$, $(NR^6R^7)mC(O)R^8$, COR^6, CO_2R^6, $CONR^6R^7$, NR^6COR^7, NR^6SOR^7, $NR^6SO_2R^7$, SOR^6, SO_2R^6, $SO_2NR^6R^7$, (CR^6R^7)m-aryl, or (CR^6R^7)m-heteroaryl,

Z^1-Z^2 is CR^{10}=CH, N+CH, or CR^{10}=N,

R^1 is hydrogen, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkoxy, C_1-C_8 alkoxyalkyl, aryl, C_1-C_8 alkylaryl, haloaryl, arylalkyl, heteroaryl, or heteroarylalkyl,

R^2, R^3, and R^4 are independently hydrogen, halogen, amino, C_1-C_8 alkylamino, arylamino, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkoxy, or C_1-C_8 alkoxyalkyl,

R^6, R^7, R^8, and R^9 are independently H, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkoxy, C_2-C_8

alkenyl, C_2-C_8 alkynyl, arylalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, or heteroarylalkyl,

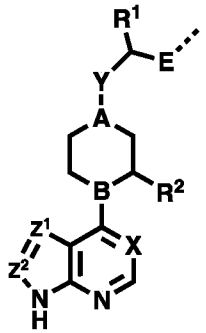
R^6 and R^7, R^8 and R^9 can independently form 4-8 membered alkyl or heterocyclyl rings,

R^{10} is hydrogen, halogen, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkoxy, C_1-C_8 alkoxyalkyl,

m = 0-8,

and

n = 0-8.



FORMULA 4

wherein

A, B and X are independently selected from N and CR^3, wherein

R^3 is independently selected from hydrogen, halogen, cyano, nitro, hydroxyl, 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 alkoxyC_1-C_8 alkyl, optionally substituted amino, optionally substituted C_1-C_8 alkylamino C_1-C_8 alkyl, optionally substituted 3-10 membered carbocyclyl, and optionally substituted 4-10 membered heterocyclyl;

Z^1 is selected for CR^8 and N, wherein

R^8 is selected from hydrogen, halogen, cyano, nitro, hydroxyl, 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 alkoxyC_1-C_8 alkyl, optionally substituted amino, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-10 membered carbocyclyl, and optionally substituted 4-10 membered heterocyclyl;

Z^2 is selected for CH and N;

Y is selected from CO, SO, SO_2, CR^4R^5, $CONR^4$, and SO_2NR^4, wherein

R^4 and R^5 is independently selected from hydrogen and 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 alkoxyC_1-C_8 alkyl, optionally substituted amino, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3 to 10 membered carbocyclyl, and optionally substituted 4-10 membered heterocyclyl;

E is connected to the "linker" moiety of the bivalent compound, and is selected from null, R'-R'', R'OR'', R'SR'', R'NR^{6}R'', R'OC(O)R'', R'OC(O)OR'', R'OCONR^{6}R'', R'C(O)R'', R'C(O)OR'', R'CONR^{6}R'', R'S(O)R'', R'S(O)$_2$R'', R'SO$_2$NR^{6}R'', R'NR^{7}C(O)OR'', R'NR^{7}C(O)R'', R'NR^{7}C(O)NR^{6}R'', R'NR^{7}S(O)R'', R'NR^{7}S(O)$_2$R'', and R'NR^{7}S(O)$_2$NR^{6}R'', wherein

R' and R'' are independently selected form null, 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 haloalkylene, optionally substituted C_1-C_8 hydroxyalkylene, optionally substituted C_1-C_8alkoxyC_1-C_8alkylene, optionally substituted (C_1-C_8 alkylene)O(C_1-C_8 alkylene), optionally substituted (C_1-C_8 alkylene)N(C_1-C_8 alkylene), optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted C_3-C_{13} fused carbocyclyl, optionally substituted C_3-C_{13} fused heterocyclyl, optionally substituted C_3-C_{13} bridged carbocyclyl, optionally substituted C_3-C_{13} bridged heterocyclyl, optionally substituted C_3-C_{13} spiro carbocyclyl, optionally substituted C_3-C_{13} spiro heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^6 and R^7 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 carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R' and R'', R^6 and R^7, R' and R^6, R' and R^7, R'' and R^6, R'' and R^7 together with the atom to which they are connected form a 4-20 membered heterocyclyl ring;

R^1 is selected from selected from hydrogen, halogen, and 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 alkoxyC_1-C_8 alkyl, optionally

substituted amino, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl; and

R^2 is selected from hydrogen, halogen, cyano, nitro, hydroxyl, 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, or optionally substituted C_1-C_8 alkoxy C_1-C_8 alkyl, optionally substituted amino, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-10 membered carbocyclyl, and optionally substituted 4-10 membered heterocyclyl;

In one embodiment, A is selected from N, CH and CNH_2.

In another embodiment, A is CNH_2.

In one embodiment, B and X are independently selected from N and CH.

In another embodiment, B is N.

In another embodiment, X is N.

In another embodiment, Z^1 is selected from CH and CCH_3.

In another embodiment, Z^1 is CH.

In another embodiment, Z^2 is CH.

In another embodiment, Y is selected from CH_2, CO, CONH and NHCO.

In another embodiment, Y is CONH.

In another embodiment, E is selected from null, O, N, optionally substituted C_1-C_8 alkylene, optionally substituted (C_1-C_8 alkylene)O, optionally substituted (C_1-C_8 alkylene)N, optionally substituted 3-10 membered carbocyclylene, optionally substituted (3-10 membered carbocyclylene)O, optionally substituted (3-10 membered carbocyclylene)N, optionally substituted 4-10 membered heterocyclylene, optionally substituted (4-10 membered heterocyclylene)O, optionally substituted (4-10 membered heterocyclylene)N, optionally substituted aryl, and optionally substituted heteroaryl.

In another embodiment, R^1 is selected from optionally substituted aryl and optionally substituted heteroaryl.

In another embodiment, R^1 is selected from optionally substituted phenyl.

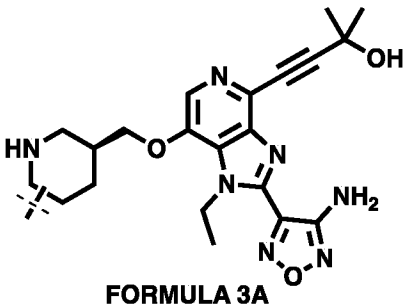
In another embodiment, R^1 is 4-chlorophenyl.

In another embodiment, R^2 is selected from H, F, Cl, CN, NO_2, CH_3, CF_3, iPr, and cPr,

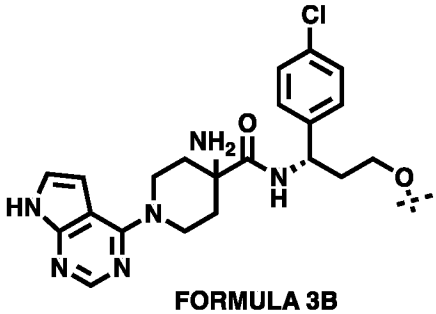
In another embodiment, R^2 is H.

The AKT ligand can be an AKT inhibitor, such as, for example, GSK690693 (Heerding et al., 2008), GSK2110183 (Dumble et al., 2014), GSK2141795 (Dumble et al., 2014), AZD5363 (Addie et al., 2013), GDC0068 (Blake et al., 2012), MK-2206 (Hirai et al., 2010), and ARQ-092 (Yu et al., 2015), and/or analogs thereof.

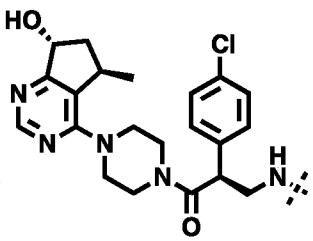
In some aspects, the AKT ligand can be, e.g.:



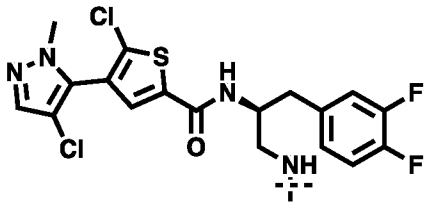
FORMULA 3A



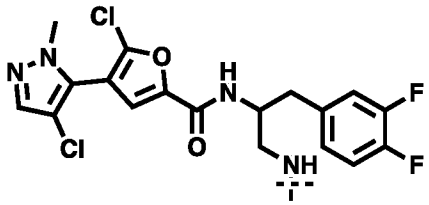
FORMULA 3B



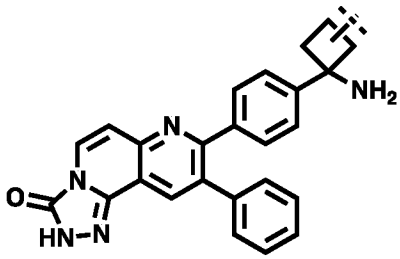
FORMULA 3C



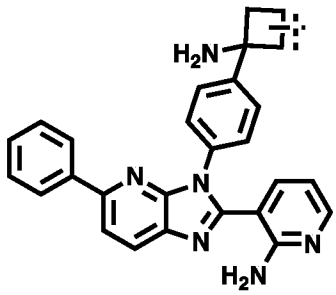
FORMULA 3D



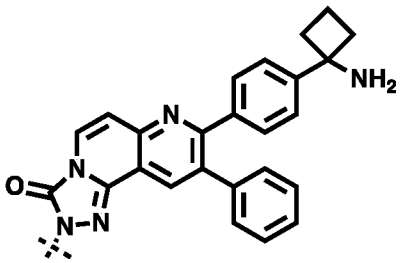
FORMULA 3E



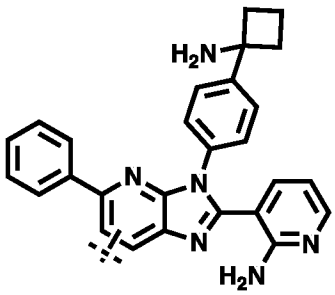
FORMULA 3F



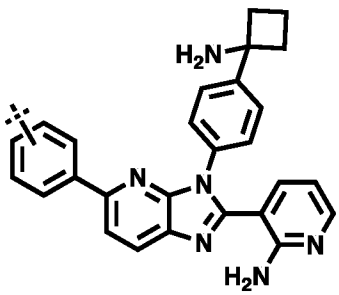
FORMULA 3G



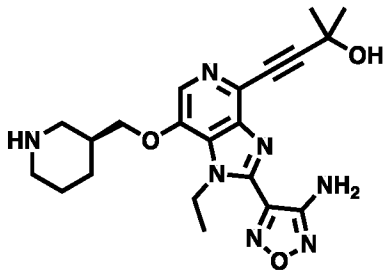
FORMULA 3H



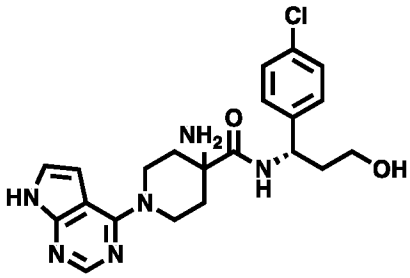
FORMULA 3I



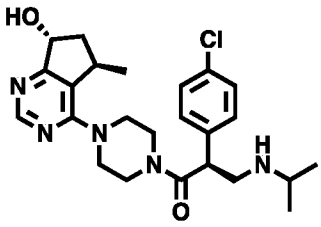
FORMULA 3J



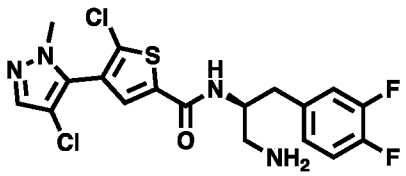
GSK690693



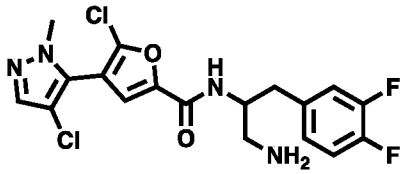
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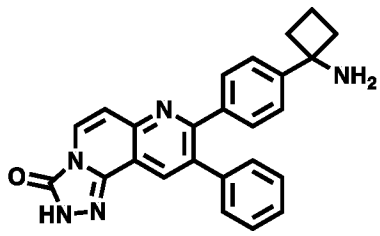
GDC0068



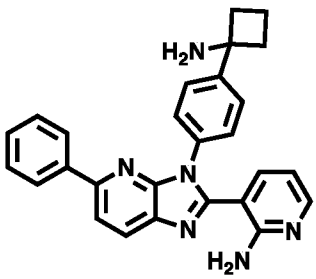
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GSK2141795



MK2206

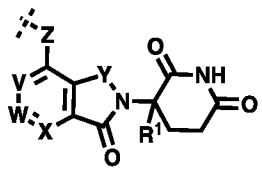


ARQ 092

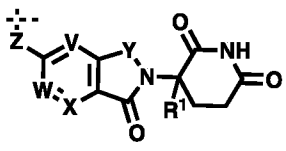
The AKT ligand can be bound to AKT and/or AKT mutant proteins, such as, e.g., AKT with an E17K mutation.

Degradation / Disruption Tags

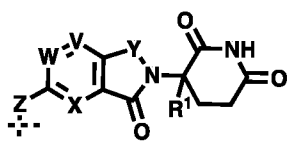
Degradation / Disruption Tags (**EL**) include but are not limited to:



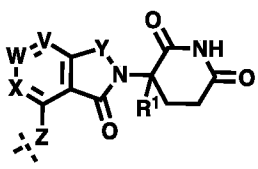
FORMULA 5A



FORMULA 5B



FORMULA 5C



FORMULA 5D

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;

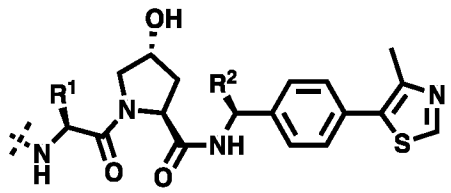
wherein

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

Y is selected from CO, CH_2, and N=N;

Z is selected from CH_2, NH and O; and

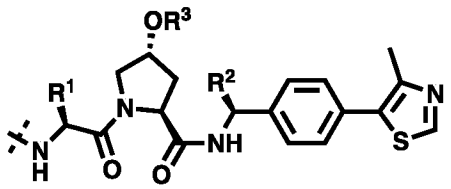
R^1 and R^2 are independently selected from hydrogen, halogen, cyano, nitro, and C_1-C_5 alkyl.



FORMULA 6

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_3-C_7 cycloalkyl, C_3-C_7 heterocyclyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl;



FORMULA 7,

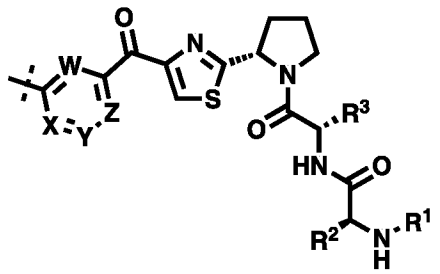
wherein

R^1 and R^2 are independently selected from hydrogen, hydroxyl, amino, cyano, nitro, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, and optionally substituted C_2-C_8 alkynyl, 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 3-10 membered carbocyclyl, and optionally substituted 4-10 membered heterocyclyl.

R^3 is selected from 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)(3-10 membered carbocyclyl), optionally substituted C(O)(4-10 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)O(3-10 membered carbocyclyl), optionally substituted C(O)O(4-10 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)N(3-10 membered carbocyclyl), optionally substituted C(O)N(4-10 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



FORMULA 8

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.

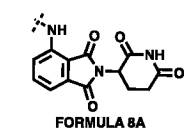
wherein

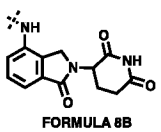
V, W, X, and Z are independently selected from CR^4 and N; and

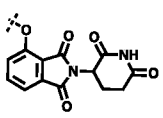
R^1, R^2, R^3, and R^4 are independently selected from hydrogen, halogen, cyano, nitro, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, and optionally substituted C_2-C_8 alkynyl; optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-C_8 hydroxyalkyl, optionally substituted C_1-C_8alkoxy, optionally substituted C_1-C_8alkylamino, optionally substituted 3-10 membered carbocyclyl, and optionally substituted 4-10 membered heterocyclyl.

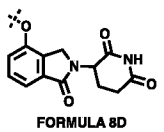
In some aspects, the degradation/disruption tag can be, for example, pomalidomide (Fischer et al., 2014), thalidomide (Fischer et al., 2014), lenalidomide (Fischer et al., 2014), VH032 (Galdeano et al., 2014; Maniaci et al., 2017), adamantine (Xie et al., 2014), 1-((4,4,5,5,5-pentafluoropentyl)sulfinyl)nonane (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), and/or analogs thereof.

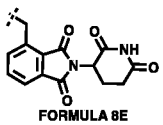
In some aspects, the degradation/disruption tag can be, e.g., one of the following structures:

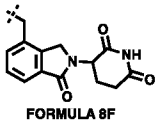

FORMULA 8A

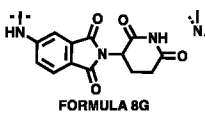

FORMULA 8B

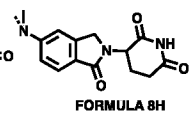

FORMULA 8C

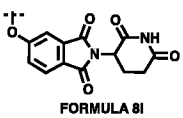

FORMULA 8D

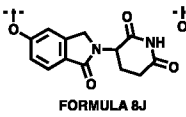

FORMULA 8E

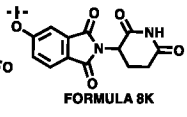

FORMULA 8F

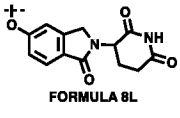

FORMULA 8G

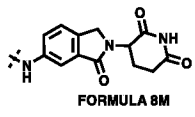

FORMULA 8H

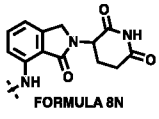

FORMULA 8I

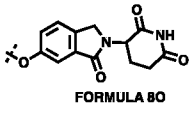

FORMULA 8J

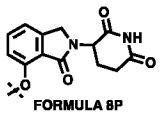

FORMULA 8K

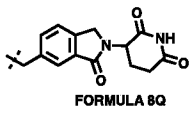

FORMULA 8L

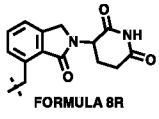

FORMULA 8M

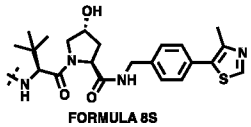

FORMULA 8N

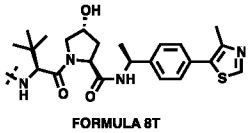

FORMULA 8O

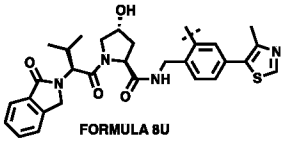

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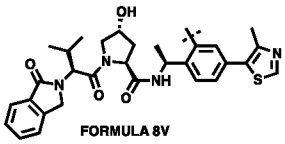

FORMULA 8Q

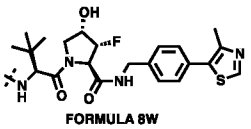

FORMULA 8R

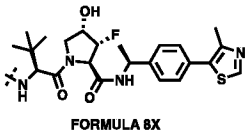

FORMULA 8S

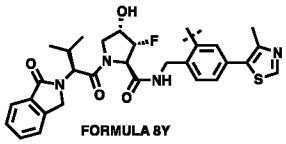

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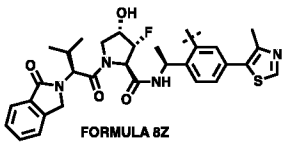

FORMULA 8U

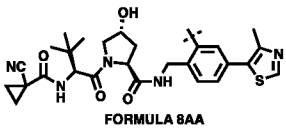

FORMULA 8V

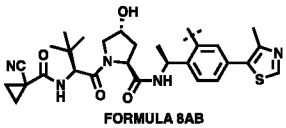

FORMULA 8W

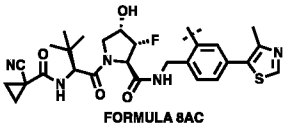

FORMULA 8X

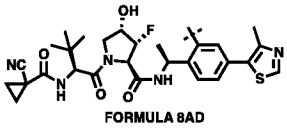

FORMULA 8Y

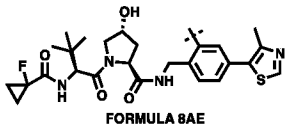

FORMULA 8Z

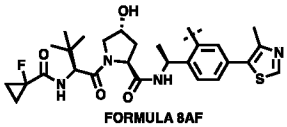

FORMULA 8AA

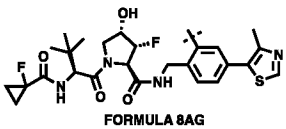

FORMULA 8AB

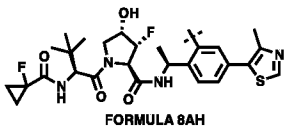

FORMULA 8AC

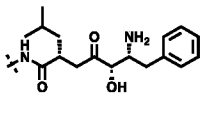

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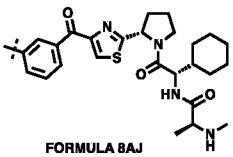

FORMULA 8AE

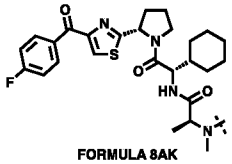

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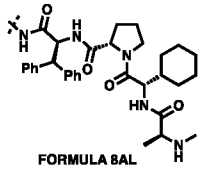

FORMULA 8AG

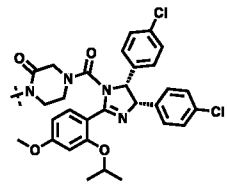

FORMULA 8AH

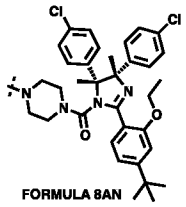

FORMULA 8AI

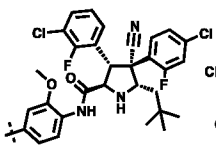

FORMULA 8AJ

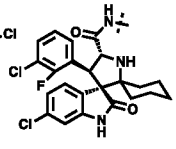

FORMULA 8AK

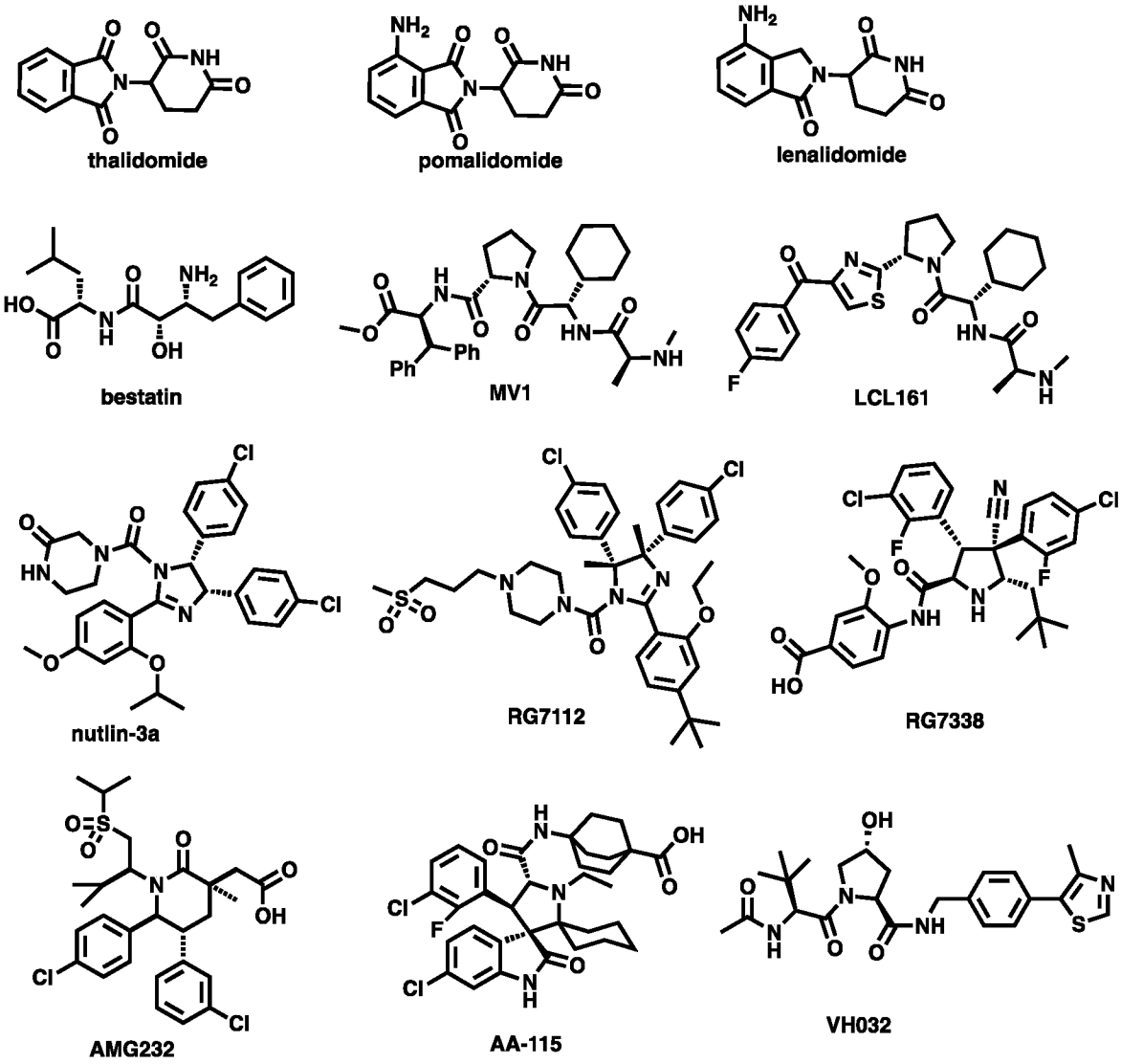

FORMULA 8AL


FORMULA 8AM


FORMULA 8AN


FORMULA 8AO


FORMULA 8AP

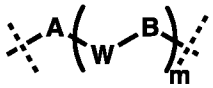


In some aspects, the degradation/disruption tag can bind to a ubiquitin ligase (e.g., an E3 ligase such as a cereblon E3 ligase, a VHL E3 ligase, a MDM2 ligase, a TRIM21 ligase, a TRIM24 ligase, and/or an IAP ligase) and/or serve as a hydrophobic group that leads to AKT protein misfolding.

Linkers

In all of the above-described compounds, the AKT 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 9,

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)NR"R^1, R'C(S)NR"R^1, R'OR", R'OC(O)R", R'OC(O)OR", R'OCONR^{1}R", R'SR", R'SOR", R'SO_2R", R'SO_2NR"R^1, R'NR"R^1, R'NR^{1}COR", R'NR^{1}C(O)OR", R'NR^{1}CONR"R^2, R'NR^{1}C(S)R", R'NR^{1}S(O)R", R'NR^1$S(O)_2$R", and R'NR^1$S(O)_2$NR^{2}R", wherein

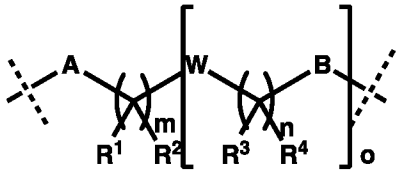
R' and R" are independently selected from null, or a moiety comprising of optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 hydroxyalkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted 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^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.

In one embodiment, the linker moiety is of FORMULA 9A:



FORMULA 9A,

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 3-10 membered cycloalkoxy, optionally substituted 3-10 membered carbocyclylamino, optionally substituted 4-8 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)NR''R^1, R'C(S)NR''R^1, R'OR'', R'OC(O)R'', R'OC(O)OR'', R'OCONR^{1}R'', R'SR'', R'SOR'', R'SO_2R'', R'SO_2NR''R^1, R'NR''R^1, R'NR^{1}COR'', R'NR^{1}C(O)OR'', R'NR^{1}CONR''R^2, R'NR^{1}C(S)R'', R'NR^{1}S(O)R'', R'NR^{1}S(O)$_2$R'', and R'NR^{1}S(O)$_2$NR^{2}R'', wherein

R' and R'' are independently selected from null, 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^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;

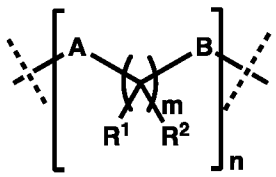
$R^{'}$ and $R^{''}$, R^5 and R^6, $R^{'}$ and R^5, $R^{'}$ and R^6, $R^{''}$ and R^5, $R^{''}$ and R^6 together with the atom to which they are connected form a 3-20 membered cycloalkyl or 4-20 membered heterocyclyl ring;

m is 0 to 15;

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

o is 0 to 15.

In another embodiment, the linker moiety is of FORMULA 9B:



FORMULA 9B,

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 3-10 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"R^1, R'C(S)NR"R^1, R'OR", R'OC(O)R", R'OC(O)OR", R'OCONR^{1}R", R'SR", R'SOR", R'SO_2R", R'SO_2NR"R^1, R'NR"R^1, R'NR^{1}COR", R'NR^{1}C(O)OR", R'NR^{1}CONR"R^2, R'NR^{1}C(S)R", R'NR^{1}S(O)R", R'NR^{1}S(O)$_2$R", and R'NR^{1}S(O)$_2$NR^{2}R", wherein

R' and R" are independently selected from null, 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;

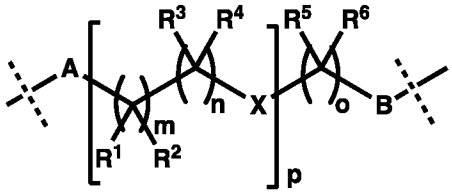
R^3 and R^4 are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxyalkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-C_8 hydroxyalkyl, 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;

each m is 0 to 15; and

n is 0 to 15.

In another embodiment, the linker moiety is of FORMULA 9C:



FORMULA 9C,

wherein

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

R^1, R^2, R^3, R^4, R^5, R^6, and R^7, 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 3-10 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)NR''R^1, R'C(S)NR''R^1, R'OR'', R'OC(O)R'', R'OC(O)OR'', R'OCONR^{1}R'', R'SR'', R'SOR'', R'SO_2R'', R'SO_2NR''R^1, R'NR''R^1, R'NR^{1}COR'', R'NR^{1}C(O)OR'', R'NR^{1}CONR''R^2, R'NR^{1}C(S)R'', R'NR^{1}S(O)R'', R'NR^{1}S(O)$_2$R'', and R'NR^{1}S(O)$_2$NR^{2}R'', wherein

R' and R'' are independently selected from null, 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^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

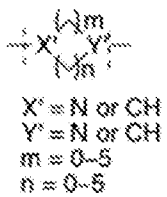
p is 0 to 15.

In another embodiment, 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, CH_2-NH-CH_2。

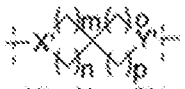
In another embodiment, o is 0 to 5.

In another embodiment, 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 another embodiment, the linker moiety comprises one or more rings selected from the group consisting of FORMULAE C1, C2, C3, C4 and C5:

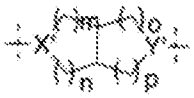


FORMULA C1,



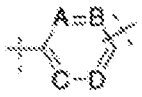
X' = N or CH
Y' = N or CH
m = 0-5
n = 0-5
o = 0-5
p = 0-5

FORMULA C2,



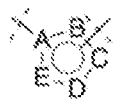
X' = N or CH
Y' = N or CH
m = 0-5
n = 0-5
o = 0-5
p = 0-5

FORMULA C3,



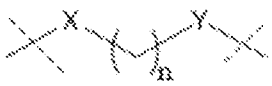
A = CH, C(C_{1-3} alkyl), or N
B = CH, C(C_{1-3} alkyl), or N
C = CH, C(C_{1-3} alkyl), or N
D = CH, C(C_{1-3} alkyl), or N

FORMULA C4, 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.

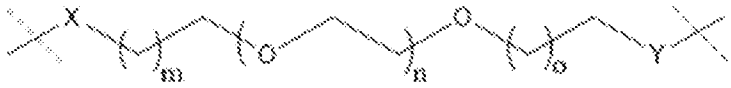


Formula A,

wherein X is C=O or CH_2,

Y is C=O or CH_2, and

n is 0-15;



Formula B,

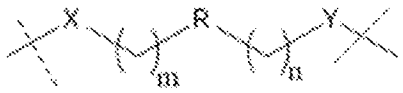
wherein X is C=O or CH_2,

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,

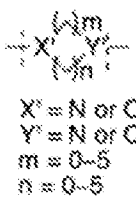
R is $–CH_2–$, $–CF_2–$, $–CH(C_{1-3}$ alkyl)–, $–C(C_{1-3}$ alkyl)(C_{1-3} alkyl)–, –CH=CH–, $–C(C_{1-3}$ alkyl)=C(C_{1-3} alkyl)–, –C=C–, –O–, –NH–, $–N(C_{1-3}$ alkyl)–, $–C(O)NH–$, $–C(O)N(C_{1-3}$ alkyl)–, a 3-13 membered ring, a 3-13 membered fused ring, a 3-13 membered bridged ring, and/or a 3-13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

m is 0-15, and

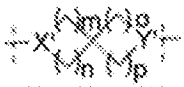
n is 0-15.

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:

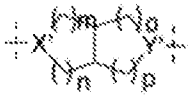


Formula C1,



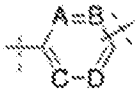
X' = N or CH
Y' = N or CH
m = 0–5
n = 0–5
o = 0–5
p = 0–5

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.

In some aspects, the bivalent compound is a compound selected from the following compounds, as identified in Table 1 below: XF038-157A, XF038-158A, XF038-159A, XF038-160A, XF038-161A, XF038-162A, XF038-164A, XF038-165A, XF038-166A, XF038-176A, XF038-177A, XF042-162, XF042-164, XF042-165, XF042-166, XF042-167, XF042-168, XF042-170, XF042-171, XF048-1, XF048-2, XF048-3, XF048-4, XF048-5, XF048-7, XF048-8, XF050-5, XF050-6, XF050-7, XF050-8, XF050-9, XF050-10, XF050-11, XF050-12, XF050-13, XF050-14, XF050-15, XF050-16, XF050-17, XF050-18, XF050-19, XF050-20, XF050-21, XF050-22, XF050-23, XF050-24, XF050-25, XF050-26, XF050-27, XF050-28, XF050-29, XF050-30, XF050-31, XF050-32, XF050-33, XF050-98, XF050-132, XF050-133. XF050-134, XF056-93, XF050-143, XF050-144, XF050-145, XF050-167, XF056-33, XF056-

34, XF056-35, XF056-36, XF056-37, XF056-73, XF061-10, XF067-1, XF067-2, XF067-3, XF067-4, XF067-5, XF067-6, XF067-7, XF067-8, XF067-9, XF067-10, XF067-11, XF067-12, XF067-13, XF067-14, XF067-15, XF067-16, XF067-17, XF067-18, XF067-19, XF067-20, XF067-21, XF067-22, XF067-23, XF067-24, XF067-25, XF067-26, XF067-27, XF067-28, XF067-29, XF067-30, XF067-31, XF067-32, XF067-33, XF067-34, XF067-35, XF067-36, XF067-37, XF067-38, XF067-39, XF067-40, XF067-41, XF067-42, XF067-43, XF067-44, XF067-45, XF067-46, XF067-47, XF067-48, XF067-49, XF067-50, XF067-51, XF067-52, XF067-53, XF067-54, XF067-55, XF067-56, XF067-57, XF067-58, XF067-59, XF067-84, XF067-85, XF067-86, XF067-87, XF067-88, XF067-89, XF067-90, XF067-91, XF067-92, XF067-93, XF067-94, XF067-95, XF067-96, XF067-97, XF067-98, XF067-99, XF067-100, XF067-101, XF067-102, XF067-103, XF067-104, XF067-105, XF067-106, XF067-107, XF067-108, XF067-109, XF067-110, XF067-111, XF067-112, XF067-113, or analogs thereof.

In some aspects, this disclosure provides a method of treating AKT-mediated cancers, the method including administering to a subject in need thereof one or more bivalent compounds including an AKT ligand conjugated to a degradation/disruption tag via a linker. The AKT-mediated cancer can be a cancer resulting from (aberrant) AKT activation. The AKT-mediated cancer can have elevated AKT enzymatic activity relative to a wild-type tissue of the same species and tissue type. Non-limiting examples of AKT-mediated diseases include inflammatory, hyperproliferative cardiovascular, neurodegenerative, gynecological, and dermatological diseases and disorders. In an aspect, the AKT degraders of the present disclosure can be employed for the treatment of hyperproliferative disorders, including cancers angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma, myxoma, rhabdomyoma, fibroma, lipoma, teratoma, squamous cell carcinoma, undifferentiated small cell carcinoma, undifferentiated large cell carcinoma, adenocarcinoma, alveolar carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma, non-small cell lung cancer, small cell lung cancer, leiomyosarcoma, stomach carcinoma, ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, neurofibroma, tubular adenoma, villous adenoma, hamartoma, kidney cancer, Wilm's tumor, nephroblastoma, leukemia, bladder cancer, urethra cancer, transitional cell carcinoma, prostate cancer, seminoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, interstitial cell carcinoma, fibroadenoma, adenomatoid tumors, hepatoma, hepatocellular carcinoma, cholangiocarcinoma, hepatoblastoma, hepatocellular adenoma, osteogenic sarcoma, osteosarcoma, malignant

fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma, reticulum cell sarcoma, multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma, osteocartilaginous exostoses, benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma, giant cell tumors, osteoma, granuloma, xanthoma, osteitis deformans, meningioma, meningiosarcoma, gliomatosis, astrocytoma, medulloblastoma, glioma, ependymoma, germinoma, pinealoma, glioblastoma multiforme, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors, spinal cord neurofibroma, endometrial carcinoma, cervical carcinoma, pre-tumor cervical dysplasia, ovarian carcinoma, serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma, granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, intraepithelial carcinoma, melanoma, clear cell carcinoma, botryoid sarcoma, embryonal fallopian tubes carcinoma, acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, myelodysplastic syndrome, Hodgkin's disease, non-Hodgkin's lymphoma, advanced melanoma, malignant melanoma, basal cell carcinoma, moles dysplastic nevi, angioma, dermatofibroma, keloids, psoriasis, neuroblastoma, metastatic breast cancer, colon cancer, oral cancer, hairy cell leukemia, head and neck cancer, refractory metastatic disease; Kaposi's sarcoma, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease.

The compounds and methods of this disclosure can be also used to treat diseases and conditions such as rheumatoid arthritis, osteoarthritis, Crohn's disease, angiofibroma, retinal vascularization, diabetic retinopathy, age-related macular degeneration, macular degeneration, multiple sclerosis, obesity, Alzheimer's disease, restenosis, autoimmune diseases, allergy, asthma, endometriosis, atherosclerosis, vein graft stenosis, peri-anastomatic prosthetic graft stenosis, prostate hyperplasia, chronic obstructive pulmonary disease, psoriasis, inhibition of neurological damage due to tissue repair, scar tissue formation, multiple sclerosis, inflammatory bowel disease, infections, particularly bacterial, viral, retroviral or parasitic infections, pulmonary disease, neoplasm, Parkinson's disease, transplant rejection, and septic shock.

The AKT-mediated disease can be a relapsed disease. The AKT-mediated disease 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 XF038-157A, XF038-158A, XF038-159A, XF038-160A, XF038-161A, XF038-162A, XF038-164A, XF038-165A, XF038-166A, XF038-176A, XF038-177A, XF042-162, XF042-164, XF042-

165, XF042-166, XF042-167, XF042-168, XF042-170, XF042-171, XF048-1, XF048-2, XF048-3, XF048-4, XF048-5, XF048-7, XF048-8, XF050-5, XF050-6, XF050-7, XF050-8, XF050-9, XF050-10, XF050-11, XF050-12, XF050-13, XF050-14, XF050-15, XF050-16, XF050-17, XF050-18, XF050-19, XF050-20, XF050-21, XF050-22, XF050-23, XF050-24, XF050-25, XF050-26, XF050-27, XF050-28, XF050-29, XF050-30, XF050-31, XF050-32, XF050-33, XF050-98, XF050-132, XF050-133. XF050-134, XF056-93, XF050-143, XF050-144, XF050-145, XF050-167, XF056-33, XF056-34, XF056-35, XF056-36, XF056-37, XF056-73, XF061-10, XF067-1, XF067-2, XF067-3, XF067-4, XF067-5, XF067-6, XF067-7, XF067-8, XF067-9, XF067-10, XF067-11, XF067-12, XF067-13, XF067-14, XF067-15, XF067-16, XF067-17, XF067-18, XF067-19, XF067-20, XF067-21, XF067-22, XF067-23, XF067-24, XF067-25, XF067-26, XF067-27, XF067-28, XF067-29, XF067-30, XF067-31, XF067-32, XF067-33, XF067-34, XF067-35, XF067-36, XF067-37, XF067-38, XF067-39, XF067-40, XF067-41, XF067-42, XF067-43, XF067-44, XF067-45, XF067-46, XF067-47, XF067-48, XF067-49, XF067-50, XF067-51, XF067-52, XF067-53, XF067-54, XF067-55, XF067-56, XF067-57, XF067-58, XF067-59, XF067-84, XF067-85, XF067-86, XF067-87, XF067-88, XF067-89, XF067-90, XF067-91, XF067-92, XF067-93, XF067-94, XF067-95, XF067-96, XF067-97, XF067-98, XF067-99, XF067-100, XF067-101, XF067-102, XF067-103, XF067-104, XF067-105, XF067-106, XF067-107, XF067-108, XF067-109, XF067-110, XF067-111, XF067-112, XF067-113, 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 AKT, the method including providing a heterobifunctional test compound including a AKT 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 AKT-mediated cancer cell) including a ubiquitin ligase and AKT.

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

Figures 1A-C are a series of Western blots showing the effect of various AKT degraders on reducing AKT, p-AKT, P-PRAS40 (T246), and P-S6 (S240/244) protein levels at various concentrations in BT474 cells. (Note: "XF" portion of the degrader compound code was omitted).

Figure 2 is a Western blot showing that XF038-166A time-dependently reduces AKT, p-AKT, P-PRAS40 (T246), and P-S6 (S240/244) protein levels in BT474 cells.

Figure 3A-C are a series of Western blots showing the effect of various AKT degraders on reducing AKT, p-AKT, P-PRAS40 (T246), and P-S6 (S240/244) protein levels at various concentrations in BT474 cells. (Note: "XF" portion of the degrader compound code was omitted)

Figure 4A is a series of Western blots showing the effect of selected AKT degraders on reducing AKT, p-AKT, P-PRAS40 (T246), and P-S6 (S240/244) protein levels at various concentrations in BT474 cells.

Figure 4B is a series of Western blots showing the effect of XF050-21 on reducing AKT, p-AKT, P-PRAS40 (T246), and P-S6 (S240/244) protein levels at various concentrations in PC-3, MDA-MB-468, and U87MG cells.

Figure 5A is a series of Western blots showing that XF050-21, XF050-33, XF042-162 and XF042-170 time-dependently reduce AKT, p-AKT, P-PRAS40 (T246), and P-S6 (S240/244) protein levels in BT474 cells.

Figure 5B is a Western blot showing that XF050-21 time-dependently reduces AKT, p-AKT, P-PRAS40 (T246), and P-S6 (S240/244) protein levels in PC3 cells.

Figure 6 is a Western blot showing the effect of XF050-21 on reducing the AKT and p-AKT levels can be blocked by pretreatment of VHL-1, MLN4924, MG132, and AZD5363 in BT474 cells.

Figure 7 is a series of concentration-response curves showing that XF050-21 was more effective than AZD5363 in inhibiting cell growth of PC-3 and MDA-MB-468 cells.

Figure 8A-B are a series of cell culture dish pictures showing that XF050-21 was more effective than AZD5363 in inhibiting colony formation of PC-3, MDA-MB-468, HCC 1143, and MDA-MB-231 cells.

Figure 9 is a series of Western blots showing the combination effect of an AKT degrader (XF050-21 or XF041-170) with an mTOR inhibitor (Torin1 or Rapamycin) in BT474 cells.

Figure 10 is the mouse plasma exposure curve of XF050-21.

Figure 11 is a series of Western blots showing the effect of various AKT degraders on reducing AKT, p-AKT, P-PRAS40 (T246), and P-S6 (S240/244) protein levels at 1 μM compound concentration in PC-3 cells.

Figure 12 is a series of Western blots showing the effect of various AKT degraders on reducing AKT, p-AKT, P-PRAS40 and P-S6 (S240/244) protein levels at 1 μM compound concentration in PC-3 cells.

DEFINITION OF TERMS

As used herein, the terms “comprising” and “including” are used in their open, non-limiting sense.

"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. 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 8 ring atoms (C_3-C_8 heterocyclyl; or 3-8 membered heterocyclyl). In certain embodiments, a heterocyclyl group comprises 3 to 10 ring atoms (C_3-C_{10} heterocyclyl; or 3-10 membered heterocyclyl). In certain embodiments, a heterocyclyl group comprises 4 to 8 ring atoms (C_4-C_8 heterocyclyl; or 4-8 membered heterocyclyl). In certain embodiments, a heterocyclyl group comprises 4 to 10 ring atoms (C_4-C_{10} heterocyclyl; or 4-10 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" or "carbocyclyl" 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 6 carbon ring atoms (C_3-C_6 cycloalkyl; 3-6 membered cycloalkyl; or 3-6 membered carbocyclyl). In certain embodiments, a cycloalkyl comprises 3 to 8 carbon ring atoms (C_3-C_8 cycloalkyl; 3-8 membered cycloalkyl; or 3-8 membered carbocyclyl). In certain embodiments, a cycloalkyl comprises 3 to 10 carbon ring atoms (C_3-C_{10} cycloalkyl; 3-10 membered cycloalkyl; or 3-10 membered carbocyclyl). 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" or "bond" 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 different FORMULAE refers to 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.

DETAILED DESCRIPTION

The present disclosure is based in part, on the discovery that novel heterobifunctional small molecules which degrade AKT and/or AKT mutant proteins are useful in the treatment of AKT-mediated diseases, particularly developmental and over-growth syndromes, cardiovascular disease, diabetes, inflammatory and autoimmune disorders, neurological disorders, and cancer, including but not limited to colon cancer, ovarian cancer, brain cancer, lung cancer, pancreatic cancer, breast cancer, prostate cancer, and gastric carcinoma.

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: 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); and 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). This bifunctional molecule technology has been successfully applied to degradation of multiple 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). Recently, peptidic VHL-recruiting bifunctional molecule has been reported (Henning et al., 2016). However, there are no reported small molecule-based bifunctional molecules that lead to the degradation of AKT or AKT 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 successfully applied to selective degradation of the pseudokinase Her3 (Xie et al., 2014), but not to degradation of AKT or AKT mutant proteins.

As discussed in the following examples, this disclosure provides specific examples of novel AKT degraders/disruptors, and examines the effect of exemplary degraders/disruptors on reducing AKT protein levels, inhibiting/disrupting AKT activity, and inhibiting cancer cell proliferation. The results indicate that these novel small molecules can be beneficial in treating human disease, especially developmental and over-growth syndromes, cardiovascular disease, diabetes, inflammatory and autoimmune disorders, neurological disorders, and cancer, including but not limited to colon cancer, ovarian cancer, brain cancer, lung cancer, pancreatic cancer, breast cancer, prostate cancer, and gastric carcinoma.

A number of selective small-molecule AKT catalytic inhibitors, such as GSK690693 (Heerding et al., 2008), GSK2110183 (Dumble et al., 2014), GSK2141795 (Dumble et al., 2014), AZD5363 (Addie et al., 2013), GDC0068 (Blake et al., 2012), MK-2206 (Hirai et al., 2010), and ARQ-092 (Yu et al., 2015) have been in clinical trials for treating ovarian cancer,

fallopian tube cancer, peritoneal cancer, neuroendocrine tumor, acute myelogenous leukemia, lymphoma, gastric and gastroesophageal junction cancer, biliary cancer, non-small cell lung cancer, pancreatic cancer, nasopharyngeal carcinoma, adenoid cystic carcinoma, endometrial cancer, colorectal cancer, breast cancer, renal cell carcinoma, prostate, glioblastoma, gliosarcoma, chronic lymphocytic leukemia, melanoma (Pretre and Wicki, 2017). Despite effectiveness in preclinical animal models, the majority of these inhibitors lack efficacy in human patients (Manning and Toker, 2017).

Currently compounds targeting AKT generally focus on inhibition of its catalytic activity. In the present disclosure, a different approach is taken: to develop compounds that directly and selectively target not only the catalytic function of AKT, but also its protein level in cells. 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 knockdown via RNA interference. Unlike gene knockout or knockdown, this chemical 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 compound.

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.

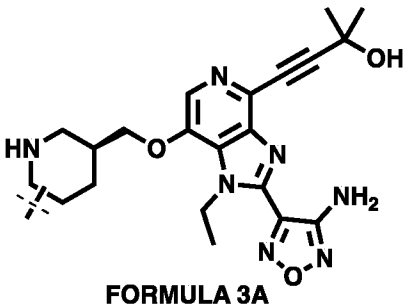
Degraders

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

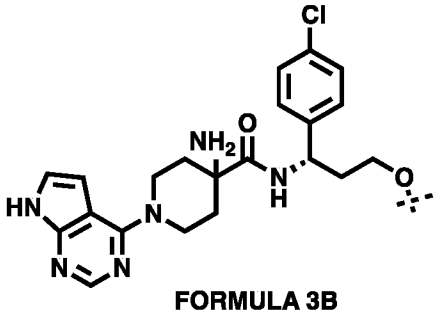
As used herein, the terms "serine threonine kinase (AKT) ligand" or "AKT ligand" or "AKT targeting moiety" are to be construed broadly, and encompass a wide variety of molecules ranging from small molecules to large proteins that associate with or bind to AKT. The AKT ligand or targeting moiety can be, 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 AKT ligand or targeting moiety can be an AKT inhibitor (e.g., GSK690693 (Heerding et al., 2008), GSK2110183 (Dumble et al., 2014), GSK2141795 (Dumble et al., 2014), AZD5363 (Addie et al., 2013), GDC0068 (Blake et al., 2012), MK-2206 (Hirai et al., 2010), and ARQ-092 (Yu et al., 2015), and analogs thereof), which is capable of interfering with the enzymatic activity of AKT. As used herein, an "inhibitor" refers to an agent that restrains, retards, or otherwise causes inhibition of a physiological, chemical or enzymatic action or function and causes a decrease in enzyme activity 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.

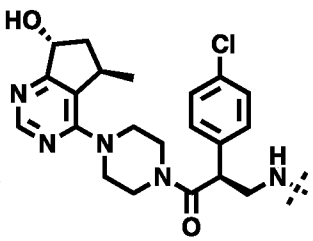
Exemplary AKT ligands include, but are not limited to, the compounds listed below:



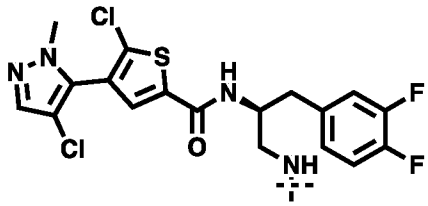
FORMULA 3A



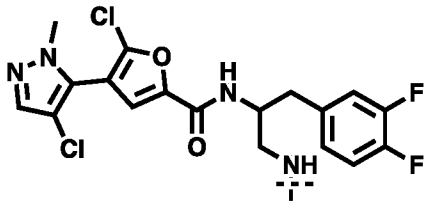
FORMULA 3B



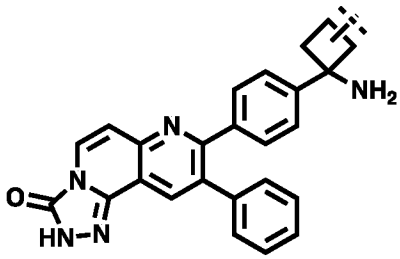
FORMULA 3C



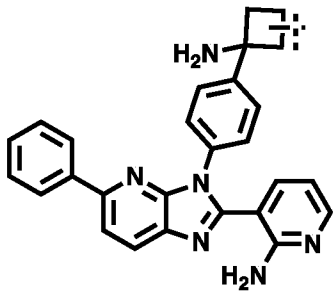
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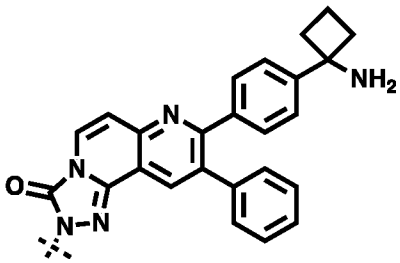
FORMULA 3E



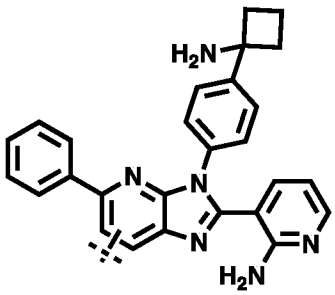
FORMULA 3F



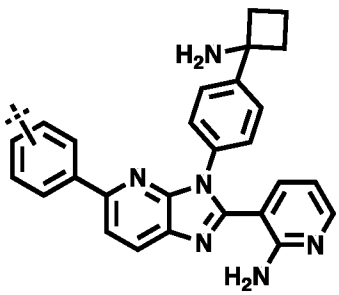
FORMULA 3G



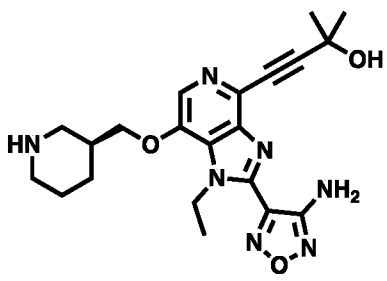
FORMULA 3H



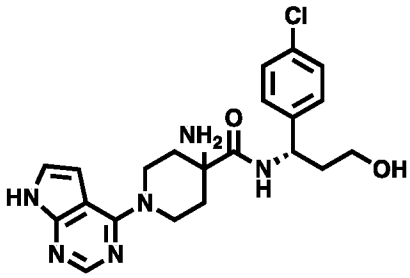
FORMULA 3I



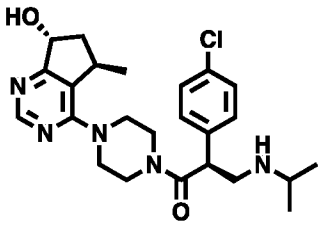
FORMULA 3J



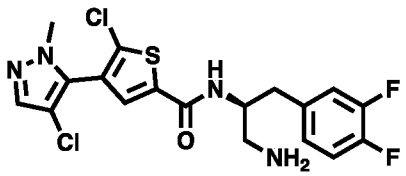
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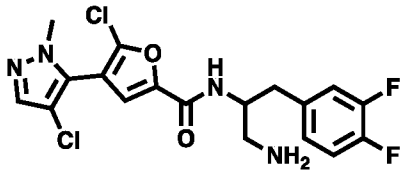
AZD5363



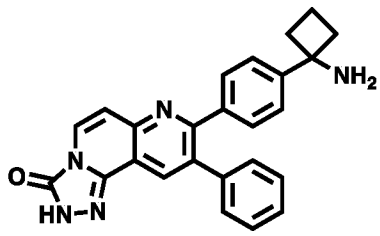
GDC0068



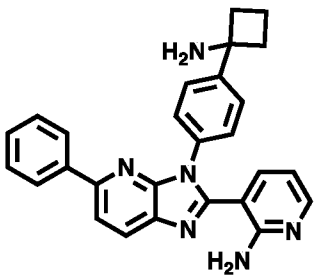
GSK2110183



GSK2141795



MK2206



ARQ 092

As used herein, the term "degradation/disruption tag" refers to a compound which associates with or binds to a ubiquitin ligase for recruitment of the corresponding ubiquitination machinery to AKT or induces AKT 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), 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 AKT ligand to the degradation/disruption tag. One of ordinary skill in the art recognizes that sites on the AKT

ligand or the degradation/disruption tag, which are not necessary for the function of the bifunctional molecule 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 bifunctional molecule, i.e., its ability to target AKT, and 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 AKT ligand or targeting moiety with the ubiquitin ligase or induce AKT 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), and analogs thereof. The degradation/disruption tags can be attached to each portion of interest in the structure of an AKT ligand or targeting moiety (e.g., GSK690693 (Heerding et al., 2008), GSK2110183 (Dumble et al., 2014), GSK2141795 (Dumble et al., 2014), AZD5363 (Addie et al., 2013), GDC0068 (Blake et al., 2012), MK-2206 (Hirai et al., 2010), and ARQ-092 (Yu et al., 2015)) 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 to AKT.

The bivalent compounds disclosed herein can selectively affect AKT-mediated disease cells compared to WT (wild type) cells (i.e., an AKT degrader/disruptor able to kill or inhibit the growth of an AKT-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 AKT-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 AKT-mediated disease cells.

Additional bivalent compounds (i.e., AKT degraders/disruptors) can be developed using the principles and methods disclosed herein. For example, other linkers, degradation/disruption tags, and AKT binding/inhibiting moieties (not limited to GSK690693

(Heerding et al., 2008), GSK2110183 (Dumble et al., 2014), GSK2141795 (Dumble et al., 2014), AZD5363 (Addie et al., 2013), GDC0068 (Blake et al., 2012), MK-2206 (Hirai et al., 2010), and ARQ-092 (Yu et al., 2015)) can be synthesized and tested.

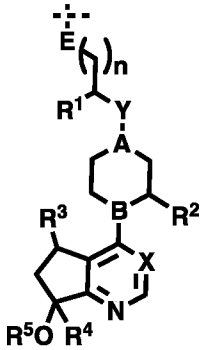
In some aspects, the AKT degraders/disruptors have the form "**PI-Linker-EL**", as shown below:



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

AKT Ligands

AKT Ligands (PI) include but are not limited to:



FORMULA 1

wherein

A, B, and X are independently N, CH, or CR^6,

Y is CH_2, CO, SO, SO_2, CR^7R^8, $CONR^7$, or SO_2NR^7,

E is NH, NR^9, O, C_1-C_8 alkyl, C_1-C_8 alkoxy, C_1-C_8 alkoxyalkyl, C_1-C_8 haloalkyl, C_1-C_8 hydroxyalkyl, C_3-C_8 cycloalkyl, C_3-C_7 heterocyclyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, OR^9, SR^9, NR^9R^{10}, CN, NO_2, $(CR^9R^{10})mNR^{11}R^{12}$, $(CR^9R^{10})mC(O)R^{11}$, $(N\ R^9R^{10})mNR^{11}R^{12}$, $(NR^9R^{10})mC(O)R^{11}$, COR^9, CO_2R^9, $CONR^9R^{10}$, NR^9COR^{10}, NR^9SOR^{10}, $NR^9SO_2R^{10}$, SOR^9, SO_2R^9, $SO_2NR^9R^{10}$, (CR^9R^{10})m-aryl, or (CR^9R^{10})m-heteroaryl,

R^1 is H, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkoxy, C_1-C_8 alkoxyalkyl, aryl, C_1-C_8 alkylaryl, haloaryl, arylalkyl, heteroaryl, or heteroarylalkyl,

R^2, R^3, R^4, and R^6 are independently hydrogen, halogen, amino, C_1-C_8 alkylamino, arylamino, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkoxy, or C_1-C_8 alkoxyalkyl,

R^5, R^7, and R^8 are independently H, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, or C_1-C_8 alkoxyalkyl,

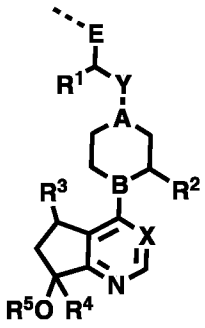
R^9, R^{10}, R^{11}, and R^{12} are independently H, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkoxy, C_2-C_8 alkenyl, C_2-C_8 alkynyl, arylalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, or heteroarylalkyl,

R^9 and R^{10}, R^{11} and R^{12} can independently form 4-8 membered alkyl or heterocyclyl rings,

m = 0-8,

and

n = 0-8; and



FORMULA 2

wherein

A, B and X are independently selected from N and CR^6, wherein

R^6 is independently selected from hydrogen, halogen, cyano, nitro, hydroxyl, amino, 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 amino, optionally substituted C_1-C_8 alkylamino, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-10 membered carbocyclyl, and optionally substituted 4-10 membered heterocyclyl;

Y is selected from CR^7R^8, CO, SO, SO_2, $CONR^7$, and SO_2NR^7, wherein

R^7 and R^8 is independently selected from hydrogen, halogen, 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 alkylamino, optionally substituted C_1-C_8 alkylamino C_1-C_8 alkyl, optionally substituted 3 to 10 membered carbocyclyl, and optionally substituted 4-10 membered heterocyclyl, or

R^7 and R^8 together with the atom to which they are connected form an optionally substituted 3-10 membered carbocyclyl or an optionally substituted 4-10 membered heterocyclyl ring;

E is connected to the "linker" moiety of the bivalent compound, and is selected from null, R'-R" R'OR", R'SR", R'NR^{9}R", R'OC(O)R", R'OC(O)OR", R'OCONR^{9}R", R'C(O)R", R'C(O)OR", R'CONR^{9}R", R'S(O)R", R'S(O)$_2$R", R'SO$_2$NR^{9}R", R'NR^{10}C(O)OR", R'NR^{10}C(O)R", R'NR^{10}C(O)NR^{9}R", R'NR^{10}S(O)R", R'NR^{10}S(O)$_2$R", and R'NR^{10}S(O)$_2$NR^{9}R", wherein

R' and R" are independently selected from null, 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$_8$alkoxyC$_1$-C$_8$alkyl, optionally substituted C$_1$-C$_8$alkylaminoC$_1$-C$_8$alkyl, 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$_8$ haloalkylene, optionally substituted C$_1$-C$_8$ hydroxyalkylene, optionally substituted C$_1$-C$_8$alkoxyC$_1$-C$_8$alkylene, optionally substituted C$_1$-C$_8$alkylaminoC$_1$-C$_8$alkylene, optionally substituted (C$_1$-C$_8$ alkylene)O(C$_1$-C$_8$ alkylene), optionally substituted (C$_1$-C$_8$ alkylene)N(C$_1$-C$_8$ alkylene), optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted C$_3$-C$_{13}$ fused carbocyclyl, optionally substituted C$_3$-C$_{13}$ fused heterocyclyl, optionally substituted C$_3$-C$_{13}$ bridged carbocyclyl, optionally substituted C$_3$-C$_{13}$ bridged heterocyclyl, optionally substituted C$_3$-C$_{13}$ spiro carbocyclyl, optionally substituted C$_3$-C$_{13}$ spiro heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^9 and R^{10} 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$_8$alkoxyC$_1$-C$_8$alkyl, optionally substituted C$_1$-C$_8$alkylaminoC$_1$-C$_8$alkyl, optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

R' and R", R^9 and R^{10}, R' and R^9, R' and R^{10}, R" and R^9, R" and R^{10} together with the atom to which they are connected form a 4-20 membered heterocyclyl ring;

R^1 is selected from hydrogen, halogen, and 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$_8$ alkylamino, optionally substituted C$_1$-C$_8$ alkylamino C$_1$-C$_8$ alkyl, optionally substituted 3-

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

R^2, R^3 and R^4 are independently selected from hydrogen, halogen, cyano, nitro, hydroxyl, 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 aryloxy, optionally substituted C_1-C_8 alkoxyC_1-C_8 alkyl, optionally substituted amino, optionally substituted C_1-C_8 alkylamino, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted arylamino, optionally substituted 3-10 membered carbocyclyl, and optionally substituted 4-10 membered heterocyclyl;

R^5 is 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 alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-10 membered carbocyclyl, and optionally substituted 4-10 membered heterocyclyl; and

In one embodiment, A is selected from N, CH and CNH_2.

In another embodiment, A is N.

In one embodiment, B and X are independently selected from N and CH.

In another embodiment, B is N.

In another embodiment, X is N.

In another embodiment, Y is selected from CH_2, CO, CONH and NHCO.

In another embodiment, Y is CO.

In another embodiment, E is selected from null, O, N, optionally substituted C_1-C_8 alkylene, optionally substituted (C_1-C_8 alkylene)O, optionally substituted (C_1-C_8 alkylene)N, optionally substituted 3-10 membered carbocyclylene, optionally substituted (3-10 membered carbocyclylene)O, optionally substituted (3-10 membered carbocyclylene)N, optionally substituted 4-10 membered heterocyclylene, optionally substituted (4-10 membered heterocyclylene)O, optionally substituted (4-10 membered heterocyclylene)N, optionally substituted aryl, and optionally substituted heteroaryl.

In another embodiment, R^1 is selected from optionally substituted aryl and optionally substituted heteroaryl.

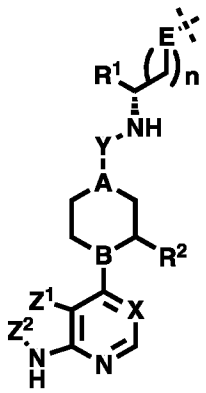
In another embodiment, R^1 is selected from optionally substituted phenyl.

In another embodiment, R^1 is 4-chlorophenyl.

In another embodiment, R^2, R^3, R^4 and R^5 are independently selected from H, F, Cl, CN, NO_2, CH_3, CF_3, iPr, and cPr.

In another embodiment, R^2, R^4 and R^5 are H.

In another embodiment, R^3 is CH_3.



FORMULA 3

wherein

A, B, and X are independently N or CR^3,

Y is CH_2, CO, SO, SO_2, CR^4R^5, $CONR^4$, or SO_2NR^4,

E is NH, NR^6, O, C_1-C_8 alkyl, C_1-C_8 alkoxy, C_1-C_8 alkoxyalkyl, C_1-C_8 haloalkyl, C_1-C_8 hydroxyalkyl, C_3-C_8 cycloalkyl, C_3-C_8 heterocyclyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, OR^6, SR^6, NR^6R^7, CN, NO_2, $(CR^6R^7)mNR^8R^9$, $(CR^6R^7)mC(O)R^8$, $(N\ R^6R^7)mNR^8R^9$, $(NR^6R^7)mC(O)R^8$, COR^6, CO_2R^6, $CONR^6R^7$, NR^6COR^7, NR^6SOR^7, $NR^6SO_2R^7$, SOR^6, SO_2R^6, $SO_2NR^6R^7$, (CR^6R^7)m-aryl, or (CR^6R^7)m-heteroaryl,

Z^1-Z^2 is CR^{10}=CH, N+CH, or CR^{10}=N,

R^1 is hydrogen, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkoxy, C_1-C_8 alkoxyalkyl, aryl, C_1-C_8 alkylaryl, haloaryl, arylalkyl, heteroaryl, or heteroarylalkyl,

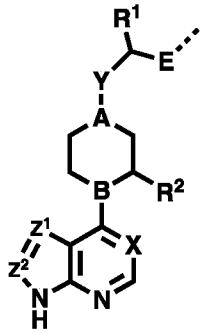
R^2, R^3, and R^4 are independently hydrogen, halogen, amino, C_1-C_8 alkylamino, arylamino, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkoxy, or C_1-C_8 alkoxyalkyl,

R^6, R^7, R^8, and R^9 are independently H, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkoxy, C_2-C_8 alkenyl, C_2-C_8 alkynyl, arylalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, or heteroarylalkyl,

R^6 and R^7, R^8 and R^9 can independently form 4-8 membered alkyl or heterocyclyl rings,

R^{10} is hydrogen, halogen, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkoxy, C_1-C_8 alkoxyalkyl, and

n = 0-8.



FORMULA 4

wherein

A, B and X are independently selected from N and CR^3, wherein

R^3 is independently selected from hydrogen, halogen, cyano, nitro, hydroxyl, 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 alkoxyC_1-C_8 alkyl, optionally substituted amino, optionally substituted C_1-C_8 alkylamino C_1-C_8 alkyl, optionally substituted 3-10 membered carbocyclyl, and optionally substituted 4-10 membered heterocyclyl;

Z^1 is selected for CR^8 and N, wherein

R^8 is selected from hydrogen, halogen, cyano, nitro, hydroxyl, 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 alkoxyC_1-C_8 alkyl, optionally substituted amino, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-10 membered carbocyclyl, and optionally substituted 4-10 membered heterocyclyl;

Z^2 is selected for CH and N;

Y is selected from CO, SO, SO_2, CR^4R^5, $CONR^4$, and SO_2NR^4, wherein

R^4 and R^5 is independently selected from hydrogen and 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 alkoxyC_1-C_8 alkyl, optionally substituted amino, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3 to 10 membered carbocyclyl, and optionally substituted 4-10 membered heterocyclyl;

E is connected to the "linker" moiety of the bivalent compound, and is selected from null, R'-R'', R'OR'', R'SR'', R'NR^6R'', R'OC(O)R'', R'OC(O)OR'', R'OCONR^6R'', R'C(O)R'', R'C(O)OR'', R'$CONR^6$R'', R'S(O)R'', R'$S(O)_2$R'', R'SO_2NR^6R'', R'NR^7C(O)OR'',

$R'NR^7C(O)R''$, $R'NR^7C(O)NR^6R''$, $R'NR^7S(O)R''$, $R'NR^7S(O)_2R''$, and $R'NR^7S(O)_2NR^6R''$, wherein

R' and R'' are independently selected form null, 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 haloalkylene, optionally substituted C_1-C_8 hydroxyalkylene, optionally substituted C_1-C_8alkoxyC_1-C_8alkylene, optionally substituted (C_1-C_8 alkylene)O(C_1-C_8 alkylene), optionally substituted (C_1-C_8 alkylene)N(C_1-C_8 alkylene), optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted C_3-C_{13} fused carbocyclyl, optionally substituted C_3-C_{13} fused heterocyclyl, optionally substituted C_3-C_{13} bridged carbocyclyl, optionally substituted C_3-C_{13} bridged heterocyclyl, optionally substituted C_3-C_{13} spiro carbocyclyl, optionally substituted C_3-C_{13} spiro heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^6 and R^7 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 carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R' and R'', R^6 and R^7, R' and R^6, R' and R^7, R'' and R^6, R'' and R^7 together with the atom to which they are connected form a 4-20 membered heterocyclyl ring;

R^1 is selected from selected from hydrogen, halogen, and 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 alkoxyC_1-C_8 alkyl, optionally substituted amino, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl; and

R^2 is selected from hydrogen, halogen, cyano, nitro, hydroxyl, 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, or optionally substituted C_1-C_8 alkoxy C_1-C_8 alkyl, optionally substituted amino, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-10 membered carbocyclyl, and optionally substituted 4-10

membered heterocyclyl;

In one embodiment, A is selected from N, CH and CNH_2.

In another embodiment, A is CNH_2.

In one embodiment, B and X are independently selected from N and CH.

In another embodiment, B is N.

In another embodiment, X is N.

In another embodiment, Z^1 is selected from CH and CCH_3.

In another embodiment, Z^1 is CH.

In another embodiment, Z^2 is CH.

In another embodiment, Y is selected from CH_2, CO, CONH and NHCO.

In another embodiment, Y is CONH.

In another embodiment, E is selected from null, O, N, optionally substituted C_1-C_8 alkylene, optionally substituted (C_1-C_8 alkylene)O, optionally substituted (C_1-C_8 alkylene)N, optionally substituted 3-10 membered carbocyclylene, optionally substituted (3-10 membered carbocyclylene)O, optionally substituted (3-10 membered carbocyclylene)N, optionally substituted 4-10 membered heterocyclylene, optionally substituted (4-10 membered heterocyclylene)O, optionally substituted (4-10 membered heterocyclylene)N, optionally substituted aryl, and optionally substituted heteroaryl.

In another embodiment, R^1 is selected from optionally substituted aryl and optionally substituted heteroaryl.

In another embodiment, R^1 is selected from optionally substituted phenyl.

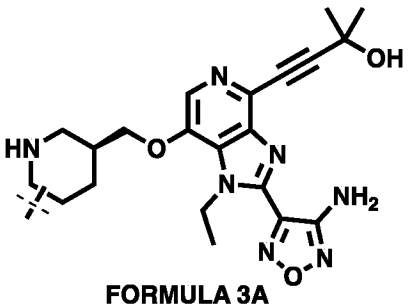
In another embodiment, R^1 is 4-chlorophenyl.

In another embodiment, R^2 is selected from H, F, Cl, CN, NO_2, CH_3, CF_3, iPr, and cPr,

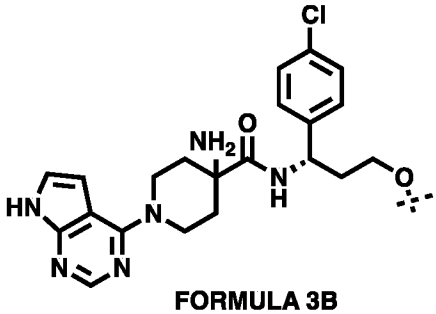
In another embodiment, R^2 is H.

The AKT ligand can be an AKT inhibitor, such as, for example, GSK690693 (Heerding et al., 2008), GSK2110183 (Dumble et al., 2014), GSK2141795 (Dumble et al., 2014), AZD5363 (Addie et al., 2013), GDC0068 (Blake et al., 2012), MK-2206 (Hirai et al., 2010), and ARQ-092 (Yu et al., 2015), and/or analogs thereof.

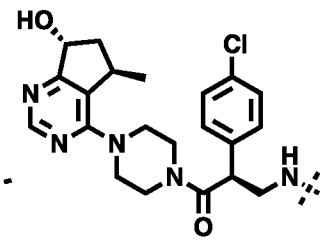
In some aspects, the AKT ligand can be, e.g.:



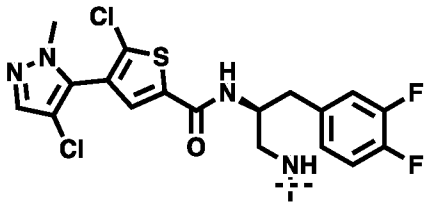
FORMULA 3A



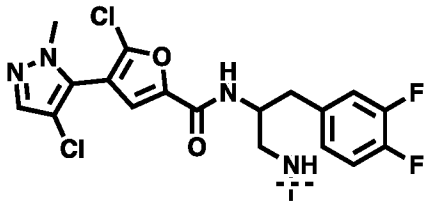
FORMULA 3B



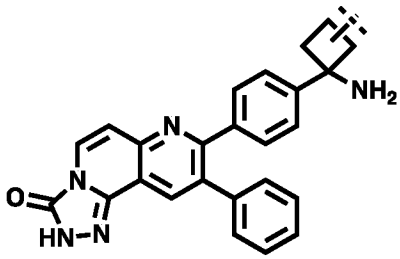
FORMULA 3C



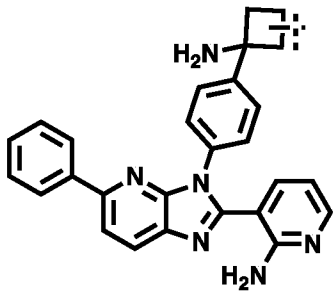
FORMULA 3D



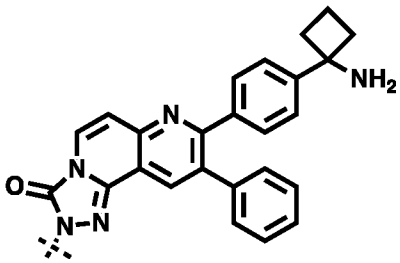
FORMULA 3E



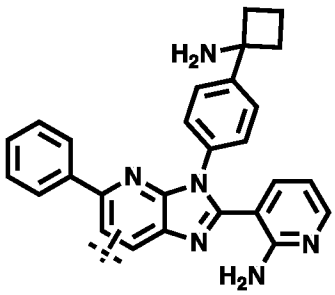
FORMULA 3F



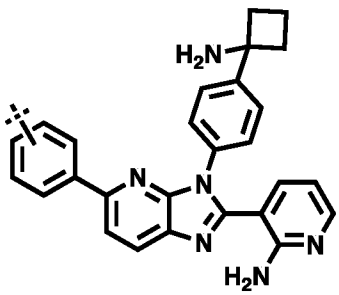
FORMULA 3G



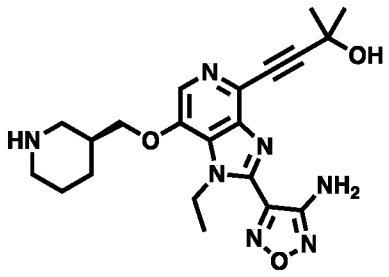
FORMULA 3H



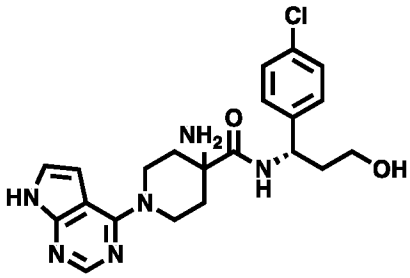
FORMULA 3I



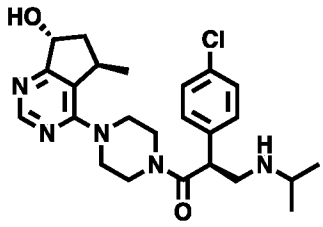
FORMULA 3J



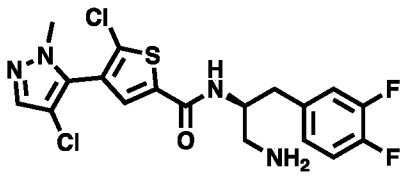
GSK690693



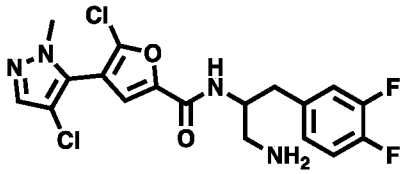
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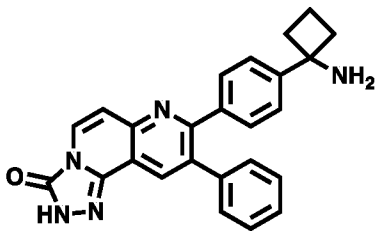
GDC0068



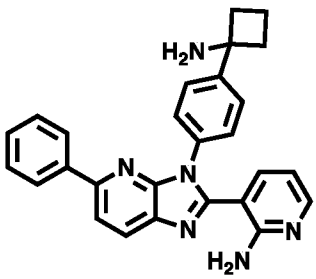
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GSK2141795



MK2206

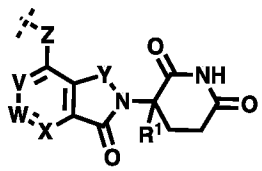


ARQ 092

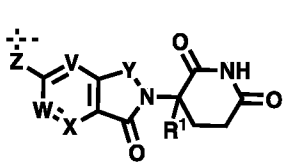
The AKT ligand can be bound to AKT and/or AKT mutant proteins, such as, e.g., AKT with an E17K mutation.

Degradation / Disruption Tags

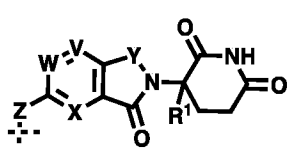
Degradation / Disruption Tags (**EL**) include but are not limited to:



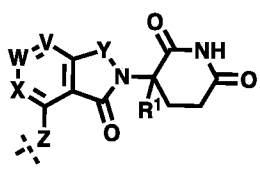
FORMULA 5A



FORMULA 5B



FORMULA 5C



FORMULA 5D

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;

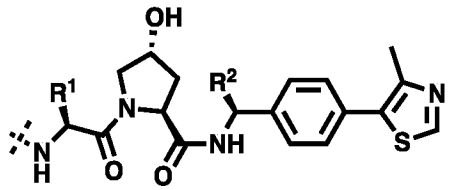
wherein

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

Y is selected from CO, CH_2, and N=N;

Z is selected from CH_2, NH and O; and

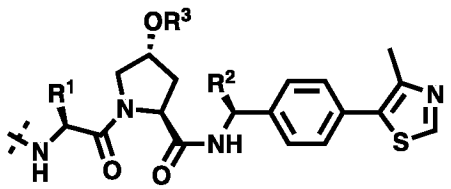
R^1 and R^2 are independently selected from hydrogen, halogen, cyano, nitro, and C_1-C_5 alkyl.



FORMULA 6

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_3-C_7 cycloalkyl, C_3-C_7 heterocyclyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl;



FORMULA 7,

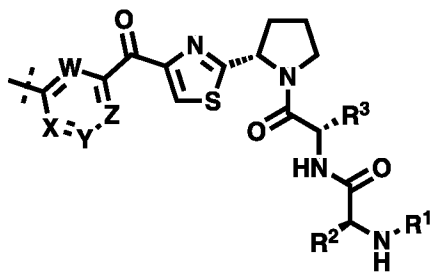
wherein

R^1 and R^2 are independently selected from hydrogen, hydroxyl, amino, cyano, nitro, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, and optionally substituted C_2-C_8 alkynyl, 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 3-10 membered carbocyclyl, and optionally substituted 4-10 membered heterocyclyl.

R^3 is selected from 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)(3-10 membered carbocyclyl), optionally substituted C(O)(4-10 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)O(3-10 membered carbocyclyl), optionally substituted C(O)O(4-10 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)N(3-10 membered carbocyclyl), optionally substituted C(O)N(4-10 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



FORMULA 8

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.

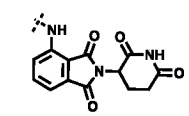
wherein

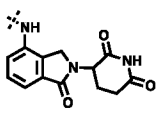
V, W, X, and Z are independently selected from CR^4 and N; and

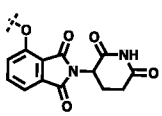
R^1, R^2, R^3, and R^4 are independently selected from hydrogen, halogen, cyano, nitro, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, and optionally substituted C_2-C_8 alkynyl; optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-C_8 hydroxyalkyl, optionally substituted C_1-C_8alkoxy, optionally substituted C_1-C_8alkylamino, optionally substituted 3-10 membered carbocyclyl, and optionally substituted 4-10 membered heterocyclyl.

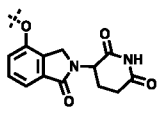
In some aspects, the degradation/disruption tag can be, for example, pomalidomide (Fischer et al., 2014), thalidomide (Fischer et al., 2014), lenalidomide (Fischer et al., 2014), VH032 (Galdeano et al., 2014; Maniaci et al., 2017), adamantine (Xie et al., 2014), 1-((4,4,5,5,5-pentafluoropentyl)sulfinyl)nonane (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), and/or analogs thereof.

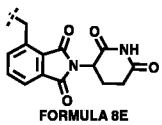
In some aspects, the degradation/disruption tag can be, e.g., one of the following structures:

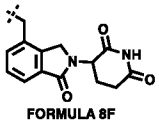

FORMULA 8A

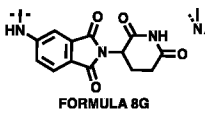

FORMULA 8B

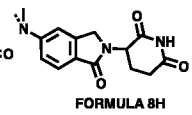

FORMULA 8C

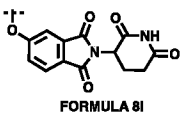

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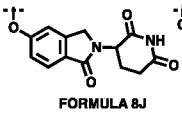

FORMULA 8E

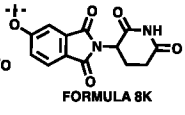

FORMULA 8F

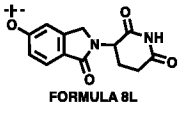

FORMULA 8G

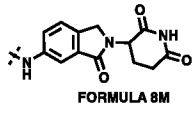

FORMULA 8H

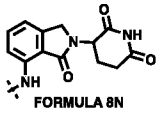

FORMULA 8I

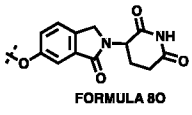

FORMULA 8J

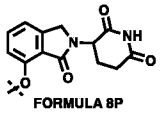

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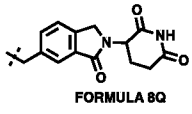

FORMULA 8L

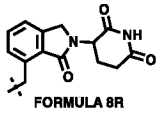

FORMULA 8M

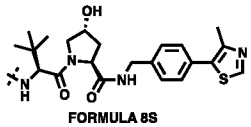

FORMULA 8N

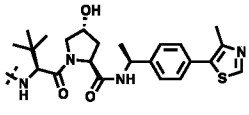

FORMULA 8O

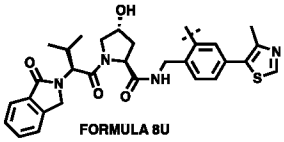

FORMULA 8P

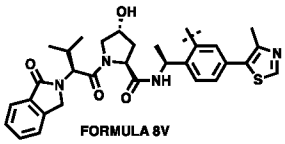

FORMULA 8Q

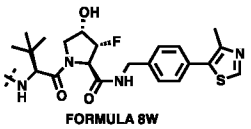

FORMULA 8R

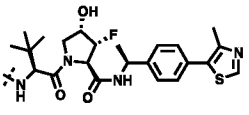

FORMULA 8S

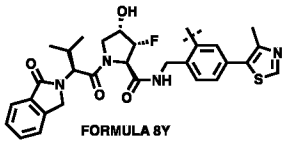

FORMULA 8T

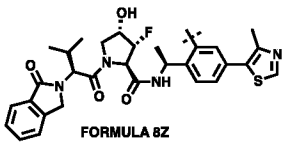

FORMULA 8U

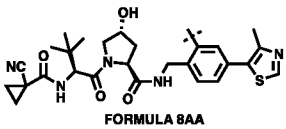

FORMULA 8V

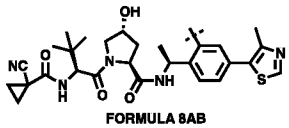

FORMULA 8W

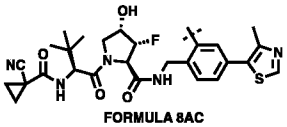

FORMULA 8X

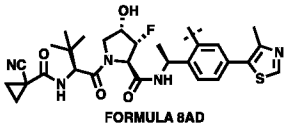

FORMULA 8Y

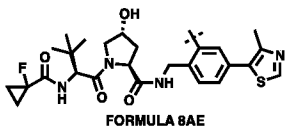

FORMULA 8Z

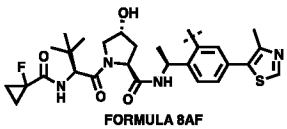

FORMULA 8AA

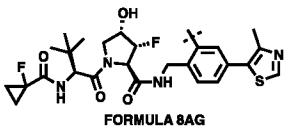

FORMULA 8AB

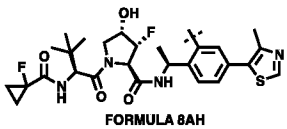

FORMULA 8AC

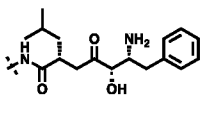

FORMULA 8AD

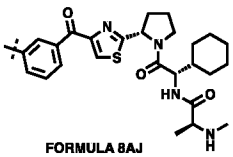

FORMULA 8AE

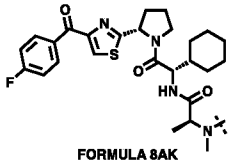

FORMULA 8AF

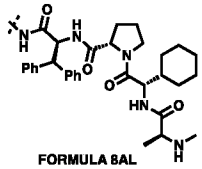

FORMULA 8AG

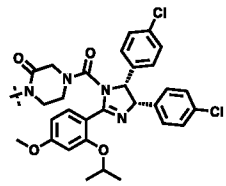

FORMULA 8AH

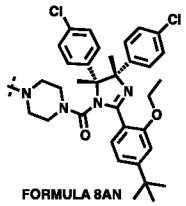

FORMULA 8AI

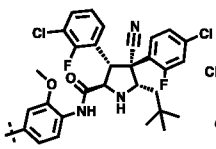

FORMULA 8AJ

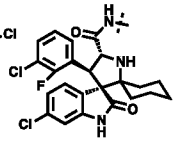

FORMULA 8AK

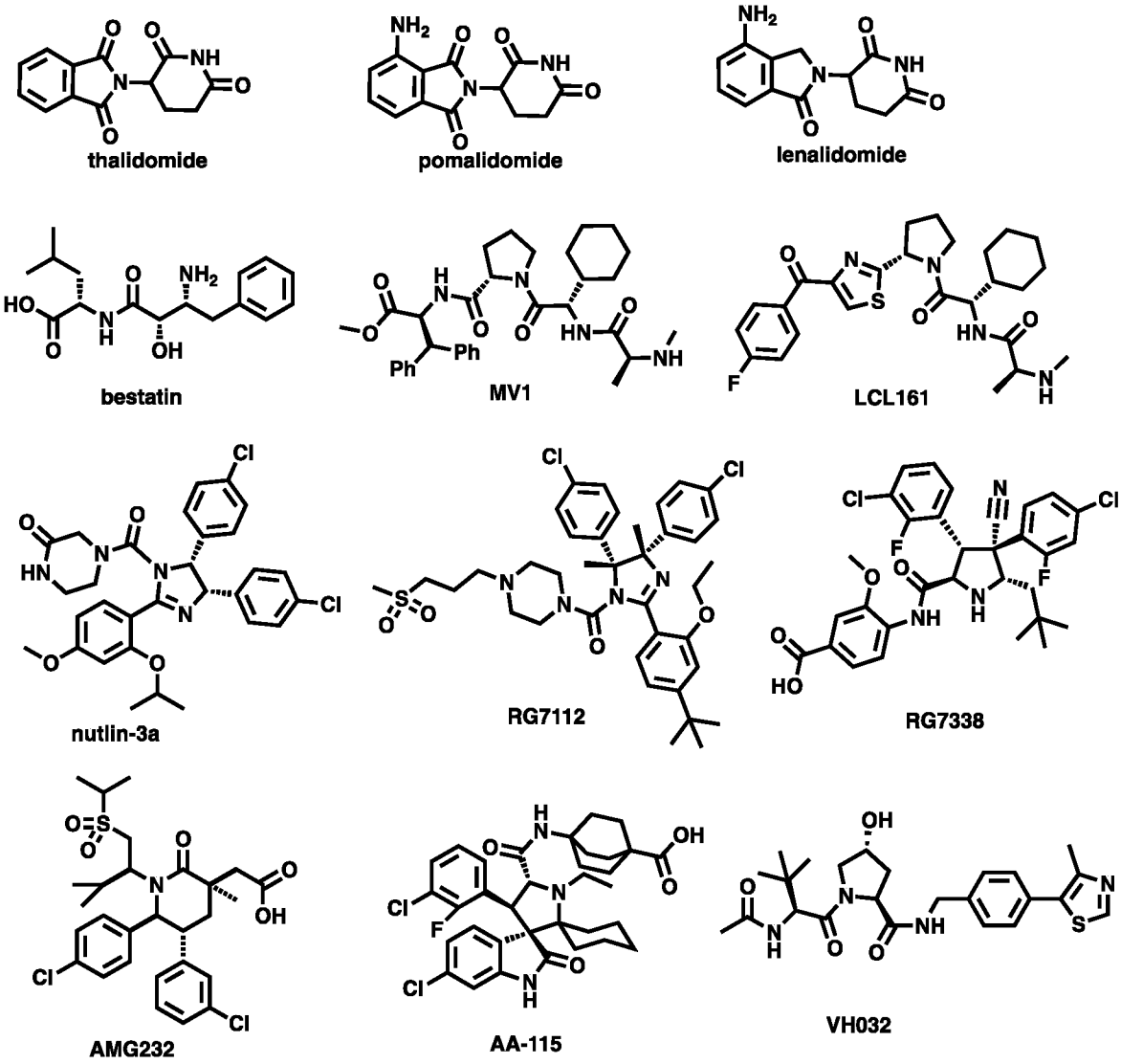

FORMULA 8AL


FORMULA 8AM


FORMULA 8AN


FORMULA 8AO


FORMULA 8AP



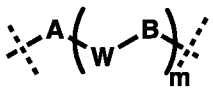
In some aspects, the degradation/disruption tag can bind to a ubiquitin ligase (e.g., an E3 ligase such as a cereblon E3 ligase, a VHL E3 ligase, a MDM2 ligase, a TRIM21 ligase, a TRIM24 ligase, and/or an IAP ligase) and/or serve as a hydrophobic group that leads to AKT protein misfolding.

Linkers

In all of the above-described compounds, the AKT 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 9,

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)NR''R^1, R'C(S)NR''R^1, R'OR'', R'OC(O)R'', R'OC(O)OR'', R'OCONR^{1}R'', R'SR'', R'SOR'', R'SO_2R'', R'SO_2NR''R^1, R'NR''R^1, R'NR^{1}COR'', R'NR^{1}C(O)OR'', R'NR^{1}CONR''R^2, R'NR^{1}C(S)R'', R'NR^{1}S(O)R'', R'NR^1$S(O)_2$R'', and R'NR^1$S(O)_2$NR^{2}R'', wherein

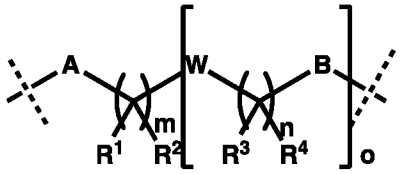
R' and R'' are independently selected from null, or a moiety comprising of optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 hydroxyalkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted 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^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.

In one embodiment, the linker moiety is of FORMULA 9A:



FORMULA 9A,

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 3-10 membered cycloalkoxy, optionally substituted 3-10 membered carbocyclylamino, optionally substituted 4-8 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)NR''R^1, R'C(S)NR''R^1, R'OR'', R'OC(O)R'', R'OC(O)OR'', R'OCONR^{1}R'', R'SR'', R'SOR'', R'SO_2R'', R'SO_2NR''R^1, R'NR''R^1, R'NR^{1}COR'', R'NR^{1}C(O)OR'', R'NR^{1}CONR''R^2, R'NR^{1}C(S)R'', R'NR^{1}S(O)R'', R'NR^{1}S(O)$_2$R'', and R'NR^{1}S(O)$_2$NR^{2}R'', wherein

R' and R'' are independently selected from null, 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^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;

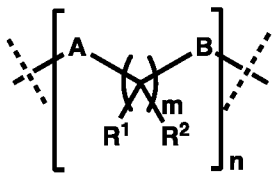
$R^{'}$ and $R^{''}$, R^5 and R^6, $R^{'}$ and R^5, $R^{'}$ and R^6, $R^{''}$ and R^5, $R^{''}$ and R^6 together with the atom to which they are connected form a 3-20 membered cycloalkyl or 4-20 membered heterocyclyl ring;

m is 0 to 15;

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

o is 0 to 15.

In another embodiment, the linker moiety is of FORMULA 9B:



FORMULA 9B,

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 3-10 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"R^1, R'C(S)NR"R^1, R'OR", R'OC(O)R", R'OC(O)OR", R'OCONR^{1}R", R'SR", R'SOR", R'SO_2R", R'SO_2NR"R^1, R'NR"R^1, R'NR^{1}COR", R'NR^{1}C(O)OR", R'NR^{1}CONR"R^2, R'NR^{1}C(S)R", R'NR^{1}S(O)R", R'NR^{1}S(O)$_2$R", and R'NR^{1}S(O)$_2$NR^{2}R", wherein

R' and R" are independently selected from null, 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;

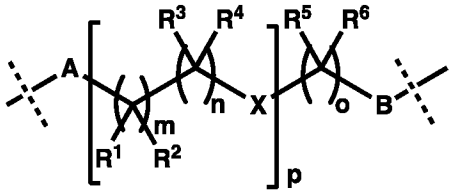
R^3 and R^4 are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxyalkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-C_8 hydroxyalkyl, 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;

each m is 0 to 15; and

n is 0 to 15.

[0032] In another embodiment, the linker moiety is of FORMULA 9C:



FORMULA 9C,

wherein

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

R^1, R^2, R^3, R^4, R^5, R^6, and R^7, 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 3-10 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)NR''R^1, R'C(S)NR''R^1, R'OR'', R'OC(O)R'', R'OC(O)OR'', R'OCONR^{1}R'', R'SR'', R'SOR'', R'SO_2R'', R'SO_2NR''R^1, R'NR''R^1, R'NR^{1}COR'', R'NR^{1}C(O)OR'', R'NR^{1}CONR''R^2, R'NR^{1}C(S)R'', R'NR^{1}S(O)R'', R'NR^{1}S(O)$_2$R'', and R'NR^{1}S(O)$_2$NR^{2}R'', wherein

R' and R'' are independently selected from null, 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^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

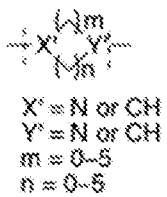
p is 0 to 15.

In another embodiment, 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, CH_2-NH-CH_2.

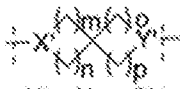
In another embodiment, o is 0 to 5.

In another embodiment, 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 another embodiment, the linker moiety comprises one or more rings selected from the group consisting of FORMULAE C1, C2, C3, C4 and C5:

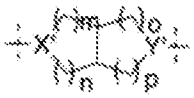


FORMULA C1,



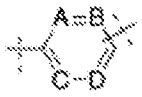
X' = N or CH
Y' = N or CH
m = 0-5
n = 0-5
o = 0-5
p = 0-5

FORMULA C2,



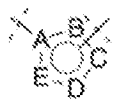
X' = N or CH
Y' = N or CH
m = 0-5
n = 0-5
o = 0-5
p = 0-5

FORMULA C3,



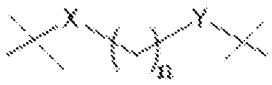
A = CH, C(C_{1-3} alkyl), or N
B = CH, C(C_{1-3} alkyl), or N
C = CH, C(C_{1-3} alkyl), or N
D = CH, C(C_{1-3} alkyl), or N

FORMULA C4, 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.



Formula A,

wherein X is C=O or CH_2,

Y is C=O or CH_2, and

n is 0-15;



Formula B,

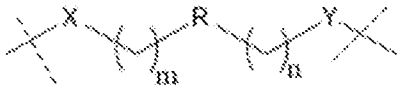
wherein X is C=O or CH_2,

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,

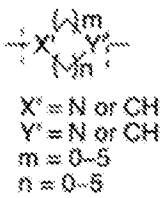
R is $–CH_2–$, $–CF_2–$, $–CH(C_{1-3}$ alkyl)–, $–C(C_{1-3}$ alkyl)(C_{1-3} alkyl)–, –CH=CH–, $–C(C_{1-3}$ alkyl)=C(C_{1-3} alkyl)–, –C=C–, –O–, –NH–, $–N(C_{1-3}$ alkyl)–, $–C(O)NH–$, $–C(O)N(C_{1-3}$ alkyl)–, a 3-13 membered ring, a 3-13 membered fused ring, a 3-13 membered bridged ring, and/or a 3-13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

m is 0-15, and

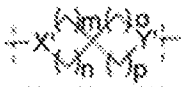
n is 0-15.

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:

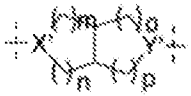


Formula C1,



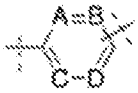
X' = N or CH
Y' = N or CH
m = 0–5
n = 0–5
o = 0–5
p = 0–5

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., AKT degraders/disruptors) can be assessed using standard biophysical assays known in the art (e.g., isothermal titration calorimetry (ITC)). Cellular assays can then be used to assess the bivalent compound's ability to induce AKT degradation and inhibit cancer cell proliferation. Besides evaluating a bivalent compound's induced changes in the protein expression of AKT or AKT 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, e.g., LNCaP cells (androgen-sensitive human prostate adenocarcinoma cells), PC3 (PC-3) cells (PTEN homozygous deletion mutant human prostate cancer cell lines), MCF7-neo/HER2 cells (PIK3CAE545K mutant stably expressing a HER2 transgene breast cancer cells), BT474M1 cells (PIK3CAK111N mutant and HER2-amplified human breast carcinoma), and IGROV-1 cells (PTENT319fsX1/Y155C and PIK3CA1069 Wovarian cancer cells), MDA-MB-468 cells (PTEN loss breast cancer cells), HCC1143 cells (Triple Negative Breast Cancer cells, TP53R248Q mutant), MDA-MB-231 (Triple Negative Breast Cancer cells), and U87MG cells (PTEN Loss Glioblastoma cells). Suitable mouse models for use in any or all of these steps are known in the art and include, e.g., PC3 prostate cancer model, MCF7-neo/HER2 breast cancer model, LNCaP prostate adenocarcinoma model, MDA-MB-468 breast cancer model, HCC1143 breast cancer model, and TOV-21G.x1 ovarian cancer xenograft model.

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

Characterization of Exemplary AKT Degraders/Disruptors

Specific exemplary AKT degraders/disruptors were characterized in various cells and mice (Examples 167-178, Figures 1-12). Bifunctional compounds XF038-165A, XF038-166A, XF038-176A, XF038-177A, XF042-162, XF042-168, XF042-170, XF048-1, XF048-2, XF048-3, XF048-4, XF048-5, XF048-7, XF048-8, XF050-5, XF050-7, XF050-16, XF050-17, XF050-18, XF050-19, XF050-20, XF050-21, XF050-30, XF050-31, XF050-32, XF050-33, XF050-98, XF050-133, XF056-93, XF050-143, XF050-144, XF050-145, XF050-167, XF056-33, XF056-34, XF056-35, and XF056-37, in particular were found to be effective in suppressing both AKT protein level and AKT activity in BT474 cells (Figures 1, 3, and 4). We further demonstrated that XF038-166A, XF042-162, XF042-170, XF050-21, and XF050-33 induced AKT degradation is time-dependent with 24 h being the time point for the most significant AKT degradation in BT474 cells (Figures 2 and 5). Using XF050-21, we showed that the observed AKT degradation can be rescued by pretreatment of the cells with VHL-1, MLN4924, MG132 and AZD5363 (Figure 6). In Figure 7, we compared the cell proliferation inhibition effects of AZD5363 and XF050-21. XF050-21 displayed better cell proliferation inhibition activity than AZD5363 in PC3 and MDA-MB-468 cells. In Figure 8, XF050-21 showed better colony formation inhibition than AZD5363 in PC3, MDA-MB-468, HCC1143, and MDA-MB-231 cells. In Figure 9, we showed that the combination treatment using an AKT degrader (XF050-21 or XF041-170) and a MTOR inhibitor (torin1 or rapamycin) significantly reduced the AKT protein levels and AKT downstream signaling in BT474 cells. In mice, XF050-21-22 was bioavailable at 75 mg/kg via IP administration (Figure 10). Additional bifunctional compounds were tested at 1 uM concentration in PC-3 cells. Compounds XF067-15, XF067-16, XF067-17, XF067-18, XF067-44, XF067-45, XF067-46, XF067-47, XF067-98, XF067-99, XF067-100, XF067-101, XF067-112 and XF067-113 were found to be effective in suppressing AKT protein level and AKT activity at 1 μM concentration in PC-3 cells (Figures 11 and 12).

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, AKT 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 AKT 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 AKT 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 AKT 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 AKT 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 AKT 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 AKT 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 AKT 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 an AKT 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 AKT-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 AKT 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 AKT-mediated diseases that can be treated with AKT degraders/disruptors include, for example, cancer, inflammatory, hyperproliferative cardiovascular, neurodegenerative, gynecological, and dermatological diseases and disorders.

In an aspect, the AKT degraders of the present disclosure can be employed for the treatment of hyperproliferative disorders, including cancers angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma, myxoma, rhabdomyoma, fibroma, lipoma, teratoma, squamous cell carcinoma, undifferentiated small cell carcinoma, undifferentiated large cell carcinoma, adenocarcinoma, alveolar carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma, non-small cell lung cancer, small cell lung cancer, leiomyosarcoma, stomach carcinoma, ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma, carcinoid tumors, Karposi's sarcoma, leiomyoma, hemangioma, neurofibroma, tubular adenoma, villous adenoma, hamartoma, kidney cancer, Wilm's tumor, nephroblastoma, leukemia, bladder cancer, urethra cancer, transitional cell carcinoma, prostate cancer, seminoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, interstitial cell carcinoma, fibroadenoma, adenomatoid tumors, hepatoma, hepatocellular carcinoma, cholangiocarcinoma, hepatoblastoma, hepatocellular adenoma, osteogenic sarcoma, osteosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma, reticulum cell sarcoma, multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma, osteocartilaginous exostoses, benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma, giant cell tumors, osteoma, granuloma, xanthoma, osteitis deformans, meningioma, meningiosarcoma, gliomatosis, astrocytoma, medulloblastoma, glioma, ependymoma, germinoma, pinealoma, glioblastoma multiforme, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors, spinal cord neurofibroma, endometrial carcinoma, cervical carcinoma, pre-tumor cervical dysplasia, ovarian carcinoma, serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma, granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, intraepithelial carcinoma, melanoma, clear cell carcinoma, botryoid sarcoma, embryonal fallopian tubes carcinoma, acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, myelodysplastic syndrome, Hodgkin's disease, non-Hodgkin's lymphoma, advanced

melanoma, malignant melanoma, basal cell carcinoma, moles dysplastic nevi, angioma, dermatofibroma, keloids, psoriasis, neuroblastoma, metastatic breast cancer, colon cancer, oral cancer, hairy cell leukemia, head and neck cancer, refractory metastatic disease; Kaposi's sarcoma, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease.

The compounds and methods of this disclosure can be also used to treat diseases and conditions such as rheumatoid arthritis, osteoarthritis, Crohn's disease, angiofibroma, retinal vascularization, diabetic retinopathy, age-related macular degeneration, macular degeneration, multiple sclerosis, obesity, Alzheimer's disease, restenosis, autoimmune diseases, allergy, asthma, endometriosis, atherosclerosis, vein graft stenosis, peri-anastomatic prosthetic graft stenosis, prostate hyperplasia, chronic obstructive pulmonary disease, psoriasis, inhibition of neurological damage due to tissue repair, scar tissue formation, multiple sclerosis, inflammatory bowel disease, infections, particularly bacterial, viral, retroviral or parasitic infections, pulmonary disease, neoplasm, Parkinson's disease, transplant rejection, and septic shock.

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

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

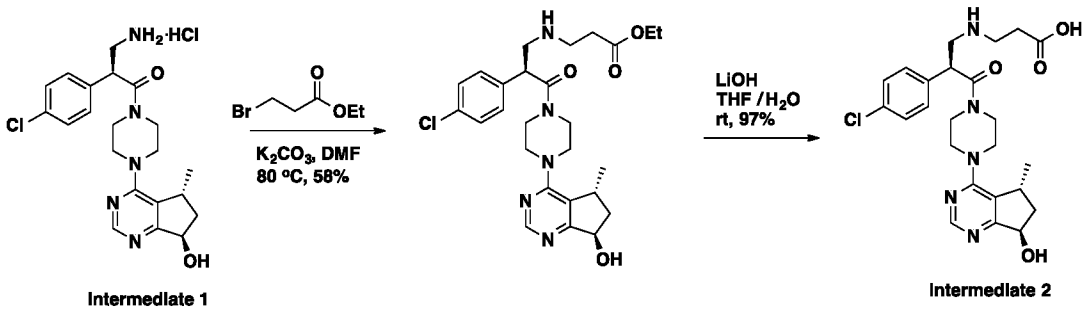
administered at least once. The compositions can be administered from one or more times per day to one or more times per week; including once every other day. The skilled artisan will appreciate that certain factors can influence the dosage and timing required to effectively treat a subject, including 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

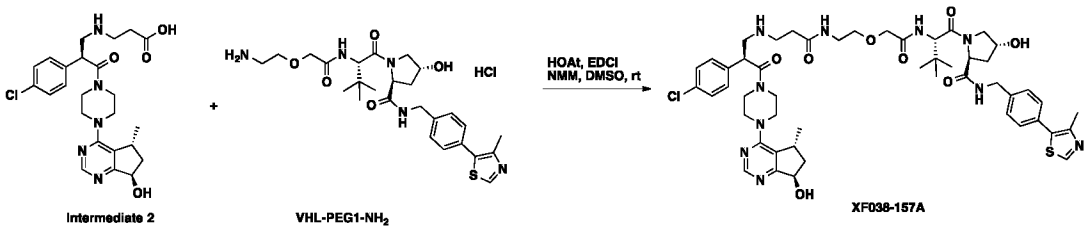
Example 1: Synthesis of intermediate 2



To a solution of intermediate 1 (Blake et al., 2012) (360 mg, 0.86 mmol) in DMF (10 mL) was added potassium carbonate (358 mg, 2.6 mmol, 3 equiv). The resulting suspension was stirred at 80 °C for 15 min, before ethyl 3-bromopropanoate (310 mg, 1.72 mmol, 2 equiv) was added to the solution. After the reaction was stirred overnight, water was added to quench the reaction. The mixture was extracted with ethyl acetate (3 x 10 mL), dried over Na_2SO_4, filtered and evaporated. The resulting residue was purified by silica gel column (DCM / MeOH = 10:1) to afford the pure product ethyl 3-(((*S*)-2-(4-chlorophenyl)-3-(4-((5*R*,7*R*)-7-hydroxy-5-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-yl)piperazin-1-yl)-3-oxopropyl)amino)propanoate (257 mg, yield 58%). The obtained intermediate was dissolved in THF/H_2O (1:1). To the resulting solution was added lithium hydroxide (12 mg, 0.5 mmol). After being stirred overnight at room temperature, the reaction mixture was concentrated and the residue was purified by reverse phase C18 column (10% – 100% methanol / 0.1% TFA in H_2O) to afford intermediate 2 as white solid in TFA salt form (238 mg, 97% yield). ^{1}H NMR (600 MHz, CD_3OD) δ 8.57 (d, *J* = 4.5 Hz, 1H), 7.47 (dt, *J* = 8.7, 2.3 Hz, 2H), 7.36 (dd, *J* = 8.4, 6.0 Hz, 2H), 5.28 (t, *J* = 7.9 Hz, 1H), 4.50 (ddd, *J* = 9.7, 6.6, 4.1 Hz, 1H), 4.37 (td, *J* = 7.9, 4.6 Hz, 1H), 4.24 – 4.10 (m, 1H), 4.09 – 4.01 (m, 1H), 3.95 – 3.81 (m, 4H), 3.65 (dd, *J* = 12.9, 8.9 Hz, 3H), 3.52 – 3.38 (m, 2H), 3.21 (dd, *J* = 12.8, 4.6 Hz, 1H), 2.78 (t, *J* = 6.4 Hz, 2H), 2.28 (dd, *J* = 12.9, 7.4 Hz, 1H), 2.17 (ddt, *J* = 12.6, 8.3, 4.1 Hz, 1H), 1.19 (dd, *J* = 21.1, 7.0 Hz, 3H). HRMS (m/z) for $C_{24}H_{31}ClN_5O_4^+$ $[M + H]^+$: molecular weight calculated 488.2059, found 488.2057.

Example 2

Synthesis of XF038-157A

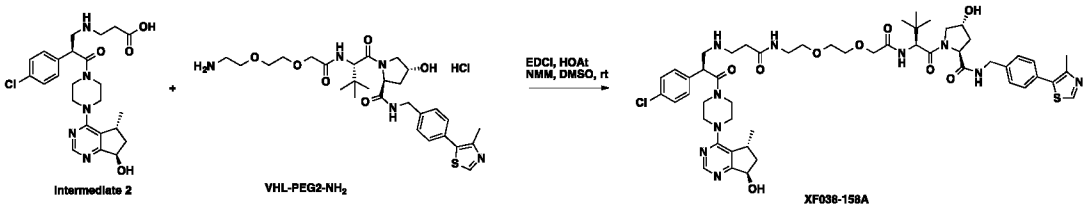


To a solution of Intermediate 2 (12 mg, 0.02 mmol) in DMSO (1 mL) were added VHL-PEG1-NH_2 (11.3 mg, 0.02 mmol, 1.0 equiv), EDCI (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide) (5.8 mg, 0.03 mmol, 1.5 equiv), HOAt (1-hydroxy-7-azabenzo-triazole) (4.1 mg, 0.03 mmol, 1.5 equiv), and NMM (N-Methylmorpholine) (6.1 mg, 0.06 mmol, 3.0 equiv). After being stirred overnight at room temperature, the resulting mixture

was purified by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O) to afford XF038-157A as white solid in TFA salt form (18.2 mg, 91%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.97 (s, 1H), 8.58 (s, 1H), 7.54 – 7.39 (m, 6H), 7.39 – 7.30 (m, 2H), 5.31 (t, J = 8.0 Hz, 1H), 4.71 (s, 1H), 4.61 – 4.45 (m, 4H), 4.42 – 4.36 (m, 1H), 4.17 (s, 1H), 4.08 – 4.03 (m, 1H), 3.99 – 3.76 (m, 7H), 3.71 – 3.54 (m, 7H), 3.47 – 3.36 (m, 3H), 3.28 – 3.23 (m, 1H), 2.80 – 2.64 (m, 3H), 2.48 (s, 3H), 2.33 – 2.22 (m, 2H), 2.17 (dt, J = 12.7, 8.2 Hz, 1H), 2.09 (ddd, J = 13.4, 9.4, 4.4 Hz, 1H), 1.17 (d, J = 6.9 Hz, 3H), 1.04 (s, 9H). HRMS (m/z) for $C_{50}H_{66}ClN_{10}O_8S^+$ $[M + H]^+$: molecular weight calculated 1001.4469, found 1001.4472.

Example 3

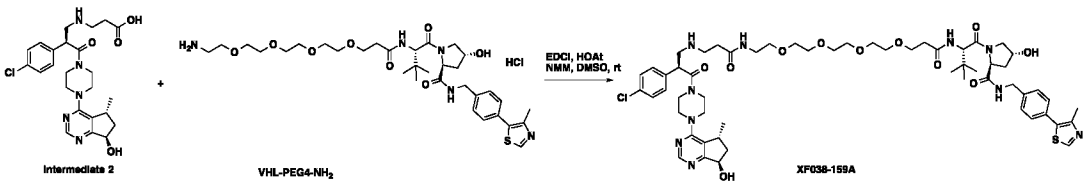
Synthesis of XF038-158A



XF038-158A was synthesized following the standard procedure for preparing XF038-157A from intermediate 2 (12 mg, 0.02 mmol), VHL-PEG2-NH_2 (12.3 mg, 0.02 mmol, 1.0 equiv), EDCI (5.8 mg, 0.03 mmol, 1.5 equiv), HOAt (4.1 mg, 0.03 mmol, 1.5 equiv), and NMM (6.1 mg, 0.06 mmol, 3.0 equiv) in DMSO (1 mL). XF038-158A was obtained as white solid in TFA salt form (9.4 mg, 45%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.95 (s, 1H), 8.57 (s, 1H), 7.53 – 7.37 (m, 6H), 7.34 (dd, J = 8.5, 2.1 Hz, 2H), 5.31 (t, J = 7.9 Hz, 1H), 4.75 (s, 1H), 4.63 – 4.45 (m, 4H), 4.40 (d, J = 15.5 Hz, 1H), 4.17 (s, 1H), 4.03 (d, J = 2.0 Hz, 2H), 3.96 – 3.79 (m, 6H), 3.74 – 3.47 (m, 13H), 3.39 (t, J = 9.5 Hz, 1H), 3.28 – 3.22 (m, 3H), 2.68 (t, J = 6.3 Hz, 1H), 2.47 (s, 3H), 2.32 – 2.24 (m, 2H), 2.17 (dt, J = 12.7, 8.1 Hz, 1H), 2.08 (ddd, J = 13.5, 9.6, 4.3 Hz, 1H), 1.17 (dd, J = 7.0, 2.0 Hz, 3H), 1.04 (s, 9H). HRMS (m/z) for $C_{52}H_{70}ClN_{10}O_9S^+$ $[M + H]^+$: molecular weight calculated 1045.4731, found 1045.4738.

Example 4

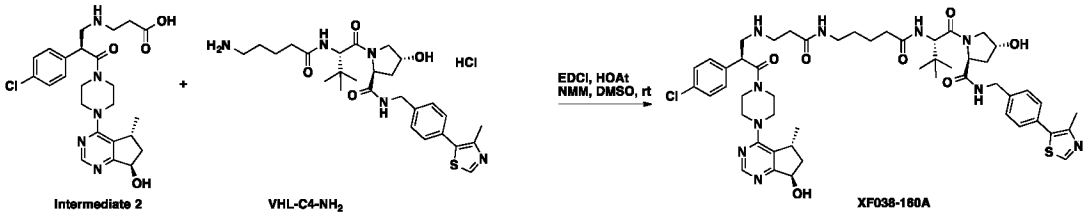
Synthesis of XF038-159A



XF038-159A was synthesized following the standard procedure for preparing XF038-157A from intermediate 2 (12 mg, 0.02 mmol), VHL-PEG4-NH_2 (14.3 mg, 0.02 mmol, 1.0 equiv), EDCI (5.8 mg, 0.03 mmol, 1.5 equiv), HOAt (4.1 mg, 0.03 mmol, 1.5 equiv), and NMM (6.1 mg, 0.06 mmol, 3.0 equiv) in DMSO (1 mL). XF038-159A was obtained as white solid in TFA salt form (11.2 mg, 48%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.95 (s, 1H), 8.58 (s, 1H), 7.54 – 7.39 (m, 6H), 7.39 – 7.28 (m, 2H), 5.31 (t, J = 8.0 Hz, 1H), 4.65 (s, 1H), 4.60 – 4.47 (m, 4H), 4.36 (d, J = 15.5 Hz, 1H), 4.18 (s, 1H), 3.98 – 3.77 (m, 6H), 3.76 – 3.57 (m, 19H), 3.53 (t, J = 5.4 Hz, 2H), 3.44 – 3.33 (m, 4H), 3.29 – 3.23 (m, 2H), 2.67 (t, J = 6.3 Hz, 2H), 2.58 (ddd, J = 15.0, 7.5, 5.2 Hz, 1H), 2.48 (s, 3H), 2.33 – 2.26 (m, 1H), 2.25 – 2.15 (m, 2H), 2.12 – 2.04 (m, 1H), 1.17 (d, J = 6.9 Hz, 3H), 1.04 (s, 9H). HRMS (m/z) for $C_{57}H_{80}ClN_{10}O_{11}S^+$ [M + H]$^+$: molecular weight calculated 1147.5412, found 1147.5412.

Example 5

Synthesis of XF038-160A

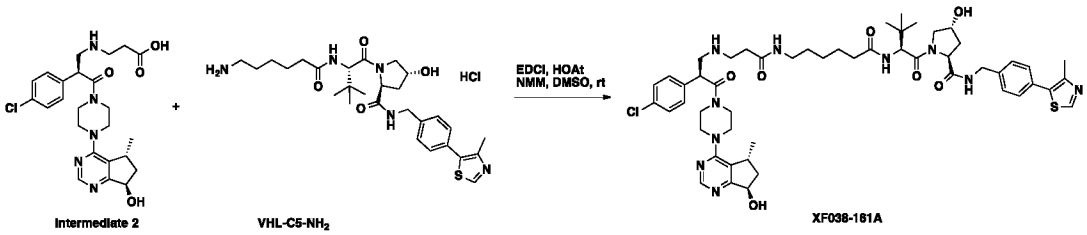


Intermediate 2 VHL-C4-NH_2 XF038-160A

XF038-160A was synthesized following the standard procedure for preparing XF038-157A from intermediate 2 (12 mg, 0.02 mmol), VHL-C4-NH_2 (11.3 mg, 0.02 mmol, 1.0 equiv), EDCI (5.8 mg, 0.03 mmol, 1.5 equiv), HOAt (4.1 mg, 0.03 mmol, 1.5 equiv), and NMM (6.1 mg, 0.06 mmol, 3.0 equiv) in DMSO (1 mL). XF038-160A was obtained as white solid in TFA salt form (7.6 mg, 38%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.93 (s, 1H), 8.57 (s, 1H), 7.51 – 7.39 (m, 6H), 7.39 – 7.32 (m, 2H), 5.31 (t, J = 7.9 Hz, 1H), 4.62 (s, 1H), 4.59 – 4.48 (m, 4H), 4.36 (d, J = 15.4 Hz, 1H), 4.18 (s, 1H), 3.96 – 3.86 (m, 4H), 3.81 (dt, J = 10.9, 6.1 Hz, 2H), 3.70 – 3.60 (m, 5H), 3.40 (t, J = 8.9 Hz, 1H), 3.27 (dd, J = 12.6, 3.8 Hz, 2H), 3.22 – 3.16 (m, 2H), 2.67 – 2.63 (m, 2H), 2.47 (s, 3H), 2.33 – 2.26 (m, 3H), 2.23 – 2.16 (m, 2H), 2.08 (ddd, J = 13.3, 9.1, 4.5 Hz, 1H), 1.65 – 1.57 (m, 2H), 1.51 (t, J = 7.4 Hz, 2H), 1.17 (d, J = 7.3 Hz, 3H), 1.03 (s, 9H). HRMS (m/z) for $C_{51}H_{68}ClN_{10}O_7S^+$ [M + H]$^+$: molecular weight calculated 999.4676, found 999.4678.

Example 6

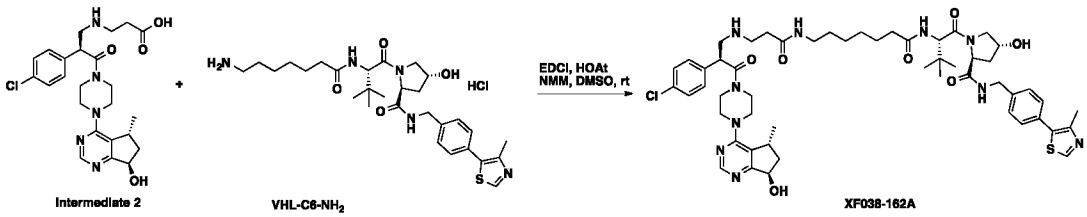
Synthesis of XF038-161A



XF038-161A was synthesized following the standard procedure for preparing XF038-157A from intermediate 2 (12 mg, 0.02 mmol), VHL-C5-NH_2 (11.6 mg, 0.02 mmol, 1.0 equiv), EDCI (5.8 mg, 0.03 mmol, 1.5 equiv), HOAt (4.1 mg, 0.03 mmol, 1.5 equiv), and NMM (6.1 mg, 0.06 mmol, 3.0 equiv) in DMSO (1 mL). XF038-161A was obtained as white solid in TFA salt form (12.7 mg, 63%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.97 (s, 1H), 8.58 (d, J = 4.4 Hz, 1H), 7.54 – 7.38 (m, 6H), 7.38 – 7.32 (m, 2H), 5.31 (t, J = 8.0 Hz, 1H), 4.63 (s, 1H), 4.60 – 4.47 (m, 4H), 4.37 (d, J = 15.4 Hz, 1H), 4.18 (s, 1H), 3.97 – 3.78 (m, 6H), 3.72 – 3.54 (m, 5H), 3.40 (dd, J = 10.8, 7.1 Hz, 1H), 3.29 – 3.24 (m, 2H), 3.18 (t, J = 7.1 Hz, 2H), 2.67 – 2.61 (m, 2H), 2.48 (s, 3H), 2.34 – 2.14 (m, 5H), 2.08 (ddd, J = 13.3, 9.2, 4.5 Hz, 1H), 1.66 – 1.57 (m, 2H), 1.50 (q, J = 7.3 Hz, 2H), 1.38 – 1.30 (m, 2H), 1.17 (d, J = 7.1 Hz, 3H), 1.03 (s, 9H). HRMS (m/z) for $C_{52}H_{70}ClN_{10}O_7S^+$ $[M + H]^+$: molecular weight calculated 1013.4833, found 1013.4847.

Example 7

Synthesis of XF038-162A

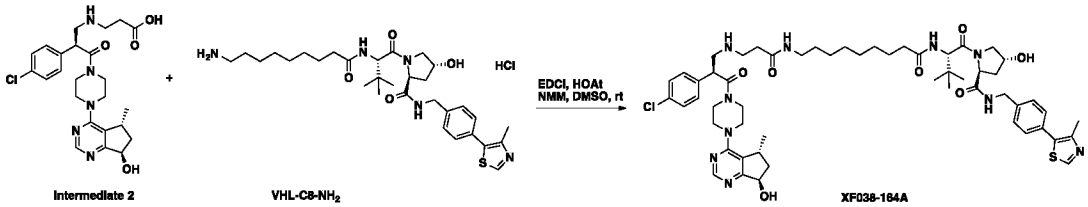


XF038-162A was synthesized following the standard procedure for preparing XF038-157A from intermediate 2 (12 mg, 0.02 mmol), VHL-C6-NH_2 (11.9 mg, 0.02 mmol, 1.0 equiv), EDCI (5.8 mg, 0.03 mmol, 1.5 equiv), HOAt (4.1 mg, 0.03 mmol, 1.5 equiv), and NMM (6.1 mg, 0.06 mmol, 3.0 equiv) in DMSO (1 mL). XF038-162A was obtained as white solid in TFA salt form (8.6 mg, 42%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.95 (s, 1H), 8.58 (s, 1H), 7.54 – 7.38 (m, 6H), 7.36 (t, J = 6.6 Hz, 2H), 5.38 – 5.26 (m, 1H), 4.64 (s, 1H), 4.61 – 4.48 (m, 4H), 4.37 (d, J

= 15.6 Hz, 1H), 4.18 (s, 1H), 3.86 (dd, *J* = 58.9, 15.4 Hz, 6H), 3.73 – 3.53 (m, 5H), 3.41 (s, 1H), 3.27 (d, *J* = 6.0 Hz, 2H), 3.23 – 3.10 (m, 2H), 2.72 – 2.57 (m, 2H), 2.48 (s, 3H), 2.33 – 2.17 (m, 5H), 2.10 (s, 1H), 1.66 – 1.58 (m, 2H), 1.53 – 1.46 (m, 2H), 1.39 – 1.31 (m, 4H), 1.17 (d, *J* = 7.5 Hz, 3H), 1.03 (s, 9H). HRMS (m/z) for $C_{53}H_{72}ClN_{10}O_7S^+$ $[M + H]^+$: molecular weight calculated 1027.4989, found 1027.4983.

Example 8

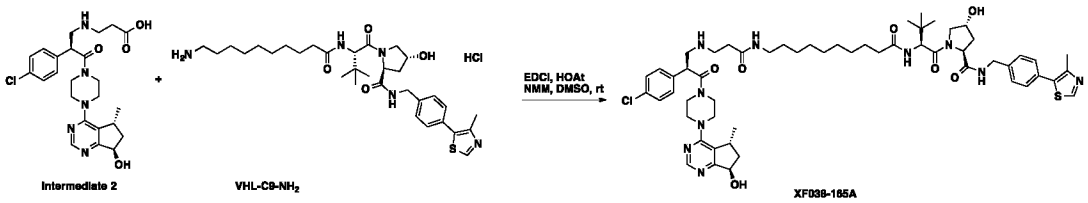
Synthesis of XF038-164A



XF038-164A was synthesized following the standard procedure for preparing XF038-157A from intermediate 2 (12 mg, 0.02 mmol), VHL-C8-NH_2 (12.4 mg, 0.02 mmol, 1.0 equiv), EDCI (5.8 mg, 0.03 mmol, 1.5 equiv), HOAt (4.1 mg, 0.03 mmol, 1.5 equiv), and NMM (6.1 mg, 0.06 mmol, 3.0 equiv) in DMSO (1 mL). XF038-164A was obtained as white solid in TFA salt form (9.9 mg, 47%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.96 (s, 1H), 8.58 (d, *J* = 3.7 Hz, 1H), 7.55 – 7.39 (m, 6H), 7.39 – 7.32 (m, 2H), 5.31 (t, *J* = 8.0 Hz, 1H), 4.63 (s, 1H), 4.60 – 4.48 (m, 4H), 4.36 (d, *J* = 15.5 Hz, 1H), 4.18 (s, 1H), 3.97 – 3.78 (m, 6H), 3.73 – 3.60 (m, 5H), 3.40 (t, *J* = 8.9 Hz, 1H), 3.29 – 3.23 (m, 2H), 3.17 (dd, *J* = 7.8, 6.3 Hz, 2H), 2.67 – 2.61 (m, 2H), 2.48 (s, 3H), 2.34 – 2.14 (m, 5H), 2.08 (s, 1H), 1.59 (d, *J* = 7.0 Hz, 2H), 1.48 (d, *J* = 7.1 Hz, 2H), 1.35 – 1.29 (m, 8H), 1.18 (d, *J* = 7.0 Hz, 3H), 1.03 (s, 9H). HRMS (m/z) for $C_{55}H_{76}ClN_{10}O_7S^+$ $[M + H]^+$: molecular weight calculated 1055.5302, found 1055.5303.

Example 9

Synthesis of XF038-165A

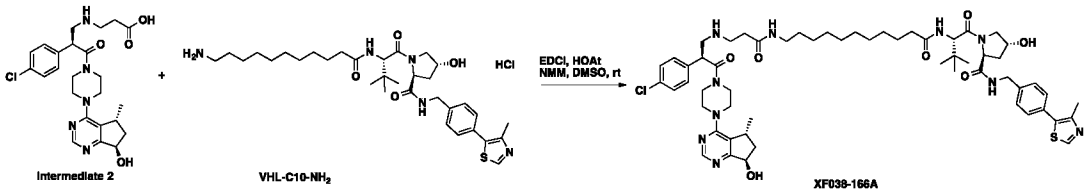


XF038-165A was synthesized following the standard procedure for preparing XF038-157A from intermediate 2 (12 mg, 0.02 mmol), VHL-C9-NH_2 (12.7 mg, 0.02 mmol, 1.0 equiv), EDCI (5.8 mg, 0.03 mmol, 1.5 equiv), HOAt (4.1 mg, 0.03 mmol, 1.5 equiv), and NMM (6.1 mg,

0.06 mmol, 3.0 equiv) in DMSO (1 mL). XF038-165A was obtained as white solid in TFA salt form (2.8 mg, 13%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.93 (s, 1H), 8.58 (s, 1H), 7.44 (d, J = 25.3 Hz, 6H), 7.36 (d, J = 8.5 Hz, 2H), 5.31 (d, J = 8.2 Hz, 1H), 4.63 (s, 1H), 4.61 – 4.43 (m, 4H), 4.36 (d, J = 15.3 Hz, 1H), 4.19 (s, 1H), 4.03 – 3.78 (m, 6H), 3.76 – 3.56 (m, 5H), 3.49 – 3.39 (m, 1H), 3.17 (d, J = 7.7 Hz, 2H), 3.03 – 2.95 (m, 1H), 2.91 – 2.83 (m, 1H), 2.65 (d, J = 8.9 Hz, 2H), 2.47 (s, 3H), 2.36 – 2.14 (m, 5H), 2.13 – 2.06 (m, 1H), 1.69 – 1.56 (m, 2H), 1.56 – 1.46 (m, 2H), 1.41 – 1.25 (m, 10H), 1.18 (d, J = 7.0 Hz, 3H), 1.04 (s, 9H). HRMS (m/z) for $C_{56}H_{78}ClN_{10}O_7S^+$ $[M + H]^+$: molecular weight calculated 1069.5459, found 1069.5464.

Example 10

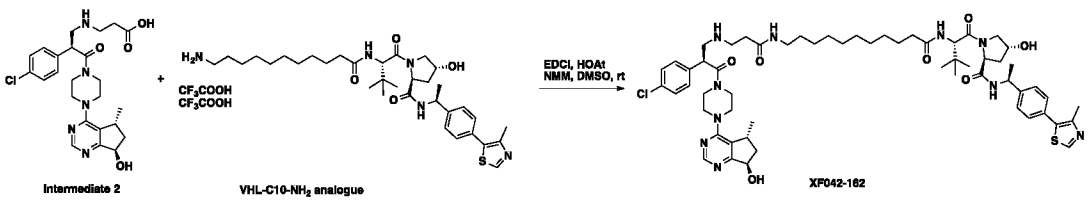
Synthesis of XF038-166A



XF038-166A was synthesized following the standard procedure for preparing XF038-157A from intermediate 2 (12 mg, 0.02 mmol), VHL-C10-NH_2 (13.0 mg, 0.02 mmol, 1.0 equiv), EDCI (5.8 mg, 0.03 mmol, 1.5 equiv), HOAt (4.1 mg, 0.03 mmol, 1.5 equiv), and NMM) (6.1 mg, 0.06 mmol, 3.0 equiv) in DMSO (1 mL). XF038-166A was obtained as white solid in TFA salt form (11.3 mg, 52%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.96 (s, 1H), 8.58 (d, J = 3.9 Hz, 1H), 7.53 – 7.38 (m, 6H), 7.38 – 7.28 (m, 2H), 5.31 (t, J = 8.0 Hz, 1H), 4.63 (s, 1H), 4.60 – 4.44 (m, 4H), 4.36 (d, J = 15.5 Hz, 1H), 4.18 (s, 1H), 3.97 – 3.78 (m, 6H), 3.72 – 3.59 (m, 5H), 3.45 – 3.36 (m, 1H), 3.29 – 3.24 (m, 2H), 3.17 (t, J = 7.1 Hz, 2H), 2.67 – 2.62 (m, 2H), 2.48 (s, 3H), 2.34 – 2.16 (m, 5H), 2.12 – 2.04 (m, 1H), 1.60 (dt, J = 15.2, 7.4 Hz, 2H), 1.49 (t, J = 7.0 Hz, 2H), 1.36 – 1.26 (m, 12H), 1.18 (d, J = 6.9 Hz, 3H), 1.03 (s, 9H). HRMS (m/z) for $C_{57}H_{80}ClN_{10}O_7S^+$ $[M + H]^+$: molecular weight calculated 1083.5615, found 1083.5617.

Example 11

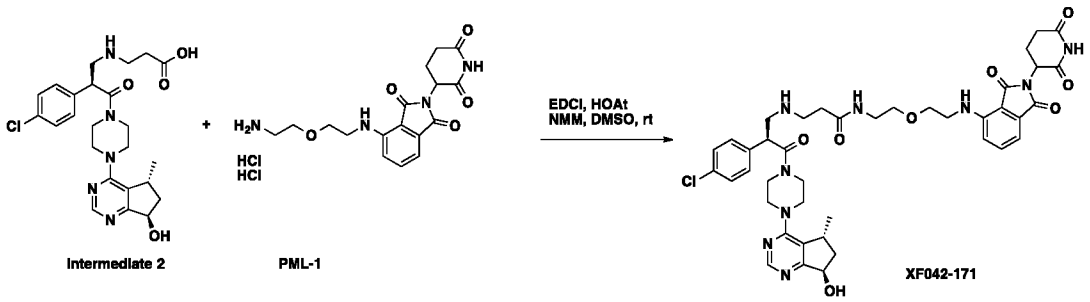
Synthesis of XF042-162



XF042-162 was synthesized following the standard procedure for preparing XF038-157A from intermediate 2 (6.01 mg, 0.01 mmol), VHL-C10-NH_2 analog (7.4 mg, 0.01 mmol, 1.0 equiv), EDCI (2.9 mg, 0.015 mmol, 1.5 equiv), HOAt (2.1 mg, 0.015 mmol, 1.5 equiv), and NMM (3.1 mg, 0.03 mmol, 3.0 equiv) in DMSO (1 mL). XF042-162 was obtained as white solid in TFA salt form (6.5 mg, 59%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.87 (s, 1H), 8.52 (s, 1H), 7.43 (dt, *J* = 15.8, 8.5 Hz, 6H), 7.37 (dd, *J* = 8.6, 6.8 Hz, 2H), 5.19 (t, *J* = 7.5 Hz, 1H), 5.00 (q, *J* = 7.0 Hz, 1H), 4.62 (s, 1H), 4.59 – 4.50 (m, 2H), 4.43 (s, 1H), 4.13 – 4.03 (m, 1H), 4.02 – 3.90 (m, 1H), 3.91 – 3.70 (m, 7H), 3.62 (t, *J* = 11.0 Hz, 4H), 3.59 – 3.51 (m, 1H), 3.43 – 3.37 (m, 1H), 3.26 (dd, *J* = 12.6, 3.9 Hz, 1H), 3.17 (t, *J* = 7.2 Hz, 2H), 2.65 (t, *J* = 6.0 Hz, 2H), 2.47 (s, 3H), 2.29 (td, *J* = 16.3, 15.4, 8.2 Hz, 1H), 2.26 – 2.14 (m, 3H), 1.95 (ddd, *J* = 13.3, 9.1, 4.5 Hz, 1H), 1.50 (d, *J* = 7.0 Hz, 3H), 1.31 (s, 16H), 1.15 (d, *J* = 7.0 Hz, 3H), 1.04 (s, 9H). HRMS (m/z) for $C_{58}H_{82}ClN_{10}O_7S^+$ $[M + H]^+$: molecular weight calculated 1097.5772, found 1083.5767.

Example 12

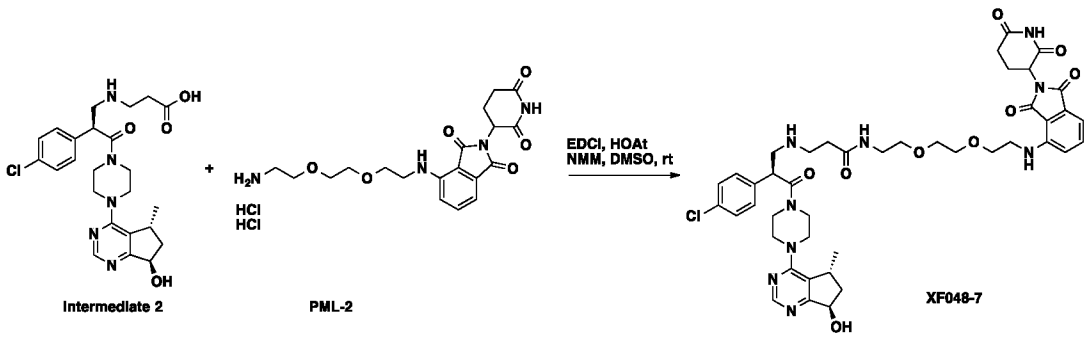
Synthesis of XF042-171



XF042-171 was synthesized following the standard procedure for preparing XF038-157A from intermediate 2 (6.0 mg, 0.01 mmol), PML-1 (4.8 mg, 0.01 mmol, 1.0 equiv), EDCI (2.0 mg, 0.015 mmol, 1.5 equiv), HOAt (2.0 mg, 0.015 mmol, 1.5 equiv), and NMM (3.0 mg, 0.03 mmol, 3.0 equiv) in DMSO (1 mL). XF042-171 was obtained as yellow solid in TFA salt form (2.1 mg, 25%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.56 (s, 1H), 7.57 (t, *J* = 8.4 Hz, 1H), 7.43 (d, *J* = 6.5 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 7.16 – 6.96 (m, 2H), 5.29 (t, *J* = 7.8 Hz, 1H), 5.07 (d, *J* = 12.1 Hz, 1H), 4.49 (s, 1H), 4.22 – 3.93 (m, 3H), 3.92 – 3.75 (m, 4H), 3.71 (s, 2H), 3.67 – 3.53 (m, 5H), 3.50 (s, 2H), 3.46 – 3.33 (m, 3H), 3.27 – 3.14 (m, 2H), 2.87 (t, *J* = 14.8 Hz, 1H), 2.79 – 2.62 (m, 4H), 2.31 – 2.22 (m, 1H), 2.22 – 2.05 (m, 2H), 1.16 (d, *J* = 6.9 Hz, 3H). HRMS (m/z) for $C_{41}H_{49}ClN_9O_8^+$ $[M + H]^+$: molecular weight calculated 830.3387, found 830.3385.

Example 13

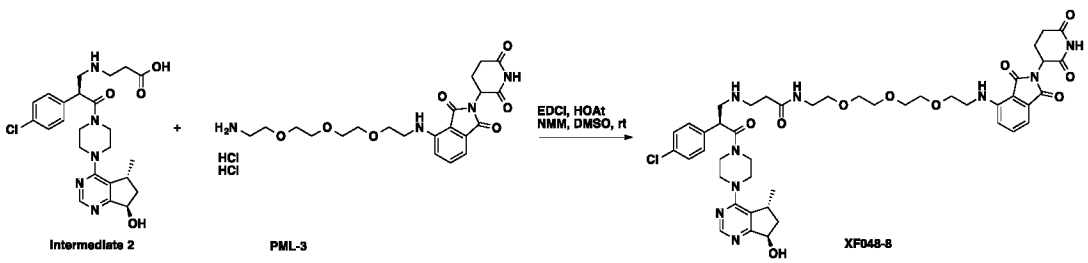
Synthesis of XF048-7



XF048-7 was synthesized following the standard procedure for preparing XF038-157A from intermediate 2 (6.0 mg, 0.01 mmol), PML-2 (5.0 mg, 0.01 mmol, 1.0 equiv), EDCI (3.0 mg, 0.015 mmol, 1.5 equiv), HOAt (2.0 mg, 0.015 mmol, 1.5 equiv), and NMM (3.0 mg, 0.03 mmol, 3.0 equiv) in DMSO (1 mL). XF048-7 was obtained as yellow solid in TFA salt form (5.8 mg, 64%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.57 (s, 1H), 7.59 – 7.53 (m, 1H), 7.45 (dd, J = 8.5, 1.8 Hz, 2H), 7.39 – 7.29 (m, 2H), 7.13 – 7.03 (m, 2H), 5.30 (t, J = 7.9 Hz, 1H), 5.07 (dd, J = 12.7, 5.5 Hz, 1H), 4.58 – 4.45 (m, 1H), 4.20 – 3.97 (m, 2H), 3.96 – 3.77 (m, 4H), 3.74 – 3.70 (m, 2H), 3.71 – 3.58 (m, 8H), 3.56 (t, J = 5.5 Hz, 2H), 3.51 (t, J = 5.2 Hz, 2H), 3.43 – 3.33 (m, 3H), 3.29 – 3.22 (m, 2H), 2.88 (ddd, J = 17.7, 13.8, 5.3 Hz, 1H), 2.80 – 2.67 (m, 2H), 2.67 – 2.60 (m, 2H), 2.28 (dd, J = 12.8, 7.5 Hz, 1H), 2.22 – 2.08 (m, 2H), 1.23 – 1.12 (m, 3H). HRMS (m/z) for $C_{43}H_{53}ClN_9O_9^+$ $[M + H]^+$: molecular weight calculated 874.3649, found 874.3650.

Example 14

Synthesis of XF048-8

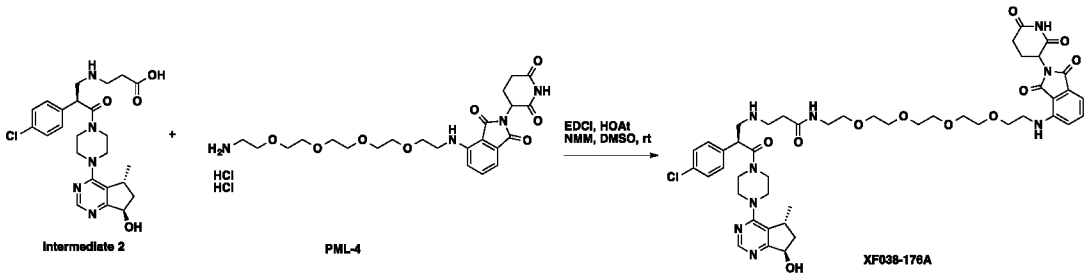


XF048-8 was synthesized following the standard procedure for preparing XF038-157A from intermediate 2 (6.1 mg, 0.01 mmol), PML-3 (5.4 mg, 0.01 mmol, 1.0 equiv), EDCI (3.0 mg, 0.015 mmol, 1.5 equiv), HOAt (2.0 mg, 0.015 mmol, 1.5 equiv), and NMM (3.0 mg, 0.03 mmol, 3.0 equiv) in DMSO (1 mL). XF048-8 was obtained as yellow solid in TFA salt form

(4.7 mg, 50%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.57 (s, 1H), 7.56 (ddd, *J* = 8.5, 7.0, 1.3 Hz, 1H), 7.49 – 7.41 (m, 2H), 7.39 – 7.29 (m, 2H), 7.15 – 6.99 (m, 2H), 5.30 (t, *J* = 7.9 Hz, 1H), 5.07 (dd, *J* = 12.9, 5.4 Hz, 1H), 4.56 – 4.48 (m, 1H), 4.16 (s, 1H), 4.05 (s, 1H), 3.95 – 3.78 (m, 4H), 3.72 (t, *J* = 5.1 Hz, 2H), 3.70 – 3.55 (m, 12H), 3.56 – 3.48 (m, 4H), 3.43 – 3.37 (m, 1H), 3.35 (q, *J* = 3.9, 2.6 Hz, 2H), 3.29 – 3.20 (m, 2H), 2.92 – 2.83 (m, 1H), 2.80 – 2.68 (m, 2H), 2.68 – 2.61 (m, 2H), 2.29 (dd, *J* = 12.8, 7.5 Hz, 1H), 2.21 – 2.09 (m, 2H), 1.17 (d, *J* = 7.0 Hz, 3H). HRMS (m/z) for $C_{45}H_{57}ClN_9O_{10}^+$ $[M + H]^+$: molecular weight calculated 918.3911, found 918.3916.

Example 15

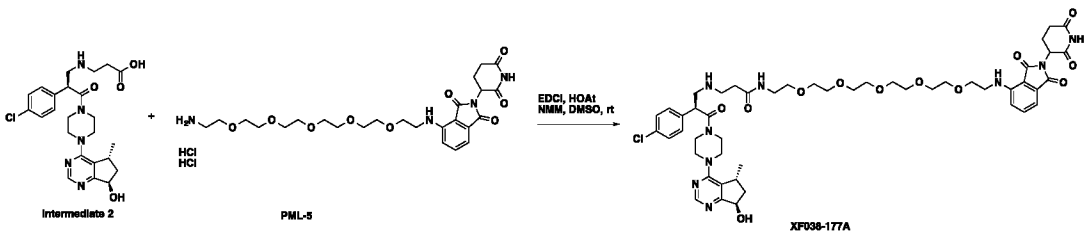
Synthesis of XF038-176A



XF038-176A was synthesized following the standard procedure for preparing XF038-157A from intermediate 2 (9.9 mg, 0.0165 mmol), PML-4 (9.3 mg, 0.0165 mmol, 1.0 equiv), EDCI (4.8 mg, 0.025 mmol, 1.5 equiv), HOAt (3.4 mg, 0.025 mmol, 1.5 equiv), and NMM (5.1 mg, 0.05 mmol, 3.0 equiv) in DMSO (1 mL). XF038-176A was obtained as yellow solid in TFA salt form (3.5 mg, 22%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.57 (s, 1H), 7.56 (tt, *J* = 9.9, 7.1, 2.8 Hz, 1H), 7.49 – 7.41 (m, 1H), 7.37 – 7.24 (m, 3H), 7.10 (d, *J* = 8.6 Hz, 1H), 7.06 (d, *J* = 7.1 Hz, 1H), 5.29 (s, 1H), 5.13 – 5.00 (m, 1H), 4.58 – 4.42 (m, 1H), 4.16 (s, 1H), 4.03 (s, 1H), 3.95 – 3.74 (m, 4H), 3.72 (t, *J* = 5.2 Hz, 2H), 3.70 – 3.54 (m, 14H), 3.52 (dq, *J* = 10.3, 5.4 Hz, 4H), 3.44 – 3.32 (m, 4H), 3.30 – 3.22 (m, 3H), 2.93 – 2.80 (m, 1H), 2.79 – 2.68 (m, 2H), 2.68 – 2.59 (m, 2H), 2.34 – 2.25 (m, 1H), 2.22 – 2.08 (m, 2H), 1.17 (d, *J* = 7.0 Hz, 3H). HRMS (m/z) for $C_{47}H_{61}ClN_9O_{11}^+$ $[M + H]^+$: molecular weight calculated 962.4174, found 962.4167.

Example 16

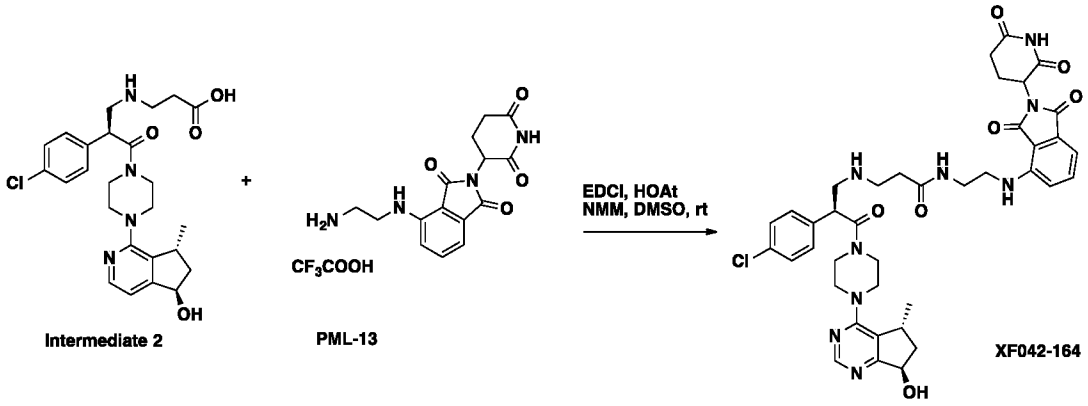
Synthesis of XF038-177A



XF038-177A was synthesized following the standard procedure for preparing XF038-157A from intermediate 2 (9.9 mg, 0.0165 mmol), PML-5 (10.0 mg, 0.0165 mmol, 1.0 equiv), EDCI (4.8 mg, 0.025 mmol, 1.5 equiv), HOAt (3.4 mg, 0.025 mmol, 1.5 equiv), and NMM (5.1 mg, 0.05 mmol, 3.0 equiv) in DMSO (1 mL). XF038-177A was obtained as yellow solid in TFA salt form (5.0 mg, 30%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.58 (d, J = 3.6 Hz, 1H), 7.56 (dd, J = 8.6, 7.0 Hz, 1H), 7.49 – 7.42 (m, 1H), 7.39 – 7.22 (m, 3H), 7.10 (d, J = 8.5 Hz, 1H), 7.05 (d, J = 7.1 Hz, 1H), 5.30 (t, J = 8.0 Hz, 1H), 5.07 (ddd, J = 12.9, 5.5, 2.1 Hz, 1H), 4.56 – 4.44 (m, 1H), 4.16 (s, 1H), 4.11 – 3.97 (m, 1H), 3.96 – 3.77 (m, 4H), 3.72 (t, J = 5.2 Hz, 2H), 3.70 – 3.55 (m, 18H), 3.52 (dq, J = 14.4, 5.3 Hz, 4H), 3.43 – 3.32 (m, 4H), 3.30 – 3.22 (m, 3H), 2.94 – 2.82 (m, 1H), 2.79 – 2.69 (m, 2H), 2.67 (dd, J = 10.2, 4.0 Hz, 2H), 2.34 – 2.23 (m, 1H), 2.22 – 2.06 (m, 2H), 1.17 (d, J = 7.0 Hz, 3H). HRMS (m/z) for $C_{49}H_{65}ClN_9O_{12}^+$ [M + H]$^+$: molecular weight calculated 1006.4436, found 1006.4449.

Example 17

Synthesis of XF042-164

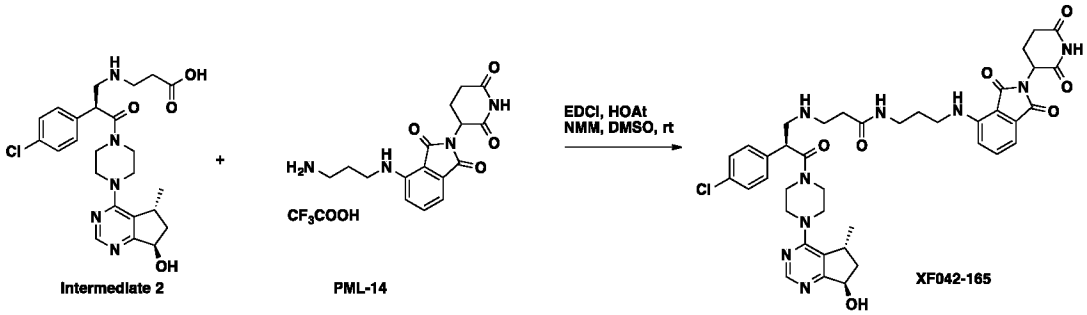


XF042-164 was synthesized following the standard procedure for preparing XF038-157A from intermediate 2 (6.1 mg, 0.01 mmol), PML-13 (4.3 mg, 0.01 mmol, 1.0 equiv), EDCI (2.9 mg, 0.015 mmol, 1.5 equiv), HOAt (2.0 mg, 0.015 mmol, 1.5 equiv), and NMM (3.0 mg, 0.03 mmol, 3.0 equiv) in DMSO (1 mL). XF042-164 was obtained as yellow solid in TFA salt form

(5.8 mg, 74%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.55 (s, 1H), 7.62 – 7.54 (m, 1H), 7.39 (ddd, *J* = 46.1, 8.2, 3.3 Hz, 4H), 7.13 (d, *J* = 8.6 Hz, 1H), 7.05 (dd, *J* = 7.0, 2.3 Hz, 1H), 5.26 (t, *J* = 7.7 Hz, 1H), 5.08 (dt, *J* = 12.3, 5.9 Hz, 1H), 4.57 (d, *J* = 9.1 Hz, 1H), 4.06 (s, 2H), 3.85 (t, *J* = 14.7 Hz, 3H), 3.76 – 3.56 (m, 4H), 3.56 – 3.40 (m, 4H), 3.39 – 3.32 (m, 2H), 3.29 – 3.24 (m, 2H), 2.92 – 2.79 (m, 1H), 2.73 (t, *J* = 18.1 Hz, 2H), 2.66 (t, *J* = 5.6 Hz, 2H), 2.25 (t, *J* = 10.2 Hz, 1H), 2.20 – 2.08 (m, 2H), 1.14 (dd, *J* = 7.0, 1.7 Hz, 3H). HRMS (m/z) for $C_{39}H_{45}ClN_9O_7^+$ $[M + H]^+$: molecular weight calculated 786.3125, found 786.3130.

Example 18

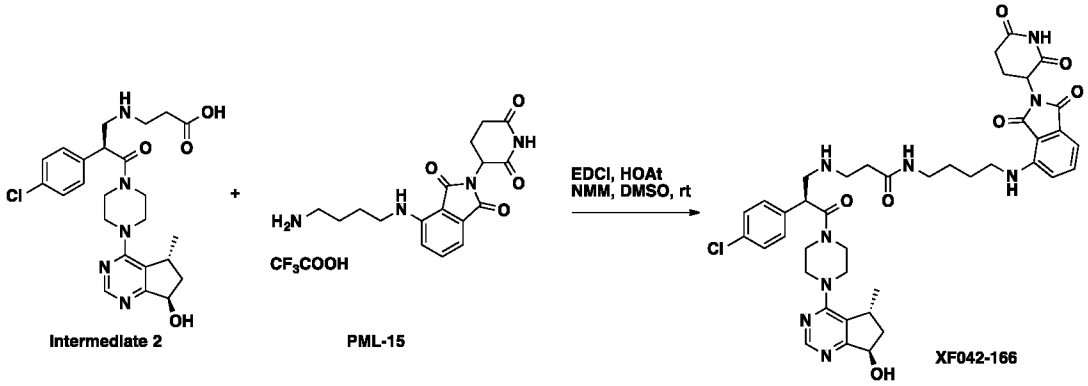
Synthesis of XF042-165



XF042-165 was synthesized following the standard procedure for preparing XF038-157A from intermediate 2 (6.1 mg, 0.01 mmol), PML-14 (4.4 mg, 0.01 mmol, 1.0 equiv), EDCI (2.9 mg, 0.015 mmol, 1.5 equiv), HOAt (2.0 mg, 0.015 mmol, 1.5 equiv), and NMM (3.0 mg, 0.03 mmol, 3.0 equiv) in DMSO (1 mL). XF042-165 was obtained as yellow solid in TFA salt form (7.8 mg, 97%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.51 (s, 1H), 7.55 (q, *J* = 7.0, 6.6 Hz, 1H), 7.44 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 2H), 7.05 (td, *J* = 8.0, 6.9, 3.6 Hz, 2H), 5.20 (t, *J* = 7.6 Hz, 1H), 5.13 – 5.02 (m, 1H), 4.61 – 4.48 (m, 1H), 4.11 – 3.89 (m, 2H), 3.90 – 3.67 (m, 4H), 3.68 – 3.46 (m, 4H), 3.41 (t, *J* = 6.5 Hz, 2H), 3.39 – 3.31 (m, 3H), 3.28 – 3.21 (m, 2H), 2.91 – 2.81 (m, 1H), 2.81 – 2.55 (m, 4H), 2.28 – 2.02 (m, 3H), 1.85 (t, *J* = 6.6 Hz, 2H), 1.11 (d, *J* = 7.0 Hz, 3H). HRMS (m/z) for $C_{40}H_{47}ClN_9O_7^+$ $[M + H]^+$: molecular weight calculated 800.3281, found 800.3284.

Example 19

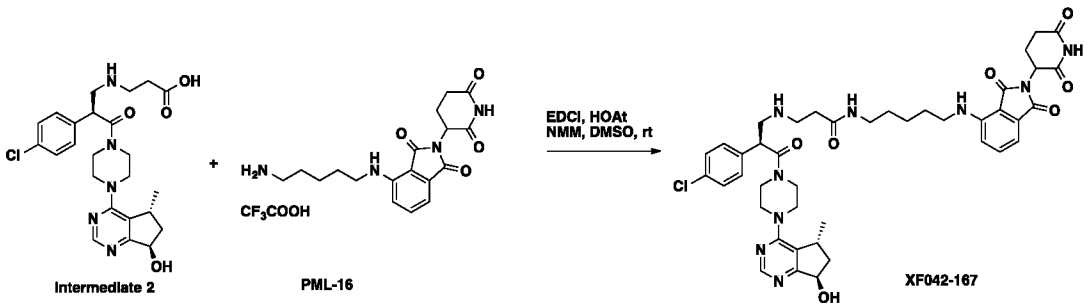
Synthesis of XF042-166



XF042-166 was synthesized following the standard procedure for preparing XF038-157A from intermediate 2 (6.1 mg, 0.01 mmol), PML-15 (4.6 mg, 0.01 mmol, 1.0 equiv), EDCI (2.9 mg, 0.015 mmol, 1.5 equiv), HOAt (2.0 mg, 0.015 mmol, 1.5 equiv), and NMM (3.0 mg, 0.03 mmol, 3.0 equiv) in DMSO (1 mL). XF042-166 was obtained as yellow solid in TFA salt form (5.7 mg, 70%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.53 (s, 1H), 7.56 (t, J = 7.8 Hz, 1H), 7.44 (d, J = 8.4 Hz, 2H), 7.35 (dd, J = 8.4, 4.1 Hz, 2H), 7.05 (t, J = 9.5 Hz, 2H), 5.23 (s, 1H), 5.10 – 5.02 (m, 1H), 4.52 (s, 1H), 4.07 (d, J = 11.6 Hz, 1H), 4.03 – 3.89 (m, 1H), 3.89 – 3.71 (m, 4H), 3.71 – 3.50 (m, 4H), 3.42 – 3.33 (m, 3H), 3.26 (d, J = 15.5 Hz, 4H), 2.91 – 2.80 (m, 1H), 2.80 – 2.56 (m, 4H), 2.30 – 2.02 (m, 3H), 1.79 – 1.55 (m, 4H), 1.14 (d, J = 6.8 Hz, 3H). HRMS (m/z) for $C_{41}H_{49}ClN_9O_7^+$ $[M + H]^+$: molecular weight calculated 814.3438, found 814.3443.

Example 20

Synthesis of XF042-167

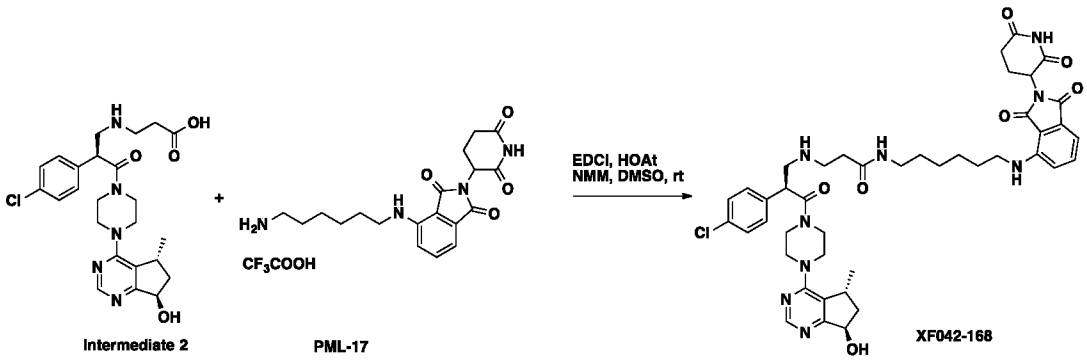


XF042-167 was synthesized following the standard procedure for preparing XF038-157A from intermediate 2 (6.1 mg, 0.01 mmol), PML-16 (4.7 mg, 0.01 mmol, 1.0 equiv), EDCI (2.9 mg, 0.015 mmol, 1.5 equiv), HOAt (2.0 mg, 0.015 mmol, 1.5 equiv), and NMM (3.0 mg, 0.03 mmol, 3.0 equiv) in DMSO (1 mL). XF042-167 was obtained as yellow solid in TFA salt form (4.7 mg, 57%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.54 (s, 1H), 7.55 (t, J = 7.8 Hz, 1H), 7.44 (d,

J = 8.1 Hz, 2H), 7.35 (dd, J = 8.4, 2.8 Hz, 2H), 7.04 (t, J = 7.8 Hz, 2H), 5.25 (s, 1H), 5.13 – 5.00 (m, 1H), 4.58 – 4.45 (m, 1H), 4.16 – 3.91 (m, 2H), 3.91 – 3.72 (m, 4H), 3.70 – 3.54 (m, 4H), 3.35 (q, J = 9.8, 6.8 Hz, 4H), 3.28 – 3.17 (m, 3H), 2.91 – 2.82 (m, 1H), 2.79 – 2.68 (m, 2H), 2.65 (d, J = 6.2 Hz, 2H), 2.28 – 2.21 (m, 1H), 2.21 – 2.14 (m, 1H), 2.13 – 2.07 (m, 1H), 1.73 – 1.65 (m, 2H), 1.57 (t, J = 7.5 Hz, 2H), 1.46 (d, J = 7.7 Hz, 2H), 1.22 – 1.07 (m, 3H). HRMS (m/z) for $C_{42}H_{51}ClN_9O_7^+$ $[M + H]^+$: molecular weight calculated 828.3594, found 828.3597.

Example 21

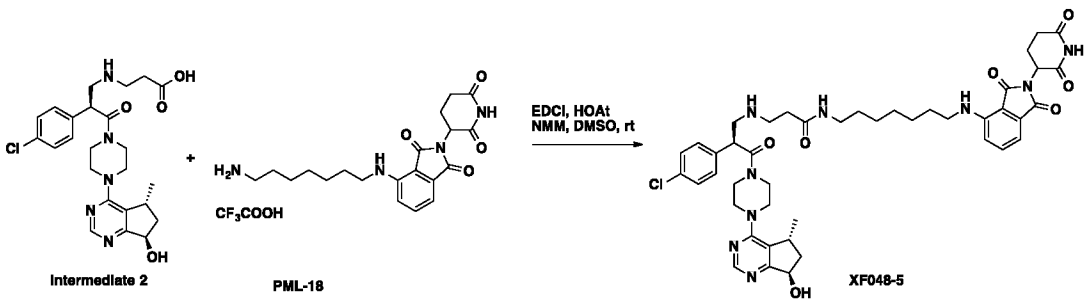
Synthesis of XF042-168



XF042-168 was synthesized following the standard procedure for preparing XF038-157A from intermediate 2 (6.1 mg, 0.01 mmol), PML-17 (4.9 mg, 0.01 mmol, 1.0 equiv), EDCI (2.9 mg, 0.015 mmol, 1.5 equiv), HOAt (2.0 mg, 0.015 mmol, 1.5 equiv), and NMM (3.0 mg, 0.03 mmol, 3.0 equiv) in DMSO (1 mL). XF042-168 was obtained as yellow solid in TFA salt form (4.7 mg, 57%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.55 (s, 1H), 7.55 (dd, J = 8.6, 7.1 Hz, 1H), 7.45 (d, J = 8.0 Hz, 2H), 7.39 – 7.27 (m, 2H), 7.04 (t, J = 7.2 Hz, 2H), 5.28 (t, J = 7.8 Hz, 1H), 5.05 (dd, J = 12.8, 5.5 Hz, 1H), 4.56 – 4.48 (m, 1H), 4.14 (s, 1H), 4.09 – 3.97 (m, 1H), 3.92 – 3.73 (m, 4H), 3.70 – 3.56 (m, 4H), 3.42 – 3.32 (m, 4H), 3.28 – 3.23 (m, 1H), 3.19 (t, J = 7.0 Hz, 2H), 2.90 – 2.81 (m, 1H), 2.77 – 2.68 (m, 2H), 2.68 – 2.60 (m, 2H), 2.27 (dd, J = 12.9, 7.4 Hz, 1H), 2.21 – 2.13 (m, 1H), 2.13 – 2.06 (m, 1H), 1.68 (p, J = 7.2 Hz, 2H), 1.53 (p, J = 7.2 Hz, 2H), 1.49 – 1.43 (m, 2H), 1.40 (d, J = 7.2 Hz, 2H), 1.16 (d, J = 7.0 Hz, 3H). HRMS (m/z) for $C_{43}H_{53}ClN_9O_7^+$ $[M + H]^+$: molecular weight calculated 842.3751, found 842.3758.

Example 22

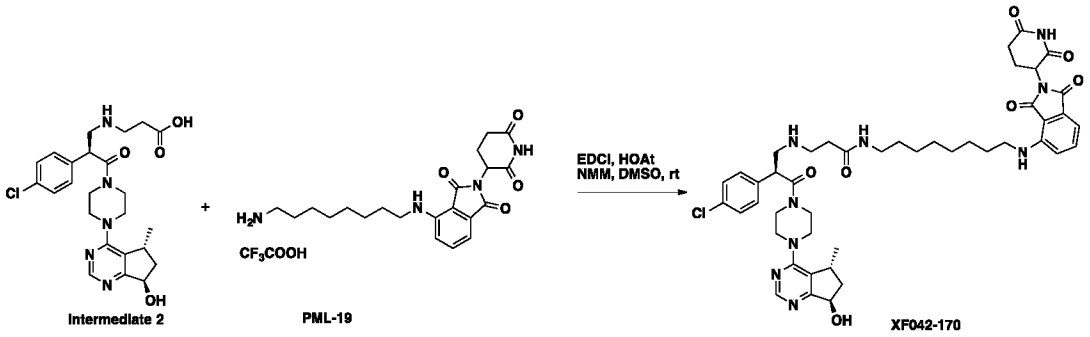
Synthesis of XF048-5



XF048-5 was synthesized following the standard procedure for preparing XF038-157A from intermediate 2 (6.1 mg, 0.01 mmol), PML-18 (5.2 mg, 0.01 mmol, 1.0 equiv), EDCI (2.9 mg, 0.015 mmol, 1.5 equiv), HOAt (2.0 mg, 0.015 mmol, 1.5 equiv), and NMM (3.0 mg, 0.03 mmol, 3.0 equiv) in DMSO (1 mL). XF048-5 was obtained as yellow solid in TFA salt form (8.8 mg, 98%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.57 (d, J = 4.4 Hz, 1H), 7.55 (dd, J = 8.6, 7.1 Hz, 1H), 7.45 (d, J = 8.4 Hz, 2H), 7.39 – 7.29 (m, 2H), 7.04 (dd, J = 7.8, 6.1 Hz, 2H), 5.30 (t, J = 7.9 Hz, 1H), 5.05 (dd, J = 12.8, 5.5 Hz, 1H), 4.52 (dt, J = 9.6, 5.0 Hz, 1H), 4.16 (s, 1H), 4.04 (d, J = 22.0 Hz, 1H), 3.97 – 3.76 (m, 4H), 3.71 – 3.58 (m, 4H), 3.40 (t, J = 8.9 Hz, 1H), 3.34 (d, J = 6.9 Hz, 2H), 3.29 – 3.25 (m, 2H), 3.18 (t, J = 6.8 Hz, 2H), 2.86 (ddd, J = 17.6, 14.0, 5.4 Hz, 1H), 2.79 – 2.67 (m, 2H), 2.63 (t, J = 6.3 Hz, 2H), 2.28 (dd, J = 12.7, 7.5 Hz, 1H), 2.17 (dt, J = 12.5, 8.1 Hz, 1H), 2.14 – 2.08 (m, 1H), 1.67 (p, J = 7.0 Hz, 2H), 1.50 (p, J = 7.2 Hz, 2H), 1.47 – 1.30 (m, 6H), 1.17 (d, J = 6.9 Hz, 3H). HRMS (m/z) for $C_{44}H_{55}ClN_9O_7^+$ [M + H]$^+$: molecular weight calculated 856.3907, found 856.3912.

Example 23

Synthesis of XF042-170

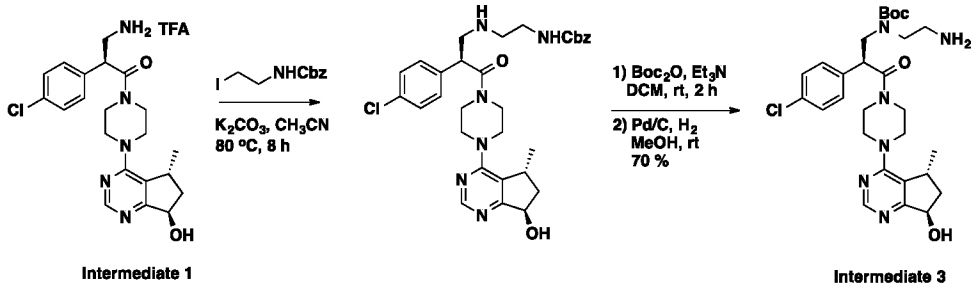


XF042-170 was synthesized following the standard procedure for preparing XF038-157A from intermediate 2 (6.1 mg, 0.01 mmol), PML-19 (5.3 mg, 0.01 mmol, 1.0 equiv), EDCI (2.9 mg, 0.015 mmol, 1.5 equiv), HOAt (2.0 mg, 0.015 mmol, 1.5 equiv), and NMM (3.0 mg, 0.03

mmol, 3.0 equiv) in DMSO (1 mL). XF042-170 was obtained as yellow solid in TFA salt form (2.8 mg, 32%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.56 (s, 1H), 7.55 (dd, J = 8.6, 7.0 Hz, 1H), 7.45 (d, J = 8.2 Hz, 2H), 7.41 – 7.29 (m, 2H), 7.04 (dd, J = 7.8, 3.6 Hz, 2H), 5.28 (t, J = 7.8 Hz, 1H), 5.05 (dd, J = 12.8, 5.5 Hz, 1H), 4.52 (dd, J = 9.3, 4.1 Hz, 1H), 4.15 (s, 1H), 4.10 – 3.97 (m, 1H), 3.94 – 3.74 (m, 4H), 3.74 – 3.50 (m, 4H), 3.44 – 3.32 (m, 4H), 3.28 – 3.24 (m, 1H), 3.17 (t, J = 7.2 Hz, 2H), 2.86 (ddd, J = 18.5, 13.8, 5.4 Hz, 1H), 2.78 – 2.67 (m, 2H), 2.63 (t, J = 6.2 Hz, 2H), 2.27 (dd, J = 12.9, 7.4 Hz, 1H), 2.21 – 2.14 (m, 1H), 2.14 – 2.06 (m, 1H), 1.67 (p, J = 7.0 Hz, 2H), 1.53 – 1.25 (m, 10H), 1.16 (d, J = 7.0 Hz, 3H). HRMS (m/z) for $C_{45}H_{57}ClN_9O_7^+$ [M + H]$^+$: molecular weight calculated 870.4064, found 870.4062.

Example 24

Synthesis of intermediate 3

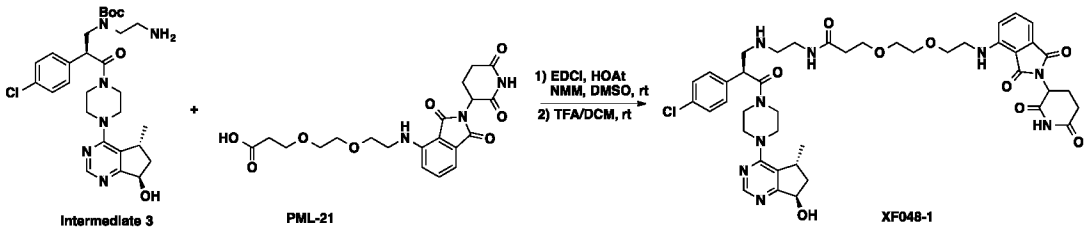


To a solution of intermediate 1 (467 mg, 1.12 mmol, 1.1 equiv) in CH_3CN was added potassium carbonate (706 mg, 5 mmol, 5 equiv). After the resulting suspension was stirred at 80 °C for 15 min, benzyl (2-iodoethyl)carbamate (305 mg, 1.0 mmol) was added. The reaction was stirred at 80 °C for 8 h, before the reaction was filtered, and the filtrate was concentrated. The resulting residue was purified by preparative HPLC to afford the desired product as white solid (201 mg, yield 30%). The white solid (201 mg, 0.34 mmol) was dissolved in DCM (5 mL). To the resulting solution was added Triethylamine (92 μL, 0.68 mmol, 2 equiv) and Di-*tert*-butyl dicarbonate (89 mg, 0.4 mmol, 1.2 equiv). The reaction was stirred at rt for 2 h, before the solvent was removed. The resulting residue was purified by silica gel column (MeOH / DCM = 1:9). The desired product was obtained (160 mg, 68% yield). After this product was dissolved in methanol (6 mL), 10% palladium on carbon was added. This reaction was stirred under H_2 for 4 h, before it was filtered. After the filtrate was concentrated, the resulting residue was purified by preparative HPLC to afford the desired product as white solid in TFA salt form (91 mg, yield 71%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.58 (d, J = 3.7 Hz, 1H), 7.44 – 7.35 (m, 2H), 7.32 (s, 2H), 5.31 (t, J = 8.0 Hz, 1H), 4.32 (s, 1H), 4.21 (s, 1H), 3.98 (d, J = 8.2 Hz, 1H), 3.85

(s, 2H), 3.79 – 3.65 (m, 6H), 3.57 (d, J = 13.4 Hz, 2H), 3.51 – 3.41 (m, 2H), 3.03 (s, 1H), 2.29 (ddd, J = 12.7, 7.3, 1.1 Hz, 1H), 2.18 (dtd, J = 10.7, 7.6, 7.0, 2.9 Hz, 1H), 1.41 (s, 9H), 1.17 (d, J = 7.0 Hz, 3H). HRMS (m/z) for $C_{28}H_{40}ClN_6O_4^+$ $[M + H]^+$: molecular weight calculated 559.2794, found 559.2792.

Example 25

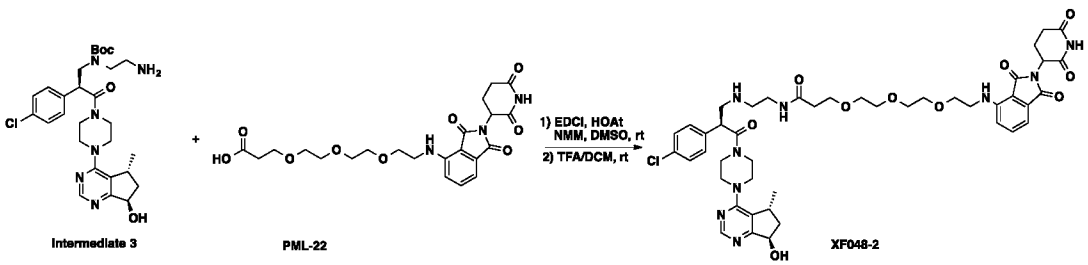
Synthesis of XF048-1



XF048-1 was synthesized following the standard procedure for preparing XF038-157A from intermediate 3 (7.8 mg, 0.012 mmol), PML-21 (5.2 mg, 0.012 mmol, 1.0 equiv), EDCI (3.5 mg, 0.018 mmol, 1.5 equiv), HOAt (2.5 mg, 0.018 mmol, 1.5 equiv), and NMM (3.6 mg, 0.036 mmol, 3.0 equiv) in DMSO (1 mL). Yellow solid in TFA salt form was obtained (8.0 mg, 68%). After this solid was dissolved in DCM (1 mL), TFA (1 mL) was added. The reaction was stirred at rt for 30 min, before the solvent was evaporated. The resulting residue was purified by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O) to afford XF048-1 as yellow solid in TFA salt form (9.6 mg, 95%). ^1H NMR (600 MHz, CD_3OD) δ 8.56 (d, J = 1.5 Hz, 1H), 7.56 (dd, J = 8.6, 7.1 Hz, 1H), 7.49 – 7.39 (m, 2H), 7.34 (dd, J = 8.5, 3.5 Hz, 2H), 7.08 (dd, J = 19.9, 7.8 Hz, 2H), 5.30 (t, J = 7.9 Hz, 1H), 5.13 – 5.00 (m, 1H), 4.47 (dd, J = 8.8, 4.3 Hz, 1H), 4.16 (s, 1H), 3.95 – 3.85 (m, 2H), 3.82 (s, 2H), 3.74 (dt, J = 15.1, 5.5 Hz, 4H), 3.67 – 3.58 (m, 8H), 3.53 – 3.44 (m, 4H), 3.44 – 3.37 (m, 1H), 3.17 (t, J = 5.7 Hz, 2H), 2.91 – 2.82 (m, 1H), 2.78 – 2.63 (m, 3H), 2.48 (t, J = 5.9 Hz, 2H), 2.28 (dd, J = 12.9, 7.4 Hz, 1H), 2.20 – 2.07 (m, 2H), 1.16 (d, J = 6.9 Hz, 3H). HRMS (m/z) for $C_{43}H_{53}ClN_9O_9^+$ $[M + H]^+$: molecular weight calculated 874.3649, found 874.3638.

Example 26

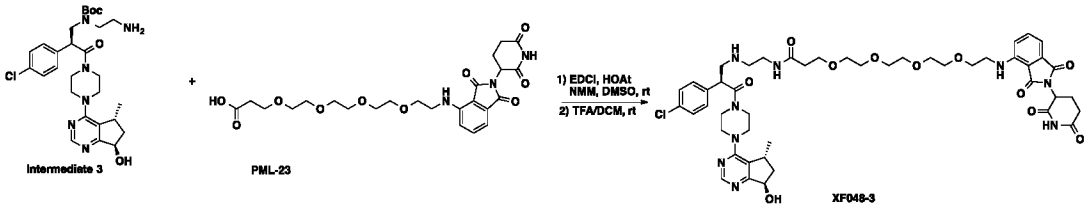
Synthesis of XF048-2



XF048-2 was synthesized following the standard procedure for preparing XF048-1 from intermediate 3 (7.8 mg, 0.012 mmol), PML-22 (5.7 mg, 0.012 mmol, 1.0 equiv), EDCI (3.5 mg, 0.018 mmol, 1.5 equiv), HOAt (2.5 mg, 0.018 mmol, 1.5 equiv), and NMM (3.6 mg, 0.036 mmol, 3.0 equiv) in DMSO (1 mL). Yellow solid in TFA salt form was obtained (11.5 mg, 94%). After this solid was dissolved in DCM (1 mL), TFA (1 mL) was added. The reaction was stirred at rt for 30 min, before the solvent was evaporated. The resulting residue was purified by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O) to afford XF048-2 as yellow solid in TFA salt form (8.3 mg, 82%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.56 (s, 1H), 7.66 – 7.51 (m, 1H), 7.51 – 7.41 (m, 2H), 7.41 – 7.29 (m, 2H), 7.07 (dd, J = 20.2, 8.0 Hz, 2H), 5.41 – 5.22 (m, 1H), 5.17 – 5.00 (m, 1H), 4.47 (dd, J = 9.2, 4.7 Hz, 1H), 4.17 (s, 1H), 4.01 – 3.78 (m, 4H), 3.79 – 3.56 (m, 16H), 3.50 (p, J = 8.8, 7.6 Hz, 4H), 3.41 (d, J = 8.6 Hz, 2H), 3.26 – 3.15 (m, 2H), 2.86 (d, J = 15.4 Hz, 1H), 2.82 – 2.63 (m, 2H), 2.55 – 2.43 (m, 2H), 2.28 (dd, J = 12.8, 7.5 Hz, 1H), 2.24 – 2.05 (m, 2H), 1.16 (d, J = 7.1 Hz, 3H). HRMS (m/z) for $C_{45}H_{57}ClN_9O_{10}^+$ $[M + H]^+$: molecular weight calculated 918.3911, found 918.3914.

Example 27

Synthesis of XF048-3

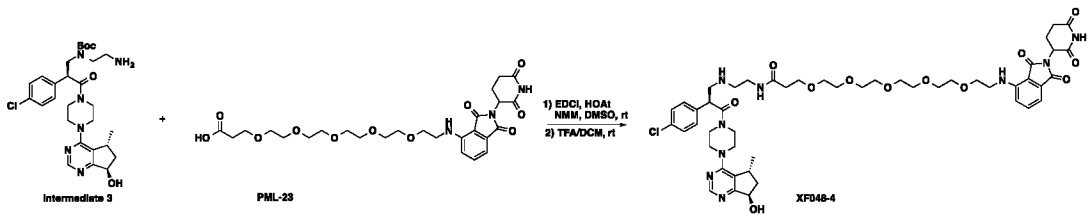


XF048-3 was synthesized following the standard procedure for preparing XF048-1 from intermediate 3 (7.8 mg, 0.012 mmol), PML-23 (6.3 mg, 0.012 mmol, 1.0 equiv), EDCI (3.5 mg, 0.018 mmol, 1.5 equiv), HOAt (2.5 mg, 0.018 mmol, 1.5 equiv), and NMM (3.6 mg, 0.036 mmol, 3.0 equiv) in DMSO (1 mL). Yellow solid in TFA salt form was obtained (9.9 mg, 78%). After this solid was dissolved in DCM (1 mL), TFA (1 mL) was added. The reaction was stirred

at rt for 30 min, before the solvent was evaporated. The resulting residue was purified by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O) to afford XF048-3 as yellow solid in TFA salt form (6.9 mg, 80%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.57 (t, J = 1.6 Hz, 1H), 7.62 – 7.51 (m, 1H), 7.48 – 7.39 (m, 2H), 7.34 (ddd, J = 8.5, 4.0, 1.9 Hz, 2H), 7.15 – 7.00 (m, 2H), 5.30 (t, J = 7.9 Hz, 1H), 5.13 – 5.02 (m, 1H), 4.44 (d, J = 8.6 Hz, 1H), 4.17 (s, 1H), 3.96 – 3.82 (m, 3H), 3.82 – 3.69 (m, 5H), 3.69 – 3.52 (m, 16H), 3.52 – 3.44 (m, 3H), 3.42 (d, J = 6.4 Hz, 1H), 3.37 – 3.32 (m, 1H), 3.26 (d, J = 5.9 Hz, 1H), 3.21 (d, J = 5.8 Hz, 2H), 2.91 – 2.83 (m, 1H), 2.80 – 2.64 (m, 2H), 2.47 (t, J = 6.8 Hz, 2H), 2.29 (dd, J = 12.8, 7.5 Hz, 1H), 2.21 – 2.07 (m, 2H), 1.16 (d, J = 6.9 Hz, 3H). HRMS (m/z) for $C_{47}H_{61}ClN_9O_{11}^+$ [M + H]$^+$: molecular weight calculated 962.4174, found 962.4154.

Example 28

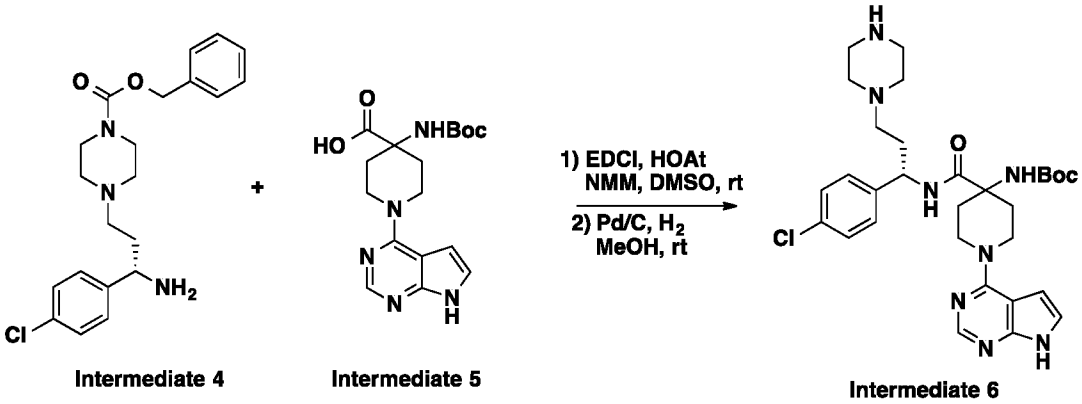
Synthesis of XF048-4



XF048-4 was synthesized following the standard procedure for preparing XF048-1 from intermediate 3 (7.8 mg, 0.012 mmol), PML-23 (6.6 mg, 0.012 mmol, 1.0 equiv), EDCI (3.5 mg, 0.018 mmol, 1.5 equiv), HOAt (2.5 mg, 0.018 mmol, 1.5 equiv), and NMM (3.6 mg, 0.036 mmol, 3.0 equiv) in DMSO (1 mL). Yellow solid in TFA salt form was obtained (3.0 mg, 23%). After this solid was dissolved in DCM (1 mL), TFA (1 mL) was added. The reaction was stirred at rt for 30 min, before the solvent was evaporated. The resulting residue was purified by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O) to afford XF048-4 as yellow solid in TFA salt form (1.2 mg, 38%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.56 (s, 1H), 7.59 – 7.53 (m, 1H), 7.45 (dd, J = 8.5, 2.9 Hz, 2H), 7.35 (dd, J = 8.5, 3.2 Hz, 2H), 7.08 (dd, J = 18.9, 7.8 Hz, 2H), 5.29 (t, J = 7.9 Hz, 1H), 5.07 (dd, J = 12.8, 5.5 Hz, 1H), 4.42 (dd, J = 8.9, 4.3 Hz, 1H), 4.17 (s, 1H), 3.95 – 3.82 (m, 3H), 3.80 – 3.69 (m, 5H), 3.68 – 3.51 (m, 21H), 3.49 (t, J = 5.2 Hz, 3H), 3.42 (s, 1H), 3.39 – 3.34 (m, 1H), 3.22 (t, J = 5.6 Hz, 2H), 2.91 – 2.83 (m, 1H), 2.78 – 2.69 (m, 2H), 2.48 (t, J = 5.2 Hz, 2H), 2.28 (dd, J = 12.8, 7.5 Hz, 1H), 2.20 – 2.15 (m, 1H), 2.15 – 2.09 (m, 1H), 1.16 (d, J = 6.9 Hz, 3H). HRMS (m/z) for $C_{49}H_{65}ClN_9O_{11}^+$ [M + H]$^+$: molecular weight calculated 1006.4436, found 1006.4441.

Example 29

Synthesis of Intermediate 6

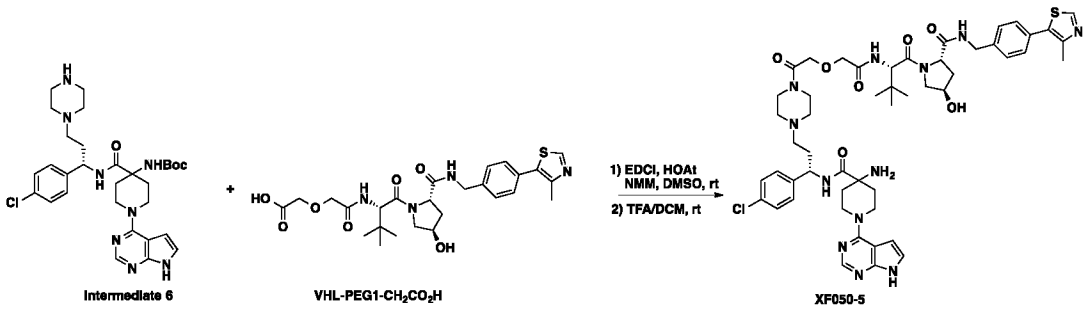


Intermediate 4 Intermediate 5 Intermediate 6

To a solution of Intermediate 4 (210 mg, 0.54 mmol) and Intermediate 5 (195 mg, 0.54 mmol, 1.0 equiv) (Addie et al.). in DMSO (5 mL) were added EDCI (159 mg, 0.81 mmol, 1.5 equiv), HOAt (110 mg, 0.81 mmol, 1.5 equiv), and NMM (164 mg, 1.61 mmol, 3.0 equiv). After being stirred overnight at room temperature, the resulting mixture was purified by reverse phase column (0%-100% methanol / 0.1% TFA in H_2O) to afford the desired product as white solid in TFA salt form (416 mg, 99%). After this product was dissolved in methanol (6 mL), 10% palladium on carbon was added. After this reaction was stirred under H_2 for 4 h, it was filtered through a pad of celite. The filtrate was concentrated. The resulting residue was purified by reverse phase column (0%-100% methanol / 0.1% TFA in H_2O) to afford the Intermediate 6 as white solid in TFA salt form (172 mg, yield 51%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.47 – 8.31 (m, 1H), 8.28 (s, 1H), 7.35 (dt, J = 16.0, 5.8 Hz, 4H), 6.93 (s, 1H), 5.15 – 5.00 (m, 1H), 4.46 – 4.19 (m, 2H), 3.91 – 3.75 (m, 2H), 3.60 – 3.33 (m, 6H), 3.18 – 2.76 (m, 4H), 2.46 – 2.07 (m, 6H), 1.44 (s, 9H). HRMS (m/z) for $C_{30}H_{42}ClN_8O_3^+$ $[M + H]^+$: calculated 597.3063, found 597.3079.

Example 30

Synthesis of XF050-5

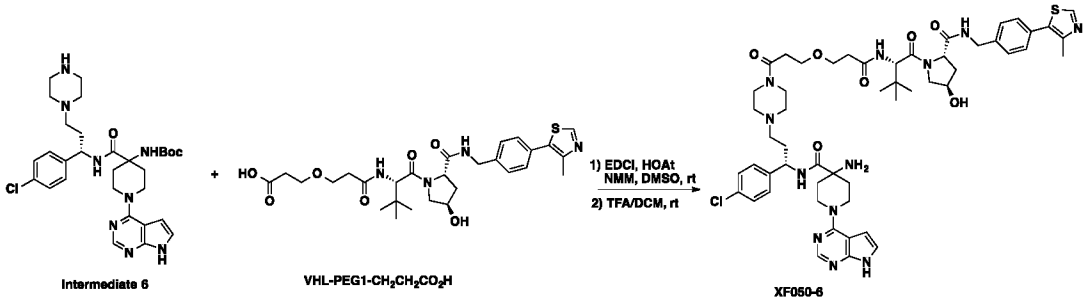


Intermediate 6 VHL-PEG1-CH_2CO_2H XF050-5

XF050-5 was synthesized following the standard procedure for preparing XF038-157A from intermediate 6 (15.9 mg, 0.022 mmol), VHL-PEG1-CH_2CO_2H (12.2 mg, 0.022 mmol, 1.0 equiv), EDCI (6.5 mg, 0.033 mmol, 1.5 equiv), HOAt (4.5 mg, 0.033 mmol, 1.5 equiv), and NMM (6.7 mg, 0.066 mmol, 3.0 equiv) in DMSO (1 mL). White solid in TFA salt form was isolated by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O). After this solid was dissolved in DCM (1 mL), TFA (1 mL) was added. The reaction was stirred at rt for 2 h, before the solvent was evaporated. The resulting residue was purified by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O) to afford XF050-5 as white solid in TFA salt form (19.4 mg, 86%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.98 (s, 1H), 8.39 (s, 1H), 7.47 – 7.43 (m, 2H), 7.41 (d, J = 8.3 Hz, 2H), 7.39 (d, J = 3.7 Hz, 1H), 7.37 – 7.31 (m, 4H), 6.94 (d, J = 3.7 Hz, 1H), 5.00 (dd, J = 9.3, 5.8 Hz, 1H), 4.67 (s, 1H), 4.66 – 4.61 (m, 2H), 4.58 – 4.53 (m, 1H), 4.53 – 4.46 (m, 2H), 4.42 – 4.34 (m, 4H), 4.17 – 4.03 (m, 3H), 3.92 – 3.78 (m, 5H), 3.27 (dd, J = 12.2, 4.4 Hz, 2H), 3.14 (td, J = 12.1, 5.3 Hz, 2H), 2.72 – 2.58 (m, 3H), 2.47 (s, 3H), 2.39 – 2.14 (m, 5H), 2.12 – 2.00 (m, 3H), 1.04 (s, 9H). HRMS (m/z) for $C_{51}H_{66}ClN_{12}O_7S^+$ $[M + H]^+$: calculated 1025.4581, found 1025.4590.

Example 31

Synthesis of XF050-6

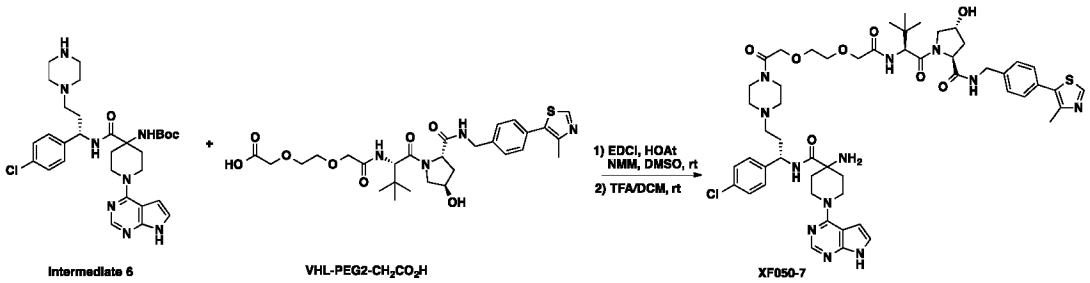


XF050-6 was synthesized following the standard procedure for preparing XF050-5 from intermediate 6 (15.9 mg, 0.022 mmol), VHL-PEG1-$CH_2CH_2CO_2H$ (12.7 mg, 0.022 mmol, 1.0 equiv), EDCI (6.5 mg, 0.033 mmol, 1.5 equiv), HOAt (4.5 mg, 0.033 mmol, 1.5 equiv), and NMM (6.7 mg, 0.066 mmol, 3.0 equiv) in DMSO (1 mL). White solid in TFA salt form was isolated by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O). After this solid was dissolved in DCM (1 mL), TFA (1 mL) was added. The reaction was stirred at rt for 2h, before the solvent was evaporated. The resulting residue was purified by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O) to afford XF050-6 as white solid in TFA salt form (11.9 mg, 52%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.95 (s, 1H), 8.39 (s, 1H), 7.47 – 7.30 (m, 9H), 6.94

(d, J = 3.8 Hz, 1H), 5.01 (dd, J = 9.2, 5.9 Hz, 1H), 4.70 – 4.60 (m, 4H), 4.53 (dd, J = 9.4, 7.5 Hz, 1H), 4.49 – 4.36 (m, 4H), 3.90 – 3.76 (m, 5H), 3.75 – 3.66 (m, 5H), 3.26 (dd, J = 12.2, 4.5 Hz, 2H), 3.18 – 3.09 (m, 2H), 2.71 – 2.57 (m, 4H), 2.50 (t, J = 5.9 Hz, 2H), 2.47 (s, 3H), 2.39 – 2.13 (m, 5H), 2.11 – 1.98 (m, 3H), 1.02 (s, 9H). HRMS (m/z) for $C_{53}H_{70}ClN_{12}O_7S^+$ [M + H]$^+$: calculated 1053.4894, found 1053.4895.

Example 32

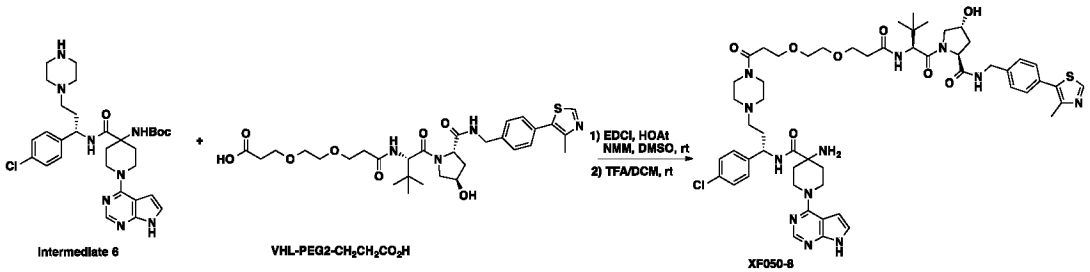
Synthesis of XF050-7



XF050-7 was synthesized following the standard procedure for preparing XF050-5 from intermediate 6 (15.9 mg, 0.022 mmol), VHL-PEG2-CH_2CO_2H (13.0 mg, 0.022 mmol, 1.0 equiv), EDCI (6.5 mg, 0.033 mmol, 1.5 equiv), HOAt (4.5 mg, 0.033 mmol, 1.5 equiv), and NMM (6.7 mg, 0.066 mmol, 3.0 equiv) in DMSO (1 mL). White solid in TFA salt form was isolated by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O). After this solid was dissolved in DCM (1 mL), TFA (1 mL) was added. The reaction was stirred at rt for 2h, before the solvent was evaporated. The resulting residue was purified by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O) to afford XF050-7 as white solid in TFA salt form (21.1 mg, 89%). ^{1}H NMR (600 MHz, CD_3OD) δ 9.00 (s, 1H), 8.40 (d, J = 2.8 Hz, 1H), 7.48 – 7.29 (m, 9H), 6.94 (d, J = 3.6 Hz, 1H), 5.01 (dd, J = 9.2, 5.8 Hz, 1H), 4.69 (d, J = 2.7 Hz, 1H), 4.66 – 4.61 (m, 2H), 4.56 – 4.51 (m, 1H), 4.47 (d, J = 17.9 Hz, 2H), 4.41 – 4.23 (m, 4H), 4.04 (t, J = 2.9 Hz, 2H), 3.90 – 3.78 (m, 5H), 3.75 – 3.68 (m, 5H), 3.26 (dd, J = 12.1, 4.3 Hz, 2H), 3.19 – 3.10 (m, 2H), 2.72 – 2.57 (m, 3H), 2.48 (s, 3H), 2.39 – 2.14 (m, 5H), 2.12 – 1.97 (m, 3H), 1.02 (s, 9H). HRMS (m/z) for $C_{53}H_{70}ClN_{12}O_8S^+$ [M + H]$^+$: calculated 1069.4843, found 1069.4850.

Example 33

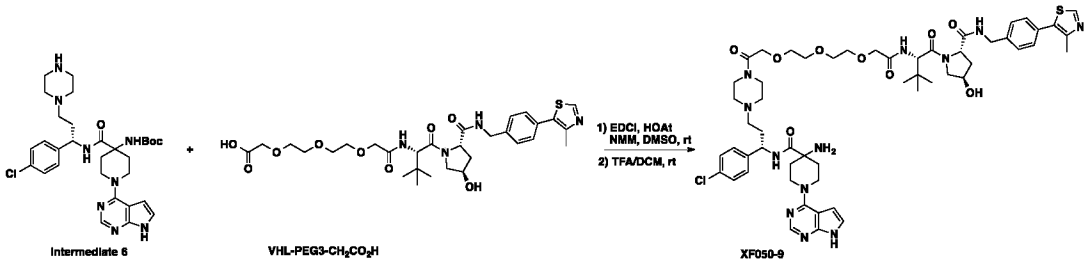
Synthesis of XF050-8



XF050-8 was synthesized following the standard procedure for preparing XF050-5 from intermediate 6 (15.9 mg, 0.022 mmol), VHL-PEG2-$CH_2CH_2CO_2H$ (13.6 mg, 0.022 mmol, 1.0 equiv), EDCI (6.5 mg, 0.033 mmol, 1.5 equiv), HOAt (4.5 mg, 0.033 mmol, 1.5 equiv), and NMM (6.7 mg, 0.066 mmol, 3.0 equiv) in DMSO (1 mL). White solid in TFA salt form was isolated by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O). After this solid was dissolved in DCM (1 mL), TFA (1 mL) was added. The reaction was stirred at rt for 2h, before the solvent was evaporated. The resulting residue was purified by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O) to afford XF050-8 as white solid in TFA salt form (18.3 mg, 76%). ^1H NMR (600 MHz, CD_3OD) δ 9.00 (s, 1H), 8.39 (s, 1H), 7.49 – 7.31 (m, 9H), 6.94 (d, J = 3.7 Hz, 1H), 5.02 (dd, J = 9.2, 5.8 Hz, 1H), 4.64 (s, 4H), 4.59 – 4.45 (m, 4H), 4.36 (d, J = 15.5 Hz, 1H), 3.91 – 3.77 (m, 5H), 3.75 – 3.66 (m, 5H), 3.59 – 3.55 (m, 4H), 3.26 (dd, J = 12.3, 4.5 Hz, 2H), 3.13 (td, J = 12.1, 5.2 Hz, 2H), 2.74 – 2.58 (m, 5H), 2.54 (dt, J = 15.0, 5.9 Hz, 1H), 2.49 – 2.42 (m, 4H), 2.40 – 2.15 (m, 5H), 2.11 – 2.01 (m, 2H), 1.03 (s, 9H). HRMS (m/z) for $C_{55}H_{74}ClN_{12}O_8S^+$ $[M + H]^+$: calculated 1097.5156, found 1097.5160.

Example 34

Synthesis of XF050-9

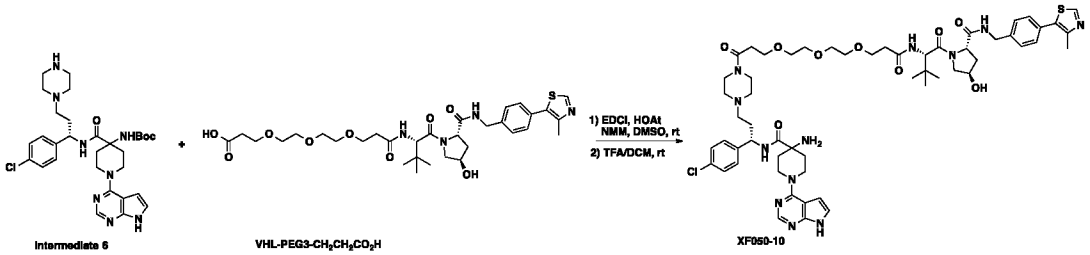


XF050-9 was synthesized following the standard procedure for preparing XF050-5 from intermediate 6 (15.9 mg, 0.022 mmol), VHL-PEG3-CH_2CO_2H (14.0 mg, 0.022 mmol, 1.0 equiv), EDCI (6.5 mg, 0.033 mmol, 1.5 equiv), HOAt (4.5 mg, 0.033 mmol, 1.5 equiv), and NMM (6.7 mg, 0.066 mmol, 3.0 equiv) in DMSO (1 mL). White solid in TFA salt form was

isolated by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O). After this solid was dissolved in DCM (1 mL), TFA (1 mL) was added. The reaction was stirred at rt for 2h, before the solvent was evaporated. The resulting residue was purified by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O) to afford XF050-9 as white solid in TFA salt form (19.2 mg, 78%). ^{1}H NMR (600 MHz, CD_3OD) δ 9.01 (d, J = 3.0 Hz, 1H), 8.39 (d, J = 3.0 Hz, 1H), 7.48 – 7.30 (m, 9H), 6.95 (d, J = 3.7 Hz, 1H), 5.01 (dd, J = 9.2, 5.9 Hz, 1H), 4.66 (brs, 4H), 4.57 – 4.48 (m, 3H), 4.37 (d, J = 15.5 Hz, 1H), 4.30 – 4.17 (m, 2H), 4.04 (s, 2H), 3.93 – 3.77 (m, 5H), 3.72 – 3.62 (m, 9H), 3.26 (dd, J = 12.2, 4.5 Hz, 2H), 3.12 (td, J = 12.1, 5.2 Hz, 2H), 2.73 – 2.57 (m, 3H), 2.48 (d, J = 2.9 Hz, 3H), 2.39 – 2.15 (m, 5H), 2.13 – 1.98 (m, 3H), 1.03 (s, 9H). HRMS (m/z) for $C_{55}H_{74}ClN_{12}O_9S^+$ $[M + H]^+$: calculated 1113.5105, found 1113.5120.

Example 35

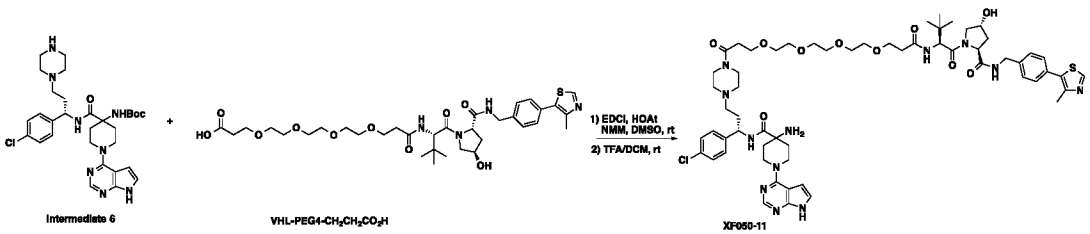
Synthesis of XF050-10



XF050-10 was synthesized following the standard procedure for preparing XF050-5 from intermediate 6 (15.9 mg, 0.022 mmol), VHL-PEG3-$CH_2CH_2CO_2H$ (14.6 mg, 0.022 mmol, 1.0 equiv), EDCI (6.5 mg, 0.033 mmol, 1.5 equiv), HOAt (4.5 mg, 0.033 mmol, 1.5 equiv), and NMM (6.7 mg, 0.066 mmol, 3.0 equiv) in DMSO (1 mL). White solid in TFA salt form was isolated by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O). After this solid was dissolved in DCM (1 mL), TFA (1 mL) was added. The reaction was stirred at rt for 2h, before the solvent was evaporated. The resulting residue was purified by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O) to afford XF050-10 as white solid in TFA salt form (13.2 mg, 53%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.99 (s, 1H), 8.40 (s, 1H), 7.51 – 7.28 (m, 9H), 6.94 (d, J = 3.6 Hz, 1H), 5.01 (dd, J = 8.9, 6.1 Hz, 1H), 4.74 – 4.61 (m, 4H), 4.60 – 4.46 (m, 4H), 4.37 (d, J = 15.5 Hz, 1H), 3.91 – 3.75 (m, 5H), 3.70 (dq, J = 16.1, 5.1, 4.1 Hz, 5H), 3.60 – 3.54 (m, 8H), 3.25 (dd, J = 12.2, 4.5 Hz, 2H), 3.11 (td, J = 12.1, 5.2 Hz, 2H), 2.73 – 2.52 (m, 6H), 2.48 (d, J = 7.7 Hz, 4H), 2.41 – 2.14 (m, 5H), 2.12 – 2.00 (m, 2H), 1.03 (s, 9H). HRMS (m/z) for $C_{57}H_{78}ClN_{12}O_9S^+$ $[M + H]^+$: calculated 1141.5418, found 1141.5438.

Example 36

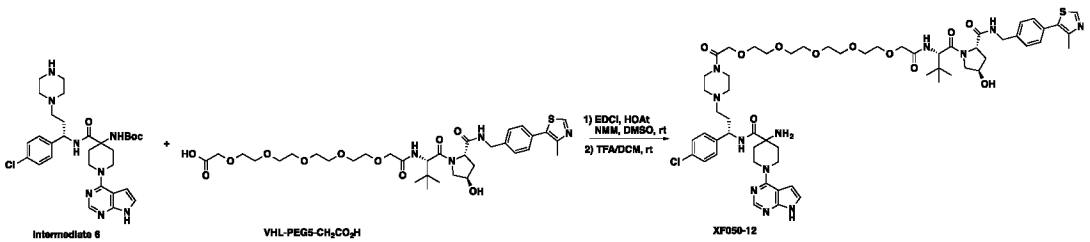
Synthesis of XF050-11



XF050-11 was synthesized following the standard procedure for preparing XF050-5 from intermediate 6 (15.9 mg, 0.022 mmol), VHL-PEG4-$CH_2CH_2CO_2H$ (15.6 mg, 0.022 mmol, 1.0 equiv), EDCI (6.5 mg, 0.033 mmol, 1.5 equiv), HOAt (4.5 mg, 0.033 mmol, 1.5 equiv), and NMM (6.7 mg, 0.066 mmol, 3.0 equiv) in DMSO (1 mL). White solid in TFA salt form was isolated by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O). After this solid was dissolved in DCM (1 mL), TFA (1 mL) was added. The reaction was stirred at rt for 2h, before the solvent was evaporated. The resulting residue was purified by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O) to afford XF050-11 as white solid in TFA salt form (14.0 mg, 54%). ^1H NMR (600 MHz, CD_3OD) δ 8.95 (s, 1H), 8.39 (s, 1H), 7.51 – 7.26 (m, 9H), 6.93 (d, J = 3.7 Hz, 1H), 5.00 (dd, J = 8.8, 6.3 Hz, 1H), 4.70 – 4.60 (m, 4H), 4.60 – 4.45 (m, 4H), 4.36 (d, J = 15.5 Hz, 1H), 3.90 – 3.76 (m, 5H), 3.75 – 3.66 (m, 5H), 3.62 – 3.51 (m, 12H), 3.26 (td, J = 12.4, 4.7 Hz, 2H), 3.10 (td, J = 12.1, 5.3 Hz, 2H), 2.72 – 2.55 (m, 6H), 2.51 – 2.42 (m, 4H), 2.39 – 2.14 (m, 5H), 2.11 – 1.99 (m, 2H), 1.02 (s, 9H). HRMS (m/z) for $C_{59}H_{82}ClN_{12}O_{10}S^+$ $[M + H]^+$: calculated 1185.5681, found 1185.5665.

Example 37

Synthesis of XF050-12

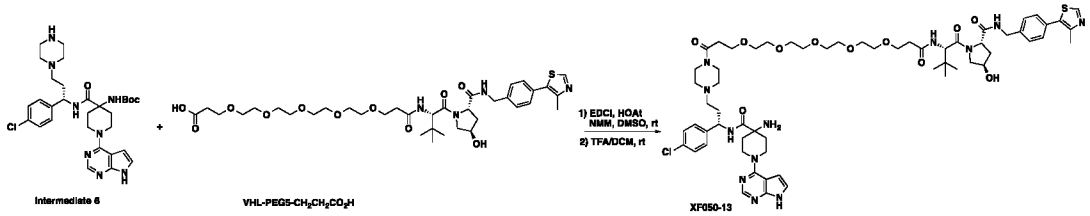


XF050-12 was synthesized following the standard procedure for preparing XF050-5 from intermediate 6 (15.9 mg, 0.022 mmol), VHL-PEG5-CH_2CO_2H (15.9 mg, 0.022 mmol, 1.0 equiv), EDCI (6.5 mg, 0.033 mmol, 1.5 equiv), HOAt (4.5 mg, 0.033 mmol, 1.5 equiv), and NMM (6.7 mg, 0.066 mmol, 3.0 equiv) in DMSO (1 mL). White solid in TFA salt form was isolated by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O). After this solid was

dissolved in DCM (1 mL), TFA (1 mL) was added. The reaction was stirred at rt for 2h, before the solvent was evaporated. The resulting residue was purified by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O) to afford XF050-12 as white solid in TFA salt form (16.3 mg, 62%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.96 (s, 1H), 8.39 (s, 1H), 7.55 – 7.17 (m, 9H), 6.93 (d, J = 3.7 Hz, 1H), 5.01 (t, J = 7.7 Hz, 1H), 4.68 – 4.46 (m, 8H), 4.36 (d, J = 15.5 Hz, 2H), 4.16 – 4.02 (m, 3H), 3.93 – 3.82 (m, 4H), 3.78 (dd, J = 10.9, 3.8 Hz, 1H), 3.68 – 3.54 (m, 16H), 3.29 – 3.20 (m, 2H), 3.17 – 3.09 (m, 2H), 2.74 – 2.57 (m, 3H), 2.47 (s, 3H), 2.41 – 2.13 (m, 5H), 2.12 – 1.99 (m, 3H), 1.04 (s, 9H). HRMS (m/z) for $C_{59}H_{82}ClN_{12}O_{11}S^+$ $[M+H]^+$: calculated 1201.5630, found 1201.5651.

Example 38

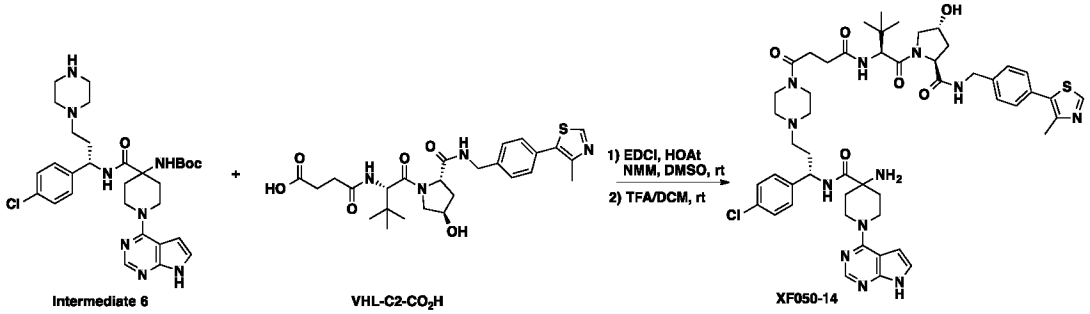
Synthesis of XF050-13



XF050-13 was synthesized following the standard procedure for preparing XF050-5 from intermediate 6 (15.9 mg, 0.022 mmol), VHL-PEG5-$CH_2CH_2CO_2H$ (16.5 mg, 0.022 mmol, 1.0 equiv), EDCI (6.5 mg, 0.033 mmol, 1.5 equiv), HOAt (4.5 mg, 0.033 mmol, 1.5 equiv), and NMM (6.7 mg, 0.066 mmol, 3.0 equiv) in DMSO (1 mL). White solid in TFA salt form was isolated by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O). After this solid was dissolved in DCM (1 mL), TFA (1 mL) was added. The reaction was stirred at rt for 2h, before the solvent was evaporated. The resulting residue was purified by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O) to afford XF050-13 as white solid in TFA salt form (17.3 mg, 64%). ^{1}H NMR (600 MHz, CD_3OD) δ 9.00 (s, 1H), 8.40 (s, 1H), 7.53 – 7.28 (m, 9H), 6.94 (d, J = 3.7 Hz, 1H), 5.00 (dd, J = 8.9, 6.3 Hz, 1H), 4.70 – 4.60 (m, 4H), 4.60 – 4.46 (m, 4H), 4.36 (d, J = 15.5 Hz, 1H), 3.91 – 3.76 (m, 5H), 3.76 – 3.67 (m, 5H), 3.65 – 3.49 (m, 16H), 3.26 (dd, J = 12.3, 4.5 Hz, 2H), 3.11 (td, J = 12.2, 5.4 Hz, 2H), 2.72 – 2.54 (m, 6H), 2.52 – 2.43 (m, 4H), 2.40 – 2.13 (m, 5H), 2.12 – 1.99 (m, 2H), 1.02 (s, 9H). HRMS (m/z) for $C_{61}H_{86}ClN_{12}O_{11}S^+$ $[M+H]^+$: calculated 1229.5943, found 1229.5950.

Example 39

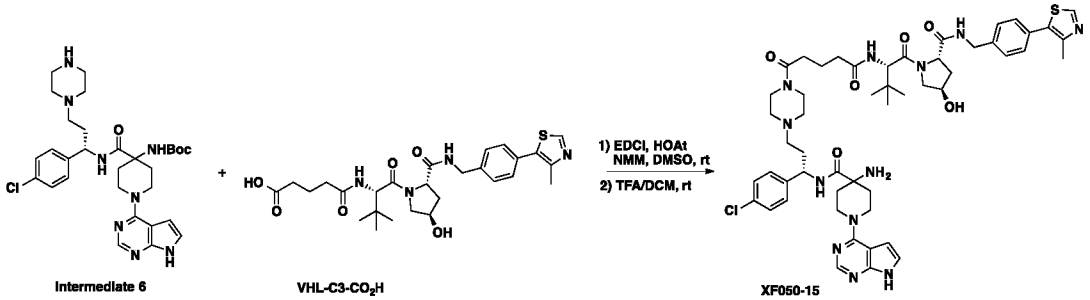
Synthesis of XF050-14



XF050-14 was synthesized following the standard procedure for preparing XF050-5 from intermediate 6 (15.9 mg, 0.022 mmol), VHL-C2-CO_2H (11.7 mg, 0.022 mmol, 1.0 equiv), EDCI (6.5 mg, 0.033 mmol, 1.5 equiv), HOAt (4.5 mg, 0.033 mmol, 1.5 equiv), and NMM (6.7 mg, 0.066 mmol, 3.0 equiv) in DMSO (1 mL). White solid in TFA salt form was isolated by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O). After this solid was dissolved in DCM (1 mL), TFA (1 mL) was added. The reaction was stirred at rt for 2h, before the solvent was evaporated. The resulting residue was purified by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O) to afford XF050-14 as white solid in TFA salt form (19.9 mg, 90%). ^1H NMR (600 MHz, CD_3OD) δ 8.99 (s, 1H), 8.40 (s, 1H), 7.52 – 7.25 (m, 9H), 6.95 (d, J = 3.8 Hz, 1H), 5.01 (dd, J = 9.2, 5.9 Hz, 1H), 4.71 – 4.60 (m, 3H), 4.60 – 4.45 (m, 5H), 4.37 (d, J = 15.6 Hz, 1H), 3.92 – 3.74 (m, 5H), 3.27 (dd, J = 12.3, 4.4 Hz, 2H), 3.13 (td, J = 12.2, 5.2 Hz, 2H), 2.74 – 2.52 (m, 7H), 2.48 (s, 3H), 2.41 – 2.13 (m, 5H), 2.13 – 1.98 (m, 3H), 1.02 (s, 9H). HRMS (m/z) for $C_{51}H_{66}ClN_{12}O_6S^+$ $[M + H]^+$: calculated 1009.4632, found 1009.4638.

Example 40

Synthesis of XF050-15

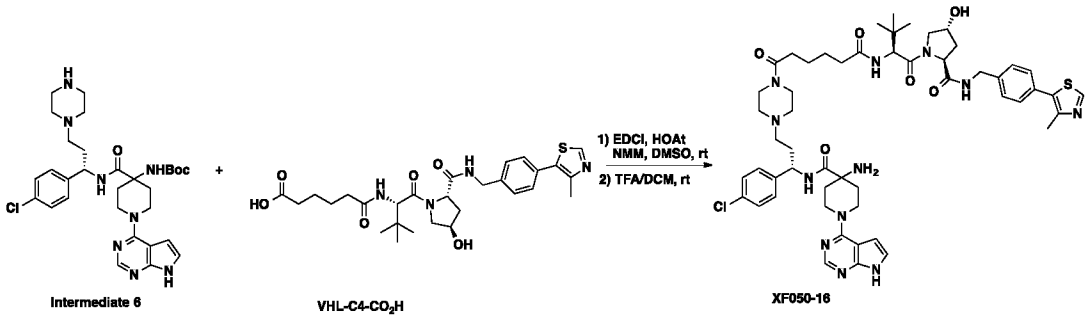


XF050-15 was synthesized following the standard procedure for preparing XF050-5 from intermediate 6 (15.9 mg, 0.022 mmol), VHL-C3-CO_2H (12.0 mg, 0.022 mmol, 1.0 equiv), EDCI (6.5 mg, 0.033 mmol, 1.5 equiv), HOAt (4.5 mg, 0.033 mmol, 1.5 equiv), and NMM

(6.7 mg, 0.066 mmol, 3.0 equiv) in DMSO (1 mL). White solid in TFA salt form was isolated by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O). After this solid was dissolved in DCM (1 mL), TFA (1 mL) was added. The reaction was stirred at rt for 2h, before the solvent was evaporated. The resulting residue was purified by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O) to afford XF050-15 as white solid in TFA salt form (13.9 mg, 62%). ^1H NMR (600 MHz, CD_3OD) δ 9.00 (s, 1H), 8.40 (s, 1H), 7.51 – 7.26 (m, 9H), 6.95 (dd, J = 3.7, 1.7 Hz, 1H), 5.00 (dd, J = 9.2, 5.9 Hz, 1H), 4.70 – 4.61 (m, 3H), 4.60 – 4.45 (m, 5H), 4.37 (d, J = 15.4 Hz, 1H), 3.94 – 3.75 (m, 5H), 3.26 (dd, J = 12.2, 4.3 Hz, 2H), 3.12 (td, J = 12.1, 5.2 Hz, 2H), 2.72 – 2.57 (m, 3H), 2.48 (d, J = 1.5 Hz, 3H), 2.45 – 2.38 (m, 2H), 2.38 – 2.12 (m, 8H), 2.12 – 1.98 (m, 2H), 1.88 (p, J = 7.3 Hz, 2H), 1.03 (d, J = 1.7 Hz, 9H). HRMS (m/z) for $C_{52}H_{68}ClN_{12}O_6S^+$ $[M + H]^+$: calculated 1023.4789, found 1023.4794.

Example 41

Synthesis of XF050-16

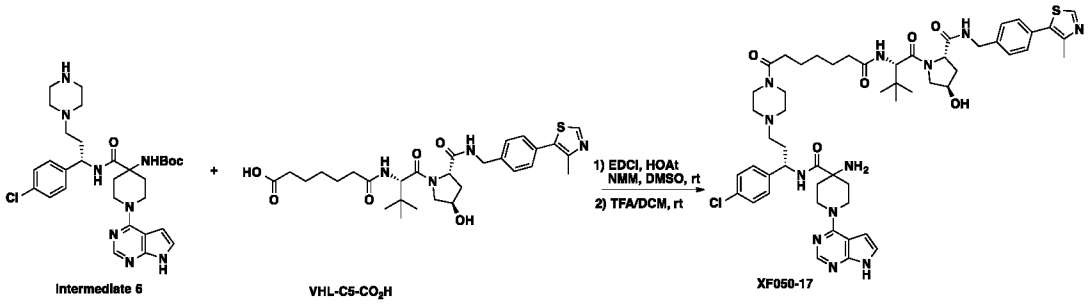


XF050-16 was synthesized following the standard procedure for preparing XF050-5 from intermediate 6 (15.9 mg, 0.022 mmol), VHL-C4-CO_2H (12.3 mg, 0.022 mmol, 1.0 equiv), EDCI (6.5 mg, 0.033 mmol, 1.5 equiv), HOAt (4.5 mg, 0.033 mmol, 1.5 equiv), and NMM (6.7 mg, 0.066 mmol, 3.0 equiv) in DMSO (1 mL). White solid in TFA salt form was isolated by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O). After this solid was dissolved in DCM (1 mL), TFA (1 mL) was added. The reaction was stirred at rt for 2h, before the solvent was evaporated. The resulting residue was purified by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O) to afford XF050-16 as white solid in TFA salt form (14.0 mg, 61%). ^1H NMR (600 MHz, CD_3OD) δ 9.00 (s, 1H), 8.39 (s, 1H), 7.53 – 7.22 (m, 9H), 6.95 (d, J = 3.7 Hz, 1H), 5.00 (dd, J = 9.2, 5.9 Hz, 1H), 4.69 – 4.59 (m, 4H), 4.59 – 4.44 (m, 4H), 4.36 (d, J = 15.5 Hz, 1H), 3.91 – 3.76 (m, 5H), 3.26 (dd, J = 12.3, 4.4 Hz, 2H), 3.13 (td, J = 12.1, 5.2 Hz, 2H), 2.73 – 2.57 (m, 3H), 2.48 (s, 3H), 2.43 (td, J = 7.1, 4.8 Hz, 2H), 2.40 – 2.13 (m, 8H), 2.11

– 2.01 (m, 2H), 1.68 – 1.57 (m, 4H), 1.03 (s, 9H). HRMS (m/z) for $C_{53}H_{70}ClN_{12}O_6S^+$ [M + H]$^+$: calculated 1037.4945, found 1037.4923.

Example 42

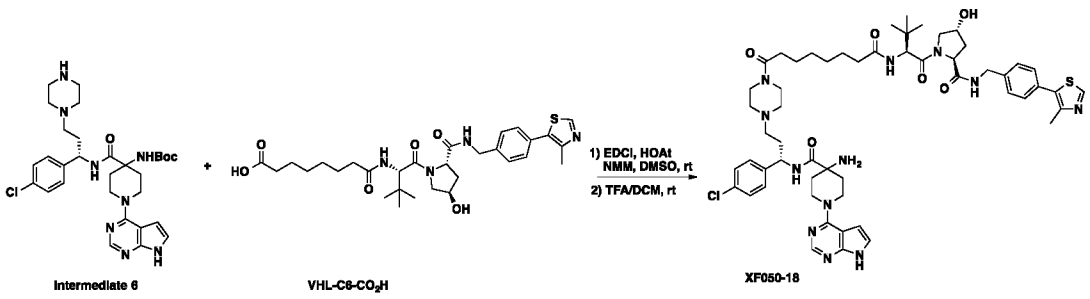
Synthesis of XF050-17



XF050-17 was synthesized following the standard procedure for preparing XF050-5 from intermediate 6 (15.9 mg, 0.022 mmol), VHL-C5-CO_2H (12.6 mg, 0.022 mmol, 1.0 equiv), EDCI (6.5 mg, 0.033 mmol, 1.5 equiv), HOAt (4.5 mg, 0.033 mmol, 1.5 equiv), and NMM (6.7 mg, 0.066 mmol, 3.0 equiv) in DMSO (1 mL). White solid in TFA salt form was isolated by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O). After this solid was dissolved in DCM (1 mL), TFA (1 mL) was added. The reaction was stirred at rt for 2h, before the solvent was evaporated. The resulting residue was purified by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O) to afford XF050-17 as white solid in TFA salt form (16.3 mg, 70%). ^{1}H NMR (600 MHz, CD_3OD) δ 9.04 (s, 1H), 8.40 (s, 1H), 7.55 – 7.25 (m, 9H), 6.95 (d, J = 3.7 Hz, 1H), 5.01 (dd, J = 9.3, 5.8 Hz, 1H), 4.64 (d, J = 18.7 Hz, 4H), 4.58 – 4.45 (m, 4H), 4.37 (d, J = 15.5 Hz, 1H), 3.93 – 3.77 (m, 5H), 3.27 (dd, J = 12.3, 4.5 Hz, 2H), 3.14 (td, J = 12.2, 5.2 Hz, 2H), 2.74 – 2.55 (m, 3H), 2.48 (s, 3H), 2.41 (t, J = 7.5 Hz, 2H), 2.39 – 2.14 (m, 8H), 2.12 – 2.00 (m, 2H), 1.66 – 1.56 (m, 4H), 1.41 – 1.29 (m, 2H), 1.02 (s, 9H). HRMS (m/z) for $C_{54}H_{72}ClN_{12}O_6S^+$ [M + H]$^+$: calculated 1051.5102, found 1051.5094.

Example 43

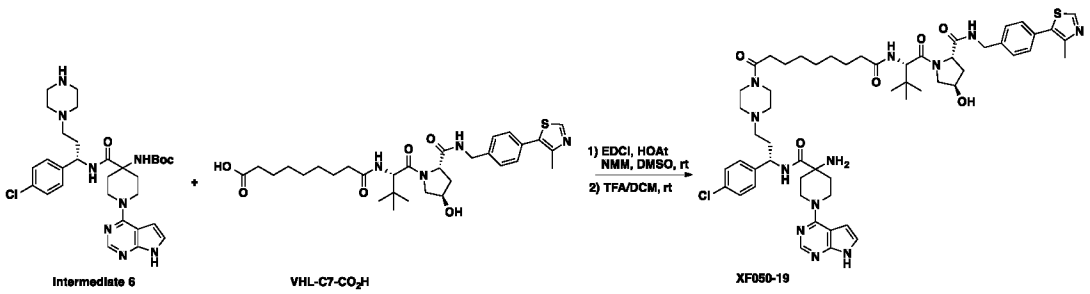
Synthesis of XF050-18



XF050-18 was synthesized following the standard procedure for preparing XF050-5 from intermediate 6 (15.9 mg, 0.022 mmol), VHL-C6-CO_2H (12.9 mg, 0.022 mmol, 1.0 equiv), EDCI (6.5 mg, 0.033 mmol, 1.5 equiv), HOAt (4.5 mg, 0.033 mmol, 1.5 equiv), and NMM (6.7 mg, 0.066 mmol, 3.0 equiv) in DMSO (1 mL). White solid in TFA salt form was isolated by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O). After this solid was dissolved in DCM (1 mL), TFA (1 mL) was added. The reaction was stirred at rt for 2h, before the solvent was evaporated. The resulting residue was purified by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O) to afford XF050-18 as white solid in TFA salt form (11.9 mg, 51%). ^1H NMR (600 MHz, CD_3OD) δ 8.97 (s, 1H), 8.39 (s, 1H), 7.53 – 7.19 (m, 9H), 6.94 (d, J = 3.8 Hz, 1H), 5.01 (dd, J = 9.2, 5.9 Hz, 1H), 4.71 – 4.61 (m, 4H), 4.59 – 4.45 (m, 4H), 4.36 (d, J = 15.4 Hz, 1H), 3.92 – 3.76 (m, 5H), 3.26 (dd, J = 12.3, 4.5 Hz, 2H), 3.13 (td, J = 12.2, 5.3 Hz, 2H), 2.73 – 2.55 (m, 3H), 2.48 (s, 3H), 2.40 (t, J = 7.6 Hz, 3H), 2.37 – 2.14 (m, 7H), 2.11 – 2.00 (m, 2H), 1.64 – 1.55 (m, 4H), 1.35 (dd, J = 7.5, 4.0 Hz, 4H), 1.03 (s, 9H). HRMS (m/z) for $C_{55}H_{74}ClN_{12}O_6S^+$ $[M + H]^+$: calculated 1065.5258, found 1065.5272.

Example 44

Synthesis of XF050-19

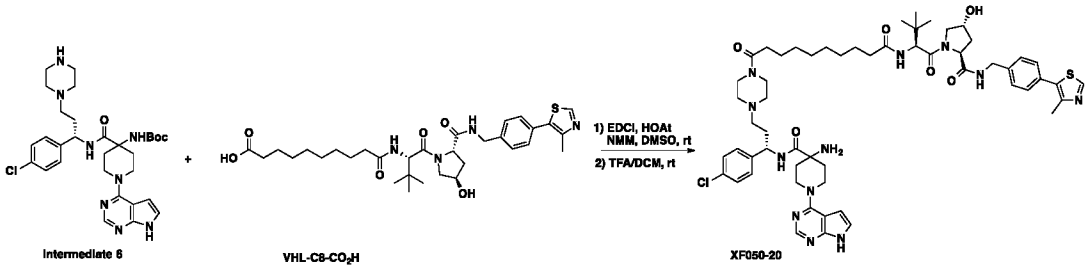


XF050-19 was synthesized following the standard procedure for preparing XF050-5 from intermediate 6 (15.9 mg, 0.022 mmol), VHL-C7-CO_2H (13.2 mg, 0.022 mmol, 1.0 equiv), EDCI (6.5 mg, 0.033 mmol, 1.5 equiv), HOAt (4.5 mg, 0.033 mmol, 1.5 equiv), and NMM (6.7 mg, 0.066 mmol, 3.0 equiv) in DMSO (1 mL). White solid in TFA salt form was isolated by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O). After this solid was dissolved in DCM (1 mL), TFA (1 mL) was added. The reaction was stirred at rt for 2h, before the solvent was evaporated. The resulting residue was purified by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O) to afford XF050-19 as white solid in TFA salt form (10.4 mg, 44%). ^1H NMR (600 MHz, CD_3OD) δ 8.98 (s, 1H), 8.40 (d, J = 1.9 Hz, 1H), 7.56 – 7.25 (m, 9H), 6.95 (dd, J = 3.7, 1.9 Hz, 1H), 5.01 (dd, J = 9.3, 5.8 Hz, 1H), 4.70 – 4.61 (m, 4H), 4.59 – 4.47 (m, 4H), 4.36 (d, J = 15.5 Hz, 1H), 3.92 – 3.78 (m, 5H), 3.26 (dd, J = 12.3, 4.3 Hz, 2H), 3.13 (td,

J = 12.0, 5.0 Hz, 2H), 2.73 – 2.58 (m, 3H), 2.48 (s, 3H), 2.43 – 2.37 (m, 3H), 2.37 – 2.14 (m, 7H), 2.11 – 2.00 (m, 2H), 1.65 – 1.54 (m, 4H), 1.34 (s, 6H), 1.03 (d, J = 1.9 Hz, 9H). HRMS (m/z) for $C_{56}H_{76}ClN_{12}O_6S^+$ $[M + H]^+$: calculated 1079.5415, found 1079.5414.

Example 45

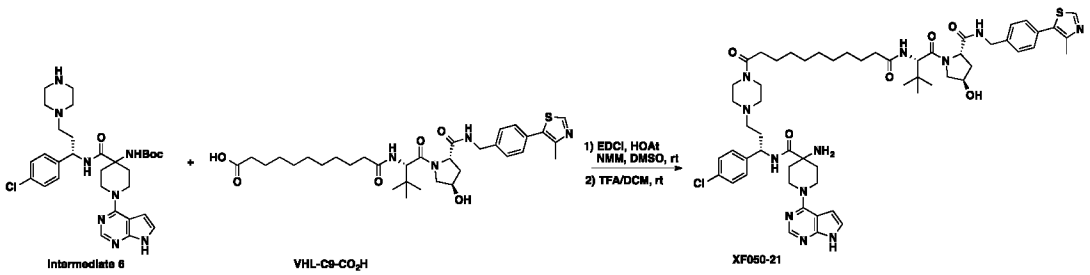
Synthesis of XF050-20



XF050-20 was synthesized following the standard procedure for preparing XF050-5 from intermediate 6 (15.9 mg, 0.022 mmol), VHL-C8-CO_2H (13.5 mg, 0.022 mmol, 1.0 equiv), EDCI (6.5 mg, 0.033 mmol, 1.5 equiv), HOAt (4.5 mg, 0.033 mmol, 1.5 equiv), and NMM (6.7 mg, 0.066 mmol, 3.0 equiv) in DMSO (1 mL). White solid in TFA salt form was isolated by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O). After this solid was dissolved in DCM (1 mL), TFA (1 mL) was added. The reaction was stirred at rt for 2h, before the solvent was evaporated. The resulting residue was purified by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O) to afford XF050-20 as white solid in TFA salt form (13.6 mg, 60%). ^1H NMR (600 MHz, CD_3OD) δ 9.00 (s, 1H), 8.40 (s, 1H), 7.53 – 7.22 (m, 9H), 6.95 (d, J = 3.8 Hz, 1H), 5.01 (dd, J = 9.3, 5.8 Hz, 1H), 4.71 – 4.61 (m, 4H), 4.59 – 4.46 (m, 4H), 4.36 (d, J = 15.5 Hz, 1H), 3.93 – 3.76 (m, 5H), 3.26 (dd, J = 12.3, 4.4 Hz, 2H), 3.13 (td, J = 12.2, 5.1 Hz, 2H), 2.73 – 2.57 (m, 3H), 2.48 (s, 3H), 2.40 (t, J = 7.6 Hz, 3H), 2.37 – 2.14 (m, 7H), 2.11 – 2.00 (m, 2H), 1.63 – 1.53 (m, 4H), 1.32 (s, 8H), 1.03 (s, 9H). HRMS (m/z) for $C_{57}H_{78}ClN_{12}O_6S^+$ $[M + H]^+$: calculated 1093.5571, found 1093.5561.

Example 46

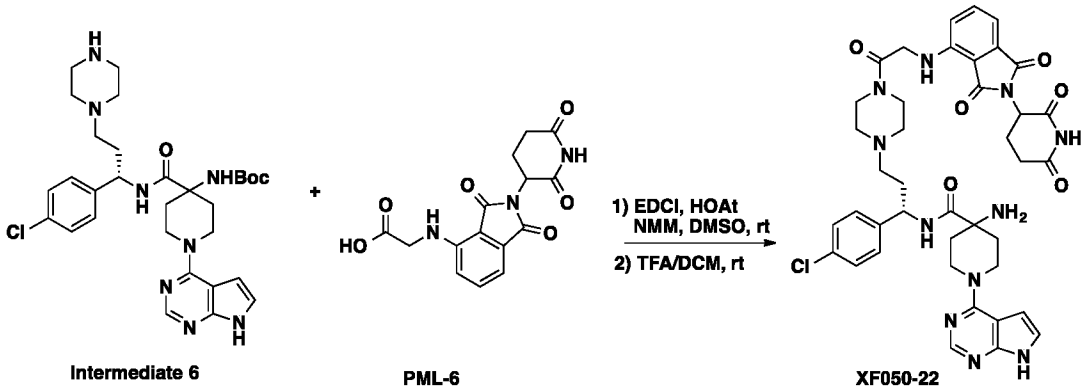
Synthesis of XF050-21



XF050-21 was synthesized following the standard procedure for preparing XF050-5 from intermediate 6 (15.9 mg, 0.022 mmol), VHL-C9-CO_2H (13.8 mg, 0.022 mmol, 1.0 equiv), EDCI (6.5 mg, 0.033 mmol, 1.5 equiv), HOAt (4.5 mg, 0.033 mmol, 1.5 equiv), and NMM (6.7 mg, 0.066 mmol, 3.0 equiv) in DMSO (1 mL). White solid in TFA salt form was isolated by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O). After this solid was dissolved in DCM (1 mL), TFA (1 mL) was added. The reaction was stirred at rt for 2h, before the solvent was evaporated. The resulting residue was purified by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O) to afford XF050-21 as white solid in TFA salt form (16.0 mg, 66%). ^1H NMR (600 MHz, CD_3OD) δ 8.97 (s, 1H), 8.39 (s, 1H), 7.53 – 7.25 (m, 9H), 6.94 (d, J = 3.8 Hz, 1H), 5.01 (dd, J = 9.4, 5.8 Hz, 1H), 4.69 – 4.59 (m, 4H), 4.59 – 4.47 (m, 4H), 4.36 (d, J = 15.5 Hz, 1H), 3.93 – 3.78 (m, 5H), 3.26 (dd, J = 12.3, 4.5 Hz, 2H), 3.14 (td, J = 12.2, 5.1 Hz, 2H), 2.74 – 2.57 (m, 3H), 2.48 (s, 3H), 2.40 (t, J = 7.6 Hz, 3H), 2.37 – 2.15 (m, 7H), 2.11 – 2.00 (m, 2H), 1.58 (td, J = 10.8, 8.0, 4.1 Hz, 4H), 1.31 (s, 10H), 1.03 (s, 9H). HRMS (m/z) for $C_{58}H_{80}ClN_{12}O_6S^+$ $[M + H]^+$: calculated 1107.5928, found 1107.5926.

Example 47

Synthesis of XF050-22

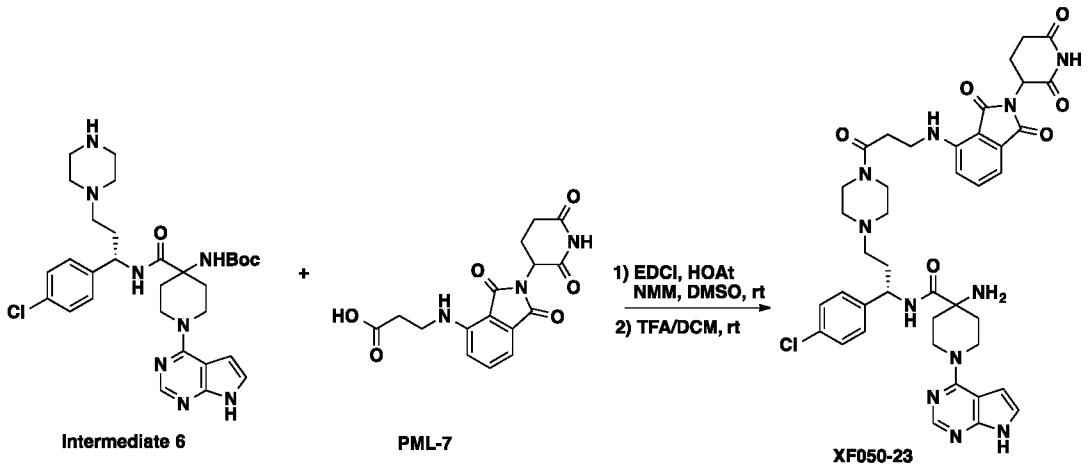


XF050-22 was synthesized following the standard procedure for preparing XF050-5 from intermediate 6 (15.9 mg, 0.022 mmol), PML-6 (7.3 mg, 0.022 mmol, 1.0 equiv), EDCI (6.5 mg, 0.033 mmol, 1.5 equiv), HOAt (4.5 mg, 0.033 mmol, 1.5 equiv), and NMM (6.7 mg, 0.066 mmol, 3.0 equiv) in DMSO (1 mL). Yellow solid in TFA salt form was isolated by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O). After this solid was dissolved in DCM (1 mL), TFA (1 mL) was added. The reaction was stirred at rt for 2h, before the solvent was evaporated. The resulting residue was purified by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O) to afford XF050-22 as yellow solid in TFA salt form (2.9 mg, 16%). ^1H NMR (600 MHz, CD_3OD) δ 8.36 (s, 1H), 7.55 (t, J = 7.8 Hz, 1H), 7.44 (dd, J = 8.5, 7.0 Hz,

1H), 7.36 (dd, J = 12.3, 2.7 Hz, 3H), 7.10 (d, J = 7.2 Hz, 1H), 7.04 (d, J = 7.0 Hz, 1H), 6.99 (dd, J = 8.4, 3.6 Hz, 1H), 6.89 (d, J = 3.7 Hz, 1H), 5.10 – 4.99 (m, 2H), 4.75 – 4.64 (m, 2H), 4.24 (s, 2H), 3.76 (q, J = 12.1 Hz, 4H), 3.44 – 3.32 (m, 2H), 3.28 – 3.22 (m, 2H), 3.12 (td, J = 12.2, 5.2 Hz, 2H), 2.90 – 2.80 (m, 2H), 2.78 – 2.51 (m, 5H), 2.40 – 2.24 (m, 2H), 2.17 – 2.06 (m, 2H), 2.04 – 1.96 (m, 1H). HRMS (m/z) for $C_{40}H_{45}ClN_{11}O_6^+$ $[M + H]^+$: calculated 810.3237, found 810.3246.

Example 48

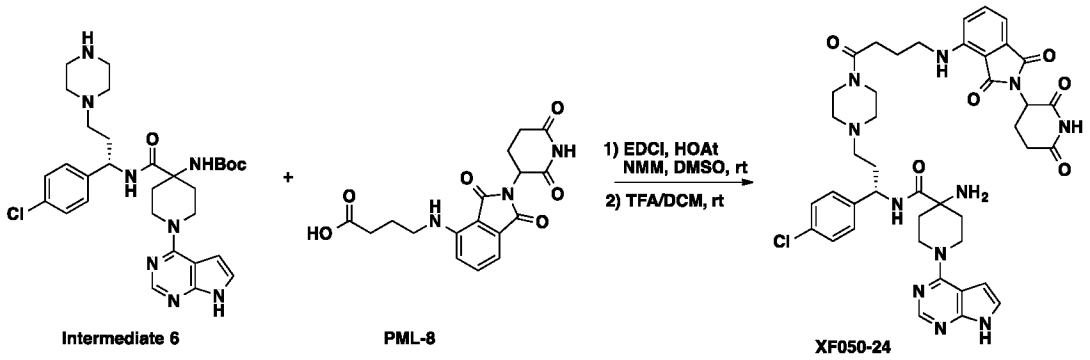
Synthesis of XF050-23



XF050-23 was synthesized following the standard procedure for preparing XF050-5 from intermediate 6 (15.9 mg, 0.022 mmol), PML-7 (7.6 mg, 0.022 mmol, 1.0 equiv), EDCI (6.5 mg, 0.033 mmol, 1.5 equiv), HOAt (4.5 mg, 0.033 mmol, 1.5 equiv), and NMM (6.7 mg, 0.066 mmol, 3.0 equiv) in DMSO (1 mL). Yellow solid in TFA salt form was isolated by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O). After this solid was dissolved in DCM (1 mL), TFA (1 mL) was added. The reaction was stirred at rt for 2h, before the solvent was evaporated. The resulting residue was purified by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O) to afford XF050-23 as yellow solid in TFA salt form (16.2 mg, 89%). ^1H NMR (600 MHz, CD_3OD) δ 8.38 (s, 1H), 7.56 (dd, J = 8.5, 7.2 Hz, 1H), 7.39 – 7.31 (m, 5H), 7.11 (d, J = 8.6 Hz, 1H), 7.05 (d, J = 7.1 Hz, 1H), 6.93 (d, J = 3.7 Hz, 1H), 5.07 – 4.97 (m, 2H), 4.64 (s, 2H), 3.84 (q, J = 12.2 Hz, 4H), 3.68 – 3.63 (m, 4H), 3.26 – 3.15 (m, 2H), 3.08 (td, J = 11.9, 4.9 Hz, 2H), 2.90 – 2.79 (m, 2H), 2.77 – 2.71 (m, 3H), 2.71 – 2.58 (m, 3H), 2.37 – 1.98 (m, 6H). HRMS (m/z) for $C_{41}H_{47}ClN_{11}O_6^+$ $[M + H]^+$: calculated 824.3394, found 824.3394.

Example 49

Synthesis of XF050-24

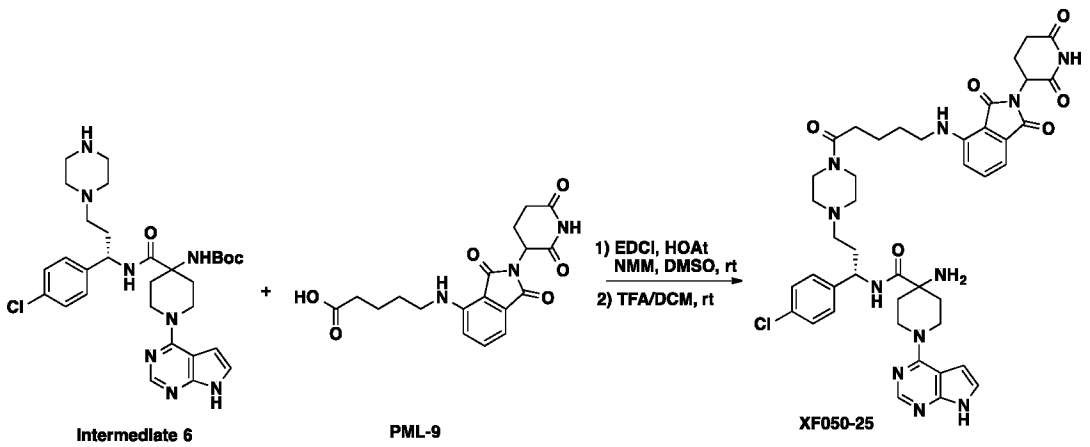


Intermediate 6 PML-8 XF050-24

XF050-24 was synthesized following the standard procedure for preparing XF050-5 from intermediate 6 (15.9 mg, 0.022 mmol), PML-8 (7.9 mg, 0.022 mmol, 1.0 equiv), EDCI (6.5 mg, 0.033 mmol, 1.5 equiv), HOAt (4.5 mg, 0.033 mmol, 1.5 equiv), and NMM (6.7 mg, 0.066 mmol, 3.0 equiv) in DMSO (1 mL). Yellow solid in TFA salt form was isolated by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O). After this solid was dissolved in DCM (1 mL), TFA (1 mL) was added. The reaction was stirred at rt for 2h, before the solvent was evaporated. The resulting residue was purified by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O) to afford XF050-24 as yellow solid in TFA salt form (12.5 mg, 68%). ^1H NMR (600 MHz, CD_3OD) δ 8.39 (s, 1H), 7.54 (dd, J = 8.5, 7.2 Hz, 1H), 7.37 (dd, J = 17.5, 3.5 Hz, 5H), 7.10 (d, J = 8.6 Hz, 1H), 7.04 (d, J = 7.1 Hz, 1H), 6.94 (d, J = 3.7 Hz, 1H), 5.05 (dd, J = 12.8, 5.5 Hz, 1H), 5.00 (dd, J = 9.2, 5.9 Hz, 1H), 4.70 – 4.60 (m, 2H), 3.84 (dd, J = 13.8, 10.5 Hz, 4H), 3.39 (t, J = 6.7 Hz, 4H), 3.23 (t, J = 12.2 Hz, 2H), 3.08 (ddd, J = 17.1, 11.5, 4.9 Hz, 2H), 2.93 – 2.79 (m, 2H), 2.78 – 2.57 (m, 5H), 2.53 (t, J = 6.9 Hz, 2H), 2.34 (d, J = 11.8 Hz, 1H), 2.26 (dd, J = 12.3, 6.2 Hz, 1H), 2.17 (d, J = 14.9 Hz, 1H), 2.10 (ddd, J = 10.5, 5.5, 3.0 Hz, 1H), 2.04 (d, J = 14.7 Hz, 1H), 1.99 – 1.94 (m, 2H). HRMS (m/z) for $C_{42}H_{49}ClN_{11}O_6^+$ $[M + H]^+$: calculated 838.3550, found 838.3552.

Example 50

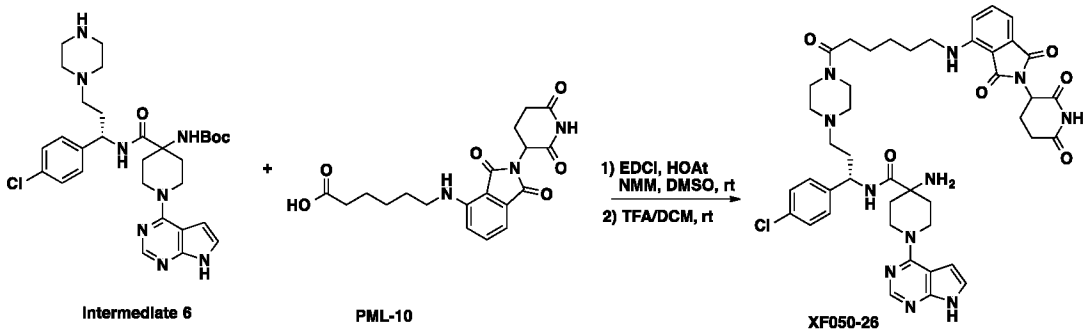
Synthesis of XF050-25



XF050-25 was synthesized following the standard procedure for preparing XF050-5 from intermediate 6 (15.9 mg, 0.022 mmol), PML-9 (8.2 mg, 0.022 mmol, 1.0 equiv), EDCI (6.5 mg, 0.033 mmol, 1.5 equiv), HOAt (4.5 mg, 0.033 mmol, 1.5 equiv), and NMM (6.7 mg, 0.066 mmol, 3.0 equiv) in DMSO (1 mL). Yellow solid in TFA salt form was isolated by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O). After this solid was dissolved in DCM (1 mL), TFA (1 mL) was added. The reaction was stirred at rt for 2h, before the solvent was evaporated. The resulting residue was purified by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O) to afford XF050-25 as yellow solid in TFA salt form (9.6 mg, 51%). ^1H NMR (600 MHz, CD_3OD) δ 8.38 (s, 1H), 7.54 (dd, J = 8.4, 7.2 Hz, 1H), 7.36 (dd, J = 6.5, 3.5 Hz, 5H), 7.07 – 7.00 (m, 2H), 6.91 (d, J = 3.7 Hz, 1H), 5.05 (ddd, J = 12.8, 5.5, 2.0 Hz, 1H), 5.00 (dd, J = 9.2, 5.9 Hz, 1H), 4.71 – 4.61 (m, 2H), 3.82 (q, J = 12.0 Hz, 4H), 3.36 (d, J = 5.8 Hz, 4H), 3.24 (td, J = 12.3, 4.5 Hz, 2H), 3.10 (td, J = 11.9, 4.9 Hz, 2H), 2.85 (dddd, J = 19.5, 14.1, 5.3, 2.2 Hz, 2H), 2.78 – 2.55 (m, 5H), 2.48 (s, 2H), 2.38 – 2.29 (m, 1H), 2.25 (tt, J = 12.2, 5.5 Hz, 1H), 2.19 – 2.06 (m, 2H), 2.02 (d, J = 14.6 Hz, 1H), 1.75 – 1.67 (m, 4H). HRMS (m/z) for $C_{43}H_{51}ClN_{11}O_6^+$ $[M + H]^+$: calculated 852.3707, found 852.3710.

Example 51

Synthesis of XF050-26

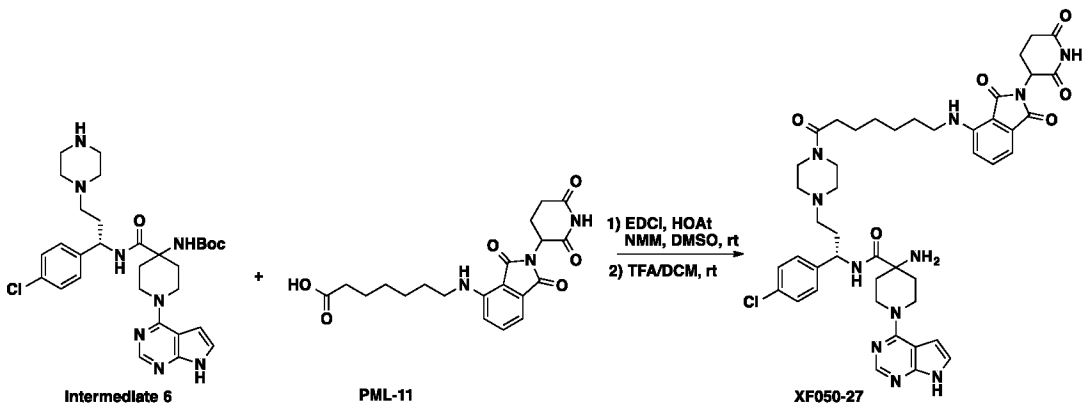


Intermediate 6 PML-10 XF050-26

XF050-26 was synthesized following the standard procedure for preparing XF050-5 from intermediate 6 (15.9 mg, 0.022 mmol), PML-10 (8.5 mg, 0.022 mmol, 1.0 equiv), EDCI (6.5 mg, 0.033 mmol, 1.5 equiv), HOAt (4.5 mg, 0.033 mmol, 1.5 equiv), and NMM (6.7 mg, 0.066 mmol, 3.0 equiv) in DMSO (1 mL). Yellow solid in TFA salt form was isolated by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O). After this solid was dissolved in DCM (1 mL), TFA (1 mL) was added. The reaction was stirred at rt for 2h, before the solvent was evaporated. The resulting residue was purified by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O) to afford XF050-26 as yellow solid in TFA salt form (13.9 mg, 73%). ^1H NMR (600 MHz, CD_3OD) δ 8.39 (s, 1H), 7.59 – 7.48 (m, 1H), 7.43 – 7.24 (m, 5H), 7.03 (dd, J = 7.8, 5.8 Hz, 2H), 6.93 (d, J = 3.7 Hz, 1H), 5.09 – 4.96 (m, 2H), 4.70 – 4.57 (m, 2H), 3.85 (q, J = 12.1 Hz, 4H), 3.33 (t, J = 6.8 Hz, 4H), 3.29 – 3.22 (m, 2H), 3.11 (td, J = 12.2, 5.1 Hz, 2H), 2.92 – 2.79 (m, 2H), 2.78 – 2.57 (m, 5H), 2.43 (t, J = 7.4 Hz, 2H), 2.38 – 2.30 (m, 1H), 2.26 (tt, J = 12.1, 5.5 Hz, 1H), 2.17 (d, J = 14.7 Hz, 1H), 2.13 – 2.07 (m, 1H), 2.07 – 1.99 (m, 1H), 1.73 – 1.61 (m, 4H), 1.46 (tt, J = 9.9, 6.4 Hz, 2H). HRMS (m/z) for $C_{44}H_{53}ClN_{11}O_6^+$ [M + H]$^+$: calculated 866.3863, found 866.3859.

Example 52

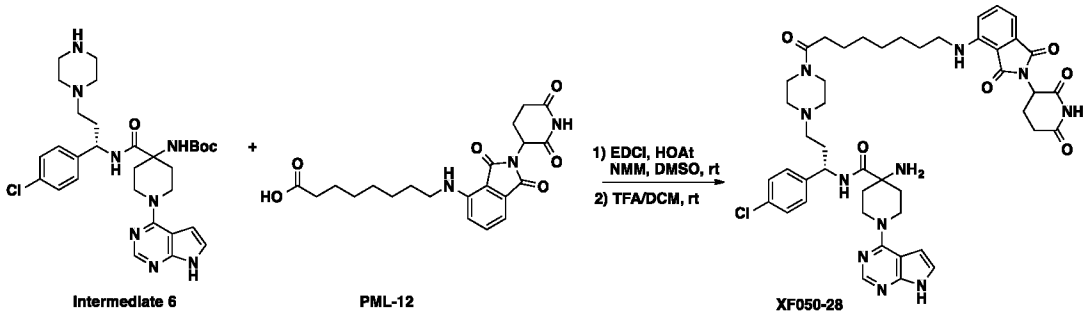
Synthesis of XF050-27



XF050-27 was synthesized following the standard procedure for preparing XF050-5 from intermediate 6 (15.9 mg, 0.022 mmol), PML-11 (8.8 mg, 0.022 mmol, 1.0 equiv), EDCI (6.5 mg, 0.033 mmol, 1.5 equiv), HOAt (4.5 mg, 0.033 mmol, 1.5 equiv), and NMM (6.7 mg, 0.066 mmol, 3.0 equiv) in DMSO (1 mL). Yellow solid in TFA salt form was isolated by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O). After this solid was dissolved in DCM (1 mL), TFA (1 mL) was added. The reaction was stirred at rt for 2h, before the solvent was evaporated. The resulting residue was purified by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O) to afford XF050-27 as yellow solid in TFA salt form (14.5 mg, 75%). ^1H NMR (600 MHz, CD_3OD) δ 8.39 (s, 1H), 7.54 (dd, J = 8.6, 7.1 Hz, 1H), 7.40 – 7.30 (m, 5H), 7.03 (t, J = 7.3 Hz, 2H), 6.94 (d, J = 3.7 Hz, 1H), 5.08 – 4.96 (m, 2H), 4.65 (d, J = 13.8 Hz, 2H), 3.85 (q, J = 12.1 Hz, 4H), 3.36 – 3.30 (m, 4H), 3.27 (td, J = 12.4, 4.5 Hz, 2H), 3.12 (td, J = 12.1, 5.1 Hz, 2H), 2.91 – 2.78 (m, 2H), 2.77 – 2.59 (m, 5H), 2.41 (d, J = 1.6 Hz, 2H), 2.37 – 2.31 (m, 1H), 2.26 (d, 1H), 2.17 (d, J = 15.0 Hz, 1H), 2.14 – 2.07 (m, 1H), 2.07 – 1.98 (m, 1H), 1.64 (dp, J = 37.0, 7.2 Hz, 4H), 1.49 – 1.35 (m, 4H). HRMS (m/z) for $C_{45}H_{55}ClN_{11}O_6^+$ [M + H]$^+$: calculated 880.4020, found 880.4026.

Example 53

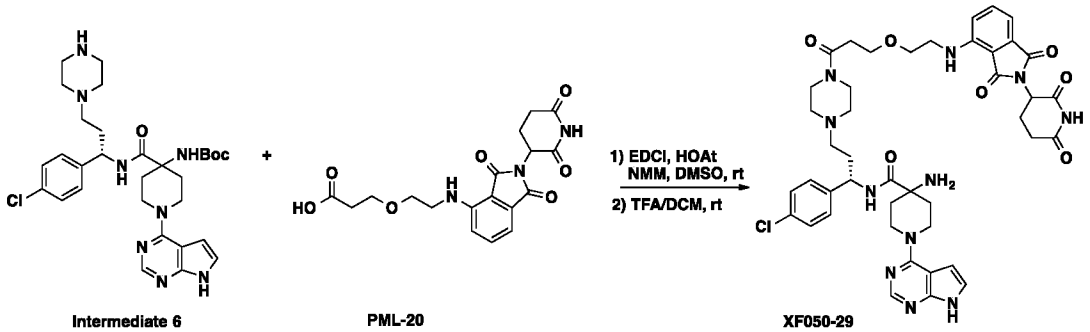
Synthesis of XF050-28



XF050-28 was synthesized following the standard procedure for preparing XF050-5 from intermediate 6 (15.9 mg, 0.022 mmol), PML-12 (9.1 mg, 0.022 mmol, 1.0 equiv), EDCI (6.5 mg, 0.033 mmol, 1.5 equiv), HOAt (4.5 mg, 0.033 mmol, 1.5 equiv), and NMM (6.7 mg, 0.066 mmol, 3.0 equiv) in DMSO (1 mL). Yellow solid in TFA salt form was isolated by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O). After this solid was dissolved in DCM (1 mL), TFA (1 mL) was added. The reaction was stirred at rt for 2h, before the solvent was evaporated. The resulting residue was purified by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O) to afford XF050-28 as yellow solid in TFA salt form (15.5 mg, 78%). ^1H NMR (600 MHz, CD_3OD) δ 8.39 (s, 1H), 7.54 (dd, J = 8.6, 7.1 Hz, 1H), 7.39 – 7.32 (m, 5H), 7.03 (dd, J = 7.8, 4.3 Hz, 2H), 6.94 (d, J = 3.7 Hz, 1H), 5.08 – 4.97 (m, 2H), 4.68 – 4.62 (m, 2H), 3.84 (q, J = 12.2 Hz, 4H), 3.35 – 3.31 (m, 4H), 3.28 – 3.24 (m, 2H), 3.12 (td, J = 12.2, 5.2 Hz, 2H), 2.85 (ddd, J = 17.6, 13.9, 5.4 Hz, 2H), 2.78 – 2.56 (m, 5H), 2.39 (t, J = 7.5 Hz, 2H), 2.34 (t, J = 10.4 Hz, 1H), 2.26 (tt, J = 12.1, 5.5 Hz, 1H), 2.17 (d, J = 14.8 Hz, 1H), 2.10 (ddt, J = 13.1, 5.6, 2.8 Hz, 1H), 2.03 (d, J = 14.6 Hz, 1H), 1.66 (p, J = 7.1 Hz, 2H), 1.58 (p, J = 7.5 Hz, 2H), 1.47 – 1.33 (m, 6H). HRMS (m/z) for $C_{46}H_{57}ClN_{11}O_6^+$ $[M + H]^+$: calculated 894.4176, found 894.4192.

Example 54

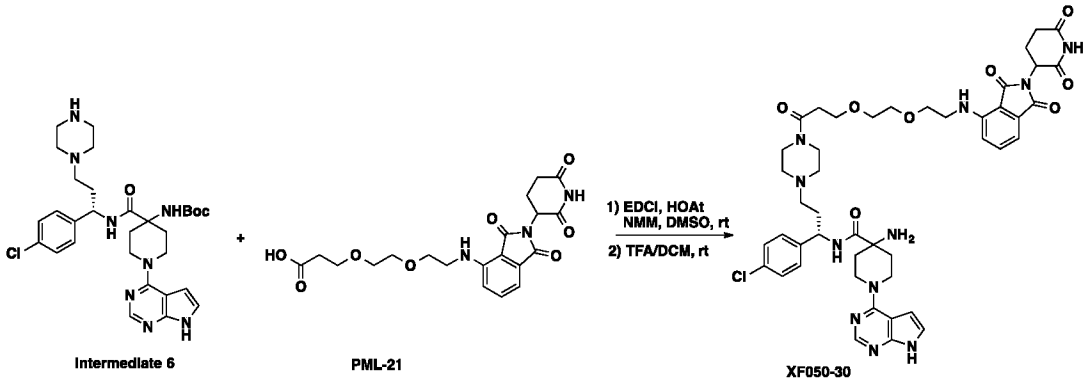
Synthesis of XF050-29



XF050-29 was synthesized following the standard procedure for preparing XF050-5 from intermediate 6 (15.9 mg, 0.022 mmol), PML-20 (8.6 mg, 0.022 mmol, 1.0 equiv), EDCI (6.5 mg, 0.033 mmol, 1.5 equiv), HOAt (4.5 mg, 0.033 mmol, 1.5 equiv), and NMM (6.7 mg, 0.066 mmol, 3.0 equiv) in DMSO (1 mL). Yellow solid in TFA salt form was isolated by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O). After this solid was dissolved in DCM (1 mL), TFA (1 mL) was added. The reaction was stirred at rt for 2h, before the solvent was evaporated. The resulting residue was purified by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O) to afford XF050-29 as yellow solid in TFA salt form (16.7 mg, 87%). ^1H NMR (600 MHz, CD_3OD) δ 8.39 (s, 1H), 7.57 (ddd, J = 8.6, 7.1, 3.9 Hz, 1H), 7.37 (dd, J = 3.9, 1.1 Hz, 1H), 7.34 – 7.28 (m, 4H), 7.10 – 7.03 (m, 2H), 6.93 (dd, J = 3.7, 1.5 Hz, 1H), 5.04 (ddd, J = 12.7, 5.5, 2.3 Hz, 1H), 4.68 – 4.59 (m, 3H), 3.91 – 3.74 (m, 6H), 3.70 (tt, J = 4.7, 2.2 Hz, 3H), 3.48 (td, J = 4.9, 4.3, 2.3 Hz, 3H), 3.15 (td, J = 15.0, 13.5, 8.3 Hz, 2H), 2.95 (dq, J = 12.2, 5.7 Hz, 2H), 2.88 – 2.78 (m, 2H), 2.77 – 2.54 (m, 6H), 2.32 – 2.06 (m, 5H), 2.02 (d, J = 14.6 Hz, 1H). HRMS (m/z) for $C_{43}H_{51}ClN_{11}O_7^+$ $[M + H]^+$: calculated 868.3656, found 868.3661.

Example 55

Synthesis of XF050-30

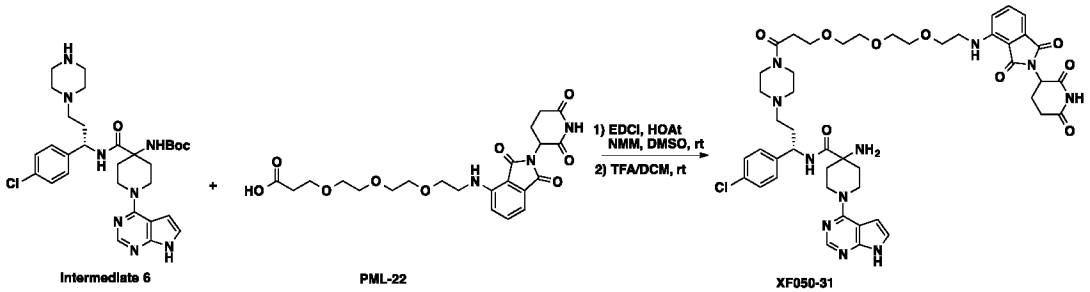


XF050-30 was synthesized following the standard procedure for preparing XF050-5 from intermediate 6 (15.9 mg, 0.022 mmol), PML-21 (9.5 mg, 0.022 mmol, 1.0 equiv), EDCI (6.5 mg, 0.033 mmol, 1.5 equiv), HOAt (4.5 mg, 0.033 mmol, 1.5 equiv), and NMM (6.7 mg, 0.066 mmol, 3.0 equiv) in DMSO (1 mL). Yellow solid in TFA salt form was isolated by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O). After this solid was dissolved in DCM (1 mL), TFA (1 mL) was added. The reaction was stirred at rt for 2h, before the solvent was evaporated. The resulting residue was purified by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O) to afford XF050-30 as yellow solid in TFA salt form (15.8 mg, 79%). ^1H

NMR (600 MHz, CD_3OD) δ 8.38 (s, 1H), 7.54 (ddt, *J* = 8.6, 7.1, 1.4 Hz, 1H), 7.37 (dd, *J* = 3.8, 1.3 Hz, 1H), 7.34 – 7.28 (m, 4H), 7.08 (d, *J* = 8.5 Hz, 1H), 7.04 (dd, *J* = 7.0, 2.7 Hz, 1H), 6.92 (dd, *J* = 3.8, 1.6 Hz, 1H), 5.05 (ddd, *J* = 12.6, 5.4, 3.8 Hz, 1H), 4.96 (dt, *J* = 9.6, 3.9 Hz, 1H), 4.68 – 4.54 (m, 3H), 3.89 – 3.80 (m, 3H), 3.73 (td, *J* = 6.0, 1.7 Hz, 2H), 3.68 (td, *J* = 5.2, 2.3 Hz, 2H), 3.65 – 3.54 (m, 5H), 3.46 (t, *J* = 5.1 Hz, 3H), 3.22 (td, *J* = 12.3, 4.4 Hz, 2H), 3.10 – 3.01 (m, 2H), 2.84 (ddt, *J* = 17.7, 13.8, 4.6 Hz, 2H), 2.77 – 2.57 (m, 6H), 2.35 – 2.07 (m, 5H), 2.02 (d, *J* = 14.7 Hz, 1H). HRMS (m/z) for $C_{45}H_{55}ClN_{11}O_8^+$ $[M + H]^+$: calculated 912.3918, found 912.3902.

Example 56

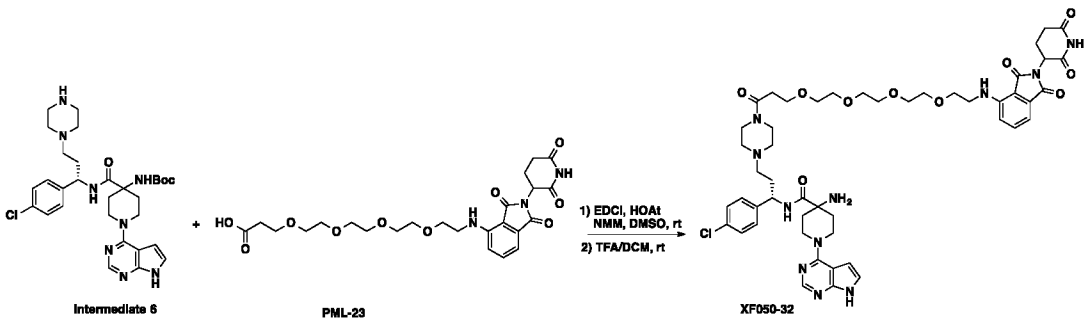
Synthesis of XF050-31



XF050-31 was synthesized following the standard procedure for preparing XF050-5 from intermediate 6 (15.9 mg, 0.022 mmol), PML-22 (10.5 mg, 0.022 mmol, 1.0 equiv), EDCI (6.5 mg, 0.033 mmol, 1.5 equiv), HOAt (4.5 mg, 0.033 mmol, 1.5 equiv), and NMM (6.7 mg, 0.066 mmol, 3.0 equiv) in DMSO (1 mL). Yellow solid in TFA salt form was isolated by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O). After this solid was dissolved in DCM (1 mL), TFA (1 mL) was added. The reaction was stirred at rt for 2h, before the solvent was evaporated. The resulting residue was purified by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O) to afford XF050-31 as yellow solid in TFA salt form (16.2 mg, 77%). ^1H NMR (600 MHz, CD_3OD) δ 8.38 (s, 1H), 7.54 (ddd, *J* = 8.6, 7.1, 1.5 Hz, 1H), 7.39 – 7.28 (m, 5H), 7.07 (d, *J* = 8.6 Hz, 1H), 7.04 (s, 1H), 6.92 (dd, *J* = 3.7, 1.6 Hz, 1H), 5.05 (ddd, *J* = 12.6, 5.4, 1.5 Hz, 1H), 4.99 (ddd, *J* = 9.4, 6.2, 3.8 Hz, 1H), 4.67 – 4.53 (m, 3H), 3.91 – 3.80 (m, 3H), 3.73 – 3.67 (m, 4H), 3.64 – 3.53 (m, 8H), 3.53 – 3.44 (m, 4H), 3.25 (t, *J* = 12.8 Hz, 2H), 3.09 (td, *J* = 11.9, 5.7 Hz, 2H), 2.91 – 2.80 (m, 2H), 2.77 – 2.57 (m, 7H), 2.37 – 2.23 (m, 2H), 2.20 – 2.07 (m, 2H), 2.03 (d, *J* = 14.7 Hz, 1H). HRMS (m/z) for $C_{47}H_{59}ClN_{11}O_9^+$ $[M + H]^+$: calculated 956.4180, found 956.4183.

Example 57

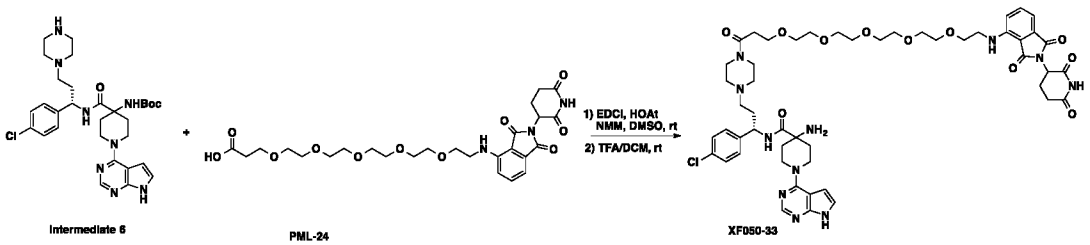
Synthesis of XF050-32



XF050-32 was synthesized following the standard procedure for preparing XF050-5 from intermediate 6 (15.9 mg, 0.022 mmol), PML-23 (11.5 mg, 0.022 mmol, 1.0 equiv), EDCI (6.5 mg, 0.033 mmol, 1.5 equiv), HOAt (4.5 mg, 0.033 mmol, 1.5 equiv), and NMM (6.7 mg, 0.066 mmol, 3.0 equiv) in DMSO (1 mL). Yellow solid in TFA salt form was isolated by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O). After this solid was dissolved in DCM (1 mL), TFA (1 mL) was added. The reaction was stirred at rt for 2h, before the solvent was evaporated. The resulting residue was purified by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O) to afford XF050-32 as yellow solid in TFA salt form (12.8 mg, 58%). ^1H NMR (600 MHz, CD_3OD) δ 8.38 (s, 1H), 7.54 (ddd, J = 8.6, 7.1, 1.5 Hz, 1H), 7.38 – 7.31 (m, 5H), 7.08 (d, J = 8.5 Hz, 1H), 7.04 (dd, J = 7.1, 2.1 Hz, 1H), 6.92 (dd, J = 3.8, 1.3 Hz, 1H), 5.05 (dd, J = 12.8, 5.5 Hz, 1H), 5.02 – 4.96 (m, 1H), 4.68 – 4.57 (m, 3H), 3.85 (dt, J = 15.4, 9.3 Hz, 3H), 3.73 – 3.68 (m, 4H), 3.62 (ttt, J = 5.6, 3.6, 1.9 Hz, 4H), 3.59 – 3.53 (m, 9H), 3.49 (t, J = 5.2 Hz, 3H), 3.25 (td, J = 12.1, 4.3 Hz, 2H), 3.09 (td, J = 12.1, 5.4 Hz, 2H), 2.89 – 2.80 (m, 2H), 2.77 – 2.56 (m, 7H), 2.38 – 2.24 (m, 2H), 2.19 – 2.08 (m, 2H), 2.03 (d, J = 14.7 Hz, 1H). HRMS (m/z) for $C_{49}H_{63}ClN_{11}O_{10}^+$ $[M + H]^+$: calculated 1000.4442, found 1000.4462.

Example 58

Synthesis of XF050-33

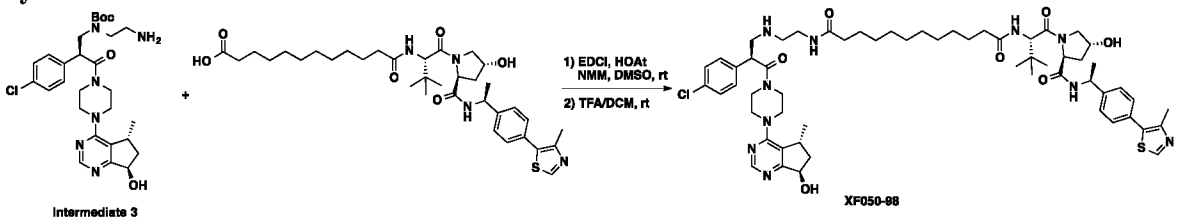


XF050-33 was synthesized following the standard procedure for preparing XF050-5 from intermediate 6 (15.9 mg, 0.022 mmol), PML-24 (12.5 mg, 0.022 mmol, 1.0 equiv), EDCI (6.5

mg, 0.033 mmol, 1.5 equiv), HOAt (4.5 mg, 0.033 mmol, 1.5 equiv), and NMM (6.7 mg, 0.066 mmol, 3.0 equiv) in DMSO (1 mL). Yellow solid in TFA salt form was isolated by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O). After this solid was dissolved in DCM (1 mL), TFA (1 mL) was added. The reaction was stirred at rt for 2h, before the solvent was evaporated. The resulting residue was purified by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O) to afford XF050-33 as yellow solid in TFA salt form (5.0 mg, 22%). ^{1}H NMR (600 MHz, CD_3OD) 8.37 (s, 1H), 7.55 (ddd, J = 8.4, 7.2, 0.9 Hz, 1H), 7.38 – 7.31 (m, 5H), 7.08 (d, J = 8.6 Hz, 1H), 7.05 (dd, J = 7.1, 1.3 Hz, 1H), 6.89 (d, J = 3.7 Hz, 1H), 5.05 (dd, J = 12.8, 5.5 Hz, 1H), 5.02 – 4.97 (m, 1H), 4.71 – 4.59 (m, 3H), 3.84 – 3.75 (m, 3H), 3.71 (t, J = 5.3 Hz, 4H), 3.66 – 3.58 (m, 7H), 3.58 – 3.51 (m, 10H), 3.49 (t, J = 5.2 Hz, 3H), 3.24 (td, J = 12.0, 4.2 Hz, 2H), 3.08 (td, J = 12.1, 5.4 Hz, 2H), 2.90 – 2.80 (m, 2H), 2.78 – 2.55 (m, 7H), 2.37 – 2.22 (m, 2H), 2.16 – 2.07 (m, 2H), 2.01 (d, J = 14.6 Hz, 1H). HRMS (m/z) for $C_{51}H_{67}ClN_{11}O_{11}^+$ $[M + H]^+$: calculated 1044.4705, found 1044.4711.

Example 59

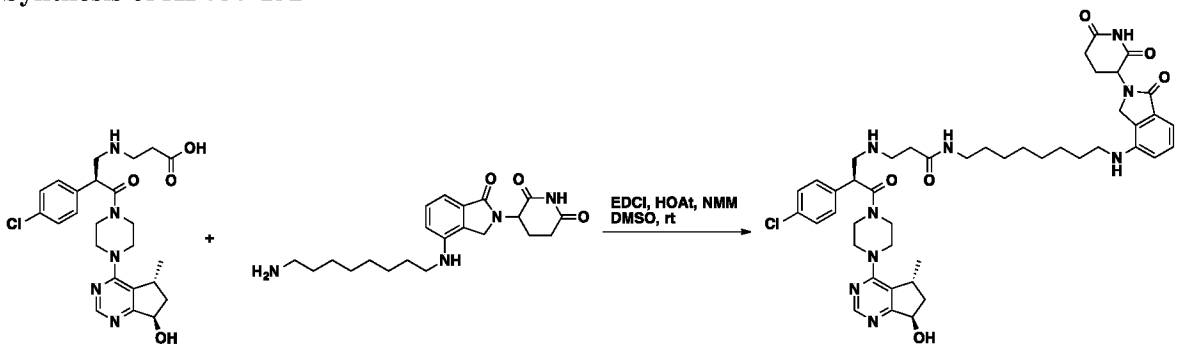
Synthesis of XF050-98



To a solution of Intermediate 3 (11.2 mg, 0.02 mmol) in DMSO (1 mL) were added 12-(((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-(((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-12-oxododecanoic acid (13.1 mg, 0.02 mmol, 1.0 equiv), EDCI (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide) (5.8 mg, 0.03 mmol, 1.5 equiv), HOAt (1-hydroxy-7-azabenzo-triazole) (4.1 mg, 0.03 mmol, 1.5 equiv), and NMM (N-Methylmorpholine) (6.1 mg, 0.06 mmol, 3.0 equiv). After being stirred overnight at room temperature, the resulting mixture was purified by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O) to afford the corresponding product. This product was dissolved in DCM (1mL), before the reaction mixture was treated with TFA (1 mL) for 30 min. After the solvent was evaporated, the residue was purified by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O) to afford XF050-98 as white solid in TFA salt form (17.4 mg, 79%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.98 (s, 1H), 8.58 (s, 1H), 7.49 – 7.41 (m, 6H), 7.36 (dd, J = 8.5, 1.8 Hz, 2H), 5.31 (t, J = 8.0 Hz, 1H), 5.00 (q, J = 7.0 Hz, 1H), 4.62 (s, 1H), 4.59 – 4.50 (m, 2H), 4.43 (dp, J = 4.3, 1.9 Hz, 1H), 4.18 (d, J = 13.7 Hz, 1H), 4.13 – 3.99 (m, 1H), 3.93 (ddt, J = 12.8,

9.8, 4.9 Hz, 2H), 3.90 – 3.78 (m, 3H), 3.75 (dd, *J* = 11.0, 4.0 Hz, 1H), 3.73 – 3.59 (m, 4H), 3.51 – 3.46 (m, 2H), 3.46 – 3.36 (m, 1H), 3.35 – 3.27 (m, 2H), 3.19 (t, *J* = 5.7 Hz, 2H), 2.48 (s, 3H), 2.36 – 2.14 (m, 5H), 1.95 (ddd, *J* = 13.3, 9.0, 4.6 Hz, 1H), 1.67 – 1.53 (m, 4H), 1.50 (d, *J* = 7.0 Hz, 3H), 1.31 (d, *J* = 4.9 Hz, 12H), 1.19 (d, *J* = 21.4, 7.0 Hz, 3H), 1.04 (s, 9H). HRMS (m/z) for $C_{58}H_{82}ClN_{10}O_7S^+$ $[M + H]^+$: calculated 1097.5772, found 1097.5768.

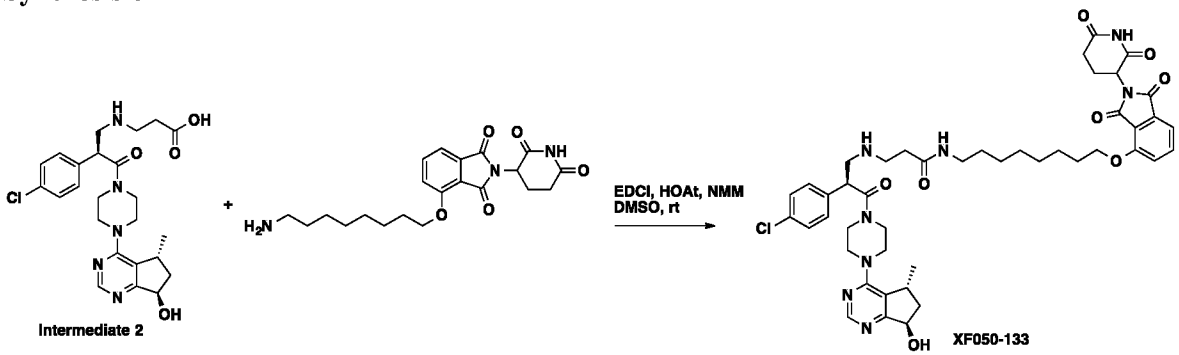
Example 60
Synthesis of XF050-132



Intermediate 2 XF050-132

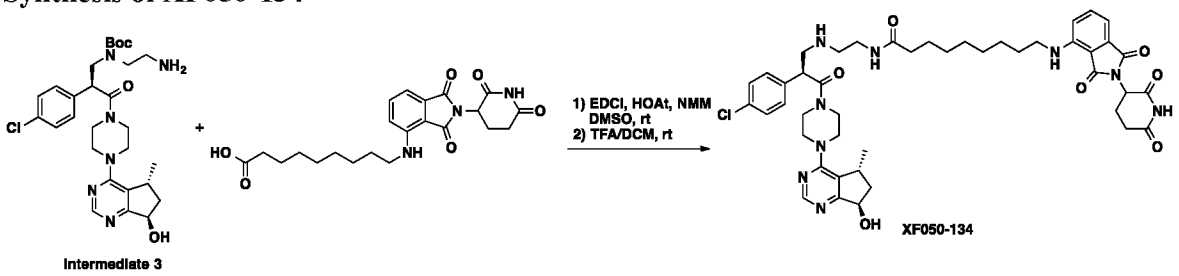
To a solution of Intermediate 2 (12.2 mg, 0.025 mmol) in DMSO (1 mL) were added 3-(4-((8-aminooctyl)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (9.7 mg, 0.025 mmol, 1.0 equiv), EDCI (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide) (7.4 mg, 0.038 mmol, 1.5 equiv), HOAt (1-hydroxy-7-azabenzo-triazole) (5.2 mg, 0.038 mmol, 1.5 equiv), and NMM (N-Methylmorpholine) (7.7 mg, 0.076 mmol, 3.0 equiv). After being stirred overnight at room temperature, the resulting mixture was purified by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O) to afford the XF050-132 as white solid in TFA salt form (8.8 mg, 41%). ^1H NMR (600 MHz, CD_3OD) δ 8.57 (s, 1H), 7.51 – 7.42 (m, 2H), 7.38 – 7.33 (m, 2H), 7.27 (ddd, *J* = 8.9, 6.9, 1.3 Hz, 1H), 7.21 – 7.12 (m, 1H), 7.00 – 6.90 (m, 1H), 5.30 (t, *J* = 7.9 Hz, 1H), 5.13 (dd, *J* = 13.4, 5.1 Hz, 1H), 4.57 – 4.48 (m, 1H), 4.36 (dd, *J* = 16.7, 1.1 Hz, 1H), 4.27 (d, *J* = 16.7 Hz, 1H), 4.19 – 4.12 (m, 1H), 3.97 – 3.46 (m, 8H), 3.44 – 3.23 (m, 6H), 3.21 – 3.10 (m, 2H), 3.02 – 2.81 (m, 2H), 2.68 – 2.59 (m, 2H), 2.46 (qd, *J* = 13.1, 5.1 Hz, 1H), 2.32 – 2.24 (m, 1H), 2.21 – 2.10 (m, 2H), 1.56 – 1.43 (m, 4H), 1.39 – 1.24 (m, 8H), 1.24 – 1.08 (m, 3H). HRMS (m/z) for $C_{45}H_{59}ClN_9O_6^+$ $[M + H]^+$: calculated 856.4271, found 856.4277.

Example 61
Synthesis of XF050-133



XF050-133 was synthesized following the standard procedure for preparing XF050-132 from intermediate 2 (12.2 mg, 0.025 mmol), 4-((8-aminooctyl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (10 mg, 0.025 mmol, 1.0 equiv), EDCI (7.4 mg, 0.038 mmol, 1.5 equiv), HOAt (5.2 mg, 0.038 mmol, 1.5 equiv), and NMM (7.7 mg, 0.06 mmol, 3.0 equiv) in DMSO (1 mL). XF050-133 was obtained as white solid in TFA salt form (10.2 mg, 47%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.57 (d, J = 2.2 Hz, 1H), 7.81 – 7.74 (m, 1H), 7.49 – 7.38 (m, 4H), 7.38 – 7.33 (m, 2H), 5.30 (t, J = 8.0 Hz, 1H), 5.10 (dd, J = 12.8, 5.5 Hz, 1H), 4.61 – 4.49 (m, 1H), 4.25 – 4.13 (m, 3H), 3.98 – 3.76 (m, 3H), 3.73 – 3.58 (m, 4H), 3.43 – 3.36 (m, 1H), 3.35 – 3.28 (m, 2H), 3.21 – 3.16 (m, 2H), 2.96 – 2.82 (m, 1H), 2.79 – 2.67 (m, 2H), 2.64 (t, J = 6.2 Hz, 2H), 2.31 – 2.24 (m, 1H), 2.23 – 2.03 (m, 2H), 1.86 – 1.81 (m, 2H), 1.59 – 1.45 (m, 4H), 1.46 – 1.33 (m, 8H), 1.17 (d, J = 7.0 Hz, 3H). HRMS (m/z) for $C_{45}H_{56}ClN_8O_8^+$ $[M + H]^+$: calculated 871.3904, found 871.3938.

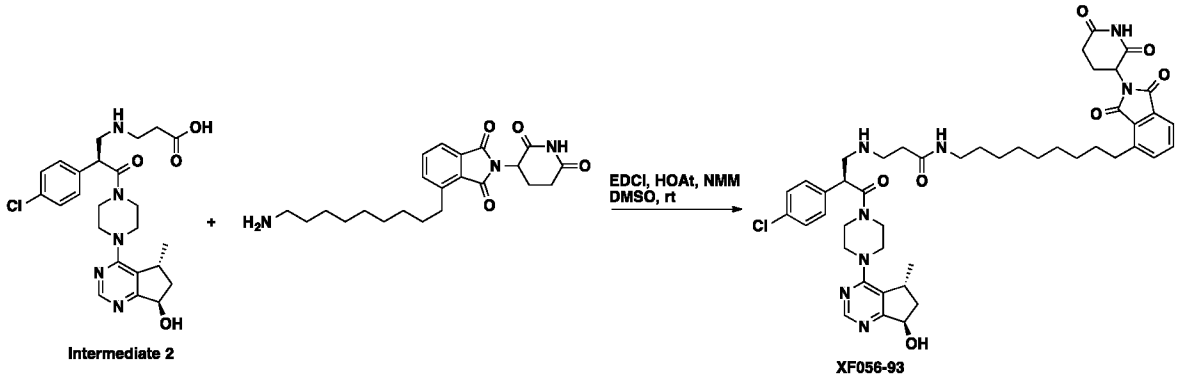
Example 62
Synthesis of XF050-134



XF050-134 was synthesized following the standard procedure for preparing XF050-98 from intermediate 3 (19.2 mg, 0.034 mmol), 9-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)nonanoic acid (14.7 mg, 0.034 mmol, 1.0 equiv), EDCI (10 mg, 0.051 mmol, 1.5 equiv), HOAt (7 mg, 0.051 mmol, 1.5 equiv), and NMM (10.1 mg, 0.1 mmol, 3.0 equiv) in DMSO (1 mL). XF050-134 was obtained as yellow solid in TFA salt form (22.1 mg, 74%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.57 (d, J = 3.9 Hz, 1H), 7.58 – 7.32 (m, 5H), 7.12 – 6.90 (m, 2H),

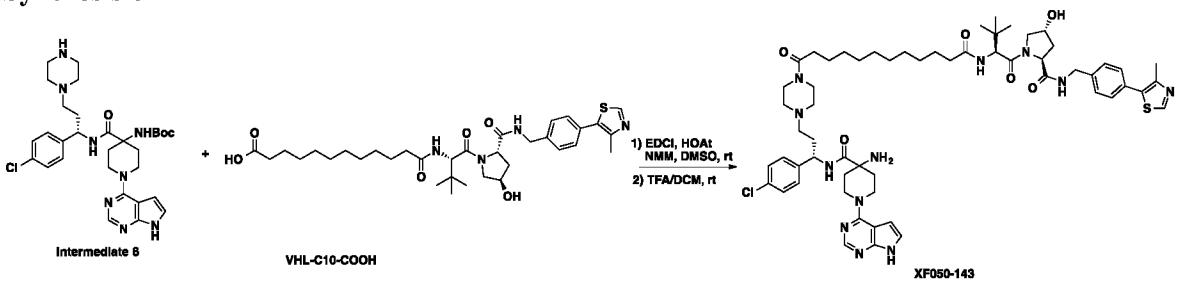
5.30 (t, J = 7.9 Hz, 1H), 5.06 (ddd, J = 12.9, 5.6, 3.4 Hz, 1H), 4.64 – 4.52 (m, 1H), 4.24 – 3.31 (m, 15H), 3.24 – 3.15 (m, 2H), 2.94 – 2.79 (m, 2H), 2.76 – 2.57 (m, 1H), 2.34 – 2.02 (m, 5H), 1.71 – 1.49 (m, 4H), 1.41 – 1.27 (m, 8H), 1.16 (d, J = 7.0 Hz, 3H). HRMS (m/z) for $C_{45}H_{57}ClN_9O_7^+$ $[M + H]^+$: calculated 870.4064, found 870.4056.

Example 63
Synthesis of XF050-93



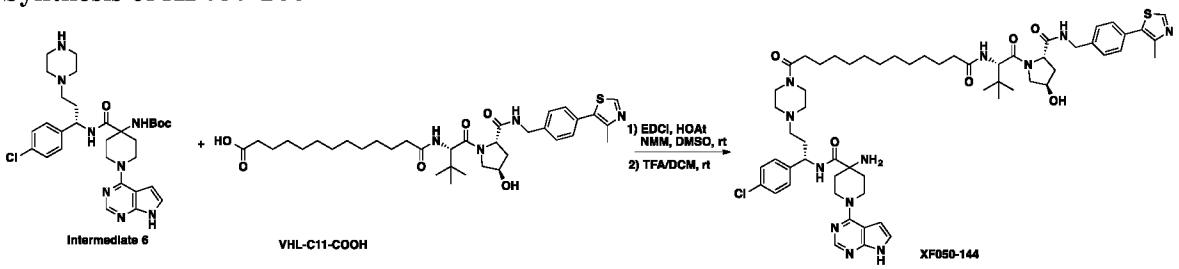
XF056-93 was synthesized following the standard procedure for preparing XF050-132 from intermediate 2 (9.7 mg, 0.02 mmol), 4-(9-aminononyl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (8 mg, 0.025 mmol, 1.0 equiv), EDCI (5.8 mg, 0.038 mmol, 1.5 equiv), HOAt (4.1 mg, 0.038 mmol, 1.5 equiv), and NMM (6.1 mg, 0.06 mmol, 3.0 equiv) in DMSO (1 mL). XF056-93 was obtained as white solid in TFA salt form (11.2 mg, 64%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.57 (d, J = 4.1 Hz, 1H), 7.74 – 7.68 (m, 2H), 7.65 – 7.59 (m, 1H), 7.47 – 7.42 (m, 2H), 7.36 (dd, J = 8.4, 1.2 Hz, 2H), 5.31 (t, J = 8.0 Hz, 1H), 5.13 (ddd, J = 12.8, 5.5, 2.7 Hz, 1H), 4.54 (dd, J = 9.4, 4.1 Hz, 1H), 4.17-4.10(m, 1H), 3.95 – 3.86 (m, 2H), 3.82 (s, 1H), 3.71 – 3.59 (m, 3H), 3.47 – 3.23 (m, 6H), 3.16 (t, J = 7.2 Hz, 2H), 3.12 – 3.06 (m, 2H), 2.94 – 2.84 (m, 1H), 2.80 – 2.69 (m, 2H), 2.67 – 2.62 (m, 2H), 2.29 (dd, J = 12.8, 7.5 Hz, 1H), 2.21 – 2.11 (m, 2H), 1.65 (q, J = 7.5 Hz, 2H), 1.48 (t, J = 7.1 Hz, 2H), 1.36 (s, 5H), 1.30 (d, J = 3.4 Hz, 5H), 1.17 (d, J = 7.0 Hz, 3H). HRMS (m/z) for $C_{46}H_{58}ClN_8O_7^+$ $[M + H]^+$: calculated 869.4112, found 869.4123.

Example 64
Synthesis of XF050-143



XF050-143 was synthesized following the standard procedure for preparing XF050-5 from intermediate 6 (14.2 mg, 0.02 mmol), VHL-C10-COOH (12.8 mg, 0.02 mmol, 1.0 equiv), EDCI (5.8 mg, 0.03 mmol, 1.5 equiv), HOAt (4.1 mg, 0.03 mmol, 1.5 equiv), and NMM (6.1 mg, 0.06 mmol, 3.0 equiv) in DMSO (1 mL). XF050-143 was obtained as white solid in TFA salt form (13.5 mg, 60%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.93 (s, 1H), 8.39 (s, 1H), 7.57 – 7.29 (m, 9H), 6.93 (d, J = 3.7 Hz, 1H), 5.01 (dd, J = 9.3, 5.8 Hz, 1H), 4.64 (d, J = 12.5 Hz, 3H), 4.60 – 4.47 (m, 3H), 4.35 (d, J = 15.4 Hz, 1H), 3.95 – 3.75 (m, 4H), 3.30 – 3.24 (m, 9H), 3.13 (td, J = 12.2, 5.1 Hz, 1H), 2.68 (ddd, J = 15.2, 10.9, 4.7 Hz, 1H), 2.61 (ddd, J = 15.0, 10.8, 4.6 Hz, 1H), 2.47 (s, 3H), 2.43 – 2.32 (m, 4H), 2.32 – 2.14 (m, 4H), 2.12 – 2.00 (m, 2H), 1.58 (dp, J = 14.4, 7.3, 6.6 Hz, 4H), 1.38 – 1.25 (m, 12H), 1.03 (s, 9H). HRMS (m/z) for $C_{59}H_{82}ClN_{12}O_6S^+$ $[M + H]^+$: calculated 1121.5884, found 1121.5898.

Example 65
Synthesis of XF050-144

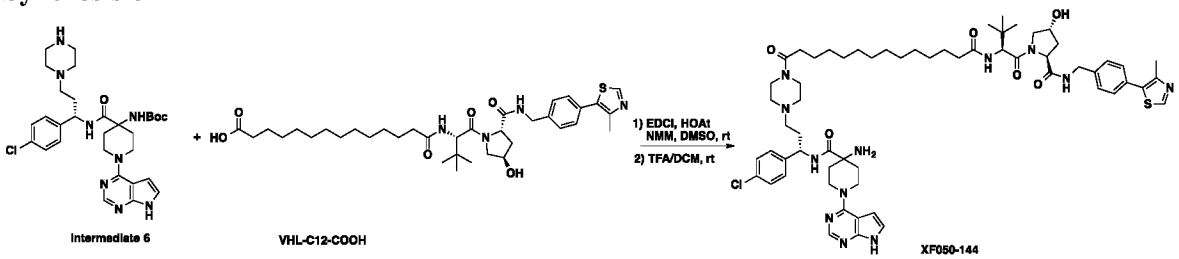


XF050-144 was synthesized following the standard procedure for preparing XF050-5 from intermediate 6 (14.2 mg, 0.02 mmol), VHL-C11-COOH (13.1 mg, 0.02 mmol, 1.0 equiv), EDCI (5.8 mg, 0.03 mmol, 1.5 equiv), HOAt (4.1 mg, 0.03 mmol, 1.5 equiv), and NMM (6.1 mg, 0.06 mmol, 3.0 equiv) in DMSO (1 mL). XF050-144 was obtained as white solid in TFA salt form (15 mg, 66%). ^{1}H NMR (600 MHz, CD_3OD) δ 9.06 – 8.86 (m, 1H), 8.41 – 8.34 (m, 1H), 7.57 – 7.27 (m, 9H), 6.94 (q, J = 3.9 Hz, 1H), 5.00 (td, J = 8.9, 5.1 Hz, 1H), 4.71 – 4.64 (m, 3H), 4.63 – 4.46 (m, 3H), 4.35 (dd, J = 15.5, 7.0 Hz, 1H), 3.95 – 3.76 (m, 4H), 3.61 – 2.89 (m, 10H), 2.65 – 1.95 (m, 15H), 1.58 (dh, J = 15.0, 7.3 Hz, 4H), 1.30 (dd, J = 13.9, 6.9 Hz,

14H), 1.09 – 0.89 (m, 9H). HRMS (m/z) for $C_{60}H_{84}ClN_{12}O_6S^+$ $[M + H]^+$: calculated 1135.6041, found 1135.6034.

Example 66

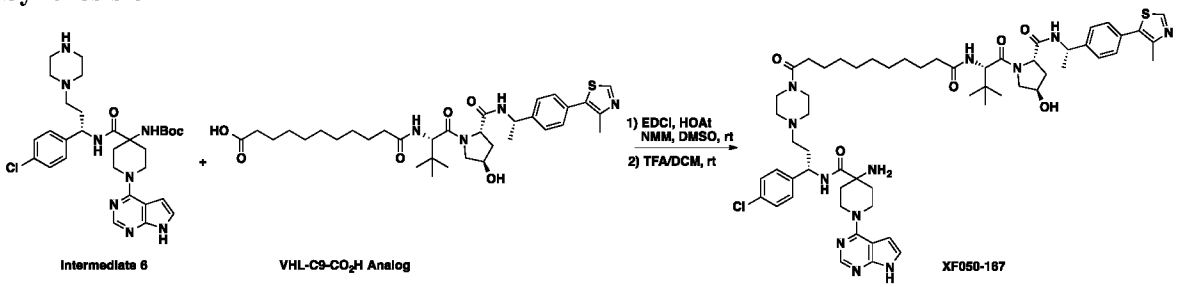
Synthesis of XF050-145



XF050-145 was synthesized following the standard procedure for preparing XF050-5 from intermediate 6 (14.2 mg, 0.02 mmol), VHL-C12-COOH (13.4 mg, 0.02 mmol, 1.0 equiv), EDCI (5.8 mg, 0.03 mmol, 1.5 equiv), HOAt (4.1 mg, 0.03 mmol, 1.5 equiv), and NMM (6.1 mg, 0.06 mmol, 3.0 equiv) in DMSO (1 mL). XF050-145 was obtained as white solid in TFA salt form (20.2 mg, 88%). ^{1}H NMR (600 MHz, CD_3OD) δ 9.04 (s, 1H), 8.40 (s, 1H), 7.55 – 7.24 (m, 9H), 7.07 – 6.84 (m, 1H), 5.01 (dd, J = 9.3, 5.8 Hz, 1H), 4.71 – 4.63 (m, 3H), 4.63 – 4.43 (m, 3H), 4.36 (d, J = 15.5 Hz, 1H), 3.95 – 3.77 (m, 4H), 3.61 – 2.95 (m, 10H), 2.66 (dddd, J = 44.2, 15.0, 10.8, 4.6 Hz, 2H), 2.49 (s, 3H), 2.45 – 2.14 (m, 8H), 2.12 – 1.97 (m, 2H), 1.63 – 1.53 (m, 4H), 1.39 – 1.19 (m, 16H), 1.03 (s, 9H). HRMS (m/z) for $C_{61}H_{86}ClN_{12}O_6S^+$ $[M + H]^+$: calculated 1149.6197, found 1149.6176.

Example 67

Synthesis of XF050-167

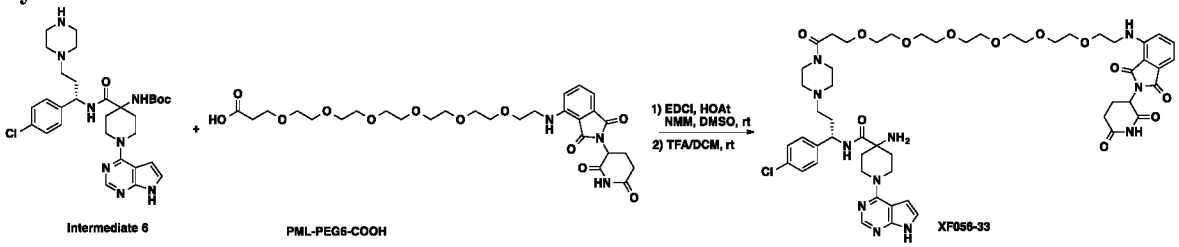


XF050-167 was synthesized following the standard procedure for preparing XF050-5 from intermediate 6 (23.5 mg, 0.033 mmol), VHL-C9-COOH Analog (21.2 mg, 0.033 mmol, 1.0 equiv), EDCI (9.6 mg, 0.05 mmol, 1.5 equiv), HOAt (6.8 mg, 0.05 mmol, 1.5 equiv), and NMM (10.1 mg, 0.1 mmol, 3.0 equiv) in DMSO (1 mL). XF050-167 was obtained as white solid in TFA salt form (22.4 mg, 61%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.95 (d, J = 6.3 Hz, 1H), 8.39 (s, 1H), 7.47 – 7.40 (m, 4H), 7.40 – 7.30 (m, 5H), 6.94 (d, J = 3.8 Hz, 1H), 5.08 – 4.95 (m, 1H), 4.69 – 4.63 (m, 3H), 4.61 – 4.52 (m, 1H), 4.46 – 4.35 (m, 1H), 3.98 – 3.81 (m, 4H), 3.74

(dd, J = 11.0, 4.0 Hz, 1H), 3.64 – 2.91 (m, 10H), 2.69 (ddd, J = 15.1, 10.9, 4.7 Hz, 1H), 2.62 (ddd, J = 15.1, 10.8, 4.7 Hz, 1H), 2.48 (s, 3H), 2.44 – 2.13 (m, 8H), 2.04 (dq, J = 14.7, 3.2, 2.2 Hz, 1H), 1.95 (ddd, J = 13.3, 9.1, 4.5 Hz, 1H), 1.66 – 1.53 (m, 4H), 1.50 (d, J = 7.0 Hz, 3H), 1.41 – 1.23 (m, 10H), 1.04 (s, 9H). HRMS (m/z) for $C_{59}H_{82}ClN_{12}O_6S^+$ [M + H]$^+$: calculated 1121.5884, found 1121.5869.

Example 68

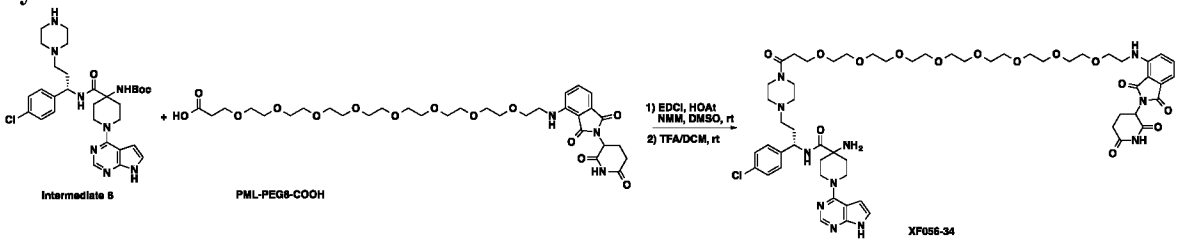
Synthesis of XF056-33



XF056-33 was synthesized following the standard procedure for preparing XF050-5 from intermediate 6 (12 mg, 0.02 mmol), PML-PEG6-COOH (12.2 mg, 0.02 mmol, 1.0 equiv), EDCI (5.8 mg, 0.03 mmol, 1.5 equiv), HOAt (4.1 mg, 0.03 mmol, 1.5 equiv), and NMM (6.1 mg, 0.06 mmol, 3.0 equiv) in DMSO (1 mL). XF056-33 was obtained as yellow solid in TFA salt form (10.3 mg, 47%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.38 (s, 1H), 7.61 – 7.51 (m, 1H), 7.44 – 7.28 (m, 4H), 7.07 (dd, J = 20.2, 7.8 Hz, 2H), 6.92 (d, J = 3.6 Hz, 1H), 5.09 – 4.98 (m, 2H), 4.65 (d, J = 12.4 Hz, 2H), 3.91 – 3.79 (m, 2H), 3.79 – 3.69 (m, 4H), 3.69 – 3.48 (m, 23H), 3.41 – 3.07 (m, 10H), 2.87 (t, J = 14.8 Hz, 1H), 2.80 – 2.53 (m, 5H), 2.41 – 2.24 (m, 3H), 2.15 (dd, J = 29.7, 13.5 Hz, 2H), 2.04 (d, J = 14.7 Hz, 1H). HRMS (m/z) for $C_{53}H_{71}ClN_{11}O_{12}^+$ [M + H]$^+$: calculated 1088.4967, found 1088.4974.

Example 69

Synthesis of XF056-34

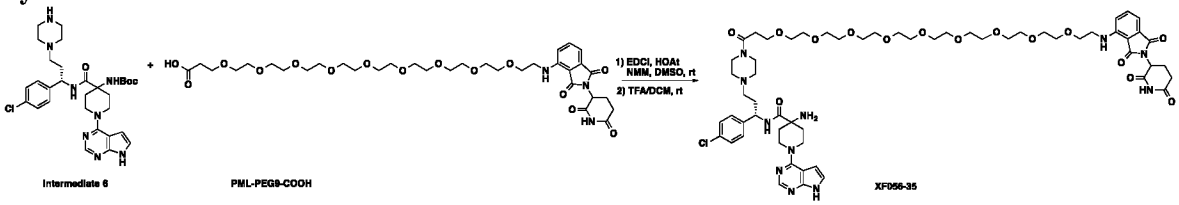


XF056-34 was synthesized following the standard procedure for preparing XF050-5 from intermediate 6 (12.2 mg, 0.02 mmol), PML-PEG8-COOH (14.1 mg, 0.02 mmol, 1.0 equiv), EDCI (5.8 mg, 0.03 mmol, 1.5 equiv), HOAt (4.1 mg, 0.03 mmol, 1.5 equiv), and NMM (6.1 mg, 0.06 mmol, 3.0 equiv) in DMSO (1 mL). XF056-34 was obtained as yellow solid in TFA salt form (16.1 mg, 68%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.39 (s, 1H), 7.54 (t, J = 7.8 Hz,

1H), 7.41 – 7.26 (m, 4H), 7.06 (dd, J = 21.5, 7.8 Hz, 2H), 6.93 (d, J = 3.7 Hz, 1H), 5.13 – 5.01 (m, 2H), 4.61 (d, J = 14.1 Hz, 2H), 3.94 – 3.79 (m, 2H), 3.80 – 3.37 (m, 36H), 3.36 – 3.00 (m, 10H), 2.91 – 2.83 (m, 1H), 2.79 – 2.53 (m, 5H), 2.40 – 2.26 (m, 2H), 2.22 – 2.00 (m, 3H). HRMS (m/z) for $C_{57}H_{79}ClN_{11}O_{14}^+$ $[M + H]^+$: calculated 1176.5491, found 1176.5475.

Example 70

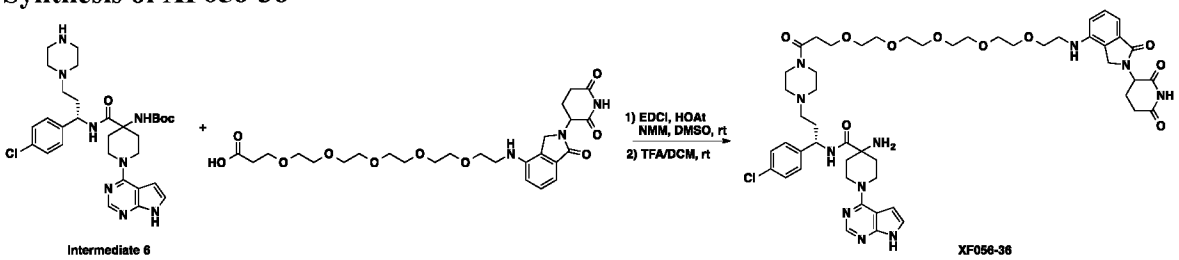
Synthesis of XF056-35



XF056-35 was synthesized following the standard procedure for preparing XF050-5 from intermediate 6 (12.2 mg, 0.034 mmol), PML-PEG9-COOH (14.8 mg, 0.02 mmol, 1.0 equiv), EDCI (5.8 mg, 0.03 mmol, 1.5 equiv), HOAt (4.1 mg, 0.03 mmol, 1.5 equiv), and NMM (6.1 mg, 0.1 mmol, 3.0 equiv) in DMSO (1 mL). XF056-35 was obtained as yellow solid in TFA salt form (15.9 mg, 65%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.40 (s, 1H), 7.56 (t, J = 7.8 Hz, 1H), 7.46 – 7.30 (m, 4H), 7.08 (dd, J = 22.3, 7.9 Hz, 2H), 6.94 (d, J = 3.6 Hz, 1H), 5.15 – 4.98 (m, 2H), 4.64 (d, J = 14.3 Hz, 2H), 3.87 (q, J = 10.9 Hz, 2H), 3.81 – 3.39 (m, 40H), 3.39 – 2.96 (m, 10H), 2.87 (td, J = 16.2, 14.3, 5.3 Hz, 1H), 2.81 – 2.57 (m, 5H), 2.41 – 2.24 (m, 2H), 2.24 – 1.97 (m, 3H). HRMS (m/z) for $C_{59}H_{83}ClN_{11}O_{15}^+$ $[M + H]^+$: calculated 1220.5753, found 1220.5767.

Example 71

Synthesis of XF056-36

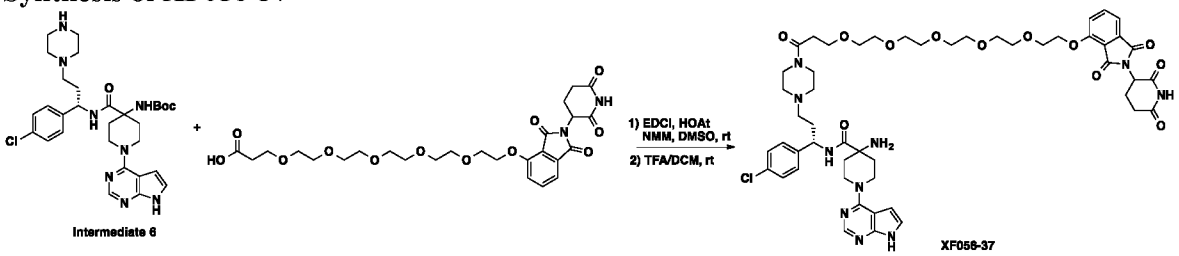


XF056-36 was synthesized following the standard procedure for preparing XF050-5 from intermediate 6 (12.2 mg, 0.02 mmol), 1-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)amino)-3,6,9,12,15-pentaoxaoctadecan-18-oic acid (14.7 mg, 0.02 mmol, 1.0 equiv), EDCI (5.8 mg, 0.03 mmol, 1.5 equiv), HOAt (4.1 mg, 0.03 mmol, 1.5 equiv), and NMM (6.1 mg, 0.06 mmol, 3.0 equiv) in DMSO (1 mL). XF056-36 was obtained as yellow solid in TFA salt form (16.1 mg, 78%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.39 (d, J = 8.9 Hz, 1H), 7.41 – 7.32 (m,

6H), 7.00 – 6.97 (m, 1H), 6.96 – 6.92 (m, 1H), 5.18 (d, J = 13.2 Hz, 1H), 5.05 – 4.98 (m, 1H), 4.65 (s, 2H), 4.37 (d, J = 16.8 Hz, 1H), 4.27 (dd, J = 16.8, 3.3 Hz, 1H), 4.07 – 3.92 (m, 2H), 3.92 – 3.80 (m, 2H), 3.79 – 3.68 (m, 2H), 3.67 – 3.36 (m, 20H), 3.38 – 3.04 (m, 10H), 3.02 – 2.80 (m, 2H), 2.67 (dd, J = 31.5, 17.7 Hz, 4H), 2.53 – 2.42 (m, 1H), 2.33 (s, 2H), 2.18 (d, J = 14.2 Hz, 1H), 2.10 – 1.99 (m, 1H). HRMS (m/z) for $C_{51}H_{69}ClN_{11}O_{10}^+$ [M + H]$^+$: calculated 1030.4912, found 1030.4945.

Example 72

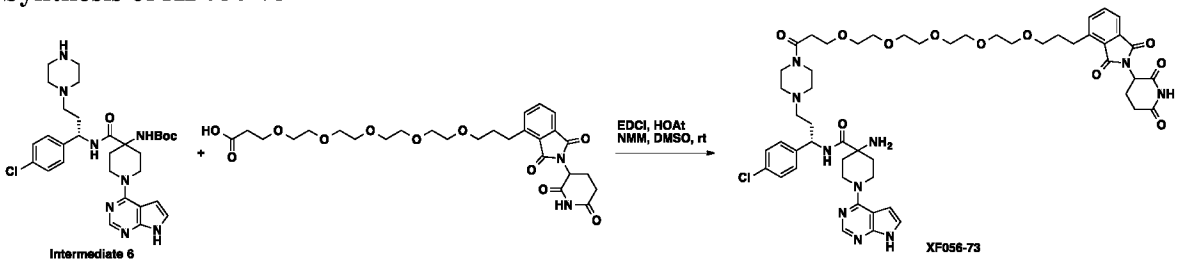
Synthesis of XF056-37



XF056-37 was synthesized following the standard procedure for preparing XF050-5 from intermediate 6 (12.2 mg, 0.034 mmol), 1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)-3,6,9,12,15-pentaoxaoctadecan-18-oic acid (11.2 mg, 0.02 mmol, 1.0 equiv), EDCI (5.8 mg, 0.03 mmol, 1.5 equiv), HOAt (4.1 mg, 0.03 mmol, 1.5 equiv), and NMM (6.1 mg, 0.06 mmol, 3.0 equiv) in DMSO (1 mL). XF056-37 was obtained as yellow solid in TFA salt form (13.4 mg, 64%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.39 (s, 1H), 7.78 (t, J = 7.5 Hz, 1H), 7.47 (d, J = 8.2 Hz, 2H), 7.36 (q, J = 8.4 Hz, 4H), 6.92 (d, J = 3.6 Hz, 1H), 5.11 (dd, J = 12.8, 5.4 Hz, 1H), 5.01 (d, J = 8.2 Hz, 1H), 4.79 – 4.60 (m, 2H), 4.38 (s, 2H), 3.92 (d, J = 4.5 Hz, 2H), 3.88 – 3.78 (m, 2H), 3.78 – 3.69 (m, 4H), 3.60 (q, J = 17.4, 13.4 Hz, 16H), 3.37 – 3.02 (m, 10H), 2.88 (t, J = 15.1 Hz, 1H), 2.81 – 2.54 (m, 5H), 2.43 – 2.25 (m, 2H), 2.22 – 2.10 (m, 2H), 2.04 (d, J = 14.6 Hz, 1H). HRMS (m/z) for $C_{51}H_{66}ClN_{10}O_{12}^+$ [M + H]$^+$: calculated 1045.4545, found 1045.4534.

Example 73

Synthesis of XF056-73

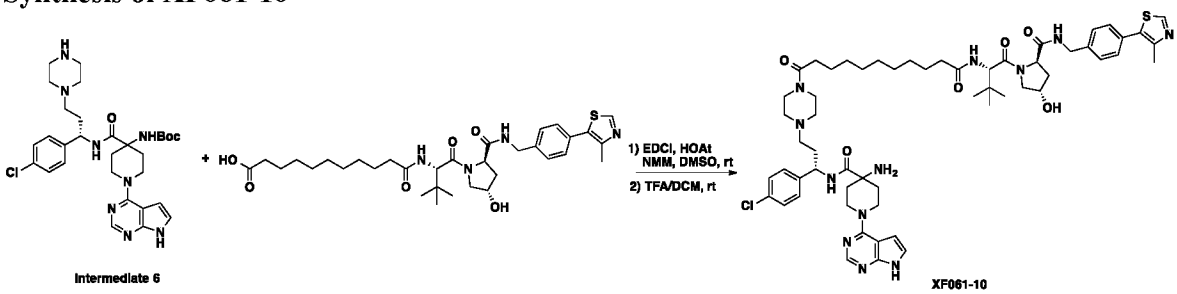


XF056-73 was synthesized following the standard procedure for preparing XF050-5 from intermediate 6 (12.7 mg, 0.02 mmol), 19-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-

yl)-4,7,10,13,16-pentaoxanonadecanoic acid (11.4 mg, 0.02 mmol, 1.0 equiv), EDCI (5.8 mg, 0.03 mmol, 1.5 equiv), HOAt (4.1 mg, 0.03 mmol, 1.5 equiv), and NMM (6.1 mg, 0.06 mmol, 3.0 equiv) in DMSO (1 mL). XF056-73 was obtained as yellow solid in TFA salt form (12.1 mg, 58%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.40 (s, 1H), 7.80 – 7.71 (m, 2H), 7.66 (dd, J = 6.1, 2.8 Hz, 1H), 7.45 – 7.26 (m, 4H), 6.95 (d, J = 3.6 Hz, 1H), 5.13 (dd, J = 12.8, 5.4 Hz, 1H), 5.02 (t, J = 7.7 Hz, 1H), 4.66 (s, 2H), 3.86 (q, J = 11.8 Hz, 2H), 3.73 (t, J = 6.1 Hz, 2H), 3.59 (dt, J = 17.2, 4.5 Hz, 17H), 3.51 (t, J = 6.4 Hz, 2H), 3.36 – 3.24 (m, 9H), 3.23 – 3.06 (m, 3H), 2.94 – 2.84 (m, 1H), 2.81 – 2.55 (m, 5H), 2.42 – 2.25 (m, 2H), 2.16 (t, J = 17.3 Hz, 2H), 2.04 (d, J = 14.8 Hz, 1H), 1.94 (p, J = 6.8 Hz, 2H). HRMS (m/z) for $C_{52}H_{68}ClN_{10}O_{11}^+$ [M + H]$^+$: calculated 1043.4752, found 1043.4746.

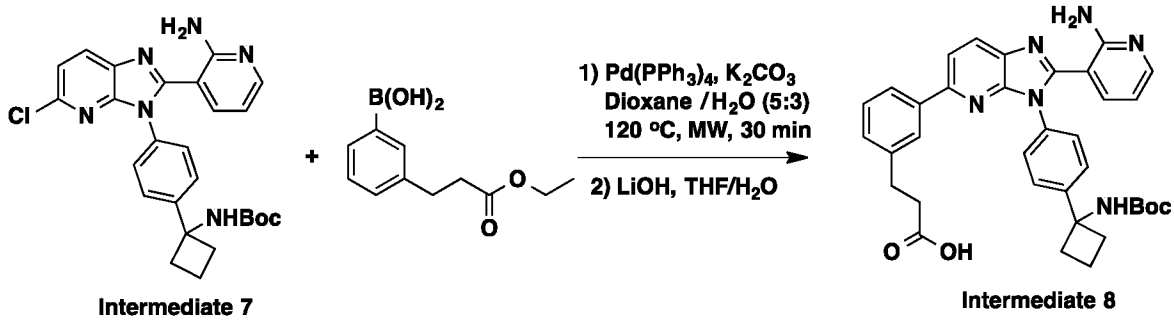
Example 74

Synthesis of XF061-10



XF061-10 was synthesized following the standard procedure for preparing XF050-5 from intermediate 6 (12.1 mg, 0.02 mmol), 11-(((*S*)-1-((2*R*,4*S*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-11-oxoundecanoic acid (12.5 mg, 0.02 mmol, 1.0 equiv), EDCI (5.8 mg, 0.03 mmol, 1.5 equiv), HOAt (4.1 mg, 0.03 mmol, 1.5 equiv), and NMM (6.1 mg, 0.06 mmol, 3.0 equiv) in DMSO (1 mL). XF061-10 was obtained as white solid in TFA salt form (9.3 mg, 42%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.94 (s, 1H), 8.39 (s, 1H), 7.50 – 7.42 (m, 2H), 7.42 – 7.32 (m, 7H), 6.94 (d, J = 3.7 Hz, 1H), 5.01 (dd, J = 9.3, 5.9 Hz, 1H), 4.67 (dd, J = 14.4, 8.6 Hz, 2H), 4.57 (dd, J = 8.4, 6.5 Hz, 1H), 4.54 – 4.45 (m, 2H), 4.43 (s, 1H), 4.35 (d, J = 15.6 Hz, 1H), 3.99 (dd, J = 10.8, 4.9 Hz, 1H), 3.83 (q, J = 10.9 Hz, 2H), 3.76 – 3.71 (m, 1H), 3.58 – 2.97 (m, 10H), 2.75 – 2.55 (m, 2H), 2.49 (s, 3H), 2.37 (q, J = 7.0, 6.5 Hz, 3H), 2.32 – 2.23 (m, 2H), 2.23 – 2.12 (m, 3H), 2.02 (ddd, J = 14.6, 9.1, 5.8 Hz, 2H), 1.59 – 1.13 (m, 14H), 1.07 (s, 9H). HRMS (m/z) for $C_{58}H_{80}ClN_{12}O_6S^+$ [M + H]$^+$: calculated 1107.5728, found 1107.5745.

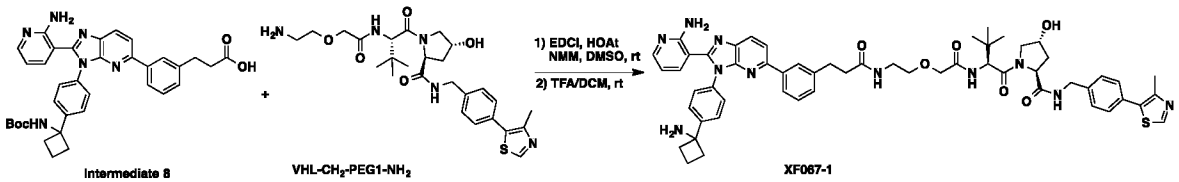
Example 75
Synthesis of Intermediate 8



Intermediate 7 Intermediate 8

To a suspension of Intermediate 7 (Lapierre et al., 2016) (152 mg, 0.31 mmol) and (3-(3-ethoxy-3-oxopropyl)phenyl)boronic acid (137 mg, 0.62 mmol) in 2.5 mL of dioxane and 1.5 mL of H_2O was added potassium carbonate (128 mg, 0.93 mmol). The mixture was degassed for 5 min, before the catalyst $Pd(PPh_3)_4$ (18 mg, 5 mol %) was added. After the reaction mixture was stirred at 120 °C for 30 min in microwave, the solvent was removed and the mixture was purified by reverse phase C18 column (10% – 100% methanol / 0.1% TFA in H_2O) to afford the desired product as white solid in TFA salt form (206 mg, 97% yield). After this product was dissolved in THF (5 mL) and H_2O (2 mL), lithium hydroxide (15 mg, 0.64 mmol) was added. The reaction mixture was stirred at rt overnight. The solvent was removed and the mixture was purified by reverse phase C18 column (10% – 100% methanol / 0.1% TFA in H_2O) to afford the intermediate 8 as white solid in TFA salt form (193 mg, 99% yield). ^1H NMR (600 MHz, DMSO-d_6) δ 8.31 (d, J = 8.4 Hz, 1H), 8.05 (dd, J = 5.8, 1.7 Hz, 1H), 8.01 (d, J = 8.5 Hz, 1H), 7.87 (d, J = 1.7 Hz, 1H), 7.84 (dt, J = 7.7, 1.5 Hz, 1H), 7.64 – 7.57 (m, 3H), 7.57 – 7.51 (m, 4H), 7.50 – 7.45 (m, 1H), 2.87 (t, J = 7.7 Hz, 2H), 2.57 (t, J = 7.7 Hz, 2H), 2.07 – 1.91 (m, 1H), 1.84 – 1.77 (m, 1H), 1.33 (s, 9H), 1.13 – 1.08 (m, 4H). ESI-MS (m/z) $[M + H]^+$: 605.2878.

Example 76
Synthesis of XF067-1

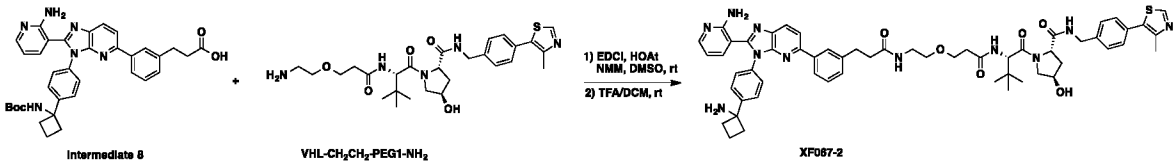


Intermediate 8 VHL-CH_2-PEG1-NH_2 XF067-1

To a solution of Intermediate 8 (12 mg, 0.02 mmol) in DMSO (1 mL) were added VHL-PEG1-NH_2 (11.4 mg, 0.02 mmol, 1.0 equiv), EDCI (1-ethyl-3-(3-

dimethylaminopropyl)carbodiimide) (5.8 mg, 0.03 mmol, 1.5 equiv), HOAt (1-hydroxy-7-azabenzo-triazole) (4.1 mg, 0.03 mmol, 1.5 equiv), and NMM (N-Methylmorpholine) (6.1 mg, 0.06 mmol, 3.0 equiv). After being stirred overnight at rt, the resulting mixture was purified by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O) to afford the corresponding product. After this product was dissolved in DCM (1mL), the reaction mixture was treated with TFA (1 mL) for 30 min. After the solvent was evaporated, the residue was purified by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O) to afford XF067-1 as white solid in TFA salt form (7.8 mg, 38%). ^{1}H NMR (800 MHz, CD_3OD) δ 8.88 (s, 1H), 8.30 (d, J = 8.3 Hz, 1H), 8.03 (d, J = 17.2 Hz, 1H), 7.99 (d, J = 8.3 Hz, 1H), 7.91 – 7.78 (m, 5H), 7.72 (d, J = 8.0 Hz, 2H), 7.42 (d, J = 7.9 Hz, 2H), 7.38 (d, J = 7.8 Hz, 2H), 7.33 (t, J = 7.7 Hz, 1H), 7.27 (d, J = 7.6 Hz, 1H), 6.83 (s, 1H), 4.70 (s, 1H), 4.60 (t, J = 8.3 Hz, 1H), 4.56 – 4.47 (m, 2H), 4.32 (d, J = 15.4 Hz, 1H), 3.93 – 3.86 (m, 2H), 3.86 – 3.78 (m, 2H), 3.48 (dd, J = 10.1, 5.3 Hz, 1H), 3.40 (dt, J = 9.7, 5.2 Hz, 1H), 3.35 – 3.29 (m, 2H), 3.00 (t, J = 7.6 Hz, 2H), 2.91 (dt, J = 14.3, 8.4 Hz, 2H), 2.71 (q, J = 11.7, 10.2 Hz, 2H), 2.58 (t, J = 7.6 Hz, 2H), 2.44 (s, 3H), 2.42 – 2.30 (m, 1H), 2.26 (dd, J = 13.2, 7.6 Hz, 1H), 2.15 – 2.03 (m, 2H), 1.03 (s, 9H). ESI-MS (m/z) $[M + H]^+$: 1018.4762.

Example 77
Synthesis of XF067-2

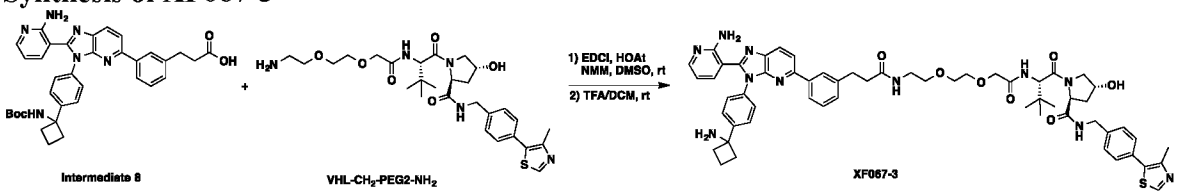


XF067-2 was synthesized following the standard procedure for preparing XF067-1 from intermediate 8 (12 mg, 0.02 mmol), VHL-CH_2CH_2PEG1-NH_2 (15.5 mg, 0.02 mmol, 1.0 equiv), EDCI (5.8 mg, 0.03 mmol, 1.5 equiv), HOAt (4.1 mg, 0.03 mmol, 1.5 equiv), and NMM (6.1 mg, 0.06 mmol, 3.0 equiv) in DMSO (1 mL). XF067-2 was obtained as white solid in TFA salt form (14.6 mg, 71%). ^{1}H NMR (800 MHz, CD_3OD) δ 8.96 (s, 1H), 8.31 (dd, J = 8.5, 4.3 Hz, 1H), 8.05 – 7.97 (m, 2H), 7.91 – 7.85 (m, 2H), 7.84 (d, J = 7.6 Hz, 1H), 7.81 (d, J = 8.0 Hz, 2H), 7.72 (d, J = 8.1 Hz, 2H), 7.42 (d, J = 7.9 Hz, 2H), 7.37 (dd, J = 23.2, 7.8 Hz, 3H), 7.29 (d, J = 7.5 Hz, 1H), 6.84 (t, J = 6.9 Hz, 1H), 4.64 (s, 1H), 4.63 – 4.54 (m, 1H), 4.52 – 4.44 (m, 2H), 4.33 (d, J = 15.4 Hz, 1H), 3.88 (d, J = 10.9 Hz, 1H), 3.79 (dd, J = 11.2, 4.0 Hz, 1H), 3.53 (dq, J = 9.8, 4.7, 4.1 Hz, 1H), 3.48 (dt, J = 10.1, 5.5 Hz, 1H), 3.38 (ddt, J = 26.6, 10.1, 5.3 Hz,

2H), 3.30 (t, J = 5.3 Hz, 2H), 2.98 (t, J = 7.6 Hz, 2H), 2.91 (tt, J = 9.1, 5.8 Hz, 2H), 2.77 – 2.67 (m, 2H), 2.56 (t, J = 7.6 Hz, 2H), 2.47 (s, 3H), 2.41 – 2.31 (m, 3H), 2.24 (dd, J = 13.3, 7.6 Hz, 1H), 2.08 (ddt, J = 12.2, 7.9, 3.9 Hz, 2H), 1.01 (s, 9H). ESI-MS (m/z) $[M + H]^+$: 1032.4912.

Example 78

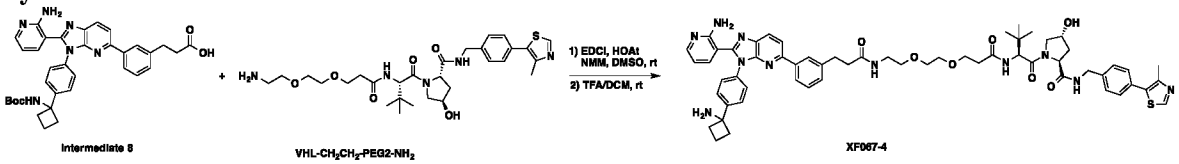
Synthesis of XF067-3



XF067-3 was synthesized following the standard procedure for preparing XF067-1 from intermediate 8 (12 mg, 0.02 mmol), VHL-CH_2PEG2-NH_2 (12.2 mg, 0.02 mmol, 1.0 equiv), EDCI (5.8 mg, 0.03 mmol, 1.5 equiv), HOAt (4.1 mg, 0.03 mmol, 1.5 equiv), and NMM (6.1 mg, 0.06 mmol, 3.0 equiv) in DMSO (1 mL). XF067-3 was obtained as white solid in TFA salt form (10.5 mg, 49%). ^{1}H NMR (800 MHz, CD_3OD) δ 8.94 (s, 1H), 8.31 (dd, J = 8.3, 3.7 Hz, 1H), 8.02 (dd, J = 18.9, 7.4 Hz, 2H), 7.93 – 7.86 (m, 2H), 7.82 (dd, J = 20.7, 8.0 Hz, 3H), 7.72 (d, J = 8.0 Hz, 2H), 7.49 – 7.32 (m, 5H), 7.28 (d, J = 7.7 Hz, 1H), 6.84 (t, J = 6.8 Hz, 1H), 4.73 (s, 1H), 4.62 – 4.56 (m, 1H), 4.54 – 4.45 (m, 2H), 4.40 – 4.32 (m, 1H), 4.01 – 3.93 (m, 1H), 3.93 – 3.86 (m, 2H), 3.82 (dd, J = 11.2, 4.1 Hz, 1H), 3.66 – 3.54 (m, 2H), 3.52 – 3.36 (m, 5H), 3.25 (ddd, J = 14.2, 7.3, 3.8 Hz, 1H), 3.02 – 2.95 (m, 2H), 2.90 (dd, J = 12.7, 7.3 Hz, 2H), 2.75 – 2.69 (m, 2H), 2.59 (dt, J = 15.1, 7.8 Hz, 1H), 2.53 (dt, J = 14.2, 7.5 Hz, 1H), 2.47 (s, 3H), 2.34 (td, J = 11.1, 6.7 Hz, 1H), 2.25 (dd, J = 13.4, 7.7 Hz, 1H), 2.09 (ddt, J = 25.6, 11.5, 4.7 Hz, 2H), 1.02 (s, 9H). ESI-MS (m/z) $[M + H]^+$: 1062.5023.

Example 79

Synthesis of XF067-4

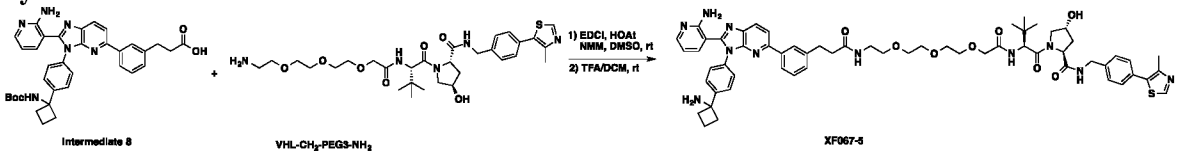


XF067-4 was synthesized following the standard procedure for preparing XF067-1 from intermediate 8 (12 mg, 0.02 mmol), VHL- CH_2CH_2PEG2-NH_2 (16.3 mg, 0.02 mmol, 1.0 equiv), EDCI (5.8 mg, 0.03 mmol, 1.5 equiv), HOAt (4.1 mg, 0.03 mmol, 1.5 equiv), and NMM (6.1 mg, 0.06 mmol, 3.0 equiv) in DMSO (1 mL). XF067-4 was obtained as white solid in TFA salt form (12.6 mg, 58%). ^{1}H NMR (800 MHz, CD_3OD) δ 8.95 (d, J = 7.0 Hz, 1H), 8.31 (d, J

= 8.4 Hz, 1H), 8.03 (t, *J* = 6.4 Hz, 2H), 7.92 – 7.86 (m, 2H), 7.83 (dd, *J* = 20.3, 7.9 Hz, 3H), 7.73 (d, *J* = 8.0 Hz, 2H), 7.48 – 7.38 (m, 4H), 7.40 – 7.33 (m, 1H), 7.29 (d, *J* = 7.6 Hz, 1H), 6.84 (t, *J* = 7.0 Hz, 1H), 4.65 (s, 1H), 4.61 – 4.56 (m, 1H), 4.56 – 4.49 (m, 2H), 4.40 – 4.34 (m, 1H), 3.89 (d, *J* = 10.9 Hz, 1H), 3.80 (dd, *J* = 11.1, 4.1 Hz, 1H), 3.72 – 3.62 (m, 2H), 3.52 (t, *J* = 4.5 Hz, 2H), 3.47 (t, *J* = 5.1 Hz, 2H), 3.40 (t, *J* = 5.4 Hz, 2H), 3.29 (t, *J* = 5.4 Hz, 2H), 2.99 (t, *J* = 7.6 Hz, 2H), 2.91 (ddd, *J* = 14.6, 9.0, 5.8 Hz, 2H), 2.72 (ddd, *J* = 13.3, 9.0, 5.9 Hz, 2H), 2.53 (s, 3H), 2.49 – 2.42 (m, 4H), 2.36 – 2.30 (m, 1H), 2.23 (dd, *J* = 13.4, 7.6 Hz, 1H), 2.12 – 2.03 (m, 2H), 1.03 (s, 9H). ESI-MS (m/z) $[M + H]^+$: 1076.5164.

Example 80

Synthesis of XF067-5

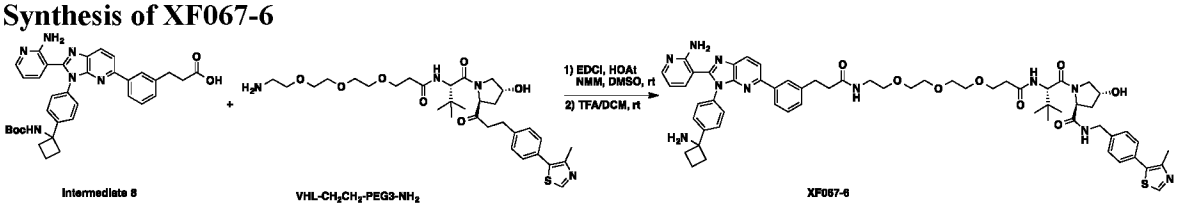


Intermediate 8 VHL-CH_2-PEG3-NH_2 XF067-5

XF067-5 was synthesized following the standard procedure for preparing XF067-1 from intermediate 8 (12 mg, 0.02 mmol), VHL-CH_2PEG3-NH_2 (16.9 mg, 0.02 mmol, 1.0 equiv), EDCI (5.8 mg, 0.03 mmol, 1.5 equiv), HOAt (4.1 mg, 0.03 mmol, 1.5 equiv), and NMM (6.1 mg, 0.06 mmol, 3.0 equiv) in DMSO (1 mL). XF067-5 was obtained as white solid in TFA salt form (16.4 mg, 74%). ^{1}H NMR (800 MHz, CD_3OD) δ 8.93 (s, 1H), 8.31 (d, *J* = 8.3 Hz, 1H), 8.03 (t, *J* = 6.9 Hz, 2H), 7.91 (s, 1H), 7.88 (d, *J* = 7.8 Hz, 1H), 7.83 (dd, *J* = 19.6, 7.8 Hz, 3H), 7.73 (d, *J* = 5.3 Hz, 2H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.41 (d, *J* = 7.9 Hz, 2H), 7.37 (t, *J* = 7.7 Hz, 1H), 7.29 (d, *J* = 7.5 Hz, 1H), 6.84 (t, *J* = 6.9 Hz, 1H), 4.70 (s, 1H), 4.59 (t, *J* = 8.6 Hz, 1H), 4.52 (d, *J* = 4.3 Hz, 2H), 4.37 (d, *J* = 15.4 Hz, 1H), 4.06 – 3.96 (m, 4H), 3.88 (d, *J* = 11.0 Hz, 1H), 3.81 (dd, *J* = 11.2, 4.0 Hz, 1H), 3.69 – 3.62 (m, 4H), 3.57 (q, *J* = 4.5 Hz, 2H), 3.47 (t, *J* = 4.7 Hz, 2H), 3.38 (t, *J* = 5.5 Hz, 2H), 3.27 (t, *J* = 5.4 Hz, 2H), 2.99 (t, *J* = 7.6 Hz, 2H), 2.91 (dt, *J* = 14.3, 8.7 Hz, 2H), 2.76 – 2.68 (m, 2H), 2.53 (t, *J* = 7.6 Hz, 2H), 2.47 (s, 3H), 2.38 – 2.29 (m, 1H), 2.25 (dd, *J* = 12.8, 7.9 Hz, 1H), 2.14 – 2.04 (m, 2H), 1.04 (s, 9H). ESI-MS (m/z) $[M + H]^+$: 1106.5268.

Example 81

Synthesis of XF067-6

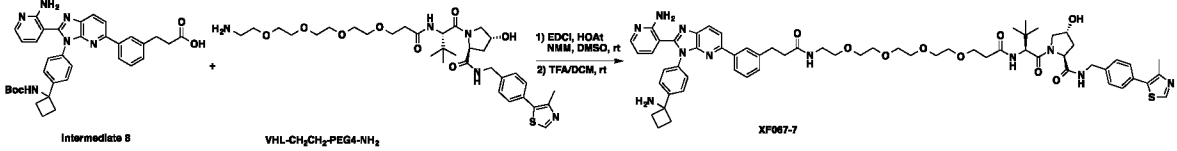


Intermediate 8 VHL-CH_2CH_2-PEG3-NH_2 XF067-6

XF067-6 was synthesized following the standard procedure for preparing XF067-1 from intermediate 8 (12 mg, 0.02 mmol), VHL-CH_2CH_2PEG3-NH_2 (17.2 mg, 0.02 mmol, 1.0 equiv), EDCI (5.8 mg, 0.03 mmol, 1.5 equiv), HOAt (4.1 mg, 0.03 mmol, 1.5 equiv), and NMM (6.1 mg, 0.06 mmol, 3.0 equiv) in DMSO (1 mL). XF067-6 was obtained as white solid in TFA salt form (12.2 mg, 54%). ^{1}H NMR (800 MHz, CD_3OD) δ 8.95 (s, 1H), 8.32 (d, J = 8.4 Hz, 1H), 8.04 (t, J = 6.5 Hz, 2H), 7.92 (s, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.85 (d, J = 7.6 Hz, 1H), 7.82 (d, J = 8.0 Hz, 2H), 7.73 (d, J = 8.0 Hz, 2H), 7.47 (d, J = 7.8 Hz, 2H), 7.42 (d, J = 7.8 Hz, 2H), 7.37 (t, J = 7.7 Hz, 1H), 7.30 (d, J = 7.5 Hz, 1H), 6.84 (t, J = 6.9 Hz, 1H), 4.65 (s, 1H), 4.58 (t, J = 8.5 Hz, 1H), 4.54 (d, J = 15.4 Hz, 1H), 4.52 – 4.50 (m, 1H), 4.40 – 4.34 (m, 1H), 3.90 (d, J = 10.9 Hz, 1H), 3.81 (dd, J = 11.1, 4.1 Hz, 1H), 3.74 – 3.66 (m, 2H), 3.63 – 3.55 (m, 4H), 3.53 (t, J = 4.7 Hz, 2H), 3.44 (t, J = 4.7 Hz, 2H), 3.39 (d, J = 5.4 Hz, 2H), 3.28 (t, J = 5.5 Hz, 2H), 3.00 (t, J = 7.6 Hz, 2H), 2.91 (dt, J = 14.4, 8.6 Hz, 2H), 2.72 (ddd, J = 13.7, 9.1, 6.0 Hz, 2H), 2.60 – 2.51 (m, 3H), 2.51 – 2.43 (m, 4H), 2.37 – 2.32 (m, 1H), 2.24 (dd, J = 13.4, 7.6 Hz, 1H), 2.09 (dtd, J = 15.6, 11.0, 10.1, 5.2 Hz, 2H), 1.04 (s, 9H). ESI-MS (m/z) $[M + H]^+$: 1120.5423.

Example 82

Synthesis of XF067-7

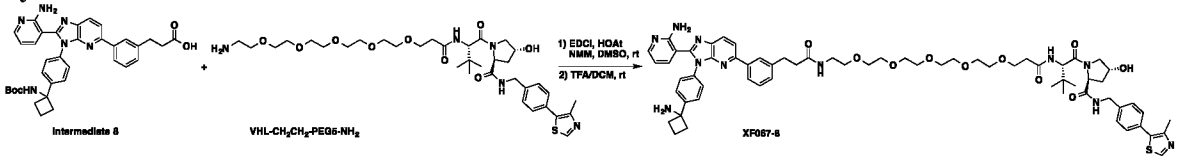


XF067-7 was synthesized following the standard procedure for preparing XF067-1 from intermediate 8 (12 mg, 0.02 mmol), VHL-CH_2CH_2PEG4-NH_2 (14.2 mg, 0.02 mmol, 1.0 equiv), EDCI (5.8 mg, 0.03 mmol, 1.5 equiv), HOAt (4.1 mg, 0.03 mmol, 1.5 equiv), and NMM (6.1 mg, 0.06 mmol, 3.0 equiv) in DMSO (1 mL). XF067-7 was obtained as white solid in TFA salt form (12.2 mg, 52%). ^{1}H NMR (800 MHz, CD_3OD) δ 8.92 (s, 1H), 8.31 (d, J = 8.3 Hz, 1H), 8.08 – 8.00 (m, 2H), 7.92 (s, 1H), 7.89 (d, J = 7.8 Hz, 1H), 7.83 (dd, J = 12.6, 7.9 Hz, 3H), 7.73 (d, J = 8.0 Hz, 2H), 7.47 (d, J = 7.9 Hz, 2H), 7.42 (d, J = 7.9 Hz, 2H), 7.37 (t, J = 7.7 Hz, 1H), 7.30 (d, J = 7.6 Hz, 1H), 6.83 (t, J = 6.9 Hz, 1H), 4.65 (s, 1H), 4.62 – 4.47 (m, 3H), 4.37 (d, J = 15.4 Hz, 1H), 3.90 (d, J = 10.9 Hz, 1H), 3.81 (dd, J = 11.1, 4.1 Hz, 1H), 3.70 (ddq, J = 28.0, 10.3, 5.4 Hz, 2H), 3.64 – 3.55 (m, 8H), 3.52 (t, J = 4.6 Hz, 2H), 3.44 (t, J = 4.7 Hz, 2H), 3.39 (t, J = 5.5 Hz, 2H), 3.28 (t, J = 5.4 Hz, 2H), 3.00 (t, J = 7.6 Hz, 2H), 2.95 – 2.87 (m, 2H), 2.77 – 2.68 (m, 2H), 2.59 – 2.51 (m, 3H), 2.51 – 2.44 (m, 4H), 2.33 (dd, J = 13.4, 8.2 Hz, 1H),

2.24 (dd, J = 13.2, 7.7 Hz, 1H), 2.12 – 2.04 (m, 2H), 1.04 (s, 9H). ESI-MS (m/z) [M + H]$^+$:1164.5673.

Example 83

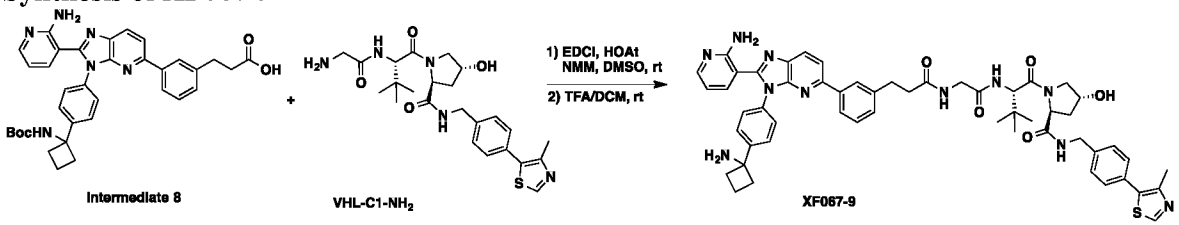
Synthesis of XF067-8



XF067-8 was synthesized following the standard procedure for preparing XF067-1 from intermediate 8 (12 mg, 0.02 mmol), VHL-CH_2CH_2PEG5-NH_2 (18.9 mg, 0.02 mmol, 1.0 equiv), EDCI (5.8 mg, 0.03 mmol, 1.5 equiv), HOAt (4.1 mg, 0.03 mmol, 1.5 equiv), and NMM (6.1 mg, 0.06 mmol, 3.0 equiv) in DMSO (1 mL). XF067-8 was obtained as white solid in TFA salt form (13.9 mg, 58%). ^{1}H NMR (800 MHz, CD_3OD) δ 8.91 (s, 1H), 8.32 (d, J = 8.4 Hz, 1H), 8.04 (d, J = 8.0 Hz, 2H), 7.92 (s, 1H), 7.89 (d, J = 7.8 Hz, 1H), 7.83 (dd, J = 12.5, 7.9 Hz, 3H), 7.73 (d, J = 8.0 Hz, 2H), 7.48 (d, J = 7.8 Hz, 2H), 7.42 (d, J = 7.8 Hz, 2H), 7.38 (t, J = 7.7 Hz, 1H), 7.30 (d, J = 7.5 Hz, 1H), 6.83 (t, J = 6.9 Hz, 1H), 4.66 (s, 1H), 4.63 – 4.53 (m, 2H), 4.51 (s, 1H), 4.37 (d, J = 15.4 Hz, 1H), 3.90 (d, J = 10.9 Hz, 1H), 3.81 (dd, J = 11.1, 4.1 Hz, 1H), 3.72 (dtt, J = 21.3, 10.3, 5.4 Hz, 2H), 3.59 (ddt, J = 15.3, 10.8, 4.4 Hz, 12H), 3.52 (t, J = 4.6 Hz, 2H), 3.44 (t, J = 4.6 Hz, 2H), 3.39 (t, J = 5.5 Hz, 2H), 3.27 (t, J = 5.5 Hz, 2H), 3.00 (t, J = 7.6 Hz, 2H), 2.95 – 2.88 (m, 2H), 2.78 – 2.69 (m, 2H), 2.60 – 2.51 (m, 3H), 2.51 – 2.41 (m, 4H), 2.34 (dq, J = 13.7, 7.8, 5.9 Hz, 1H), 2.24 (dd, J = 13.1, 7.7 Hz, 1H), 2.13 – 2.03 (m, 2H), 1.04 (s, 9H). ESI-MS (m/z) [M + H]$^+$: 1208.5948.

Example 84

Synthesis of XF067-9

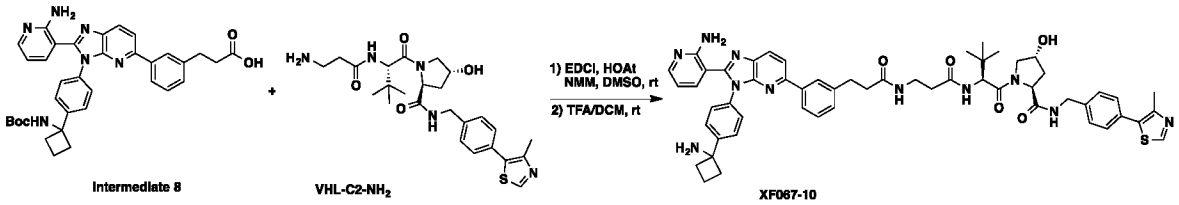


XF067-9 was synthesized following the standard procedure for preparing XF067-1 from intermediate 8 (12 mg, 0.02 mmol), VHL-C1-NH_2 (14.3 mg, 0.02 mmol, 1.0 equiv), EDCI (5.8 mg, 0.03 mmol, 1.5 equiv), HOAt (4.1 mg, 0.03 mmol, 1.5 equiv), and NMM (6.1 mg, 0.06 mmol, 3.0 equiv) in DMSO (1 mL). XF067-9 was obtained as white solid in TFA salt form

(11.7 mg, 60%). ^{1}H NMR (800 MHz, CD_3OD) δ 8.88 (s, 1H), 8.30 (d, J = 8.4 Hz, 1H), 8.07 – 7.98 (m, 2H), 7.92 (s, 1H), 7.87 (d, J = 7.8 Hz, 1H), 7.83 – 7.80 (m, 3H), 7.73 (s, 2H), 7.48 (d, J = 7.9 Hz, 2H), 7.41 (d, J = 7.8 Hz, 2H), 7.36 (t, J = 7.6 Hz, 1H), 7.31 (d, J = 7.5 Hz, 1H), 6.83 (t, J = 6.9 Hz, 1H), 4.64 (s, 1H), 4.61 – 4.53 (m, 2H), 4.52 (d, J = 4.4 Hz, 1H), 4.36 (d, J = 15.4 Hz, 1H), 3.89 – 3.79 (m, 4H), 3.03 (t, J = 7.8 Hz, 2H), 2.91 (tt, J = 9.3, 5.6 Hz, 2H), 2.72 (dq, J = 14.3, 9.3, 7.6 Hz, 2H), 2.63 (t, J = 7.8 Hz, 2H), 2.46 (s, 3H), 2.34 (dd, J = 10.8, 6.3 Hz, 1H), 2.25 (dd, J = 13.3, 7.6 Hz, 1H), 2.16 – 2.02 (m, 2H), 1.03 (s, 9H). ESI-MS (m/z) $[M + H]^+$: 974.4486.

Example 85

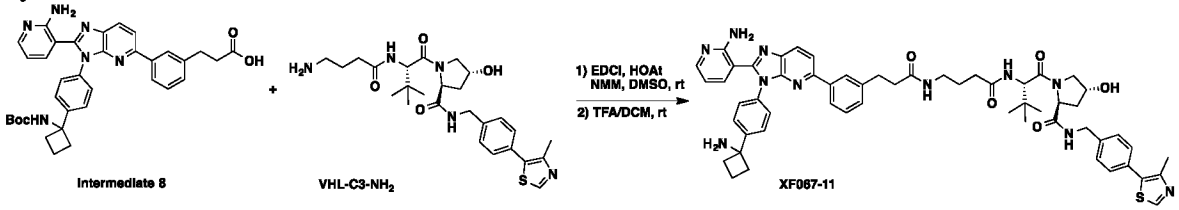
Synthesis of XF067-10



XF067-10 was synthesized following the standard procedure for preparing XF067-1 from intermediate 8 (12 mg, 0.02 mmol), VHL-C2-NH_2 (14.6 mg, 0.02 mmol, 1.0 equiv), EDCI (5.8 mg, 0.03 mmol, 1.5 equiv), HOAt (4.1 mg, 0.03 mmol, 1.5 equiv), and NMM (6.1 mg, 0.06 mmol, 3.0 equiv) in DMSO (1 mL). XF067-10 was obtained as white solid in TFA salt form (13.5 mg, 68%). ^{1}H NMR (800 MHz, CD_3OD) δ 8.93 (s, 1H), 8.30 (d, J = 8.4 Hz, 1H), 8.02 (dd, J = 11.7, 7.3 Hz, 2H), 7.94 – 7.79 (m, 5H), 7.72 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 7.9 Hz, 2H), 7.40 (d, J = 7.9 Hz, 2H), 7.38 – 7.35 (m, 1H), 7.29 (d, J = 7.6 Hz, 1H), 6.84 (t, J = 6.9 Hz, 1H), 4.61 – 4.46 (m, 4H), 4.35 (d, J = 15.4 Hz, 1H), 3.91 (d, J = 10.9 Hz, 1H), 3.80 (dd, J = 11.1, 4.1 Hz, 1H), 3.42 – 3.35 (m, 2H), 2.99 (t, J = 7.6 Hz, 2H), 2.95 – 2.88 (m, 2H), 2.76 – 2.64 (m, 2H), 2.51 (t, J = 7.6 Hz, 2H), 2.47 (s, 3H), 2.40 – 2.28 (m, 3H), 2.23 (dd, J = 13.3, 7.5 Hz, 1H), 2.09 (tdd, J = 17.2, 10.8, 6.6 Hz, 2H), 1.01 (s, 9H). ESI-MS (m/z) $[M + H]^+$: 988.4638.

Example 86

Synthesis of XF067-11

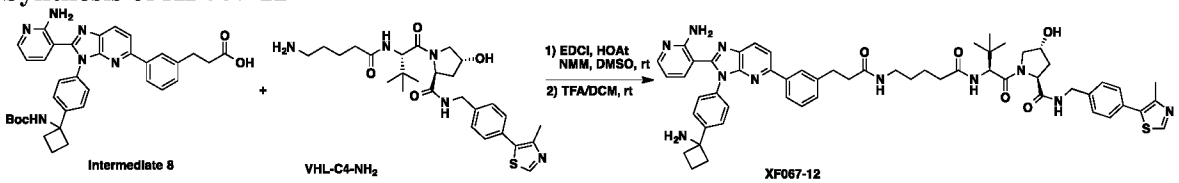


XF067-11 was synthesized following the standard procedure for preparing XF067-1 from intermediate 8 (12 mg, 0.02 mmol), VHL-C3-NH_2 (14.8 mg, 0.02 mmol, 1.0 equiv), EDCI (5.8

mg, 0.03 mmol, 1.5 equiv), HOAt (4.1 mg, 0.03 mmol, 1.5 equiv), and NMM (6.1 mg, 0.06 mmol, 3.0 equiv) in DMSO (1 mL). XF067-11 was obtained as white solid in TFA salt form (13.8 mg, 69%). ^{1}H NMR (800 MHz, CD_3OD) δ 8.94 (s, 1H), 8.31 (d, J = 8.4 Hz, 1H), 8.03 (dd, J = 11.1, 7.1 Hz, 2H), 7.92 (s, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.85 (d, J = 7.7 Hz, 1H), 7.81 (d, J = 8.1 Hz, 2H), 7.73 (d, J = 8.1 Hz, 2H), 7.48 (d, J = 7.8 Hz, 2H), 7.42 (d, J = 7.9 Hz, 2H), 7.37 (q, J = 7.9 Hz, 1H), 7.30 (d, J = 7.7 Hz, 1H), 6.84 (t, J = 7.0 Hz, 1H), 4.60 – 4.56 (m, 2H), 4.55 (s, 1H), 4.52 (d, J = 3.2 Hz, 1H), 4.37 (d, J = 15.4 Hz, 1H), 3.90 (d, J = 10.9 Hz, 1H), 3.81 (dd, J = 11.1, 4.1 Hz, 1H), 3.16 – 3.10 (m, 2H), 3.02 – 2.98 (m, 2H), 2.94 – 2.89 (m, 2H), 2.72 (td, J = 14.3, 11.7, 7.2 Hz, 2H), 2.53 (t, J = 7.5 Hz, 2H), 2.48 (s, 3H), 2.39 – 2.29 (m, 1H), 2.28 – 2.21 (m, 1H), 2.17 – 2.02 (m, 4H), 1.73 – 1.64 (m, 2H), 1.03 (s, 9H). ESI-MS (m/z) [M + H]$^+$: 1002.4804.

Example 87

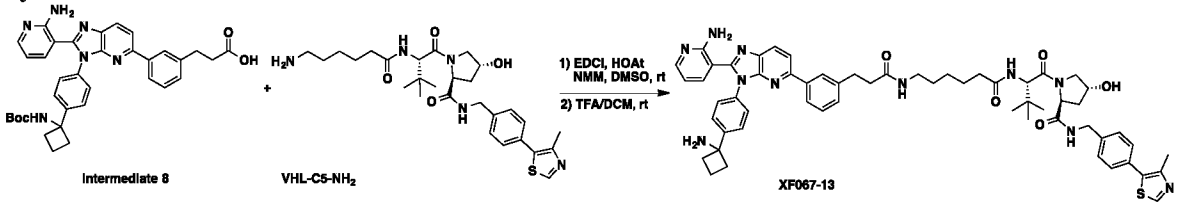
Synthesis of XF067-12



XF067-12 was synthesized following the standard procedure for preparing XF067-1 from intermediate 8 (12 mg, 0.02 mmol), VHL-C4-NH_2 (11.3 mg, 0.02 mmol, 1.0 equiv), EDCI (5.8 mg, 0.03 mmol, 1.5 equiv), HOAt (4.1 mg, 0.03 mmol, 1.5 equiv), and NMM (6.1 mg, 0.06 mmol, 3.0 equiv) in DMSO (1 mL). XF067-12 was obtained as white solid in TFA salt form (15.5 mg, 76%). ^{1}H NMR (800 MHz, CD_3OD) δ 8.93 (s, 1H), 8.32 (d, J = 8.4 Hz, 1H), 8.03 (dd, J = 8.4, 4.5 Hz, 2H), 7.92 (s, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.85 (d, J = 7.5 Hz, 1H), 7.81 (d, J = 8.0 Hz, 2H), 7.77 – 7.67 (m, 2H), 7.47 (d, J = 7.8 Hz, 2H), 7.44 – 7.33 (m, 3H), 7.32 – 7.25 (m, 1H), 6.84 (t, J = 7.0 Hz, 1H), 4.60 (s, 1H), 4.60 – 4.49 (m, 3H), 4.37 (d, J = 15.4 Hz, 1H), 3.90 (d, J = 10.9 Hz, 1H), 3.81 (dd, J = 11.1, 4.1 Hz, 1H), 3.11 (t, J = 6.9 Hz, 2H), 3.00 (t, J = 7.5 Hz, 2H), 2.92 (dt, J = 14.5, 8.6 Hz, 2H), 2.72 (dt, J = 13.2, 8.0 Hz, 2H), 2.56 – 2.50 (m, 2H), 2.48 (s, 3H), 2.37 – 2.30 (m, 1H), 2.26 – 2.21 (m, 1H), 2.19 – 2.14 (m, 1H), 2.13 – 2.05 (m, 2H), 1.50 – 1.41 (m, 2H), 1.40 – 1.32 (m, 2H), 1.03 (s, 9H). ESI-MS (m/z) [M + H]$^+$: 1016.4976.

Example 88

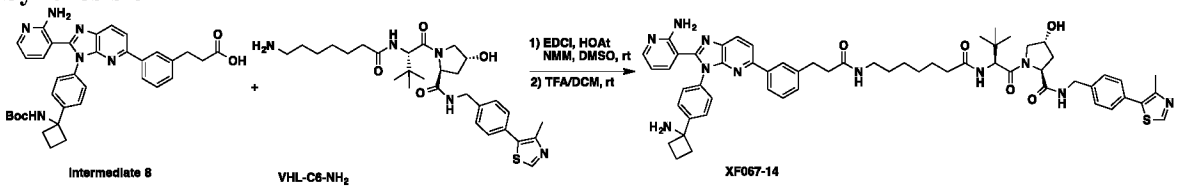
Synthesis of XF067-13



XF067-13 was synthesized following the standard procedure for preparing XF067-1 from intermediate 8 (12 mg, 0.02 mmol), VHL-C5-NH_2 (11.6 mg, 0.02 mmol, 1.0 equiv), EDCI (5.8 mg, 0.03 mmol, 1.5 equiv), HOAt (4.1 mg, 0.03 mmol, 1.5 equiv), and NMM (6.1 mg, 0.06 mmol, 3.0 equiv) in DMSO (1 mL). XF067-13 was obtained as white solid in TFA salt form (13.6 mg, 66%). ^{1}H NMR (800 MHz, CD_3OD) δ 8.97 (s, 1H), 8.31 (d, J = 8.4 Hz, 1H), 8.03 (t, J = 6.8 Hz, 2H), 7.92 (s, 1H), 7.88 (dd, J = 18.0, 7.8 Hz, 2H), 7.83 – 7.79 (m, 2H), 7.74 (d, J = 8.1 Hz, 2H), 7.48 (d, J = 7.8 Hz, 2H), 7.43 (d, J = 7.8 Hz, 2H), 7.38 (t, J = 7.7 Hz, 1H), 7.30 (d, J = 7.6 Hz, 1H), 6.85 (t, J = 7.0 Hz, 1H), 4.62 (s, 1H), 4.61 – 4.57 (m, 1H), 4.55 (d, J = 15.4 Hz, 1H), 4.52 (s, 1H), 4.38 (d, J = 15.4 Hz, 1H), 3.91 (d, J = 10.9 Hz, 1H), 3.81 (dd, J = 11.1, 4.1 Hz, 1H), 3.09 (td, J = 7.5, 2.5 Hz, 2H), 2.99 (t, J = 7.5 Hz, 2H), 2.92 (ddd, J = 14.7, 11.9, 7.2 Hz, 2H), 2.77 – 2.69 (m, 2H), 2.52 (d, J = 7.5 Hz, 2H), 2.48 (s, 3H), 2.39 – 2.30 (m, 1H), 2.24 (dd, J = 13.4, 7.6 Hz, 1H), 2.19 – 2.16 (m, 1H), 2.15 – 2.01 (m, 3H), 1.46 (dp, J = 15.1, 7.1 Hz, 2H), 1.35 (p, J = 7.5 Hz, 2H), 1.20 – 1.14 (m, 2H), 1.03 (s, 9H). ESI-MS (m/z) $[M + H]^+$: 1030.5111.

Example 89

Synthesis of XF067-14

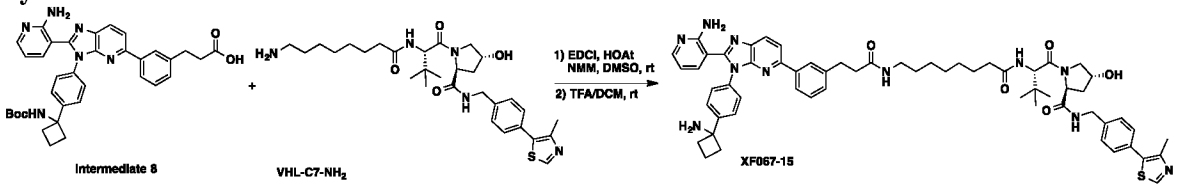


XF067-14 was synthesized following the standard procedure for preparing XF067-1 from intermediate 8 (12 mg, 0.02 mmol), VHL-C6-NH_2 (11.8 mg, 0.02 mmol, 1.0 equiv), EDCI (5.8 mg, 0.03 mmol, 1.5 equiv), HOAt (4.1 mg, 0.03 mmol, 1.5 equiv), and NMM (6.1 mg, 0.06 mmol, 3.0 equiv) in DMSO (1 mL). XF067-14 was obtained as white solid in TFA salt form (8.4 mg, 40%). ^{1}H NMR (800 MHz, CD_3OD) δ 8.95 (s, 1H), 8.32 (d, J = 8.3 Hz, 1H), 8.04 (q, J = 3.7 Hz, 2H), 7.93 – 7.87 (m, 2H), 7.86 (d, J = 7.6 Hz, 1H), 7.82 (d, J = 8.0 Hz, 2H), 7.74 (d, J = 8.0 Hz, 2H), 7.48 (d, J = 7.8 Hz, 2H), 7.43 (d, J = 7.8 Hz, 2H), 7.41 – 7.35 (m, 1H), 7.29 (d, J = 7.5 Hz, 1H), 6.85 (t, J = 6.9 Hz, 1H), 4.63 (s, 1H), 4.60 (t, J = 8.0 Hz, 1H), 4.57 – 4.49 (m, 2H), 4.38 (d, J = 15.4 Hz, 1H), 3.92 (d, J = 10.9 Hz, 1H), 3.82 (dd, J = 11.1, 4.1 Hz,

1H), 3.08 (t, J = 7.1 Hz, 2H), 2.99 (t, J = 7.5 Hz, 2H), 2.92 (dt, J = 14.6, 8.3 Hz, 2H), 2.76 – 2.67 (m, 2H), 2.52 (d, J = 7.5 Hz, 2H), 2.48 (s, 3H), 2.34 (tq, J = 16.4, 10.0, 7.7 Hz, 1H), 2.28 – 2.03 (m, 5H), 1.53 – 1.44 (m, 2H), 1.34 (p, J = 7.1 Hz, 2H), 1.21 – 1.12 (m, 4H), 1.04 (s, 9H). ESI-MS (m/z) $[M + H]^+$: 1044.5284.

Example 90

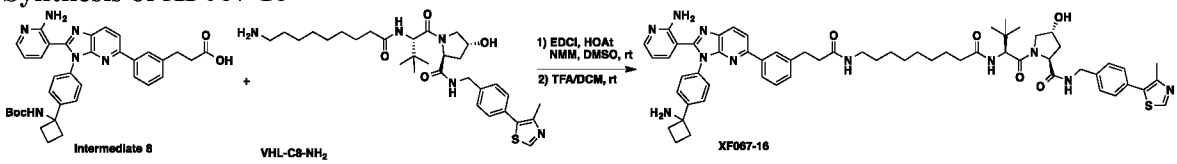
Synthesis of XF067-15



XF067-15 was synthesized following the standard procedure for preparing XF067-1 from intermediate 8 (12 mg, 0.02 mmol), VHL-C7-NH_2 (16 mg, 0.02 mmol, 1.0 equiv), EDCI (5.8 mg, 0.03 mmol, 1.5 equiv), HOAt (4.1 mg, 0.03 mmol, 1.5 equiv), and NMM (6.1 mg, 0.06 mmol, 3.0 equiv) in DMSO (1 mL). XF067-15 was obtained as white solid in TFA salt form (9.6 mg, 45%). ^{1}H NMR (800 MHz, CD_3OD) δ 8.96 (s, 1H), 8.32 (d, J = 8.3 Hz, 1H), 8.07 – 8.00 (m, 2H), 7.92 (s, 1H), 7.89 (d, J = 7.8 Hz, 1H), 7.86 (d, J = 7.6 Hz, 1H), 7.82 (d, J = 8.0 Hz, 2H), 7.73 (d, J = 8.1 Hz, 2H), 7.48 (d, J = 7.8 Hz, 2H), 7.43 (d, J = 7.8 Hz, 2H), 7.37 (t, J = 7.7 Hz, 1H), 7.29 (d, J = 7.6 Hz, 1H), 6.84 (t, J = 6.9 Hz, 1H), 4.64 (s, 1H), 4.59 (t, J = 8.3 Hz, 1H), 4.56 (d, J = 15.4 Hz, 1H), 4.52 (d, J = 4.2 Hz, 1H), 4.38 (d, J = 15.4 Hz, 1H), 3.91 (d, J = 11.0 Hz, 1H), 3.82 (dd, J = 11.1, 4.1 Hz, 1H), 3.08 (q, J = 6.7 Hz, 2H), 2.99 (t, J = 7.4 Hz, 2H), 2.92 (tt, J = 9.3, 5.8 Hz, 2H), 2.75 – 2.68 (m, 2H), 2.52 (t, J = 7.4 Hz, 2H), 2.49 (s, 3H), 2.37 – 2.31 (m, 1H), 2.28 – 2.21 (m, 2H), 2.18 (dt, J = 14.6, 7.5 Hz, 1H), 2.14 – 2.04 (m, 2H), 1.57 – 1.45 (m, 2H), 1.33 (p, J = 7.1 Hz, 2H), 1.24 – 1.09 (m, 6H), 1.04 (s, 9H). ESI-MS (m/z) $[M + H]^+$: 1058.5425.

Example 91

Synthesis of XF067-16

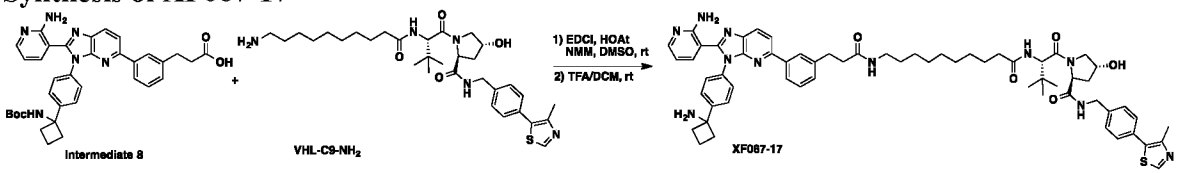


XF067-16 was synthesized following the standard procedure for preparing XF067-1 from intermediate 8 (12 mg, 0.02 mmol), VHL-C8-NH_2 (12.4 mg, 0.02 mmol, 1.0 equiv), EDCI (5.8 mg, 0.03 mmol, 1.5 equiv), HOAt (4.1 mg, 0.03 mmol, 1.5 equiv), and NMM (6.1 mg, 0.06 mmol, 3.0 equiv) in DMSO (1 mL). XF067-16 was obtained as white solid in TFA salt form (8.6 mg, 40%). ^{1}H NMR (800 MHz, CD_3OD) δ 8.92 (s, 1H), 8.32 (d, J = 8.4 Hz, 1H), 8.07 –

8.00 (m, 2H), 7.92 (s, 1H), 7.89 (d, J = 7.7 Hz, 1H), 7.83 (dd, J = 14.8, 7.8 Hz, 3H), 7.77 – 7.69 (m, 2H), 7.48 (d, J = 7.8 Hz, 2H), 7.43 (d, J = 7.8 Hz, 2H), 7.37 (t, J = 7.7 Hz, 1H), 7.29 (d, J = 7.6 Hz, 1H), 6.83 (t, J = 6.9 Hz, 1H), 4.65 (s, 1H), 4.60 (t, J = 8.1 Hz, 1H), 4.57 – 4.50 (m, 2H), 4.38 (d, J = 15.4 Hz, 1H), 3.92 (d, J = 10.9 Hz, 1H), 3.82 (dd, J = 11.1, 4.1 Hz, 1H), 3.08 (t, J = 7.1 Hz, 2H), 2.99 (t, J = 7.4 Hz, 2H), 2.92 (dt, J = 14.6, 6.1 Hz, 2H), 2.76 – 2.67 (m, 2H), 2.52 (t, J = 7.6 Hz, 2H), 2.48 (s, 3H), 2.34 (tqd, J = 10.8, 6.8, 3.3 Hz, 1H), 2.23 (ddq, J = 29.7, 14.6, 7.3 Hz, 3H), 2.10 (dddd, J = 23.5, 17.8, 10.5, 5.8 Hz, 2H), 1.54 (qq, J = 13.9, 7.0 Hz, 2H), 1.32 (dp, J = 13.9, 7.1 Hz, 2H), 1.27 – 1.09 (m, 8H), 1.05 (s, 9H). ESI-MS (m/z) $[M + H]^+$: 1072.5598.

Example 92

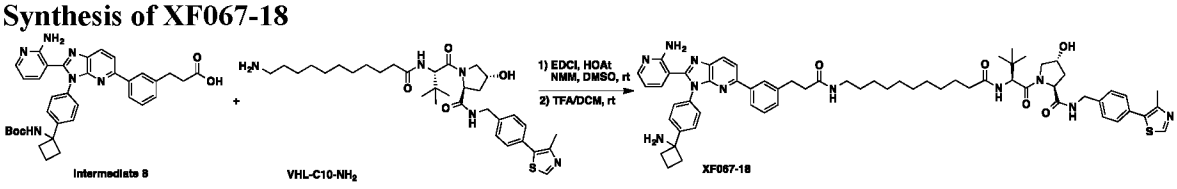
Synthesis of XF067-17



XF067-17 was synthesized following the standard procedure for preparing XF067-1 from intermediate 8 (12 mg, 0.02 mmol), VHL-C9-NH_2 (16.5 mg, 0.02 mmol, 1.0 equiv), EDCI (5.8 mg, 0.03 mmol, 1.5 equiv), HOAt (4.1 mg, 0.03 mmol, 1.5 equiv), and NMM (6.1 mg, 0.06 mmol, 3.0 equiv) in DMSO (1 mL). XF067-17 was obtained as white solid in TFA salt form (7.3 mg, 34%). ^{1}H NMR (800 MHz, CD_3OD) δ 8.92 (s, 1H), 8.32 (d, J = 8.3 Hz, 1H), 8.09 – 8.00 (m, 2H), 7.92 (s, 1H), 7.89 (d, J = 7.8 Hz, 1H), 7.82 (t, J = 7.9 Hz, 3H), 7.73 (d, J = 8.1 Hz, 2H), 7.48 (d, J = 7.8 Hz, 2H), 7.43 (d, J = 7.9 Hz, 2H), 7.37 (t, J = 7.7 Hz, 1H), 7.30 (d, J = 7.4 Hz, 1H), 6.83 (t, J = 6.9 Hz, 1H), 4.65 (s, 1H), 4.62 – 4.51 (m, 3H), 4.38 (d, J = 15.4 Hz, 1H), 3.92 (d, J = 10.9 Hz, 1H), 3.83 (dd, J = 11.1, 4.1 Hz, 1H), 3.08 (t, J = 7.1 Hz, 2H), 2.99 (t, J = 7.5 Hz, 2H), 2.92 (q, J = 9.8, 7.7 Hz, 2H), 2.72 (dt, J = 14.0, 8.5 Hz, 2H), 2.54 – 2.46 (m, 5H), 2.38 – 2.31 (m, 1H), 2.30 – 2.18 (m, 3H), 2.15 – 2.02 (m, 2H), 1.56 (ddq, J = 20.4, 13.5, 6.8 Hz, 2H), 1.32 (t, J = 7.1 Hz, 2H), 1.29 – 1.23 (m, 2H), 1.23 – 1.19 (m, 2H), 1.18 – 1.14 (m, 2H), 1.14 – 1.11 (m, 4H), 1.06 (s, 9H). ESI-MS (m/z) $[M + H]^+$: 1086.5721.

Example 93

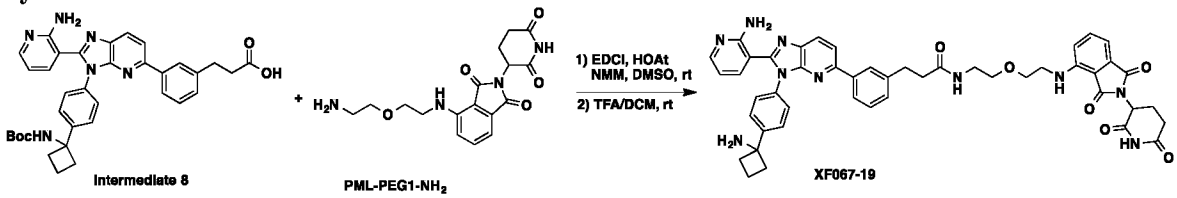
Synthesis of XF067-18



XF067-18 was synthesized following the standard procedure for preparing XF067-1 from intermediate 8 (12 mg, 0.02 mmol), VHL-C10-NH_2 (16.5 mg, 0.02 mmol, 1.0 equiv), EDCI (5.8 mg, 0.03 mmol, 1.5 equiv), HOAt (4.1 mg, 0.03 mmol, 1.5 equiv), and NMM (6.1 mg, 0.06 mmol, 3.0 equiv) in DMSO (1 mL). XF067-18 was obtained as white solid in TFA salt form (8.7 mg, 37%). ^{1}H NMR (800 MHz, CD_3OD) δ 8.92 (s, 1H), 8.31 (d, J = 8.3 Hz, 1H), 8.05 – 8.01 (m, 2H), 7.93 (s, 1H), 7.89 (d, J = 7.7 Hz, 1H), 7.82 (t, J = 6.9 Hz, 3H), 7.75 – 7.68 (m, 2H), 7.48 (d, J = 7.9 Hz, 2H), 7.43 (d, J = 7.9 Hz, 2H), 7.37 (t, J = 7.6 Hz, 1H), 7.30 (d, J = 7.4 Hz, 1H), 6.83 (t, J = 6.9 Hz, 1H), 4.65 (s, 1H), 4.62 – 4.58 (m, 1H), 4.56 (d, J = 15.5 Hz, 1H), 4.52 (d, J = 3.8 Hz, 1H), 4.41 – 4.35 (m, 1H), 3.92 (d, J = 10.9 Hz, 1H), 3.85 – 3.79 (m, 1H), 3.08 (t, J = 7.1 Hz, 2H), 3.00 (t, J = 7.5 Hz, 2H), 2.92 (tt, J = 9.4, 5.6 Hz, 2H), 2.77 – 2.68 (m, 2H), 2.52 (t, J = 7.5 Hz, 2H), 2.49 (s, 3H), 2.35 (tt, J = 10.8, 5.8 Hz, 1H), 2.29 (dt, J = 14.9, 7.7 Hz, 1H), 2.24 (dt, J = 14.8, 7.8 Hz, 2H), 2.14 – 2.02 (m, 2H), 1.64 – 1.52 (m, 2H), 1.37 – 1.23 (m, 6H), 1.22 – 1.10 (m, 8H), 1.05 (s, 9H). ESI-MS (m/z) $[M + H]^+$: 1110.5912.

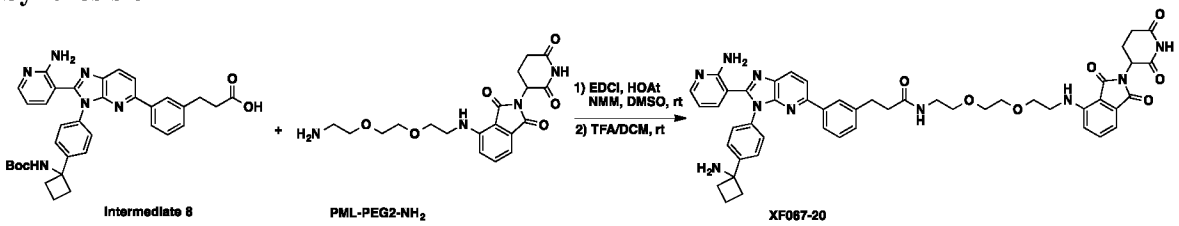
Example 94

Synthesis of XF067-19



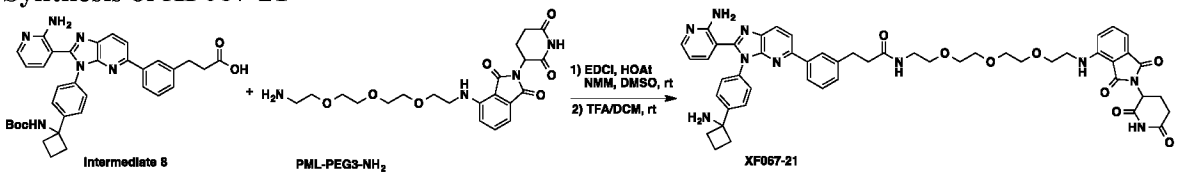
XF067-19 was synthesized following the standard procedure for preparing XF067-1 from intermediate 8 (12 mg, 0.02 mmol), PML-PEG1-NH_2 (9.4 mg, 0.02 mmol, 1.0 equiv), EDCI (5.8 mg, 0.03 mmol, 1.5 equiv), HOAt (4.1 mg, 0.03 mmol, 1.5 equiv), and NMM (6.1 mg, 0.06 mmol, 3.0 equiv) in DMSO (1 mL). XF067-19 was obtained as yellow solid in TFA salt form (10.9 mg, 64%). ^{1}H NMR (800 MHz, CD_3OD) δ 8.22 (d, J = 8.4 Hz, 1H), 8.03 (d, J = 6.2 Hz, 1H), 8.02 – 7.96 (m, 1H), 7.92 (s, 1H), 7.86 (d, J = 7.8 Hz, 1H), 7.79 (t, J = 8.0 Hz, 3H), 7.77 – 7.67 (m, 2H), 7.45 (t, J = 7.8 Hz, 1H), 7.32 (q, J = 7.8 Hz, 1H), 7.27 (d, J = 7.5 Hz, 1H), 6.98 – 6.93 (m, 1H), 6.88 (d, J = 8.5 Hz, 1H), 6.82 (t, J = 7.0 Hz, 1H), 4.93 (dd, J = 21.3, 10.7, 7.4, 3.5 Hz, 1H), 3.48 – 3.37 (m, 3H), 3.35 – 3.32 (m, 1H), 3.33 – 3.23 (m, 2H), 3.27 – 3.25 (m, 2H), 3.01 (h, J = 6.8 Hz, 2H), 2.90 (dt, J = 14.1, 8.1 Hz, 2H), 2.70 (ddd, J = 18.2, 13.5, 6.6 Hz, 3H), 2.67 – 2.53 (m, 4H), 2.32 (ddd, J = 16.4, 10.8, 6.3 Hz, 1H), 2.07 (dp, J = 16.5, 7.9 Hz, 1H), 1.96 (dd, J = 12.5, 6.4 Hz, 1H). ESI-MS (m/z) $[M + H]^+$: 847.3668.

Example 95
Synthesis of XF067-20



XF067-20 was synthesized following the standard procedure for preparing XF067-1 from intermediate 8 (12 mg, 0.02 mmol), PML-PEG2-NH_2 (10.3 mg, 0.02 mmol, 1.0 equiv), EDCI (5.8 mg, 0.03 mmol, 1.5 equiv), HOAt (4.1 mg, 0.03 mmol, 1.5 equiv), and NMM (6.1 mg, 0.06 mmol, 3.0 equiv) in DMSO (1 mL). XF067-20 was obtained as yellow solid in TFA salt form (13.4 mg, 75%). ^{1}H NMR (800 MHz, CD_3OD) δ 8.28 (d, J = 8.4 Hz, 1H), 8.01 (dd, J = 14.4, 7.2 Hz, 2H), 7.92 – 7.85 (m, 2H), 7.80 (t, J = 7.8 Hz, 3H), 7.71 (d, J = 8.0 Hz, 2H), 7.46 (t, J = 7.8 Hz, 1H), 7.35 (t, J = 7.7 Hz, 1H), 7.27 (d, J = 7.5 Hz, 1H), 6.98 (t, J = 8.3 Hz, 2H), 6.81 (t, J = 6.9 Hz, 1H), 5.01 (dd, J = 12.8, 5.4 Hz, 1H), 3.64 (t, J = 5.2 Hz, 2H), 3.55 (t, J = 4.4 Hz, 2H), 3.48 (t, J = 4.5 Hz, 2H), 3.41 (dt, J = 10.5, 5.4 Hz, 4H), 3.30 (q, J = 5.8 Hz, 2H), 2.98 (t, J = 7.5 Hz, 2H), 2.94 – 2.87 (m, 2H), 2.81 (ddd, J = 18.1, 13.7, 5.3 Hz, 1H), 2.75 – 2.67 (m, 3H), 2.68 – 2.62 (m, 1H), 2.52 (t, J = 7.5 Hz, 2H), 2.33 (qt, J = 10.5, 6.4 Hz, 1H), 2.06 (ddq, J = 18.7, 12.1, 6.9, 6.1 Hz, 2H). ESI-MS (m/z) $[M + H]^+$: 891.3945.

Example 96
Synthesis of XF067-21

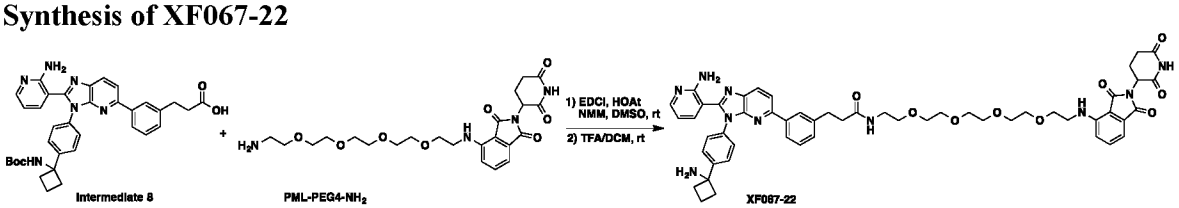


XF067-21 was synthesized following the standard procedure for preparing XF067-1 from intermediate 8 (12 mg, 0.02 mmol), PML-PEG3-NH_2 (11.2 mg, 0.02 mmol, 1.0 equiv), EDCI (5.8 mg, 0.03 mmol, 1.5 equiv), HOAt (4.1 mg, 0.03 mmol, 1.5 equiv), and NMM (6.1 mg, 0.06 mmol, 3.0 equiv) in DMSO (1 mL). XF067-21 was obtained as yellow solid in TFA salt form (11.9 mg, 64%). ^{1}H NMR (800 MHz, CD_3OD) δ 8.28 (d, J = 8.4 Hz, 1H), 8.02 (dd, J = 14.8, 7.2 Hz, 2H), 7.90 (s, 1H), 7.87 (d, J = 7.8 Hz, 1H), 7.81 (d, J = 7.9 Hz, 3H), 7.71 (d, J = 8.0 Hz, 2H), 7.47 (t, J = 7.8 Hz, 1H), 7.36 (t, J = 7.7 Hz, 1H), 7.28 (d, J = 7.6 Hz, 1H), 7.07 – 6.94 (m, 2H), 6.81 (t, J = 6.9 Hz, 1H), 5.01 (dd, J = 12.7, 5.3 Hz, 1H), 3.66 (t, J = 5.2 Hz, 2H), 3.62 (p, J = 4.5, 3.8 Hz, 4H), 3.55 (t, J = 4.5 Hz, 2H), 3.46 (t, J = 4.5 Hz, 2H), 3.41 (dt, J = 21.3, 5.3 Hz, 4H), 3.27 (t, J = 5.4 Hz, 2H), 2.99 (t, J = 7.6 Hz, 2H), 2.94 – 2.87 (m, 2H), 2.82

(ddd, J = 18.2, 13.7, 5.3 Hz, 1H), 2.74 – 2.62 (m, 4H), 2.54 (t, J = 7.6 Hz, 2H), 2.34 (qd, J = 10.4, 5.3 Hz, 1H), 2.07 (ddt, J = 17.7, 11.6, 6.9 Hz, 2H). ESI-MS (m/z) $[M + H]^+$: 935.4187.

Example 97

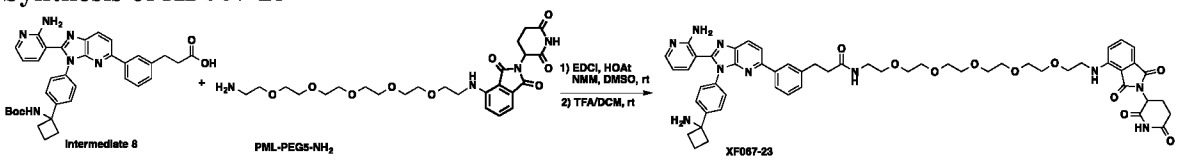
Synthesis of XF067-22



XF067-22 was synthesized following the standard procedure for preparing XF067-1 from intermediate 8 (12 mg, 0.02 mmol), PML-PEG4-NH_2 (11.3 mg, 0.02 mmol, 1.0 equiv), EDCI (5.8 mg, 0.03 mmol, 1.5 equiv), HOAt (4.1 mg, 0.03 mmol, 1.5 equiv), and NMM (6.1 mg, 0.06 mmol, 3.0 equiv) in DMSO (1 mL). XF067-22 was obtained as yellow solid in TFA salt form (9.5 mg, 49%). ^{1}H NMR (800 MHz, CD_3OD) δ 8.29 (s, 1H), 8.02 (d, J = 8.0 Hz, 2H), 7.91 (s, 1H), 7.87 (d, J = 7.9 Hz, 1H), 7.79 (d, J = 8.0 Hz, 2H), 7.71 (t, J = 11.1 Hz, 3H), 7.49 (t, J = 7.9 Hz, 1H), 7.37 (t, J = 7.8 Hz, 1H), 7.29 (d, J = 7.6 Hz, 1H), 7.04 – 6.99 (m, 2H), 6.76 (s, 1H), 5.01 (dd, J = 12.6, 5.3 Hz, 1H), 3.71 – 3.59 (m, 8H), 3.59 – 3.56 (m, 2H), 3.52 (t, J = 4.6 Hz, 2H), 3.43 (q, J = 4.9 Hz, 4H), 3.38 (t, J = 5.4 Hz, 2H), 3.27 (t, J = 5.4 Hz, 2H), 2.99 (t, J = 7.6 Hz, 2H), 2.91 (dd, J = 13.1, 7.1 Hz, 2H), 2.86 – 2.78 (m, 1H), 2.73 – 2.65 (m, 4H), 2.54 (t, J = 7.6 Hz, 2H), 2.33 (d, J = 10.2 Hz, 1H), 2.10 – 2.03 (m, 2H). ESI-MS (m/z) $[M + H]^+$: 979.4463.

Example 98

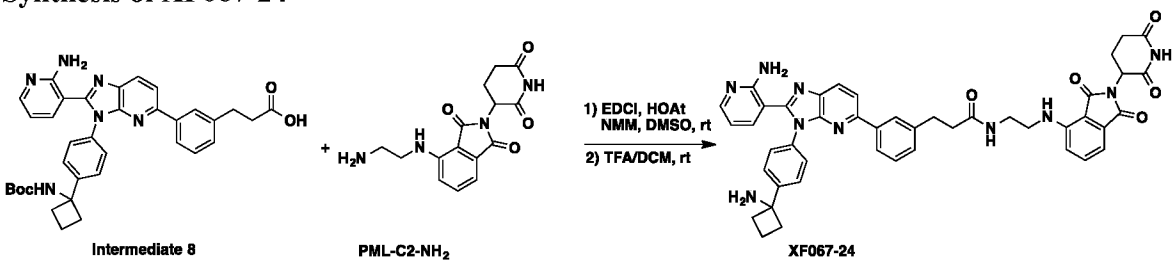
Synthesis of XF067-23



XF067-23 was synthesized following the standard procedure for preparing XF067-1 from intermediate 8 (12 mg, 0.02 mmol), PML-PEG5-NH_2 (12.2 mg, 0.02 mmol, 1.0 equiv), EDCI (5.8 mg, 0.03 mmol, 1.5 equiv), HOAt (4.1 mg, 0.03 mmol, 1.5 equiv), and NMM (6.1 mg, 0.06 mmol, 3.0 equiv) in DMSO (1 mL). XF067-23 was obtained as yellow solid in TFA salt form (11.3 mg, 55%). ^{1}H NMR (800 MHz, CD_3OD) δ 8.30 (d, J = 8.3 Hz, 1H), 8.08 – 7.97 (m, 2H), 7.91 (s, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.81 (d, J = 8.3 Hz, 3H), 7.72 (d, J = 8.0 Hz, 2H), 7.50 (t, J = 7.8 Hz, 1H), 7.37 (t, J = 7.7 Hz, 1H), 7.29 (d, J = 7.5 Hz, 1H), 7.02 (dd, J = 17.2, 7.9 Hz, 2H), 6.82 (t, J = 6.9 Hz, 1H), 5.02 (dd, J = 12.6, 5.4 Hz, 1H), 3.68 (t, J = 5.1 Hz, 2H),

3.66 – 3.54 (m, 12H), 3.52 (q, J = 4.6 Hz, 2H), 3.44 (dt, J = 9.4, 4.8 Hz, 4H), 3.38 (t, J = 5.4 Hz, 2H), 3.26 (t, J = 5.4 Hz, 2H), 2.99 (t, J = 7.5 Hz, 2H), 2.91 (dq, J = 14.4, 8.5, 7.2 Hz, 2H), 2.82 (ddd, J = 18.0, 13.6, 5.3 Hz, 1H), 2.75 – 2.64 (m, 4H), 2.54 (t, J = 7.6 Hz, 2H), 2.34 (tt, J = 12.1, 6.4 Hz, 1H), 2.08 (dq, J = 12.6, 7.5, 6.6 Hz, 2H). ESI-MS (m/z) $[M + H]^+$: 1023.4738.

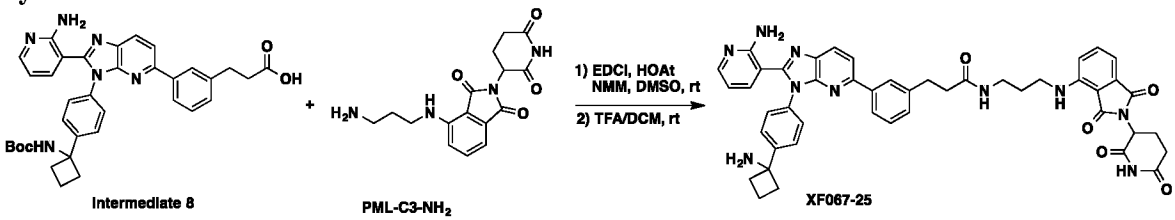
Example 99
Synthesis of XF067-24



Intermediate 8 PML-C2-NH_2 XF067-24

XF067-24 was synthesized following the standard procedure for preparing XF067-1 from intermediate 8 (12 mg, 0.02 mmol), PML-C2-NH_2 (8.6 mg, 0.02 mmol, 1.0 equiv), EDCI (5.8 mg, 0.03 mmol, 1.5 equiv), HOAt (4.1 mg, 0.03 mmol, 1.5 equiv), and NMM (6.1 mg, 0.06 mmol, 3.0 equiv) in DMSO (1 mL). XF067-24 was obtained as yellow solid in TFA salt form (10.5 mg, 65%). ^{1}H NMR (800 MHz, CD_3OD) δ 8.22 (d, J = 8.4 Hz, 1H), 8.03 (d, J = 6.2 Hz, 1H), 7.99 – 7.93 (m, 1H), 7.91 (s, 1H), 7.85 (d, J = 7.8 Hz, 1H), 7.80 (t, J = 7.1 Hz, 3H), 7.66 (d, J = 8.0 Hz, 2H), 7.38 – 7.33 (m, 1H), 7.31 – 7.25 (m, 2H), 6.92 – 6.87 (m, 1H), 6.82 (t, J = 6.9 Hz, 1H), 6.70 (d, J = 8.5 Hz, 1H), 5.01 (dd, J = 12.7, 5.4 Hz, 1H), 3.27 (hept, J = 6.5, 5.8 Hz, 2H), 3.16 – 3.10 (m, 2H), 3.01 (t, J = 7.2 Hz, 2H), 2.92 (dt, J = 11.1, 7.2 Hz, 2H), 2.82 (ddd, J = 18.2, 13.7, 5.3 Hz, 1H), 2.75 – 2.63 (m, 4H), 2.53 (t, J = 7.3 Hz, 2H), 2.33 (qt, J = 10.6, 6.3 Hz, 1H), 2.07 (dq, J = 13.7, 7.8, 6.7 Hz, 2H). ESI-MS (m/z) $[M + H]^+$: 803.3417.

Example 100
Synthesis of XF067-25



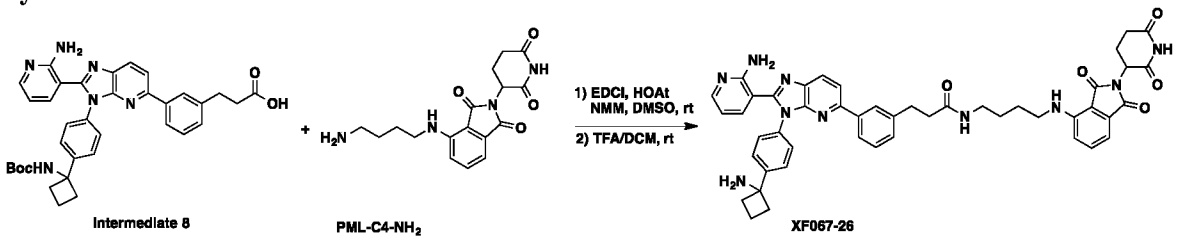
Intermediate 8 PML-C3-NH_2 XF067-25

XF067-25 was synthesized following the standard procedure for preparing XF067-1 from intermediate 8 (12 mg, 0.02 mmol), PML-C3-NH_2 (8.9 mg, 0.02 mmol, 1.0 equiv), EDCI (5.8 mg, 0.03 mmol, 1.5 equiv), HOAt (4.1 mg, 0.03 mmol, 1.5 equiv), and NMM (6.1 mg, 0.06 mmol, 3.0 equiv) in DMSO (1 mL). XF067-25 was obtained as yellow solid in TFA salt form (16.3 mg, 99%). ^{1}H NMR (800 MHz, CD_3OD) δ 8.20 (d, J = 8.4 Hz, 1H), 8.03 (d, J = 6.2 Hz,

1H), 7.93 (s, 1H), 7.92 – 7.86 (m, 1H), 7.80 (dq, J = 19.8, 7.5, 6.0 Hz, 4H), 7.68 (d, J = 8.0 Hz, 2H), 7.39 (t, J = 7.7 Hz, 1H), 7.35 – 7.28 (m, 2H), 6.87 (d, J = 7.1 Hz, 1H), 6.83 (q, J = 6.6 Hz, 1H), 6.62 (d, J = 8.5 Hz, 1H), 5.00 (dd, J = 12.8, 5.5 Hz, 1H), 3.18 (pt, J = 12.8, 6.6 Hz, 2H), 3.03 (t, J = 7.1 Hz, 2H), 2.92 (dt, J = 14.5, 8.2 Hz, 2H), 2.87 – 2.79 (m, 3H), 2.77 – 2.66 (m, 4H), 2.56 (t, J = 7.0 Hz, 2H), 2.34 (dtd, J = 16.2, 10.3, 6.5 Hz, 1H), 2.13 (dt, J = 12.6, 6.2 Hz, 1H), 2.07 (dq, J = 16.4, 8.3 Hz, 1H), 1.54 (p, J = 6.8 Hz, 2H). ESI-MS (m/z) $[M + H]^+$: 817.3578.

Example 101

Synthesis of XF067-26

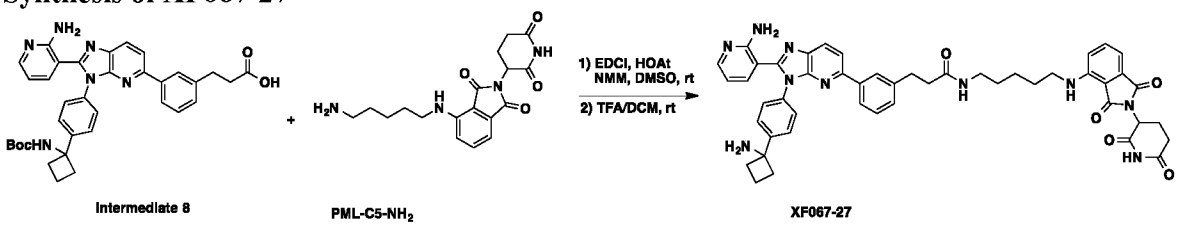


Intermediate 8 PML-C4-NH_2 XF067-26

XF067-26 was synthesized following the standard procedure for preparing XF067-1 from intermediate 8 (12 mg, 0.02 mmol), PML-C4-NH_2 (9.2 mg, 0.02 mmol, 1.0 equiv), EDCI (5.8 mg, 0.03 mmol, 1.5 equiv), HOAt (4.1 mg, 0.03 mmol, 1.5 equiv), and NMM (6.1 mg, 0.06 mmol, 3.0 equiv) in DMSO (1 mL). XF067-26 was obtained as yellow solid in TFA salt form (10.5 mg, 63%). ^{1}H NMR (800 MHz, CD_3OD) δ 8.23 (d, J = 8.3 Hz, 1H), 8.02 (d, J = 6.3 Hz, 1H), 7.97 (d, J = 8.3 Hz, 1H), 7.90 – 7.85 (m, 2H), 7.78 (dd, J = 21.0, 7.8 Hz, 3H), 7.66 (d, J = 8.0 Hz, 2H), 7.38 (t, J = 7.7 Hz, 2H), 7.31 (d, J = 7.6 Hz, 1H), 6.97 – 6.91 (m, 1H), 6.82 (q, J = 9.2, 6.9 Hz, 1H), 6.67 (d, J = 8.4 Hz, 1H), 5.09 – 5.03 (m, 1H), 3.10 (t, J = 6.6 Hz, 2H), 3.01 (t, J = 7.1 Hz, 2H), 2.94 – 2.83 (m, 5H), 2.80 – 2.67 (m, 4H), 2.54 (t, J = 7.1 Hz, 2H), 2.33 (qt, J = 10.3, 6.4 Hz, 1H), 2.13 (dt, J = 12.6, 5.8 Hz, 1H), 2.06 (dq, J = 14.0, 8.4 Hz, 1H), 1.32 (dq, J = 11.4, 6.6 Hz, 2H), 1.24 (q, J = 7.6 Hz, 2H). ESI-MS (m/z) $[M + H]^+$: 831.3721.

Example 102

Synthesis of XF067-27



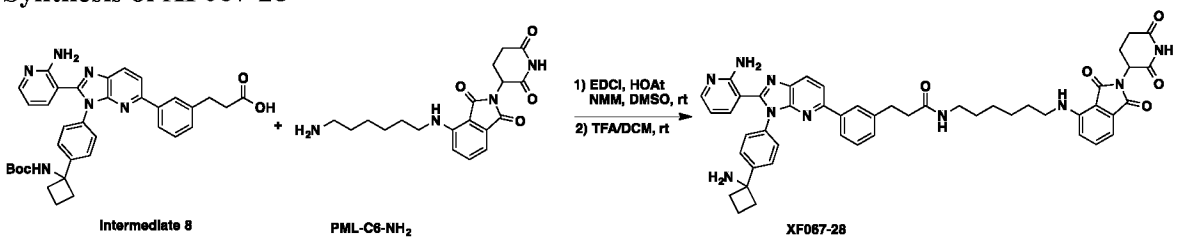
Intermediate 8 PML-C5-NH_2 XF067-27

XF067-27 was synthesized following the standard procedure for preparing XF067-1 from intermediate 8 (12 mg, 0.02 mmol), PML-C5-NH_2 (9.7 mg, 0.02 mmol, 1.0 equiv), EDCI (5.8

mg, 0.03 mmol, 1.5 equiv), HOAt (4.1 mg, 0.03 mmol, 1.5 equiv), and NMM (6.1 mg, 0.06 mmol, 3.0 equiv) in DMSO (1 mL). XF067-27 was obtained as yellow solid in TFA salt form (11.1 mg, 66%). ^{1}H NMR (800 MHz, CD_3OD) δ 8.27 (d, J = 8.4 Hz, 1H), 8.01 (dd, J = 10.1, 7.0 Hz, 2H), 7.94 – 7.88 (m, 2H), 7.79 (d, J = 8.1 Hz, 2H), 7.71 (d, J = 7.7 Hz, 1H), 7.65 (d, J = 8.1 Hz, 2H), 7.41 (t, J = 7.7 Hz, 1H), 7.38 (t, J = 7.7 Hz, 1H), 7.31 (d, J = 7.6 Hz, 1H), 6.94 – 6.88 (m, 1H), 6.79 (t, J = 7.0 Hz, 1H), 6.76 (d, J = 8.5 Hz, 1H), 5.02 (dd, J = 12.7, 5.4 Hz, 1H), 3.11 (td, J = 7.2, 2.3 Hz, 2H), 3.01 (t, J = 7.2 Hz, 2H), 2.97 (t, J = 7.3 Hz, 2H), 2.93 – 2.87 (m, 2H), 2.86 – 2.79 (m, 1H), 2.77 – 2.64 (m, 4H), 2.54 (t, J = 7.2 Hz, 2H), 2.33 (dq, J = 11.8, 6.1, 5.2 Hz, 1H), 2.07 (tt, J = 13.3, 6.0 Hz, 2H), 1.38 – 1.29 (m, 4H), 1.11 (q, J = 7.8 Hz, 2H). ESI-MS (m/z) $[M + H]^+$: 845.3867.

Example 103

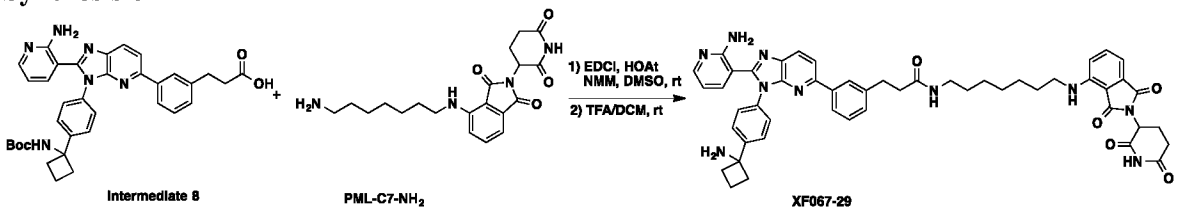
Synthesis of XF067-28



XF067-28 was synthesized following the standard procedure for preparing XF067-1 from intermediate 8 (12 mg, 0.02 mmol), PML-C6-NH_2 (8.2 mg, 0.02 mmol, 1.0 equiv), EDCI (5.8 mg, 0.03 mmol, 1.5 equiv), HOAt (4.1 mg, 0.03 mmol, 1.5 equiv), and NMM (6.1 mg, 0.06 mmol, 3.0 equiv) in DMSO (1 mL). XF067-28 was obtained as yellow solid in TFA salt form (10.9 mg, 63%). ^{1}H NMR (800 MHz, CD_3OD) δ 8.28 (d, J = 8.3 Hz, 1H), 8.05 – 7.99 (m, 2H), 7.93 – 7.88 (m, 2H), 7.80 (d, J = 8.0 Hz, 2H), 7.70 (dd, J = 27.6, 7.9 Hz, 3H), 7.46 (t, J = 7.8 Hz, 1H), 7.37 (t, J = 7.7 Hz, 1H), 7.30 (d, J = 7.6 Hz, 1H), 6.95 (d, J = 7.1 Hz, 1H), 6.86 (d, J = 8.5 Hz, 1H), 6.78 (t, J = 6.9 Hz, 1H), 5.07 (dd, J = 12.6, 5.4 Hz, 1H), 3.09 (t, J = 6.8 Hz, 2H), 3.04 (t, J = 7.3 Hz, 2H), 3.01 (t, J = 7.2 Hz, 2H), 2.94 – 2.83 (m, 3H), 2.80 – 2.68 (m, 4H), 2.54 (t, J = 7.2 Hz, 2H), 2.33 (qt, J = 10.3, 6.4 Hz, 1H), 2.13 (dq, J = 12.7, 6.6, 5.5 Hz, 1H), 2.07 (dq, J = 13.6, 8.4, 7.8 Hz, 1H), 1.38 (p, J = 7.4 Hz, 2H), 1.31 (q, J = 7.3 Hz, 2H), 1.18 – 1.14 (m, 2H), 1.08 (q, J = 7.9 Hz, 2H). ESI-MS (m/z) $[M + H]^+$: 859.4043.

Example 104

Synthesis of XF067-29

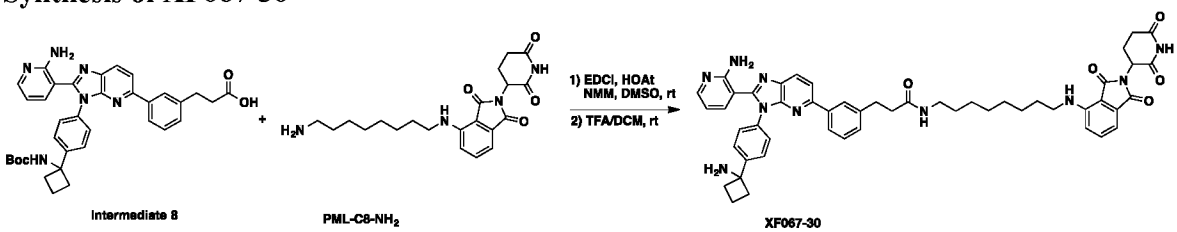


Intermediate 8 PML-C7-NH_2 XF067-29

XF067-29 was synthesized following the standard procedure for preparing XF067-1 from intermediate 8 (12 mg, 0.02 mmol), PML-C7-NH_2 (10 mg, 0.02 mmol, 1.0 equiv), EDCI (5.8 mg, 0.03 mmol, 1.5 equiv), HOAt (4.1 mg, 0.03 mmol, 1.5 equiv), and NMM (6.1 mg, 0.06 mmol, 3.0 equiv) in DMSO (1 mL). XF067-29 was obtained as yellow solid in TFA salt form (15.2 mg, 87%). ^{1}H NMR (800 MHz, CD_3OD) δ 8.29 (d, J = 8.4 Hz, 1H), 8.03 (d, J = 8.4 Hz, 1H), 8.00 (d, J = 6.3 Hz, 1H), 7.93 – 7.88 (m, 2H), 7.81 (d, J = 8.1 Hz, 2H), 7.74 (d, J = 7.6 Hz, 1H), 7.69 (d, J = 8.0 Hz, 2H), 7.50 (t, J = 7.8 Hz, 1H), 7.37 (t, J = 7.6 Hz, 1H), 7.30 (d, J = 7.5 Hz, 1H), 7.01 – 6.96 (m, 1H), 6.92 (d, J = 8.5 Hz, 1H), 6.78 (t, J = 6.9 Hz, 1H), 5.05 (dd, J = 12.7, 5.4 Hz, 1H), 3.14 – 3.05 (m, 4H), 3.00 (t, J = 7.2 Hz, 2H), 2.94 – 2.82 (m, 3H), 2.78 – 2.67 (m, 4H), 2.53 (t, J = 7.2 Hz, 2H), 2.33 (dtd, J = 16.3, 10.4, 6.5 Hz, 1H), 2.13 – 2.03 (m, 2H), 1.44 (p, J = 7.4 Hz, 2H), 1.29 (p, J = 7.2 Hz, 2H), 1.19 (p, J = 7.3 Hz, 2H), 1.13 – 1.03 (m, 4H). ESI-MS (m/z) $[M + H]^+$: 873.4186.

Example 105

Synthesis of XF067-30



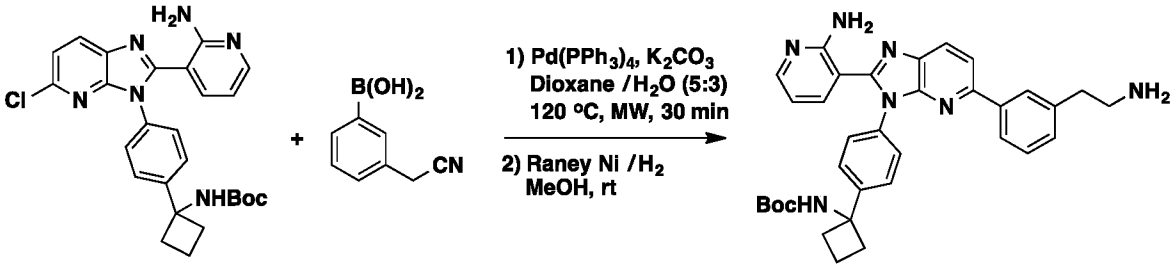
Intermediate 8 PML-C8-NH_2 XF067-30

XF067-30 was synthesized following the standard procedure for preparing XF067-1 from intermediate 8 (12 mg, 0.02 mmol), PML-C8-NH_2 (10.2 mg, 0.02 mmol, 1.0 equiv), EDCI (5.8 mg, 0.03 mmol, 1.5 equiv), HOAt (4.1 mg, 0.03 mmol, 1.5 equiv), and NMM (6.1 mg, 0.06 mmol, 3.0 equiv) in DMSO (1 mL). XF067-30 was obtained as yellow solid in TFA salt form (11.1 mg, 63%). ^{1}H NMR (800 MHz, CD_3OD) δ 8.32 – 8.26 (m, 1H), 8.05 – 7.98 (m, 2H), 7.92 – 7.87 (m, 2H), 7.85 – 7.78 (m, 2H), 7.76 (d, J = 7.7 Hz, 1H), 7.70 (d, J = 8.1 Hz, 2H), 7.50 (t, J = 7.8 Hz, 1H), 7.40 – 7.33 (m, 1H), 7.30 (d, J = 7.6 Hz, 1H), 7.02 – 6.97 (m, 1H), 6.94 (d, J = 8.4 Hz, 1H), 6.79 (t, J = 7.0 Hz, 1H), 5.06 (dd, J = 12.8, 5.3 Hz, 1H), 3.17 (t, J = 7.2 Hz, 2H), 3.09 (t, J = 7.0 Hz, 2H), 3.00 (t, J = 7.3 Hz, 2H), 2.94 – 2.82 (m, 3H), 2.79 – 2.66 (m, 4H), 2.53 (t, J = 7.3 Hz, 2H), 2.34 (qt, J = 10.4, 6.3 Hz, 1H), 2.13 – 2.04 (m, 2H), 1.49 (p,

J = 7.3 Hz, 2H), 1.31 (p, J = 7.2 Hz, 2H), 1.26 (q, J = 7.4 Hz, 2H), 1.15 (q, J = 7.3 Hz, 2H), 1.09 (ddt, J = 21.5, 14.5, 7.8 Hz, 4H). ESI-MS (m/z) $[M + H]^+$: 887.4367.

Example 106

Synthesis of Intermediate 9

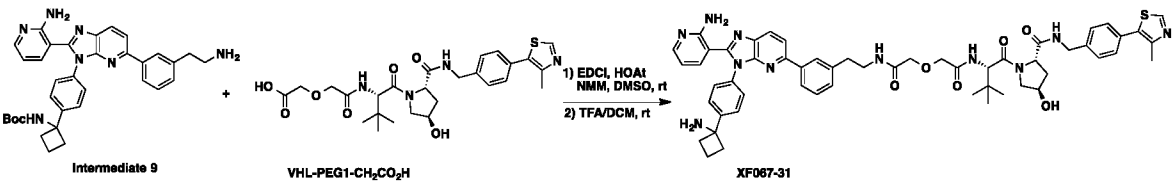


Intermediate 7 Intermediate 9

To a suspension of Intermediate 7 (156.4 mg, 0.32 mmol) and (3-(cyanomethyl)phenyl)boronic acid (102 mg, 0.64 mmol) in dioxane (2.5 mL) and H_2O (1.5 mL) was added potassium carbonate (144 mg, 0.93 mmol). The mixture was degassed for 5 min, before the catalyst $Pd(PPh_3)_4$ (19 mg, 5 mol %) was added. After the reaction mixture was stirred at 120 °C for 30 min in microwave, the solvent was removed and the mixture was purified by reverse phase C18 column (10% – 100% methanol / 0.1% TFA in H_2O) to afford the desired product as white solid in TFA salt form (206 mg, 97% yield). After this product was dissolved in 5 mL of methanol, the catalyst Raney nickel and $NH_3 \cdot H_2O$ (a few drops) were added. The reaction was stirred at rt for 1 h, before the mixture was filtered through a pad of Celite. After the filtrate was concentrated, the resulting residue was purified by reverse phase C18 column (10% – 100% methanol / 0.1% TFA in H_2O) to afford the intermediate 9 as yellow solid in TFA salt form (272.5 mg, 43% yield). ^1H NMR (500 MHz, CD_3OD) δ 8.31 (d, J = 8.4 Hz, 1H), 8.09 – 7.93 (m, 5H), 7.81 – 7.68 (m, 2H), 7.53 (d, J = 8.1 Hz, 2H), 7.46 (t, J = 7.7 Hz, 1H), 7.36 (dt, J = 7.7, 1.4 Hz, 1H), 6.77 (t, J = 6.9 Hz, 1H), 3.25 (t, J = 7.7 Hz, 2H), 3.06 (t, J = 7.7 Hz, 2H), 2.61 (ddd, J = 12.2, 6.2, 2.5 Hz, 2H), 2.55 (d, J = 13.8 Hz, 2H), 2.20 (s, 1H), 2.00 (s, 1H), 1.56 – 1.06 (m, 9H). ESI-MS (m/z) $[M + H]^+$: 576.3062.

Example 107

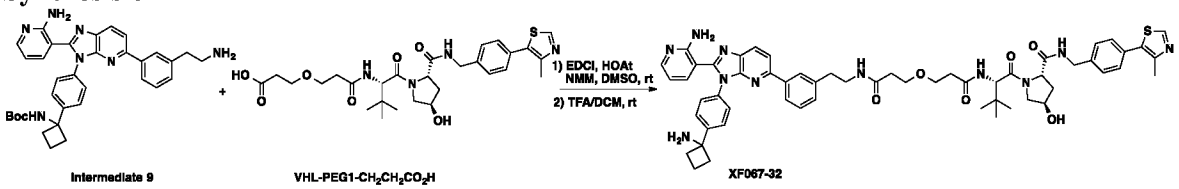
Synthesis of XF067-31



To a solution of Intermediate 9 (9.3 mg, 0.016 mmol) in DMSO (1 mL) were added VHL-PEG1-CH_2COOH (8.3 mg, 0.016 mmol, 1.0 equiv), EDCI (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide) (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (1-hydroxy-7-azabenzo-triazole) (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (N-Methylmorpholine) (4.8 mg, 0.048 mmol, 3.0 equiv). After being stirred overnight at room temperature, the resulting mixture was purified by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O) to afford the corresponding product. After this product was dissolved in DCM (1mL), the reaction mixture was treated with TFA (1 mL) for 30 min. After the solvent was evaporated, the residue was purified by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O) to afford XF067-31 as white solid in TFA salt form (7.8 mg, 38%). ^1H NMR (800 MHz, CD_3OD) δ 8.88 (d, J = 25.3 Hz, 1H), 8.43 – 7.64 (m, 10H), 7.61 – 7.20 (m, 6H), 6.83 (t, J = 25.0 Hz, 1H), 4.77 – 4.27 (m, 5H), 4.20 – 3.78 (m, 6H), 3.70 – 3.43 (m, 2H), 2.92 (t, J = 21.5 Hz, 6H), 2.56 – 1.98 (m, 7H), 1.03 (s, 9H). ESI-MS (m/z) $[M + H]^+$: 1004.4613.

Example 108

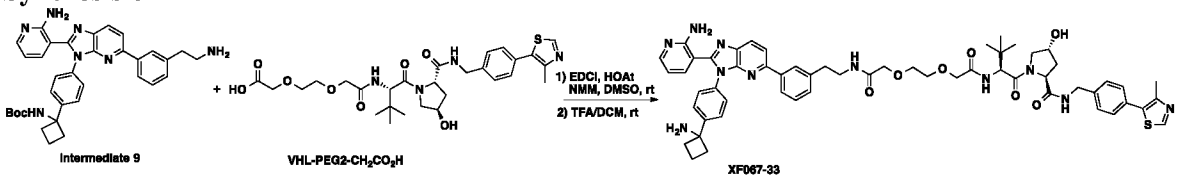
Synthesis of XF067-32



XF067-32 was synthesized following the standard procedure for preparing XF067-31 from intermediate 9 (9.3 mg, 0.016 mmol), VHL-PEG1-CH_2CH_2-CO_2H (9.3 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-32 was obtained as white solid in TFA salt form (9.1 mg, 55%). ^1H NMR (800 MHz, CD_3OD) δ 8.95 (s, 1H), 8.32 (d, J = 8.3 Hz, 1H), 8.04 (d, J = 8.1 Hz, 2H), 7.96 (s, 1H), 7.88 (dd, J = 22.4, 7.7 Hz, 2H), 7.82 (d, J = 8.0 Hz, 2H), 7.73 (d, J = 8.0 Hz, 2H), 7.48 – 7.35 (m, 5H), 7.30 (d, J = 7.5 Hz, 1H), 6.85 (t, J = 6.9 Hz, 1H), 4.64 (s, 1H), 4.58 (t, J = 8.4 Hz, 1H), 4.56 – 4.49 (m, 2H), 4.39 – 4.34 (m, 1H), 3.89 (d, J = 10.9 Hz, 1H), 3.80 (dd, J = 11.1, 4.0 Hz, 1H), 3.69 – 3.63 (m, 3H), 3.60 (dt, J = 10.2, 5.7 Hz, 1H), 3.48 (t, J = 7.6 Hz, 2H), 2.90 (dt, J = 19.6, 7.5 Hz, 4H), 2.73 (dt, J = 12.4, 7.7 Hz, 2H), 2.52 – 2.38 (m, 7H), 2.35 (s, 1H), 2.24 (dd, J = 13.3, 7.6 Hz, 1H), 2.09 (dtd, J = 12.8, 8.8, 4.4 Hz, 2H), 1.03 (s, 9H). ESI-MS (m/z) for $[M + H]^+$: 1032.4904.

Example 109

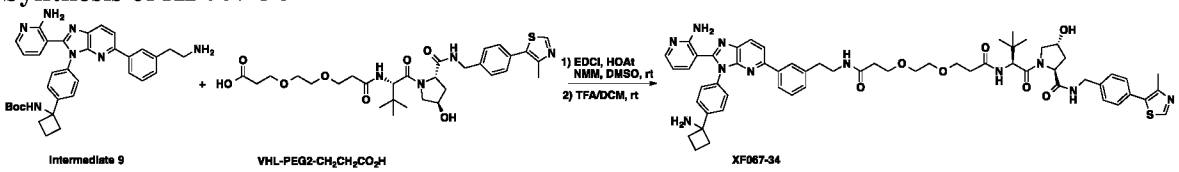
Synthesis of XF067-33



XF067-33 was synthesized following the standard procedure for preparing XF067-31 from intermediate 9 (9.3 mg, 0.016 mmol), VHL-PEG2-CH_2-CO_2H (9.4 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-33 was obtained as white solid in TFA salt form (6.2 mg, 37%). ^{1}H NMR (800 MHz, CD_3OD) δ 8.90 (s, 1H), 8.31 (d, J = 8.3 Hz, 1H), 8.07 – 8.02 (m, 2H), 7.97 (s, 1H), 7.90 (d, J = 7.8 Hz, 1H), 7.86 (d, J = 7.8 Hz, 1H), 7.82 (d, J = 7.9 Hz, 2H), 7.73 (d, J = 8.1 Hz, 2H), 7.39 – 7.35 (m, 5H), 7.31 (d, J = 7.5 Hz, 1H), 6.85 (t, J = 6.9 Hz, 1H), 4.73 (s, 1H), 4.61 (t, J = 8.5 Hz, 1H), 4.53 (s, 1H), 4.41 (d, J = 15.3 Hz, 1H), 4.35 (d, J = 15.4 Hz, 1H), 4.05 – 3.88 (m, 6H), 3.86 – 3.81 (m, 1H), 3.70 – 3.50 (m, 5H), 2.96 – 2.86 (m, 4H), 2.75 – 2.69 (m, 2H), 2.45 (s, 3H), 2.38 – 2.31 (m, 1H), 2.27 (dd, J = 13.0, 7.6 Hz, 1H), 2.12 – 2.04 (m, 2H), 1.04 (s, 9H). ESI-MS (m/z) $[M + H]^+$: 1048.4877.

Example 110

Synthesis of XF067-34

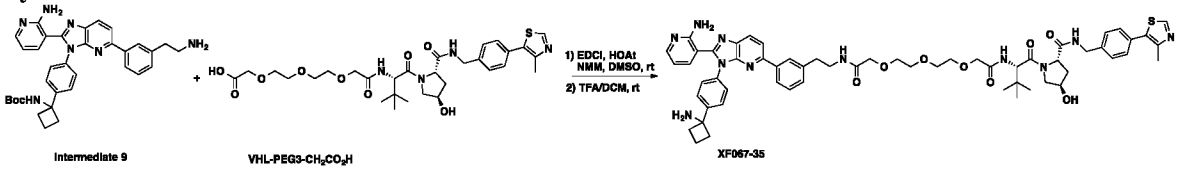


XF067-34 was synthesized following the standard procedure for preparing XF067-31 from intermediate 9 (9.3 mg, 0.016 mmol), VHL-PEG2-CH_2CH_2-CO_2H (9.9 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-34 was obtained as white solid in TFA salt form (9.1 mg, 53%). ^{1}H NMR (800 MHz, CD_3OD) δ 8.94 (s, 1H), 8.32 (d, J = 8.3 Hz, 1H), 8.05 (t, J = 7.7 Hz, 2H), 7.96 (s, 1H), 7.90 (d, J = 7.8 Hz, 1H), 7.86 (d, J = 7.6 Hz, 1H), 7.82 (d, J = 8.1 Hz, 2H), 7.74 (d, J = 8.0 Hz, 2H), 7.47 (d, J = 7.9 Hz, 2H), 7.40 (dt, J = 26.0, 8.4 Hz, 3H), 7.31 (d, J = 7.5 Hz, 1H), 6.85 (t, J = 7.0 Hz, 1H), 4.65 (s, 1H), 4.58 (t, J = 8.2 Hz, 1H), 4.54 (d, J = 15.4 Hz, 1H), 4.50 (s, 1H), 4.37 (d, J = 15.4 Hz, 1H), 3.89 (d, J = 10.9 Hz, 1H), 3.80 (dd, J = 11.1, 4.1 Hz, 1H), 3.68 (dhept, J = 11.5, 5.2 Hz, 4H), 3.58 – 3.51 (m, 4H), 3.48 (t, J = 7.5 Hz, 2H), 2.90 (dt, J = 24.4, 7.0 Hz, 4H), 2.76 – 2.70 (m, 2H), 2.53 (dt,

J = 13.6, 6.8 Hz, 1H), 2.49 – 2.39 (m, 6H), 2.34 (dd, J = 11.3, 6.1 Hz, 1H), 2.23 (dd, J = 13.3, 7.6 Hz, 1H), 2.09 (ddt, J = 17.0, 12.3, 6.3 Hz, 2H), 1.03 (s, 9H). ESI-MS (m/z) $[M + H]^+$: 1076.5189.

Example 111

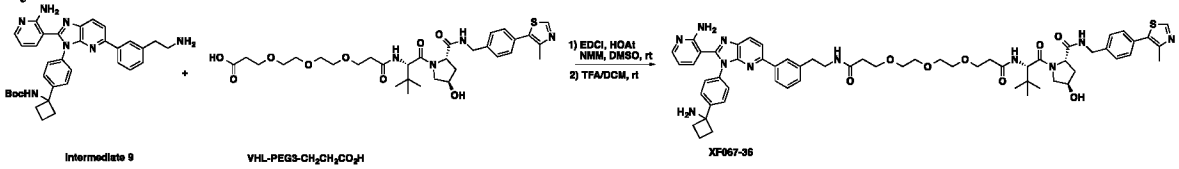
Synthesis of XF067-35



XF067-35 was synthesized following the standard procedure for preparing XF067-31 from intermediate 9 (9.3 mg, 0.016 mmol), VHL-PEG3-CH_2-CO_2H (10.1 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-35 was obtained as white solid in TFA salt form (6.8 mg, 39%). ^{1}H NMR (800 MHz, CD_3OD) δ 8.91 (s, 1H), 8.32 (d, J = 8.4 Hz, 1H), 8.05 (dd, J = 8.3, 4.2 Hz, 2H), 7.99 (s, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.84 (dd, J = 29.9, 7.9 Hz, 3H), 7.76 – 7.69 (m, 2H), 7.45 (d, J = 7.9 Hz, 2H), 7.40 (dp, J = 15.2, 7.7 Hz, 3H), 7.30 (d, J = 7.6 Hz, 1H), 6.84 (s, 1H), 4.70 (s, 1H), 4.62 – 4.47 (m, 3H), 4.35 (d, J = 15.3 Hz, 1H), 4.09 – 3.84 (m, 5H), 3.80 (dd, J = 11.1, 4.0 Hz, 1H), 3.70 – 3.58 (m, 8H), 3.58 – 3.47 (m, 2H), 2.91 (dt, J = 15.0, 7.1 Hz, 4H), 2.73 (q, J = 12.1, 9.9 Hz, 2H), 2.47 (s, 3H), 2.38 – 2.30 (m, 1H), 2.23 (dd, J = 13.3, 7.6 Hz, 1H), 2.13 – 2.02 (m, 2H), 1.03 (s, 9H). ESI-MS (m/z) $[M + H]^+$: 1092.5135.

Example 112

Synthesis of XF067-36

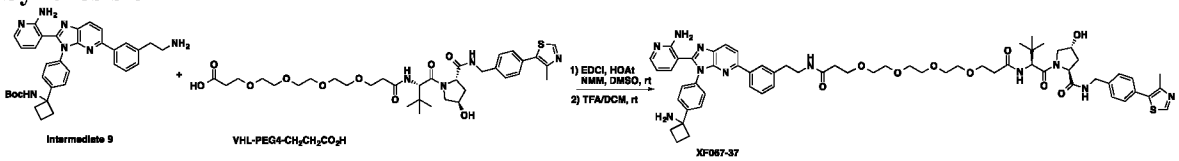


XF067-36 was synthesized following the standard procedure for preparing XF067-31 from intermediate 9 (9.3 mg, 0.016 mmol), VHL-PEG3-CH_2CH_2-CO_2H (10.6 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-36 was obtained as white solid in TFA salt form (8.3 mg, 46%). ^{1}H NMR (800 MHz, CD_3OD) δ 8.93 (s, 1H), 8.32 (d, J = 8.4 Hz, 1H), 8.05 (t, J = 8.1 Hz, 2H), 7.97 (s, 1H), 7.90 (d, J = 7.8 Hz, 1H), 7.84 (dd, J = 25.3, 7.8 Hz, 3H), 7.74 (d, J = 8.0 Hz, 2H), 7.47 (d, J = 7.9 Hz, 2H), 7.41 (tt, J = 15.4, 6.9 Hz,

3H), 7.31 (d, J = 7.5 Hz, 1H), 6.84 (t, J = 7.0 Hz, 1H), 4.64 (s, 1H), 4.59 – 4.47 (m, 3H), 4.37 (d, J = 15.4 Hz, 1H), 3.89 (d, J = 10.9 Hz, 1H), 3.80 (dd, J = 11.1, 4.0 Hz, 1H), 3.74 – 3.63 (m, 4H), 3.63 – 3.51 (m, 8H), 3.48 (t, J = 7.5 Hz, 2H), 2.94 – 2.86 (m, 4H), 2.76 – 2.70 (m, 2H), 2.58 – 2.51 (m, 1H), 2.49 – 2.39 (m, 6H), 2.38 – 2.31 (m, 1H), 2.23 (dd, J = 13.1, 7.7 Hz, 1H), 2.12 – 2.03 (m, 2H), 1.03 (s, 9H). ESI-MS (m/z) $[M + H]^+$: 1120.5442.

Example 113

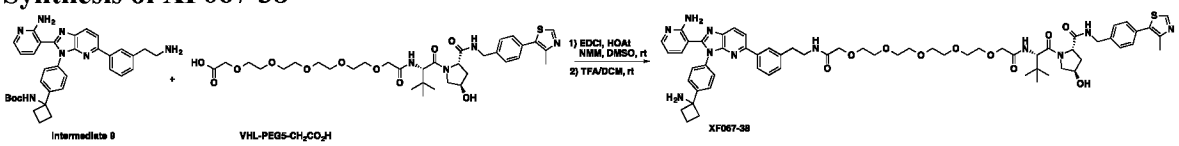
Synthesis of XF067-37



XF067-37 was synthesized following the standard procedure for preparing XF067-31 from intermediate 9 (9.3 mg, 0.016 mmol), VHL-PEG4-CH_2CH_2-CO_2H (11.3 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-37 was obtained as white solid in TFA salt form (8.4 mg, 45%). ^{1}H NMR (800 MHz, CD_3OD) δ 8.92 (s, 1H), 8.32 (d, J = 8.4 Hz, 1H), 8.05 (dd, J = 11.9, 7.2 Hz, 2H), 7.98 (s, 1H), 7.91 (d, J = 7.8 Hz, 1H), 7.86 (d, J = 7.6 Hz, 1H), 7.82 (d, J = 8.0 Hz, 2H), 7.74 (d, J = 8.1 Hz, 2H), 7.47 (d, J = 7.8 Hz, 2H), 7.45 – 7.37 (m, 3H), 7.31 (d, J = 7.5 Hz, 1H), 6.84 (t, J = 7.0 Hz, 1H), 4.64 (s, 1H), 4.59 – 4.48 (m, 3H), 4.37 (d, J = 15.4 Hz, 1H), 3.89 (d, J = 10.9 Hz, 1H), 3.81 (dd, J = 11.1, 4.0 Hz, 1H), 3.73 – 3.63 (m, 4H), 3.63 – 3.50 (m, 12H), 3.48 (t, J = 7.5 Hz, 2H), 2.93 – 2.87 (m, 4H), 2.79 – 2.68 (m, 2H), 2.57 – 2.40 (m, 7H), 2.33 (q, J = 8.7, 7.0 Hz, 1H), 2.23 (dd, J = 13.3, 7.6 Hz, 1H), 2.12 – 2.04 (m, 2H), 1.03 (s, 9H). ESI-MS (m/z) $[M + H]^+$: 1164.5682.

Example 114

Synthesis of XF067-38

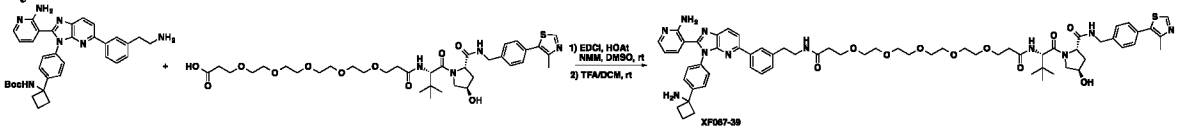


XF067-38 was synthesized following the standard procedure for preparing XF067-31 from intermediate 9 (9.3 mg, 0.016 mmol), VHL-PEG5-CH_2-CO_2H (11.6 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-38 was obtained as white solid in TFA salt form (9.7 mg, 51%). ^{1}H NMR (800 MHz, CD_3OD) δ 8.95 (d, J = 13.9 Hz, 1H), 8.32 (d, J = 8.3 Hz, 1H), 8.11 – 7.98 (m, 3H), 7.92 (d, J = 7.8 Hz, 1H), 7.88 (d, J = 7.8

Hz, 1H), 7.82 (d, J = 8.0 Hz, 2H), 7.74 (d, J = 7.9 Hz, 2H), 7.49 – 7.36 (m, 5H), 7.31 (d, J = 7.6 Hz, 1H), 6.86 (t, J = 7.0 Hz, 1H), 4.69 (s, 1H), 4.62 – 4.50 (m, 3H), 4.37 (d, J = 15.4 Hz, 1H), 4.05 – 3.91 (m, 4H), 3.88 (d, J = 11.2 Hz, 1H), 3.82 (dd, J = 11.2, 3.9 Hz, 1H), 3.73 – 3.50 (m, 18H), 2.91 (d, J = 7.7 Hz, 4H), 2.74 (q, J = 12.0, 10.3 Hz, 2H), 2.48 (s, 3H), 2.37 – 2.31 (m, 1H), 2.25 (dd, J = 13.4, 7.7 Hz, 1H), 2.14 – 2.02 (m, 2H), 1.04 (s, 9H). ESI-MS (m/z) $[M + H]^+$: 1180.5672.

Example 115

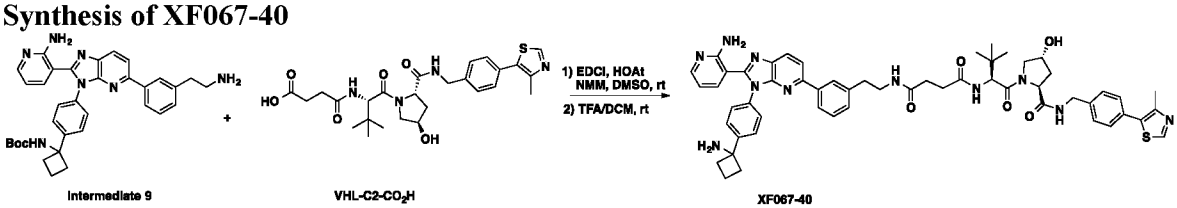
Synthesis of XF067-39



XF067-39 was synthesized following the standard procedure for preparing XF067-31 from intermediate 9 (9.3 mg, 0.016 mmol), VHL-PEG5-CH_2CH_2-CO_2H (12 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-39 was obtained as white solid in TFA salt form (10.6 mg, 55%). ^{1}H NMR (800 MHz, CD_3OD) δ 8.96 (s, 1H), 8.33 (d, J = 8.5 Hz, 1H), 8.05 (dd, J = 12.2, 7.2 Hz, 2H), 8.00 (s, 1H), 7.91 (d, J = 7.8 Hz, 1H), 7.88 (d, J = 7.6 Hz, 1H), 7.83 (d, J = 8.1 Hz, 2H), 7.75 (d, J = 8.0 Hz, 2H), 7.48 (d, J = 7.8 Hz, 2H), 7.42 (d, J = 7.9 Hz, 2H), 7.39 (t, J = 7.7 Hz, 1H), 7.31 (d, J = 7.5 Hz, 1H), 6.85 (t, J = 6.9 Hz, 1H), 4.65 (s, 1H), 4.61 – 4.47 (m, 3H), 4.37 (d, J = 15.4 Hz, 1H), 3.89 (d, J = 10.9 Hz, 1H), 3.81 (dd, J = 11.1, 4.0 Hz, 1H), 3.70 – 3.62 (m, 4H), 3.62 – 3.51 (m, 16H), 3.49 (t, J = 7.6 Hz, 2H), 2.90 (dt, J = 27.1, 6.6 Hz, 4H), 2.74 (q, J = 12.4, 10.6 Hz, 2H), 2.57 – 2.51 (m, 1H), 2.49 (s, 3H), 2.43 (h, J = 5.6 Hz, 3H), 2.38 – 2.30 (m, 1H), 2.24 (dd, J = 13.3, 7.7 Hz, 1H), 2.14 – 2.03 (m, 2H), 1.03 (s, 9H). ESI-MS (m/z) $[M + H]^+$: 1208.5978.

Example 116

Synthesis of XF067-40

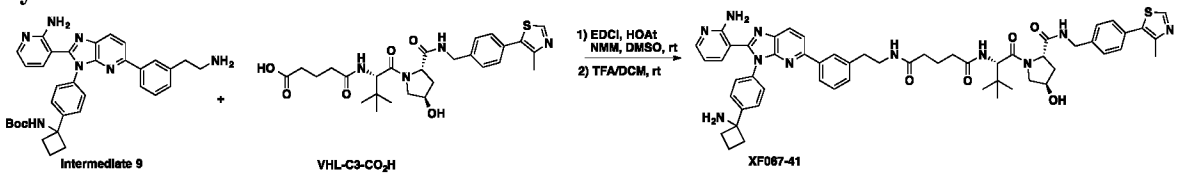


XF067-40 was synthesized following the standard procedure for preparing XF067-31 from intermediate 9 (9.3 mg, 0.016 mmol), VHL-C2-CO_2H (8.5 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-40 was obtained as white solid in TFA salt

form (10.6 mg, 67%). ^{1}H NMR (800 MHz, CD_3OD) δ 8.97 (s, 1H), 8.32 (d, *J* = 8.4 Hz, 1H), 8.04 (t, *J* = 7.8 Hz, 2H), 7.95 (s, 1H), 7.90 (d, *J* = 7.8 Hz, 1H), 7.84 (dd, *J* = 27.5, 7.8 Hz, 3H), 7.73 (d, *J* = 8.1 Hz, 2H), 7.47 (d, *J* = 7.9 Hz, 2H), 7.42 (d, *J* = 7.9 Hz, 2H), 7.41 – 7.35 (m, 1H), 7.30 (d, *J* = 7.6 Hz, 1H), 6.84 (t, *J* = 6.9 Hz, 1H), 4.64 – 4.47 (m, 4H), 4.38 (d, *J* = 15.4 Hz, 1H), 3.90 (d, *J* = 10.9 Hz, 1H), 3.85 – 3.74 (m, 1H), 3.51 – 3.41 (m, 2H), 2.96 – 2.85 (m, 4H), 2.77 – 2.69 (m, 2H), 2.58 (dt, *J* = 14.3, 7.1 Hz, 1H), 2.54 – 2.41 (m, 6H), 2.39 – 2.31 (m, 1H), 2.23 (dd, *J* = 13.2, 7.7 Hz, 1H), 2.13 – 2.03 (m, 2H), 1.07 – 0.99 (m, 9H). ESI-MS (m/z) $[M + H]^+$: 988.4659.

Example 117

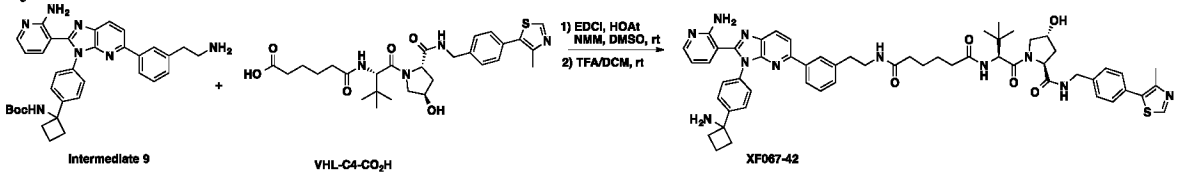
Synthesis of XF067-41



XF067-41 was synthesized following the standard procedure for preparing XF067-31 from intermediate 9 (9.3 mg, 0.016 mmol), VHL-C3-CO_2H (8.7 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-41 was obtained as white solid in TFA salt form (8.3 mg, 52%). ^{1}H NMR (800 MHz, CD_3OD) δ 8.93 (d, *J* = 29.3 Hz, 1H), 8.30 (dd, *J* = 25.1, 8.4 Hz, 1H), 8.04 (t, *J* = 6.3 Hz, 2H), 7.97 (s, 1H), 7.88 (dd, *J* = 23.2, 7.7 Hz, 2H), 7.82 (d, *J* = 8.0 Hz, 2H), 7.74 (d, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 7.8 Hz, 2H), 7.44 – 7.36 (m, 3H), 7.29 (d, *J* = 7.5 Hz, 1H), 6.85 (s, 1H), 4.63 – 4.46 (m, 4H), 4.37 (d, *J* = 15.4 Hz, 1H), 3.92 (d, *J* = 10.9 Hz, 1H), 3.83 (dd, *J* = 11.1, 4.1 Hz, 1H), 3.48 (hept, *J* = 6.9, 6.2 Hz, 2H), 2.91 (dq, *J* = 19.5, 7.9 Hz, 4H), 2.76 – 2.70 (m, 2H), 2.47 (s, 3H), 2.37 (ddt, *J* = 28.9, 13.6, 5.6 Hz, 1H), 2.29 – 2.14 (m, 5H), 2.14 – 2.03 (m, 2H), 1.85 (p, *J* = 7.5 Hz, 2H), 1.03 (s, 9H). ESI-MS (m/z) $[M + H]^+$: 1002.4811.

Example 118

Synthesis of XF067-42

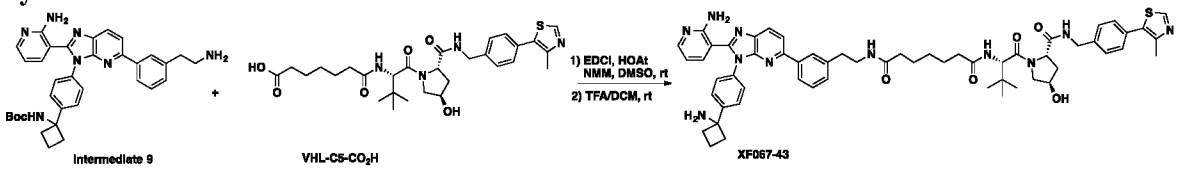


XF067-42 was synthesized following the standard procedure for preparing XF067-31 from intermediate 9 (9.3 mg, 0.016 mmol), VHL-C4-CO_2H (8.9 mg, 0.016 mmol, 1.0 equiv), EDCI

(4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-42 was obtained as white solid in TFA salt form (6.7 mg, 41%). ^{1}H NMR (800 MHz, CD_3OD) δ 8.93 (s, 1H), 8.32 (d, J = 8.4 Hz, 1H), 8.09 – 8.00 (m, 2H), 7.96 (s, 1H), 7.90 (d, J = 7.8 Hz, 1H), 7.86 (d, J = 7.7 Hz, 1H), 7.82 (d, J = 8.1 Hz, 2H), 7.74 (d, J = 8.1 Hz, 2H), 7.47 (d, J = 7.8 Hz, 2H), 7.42 (d, J = 7.9 Hz, 2H), 7.39 (q, J = 7.9 Hz, 1H), 7.30 (d, J = 7.5 Hz, 1H), 6.84 (t, J = 6.9 Hz, 1H), 4.63 (s, 1H), 4.61 – 4.50 (m, 3H), 4.37 (d, J = 15.4 Hz, 1H), 3.91 (d, J = 10.9 Hz, 1H), 3.82 (dd, J = 11.1, 4.1 Hz, 1H), 3.47 (t, J = 7.5 Hz, 2H), 2.98 – 2.83 (m, 4H), 2.77 – 2.70 (m, 2H), 2.54 – 2.45 (m, 3H), 2.39 – 2.30 (m, 1H), 2.28 – 2.12 (m, 5H), 2.13 – 2.05 (m, 2H), 1.58 (q, J = 9.0 Hz, 4H), 1.04 (s, 9H). ESI-MS (m/z) $[M + H]^+$: 1016.4956.

Example 119

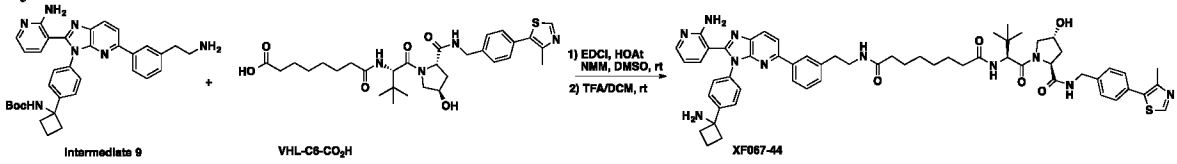
Synthesis of XF067-43



XF067-43 was synthesized following the standard procedure for preparing XF067-31 from intermediate 9 (9.3 mg, 0.016 mmol), VHL-C5-CO_2H (9.2 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-43 was obtained as white solid in TFA salt form (8.6 mg, 52%). ^{1}H NMR (800 MHz, CD_3OD) δ 8.94 (s, 1H), 8.32 (d, J = 8.3 Hz, 1H), 8.09 – 7.99 (m, 2H), 7.96 (s, 1H), 7.90 (d, J = 7.9 Hz, 1H), 7.87 (d, J = 7.7 Hz, 1H), 7.82 (d, J = 8.1 Hz, 2H), 7.74 (d, J = 8.1 Hz, 2H), 7.48 (d, J = 7.9 Hz, 2H), 7.43 (d, J = 7.9 Hz, 2H), 7.39 (t, J = 7.7 Hz, 1H), 7.30 (d, J = 7.6 Hz, 1H), 6.85 (t, J = 6.9 Hz, 1H), 4.63 (s, 1H), 4.61 – 4.49 (m, 3H), 4.40 – 4.34 (m, 1H), 3.91 (d, J = 10.9 Hz, 1H), 3.81 (dd, J = 11.1, 4.1 Hz, 1H), 3.47 (q, J = 7.8 Hz, 2H), 2.91 (dq, J = 19.4, 8.3, 7.5 Hz, 4H), 2.72 (dt, J = 14.0, 8.4 Hz, 2H), 2.49 (s, 3H), 2.34 (dp, J = 21.6, 7.1 Hz, 1H), 2.23 (tt, J = 12.3, 5.8 Hz, 2H), 2.16 (dt, J = 19.4, 7.4 Hz, 3H), 2.13 – 2.04 (m, 2H), 1.54 (dp, J = 18.7, 7.2 Hz, 4H), 1.27 (p, J = 9.1, 8.4 Hz, 2H), 1.04 (s, 9H). ESI-MS (m/z) $[M + H]^+$: 1030.5126.

Example 120

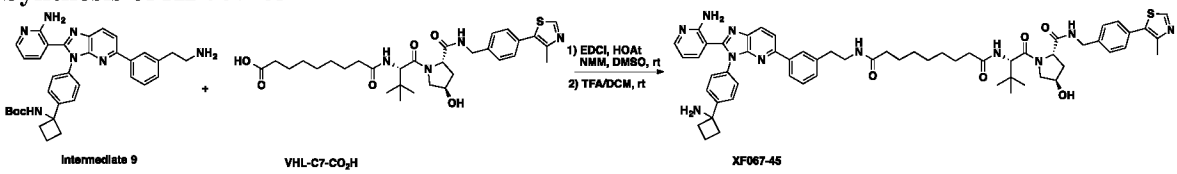
Synthesis of XF067-44



XF067-44 was synthesized following the standard procedure for preparing XF067-31 from intermediate 9 (9.3 mg, 0.016 mmol), VHL-C6-CO_2H (9.4 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-44 was obtained as white solid in TFA salt form (8.4 mg, 50%). ^1H NMR (800 MHz, CD_3OD) δ 8.95 (s, 1H), 8.32 (d, J = 8.3 Hz, 1H), 8.04 (h, J = 4.3 Hz, 2H), 7.96 (s, 1H), 7.90 (d, J = 7.9 Hz, 1H), 7.86 (d, J = 7.5 Hz, 1H), 7.82 (d, J = 8.1 Hz, 2H), 7.77 – 7.70 (m, 2H), 7.48 (d, J = 7.8 Hz, 2H), 7.43 (d, J = 7.8 Hz, 2H), 7.41 – 7.35 (m, 1H), 7.30 (d, J = 7.5 Hz, 1H), 6.85 (t, J = 6.9 Hz, 1H), 4.64 (s, 1H), 4.62 – 4.48 (m, 3H), 4.38 (d, J = 15.5 Hz, 1H), 3.92 (d, J = 10.9 Hz, 1H), 3.82 (dd, J = 11.1, 4.1 Hz, 1H), 3.47 (t, J = 7.4 Hz, 2H), 2.89 (dhept, J = 16.3, 8.1 Hz, 4H), 2.72 (dt, J = 14.1, 8.5 Hz, 2H), 2.53 – 2.44 (m, 3H), 2.39 – 2.28 (m, 1H), 2.27 – 2.03 (m, 7H), 1.59 – 1.49 (m, 4H), 1.26 (p, J = 3.8 Hz, 4H), 1.04 (s, 9H). ESI-MS (m/z) $[M + H]^+$: 1044.5289.

Example 121

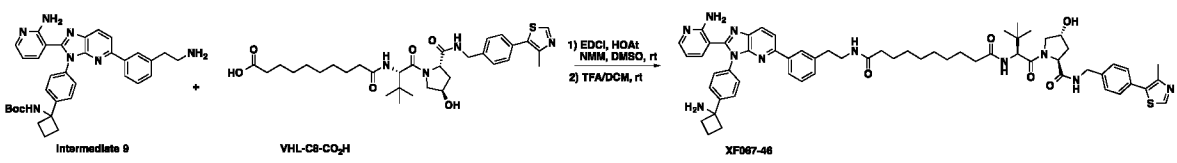
Synthesis of XF067-45



XF067-45 was synthesized following the standard procedure for preparing XF067-31 from intermediate 9 (9.3 mg, 0.016 mmol), VHL-C7-CO_2H (9.6 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-45 was obtained as white solid in TFA salt form (5.4 mg, 32%). ^1H NMR (800 MHz, CD_3OD) δ 8.93 (s, 1H), 8.32 (d, J = 7.4 Hz, 1H), 8.07 – 7.67 (m, 9H), 7.55 – 7.22 (m, 6H), 6.84 (s, 1H), 4.70 – 4.45 (m, 4H), 4.38 (dd, J = 15.3, 6.4 Hz, 1H), 3.91 (t, J = 8.7 Hz, 1H), 3.82 (p, J = 4.2 Hz, 1H), 3.47 (q, J = 7.6 Hz, 2H), 2.97 – 2.84 (m, 4H), 2.72 (dq, J = 13.8, 8.0 Hz, 2H), 2.49 (s, 3H), 2.34 (s, 1H), 2.30 – 2.01 (m, 7H), 1.54 (dd, J = 13.8, 7.0 Hz, 4H), 1.32 – 1.11 (m, 6H), 1.15 – 0.94 (m, 9H). ESI-MS (m/z) $[M + H]^+$: 1058.5451.

Example 122

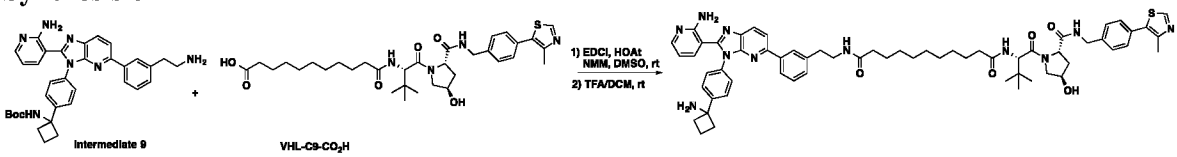
Synthesis of XF067-46



XF067-46 was synthesized following the standard procedure for preparing XF067-31 from intermediate 9 (9.3 mg, 0.016 mmol), VHL-C8-CO_2H (9.8 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-46 was obtained as white solid in TFA salt form (5.3 mg, 31%). ^1H NMR (800 MHz, CD_3OD) δ 8.94 (s, 1H), 8.33 (d, J = 8.4 Hz, 1H), 8.05 (dd, J = 8.4, 4.7 Hz, 2H), 7.96 (s, 1H), 7.90 (d, J = 7.7 Hz, 1H), 7.86 (d, J = 7.6 Hz, 1H), 7.82 (d, J = 8.0 Hz, 2H), 7.74 (d, J = 8.0 Hz, 2H), 7.48 (d, J = 7.8 Hz, 2H), 7.43 (d, J = 7.8 Hz, 2H), 7.38 (t, J = 7.7 Hz, 1H), 7.30 (d, J = 7.6 Hz, 1H), 6.84 (s, 1H), 4.68 – 4.62 (m, 1H), 4.63 – 4.47 (m, 3H), 4.38 (d, J = 15.4 Hz, 1H), 3.92 (d, J = 10.9 Hz, 1H), 3.82 (dd, J = 11.1, 4.1 Hz, 1H), 3.47 (q, J = 7.7 Hz, 2H), 2.94 – 2.86 (m, 4H), 2.72 (q, J = 12.3, 10.3 Hz, 2H), 2.49 (d, J = 4.6 Hz, 3H), 2.34 (d, J = 10.5 Hz, 1H), 2.25 (ddt, J = 36.7, 14.8, 7.5 Hz, 3H), 2.19 – 2.03 (m, 4H), 1.56 (ddd, J = 32.8, 14.0, 7.1 Hz, 4H), 1.23 (s, 8H), 1.05 (s, 9H). ESI-MS (m/z) $[M + H]^+$: 1072.5593.

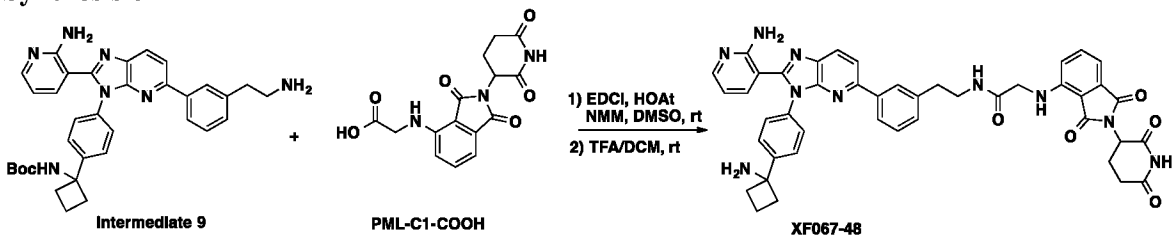
Example 123

Synthesis of XF067-47



XF067-47 was synthesized following the standard procedure for preparing XF067-31 from intermediate 9 (9.3 mg, 0.016 mmol), VHL-C9-CO_2H (10 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-47 was obtained as white solid in TFA salt form (8.4 mg, 48%). ^1H NMR (800 MHz, CD_3OD) δ 8.92 (s, 1H), 8.32 (d, J = 8.0 Hz, 1H), 8.05 (d, J = 8.2 Hz, 2H), 7.96 (s, 1H), 7.90 (d, J = 7.6 Hz, 1H), 7.82 (t, J = 8.4 Hz, 3H), 7.73 (d, J = 8.1 Hz, 2H), 7.55 – 7.35 (m, 5H), 7.30 (d, J = 7.4 Hz, 1H), 6.82 (s, 1H), 4.65 (s, 1H), 4.61 – 4.47 (m, 3H), 4.38 (d, J = 15.4 Hz, 1H), 3.92 (d, J = 10.7 Hz, 1H), 3.82 (dd, J = 11.1, 4.0 Hz, 1H), 3.48 (t, J = 7.4 Hz, 2H), 2.98 – 2.84 (m, 4H), 2.78 – 2.66 (m, 2H), 2.49 (s, 3H), 2.40 – 2.20 (m, 5H), 2.20 – 2.01 (m, 3H), 1.68 – 1.45 (m, 4H), 1.22 (s, 10H), 1.04 (s, 9H). ESI-MS (m/z) $[M + H]^+$: 1086.5765.

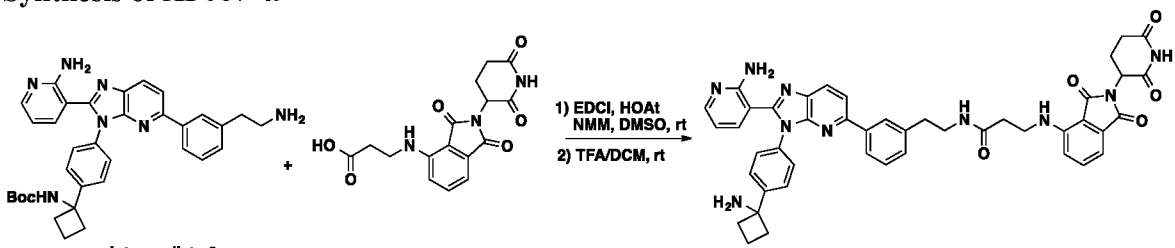
Example 124
Synthesis of XF067-48



Intermediate 9 PML-C1-COOH XF067-48

XF067-48 was synthesized following the standard procedure for preparing XF067-31 from intermediate 9 (9.3 mg, 0.016 mmol), PML-C1-CO_2H (5.3 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-48 was obtained as yellow solid in TFA salt form (5.3 mg, 42%). ^{1}H NMR (800 MHz, CD_3OD) δ 8.28 (d, J = 8.4 Hz, 1H), 8.03 (d, J = 6.0 Hz, 1H), 7.99 (d, J = 8.4 Hz, 1H), 7.88 (d, J = 5.7 Hz, 2H), 7.78 (d, J = 8.1 Hz, 2H), 7.73 (d, J = 7.7 Hz, 1H), 7.67 (d, J = 8.0 Hz, 2H), 7.35 (t, J = 7.8 Hz, 1H), 7.27 – 7.20 (m, 2H), 6.86 (d, J = 7.2 Hz, 1H), 6.77 (t, J = 6.8 Hz, 1H), 6.62 (d, J = 8.4 Hz, 1H), 5.06 (dd, J = 12.8, 5.5 Hz, 1H), 3.91 (s, 2H), 3.58 (hept, J = 6.7 Hz, 2H), 2.94 – 2.85 (m, 5H), 2.79 – 2.67 (m, 4H), 2.34 – 2.30 (m, 1H), 2.16 – 1.98 (m, 2H). ESI-MS (m/z) $[M + H]^+$: 789.3244.

Example 125
Synthesis of XF067-49



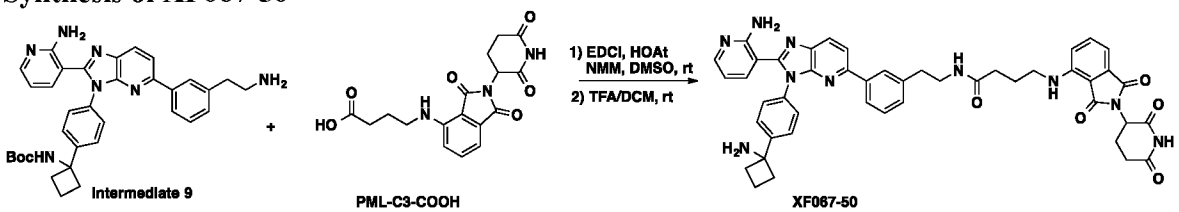
Intermediate 9 PML-C2-COOH XF067-49

XF067-49 was synthesized following the standard procedure for preparing XF067-31 from intermediate 9 (9.3 mg, 0.016 mmol), PML-C2-CO_2H (5.5 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-49 was obtained as yellow solid in TFA salt form (7.4 mg, 58%). ^{1}H NMR (800 MHz, CD_3OD) δ 8.26 (d, J = 8.4 Hz, 1H), 8.05 – 7.99 (m, 2H), 7.94 (s, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.82 – 7.78 (m, 3H), 7.68 (d, J = 8.0 Hz, 2H), 7.43 – 7.33 (m, 2H), 7.28 (d, J = 7.5 Hz, 1H), 6.97 (d, J = 7.1 Hz, 1H), 6.89 (d, J = 8.5 Hz, 1H), 6.85 – 6.76 (m, 1H), 5.01 (dd, J = 12.5, 5.3 Hz, 1H), 3.48 (q, J = 7.9 Hz, 4H), 2.94 – 2.88 (m, 2H), 2.87 (t, J = 7.3 Hz, 2H), 2.80 (ddd, J = 19.2, 14.3, 5.4 Hz, 1H), 2.71 (td, J = 14.1, 11.7,

7.2 Hz, 2H), 2.70 – 2.61 (m, 2H), 2.46 (t, J = 6.7 Hz, 2H), 2.37 – 2.30 (m, 1H), 2.06 – 2.03 (m, 2H). ESI-MS (m/z) $[M + H]^+$: 803.3419.

Example 126

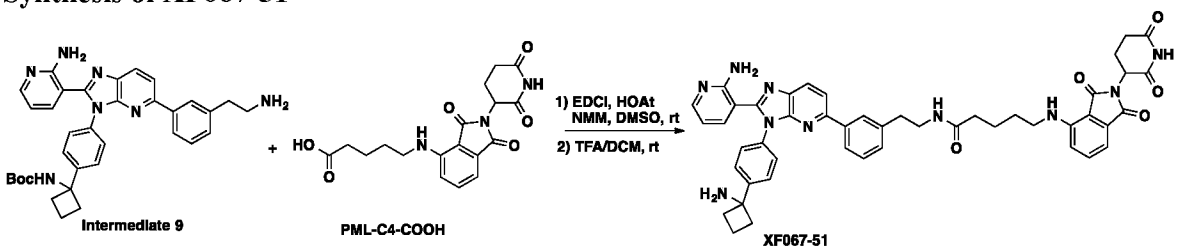
Synthesis of XF067-50



XF067-50 was synthesized following the standard procedure for preparing XF067-31 from intermediate 9 (9.3 mg, 0.016 mmol), PML-C3-CO_2H (5.7 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-50 was obtained as yellow solid in TFA salt form (8.5 mg, 65%). ^{1}H NMR (800 MHz, CD_3OD) δ 8.24 (d, J = 8.4 Hz, 1H), 8.03 (d, J = 6.2 Hz, 1H), 8.00 – 7.95 (m, 2H), 7.85 (d, J = 7.8 Hz, 1H), 7.79 (dd, J = 14.6, 7.7 Hz, 3H), 7.68 (t, J = 6.1 Hz, 2H), 7.37 (dt, J = 16.3, 7.7 Hz, 2H), 7.31 (d, J = 7.5 Hz, 1H), 6.94 – 6.87 (m, 1H), 6.82 (t, J = 6.9 Hz, 1H), 6.77 (d, J = 8.5 Hz, 1H), 4.99 (dt, J = 13.5, 6.3 Hz, 1H), 3.53 (p, J = 6.7 Hz, 2H), 3.07 (t, J = 7.3 Hz, 2H), 2.91 (p, J = 8.3, 7.8 Hz, 4H), 2.79 (ddd, J = 18.3, 13.8, 5.1 Hz, 1H), 2.76 – 2.62 (m, 4H), 2.35 – 2.30 (m, 1H), 2.22 (t, J = 7.2 Hz, 2H), 2.06 (s, 2H), 1.79 (p, J = 7.3 Hz, 2H). ESI-MS (m/z) $[M + H]^+$: 817.3576.

Example 127

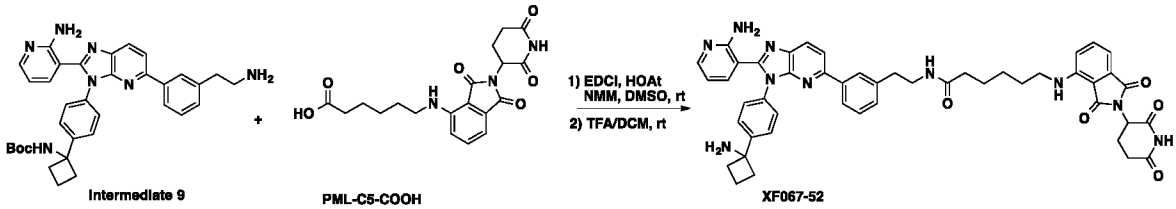
Synthesis of XF067-51



XF067-51 was synthesized following the standard procedure for preparing XF067-31 from intermediate 9 (9.3 mg, 0.016 mmol), PML-C4-CO_2H (6 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-51 was obtained as yellow solid in TFA salt form (7.6 mg, 57%). ^{1}H NMR (800 MHz, CD_3OD) δ 8.25 (d, J = 8.4 Hz, 1H), 8.02 (dd, J = 24.9, 7.3 Hz, 2H), 7.94 (s, 1H), 7.87 (d, J = 7.8 Hz, 1H), 7.79 (dd, J = 11.5, 7.6 Hz, 3H), 7.68 (d, J = 8.0 Hz, 2H), 7.43 (t, J = 7.8 Hz, 1H), 7.38 (t, J = 7.7 Hz, 1H), 7.31 (d, J = 7.6 Hz, 1H),

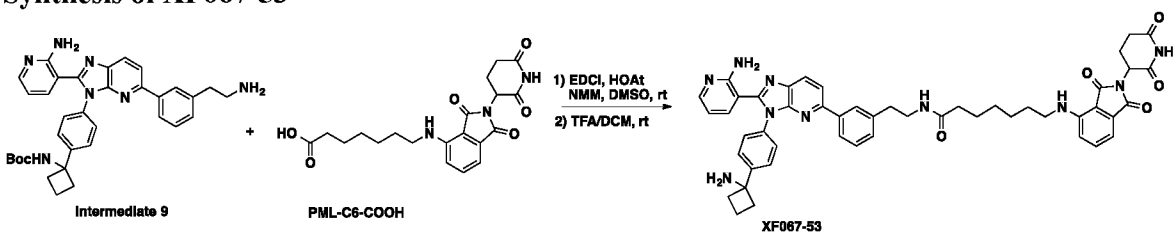
6.98 – 6.93 (m, 1H), 6.81 (dd, *J* = 20.2, 7.7 Hz, 2H), 5.08 – 5.02 (m, 1H), 3.53 (t, *J* = 7.1 Hz, 2H), 3.06 (t, *J* = 7.1 Hz, 2H), 2.95 – 2.82 (m, 5H), 2.79 – 2.68 (m, 4H), 2.33 (tq, *J* = 16.4, 7.0 Hz, 1H), 2.18 (t, *J* = 7.2 Hz, 2H), 2.12 (dd, *J* = 12.5, 5.8 Hz, 1H), 2.10 – 2.02 (m, 1H), 1.58 (p, *J* = 7.3 Hz, 2H), 1.44 (p, *J* = 7.3 Hz, 2H). ESI-MS (m/z) $[M + H]^+$: 831.3715.

Example 128
Synthesis of XF067-52



XF067-52 was synthesized following the standard procedure for preparing XF067-31 from intermediate 9 (9.3 mg, 0.016 mmol), PML-C5-CO_2H (6.2 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-52 was obtained as yellow solid in TFA salt form (9.2 mg, 68%). ^1H NMR (800 MHz, CD_3OD) δ 8.28 (d, *J* = 8.4 Hz, 1H), 8.03 (dd, *J* = 12.4, 7.3 Hz, 2H), 7.95 (s, 1H), 7.90 (d, *J* = 7.8 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 2H), 7.75 (d, *J* = 7.6 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 2H), 7.45 (t, *J* = 7.8 Hz, 1H), 7.39 (t, *J* = 7.7 Hz, 1H), 7.31 (d, *J* = 7.5 Hz, 1H), 6.97 – 6.91 (m, 1H), 6.84 – 6.78 (m, 2H), 4.99 (dd, *J* = 12.7, 5.4 Hz, 1H), 3.52 (t, *J* = 7.1 Hz, 2H), 3.07 (t, *J* = 7.2 Hz, 2H), 2.94 – 2.86 (m, 5H), 2.79 (ddd, *J* = 18.2, 13.6, 5.3 Hz, 1H), 2.74 – 2.70 (m, 2H), 2.67 (dtd, *J* = 31.0, 13.2, 11.6, 4.3 Hz, 2H), 2.33 (dt, *J* = 11.5, 6.0 Hz, 1H), 2.16 (t, *J* = 7.2 Hz, 2H), 2.10 – 2.01 (m, 1H), 1.55 (q, *J* = 7.5 Hz, 2H), 1.47 (q, *J* = 7.4 Hz, 2H), 1.27 – 1.22 (m, 2H). ESI-MS (m/z) $[M + H]^+$: 845.3876.

Example 129
Synthesis of XF067-53

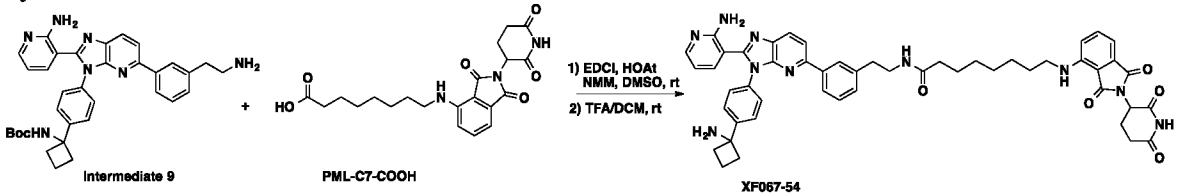


XF067-53 was synthesized following the standard procedure for preparing XF067-31 from intermediate 9 (9.3 mg, 0.016 mmol), PML-C6-CO_2H (6.4 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-53 was obtained as yellow solid in TFA salt

form (8.3 mg, 60%). ^{1}H NMR (800 MHz, CD_3OD) δ 8.29 (d, *J* = 8.4 Hz, 1H), 8.02 (dd, *J* = 12.1, 7.0 Hz, 2H), 7.94 (s, 1H), 7.89 (d, *J* = 7.8 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 2H), 7.75 (d, *J* = 7.7 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 2H), 7.47 (t, *J* = 7.8 Hz, 1H), 7.38 (t, *J* = 7.7 Hz, 1H), 7.31 (d, *J* = 7.6 Hz, 1H), 6.96 (d, *J* = 7.1 Hz, 1H), 6.90 (d, *J* = 8.5 Hz, 1H), 6.79 (s, 1H), 5.06 (dd, *J* = 12.6, 5.4 Hz, 1H), 3.52 (t, *J* = 7.1 Hz, 2H), 3.11 (t, *J* = 7.2 Hz, 2H), 2.94 – 2.83 (m, 5H), 2.78 – 2.68 (m, 4H), 2.33 (dq, *J* = 16.3, 8.6, 7.9 Hz, 1H), 2.17 – 2.08 (m, 3H), 2.07 – 2.05 (m, 1H), 1.53 (q, *J* = 7.5 Hz, 2H), 1.46 (p, *J* = 7.3 Hz, 2H), 1.26 (q, *J* = 7.5 Hz, 2H), 1.21 (q, *J* = 7.7 Hz, 2H). ESI-MS (m/z) $[M + H]^+$: 859.4025.

Example 130

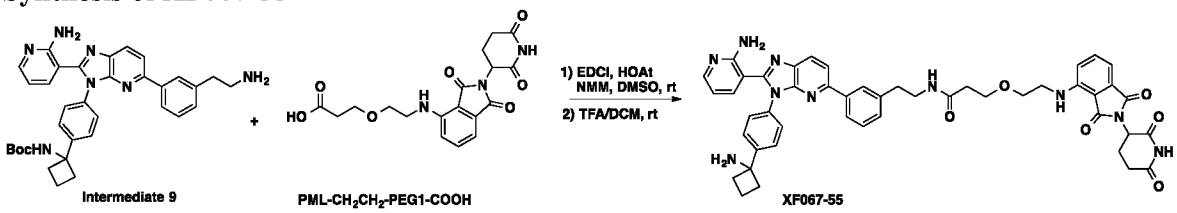
Synthesis of XF067-54



XF067-54 was synthesized following the standard procedure for preparing XF067-31 from intermediate 9 (9.3 mg, 0.016 mmol), PML-C7-CO_2H (6.6 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-54 was obtained as yellow solid in TFA salt form (9.2 mg, 66%). ^{1}H NMR (800 MHz, CD_3OD) δ 8.31 (d, *J* = 8.3 Hz, 1H), 8.05 (d, *J* = 8.3 Hz, 1H), 8.01 (d, *J* = 6.2 Hz, 1H), 7.94 (s, 1H), 7.91 (d, *J* = 7.8 Hz, 1H), 7.79 (dd, *J* = 26.9, 7.8 Hz, 3H), 7.71 (d, *J* = 8.0 Hz, 2H), 7.50 (t, *J* = 7.8 Hz, 1H), 7.38 (t, *J* = 7.7 Hz, 1H), 7.30 (d, *J* = 7.6 Hz, 1H), 6.99 (t, *J* = 5.9 Hz, 1H), 6.94 (d, *J* = 8.5 Hz, 1H), 6.80 (t, *J* = 6.9 Hz, 1H), 5.07 – 5.01 (m, 1H), 3.51 (t, *J* = 7.2 Hz, 2H), 3.16 (t, *J* = 7.2 Hz, 2H), 2.91 (h, *J* = 7.5 Hz, 4H), 2.84 (ddd, *J* = 18.0, 13.6, 5.3 Hz, 1H), 2.77 – 2.66 (m, 4H), 2.34 (tq, *J* = 15.8, 7.4, 7.0 Hz, 1H), 2.14 (t, *J* = 7.4 Hz, 2H), 2.12 – 2.05 (m, 2H), 1.51 (qt, *J* = 11.1, 5.5 Hz, 4H), 1.26 (q, *J* = 7.4 Hz, 2H), 1.21 (tq, *J* = 11.0, 6.8, 6.0 Hz, 4H). ESI-MS (m/z) $[M + H]^+$: 873.4187.

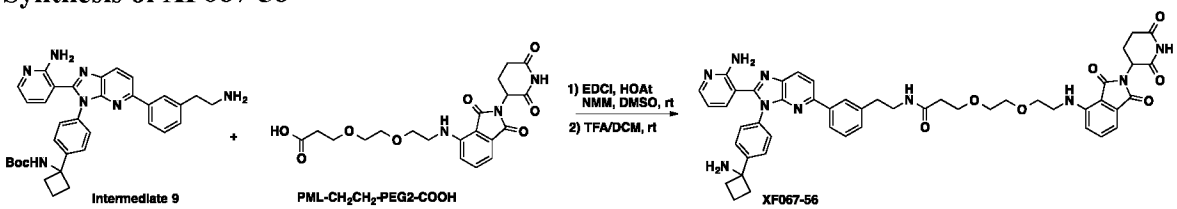
Example 131

Synthesis of XF067-55



XF067-55 was synthesized following the standard procedure for preparing XF067-31 from intermediate 9 (9.3 mg, 0.016 mmol), PML-CH_2CH_2-PEG1-CO_2H (6.2 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-55 was obtained as yellow solid in TFA salt form (7.7 mg, 57%). ^{1}H NMR (800 MHz, CD_3OD) δ 8.28 (d, J = 8.3 Hz, 1H), 8.02 (dd, J = 11.4, 7.2 Hz, 2H), 7.97 (s, 1H), 7.87 (d, J = 7.7 Hz, 1H), 7.80 (dd, J = 8.0, 5.0 Hz, 3H), 7.70 (d, J = 8.0 Hz, 2H), 7.48 (t, J = 7.8 Hz, 1H), 7.39 – 7.33 (m, 1H), 7.28 (d, J = 7.5 Hz, 1H), 6.96 (t, J = 7.6 Hz, 2H), 6.82 (t, J = 6.9 Hz, 1H), 4.88 – 4.77 (m, 1H), 3.76 – 3.70 (m, 2H), 3.58 (t, J = 5.1 Hz, 2H), 3.49 (t, J = 7.5 Hz, 2H), 3.36 (t, J = 5.2 Hz, 2H), 2.89 (dt, J = 15.1, 11.1 Hz, 5H), 2.73 – 2.69 (m, 2H), 2.62 – 2.52 (m, 2H), 2.45 (t, J = 5.8 Hz, 2H), 2.37 – 2.29 (m, 1H), 2.10 – 2.04 (m, 1H), 1.89 (d, J = 12.6 Hz, 1H). ESI-MS (m/z) $[M + H]^+$: 847.3673.

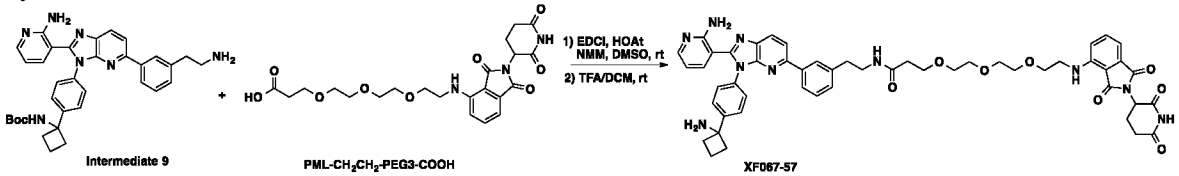
Example 132
Synthesis of XF067-56



XF067-56 was synthesized following the standard procedure for preparing XF067-31 from intermediate 9 (9.3 mg, 0.016 mmol), PML-CH_2CH_2-PEG2-CO_2H (6.9 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-56 was obtained as yellow solid in TFA salt form (8.7 mg, 61%). ^{1}H NMR (800 MHz, CD_3OD) δ 8.28 (d, J = 8.4 Hz, 1H), 8.02 (dd, J = 10.4, 6.3 Hz, 2H), 7.93 (s, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.78 (dd, J = 26.3, 7.8 Hz, 3H), 7.70 (d, J = 8.0 Hz, 2H), 7.43 (t, J = 7.8 Hz, 1H), 7.36 (t, J = 7.7 Hz, 1H), 7.27 (d, J = 7.5 Hz, 1H), 6.98 – 6.92 (m, 2H), 6.79 (t, J = 6.8 Hz, 1H), 4.99 (dq, J = 11.7, 6.6, 5.3 Hz, 1H), 3.69 (t, J = 5.9 Hz, 2H), 3.63 (t, J = 5.2 Hz, 2H), 3.56 (s, 4H), 3.47 (t, J = 7.4 Hz, 2H), 3.39 (t, J = 5.2 Hz, 2H), 2.89 (dt, J = 30.3, 6.5 Hz, 4H), 2.80 (ddd, J = 18.3, 13.7, 5.2 Hz, 1H), 2.67 (dddt, J = 53.5, 17.7, 13.2, 6.6 Hz, 4H), 2.42 (t, J = 5.9 Hz, 2H), 2.36 – 2.30 (m, 1H), 2.09 – 2.01 (m, 2H). ESI-MS (m/z) $[M + H]^+$: 891.3945.

Example 133

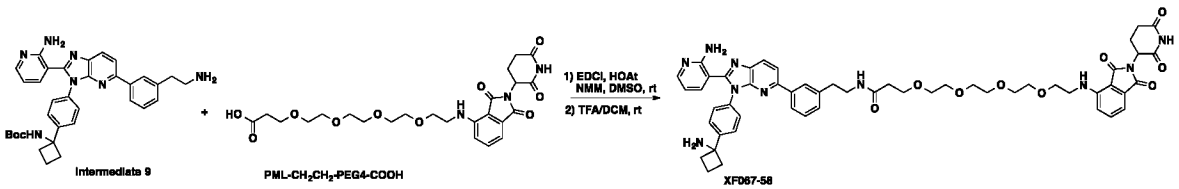
Synthesis of XF067-57



XF067-57 was synthesized following the standard procedure for preparing XF067-31 from intermediate 9 (9.3 mg, 0.016 mmol), PML-CH_2CH_2-PEG3-CO_2H (7.6 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-57 was obtained as yellow solid in TFA salt form (7.9 mg, 53%). ^{1}H NMR (800 MHz, CD_3OD) δ 8.29 (d, J = 8.4 Hz, 1H), 8.03 (d, J = 8.3 Hz, 2H), 7.96 (s, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.79 (dd, J = 15.4, 7.7 Hz, 3H), 7.71 (d, J = 8.0 Hz, 2H), 7.46 (t, J = 7.8 Hz, 1H), 7.37 (t, J = 7.7 Hz, 1H), 7.29 (d, J = 7.5 Hz, 1H), 6.98 (t, J = 7.4 Hz, 2H), 6.80 (s, 1H), 5.01 (dd, J = 12.9, 5.3 Hz, 1H), 3.67 (t, J = 6.0 Hz, 2H), 3.65 (t, J = 5.2 Hz, 2H), 3.62 (s, 4H), 3.58 (t, J = 4.5 Hz, 2H), 3.56 – 3.52 (m, 2H), 3.48 (t, J = 7.5 Hz, 2H), 3.40 (t, J = 5.2 Hz, 2H), 2.95 – 2.85 (m, 4H), 2.82 (ddd, J = 18.2, 13.7, 5.3 Hz, 1H), 2.75 – 2.60 (m, 4H), 2.41 (t, J = 5.9 Hz, 2H), 2.36 – 2.30 (m, 1H), 2.11 – 2.02 (m, 2H). ESI-MS (m/z) $[M + H]^+$: 935.4178.

Example 134

Synthesis of XF067-58

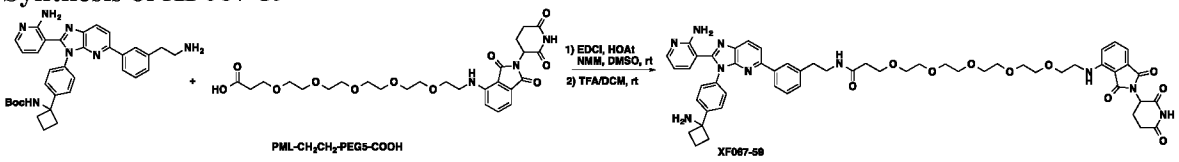


XF067-58 was synthesized following the standard procedure for preparing XF067-31 from intermediate 9 (9.3 mg, 0.016 mmol), PML-CH_2CH_2-PEG4-CO_2H (8.3 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-58 was obtained as yellow solid in TFA salt form (8 mg, 51%). ^{1}H NMR (800 MHz, CD_3OD) δ 8.28 (d, J = 8.4 Hz, 1H), 8.04 (q, J = 6.4, 4.3 Hz, 3H), 7.87 (dd, J = 23.8, 7.7 Hz, 2H), 7.83 (d, J = 8.0 Hz, 2H), 7.73 (d, J = 8.0 Hz, 2H), 7.44 – 7.34 (m, 2H), 7.28 (d, J = 7.5 Hz, 1H), 7.00 – 6.94 (m, 1H), 6.83 (dd, J = 19.1, 7.7 Hz, 2H), 5.01 (dd, J = 12.9, 5.4 Hz, 1H), 3.72 – 3.69 (m, 2H), 3.67 – 3.60 (m, 6H), 3.62 – 3.56 (m, 6H), 3.58 – 3.53 (m, 2H), 3.49 (t, J = 7.7 Hz, 2H), 3.28 (dq, J = 8.6, 5.1, 4.5 Hz, 2H), 2.92 (dt, J = 16.0, 7.7 Hz, 2H), 2.89 – 2.79 (m, 3H), 2.79 – 2.63 (m, 4H), 2.45 (t,

J = 5.8 Hz, 2H), 2.35 (qd, J = 10.1, 5.0 Hz, 1H), 2.07 (d, J = 14.0 Hz, 2H). ESI-MS (m/z) [M + H]$^+$: 979.4459.

Example 135

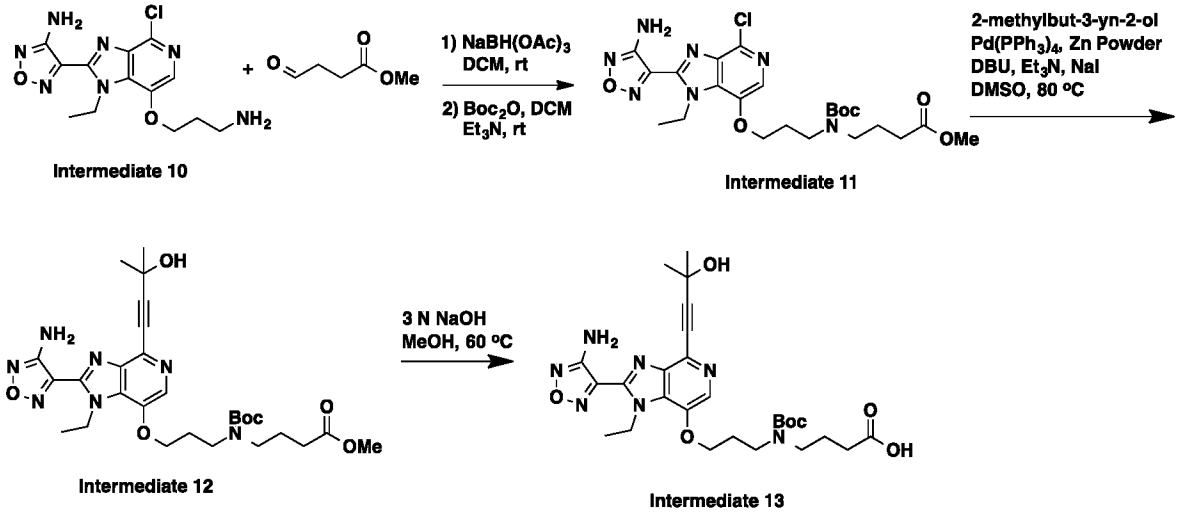
Synthesis of XF067-59



XF067-59 was synthesized following the standard procedure for preparing XF067-31 from intermediate 9 (9.3 mg, 0.016 mmol), PML-CH_2CH_2-PEG5-CO_2H (9 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-59 was obtained as yellow solid in TFA salt form (7.8 mg, 48%). ^{1}H NMR (800 MHz, CD_3OD) δ 8.30 (d, J = 8.3 Hz, 1H), 8.09 – 7.98 (m, 3H), 7.90 (d, J = 7.8 Hz, 1H), 7.84 (dd, J = 14.9, 7.9 Hz, 3H), 7.72 (d, J = 8.1 Hz, 2H), 7.50 (t, J = 7.8 Hz, 1H), 7.41 – 7.35 (m, 1H), 7.30 (d, J = 7.5 Hz, 1H), 7.02 (s, 1H), 6.98 (d, J = 8.5 Hz, 1H), 6.84 (s, 1H), 5.02 (dd, J = 12.8, 5.2 Hz, 1H), 3.70 (q, J = 5.6 Hz, 2H), 3.62 – 3.55 (m, 14H), 3.55 – 3.46 (m, 6H), 3.38 – 3.34 (m, 2H), 2.97 – 2.86 (m, 4H), 2.83 (ddd, J = 18.2, 13.8, 5.6 Hz, 1H), 2.78 – 2.72 (m, 2H), 2.71 (s, 1H), 2.70 – 2.63 (m, 1H), 2.44 (t, J = 5.8 Hz, 2H), 2.37 – 2.32 (m, 1H), 2.12 – 2.03 (m, 2H). ESI-MS (m/z) [M + H]$^+$: 1023.4716.

Example 136

Synthesis of Intermediate 13

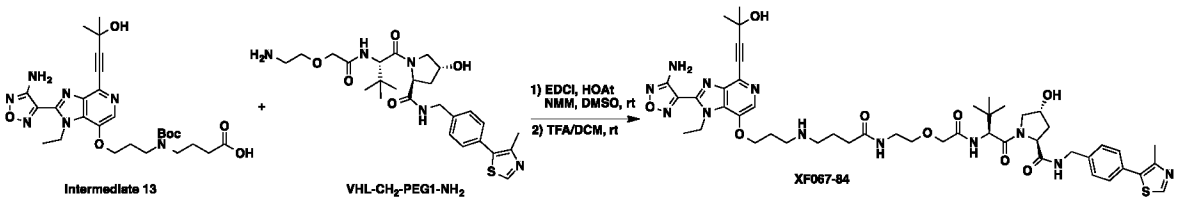


The intermediate 10 was synthesized following a known procedure (Heerding et al., 2008). To the suspension of intermediate 10 (119 mg x 3, 0.5 mmol) and methyl-4-oxobutanonate (58 mg x 3, 0.5 mmol) in 5 mL of DCM was added sodium triacetoxyborohydride (211 mg x 3, 1.0

mmol) in three times. Once the reaction mixture became clear solution, saturated $NaHCO_3$ solution was added to quench the reaction. After the organic phase was separated, the aqueous phase was extracted with DCM (10 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The resulting residue was dissolved in DCM (15 mL). To the resulting solution were added di-*tert*-butyl decarbonate (272 mg, 1.25 mmol) and triethylamine (188 mg, 1.86 mmol). The reaction was stirred for 30 min, before the reaction mixture was concentrated. The resulting residue was purified by silica gel column (Hexane / EA = 1 : 3) to afford intermediate 11 as yellow solid (178 mg, 53 %). ESI m/z 548.8 $[M + H]^+$. Intermediate 11 (178 mg, 0.34 mmol) was dissolved in DMSO (5 mL) in a pressure vessel. To the resulting solution were added 2-methylbut-3-yn-2-ol (371 μL, 4.1 mmol), zinc powder (68 mg, 1.02 mmol), NaI (16 mg, 0.11 mmol), DBU (153 μL,1.02 mmol), and triethylamine (207 μL, 1.02 mmol). The reaction was degassed for 5 min, before the catalyst $Pd(PPh_3)_4$ (40 mg, 10 mol %) was added. The reaction vessel was purged with nitrogen, sealed and heated to 80 °C for 1 h. The reaction was quenched by pouring into saturated NH_4Cl. The aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the intermediate 12, which was used in the next step without further purification. The intermediate 12 (146 mg, 0.25 mmol) was dissolved in methanol (5 mL). To the resulting solution was added NaOH (0.5 mL, 3 N). The reaction was heated to 60 °C for 1 h, before the reaction mixture was concentrated. The resulting residue was purified by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O) to afford Intermediate 13 as white solid in TFA salt form (128.3 mg, 90%). ^1H NMR (500 MHz, DMSO-d_6) δ 8.15 (s, 1H), 7.03 (s, 2H), 4.93 – 4.74 (m, 2H), 4.40 – 4.26 (m, 2H), 3.39 (t, J = 7.1 Hz, 2H), 3.22 (t, J = 7.2 Hz, 2H), 2.21 (t, J = 7.2 Hz, 2H), 2.13 – 2.02 (m, 2H), 1.82 – 1.69 (m, 2H), 1.47 (t, J = 7.0 Hz, 3H), 1.41 – 1.30 (m, 15H). ESI-MS (m/z) $[M + H]^+$: 572.3213

Example 137

Synthesis of XF067-84

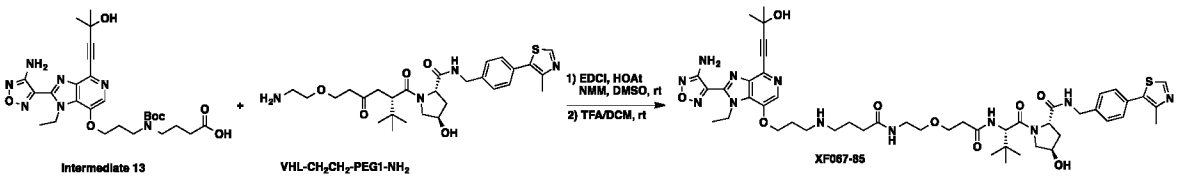


To a solution of Intermediate 13 (9.1 mg, 0.016 mmol) in DMSO (1 mL) were added VHL-CH_2-PEG1-NH_2 (9.1 mg, 0.016 mmol, 1.0 equiv), EDCI (1-ethyl-3-(3-

dimethylaminopropyl)carbodiimide) (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (1-hydroxy-7-azabenzo-triazole) (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (N-Methylmorpholine) (4.8 mg, 0.048mmol, 3.0 equiv). After being stirred overnight at room temperature, the resulting mixture was purified by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O) to afford the corresponding product. After this product was dissolved in DCM (1mL), the reaction mixture was treated with TFA (1 mL) for 30 min. After the solvent was evaporated, the residue was purified by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O) to afford XF067-84 as white solid in TFA salt form (6.1 mg, 39%). ^{1}H NMR (500 MHz, CD_3OD) δ 8.97 (d, J = 5.7 Hz, 1H), 8.23 (s, 1H), 7.51 – 7.34 (m, 4H), 5.05 (q, J = 7.0 Hz, 2H), 4.74 – 4.65 (m, 1H), 4.64 – 4.28 (m, 6H), 4.13 – 3.93 (m, 2H), 3.93 – 3.77 (m, 2H), 3.68 – 3.49 (m, 2H), 3.43 – 3.35 (m, 4H), 3.24 – 3.07 (m, 2H), 2.58 – 2.33 (m, 7H), 2.27 (dd, J = 13.2, 7.6 Hz, 1H), 2.10 (ddd, J = 13.5, 9.4, 4.4 Hz, 1H), 2.00 (h, J = 7.2 Hz, 2H), 1.69 (s, 6H), 1.58 (t, J = 7.0 Hz, 3H), 1.05 (s, 9H). ESI-MS (m/z) $[M + H]^+$: 985.4728.

Example 138

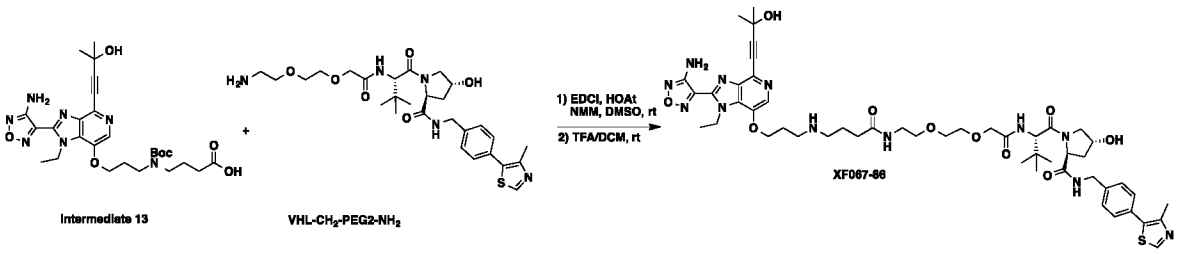
Synthesis of XF067-85



XF067-85 was synthesized following the standard procedure for preparing XF067-84 from intermediate 13 (9.1 mg, 0.016 mmol), VHL-CH_2CH_2-PEG1-NH_2 (12.4 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-85 was obtained as white solid in TFA salt form (11.8 mg, 74%). ^{1}H NMR (500 MHz, CD_3OD) δ 8.97 (s, 1H), 8.24 (s, 1H), 7.55 – 7.32 (m, 4H), 5.05 (q, J = 7.1 Hz, 2H), 4.71 – 4.63 (m, 1H), 4.64 – 4.48 (m, 5H), 4.41 (d, J = 15.4 Hz, 1H), 3.96 – 3.80 (m, 2H), 3.71 (tt, J = 10.5, 4.8 Hz, 2H), 3.50 (t, J = 5.4 Hz, 2H), 3.38 – 3.33 (m, 4H), 3.16 (t, J = 7.0 Hz, 2H), 2.56 – 2.36 (m, 9H), 2.26 (ddt, J = 13.2, 7.7, 1.9 Hz, 1H), 2.10 (ddd, J = 13.3, 9.2, 4.4 Hz, 1H), 1.98 (p, J = 6.8 Hz, 2H), 1.69 (s, 6H), 1.58 (t, J = 7.1 Hz, 3H), 1.05 (s, 9H). ESI-MS (m/z) $[M + H]^+$: 999.4875.

Example 139

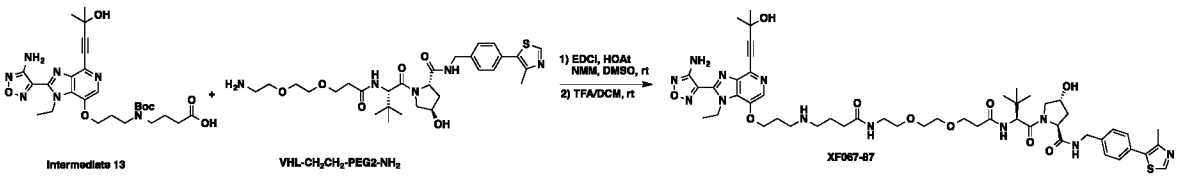
Synthesis of XF067-86



XF067-86 was synthesized following the standard procedure for preparing XF067-84 from intermediate 13 (9.1 mg, 0.016 mmol), VHL-CH_2-PEG2-NH_2 (9.8 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-86 was obtained as white solid in TFA salt form (10.6 mg, 64%). ^{1}H NMR (500 MHz, CD_3OD) δ 9.01 (d, J = 2.9 Hz, 1H), 8.26 (d, J = 3.0 Hz, 1H), 7.53 – 7.44 (m, 4H), 5.06 (q, J = 7.0 Hz, 2H), 4.95 – 4.71 (m, 1H), 4.64 – 4.31 (m, 6H), 4.03-4.01 (m, 2H), 3.94 – 3.78 (m, 2H), 3.80 – 3.58 (m, 4H), 3.56 – 3.48 (m, 2H), 3.46 – 3.26 (m, 4H), 3.22 – 3.08 (m, 2H), 2.59 – 2.35 (m, 7H), 2.36 – 2.23 (m, 1H), 2.19 – 2.06 (m, 1H), 2.03 – 1.93 (m, 2H), 1.70 (s, 6H), 1.59 (t, J = 7.0 Hz, 3H), 1.06 (s, 9H). ESI-MS (m/z) $[M + H]^+$: 1029.4983.

Example 140

Synthesis of XF067-87

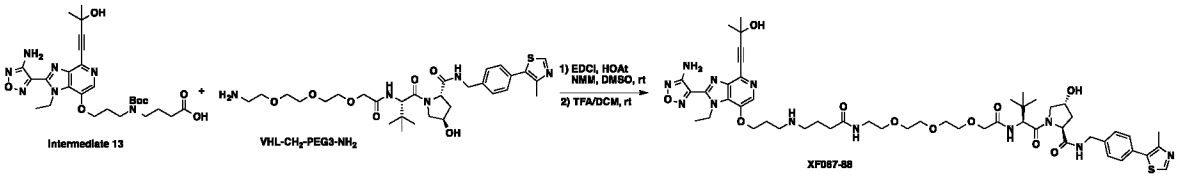


XF067-87 was synthesized following the standard procedure for preparing XF067-84 from intermediate 13 (9.1 mg, 0.016 mmol), VHL-CH_2CH_2-PEG2-NH_2 (13.1 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-87 was obtained as white solid in TFA salt form (6.4 mg, 38%). ^{1}H NMR (500 MHz, CD_3OD) δ 9.01 (s, 1H), 8.26 (s, 1H), 7.54 – 7.36 (m, 4H), 5.07 (q, J = 7.1 Hz, 2H), 4.67 (d, J = 6.2 Hz, 1H), 4.64 – 4.47 (m, 5H), 4.39 (d, J = 15.4 Hz, 1H), 3.91 (d, J = 11.0 Hz, 1H), 3.82 (dd, J = 11.0, 3.9 Hz, 1H), 3.80 – 3.69 (m, 2H), 3.66 – 3.56 (m, 4H), 3.50 (t, J = 5.4 Hz, 2H), 3.36 – 3.31 (m, 4H), 3.17 (t, J = 7.0 Hz, 2H), 2.59 (ddd, J = 15.0, 7.3, 5.2 Hz, 1H), 2.55 – 2.34 (m, 8H), 2.24 (ddt, J = 13.3, 7.6,

2.0 Hz, 1H), 2.10 (ddd, J = 13.3, 9.1, 4.5 Hz, 1H), 1.99 (p, J = 6.9 Hz, 2H), 1.70 (s, 6H), 1.59 (t, J = 7.1 Hz, 3H), 1.05 (s, 9H). ESI-MS (m/z) $[M + H]^+$: 1043.5145.

Example 141

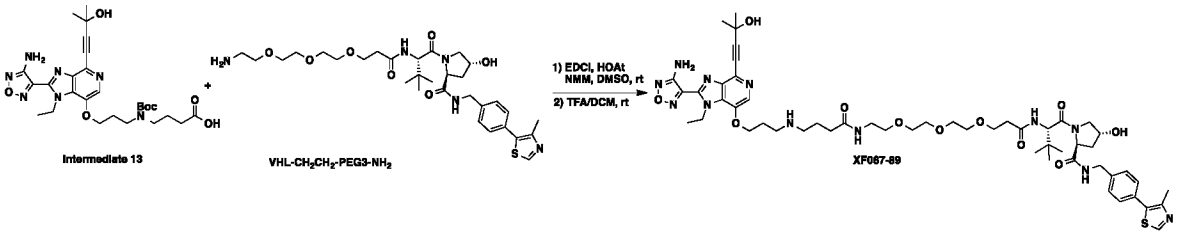
Synthesis of XF067-88



XF067-88 was synthesized following the standard procedure for preparing XF067-84 from intermediate 13 (9.1 mg, 0.016 mmol), VHL-CH_2-PEG3-NH_2 (13.5 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-88 was obtained as white solid in TFA salt form (8.1 mg, 47%). ^{1}H NMR (500 MHz, CD_3OD) δ 9.00 (s, 1H), 8.25 (s, 1H), 7.49 – 7.41 (m, 4H), 5.06 (q, J = 6.9 Hz, 2H), 4.75 – 4.64 (m, 1H), 4.64 – 4.45 (m, 5H), 4.48 – 4.30 (m, 1H), 4.15 – 3.97 (m, 2H), 3.93 – 3.78 (m, 2H), 3.78 – 3.57 (m, 8H), 3.49 (t, J = 5.4 Hz, 2H), 3.34 – 3.24 (m, 4H), 3.17 (d, J = 7.1, 2.4 Hz, 2H), 2.54 – 2.33 (m, 7H), 2.33 – 2.21 (m, 1H), 2.17 – 2.05 (m, 1H), 2.04 – 1.92 (m, 2H), 1.75 – 1.63 (m, 6H), 1.59 (t, J = 7.1 Hz, 3H), 1.06 (s, 9H). ESI-MS (m/z) $[M + H]^+$: 1073.5231.

Example 142

Synthesis of XF067-89

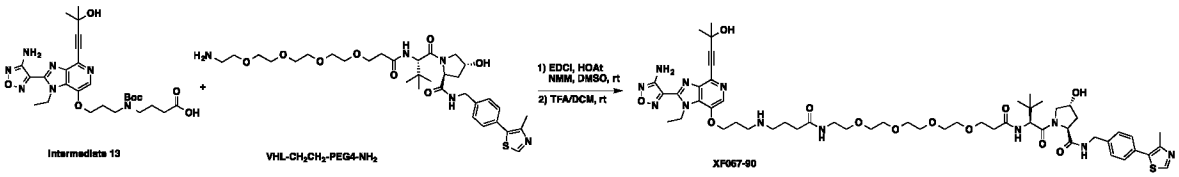


XF067-89 was synthesized following the standard procedure for preparing XF067-84 from intermediate 13 (9.1 mg, 0.016 mmol), VHL-CH_2CH_2-PEG3-NH_2 (13.8 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-89 was obtained as white solid in TFA salt form (10.7 mg, 61%). ^{1}H NMR (500 MHz, CD_3OD) δ 9.02 (s, 1H), 8.27 (s, 1H), 7.59 – 7.33 (m, 4H), 5.07 (q, J = 7.2 Hz, 2H), 4.73 – 4.62 (m, 1H), 4.62 – 4.47 (m, 5H), 4.39 (dd, J = 15.6, 2.6 Hz, 1H), 3.94 – 3.87 (m, 1H), 3.87 – 3.66 (m, 3H), 3.70 – 3.54 (m, 8H),

3.50 (t, J = 5.4 Hz, 2H), 3.37 – 3.30 (m, 4H), 3.17 (t, J = 7.0 Hz, 2H), 2.60 (ddd, J = 15.0, 7.5, 5.2 Hz, 1H), 2.52 – 2.30 (m, 8H), 2.24 (ddt, J = 13.3, 7.7, 2.1 Hz, 1H), 2.10 (ddd, J = 13.3, 9.2, 4.4 Hz, 1H), 2.00 (p, J = 6.8 Hz, 2H), 1.70 (s, 6H), 1.60 (t, J = 7.1 Hz, 3H), 1.06 (s, 9H). ESI-MS $[M + H]^+$: 1087.5383.

Example 143

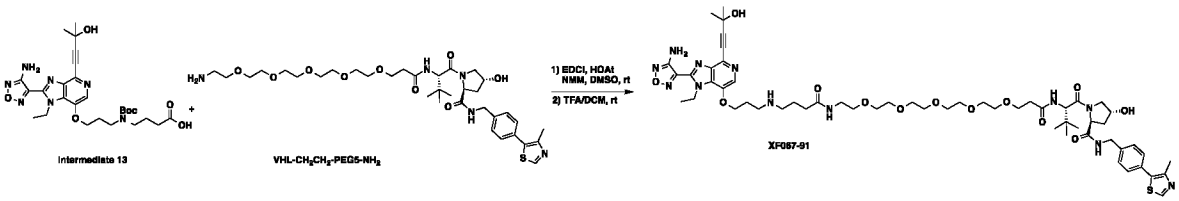
Synthesis of XF067-90



XF067-90 was synthesized following the standard procedure for preparing XF067-84 from intermediate 13 (9.1 mg, 0.016 mmol), VHL-CH_2CH_2-PEG4-NH_2 (11.4 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-90 was obtained as white solid in TFA salt form (12.6 mg, 70%). ^{1}H NMR (500 MHz, CD_3OD) δ 9.02 (s, 1H), 8.27 (s, 1H), 7.56 – 7.33 (m, 4H), 5.07 (q, J = 7.1 Hz, 2H), 4.65 (s, 1H), 4.62 – 4.46 (m, 5H), 4.38 (d, J = 15.5 Hz, 1H), 3.90 (d, J = 11.0 Hz, 1H), 3.82 (dd, J = 11.0, 3.9 Hz, 1H), 3.74 (dq, J = 9.7, 4.8, 4.2 Hz, 2H), 3.67 – 3.55 (m, 12H), 3.51 (t, J = 5.4 Hz, 2H), 3.40 – 3.32 (m, 4H), 3.17 (t, J = 7.1 Hz, 2H), 2.60 (ddd, J = 15.0, 7.3, 5.3 Hz, 1H), 2.55 – 2.29 (m, 8H), 2.24 (ddt, J = 13.2, 7.7, 2.0 Hz, 1H), 2.10 (ddd, J = 13.3, 9.1, 4.5 Hz, 1H), 2.00 (td, J = 13.7, 12.3, 5.5 Hz, 2H), 1.70 (s, 6H), 1.60 (t, J = 7.1 Hz, 3H), 1.05 (s, 9H). ESI-MS (m/z) for $[M + H]^+$: 1131.5653.

Example 144

Synthesis of XF067-91

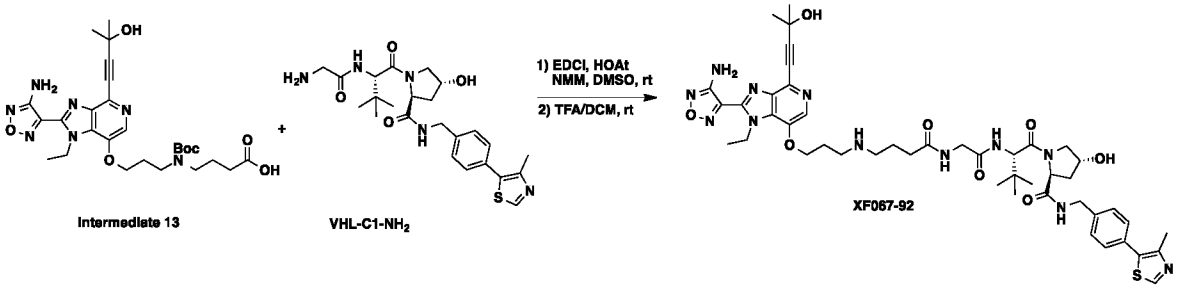


XF067-91 was synthesized following the standard procedure for preparing XF067-84 from intermediate 13 (9.1 mg, 0.016 mmol), VHL-CH_2CH_2-PEG5-NH_2 (15.2 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-91 was obtained as white

solid in TFA salt form (9.4 mg, 50%). ^{1}H NMR (500 MHz, CD_3OD) δ 8.99 (s, 1H), 8.25 (s, 1H), 7.53 – 7.36 (m, 4H), 5.07 (q, J = 7.1 Hz, 2H), 4.66 (s, 1H), 4.61 – 4.47 (m, 5H), 4.38 (d, J = 15.5 Hz, 1H), 3.90 (d, J = 11.1 Hz, 1H), 3.86 – 3.70 (m, 3H), 3.66 – 3.56 (m, 16H), 3.50 (t, J = 5.4 Hz, 2H), 3.36 – 3.28 (m, 4H), 3.18 (t, J = 7.0 Hz, 2H), 2.60 (ddd, J = 14.8, 7.4, 5.1 Hz, 1H), 2.52 – 2.32 (m, 8H), 2.24 (ddt, J = 11.7, 7.7, 1.9 Hz, 1H), 2.15 – 2.02 (m, 1H), 1.99 (q, J = 6.8 Hz, 2H), 1.69 (s, 6H), 1.59 (t, J = 7.1 Hz, 3H), 1.06 (s, 9H). ESI-MS (m/z) for $[M + H]^+$: 1175.5911.

Example 145

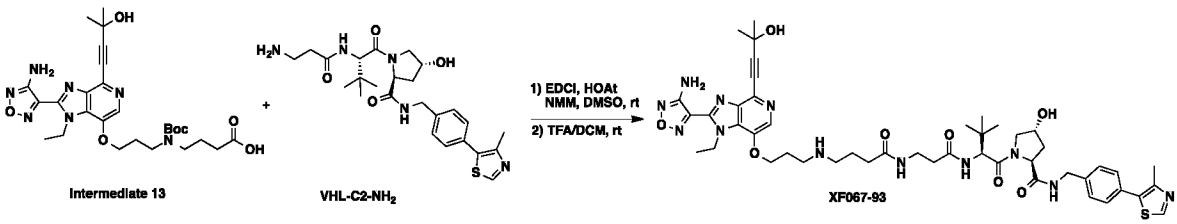
Synthesis of XF067-92



XF067-92 was synthesized following the standard procedure for preparing XF067-84 from intermediate 13 (9.1 mg, 0.016 mmol), VHL-C1-NH_2 (11.4 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-92 was obtained as white solid in TFA salt form (9.3 mg, 62%). ^{1}H NMR (500 MHz, CD_3OD) δ 9.01 (d, J = 6.5 Hz, 1H), 8.25 (d, J = 6.2 Hz, 1H), 7.56 – 7.39 (m, 4H), 5.06 (dd, J = 12.7, 5.7 Hz, 2H), 4.83 – 4.31 (m, 7H), 4.08 – 3.78 (m, 4H), 3.46 – 3.35 (m, 2H), 3.21 (q, J = 7.2, 5.9 Hz, 2H), 2.80 – 2.29 (m, 7H), 2.33 – 2.18 (m, 1H), 2.18 – 1.90 (m, 3H), 1.70 (s, 6H), 1.64 – 1.51 (m, 3H), 1.06 (d, J = 10.6 Hz, 9H). ESI-MS (m/z) for $[M + H]^+$: 941.4458.

Example 146

Synthesis of XF067-93

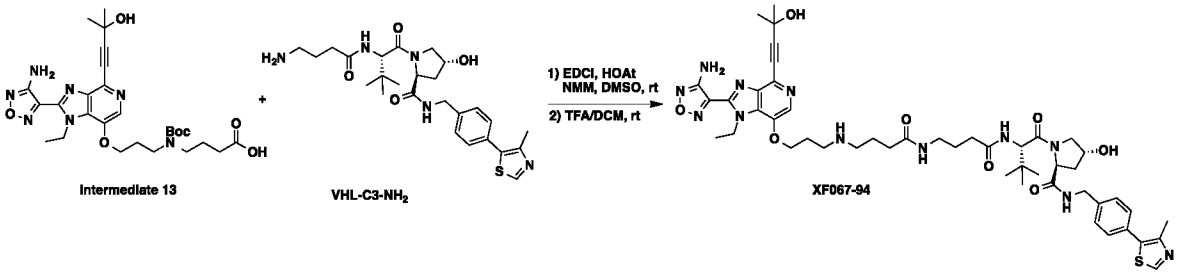


XF067-93 was synthesized following the standard procedure for preparing XF067-84 from intermediate 13 (9.1 mg, 0.016 mmol), VHL-C2-NH_2 (11.7 mg, 0.016 mmol, 1.0 equiv), EDCI

(4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-93 was obtained as white solid in TFA salt form (12.9 mg, 84%). ^{1}H NMR (500 MHz, CD_3OD) δ 9.02 (s, 1H), 8.26 (s, 1H), 7.51 – 7.28 (m, 4H), 5.07 (q, J = 7.0 Hz, 2H), 4.62 (s, 1H), 4.59 – 4.47 (m, 5H), 4.40 (d, J = 15.5 Hz, 1H), 3.95 (d, J = 11.0 Hz, 1H), 3.82 (dd, J = 11.0, 3.9 Hz, 1H), 3.47 – 3.33 (m, 4H), 3.17 (t, J = 7.2 Hz, 2H), 2.57 – 2.33 (m, 9H), 2.26 (dd, J = 13.3, 7.6 Hz, 1H), 2.11 (ddd, J = 13.4, 9.3, 4.3 Hz, 1H), 1.99 (p, J = 6.8 Hz, 2H), 1.70 (s, 6H), 1.60 (t, J = 7.1 Hz, 3H), 1.05 (s, 9H). ESI-MS (m/z) $[M + H]^+$: 955.4613.

Example 147

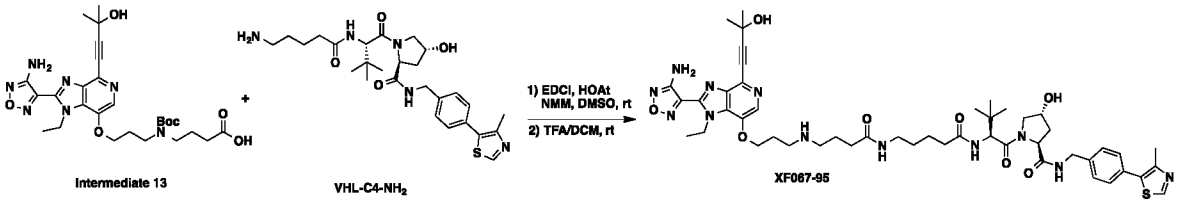
Synthesis of XF067-94



XF067-94 was synthesized following the standard procedure for preparing XF067-84 from intermediate 13 (9.1 mg, 0.016 mmol), VHL-C3-NH_2 (11.9 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-94 was obtained as white solid in TFA salt form (9.3 mg, 60%). ^{1}H NMR (500 MHz, CD_3OD) δ 9.02 (s, 1H), 8.27 (s, 1H), 7.58 – 7.34 (m, 4H), 5.07 (q, J = 7.3, 6.3 Hz, 2H), 4.75 – 4.48 (m, 6H), 4.40 (dd, J = 15.5, 4.9 Hz, 1H), 3.96 – 3.77 (m, 2H), 3.40 – 3.32 (m, 4H), 3.18 (q, J = 7.2, 6.4 Hz, 2H), 2.63 – 2.19 (m, 10H), 2.11 (ddd, J = 13.3, 9.2, 4.6 Hz, 1H), 2.00 (p, J = 6.6 Hz, 2H), 1.85 – 1.64 (m, 8H), 1.60 (t, J = 7.0 Hz, 3H), 1.06 (d, J = 4.6 Hz, 9H). ESI-MS (m/z) for $[M + H]^+$: 969.4754.

Example 148

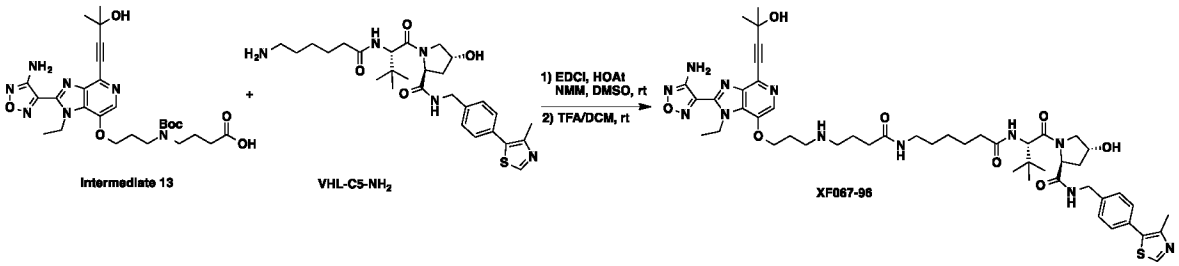
Synthesis of XF067-95



XF067-95 was synthesized following the standard procedure for preparing XF067-84 from intermediate 13 (9.1 mg, 0.016 mmol), VHL-C4-NH_2 (9.1 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-95 was obtained as white solid in TFA salt form (6.7 mg, 43%). ^{1}H NMR (500 MHz, CD_3OD) δ 8.98 (s, 1H), 8.24 (s, 1H), 7.52 – 7.37 (m, 4H), 5.06 (q, J = 7.1 Hz, 2H), 4.63 (s, 1H), 4.55 (ddt, J = 17.1, 10.3, 6.2 Hz, 5H), 4.39 (d, J = 15.4 Hz, 1H), 3.91 (d, J = 11.0 Hz, 1H), 3.82 (dd, J = 11.0, 4.0 Hz, 1H), 3.41 – 3.26 (m, 2H), 3.22 – 3.04 (m, 4H), 2.51 – 2.35 (m, 7H), 2.35 – 2.18 (m, 3H), 2.17 – 2.05 (m, 1H), 1.99 (p, J = 6.9 Hz, 2H), 1.69 (s, 6H), 1.65 – 1.40 (m, 7H), 1.04 (s, 9H). ESI-MS (m/z) $[M + H]^+$: 983.4927.

Example 149

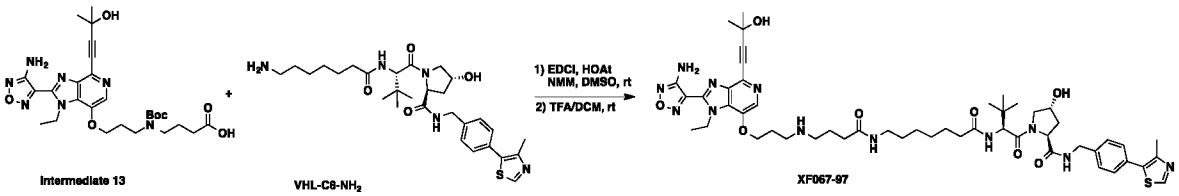
Synthesis of XF067-96



XF067-96 was synthesized following the standard procedure for preparing XF067-84 from intermediate 13 (9.1 mg, 0.016 mmol), VHL-C5-NH_2 (9.3 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-96 was obtained as white solid in TFA salt form (6.7 mg, 42%). ^{1}H NMR (500 MHz, CD_3OD) δ 8.97 (s, 1H), 8.23 (s, 1H), 7.54 – 7.35 (m, 4H), 5.06 (q, J = 7.0 Hz, 2H), 4.64 (s, 1H), 4.61 – 4.47 (m, 5H), 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), 3.39 – 3.32 (m, 2H), 3.17 (t, J = 7.0 Hz, 2H), 3.08 (t, J = 7.1 Hz, 2H), 2.50 (s, 3H), 2.48 – 2.35 (m, 4H), 2.34 – 2.20 (m, 3H), 2.11 (ddd, J = 13.3, 9.1, 4.5 Hz, 1H), 1.99 (p, J = 6.9 Hz, 2H), 1.69 (s, 6H), 1.65 – 1.54 (m, 5H), 1.48 (p, J = 7.3 Hz, 2H), 1.39 – 1.25 (m, 2H), 1.05 (s, 9H). ESI-MS (m/z) for $[M + H]^+$: 997.5079.

Example 150

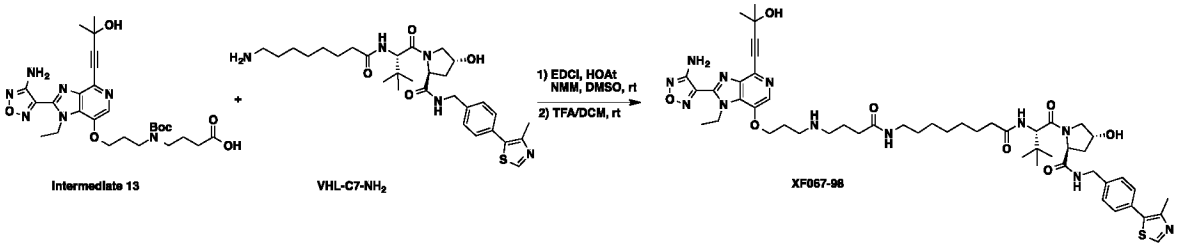
Synthesis of XF067-97



XF067-97 was synthesized following the standard procedure for preparing XF067-84 from intermediate 13 (9.1 mg, 0.016 mmol), VHL-C6-NH_2 (9.5 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-97 was obtained as white solid in TFA salt form (13.9 mg, 86%). ^{1}H NMR (500 MHz, CD_3OD) δ 9.11 – 8.85 (m, 1H), 8.25 (s, 1H), 7.58 – 7.32 (m, 4H), 5.07 (tt, J = 9.3, 4.8 Hz, 2H), 4.72 – 4.48 (m, 6H), 4.39 (dd, J = 15.4, 3.3 Hz, 1H), 3.92 (d, J = 10.7 Hz, 1H), 3.83 (d, J = 10.9, 3.6 Hz, 1H), 3.33 – 3.27 (m, 2H), 3.22 – 3.14 (m, 2H), 3.11 – 2.95 (m, 2H), 2.57 – 2.17 (m, 10H), 2.11 (ddt, J = 13.2, 8.9, 3.9 Hz, 1H), 2.00 (dtt, J = 12.8, 8.9, 4.6 Hz, 2H), 1.73 – 1.51 (m, 9H), 1.51 – 1.41 (m, 2H), 1.41 – 1.23 (m, 6H), 1.05 (s, 9H). ESI-MS (m/z) for $[M + H]^+$: 1011.5239.

Example 151

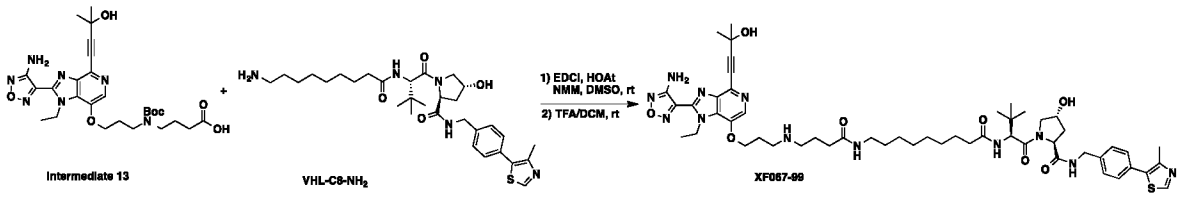
Synthesis of XF067-98



XF067-98 was synthesized following the standard procedure for preparing XF067-84 from intermediate 13 (9.1 mg, 0.016 mmol), VHL-C7-NH_2 (12.8 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-98 was obtained as white solid in TFA salt form (8.6 mg, 52%). ^{1}H NMR (500 MHz, CD_3OD) δ 8.97 (s, 1H), 8.22 (s, 1H), 7.57 – 7.19 (m, 4H), 5.14 – 4.97 (m, 2H), 4.67 – 4.43 (m, 6H), 4.38 (dd, J = 15.5, 2.6 Hz, 1H), 3.92 (d, J = 11.0 Hz, 1H), 3.82 (dd, J = 11.0, 3.9 Hz, 1H), 3.32 (d, J = 2.2 Hz, 2H), 3.17 (td, J = 7.0, 2.6 Hz, 2H), 3.06 (td, J = 7.1, 2.6 Hz, 2H), 2.54 – 2.35 (m, 8H), 2.34 – 2.18 (m, 2H), 2.13 – 2.06 (m, 1H), 2.04 – 1.93 (m, 2H), 1.77 – 1.52 (m, 9H), 1.44 (p, J = 7.2 Hz, 2H), 1.39 – 1.12 (m, 8H), 1.05 (s, 9H). ESI-MS (m/z) $[M + H]^+$: 1025.5387.

Example 152

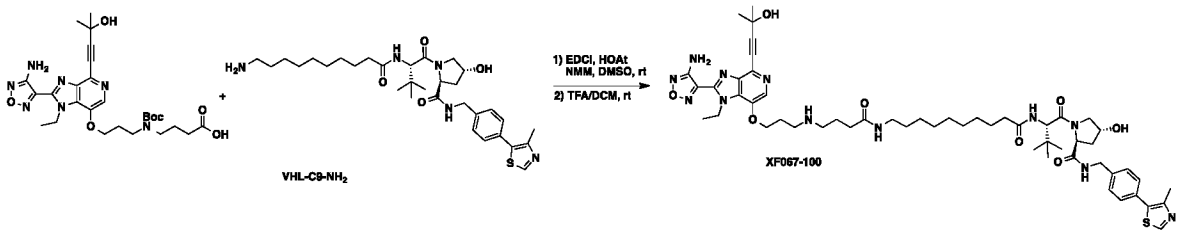
Synthesis of XF067-99



XF067-99 was synthesized following the standard procedure for preparing XF067-84 from intermediate 13 (9.1 mg, 0.016 mmol), VHL-C8-NH_2 (10 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-99 was obtained as white solid in TFA salt form (7 mg, 42%). ^{1}H NMR (500 MHz, CD_3OD) δ 8.95 (s, 1H), 8.21 (s, 1H), 7.54 – 7.31 (m, 4H), 5.06 (q, J = 7.1 Hz, 2H), 4.65 (s, 1H), 4.62 – 4.48 (m, 5H), 4.38 (d, J = 15.5 Hz, 1H), 3.92 (d, J = 11.0 Hz, 1H), 3.83 (dd, J = 11.0, 3.9 Hz, 1H), 3.37 – 3.29 (m, J = 2.8 Hz, 2H), 3.17 (t, J = 6.9 Hz, 2H), 3.05 (t, J = 7.1 Hz, 2H), 2.52 – 2.37 (m, 7H), 2.34 – 2.19 (m, 3H), 2.15 – 2.04 (m, 1H), 1.98 (p, J = 6.7 Hz, 2H), 1.69 (s, 6H), 1.65 – 1.54 (m, 3H), 1.43 (p, J = 7.1 Hz, 2H), 1.30 (d, J = 13.7 Hz, 10H), 1.05 (s, 9H). ESI-MS (m/z) $[M + H]^+$: 1039.5534.

Example 153

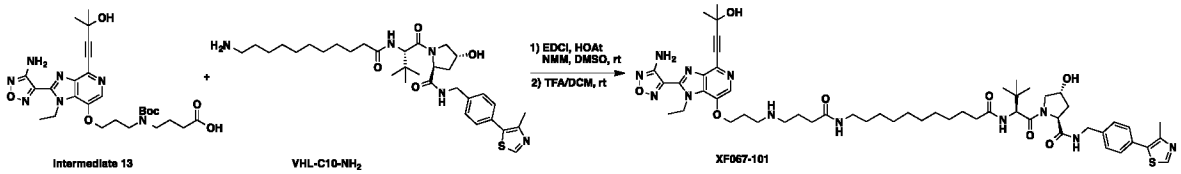
Synthesis of XF067-100



XF067-100 was synthesized following the standard procedure for preparing XF067-84 from intermediate 13 (9.1 mg, 0.016 mmol), VHL-C9-NH_2 (13.2 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-100 was obtained as white solid in TFA salt form (3.9 mg, 23%). ^{1}H NMR (500 MHz, CD_3OD) δ 8.92 (d, J = 4.5 Hz, 1H), 8.17 (d, J = 5.8 Hz, 1H), 7.62 – 7.29 (m, 4H), 5.15 – 5.00 (m, 2H), 4.65 (d, J = 2.5 Hz, 1H), 4.63 – 4.46 (m, 5H), 4.42 – 4.29 (m, 1H), 3.92 (d, J = 11.0 Hz, 1H), 3.83 (dd, J = 11.0, 3.9 Hz, 1H), 3.35 – 3.29 (m, 2H), 3.17 (dd, J = 7.8, 5.9 Hz, 2H), 3.05 (td, J = 7.3, 3.5 Hz, 2H), 2.58 – 2.18 (m, 10H), 2.11 (ddd, J = 13.2, 9.0, 4.5 Hz, 1H), 2.04 – 1.89 (m, 2H), 1.76 – 1.50 (m, 9H), 1.42 (t, J = 7.0 Hz, 2H), 1.38 – 1.12 (m, 12H), 1.05 (s, 9H). ESI-MS (m/z) $[M + H]^+$: 1053.5711.

Example 154

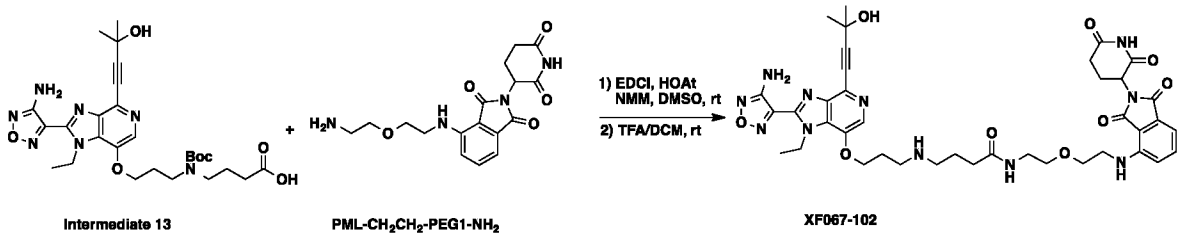
Synthesis of XF067-101



XF067-101 was synthesized following the standard procedure for preparing XF067-84 from intermediate 13 (9.1 mg, 0.016 mmol), VHL-C10-NH_2 (10.4 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-101 was obtained as white solid in TFA salt form (4.8 mg, 26%). ^{1}H NMR (500 MHz, CD_3OD) δ 8.96 (d, J = 2.6 Hz, 1H), 8.22 (d, J = 2.5 Hz, 1H), 7.58 – 7.32 (m, 4H), 5.13 – 5.00 (m, 2H), 4.65 (s, 1H), 4.63 – 4.50 (m, 5H), 4.37 (dd, J = 15.4, 2.8 Hz, 1H), 3.92 (d, J = 11.0 Hz, 1H), 3.83 (dd, J = 11.0, 3.9 Hz, 1H), 3.33 – 3.30 (m, 2H), 3.21 – 3.14 (m, 2H), 3.06 (dd, J = 9.4, 4.5 Hz, 2H), 2.54 – 2.38 (m, 7H), 2.36 – 2.20 (m, 3H), 2.11 (ddd, J = 13.3, 9.1, 4.5 Hz, 1H), 2.06 – 1.91 (m, 2H), 1.75 – 1.57 (m, 9H), 1.43 (t, J = 7.1 Hz, 2H), 1.39 – 1.22 (m, 14H), 1.05 (s, 9H). ESI-MS (m/z) $[M + H]^+$: 1067.5853.

Example 155

Synthesis of XF067-102

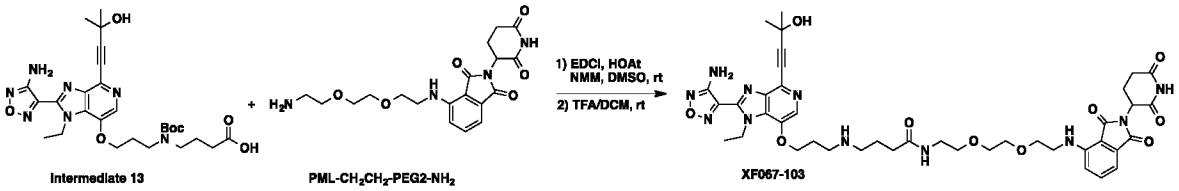


XF067-102 was synthesized following the standard procedure for preparing XF067-84 from intermediate 13 (9.1 mg, 0.016 mmol), PML-CH_2CH_2-PEG1-NH_2 (7.6 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-102 was obtained as yellow solid in TFA salt form (9.6 mg, 26%). ^{1}H NMR (500 MHz, CD_3OD) δ 8.17 (s, 1H), 7.50 (dd, J = 8.6, 7.1 Hz, 1H), 7.01 (t, J = 8.2 Hz, 2H), 5.06 (dd, J = 12.7, 5.5 Hz, 1H), 4.99 (q, J = 7.1 Hz, 2H), 4.50 (t, J = 5.8 Hz, 2H), 3.66 (t, J = 5.1 Hz, 2H), 3.52 (t, J = 5.3 Hz, 2H), 3.44 (t, J = 5.1 Hz, 2H), 3.40 – 3.26 (m, 4H), 3.14 (t, J = 6.8 Hz, 2H), 2.88 (ddd, J = 17.3, 13.8, 5.3 Hz, 1H), 2.81 – 2.63 (m, 2H), 2.48 (t, J = 6.4 Hz, 2H), 2.39 – 2.35 (m, 2H), 2.13 (dtd, J = 13.2, 5.3,

2.5 Hz, 1H), 1.97 (p, J = 6.7 Hz, 2H), 1.69 (s, 6H), 1.53 (t, J = 7.1 Hz, 3H). ESI-MS (m/z) [M + H]$^+$: 814.3611.

Example 156

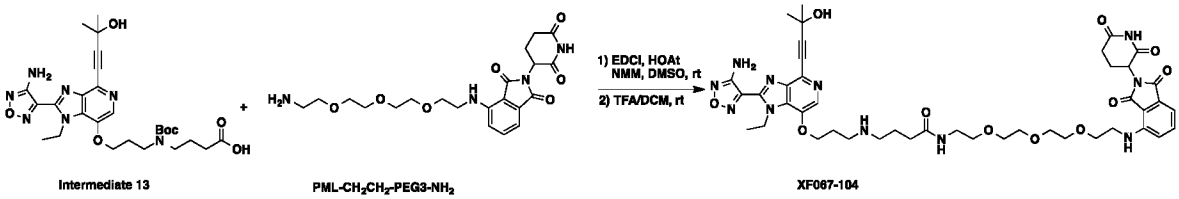
Synthesis of XF067-103



XF067-103 was synthesized following the standard procedure for preparing XF067-84 from intermediate 13 (9.1 mg, 0.016 mmol), PML-CH_2CH_2-PEG2-NH_2 (8.3 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-103 was obtained as yellow solid in TFA salt form (7.8 mg, 57%). ^{1}H NMR (500 MHz, CD_3OD) δ 8.16 (s, 1H), 7.53 (dd, J = 8.5, 7.1 Hz, 1H), 7.05 (dd, J = 15.6, 7.8 Hz, 2H), 5.09 – 4.97 (m, 3H), 4.51 (t, J = 5.9 Hz, 2H), 3.73 (t, J = 5.2 Hz, 2H), 3.70 – 3.60 (m, 4H), 3.55 – 3.46 (m, 4H), 3.34 – 3.24 (m, 4H), 3.14 (t, J = 7.0 Hz, 2H), 2.87 (ddd, J = 17.6, 14.0, 5.3 Hz, 1H), 2.80 – 2.64 (m, 2H), 2.46 – 2.34 (m, 4H), 2.13 (dtd, J = 13.1, 5.7, 2.9 Hz, 1H), 1.97 (p, J = 6.8 Hz, 2H), 1.69 (s, 6H), 1.56 (t, J = 7.1 Hz, 3H). ESI-MS (m/z) [M + H]$^+$: 858.3879.

Example 157

Synthesis of XF067-104

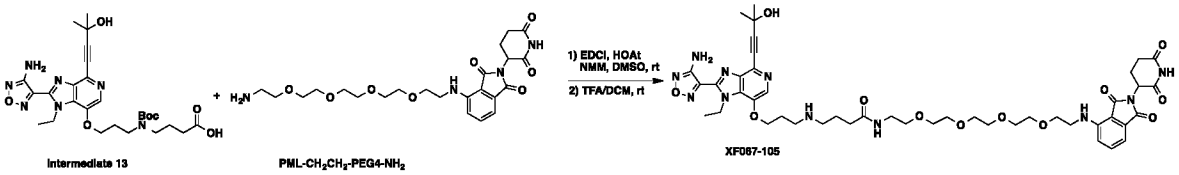


XF067-104 was synthesized following the standard procedure for preparing XF067-84 from intermediate 13 (9.1 mg, 0.016 mmol), PML-CH_2CH_2-PEG3-NH_2 (9 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-104 was obtained as yellow solid in TFA salt form (11.3 mg, 78%). ^{1}H NMR (500 MHz, CD_3OD) δ 8.23 (s, 1H), 7.51 (dd, J = 8.6, 7.1 Hz, 1H), 7.02 (dd, J = 19.2, 7.8 Hz, 2H), 5.09 – 4.99 (m, 3H), 4.52 (t, J = 5.9 Hz, 2H), 3.73 (t, J = 5.2 Hz, 2H), 3.68 (s, 4H), 3.69 – 3.63 (m, 2H), 3.66 – 3.55 (m, 2H), 3.49 (dt, J = 7.7, 5.3 Hz, 4H), 3.37 – 3.25 (m, 4H), 3.15 (t, J = 7.0 Hz, 2H), 2.88 (ddd, J = 17.6, 14.0,

5.3 Hz, 1H), 2.82 – 2.65 (m, 2H), 2.47 – 2.38 (m, 4H), 2.13 (dtd, *J* = 13.1, 5.7, 2.9 Hz, 1H), 1.98 (p, *J* = 6.9 Hz, 2H), 1.70 (s, 6H), 1.57 (t, *J* = 7.1 Hz, 3H). ESI-MS (m/z) $[M + H]^+$: 902.4134.

Example 158

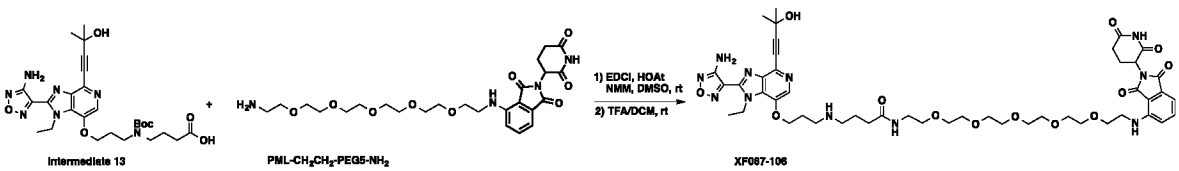
Synthesis of XF067-105



XF067-105 was synthesized following the standard procedure for preparing XF067-84 from intermediate 13 (9.1 mg, 0.016 mmol), PML-CH_2CH_2-PEG4-NH_2 (9 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-105 was obtained as yellow solid in TFA salt form (5.2 mg, 34%). ^{1}H NMR (500 MHz, CD_3OD) δ 8.19 (s, 1H), 7.52 (dd, *J* = 8.6, 7.1 Hz, 1H), 7.04 (dd, *J* = 19.6, 7.8 Hz, 2H), 5.09 – 4.98 (m, 3H), 4.51 (t, *J* = 5.8 Hz, 2H), 3.73 (t, *J* = 5.2 Hz, 2H), 3.70 – 3.60 (m, 10H), 3.58 (dd, *J* = 6.1, 3.4 Hz, 2H), 3.49 (t, *J* = 5.3 Hz, 4H), 3.34 – 3.25 (m, 4H), 3.16 (t, *J* = 7.0 Hz, 2H), 2.88 (ddd, *J* = 17.5, 14.0, 5.3 Hz, 1H), 2.81 – 2.65 (m, 2H), 2.46 (t, *J* = 6.5 Hz, 2H), 2.41 – 2.37 (m, 2H), 2.17 – 2.10 (m, 1H), 1.98 (p, *J* = 6.9 Hz, 2H), 1.69 (s, 6H), 1.57 (t, *J* = 7.1 Hz, 3H). ESI-MS (m/z) $[M + H]^+$: 946.4412.

Example 159

Synthesis of XF067-106

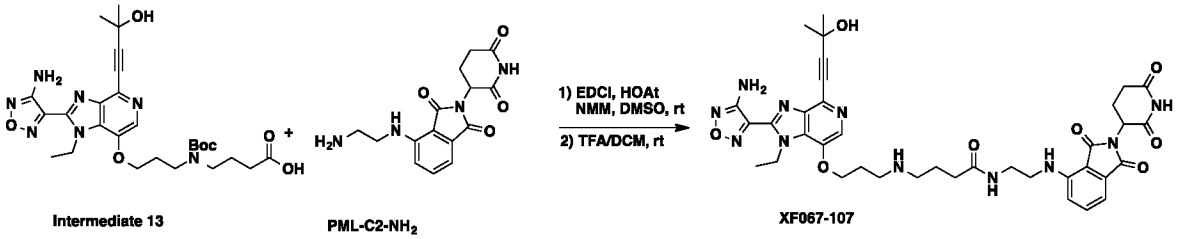


XF067-106 was synthesized following the standard procedure for preparing XF067-84 from intermediate 13 (9.1 mg, 0.016 mmol), PML-CH_2CH_2-PEG5-NH_2 (9.6 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-106 was obtained as yellow solid in TFA salt form (12.8 mg, 81%). ^{1}H NMR (500 MHz, CD_3OD) δ 8.24 (d, *J* = 3.6 Hz, 1H), 7.60 – 7.45 (m, 1H), 7.04 (ddd, *J* = 19.7, 8.0, 3.7 Hz, 2H), 5.05 (td, *J* = 8.7, 7.4, 3.8 Hz, 3H), 4.54 (q, *J* = 5.8, 5.0 Hz, 2H), 3.82 – 3.56 (m, 18H), 3.49 (q, *J* = 5.3 Hz, 4H), 3.37 – 3.27

(m, 4H), 3.23 – 3.15 (m, 2H), 2.93 – 2.82 (m, 1H), 2.83 – 2.72 (m, 2H), 2.47 – 2.37 (m, 4H), 2.13 (dtd, J = 13.0, 5.7, 2.9 Hz, 1H), 1.99 (p, J = 6.8, 5.6 Hz, 2H), 1.70 (d, J = 3.7 Hz, 6H), 1.62 – 1.53 (m, 3H). ESI-MS (m/z) $[M + H]^+$: 990.4668.

Example 160

Synthesis of XF067-107

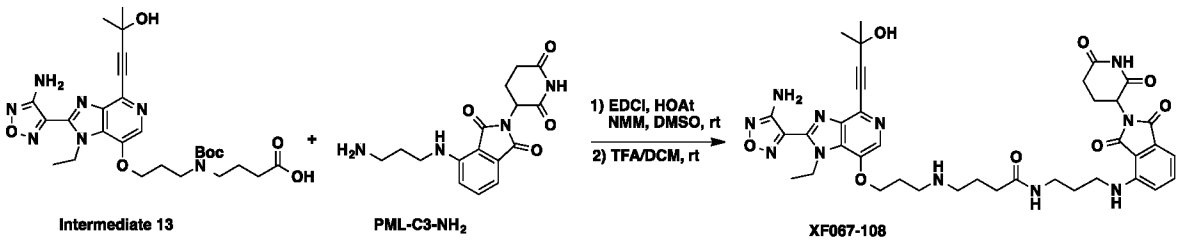


Intermediate 13 PML-C2-NH_2 XF067-107

XF067-107 was synthesized following the standard procedure for preparing XF067-84 from intermediate 13 (9.1 mg, 0.016 mmol), PML-C2-NH_2 (7 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-107 was obtained as yellow solid in TFA salt form (12.1 mg, 98%). ^{1}H NMR (500 MHz, CD_3OD) δ 8.26 (d, J = 13.2 Hz, 1H), 7.55 – 7.44 (m, 1H), 7.02 (dd, J = 14.2, 7.8 Hz, 2H), 5.09 – 4.98 (m, 3H), 4.62 – 4.51 (m, 2H), 3.36 – 3.32 (m, 6H), 3.15 (t, J = 6.6 Hz, 2H), 2.87 (ddd, J = 17.2, 13.8, 5.3 Hz, 1H), 2.81 – 2.62 (m, 2H), 2.51 – 2.43 (m, 2H), 2.39 (tq, J = 12.7, 6.8 Hz, 2H), 2.13 (dtd, J = 13.2, 5.4, 2.6 Hz, 1H), 2.01 – 1.94 (m, 2H), 1.69 (s, 6H), 1.64 – 1.52 (m, 3H).). ESI-MS (m/z) $[M + H]^+$: 770.3356.

Example 161

Synthesis of XF067-108



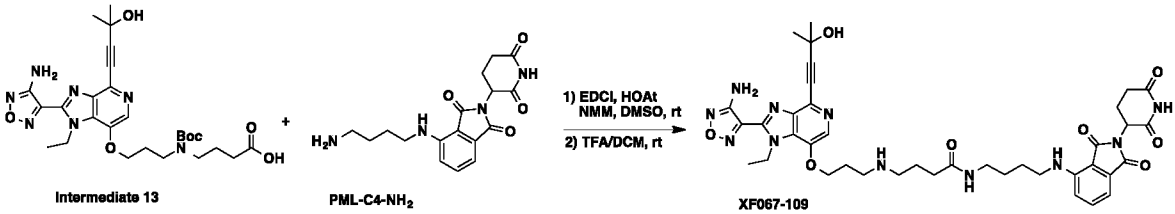
Intermediate 13 PML-C3-NH_2 XF067-108

XF067-108 was synthesized following the standard procedure for preparing XF067-84 from intermediate 13 (9.1 mg, 0.016 mmol), PML-C3-NH_2 (7.1 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-108 was obtained as yellow solid in TFA salt form (11.7 mg, 93%). ^{1}H NMR (500 MHz, CD_3OD) δ 8.25 (s, 1H), 7.51 (dd, J = 8.6, 7.1 Hz, 1H), 6.99 (dd, J = 7.8, 4.6 Hz, 2H), 5.08 – 4.98 (m, 3H), 4.54 (t, J = 5.8 Hz, 2H), 3.39 – 3.29 (m, 4H), 3.31 – 3.22 (m, 2H), 3.18 (t, J = 6.6 Hz, 2H), 2.87 (ddd, J = 17.5, 14.0, 5.4 Hz,

1H), 2.80 – 2.64 (m, 2H), 2.51 (t, J = 6.4 Hz, 2H), 2.45 – 2.38 (m, 2H), 2.12 (ddt, J = 13.1, 5.4, 2.8 Hz, 1H), 2.00 (q, J = 6.5 Hz, 2H), 1.77 (q, J = 6.4 Hz, 2H), 1.70 (s, 6H), 1.56 (t, J = 7.1 Hz, 3H). ESI-MS (m/z) $[M + H]^+$: 784.3534.

Example 162

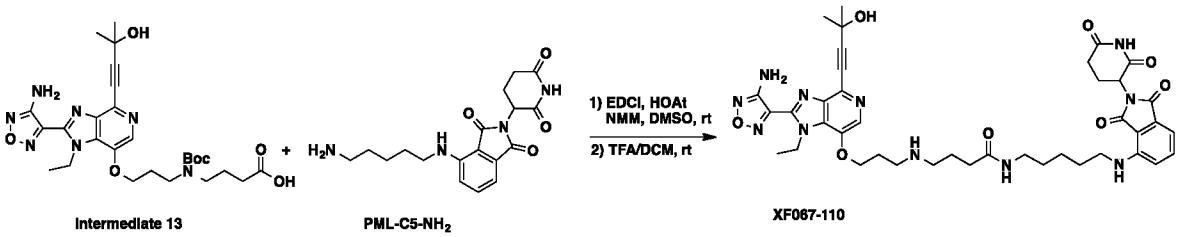
Synthesis of XF067-109



XF067-109 was synthesized following the standard procedure for preparing XF067-84 from intermediate 13 (9.1 mg, 0.016 mmol), PML-C4-NH_2 (7.3 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-109 was obtained as yellow solid in TFA salt form (9.6 mg, 75%). ^{1}H NMR (500 MHz, CD_3OD) δ 8.25 (s, 1H), 7.51 (t, J = 7.8 Hz, 1H), 7.03 – 6.96 (m, 2H), 5.04 (q, J = 7.1, 6.3 Hz, 3H), 4.54 (t, J = 5.8 Hz, 2H), 3.47 – 3.01 (m, 8H), 2.93 – 2.62 (m, 3H), 2.59 – 2.31 (m, 4H), 2.18 – 2.07 (m, 1H), 1.99 (p, J = 6.4 Hz, 2H), 1.82 – 1.45 (m, 13H). ESI -MS (m/z) $[M + H]^+$: 798.3667.

Example 163

Synthesis of XF067-110

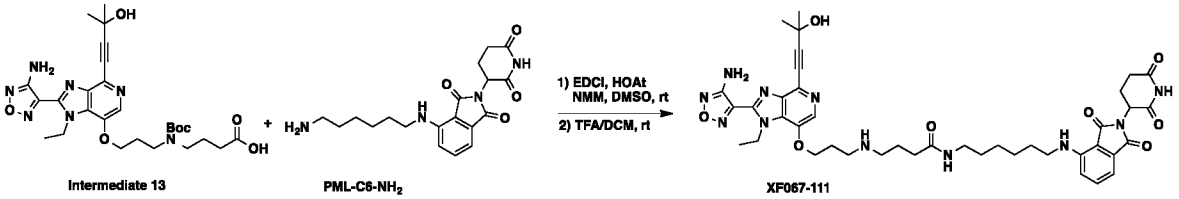


XF067-110 was synthesized following the standard procedure for preparing XF067-84 from intermediate 13 (9.1 mg, 0.016 mmol), PML-C5-NH_2 (7.6 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-110 was obtained as yellow solid in TFA salt form (10.6 mg, 82%). ^{1}H NMR (500 MHz, CD_3OD) δ 8.18 (s, 1H), 7.49 (dd, J = 8.5, 7.1 Hz, 1H), 6.98 (dd, J = 7.8, 6.4 Hz, 2H), 5.08 – 4.96 (m, 3H), 4.51 (t, J = 5.8 Hz, 2H), 3.34 – 3.23 (m, 3H), 3.20 – 3.07 (m, 4H), 2.88 (ddd, J = 17.0, 13.7, 5.2 Hz, 1H), 2.81 – 2.64 (m, 2H), 2.47 (t, J = 6.5 Hz, 2H), 2.39 (p, J = 6.4 Hz, 2H), 2.18 – 2.08 (m, 1H), 1.98 (p, J = 6.7 Hz, 2H),

1.69 (s, 6H), 1.69 – 1.60 (m, 2H), 1.58 – 1.47 (m, 5H), 1.40 (qd, J = 8.5, 5.6 Hz, 2H). ESI-MS (m/z) $[M + H]^+$: 812.3854.

Example 164

Synthesis of XF067-111

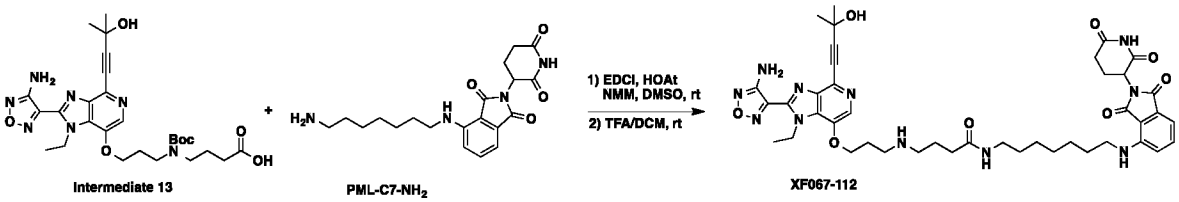


Intermediate 13 PML-C6-NH_2 XF067-111

XF067-111 was synthesized following the standard procedure for preparing XF067-84 from intermediate 13 (9.1 mg, 0.016 mmol), PML-C6-NH_2 (6.5 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-111 was obtained as yellow solid in TFA salt form (11.9 mg, 90%). ^{1}H NMR (500 MHz, CD_3OD) δ 8.24 (s, 1H), 7.60 – 7.48 (m, 1H), 7.15 – 6.86 (m, 2H), 5.04 (dt, J = 12.3, 5.2 Hz, 3H), 4.54 (q, J = 5.8, 4.9 Hz, 2H), 3.14 (dt, J = 25.1, 7.0 Hz, 8H), 2.98 – 2.67 (m, 3H), 2.43 (dq, J = 19.2, 7.8, 6.4 Hz, 4H), 2.19 – 2.10 (m, 1H), 1.99 (p, J = 6.7 Hz, 2H), 1.83 – 1.15 (m, 17H). ESI-MS (m/z) $[M + H]^+$: 826.3987.

Example 165

Synthesis of XF067-112



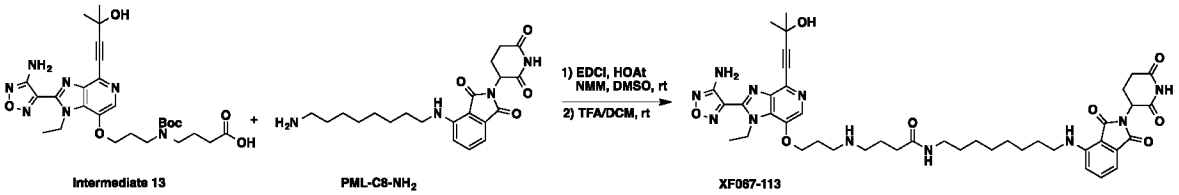
Intermediate 13 PML-C7-NH_2 XF067-112

XF067-112 was synthesized following the standard procedure for preparing XF067-84 from intermediate 13 (9.1 mg, 0.016 mmol), PML-C7-NH_2 (8 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-112 was obtained as yellow solid in TFA salt form (12.5 mg, 93%). ^{1}H NMR (500 MHz, CD_3OD) δ 8.22 (s, 1H), 7.53 (ddd, J = 8.5, 7.2, 2.0 Hz, 1H), 7.01 (td, J = 6.9, 2.2 Hz, 2H), 5.09 – 5.00 (m, 3H), 4.53 (t, J = 5.9 Hz, 2H), 3.39 – 3.27 (m, 4H), 3.16 (t, J = 6.9 Hz, 2H), 3.09 (t, J = 7.1 Hz, 2H), 2.93 – 2.82 (m, 1H), 2.81 – 2.66 (m, 2H), 2.43 (dt, J = 20.7, 6.9 Hz, 4H), 2.12 (dtd, J = 13.0, 5.6, 2.8 Hz, 1H), 1.99 (p, J =

6.9 Hz, 2H), 1.72 – 1.62 (m, 8H), 1.58 (t, J = 7.1 Hz, 3H), 1.49 – 1.29 (m, 8H). ESI-MS (m/z) $[M + H]^+$: 840.4157.

Example 166

Synthesis of XF067-113



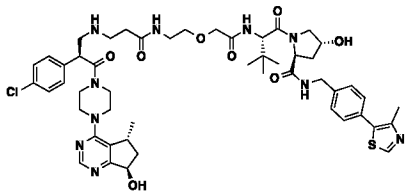
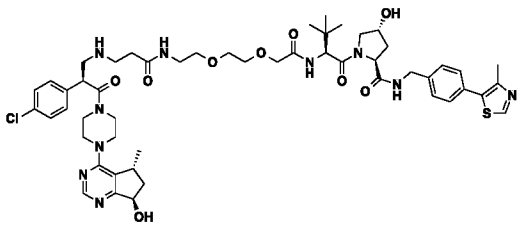
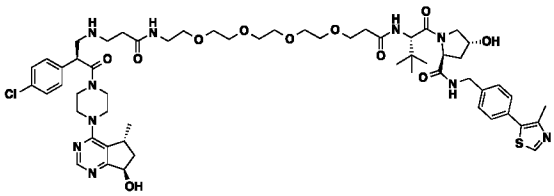
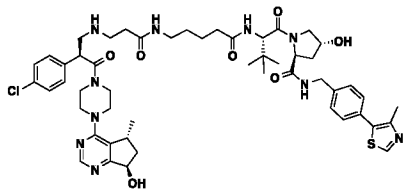
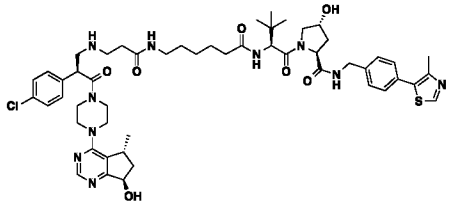
Intermediate 13 PML-C8-NH_2 XF067-113

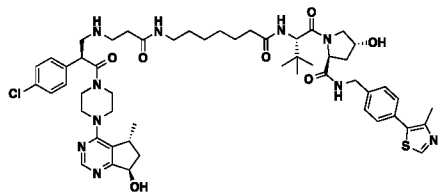
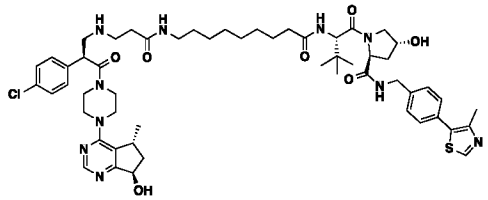
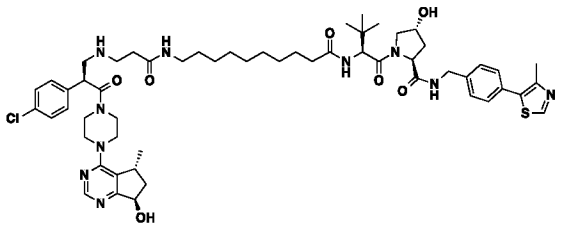
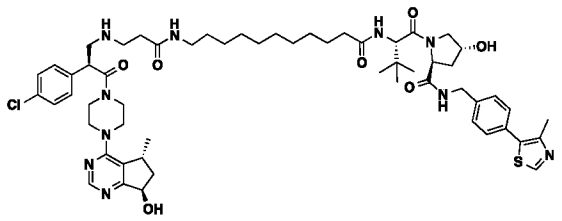
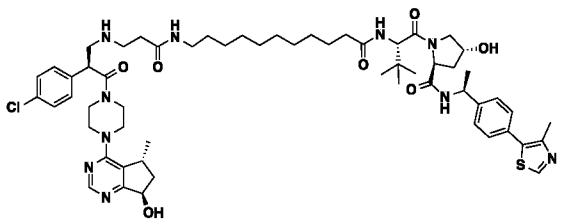
XF067-113 was synthesized following the standard procedure for preparing XF067-84 from intermediate 13 (9.1 mg, 0.016 mmol), PML-C8-NH_2 (8.2 mg, 0.016 mmol, 1.0 equiv), EDCI (4.6 mg, 0.024 mmol, 1.5 equiv), HOAt (3.3 mg, 0.024 mmol, 1.5 equiv), and NMM (4.8 mg, 0.048 mmol, 3.0 equiv) in DMSO (1 mL). XF067-113 was obtained as yellow solid in TFA salt form (12.6 mg, 98%). ^{1}H NMR (500 MHz, CD_3OD) δ 8.25 (d, J = 2.8 Hz, 1H), 7.54 (ddd, J = 8.5, 7.1, 2.3 Hz, 1H), 7.02 (dd, J = 7.8, 3.0 Hz, 2H), 5.10 – 5.01 (m, 3H), 4.54 (t, J = 5.8 Hz, 2H), 3.34 – 3.27 (m, 4H), 3.17 (td, J = 7.3, 2.6 Hz, 2H), 3.09-3.07 (m, 2H), 2.92 – 2.82 (m, 1H), 2.81 – 2.66 (m, 2H), 2.48 – 2.36 (m, 4H), 2.12 (dtd, J = 13.1, 5.6, 2.8 Hz, 1H), 2.03 – 1.92 (m, 2H), 1.75 – 1.62 (m, 8H), 1.65 – 1.55 (m, 3H), 1.49 – 1.25 (m, 10H). ESI-MS (m/z) $[M + H]^+$: 854.4313.

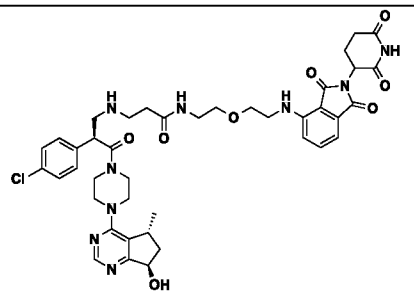
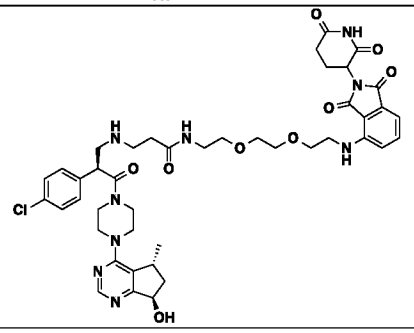
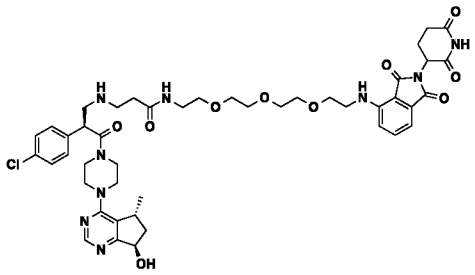
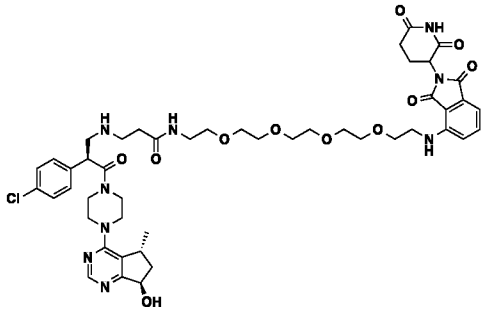
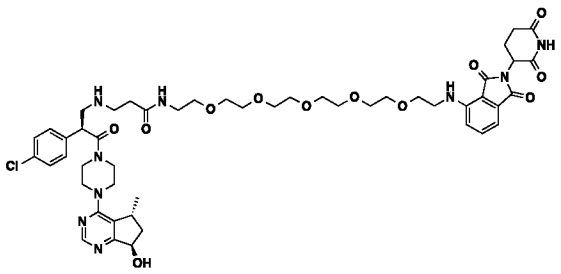
Compounds synthesized in the Examples above are set forth in Table 1, below.

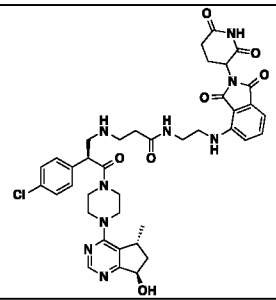
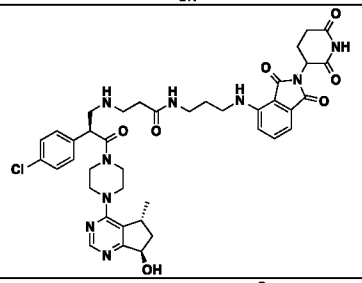
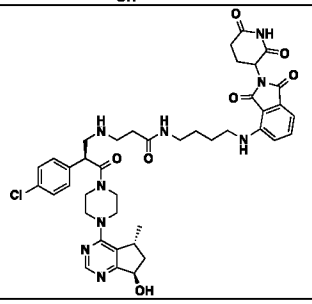
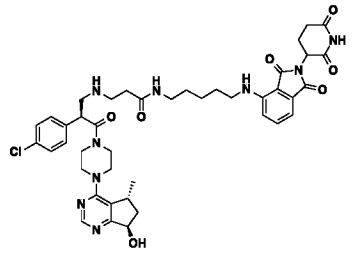
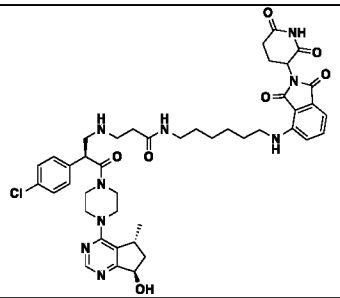
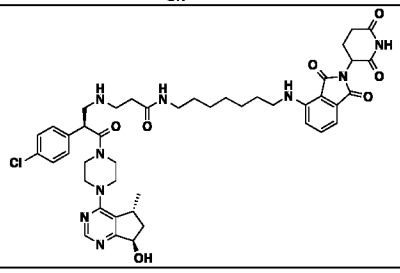
In Table 1, the left portion of the structure of the AKT disruptors/degraders binds to AKT (as, e.g., GSK690693 (Heerding et al., 2008), GSK2110183 (Dumble et al., 2014), GSK2141795 (Dumble et al., 2014), AZD5363 (Addie et al., 2013), GDC0068 (Blake et al., 2012), MK-2206 (Hirai et al., 2010), and ARQ-092 (Yu et al., 2015) do), and the right portion of the structure recruits the ubiquitination machinery to AKT, which induces poly-ubiquitination and degradation of AKT at the proteasome.

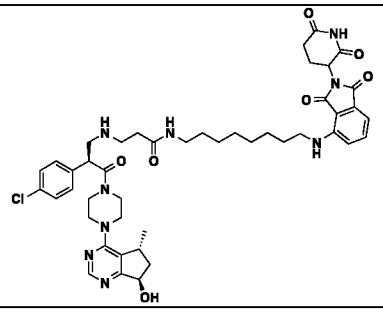
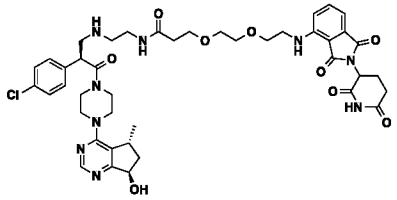
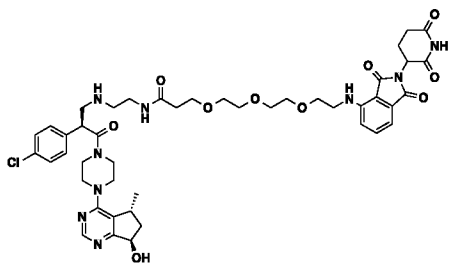
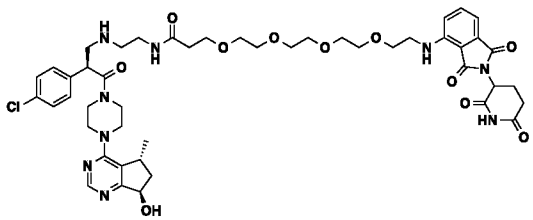
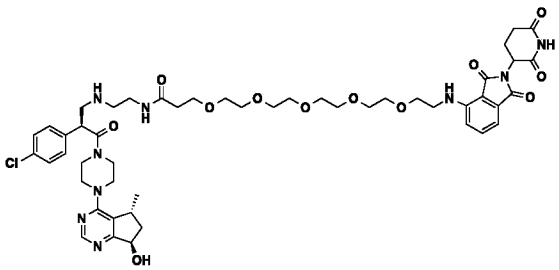
Table 1

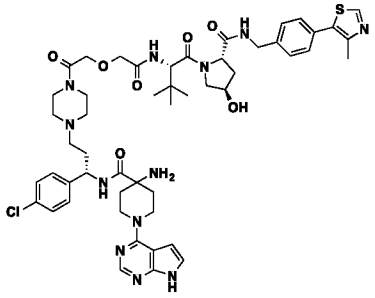
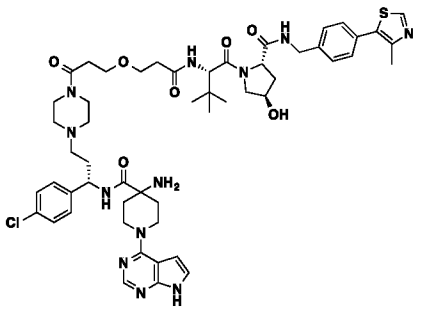
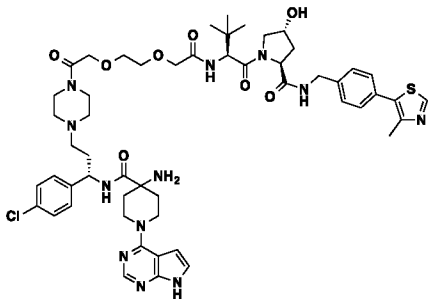
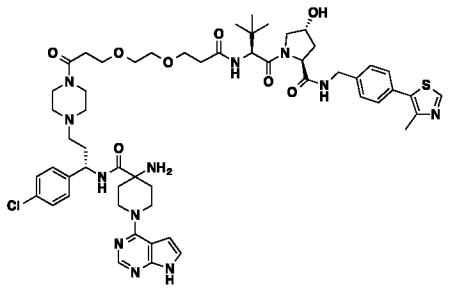
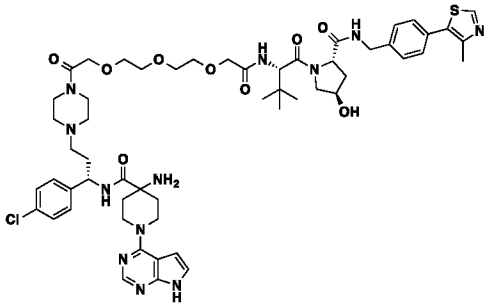
Compound ID	Structure	Chemical Name
XF038-157A		**(2*S*,4*R*)-1-((2*S*,15*S*)-2-(*tert*-butyl)-15-(4-chlorophenyl)-16-(4-((5*R*,7*R*)-7-hydroxy-5-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-yl)piperazin-1-yl)-4,10,16-trioxo-6-oxa-3,9,13-triazahexadecanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**
XF038-158A		**(2*S*,4*R*)-1-((2*S*,18*S*)-2-(*tert*-butyl)-18-(4-chlorophenyl)-19-(4-((5*R*,7*R*)-7-hydroxy-5-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-yl)piperazin-1-yl)-4,13,19-trioxo-6,9-dioxa-3,12,16-triazanonadecanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**
XF038-159A		**(2*S*,4*R*)-1-((2*S*,25*S*)-2-(*tert*-butyl)-25-(4-chlorophenyl)-26-(4-((5*R*,7*R*)-7-hydroxy-5-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-yl)piperazin-1-yl)-4,20,26-trioxo-7,10,13,16-tetraoxa-3,19,23-triazahexacosanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**
XF038-160A		**(2*S*,4*R*)-1-((*S*)-2-(5-(3-(((*S*)-2-(4-chlorophenyl)-3-(4-((5*R*,7*R*)-7-hydroxy-5-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-yl)piperazin-1-yl)-3-oxopropyl)amino)propanamido)pentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**
XF038-161A		**(2*S*,4*R*)-1-((*S*)-2-(6-(3-(((*S*)-2-(4-chlorophenyl)-3-(4-((5*R*,7*R*)-7-hydroxy-5-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-yl)piperazin-1-yl)-3-oxopropyl)amino)propanamido)hexanamido)-3,3-dimethylbutanoyl)-4-hydroxy-**

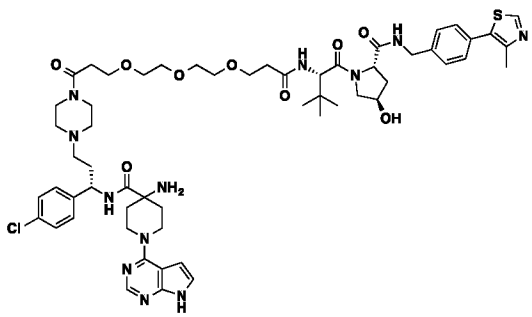
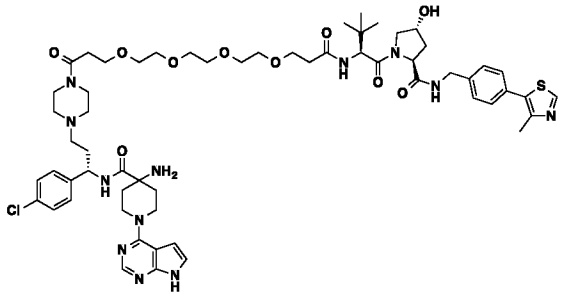
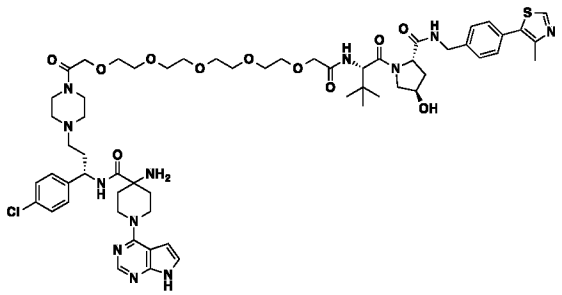
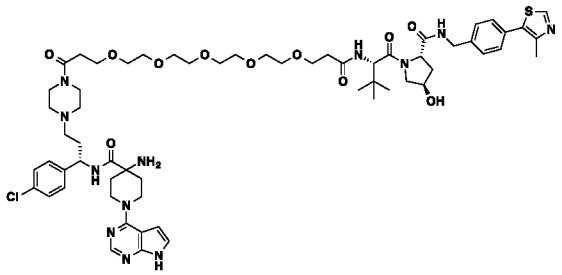
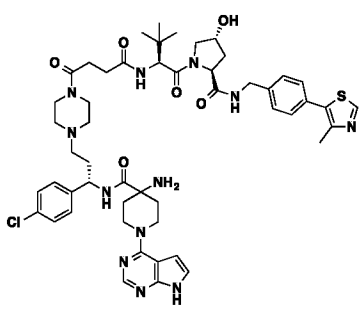
		***N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**
XF038-162A		**(2*S*,4*R*)-1-((*S*)-2-(7-(3-(((*S*)-2-(4-chlorophenyl)-3-(4-((5*R*,7*R*)-7-hydroxy-5-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-yl)piperazin-1-yl)-3-oxopropyl)amino)propanamido)heptanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**
XF038-164A		**(2*S*,4*R*)-1-((*S*)-2-(9-(3-(((*S*)-2-(4-chlorophenyl)-3-(4-((5*R*,7*R*)-7-hydroxy-5-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-yl)piperazin-1-yl)-3-oxopropyl)amino)propanamido)nonanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**
XF038-165A		**(2*S*,4*R*)-1-((*S*)-2-(10-(3-(((*S*)-2-(4-chlorophenyl)-3-(4-((5*R*,7*R*)-7-hydroxy-5-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-yl)piperazin-1-yl)-3-oxopropyl)amino)propanamido)decanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**
XF038-166A		**(2*S*,4*R*)-1-((*S*)-2-(11-(3-(((*S*)-2-(4-chlorophenyl)-3-(4-((5*R*,7*R*)-7-hydroxy-5-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-yl)piperazin-1-yl)-3-oxopropyl)amino)propanamido)undecanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**
XF042-162		**(2*S*,4*R*)-1-((*S*)-2-(11-(3-(((*S*)-2-(4-chlorophenyl)-3-(4-((5*R*,7*R*)-7-hydroxy-5-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-yl)piperazin-1-yl)-3-oxopropyl)amino)propanamido)undecanamido)-3,3-dimethylbutanoyl)-4-hydroxy-**

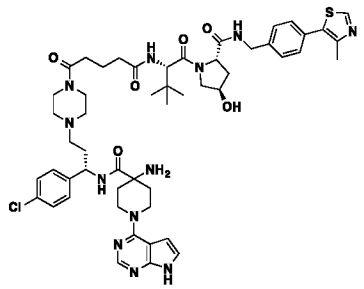
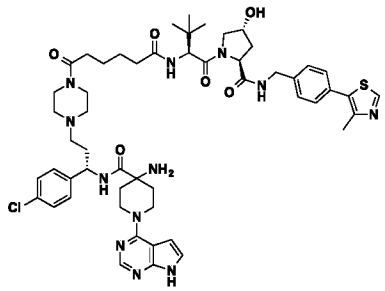
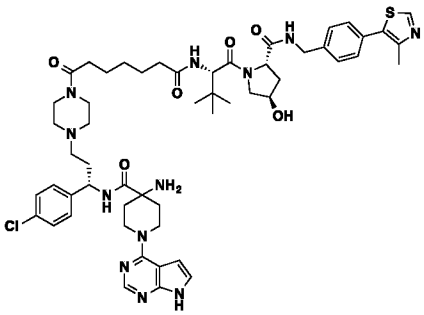
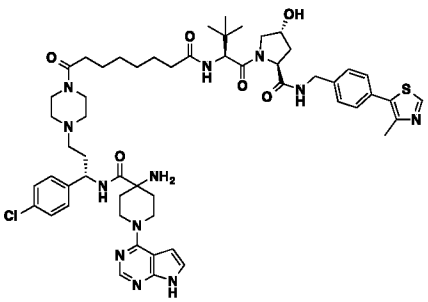
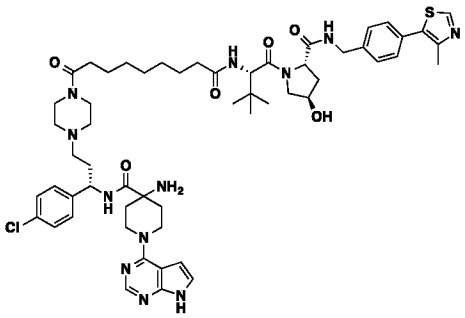
		***N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide**
XF042-171		**3-(((*S*)-2-(4-chlorophenyl)-3-(4-((5*R*,7*R*)-7-hydroxy-5-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-yl)piperazin-1-yl)-3-oxopropyl)amino)-*N*-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethyl)propanamide**
XF048-7		**3-(((*S*)-2-(4-chlorophenyl)-3-(4-((5*R*,7*R*)-7-hydroxy-5-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-yl)piperazin-1-yl)-3-oxopropyl)amino)-*N*-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethyl)propanamide**
XF048-8		**3-(((*S*)-2-(4-chlorophenyl)-3-(4-((5*R*,7*R*)-7-hydroxy-5-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-yl)piperazin-1-yl)-3-oxopropyl)amino)-*N*-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethoxy)ethyl)propanamide**
XF038-176A		**3-(((*S*)-2-(4-chlorophenyl)-3-(4-((5*R*,7*R*)-7-hydroxy-5-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-yl)piperazin-1-yl)-3-oxopropyl)amino)-*N*-(14-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12-tetraoxatetradecyl)propanamide**
XF038-177A		**3-(((*S*)-2-(4-chlorophenyl)-3-(4-((5*R*,7*R*)-7-hydroxy-5-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-yl)piperazin-1-yl)-3-oxopropyl)amino)-*N*-(17-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12,15-pentaoxaheptadecyl)propanamide**

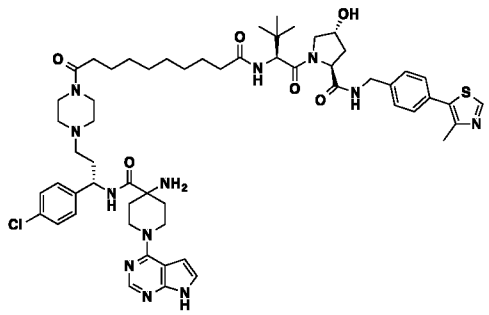
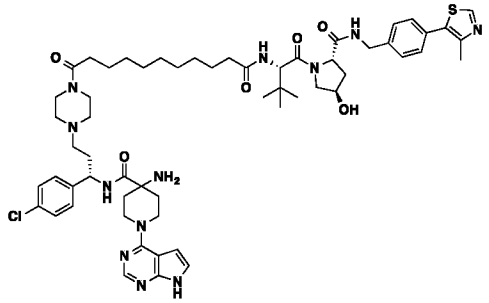
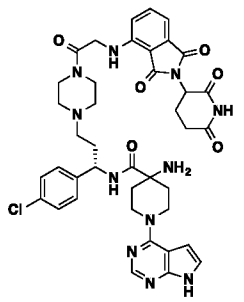
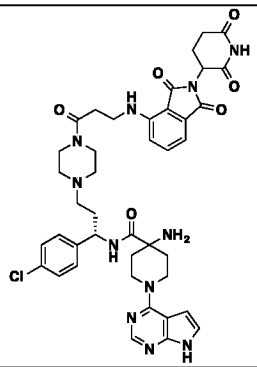
XF042-164		**3-(((*S*)-2-(4-chlorophenyl)-3-(4-((5*R*,7*R*)-7-hydroxy-5-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-yl)piperazin-1-yl)-3-oxopropyl)amino)-*N*-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethyl)propanamide**
XF042-165		**3-(((*S*)-2-(4-chlorophenyl)-3-(4-((5*R*,7*R*)-7-hydroxy-5-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-yl)piperazin-1-yl)-3-oxopropyl)amino)-*N*-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propyl)propanamide**
XF042-166		**3-(((*S*)-2-(4-chlorophenyl)-3-(4-((5*R*,7*R*)-7-hydroxy-5-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-yl)piperazin-1-yl)-3-oxopropyl)amino)-*N*-(4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)butyl)propanamide**
XF042-167		**3-(((*S*)-2-(4-chlorophenyl)-3-(4-((5*R*,7*R*)-7-hydroxy-5-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-yl)piperazin-1-yl)-3-oxopropyl)amino)-*N*-(5-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)pentyl)propanamide**
XF042-168		**3-(((*S*)-2-(4-chlorophenyl)-3-(4-((5*R*,7*R*)-7-hydroxy-5-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-yl)piperazin-1-yl)-3-oxopropyl)amino)-*N*-(6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)hexyl)propanamide**
XF048-5		**3-(((*S*)-2-(4-chlorophenyl)-3-(4-((5*R*,7*R*)-7-hydroxy-5-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-yl)piperazin-1-yl)-3-oxopropyl)amino)-*N*-(7-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)heptyl)propanamide**

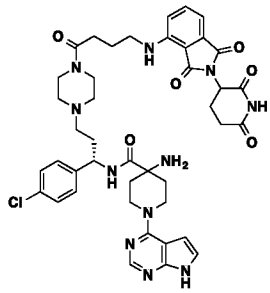
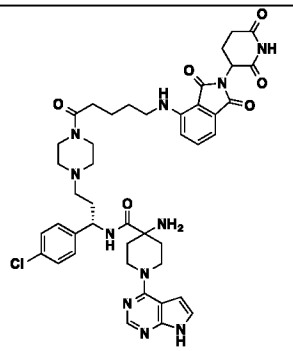
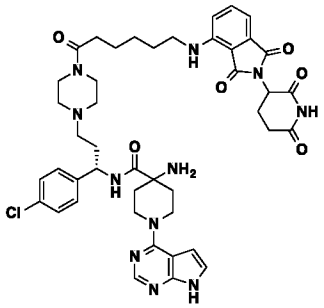
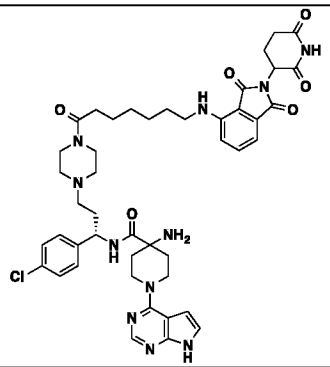
XF042-170		**3-(((*S*)-2-(4-chlorophenyl)-3-(4-((5*R*,7*R*)-7-hydroxy-5-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-yl)piperazin-1-yl)-3-oxopropyl)amino)-*N*-(8-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)octyl)propanamide**
XF048-1		***N*-(2-(((*S*)-2-(4-chlorophenyl)-3-(4-((5*R*,7*R*)-7-hydroxy-5-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-yl)piperazin-1-yl)-3-oxopropyl)amino)ethyl)-3-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)propanamide**
XF048-2		***N*-(2-(((*S*)-2-(4-chlorophenyl)-3-(4-((5*R*,7*R*)-7-hydroxy-5-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-yl)piperazin-1-yl)-3-oxopropyl)amino)ethyl)-3-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethoxy)propanamide**
XF048-3		***N*-(2-(((*S*)-2-(4-chlorophenyl)-3-(4-((5*R*,7*R*)-7-hydroxy-5-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-yl)piperazin-1-yl)-3-oxopropyl)amino)ethyl)-1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12-tetraoxapentadecan-15-amide**
XF048-4		***N*-(2-(((*S*)-2-(4-chlorophenyl)-3-(4-((5*R*,7*R*)-7-hydroxy-5-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-yl)piperazin-1-yl)-3-oxopropyl)amino)ethyl)-1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12,15-pentaoxaoctadecan-18-amide**

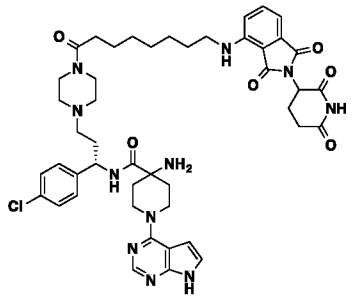
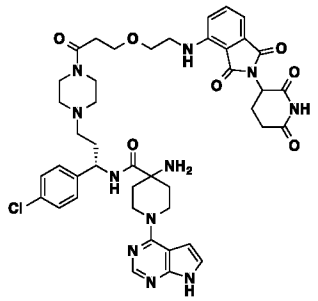
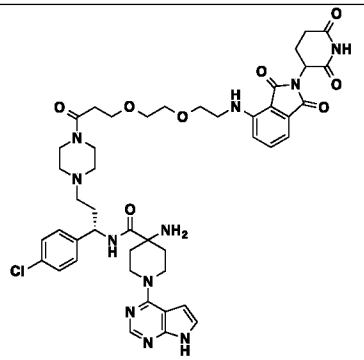
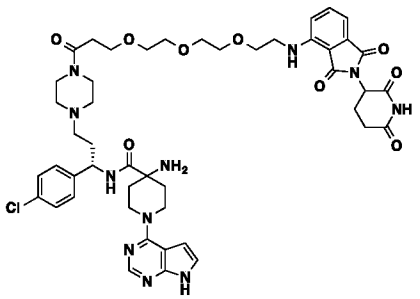
XF050-5		**4-amino-*N*-((*S*)-1-(4-chlorophenyl)-3-(4-(2-(2-(((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-2-oxoethoxy)acetyl)piperazin-1-yl)propyl)-1-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)piperidine-4-carboxamide**
XF050-6		**4-amino-*N*-((*S*)-1-(4-chlorophenyl)-3-(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)propanoyl)piperazin-1-yl)propyl)-1-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)piperidine-4-carboxamide**
XF050-7		**4-amino-*N*-((*S*)-1-(4-chlorophenyl)-3-(4-(2-(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)ethoxy)acetyl)piperazin-1-yl)propyl)-1-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)piperidine-4-carboxamide**
XF050-8		**4-amino-*N*-((*S*)-1-(4-chlorophenyl)-3-(4-(3-(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)ethoxy)propanoyl)piperazin-1-yl)propyl)-1-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)piperidine-4-carboxamide**
XF050-9		**4-amino-*N*-((*S*)-1-(4-chlorophenyl)-3-(4-((*S*)-13-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-14,14-dimethyl-11-oxo-3,6,9-trioxa-12-azapentadecanoyl)piperazin-1-yl)propyl)-1-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)piperidine-4-carboxamide**

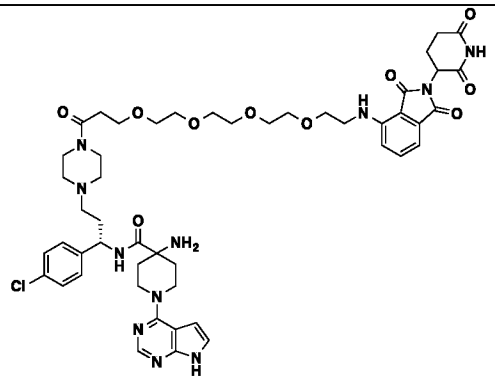
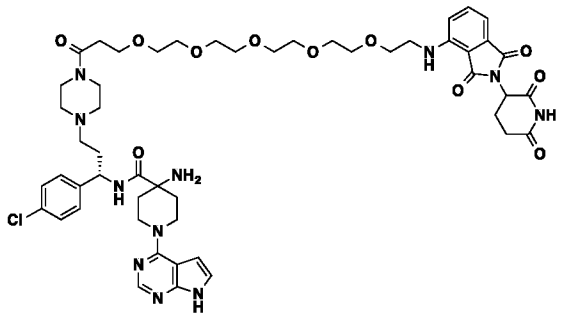
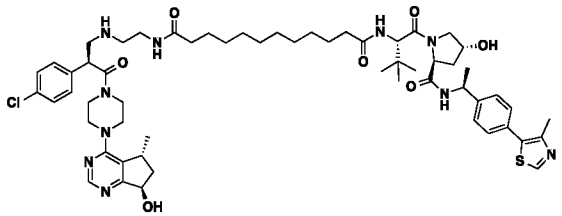
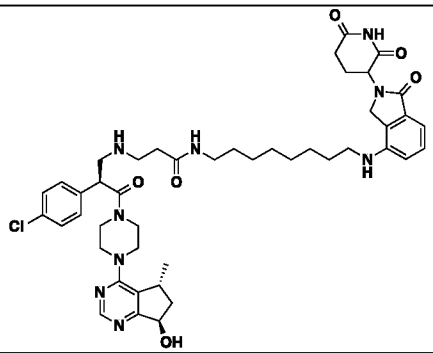
XF050-10		**4-amino-*N*-((*S*)-1-(4-chlorophenyl)-3-(4-((*S*)-15-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-16,16-dimethyl-13-oxo-4,7,10-trioxa-14-azaheptadecanoyl)piperazin-1-yl)propyl)-1-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)piperidine-4-carboxamide**
XF050-11		**4-amino-*N*-((*S*)-1-(4-chlorophenyl)-3-(4-((*S*)-18-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-19,19-dimethyl-16-oxo-4,7,10,13-tetraoxa-17-azaicosanoyl)piperazin-1-yl)propyl)-1-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)piperidine-4-carboxamide**
XF050-12		**4-amino-*N*-((*S*)-1-(4-chlorophenyl)-3-(4-((*S*)-19-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-20,20-dimethyl-17-oxo-3,6,9,12,15-pentaoxa-18-azahenicosanoyl)piperazin-1-yl)propyl)-1-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)piperidine-4-carboxamide**
XF050-13		**4-amino-*N*-((*S*)-1-(4-chlorophenyl)-3-(4-((*S*)-21-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-22,22-dimethyl-19-oxo-4,7,10,13,16-pentaoxa-20-azatricosanoyl)piperazin-1-yl)propyl)-1-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)piperidine-4-carboxamide**
XF050-14		**4-amino-*N*-((*S*)-1-(4-chlorophenyl)-3-(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-oxobutanoyl)piperazin-1-yl)propyl)-1-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)piperidine-4-carboxamide**

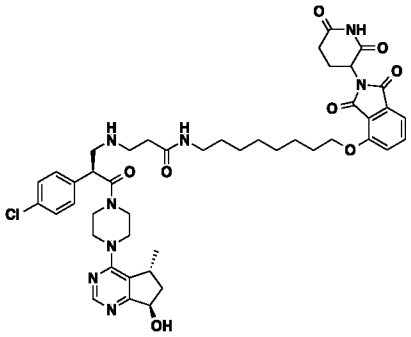
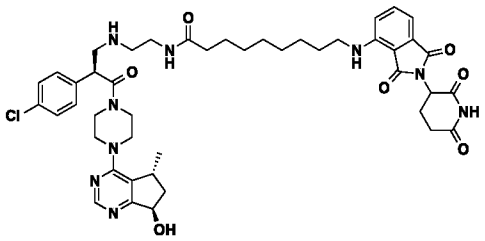
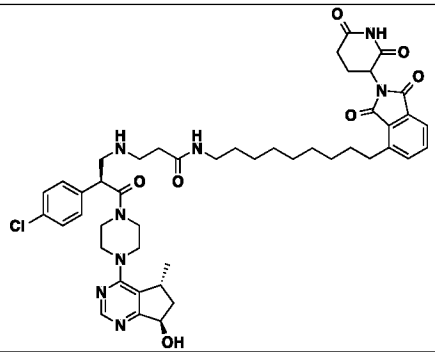
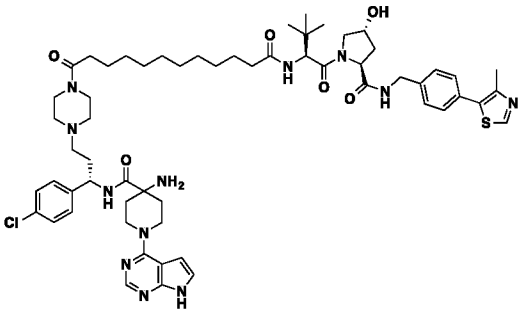
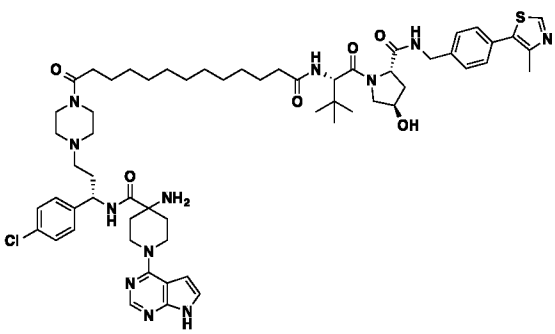
XF050-15		**4-amino-*N*-((*S*)-1-(4-chlorophenyl)-3-(4-(5-(((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-5-oxopentanoyl)piperazin-1-yl)propyl)-1-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)piperidine-4-carboxamide**
XF050-16		**4-amino-*N*-((*S*)-1-(4-chlorophenyl)-3-(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-oxohexanoyl)piperazin-1-yl)propyl)-1-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)piperidine-4-carboxamide**
XF050-17		**4-amino-*N*-((*S*)-1-(4-chlorophenyl)-3-(4-(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)amino)-7-oxoheptanoyl)piperazin-1-yl)propyl)-1-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)piperidine-4-carboxamide**
XF050-18		**4-amino-*N*-((*S*)-1-(4-chlorophenyl)-3-(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-oxooctanoyl)piperazin-1-yl)propyl)-1-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)piperidine-4-carboxamide**
XF050-19		**4-amino-*N*-((*S*)-1-(4-chlorophenyl)-3-(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-oxononanoyl)piperazin-1-yl)propyl)-1-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)piperidine-4-carboxamide**

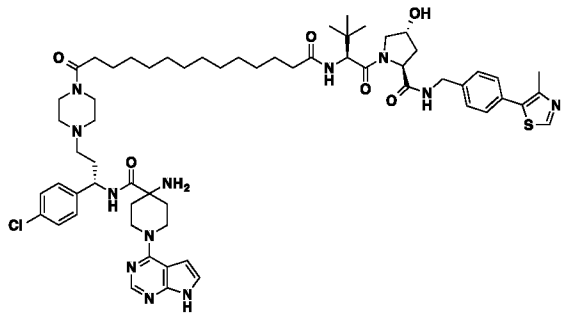
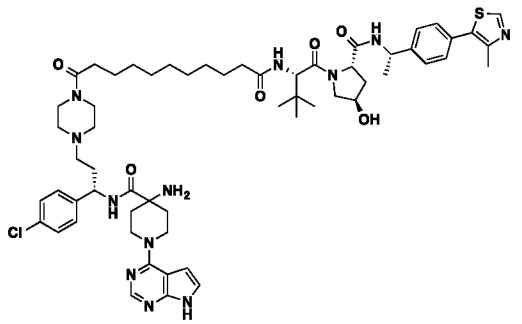
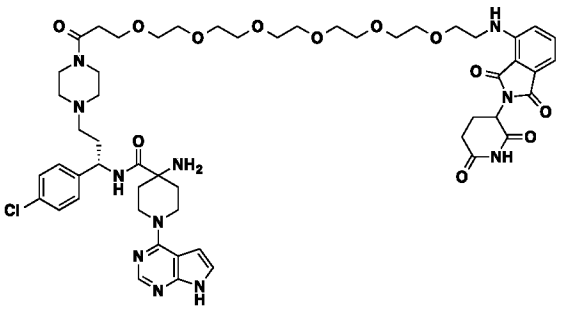
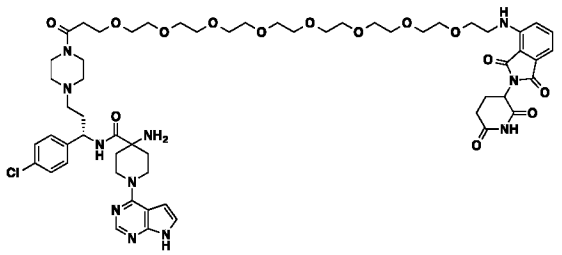
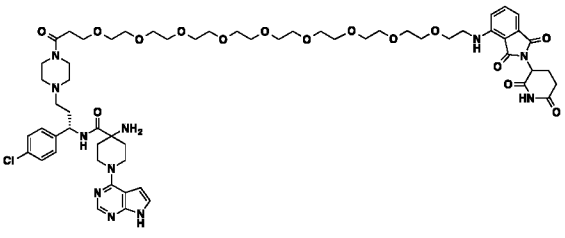
XF050-20		**4-amino-*N*-((*S*)-1-(4-chlorophenyl)-3-(4-(10-(((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-10-oxodecanoyl)piperazin-1-yl)propyl)-1-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)piperidine-4-carboxamide**
XF050-21		**4-amino-*N*-((*S*)-1-(4-chlorophenyl)-3-(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-oxoundecanoyl)piperazin-1-yl)propyl)-1-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)piperidine-4-carboxamide**
XF050-22		**4-amino-*N*-((1*S*)-1-(4-chlorophenyl)-3-(4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)glycyl)piperazin-1-yl)propyl)-1-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)piperidine-4-carboxamide**
XF050-23		**4-amino-*N*-((1*S*)-1-(4-chlorophenyl)-3-(4-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propanoyl)piperazin-1-yl)propyl)-1-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)piperidine-4-carboxamide**

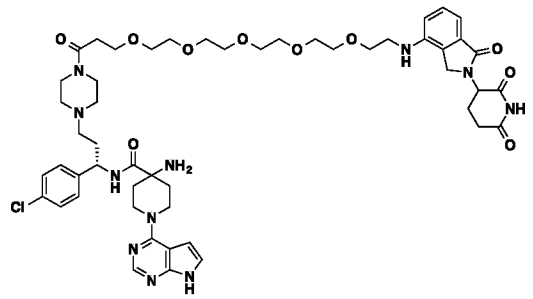
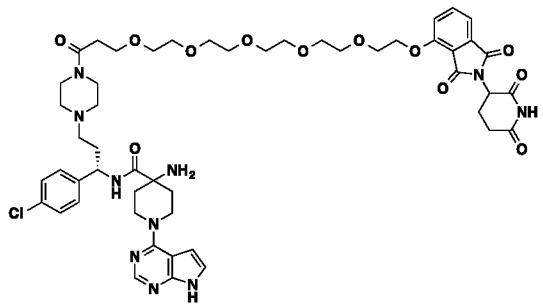
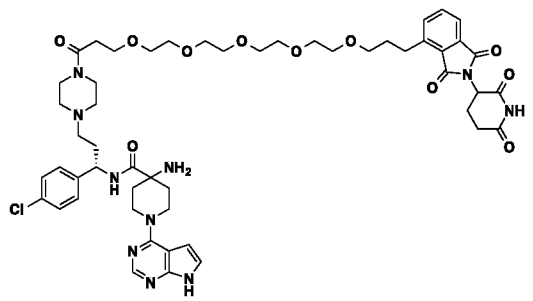
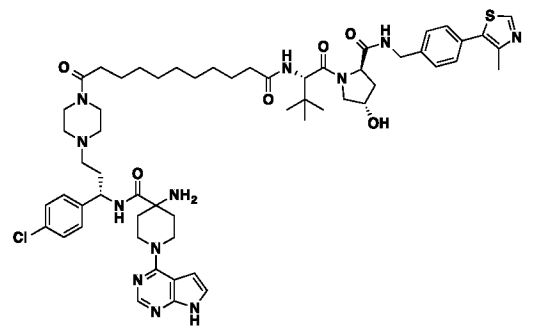
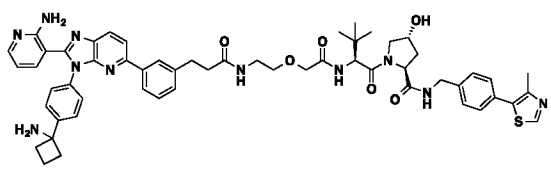
XF050-24		**4-amino-*N*-((1*S*)-1-(4-chlorophenyl)-3-(4-(4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)butanoyl)piperazin-1-yl)propyl)-1-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)piperidine-4-carboxamide**
XF050-25		**4-amino-*N*-((1*S*)-1-(4-chlorophenyl)-3-(4-(5-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)pentanoyl)piperazin-1-yl)propyl)-1-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)piperidine-4-carboxamide**
XF050-26		**4-amino-*N*-((1*S*)-1-(4-chlorophenyl)-3-(4-(6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)hexanoyl)piperazin-1-yl)propyl)-1-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)piperidine-4-carboxamide**
XF050-27		**4-amino-*N*-((1*S*)-1-(4-chlorophenyl)-3-(4-(7-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)heptanoyl)piperazin-1-yl)propyl)-1-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)piperidine-4-carboxamide**

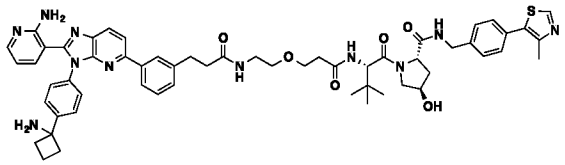
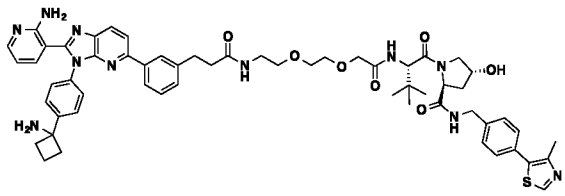
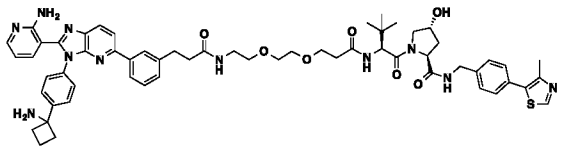
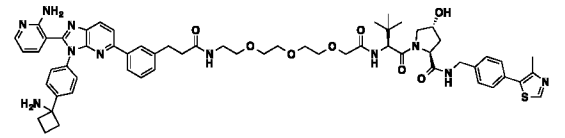
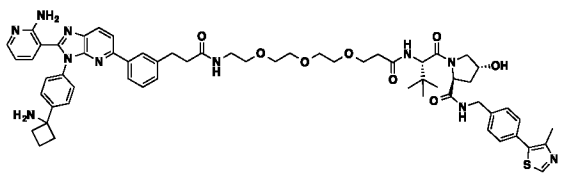
XF050-28		**4-amino-*N*-((1*S*)-1-(4-chlorophenyl)-3-(4-(8-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)octanoyl)piperazin-1-yl)propyl)-1-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)piperidine-4-carboxamide**
XF050-29		**4-amino-*N*-((1*S*)-1-(4-chlorophenyl)-3-(4-(3-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)propanoyl)piperazin-1-yl)propyl)-1-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)piperidine-4-carboxamide**
XF050-30		**4-amino-*N*-((1*S*)-1-(4-chlorophenyl)-3-(4-(3-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)propanoyl)piperazin-1-yl)propyl)-1-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)piperidine-4-carboxamide**
XF050-31		**4-amino-*N*-((1*S*)-1-(4-chlorophenyl)-3-(4-(3-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethoxy)propanoyl)piperazin-1-yl)propyl)-1-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)piperidine-4-carboxamide**

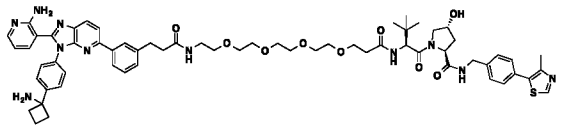
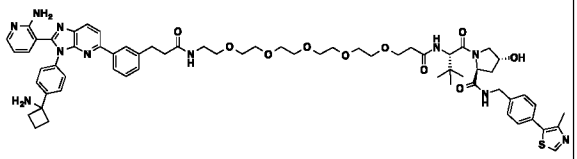
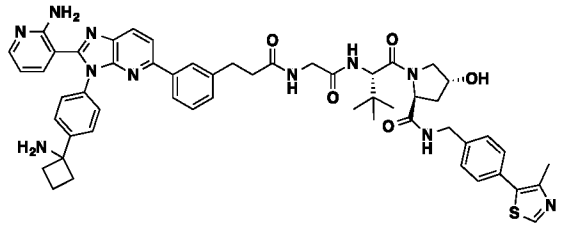
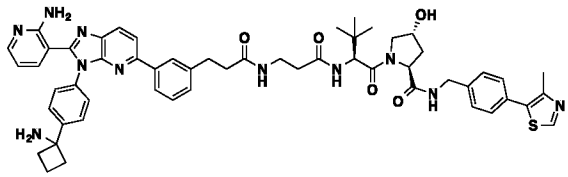
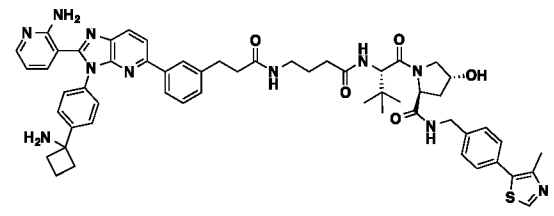
XF050-32		4-amino-*N*-((1*S*)-1-(4-chlorophenyl)-3-(4-(1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12-tetraoxapentadecan-15-oyl)piperazin-1-yl)propyl)-1-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)piperidine-4-carboxamide
XF050-33		4-amino-*N*-((1*S*)-1-(4-chlorophenyl)-3-(4-(1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12,15-pentaoxaoctadecan-18-oyl)piperazin-1-yl)propyl)-1-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)piperidine-4-carboxamide
XF050-98		N^1-(2-(((*S*)-2-(4-chlorophenyl)-3-(4-((5*R*,7*R*)-7-hydroxy-5-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-yl)piperazin-1-yl)-3-oxopropyl)amino)ethyl)-N^{12}-((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-(((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)dodecanediamide
XF050-132		3-(((*S*)-2-(4-chlorophenyl)-3-(4-((5*R*,7*R*)-7-hydroxy-5-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-yl)piperazin-1-yl)-3-oxopropyl)amino)-*N*-(8-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)amino)octyl)propanamide

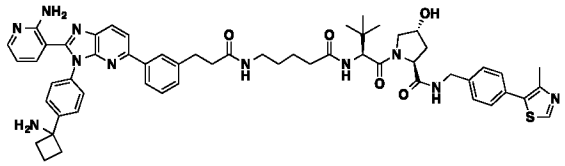
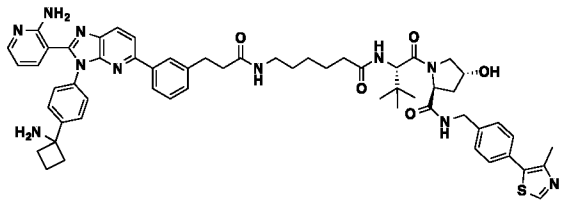
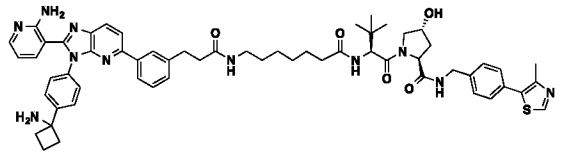
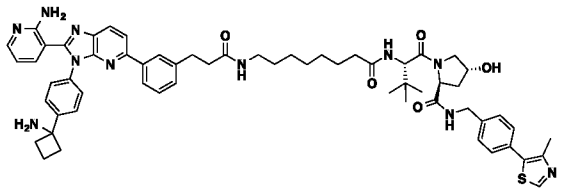
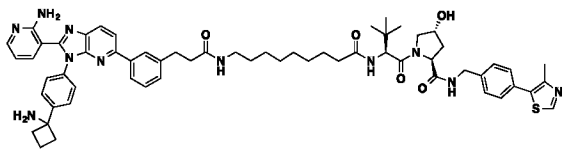
XF050-133		3-(((*S*)-2-(4-chlorophenyl)-3-(4-((5*R*,7*R*)-7-hydroxy-5-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-yl)piperazin-1-yl)-3-oxopropyl)amino)-*N*-(8-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)octyl)propanamide
XF050-134		*N*-(2-(((*S*)-2-(4-chlorophenyl)-3-(4-((5*R*,7*R*)-7-hydroxy-5-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-yl)piperazin-1-yl)-3-oxopropyl)amino)ethyl)-9-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)nonanamide
XF056-93		3-(((*S*)-2-(4-chlorophenyl)-3-(4-((5*R*,7*R*)-7-hydroxy-5-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-yl)piperazin-1-yl)-3-oxopropyl)amino)-*N*-(9-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)nonyl)propanamide
XF050-143		4-amino-*N*-((*S*)-1-(4-chlorophenyl)-3-(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-oxododecanoyl)piperazin-1-yl)propyl)-1-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)piperidine-4-carboxamide
XF050-144		4-amino-*N*-((*S*)-1-(4-chlorophenyl)-3-(4-(13-(((*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)-13-oxotridecanoyl)piperazin-1-yl)propyl)-1-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)piperidine-4-carboxamide

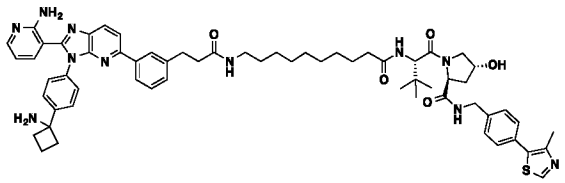
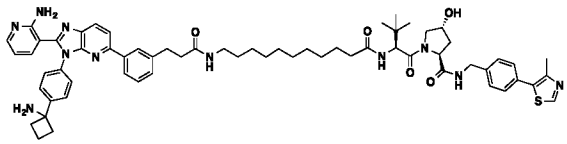
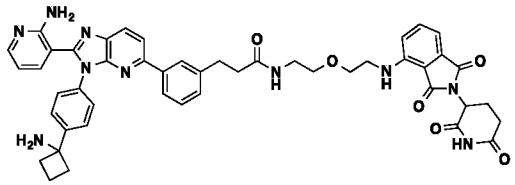
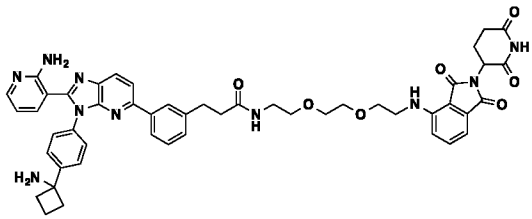
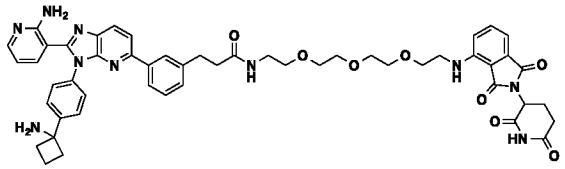
XF050-145		**4-amino-*N*-((*S*)-1-(4-chlorophenyl)-3-(4-(14-(((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-14-oxotetradecanoyl)piperazin-1-yl)propyl)-1-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)piperidine-4-carboxamide**
XF050-167		**4-amino-*N*-((*S*)-1-(4-chlorophenyl)-3-(4-(11-(((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-(((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-11-oxoundecanoyl)piperazin-1-yl)propyl)-1-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)piperidine-4-carboxamide**
XF056-33		**4-amino-*N*-((1*S*)-1-(4-chlorophenyl)-3-(4-(1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12,15,18-hexaoxahenicosan-21-oyl)piperazin-1-yl)propyl)-1-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)piperidine-4-carboxamide**
XF056-34		**4-amino-*N*-((1*S*)-1-(4-chlorophenyl)-3-(4-(1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12,15,18,21,24-octaoxaheptacosan-27-oyl)piperazin-1-yl)propyl)-1-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)piperidine-4-carboxamide**
XF056-35		**4-amino-*N*-((1*S*)-1-(4-chlorophenyl)-3-(4-(1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12,15,18,21,24,27-nonaoxatriacontan-30-oyl)piperazin-1-yl)propyl)-1-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)piperidine-4-carboxamide**

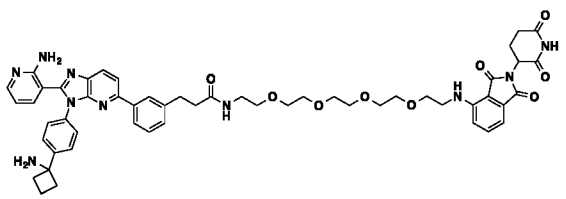
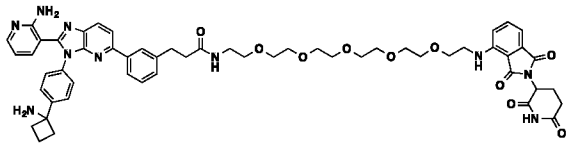
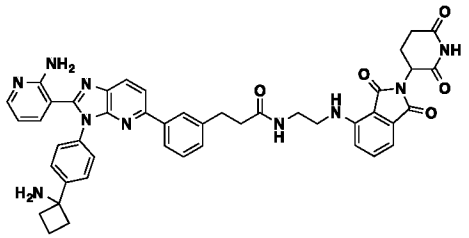
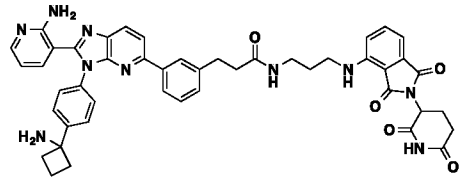
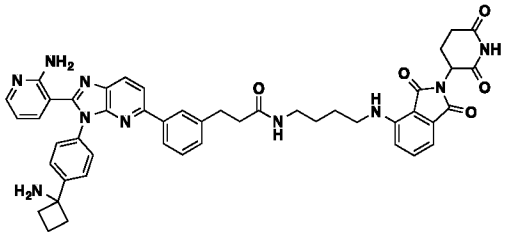
XF056-36		4-amino-*N*-((1*S*)-1-(4-chlorophenyl)-3-(4-(1-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)amino)-3,6,9,12,15-pentaoxaoctadecan-18-oyl)piperazin-1-yl)propyl)-1-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)piperidine-4-carboxamide
XF056-37		4-amino-*N*-((1*S*)-1-(4-chlorophenyl)-3-(4-(1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)-3,6,9,12,15-pentaoxaoctadecan-18-oyl)piperazin-1-yl)propyl)-1-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)piperidine-4-carboxamide
XF056-73		4-amino-*N*-((1*S*)-1-(4-chlorophenyl)-3-(4-(19-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)-4,7,10,13,16-pentaoxanonadecanoyl)piperazin-1-yl)propyl)-1-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)piperidine-4-carboxamide
XF061-10		4-amino-*N*-((*S*)-1-(4-chlorophenyl)-3-(4-(11-(((*S*)-1-((2*R*,4*S*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-11-oxoundecanoyl)piperazin-1-yl)propyl)-1-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)piperidine-4-carboxamide
XF067-1		(2*S*,4*R*)-1-((*S*)-2-(2-(2-(3-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenyl)propanamido)ethoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide

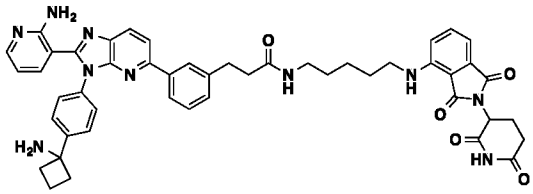
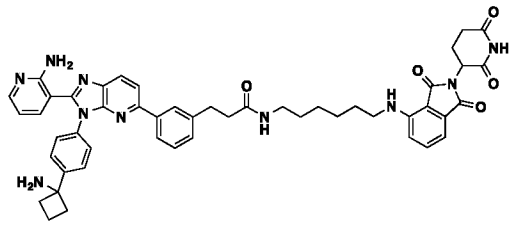
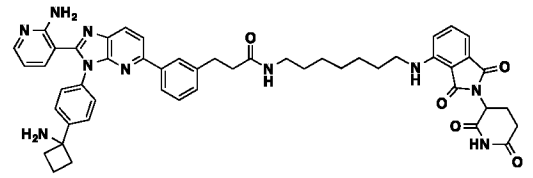
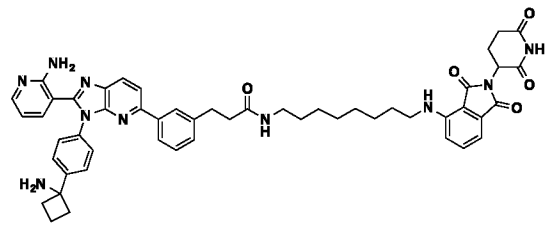
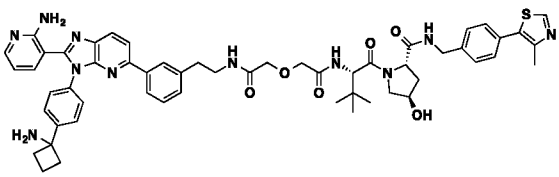
XF067-2		**(2*S*,4*R*)-1-((*S*)-2-(3-(2-(3-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenyl)propanamido)ethoxy)propanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**
XF067-3		**(2*S*,4*R*)-1-((*S*)-15-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenyl)-2-(*tert*-butyl)-4,13-dioxo-6,9-dioxa-3,12-diazapentadecanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**
XF067-4		**(2*S*,4*R*)-1-((*S*)-16-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenyl)-2-(*tert*-butyl)-4,14-dioxo-7,10-dioxa-3,13-diazahexadecanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**
XF067-5		**(2*S*,4*R*)-1-((*S*)-18-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenyl)-2-(*tert*-butyl)-4,16-dioxo-6,9,12-trioxa-3,15-diazaoctadecanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**
XF067-6		**(2*S*,4*R*)-1-((*S*)-19-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenyl)-2-(*tert*-butyl)-4,17-dioxo-7,10,13-trioxa-3,16-diazanonadecanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**

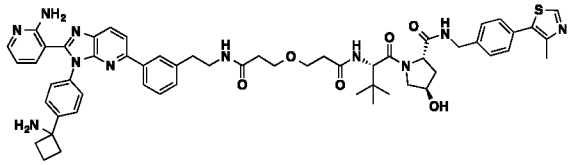
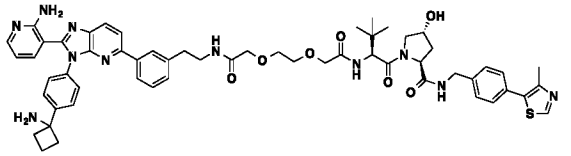
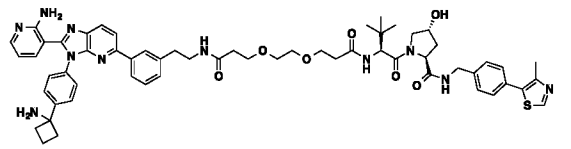
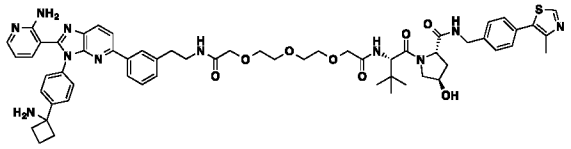
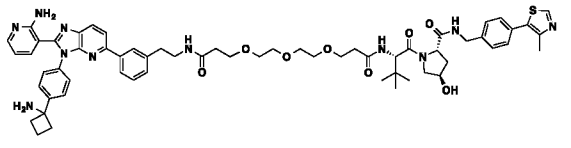
XF067-7		**(2*S*,4*R*)-1-((*S*)-22-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenyl)-2-(*tert*-butyl)-4,20-dioxo-7,10,13,16-tetraoxa-3,19-diazadocosanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**
XF067-8		**(2*S*,4*R*)-1-((*S*)-25-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenyl)-2-(*tert*-butyl)-4,23-dioxo-7,10,13,16,19-pentaoxa-3,22-diazapentacosanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**
XF067-9		**(2*S*,4*R*)-1-((*S*)-2-(2-(3-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenyl)propanamido)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**
XF067-10		**(2*S*,4*R*)-1-((*S*)-2-(3-(3-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenyl)propanamido)propanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**
XF067-11		**(2*S*,4*R*)-1-((*S*)-2-(4-(3-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenyl)propanamido)butanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**

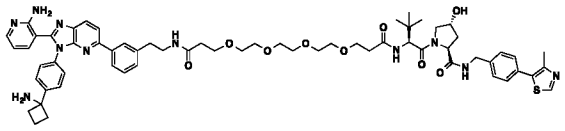
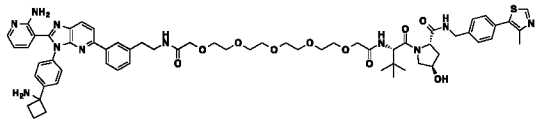
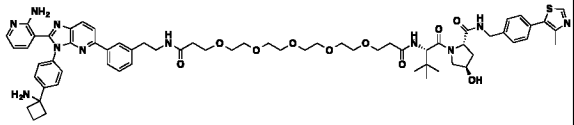
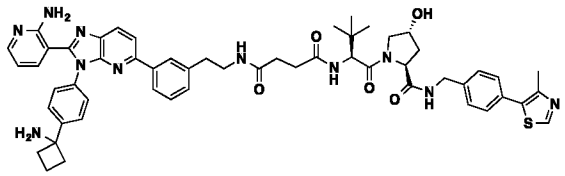
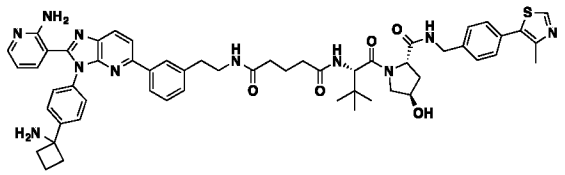
XF067-12		**(2*S*,4*R*)-1-((*S*)-2-(5-(3-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenyl)propanamido)pentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**
XF067-13		**(2*S*,4*R*)-1-((*S*)-2-(6-(3-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenyl)propanamido)hexanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**
XF067-14		**(2*S*,4*R*)-1-((*S*)-2-(7-(3-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenyl)propanamido)heptanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**
XF067-15		**(2*S*,4*R*)-1-((*S*)-2-(8-(3-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenyl)propanamido)octanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**
XF067-16		**(2*S*,4*R*)-1-((*S*)-2-(9-(3-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenyl)propanamido)nonanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**

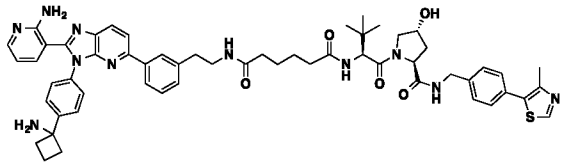
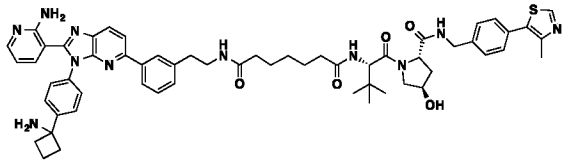
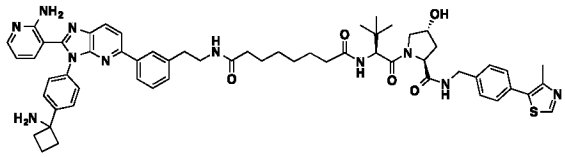
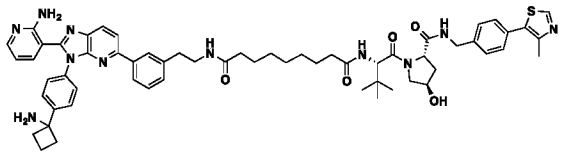
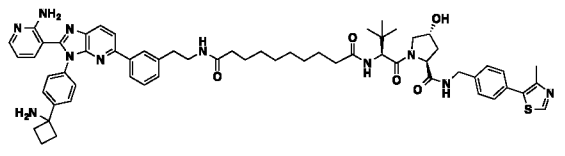
XF067-17		**(2*S*,4*R*)-1-((*S*)-2-(10-(3-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenyl)propanamido)decanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**
XF067-18		**(2*S*,4*R*)-1-((*S*)-2-(11-(3-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenyl)propanamido)undecanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**
XF067-19		**3-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenyl)-*N*-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethyl)propanamide**
XF067-20		**3-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenyl)-*N*-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethyl)propanamide**
XF067-21		**3-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenyl)-*N*-(2-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethoxy)ethyl)propanamide**

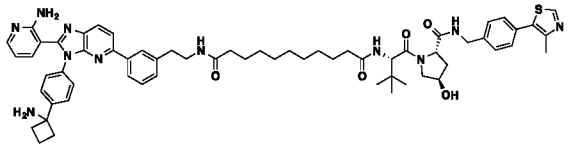
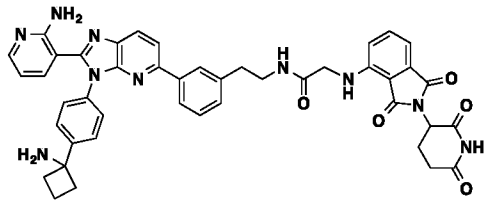
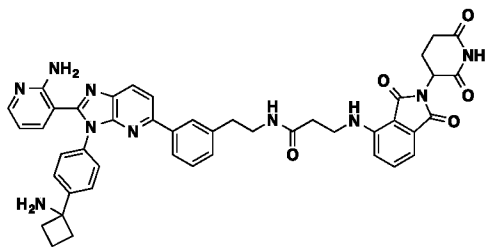
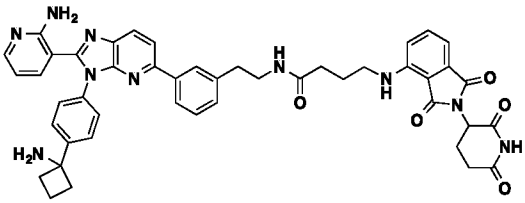
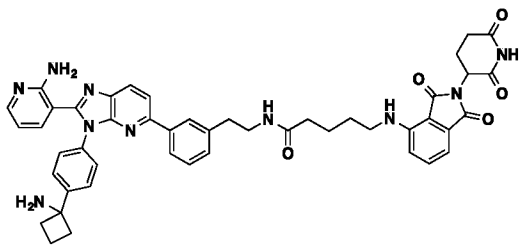
XF067-22		**3-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenyl)-*N*-(14-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12-tetraoxatetradecyl)propanamide**
XF067-23		**3-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenyl)-*N*-(17-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12,15-pentaoxaheptadecyl)propanamide**
XF067-24		**3-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenyl)-*N*-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethyl)propanamide**
XF067-25		**3-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenyl)-*N*-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propyl)propanamide**
XF067-26		**3-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenyl)-*N*-(4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)butyl)propanamide**

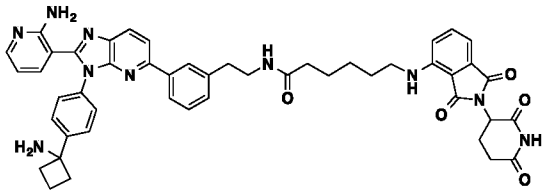
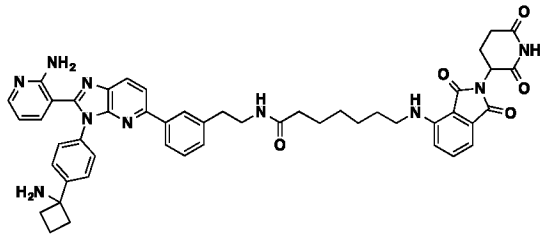
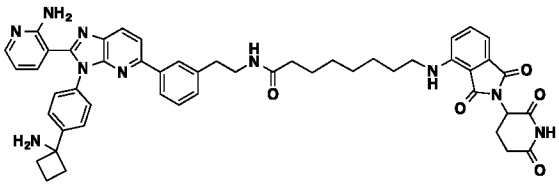
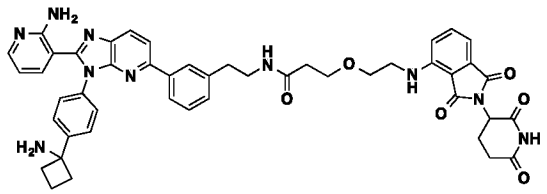
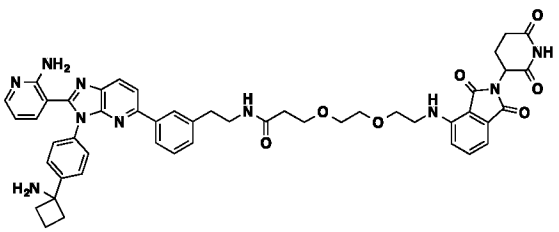
XF067-27		**3-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenyl)-*N*-(5-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)pentyl)propanamide**
XF067-28		**3-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenyl)-*N*-(6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)hexyl)propanamide**
XF067-29		**3-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenyl)-*N*-(7-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)heptyl)propanamide**
XF067-30		**3-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenyl)-*N*-(8-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)octyl)propanamide**
XF067-31		**(2*S*,4*R*)-1-((*S*)-2-(2-(2-((3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenethyl)amino)-2-oxoethoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**

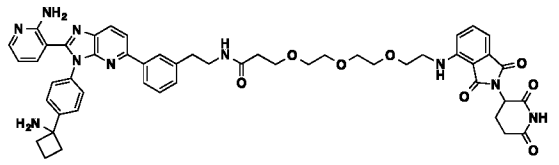
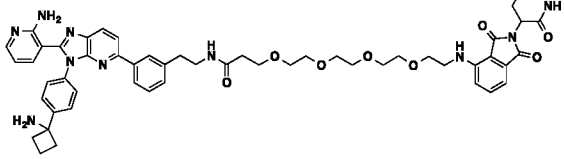
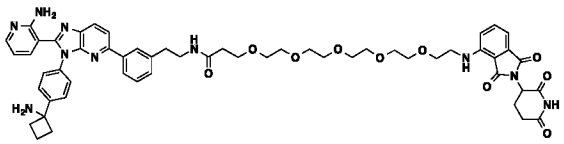
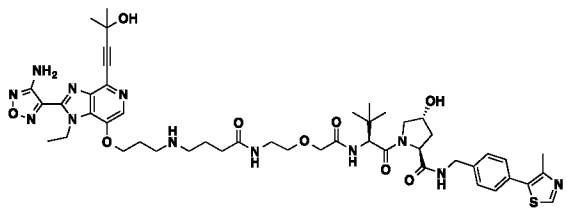
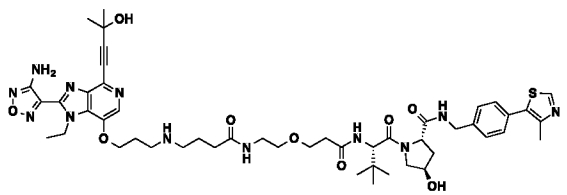
XF067-32		**(2*S*,4*R*)-1-((*S*)-2-(3-(3-((3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenethyl)amino)-3-oxopropoxy)propanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**
XF067-33		**(2*S*,4*R*)-1-((*S*)-14-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenyl)-2-(*tert*-butyl)-4,11-dioxo-6,9-dioxa-3,12-diazatetradecanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**
XF067-34		**(2*S*,4*R*)-1-((*S*)-16-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenyl)-2-(*tert*-butyl)-4,13-dioxo-7,10-dioxa-3,14-diazahexadecanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**
XF067-35		**(2*S*,4*R*)-1-((*S*)-17-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenyl)-2-(*tert*-butyl)-4,14-dioxo-6,9,12-trioxa-3,15-diazaheptadecanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**
XF067-36		**(2*S*,4*R*)-1-((*S*)-19-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenyl)-2-(*tert*-butyl)-4,16-dioxo-7,10,13-trioxa-3,17-diazanonadecanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**

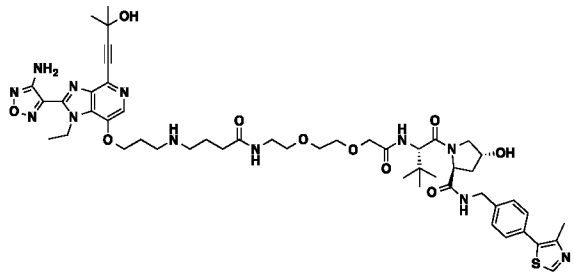
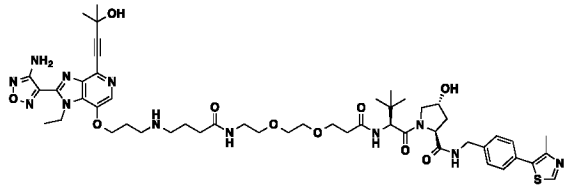
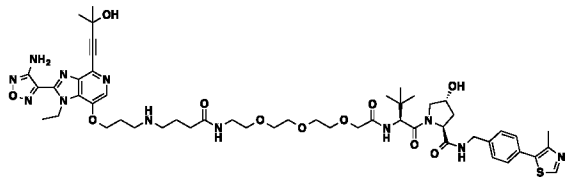
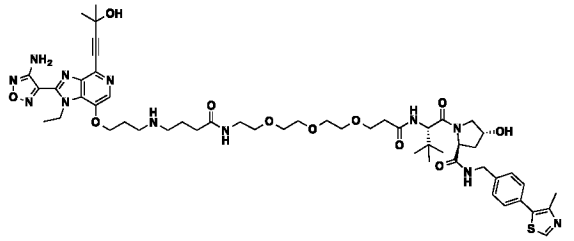
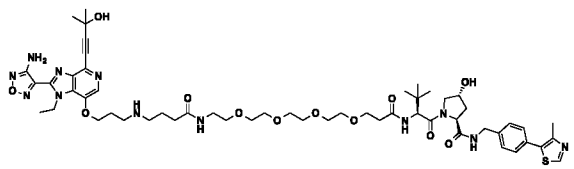
XF067-37		***N*^{1}-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenethyl)-*N*^{16}-((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-4,7,10,13-tetraoxahexadecanediamide**
XF067-38		***N*^{1}-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenethyl)-*N*^{17}-((*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-pentaoxaheptadecanediamide**
XF067-39		***N*^{1}-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenethyl)-*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**
XF067-40		***N*^{1}-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenethyl)-*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**
XF067-41		***N*^{1}-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenethyl)-*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**

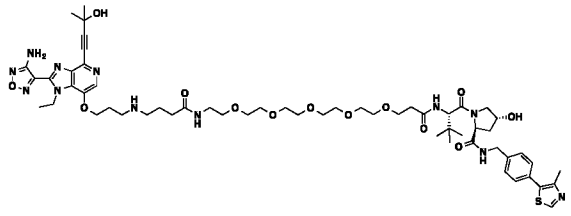
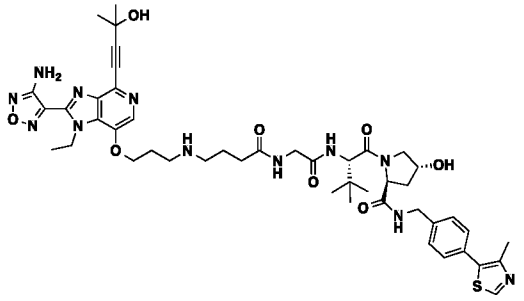
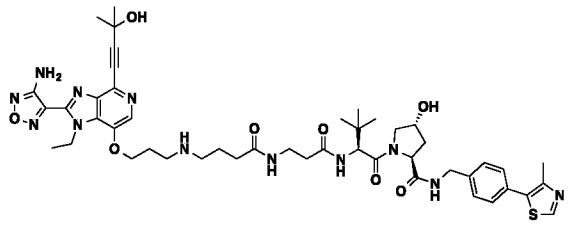
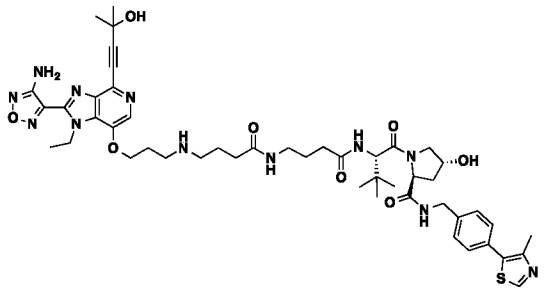
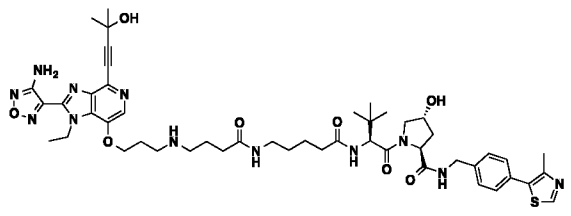
XF067-42		***N*^{1}-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenethyl)-*N*^{6}-((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)adipamide**
XF067-43		***N*^{1}-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenethyl)-*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**
XF067-44		***N*^{1}-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenethyl)-*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**
XF067-45		***N*^{1}-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenethyl)-*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**
XF067-46		***N*^{1}-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenethyl)-*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**

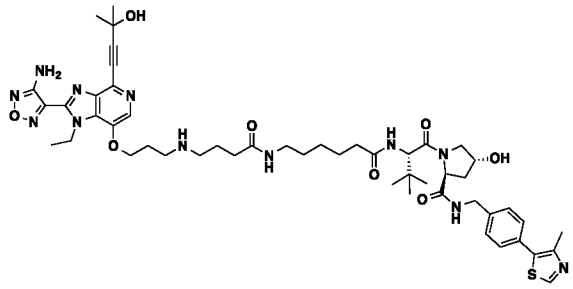
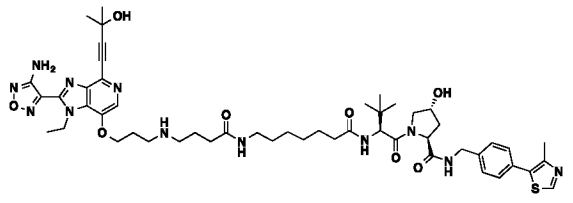
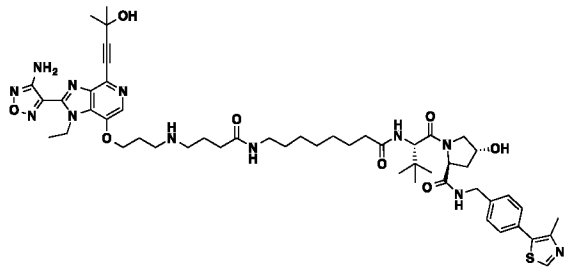
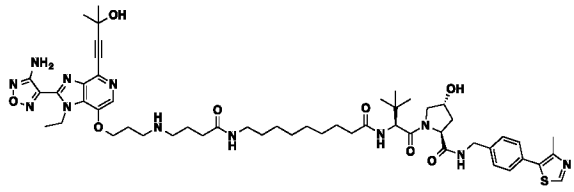
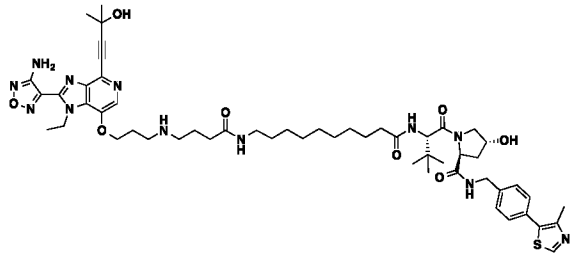
XF067-47		***N*^{1}-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenethyl)-*N*^{11}-((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)undecanediamide**
XF067-48		***N*-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenethyl)-2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)acetamide**
XF067-49		***N*-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenethyl)-3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propanamide**
XF067-50		***N*-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenethyl)-4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)butanamide**
XF067-51		***N*-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenethyl)-5-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)pentanamide**

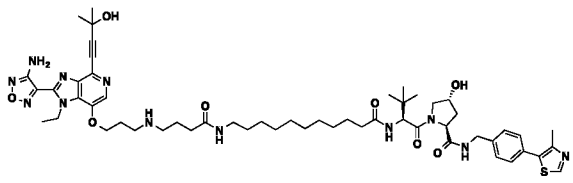
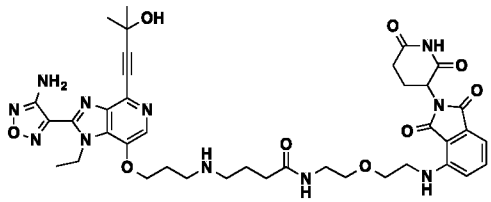
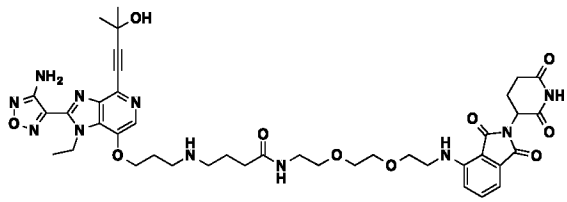
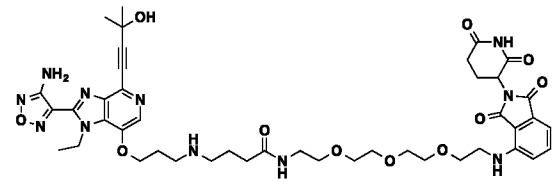
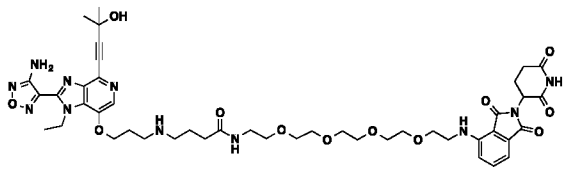
XF067-52		***N*-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenethyl)-6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)hexanamide**
XF067-53		***N*-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenethyl)-7-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)heptanamide**
XF067-54		***N*-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenethyl)-8-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)octanamide**
XF067-55		***N*-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenethyl)-3-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)propanamide**
XF067-56		***N*-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenethyl)-3-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)propanamid**

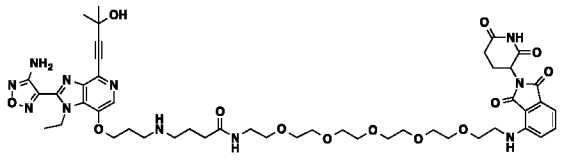
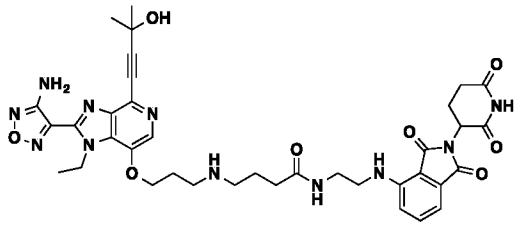
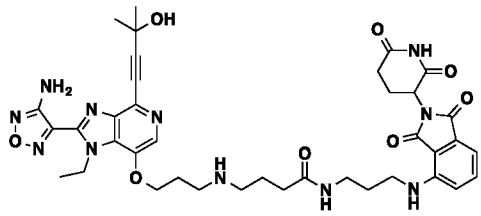
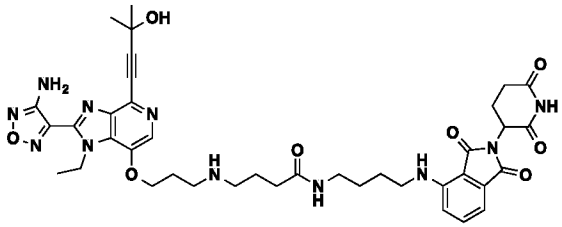
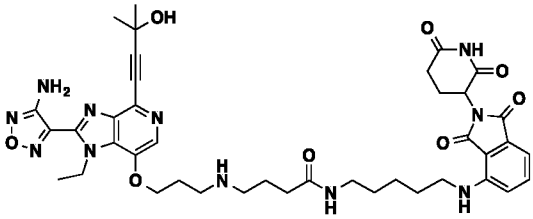
XF067-57		***N*-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenethyl)-3-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethoxy)propanamide**
XF067-58		***N*-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenethyl)-1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12-tetraoxapentadecan-15-amide**
XF067-59		***N*-(3-(3-(4-(1-aminocyclobutyl)phenyl)-2-(2-aminopyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenethyl)-1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12,15-pentaoxaoctadecan-18-amide**
XF067-84		**(2*S*,4*R*)-1-((*S*)-17-((2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-4-(3-hydroxy-3-methylbut-1-yn-1-yl)-1*H*-imidazo[4,5-*c*]pyridin-7-yl)oxy)-2-(*tert*-butyl)-4,10-dioxo-6-oxa-3,9,14-triazaheptadecanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**
XF067-85		**(2*S*,4*R*)-1-((*S*)-18-((2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-4-(3-hydroxy-3-methylbut-1-yn-1-yl)-1*H*-imidazo[4,5-*c*]pyridin-7-yl)oxy)-2-(*tert*-butyl)-4,11-dioxo-7-oxa-3,10,15-triazaoctadecanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**

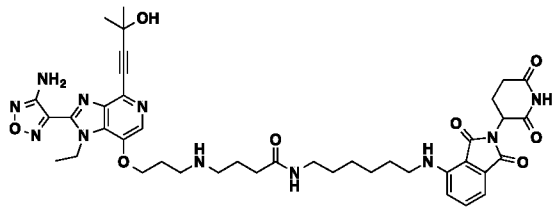
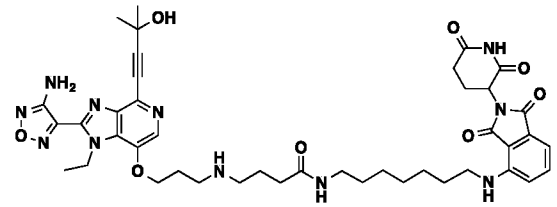
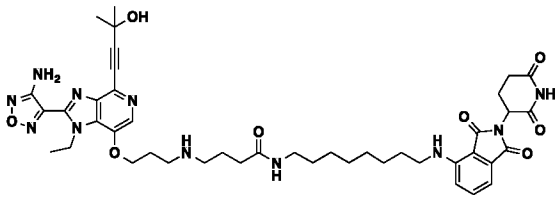
XF067-86		**(2*S*,4*R*)-1-((*S*)-20-((2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-4-(3-hydroxy-3-methylbut-1-yn-1-yl)-1*H*-imidazo[4,5-*c*]pyridin-7-yl)oxy)-2-(*tert*-butyl)-4,13-dioxo-6,9-dioxa-3,12,17-triazaicosanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**
XF067-87		**(2*S*,4*R*)-1-((*S*)-21-((2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-4-(3-hydroxy-3-methylbut-1-yn-1-yl)-1*H*-imidazo[4,5-*c*]pyridin-7-yl)oxy)-2-(*tert*-butyl)-4,14-dioxo-7,10-dioxa-3,13,18-triazahenicosanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**
XF067-88		**(2*S*,4*R*)-1-((*S*)-23-((2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-4-(3-hydroxy-3-methylbut-1-yn-1-yl)-1*H*-imidazo[4,5-*c*]pyridin-7-yl)oxy)-2-(*tert*-butyl)-4,16-dioxo-6,9,12-trioxa-3,15,20-triazatricosanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**
XF067-89		**(2*S*,4*R*)-1-((*S*)-24-((2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-4-(3-hydroxy-3-methylbut-1-yn-1-yl)-1*H*-imidazo[4,5-*c*]pyridin-7-yl)oxy)-2-(*tert*-butyl)-4,17-dioxo-7,10,13-trioxa-3,16,21-triazatetracosanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**
XF067-90		**(2*S*,4*R*)-1-((*S*)-27-((2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-4-(3-hydroxy-3-methylbut-1-yn-1-yl)-1*H*-imidazo[4,5-*c*]pyridin-7-yl)oxy)-2-(*tert*-butyl)-4,20-dioxo-7,10,13,16-tetraoxa-3,19,24-triazaheptacosanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**

XF067-91		**(2*S*,4*R*)-1-((*S*)-30-((2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-4-(3-hydroxy-3-methylbut-1-yn-1-yl)-1*H*-imidazo[4,5-*c*]pyridin-7-yl)oxy)-2-(*tert*-butyl)-4,23-dioxo-7,10,13,16,19-pentaoxa-3,22,27-triazatriacontanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**
XF067-92		**(2*S*,4*R*)-1-((*S*)-2-(2-(4-((3-((2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-4-(3-hydroxy-3-methylbut-1-yn-1-yl)-1*H*-imidazo[4,5-*c*]pyridin-7-yl)oxy)propyl)amino)butanamido)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**
XF067-93		**(2*S*,4*R*)-1-((*S*)-2-(3-(4-((3-((2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-4-(3-hydroxy-3-methylbut-1-yn-1-yl)-1*H*-imidazo[4,5-*c*]pyridin-7-yl)oxy)propyl)amino)butanamido)propanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**
XF067-94		**(2*S*,4*R*)-1-((*S*)-2-(4-(4-((3-((2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-4-(3-hydroxy-3-methylbut-1-yn-1-yl)-1*H*-imidazo[4,5-*c*]pyridin-7-yl)oxy)propyl)amino)butanamido)butanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**
XF067-95		**(2*S*,4*R*)-1-((*S*)-2-(5-(4-((3-((2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-4-(3-hydroxy-3-methylbut-1-yn-1-yl)-1*H*-imidazo[4,5-*c*]pyridin-7-yl)oxy)propyl)amino)butanamido)pentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**

XF067-96		**(2*S*,4*R*)-1-((*S*)-2-(6-(4-((3-((2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-4-(3-hydroxy-3-methylbut-1-yn-1-yl)-1*H*-imidazo[4,5-*c*]pyridin-7-yl)oxy)propyl)amino)butanamido)hexanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**
XF067-97		**(2*S*,4*R*)-1-((*S*)-2-(7-(4-((3-((2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-4-(3-hydroxy-3-methylbut-1-yn-1-yl)-1*H*-imidazo[4,5-*c*]pyridin-7-yl)oxy)propyl)amino)butanamido)heptanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**
XF067-98		**(2*S*,4*R*)-1-((*S*)-2-(8-(4-((3-((2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-4-(3-hydroxy-3-methylbut-1-yn-1-yl)-1*H*-imidazo[4,5-*c*]pyridin-7-yl)oxy)propyl)amino)butanamido)octanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**
XF067-99		**(2*S*,4*R*)-1-((*S*)-2-(9-(4-((3-((2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-4-(3-hydroxy-3-methylbut-1-yn-1-yl)-1*H*-imidazo[4,5-*c*]pyridin-7-yl)oxy)propyl)amino)butanamido)nonanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**
XF067-100		**(2*S*,4*R*)-1-((*S*)-2-(10-(4-((3-((2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-4-(3-hydroxy-3-methylbut-1-yn-1-yl)-1*H*-imidazo[4,5-*c*]pyridin-7-yl)oxy)propyl)amino)butanamido)decanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**

XF067-101		**(2*S*,4*R*)-1-((*S*)-2-(11-(4-((3-((2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-4-(3-hydroxy-3-methylbut-1-yn-1-yl)-1*H*-imidazo[4,5-*c*]pyridin-7-yl)oxy)propyl)amino)butanamido)undecanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**
XF067-102		**4-((3-((2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-4-(3-hydroxy-3-methylbut-1-yn-1-yl)-1*H*-imidazo[4,5-*c*]pyridin-7-yl)oxy)propyl)amino)-*N*-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethyl)butanamide**
XF067-103		**4-((3-((2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-4-(3-hydroxy-3-methylbut-1-yn-1-yl)-1*H*-imidazo[4,5-*c*]pyridin-7-yl)oxy)propyl)amino)-*N*-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethyl)butanamide**
XF067-104		**4-((3-((2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-4-(3-hydroxy-3-methylbut-1-yn-1-yl)-1*H*-imidazo[4,5-*c*]pyridin-7-yl)oxy)propyl)amino)-*N*-(2-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethoxy)ethyl)butanamide**
XF067-105		**4-((3-((2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-4-(3-hydroxy-3-methylbut-1-yn-1-yl)-1*H*-imidazo[4,5-*c*]pyridin-7-yl)oxy)propyl)amino)-*N*-(14-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12-tetraoxatetradecyl)butanamide**

XF067-106		**4-((3-((2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-4-(3-hydroxy-3-methylbut-1-yn-1-yl)-1*H*-imidazo[4,5-*c*]pyridin-7-yl)oxy)propyl)amino)-*N*-(17-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12,15-pentaoxaheptadecyl)butanamide**
XF067-107		**4-((3-((2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-4-(3-hydroxy-3-methylbut-1-yn-1-yl)-1*H*-imidazo[4,5-*c*]pyridin-7-yl)oxy)propyl)amino)-*N*-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethyl)butanamide**
XF067-108		**4-((3-((2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-4-(3-hydroxy-3-methylbut-1-yn-1-yl)-1*H*-imidazo[4,5-*c*]pyridin-7-yl)oxy)propyl)amino)-*N*-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propyl)butanamide**
XF067-109		**4-((3-((2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-4-(3-hydroxy-3-methylbut-1-yn-1-yl)-1*H*-imidazo[4,5-*c*]pyridin-7-yl)oxy)propyl)amino)-*N*-(4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)butyl)butanamide**
XF067-110		**4-((3-((2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-4-(3-hydroxy-3-methylbut-1-yn-1-yl)-1*H*-imidazo[4,5-*c*]pyridin-7-yl)oxy)propyl)amino)-*N*-(5-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)pentyl)butanamide**

XF067-111		**4-((3-((2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-4-(3-hydroxy-3-methylbut-1-yn-1-yl)-1*H*-imidazo[4,5-*c*]pyridin-7-yl)oxy)propyl)amino)-*N*-(6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)hexyl)butanamide**
XF067-112		**4-((3-((2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-4-(3-hydroxy-3-methylbut-1-yn-1-yl)-1*H*-imidazo[4,5-*c*]pyridin-7-yl)oxy)propyl)amino)-*N*-(7-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)heptyl)butanamide**
XF067-113		**4-((3-((2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-4-(3-hydroxy-3-methylbut-1-yn-1-yl)-1*H*-imidazo[4,5-*c*]pyridin-7-yl)oxy)propyl)amino)-*N*-(8-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)octyl)butanamide**

As used herein, in case of discrepancy between the structure and chemical name provided for a particular compound, the structure shall control.

Example 167. AKT degraders reduced AKT protein levels in BT474 cells (Fig. 1).

BT474 cells were treated with DMSO or indicated compounds at 1 μM, 5 μM, or 10 μM for 24 h. The Western blot results showed that various AKT degraders significantly reduced AKT protein levels at 1 μM, while the AKT activity inhibitor GDC0068 had no effect on AKT protein levels but increased pAKT levels.

Example 168. AKT degraders reduced AKT protein levels in BT474 cells in a time-dependent manner (Fig. 2).

BT474 cells were treated with DMSO or the indicated compounds at a fixed concentration of 1 μM for 1, 2, 3, 6, 12, or 24 h. The maximum degradation of AKT and inhibition of downstream signaling were observed after 12 h of treatment.

Example 169. AKT degraders reduced AKT protein levels in BT474 cells (Fig. 3).

BT474 cells were treated with DMSO or indicated compounds at 1 μM, 5 μM, or 10 μM for 24 h. The Western blot results showed that various AKT degraders significantly reduced AKT protein levels at 1 μM, while the AKT activity inhibitor AZD5363 had no effect on AKT protein levels but increased pAKT levels.

Example 170. AKT degraders reduced AKT protein levels in BT474 cells (Fig. 4).

BT474 cells were treated with DMSO or indicated compounds at 0.01 μM, 0.03 μM, 0.1 μM, 0.3 μM, or 1 μM for 24 h. The Western blot results showed that various AKT degraders significantly reduced AKT protein levels at 1 μM, while the AKT activity inhibitor AZD5363 or GDC0068 had no effect on AKT protein levels but increased pAKT levels (Fig. 4A). PC-3 cells, MDA-MB-468 cells, U87MG cells were treated with DMSO or indicated compounds at 0.3 μM, 1 μM, 3 μM, or 10 μM for 24 h. The Western blot results showed that AKT degrader XF050-21 significantly reduced AKT protein levels in these cell lines, while the AKT activity inhibitor AZD5363 had no effect on AKT protein levels but increased pAKT levels (Fig. 4B).

Example 171. AKT degraders reduced AKT protein levels in BT474 cells and PC-3 cells in a time-dependent manner (Fig. 5).

BT474 cells and PC-3 cells were treated with DMSO or the indicated compounds at a fixed concentration of 1 μM for 1, 2, 4, 8, 12, or 24 h. The maximum degradation of AKT and inhibition of downstream signaling were observed after 24 h of treatment in BT474 cells (Fig. 5A). The maximum degradation of AKT and inhibition of downstream signaling were observed after 12 h of treatment in PC-3 cells (Fig. 5B).

Example 172. AKT degraders reduced AKT protein levels through E3 ubiquitin ligase (Fig. 6).

BT474 Cells were pre-treated with DMSO, VHL-1 (1 mM), MLN4924 (1 μM), MG-132 (20 μM) or AZD5363 (1 μM) for 2 h, before being treated with the 1 μM XF050-21 compounds

for 24 h. XF050-21 induced AKT protein degradation is mediated by hijacking the E3 ubiquitin ligase VHL, and it can be rescued by VHL-1, MLN4924, MG-132 or AZD5363 pretreatment.

Example 173: AKT degraders inhibit cancer cell proliferation (Fig. 7)

1-3 × 10^3 PC-3 or MDA-MB-468 cells were seeded in 96-well plates in triplicates and treated at the indicated compound concentrations. Cells were monitored using the IncuCyte® live cell imaging system (Essen Bioscience™, Ann Arbor, MI) which was placed in a cell culture incubator operated at 37 °C and 5% CO_2. Cell confluence was determined using calculations derived from phase-contrast images. The concentration for 50% of maximal inhibition of cell proliferation (GI50) values were determined by fitting to a standard four-parameter logistic using GraphPad Prism® v5. Graphs depicting the GI_{50} of AKT degraders XF050-21 for these cancer cell lines are shown in Figures 7.

Example 174. AKT Degraders inhibit cancer cell proliferation (Fig. 8).

PC-3, MDA-MB-468, HCC1143, and MDA-MB-231 cells were treated with DMSO, AZD5363 or XF050-21 at 0.1 μM, 0.3 μM, 1 μM, 3 μM, or 10 μM for 2 weeks. Cells were stained with Crystal Violet and the Bright field imaging indicated that XF050-21 was more effective in inhibiting cancer cell proliferation than AZD5363 at the same concentration in these cells.

Example 175. Combination treatment of an AKT degrader and an mTOR inhibitor reduced AKT protein levels and inhibited downstream signaling in BT474 cells (Fig. 9).

BT474 cells were treated with DMSO or indicated compounds combination at indicated concentration for 24 h. The Western blot results showed that the combination treatment of AKT degrader (XF050-21 or XF042-170) and an mTOR inhibitor (Torin1 or Rapamycin) reduced AKT protein levels and inhibited downstream signaling in BT474 cells.

Example 176. XF050-21 was bioavailable in mice (Fig. 10).

Standard PK studies were conducted using male Swiss Albino mice. A single 75 mg/kg intraperitoneal (IP) injection of XF050-21 was evaluated. Plasma concentrations of XF050-21 reported at each of the six time points (30 min, 1 h, 2 h, 4 h, 8 h, and 12 h post dosing) are the average values from 3 test animals. There were no abnormal clinical observations noted during the course of the study.

Example 177. AKT degraders reduced AKT protein levels in PC-3 cells (Fig. 11).

PC-3 cells were treated with DMSO or indicated compounds at 1 μM for 24 h. The Western blot results showed that various AKT degraders significantly reduced AKT protein levels at 1 μM, while the AKT activity inhibitor ARQ-092 had no effect on reducing AKT protein levels.

Example 178. AKT degraders reduced AKT protein levels in PC-3 cells (Fig. 12).

PC-3 cells were treated with DMSO or indicated compounds at 1 μM for 24 h. The Western blot results showed that various AKT degraders significantly reduced AKT protein levels at 1 μM, while the AKT activity inhibitor GSK690693 had no effect on reducing AKT protein levels.

Materials And Methods:

General Chemistry Methods

HPLC spectra for all compounds were acquired using an Agilent 1200 Series system with DAD detector. Chromatography was performed on a 2.1×150 mm Zorbax 300SB-C18 5 μm column with water containing 0.1% formic acid as solvent A and acetonitrile containing 0.1% formic acid as solvent B at a flow rate of 0.4 ml/min. The gradient program was as follows: 1% B (0−1 min), 1−99% B (1−4 min), and 99% B (4−8 min). High-resolution mass spectra (HRMS) data were acquired in positive ion mode using an Agilent G1969A API-TOF with an electrospray ionization (ESI) source. Nuclear Magnetic Resonance (NMR) spectra were acquired on a Bruker DRX-600 spectrometer with 600 MHz for proton (^{1}H NMR) and 150 MHz for carbon (^{13}C NMR); chemical shifts are reported in (δ). Preparative HPLC was performed on Agilent Prep 1200 series with UV detector set to 254 nm. Samples were injected onto a Phenomenex Luna 250 x 30 mm, 5 μm, C_{18} column at room temperature. The flow rate was 40 ml/min. A linear gradient was used with 10% (or 50%) of MeOH (A) in H_2O (with 0.1 % TFA) (B) to 100% of MeOH (A). HPLC was used to establish the purity of target compounds. All final compounds had > 95% purity using the HPLC methods described above.

Cell Culture and Treatment

PC-3, U87MG, HCC1143, MDA-MB-231, MDA-MB-468, BT474 and MCF-7 cell lines were purchased from ATCC. Cell lines were regularly tested in the lab for mycoplasma. All cells were cultured at 37°C and 5% CO2. PC-3, U87MG, MDA-MB-231, MCF-7 and BT474 cells were cultured in 1X DMEM (Corning, 10-013-CV) with 10% fetal bovine serum

(Atlanta Biologicals S11150) and 1X Penicillin/Streptomycin. HCC1143 cells were cultured in RPMI (Corning, 10-040-CV) medium with 10% fetal bovine serum (Atlanta Biologicals S11150) and 1X Penicillin/Streptomycin. Cells were split using 0.05% or 0.25% trypsin (Corning 25-051-Cl or 25-053-Cl, respectively) before they reached full confluence and media was changed every 3-4 days. Cells were treated with compounds individually at different concentrations for 24 hrs. Cells were treated with DMSO, VHL, or PML alone as controls.

Immunoblotting

Cells were lysed in 2X sample buffer (125 mM Tris-HCl at pH 6.8, 10% βME, 2% SDS, 20% glycerol, 0.05% Bromophenol Blue, 8 M urea). Protein lysates were loaded into 4-12% Bis-Tris gels and resolved by electrophoresis. Samples were then blotted on PVDF membrane (Millipore IPVH00010) using the wet transfer technique (Invitrogen). Membranes were blocked in 5% milk-TBST for 1 hour, washed in TBST for 10 min, and incubated in primary antibody in 5% milk-TBST or 5% BSA-TBST at 4 °C for 16 h. Membranes were rinsed (3 x 6 min) in TBST and incubated in horseradish peroxidase-conjugated secondary antibodies in 5% milk-TBST for 1 hour and rinsed again in TBST (3 x 6 min). Membranes were visualized using the chemiluminescence system (Thermo 34080, 37075) on autoradiography film (Denville E3018). Primary Antibodies: β-actin (Sigma A5316), p-AKT (Ser473 CST-9721), total AKT (CST-9272), p-S6 (Ser240/244, CST-5364), p-PRAS40 (Thr246, CST-2997). Secondary Antibodies: Mouse (Thermo 31432), Rabbit (Thermo 31460).

Cell Viability Assay

Cells were cultured for 12 – 17 days in the presence of different compounds. Media with compound was replenished every two days. At the end of the experiment, media was aspirated and viable cells were stained with 0.5% crystal violet dye.

Proliferation and apoptosis assays

Experiments were carried out in 96-well plates in triplicates. A total of $1–3 \times 10^3$ cells per well were grown in the presence of 1 μM of AZD5363 (Selleckchem), 1 μM of selected degrader compounds. Cells were then monitored for 3 – 4 days using the IncuCyte live cell imaging system (Essen BioScience, Ann Arbor, MI, USA), which was placed in a cell culture incubator operated at 37 °C and 5% CO_2. Cell confluence was determined using calculations derived from phase-contrast images. For measurement of cell death DRAQ7 (Cell Signaling # 7406) at

1.5 μM was included in the medium and apoptotic red counts were measured in IncuCyteTM FLR automated incubator microscope.

Xenograft studies

Thirty male immunocompromised nu/nu mice (The Jackson Laboratory) was engrafted with PC-3 human prostate cancer cells that have never been passed through animals and was used under blood-born pathogen laboratory procedures. After tumor volumes reach ~100 mm^3, 3 treatment arms (10 animals per group) were administrated with vehicle control, AZD5363, or a selected degrader compound daily for 3-4 weeks via intraperitoneal (IP) injections. Tumor volume was calculated as follows: tumor size (mm^3) = (longer measurement × shorter measurement^2) × 0.5. Tumor sizes were recorded every other day over the course of the studies. Engraftment and monitoring of tumor growth and toxicity in mice were be performed. Treatments would be discontinued if toxicity or distress is encountered. All procedures involving mice and experimental protocols (LA13-00024) were approved by the Institutional Animal Care and Use Committee (IACUC) of Icahn School of Medicine at Mount Sinai (ISMMS).

Immunohistochemistry

Paraffin sections were dewaxed as previously described. If necessary, antigen retrieval was performed, typically, the sections were boiled in 0.01M sodium citrate, pH 6.0, 0.05% Tween-20 twice for 10min, and then cooled at room temperature for 20min. After that, the sections were washed with dd H_2O for 3 times of 5min each and then washed with PBS for 5min. HRP conjugated secondary antibody was used to detect the signal. Endogenous HRP was blocked with 3% H_2O_2 in PBS or methanol for 10min. Then the slide was washed in PBS for 3times of 5mins each. At this time, the section on slide was circled with a PAP pen. For cryosections, the sections were warmed from -80 °C freezer to room temperature and dried at room temperature for 30mins or 15mins at 50 °C. Then sections were fixed in ice-cold acetone for 5min on ice, and then air dried at room temperature for 30mins, followed by washing with 1x PBS for 5mins. Afterwards, the endogenous HRP was blocked with 3% H_2O_2 if necessary. The sections were washed again with PBS for 3 times of 5mins each before circled with a PAP pen.

Statistics

No statistical methods were used to determine sample size, and experiments were not randomized. The experimenters were not blinded. Aside from traditional Mann-Whitney (non-

parametric), Spearman correlation test (non-parametric), student t-tests (parametric) to compare two data sets, and Chi-squared test (non-parametric), parametric statistical methods were used in order to make appropriate multiple comparisons of repeated measures of data (following 1-way or 2-way ANOVA). Graphpad Prism was used to make these simple predetermined statistical comparisons. Tukey's Multiple Comparisons Correction: Used for making all possible pairwise comparisons in a data set. Dunnett's Multiple Comparisons Correction: Used for comparing all samples to a control sample, but not for comparing the non-control samples to one another. Sidak's Multiple Comparisons Correction: Used when specific multiple comparisons are pre-selected. Fischer's Exact Test: Used to analyze items in a contingency table.

OTHER EMBODIMENTS

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

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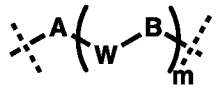
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What is claimed is:

What is claimed is:

1. A bivalent compound comprising a serine threonine kinase AKT ligand conjugated to a degradation/disruption tag through a linker, said linker selected from the group consisting of:

a.  FORMULA 9, wherein

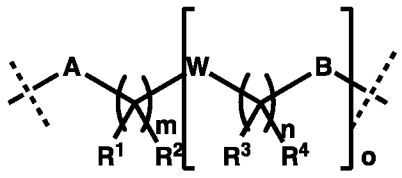
A, W and B, at each occurrence, are independently selected from null, or bivalent moiety selected from R'-R'', R'COR'', R'CO_2R'', R'C(O)NR''R^1, R'C(S)NR''R^1, R'OR'', R'OC(O)R'', R'OC(O)OR'', R'OCONR^{1}R'', R'SR'', R'SOR'', R'SO_2R'', R'SO_2NR''R^1, R'NR''R^1, R'NR^{1}COR'', R'NR^{1}C(O)OR'', R'NR^{1}CONR''R^2, R'NR^{1}C(S)R'', R'NR^{1}S(O)R'', R'NR^{1}S(O)$_2$R'', and R'NR^{1}S(O)$_2$NR^{2}R'', wherein

R' and R'' are independently selected from null, 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^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 9A, 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 3-10 membered cycloalkoxy, optionally substituted 3-10 membered carbocyclylamino, optionally substituted 4-8 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)NR''R^1, R'C(S)NR''R^1, R'OR'', R'OC(O)R'', R'OC(O)OR'', R'OCONR^{1}R'', R'SR'', R'SOR'', R'SO_2R'', R'SO_2NR''R^1, R'NR''R^1, R'NR^{1}COR'', R'NR^{1}C(O)OR'', R'NR^{1}CONR''R^2, R'NR^{1}C(S)R'', R'NR^{1}S(O)R'', R'NR^{1}S(O)$_2$R'', and R'NR^{1}S(O)$_2$NR^{2}R'', wherein

R' and R'' are independently selected from null, 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;

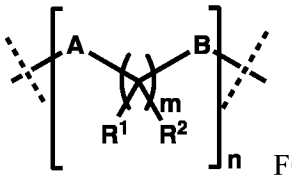
R^5 and R^6 are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxyalkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-C_8 hydroxyalkyl, 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 9B, 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 3-10 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''R^1, R'C(S)NR''R^1, R'OR'', R'OC(O)R'', R'OC(O)OR'', R'OCONR^{1}R'', R'SR'', R'SOR'', R'SO_2R'', R'SO_2NR''R^1, R'NR''R^1,

$R'NR^1COR''$, $R'NR^1C(O)OR''$, $R'NR^1CONR''R^2$, $R'NR^1C(S)R''$, $R'NR^1S(O)R''$, $R'NR^1S(O)_2R''$, and $R'NR^1S(O)_2NR^2R''$, wherein

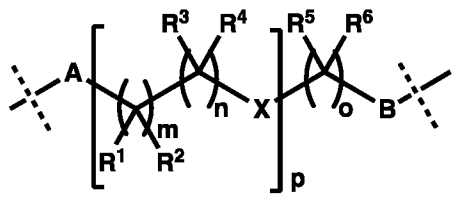
R' and R'' are independently selected from null, or a moiety comprising of optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 hydroxyalkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted 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^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;

each m is 0 to 15; and

n is 0 to 15;

d. 

FORMULA 9C, wherein

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

R^1, R^2, R^3, R^4, R^5, R^6, and R^7, 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 3-10 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)NR''R^1, R'C(S)NR''R^1, R'OR'', R'OC(O)R'', R'OC(O)OR'', R'OCONR^{1}R'', R'SR'', R'SOR'', R'SO_2R'', R'SO_2NR''R^1, R'NR''R^1, R'NR^{1}COR'', R'NR^{1}C(O)OR'', R'NR^{1}CONR''R^2, R'NR^{1}C(S)R'', R'NR^{1}S(O)R'', R'NR^{1}S(O)$_2$R'', and R'NR^{1}S(O)$_2$NR^{2}R'', wherein

R' and R'' are independently selected from null, 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^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;

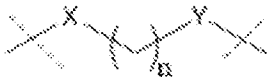
m, at each occurrence, is 0 to 15;

n, at each occurrence, is 0 to 15;

o is 0 to 15; and

p is 0 to 15;

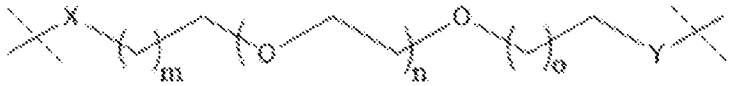
e. the linker comprises one or more rings selected from the group consisting of a 3 to 13 membered ring, a 3 to 13 membered fused ring, a 3 to 13 membered bridged ring, and a 3 to 13 membered spiro ring;

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; and

h.  FORMULA C, wherein

X is C=O or CH_2,

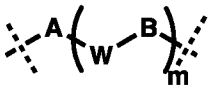
Y is C=O or CH_2,

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=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 9, 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)NR''R^1, R'C(S)NR''R^1, R'OR'', R'OC(O)R'', R'OC(O)OR'', R'OCONR^{1}R'', R'SR'', R'SOR'', R'SO_2R'', R'SO_2NR''R^1, R'NR''R^1, R'NR^{1}COR'', R'NR^{1}C(O)OR'', R'NR^{1}CONR''R^2, R'NR^{1}C(S)R'', R'NR^{1}S(O)R'', R'NR^{1}S(O)$_2$R'', and R'NR^{1}S(O)$_2$NR^{2}R'', wherein

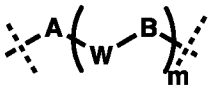
R' and R'' are independently selected from null, or a moiety comprising of optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 hydroxyalkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted 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^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 9, 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 $-CH_2CH_2-$;

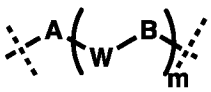
W is –O-;

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 9, 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 $–CH_2CH_2-$;

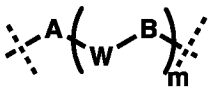
W is –O-;

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 9, 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

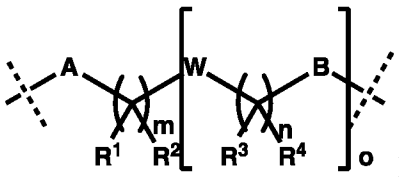
A is R'C(O)NR''R^1, wherein R' is piperazine and R" is $–CH_2-$;

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 9A, 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 3-10 membered cycloalkoxy, optionally substituted 3-10 membered carbocyclylamino, optionally substituted 4-8 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'', $R'COR''$, $R'CO_2R''$, $R'C(O)NR''R^1$, $R'C(S)NR''R^1$, $R'OR''$, $R'OC(O)R''$, $R'OC(O)OR''$, $R'OCONR^1R''$, $R'SR''$, $R'SOR''$, $R'SO_2R''$, $R'SO_2NR''R^1$, $R'NR''R^1$, $R'NR^1COR''$, $R'NR^1C(O)OR''$, $R'NR^1CONR''R^2$, $R'NR^1C(S)R''$, $R'NR^1S(O)R''$, $R'NR^1S(O)_2R''$, and $R'NR^1S(O)_2NR^2R''$, wherein

R' and R'' are independently selected from null, 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^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;

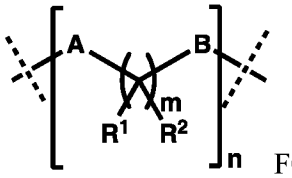
R' and R'', R^5 and R^6, R' and R^5, R' and R^6, R'' and R^5, R'' and R^6 together with the atom to which they are connected form a 3-20 membered cycloalkyl or 4-20 membered heterocyclyl ring;

m is 0 to 15;

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

o is 0 to 15.

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



FORMULA 9B, 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 3-10 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''R^1, R'C(S)NR''R^1, R'OR'', R'OC(O)R'', R'OC(O)OR'', R'OCONR^{1}R'', R'SR'', R'SOR'', R'SO_2R'', R'SO_2NR''R^1, R'NR''R^1, R'NR^{1}COR'', R'NR^{1}C(O)OR'', R'NR^{1}CONR''R^2, R'NR^{1}C(S)R'', R'NR^{1}S(O)R'', R'NR^{1}S(O)$_2$R'', and R'NR^{1}S(O)$_2$NR^{2}R'', wherein

R' and R'' are independently selected from null, 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;

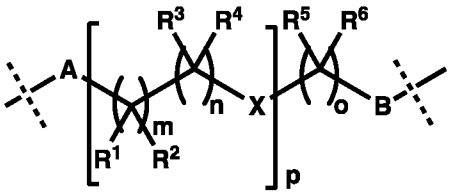
R^3 and R^4 are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxyalkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-C_8 hydroxyalkyl, 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;

each m is 0 to 15; and

n is 0 to 15.

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



FORMULA 9C, wherein

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

R^1, R^2, R^3, R^4, R^5, R^6, and R^7, 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 3-10 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)NR''R^1, R'C(S)NR''R^1, R'OR'', R'OC(O)R'', R'OC(O)OR'', R'OCONR^{1}R'', R'SR'', R'SOR'', R'SO_2R'', R'SO_2NR''R^1, R'NR''R^1, R'NR^{1}COR'', R'NR^{1}C(O)OR'', R'NR^{1}CONR''R^2, R'NR^{1}C(S)R'', R'NR^{1}S(O)R'', R'NR^{1}S(O)$_2$R'', and R'NR^{1}S(O)$_2$NR^{2}R'', wherein

R' and R'' are independently selected from null, 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^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;

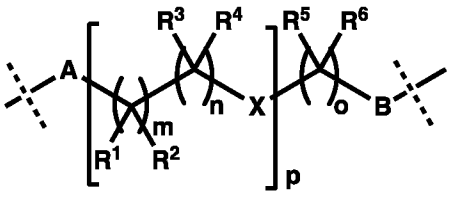
m, at each occurrence, is 0 to 15;

n, at each occurrence, is 0 to 15;

o is 0 to 15; and

p is 0 to 15.

15. The bivalent compound of claim 14, wherein the linker comprises:



FORMULA 9C, 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;

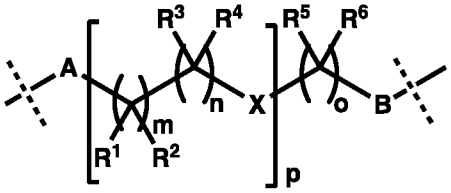
B is null;

R^1 is hydrogen; and

o is 8; and

p is 0.

23. The bivalent compound of claim 14, wherein the linker comprises:



FORMULA 9C, 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

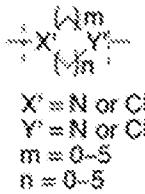
p is 0.

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.

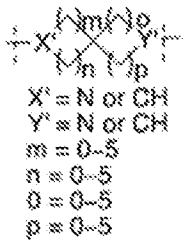
27. The bivalent compound of any one of claims 1, 2, 12, 13 or 14, wherein o is 0 to 5.

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.

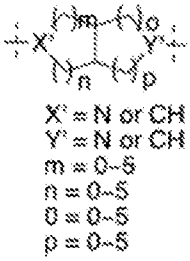
29. The bivalent compound of any one of claims 1, 2, 12, 13 or 14, wherein the linker comprises one or more rings selected from the group consisting of:



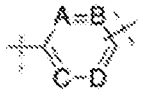
(a) FORMULA C1,



(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

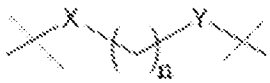
(d) FORMULA C4, and



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:



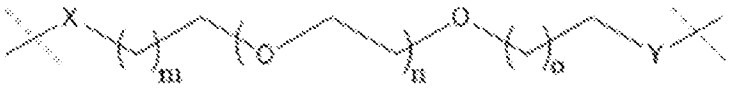
FORMULA A, wherein

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,

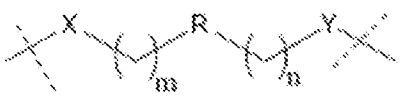
Y is C=O or CH_2,

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,

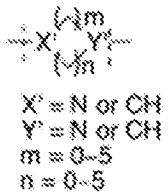
R is $-CH_2-$, $-CF_2-$, $-CH(C_{1-3}$ alkyl)–, $-C(C_{1-3}$ alkyl)$(C_{1-3}$ alkyl)–, –CH=CH–, $-C(C_{1-3}$ alkyl)$=C(C_{1-3}$ alkyl)–, –C=C–, –O–, –NH–, $-N(C_{1-3}$ alkyl)–, $-C(O)NH-$, $-C(O)N(C_{1-3}$ alkyl)–, a 3-13 membered ring, a 3-13 membered fused ring, a 3-13 membered bridged ring, and/or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

m is 0-15, and

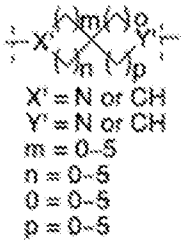
n is 0-15.

33. The bivalent compound of claim 1, 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.

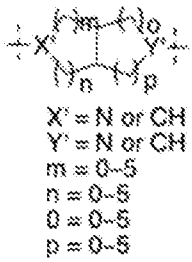
34. The bivalent compound of claim 1, subpart (h), or claim 32, wherein R has a structure of

(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, or



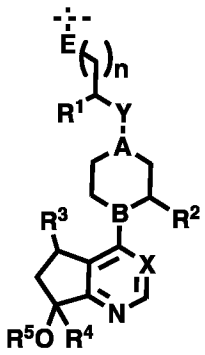
A = C, CH, C(C_{1-3} alkyl), N, NH, N(C_{1-3} alkyl), O, S
B = C, CH, C(C_{1-3} alkyl), N, NH, N(C_{1-3} alkyl), O, S
C = C, CH, C(C_{1-3} alkyl), N, NH, N(C_{1-3} alkyl), O, S
D = C, CH, C(C_{1-3} alkyl), N, NH, N(C_{1-3} alkyl), O, S
E = C, CH, C(C1-3 alkyl), N, NH, N(C1-3alkyl), O, S

(e) FORMULA C5.

35. The bivalent compound of any one of claims 1 to 34, wherein the linker is covalently bonded to the AKT ligand.

36. The bivalent compound of claim 35, wherein the covalent bond is an amide bond or an amino bond.

37. The bivalent compound of any one of claims 1 to 36, wherein the AKT ligand is selected from the group consisting of:



a. FORMULA 1

wherein

A, B, and X are independently N, CH, or CR^6,

Y is CH_2, CO, SO, SO_2, CR^7R^8, $CONR^7$, or SO_2NR^7,

E is NH, NR^9, O, C_1-C_8 alkyl, C_1-C_8 alkoxy, C_1-C_8 alkoxyalkyl, C_1-C_8 haloalkyl, C_1-C_8 hydroxyalkyl, C_3-C_8 cycloalkyl, C_3-C_7 heterocyclyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, OR^9, SR^9, NR^9R^{10}, CN, NO_2, $(CR^9R^{10})_mNR^{11}R^{12}$, $(CR^9R^{10})_mC(O)R^{11}$, $(N\ R^9R^{10})_mNR^{11}R^{12}$,

$(NR^9R^{10})_mC(O)R^{11}$, COR^9, CO_2R^9, $CONR^9R^{10}$, NR^9COR^{10}, NR^9SOR^{10}, $NR^9SO_2R^{10}$, SOR^9, SO_2R^9, $SO_2NR^9R^{10}$, $(CR^9R^{10})_m$-aryl, or $(CR^9R^{10})_m$-heteroaryl,

R^1 is H, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkoxy, C_1-C_8 alkoxyalkyl, aryl, C_1-C_8 alkylaryl, haloaryl, arylalkyl, heteroaryl, or heteroarylalkyl,

R^2, R^3, R^4, and R^6 are independently hydrogen, halogen, amino, C_1-C_8 alkylamino, arylamino, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkoxy, or C_1-C_8 alkoxyalkyl,

R^5, R^7, and R^8 are independently H, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, or C_1-C_8 alkoxyalkyl,

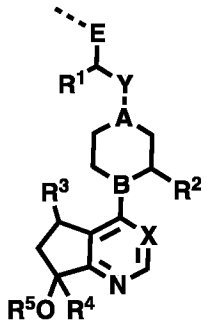
R^9, R^{10}, R^{11}, and R^{12} are independently H, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkoxy, C_2-C_8 alkenyl, C_2-C_8 alkynyl, arylalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, or heteroarylalkyl,

R^9 and R^{10}, R^{11} and R^{12} can independently form 4-8 membered alkyl or heterocyclyl rings,

m = 0-8,

and

n = 0-8;

b. 

FORMULA 2

wherein

A, B and X are independently selected from N and CR^6, wherein

R^6 is independently selected from hydrogen, halogen, cyano, nitro, hydroxyl, amino, 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 amino, optionally substituted C_1-C_8 alkylamino, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-10 membered carbocyclyl, and optionally substituted 4-10 membered heterocyclyl;

Y is selected from CR^7R^8, CO, SO, SO_2, $CONR^7$, and SO_2NR^7, wherein

R^7 and R^8 is independently selected from hydrogen, halogen, 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 alkylamino, optionally substituted C_1-C_8 alkylamino C_1-C_8 alkyl, optionally

substituted 3 to 10 membered carbocyclyl, and optionally substituted 4-10 membered heterocyclyl, or

R^7 and R^8 together with the atom to which they are connected form an optionally substituted 3-10 membered carbocyclyl or an optionally substituted 4-10 membered heterocyclyl ring;

E is connected to the "linker" moiety of the bivalent compound, and is selected from null, R'-R" R'OR", R'SR", R'NR^{9}R", R'OC(O)R", R'OC(O)OR", R'OCONR^{9}R", R'C(O)R", R'C(O)OR", R'CONR^{9}R", R'S(O)R", R'S(O)$_2$R", R'SO$_2$NR^{9}R", R'NR^{10}C(O)OR", R'NR^{10}C(O)R", R'NR^{10}C(O)NR^{9}R", R'NR^{10}S(O)R", R'NR^{10}S(O)$_2$R", and R'NR^{10}S(O)$_2$NR^{9}R", wherein

R' and R" are independently selected from null, 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 haloalkylene, 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 alkylene)O(C_1-C_8 alkylene), optionally substituted (C_1-C_8 alkylene)N(C_1-C_8 alkylene), optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted C_3-C_{13} fused carbocyclyl, optionally substituted C_3-C_{13} fused heterocyclyl, optionally substituted C_3-C_{13} bridged carbocyclyl, optionally substituted C_3-C_{13} bridged heterocyclyl, optionally substituted C_3-C_{13} spiro carbocyclyl, optionally substituted C_3-C_{13} spiro heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^9 and R^{10} 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 carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

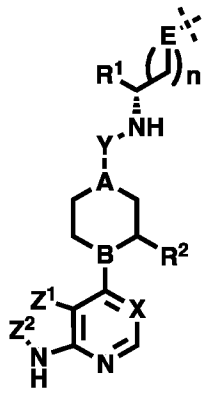
R' and R", R^9 and R^{10}, R' and R^9, R' and R^{10}, R" and R^9, R" and R^{10} together with the atom to which they are connected form a 4-20 membered heterocyclyl ring;

R^1 is selected from hydrogen, halogen, and 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 alkylamino, optionally substituted C_1-C_8 alkylamino C_1-C_8 alkyl, optionally substituted 3-10

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

R^2, R^3 and R^4 are independently selected from hydrogen, halogen, cyano, nitro, hydroxyl, 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 aryloxy, optionally substituted C_1-C_8 alkoxyC_1-C_8 alkyl, optionally substituted amino, optionally substituted C_1-C_8 alkylamino, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted arylamino, optionally substituted 3-10 membered carbocyclyl, and optionally substituted 4-10 membered heterocyclyl;

R^5 is 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 alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-10 membered carbocyclyl, and optionally substituted 4-10 membered heterocyclyl;

c.  FORMULA 3

wherein

A, B, and X are independently N or CR^3,

Y is CH_2, CO, SO, SO_2, CR^4R^5, $CONR^4$, or SO_2NR^4,

E is NH, NR^6, O, C_1-C_8 alkyl, C_1-C_8 alkoxy, C_1-C_8 alkoxyalkyl, C_1-C_8 haloalkyl, C_1-C_8 hydroxyalkyl, C_3-C_8 cycloalkyl, C_3-C_8 heterocyclyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, OR^6, SR^6, NR^6R^7, CN, NO_2, $(CR^6R^7)_mNR^8R^9$, $(CR^6R^7)_mC(O)R^8$, (N $R^6R^7)_mNR^8R^9$, $(NR^6R^7)_mC(O)R^8$, COR^6, CO_2R^6, $CONR^6R^7$, NR^6COR^7, NR^6SOR^7, $NR^6SO_2R^7$, SOR^6, SO_2R^6, $SO_2NR^6R^7$, $(CR^6R^7)_m$-aryl, or $(CR^6R^7)_m$-heteroaryl,

Z^1-Z^2 is CR^{10}=CH, N+CH, or CR^{10}=N,

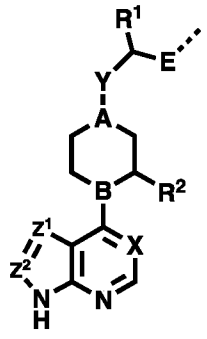
R^1 is hydrogen, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkoxy, C_1-C_8 alkoxyalkyl, aryl, C_1-C_8 alkylaryl, haloaryl, arylalkyl, heteroaryl, or heteroarylalkyl,

R^2, R^3, and R^4 are independently hydrogen, halogen, amino, C_1-C_8 alkylamino, arylamino, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkoxy, or C_1-C_8 alkoxyalkyl,

R^6, R^7, R^8, and R^9 are independently H, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkoxy, C_2-C_8 alkenyl, C_2-C_8 alkynyl, arylalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, or heteroarylalkyl,

R^6 and R^7, R^8 and R^9 can independently form 4-8 membered alkyl or heterocyclyl rings,

R^{10} is hydrogen, halogen, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkoxy, C_1-C_8 alkoxyalkyl, and n = 0-8;

d. 

FORMULA 4

wherein

A, B and X are independently selected from N and CR^3, wherein

R^3 is independently selected from hydrogen, halogen, cyano, nitro, hydroxyl, 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 alkoxyC_1-C_8 alkyl, optionally substituted amino, optionally substituted C_1-C_8 alkylamino C_1-C_8 alkyl, optionally substituted 3-10 membered carbocyclyl, and optionally substituted 4-10 membered heterocyclyl;

Z^1 is selected from CR^8 and N, wherein

R^8 is selected from hydrogen, halogen, cyano, nitro, hydroxyl, 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 alkoxyC_1-C_8 alkyl, optionally substituted amino, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-10 membered carbocyclyl, and optionally substituted 4-10 membered heterocyclyl;

Z^2 is selected from CH and N;

Y is selected from CO, SO, SO_2, CR^4R^5, $CONR^4$, and SO_2NR^4, wherein

R^4 and R^5 is independently selected from hydrogen and 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 alkoxyC_1-C_8 alkyl, optionally substituted amino, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3 to 10 membered carbocyclyl, and optionally substituted 4-10 membered heterocyclyl;

E is connected to the "linker" moiety of the bivalent compound, and is selected from null, R'-R", R'OR", R'SR", R'NR^{6}R", R'OC(O)R", R'OC(O)OR", R'OCONR^{6}R", R'C(O)R", R'C(O)OR", R'CONR^{6}R", R'S(O)R", R'S(O)$_2$R", R'SO$_2$NR^{6}R", R'NR^{7}C(O)OR", R'NR^{7}C(O)R", R'NR^{7}C(O)NR^{6}R", R'NR^{7}S(O)R", R'NR^{7}S(O)$_2$R", and R'NR^{7}S(O)$_2$NR^{6}R", wherein

R' and R" are independently selected from null, 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 haloalkylene, optionally substituted C_1-C_8 hydroxyalkylene, optionally substituted C_1-C_8alkoxyC_1-C_8alkylene, optionally substituted (C_1-C_8 alkylene)O(C_1-C_8 alkylene), optionally substituted (C_1-C_8 alkylene)N(C_1-C_8 alkylene), optionally substituted 3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted C_3-C_{13} fused carbocyclyl, optionally substituted C_3-C_{13} fused heterocyclyl, optionally substituted C_3-C_{13} bridged carbocyclyl, optionally substituted C_3-C_{13} bridged heterocyclyl, optionally substituted C_3-C_{13} spiro carbocyclyl, optionally substituted C_3-C_{13} spiro heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^6 and R^7 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 carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or

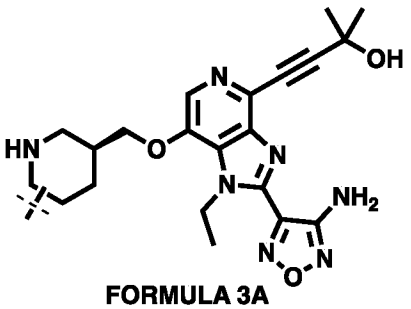
R' and R", R^6 and R^7, R' and R^6, R' and R^7, R" and R^6, R" and R^7 together with the atom to which they are connected form a 4-20 membered heterocyclyl ring;

R^1 is selected from selected from hydrogen, halogen, and 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 alkoxyC_1-C_8 alkyl, optionally substituted amino, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted

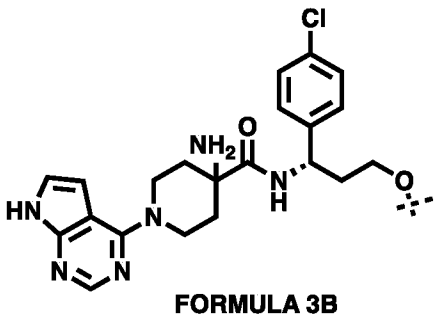
3-10 membered carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl; and

R^2 is selected from hydrogen, halogen, cyano, nitro, hydroxyl, 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, or optionally substituted C_1-C_8 alkoxy C_1-C_8 alkyl, optionally substituted amino, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-10 membered carbocyclyl, and optionally substituted 4-10 membered heterocyclyl; and

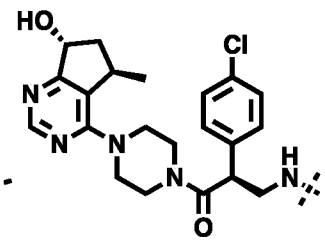
e. a compound selected from the group consisting of:



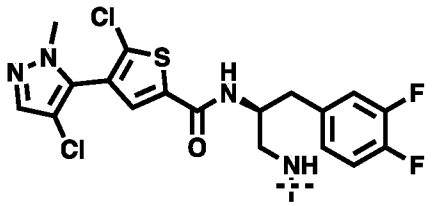
FORMULA 3A



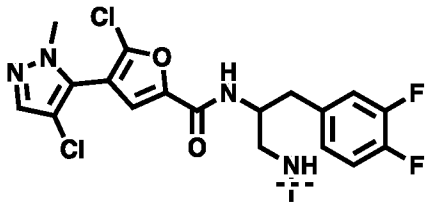
FORMULA 3B



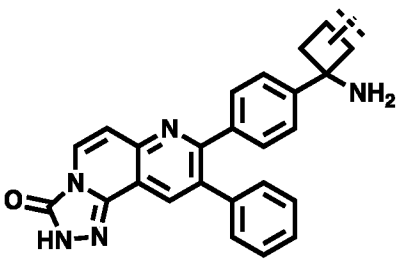
FORMULA 3C



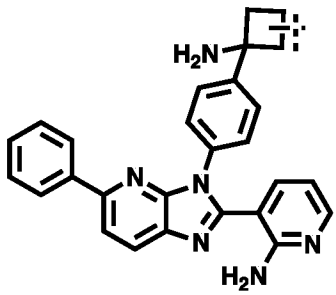
FORMULA 3D



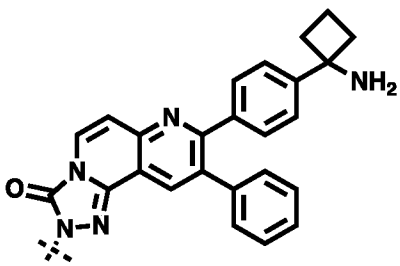
FORMULA 3E



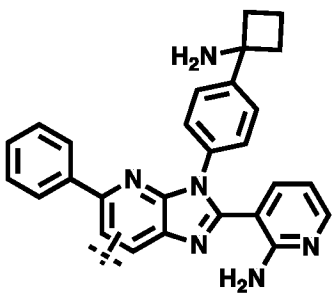
FORMULA 3F



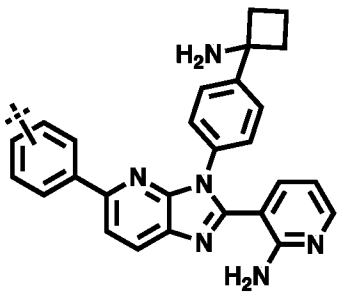
FORMULA 3G



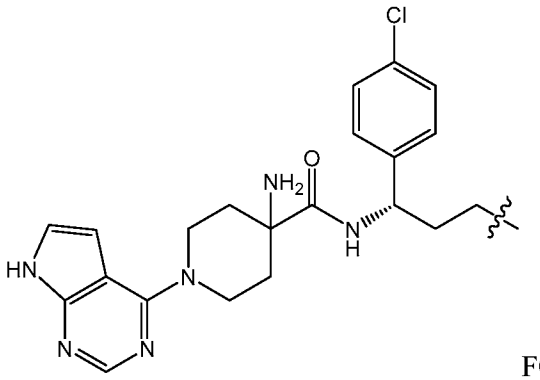
FORMULA 3H



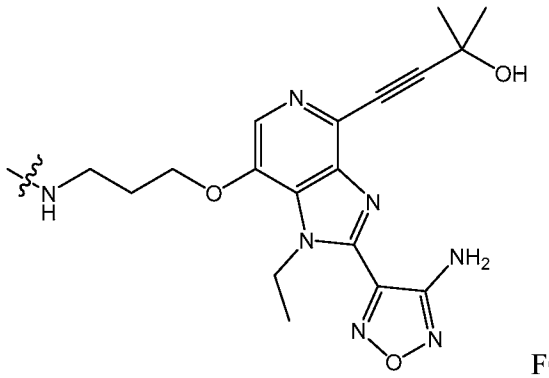
FORMULA 3I



FORMULA 3J

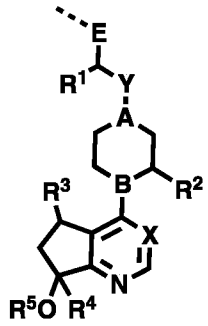


FORMULA 3K;



and FORMULA 3L.

38. The bivalent ligand of claim 37, subpart (b), wherein the AKT ligand comprises:



FORMULA 2

wherein

A, B and X are each N;

Y is CO;

E is connected to the "linker" moiety of the bivalent compound, and is $R'NR^9R''$, wherein

R' is optionally substituted C_1-C_8 alkyl;

R^9 is hydrogen;

R'' is null;

R^1 is optionally substituted aryl;

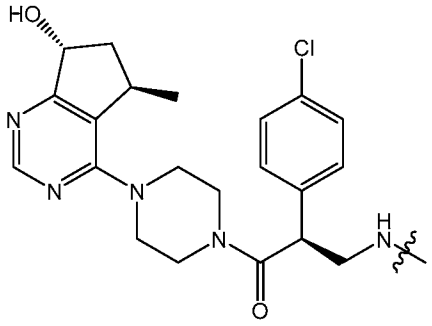
R^2 is hydrogen;

R^3 is optionally substituted C_1-C_8 alkyl;

R^4 is hydrogen; and

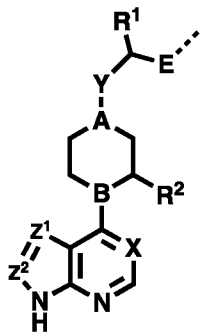
R^5 is hydrogen.

39. The bivalent compound of claim 37, subpart (e), wherein the AKT ligand comprises:



FORMULA 3C.

40. The bivalent ligand of claim 37, subpart (d), wherein the AKT ligand comprises:



FORMULA 4

wherein

A is CR^3, wherein

B and X are each N, wherein

R^3 is optionally substituted amino;

Z^1 is CR^8, wherein

R^8 is hydrogen;

Z^2 is CH;

Y is $CONR^4$, wherein

R^4 is hydrogen;

E is connected to the "linker" moiety of the bivalent compound, and is R'-R", wherein

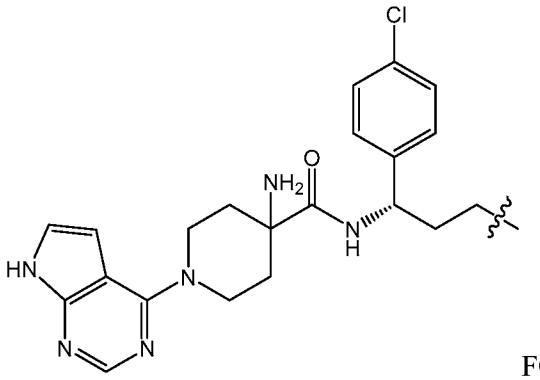
R' is optionally substituted C_1-C_8 alkyl;

R" is null;

R^1 is optionally substituted aryl; and

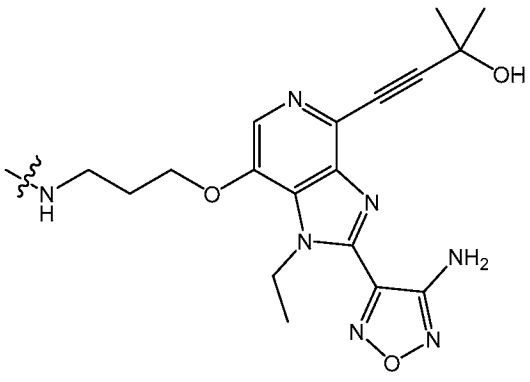
R^2 is hydrogen.

41. The bivalent compound of claim 37, subpart (e), wherein the AKT ligand comprises:



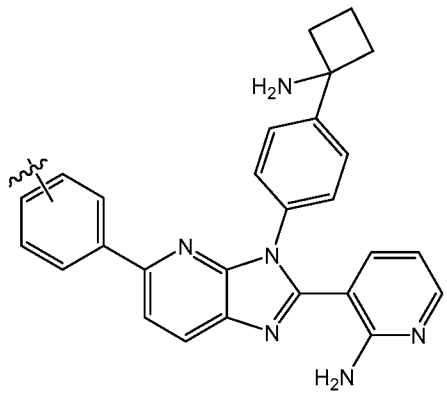
FORMULA 3K.

42. The bivalent compound of claim 37, subpart (e), wherein the AKT ligand comprises:



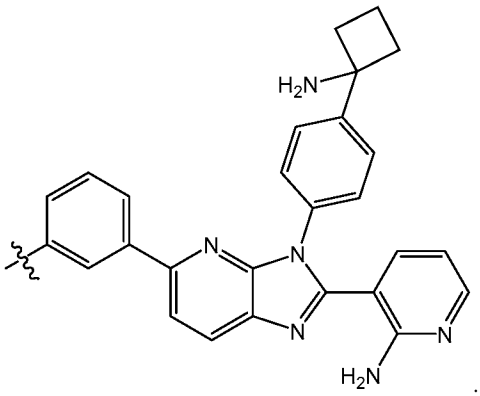
FORMULA 3L.

43. The bivalent compound of claim 37, subpart (e), wherein the AKT ligand comprises:

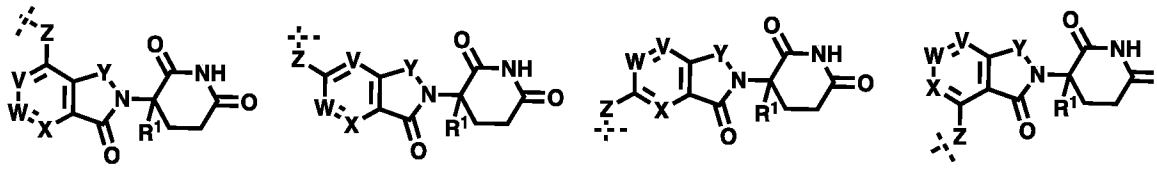


FORMULA 3J.

44. The bivalent compound of claim 37, subpart (e), wherein the AKT ligand comprises:



45. The bivalent compound of any one of claims 1-44, wherein the degradation/disruption tag is selected from the group consisting of:

a. 

FORMULA 5A FORMULA 5B FORMULA 5C FORMULA 5D

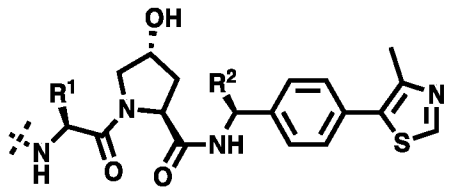
wherein

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

Y is selected from CO, CH_2, and N=N;

Z is selected from CH_2, NH and O; and

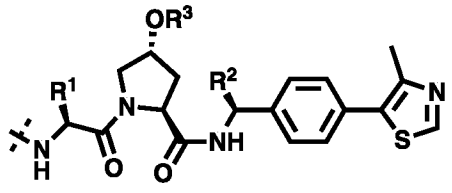
R^1 and R^2 are independently selected from hydrogen, halogen, cyano, nitro, and C_1-C_5 alkyl;

b. 

FORMULA 6

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_3-C_7 cycloalkyl, C_3-C_7 heterocyclyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl;

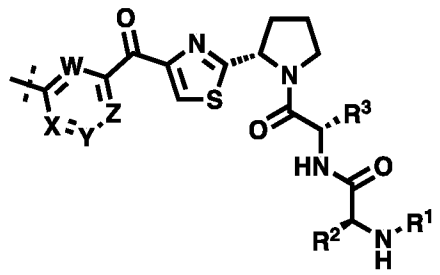
c. 

FORMULA 7,

wherein

R^1 and R^2 are independently selected from hydrogen, hydroxyl, amino, cyano, nitro, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, and optionally substituted C_2-C_8 alkynyl, 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 3-10 membered carbocyclyl, and optionally substituted 4-10 membered heterocyclyl.

R^3 is selected from 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)(3-10 membered carbocyclyl), optionally substituted C(O)(4-10 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)O(3-10 membered carbocyclyl), optionally substituted C(O)O(4-10 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)N(3-10 membered carbocyclyl), optionally substituted C(O)N(4-10 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$)_2$;

d. 

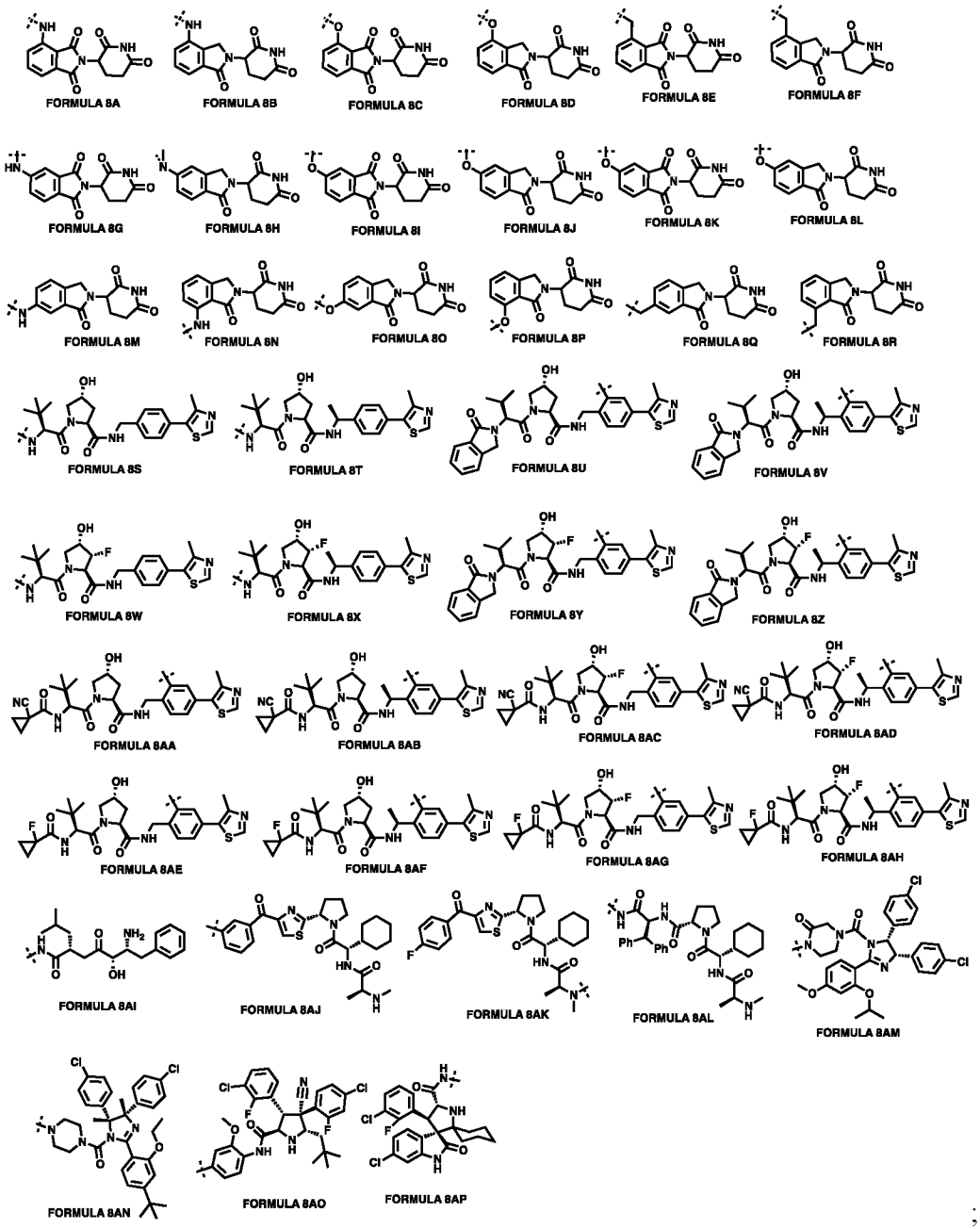
FORMULA 8

wherein

V, W, X, and Z are independently selected from CR^4 and N; and

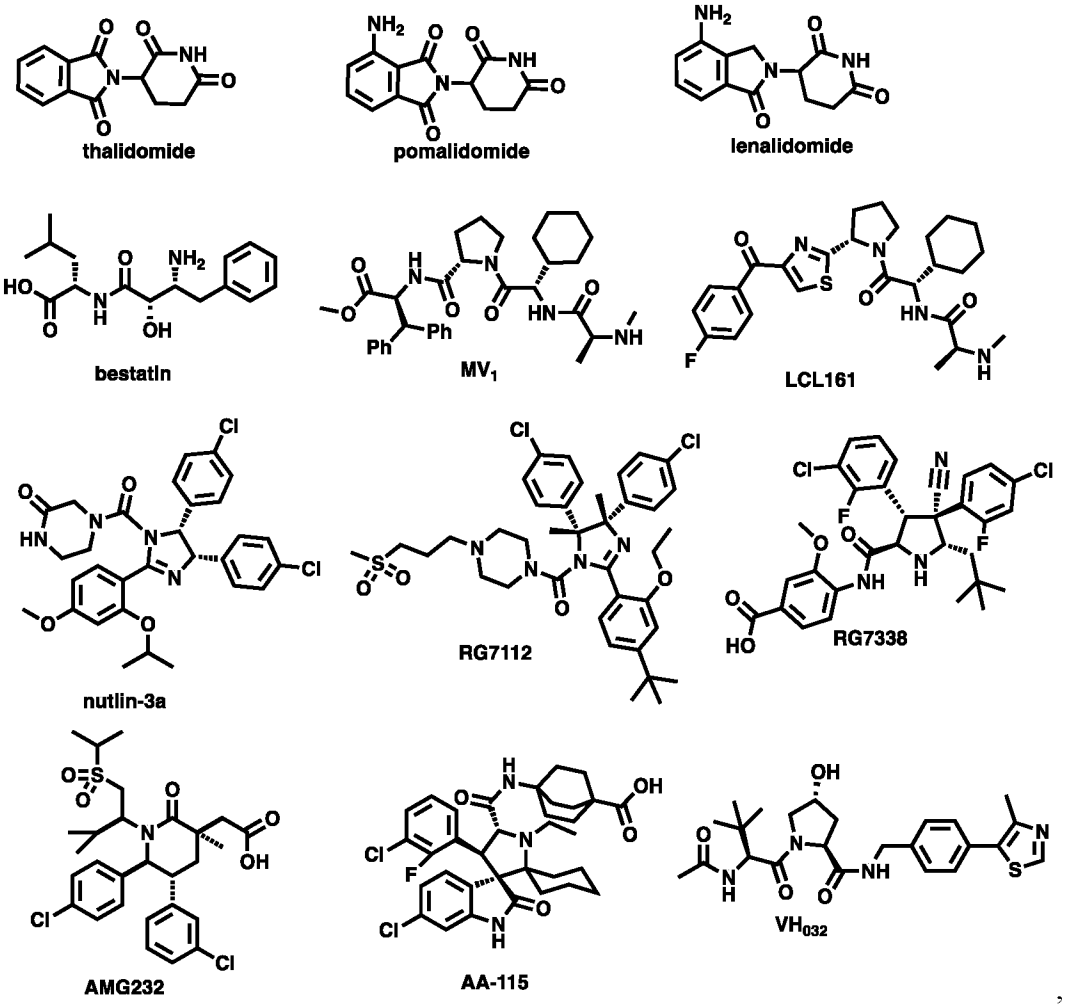
R^1, R^2, R^3, and R^4 are independently selected from hydrogen, halogen, cyano, nitro, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, and optionally substituted C_2-C_8 alkynyl; optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8 haloalkyl, optionally substituted C_1-C_8 hydroxyalkyl, optionally substituted C_1-C_8alkoxy, optionally substituted C_1-C_8alkylamino, optionally substituted 3-10 membered carbocyclyl, and optionally substituted 4-10 membered heterocyclyl;

e. a compound selected from the group consisting of:



; and

f. a compound selected from the group consisting of:



or a pharmaceutically acceptable salt thereof.

46. The bivalent compound of any one of claims 1 to 45, wherein the degradation/disruption tag binds to a ubiquitin ligase and/or serves as a hydrophobic group that leads to AKT protein misfolding.

47. The bivalent compound of claim 46, wherein the ubiquitin ligase is an E3 ligase.

48. The bivalent compound of claim 47, wherein the E3 ligase is a cereblon E3 ligase, a VHL E3 ligase, a MDM2 ligase, a TRIM21 ligase, a TRIM24 ligase, and/or an IAP ligase.

49. The bivalent compound of any one of claims 1 to 48, wherein the bivalent compound is selected from the group consisting of: XF038-157A, XF038-158A, XF038-159A,

XF038-160A, XF038-161A, XF038-162A, XF038-164A, XF038-165A, XF038-166A, XF038-176A, XF038-177A, XF042-162, XF042-164, XF042-165, XF042-166, XF042-167, XF042-168, XF042-170, XF042-171, XF048-1, XF048-2, XF048-3, XF048-4, XF048-5, XF048-7, XF048-8, XF050-5, XF050-6, XF050-7, XF050-8, XF050-9, XF050-10, XF050-11, XF050-12, XF050-13, XF050-14, XF050-15, XF050-16, XF050-17, XF050-18, XF050-19, XF050-20, XF050-21, XF050-22, XF050-23, XF050-24, XF050-25, XF050-26, XF050-27, XF050-28, XF050-29, XF050-30, XF050-31, XF050-32, XF050-33, XF050-98, XF050-132, XF050-133. XF050-134, XF056-93, XF050-143, XF050-144, XF050-145, XF050-167, XF056-33, XF056-34, XF056-35, XF056-36, XF056-37, XF056-73, XF061-10, XF067-1, XF067-2, XF067-3, XF067-4, XF067-5, XF067-6, XF067-7, XF067-8, XF067-9, XF067-10, XF067-11, XF067-12, XF067-13, XF067-14, XF067-15, XF067-16, XF067-17, XF067-18, XF067-19, XF067-20, XF067-21, XF067-22, XF067-23, XF067-24, XF067-25, XF067-26, XF067-27, XF067-28, XF067-29, XF067-30, XF067-31, XF067-32, XF067-33, XF067-34, XF067-35, XF067-36, XF067-37, XF067-38, XF067-39, XF067-40, XF067-41, XF067-42, XF067-43, XF067-44, XF067-45, XF067-46, XF067-47, XF067-48, XF067-49, XF067-50, XF067-51, XF067-52, XF067-53, XF067-54, XF067-55, XF067-56, XF067-57, XF067-58, XF067-59, XF067-84, XF067-85, XF067-86, XF067-87, XF067-88, XF067-89, XF067-90, XF067-91, XF067-92, XF067-93, XF067-94, XF067-95, XF067-96, XF067-97, XF067-98, XF067-99, XF067-100, XF067-101, XF067-102, XF067-103, XF067-104, XF067-105, XF067-106, XF067-107, XF067-108, XF067-109, XF067-110, XF067-111, XF067-112, XF067-113, and analogs thereof.

50. The bivalent compound of claim 1, wherein the bivalent compound is selected from the group consisting of: XF038-165A, XF038-166A, XF038-176A, XF038-177A, XF042-162, XF042-168, XF042-170, XF048-1, XF048-2, XF048-3, XF048-4, XF048-5, XF048-7, XF048-8, XF050-5, XF050-7, XF050-16, XF050-17, XF050-18, XF050-19, XF050-20, XF050-21, XF050-30, XF050-31, XF050-32, XF050-33, XF050-98, XF050-133, XF056-93, XF050-143, XF050-144, XF050-145, XF050-167, XF056-33, XF056-34, XF056-35, XF056-37, XF067-15, XF067-16, XF067-17, XF067-18, XF067-44, XF067-45, XF067-46, XF067-47, XF067-98, XF067-99, XF067-100, XF067-101, XF067-112 and XF067-113.

51. The bivalent compound of claim 1, wherein the bivalent compound is selected from the group consisting of: XF050-21, XF050-32, XF050-33, XF050-143, XF050-144, XF050-145, XF050-167, XF056-33, XF056-34, XF056-35, and XF056-73.

52. The bivalent compound of claim 51, wherein the bivalent compound is selected from the group consisting of: XF050-21, XF050-143, XF050-144, XF050-145, and XF050-167.

53. The bivalent compound of claim 51, wherein the bivalent compound is selected from the group consisting of: XF050-32, XF050-33, XF056-33, XF056-34, XF056-35, and XF056-73.

54. The bivalent compound of claim 1, wherein the bivalent compound is selected from the group consisting of: XF038-162A, XF038-165A, XF038-166A, XF038-176A, XF038-177A, XF042-162, XF042-170, XF050-98, XF050-133, and XF056-93.

55. The bivalent compound of claim 54, wherein the bivalent compound is selected from the group consisting of: XF038-162A, XF038-165A, XF038-166A, XF042-162, and XF050-98.

56. The bivalent compound of claim 54, wherein the bivalent compound is selected from the group consisting of: XF038-176A and XF038-177A.

57. The bivalent compound of claim 54, wherein the bivalent compound is selected from the group consisting of: XF042-170, XF050-133, and XF056-93.

58. The bivalent compound of claim 1, wherein the bivalent compound is selected from the group consisting of: XF067-15, XF067-16, XF067-17, XF067-18, XF067-44, XF067-45, XF067-46, and XF067-47.

59. The bivalent compound of claim 1, wherein the bivalent compound is selected from the group consisting of: XF067-98, XF067-99, XF067-100, XF067-101, XF067-112, and XF067-113.

60. The bivalent compound of claim 59, wherein the bivalent compound is selected from the group consisting of: XF067-98, XF067-99, XF067-100, and XF067-101.

61. The bivalent compound of claim 59, wherein the bivalent compound is selected from the group consisting of: XF067-112, and XF067-113.

62. A bivalent compound selected from the group consisting of: XF038-157A, XF038-158A, XF038-159A, XF038-160A, XF038-161A, XF038-162A, XF038-164A, XF038-165A, XF038-166A, XF038-176A, XF038-177A, XF042-162, XF042-164, XF042-165, XF042-166, XF042-167, XF042-168, XF042-170, XF042-171, XF048-1, XF048-2, XF048-3, XF048-4, XF048-5, XF048-7, XF048-8, XF050-5, XF050-6, XF050-7, XF050-8, XF050-9, XF050-10, XF050-11, XF050-12, XF050-13, XF050-14, XF050-15, XF050-16, XF050-17, XF050-18, XF050-19, XF050-20, XF050-21, XF050-22, XF050-23, XF050-24, XF050-25, XF050-26, XF050-27, XF050-28, XF050-29, XF050-30, XF050-31, XF050-32, XF050-33, XF050-98, XF050-132, XF050-133. XF050-134, XF056-93, XF050-143, XF050-144, XF050-145, XF050-167, XF056-33, XF056-34, XF056-35, XF056-36, XF056-37, XF056-73, XF061-10, XF067-1, XF067-2, XF067-3, XF067-4, XF067-5, XF067-6, XF067-7, XF067-8, XF067-9, XF067-10, XF067-11, XF067-12, XF067-13, XF067-14, XF067-15, XF067-16, XF067-17, XF067-18, XF067-19, XF067-20, XF067-21, XF067-22, XF067-23, XF067-24, XF067-25, XF067-26, XF067-27, XF067-28, XF067-29, XF067-30, XF067-31, XF067-32, XF067-33, XF067-34, XF067-35, XF067-36, XF067-37, XF067-38, XF067-39, XF067-40, XF067-41, XF067-42, XF067-43, XF067-44, XF067-45, XF067-46, XF067-47, XF067-48, XF067-49, XF067-50, XF067-51, XF067-52, XF067-53, XF067-54, XF067-55, XF067-56, XF067-57, XF067-58, XF067-59, XF067-84, XF067-85, XF067-86, XF067-87, XF067-88, XF067-89, XF067-90, XF067-91, XF067-92, XF067-93, XF067-94, XF067-95, XF067-96, XF067-97, XF067-98, XF067-99, XF067-100, XF067-101, XF067-102, XF067-103, XF067-104, XF067-105, XF067-106, XF067-107, XF067-108, XF067-109, XF067-110, XF067-111, XF067-112, XF067-113, and analogs thereof.

63. A bivalent compound selected from the group consisting of: XF050-21, XF050-32, XF050-33, XF050-143, XF050-144, XF050-145, XF050-167, XF056-33, XF056-34, XF056-35, and XF056-73.

64. The bivalent compound of claim 63, wherein the bivalent compound is selected from the group consisting of: XF050-21, XF050-143, XF050-144, XF050-145, and XF050-167.

65. The bivalent compound of claim 63, wherein the bivalent compound is selected from the group consisting of: XF050-32, XF050-33, XF056-33, XF056-34, XF056-35, and XF056-73.

66. A bivalent compound selected from the group consisting of: XF038-162A, XF038-165A, XF038-166A, XF038-176A, XF038-177A, XF042-162, XF042-170, XF050-98, XF050-133, and XF056-93.

67. The bivalent compound of claim 66, wherein the bivalent compound is selected from the group consisting of: XF038-162A, XF038-165A, XF038-166A, XF042-162, and XF050-98.

68. The bivalent compound of claim 66, wherein the bivalent compound is selected from the group consisting of: XF038-176A and XF038-177A.

69. The bivalent compound of claim 66, wherein the bivalent compound is selected from the group consisting of: XF042-170, XF050-133, and XF056-93.

70. A bivalent compound selected from the group consisting of: XF067-15, XF067-16, XF067-17, XF067-18, XF067-44, XF067-45, XF067-46, and XF067-47.

71. A bivalent compound selected from the group consisting of: XF067-98, XF067-99, XF067-100, XF067-101, XF067-112, and XF067-113.

72. The bivalent compound of claim 71, wherein the bivalent compound is selected from the group consisting of: XF067-98, XF067-99, XF067-100, and XF067-101.

73. The bivalent compound of claim 71, wherein the bivalent compound is selected from the group consisting of: XF067-112, and XF067-113.

74. A method of treating a serine threonine kinase (AKT)-mediated disease, comprising administering, to a subject with an AKT-mediated disease, a bivalent compound comprising an AKT ligand conjugated to a degradation/disruption tag through a linker.

75. The method of claim 74, wherein the AKT-mediated disease results from ALK activation or mutation.

76. The method of claim 74 or 75, wherein a tissue from the subject has elevated AKT enzymatic activity relative to a wild-type tissue of the same species and tissue type.

77. The method of any one of claims 74-76, wherein the bivalent compound is selected from the group consisting of XF038-157A, XF038-158A, XF038-159A, XF038-160A, XF038-161A, XF038-162A, XF038-164A, XF038-165A, XF038-166A, XF038-176A, XF038-177A, XF042-162, XF042-164, XF042-165, XF042-166, XF042-167, XF042-168, XF042-170, XF042-171, XF048-1, XF048-2, XF048-3, XF048-4, XF048-5, XF048-7, XF048-8, XF050-5, XF050-6, XF050-7, XF050-8, XF050-9, XF050-10, XF050-11, XF050-12, XF050-13, XF050-14, XF050-15, XF050-16, XF050-17, XF050-18, XF050-19, XF050-20, XF050-21, XF050-22, XF050-23, XF050-24, XF050-25, XF050-26, XF050-27, XF050-28, XF050-29, XF050-30, XF050-31, XF050-32, XF050-33, XF050-98, XF050-132, XF050-133. XF050-134, XF056-93, XF050-143, XF050-144, XF050-145, XF050-167, XF056-33, XF056-34, XF056-35, XF056-36, XF056-37, XF056-73, XF061-10, XF067-1, XF067-2, XF067-3, XF067-4, XF067-5, XF067-6, XF067-7, XF067-8, XF067-9, XF067-10, XF067-11, XF067-12, XF067-13, XF067-14, XF067-15, XF067-16, XF067-17, XF067-18, XF067-19, XF067-20, XF067-21, XF067-22, XF067-23, XF067-24, XF067-25, XF067-26, XF067-27, XF067-28, XF067-29, XF067-30, XF067-31, XF067-32, XF067-33, XF067-34, XF067-35, XF067-36, XF067-37, XF067-38, XF067-39, XF067-40, XF067-41, XF067-42, XF067-43, XF067-44, XF067-45, XF067-46, XF067-47, XF067-48, XF067-49, XF067-50, XF067-51, XF067-52, XF067-53, XF067-54, XF067-55, XF067-56, XF067-57, XF067-58, XF067-59, XF067-84, XF067-85, XF067-86, XF067-87, XF067-88, XF067-89, XF067-90, XF067-91, XF067-92, XF067-93, XF067-94, XF067-95, XF067-96, XF067-97, XF067-98, XF067-99, XF067-100, XF067-101, XF067-102, XF067-103, XF067-104, XF067-105, XF067-

106, XF067-107, XF067-108, XF067-109, XF067-110, XF067-111, XF067-112, XF067-113, and analogs thereof.

78. The method of any one of claims 74-77, wherein the bivalent compound is administered to the subject orally, parenterally, intradermally, subcutaneously, topically, or rectally.

79. The method of any one of claims 74-78, further comprising treating the subject with an additional therapeutic regimen for treating cancer.

80. The method of claim 79, wherein the additional therapeutic regimen is selected from the group consisting of surgery, chemotherapy, radiation therapy, hormone therapy, and immunotherapy.

81. The method of any one of claims 74-80, wherein the AKT-mediated disease is selected from the group consisting of inflammatory, hyperproliferative, cardiovascular, neurodegenerative, gynecological, and dermatological diseases and disorders.

82. The method of claim 81, wherein the hyperproliferative disease or disorder is selected from the group consisting of cancers angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma, myxoma, rhabdomyoma, fibroma, lipoma, teratoma, squamous cell carcinoma, undifferentiated small cell carcinoma, undifferentiated large cell carcinoma, adenocarcinoma, alveolar carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma, non-small cell lung cancer, small cell lung cancer, leiomyosarcoma, stomach carcinoma, ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma, carcinoid tumors, Karposi's sarcoma, leiomyoma, hemangioma, neurofibroma, tubular adenoma, villous adenoma, hamartoma, kidney cancer, Wilm's tumor, nephroblastoma, leukemia, bladder cancer, urethra cancer, transitional cell carcinoma, prostate cancer, seminoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, interstitial cell carcinoma, fibroadenoma, adenomatoid tumors, hepatoma, hepatocellular carcinoma, cholangiocarcinoma, hepatoblastoma, hepatocellular adenoma, osteogenic sarcoma, osteosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma, reticulum cell sarcoma, multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma, osteocartilaginous exostoses, benign chondroma,

chondroblastoma, chondromyxofibroma, osteoid osteoma, giant cell tumors, osteoma, granuloma, xanthoma, osteitis deformans, meningioma, meningiosarcoma, gliomatosis, astrocytoma, medulloblastoma, glioma, ependymoma, germinoma, pinealoma, glioblastoma multiforme, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors, spinal cord neurofibroma, endometrial carcinoma, cervical carcinoma, pre-tumor cervical dysplasia, ovarian carcinoma, serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma, granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, intraepithelial carcinoma, melanoma, clear cell carcinoma, botryoid sarcoma, embryonal fallopian tubes carcinoma, acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, myelodysplastic syndrome, Hodgkin's disease, non-Hodgkin's lymphoma, advanced melanoma, malignant melanoma, basal cell carcinoma, moles dysplastic nevi, angioma, dermatofibroma, keloids, psoriasis, neuroblastoma, metastatic breast cancer, colon cancer, oral cancer, hairy cell leukemia, head and neck cancer, refractory metastatic disease; Kaposi's sarcoma, Bannayan-Zonana syndrome, Cowden disease, and Lhermitte-Duclos disease.

83. The method of any one of claims 74-82, wherein the AKT-mediated disease is a relapsed cancer.

84. The method of any one of claims 74-81, wherein the AKT-mediated disease is selected from the group consisting of rheumatoid arthritis, osteoarthritis, Crohn's disease, angiofibroma, retinal vascularization, diabetic retinopathy, age-related macular degeneration, macular degeneration, multiple sclerosis, obesity, Alzheimer's disease, restenosis, autoimmune diseases, allergy, asthma, endometriosis, atherosclerosis, vein graft stenosis, peri-anastomatic prosthetic graft stenosis, prostate hyperplasia, chronic obstructive pulmonary disease, psoriasis, inhibition of neurological damage due to tissue repair, scar tissue formation, multiple sclerosis, inflammatory bowel disease, infections, particularly bacterial, viral, retroviral or parasitic infections, pulmonary disease, neoplasm, Parkinson's disease, transplant rejection, and septic shock.

85. The method of any one of claims 74-82 or 84, wherein the AKT-mediated disease is a relapsed disease.

86. The method of any one of claims 74-85, wherein the AKT-mediated disease is refractory to one or more previous treatments.

87. The method of any one of claims 74-85, wherein the AKT-mediated disease is refractory to one or more previous treatments by different therapies.

88. The method of any one of claims 74-87, further comprising treatment with an m-TOR inhibitor.

89. The method of claim 88, wherein the m-Tor inhibitor is Torin 1 or rapamycin.

90. A bivalent compound comprising a serine threonine kinase (AKT) ligand conjugated to a degradation/disruption tag through a linker.

91. The bivalent compound of claim 88, wherein the AKT ligand is an AKT inhibitor.

92. The bivalent compound of claim 89, wherein the AKT ligand is selected from the group consisting of GSK690693, GSK2110183, GSK2141795, AZD5363, GDC-0068, MK-2206, ARQ-092, and analogs thereof.

93. The bivalent compound of any one of claims 88-90, wherein the AKT ligand is bound to AKT or AKT mutant proteins.

94. The bivalent compound of any one of claims 88-91, wherein the degradation/disruption tag is selected from the group consisting of pomalidomide, thalidomide, lenalidomide, VHL-1, adamantane, 1-((4,4,5,5,5-pentafluoropentyl)sulfinyl)nonane, nutlin-3a, RG7112, RG7338, AMG232, AA-115, bestatin, MV-1, LCL161, and analogs thereof.

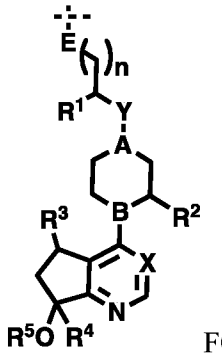
95. The bivalent compound of any one of claims 88-92, wherein the degradation/disruption tag binds to a ubiquitin ligase or serves as a hydrophobic group that leads to AKT protein misfolding.

96. The bivalent compound of any one of claims 88-93, wherein the bivalent compound has the form 

,

wherein PI comprises an AKT ligand and EL comprises a degradation/disruption tag.

97. The bivalent compound of claim 94, wherein PI comprises:



FORMULA 1,

wherein

A, B, and X are independently N, CH, or CR^6,

Y is CH_2, CO, SO, SO_2, CR^7R^8, $CONR^7$, or SO_2NR^7,

E is NH, NR^9, O, C_1-C_8 alkyl, C_1-C_8 alkoxy, C_1-C_8 alkoxyalkyl, C_1-C_8 haloalkyl, C_1-C_8 hydroxyalkyl, C_3-C_8 cycloalkyl, C_3-C_7 heterocyclyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, OR^9, SR^9, NR^9R^{10}, CN, NO_2, $(CR^9R^{10})_mNR^{11}R^{12}$, $(CR^9R^{10})_mC(O)R^{11}$, $(N\ R^9R^{10})_mNR^{11}R^{12}$, $(NR^9R^{10})_mC(O)R^{11}$, COR^9, CO_2R^9, $CONR^9R^{10}$, NR^9COR^{10}, NR^9SOR^{10}, $NR^9SO_2R^{10}$, SOR^9, SO_2R^9, $SO_2NR^9R^{10}$, $(CR^9R^{10})_m$-aryl, or $(CR^9R^{10})_m$-heteroaryl,

R^1 is H, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkoxy, C_1-C_8 alkoxyalkyl, aryl, C_1-C_8 alkylaryl, haloaryl, arylalkyl, heteroaryl, or heteroarylalkyl,

R^2, R^3, R^4, and R^6 are independently hydrogen, halogen, amino, C_1-C_8 alkylamino, arylamino, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkoxy, or C_1-C_8 alkoxyalkyl,

R^5, R^7, and R^8 are independently H, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, or C_1-C_8 alkoxyalkyl,

R^9, R^{10}, R^{11}, and R^{12} are independently H, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkoxy, C_2-C_8 alkenyl, C_2-C_8 alkynyl, arylalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, or heteroarylalkyl,

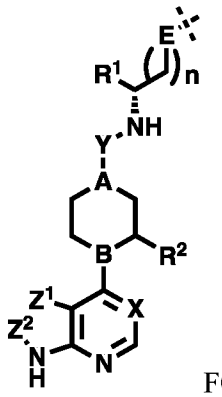
R^9 and R^{10}, R^{11} and R^{12} can independently form 4-8 membered alkyl or heterocyclyl rings,

m = 0-8,

and

n = 0-8.

98. The bivalent compound of claim 94, wherein PI comprises:



FORMULA 3,

wherein

A, B, and X are independently N or CR^3,

Y is CH_2, CO, SO, SO_2, CR^4R^5, $CONR^4$, or SO_2NR^4,

E is NH, NR^6, O, C_1-C_8 alkyl, C_1-C_8 alkoxy, C_1-C_8 alkoxyalkyl, C_1-C_8 haloalkyl, C_1-C_8 hydroxyalkyl, C_3-C_8 cycloalkyl, C_3-C_8 heterocyclyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, OR^6, SR^6, NR^6R^7, CN, NO_2, $(CR^6R^7)_mNR^8R^9$, $(CR^6R^7)_mC(O)R^8$, $(NR^6R^7)_mNR^8R^9$, $(NR^6R^7)_mC(O)R^8$, COR^6, CO_2R^6, $CONR^6R^7$, NR^6COR^7, NR^6SOR^7, $NR^6SO_2R^7$, SOR^6, SO_2R^6, $SO_2NR^6R^7$, $(CR^6R^7)_m$-aryl, or $(CR^6R^7)_m$-heteroaryl,

Z^1-Z^2 is CR^{10}=CH, N+CH, or CR^{10}=N,

R^1 is hydrogen, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkoxy, C_1-C_8 alkoxyalkyl, aryl, C_1-C_8 alkylaryl, haloaryl, arylalkyl, heteroaryl, or heteroarylalkyl,

R^2, R^3, and R^4 are independently hydrogen, halogen, amino, C_1-C_8 alkylamino, arylamino, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkoxy, or C_1-C_8 alkoxyalkyl,

R^6, R^7, R^8, and R^9 are independently H, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkoxy, C_2-C_8 alkenyl, C_2-C_8 alkynyl, arylalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, or heteroarylalkyl,

R^6 and R^7, R^8 and R^9 can independently form 4-8 membered alkyl or heterocyclyl rings,

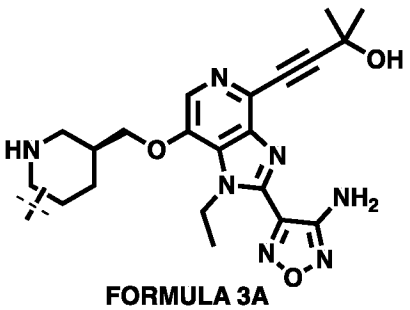
R^{10} is hydrogen, halogen, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkoxy, C_1-C_8 alkoxyalkyl,

m = 0-8,

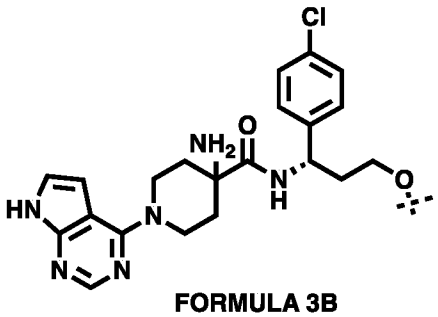
and

n = 0-8.

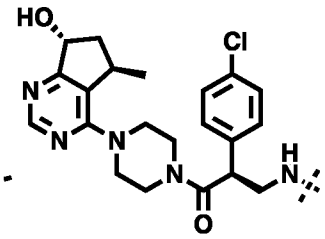
99. The bivalent compound of claim 94, wherein PI is selected from the group consisting of:



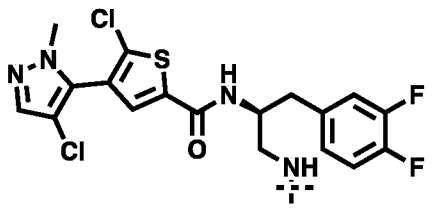
FORMULA 3A



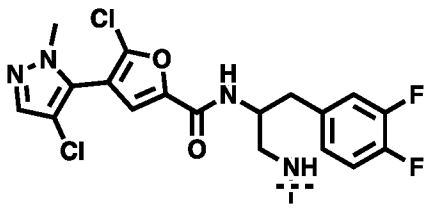
FORMULA 3B



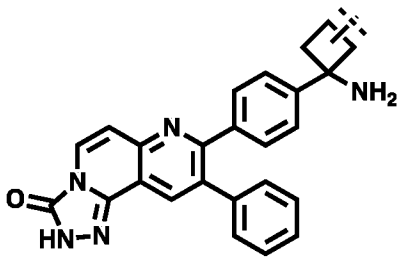
FORMULA 3C



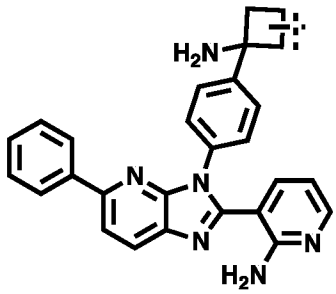
FORMULA 3D



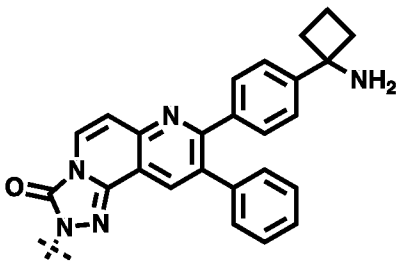
FORMULA 3E



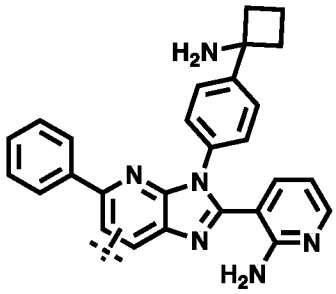
FORMULA 3F



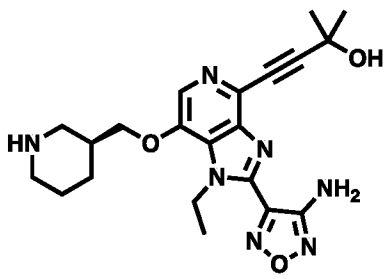
FORMULA 3G



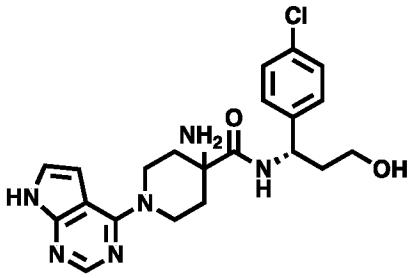
FORMULA 3H



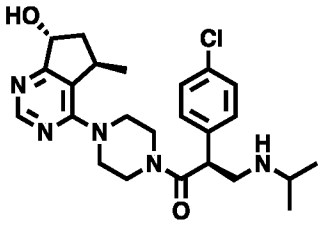
FORMULA 3I



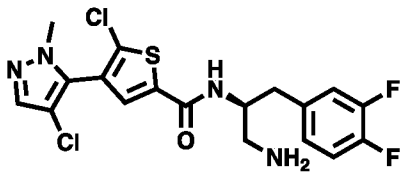
GSK690693



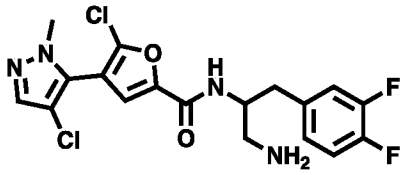
AZD5363



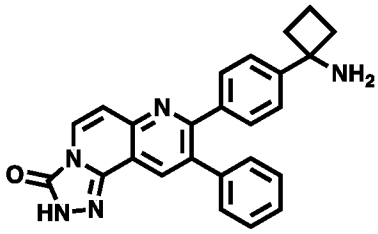
GDC0068



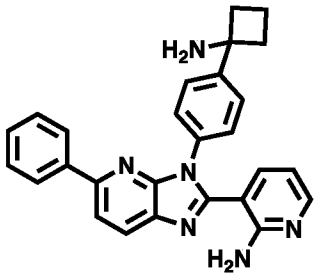
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GSK2141795



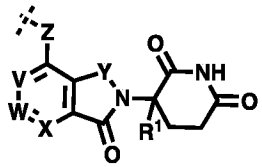
MK2206



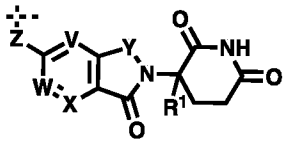
ARQ 092

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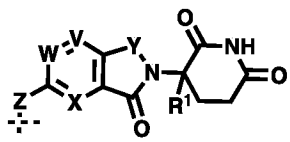
100. The bivalent compound of claim 94, wherein EL is selected from the group consisting of:



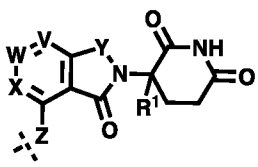
FORMULA 5A,



FORMULA 5B,



FORMULA 5C,



FORMULA 5D,

wherein

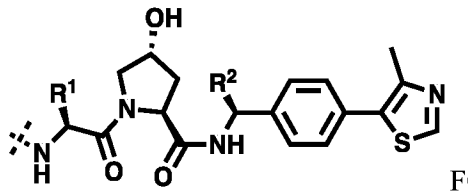
V, W, and X are independently CR^2 or N,

Y is CO or CH_2,

Z is CH_2, NH, or O,

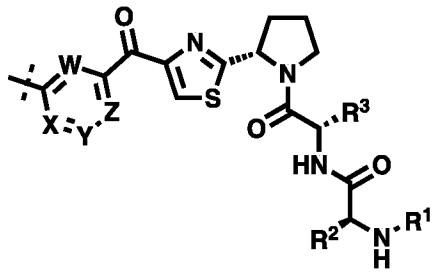
R^1 is hydrogen, methyl, or fluoro, and

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



FORMULA 6,

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_3-C_7 cycloalkyl, C_3-C_7 heterocyclyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl; and



FORMULA 8,

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.

101. The bivalent compound of claim 94, wherein EL binds to an ubiquitin ligase selected from the group consisting of a cereblon E3 ligase, a VHL E3 ligase, a MDM2 ligase, a TRIM21 ligase, a TRIM24 ligase, and an IAP ligase, or EL is a hydrophobic group that leads to ALK protein misfolding.

102. The bivalent compound of claim 94, wherein the linker comprises acyclic or cyclic saturated or unsaturated carbon, ethylene glycol, amide, amino, ether, urea, carbamate, aromatic, heteroaromatic, heterocyclic or carbonyl containing groups with different lengths.

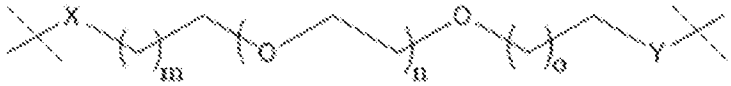
103. The bivalent compound of claim 99, wherein the linker is selected from the group consisting of:


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; and


Formula C,

wherein

X is C=O or CH_2,

Y is C=O or CH_2,

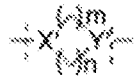
R is $–CH_2–$, $–CF_2–$, $–CH(C_{1-3}$ alkyl)–, $–C(C_{1-3}$ alkyl)(C_{1-3} alkyl)–, –CH=CH–, $–C(C_{1-3}$ alkyl)=$C(C_{1-3}$ alkyl)–, –C=C–, –O–, –NH–, $–N(C_{1-3}$ alkyl)–, $–C(O)NH–$, $–C(O)N(C_{1-3}$ alkyl)–, a 3-13 membered ring, a 3-13 membered fused ring, a 3-13 membered bridged ring, or a 3-13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

m is 0-15, and

n is 0-15.

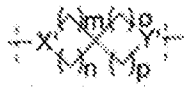
104. The bivalent compound of claim 101, wherein the linker is Formula C and R is selected from the group consisting of 3-13 membered rings, 3-13 membered fused rings, 3-13 membered bridged rings, and 3-13 membered spiro rings, wherein R contains one or more heteroatoms.

105. The bivalent compound of claim 101, wherein the linker is Formula C and R is selected from the group consisting of:



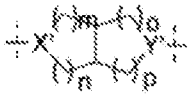
X' = N or CH
Y' = N or CH
m = 0-5
n = 0-5

Formula C1,



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

Formula C2,



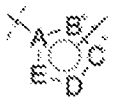
X' = N or CH
Y' = N or CH
m = 0-5
n = 0-5
o = 0-5
p = 0-5

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

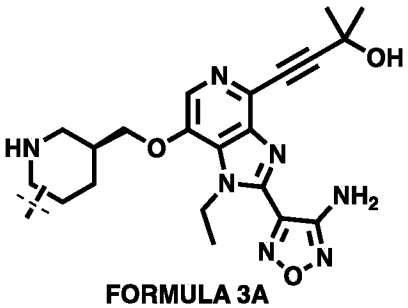
Formula C4, and



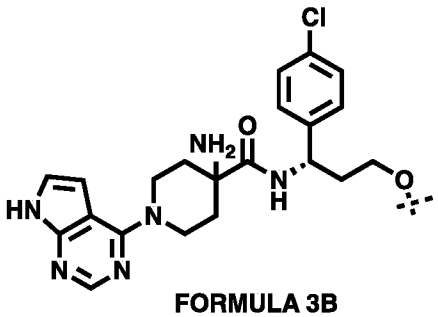
A = C, CH, C(C_{1-3} alkyl), N, NH, N(C_{1-3} alkyl), O, S
B = C, CH, C(C_{1-3} alkyl), N, NH, N(C_{1-3} alkyl), O, S
C = C, CH, C(C_{1-3} alkyl), N, NH, N(C_{1-3} alkyl), O, S
D = C, CH, C(C_{1-3} alkyl), N, NH, N(C_{1-3} alkyl), O, S
E = C, CH, C(C1-3 alkyl), N, NH, N(C1-3alkyl), O, S

Formula C5.

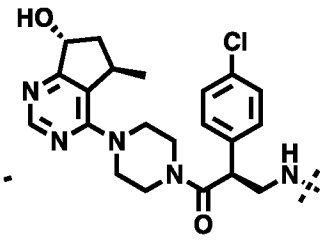
106. The bivalent compound of claim 88, wherein the AKT ligand is selected from the group consisting of:



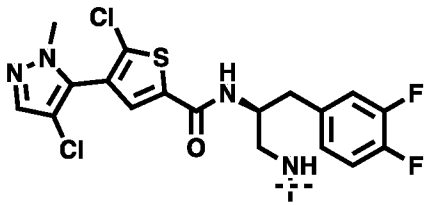
FORMULA 3A



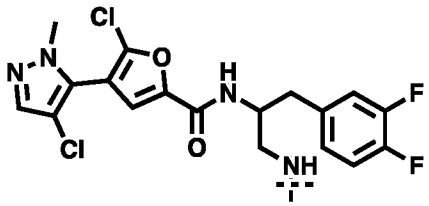
FORMULA 3B



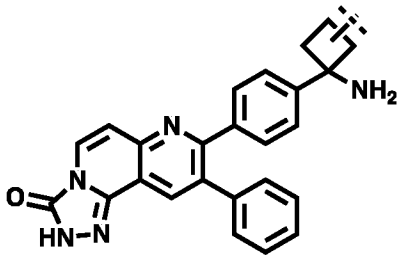
FORMULA 3C



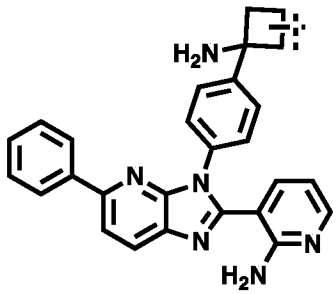
FORMULA 3D



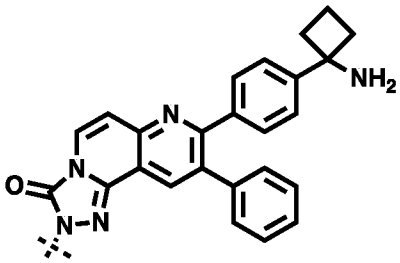
FORMULA 3E



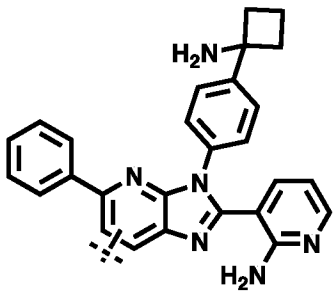
FORMULA 3F



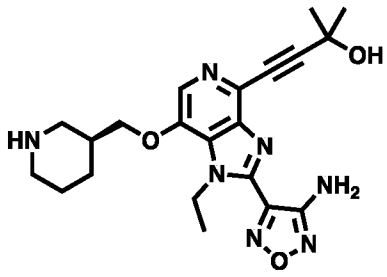
FORMULA 3G



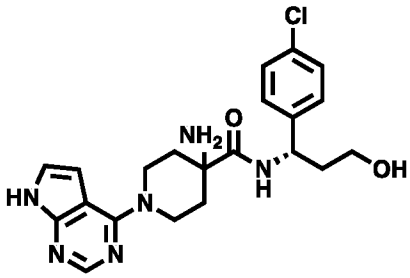
FORMULA 3H



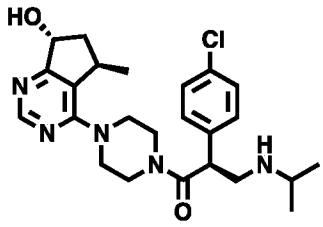
FORMULA 3I



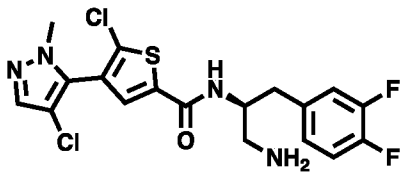
GSK690693



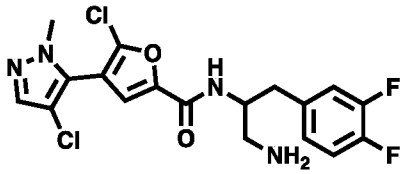
AZD5363



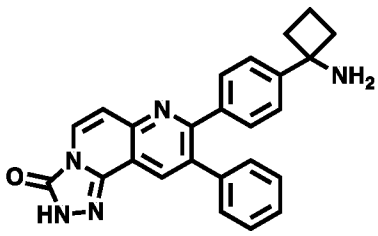
GDC0068



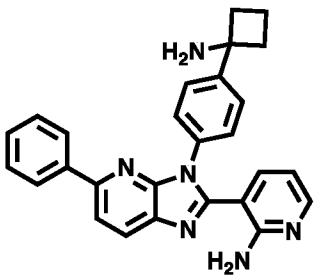
GSK2110183



GSK2141795



MK2206



ARQ 092

107. The bivalent compound of claim 93, wherein the ubiquitin ligase is an E3 ligase.

108. The bivalent compound of claim 105, 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, and an IAP ligase.

109. The bivalent compound of any one of claims 88-106, wherein the bivalent compound is selected from the group consisting of XF038-157A, XF038-158A, XF038-159A, XF038-160A, XF038-161A, XF038-162A, XF038-164A, XF038-165A, XF038-166A, XF038-176A, XF038-177A, XF042-162, XF042-164, XF042-165, XF042-166, XF042-167, XF042-168, XF042-170, XF042-171, XF048-1, XF048-2, XF048-3, XF048-4, XF048-5, XF048-7, XF048-8, XF050-5, XF050-6, XF050-7, XF050-8, XF050-9, XF050-10, XF050-11, XF050-12, XF050-13, XF050-14, XF050-15, XF050-16, XF050-17, XF050-18, XF050-19, XF050-20, XF050-21, XF050-22,

XF050-23, XF050-24, XF050-25, XF050-26, XF050-27, XF050-28, XF050-29, XF050-30, XF050-31, XF050-32, XF050-33, XF050-98, XF050-132, XF050-133. XF050-134, XF056-93, XF050-143, XF050-144, XF050-145, XF050-167, XF056-33, XF056-34, XF056-35, XF056-36, XF056-37, XF056-73, XF061-10, XF067-1, XF067-2, XF067-3, XF067-4, XF067-5, XF067-6, XF067-7, XF067-8, XF067-9, XF067-10, XF067-11, XF067-12, XF067-13, XF067-14, XF067-15, XF067-16, XF067-17, XF067-18, XF067-19, XF067-20, XF067-21, XF067-22, XF067-23, XF067-24, XF067-25, XF067-26, XF067-27, XF067-28, XF067-29, XF067-30, XF067-31, XF067-32, XF067-33, XF067-34, XF067-35, XF067-36, XF067-37, XF067-38, XF067-39, XF067-40, XF067-41, XF067-42, XF067-43, XF067-44, XF067-45, XF067-46, XF067-47, XF067-48, XF067-49, XF067-50, XF067-51, XF067-52, XF067-53, XF067-54, XF067-55, XF067-56, XF067-57, XF067-58, XF067-59, XF067-84, XF067-85, XF067-86, XF067-87, XF067-88, XF067-89, XF067-90, XF067-91, XF067-92, XF067-93, XF067-94, XF067-95, XF067-96, XF067-97, XF067-98, XF067-99, XF067-100, XF067-101, XF067-102, XF067-103, XF067-104, XF067-105, XF067-106, XF067-107, XF067-108, XF067-109, XF067-110, XF067-111, XF067-112, XF067-113, and analogs thereof.

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

providing a heterobifunctional test compound comprising an AKT ligand conjugated to a degradation/disruption tag through a linker;

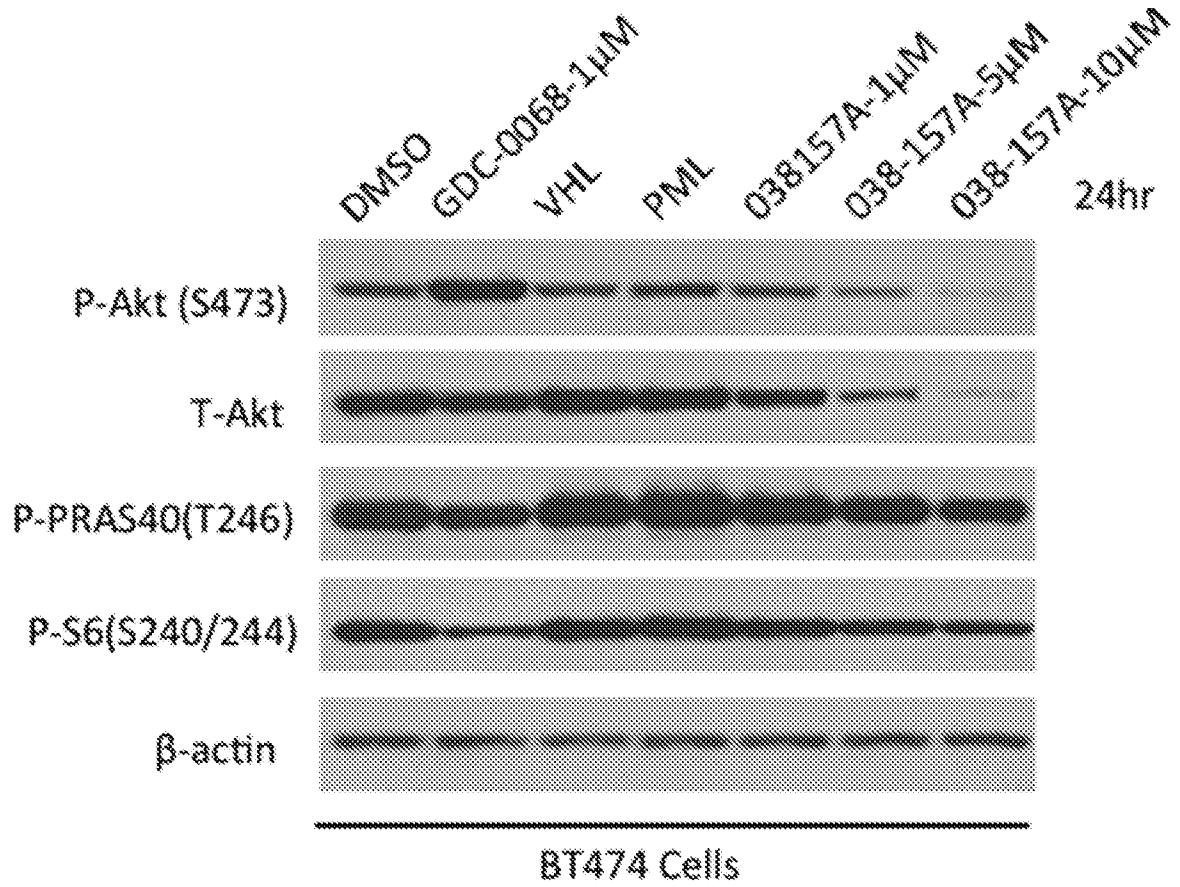
contacting the heterobifunctional test compound with a cell comprising a ubiquitin ligase and AKT;

determining whether AKT levels decrease in the cell; and

identifying the heterobifunctional test compound as a bivalent compound which mediates degradation/reduction of AKT levels decrease in the cell.

111. The method of claim 108, wherein the cell is a cancer cell.

112. The method of claim 109, wherein the cancer cell is an AKT-mediated cancer cell.


DMSO
GDC-0068-1μM
VHL
PML
038157A-1μM
038-157A-5μM
038-157A-10μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells

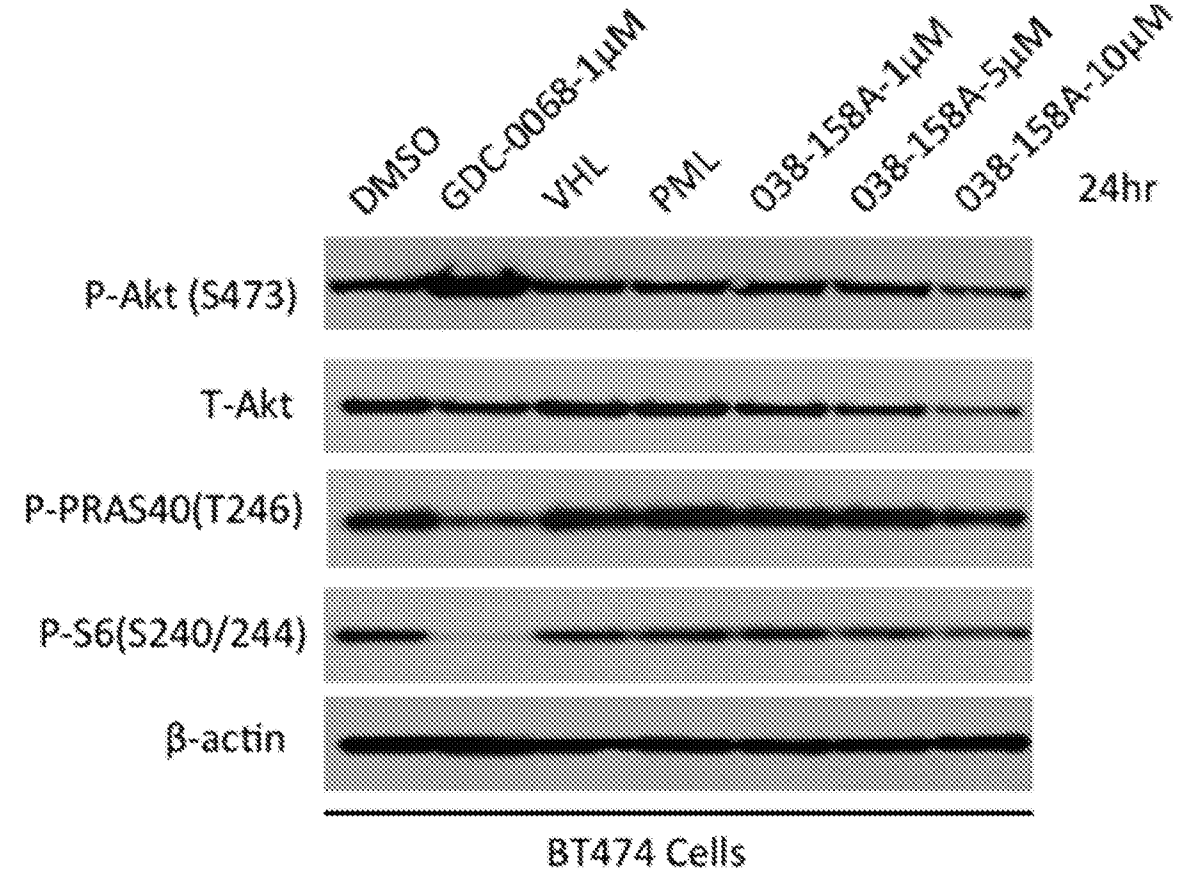
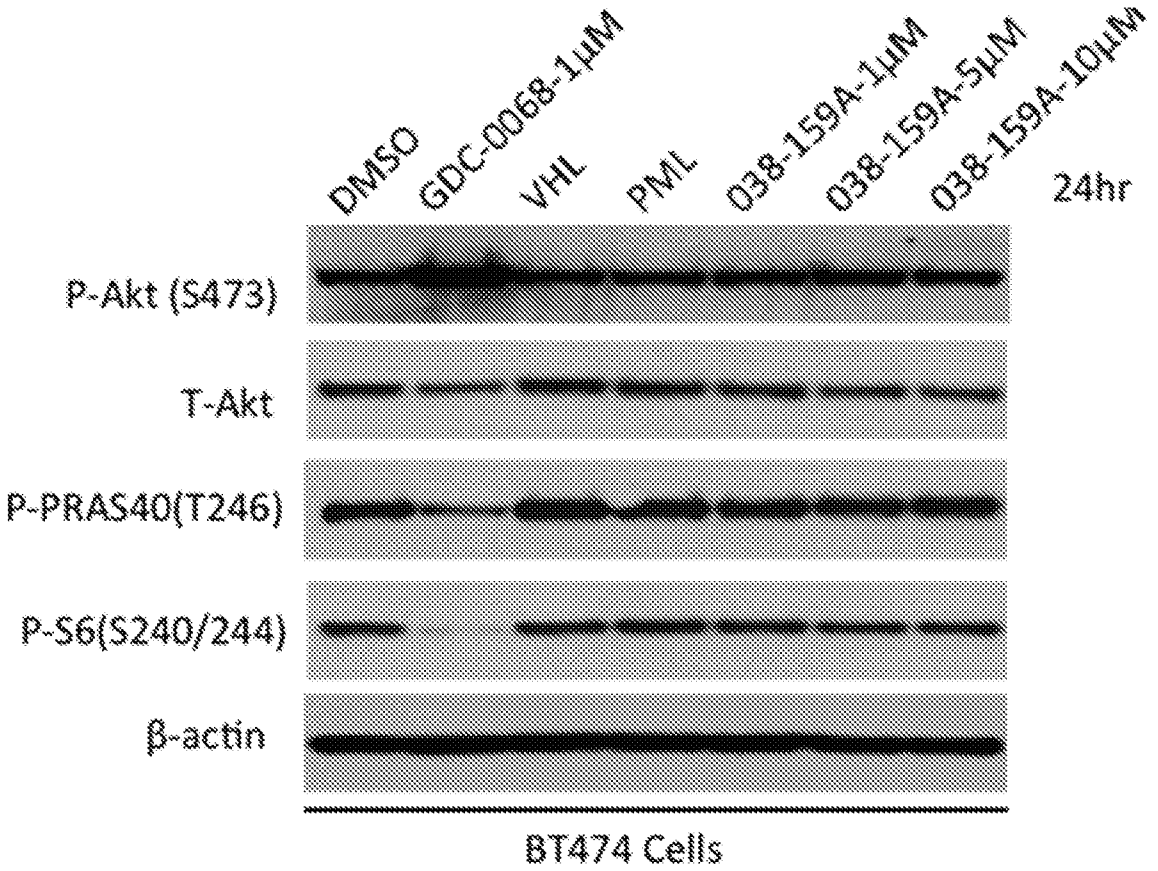

DMSO
GDC-0068-1μM
VHL
PML
038-158A-1μM
038-158A-5μM
038-158A-10μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells

FIG. 1A-1


DMSO
GDC-0068-1μM
VHL
PML
038-159A-1μM
038-159A-5μM
038-159A-10μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells

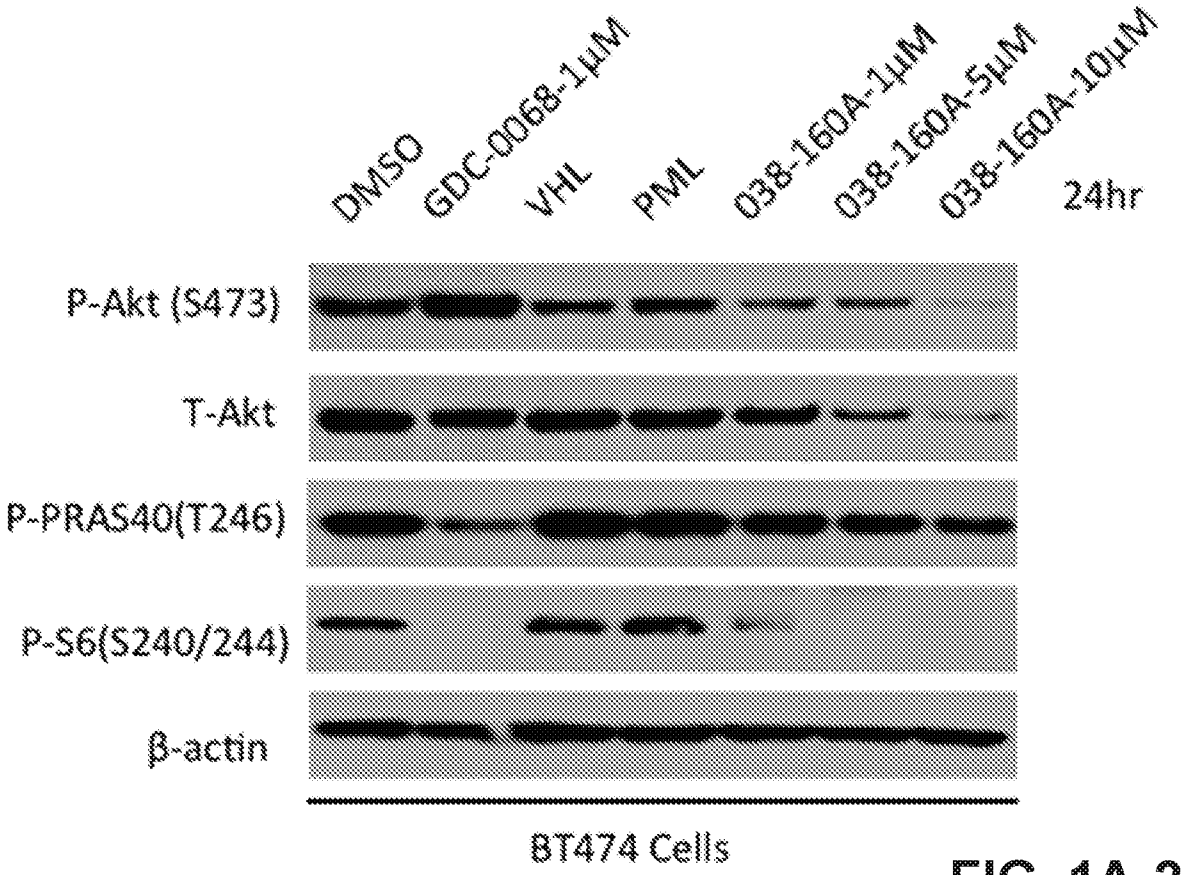
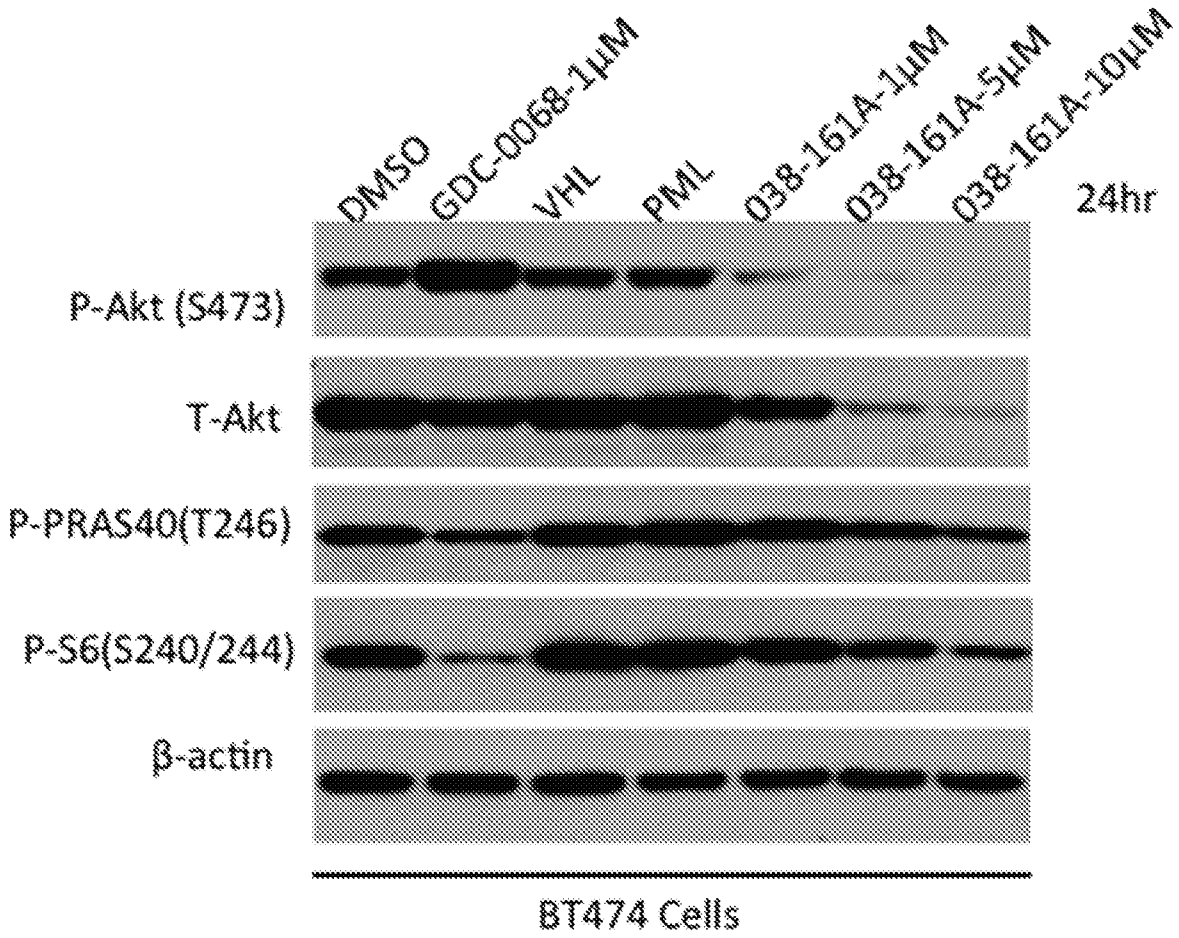

DMSO
GDC-0068-1μM
VHL
PML
038-160A-1μM
038-160A-5μM
038-160A-10μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells

FIG. 1A-2


DMSO
GDC-0068-1μM
VHL
PML
038-161A-1μM
038-161A-5μM
038-161A-10μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells

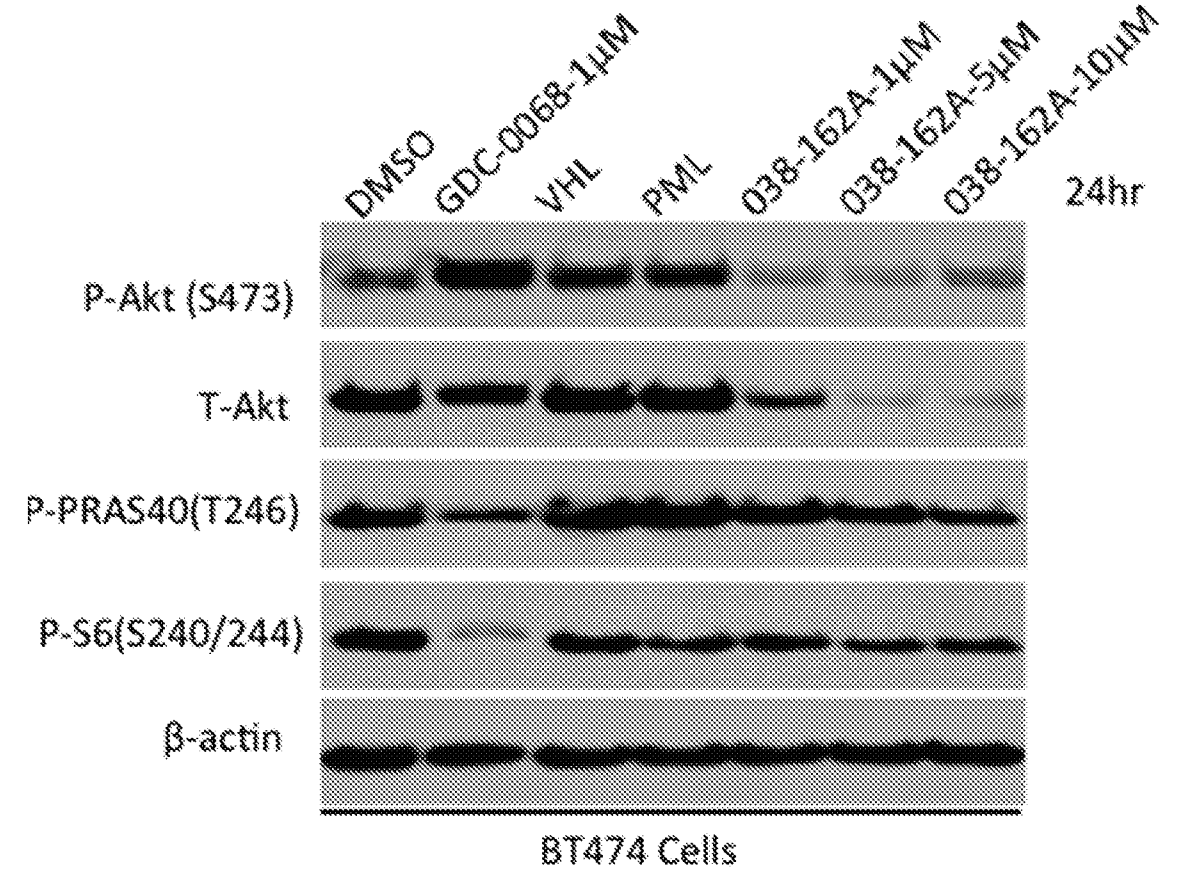
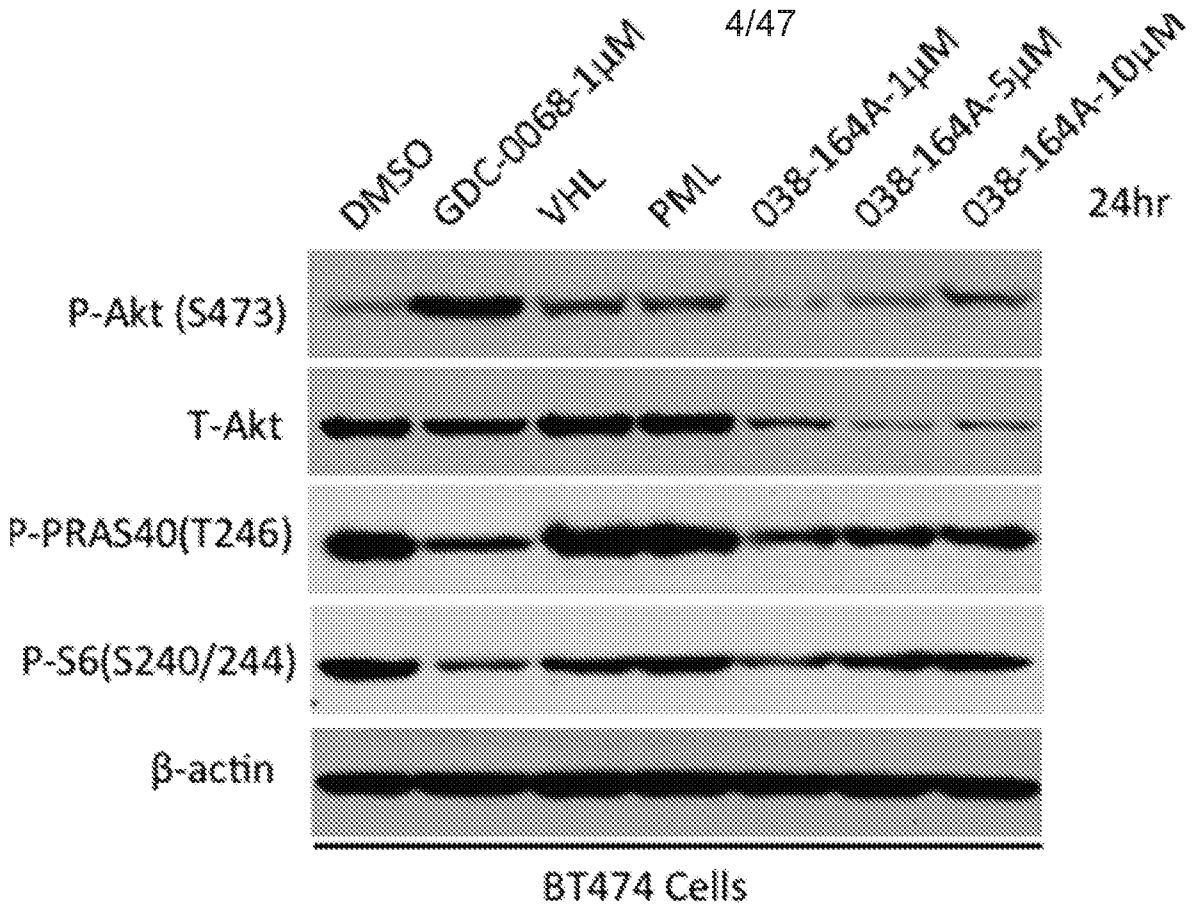

DMSO
GDC-0068-1μM
VHL
PML
038-162A-1μM
038-162A-5μM
038-162A-10μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells

FIG. 1A-3


DMSO
GDC-0068-1μM
VHL
PML
038-164A-1μM
038-164A-5μM
038-164A-10μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells

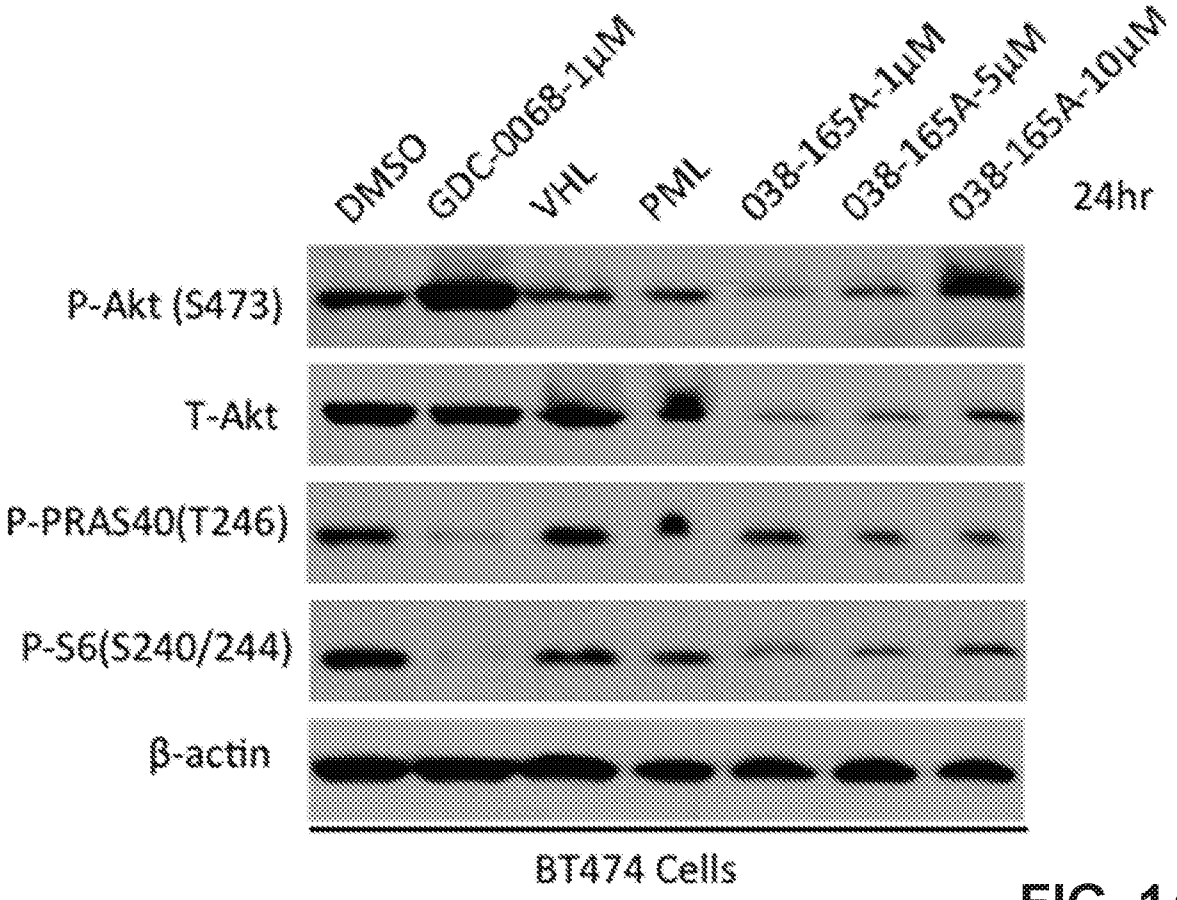

DMSO
GDC-0068-1μM
VHL
PML
038-165A-1μM
038-165A-5μM
038-165A-10μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells

FIG. 1A-4

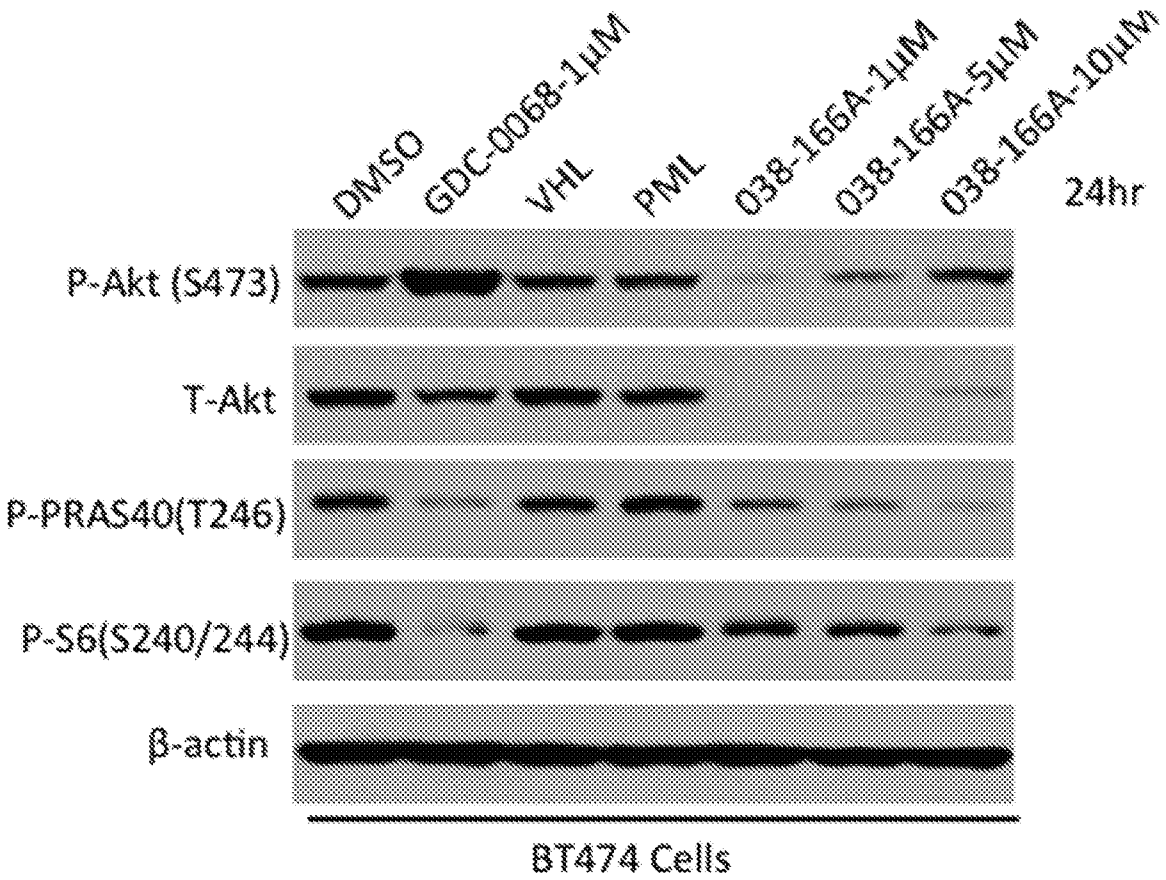
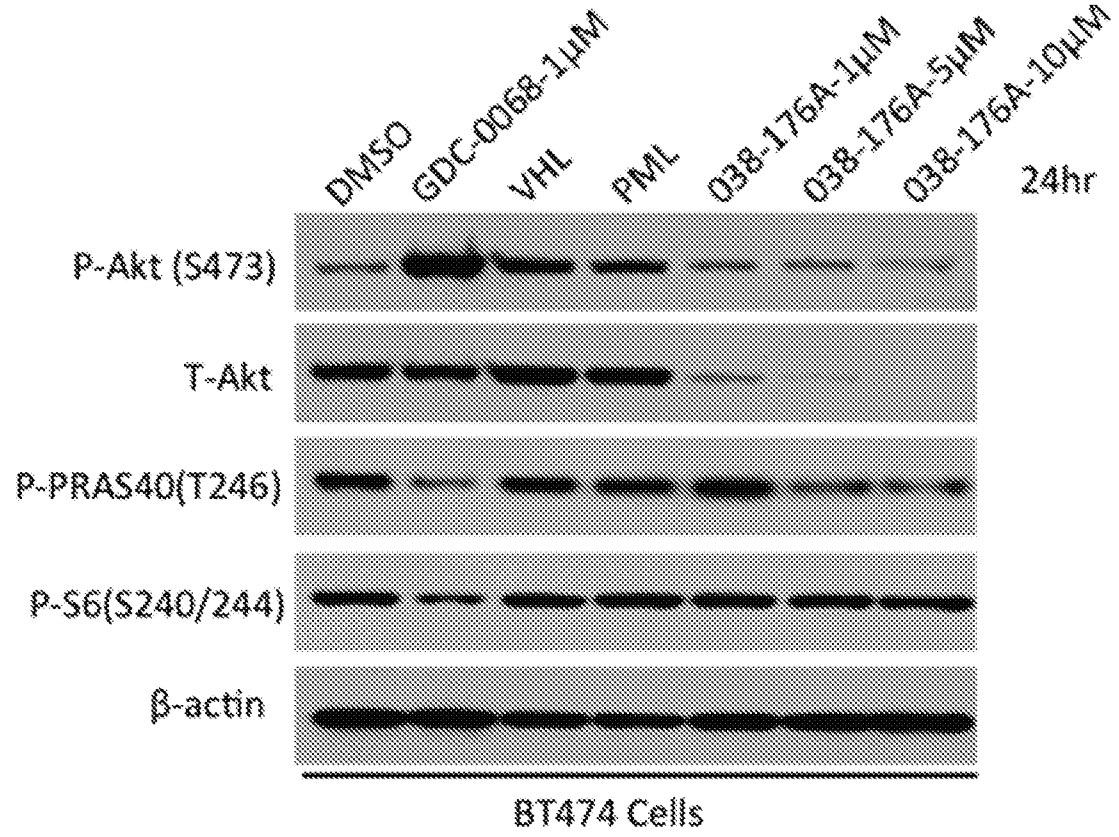

DMSO
GDC-0068-1μM
VHL
PML
038-166A-1μM
038-166A-5μM
038-166A-10μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells

FIG. 1A-5


DMSO
GDC-0068-1μM
VHL
PML
038-176A-1μM
038-176A-5μM
038-176A-10μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells

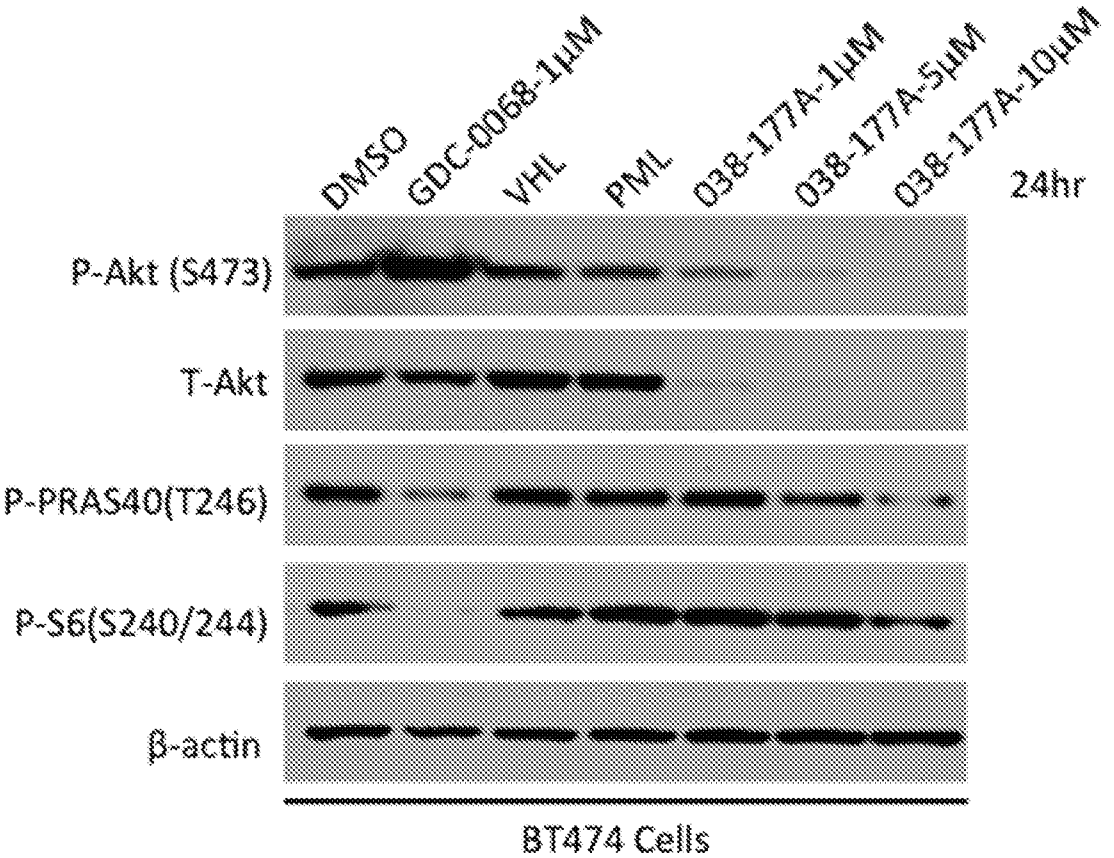

DMSO
GDC-0068-1μM
VHL
PML
038-177A-1μM
038-177A-5μM
038-177A-10μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells

FIG. 1B-1

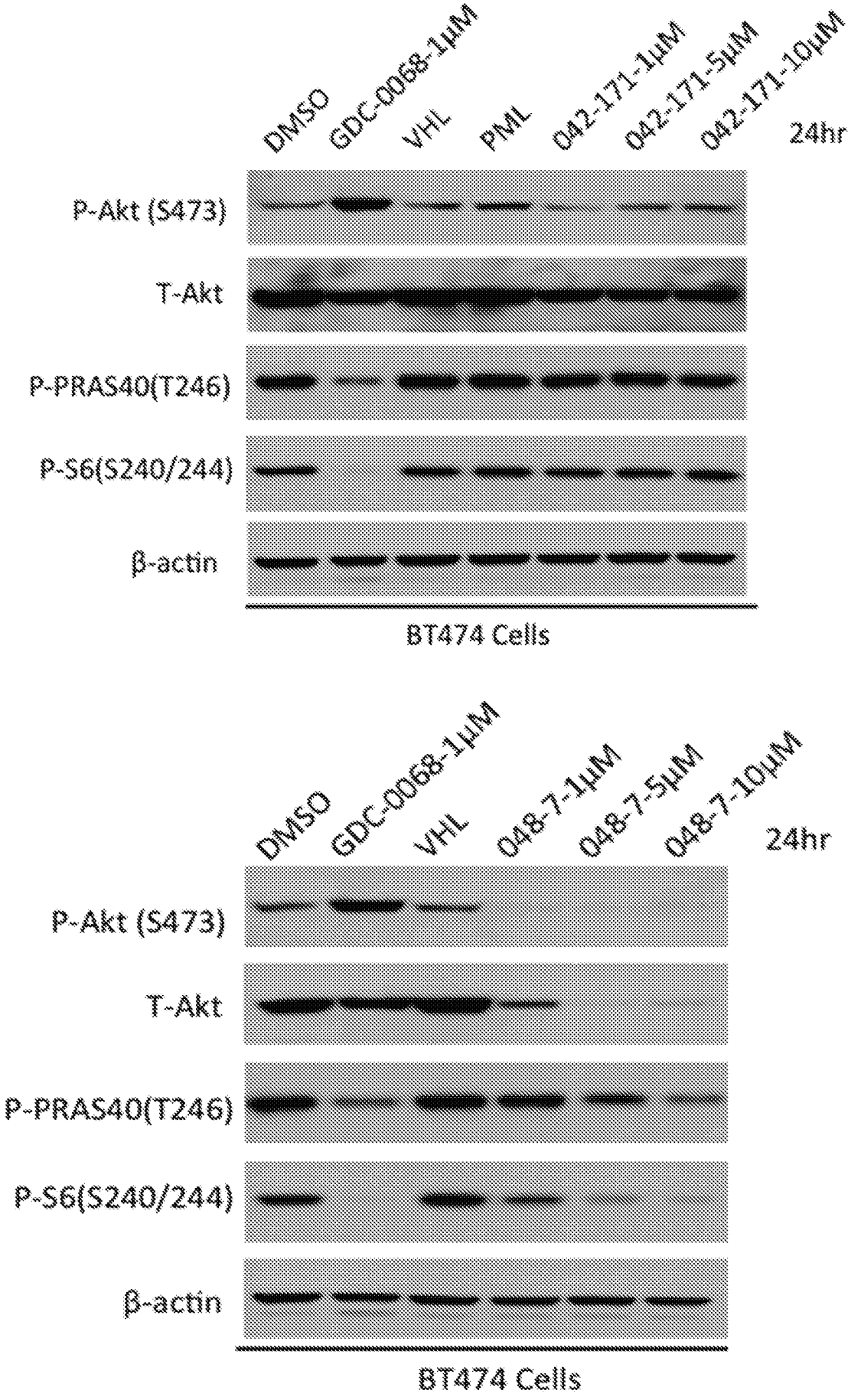

DMSO
GDC-0068-1μM
VHL
PML
042-171-1μM
042-171-5μM
042-171-10μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells
DMSO
GDC-0068-1μM
VHL
048-7-1μM
048-7-5μM
048-7-10μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells

FIG. 1B-2

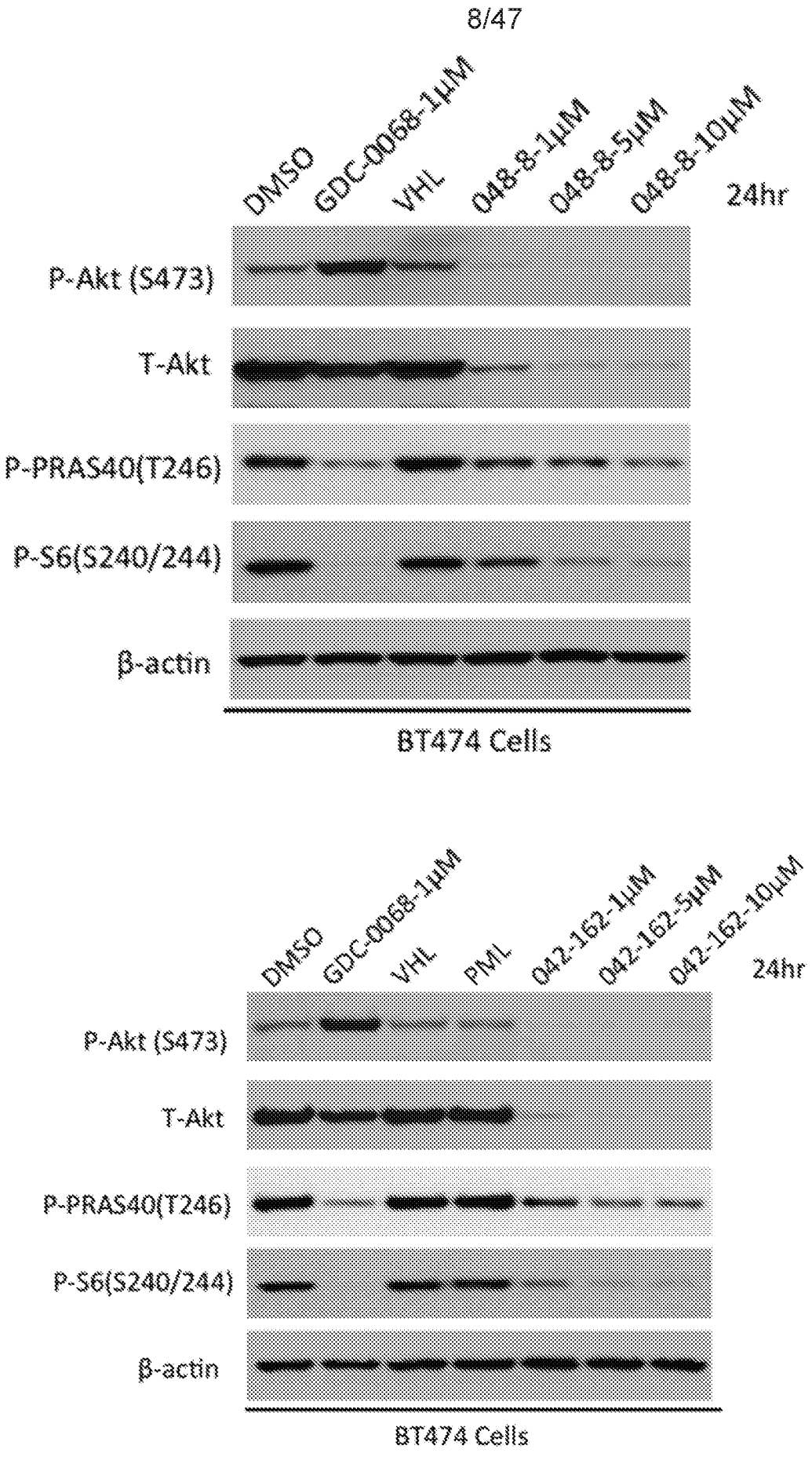
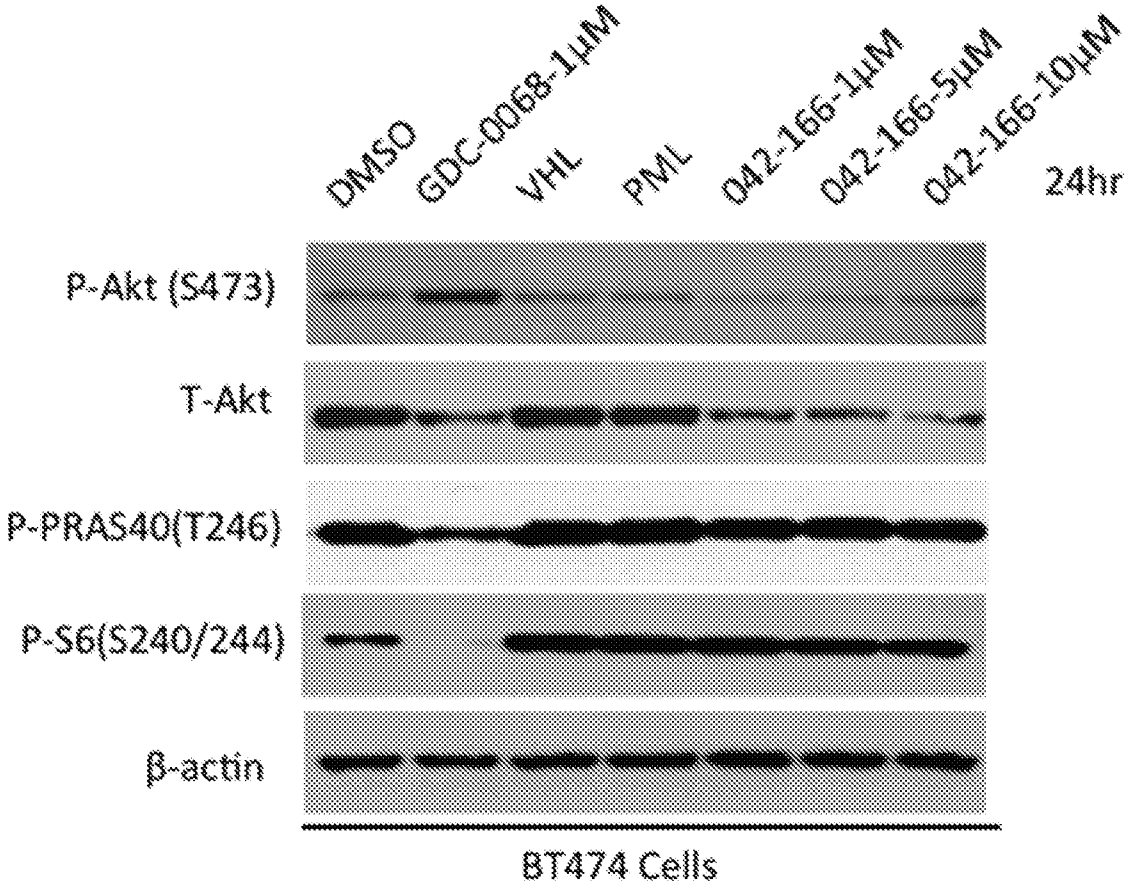

DMSO
GDC-0068-1μM
VHL
048-8-1μM
048-8-5μM
048-8-10μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells
DMSO
GDC-0068-1μM
VHL
PML
042-162-1μM
042-162-5μM
042-162-10μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells

FIG. 1B-3


DMSO
GDC-0068-1μM
VHL
PML
042-166-1μM
042-166-5μM
042-166-10μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells

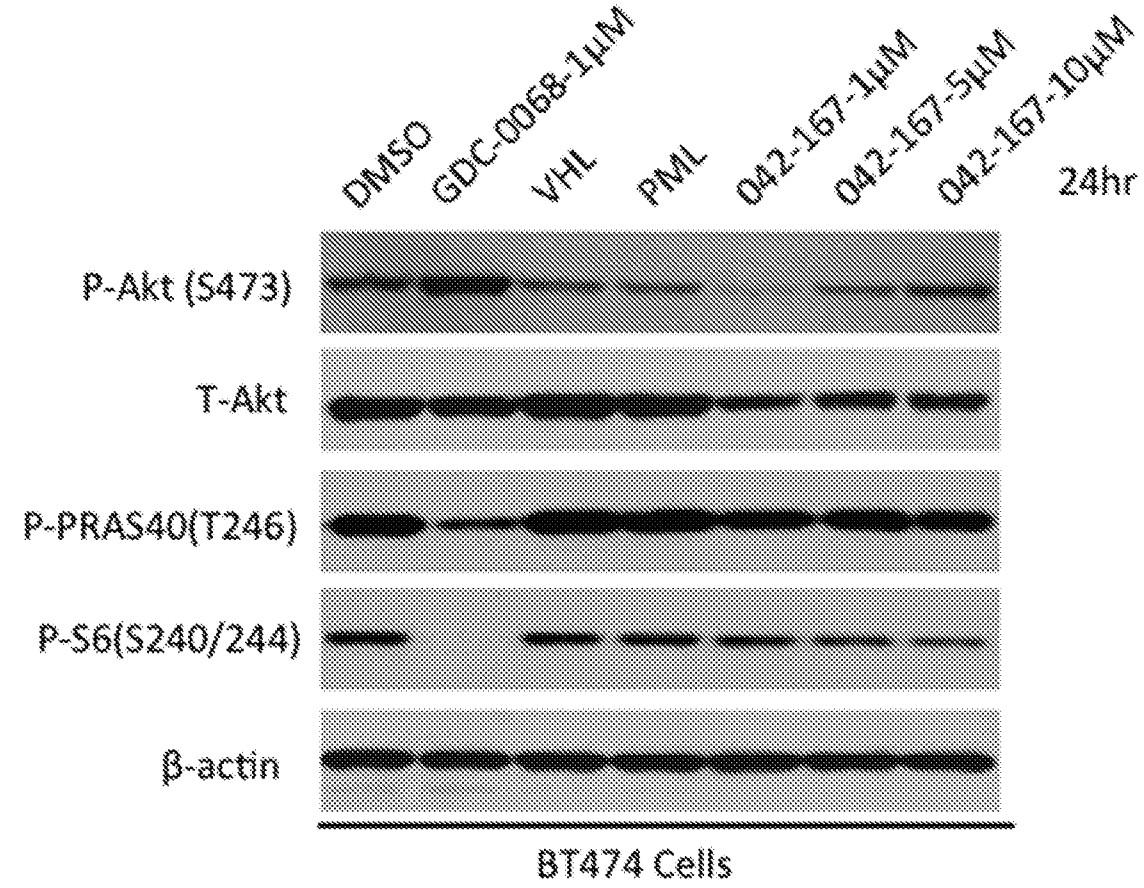

DMSO
GDC-0068-1μM
VHL
PML
042-167-1μM
042-167-5μM
042-167-10μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells

FIG. 1B-4

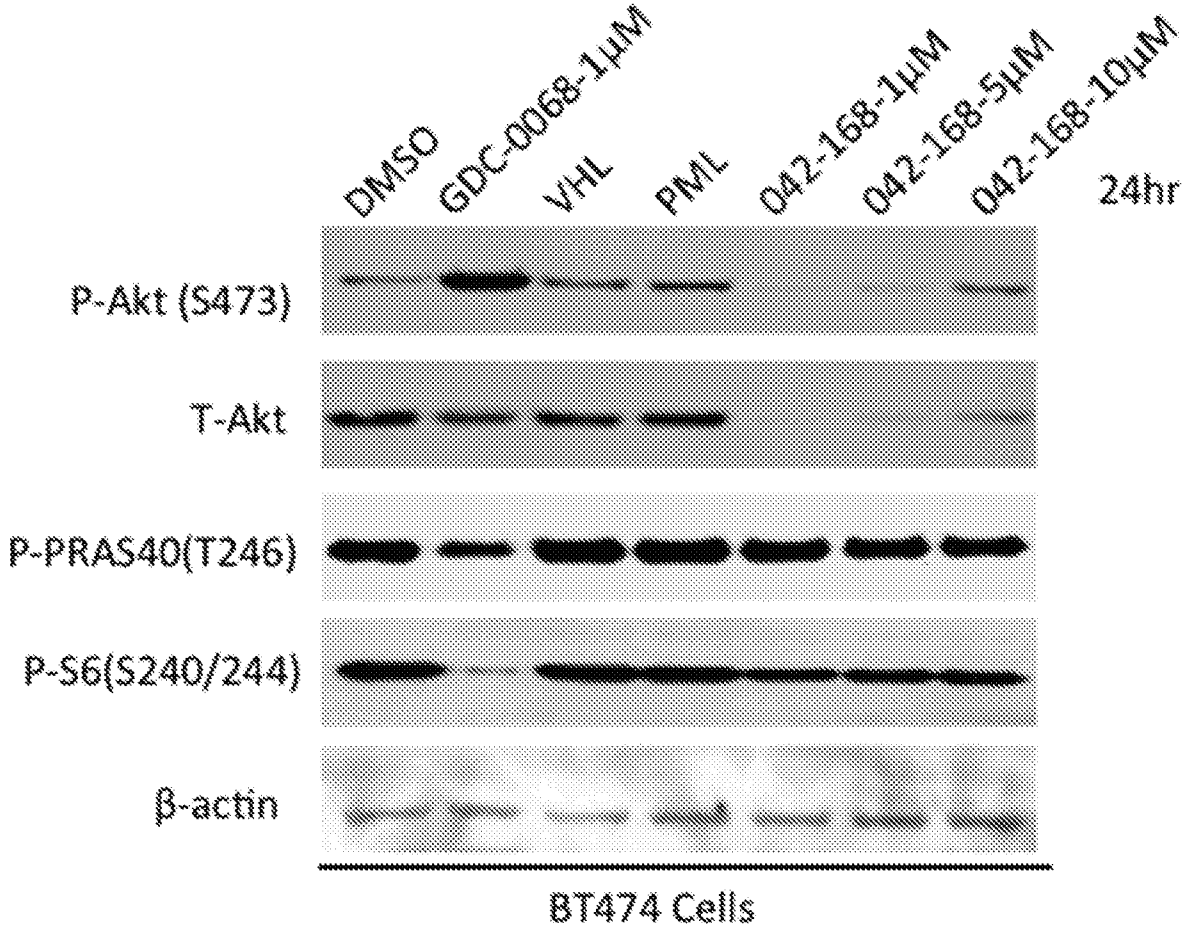
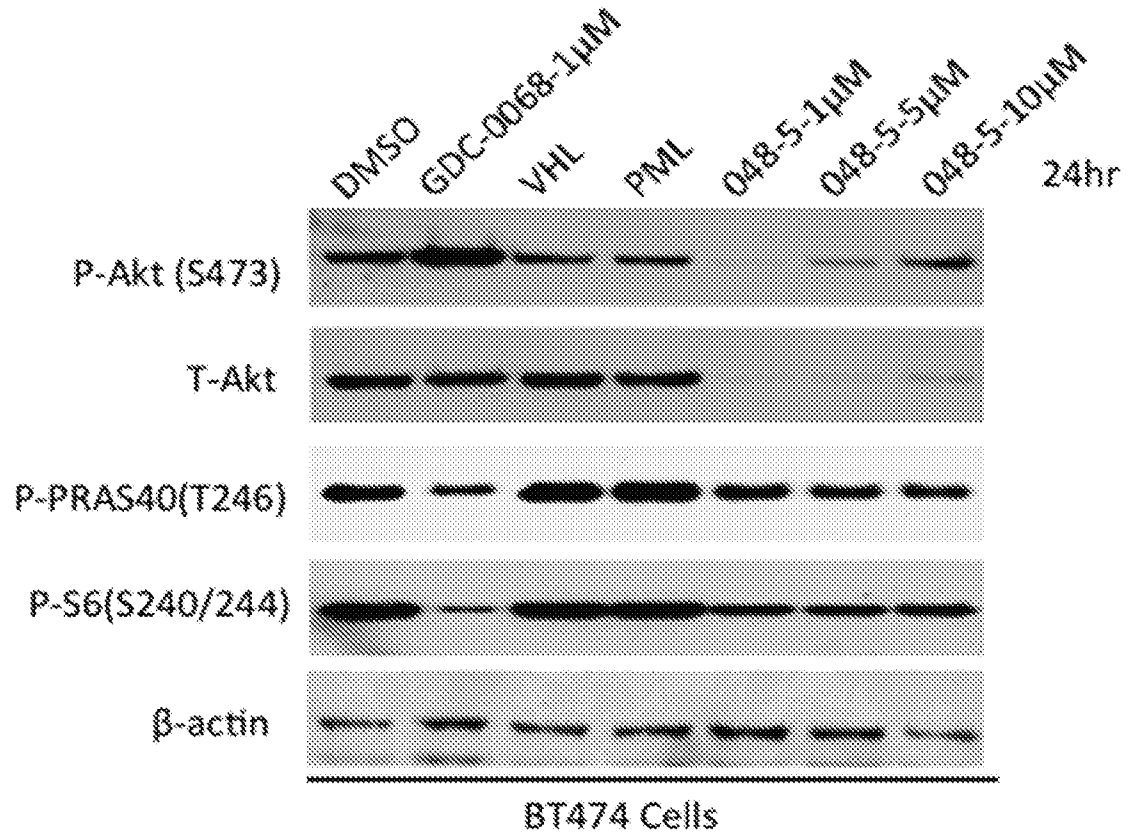

DMSO
GDC-0068-1μM
VHL
PML
042-168-1μM
042-168-5μM
042-168-10μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells

FIG. 1B-5


DMSO
GDC-0068-1μM
VHL
PML
048-5-1μM
048-5-5μM
048-5-10μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells

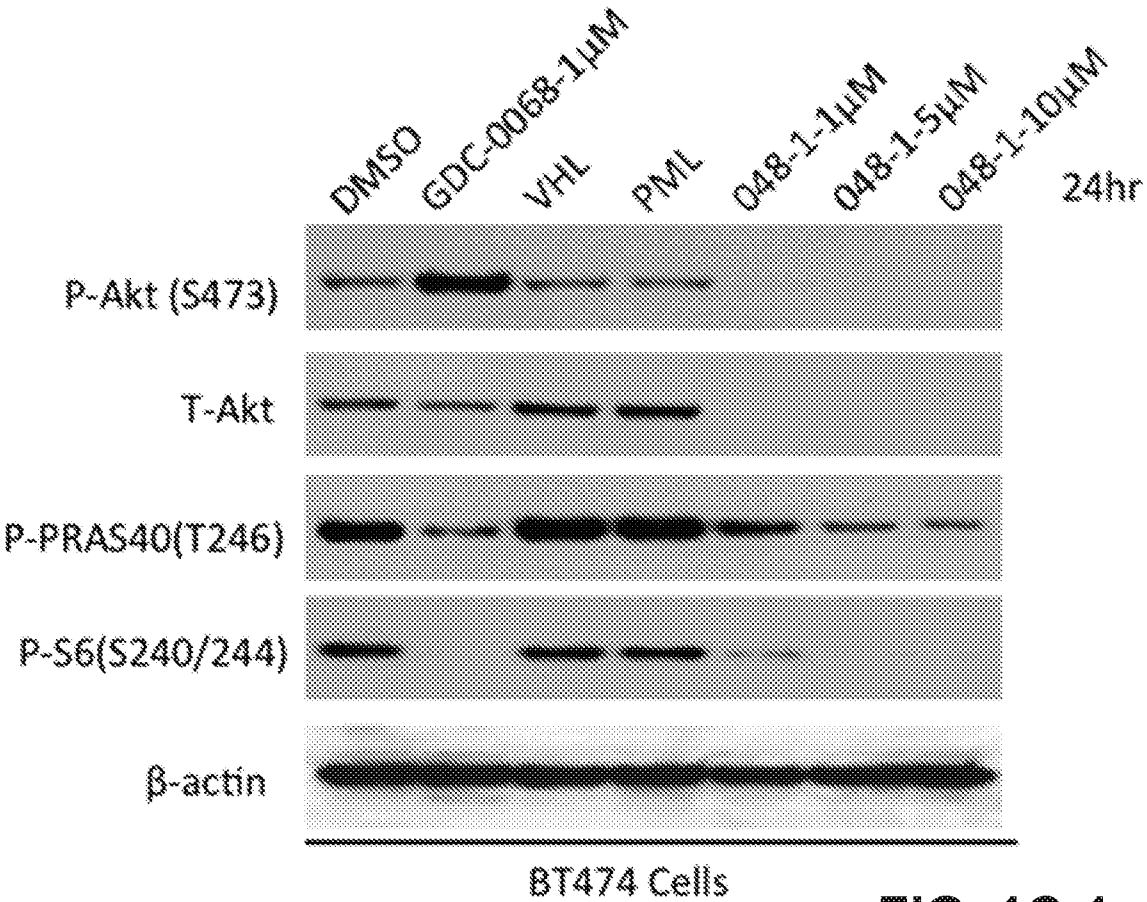
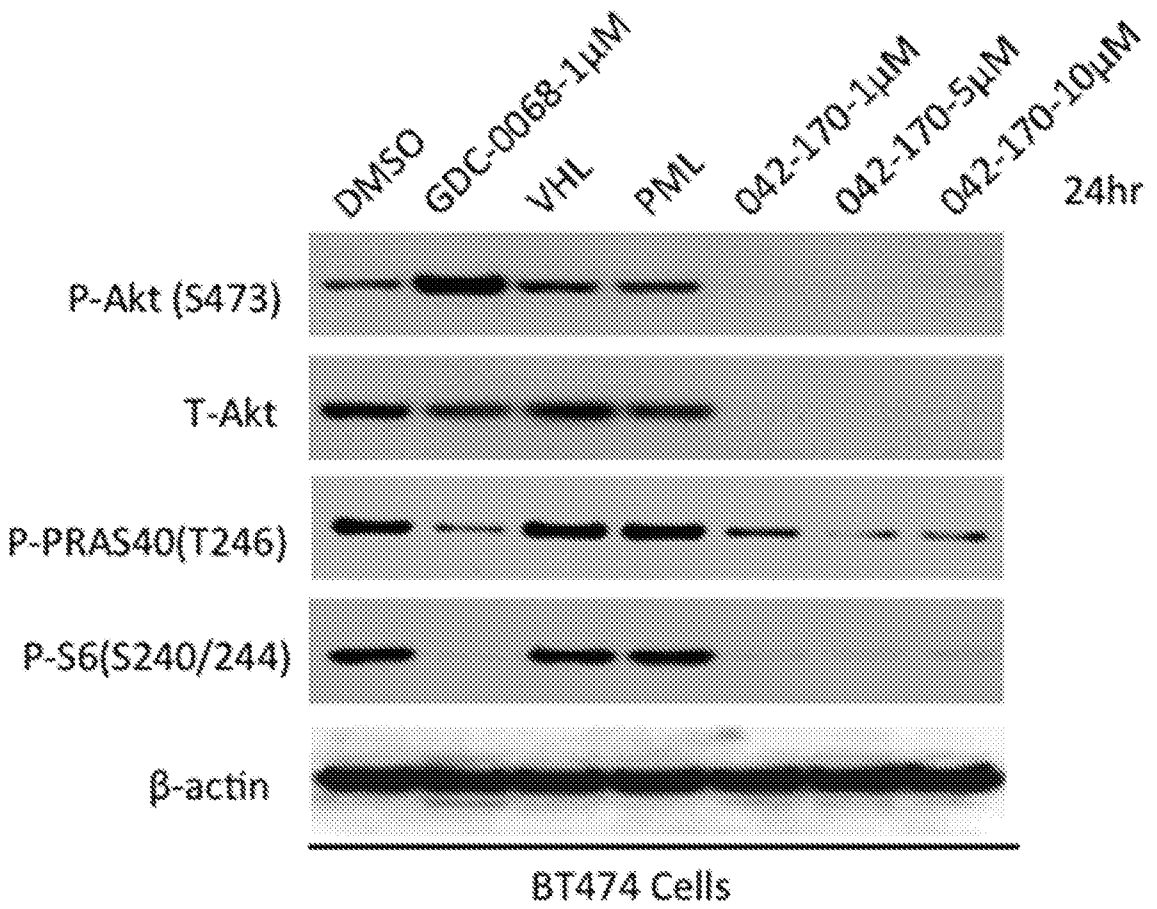

DMSO
GDC-0068-1μM
VHL
PML
048-1-1μM
048-1-5μM
048-1-10μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells

FIG. 1C-1


DMSO
GDC-0068-1μM
VHL
PML
042-170-1μM
042-170-5μM
042-170-10μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells

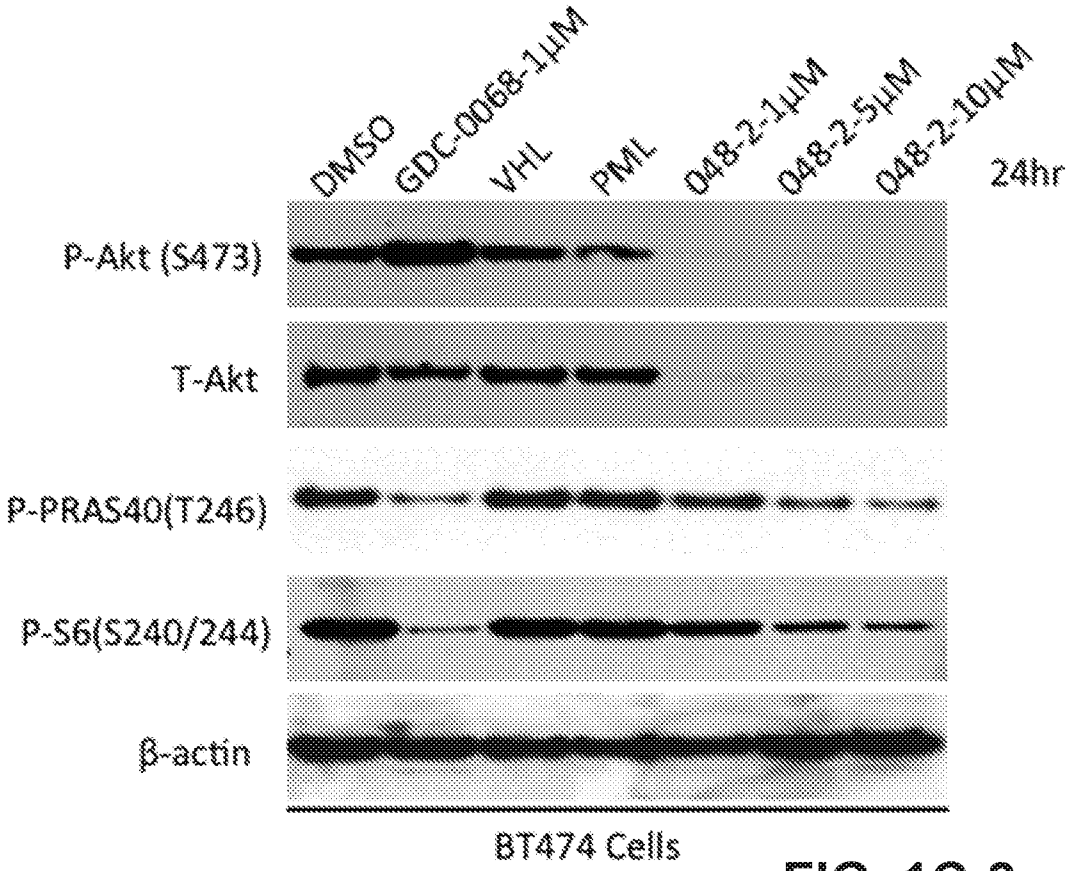
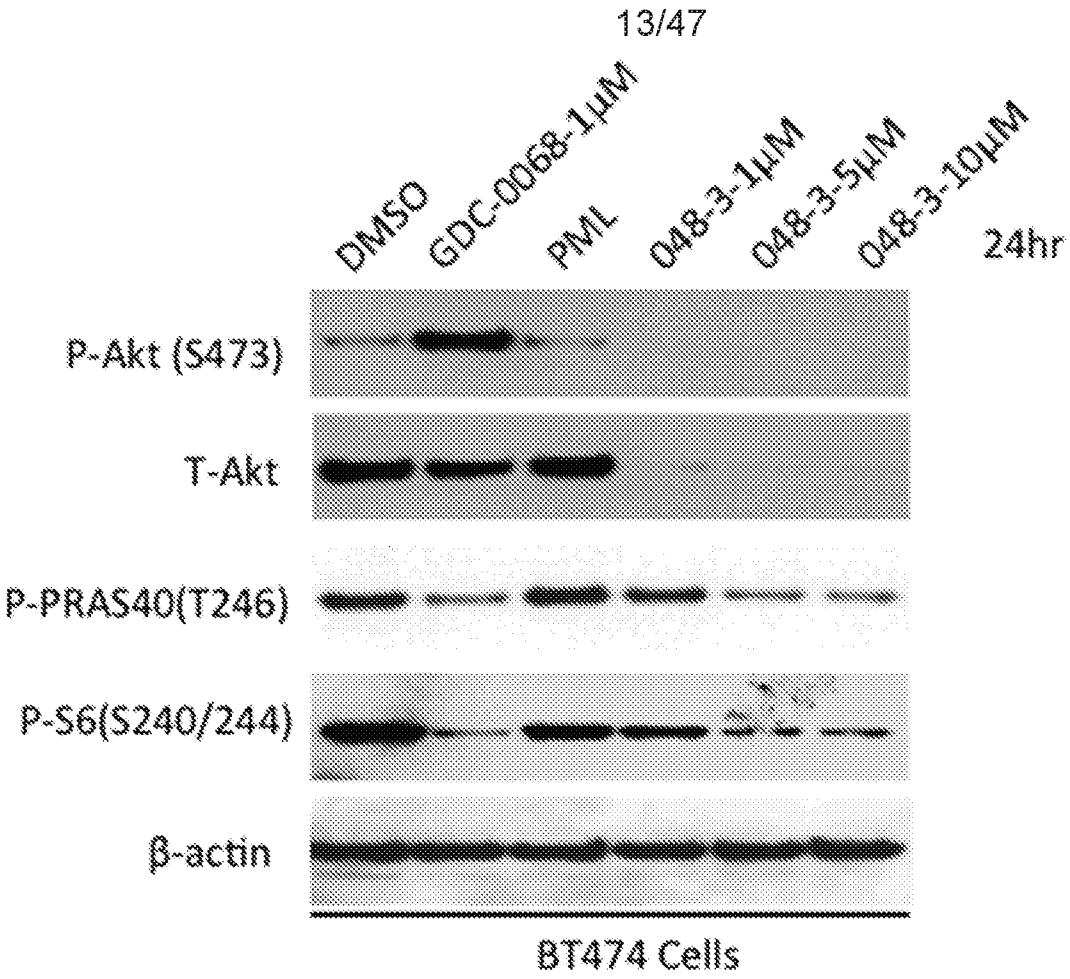

DMSO
GDC-0068-1μM
VHL
PML
048-2-1μM
048-2-5μM
048-2-10μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells

FIG. 1C-2


DMSO
GDC-0068-1μM
PML
048-3-1μM
048-3-5μM
048-3-10μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells

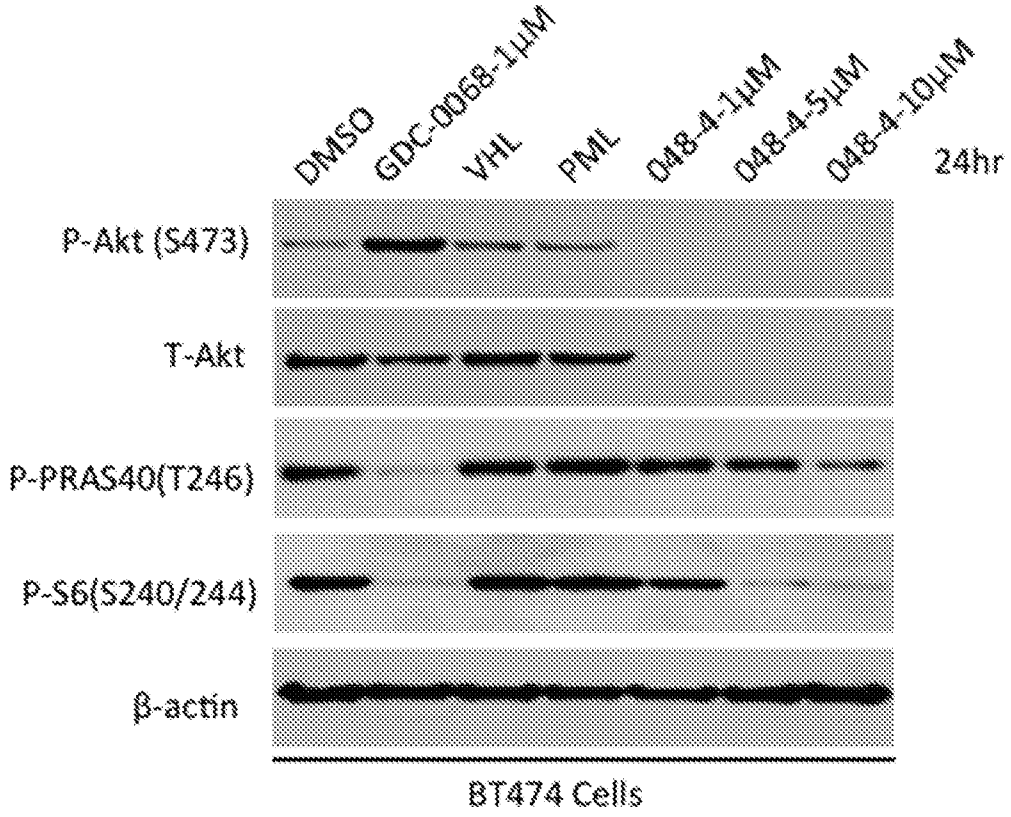
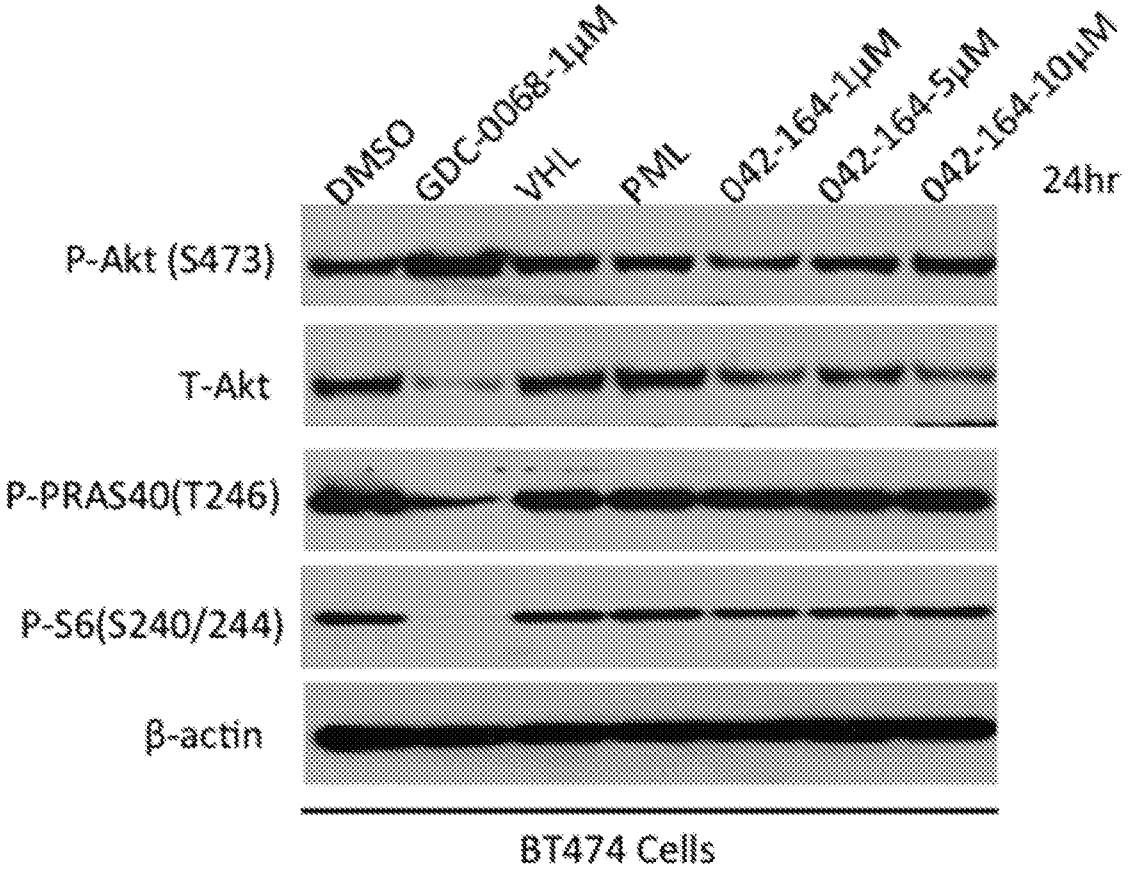

DMSO
GDC-0068-1μM
VHL
PML
048-4-1μM
048-4-5μM
048-4-10μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells

FIG. 1C-3


DMSO
GDC-0068-1μM
VHL
PML
042-164-1μM
042-164-5μM
042-164-10μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells

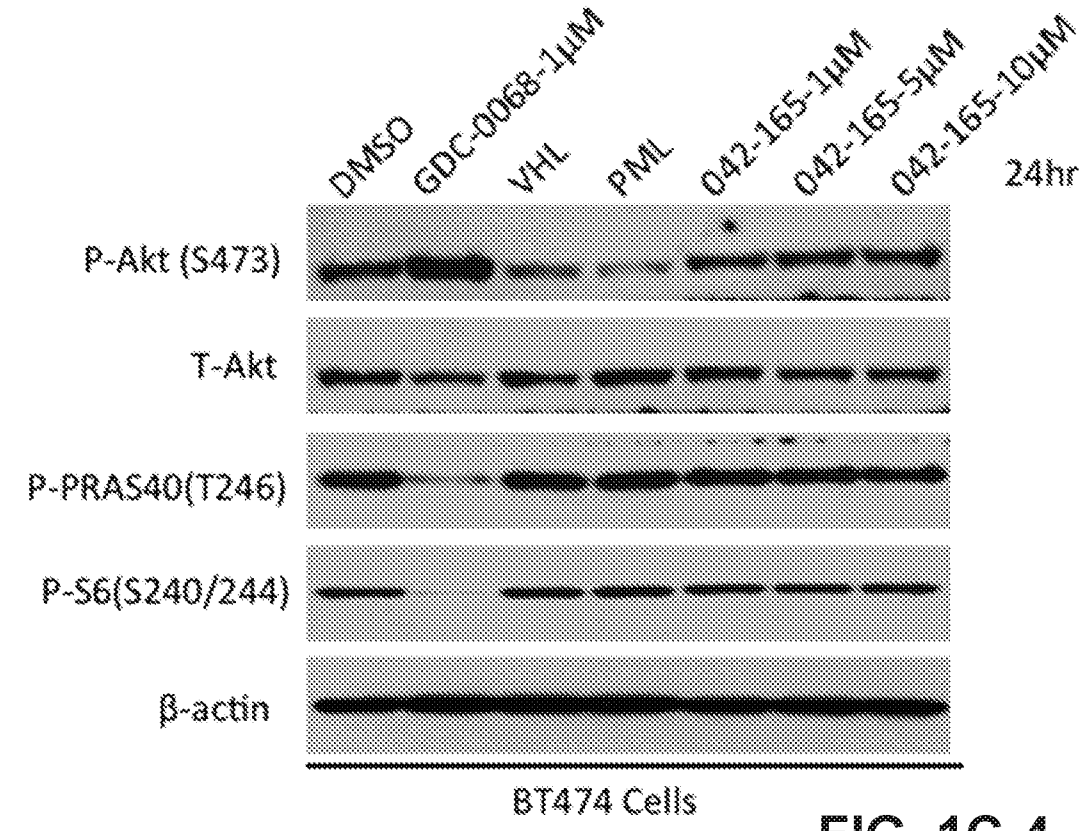

DMSO
GDC-0068-1μM
VHL
PML
042-165-1μM
042-165-5μM
042-165-10μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells

FIG. 1C-4

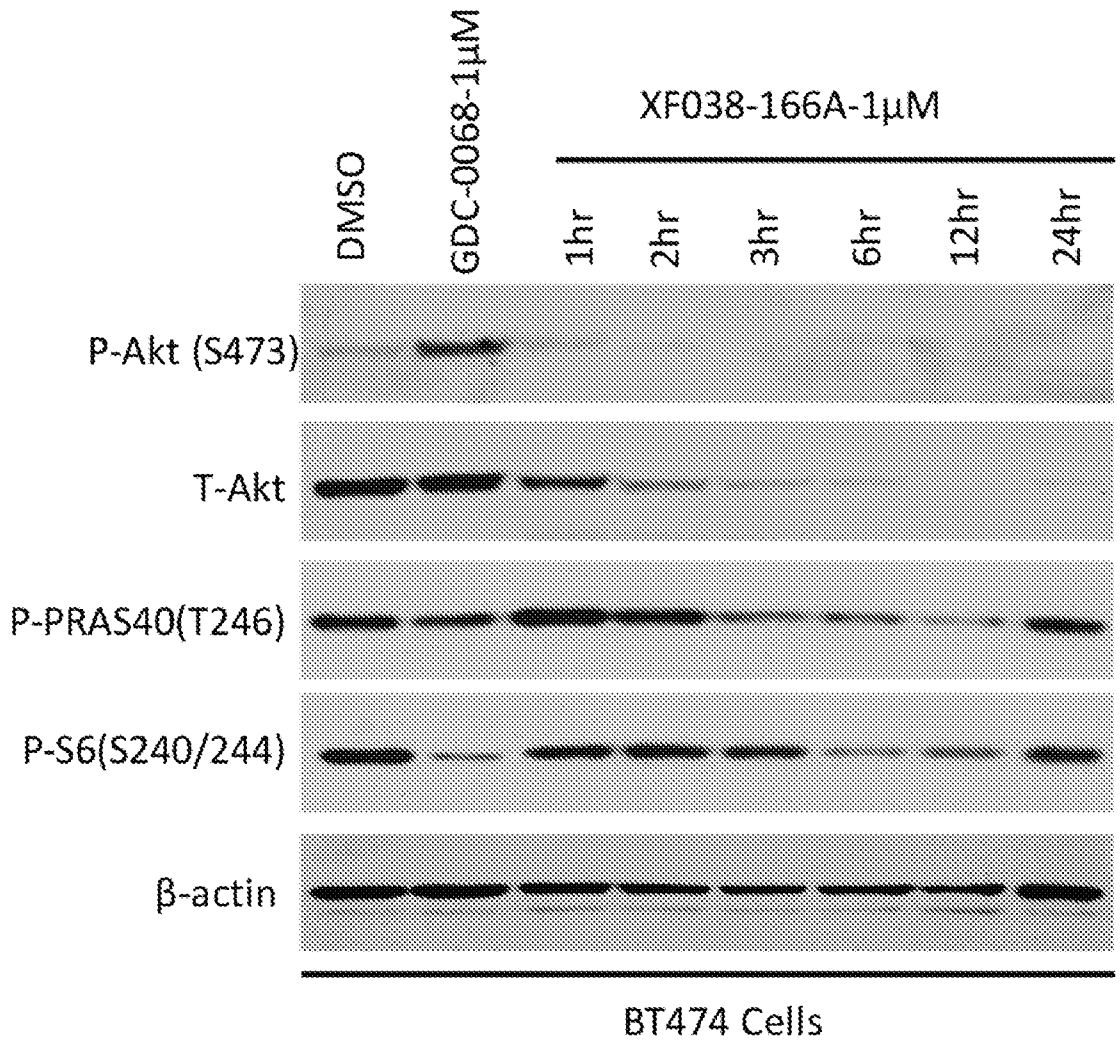
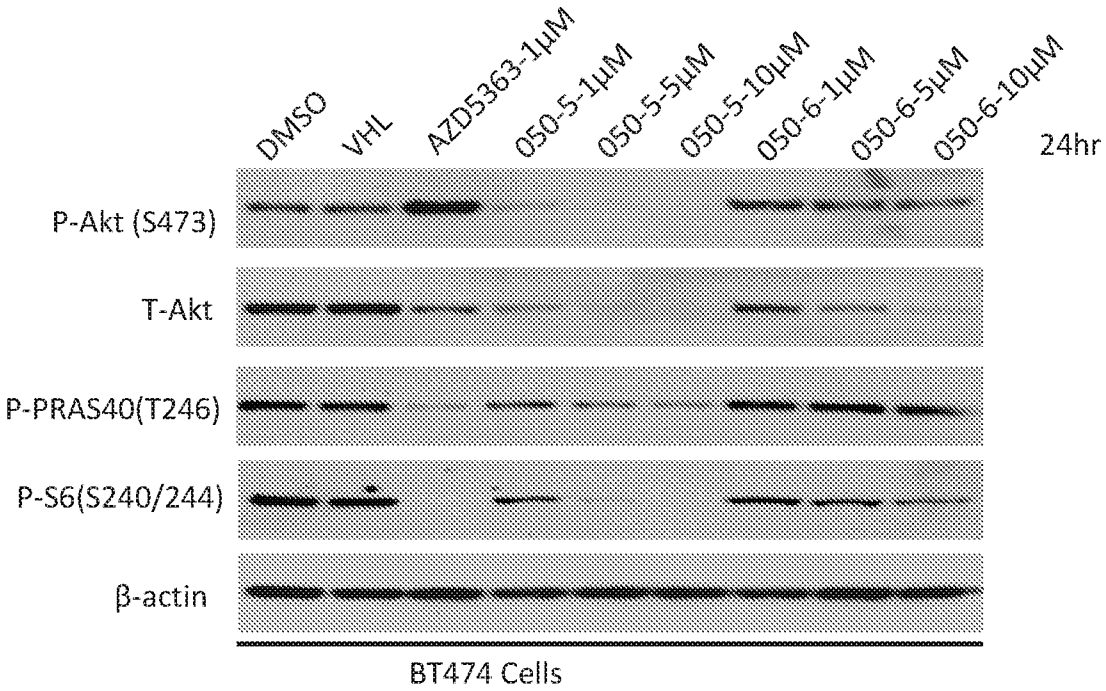

DMSO
GDC-0068-1μM
XF038-166A-1μM
1hr
2hr
3hr
6hr
12hr
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells

FIG. 2


DMSO
VHL
AZD5363-1μM
050-5-1μM
050-5-5μM
050-5-10μM
050-6-1μM
050-6-5μM
050-6-10μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells

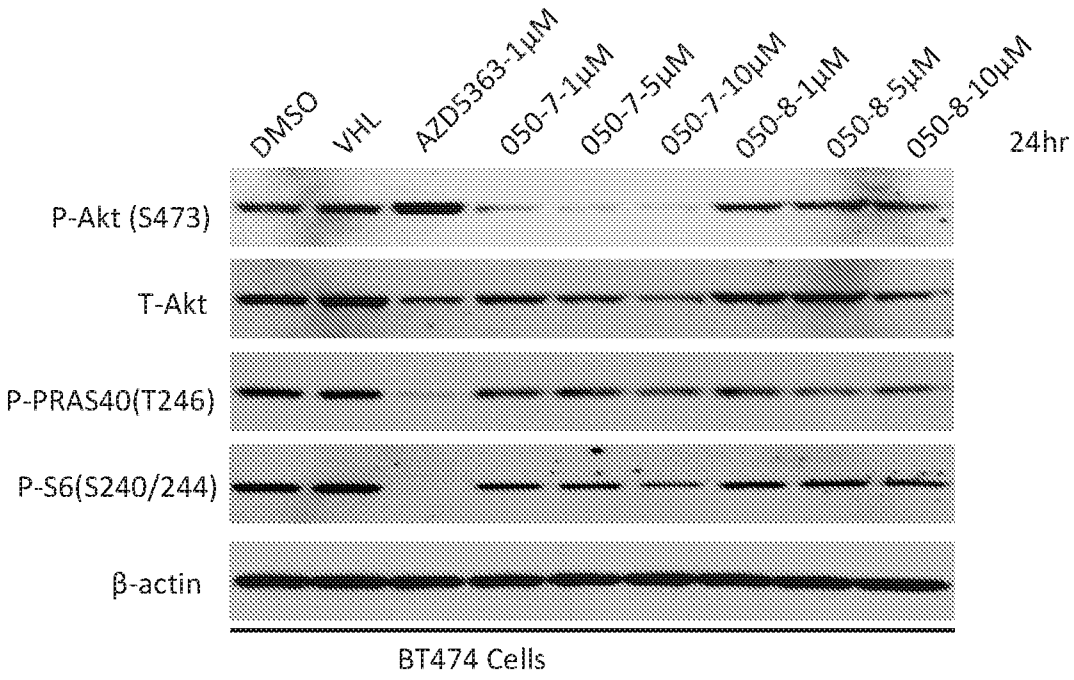
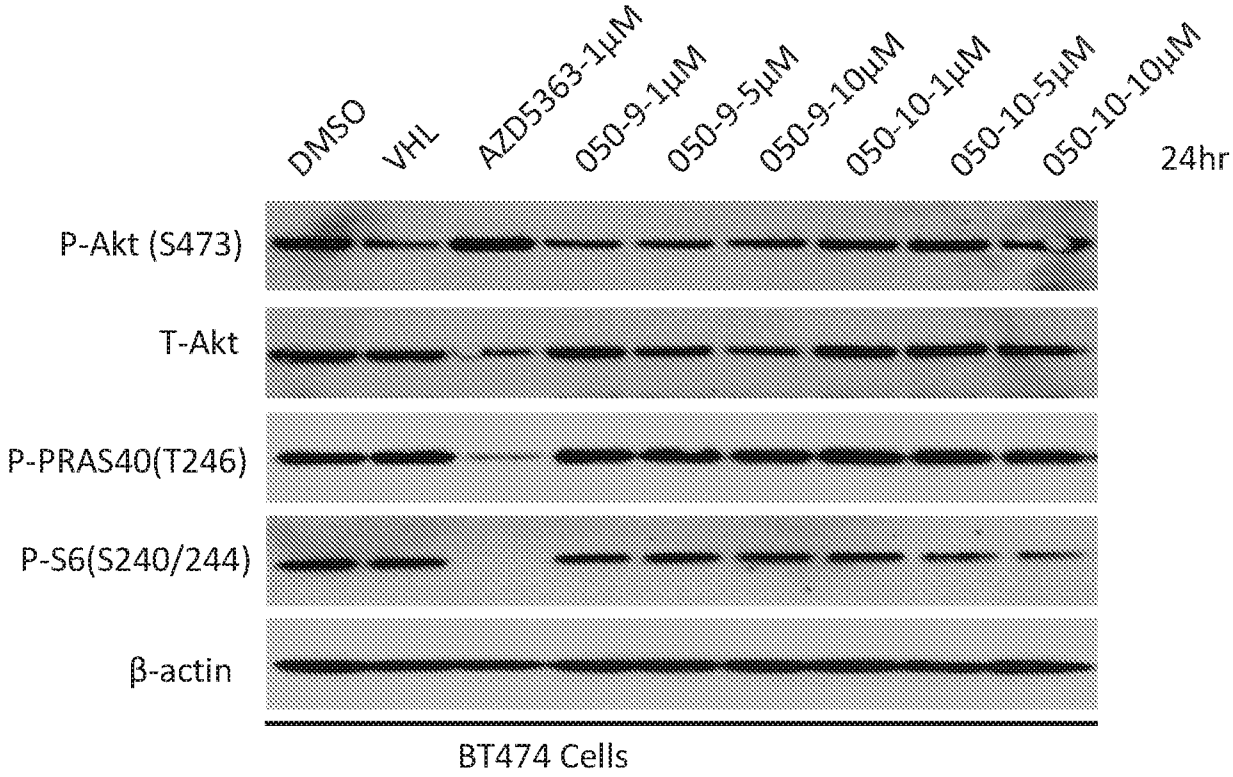

DMSO
VHL
AZD5363-1μM
050-7-1μM
050-7-5μM
050-7-10μM
050-8-1μM
050-8-5μM
050-8-10μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells

FIG. 3A-1


DMSO
VHL
AZD5363-1μM
050-9-1μM
050-9-5μM
050-9-10μM
050-10-1μM
050-10-5μM
050-10-10μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells

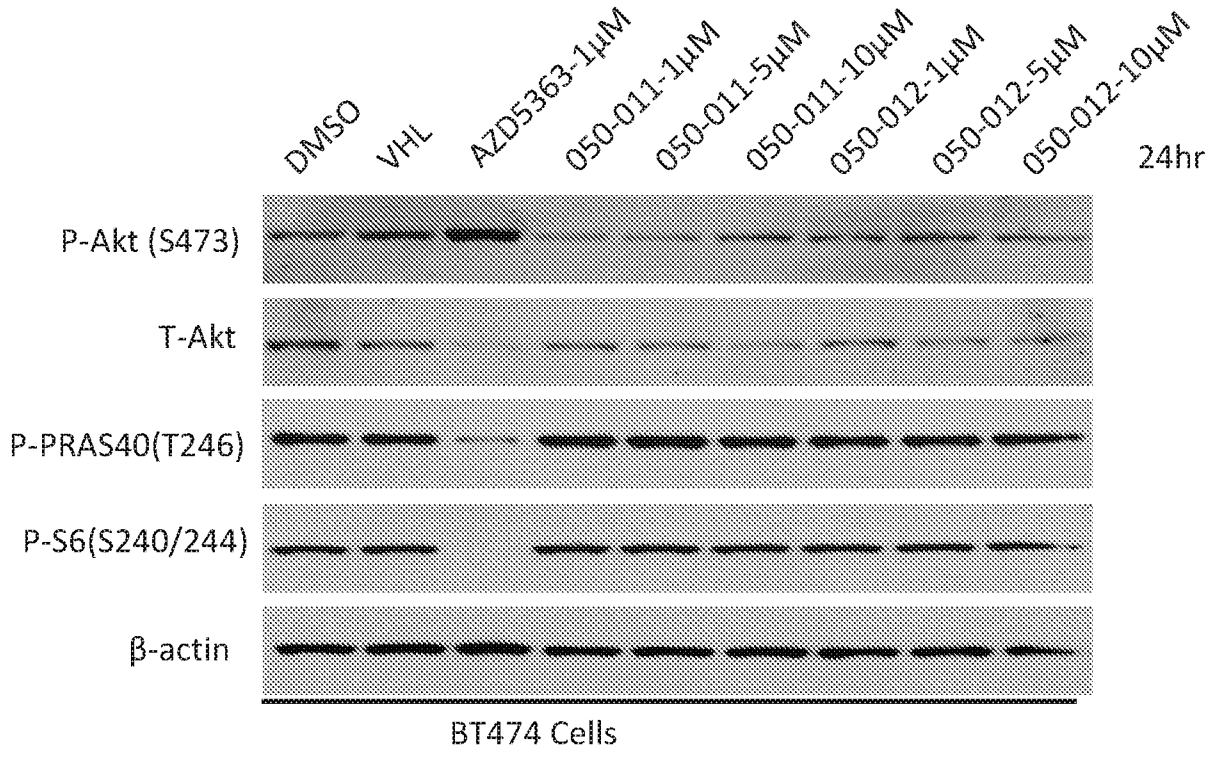
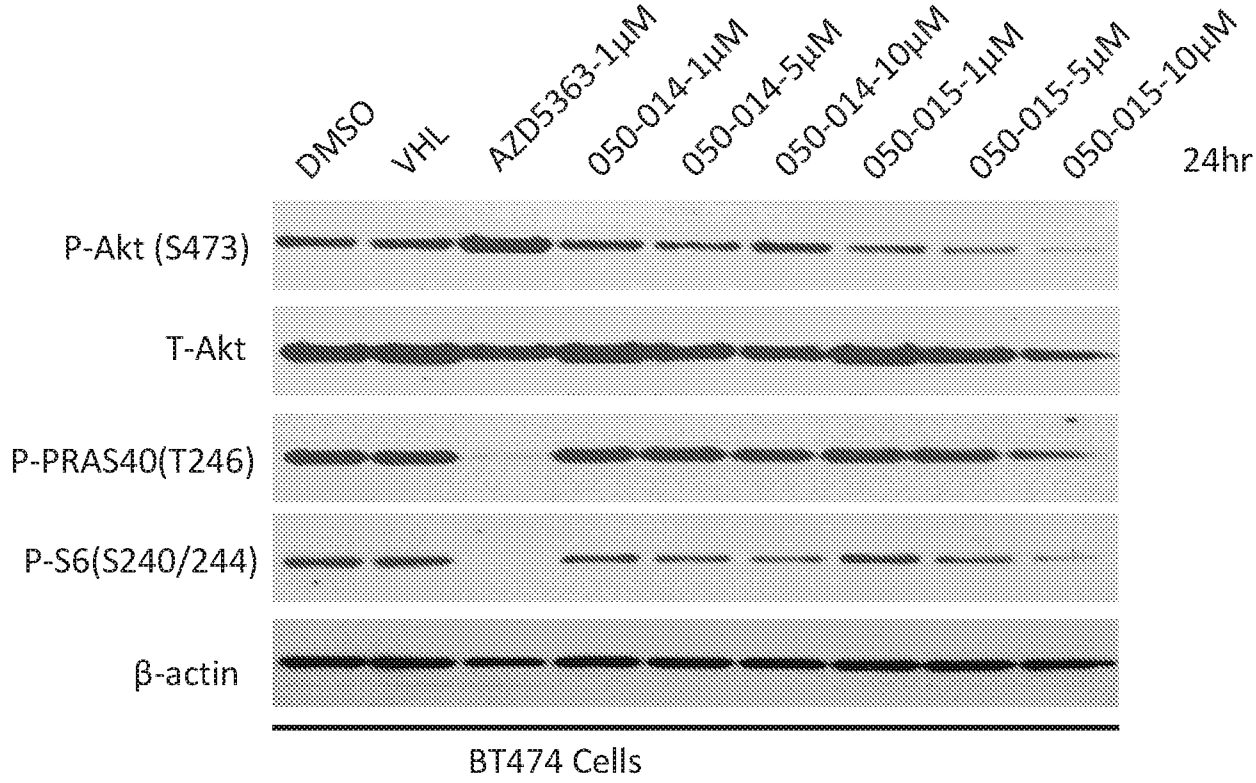

DMSO
VHL
AZD5363-1μM
050-011-1μM
050-011-5μM
050-011-10μM
050-012-1μM
050-012-5μM
050-012-10μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells

FIG. 3A-2


DMSO
VHL
AZD5363-1μM
050-014-1μM
050-014-5μM
050-014-10μM
050-015-1μM
050-015-5μM
050-015-10μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells

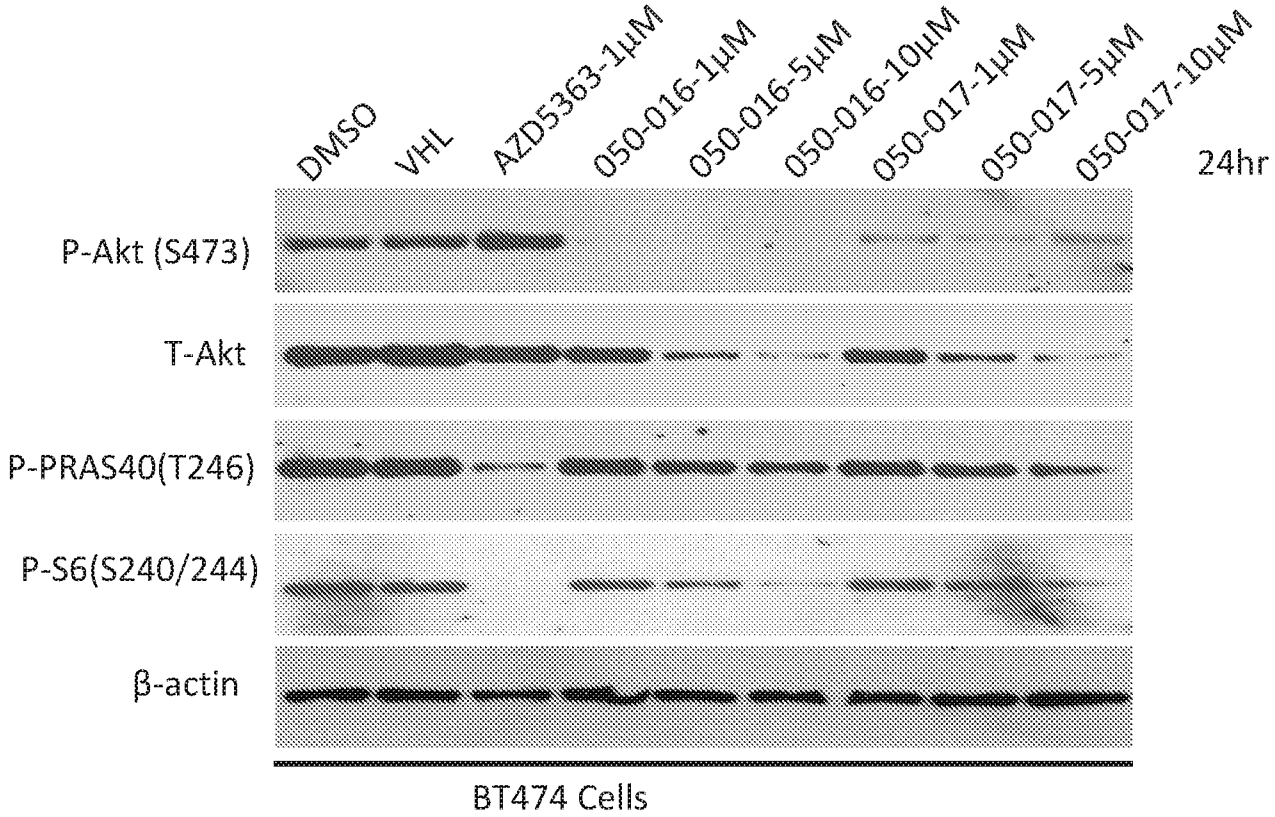
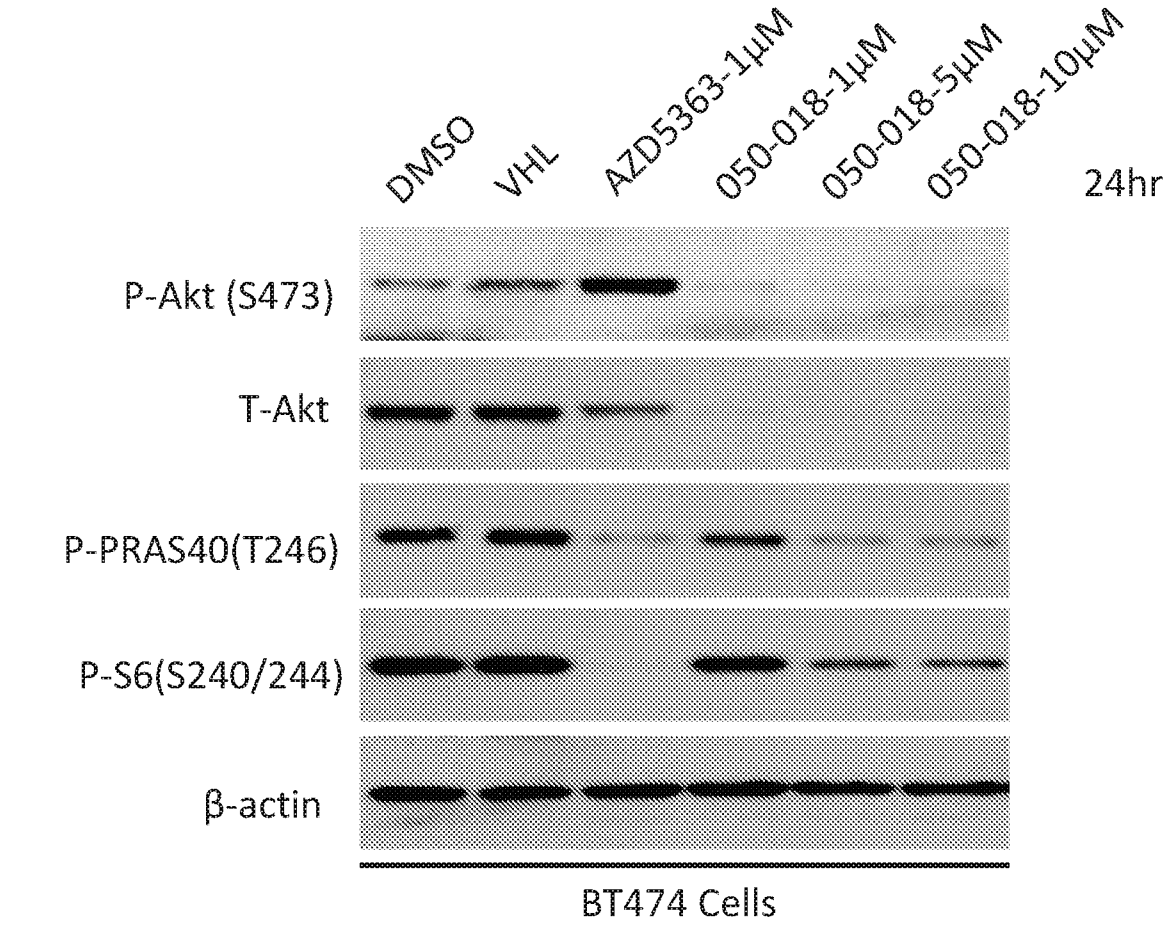

DMSO
VHL
AZD5363-1μM
050-016-1μM
050-016-5μM
050-016-10μM
050-017-1μM
050-017-5μM
050-017-10μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells

FIG. 3A-3


DMSO
VHL
AZD5363-1μM
050-018-1μM
050-018-5μM
050-018-10μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells

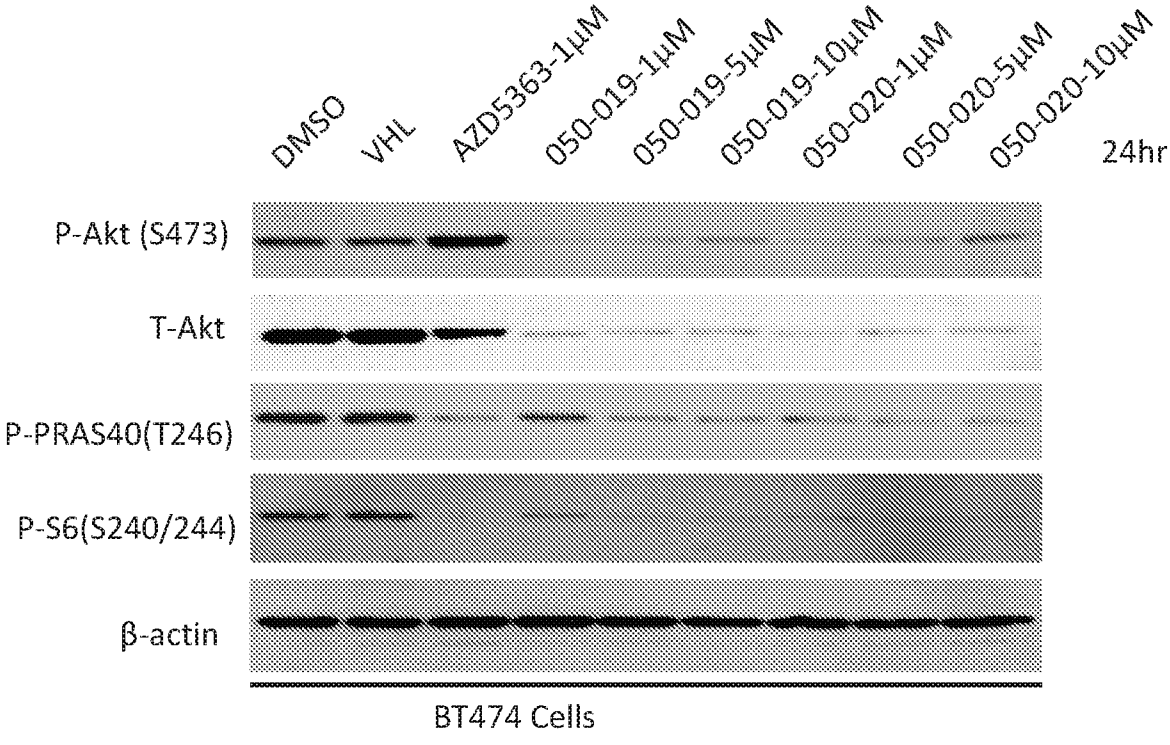

DMSO
VHL
AZD5363-1μM
050-019-1μM
050-019-5μM
050-019-10μM
050-020-1μM
050-020-5μM
050-020-10μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells

FIG. 3A-4

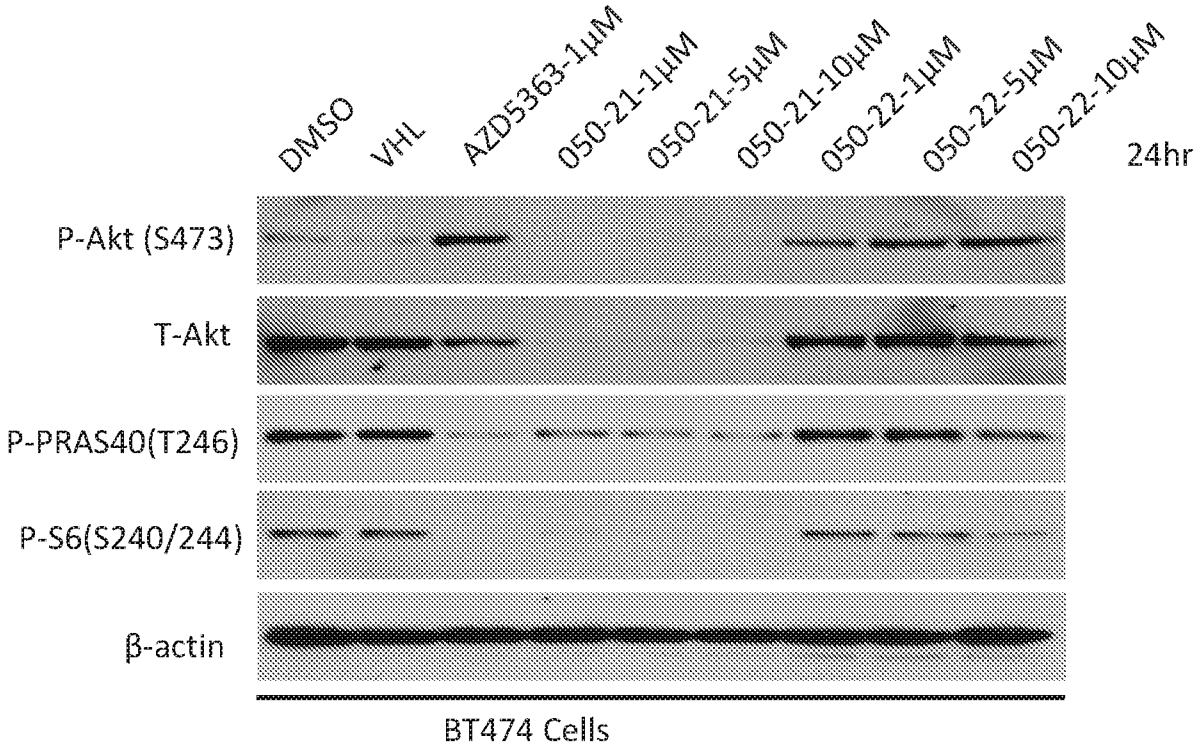
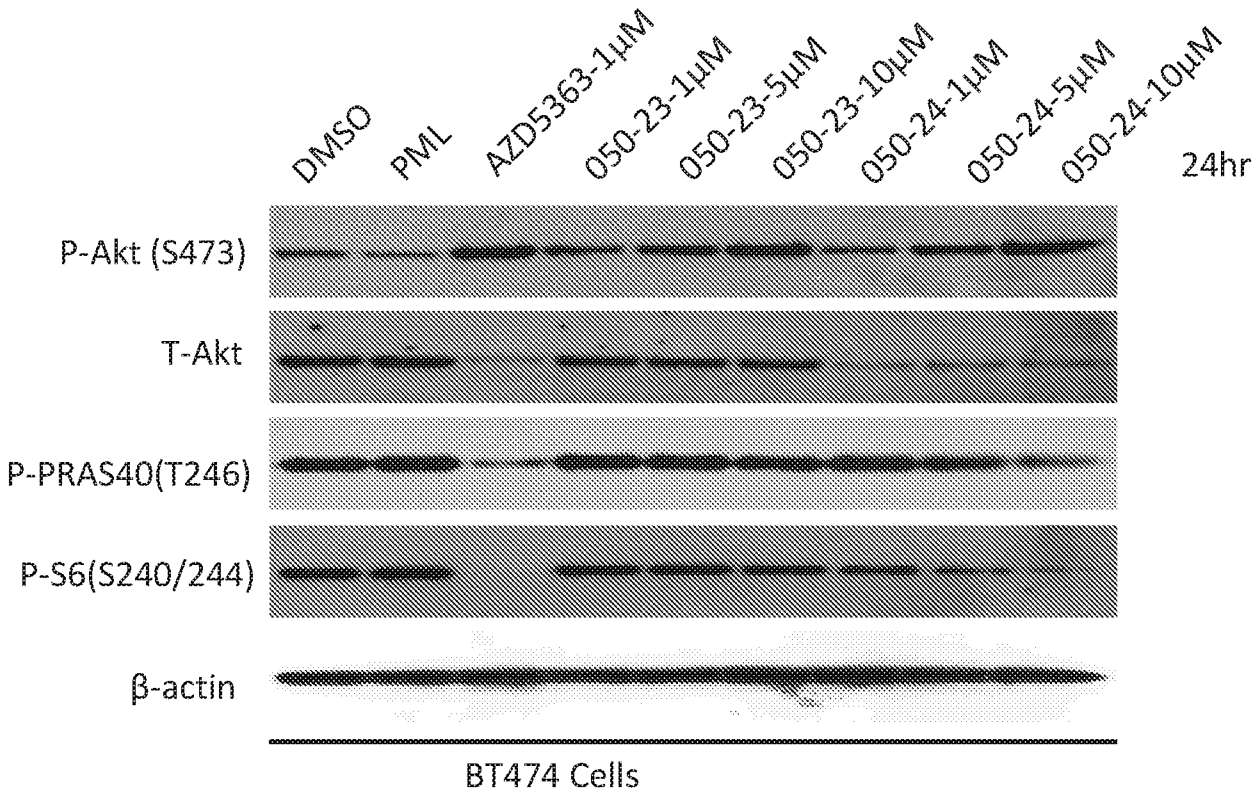

DMSO
VHL
AZD5363-1μM
050-21-1μM
050-21-5μM
050-21-10μM
050-22-1μM
050-22-5μM
050-22-10μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells

FIG. 3A-5


DMSO
PML
AZD5363-1μM
050-23-1μM
050-23-5μM
050-23-10μM
050-24-1μM
050-24-5μM
050-24-10μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells

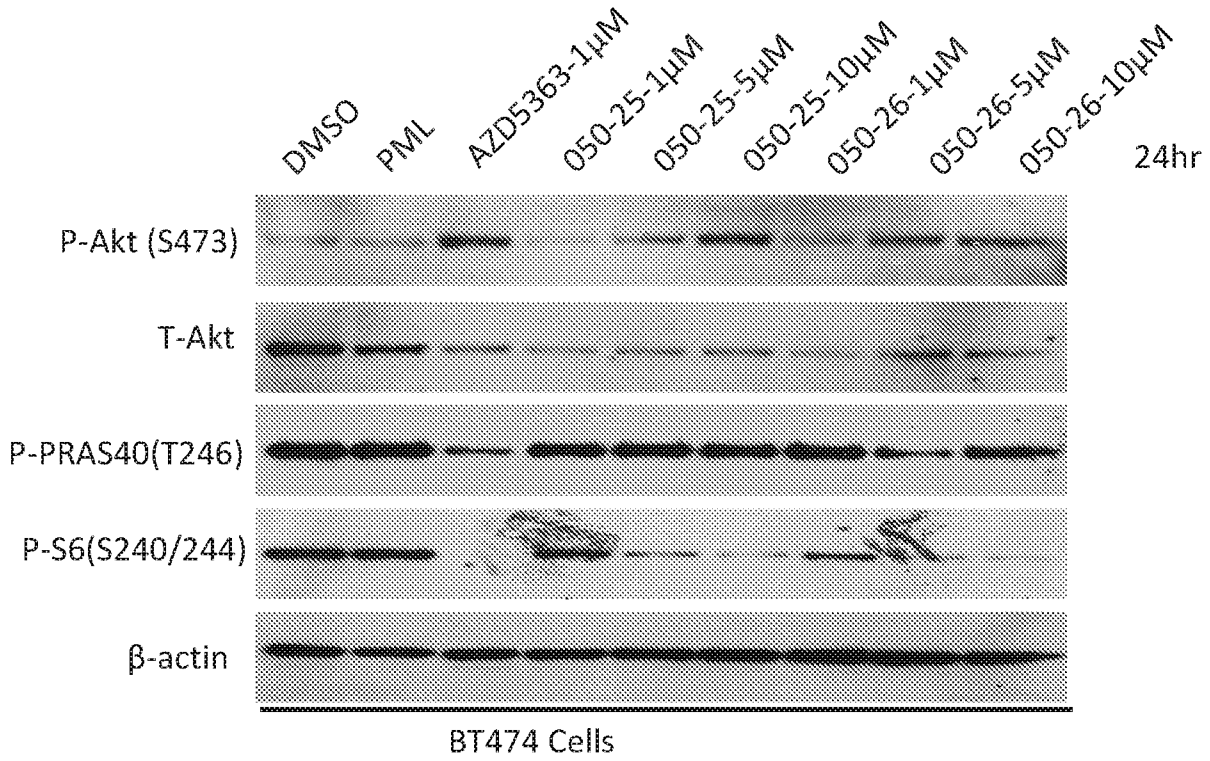
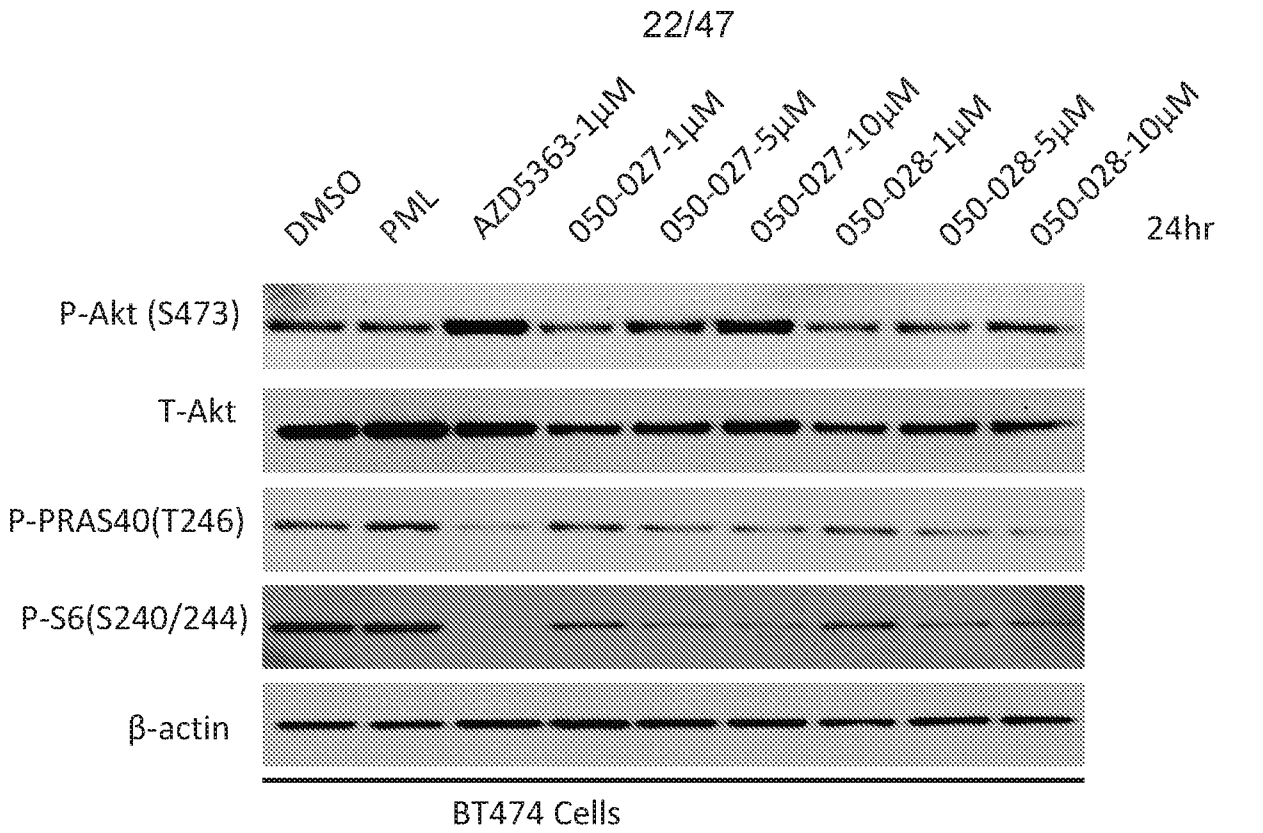

DMSO
PML
AZD5363-1μM
050-25-1μM
050-25-5μM
050-25-10μM
050-26-1μM
050-26-5μM
050-26-10μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells

FIG. 3B-1


DMSO
PML
AZD5363-1μM
050-027-1μM
050-027-5μM
050-027-10μM
050-028-1μM
050-028-5μM
050-028-10μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells

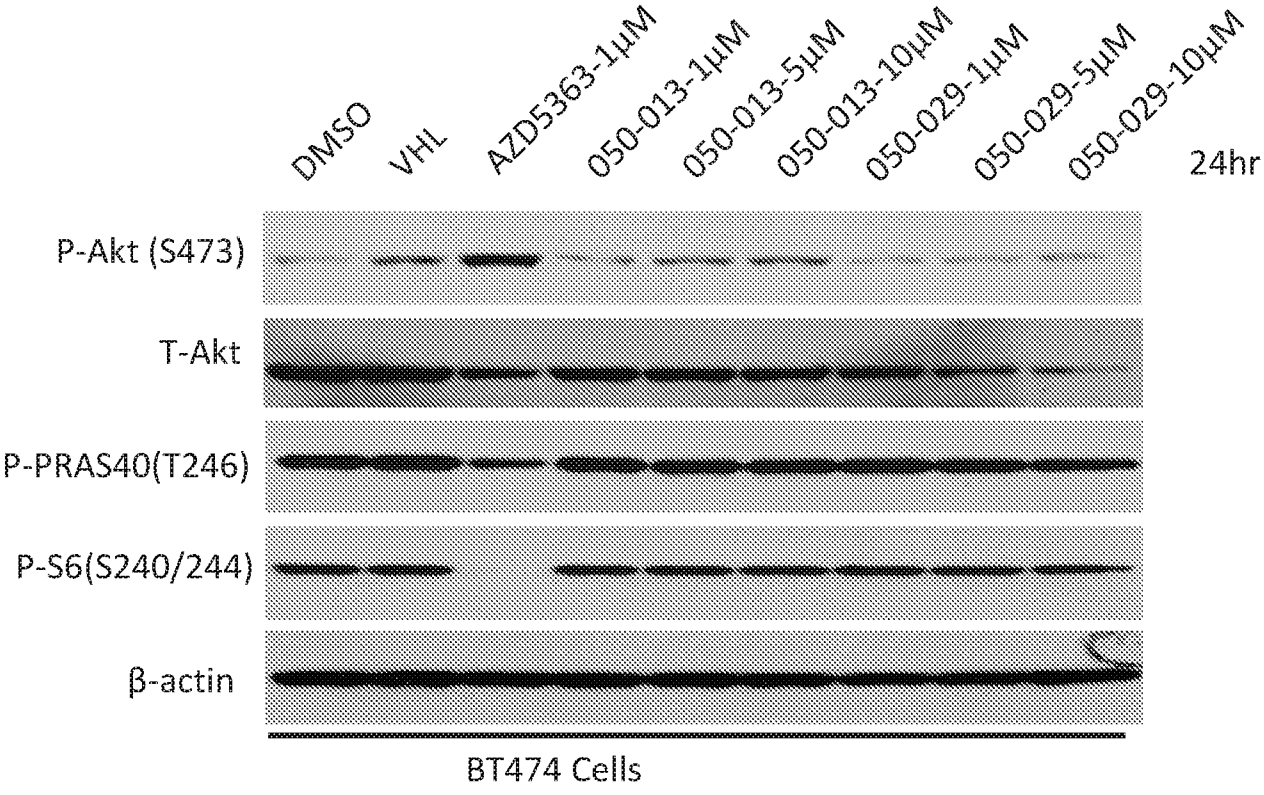
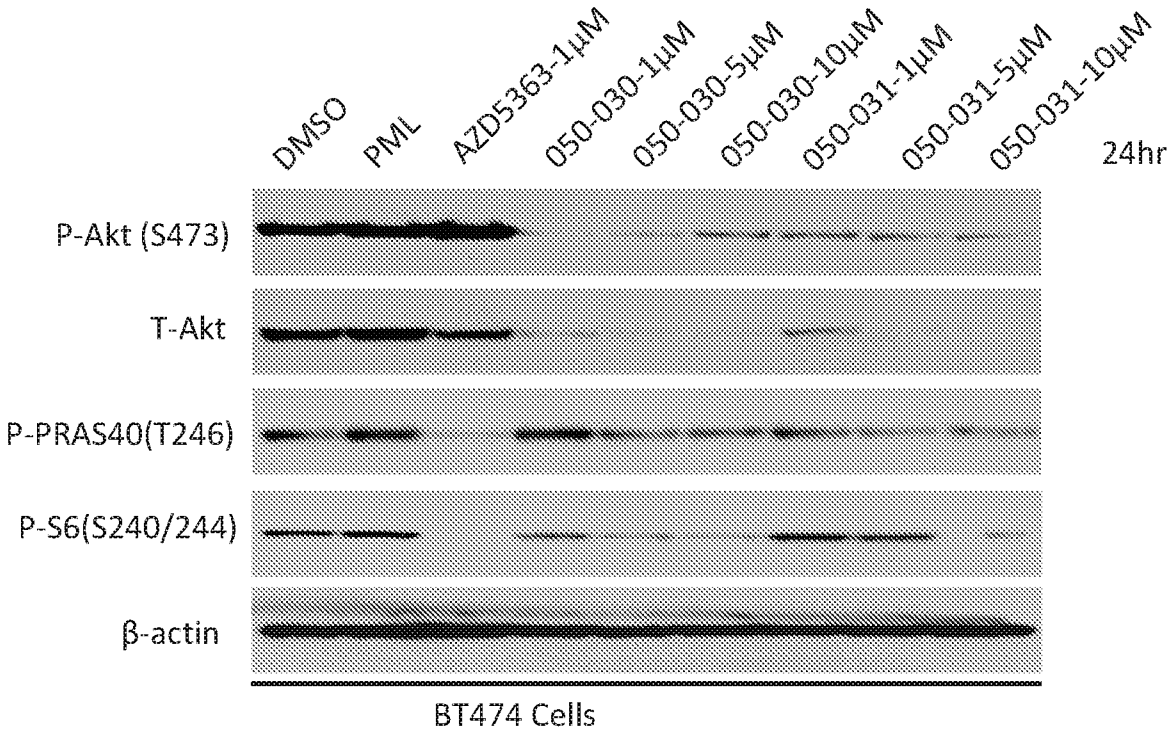

DMSO
VHL
AZD5363-1μM
050-013-1μM
050-013-5μM
050-013-10μM
050-029-1μM
050-029-5μM
050-029-10μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells

FIG. 3B-2


DMSO
PML
AZD5363-1μM
050-030-1μM
050-030-5μM
050-030-10μM
050-031-1μM
050-031-5μM
050-031-10μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells

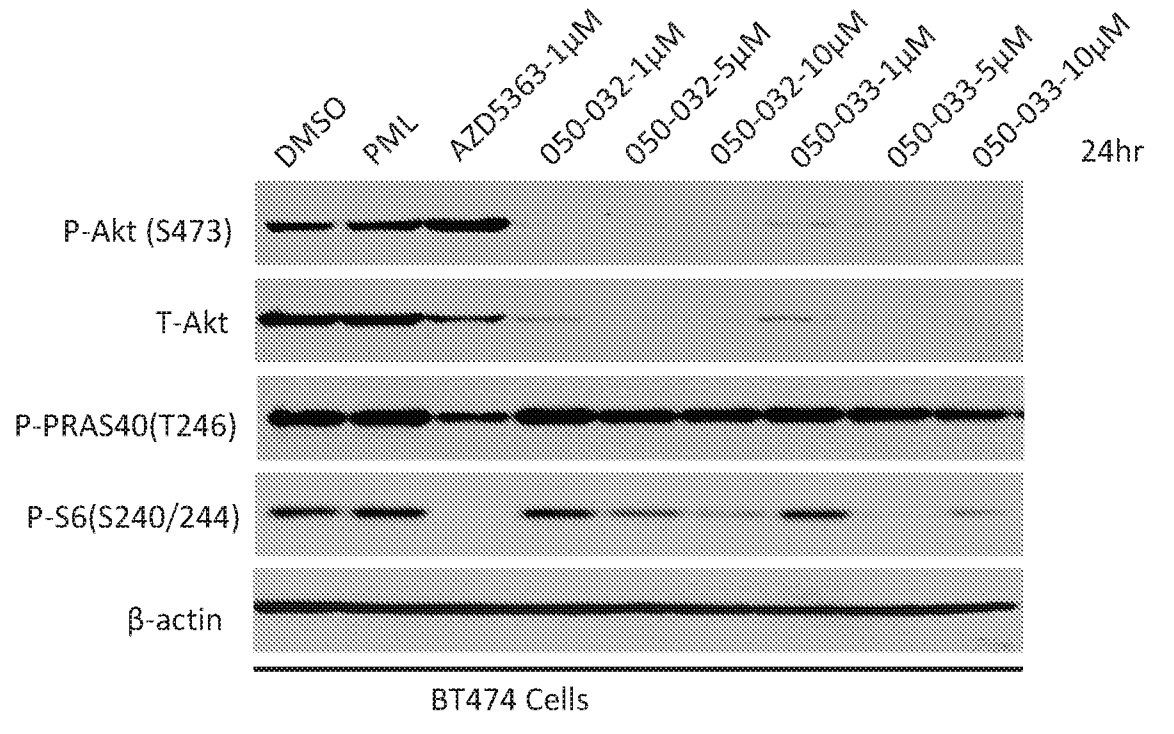

DMSO
PML
AZD5363-1μM
050-032-1μM
050-032-5μM
050-032-10μM
050-033-1μM
050-033-5μM
050-033-10μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells

FIG. 3B-3

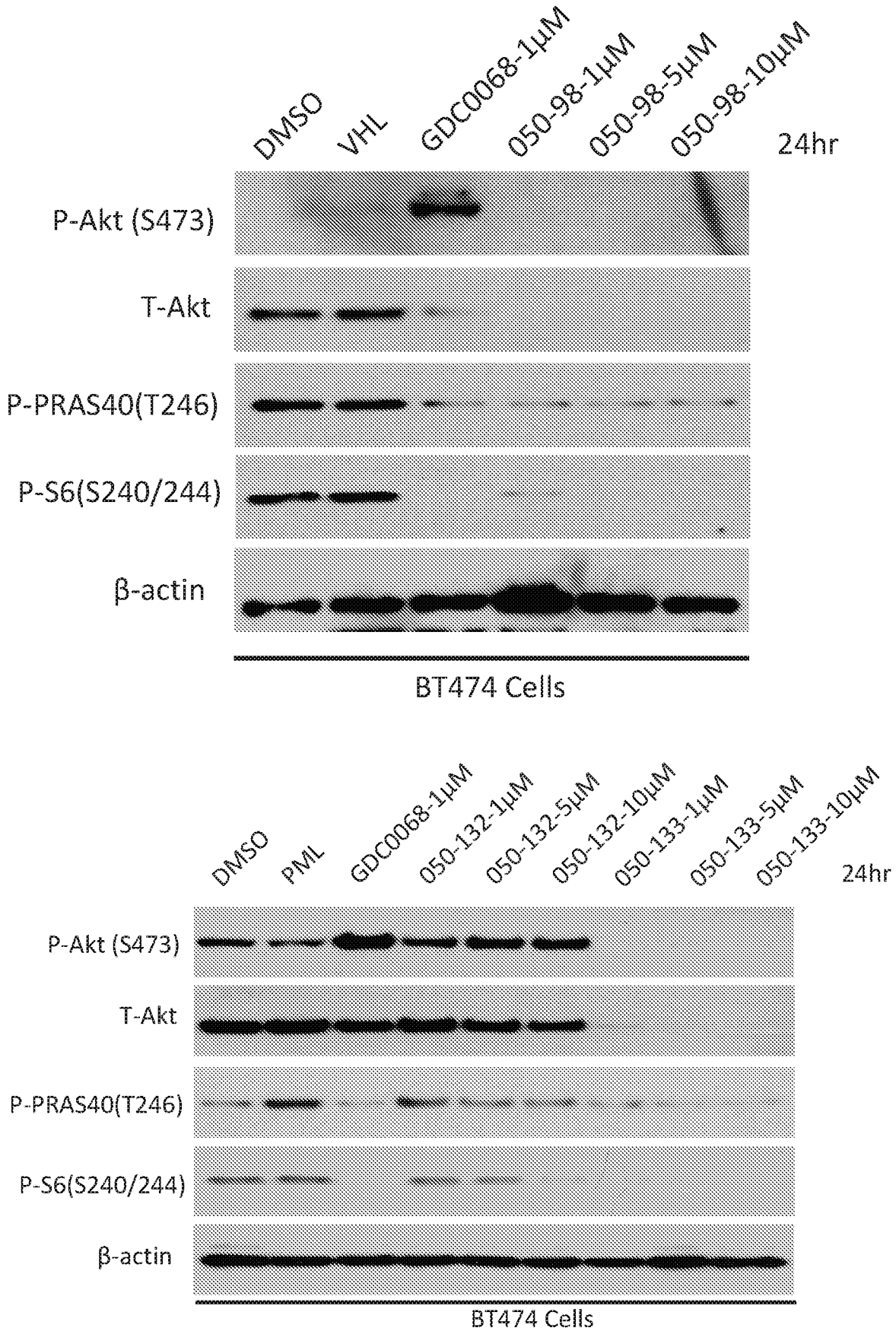

DMSO
VHL
GDC0068-1μM
050-98-1μM
050-98-5μM
050-98-10μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells
DMSO
PML
GDC0068-1μM
050-132-1μM
050-132-5μM
050-132-10μM
050-133-1μM
050-133-5μM
050-133-10μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells

FIG. 3B-4

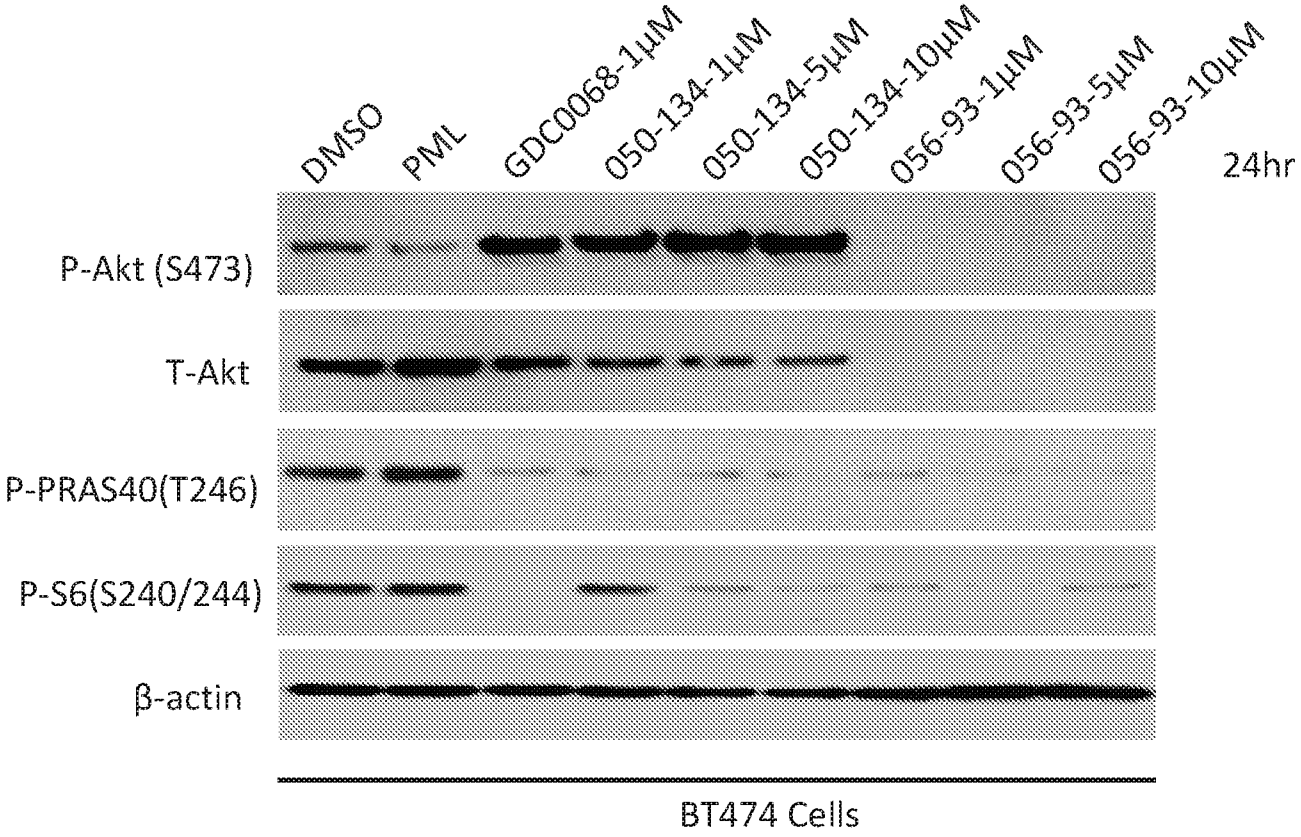

DMSO
PML
GDC0068-1μM
050-134-1μM
050-134-5μM
050-134-10μM
056-93-1μM
056-93-5μM
056-93-10μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells

FIG. 3B-5

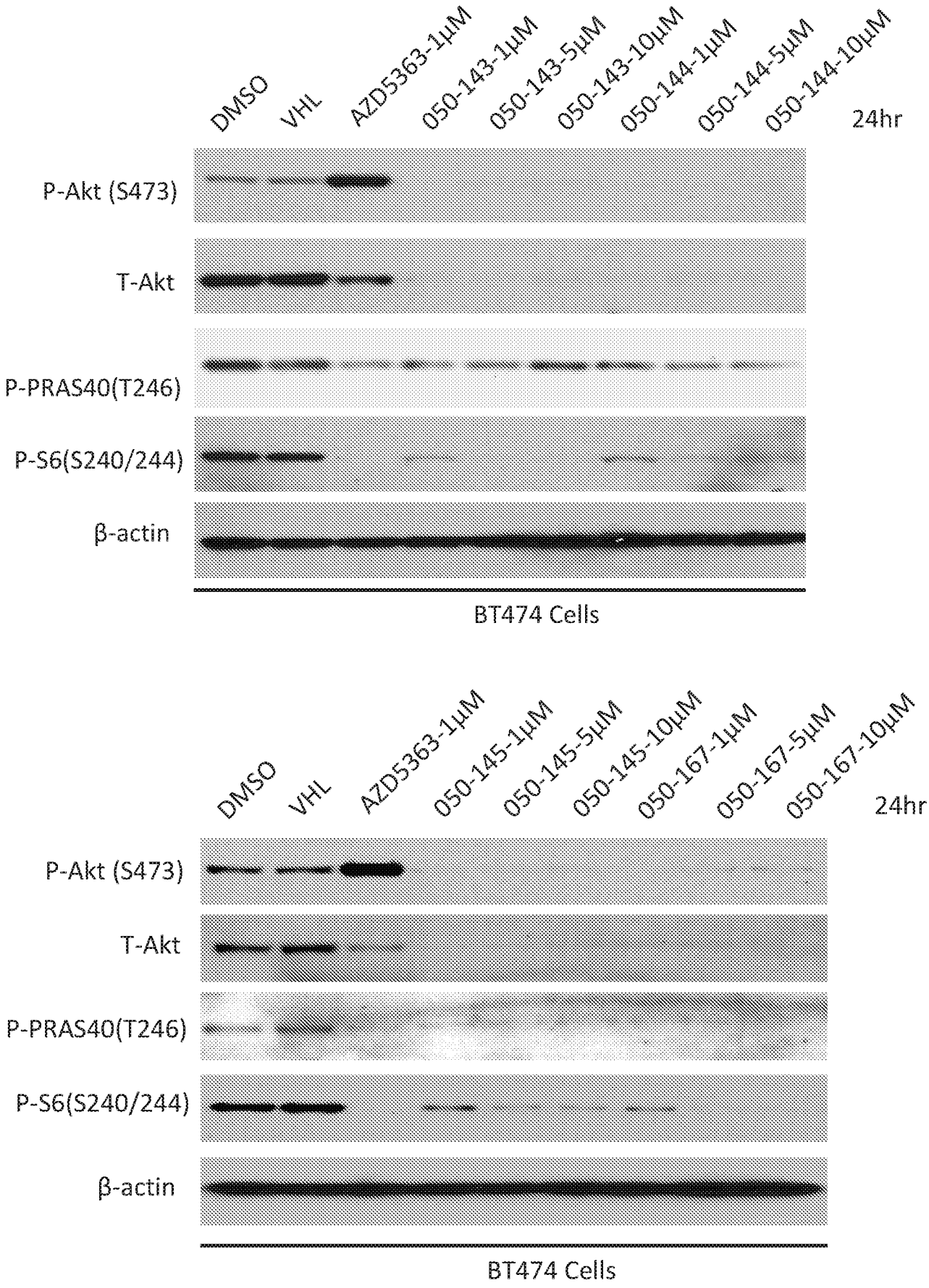

DMSO
VHL
AZD5363-1μM
050-143-1μM
050-143-5μM
050-143-10μM
050-144-1μM
050-144-5μM
050-144-10μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells
DMSO
VHL
AZD5363-1μM
050-145-1μM
050-145-5μM
050-145-10μM
050-167-1μM
050-167-5μM
050-167-10μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells

FIG. 3C-1

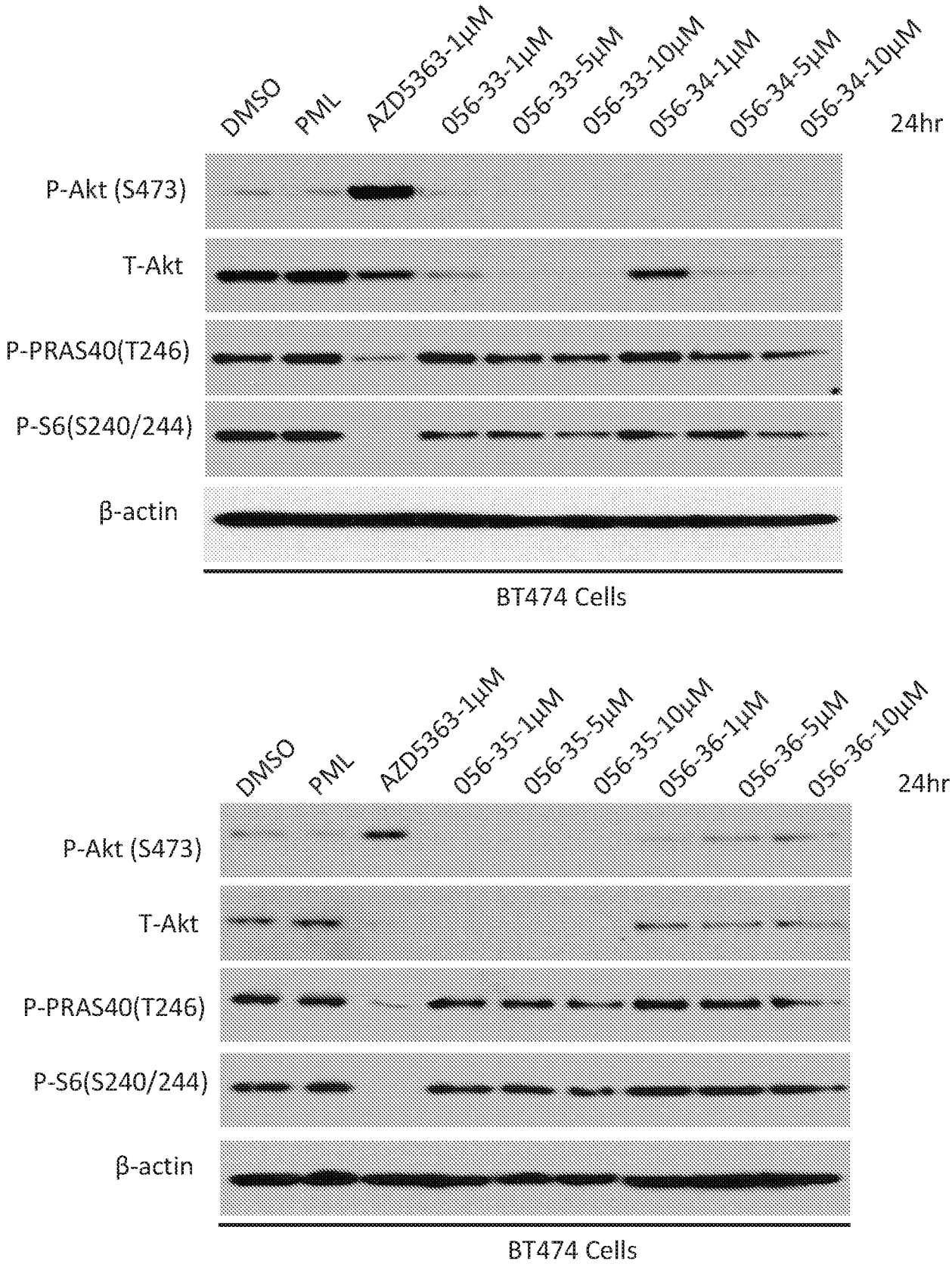

DMSO
PML
AZD5363-1μM
056-33-1μM
056-33-5μM
056-33-10μM
056-34-1μM
056-34-5μM
056-34-10μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells
DMSO
PML
AZD5363-1μM
056-35-1μM
056-35-5μM
056-35-10μM
056-36-1μM
056-36-5μM
056-36-10μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells

FIG. 3C-2

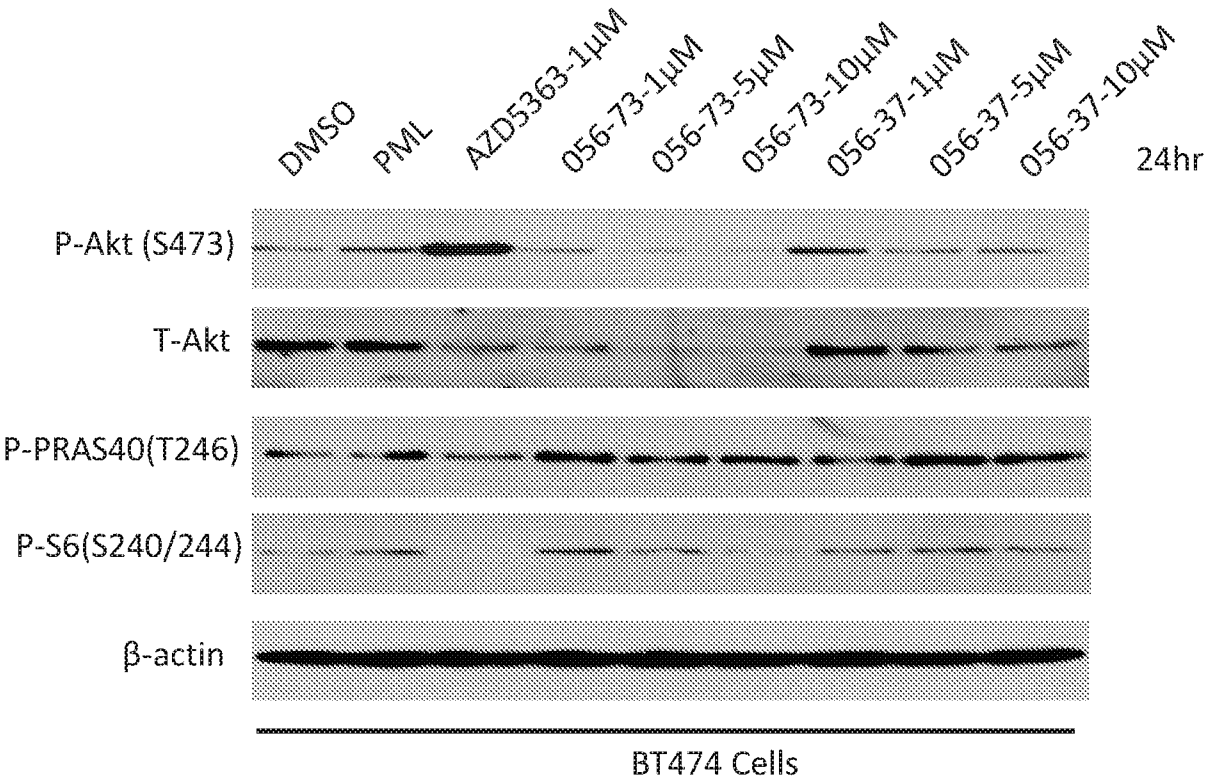

DMSO
PML
AZD5363-1μM
056-73-1μM
056-73-5μM
056-73-10μM
056-37-1μM
056-37-5μM
056-37-10μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells

FIG. 3C-3

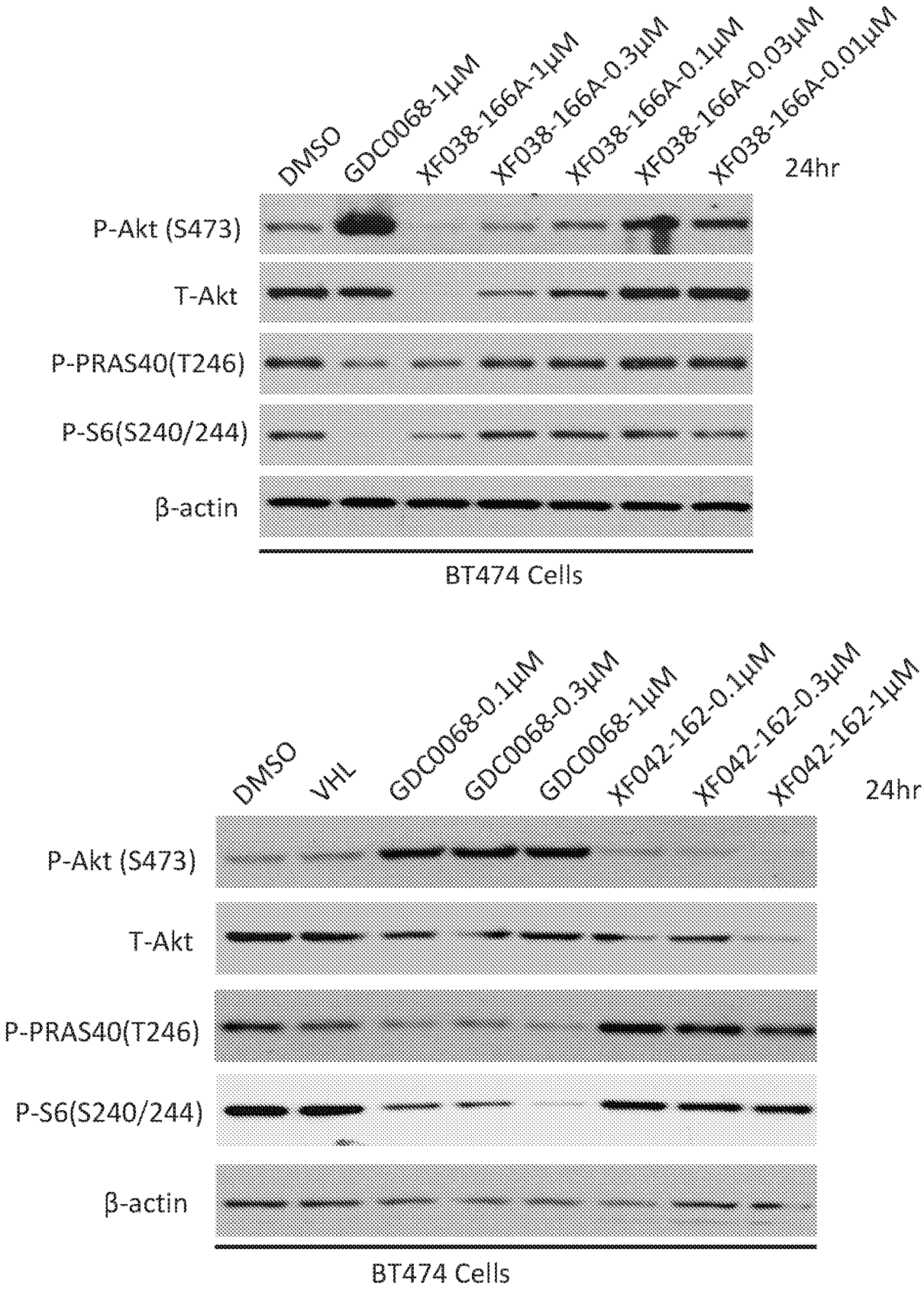
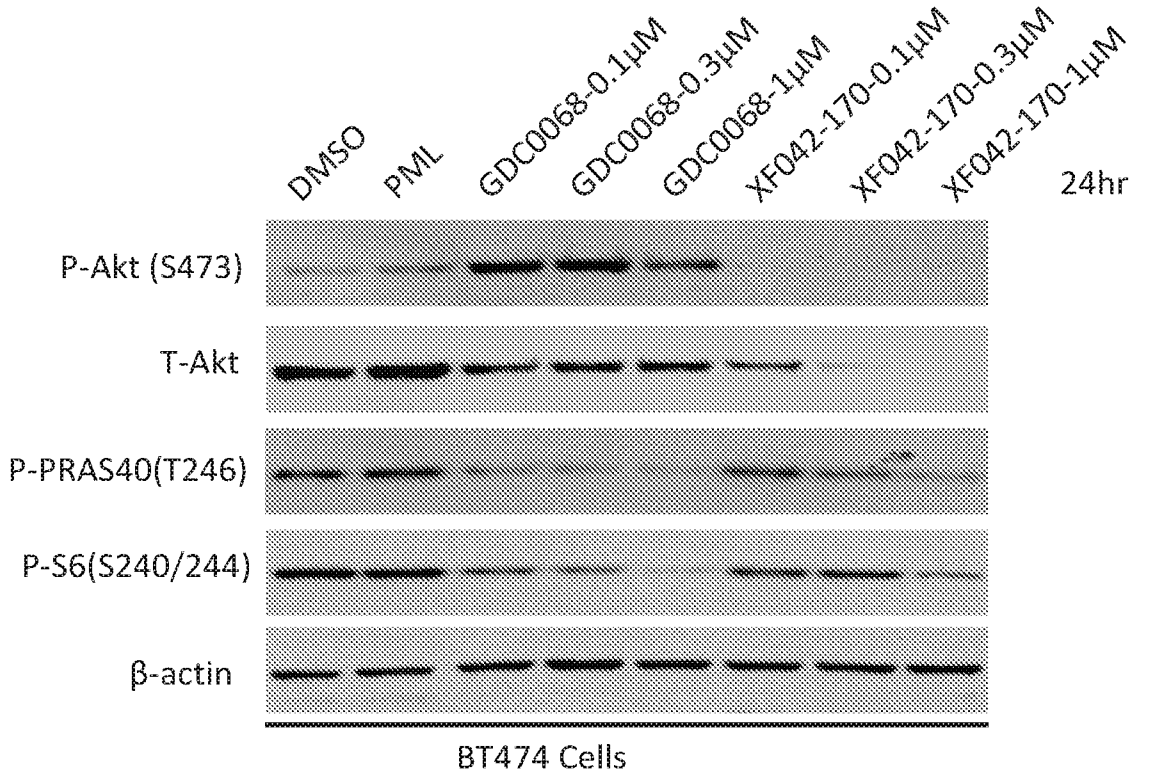

DMSO
GDC0068-1μM
XF038-166A-1μM
XF038-166A-0.3μM
XF038-166A-0.1μM
XF038-166A-0.03μM
XF038-166A-0.01μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells
DMSO
VHL
GDC0068-0.1μM
GDC0068-0.3μM
GDC0068-1μM
XF042-162-0.1μM
XF042-162-0.3μM
XF042-162-1μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells

FIG. 4A-1


DMSO
PML
GDC0068-0.1μM
GDC0068-0.3μM
GDC0068-1μM
XF042-170-0.1μM
XF042-170-0.3μM
XF042-170-1μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells

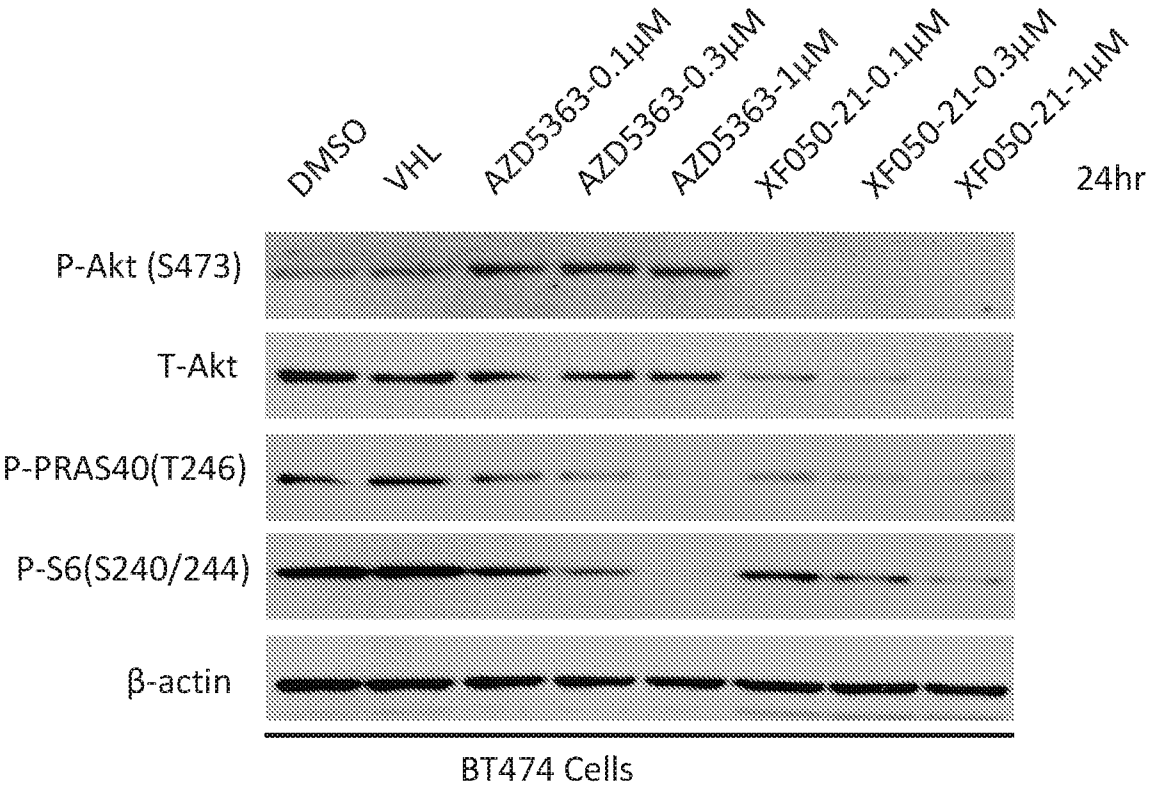

DMSO
VHL
AZD5363-0.1μM
AZD5363-0.3μM
AZD5363-1μM
XF050-21-0.1μM
XF050-21-0.3μM
XF050-21-1μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells

FIG. 4A-2

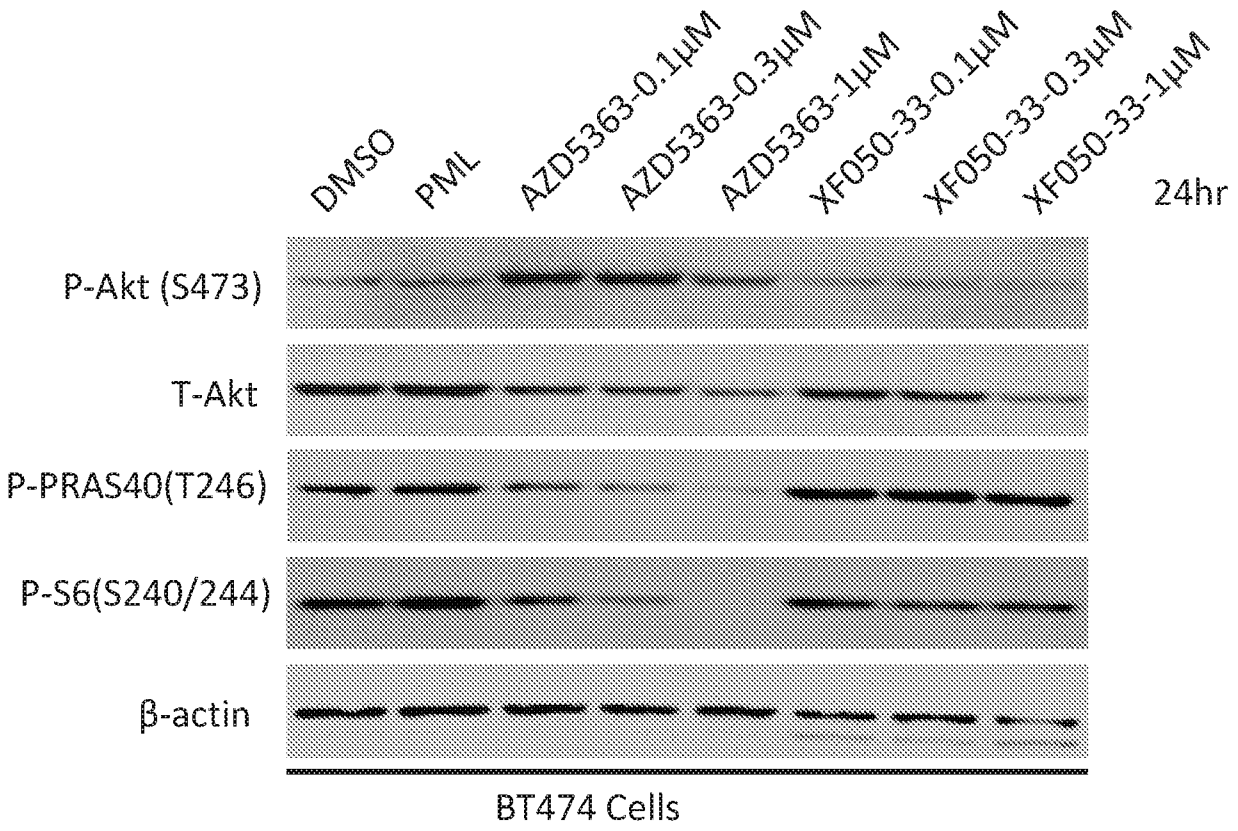

DMSO
PML
AZD5363-0.1μM
AZD5363-0.3μM
AZD5363-1μM
XF050-33-0.1μM
XF050-33-0.3μM
XF050-33-1μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells

FIG. 4A-3

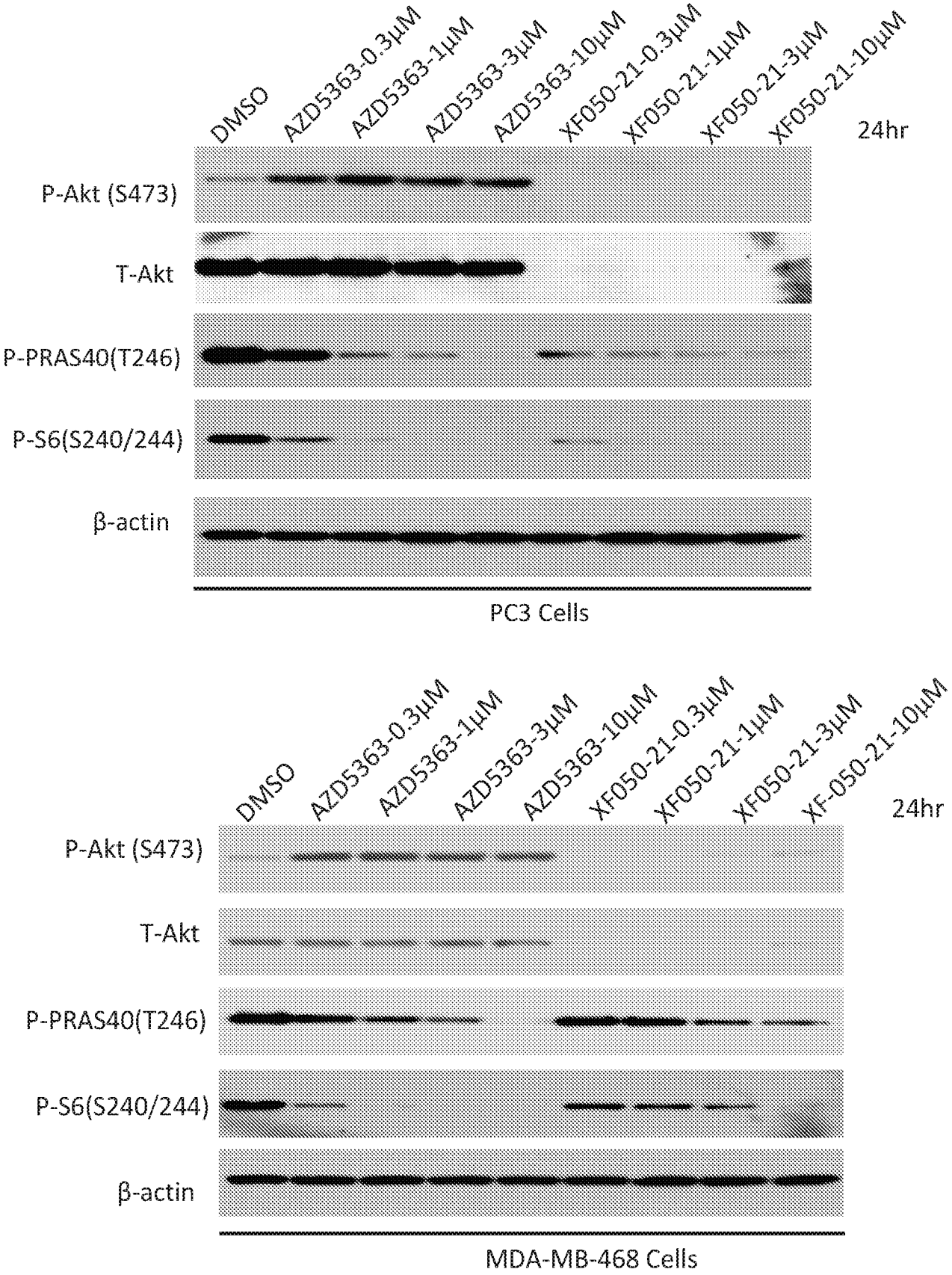

DMSO
AZD5363-0.3μM
AZD5363-1μM
AZD5363-3μM
AZD5363-10μM
XF050-21-0.3μM
XF050-21-1μM
XF050-21-3μM
XF050-21-10μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
PC3 Cells
DMSO
AZD5363-0.3μM
AZD5363-1μM
AZD5363-3μM
AZD5363-10μM
XF050-21-0.3μM
XF050-21-1μM
XF050-21-3μM
XF-050-21-10μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
MDA-MB-468 Cells

FIG. 4B-1

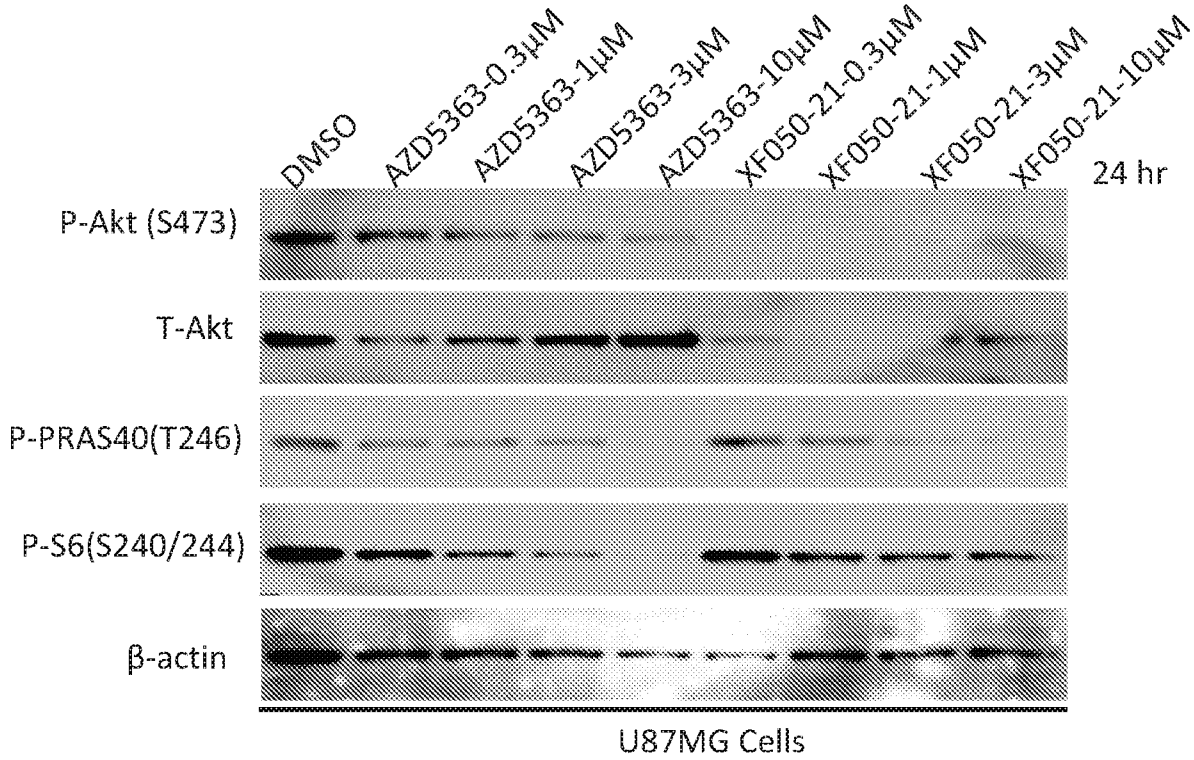

DMSO
AZD5363-0.3μM
AZD5363-1μM
AZD5363-3μM
AZD5363-10μM
XF050-21-0.3μM
XF050-21-1μM
XF050-21-3μM
XF050-21-10μM
24 hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
U87MG Cells

FIG. 4B-2

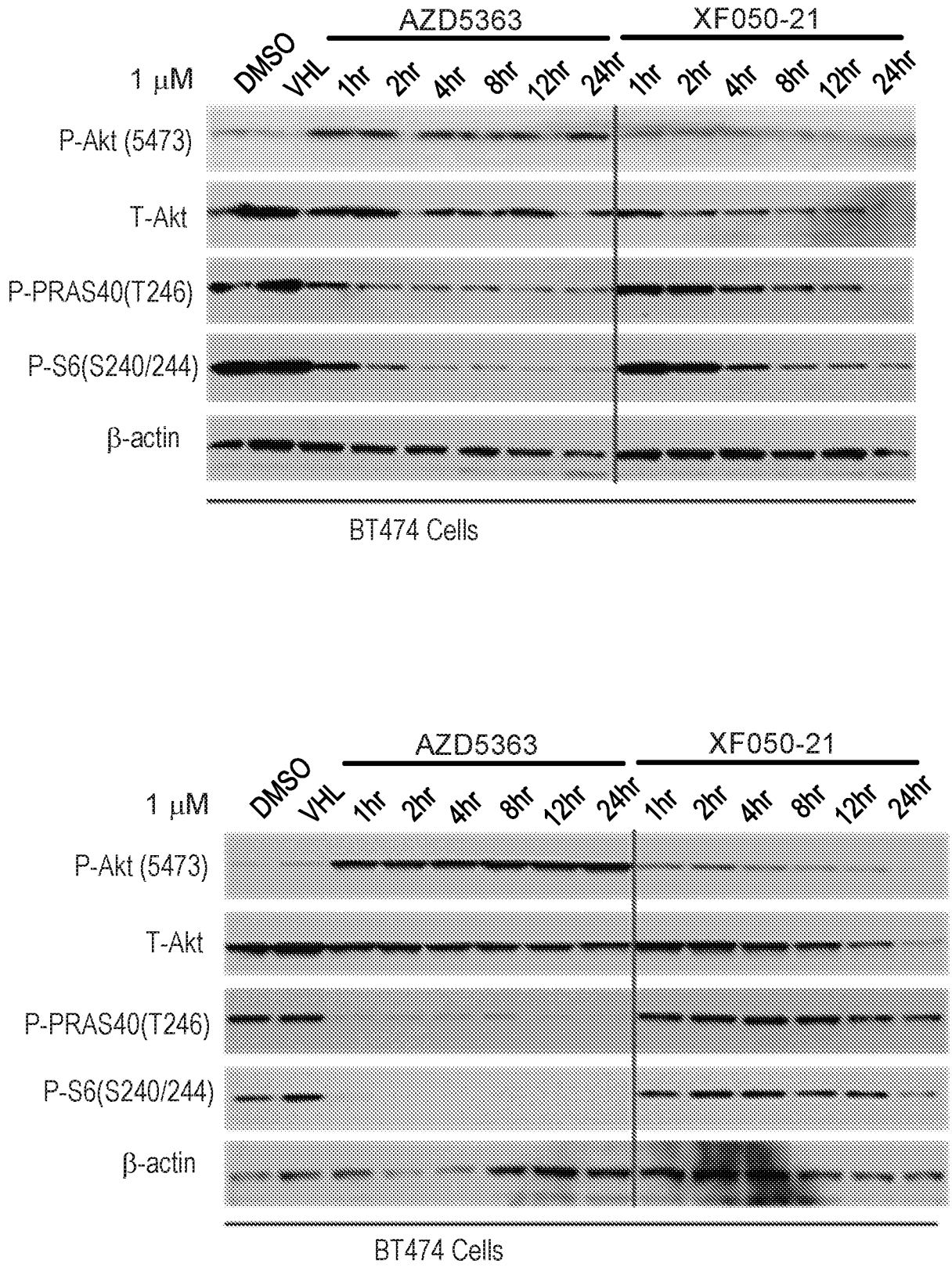
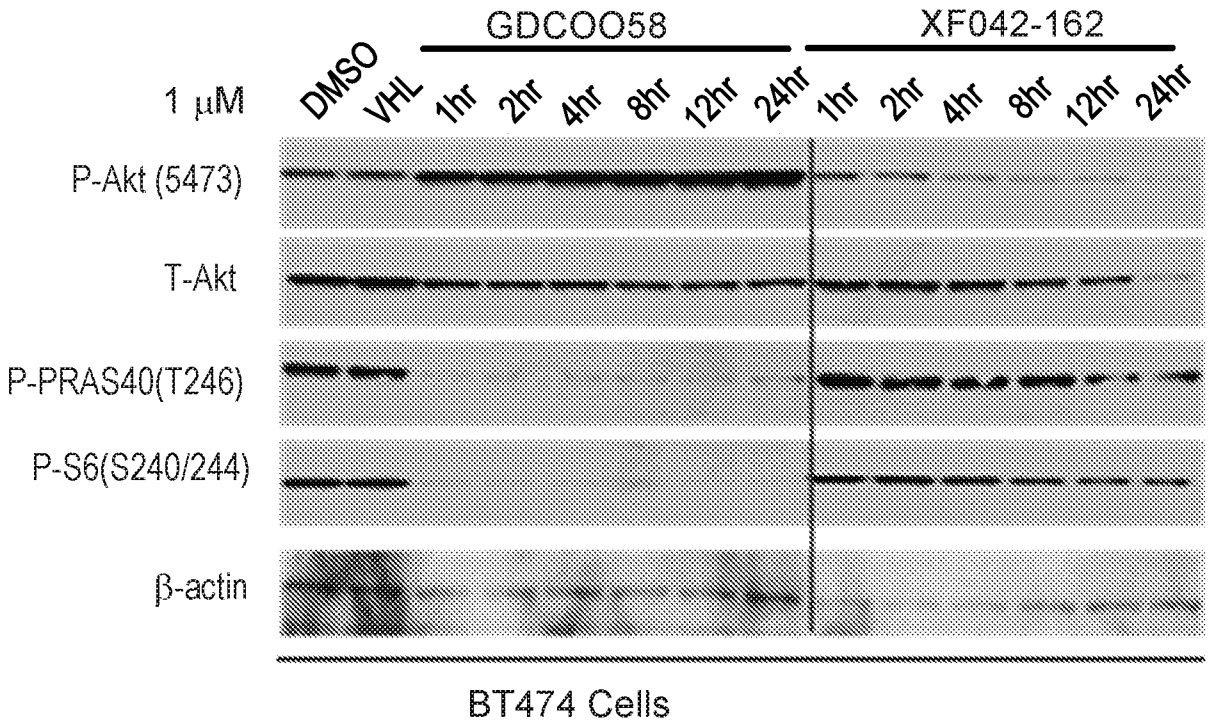

AZD5363
XF050-21
1 μM
DMSO
VHL
1hr
2hr
4hr
8hr
12hr
24hr
P-Akt (5473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells

FIG. 5A-1


GDCOO58
XF042-162
1 μM
DMSO
VHL
1hr
2hr
4hr
8hr
12hr
24hr
1hr
2hr
4hr
8hr
12hr
24hr
P-Akt (5473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells

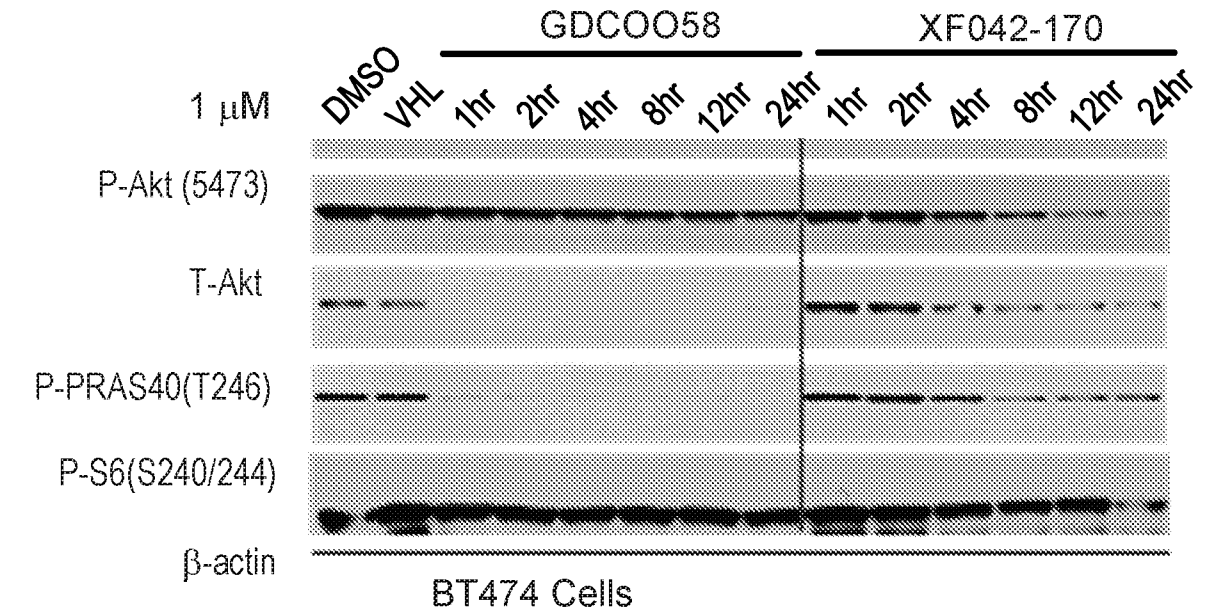

GDCOO58
XF042-170
1 μM
DMSO
VHL
1hr
2hr
4hr
8hr
12hr
24hr
1hr
2hr
4hr
8hr
12hr
24hr
P-Akt (5473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells

FIG. 5A-2

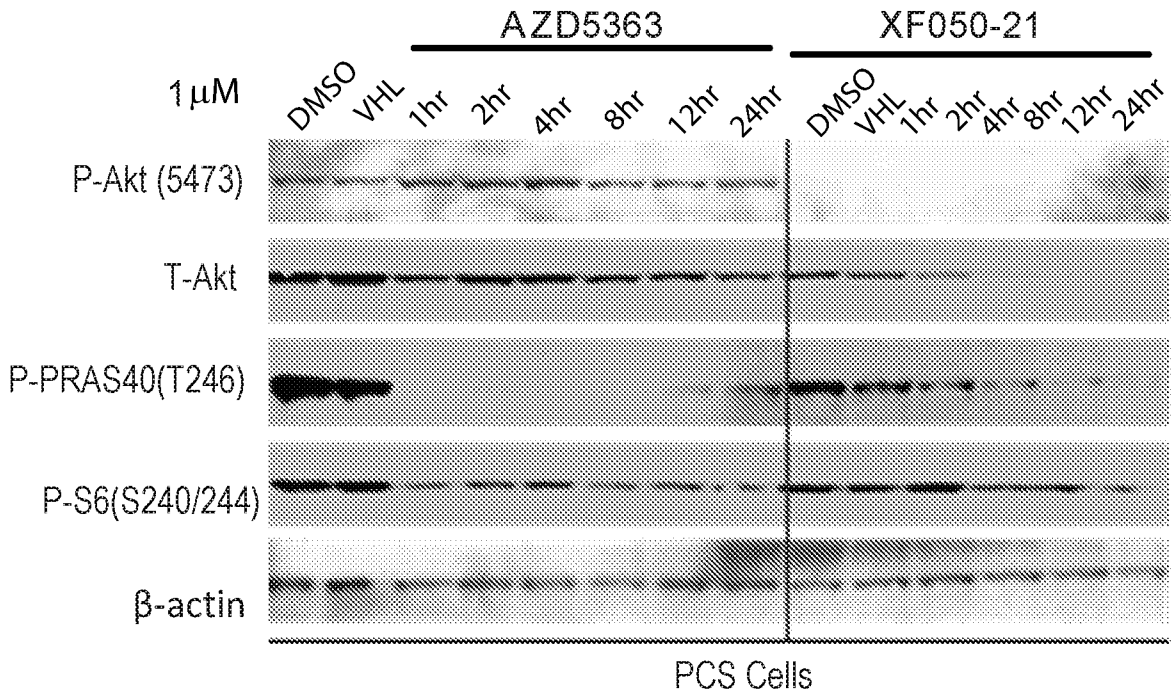

AZD5363
XF050-21
1 μM
DMSO
VHL
1hr
2hr
4hr
8hr
12hr
24hr
DMSO
VHL
1hr
2hr
4hr
8hr
12hr
24hr
P-Akt (5473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
PCS Cells

FIG. 5B

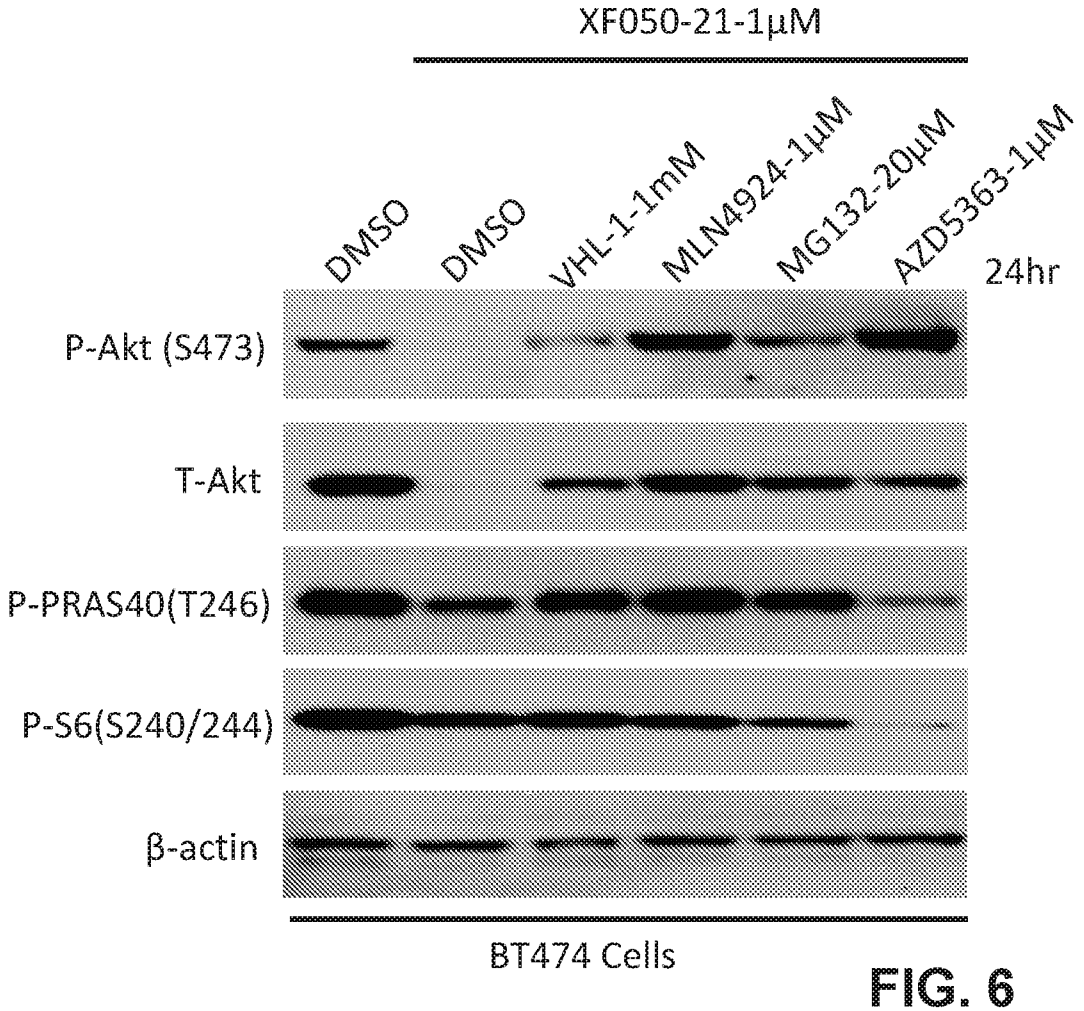

XF050-21-1μM
DMSO
DMSO
VHL-1-1mM
MLN4924-1μM
MG132-20μM
AZD5363-1μM
24hr
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells

FIG. 6

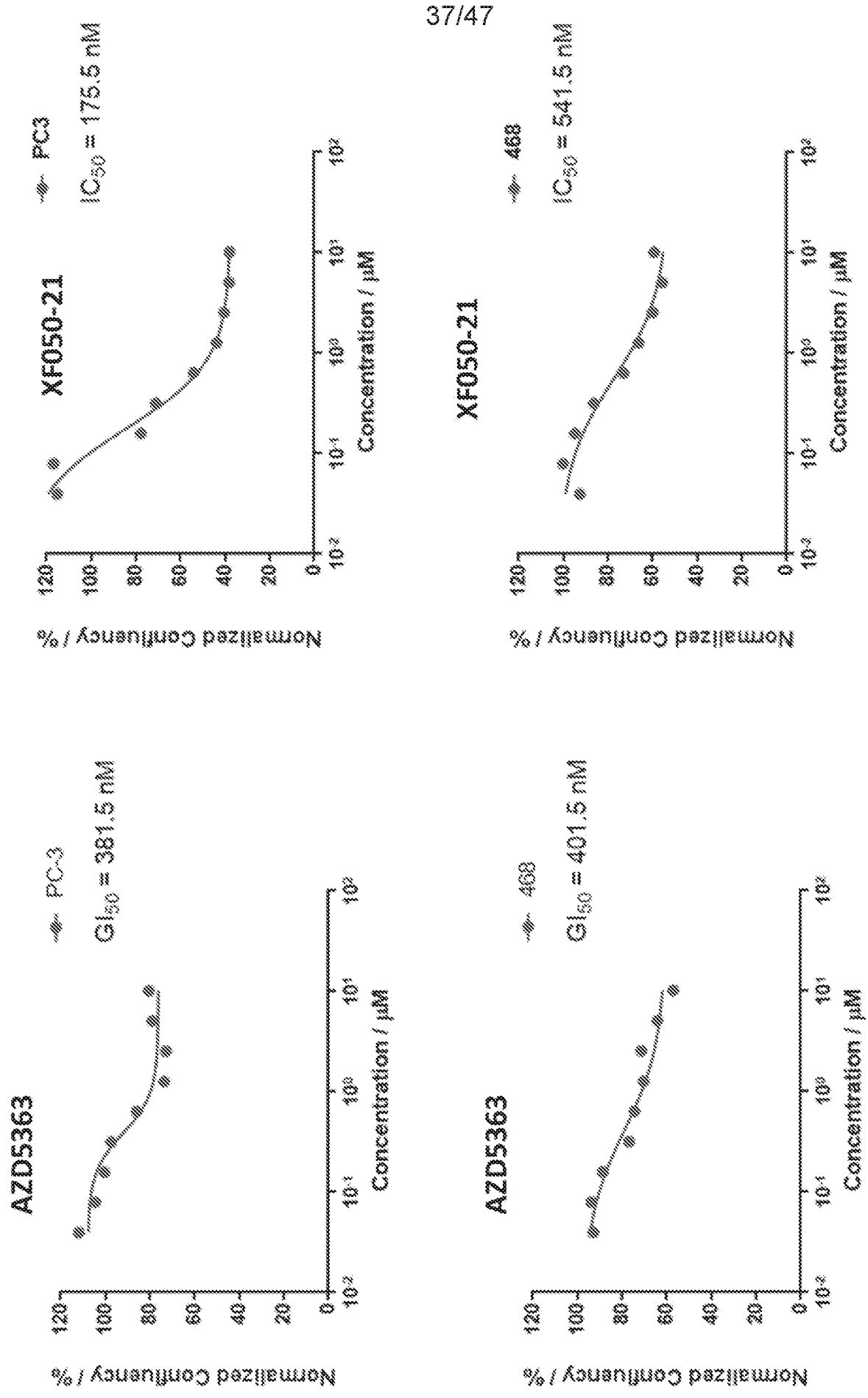

XF050-21
PC3
IC_{50} = 175.5 nM
468
IC_{50} = 541.5 nM
AZD5363
PC-3
GI_{50} = 381.5 nM
468
GI_{50} = 401.5 nM
Normalized Confluency / %
Concentration / μM

FIG. 7

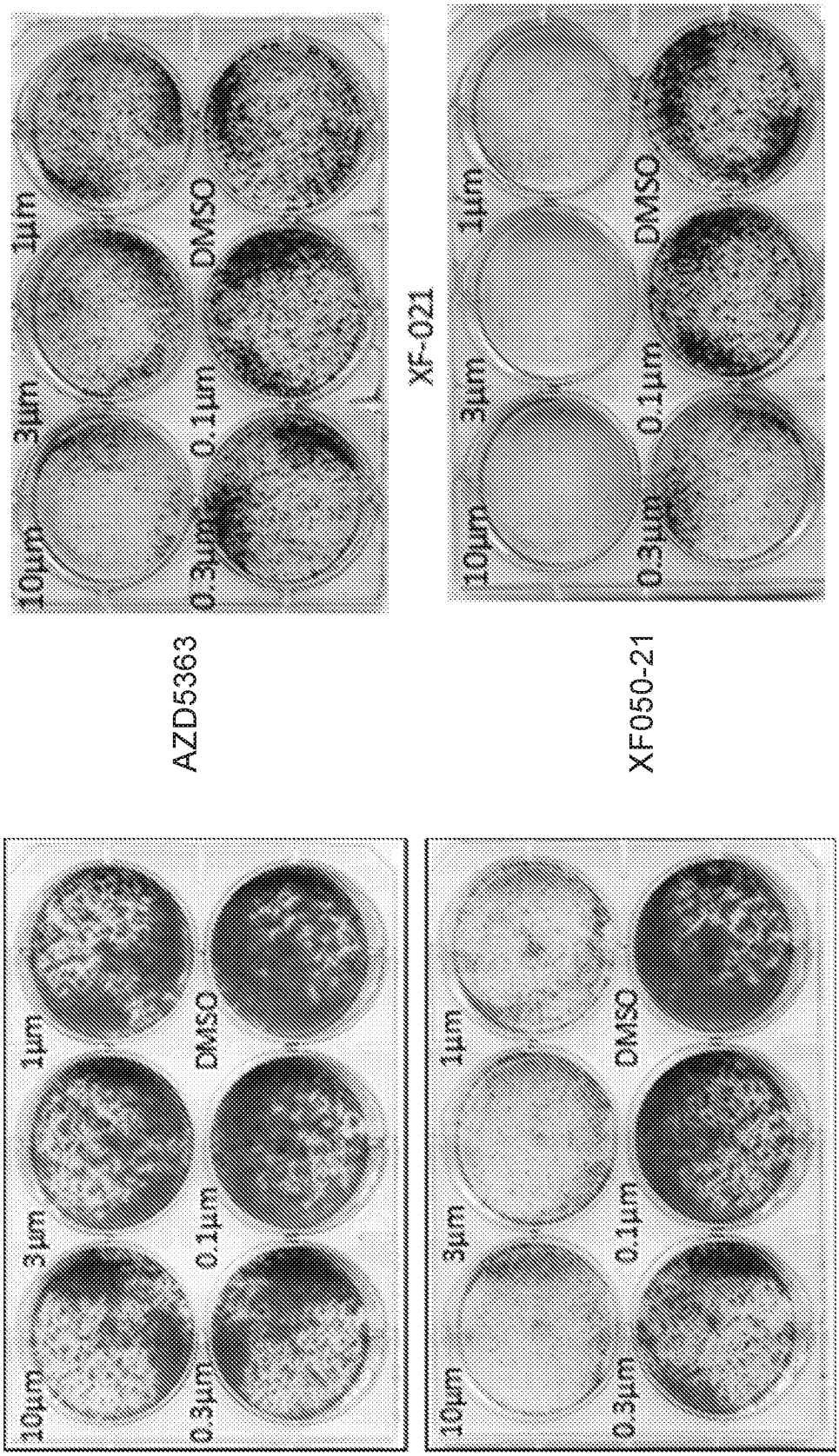


FIG. 8A

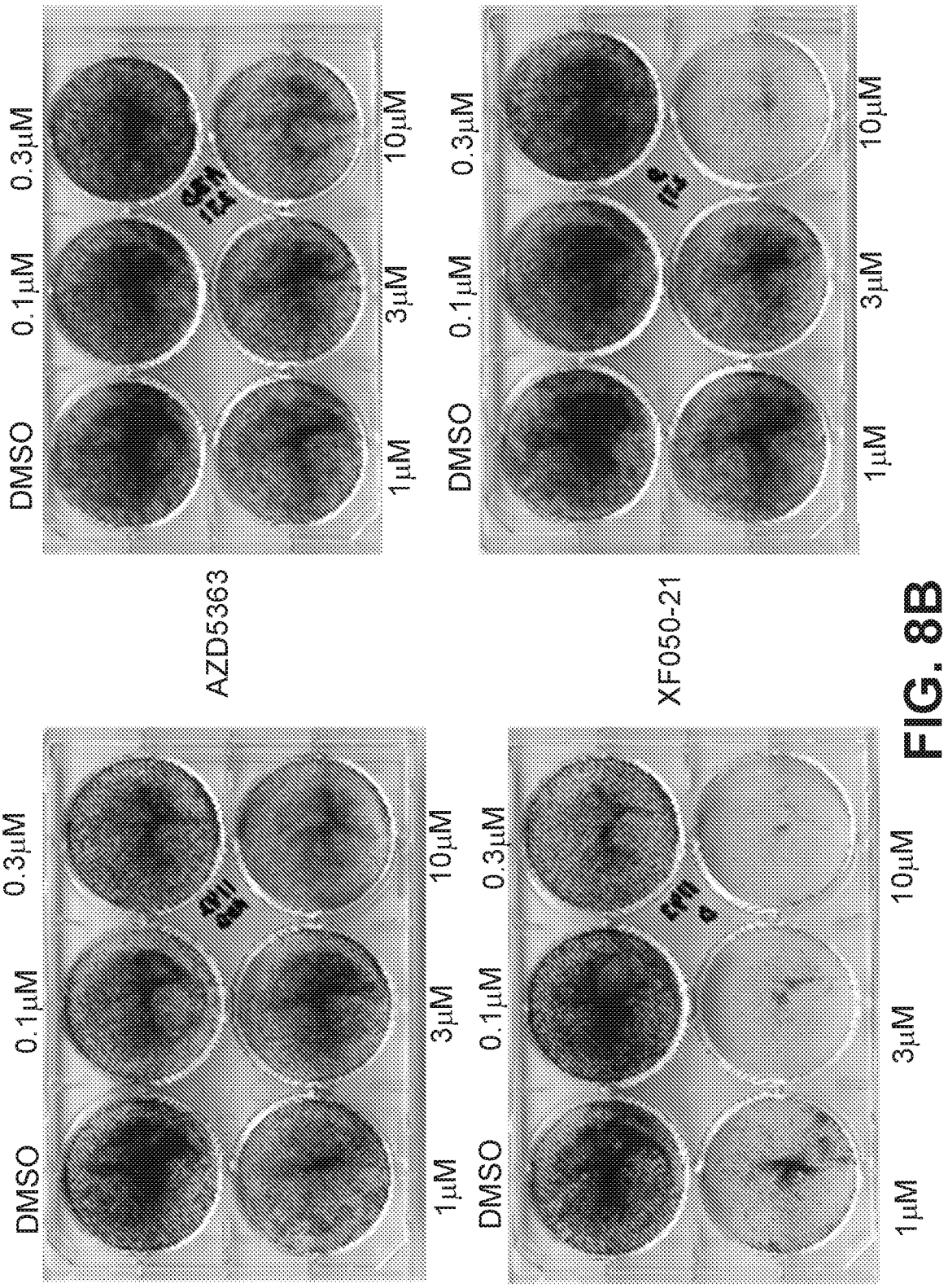


FIG. 8B

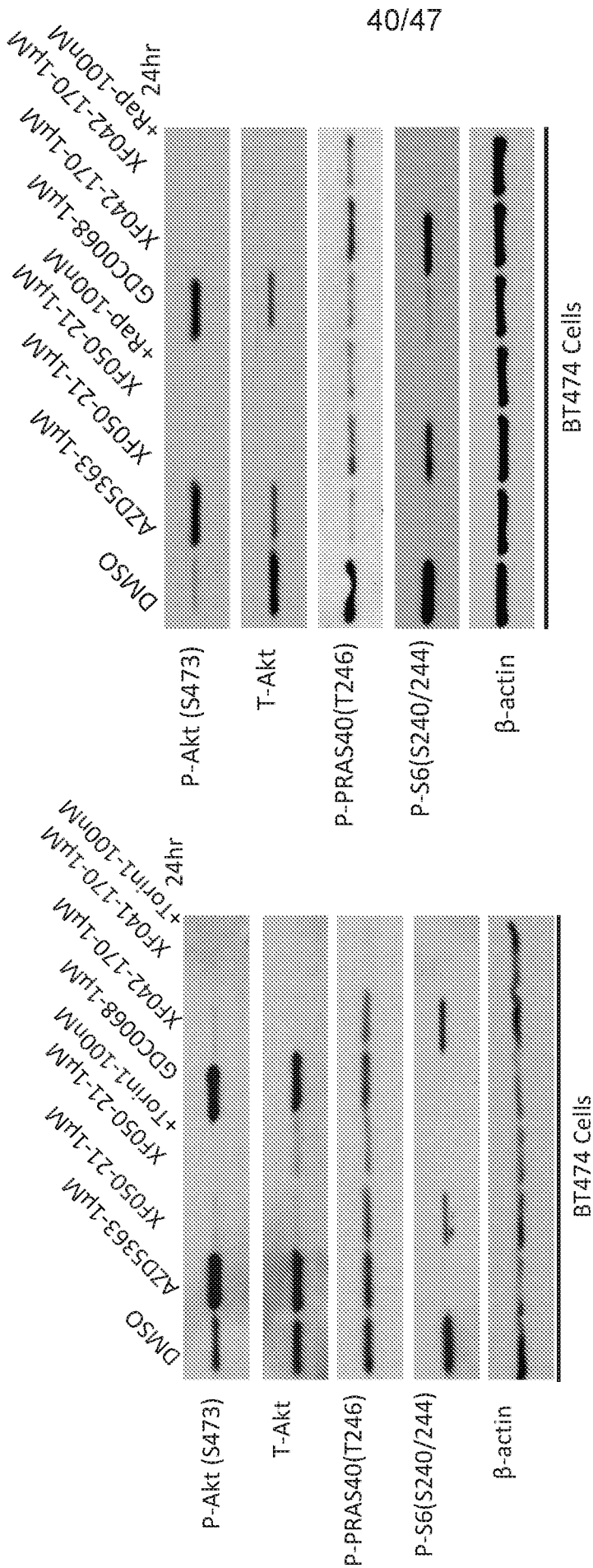

24hr
+Rap-100nM
XF042-170-1μM
XF042-170-1μM
GDC0068-1μM
+Rap-100nM
XF050-21-1μM
XF050-21-1μM
AZD5363-1μM
DMSO
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells
24hr
+Torin1-100nM
XF041-170-1μM
XF042-170-1μM
GDC0068-1μM
+Torin1-100nM
XF050-21-1μM
XF050-21-1μM
AZD5363-1μM
DMSO
P-Akt (S473)
T-Akt
P-PRAS40(T246)
P-S6(S240/244)
β-actin
BT474 Cells

FIG. 9

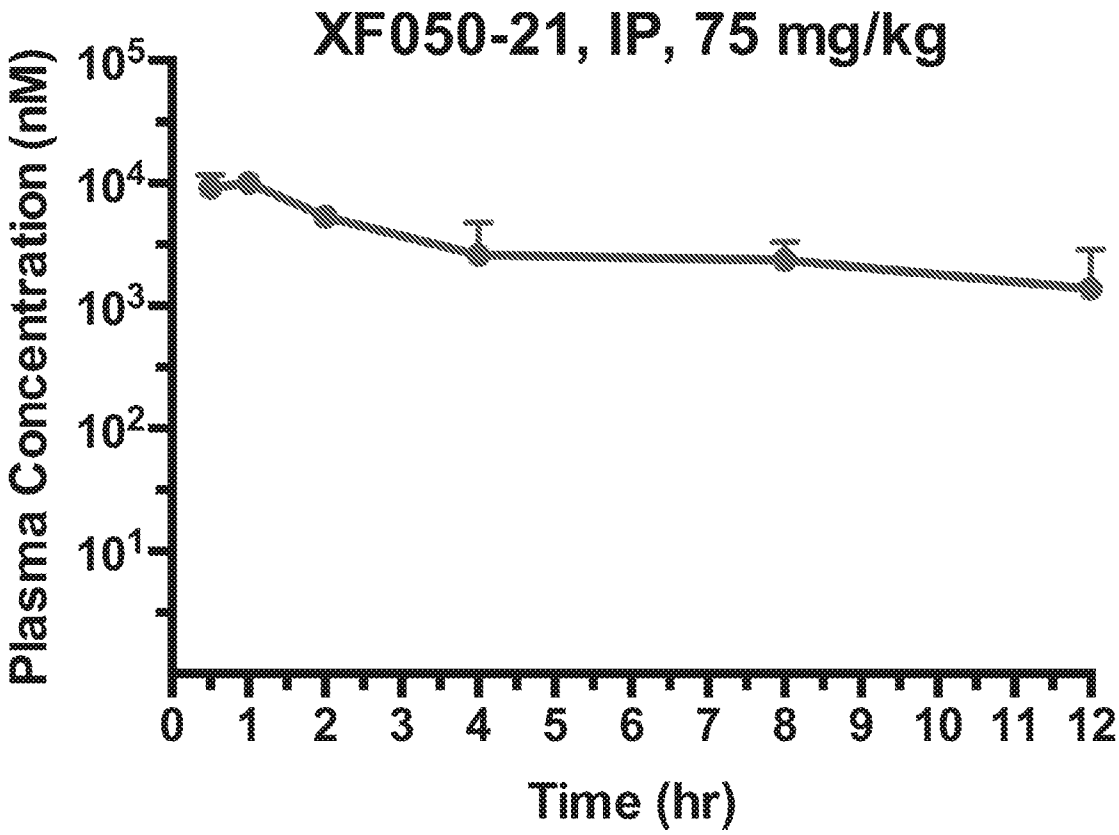

XF050-21, IP, 75 mg/kg
Plasma Concentration (nM)
10^5
10^4
10^3
10^2
10^1
0 1 2 3 4 5 6 7 8 9 10 11 12
Time (hr)

FIG. 10

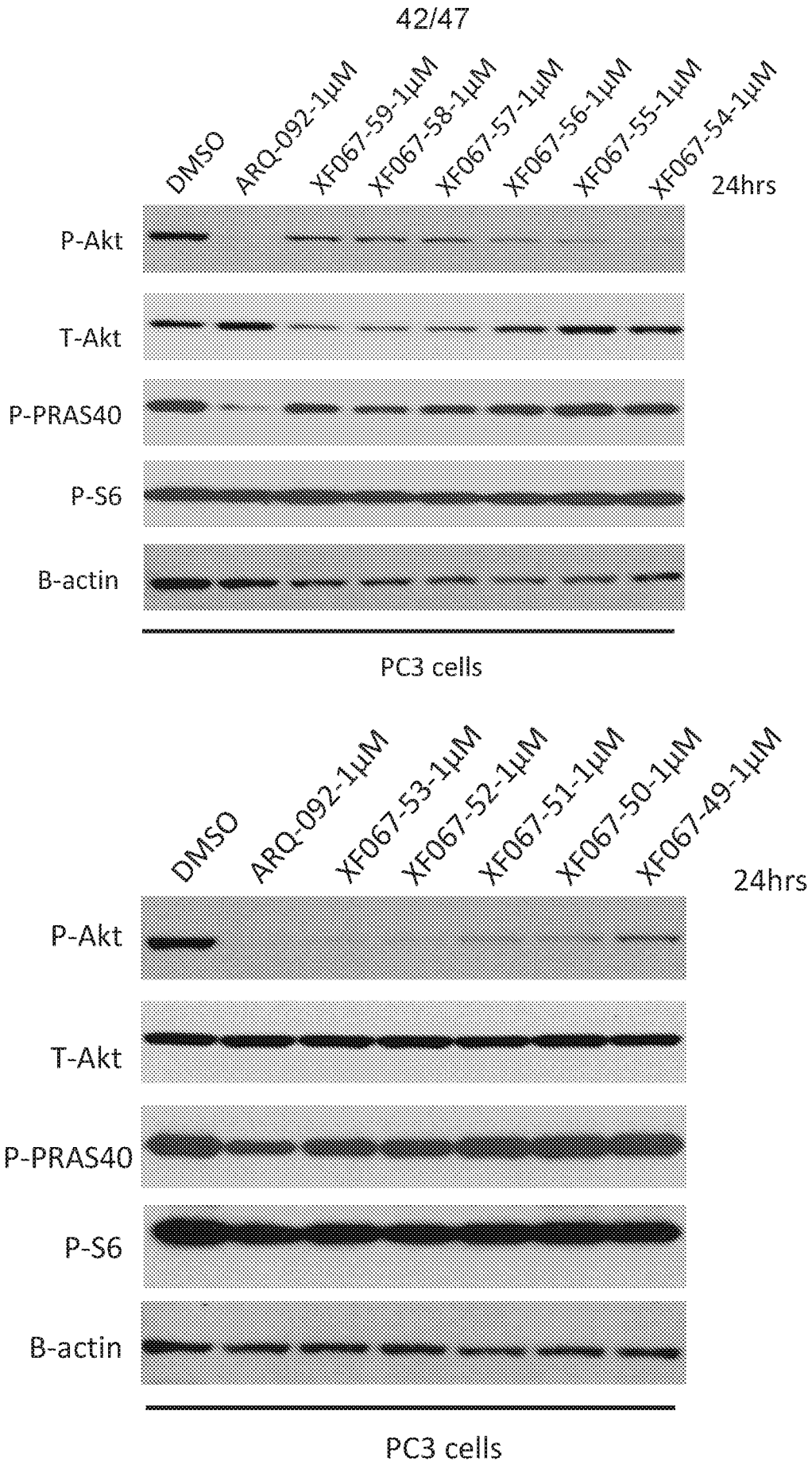

DMSO
ARQ-092-1μM
XF067-59-1μM
XF067-58-1μM
XF067-57-1μM
XF067-56-1μM
XF067-55-1μM
XF067-54-1μM
24hrs
P-Akt
T-Akt
P-PRAS40
P-S6
B-actin
PC3 cells
DMSO
ARQ-092-1μM
XF067-53-1μM
XF067-52-1μM
XF067-51-1μM
XF067-50-1μM
XF067-49-1μM
24hrs
P-Akt
T-Akt
P-PRAS40
P-S6
B-actin
PC3 cells

FIG. 11-1

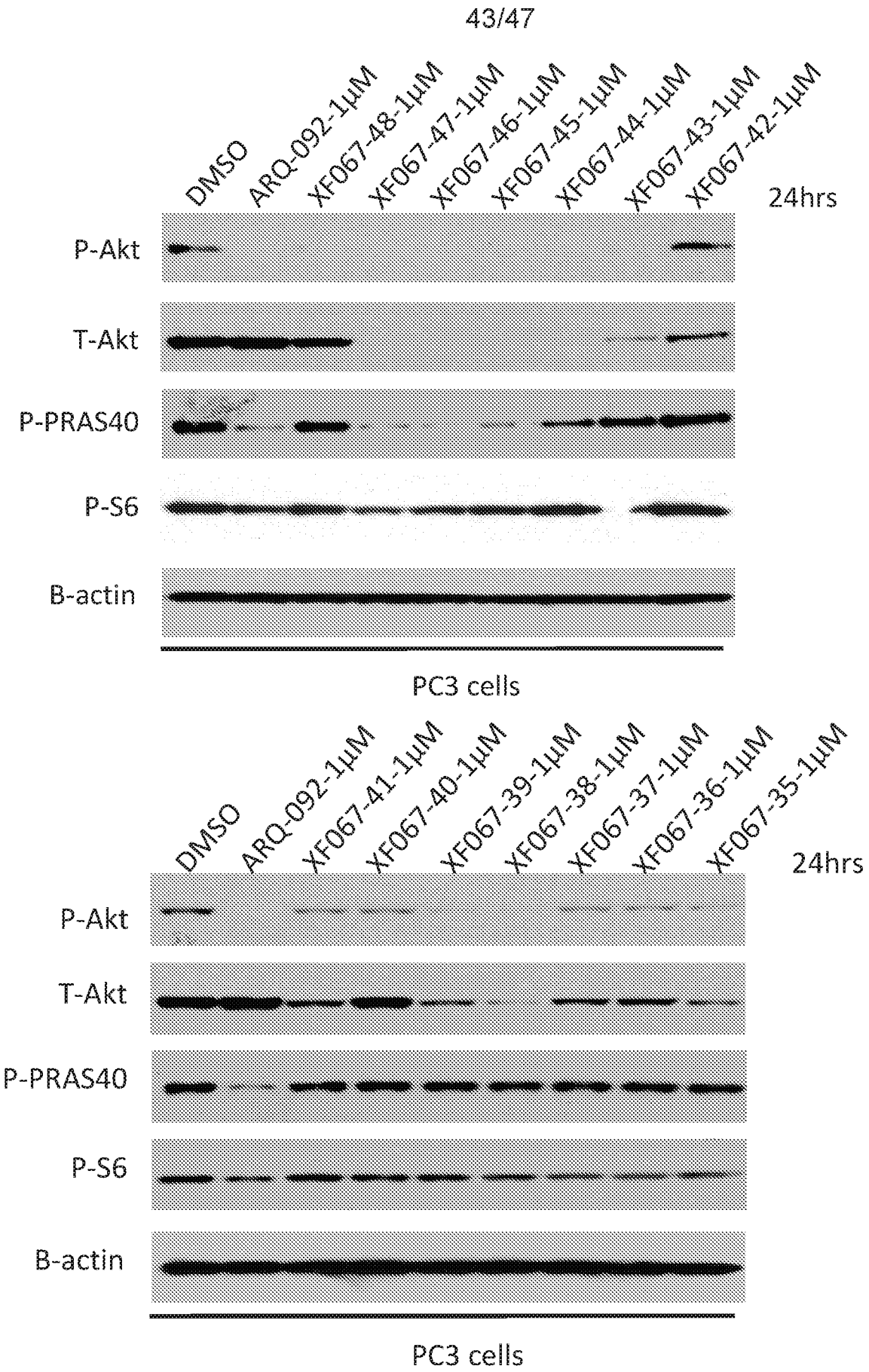
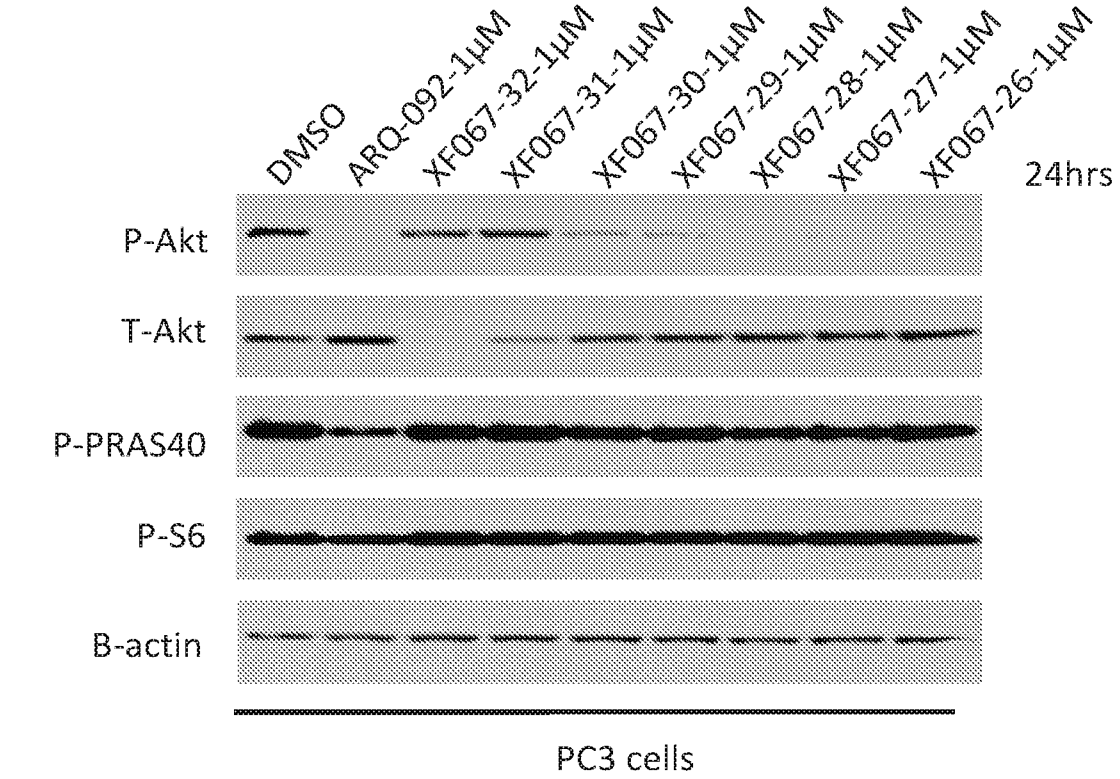

DMSO
ARQ-092-1μM
XF067-48-1μM
XF067-47-1μM
XF067-46-1μM
XF067-45-1μM
XF067-44-1μM
XF067-43-1μM
XF067-42-1μM
24hrs
P-Akt
T-Akt
P-PRAS40
P-S6
B-actin
PC3 cells
DMSO
ARQ-092-1μM
XF067-41-1μM
XF067-40-1μM
XF067-39-1μM
XF067-38-1μM
XF067-37-1μM
XF067-36-1μM
XF067-35-1μM
24hrs
P-Akt
T-Akt
P-PRAS40
P-S6
B-actin
PC3 cells

FIG. 11-2


DMSO
ARQ-092-1μM
XF067-32-1μM
XF067-31-1μM
XF067-30-1μM
XF067-29-1μM
XF067-28-1μM
XF067-27-1μM
XF067-26-1μM
24hrs
P-Akt
T-Akt
P-PRAS40
P-S6
B-actin
PC3 cells

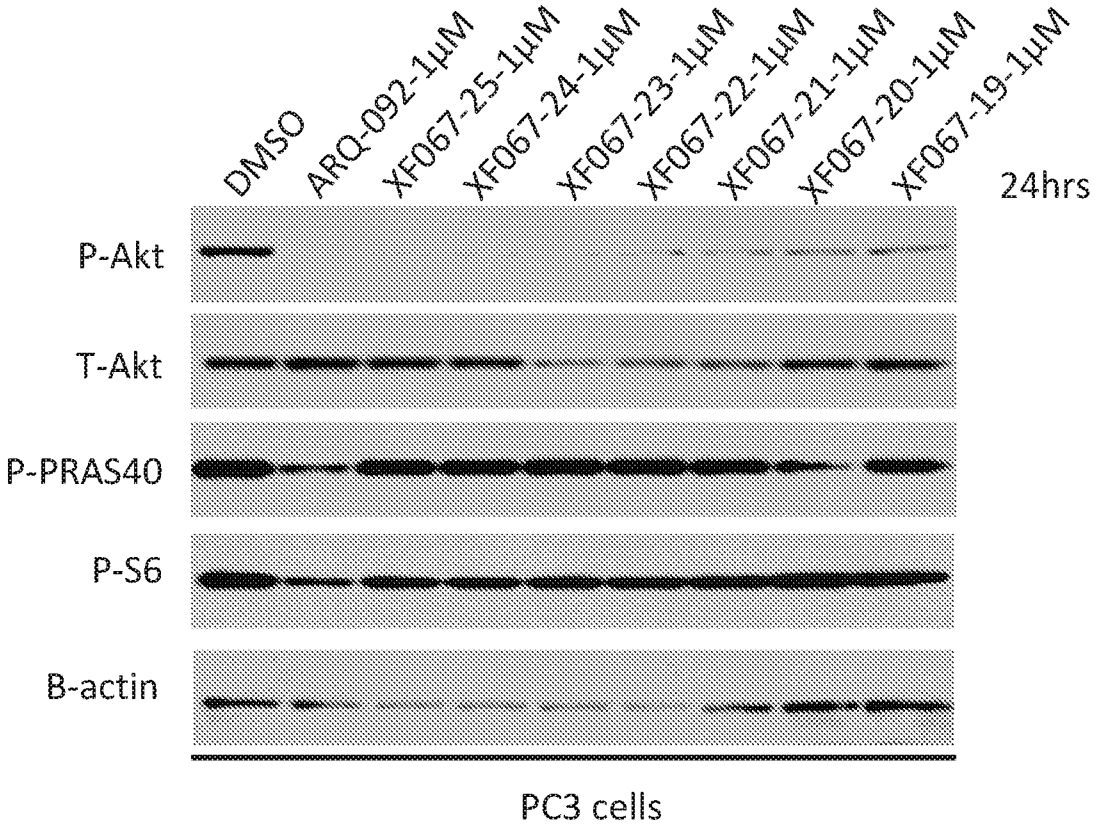

DMSO
ARQ-092-1μM
XF067-25-1μM
XF067-24-1μM
XF067-23-1μM
XF067-22-1μM
XF067-21-1μM
XF067-20-1μM
XF067-19-1μM
24hrs
P-Akt
T-Akt
P-PRAS40
P-S6
B-actin
PC3 cells

FIG. 11-3

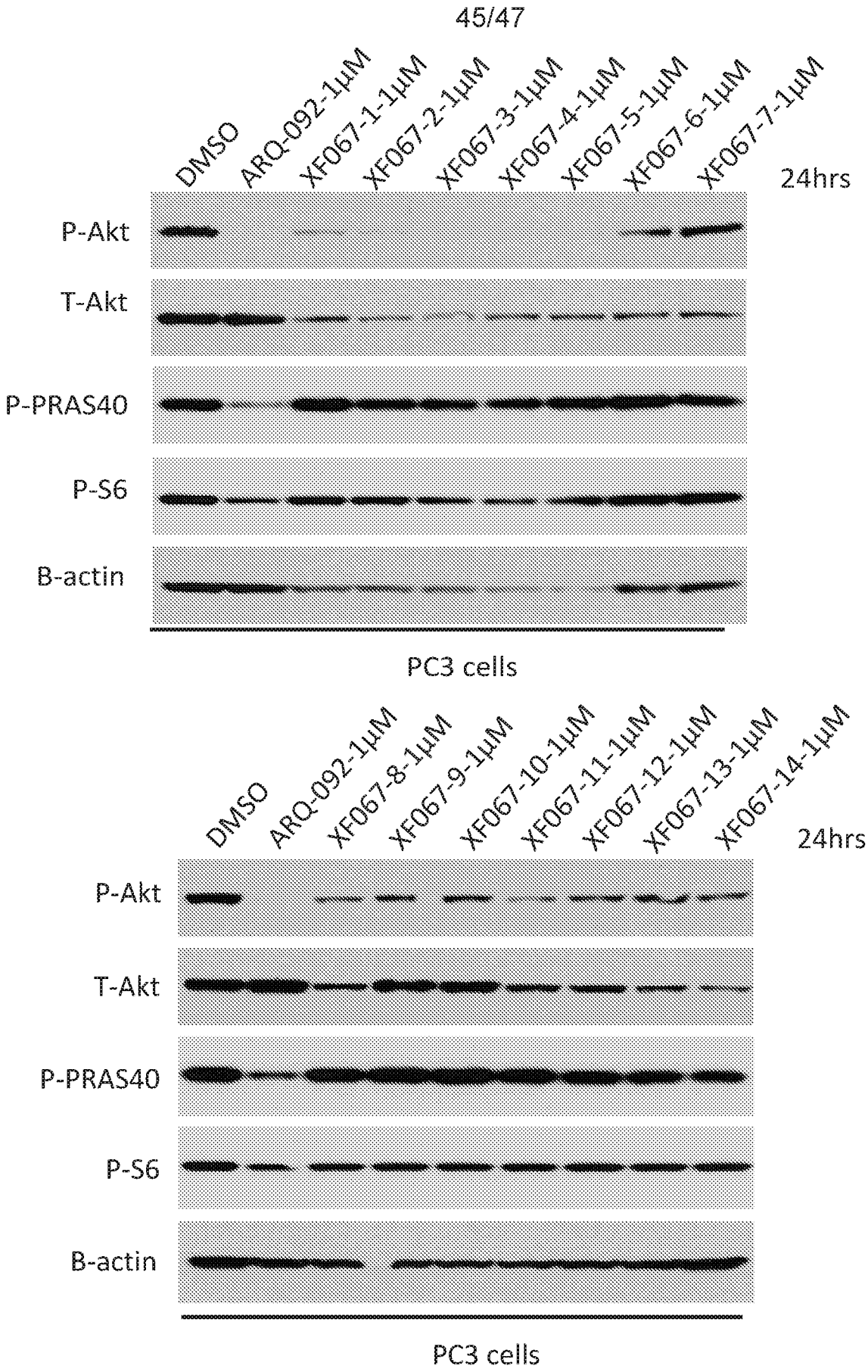

DMSO
ARQ-092-1μM
XF067-1-1μM
XF067-2-1μM
XF067-3-1μM
XF067-4-1μM
XF067-5-1μM
XF067-6-1μM
XF067-7-1μM
24hrs
P-Akt
T-Akt
P-PRAS40
P-S6
B-actin
PC3 cells
DMSO
ARQ-092-1μM
XF067-8-1μM
XF067-9-1μM
XF067-10-1μM
XF067-11-1μM
XF067-12-1μM
XF067-13-1μM
XF067-14-1μM
24hrs
P-Akt
T-Akt
P-PRAS40
P-S6
B-actin
PC3 cells

FIG. 11-4

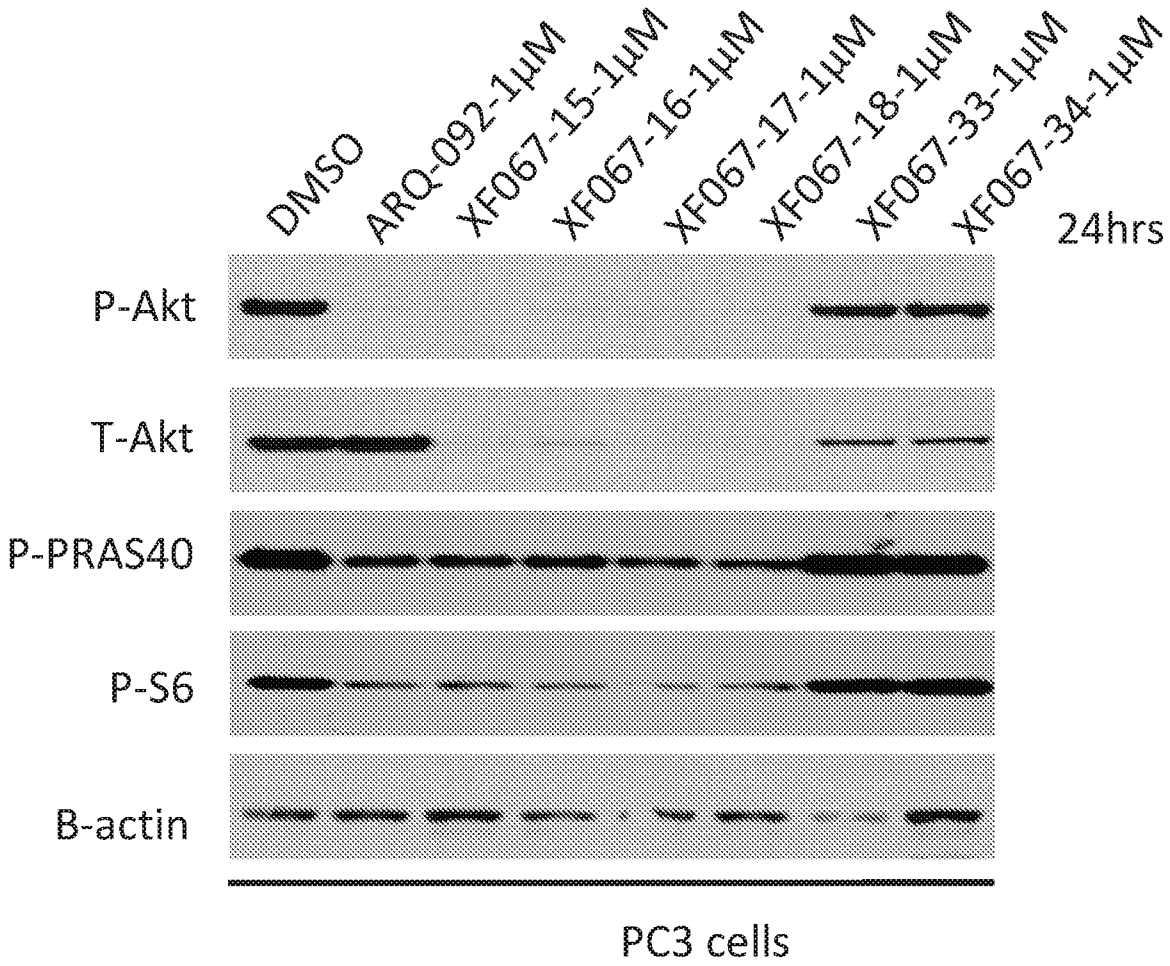

DMSO
ARQ-092-1μM
XF067-15-1μM
XF067-16-1μM
XF067-17-1μM
XF067-18-1μM
XF067-33-1μM
XF067-34-1μM
24hrs
P-Akt
T-Akt
P-PRAS40
P-S6
B-actin
PC3 cells

FIG. 11-5

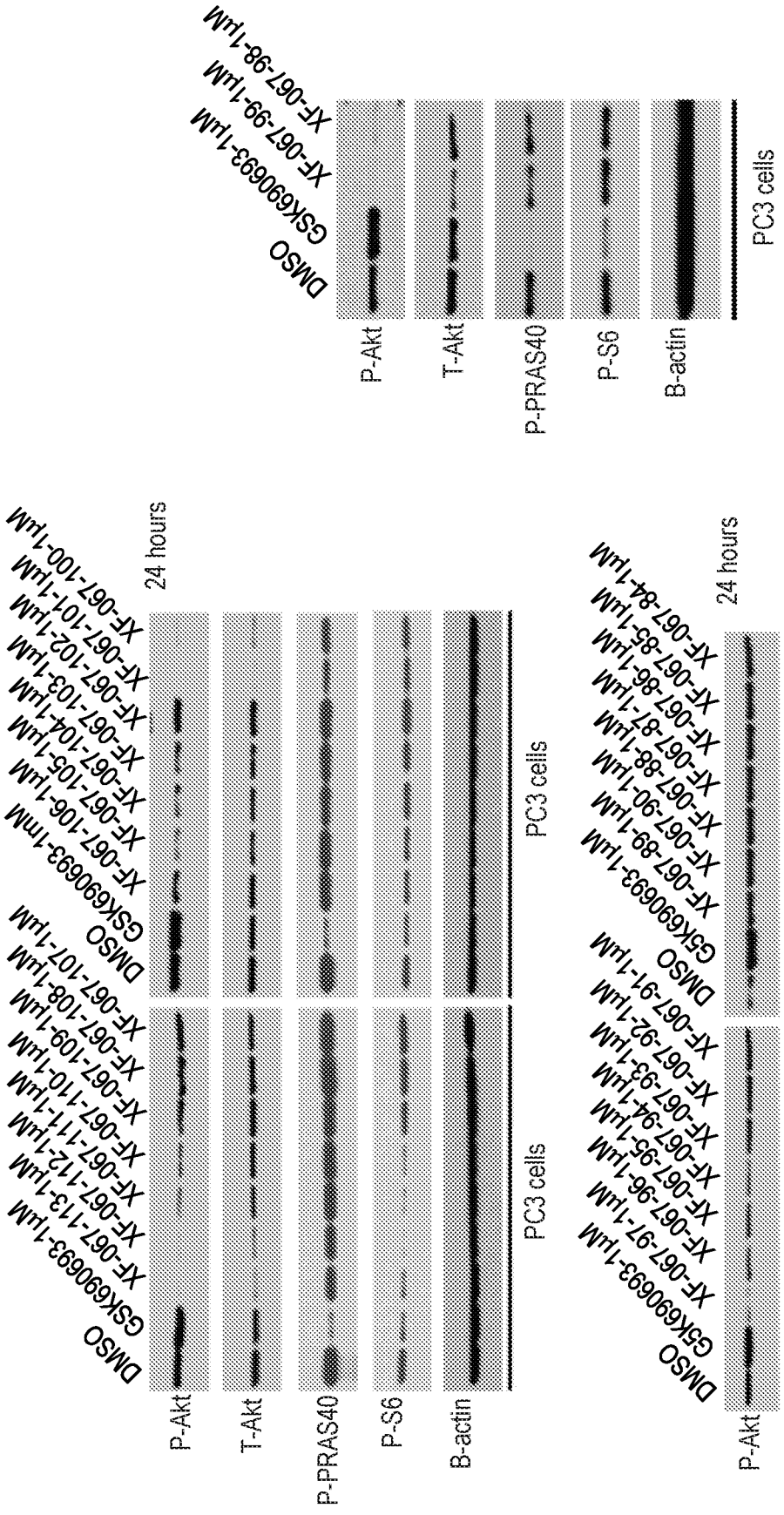

DMSO
GSK690693-1μM
XF-067-99-1μM
XF-067-98-1μM
P-Akt
T-Akt
P-PRAS40
P-S6
B-actin
PC3 cells
24 hours
DMSO
GSK690693-1μM
XF-067-89-1μM
XF-067-90-1μM
XF-067-88-1μM
XF-067-87-1μM
XF-067-86-1μM
XF-067-85-1μM
XF-067-84-1μM
DMSO
GSK690693-1μM
XF-067-97-1μM
XF-067-96-1μM
XF-067-95-1μM
XF-067-94-1μM
XF-067-93-1μM
XF-067-92-1μM
XF-067-91-1μM
DMSO
GSK690693-1mM
XF-067-106-1μM
XF-067-105-1μM
XF-067-104-1μM
XF-067-103-1μM
XF-067-102-1μM
XF-067-101-1μM
XF-067-100-1μM
DMSO
GSK690693-1μM
XF-067-113-1μM
XF-067-112-1μM
XF-067-111-1μM
XF-067-110-1μM
XF-067-109-1μM
XF-067-108-1μM
XF-067-107-1μM

FIG. 12

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2019/021014

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 35-49, 77-89, 91-109, 111, 112
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See Extra Sheet.

Claims 1, 2, 12-14, 26, 27, and 90 have been analyzed subject to the restriction as described in the Lack of Unity of Invention (See Extra Sheet). The claims are restricted to a bivalent compound comprising a serine threonine kinase AKT ligand conjugated to a degradation/disruption tag through a linker, said linker selected from the group consisting of the formula shown, wherein A, W, and B at each occurrence, are independently null; m is 0; wherein the AKT ligand is selected from the group consisting of Formula 1, shown in claim 37 of the instant invention, wherein A, B, and X are independently N; Y is CH2; E is NH; R1 is H; R2, R3, and R4 are independently hydrogen; R5 is H, wherein the AKT ligand is attached to the degradation/disruption tag through E, as shown; and the degradation/disruption tag is the Formula 5A as shown in claim 45 of the instant invention, wherein V, W, and X are independently CR2; Y is CO; Z is CH2; and R1 and R2 are independently hydrogen, wherein the degradation/disruption tag is attached to the AKT ligand through Z, as shown; and bivalent compounds thereof.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1, 2, 12-14, 26, 27, 90

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2019/021014

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07D 403/14; C07D 401/14; C07D 417/14 (2019.01)
CPC - C07D 401/14; C07D 403/14; C07D 417/14 (2019.05)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2015/192123 A1 (TRUSTEES OF TUFTS COLLEGE) 17 December 2015 (17.12.2015) entire document	1, 2, 12-14, 26, 27, 90
A	US 2017/0114098 A1 (AILERON THERAPEUTICS INC) 27 April 2017 (27.04.2017) entire document	1, 2, 12-14, 26, 27, 90
A	US 8,377,937 B2 (BENCSIK et al) 19 February 2013 (19.02.2013) entire document	1, 2, 12-14, 26, 27, 90
A	US 8,648,096 B2 (MULLER et al) 11 February 2014 (11.02.2014) entire document	1, 2, 12-14, 26, 27, 90

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
07 June 2019	27 JUN 2019
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Continued from Box No. III Observations where unity of invention is lacking

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-34, 50-73, and 90 are drawn to bivalent compounds.

Group II: claims 74-76 and 110 are drawn to methods of treating a serine threonine kinase (AKT)-mediated disease and method for identifying a bivalent compound which mediates degradation/disruption of AKT.

The first invention of Group I+ is restricted to a bivalent compound comprising a serine threonine kinase AKT ligand conjugated to a degradation/disruption tag through a linker, said linker selected from the group consisting of the formula shown, wherein A, W, and B at each occurrence, are independently null; m is 0; wherein the AKT ligand is selected from the group consisting of Formula 1, shown in claim 37 of the instant invention, wherein A, B, and X are independently N; Y is CH2; E is NH; R1 is H; R2, R3, and R4 are independently hydrogen; R5 is H, wherein the AKT ligand is attached to the degradation/disruption tag through E, as shown; and the degradation/disruption tag is the Formula 5A as shown in claim 45 of the instant invention, wherein V, W, and X are independently CR2; Y is CO; Z is CH2; and R1 and R2 are independently hydrogen, wherein the degradation/disruption tag is attached to the AKT ligand through Z, as shown; and bivalent compounds thereof. It is believed that claims 1, 2, 12-14, 26, 27, and 90 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. Each additional elected formula(e) requires the selection of a single definition for each compound variable. An exemplary election would be a bivalent compound comprising a serine threonine kinase AKT ligand conjugated to a degradation/disruption tag through a linker, said linker selected from the group consisting of the formula shown, wherein A, W, and B at each occurrence, are independently null; m is 0; wherein the AKT ligand is selected from the group consisting of Formula 1, shown in claim 37 of the instant invention, wherein A, B, and X are independently N; Y is CH2; E is NH; R1 is H; R2, R3, and R4 are independently hydrogen; R5 is H, wherein the AKT ligand is attached to the degradation/disruption tag through E, as shown; and the degradation/disruption tag is the Formula 5A as shown in claim 45 of the instant invention, wherein V, W, and X are independently CR2; Y is N=N; Z is CH2; and R1 and R2 are independently hydrogen, wherein the degradation/disruption tag is attached to the AKT ligand through Z, as shown; and bivalent compounds thereof. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ and II do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The special technical features of Group I+, bivalent compounds, are not present in Group II; and the special technical features of Group II, methods of treating a serine threonine kinase (AKT)-mediated disease and method for identifying a bivalent compound which mediates degradation/disruption of AKT, are not present in Group I+.

The Groups I+ and II formulae do not share a significant structural element requiring the selection of alternatives for the AKT ligand, degradation/disruption tag and compound variables A, W, B, m and accordingly these groups lack unity a priori.

Additionally, even if Groups I+ and II were considered to share the technical features of a bivalent compound comprising a serine threonine kinase AKT ligand conjugated to a degradation/disruption tag through a linker; and a bivalent compound comprising a serine threonine kinase (AKT) ligand conjugated to a degradation/disruption tag through a linker, these shared technical features do not represent a contribution over the prior art as disclosed by WO 2015/192123 A1 to Trustees of Tufts College.

WO 2015/192123 A1 to Trustees of Tufts College teaches a bivalent compound comprising a serine threonine kinase AKT ligand conjugated to a degradation/disruption tag through a linker (Fig. 13, Compound 5155, see shown structure; Pg. 13, Lns. 3-4, Figure 13 shows the structures of two Akt inhbitor prodrugs, and a graph showing that the Akt inhibitor prodrugs...); and a bivalent compound comprising a serine threonine kinase (AKT) ligand conjugated to a degradation/disruption tag through a linker (Fig. 13, Compound 5155, see shown structure; Pg. 13, Lns. 3-4).

The inventions listed in Groups I+ and II therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.