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(54) Title: COMPOSITIONS AND METHODS FOR TREATING CDK4/6-MEDIATED CANCER

(57) Abstract: Methods for designing heterobifunctional small molecules which selectively degrade/disrupt CDK4/6 and compositions and methods of using such degraders/disruptors to treat CDK4/6-mediated cancer are provided.

COMPOSITIONS AND METHODS FOR TREATING CDK4/6-MEDIATED CANCER

TECHNICAL FIELD

This disclosure relates to bivalent compounds (e.g., bi-functional small molecule compounds) which selectively degrade and/or disrupt cyclin-dependent kinase (CDK) 4 and/or 6, compositions comprising one or more of the bivalent compounds, and to methods of use thereof for the treatment of CDK4/6-mediated cancer in a subject in need thereof. The disclosure also relates to methods for designing such bivalent compounds.

BACKGROUND OF THE INVENTION

Cyclin-dependent kinase 4 (CDK4, also known as CMM3 and PSK-J3) (Matsushime et al., 1992) and cyclin-dependent kinase 6 (CDK6, also known as MCPH12 and PLSTIRE) (Meyerson and Harlow, 1994) are related serine/threonine kinases (referred to together as "CDK4/6") that play a critical role in the cyclin D/CDK4/6/Rb/E2F signaling pathway ("CDK4/6/Rb signaling") (Sherr et al., 2016). CDK4/6/Rb signaling mediates physiological cell cycle progression and cell proliferation. Dephosphorylated Rb binds transcription factors of the E2F family, thus preventing transition through the S phase. CDK4 and CDK6 promote cell cycle progression by phosphorylating Rb. Phosphorylation of Rb allows E2F to dissociate from Rb and promote transition through the S phase of the cell cycle (Burkhart and Sage, 2008).

Multiple types of cancer, including breast cancer, have been found to depend on aberrant activation of CDK4/6/Rb signaling for their progression ("CDK4/6-mediated cancer") (Yu et al., 2006; Hamilton and Infante, 2016; Lim et al., 2016). Conventional cancer treatments include surgery, radiation therapy, chemotherapy (e.g., gemcitabine HCl and temozolomide, a cytotoxic DNA alkylating agent), hormonal therapy, targeted antibody therapy, and combinations thereof. Among women, breast cancer has a considerably higher incident rate (43.3 per 100,000) than any other cancer. In North America, breast cancer is one of the leading causes of cancer death among women (about 15%), only second to lung cancer.

Significant effort has been spent on developing therapeutics capable of inhibiting the activity of CDK4/6. Three CDK4/6 inhibitors (palbociclib (PD-0332991; Pfizer), abemaciclib (LY2835219; Lilly), and ribociclib (LEE011; Novartis)) have been approved. All three compounds have shown preclinical activity in a range of tumor models, dependent on the

expression of intact Rb in the tumor. Recently, three additional CDK4/6 inhibitors, trilaciclib (G1T28), G1T38, and SHR6390, have entered phase I clinical trials.

Clinical results have shown that patients with estrogen receptor (ER) positive (ER+) breast tumors show remarkable responses and increased progression-free survival when treated with CDK4/6 inhibitors coupled with endocrine therapy (i.e., treatment with one or more aromatase inhibitors or ER antagonists) (Finn et al., 2015; Turner et al., 2015). Despite the initial response to such treatments, however, the majority of these patients eventually develop resistance to such treatment within 14-28 months (Finn et al., 2015). Preliminary data suggest that such acquired resistance can arise from failure of inhibitor to suppress CDK4/6/Rb signaling or from loss of Rb (Herrera-Abreu et al., 2016). Overall, the clinical efficacy of CDK4/6 inhibitor monotherapy (i.e., CDK4/6 treatment alone without endocrine or other therapy) appears to be modest (Sherr et al., 2016). Toxicity can limit the administration of these inhibitors at a concentration high enough to sufficiently inhibit Rb phosphorylation in the tumor.

SUMMARY

The present disclosure relates generally to bivalent compounds (e.g., bi-functional small molecule compounds) which selectively degrade and/or disrupt CDK4/6, and to methods for the treatment of CDK4/6-mediated cancer (i.e., a cancer that overexpresses CDK4, CDK6 or both; cancer which depends on CDK4, CDK6, or both activity; or cancer having elevated levels of CDK4, CDK6, or both, activity relative to a wild-type tissue of the same species and tissue type). It is important to note, because the CDK4/6 degraders/disruptors have dual functions (enzyme inhibition plus protein degradation/disruption), the bivalent compounds disclosed/claimed here can be significantly more effective therapeutic agents than current CDK4/6 inhibitors, which inhibit the enzymatic activity of CDK4/6 but do not affect CDK4/6 protein levels. The present disclosure further provides methods for identifying CDK4/6 degraders/disruptors as described herein.

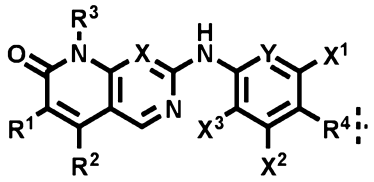
More specifically, the present disclosure provides a bivalent compound including a cyclin-dependent kinase 4/6 (CDK4/6) ligand conjugated to a degradation/disruption tag.

In an aspect, the CDK4/6 degraders/disruptors have the form "**PI-linker-EL**" as shown below:

Formula I,

wherein **PI** comprises a CDK4/6 ligand (e.g., a CDK4/6 inhibitor) and **EL** comprises a degradation/disruption tag (e.g., E3 ligase ligand). Exemplary CDK4/6 ligands (**PI**) and exemplary degradation/disruption tags (**EL**) are disclosed herein.

For example, **PI** can include, but is not limited to:



Formula II,

wherein X^1, X^2, and X^3 are independently hydrogen, halogen, C1-C8 alkyl, C1-C8 alkoxy, C1-C8 alkoxyalkyl, NR^5R^6, CN, NO_2, COR^5, CO_2R^5, $CONR^5R^6$, or NR^5COR^6;

R^1 and R^4 are independently hydrogen, halogen, C1-C8 alkyl, C1-C8 alkoxy, C1-C8 alkoxyalkyl, C1-C8 haloalkyl, C1-C8 hydroxyalkyl, C3-C7 cycloalkyl, C3-C7 heterocyclyl, C2-C8 alkenyl, C2-C8 alkynyl, OR^5, SR^5, NR^5R^6, CN, NO_2, $(CR^5R^6)mNR^7R^8$, $(CR^5R^6)mC(O)R^7$, COR^5, CO_2R^5, $CONR^5R^6$, NR^5COR^6, NR^5SOR^6, $NR^5SO_2R^6$, SOR^5, SO_2R^5, $SO_2NR^5R^6$, (CR^5R^6)m-aryl, or (CR^5R^6)m-heteroaryl, wherein m is 0-8;

R^2 is hydrogen, halogen, C1-C8 alkyl, C1-C8 alkoxy, C3-C7 cycloalkyl, or C3-C7 heterocyclyl;

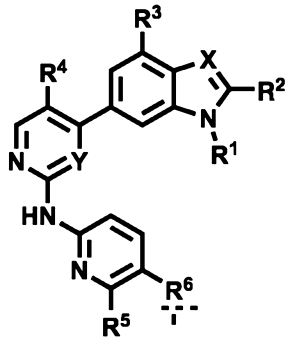
R^3 is hydrogen, aryl, C1-C8 alkyl, C1-C8 alkoxy, C3-C7 cycloalkyl, or C3-C7 heterocyclyl;

R^5, R^6, R^7, R^8 are independently hydrogen, C1-C8 alkyl, C2-C8 alkenyl, C2-C8 alkynyl, arylalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, or heteroarylalkyl;

optionally, R^1 and R^2; R^5 and R^6; or $R^7$and R^8 independently form 4-8 membered alkyl or heterocyclyl rings; and

X and Y are independently CR^5R^6 or N.

For example, **PI** can include:



Formula III,

wherein R^1 is independently hydrogen, C1-C8 alkyl, C1-C8 alkoxyalkyl, C1-C8 haloalkyl, C1-C8 hydroxyalkyl, C3-C7 cycloalkyl, C3-C7 heterocyclyl, C2-C8 alkenyl, or C2-C8 alkynyl;

R^2 is hydrogen, C1-C3 alkyl, or cyclopropyl;

R^3, R^4, and R^5 are independently hydrogen, halogen, C1-C8 alkyl, C1-C8 alkoxy, C3-C7 cycloalkyl, or C3-C7 heterocyclyl;

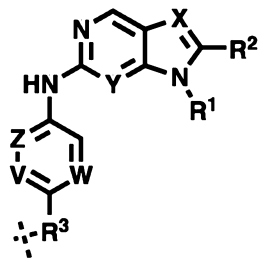
R^6 is hydrogen, halogen,C1-C8 alkyl, C1-C8 alkoxy, C1-C8 alkoxyalkyl, C1-C8 haloalkyl, C1-C8 hydroxyalkyl, C3-C7 cycloalkyl, C3-C7 heterocyclyl, C2-C8 alkenyl, C2-C8 alkynyl, OR^7, SR^7, NR^7R^8, CN, NO_2, $(CR^7R^8)mNR^9R^{10}$, $(CR^7R^8)mC(O)R^9$, COR^7, CO_2R^7, $CONR^7R^8$, NR^7COR^8, NR^7SOR^8, $NR^7SO_2R^8$, SOR^7, SO_2R^7, $SO_2NR^7R^8$, (CR^7R^8)m-aryl, or (CR^7R^8)m-heteroaryl, wherein m is 0-8;

R^7, R^8, R^9, R^{10} are independently hydrogen, C1-C8 alkyl, C2-C8 alkenyl, C2-C8 alkynyl, arylalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, or heteroarylalkyl;

optionally, R^7 and R^8; R^9 and R^{10} independently form 4-8 membered alkyl or heterocyclyl rings; and

X and Y are independently CR^7R^8 or N.

For example, **PI** can include:



Formula IV,

wherein R^1 is independently hydrogen, C1-C8 alkyl, C1-C8 alkoxyalkyl, C1-C8 haloalkyl, C1-C8 hydroxyalkyl, C3-C7 cycloalkyl, C3-C7 heterocyclyl, C2-C8 alkenyl, or C2-C8 alkynyl;

R^2 is hydrogen, C1-C8 alkyl, C1-C8 alkoxyalkyl, C1-C8 haloalkyl, C1-C8 hydroxyalkyl, C3-C7 cycloalkyl, C3-C7 heterocyclyl, C2-C8 alkenyl, C2-C8 alkynyl, CN, COR^4, CO_2R^4, or $CONR^4R^5$;

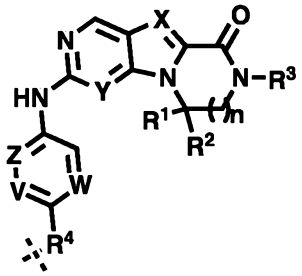
R^3 is hydrogen, halogen, C1-C8 alkyl, C1-C8 alkoxy, C1-C8 alkoxyalkyl, C1-C8 haloalkyl, C1-C8 hydroxyalkyl, C3-C7 cycloalkyl, C3-C7 heterocyclyl, C2-C8 alkenyl, C2-C8 alkynyl, OR^4, SR^4, NR^4R^5, CN, NO_2, $(CR^4R^5)mNR^6R^7$, $(CR^4R^5)mC(O)R^6$, COR^4, CO_2R^4, $CONR^4R^5$, NR^4COR^5, NR^4SOR^5, $NR^4SO_2R^5$, SOR^4, SO_2R^4, $SO_2NR^4R^5$, (CR^4R^5)m-aryl, or (CR^4R^5)m-heteroaryl, wherein m is 0-8;

R^4, R^5, R^6, R^7 are independently hydrogen, C1-C8 alkyl, C2-C8 alkenyl, C2-C8 alkynyl, arylalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, or heteroarylalkyl;

optionally, R^1 and R^2; R^4 and R^5; $R^6$and R^7 independently form 4-8 membered alkyl or heterocyclyl rings; and

V, W, X, Y, and Z are independently CR^4R^5 or N.

For example, **PI** can include:



Formula VI,

wherein R^1 and R^2 are independently hydrogen, C1-C8 alkyl, C1-C8 alkoxyalkyl, C1-C8 haloalkyl, C1-C8 hydroxyalkyl, C3-C7 cycloalkyl, C3-C7 heterocyclyl, C2-C8 alkenyl, or C2-C8 alkynyl;

R^3 is hydrogen, C1-C6 alkyl, C1-C6 alkoxyalkyl, C1-C6 haloalkyl, C1-C6 hydroxyalkyl, C3-C6 cycloalkyl, C3-C6 heterocyclyl, C2-C6 alkenyl, or C2-C6 alkynyl;

R^4 is hydrogen, halogen, C1-C8 alkyl, C1-C8 alkoxy, C1-C8 alkoxyalkyl, C1-C8 haloalkyl, C1-C8 hydroxyalkyl, C3-C7 cycloalkyl, C3-C7 heterocyclyl, C2-C8 alkenyl, C2-C8 alkynyl, OR^5, SR^5, NR^5R^6, CN, NO_2, $(CR^5R^6)mNR^7R^8$, $(CR^5R^6)mC(O)R^7$, COR^5,

CO_2R^5, $CONR^5R^6$, NR^5COR^6, NR^5SOR^6, $NR^5SO_2R^6$, SOR^5, SO_2R^5, $SO_2NR^5R^6$, (CR^5R^6)m-aryl, or (CR^5R^6)m-heteroaryl, wherein m is 0-8;

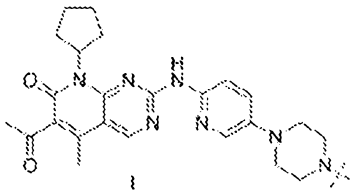
n is independently 0-4;

optionally, R^1 and R^2; R^5 and R^6; $R^7$and R^8 independently form 4-8 membered alkyl or heterocyclyl rings; and

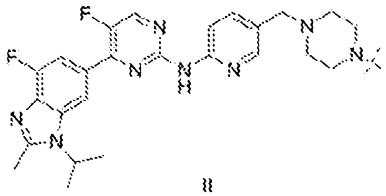
V, W, X, Y, and Z are independently CR^5R^6 or N.

The CDK4/6 ligand can be a CDK4/6 inhibitor, such as, e.g., abemaciclib, palbociclib, ribociclib, trilaciclib (G1T28), G1T38, SHR6390, and/or analogs thereof.

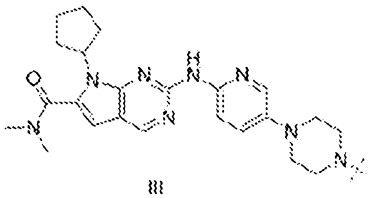
In some aspects, the CDK4/6 ligand can be, e.g.,



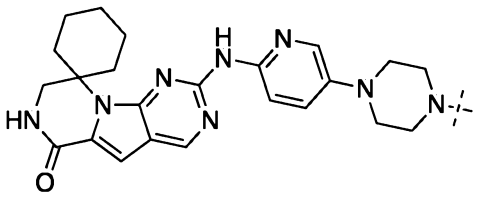
I



II



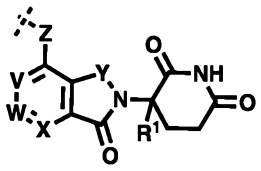
III



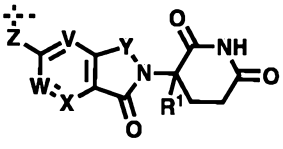
IV.

The CDK4/6 ligand can be bound to CDK4/6.

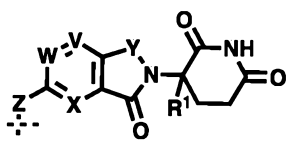
EL includes, but is not limited to:



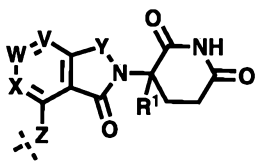
Formula VII,



Formula VIII,



Formula IX,



Formula XI,

wherein V, W, X are independently CR^2 or N;

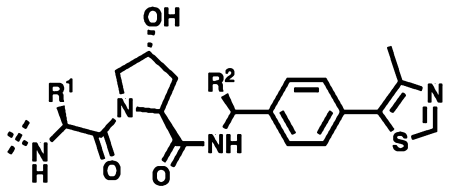
Y is CO or CH_2;

Z is CH_2, NH, or O;

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

R^2 is hydrogen, halogen, or C1-C5 alkyl.

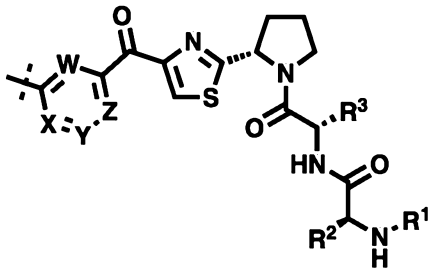
For example, **EL** can include:



Formula XII,

wherein R^1 and R^2 are independently hydrogen, C1-C8 alkyl, C1-C8 alkoxyalkyl, C1-C8 haloalkyl, C1-C8 hydroxyalkyl, C3-C7 cycloalkyl, C3-C7 heterocyclyl, C2-C8 alkenyl, or C2-C8 alkynyl.

For example, **EL** can include:



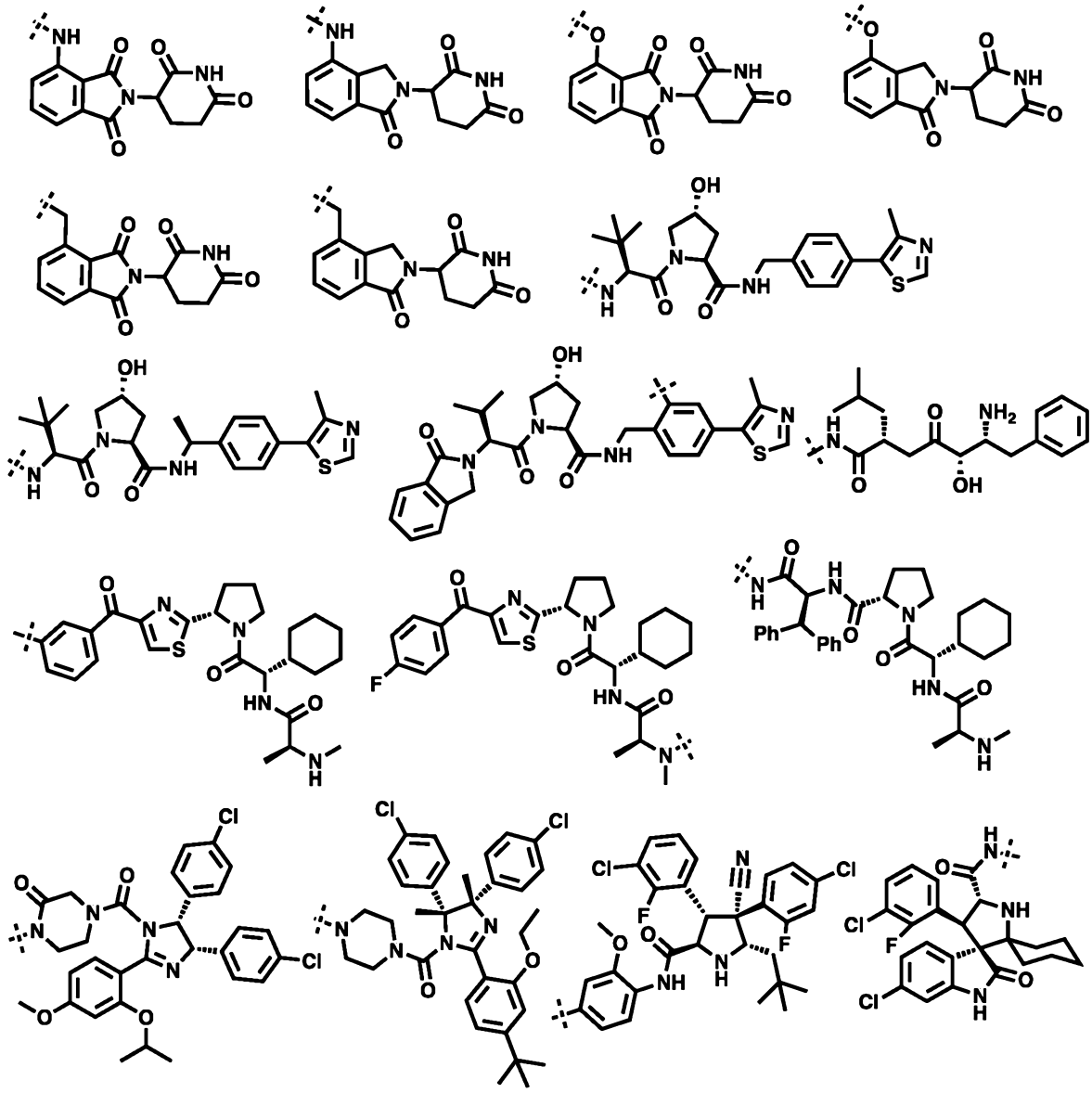
Formula XIII,

wherein R^1, R^2, R^3 and R^4 are independently hydrogen, C1-C8 alkyl, C1-C8 alkoxyalkyl, C1-C8 haloalkyl, C1-C8 hydroxyalkyl, C3-C7 cycloalkyl, C3-C7 heterocyclyl, C2-C8 alkenyl, or C2-C8 alkynyl; and

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

In some aspects, the degradation/disruption tag can be, e.g., pomalidomide, thalidomide, lenalidomide, VHL-1, adamantane, 1-((4,4,5,5,5-pentafluoropentyl)sulfinyl)nonane, nutlin-3a, RG7112, RG7338, AMG 232, AA-115, bestatin, MV-1, LCL161, and/or analogs thereof.

In some aspects, the degradation/disruption tag can be, e.g.,

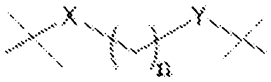


Formulas XIV-XXX (left to right, then top to bottom, starting with Formula XIV at the top left corner and ending with Formula XXX at the bottom right corner).

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 a IAP ligase) and/or serve as a hydrophobic group that leads to CDK4 or CDK6 protein misfolding.

In any of the above-described compounds, the CDK4/6 ligand can be 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 embodiments, the linker can be a moiety of:

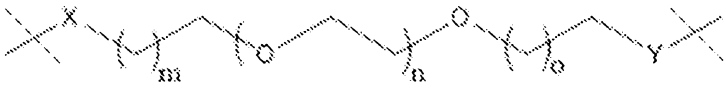


Formula A

wherein X is C=O or CH_2,

Y is C=O or CH_2, and

n is 0-15;



Formula B,

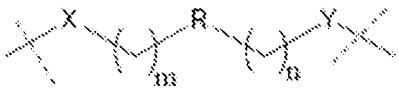
wherein X is C=O or CH_2,

Y is C=O or CH_2,

m is 0-15,

n is 0-6, and

o is 0-15; or



Formula C,

wherein

X is C=O or CH_2,

Y is C=O or CH_2,

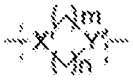
R is $-CH_2-$, $-CF_2-$, $-CH(C_{1-3}$ alkyl)–, $-C(C_{1-3}$ alkyl)$(C_{1-3}$ alkyl)–, –CH=CH–, $-C(C_{1-3}$ alkyl)$=C(C_{1-3}$ alkyl)–, –C=C–, –O–, –NH–, $-N(C_{1-3}$ alkyl)–, $-C(O)NH-$, $-C(O)N(C_{1-3}$ alkyl)–, a 3-13 membered ring, a 3-13 membered fused ring, a 3-13 membered bridged ring, and/or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

m is 0-15, and

n is 0-15.

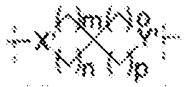
In some embodiments of Formula C, R is a 3-13 membered ring, a 3-13 membered fused ring, a 3-13 membered bridged ring, and/or a 3-13 membered spiro ring, one or more of which can contain one or more heteroatoms.

In some embodiments of Formula C, R has a structure of



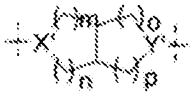
X' = N or CH
Y' = N or CH
m = 0~5
n = 0~5

Formula V,



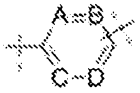
X' = N or CH
Y' = N or CH
m = 0~5
n = 0~5
o = 0~5
p = 0~5

Formula W,



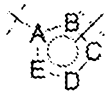
X' = N or CH
Y' = N or CH
m = 0~5
n = 0~5
o = 0~5
p = 0~5

Formula X,



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 Y, 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

Formula Z.

In some aspects, the bivalent compound is a compound selected from XY028-082, XY028-003, XY028-004, XY028-005, XY019-098, XY028-006, XY028-007, XY028-008, XY028-009, XY028-085, XY028-084, XY028-083, XY028-132, XY028-133, XY019-106, XY028-162, XY028-163, XY028-002, XY028-114, XY028-097, XY019-108, XY028-105, XY028-106, XY028-140, XY028-141, XY028-142, XY028-143, XY028-144, XY028-145,

YX26-56, YX26-66, YX26-58, YX30-108, YX30-107, YX30-85, YX30-86, YX30-117, YX30-118, YX30-126, YX30-125, XY028-186, YX33-29, YX33-31, YX33-74, YX33-94, YX33-108, YX33-96, YX33-97, YX33-109, YX33-110, YX33-112, YX33-123, YX35-48, YX39-47, YX39-48, YX39-56, YX39-65, YX39-74, YX39-123, YX39-124, YX39-147, YX44-18, YX44-19, YX44-22, YX44-46, YX44-48, YX44-78, YS36-95, YS36-60, YS36-61, YS36-62, YS36-63, YS36-64, YS36-65, YS36-66, YS36-67, YS36-68, YS36-69, YS36-70, YS36-71, and compound examples 80-135, or analogs thereof.

In some aspects, the document provides a method of treating a cyclin-dependent kinase 4/6 (CDK4/6)-mediated cancer, the method including administering to a subject in need thereof with a CDK4/6-mediated cancer one or more bivalent compounds including a CDK4/6 ligand conjugated to a degradation/disruption tag. The CDK4/6-mediated cancer may be a cancer which overexpresses cyclin-dependent kinase 4 (CDK4) and/or cyclin-dependent kinase 6 (CDK6) relative to a wild-type tissue of the same species and tissue type. The CDK4/6-mediated cancer can have elevated CDK4 and/or CDK6 enzymatic activity relative to a wild-type tissue of the same species and tissue type. Non-limiting examples of CDK4/6-mediated cancer include mesothelioma, hepatocellular cancer, central nervous system neoplasm, lung cancer, bone cancer, pancreatic cancer, skin cancer, head and neck cancer, melanoma, ovarian cancer, colon cancer, rectal cancer, anal cancer, stomach cancer, gastrointestinal cancer, breast cancer (e.g., estrogen receptor positive (ER+) breast cancer), uterine cancer, fallopian tube cancer, endometrial cancer, cervical cancer, vaginal cancer, vulvar cancer, esophageal cancer, gastrointestinal cancer, endocrine cancer, thyroid cancer, parathyroid cancer, adrenal cancer, soft tissue sarcoma, urethral cancer, penile cancer, prostate cancer, testicular cancer, leukemia, lymphoma, bladder cancer, renal cell cancer, brain stem glioma, pituitary cancer, adrenocortical cancer, gallbladder cancer, multiple myeloma, cholangiocarcinoma, fibrosarcoma, neuroblastoma, and/or retinoblastoma. The CDK4/6-mediated cancer can be a relapsed cancer. The CDK4/6-mediated cancer can have been refractory to one or more previous treatments.

In any of the above-described methods, the bivalent compounds can be XY028-082, XY028-003, XY028-004, XY028-005, XY019-098, XY028-006, XY028-007, XY028-008, XY028-009, XY028-085, XY028-084, XY028-083, XY028-132, XY028-133, XY019-106, XY028-162, XY028-163, XY028-002, XY028-114, XY028-097, XY019-108, XY028-105, XY028-106, XY028-140, XY028-141, XY028-142, XY028-143, XY028-144, XY028-145, YX26-56, YX26-66, YX26-58, YX30-108, YX30-107, YX30-85, YX30-86, YX30-117, YX30-118, YX30-126, YX30-125, XY028-186, YX33-29, YX33-31, YX33-74, YX33-94,

YX33-108, YX33-96, YX33-97, YX33-109, YX33-110, YX33-112, YX33-123, YX35-48, YX39-47, YX39-48, YX39-56, YX39-65, YX39-74, YX39-123, YX39-124, YX39-147, YX44-18, YX44-19, YX44-22, YX44-46, YX44-48, YX44-78, YS36-95, YS36-60, YS36-61, YS36-62, YS36-63, YS36-64, YS36-65, YS36-66, YS36-67, YS36-68, YS36-69, YS36-70, YS36-71, and compound examples 80-135, or analogs thereof.

In some embodiments of the disclosed methods, 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 the 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.

The document additionally provides a method for identifying a bivalent compound which mediates degradation/disruption of CDK4 and/or CDK6, the method including providing a heterobifunctional test compound including a CDK4/6 ligand conjugated to a degradation/disruption tag, contacting the heterobifunctional test compound with a cell (e.g., a cancer cell such as a CDK4/6-mediated cancer cell) including a ubiquitin ligase and at least one of CDK4 and CDK6. The method can include determining whether CDK4 or CDK6 levels decrease in the cell, and (i) identifying the heterobifunctional test compound as a bivalent compound which mediates degradation/reduction of CDK4 if CDK4 levels decrease in the cell and CDK6 levels do not decrease in the cell, (ii) identifying the heterobifunctional test compound as a bivalent compound which mediates degradation/reduction of CDK6 if CDK6 levels decrease in the cell and CDK4 levels do not decrease in the cell, or (iii) identifying the heterobifunctional test compound as a bivalent compound which mediates degradation/reduction of CDK4 and CDK6 if both CDK4 and CDK6 levels decrease in the cell.

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.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Methods and materials are described herein for use in the present invention; other, suitable methods and materials known in the art can also be used. The materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent

applications, patents, sequences, database entries, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control.

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

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a series of Western blots showing the effect of various CDK4/6 inhibitors on CDK4/6 activity (as evidenced by Rb phosphorylation (pRb level)) and expression of Rb/E2F downstream targets PLK1 and cyclin A at different concentrations. palbociclib (PB)-treated breast cancer cells (**A**); abemaciclib (AB)-treated breast cancer cells (**B**); PB-treated melanoma cells (**C**); AB-treated melanoma cells (**D**); 219476-treated breast cancer cells (**E**).

Figure 2 is a series of bar graphs showing the effect of various CDK4/6 inhibitors on PLK1 and cyclin A (CCNA2) mRNA levels in indicated breast cancer cells at different concentrations.

Figure 3 is a series of bar graphs showing the effect of PB on PLK1 and cyclin A (CCNA2) mRNA levels in melanoma cancer cells at different concentrations.

Figure 4 is a series of bar graphs showing the effect of various CDK4/6 inhibitors on cell cycle progression at different concentrations.

Figure 5 is a series of Western blots showing the effect of various CDK4/6 inhibitors on CDK4 or CDK6 expression at different concentrations. PB- or AB-treated breast cancer cells (**A**); PB-treated melanoma cells (**B**); AB-treated melanoma cells (**C**).

Figure 6 is a series of bar graphs showing the effect of various CDK4/6 inhibitors on CDK4 mRNA levels at different concentrations.

Figure 7 is a series of Western blots showing the effect of various CDK4/6 inhibitors on ectopically expressed of V5-tagged CDK4 or CDK6 at different concentrations.

Figure 8 is a series of pull-down assays showing the effect of various CDK4/6 inhibitors on the ubiquitination of either ectopically expressed (**A**), or endogenous (**B**) CDK4 at different concentrations.

Figure 9 is a series of Western blots showing the efficacy of palbociclib in inhibiting Rb phosphorylation in ER+ breast cancer cells, palbociclib-resistant ER+ breast cancer cells (a) and melanoma cells (b).

Figure 10 is a series of Western blots showing the efficacy of various CDK4/6 degraders in inhibiting CDK4/6 activity and suppressing CDK4/6 expression in either MCF7 (**A**) or T47D (**B**) breast cancer cells.

Figure 11 is a series of Western blots (**A, B,** and **C**) showing the efficacy of various CDK4/6 degraders with different linkers in inhibiting CDK4/6 activity and suppressing CDK4/6 expression in melanoma cells.

Figure 12 is a series of Western blots (**A, B, C,** and **D**) showing the efficacy of various CDK4/6 degraders with different linkers in inhibiting CDK4/6 activity and suppressing CDK4/6 expression in melanoma cells.

Figure 13 is a series of Western blots showing the effect of various CDK4/6 degraders in inhibiting CDK4/6 activity and suppressing CDK4/6 expression in melanoma cells.

Figure 14 is a series of Western blots showing the effect of various CDK4/6 degraders in inhibiting CDK4/6 activity and suppressing CDK4/6 expression in melanoma cells.

Figure 15 is a series of Western blots showing the effect of various CDK4/6 degraders in inhibiting CDK4/6 activity and suppressing CDK4/6 expression in breast cancer (**A**) and melanoma (**B**) cells.

Figure 16 is a series of Western blots (**A** and **B**) showing the effect of various CDK4/6 degraders in inhibiting CDK4/6 activity and suppressing CDK4/6 expression in melanoma cells.

Figure 17 is a series of Western blots showing the effect of various CDK4/6 degraders in inhibiting CDK4/6 activity and suppressing CDK4/6 expression in breast cancer cells.

Figure 18 is a series of Western blots showing the effect of various CDK4/6 degraders in inhibiting CDK4/6 activity and suppressing CDK4/6 expression in melanoma cells.

Figure 19 is a series of Western blots showing the effect of various CDK4/6 degraders in inhibiting CDK4/6 activity and suppressing CDK4/6 expression in breast cancer cells.

Figure 20 is a series of images showing the effect of the CDK4/6 degrader XY028-133 in suppressing cell proliferation of melanoma cells.

Figure 21 is a series of clonogenic assays showing the effect of the CDK4/6 degrader XY028-133 in suppressing cell proliferation of melanoma cells.

Figure 22 is a series of clonogenic assays showing the effect of various CDK4/6 degraders in suppressing cell proliferation of breast cancer cells.

Figure 23 is a series of clonogenic assays showing the effect of various CDK4/6 degraders in suppressing cell proliferation of breast cancer cells.

DETAILED DESCRIPTION

The present disclosure is based, in part, on the discovery that novel heterobifunctional small molecules which selectively degrade CDK4, CDK6, or both CDK4 and CDK6 ("PROteolysis TArgeting Chimeras" or "PROTACs") are useful in the treatment of CDK4/6-mediated cancers, particularly estrogen receptor (ER) positive (ER+) breast cancer.

Successful strategies for selective degradation/disruption of the target protein induced by a small molecule include recruiting an E3 ubiquitin ligase and mimicking protein misfolding with a hydrophobic tag (Buckley and Crews, 2014). PROTACs are bivalent inhibitors with one moiety that binds an E3 ubiquitin ligase and another moiety that binds the protein target of interest (Buckley and Crews, 2014). The induced proximity leads to ubiquitination of the target followed by their degradation at proteasome. Two 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 (Ito et al., 2010; Chamberlain et al., 2014; Fischer et al., 2014; Bondeson et al., 2015; 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 (Buckley et al., 2012; Buckley et al., 2012; Galdeano et al., 2014; Bondeson et al., 2015; Zengerle et al., 2015). The PROTAC technology has been successfully applied to degradation of multiple targets (Bondeson et al., 2015; Buckley et al., 2015; Lu et al., 2015; Winter et al., 2015; Zengerle et al., 2015; Lai et al., 2016), but not to degradation of CDK4/6. 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 also been successfully applied to selective degradation of the pseudokinase Her3 (Xie et al., 2014), but not to degradation of CDK4/6.

As discussed in the following examples, this disclosure provides specific examples of novel CDK4/6 degraders/disruptors, and examined the effect of exemplary degraders/disruptors in inhibiting/disrupting CDK4/6 activity, suppressing CDK4/6 expression, and inhibiting cancer cell proliferation. The results indicated that these novel small molecules can be beneficial in treating cancer, especially breast cancer, melanoma, and lung cancer.

A number of selective small-molecule CDK4/6 catalytic inhibitors, such as palbociclib, abemaciclib, ribociclib, trilaciclib (G1T28), G1T38, and SHR6390, have recently been discovered. Some of these inhibitors have been in clinical trials for treating ER+ breast cancer.

However, these inhibitors have exhibited very limited success when administered alone; rather, they must be co-administered with a second therapy such as endocrine therapy, causing increased off-target effects and toxicity. Further, even when co-administered with a second therapy, the majority of patients treated in the trials have developed resistance as early as 14 months.

Surprisingly, it was discovered that in addition to toxicity issues, CDK4/6 inhibitors weren't even able to suppress CDK4/6 activity when they were administered at high concentrations (Example 5, Fig. 1). In fact, there was a positive correlation between palbociclib or abemaciclib concentration and expression of the Rb/E2F downstream targets PLK1 and cyclin A (Example 6, Figs. 2 and 3), and a corresponding inverse correlation between inhibitor concentration and suppression of cell cycle progression (Example 7, Fig. 4). It was found that this was because, although CDK4/6 inhibitors are able to inhibit the activity of CDK4 and CDK6, the inhibitors actually (unexpectedly) upregulate the expression of both CDK4 and CDK6, with a positive correlation between inhibitor concentration and CDK4/6 expression (Example 8, Fig. 5). CDK4/6 inhibitors don't upregulate the expression of CDK4 and CDK6 at the mRNA level (Example 8, Figs. 6 and 7); rather, the inhibitors protect CDK4/6 from degradation by blocking them from ubiquitination (Example 9, Fig. 8). Consistent with the above results, increased CDK4/6 expression was associated with decreased CDK4/6 inhibitor efficacy (Example 10, Fig. 9). This indicates that CDK4/6 inhibitors only have a narrow window of activity and suggests that if cancer cells develop resistance to the inhibitors, inhibitor dosage cannot simply be increased to overcome the resistance.

Current drugs targeting CDK4/6 generally focus on inhibition of its catalytic function. Here, a different approach was taken: to develop compounds that directly and selectively target not only the catalytic function of CDK4/6, but also their level of expression at the protein level. Strategies for inducing protein degradation include recruiting E3 ubiquitin ligases, mimicking protein misfolding with hydrophobic tags, and inhibiting chaperones. For example, a thalidomide-JQ1 bivalent compound has been used to hijack the cereblon E3 ligase, inducing highly selective BET protein degradation *in vitro* and *in vivo* and resulting in a demonstrated delay in leukemia progression in mice (Winter et al., 2015). Similarly, BET protein degradation has also been induced via another E3 ligase, VHL (Zengerle et al., 2015). Partial degradation of Her3 has been induced using an adamantane-modified compound (Xie et al., 2014). Such an approach, based on the use of bivalent small molecule compounds, permits more flexible regulation of protein expression *in vitro* and *in vivo* compared with techniques such as gene knockout or shRNA knockdown. Unlike gene knockout or shRNA knockdown, a small

molecule approach further provides an opportunity to study dose and time dependency in a disease model through varying the concentrations and frequencies of administration of the relevant small molecule.

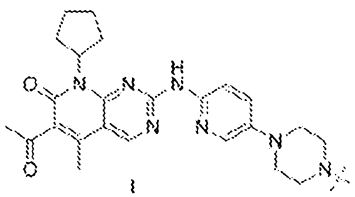
PROTACs

In some aspects, the present disclosure provides bivalent compounds, also referred to herein as PROTACs, comprising a CDK4/6 ligand (or targeting moiety) conjugated to a degradation tag. Linkage of the CDK4/6 ligand to the degradation tag can be direct, or indirect via a linker.

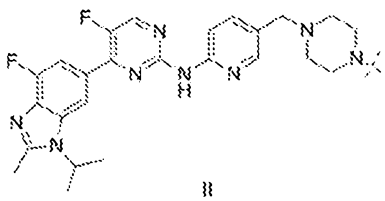
As used herein, the terms "**cyclin-dependent kinase 4/6 (CDK4/6) ligand**" or "**CDK4/6 ligand**" or "**CDK4/6 targeting moiety**" are to be construed broadly, and encompass a wide variety of molecules ranging from small molecules to large proteins that associates with or binds to CDK4, CDK6, or both CDK4 and CDK6. The CDK4/6 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 CDK4/6 ligand or targeting moiety can be a **CDK4/6 inhibitor** (e.g., abemaciclib, palbociclib, ribociclib, trilaciclib (G1T28), G1T38, SHR6390, and analogs thereof) which is capable of interfering with the enzymatic activity of CDK4, CDK6, or both CDK4 and CDK6. As used herein, an "inhibitor" refers to an agent that restrains, retards, or otherwise causes inhibition of a physiological, chemical or enzymatic action or function. An inhibitor can cause an at least 5% decrease in enzyme activity. 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.

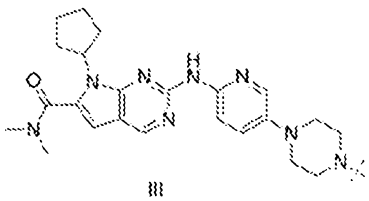
Exemplary CDK4/6 ligands include, but are not limited to, the compounds shown below.



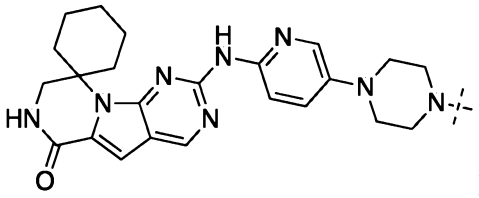
I



II



III



IV.

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 CDK4, CDK6, or both CDK4 and CDK6 or induces CDK4, CDK6, or both CDK4 and CDK6 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., thalidomide, pomalidomide, lenalidomide, VHL-1, adamantane, 1-((4,4,5,5,5-pentafluoropentyl)sulfinyl)nonane, nutlin-3a, RG7112, RG7338, AMG 232, AA-115, bestatin, MV-1, LCL161, 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 can provide for optimal spacing of the two entities. The term "linker" in some aspects refers to any agent or molecule that bridges the CDK4/6 ligand to the degradation/disruption tag. One of ordinary skill in the art recognizes that sites on the CDK4/6 ligand or the degradation/disruption tag, which are not necessary for the function of the PROTACs 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 PROTAC, i.e., its ability to target CDK4/6 and 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 CDK4/6 ligand or targeting moiety with the ubiquitin ligase or induce CDK4/6 misfolding by the hydrophobic tag at the same time.

In some embodiments, the degradation/disruption tags of the present disclosure include, for example, thalidomide, pomalidomide, lenalidomide, VHL-1, adamantane, 1-((4,4,5,5,5-pentafluoropentyl)sulfinyl)nonane, nutlin-3a, RG7112, RG7338, AMG 232, AA-115, bestatin, MV-1, LCL161, and analogs thereof. The degradation/disruption tags can be attached to each portion of interest in the structure of a CDK4/6 ligand or targeting moiety (e.g., abemaciclib, palbociclib, ribociclib, trilaciclib (G1T28), G1T38, or SHR6390) with linkers of different types and lengths in order to generate effective bivalent compounds. In particular, attaching

thalidomide to either portion of the molecule can recruit the cereblon E3 ligase to CDK4/6 without causing destructive steric interactions with the CDK4/6/HSP90/CDC37 complex.

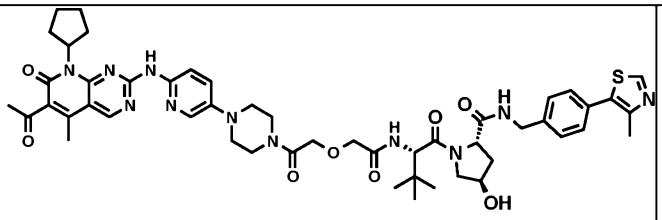
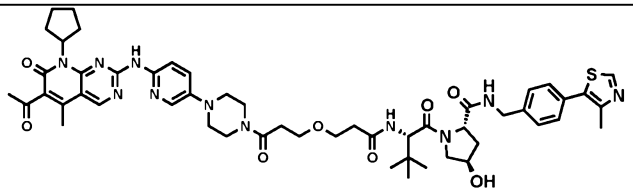
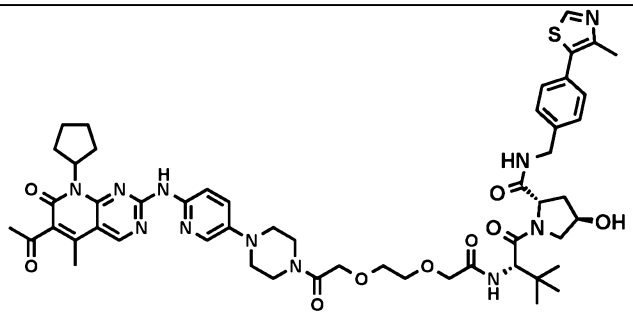
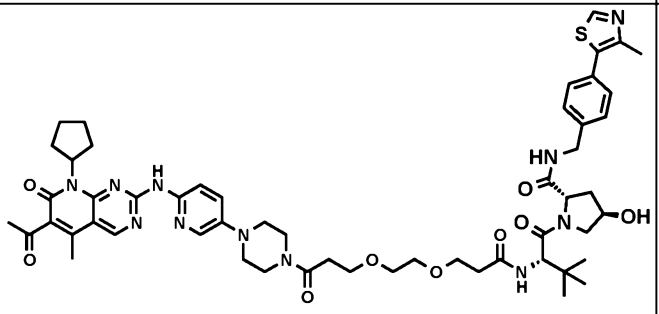
The bivalent compounds disclosed herein can selectively affect CDK4/6-mediated cancer cells (e.g., ER+ cells) compared to WT cells (i.e., a CDK4/6 degrader disruptor able to kill or inhibit the growth of a CDK4/6-mediated cancer cell while also having a relatively low ability to lyse or inhibit the growth of a WT cell), e.g., possess a GI_{50} for one or more CDK4/6-mediated cancer cells more than 1.5-fold lower, more than 2-fold lower, more than 2.5-fold lower, more than 3-fold lower, more than 4-fold lower, more than 5-fold lower, more than 6-fold lower, more than 7-fold lower, more than 8-fold lower, more than 9-fold lower, more than 10-fold lower, more than 15-fold lower, or more than 20-fold lower than its GI_{50} for one or more WT cells, e.g., WT cells of the same species and tissue type as the CDK4/6-mediated cancer cells.

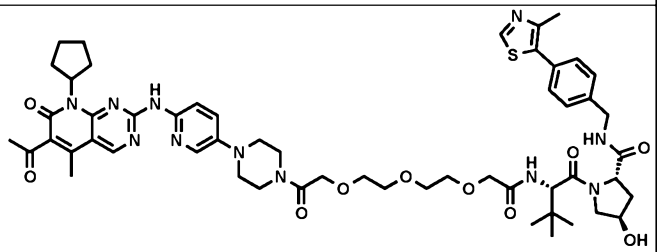
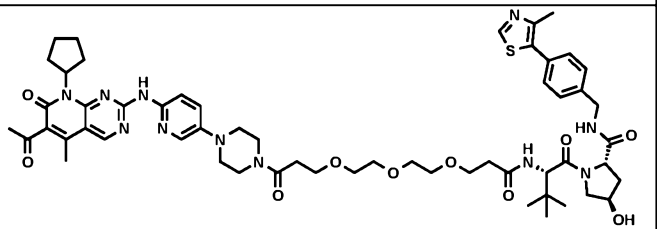
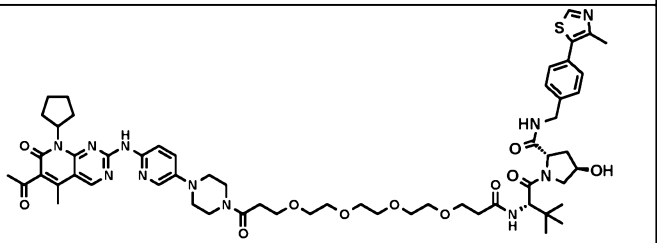
Additional bivalent compounds (i.e., CDK4/6 degraders/disruptors) can be developed using the principles and methods disclosed herein. For example, other linkers, degradation tags, and CDK4/6 binding/inhibiting moieties (not limited to abemaciclib, palbociclib, ribociclib, trilaciclib (G1T28), G1T38, and SHR6390) can be synthesized and tested. Non-limiting examples of CDK4/6 disruptors/degraders (e.g., bivalent compounds) are shown in Table 1 (below). The left portion of the CDK4/6 disruptors/degraders bind to CDK4/6 (as abemaciclib, palbociclib, ribociclib, trilaciclib (G1T28), G1T38, and SHR6390 do), and the right portion recruits for the ubiquitination machinery to CDK4/6, which induces the poly-ubiquitination and degradation of CDK4 and CDK6, or induces CDK4/6 misfolding and subsequent loss of function or degradation at the proteasome.

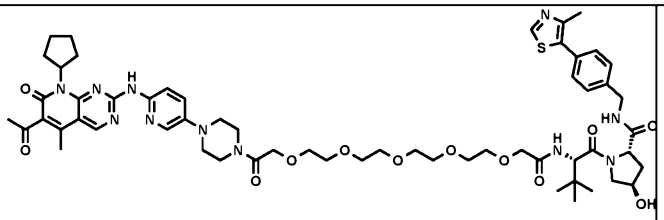
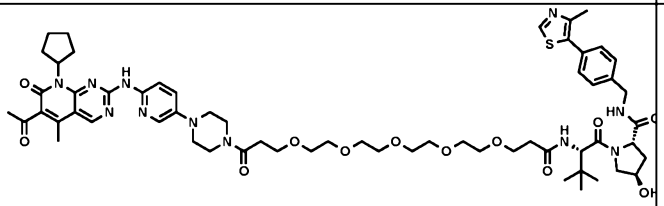
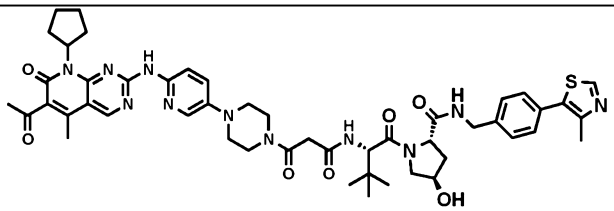
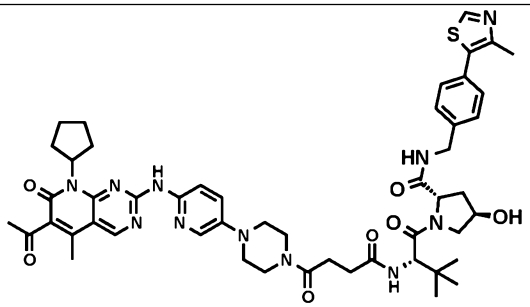
Non-limiting examples of bivalent compounds are set forth in Table 1, below.

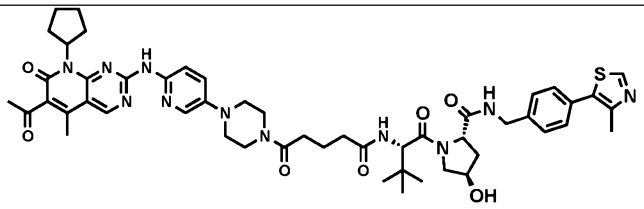
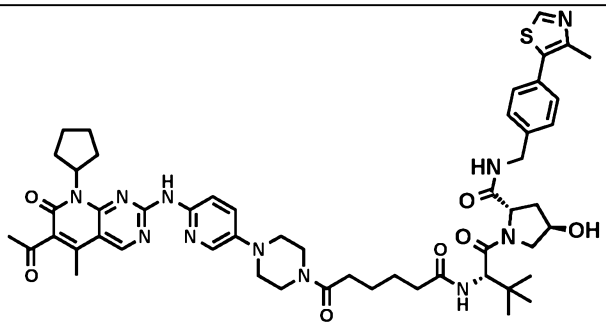
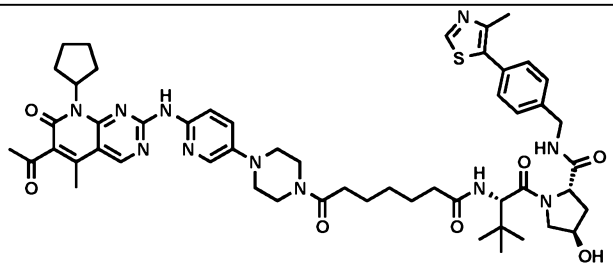
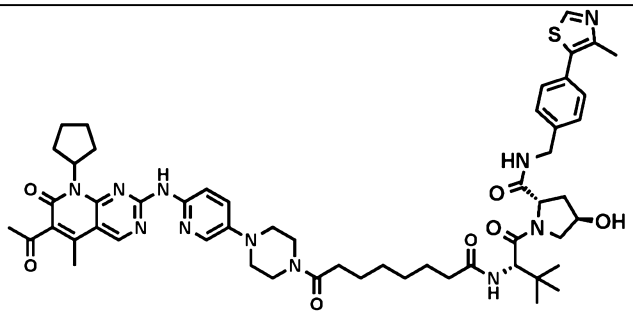
Table 1

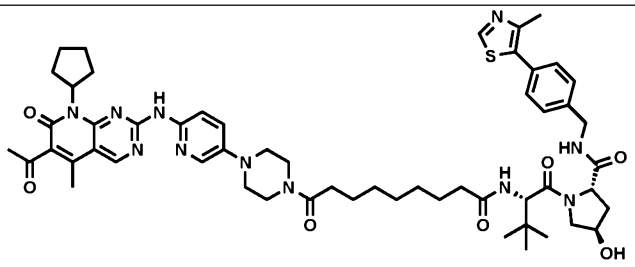
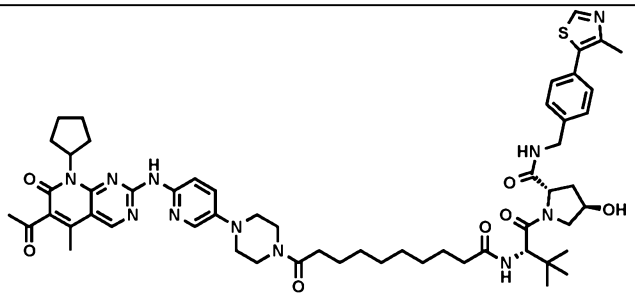
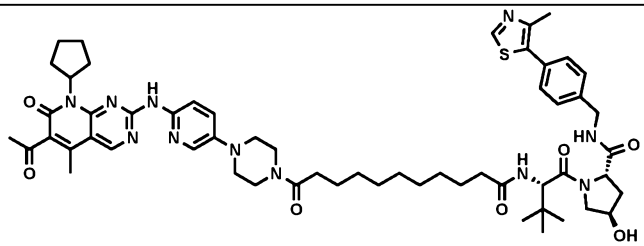
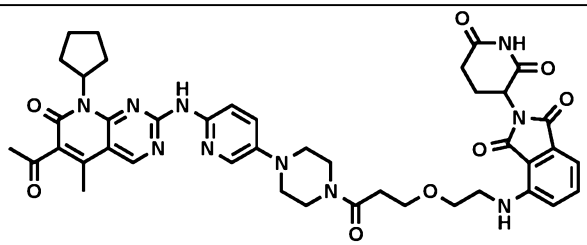
Cpd. Example Number	Cpd. Code	Structure	Chemical Name

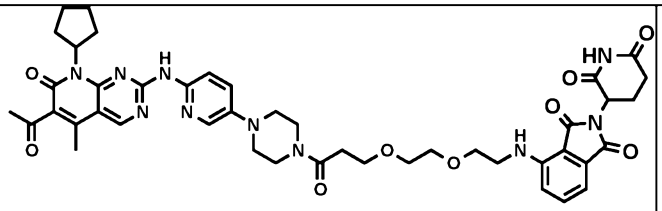
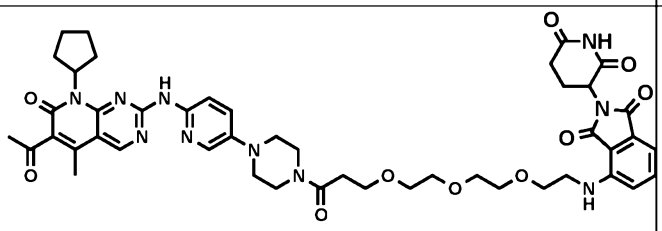
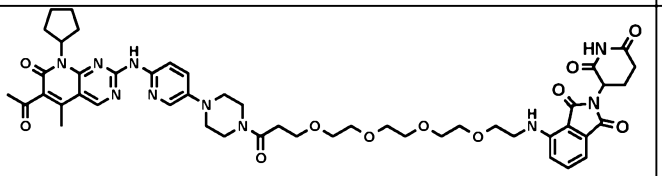
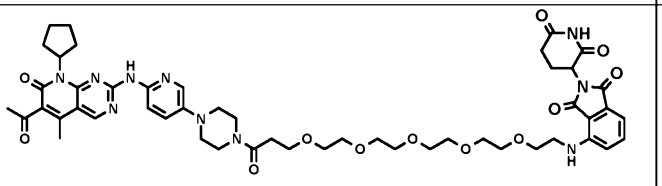
1	XY028-082		(2*S*,4*R*)-1-((*S*)-2-(2-(2-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-2-oxoethoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide
2	XY028-003		(2*S*,4*R*)-1-((*S*)-2-(3-(3-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-3-oxopropoxy)propanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide
3	XY028-004		(2*S*,4*R*)-1-((*S*)-2-(2-(2-(2-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-2-oxoethoxy)ethoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide
4	XY028-005		(2*S*,4*R*)-1-((*S*)-2-(3-(2-(3-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-3-oxopropoxy)ethoxy)propanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-

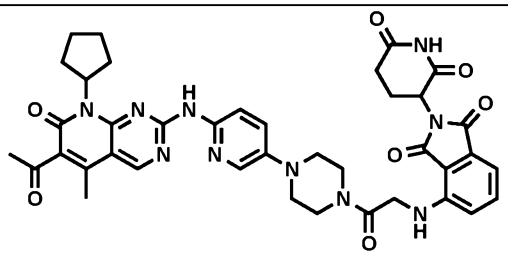
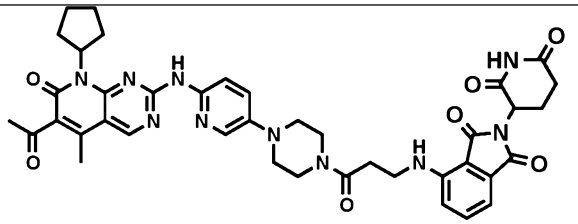
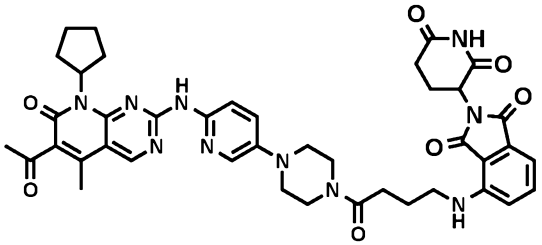
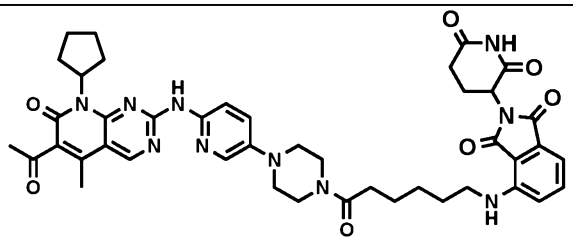
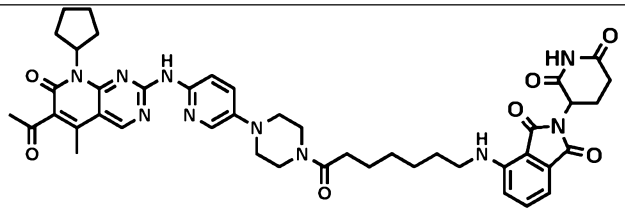
			yl)benzyl)pyrrolidine-2-carboxamide
5	XY019-098		(2*S*,4*R*)-1-((*S*)-14-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-2-(*tert*-butyl)-4,14-dioxo-6,9,12-trioxa-3-azatetradecanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide
6	XY028-006		(2*S*,4*R*)-1-((*S*)-16-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-2-(*tert*-butyl)-4,16-dioxo-7,10,13-trioxa-3-azahexadecanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide
7	XY028-007		(2*S*,4*R*)-1-((*S*)-19-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-2-(*tert*-butyl)-4,19-dioxo-7,10,13,16-tetraoxa-3-azanonadecanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide

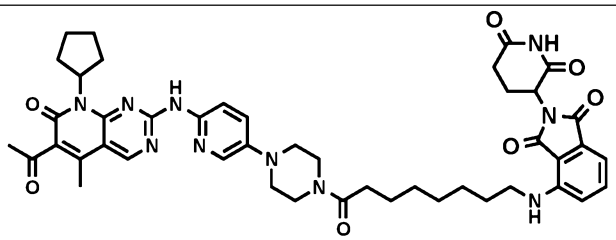
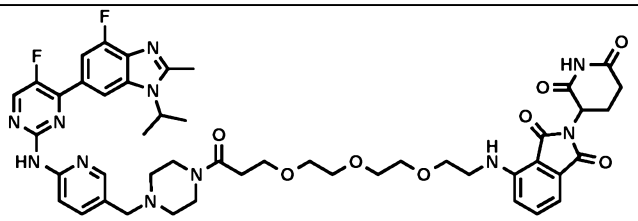
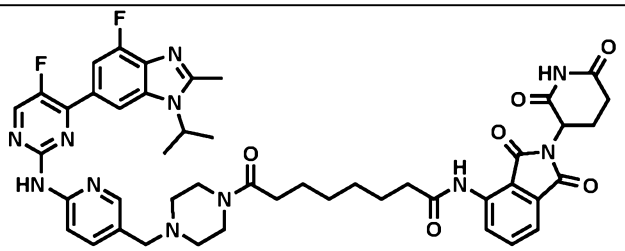
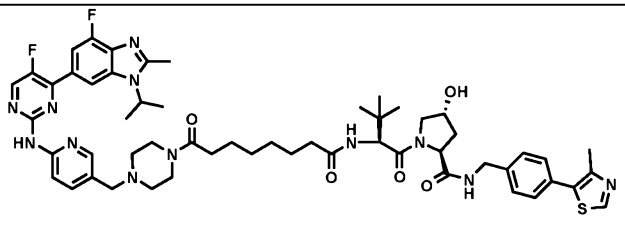
8	XY028-008		(2*S*,4*R*)-1-((*S*)-20-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-2-(*tert*-butyl)-4,20-dioxo-6,9,12,15,18-pentaoxa-3-azaicosanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide
9	XY028-009		(2*S*,4*R*)-1-((*S*)-22-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-2-(*tert*-butyl)-4,22-dioxo-7,10,13,16,19-pentaoxa-3-azadocosanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide
10	XY028-085		(2*S*,4*R*)-1-((*S*)-2-(3-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-3-oxopropanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide
11	XY028-084		(2*S*,4*R*)-1-((*S*)-2-(4-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-4-oxobutanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-

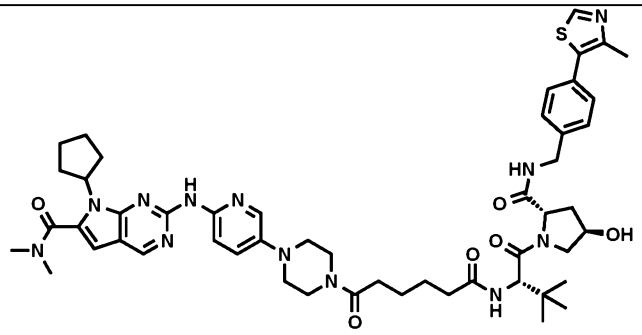
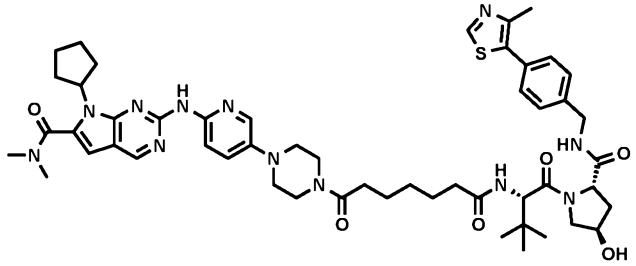
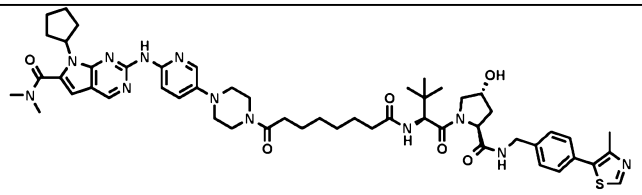
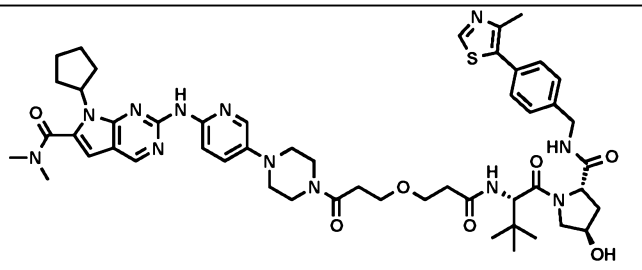
			yl)benzyl)pyrrolidine-2-carboxamide
12	XY028-083		(2*S*,4*R*)-1-((*S*)-2-(5-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-5-oxopentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide
13	XY028-132		(2*S*,4*R*)-1-((*S*)-2-(6-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-6-oxohexanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide
14	XY028-133		(2*S*,4*R*)-1-((*S*)-2-(7-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-7-oxoheptanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide
15	XY019-106		(2*S*,4*R*)-1-((*S*)-2-(8-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-8-oxooctanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-

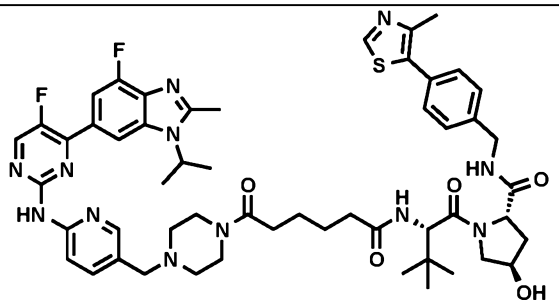
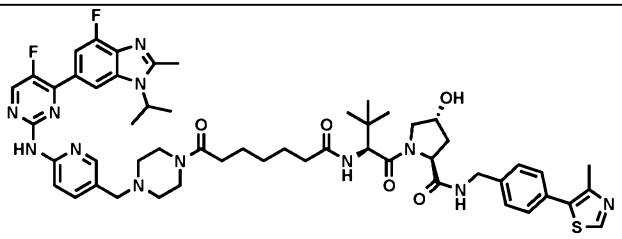
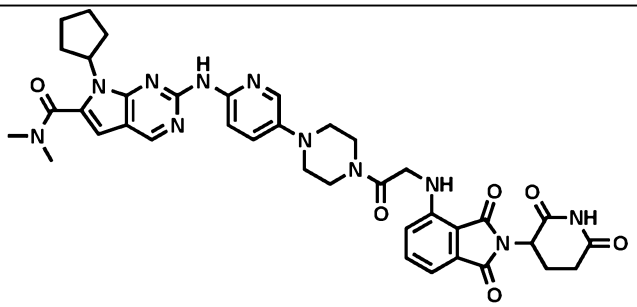
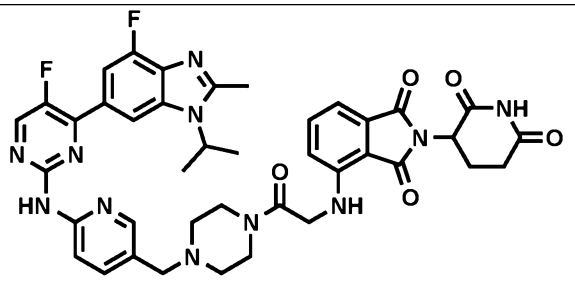
			yl)benzyl)pyrrolidine-2-carboxamide
16	XY028-162		(2*S*,4*R*)-1-((*S*)-2-(9-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-9-oxononanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide
17	XY028-163		(2*S*,4*R*)-1-((*S*)-2-(10-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-10-oxodecanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide
18	XY028-002		(2*S*,4*R*)-1-((*S*)-2-(11-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-11-oxoundecanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide
19	XY028-114		4-((2-(3-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-3-oxopropoxy)ethyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione

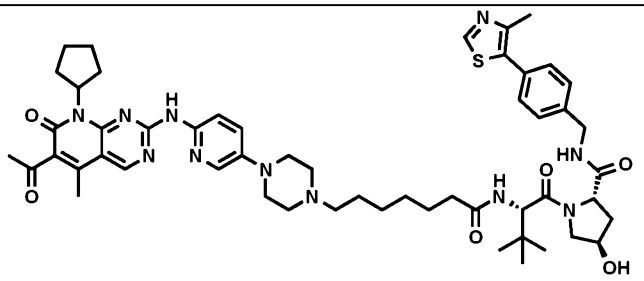
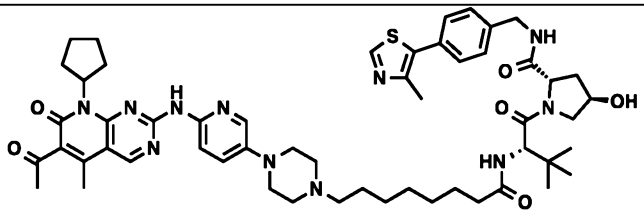
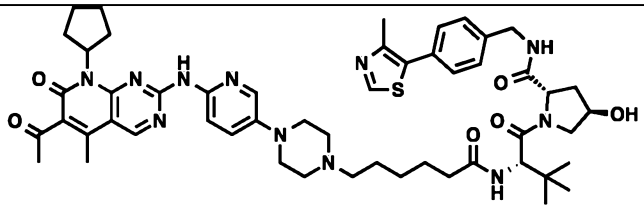
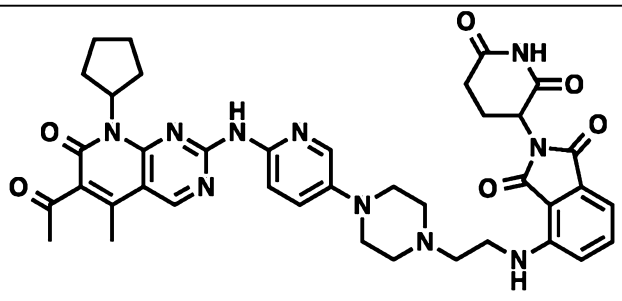
20	XY028-097		4-((2-(2-(3-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-3-oxopropoxy)ethoxy)ethyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione
21	XY019-108		4-((2-(2-(2-(3-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-3-oxopropoxy)ethoxy)ethoxy)ethyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione
22	XY028-105		4-((15-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-15-oxo-3,6,9,12-tetraoxapentadecyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione
23	XY028-106		4-((18-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-18-oxo-3,6,9,12,15-pentaoxaoctadecyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione

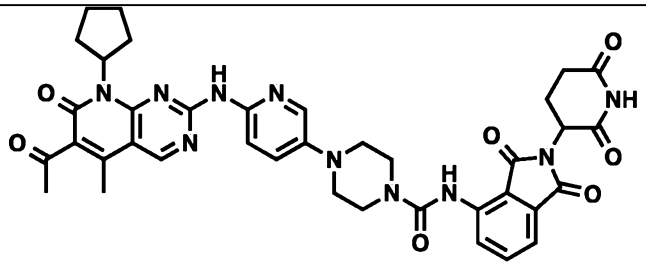
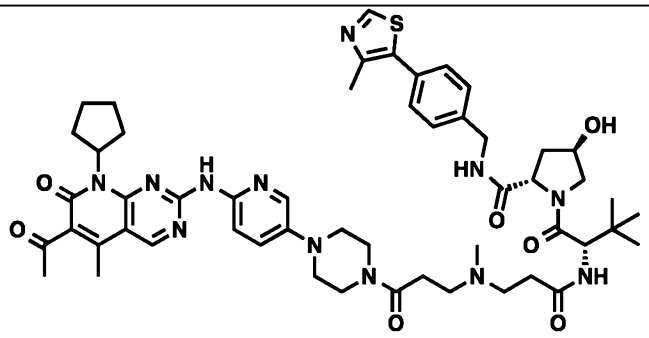
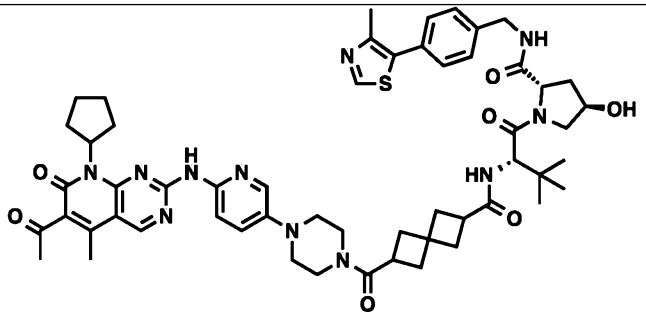
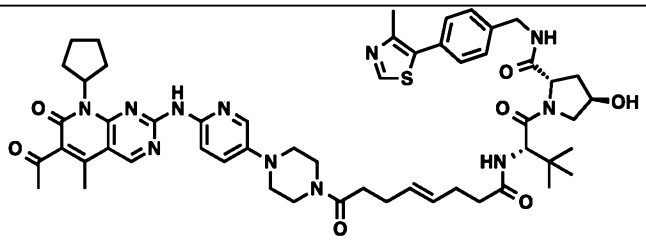
24	XY028-140		4-((2-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-2-oxoethyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione
25	XY028-141		4-((3-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-3-oxopropyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione
26	XY028-142		4-((4-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-4-oxobutyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione
27	XY028-143		4-((6-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-6-oxohexyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione
28	XY028-144		4-((7-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-7-oxoheptyl)amino)-2-(2,6-

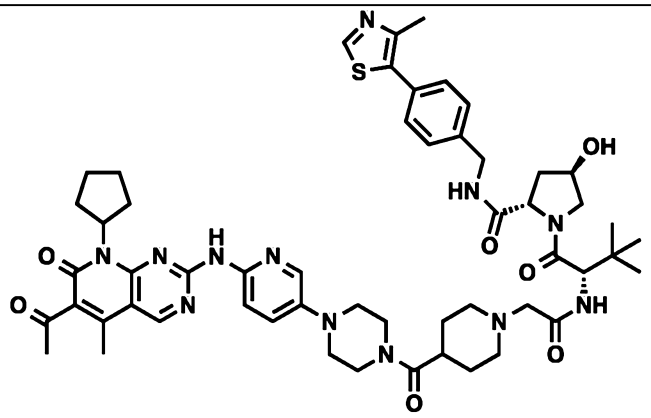
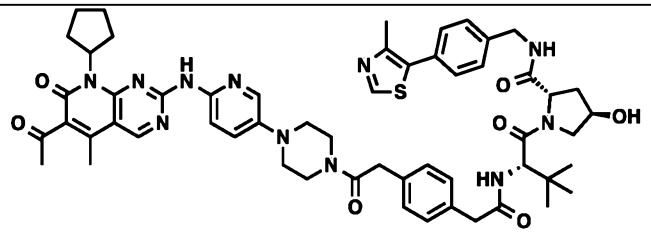
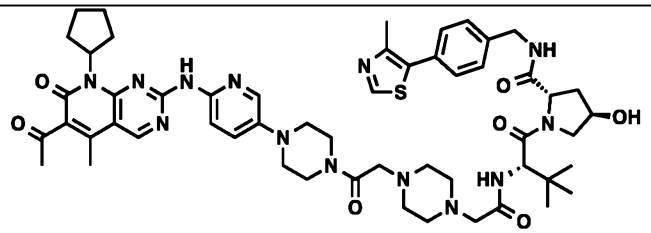
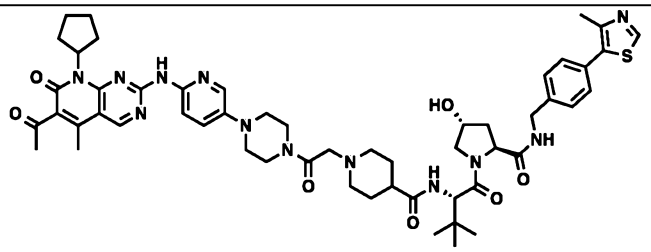
			dioxopiperidin-3-yl)isoindoline-1,3-dione
29	XY028-145		4-((8-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-8-oxooctyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione
30	YX26-56		2-(2,6-dioxopiperidin-3-yl)-4-((2-(2-(2-(3-(4-((6-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1*H*-benzo[*d*]imidazol-6-yl)pyrimidin-2-yl)amino)pyridin-3-yl)methyl)piperazin-1-yl)-3-oxopropoxy)ethoxy)ethoxy)ethyl)amino)isoindoline-1,3-dione
31	YX26-66		*N*-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)-8-(4-((6-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1*H*-benzo[*d*]imidazol-6-yl)pyrimidin-2-yl)amino)pyridin-3-yl)methyl)piperazin-1-yl)-8-oxooctanamide
32	YX26-58		(2*S*,4*R*)-1-((*S*)-2-(8-(4-((6-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1*H*-benzo[*d*]imidazol-6-yl)pyrimidin-2-yl)amino)pyridin-3-yl)methyl)piperazin-1-yl)-8-oxooctanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide

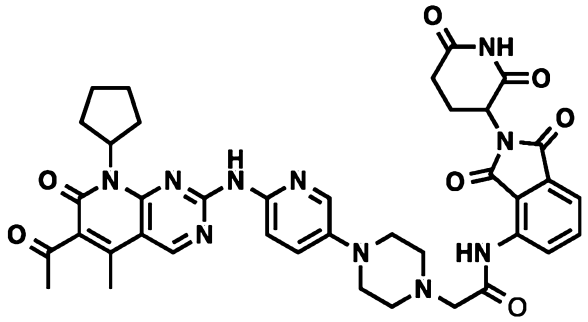
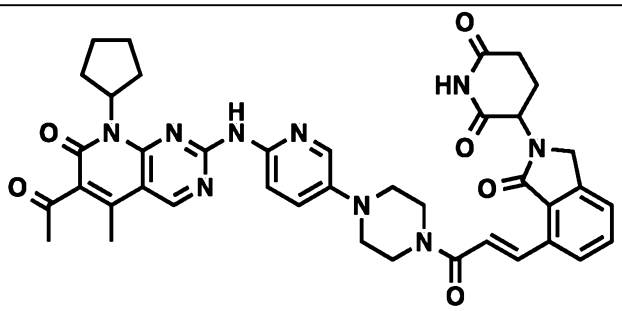
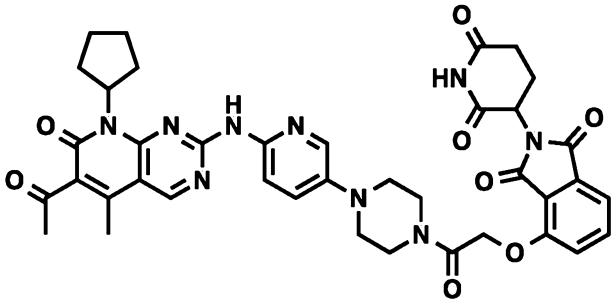
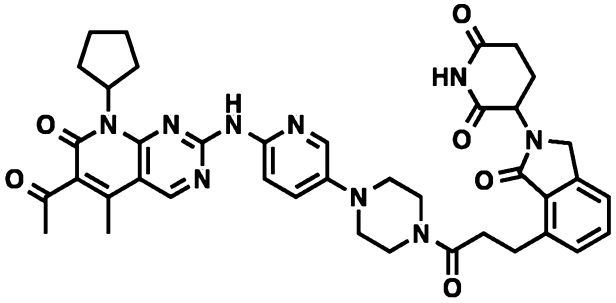
33	YX30-108		7-cyclopentyl-2-((5-(4-(6-(((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-6-oxohexanoyl)piperazin-1-yl)pyridin-2-yl)amino)-*N*,*N*-dimethyl-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide
34	YX30-107		7-cyclopentyl-2-((5-(4-(7-(((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-7-oxoheptanoyl)piperazin-1-yl)pyridin-2-yl)amino)-*N*,*N*-dimethyl-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide
35	YX30-85		7-cyclopentyl-2-((5-(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)pyridin-2-yl)amino)-*N*,*N*-dimethyl-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide
36	YX30-86		7-cyclopentyl-2-((5-(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)pyridin-2-yl)amino)-*N*,*N*-dimethyl-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide

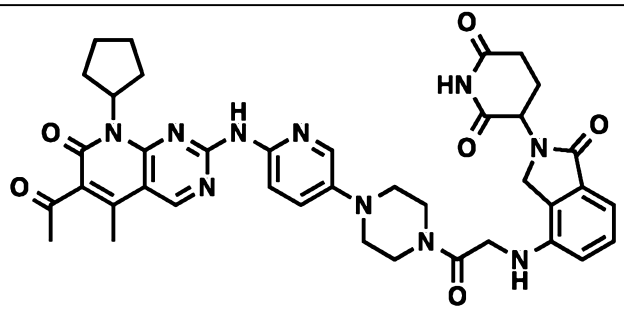
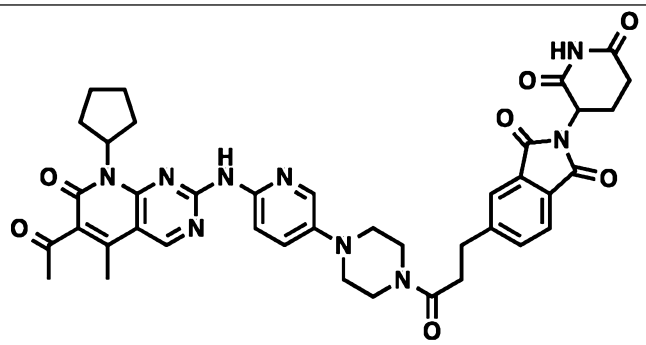
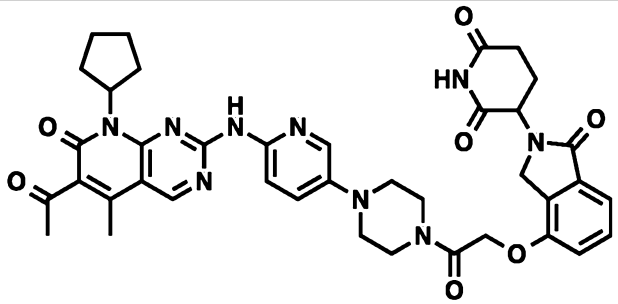
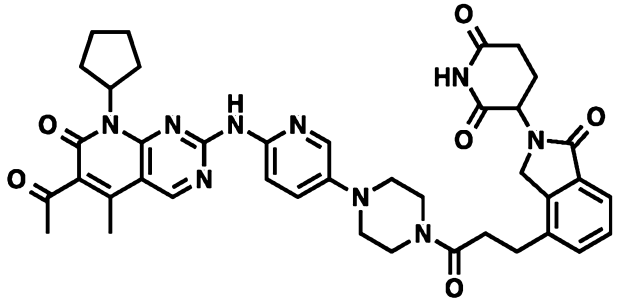
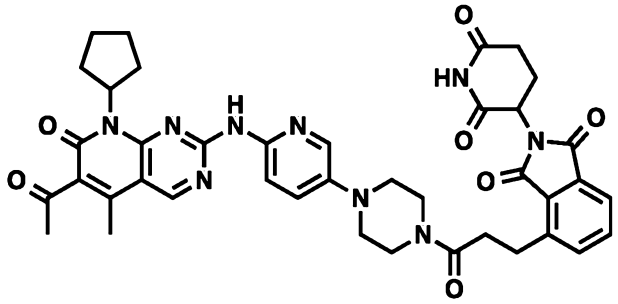
37	YX30-117		(2*S*,4*R*)-1-((*S*)-2-(6-(4-((6-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1*H*-benzo[*d*]imidazol-6-yl)pyrimidin-2-yl)amino)pyridin-3-yl)methyl)piperazin-1-yl)-6-oxohexanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide
38	YX30-118		(2*S*,4*R*)-1-((*S*)-2-(7-(4-((6-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1*H*-benzo[*d*]imidazol-6-yl)pyrimidin-2-yl)amino)pyridin-3-yl)methyl)piperazin-1-yl)-7-oxoheptanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide
39	YX30-126		7-cyclopentyl-2-((5-(4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)glycyl)piperazin-1-yl)pyridin-2-yl)amino)-*N*,*N*-dimethyl-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide
40	YX30-125		2-(2,6-dioxopiperidin-3-yl)-4-((2-(4-((6-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1*H*-benzo[*d*]imidazol-6-yl)pyrimidin-2-yl)amino)pyridin-3-yl)methyl)piperazin-1-yl)-2-oxoethyl)amino)isoindoline-1,3-dione

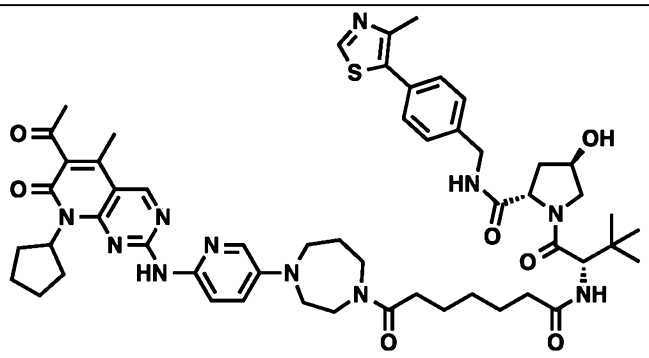
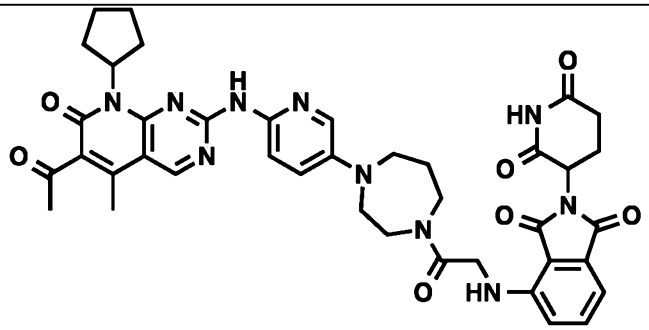
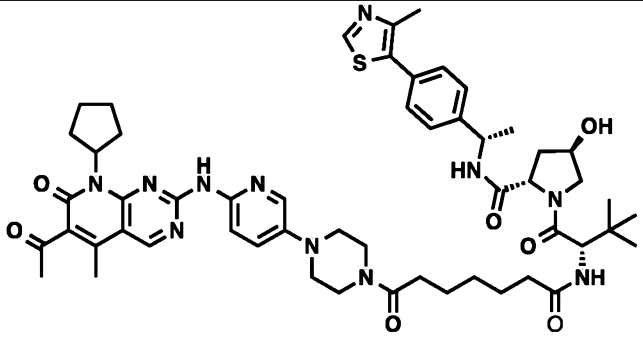
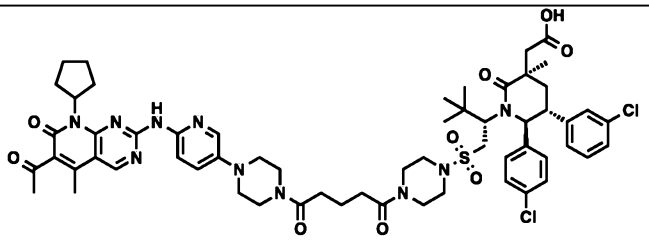
41	XY028-186		(2S,4R)-1-((S)-2-(7-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)heptanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide
42	YX33-29		(2*S*,4*R*)-1-((*S*)-2-(8-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)octanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide
43	YX33-31		(2*S*,4*R*)-1-((*S*)-2-(6-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)hexanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide
44	YX33-74		4-((2-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)ethyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione

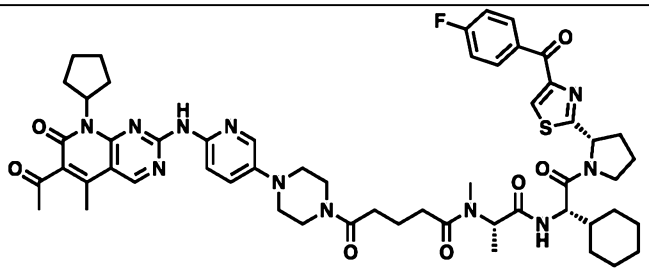
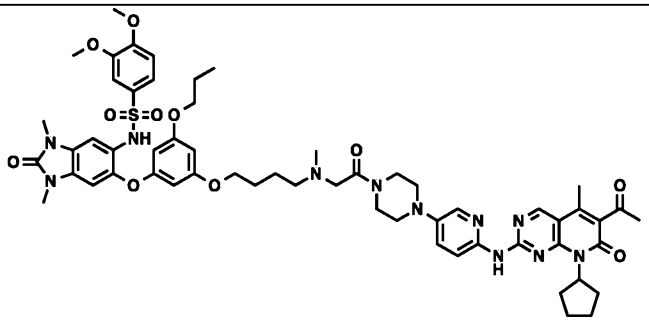
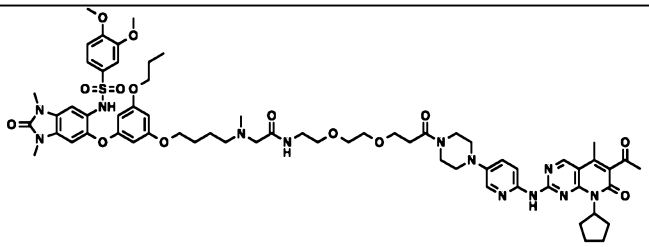
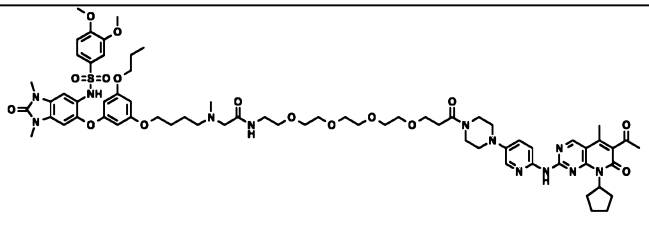
45	YX33-94		4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)-*N*-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)piperazine-1-carboxamide
46	YX33-108		(2*S*,4*R*)-1-((*S*)-2-(3-((3-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-3-oxopropyl)(methyl)amino)propanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide
47	YX33-96		(2*S*,4*R*)-1-((*S*)-2-(6-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazine-1-carbonyl)spiro[3.3]heptane-2-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide
48	YX33-97		(2*S*,4*R*)-1-((*S*)-2-((*E*)-8-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-8-oxooct-4-enamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide

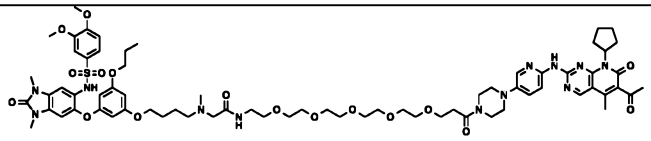
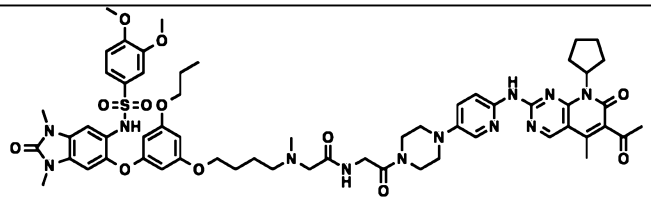
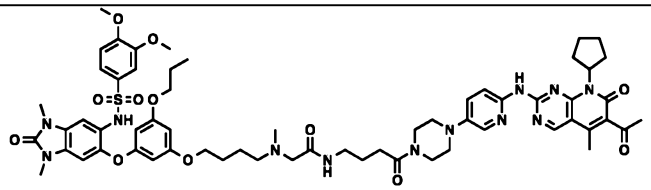
49	YX33-109		(2*S*,4*R*)-1-((*S*)-2-(2-(4-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazine-1-carbonyl)piperidin-1-yl)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide
50	YX33-110		(2*S*,4*R*)-1-((*S*)-2-(2-(4-(2-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-2-oxoethyl)phenyl)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide
51	YX33-122		(2*S*,4*R*)-1-((*S*)-2-(2-(4-(2-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-2-oxoethyl)piperazin-1-yl)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide
52	YX33-123		1-(2-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-2-oxoethyl)-*N*-((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-

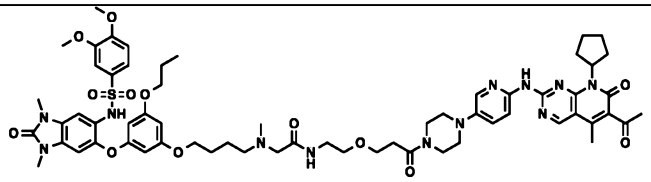
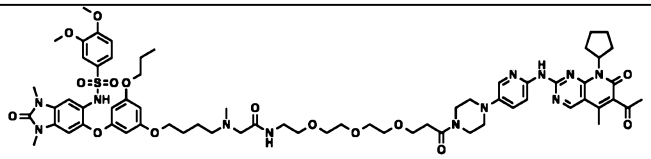
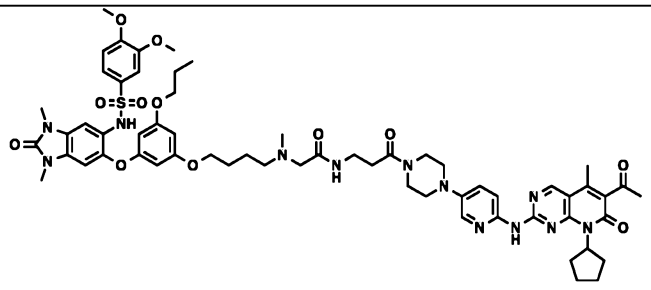
			yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)piperidine-4-carboxamide
53	YX35-48		2-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-*N*-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)acetamide
54	YX39-47		(*E*)-3-(7-(3-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-3-oxoprop-1-en-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione
55	YX39-48		4-(2-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-2-oxoethoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione
56	YX39-56		3-(7-(3-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-3-oxopropyl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione

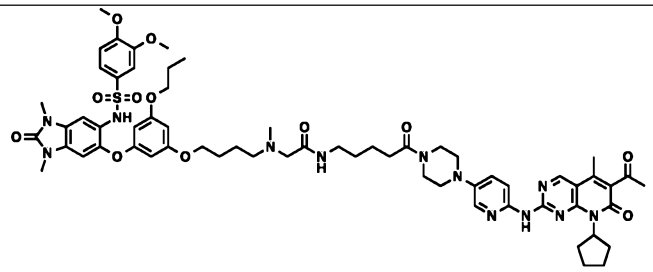
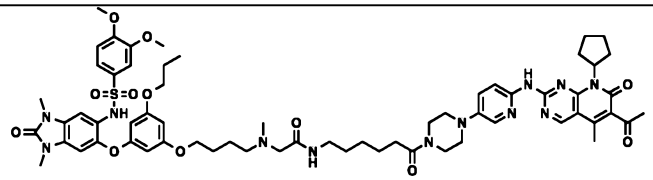
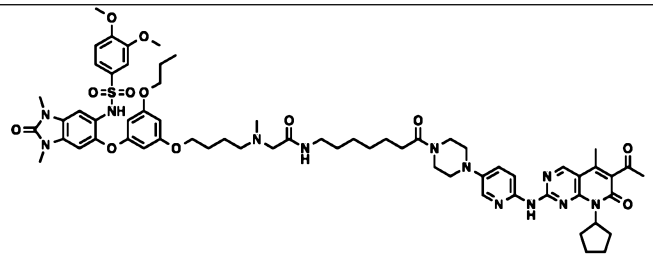
57	YX39-65		3-(4-((2-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-2-oxoethyl)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione
58	YX39-74		5-(3-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-3-oxopropyl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione
59	YX39-123		3-(4-(2-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-2-oxoethoxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione
60	YX39-124		3-(4-(3-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-3-oxopropyl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione
61	YX39-147		4-(3-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-3-oxopropyl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione

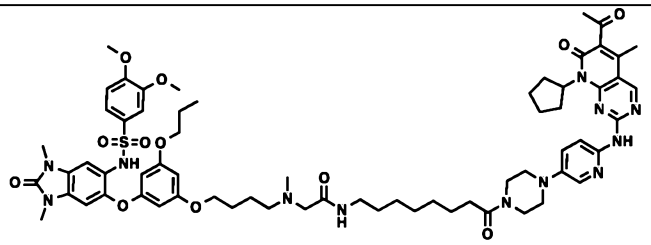
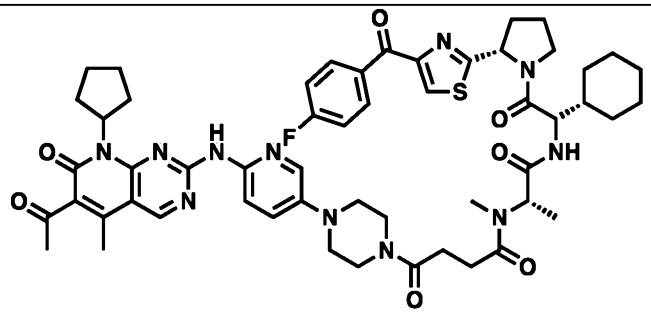
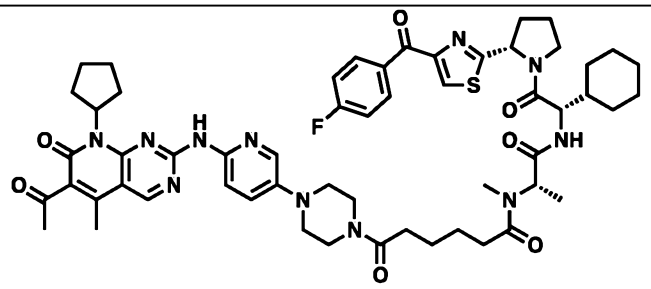
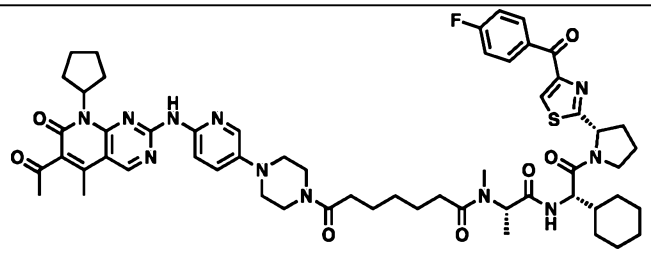
62	YX44-18		(2*S*,4*R*)-1-((*S*)-2-(7-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)-1,4-diazepan-1-yl)-7-oxoheptanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide
63	YX44-19		4-((2-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)-1,4-diazepan-1-yl)-2-oxoethyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione
64	YX44-22		(2*S*,4*R*)-1-((*S*)-2-(7-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-7-oxoheptanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide
65	YX44-46		2-((3*R*,5*R*,6*S*)-1-((*S*)-1-((4-(5-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-5-oxopentanoyl)piperazin-1-yl)sulfonyl)-3,3-dimethylbutan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid

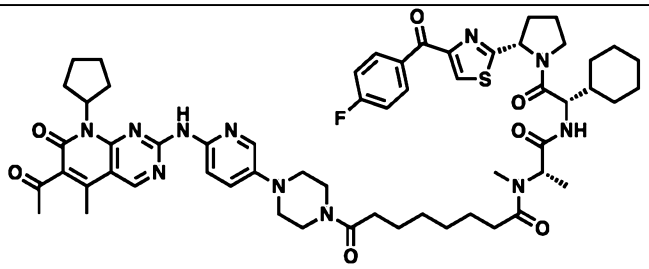
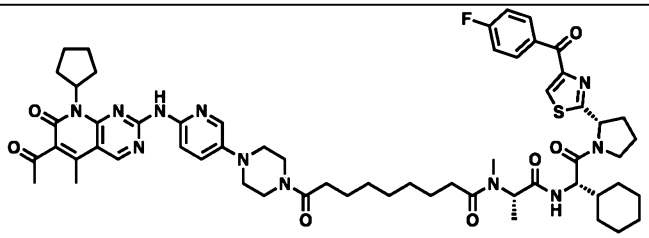
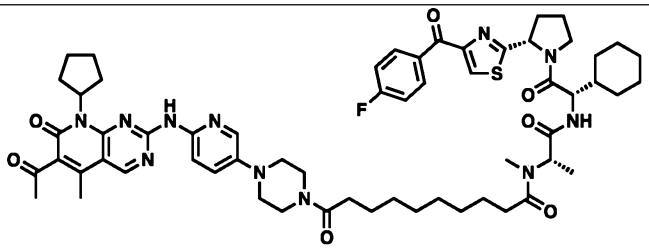
66	YX44-48		5-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-*N*-((*S*)-1-(((*S*)-1-cyclohexyl-2-((*S*)-2-(4-(4-fluorobenzoyl)thiazol-2-yl)pyrrolidin-1-yl)-2-oxoethyl)amino)-1-oxopropan-2-yl)-*N*-methyl-5-oxopentanamide
67	YS36-95		*N*-(6-(3-(4-((2-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-2-oxoethyl)(methyl)amino)butoxy)-5-propoxyphenoxy)-1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)-3,4-dimethoxybenzenesulfonamide
68	YS36-60		*N*-(2-(2-(3-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-3-oxopropoxy)ethoxy)ethyl)-2-((4-(3-((6-((3,4-dimethoxyphenyl)sulfonamido)-1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)oxy)-5-propoxyphenoxy)butyl)(methyl)amino)acetamide
69	YS36-61		*N*-(15-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-15-oxo-

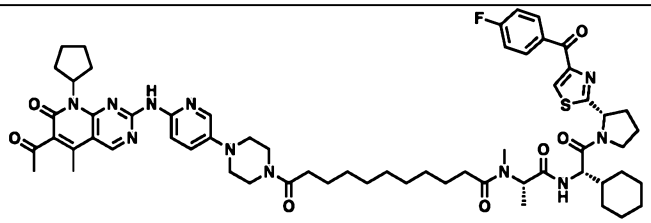
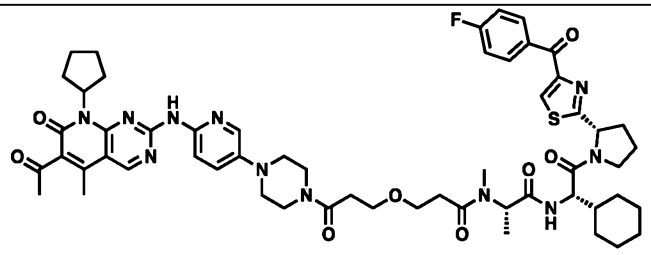
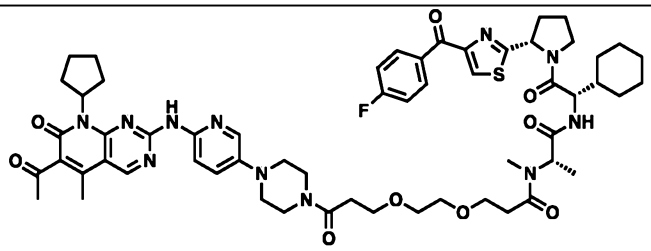
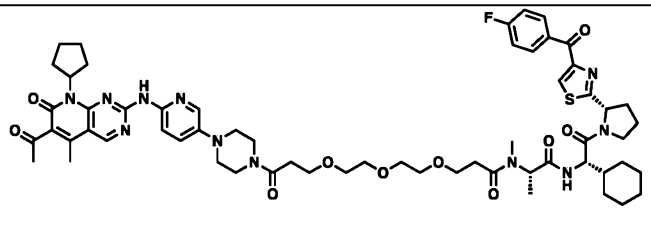
			3,6,9,12-tetraoxapentadecyl)-2-((4-(3-((6-((3,4-dimethoxyphenyl)sulfonamido)-1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)oxy)-5-propoxyphenoxy)butyl)(methyl)amino)acetamide
70	YS36-62		*N*-(18-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-18-oxo-3,6,9,12,15-pentaoxaoctadecyl)-2-((4-(3-((6-((3,4-dimethoxyphenyl)sulfonamido)-1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)oxy)-5-propoxyphenoxy)butyl)(methyl)amino)acetamide
71	YS36-63		*N*-(2-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-2-oxoethyl)-2-((4-(3-((6-((3,4-dimethoxyphenyl)sulfonamido)-1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)oxy)-5-propoxyphenoxy)butyl)(methyl)amino)acetamide
72	YS36-64		*N*-(4-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-4-oxobutyl)-2-((4-(3-((6-((3,4-dimethoxyphenyl)sulfonamido)

			-1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)oxy)-5-propoxyphenoxy)butyl)(methyl)amino)acetamide
73	YS36-65		*N*-(2-(3-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-3-oxopropoxy)ethyl)-2-((4-(3-((6-((3,4-dimethoxyphenyl)sulfonamido)-1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)oxy)-5-propoxyphenoxy)butyl)(methyl)amino)acetamide
74	YS36-66		*N*-(2-(2-(2-(3-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-3-oxopropoxy)ethoxy)ethoxy)ethyl)-2-((4-(3-((6-((3,4-dimethoxyphenyl)sulfonamido)-1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)oxy)-5-propoxyphenoxy)butyl)(methyl)amino)acetamide
75	YS36-67		*N*-(3-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-3-oxopropyl)-2-((4-(3-((6-((3,4-dimethoxyphenyl)sulfonamido)-1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)oxy)-5-

			propoxyphenoxy)butyl)(methyl)amino)acetamide
76	YS36-68		*N*-(5-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-5-oxopentyl)-2-((4-(3-((6-((3,4-dimethoxyphenyl)sulfonamido)-1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)oxy)-5-propoxyphenoxy)butyl)(methyl)amino)acetamide
77	YS36-69		*N*-(6-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-6-oxohexyl)-2-((4-(3-((6-((3,4-dimethoxyphenyl)sulfonamido)-1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)oxy)-5-propoxyphenoxy)butyl)(methyl)amino)acetamide
78	YS36-70		*N*-(7-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-7-oxoheptyl)-2-((4-(3-((6-((3,4-dimethoxyphenyl)sulfonamido)-1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)oxy)-5-propoxyphenoxy)butyl)(methyl)amino)acetamide

79	YS36-71		*N*-(8-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-8-oxooctyl)-2-((4-(3-((6-((3,4-dimethoxyphenyl)sulfonamido)-1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)oxy)-5-propoxyphenoxy)butyl)(methyl)amino)acetamide
80			4-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-*N*-((*S*)-1-(((*S*)-1-cyclohexyl-2-((*S*)-2-(4-(4-fluorobenzoyl)thiazol-2-yl)pyrrolidin-1-yl)-2-oxoethyl)amino)-1-oxopropan-2-yl)-*N*-methyl-4-oxobutanamide
81			6-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-*N*-((*S*)-1-(((*S*)-1-cyclohexyl-2-((*S*)-2-(4-(4-fluorobenzoyl)thiazol-2-yl)pyrrolidin-1-yl)-2-oxoethyl)amino)-1-oxopropan-2-yl)-*N*-methyl-6-oxohexanamide
82			7-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-*N*-((*S*)-1-(((*S*)-1-cyclohexyl-2-((*S*)-2-(4-

			(4-fluorobenzoyl)thiazol-2-yl)pyrrolidin-1-yl)-2-oxoethyl)amino)-1-oxopropan-2-yl)-*N*-methyl-7-oxoheptanamide
83			8-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-*N*-((*S*)-1-(((*S*)-1-cyclohexyl-2-((*S*)-2-(4-(4-fluorobenzoyl)thiazol-2-yl)pyrrolidin-1-yl)-2-oxoethyl)amino)-1-oxopropan-2-yl)-*N*-methyl-8-oxooctanamide
84			9-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-*N*-((*S*)-1-(((*S*)-1-cyclohexyl-2-((*S*)-2-(4-(4-fluorobenzoyl)thiazol-2-yl)pyrrolidin-1-yl)-2-oxoethyl)amino)-1-oxopropan-2-yl)-*N*-methyl-9-oxononanamide
85			10-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-*N*-((*S*)-1-(((*S*)-1-cyclohexyl-2-((*S*)-2-(4-(4-fluorobenzoyl)thiazol-2-yl)pyrrolidin-1-yl)-2-oxoethyl)amino)-1-oxopropan-2-yl)-*N*-methyl-10-oxodecanamide

86			11-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-*N*-((*S*)-1-(((*S*)-1-cyclohexyl-2-((*S*)-2-(4-(4-fluorobenzoyl)thiazol-2-yl)pyrrolidin-1-yl)-2-oxoethyl)amino)-1-oxopropan-2-yl)-*N*-methyl-11-oxoundecanamide
87			3-(3-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-3-oxopropoxy)-*N*-((*S*)-1-(((*S*)-1-cyclohexyl-2-((*S*)-2-(4-(4-fluorobenzoyl)thiazol-2-yl)pyrrolidin-1-yl)-2-oxoethyl)amino)-1-oxopropan-2-yl)-*N*-methylpropanamide
88			3-(2-(3-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-3-oxopropoxy)ethoxy)-*N*-((*S*)-1-(((*S*)-1-cyclohexyl-2-((*S*)-2-(4-(4-fluorobenzoyl)thiazol-2-yl)pyrrolidin-1-yl)-2-oxoethyl)amino)-1-oxopropan-2-yl)-*N*-methylpropanamide
89			3-(2-(2-(3-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-3-oxopropoxy)ethoxy)ethoxy)-*N*-((*S*)-1-(((*S*)-1-cyclohexyl-2-

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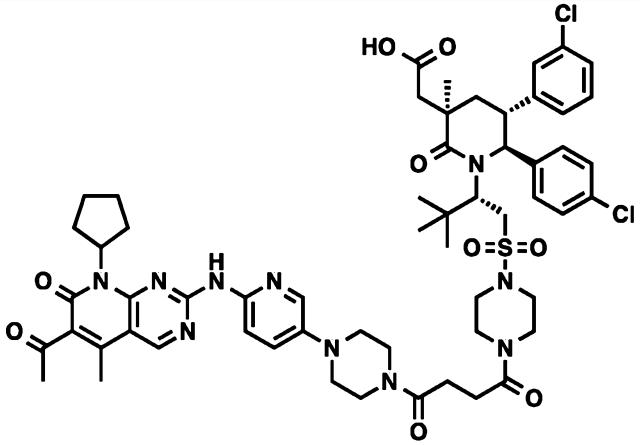
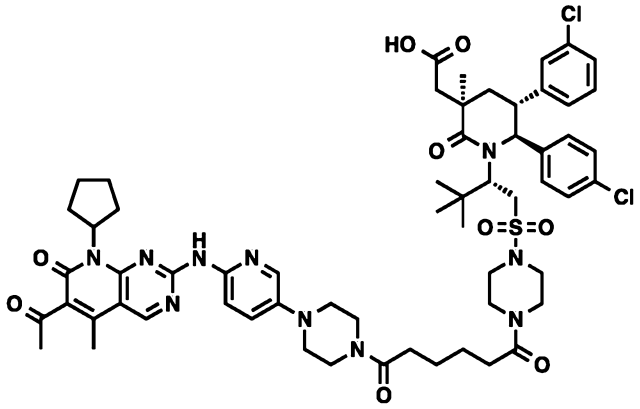
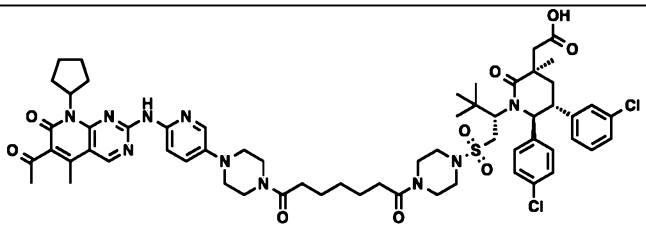
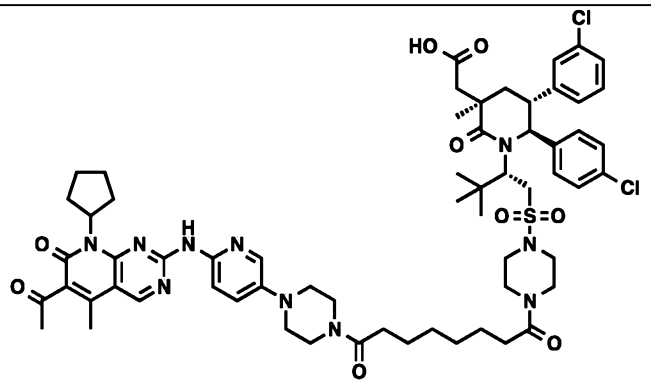
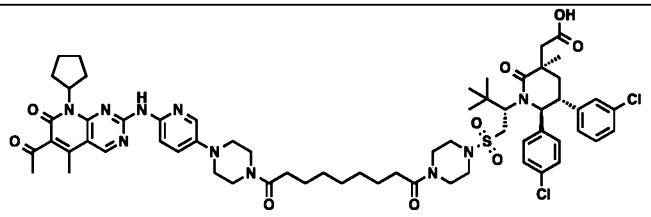
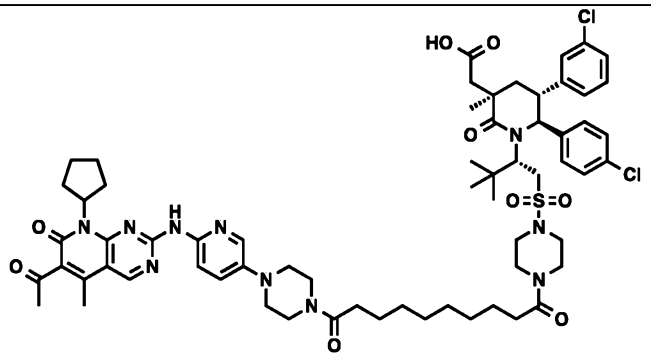
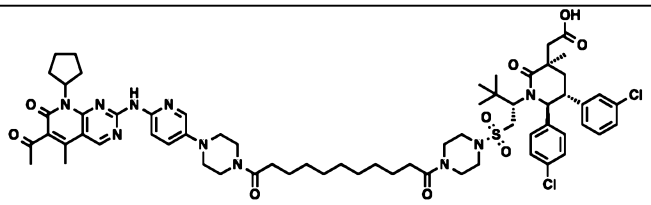
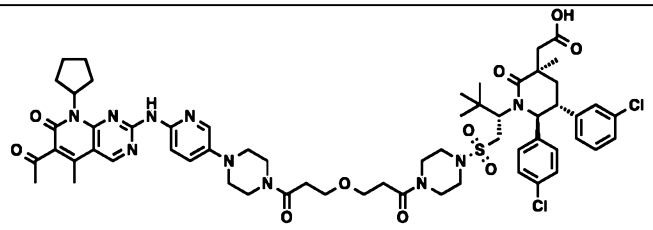
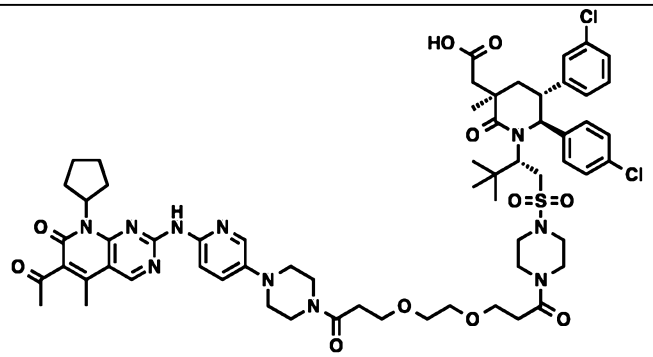
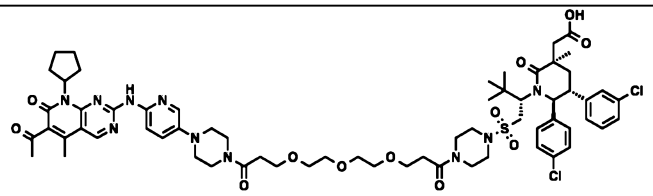
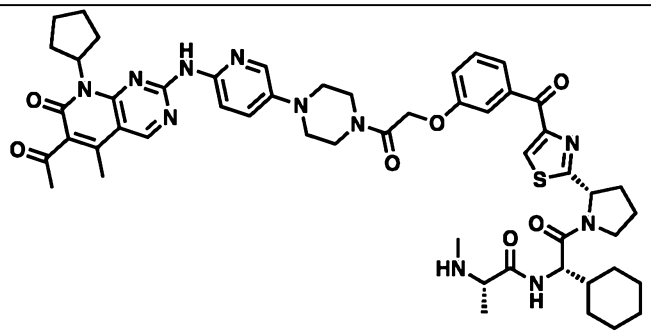
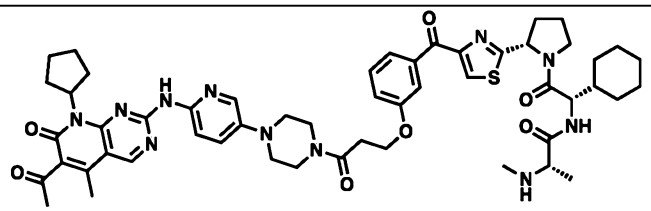
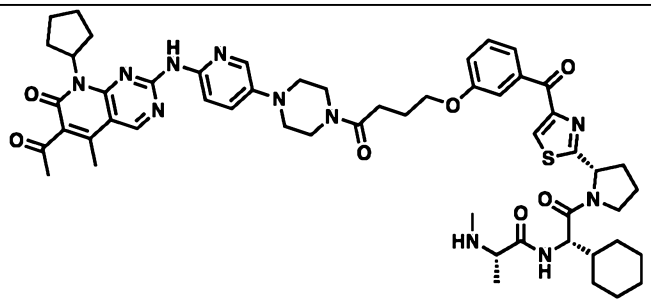
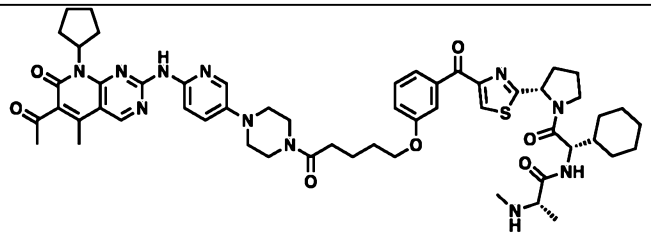
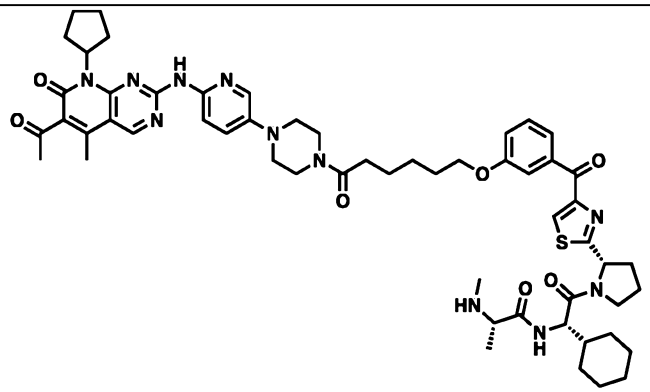
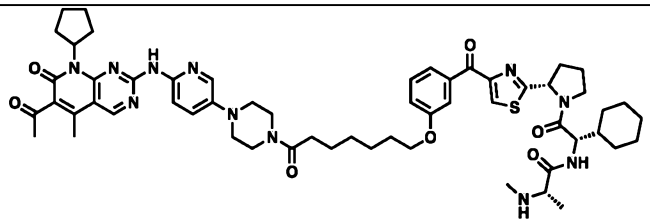
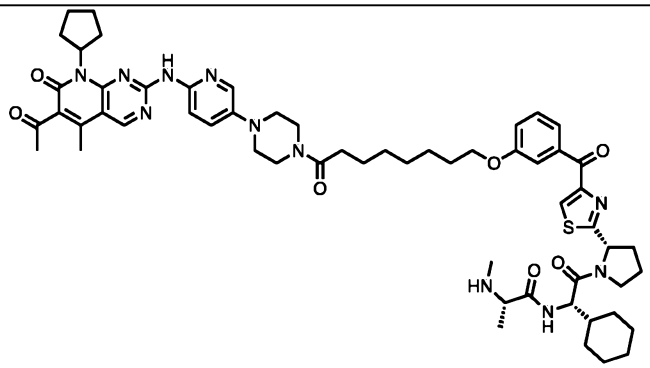
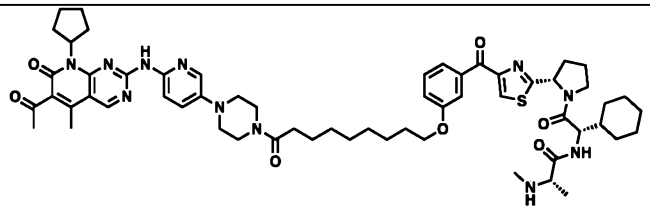
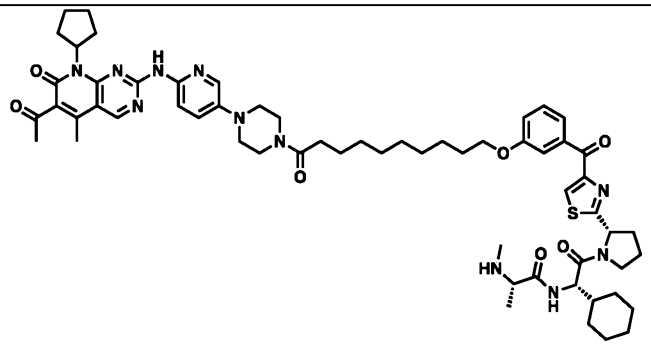
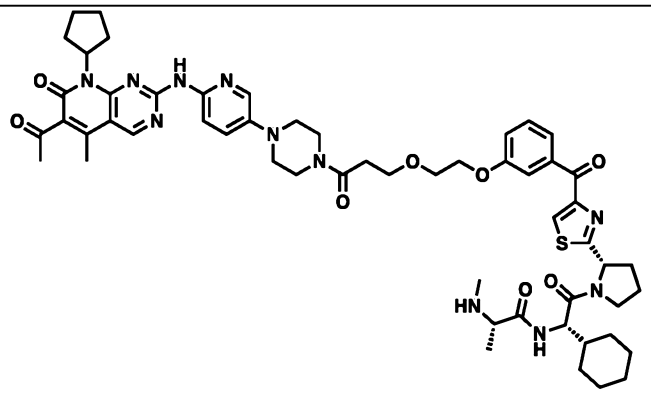
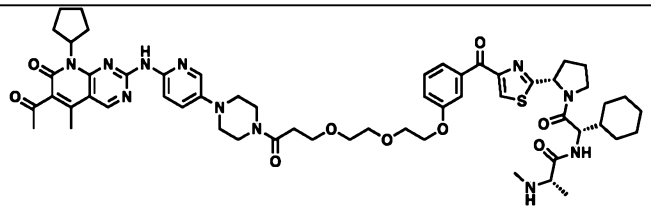
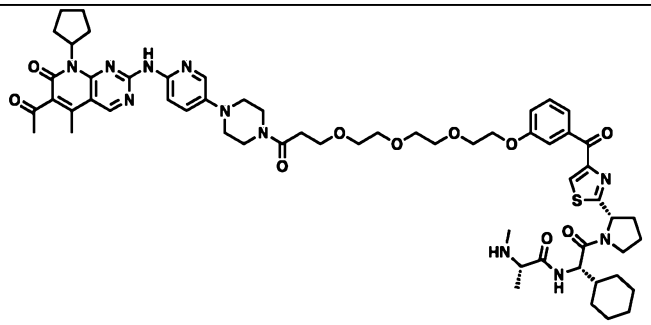
90			2-((3*R*,5*R*,6*S*)-1-((*S*)-1-((4-(4-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-4-oxobutanoyl)piperazin-1-yl)sulfonyl)-3,3-dimethylbutan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid
91			2-((3*R*,5*R*,6*S*)-1-((*S*)-1-((4-(6-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-6-oxohexanoyl)piperazin-1-yl)sulfonyl)-3,3-dimethylbutan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid
92			2-((3*R*,5*R*,6*S*)-1-((*S*)-1-((4-(7-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-7-oxoheptanoyl)piperazin-1-yl)sulfonyl)-3,3-dimethylbutan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid

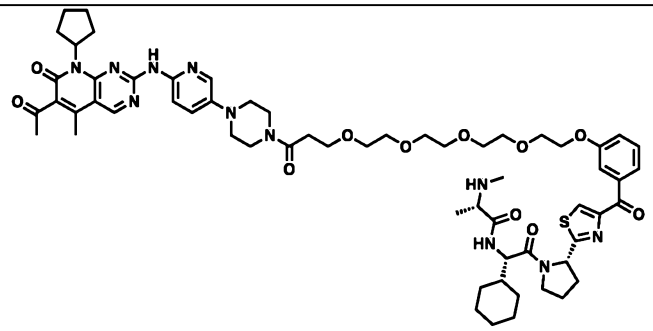
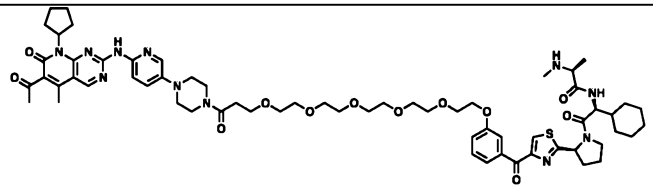
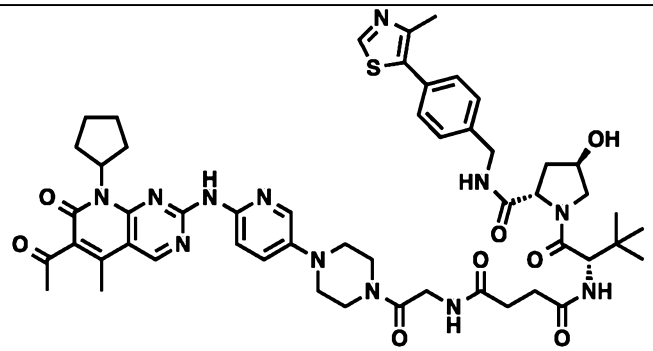
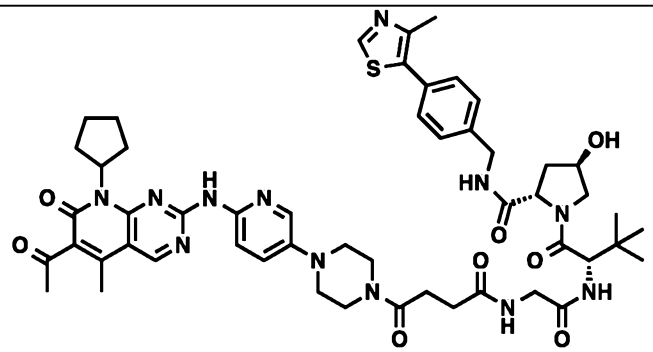
93			2-((3*R*,5*R*,6*S*)-1-((*S*)-1-((4-(8-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-8-oxooctanoyl)piperazin-1-yl)sulfonyl)-3,3-dimethylbutan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid
94			2-((3*R*,5*R*,6*S*)-1-((*S*)-1-((4-(9-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-9-oxononanoyl)piperazin-1-yl)sulfonyl)-3,3-dimethylbutan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid
95			2-((3*R*,5*R*,6*S*)-1-((*S*)-1-((4-(10-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-10-oxodecanoyl)piperazin-1-yl)sulfonyl)-3,3-dimethylbutan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid
96			2-((3*R*,5*R*,6*S*)-1-((*S*)-1-((4-(11-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-11-oxoundecanoyl)piperazin-1-yl)sulfonyl)-3,3-dimethylbutan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid

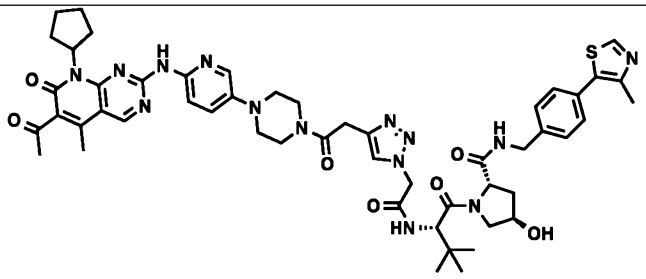
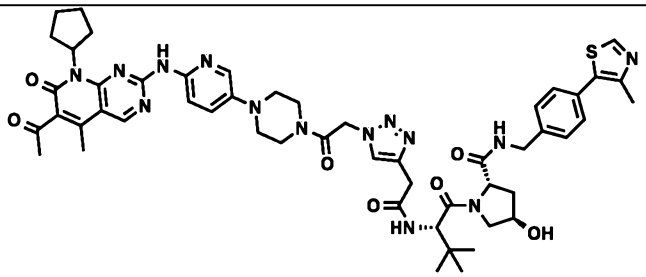
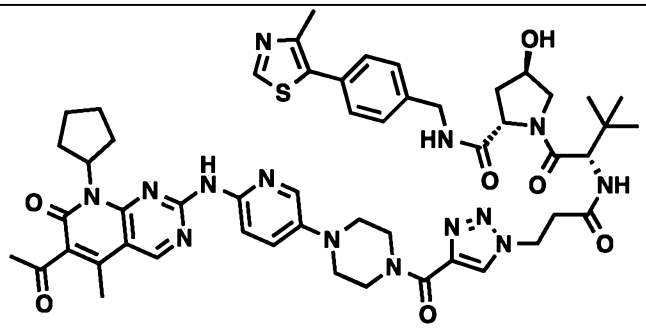
97			2-((3*R*,5*R*,6*S*)-1-((*S*)-1-((4-(3-(3-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-3-oxopropoxy)propanoyl)piperazin-1-yl)sulfonyl)-3,3-dimethylbutan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid
98			2-((3*R*,5*R*,6*S*)-1-((*S*)-1-((4-(3-(2-(3-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-3-oxopropoxy)ethoxy)propanoyl)piperazin-1-yl)sulfonyl)-3,3-dimethylbutan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid
99			2-((3*R*,5*R*,6*S*)-1-((*S*)-1-((4-(3-(2-(2-(3-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-3-oxopropoxy)ethoxy)ethoxy)propanoyl)piperazin-1-yl)sulfonyl)-3,3-dimethylbutan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid

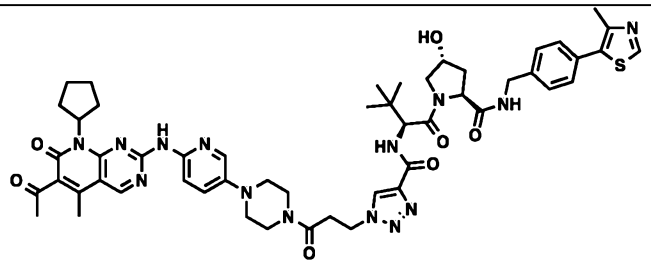
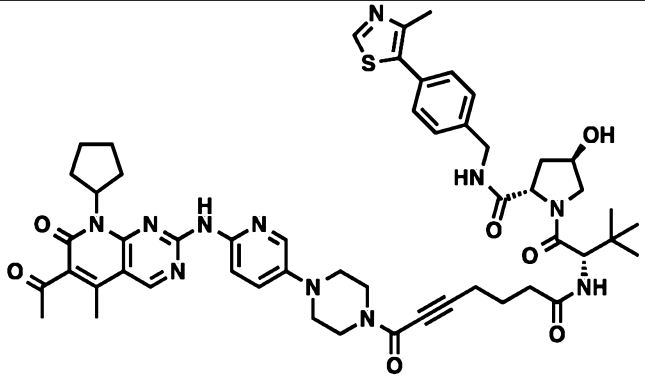
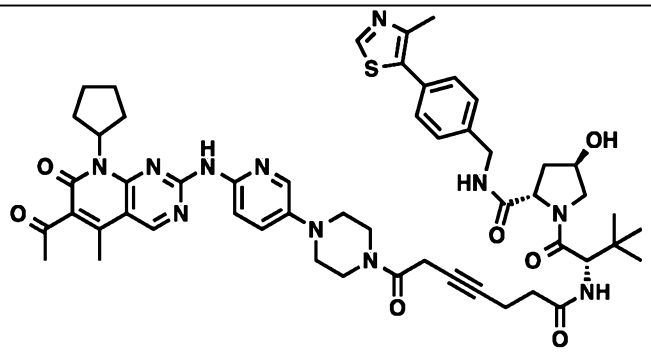
100			(*S*)-*N*-((*S*)-2-((*S*)-2-(4-(3-(2-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-2-oxoethoxy)benzoyl)thiazol-2-yl)pyrrolidin-1-yl)-1-cyclohexyl-2-oxoethyl)-2-(methylamino)propanamide
101			(*S*)-*N*-((*S*)-2-((*S*)-2-(4-(3-(3-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-3-oxopropoxy)benzoyl)thiazol-2-yl)pyrrolidin-1-yl)-1-cyclohexyl-2-oxoethyl)-2-(methylamino)propanamide
102			(*S*)-*N*-((*S*)-2-((*S*)-2-(4-(3-(4-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-4-oxobutoxy)benzoyl)thiazol-2-yl)pyrrolidin-1-yl)-1-cyclohexyl-2-oxoethyl)-2-(methylamino)propanamide
103			(*S*)-*N*-((*S*)-2-((*S*)-2-(4-(3-((5-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-5-oxopentyl)oxy)benzoyl)thiazol-2-yl)pyrrolidin-1-yl)-1-cyclohexyl-2-oxoethyl)-2-(methylamino)propanamide

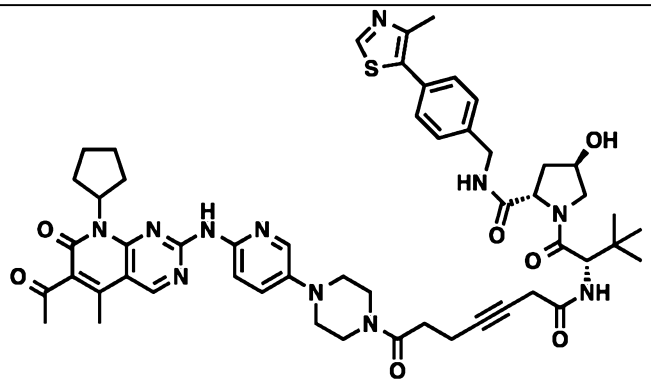
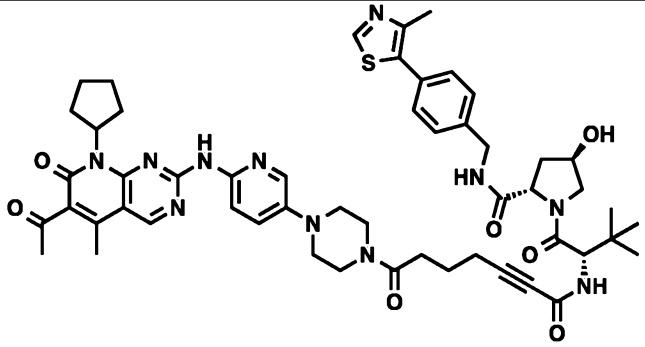
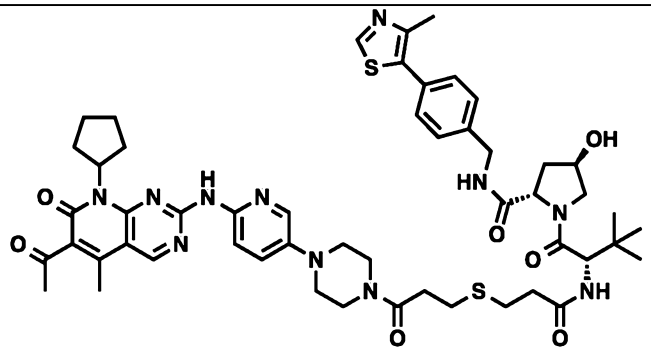
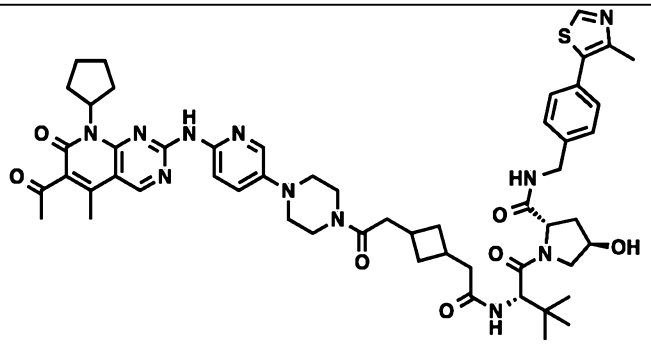
104			(*S*)-*N*-((*S*)-2-((*S*)-2-(4-(3-((6-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-6-oxohexyl)oxy)benzoyl)thiazol-2-yl)pyrrolidin-1-yl)-1-cyclohexyl-2-oxoethyl)-2-(methylamino)propanamide
105			(*S*)-*N*-((*S*)-2-((*S*)-2-(4-(3-((7-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-7-oxoheptyl)oxy)benzoyl)thiazol-2-yl)pyrrolidin-1-yl)-1-cyclohexyl-2-oxoethyl)-2-(methylamino)propanamide
106			(*S*)-*N*-((*S*)-2-((*S*)-2-(4-(3-((8-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-8-oxooctyl)oxy)benzoyl)thiazol-2-yl)pyrrolidin-1-yl)-1-cyclohexyl-2-oxoethyl)-2-(methylamino)propanamide
107			(*S*)-*N*-((*S*)-2-((*S*)-2-(4-(3-((9-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-9-oxononyl)oxy)benzoyl)thiazol-2-yl)pyrrolidin-1-yl)-1-cyclohexyl-2-oxoethyl)-2-(methylamino)propanamide

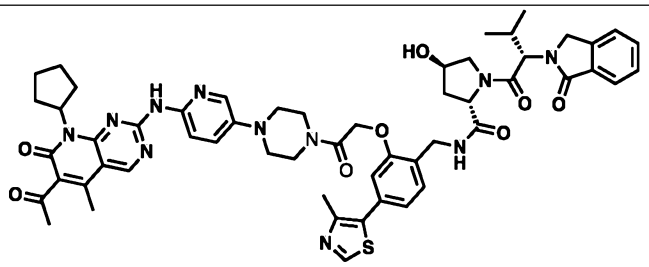
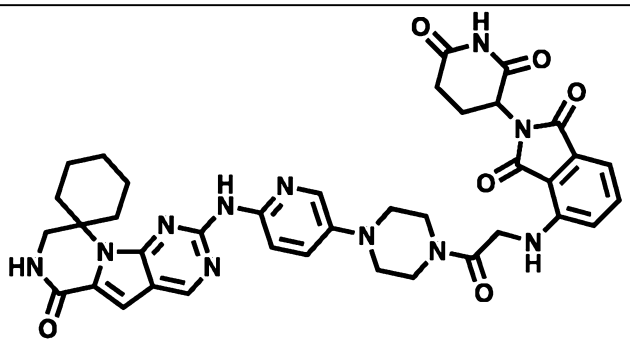
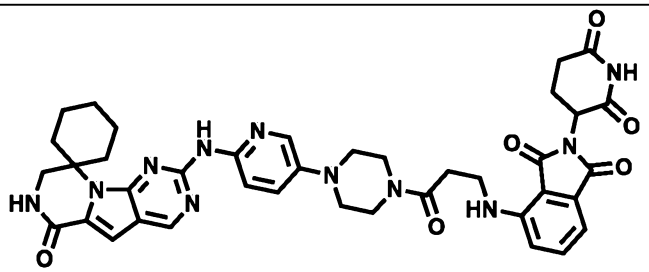
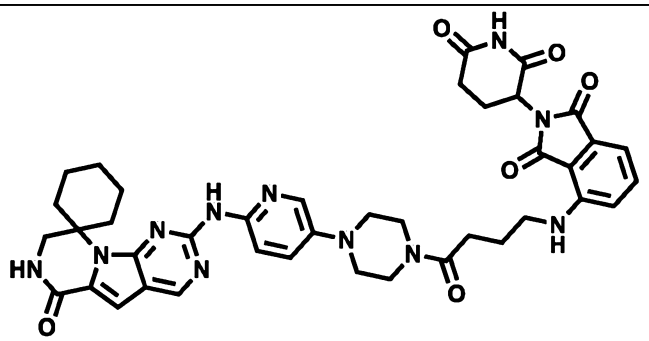
108			(*S*)-*N*-((*S*)-2-((*S*)-2-(4-(3-((10-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-10-oxodecyl)oxy)benzoyl)thiazol-2-yl)pyrrolidin-1-yl)-1-cyclohexyl-2-oxoethyl)-2-(methylamino)propanamide
109			(*S*)-*N*-((*S*)-2-((*S*)-2-(4-(3-(2-(3-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-3-oxopropoxy)ethoxy)benzoyl)thiazol-2-yl)pyrrolidin-1-yl)-1-cyclohexyl-2-oxoethyl)-2-(methylamino)propanamide
110			(*S*)-*N*-((*S*)-2-((*S*)-2-(4-(3-(2-(2-(3-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-3-oxopropoxy)ethoxy)ethoxy)benzoyl)thiazol-2-yl)pyrrolidin-1-yl)-1-cyclohexyl-2-oxoethyl)-2-(methylamino)propanamide
111			(*S*)-*N*-((*S*)-2-((*S*)-2-(4-(3-(2-(2-(2-(3-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-3-oxopropoxy)ethoxy)ethoxy)ethoxy)benzoyl)thiazol-2-yl)pyrrolidin-1-yl)-1-cyclohexyl-2-oxoethyl)-2-(methylamino)propanamide

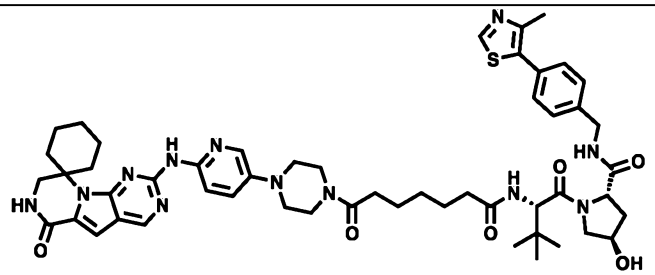
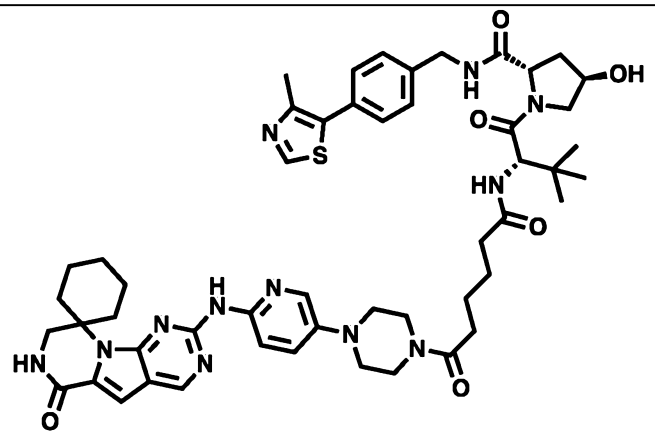
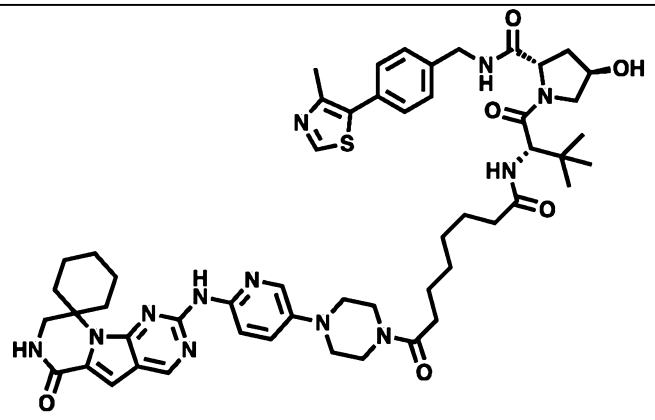
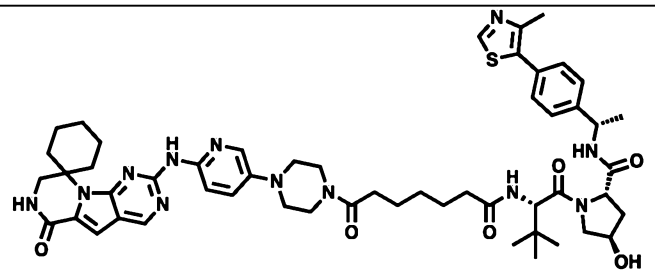
112			(*S*)-*N*-((*S*)-2-((*S*)-2-(4-(3-((15-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-15-oxo-3,6,9,12-tetraoxapentadecyl)oxy)benzoyl)thiazol-2-yl)pyrrolidin-1-yl)-1-cyclohexyl-2-oxoethyl)-2-(methylamino)propanamide
113			(*S*)-*N*-((*S*)-2-((*S*)-2-(4-(3-((18-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-18-oxo-3,6,9,12,15-pentaoxaoctadecyl)oxy)benzoyl)thiazol-2-yl)pyrrolidin-1-yl)-1-cyclohexyl-2-oxoethyl)-2-(methylamino)propanamide
114			N^1-(2-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-2-oxoethyl)-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
115			(2*S*,4*R*)-1-((*S*)-2-(2-(4-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-4-oxobutanamido)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-

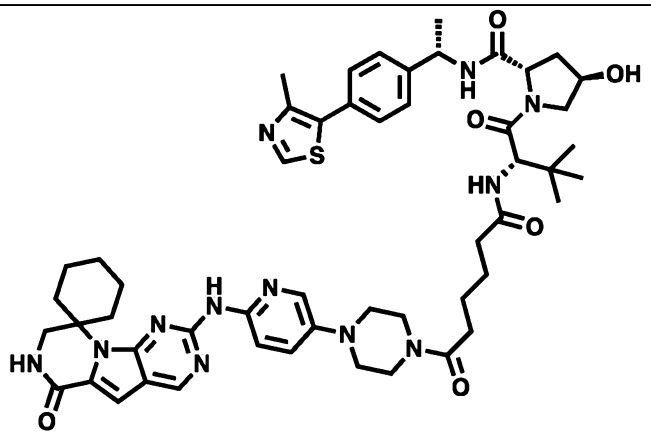
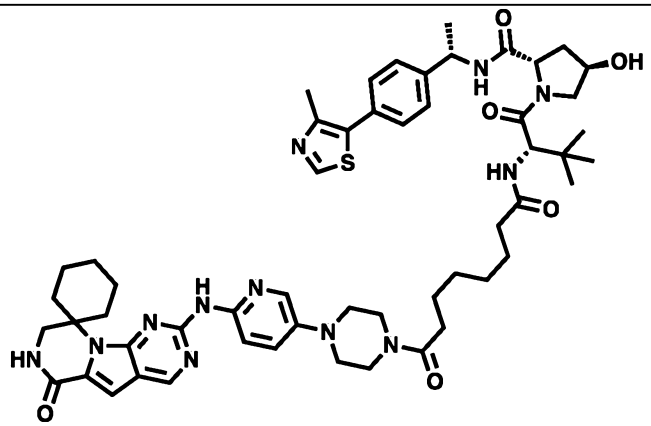
			yl)benzyl)pyrrolidine-2-carboxamide
116			(2*S*,4*R*)-1-((*S*)-2-(2-(4-(2-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-2-oxoethyl)-1*H*-1,2,3-triazol-1-yl)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide
117			(2*S*,4*R*)-1-((*S*)-2-(2-(1-(2-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-2-oxoethyl)-1*H*-1,2,3-triazol-4-yl)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide
118			(2*S*,4*R*)-1-((*S*)-2-(3-(4-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazine-1-carbonyl)-1*H*-1,2,3-triazol-1-yl)propanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide

119			1-(3-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-3-oxopropyl)-*N*-((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-1*H*-1,2,3-triazole-4-carboxamide
120			(2*S*,4*R*)-1-((*S*)-2-(7-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-7-oxohept-5-ynamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide
121			(2*S*,4*R*)-1-((*S*)-2-(7-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-7-oxohept-4-ynamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide

122			(2*S*,4*R*)-1-((*S*)-2-(7-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-7-oxohept-3-ynamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide
123			(2*S*,4*R*)-1-((*S*)-2-(7-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-7-oxohept-2-ynamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide
124			(2*S*,4*R*)-1-((*S*)-2-(3-((3-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-3-oxopropyl)thio)propanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide
125			(2*S*,4*R*)-1-((*S*)-2-(2-(3-(2-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-2-oxoethyl)cyclobutyl)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-

			yl)benzyl)pyrrolidine-2-carboxamide
126	YX44-78		(2S,4R)-N-(2-(2-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-2-oxoethoxy)-4-(4-methylthiazol-5-yl)benzyl)-4-hydroxy-1-((S)-3-methyl-2-(1-oxoisoindolin-2-yl)butanoyl)pyrrolidine-2-carboxamide
127			2-(2,6-dioxopiperidin-3-yl)-4-((2-oxo-2-(4-(6-((6'-oxo-7',8'-dihydro-6'*H*-spiro[cyclohexane-1,9'-pyrazino[1',2':1,5]pyrrolo[2,3-*d*]pyrimidin]-2'-yl)amino)pyridin-3-yl)piperazin-1-yl)ethyl)amino)isoindoline-1,3-dione
128			2-(2,6-dioxopiperidin-3-yl)-4-((3-oxo-3-(4-(6-((6'-oxo-7',8'-dihydro-6'*H*-spiro[cyclohexane-1,9'-pyrazino[1',2':1,5]pyrrolo[2,3-*d*]pyrimidin]-2'-yl)amino)pyridin-3-yl)piperazin-1-yl)propyl)amino)isoindoline-1,3-dione
129			2-(2,6-dioxopiperidin-3-yl)-4-((4-oxo-4-(4-(6-((6'-oxo-7',8'-dihydro-6'*H*-spiro[cyclohexane-1,9'-pyrazino[1',2':1,5]pyrrolo[2,3-*d*]pyrimidin]-2'-yl)amino)pyridin-3-yl)piperazin-1-yl)butyl)amino)isoindoline-1,3-dione

130			(2*S*,4*R*)-1-((*S*)-3,3-dimethyl-2-(7-oxo-7-(4-(6-((6'-oxo-7',8'-dihydro-6'*H*-spiro[cyclohexane-1,9'-pyrazino[1',2':1,5]pyrrolo[2,3-*d*]pyrimidin]-2'-yl)amino)pyridin-3-yl)piperazin-1-yl)heptanamido)butanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide
131			(2*S*,4*R*)-1-((*S*)-3,3-dimethyl-2-(6-oxo-6-(4-(6-((6'-oxo-7',8'-dihydro-6'*H*-spiro[cyclohexane-1,9'-pyrazino[1',2':1,5]pyrrolo[2,3-*d*]pyrimidin]-2'-yl)amino)pyridin-3-yl)piperazin-1-yl)hexanamido)butanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide
132			(2*S*,4*R*)-1-((*S*)-3,3-dimethyl-2-(8-oxo-8-(4-(6-((6'-oxo-7',8'-dihydro-6'*H*-spiro[cyclohexane-1,9'-pyrazino[1',2':1,5]pyrrolo[2,3-*d*]pyrimidin]-2'-yl)amino)pyridin-3-yl)piperazin-1-yl)octanamido)butanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide
133			(2*S*,4*R*)-1-((*S*)-3,3-dimethyl-2-(7-oxo-7-(4-(6-((6'-oxo-7',8'-dihydro-6'*H*-spiro[cyclohexane-1,9'-pyrazino[1',2':1,5]pyrrolo[2,3-*d*]pyrimidin]-2'-yl)amino)pyridin-3-yl)piperazin-1-

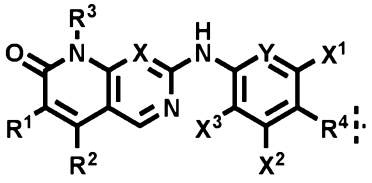
			yl)heptanamido)butanoyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide
134			(2*S*,4*R*)-1-((*S*)-3,3-dimethyl-2-(6-oxo-6-(4-(6-((6'-oxo-7',8'-dihydro-6'*H*-spiro[cyclohexane-1,9'-pyrazino[1',2':1,5]pyrrolo[2,3-*d*]pyrimidin]-2'-yl)amino)pyridin-3-yl)piperazin-1-yl)hexanamido)butanoyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide
135			(2*S*,4*R*)-1-((*S*)-3,3-dimethyl-2-(8-oxo-8-(4-(6-((6'-oxo-7',8'-dihydro-6'*H*-spiro[cyclohexane-1,9'-pyrazino[1',2':1,5]pyrrolo[2,3-*d*]pyrimidin]-2'-yl)amino)pyridin-3-yl)piperazin-1-yl)octanamido)butanoyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide

In an aspect, the CDK4/6 degraders/disruptors have the form "**PI-linker-EL**" as shown below:

Formula I,

wherein **PI** comprises a CDK4/6 ligand (e.g., a CDK4/6 inhibitor) and **EL** comprises a degradation/disruption tag (e.g., E3 ligase ligand). Exemplary CDK4/6 ligands (**PI**) and exemplary degradation/disruption tags (**EL**) are disclosed herein.

For example, **PI** can include, but is not limited to:



Formula II,

wherein X^1, X^2, and X^3 are independently hydrogen, halogen, C1-C8 alkyl, C1-C8 alkoxy, C1-C8 alkoxyalkyl, NR^5R^6, CN, NO_2, COR^5, CO_2R^5, $CONR^5R^6$, or NR^5COR^6;

R^1 and R^4 are independently hydrogen, halogen, C1-C8 alkyl, C1-C8 alkoxy, C1-C8 alkoxyalkyl, C1-C8 haloalkyl, C1-C8 hydroxyalkyl, C3-C7 cycloalkyl, C3-C7 heterocyclyl, C2-C8 alkenyl, C2-C8 alkynyl, OR^5, SR^5, NR^5R^6, CN, NO_2, $(CR^5R^6)mNR^7R^8$, $(CR^5R^6)mC(O)R^7$, COR^5, CO_2R^5, $CONR^5R^6$, NR^5COR^6, NR^5SOR^6, $NR^5SO_2R^6$, SOR^5, SO_2R^5, $SO_2NR^5R^6$, (CR^5R^6)m-aryl, or (CR^5R^6)m-heteroaryl, wherein m is 0-8;

R^2 is hydrogen, halogen, C1-C8 alkyl, C1-C8 alkoxy, C3-C7 cycloalkyl, or C3-C7 heterocyclyl;

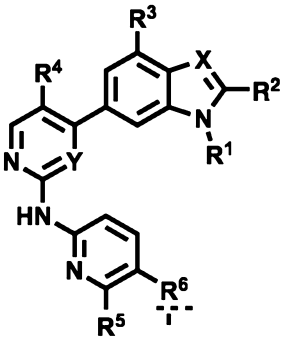
R^3 is hydrogen, aryl, C1-C8 alkyl, C1-C8 alkoxy, C3-C7 cycloalkyl, or C3-C7 heterocyclyl;

R^5, R^6, R^7, R^8 are independently hydrogen, C1-C8 alkyl, C2-C8 alkenyl, C2-C8 alkynyl, arylalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, or heteroarylalkyl;

optionally, R^1 and R^2; R^5 and R^6; or $R^7$and R^8 independently form 4-8 membered alkyl or heterocyclyl rings; and

X and Y are independently CR^5R^6 or N.

For example, **PI** can include:



Formula III,

wherein R^1 is independently hydrogen, C1-C8 alkyl, C1-C8 alkoxyalkyl, C1-C8 haloalkyl, C1-C8 hydroxyalkyl, C3-C7 cycloalkyl, C3-C7 heterocyclyl, C2-C8 alkenyl, or C2-C8 alkynyl;

R^2 is hydrogen, C1-C3 alkyl, or cyclopropyl;

R^3, R^4, and R^5 are independently hydrogen, halogen, C1-C8 alkyl, C1-C8 alkoxy, C3-C7 cycloalkyl, or C3-C7 heterocyclyl;

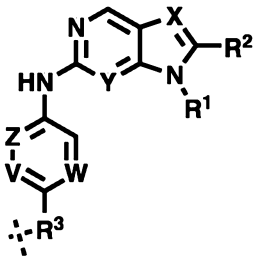
R^6 is hydrogen, halogen,C1-C8 alkyl, C1-C8 alkoxy, C1-C8 alkoxyalkyl, C1-C8 haloalkyl, C1-C8 hydroxyalkyl, C3-C7 cycloalkyl, C3-C7 heterocyclyl, C2-C8 alkenyl, C2-C8 alkynyl, OR^7, SR^7, NR^7R^8, CN, NO_2, $(CR^7R^8)mNR^9R^{10}$, $(CR^7R^8)mC(O)R^9$, COR^7, CO_2R^7, $CONR^7R^8$, NR^7COR^8, NR^7SOR^8, $NR^7SO_2R^8$, SOR^7, SO_2R^7, $SO_2NR^7R^8$, (CR^7R^8)m-aryl, or (CR^7R^8)m-heteroaryl, wherein m is 0-8;

R^7, R^8, R^9, R^{10} are independently hydrogen, C1-C8 alkyl, C2-C8 alkenyl, C2-C8 alkynyl, arylalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, or heteroarylalkyl;

optionally, R^7 and R^8; R^9 and R^{10} independently form 4-8 membered alkyl or heterocyclyl rings; and

X and Y are independently CR^7R^8 or N.

For example, **PI** can include:



Formula IV,

wherein R^1 is independently hydrogen, C1-C8 alkyl, C1-C8 alkoxyalkyl, C1-C8 haloalkyl, C1-C8 hydroxyalkyl, C3-C7 cycloalkyl, C3-C7 heterocyclyl, C2-C8 alkenyl, or C2-C8 alkynyl;

R^2 is hydrogen, C1-C8 alkyl, C1-C8 alkoxyalkyl, C1-C8 haloalkyl, C1-C8 hydroxyalkyl, C3-C7 cycloalkyl, C3-C7 heterocyclyl, C2-C8 alkenyl, C2-C8 alkynyl, CN, COR^4, CO_2R^4, or $CONR^4R^5$;

R^3 is hydrogen, halogen, C1-C8 alkyl, C1-C8 alkoxy, C1-C8 alkoxyalkyl, C1-C8 haloalkyl, C1-C8 hydroxyalkyl, C3-C7 cycloalkyl, C3-C7 heterocyclyl, C2-C8 alkenyl, C2-

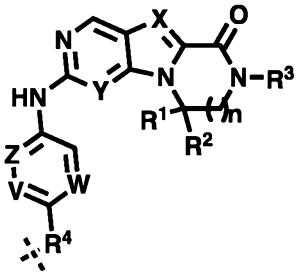
C8 alkynyl, OR^4, SR^4, NR^4R^5, CN, NO_2, $(CR^4R^5)mNR^6R^7$, $(CR^4R^5)mC(O)R^6$, COR^4, CO_2R^4, $CONR^4R^5$, NR^4COR^5, NR^4SOR^5, $NR^4SO_2R^5$, SOR^4, SO_2R^4, $SO_2NR^4R^5$, (CR^4R^5)m-aryl, or (CR^4R^5)m-heteroaryl, wherein m is 0-8;

R^4, R^5, R^6, R^7 are independently hydrogen, C1-C8 alkyl, C2-C8 alkenyl, C2-C8 alkynyl, arylalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, or heteroarylalkyl;

optionally, R^1 and R^2; R^4 and R^5; $R^6$and R^7 independently form 4-8 membered alkyl or heterocyclyl rings; and

V, W, X, Y, and Z are independently CR^4R^5 or N.

For example, **PI** can include:



Formula VI,

wherein R^1 and R^2 are independently hydrogen, C1-C8 alkyl, C1-C8 alkoxyalkyl, C1-C8 haloalkyl, C1-C8 hydroxyalkyl, C3-C7 cycloalkyl, C3-C7 heterocyclyl, C2-C8 alkenyl, or C2-C8 alkynyl;

R^3 is hydrogen, C1-C6 alkyl, C1-C6 alkoxyalkyl, C1-C6 haloalkyl, C1-C6 hydroxyalkyl, C3-C6 cycloalkyl, C3-C6 heterocyclyl, C2-C6 alkenyl, or C2-C6 alkynyl;

R^4 is hydrogen, halogen, C1-C8 alkyl, C1-C8 alkoxy, C1-C8 alkoxyalkyl, C1-C8 haloalkyl, C1-C8 hydroxyalkyl, C3-C7 cycloalkyl, C3-C7 heterocyclyl, C2-C8 alkenyl, C2-C8 alkynyl, OR^5, SR^5, NR^5R^6, CN, NO_2, $(CR^5R^6)mNR^7R^8$, $(CR^5R^6)mC(O)R^7$, COR^5, CO_2R^5, $CONR^5R^6$, NR^5COR^6, NR^5SOR^6, $NR^5SO_2R^6$, SOR^5, SO_2R^5, $SO_2NR^5R^6$, (CR^5R^6)m-aryl, or (CR^5R^6)m-heteroaryl, wherein m is 0-8;

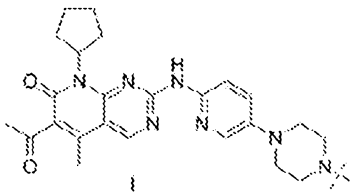
n is 0-4;

optionally, R^1 and R^2; R^5 and R^6; $R^7$and R^8 independently form 4-8 membered alkyl or heterocyclyl rings; and

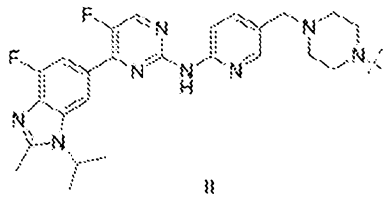
V, W, X, Y, and Z are independently CR^5R^6 or N.

The CDK4/6 ligand can be a CDK4/6 inhibitor, such as, for example, abemaciclib, palbociclib, ribociclib, trilaciclib (G1T28), G1T38, SHR6390, and/or analogs thereof.

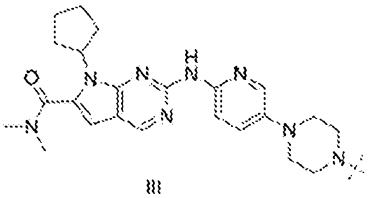
In some aspects, the CDK4/6 ligand can be, e.g.,



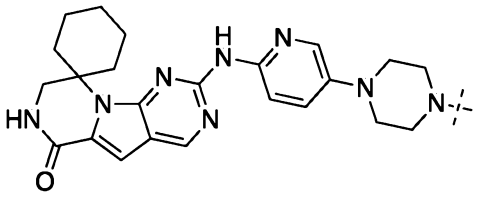
I



II



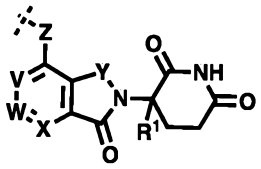
III



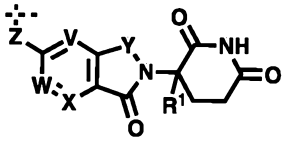
IV.

The CDK4/6 ligand can be bound to CDK4/6.

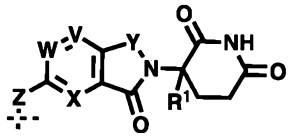
EL includes, but is not limited to:



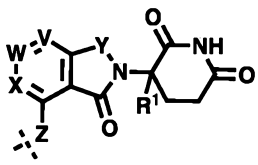
Formula VII,



Formula VIII,



Formula IX,



Formula XI.

wherein V, W, X are independently CR^2 or N;

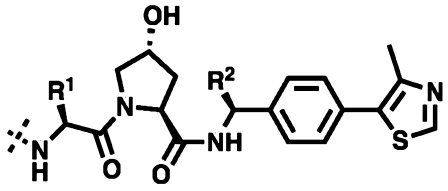
Y is CO or CH_2;

Z is CH_2, NH, or O;

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

R^2 is hydrogen, halogen, or C1-C5 alkyl.

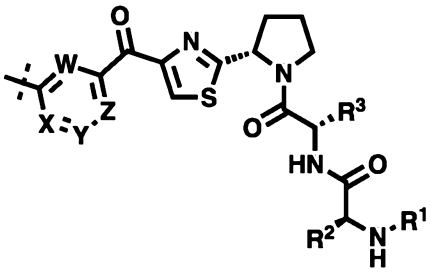
For example, **EL** can include:



Formula XII,

wherein R^1 and R^2 are independently hydrogen, C1-C8 alkyl, C1-C8 alkoxyalkyl, C1-C8 haloalkyl, C1-C8 hydroxyalkyl, C3-C7 cycloalkyl, C3-C7 heterocyclyl, C2-C8 alkenyl, or C2-C8 alkynyl.

For example, **EL** can include:



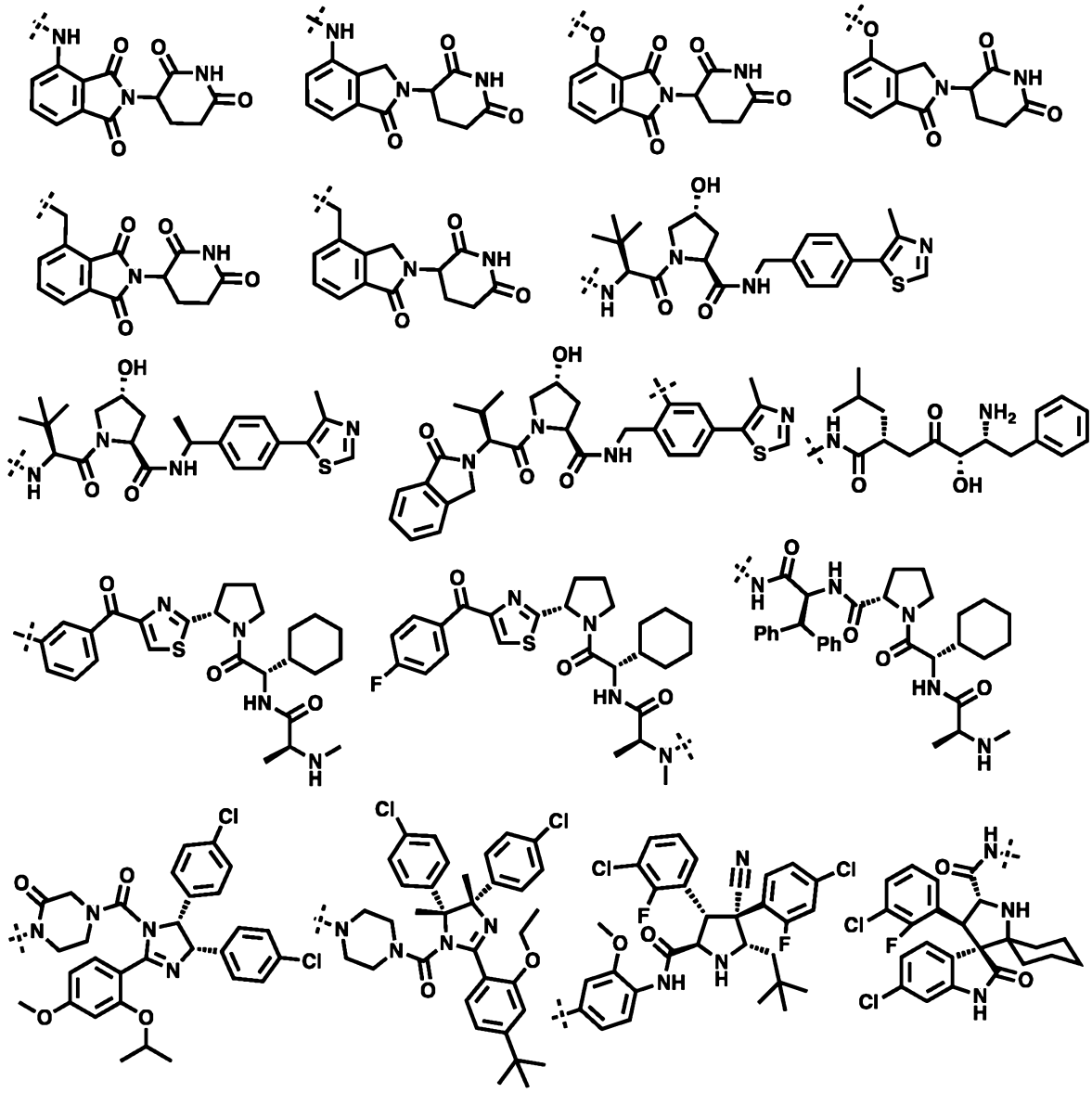
Formula XIII,

wherein R^1, R^2, R^3 and R^4 are independently hydrogen, C1-C8 alkyl, C1-C8 alkoxyalkyl, C1-C8 haloalkyl, C1-C8 hydroxyalkyl, C3-C7 cycloalkyl, C3-C7 heterocyclyl, C2-C8 alkenyl, or C2-C8 alkynyl; and

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

In some aspects, the degradation/disruption tag can be, for example, pomalidomide, thalidomide, lenalidomide, VHL-1, adamantane, 1-((4,4,5,5,5-pentafluoropentyl)sulfinyl)nonane, nutlin-3a, RG7112, RG7338, AMG 232, AA-115, bestatin, MV-1, LCL161, and/or analogs thereof.

In some aspects, the degradation/disruption tag can be, e.g.,



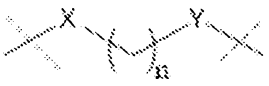
Formulas XIV-XXX (left to right, then top to bottom, starting with Formula XIV at the top left corner and ending with Formula XXX at the bottom right corner).

In some aspects, the degradation/disruption tag can bind to a ubiquitin ligase, such as, for example, an E3 ligase. Exemplary E3 ligases include, for example, a cereblon E3 ligase, a VHL E3 ligase, a MDM2 ligase, a TRIM21 ligase, a TRIM24 ligase, and/or a IAP ligase. In some aspects, the degradation/disruption tag can serve as a hydrophobic group that leads to CDK4 or CDK6 protein misfolding.

In any of the above-described compounds, the CDK4/6 ligand can be 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 embodiments, the linker can be a moiety of:

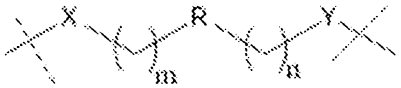


Formula A

wherein X is C=O or CH_2,
Y is C=O or CH_2, and
n is 0-15;

Formula B,

wherein X is C=O or CH_2,
Y is C=O or CH_2,
m is 0-15,
n is 0-6, and
o is 0-15; or



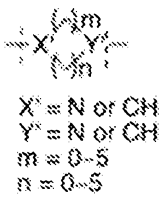
Formula C,

wherein

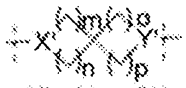
X is C=O or CH_2,
Y is C=O or CH_2,
R is $-CH_2-$, $-CF_2-$, $-CH(C_{1-3}$ alkyl)–, $-C(C_{1-3}$ alkyl)(C_{1-3} alkyl)–, –CH=CH–, $-C(C_{1-3}$ alkyl)=C(C_{1-3} alkyl)–, –C=C–, –O–, –NH–, $-N(C_{1-3}$ alkyl)–, $-C(O)NH-$, $-C(O)N(C_{1-3}$ alkyl)–, a 3-13 membered ring, a 3-13 membered fused ring, a 3-13 membered bridged ring, and/or a 3-13 membered spiro ring,
m is 0-15, and
n is 0-15.

In some embodiments 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 embodiments of Formula C, R has a structure of

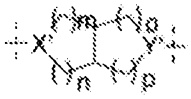


Formula V,



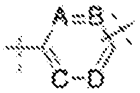
X' = N or CH
Y' = N or CH
m = 0-5
n = 0-5
o = 0-5
p = 0-5

Formula W,



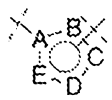
X' = N or CH
Y' = N or CH
m = 0-5
n = 0-5
o = 0-5
p = 0-5

Formula X,



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 Y, 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

Formula Z.

Synthesis and Testing of Bivalent Compounds

The binding affinity of novel synthesized bivalent compounds (i.e., CDK4/6 degraders/disruptors) can be assessed using standard biophysical assays known in the art (e.g., ITC). Cellular assays can then be used to assess the bivalent compound's ability to induce CDK4/6 degradation and inhibit cancer cell proliferation. Besides evaluating bivalent compound's induced changes in the protein expression of CDK4/6, CDK4/6 enzymatic activity can also be assessed. Multiple cycles of designs, syntheses, and biological tests can be performed. Promising bivalent compounds can then be further optimized using methods known

in the art to improve their pharmacokinetic/pharmacodynamic properties (e.g., absorption, distribution, metabolism, and excretion (ADME) properties). Assays suitable for use in any or all of these steps are known in the art, and include, for example, Western blotting, quantitative mass spectrometry (MS) analysis, flow cytometry, enzymatic inhibition, isothermal titration calorimetry (ITC), surface plasmon resonance (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, for example, breast cancer cell lines (e.g., ER+ breast cancer cell lines such as MCF7, T47D, and ZR-75-1) and melanoma cell lines (e.g., A375, SK-MEL-2, SK-MEL-30, and WM1382).

By way of non-limiting example, detailed synthesis protocols are described in the Examples for specific exemplary CDK4/6 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, for example, ^{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, 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 CDK4/6 Degraders/Disruptors

Specific exemplary abemaciclib-, ribociclib-, and palbociclib-based CDK4/6 degraders/disruptors were characterized in various different breast cancer and melanoma cells (Examples 12 and 13, Figs. 10-23). XY019-098, XY019-106, XY028-003, XY019-108, XY028-132, XY028-133, YX26-66, XY028-140, XY028-144, YX039-48, YX039-124, YX039-123, YX039-147, YX039-56, and YX039-65 in particular were found to be especially effective in suppressing both CDK4/6 expression and CDK4/6 activity. This efficacy in suppressing CDK4/6 expression and CDK4/6 activity correlated with efficacy in inhibiting cancer cell proliferation.

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, for example, conventional chemotherapeutic agents known in the art (e.g., gemcitabine HCl and temozolomide). When co-administered, CDK4/6 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 CDK4/6 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 CDK4/6 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 CDK4/6 degraders/disruptors disclosed herein include pure enantiomers, mixtures of enantiomers, pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixtures of diastereoisomeric racemates and the meso-form and pharmaceutically acceptable salts, solvent complexes, morphological forms, or deuterated derivative thereof

In particular, pharmaceutically acceptable salts of the CDK4/6 degraders/disruptors disclosed herein include, for example, 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, for example, 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 CDK4/6 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 CDK4/6 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, for example, 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, for example, 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 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., a CDK4/6 degraders/disruptors) and one or more additional compounds (e.g., one or more additional compounds, drugs, or agents used for the treatment of cancer or any other condition or disease, including conditions or diseases known to be associated with or caused by cancer), both the compound and the additional compound should be present at dosage levels of between about 1 to 100%, and more preferably between about 5 to 95% of the dosage normally administered in a monotherapy regimen. The additional agents can be administered separately, as part of a multiple dose regimen, from the compounds of this invention. Alternatively, those agents can be part of a single dosage form, mixed together with the compounds of this invention in a single composition.

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

Methods of Treatment

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

In some aspects, the present disclosure provides methods for using a composition comprising a CDK4/6 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., a CDK4/6-mediated cancer, e.g., ER+ breast cancer). 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 CDK4/6 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 CDK4/6-mediated cancers that can be treated with CDK4/6 degraders/disruptors include, for example, solid tumors (e.g., breast cancer (e.g., ER+ breast cancer) and prostate cancer), leukemia (e.g., acute lymphoblastic leukemia, acute myeloid leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, hairy cell leukemia, and myeloid leukemia), lymphoma (e.g., Burkitt's lymphoma, cutaneous T-cell lymphoma, diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), Hodgkin's lymphoma, mantel cell lymphoma, and non-Hodgkin's lymphoma (NHL)), adrenocortical cancer, AIDS-related cancer, anal cancer, astrocytoma, basal cell carcinoma, skin cancer (non-melanoma), bile duct cancer, bladder cancer, bone cancer (e.g., fibrosarcoma/osteosarcoma/malignant fibrous histiocytoma), brain tumor (e.g., cerebral astrocytoma, ependymoma, glioma, medulloblastoma, and supratentorial primitive neuroectodermal tumors (PNETs)), brainstem glioma, bronchial adenomas/carcinoids, carcinoid tumors, central nervous system neoplasms, cervical cancer, cholangiocarcinoma, chronic myeloproliferative disorder, colon cancer, endometrial cancer, esophageal cancer, melanoma (e.g., cutaneous or intraocular), gallbladder cancer, gastrointestinal cancer (e.g., colorectal, duodenal, and gastric (stomach) cancer), germ cell tumors, head and neck cancer, hepatocellular (liver) cancer, hypopharyngeal cancer, islet cell carcinoma, Kaposi's sarcoma, kidney (renal cell) cancer, laryngeal cancer, lip and oral cavity cancer, lung cancer (small cell and non-small cell), Merkel cell carcinoma, mesothelioma, endocrine cancer (e.g., multiple endocrine neoplasia syndrome), multiple myeloma/plasma cell neoplasm mycosis fungoides, myelodysplastic syndrome, myeloproliferative disorders, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer,

neuroblastoma, oropharyngeal cancer, ovarian cancer, pancreatic cancer, parathyroid cancer, penile cancer, pituitary cancer, pleuropulmonary blastoma, rectal cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, Ewing sarcoma, soft tissue sarcoma, Sezary syndrome, squamous cell carcinoma, squamous neck cancer, synovial sarcoma, testicular cancer, thymoma, thymic carcinoma, thyroid cancer, transitional cell cancer, trophoblastic tumors, urethral cancer, uterine cancer, fallopian tube cancer, vaginal cancer, visual pathway and hypothalamic glioma, vulvar cancer, Waldenstrom's macroglobulinemia, and Wilms' tumor.

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 one from one or more times per day to one or more times per week; including once every other day. The skilled artisan will appreciate that certain factors 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.

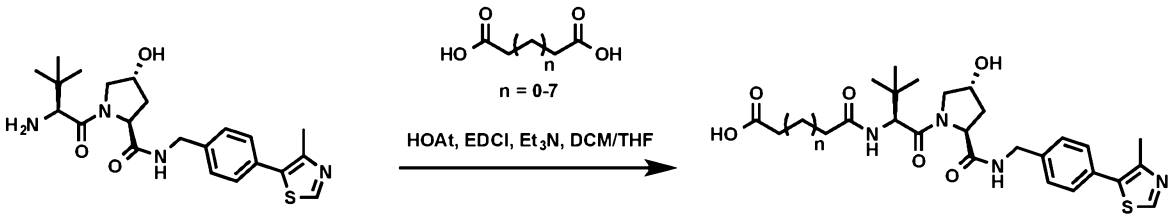
Following administration, the subject can be evaluated to detect, assess, or determine their level of disease. In some instances, treatment can continue until a change (e.g., reduction) in the level of disease in the subject is detected. Upon improvement of a patient's condition (e.g., a change (e.g., 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.

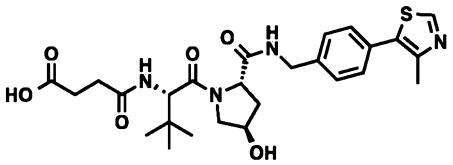
EXAMPLES

Example 1:

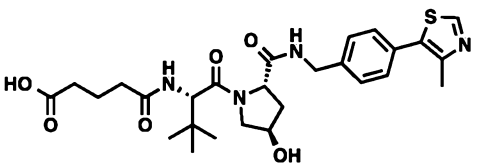
Procedures for the Synthesis of VHL-1 Alkyl Linkers



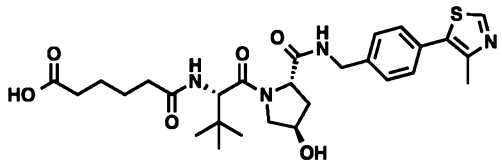
To a solution of diacid (10 mmol) in DCM/THF (1:1, 200 ml) was added VHL-1 (2 mmol), triethylamine (1 ml, 7.1 mmol), HOAt (300 mg, 2.2 mmol), and EDCI (420 mg, 2.2 mmol) sequentially at 0 °C. The resulting solution was stirred for 2 h at 0 °C, before being warmed to room temperature (RT). After stirring overnight at RT, the reaction was quenched with water. After concentration under reduced pressure, the resulting residue was purified by reverse-phase chromatography to yield the desired product.



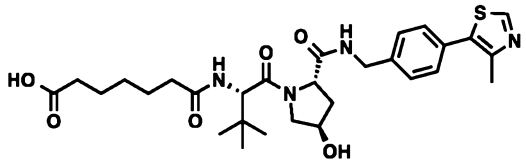
Linker 1: 4-(((S)-1-((2S,4R)-4-Hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl) pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-4-oxobutanoic acid (810 mg, 85%) as white solid. ^{1}H NMR (600 MHz CD_3OD) δ 9.10 (s, 1H), 7.51 (d, J = 7.8 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 4.64 (s, 1H), 4.60-4.49 (m, 3H), 4.39 (d, J = 15.6 Hz, 1H), 3.91 (d, J = 10.8 Hz, 1H), 3.82 (dd, J = 9.6, 3.6 Hz, 1H), 2.67 – 2.55 (m, 4H), 2.52 (s, 3H), 2.25 – 2.22 (m, 1H), 2.12 – 2.07 (m, 1H), 1.06 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{26}H_{35}N_4O_6S$, 531.2272, found 531.2280.



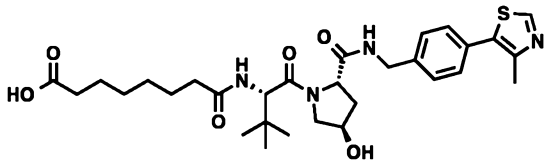
Linker 2: 5-(((S)-1-((2S,4R)-4-Hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl) pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-5-oxopentanoic acid (230 mg, 43%) as white solid. ^{1}H NMR (600 MHz CD_3OD) δ 9.14 (s, 1H), 7.51 (d, J = 9.0 Hz, 2H), 7.46 (d, J = 8.4 Hz, 2H), 4.65 (s, 1H), 4.60 – 4.57 (m, 1H), 4.56 (d, J = 15.6 Hz, 1H), 4.53 – 4.50 (m, 1H), 4.38 (d, J = 15.6 Hz, 1H), 3.94 (d, J = 11.4 Hz, 1H), 3.82 (dd, J = 11.4, 3.6 Hz, 1H), 2.52 (s, 3H), 2.40 – 2.30 (m, 4H), 2.26 – 2.22 (m, 1H), 2.12-2.08 (m, 1H), 1.91 (t, J = 7.8 Hz, 2H), 1.06 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{27}H_{37}N_4O_6S$, 545.2428, found 545.2432.



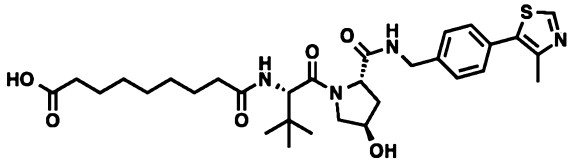
Linker 3: 6-(((S)-1-((2S,4R)-4-Hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl) pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-6-oxohexanoic acid (700 mg, 63%) as white solid. ^{1}H NMR (600 MHz CD_3OD) δ 9.12 (s, 1H), 7.51 (d, J = 9.0 Hz, 2H), 7.46 (d, J = 8.4 Hz, 2H), 4.65 (s, 1H), 4.60 – 4.55 (m, 2H), 4.53 – 4.50 (m, 1H), 4.38 (d, J = 16.8 Hz, 1H), 3.93 (d, J = 10.8 Hz, 1H), 3.82 (dd, J = 11.4, 3.6 Hz, 1H), 2.52 (s, 3H), 2.38 – 2.21 (m, 5H), 2.12-2.08 (m, 1H), 1.71-1.62 (m, 4H), 1.06 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{28}H_{39}N_4O_6S$, 559.2585, found 559.2605.



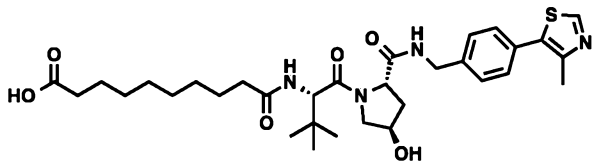
Linker 4: 7-(((S)-1-((2S,4R)-4-Hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl) pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-7-oxoheptanoic acid (810 mg, 79%) as white solid. ^{1}H NMR (600 MHz CD_3OD) δ 8.98 (s, 1H), 7.50 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 9.0 Hz, 2H), 4.65 (s, 1H), 4.60 – 4.49 (m, 3H), 4.38 (d, J = 15.6 Hz, 1H), 3.93 (d, J = 10.8 Hz, 1H), 3.82 (dd, J = 11.4, 3.6 Hz, 1H), 2.51 (s, 3H), 2.35 – 2.22 (m, 5H), 2.13 – 2.08 (m, 1H), 1.68 – 1.59 (m, 4H),1.42 – 1.34 (m, 2H), 1.06 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{29}H_{41}N_4O_6S$, 573.2741, found 573.2754.



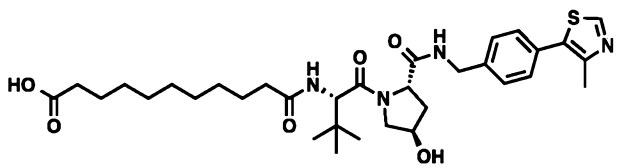
Linker 5: 8-(((S)-1-((2S,4R)-4-Hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl) pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-8-oxooctanoic acid (980 mg, 78%) as white solid. ^{1}H NMR (600 MHz, CD_3OD) δ 8.94 (s, 1H), 7.47 (d, J = 8.1 Hz, 2H), 7.42 (d, J = 8.2 Hz, 2H), 4.63 (s, 1H), 4.59 – 4.47 (m, 3H), 4.35 (d, J = 15.4 Hz, 1H), 3.90 (d, J = 11.0 Hz, 1H), 3.80 (dd, J = 10.9, 3.9 Hz, 1H), 2.48 (s, 3H), 2.32 – 2.17 (m, 5H), 2.08 (ddd, J = 13.3, 9.1, 4.5 Hz, 1H), 1.67 – 1.55 (m, 4H), 1.40 – 1.28 (m, 4H), 1.03 (s, 9H). HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{30}H_{43}N_4O_6S$, 587.2898; found: 587.2903.



Linker 6: 9-(((S)-1-((2S,4R)-4-Hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl) pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-9-oxononanoic acid (750 mg, 66%) as white solid. ^{1}H NMR (600 MHz CD_3OD) δ 9.09 (s, 1H), 7.51 (d, J = 9.0 Hz, 2H), 7.46 (d, J = 8.4 Hz, 2H), 4.66 (s, 1H), 4.61 – 4.50 (m, 3H), 4.38 (d, J = 15.6 Hz,1 1H), 3.93 (d, J = 10.8 Hz, 1H), 3.82 (dd, J = 11.4, 3.6 Hz, 1H), 2.52 (s, 3H), 2.36 – 2.22 (m, 5H), 2.12 – 2.07 (m, 1H), 1.68 – 1.59 (m, 4H),1.40 – 1.34 (m, 8H), 1.06 (s, 9H); HPLC 98%; t_R = 4.24 min; HRMS(TOF) calculated for $C_{31}H_{45}N_4O_6S$ $[M+H]^+$, 601.3054, found 601.3064.



Linker 7: 10-(((S)-1-((2S,4R)-4-Hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl) pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-10-oxodecanoic acid (900 mg, 73%) as white solid. ^{1}H NMR (600 MHz CD_3OD) δ 8.98 (s, 1H), 7.50 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 9.0 Hz, 2H), 4.66 (s, 1H), 4.61 – 4.50 (m, 3H), 4.38 (d, J = 14.4 Hz,1 1H), 3.93 (d, J = 10.8 Hz, 1H), 3.83 (dd, J = 11.4, 3.6 Hz, 1H), 2.51 (s, 3H), 2.35 – 2.22 (m, 5H), 2.13 – 2.08 (m, 1H), 1.66 – 1.58 (m, 4H),1.38 – 1.32 (m, 10H), 1.06 (s, 9H). HRMS(TOF) calculated for $C_{32}H_{47}N_4O_6S$ $[M+H]^+$, 615.3211, found 615.3224.

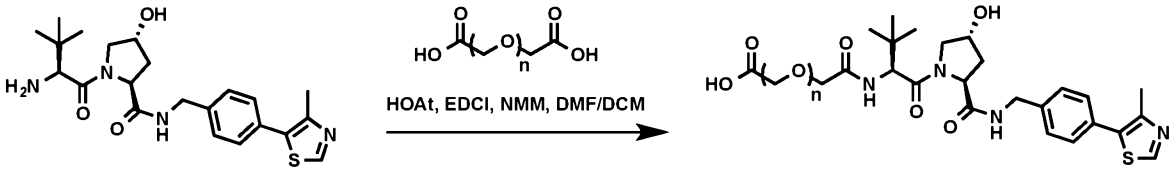


Linker 8: 11-(((S)-1-((2S,4R)-4-Hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl) pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-11-oxoundecanoic acid (930 mg,

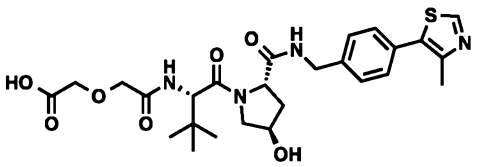
78%) as white solid. ^{1}H NMR (600 MHz CD_3OD) δ 8.95 (s, 1H), 7.49 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 7.8 Hz, 2H), 4.66 (s, 1H), 4.61 – 4.50 (m, 3H), 4.38 (d, J = 15.6 Hz, 1H), 3.93 (d, J = 9.6 Hz, 1H), 3.82 (dd, J = 11.4, 3.6 Hz, 1H), 2.50 (s, 3H), 2.35 – 2.21 (m, 5H), 2.12 – 2.07 (m, 1H), 1.66 – 1.57 (m, 4H),1.37 – 1.29 (m, 12H), 1.06 (s, 9H). HRMS (ESI-TOF) calculated for $C_{33}H_{49}N_4O_6S$, 629.3367, found 629.3368.

Example 2:

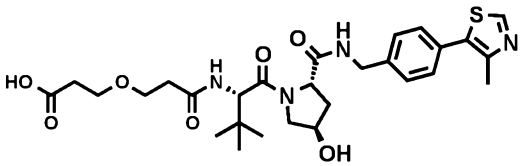
Procedures for the synthesis of VHL-1 PEG linkers



To a solution of diacid (4 mmol) in DMF (10 ml) and DCM (250 ml) was added NMM (10 mmol), VHL-1 (2 mmol), HOAt (2.4 mmol), and EDCI (2.4 mmol) at 0 °C. The resulting reaction solution was stirred at 0 °C for 6 h and then at RT overnight. The progress of the reaction was monitored by LC/MS. After VHL-1 was totally consumed, the reaction was concentrated and the resulting residue was purified by reverse-phase chromatography to yield the product.

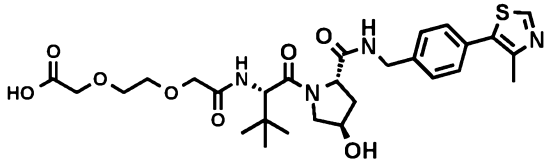


Linker 9: 2-(2-(((*S*)-1-((2*S*,4*R*)-4-Hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl) pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-2-oxoethoxy)acetic acid (810 mg, 69%) as white soild. ^{1}H NMR (600 MHz, CD_3OD) δ 8.97 (s, 1H), 7.47 (d, J = 8.2 Hz, 2H), 7.43 (d, J = 8.1 Hz, 2H), 4.69 (s, 1H), 4.60 – 4.47 (m, 3H), 4.36 (d, J = 15.5 Hz, 1H), 4.27 – 4.17 (m, 2H), 4.16 – 4.07 (m, 2H), 3.89 (d, J = 11.0 Hz, 1H), 3.81 (dd, J = 11.0, 3.8 Hz, 1H), 2.48 (s, 3H), 2.22 (dd, J = 13.1, 7.6 Hz, 1H), 2.08 (ddd, J = 13.3, 9.2, 4.5 Hz, 1H), 1.05 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{26}H_{35}N_4O_7S$, 547.2221; found: 547.2230.

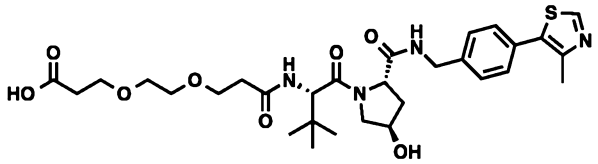


Linker 10: 3-(3-(((*S*)-1-((2*S*,4*R*)-4-Hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl) pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-3-

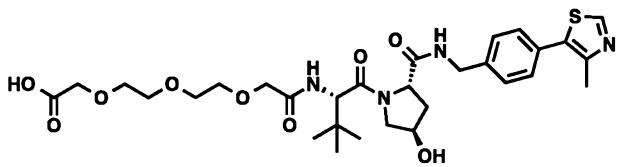
oxopropoxy)propanoic acid (450 mg, 63%) as white solid. ^{1}H NMR (600 MHz, CD_3OD) δ 9.00 (s, 1H), 7.45 (d, J = 22.1 Hz, 4H), 4.64 (s, 1H), 4.61 – 4.44 (m, 3H), 4.36 (d, J = 15.4 Hz, 1H), 3.84 (dd, J = 57.3, 10.5 Hz, 2H), 3.75 – 3.56 (m, 4H), 2.60 – 2.39 (m, 7H), 2.24 – 2.17 (m, 1H), 2.11 – 2.03 (m, 1H), 1.03 (s, 9H). HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{28}H_{39}N_4O_7S$, 575.2534; found: 575.2543.



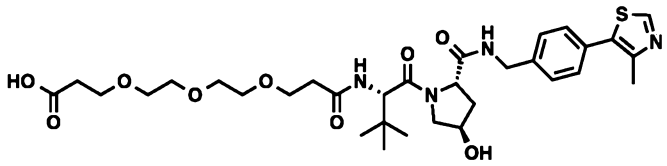
Linker 11: 2-(2-(2-(((*S*)-1-((2*S*,4*R*)-4-Hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl) carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-2-oxoethoxy)ethoxy)acetic acid (680 mg, 54%) as white solid. ^{1}H NMR (600 MHz, CD_3OD) δ 9.05 (s, 1H), 7.48 (d, J = 8.1 Hz, 2H), 7.44 (d, J = 8.2 Hz, 2H), 4.69 (s, 1H), 4.56 (dd, J = 18.6, 12.1 Hz, 2H), 4.50 (s, 1H), 4.36 (d, J = 15.5 Hz, 1H), 4.21 (d, J = 16.8 Hz, 1H), 4.13 (d, J = 16.9 Hz, 1H), 4.08 (d, J = 15.6 Hz, 1H), 4.04 (d, J = 15.7 Hz, 1H), 3.88 (d, J = 11.0 Hz, 1H), 3.83 – 3.69 (m, 5H), 2.49 (s, 3H), 2.25 – 2.19 (m, 1H), 2.08 (ddd, J = 13.3, 9.2, 4.4 Hz, 1H), 1.04 (s, 9H). HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{28}H_{39}N_4O_8S$, 591.2483; found: 591.2477.



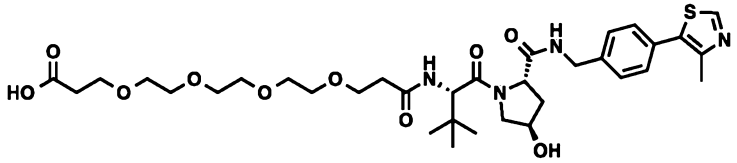
Linker 12: 3-(2-(3-(((*S*)-1-((2*S*,4*R*)-4-Hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl) carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-3-oxopropoxy)ethoxy) propanoic acid (680 mg, 64%) as white solid. ^{1}H NMR (600 MHz, CD_3OD) δ 8.98 (d, J = 20.1 Hz, 1H), 7.48 (d, J = 8.0 Hz, 2H), 7.43 (d, J = 8.1 Hz, 2H), 4.64 (s, 1H), 4.59 – 4.51 (m, 2H), 4.49 (s, 1H), 4.35 (d, J = 15.5 Hz, 1H), 3.89 (d, J = 11.0 Hz, 1H), 3.80 (dd, J = 10.9, 3.8 Hz, 1H), 3.76 – 3.67 (m, 4H), 3.63 – 3.55 (m, 4H), 2.60 – 2.43 (m, 7H), 2.21 (dd, J = 13.1, 7.6 Hz, 1H), 2.08 (ddd, J = 13.2, 9.1, 4.5 Hz, 1H), 1.04 (s, 9H). HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{30}H_{43}N_4O_8S$, 619.2796; found: 619.2800.



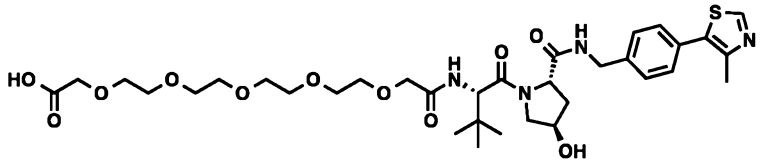
Linker 13: (*S*)-13-((2*S*,4*R*)-4-Hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl) pyrrolidine-1-carbonyl)-14,14-dimethyl-11-oxo-3,6,9-trioxa-12-azapentadecanoic acid (880 mg, 54%) as white solid. ^{1}H NMR (600 MHz, CD_3OD) δ 9.05 (s, 1H), 7.48 (d, *J* = 8.2 Hz, 2H), 7.44 (d, *J* = 8.3 Hz, 2H), 4.69 (s, 1H), 4.60 – 4.51 (m, 2H), 4.50 (s, 1H), 4.36 (d, *J* = 15.5 Hz, 1H), 4.10 (s, 1H), 4.07 (d, *J* = 15.6 Hz, 1H), 4.03 (d, *J* = 15.6 Hz, 1H), 3.87 (d, *J* = 11.0 Hz, 1H), 3.80 (dd, *J* = 11.0, 3.8 Hz, 1H), 3.76 – 3.64 (m, 9H), 2.50 (s, 3H), 2.22 (dd, *J* = 13.1, 7.6 Hz, 1H), 2.08 (ddd, *J* = 13.3, 9.2, 4.4 Hz, 1H), 1.04 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{30}H_{43}N_4O_9S$, 635.2745; found: 635.2751.



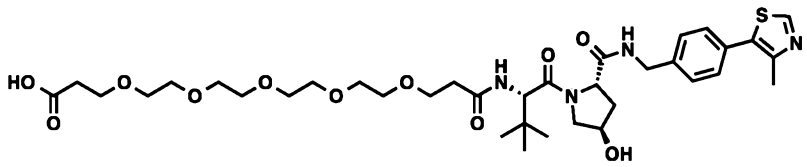
Linker 14: (*S*)-15-((2*S*,4*R*)-4-Hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl) pyrrolidine-1-carbonyl)-16,16-dimethyl-13-oxo-4,7,10-trioxa-14-azaheptadecanoic acid (677 mg, 57%) as white solid. ^{1}H NMR (600 MHz, CD_3OD) δ 8.95 (s, 1H), 7.47 (d, *J* = 8.1 Hz, 2H), 7.42 (d, *J* = 8.1 Hz, 2H), 4.65 (s, 1H), 4.59 – 4.51 (m, 2H), 4.49 (s, 1H), 4.35 (d, *J* = 15.5 Hz, 1H), 3.89 (d, *J* = 11.1 Hz, 1H), 3.80 (dd, *J* = 10.9, 3.9 Hz, 1H), 3.76 – 3.67 (m, 4H), 3.66 – 3.54 (m, 8H), 2.60 – 2.50 (m, 3H), 2.50 – 2.43 (m, 4H), 2.21 (dd, *J* = 13.1, 7.6 Hz, 1H), 2.08 (ddd, *J* = 13.3, 9.1, 4.5 Hz, 1H), 1.04 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{32}H_{47}N_4O_9S$, 663.3058; found: 663.3059.



Linker 15: (*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-azaicosanoic acid (590 mg, 65%) as white solid. ^{1}H NMR (600 MHz, CD_3OD) δ 8.99 (s, 1H), 7.48 (d, *J* = 8.1 Hz, 2H), 7.42 (d, *J* = 8.2 Hz, 2H), 4.65 (s, 1H), 4.59 – 4.51 (m, 2H), 4.49 (s, 1H), 4.35 (d, *J* = 15.5 Hz, 1H), 3.89 (d, *J* = 11.0 Hz, 1H), 3.80 (dd, *J* = 10.9, 3.8 Hz, 1H), 3.77 – 3.67 (m, 4H), 3.67 – 3.54 (m, 12H), 2.61 – 2.43 (m, 7H), 2.21 (dd, *J* = 13.0, 7.6 Hz, 1H), 2.08 (ddd, *J* = 13.2, 9.1, 4.4 Hz, 1H), 1.04 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{34}H_{51}N_4O_{10}S$, 707.3320; found: 707.3321.



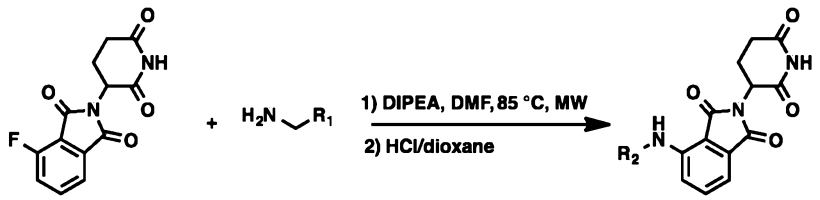
Linker 16: (*S*)-19-((2*S*,4*R*)-4-Hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl) pyrrolidine-1-carbonyl)-20,20-dimethyl-17-oxo-3,6,9,12,15-pentaoxa-18-azahenicosanoic acid (496 mg, 54%) as white solid. ^{1}H NMR (600 MHz, CD_3OD) δ 8.89 (s, 1H), 7.47 (d, *J* = 8.1 Hz, 2H), 7.42 (d, *J* = 8.1 Hz, 2H), 4.69 (s, 1H), 4.59 – 4.46 (m, 3H), 4.36 (d, *J* = 15.5 Hz, 1H), 4.16 – 4.00 (m, 4H), 3.87 (d, *J* = 11.0 Hz, 1H), 3.80 (dd, *J* = 11.0, 3.7 Hz, 1H), 3.76 – 3.53 (m, 16H), 2.48 (s, 3H), 2.22 (dd, *J* = 13.1, 7.6 Hz, 1H), 2.08 (ddd, *J* = 13.3, 9.2, 4.4 Hz, 1H), 1.04 (s, 7H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{34}H_{51}N_4O_{11}S$, 723.3270; found: 723.3269.



Linker 17: (*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-azatricosanoic acid (420 mg, 42%) as white solid.^{1}H NMR (600 MHz, CD_3OD) δ 8.89 (s, 1H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.42 (d, *J* = 8.1 Hz, 2H), 4.65 (s, 1H), 4.59 – 4.51 (m, 2H), 4.49 (s, 1H), 4.35 (d, *J* = 15.5 Hz, 1H), 3.89 (d, *J* = 11.0 Hz, 1H), 3.80 (dd, *J* = 10.9, 3.8 Hz, 1H), 3.77 – 3.67 (m, 4H), 3.67 – 3.51 (m, 16H), 2.61 – 2.42 (m, 7H), 2.24 – 2.18 (m, 1H), 2.08 (ddd, *J* = 13.2, 9.1, 4.4 Hz, 1H), 1.02 (d, *J* = 14.3 Hz, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{36}H_{55}N_4O_{11}S$, 751.3583; found: 751.3589.

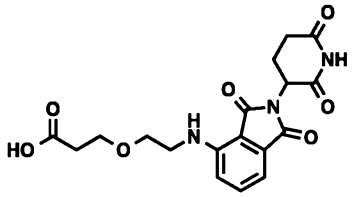
Example 3:

Procedures for the synthesis of pomalidomide linkers

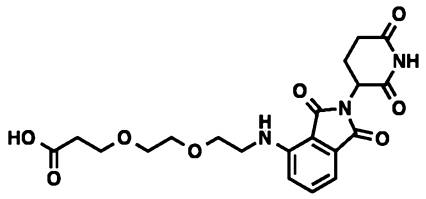


A solution of pomalidomide analogue (1 eq.), amine (1 eq.), and *N*,*N*-diisopropylethylamine (1.5 eq.) in DMF (2.0 ml per mmol of pomalidamide) was heated to 85 °C in a microwave reactor for 40 min. After cooling to RT, the reaction was quenched with water and extracted with ethyl acetate (3X). The combined organic phase was dried over anhydrous sodium sulfate

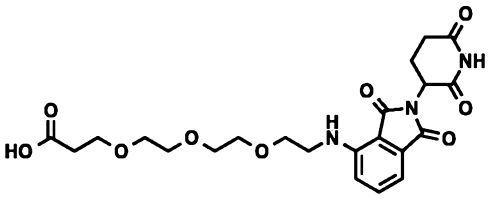
and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (eluted with hexanes/EtOAc: 0-100%) to give the desired *t*-Bu ester intermediate as oil. This intermediate was treated with a solution of hydrogen chloride in dioxane (4 M, 5 ml per mmol of pomalidamide) for overnight. After concentration under reduced pressure, the desired acid product was obtained as yellow oil.



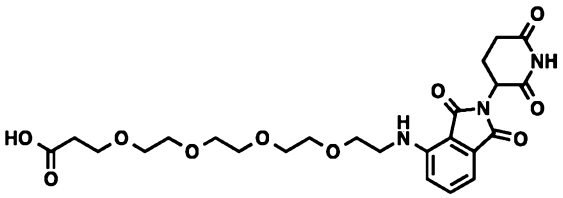
Linker 18: 3-(2-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy) propanoic acid. *tert*-Butyl 3-(2-aminoethoxy)propanoate (1.0 g, 5.3 mmol) was used to prepare the title compound (500 mg, 24%) according to the above procedures. ^{1}H NMR (600 MHz, CD_3OD) δ 7.54 (dd, *J* = 8.3, 7.0, 1.2 Hz, 1H), 7.09 (d, 1H), 7.04 (d, *J* = 7.0, 1.1 Hz, 1H), 5.05 (dd, *J* = 12.5, 5.4, 1.2 Hz, 1H), 3.75 (t, *J* = 6.2, 1.2 Hz, 2H), 3.65-3.69 (m, 2H), 3.45-3.49 (m, 2H), 2.88 – 2.82 (m, 1H), 2.76 – 2.70 (m, 2H), 2.56 (t, *J* = 6.2, 1.2 Hz, 2H), 2.10 (ddt, *J* = 14.9, 7.6, 3.7, 1.6 Hz, 1H). MS (ESI) *m/z* 390.2 $[M+H]^+$.



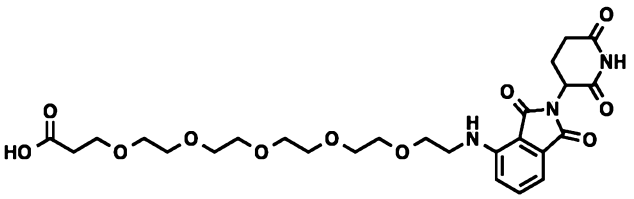
Linker 19: 3-(2-(2-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy) ethoxy)-propanoic acid. *tert*-Butyl 3-(2-(2-aminoethoxy)ethoxy)propanoate (0.70 g, 3.0 mmol) was used to prepare *tert*-butyl 3-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-ethoxy)ethoxy)propanoate (575 mg, 39%) according to the above procedures. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.53 – 7.45 (m, 1H), 7.10 (d, *J* = 7.1 Hz, 1H), 6.92 (d, *J* = 8.5 Hz, 1H), 6.49 (t, *J* = 5.6 Hz, 1H), 4.91 (dd, *J* = 12.4, 5.3 Hz, 1H), 3.76 – 3.69 (m, 4H), 3.67 – 3.60 (m, 4H), 3.46 (q, *J* = 5.5 Hz, 2H), 2.89 (dt, *J* = 16.8, 3.2 Hz, 1H), 2.84 – 2.69 (m, 2H), 2.51 (t, *J* = 6.6 Hz, 2H), 2.16 – 2.08 (m, 1H), 1.44 (s, 9H). MS (ESI) m/z 490.2 $[M+H]^+$. The *t*-Bu ester intermediate was dissolved in formic acid (10 ml) and the resulting solution was stirred at RT overnight. After removal of the solvent under reduced pressure, the tittle compound (512 mg, 100%) was obtained and used for the following reactions without further purification.



Linker 20: 3-(2-(2-(2-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy) ethoxy)ethoxy)propanoic acid. *tert*-Butyl 3-(2-(2-(2-aminoethoxy)ethoxy)ethoxy)propanoate (1.0 g, 3.6 mmol) was used to prepare the title compound (240 mg, 10%) according to the above procedures. ^{1}H NMR (600 MHz, CD_3OD) δ 7.55 (dd, *J* = 8.4, 7.2 Hz, 1H), 7.10 (d, *J* = 8.6 Hz, 1H), 7.05 (d, *J* = 7.1 Hz, 1H), 5.05 (dd, *J* = 12.4, 5.4 Hz, 1H), 3.71 (dt, *J* = 9.4, 5.7 Hz, 4H), 3.66 – 3.63 (m, 4H), 3.62 (dd, *J* = 6.0, 3.5 Hz, 2H), 3.58 (dd, *J* = 6.1, 3.5 Hz, 2H), 3.50 (t, *J* = 5.3 Hz, 2H), 2.86 (ddd, *J* = 19.1, 14.1, 5.3 Hz, 1H), 2.77 – 2.66 (m, 2H), 2.52 (t, *J* = 6.3 Hz, 2H), 2.11 (ddt, *J* = 10.3, 5.0 Hz, 1H). MS (ESI) *m/z* 478.3 $[M+H]^+$.

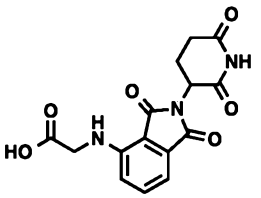


Linker 21: 1-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12-tetraoxapentadecan-15-oic acid. *tert*-Butyl 1-amino-3,6,9,12-tetraoxapentadecan-15-oate (0.96 g, 3.0 mmol) was used to prepare the *t*-Bu ester intermediate according to the general procedures. The *t*-Bu ester intermediate was dissolved in formic acid (10 ml) and the resulting solution was stirred at RT overnight. After removal of the solvent under reduced pressure, the title compound (950 mg, 61%) was obtained and used for the following reactions without further purification. ^{1}H NMR (600 MHz, CD_3OD) δ 7.55 (t, *J* = 7.8 Hz, 1H), 7.10 (d, *J* = 8.5 Hz, 1H), 7.06 (d, *J* = 7.0 Hz, 1H), 5.05 (dd, *J* = 12.6, 5.3 Hz, 1H), 3.75 – 3.68 (m, 4H), 3.68 – 3.55 (m, 12H), 3.50 (t, *J* = 4.9 Hz, 2H), 2.90 – 2.81 (m, 1H), 2.78 – 2.66 (m, 2H), 2.52 (t, *J* = 6.0 Hz, 2H), 2.14 – 2.07 (m, 1H). MS (ESI) m/z 522.2 $[M+H]^+$.

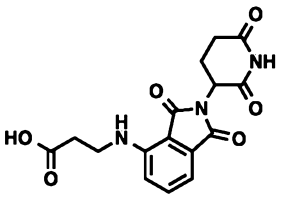


Linker 22: 1-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12,15-pentaoxaoctadecan-18-oic acid. *tert*-Butyl 1-amino-3,6,9,12,15-pentaoxaoctadecan-18-oate

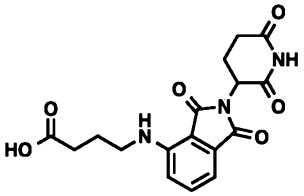
(1.10 g, 3.0 mmol) was used to prepare *tert*-butyl 1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12,15-pentaoxaoctadecan-18-oate (1.35 g, 72%) according to the above procedures. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.48 (dd, J = 8.5, 7.1 Hz, 1H), 7.10 (d, J = 7.1 Hz, 1H), 6.91 (d, J = 8.6 Hz, 1H), 6.49 (t, J = 5.7 Hz, 1H), 4.91 (dd, J = 12.4, 5.3 Hz, 1H), 3.74 – 3.68 (m, 4H), 3.68 – 3.63 (m, 12H), 3.63 – 3.58 (m, 4H), 3.46 (q, J = 5.6 Hz, 2H), 2.92 – 2.85 (m, 1H), 2.83 – 2.68 (m, 2H), 2.49 (t, J = 6.6 Hz, 2H), 2.15 – 2.08 (m, 1H), 1.43 (s, 9H). MS (ESI) m/z 622.2 $[M+H]^+$. The *t*-Bu ester intermediate was dissolved in formic acid (10 ml) and the resulting solution was stirred at RT overnight. After removal of the solvent under reduced pressure, the tittle compound (1.23 g, 100%) was obtained and used for the following reactions without further purification.



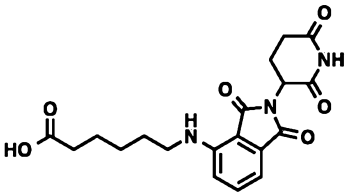
Linker 23: (2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)glycine. *tert*-Butyl glycinate (838 mg, 5.0 mmol) was used to prepare the title compound (240 mg, 14%) according to the general procedures. ^{1}H NMR (600 MHz, CD_3OD) δ 7.57 (dd, J = 8.5, 7.1 Hz, 1H), 7.11 (d, J = 7.1 Hz, 1H), 6.95 (d, J = 8.5 Hz, 1H), 5.07 (dd, J = 12.6, 5.5 Hz, 1H), 4.12 (s, 2H), 2.86 (ddd, J = 18.0, 14.4, 5.4 Hz, 1H), 2.74 – 2.67 (m, 2H), 2.15 – 2.08 (m, 1H). MS (ESI) *m/z* 332.1 $[M+H]^+$.



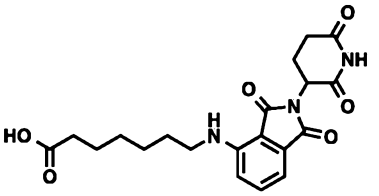
Linker 24: 3-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propanoic acid. *tert*-Butyl 3-aminopropanoate HCl salt (1.0 g, 5.97 mmol) was used to prepare the title compound (700 mg, 4%) according to the above procedures. ^{1}H NMR (600 MHz, CD_3OD) δ 7.57 (dd, J = 8.6, 7.1 Hz, 1H), 7.11 (d, J = 8.6 Hz, 1H), 7.06 (d, J = 7.1 Hz, 1H), 5.05 (dd, J = 12.6, 5.5 Hz, 1H), 3.62 (t, J = 6.5 Hz, 2H), 2.88 – 2.82 (m, 1H), 2.76 – 2.69 (m, 2H), 2.64 (t, J = 6.5 Hz, 2H), 2.13 – 2.07 (m, 1H). MS (ESI) *m/z* 346.2 $[M+H]^+$.



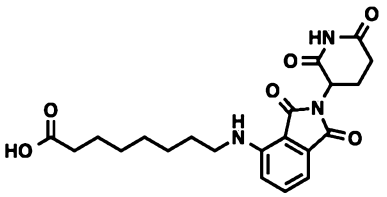
Linker 25: 4-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)butanoic acid. *tert*-Butyl 4-aminobutanoate (1.0 g, 6.2 mmol) was used to prepare the title compound (550 mg, 25%) according to the above procedures. ^{1}H NMR (600 MHz, CD_3OD) δ 7.55 (dd, J = 8.6, 7.1 Hz, 1H), 7.10 (d, J = 8.5 Hz, 1H), 7.04 (d, J = 7.1 Hz, 1H), 5.05 (dd, J = 12.4, 5.5 Hz, 1H), 3.39 (t, J = 7.2 Hz, 2H), 2.85 – 2.82 (m, 1H), 2.76 – 2.69 (m, 2H), 2.42 (t, J = 7.1 Hz, 2H), 2.10 (tq, J = 8.0, 3.8 Hz, 1H), 1.94 (dp, J = 14.3, 7.0 Hz, 2H). MS (ESI) *m/z* 360.1 $[M+H]^+$.



Linker 26: 6-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)hexanoic acid. *tert*-Butyl 6-aminohexanoate (1.0 g, 4.47 mmol) was used to prepare the title compound (460 mg, 27%) according to the above procedures. ^{1}H NMR (600 MHz, CD_3OD) δ 7.54 (dd, J = 8.6, 7.1 Hz, 1H), 7.03 (dd, J = 7.8, 3.8 Hz, 2H), 5.05 (dd, J = 12.5, 5.4 Hz, 1H), 3.33 (t, J = 7.1 Hz, 2H), 2.88 – 2.82 (m, 1H), 2.75 – 2.67 (m, 2H), 2.31 (t, J = 7.4 Hz, 2H), 2.10 (tdd, J = 10.1, 5.3, 3.1 Hz, 1H), 1.70 – 1.64 (m, 4H), 1.46 (dddd, J = 13.0, 8.9, 7.1, 4.2 Hz, 2H). MS (ESI) *m/z* 388.1 $[M+H]^+$.



Linker 27: 7-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)heptanoic acid. *tert*-Butyl 7-aminoheptanoate (1.0 g, 4.96 mmol) was used to prepare the title compound (500 mg, 25%) according to the above procedures. ^{1}H NMR (600 MHz, CD_3OD) δ 7.54 (dd, 1H), 7.03 (dd, J = 7.8, 3.7 Hz, 2H), 5.05 (dd, J = 12.5, 5.5 Hz, 1H), 3.30-3.33 (m, 2H), 2.90 – 2.79 (m, 1H), 2.77 – 2.68 (m, 2H), 2.29 (t, J = 7.4 Hz, 2H), 2.13 – 2.07 (m, 1H), 1.68 – 1.61 (m, 4H), 1.46 – 1.40 (m, 4H). MS (ESI) *m/z* 402.3 $[M+H]^+$.

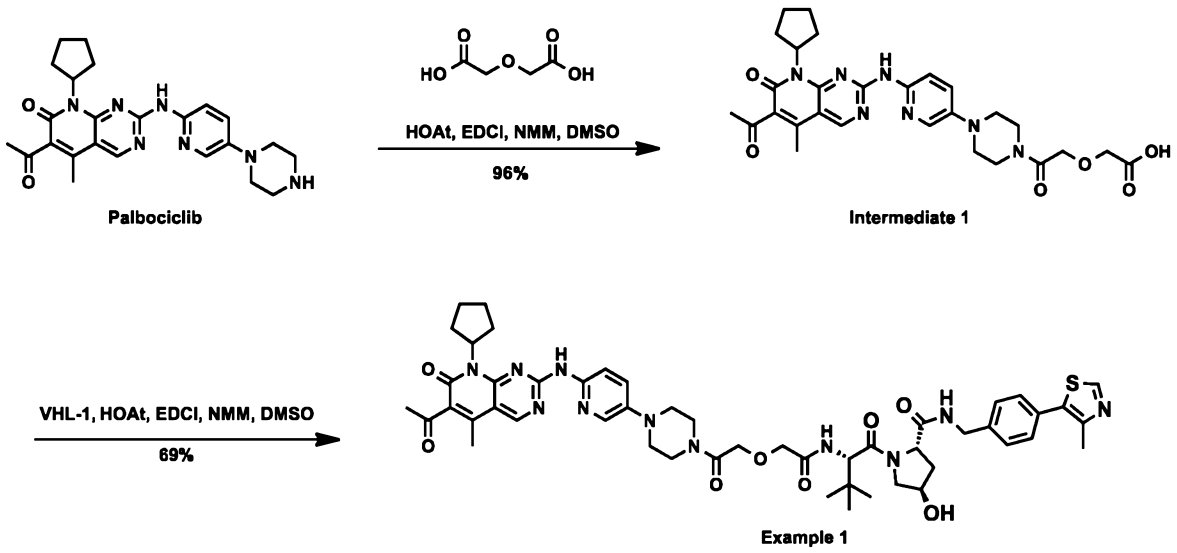


Linker 28: 8-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)octanoic acid. *tert*-Butyl 8-aminooctanoate (1.0 g, 4.6 mmol) was used to prepare the title compound (620 mg, 32%) according to the above procedures. ^{1}H NMR (600 MHz, CD_3OD) δ 7.53 (dd, J = 8.6, 7.0, 1.5 Hz, 1H), 7.08 – 6.93 (m, 2H), 5.05 (dd, J = 12.5, 5.5, 1.5 Hz, 1H), 3.31 (t, 2H), 2.90 – 2.79 (m, 1H), 2.75 – 2.66 (m, 2H), 2.28 (t, J = 7.5, 1.5 Hz, 2H), 2.13 – 2.07 (m, 1H), 1.66 – 1.51 (m, 4H), 1.43 – 1.33 (m, 6H). MS (ESI) m/z 416.4[M+H]$^+$.

Example 4:

Procedures for the synthesis of bivalent compounds

Scheme 1: Synthesis of example 1

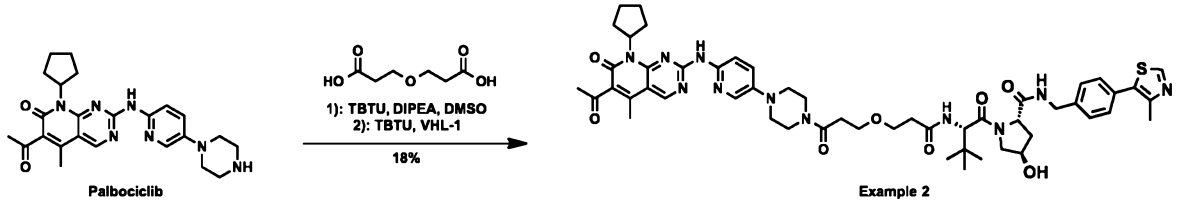


2-(2-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-2-oxoethoxy)acetic acid (Intermediate 1). To a solution of palbociclib (25 mg, 0.0559 mmol) in DMSO (1 ml) and DCM (10 ml) were added NMM (34 mg, 0.335 mmol), 2,2'-oxydiacetic acid (18 mg, 0.135 mmol), HOAt (20 mg, 0.134 mmol), and EDCI (28 mg, 0.134 mmol). The mixture was allowed to stir at room temperature overnight. After palbociclib was consumed, the reaction was concentrated under reduced pressure. The resulting residue was purified by prep-HPLC to yield the product (30 mg, 96%). ^{1}H NMR (600 MHz, CD_3OD) δ 9.10 (s, 1H), 8.20 (d, J = 9.5 Hz, 1H), 7.88 (s, 1H), 7.55 (d, J

= 9.5 Hz, 1H), 6.00 (p, *J* = 8.9 Hz, 1H), 4.41 (s, 2H), 4.21 (s, 2H), 3.85 – 3.70 (m, 4H), 3.39 – 3.26 (m, 4H), 2.49 (s, 3H), 2.43 (s, 3H), 2.35 – 2.25 (m, 2H), 2.13 – 2.04 (m, 2H), 1.95 – 1.85 (m, 2H), 1.74 – 1.64 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{28}H_{34}N_7O_6$, 564.2565; found: 564.2560.

(2*S*,4*R*)-1-((*S*)-2-(2-(2-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-2-oxoethoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (compound Example 1). To a solution of intermediate **1** (30 mg, 0.0553 mmol) in DMSO (1 mL) were added NMM (27 mg, 0.266 mmol), VHL-1 (30 mg, 0.0639 mmol), HOAt (11 mg, 0.0799 mmol), and EDCI (15 mg, 0.0799 mmol). The mixture was allowed to stir at room temperature overnight. After VHL-1 was consumed, the reaction was concentrated under reduced pressure. The resulting residue was purified by prep-HPLC to yield the product (36 mg, 69%) as yellow solid. ^{1}H NMR (600 MHz, CD_3OD) δ 9.07 (s, 1H), 9.03 (s, 1H), 8.17 (dd, *J* = 2.9, 9.6 Hz, 1H), 7.86 (d, *J* = 2.9 Hz, 1H), 7.52 (d, *J* = 9.6 Hz, 1H), 7.46 – 7.42 (m, 2H), 7.38 (d, *J* = 8.3 Hz, 2H), 5.99 (p, *J* = 8.9 Hz, 1H), 4.69 (s, 1H), 4.62 – 4.30 (m, 6H), 4.17 (d, *J* = 15.1 Hz, 1H), 4.10 (d, *J* = 15.0 Hz, 1H), 3.90 (d, *J* = 10.9 Hz, 1H), 3.85 – 3.74 (m, 3H), 3.72 – 3.62 (m, 2H), 3.37 – 3.25 (m, 4H), 2.49 (s, 3H), 2.47 (s, 3H), 2.41 (s, 3H), 2.35 – 2.21 (m, 3H), 2.14 – 2.04 (m, 3H), 1.94 – 1.85 (m, 2H), 1.75 – 1.63 (m, 2H), 1.06 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{50}H_{62}N_{11}O_8S$, 976.4498; found: 976.4492.

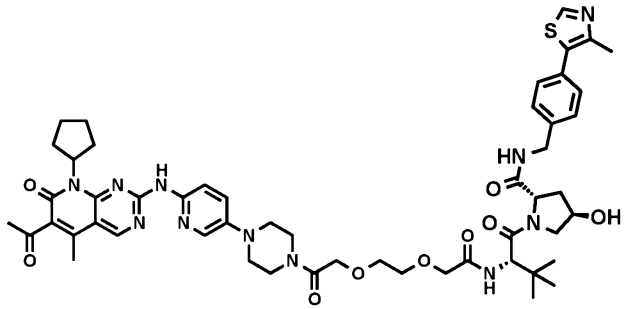
Scheme 2: Synthesis of example 2



(2*S*,4*R*)-1-((*S*)-2-(3-(3-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-3-oxopropoxy)propanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (compound Example 2). To a solution of palbociclib (53 mg, 0.119 mmol) in DMSO (2 ml) were added DIPEA (76 mg, 0.594 mmol), 3,3'-oxydipropionic acid (25 mg, 0.154 mmol), and TBTU (57 mg, 0.178 mmol). The mixture was allowed to stir at RT overnight, at which time TBTU (57 mg, 0.178 mmol) and VHL-1 (55 mg, 0.119 mmol) were added. The reaction mixture was allowed to stir at RT overnight. After VHL-

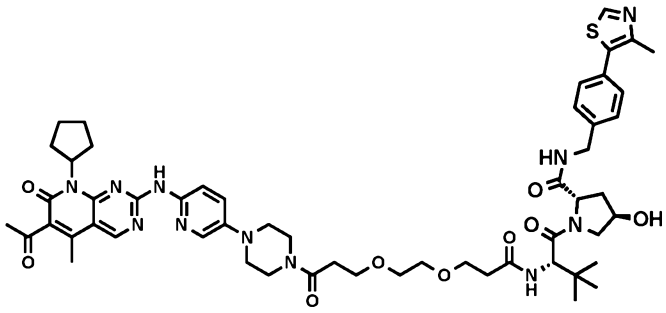
1 was consumed, the reaction was concentrated under reduced pressure. The resulting residue was purified by prep-HPLC to yield the product (22 mg, 18%) as yellow solid. ^{1}H NMR (600 MHz, CD_3OD) δ 8.92 (s, 1H), 8.79 (s, 1H), 7.98 (s, 1H), 7.95 (d, J = 8.9 Hz, 1H), 7.41 (d, J = 8.1 Hz, 1H), 7.37 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 7.7 Hz, 2H), 5.88 (p, J = 9.1 Hz, 1H), 4.66 (s, 1H), 4.56 (t, J = 8.4 Hz, 1H), 4.49 (s, 1H), 4.45 (d, J = 15.6 Hz, 1H), 4.33 (d, J = 15.4 Hz, 1H), 3.88 (d, J = 11.1 Hz, 1H), 3.80-3.70 (m, 9H), 3.15 (dt, J = 5.1, 29.0 Hz, 4H), 2.73 (d, J = 2.7 Hz, 2H), 2.57-2.49 (m, 2H), 2.47 (s, 3H), 2.39 (s, 3H), 2.34-2.25 (m, 5H), 2.24-2.18 (m, 1H), 2.12-2.03 (m, 1H), 2.03-1.95 (m, 2H), 1.89-1.80 (m, 2H), 1.71-1.61 (m, 2H), 1.03 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{52}H_{66}N_{11}O_8S$, 1004.4811; found: 1004.4813.

The Example **3, 4, 5, 6, 7, 8, 9,** and **18** compounds (below) were synthesized according to the procedures for the preparation of the Example **2** compound (above).



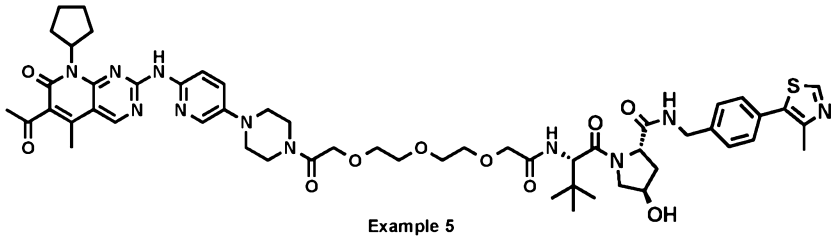
Example 3

(2*S*,4*R*)-1-((*S*)-2-(2-(2-(2-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-2-oxoethoxy)ethoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (compound Example 3) (9 mg, 4%) as yellow solid. ^{1}H NMR (600 MHz, CD_3OD) δ 9.06 (s, 1H), 8.94 (s, 1H), 8.16 (dd, J = 2.9, 9.6 Hz, 1H), 7.82 (d, J = 2.9 Hz, 1H), 7.50 (d, J = 9.6 Hz, 1H), 7.41 (d, J = 8.2 Hz, 2H), 7.38 (d, J = 8.2 Hz, 2H), 6.00 (p, J = 8.8 Hz, 1H), 4.73 (d, J = 9.5 Hz, 1H), 4.57 (dd, J = 7.5, 9.5 Hz, 1H), 4.53 – 4.45 (m, 2H), 4.41 – 4.31 (m, 3H), 4.06 (d, J = 8.3 Hz, 2H), 3.89 (d, J = 11.1 Hz, 1H), 3.85 – 3.70 (m, 9H), 3.37 – 3.24 (m, 4H), 2.50 (s, 3H), 2.45 (s, 3H), 2.42 (s, 3H), 2.34 – 2.23 (m, 3H), 2.14 – 2.05 (m, 3H), 1.94 – 1.86 (m, 2H), 1.74 – 1.65 (m, 2H), 1.04 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{52}H_{66}N_{11}O_9S$, 1020.4760; found: 1020.4769.



Example 4

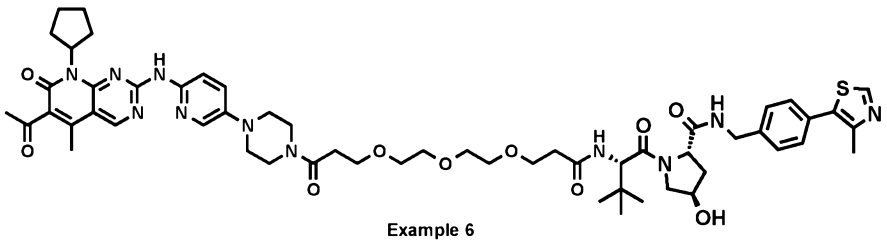
(2*S*,4*R*)-1-((*S*)-2-(3-(2-(3-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-3-oxopropoxy)ethoxy)propanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (compound Example 4) (13 mg, 11%) as yellow solid. ^{1}H NMR (600 MHz, CD_3OD) δ 9.09 (s, 1H), 8.98 (s, 1H), 8.20 (dd, *J* = 3.1, 9.6 Hz, 1H), 7.85 (d, *J* = 2.9 Hz, 1H), 7.53 (d, *J* = 9.5 Hz, 1H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.40 (d, *J* = 8.2 Hz, 2H), 6.00 (p, *J* = 8.9 Hz, 1H), 4.64 (s, 1H), 4.60 – 4.47 (m, 3H), 4.35 (d, *J* = 15.5 Hz, 1H), 3.88 (d, *J* = 11.0 Hz, 1H), 3.82 – 3.75 (m, 7H), 3.74 – 3.67 (m, 2H), 3.65 – 3.57 (m, 5H), 3.33 (t, *J* = 5.4 Hz, 2H), 3.26 (t, *J* = 5.3 Hz, 2H), 2.72 (t, *J* = 6.1 Hz, 2H), 2.56 – 2.51 (m, 1H), 2.50 (s, 3H), 2.47 (s, 3H), 2.43 (s, 3H), 2.35 – 2.26 (m, 2H), 2.25 – 2.20 (m, 1H), 2.14 – 2.04 (m, 3H), 1.94 – 1.86 (m, 2H), 1.74 – 1.66 (m, 2H), 1.03 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{54}H_{70}N_{11}O_9S$, 1048.5073; found: 1048.5069.



Example 5

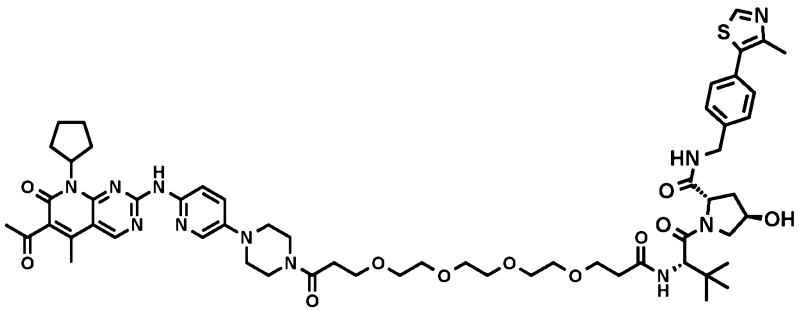
(2*S*,4*R*)-1-((*S*)-14-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-2-(*tert*-butyl)-4,14-dioxo-6,9,12-trioxa-3-azatetradecanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (compound Example 5) (15 mg, 17%) as yellow solid. ^{1}H NMR (600 MHz, CD_3OD) δ 9.08 (s, 1H), 9.07 (s, 1H), 8.18 (dd, *J* = 3.0, 9.6 Hz, 1H), 7.85 (d, *J* = 2.9 Hz, 1H), 7.53 (d, *J* = 9.6 Hz, 1H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.42 (d, *J* = 8.1 Hz, 2H), 6.00 (p, *J* = 8.9 Hz, 1H), 4.69 (s, 1H), 4.60 – 4.48 (m, 3H), 4.39 – 4.26 (m, 3H), 4.09 – 3.96 (m, 2H), 3.88 (d, *J* = 10.9 Hz, 1H), 3.83 – 3.63 (m, 12H), 3.27 (t, *J* = 5.0 Hz, 4H), 2.49 (s, 3H), 2.48 (s, 3H), 2.42 (s, 3H), 2.34 – 2.21 (m, 3H), 2.13 – 2.04 (m, 3H), 1.93 – 1.86 (m, 2H), 1.72 – 1.66 (m, 2H), 1.04

(s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{54}H_{70}N_{11}O_{10}S$, 1064.5022; found: 1064.5026.



Example 6

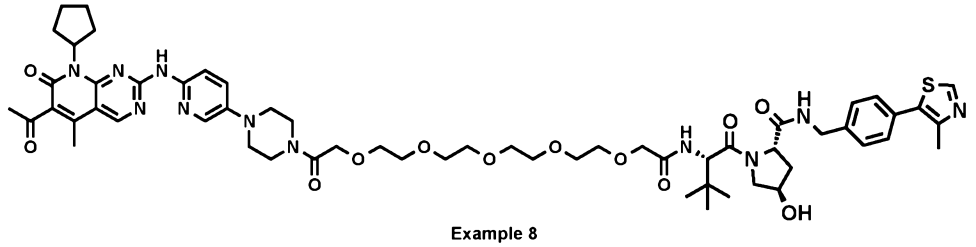
(2*S*,4*R*)-1-((*S*)-16-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-2-(*tert*-butyl)-4,16-dioxo-7,10,13-trioxa-3-azahexadecanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (compound Example 6) (13 mg, 13%) as yellow solid. ^{1}H NMR (600 MHz, CD_3OD) δ 9.09 (s, 1H), 8.97 (s, 1H), 8.20 (dd, *J* = 3.0, 9.7 Hz, 1H), 7.86 (d, *J* = 3.0 Hz, 1H), 7.53 (d, *J* = 9.7 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.40 (d, *J* = 8.0 Hz, 2H), 6.01 (p, *J* = 8.8 Hz, 1H), 4.64 (s, 1H), 4.58 – 4.47 (m, 3H), 4.35 (d, *J* = 15.5 Hz, 1H), 3.88 (d, *J* = 11.0 Hz, 1H), 3.83 – 3.75 (m, 7H), 3.74 – 3.65 (m, 2H), 3.64 – 3.55 (m, 8H), 3.33 (t, *J* = 5.2 Hz, 2H), 3.27 (d, *J* = 7.2 Hz, 2H), 2.71 (t, *J* = 6.2 Hz, 2H), 2.59 – 2.52 (m, 1H), 2.50 (s, 3H), 2.47 (s, 3H), 2.43 (s, 3H), 2.34 – 2.26 (m, 2H), 2.24 – 2.19 (m, 1H), 2.13 – 2.04 (m, 3H), 1.94 – 1.86 (m, 2H), 1.74 – 1.65 (m, 2H), 1.03 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{56}H_{74}N_{11}O_{10}S$, 1092.5335; found: 1092.5339.



Example 7

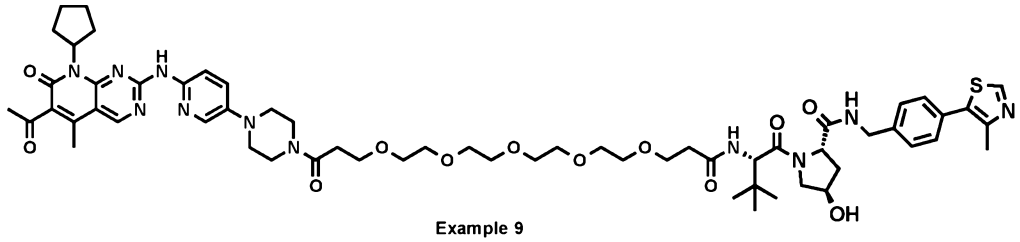
(2*S*,4*R*)-1-((*S*)-19-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-2-(*tert*-butyl)-4,19-dioxo-7,10,13,16-tetraoxa-3-azanonadecanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (compound Example 7) (12 mg, 12%) as yellow solid. ^{1}H NMR (600 MHz, CD_3OD) δ 9.08 (s, 1H), 8.99 (s, 1H), 8.21 (dd, *J* = 3.0, 9.5 Hz, 1H), 7.87 (d, *J* = 2.9 Hz, 1H), 7.53 (d, *J* = 9.6 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.40 (d, *J* = 8.1 Hz, 2H), 6.00 (p, *J* = 8.9 Hz, 1H), 4.64 (s, 1H), 4.59 – 4.47 (m, 3H), 4.35 (d, *J* = 15.5 Hz, 1H), 3.88 (d, *J* = 11.0 Hz, 1H), 3.83 – 3.75 (m, 7H), 3.75 – 3.66 (m, 2H), 3.64 – 3.53 (m, 13H), 3.34 (t,

J = 5.2 Hz, 2H), 3.28 (t, *J* = 5.3 Hz, 2H), 2.72 (t, *J* = 6.2 Hz, 2H), 2.59 – 2.52 (m, 1H), 2.50 (s, 3H), 2.47 (s, 3H), 2.43 (s, 3H), 2.35 – 2.26 (m, 2H), 2.24 – 2.19 (m, 1H), 2.13 – 2.04 (m, 3H), 1.94 – 1.86 (m, 2H), 1.73 – 1.64 (m, 2H), 1.03 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{58}H_{78}N_{11}O_{11}S$, 1136.5597; found: 1136.5595.



Example 8

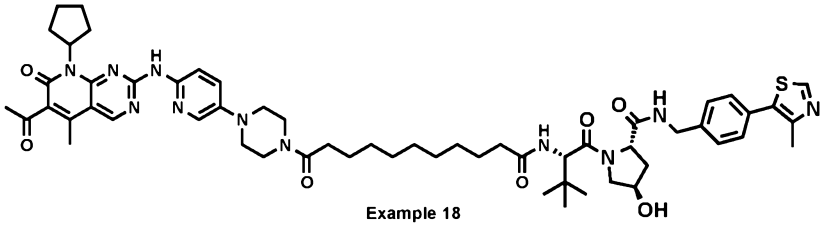
(2*S*,4*R*)-1-((*S*)-20-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-2-(*tert*-butyl)-4,20-dioxo-6,9,12,15,18-pentaoxa-3-azaicosanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (compound Example 8) (6 mg, 7%) as yellow solid. ^{1}H NMR (600 MHz, CD_3OD) δ 9.08 (s, 1H), 8.93 (s, 1H), 8.20 (dd, *J* = 3.0, 9.6 Hz, 1H), 7.87 (d, *J* = 3.0 Hz, 1H), 7.53 (d, *J* = 9.6 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 2H), 6.00 (p, *J* = 8.7 Hz, 1H), 4.69 (s, 1H), 4.59 – 4.48 (m, 3H), 4.36 (d, *J* = 15.7 Hz, 1H), 4.30 (s, 2H), 4.05 (d, *J* = 15.8 Hz, 1H), 4.00 (d, *J* = 15.5 Hz, 1H), 3.88 (d, *J* = 11.1 Hz, 1H), 3.83 – 3.72 (m, 5H), 3.72 – 3.58 (m, 16H), 3.36 – 3.25 (m, 4H), 2.50 (s, 3H), 2.47 (s, 3H), 2.43 (s, 3H), 2.34 – 2.27 (m, 2H), 2.26 – 2.21 (m, 1H), 2.15 – 2.05 (m, 3H), 1.94 – 1.86 (m, 2H), 1.73 – 1.65 (m, 2H), 1.03 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{58}H_{78}N_{11}O_{12}S$, 1152.5547; found: 1152.5548.



Example 9

(2*S*,4*R*)-1-((*S*)-22-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-2-(*tert*-butyl)-4,22-dioxo-7,10,13,16,19-pentaoxa-3-azadocosanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (compound Example 9) (25 mg, 19%) as yellow solid. ^{1}H NMR (600 MHz, CD_3OD) δ 9.09 (s, 1H), 9.06 (s, 1H), 8.21 (dd, *J* = 3.0, 9.6 Hz, 1H), 7.88 (d, *J* = 3.0 Hz, 1H), 7.54 (d, *J* = 9.6 Hz, 1H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.41 (d, *J* = 8.2 Hz, 2H), 6.00 (p, *J* = 8.9 Hz, 1H), 4.64 (s, 1H), 4.60 – 4.46 (m, 3H), 4.35 (d, *J* = 15.6 Hz, 1H), 3.88 (d, *J* = 10.8 Hz, 1H), 3.84 – 3.66 (m, 10H), 3.65 – 3.55 (m, 16H), 3.35 (t, *J* = 5.1 Hz, 2H), 3.28

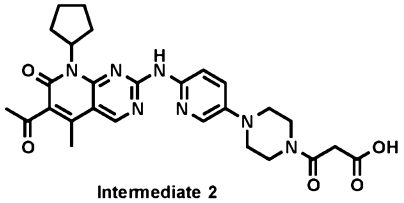
(t, J = 5.3 Hz, 2H), 2.72 (t, J = 6.1 Hz, 2H), 2.61 – 2.53 (m, 1H), 2.49 (s, 3H), 2.48 (s, 3H), 2.42 (s, 3H), 2.34 – 2.26 (m, 2H), 2.25 – 2.19 (m, 1H), 2.12 – 2.03 (m, 3H), 1.94 – 1.86 (m, 2H), 1.73 – 1.65 (m, 2H), 1.03 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{60}H_{82}N_{11}O_{12}S$, 1180.5860; found: 1180.5859.



Example 18

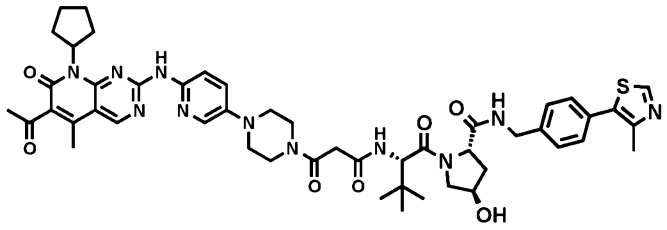
(2*S*,4*R*)-1-((*S*)-2-(11-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-11-oxoundecanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (compound Example 18) (17 mg, 13%) as yellow solid. ^{1}H NMR (600 MHz, CD_3OD) δ 9.10 (s, 1H), 8.94 (s, 1H), 8.20 (dd, J = 2.9, 9.6 Hz, 1H), 7.86 (d, J = 3.0 Hz, 1H), 7.54 (d, J = 9.6 Hz, 1H), 7.46 (d, J = 8.2 Hz, 2H), 7.41 (d, J = 8.1 Hz, 2H), 6.01 (p, J = 8.9 Hz, 1H), 4.63 (s, 1H), 4.59 – 4.46 (m, 3H), 4.35 (d, J = 15.5 Hz, 1H), 3.90 (d, J = 11.0 Hz, 1H), 3.84 – 3.72 (m, 5H), 3.36 – 3.24 (m, 4H), 2.53 – 2.40 (m, 10H), 2.36 – 2.18 (m, 5H), 2.15 – 2.03 (m, 3H), 1.95 – 1.86 (m, 2H), 1.74 – 1.53 (m, 6H), 1.42 – 1.27 (m, 11H), 1.03 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{57}H_{76}N_{11}O_7S$, 1058.5644; found: 1058.5640.

The Intermediate **2, 3,** and **4** and Example **10, 11,** and **12** compounds were synthesized according to the procedures for the preparation of the Example **1** compound (above).



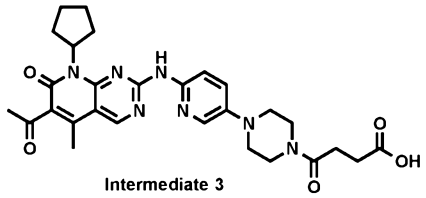
Intermediate 2

3-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-3-oxopropanoic acid (Intermediate 2) (18 mg, 51%). ^{1}H NMR (600 MHz, CD_3OD) δ 9.07 (s, 1H), 8.09 (d, J = 10.2 Hz, 1H), 7.90 (s, 1H), 7.62 (d, J = 9.5 Hz, 1H), 6.06 – 5.95 (m, 1H), 3.86 – 3.72 (m, 4H), 3.59 (d, J = 9.0 Hz, 2H), 3.40 – 3.22 (m, 4H), 2.50 (s, 3H), 2.42 (s, 3H), 2.37 – 2.27 (m, 2H), 2.14 – 2.03 (m, 2H), 1.95 – 1.85 (m, 2H), 1.75 – 1.66 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{27}H_{32}N_7O_5$, 534.2459; found: 534.2450.



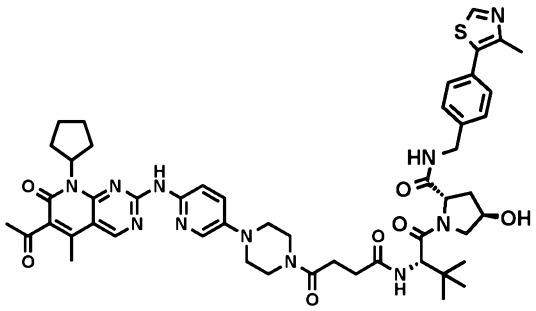
Example 10

6-Acetyl-8-cyclopentyl-*N*-(5-(4-(3-(((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-3-oxopropanoyl)piperazin-1-yl)pyridin-2-yl)-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-aminium (compound Example 10) (19 mg, 59%) as yellow solid. ^{1}H NMR (600 MHz, CD_3OD) δ 9.10 (s, 1H), 9.00 (s, 1H), 8.20 (dd, *J* = 3.0, 9.7 Hz, 1H), 7.86 (d, *J* = 3.0 Hz, 1H), 7.53 (d, *J* = 9.5 Hz, 1H), 7.47 (d, *J* = 8.2 Hz, 2H), 7.41 (d, *J* = 8.3 Hz, 2H), 6.00 (p, *J* = 9.0 Hz, 1H), 4.63 (s, 1H), 4.59 – 4.43 (m, 4H), 4.37 (d, *J* = 15.5 Hz, 1H), 3.94 – 3.84 (m, 2H), 3.84 – 3.68 (m, 5H), 3.41 – 3.20 (m, 4H), 2.49 (s, 3H), 2.48 (s, 3H), 2.42 (s, 3H), 2.34 – 2.27 (m, 2H), 2.24 – 2.18 (m, 1H), 2.13 – 2.04 (m, 3H), 1.93 – 1.86 (m, 2H), 1.73 – 1.66 (m, 2H), 1.06 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{49}H_{60}N_{11}O_7S$, 946.4392; found: 946.4391.



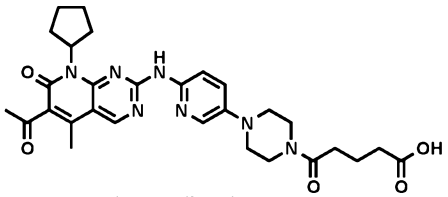
Intermediate 3

4-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-4-oxobutanoic acid (Intermediate 3) (27 mg, 88%). ^{1}H NMR (600 MHz, CD_3OD) δ 9.09 (s, 1H), 8.17 (d, *J* = 9.5 Hz, 1H), 7.88 (s, 1H), 7.57 (d, *J* = 9.6 Hz, 1H), 6.00 (p, *J* = 9.0 Hz, 1H), 3.78 (t, *J* = 5.8 Hz, 4H), 3.35 (t, *J* = 4.9 Hz, 2H), 3.28 (t, *J* = 4.9 Hz, 2H), 2.73 (t, *J* = 6.5 Hz, 2H), 2.64 (t, *J* = 6.5 Hz, 2H), 2.49 (s, 3H), 2.42 (s, 3H), 2.36 – 2.27 (m, 2H), 2.13 – 2.04 (m, 2H), 1.95 – 1.86 (m, 2H), 1.75 – 1.64 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{28}H_{34}N_7O_5$, 548.2616; found: 548.2612.



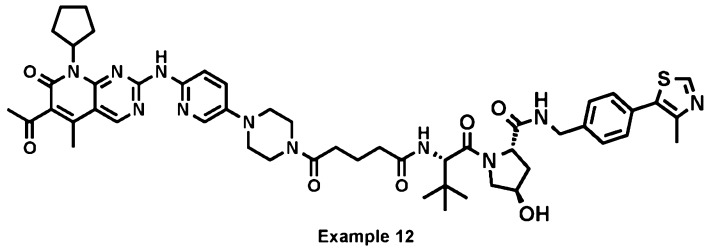
Example 11

(2*S*,4*R*)-1-((*S*)-2-(4-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-4-oxobutanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (compound Example 11) (32 mg, 68%) as yellow solid. ^{1}H NMR (600 MHz, CD_3OD) δ 9.09 (s, 1H), 9.01 (s, 1H), 8.20 (dd, *J* = 3.0, 9.6 Hz, 1H), 7.86 (d, *J* = 2.9 Hz, 1H), 7.53 (d, *J* = 9.6 Hz, 1H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.41 (d, *J* = 8.2 Hz, 2H), 6.00 (p, *J* = 8.8 Hz, 1H), 4.61 (s, 1H), 4.58 – 4.54 (m, 1H), 4.52 (d, *J* = 15.4 Hz, 1H), 4.50 – 4.47 (m, 1H), 4.36 (d, *J* = 15.5 Hz, 1H), 3.88 (d, *J* = 11.3 Hz, 1H), 3.84 – 3.70 (m, 5H), 3.34 (t, *J* = 5.1 Hz, 2H), 3.27 (t, *J* = 5.5 Hz, 2H), 2.80 – 2.62 (m, 3H), 2.60 – 2.54 (m, 1H), 2.49 (s, 3H), 2.48 (s, 3H), 2.42 (s, 3H), 2.35 – 2.26 (m, 2H), 2.24 – 2.19 (m, 1H), 2.13 – 2.05 (m, 3H), 1.93 – 1.86 (m, 2H), 1.73 – 1.66 (m, 2H), 1.03 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{50}H_{62}N_{11}O_7S$, 960.4549; found: 960.4545.



Intermediate 4

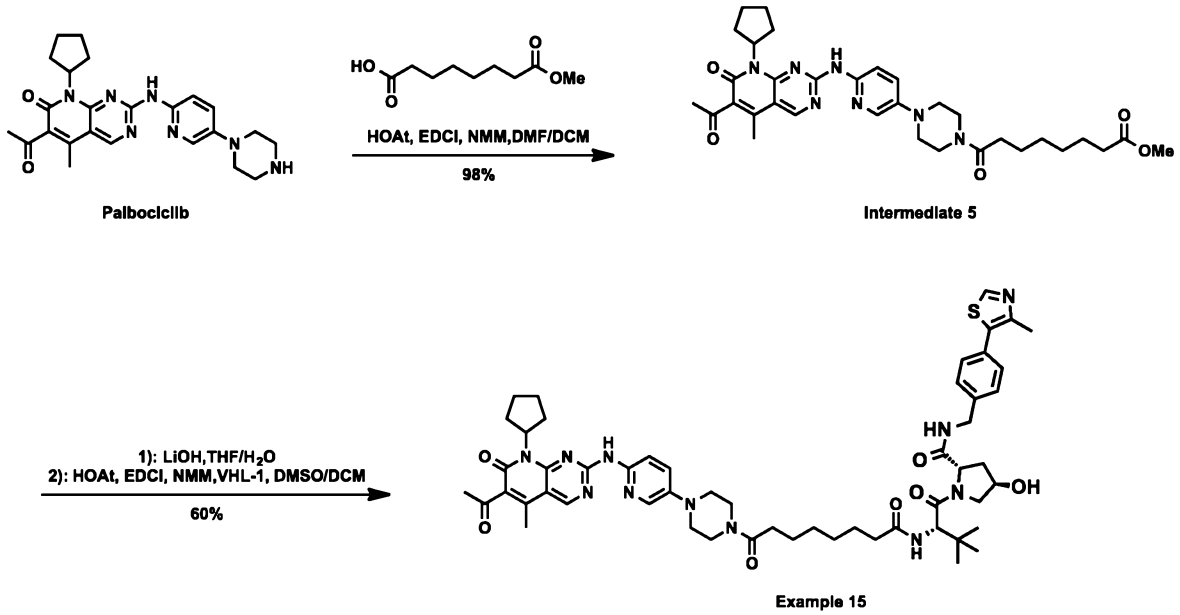
5-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-5-oxopentanoic acid (Intermediate 4) (30 mg, 96%). ^{1}H NMR (600 MHz, CD_3OD) δ 9.14 (s, 1H), 8.21 (d, *J* = 9.4 Hz, 1H), 7.92 (s, 1H), 7.56 (d, *J* = 9.3 Hz, 1H), 6.00 (p, *J* = 8.9 Hz, 1H), 4.04 (d, *J* = 13.3 Hz, 2H), 3.77 (t, *J* = 12.2 Hz, 2H), 3.44 (d, *J* = 12.5 Hz, 2H), 3.15 (td, *J* = 3.4, 12.3 Hz, 2H), 2.53 (t, *J* = 7.5 Hz, 2H), 2.49 (s, 3H), 2.43 (s, 3H), 2.40 (t, *J* = 7.3 Hz, 2H), 2.35 – 2.26 (m, 2H), 2.13 – 2.05 (m, 2H), 1.95 – 1.86 (m, 4H), 1.74 – 1.65 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{29}H_{36}N_7O_5$, 562.2772; found: 562.2775.



Example 12

(2*S*,4*R*)-1-((*S*)-2-(5-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-5-oxopentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (compound Example 12) (40 mg, 77%) as yellow solid. ^{1}H NMR (600 MHz, CD_3OD) δ 9.12 (s, 1H), 9.09 (s, 1H), 8.17 (dd, *J* = 2.9, 9.6 Hz, 1H), 7.86 (d, *J* = 2.9 Hz, 1H), 7.53 (d, *J* = 9.6 Hz, 1H), 7.47 (d, *J* = 7.9 Hz, 2H), 7.41 (d, *J* = 8.3 Hz, 2H), 5.99 (p, *J* = 8.8 Hz, 1H), 4.62 (s, 1H), 4.59 – 4.49 (m, 3H), 4.37 (d, *J* = 15.6 Hz, 1H), 3.94 (d, *J* = 11.1 Hz, 1H), 3.83 – 3.71 (m, 6H), 3.34 – 3.25 (m, 4H), 2.49 (s, 3H), 2.48 (s, 3H), 2.42 (s, 3H), 2.39 – 2.20 (m, 6H), 2.11 – 2.05 (m, 3H), 1.95 – 1.85 (m, 4H), 1.72 – 1.65 (m, 2H), 1.04 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{51}H_{64}N_{11}O_7S$, 974.4705; found: 974.4703.

Scheme 3: Synthesis of example 15



Palbociclib

Intermediate 5

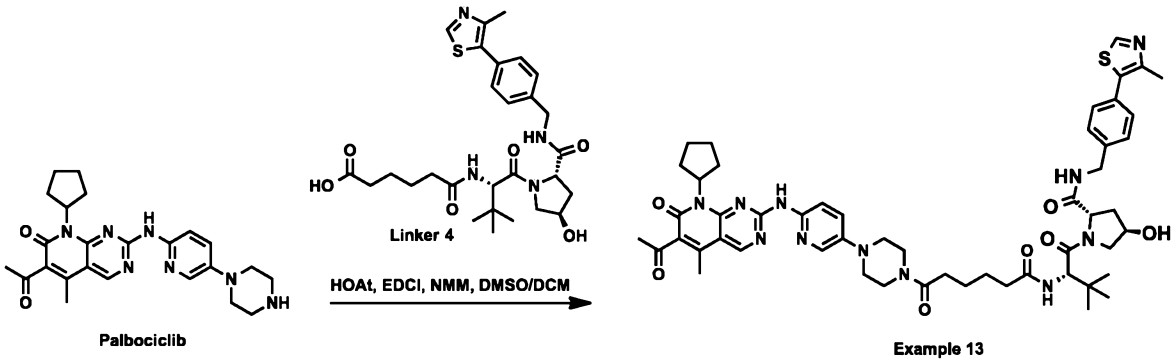
Example 15

Methyl 8-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-8-oxooctanoate (Intermediate 5). To a solution of palbociclib (50 mg, 0.112 mmol) in DMF (5 ml) and DCM (20 ml) were added NMM (34 mg, 0.335 mmol), 8-methoxy-8-oxooctanoic acid (25 mg, 0.134 mmol), HOAt (20 mg, 0.146 mmol), and EDCI (28 mg, 0.146 mmol). The mixture was allowed to stir at RT

overnight. After palbociclib was consumed, the reaction was concentrated under reduced pressure. The resulting residue was purified by prep-HPLC to yield the product (69 mg, 98%) as yellow solid. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{33}H_{44}N_7O_5$, 618.3398; found: 618.3401.

(2*S*,4*R*)-1-((*S*)-2-(8-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-8-oxooctanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (compound Example 15) To a stirring solution of intermediate **5** (69 mg, 0.112 mmol) in THF/H_2O (20 ml/5 ml) was added anhydrous LiOH (6 mg, 0.223 mmol) and the resulting mixture was stirred overnight at RT. The disappearance of starting material was monitored by LC/MS. The reaction mixture was concentrated under reduced pressure and the resulting residue was dissolved in DCM/DMSO (10 ml/3 ml). To the resulting solution were added NMM (13 mg, 0.335 mmol), VHL-1 (57 mg, 0.123 mmol), HOAt (20 mg, 0.145 mmol) and EDCI (28 mg, 0.145 mmol). The mixture was allowed to stir at room temperature overnight. After the starting materials were consumed, the reaction was concentrated under reduced pressure. The resulting residue was purified by prep-HPLC to yield the product (68 mg, 60%) as yellow solid. ^1H NMR (600 MHz, CD_3OD) δ 9.10 (s, 1H), 9.05 (s, 1H), 8.21 (dd, *J* = 3.0, 9.7 Hz, 1H), 7.86 (s, 1H), 7.53 (d, *J* = 9.7 Hz, 1H), 7.47 (d, *J* = 7.9 Hz, 2H), 7.42 (d, *J* = 7.9 Hz, 2H), 6.01 (p, *J* = 8.9 Hz, 1H), 4.63 (s, 1H), 4.59-4.45 (m, 3H), 4.36 (d, *J* = 15.5 Hz, 1H), 3.90 (d, *J* = 11.0 Hz, 1H), 3.84-3.72 (m, 5H), 3.33-3.25 (m, 4H), 2.53 – 2.40 (m, 10H), 2.36-2.18 (m, 6H), 2.13-2.03 (m, 3H), 1.95-1.85 (m, 2H), 1.74-1.58 (m, 6H), 1.45-1.32 (m, 4H), 1.03 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{54}H_{70}N_{11}O_7S$, 1016.5175; found: 1016.5180.

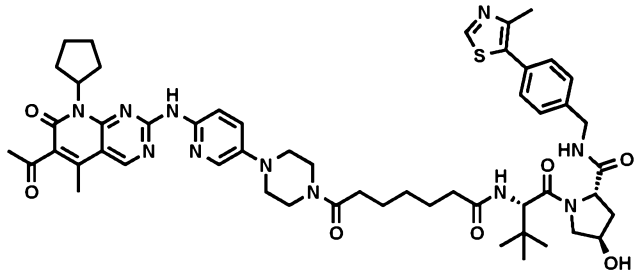
Scheme 4: Synthesis of example 13



(2*S*,4*R*)-1-((*S*)-2-(6-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-6-oxohexanamido)-3,3-

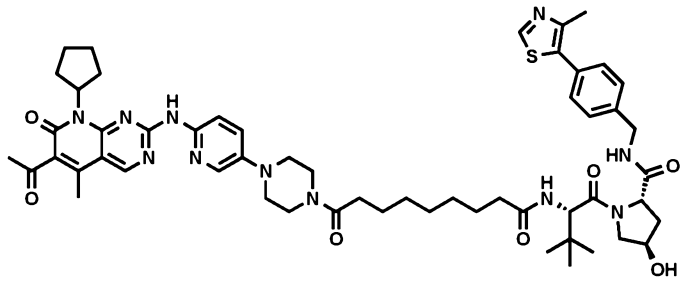
dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (compound Example 13). To a solution of palbociclib (12 mg, 0.0268 mmol) in DMSO (1 mL) and DCM (5 mL) were added NMM (13.6 mg, 0.134 mmol), linker **4** (15 mg, 0.0268 mmol), HOAt (5.5 mg, 0.042 mmol) and EDCI (7.7 mg, 0.042 mmol). The mixture was allowed to stir at rt overnight. After the starting materials were consumed, the reaction was concentrated under reduced pressure. The resulting residue was purified by prep-HPLC to yield the product (24 mg, 81%) as yellow solid. ^{1}H NMR (600 MHz, CD_3OD) δ 9.09 (s, 1H), 8.95 (s, 1H), 8.19 (dd, J = 9.6, 2.9 Hz, 1H), 7.86 (d, J = 2.8 Hz, 1H), 7.54 (d, J = 9.6 Hz, 1H), 7.46 (d, J = 8.2 Hz, 2H), 7.40 (d, J = 8.2 Hz, 2H), 6.00 (p, J = 8.9 Hz, 1H), 4.63 (s, 1H), 4.60 – 4.48 (m, 3H), 4.36 (d, J = 15.6 Hz, 1H), 3.90 (d, J = 11.1 Hz, 1H), 3.83 – 3.73 (m, 5H), 3.35 – 3.31 (m, 2H), 3.29 – 3.25 (m, 2H), 2.50 (s, 3H), 2.47 (s, 3H), 2.43 (s, 3H), 2.36 – 2.27 (m, 4H), 2.24 – 2.19 (m, 1H), 2.13 – 2.05 (m, 3H), 1.94 – 1.86 (m, 2H), 1.73 – 1.61 (m, 6H), 1.41 – 1.24 (m, 2H), 1.04 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{52}H_{66}N_{11}O_7S$, 988.4862; found: 988.4871.

The Example **14, 16,** and **17** compounds were synthesized using the procedures for the preparation of the Example **13** compound (above).



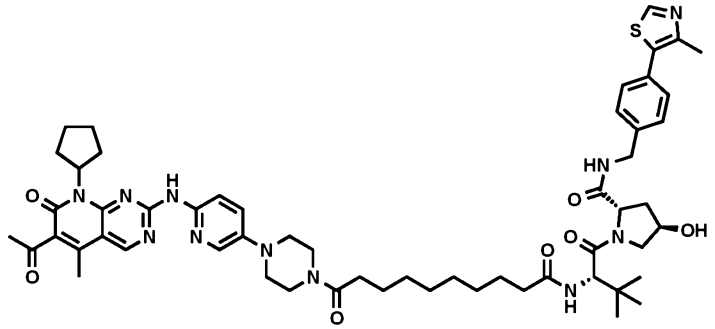
Example 14

(2*S*,4*R*)-1-((*S*)-2-(7-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-7-oxoheptanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (compound Example 14) (20 mg, 68%) as yellow solid. ^{1}H NMR (600 MHz, CD_3OD) δ 9.09 (s, 1H), 8.93 (s, 1H), 8.20 (dd, J = 9.6, 2.9 Hz, 1H), 7.86 (d, J = 2.9 Hz, 1H), 7.53 (d, J = 9.6 Hz, 1H), 7.46 (d, J = 8.1 Hz, 2H), 7.40 (d, J = 8.2 Hz, 2H), 6.01 (p, J = 8.8 Hz, 1H), 4.63 (s, 1H), 4.58 – 4.48 (m, 3H), 4.36 (d, J = 15.5 Hz, 1H), 3.90 (d, J = 11.1 Hz, 1H), 3.83 – 3.72 (m, 5H), 3.32 (t, J = 5.0 Hz, 2H), 3.28 (t, J = 5.0 Hz, 2H), 2.50 (s, 3H), 2.47 (s, 3H), 2.48 – 2.44 (m, 2H), 2.43 (s, 3H), 2.35 – 2.24 (m, 4H), 2.24 – 2.19 (m, 1H), 2.13 – 2.05 (m, 3H), 1.94 – 1.86 (m, 2H), 1.74 – 1.60 (m, 6H), 1.40 (dt, J = 8.7, 7.4 Hz, 2H), 1.03 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{53}H_{68}N_{11}O_7S$, 1002.5018; found: 1002.5019.



Example 16

(2*S*,4*R*)-1-((*S*)-2-(9-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-9-oxononanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (compound Example 16) (18 mg, 63%) as yellow solid. ^{1}H NMR (600 MHz, CD_3OD) δ 9.10 (s, 1H), 9.00 (s, 1H), 8.20 (dd, *J* = 9.6, 2.8 Hz, 1H), 7.86 (d, *J* = 2.8 Hz, 1H), 7.54 (d, *J* = 9.6 Hz, 1H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.41 (d, *J* = 8.1 Hz, 2H), 6.00 (p, *J* = 8.8 Hz, 1H), 4.63 (s, 1H), 4.60 – 4.47 (m, 3H), 4.36 (d, *J* = 15.5 Hz, 1H), 3.90 (d, *J* = 11.0 Hz, 1H), 3.82 – 3.72 (m, 5H), 3.34 – 3.23 (m, 4H), 2.50 (s, 3H), 2.48 (s, 3H), 2.48 – 2.44 (m, 2H), 2.43 (s, 3H), 2.34 – 2.18 (m, 5H), 2.13 – 2.04 (m, 3H), 1.94 – 1.85 (m, 2H), 1.73 – 1.57 (m, 6H), 1.41 – 1.30 (m, 6H), 1.03 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{55}H_{72}N_{11}O_7S$, 1030.5331; found: 1030.5335.

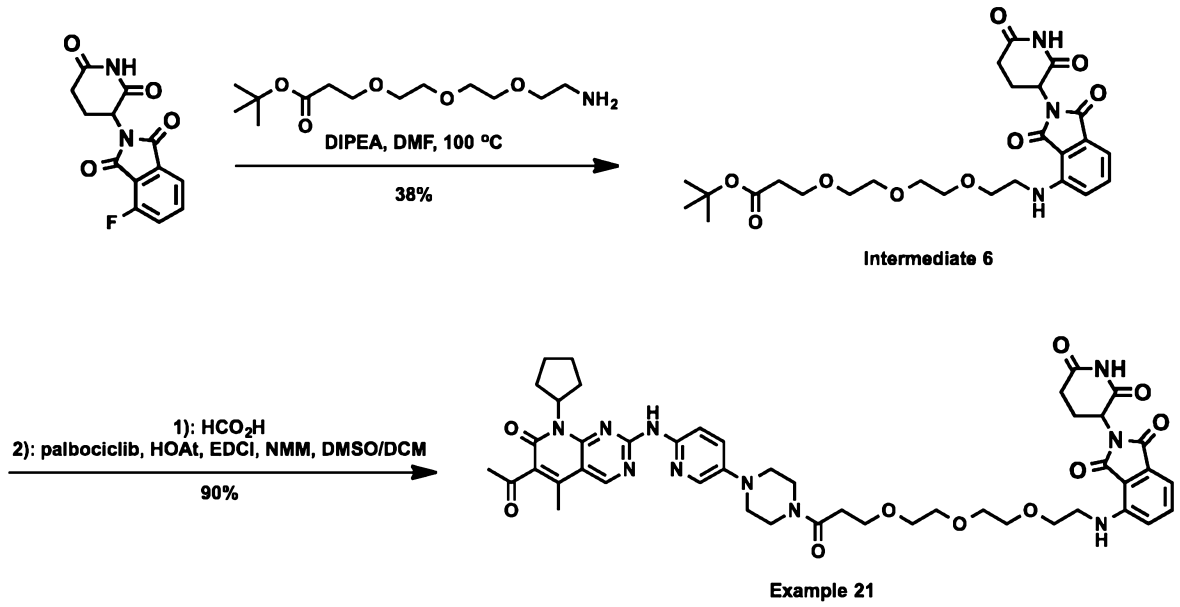


Example 17

(2*S*,4*R*)-1-((*S*)-2-(10-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-10-oxodecanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (compound Example 17) (18 mg, 64%) as yellow solid. ^{1}H NMR (600 MHz, CD_3OD) δ 9.09 (s, 1H), 8.93 (s, 1H), 8.19 (dd, *J* = 9.6, 2.9 Hz, 1H), 7.87 (d, *J* = 2.9 Hz, 1H), 7.54 (d, *J* = 9.6 Hz, 1H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.41 (d, *J* = 8.2 Hz, 2H), 6.00 (p, *J* = 8.8 Hz, 1H), 4.63 (s, 1H), 4.60 – 4.47 (m, 3H), 4.35 (d, *J* = 15.5 Hz, 1H), 3.90 (d, *J* = 11.0 Hz, 1H), 3.83 – 3.70 (m, 5H), 3.36 – 3.23 (m, 4H), 2.50 (s, 3H), 2.47 (s, 3H), 2.48

– 2.44 (m, 2H), 2.43 (s, 3H), 2.34 – 2.19 (m, 5H), 2.12 – 2.05 (m, 3H), 1.93 – 1.86 (m, 2H), 1.73 – 1.66 (m, 2H), 1.65 – 1.56 (m, 4H), 1.40 – 1.28 (m, 8H), 1.03 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{56}H_{74}N_{11}O_7S$, 1044.5488; found: 1044.5487.

Scheme 5: Synthesis of example 21

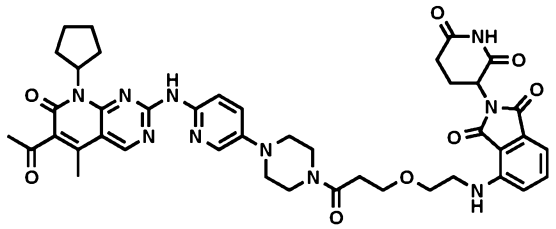


***tert*-Butyl 3-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy) ethoxy)ethoxy)propanoate (Intermediate 6).** A solution of 2-(2,6-dioxopiperidin-3-yl)-4-fluoroisoindoline-1,3-dione (100 mg, 0.362 mmol), *tert*-butyl 3-(2-(2-(2-aminoethoxy)ethoxy) ethoxy)propanoate (100 mg, 0.362 mmol) and DIPEA (0.5 ml) in DMF (5 ml) was heated at 100 °C overnight. After the starting materials were consumed, the reaction was concentrated under reduced pressure. The resulting residue was purified by prep-HPLC to yield the product (72 mg, 37%) as yellow solid. ^{1}H NMR (600 MHz, CD_3OD) δ 7.55 (dd, J = 7.1, 8.6 Hz, 1H), 7.10 (d, J = 8.5 Hz, 1H), 7.05 (d, J = 7.0 Hz, 1H), 5.06 (dd, J = 5.4, 12.4 Hz, 1H), 4.10 (q, J = 7.1 Hz, 1H), 3.72 (t, J = 5.3 Hz, 2H), 3.69 – 3.59 (m, 8H), 3.59 – 3.55 (m, 2H), 3.50 (t, J = 5.3 Hz, 2H), 2.91 – 2.82 (m, 1H), 2.78 – 2.68 (m, 2H), 2.45 (t, J = 6.2 Hz, 2H), 1.43 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{26}H_{36}N_3O_9$, 534.2446; found: 534.2459.

4-((2-(2-(2-(3-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-3-oxopropoxy)ethoxy)ethoxy)ethyl) amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (compound Example 21). A solution of intermediate **6** (20 mg, 0.0308 mmol) in HCO_2H (5 mL) was stirred overnight at RT. The reaction was concentrated under reduced pressure and the resulting residue was dissolved in DCM/DMSO (10 ml/2 ml). To the resulting solution were added palbociclib (13.7

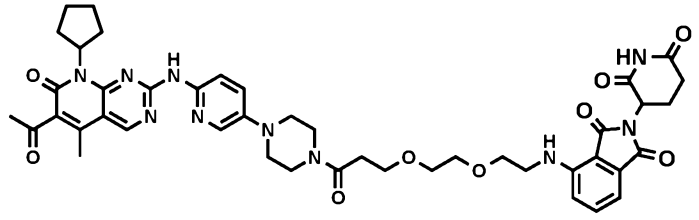
mg, 0.0308 mmol), NMM (16 mg, 0.154 mmol), HOAt (5.4 mg, 0.0399 mmol), and EDCI (7.6 mg, 0.0399 mmol). The reaction mixture was allowed to stir at RT overnight. After palbociclib was consumed, the reaction was concentrated under reduced pressure. The resulting residue was purified by prep-HPLC to yield the product (25 mg, 90%) as yellow solid. ^{1}H NMR (600 MHz, CD_3OD) δ 8.98 (s, 1H), 8.13 (d, J = 9.7 Hz, 1H), 7.72 (d, J = 2.9 Hz, 1H), 7.44 – 7.35 (m, 2H), 6.94 (d, J = 8.6 Hz, 1H), 6.77 (d, J = 7.1 Hz, 1H), 6.03 – 5.93 (m, 1H), 5.09 (dd, J = 5.5, 12.7 Hz, 1H), 3.87 – 3.75 (m, 8H), 3.67 (t, J = 5.2 Hz, 2H), 3.65 – 3.58 (m, 9H), 3.41 – 3.37 (m, 2H), 2.92 – 2.84 (m, 1H), 2.79 – 2.63 (m, 4H), 2.52 (s, 3H), 2.42 (s, 3H), 2.36 – 2.28 (m, 2H), 2.13 – 2.07 (m, 4H), 1.97 – 1.88 (m, 2H), 1.75 – 1.67 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{46}H_{55}N_{10}O_{10}$, 907.4097; found: 907.4095.

The Example **19, 20, 22, 23, 24, 25, 26, 27, 28,** and **29** compounds were synthesized according to the procedures for the preparation of the Example **21** compound (above).



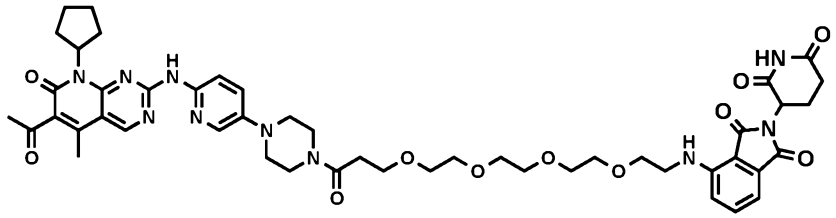
Example 19

4-((2-(3-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-3-oxopropoxy)ethyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (compound Example 19) (28 mg, 88%) as yellow solid. ^{1}H NMR (600 MHz, CD_3OD) δ 9.08 (s, 1H), 7.99 (dd, J = 9.6, 2.8 Hz, 1H), 7.64 (d, J = 2.8 Hz, 1H), 7.44 (dd, J = 8.3, 7.2 Hz, 1H), 7.30 (d, J = 9.6 Hz, 1H), 6.96 (d, J = 8.6 Hz, 1H), 6.80 (d, J = 7.0 Hz, 1H), 6.02 (p, J = 8.9 Hz, 1H), 5.07 (dd, J = 12.8, 5.6 Hz, 1H), 3.99 – 3.79 (m, 4H), 3.79 – 3.61 (m, 4H), 3.48 – 3.36 (m, 2H), 3.30 – 3.24 (m, 1H), 3.23 – 3.13 (m, 2H), 3.13 – 3.05 (m, 1H), 2.90 – 2.77 (m, 2H), 2.76 – 2.70 (m, 1H), 2.70 – 2.60 (m, 2H), 2.51 (s, 3H), 2.45 (s, 3H), 2.37 – 2.27 (m, 2H), 2.15 – 2.04 (m, 3H), 1.96 – 1.87 (m, 2H), 1.75 – 1.66 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{42}H_{47}N_{10}O_8$, 819.3573; found: 819.3573.



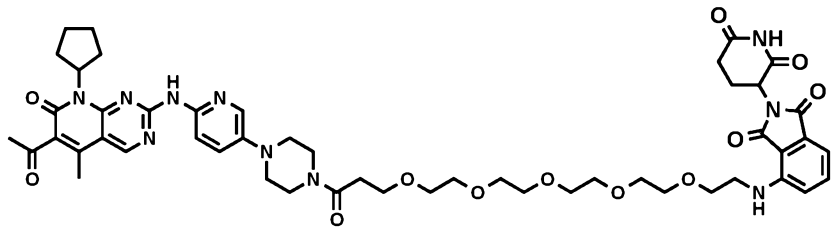
Example 20

4-((2-(2-(3-(4-(6-(((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-3-oxopropoxy)ethoxy)ethyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (compound Example 20) (22 mg, 73%) as yellow solid. ^{1}H NMR (600 MHz, CD_3OD) δ 8.99 (s, 1H), 8.08 (dd, *J* = 9.6, 2.8 Hz, 1H), 7.68 (d, *J* = 2.6 Hz, 1H), 7.40 (dd, *J* = 8.4, 7.2 Hz, 1H), 7.37 (d, *J* = 9.6 Hz, 1H), 6.94 (d, *J* = 8.6 Hz, 1H), 6.72 (d, *J* = 7.1 Hz, 1H), 5.99 (p, *J* = 8.9 Hz, 1H), 5.08 (dd, *J* = 12.8, 5.6 Hz, 1H), 3.86 – 3.70 (m, 6H), 3.69 – 3.61 (m, 6H), 3.41 – 3.31 (m, 4H), 3.26 – 3.17 (m, 2H), 2.92 – 2.82 (m, 1H), 2.78 – 2.63 (m, 4H), 2.51 (s, 3H), 2.43 (s, 3H), 2.36 – 2.28 (m, 2H), 2.13 – 2.07 (m, 3H), 1.96 – 1.87 (m, 2H), 1.74 – 1.66 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{44}H_{51}N_{10}O_9$, 863.3835; found: 863.3842.



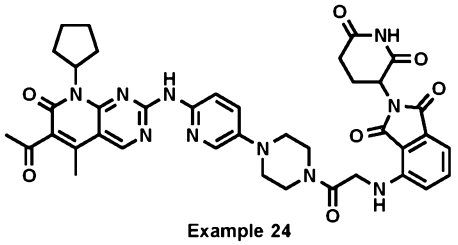
Example 22

4-((15-(4-(6-(((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-15-oxo-3,6,9,12-tetraoxapentadecyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (compound Example 22) (34 mg, 85%) as yellow solid. ^{1}H NMR (600 MHz, CD_3OD) δ 8.97 (s, 1H), 8.17 (d, *J* = 9.6 Hz, 1H), 7.75 (s, 1H), 7.44 (d, *J* = 9.6 Hz, 1H), 7.39 (t, *J* = 7.8 Hz, 1H), 6.92 (d, *J* = 8.5 Hz, 1H), 6.80 (d, *J* = 7.0 Hz, 1H), 5.96 (p, *J* = 8.7 Hz, 1H), 5.07 (dd, *J* = 12.8, 5.4 Hz, 1H), 3.87 – 3.73 (m, 6H), 3.70 – 3.51 (m, 14H), 3.42 – 3.32 (m, 4H), 3.30 – 3.22 (m, 2H), 2.91 – 2.83 (m, 1H), 2.78 – 2.59 (m, 4H), 2.50 (s, 3H), 2.39 (s, 3H), 2.34 – 2.24 (m, 2H), 2.15 – 2.03 (m, 3H), 1.95 – 1.86 (m, 2H), 1.74 – 1.64 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{48}H_{59}N_{10}O_{11}$, 951.4359; found: 951.4353.



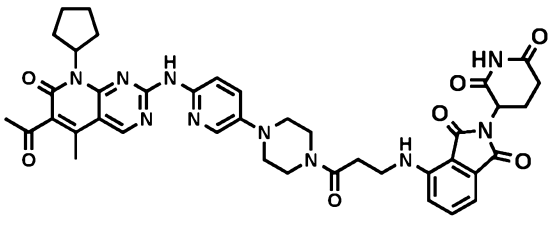
Example 23

4-((18-(4-(6-(((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-18-oxo-3,6,9,12,15-pentaoxaoctadecyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (compound Example 23) (18 mg, 51%) as yellow solid. ^{1}H NMR (600 MHz, CD_3OD) δ 9.03 – 8.97 (m, 1H), 8.20 (dd, *J* = 9.6, 2.9 Hz, 1H), 7.78 (d, *J* = 2.9 Hz, 1H), 7.45 (d, *J* = 9.7 Hz, 1H), 7.43 (dd, *J* = 8.5, 7.2 Hz, 1H), 6.97 (d, *J* = 8.6 Hz, 1H), 6.85 (d, *J* = 7.0 Hz, 1H), 5.97 (p, *J* = 8.8 Hz, 1H), 5.06 (dd, *J* = 12.8, 5.5 Hz, 1H), 3.84 – 3.78 (m, 4H), 3.77 (t, *J* = 6.0 Hz, 2H), 3.68 (t, *J* = 5.1 Hz, 2H), 3.66 – 3.53 (m, 16H), 3.44 – 3.38 (m, 2H), 3.37 – 3.32 (m, 2H), 3.29 – 3.22 (m, 2H), 2.90 – 2.82 (m, 1H), 2.77 – 2.62 (m, 4H), 2.51 (s, 3H), 2.41 (s, 3H), 2.34 – 2.26 (m, 2H), 2.13 – 2.05 (m, 3H), 1.95 – 1.87 (m, 2H), 1.74 – 1.65 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{50}H_{63}N_{10}O_{12}$, 995.4621; found: 995.4628.



Example 24

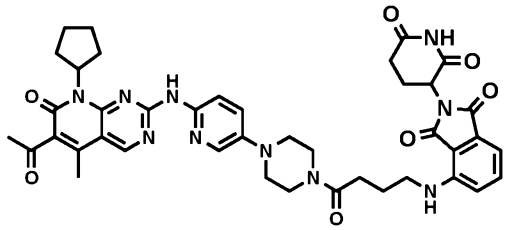
4-((2-(4-(6-(((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-2-oxoethyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (compound Example 24) (28 mg, 72%) as yellow solid. ^{1}H NMR (600 MHz, CD_3OD) δ 9.08 (s, 1H), 8.21 (dd, *J* = 9.6, 2.8 Hz, 1H), 7.86 (d, *J* = 2.8 Hz, 1H), 7.55 – 7.50 (m, 2H), 7.03 (d, *J* = 7.0 Hz, 1H), 6.99 (d, *J* = 8.5 Hz, 1H), 6.04 – 5.97 (m, 1H), 5.08 (dd, *J* = 12.7, 5.5 Hz, 1H), 4.24 (s, 2H), 3.88 – 3.73 (m, 4H), 3.42 – 3.31 (m, 4H), 2.92 – 2.82 (m, 1H), 2.80 – 2.67 (m, 2H), 2.50 (s, 3H), 2.43 (s, 3H), 2.35 – 2.27 (m, 2H), 2.15 – 2.06 (m, 3H), 1.94 – 1.87 (m, 2H), 1.73 – 1.66 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{39}H_{41}N_{10}O_7$, 761.3154; found: 761.3150.



Example 25

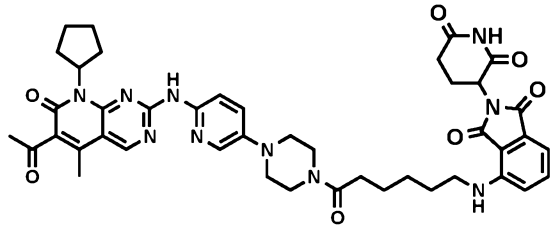
4-((3-(4-(6-(((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-3-oxopropyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (compound Example 25) (26 mg, 67%) as yellow solid. ^{1}H NMR

(600 MHz, CD_3OD) δ 9.07 (s, 1H), 8.13 (dd, *J* = 9.6, 2.9 Hz, 1H), 7.77 (d, *J* = 2.9 Hz, 1H), 7.52 (dd, *J* = 8.5, 7.1 Hz, 1H), 7.49 (d, *J* = 9.6 Hz, 1H), 7.09 (d, *J* = 8.6 Hz, 1H), 6.95 (d, *J* = 7.0 Hz, 1H), 6.00 (p, *J* = 8.9 Hz, 1H), 5.03 (dd, *J* = 12.7, 5.5 Hz, 1H), 3.76 (dt, *J* = 10.3, 4.7 Hz, 4H), 3.68 (t, *J* = 6.1 Hz, 2H), 3.18 (br. s, 4H), 2.88 – 2.80 (m, 1H), 2.79 (td, *J* = 5.9, 1.9 Hz, 2H), 2.75 – 2.62 (m, 2H), 2.50 (s, 3H), 2.42 (s, 3H), 2.34 – 2.26 (m, 2H), 2.13 – 2.03 (m, 3H), 1.94 – 1.86 (m, 2H), 1.73 – 1.64 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{40}H_{43}N_{10}O_7$, 775.3311; found: 775.3316.



Example 26

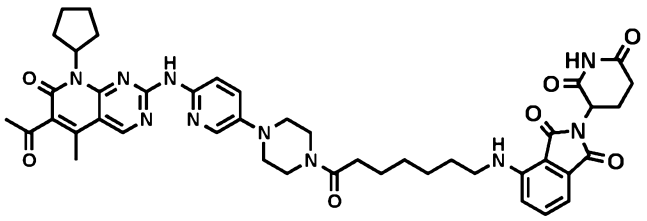
4-((4-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-4-oxobutyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (compound Example 26) (17 mg, 45%) as yellow solid. ^1H NMR (600 MHz, CD_3OD) δ 9.09 (s, 1H), 8.13 (dd, *J* = 9.6, 2.9 Hz, 1H), 7.79 (d, *J* = 2.8 Hz, 1H), 7.54 – 7.45 (m, 2H), 7.08 (d, *J* = 8.6 Hz, 1H), 6.92 (d, *J* = 7.0 Hz, 1H), 6.00 (p, *J* = 8.8 Hz, 1H), 5.05 (dd, *J* = 12.7, 5.5 Hz, 1H), 3.80 – 3.70 (m, 4H), 3.41 (td, *J* = 6.5, 1.3 Hz, 2H), 3.25 – 3.16 (m, 4H), 2.90 – 2.82 (m, 1H), 2.77 – 2.65 (m, 2H), 2.58 (t, *J* = 6.9 Hz, 2H), 2.50 (s, 3H), 2.43 (s, 3H), 2.35 – 2.27 (m, 2H), 2.13 – 2.06 (m, 3H), 2.00 (p, *J* = 6.7 Hz, 2H), 1.95 – 1.86 (m, 2H), 1.70 (dt, *J* = 10.1, 8.6 Hz, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{41}H_{45}N_{10}O_7$, 789.3467; found: 789.3474.



Example 27

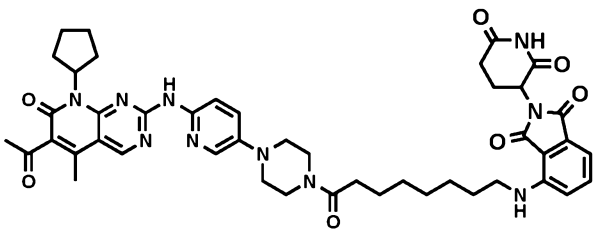
4-((6-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-6-oxohexyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (compound Example 27) (24 mg, 66%) as yellow solid. ^1H NMR (600 MHz, CD_3OD) δ 9.09 (s, 1H), 8.13 (dd, *J* = 9.6, 2.9 Hz, 1H), 7.78 (d, *J* = 2.8 Hz, 1H), 7.52 – 7.46 (m, 2H), 7.02 (d, *J* = 8.6 Hz, 1H), 6.90 (d, *J* = 7.0 Hz, 1H), 6.01 (p, *J* = 8.8 Hz,

1H), 5.04 (dd, *J* = 12.7, 5.5 Hz, 1H), 3.83 – 3.69 (m, 4H), 3.36 – 3.29 (m, 2H), 3.27 – 3.16 (m, 4H), 2.85 (ddd, *J* = 17.5, 13.9, 5.4 Hz, 1H), 2.76 – 2.62 (m, 2H), 2.54 – 2.45 (m, 5H), 2.43 (s, 3H), 2.36 – 2.27 (m, 2H), 2.14 – 2.04 (m, 3H), 1.95 – 1.86 (m, 2H), 1.75 – 1.63 (m, 6H), 1.54 – 1.44 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{43}H_{49}N_{10}O_7$, 817.3780; found: 817.3773.



Example 28

4-((7-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-7-oxoheptyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (compound Example 28) (26 mg, 74%) as yellow solid. ^{1}H NMR (600 MHz, CD_3OD) δ 9.07 (s, 1H), 8.16 (dd, *J* = 9.7, 2.9 Hz, 1H), 7.80 (d, *J* = 2.8 Hz, 1H), 7.55 – 7.45 (m, 2H), 7.00 (d, *J* = 8.6 Hz, 1H), 6.93 (d, *J* = 7.1 Hz, 1H), 6.00 (p, *J* = 8.9 Hz, 1H), 5.04 (dd, *J* = 12.8, 5.5 Hz, 1H), 3.82 – 3.69 (m, 4H), 3.32 – 3.20 (m, 6H), 2.84 (ddd, *J* = 17.8, 14.1, 5.3 Hz, 1H), 2.77 – 2.63 (m, 2H), 2.50 (s, 3H), 2.46 (t, *J* = 7.4 Hz, 2H), 2.42 (s, 3H), 2.35 – 2.25 (m, 2H), 2.13 – 2.05 (m, 3H), 1.95 – 1.85 (m, 2H), 1.74 – 1.60 (m, 6H), 1.50 – 1.39 (m, 4H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{44}H_{51}N_{10}O_7$, 831.3937; found: 831.3929.

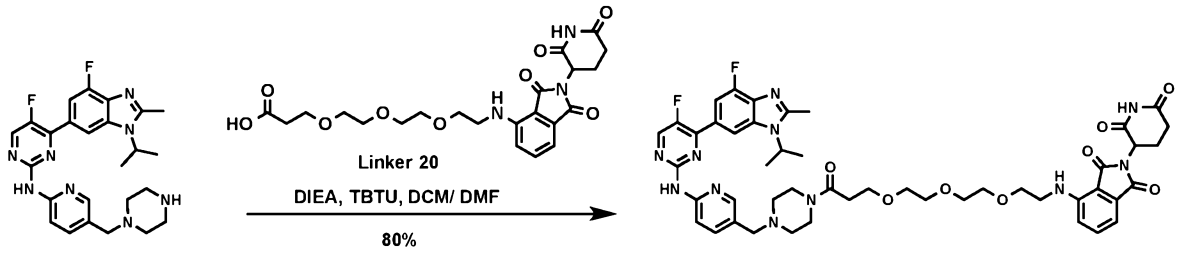


Example 29

4-((8-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-8-oxooctyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (compound Example 29) (23 mg, 66%) as yellow solid. ^{1}H NMR (600 MHz, CD_3OD) δ 9.07 (s, 1H), 8.16 (dd, *J* = 9.6, 2.9 Hz, 1H), 7.82 (d, *J* = 2.8 Hz, 1H), 7.54 – 7.48 (m, 2H), 7.01 (d, *J* = 8.6 Hz, 1H), 6.95 (d, *J* = 7.1 Hz, 1H), 6.01 (p, *J* = 8.8 Hz, 1H), 5.05 (dd, *J* = 12.8, 5.5 Hz, 1H), 3.82 – 3.71 (m, 4H), 3.33 – 3.22 (m, 6H), 2.85 (ddd, *J* = 17.7, 14.1, 5.3 Hz, 1H), 2.76 – 2.64 (m, 2H), 2.50 (s, 3H), 2.46 (t, *J* = 7.4 Hz, 2H), 2.43 (s, 3H), 2.32 (td, *J* = 15.4, 7.8 Hz, 2H), 2.14 – 2.04 (m, 3H), 1.95 – 1.86 (m, 2H), 1.74 – 1.60 (m, 6H),

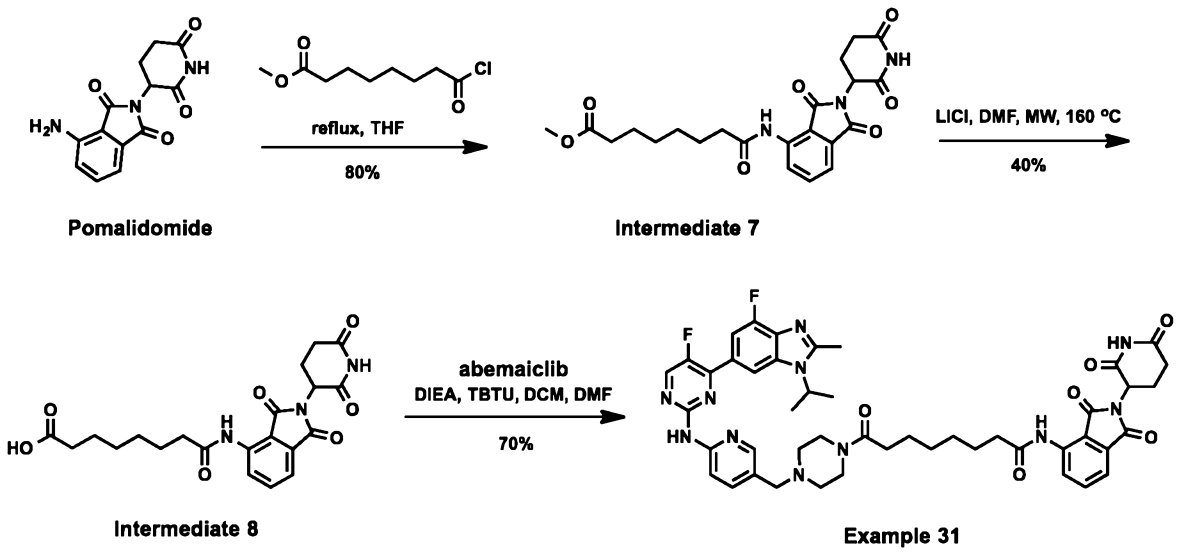
1.50 – 1.36 (m, 6H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{45}H_{53}N_{10}O_7$, 845.4093; found: 845.4101.

Scheme 6: Synthesis of example 30



2-(2,6-Dioxopiperidin-3-yl)-4-((2-(2-(2-(3-(4-((6-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-yl)amino)pyridin-3-yl)methyl)piperazin-1-yl)-3-oxopropoxy)ethoxy)ethoxy)ethyl)amino)isoindoline-1,3-dione (compound Example 30). To a solution of linker **20** (32 mg, 0.07 mmol) and abemaciclib (24 mg, 0.05 mmol) in CH_2Cl_2 (4 ml) and DMF (1 ml) were added DIEA (17 µl, 0.1 mmol) and TBTU (22 mg, 0.07 mmol). The reaction was stirred at RT for 1 h before being concentrated under reduced pressure. The resulting residue was purified by prep-HPLC to provide the title compound (37 mg, 80% over 2 steps). ^{1}H NMR (600 MHz, CD_3OD) δ 8.52 (d, *J* = 3.6 Hz, 1H), 8.32 (d, *J* = 8.4 Hz, 1H), 8.28 (s, 1H), 8.24 (s, 1H), 7.80 – 7.78 (m, 2H), 7.49 (t, *J* = 7.8 Hz, 1H), 7.02 (dd, *J* = 6.6 Hz, *J* = 3.0 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 5.00 (dd, J = 12.6 Hz, *J* = 6.0 Hz, 1 H), 3.75 (t, *J* = 6.0 Hz, 2H), 3.71 (t, *J* = 5.4 Hz, 2H), 3.66 – 3.60 (m, 14H), 3.46 (t, *J* = 5.4 Hz, 2H), 2.88 – 2.73 (m, 4H), 2.70 (s, 3H), 2.64 (t, *J* = 6.0 Hz, 2H), 2.65 – 2.50 (m, 4H), 2.12 – 2.10 (m, 1H), 1.74 (d, *J* =6.6 Hz, 6H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{47}H_{54}F_2N_{11}O_8$, 938.4119; found: 938.4148.

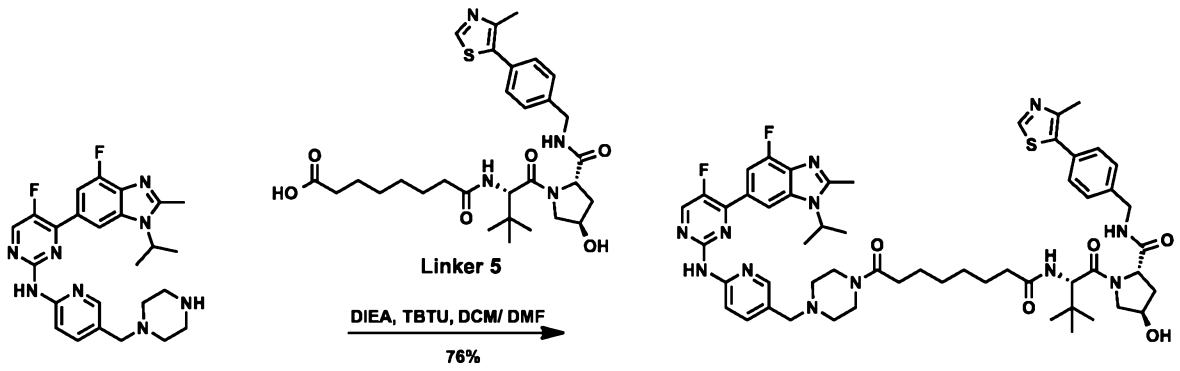
Scheme 7: Synthesis of example 31



***N*-(2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)-8-(4-((6-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-yl)amino)pyridin-3-yl)methyl)piperazin-1-yl)-8-oxooctanamide (compound Example 31).** Methyl 8-chloro-8-oxooctanoate (30 mg, 0.15 mmol) and pomalidomide (40 mg, 0.15 mmol) were dissolved in THF (5 ml). The resulting solution was heated at reflux for 3 h before the solvent was evaporated under reduced pressure. The residue was purified by prep-HPLC to provide intermediate **7** (53 mg, 0.12 mmol) as yellow oil. A solution of intermediate **7** (53 mg, 0.12 mmol) in DMF (1 ml) was treated with LiCl (25 mg, 0.6 mmol) at 160 °C in microwave reactor for 2 h. After being cooled to RT, the reaction mixture was poured into water (5 mL) and extracted with DCM (3X 5 ml). The organic phase was combined, dried over Na_2SO_4, and concentrated. The resulting residue was purified by prep-HPLC to provide intermediate **8** (21 mg, 40%) as yellow oil. To a solution of intermediate **8** (21 mg, 0.05 mmol) and abemaiclib (19 mg, 0.04 mmol) in CH_2Cl_2 (4 ml) and DMF (1 ml) were added DIEA (17 µl, 0.1 mmol) and TBTU (15 mg, 0.05 mmol). The reaction was stirred at RT for 1 h before being concentrated under reduced pressure. The resulting residue was purified by prep-HPLC to provide the title compound (25 mg, 70%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.47 (s, 1H), 8.95 (s, 1H), 8.86 (d, J = 8.4 Hz, 1H), 8.50 – 8.49 (m, 2H), 8.28 (s, 1H), 8.23 (s, 1H), 7.84 (d, J = 12.0 Hz, 1 H), 7.75 – 7.73 (m, 2H), 7.58 (d, J = 7.2 Hz, 1H), 5.02 – 4.99 (m, 1H), 4.79 – 4.74 (m, 1H), 3.86 – 3.85 (m, 1H), 3.61 (d, J = 12.6 Hz, 1H), 3.52 – 3.33 (m, 3H), 3.41 – 3.37 (m, 1H), 3.03 – 3.01 (m, 1H), 2.89 – 2.81(m, 2H), 2.72 (s, 3H), 2.63 – 2.56 (m, 1H), 2.53 – 2.37 (m, 4H), 2.36 – 2.28 (m, 3H), 2.25 – 2.18 (m, 1H), 1.86 – 1.78 (m, 2H), 1.74 (d. J = 6.6 Hz, 6H),

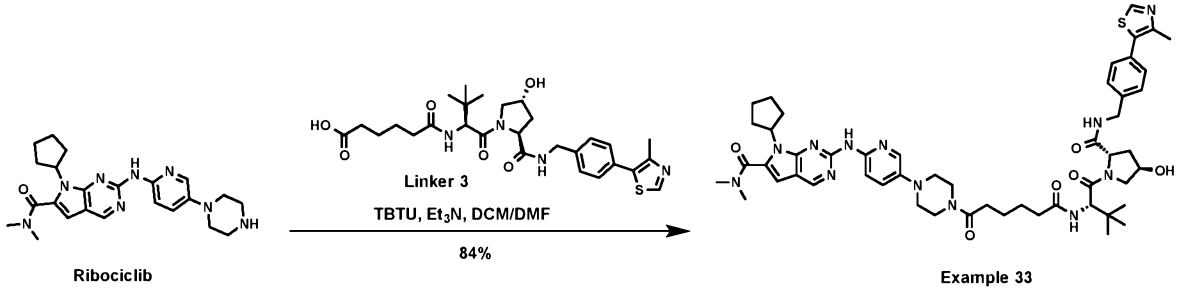
1.70 – 1.60 (m, 2H), 1.46 – 1.35 (5H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{46}H_{50}F_2N_{11}O_6$, 890.3908; found: 890.3931.

Scheme 8: Synthesis of example 32



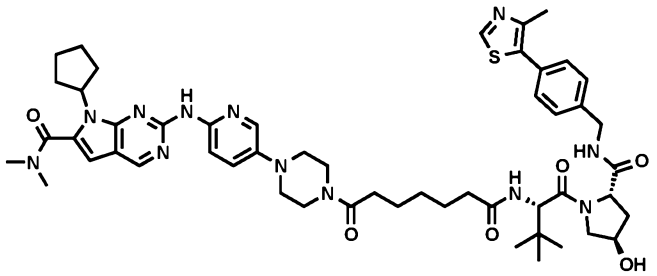
(2S,4R)-1-((S)-2-(8-(4-((6-((5-Fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-yl)amino)pyridin-3-yl)methyl)piperazin-1-yl)-8-oxooctanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (compound Example 32). To a solution of linker **5** (29 mg, 0.05 mmol) and abemaiclib (19 mg, 0.04 mmol) in CH_2Cl_2 (4 ml) and DMF (1 ml) were added DIEA (17 µl, 0.1 mmol) and TBTU (15 mg, 0.05 mmol). The reaction was stirred at RT for 1 h before being concentrated under reduced pressure. The resulting residue was purified by prep-HPLC to provide the Example **32** compound (31 mg, 76% over 2 steps). ^1H NMR (600 MHz, CD_3OD) δ 8.88 (s, 1H), 8.55 (d, J = 3.6 Hz, 1H), 8.36-8.35 (m, 2H), 8.25 (s, 1H), 7.86 (d, J = 9.0 Hz, 1H), 7.81 – 7.78 (m, 2H), 7.48 – 7.41 (m, 3H), 4.66 – 4.51 (m, 4 H), 4.36 (d, J = 8.4 Hz, 1H), 3.91 (d, J = 10.8 Hz, 1H), 3.81 (dd, J = 10.8 Hz, 3.6 Hz, 1H), 3.66 – 3.54 (m, 7H), 2.71 (s, 3H), 2.51 – 2.48 (m, 6H), 2.40 (t, J = 7.8 Hz, 2H), 2.34 – 2.21 (m, 3H), 2.12 – 2.06 (m, 1H), 1.73 (d, J = 6.6 Hz, 6H), 1.63 – 1.60 (m, 4H), 1.37 – 1.27 (m, 5H), 1.05 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{55}H_{69}F_2N_{12}O_5S$, 1047.5197; found: 1047.5192.

Scheme 9: synthesis of example 33



7-Cyclopentyl-2-((5-(4-(6-(((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl) carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-6-oxohexanoyl)piperazin-1-yl)pyridin-2-yl)amino)-*N*,*N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (compound Example 33). To a solution of ribociclib (9 mg, 0.021 mmol) and linker **3** (14 mg, 0.025 mmol) in DCM/DMF (1:1, 2 ml) were added triethylamine (17 µl, 0.12 mmol) and TBTU (8 mg, 0.025 mmol). The reaction was stirred at RT for 1 h before being concentrated under reduced pressure. The resulting residue was dissolved in MeOH, and purified by prep-HPLC to yield the product (19 mg, 84%) as yellow solid. ^{1}H NMR (600 MHz, CD_3OD) of major isomer (rotamer ratio 6:1) δ 9.02 (s, 1H), 8.97 (s, 1H), 8.08 (dd, J = 9.6, 2.4 Hz, 1H), 7.87 (d, J = 2.4 Hz, 1H), 7.48 (d, J = 7.8 Hz, 2H), 7.45 (d, J = 10.2 Hz, 1H), 7.43 (d, J = 8.4 Hz, 1H), 6.82 (s, 1H), 4.86-4.80 (m, 1H), 4.65 (s, 1H), 4.62-4.52 (m, 3H), 4.38 (d, J = 16.8 Hz, 1H), 3.93 (d, J = 10.8 Hz, 1H), 3.84-3.76 (m, 5H), 3.29 (t, J = 4.8 Hz, 2H), 3.24 (t, J = 4.8 Hz, 2H), 3.19 (s, 3H), 3.17 (s, 3H), 2.52-2.47 (m, 7H), 2.39-2.30 (m, 3H), 2.14-2.08 (m, 5H), 1.77-1.64 (m, 6H), 1.06 (s, 9H); HRMS(ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{51}H_{67}N_{12}O_6S$, 975.5022, found 975.5024.

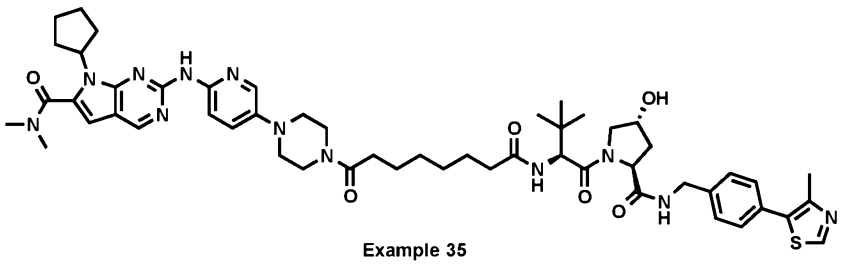
The Example **34, 35,** and **36** compounds were synthesized according to the procedures for the preparation of the Example **33** compound (above).



Example 34

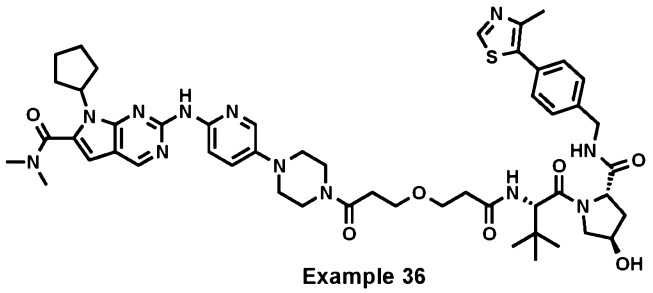
7-Cyclopentyl-2-((5-(4-(7-(((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl) carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-7-oxoheptanoyl) piperazin-1-yl)pyridin-2-yl)amino)-*N*,*N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (compound Example 34) (17 mg, 83%) as yellow solid. ^{1}H NMR (600 MHz, CD_3OD) of major isomer (rotamer ratio 7:2) δ 9.03 (s, 1H), 8.97 (s, 1H), 8.08 (dd, J = 9.6, 2.4 Hz, 1H), 7.88 (d, J = 2.4 Hz, 1H), 7.49 (d, J = 8.4 Hz, 2H), 7.46-7.43 (m, 3H), 6.82 (s, 1H), 4.86-4.80 (m, 1H), 4.66 (s, 1H), 4.61-4.51 (m, 3H), 4.39 (d, J = 14.4 Hz, 1H), 3.93 (d, J = 10.8 Hz, 1H), 3.84-3.77 (m, 5H), 3.29 (t, J = 4.8 Hz, 2H), 3.24 (t, J = 4.8 Hz, 2H), 3.19 (s, 3H), 3.17 (s, 3H), 2.51-2.47 (m, 7H), 2.37-2.23 (m, 3H), 2.16-2.08 (m, 5H), 1.79-1.73 (m, 2H), 1.70-1.63

(m, 4H), 1.45-1.39 (m, 2H), 1.06 (s, 9H). HRMS(ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{52}H_{69}N_{12}O_6S$, 989.5178, found 989.5180.



Example 35

7-Cyclopentyl-2-((5-(4-(8-(((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl) carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-8-oxooctanoyl)piperazin-1-yl)pyridin-2-yl)amino)-*N*,*N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (compound Example 35) (25 mg, 98%) as yellow solid. ^{1}H NMR (600 MHz, CD_3OD) of major isomer rotamer ration 8:1) δ 9.02 (s, 1H), 8.97 (s, 1H), 8.08 (dd, *J* = 9.6, 2.4 Hz, 1H), 7.87 (d, *J* = 2.4 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 11.2 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 2H), 6.82 (s, 1H), 4.86-4.79 (m, 1H), 4.66 (s, 1H), 4.62-4.52 (m, 3H), 4.38 (d, *J* = 15.6 Hz, 1H), 3.93 (d, *J* = 10.8 Hz, 1H), 3.84-3.77 (m, 5H), 3.29-3.28 (m, 2H), 3.24-3.22 (m, 2H), 3.19 (s, 3H), 3.17 (s, 3H), 2.50 (s, 3H), 2.49-2.47 (m, 4H), 2.36-2.32 (m, 3H), 2.16-2.08 (m, 5H), 1.80-1.72 (m, 2H), 1.69-1.62 (m, 4H), 1.46-1.36 (m, 4H), 1.06 (s, 9H). HRMS(ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{53}H_{71}N_{12}O_6S$, 1003.5335, found 1003.5361.

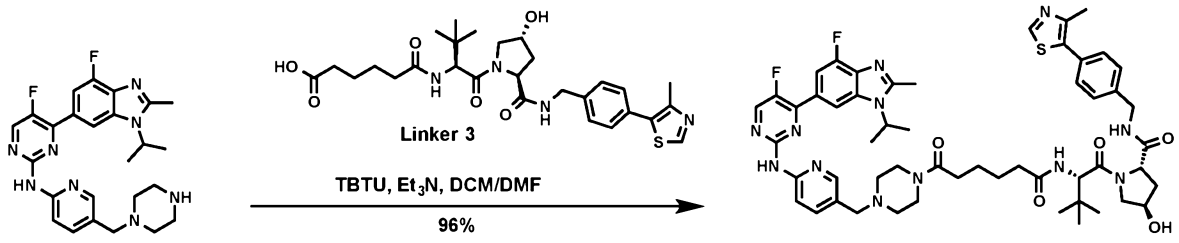


Example 36

7-Cyclopentyl-2-((5-(4-(3-(3-(((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl) carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-3-oxopropoxy) propanoyl)piperazin-1-yl)pyridin-2-yl)amino)-*N*,*N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (compound Example 36) (17 mg, 74%) as yellow solid. ^{1}H NMR (600 MHz, CD_3OD) of major isomer (rotamer ration 7:2) δ 9.04 (s, 1H), 8.96 (s, 1H), 8.07 (dd, *J* = 9.6, 2.4 Hz, 1H), 7.85 (d, *J* = 2.4 Hz, 1H), 7.45 (d, *J* = 9.0 Hz, 2H), 7.43 (d, *J* = 9.6 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 2H), 6.81 (s, 1H), 4.85-4.79 (m, 1H), 4.70 (s, 1H), 4.58 (t, *J*

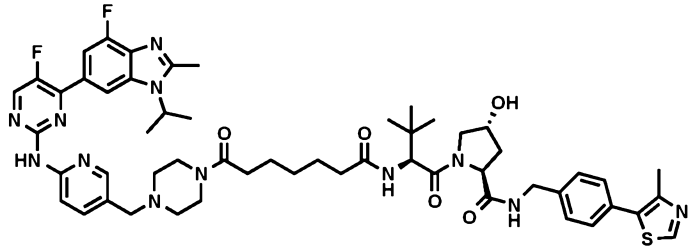
= 8.4 Hz, 1H), 4.54-4.51 (m, 1H), 4.49 (d, *J* = 15.6 Hz, 1H), 4.38 (d, *J* = 14.4Hz, 1H), 3.93 (d, *J* = 10.8 Hz, 1H), 3.84-3.78 (m, 7H), 3.74 (t, *J* = 6.0 Hz, 2H), 3.28-3.22 (m, 4H), 3.19 (s, 3H), 3.17 (s, 3H), 2.81-2.71 (m, 2H), 2.60-2.48 (m, 7H), 2.28-2.25 (m, 1H), 2.16-2.08 (m, 5H), 1.79-1.72 (m, 2H), 1.07 (s, 9H). HRMS(ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{51}H_{67}N_{12}O_7S$, 991.4971, found 991.4975.

Scheme 10: synthesis of example 37



(2S,4R)-1-((S)-2-(6-(4-((6-((5-Fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-yl)amino)pyridin-3-yl)methyl)piperazin-1-yl)-6-oxohexanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (compound Example 37). To a solution of abemaciclib (13 mg, 0.028 mmol) and linker **3** (18 mg, 0.032 mmol) in DCM/DMF (1:1, 2 ml) were added triethylamine (17 µl, 0.12 mmol) and TBTU (10 mg, 0.031 mmol). The reaction was stirred at RT for 1 h before being concentrated under reduced pressure. The resulting residue was dissolved in MeOH and purified by prep-HPLC to yield the desired product (31 mg, 96%) as white solid. ^{1}HNMR (CD_3OD, 600 MHz) (1H buried in solvent peak) 9.13 (s, 1H), 8.85 (d, *J* = 3.6 Hz, 1H), 8.57 (d, *J*= 11.4 Hz, 1H), 8.36 (d, *J* = 8.4 Hz, 1H), 8.14 (d, *J* = 10.8 Hz, 1H), 7.86 (d, *J*= 8.4 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 7.8 Hz, 2H), 5.15-5.10 (m, 1 H), 4.65 (s, 1H), 4.62-4.51 (m, 5H), 4.39 (d, *J* = 15.6 Hz, 1H), 3.93-3.82 (m, 6H), 3.41-3.33 (m, 4H), 2.94 (s, 3H), 2.51-2.45 (m, 5H), 2.39-2.29 (m, 2H), 2.26-2.23 (m, 1H), 2.12-2.08 (m, 1H), 1.82 (d, *J* = 6.0 Hz, 6H), 1.72-1.62 (m, 4H), 1.06 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{53}H_{65}F_2N_{12}O_5S$ $[M+H]^+$, 1019.4884, found 1019.4881.

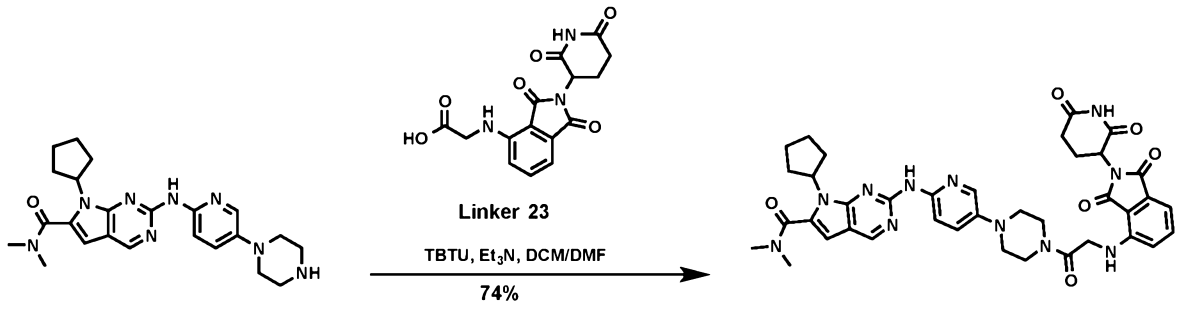
The Example **38** compound was synthesized according to the procedures for the preparation of the Example **37** compound (above).



Example 38

(2S,4R)-1-((S)-2-(7-(4-((6-((5-Fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-yl)amino)pyridin-3-yl)methyl)piperazin-1-yl)-7-oxoheptanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (compound Example 38) (24 mg, 98%) as white solid. ^{1}H NMR (CD_3OD, 600 MHz) (1H buried in solvent peak) δ 9.11 (s, 1H), 8.85 (d, *J* = 3.6 Hz, 1H), 8.56 (d, *J*= 9.6 Hz, 1H), 8.35 (d, *J* = 8.4 Hz, 1H), 8.14 (d, *J* = 10.8 Hz, 1H), 7.87 (d, *J*= 8.4 Hz, 1H), 7.50 (d, *J* = 7.2 Hz, 2H), 7.44 (d, *J* = 9.0 Hz, 2H), 5.14-5.10 (m, 1 H), 4.66 (s, 1H), 4.62-4.51 (m, 5H), 4.39 (d, *J* = 15.6 Hz, 1H), 3.94-3.82 (m, 6H), 3.46-3.30 (m, 4H), 2.95 (s, 3H), 2.51 (s, 3H), 2.47 (t, *J* = 7.8 Hz, 2H), 2.36-2.23 (m, 3H), 2.13-2.08 (m, 1H), 1.82 (d, *J* = 6.0 Hz, 6H), 1.69-1.62 (m, 4H), 1.41-1.39 (m, 2H), 1.06 (s, 9H). HRMS(ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{54}H_{67}F_2N_{12}O_5S$, 1033.5041, found 1033.5053.

Scheme 11: synthesis of example 39

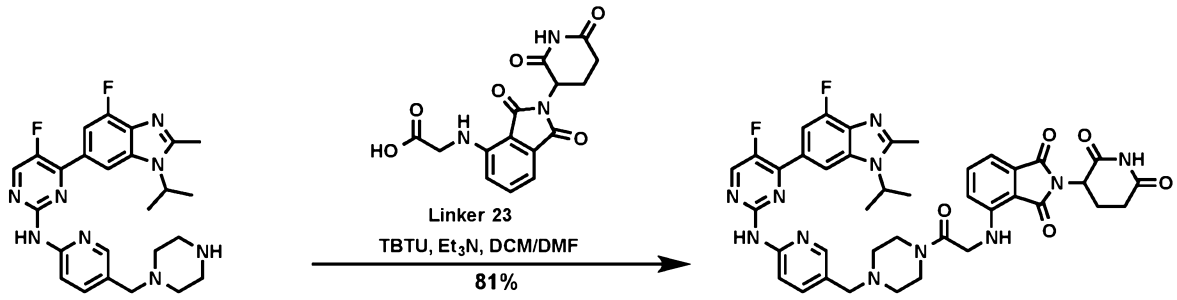


Ribociclib Example 39

7-Cyclopentyl-2-((5-(4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)glycyl) piperazin-1-yl)pyridin-2-yl)amino)-*N*,*N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (compound Example 39). To a solution of ribociclib (12 mg, 0.027 mmol) and linker **23** (11 mg, 0.034 mmol) in DCM/DMF (1:1, 2 ml) were added triethylamine (17 µl, 0.12 mmol) and TBTU (12 mg, 0.038 mmol). The reaction solution was stirred at RT for 1 h before being concentrated under reduced pressure. The resulting residue was dissolved in MeOH and purified by prep-HPLC to yield the desired product (15 mg, 74%) as yellow solid. ^{1}H NMR (CD_3OD, 600 MHz) δ 8.86 (s, 1H), 7.89 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.82 (d, *J* = 2.4 Hz, 1H),

7.52-7.49 (m, 2H), 7.08 (d, J = 7.2 Hz, 1H), 6.90 (d, J = 8.4 Hz, 1H), 6.65 (s, 1H), 4.96-4.93 (m, 1H), 4.78-4.72 (m, 1H), 4.17 (s, 2H), 3.85-3.83 (m, 2H), 3.72-3.72 (m, 2H), 3.30-3.28 (m, 2H), 3.23-3.21 (m, 2H), 3.18 (s, 3H), 3.15 (s, 3H), 2.84-2.73 (m, 3H), 2.46-2.40 (m, 2H), 2.15-2.02 (m, 5H), 1.75-1.67 (m, 2H). HRMS(ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{38}H_{41}N_{11}O_6$, 748.3314, found 748.3391.

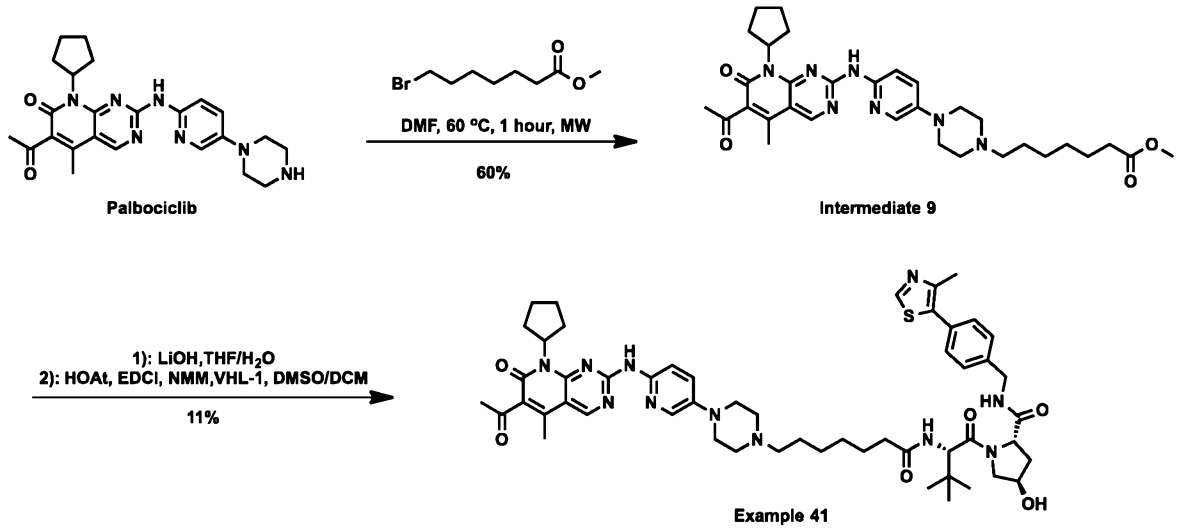
Scheme 12: synthesis of example 40



Abemaciclib Example 40

2-(2,6-Dioxopiperidin-3-yl)-4-((2-(4-((6-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-yl)amino)pyridin-3-yl)methyl)piperazin-1-yl)-2-oxoethyl)amino)isoindoline-1,3-dione (compound Example 40). To a solution of abemaciclib (12 mg, 0.025 mmol) and compound **23** (10 mg, 0.032 mmol) in DCM/DMF (1:1, 2 ml) were added triethylamine (17 µl, 0.12 mmol) and TBTU (11 mg, 0.034 mmol). The reaction was stirred at RT for 1 h before being concentrated under reduced pressure. The resulting residue was dissolved in MeOH and purified by prep-HPLC to yield the desired product (16 mg, 81%) as yellow solid. ^{1}H NMR (CD_3OD, 600 MHz) δ 8.59 (d, J = 2.4 Hz, 1H), 8.44 (s, 1H), 8.30 (s, 1H), 8.13 (s, 2H), 7.89 (d, J = 10.8 Hz, 1H), 7.36 (t, J = 7.2 Hz, 1H), 6.98 (d, J = 7.2 Hz, 1H), 6.75 (d, J = 8.4 Hz, 1H), 4.95-4.92 (m, 1H), 4.89-4.84 (m, 1H), 4.29 (s, 2H), 4.04 (s, 2H), 3.98-3.74 (m, 4H), 3.31-3.20 (m, 4H), 3.18 (s, 3H), 2.85-2.69 (m, 6H), 2.13-2.11 (m, 1H), 1.73 (d, J = 7.8 Hz, 6H); HRMS(ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{38}H_{41}N_{11}O_6$, 792.3176, found 792.3180.

Scheme 13: Synthesis of example 41

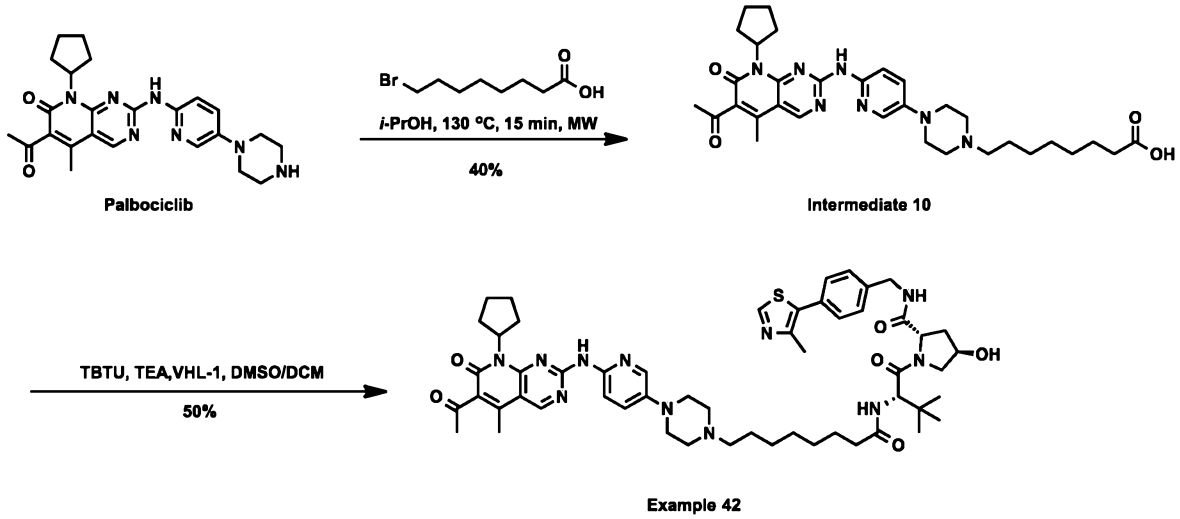


Methyl 7-(4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)heptanoate (Intermediate 9). A solution of palbociclib (50 mg, 0.112 mmol), methyl 7-bromoheptanoate (75 mg, 0.335 mmol) and K_2CO_3 (46 mg, 0.335 mmol) in DMF (5 ml) was heated at 60 °C in a microwave reactor for 1 h. After being cooled to RT, the reaction mixture was filtered and concentrated, and the resulting residue was purified by prep-HPLC to yield the title compound (40 mg, 60%) as yellow solid. ^{1}H NMR (600 MHz, CD_3OD) δ 9.10 (s, 1H), 8.21 (dd, J = 9.6, 2.7 Hz, 1H), 7.98 (d, J = 2.5 Hz, 1H), 7.59 (d, J = 9.6 Hz, 1H), 5.99 (p, J = 8.8 Hz, 1H), 3.93 (s, 2H), 3.75 (s, 2H), 3.65 (s, 3H), 3.38 – 3.16 (m, 6H), 2.49 (s, 3H), 2.42 (s, 3H), 2.37 – 2.25 (m, 4H), 2.13 – 2.03 (m, 2H), 1.94 – 1.86 (m, 2H), 1.85 – 1.78 (m, 2H), 1.72 – 1.59 (m, 4H), 1.47 – 1.36 (m, 4H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{32}H_{44}N_7O_4$, 590.3449; found: 590.3446.

(2*S*,4*R*)-1-((*S*)-2-(7-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)heptanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (compound Example 41) To a stirring solution of intermediate **9** (40 mg, 0.0678 mmol) in THF/H_2O (10 ml/2 ml) was added anhydrous LiOH (3.3 mg, 0.136 mmol). After the resulting mixture was stirred overnight at RT, the reaction mixture was concentrated under reduced pressure and the resulting residue was dissolved in DCM/DMSO (5 ml/1 ml). To the resulting solution were added NMM (68 mg, 0.678 mmol), VHL-1 (32 mg, 0.0678 mmol), HOAt (14 mg, 0.102 mmol), and EDCI (19.5 mg, 0.102 mmol). After the mixture was stirred at RT overnight, the reaction was concentrated. The resulting residue was purified by prep-HPLC to yield the title compound (8 mg, 11%) as yellow solid. ^{1}H NMR (600 MHz, CD_3OD)

δ 9.10 (s, 1H), 8.98 (s, 1H), 8.20 (dd, *J* = 9.5, 2.6 Hz, 1H), 7.97 (d, *J* = 2.4 Hz, 1H), 7.58 (d, *J* = 9.5 Hz, 1H), 7.47 (d, *J* = 8.2 Hz, 2H), 7.42 (d, *J* = 8.0 Hz, 2H), 6.05 – 5.96 (m, 1H), 4.64 (s, 1H), 4.58 – 4.47 (m, 3H), 4.37 (d, *J* = 15.5 Hz, 1H), 3.99 – 3.84 (m, 3H), 3.84 – 3.79 (m, 1H), 3.80 – 3.66 (m, 2H), 3.34 – 3.18 (m, 6H), 2.50 (s, 3H), 2.48 (s, 3H), 2.43 (s, 3H), 2.36 – 2.26 (m, 4H), 2.23 (dd, *J* = 13.1, 7.6 Hz, 1H), 2.14 – 2.05 (m, 3H), 1.94 – 1.86 (m, 2H), 1.84 – 1.75 (m, 2H), 1.74 – 1.61 (m, 4H), 1.48 – 1.38 (m, 4H), 1.04 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{53}H_{70}N_{11}O_6S$, 988.5226; found: 988.5226.

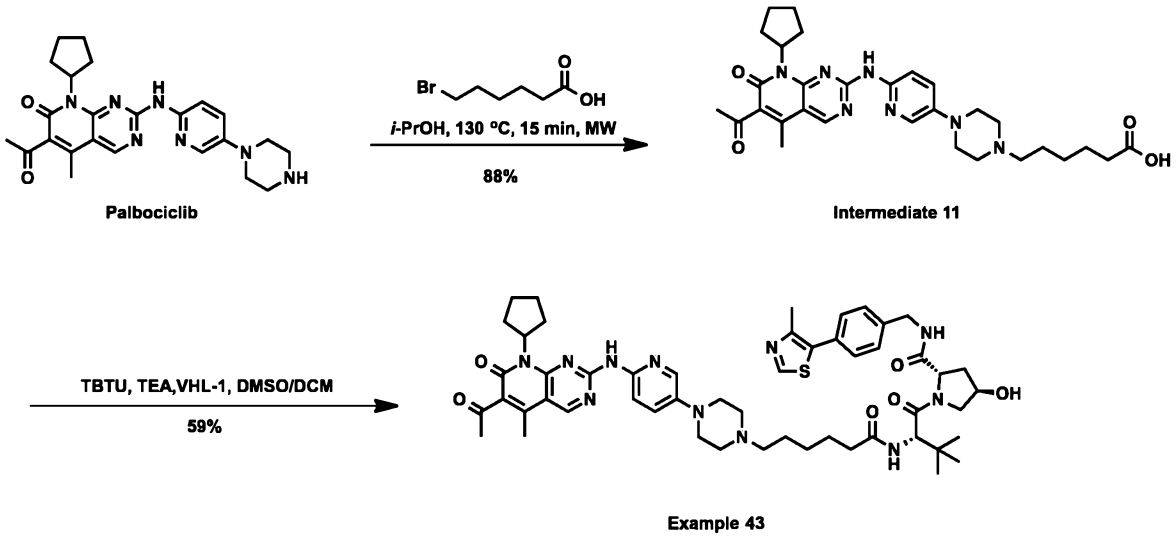
Scheme 14: Synthesis of example 42



(2*S*,4*R*)-1-((*S*)-2-(8-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)octanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (example 42) A solution of palbociclib (45 mg, 0.1 mmol), 8-bromooctanoic acid (64 mg, 0.28 mmol) and TEA (0.05 mL, 0.36 mmol) in *i*-PrOH (1 ml) was heated at 130 °C in a microwave reactor for 15 min. After being cooled to RT, the reaction mixture was concentrated, and the resulting residue was purified by prep-HPLC to yield the intermediate **10** (24 mg, 40%) as yellow solid. To a stirring solution of intermediate **10** (24 mg, 0.04 mmol) in DCM/DMSO (5 ml/1 ml) were added TEA (0.05 mL, 0.36 mmol), VHL-1 (20 mg, 0.043 mmol), and TBTU (12 mg, 0.038 mmol). After the mixture was stirred at RT overnight, the reaction was concentrated. The resulting residue was purified by prep-HPLC to yield the title compound (20 mg, 50%) as yellow solid. ^{1}H NMR (600 MHz, CD_3OD) δ 9.13 (s, 1H), 9.07 (s, 1H), 8.23 (dd, *J* = 9.6, 3.0 Hz, 1H), 8.00 (d, *J* = 2.8 Hz, 1H), 7.60 (d, *J* = 9.6 Hz, 1H), 7.50 (d, *J* = 8.1 Hz, 2H), 7.45 (d, *J* = 8.2 Hz, 2H), 6.03 (p, *J* = 8.7 Hz, 1H), 4.67 (s, 1H), 4.60 – 4.53 (m, 3H), 4.40 (d, *J* = 15.5 Hz, 1H), 3.96 – 3.71 (m, 6H), 3.30 – 3.20 (m, 6H), 2.52 (s, 3H), 2.51

(s, 3H), 2.45 (s, 3H), 2.37 – 2.24 (m, 5H), 2.17 – 2.03 (m, 3H), 1.97 – 1.87 (m, 2H), 1.84 – 1.80 (m, 2H), 1.77 – 1.60 (m, 4H), 1.50 – 1.33 (m, 6H), 1.05 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{54}H_{72}N_{11}O_6S$, 1002.5389; found: 1002.5390.

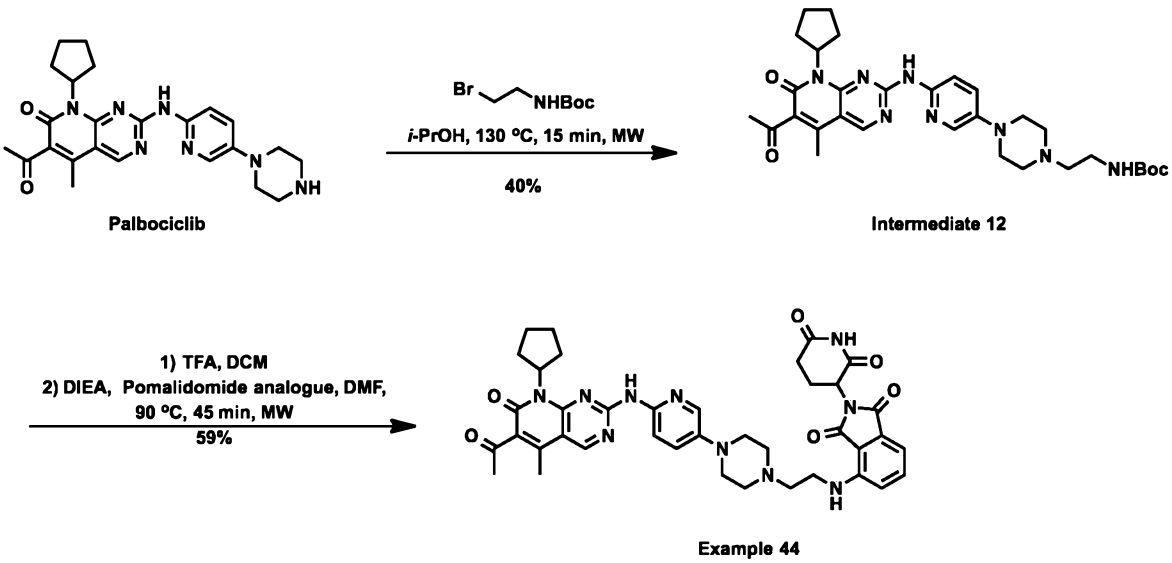
Scheme 15: Synthesis of example 43



(2*S*,4*R*)-1-((*S*)-2-(6-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)hexanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (example 43) A solution of palbociclib (40 mg, 0.09 mmol), 6-bromohexanoic acid (55 mg, 0.28 mmol) and TEA (0.05 mL, 0.36 mmol) in *i*-PrOH (1 ml) was heated at 130 °C in a microwave reactor for 15 min. After being cooled to RT, the reaction mixture was concentrated, and the resulting residue was purified by prep-HPLC to yield the intermediate **11** (44 mg, 88%) as yellow solid. To a stirring solution of intermediate **11** (44 mg, 0.065 mmol) in DCM/DMSO (5 ml/1 ml) were added TEA (0.05 mL, 0.36 mmol), VHL-1 (34 mg, 0.073 mmol), and TBTU (22 mg, 0.070 mmol). After the mixture was stirred at RT overnight, the reaction was concentrated. The resulting residue was purified by prep-HPLC to yield the title compound (37 mg, 59%) as yellow solid. ^{1}H NMR (600 MHz, CD_3OD) δ 9.12 (s, 1H), 9.12 (s, 1H), 8.23 (dd, *J* = 9.8, 2.4 Hz, 1H), 8.00 (d, *J* = 2.7 Hz, 1H), 7.60 (d, *J* = 9.6 Hz, 1H), 7.49 (d, *J* = 7.8 Hz, 2H), 7.44 (d, *J* = 8.1 Hz, 2H), 6.02 (p, *J* = 8.8 Hz, 1H), 4.67 (s, 1H), 4.62 – 4.49 (m, 3H), 4.40 (d, *J* = 15.5 Hz, 1H), 3. 96 – 3.71 (m, 6H), 3.30 – 3.20 (m, 6H), 2.52 (s, 3H), 2.51 (s, 3H), 2.45 (s, 3H), 2.40 – 2.21 (m, 5H), 2.16 – 2.05 (m, 3H), 1.97 – 1.88 (m, 2H), 1.88

– 1.78 (m, 2H), 1.72 – 1.67 (m 4H), 1.49 – 1.40 (m, 2H), 1.07 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{52}H_{68}N_{11}O_6S$, 974.5069; found: 974.5069.

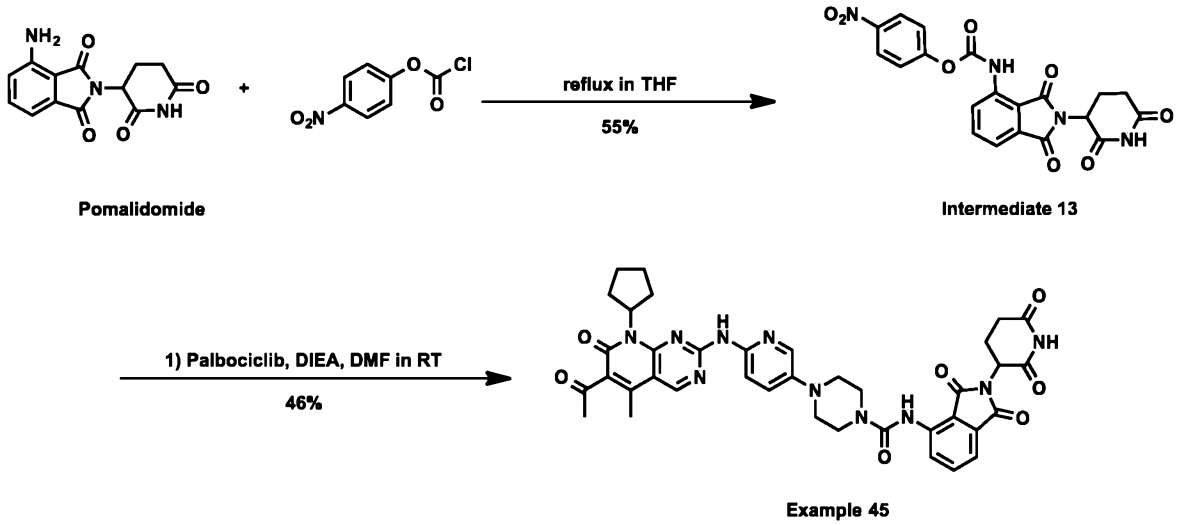
Scheme 16: Synthesis of example 44



4-((2-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)ethyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (example 44) A solution of palbociclib (45 mg, 0.1 mmol), *tert*-butyl (2-bromoethyl)carbamate (69 mg, 0.31 mmol) and TEA (0.05 mL, 0.36 mmol) in *i*-PrOH (1 ml) was heated at 130 °C in a microwave reactor for 15 min. After being cooled to RT, the reaction mixture was concentrated. The resulting residue was purified by prep-HPLC to yield the intermediate **12** (24 mg, 40%) as yellow solid. To a stirring solution of intermediate **12** (24 mg, 0.04 mmol) in DCM (2mL) was added TFA (1 mL). The mixture was stirred at RT and the reaction progress was monitored by LC/MS. After completion of the reaction, the reaction solution was concentrated, and the resulting residue was dissolved in DMF (1 ml). To this solution were added TEA (0.05 mL, 0.36 mmol) and pomalidomide analogue (17 mg, 0.06 mmol). The resulting mixture was heated at 90 °C in a microwave reactor for 45 min. After being cooled to RT, the reaction mixture was concentrated, and the resulting residue was purified by prep-HPLC to yield the title compound (4 mg, 13%) as yellow solid. ^{1}H NMR (600 MHz, CD_3OD) δ 9.10 (s, 1H), 8.14 (dd, J = 9.5, 2.7 Hz, 1H), 8.01 (d, J = 2.8 Hz, 1H), 7.70 – 7.65 (m, 2H), 7.22 (d, J = 7.8 Hz, 1H), 7.21 (d, J = 6.6 Hz, 1H), 6.02 (p, J = 8.9 Hz, 1H), 5.11 (dd, J = 12.5, 5.5 Hz, 1H), 3.90 (t, J = 6.2 Hz, 2H), 3.63 (br, 8H), 3.55 (t, J = 6.1 Hz, 2H), 2.94 – 2.86 (m, 1H), 2.80 – 2.65 (m, 2H), 2.52 (s, 3H), 2.43 (s, 3H), 2.38 – 2.26 (m, 42H), 2.17 –

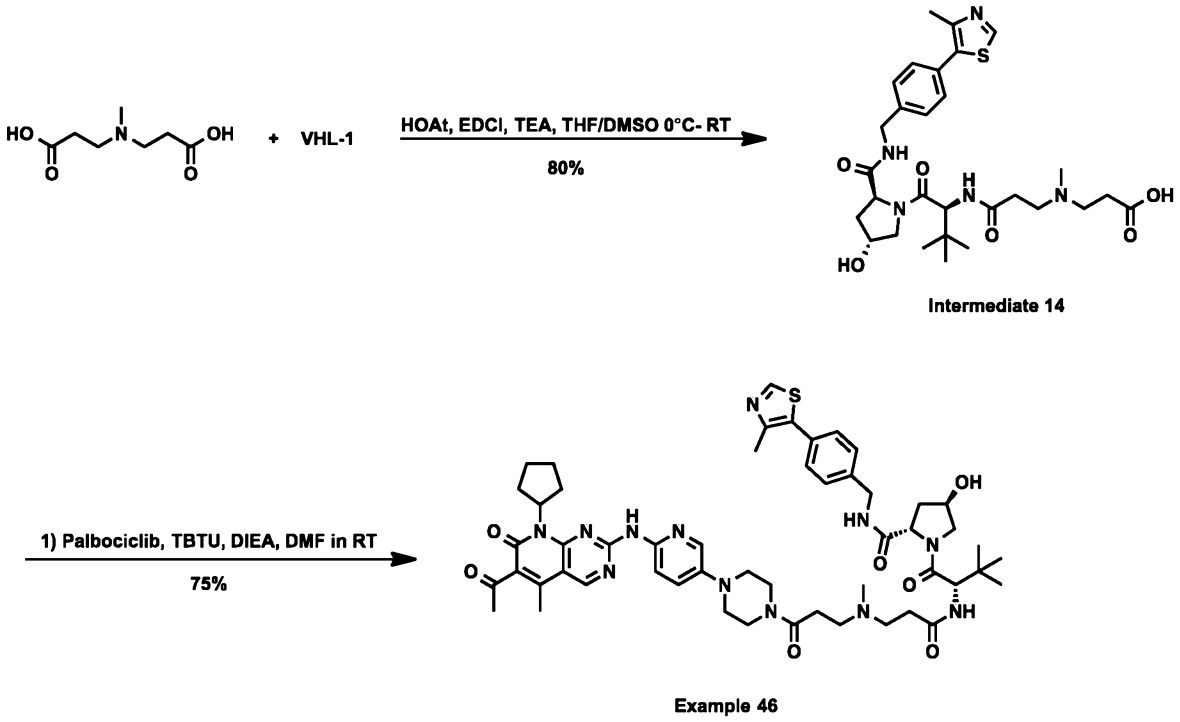
2.05 (m, 3H), 1.99 – 1.84 (m, 2H), 1.77 – 1.64 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{39}H_{43}N_{10}O_6$, 747.3362; found: 747.3342.

Scheme 17: Synthesis of example 45



4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)-*N*-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)piperazine-1-carboxamide (example 45) A solution of pomalidomide (278 mg, 1 mmol), 4-nitrophenyl carbonochloridate (307 mg, 1.52 mmol) in THF (5 ml) was heated at reflux overnight. After being cooled to RT, the reaction mixture was concentrated. The resulting residue was washed with ethyl acetate, dried over $NaSO_4$, and concentrated to yield the intermediate **13** (240 mg, 55%) as yellow solid. To a stirring solution of intermediate **13** (19 mg, 0.043 mmol) in DMF (1 mL) were added DIEA (0.014 mL, 0.1 mmol) and palbociclib (18 mg, 0.041 mmol). The mixture was stirred at RT overnight, before being concentrated. The resulting residue was purified by prep-HPLC to yield the title compound (14 mg, 46%) as yellow solid. ^1H NMR (600 MHz, CD_3OD) δ 9.07 (s, 1H), 8.56 (d, J = 8.5 Hz, 1H), 8.10 (dd, J = 9.6, 2.6 Hz, 1H), 7.78 – 7.70 (m, 1H), 7.64 (d, J = 8.8 Hz, 1H), 7.51 (d, J = 7.3 Hz, 1H), 5.97 (p, J = 8.9 Hz, 1H), 5.07 (dd, J = 12.5, 5.5 Hz, 1H), 3.86 – 3.79 (m, 4H), 3.45 – 3.40 (m, 4H), 2.89 – 2.72 (m, 3H), 2.54 (s, 3H), 2.44 (s, 3H), 2.33 – 2.27 (m, 2H), 2.22 – 2.15 (m, 1H), 2.11 – 2.06 (m, 2H), 1.96 – 1.86 (m, 2H), 1.73 – 1.59 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{38}H_{39}N_{10}O_7$, 747.2998; found: 747.2970.

Scheme 18: Synthesis of example 46

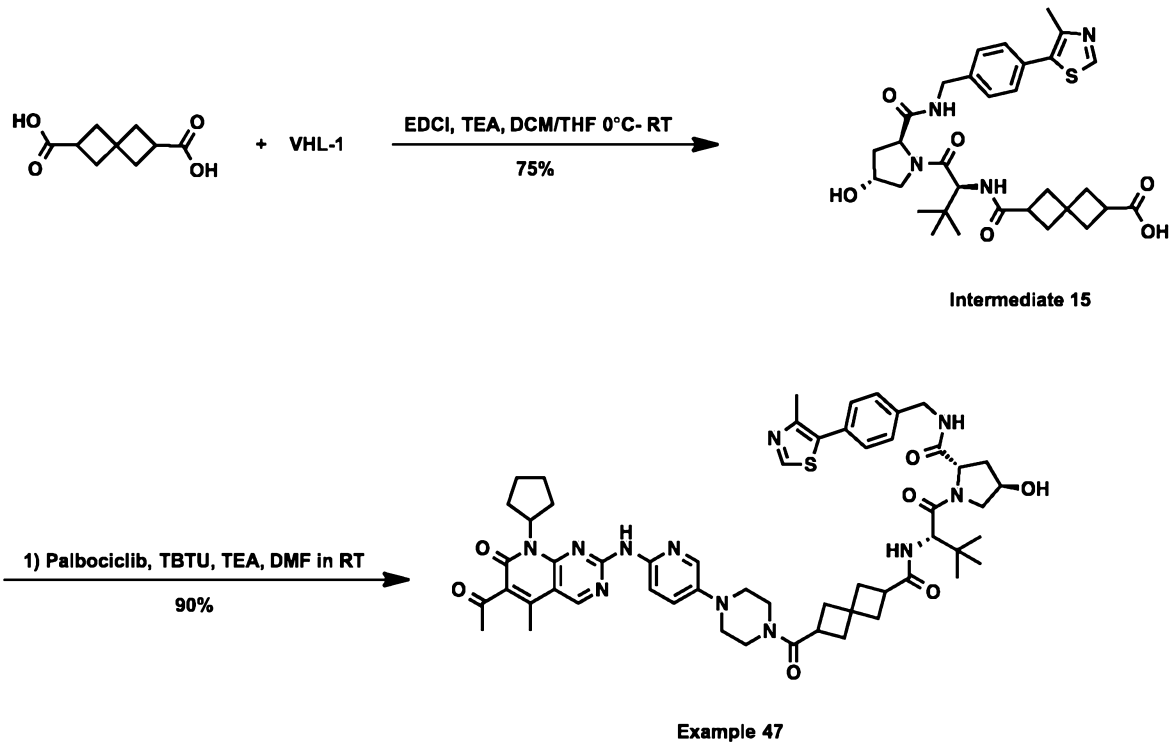


3-((3-(((*S*)-1-((2*S*,4*R*)-4-Hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-3-oxopropyl)(methyl)amino)propanoic acid (intermediate 14) To a solution of 3,3'-(methylazanediyl)dipropionic acid (700 mg, 4 mmol) in DMSO/THF (1:1, 10 ml) were added VHL-1 (472 mg, 1 mmol), triethylamine (0.5 ml, 3.5 mmol), HOAt (173 mg, 1.3 mmol), and EDCI (242 mg, 1.3 mmol) sequentially at 0 °C. The resulting solution was stirred for 2 h at 0 °C, before being warmed to room temperature (RT). After being stirred overnight at RT, the reaction was quenched with water, and concentrated under reduced pressure. The resulting residue was purified by reverse-phase chromatography to yield the title compound (470 mg, 80%) as white solid. ^{1}H NMR (600 MHz, CD_3OD) δ 8.93 (s, 1H), 7.49 (d, *J* = 8.7 Hz, 2H), 7.44 (d, *J* = 8.1 Hz, 2H), 4.61 – 4.54(m, 4H), 4.37 (d, *J* = 15.4 Hz, 1H), 3.98 (d, *J* = 11.0 Hz, 1H), 3.82 (dd, *J* = 10.9, 3.8 Hz, 1H), 3.37 (s, 4H), 2.92 (s, 3H), 2.87 (dt, *J* = 18.1, 6.5 Hz, 4H), 2.50 (s, 3H), 2.28 – 2.22 (m, 1H), 2.16 – 2.09 (m, 1H), 1.08 (s, 9H).

(2*S*,4*R*)-1-((*S*)-2-(3-((3-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-3-oxopropyl)(methyl)amino)propanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (example 46) To a stirring solution

of intermediate **14** (22 mg, 0.031 mmol) in DMF (1 ml) were added TEA (0.015 mL, 0.11 mmol), palbociclib (13.1 mg, 0.029 mmol), and TBTU (11.3 mg, 0.035 mmol). The mixture was stirred at RT overnight before being concentrated. The resulting residue was purified by prep-HPLC to yield the title compound (22mg, 75%) as yellow solid. ^{1}H NMR (600 MHz, CD_3OD) δ 9.11 (s, 1H), 8.92 (s, 1H), 8.19 (d, J = 7.9 Hz, 1H), 7.93 (d, J = 2.7 Hz, 1H), 7.59 (d, J = 9.6 Hz, 1H), 7.47 (d, J = 7.8 Hz, 2H), 7.42 (d, J = 8.1 Hz, 2H), 6.03 (p, J = 8.8 Hz, 1H), 4.65 – 4.49 (m, 4H), 4.38 (d, J = 15.5 Hz, 1H), 3.97 (d, J = 10.8 Hz, 1H), 3.90 – 3.64 (m, 5H), 3.64 – 3.51 (m, 2H), 3.43 – 3.36 (m, 4H), 3.10 – 3.02 (m, 2H), 2.93 (s, 3H), 2.93 – 2.85 (m, 4H), 2.52 (s, 3H), 2.49 (s, 3H), 2.45 (s, 3H), 2.37 – 2.29 (m, 2H), 2.29 – 2.20 (m, 1H), 2.16 – 2.07 (m, 3H), 1.97 – 1.88 (m, 2H), 1.76 – 1.66 (m, 2H), 1.07 (d, J = 10.7 Hz, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{53}H_{69}N_{12}O_7S$, 1017.5127; found: 1017.5013.

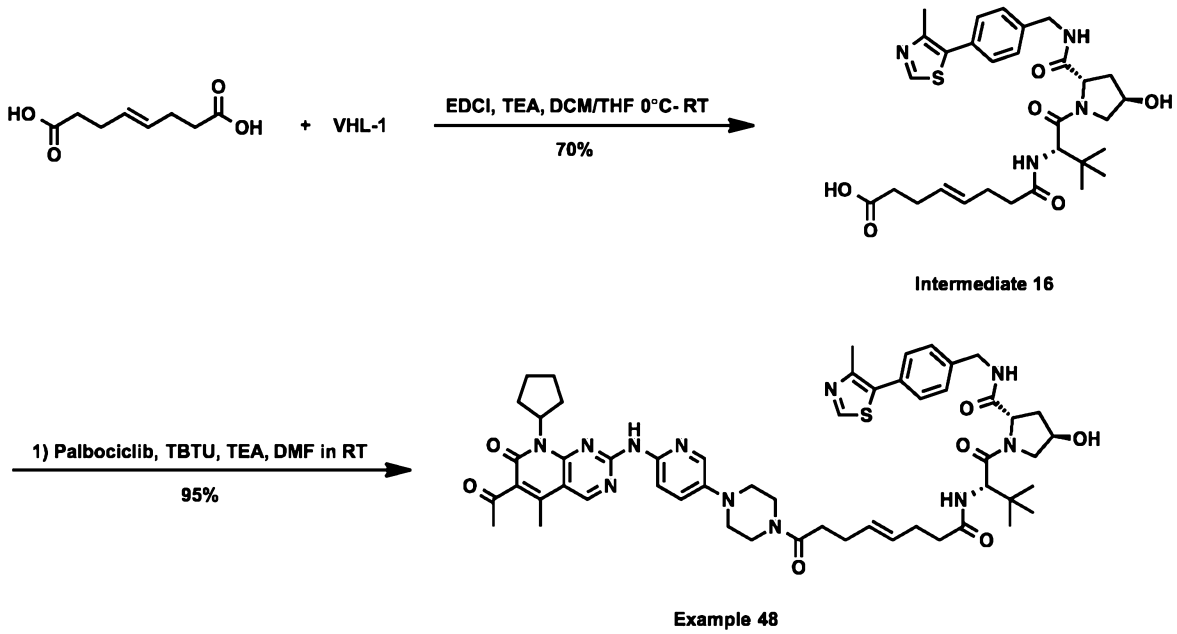
Scheme 18: Synthesis of example 47



(2*S*,4*R*)-1-((*S*)-2-(6-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazine-1-carbonyl)spiro[3.3]heptane-2-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (example 47) To a solution of spiro[3.3]heptane-2,6-dicarboxylic acid (250 mg, 1.36 mmol) in DCM/THF (1:1, 5 ml) were added VHL-1 (218 mg, 0.47 mmol), triethylamine (0.21 ml, 1.4 mmol), and EDCI (112 mg, 0.59 mmol) sequentially

at 0 °C. The resulting solution was stirred for 2 h at 0 °C, before being warmed to room temperature (RT). After stirring overnight at RT, the reaction was quenched with water, and concentrated under reduced pressure. The resulting residue was purified by reverse-phase chromatography to yield the intermediate **15** (210 mg, 75%) as white solid. To a stirring solution of intermediate **15** (19 mg, 0.031 mmol) in DMF (1 ml) were added TEA (0.01 mL, 0.07 mmol), palbociclib (12.7 mg, 0.028 mmol), and TBTU (14.2 mg, 0.044 mmol). The mixture was stirred at RT overnight before being concentrated. The resulting residue was purified by prep-HPLC to yield the title compound (26 mg, 90%) as yellow solid. ^{1}H NMR (600 MHz, CD_3OD) δ 9.11 (s, 1H), 8.97 (s, 1H), 8.21 (dd, J = 9.6, 3.0 Hz, 1H), 7.88 (d, J = 2.4 Hz, 1H), 7.57 (d, J = 9.6 Hz, 1H), 7.48 (dd, J = 8.0, 1.6 Hz, 2H), 7.45 – 7.42 (m, 2H), 6.02 (p, J = 8.8 Hz, 1H), 4.69 – 4.62 (m, 1H), 4.62 – 4.47 (m, 3H), 4.41 – 4.27 (m, 1H), 3.92 (dd, J = 11.0, 4.4 Hz, 1H), 3.86 – 3.70 (m, 3H), 3.71 – 3.56 (m, 2H), 3.37 – 3.22 (m, 6H), 3.17 – 3.03 (m, 1H), 2.52 (s, 3H), 2.50 (s, 3H), 2.45 (s, 3H), 2.40 – 2.04 (m, 13H), 1.96 – 1.88 (m, 2H), 1.76 – 1.68 (m, 2H), 1.04 (d, J = 3.4 Hz, 9H). HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{55}H_{68}N_{11}O_7S$, 1026.5018; found: 1026.4985.

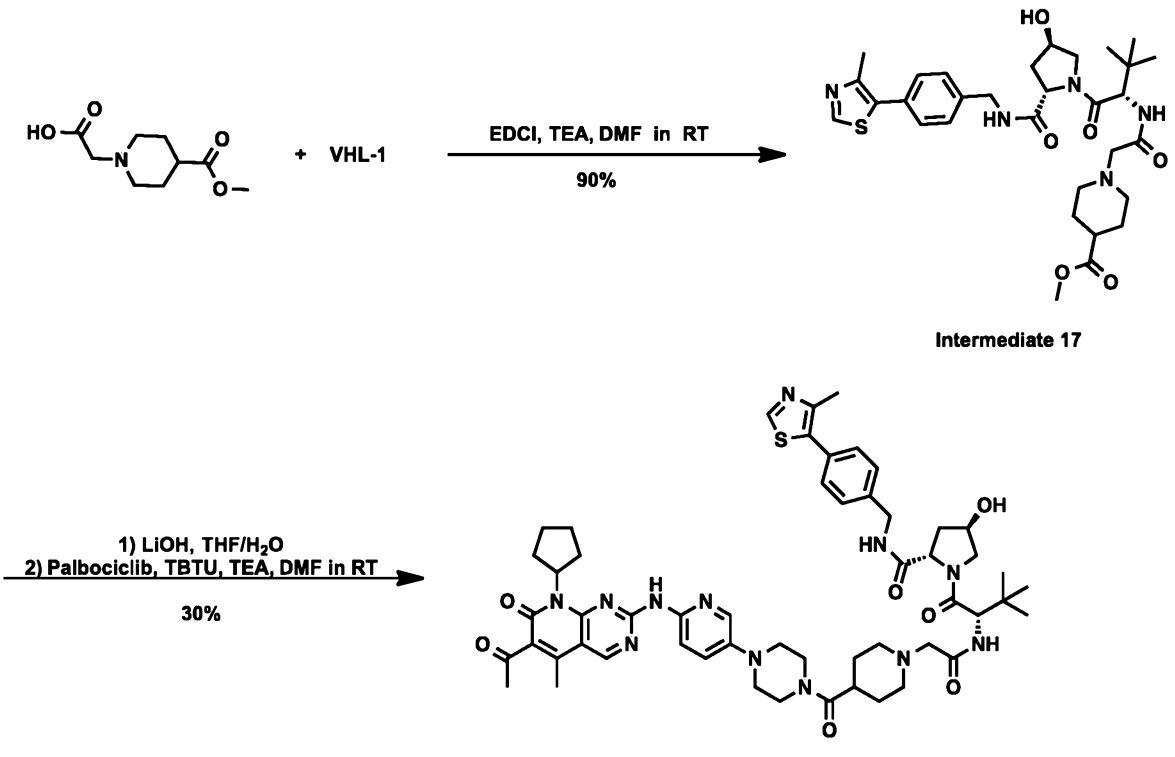
Scheme 19: Synthesis of example 48



(2*S*,4*R*)-1-((*S*)-2-((*E*)-8-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-8-oxooct-4-enamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (example 48) To a solution of (*E*)-oct-4-enedioic acid (250 mg, 1.45 mmol) in THF (5 ml) were added VHL-1 (239 mg, 0.51 mmol), triethylamine

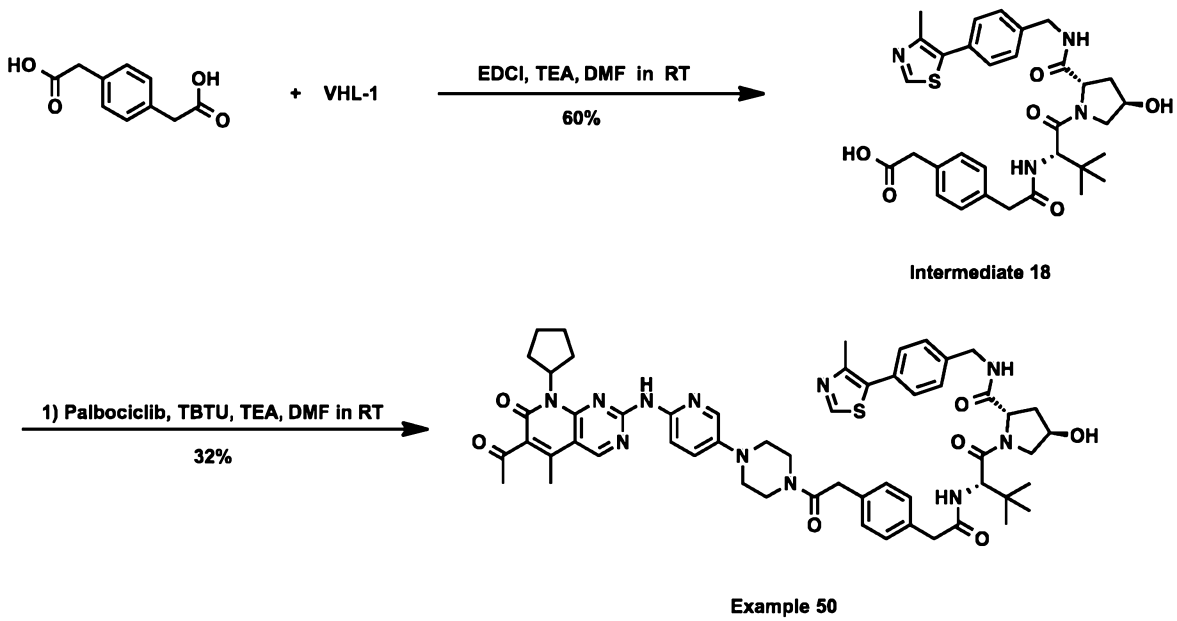
(0.21 ml, 1.4 mmol), and EDCI (104 mg, 0.54mmol) sequentially at 0 °C. The resulting solution was stirred for 2 h at 0 °C, before being warmed to room temperature (RT). After stirring overnight at RT, the reaction was quenched with water and concentrated under reduced pressure. The resulting residue was purified by reverse-phase chromatography to yield the intermediate **16** (208 mg, 70%) as white solid. To a stirring solution of intermediate **16** (19 mg, 0.032 mmol) in DMF (1 ml) were added TEA (0.01 mL, 0.07 mmol), palbociclib (11.1 mg, 0.025 mmol), and TBTU (10.4 mg, 0.032 mmol). The mixture was stirred at RT overnight before being concentrated. The resulting residue was purified by prep-HPLC to yield the title compound (24 mg, 95%) as yellow solid. ^{1}H NMR (600 MHz, CD_3OD) δ 9.12 (s, 1H), 9.00 (s, 1H), 8.21 (dd, J = 9.6, 2.9 Hz, 1H), 7.88 (d, J = 2.8 Hz, 1H), 7.56 (d, J = 9.6 Hz, 1H), 7.49 (d, J = 8.1 Hz, 2H), 7.43 (d, J = 8.1 Hz, 2H), 6.03 (p, J = 8.8 Hz, 1H), 5.61 – 5.50 (m, 2H), 4.66 (s, 1H), 4.60 – 4.48 (m, 3H), 4.37 (dd, J = 15.3, 8.6 Hz, 1H), 3.92 (d, J = 11.0 Hz, 1H), 3.83 – 3.77 (m, 5H), 3.31 – 3.25 (m, 3H), 2.54 (t, J = 7.8 Hz, 2H), 2.51 (s, 3H), 2.49 (s, 3H), 2.45 (s, 3H), 2.40 – 2.28 (m, 9H), 2.26 – 2.23 (m, 1H), 2.16 – 2.07 (m, 3H), 1.96 – 1.87 (m, 2H), 1.76 – 1.66 (m, 2H), 1.04 (s, 9H). HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{54}H_{68}N_{11}O_7S$, 1014.5018; found: 1014.5011.

Scheme 20: Synthesis of example 49



(2*S*,4*R*)-1-((*S*)-2-(2-(4-(4-(6-(((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazine-1-carbonyl)piperidin-1-yl)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (example 49) To a solution of 2-(4-(methoxycarbonyl)piperidin-1-yl)acetic acid (300 mg, 1.5 mmol) in DMF (10 ml) were added VHL-1 (715 mg, 1.5 mmol), triethylamine (1.07 ml, 7.7 mmol), and TBTU (513 mg, 1.6 mmol) sequentially at RT. After being stirred overnight at RT, the reaction was quenched with water and concentrated under reduced pressure, the resulting residue was purified by reverse-phase chromatography to yield the intermediate **17** (552 mg, 90%) as white solid. To a stirring solution of intermediate **17** (52 mg, 0.085 mmol) in THF/H_2O (5:1, 3 ml) was added anhydrous LiOH (3.3 mg, 0.136 mmol). The resulting mixture was stirred overnight at RT before being concentrated under reduced pressure. The resulting residue was dissolved in DMF (1 ml). To the resulting solution, TEA (0.015 mL, 0.11 mmol), palbociclib (13.3 mg, 0.030 mmol), and TBTU (14 mg, 0.044 mmol) were added. After the mixture was stirred at RT overnight, the reaction was concentrated. The resulting residue was purified by prep-HPLC to yield the title compound (25 mg, 30%) as yellow solid. ^{1}H NMR (600 MHz, CD_3OD) δ 9.12 (s, 1H), 8.97 (s, 1H), 8.22 (dd, J = 10.1, 3.0 Hz, 1H), 7.91 (d, J = 3.0 Hz, 1H), 7.58 (dd, J = 9.6, 5.5 Hz, 1H), 7.50 (d, J = 8.0Hz, 2H), 7.43 (d, J = 8.2 Hz, 2H), 6.03 (p, J = 8.8 Hz, 1H), 4.69 – 4.65 (m, 1H), 4.61 – 4.54 (m, 3H), 4.38 (d, J = 15.5 Hz, 1H), 4.13 – 3.90 (m, 3H), 3.90 – 3.76 (m, 5H), 3.72 – 3.64 (m, 2H), 3.40 –3.32 (m, 2H), 3.30 – 3.28 (m, 2H), 3.15 (br, 2H), 2.52 (s, 3H), 2.50 (s, 3H), 2.45 (s, 3H), 2.37 – 2.29 (m, 2H), 2.29 – 2.23 (m, 1H), 2.16 – 1.99 (m, 9H), 1.98 – 1.88 (m, 2H), 1.77 – 1.65 (m, 2H), 1.09 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{54}H_{69}N_{12}O_7S$, 1029.5127; found: 1029.5048.

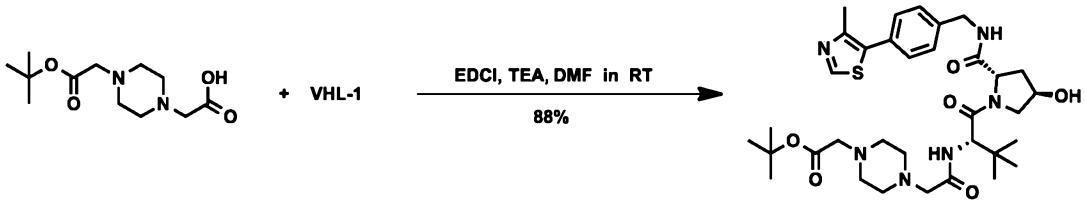
Scheme 21: Synthesis of example 50



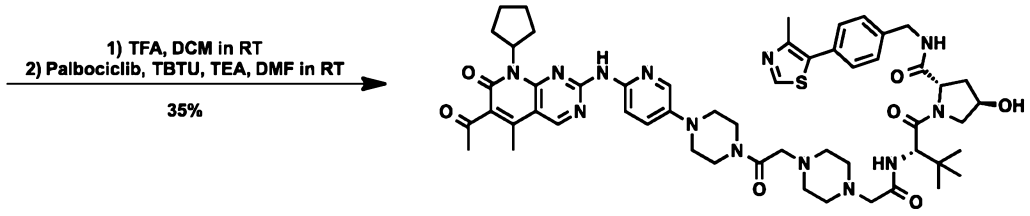
(2*S*,4*R*)-1-((*S*)-2-(2-(4-(2-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-2-oxoethyl)phenyl)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (example 50) To a solution of 2,2'-(1,4-phenylene)diacetic acid (414 mg, 2.13 mmol) in THF (10 ml) were added VHL-1 (217 mg, 0.47 mmol), triethylamine (0.21 ml, 1.4 mmol), and EDCI (110 mg, 0.58mmol) sequentially at 0 °C. The resulting solution was stirred for 2 h at 0 °C, before being warmed to room temperature (RT). After stirring overnight at RT, the reaction was quenched with water and concentrated under reduced pressure. The resulting residue was purified by reverse-phase chromatography to yield the intermediate **18** (170 mg, 60%) as white solid. To a stirring solution of intermediate **18** (20 mg, 0.033 mmol) in DMF (1 ml) were added TEA (0.015 mL, 0.11 mmol), palbociclib (12 mg, 0.027 mmol), and TBTU (12.2 mg, 0.038 mmol). After the mixture was stirred at RT overnight, the reaction was concentrated under reduced pressure. The resulting residue was purified by prep-HPLC to yield the title compound (9 mg, 32%) as yellow solid. ^{1}H NMR (600 MHz, CD_3OD) δ 9.08 (s, 1H), 8.95 (s, 1H), 8.15 (dd, J = 9.7, 2.8 Hz, 1H), 7.78 (d, J = 2.6 Hz, 1H), 7.51 (d, J = 11.4 Hz, 1H), 7.46 – 7.38 (m, 4H), 7.34 – 7.25 (m, 4H), 6.06 – 5.97 (m, 1H), 4.66 – 4.61 (m, 1H), 4.59 – 4.46 (m, 3H), 4.38 – 4.32 (m, 1H), 3.92 – 3.83 (m, 3H), 3.81 – 3.70 (m, 4H), 3.64 (d, J = 14.4 Hz, 1H), 3.58 (d, J = 14.7 Hz, 1H), 3.24 – 3.18 (m, 1H), 3.16 – 3.09 (m, 1H), 3.08 – 3.02 (m, 1H), 2.52 (s, 3H), 2.49 (s, 3H), 2.44 (s, 3H), 2.37

– 2.31 (m, 2H), 2.26 – 2.20 (m, 1H), 2.15 – 2.08 (m, 3H), 1.96 – 1.87 (m, 2H), 1.76 – 1.68 (m, 2H), 0.97 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{56}H_{66}N_{11}O_7S$, 1036.4862; found: 1036.4860.

Scheme 22: Synthesis of example 51



Intermediate 19

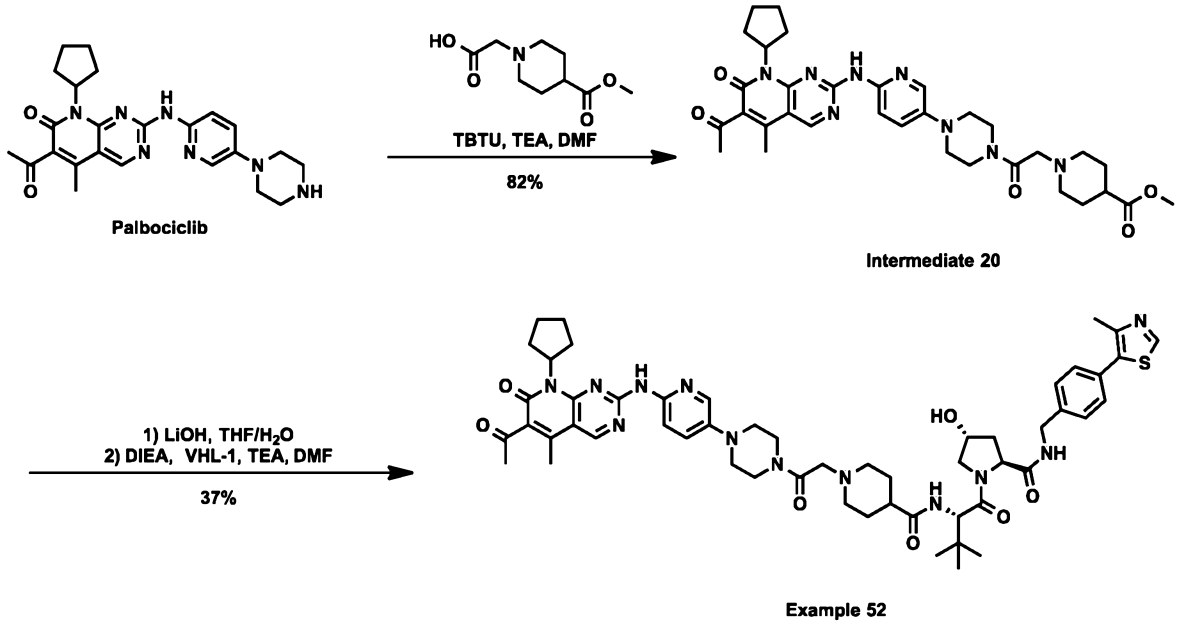


Example 51

(2*S*,4*R*)-1-((*S*)-2-(2-(4-(2-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-2-oxoethyl)piperazin-1-yl)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (example 51) To a solution of 2-(4-(2-(*tert*-butoxy)-2-oxoethyl)piperazin-1-yl)acetic acid (340 mg, 0.7 mmol) in DMF (5 ml) were added VHL-1 (277 mg, 0.6 mmol), triethylamine (0.7 ml, 5 mmol), and EDCI (224 mg, 1.2 mmol) sequentially at RT. After being stirred overnight at RT, the reaction was quenched with water, and concentrated under reduced pressure. The resulting residue was purified by reverse-phase chromatography to yield the intermediate **17** (350 mg, 88%) as white solid. To a stirring solution of intermediate **19** (15 mg, 0.023 mmol) in DCM (1 ml) was added TFA (1 mL). The resulting mixture was stirred at RT. The disappearance of starting material was monitored by LC/MS. The reaction mixture was concentrated under reduced pressure and the resulting residue was dissolved in DMF (1 ml). To the resulting solution, TEA (0.015 mL, 0.11 mmol), palbociclib (8.3 mg, 0.019 mmol), and TBTU (7 mg, 0.022 mmol) were added. The mixture was stirred at RT overnight before being concentrated. The resulting residue was purified by prep-HPLC to yield the title compound (7 mg, 35%) as yellow solid. ^{1}H NMR (600 MHz,

CD_3OD) δ 9.13 (s, 1H), 8.99 (s, 1H), 8.24 (dd, J = 9.6, 2.4 Hz, 1H), 7.93 (s, 1H), 7.59 (d, J = 9.6 Hz, 1H), 7.49 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.2 Hz, 2H), 6.08 – 5.98 (m, 1H), 4.69 (s, 1H), 4.61 – 4.50 (m, 3H), 4.44 – 4.38 (m, 1H), 4.25 (s, 2H), 3.92 (d, J = 11.1 Hz, 1H), 3.88 – 3.79 (m, 3H), 3.68 (br, 2H), 3.50 – 3.37 (m, 8H), 3.37 – 3.34 (m, 2H), 3.06 (br, 4H), 2.53 (s, 2H), 2.51 (s, 2H), 2.46 (s, 3H), 2.37 – 2.25 (m, 3H), 2.17 – 2.07 (m, 3H), 1.97 – 1.87 (m, 2H), 1.76 – 1.69 (m, 2H), 1.07 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{54}H_{70}N_{13}O_7S$, 1044.5236; found: 1044.5226.

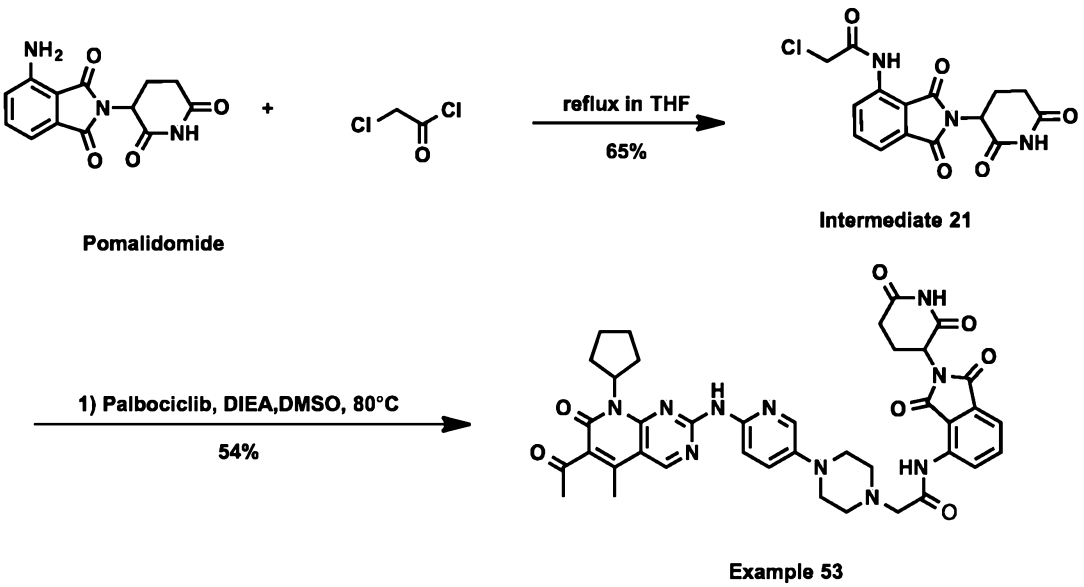
Scheme 23: Synthesis of example 52



1-(2-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-2-oxoethyl)-*N*-((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)piperidine-4-carboxamide (example 52) A solution of palbociclib (43 mg, 0.096 mmol) in DMF were added 2-(4-(methoxycarbonyl)piperidin-1-yl)acetic acid (20 mg, 0.1 mmol), TEA (0.035 mL, 0.25 mmol), and TBTU (42 mg, 0.13 mmol) sequentially at RT. After being stirred overnight at RT, the reaction was quenched with water. After concentration under reduced pressure, the resulting residue was purified by reverse-phase chromatography to yield the intermediate **20** (50 mg, 82%) as white solid. To a stirring solution of intermediate **20** (50 mg, 0.079 mmol) in THF/H_2O (5:1, 3 mL) was added anhydrous LiOH (6 mg, 0.025 mmol). The mixture was stirred at RT and the reaction progress was monitored by LC/MS. After total consumption of intermediate **20**, the reaction was concentrated. The resulting residue was

dissolved in DMF (1 ml). To the solution were added TEA (0.02 mL, 0.14 mmol), VHL-1 (26 mg, 0.055 mmol), and TBTU (16 mg, 0.05 mmol). The reaction mixture was stirred at RT overnight before being concentrated. The resulting residue was purified by prep-HPLC to yield the title compound (30 mg, 37%) as yellow solid. ^{1}H NMR (600 MHz, CD_3OD) δ 9.15 (s, 1H), 9.13 (s, 1H), 8.24 (dd, J = 9.6, 2.7 Hz, 1H), 7.93 (d, J = 2.2 Hz, 1H), 7.58 (d, J = 9.6 Hz, 1H), 7.51 (d, J = 8.1 Hz, 2H), 7.46 (d, J = 8.2 Hz, 2H), 6.03 (p, J = 8.8 Hz, 1H), 4.65 (d, J = 8.3 Hz, 1H), 4.62 – 4.51 (m, 3H), 4.42 – 4.32 (m, 3H), 3.91 (d, J = 9.6 Hz, 1H), 3.87 – 3.82 (m, 3H), 3.79 – 3.70 (m, 1H), 3.65 (br, 2H), 3.50 (br, 1H), 3.40 (br, 2H), 3.37 – 3.34 (m, 3H), 3.20 – 3.07 (m, 1H), 2.74 (br, 1H), 2.52 (s, 3H), 2.52 (s, 3H), 2.45 (s, 3H), 2.36 – 2.24 (m, 3H), 2.21 – 2.03 (m, 7H), 1.97 – 1.88 (m, 2H), 1.77 – 1.64 (m, 2H), 1.07 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{54}H_{69}N_{12}O_7S$, 1029.5127; found: 1029.5106.

Scheme 24: Synthesis of example 53

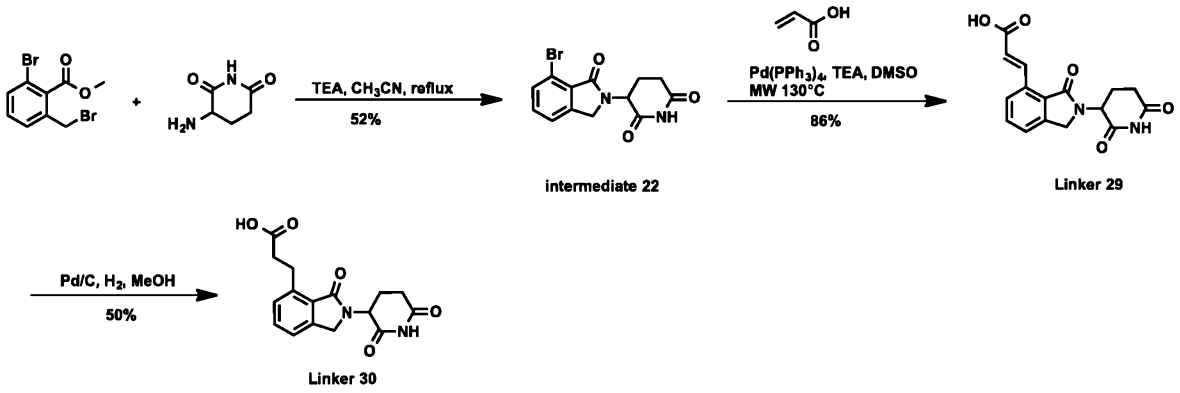


2-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-*N*-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)acetamide (example 53) A solution of pomalidomide (90 mg, 0.33 mmol) and 2-chloroacetyl chloride (0.026 mL, 0.33 mmol) in THF (2 ml) was heated at reflux overnight. After being cooled to RT, the reaction mixture was concentrated, and the resulting residue was washed with ethyl acetate to yield the intermediate **21** (75 mg, 65%) as yellow solid. To a stirring solution of intermediate **13** (36 mg, 0.082 mmol) in DMSO (1mL) were added DIEA (0.043 mL, 0.24 mmol) and palbociclib (39 mg, 0.087 mmol). The mixture was heated at 80°C. After the starting materials were consumed, the reaction was concentrated

under reduced pressure. The resulting residue was purified by prep-HPLC to yield the title compound (36 mg, 54%) as yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 11.19 (s, 1H), 8.89 (d, J = 8.5 Hz, 1H), 8.81 (s, 1H), 8.20 (d, J = 9.1 Hz, 1H), 8.14 (d, J = 2.8 Hz, 1H), 7.71 (t, J = 4.2 Hz, 1H), 7.55 (d, J = 7.3 Hz, 1H), 7.38 (dd, J = 9.1, 2.9 Hz, 1H), 5.87 (p, J = 9.0 Hz, 1H), 4.94 (dd, J = 12.7, 5.3 Hz, 1H), 3.39 (br, 4H), 3.34 (AB, J_{ab} = 17.4 Hz, 1H), 3.27 (AB, J_{ab} = 17.4 Hz, 1H), 2.92 – 2.73 (m, 8H), 2.54 (s, 3H), 2.40 – 2.29 (m, 4H), 2.14 – 2.09 (m, 1H), 2.08 – 2.00 (m, 2H), 1.90 – 1.81 (m, 2H), 1.70 – 1.59 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{39}H_{41}N_{10}O_7$, 761.3154; found: 761.3157.

Synthesis of various linkers of pomalidomide analogues.

Scheme 25: Synthesis of Linker 29 and 30



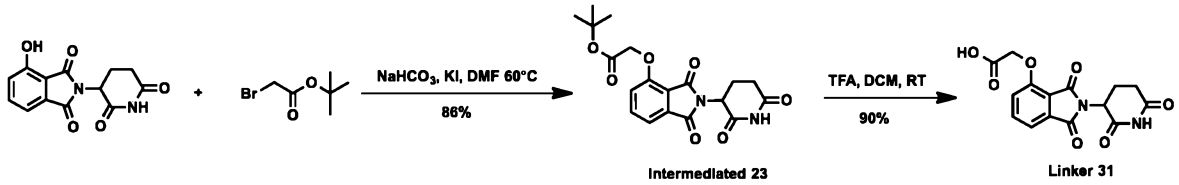
3-(7-Bromo-1-oxoisoindolin-2-yl)piperidine-2,6-dione (intermediate 22) A solution of methyl 2-bromo-6-(bromomethyl)benzoate (970 mg, 3.16 mmol), 3-aminopiperidine-2,6-dione (667 mg, 4.06 mmol) and TEA (0.62 mL, 4.4 mmol) in CH_3CN (10 mL) was heated at reflux for 16 h. After being cooled to RT, the reaction was concentrated. To the resulting residue were added ethyl acetate (10 mL) and H_2O (10 mL). After filtration, the solid was collected and dried to yield the title compound (534 mg, 54%) as purple solid.

(*E*)-3-(2-(2,6-Dioxopiperidin-3-yl)-3-oxoisoindolin-4-yl)acrylic acid (linker 29) A solution of intermediate **22** (46 mg, 0.14 mmol), acrylic acid (0.02 mL, 0.29 mmol), tetrakis(triphenylphosphine)palladium (23.3 mg, 0.02 mmol) and TEA (0.02 mL, 0.14 mmol) in DMSO (1 mL) was heated in a microwave reactor at 130°C for 30 min. After being cooled to RT, the mixture was filtered. The solution was concentrated and purified by prep-HPLC to yield the title compound (38mg, 86%) as yellow solid. ^{1}H NMR (600 MHz, DMSO-*d*$_6$) δ 12.51 (sbr, 1H), 11.03 (s, 1H), 8.87 (d, J = 16.2 Hz, 1H), 7.98 (t, J = 6.0 Hz, 1H), 7.64 (d, J = 4.7 Hz, 2H), 6.69 (d, J = 16.3 Hz, 1H), 5.10 (dd, J = 13.3, 5.1 Hz, 1H), 4.47 (d, J = 17.4 Hz, 1H), 4.35

(d, J = 17.4 Hz, 1H), 2.98 – 2.86 (m, 1H), 2.62 (d, J = 17.1 Hz, 1H), 2.42 (qd, J = 13.2, 4.5 Hz, 1H), 2.07 – 1.99 (m, 1H).

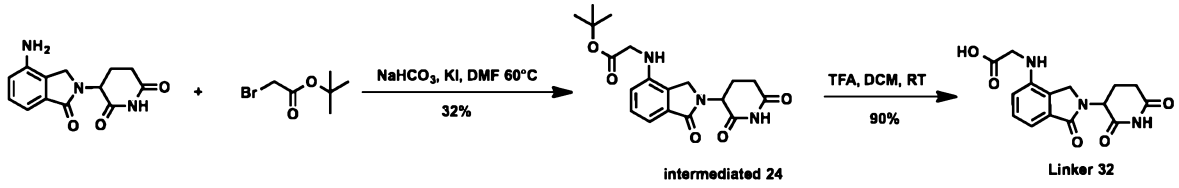
3-(2-(2,6-Dioxopiperidin-3-yl)-3-oxoisoindolin-4-yl)propanoic acid (linker 30) A mixture of linker **29** (20 mg, 0.064 mmol) and Pd/C (5 mg) in MeOH/DMSO (1:1, 2 mL) was stirred for 16 h under H_2 atmosphere. After removal of Pd/C through filtration, the solution was concentrated under reduced pressure. The resulting residue was purified by prep-HPLC to yield the title compound (11 mg, 50%) as yellow solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.99 (br, 2H), 7.55 – 7.47 (m, 1H), 7.43 (d, J = 7.5 Hz, 1H), 7.31 (d, J = 7.7 Hz, 1H), 5.13 – 5.03 (m, 1H), 4.41 (dd, J = 16.8, 8.8 Hz, 1H), 4.30 (dd, J = 16.8, 8.8 Hz, 1H), 3.33 – 3.27 (m, 2H), 2.97 – 3.84 (m, 1H), 2.63 – 2.55 (m, 3H), 2.43 – 2.38 (m, 1H), 2.06 – 1.98 (m, 1H).

Scheme 26: Synthesis of Linker 31



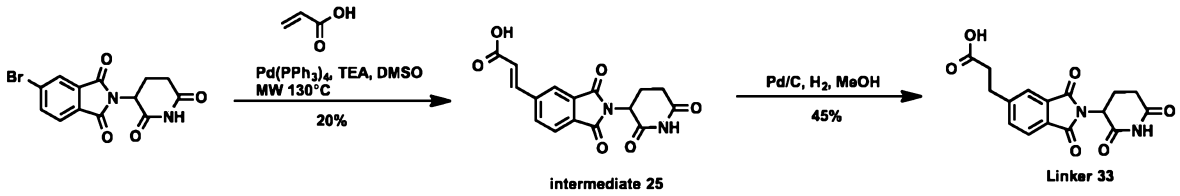
2-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetic acid (linker 31) A round bottom flash was charged with 2-(2,6-dioxopiperidin-3-yl)-4-hydroxyisoindoline-1,3-dione (68 mg, 0.25 mmol), DMF (2 mL), *tert*-butyl-2-bromo acetate ester (0.045 mL, 0.3 mmol), sodium bicarbonate (49 mg, 0.058 mmol), and potassium iodide (10 mg, 0.06 mmol). The reaction mixture was heated at 60 °C overnight. After being cooled to RT, the insoluble solid was removed by filtration. The solution was collected and concentrated. The resulting residue was purified by reverse-ISCO to yield intermediated **23** (83 mg, 86%). Intermediate **23** (83 mg, 0.21 mmol) was dissolved in DCM/TFA (2:1, 3 mL). After the reaction was stirred for 3 h at RT, the solvent was removed to yield the title compound (60 mg, 90%) as white solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.11 (br, 2H), 7.82 – 7.77 (m, 1H), 7.48 (d, J = 7.2 Hz, 1H), 7.40 (d, J = 8.6 Hz, 1H), 5.11 (ddd, J = 12.8, 5.4, 1.2 Hz, 1H), 5.00 (s, 2H), 2.95 – 2.80 (m, 1H), 2.63 – 2.53 (m, 2H), 2.08 – 2.00 (m, 1H).

Scheme 27: Synthesis of Linker 32



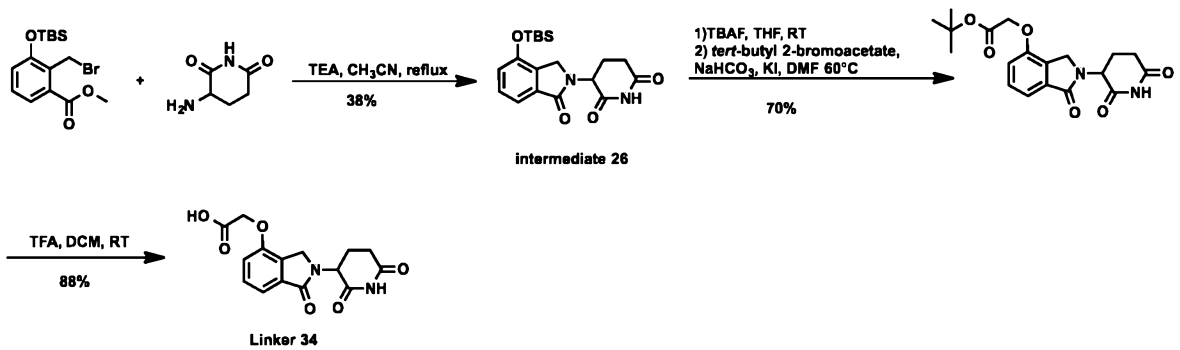
(2-(2,6-Dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)glycine (linker 32) The title compound was synthesized using the same procedures for the preparation of linker **31**. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.66 (br, 1H), 11.03 (s, 1H), 7.29 (t, J = 7.7 Hz, 1H), 6.99 (d, J = 7.4 Hz, 1H), 6.66 (d, J = 8.0 Hz, 1H), 5.13 (dd, J = 13.3, 4.9 Hz, 1H), 4.27 (d, J = 17.0 Hz, 1H), 4.18 (d, J = 17.4 Hz, 1H), 3.93 (s, 2H), 2.98 – 2.84 (m, 1H), 2.63 (d, J = 17.0 Hz, 1H), 2.34 (qd, J = 13.2, 4.1 Hz, 1H), 2.08 – 1.97 (m, 1H).

Scheme 28: Synthesis of Linker 33



3-(2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)propanoic acid (linker 33) The title compound was synthesized using the same procedures for the preparation of linker **30**. ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.15 (br, 2H), 7.85 (d, J = 7.7 Hz, 1H), 7.82 (s, 1H), 7.76 (d, J = 7.7 Hz, 1H), 5.14 (dd, J = 12.9, 5.4 Hz, 1H), 3.02 (t, J = 7.4 Hz, 2H), 2.93 – 2.84 (m, 1H), 2.65 (t, J = 7.5 Hz, 2H), 2.60 – 2.53 (m, 2H), 2.08 – 2.04 (m, 1H).

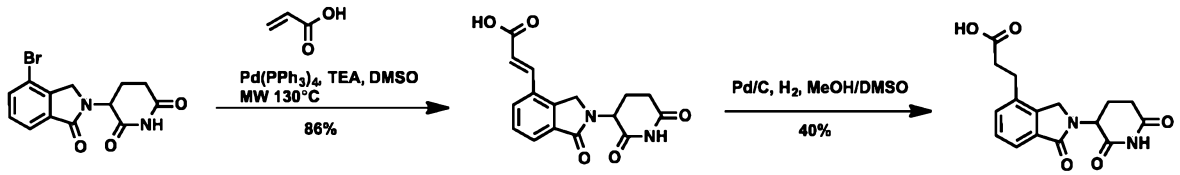
Scheme 29: Synthesis of Linker 34



3-(4-((*tert*-Butyldimethylsilyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (intermediate 26) The title compound was synthesized using the same procedures for the preparation of intermediate **22** (38%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.98 (s, 1H), 7.44 (t, J = 7.7 Hz, 1H), 7.36 (d, J = 7.4 Hz, 1H), 7.11 (d, J = 7.9 Hz, 1H), 5.11 (dd, J = 13.2, 4.8 Hz, 1H), 4.34 (d, J = 17.3 Hz, 1H), 4.25 (d, J = 17.2 Hz, 1H), 2.96 – 2.82 (m, 1H), 2.66 – 2.53 (m, 2H), 2.02 – 1.96 (m, 1H), 0.99 (s, 9H), 0.26 (s, 6H).

2-((2-(2,6-Dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)oxy)acetic acid (linker 34) The title compound was synthesized using the same procedures for the preparation of linker **31**. ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.00 (s, 1H), 7.47 (t, J = 7.8 Hz, 1H), 7.36 (d, J = 8.6 Hz, 1H), 7.17 (d, J = 8.2 Hz, 1H), 5.19 – 5.05 (m, 2H), 4.84 (s, 2H), 4.41 (d, J = 17.4 Hz, 1H), 4.28 (d, J = 17.3 Hz, 1H), 3.00 – 2.84 (m, 1H), 2.63 – 2.58 (m, 1H), 2.49 – 2.38 (m, 1H), 2.04 – 1.92 (m, 1H).

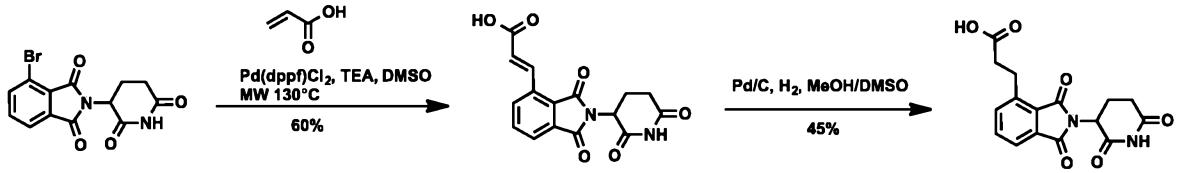
Scheme 30: Synthesis of Linker 35



Linker 35

3-(2-(2,6-Dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)propanoic acid (linker 35) The title compound was synthesized using the same procedures for the preparation of linker **30**. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.23 (br, 1H), 11.01 (s, 1H), 7.59 (d, J = 7.1 Hz, 1H), 7.51 – 7.46 (m, 2H), 5.14 (dd, J = 13.3, 5.1 Hz, 1H), 4.51 (d, J = 17.0 Hz, 1H), 4.36 (d, J = 17.1 Hz, 1H), 2.97 – 2.83 (m, 3H), 2.67 – 2.58 (m, 3H), 2.49 – 2.39 (m, 1H), 2.05 – 1.99 (m, 1H).

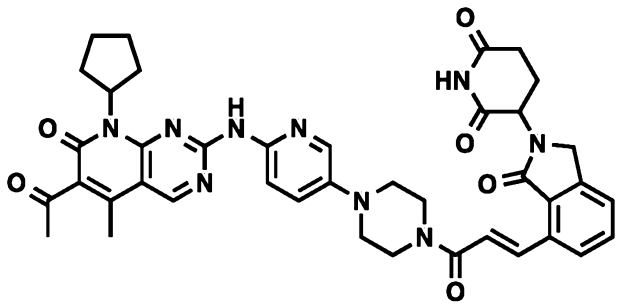
Scheme 31: Synthesis of Linker 36



Linker 36

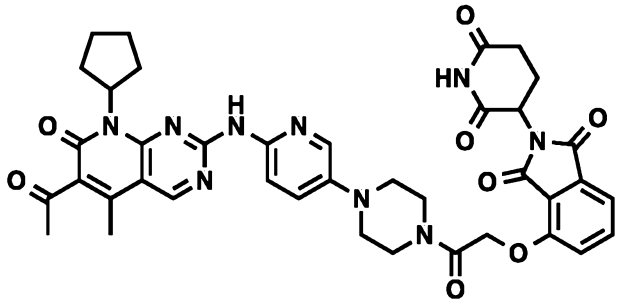
3-(2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)propanoic acid (linker 36) The title compound was synthesized using the same procedures for the preparation of linker **30**. ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.15 (br, 2H), 7.79 – 7.73 (m, 3H), 5.14 (dd, J = 12.9, 5.4 Hz, 1H), 3.27 (t, J = 7.2 Hz, 2H), 2.95 – 2.83 (m, 1H), 2.67 – 2.52 (m, 4H), 2.12 – 2.01 (m, 1H).

The example **54–61** compounds were synthesized using the same procedures for the preparation of the example **40** compound with linkers **29** – **36**.



example 54

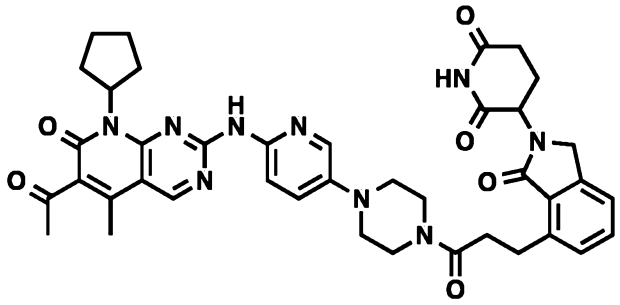
(*E*)-3-(7-(3-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-3-oxoprop-1-en-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (example 54) (52 mg, 58%) as yellow solid. ^{1}H NMR (600 MHz, CD_3OD) δ 9.08 (s, 1H), 8.74 (d, J = 15.7 Hz, 1H), 8.17 (dd, J = 9.7, 2.7 Hz, 1H), 7.90 (d, J = 2.7 Hz, 1H), 7.84 (d, J = 7.7 Hz, 1H), 7.62 – 7.54 (m, 2H), 7.51 (d, J = 7.5 Hz, 1H), 7.27 (d, J = 15.7 Hz, 1H), 5.98 (p, J = 8.8 Hz, 1H), 5.13 (dd, J = 12.6, 5.4 Hz, 1H), 4.47 (AB, J_{ab} = 16.8 Hz, 1H), 4.43 (AB, J_{ab} = 16.8 Hz, 1H), 3.97 (br, 2H), 3.90 (br, 2H), 3.28 (br, 2H), 3.34 (br, 2H), 2.87 – 2.75 (m, 1H), 2.52(s, 3H), 2.50 – 2.44 (m, 1H), 2.43 (s, 3H), 2.35 – 2.25 (m, 2H), 2.25 – 2.15 (m, 2H), 2.14 – 2.03 (m, 3H), 1.94 – 1.86 (m, 2H), 1.73 – 1.64 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{40}H_{42}N_9O_6$, 744.3253; found: 744.3274.



example 55

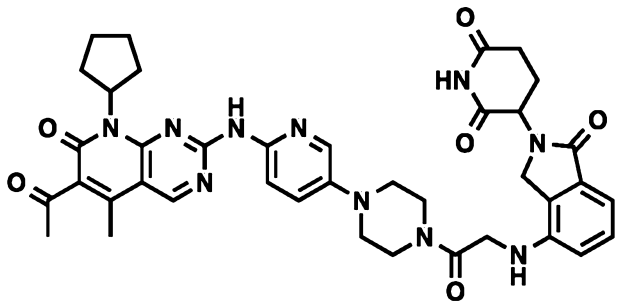
4-(2-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-2-oxoethoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (example 55) (27 mg, 51%) as yellow solid. ^{1}H NMR (600 MHz, CD_3OD) δ 9.11 (s, 1H), 8.19 (d, J = 8.6 Hz, 1H), 7.88 (br, 1H), 7.76 (t, J = 7.9 Hz, 1H), 7.57 (d, J = 7.9 Hz, 1H), 7.49 (d, J = 7.2 Hz, 1H), 7.41 (d, J = 8.5 Hz, 1H), 6.06 – 5.96 (m, 1H), 5.22 – 5.15 (m, 2H), 5.12 (dd, J = 12.7, 5.4 Hz, 1H), 3.93 – 3.76 (m, 4H), 3.45 – 3.24 (m, 4H), 2.95 – 2.69 (m, 3H), 2.53 (s, 3H), 2.45 (s, 3H), 2.37 – 2.27 (m, 2H), 2.20 – 2.05 (m, 3H), 1.96

– 1.87 (m, 2H), 1.77 – 1.62 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{39}H_{40}N_9O_8$, 762.2994; found: 762.3008.



example 56

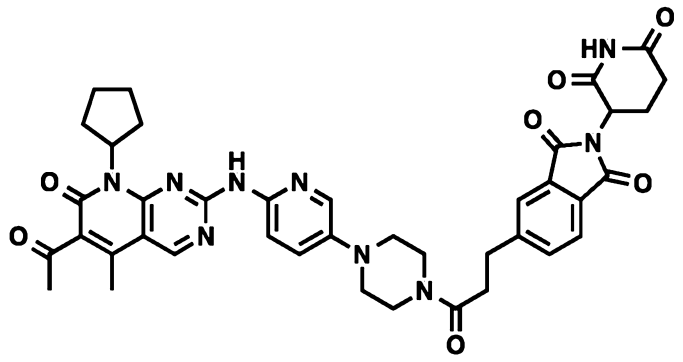
3-(7-(3-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-3-oxopropyl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (example 56) (9 mg, 48%) as yellow solid. ^{1}H NMR (600 MHz, CD_3OD) δ 8.81 (s, 1H), 7.73 – 7.65 (m, 2H), 7.63 (s, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), , 7.18 (d, *J* = 7.4 Hz, 1H), 7.13 (d, *J* = 7.4 Hz, 1H), 5.75 –5.70 (m, 1H), 4.93 (dd, *J* = 13.2, 5.1 Hz, 1H), 3.69 – 3.48 (m, 4H), 3.31 – 3.21 (m, 1H), 3.21 – 3.09 (m, 3H), 3.07 – 3.00 (m, 2H), 2.99 – 2.77 (m, 2H), 2.76 – 2.63 (m, 3H), 2.63 – 2.54 (m, 1H), 2.34 (s, 3H), 2.28 – 2.16 (m, 4H), 2.15 – 2.02 (m, 3H), 1.94 – 1.85 (m, 2H), 1.75 – 1.65 (m, 2H), 1.55 – 1.44 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{40}H_{44}N_9O_6$, 746.3409; found: 746.3427.



example 57

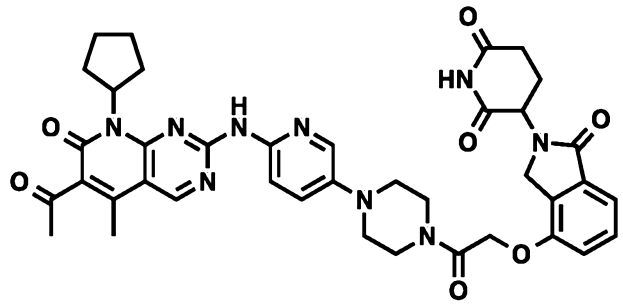
3-(4-((2-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-2-oxoethyl)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (example 57) (39 mg, 80%) ^{1}H NMR (600 MHz, CD_3OD) δ 9.07 (s, 1H), 8.09 (d, *J* = 9.5 Hz, 1H), 7.89 (s, 1H), 7.61 (d, *J* = 8.7 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.16 (d, *J* = 7.4 Hz, 1H), 6.79 (d, *J* = 7.9 Hz, 1H), 5.96 (p, *J* = 8.7 Hz, 1H), 5.14 (dd, *J* = 13.2, 4.1 Hz, 1H), 4.37 (s, 2H), 4.18 – 4.06 (m, 2H), 3.85 – 3.79 (m, 4H), 3.38 – 3.22 (m, 4H), 2.90 – 2.76 (m, 2H), 2.56 – 2.48 (m, 3H), 2.49 – 2.38 (m, 4H), 2.27 (t, *J* = 18.1 Hz, 2H), 2.24 – 2.14

(m, 1H), 2.09 (s, 2H), 1.90 (s, 2H), 1.68 (d, J = 3.0 Hz, 2H). HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{39}H_{43}N_{10}O_6$, 747.3362; found: 747.3370.



example 58

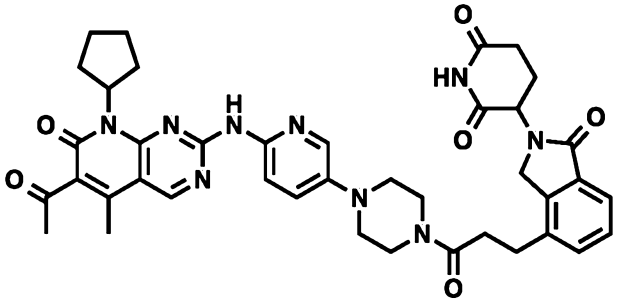
5-(3-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-3-oxopropyl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (example 58) (4 mg, 33%). ^{1}H NMR (600 MHz, CD_3OD) δ 9.04 (s, 1H), 7.99 – 7.96 (m, 1H), 7.85 (s, 1H), 7.82 – 7.78 (m, 1H), 7.74 – 7.70 (m, 1H), 7.67 – 7.63 (m, 1H), 6.31 (s, 1H), 5.99 – 5.93 (m, 1H), 5.04 (dd, J = 11.8, 6.0 Hz, 1H), 3.87 – 3.63 (m, 4H), 3.26 – 3.01 (m, 5H), 2.88 – 2.72 (m, 4H), 2.54 (s, 3H), 2.43 (s, 3H), 2.35 – 2.22 (m, 2H), 2.19 – 2.10 (m, 1H), 2.08 – 2.04 (m, 2H), 1.92 – 1.87 (m, 2H), 1.74 – 1.63 (m, 2H), 1.30 – 1.26 (m, 2H). HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{40}H_{42}N_9O_7$, 760.3202; found: 760.3226.



example 59

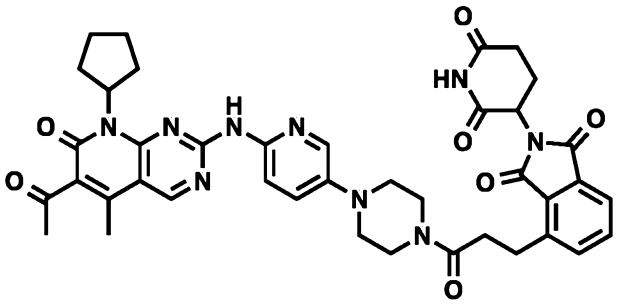
3-(4-(2-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-2-oxoethoxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (example 59) (43 mg, 90%) ^{1}H NMR (600 MHz, CD_3OD) δ 9.09 (s, 1H), 8.14 (dd, J = 9.7, 2.8 Hz, 1H), 7.89 (d, J = 2.5 Hz, 1H), 7.59 (d, J = 9.6 Hz, 1H), 7.48 – 7.40 (m, 2H), 7.15 (d, J = 8.0 Hz, 1H), 5.98 (p, J = 8.8 Hz, 1H), 5.15 (dd, J = 13.3, 5.1 Hz,

1H), 5.03 (AB, J_{ab} = 14.4 Hz, 1H), 4.99 (AB, J_{ab} = 14.4 Hz, 1H), 4.53 (AB, J_{ab} = 17.4 Hz, 1H), 4.49 (AB, J_{ab} = 17.4 Hz, 1H), 3.90 – 3.67 (m, 4H), 3.42 – 3.20 (m, 4H), 2.96 – 2.73 (m, 2H), 2.54 (s, 3H), 2.52 – 2.47 (m, 1H), 2.44 (s, 3H), 2.34 – 2.28 (m, 2H), 2.26 – 2.16 (m, 1H), 2.12 – 2.05 (m, 2H), 1.96 – 1.83 (m, 2H), 1.74 – 1.59 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{39}H_{49}N_9O_7$, 748.3202; found: 748.3236.



example 60

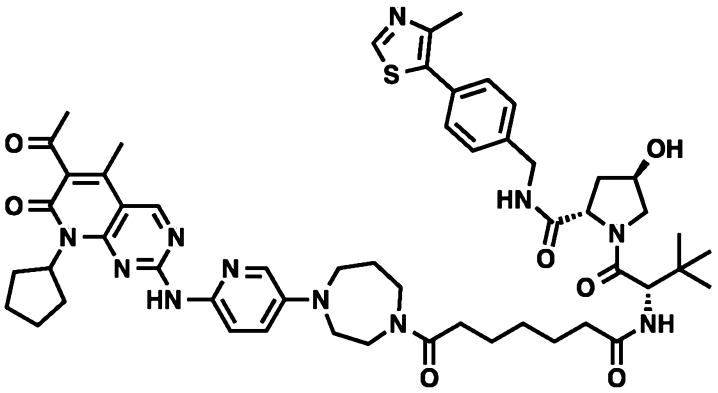
3-(4-(3-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-3-oxopropyl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (example 60) (15 mg, 75%). ^{1}H NMR (600 MHz, CD_3OD) δ 9.12 (s, 1H), 8.11 (dd, *J* = 9.7, 2.9 Hz, 1H), 7.79 (d, *J* = 2.8 Hz, 1H), 7.65 (d, *J* = 4.8 Hz, 1H), 7.58 – 7.52 (m, 2H), 7.49 (t, *J* = 7.5 Hz, 1H), 6.01 (p, *J* = 8.9 Hz, 1H), 5.17 (dd, *J* = 13.3, 5.2 Hz, 1H), 4.56 (q, *J* = 16.9 Hz, 2H), 3.83 – 3.72 (m, 2H), 3.63 (t, *J* = 5.1 Hz, 2H), 3.22 – 3.13 (m, 2H), 3.08 (t, *J* = 7.1 Hz, 2H), 3.03 – 2.97 (m, 1H), 2.94 – 2.82 (m, 5H), 2.59 – 2.49 (m, 4H), 2.45 (s, 3H), 2.35 – 2.29 (m, 2H), 2.27 – 2.16 (m, 1H), 2.14 – 2.04 (m, 2H), 1.95 – 1.83 (m, 2H), 1.75 – 1.63 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{40}H_{44}N_9O_6$, 746.3409; found: 746.3382.



example 61

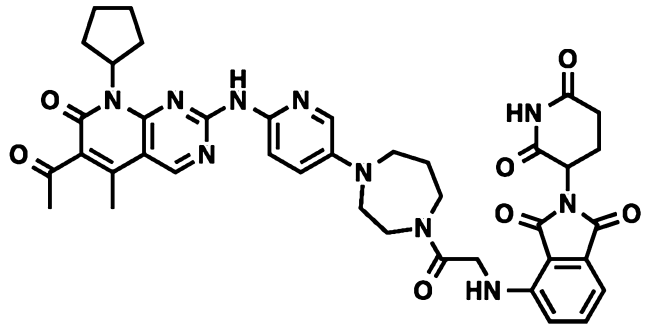
4-(3-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-3-oxopropyl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (example 61) (17 mg, 43%). ^{1}H NMR (600 MHz, CD_3OD) δ 9.10 (s,

1H), 8.14 (d, J = 9.4 Hz, 1H), 7.86 (s, 1H), 7.81 – 7.65 (m, 3H), 7.59 (d, J = 9.5 Hz, 1H), 6.00 (p, J = 8.8 Hz, 1H), 5.13 (dd, J = 12.5, 5.3 Hz, 1H), 3.82 – 3.74 (m, 4H), 3.47 – 3.37 (m, 2H), 3.31 – 3.20 (m, 4H), 2.92 – 2.69 (m, 5H), 2.54 (s, 3H), 2.45 (s, 3H), 2.39 – 2.26 (m, 2H), 2.22 – 2.16 (m, 1H), 2.14 – 2.06 (m, 2H), 1.96 – 1.86 (m, 2H), 1.76 – 1.65 (m, 2H). HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{40}H_{42}N_9O_7$, 760.3202; found: 760.3210.



example 62

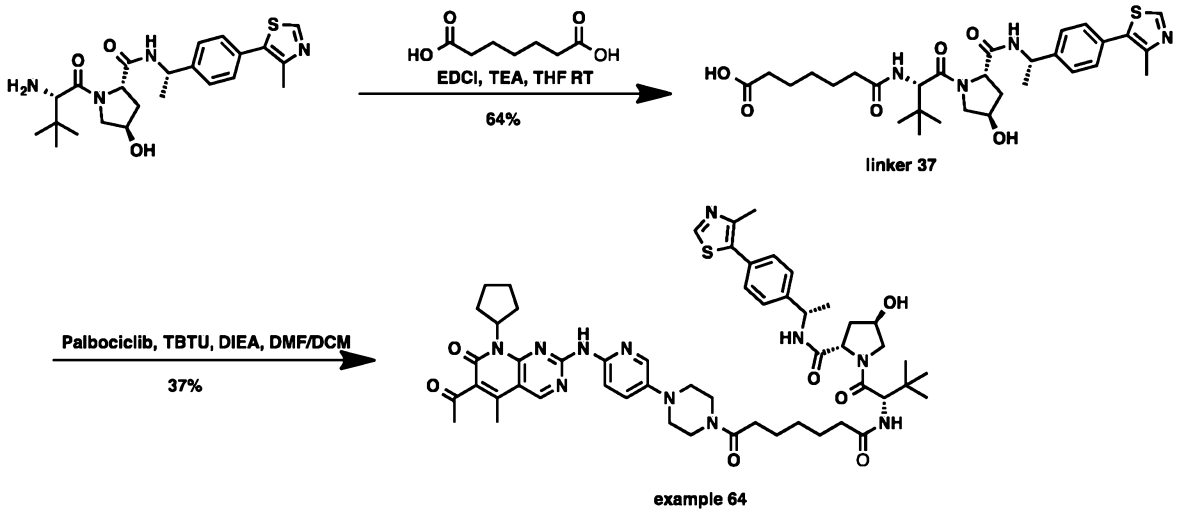
(2*S*,4*R*)-1-((*S*)-2-(7-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)-1,4-diazepan-1-yl)-7-oxoheptanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (example 62) The title compound was synthesized using the same procedures for the preparation of the example **40** compound with linker **4** (9 mg, 74%) as white solid. ^{1}H NMR (600 MHz, CD_3OD) δ 9.10 (s, 1H), 9.01 (s, 1H), 8.06 – 8.01 (m, 1H), 7.80 – 7.75 (m, 1H), 7.55 – 7.41 (m, 5H), 6.06 – 5.98 (m, 1H), 4.66 – 4.49 (m, 5H), 4.38 (dd, J = 15.4, 4.1 Hz, 1H), 3.93 – 3.77 (m, 5H), 3.77 – 3.54 (m, 4H), 2.52 (s, 3H), 2.50 (s, 3H), 2.45 (s, 3H), 2.40 – 2.05 (m, 9H), 2.00 – 1.88 (m, 4H), 1.76 – 1.46 (m, 6H), 1.40 – 1.23 (m, 3H), 1.06 – 1.01 (m, 9H). HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{54}H_{70}N_{11}O_7S$, 1016.5175; found: 1016.5166.



example 63

4-((2-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)-1,4-diazepan-1-yl)-2-oxoethyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (example 63) The title compound was synthesized using the same procedures for the preparation of the example **40** compound with linker **24** (4 mg, 44%) as yellow solid. Rotamer (3:2) major one ^{1}H NMR (600 MHz, CD_3OD) δ 9.02 (s, 1H), 7.81 (dd, J = 9.6, 3.0 Hz, 1H), 7.51 (d, J = 2.9 Hz, 1H), 7.37 – 7.33 (m, 2H), 6.92 (d, J = 8.6 Hz, 1H), 6.87 (d, J = 7.8 Hz, 1H), 6.06 – 6.00 (m, 1H), 5.05 (dd, J = 12.8, 5.5 Hz, 1H), 4.24 (d, J = 16.2 Hz, 1H), 4.16 – 4.14 (m, 1H), 3.96 – 3.79 (m, 4H), 3.74 –3.65 (m, 4H), 2.90 – 2.63 (m, 4H), 2.54 (s, 3H), 2.44 (s, 3H), 2.40 – 2.28 (m, 2H), 2.16 – 2.06 (m, 2H), 1.98 – 1.87 (m, 4H), 1.78 – 1.65 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{40}H_{43}N_{10}O_7$, 775.3311; found: 775.3314.

Scheme 32: synthesis of example 64



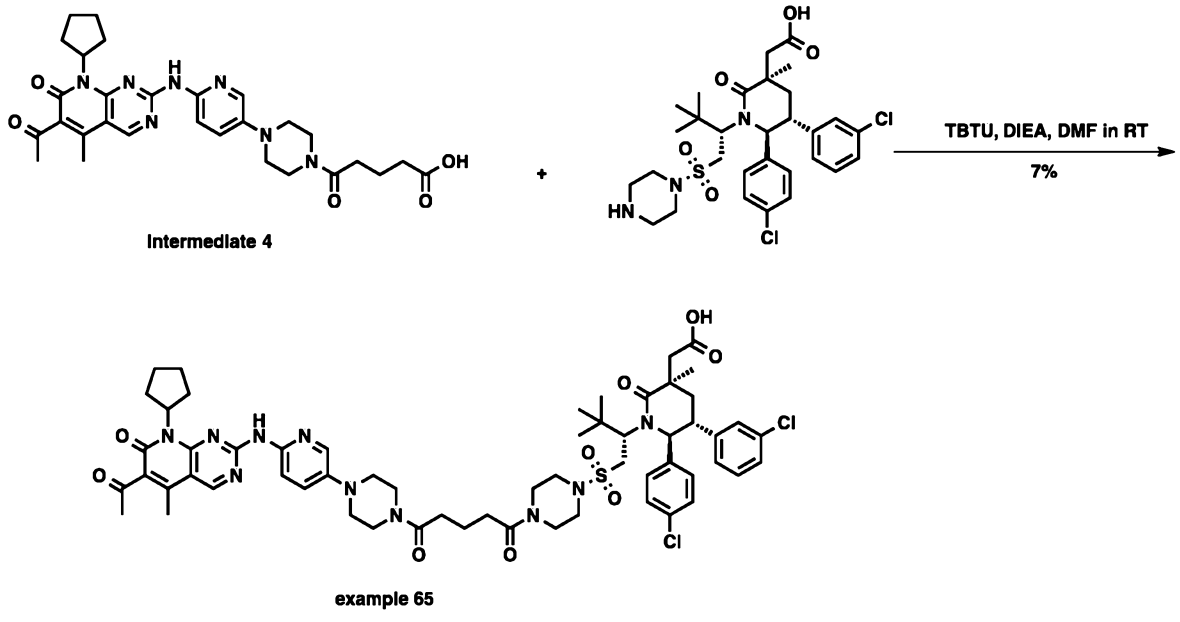
example 64

7-(((*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)-7-

oxoheptanoic acid (linker 37) The title compound was synthesis using the same procedures for the preparation of linker **1** (22 mg, 64%). ^{1}H NMR (600 MHz, CD_3OD) δ 9.23 (s, 1H), 7.48 (dd, *J* = 12.0, 7.3 Hz, 4H), 5.06 – 5.00 (m, 1H), 4.64 (s, 1H), 4.59 (t, *J* = 8.4 Hz, 1H), 4.46 – 4.42 (m, 1H), 3.91 (d, *J* = 11.1 Hz, 1H), 3.77 (dd, *J* = 11.0, 4.0 Hz, 1H), 2.53 (s, 3H), 2.35 – 2.26 (m, 4H), 2.24 – 2.16 (m, 1H), 1.99 – 1.94 (m, 1H), 1.67 – 1.62 (m, 4H), 1.52 (d, *J* = 7.2 Hz, 3H), 1.45 – 1.34 (m, 2H), 1.06 (s, 9H).

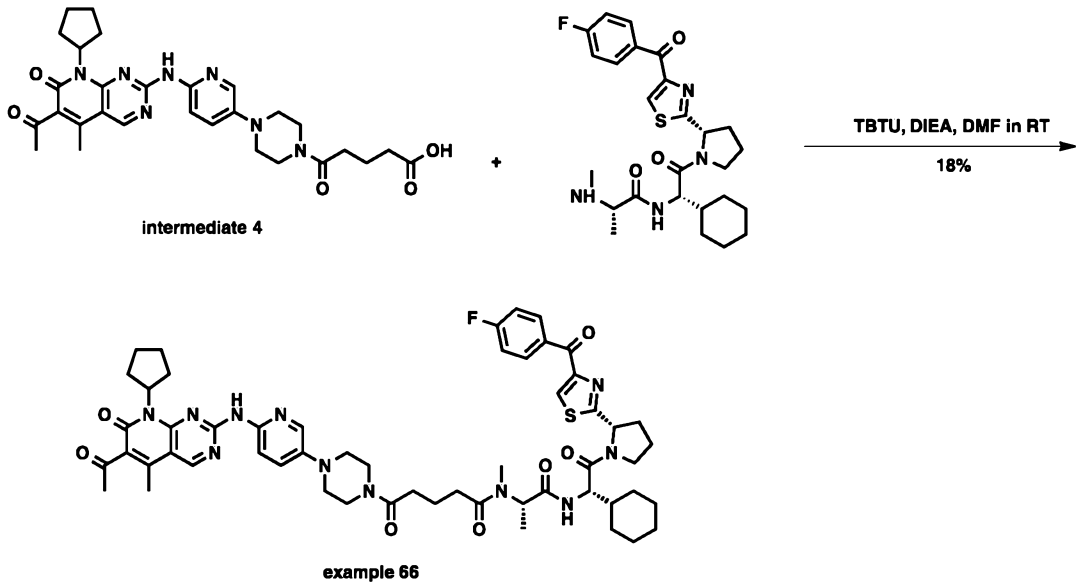
(2*S*,4*R*)-1-((*S*)-2-(7-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-7-oxoheptanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (example 64) the title compound was synthesized using the same procedures for the preparation of the example **40** compound with linker **37** (15 mg, 37%). ^{1}H NMR (600 MHz, CD_3OD) δ 9.12 (s, 1H), 8.98 (s, 1H), 8.23 (dd, *J* = 9.6, 2.9 Hz, 1H), 7.90 (d, *J* = 2.6 Hz, 1H), 7.57 (d, *J* = 9.5 Hz, 1H), 7.45 (q, *J* = 8.3 Hz, 4H), 6.03 (p, *J* = 8.8 Hz, 1H), 5.02 (q, *J* = 6.6 Hz, 1H), 4.66 (s, 1H), 4.60 (t, *J* = 7.7 Hz, 1H), 4.46 (br, 1H), 3.90 (d, *J* = 11.0 Hz, 1H), 3.85 – 3.74 (m, 5H), 3.39 – 3.34 (m, 2H), 3.33 – 3.30 (m, 2H), 2.52 (s, 3H), 2.50 (s, 3H), 2.45 (s, 3H), 2.39 – 2.26 (m, 5H), 2.26 – 2.18 (m, 1H), 2.14 – 2.09 (m, 2H), 2.01 – 1.88 (m, 3H), 1.76 – 1.62 (m, 7H), 1.51 (d, *J* = 6.6 Hz, 3H), 1.46 – 1.41 (m, 2H), 1.06 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{54}H_{70}N_{11}O_7S$, 1016.5175; found: 1016.5154.

Scheme 33: synthesis of example 65



2-((3*R*,5*R*,6*S*)-1-((*S*)-1-((4-(5-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-5-oxopentanoyl)piperazin-1-yl)sulfonyl)-3,3-dimethylbutan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid (example 65) The title compound was synthesized using the same procedures for the preparation of the example **15** compound (4 mg, 7%). ^{1}H NMR (600 MHz, CD_3OD) δ 9.13 (s, 1H), 8.24 (dd, *J* = 9.6, 2.8 Hz, 1H), 7.89 (d, *J* = 2.8 Hz, 1H), 7.79 (br, 1H), 7.57 (d, *J* = 9.6 Hz, 1H), 7.47 (br, 1H), 7.19 (br, 1H), 7.16 – 7.07 (m, 3H), 7.07 (br, 1H), 7.02 (d, *J* = 7.4 Hz, 1H), 6.08 – 5.98 (m, 1H), 5.09 (d, *J* = 11.2 Hz, 1H), 3.96 (dd, *J* = 13.6, 11.5 Hz, 1H), 3.87 – 3.67 (m, 8H), 3.55 (dd, *J* = 11.4, 2.2 Hz, 1H), 3.43 – 3.36 (m, 9H), 3.03 (d, *J* = 13.4 Hz, 1H), 2.94 (dd, *J* = 13.6, 2.2 Hz, 1H), 2.66 (d, *J* = 13.5 Hz, 1H), 2.56 (dd, *J* = 13.6, 7.0 Hz, 4H), 2.53 (s, 3H), 2.46 (s, 3H), 2.89 – 2.35 (m, 3H), 2.16 – 2.08 (m, 3H), 2.01 – 1.90 (m, 4H), 1.72 (dd, *J* = 10.5, 5.4 Hz, 2H), 1.40 (s, 3H), 0.73 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{59}H_{73}Cl_2N_{10}O_9S$, 1167.4654; found: 1167.4653.

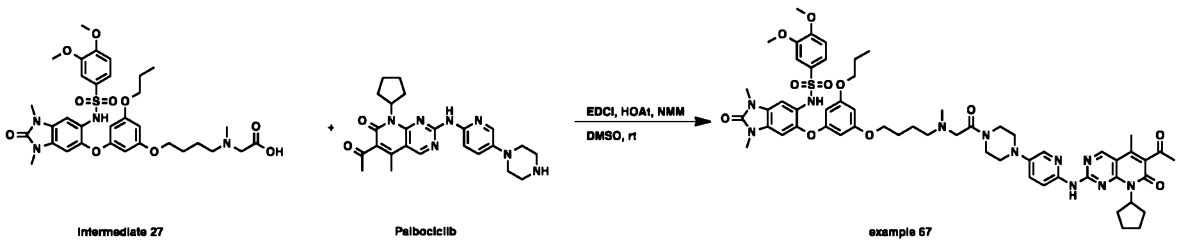
Scheme 34: synthesis of example 66



5-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-*N*-((*S*)-1-(((*S*)-1-cyclohexyl-2-((*S*)-2-(4-(4-fluorobenzoyl)thiazol-2-yl)pyrrolidin-1-yl)-2-oxoethyl)amino)-1-oxopropan-2-yl)-*N*-methyl-5-oxopentanamide (example 66) The title compound was synthesized using the same procedures for the preparation of the example **15** compound (9 mg, 18%). Rotamer (4:3) major

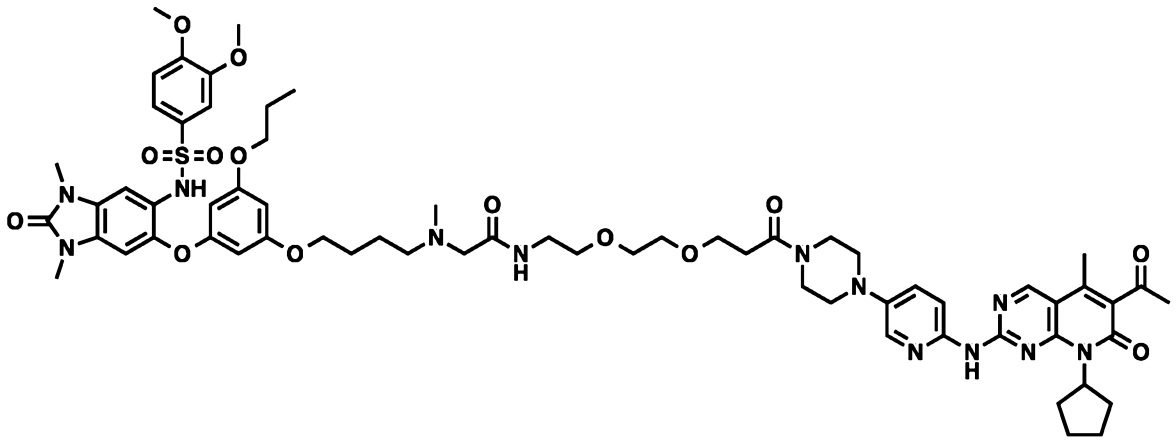
one ^{1}H NMR (600 MHz, CD_3OD) δ 9.10 (s, 1H), 8.41 – 8.15 (m, 3H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.83 (s, 1H), 7.56 – 7.50 (m, 1H), 7.30 – 7.20 (m, 2H), 6.08 – 6.00 (m, 1H), 5.46 (d, *J* = 7.8 Hz, 1H), 5.17 – 5.13 (m, 1H), 4.58 – 4.52 (m, 1H), 4.28 – 4.23 (m, 1H), 3.85 – 3.69 (m, 5H), 3.36 – 3.19 (m, 4H), 2.88 (s, 3H), 2.56 – 2.25 (m, 12H), 2.21 – 2.06 (m, 4H), 2.01 – 1.66 (m, 11H), 1.35 (d, *J* = 7.1 Hz, 4H), 1.34 – 0.84 (m, 7H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{55}H_{67}FN_{11}O_7S$, 1044.4924; found: 1044.4940.

Scheme 35: synthesis of example 67



Intermediate 27 Palbociclib example 67

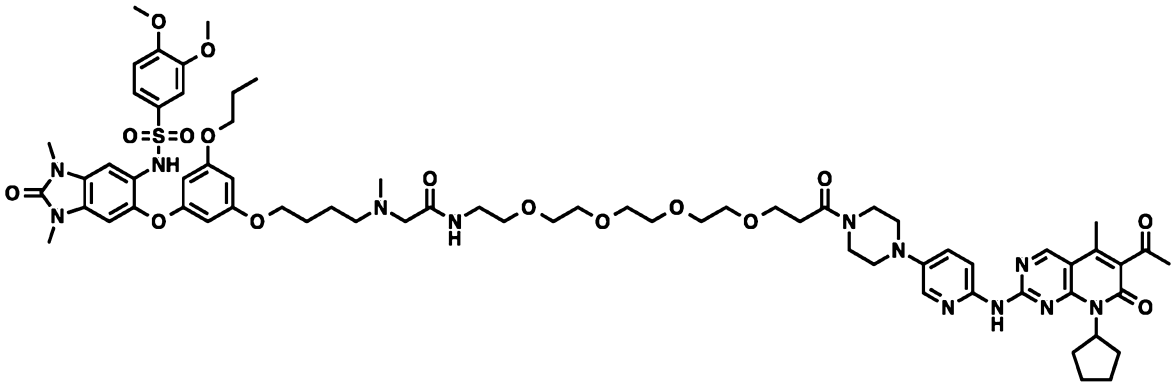
***N*-(6-(3-(4-((2-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-2-oxoethyl)(methyl)amino)butoxy)-5-propoxyphenoxy)-1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)-3,4-dimethoxybenzenesulfonamide (example 67)** To a solution of intermediate **27** (10 mg, 0.01 mmol), HOAt (1-hydroxy-7-azabenzo-triazole) (4.3 mg, 0.03 mmol), and intermediate **2** (5 mg, 0.01 mmol) in DMSO (1 mL) were added NMM (14 μL, 0.13 mmol) and EDCI (6.05 mg, 0.03 mmol) at room temperature. After being stirred overnight at room temperature, the mixture was purified by preparative HPLC (10%-100% methanol / 0.1% TFA in H_2O) to afford example **67** as white solid (6 mg, 54%). ^{1}H NMR (600 MHz, CD_3OD) δ 9.07 (s, 1H), 8.15 (dd, *J* = 10.0, 2.7 Hz, 1H), 7.83 (s, 1H), 7.51 (d, *J* = 9.6 Hz, 1H), 7.29 (s, 1H), 7.18 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.13 (d, *J* = 2.1 Hz, 1H), 6.77 (d, *J* = 8.5 Hz, 1H), 6.59 (s, 1H), 6.14 (s, 1H), 6.04 – 5.97 (m, 1H), 5.72 (t, *J* = 2.1 Hz, 1H), 5.61 (t, *J* = 2.1 Hz, 1H), 4.52 – 4.25 (m, 2H), 3.97 – 3.83 (m, 4H), 3.82 – 3.78 (m, 3H), 3.75 (t, *J* = 6.5 Hz, 2H), 3.60 (s, 6H), 3.39 (s, 5H), 3.24 (s, 6H), 2.99 (s, 3H), 2.50 (s, 3H), 2.43 (s, 3H), 2.31 (dt, *J* = 15.7, 8.4 Hz, 2H), 2.09 (dq, *J* = 12.3, 7.0 Hz, 2H), 2.02 – 1.87 (m, 4H), 1.83 (p, *J* = 6.8 Hz, 2H), 1.76 – 1.65 (m, 4H), 1.00 (t, *J* = 7.4 Hz, 3H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{57}H_{70}N_{11}O_{11}S^+$, 1116.4971; found, 1116.4961.



example 68

***N*-(2-(2-(3-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-3-oxopropoxy)ethoxy)ethyl)-2-((4-(3-((6-((3,4-dimethoxyphenyl)sulfonamido)-1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)oxy)-5-propoxyphenoxy)butyl)(methyl)amino)acetamide**

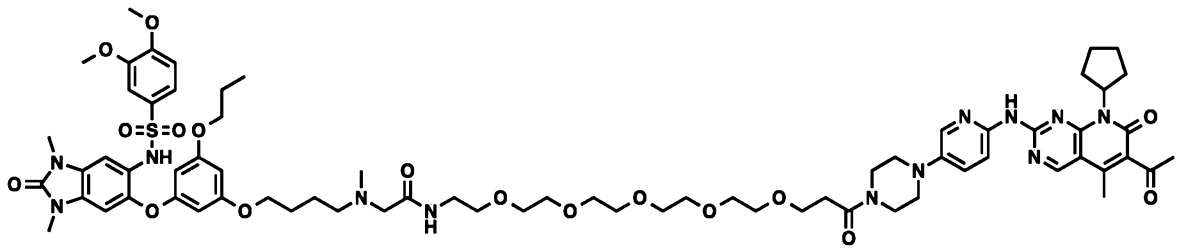
(example 68) The title compound was synthesized using the same procedures for the preparation of the example **67** compound as white solid (7 mg, 55%). ^{1}H NMR (600 MHz, CD_3OD) δ 9.05 (s, 1H), 8.16 (dd, *J* = 9.7, 2.9 Hz, 1H), 7.84 (d, *J* = 2.9 Hz, 1H), 7.52 (d, *J* = 9.5 Hz, 1H), 7.29 (s, 1H), 7.17 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.12 (d, *J* = 2.1 Hz, 1H), 6.78 (d, *J* = 8.5 Hz, 1H), 6.60 (s, 1H), 6.14 (d, *J* = 2.7 Hz, 1H), 6.00 (p, *J* = 8.9 Hz, 1H), 5.73 (d, *J* = 2.3 Hz, 1H), 5.62 (d, *J* = 2.4 Hz, 1H), 3.96 (d, *J* = 45.2 Hz, 2H), 3.86 (t, *J* = 5.9 Hz, 2H), 3.82 – 3.71 (m, 14H), 3.59 (d, *J* = 3.9 Hz, 7H), 3.54 (t, *J* = 5.3 Hz, 2H), 3.45 – 3.37 (m, 5H), 3.28 – 3.22 (m, 6H), 2.95 (d, *J* = 1.1 Hz, 3H), 2.72 (t, *J* = 6.2 Hz, 2H), 2.50 (d, *J* = 1.1 Hz, 3H), 2.42 (s, 3H), 2.31 (dt, *J* = 15.2, 7.6 Hz, 2H), 2.09 (s, 2H), 1.92 (dt, *J* = 15.9, 8.2 Hz, 4H), 1.82 (p, *J* = 6.3 Hz, 2H), 1.71 (dq, *J* = 20.6, 6.3, 5.6 Hz, 4H), 1.00 (dd, *J* = 7.9, 6.8 Hz, 3H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{64}H_{83}N_{12}O_{14}S^+$, 1275.5867; found, 1275.5887.



example 69

***N*-(15-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-15-oxo-3,6,9,12-tetraoxapentadecyl)-2-((4-(3-((6-((3,4-dimethoxyphenyl)sulfonamido)-1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)oxy)-5-propoxyphenoxy)butyl)(methyl)amino)acetamide**

(example 69) The title compound was synthesized using the same procedures for the preparation of the example **67** compound as white solid (6 mg, 44%). ^{1}H NMR (600 MHz, CD_3OD) δ 9.06 (d, *J* = 1.2 Hz, 1H), 8.17 (dd, *J* = 9.6, 3.0 Hz, 1H), 7.85 (d, *J* = 2.9 Hz, 1H), 7.53 (d, *J* = 9.6 Hz, 1H), 7.31 (d, *J* = 1.2 Hz, 1H), 7.18 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.13 (d, *J* = 2.0 Hz, 1H), 6.78 (d, *J* = 8.5 Hz, 1H), 6.60 (d, *J* = 1.2 Hz, 1H), 6.20 – 6.11 (m, 1H), 6.05 – 5.92 (m, 1H), 5.75 (d, *J* = 2.3 Hz, 1H), 5.63 – 5.41 (m, 1H), 3.97 (d, *J* = 43.7 Hz, 2H), 3.88 – 3.84 (m, 2H), 3.83 – 3.68 (m, 13H), 3.62 – 3.56 (m, 14H), 3.54 (t, *J* = 5.3 Hz, 2H), 3.45 – 3.38 (m, 5H), 3.35 – 3.19 (m, 8H), 2.95 (d, *J* = 1.3 Hz, 3H), 2.72 (t, *J* = 6.2 Hz, 2H), 2.50 (d, *J* = 1.3 Hz, 3H), 2.42 (d, *J* = 1.2 Hz, 3H), 2.30 (d, *J* = 9.6 Hz, 2H), 2.09 (s, 2H), 1.95 – 1.87 (m, 4H), 1.82 (q, *J* = 7.1, 6.7 Hz, 2H), 1.72 (dq, *J* = 20.9, 7.2 Hz, 4H), 1.01 (td, *J* = 7.4, 1.2 Hz, 3H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{68}H_{91}N_{12}O_{16}S^+$, 1363.6391; found, 1363.6387.

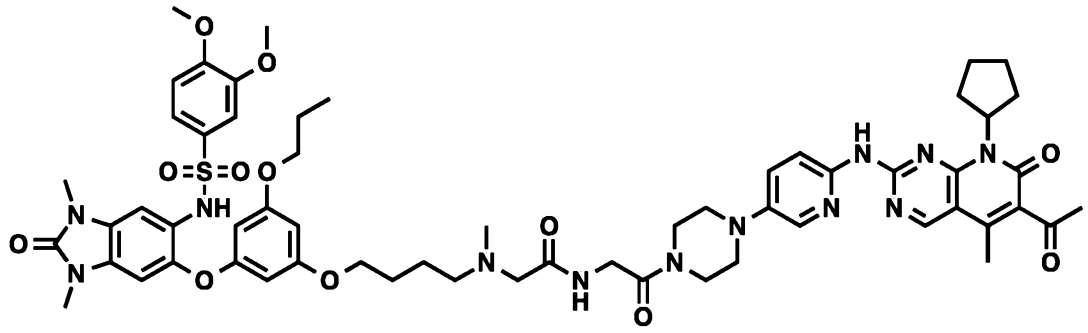


example 70

***N*-(18-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-18-oxo-3,6,9,12,15-pentaoxaoctadecyl)-2-((4-(3-((6-((3,4-dimethoxyphenyl)sulfonamido)-1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)oxy)-5-propoxyphenoxy)butyl)(methyl)amino)acetamide**

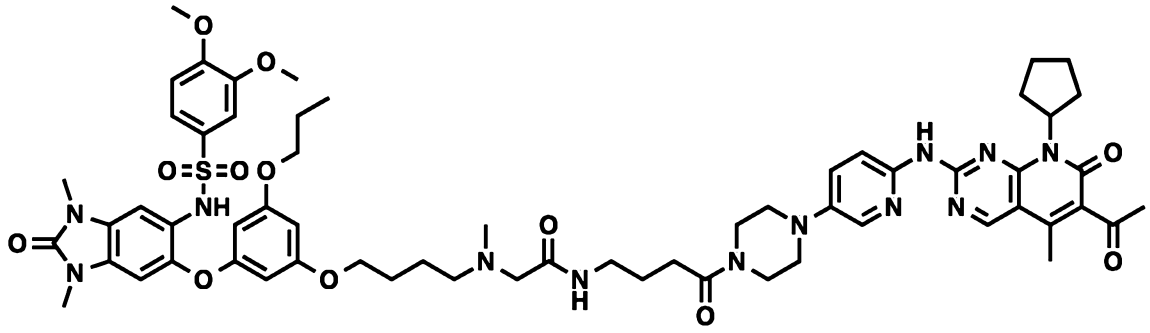
(example 70) The title compound was synthesized using the same procedures for the preparation of the example **67** compound as white solid (9 mg, 64%). ^{1}H NMR (600 MHz, CD_3OD) δ 9.09 – 9.04 (m, 1H), 8.18 (dd, *J* = 9.6, 2.9 Hz, 1H), 7.86 (d, *J* = 2.9 Hz, 1H), 7.53 (d, *J* = 9.6 Hz, 1H), 7.31 (d, *J* = 0.9 Hz, 1H), 7.18 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.13 (d, *J* = 2.2 Hz, 1H), 6.78 (d, *J* = 8.5 Hz, 1H), 6.60 (d, *J* = 0.9 Hz, 1H), 6.15 (d, *J* = 2.3 Hz, 1H), 6.00 (p, *J* = 8.9 Hz, 1H), 5.75 (d, *J* = 2.3 Hz, 1H), 5.61 (d, *J* = 2.5 Hz, 1H), 3.97 (d, *J* = 42.8 Hz, 2H), 3.86 (t, *J* = 5.9 Hz, 2H), 3.83 – 3.73 (m, 13H), 3.63 – 3.56 (m, 18H), 3.54 (t, *J* = 5.3 Hz, 2H), 3.48 – 3.38 (m, 5H), 3.36 – 3.21 (m, 8H), 2.95 (d, *J* = 1.0 Hz, 3H), 2.72 (t, *J* = 6.2 Hz, 2H),

2.50 (d, *J* = 1.0 Hz, 3H), 2.42 (s, 3H), 2.31 (dd, *J* = 12.5, 7.3 Hz, 2H), 2.09 (s, 2H), 1.96 – 1.88 (m, 4H), 1.82 (q, *J* = 7.2, 6.6 Hz, 2H), 1.72 (dq, *J* = 25.3, 6.3, 5.6 Hz, 4H), 1.07 – 0.88 (m, 3H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{70}H_{94}N_{12}O_{17}S^+$, 1407.6653; found, 1407.6628.



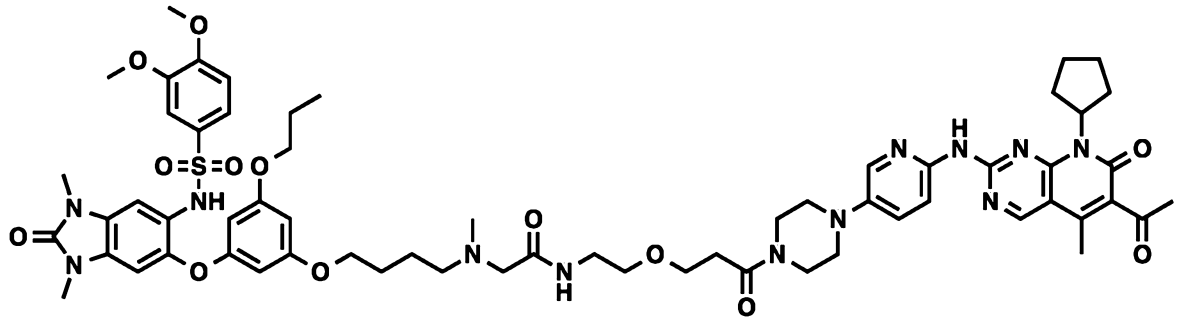
example 71

***N*-(2-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-2-oxoethyl)-2-((4-(3-((6-((3,4-dimethoxyphenyl)sulfonamido)-1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)oxy)-5-propoxyphenoxy)butyl)(methyl)amino)acetamide (example 71)** The title compound was synthesized using the same procedures for the preparation of the example **67** compound as white solid (7 mg, 60%). ^{1}H NMR (600 MHz, CD_3OD) δ 9.08 (s, 1H), 8.13 (d, *J* = 9.6 Hz, 1H), 7.84 (s, 1H), 7.54 (d, *J* = 9.6 Hz, 1H), 7.32 (d, *J* = 1.6 Hz, 1H), 7.18 (d, *J* = 8.5 Hz, 1H), 7.13 (d, *J* = 1.9 Hz, 1H), 6.78 (dd, *J* = 8.6, 1.6 Hz, 1H), 6.62 (d, *J* = 1.6 Hz, 1H), 6.14 (d, *J* = 2.0 Hz, 1H), 6.01 (t, *J* = 8.8 Hz, 1H), 5.73 (d, *J* = 2.1 Hz, 1H), 5.64 (d, *J* = 2.1 Hz, 1H), 4.23 (d, *J* = 37.0 Hz, 2H), 4.08 (d, *J* = 31.5 Hz, 2H), 3.87 (t, *J* = 5.9 Hz, 2H), 3.82 – 3.68 (m, 10H), 3.60 (d, *J* = 1.6 Hz, 3H), 3.41 (d, *J* = 1.6 Hz, 3H), 3.25 (d, *J* = 1.6 Hz, 8H), 2.98 (d, *J* = 1.6 Hz, 3H), 2.50 (d, *J* = 1.6 Hz, 3H), 2.43 (d, *J* = 1.7 Hz, 3H), 2.31 (d, *J* = 9.0 Hz, 2H), 2.09 (s, 2H), 1.93 (dd, *J* = 16.5, 9.0 Hz, 4H), 1.83 (d, *J* = 7.2 Hz, 2H), 1.73 (dt, *J* = 19.8, 9.9 Hz, 4H), 1.00 (td, *J* = 7.4, 1.7 Hz, 3H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{59}H_{73}N_{12}O_{12}S^+$, 1173.5186; found, 1173.5195.



example 72

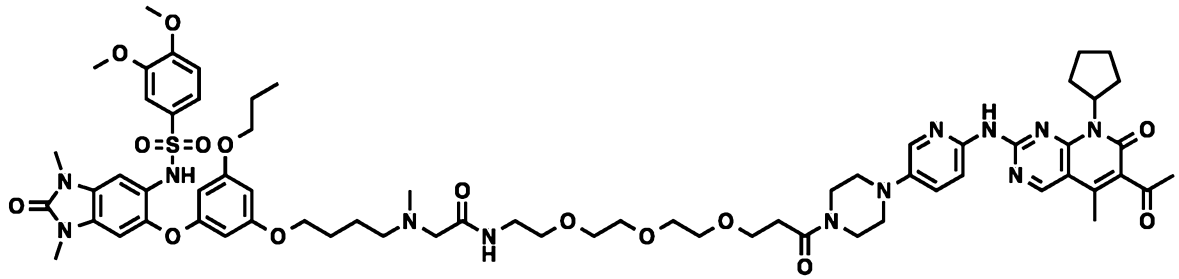
***N*-(4-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-4-oxobutyl)-2-((4-(3-((6-((3,4-dimethoxyphenyl)sulfonamido)-1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)oxy)-5-propoxyphenoxy)butyl)(methyl)amino)acetamide (example 72)** The title compound was synthesized using the same procedures for the preparation of the example **67** compound as white solid (7 mg, 58%). ^{1}H NMR (600 MHz, CD_3OD) δ 9.07 (s, 1H), 8.14 (dd, *J* = 9.5, 2.9 Hz, 1H), 7.84 (s, 1H), 7.54 (d, *J* = 9.5 Hz, 1H), 7.31 (s, 1H), 7.18 (d, *J* = 8.5 Hz, 1H), 7.13 (d, *J* = 2.2 Hz, 1H), 6.78 (d, *J* = 8.5 Hz, 1H), 6.61 (s, 1H), 6.14 (d, *J* = 2.5 Hz, 1H), 6.00 (p, *J* = 8.9 Hz, 1H), 5.74 (s, 1H), 5.62 (d, *J* = 2.5 Hz, 1H), 3.98 (d, *J* = 50.2 Hz, 2H), 3.86 (t, *J* = 5.9 Hz, 2H), 3.80 (s, 3H), 3.78 – 3.66 (m, 7H), 3.61 (s, 3H), 3.41 (d, *J* = 1.1 Hz, 3H), 3.31 – 3.18 (m, 10H), 2.95 (s, 3H), 2.52 – 2.46 (m, 5H), 2.42 (s, 3H), 2.31 (q, *J* = 9.1, 7.5 Hz, 2H), 2.09 (s, 2H), 1.94 – 1.88 (m, 4H), 1.83 (dt, *J* = 14.3, 7.4 Hz, 4H), 1.76 – 1.66 (m, 4H), 1.00 (t, *J* = 7.4 Hz, 3H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{61}H_{77}N_{12}O_{12}S^+$, 1201.5499; found, 1201.5489.



example 73

***N*-(2-(3-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-3-oxopropoxy)ethyl)-2-((4-(3-((6-((3,4-dimethoxyphenyl)sulfonamido)-1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)oxy)-5-propoxyphenoxy)butyl)(methyl)amino)acetamide**

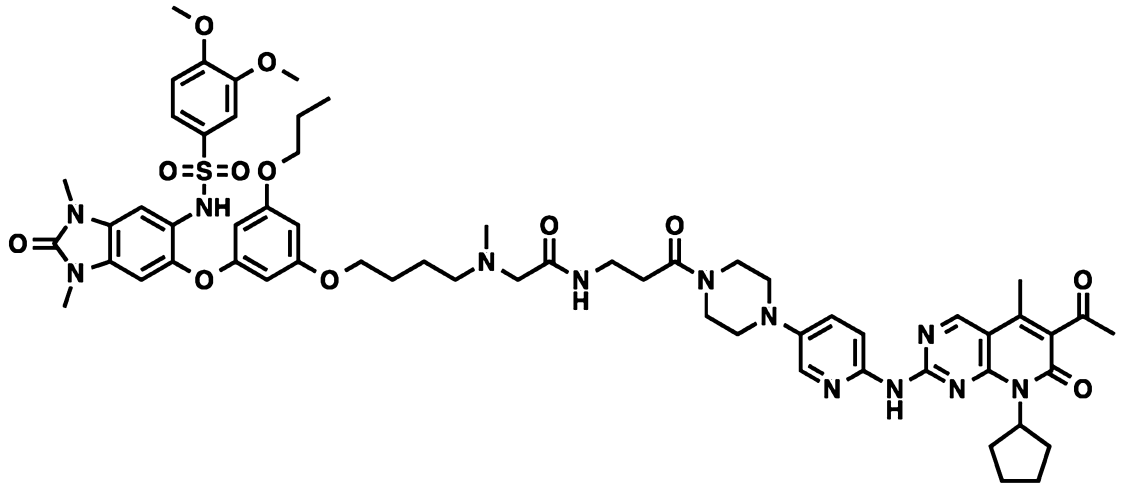
(example 73) The title compound was synthesized using the same procedures for the preparation of the example **67** compound as white solid (8 mg, 65%). ^{1}H NMR (600 MHz, CD_3OD) δ 9.05 (s, 1H), 8.10 (d, *J* = 9.6 Hz, 1H), 7.84 (s, 1H), 7.56 (d, *J* = 9.4 Hz, 1H), 7.34 – 7.26 (m, 1H), 7.18 (d, *J* = 8.4 Hz, 1H), 7.13 (d, *J* = 1.7 Hz, 1H), 6.84 – 6.72 (m, 1H), 6.67 – 6.50 (m, 1H), 6.14 (s, 1H), 6.00 (p, *J* = 8.9 Hz, 1H), 5.74 (s, 1H), 5.63 (s, 1H), 3.99 (s, 2H), 3.86 (t, *J* = 5.8 Hz, 2H), 3.83 – 3.72 (m, 15H), 3.60 (d, *J* = 1.1 Hz, 3H), 3.56 (t, *J* = 5.4 Hz, 2H), 3.40 (d, *J* = 1.1 Hz, 4H), 3.26 – 3.22 (m, 5H), 2.96 (d, *J* = 1.2 Hz, 3H), 2.70 (t, *J* = 5.9 Hz, 2H), 2.50 (d, *J* = 1.2 Hz, 3H), 2.42 (d, *J* = 1.2 Hz, 3H), 2.31 (dd, *J* = 12.5, 7.3 Hz, 2H), 2.09 (s, 3H), 1.93 (dt, *J* = 16.9, 8.3 Hz, 4H), 1.86 – 1.79 (m, 2H), 1.72 (dt, *J* = 19.2, 9.6 Hz, 4H), 1.00 (td, *J* = 7.5, 1.2 Hz, 3H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{62}H_{79}N_{12}O_{13}S^+$, 1231.5605; found, 1231.5621.



example 74

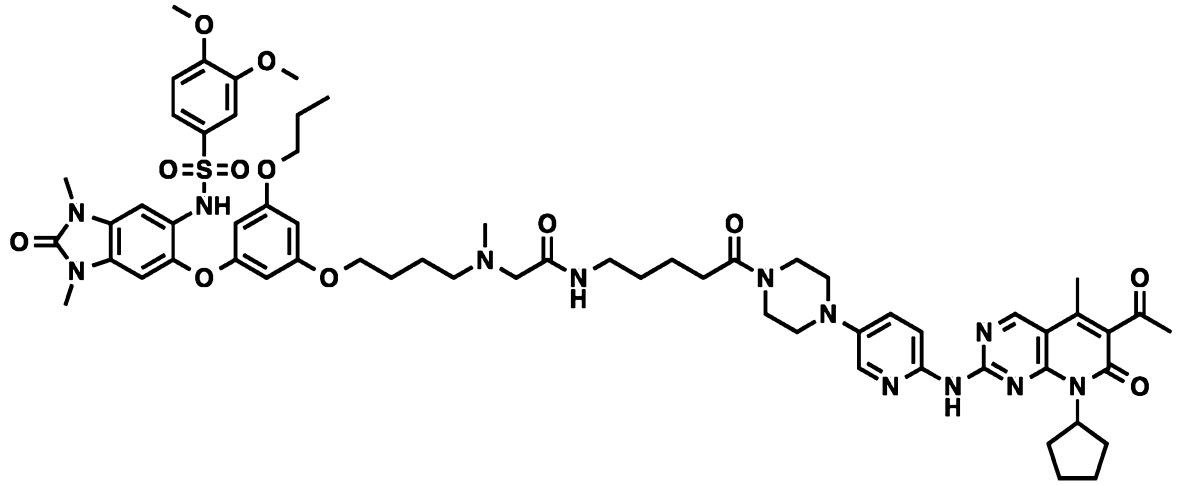
***N*-(2-(2-(2-(3-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-3-oxopropoxy)ethoxy)ethoxy)ethyl)-2-((4-(3-((6-((3,4-dimethoxyphenyl)sulfonamido)-1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)oxy)-5-propoxyphenoxy)butyl)(methyl)amino)acetamide (example 74)** The title compound was synthesized using the same procedures for the preparation of the example **67** compound as white solid (8 mg, 61%). ^{1}H NMR (600 MHz, CD_3OD) δ 9.06 (s, 1H), 8.16 (dd, *J* = 9.6, 2.9 Hz, 1H), 7.85 (s, 1H), 7.53 (d, *J* = 9.6 Hz, 1H), 7.30 (s, 1H), 7.18 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.12 (d, *J* = 2.1 Hz, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 6.60 (s, 1H), 6.14 (d, *J* = 2.6 Hz, 1H), 6.00 (p, *J* = 9.0 Hz, 1H), 5.74 (d, *J* = 2.4 Hz, 1H), 5.61 (d, *J* = 2.5 Hz, 1H), 3.98 (d, *J* = 36.9 Hz, 2H), 3.85 (t, *J* = 5.9 Hz, 2H), 3.82 – 3.70 (m, 13H), 3.63 – 3.52 (m, 15H), 3.45 – 3.36 (m, 5H),

3.29 – 3.19 (m, 5H), 2.95 (d, J = 1.1 Hz, 3H), 2.72 (t, J = 6.2 Hz, 2H), 2.50 (d, J = 1.2 Hz, 3H), 2.42 (s, 3H), 2.30 (d, J = 9.4 Hz, 2H), 2.09 (s, 2H), 1.92 (q, J = 8.3, 7.9 Hz, 4H), 1.81 (p, J = 6.3 Hz, 2H), 1.71 (ddd, J = 23.2, 12.4, 6.2 Hz, 4H), 1.00 (t, J = 7.4 Hz, 3H). HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{66}H_{87}N_{12}O_{15}S^+$, 1319.6129; found, 1319.6132.



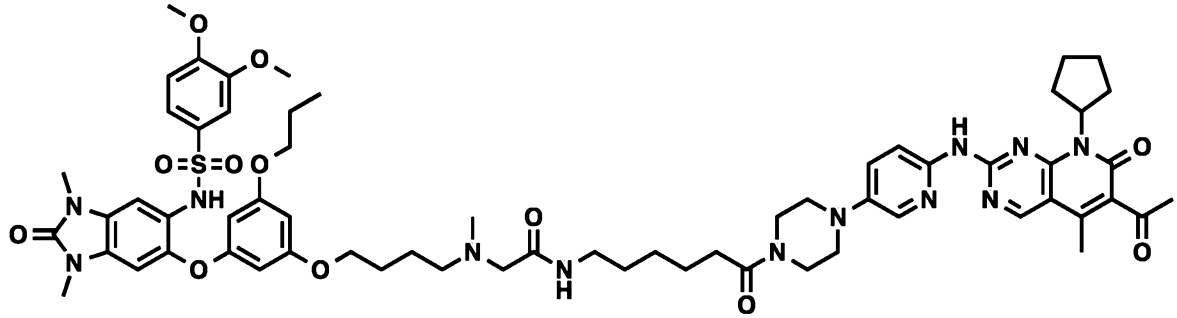
example 75

***N*-(3-(4-(6-(((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-3-oxopropyl)-2-((4-(3-((6-((3,4-dimethoxyphenyl)sulfonamido)-1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)oxy)-5-propoxyphenoxy)butyl)(methyl)amino)acetamide (example 75)** The title compound was synthesized using the same procedures for the preparation of the example **67** compound as white solid (9 mg, 76%). ^{1}H NMR (600 MHz, CD_3OD) δ 9.07 (s, 1H), 8.15 (dd, J = 9.6, 2.9 Hz, 1H), 7.82 (d, J = 2.9 Hz, 1H), 7.52 (d, J = 9.5 Hz, 1H), 7.30 (d, J = 1.2 Hz, 1H), 7.17 (dd, J = 8.4, 2.0 Hz, 1H), 7.12 (d, J = 2.2 Hz, 1H), 6.77 (d, J = 8.4 Hz, 1H), 6.60 (d, J = 1.2 Hz, 1H), 6.14 (t, J = 1.9 Hz, 1H), 6.01 (p, J = 8.9 Hz, 1H), 5.74 (t, J = 1.9 Hz, 1H), 5.61 (t, J = 1.9 Hz, 1H), 3.96 (d, J = 48.7 Hz, 2H), 3.86 (t, J = 5.9 Hz, 2H), 3.80 (d, J = 1.3 Hz, 3H), 3.76 (t, J = 6.6 Hz, 6H), 3.69 (t, J = 5.2 Hz, 2H), 3.60 (d, J = 1.2 Hz, 5H), 3.40 (d, J = 1.3 Hz, 3H), 3.30 – 3.21 (m, 7H), 2.95 (d, J = 1.2 Hz, 3H), 2.68 (t, J = 6.4 Hz, 2H), 2.51 (d, J = 1.2 Hz, 3H), 2.43 (d, J = 1.2 Hz, 3H), 2.37 – 2.27 (m, 2H), 2.10 (s, 2H), 1.91 (q, J = 8.1 Hz, 4H), 1.86 – 1.79 (m, 2H), 1.72 (dq, J = 14.0, 7.1 Hz, 4H), 1.00 (td, J = 7.4, 1.2 Hz, 3H). HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{57}H_{70}N_{11}O_{11}S^+$, 1187.5343; found, 1187.5355.



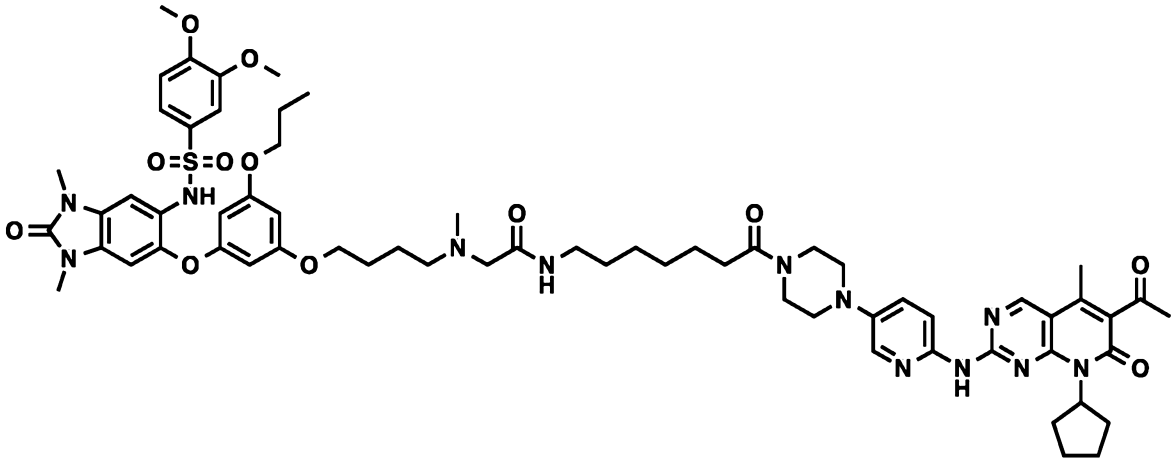
example 76

***N*-(5-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-5-oxopentyl)-2-((4-(3-((6-((3,4-dimethoxyphenyl)sulfonamido)-1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)oxy)-5-propoxyphenoxy)butyl)(methyl)amino)acetamide (example 76)** The title compound was synthesized using the same procedures for the preparation of the example **67** compound as white solid (5 mg, 41%). ^{1}H NMR (600 MHz, CD_3OD) δ 9.08 (d, *J* = 1.2 Hz, 1H), 8.17 (dd, *J* = 9.6, 2.9 Hz, 1H), 7.83 (d, *J* = 2.9 Hz, 1H), 7.52 (d, *J* = 9.5 Hz, 1H), 7.31 (d, *J* = 1.2 Hz, 1H), 7.18 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.13 (d, *J* = 2.0 Hz, 1H), 6.78 (dd, *J* = 8.5, 1.2 Hz, 1H), 6.61 (d, *J* = 1.1 Hz, 1H), 6.14 (t, *J* = 2.0 Hz, 1H), 6.01 (p, *J* = 8.9 Hz, 1H), 5.73 (t, *J* = 2.0 Hz, 1H), 5.62 (t, *J* = 2.0 Hz, 1H), 4.07 – 3.93 (m, 2H), 3.86 (t, *J* = 5.9 Hz, 2H), 3.80 (d, *J* = 1.2 Hz, 3H), 3.79 – 3.68 (m, 10H), 3.60 (d, *J* = 1.2 Hz, 3H), 3.40 (d, *J* = 1.2 Hz, 3H), 3.34 – 3.23 (m, 7H), 2.95 (d, *J* = 1.3 Hz, 3H), 2.50 (d, *J* = 1.3 Hz, 3H), 2.48 – 2.38 (m, 5H), 2.31 (q, *J* = 9.0, 7.5 Hz, 2H), 2.10 (s, 2H), 1.92 (dt, *J* = 15.5, 7.9 Hz, 4H), 1.82 (p, *J* = 6.3 Hz, 2H), 1.72 (dq, *J* = 20.1, 6.3, 5.5 Hz, 4H), 1.61 (dq, *J* = 28.9, 7.8 Hz, 4H), 1.00 (td, *J* = 7.5, 1.3 Hz, 3H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{62}H_{79}N_{12}O_{12}S^+$, 1215.5656; found, 1215.5637.



example 77

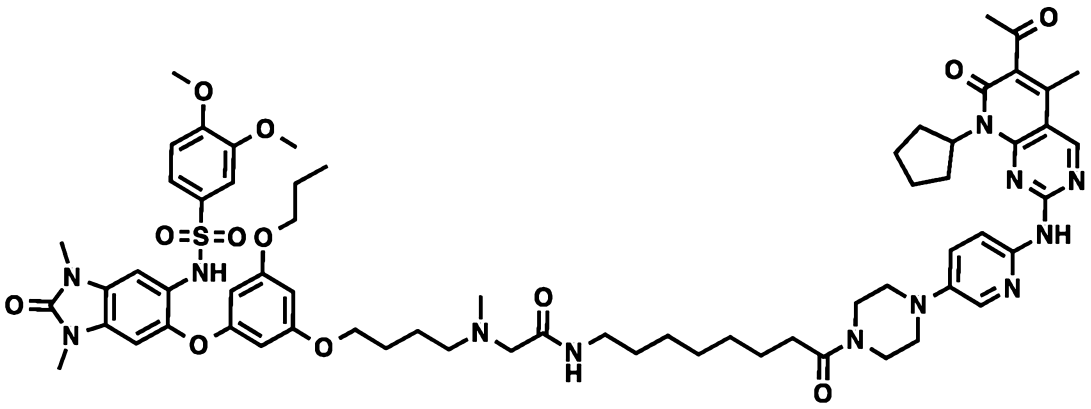
***N*-(6-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-6-oxohexyl)-2-((4-(3-((6-((3,4-dimethoxyphenyl)sulfonamido)-1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)oxy)-5-propoxyphenoxy)butyl)(methyl)amino)acetamide (example 77)** The title compound was synthesized using the same procedures for the preparation of the example **67** compound as white solid (6 mg, 41%). ^{1}H NMR (600 MHz, CD_3OD) δ 9.07 (s, 1H), 8.16 (d, *J* = 9.6 Hz, 1H), 7.85 (s, 1H), 7.53 (d, *J* = 9.5 Hz, 1H), 7.31 (d, *J* = 1.2 Hz, 1H), 7.18 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.13 (d, *J* = 2.1 Hz, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 6.61 (d, *J* = 1.2 Hz, 1H), 6.14 (t, *J* = 1.9 Hz, 1H), 6.05 – 5.93 (m, 1H), 5.74 (t, *J* = 1.9 Hz, 1H), 5.62 (t, *J* = 1.9 Hz, 1H), 3.96 (d, *J* = 46.5 Hz, 2H), 3.86 (t, *J* = 5.9 Hz, 2H), 3.81 (d, *J* = 1.3 Hz, 3H), 3.79 – 3.69 (m, 10H), 3.60 (d, *J* = 1.3 Hz, 3H), 3.41 (d, *J* = 1.3 Hz, 3H), 3.25 (d, *J* = 1.3 Hz, 7H), 2.95 (d, *J* = 1.3 Hz, 3H), 2.50 (d, *J* = 1.3 Hz, 3H), 2.43 (d, *J* = 6.8 Hz, 5H), 2.31 (q, *J* = 9.0, 7.5 Hz, 2H), 2.09 (s, 2H), 1.92 (dt, *J* = 15.7, 8.0 Hz, 4H), 1.82 (q, *J* = 7.1, 6.6 Hz, 2H), 1.73 (ddt, *J* = 16.9, 10.7, 6.1 Hz, 4H), 1.59 (dp, *J* = 38.0, 7.4 Hz, 4H), 1.38 (p, *J* = 7.8 Hz, 2H), 1.01 (td, *J* = 7.4, 1.3 Hz, 3H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{63}H_{80}N_{12}O_{12}S^+$, 1229.5812; found, 1229.5802.



example 78

***N*-(7-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-7-oxoheptyl)-2-((4-(3-((6-((3,4-dimethoxyphenyl)sulfonamido)-1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)oxy)-5-propoxyphenoxy)butyl)(methyl)amino)acetamide (example 78)** The title compound was synthesized using the same procedures for the preparation of the example **67** compound as white solid (8mg, 64%). ^{1}H NMR (600 MHz, CD_3OD) δ 9.08 (s, 1H), 8.18 (d, *J* = 9.5 Hz, 1H), 7.85 (s, 1H), 7.53 (d, *J* = 9.5 Hz, 1H), 7.32 (s, 1H), 7.22 – 7.16 (m, 1H), 7.13 (d, *J* = 2.1 Hz, 1H), 6.78 (d, *J* = 8.5 Hz, 1H), 6.61 (s, 1H), 6.14 (t, *J* = 1.9 Hz, 1H), 6.00 (p, *J* =

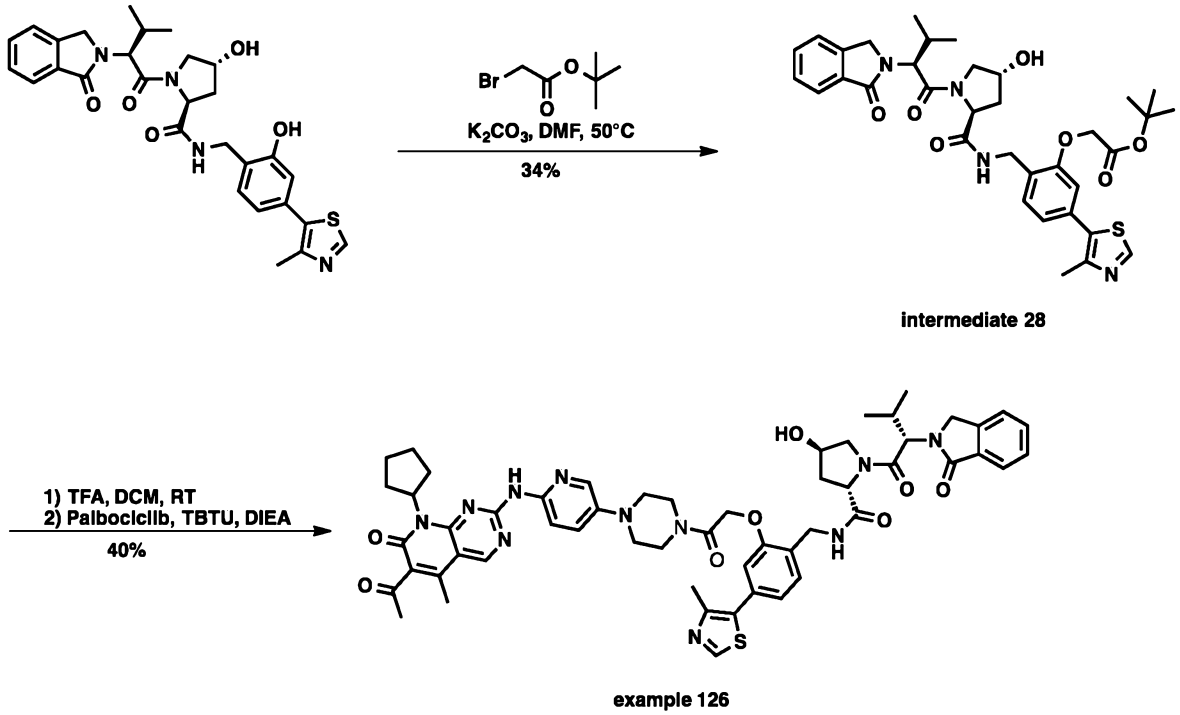
8.9 Hz, 1H), 5.74 (t, *J* = 1.9 Hz, 1H), 5.61 (d, *J* = 1.8 Hz, 1H), 3.96 (d, *J* = 44.8 Hz, 2H), 3.85 (t, *J* = 5.8 Hz, 2H), 3.82 – 3.67 (m, 13H), 3.60 (d, *J* = 1.3 Hz, 3H), 3.41 (d, *J* = 1.2 Hz, 3H), 3.26 (dd, *J* = 10.4, 3.4 Hz, 7H), 2.94 (d, *J* = 1.3 Hz, 3H), 2.50 (d, *J* = 1.3 Hz, 3H), 2.43 (d, *J* = 5.7 Hz, 5H), 2.36 – 2.29 (m, 2H), 2.09 (s, 2H), 1.92 (p, *J* = 7.6 Hz, 4H), 1.81 (p, *J* = 6.4 Hz, 2H), 1.72 (dq, *J* = 19.2, 6.7 Hz, 4H), 1.59 (d, *J* = 6.9 Hz, 2H), 1.53 (t, *J* = 6.9 Hz, 2H), 1.36 (s, 4H), 1.03 – 0.89 (m, 3H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{64}H_{83}N_{12}O_{12}S^+$, 1243.5969; found, 1243.5967.



example 79

***N*-(8-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-8-oxooctyl)-2-((4-(3-((6-((3,4-dimethoxyphenyl)sulfonamido)-1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)oxy)-5-propoxyphenoxy)butyl)(methyl)amino)acetamide (example 79)** The title compound was synthesized using the same procedures for the preparation of the example **67** compound as white solid (8mg, 64%). ^{1}H NMR (600 MHz, CD_3OD) δ 9.08 (s, 1H), 8.19 (dd, *J* = 9.6, 2.9 Hz, 1H), 7.85 (d, *J* = 2.9 Hz, 1H), 7.52 (d, *J* = 9.6 Hz, 1H), 7.32 (s, 1H), 7.18 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.14 (d, *J* = 2.1 Hz, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 6.61 (s, 1H), 6.14 (d, *J* = 2.4 Hz, 1H), 6.01 (p, *J* = 8.9 Hz, 1H), 5.75 (d, *J* = 2.4 Hz, 1H), 5.60 (d, *J* = 2.4 Hz, 1H), 3.96 (d, *J* = 48.0 Hz, 2H), 3.85 (t, *J* = 5.9 Hz, 2H), 3.83 – 3.69 (m, 13H), 3.61 (d, *J* = 1.0 Hz, 3H), 3.41 (d, *J* = 1.0 Hz, 3H), 3.28 – 3.21 (m, 7H), 2.94 (d, *J* = 1.1 Hz, 3H), 2.50 (d, *J* = 1.0 Hz, 3H), 2.43 (q, *J* = 3.4 Hz, 5H), 2.31 (dd, *J* = 12.5, 7.5 Hz, 2H), 2.10 (s, 2H), 1.96 – 1.87 (m, 4H), 1.82 (q, *J* = 7.1, 6.6 Hz, 2H), 1.78 – 1.66 (m, 4H), 1.59 (d, *J* = 7.4 Hz, 2H), 1.56 – 1.48 (m, 2H), 1.34 (s, 6H), 1.03 – 0.90 (m, 3H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{65}H_{85}N_{12}O_{12}S^+$, 1257.6125; found, 1257.6103.

Scheme 36: synthesis of example 126



***tert*-Butyl 2-(2-(((2*S*,4*R*)-4-hydroxy-1-((*S*)-3-methyl-2-(1-oxoisoindolin-2-yl)butanoyl)pyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)acetate (intermediate 28)** To a solution of (2*S*,4*R*)-4-hydroxy-*N*-(2-hydroxy-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-3-methyl-2-(1-oxoisoindolin-2-yl)butanoyl)pyrrolidine-2-carboxamide (124 mg, 0.23 mmol) in DMF (2 mL) were added K_2CO_3 (130 mg, 0.94 mmol) and *tert*-butyl-2-bromo-acetate ester (0.037 mmL, 0.25 mmol). The mixture was stirred at 50°C for 18 h. After cooling to RT, the mixture was filtered to remove the unsolvable materials. The filtrate was concentrated under reduce pressure. The resulting residue was purified by prep-HPLC to yield the title compound (52 mg, 34%) as brown oil. ^{1}H NMR (600 MHz, CD_3OD) δ 9.10 (s, 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.67 – 7.57 (m, 2H), 7.56 – 7.47 (m, 2H), 7.11 (d, *J* = 7.9 Hz, 1H), 6.98 (s, 1H), 4.88 – 4.85 (m, 1H), 4.78 (s, 2H), 4.68 – 4.46 (m, 6H), 3.99 (d, *J* = 11.2 Hz, 1H), 3.91 (d, *J* = 11.1 Hz, 1H), 2.53 (s, 3H), 2.50 – 2.40 (m, 1H), 2.27 – 2.18 (m, 1H), 2.15 – 2.05 (m, 1H), 1.50 (s, 9H), 1.04 (d, *J* = 6.6 Hz, 3H), 0.84 (d, *J* = 6.6 Hz, 3H).

(2*S*,4*R*)-*N*-(2-(2-(4-(6-((6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)-2-oxoethoxy)-4-(4-methylthiazol-5-yl)benzyl)-4-hydroxy-1-((*S*)-3-methyl-2-(1-oxoisoindolin-2-yl)butanoyl)pyrrolidine-2-

carboxamide (example 126) Intermediate **28** (52 mg, 0.078 mmol) was dissolved in DCM/TFA (2:1, 3 mL). The solution was stirred at RT for 3 h before being concentrated. The residue was dissolved in DCM/DMF (3:1, 2 mL). To the resulting solution were added palbociclib (33 mg, 0.074 mmol), TBTU (25 mg, 0.076 mmol), and DIEA (0.04 mL, 0.24 mmol). The reaction mixture was stirred at RT for 18 h. After concentration, the resulting residue was purified by prep-HPLC to yield the title compound (32 mg, 40%) as yellow solid. ^{1}H NMR (600 MHz, Methanol-d_4) δ 9.07 (s, 1H), 8.96 (s, 1H), 8.18 (dd, J = 9.7, 2.9 Hz, 1H), 7.89 (d, J = 2.9 Hz, 1H), 7.74 (d, J = 7.6 Hz, 1H), 7.58 (t, J = 7.5 Hz, 1H), 7.55 (d, J = 9.6 Hz, 1H), 7.51 (d, J = 7.7 Hz, 1H), 7.48 – 7.44 (m, 2H), 7.12 – 7.07 (m, 2H), 5.99 (p, J = 8.9 Hz, 1H), 5.14 – 5.00 (m, 2H), 4.88 (d, J = 11.2 Hz, 1H), 4.62 – 4.41 (m, 6H), 4.02 (d, J = 11.1 Hz, 1H), 3.96 (dd, J = 11.1, 3.9 Hz, 1H), 3.91 – 3.83 (m, 4H), 3.39 – 3.30 (m, 4H), 2.53 (s, 3H), 2.52 (s, 3H), 2.44 (s, 3H), 2.43 – 2.38 (m, 1H), 2.37 – 2.23 (m, 3H), 2.16 – 2.05 (m, 3H), 1.98 – 1.85 (m, 2H), 1.76 – 1.66 (m, 2H), 1.03 (d, J = 6.5 Hz, 3H), 0.83 (d, J = 6.6 Hz, 3H). HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{55}H_{62}N_{11}O_8S^+$, 1036.4498; found, 1036.4508.

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 75 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

Breast cancer cell lines (MCF7, T47D, and ZR-75-1) and melanoma cell lines (A375, SK-MEL-2, SK-MEL-30, and WM1382) were cultured in the presence of DMEM or RPMI supplemented with 10% FBS in the presence of penicillin and streptomycin.

Cell Viability Assay

Cells were cultured for 7-11 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.

BrdU Cell Proliferation Assay

BrdU incorporation was measured using a BrdU cell proliferation kit (Millipore) according to the manufacturer's instructions. Briefly, ER+ or melanoma cells were seeded at $1*10^5$ cells/ml in 96-well plates. The following day, cultured cells were treated with different concentrations of abemaciclib or palbociclib for 12 h, followed by incubation with BrdU labeling solution for 4 h. BrdU absorbance was measured with a spectrophotometer microplate reader at a dual wavelength of 450/550 nm. The measured absorbance reflected the degree of cell proliferation. Each group was cultured in triplicate.

Quantitative Real-Time PCR Analysis

Cells were treated with CDK4/6i for 24 h, and total RNA was extracted using an RNeasy Mini kit (Qiagen). Complementary DNA (cDNA) was synthesized with a SuperScript III First Strand Synthesis System (Thermo Fisher). Quantitative real-time PCR was performed using a Fast SYBR Green Master Mix with an ABI-7500 Fast Real-Time PCR System. Samples were normalized using the housekeeping gene GAPDH. Differences in expression were calculated using the ΔΔCT method.

The following primer sequences were used in PCR analyses:

GAPDH:

F: 5'- ACAACTTTGGTATCGTGGAAGG-3' (SEQ ID NO: 1);

R: 5'- GCCATCACGCCACAGTTTC-3' (SEQ ID NO: 2)

CDK4:

F: 5'- CTGGTGTTTGAGCATGTAGACC-3' (SEQ ID NO: 3);

R: 5'- GATCCTTGATCGTTTCGGCTG-3' (SEQ ID NO: 4)

CDK6:

F: 5'- TCTTCATTCACACCGAGTAGTGC-3' (SEQ ID NO: 5);

R: 5'- TGAGGTTAGAGCCATCTGGAAA-3' (SEQ ID NO: 6)

CCNA2:

F: 5'- CGCTGGCGGTACTGAAGTC-3' (SEQ ID NO: 7);

R: 5'- GAGGAACGGTGACATGCTCAT-3' (SEQ ID NO: 8)

PLK1:

F: 5'- CACCAGCACGTCGTAGGATTC-3' (SEQ ID NO: 9);

R: 5'- CCGTAGGTAGTATCGGGCCTC-3' (SEQ ID NO: 10)

Western Blot Assay

Protein concentrations were determined by BCA from cell lysates and equal amounts of protein are loaded to a Bis-Tris 4-12% gel. Gels were run at 80 V for 4 h using 1X running buffer (25 mM Tris, pH 8.3, 1.92 M glycine, 0.1% SDS). Proteins were transferred to a nitrocellulose membrane for 2 h at 100 V using transfer buffer (25 mM Tris, pH 8.3, 1.92 M glycine, 20% methanol). Ponceau S staining (0.1% Ponceau S, 1% acetic acid) was used to confirm transfer of proteins to the membrane followed by blocking of the membrane for 30 min at room temperature using blocking buffer (5% dry nonfat milk, 0.1% Tween, 0.02% sodium azide in TBS). The blocked membrane is incubated with primary antibodies (1:1000 dilution) in blocking buffer at 4 °C overnight. When primary phosphor-antibodies were used, then the membrane is incubated with 5% BSA instead of milk. The membrane was washed three times, 10 min each, with wash buffer (0.1% Tween in TBS) followed by incubation with secondary HRP conjugated antibody (1:5000 dilution) in 2.5% dry nonfat milk, 0.1% Tween in TBS for 1 h at room temperature. The membrane was washed three times, 10 min each, with wash buffer (0.1% Tween in TBS). Membranes are incubated with ECL for 1 min and proteins are detected after exposure to a blue autoradiographic film.

Example 5. CDK4/6 Inhibitors Fail to Suppress CDK4/6 Activity at High Concentrations

MCF7, T47D, or ZR-75-1 breast cancer cells were treated with 0, 0.1, 0.3, 1, 3, 10, or 30 μM palbociclib (PB) or abemaciclib (AB) for 24 h, then lysed and immunoblotted with antibodies to phospho-Rb, PLK1, cyclin A, and total Rb and actin (as controls) (Fig. 1, panels A and B). Similarly, SK-MEL-2, SK-MEL-30, or MCF7 melanoma cells were treated with 0, 0.1, 0.3, 1, 3, 10, or 30 μM palbociclib (PB), abemaciclib (AB), or 219476 for 24 h, then lysed and immunoblotted with antibodies to phospho-Rb, PLK1, cyclin A, and total Rb and actin (as controls) (Fig. 1, panels C, D, and E). The results indicated that all three CDK4/6 inhibitors tested only had a narrow window of activity. As expected, they failed to suppress CDK4/6 activity (as evidenced by Rb phosphorylation (pRb level)) in breast cancer or melanoma cells when administered at low concentrations; surprisingly, they also failed to suppress CDK4/6 activity when administered at high concentrations (e.g., a concentration ≥ about 10 μM).

Example 6. CDK4/6 Inhibitors Increase Expression of PLK1 and Cyclin A mRNA

MCF7, T47D, or ZR-75-1 breast cancer cells or SK-MEL-2 or SK-MEL-30 melanoma cells were treated with 0, 1, 7.5, 15, or 30 μM palbociclib or abemaciclib for 24 h, then lysed and subjected to PCR analysis of expression of the Rb/E2F downstream targets PLK1 and cyclin A (CCNA2). Neither palbociclib nor abemaciclib suppressed expression of PLK1 or cyclin A at the mRNA level; in fact, there was a positive correlation between increased inhibitor concentration and increased gene expression (Figs. 2 and 3). This data suggests a mechanistic explanation for the failure of CDK4/6 inhibitors to suppress CDK4/6 activity when administered at high concentrations.

Example 7. CDK4/6 Inhibitors Suppress Cell Proliferation Less Effectively at High Concentrations

MCF7, T47D, or ZR-75-1 breast cancer cells or SK-MEL-2 or SK-MEL-30 melanoma cells were treated with 0, 0.3, 1, 3, 10, 20, or 30 μM palbociclib or abemaciclib for 16 h; cell cycle progression through S phase was determined using the BrdU incorporation assay. Consistent with the results in Examples 5 and 6 (above), the results indicated that there was an inverse correlation between increased inhibitor concentration and suppression of cell cycle progression (Fig. 4).

Example 8. CDK4/6 Inhibitors Increase Expression of CDK4/6

MCF7, T47D, or ZR-75-1 breast cancer cells or SK-MEL-2 melanoma cells were treated with 0, 0.1, 0.3, 1, 3, 10, or 30 μM palbociclib or abemaciclib for 24 h, then lysed and immunoblotted with antibodies to CDK4, CDK6, and actin. The results indicated that, despite the CDK4/6 inhibitors' ability to inhibit the *activity* of CDK4 and CDK6, the inhibitors actually *upregulate* the expression of both CDK4 and CDK6, with a positive correlation between increased inhibitor concentration and increased CDK4/6 expression (Fig. 5, panels A-C). This data suggests a mechanistic explanation for the positive correlation between CDK4/6 inhibitor concentration and increased expression of PLK1 and cyclin A mRNA.

MCF7, T47D, or ZR-75-1 breast cancer cells were treated with 0, 1, 7.5, 15, or 30 μM palbociclib or abemaciclib for 24 h, then lysed and subjected to PCR analysis of expression of CDK4. The CDK4/6 inhibitors did *not* upregulate the expression of CDK4 mRNA (Fig. 6), indicating that the CDK4/6 inhibitors increase CDK4/6 protein expression by inhibiting protein degradation (instead of by increasing transcription or extending mRNA half-life).

To confirm the above findings, 293H cells ectopically expressing V5-tagged CDK4 or V5-tagged CDK6 were treated with 1, 3, or 10 μM palbociclib (PB), abemaciclib (AB), or ribociclib (RIB) for 24 h, then lysed and immunoblotted with antibodies to V5 (to detect V5-

tagged CDK4 or CDK6) and actin. Consistent with Fig. 5, all three CDK4/6 inhibitors examined upregulated the expression of V5-tagged CDK4 and CDK6 (Fig. 7).

Example 9. CDK4/6 Inhibitors Prevent Ubiquitination of CDK4

293H cells ectopically co-expressing V5-tagged CDK4 and HA-tagged ubiquitin were treated with 1 or 10 μM palbociclib or abemaciclib for 24 h, then lysed and either 1) subjected to immunoprecipitation with a V5 antibody (to pull down V5-tagged CDK4) followed by immunoblotting for HA (to detect HA-tagged ubiquitin), or 2) directly immunoblotted with antibodies to V5, HA, and actin. The data indicated that CDK4/6 inhibitors inhibit the ubiquitination of CDK4, thus protecting it from degradation and inducing elevated cellular levels of CDK4 (Fig. 8, panel A).

T47D breast cancer cells were treated with the proteasome inhibitor MG132 for 24 h in the presence or absence of 1 or 10 μM abemaciclib, then lysed and either 1) subjected to immunoprecipitation with a CDK4 antibody followed by immunoblotting for ubiquitin, or 2) directly immunoblotted with antibodies to ubiquitin, CDK4, and actin. Consistent with the results above for V5-tagged CDK4, the data indicated that CDK4/6 inhibitors inhibit the ubiquitination of native CDK4 (Fig. 8, panel B).

Example 10 Increased CDK4/6 Expression is Associated with Decreased CDK4/6 Inhibitor Efficacy

MCF7 breast cancer cells resistant to palbociclib (MCF7-PBR) were generated by treating MCF7 cells with 1 μM palbociclib for 12 weeks. MCF7-PBR cells were then treated with 1, 3, or 10 μM palbociclib (PB) for 24 h, then lysed and immunoblotted with antibodies to phospho-Rb (pRB), Rb (RB), PLK1, cyclin A, CDK2, CDK6, and actin (Fig. 9). These results confirmed the resistance of the MCF7-PBR cells to palbociclib and demonstrated that this resistance is associated with elevated expression of CDK6 (compare CDK6 levels in the MCF7 lane with CDK6 levels in any of the MCF7-PBR lanes, noting that the actin control indicates equal amounts of total protein in the MCF7 and MCF7-PBR lanes).

Example 11. Palbociclib Suppresses Rb Phosphorylation More Effectively in ER+ Breast Cancer Cells

MCF7 or T47D breast cancer cells or SK-MEL-2, A375, or WM1382 melanoma cells were treated with or without 0.5 μM palbociclib for 24 h, then lysed and immunoblotted with antibodies to phospho-Rb (pRb), cyclin A, PLK1, CDK4, CDK6, and actin (Fig. 9). The results indicated that palbociclib suppresses Rb phosphorylation more effectively in ER+ breast cancer cells than melanoma cells.

Example 12. CDK4/6 degraders/disruptors Inhibit CDK4/6 Activity and Suppress CDK4/6 Expression

MCF7 breast cancer cells were treated with 1 or 5 μM XY019-095, XY019-098, XY019-0100, XY019-105A, XY019-105B, XY019-106, or XY019-108 for 24 h, then lysed and immunoblotted with antibodies to CDK4, CDK6, and actin (Fig. 10, panel A). The results indicated that XY019-098, XY019-106, and XY019-108 were especially effective in suppressing CDK4/6 expression even at 1 μM; this effect did not diminish at 5 μM. T47D breast cancer cells were treated with 0.1, 0.3, 1, 3, 10, or 30 μM XY019-106 for 24 h, then lysed and immunoblotted with antibodies to phospho-Rb (pRB), CDK4, and actin (Fig. 10, panel B). The results showed that XY019-106 both suppresses CDK4 expression and inhibit CDK4 activity (as evidenced by decreased Rb phosphorylation), with significant effects at concentrations as low as 0.3 μM. Further, unlike CDK4/6 inhibitors such as palbociclib, XY019-106 inhibited Rb phosphorylation even when administered at high concentrations (e.g., at concentrations as high as 30 μM).

SK-MEL-2 or A375 melanoma cells (Fig. 11, panels A and B) were treated with 1 or 3 μM XY019-106, XY028-002, XY028-003, XY028-004, XY028-005, XY028-006, or XY028-007 for 24 h, then lysed and immunoblotted with antibodies to CDK4, CDK6, phospho-Rb (pRb), and actin. Similarly, A375 melanoma cells were treated with 1 or 3 μM palbociclib (PB), XY019-106, XY028-003, XY028-082, XY028-083, XY028-084, or XY028-085 for 24 h, then lysed and immunoblotted with antibodies to CDK6, CDK4, phospho-Rb (pRb), cyclin A, PLK1, and actin (Fig. 11, panel C).

The results confirmed the efficacy of CDK4/6 degraders/disruptors, particularly XY019-106 and XY028-003, in inhibiting both CDK4/6 expression and CDK4/6 activity (as evidenced by decreased Rb phosphorylation).

A375 melanoma cells (Fig. 12, panel A) were treated with 1 or 3 μM palbociclib (PB), XY019-106, XY028-003, XY028-132, XY028-133, XY028-114, XY028-097, XY028-105, or XY028-106 for 24 h, then lysed and immunoblotted with antibodies to CDK4, CDK6, phospho-Rb (pRb), and actin. Similarly, A375 melanoma cells were treated with 1 or 3 μM palbociclib (PB), XY019-106, XY028-003, XY028-132, XY028-133, XY028-140, XY028-141, XY028-142, or XY028-143 for 24 h, then lysed and immunoblotted with antibodies to CDK6, CDK4, phospho-Rb (pRb), cyclin A, PLK1, and actin (Fig. 12, panel B). Similarly, A375 melanoma cells were treated with 1 or 3 μM XY028-132, XY028-133, XY028-140, XY028-141, XY028-142, XY028-143, XY028-144, or XY028-145 for 24 h, then lysed and immunoblotted with antibodies to CDK6, CDK4, cyclin A, PLK1, and actin (Fig. 12, panel C).

Similarly, A375 melanoma cells were treated with 1 or 3 μM palbociclib (PB), XY019-106, XY028-103, XY028-108, XY028-132, XY028-133, or XY028-140 for 24 h, then lysed and immunoblotted with antibodies to CDK6, CDK4, phospho-Rb (pRb), cyclin A, PLK1, and actin (Fig. 12, panel D).

The results confirmed the efficacy of CDK4/6 degraders, particularly XY028-133, XY028-140, XY019-106 and XY028-003, in inhibiting both CDK4/6 expression and CDK4/6 activity (as evidenced by decreased Rb phosphorylation).

A375 melanoma cells (Fig. 13) were treated with 1 or 3 μM Ribociclib (RB), YX030-126, YX030-108, YX030-107, YX030-086, YX030-085 or XY028-133 for 24 h, then lysed and immunoblotted with antibodies to CDK4, CDK6, cyclin A, PLK1, phospho-Rb (pRb), and actin.

The results demonstrated that ribociclib-based CDK4/6 degraders, in particular YX-085, are likewise effective in inhibiting both CDK4/6 expression and CDK4/6 activity (as evidenced by decreased Rb phosphorylation).

A375 melanoma cells (Fig. 14) were treated with 1 or 3 μM Abemaciclib (AB), YX030-125, YX030-117, YX030-118 or XY028-133 for 24 h, then lysed and immunoblotted with antibodies to CDK4, CDK6, cyclin A, PLK1, phospho-Rb (pRb), and actin.

ZR-75-1 breast cancer cells (Fig. 15, panel A) or SK-MEL-2 melanoma cells (Fig. 15, panel B) were treated with 1 or 5 μM abemaciclib (AB), YX26-56, YX26-58, or YX26-66 for 24 h, then lysed and immunoblotted with antibodies to phospho-Rb (pRb), total Rb, PLK1, cyclin A, CDK4, CDK6, and actin. The results demonstrated that ademaciclib-based CDK4/6 degraders/ disruptors are likewise effective in inhibiting both CDK4/6 expression and CDK4/6 activity (as evidenced by decreased Rb phosphorylation).

A375 melanoma cells (Fig. 16, panel A) were treated with 0.3 or 1 μM XY028-140, YX039-65, YX039-48, YX039-123, YX039-56, YX039-124 or YX039-147 for 24 h. A375 melanoma cells were treated with 1 or 3 μM XY028-140, YX039-56, YX039-65 or XY028-133 (Fig 16, panel B). Cells were lysed and immunoblotted with antibodies to phospho-Rb (pRb), total Rb, PLK1, cyclin A, CDK4, CDK6, and actin. The results confirmed the efficacy of CDK4/6 degraders, particularly XY028-133 in inhibiting both CDK4/6 expression and CDK4/6 activity (as evidenced by decreased Rb phosphorylation).

T47D breast cancer cells (Fig. 17) were treated with 0.3 or 1 μM XY028-140, YX039-48, YX039-123, YX039-56, YX039-124, YX039-65, YX039-147 or YX039-74 for 24 h, then lysed and immunoblotted with antibodies to phospho-Rb (pRb), total Rb, PLK1, cyclin A, CDK4, CDK6, and actin. The results confirmed the efficacy of CDK4/6 degraders, particularly

XY028-140 and YX039-123, in inhibiting both CDK4/6 expression and CDK4/6 activity (as evidenced by decreased Rb phosphorylation).

A375 melanoma cells (Fig. 18) were treated with 1 or 3 μM XY028-133, YX044-18, YX044-22, XY028-140, YX044-19 or YX044-38 for 24 h, then lysed and immunoblotted with antibodies to phospho-Rb (pRb), total Rb, PLK1, cyclin A, CDK4, CDK6, and actin. The results confirmed the efficacy of CDK4/6 degraders, particularly XY028-133 and YX044-18, in inhibiting both CDK4/6 expression and CDK4/6 activity (as evidenced by decreased Rb phosphorylation).

T47D breast cancer cells (Fig. 19) were treated with 0.3 or 1 μM XY028-133, YX044-18, YX044-22, XY028-140, YX044-19 or YX044-38 for 24 h, then lysed and immunoblotted with antibodies to phospho-Rb (pRb), total Rb, PLK1, cyclin A, CDK4, CDK6, and actin. The results confirmed the efficacy of CDK4/6 degraders, particularly XY028-140 and YX044-22 and YX044-19, in inhibiting both CDK4/6 expression and CDK4/6 activity (as evidenced by decreased Rb phosphorylation).

Example 13. CDK4/6 Degraders/Disruptors Inhibit Cancer Cell Proliferation.

A375 melanoma cells (Fig. 20) were treated with 1 or 2 μM palbociclib or XY028-133 for 7 days. Bright field imaging indicated that XY028-133 was more effective in inhibiting cancer cell proliferation than palbociclib at the same concentration in melanoma cells.

A375 melanoma cells (Fig. 21) were treated with 0.03, 0.1, 0.3, 1, or 3 μM palbociclib or XY028-133 for 11 days. Crystal violet staining indicated that XY028-133 was more effective in inhibiting cancer cell proliferation than palbociclib at 1 and 3 μM in melanoma cells.

T47D breast cancer cells (Fig. 22) were treated with 0.03, 0.1, 0.3, 1, or 3 μM palbociclib, XY028-140, YX039-48, YX039-124, YX039-123, YX039-147, YX039-56, or YX039-65 for 11 days. Crystal violet staining indicated that CDK4/6 degraders and particularly XY028-140, YX039-123, YX039-56, and YX039-65 inhibited cancer cell proliferation more effective that palbociclib at the same concentration in breast cancer cells.

T47D breast cancer cells (Fig. 23) were treated with 0.003, 0.01, or 0.03 μM palbociclib, XY028-140, YX039-123, YX039-56, or YX039-65 for 11 days. Crystal violet staining indicated that CDK4/6 degraders inhibited cancer cell proliferation more effective that palbociclib at the same concentration in breast cancer cells.

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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CLAIMS

What is claimed is:

1. A bivalent compound comprising a cyclin-dependent kinase 4/6 (CDK4/6) ligand conjugated to a degradation/disruption tag.

2. The bivalent compound of claim 1, wherein the CDK4/6 ligand is a CDK4/6 inhibitor.

3. The bivalent compound of claim 2, wherein the CDK4/6 ligand is selected from the group consisting of abemaciclib, palbociclib, ribociclib, trilaciclib, G1T38, SHR6390, and analogs thereof.

4. The bivalent compound of any one of claims 1-3, wherein the CDK4/6 ligand is bound to CDK4/6.

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

6. The bivalent compound of any one of claims 1-5, wherein the degradation/disruption tag binds to a ubiquitin ligase or serves as a hydrophobic group that leads to CDK4 or CDK6 protein misfolding.

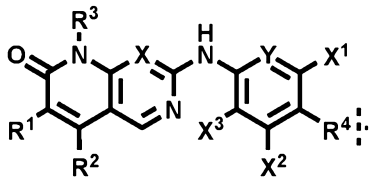
7. The bivalent compound of any one of claims 1-6, wherein the CDK4/6 ligand is conjugated to the degradation/disruptor tag through a linker.

8. The bivalent compound of any one of claims 1-7, wherein the bivalent compound has the structure of formula I:

Formula I,

wherein **PI** comprises a CDK4/6 ligand and **EL** comprises a degradation/disruption tag.

9. The bivalent compound of claim 8, wherein **PI** has the structure of Formula II,



Formula II,

wherein X^1, X^2, and X^3 are independently hydrogen, halogen, C1-C8 alkyl, C1-C8 alkoxy, C1-C8 alkoxyalkyl, NR^5R^6, CN, NO_2, COR^5, CO_2R^5, $CONR^5R^6$, or NR^5COR^6;

R^1 and R^4 are independently hydrogen, halogen, C1-C8 alkyl, C1-C8 alkoxy, C1-C8 alkoxyalkyl, C1-C8 haloalkyl, C1-C8 hydroxyalkyl, C3-C7 cycloalkyl, C3-C7 heterocyclyl, C2-C8 alkenyl, C2-C8 alkynyl, OR^5, SR^5, NR^5R^6, CN, NO_2, $(CR^5R^6)mNR^7R^8$, $(CR^5R^6)mC(O)R^7$, COR^5, CO_2R^5, $CONR^5R^6$, NR^5COR^6, NR^5SOR^6, $NR^5SO_2R^6$, SOR^5, SO_2R^5, $SO_2NR^5R^6$, (CR^5R^6)m-aryl, or (CR^5R^6)m-heteroaryl, wherein m is 0-8;

R^2 is hydrogen, halogen, C1-C8 alkyl, C1-C8 alkoxy, C3-C7 cycloalkyl, or C3-C7 heterocyclyl;

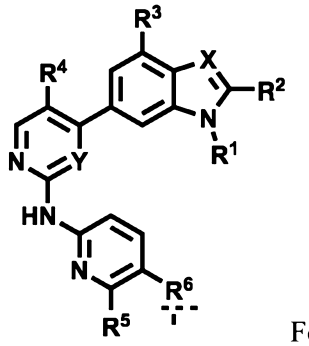
R^3 is hydrogen, aryl, C1-C8 alkyl, C1-C8 alkoxy, C3-C7 cycloalkyl, or C3-C7 heterocyclyl;

R^5, R^6, R^7, and R^8 are independently hydrogen, C1-C8 alkyl, C2-C8 alkenyl, C2-C8 alkynyl, arylalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, or heteroarylalkyl;

optionally, R^1 and R^2, R^5 and R^6, or $R^7$and R^8 independently form 4-8 membered alkyl or heterocyclyl rings; and

X and Y are independently CR^5R^6 or N;

the structure of Formula III,



Formula III,

wherein R^1 is hydrogen, C1-C8 alkyl, C1-C8 alkoxyalkyl, C1-C8 haloalkyl, C1-C8 hydroxyalkyl, C3-C7 cycloalkyl, C3-C7 heterocyclyl, C2-C8 alkenyl, or C2-C8 alkynyl;

R^2 is hydrogen, C1-C3 alkyl, or cyclopropyl;

R^3, R^4, and R^5 are independently hydrogen, halogen, C1-C8 alkyl, C1-C8 alkoxy, C3-C7 cycloalkyl, or C3-C7 heterocyclyl;

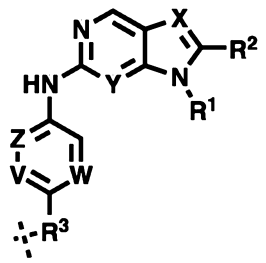
R^6 is hydrogen, halogen,C1-C8 alkyl, C1-C8 alkoxy, C1-C8 alkoxyalkyl, C1-C8 haloalkyl, C1-C8 hydroxyalkyl, C3-C7 cycloalkyl, C3-C7 heterocyclyl, C2-C8 alkenyl, C2-C8 alkynyl, OR^7, SR^7, NR^7R^8, CN, NO_2, $(CR^7R^8)mNR^9R^{10}$, $(CR^7R^8)mC(O)R^9$, COR^7, CO_2R^7, $CONR^7R^8$, NR^7COR^8, NR^7SOR^8, $NR^7SO_2R^8$, SOR^7, SO_2R^7, $SO_2NR^7R^8$, (CR^7R^8)m-aryl, or (CR^7R^8)m-heteroaryl; wherein m is 0-8;

R^7, R^8, R^9, and R^{10} are independently hydrogen, C1-C8 alkyl, C2-C8 alkenyl, C2-C8 alkynyl, arylalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, or heteroarylalkyl;

optionally, R^7 and R^8 or R^9 and R^{10} independently form 4-8 membered alkyl or heterocyclyl rings; and

X and Y are independently CR^7R^8, or N;

the structure of Formula IV,



Formula IV,

wherein R^1 is hydrogen, C1-C8 alkyl, C1-C8 alkoxyalkyl, C1-C8 haloalkyl, C1-C8 hydroxyalkyl, C3-C7 cycloalkyl, C3-C7 heterocyclyl, C2-C8 alkenyl, or C2-C8 alkynyl;

R^2 is hydrogen, C1-C8 alkyl, C1-C8 alkoxyalkyl, C1-C8 haloalkyl, C1-C8 hydroxyalkyl, C3-C7 cycloalkyl, C3-C7 heterocyclyl, C2-C8 alkenyl, or C2-C8 alkynyl, CN, COR^4, CO_2R^4, or $CONR^4R^5$;

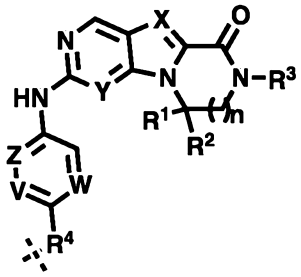
R^3 is hydrogen, halogen, C1-C8 alkyl, C1-C8 alkoxy, C1-C8 alkoxyalkyl, C1-C8 haloalkyl, C1-C8 hydroxyalkyl, C3-C7 cycloalkyl, C3-C7 heterocyclyl, C2-C8 alkenyl, C2-C8 alkynyl, OR^4, SR^4, NR^4R^5, CN, NO_2, $(CR^4R^5)mNR^6R^7$, $(CR^4R^5)mC(O)R^6$, COR^4, CO_2R^4, $CONR^4R^5$, NR^4COR^5, NR^4SOR^5, $NR^4SO_2R^5$, SOR^4, SO_2R^4, $SO_2NR^4R^5$, (CR^4R^5)m-aryl, or (CR^4R^5)m-heteroaryl, wherein m is 0-8;

R^4, R^5, R^6, and R^7 are independently hydrogen, C1-C8 alkyl, C2-C8 alkenyl, C2-C8 alkynyl, arylalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, or heteroarylalkyl;

optionally, R^1 and R^2, R^4 and R^5, or $R^6$and R^7 independently form 4-8 membered alkyl or heterocyclyl rings; and

V, W, X, Y, and Z are independently CR^4R^5 or N;

or the structure of Formula VI,



Formula VI,

wherein R^1 and R^2 are independently hydrogen, C1-C8 alkyl, C1-C8 alkoxyalkyl, C1-C8 haloalkyl, C1-C8 hydroxyalkyl, C3-C7 cycloalkyl, C3-C7 heterocyclyl, C2-C8 alkenyl, or C2-C8 alkynyl;

R^3 is hydrogen, C1-C6 alkyl, C1-C6 alkoxyalkyl, C1-C6 haloalkyl, C1-C6 hydroxyalkyl, C3-C6 cycloalkyl, C3-C6 heterocyclyl, C2-C6 alkenyl, or C2-C6 alkynyl;

R^4 is hydrogen, halogen,C1-C8 alkyl, C1-C8 alkoxy, C1-C8 alkoxyalkyl, C1-C8 haloalkyl, C1-C8 hydroxyalkyl, C3-C7 cycloalkyl, C3-C7 heterocyclyl, C2-C8 alkenyl, C2-C8 alkynyl, OR^5, SR^5, NR^5R^6, CN, NO_2, $(CR^5R^6)mNR^7R^8$, $(CR^5R^6)mC(O)R^7$, COR^5,

CO_2R^5, $CONR^5R^6$, NR^5COR^6, NR^5SOR^6, $NR^5SO_2R^6$, SOR^5, SO_2R^5, $SO_2NR^5R^6$, (CR^5R^6)m-aryl, or (CR^5R^6)m-heteroaryl, wherein m is 0-8;

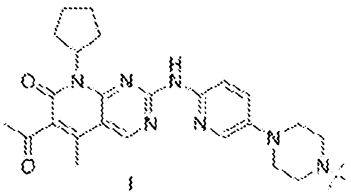
n is 0-4;

optionally, R^1 and R^2, R^5 and R^6, or $R^7$and R^8 independently form 4-8 membered alkyl or heterocyclyl rings; and

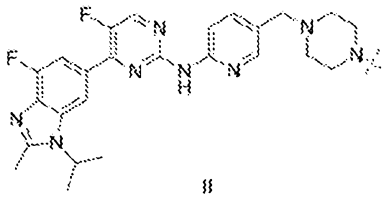
V, W, X, Y, and Z are independently CR^5R^6 or N.

10. The bivalent compound of claim 8 or 9, wherein the CDK4/6 ligand is selected from the group consisting of abemaciclib, palbociclib, ribociclib, trilaciclib (G1T28), G1T38, SHR6390, and analogs thereof.

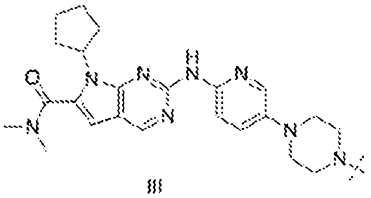
11. The bivalent compound of claim 8 or 9, wherein the CDK4/6 ligand is selected from the group consisting of:



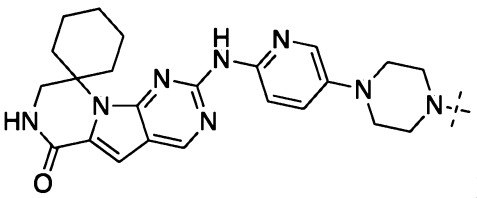
I



II



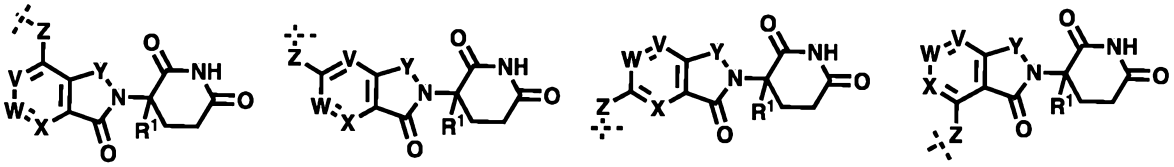
III



IV.

12. The bivalent compound of any one of claims 8-11, wherein the CDK4/6 ligand is bound to CDK4/6.

13. The bivalent compound of any one of claims 8-12, wherein **EL** is selected from:



Formula VII, Formula VIII, Formula IX, Formula XI,

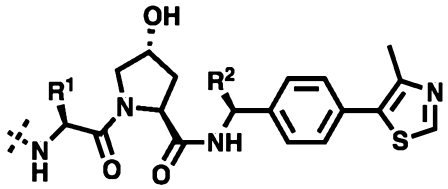
wherein V, W, and X are independently CR^2 or N;

Y is CO or CH_2;

Z is CH_2, NH, or O;

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

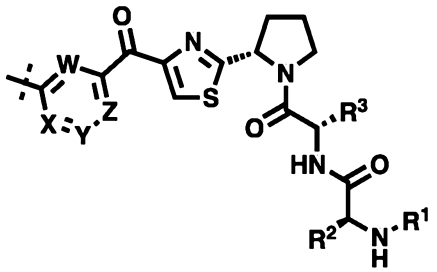
R^2 is hydrogen, halogen, or C1-C5 alkyl;



Formula XII,

wherein R^1 and R^2 are independently hydrogen, C1-C8 alkyl, C1-C8 alkoxyalkyl, C1-C8 haloalkyl, C1-C8 hydroxyalkyl, C3-C7 cycloalkyl, C3-C7 heterocyclyl, C2-C8 alkenyl, or C2-C8 alkynyl;

or



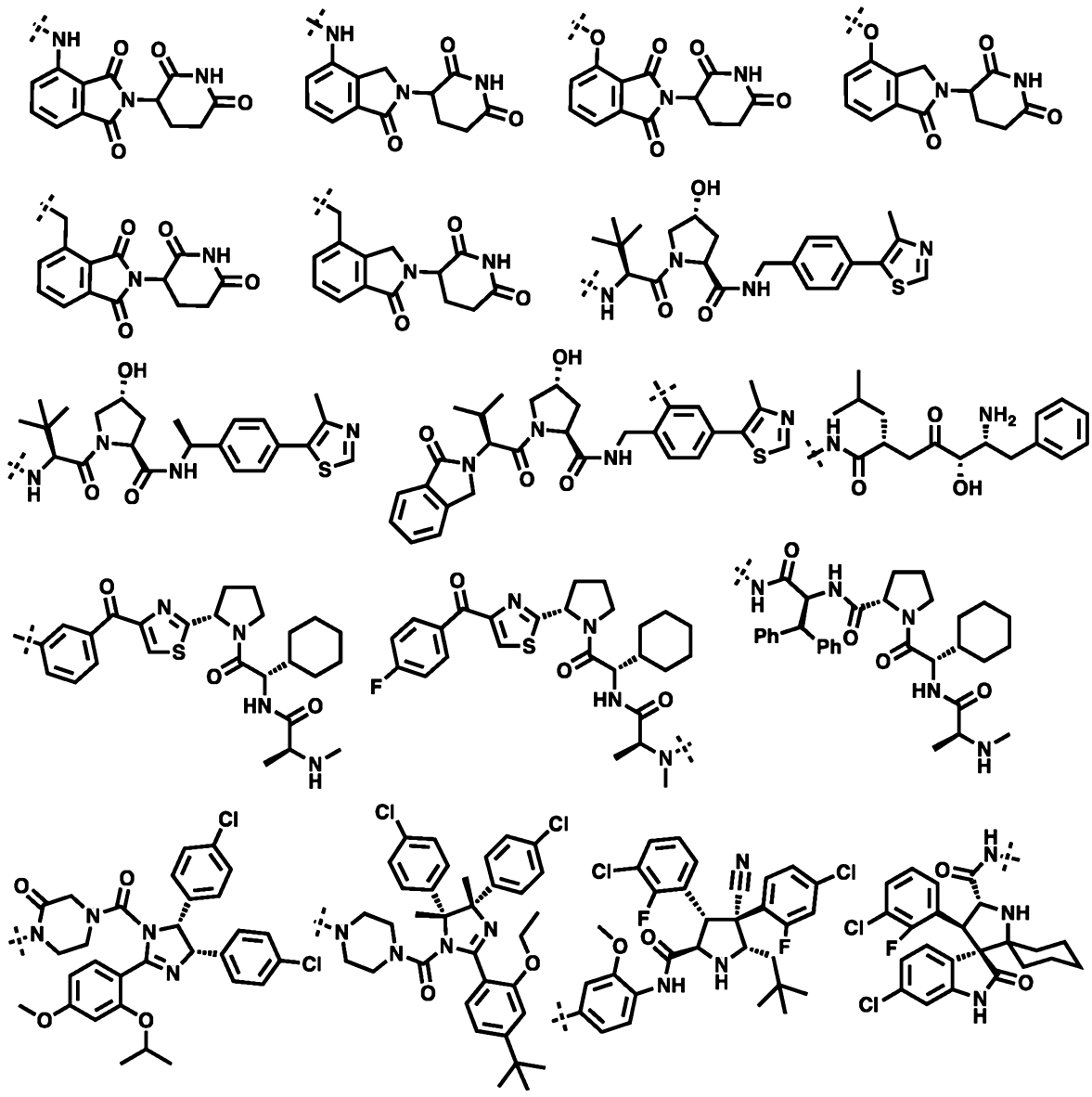
Formula XIII,

wherein R^1, R^2, R^3 and R^4 are independently hydrogen, C1-C8 alkyl, C1-C8 alkoxyalkyl, C1-C8 haloalkyl, C1-C8 hydroxyalkyl, C3-C7 cycloalkyl, C3-C7 heterocyclyl, C2-C8 alkenyl, or C2-C8 alkynyl; and

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

14. The bivalent compound of any one of claims 1-13, 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, AMG 232, AA-115, bestatin, MV-1, LCL161, and analogs thereof.

15. The bivalent compound of any one of claims 1-13, wherein the degradation/disruption tag is selected from the group consisting of:



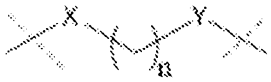
Formulas XIV-XXX.

16. The bivalent compound of any one of claims 1-15, wherein the degradation/disruption tag is bound to a ubiquitin ligase.

17. The bivalent compound of any one of claims 1-16, wherein the degradation/disruption tag functions as a hydrophobic group that leads to CDK4 or CDK6 protein misfolding.

18. The bivalent compound of any one of claims 8-17, 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.

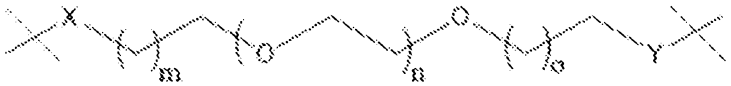
19. The bivalent compound of any one of claims 8-17, wherein the linker is selected from the group consisting of:


Formula A

wherein X is C=O or CH_2;

Y is C=O or CH_2; and

n is 0-15;


Formula B,

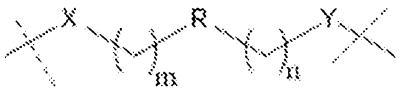
wherein X is C=O or CH_2;

Y is C=O or CH_2;

m is 0-15;

n is 0-6; and

o is 0-15; or


Formula C,

wherein X is C=O or CH_2;

Y is C=O or CH_2;

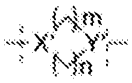
R is $–CH_2–$, $–CF_2–$, $–CH(C_{1-3}$ alkyl$)–$, $–C(C_{1-3}$ alkyl$)(C_{1-3}$ alkyl$)–$, –CH=CH–, $–C(C_{1-3}$ alkyl$)=C(C_{1-3}$ alkyl$)–$, –C=C–, –O–, –NH–, $–N(C_{1-3}$ alkyl$)–$, $–C(O)NH–$, $–C(O)N(C_{1-3}$ alkyl$)–$, a 3-13 membered ring, a 3-13 membered fused ring, a 3-13 membered bridged ring,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

m is 0-15; and

n is 0-15.

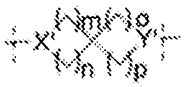
20. The bivalent compound of claim 19, wherein the linker is Formula C and R is selected from the group consisting of 3-13 membered rings, 3-13 membered fused rings, 3-13 membered bridged rings, and 3-13 membered spiro rings,
wherein R contains one or more heteroatoms.

21. The bivalent compound of claim 19, wherein the linker is Formula C and R is selected from the group consisting of:



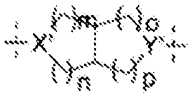
X' = N or CH
Y' = N or CH
m = 0-5
n = 0-5

Formula V,



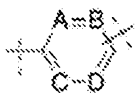
X' = N or CH
Y' = N or CH
m = 0-5
n = 0-5
o = 0-5
p = 0-5

Formula W,



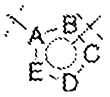
X' = N or CH
Y' = N or CH
m = 0-5
n = 0-5
o = 0-5
p = 0-5

Formula X,



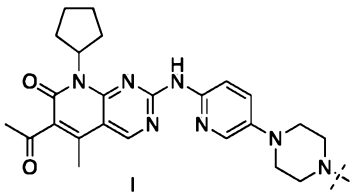
A = CH, C(C_{1-3} alkyl), or N
B = CH, C(C_{1-3} alkyl), or N
C = CH, C(C_{1-3} alkyl), or N
D = CH, C(C_{1-3} alkyl), or N

Formula Y, and

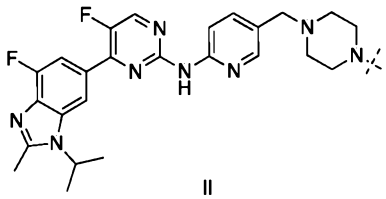


A = C, CH, C(C_{1-3} alkyl), N, NH, N(C_{1-3} alkyl), O, S
B = C, CH, C(C_{1-3} alkyl), N, NH, N(C_{1-3} alkyl), O, S
C = C, CH, C(C_{1-3} alkyl), N, NH, N(C_{1-3} alkyl), O, S
D = C, CH, C(C_{1-3} alkyl), N, NH, N(C_{1-3} alkyl), O, S Formula Z.

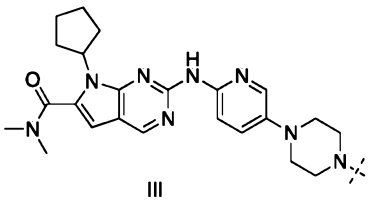
22. The bivalent compound of claim 1, wherein the CDK4/6 ligand is selected from the group consisting of:



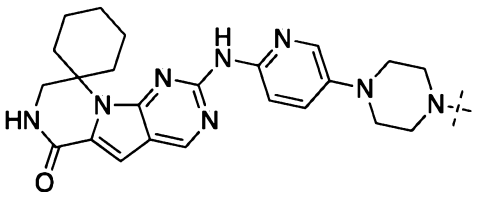
I



II



III



IV.

23. The bivalent compound of any one of claims 6-22, wherein the ubiquitin ligase is an E3 ligase.

24. The bivalent compound of claim 23, wherein the E3 ligase is selected from the group consisting of cereblon E3 ligase, VHL E3 ligase, MDM2 ligase, TRIM24 ligase, TRIM21 ligase, and IAP ligase.

25. The bivalent compound of any one of claims 1-8, wherein the bivalent compound is selected from the group consisting of XY028-082, XY028-003, XY028-004, XY028-005, XY019-098, XY028-006, XY028-007, XY028-008, XY028-009, XY028-085, XY028-084, XY028-083, XY028-132, XY028-133, XY019-106, XY028-162, XY028-163, XY028-002, XY028-114, XY028-097, XY019-108, XY028-105, XY028-106, XY028-140, XY028-141, XY028-142, XY028-143, XY028-144, XY028-145, YX26-56, YX26-66, YX26-58, YX30-108, YX30-107, YX30-85, YX30-86, YX30-117, YX30-118, YX30-126, YX30-125, XY028-186, YX33-29, YX33-31, YX33-74,

YX33-94, YX33-108, YX33-96, YX33-97, YX33-109, YX33-110, YX33-112, YX33-123, YX35-48, YX39-47, YX39-48, YX39-56, YX39-65, YX39-74, YX39-123, YX39-124, YX39-147, YX44-18, YX44-19, YX44-22, YX44-46, YX44-48, YX44-78, YS36-95, YS36-60, YS36-61, YS36-62, YS36-63, YS36-64, YS36-65, YS36-66, YS36-67, YS36-68, YS36-69, YS36-70, YS36-71, compound examples 80-135, and analogs thereof.

26. A bivalent compound selected from the group consisting of XY028-082, XY028-003, XY028-004, XY028-005, XY019-098, XY028-006, XY028-007, XY028-008, XY028-009, XY028-085, XY028-084, XY028-083, XY028-132, XY028-133, XY019-106, XY028-162, XY028-163, XY028-002, XY028-114, XY028-097, XY019-108, XY028-105, XY028-106, XY028-140, XY028-141, XY028-142, XY028-143, XY028-144, XY028-145, YX26-56, YX26-66, YX26-58, YX30-108, YX30-107, YX30-85, YX30-86, YX30-117, YX30-118, YX30-126, YX30-125, XY028-186, YX33-29, YX33-31, YX33-74, YX33-94, YX33-108, YX33-96, YX33-97, YX33-109, YX33-110, YX33-112, YX33-123, YX35-48, YX39-47, YX39-48, YX39-56, YX39-65, YX39-74, YX39-123, YX39-124, YX39-147, YX44-18, YX44-19, YX44-22, YX44-46, YX44-48, YX44-78, YS36-95, YS36-60, YS36-61, YS36-62, YS36-63, YS36-64, YS36-65, YS36-66, YS36-67, YS36-68, YS36-69, YS36-70, YS36-71, compound examples 80-135, and analogs thereof.

27. A method of treating a cyclin-dependent kinase 4/6 (CDK4/6)-mediated cancer, which comprises administering to a subject in need thereof with a CDK4/6-mediated cancer a bivalent compound comprising a CDK4/6 ligand conjugated to a degradation/disruption tag.

28. The method of claim 27, wherein the CDK4/6-mediated cancer overexpresses cyclin-dependent kinase 4 (CDK4) or cyclin-dependent kinase 6 (CDK6) relative to a wild-type tissue of the same species and tissue type.

29. The method of claim 27, wherein the CDK4/6-mediated cancer comprises higher CDK4 or CDK6 enzymatic activity relative to a wild-type tissue of the same species and tissue type.

30. The method of any one of claims 27-29, wherein at least one bivalent compound is selected from the group consisting of XY028-082, XY028-003, XY028-004, XY028-005, XY019-098, XY028-006, XY028-007, XY028-008, XY028-009, XY028-085, XY028-084, XY028-083, XY028-132, XY028-133, XY019-106, XY028-162, XY028-163, XY028-002, XY028-114, XY028-097, XY019-108, XY028-105, XY028-106, XY028-140, XY028-141, XY028-142, XY028-143, XY028-144, XY028-145, YX26-56, YX26-66, YX26-58, YX30-108, YX30-107, YX30-85, YX30-86, YX30-117, YX30-118, YX30-126, YX30-125, XY028-186, YX33-29, YX33-31, YX33-74, YX33-94, YX33-108, YX33-96, YX33-97, YX33-109, YX33-110, YX33-112, YX33-123, YX35-48, YX39-47, YX39-48, YX39-56, YX39-65, YX39-74, YX39-123, YX39-124, YX39-147, YX44-18, YX44-19, YX44-22, YX44-46, YX44-48, YX44-78, YS36-95, YS36-60, YS36-61, YS36-62, YS36-63, YS36-64, YS36-65, YS36-66, YS36-67, YS36-68, YS36-69, YS36-70, YS36-71, compound examples 80-135, and analogs thereof.

31. The method of any one of claims 27-30, wherein at least one bivalent compound is administered orally, parenterally, intradermally, subcutaneously, topically, or rectally.

32. The method of any one of claims 28-31, further comprising treating the subject with one or more additional therapeutic regimens for treating cancer.

33. The method of claim 32, wherein the one or more additional therapeutic regimens are selected from the group consisting of surgery, chemotherapy, radiation therapy, hormone therapy, and immunotherapy.

34. The method of any of claims 27-33, wherein the CDK4/6-mediated cancer is selected from the group consisting of mesothelioma, hepatocellular cancer, central nervous system neoplasm, lung cancer, bone cancer, pancreatic cancer, skin cancer, head and neck cancer, melanoma, ovarian cancer, colon cancer, rectal cancer, anal cancer, stomach cancer, gastrointestinal cancer, breast cancer, uterine cancer, fallopian tube cancer, endometrial cancer, cervical cancer, vaginal cancer, vulvar cancer, esophageal cancer, gastrointestinal cancer, endocrine cancer, thyroid cancer, parathyroid cancer, adrenal cancer, soft tissue sarcoma, urethral cancer, penile cancer, prostate cancer, testicular cancer, leukemia, lymphoma, bladder cancer, renal cell cancer, brain stem

glioma, pituitary cancer, adrenocortical cancer, gallbladder cancer, multiple myeloma, cholangiocarcinoma, fibrosarcoma, neuroblastoma, and retinoblastoma.

35. The method of claim 34, wherein the breast cancer is estrogen receptor positive (ER+).

36. The method of any of claims 27-35, wherein the CDK4/6-mediated cancer is a relapsed cancer.

37. The method of any of claims 27-36, wherein the CDK4/6-mediated cancer was refractory to one or more previous treatments.

38. A method for identifying a bivalent compound which mediates degradation/disruption of CDK4 or CDK6, the method comprising:

providing a heterobifunctional test compound comprising a CDK4/6 ligand conjugated to a degradation/disruption tag;

contacting the heterobifunctional test compound with a cell comprising a ubiquitin ligase and at least one of CDK4 and CDK6;

determining whether CDK4 or CDK6 levels decrease in the cell; and

(i) identifying the heterobifunctional test compound as a bivalent compound which mediates degradation/reduction of CDK4 if CDK4 levels decrease in the cell and CDK6 levels do not decrease in the cell,

(ii) identifying the heterobifunctional test compound as a bivalent compound which mediates degradation/reduction of CDK6 if CDK6 levels decrease in the cell and CDK4 levels do not decrease in the cell, or

(iii) identifying the heterobifunctional test compound as a bivalent compound which mediates degradation/reduction of CDK4 and CDK6 if both CDK4 and CDK6 levels decrease in the cell.

39. The method of claim 38, wherein the cell is a cancer cell.

40. The method of claim 39, wherein the cancer cell is a CDK4/6-mediated cancer cell.

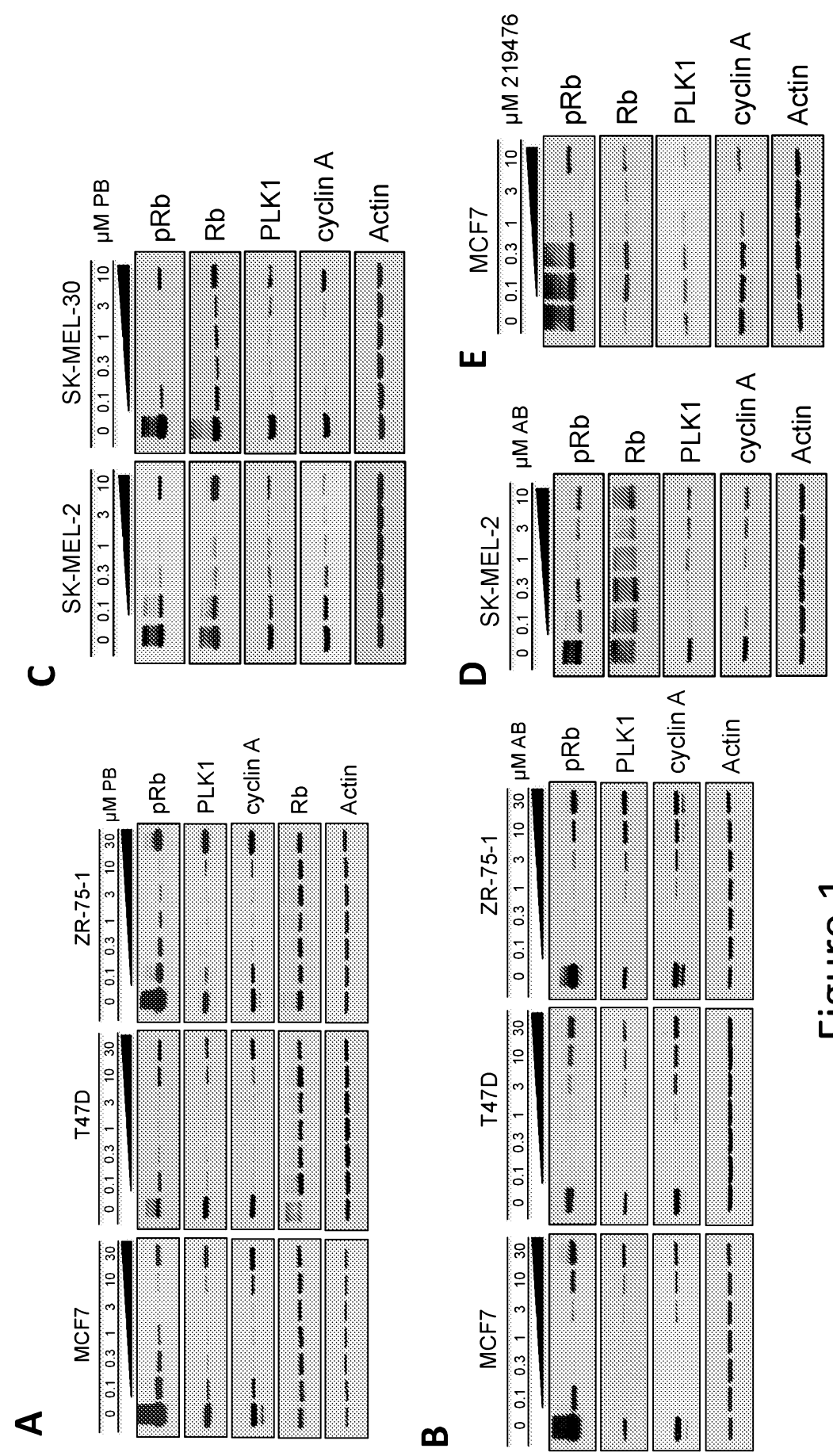

A
MCF7
T47D
ZR-75-1
0 0.1 0.3 1 3 10 30
μM PB
pRb
PLK1
cyclin A
Rb
Actin
B
MCF7
T47D
ZR-75-1
0 0.1 0.3 1 3 10 30
μM AB
pRb
PLK1
cyclin A
Actin
C
SK-MEL-2
SK-MEL-30
0 0.1 0.3 1 3 10
μM PB
pRb
Rb
PLK1
cyclin A
Actin
D
SK-MEL-2
0 0.1 0.3 1 3 10
μM AB
pRb
Rb
PLK1
cyclin A
Actin
E
MCF7
0 0.1 0.3 1 3 10
μM 219476
pRb
Rb
PLK1
cyclin A
Actin

Figure 1

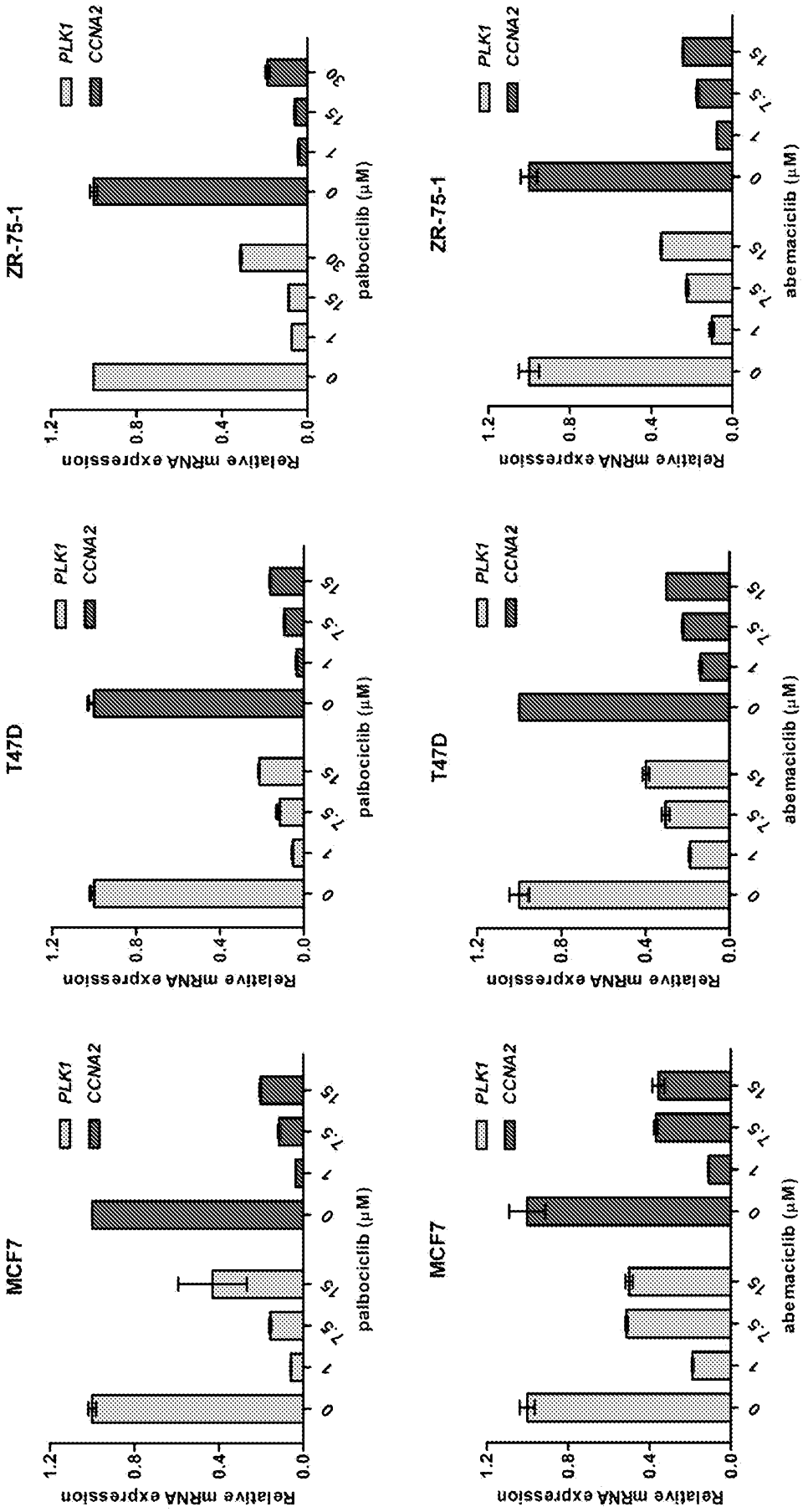

ZR-75-1
T47D
MCF7
PLK1
CCNA2
Relative mRNA expression
palbociclib (μM)
abemaciclib (μM)
0
1
1.5
15
30
0.0
0.4
0.8
1.2

Figure 2

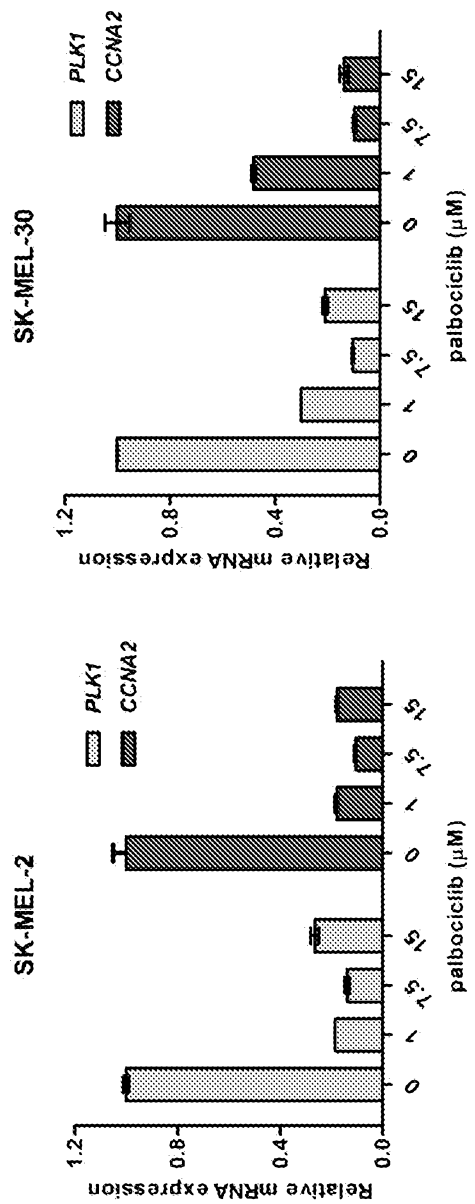

SK-MEL-30
SK-MEL-2
PLK1
CCNA2
Relative mRNA expression
1.2
0.8
0.4
0.0
0
1
1.5
1.75
palbociclib (μM)

Figure 3

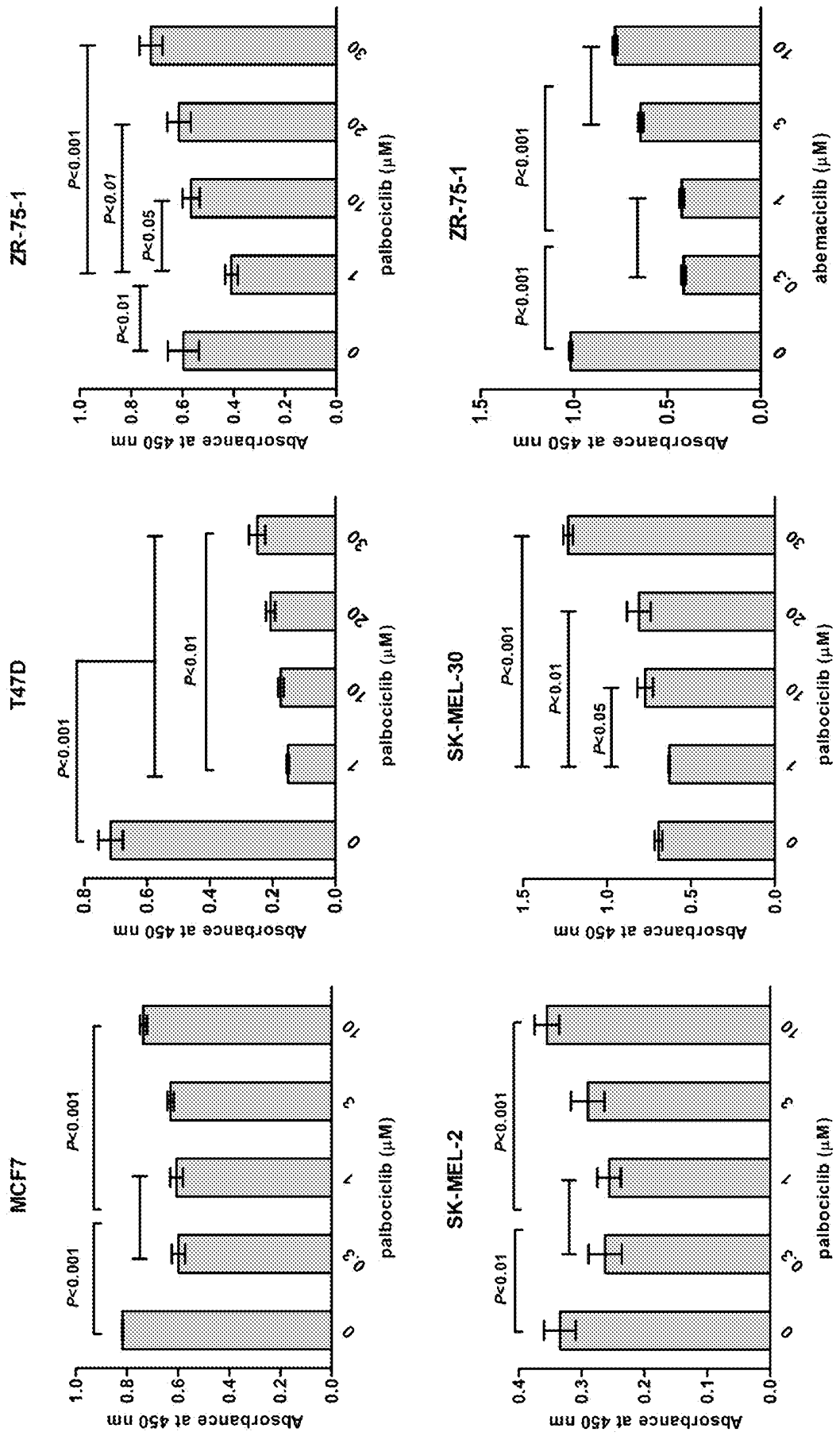

MCF7
T47D
ZR-75-1
SK-MEL-2
SK-MEL-30
ZR-75-1
Absorbance at 450 nm
palbociclib (μM)
abemaciclib (μM)
P<0.001
P<0.01
P<0.05

Figure 4

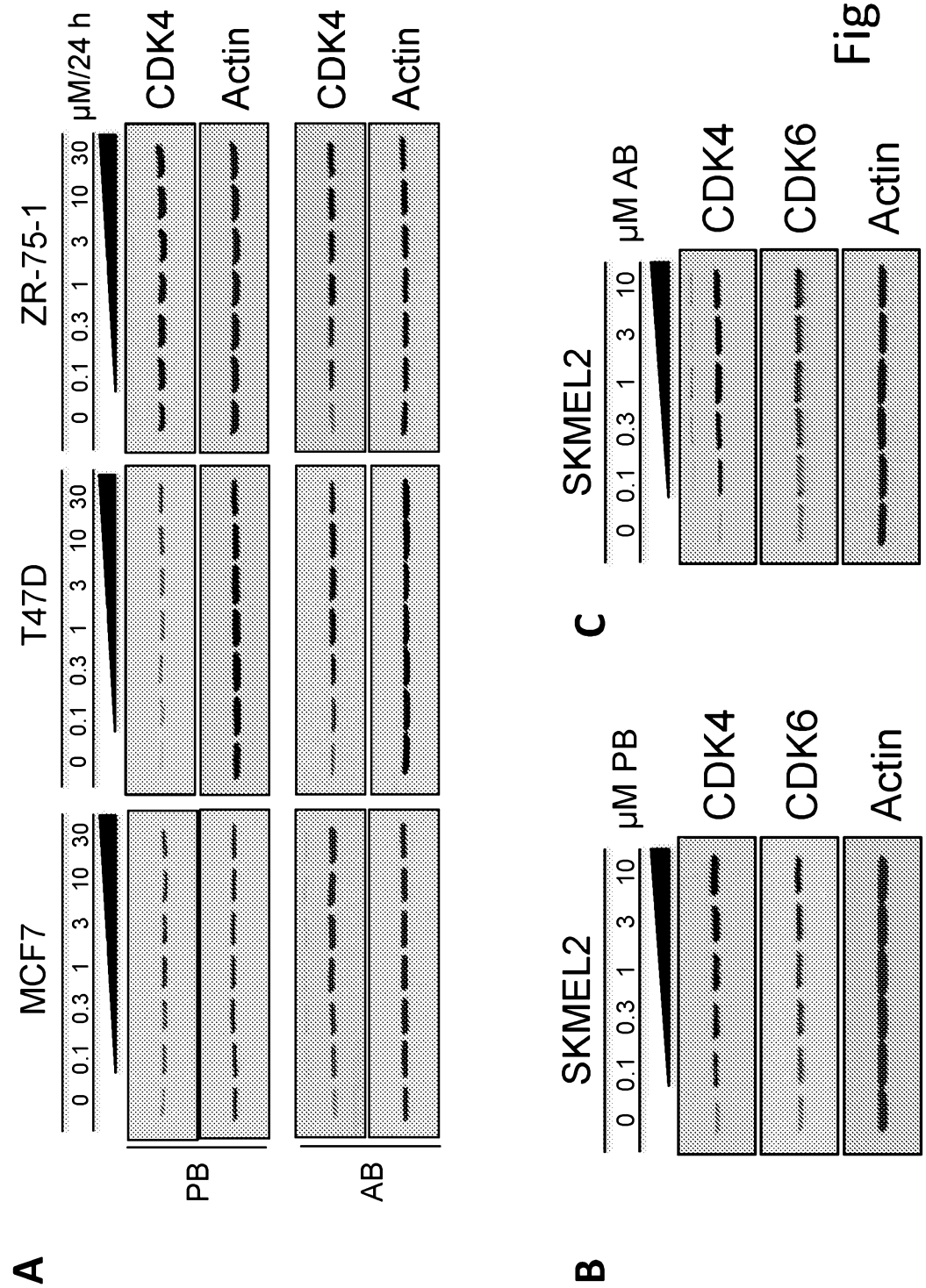

A
MCF7
T47D
ZR-75-1
0 0.1 0.3 1 3 10 30 µM/24 h
CDK4
Actin
PB
AB
B
SKMEL2
0 0.1 0.3 1 3 10 µM PB
CDK4
CDK6
Actin
C
SKMEL2
0 0.1 0.3 1 3 10 µM AB
CDK4
CDK6
Actin

Figure 5

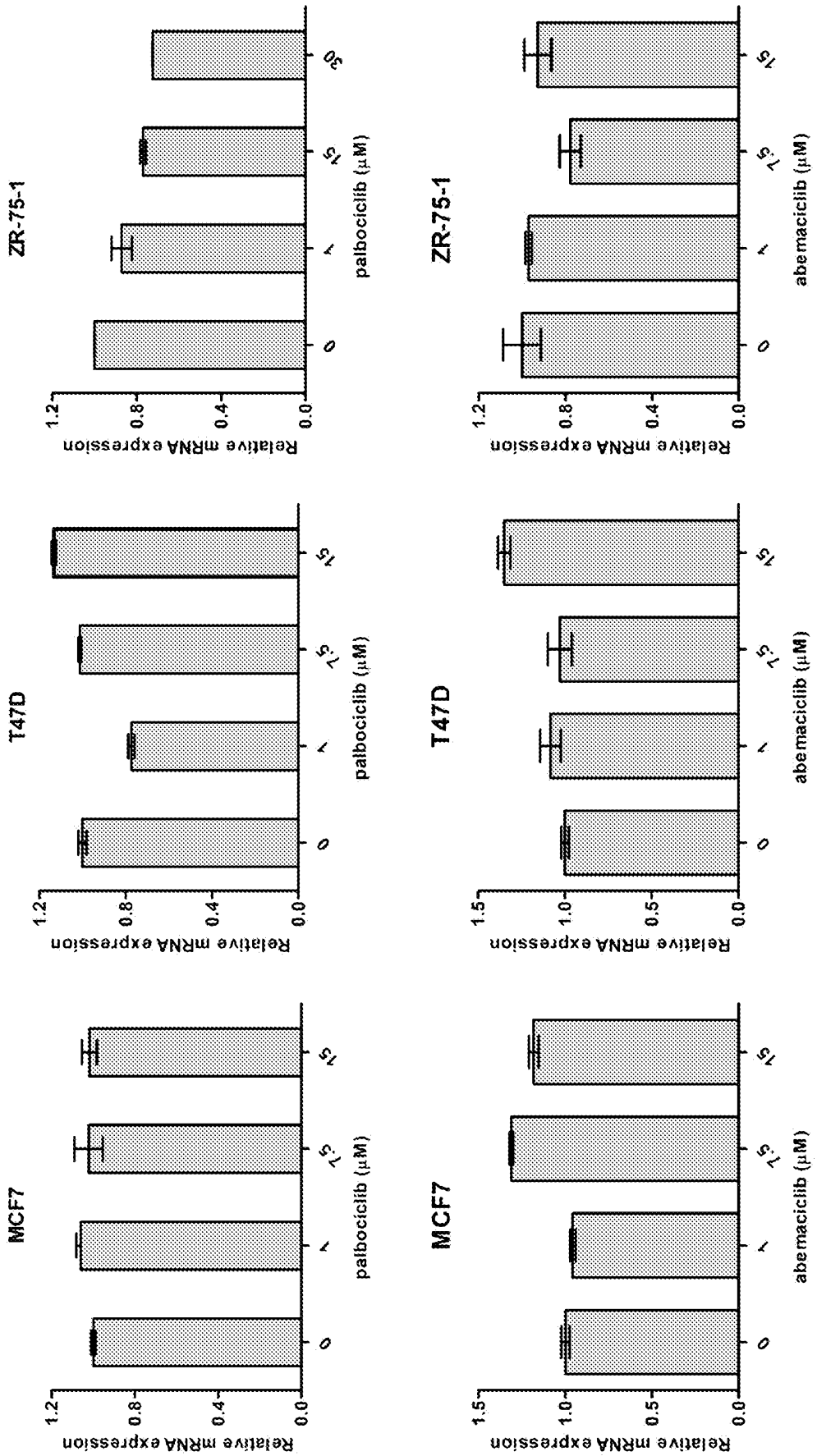

MCF7
T47D
ZR-75-1
MCF7
T47D
ZR-75-1
Relative mRNA expression
palbociclib (μM)
abemaciclib (μM)
0
1
1.5
15
30

Figure 6

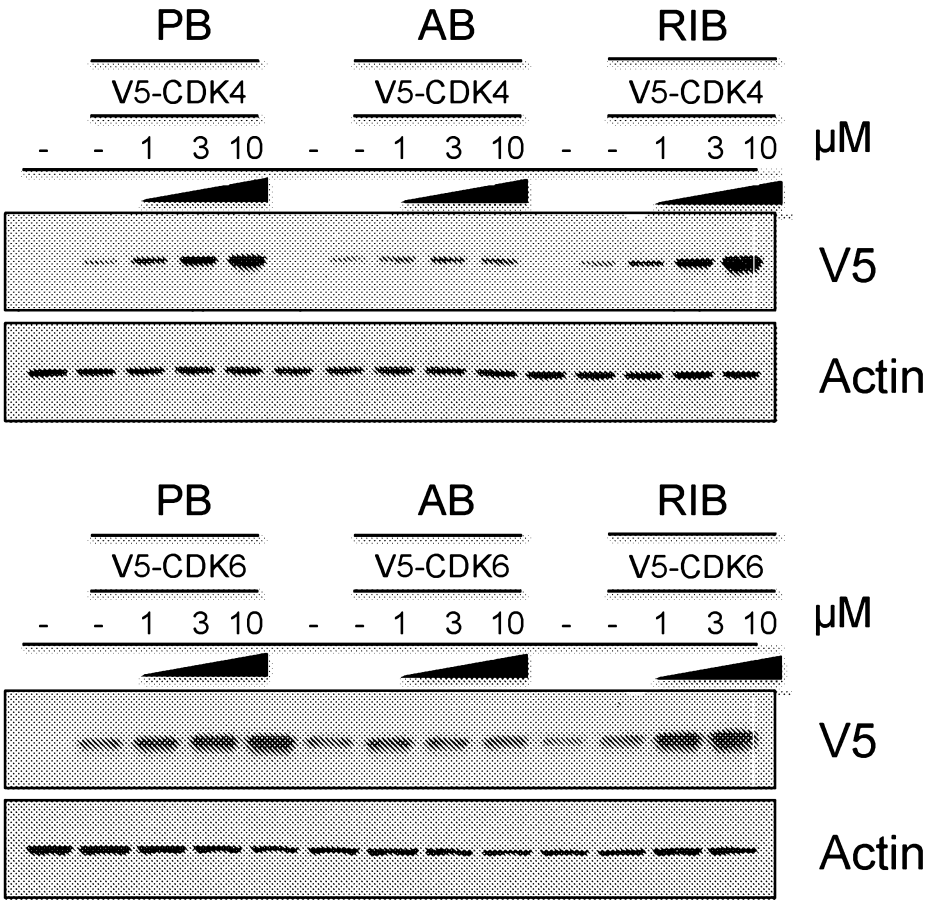

PB
AB
RIB
V5-CDK4
V5-CDK4
V5-CDK4
- - 1 3 10 - - 1 3 10 - - 1 3 10
μM
V5
Actin
PB
AB
RIB
V5-CDK6
V5-CDK6
V5-CDK6
- - 1 3 10 - - 1 3 10 - - 1 3 10
μM
V5
Actin

Figure 7

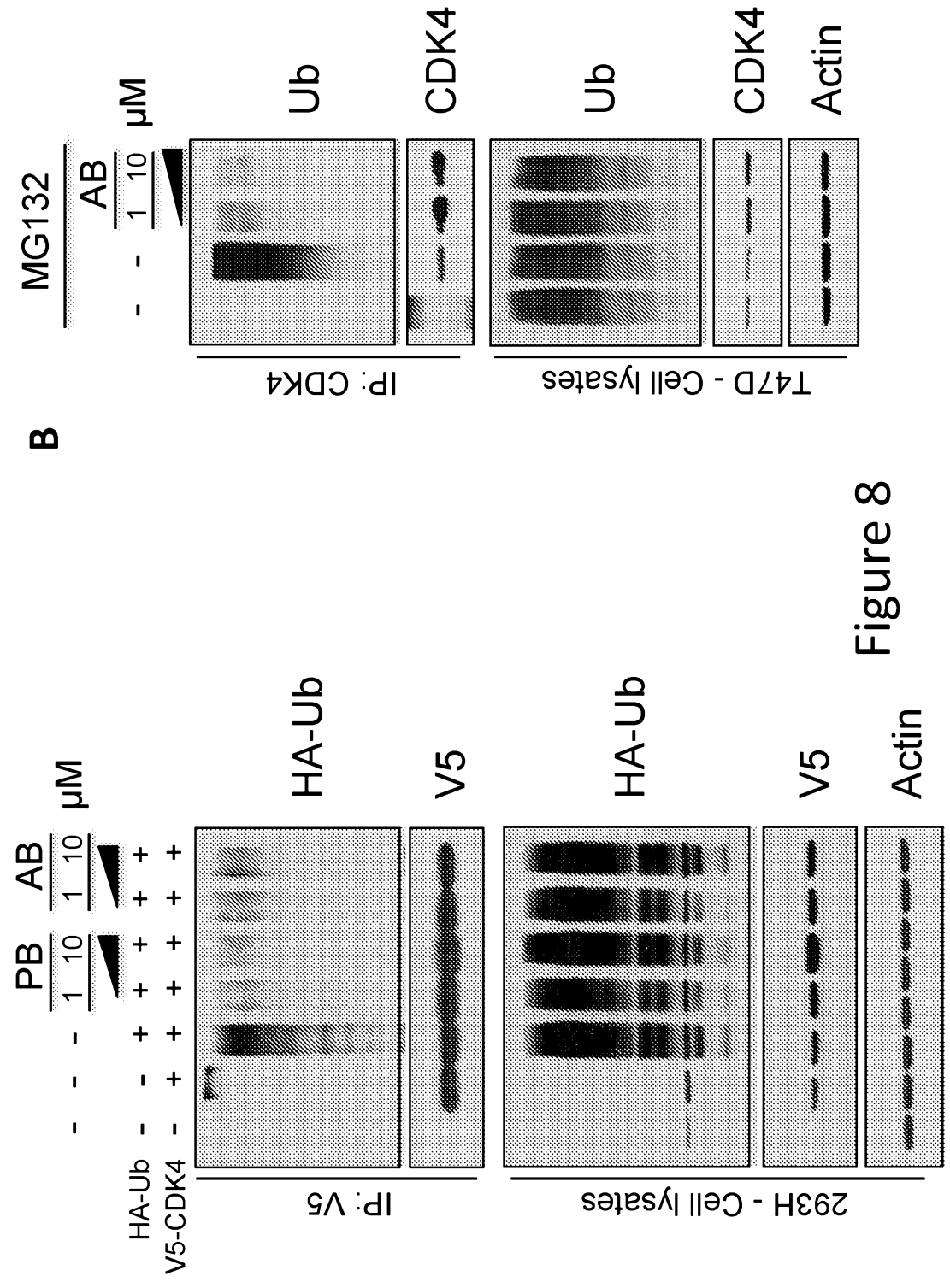

A
HA-Ub
V5-CDK4
PB
AB
μM
1 10
IP: V5
293H - Cell lysates
HA-Ub
V5
Actin
B
MG132
IP: CDK4
T47D - Cell lysates
Ub
CDK4
Actin

Figure 8

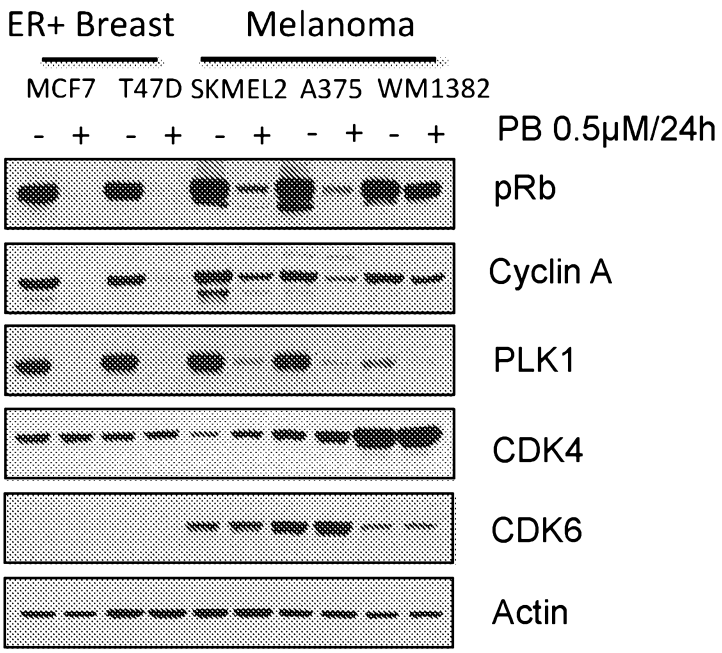
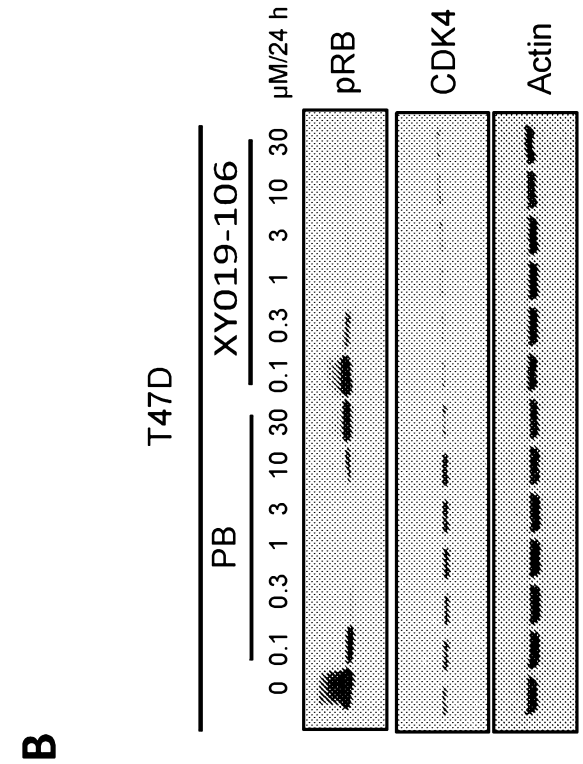

ER+ Breast
Melanoma
MCF7 T47D SKMEL2 A375 WM1382
- + - + - + - + - +
PB 0.5μM/24h
pRb
Cyclin A
PLK1
CDK4
CDK6
Actin

Figure 9


B
T47D
PB
XY019-106
0 0.1 0.3 1 3 10 30 0 0.1 0.3 1 3 10 30 μM/24 h
pRB
CDK4
Actin

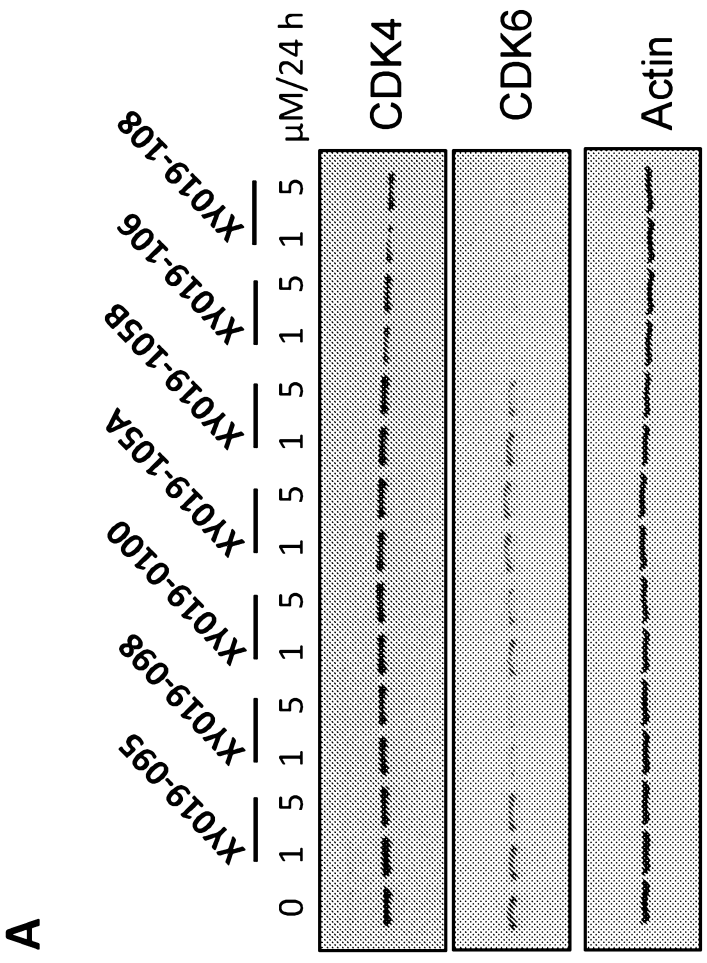
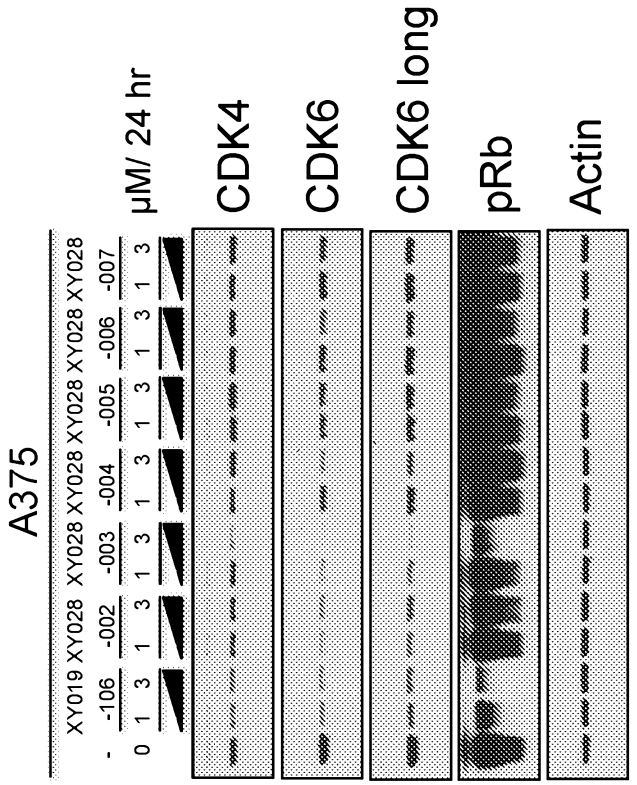
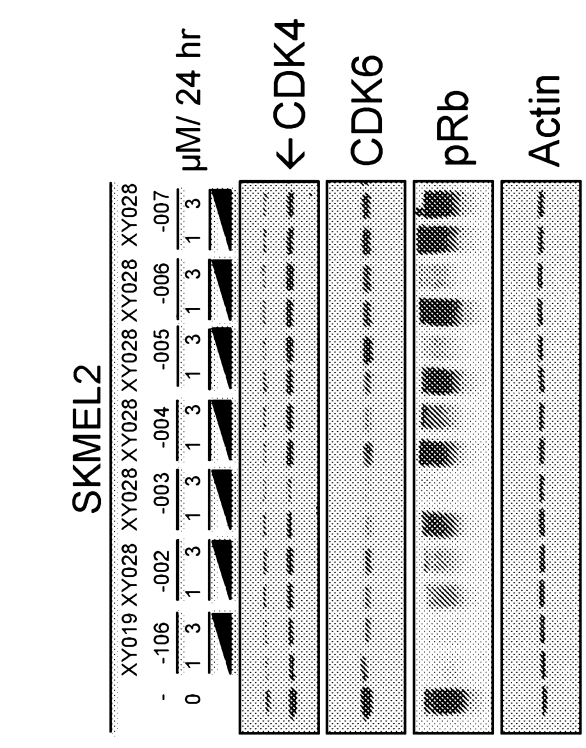

A
0 1 5 1 5 1 5 1 5 1 5 1 5 μM/24 h
XY019-095
XY019-098
XY019-0100
XY019-105A
XY019-105B
XY019-106
XY019-108
CDK4
CDK6
Actin

Figure 10


B
A375
XY019 XY028 XY028 XY028 XY028 XY028 XY028 XY028
- -106 -002 -003 -004 -005 -006 -007
0 1 3 1 3 1 3 1 3 1 3 1 3 1 3
µM/ 24 hr
CDK4
CDK6
CDK6 long
pRb
Actin


A
SKMEL2
XY019 XY028 XY028 XY028 XY028 XY028 XY028 XY028
- -106 -002 -003 -004 -005 -006 -007
0 1 3 1 3 1 3 1 3 1 3 1 3 1 3
µM/ 24 hr
← CDK4
CDK6
pRb
Actin

C
A375
XY019 XY028 XY028 XY028 XY028 XY028 XY028
- PB -106 -003 -082 -083 -084 -085
0 1 3 1 3 1 3 1 3 1 3 1 3
µM/ 24 hr
CDK4
CDK6
pRb
Cyclin A
PLK1
Actin

Figure 11

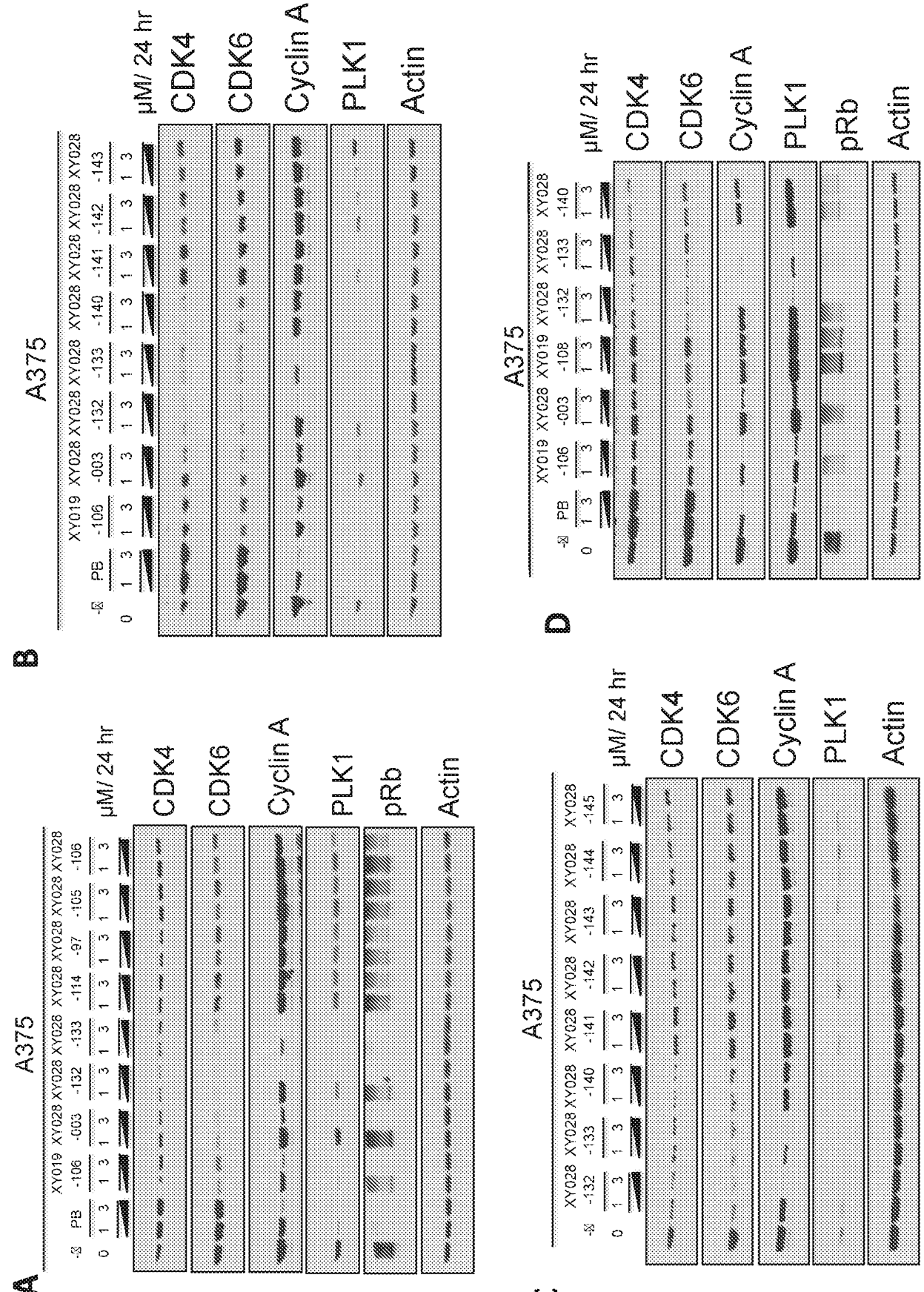

A
A375
XY019 XY028 XY028 XY026 XY028 XY028 XY028 XY028
-% PB -106 -003 -132 -133 -114 -97 -105 -106
0 1 3 1 3 1 3 1 3 1 3 1 3 1 3 1 3
µM/ 24 hr
CDK4
CDK6
Cyclin A
PLK1
pRb
Actin
B
A375
XY019 XY028 XY028 XY028 XY028 XY028 XY028 XY028
-% PB -106 -003 -132 -133 -140 -141 -142 -143
0 1 3 1 3 1 3 1 3 1 3 1 3 1 3 1 3
µM/ 24 hr
CDK4
CDK6
Cyclin A
PLK1
Actin
C
A375
XY028 XY028 XY028 XY026 XY028 XY028 XY028 XY028
-% -132 -133 -140 -141 -142 -143 -144 -145
0 1 3 1 3 1 3 1 3 1 3 1 3 1 3 1 3
µM/ 24 hr
CDK4
CDK6
Cyclin A
PLK1
Actin
D
A375
XY019 XY026 XY019 XY028 XY028 XY028
-% PB -106 -003 -108 -132 -133 -140
0 1 3 1 3 1 3 1 3 1 3 1 3
µM/ 24 hr
CDK4
CDK6
Cyclin A
PLK1
pRb
Actin

Figure 12

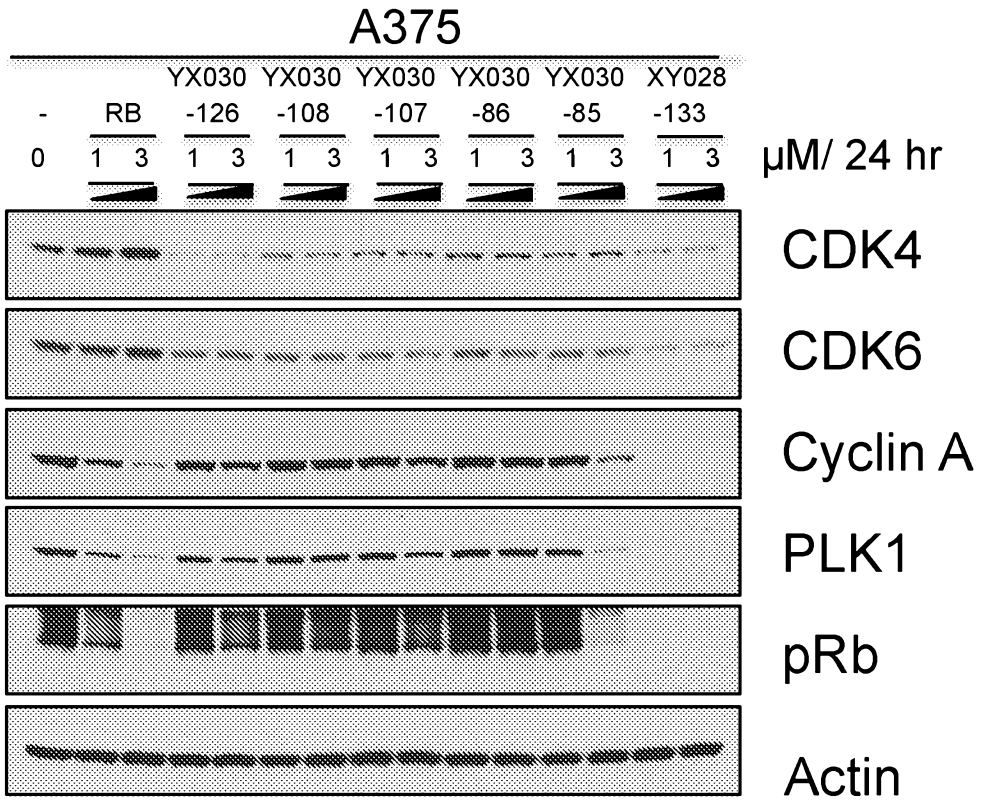

A375
YX030 YX030 YX030 YX030 YX030 XY028
- RB -126 -108 -107 -86 -85 -133
0 1 3 1 3 1 3 1 3 1 3 1 3 1 3
μM/ 24 hr
CDK4
CDK6
Cyclin A
PLK1
pRb
Actin

Figure 13

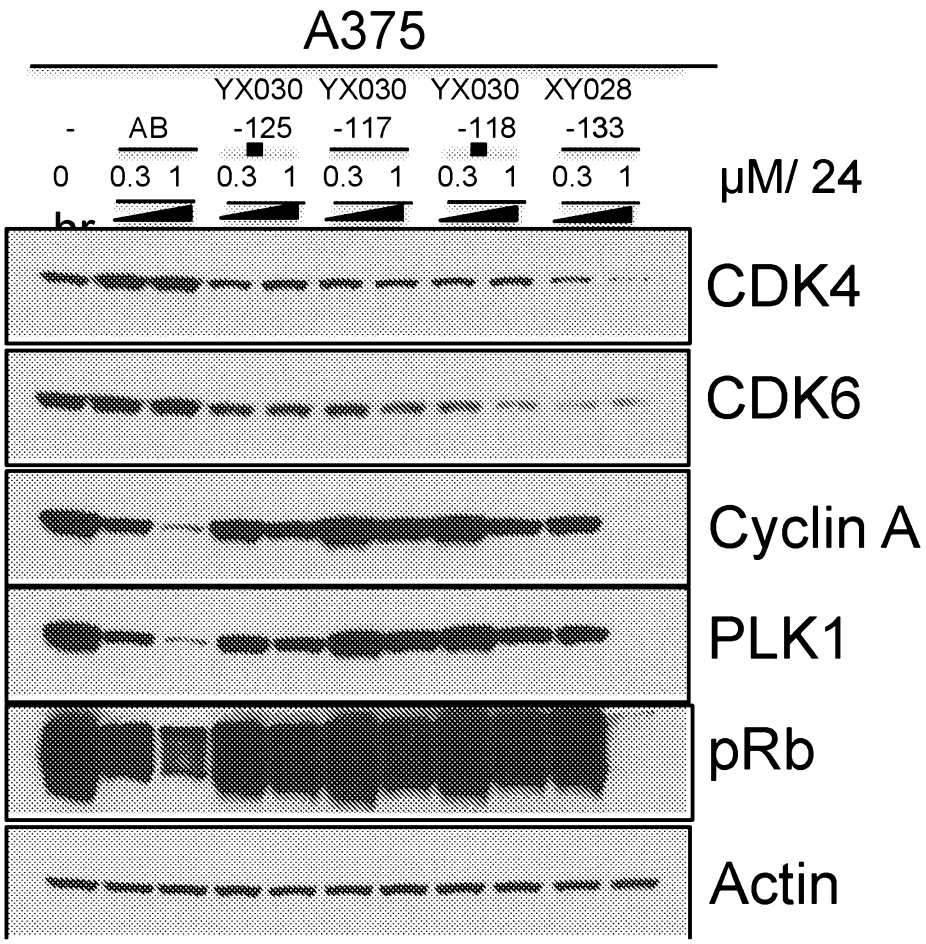

A375
YX030 YX030 YX030 XY028
- AB -125 -117 -118 -133
0 0.3 1 0.3 1 0.3 1 0.3 1 0.3 1
μM/ 24
CDK4
CDK6
Cyclin A
PLK1
pRb
Actin

Figure 14

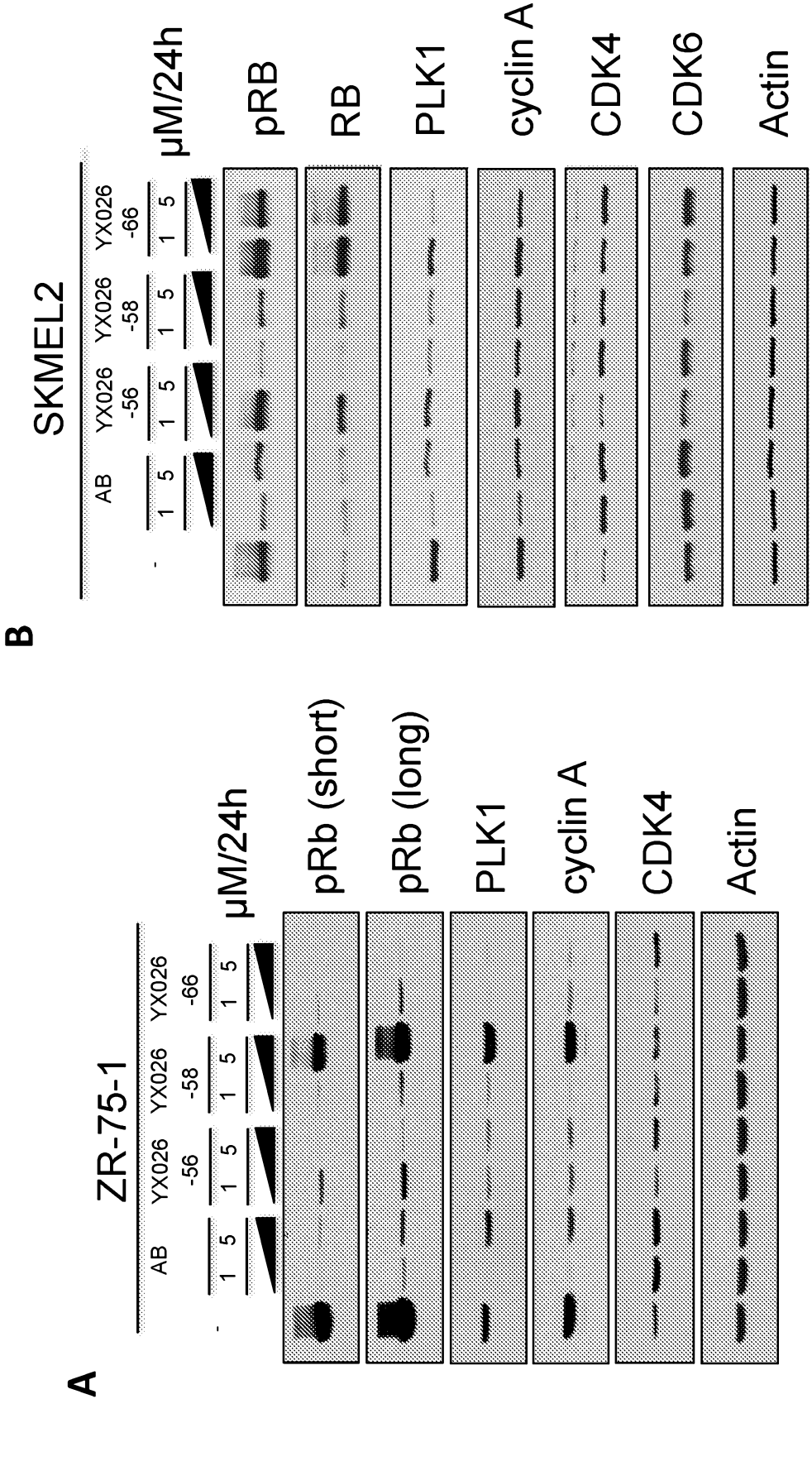

A
ZR-75-1
AB
YX026 -56
YX026 -58
YX026 -66
1 5
µM/24h
pRb (short)
pRb (long)
PLK1
cyclin A
CDK4
Actin
B
SKMEL2
AB
YX026 -56
YX026 -58
YX026 -66
1 5
µM/24h
pRB
RB
PLK1
cyclin A
CDK4
CDK6
Actin

Figure 15

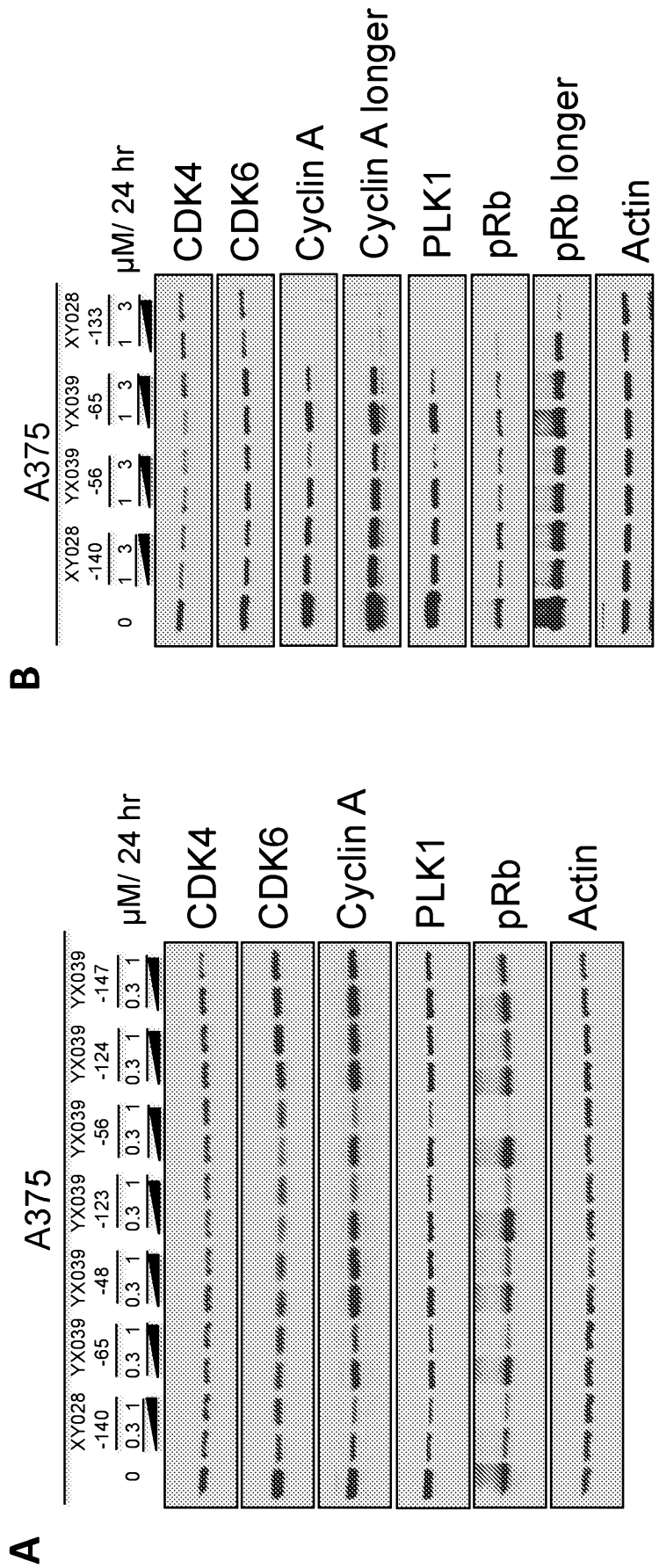

A
A375
XY028
YX039
YX039
YX039
YX039
YX039
-140
-65
-48
-123
-56
-124
-147
0
0.3 1
0.3 1
0.3 1
0.3 1
0.3 1
0.3 1
0.3 1
µM/ 24 hr
CDK4
CDK6
Cyclin A
PLK1
pRb
Actin
B
A375
XY028
YX039
YX039
YX039
XY028
-140
-56
-65
-133
0
1 3
1 3
1 3
1 3
µM/ 24 hr
CDK4
CDK6
Cyclin A
Cyclin A longer
PLK1
pRb
pRb longer
Actin

Figure 16

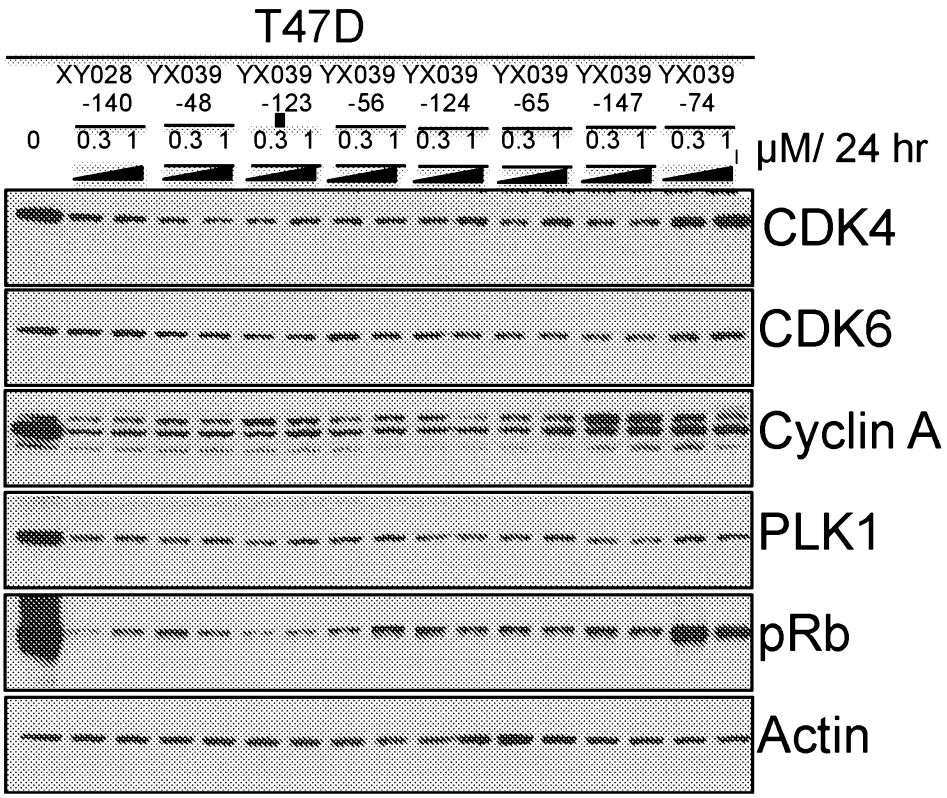

T47D
XY028 -140
YX039 -48
YX039 -123
YX039 -56
YX039 -124
YX039 -65
YX039 -147
YX039 -74
0
0.3 1 0.3 1 0.3 1 0.3 1 0.3 1 0.3 1 0.3 1 0.3 1
μM/ 24 hr
CDK4
CDK6
Cyclin A
PLK1
pRb
Actin

Figure 17

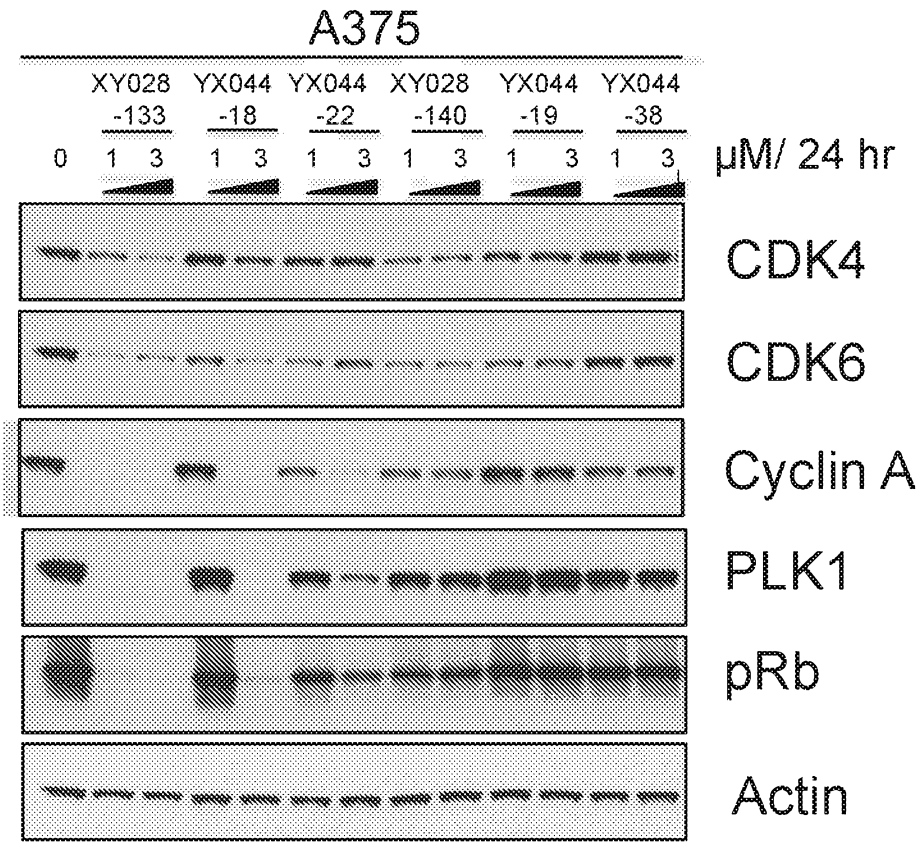

A375
XY028 -133
YX044 -18
YX044 -22
XY028 -140
YX044 -19
YX044 -38
0 1 3 1 3 1 3 1 3 1 3 1 3
μM/ 24 hr
CDK4
CDK6
Cyclin A
PLK1
pRb
Actin

Figure 18

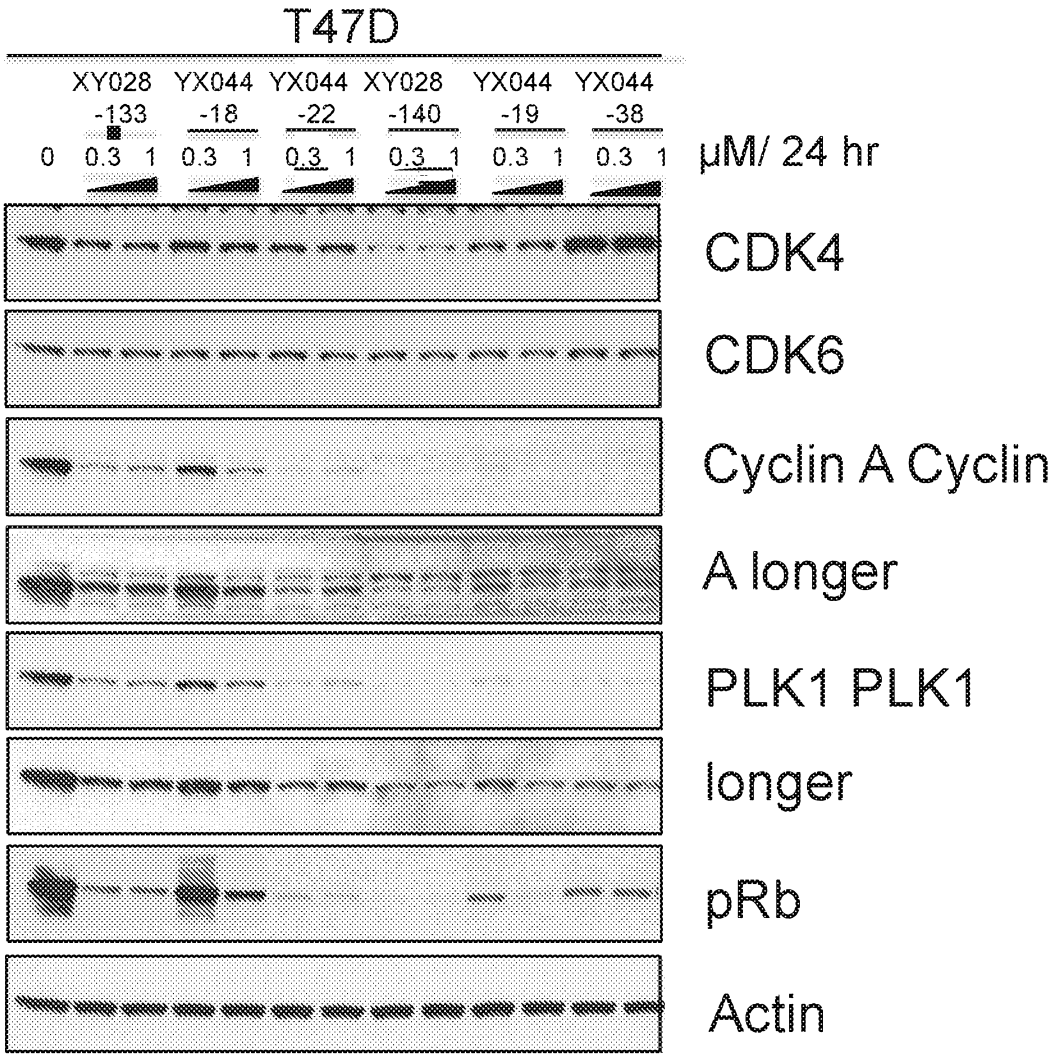

T47D
XY028 -133
YX044 -18
YX044 -22
XY028 -140
YX044 -19
YX044 -38
0 0.3 1 0.3 1 0.3 1 0.3 1 0.3 1 0.3 1
μM/ 24 hr
CDK4
CDK6
Cyclin A Cyclin
A longer
PLK1 PLK1
longer
pRb
Actin

Figure 19

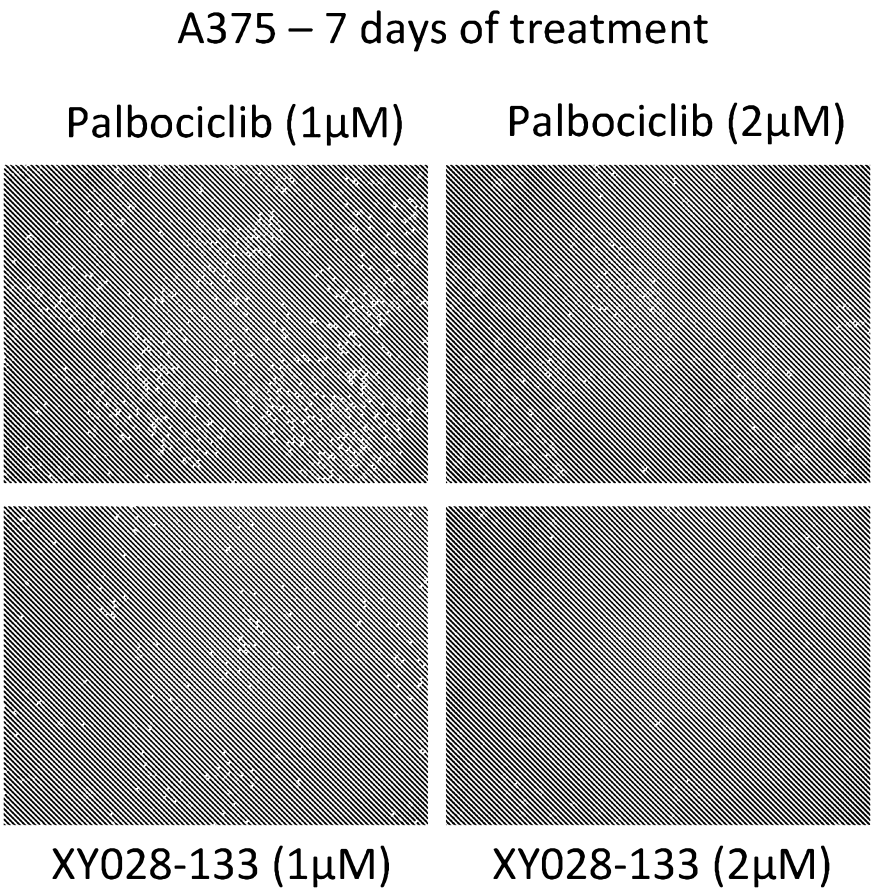

A375 – 7 days of treatment
Palbociclib (1µM)
Palbociclib (2µM)
XY028-133 (1µM)
XY028-133 (2µM)

Figure 20

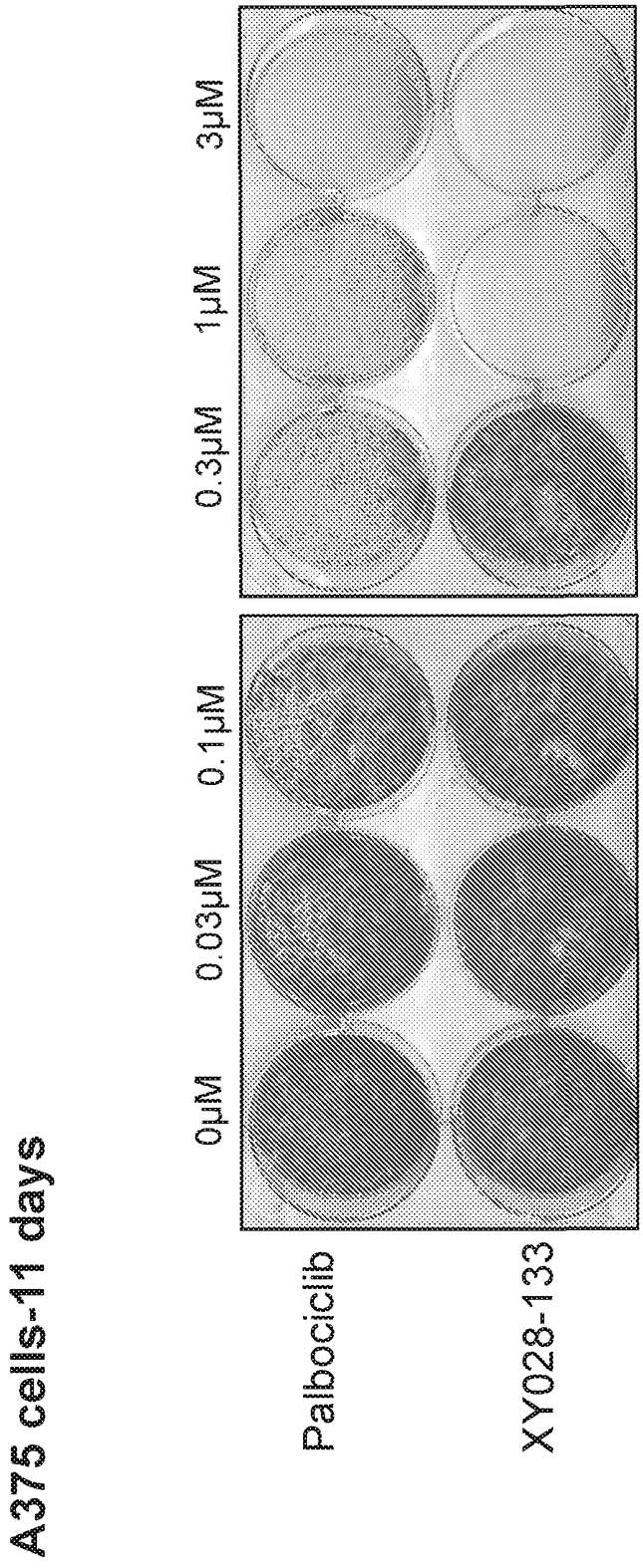

A375 cells-11 days
0μM
0.03μM
0.1μM
0.3μM
1μM
3μM
Palbociclib
XY028-133

Figure 21

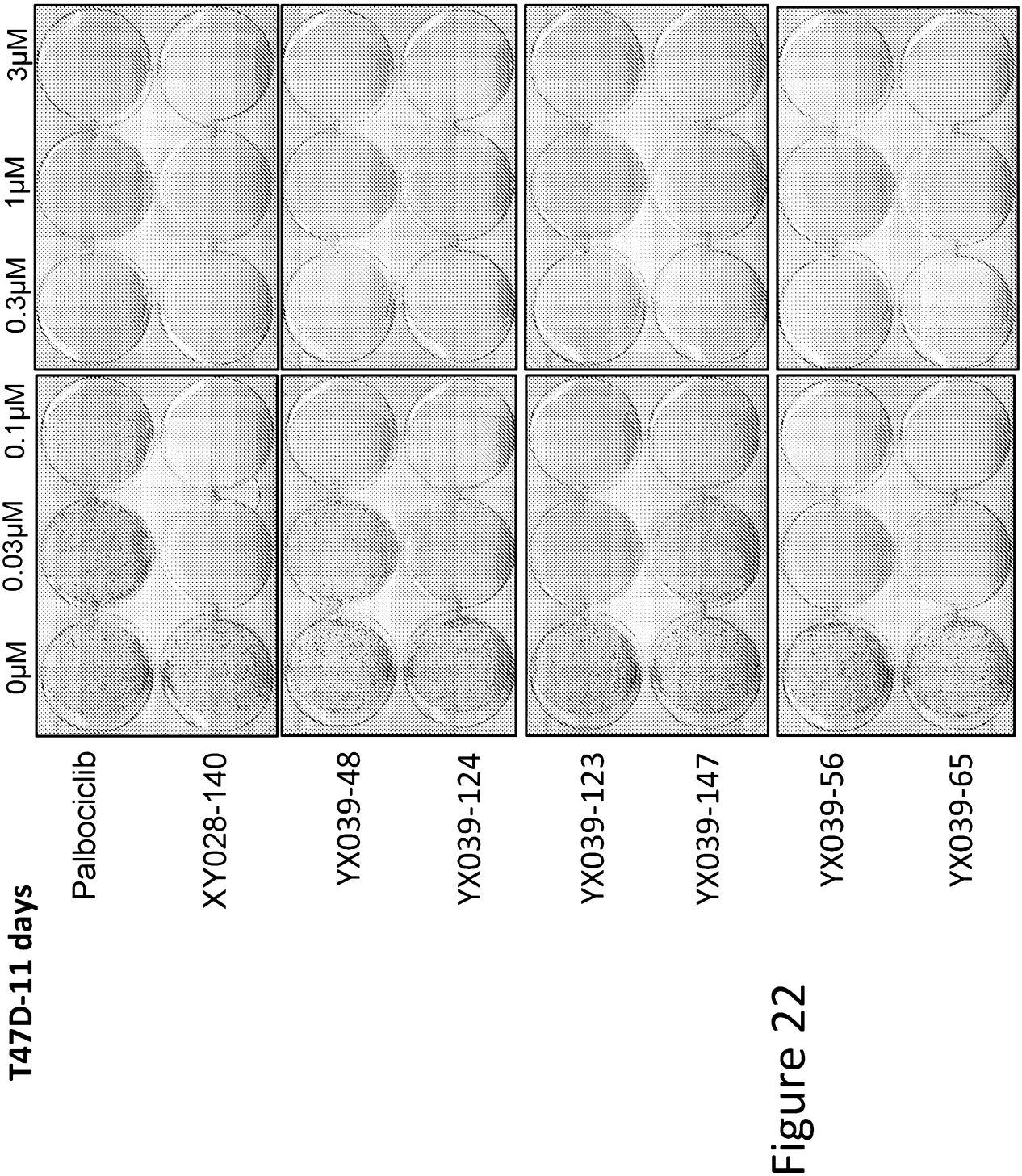

T47D-11 days
0μM
0.03μM
0.1μM
0.3μM
1μM
3μM
Palbociclib
XY028-140
YX039-48
YX039-124
YX039-123
YX039-147
YX039-56
YX039-65

Figure 22

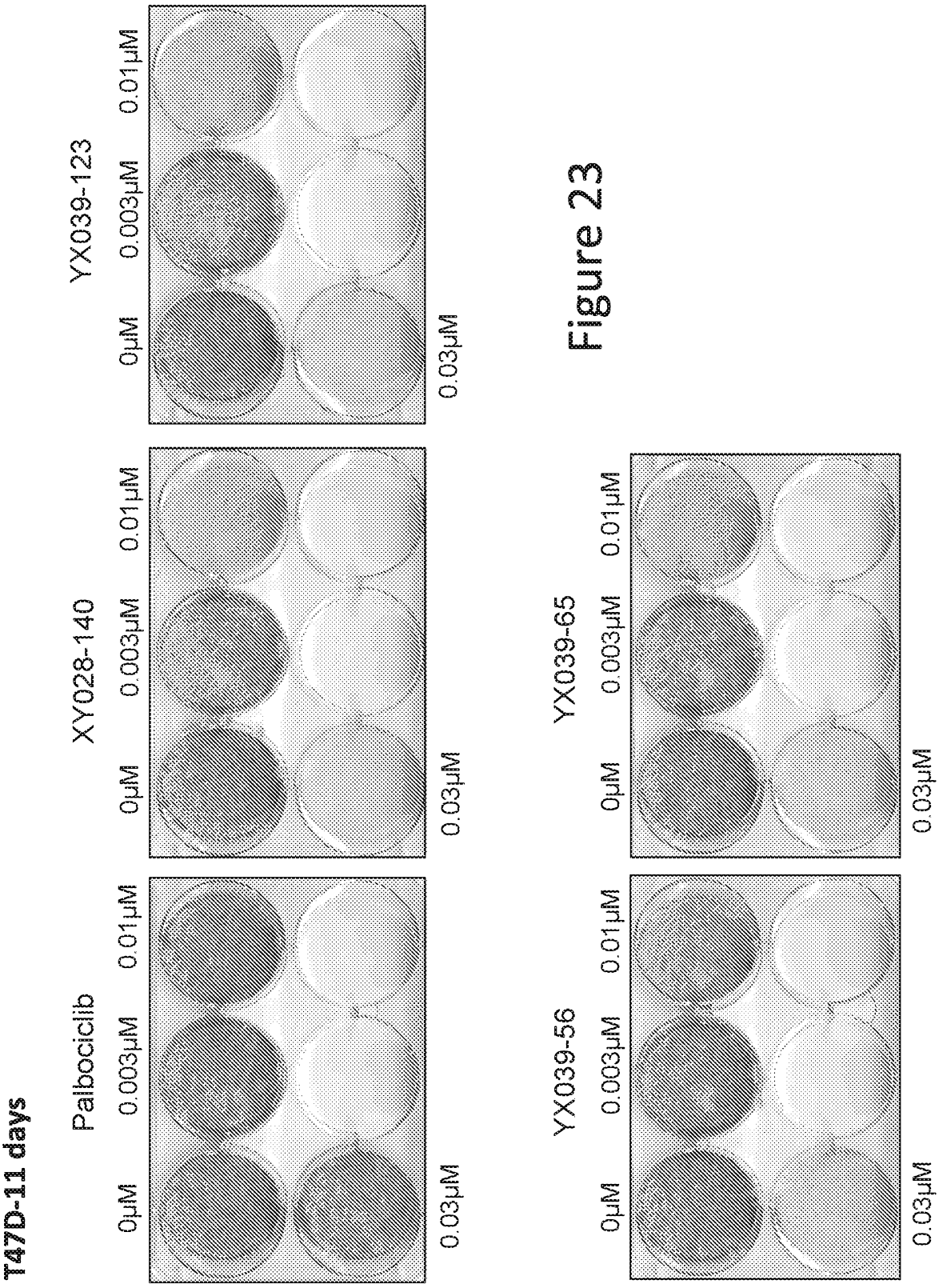

T47D-11 days
Palbociclib
XY028-140
YX039-123
YX039-56
YX039-65
0μM
0.003μM
0.01μM
0.03μM

Figure 23

SEQUENCE LISTING

<110> Icahn School of Medicine at Mount Sinai

<120> COMPOSITIONS AND METHODS FOR TREATING CDK4/6-MEDIATED CANCER

<130> 27527-0152WO1

<150> US 62/431,806
<151> 2016-12-08

<160> 10

<170> PatentIn version 3.5

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<213> Artificial Sequence

<220>
<223> Amplification Primer

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<220>
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<223> Amplification Primer

<400> 10
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