

KRAS G12C INHIBITORS

CROSS REFERENCE

[0001] This application claims benefit of priority under 35 U.S.C. §119(e) from U.S. Provisional Application No. 62/338,116, filed May 18, 2016, and U.S. Provisional Application No. 62/444,614 filed January 10, 2017, the entire content of each application is hereby incorporated by reference in their entirety.

FIELD OF THE INVENTION

[0002] The present invention relates to compounds that inhibit KRas G12C. In particular, the present invention relates to compounds that irreversibly inhibit the activity of KRas G12C, pharmaceutical compositions comprising the compounds and methods of use therefor.

BACKGROUND OF THE INVENTION

[0003] Kirsten Rat Sarcoma 2 Viral Oncogene Homolog (“KRas”) is a small GTPase and a member of the Ras family of oncogenes. KRas serves a molecular switch cycling between inactive (GDP-bound) and active (GTP-bound) states to transduce upstream cellular signals received from multiple tyrosine kinases to downstream effectors to regulate a wide variety of processes, including cellular proliferation (e.g., see Alamgeer et al., (2013) Current Opin Pharmacol. 13:394-401).

[0004] The role of activated KRas in malignancy was observed over thirty years ago (e.g., see Santos et al., (1984) Science 223:661-664). Aberrant expression of KRas accounts for up to 20% of all cancers and oncogenic KRas mutations that stabilize GTP binding and lead to constitutive activation of KRas and downstream signaling have been reported in 25 -30% of lung adenocarcinomas. (e.g., see Samatar and Poulikakos (2014) Nat Rev Drug Disc 13(12): 928-942 doi: 10.1038/nrd428). Single nucleotide substitutions that result in missense mutations at codons 12 and 13 of the KRas primary amino acid sequence comprise approximately 40% of these KRas driver mutations in lung adenocarcinoma, with a G12C transversion being the most common activating mutation (e.g., see Dogan et al., (2012) Clin

Cancer Res. 18(22):6169-6177, published online 2012 Sep 26. doi: 10.1158/1078-0432.CCR-11-3265).

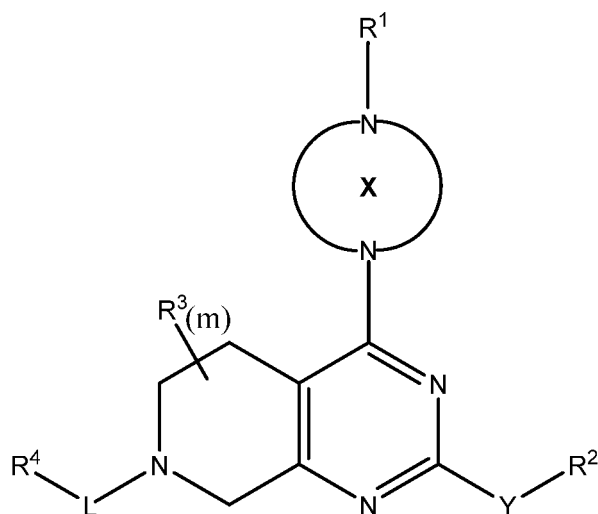
[0005] The well-known role of KRAs in malignancy and the discovery of these frequent mutations in KRas in various tumor types made KRas a highly attractable target of the pharmaceutical industry for cancer therapy. Notwithstanding thirty years of large scale discovery efforts to develop inhibitors of KRas for treating cancer, no KRas inhibitor has demonstrated sufficient safety and/or efficacy to obtain regulatory approval (e.g., see McCormick (2015) Clin Cancer Res. 21 (8):1797-1801).

[0006] Despite many failed efforts to target KRas, compounds that inhibit KRas activity are still highly desirable and under investigation, including those that disrupt effectors such as guanine nucleotide exchange factors (e.g., see Sun et al., (2012) Agnew Chem Int Ed Engl. 51(25):6140-6143 doi: 10.1002/anie.201201358) as well target KRas G12C (e.g., see Ostrem et al., (2013) Nature 503:548-551). Clearly there remains a continued interest and effort to develop inhibitors of KRas, particularly inhibitors of activating KRas mutants, including KRas G12C.

[0007] Thus, there is a need to develop new KRas G12C inhibitors that demonstrate sufficient efficacy, stability and/or safety for treating KRas G12C-mediated cancer. The compounds and compositions of the present invention advantageously overcome one or more of the previous shortcomings by providing selective KRas G12C inhibitors.

SUMMARY OF THE INVENTION

[0008] In one aspect of the invention, compounds are provided that inhibit KRas G12C activity. In certain embodiments, the compounds are represented by formula (I):



Formula (I)

[0009] or a pharmaceutically acceptable salt thereof, wherein:

[0010] X is a 4-12 membered saturated or partially saturated monocyclic, bridged or spirocyclic ring, wherein the saturated or partially saturated monocyclic ring is optionally substituted with one or more R⁸;

[0011] Y is a bond, O, S or NR⁵;

[0012] R¹ is $-\text{C}(\text{O})\text{C}(\text{R}^{\text{A}}) \text{---} \text{C}(\text{R}^{\text{B}})_p$ or $-\text{SO}_2\text{C}(\text{R}^{\text{A}}) \text{---} \text{C}(\text{R}^{\text{B}})_p$;

[0013] R² is hydrogen, alkyl, hydroxyalkyl, dihydroxyalkyl, alkylaminylalkyl, dialkylaminylalkyl, -Z-NR⁵R¹⁰, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, or heteroarylalkyl, wherein each of the Z, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl may be optionally substituted with one or more R⁹;

[0014] Z is C1 – C4 alkylene;

[0015] each R³ is independently C1 – C3 alkyl, oxo, or haloalkyl;

[0016] L is a bond, -C(O)-, or C1 – C3 alkylene;

[0017] R⁴ is hydrogen, cycloalkyl, heterocyclyl, aryl, aralkyl or heteroaryl, wherein each of the cycloalkyl, heterocyclyl, aryl, aralkyl and heteroaryl may be optionally substituted with one or more R⁶ or R⁷;

[0018] each R⁵ is independently hydrogen or C1 – C3 alkyl;

[0019] R⁶ is cycloalkyl, heterocyclyl, heterocyclylalkyl, aryl, or heteroaryl, wherein each of the cycloalkyl, heterocyclyl, aryl, or heteroaryl may be optionally substituted with one or more R⁷;

[0020] each R⁷ is independently halogen, hydroxyl, C1 – C6 alkyl, cycloalkyl, alkoxy, haloalkyl, amino, cyano, heteroalkyl, hydroxyalkyl or Q-haloalkyl, wherein Q is O or S;

[0021] R⁸ is oxo, C1 – C3 alkyl, C2 – C4 alkynyl, heteroalkyl, cyano, -C(O)OR⁵, -C(O)N(R⁵)₂, -N(R⁵)₂, wherein the C1 – C3 alkyl may be optionally substituted with cyano, halogen, -OR⁵, -N(R⁵)₂, or heteroaryl

[0022] each R⁹ is independently hydrogen, oxo, acyl, hydroxyl, hydroxyalkyl, cyano, halogen, C1 – C6 alkyl, aralkyl, haloalkyl, heteroalkyl, cycloalkyl, heterocyclylalkyl, alkoxy, dialkylaminyl, dialkylamidoalkyl, or dialkylaminylalkyl, wherein the C1 – C6 alkyl may be optionally substituted with cycloalkyl;

[0023] each R¹⁰ is independently hydrogen, acyl, C1 – C3 alkyl, heteroalkyl or hydroxyalkyl;

[0024] R^A is absent, hydrogen, or C1 – C3 alkyl;

[0025] each R^B is independently hydrogen, C1 – C3 alkyl, alkylaminylalkyl, dialkylaminylalkyl or heterocyclylalkyl;

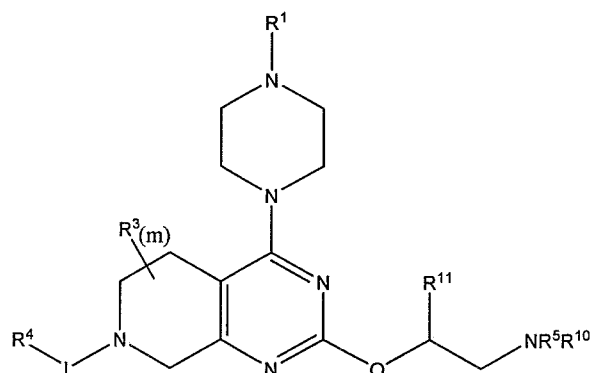
[0026] m is zero or an integer between 1 and 2;

[0027] p is one or two; and wherein,

[0028] when $\equiv$ is a triple bond then R^A is absent, R^B is present and p equals one,

[0029] or when = is a double bond then R^A is present, R^B is present and p equals two, or R^A, R^B and the carbon atoms to which they are attached form a 5-8 membered partially saturated cycloalkyl optionally substituted with one or more R⁷.

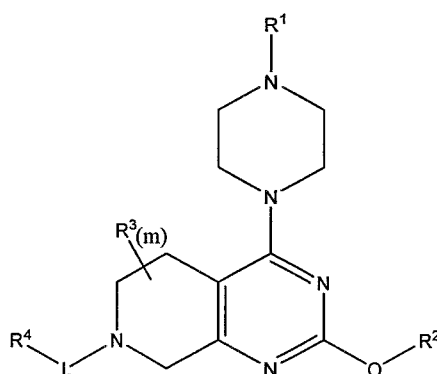
[0030] Also included are compounds of Formula I having the Formula I-A:



Formula I-A

[0031] wherein R¹, R³, R⁴, R⁵, R¹⁰, L and m are as defined for Formula I, R¹¹ is hydrogen, C1 – C3 alkyl or hydroxyalkyl, and the piperidiny ring is optionally substituted with R⁸ wherein R⁸ is as defined for Formula I.

[0032] Also included are compounds of Formula I having the Formula I-B:



Formula I-B

[0033] where R¹, R³, R⁴, R⁹, L and m are as defined for Formula I, R² is heterocyclalkyl optionally substituted with one or more R⁹, and the piperidiny ring is optionally substituted with R⁸, where R⁸ is as defined for Formula I.

[0034] In another aspect of the invention, there is provided a pharmaceutical composition comprising a therapeutically effective amount of a compound as described herein and a pharmaceutically acceptable excipient.

[0034a] In one embodiment, pharmaceutical compositions are provided comprising a therapeutically effective amount of a compound of the present invention or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient.

[0035] In yet another aspect of the invention, there is provided a method for inhibiting KRas G12C activity in a cell, comprising contacting the cell in which inhibition of KRas G12C activity is desired with an effective amount of a compound as described herein, pharmaceutically acceptable salts thereof or pharmaceutical compositions containing the compound of Formula (I) or Formula I-B, or pharmaceutically acceptable salt thereof.

[0035a] In one embodiment, methods for inhibiting KRas G12C activity in a cell are provided, comprising contacting the cell with a compound of Formula I, Formula I-A or Formula I-B. In one embodiment, the contacting is in vitro. In one embodiment, the contacting is in vivo.

[0035b] In another aspect of the invention, there is provided a use of a compound as described herein or a pharmaceutically acceptable salt thereof, alone or combined with a pharmaceutically acceptable carrier, excipient or diluents, in the manufacture of a medicament for the treatment of cancer, wherein a therapeutically effective amount is to be administered to a patient in need thereof.

[0035c] In another aspect of the invention, there is provided a use of compound as described herein or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of cancer in a patient in need thereof, wherein the cancer is associated with a KRas G12C mutation (e.g., a KRas G12C-associated cancer); and wherein a therapeutically effective amount of the compound or a pharmaceutically acceptable salt thereof is to be administered.

[0036] Also provided herein is a method of inhibiting cell proliferation, in vitro or in vivo, the method comprising contacting a cell with an effective amount of a compound of Formula I, Formula I-A or Formula I-B, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof as defined herein.

[0037] Also provided are methods for treating cancer in a patient comprising administering a therapeutically effective amount of a compound or pharmaceutical composition of the present invention or a pharmaceutically acceptable salt thereof to a patient in need thereof.

[0038] Also provided herein is a method of treating a KRas G12C -associated disease or disorder in a patient in need of such treatment, the method comprising administering to the patient a therapeutically effective amount of a compound of Formula I, Formula I-A or Formula 1-B, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition thereof as defined herein.

[0039] Also provided herein is a compound of Formula I, Formula I-A or Formula 1-B, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition thereof as defined herein for use in therapy.

[0040] Also provided herein is a compound of Formula I, Formula I-A or Formula 1-B, or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition thereof as defined herein for use in the treatment of cancer.

[0041] Also provided herein is a compound of Formula I, Formula I-A or Formula 1-B, or a pharmaceutically acceptable salt or solvate thereof for use in the inhibition of KRas G12C.

[0042] Also provided herein is a compound of Formula I, Formula I-A or Formula 1-B, or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition thereof as defined herein, for use in the treatment of a KRas G12C-associated disease or disorder.

[0043] Also provided herein is the use of a compound of Formula I, Formula I-A or Formula 1-B or a pharmaceutically acceptable salt or solvate thereof, as defined herein in the manufacture of a medicament for the treatment of cancer.

[0044] Also provided herein is a use of a compound of Formula I, Formula I-A or Formula 1-B, or a pharmaceutically acceptable salt or solvate thereof, as defined herein in the manufacture of a medicament for the inhibition of activity of KRas G12C.

[0045] Also provided herein is the use of a compound of Formula I, Formula I-A or Formula 1-B, or a pharmaceutically acceptable salt or solvate thereof, as defined herein, in the manufacture of a medicament for the treatment of a KRas G12C-associated disease or disorder.

[0046] Also provided herein is a method for treating cancer in a patient in need thereof, the method comprising (a) determining that the cancer is associated with a KRas G12C mutation (e.g., a KRas G12C-associated cancer); and (b) administering to the patient a therapeutically effective amount of a compound of Formula I, Formula I-A or Formula 1-B or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof.

[0047] Also provided herein is a process for preparing a compound of Formula I, Formula I-A or Formula 1-B, or a pharmaceutically acceptable salt or solvate thereof.

[0048] Also provided herein is a compound of Formula I, Formula I-A or Formula 1-B, or a pharmaceutically acceptable salt thereof obtained by a process of preparing the compound as defined herein.

DETAILED DESCRIPTION OF THE INVENTION

[0049] The present invention relates to inhibitors of KRas G12C. In particular, the present invention relates to compounds that irreversibly inhibit the activity of KRas G12C, pharmaceutical compositions comprising a therapeutically effective amount of the compounds and methods of use therefor.

DEFINITIONS

[0050] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs.

All patents, patent applications, and publications referred to herein are incorporated by reference.

[0051] As used herein, "KRas G12C" refers to a mutant form of a mammalian KRas protein that contains an amino acid substitution of a cysteine for a glycine at amino acid position 12. The assignment of amino acid codon and residue positions for human KRas is based on the amino acid sequence identified by UniProtKB/Swiss-Prot P01116: Variant p.Gly12Cys.

[0052] As used herein, a "KRas G12C inhibitor" refers to compounds of the present invention that are represented by formulae (I) as described herein. These compounds are capable of negatively modulating or inhibiting all or a portion of the enzymatic activity of KRas G12C. The KRas G12C inhibitors of the present invention interact with and irreversibly bind to KRas G12C by forming a covalent adduct with the sulfhydryl side chain of the cysteine residue at position 12 resulting in the inhibition of the enzymatic activity of KRas G12C.

[0053] A "KRas G12C-associated disease or disorder" as used herein refers to diseases or disorders associated with or mediated by or having a KRas G12C mutation. A non-limiting example of a KRas G12C-associated disease or disorder is a KRas G12C-associated cancer.

[0054] As used herein, the term "subject," "individual," or "patient," used interchangeably, refers to any animal, including mammals such as mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, primates, and humans. In some embodiments, the patient is a human. In some embodiments, the subject has experienced and/or exhibited at least one symptom of the disease or disorder to be treated and/or prevented. In some embodiments, the subject has been identified or diagnosed as having a cancer having a KRas G12C mutation (e.g., as determined using a regulatory agency-approved, e.g., FDA-approved, assay or kit). In some embodiments, the subject has a tumor that is positive for a KRas G12C mutation (e.g., as determined using a regulatory agency-approved assay or kit). The subject can be a subject with a tumor(s) that is positive for a KRas G12C mutation (e.g., identified as positive using a regulatory agency-approved, e.g., FDA-approved, assay or kit). The subject can be a subject whose tumors have a KRas G12C mutation (e.g., where the tumor is identified as such using a regulatory agency-approved, e.g., FDA-approved, kit or assay). In some embodiments, the subject is suspected of having a KRas G12C gene-associated cancer. In some embodiments, the

subject has a clinical record indicating that the subject has a tumor that has a KRas G12C mutation (and optionally the clinical record indicates that the subject should be treated with any of the compositions provided herein).

[0055] In some embodiments of any of the methods or uses described herein, an assay is used to determine whether the patient has KRas G12C mutation using a sample (e.g., a biological sample or a biopsy sample (e.g., a paraffin-embedded biopsy sample) from a patient (e.g., a patient suspected of having a KRas G12C-associated cancer, a patient having one or more symptoms of a KRas G12C-associated cancer, and/or a patient that has an increased risk of developing a KRas G12C-associated cancer) can include, for example, next generation sequencing, immunohistochemistry, fluorescence microscopy, break apart FISH analysis, Southern blotting, Western blotting, FACS analysis, Northern blotting, and PCR-based amplification (e.g., RT-PCR and quantitative real-time RT-PCR). As is well-known in the art, the assays are typically performed, e.g., with at least one labelled nucleic acid probe or at least one labelled antibody or antigen-binding fragment thereof.

[0056] The term “regulatory agency” is a country’s agency for the approval of the medical use of pharmaceutical agents with the country. For example, a non-limiting example of a regulatory agency is the U.S. Food and Drug Administration (FDA).

[0057] The term “amino” refers to $-NH_2$;

[0058] The term "acyl" refers to $-C(O)CH_3$.

[0059] The term "alkyl" as employed herein refers to straight and branched chain aliphatic groups having from 1 to 12 carbon atoms, 1-8 carbon atoms 1-6 carbon atoms, or 1-3 carbon atoms which is optionally substituted with one, two or three substituents. Examples of alkyl groups include, without limitation, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, and hexyl.

[0060] The term “haloalkyl” refers to an alkyl chain in which one or more hydrogen has been replaced by a halogen. Examples of haloalkyls are trifluoromethyl, difluoromethyl and fluoromethyl.

[0061] The term “haloalkyloxy” refers to $-O$ -haloalkyl.

[0062] An "alkylene," group is an alkyl group, as defined hereinabove, that is positioned between and serves to connect two other chemical groups. Exemplary alkylene groups include, without limitation, methylene, ethylene, propylene, and butylene.

[0063] The term "alkoxy" refers to --OC1--C6 alkyl .

[0064] The term "cycloalkyl" as employed herein includes saturated and partially unsaturated cyclic hydrocarbon groups having 3 to 12 carbons, for example 3 to 8 carbons, and as a further example 3 to 6 carbons, wherein the cycloalkyl group additionally is optionally substituted. Examples of cycloalkyl groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl.

[0065] The term "heteroalkyl" refers to an alkyl group, as defined hereinabove, wherein one or more carbon atoms in the chain are replaced by a heteroatom selected from the group consisting of O, S, and N.

[0066] As used herein, the term "hydroxyalkyl" refers to --alkyl--OH .

[0067] The term "dihydroxyalkyl" refers to an alkyl group as defined herein wherein two carbon atoms are each substituted with a hydroxyl group.

[0068] The term "alkylaminyl" refers to $\text{--NR}^x\text{--alkyl}$, wherein R^x is hydrogen. In one embodiment, R^x is hydrogen.

[0069] The term "dialkylaminyl" refers to $\text{--N(R}^y)_2$, wherein each R^y is C1 – C3 alkyl.

[0070] The term "alkylaminylalkyl" refers to $\text{--alkyl--NR}^x\text{--alkyl}$, wherein R^x is hydrogen. In one embodiment, R^x is hydrogen.

[0071] The term "dialkylaminylalkyl" refers to $\text{--alkyl--N(R}^y)_2$, wherein each R^y is C1 – C4 alkyl, wherein the alkyl of the $\text{--alkyl--N(R}^y)_2$ may be optionally substituted with hydroxy or hydroxyalkyl.

[0072] An "aryl" group is a C₆-C₁₄ aromatic moiety comprising one to three aromatic rings, which is optionally substituted. As one embodiment, the aryl group is a C₆-C₁₀ aryl group.

Examples of aryl groups include, without limitation, phenyl, naphthyl, anthracenyl, and fluorenyl.

[0073] An "aralkyl" or "arylalkyl" group comprises an aryl group covalently linked to an alkyl group, either of which may independently be optionally substituted or unsubstituted. An example of an aralkyl group is (C₁-C₆)alkyl(C₆-C₁₀)aryl, including, without limitation, benzyl, phenethyl, and naphthylmethyl. An example of a substituted aralkyl is wherein the alkyl group is substituted with hydroxyalkyl.

[0074] A "heterocyclyl" or "heterocyclic" group is a ring structure having from about 3 to about 12 atoms, for example 4 to 8 atoms, wherein one or more atoms are selected from the group consisting of N, O, and S, the remainder of the ring atoms being carbon. The heterocyclyl may be a monocyclic, a bicyclic, a spirocyclic or a bridged ring system. The heterocyclic group is optionally substituted with R⁷ on carbon or nitrogen at one or more positions, wherein R⁷ is as defined for Formula I. The heterocyclic group is also independently optionally substituted on nitrogen with alkyl, aryl, aralkyl, alkylcarbonyl, alkylsulfonyl, arylcarbonyl, arylsulfonyl, alkoxy carbonyl, aralkoxy carbonyl, or on sulfur with oxo or lower alkyl. Examples of heterocyclic groups include, without limitation, epoxy, azetidiny, aziridiny, tetrahydrofurany, tetrahydropyrany, pyrrolidiny, pyrrolidinony, piperidiny, piperaziny, imidazolidiny, thiazolidiny, dithianyl, trithianyl, dioxolany, oxazolidiny, oxazolidinony, decahydroquinolinyl, piperidony, 4-piperidinony, thiomorpholinyl, thiomorpholinyl 1,1 dioxide, morpholinyl, oxazepany, azabicyclohexanes, azabicycloheptanes and oxa azabiocycloheptanes. Specifically excluded from the scope of this term are compounds having adjacent annular O and/or S atoms.

[0075] The term "heterocyclylalkyl" refers to a heterocyclyl group as defined herein linked to the remaining portion of the molecule via an alkyl linker, wherein the alkyl linker of the heterocyclylalkyl may be optionally substituted with hydroxy or hydroxyalkyl.

[0076] As used herein, the term "heteroaryl" refers to groups having 5 to 14 ring atoms, preferably 5, 6, 9, or 10 ring atoms; having 6, 10, or 14 π electrons shared in a cyclic array; and having, in addition to carbon atoms, from one to three heteroatoms per ring selected from the group consisting of N, O, and S. Examples of heteroaryl groups include acridinyl, azocinyl,

benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, furanyl, furazanyl, imidazolyl, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indoliziny, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, methylenedioxyphenyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinoliziny, quinoxalinyl, quinuclidinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl.

[0077] A "heteroarylalkyl" group comprises a heteroaryl group covalently linked to an alkyl group, wherein the radical is on the alkyl group, either of which is independently optionally substituted or unsubstituted. Examples of heteroarylalkyl groups include a heteroaryl group having 5, 6, 9, or 10 ring atoms bonded to a C1-C6 alkyl group. Examples of heteroarylalkyl groups include pyridylmethyl, pyridylethyl, pyrrolylmethyl, pyrrolylethyl, imidazolylmethyl, imidazolylethyl, thiazolylmethyl, thiazolylethyl, benzimidazolylmethyl, benzimidazolylethyl, quinazolinylmethyl, quinolinylmethyl, quinolinylethyl, benzofuranylmethyl, indolinylethyl, isoquinolinylmethyl, isoinodolylmethyl, cinnolinylmethyl, and benzothiophenylethyl. Specifically excluded from the scope of this term are compounds having adjacent annular O and/or S atoms.

[0078] As used herein, "an effective amount" of a compound is an amount that is sufficient to negatively modulate or inhibit the activity of KRas G12C. Such amount may be administered as a single dosage or may be administered according to a regimen, whereby it is effective.

[0079] As used herein, a "therapeutically effective amount" of a compound is an amount that is sufficient to ameliorate, or in some manner reduce a symptom or stop or reverse progression of

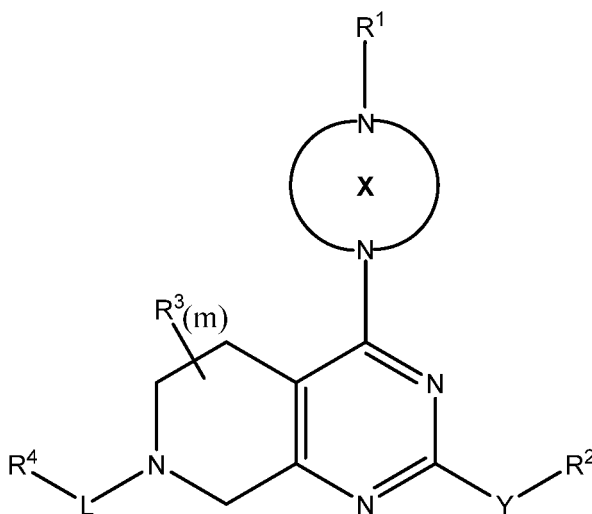
a condition, or negatively modulate or inhibit the activity of KRas G12C. Such amount may be administered as a single dosage or may be administered according to a regimen, whereby it is effective.

[0080] As used herein, treatment means any manner in which the symptoms or pathology of a condition, disorder or disease are ameliorated or otherwise beneficially altered. Treatment also encompasses any pharmaceutical use of the compositions herein.

[0081] As used herein, amelioration of the symptoms of a particular disorder by administration of a particular pharmaceutical composition refers to any lessening, whether permanent or temporary, lasting or transient that can be attributed to or associated with administration of the composition.

COMPOUNDS

[0082] In one aspect of the invention, compounds are provided represented by formula (I):



Formula (I)

[0083] or a pharmaceutically acceptable salt thereof, wherein:

[0084] X is a 4-12 membered saturated or partially saturated monocyclic, bridged or spirocyclic ring, wherein the saturated or partially saturated monocyclic ring is optionally substituted with one or more R⁸;

[0085] Y is a bond, O, S or NR⁵;

[0086] R¹ is $-C(O)C(R^A) \overset{\text{-----}}{\parallel} C(R^B)_p$ or $-SO_2C(R^A) \overset{\text{-----}}{\parallel} C(R^B)_p$;

[0087] R² is hydrogen, alkyl, hydroxyalkyl, dihydroxyalkyl, alkylaminylalkyl, dialkylaminylalkyl, -Z-NR⁵R¹⁰, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, or heteroarylalkyl, wherein each of the Z, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl may be optionally substituted with one or more R⁹;

[0088] Z is C1 – C4 alkylene;

[0089] each R³ is independently C1 – C3 alkyl, oxo, or haloalkyl;

[0090] L is a bond, -C(O)-, or C1 – C3 alkylene;

[0091] R⁴ is hydrogen, cycloalkyl, heterocyclyl, aryl, aralkyl or heteroaryl, wherein each of the cycloalkyl, heterocyclyl, aryl, aralkyl and heteroaryl may be optionally substituted with one or more R⁶ or R⁷;

[0092] each R⁵ is independently hydrogen or C1 – C3 alkyl;

[0093] R⁶ is cycloalkyl, heterocyclyl, heterocyclylalkyl, aryl, or heteroaryl, wherein each of the cycloalkyl, heterocyclyl, aryl, or heteroaryl may be optionally substituted with one or more R⁷;

[0094] each R⁷ is independently halogen, hydroxyl, C1 – C6 alkyl, cycloalkyl, alkoxy, haloalkyl, amino, cyano, heteroalkyl, hydroxyalkyl or Q-haloalkyl, wherein Q is O or S;

[0095] R⁸ is oxo, C1 – C3 alkyl, C2 – C4 alkynyl, heteroalkyl, cyano, -C(O)OR⁵, -C(O)N(R⁵)₂, -N(R⁵)₂, wherein the C1 – C3 alkyl may be optionally substituted with cyano, halogen, -OR⁵, -N(R⁵)₂, or heteroaryl;

[0096] each R⁹ is independently hydrogen, oxo, acyl, hydroxyl, hydroxyalkyl, cyano, halogen, C1 – C6 alkyl, aralkyl, haloalkyl, heteroalkyl, cycloalkyl, heterocyclylalkyl, alkoxy, dialkylaminyl, dialkylamidoalkyl, or dialkylaminylalkyl, wherein the C1 – C6 alkyl may be optionally substituted with cycloalkyl;

[0097] each R¹⁰ is independently hydrogen, acyl, C1 – C3 alkyl, heteroalkyl or hydroxyalkyl;

[0098] R^A is absent, hydrogen, or C1 – C3 alkyl;

[0099] each R^B is independently hydrogen, C1 – C3 alkyl, alkylaminylalkyl, dialkylaminylalkyl or heterocyclalkyl;

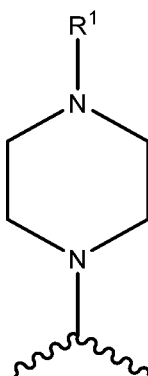
[0100] m is zero or an integer between 1 and 2;

[0101] p is one or two; and wherein,

[0102] when $\equiv$ is a triple bond then R^A is absent, R^B is present and p equals one;

[0103] or when $=$ is a double bond then R^A is present, R^B is present and p equals two, or R^A , R^B and the carbon atoms to which they are attached form a 5-8 membered partially saturated cycloalkyl optionally substituted with one or more R^7 .

[0104] In certain embodiments, R^1 -X is:



[0105] wherein R^1 is defined for Formula I and the piperazinyl ring is optionally substituted with R^8 , where R^8 is as defined for Formula I. In certain embodiments, R^8 is C1 – C3 alkyl wherein the alkyl is optionally substituted with cyano or OR^5 , or $-C(O)N(R^5)_2$, wherein each R^5 is independently hydrogen or C1 – C3 alkyl.

[0106] In particular embodiments, R^1 is $-C(O)C(R^A)\equiv C(R^B)_p$ where R^A , R^B and p are as defined for Formula I. In one embodiment, R^1 is $-C(O)C(R^A)\equiv C(R^B)_p$, wherein $\equiv$ is a triple bond and R^A is absent, p is one and R^B is C1 – C3 alkyl. In one embodiment, R^1 is $-C(O)C(R^A)=C(R^B)_p$, wherein $=$ is a double bond and R^A is hydrogen or C1 – C3alkyl, p is two and each R^B is independently hydrogen, C1 – C3alkyl, dialkylaminylalkyl or

heterocyclalkyl. In one embodiment, R^1 is $-C(O)C(R^A)=C(R^B)_p$, wherein R^A is hydrogen or C1 – C3alkyl, p is two, one of said R^B is hydrogen, C1 – C3alkyl, dialkylaminylalkyl or heterocyclalkyl and the other R^B is hydrogen or C1 – C3alkyl. In one embodiment, R^1 is $-C(O)CH=CH_2$.

[0107] In one embodiment, Y is O or NR^5 and R^2 is selected from the group consisting of alkyl, hydroxyalkyl, dihydroxyalkyl, alkylaminylalkyl, dialkylaminylalkyl, heterocycl, heterocyclalkyl, and heteroaryl. In one embodiment, Y is O and R^2 is hydroxyalkyl, dihydroxyalkyl, alkylaminylalkyl, or dialkylaminylalkyl, wherein the alkylaminylalkyl or dialkylaminylalkyl is optionally substituted with one or more R^9 . In one embodiment, the optionally substituted alkylaminylalkyl or dialkylaminylalkyl is independently selected from methylaminylpropan-2-yl, dimethylaminylethyl, methylethylaminylethyl, dimethylaminylpropanyl, dimethylaminylpropan-2-yl, dimethylaminylbutanyl, dimethylaminylbutan-2-yl, 2-dimethylaminylpropanol, or diethylaminylethyl. In one embodiment, Y is O or NR^5 and R^2 is heterocycl or heterocyclalkyl optionally substituted with one or more R^9 . Nonlimiting examples of one or more R^9 when R^2 is heterocycl or heterocyclalkyl include C1 – C3 alkyl, acyl, oxo, cyano, alkoxy, cycloalkyl, cycloalkylmethyl, halogen, and hydroxyl. Nonlimiting examples of R^2 heterocycls optionally substituted with one or more R^9 include azetidiny, C1-C3alkyl-substituted azetidiny (e.g., methylazetidiny), halo-substituted azetidiny (e.g., difluoroazetidiny), tetrahydropyran, pyrrolidiny, C1-C3 alkyl-substituted pyrrolidiny (e.g., methylpyrrolidiny, dimethylpyrrolidiny, and isopropylpyrrolidiny), cycloalkylalkylpyrrolidiny, hydroxypyrrolidiny, halo-substituted pyrrolidiny (e.g., fluoropyrrolidiny and difluoropyrrolidiny), methoxyethylpyrrolidiny, (N-methyl)methoxypyrrolidiny, piperaziny, dimethylaminylpyrrolidiny, morpholiny, methylmorpholiny, 1,4-oxazepany, piperdiny, C1-C3 alkyl-substituted piperidiny (e.g., methylpiperidiny), acylpiperdiny, cyanopiperdiny, cycloalkylpiperdiny, halopiperdiny (e.g., fluoropiperdiny), dihalopiperdiny (e.g., difluoropiperdiny), alkoxypiperdiny, pyrrolidony, piperidony, thiomorpholiny-1,1-dioxide, 3-azabicyclo[3.1.0]hexany, oxa-5-azabicyclo[2.2.1]heptan-5-yl, and azabicyclo[2.2.1]heptan-2-yl.

[0108] In one embodiment, Y is O and R^2 is heteroarylalkyl optionally substituted with one or more R^9 . In one embodiment, the heteroaryl portion of the heteroarylalkyl is pyridiny.

[0109] In one embodiment, Y is O and R^2 is $-ZR^5R^{10}$. In one embodiment, R^5 is C1 – C3 alkyl and R^{10} is independently selected from acyl, hydroxyalkyl or alkoxy.

[0110] In one embodiment, Y is a bond and R^2 is hydrogen, heterocyclyl or aryl, wherein said heterocyclyl and aryl are optionally substituted with one or more R^9 .

[0111] In one embodiment, Y is a bond and R^2 is hydrogen.

[0112] In one embodiment, Y is a bond and R^2 is heterocyclyl optionally substituted with one or more R^9 . In one embodiment, Y is a bond and R^2 is heterocyclyl optionally substituted with methyl, halogen or dimethylamino. Nonlimiting examples of R^2 heterocyclyls include azetidiny, piperidiny, piperaziny, morpholinyl, and pyrrolidinyl.

[0113] In one embodiment, Y is a bond and R^2 is aryl optionally substituted with one or more R^9 . In one embodiment, the aryl is phenyl substituted with heterocyclylalkyl.

[0114] In certain other embodiments when X is a monocyclic ring, R^4 is aryl. In one embodiment, R^4 is selected from the group consisting of phenyl and naphthyl and is optionally substituted with one or more R^6 or R^7 . Examples of R^7 substituents include halogen, hydroxyl, C1- C6 alkyl (e.g., C1- C3 alkyl), cycloalkyl, haloalkyl, Q-haloalkyl, amino, cyano, hydroxyalkyl and alkoxy. In one embodiment, the aryl is phenyl substituted with one or more R^7 groups independently selected from halogen, hydroxyl, C1- C3 alkyl, haloalkyl, Q-haloalkyl, and alkoxy. In one embodiment, the aryl is phenyl substituted with one or more R^7 groups independently selected from halogen, haloalkyl, methyl, isopropyl, methoxy, Q-haloalkyl and hydroxyl. In one embodiment, the aryl is phenyl substituted with one or more R^7 groups independently selected from methyl, trifluoromethyl, 2,2,2-trifluoroethyl, hydroxyl, trifluoromethoxy, hydroxyl, fluoro, chloro, isopropyl, cyclopropyl and trifluoromethylthio. In one embodiment, the aryl is phenyl substituted with one to three R^7 groups independently selected from hydroxyl, fluorine and chlorine. In one embodiment, the aryl is phenyl substituted with hydroxyl and C1 – C3 alkyl or two C1 – C3 alkyl. In one embodiment, the aryl is phenyl substituted with Q-haloalkyl and hydroxyl or fluorine.

[0115] In one embodiment, R^4 is aryl wherein aryl is naphthyl optionally substituted with one or more R^7 . In one embodiment, the aryl is naphthyl substituted with one or more R^7 groups

independently selected from halogen, hydroxyl, C1- C3 alkyl, haloalkyl, Q-haloalkyl, and alkoxy. In one embodiment, the aryl is naphthyl substituted with one or more R⁷ groups independently selected from halogen, haloalkyl, methyl, isopropyl, methoxy, Q-haloalkyl and hydroxyl. In one embodiment, R⁴ is naphthyl optionally substituted with one or more R⁷ substituents independently selected from hydroxyl, halogen, C1 – C3 alkyl, amino, and haloalkyl. In one embodiment, R⁴ is naphthyl optionally substituted with one to three R⁷ substituents independently selected from difluoromethyl, methyl, hydroxyl, amino, fluoro, and chloro.

[0116] In one embodiment, the aryl is naphthyl optionally substituted with one or more halogen. In one embodiment, the aryl is naphthyl substituted with hydroxyl and trifluoromethyl or C1 – C3alkyl. In one embodiment, the aryl is naphthyl substituted with hydroxyl.

[0117] In one embodiment, R⁴ is heteroaryl optionally substituted with one or more R⁷. In one embodiment, R⁴ is heteroaryl optionally substituted with one or more R⁷ independently selected from halogen, hydroxyl, C1- C3 alkyl, haloalkyl, Q-haloalkyl, alkoxy and amino. In one embodiment, R⁴ is indoyl, indazolyl, quinolinyl, isoquinolinyl, pyridinyl or benzo[d]thiazolyl optionally substituted with one or more R⁷. In one embodiment, R⁴ is indoyl, indazolyl, quinolinyl, isoquinolinyl, pyridinyl or benzo[d]thiazolyl optionally substituted with one or more R⁷ independently selected from halogen, hydroxyl, C1- C3 alkyl, haloalkyl, Q-haloalkyl, alkoxy and amino.

[0118] In yet other embodiments, R⁴ is heteroaryl, optionally an indoyl or an indazolyl, each of which may be substituted with one or more R⁷. In one embodiment, R⁴ is heteroaryl optionally substituted with one or more R⁷ substituents independently selected from the group consisting of halogen, hydroxyl, C1- C3 alkyl, haloalkyl, Q-haloalkyl and alkoxy. In one embodiment, the R⁴ heteroaryl is indazolyl optionally substituted with one or two R⁷ independently selected from alkoxy, haloalkyl, and C1-C6 alkyl. In other embodiments, the R⁴ heteroaryl is a quinolinyl or isoquinolinyl, each optionally substituted with one or more R⁷. In one embodiment, the R⁴ heteroaryl is a quinolinyl or isoquinolinyl, each optionally substituted with one or more R⁷ independently selected from amino, hydroxyl, C1 – C3 alkyl, and hydroxyl. In one embodiment, the R⁴ heteroaryl is a quinolinyl or isoquinolinyl, each optionally substituted with R⁷ selected from hydroxyl and amino. In one embodiment, the R⁴ heteroaryl is a pyridinyl

optionally substituted with one or more R^7 . In one embodiment, the R^4 heteroaryl is pyridinyl optionally substituted with one or more R^7 independently selected from C1 – C3 alkyl, halogen and haloalkyl. In other embodiments, the R^4 heteroaryl is benzo[d]thiazolyl optionally substituted with one or more R^7 , such as hydroxyl, one or two C1 – C3 alkyl, or hydroxyl and one or two C1 – C3 alkyl. In one embodiment, the R^4 heteroaryl is indolyl optionally substituted with one or more R^7 . In one embodiment, the R^4 heteroaryl is indolyl optionally substituted with one or two R^7 independently selected from hydroxyl and C1 – C3alkyl.

[0119] In one embodiment, where X is a monocyclic ring, R^4 is aralkyl. In certain embodiments, the aralkyl is benzyl. In other embodiments, the alkyl of the benzyl group is optionally substituted with hydroxyalkyl.

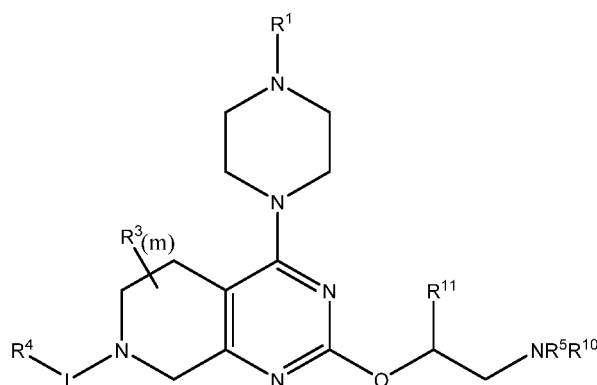
[0120] In one embodiment, L is a bond.

[0121] In one embodiment, m is one and R^3 is C1 – C3 alkyl.

[0122] In one embodiment, m is one and R^3 is oxo.

[0123] In one embodiment, R^8 is heteroalkyl, C2-C4 alkynyl or C1 – C3 alkyl optionally substituted with $-OR^5$, cyano or heteroaryl. In one embodiment, R^8 is methyl, cyanomethyl, methoxymethyl, hydroxymethyl. In one embodiment, R^8 is methyl. In one embodiment, R^8 is cyanomethyl. In one embodiment, R^8 is hydroxymethyl.

[0124] In one embodiment, Formula I includes compounds having the Formula I-A:

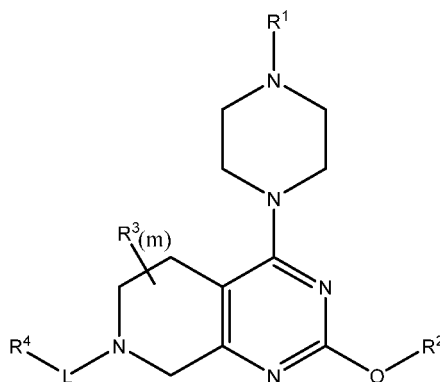


[0125] wherein R^1 , R^3 , R^4 , R^5 , R^{10} , L and m are as defined for Formula I, R^{11} is hydrogen, methyl or hydroxyalkyl, and the piperidinyl ring is optionally substituted with R^8 wherein R^8 is

as defined for Formula I. In one embodiment, L is a bond. In one embodiment, R⁴ is aryl or heteroaryl, each of which is optionally substituted with one or more R⁶ or R⁷. In one embodiment, R⁴ is aryl or heteroaryl, each of which is optionally substituted with one or more R⁷. In one embodiment, each R⁷ is independently selected from hydroxyl, amino, halogen, C1 – C3 alkyl, haloalkyl, Q-haloalkyl, cycloalkyl and alkoxy. In one embodiment, R⁵ and R¹⁰ are each C1 – C3 alkyl. In one embodiment, the aryl is phenyl substituted with one or more R⁷ groups independently selected from halogen, hydroxyl, C1- C3 alkyl, haloalkyl, Q-haloalkyl, and alkoxy. In one embodiment, the aryl is phenyl substituted with one or more R⁷ groups independently selected from halogen, haloalkyl, methyl, isopropyl, methoxy, Q-haloalkyl and hydroxyl. In one embodiment, the aryl is phenyl substituted with one or more R⁷ groups independently selected from methyl, trifluoromethyl, 2,2,2-trifluoroethyl, hydroxyl, trifluoromethoxy, hydroxyl, fluoro, chloro, isopropyl, cyclopropyl and trifluoromethylthio. In one embodiment, the aryl is phenyl substituted with one to three R⁷ groups independently selected from hydroxyl, fluorine and chlorine. In one embodiment, the aryl is phenyl substituted with hydroxyl and C1 – C3 alkyl or two C1 – C3 alkyl. In one embodiment, the aryl is phenyl substituted with Q-haloalkyl and hydroxyl or fluorine. In one embodiment, the aryl is naphthyl substituted with one or more R⁷ groups independently selected from halogen, hydroxyl, C1- C3 alkyl, haloalkyl, Q-haloalkyl, and alkoxy. In one embodiment, the aryl is naphthyl substituted with one or more R⁷ groups independently selected from halogen, haloalkyl, methyl, isopropyl, methoxy, Q-haloalkyl and hydroxyl. In one embodiment, R⁴ is naphthyl optionally substituted with one or more R⁷ substituents independently selected from hydroxyl, halogen, C1 – C3 alkyl, amino, and haloalkyl. In one embodiment, R⁴ is naphthyl optionally substituted with one to three R⁷ substituents independently selected from difluoromethyl, methyl, hydroxyl, amino, fluoro, and chloro. In one embodiment, the aryl is naphthyl optionally substituted with one or more halogen. In one embodiment, the aryl is naphthyl substituted with hydroxyl and trifluoromethyl or C1 – C3alkyl. In one embodiment, the aryl is naphthyl substituted with hydroxyl. In one embodiment, R⁴ is heteroaryl, wherein the heteroaryl is indazolyl optionally substituted with one or two R⁷ independently selected from alkoxy, haloalkyl, and C1-C6 alkyl. In one embodiment, R⁴ is heteroaryl, wherein the heteroaryl is quinolinyl or isoquinolinyl, each optionally substituted with one or more R⁷. In one embodiment, R⁴ is heteroaryl, wherein the heteroaryl is quinolinyl or isoquinolinyl, each

optionally substituted with one or more R^7 independently selected from amino, hydroxyl, C1 – C3alkyl, and hydroxyl. In one embodiment, the R^4 heteroaryl is a pyridinyl optionally substituted with one or more R^7 . In one embodiment, the R^4 heteroaryl is pyridinyl optionally substituted with one or more R^7 independently selected from C1 – C3 alkyl, halogen and haloalkyl. In one embodiment, the R^4 heteroaryl is benzo[d]thiazolyl optionally substituted with one or more R^7 , such as hydroxyl, one or two C1 – C3 alkyl, or hydroxyl and one or two C1 – C3 alkyl. In one embodiment, the R^4 heteroaryl is indolyl optionally substituted with one or more R^7 . In one embodiment, the R^4 heteroaryl is indolyl optionally substituted with one or two R^7 independently selected from hydroxyl and C1 – C3alkyl. In one embodiment, R^{11} is methyl. In one embodiment, the piperidinyl ring is unsubstituted. In one embodiment, the piperidinyl ring is substituted with R^8 . In one embodiment, R^8 is C1 – C3 alkyl optionally substituted with cyano or hydroxyl. In one embodiment, R^8 is methyl, cyanomethyl or hydroxymethyl. In one embodiment, R^8 is methyl. In one embodiment, R^8 is cyanomethyl. In one embodiment, R^8 is hydroxymethyl. In another embodiment, R^5 and R^{10} are each C1 – C3 alkyl, R^{11} is methyl, R^8 is methyl, cyanomethyl or hydroxymethyl, L is a bond, and R^4 is aryl or heteroaryl, each optionally substituted with one or more R^6 or R^7 .

[0126] In one embodiment, Formula I includes compounds having the Formula I-B:



Formula I-B

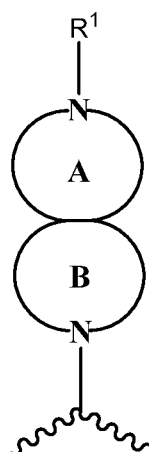
and R^1 , R^3 , R^4 , R^9 , L and m are as defined for Formula I, R^2 is heterocyclalkyl optionally substituted with one or more R^9 , and the piperidinyl ring is optionally substituted with R^8 , where R^8 is as defined for Formula I. In one embodiment, the heterocycl portion of the R^2

heterocyclalkyl is a monocyclic, bicyclic, or bridged ring system having one or two ring heteroatoms independently selected from N and O. In one embodiment, R² heterocycl is pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, 1,4-oxazepanyl, thiomorpholinyl-1,1-dioxide, 3-azabicyclo[3.1.0]hexanyl, 2-oxa-5-azabicyclo[2.2.1]heptan-5-yl, and azabicyclo[2.2.1]heptan-2-yl, optionally substituted with one or more R⁹. In one embodiment, each R⁹ is selected from acyl, oxo, halogen, cyano, C1 – C3 alkyl, alkoxy, hydroxyalkyl, heteroalkyl, cycloalkyl, aralkyl and dialkylamidoalkyl. In one embodiment, L is a bond. In one embodiment, R⁴ is aryl or heteroaryl, each of which is optionally substituted with one or more R⁶ or R⁷. In one embodiment, R⁴ is aryl or heteroaryl, each of which is optionally substituted with one or more R⁷. In one embodiment, each R⁷ is independently selected from hydroxyl, amino, halogen, C1 – C3 alkyl, haloalkyl, Q-haloalkyl, cycloalkyl and alkoxy. In one embodiment, the aryl is phenyl substituted with one or more R⁷ groups independently selected from halogen, hydroxyl, C1- C3 alkyl, haloalkyl, Q-haloalkyl, and alkoxy. In one embodiment, the aryl is phenyl substituted with one or more R⁷ groups independently selected from halogen, haloalkyl, methyl, isopropyl, methoxy, Q-haloalkyl and hydroxyl. In one embodiment, the aryl is phenyl substituted with one or more R⁷ groups independently selected from methyl, trifluoromethyl, 2,2,2-trifluoroethyl, hydroxyl, trifluoromethoxy, hydroxyl, fluoro, chloro, isopropyl, cyclopropyl and trifluoromethylthio. In one embodiment, the aryl is phenyl substituted with one to three R⁷ groups independently selected from hydroxyl, fluorine and chlorine. In one embodiment, the aryl is phenyl substituted with hydroxyl and C1 – C3 alkyl or two C1 – C3 alkyl. In one embodiment, the aryl is phenyl substituted with Q-haloalkyl and hydroxyl or fluorine. In one embodiment, the aryl is naphthyl substituted with one or more R⁷ groups independently selected from halogen, hydroxyl, C1- C3 alkyl, haloalkyl, Q-haloalkyl, and alkoxy. In one embodiment, the aryl is naphthyl substituted with one or more R⁷ groups independently selected from halogen, haloalkyl, methyl, isopropyl, methoxy, Q-haloalkyl and hydroxyl. In one embodiment, R⁴ is naphthyl optionally substituted with one or more R⁷ substituents independently selected from hydroxyl, halogen, C1 – C3 alkyl, amino, and haloalkyl. In one embodiment, R⁴ is naphthyl optionally substituted with one to three R⁷ substituents independently selected from difluoromethyl, methyl, hydroxyl, amino, fluoro, and chloro. In one embodiment, the aryl is naphthyl optionally substituted with one or more halogen. In one embodiment, the aryl is naphthyl substituted with hydroxyl and trifluoromethyl

or C1 – C3alkyl. In one embodiment, the aryl is naphthyl substituted with hydroxyl. In one embodiment, R⁴ is heteroaryl, wherein the heteroaryl is indazolyl optionally substituted with one or two R⁷ independently selected from alkoxy, haloalkyl, and C1-C6 alkyl. In one embodiment, R⁴ is heteroaryl, wherein the heteroaryl is quinolinyl or isoquinolinyl, each optionally substituted with one or more R⁷. In one embodiment, R⁴ is heteroaryl, wherein the heteroaryl is quinolinyl or isoquinolinyl, each optionally substituted with one or more R⁷ independently selected from amino, hydroxyl, C1 – C3 alkyl, and hydroxyl. In one embodiment, the R⁴ heteroaryl is a pyridinyl optionally substituted with one or more R⁷. In one embodiment, the R⁴ heteroaryl is pyridinyl optionally substituted with one or more R⁷ independently selected from C1 – C3 alkyl, halogen and haloalkyl. In one embodiment, the R⁴ heteroaryl is benzo[d]thiazolyl optionally substituted with one or more R⁷, such as hydroxyl, one or two C1 – C3 alkyl, or hydroxyl and one or two C1 – C3 alkyl. In one embodiment, the R⁴ heteroaryl is indolyl optionally substituted with one or more R⁷. In one embodiment, the R⁴ heteroaryl is indolyl optionally substituted with one or two R⁷ independently selected from hydroxyl and C1 – C3 alkyl. In one embodiment, R¹¹ is methyl. In one embodiment, the piperidinyl ring is unsubstituted. In one embodiment, the piperidinyl ring is substituted with R⁸. In one embodiment, the piperidinyl ring is unsubstituted. In one embodiment, the piperidinyl ring is substituted with R⁸. In one embodiment, R⁸ is C1 – C3 alkyl optionally substituted with cyano, hydroxyl or methoxy. In one embodiment, R⁸ is methyl, cyanomethyl, hydroxymethyl or methoxymethyl.

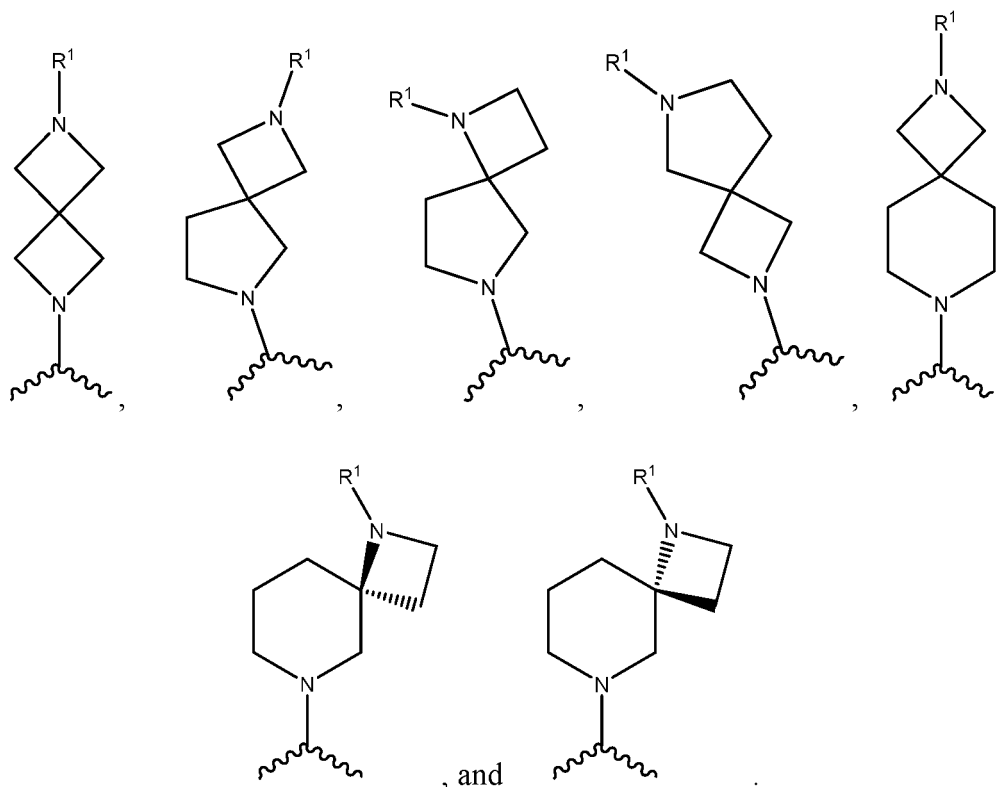
[0127] In one embodiment, X is a saturated bridged ring system. Nonlimiting examples of bridged ring systems include diazabicycloheptanes and diazabicyclooctanes. In certain embodiments, when X is a saturated bridged ring system, R¹ is –C(O)CH=CH₂. In one embodiment, the bridged ring system is substituted with one or two groups independently selected from R⁸, where R⁸ is as defined for Formula I. In one embodiment, the bridged ring system is unsubstituted. In one embodiment, the bridged ring system is diazabicyclo[3.2.1]octan-8-yl or diazabicyclo[3.2.1]octan-3-yl.

[0128] In one embodiment, R¹-X is:



[0129] wherein A and B are a spirocyclic ring system, wherein A and B are the same or different and independently represent a 4-6 membered saturated ring systems, wherein the rings are optionally substituted with one or more R^8 , wherein R^8 is as defined for Formula I. In certain embodiments, R^1 is $-C(O)CH=CH_2$. In certain embodiments, rings A and B are unsubstituted.

[0130] In one embodiment, the spirocyclic ring system is unsubstituted. Non-limiting examples of spirocyclic ring systems include:



[0131] In certain embodiments when A and B represent a spirocyclic ring system, R^1 is – $C(O)CH=CH_2$.

[0132] In one embodiment of Formula I, R^2 is selected from the group consisting of hydroxyalkyl, dialkylaminylalkyl, heterocyclyl and heterocyclylalkyl, wherein each of the heterocyclyl or heterocyclylalkyl are independently optionally substituted with R^9 . In another embodiment, R^2 is heterocyclyl and heterocyclylalkyl, wherein each of the heterocyclyl or heterocyclylalkyl are independently optionally substituted with one or more R^9 . In certain embodiments, R^2 is dialkylaminylalkyl optionally substituted with one or more R^9 . Non-limiting examples include dimethylaminylethyl, dimethylaminylpropyl, dimethylaminylpropan-2-yl, dimethylaminylbutyl, dimethylaminylbutan-2-yl, 2-dimethylaminylpropanol, or diethylaminylethyl.

[0133] In one embodiment, Y is O and R^2 is selected from the group consisting of hydroxyalkyl, dialkylaminylalkyl, heterocyclyl, heterocyclylalkyl, and $-ZR^5R^{10}$, wherein R^5 and R^{10} are as defined for Formula I.

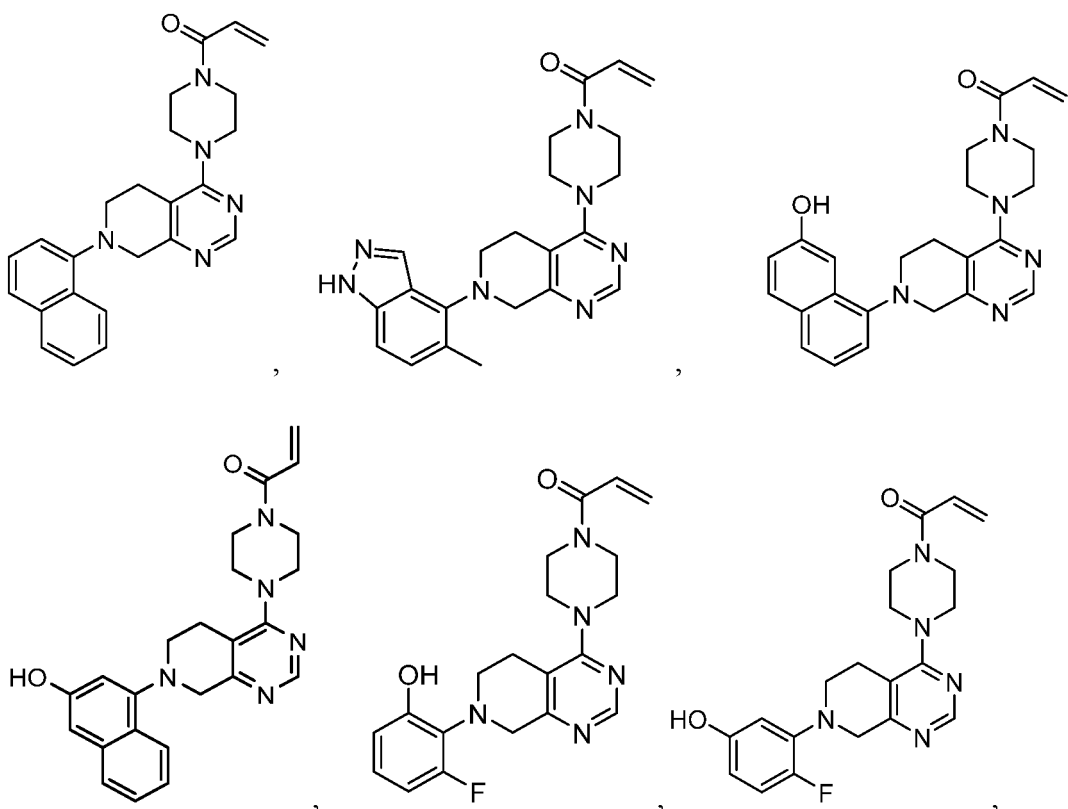
[0134] In one embodiment, Y is O and R^2 is selected from the group consisting of hydroxyalkyl, dialkylaminylalkyl, heterocyclyl and heterocyclylalkyl, wherein each of the heterocyclyl or heterocyclylalkyl are independently optionally substituted with R^9 . In another embodiment, R^2 is heterocyclyl and heterocyclylalkyl, wherein each of the heterocyclyl or heterocyclylalkyl are independently optionally substituted with one or more R^9 . Non-limiting examples of R^9 include acyl, oxo, halogen, cyano, C1 – C6 alkyl, alkoxy, hydroxyalkyl, heteroalkyl, cycloalkyl, aralkyl or dialkylamidoalkyl. In certain embodiments, R^2 is dialkylaminylalkyl optionally substituted with one or more R^9 . Non-limiting examples include dimethylaminylethyl, dimethylaminylpropyl, dimethylaminylpropan-2-yl, dimethylaminylbutyl, dimethylaminylbutan-2-yl, 2-dimethylaminylpropanol, or diethylaminylethyl.

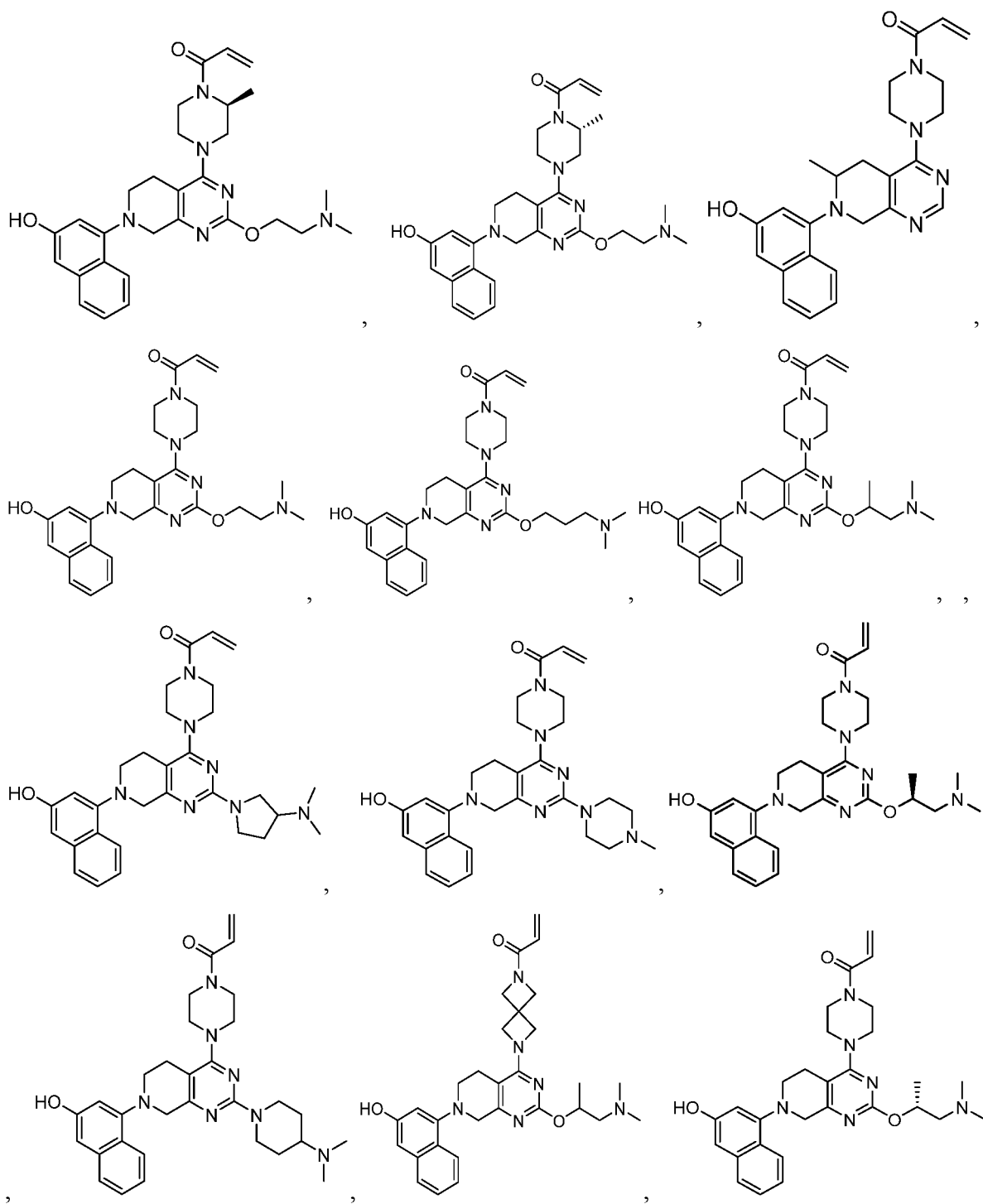
[0135] In one embodiment of Formula I, R^4 is aryl optionally substituted with one or more R^6 or R^7 . In one embodiment, R^4 is phenyl or naphthyl optionally substituted with one or more R^6 or R^7 . In one embodiment, R^4 is phenyl or naphthyl optionally substituted with one or more R^7 . In one embodiment, R^4 is phenyl or naphthyl optionally substituted with one or more R^7 .

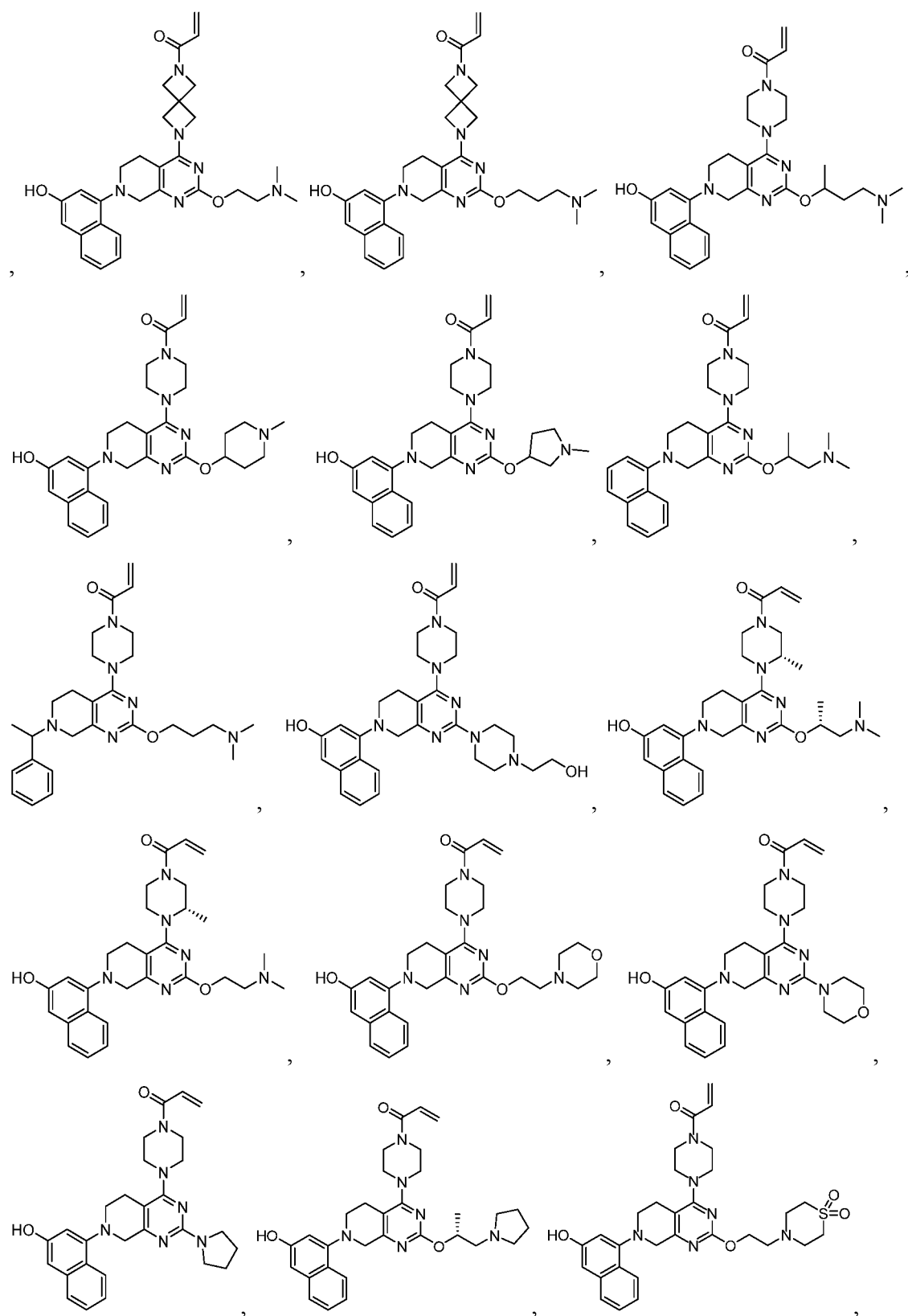
substituents independently selected from halogen, hydroxyl, C1 – C3alkyl, cycloalkyl, alkoxy, haloalkyl, or Q-haloalkyl wherein Q is O or S. In one embodiment, R⁴ is phenyl or naphthyl optionally substituted with one or more R⁷ substituents independently selected from methyl, trifluoromethyl, hydroxyl, trifluoromethoxy, hydroxyl, fluoro, chloro, isopropyl, cyclopropyl and methylthio.

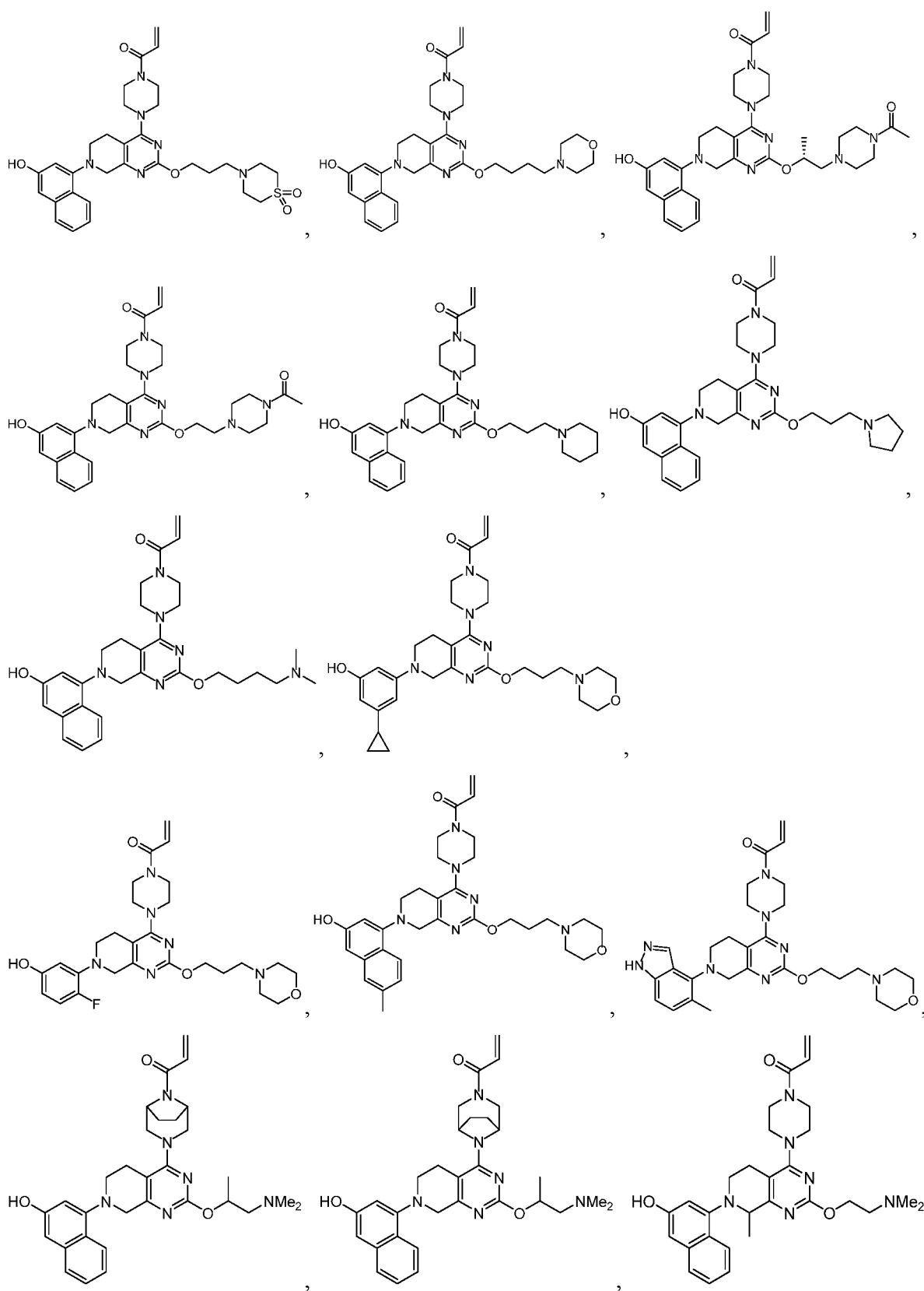
[0136] In one embodiment, R⁴ is isoquinolinyl which is optionally substituted with amino. In one embodiment, R⁴ is aralkyl. In certain embodiments, the aralkyl is benzyl. In one embodiment, the aralkyl is benzyl wherein the alkyl portion is substituted with hydroxyl or hydroxyalkyl.

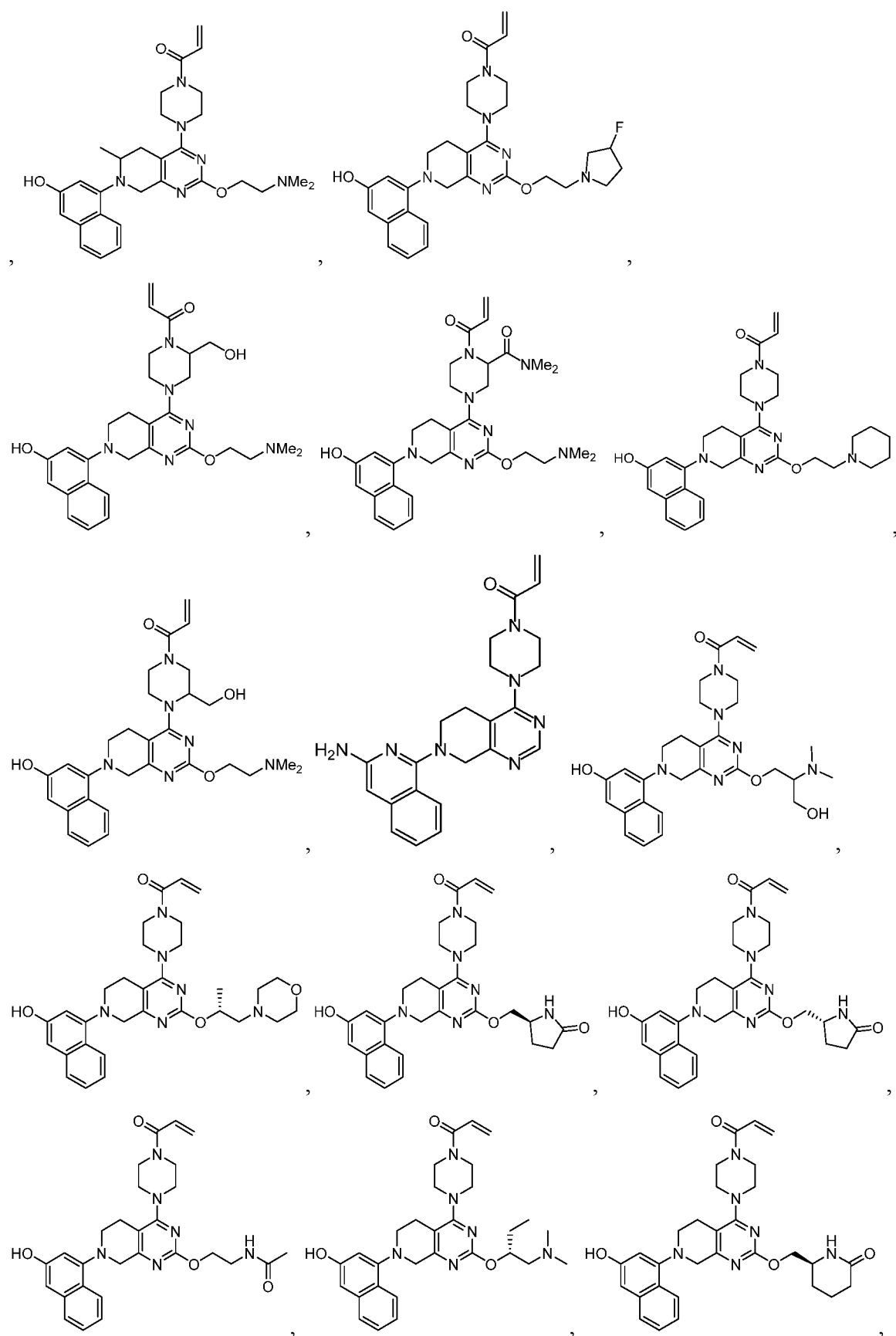
[0137] Nonlimiting examples of compounds of Formula (I), Formula I-A and Formula I-B are selected from the group consisting of:

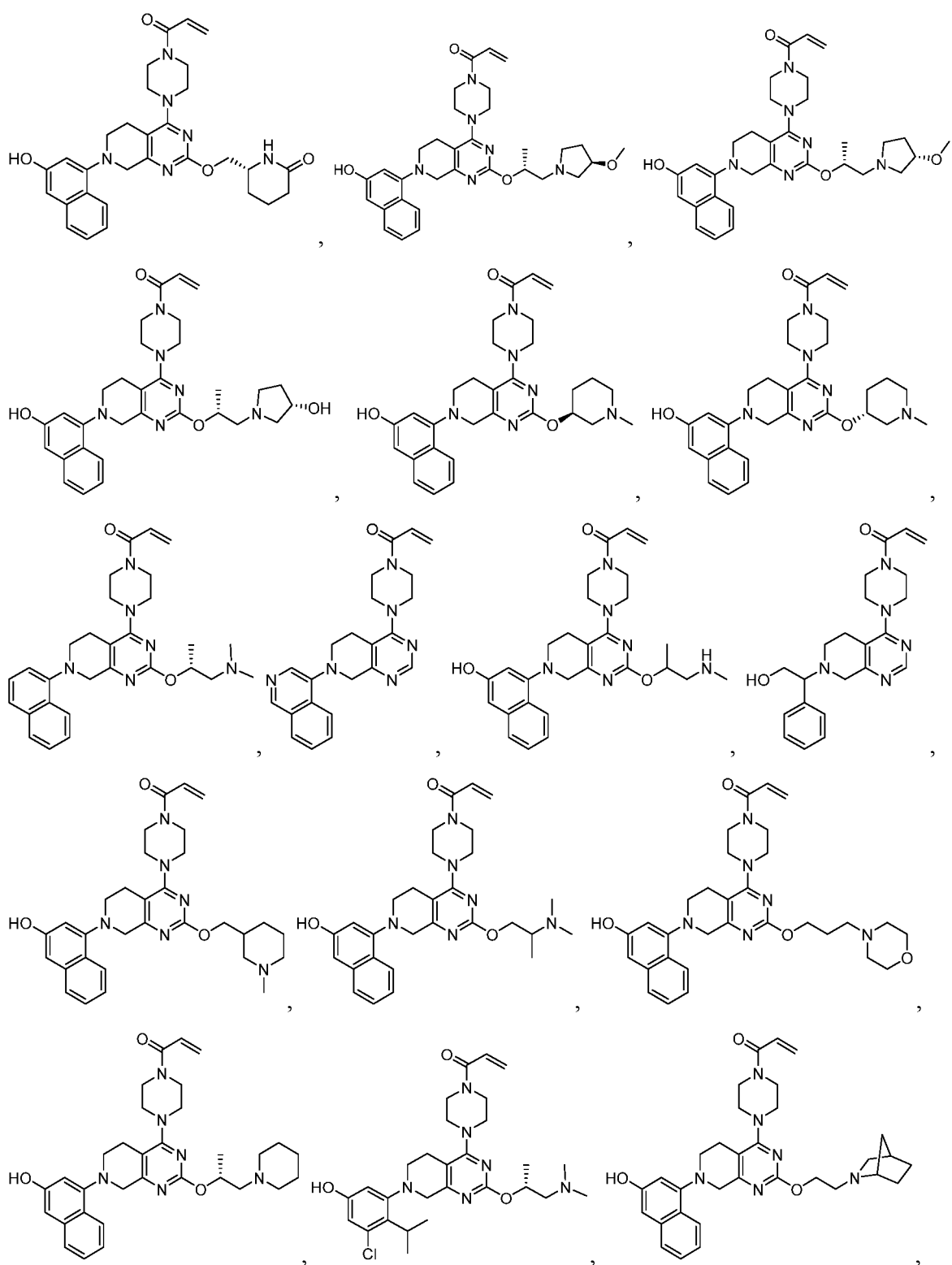


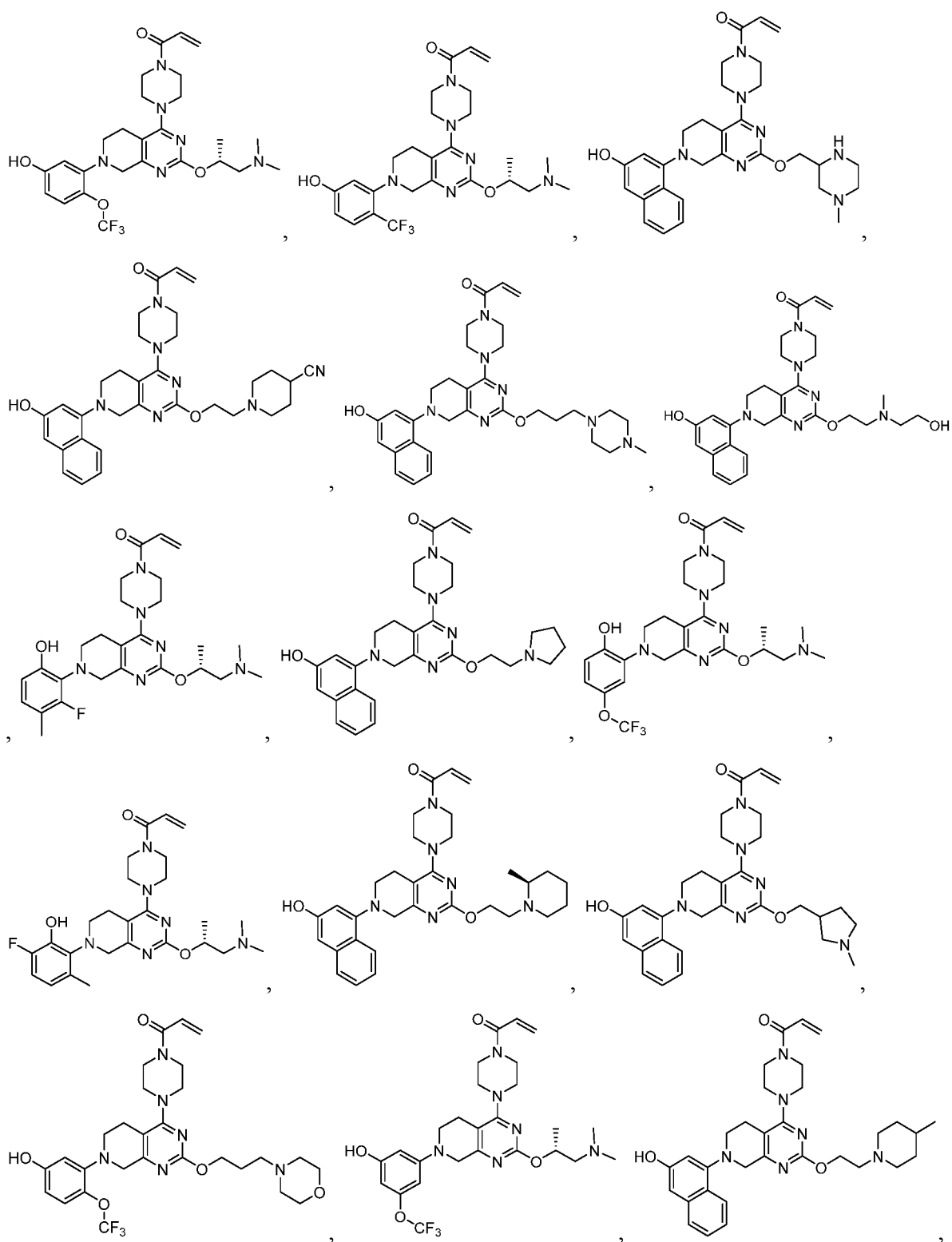


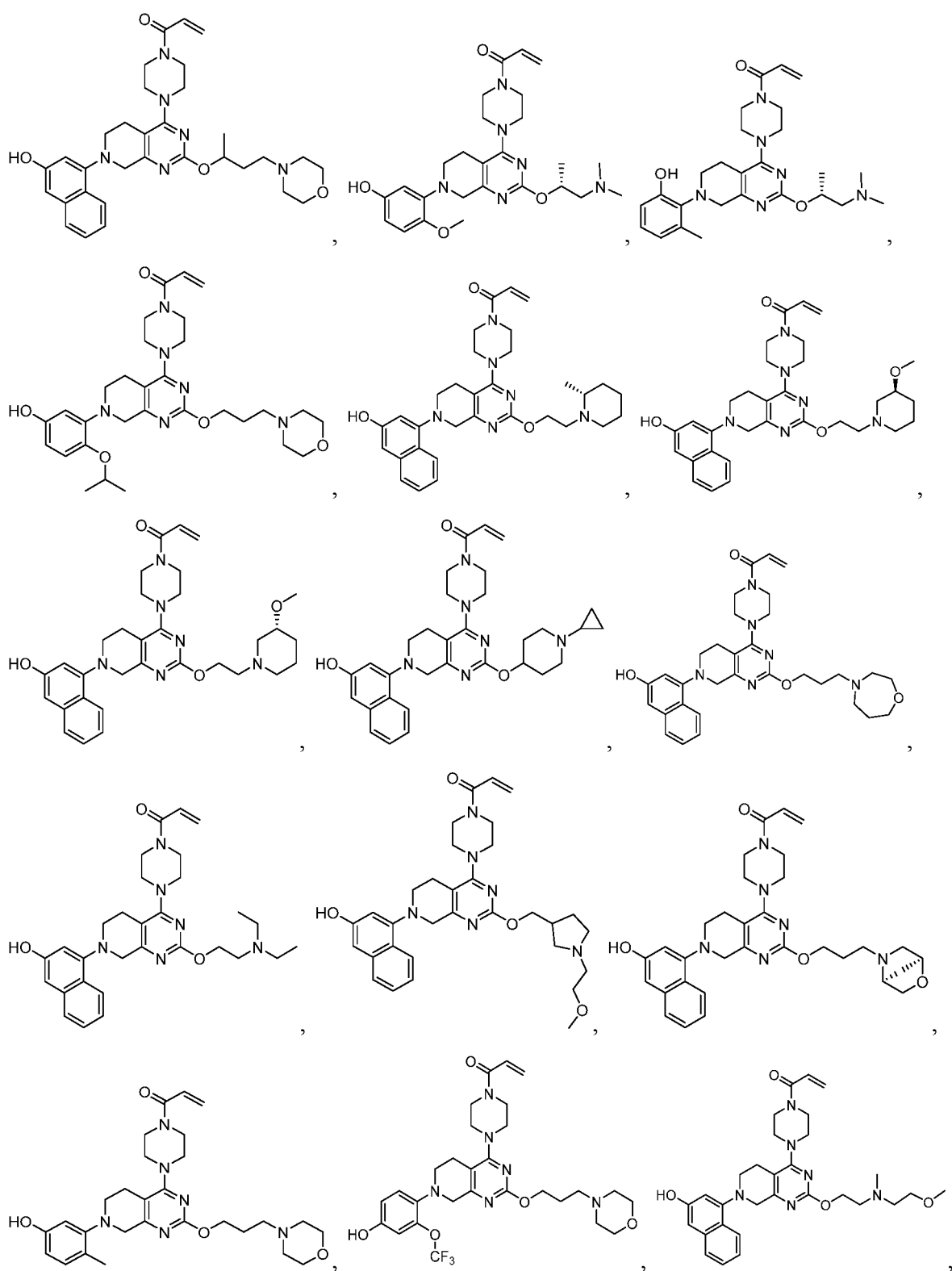


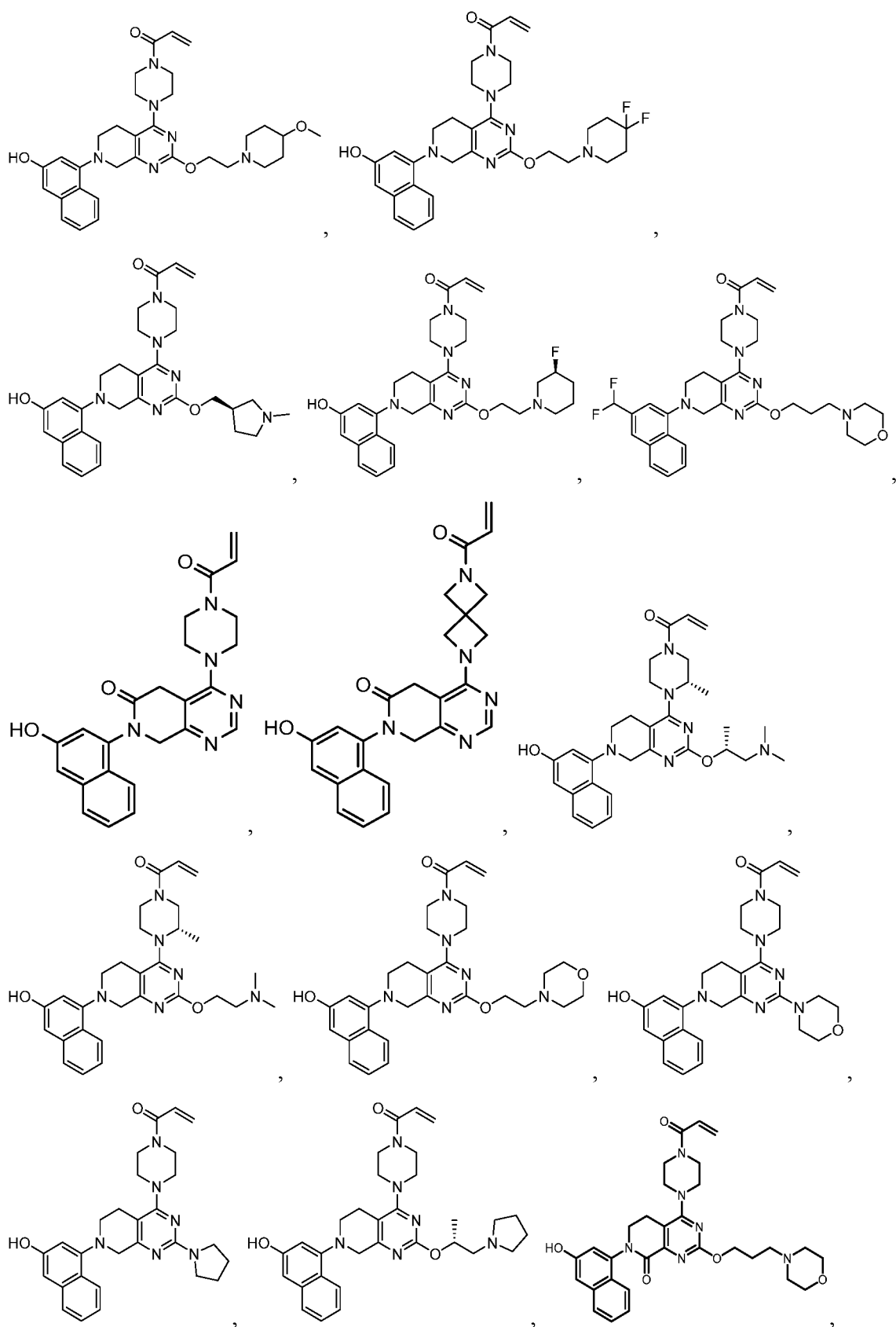


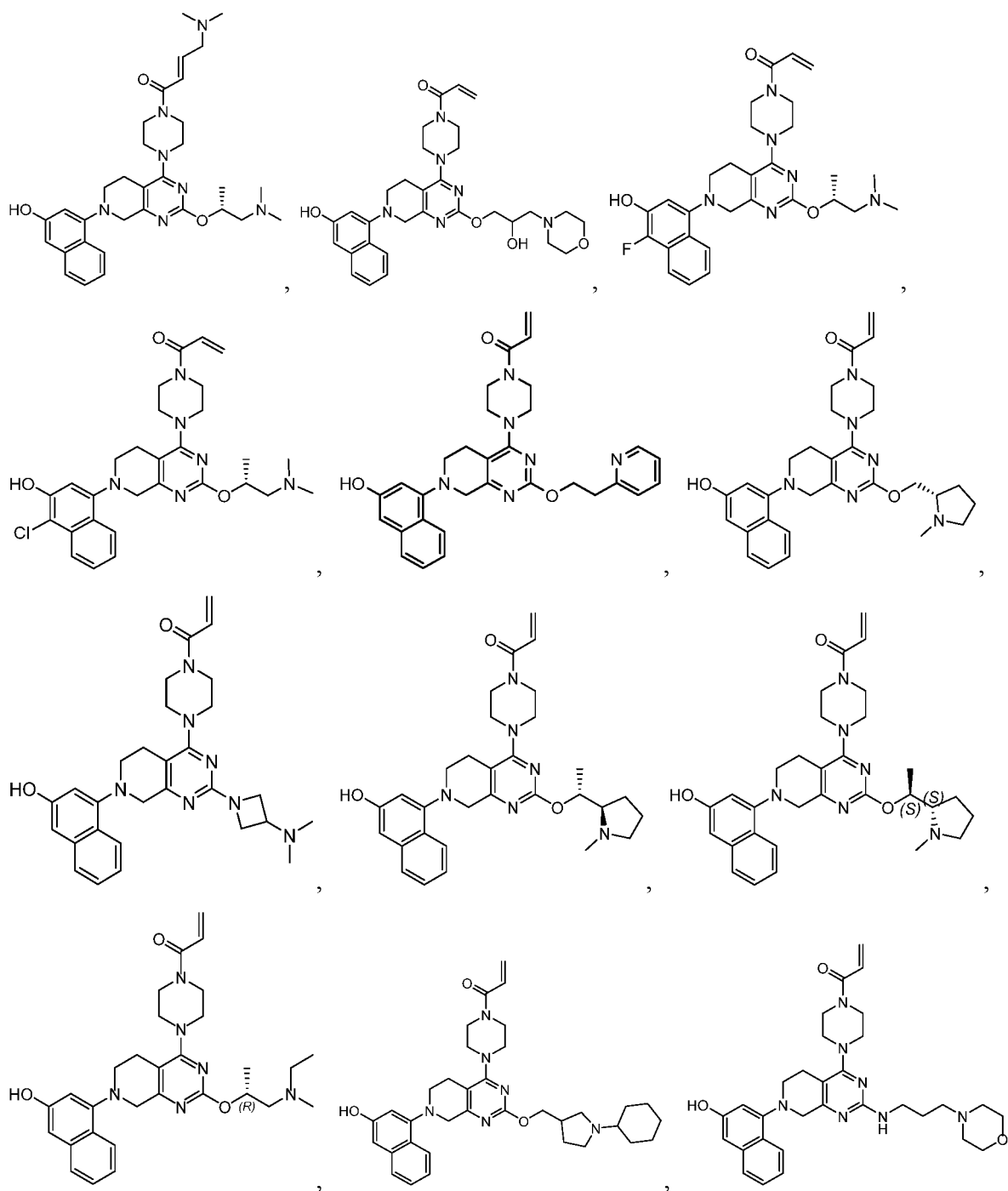


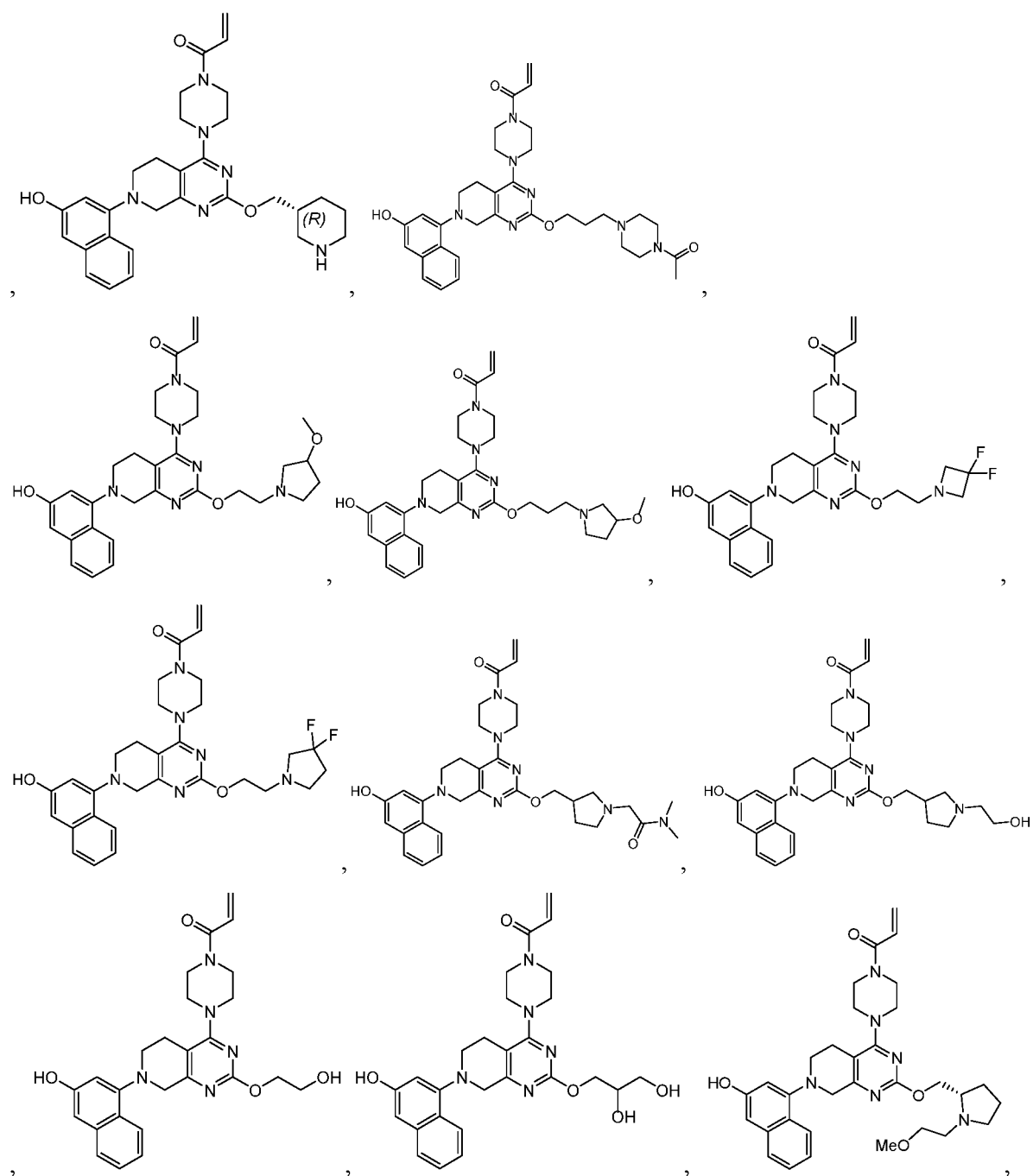


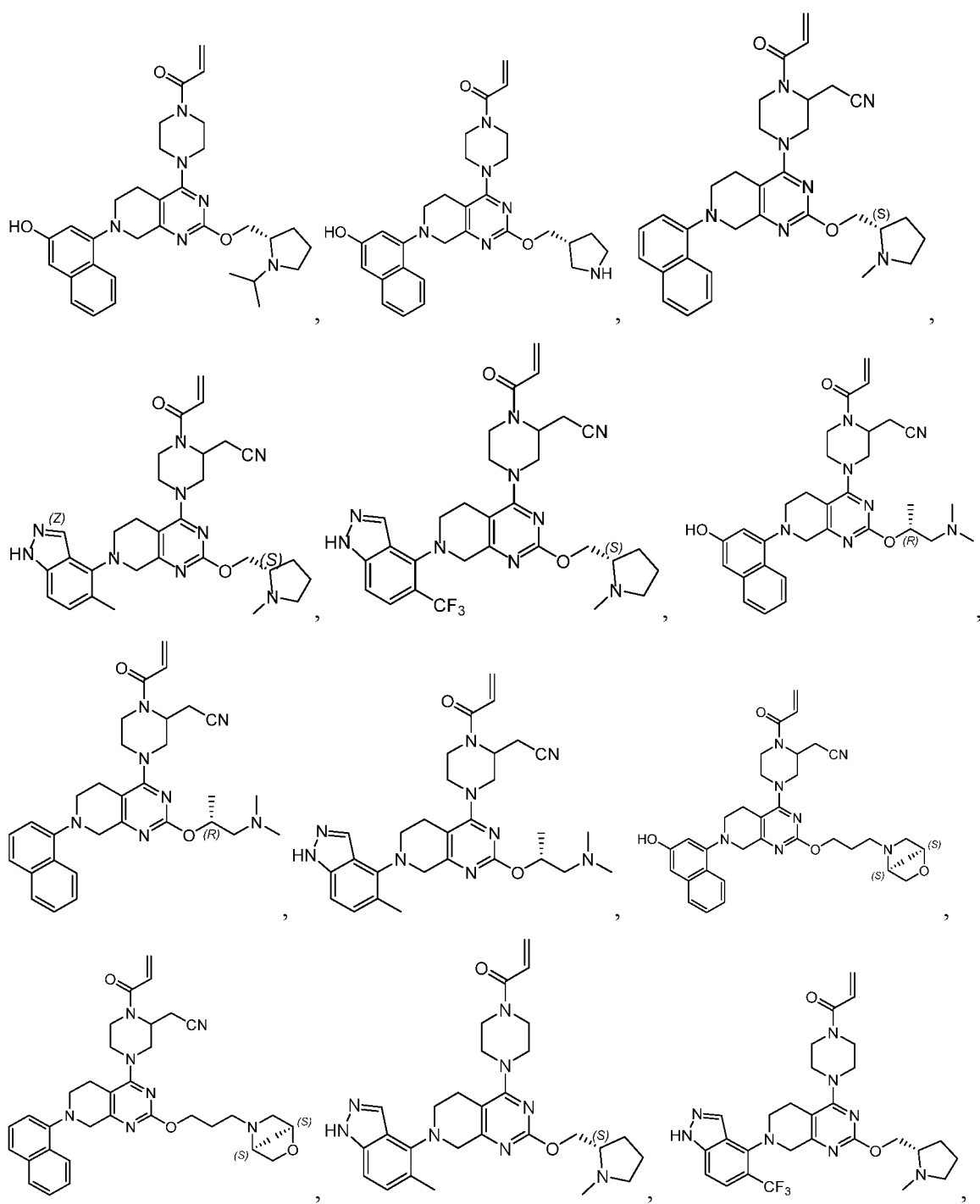


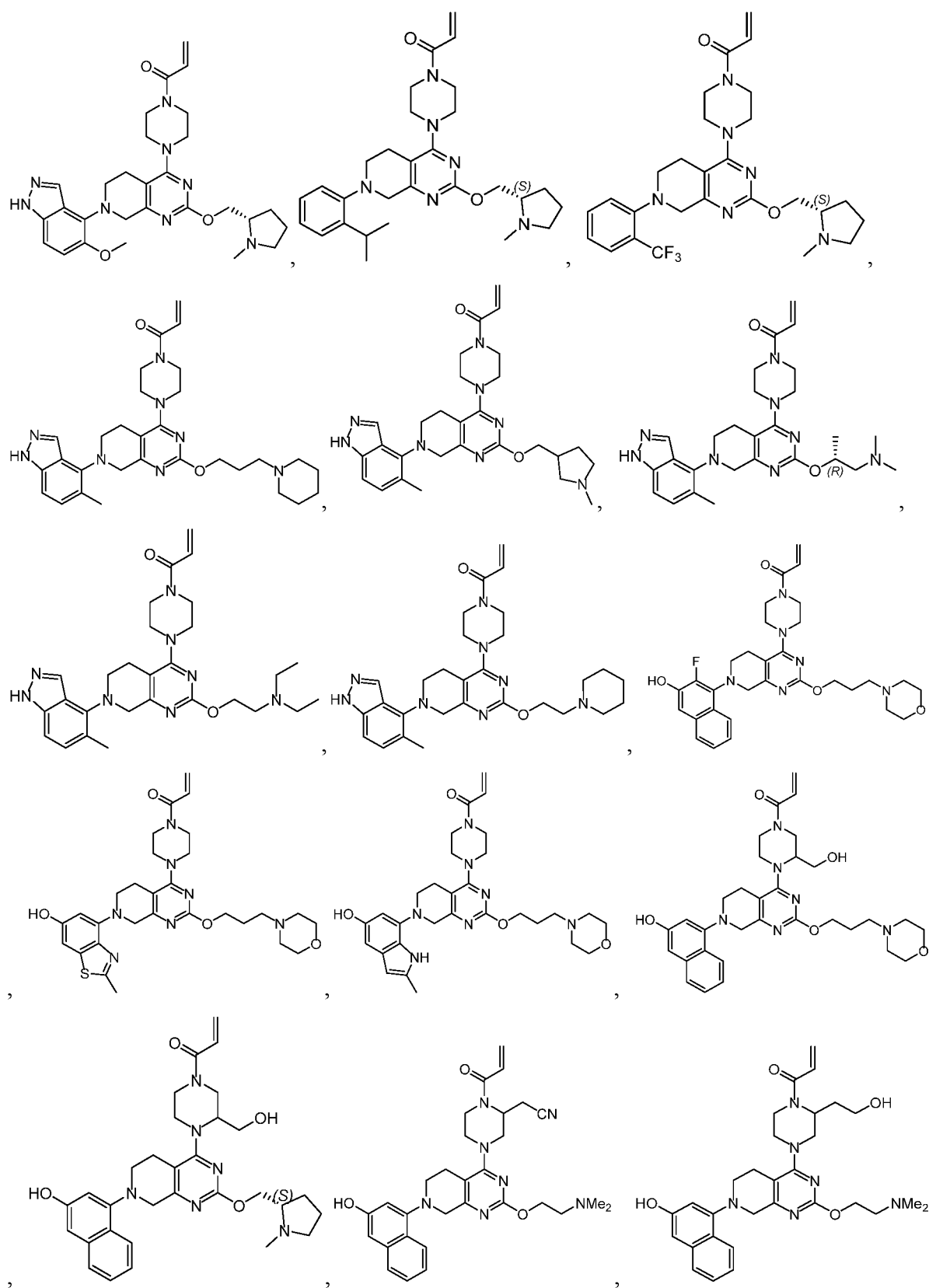


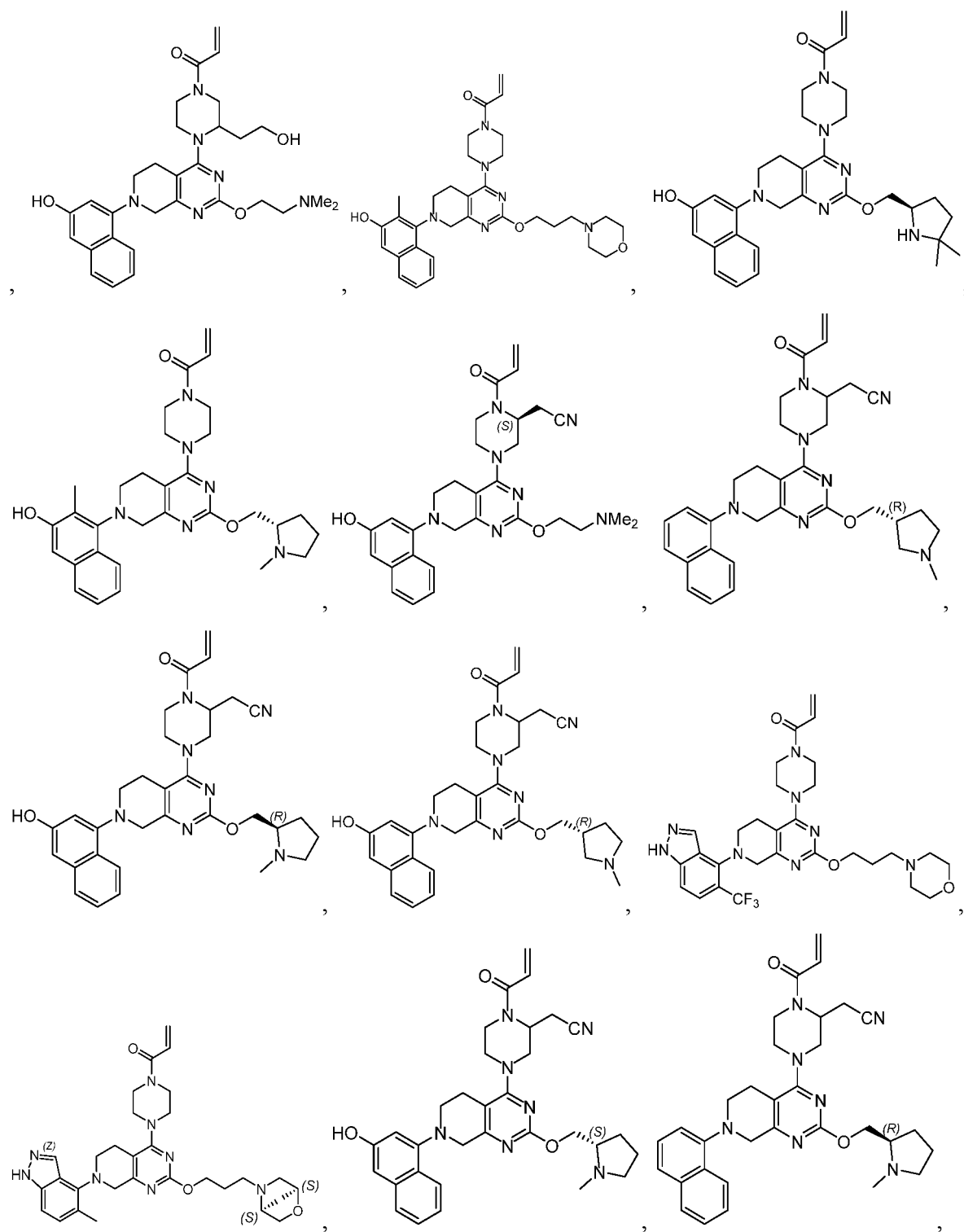


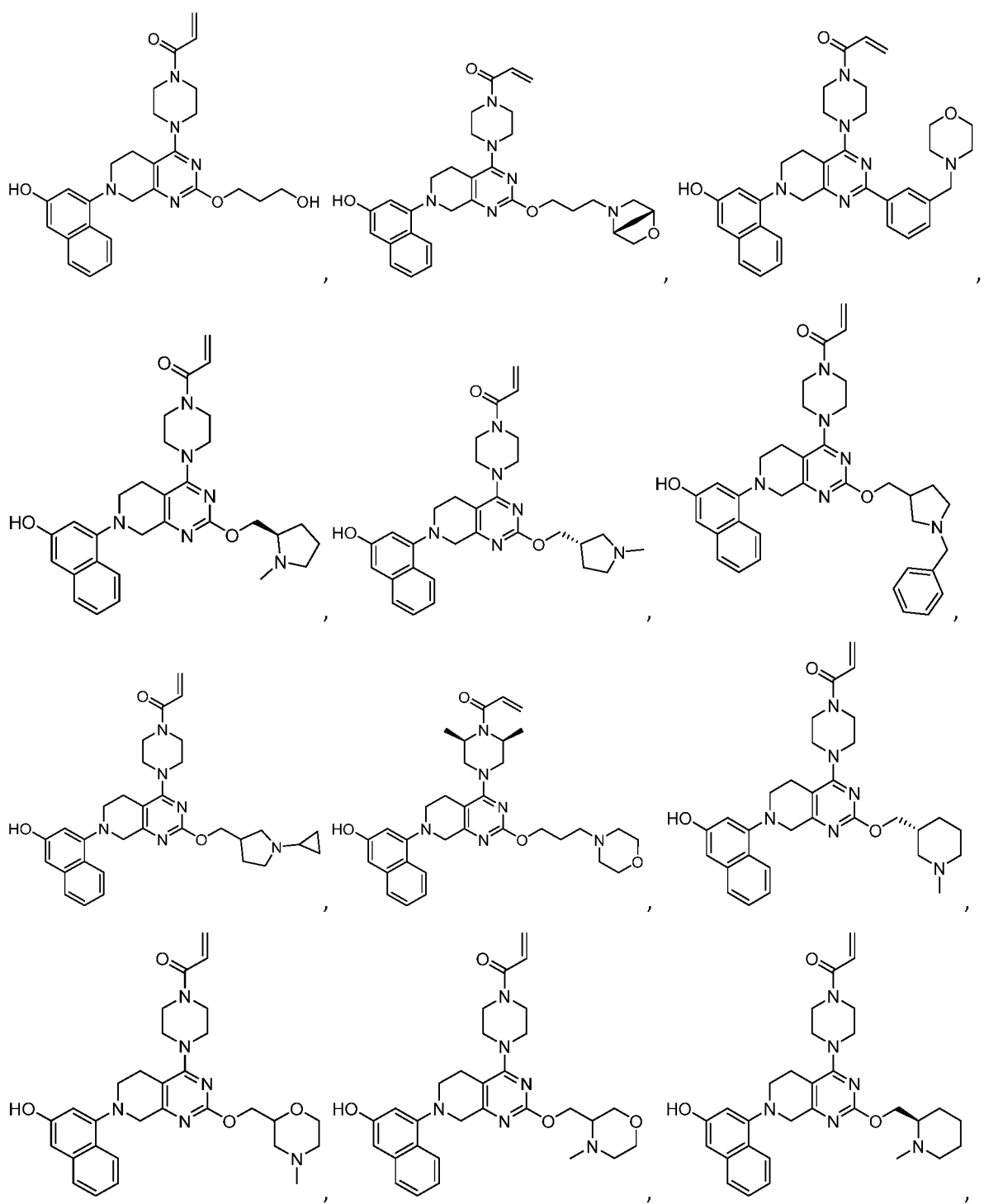


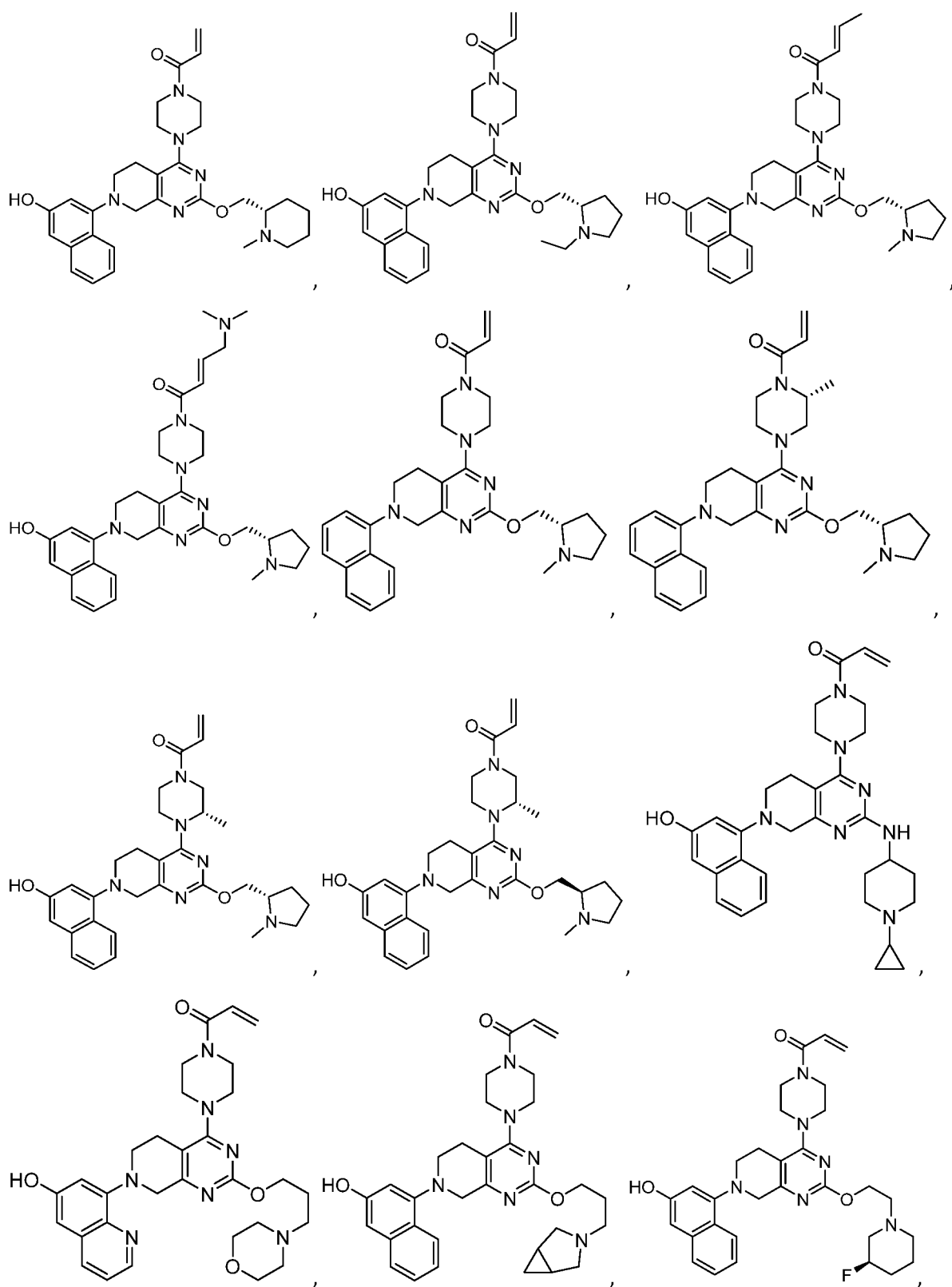


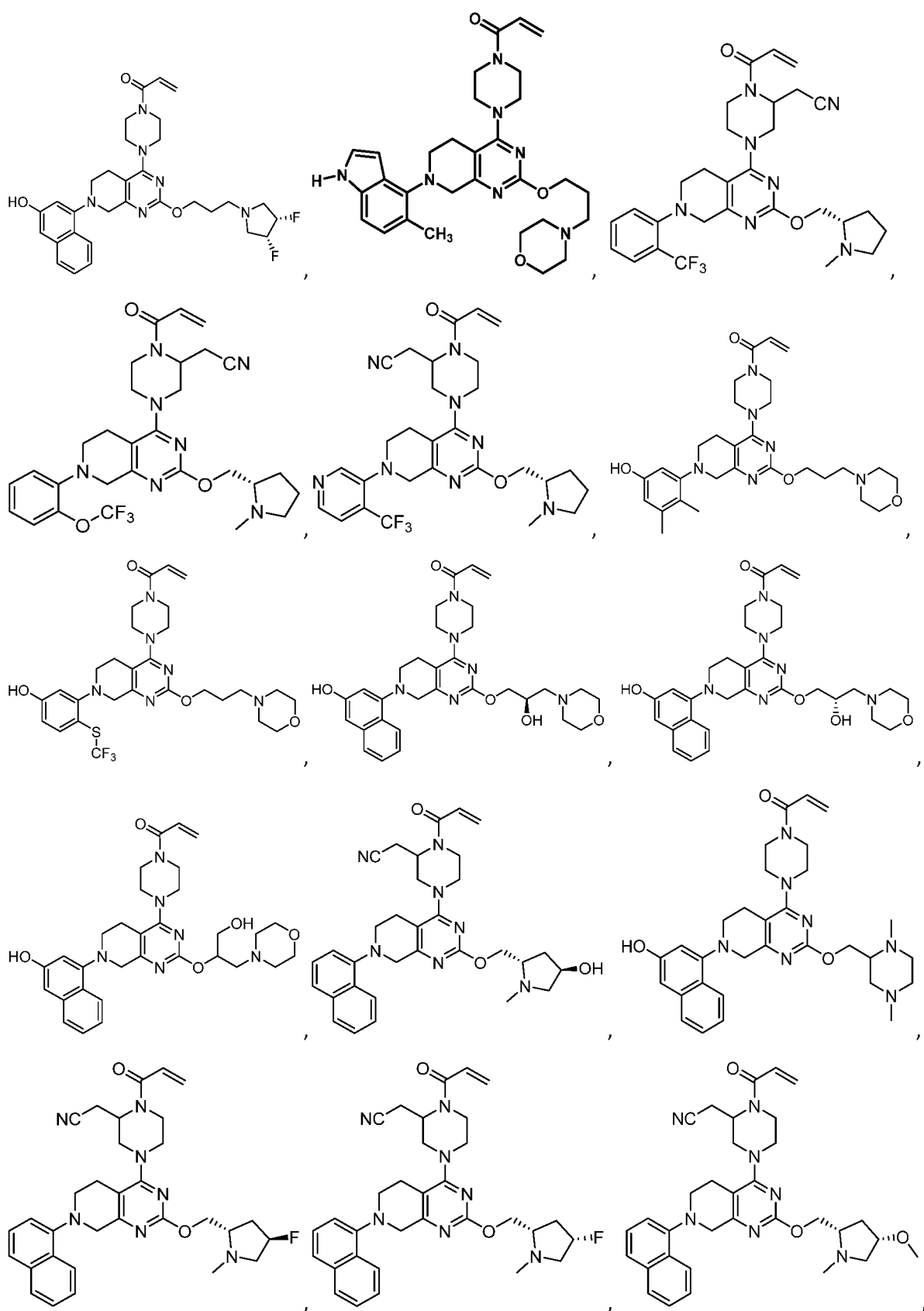


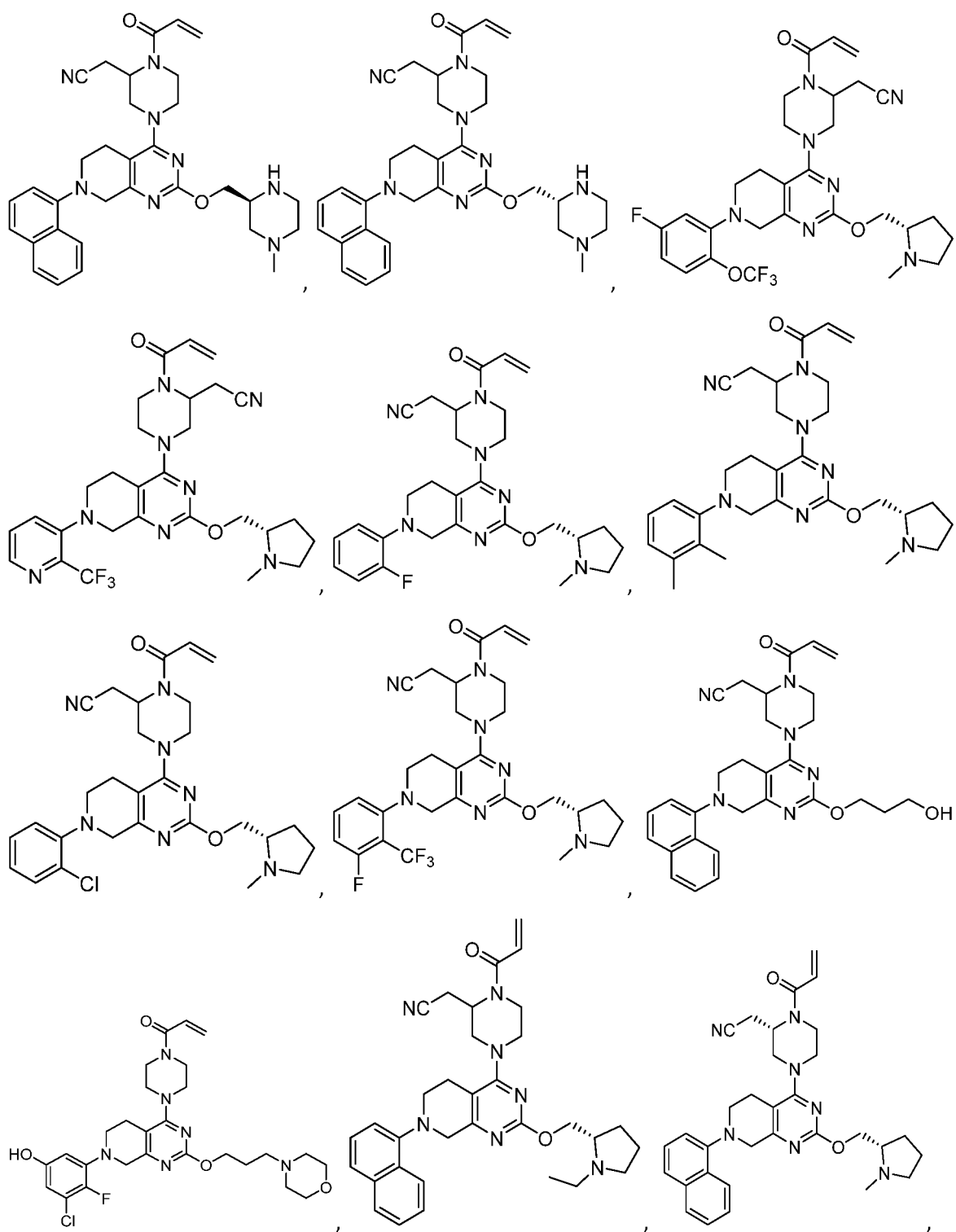


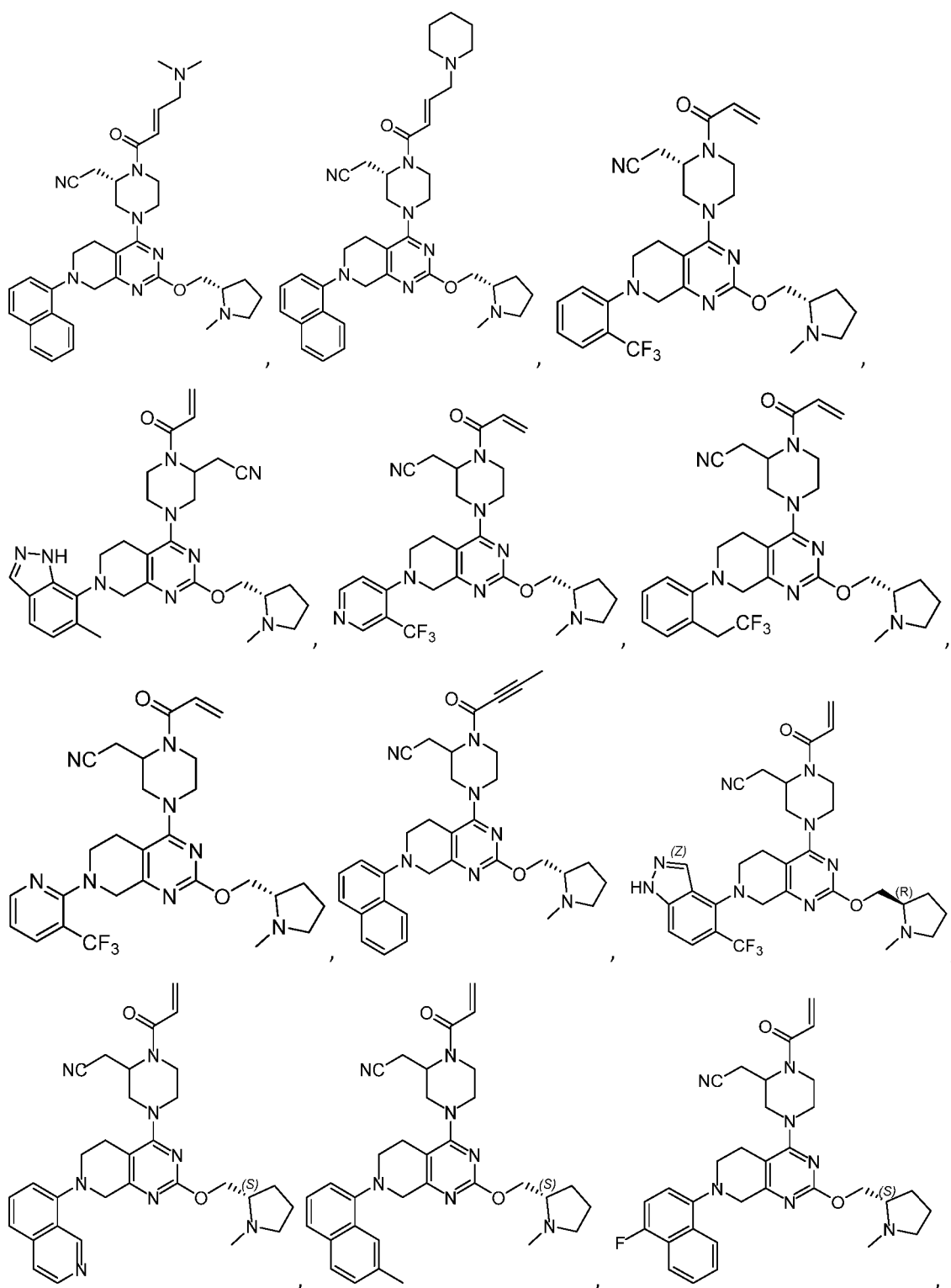


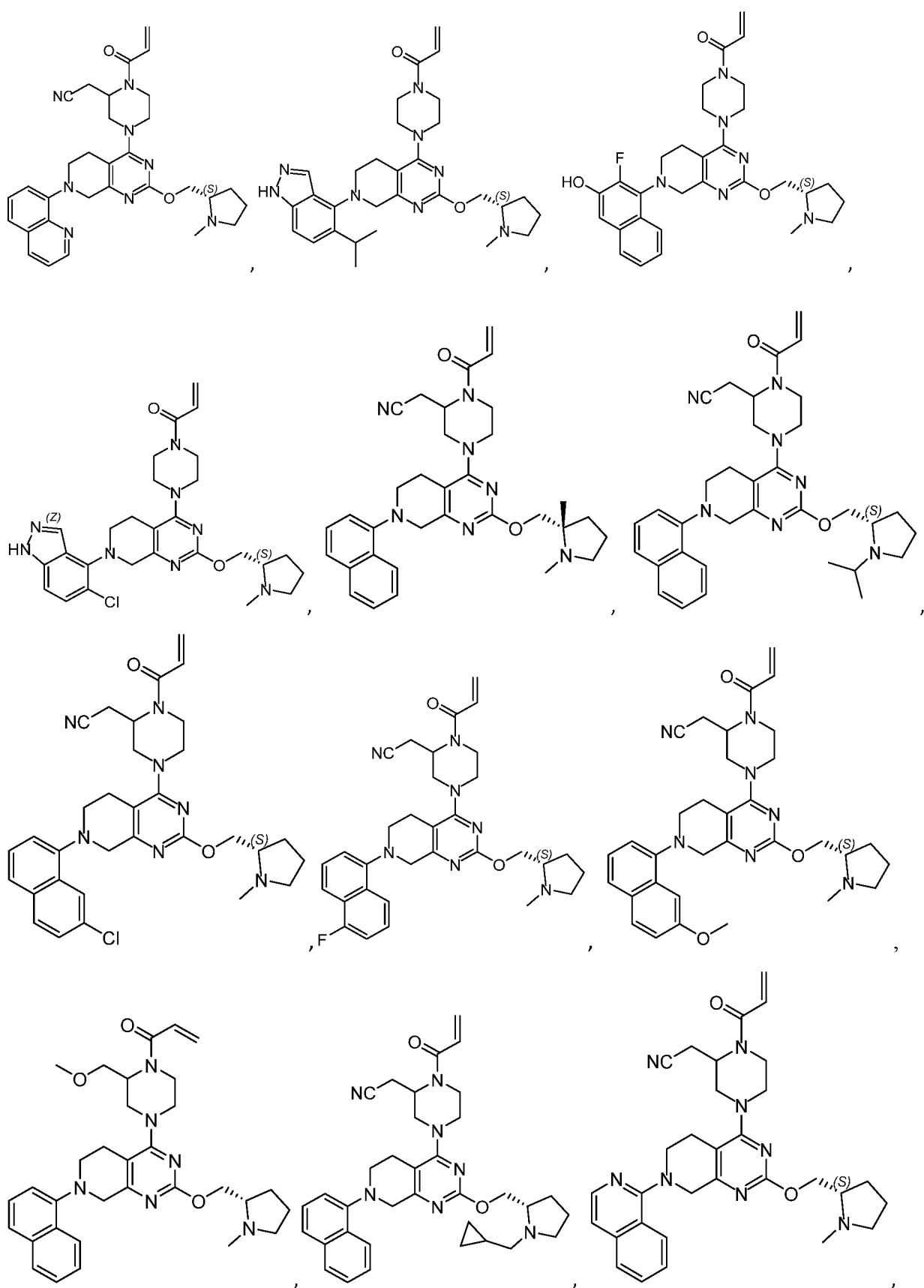


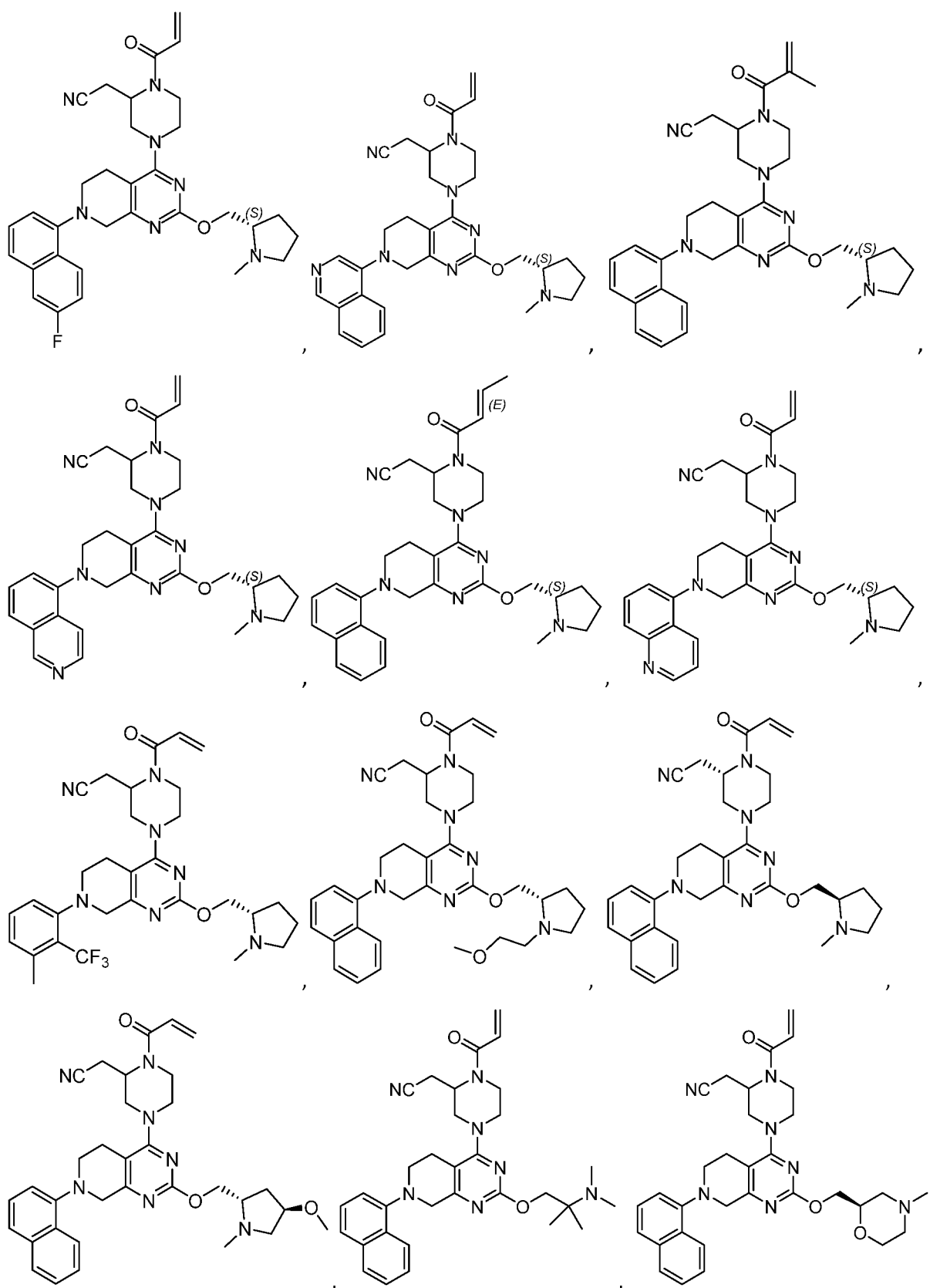


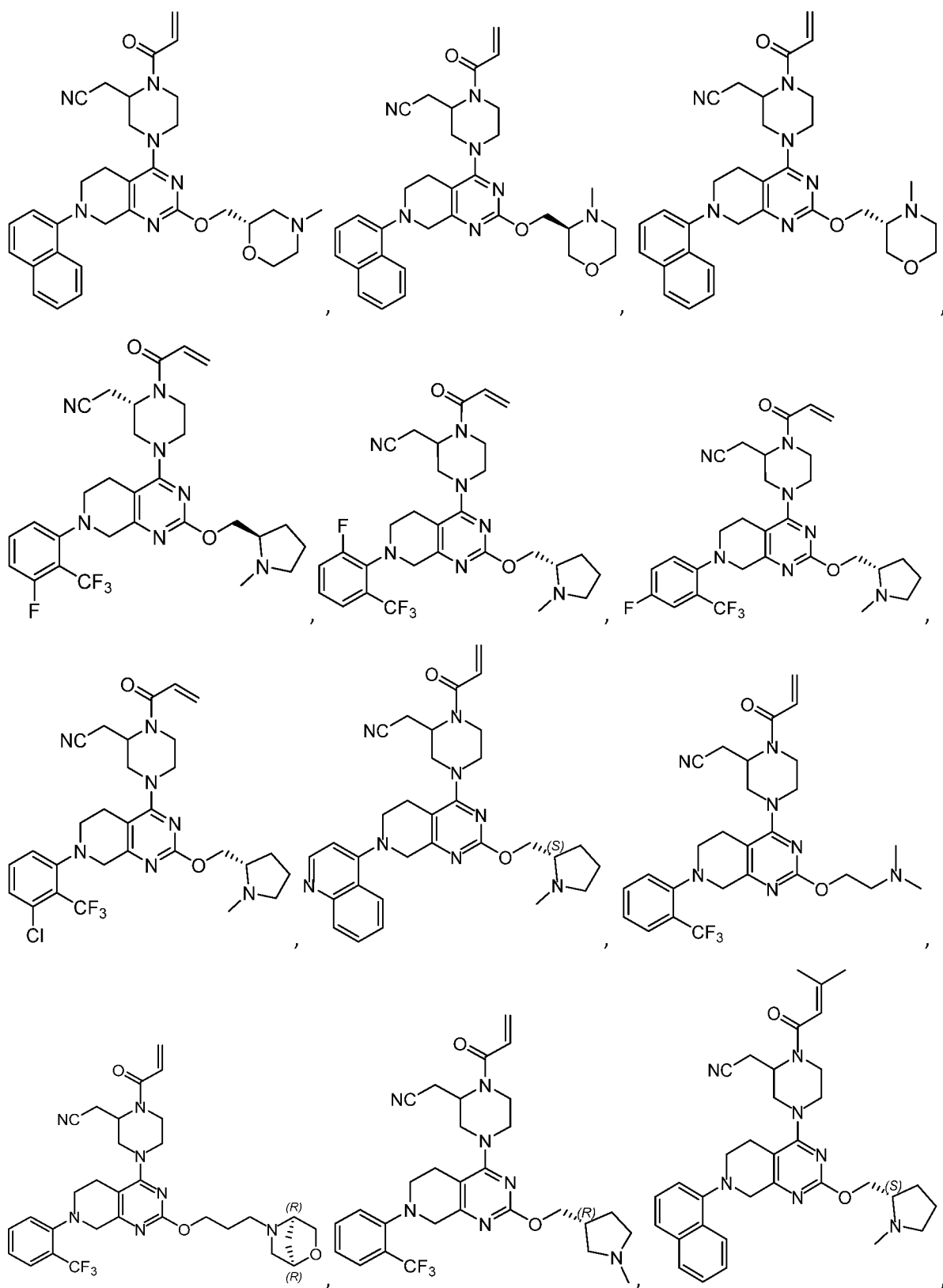


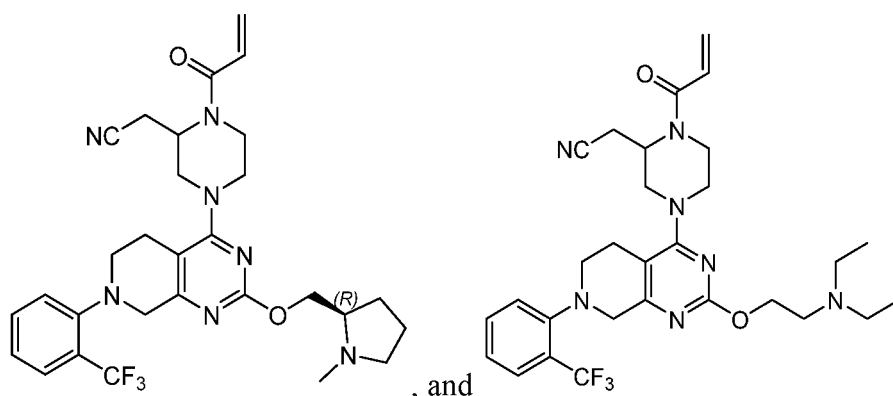












[0138] and pharmaceutically acceptable salts thereof. In one embodiment, the compounds of Formula I include trifluoroacetic acid salts of the above compounds. The compounds of Formula (I), Formula I-A, or Formula I-B may be formulated into pharmaceutical compositions.

PHARMACEUTICAL COMPOSITIONS

[0139] In another aspect, the invention provides pharmaceutical compositions comprising a KRas G12C inhibitor according to the invention and a pharmaceutically acceptable carrier, excipient, or diluent. Compounds of the invention may be formulated by any method well known in the art and may be prepared for administration by any route, including, without limitation, parenteral, oral, sublingual, transdermal, topical, intranasal, intratracheal, or intrarectal. In certain embodiments, compounds of the invention are administered intravenously in a hospital setting. In one embodiment, administration may be by the oral route.

[0140] The characteristics of the carrier will depend on the route of administration. As used herein, the term "pharmaceutically acceptable" means a non-toxic material that is compatible with a biological system such as a cell, cell culture, tissue, or organism, and that does not interfere with the effectiveness of the biological activity of the active ingredient(s). Thus, compositions according to the invention may contain, in addition to the inhibitor, diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The preparation of pharmaceutically acceptable formulations is described in, e.g., Remington's Pharmaceutical Sciences, 18th Edition, ed. A. Gennaro, Mack Publishing Co., Easton, Pa., 1990.

[0141] As used herein, the term pharmaceutically acceptable salt refers to salts that retain the desired biological activity of the above-identified compounds and exhibit minimal or no undesired toxicological effects. Examples of such salts include, but are not limited to acid addition salts formed with inorganic acids (for example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and the like), and salts formed with organic acids such as acetic acid, oxalic acid, tartaric acid, succinic acid, malic acid, ascorbic acid, benzoic acid, tannic acid, pamoic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid, naphthalenedisulfonic acid, and polygalacturonic acid. The compounds can also be administered as pharmaceutically acceptable quaternary salts known by those skilled in the art, which specifically include the quaternary ammonium salt of the formula $--NR^+Z^-$, wherein R is hydrogen, alkyl, or benzyl, and Z is a counterion, including chloride, bromide, iodide, $--O$ -alkyl, toluenesulfonate, methylsulfonate, sulfonate, phosphate, or carboxylate (such as benzoate, succinate, acetate, glycolate, maleate, malate, citrate, tartrate, ascorbate, benzoate, cinnamate, mandelate, benzyloate, and diphenylacetate).

[0142] The active compound is included in the pharmaceutically acceptable carrier or diluent in an amount sufficient to deliver to a patient a therapeutically effective amount without causing serious toxic effects in the patient treated. In one embodiment, a dose of the active compound for all of the above-mentioned conditions is in the range from about 0.01 to 300 mg/kg, for example 0.1 to 100 mg/kg per day, and as a further example 0.5 to about 25 mg per kilogram body weight of the recipient per day. A typical topical dosage will range from 0.01-3% wt/wt in a suitable carrier. The effective dosage range of the pharmaceutically acceptable derivatives can be calculated based on the weight of the parent compound to be delivered. If the derivative exhibits activity in itself, the effective dosage can be estimated as above using the weight of the derivative, or by other means known to those skilled in the art.

[0143] The pharmaceutical compositions comprising compounds of the present invention may be used in the methods of use described herein.

METHODS OF USE

[0144] In yet another aspect, the invention provides for methods for inhibiting KRas G12C activity in a cell, comprising contacting the cell in which inhibition of KRas G12C activity is

desired with an effective amount of a compound of Formula (I), Formula I-A, or Formula I-B, pharmaceutically acceptable salts thereof or pharmaceutical compositions containing the compound or pharmaceutically acceptable salt thereof. In one embodiment, the contacting is in vitro. In one embodiment, the contacting is in vivo.

[0145] As used herein, the term "contacting" refers to the bringing together of indicated moieties in an in vitro system or an in vivo system. For example, "contacting" a KRas G12C with a compound provided herein includes the administration of a compound provided herein to an individual or patient, such as a human, having KRas G12C, as well as, for example, introducing a compound provided herein into a sample containing a cellular or purified preparation containing the KRas G12C.

[0146] In one embodiment, a cell in which inhibition of KRas G12C activity is desired is contacted with an effective amount of a compound of Formula (I), Formula I-A, or Formula I-B, to negatively modulate the activity of KRas G12C. In other embodiments, a therapeutically effective amount of pharmaceutically acceptable salt or pharmaceutical compositions containing the compound of Formula (I), Formula I-A, or Formula I-B, may be used.

[0147] By negatively modulating the activity of KRas G12C, the methods described herein are designed to inhibit undesired cellular proliferation resulting from enhanced KRas G12C activity within the cell. The cells may be contacted in a single dose or multiple doses in accordance with a particular treatment regimen to effect the desired negative modulation of KRas G12C. The degree of covalent modification of KRas G12C may be monitored in vitro using well known methods, including those described in Example A below. In addition, the inhibitory activity of exemplary compounds in cells may be monitored, for example, by measuring the inhibition of KRas G12C activity of the amount of phosphorylated ERK, including those described in Example B below, to assess the effectiveness of treatment and dosages may be adjusted accordingly by the attending medical practitioner.

[0148] In another aspect, methods of treating cancer in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a compound of Formula (I), Formula I-A, or Formula I-B, pharmaceutically acceptable salts thereof or pharmaceutical

compositions comprising the compound or pharmaceutically acceptable salts thereof are provided.

[0149] The compositions and methods provided herein may be used for the treatment of a KRas G12C-associated cancer in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a compound of Formula (I), Formula I-A, or Formula I-B, pharmaceutically acceptable salts thereof or pharmaceutical compositions comprising the compound or pharmaceutically acceptable salts thereof are provided. In one embodiment, the KRas G12C-associated cancer is lung cancer.

[0150] The compositions and methods provided herein may be used for the treatment of a wide variety of cancers including tumors such as lung, prostate, breast, brain, skin, cervical carcinomas, testicular carcinomas, etc. More particularly, cancers that may be treated by the compositions and methods of the invention include, but are not limited to tumor types such as astrocytic, breast, cervical, colorectal, endometrial, esophageal, gastric, head and neck, hepatocellular, laryngeal, lung, oral, ovarian, prostate and thyroid carcinomas and sarcomas. More specifically, these compounds can be used to treat: Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor (nephroblastoma), lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma,

hepatocellular adenoma, hemangioma; Biliary tract: gall bladder carcinoma, ampullary carcinoma, cholangiocarcinoma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochondroma (osteochondrogenous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma (pinealoma), glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma (serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma), granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia (acute and chronic), acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma (malignant lymphoma); Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and Adrenal glands: neuroblastoma. In certain embodiments, the cancer is non-small cell lung cancer.

[0151] The concentration and route of administration to the patient will vary depending on the cancer to be treated. The compounds, pharmaceutically acceptable salts thereof and pharmaceutical compositions comprising such compounds and salts also may be co-administered with other anti-neoplastic compounds, e.g., chemotherapy, or used in combination with other treatments, such as radiation or surgical intervention, either as an adjuvant prior to surgery or post-operatively.

[0152] Also provided herein is a compound of Formula (I), Formula I-A, or Formula I-B, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition thereof as defined herein for use in therapy.

[0153] Also provided herein is a compound of Formula (I), Formula I-A, or Formula I-B, or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition thereof as defined herein for use in the treatment of cancer.

[0154] Also provided herein is a compound of Formula (I), Formula I-A, or Formula I-B, or a pharmaceutically acceptable salt or solvate thereof for use in the inhibition of KRas G12C.

[0155] Also provided herein is a compound of Formula (I), Formula I-A, or Formula I-B, or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition thereof as defined herein, for use in the treatment of a KRas G12C-associated disease or disorder.

[0156] Also provided herein is the use of a compound of Formula (I), Formula I-A, or Formula I-B, or a pharmaceutically acceptable salt or solvate thereof, as defined herein in the manufacture of a medicament for the treatment of cancer.

[0157] Also provided herein is a use of a compound of Formula (I), Formula I-A, or Formula I-B, or a pharmaceutically acceptable salt or solvate thereof, as defined herein in the manufacture of a medicament for the inhibition of activity of KRas G12C.

[0158] Also provided herein is the use of a compound of Formula (I), Formula I-A, or Formula I-B, or a pharmaceutically acceptable salt or solvate thereof, as defined herein, in the manufacture of a medicament for the treatment of a KRas G12C-associated disease or disorder.

[0159] Also provided herein is a method for treating cancer in a patient in need thereof, the method comprising (a) determining that cancer is associated with a KRas G12C mutation (e.g., a KRas G12C-associated cancer) (e.g., as determined using a regulatory agency-approved, e.g., FDA-approved, assay or kit); and (b) administering to the patient a therapeutically effective amount of a compound of Formula (I), Formula I-A, or Formula I-B, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof.

[0160] One skilled in the art will recognize that, both in vivo and in vitro trials using suitable, known and generally accepted cell and/or animal models are predictive of the ability of a test compound to treat or prevent a given disorder.

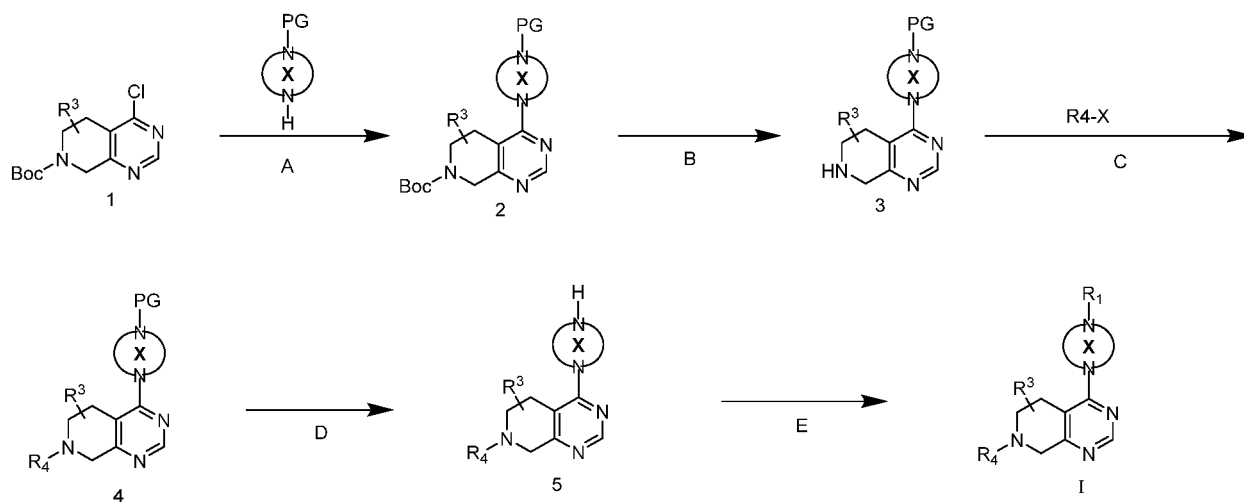
[0161] One skilled in the art will further recognize that human clinical trials including first-in-human, dose ranging and efficacy trials, in healthy patients and/or those suffering from a given disorder, may be completed according to methods well known in the clinical and medical arts.

REACTION SCHEMES AND EXAMPLES

[0162] The compounds of the present invention may be prepared from commercially available reagents using the synthetic methods and reaction schemes described herein, or using other reagents and conventional methods well known to those skilled in the art.

[0163] For instance, compounds of the present invention may be prepared according to the General Reaction Schemes I and II.

GENERAL REACTION SCHEMES

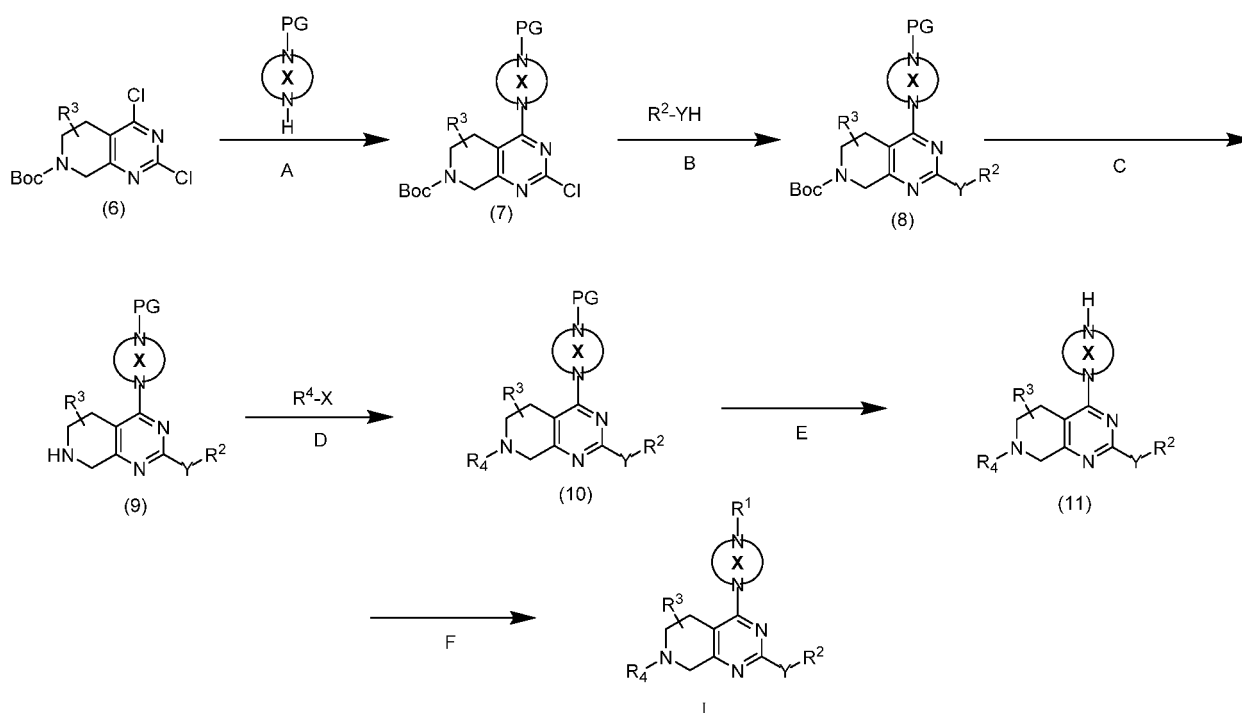


SCHEME I

[0164] Compounds of Formula I wherein L and Y are bonds, R² is hydrogen and R⁴ is aryl or heteroaryl can be prepared according to Scheme I. In step A, an appropriately functionalized dihydropyridopyrimidine (1) is coupled to a heterocycle containing one nucleophilic amine species, with the other bound to a protecting group to provide compound (2). This coupling

proceeds in a solvent such as dichloromethane in the presence of a base such as triethylamine or Hunig's base. In step B, the Boc group of compound (2) is removed using conditions known in the art, for example with trifluoroacetic acid in a solvent such as dichloromethane, to provide compound (3). In step C, the substituent R^4 is introduced with a palladium coupling, using a suitable functionalized aryl or heteroaryl system, for example an aryl triflate, in the presence of a palladium catalyst such as Pd_2DBA_3 /Xantphos in a solvent such as toluene with a base such as sodium tert-butoxide to provide compound (4). In step D, the protecting group of ring X compound (4) is removed, for example hydrogenolysis by Pd/C in the presence of H_2 in a polar solvent such as EtOH/THF to provide compound (5). In the final step, E, R^1 is introduced to provide a compound of Formula I, for example by treating with an acid chloride having the formula $Cl-C(O)C(R^A) \text{---} C(R^B)_p$ or $Cl-SO_2C(R^A) \text{---} C(R^B)_p$, or an anhydride having the formula $C(R^B)_p \text{---} C(R^A)C(O)OC(O)C(R^A) \text{---} C(R^B)_p$, where R^A , R^B and p are as defined for Formula I. For example, in the case where R^1 is an acryloyl group, this reaction proceeds, for example, in a solvent such as methylene chloride in the presence of acryloyl chloride or an acryloyl anhydride and a base such as Hunig's base. In some cases, the species R^4 will also contain a protecting group, which can be removed at a subsequent step in the synthetic sequence.

[0165] Compounds (1), (2), (3), (4) and (5) as shown and described above for Scheme 1 are useful as intermediates for preparing compounds of Formula I and are provided as further aspects of the invention.



SCHEME II

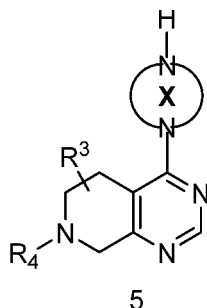
[0166] Compounds of Formula I wherein L is a bond, $-Y-R^2$ is other than hydrogen and R^4 is aryl or heteroaryl can be prepared according to Scheme II. In step A, an appropriately functionalized dihydropyridopyrimidine (6) is coupled to a heterocycle containing one nucleophilic amine species, with the other bound to a protecting group to provide compound (7). This coupling proceeds in a solvent such as dichloromethane in the presence of a base such as triethylamine or Hunig's base. In step B, the substituent $-Y-R^2$ is introduced by substitution of the chlorine by a nucleophile, for example (S)-1-(dimethylamino-propan-2-ol in a polar solvent such as dioxane to provide compound (8). In step C, the Boc group is removed using conditions known in the art, for example with trifluoroacetic acid in a solvent such as dichloromethane to provide compound (9). In step D, the substituent R^4 is introduced with a palladium coupling, using a suitable functionalized aryl or heteroaryl system, for example an aryl triflate, in the presence of a palladium catalyst such as $Pd_2DBA_3/BINAP$ in a solvent such as toluene with a base such as sodium tert-butoxide to provide compound (10). In step E, the protecting group of ring X is removed, for example hydrogenolysis by Pd/C in the presence of H_2 in a polar solvent such as EtOH/THF to provide compound (11). In step F, R^1 is introduced to provide a compound of Formula I, for example by treating with an acid chloride having the

formula $\text{Cl}-\text{C}(\text{O})\text{C}(\text{R}^{\text{A}}) \equiv \text{C}(\text{R}^{\text{B}})_p$ or $\text{Cl}-\text{SO}_2\text{C}(\text{R}^{\text{A}}) \equiv \text{C}(\text{R}^{\text{B}})_p$, or an anhydride having the formula $\text{C}(\text{R}^{\text{B}})_p \equiv \text{C}(\text{R}^{\text{A}})\text{C}(\text{O})\text{OC}(\text{O})\text{C}(\text{R}^{\text{A}}) \equiv \text{C}(\text{R}^{\text{B}})_p$, where R^{A} , R^{B} and p are as defined for Formula I. For example, in the case where R^1 is an acryloyl group, this reaction proceeds, for example, in a solvent such as methylene chloride in the presence of acryloyl chloride acryloyl anhydride and a base such as Hunig's base. In some cases, the species R^4 and R^2 may also contain protecting groups, which can be removed at a subsequent step in the synthetic sequence.

[0167] Compounds (6), (7), (8), (9), (10) and (11) as shown and described above for Scheme 2 are useful as intermediates for preparing compounds of Formula I, Formula I-A or Formula I-B and are provided as further aspects of the invention.

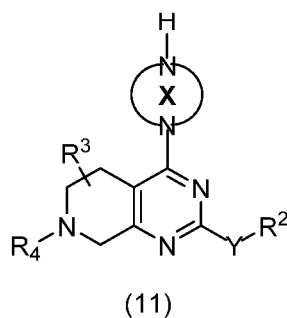
[0168] Accordingly, also provide is a process for preparing a compound of Formula I, comprising:

[0169] (a) for a compound of Formula I where Y is a bond and R^2 is hydrogen, reacting a compound of formula 5



[0170] where X, R^3 and R^4 are as defined for Formula I, with an acid chloride having the formula $\text{Cl}-\text{C}(\text{O})\text{C}(\text{R}^{\text{A}}) \equiv \text{C}(\text{R}^{\text{B}})_p$ or $\text{Cl}-\text{SO}_2\text{C}(\text{R}^{\text{A}}) \equiv \text{C}(\text{R}^{\text{B}})_p$ or an anhydride having the formula $\text{C}(\text{R}^{\text{B}})_p \equiv \text{C}(\text{R}^{\text{A}})\text{C}(\text{O})\text{OC}(\text{O})\text{C}(\text{R}^{\text{A}}) \equiv \text{C}(\text{R}^{\text{B}})_p$, where R^{A} , R^{B} and p are as defined for Formula I, in the presence of a base; or

[0171] (b) for a compound of Formula I wherein L is a bond and $-\text{Y}-\text{R}^2$ is other than hydrogen, reacting a compound of formula (11)



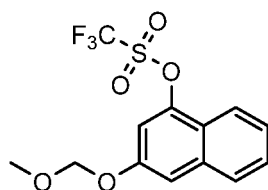
[0172] wherein L is a bond, $-Y-R^2$ is other than hydrogen, and X, R^3 and R^4 are as defined for Formula I, with an acid chloride having the formula $Cl-C(O)C(R^A) \text{---} C(R^B)_p$ or $Cl-SO_2C(R^A) \text{---} C(R^B)_p$, or an anhydride having the formula $C(R^B)_p \text{---} C(R^A)C(O)OC(O)C(R^A) \text{---} C(R^B)_p$, where R^A , R^B and p are as defined for Formula I, in the presence of a base; and

[0173] optionally forming a salt thereof.

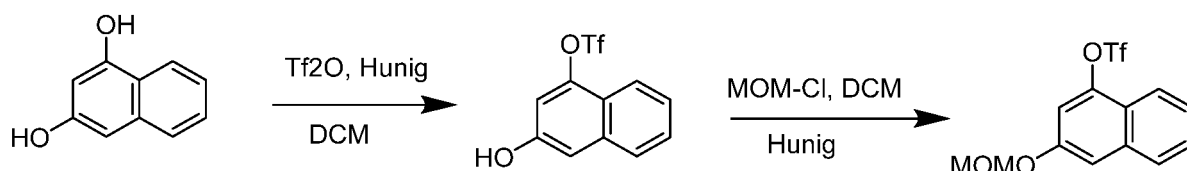
[0174] The compounds of the present invention may have one or more chiral center and may be synthesized as stereoisomeric mixtures, isomers of identical constitution that differ in the arrangement of their atoms in space. The compounds may be used as mixtures or the individual components/isomers may be separated using commercially available reagents and conventional methods for isolation of stereoisomers and enantiomers well-known to those skilled in the art, e.g., using CHIRALPAK® (Sigma-Aldrich) or CHIRALCEL® (Diacel Corp) chiral chromatographic HPLC columns according to the manufacturer's instructions. Alternatively, compounds of the present invention may be synthesized using optically pure, chiral reagents and intermediates to prepare individual isomers or enantiomers. Unless otherwise indicated, all chiral (enantiomeric and diastereomeric) and racemic forms are within the scope of the invention. Unless otherwise indicated, whenever the specification, including the claims, refers to compounds of the invention, the term "compound" is to be understood to encompass all chiral (enantiomeric and diastereomeric) and racemic forms.

[0175] The following Examples are intended to illustrate further certain embodiments of the invention and are not intended to limit the scope of the invention.

Intermediate 1

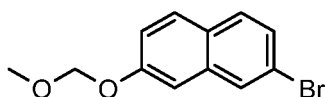


3-(methoxymethoxy)naphthalen-1-yl trifluoromethanesulfonate

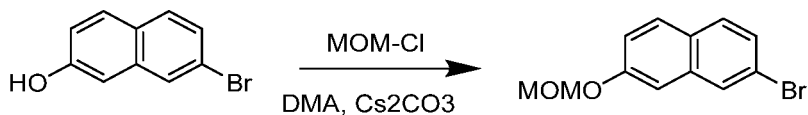


[0176] 3-Hydroxynaphthalen-1-yl trifluoromethanesulfonate (13.101 g, 44.831 mmol) was dissolved in dichloromethane (100 mL) and stirred at 0 °C. To this solution was added chloro(methoxy)methane (3.7456 mL, 49.315 mmol) and Hunig's base (11.745 mL, 67.247 mmol). The reaction was stirred at 0 °C for 4 hrs. The reaction was partitioned with 1M HCl and washed with saturated sodium bicarbonate. The combined organic layers were dried over magnesium sulfate and concentrated under vacuum. The concentrated material was loaded onto a 120 g RediSep® gold silica gel column with dichloromethane and purified by normal phase chromatography (CombiFlash®, 0%-20% ethyl acetate/hexanes as the eluent) to give 3-(methoxymethoxy)naphthalen-1-yl trifluoromethanesulfonate (11.785 g, 35.045 mmol, 78.171 % yield).

Intermediate 2



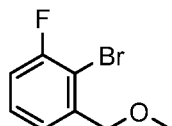
2-bromo-7-(methoxymethoxy)naphthalene



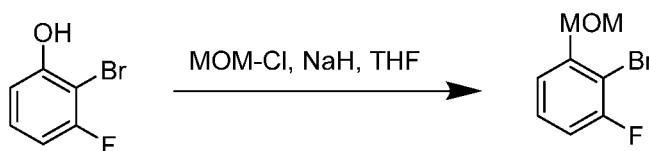
[0177] To a solution of 7-bromonaphthalen-2-ol (2.0 g, 9.0 mmol) in dimethyl acetamide (40 mL) was added chloro(methoxy)methane (1.4 g, 18 mmol) and cesium carbonate (5.8 g, 18 mmol) and the reaction mixture was stirred overnight at room temperature. The reaction was diluted with water and the aqueous layer washed with ethyl acetate. The combined organic

layers were washed with water and brine, dried over magnesium sulfate and concentrated under vacuum. The crude material was purified by normal phase chromatography using 5-50% ethyl acetate/hexanes as the eluent to give 2-bromo-7-(methoxymethoxy)naphthalene (1.0 g, 3.7 mmol, 42 % yield).

Intermediate 3

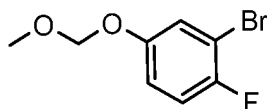


2-bromo-1-fluoro-3-(methoxymethyl)benzene

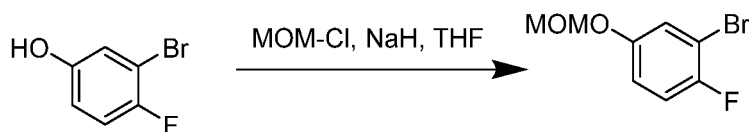


[0178] To a stirred solution of 2-bromo-3-fluorophenol (1422 mg, 7.445 mmol) in 22 mL tetrahydrofuran at room temperature under nitrogen was added NaH (327.6 mg, 8.190 mmol) neat as a solid portion wise. After 15 minutes, a solution had formed. Chloro(methoxy)methane (678.6 μ L, 8.934 mmol) was added by syringe. After stirring for 2 hours, the reaction was quenched with saturated ammonium chloride solution and then partitioned between ethyl acetate (30 mL) and water (30 mL). The combined organic layers were isolated, washed with brine, dried over MgSO_4 , filtered and concentrated. The crude product was loaded in a minimum of dichloromethane onto a 40 gram RediSep® column pre-wet with hexanes and eluted with an ethyl acetate/hexanes gradient (0% to 20% ethyl acetate). Fractions containing the product were combined and concentrated to provide the product as a clear oil (1.45g, 83%).

Intermediate 4

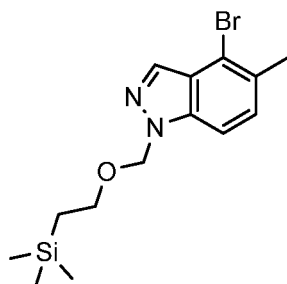


2-bromo-1-fluoro-4-(methoxymethoxy)benzene

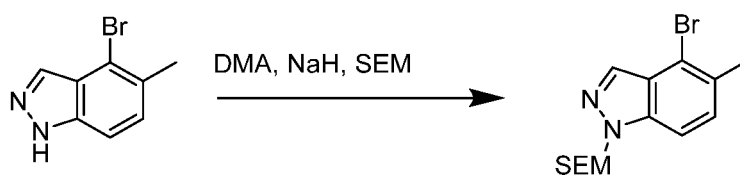


[0179] To a stirred solution of 3-bromo-4-fluorophenol (327 mg, 1.71 mmol) in 5.1 mL tetrahydrofuran at room temperature under nitrogen was added NaH (75.3 mg, 1.88 mmol) neat as a solid portion wise. After 15 minutes, a solution had formed. Chloro(methoxy)methane (156 μ L, 2.05 mmol) was added by syringe. After stirring for 2 hours, the reaction was quenched with saturated ammonium chloride solution and partitioned between ethyl acetate and water. The combined organic layers were washed with brine, dried over MgSO_4 , filtered and concentrated. The crude product was loaded in a minimum of dichloromethane onto a 24 gram RediSep® column pre-wet with hexanes and eluted with an ethyl acetate/hexanes gradient (0% to 20% ethyl acetate). Fractions containing the product were combined and concentrated to provide the product as a clear oil (120 mg, 29.8%)

Intermediate 5



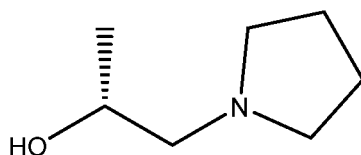
4-bromo-5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole



[0180] To a solution of 4-bromo-5-methyl-1H-indazole (0.7 g, 3.3 mmol) in dimethyl acetamide (30 mL) cooled to 0 °C was added NaH (0.19 g, 4.6 mmol) in portions and the reaction mixture was purged with nitrogen. The reaction was stirred for 20 minutes, and then (2-(chloromethoxy)ethyl)trimethylsilane (0.83 g, 5.0 mmol) was added and the reaction was stirred for 2 hours while warming to room temperature. The reaction was quenched by pouring into water and the aqueous layer was extracted into ethyl acetate. The combined organic layers were

washed with water and brine, dried over MgSO_4 and concentrated under vacuum. The crude material was purified by chromatography using 10-50% ethyl acetate/hexanes as the eluent to give 4-bromo-5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole (0.87 g, 79%).

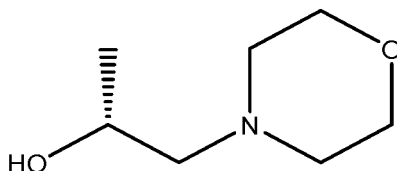
Intermediate 6



(R)-1-(pyrrolidin-1-yl)propan-2-ol

[0181] In a sealed tube, R-(+)-Propylene oxide (3.69 mL, 52.7 mmol) was cooled to -78°C and then sparged with anhydrous dimethyl amine for a few minutes. The reaction mixture was heated to 70°C for 16 hours. The reaction was cooled and concentrated in vacuo for 20 minutes to provide (R)-1-(pyrrolidin-1-yl)propan-2-ol (5.35 g, 41.4 mmol, 98.2% yield).

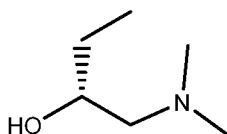
Intermediate 7



(R)-1-morpholinopropan-2-ol

[0182] In a sealed tube, R-(+)-Propylene oxide (2.111 mL, 30.13 mmol) and morpholine (1.490 mL, 17.22 mmol) were heated to 70°C for 20 hours. The reaction was cooled and concentrated in vacuo to provide (R)-1-morpholinopropan-2-ol (2.47 g, 17.01 mmol, 98.80 % yield).

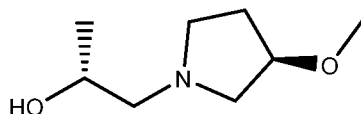
Intermediate 8



(R)-1-(dimethylamino)butan-2-ol

[0183] In a sealed tube, R-(+)-Propylene oxide (4.00 g, 55.5 mmol) and dimethylamine (1.00 g, 22.2 mmol), were heated to 65°C for 18 hours. The reaction was cooled and concentrated in vacuo. The resulting residue was purified by silica gel (0-12% MeOH in DCM) to provide (R)-1-(dimethylamino)butan-2-ol (1.38 g, 11.8 mmol, 53.1 % yield).

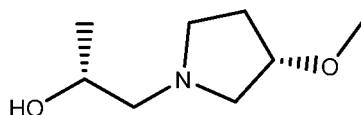
Intermediate 9



(R)-1-((R)-3-methoxypyrrolidin-1-yl)propan-2-ol

[0184] In a sealed tube, (R)-3-methoxypyrrolidine hydrochloride (1.00 g, 7.27 mmol), TEA (2.03 mL, 14.5 mmol) and R-(+)-Propylene oxide (1.27 mL, 18.2 mmol) were heated to 65°C for 18 hours. The reaction was cooled and concentrated in vacuo. The resulting residue was purified by silica gel (0-12% MeOH in DCM) to provide (R)-1-((R)-3-methoxypyrrolidin-1-yl)propan-2-ol (775 mg, 4.87 mmol, 67.0 % yield).

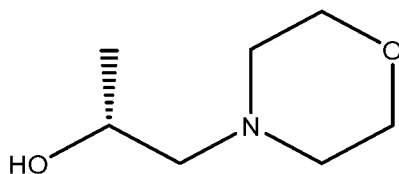
Intermediate 10



(R)-1-((S)-3-methoxypyrrolidin-1-yl)propan-2-ol

[0185] In a sealed tube, (S)-3-methoxypyrrolidine hydrochloride (1.00 g, 7.27 mmol), TEA (2.03 mL, 14.5 mmol) and R-(+)-Propylene oxide (1.27 mL, 18.2 mmol) were heated to 65°C for 18 hours. The reaction was cooled and concentrated in vacuo. The resulting residue was purified by silica gel (0-12% MeOH in DCM) to provide (R)-1-((S)-3-methoxypyrrolidin-1-yl)propan-2-ol (781 mg, 4.90 mmol, 67.5 % yield).

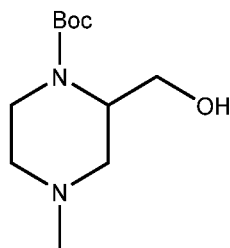
Intermediate 11



(R)-1-((S)-3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)propan-2-ol

[0186] In a sealed tube, R-(+)-Propylene oxide (0.609 mL, 8.69 mmol) and (S)-3-((tert-butyldimethylsilyl)oxy)pyrrolidine (1.00 g, 4.97 mmol) were heated to 70°C for 20 hours. The reaction was cooled and concentrated in vacuo to provide (R)-1-((S)-3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)propan-2-ol (1.29 g, 4.20 mmol, 84.6 % yield).

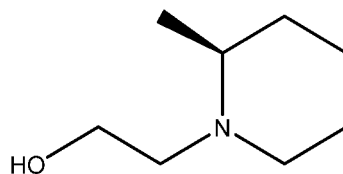
Intermediate 12



tert-butyl 2-(hydroxymethyl)-4-methylpiperazine-1-carboxylate

[0187] To a suspension of lithium chloride (246 mg, 5.81 mmol) and Lithium Borohydride (126 mg, 5.81 mmol) in ethanol (9 mL), at 0°C under nitrogen, a solution of 1-(tert-butyl) 2-methyl 4-methylpiperazine-1,2-dicarboxylate (750 mg, 2.90 mmol) in dry THF (6 mL) was added dropwise. The reaction was stirred overnight forming a white precipitate. The precipitate was filtered and washed with ethanol. The combined filtrate and organic extracts were concentrated to provide a white residue which was extracted with ethyl acetate. The combined organic layers were washed with saturated sodium chloride solution, dried over sodium sulfate and concentrated in vacuo. The residue was purified by chromatography with isocratic 10% MeOH in DCM with 0.2% NH₄OH to provide tert-butyl 2-(hydroxymethyl)-4-methylpiperazine-1-carboxylate (104 mg, 0.452 mmol, 15.6 % yield).

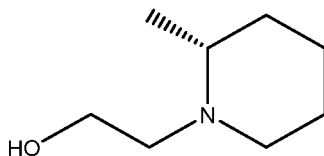
Intermediate 13



(S)-2-(2-methylpiperidin-1-yl)ethan-1-ol

[0188] A mixture of (S)-2-methylpiperidine (100 mg, 1.01 mmol), 2-bromoethanol (78 μ L, 139 mg, 1.11 mmol, 1.1 eq.), sodium iodide (151 mg, 1 eq.), potassium carbonate (418 mg, 3 eq.) and acetonitrile (1 mL) in a 4-mL vial was purged with nitrogen, sealed and stirred at room temperature for 2 days. The reaction mixture was partitioned between diethyl ether (15 mL) and water (2 mL). The ether layer was washed with brine (2 mL), acidified with TFA and dried under high vacuum for 2 days. The residue was washed with ether (3 mL), diluted with water (0.5 mL) and basified with 10M NaOH (0.2 mL). The layers were separated and the upper layer was carefully dried over NaOH. The ether solution was evaporated under nitrogen to yield crude (S)-2-(2-methylpiperidin-1-yl)ethan-1-ol (100 mg, 0.698 mmol, 69.24% yield) as colorless oil.

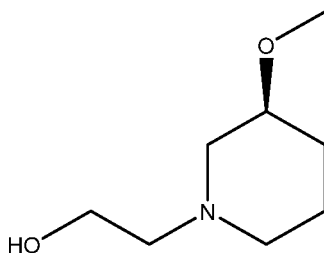
Intermediate 14



(R)-2-(2-methylpiperidin-1-yl)ethan-1-ol

[0189] Synthesized according to the method of Intermediate 13, using (R)-2-methylpiperidine (99 mg, 1 mmol) in place of (S)-2-methylpiperidine.

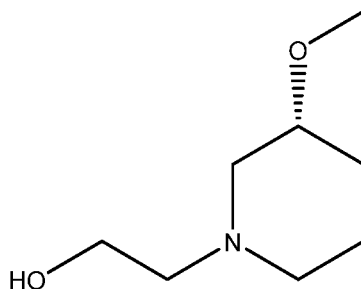
Intermediate 15



(S)-2-(3-methoxypiperidin-1-yl)ethan-1-ol

[0190] Synthesized according to the method of Intermediate 13, using (S)-3-methoxypiperidine (173 mg, 1.50 mmol) in place of (S)-2-methylpiperidine.

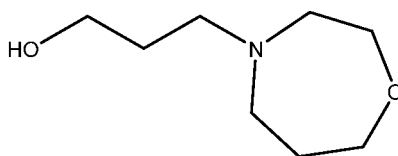
Intermediate 16



(R)-2-(3-methoxypiperidin-1-yl)ethan-1-ol

[0191] Synthesized according to the method of Intermediate 13, using R-3-methoxypiperidine (173 mg, 1.50 mmol) in place of (S)-2-methylpiperidine.

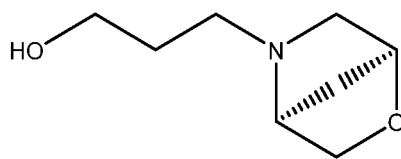
Intermediate 17



3-(1,4-oxazepan-4-yl)propan-1-ol

[0192] To a vial was added homomorpholine (0.250 g, 2.472 mmol), Acetonitrile (4.943 mL, 2.472 mmol) and 3-Bromo-1-propanol (0.2459 mL, 2.719 mmol). Potassium carbonate (0.6832 g, 4.943 mmol) was added and the mixture was warmed to 50 °C and stirred for 6 hours. The mixture was cooled to ambient temperature, diluted with DCM, filtered and the collected solids were washed with DCM. The filtrate was concentrated in vacuo and the crude oil was purified via column chromatography (Biotage Isolera, 12g Isco RediSep Gold, 10-20% MeOH/DCM with 0.2% NH₄OH) to afford 3-(1,4-oxazepan-4-yl)propan-1-ol (0.272 g, 1.708 mmol) as a colorless oil.

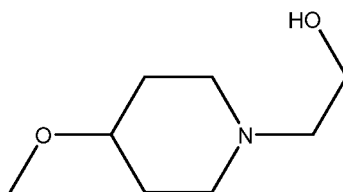
Intermediate 18



3-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)propan-1-ol

[0193] Synthesized according to the method of Intermediate 17, using (1S,4S)-2-Oxa-5-azabicyclo[2.2.1]heptane (0.250 g, 2.522 mmol) in place of homomorpholine.

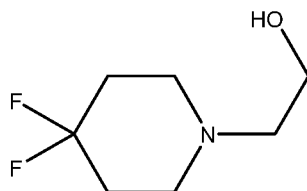
Intermediate 19



2-(4-methoxypiperidin-1-yl)ethan-1-ol

[0194] Synthesized according to the method of Intermediate 13, using 4-methoxypiperidine (173 mg, 1.50 mmol) in place of (S)-2-methylpiperidine.

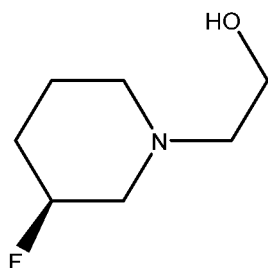
Intermediate 20



2-(4,4-difluoropiperidin-1-yl)ethan-1-ol

[0195] Synthesized according to the method of Intermediate 13, using 4,4-difluoropiperidine hydrochloride (173 mg, 1.50 mmol) in place of (S)-2-methylpiperidine.

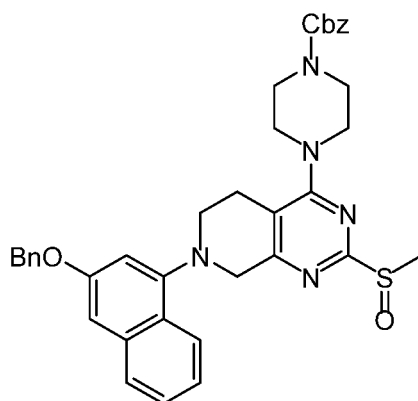
Intermediate 21



(S)-2-(3-fluoropiperidin-1-yl)ethan-1-ol

[0196] Synthesized according to the method of Intermediate 13, using S-3-fluoropiperidine hydrochloride (209 mg, 1.50 mmol) in place of (S)-2-methylpiperidine.

Intermediate 22



benzyl 4-(7-(3-(benzyloxy)naphthalen-1-yl)-2-(methylsulfinyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate

[0197] Step A: tert-butyl 4-hydroxy-2-(methylthio)-5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate: To a stirred solution of 1-*tert*-butyl 4-ethyl 3-oxopiperidine-1,4-dicarboxylate (50.0 g, 184 mmol, 1.00 *eq*) in MeOH (1.00 L) at 25 °C under nitrogen was added NaOMe (49.8 g, 921 mmol, 5.00 *eq*), followed by 2-methylisothiurea (62.4 g, 331 mmol, 1.80 *eq*, H₂SO₄) as a solid. The reaction mixture was stirred at 25 °C for 16 hours. The reaction mixture was adjusted to pH 5 with HCl (2 M), and the mixture was concentrated under reduced pressure to removed MeOH. The residue was suspended in 300 mL of ethyl acetate and 300 mL of water and stirred rapidly. The suspension was filtered and the white solid was collected. The filtrate was separated and the organic layer was washed with water (1 × 300 mL) and brine (1 × 200

mL). The combined organic layers were isolated, dried over Na₂SO₄, filtered and concentrated to provide *tert*-butyl 4-hydroxy-2-methylsulfanyl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidine-7-carboxylate (51.0 g, 138 mmol, 75.4 % yield, 81.0 % purity) as a white solid which as used directly in the next step without further purification. **ESI MS** *m/z* 298.2 [M+H]⁺.

[0198] Step B: *tert*-butyl 2-methylsulfanyl-4-(trifluoromethylsulfonyloxy)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidine-7-carboxylate: To a stirred suspension of *tert*-butyl 4-hydroxy-2-methylsulfanyl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidine-7-carboxylate (51.0 g, 171 mmol, 1.00 *eq*) in DCM (500 mL) at 0 °C was added DIEA (44.3 g, 343 mmol, 59.9 mL, 2.00 *eq*), followed by trifluoromethanesulfonic anhydride (72.6 g, 257 mmol, 42.4 mL, 1.50 *eq*) under nitrogen. Immediately a brown solution formed. After stirring at 25 °C for 16 hours, the reaction was concentrated to give a brown oil. The brown oil was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 1:0 to 10:1) to provide *tert*-butyl 2-methylsulfanyl-4-(trifluoromethylsulfonyloxy)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidine-7-carboxylate (46.0 g, 107 mmol, 62.4 % yield) as a yellow solid **ESI MS** *m/z* 430.2 [M+H]⁺.

[0199] Step C: *tert*-butyl 4-(4-benzyloxycarbonylpiperazin-1-yl)-2-methylsulfanyl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidine-7-carboxylate: To a stirred solution of *tert*-butyl 2-methylsulfanyl-4-(trifluoromethylsulfonyloxy)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidine-7-carboxylate (46.0 g, 107 mmol, 1.00 *eq*) in DMF (500 mL) was added DIEA (27.7 g, 214 mmol, 37.4 mL, 2.00 *eq*) followed by benzyl piperazine-1-carboxylate (25.9 g, 117 mmol, 22.7 mL, 1.10 *eq*). The reaction was heated to 100 °C for 1 hour under a nitrogen atmosphere. The reaction mixture was poured into ethyl acetate (300 mL), washed with H₂O (300 mL × 3) and brine (200 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 1:0 to 5:1) to give *tert*-butyl 4-(4-benzyloxycarbonylpiperazin-1-yl)-2-methylsulfanyl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidine-7-carboxylate (51.0 g, 96.9 mmol, 90.5 % yield, 92.0 % purity) as a white solid **ESI MS** *m/z* 500.3 [M+H]⁺.

[0200] Step D: Benzyl 4-(2-methylsulfanyl-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl)piperazine-1-carboxylate: To a solution of *tert*-butyl 4-(4-benzyloxycarbonylpiperazin-1-yl)-2-methylsulfanyl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidine-7-carboxylate (25.0 g, 50.0 mmol, 1.00 *eq*) in DCM (50.0 mL) was added TFA (85.6 g, 750 mmol, 55.6 mL, 15.0 *eq*). After

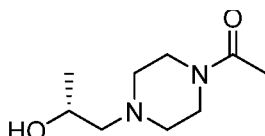
stirring at 25 °C for 1 hour, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in 300 mL of ethyl acetate and 300 mL of water and stirred rapidly. The mixture was adjusted to pH 8 with Na₂CO₃. The organic layer was washed with water (1 × 300 mL) and brine (1 × 200 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to provide benzyl 4-(2-methylsulfanyl-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (19.0 g, 46.6 mmol, 93.2 % yield, 98.0 % purity) as a yellow oil. **ESI MS** m/z 400.2 [M+H]⁺.

[0201] Step E : Benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-methylsulfanyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate: A mixture of 3-benzyloxy-1-bromonaphthalene (16.3 g, 52.1 mmol, 1.30 *eq*), benzyl 4-(2-methylsulfanyl-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (16.0 g, 40.1 mmol, 1.00 *eq*), Cs₂CO₃ (32.6 g, 100 mmol, 2.50 *eq*), Pd₂(dba)₃ (5.50 g, 6.01 mmol, 0.15 *eq*) and 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl (RuPhos) (3.74 g, 8.01 mmol, 0.20 *eq*) in dioxane (300 mL) was degassed and purged with nitrogen 3 times. The mixture was stirred at 85 °C for 5 hours under a nitrogen atmosphere. The reaction mixture was quenched by adding water (200 mL) at 0 °C, and extracted with ethyl acetate (3 × 200 mL). The combined organic layers were washed with brine (3 × 150 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, DCM/MeOH = 10/1 to 5/1) to provide benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-methylsulfanyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (16.0 g, 22.8 mmol, 56.9 % yield, 90.0 % purity) as a yellow solid. **ESI MS** m/z 632.5 [M+H]⁺.

[0202] Step F: Benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-methylsulfinyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate: To a stirred solution of benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-methylsulfanyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (8.00 g, 12.7 mmol, 1.00 *eq*) in DCM (200 mL) was added m-CPBA (2.73 g, 12.7 mmol, 80.0 % purity, 1.00 *eq*) at 0 °C under nitrogen. After stirring at 0 °C for 2 hours under a nitrogen atmosphere, the reaction mixture was quenched by adding Na₂S₂O₃ (10.0 mL) at 0 °C, diluted with water (100 mL) and extracted with DCM (200 mL). The combined organic layers were washed with brine (200 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column

chromatography (SiO₂, DCM/MeOH = 1/0 to 10/1) to provide benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-methylsulfinyl-6,8-dihydro-5*H*-pyrido [3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (3.50 g, 4.92 mmol, 38.8 % yield, 91.0 % purity) as a yellow solid. **ESI MS** *m/z* 648.5 [M+H]⁺.

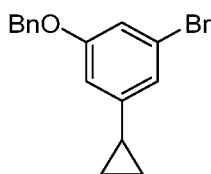
Intermediate 23



(R)-1-(4-(2-hydroxypropyl)piperazin-1-yl)ethan-1-one

[0203] Step A: 1-[4-[(2*R*)-2-hydroxypropyl]piperazin-1-yl]ethanone: (2*R*)-2-methyloxirane (1.00 g, 17.2 mmol, 1.20 mL, 1.00 *eq*) and 1-piperazin-1-ylethanone (8.00 g, 62.4 mmol, 3.62 *eq*) were taken up into a microwave tube. The sealed tube was heated at 150 °C for 1 hour under microwave. The mixture was dissolved in DCM (80.0 mL), added (Boc)₂O (3.62 *eq*, 13.6 g) and stirred at 20 °C for 1 hour. The residue was purified by column chromatography (DCM/MeOH 100/1 to 10/1) to give 1-[4-[(2*R*)-2-hydroxypropyl]piperazin-1-yl]ethanone (3.80 g, 13.5 mmol, 78.2 % yield, 66.0 % purity) as a yellow oil.

Intermediate 24

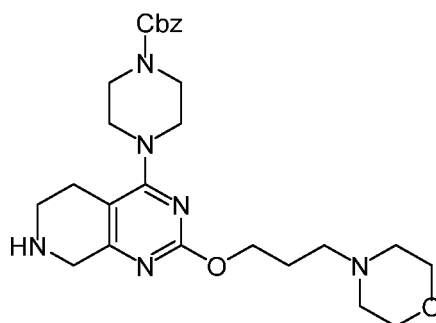


1-(benzyloxy)-3-bromo-5-cyclopropylbenzene

[0204] Step A: 1-benzyloxy-3,5-dibromo-benzene: To a mixture of 3,5-dibromophenol (1.50 g, 5.95 mmol, 1.00 *eq*) and K₂CO₃ (2.47 g, 17.9 mmol, 3.00 *eq*) in MeCN (30.0 mL) was added benzyl bromide (1.07 g, 6.25 mmol, 742 μL, 1.05 *eq*), the reaction mixture was stirred at 80 °C for 2 hours. The reaction mixture was filtered and concentrated. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 1:1 to give 1-benzyloxy-3,5-dibromobenzene (1.60 g, 4.68 mmol, 78.6 % yield) as colorless oil.

[0205] Step B: 1-benzyloxy-3-bromo-5-cyclopropylbenzene: To a mixture of 1-benzyloxy-3,5-dibromobenzene (1.20 g, 3.51 mmol, 1.00 *eq*) and cyclopropylboronic acid (392 mg, 4.56 mmol, 1.30 *eq*) in H₂O (4.00 mL) and dioxane (20.0 mL) was added Pd(dppf)Cl₂ (513 mg, 702 μ mol, 0.20 *eq*) and Cs₂CO₃ (2.29 g, 7.02 mmol, 2.00 *eq*). The reaction mixture was stirred at 90 °C for 12 hours under N₂. The reaction mixture was added to water (20 mL) and extracted with ethyl acetate (2 $\times$ 15 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 1:1 to give 1-benzyloxy-3-bromo-5-cyclopropyl -benzene (270 mg, 890 μ mol, 25.4 % yield) as colorless oil.

Intermediate 25



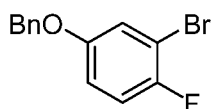
benzyl 4-(2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate

[0206] Step A: tert-butyl 4-(4-benzyloxycarbonylpiperazin-1-yl)-2-(3-morpholinopropoxy)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidine-7-carboxylate: To a mixture of 3-morpholinopropan-1-ol (5.46 g, 37.6 mmol, 2.00 *eq*) in THF (100 mL) was added NaH (2.26 g, 56.4 mmol, 60.0 % purity, 3.00 *eq*) in portions at 0 °C. After the mixture was stirred at 0 °C for 0.5 hour, a solution of *tert*-butyl 4-(4-benzyloxycarbonylpiperazin-1-yl)-2-methylsulfonyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidine-7-carboxylate (10.0 g, 18.8 mmol, 1.00 *eq*) in THF (100 mL) was added, and the reaction mixture was stirred at 0 °C for 1.5 hours under N₂. The mixture was poured into NH₄Cl aqueous (300 mL), and extracted with DCM (2 $\times$ 200 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=50:1 to 10:1) to give *tert*-butyl 4-(4-benzyloxycarbonylpiperazin-1-yl)-2-(3-morpholinopropoxy)-6,8-dihydro-5H-pyrido[3,4-

d]pyrimidine-7-carboxylate (7.70 g, 12.8 mmol, 67.8 % yield, 98.8 % purity) as a yellow oil. **ESI MS** m/z 597.4 $[M+H]^+$.

[0207] Step B: benzyl 4-[2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate: To a mixture of *tert*-butyl 4-(4-benzyloxycarbonylpiperazin-1-yl)-2-(3-morpholinopropoxy)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidine-7-carboxylate (7.70 g, 12.9 mmol, 1.00 *eq*) in DCM (80.0 mL) was added TFA (119 g, 1.04 mol, 76.9 mL, 80.6 *eq*), and the reaction mixture was stirred at 15 °C for 1 hour. The reaction mixture was concentrated, then diluted with DCM (100 mL) and adjusted to pH 8 with aqueous NaOH. The organic layer was separated, dried over Na₂SO₄, filtered and concentrated to give benzyl 4-[2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (6.00 g, 11.2 mmol, 86.9 % yield, 92.8 % purity) as yellow oil. **ESI MS** m/z 497.4 $[M+H]^+$.

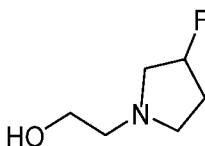
Intermediate 26



4-(benzyloxy)-2-bromo-1-fluorobenzene

[0208] To a solution of 3-bromo-4-fluorophenol (4.00 g, 20.9 mmol, 1.00 *eq*) and K₂CO₃ (8.68 g, 62.8 mmol, 3.00 *eq*) in ACN (80.0 mL) was added benzyl bromide (3.65 g, 21.4 mmol, 2.54 mL, 1.02 *eq*) and the reaction mixture was stirred at 60 °C for 2 hrs. The reaction mixture was filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (petroleum ether:ethyl acetate; gradient from 1:0 to 10:1) to give 4-benzyloxy-2-bromo-1-fluoro-benzene (5.02 g, 17.0 mmol, 81.0 % yield, 95 % purity) was obtained as white solid.

Intermediate 27



2-(3-fluoropyrrolidin-1-yl)ethan-1-ol

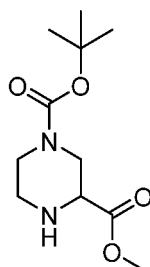
[0209] Step A: tert-butyl 3-fluoropyrrolidine-1-carboxylate: To a solution of *tert*-butyl 3-hydroxypyrrolidine-1-carboxylate (10.0 g, 53.4 mmol, 1.00 *eq*) in DCM (150.00 mL) was added diethylaminosulfur trifluoride (DAST) (12.9 g, 80.1 mmol, 10.6 mL, 1.50 *eq*) at -40 °C under a nitrogen atmosphere. After stirring at -40 °C for 2 hours, the mixture was warmed to 20 °C and stirred for 16 hours. The mixture was poured into 5% aqueous sodium bicarbonate (200 mL) and extracted with dichloromethane (2 × 100 mL). The organic layer was dried over sodium sulfate, filtered and concentrated under vacuum. The residue was purified by column chromatography over silica gel (petroleum ether/ethyl acetate 100:1 to 5:1). The desired fractions were collected and concentrated under vacuum to give *tert*-butyl 3-fluoropyrrolidine-1-carboxylate (4.30 g, 22.7 mmol, 42.6 % yield) as a colorless oil. ¹H NMR (400 MHz, Chloroform-d) δ = 5.27 (t, *J* = 3.6 Hz, 0.5H), 5.13 (t, *J* = 3.6 Hz, 0.5H), 3.77 - 3.38 (m, 4H), 2.26 - 2.15 (m, 1H), 2.08 - 1.85 (m, 1H), 1.46 (s, 9H).

[0210] Step B: 3-fluoropyrrolidine: To a solution of *tert*-butyl 3-fluoropyrrolidine-1-carboxylate (4.30 g, 22.7 mmol, 1.00 *eq*) in DCM (50.00 mL) was added HCl/dioxane (4 M, 35.0 mL, 6.16 *eq*) dropwise at 0 °C. The mixture was warmed to 20 °C and stirred for 1 hour. The mixture was concentrated under vacuum. The residue was triturated with diisopropyl ether (20 mL) and the precipitate was filtered and dried under vacuum to provide 3-fluoropyrrolidine (2.70 g, 21.5 mmol, 94.6 % yield, HCl) as a white solid. ¹H NMR (400 MHz, Methanol-d₄) δ = 5.51 (t, *J* = 3.6 Hz, 0.5H), 5.38 (t, *J* = 3.6 Hz, 1H), 3.66 - 3.27 (m, 5H), 2.45 - 2.12 (m, 2H).

[0211] Step C: methyl 2-(3-fluoropyrrolidin-1-yl)acetate: A suspension of 3-fluoropyrrolidine (2.70 g, 21.5 mmol, 1.00 *eq*, HCl) in DCM (27.00 mL) was cooled to 0° C. Triethylamine (5.44 g, 53.8 mmol, 7.45 mL, 2.50 *eq*) and methyl 2-bromoacetate (3.62 g, 23.7 mmol, 2.23 mL, 1.10 *eq*) were added and the reaction mixture was stirred at 20 °C for 16 h. The reaction mixture was diluted with CH₂Cl₂ (100 mL) and water (50 mL). The organic layer was washed with 5% aqueous citric acid solution (1 × 50 mL). The water layer was basified by saturated aqueous sodium carbonate solution (20 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried over sodium sulfate and concentrated in vacuo to give methyl 2-(3-fluoropyrrolidin-1-yl)acetate (2.20 g, 13.7 mmol, 63.5 % yield). ¹H NMR (400 MHz, Chloroform-d) δ = 5.22 - 5.02 (m, 1H), 3.66 (s, 3H), 3.35 (s, 2H), 3.07 - 2.93 (m, 1H), 2.91 - 2.77 (m, 2H), 2.67 (dt, *J* = 5.2, 8.4 Hz, 1H), 2.21 - 1.93 (m, 2H).

[0212] Step D: 2-(3-fluoropyrrolidin-1-yl)ethanol: To a solution of LiAlH_4 (706 mg, 18.6 mmol, 1.50 eq) in THF (20 mL) was added a solution of methyl 2-(3-fluoropyrrolidin-1-yl)acetate (2.00 g, 12.4 mmol, 1.00 eq) in THF (10 mL) dropwise at 0 °C. The mixture was warmed up to 20 °C and stirred for 3 hours. The mixture was quenched with saturated aqueous sodium sulfate solution (1 mL). The mixture was filtered and the filtrate was concentrated under vacuum. The product was purified by silica gel chromatography using 5% MeOH in DMC. The desired fractions were collected and concentrated under vacuum to give 2-(3-fluoropyrrolidin-1-yl)ethanol (1.20 g, 9.01 mmol, 72.6 % yield) as a colorless oil. ^1H NMR (400 MHz, Chloroform- d) δ = 5.28 - 5.05 (m, 1H), 3.68 - 3.61 (m, 2H), 2.99 - 2.73 (m, 4H), 2.72 - 2.67 (m, 2H), 2.58 - 2.45 (m, 1H), 2.28 - 1.97 (m, 2H).

Intermediate 28



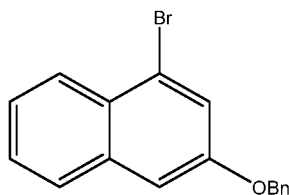
1-(tert-butyl) 3-methyl piperazine-1,3-dicarboxylate

[0213] Step A: methyl piperazine-2-carboxylate: To a mixture of 1-tert-butyl 2-methyl piperazine-1,2-dicarboxylate (5.0 g, 22.6 mmol, 1.00 eq) in MeOH (50.0 mL) was added HCl/dioxane (4.0 M, 134 mL). The reaction mixture was degassed and purged with nitrogen 3 times, and the mixture was stirred at 25 °C for 12 hours under a nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure to dryness to give methyl piperazine-2-carboxylate (4.89 g, 2HCl, crude) as a white solid, which was used directly in the next step without further purification.

[0214] Step B: 1-(tert-butyl) 3-methyl piperazine-1,3-dicarboxylate: To a solution of methyl piperazine-2-carboxylate (4.30 g, crude) and TEA (8.02 g, 79.2 mmol, 11.0 mL) in MeOH (50.0 mL) was added di-tert-butyl dicarbonate (4.32 g, 19.8 mmol, 4.55 mL). After stirring at 25 °C for 12 hours, the reaction mixture was filtered and concentrated under reduced pressure to dryness. The residue was purified by column chromatography (SiO_2 , DCM / MeOH = 1:0 to

20:1) to give 1-(tert-butyl) 3-methyl piperazine-1,3-dicarboxylate (4.80 g, 19.7 mmol, two steps, 99.0 % yield) as a colorless oil. ^1H NMR (400 MHz, chloroform- d) δ = 4.10 - 3.85 (m, 1H), 3.73 (s, 3H), 3.71 - 3.65 (m, 1H), 3.47 - 3.38 (m, 1H), 3.10 - 2.98 (m, 2H), 2.78 - 2.66 (m, 1H), 2.17 (s, 1H), 1.46 (s, 9H).

Intermediate 29



4-bromonaphthalen-2-ol

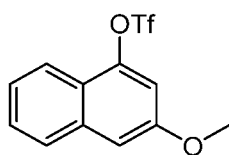
[0215] Step A: 2,4-dibromonaphthalen-1-amine: To a solution of Br_2 (246 g, 1.54 mol, 79.3 mL, 2.18 *eq*) in AcOH (750 mL) was added a solution of naphthalen-1-amine (101 g, 705 mmol, 99.0 mL, 1.00 *eq*) in AcOH (500 mL) at ambient temperature, and the reaction was stirred at 70 °C for 1 hour. The reaction mixture was cooled at room temperature and filtered. The filter cake was washed with AcOH (300 mL), then added to 20 % aqueous of NaOH (1.2 L). The mixture was stirred for 20 min and filtered. The isolated solid was washed with water (1 L) and dried under vacuum to provide 2,4-dibromonaphthalen-1-amine (200 g, 664 mmol, 94.2% yield) as gray solid. **ESI MS** m/z 301. 9 $[\text{M}+\text{H}]^+$.

[0216] Step B: 4-bromo-1-diazonio-naphthalen-2-olate: To a solution of 2,4-dibromonaphthalen-1-amine (60.0 g, 199 mmol, 1.00 *eq*) in AcOH (900 mL) and propionic acid (150 mL) was added NaNO_2 (16.5 g, 239 mmol, 13.0 mL, 1.20 *eq*) portionwise at 5-8 °C over 30 min, and then the reaction mixture was stirred at 5-8 °C for 30 min. The reaction mixture was poured into ice-water (4000 mL), and the resulting solid was collected and washed with water (2×50 mL) to provide 4-bromo-1-diazonio-naphthalen-2-olate (150 g, wet crude) as gray solid which was used directly in the next step. ^1H NMR (400 MHz, CDCl_3) δ 8.12 - 8.10 (d, $J=8.4$ Hz, 1H), 7.62 - 7.58 (t, $J=7.6$ Hz, 1H), 7.41 - 7.37 (t, $J=7.6$ Hz, 1H), 7.31 - 7.29 (d, $J=8.0$ Hz, 1H), 7.20 (s, 1H).

[0217] Step C: 4-bromonaphthalen-2-ol: To a solution of 4-bromo-1-diazonio-naphthalen-2-olate (100 g, 402 mmol, 1.00 *eq*) in EtOH (2.00 L) was added portionwise NaBH₄ (30.4 g, 803 mmol, 2.00 *eq*) at 13-15 °C over 1 h, and the reaction mixture was stirred at 15-18 °C for 3 hrs. The reaction was filtered and concentrated to dryness. The residue was dissolved in DCM (1000 mL) and washed with water (500 mL × 2). The organic phase was dried over Na₂SO₄ and concentrated to dryness. The residue was purified by silica gel column chromatograph, eluting with diethyl ether/ethyl acetate (60:1 to 10:1). The isolated product was further purified by reversed phase HPLC to provide 4-bromonaphthalen-2-ol (40.0 g, 139 mmol, 17.3 % yield, 77.4% purity) as a gray solid. ¹H NMR (400 MHz, CDCl₃) δ 8.07 – 8.05 (d, *J*=8.0 Hz, 1H), 7.60 – 7.58 (d, *J*=7.6 Hz, 1H), 7.41 - 7.36 (m, 3H), 7.07 (s, 1H).

[0218] Step D: 3-benzyloxy-1-bromo-naphthalene: A mixture of 4-bromonaphthalen-2-ol (30.0 g, 134 mmol, 1.00 *eq*), benzyl bromide (25.3 g, 148 mmol, 17.6 mL, 1.10 *eq*) and K₂CO₃ (55.7 g, 403 mmol, 3.00 *eq*) in MeCN (500 mL) was heated at 80 °C for 1 hr. The reaction mixture was filtered and concentrated to dryness. The residue was purified by silica gel column chromatography, eluting with diethyl ether/ethyl acetate (100:1 to 60:1) to provide 3-benzyloxy-1-bromo-naphthalene (40.0 g, 128 mmol, 95 % yield) as yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 8.19 – 8.17 (d, *J*=8.0 Hz, 1H), 7.75 – 7.32 (d, *J*=8.8 Hz, 1H), 7.64 - 7.63 (d, *J*=2.4 Hz, 1H), 7.52 – 7.37 (m, 7H), 7.23 – 7.21 (d, *J*=2.0 Hz, 1H), 5.2 (s, 2H).

Intermediate 30



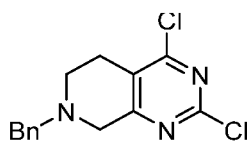
3-methoxynaphthalen-1-yl trifluoromethanesulfonate

[0219] Step A: 3-methoxynaphthalen-1-ol : To a solution of naphthalene-1,3-diol (3.00 g, 18.7 mmol, 1.00 *eq*) in MeOH (60.0 mL) was added HCl/MeOH (4 M, 60.0 mL, 12.8 *eq*) at 0 °C. The mixture was stirred at 25 °C for 60 hours. The solvent was removed under vacuum. The residue was purified by silica gel chromatography (diethyl ether:ethyl acetate=10:1 to 5:1) to give 3-methoxynaphthalen-1-ol (2.10 g, 12.1 mmol, 64.4% yield) as a brown solid. ¹H NMR (400 MHz, CDCl₃-d₆) δ = 8.10 - 8.08 (d, *J*=8.4 Hz, 1H), 7.73 - 7.71 (d, *J*=8.4 Hz, 1H), 7.47 -

7.45(m, 1H), 7.38 - 7.35(m, 1H), 6.80 - 6.79 (d, $J=2.0$ Hz, 1H), 6.56 - 6.55 (d, $J=2.4$ Hz, 1H), 3.92 (s, 3H).

[0220] Step B: (3-methoxy-1-naphthyl) trifluoromethanesulfonate: To a solution of 3-methoxynaphthalen-1-ol (2.10 g, 12.0 mmol, 1.00 eq) in DCM (40.0 mL) was added DIEA (7.79 g, 60.3 mmol, 10.5 mL, 5.00 eq) and trifluoromethanesulfonic anhydride (5.10 g, 18.1 mmol, 2.98 mL, 1.50 eq) at 0 °C. The mixture was stirred at 25 °C for 1 hour. The mixture was diluted with DCM (30 mL) and water (10 mL) and extracted with DCM (20 mL). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by silica gel chromatography (diethyl ether:ethyl acetate=20:1 to 10 :1) to give (3-methoxy-1-naphthyl) trifluoromethanesulfonate (3.00 g, 8.52 mmol, 70.7 % yield, 87.0 % purity) as a brown oil. ESI MS m/z 307.1 [M+H]⁺.

Intermediate 31

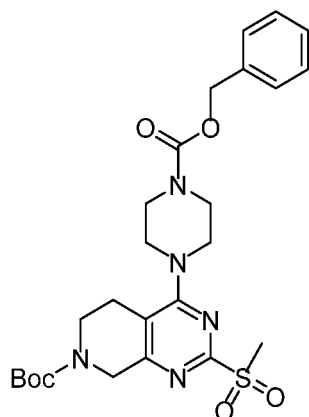


7-benzyl-2,4-dichloro-6,8-dihydro-5H-pyrido[3,4-d]pyrimidine

[0221] Step A: 7-benzyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidine-2,4-diol: To EtOH (600 mL) was added Na (5.56 g, 241 mmol, 5.73 mL, 2.40 eq) in portions. The reaction mixture was stirred for 1 hour. To the mixture was added ethyl 1-benzyl-3-oxo-piperidine-4-carboxylate (30.0 g, 100 mmol, 1.00 eq, HCl) and urea (14.5 g, 242 mmol, 13.0 mL, 2.40 eq). The reaction mixture was stirred at 75 °C for 36 hours, and then the solvent was removed under vacuum. The residue was dissolved in water (50 mL) and acidified with HCl (120 mL, 2M). A white solid precipitated from the solution and was collected by filtration. The filter cake was dried under vacuum to provide 7-benzyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidine-2,4-diol (22.0 g, 83.8 mmol, 83.2 % yield, 98 % purity) as a white solid. ¹HNMR (400 MHz, DMSO-d₆) δ = 10.97 (br s, 1H), 10.66 (br s, 1H), 7.55 - 6.95 (m, 5H), 3.81 - 3.50 (m, 2H), 3.26 - 2.91 (m, 2H), 2.77 - 2.58 (m, 2H), 2.34 - 2.09 (m, 2H).

[0222] Step B: 7-benzyl-2,4-dichloro-6,8-dihydro-5H-pyrido[3,4-d]pyrimidine: To a solution of DIEA (30.1 g, 233 mmol, 40.7 mL, 3.00 eq) in POCl₃ (330 g, 2.15 mol, 200 mL) was added 7-benzyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidine-2,4-diol (20.0 g, 77.7 mmol, 1.00 eq). The reaction mixture was stirred at 110 °C for 5 hours. The reaction mixture was concentrated under vacuum. The residue was dissolved in DCM (400 mL) and poured into saturated NaHCO₃ (200 mL). The mixture was extracted with DCM (2 × 400 mL). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by silica gel chromatography (diethyl ether: DCM=10:1 to 0:1) to give 7-benzyl-2,4-dichloro-6,8-dihydro-5H-pyrido[3,4-d]pyrimidine (7.70 g, 26.2 mmol, 33.7 % yield) as a brown oil. ¹HNMR (300 MHz, chloroform-d) δ = 7.43 – 7.28 (m, 5H), 3.73 (s, 2H), 3.66 (br s, 2H), 2.84 (br s, 4H)

Intermediate 32



tert-butyl 4-((benzyloxy)carbonyl)piperazin-1-yl-2-(methylsulfonyl)-5,6-dihydropyrido[3,4-d]pyrimidine-7(8H)-carboxylate

[0223] Step A: *tert*-butyl 4-hydroxy-2-methylsulfanyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidine-7-carboxylate: To a stirred solution of 1-*tert*-butyl 4-ethyl-3-oxopiperidine-1,4-dicarboxylate (44.0 g, 162 mmol, 1.00 eq) in MeOH (1.00 mL) at 25 °C under nitrogen was added a solution of NaOMe (35.0 g, 649 mmol, 4.00 eq) in MeOH (600 mL) by syringe followed by 2-methylisothiurea (61.1 g, 324 mmol, 2.00 eq, H₂SO₄). After stirring at 25 °C for 16 hours, the reaction mixture was concentrated under reduced pressure to removed MeOH. The residue was suspended in 500 mL of ethyl acetate and 500 mL of water and stirred rapidly. The reaction

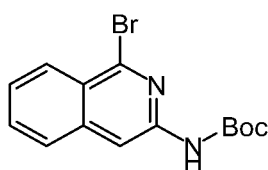
mixture was adjusted to pH 5 with HCl (2 M). The precipitate was filtered and the white solid was washed with ethyl acetate and dried under vacuum to give *tert*-butyl 4-hydroxy-2-methylsulfanyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidine-7-carboxylate (33.0 g, 103 mmol, 63.8 % yield, 93.2 % purity) as a white solid, which was used directly in the next step without further purification. ¹H NMR (400 MHz, DMSO-d₆) δ = 4.19 (s, 2 H), 3.49 (br s, 2 H), 2.46 (s, 3 H), 2.35 (br t, *J* = 5.2 Hz, 2 H), 1.42 (s, 9 H).

[0224] Step B: give *tert*-butyl 2-methylsulfanyl-4-(trifluoromethylsulfonyloxy)-6,8-dihydro-5H-pyrido [3,4-d]pyrimidine-7-carboxylate: To a stirred suspension of *tert*-butyl 4-hydroxy-2-methylsulfanyl -6,8-dihydro-5H-pyrido[3,4-d]pyrimidine-7-carboxylate (15.0 g, 50.4 mmol, 1.00 *eq*) in DCM (200 mL) was added DIEA (26.1 g, 202 mmol, 35.2 mL, 4.00 *eq*) at 0 °C under nitrogen and followed by trifluoromethanesulfonic anhydride (28.5 g, 101 mmol, 16.6 mL, 2.00 *eq*) by syringe. Immediately a brown solution formed. The reaction mixture was stirred at 25 °C for 12 hours. The reaction mixture was purified by column chromatography (SiO₂, Petroleum ether / Ethyl acetate = 1:0 to 10:1) to give *tert*-butyl 2-methylsulfanyl-4-(trifluoromethylsulfonyloxy)-6,8-dihydro-5H-pyrido [3,4-d]pyrimidine-7-carboxylate (16.7 g, 35.7 mmol, 70.9 % yield, 91.9 % purity) as a white solid. ESI MS *m/z* 374.0 [M+H]⁺.

[0225] Step C: *tert*-butyl 4-(4-benzyloxycarbonylpiperazin-1-yl)-2-methylsulfanyl-6,8- dihydro-5H-pyrido[3,4-d]pyrimidine-7-carboxylate: To a stirred solution of *tert*-butyl 2-methylsulfanyl-4-(trifluoromethyl sulfonyloxy)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidine-7-carboxylate (16.7 g, 38.9 mmol, 1.00 *eq*) in DMF (100 mL) was added DIEA (10.0 g, 77.9 mmol, 2.00 *eq*) and benzyl piperazine-1-carboxylate (9.41 g, 42.8 mmol, 1.10 *eq*). The reaction was heated to 100 °C and stirred for 1 hour under a nitrogen atmosphere. The reaction mixture was diluted with water (150 mL) and the reaction mixture was adjusted to pH 5 with HCl (2 M) and extracted with DCM (3 × 200 mL). The combined organic layers were washed with saturated NaHCO₃ (3 × 150 mL), brine (3 × 150 mL) and H₂O (3 × 150 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give *tert*-butyl 4-(4-benzyloxycarbonylpiperazin-1-yl)-2-methylsulfanyl-6,8- dihydro-5H-pyrido[3,4-d]pyrimidine-7-carboxylate (18.1 g, 36.2 mmol, 93.0 % yield, 94.1 % purity) as a yellow solid, which was used directly in the next step without further purification. ESI MS *m/z* 500.1 [M+H]⁺.

[0226] Step D: tert-butyl 4-(4-benzyloxycarbonylpiperazin-1-yl)-2-methylsulfonyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidine-7-carboxylate: To a stirred solution of tert-butyl 4-(4-benzyloxycarbonylpiperazin-1-yl)-2-methylsulfonyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidine-7-carboxylate (14.4 g, 28.9 mmol, 1.00 eq) in DCM (150 mL) at 0 °C under nitrogen was added meta-chloroperoxybenzoic acid (17.4 g, 101 mmol, 3.50 eq) as a solid. After stirring at 0 °C for 2 hours under a nitrogen atmosphere, the reaction mixture was diluted with water (300 mL) and the reaction mixture was adjusted to pH 8 with saturated aqueous NaHCO₃ and extracted with DCM (3 × 200 mL). The combined organic layers were washed with brine (3 × 200 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to dryness. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 10:1 to 1:2) to give tert-butyl 4-(4-benzyloxycarbonylpiperazin-1-yl)-2-methylsulfonyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidine-7-carboxylate (11.0 g, 19.7 mmol, 68.6 % yield, 95.4 % purity) as a white solid. **ESI MS** m/z 532.1 [M+H]⁺.

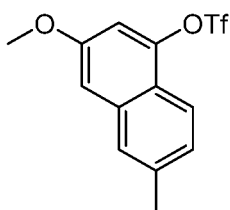
Intermediate 33



tert-butyl (1-bromoisoquinolin-3-yl)carbamate

[0227] Step A: A mixture of 1-bromoisoquinolin-3-amine (400 mg, 1.79 mmol, 1.00 eq) and *tert*-butoxycarbonyl tert-butyl carbonate (3.91 g, 17.9 mmol, 4.12 mL, 10.0 eq) was stirred at 70 °C for 16 hours. The residue was purified by column chromatography (SiO₂, diethyl ether/ethyl acetate = 5:1) to give *tert*-butyl N-(1-bromo-3-isoquinolyl) carbamate (400 mg, 1.24 mmol, 69.2 % yield) as a yellow solid. **ESI MS** m/z 322.1, 324.1 [M+H]⁺.

Intermediate 34



3-methoxy-6-methylnaphthalen-1-yl trifluoromethanesulfonate

[0228] Step A: 3-methoxynaphthalen-1-ol: To a solution of naphthalene-1,3-diol (40.0 g, 250 mmol, 1.00 *eq*) in MeOH (800 mL) was added HCl (4 M, 750 mL, 12.0 *eq*, 4 M in MeOH) at 0 °C. The mixture was warmed up to 18 °C and stirred for 30 hours. The mixture was concentrated under vacuum. The residue was purified by column chromatography over silica gel (petroleum ether/ethyl acetate 100/1 to 1/1). The desired fractions were collected and concentrated under vacuum to give 3-methoxynaphthalen-1-ol (17.7 g, 96.5 mmol, 38.6 % yield, 95 % purity) as a red oil. ¹H NMR (400MHz, Chloroform-d) δ = 8.17 (d, *J* = 8.4 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.50 (ddd, *J* = 1.2, 6.8, 8.0 Hz, 1H), 7.38 (ddd, *J* = 1.2, 6.8, 8.0 Hz, 1H), 6.81 (d, *J* = 2.0 Hz, 1H), 6.76 (br s, 1H), 6.62 (d, *J* = 2.4 Hz, 1H), 3.91 (s, 3H).

[0229] Step B: *tert*-butyl-[(3-methoxy-1-naphthyl)oxy]-dimethyl-silane: To a solution of 3-methoxynaphthalen-1-ol (20.0 g, 115 mmol, 1.00 *eq*) and imidazole (23.5 g, 344 mmol, 3.00 *eq*) in THF (400 mL) was added TBSCl (26.0 g, 172 mmol, 21.1 mL, 1.50 *eq*) dropwise at 0 °C. The mixture was warmed up to 25 °C and stirred for 16 hours. The mixture was diluted with petroleum ether (600 mL) and ethyl acetate (200 mL), and then washed with water (1 × 200 mL) and brine (1 × 200 mL). The separated organic layer was dried over sodium sulfate, filtered and concentrated under vacuum. The residue was purified by column chromatography over silica gel (petroleum ether/ethyl acetate 100/1 to 10/1). *tert*-butyl-[(3-methoxy-1-naphthyl)oxy]-dimethyl-silane (28.0 g, 97.1 mmol, 84.6 % yield) was obtained as a colorless oil. ¹H NMR (400MHz, Chloroform-d) δ = 8.01 (d, *J* = 8.4 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.35 (dt, *J* = 1.2, 7.6 Hz, 1H), 7.24 (dt, *J* = 1.2, 7.6 Hz, 1H), 6.71 (d, *J* = 2.0 Hz, 1H), 6.48 (d, *J* = 2.4 Hz, 1H), 3.82 (s, 3H), 1.02 (s, 9H), 0.23 (s, 6H).

[0230] Step C: *tert*-butyl-[[3-methoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-naphthyl]oxy]-dimethyl-silane and *tert*-butyl((3-methoxy-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)oxy)dimethylsilane: A mixture of *tert*-butyl-[(3-methoxy-1-naphthyl)oxy]-dimethyl-silane (26.0 g, 90.1 mmol, 1.00 *eq*), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (45.8 g, 180 mmol, 2.00 *eq*), (1*Z*,5*Z*)-cycloocta-1,5-diene;2,4-dimethyl-BLAHbicyclo[1.1.0]butane (2.39 g, 3.61 mmol, 0.04 *eq*) and 4-*tert*-butyl-2-(4-*tert*-butyl-2-pyridyl)pyridine (1.45 g, 5.41 mmol, 0.06 *eq*) in hexane (500 mL) was stirred at 100 °C under nitrogen atmosphere for 16 hours. The mixture was diluted with

water (500 mL) and ethyl acetate (1000 mL). The separated organic layer was washed with brine (1 × 500 mL), dried over sodium sulfate, filtered and concentrated under vacuum. The residue was purified by column chromatography over silica gel (petroleum ether/ethyl acetate 100/1 to 10/1). The desired fractions were collected and concentrated under vacuum to give a mixture of *tert*-butyl-[[3-methoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-naphthyl]oxy]-dimethyl-silane and *tert*-butyl((3-methoxy-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)oxy)dimethylsilane (38.0 g, 85.3 mmol, 94.6 % yield, 93 % purity) as a light yellow oil. ESI MS *m/z* 415.5 [M+H]⁺

[0231] Step D: 8-[*tert*-butyl(dimethyl)silyl]oxy-6-methoxy-naphthalen-2-ol: To a solution of mixture (36.0 g, 86.9 mmol, 1.00 *eq*) of *tert*-butyl-[[3-methoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-naphthyl]oxy]-dimethyl-silane and *tert*-butyl((3-methoxy-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)oxy)dimethylsilane in acetone (400 mL) was added a solution of Oxone (58.7 g, 95.6 mmol, 1.10 *eq*) in H₂O (400 mL) at 0 °C. The mixture was stirred at 0 °C for 1 hour. The mixture was quenched with 5% aqueous sodium thiosulfate solution (50 mL) and extracted with ethyl acetate (2 × 300 mL). The extracts were combined and washed with water (1 × 200 mL), brine (1 × 200 mL), dried over magnesium sulfate, filtered and the filtrate was concentrated under vacuum. The residue was purified by column chromatography over silica gel (petroleum ether/ethyl acetate 200/1 to 20/1). The desired fractions were collected and concentrated under vacuum to give 8-[*tert*-butyl(dimethyl)silyl]oxy-6-methoxy-naphthalen-2-ol (9.00 g, 28.4 mmol, 32.7 % yield, 96 % purity) as a colorless oil and 5-[*tert*-butyl(dimethyl)silyl]oxy-7-methoxy-naphthalen-2-ol (9.00 g, 29.0 mmol, 33.4 % yield, 98 % purity) as a white solid. ESI MS *m/z* 305.2 [M+H]⁺

[0232] Step E: 5-[*tert*-butyl(dimethyl)silyl]oxy-7-methoxy-2-naphthyl trifluoromethanesulfonate: To a solution of 5-[*tert*-butyl(dimethyl)silyl]oxy-7-methoxy-naphthalen-2-ol (11.0 g, 36.1 mmol, 1.00 *eq*) and DIEA (14.0 g, 108 mmol, 18.9 mL, 3.00 *eq*) in DCM (150 mL) was added Tf₂O (12.2 g, 43.4 mmol, 7.15 mL, 1.20 *eq*) dropwise at -40 °C. The mixture was stirred for 1 hour. The mixture was diluted with dichloromethane (200 mL) and washed with water (1 × 200 mL) and brine (1 × 200 mL). The separated organic layer was dried over sodium sulfate, filtered and concentrated under vacuum. The residue was purified by column chromatography over silica gel (petroleum ether/ethyl acetate 100/1 to 10/1). The

desired fractions were collected and concentrated under vacuum to give [5-[*tert*-butyl(dimethyl)silyl]oxy-7-methoxy-2-naphthyl] trifluoromethanesulfonate (13.0 g, 29.8 mmol, 82.4 % yield, 100 % purity) as a white solid. **ESI MS** m/z 436.9 $[M+H]^+$

[0233] Step F: *tert*-butyl-[(3-methoxy-6-methyl-1-naphthyl)oxy]-dimethyl-silane: To a solution of [5-[*tert*-butyl(dimethyl)silyl]oxy-7-methoxy-2-naphthyl]trifluoromethanesulfonate (12.5 g, 28.6 mmol, 1.00 eq) and K_2CO_3 (11.9 g, 85.9 mmol, 3.00 eq) in dioxane (160 mL) was added $Pd(PPh_3)_4$ (3.31 g, 2.86 mmol, 0.10 eq) and trimethylboroxine (14.4 g, 57.3 mmol, 16.0 mL, 2.00 eq) under nitrogen atmosphere. The reaction was heated to 100 °C for 16 hours. The mixture was diluted with ethyl acetate (200 mL) and then washed with water (1 × 200 mL) and brine (1 × 200 mL). The separated organic layer was dried over sodium sulfate, filtered and concentrated under vacuum. The residue was purified by column chromatography over silica gel (petroleum ether/ethyl acetate 100/1 to 5/1). The desired fractions were collected and concentrated under vacuum to give *tert*-butyl-[(3-methoxy-6-methyl-1-naphthyl)oxy]-dimethyl-silane (8.00 g, 24.6 mmol, 85.9 % yield, 93 % purity) as a colorless oil as red solid. **ESI MS** m/z 303.2 $[M+H]^+$

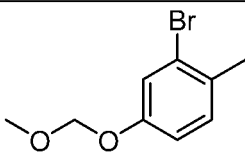
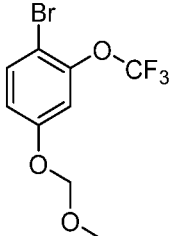
[0234] Step G: 3-methoxy-6-methyl-naphthalen-1-ol: To a solution of *tert*-butyl-[(3-methoxy-6-methyl-1-naphthyl)oxy]-dimethyl-silane (8.00 g, 26.5 mmol, 1.00 eq) in THF (100 mL) was added TBAF (10.4 g, 39.7 mmol, 1.50 eq) at 0 °C. The mixture was stirred at 0 °C for 3 hours. The mixture was diluted with water (100 mL) and ethyl acetate (200 mL). The separated organic layer was washed with brine (1 × 100 mL), dried over sodium sulfate, filtered and concentrated under vacuum. The residue was purified by column chromatography over silica gel (petroleum ether/ethyl acetate 50/1 to 5/1). The desired fractions were collected and concentrated under vacuum to give 3-methoxy-6-methyl-naphthalen-1-ol (4.70 g, 25.0 mmol, 94.4 % yield) as a red solid. **ESI MS** m/z 188.4 $[M+H]^+$

[0235] Step H: 3-methoxy-6-methyl-1-naphthyl trifluoromethanesulfonate: To a solution of 3-methoxy-6-methyl-naphthalen-1-ol (4.70 g, 25.0 mmol, 1.00 eq) and DIEA (9.68 g, 74.9 mmol, 13.1 mL, 3.00 eq) in DCM (3.00 mL) was added Tf_2O (8.45 g, 30.0 mmol, 4.94 mL, 1.20 eq) dropwise at -40 °C. The mixture was stirred for 1 hour. The mixture was diluted with dichloromethane (200 mL) and washed with water (1 × 200 mL) and brine (1 × 200 mL). The separated organic layer was dried over sodium sulfate, filtered and concentrated under vacuum.

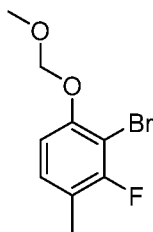
The residue was purified by column chromatography over silica gel (petroleum ether/ethyl acetate 100/1 to 10/1). 3-methoxy-6-methyl-1-naphthyl trifluoromethanesulfonate (7.70 g, 24.0 mmol, 96.2 % yield, 99.9 % purity) was obtained as a colorless oil. **ESI MS** m/z 320.7 $[M+H]^+$.

[0236] The following intermediates were prepared according to the preparation for Intermediate 3, substituting the appropriate phenol for 2-bromo-3-fluorophenol.

Intermediate No.	Structure	Name
Intermediate 35		2-bromo-4-(methoxymethoxy)-1-(trifluoromethoxy)benzene
Intermediate 36		2-bromo-4-(methoxymethoxy)-1-(trifluoromethyl)benzene
Intermediate 37		2-bromo-1-(methoxymethoxy)-4-(trifluoromethoxy)benzene
Intermediate 38		2-bromo-4-fluoro-3-(methoxymethoxy)-1-methylbenzene
Intermediate 39		1-bromo-3-(methoxymethoxy)-5-(trifluoromethoxy)benzene
Intermediate 40		2-bromo-1-methoxy-4-(methoxymethoxy)benzene
Intermediate 41		2-bromo-1-(methoxymethoxy)-3-methylbenzene

Intermediate 42		2-bromo-4-(methoxymethoxy)-1-methylbenzene
Intermediate 43		1-bromo-4-(methoxymethoxy)-2-(trifluoromethoxy)benzene

Intermediate 44

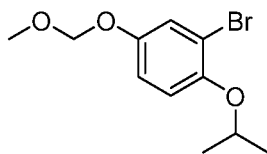


2-bromo-3-fluoro-1-(methoxymethoxy)-4-methylbenzene

[0237] Step 1: 3-fluoro-4-methylphenol (1.016 g, 8.055 mmol) was placed in CS_2 (3.9 mL, 64.44 mmol) and was cooled to 0°C . Br_2 (0.4150 mL, 8.055 mmol) was added and the mixture was stirred at room temperature for 2 hrs. 10% $\text{Na}_2\text{S}_2\text{O}_2$ was added and the mixture was extracted with DCM. The organic layers were combined, dried and filtered to provide 2-bromo-3-fluoro-4-methylphenol (1.389 g, 6.775 mmol, 84.10 % yield) which was used directly in the next step.

[0238] Step 2: 2-bromo-3-fluoro-1-(methoxymethoxy)-4-methylbenzene was prepared according to the procedure for Intermediate 8 using 2-bromo-3-fluoro-4-methylphenol in place of 2-bromo-3-fluorophenol.

Intermediate 45



2-bromo-1-isopropoxy-4-(methoxymethoxy)benzene

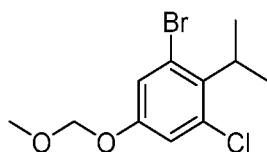
[0239] Step 1: 4-isopropoxyphenol (1.00 g, 6.57 mmol) and TEA (1.83 mL, 13.1 mmol) were placed in DCM (25 mL). Acetyl chloride (7.56 mL, 7.56 mmol) was added dropwise and the reaction was stirred at room temperature for 2hr. Water was added and the mixture was extracted with DCM. The organic layer was dried, filtered and concentrated to provide 4-isopropoxyphenyl acetate (1.24 g, 6.38 mmol, 97.2 % yield) which was directly in the next step.

[0240] Step2: 4-Isopropoxyphenyl acetate (1.24 g, 6.585 mmol) was placed in ACN (20 mL) and N-bromosuccinimide (1.173 g, 6.590 mmol) was added. The mixture was stirred for 18 hr. Water was added and the mixture was extracted with ether. The organic layers were combined, dried, and concentrated to provide 3-bromo-4-isopropoxyphenyl acetate (1.584 g, 5.800 mmol, 88.00 % yield) which was directly in the next step.

[0241] Step 3: 3-Bromo-4-isopropoxyphenyl acetate (500 mg, 1.83 mmol) was placed in MeOH (7 mL). A solution of KOH (111 mg, 1.98 mmol) in water (2 mL) was added to mixture and was stirred for 1 hr at room temperature. The reaction mixture was adjusted to pH 3 by the addition of 1N HCl. The mixture was extracted with DCM. The extracts were combined, dried, filtered and concentrated to provide crude 3-bromo-4-isopropoxyphenol which was used directly the next reaction.

[0242] Step 4: 2-Bromo-1-isopropoxy-4-(methoxymethoxy)benzene was prepared according to the procedure for Intermediate 8 using 3-bromo-4-isopropoxyphenol in place of 2-bromo-3-fluorophenol

Intermediate 46

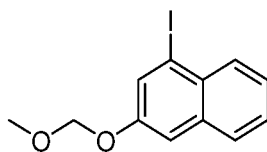


1-bromo-3-chloro-2-isopropyl-5-(methoxymethoxy)benzene

[0243] Step 1: 1-bromo-3-chloro-2-isopropyl-5-methoxybenzene (952 mg, 3.61 mmol) was placed in DCM (3 mL) and was cooled to 0°C. BBr₃ (9030 µL, 9.03 mmol) was added and the reaction was stirred at 0°C for 2 hr. Water was added and the mixture was extracted with DCM. The extracts were combined and concentrated. The resulting residue was purified by silica gel (0-20% EtOAc in hexane) to provide 3-bromo-5-chloro-4-isopropylphenol (575 mg, 2.30 mmol, 63.8 % yield)

[0244] Step 2: 1-bromo-3-chloro-2-isopropyl-5-(methoxymethoxy)benzene was prepared according to the procedure for Intermediate 8 using 3-bromo-5-chloro-4-isopropylphenol in place of 2-

Intermediate 47

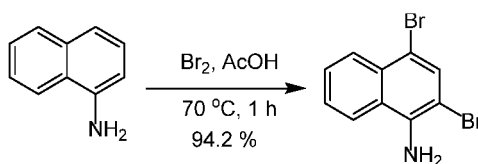
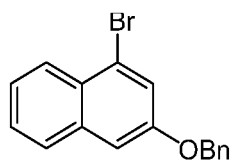


1-iodo-3-(methoxymethoxy)naphthalene

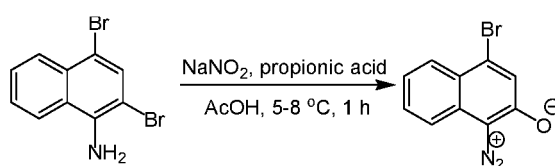
[0245] To a solution of 4-iodonaphthalen-2-ol (0.80 g, 3.0 mmol) in DCM (20 mL) was added N-ethyl-N-isopropylpropan-2-amine (1.1 mL, 5.9 mmol) and chloro(methoxy)methane (0.29 g, 3.6 mmol) and the reaction stirred at room temperature for 4 hours, with additional chloro(methoxy)methane (0.15 g) being added after 2 hours. The reaction was washed with brine and concentrated *in vacuo*. The material was purified by chromatography using a gradient of 0 to 10% EtOAc/hexanes as the eluent to give 1-iodo-3-(methoxymethoxy)naphthalene (0.80 g, 2.5 mmol, 86 % yield).

Intermediate 48

3-benzyloxy-1-bromo-naphthalene

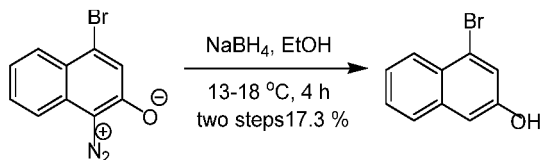


[0246] Step A: 2,4-dibromonaphthalen-1-amine: To a solution of Br₂ (246 g, 1.54 mol, 79.3 mL) in AcOH (750 mL) was added a solution of naphthalen-1-amine (101 g, 705 mmol, 99.0 mL) in AcOH (500 mL) at room temperature and the reaction stirred at 70 °C for 1 hour. The reaction mixture was cooled to room temperature and filtered. The filter cake was washed with AcOH (300 mL). The solid was next suspended in 20 % aqueous of NaOH (1.2 L). The mixture was stirred for 20 minutes and filtered. The solid was washed with water (1 L) and dried under vacuum to give 2,4-dibromonaphthalen-1-amine (200 g, 664 mmol, 94.2% yield) as gray solid. ES+APCI MS m/z 301.9 [M+H]⁺.

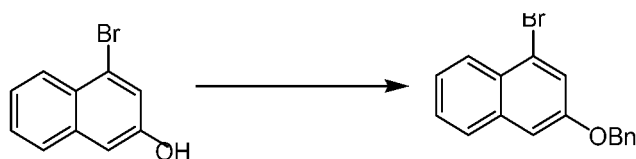


[0247] Step B: 4-bromo-1-diazonio-naphthalen-2-olate: To a solution of 2,4-dibromonaphthalen-1-amine (60.0 g, 199 mmol) in AcOH (900 mL) and propionic acid (150 mL) was added NaNO₂ (16.5 g, 239 mmol, 13.0 mL) portionwise at 5-8 °C over 30 minutes and the reaction mixture stirred at 5-8 °C for 30 minutes. The reaction mixture was poured into ice-water (4000 mL), the slurry filtered and the solid washed with water (2 × 50 mL) to give 4-bromo-1-diazonio-naphthalen-2-olate (150 g, wet crude) which was used crude in the next step immediately. ¹H

NMR (400 MHz, CDCl₃) δ 8.12 - 8.10 (d, $J=8.4$ Hz, 1H), 7.62 - 7.58 (t, $J=7.6$ Hz, 1H), 7.41 - 7.37 (t, $J=7.6$ Hz, 1H), 7.31 - 7.29 (d, $J=8.0$ Hz, 1H), 7.20 (s, 1H).



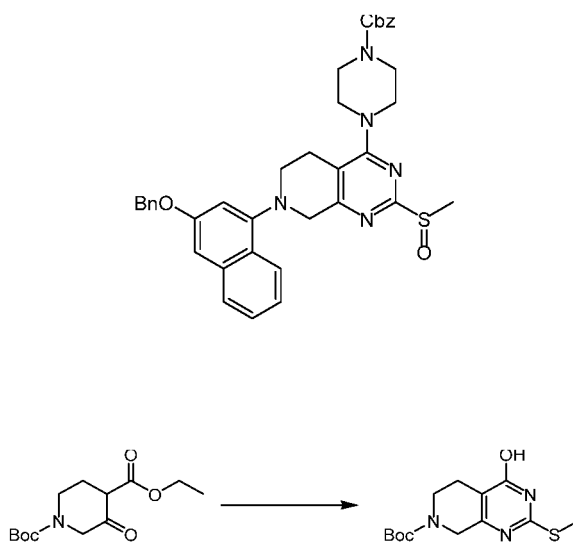
[0248] Step C: 4-bromonaphthalen-2-ol: To a solution of 4-bromo-1-diazonio-naphthalen-2-olate (100 g, 402 mmol) in EtOH (2.00 L) was added portion-wise NaBH₄ (30.4 g, 803 mmol) at 13-15 °C over 1 hour and the reaction stirred at 15-18 °C for 3 hours. The reaction was filtered and concentrated to dryness. The residue was dissolved in DCM (1000 mL) and washed with water (500 mL $\times$ 2). The organics were dried over Na₂SO₄ and concentrated to dryness. The residue was purified by chromatography eluting with petroleum ether/EtOAc (60/1 $\rightarrow$ 10/1) and material re-purified by reversed phase HPLC to give 4-bromonaphthalen-2-ol (40.0 g, 139 mmol, 17.3 % yield, 77.4% purity) as a gray solid. ¹H NMR (400 MHz, CDCl₃) δ 8.07 – 8.05 (d, $J=8.0$ Hz, 1H), 7.60 – 7.58 (d, $J=7.6$ Hz, 1H), 7.41 - 7.36 (m, 3H), 7.07 (s, 1H).



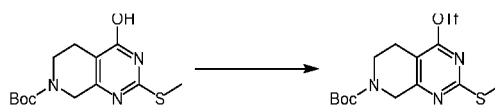
[0249] Step D: 3-benzyloxy-1-bromo-naphthalene: A mixture of 4-bromonaphthalen-2-ol (30.0 g, 134 mmol), BnBr (25.3 g, 148 mmol, 17.6 mL) and K₂CO₃ (55.7 g, 403 mmol) in MeCN (500 mL) was heated at 80 °C for 1 hr. The reaction mixture was filtered and concentrated to dryness. The residue was purified by silica gel column eluting with PE/EA (100/1 to 60/1) to give 3-benzyloxy-1-bromo-naphthalene (40.0 g, 128 mmol, 95 % yield). ¹H NMR (400 MHz, CDCl₃) δ 8.19 – 8.17 (d, $J=8.0$ Hz, 1H), 7.75 – 7.32 (d, $J=8.8$ Hz, 1H), 7.64 - 7.63 (d, $J=2.4$ Hz, 1H), 7.52 – 7.37 (m, 7H), 7.23 – 7.21 (d, $J=2.0$ Hz, 1H), 5.2 (s, 2H).

Intermediate 49

benzyl 4-(7-(3-(benzyloxy)naphthalen-1-yl)-2-(methylsulfinyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate

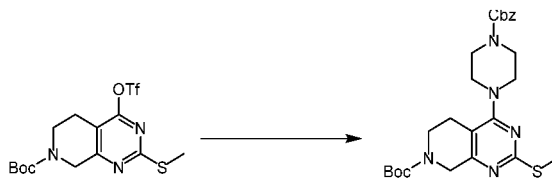


[0250] Step A: *tert*-butyl 4-hydroxy-2-methylsulfanyl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidine-7- carboxylate: To a solution of 1-*tert*-butyl 4-ethyl 3-oxopiperidine-1,4-dicarboxylate (50.0 g, 184 mmol) in MeOH (1.00 L) under nitrogen was added NaOMe (49.8 g, 921 mmol) and 2-methylisothiurea (62.4 g, 331 mmol, H₂SO₄). The reaction mixture was stirred at 25 °C for 16 hours. HCl (2 M) was added to the reaction mixture until pH~5 and then the mixture was concentrated under reduced pressure. The residue was suspended in 300 mL of ethyl acetate and 300 mL of water. The suspension was filtered. The organic phase was washed with water (1 × 300 mL), brine (1× 200 mL), dried over Na₂SO₄, filtered and concentrated to give *tert*-butyl 4-hydroxy-2-methylsulfanyl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidine-7- carboxylate (51.0 g, 138 mmol, 75.4 % yield, 81.0 % purity) which was used directly in the next reaction. ES+APCI MS *m/z* 298.2 [M+H]⁺.

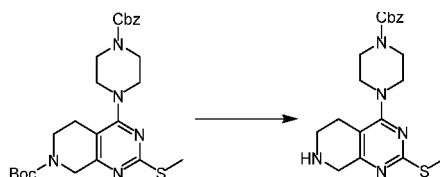


[0251] Step B: *tert*-butyl 2-methylsulfanyl-4-(trifluoromethylsulfonyloxy)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidine-7-carboxylate: To a solution of *tert*-butyl 4-hydroxy-2-methylsulfanyl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidine-7-carboxylate (51.0 g, 171 mmol) in DCM (500 mL) was added DIEA (44.3 g, 343 mmol, 59.9 mL) and Tf₂O (72.6 g, 257 mmol, 42.4 mL) sequentially at 0 °C under nitrogen. The reaction mixture was warmed up to 25 °C and stirred for 16 hours. The reaction mixture was concentrated and the residue purified by column chromatography eluting with EtOAc/Petroleum 0 → 10% to give *tert*-butyl 2-methylsulfanyl-4-

(trifluoromethylsulfonyloxy)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidine-7-carboxylate (46.0 g, 107 mmol, 62.4 % yield). ES+APCI MS m/z 430.2 $[M+H]^+$.

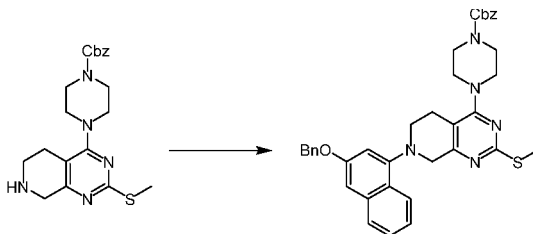


[0252] Step C: tert-butyl 4-(4-benzyloxycarbonylpiperazin-1-yl)-2-methylsulfanyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidine-7-carboxylate: To a solution of *tert*-butyl 2-methylsulfanyl-4-(trifluoromethylsulfonyloxy)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidine-7-carboxylate (46.0 g, 107 mmol) in DMF (500 mL) was added DIEA (27.7 g, 214 mmol, 37.4 mL) and benzyl piperazine-1-carboxylate (25.9 g, 117 mmol, 22.7 mL). The reaction was heated to 100 °C for one hour under N₂ atmosphere. The reaction mixture was poured into ethyl acetate (300 mL). The mixture was washed with H₂O (300 mL × 3). The organic phase was washed with brine (200 mL), dried over anhydrous Na₂SO₄, concentrated in vacuo. The residue was purified by column chromatography using 0→20% EtOAc/Petroleum as eluent to give *tert*-butyl 4-(4-benzyloxycarbonylpiperazin-1-yl)-2-methylsulfanyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidine-7-carboxylate (51.0 g, 96.9 mmol, 90.5 % yield, 92.0 % purity) ES+APCI MS m/z 500.3 $[M+H]^+$.

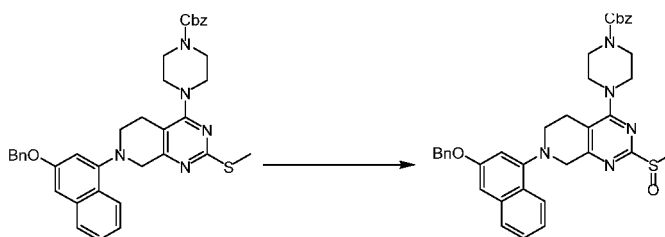


[0253] Step D: Benzyl 4-(2-methylsulfanyl-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate: To a solution of *tert*-butyl 4-(4-benzyloxycarbonylpiperazin-1-yl)-2-methylsulfanyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidine-7-carboxylate (25.0 g, 50 mmol) in DCM (50 mL) was added TFA (85.6 g, 750 mmol, 55.6 mL). The mixture was stirred at 25 °C for 1 hour. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in 300 mL of ethyl acetate and 300 mL of water and Na₂CO₃ added until pH~8. The organic layer was washed with water (1 × 300 mL), brine (1 × 200 mL) and dried over Na₂SO₄, filtered and concentrated under reduced pressure to give benzyl 4-(2-

methylsulfanyl-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate. The product was used directly to the next step without further purification. ES+APCI MS m/z 400.2 $[M+H]^+$.



[0254] Step E: benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-methylsulfanyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate: A mixture of 3-benzyloxy-1-bromonaphthalene (16.3 g, 52.1 mmol), benzyl 4-(2-methylsulfanyl-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (16.0 g, 40.1 mmol), Cs_2CO_3 (32.6 g, 100 mmol), $\text{Pd}_2(\text{dba})_3$ (5.50 g, 6.01 mmol) and RuPhos (3.74 g, 8.01 mmol) in dioxane (300 mL) was degassed with N_2 3 times and the mixture stirred at 85 °C for 5 hour under N_2 atmosphere. The reaction mixture was quenched by addition water (200 mL) at 0 °C, and extracted with EtOAc (3×200 mL). The combined organic layers were washed with brine (3×150 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by column chromatography eluting with 10→20% MeOH/DCM to give benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-methylsulfanyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (16.0 g, 22.8 mmol, 56.9 % yield, 90.0 % purity ES+APCI MS m/z 632.5 $[M+H]^+$).

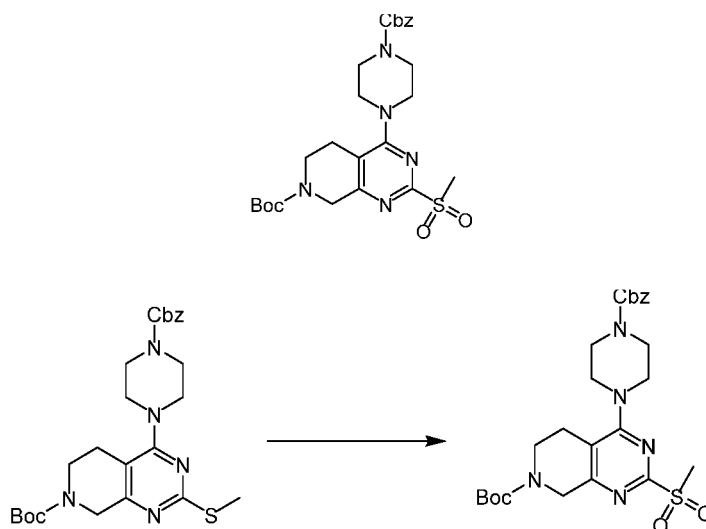


[0255] Step F: benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-methylsulfinyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate: To a solution of benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-methylsulfanyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (8.00 g, 12.7 mmol) in DCM (200 mL) was added m-CPBA (2.73 g, 12.7 mmol, 80.0 % purity) at 0 °C under nitrogen atmosphere. The reaction mixture was

stirred for two hours under 0 °C. The reaction mixture was quenched by addition Na₂S₂O₃ (10 mL) at 0 °C, and then diluted with water (100 mL) and extracted with DCM (200 mL). The combined organic layers were washed with brine (200 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography eluting with 0→10% MeOH/DCM to benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-methylsulfinyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (3.50 g, 4.92 mmol, 38.8 % yield, 91.0 % purity) ES+APCI MS m/z 648.5 [M+H]⁺.

Intermediate 50

tert-butyl 4-(4-benzyloxycarbonylpiperazin-1-yl)-2-methylsulfonyl-6,8-dihydro- 5H-pyrido[3,4-d]pyrimidine-7-carboxylate

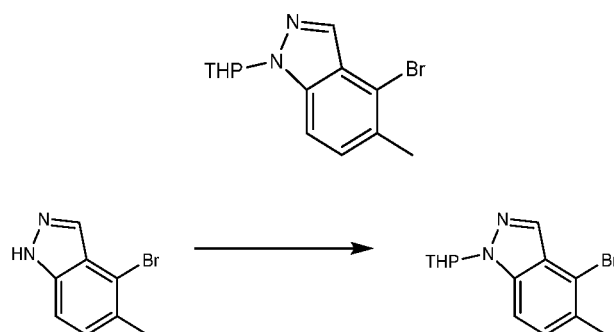


[0256] Step A: *tert*-butyl 4-(4-benzyloxycarbonylpiperazin-1-yl)-2-methylsulfonyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidine-7-carboxylate: To a stirred solution of *tert*-butyl 4-(4-benzyloxycarbonylpiperazin-1-yl)-2-methylsulfonyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidine-7-carboxylate (14.4 g, 28.9 mmol) in DCM (150 mL) was added m-CPBA solid (17.4 g, 101 mmol) at 0 °C under nitrogen. After stirring at 0 °C for 2 hours, the reaction mixture was diluted with water (300 mL) and basified with saturated NaHCO₃ aqueous solution to pH ~ 8 and then extracted with DCM (3 × 200 mL). The combined organic layers were washed with brine (3 × 200 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate 10/1 to 1/2) to give

tert-butyl 4-(4-benzyloxycarbonylpiperazin-1-yl)-2-methylsulfonyl-6,8-dihydro- 5*H*-pyrido[3,4-*d*]pyrimidine-7-carboxylate (11.0 g, 19.7 mmol, 68.6 % yield, 95.4 % purity). ES+APCI MS m/z 532.1 $[M+H]^+$.

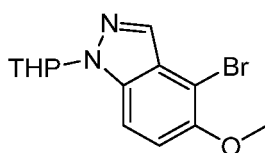
Intermediate 51

4-bromo-5-methyl-1-(tetrahydropyran-2-yl)-indazole



[0257] Step A: 4-bromo-5-methyl-1-(tetrahydropyran-2-yl)-indazole: To a mixture of 4-bromo-5-methyl-1*H*-indazole (3 g, 14.2 mmol) and 3,4-dihydro-2*H*-pyran (2.39 g, 28.4 mmol, 2.60 mL) in DCM (30 mL) was added TsOH·H₂O (270 mg, 1.42 mmol) and the mixture stirred at 15 °C for 2 hours. After completion, the reaction mixture was concentrated under vacuum and the residue purified by column chromatography using 5→20% EtOAc/Petroleum Ether as eluent to give 4-bromo-5-methyl-1-(tetrahydropyran-2-yl)-indazole (4 g, 13.6 mmol, 95.3% yield) as white solid. ¹H NMR (400 MHz, chloroform-*d*) δ 8.01 (s, 1H), 7.47 (d, $J=8.4$ Hz, 1H), 7.25 (d, $J=8.4$ Hz, 1H), 5.70 (dd, $J=2.8, 9.2$ Hz, 1H), 4.05 - 3.96 (m, 1H), 3.79 - 3.70 (m, 1H), 2.66 - 2.44 (m, 4H), 2.25 - 2.04 (m, 2H), 1.84 - 1.56 (m, 3H).

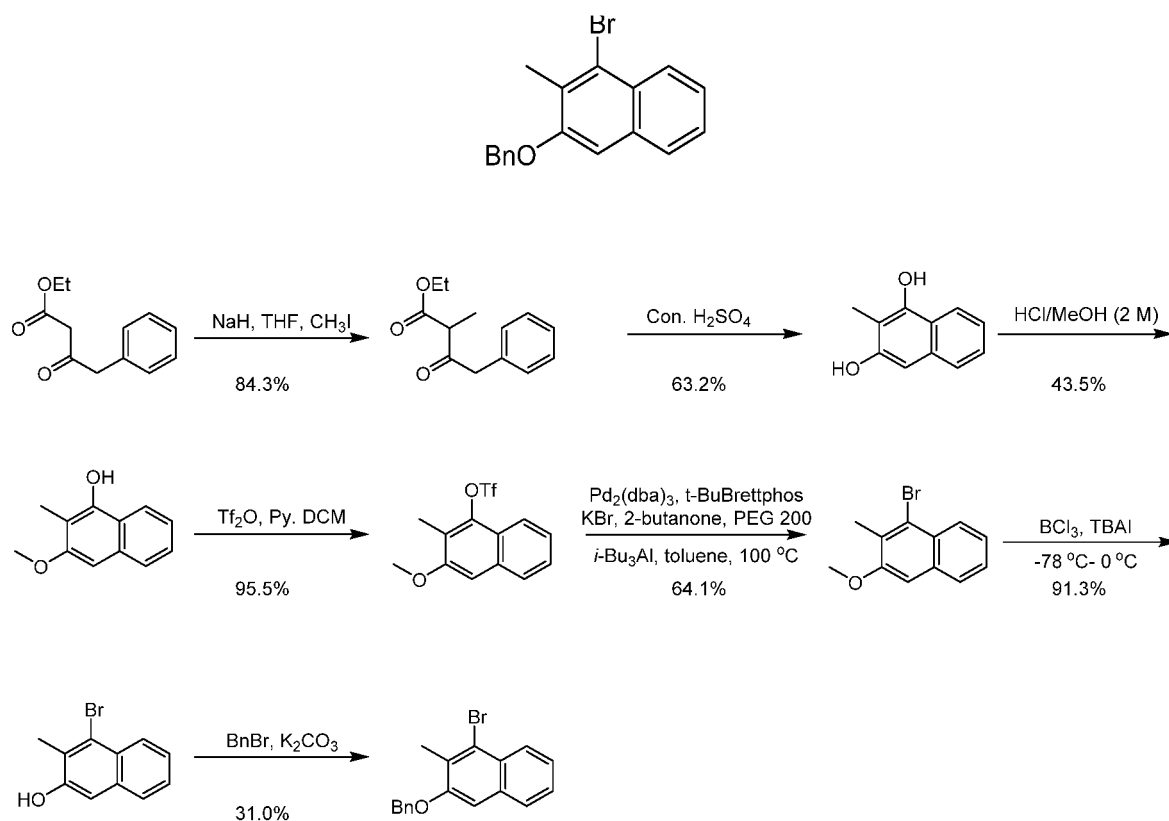
Intermediate 52

4-bromo-5-methoxy-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole

[0258] 4-bromo-5-methoxy-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole was prepared following Intermediate 51 substituting 4-bromo-5-methoxy-1H-indazole for 4-bromo-5-methyl-1H-indazole in Step A. ¹H NMR (400 MHz, chloroform-d) δ 8.00 (s, 1H), 7.53 (d, $J=9.2$ Hz, 1H), 7.16 (d, $J=9.2$ Hz, 1H), 5.70 (dd, $J=2.8, 9.2$ Hz, 1H), 4.04 - 3.98 (m, 1H), 3.96 (s, 3H), 2.55 - 2.49 (m, 1H), 2.23 - 2.05 (m, 2H), 1.83 - 1.69 (m, 3H).

Intermediate 53

3-(benzyloxy)-1-bromo-2-methylnaphthalene



[0259] Step A: ethyl 2-methyl-3-oxo-4-phenyl-butanoate. To a dried 250 ml three-necked flask was added ethyl 3-oxo-4-phenyl-butanoate (4.00 g, 19.4 mmol.), THF (50.0 mL), sodium hydride (931 mg, 23.3 mmol) and the reaction stirred for 0.5 hours at 0°C. A solution of methyl iodide (3.03 g, 21.3) was next added drop-wise. After addition was completed, the reaction mixture was warmed to 20 °C and stirred for two hours at 20°C. The reaction mixture was quenched by addition of water (10.0 mL) at 20 °C and then diluted with ethyl acetate (20.0 mL) and the layers separated. The aqueous layer was next extracted with ethyl acetate (20.0 mL $\times$ 3).

The combined organic layers were washed with brine (30.0 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether : Ethyl acetate 20:1 to 10:1) to give ethyl 2-methyl-3-oxo-4-phenyl-butanoate (3.60 g, 16.3 mmol, 84.3% yield) as a colorless oil.

¹H NMR (400 MHz, CDCl₃) δ = 7.38 - 7.28 (m, 3H), 7.25 - 7.19 (m, 2H), 4.22 - 4.15 (m, 2H), 3.87 (d, J = 2.0 Hz, 2H), 3.65 (q, J = 7.2 Hz, 1H), 1.34 (d, J = 7.2 Hz, 3H), 1.30 - 1.26 (m, 3H).

[0260] Step B: 2-methylnaphthalene-1,3-diol. A solution of ethyl 2-methyl-3-oxo-4-phenyl-butanoate (3.60 g, 16.3 mmol) in concentrated sulfuric acid (19.9 g, 203 mmol) was stirred at 15 °C for 12 hours. The reaction mixture was poured into ice-water (30.0 mL) and the resulting solid collected by filtration and dried under vacuum to afford 2-methylnaphthalene-1,3-diol (1.80 g, 10.3 mmol, 63.2% yield) as a red solid. ¹H NMR (400 MHz, CDCl₃) δ = 8.02 (d, J = 8.0 Hz, 1H), 7.65 - 7.54 (m, 1H), 7.41 (t, J = 7.2 Hz, 1H), 7.36 - 7.31 (m, 1H), 6.80 (s, 1H), 4.29 - 4.20 (s, 2H), 2.41 - 2.24 (s, 3H).

[0261] Step C: 3-methoxy-2-methyl-naphthalen-1-ol. 2-methylnaphthalene-1,3-diol (1.70 g, 9.76 mmol) was added to HCl/MeOH (2 M, 35.0 mL) and the result mixture was stirred at 30 °C for 3 days. The reaction was concentrated in vacuo and the residue purified by Prep-TLC (Petroleum ether : Ethyl acetate 1:1) to give 3-methoxy-2-methyl-naphthalen-1-ol (800 mg, 4.25 mmol, 43.5% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ = 8.02 (d, J = 8.4 Hz, 1H), 7.69 (d, J = 8.4 Hz, 1H), 7.44 - 7.38 (m, 1H), 7.37 - 7.31 (m, 1H), 6.79 (s, 1H), 5.14 (s, 1H), 3.94 (s, 3H), 2.29 (s, 3H).

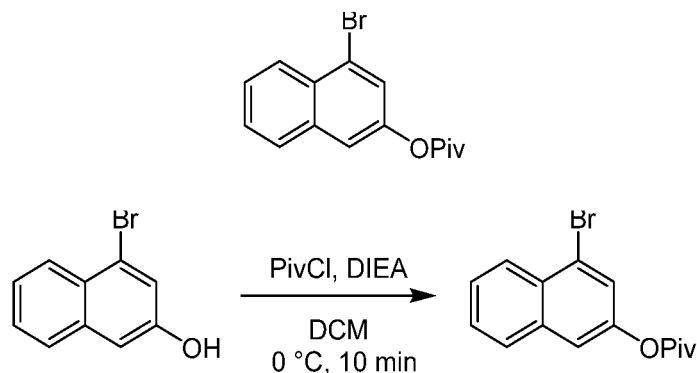
[0262] Step D: (3-methoxy-2-methyl-1-naphthyl)trifluoromethanesulfonate. To a mixture of 3-methoxy-2-methyl-naphthalen-1-ol (800 mg, 4.25 mmol.) and pyridine (504 mg, 6.38 mmol) in DCM (10.0 mL) was added trifluoroacetic anhydride (1.44 g, 5.10 mmol) dropwise at 0 °C under N₂ atmosphere. The mixture was warmed to 20 °C and stirred for an additional 5 hours. The solvent was removed under vacuum and the residue purified by Prep-TLC (Petroleum ether : Ethyl acetate 1:1) to give (3-methoxy-2-methyl-1-naphthyl)trifluoromethanesulfonate (1.30 g, 4.06 mmol, 95.5% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ = 7.97 (d, J = 7.6 Hz, 1H), 7.79 - 7.74 (m, 1H), 7.52 - 7.43 (m, 2H), 7.14 (s, 1H), 3.99 (s, 3H), 2.42 (s, 3H)

[0263] Step E: 1-bromo-3-methoxy-2-methyl-naphthalene : In a sealed tube was added (3-methoxy-2-methyl-1-naphthyl)trifluoromethanesulfonate (466 mg, 1.45 mmol), t-Bu-Brettphos (154 mg, 290 μ mol), potassium bromide (259 mg, 2.17 mmol), PEG-200 (175 mg), 2-butanone (157 mg, 2.17 mmol) and $\text{Pd}_2(\text{dba})_3$ (133 mg, 145 μ mol) in toluene (10.0 mL) and the mixture de-gassed with N_2 for 5 minutes. Next, triisobutylaluminum (431 mg, 2.17 mmol) was added drop-wise at 20 °C. The mixture was heated to 100 °C for 24 hrs. The reaction mixture was poured into water (30.0 mL) and the aqueous layer extracted with ethyl acetate (20.0 mL $\times$ 3). The combined organics were washed with brine (30.0 mL), dried over anhydrous sodium sulfate and concentrated in vacuo to give a residue which was pre-purified by column chromatography (Petroleum ether:Ethyl acetate 10:1) and then by Prep-TLC (Petroleum ether : Ethyl acetate 10:1) to give 1-bromo-3-methoxy-2-methyl-naphthalene (700 mg, 2.79 mmol, 64.1% yield) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ = 8.26 - 8.17 (m, 1H), 7.73 - 7.69 (m, 1H), 7.47 - 7.40 (m, 2H), 7.09 (s, 1H), 3.98 - 3.95 (m, 3H), 2.56 (s, 3H).

[0264] Step F: 4-bromo-3-methyl-naphthalen-2-ol: To a solution of 1-bromo-3-methoxy-2-methyl-naphthalene (580 mg, 2.31 mmol) and tetrabutylammonium iodide (2.13 g, 5.78 mmol) in DCM (11.0 mL) cooled to -78 °C was added a solution of BCl_3 (1 M, 5.78 mL) dropwise over a period of 10 minutes while under N_2 . The reaction mixture was warmed to 0 °C and stirred for 2 hours at room temperature. Next the solvent was removed under vacuum and the residue was purified by Prep-TLC (Petroleum ether : Ethyl acetate 5:1) to give 4-bromo-3-methyl-naphthalen-2-ol (500 mg, 2.11 mmol, 91.3% yield) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ = 8.26 - 8.15 (m, 1H), 7.63 (dd, J = 3.6, 6.0 Hz, 1H), 7.45 - 7.38 (m, 2H), 7.11 (s, 1H), 5.09 (s, 1H), 2.60 (s, 3H), 1.56 (s, 3H).

[0265] Step G: 3-benzyloxy-1-bromo-2-methyl-naphthalene. To a mixture of 4-bromo-3-methyl-naphthalen-2-ol (265 mg, 1.12 mmol) and benzyl bromide (201 mg, 1.18 mmol) in acetonitrile (3.00 mL) was added potassium carbonate (310 mg, 2.24 mmol) in one portion at 20 °C under N_2 . The mixture was next stirred at 60 °C for two hours. The solvent was removed under vacuum and the residue purified by Prep-TLC (Petroleum ether : Ethyl acetate 5:1) to give the 3-benzyloxy-1-bromo-2-methyl-naphthalene (250 mg, 695 μ mol, 31.0% yield, 91.0% purity) as a white solid. ES+APCI MS m/z 327.0, 329.0 $[\text{M}+\text{H}]^+$.

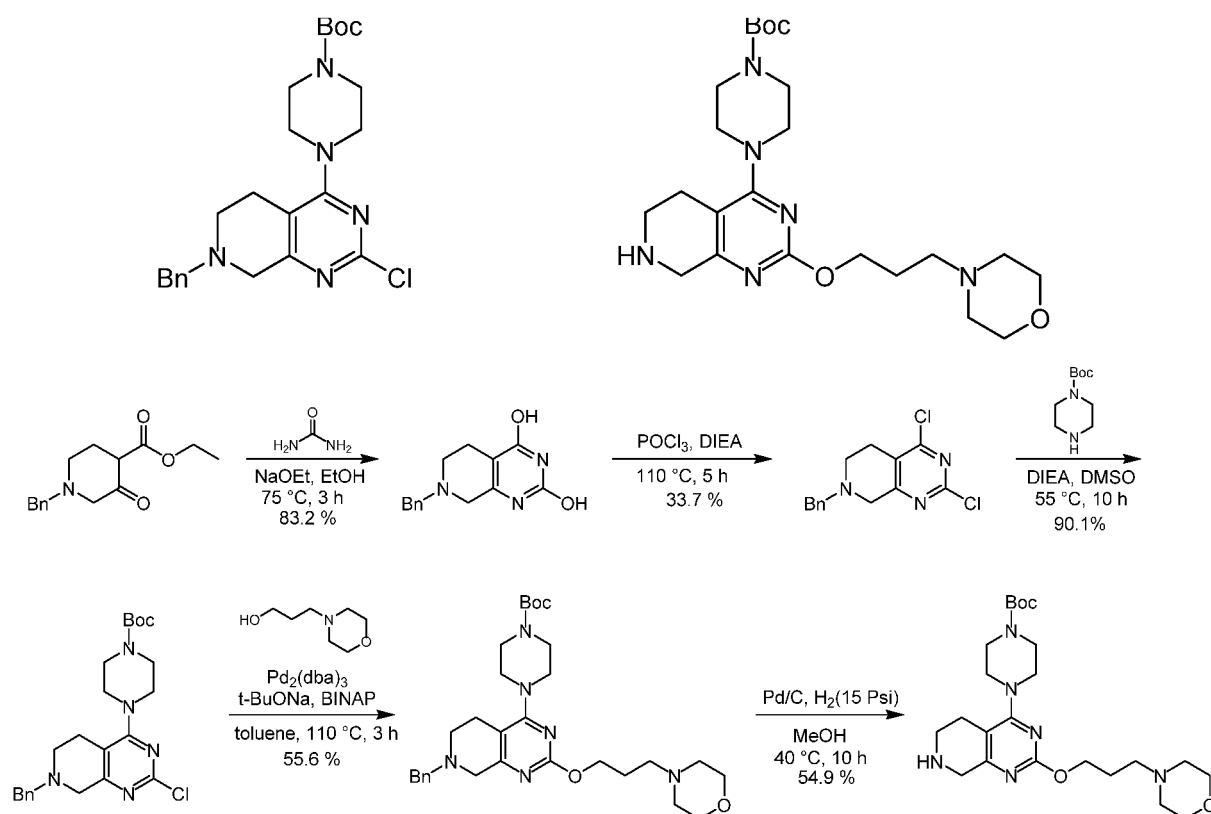
tert-butyl-2-(cyanomethyl)-4-[2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate



[0266] Step A: (4-bromo-2-naphthyl) 2,2-dimethylpropanoate. To a solution of 4-bromonaphthalen-2-ol (10 g, 44.8 mmol) and TEA (9.07 g, 89.7 mmol) in DCM (200 mL) was added 2,2-dimethylpropanoyl chloride (8.11 g, 67.2 mmol) at 0°C. The reaction mixture was stirred at 0 °C for 10 min. The reaction mixture was quenched by addition of water (50 mL) and the layers separated. The organic layer was washed with brine (30 mL), dried over Na₂SO₄ filtered and concentrated under vacuum. The residue was purified by silica gel chromatography (PE: EA =1:0 to 100:1) to give (4-bromo-2-naphthyl) 2,2-dimethylpropanoate (9 g, 29.3 mmol, 65.4% yield) as a red oil. ¹H NMR (400MHz, CHLOROFORM-*d*) δ = 8.22 (d, *J*=8.0 Hz, 1H), 7.83 - 7.77 (m, 1H), 7.63 - 7.49 (m, 4H), 1.41 (s, 9H).

Intermediate 55

tert-butyl 4-(2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl)piperazine-1-carboxylate.



[0267] Step A: 7-benzyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidine-2,4-diol. To EtOH (600 mL) was added Na (5.56 g, 241 mmol) in portions and the mixture stirred for 1 hour. To this solution was added ethyl 1-benzyl-3-oxopiperidine-4-carboxylate (30.0 g, 100 mmol) and urea (14.5 g, 242 mmol) and the reaction mixture stirred at 75 °C for 36 hours. The solvent was removed under vacuum and the residue dissolved in water (50 mL) and acidified by addition of HCl (120 mL, 2M) at which point a solid precipitated. The solid was filtered and the filter cake dried under vacuum to give 7-benzyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidine-2,4-diol (22.0 g, 83.8 mmol). ¹HNMR (400MHz, DMSO-d₆) δ = 10.97 (br s, 1H), 10.66 (br s, 1H), 7.55 - 6.95 (m, 5H), 3.81 - 3.50 (m, 2H), 3.26 - 2.91 (m, 2H), 2.77 - 2.58 (m, 2H), 2.34 - 2.09 (m, 2H).

[0268] Step B: 7-benzyl-2,4-dichloro-6,8-dihydro-5H-pyrido[3,4-d]pyrimidine. To a solution of DIEA (30.1 g, 233 mmol) in POCl₃ (330 g, 2.15 mol) was added 7-benzyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidine-2,4-diol (20.0 g, 77.7 mmol) and the reaction mixture stirred at 110 °C for 5 hours. Upon completion, the reaction mixture was concentrated under vacuum. The residue was dissolved in DCM (400 mL) and poured into sat. NaHCO₃ (200 mL) and the layers separated. The aqueous layer was extracted with DCM (2 × 400 mL). The combined organics

were washed with brine (100 mL), dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by silica gel chromatography (PE/DCM = 10/1 to 0/1) to give 7-benzyl-2,4-dichloro-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidine (7.70 g, 26.2 mmol). ¹HNMR (300MHz, chloroform-*d*) δ = 7.43 - 7.28 (m, 5H), 3.73 (s, 2H), 3.66 (br s, 2H), 2.84 (br s, 4H).

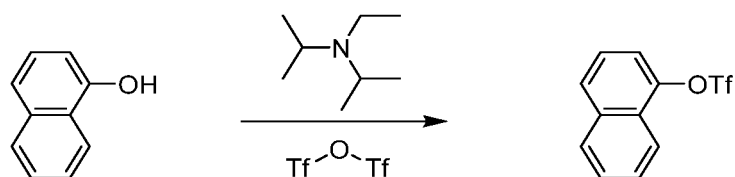
[0269] Step C: *tert*-butyl 4-(7-benzyl-2-chloro-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl) piperazine-1-carboxylate. To a solution of 7-benzyl-2,4-dichloro-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidine (17.3 g, 58.8 mmol) in DMSO (200 mL) was added DIEA (19.0 g, 147 mmol) and *tert*-butyl piperazine-1-carboxylate (11.5 g, 61.7 mmol) and the mixture stirred at 55 °C for 10 hours. The reaction mixture was poured into ethyl acetate (200 mL) and washed with water (3x200mL). The combined organics were washed with brine (200 mL), dried over anhydrous Na₂SO₄ and concentrated under vacuum to give a residue. The residue was purified by trituration from MTBE (200 mL) to give *tert*-butyl 4-(7-benzyl-2-chloro-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl) piperazine-1-carboxylate (24 g, 52.9 mmol). ES+APCI MS *m/z* 444.2 [M+H]⁺.

[0270] Step D: *tert*-Butyl 4-[7-benzyl-2-(3-morpholinopropoxy)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl] piperazine-1-carboxylate. A mixture of 3-morpholinopropan-1-ol (11.8 g, 81.1 mmol), *tert*-butyl 4-(7-benzyl-2-chloro-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl)piperazine-1-carboxylate (18 g, 40.5 mmol), BINAP (5.05 g, 8.11 mmol), *t*-BuONa (9.74 g, 101 mmol) and Pd₂(dba)₃ (3.71 g, 4.05 mmol) in toluene (300 mL) was degassed and purged with N₂ 3 times, and the mixture stirred at 110 °C for 3 hours under N₂ atmosphere. The reaction mixture was poured into H₂O (200 mL) and the aqueous layer extracted with ethyl acetate (3x300 mL). The combined organics were washed with brine (200 mL), dried over anhydrous Na₂SO₄ and concentrated under vacuum to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 100/1 to 5/1) to give *tert*-Butyl 4-[7-benzyl-2-(3-morpholinopropoxy)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl] piperazine-1-carboxylate (14 g, 22.5 mmol). ES+APCI MS *m/z* 553.4 [M+H]⁺.

[0271] Step E: *tert*-butyl 4-[2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl] piperazine-1-carboxylate. To a solution of *tert*-butyl 4-[7-benzyl-2-(3-morpholinopropoxy)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (14 g, 25.3 mmol) in MeOH (1 L) was added dry Pd/C (3 g, 10% purity) under N₂. The

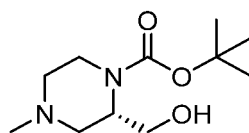
suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (15 psi) at 40 °C for 10 hours. The mixture was filtered and the filtrate concentrated in vacuo to give a residue. The residue was purified by reversed phase flash [water (0.1TFA)/acetonitrile] to give *tert*-butyl 4-[2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl] piperazine-1-carboxylate (6.5 g, 13.9 mmol). ES+APCI MS *m/z* 463.4 [M+H]⁺.

Intermediate 56

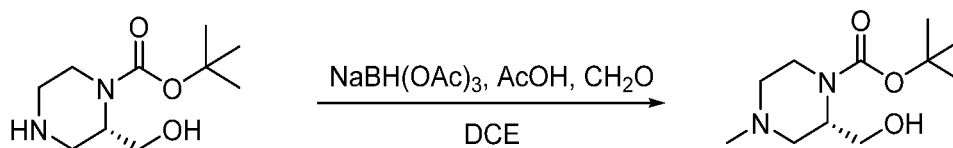


[0272] Naphthalen-1-yl trifluoromethanesulfonate. α -Naphthol (4 g, 27.74 mmol) was dissolved in DCM (200 mL) in a 3 neck flask. The reaction was cooled to 10°C in a water bath. N-ethyl-N-isopropylpropan-2-amine (4.846 mL, 27.74 mmol) and trifluoromethanesulfonic anhydride (4.668 mL, 27.74 mmol) were added to the solution dropwise. The reaction was stirred at 10°C for 2 hours. TLC (25% EtOAc, UV vis) showed reaction complete. The organics were washed with water (2X) and brine (2X). The organics were dried over MgSO₄ and concentrated in vacuo. The concentrate was purified using normal phase chromatography on the CombiFlash (0%-12% EtOAc:Hexanes). All fractions containing clean product were combined and concentrated in vacuo to give naphthalen-1-yl trifluoromethanesulfonate (6.77 g, 24.51 mmol, 88.34 % yield).

Intermediate 57

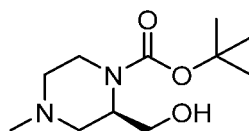


Tert-butyl (S)-2-(hydroxymethyl)-4-methylpiperazine-1-carboxylate



[0273] To a solution of (S)-1-Boc-2-hydroxymethylpiperazine (1.0 g, 4.62 mmol) in DCE (92.47 ml, 4.624 mmol) was added formaldehyde (3.474 ml, 46.24 mmol) (37% in water) followed by sodium triacetoxyborohydride (4.9 g, 23.12 mmol). The mixture was stirred vigorously at room temperature for 2.5 hours. The mixture was treated with saturated sodium bicarbonate (30 mL), stirred for 10 min then extracted with DCM (3 x 10 mL). The combined organic phases were dried over sodium sulfate, filtered and concentrated. ES+APCI MS m/z 231.1 $[M+H]^+$.

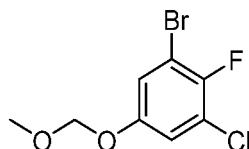
Intermediate 58



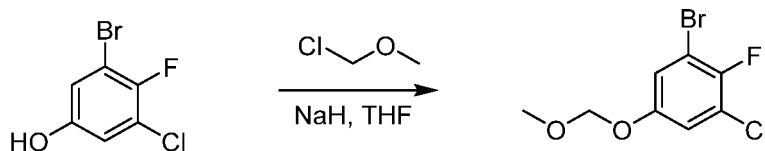
Tert-butyl (R)-2-(hydroxymethyl)-4-methylpiperazine-1-carboxylate

[0274] Title compound was prepared as in Intermediate 57, substituting tert-butyl (R)-2-(hydroxymethyl)piperazine-1-carboxylate for (S)-1-Boc-2-hydroxymethylpiperazine. ES+APCI MS m/z 231.1 $[M+H]^+$

Intermediate 59



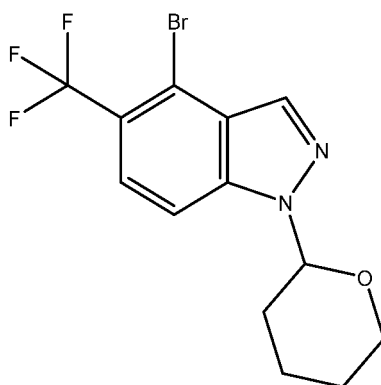
1-bromo-3-chloro-2-fluoro-5-(methoxymethoxy)benzene



[0275] To a round bottom flask was added THF (8.87 ml, 4.44 mmol) followed by sodium hydride, 60 % dispersion in mineral oil (0.213 g, 5.32 mmol). The mixture was cooled to 0 °C then 3-bromo-5-chloro-4-fluorophenol (1.0 g, 4.44 mmol) was added portionwise. Once the bubbling had ceased the resulting dark mixture was stirred at 0 °C for 30 min. Then chloromethyl methyl ether (0.421 ml, 5.54 mmol) was added and the mixture was warmed to ambient temperature where it was stirred for 2 hr. A saturated aqueous ammonium chloride solution was added and the mixture was extracted with DCM. The organic layer was dried over sodium sulfate, filtered and concentrated. Crude material was chromatographed (0-15% EtOAc in hexanes) to provide product as clear oil.

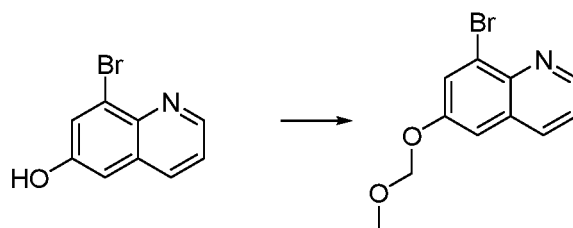
Intermediate 60

4-bromo-1-(tetrahydropyran-2-yl)-5-(trifluoromethyl)indazole



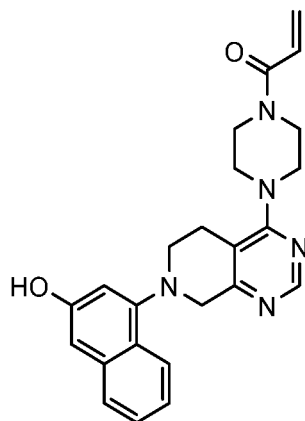
[0276] Step A: 4-bromo-1-(tetrahydropyran-2-yl)-5-(trifluoromethyl)indazole: To a solution of 4-bromo-5-(trifluoromethyl)-1H-indazole (500 mg, 1.89 mmol, 1 *eq*) in DCM (10 mL) was added 3,4-dihydro-2H-pyran (476 mg, 5.66 mmol, 517 μ L, 3 *eq*) and TsOH·H₂O (35.9 mg, 188 μ mol, 0.1 *eq*). The mixture was stirred at 15 °C for 1 hour. The mixture was concentrated. The residue was purified by column chromatography (SiO₂, PE:EA=10:1 to 1:1) to give 4-bromo-1-(tetrahydropyran-2-yl)-5-(trifluoromethyl)indazole (480 mg, 1.37 mmol, 72.9% yield) as yellow oil. ¹H NMR (400 MHz, chloroform-d) δ 8.20 (s, 1H), 7.69 - 7.63 (m, 2H), 5.70 (dd, *J*=2.8, 8.8 Hz, 1H), 4.05 - 3.96 (m, 1H), 3.79 - 3.70 (m, 1H), 2.56 - 2.50 (m, 1H), 2.27 - 2.04 (m, 2H), 1.80 - 1.74 (m, 2H), 1.60 - 1.54 (m, 1H).

Intermediate 61

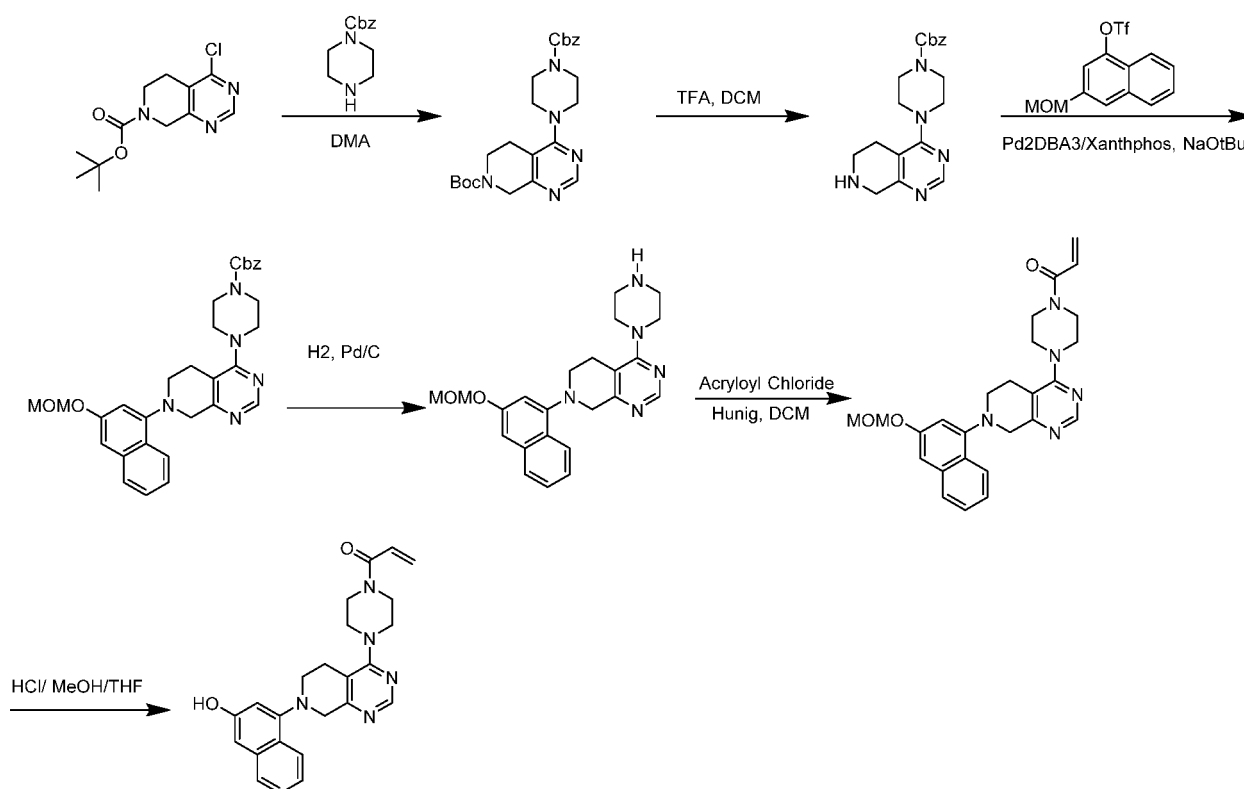


[0277] 8-bromo-6-(methoxymethoxy)quinoline: A stirred suspension of 8-bromoquinolin-6-ol (1.00 g, 4.46 mmol) in DCM (20 mL) was cooled to 0°C and diisopropylethylamine (1.2 mL, 6.7 mmol, 1.5 eq.) was added followed by chloro(methoxy)methane (0.41 mL, 5.4 mmol, 1.2 eq.) dropwise and the reaction mixture was warmed to room temperature overnight. Concentrated aqueous ammonia (0.5 mL, ~5 mmol) was next added and the resulted mixture was stirred for 1 hour at room temperature. The mixture was evaporated in vacuo and chromatographed on silica gel, Redisep 40g, using 20% EtOAc/hexane as eluent to give a colorless powder (0.52 g, 44%). ES+APCI MS m/z 268.0, $[M+H]^+$.

EXAMPLE 1



1-(4-(7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one



[0278] Step A: tert-butyl 4-(4-((benzyloxy)carbonyl)piperazin-1-yl)-5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate: In 2 mL of dimethyl acetamide were combined tert-butyl 4-chloro-5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate (1.0 g, 3.7 mmol), triethylamine (1.0 mL, 7.4 mmol), and benzyl 1-piperazinecarboxylate (0.86 mL, 4.4 mmol). The reaction vessel was sealed and the reaction mixture was heated to 90 °C with stirring. After 5 hours, the reaction was diluted with brine and extracted with methyl t-butyl ether. The combined organic layers were washed sequentially with saturated ammonium chloride and brine, dried over MgSO₄, and concentrated under reduced pressure to a thick oil. The oil was chromatographed (RediSep®, 24 g) eluting with 1:1 ethyl acetate/Hexanes to give tert-butyl 4-(4-((benzyloxy)carbonyl)piperazin-1-yl)-5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate (1.3 g, 2.9 mmol, 77 % yield). ES+APCI MS m/z 454.2 [M+H]⁺.

[0279] Step B : Benzyl 4-(5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate: To a solution of tert-butyl 4-(4-((benzyloxy)carbonyl)piperazin-1-yl)-5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate (1.58 g, 3.484 mmol) in dichloromethane (11.61 mL, 3.484 mmol) was added trifluoroacetic acid (2.668 mL, 34.84 mmol) and the reaction was stirred at room temperature for 3 hours. The reaction was concentrated under

vacuum and the residue was taken up in dichloromethane. The solution was washed with sequentially with 1M NaOH and brine, dried over Na₂SO₄, filtered and concentrated under vacuum. The crude product was purified by column chromatography (Biotage Isolera, 24G Isco RediSep® Gold, 10 to 20% methanol/dichloromethane) to afford the product (1.1 g, 89%) as an off-white foam. ES+APCI MS m/z 354.2 [M+H]⁺.

[0280] Step C: benzyl 4-(7-(3-(methoxymethoxy)naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate: To a vial was added tris(dibenzylideneacetone)dipalladium (0) (0.0069 g, 0.0075 mmol), racemic-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.0096 g, 0.015 mmol) and toluene (0.62 mL, 0.19 mmol). Argon was bubbled through the mixture for 5 minutes and then the vial was capped and the mixture was heated to 100 °C for 15 minutes. The mixture was cooled to ambient temperature and then sodium tert-butoxide (0.036 g, 0.37 mmol) was added followed by 1-bromo-3-(methoxymethoxy)naphthalene (0.050 g, 0.19 mmol) and benzyl 4-(5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (0.13 g, 0.37 mmol). The vial was capped and the mixture heated to 100 °C for 20 hours. The mixture was cooled to ambient temperature, diluted with dichloromethane and filtered through GF/F paper. The filtrate was concentrated and purified by column chromatography (Biotage Isolera, 12G Isco RediSep®, 10-50% ethyl acetate/dichloromethane) to afford the product (0.062 g, 61%) as an off-white foam. ES+APCI MS m/z 540.3 [M+H]⁺.

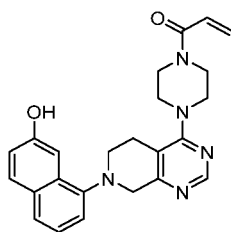
[0281] Step D : 7-(3-(methoxymethoxy)naphthalen-1-yl)-4-(piperazin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine: To a solution of benzyl 4-(7-(3-(methoxymethoxy)naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (0.061 g, 0.11 mmol) in ethanol (1.1 mL, 0.11 mmol) and tetrahydrofuran (1.1 mL, 0.11 mmol) was added palladium (0.024 g, 0.011 mmol) (Degussa Type, 10 wt.%, 50% H₂O). An atmosphere of H₂ was introduced into the reaction vessel by vacuum, and then the reaction mixture was maintained under an atmosphere of H₂. The mixture was stirred at ambient temperature for 2.5 hours, then diluted with methanol and filtered through GF/F paper. The colorless filtrate was concentrated under vacuum with toluene to provide an off-white foam (0.048 g, 105%) that was used directly in the next step. ES+APCI MS m/z 406.2 [M+H]⁺.

[0282] Step E: 1-(4-(7-(3-(methoxymethoxy)naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one: To a suspension of 7-(3-(methoxymethoxy)naphthalen-1-yl)-4-(piperazin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine (0.046 g, 0.11 mmol) in dichloromethane (1.1 mL, 0.11 mmol) at ambient temperature was added acryloyl chloride (1.2 mL, 0.12 mmol) (freshly prepared 0.1 M solution in dichloromethane) followed by triethylamine (0.032 mL, 0.23 mmol). The reaction was stirred at ambient temperature for 1 hour. The mixture was concentrated and the product was purified by column chromatography (Biotage Isolera, 12G Isco RediSep®, ethyl acetate) to afford the product (0.042 g, 79%) as an off-white solid foam. ES+APCI MS m/z 460.2 $[M+H]^+$.

[0283] Step F: 1-(4-(7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one: To a solution of 1-(4-(7-(3-(methoxymethoxy)naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one (0.034 g, 0.074 mmol) in ethyl acetate (0.74 mL, 0.074 mmol) was added hydrochloric acid (5 to 6 N solution in 2-propanol (0.44 mL, 2.2 mmol). The mixture was stirred at ambient temperature for 5 hours. The mixture was diluted with ethyl acetate (10 mL), filtered through a polypropylene filter and the collected solid was washed with ethyl acetate and hexanes to provide the product as the HCl salt. The impure material was treated with 1 mL of ammonium hydroxide/methanol to quench the acid and the mixture was concentrated. The residue was dissolved in 10% methanol/dichloromethane and purified by column chromatography (Biotage Isolera, 12G Isco RediSep®, 2 to 5% methanol/ethyl acetate) to afford the product (0.008 g, 25%) as an off-white solid. ES+APCI MS m/z 416.2 $[M+H]^+$.

[0284] 1H NMR (CD_3OD , 400 MHz) δ 8.49 (s, 1H), 8.07 (app d, J = 8.2 Hz, 1H), 7.61 (app d, J = 8.2 Hz, 1H), 7.35 (m, 1H), 7.25 (m, 1H), 6.80 (m, 3H), 6.23 (dd, J = 16.8, 1.6 Hz, 1H), 5.77 (dd, J = 10.6, 2.0 Hz, 1H), 4.22 (br s, 2H), 3.80 (app t, J = 4.7 Hz, 4H), 3.63 (br s, 4H), 3.35 (br s, 2H), 3.03 (br s, 2H).

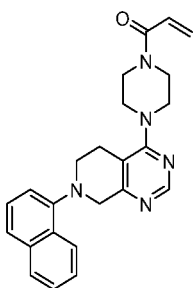
EXAMPLE 2



1-(4-(7-(7-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0285] Synthesized according to the method of **Example 1**, using 2-bromo-7-(methoxymethoxy)naphthalene in place of 1-bromo-3-(methoxymethoxy)naphthalene in Step C. ES+APCI MS m/z 416.1 [M+H]⁺.

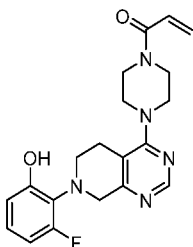
EXAMPLE 3



1-(4-(7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0286] Synthesized according to the method of **Example 1**, using 1-iodonaphthalene in place of 1-bromo-3-(methoxymethoxy)naphthalene in Step C. ES+APCI MS m/z 400.2 [M+H]⁺.

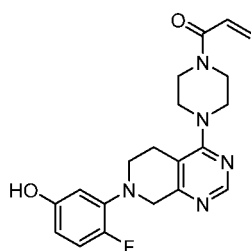
EXAMPLE 4



1-(4-(7-(2-fluoro-6-hydroxyphenyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0287] Synthesized according to the method of **Example 1**, using 2-bromo-1-fluoro-3-(methoxymethyl)benzene in place of 1-bromo-3-(methoxymethoxy)naphthalene in Step C. ES+APCI MS m/z 384.2 $[M+H]^+$.

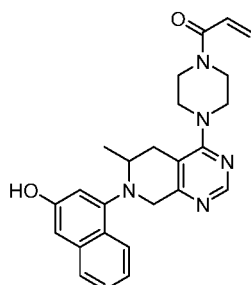
EXAMPLE 5



1-(4-(7-(2-fluoro-5-hydroxyphenyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0288] Synthesized according to the method of **Example 1**, using 2-bromo-1-fluoro-4-(methoxymethoxy)benzene in place of 1-bromo-3-(methoxymethoxy)naphthalene in Step C. ES+APCI MS m/z 384.2 $[M+H]^+$.

EXAMPLE 6



1-(4-(7-(3-hydroxynaphthalen-1-yl)-6-methyl-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

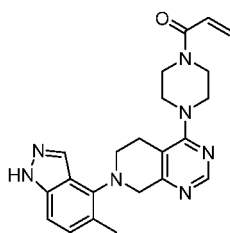
[0289] Steps A-C: benzyl 4-(7-(3-(methoxymethoxy)naphthalen-1-yl)-6-methyl-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate: Synthesized according to the method of **Example 1**, Steps A-C, using tert-butyl 4-chloro-6-methyl-5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate in place of 4-chloro-5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate in Step A. ES+APCI MS m/z 430.2 $[M+H]^+$.

[0290] Step D1: benzyl 4-(7-(3-hydroxynaphthalen-1-yl)-6-methyl-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate: To a solution of benzyl 4-(7-(3-(methoxymethoxy)naphthalen-1-yl)-6-methyl-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (0.05 g, 0.09 mmol) in isopropanol (10 mL) was added hydrogen chloride (5-6M in isopropanol) (0.02 mL, 0.09 mmol) and the reaction stirred at room temperature for 1 hour. The reaction was concentrated under vacuum and the concentrate was partitioned between ethyl acetate and water to convert the material to the free base. The combined organic layers were washed with brine, dried over MgSO_4 and concentrated under vacuum to give benzyl 4-(7-(3-hydroxynaphthalen-1-yl)-6-methyl-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (0.005 g, 0.010 mmol, 11% yield). ES+APCI MS m/z 510.3 $[\text{M}+\text{H}]^+$.

[0291] Step D2: 4-(7-(3-hydroxynaphthalen-1-yl)-6-methyl-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-ol: Prepared according to the method of **Example 1**, Step D.

[0292] Step E: 1-(4-(7-(3-hydroxynaphthalen-1-yl)-6-methyl-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one: Prepared according to the method of **Example 1**, Step E.

EXAMPLE 7



1-(4-(7-(5-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

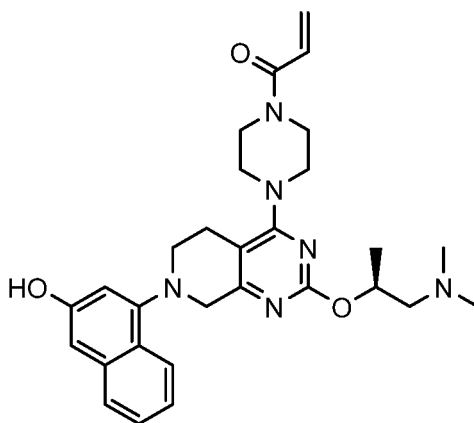
[0293] Steps A-D: benzyl 4-(7-(5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate: Synthesized according to General Scheme 1, Steps A-C, using 4-bromo-5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole in place of 1-bromo-3-(methoxymethoxy)naphthalene in Step C

[0294] Step D1: benzyl 4-(7-(5-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate: To a solution of benzyl 4-(7-(5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (0.16 g, 0.26 mmol) in dichloromethane (10 mL) was added 2,2,2-trifluoroacetic acid (0.89 g, 7.8 mmol) followed by anisole (0.028 g, 0.26 mmol), and the reaction was stirred at room temperature for 3 hours at room temperature. The reaction was concentrated under vacuum and the concentrated material was taken up in ethyl acetate and washed with basic brine. The combined organic layers were dried over MgSO₄ and concentrated under vacuum. The crude material was chromatographed using 0 to 10% methanol/dichloromethane as the eluent to give benzyl 4-(7-(5-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (0.05g, 38%). ES+APCI MS m/z 484.2 [M+H]⁺.

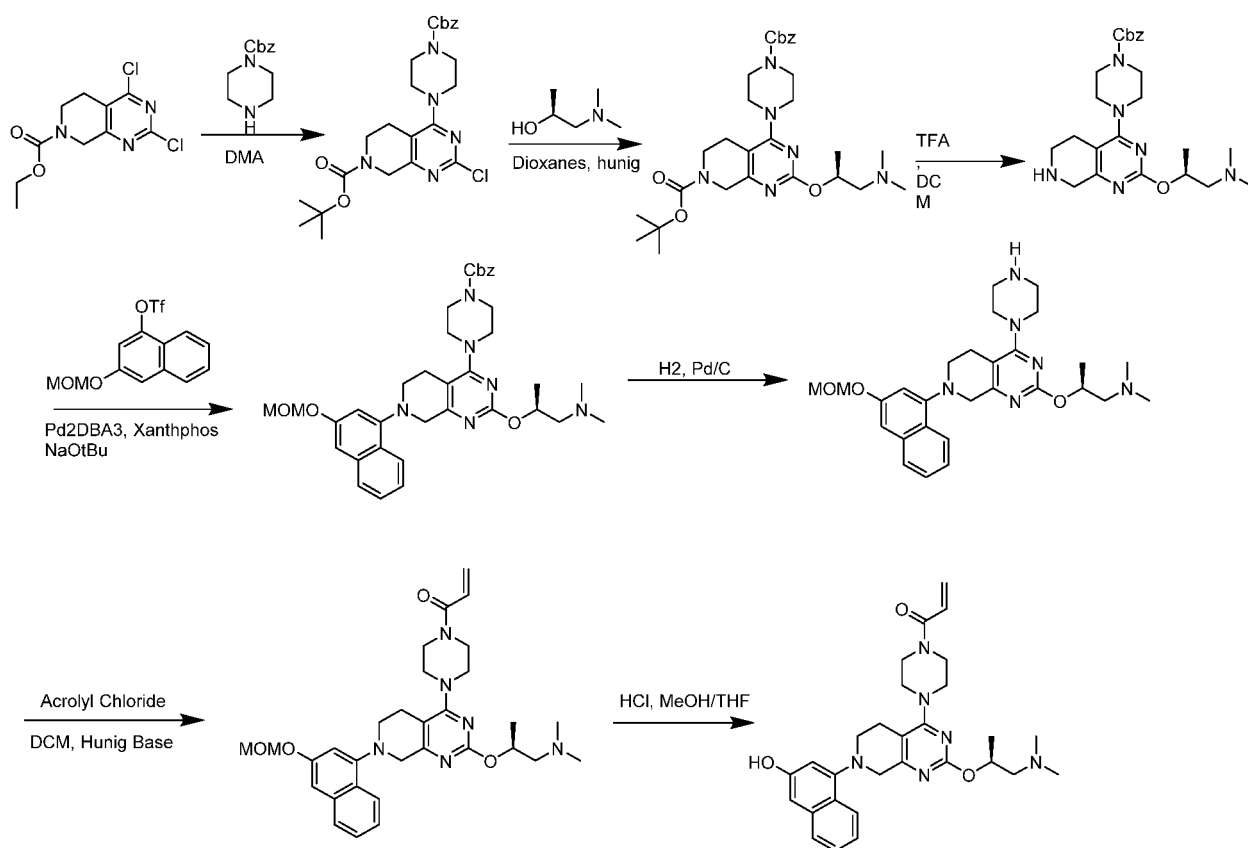
[0295] Step D2: 7-(5-methyl-1H-indazol-4-yl)-4-(piperazin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine: Prepared according to the method of **Example 1**, Step D.

[0296] Step E: 1-(4-(7-(5-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one: Prepared according to the method of **Example 1**, Step E.

EXAMPLE 8



(S)-1-(4-(2-((1-(dimethylamino)propan-2-yl)oxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one



[0297] Step A: tert-butyl 4-(4-((benzyloxy)carbonyl)piperazin-1-yl)-2-chloro-5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate: Benzyl 1-piperazinecarboxylate (1.268 mL, 6.575 mmol) and tert-Butyl 2,4-dichloro-5,6-dihydropyrido[3,4-d]pyrimidine-7(8H)-carboxylate (2 g, 6.575 mmol) were dissolved in dimethyl acetamide (10 mL) and treated with N-ethyl-N-isopropylpropan-2-amine (3.445 mL, 19.73 mmol). The reaction mixture was stirred at 85 °C for 2 hours. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, washed with water and brine, dried over MgSO₄, filtered and concentrated. The concentrate was purified by chromatography (CombiFlash®, 0%-50% ethyl acetate:Hexanes as the eluent) to provide the product (2.69g, 83%). ES+APCI MS m/z 488.2, 490.2 [M+H]⁺.

[0298] Step B: tert-butyl (S)-4-(4-((benzyloxy)carbonyl)piperazin-1-yl)-2-((1-(dimethylamino)propan-2-yl)oxy)-5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate: Tert-butyl 4-(4-((benzyloxy)carbonyl)piperazin-1-yl)-2-chloro-5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate (235 mg, 0.482 mmol), and (S)-1-(dimethylamino)propan-2-ol (497 mg, 4.82 mmol) were added to dioxane (0.5 mL) and heated to 100 °C for 3 days. The reaction was concentrated and the resulting residue was purified by silica gel (Biotage Isolera,

0-12% methanol in dichloromethane) to provide tert-butyl (S)-4-(4-((benzyloxy)carbonyl)piperazin-1-yl)-2-((1-(dimethylamino)propan-2-yl)oxy)-5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate (200 mg, 0.361 mmol, 74.9 % yield). ES+APCI MS m/z 555.3 [M+H]⁺.

[0299] Step C: benzyl (S)-4-(2-((1-(dimethylamino)propan-2-yl)oxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate: To a solution of tert-butyl (S)-4-(4-((benzyloxy)carbonyl)piperazin-1-yl)-2-((1-(dimethylamino)propan-2-yl)oxy)-5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate (200 mg, 0.3606 mmol) in dichloromethane (1202 μ L, 0.3606 mmol) was added trifluoroacetic acid (828.3 μ L, 10.82 mmol) and the reaction was stirred at room temperature for 3 hours. The reaction was concentrated under vacuum and the residue was taken up in dichloromethane. The solution was washed with 1M NaOH followed by brine and then dried over Na₂SO₄, filtered and concentrated under vacuum. The crude product was purified by column chromatography (Biotage Isolera, 24G Isco RediSep®Gold, 10 to 20% methanol/dichloromethane) to afford the product as an off-white foam (0.135 g, 83%). ES+APCI MS m/z 455.2 [M+H]⁺.

[0300] Step D : benzyl (S)-4-(2-((1-(dimethylamino)propan-2-yl)oxy)-7-(3-(methoxymethoxy)naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate: To a vial was added tris(dibenzylideneacetone)dipalladium (0) (21.8 mg, 0.0238 mmol), racemic-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl (30.4 mg, 0.0488 mmol) and toluene (991 μ L, 0.297 mmol). Argon was bubbled through the mixture for 5 minutes and then the vial was capped and the mixture was heated to 100 °C for 15 minutes. The mixture was cooled to ambient temperature and sodium tert-butoxide (57.2 mg, 0.595 mmol) was added followed by 3-(methoxymethoxy)naphthalen-1-yl trifluoromethanesulfonate (100 mg, 0.297 mmol) and benzyl (S)-4-(2-((1-(dimethylamino)propan-2-yl)oxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (135 mg, 0.297 mmol). The vial was capped and the mixture was heated to 100 °C for 18 hours. The mixture was cooled and concentrated. The crude material was purified by silica gel (Biotage Isolera, 0-11% methanol/dichloromethane to provide benzyl (S)-4-(2-((1-(dimethylamino)propan-2-yl)oxy)-7-(3-(methoxymethoxy)naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (68 mg, 0.106 mmol, 35.7 % yield). ES+APCI MS m/z 641.3 [M+H]⁺.

[0301] Step E: (S)-2-((7-(3-(methoxymethoxy)naphthalen-1-yl)-4-(piperazin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-2-yl)oxy)-N,N-dimethylpropan-1-amine: To a solution of benzyl (S)-4-(2-((1-(dimethylamino)propan-2-yl)oxy)-7-(3-(methoxymethoxy)naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (68 mg, 0.11 mmol) in ethanol (1061 μ L, 0.11 mmol) and tetrahydrofuran (1061 μ L, 0.11 mmol) was added Palladium (113 mg, 0.053 mmol) (Degussa Type, 10 wt.%, 50% H₂O). An atmosphere of H₂ was introduced by vacuum and then the reaction vessel was maintained under an atmosphere of H₂. The mixture was stirred at ambient temperature for 3 hours. The mixture was diluted with methanol and filtered through GF/F paper. The colorless filtrate was concentrated to provide (S)-2-((7-(3-(methoxymethoxy)naphthalen-1-yl)-4-(piperazin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-2-yl)oxy)-N,N-dimethylpropan-1-amine (54 mg, 100 % yield) which was used in the next step without purification. ES+APCI MS m/z 507.3 [M+H]⁺.

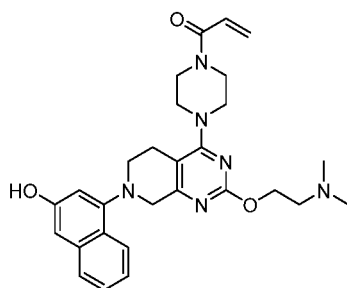
[0302] Step F: (S)-1-(4-(2-((1-(dimethylamino)propan-2-yl)oxy)-7-(3-(methoxymethoxy)naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one: To a suspension of (S)-2-((7-(3-(methoxymethoxy)naphthalen-1-yl)-4-(piperazin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-2-yl)oxy)-N,N-dimethylpropan-1-amine (54 mg, 0.11 mmol) in dichloromethane (1066 μ L, 0.11 mmol) at ambient temperature was added acryloyl chloride (1279 μ L, 0.13 mmol) (freshly prepared 0.1 M solution in DCM) followed by triethylamine (30 μ L, 0.21 mmol). The reaction was stirred at ambient temperature for 20 minutes. The mixture was concentrated and the product was purified by column chromatography (Biotage Isolera, 12G Isco RediSep®, 0-15% methanol/dichloromethane) to afford (S)-1-(4-(2-((1-(dimethylamino)propan-2-yl)oxy)-7-(3-(methoxymethoxy)naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one (51 mg, 0.091 mmol, 85 % yield). ES+APCI MS m/z 561.3 [M+H]⁺.

[0303] Step G: 1-(4-(2-(2-(dimethylamino)ethoxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one: (S)-1-(4-(2-((1-(dimethylamino)propan-2-yl)oxy)-7-(3-(methoxymethoxy)naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one (51 mg, 0.091 mmol) was added to a vial containing 350 μ L of methanol and a few drops of tetrahydrofuran and the reaction vial was capped. HCl (379 μ L, 2.3 mmol) (6M aqueous) was added with stirring, and

the mixture was heated to 55 °C for 3 hours. The reaction was cooled and concentrated under vacuum. A saturated bicarbonate solution was added and the reaction was extracted with 10% methanol in dichloromethane. The organic layers were combined and concentrated. The resulting residue was purified by silica gel (Biotage Isolera, 4-20% methanol in dichloromethane with 1% concentrated ammonium chloride) to provide the title product (25.3 mg, 54%). ES+APCI MS m/z 517.2 $[M+H]^+$.

[0304] ^1H NMR (400 MHz, CDCl_3) δ 7.90 (d, 1H, $J=8.314\text{Hz}$), 7.54 (d, 1H, $J=8.021$), 7.34 (m, 1H), 7.24 (m, 1H), 6.72 (m, 1H), 6.56-6.48 (m, 2H), 6.32 (dd, 1H, $J=16.726, 1.858$), 5.73 (dd, 1H, $J=10.368, 1.858$), 5.45 (m, 1H), 4.09-3.94 (m, 2H), 3.63 (bs, 2H), 3.47 (bs, 2H), 3.31 (m, 4H), 3.16 (bs, 2H), 2.84 (m, 1H), 2.60 (bs, 2H), 2.45 (m, 1H), 2.43 (s, 6H), 1.31 (d, 3H, $J=6.162\text{Hz}$)

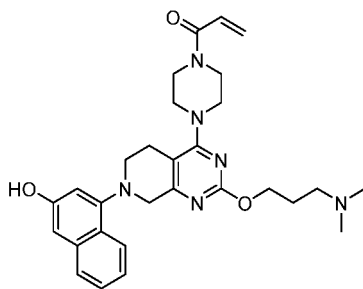
EXAMPLE 9



1-(4-(2-(2-(dimethylamino)ethoxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0305] Synthesized according to the method of **Example 8**, using 2-(dimethylamino)ethan-1-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 503.2 $[M+H]^+$.

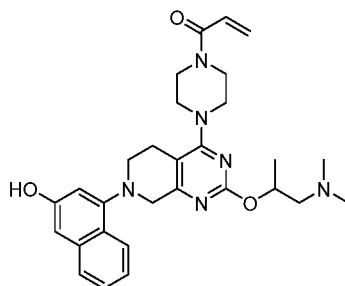
EXAMPLE 10



1-(4-(2-(3-(dimethylamino)propoxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0306] Synthesized according to the method of **Example 8**, using 3-(dimethylamino)propan-1-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 517.3 [M+H]⁺.

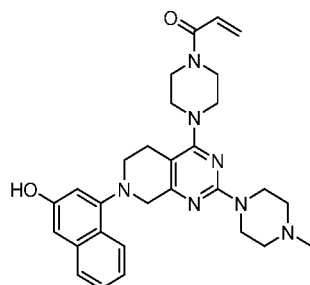
EXAMPLE 11



1-(4-(2-((1-(dimethylamino)propan-2-yl)oxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0307] Synthesized according to the method of **Example 8**, using 1-(dimethylamino)propan-2-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 517.3 [M+H]⁺.

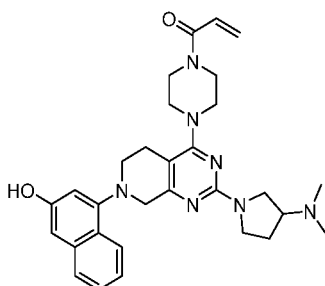
EXAMPLE 12



1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-(4-methylpiperazin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0308] Synthesized according to the method of **Example 8**, using 1-methylpiperazine in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 514.3 [M+H]⁺.

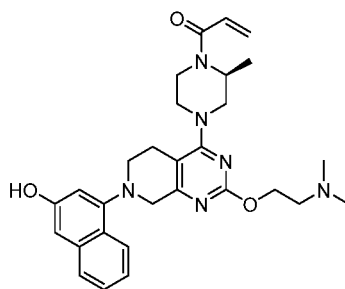
EXAMPLE 13



1-(4-(2-(3-(dimethylamino)pyrrolidin-1-yl)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0309] Synthesized according to the method of **Example 8**, using N,N-dimethylpyrrolidin-3-amine in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 528.3 [M+H]⁺.

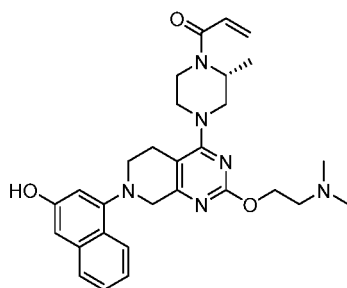
EXAMPLE 14



(S)-1-(4-(7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)-2-methylpiperazin-1-yl)prop-2-en-1-one

[0310] Synthesized according to the method of **Example 8**, using benzyl (S)-2-methylpiperazine-1-carboxylate in place of benzyl piperazine-1-carboxylate in Step A and using 2-(dimethylamino)ethan-1-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 517.3 [M+H]⁺.

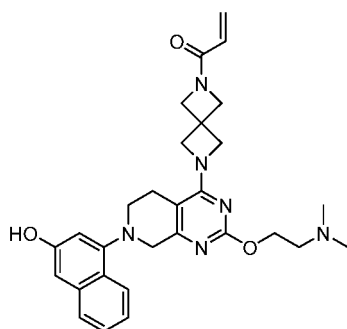
EXAMPLE 15



(R)-1-(4-(2-(2-(dimethylamino)ethoxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)-2-methylpiperazin-1-yl)prop-2-en-1-one

[0311] Synthesized according to the method of **Example 8**, substituting benzyl (R)-2-methylpiperazine-1-carboxylate for benzyl piperazine-1-carboxylate in Step A and 2-(dimethylamino)ethan-1-ol for (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 517.3 [M+H]⁺.

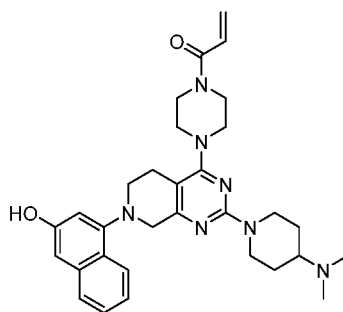
EXAMPLE 16



1-(6-(2-(2-(dimethylamino)ethoxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)-2,6-diazaspiro[3.3]heptan-2-yl)prop-2-en-1-one

[0312] Synthesized according to the method of **Example 8**, using benzyl 2,6-diazaspiro[3.3]heptane-2-carboxylate in place of benzyl piperazine-1-carboxylate in Step A and substituting 2-(dimethylamino)ethan-1-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 515.3 [M+H]⁺.

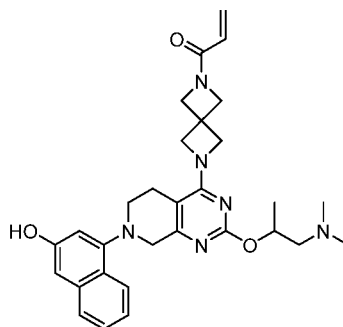
EXAMPLE 17



1-(4-(2-(4-(dimethylamino)piperidin-1-yl)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0313] Synthesized according to the method of **Example 8**, using N,N-dimethylpiperidin-4-amine in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 580.3 [M+H]⁺.

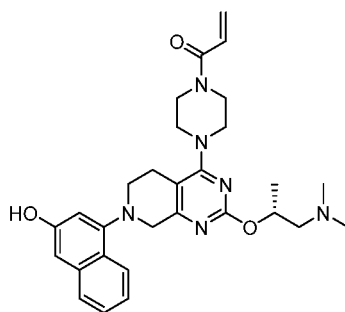
EXAMPLE 18



1-(6-(2-((1-(dimethylamino)propan-2-yl)oxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)-2,6-diazaspiro[3.3]heptan-2-yl)prop-2-en-1-one

[0314] Synthesized according to the method of **Example 8**, using benzyl 2,6-diazaspiro[3.3]heptane-2-carboxylate in place of benzyl piperazine-1-carboxylate in Step A and substituting 1-(dimethylamino)propan-2-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 529.3 [M+H]⁺.

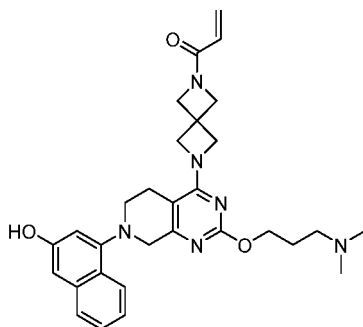
EXAMPLE 19



(R)-1-(4-(2-((1-(dimethylamino)propan-2-yl)oxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0315] Synthesized according to the method of **Example 8**, using (R)-1-(dimethylamino)propan-2-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 517.3 [M+H]⁺.

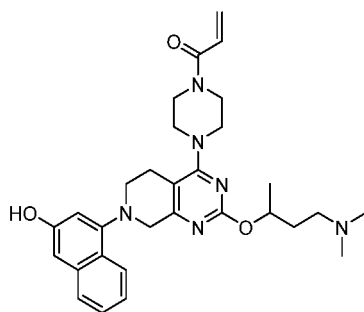
EXAMPLE 20



1-(6-(2-(3-(dimethylamino)propoxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)-2,6-diazaspiro[3.3]heptan-2-yl)prop-2-en-1-one

[0316] Synthesized according to the method of **Example 8**, using benzyl 2,6-diazaspiro[3.3]heptane-2-carboxylate in place of benzyl piperazine-1-carboxylate in Step A and substituting 3-(dimethylamino)propan-1-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 529.3 [M+H]⁺.

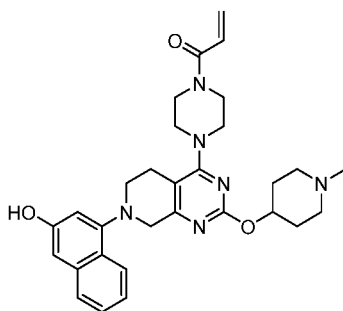
EXAMPLE 21



1-(4-(2-((4-(dimethylamino)butan-2-yl)oxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0317] Synthesized according to the method of **Example 8**, using 4-(dimethylamino)butan-2-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 531.3 [M+H]⁺.

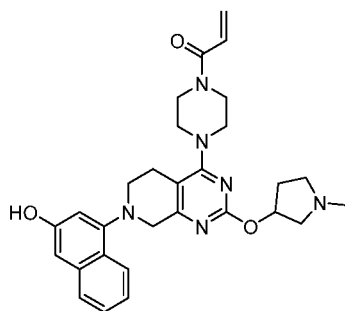
EXAMPLE 22



1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-((1-methylpiperidin-4-yl)oxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0318] Synthesized according to the method of **Example 8**, using 1-methylpiperidin-4-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 529.3 [M+H]⁺.

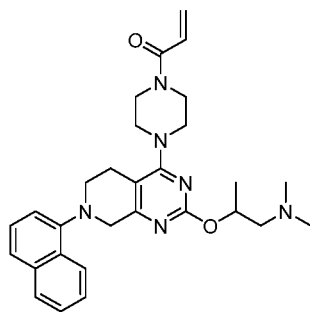
EXAMPLE 23



1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-((1-methylpyrrolidin-3-yl)oxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0319] Synthesized according to the method of **Example 8**, using 1-methylpyrrolidin-3-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 515.3 [M+H]⁺.

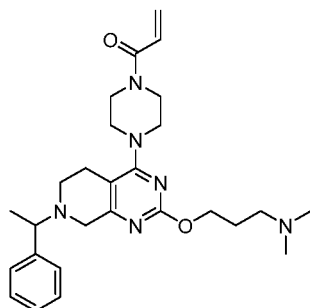
EXAMPLE 24



1-(4-(2-((1-(dimethylamino)propan-2-yl)oxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0320] Synthesized according to the method of **Example 8**, using 1-(dimethylamino)propan-2-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B, using 1-bromo naphthalene in place of 3-(methoxymethoxy)naphthalen-1-yl trifluoromethanesulfonate in step D, and eliminating Step G. ES+APCI MS m/z 501.3 [M+H]⁺.

EXAMPLE 25

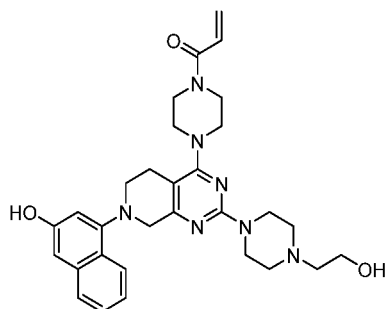


1-(4-(2-(3-(dimethylamino)propoxy)-7-(1-phenylethyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0321] Synthesized according to the method of **Example 8**, using 3-(dimethylamino)propan-1-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B, using (1-bromoethyl)benzene in place

of 3-(methoxymethoxy)naphthalen-1-yl trifluoromethanesulfonate in step D, and eliminating Step G. ES+APCI MS m/z 559.3 $[M+H]^+$.

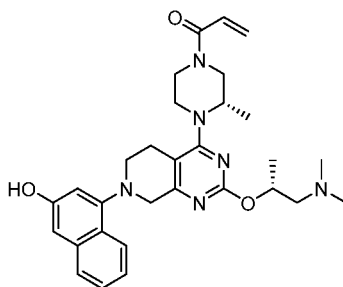
EXAMPLE 26



1-(4-(2-(4-(2-hydroxyethyl)piperazin-1-yl)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0322] Synthesized according to the method of **Example 8**, using 2-(piperazin-1-yl)ethyl acetate in place of (S)-1-(dimethylamino)propan-2-ol in Step B. After Step D, the following saponification reaction was performed: Benzyl 4-(2-(4-(2-acetoxyethyl)piperazin-1-yl)-7-(3-(methoxymethoxy)naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate was taken up in THF (5 mL) and 2 M LiOH (1 mL) was added. The mixture was stirred at ambient temperature for 24 hr. Saturated NH_4Cl was added and the reaction was extracted with DCM. The combined organic layers were concentrated and the resulting residue was purified by silica gel (Biotage Isolera Gold, eluting with 0-10% MeOH in DCM) to provide benzyl 4-(2-(4-(2-hydroxyethyl)piperazin-1-yl)-7-(3-(methoxymethoxy)naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate. The remainder of the synthesis proceeded as in Example 8, step E. ES+APCI MS m/z 544.3 $[M+H]^+$.

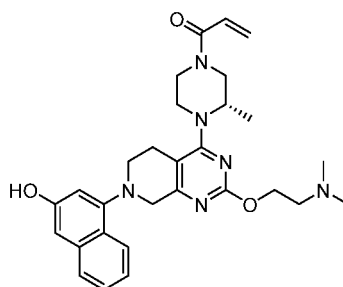
EXAMPLE 27



1-((S)-4-(2-(((R)-1-(dimethylamino)propan-2-yl)oxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)-3-methylpiperazin-1-yl)prop-2-en-1-one

[0323] Synthesized according to the method of **Example 8**, using benzyl (S)-3-methylpiperazine-1-carboxylate in place of benzyl piperazine-1-carboxylate in Step A and using (R)-1-(dimethylamino)propan-2-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 531.3 [M+H]⁺.

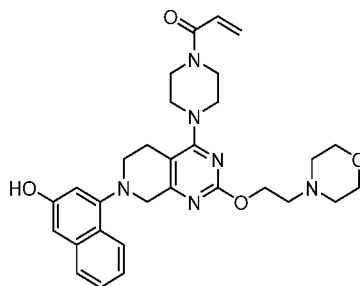
EXAMPLE 28



(S)-1-(4-(2-(2-(dimethylamino)ethoxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)-3-methylpiperazin-1-yl)prop-2-en-1-one

[0324] Synthesized according to the method of **Example 8**, using benzyl (S)-3-methylpiperazine-1-carboxylate in place of benzyl piperazine-1-carboxylate in Step A and using 2-(dimethylamino)ethan-1-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 517.2 [M+H]⁺.

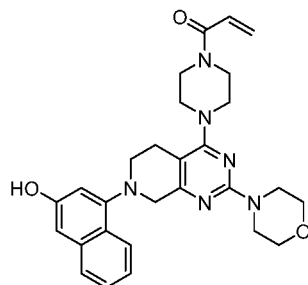
EXAMPLE 29



1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-(2-morpholinoethoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0325] Synthesized according to the method of **Example 8**, using 2-morpholinoethan-1-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 545.2 [M+H]⁺.

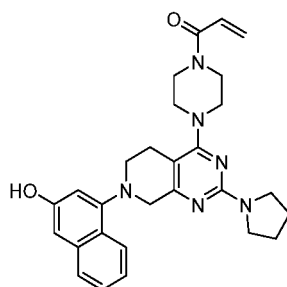
EXAMPLE 30



1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-morpholino-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0326] Synthesized according to the method of **Example 8**, using morpholine in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 501.3 $[M+H]^+$.

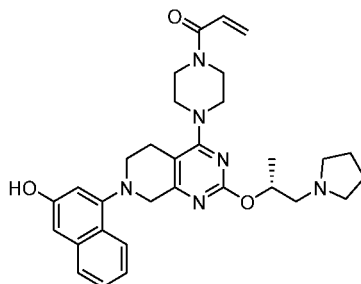
EXAMPLE 31



1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-(pyrrolidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0327] Synthesized according to the method of **Example 8**, using pyrrolidine in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 485.2 $[M+H]^+$.

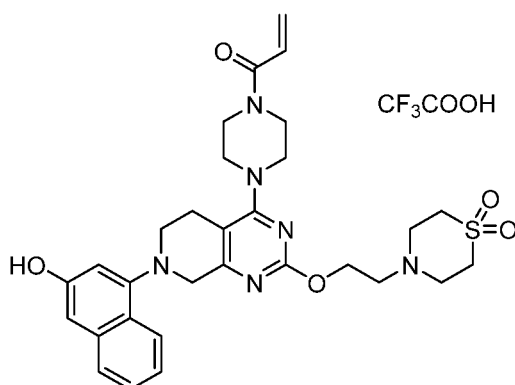
EXAMPLE 32



(R)-1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-((1-(pyrrolidin-1-yl)propan-2-yl)oxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0328] Synthesized according to the method of Example 8, using (R)-1-(pyrrolidin-1-yl)propan-2-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 543.4 $[M+H]^+$.

EXAMPLE 33



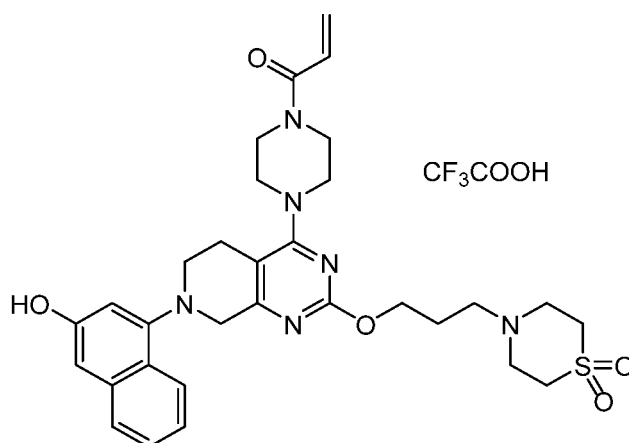
1-(4-(2-(2-(1,1-dioxidothiomorpholino)ethoxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one trifluoroacetate

[0329] Step A: benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[2-(1,1-dioxo-1,4-thiazinan-4-yl)ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate: To a mixture of benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-methylsulfinyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (300 mg, 463.12 μ mol, 1.00 eq) and 2-(1,1-dioxo-1,4-thiazinan-4-yl)ethanol (166 mg, 926 μ mol, 2.00 eq) in toluene (10.0 mL) was added NaOBu-t (133 mg, 1.39 mmol, 3.00 eq), BINAP (57.7 mg, 92.6 μ mol, 0.20 eq), $Pd_2(dba)_3$ (42.4 mg, 46.3 μ mol, 0.10 eq). The reaction mixture was stirred at 90 °C for 12 hours under N_2 . The reaction mixture was filtered and the filter cake was washed with DCM (3×10 mL). The filtrate was concentrated under vacuum. The residue was purified by reverse flash chromatography (40 % MeCN in water (0.1 % TFA) to give benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[2-(1,1-dioxo-1,4-thiazinan-4-yl)ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (230 mg, 301 μ mol, 65.1 % yield) as a brown solid. ESI MS m/z 763.5 $[M+H]^+$.

[0330] Step B: 4-[2-[2-(1,1-dioxo-1,4-thiazinan-4-yl)ethoxy]-4-piperazin-1-yl]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-7-yl]naphthalen-2-ol: To a solution of benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[2-(1,1-dioxo-1,4-thiazinan-4-yl)ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (190 mg, 249 μ mol, 1.00 eq) in MeOH (10.0 mL) was added Pd/C (100 mg) under N₂. The suspension was degassed under vacuum and purged with hydrogen several times. The mixture was stirred under hydrogen (15 psi) at 40°C for 4 hours. The reaction mixture was filtered and the filtrate was concentrated under vacuum to give 4-[2-[2-(1,1-dioxo-1,4-thiazinan-4-yl)ethoxy]-4-piperazin-1-yl]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-7-yl]naphthalen-2-ol (90.0 mg, 167 μ mol, 67.1 % yield) as a brown solid. **ESI MS** m/z 539.4 [M+H]⁺.

[0331] Step C: 1-[4-[2-[2-(1,1-dioxo-1,4-thiazinan-4-yl)ethoxy]-7-(3-hydroxy-1-naphthyl)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one: To a solution of 4-[2-[2-(1,1-dioxo-1,4-thiazinan-4-yl)ethoxy]-4-piperazin-1-yl]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-7-yl]naphthalen-2-ol (90.0 mg, 167 μ mol, 1.00 eq) and DIEA (64.8 mg, 501 μ mol, 87.5 μ L, 3.00 eq) in DCM (2.00 mL) was added prop-2-enoyl prop-2-enoate (19.0 mg, 150 μ mol, 0.90 eq) at -40 °C. The reaction mixture was stirred at -40 °C for 0.5 h. The reaction mixture was quenched with 1 mL of MeOH and concentrated under vacuum. The residue was purified by preparative HPLC column: Phenomenex Synergi C18 150*25*, 10 μ ; mobile phase: [water (0.1% TFA) -ACN]; B%: 12%-42%, 11 min to give 1-[4-[2-[2-(1,1-dioxo-1,4-thiazinan-4-yl)ethoxy]-7-(3-hydroxy-1-naphthyl)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one trifluoroacetate (32.6 mg, 50.2 μ mol, 30.0 % yield, 91.3 % purity) as a brown solid. **ESI MS** m/z 593.5 [M+H]⁺.

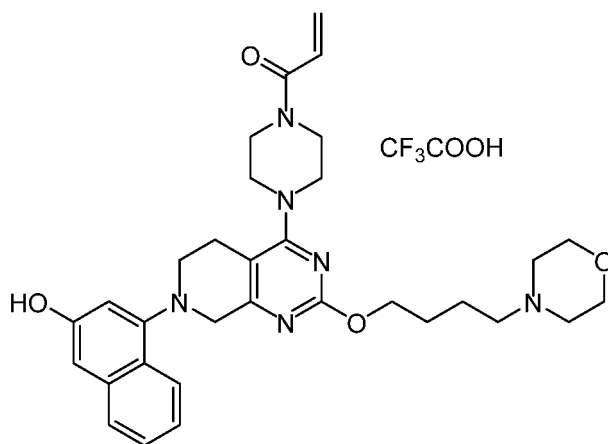
EXAMPLE 34



1-(4-(2-(3-(1,1-dioxidothiomorpholino)propoxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one trifluoroacetate

[0332] Synthesized according to the method of **Example 33**, using 3-(1,1-dioxo-1,4-thiazinan-4-yl)propan-1-ol in place of 2-(1,1-dioxo-1,4-thiazinan-4-yl)ethanol in Step A. **ESI MS** m/z 607.5 $[M+H]^+$.

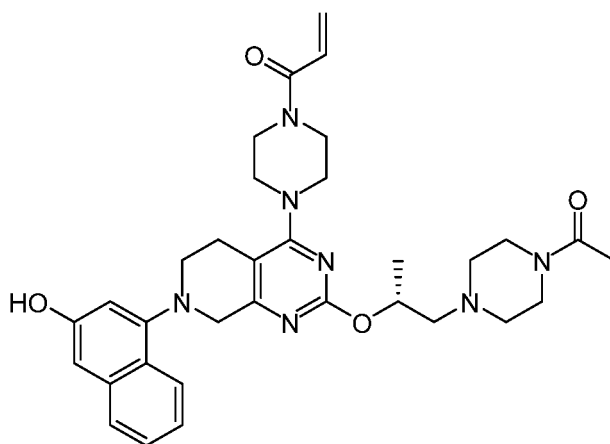
EXAMPLE 35



1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-(4-morpholinobutoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one trifluoroacetate

[0333] Synthesized according to the method of **Example 33**, using 4-morpholinobutan-1-ol in place of 2-(1,1-dioxo-1,4-thiazinan-4-yl)ethanol in Step A. **ESI MS** m/z 573.4 $[M+H]^+$.

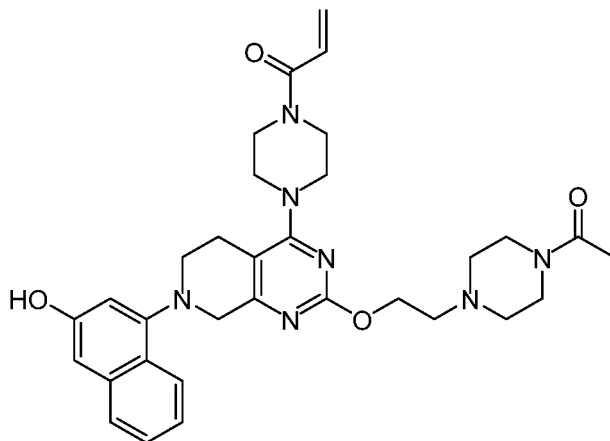
EXAMPLE 36



(R)-1-(4-(2-((1-(4-acetylpiperazin-1-yl)propan-2-yl)oxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0334] Synthesized according to the method of **Example 33**, using 1-[4-[(2R)-2-hydroxypropyl]piperazin-1-yl]ethanone in place of 2-(1,1-dioxo-1,4-thiazinan-4-yl)ethanol in Step A. **ESI MS** m/z 600.6 $[M+H]^+$.

EXAMPLE 37



1-(4-(2-(2-(4-acetylpiperazin-1-yl)ethoxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0335] Step A: benzyl 4-[2-[2-(4-acetylpiperazin-1-yl)ethoxy]-7-(3-benzyloxy-1-naphthyl)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate: To a solution of 1-[4-(2-hydroxyethyl)piperazin-1-yl]ethanone (277 mg, 1.61 mmol, 2.60 eq) in THF (8.00 mL) was added NaH (49.4 mg, 1.23 mmol, 60 % purity, 2.00 eq) at 0°C. The reaction mixture was stirred

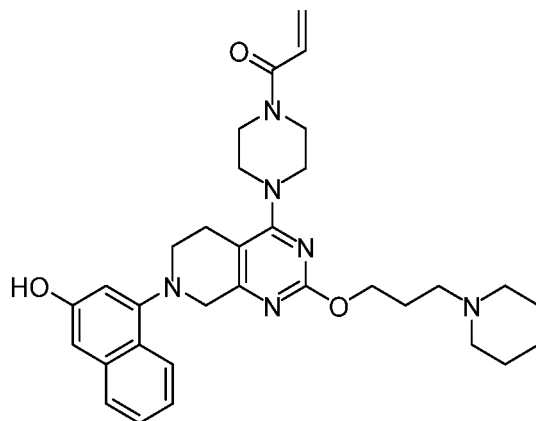
at 0 °C for 15 minutes. To the mixture was added benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-methylsulfinyl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (400 mg, 618 µmol, 1.00 eq) in THF (2.00 mL). The reaction mixture was stirred at 0 °C for 20 minutes. The reaction mixture was quenched with saturated NH₄Cl (6 mL) and water (6 mL). The reaction mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄ and concentrated under vacuum to give benzyl 4-[2-[2-(4-acetylpiperazin-1-yl)ethoxy]-7-(3-benzyloxy-1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (450 mg, 534 µmol, 86.5 % yield, 89.7 % purity) as a brown solid. ESI MS *m/z* 756.3 [M+H]⁺.

[0336] Step B: 1-[4-[2-[[7-(3-hydroxy-1-naphthyl)-4-piperazin-1-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-2-yl]oxy]ethyl]piperazin-1-yl]ethanone: To a solution of benzyl 4-[2-[2-(4-acetylpiperazin-1-yl)ethoxy]-7-(3-benzyloxy-1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (200 mg, 264 µmol, 1.00 eq) in THF (10.0 mL) was added Pd/C (100 mg, 10 % purity) under N₂. The suspension was degassed under vacuum and purged with hydrogen several times. The mixture was stirred under hydrogen (15 psi) at 40 °C for 12 hours. The reaction mixture was filtered and the filter cake was washed with THF (3 × 5 mL). The filtrate was concentrated under vacuum to give 1-[4-[2-[[7-(3-hydroxy-1-naphthyl)-4-piperazin-1-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-2-yl]oxy]ethyl]piperazin-1-yl]ethanone (80.0 mg, 150 µmol, 56.9 % yield) as a brown solid.

[0337] Step C: 1-[4-[2-[2-(4-acetylpiperazin-1-yl)ethoxy]-7-(3-hydroxy-1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one: To a solution of 1-[4-[2-[[7-(3-hydroxy-1-naphthyl)-4-piperazin-1-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-2-yl]oxy]ethyl]piperazin-1-yl]ethanone (80.0 mg, 150 µmol, 1.00 eq) and DIEA (58.3 mg, 451 µmol, 78.8 µL, 3.00 eq) in DCM (2.00 mL) was added prop-2-enoyl prop-2-enoate (14.2 mg, 113 µmol, 0.75 eq) at - 40 °C for 0.5 h. The reaction mixture was quenched with MeOH (1 mL) and diluted by DCM (20 mL) next washed with water (5 mL). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄ and concentrated under vacuum. The reaction mixture was purified by preparative HPLC : Phenomenex Gemini 150*25mm*, 10 µ; mobile phase: [water (0.05% ammonia hydroxide v/v) - ACN]; B%: 30%-55%, 10 min to give 1-[4-[2-[2-(4-acetylpiperazin-1-yl)ethoxy]-7-(3-hydroxy-1-naphthyl)-6,8-dihydro-5*H*-

pyrido[3,4-d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one (13.8 mg, 23.3 μ mol, 15.5 % yield, 98.7 % purity) as a yellow solid. **ESI MS** m/z 586.3 $[M+H]^+$.

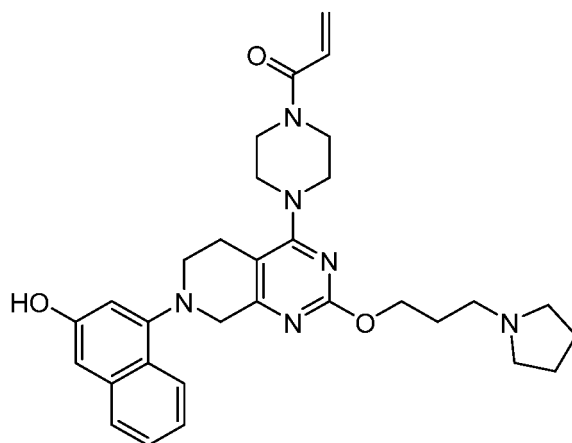
EXAMPLE 38



1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-(3-(piperidin-1-yl)propoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0338] Synthesized according to the method of **Example 37**, using 3-(1-piperidyl)propan-1-ol in place of 1-[4-(2-hydroxyethyl)piperazin-1-yl]ethanone in Step A. **ESI MS** m/z 557.5 $[M+H]^+$.

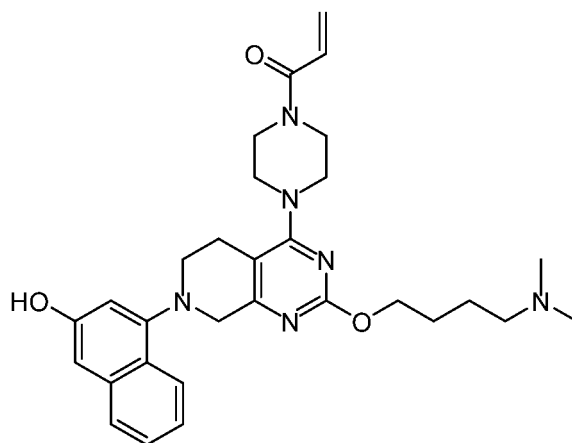
EXAMPLE 39



1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-(3-(pyrrolidin-1-yl)propoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0339] Synthesized according to the method of **Example 37**, using 3-pyrrolidin-1-ylpropan-1-ol in place of 1-[4-(2-hydroxyethyl)piperazin-1-yl]ethanone in Step A. **ESI MS** m/z 543.3 $[M+H]^+$

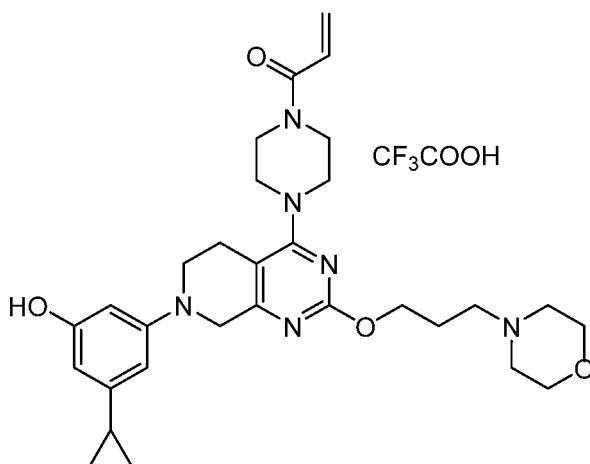
EXAMPLE 40



1-(4-(2-(4-(dimethylamino)butoxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0340] Synthesized according to the method of **Example 37**, using 4-(dimethylamino)butan-1-ol in place of 1-[4-(2-hydroxyethyl)piperazin-1-yl]ethanone in Step A. **ESI MS** m/z 531.4 $[M+H]^+$

EXAMPLE 41



1-(4-(7-(3-cyclopropyl-5-hydroxyphenyl)-2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one trifluoroacetate

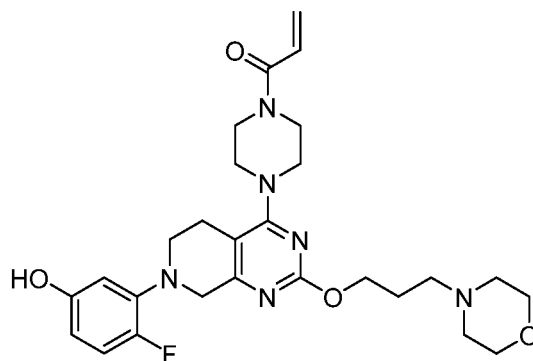
[0341] Step A: 4-[7-(3-benzyloxy-5-cyclopropyl-phenyl)-2-(3-morpholinopropoxy)-6,8-dihydro-5*H*-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate: To a mixture of benzyl 4-[2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (400 mg, 805 μ mol, 1.00 *eq*) and 1-benzyloxy-3-bromo-5-cyclopropyl-benzene (268 mg, 886 μ mol, 1.10 *eq*) in toluene (10.0 mL) was added 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl (RuPhos) (75.2 mg, 161 μ mol, 0.20 *eq*), Pd₂(dba)₃ (111 mg, 121 μ mol, 0.15 *eq*) and Cs₂CO₃ (656 mg, 2.01 mmol, 2.50 *eq*). The reaction mixture was stirred at 90 °C for 12 hours under N₂. The mixture was added to water (15 mL) and extracted with DCM (2 $\times$ 15 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The residue was purified by chromatography (SiO₂, Petroleum ether/Ethyl acetate = 3:1 to Dichloromethane: Methanol = 10:1) to give benzyl 4-[7-(3-benzyloxy-5-cyclopropyl-phenyl)-2-(3-morpholinopropoxy)-6,8-dihydro-5*H*-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (170 mg, 230 μ mol, 28.5 % yield, 97.2 % purity) as brown oil. **ESI MS** *m/z* 719.6 [M+H]⁺.

[0342] Step B: 3-cyclopropyl-5-[2-(3-morpholinopropoxy)-4-piperazin-1-yl]-6,8-dihydro-5*H*-pyrido[3,4-d]pyrimidin-7-yl]phenol To a mixture of benzyl 4-[7-(3-benzyloxy-5-cyclopropyl-phenyl)-2-(3-morpholinopropoxy)-6,8-dihydro-5*H*-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (150 mg, 209 μ mol, 1.00 *eq*) in MeOH (10.0 mL) was added Pd/C (150 mg, 10 % purity) and CH₃COOH (25.1 mg, 417.3 μ mol, 23.9 μ L, 2.00 *eq*). The suspension was degassed under vacuum and purged with hydrogen several times. The mixture was stirred under hydrogen (15 Psi) at 40 °C for 2 hours. The reaction mixture was filtered through Celite® and the filtrate was concentrated. The product 3-cyclopropyl-5-[2-(3-morpholinopropoxy)-4-piperazin-1-yl]-6,8-dihydro-5*H*-pyrido[3,4-d]pyrimidin-7-yl]phenol diacetate (80.0 mg, 130 μ mol, 62.4 % yield) was obtained as yellow solid. **ESI MS** *m/z* 495.2 [M+H]⁺.

[0343] Step C: 1-[4-[7-(3-cyclopropyl-5-hydroxy-phenyl)-2-(3-morpholinopropoxy)-6,8-dihydro-5*H*-pyrido[3,4-d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one To a mixture of 3-cyclopropyl-5-[2-(3-morpholinopropoxy)-4-piperazin-1-yl]-6,8-dihydro-5*H*-pyrido[3,4-d]pyrimidin-7-yl]phenol diacetate (80.0 mg, 130 μ mol, 1.00 *eq*) in DCM (2.00 mL) was added DIEA (168 mg, 1.30 mmol, 227 μ L, 10.0 *eq*) and prop-2-enoyl prop-2-enoate (13.1 mg, 104

μmol , 0.80 *eq*) at $-78\text{ }^{\circ}\text{C}$, the reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 0.5 hour. The reaction mixture was quenched with MeOH (2 eq, 10 mg), then concentrated. The residue was purified by preparative HPLC (Instrument: GX-K; Column: Phenomenex Synergi C18 150*25*, 10 μ ; Conditions: water (0.1 % TFA)-ACN; Begin B: 8; End B: 38; Gradient Time (min): 11; 100% B Hold Time (min): 2; FlowRate (mL/min): 25). The isolated product was concentrated by lyophilization. The product 1-[4-[7-(3-cyclopropyl-5-hydroxy-phenyl)-2-(3-morpholinopropoxy)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one trifluoroacetate (21.5 mg, 31.1 μmol , 23.9 % yield, 95.8 % purity) was obtained as yellow solid. **ESI MS** m/z 549.5 $[\text{M}+\text{H}]^{+}$.

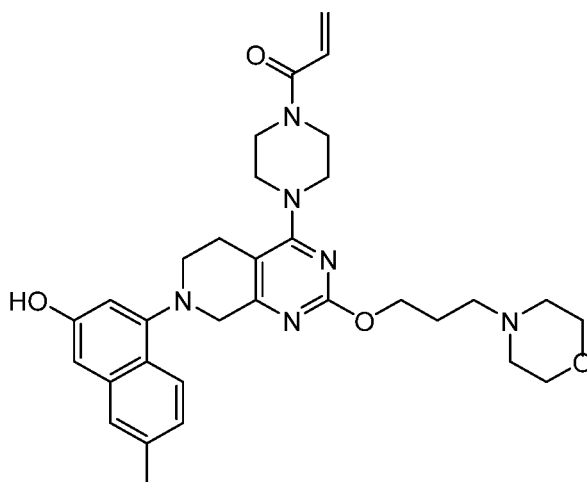
EXAMPLE 42



1-(4-(7-(2-fluoro-5-hydroxyphenyl)-2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0344] Synthesized according to the method of **Example 41**, using 4-(benzyloxy)-2-bromo-1-fluorobenzene in place of 1-benzyloxy-3-bromo-5-cyclopropyl-benzene in Step A. **ESI MS** m/z 527.4 $[\text{M}+\text{H}]^{+}$.

EXAMPLE 43



1-(4-(7-(3-hydroxy-6-methylnaphthalen-1-yl)-2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0345] Step A: benzyl 4-[7-(3-methoxy-6-methyl-1-naphthyl)-2-(3-morpholinopropoxy)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate: A mixture of benzyl 4-[2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (500 mg, 1.01 mmol, 1.00 *eq*), (3-methoxy-6-methyl-1-naphthyl)trifluoromethanesulfonate (483 mg, 1.51 mmol, 1.50 *eq*), Cs₂CO₃ (820 mg, 2.52 mmol, 2.50 *eq*), 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl (RuPhos) (93.9 mg, 201.3 μ mol, 0.20 *eq*) and Pd₂(dba)₃ (92.2 mg, 100 μ mol, 0.10 *eq*) in toluene (3.00 mL) was stirred at 90 °C for 10 hours. The mixture was diluted with ethyl acetate (50.0 mL). The precipitate was removed by filtration, and the filtrate was concentrated under vacuum. The residue was purified by reversed phase column chromatography over silica gel (0.1% TFA water/acetonitrile). The desired fractions were combined and basified with saturated aqueous sodium bicarbonate (2.00 mL), then concentrated under vacuum. The residue was extracted with ethyl acetate (2 $\times$ 100 mL). The combined extracts were washed with brine (1 $\times$ 100 mL), dried over sodium sulfate, filtered and concentrated under vacuum to give benzyl 4-[7-(3-methoxy-6-methyl-1-naphthyl)-2-(3-morpholinopropoxy)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (400. mg, 599 μ mol, 59.4 % yield, 100 % purity) as a yellow solid. **ESI MS** *m/z* 667.6 [M+H]⁺.

[0346] Step B: 4-[3-[[7-(3-methoxy-6-methyl-1-naphthyl)-4-piperazin-1-yl]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-2-yl]oxy]propyl]morpholine: To a solution of benzyl 4-[7-(3-methoxy-6-methyl-1-naphthyl)-2-(3-morpholinopropoxy)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-

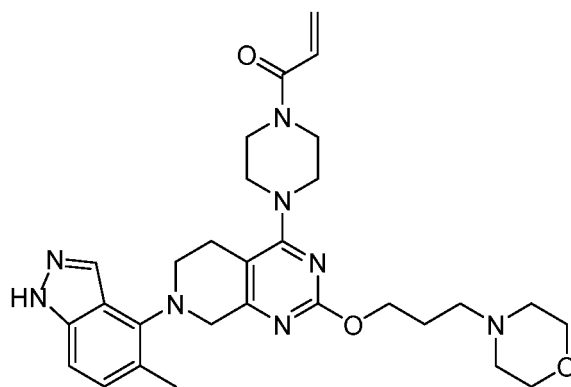
yl]piperazine-1-carboxylate (370 mg, 554 μmol , 1.00 *eq*) in MeOH (10.0 mL) was added Pd-C (100 mg, 10 % purity) and AcOH (66.6 mg, 1.11 mmol, 2.00 *eq*) under N₂. The suspension was degassed under vacuum and purged with hydrogen several times. The mixture was stirred under hydrogen (15 psi) at 40 °C for 2 hours. The reaction mixture was filtered and concentrated in vacuum to provide 4-[3-[[7-(3-methoxy-6-methyl-1-naphthyl)-4-piperazin-1-yl]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-2-yl]oxy]propyl]morpholine (295 mg, 553 μmol , 99.8 % yield) as a yellow solid which was used directly in the next step without purification. ESI MS *m/z* 533.6 [M+H]⁺

[0347] Step C: 1-[4-[7-(3-methoxy-6-methyl-1-naphthyl)-2-(3-morpholinopropoxy) -6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one: To a mixture of prop-2-enoyl prop-2-enoate (56.8 mg, 450 μmol , 0.80 *eq*) and DIEA (727 mg, 5.63 mmol, 983 μL , 10.0 *eq*) in DCM (2.00 mL) was added a solution of 4-[3-[[7-(3-methoxy-6-methyl-1-naphthyl)-4-piperazin-1-yl]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-2-yl]oxy]propyl]morpholine (300 mg, 563 μmol , 1.00 *eq*) DCM (1.00 mL) at -40 °C under a nitrogen atmosphere. The mixture was stirred for 1 hour. The reaction mixture was quenched by addition of MeOH (50 μL) at -40 °C, diluted with water (10.0 mL), extracted with DCM (10.0 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to provide 1-[4-[7-(3-methoxy-6-methyl-1-naphthyl)-2-(3-morpholinopropoxy) -6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one (270 mg, 460 μmol , 81.7 % yield) ESI MS *m/z* 587.6 [M+H]⁺.

[0348] Step D: 1-[4-[7-(3-hydroxy-6-methyl-1-naphthyl) -2-(3-morpholinopropoxy)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one: To a solution of 1-[4-[7-(3-methoxy-6-methyl-1-naphthyl)-2-(3-morpholinopropoxy)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one (100 mg, 170 μmol , 1.00 *eq*) in DCM (3.00 mL) was added BBr₃ (213 mg, 852 μmol , 82.1 μL , 5.00 *eq*) at -78 °C. The mixture was stirred at 0 °C for 1 hour. The mixture was cooled to -78 °C and diluted with DCM (20.0 mL), quenched by addition of saturated sodium bicarbonate solution (5.00 mL) and stirred at -78 °C for 10 mins, then warmed to 0 °C. The mixture was extracted with DCM (2 × 15.0 mL), washed with brine (1 × 20.0 mL), dried over Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by preparative HPLC (column: Phenomenex Gemini C18 250*50 mm*, 10 μ ; mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN]; B%: 27%-57%, 12 min) to

provide 1-[4-[7-(3-hydroxy-6-methyl-1-naphthyl)-2-(3-morpholinopropoxy)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one (11.0 mg, 18.6 μ mol, 10.9 % yield, 97.0 % purity) as a brown solid. **ESI MS** m/z 573.6 $[M+H]^+$.

EXAMPLE 44



1-(4-(7-(5-methyl-1H-indazol-4-yl)-2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0349] Step A: benzyl 4-[7-[5-methyl-1-(2-trimethylsilylethoxymethyl)indazol-4-yl]-2-(3-morpholinopropoxy)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate: A mixture of benzyl 4-[2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (500 mg, 1.01 mmol, 1.00 *eq*), 2-[(4-bromo-5-methyl-indazol-1-yl)methoxy] ethyl-trimethylsilane (448 mg, 1.31 mmol, 1.30 *eq*), Cs_2CO_3 (822 mg, 2.53 mmol, 2.50 *eq*), $\text{Pd}_2(\text{dba})_3$ (138 mg, 151 μ mol, 0.15 *eq*) and 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl (RuPhos) (94.3 mg, 202 μ mol, 0.20 *eq*) in toluene (20.0 mL) was degassed and purged with nitrogen 3 times, and stirred at 90 °C for 10 hours under a nitrogen atmosphere. The reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (3×100 mL). The combined organic layers were washed with brine (3×50.0 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by reversed phase HPLC (0.1% TFA water/acetonitrile) to provide benzyl 4-[7-[5-methyl-1-(2-trimethylsilylethoxymethyl)indazol-4-yl]-2-(3-morpholinopropoxy)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (420 mg, 554 μ mol, 54.9 % yield) as a yellow oil. **ESI MS** m/z 757.6 $[M+H]^+$.

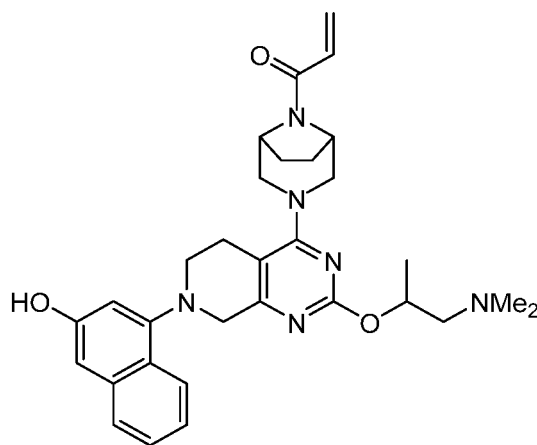
[0350] Step B: *tert*-butyl 4-[7-[5-methyl-1-(2-trimethylsilylethoxymethyl)indazol-4-yl]-2-(3-morpholinopropoxy)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate: To a solution of benzyl 4-[7-[5-methyl-1-(2-trimethylsilylethoxymethyl) indazol-4-yl]-2-(3-morpholinopropoxy)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (370 mg, 488 μ mol, 1.00 *eq*) in MeOH (10.0 mL) was added triethylamine (98.9 mg, 977 μ mol, 135 μ L, 2.00 *eq*), Pd/C(100 mg, 10 % purity) and *tert*-butoxycarbonyl *tert*-butyl carbonate (213 mg, 977 μ mol, 224 μ L, 2.00 *eq*) under N₂. The suspension was degassed under vacuum and purged with hydrogen several times. The mixture was stirred under hydrogen (15 psi) at 40 °C for 2 hours. The reaction mixture was filtrated and concentrated under vacuum. The residue was purified by column chromatography (SiO₂, DCM/MeOH = 1:0 to 10:1) to provide *tert*-butyl 4-[7-[5-methyl-1-(2-trimethylsilylethoxymethyl)indazol-4-yl]-2-(3-morpholinopropoxy)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (340 mg, 470 μ mol, 96.2 % yield) as a brown oil. **ESI MS** *m/z* 723.5 [M+H]⁺.

[0351] Step C: 4-[3-[[7-(5-methyl-1H-indazol-4-yl) -4-piperazin-1-yl]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-2-yl]oxy]propyl]morpholine trifluoroacetate : To a solution of *tert*-butyl 4-[7-[5-methyl-1- (2-trimethylsilylethoxymethyl)indazol-4-yl]-2-(3-morpholinopropoxy)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (150 mg, 207 μ mol, 1.00 *eq*) in DCM (500 μ L) was added TFA (354 mg, 3.11 mmol, 230 μ L, 15.0 *eq*). The mixture was stirred at 25 °C for 1 hour. The reaction mixture was concentrated in vacuum to provide 4-[3-[[7-(5-methyl-1H-indazol-4-yl) -4-piperazin-1-yl]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-2-yl]oxy]propyl]morpholine trifluoroacetate (125 mg, 206 μ mol, 99.3 % yield) as a brown oil and used directly in the next step without purification. **ESI MS** *m/z* 493.4 [M+H]⁺.

[0352] Step D 1-[4-[7-(5-methyl-1H-indazol-4-yl) -2-(3-morpholinopropoxy)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one : To a mixture of 4-[3-[[7-(5-methyl-1H-indazol-4-yl)-4-piperazin -1-yl]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-2-yl]oxy]propyl]morpholine trifluoroacetate (120 mg, 197 μ mol, 1.00 *eq*, TFA) and DIEA (255 mg, 1.98 mmol, 345 μ L, 10.0 *eq*) in dichloromethane (2.00 mL) was added a solution of prop-2-enoyl prop-2-enoate (19.9 mg, 158 μ mol, 0.80 *eq*) dichloromethane (1.00 mL) at -40°C under nitrogen atmosphere. The mixture was stirred for 1 hour. The reaction mixture was quenched by addition of MeOH (50.0 μ L) at -40°C, diluted with water (10.0 mL), extracted with

dichloromethane (10.0 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC (column: Phenomenex Gemini 150*25mm*, 10 μ; mobile phase: [water (0.05% ammonia hydroxide v/v) - ACN]; B%: 30%-60%, 10 min) to provide 1-[4-[7-(5-methyl-1*H*-indazol-4-yl)-2-(3-morpholinopropoxy)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one (19.0 mg, 34.4 μmol, 17.4 % yield, 99.0 % purity) as a white solid. **ESI MS** *m/z* 547.5 [M+H]⁺.

EXAMPLE 45



1-((1*R*,5*S*)-3-(2-((1-(dimethylamino)propan-2-yl)oxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)prop-2-en-1-one

[0353] Step A: *tert*-butyl 3-(7-benzyl-2-chloro-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate: To a mixture of 7-benzyl-2,4-dichloro-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidine (920 mg, 3.13 mmol, 1.00 *eq*) and *tert*-butyl 3,8-diazabicyclo[3.2.1]octane-8-carboxylate (677 mg, 3.19 mmol, 1.02 *eq*) in DMSO (18.0 mL) was added DIEA (1.21 g, 9.39 mmol, 1.64 mL, 3.00 *eq*). The reaction mixture was stirred at 60 °C for 1 hour. The mixture was diluted with extracted with EtOAc (3 × 20 mL), washed with water (10 mL), 1*N* HCl (5 mL), NaHCO₃ (15 mL), and brine (15 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under vacuum to give *tert*-butyl 3-(7-benzyl-2-chloro-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.30 g, 2.41 mmol, 76.9 % yield, 87.0 % purity) as a brown oil which was used directly in the next step without further purification. **ESI MS** *m/z* 470.2 [M+H]⁺.

[0354] Step B: *tert*-butyl 3-[7-benzyl-2-[2-(dimethylamino)-1-methyl-ethoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate: To a solution of 1-(dimethylamino)propan-2-ol (857 mg, 8.31 mmol, 942 μ L, 3.00 *eq*) in THF (40.0 mL) was added NaH (222 mg, 5.54 mmol, 60.0 % purity, 2.00 *eq*) at 15 °C under N₂. After stirring at 15 °C for 0.5 hour, *tert*-butyl 3-(7-benzyl-2-chloro-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.30 g, 2.77 mmol, 1.00 *eq*) was added. The mixture was stirred at 100 °C for 12 hours in a sealed tube. The reaction was slowly quenched with water (3 mL) and then concentrated under vacuum. The residue was purified by column chromatography (DCM/MeOH 60:1 to 10:1) to give *tert*-butyl 3-[7-benzyl-2-[2-(dimethylamino)-1-methyl-ethoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (700 mg, 1.07 mmol, 38.8 % yield, 82.4 % purity) as a yellow oil.

[0355] Step C: *tert*-butyl 3-[2-[2-(dimethylamino)-1-methyl-ethoxy]-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate : To a solution of *tert*-butyl 3-[7-benzyl-2-[2-(dimethylamino)-1-methyl-ethoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (700 mg, 1.30 mmol, 1.00 *eq*) in MeOH (30.0 mL) was added Pd/C (200 mg) under N₂. The suspension was degassed under vacuum and purged with hydrogen 4 times. The mixture was stirred under hydrogen (50 psi) at 40 °C for 12 hours. The mixture was concentrated under vacuum. The residue was purified by column chromatography (DCM/MeOH 50:1 to 5:1) to give *tert*-butyl 3-[2-[2-(dimethylamino)-1-methyl-ethoxy]-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (500 mg, 952 μ mol, 73.2 % yield, 85.0 % purity) as a yellow oil.

[0356] Step D: *tert*-butyl 3-[7-(3-benzyloxy-1-naphthyl)-2-[2-(dimethylamino)-1-methyl-ethoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate: Pd₂(dba)₃ (84.1 mg, 91.8 μ mol, 0.10 *eq*) was added to a solution of *tert*-butyl 3-[2-[2-(dimethylamino)-1-methyl-ethoxy]-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (410 mg, 918 μ mol, 1.00 *eq*), 3-benzyloxy-1-bromonaphthalene (293 mg, 936 μ mol, 1.02 *eq*), 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl (RuPhos) (85.7 mg, 184 μ mol, 0.20 *eq*) and Cs₂CO₃ (897 mg, 2.75 mmol, 3.00 *eq*) in dioxane

(9.00 mL). The reaction mixture was stirred at 100 °C for 7 hours under N₂ and then concentrated under vacuum. The residue was diluted with water (5 mL) and extracted with DCM (2 × 20 mL). The organic layers were dried over Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by column chromatography (DCM/MeOH 100:1 to 20:1) to give *tert*-butyl 3-[7-(3-benzyloxy-1-naphthyl)-2-[2-(dimethylamino)-1-methyl-ethoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (317 mg, 441 μmol, 48.1 % yield, 94.5 % purity) as a yellow oil. **ESI MS** *m/z* 679.2 [M+H]⁺.

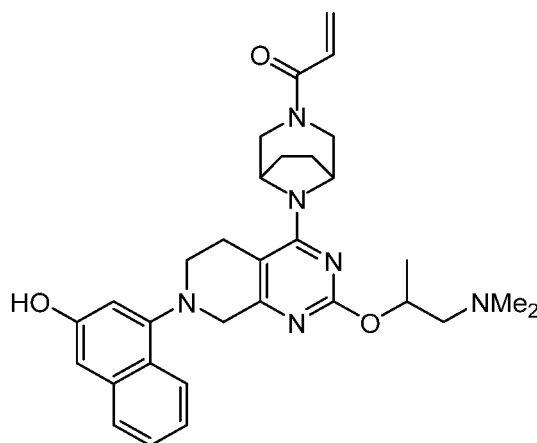
[0357] Step E: *tert*-butyl 3-[2-[2-(dimethylamino)-1-methyl-ethoxy]-7-(3-hydroxy-1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate: To a solution of *tert*-butyl 3-[7-(3-benzyloxy-1-naphthyl)-2-[2-(dimethylamino)-1-methyl-ethoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (340 mg, 501 μmol, 1.00 *eq*) in MeOH (6.80 mL) was added Pd/C (120 mg). The suspension was degassed under vacuum and purged with hydrogen 4 times. The mixture was stirred under hydrogen (15 psi) at 40 °C for 1.5 hours. The mixture was concentrated under vacuum to give *tert*-butyl 3-[2-[2-(dimethylamino)-1-methyl-ethoxy]-7-(3-hydroxy-1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (210 mg, 316 μmol, 63.1 % yield, 88.6 % purity) as a yellow solid which was used directly in the next step without further purification. **ESI MS** *m/z* 589.3 [M+H]⁺.

Step F: 4-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-2-[2-(dimethylamino)-1-methyl-ethoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]naphthalen-2-ol trifluoroacetate : To a solution of *tert*-butyl 3-[2-[2-(dimethylamino)-1-methyl-ethoxy]-7-(3-hydroxy-1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (180 mg, 306 μmol, 1.00 *eq*) in DCM (230 μL) was added TFA (349 mg, 3.06 mmol, 226 μL, 10.0 *eq*). The reaction mixture was stirred at 18 °C for 0.5 hour. The mixture was concentrated under vacuum to give 4-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-2-[2-(dimethylamino)-1-methyl-ethoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]naphthalen-2-ol trifluoroacetate (528 mg, crude) as a red oil which was used directly in the next step without further purification. **ESI MS** *m/z* 489.2 [M+H]⁺.

[0358] Step G: 1-[3-[2-[2-(dimethylamino)-1-methyl-ethoxy]-7-(3-hydroxy-1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]prop-2-en-1-one:

To a solution of 4-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-2-[2-(dimethylamino)-1-methyl-ethoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]naphthalen-2-ol trifluoroacetate (149 mg, 306 μmol , 1.00 *eq*) and DIEA (1.36 g, 10.5 mmol, 1.84 mL, 34.5 *eq*) in DCM (1.50 mL) was added prop-2-enoyl prop-2-enoate (30.9 mg, 245 μmol , 0.80 *eq*) dropwise at - 50 °C. The mixture was stirred at -40 and then -20 °C for 30 minutes. The reaction was quenched with MeOH (19.6 mg) and concentrated under vacuum. The residue was purified by preparative TLC (DCM/MeOH 7:1) to give 1-[3-[2-[2-(dimethylamino)-1-methyl-ethoxy]-7-(3-hydroxy-1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]prop-2-en-1-one (18.9 mg, 32.8 μmol , 10.7 % yield, 94.3 % purity) as a yellow solid. **ESI MS** m/z 543.3 $[\text{M}+\text{H}]^+$.

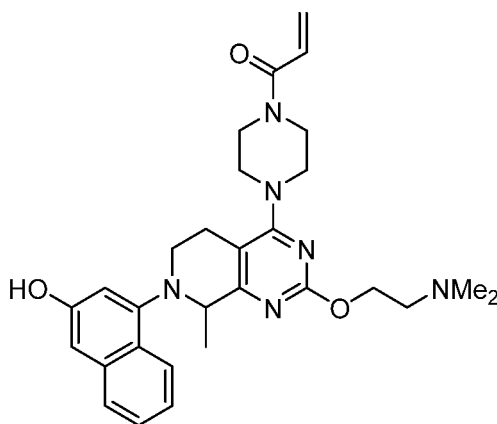
EXAMPLE 46



1-((1R,5S)-8-(2-((1-(dimethylamino)propan-2-yl)oxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)prop-2-en-1-one

[0359] Synthesized according to the method of **Example 4**, using *tert*-butyl (1R,5S)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate in place *tert*-butyl 3,8-diazabicyclo[3.2.1]octane-8-carboxylate in Step A. **ESI MS** m/z 543.4 $[\text{M}+\text{H}]^+$.

EXAMPLE 47



1-(4-(2-(2-(dimethylamino)ethoxy)-7-(3-hydroxynaphthalen-1-yl)-8-methyl-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0360] Step A: ethyl 2-(benzylamino)propanoate: To a solution of ethyl 2-bromopropanoate (30.0 g, 165 mmol, 21.6 mL, 1.00 eq), BnNH₂ (23.1 g, 215 mmol, 23.6 mL, 1.30 eq) in MeCN (600 mL) was added K₂CO₃ (45.8 g, 331 mmol, 2.00 eq). The mixture was stirred at 80 °C for 2 hour. The reaction mixture was filtered and the filter cake was washed with DCM (300 mL). The filtrate was concentrated under vacuum. The residue was purified by silica gel chromatography (diethyl ether:ethyl acetate=10:1 to 4:1) to give ethyl 2-(benzylamino)propanoate (34.0 g, 163 mmol, 98.4 % yield, 99.4 % purity) a colorless oil.

[0361] Step B: ethyl 4-[benzyl-(2-ethoxy-1-methyl-2-oxo-ethyl)amino]butanoate: To a solution of ethyl 2-(benzylamino)propanoate (31.0 g, 150 mmol, 1.00 eq) and ethyl 4-bromobutanoate (87.5 g, 449 mmol, 64.4 mL, 3.00 eq) in MeCN (600 mL) and water (60.0 mL) was added Cs₂CO₃ (97.5 g, 299.12 mmol, 2.00 eq) and KI (4.97 g, 29.9 mmol, 0.20 eq). The reaction mixture was stirred at 80-90 °C for 40 hours. The reaction mixture was filtered and the filter cake was washed with DCM (2 × 100 mL). The filtrate was concentrated under vacuum. The residue was dissolved in DCM (300 mL) and washed with brine (80 mL), dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by flash silica gel chromatography (diethyl ether:ethyl acetate = 1:0 to 20:1) to give ethyl 4-[benzyl-(2-ethoxy-1-methyl-2-oxo-ethyl)amino]butanoate (28.0 g, 87.1 mmol, 58.3 % yield) as a yellow oil.

[0362] Step C: ethyl 1-benzyl-2-methyl-3-oxo-piperidine-4-carboxylate: To a solution of ethyl 4-[benzyl-(2-ethoxy-1-methyl-2-oxo-ethyl)amino]butanoate (28.0 g, 87.1 mmol, 1.00 eq) in

THF (600 mL) was added tBuOK (19.6 g, 174 mmol, 2.00 eq). The reaction mixture was stirred at 18 °C for 1 hour. The reaction mixture was quenched with water (100 mL) and extracted with MTBE (3 × 300 mL) and DCM (2 × 200 mL). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated under vacuum. The crude product was purified by silica gel chromatography (diethyl ether:ethyl acetate=100:1 to 20:1) to give ethyl 1-benzyl-2-methyl-3-oxo-piperidine-4-carboxylate (20.0 g, 58.8 mmol, 67.5 % yield, 81.0 % purity) as a yellow oil. **ESI MS** m/z 276.0 [M+H]⁺.

[0363] Step D: 7-benzyl-8-methyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidine-2,4-diol: To EtOH (400 mL) was added Na (3.76 g, 163 mmol, 3.88 mL, 2.50 eq). The reaction mixture was stirred at 20 °C for 0.5 hour. To the mixture was added ethyl 1-benzyl-2-methyl-3-oxo-piperidine-4-carboxylate (18.0 g, 65.4 mmol, 1.00 eq) and UREA (9.82 g, 163 mmol, 8.77 mL, 2.50 eq) and the reaction mixture was stirred at 80 °C for 80 hours. The solvent was removed under vacuum. The residue was dissolved in water (100 mL) and washed with MTBE (3 × 50 mL). The aqueous phase was adjusted to pH 6-7 with HCl (15 mL, 12 M). The mixture was filtered and the filter cake was washed with water (30 mL) and dried in vacuum to give 7-benzyl-8-methyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidine-2,4-diol (12.0 g, 44.2 mmol, 67.7 % yield, 100 % purity) was obtained as a brown solid. **ESI MS** m/z 272.0 [M+H]⁺.

[0364] Step E: benzyl-2,4-dichloro-8-methyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidine: A mixture of 7-benzyl-8-methyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidine-2,4-diol (5.00 g, 18.4 mmol, 1.00 eq) in POCl₃ (305 g, 1.99 mol, 185 mL, 108 eq) was heated to 110 °C for 12 hours. The solvent was removed under vacuum. The residue was dissolved in DCM (500 mL) and poured into saturated NaHCO₃ (200 mL) while keeping the pH greater than 7. The organic layer was washed with brine (50 mL), dried over Na₂SO₄. The solution was filtered through a pad of silica gel and the filter cake was washed with DCM (3 × 400 mL). The combined organic layers were concentrated under vacuum to give 7-benzyl-2,4-dichloro-8-methyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidine (4.50 g, 14.6 mmol, 79.2 % yield) as a brown oil.

[0365] Step F: 4-(7-benzyl-2-chloro-8-methyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate: To a solution of 7-benzyl-2,4-dichloro-8-methyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidine (3.00 g, 9.73 mmol, 1.00 eq) and DIEA (2.52 g, 19.5 mmol, 3.40 mL, 2.00 eq) in dioxane (60.0 mL) was added tert-butyl piperazine-1-carboxylate (1.90 g, 10.2

mmol, 1.05 eq). The reaction mixture was stirred at 60 °C for 12 hours. The solvent was removed under vacuum. The residue was purified by silica gel chromatography (diethyl ether:ethyl acetate = 2:1) to give tert-butyl 4-(7-benzyl-2-chloro-8-methyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (3.30 g, 7.15 mmol, 73.5 % yield, 99.3 % purity) as a yellow solid. **ESI MS** m/z 458.1 [M+H]⁺.

[0366] Step G: tert-butyl-4-[7-benzyl-2-[2-(dimethylamino)ethoxy]-8-methyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate: To a solution of 2-(dimethylamino)ethanol (583 mg, 6.54 mmol, 655 µL, 3.00 eq) in toluene (20.0 mL) was added Pd(OAc)₂ (48.9 mg, 218 µmol, 0.10 eq), tert-butyl-4-(7-benzyl-2-chloro-8-methyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (1.00 g, 2.18 mmol, 1.00 eq), Cs₂CO₃ (2.13 g, 6.54 mmol, 3.00 eq) and BINAP (272 mg, 436 µmol, 0.20 eq). The reaction mixture was stirred at 110 °C for 3 hours under N₂. The reaction mixture was concentrated under vacuum. The residue was dissolved in water (10 mL) and extracted with DCM (3 × 40 mL). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by silica gel chromatography (diethyl ether:ethyl acetate = 5:1 to 2:1 then DCM:MeOH = 50:1 to 5:1) to give tert-butyl-4-[7-benzyl-2-[2-(dimethylamino)ethoxy]-8-methyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (900 mg, 1.76 mmol, 80.8 % yield) as a brown solid. **ESI MS** m/z 511.2 [M+H]⁺.

[0367] Step H: tert-butyl 4-[2-[2-(dimethylamino)ethoxy]-8-methyl-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate: To a solution of tert-butyl 4-[7-benzyl-2-[2-(dimethylamino)ethoxy]-8-methyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (800 mg, 1.57 mmol, 1.00 eq) in MeOH (20.0 mL) was added Pd/C (100 mg) under N₂. The suspension was degassed under vacuum and purged with hydrogen several times. The mixture was stirred under hydrogen (50 psi) at 40°C for 12 hours. The reaction mixture was filtered and the filter cake was washed with MeOH (3 × 200 mL). The filtrate was concentrated under vacuum to give tert-butyl 4-[2-[2-(dimethylamino)ethoxy]-8-methyl-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (450 mg, 1.07 mmol, 68.2 % yield) as brown oil which was used for next step without further purification. **ESI MS** m/z 421.3 [M+H]⁺.

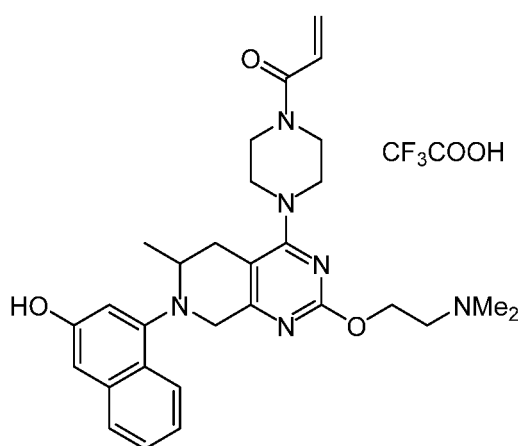
[0368] Step I: tert-butyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[2-(dimethylamino)ethoxy]-8-methyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate: To a mixture of tert-butyl 4-[2-[2-(dimethylamino)ethoxy]-8-methyl-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (380 mg, 904 μmol , 1.00 eq) and 3-benzyloxy-1-bromonaphthalene (311 mg, 994 μmol , 1.10 eq) in dioxane (8.00 mL), Cs_2CO_3 (883 mg, 2.71 mmol, 3.00 eq) and 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl (RuPhos) (84.3 mg, 181 μmol , 0.20 eq) and $\text{Pd}_2(\text{dba})_3$ (82.7 mg, 90.4 μmol , 0.10 eq) were added. The reaction mixture was stirred at 90 °C for 12 h under N_2 . The reaction mixture was concentrated under vacuum. The residue was partitioned between DCM (50 mL) and water (20 mL). The reaction mixture was extracted with DCM (50 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by silica gel chromatography (diethyl ether:ethyl acetate = 5:1 then DCM:MeOH = 100:1 to 5:1), followed by purification of the isolated product by preparative TLC (DCM: MeOH=10:1) to give tert-butyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[2-(dimethylamino)ethoxy]-8-methyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (200 mg, 306 μmol , 33.9 % yield) as brown solid. **ESI MS** m/z 653.4 $[\text{M}+\text{H}]^+$.

[0369] Step J: 4-[2-[2-(dimethylamino)ethoxy]-8-methyl-4-piperazin-1-yl]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-7-yl]naphthalen-2-ol bis-trifluoroacetate: To a solution of tert-butyl 4-[2-[2-(dimethylamino)ethoxy]-7-(3-hydroxy-1-naphthyl)-8-methyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (100 mg, 177 μmol , 1.00 eq) in DCM (130.00 μL) was added TFA (202 mg, 1.78 mmol, 132 μL , 10.00 eq). The reaction mixture was stirred at 20 °C for 1 hour. The solvent was removed under vacuum to provide 4-[2-[2-(dimethylamino)ethoxy]-8-methyl-4-piperazin-1-yl]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-7-yl]naphthalen-2-ol bis-trifluoroacetate (175.00 mg) as a brown oil which was used in the next step without further purification.

[0370] Step K: 1-[4-[2-[2-(dimethylamino)ethoxy]-7-(3-hydroxy-1-naphthyl)-8-methyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one: To a solution of 4-[2-[2-(dimethylamino)ethoxy]-8-methyl-4-piperazin-1-yl]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-7-yl]naphthalen-2-ol bis-trifluoroacetate (97.4 mg, 141 μmol , 1.00 eq) in DCM (500.00 μL) was added DIEA (222 mg, 1.72 mmol, 300 μL , 12.2 eq) and prop-2-enoyl prop-2-enoate (14.2

mg, 113 μ mol, 0.80 eq) at -40 °C. The reaction mixture was stirred at -40 °C for 0.5 h. The reaction mixture was quenched with a drop of MeOH and concentrated under vacuum. The residue was purified by preparative TLC (DCM:MeOH =10:1) and then by preparative HPLC (column: Phenomenex Synergi C18 150*25*, 10 μ ; mobile phase: [water (0.1%TFA)-ACN]; B%: 15%-45%, 13 min) to give 1-[4-[2-[2-(dimethylamino)ethoxy]-7-(3-hydroxy-1-naphthyl)-8-methyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one (10.7 mg, 20.7 μ mol, three steps 6.8 % yield) as a brown oil. **ESI MS** m/z 517.2 [M+H]⁺.

EXAMPLE 48



1-(4-(2-(2-(dimethylamino)ethoxy)-7-(3-hydroxynaphthalen-1-yl)-6-methyl-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one trifluoroacetate

[0371] Step A: ethyl 4-[benzyl-(2-ethoxy-2-oxo-ethyl)amino]pentanoate: A solution of ethyl 4-oxopentanoate (47.0 g, 326 mmol, 46.5 mL, 1.50 *eq*), ethyl 2-(benzylamino)acetate (42.0 g, 217.3 mmol, 1.00 *eq*) and AcOH (13.0 g, 217 mmol, 12.4 mL, 1.00 *eq*) in DCM (800 mL) was stirred at 12-18 °C for 30 min, then cooled at 0-5 °C, NaBH(OAc)₃ (138 g, 652 mmol, 3.00 *eq*) was added portion-wise. The mixture was warmed to 10-18 °C and stirred for 16 hours. The reaction mixture was quenched with water (1000 mL) and extracted with DCM (2 × 500 mL). The combined organic phases were dried and concentrated to dryness. The residue was purified by silica gel column eluting with diethyl ether/ethyl acetate (60:1 to 40:1) to provide ethyl 4-[benzyl-(2-ethoxy-2-oxo-ethyl)amino]pentanoate (42.0 g, 91.5 mmol, 42.1 % yield, 70 % purity) as colorless oil. **ESI MS** m/z 322.2 [M+H]⁺.

[0372] Step B: ethyl 1-benzyl-2-methyl-5-oxo-piperidine-4-carboxylate: A solution of ethyl 4-[benzyl-(2-ethoxy-2-oxo-ethyl)amino]pentanoate (37.00 g, 115.12 mmol, 1.00 *eq*) and t-BuOK (16.8 g, 150 mmol, 1.30 *eq*) in toluene (30.0 mL) was stirred at 25 °C for 5 hours. The reaction was quenched with water (50 mL) and extracted with ethyl acetate (2 x 30 mL). The combined organic extracts were dried and concentrated to dryness to provide ethyl 1-benzyl-2-methyl-5-oxo-piperidine-4-carboxylate (14.6 g, 53.0 mmol, 46 % yield) as yellow oil which was used directly in the next step.

[0373] Step C: 7-benzyl-6-methyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidine-2,4-diol: Na (3.05 g, 133 mmol, 3.14 mL, 2.50 *eq*) was dissolved in EtOH (280 mL), and then ethyl 1-benzyl-2-methyl-5-oxo-piperidine-4-carboxylate (14.6 g, 53.0 mmol, 1.00 *eq*) and urea (7.96 g, 133 mmol, 7.11 mL, 2.50 *eq*) were added. The reaction mixture was heated to reflux (78 °C) for 16 hrs under N₂. The reaction mixture was concentrated to dryness. The residue was dissolved in water (100 mL), washed with MTBE (100 mL). The pH of the water phase was adjusted to pH 6-7 with 6N HCl (2 mL). The resulting solid was collected by filtration and dried under vacuum at 60 °C to provide 7-benzyl-6-methyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidine-2,4-diol (5.00 g, 17.1 mmol, 32.3 % yield, 93 % purity) as light yellow solid.

[0374] Step D: 7-benzyl-2,4-dichloro-6-methyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidine: POCl₃ (49.5 g, 323 mmol, 30.0 mL, 58.4 *eq*) and 7-benzyl-6-methyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidine-2,4-diol (1.50 g, 5.53 mmol, 1.00 *eq*) were heated to 100 °C under reflux for 12 hours. The reaction was concentrated to dryness to remove POCl₃. The residue was dissolved in DCM (40 mL) and washed with saturated NaHCO₃ aqueous /saturated aqueous Na₂CO₃ (1/1, 60 mL). The mixture was filtered and the organic layers were dried over Na₂SO₄, filtered and concentrated under vacuum to give 7-benzyl-2,4-dichloro-6-methyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidine (2.08 g, crude) as a brown solid which was used directly in the next step without further purification. ESI MS m/z 307.9, 309.9 [M+H]⁺.

[0375] Step E: 4-(7-benzyl-2-chloro-6-methyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate: To a mixture of 7-benzyl-2,4-dichloro-6-methyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidine (2.50 g, 8.11 mmol, 1.00 *eq*) and *tert*-butyl piperazine-1-carboxylate (1.54 g, 8.27 mmol, 1.02 *eq*) in dioxane (50.0 mL) was added DIEA (3.14 g, 24.3 mmol, 4.25 mL, 3.00 *eq*). The mixture was stirred at 60 °C for 20 hours. The mixture was concentrated

under vacuum. The residue was diluted with water (20 mL) and extracted with DCM (2×80 mL). The organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by automated flash chromatography system (diethyl ether/ethyl acetate 50:1 to 2:1) to give *tert*-butyl 4-(7-benzyl-2-chloro-6-methyl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl)piperazine-1-carboxylate (2.59 g, 5.29 mmol, 65.2 % yield, 93.5 % purity) as a yellow solid.

[0376] Step F: *tert*-butyl 4-[7-benzyl-2-[2-(dimethylamino)ethoxy]-6-methyl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate: To a solution of 2-(dimethylamino)ethanol (701 mg, 7.86 mmol, 788 μL , 3.00 *eq*) in THF (45.0 mL) was added NaH (210 mg, 5.24 mmol, 60.0 % purity, 2.00 *eq*) at 15 °C under N_2 . After stirring at 15 °C for 0.5 hour, *tert*-butyl 4-(7-benzyl-2-chloro-6-methyl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl)piperazine-1-carboxylate (1.20 g, 2.62 mmol, 1.00 *eq*) was added. The mixture was stirred at 110 °C for 18 hours in a sealed tube. The mixture was concentrated under vacuum. The residue was purified by column chromatography over Al_2O_3 (DCM/MeOH 100:1 to 10:1) to give *tert*-butyl 4-[7-benzyl-2-[2-(dimethylamino)ethoxy]-6-methyl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (1.38 g, 2.36 mmol, 90.3 % yield, 87.5% purity) as a yellow oil. ESI MS m/z 511.3 $[\text{M}+\text{H}]^+$.

[0377] Step G: *tert*-butyl 4-[2-[2-(dimethylamino)ethoxy]-6-methyl-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate: To a solution of *tert*-butyl 4-[7-benzyl-2-[2-(dimethylamino)ethoxy]-6-methyl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (1.50 g, 2.94 mmol, 1.00 *eq*) in MeOH (80.0 mL) was added Pd/C (450 mg) under N_2 . The suspension was degassed under vacuum and purged with hydrogen 4 times. The mixture was stirred under hydrogen (50 psi) at 40 °C for 12 hours. The reaction mixture was filtered and the filtrate was concentrated. The residue was purified by column chromatography (DCM/MeOH 40/1 to 10/1) to give *tert*-butyl 4-[2-[2-(dimethylamino)ethoxy]-6-methyl-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (1.15 g, 2.46 mmol, 83.7 % yield, 90.0 % purity) as a yellow oil.

[0378] Step H: *tert*-butyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[2-(dimethylamino)ethoxy]-6-methyl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate: $\text{Pd}_2(\text{dba})_3$ (109 mg, 119 μmol , 0.10 *eq*) was added to a solution of *tert*-butyl 4-[2-[2-(dimethylamino)ethoxy]-6-methyl-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (500 mg, 1.19

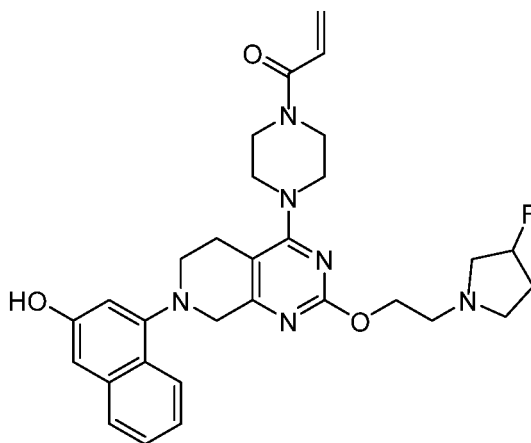
mmol, 1.00 *eq*), 3-benzyloxy-1-bromo-naphthalene (410 mg, 1.31 mmol, 1.10 *eq*), 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl (RuPhos) (111 mg, 238 μ mol, 0.20 *eq*) and Cs₂CO₃ (1.16 g, 3.57 mmol, 3.00 *eq*) in dioxane (10.0 mL). The reaction mixture was stirred at 90 °C for 12 hours under N₂. The mixture was concentrated under vacuum. The residue was diluted with water (5 mL) and extracted with DCM (2 $\times$ 20 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by column chromatography over Al₂O₃ (DCM/MeOH 100/1 to 10/1) and by preparative TLC (DCM/MeOH 5:1) to give *tert*-butyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[2-(dimethylamino)ethoxy]-6-methyl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (309 mg, 453 μ mol, 38.1 % yield, 95.8 % purity) as a yellow oil.

[0379] Step I: *tert*-butyl 4-[2-[2-(dimethylamino)ethoxy]-7-(3-hydroxy-1-naphthyl)-6-methyl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate: To a solution of *tert*-butyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[2-(dimethylamino)ethoxy]-6-methyl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (340 mg, 521 μ mol, 1.00 *eq*) in MeOH (6.80 mL) was added Pd/C (120 mg) under N₂. The suspension was degassed under vacuum and purged with hydrogen 4 times. The mixture was stirred under hydrogen (15 psi) at 40 °C for 1.5 hours. The mixture was concentrated under vacuum to give *tert*-butyl 4-[2-[2-(dimethylamino)ethoxy]-7-(3-hydroxy-1-naphthyl)-6-methyl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (210 mg, 312 μ mol, 59.8 % yield, 83.5 % purity) as a pink solid which was used directly in the next step without further purification. **ESI MS** *m/z* 563.3 [M+H]⁺.

[0380] Step J: 4-[2-[2-(dimethylamino)ethoxy]-6-methyl-4-piperazin-1-yl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]naphthalen-2-ol trifluoroacetate: To a solution of *tert*-butyl 4-[2-[2-(dimethylamino)ethoxy]-7-(3-hydroxy-1-naphthyl)-6-methyl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (180 mg, 320 μ mol, 1.00 *eq*) in DCM (240 μ L) was added TFA (365 mg, 3.20 mmol, 237 μ L, 10.0 *eq*). The mixture was stirred at 18 °C for 0.5 hour. The mixture was concentrated under vacuum to give 4-[2-[2-(dimethylamino)ethoxy]-6-methyl-4-piperazin-1-yl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]naphthalen-2-ol trifluoroacetate (273 mg) as a yellow oil which was used directly in the next step without further purification.

Step K: 1-[4-[2-[2-(dimethylamino)ethoxy]-7-(3-hydroxy-1-naphthyl)-6-methyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one: To a solution of 4-[2-[2-(dimethylamino)ethoxy]-6-methyl-4-piperazin-1-yl]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-7-yl]naphthalen-2-ol trifluoroacetate (148 mg, 320 μ mol, 1.00 *eq*) and DIEA (494 mg, 3.83 mmol, 668 μ L, 12.0 *eq*) in DCM (500 μ L) was added prop-2-enoyl prop-2-enoate (32.3 mg, 256 μ mol, 0.80 *eq*) dropwise at -50 °C. The mixture was stirred at -40 to -20 °C for 30 minutes. The reaction was quenched with MeOH (20.5 mg) and concentrated under vacuum. The residue was purified by preparative HPLC (column: Phenomenex Synergi C18 150*25*, 10 μ ; mobile phase: [water (0.1% TFA)-ACN]; B%: 8%-38%, 13 min) to give 1-[4-[2-[2-(dimethylamino)ethoxy]-7-(3-hydroxy-1-naphthyl)-6-methyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one trifluoroacetate (73.7 mg, 113 μ mol, 35.2 % yield, 96.3 % purity) as a yellow solid. **ESI MS** m/z 517.3 $[M+H]^+$.

EXAMPLE 49



1-(4-(2-(2-(3-fluoropyrrolidin-1-yl)ethoxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0381] Step A: *tert*-butyl 4-(4-benzyloxycarbonylpiperazin-1-yl)-2-[2-(3-fluoropyrrolidin-1-yl)ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidine-7-carboxylate :A mixture of 2-(3-fluoropyrrolidin-1-yl)ethanol (401 mg, 3.01 mmol, 1.60 *eq*), *tert*-butyl 4-(4-benzyloxycarbonylpiperazin-1-yl)-2-methylsulfonyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidine-7-carboxylate (1.00 g, 1.88 mmol, 1.00 *eq*), Cs₂CO₃ (1.84 g, 5.64 mmol, 3.00 *eq*), Pd(OAc)₂ (42.2 mg, 188 μ mol, 0.10 *eq*) and BINAP (234 mg, 376 μ mol, 0.20 *eq*) in toluene (50.00 mL)

was stirred at 110 °C for 3 hours. The mixture was concentrated under vacuum. The residue was purified by column chromatography over silica gel (petroleum ether/ethyl acetate 10:1 to 100:1). The desired fractions were collected and concentrated under vacuum to give *tert*-butyl 4-(4-benzyloxycarbonylpiperazin-1-yl)-2-[2-(3-fluoropyrrolidin-1-yl)ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidine-7-carboxylate (1.20 g, 1.07 mmol, 56.8 % yield, 52 % purity) as a yellow solid. **ESI MS** *m/z* 585.3 [M+H]⁺.

[0382] Step B: benzyl 4-[2-[2-(3-fluoropyrrolidin-1-yl)ethoxy]-5,6,7,8-tetrahydropyrido [3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate: To a solution of *tert*-butyl 4-(4-benzyloxycarbonylpiperazin-1-yl)-2-[2-(3-fluoropyrrolidin-1-yl)ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidine-7-carboxylate (1.20 g, 2.05 mmol, 1.00 *eq*) in DCM (10.00 mL) was added TFA (3.51 g, 30.8 mmol, 2.28 mL, 15.00 *eq*) at 0 °C. The mixture was warmed to 25 °C and stirred for 16 hours. The mixture was diluted with water (100 mL) and the solution was extracted with ethyl acetate (2 × 100 mL). The water layer was basified with saturated aqueous sodium carbonate solution (50 mL) and then extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with brine (1 × 100 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under vacuum to provide benzyl 4-[2-[2-(3-fluoropyrrolidin-1-yl)ethoxy]-5,6,7,8-tetrahydropyrido [3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (800 mg, 1.65 mmol, 80.4 % yield) as a yellow gum. **ESI MS** *m/z* 485.3 [M+H]⁺.

[0383] Step C: benzyl 4-[2-[2-(3-fluoropyrrolidin-1-yl)ethoxy]-7-(3-methoxy-1-naphthyl)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate: A mixture of benzyl 4-[2-[2-(3-fluoropyrrolidin-1-yl)ethoxy]-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (750 mg, 1.55 mmol, 1.00 *eq*), (3-methoxy-1-naphthyl) trifluoromethanesulfonate (949 mg, 3.10 mmol, 2.00 *eq*), 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl (RuPhos) (144.66 mg, 310.00 μmol, 0.20 *eq*), Pd₂(dba)₃ (141.94 mg, 155.00 μmol, 0.10 *eq*) and Cs₂CO₃ (1.52 g, 4.65 mmol, 3.00 *eq*) in toluene (70.00 mL) was stirred at 110 °C for 16 hours. The mixture was concentrated under vacuum and then diluted with ethyl acetate (100 mL) and water (100 mL). The separated organic layer was washed with brine (1 × 100 mL), dried over sodium sulfate, filtered and concentrated under vacuum. The residue was purified by column chromatography over silica gel (petroleum ether/ethyl acetate 10:1 to ethyl acetate/methanol 10:1). The desired fractions were collected and concentrated under vacuum to give benzyl 4-[2-

[2-(3-fluoropyrrolidin-1-yl)ethoxy]-7-(3-methoxy-1-naphthyl)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (700 mg, 961 μ mol, 62.0 % yield, 88% purity) as a brown solid. **ESI MS** m/z 641.3 $[M+H]^+$.

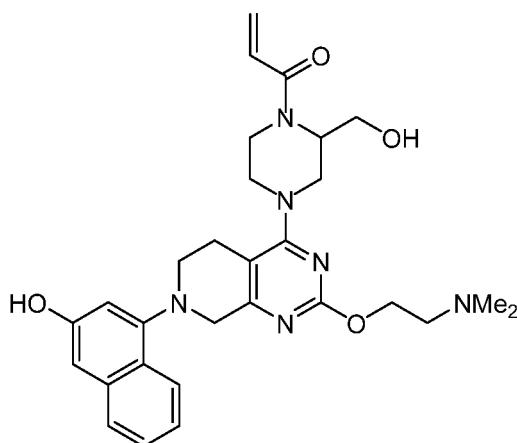
[0384] Step D: 2-[2-(3-fluoropyrrolidin-1-yl)ethoxy]-7-(3-methoxy-1-naphthyl)-4-piperazin-1-yl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidine: A mixture of benzyl 4-[2-[2-(3-fluoropyrrolidin-1-yl)ethoxy]-7-(3-methoxy-1-naphthyl)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (700.00 mg, 1.09 mmol, 1.00 *eq*) in MeOH was hydrogenated (15 psi) at 40 °C with dry Pd/C (140 mg,) as a catalyst for 4 hours. The catalyst was filtered through a Celite® pelt and the filtrate was concentrated under vacuum to provide 2-[2-(3-fluoropyrrolidin-1-yl)ethoxy]-7-(3-methoxy-1-naphthyl)-4-piperazin-1-yl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidine (500 mg, 987 μ mol, 90.6 % yield) as a brown solid.

[0385] Step E: 1-[4-[2-[2-(3-fluoropyrrolidin-1-yl)ethoxy]-7-(3-methoxy-1-naphthyl)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one: To a mixture of 2-[2-(3-fluoropyrrolidin-1-yl)ethoxy]-7-(3-methoxy-1-naphthyl)-4-piperazin-1-yl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidine (500 mg, 987 μ mol, 1.00 *eq*) and DIEA (255 mg, 1.97 mmol, 345 μ L, 2.00 *eq*) in dichloromethane (8 mL) was added a solution of prop-2-enoyl prop-2-enoate (124 mg, 987 μ mol, 1.00 *eq*) in dichloromethane (2 mL) at -40 °C under nitrogen atmosphere. The mixture was warmed to 25 °C and stirred for 1 hour. The mixture was diluted with water (20 mL) and dichloromethane (30 mL). The separated organic layer was washed with brine (1 $\times$ 30 mL), dried over magnesium sulfate, filtered and concentrated under vacuum. The residue was purified by column chromatography over silica gel (dichloromethane/methanol 100/1 to 10/1). The desired fractions were collected and concentrated under vacuum to give 1-[4-[2-[2-(3-fluoropyrrolidin-1-yl)ethoxy]-7-(3-methoxy-1-naphthyl)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one (450 mg, 714 μ mol, 72.4 % yield, 89 % purity) as a yellow solid. **ESI MS** m/z 561.2 $[M+H]^+$.

[0386] Step F: 1-[4-[2-[2-(3-fluoropyrrolidin-1-yl)ethoxy]-7-(3-hydroxy-1-naphthyl)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one: To a solution of 1-[4-[2-[2-(3-fluoropyrrolidin-1-yl)ethoxy]-7-(3-methoxy-1-naphthyl)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one (400 mg, 713 μ mol, 1.00 *eq*) in DCM (2.00 mL) was added BBr₃ (1.30 g, 5.19 mmol, 500 μ L, 7.27 *eq*) at -70 °C under nitrogen

atmosphere. The mixture was warmed to 0 °C and stirred for 1 hour. The mixture was diluted with dichloromethane (20 mL), and then quenched with saturated aqueous sodium bicarbonate solution (20 mL). The separated organic layer was washed with brine (1 × 10 mL), dried over sodium sulfate, filtered and concentrated under vacuum. The residue was purified by preparative HPLC (Phenomenex Synergi C18 150*25*, 10 μ; mobile phase: [water (0.1%TFA)-ACN]; B%: 18%-48%, 12 min.) The desired fractions were collected and lyophilized to give 1-[4-[2-[2-(3-fluoropyrrolidin-1-yl)ethoxy]-7-(3-hydroxy-1-naphthyl)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one (40.0 mg, 63.7 μmol, 8.92 % yield, 87 % purity) was a yellow solid. ESI MS m/z 547.3 [M+H]⁺.

EXAMPLE 50



1-(4-(2-(2-(dimethylamino)ethoxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)-2-(hydroxymethyl)piperazin-1-yl)prop-2-en-1-one

[0387] Step A: 1-tert-butyl 2-methyl-4-(7-benzyl-2-chloro-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl)piperazine-1,2-dicarboxylate: To a solution of 7-benzyl-2,4-dichloro-6,8-dihydro-5H-pyrido[3,4-d]pyrimidine (2.00 g, 6.80 mmol, 1.00 eq) in DMSO (40.0 mL) was added DIEA (1.76 g, 13.6 mmol, 2.38 mL, 2.00 eq) and 1-tert-butyl 2-methylpiperazine-1,2-dicarboxylate (1.74 g, 7.14 mmol, 1.05 eq). The mixture was stirred at 55 °C for 16 hours. The mixture was diluted with water (100 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with brine (3 × 100 mL), dried over Na₂SO₄, filtered and concentrated to dryness. The residue was purified by column chromatography (SiO₂, diethyl ether/ethyl acetate = 1:0 to 3:1) to give 1-tert-butyl 2-methyl-4-(7-benzyl-2-chloro-6,8-dihydro-

5H-pyrido[3,4-d]pyrimidin-4-yl)piperazine-1,2-dicarboxylate (3.10 g, 5.70 mmol, 83.8 % yield, 92.3 % purity) as a yellow semisolid. **ESI MS** m/z 502.2 $[M+H]^+$.

[0388] Step B: 1-tert-butyl 2-methyl-4-[7-benzyl-2-[2-(dimethylamino)ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1,2-dicarboxylate: A mixture of 1-tert-butyl 2-methyl-4-(7-benzyl-2-chloro-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl)piperazine-1,2-dicarboxylate (3.00 g, 5.98 mmol, 1.00 eq), 2-(dimethylamino)ethanol (1.07 g, 12.0 mmol, 1.20 mL, 2.00 eq), Cs_2CO_3 (4.87 g, 15.0 mmol, 2.50 eq), $Pd(OAc)_2$ (201 mg, 897 μ mol, 0.15 eq) and BINAP (744 mg, 1.20 mmol, 0.20 eq) in toluene (60.0 mL) was degassed and purged with nitrogen 3 times, and then the mixture was stirred at 110 °C for 3 hours under a nitrogen atmosphere. The reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (3 $\times$ 50 mL). The combined organic layers were washed with brine (3 $\times$ 50 mL), dried over Na_2SO_4 , filtered and concentrated to dryness. The residue was purified by column chromatography (SiO_2 , DCM / MeOH = 1:0 to 5:1) to give 1-tert-butyl 2-methyl-4-[7-benzyl-2-[2-(dimethylamino)ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1,2-dicarboxylate (3.10 g, 4.45 mmol, 80.4 % yield, 86.0 % purity) as a black oil. **ESI MS** m/z 555.3 $[M+H]^+$.

[0389] Step C: 1-tert-butyl 2-methyl-4-[2-[2-(dimethylamino)ethoxy]-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl]piperazine-1,2-dicarboxylate: To a solution of 1-tert-butyl 2-methyl-4-[7-benzyl-2-[2-(dimethyl amino)ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1,2-dicarboxylate (2.33 g, 4.20 mmol, 1.00 eq) in MeOH (50.0 mL) was added Pd/C (233 mg) under N_2 . The suspension was degassed under vacuum and purged with hydrogen several times. The mixture was stirred under hydrogen (50 psi) at 40 °C for 36 hours. The reaction mixture was filtered and the organic phase was concentrated to dryness to give 1-tert-butyl-2-methyl-4-[2-[2-(dimethylamino)ethoxy]-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl]piperazine-1,2-dicarboxylate (1.50 g, crude) as a colorless oil, which was used directly in the next step without further purification.

[0390] Step D: 1-tert-butyl-2-methyl-4-[7-(3-benzyloxy-1-naphthyl)-2-[2-(dimethylamino)ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1,2-dicarboxylate: A mixture of 1-tert-butyl-2-methyl-4-[2-[2-(dimethylamino)ethoxy]-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl]piperazine-1,2-dicarboxylate (1.50 g, crude), 3-

benzyloxy-1-bromo-naphthalene (1.49 g, 4.76 mmol, 1.30 eq), Cs₂CO₃ (2.98 g, 9.15 mmol, 2.50 eq), Pd₂(dba)₃ (503 mg, 549 μmol, 0.15 eq) and 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl (RuPhos) (342 mg, 732 μmol, 0.20 eq) in dioxane (100 mL) was degassed and purged with nitrogen 3 times, and the mixture was stirred at 85 °C for 5 hours under a nitrogen atmosphere. The reaction mixture was quenched by adding water (50 mL) at 0 °C, and extracted with DCM (3 × 100 mL). The combined organic layers were washed with brine (3 × 150 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to dryness. The residue was purified by column chromatography (SiO₂, DCM / MeOH = 10:1 to 5:1) to give 1-tert-butyl 2-methyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[2-(dimethylamino)ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1,2-dicarboxylate (1.72 g, 2.25 mmol, 53.5 % yield, 91% purity) as a yellow. **ESI MS** m/z 697.3 [M+H]⁺.

[0391] Step E: methyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[2-(dimethylamino)ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-2-carboxylate: To a solution of 1-tert-butyl 2-methyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[2-(dimethylamino)ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1,2-dicarboxylate (1.32 g, 1.89 mmol, 1.00 eq) in DCM (20.0 mL) was added TFA (4.31 g, 37.8 mmol, 2.80 mL, 20.0 eq) at 0 °C and the reaction mixture was stirred for 2 hours at 25 °C. The reaction mixture was concentrated under reduced pressure to dryness. The residue was dissolved in DCM (50 mL) and H₂O (20 mL) and the reaction mixture was adjusted to pH 8 with saturated NaHCO₃. The organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure to give methyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[2-(dimethylamino)ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-2-carboxylate (1.12 g, 1.87 mmol, 69.6 % yield, 70 % purity) as a brown oil, which was used directly in the next step without further purification. **ESI MS** m/z 597.4 [M+H]⁺.

[0392] Step F: 4-[7-(3-benzyloxy-1-naphthyl)-2-[2-(dimethylamino)ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-2-yl]methanol: A mixture of methyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[2-(dimethyl amino)ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-2-carboxylate (400 mg, 0.670 mmol) in THF (5.00 mL) was added LiAlH₄ (102 mg, 2.68 mmol, 4.00 eq) at 0 °C. The reaction mixture was degassed and purged with nitrogen 3 times, and stirred at 0 °C for 2 hours under a nitrogen atmosphere. The reaction mixture was

quenched by addition of $\text{Na}_2\text{SO}_4 \cdot 10 \text{ H}_2\text{O}$ (0.5 g) at 0 °C, and then diluted with DCM (50 mL). The combined organic layers were filtered, dried over Na_2SO_4 , and concentrated under reduced pressure to give [4-[7-(3-benzyloxy-1-naphthyl)-2-[2-(dimethylamino)ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazin-2-yl]methanol (280 mg, 0.493 mmol, 73.6 % yield) as a yellow semisolid, which was used directly in the next step without further purification. **ESI MS** m/z 569.3 $[\text{M}+\text{H}]^+$.

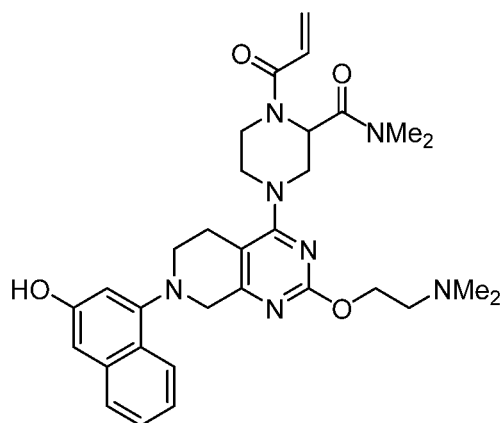
[0393] Step G: 2-[[7-(3-benzyloxy-1-naphthyl)-4-[3-[[tert-butyl(dimethyl)silyl]oxymethyl]piperazin-1-yl]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-2-yl]oxy]-N,N-dimethyl-ethanamine: To a stirred solution of [4-[7-(3-benzyloxy-1-naphthyl)-2-[2-(dimethyl amino)ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazin-2-yl]methanol (250 mg, 440 μmol , 1.00 eq) and NaH (176 mg, 4.40 mmol, 60.0 % purity, 10.0 eq) in THF (10.0 mL) was added tert-butyl(dimethyl)silyl chloride (232 mg, 1.54 mmol, 189 μL , 3.50 eq) at 0 °C. The mixture was stirred at 25 °C for 12 hours under a nitrogen atmosphere. The reaction mixture was quenched by addition of water (25 mL) at 0 °C and extracted with DCM ($3 \times 30 \text{ mL}$). The combined organic layers were washed with brine ($3 \times 30 \text{ mL}$), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to dryness. The residue was purified by preparative TLC (SiO_2 , $\text{DCM}/\text{MeOH} = 10:1$) to give 2-[[7-(3-benzyloxy-1-naphthyl)-4-[3-[[tert-butyl(dimethyl)silyl]oxymethyl] piperazin-1-yl]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-2-yl]oxy]-N,N-dimethyl-ethanamine (128 mg, 180 μmol , 40.9 % yield, 96.0 % purity) as a colorless semisolid. **ESI MS** m/z 683.3 $[\text{M}+\text{H}]^+$.

[0394] Step H: 1-[4-[7-(3-benzyloxy-1-naphthyl)-2-[2-(dimethylamino) ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]-2-[[tert-butyl(dimethyl)silyl]oxymethyl]piperazin-1-yl]prop-2-en-1-one; To a solution of 2-[[7-(3-benzyloxy-1-naphthyl)-4-[3-[[tert-butyl(dimethyl)silyl]oxymethyl]piperazin-1-yl]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-2-yl]oxy]-N,N-dimethyl-ethanamine (128 mg, 187 μmol , 1.00 eq) and triethylamine (47.4 mg, 469 μmol , 65.0 μL , 2.50 eq) in DCM (5.00 mL) was added prop-2-enoyl prop-2-enoate (35.5 mg, 281 μmol , 1.50 eq) dropwise at - 40 °C and stirred for 30 minutes. The reaction mixture was concentrated under reduced pressure to dryness. The residue was purified by preparative TLC (SiO_2 , $\text{DCM}/\text{MeOH} = 10:1$) to give 1-[4-[7-(3-benzyloxy-1-naphthyl)-2-[2-(dimethylamino) ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]-2-[[tert-

butyl(dimethyl)silyl]oxymethyl]piperazin-1-yl]prop-2-en-1-one (92.0 mg, 101 μ mol, 54.0 % yield, 81.0 % purity) as a yellow solid. **ESI MS** m/z 737.3 $[M+H]^+$.

[0395] Step I: 1-[4-[2-[2-(dimethylamino)ethoxy]-7-(3-hydroxy-1-naphthyl)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]-2-(hydroxymethyl)piperazin-1-yl]prop-2-en-1-one: A mixture of 1-[4-[7-(3-benzyloxy-1-naphthyl)-2-[2-(dimethylamino)ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]-2-[[tert-butyl(dimethyl)silyl]oxymethyl]piperazin-1-yl]prop-2-en-1-one (92.0 mg, 125 μ mol, 1.00 eq) in DCM (8.00 mL) was added BBr_3 (17.0 mg, 67.8 μ mol, 6.53 μ L, 10.0 eq). The mixture was stirred at - 40 °C for 30 minutes under a nitrogen atmosphere and then concentrated at 25 °C under reduced pressure to dryness. To the residue was added saturated $NaHCO_3$ aqueous (0.5 mL). The solution was adjusted to pH 7 at 0 °C and then MeOH (2.0 mL) was added. The solution was purified by preparative HPLC (column: Phenomenex Synergi C18 150*25*, 10 μ ; mobile phase: [water (0.1 % TFA) - ACN]; B %: 15 % - 45 %, 11 min). The desired fractions were collected and concentrated under reduced pressure to remove MeCN and lyophilized to give 1-[4-[2-[2-(dimethylamino)ethoxy]-7-(3-hydroxy-1-naphthyl)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]-2-(hydroxymethyl)piperazin-1-yl]prop-2-en-1-one (6.30 mg, 11.2 μ mol, 9.00 % yield, 95.0 % purity) as a yellow solid. **ESI MS** m/z 533.2 $[M+H]^+$.

EXAMPLE 51



1-acryloyl-4-(2-(2-(dimethylamino)ethoxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)-N,N-dimethylpiperazine-2-carboxamide

[0396] Step A: 4-[7-(3-benzyloxy-1-naphthyl)-2-[2-(dimethylamino)ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]-1-tert-butoxycarbonyl-piperazine-2-carboxylic acid: To a solution of 1-tert-butyl 2-methyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[2-(dimethylamino)ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1,2-dicarboxylate (300 mg, 431 μ mol, 1.00 eq) in THF (4.00 mL) and H₂O (1.00 mL) was added NaOH (68.9 mg, 1.72 mmol, 4.00 eq). The mixture was stirred at 25 °C for 12 hours under a nitrogen atmosphere. The reaction mixture was diluted with water (50 mL) and the reaction mixture was adjusted to pH 6 with HCl (6 M) and then extracted with DCM (3 $\times$ 50 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to dryness to give 4-[7-(3-benzyloxy-1-naphthyl)-2-[2-(dimethylamino)ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]-1-tert-butoxycarbonyl-piperazine-2-carboxylic acid (310 mg, crude) as a yellow solid which was used directly in the next step without further purification. **ESI MS** m/z 683.3 [M+H]⁺.

[0397] Step B: tert-butyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[2-(dimethylamino)ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]-2-(dimethylcarbamoyl)piperazine-1-carboxylate A mixture of 4-[7-(3-benzyloxy-1-naphthyl)-2-[2-(dimethylamino)ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]-1-tert-butoxycarbonyl-piperazine-2-carboxylic acid (310 mg, crude) and DIEA (352 mg, 2.72 mmol, 476 μ L) in DCM (10.0 mL) was added portionwise HATU (259 mg, 681 μ mol) at 0 °C. After stirring for 30 minutes, N-methylmethanamine (130 mg, 1.59 mmol, 146 μ L, HCl) was added in one portion. The reaction mixture was degassed and purged with nitrogen 3 times. After stirring at 25 °C for 12 hours under a nitrogen atmosphere, the reaction mixture was diluted with water (50 mL) at 0 °C and extracted with DCM (3 $\times$ 50 mL). The combined organic layers were adjusted to pH 6 with HCl (1 M), washed with brine (3 $\times$ 50 mL) and water (3 $\times$ 50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to dryness to give tert-butyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[2-(dimethylamino)ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]-2-(dimethylcarbamoyl)piperazine-1-carboxylate (345 mg, 428 μ mol, two steps 94.2 % yield, 88.0 % purity) as a yellow semi-solid. **ESI MS** m/z 710.3 [M+H]⁺.

[0398] Step C: tert-butyl 4-[2-[2-(dimethylamino)ethoxy]-7-(3-hydroxy-1-naphthyl)-6,8-dihydro-5H-pyrido [3,4-d]pyrimidin-4-yl]-2-(dimethylcarbamoyl)piperazine-1-carboxylate: To a solution of tert-butyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[2-(dimethylamino)ethoxy]-6,8-

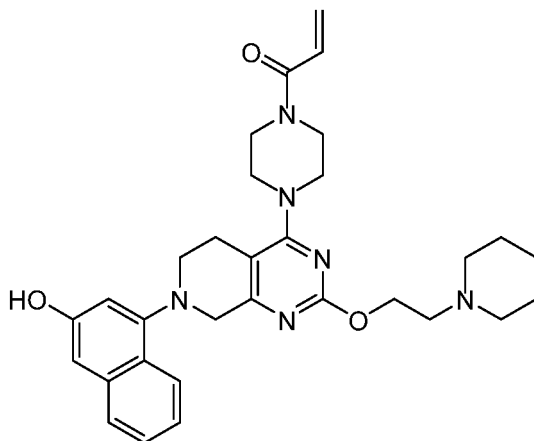
dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]-2-(dimethylcarbamoyl)piperazine-1-carboxylate (345 mg, 486 μ mol, 1.00 eq) in MeOH (5.00 mL) was added Pd/C (80.0 mg) under N₂. The suspension was degassed under vacuum and purged with hydrogen several times. The mixture was stirred under hydrogen (15 psi) at 25 °C for 8 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to dryness to give tert-butyl 4-[2-[2-(dimethylamino)ethoxy]-7-(3-hydroxy-1-naphthyl)-6,8-dihydro-5H-pyrido [3,4-d]pyrimidin-4-yl]-2-(dimethylcarbamoyl)piperazine-1-carboxylate (197 mg, crude) as a brown solid, which was used directly in the next step without further purification. **ESI MS** m/z 620.3 [M+H]⁺.

[0399] Step D: 4-[2-[2-(dimethylamino)ethoxy]-7-(3-hydroxy-1-naphthyl)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]-N,N-dimethyl-piperazine-2-carboxamide: A mixture of tert-butyl 4-[2-[2-(dimethylamino)ethoxy]-7-(3-hydroxy-1-naphthyl)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]-2-(dimethylcarbamoyl)piperazine-1-carboxylate (197 mg, crude) in DCM (5.00 mL) was added HCl/dioxane (4 M, 1.61 mL) at 0 °C. The reaction mixture was degassed and purged with nitrogen 3 times and stirred at 25 °C for 2 hours under a nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure to dryness. The residue was purified by preparative HPLC (column: Phenomenex Synergi C18 150*25*, 10 μ ; mobile phase: [water (0.05 % HCl) - ACN]; B %: 10 % - 30 %, 7.8 min). The collected water phase was lyophilized to dryness to give 4-[2-[2-(dimethylamino)ethoxy]-7-(3-hydroxy-1-naphthyl)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]-N,N-dimethyl-piperazine-2-carboxamide (90.0 mg, 171 μ mol, 53.1 % yield, 99.0 % purity) as a brown solid. **ESI MS** m/z 520.2 [M+H]⁺.

[0400] Step E: 4-[2-[2-(dimethylamino)ethoxy]-7-(3-hydroxy-1-naphthyl)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]-N,N-dimethyl-1-prop-2-enoyl-piperazine-2-carboxamide: To a solution of 4-[2-[2-(dimethylamino)ethoxy]-7-(3-hydroxy-1-naphthyl)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]-N,N-dimethyl-piperazine-2-carboxamide (70.0 mg, 135 μ mol, 1.00 eq) in DMAC (500 μ L) was added triethylamine (40.9 mg, 404 μ mol, 56.0 μ L, 3.00 eq) at 0 °C and then prop-2-enoyl prop-2-enoate (2.55 mg, 20.2 μ mol, 0.15 eq) was added. The mixture was stirred at 0 °C for 2 hours under a nitrogen atmosphere. The reaction mixture was filtered and the collected organic phase was purified by preparative HPLC (column: Phenomenex Synergi C18 150*25*, 10 μ ; mobile phase: [water (0.1 % TFA)-ACN]; B %: 15 % - 45 %, 12 min). The collected water phase was lyophilized to give 4-[2-[2-

(dimethylamino)ethoxy]-7-(3-hydroxy-1-naphthyl)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]-N,N-dimethyl-1-prop-2-enoyl-piperazine-2-carboxamide (10.0 mg, 16.5 μ mol, 12.2 % yield, 94.6 % purity) as a yellow semisolid. **ESI MS** m/z 574.2 $[M+H]^+$.

EXAMPLE 52



1-[4-[7-(3-hydroxy-1-naphthyl)-2-[2-(1-piperidyl)ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one

[0401] Step A: tert-butyl 4-[7-benzyl-2-[2-(1-piperidyl)ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate: To a solution of 2-(1-piperidyl)ethanol (872 mg, 6.75 mmol, 899 μ L, 3.00 eq) in toluene (40.0 mL) was added $Pd(OAc)_2$ (50.5 mg, 225 μ mol, 0.10 eq), Cs_2CO_3 (2.20 g, 6.75 mmol, 3.00 eq), BINAP (280 mg, 450 μ mol, 0.20 eq) and tert-butyl 4-(7-benzyl-2-chloro-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (1.00 g, 2.25 mmol, 1.00 eq). The mixture was stirred at 110 $^{\circ}C$ for 12 hours under N_2 and then concentrated under vacuum. The residue was diluted with water (10.0 mL), extracted with ethyl acetate (3×20 mL), washed with brine (1×50 mL), dried over Na_2SO_4 , filtered and concentrated under vacuum. The residue was purified by column chromatography (SiO_2 , DCM/MeOH = 10:1) to give tert-butyl 4-[7-benzyl-2-[2-(1-piperidyl)ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (700 mg, 1.30 mmol, 58.0 % yield) as a red solid. **ESI MS** m/z 537.3 $[M+H]^+$.

[0402] Step B: tert-butyl 4-[2-[2-(1-piperidyl)ethoxy]-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate: To a mixture of tert-butyl 4-[7-benzyl-2-[2-(1-

piperidyl)ethoxy]-6,8- dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (600 mg, 1.12 mmol, 1.00 eq) in MeOH (50.0 mL) was added Pd/C (67.2 mg, 10 %). The mixture was stirred at 40 °C for 24 hours at 50 psi under H₂. The mixture was filtered and concentrated under vacuum to give tert-butyl 4-[2-[2-(1-piperidyl)ethoxy]-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl] piperazine-1-carboxylate (500 mg, crude) as a brown oil and used in the next step without further purification. **ESI MS** m/z 447.3 [M+H]⁺.

[0403] Step C: tert-butyl 4-[7-(3-methoxy-1-naphthyl)-2-[2-(1-piperidyl)ethoxy]-6,8-dihydro-5H-pyrido [3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate: To a solution of tert-butyl 4-[2-[2-(1-piperidyl)ethoxy]-5,6,7,8- tetrahydropyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (250 mg) and (3-methoxy-1-naphthyl) trifluoromethanesulfonate (343 mg, 1.12 mmol) in toluene (6.00 mL) was added 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl (RuPhos) (52.3 mg, 112 μmol), Pd₂(dba)₃ (32.19 mg, 55.98 μmol) and Cs₂CO₃ (548 mg, 1.68 mmol). After stirring at 110 °C for 72 hours under N₂, the mixture was concentrated under vacuum, diluted with water (20.0 mL), extracted with ethyl acetate (3 × 30.0 mL), washed with brine (1 × 50.0 mL), dried over Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by column chromatography (SiO₂, DCM/MeOH = 10:1) to give tert-butyl 4-[7-(3-methoxy-1-naphthyl)-2-[2-(1-piperidyl)ethoxy]-6,8-dihydro-5H-pyrido [3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (140 mg, 232 μmol, two steps, 41.5 % yield) as a yellow solid. **ESI MS** m/z 603.3 [M+H]⁺.

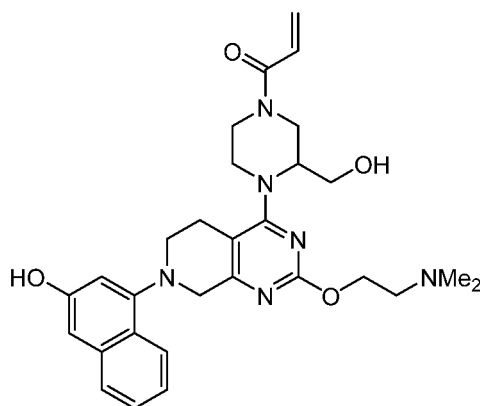
[0404] Step D: 7-(3-methoxy-1-naphthyl)-4-piperazin-1-yl-2-[2-(1-piperidyl)ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidine: A mixture of tert-butyl 4-[7-(3-methoxy-1-naphthyl)-2-[2-(1-piperidyl) ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (120 mg, 199 μmol, 1.00 eq) and TFA (340 mg, 2.99 mmol, 221 μL, 15.0 eq) in DCM (1.00 mL) was stirred at 25 °C for 1 hour. The mixture was concentrated under vacuum to give 7-(3-methoxy-1-naphthyl)-4-piperazin-1-yl-2-[2-(1-piperidyl)ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidine bis-trifluoroacetate (145 mg, crude) as a yellow solid which was used into next step without further purification. **ESI MS** m/z 503.3 [M+H]⁺.

[0405] Step E: 1-[4-[7-(3-methoxy-1-naphthyl)-2-[2-(1-piperidyl) ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one: To a solution of 7-(3-methoxy-1-naphthyl)-4-piperazin-1-yl-2-[2- (1-piperidyl)ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidine

bis-trifluoroacetate (145 mg, crude) and Et₃N (221 mg, 2.18 mmol, 303 μ L) in DCM (2.00 mL) was added prop-2-enoyl prop-2-enoate (25.0 mg, 198 μ mol) at -78 °C. After stirring at 0 °C for 0.5 h, the mixture quenched with MeOH and concentrated under vacuum. The mixture was purified by column chromatography (SiO₂, DCM/MeOH = 10:1) to give 1-[4-[7-(3-methoxy-1-naphthyl)-2-[2-(1-piperidyl)ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one (90.0 mg, 162 μ mol, two steps 81.5 % yield) a yellow solid. **ESI MS** m/z 557.3 [M+H]⁺.

[0406] Step F: 1-[4-[7-(3-hydroxy-1-naphthyl)-2-[2-(1-piperidyl)ethoxy]-6,8- dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one: To a solution of 1-[4-[7-(3-methoxy-1-naphthyl)-2-[2-(1-piperidyl) ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one (90.0 mg, 162 μ mol, 1.00 eq) in DCM (2.00 mL) was added BBr₃ (405 mg, 1.62 mmol, 156 μ L, 10.0 eq) at -78 °C. After stirring at 0 °C for 1 h, the mixture was quenched with saturated sodium bicarbonate solution at -78°C and stirred at 0 °C for 0.5 h. The mixture was extracted with ethyl acetate (3 $\times$ 20.0 mL), washed with brine (1 $\times$ 40.0 mL), dried over Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by preparative HPLC (Phenomenex Gemini 150*25mm*, 10 μ ; mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN]; B%: 55%-85%,10 min) to give 1-[4-[7-(3-hydroxy-1-naphthyl)-2-[2-(1-piperidyl)ethoxy]-6,8- dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one (6.19 mg, 10.8 μ mol, 6.71 % yield, 95 % purity) as a yellow oil. **ESI MS** m/z 543.2 [M+H]⁺.

EXAMPLE 53



1-(4-(2-(2-(dimethylamino)ethoxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)-3-(hydroxymethyl)piperazin-1-yl)prop-2-en-1-one

[0407] Step A: 1-tert-butyl 3-methyl 4-(7-benzyl-2-chloro-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1,3-dicarboxylate : A mixture of 7-benzyl-2,4-dichloro-6,8-dihydro-5H-pyrido[3,4-d] pyrimidine (3.00 g, 10.2 mmol, 1.00 eq), 1-tert-butyl-3-methyl piperazine-1,3-dicarboxylate (2.62 g, 10.7 mmol, 1.05 eq), DIEA (3.30 g, 25.5 mmol, 4.45 mL, 2.50 eq) in DMSO (50.0 mL) was degassed and purged with nitrogen 3 times. The mixture was stirred at 100 °C for 12 hours under a nitrogen atmosphere. The reaction mixture was diluted with DCM (200 mL), washed with brine (3 × 50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to dryness. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 10:1 to 3:1) to give 1-tert-butyl 3-methyl 4-(7-benzyl-2-chloro-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1,3-dicarboxylate (2.10 g, 3.81 mmol, 37.4 % yield, 91.0 % purity) as a yellow oil. **ESI MS** m/z 502.1 [M+H]⁺.

[0408] Step B: 1-tert-butyl 3-methyl 4-(7-benzyl-2-(2-(dimethylamino)ethoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1,3-dicarboxylate : A mixture of 1-tert-butyl 3-methyl 4-(7-benzyl-2-chloro-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1,3-dicarboxylate (2.10 g, 4.17 mmol, 1.00 eq), 2-(dimethylamino)ethanol (929 mg, 10.4 mmol, 1.04 mL, 2.50 eq), Pd(OAc)₂ (140 mg, 625 μmol, 0.15 eq), BINAP (519 mg, 833 μmol, 0.20 eq) and Cs₂CO₃ (3.39 g, 10.4 mmol, 2.50 eq) in toluene (60.0 mL) was degassed and purged with nitrogen for 3 times. The mixture was stirred at 110 °C for 3 hours under a nitrogen atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to dryness. The residue was purified by column chromatography (SiO₂, DCM/MeOH = 30:1 to 10:1) to give 1-tert-butyl 3-methyl 4-(7-benzyl-2-(2-(dimethylamino)ethoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1,3-dicarboxylate (1.30 g, 1.67 mmol, 40.0 % yield, 71.4 % purity) as a yellow solid. **ESI MS** m/z 555.3 [M+H]⁺.

[0409] Step C: 1-tert-butyl 3-methyl 4-(2-(2-(dimethylamino)ethoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl) piperazine-1,3-dicarboxylate : To a solution of 1-tert-butyl 3-methyl 4-(7-benzyl-2-(2-(dimethylamino)ethoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1,3-dicarboxylate (1.30 g, 2.34 mmol, 1.00 eq) in MeOH (15.0

mL) was added Pd/C (300 mg) under N₂. The suspension was degassed under vacuum and purged with hydrogen several times. The mixture was stirred under hydrogen (50 psi) at 45 °C for 48 hours. The catalyst was filtered off and the filtrate was concentrated under reduced pressure to give 1-tert-butyl 3-methyl 4-(2-(2-(dimethylamino)ethoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl) piperazine-1,3-dicarboxylate (780 mg, crude) as a colorless oil, which was used directly in the next step without further purification.

[0410] Step D: 1-tert-butyl 3-methyl 4-(7-(3-(benzyloxy)naphthalen-1-yl)-2-(2-(dimethylamino)ethoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1,3-dicarboxylate: A mixture of 1-tert-butyl 3-methyl 4-(2-(2-(dimethylamino)ethoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1,3-dicarboxylate (780 mg, crude), 3-benzyloxy-1-bromo-naphthalene (684 mg, 2.18 mmol), Pd₂(dba)₃ (231 mg, 252 μmol), Cs₂CO₃ (1.37 g, 4.20 mmol) and 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl (RuPhos) (157 mg, 336 μmol) in dioxane (20.0 mL) was degassed and purged with nitrogen 3 times. The mixture was stirred at 85 °C for 5 hours under a nitrogen atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to dryness. The residue was purified by column chromatography (SiO₂, DCM/MeOH = 10:1 to 5:1) to give 1-tert-butyl 3-methyl 4-(7-(3-(benzyloxy)naphthalen-1-yl)-2-(2-(dimethylamino)ethoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1,3-dicarboxylate (750 mg, 1.02 mmol, two steps 43.6 % yield, 95.0 % purity) as a yellow solid. ¹H NMR (400 MHz, chloroform-d) δ = 8.10 (d, J = 8.0 Hz, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.58 - 7.31 (m, 8H), 7.00 (d, J = 2.0 Hz, 1H), 6.89 (d, J = 2.0 Hz, 1H), 5.18 (s, 2H), 4.75 (br s, 1H), 4.45 (br d, J = 13.2 Hz, 1H), 4.42 - 4.34 (m, 1H), 4.34 - 4.28 (m, 1H), 4.15 (br s., 2H), 4.13 - 3.91 (m, 1H), 3.85 - 3.70 (m, 5H), 3.49 - 3.33 (m, 2H), 3.31 - 3.07 (m, 2H), 2.99 (br s, 1H), 2.83 - 2.68 (m, 3H), 2.35(s, 6H), 1.48 (s, 9H).

[0411] Step E: methyl 1-(7-(3-(benzyloxy)naphthalen-1-yl)-2-(2-(dimethylamino)ethoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-2-carboxylate: To a solution of 1-tert-butyl 3-methyl 4-(7-(3-(benzyloxy)naphthalen-1-yl)-2-(2-(dimethylamino)ethoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1,3-dicarboxylate (200 mg, 287 μmol, 1.00 eq) in DCM (5.00 mL) was added TFA (770 mg, 6.75 mmol, 500 μL, 23.5 eq) at 0 °C. The mixture was stirred at 25 °C for 2 hours under a nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure to dryness. The residue was dissolved in DCM (100 mL)

and water (50 mL) and the solution was adjusted to pH 8 with saturated Na₂CO₃ aqueous and then extracted with DCM (3 × 50 mL). The combined organic layers were washed with brine (3 × 50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give methyl 1-(7-(3-(benzyloxy)naphthalen-1-yl)-2-(2-(dimethylamino)ethoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-2-carboxylate (171 mg, 263 μmol, 91.6 % yield, 91.7 % purity) as a yellow solid. **ESI MS** m/z 597.2 [M+H]⁺.

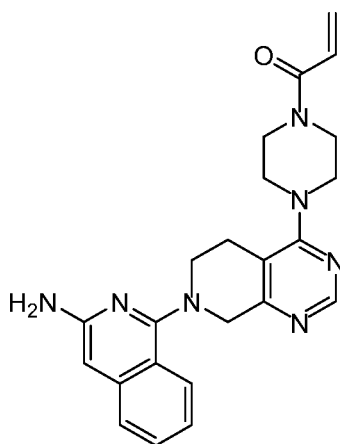
[0412] Step F: (1-(7-(3-(benzyloxy) naphthalen-1-yl)-2-(2-(dimethylamino)ethoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)methanol: To a mixture of methyl 1-(7-(3-(benzyloxy)naphthalen-1-yl)-2-(2-(dimethylamino)ethoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-2-carboxylate (171 mg, 287 μmol, 1.00 eq) in THF (5.00 mL) was added LiAlH₄ (65.3 mg, 1.72 mmol, 6.00 eq) at 0 °C. After stirring for 2 hours at 25 °C, the reaction mixture was quenched by addition of water (30 mL) at 0 °C, and extracted with DCM (3 × 30 mL). The combined organic layers were washed with brine (3 × 30 mL). The collected organic phase was dried over Na₂SO₄, filtered and concentrated under reduced pressure to give (1-(7-(3-(benzyloxy) naphthalen-1-yl)-2-(2-(dimethylamino)ethoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)methanol (160 mg, 281 μmol, 98.2 % yield, 100 % purity) as a colorless semisolid. **ESI MS** m/z 569.2 [M+H]⁺.

[0413] Step G: 2-((7-(3-(benzyloxy)naphthalen-1-yl)-4-(2-(((tert-butyl)dimethylsilyl)oxy)methyl)piperazin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-2-yl)oxy)-N,N-dimethylethanamine: To a mixture of (1-(7-(3-(benzyloxy)naphthalen-1-yl)-2-(2-(dimethyl amino)ethoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)methanol (160 mg, 281 μmol, 1.00 eq) in THF (5.00 mL) was added NaH (94.0 mg, 2.35 mmol, 60.0 % purity, 8.00 eq) at 0 °C. After stirring for 30 minutes, tert-butyl dimethylsilyl chloride (133 mg, 881 μmol, 108 μL, 3.00 eq) was added dropwise. The mixture was stirred at 25 °C for 6 hours under a nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure to give 2-((7-(3-(benzyloxy)naphthalen-1-yl)-4-(2-(((tert-butyl)dimethylsilyl)oxy)methyl)piperazin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-2-yl)oxy)-N,N-dimethylethanamine (133 mg, 165 μmol, 56.1 % yield, 84.6 % purity) as a slight yellow solid, which was used directly in the next step without further purification. **ESI MS** m/z 683.2 [M+H]⁺.

[0414] Step H: 1-(4-(7-(3-(benzyloxy) naphthalene-1-yl)-2-(2-(dimethylamino)ethoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)-3-(((tert-butyldimethylsilyl)oxy)methyl)piperazin-1-yl)prop-2-en-1-one: 1 To a solution of 2-((7-(3-(benzyloxy)naphthalen-1-yl)-4-(2-(((tert-butyl dimethylsilyl)oxy)methyl)piperazin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-2-yl)oxy)-N,N-dimethylethanamine (133 mg, 165 μ mol, 1.00 eq) and TEA (39.4 mg, 389 μ mol, 54.0 μ L, 2.00 eq) in DCM (3.00 mL) was added prop-2-enoyl prop-2-enoate (31.9 mg, 253 μ mol, 1.30 eq) at -40 °C. After stirring at -40 °C for 2 hours, the reaction mixture was quenched with MeOH (1 M) and concentrated under reduced pressure to give 1-(4-(7-(3-(benzyloxy) naphthalene-1-yl)-2-(2-(dimethylamino)ethoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)-3-(((tert-butyldimethylsilyl)oxy)methyl)piperazin-1-yl)prop-2-en-1-one (140 mg, crude) as a yellow solid. **ESI MS** m/z 737.2 [M+H]⁺.

[0415] Step I: 1-(4-(2-(2-(dimethylamino)ethoxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)-3-(hydroxymethyl)piperazin-1-yl)prop-2-en-1-one: To a solution of 1-(4-(7-(3-(benzyloxy)naphthalen-1-yl)-2-(2-(dimethylamino)ethoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)-3-(((tert-butyldimethylsilyl)oxy)methyl)piperazin-1-yl)prop-2-en-1-one (140 mg, crude) in DCM (5.00 mL) was added BBr₃ (476 mg, 1.90 mmol, 183 μ L) at -40 °C. After stirring for 2 hours at -40 °C under a nitrogen atmosphere, the mixture was concentrated under reduced pressure to dryness. Water (0.5 mL) and MeOH (2.5 mL) were added and the resulting solution was purified by preparative HPLC (column: Waters Xbridge 150*25 5u; mobile phase: [water (10 mM NH₄HCO₃) - ACN]; B %: 27 % - 57 %, 11 min). The desired fractions were collected and lyophilized to give 1-(4-(2-(2-(dimethylamino)ethoxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)-3-(hydroxymethyl)piperazin-1-yl)prop-2-en-1-one (4.32 mg, 7.94 μ mol, 4.18 % yield, 97.9 % purity) as a white solid. **ESI MS** m/z 533.4 [M+H]⁺.

EXAMPLE 54



1-[4-[7-(3-amino-1-isoquinolyl)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one

[0416] Step A: tert-butyl 4-hydroxy-6,8-dihydro-5H-pyrido [3,4-d]pyrimidine-7-carboxylate: To a solution of Na (4.24 g, 184 mmol, 4.37 mL, 2.50 eq) in EtOH (400 mL) was added 1-tert-butyl 4-ethyl 3-oxopiperidine-1,4-dicarboxylate (20.0 g, 73.7 mmol, 1.00 eq) and acetic acid methanimidamide (11.5 g, 111 mmol, 1.50 eq) under N₂. The mixture was stirred at 70 °C for 5 hours. The reaction mixture was adjusted to pH 7 with HCl (1N), extracted with DCM (3 × 200 mL), washed with brine (1 × 400 mL), dried over Na₂SO₄, filtered and concentrated under vacuum to give tert-butyl 4-hydroxy-6,8-dihydro-5H-pyrido [3,4-d]pyrimidine-7-carboxylate (16.0 g, 63.7 mmol, 86.4 % yield) as a brown solid. ESI MS m/z 274.0 [M+H]⁺.

[0417] Step B: tert-butyl 4-(4-benzyloxycarbonylpiperazin-1-yl)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidine-7-carboxylate: To a solution of tert-butyl 4-hydroxy-6,8-dihydro-5H-pyrido[3,4-d]pyrimidine-7-carboxylate (16.0 g, 63.7 mmol, 1.00 eq) in DMF (4.00 mL) was added DBU (29.1 g, 191 mmol, 28.8 mL, 3.00 eq) and benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PYBOP) (39.8 g, 76.4 mmol, 1.20 eq). The mixture was stirred at 25 °C for 1 hour. Benzyl piperazine-1-carboxylate (21.0 g, 95.5 mmol, 18.5 mL, 1.50 eq) was added and the reaction mixture was stirred at 25 °C for 16 hours. The mixture was diluted with ethyl acetate (500 mL) and washed with water (3 × 400 mL), dried over Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by column chromatography (SiO₂, diethyl ether/ethyl acetate = 1:1) to give tert-butyl 4-(4-benzyloxycarbonylpiperazin-1-yl)-6,8-dihydro-

5*H*-pyrido[3,4-*d*]pyrimidine-7-carboxylate (2.00 g, 4.41 mmol, 6.93 % yield) as a yellow oil. **ESI MS** *m/z* 454.3 [M+H]⁺.

[0418] Step C: A mixture of *tert*-butyl 4-(4-benzyloxycarbonylpiperazin-1-yl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidine-7-carboxylate (1.20 g, 2.65 mmol, 1.00 eq) and TFA (4.53 g, 39.7 mmol, 2.94 mL, 15.0 eq) in DCM (2.00 mL) was stirred at 25 °C for 1 hour. The mixture was concentrated under vacuum. The concentrated material was adjusted to pH 8 with saturated aq. NaHCO₃, then extracted with ethyl acetate (3 × 30.0 mL), washed with brine (1 × 100 mL), dried over Na₂SO₄, filtered and concentrated under vacuum to give benzyl 4-(5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl)piperazine-1-carboxylate (800 mg, 2.26 mmol, 85.4 % yield) as a yellow oil. **ESI MS** *m/z* 354.3 [M+H]⁺.

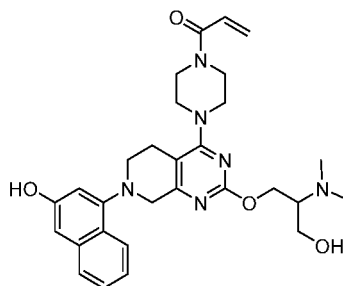
[0419] Step D: benzyl 4-[7-[3-(*tert*-butoxycarbonylamino)-1-isoquinolyl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate: A mixture of *tert*-butyl *N*-(1-bromo-3-isoquinolyl)carbamate (330 mg, 1.02 mmol, 1.00 eq), DIEA (264 mg, 2.04 mmol, 357 µL, 2.00 eq) and benzyl 4-(5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl)piperazine-1-carboxylate (541 mg, 1.53 mmol, 1.50 eq) in DMSO (3.00 mL) was stirred at 80 °C for 10 hours. The mixture was diluted with water (5.00 mL) and extracted with ethyl acetate (3 × 20 mL). The combined extracts were dried over sodium sulfate, filtered and concentrated under vacuum. The residue was purified by reverse-phase column (TFA, 0.1 %) to give benzyl 4-[7-[3-(*tert*-butoxycarbonylamino)-1-isoquinolyl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (400 mg, 665 µmol, 65.2 % yield) as a yellow solid. **ESI MS** *m/z* 596.3 [M+H]⁺.

[0420] Step E: *tert*-butyl *N*-[1-(4-piperazin-1-yl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl)-3-isoquinolyl]carbamate: A mixture of benzyl 4-[7-[3-(*tert*-butoxycarbonylamino)-1-isoquinolyl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (240 mg, 403 µmol, 1.00 eq), KOH (36.2 mg, 645 µmol, 1.60 eq) in H₂O (2.40 mL) and *n*-butyl alcohol (2.40 mL) was stirred at 100 °C for 12 hours. The mixture was diluted with ethyl acetate (3 × 5.00 mL), washed with brine (1 × 10.0 mL), dried over Na₂SO₄, filtered and concentrated under vacuum to give *tert*-butyl *N*-[1-(4-piperazin-1-yl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl)-3-isoquinolyl]carbamate (150 mg, 325 µmol, 80.7 % yield) as a yellow oil. **ESI MS** *m/z* 462.3 [M+H]⁺.

[0421] Step F: 1-(4-piperazin-1-yl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-7-yl)isoquinolin-3-amine trifluoroacetate: A solution of *tert*-butyl N-[1-(4-piperazin-1-yl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-7-yl)-3-isoquinolyl]carbamate (150 mg, 325 μ mol, 1.00 eq) and TFA (556 mg, 4.87 mmol, 361 μ L, 15.0 eq) in DCM (360 μ L) was stirred at 25 °C for 1 hours. The mixture was concentrated under vacuum to give 1-(4-piperazin-1-yl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-7-yl)isoquinolin-3-amine trifluoroacetate (154.52 mg, crude) as a yellow solid which was used into next step without further purification.

[0422] Step G: 1-[4-[7-(3-amino-1-isoquinolyl)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one: To a solution of 1-(4-piperazin-1-yl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-7-yl)isoquinolin-3-amine trifluoroacetate (150 mg, crude) and Et₃N (319 mg, 3.15 mmol, 437 μ L) in DCM (2.00 mL) was added prop-2-enoyl prop-2-enoate (31.8 mg, 252 μ mol) at -40 °C, then stirred at -40 °C for 0.5 h. The mixture was quenched by adding MeOH (20.22 mg, 630.96 μ mol) and concentrated under vacuum. The residue was purified by preparative HPLC (Phenomenex Gemini 150*25mm*, 10 μ ; mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN]; B%: 26%-56%, 10 min) to give 1-[4-[7-(3-amino-1-isoquinolyl)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one (35.4 mg, 82.5 μ mol, 26.2 % yield, 96.8 % purity) as a yellow solid. **ESI MS** *m/z* 416.3 [M+H]⁺.

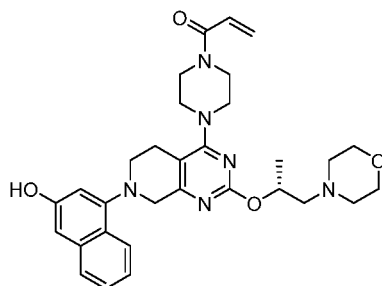
EXAMPLE 55



1-(4-(2-(2-(dimethylamino)-3-hydroxypropoxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0423] Synthesized according to the method of **Example 8**, using 2-(dimethylamino)propane-1,3-diol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. **ES+APCI MS** *m/z* 533.3[M+H]⁺.

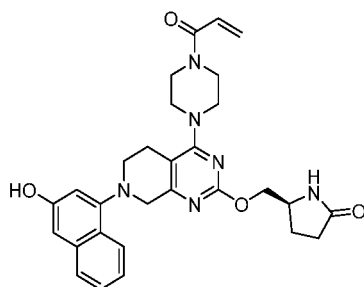
EXAMPLE 56



(R)-1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-((1-morpholinopropan-2-yl)oxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0424] Synthesized according to the method of **Example 8**, using (R)-1-morpholinopropan-2-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 559.3 $[M+H]^+$.

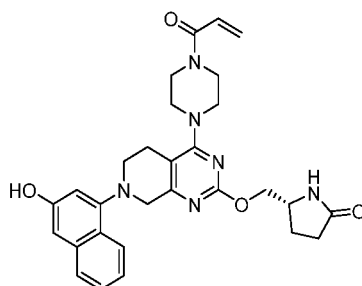
EXAMPLE 57



(S)-5-(((4-(4-acryloylpiperazin-1-yl)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-2-yl)oxy)methyl)pyrrolidin-2-one

[0425] Synthesized according to the method of **Example 8**, using (S)-5-(hydroxymethyl)pyrrolidin-2-one in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 529.3 $[M+H]^+$.

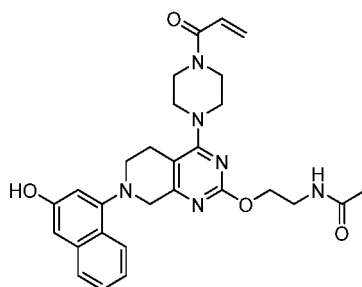
EXAMPLE 58



(R)-5-(((4-(4-acryloylpiperazin-1-yl)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-2-yl)oxy)methyl)pyrrolidin-2-one

[0426] Synthesized according to the method of **Example 8**, using (R)-5-(hydroxymethyl)pyrrolidin-2-one in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 529.2 $[M+H]^+$.

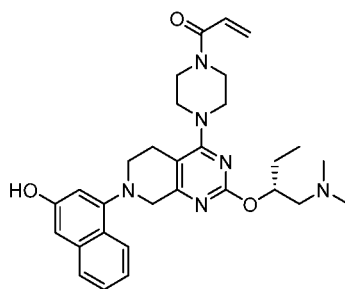
EXAMPLE 59



N-(2-(((4-(4-acryloylpiperazin-1-yl)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-2-yl)oxy)ethyl)acetamide

[0427] Synthesized according to the method of **Example 8**, using N-(2-hydroxyethyl)acetamide in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 517.3 $[M+H]^+$.

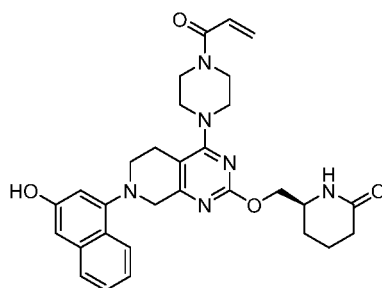
EXAMPLE 60



(R)-1-(4-(2-((1-(dimethylamino)butan-2-yl)oxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0428] Synthesized according to the method of **Example 8**, using (R)-1-(dimethylamino)butan-2-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 545.3 [M+H]⁺.

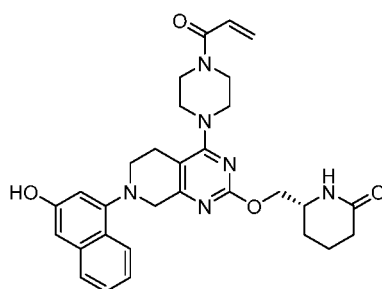
EXAMPLE 61



(S)-6-(((4-(4-acryloylpiperazin-1-yl)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-2-yl)oxy)methyl)piperidin-2-one

[0429] Synthesized according to the method of **Example 8**, using 6-(hydroxymethyl)piperidin-2-one in place of (S)-1-(dimethylamino)propan-2-ol in Step B and the product was separated by chiral chromatography. Peak 2 was given the (S) stereochemistry and this was not confirmed. ES+APCI MS m/z 543.3 [M+H]⁺.

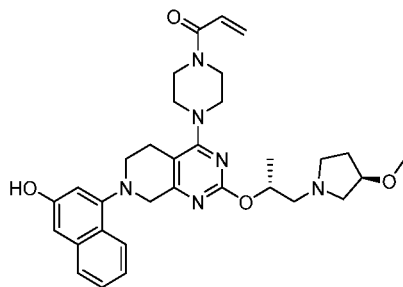
EXAMPLE 62



(R)-6-(((4-(4-acryloylpiperazin-1-yl)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-2-yl)oxy)methyl)piperidin-2-one

[0430] Synthesized according to the method of **Example 8**, using 6-(hydroxymethyl)piperidin-2-one in place of (S)-1-(dimethylamino)propan-2-ol in Step B and separated by chiral chromatography. Peak 1 was assigned the (R) stereochemistry but this stereochemistry was not confirmed. ES+APCI MS m/z 543.2 [M+H]⁺.

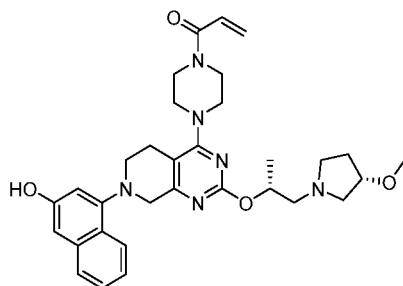
EXAMPLE 63



1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-(((R)-1-((R)-3-methoxypyrrolidin-1-yl)propan-2-yl)oxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0431] Synthesized according to the method of **Example 8**, using (R)-1-((R)-3-methoxypyrrolidin-1-yl)propan-2-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 573.3 [M+H]⁺.

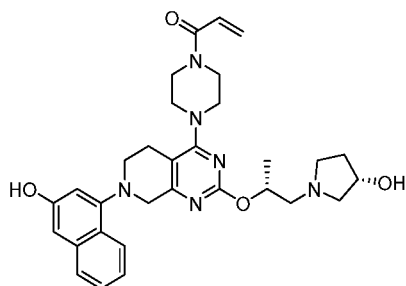
EXAMPLE 64



1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-(((R)-1-((S)-3-methoxypyrrolidin-1-yl)propan-2-yl)oxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0432] Synthesized according to the method of **Example 8**, using (R)-1-((S)-3-methoxypyrrolidin-1-yl)propan-2-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 573.3 [M+H]⁺.

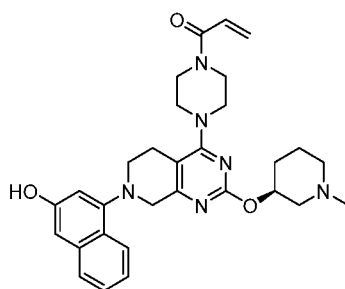
EXAMPLE 65



1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-(((R)-1-((S)-3-hydroxypyrrolidin-1-yl)propan-2-yl)oxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0433] Synthesized according to the method of **Example 8**, using (R)-1-((S)-3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)propan-2-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 559.3 [M+H]⁺.

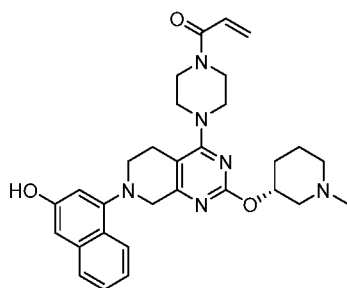
EXAMPLE 66



(S)-1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-((1-methylpiperidin-3-yl)oxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0434] Synthesized according to the method of **Example 8**, using (S)-1-methylpiperidin-3-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 529.3 [M+H]⁺.

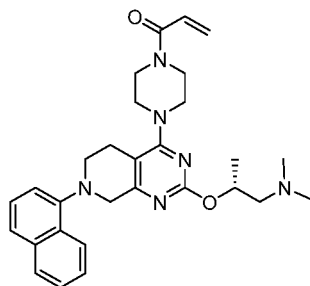
EXAMPLE 67



(R)-1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-((1-methylpiperidin-3-yl)oxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0435] Synthesized according to the method of **Example 8**, using (R)-1-methylpiperidin-3-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 529.3 $[M+H]^+$.

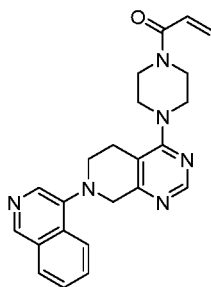
EXAMPLE 68



(R)-1-(4-(2-((1-(dimethylamino)propan-2-yl)oxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0436] Synthesized according to the method of **Example 8**, using 1-iodonaphthalene in place of (3-(methoxymethoxy)naphthalen-1-yl trifluoromethanesulfonate in Step D. ES+APCI MS m/z 501.3 $[M+H]^+$.

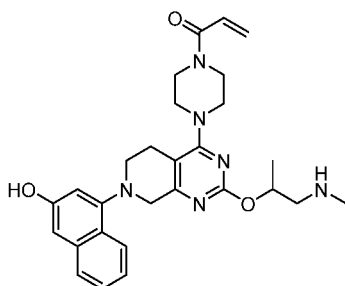
EXAMPLE 69



1-(4-(7-(isoquinolin-4-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0437] Synthesized according to the method of **Example 1**, using 4-bromoisquinoline in place of 1-bromo-3-(methoxymethoxy)naphthalene in Step C. ES+APCI MS m/z 401.2 [M+H]⁺.

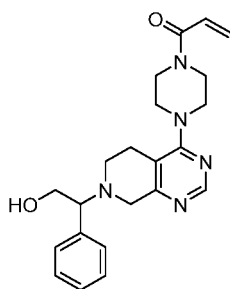
EXAMPLE 70



1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-((1-(methylamino)propan-2-yl)oxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0438] Synthesized according to the method of **Example 8**, using 1-(methylamino)propan-2-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 503.3 [M+H]⁺.

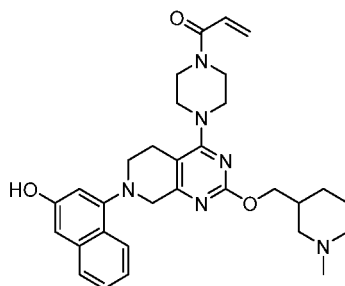
EXAMPLE 71



1-(4-(7-(2-hydroxy-1-phenylethyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0439] Synthesized according to the method of **Example 1**, using 2-((tert-butyl dimethylsilyl)oxy)-1-phenylethyl methanesulfonate in place of 1-bromo-3-(methoxymethoxy)naphthalene in Step C. ES+APCI MS m/z 394.2 [M+H]⁺.

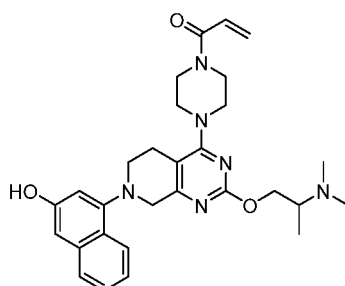
EXAMPLE 72



1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-((1-methylpiperidin-3-yl)methoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0440] Synthesized according to the method of **Example 8**, using (1-methylpiperidin-3-yl)methanol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 543.3 $[M+H]^+$.

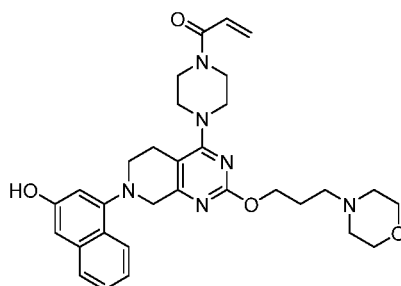
EXAMPLE 73



1-(4-(2-(2-(dimethylamino)propoxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0441] Synthesized according to the method of **Example 8**, using 2-(dimethylamino)propan-1-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 517.2 $[M+H]^+$.

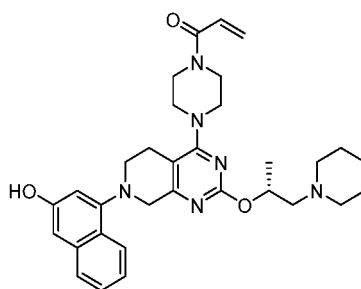
EXAMPLE 74



1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0442] Synthesized according to the method of **Example 8**, using 3-morpholinopropan-1-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 559.3 $[M+H]^+$.

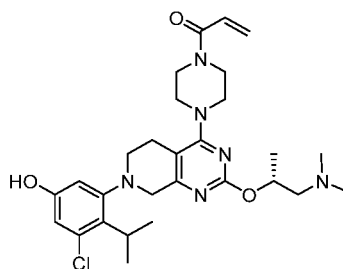
EXAMPLE 75



(R)-1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-((1-(piperidin-1-yl)propan-2-yl)oxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0443] Synthesized according to the method of **Example 8**, using (R)-1-(piperidin-1-yl)propan-2-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 557.3 $[M+H]^+$.

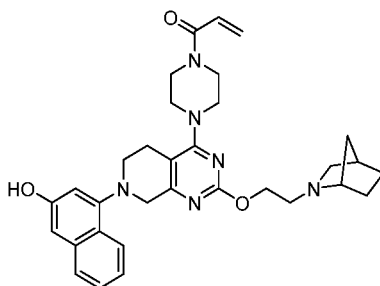
EXAMPLE 76



(R)-1-(4-(7-(3-chloro-5-hydroxy-2-isopropylphenyl)-2-((1-(dimethylamino)propan-2-yl)oxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0444] Synthesized according to the method of **Example 8**, using 1-bromo-3-chloro-2-isopropyl-5-(methoxymethoxy)benzene in place of (3-(methoxymethoxy)naphthalen-1-yl)trifluoromethanesulfonate in Step D. ES+APCI MS m/z 545.3 [M+H]⁺.

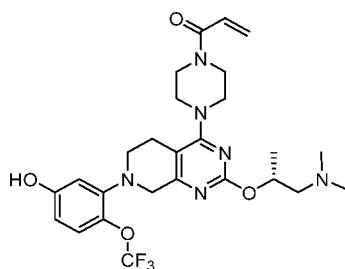
EXAMPLE 77



1-(4-(2-(2-((1S,4R)-2-azabicyclo[2.2.1]heptan-2-yl)ethoxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0445] Synthesized according to the method of **Example 8**, using 2-((1S,4R)-2-azabicyclo[2.2.1]heptan-2-yl)ethan-1-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 555.2 [M+H]⁺.

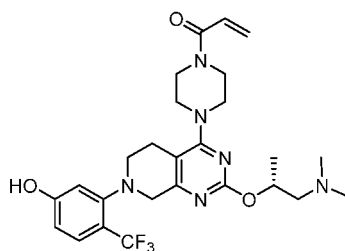
EXAMPLE 78



(R)-1-(4-(2-((1-(dimethylamino)propan-2-yl)oxy)-7-(5-hydroxy-2-(trifluoromethoxy)phenyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0446] Synthesized according to the method of **Example 8**, using 2-bromo-4-(methoxymethoxy)-1-(trifluoromethoxy)benzene in place of (3-(methoxymethoxy)naphthalen-1-yl trifluoromethanesulfonate in Step D. ES+APCI MS m/z 551.2 $[M+H]^+$.

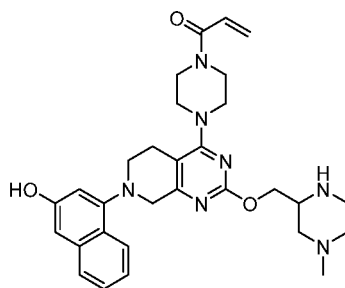
EXAMPLE 79



(R)-1-(4-(2-((1-(dimethylamino)propan-2-yl)oxy)-7-(5-hydroxy-2-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0447] Synthesized according to the method of **Example 8**, using 2-bromo-4-(methoxymethoxy)-1-(trifluoromethyl)benzene in place of (3-(methoxymethoxy)naphthalen-1-yl trifluoromethanesulfonate in Step D. ES+APCI MS m/z 535.2 $[M+H]^+$.

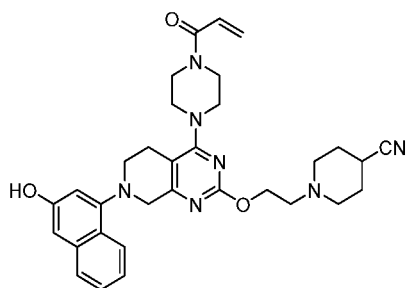
EXAMPLE 80



1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-((4-methylpiperazin-2-yl)methoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0448] Synthesized according to the method of **Example 8**, using (4-methylpiperazin-2-yl)methanol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 544.3 $[M+H]^+$.

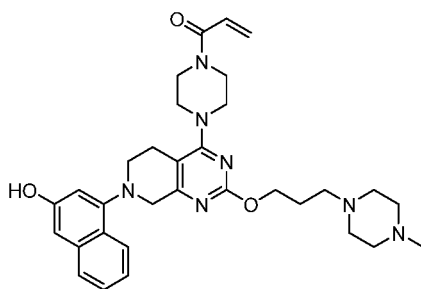
EXAMPLE 81



1-(2-((4-(4-acryloylpiperazin-1-yl)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-2-yl)oxy)ethyl)piperidine-4-carbonitrile

[0449] Synthesized according to the method of **Example 8**, using 1-(2-hydroxyethyl)piperidine-4-carbonitrile in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 568.2 [M+H]⁺.

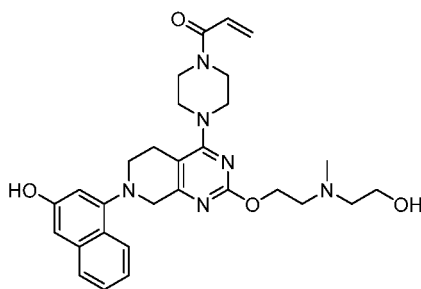
EXAMPLE 82



1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-(3-(4-methylpiperazin-1-yl)propoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0450] Synthesized according to the method of **Example 8**, 3-(4-methylpiperazin-1-yl)propan-1-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 572.4 [M+H]⁺.

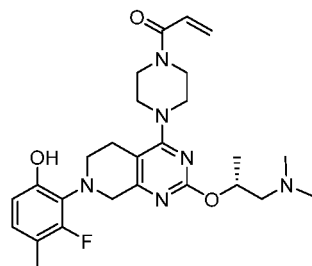
EXAMPLE 83



1-(4-(2-(2-((2-hydroxyethyl)(methyl)amino)ethoxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0451] Synthesized according to the method of **Example 8**, using 2-((2-((tert-butyl)dimethylsilyl)oxy)ethyl)(methyl)amino)ethan-1-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 533.3 [M+H]⁺.

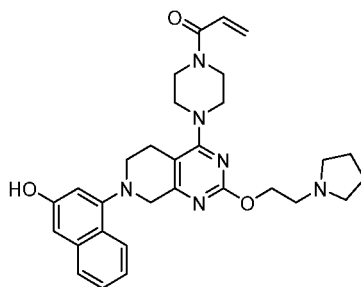
EXAMPLE 84



(R)-1-(4-(2-((1-(dimethylamino)propan-2-yl)oxy)-7-(2-fluoro-6-hydroxy-3-methylphenyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0452] Synthesized according to the method of **Example 8**, using 2-bromo-3-fluoro-1-(methoxymethoxy)-4-methylbenzene in place of (3-(methoxymethoxy)naphthalen-1-yl)trifluoromethanesulfonate in Step D. ES+APCI MS m/z 499.3 [M+H]⁺.

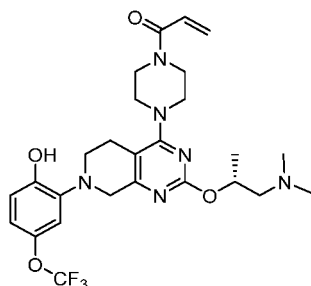
EXAMPLE 85



1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-(2-(pyrrolidin-1-yl)ethoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0453] Synthesized according to the method of **Example 8**, using 2-(pyrrolidin-1-yl)ethan-1-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 529.2 [M+H]⁺.

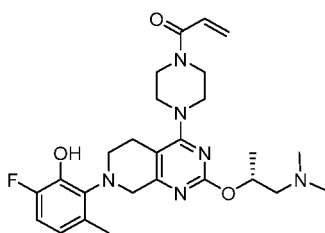
EXAMPLE 86



(R)-1-(4-(2-((1-(dimethylamino)propan-2-yl)oxy)-7-(2-hydroxy-5-(trifluoromethoxy)phenyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0454] Synthesized according to the method of **Example 8**, using 2-bromo-1-(methoxymethoxy)-4-(trifluoromethoxy)benzene in place of (3-(methoxymethoxy)naphthalen-1-yl trifluoromethanesulfonate in Step D. ES+APCI MS m/z 551.2 $[M+H]^+$.

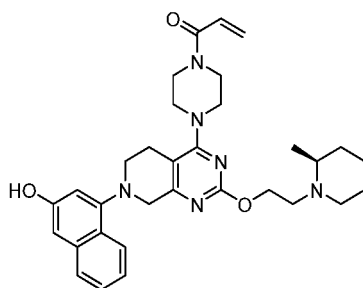
EXAMPLE 87



(R)-1-(4-(2-((1-(dimethylamino)propan-2-yl)oxy)-7-(3-fluoro-2-hydroxy-6-methylphenyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0455] Synthesized according to the method of **Example 8**, using 2-bromo-4-fluoro-3-(methoxymethoxy)-1-methylbenzene in place of (3-(methoxymethoxy)naphthalen-1-yl trifluoromethanesulfonate in Step D. ES+APCI MS m/z 499.2 $[M+H]^+$.

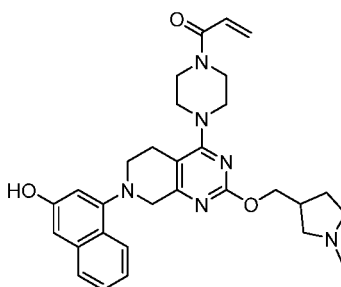
EXAMPLE 88



(S)-1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-(2-(2-methylpiperidin-1-yl)ethoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0456] Synthesized according to the method of **Example 8**, using (S)-2-(2-methylpiperidin-1-yl)ethan-1-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 557.2 [M+H]⁺.

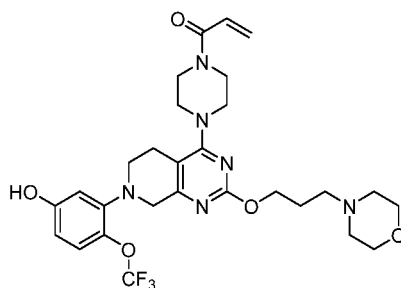
EXAMPLE 89



1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-((1-methylpyrrolidin-3-yl)methoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0457] Synthesized according to the method of **Example 8**, using (1-methylpyrrolidin-3-yl)methanol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 529.3 [M+H]⁺.

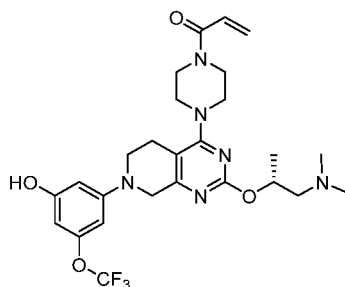
EXAMPLE 90



1-(4-(7-(5-hydroxy-2-(trifluoromethoxy)phenyl)-2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0458] Synthesized according to the method of **Example 8**, using 3-morpholinopropan-1-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B, and using 2-bromo-4-(methoxymethoxy)-1-(trifluoromethoxy)benzene in place of (3-(methoxymethoxy)naphthalen-1-yl trifluoromethanesulfonate in Step D. ES+APCI MS m/z 593.2 [M+H]⁺.

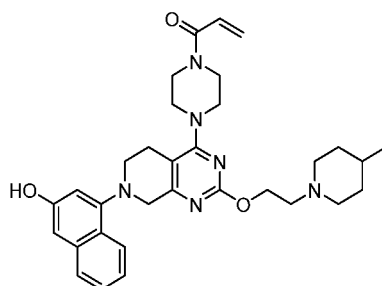
EXAMPLE 91



(R)-1-(4-(2-((1-(dimethylamino)propan-2-yl)oxy)-7-(3-hydroxy-5-(trifluoromethoxy)phenyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0459] Synthesized according to the method of **Example 8**, using 3-bromo-1-(methoxymethoxy)-5-(trifluoromethoxy)benzene in place of (3-(methoxymethoxy)naphthalen-1-yl trifluoromethanesulfonate in Step D. ES+APCI MS m/z 551.2 [M+H]⁺.

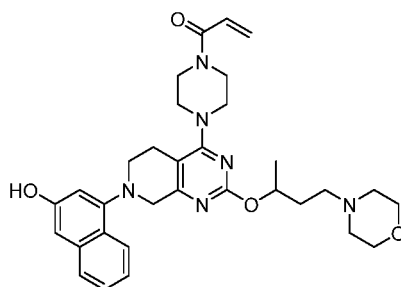
EXAMPLE 92



1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-(2-(4-methylpiperidin-1-yl)ethoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0460] Synthesized according to the method of **Example 8**, using 2-(4-methylpiperidin-1-yl)ethan-1-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 557.2 $[M+H]^+$.

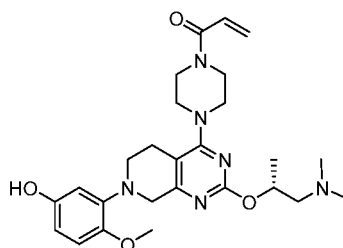
EXAMPLE 93



1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-((4-morpholinobutan-2-yl)oxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0461] Synthesized according to the method of **Example 8**, using 4-morpholinobutan-2-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 573.3 $[M+H]^+$.

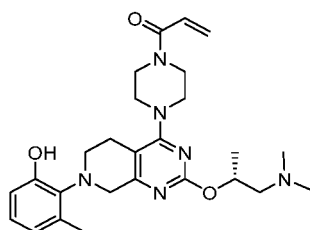
EXAMPLE 94



(R)-1-(4-(2-((1-(dimethylamino)propan-2-yl)oxy)-7-(5-hydroxy-2-methoxyphenyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0462] Synthesized according to the method of **Example 8**, using 3-bromo-1-(methoxymethoxy)-4-methoxybenzene in place of (3-(methoxymethoxy)naphthalen-1-yl trifluoromethanesulfonate in Step D. ES+APCI MS m/z 497.2 [M+H]⁺.

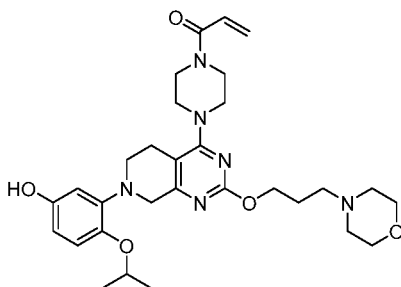
EXAMPLE 95



(R)-1-(4-(2-((1-(dimethylamino)propan-2-yl)oxy)-7-(2-hydroxy-6-methylphenyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0463] Synthesized according to the method of **Example 8**, using 2-bromo-1-(methoxymethoxy)-3-methylbenzene in place of (3-(methoxymethoxy)naphthalen-1-yl trifluoromethanesulfonate in Step D. ES+APCI MS m/z 481.2 [M+H]⁺.

EXAMPLE 96

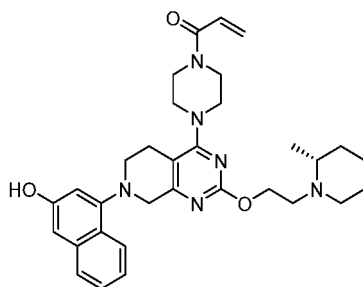


1-(4-(7-(5-hydroxy-2-isopropoxyphenyl)-2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0464] Synthesized according to the method of **Example 8**, using 3-morpholinopropan-1-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B, and using 2-bromo-4-(methoxymethoxy)-

1-(isopropoxy)benzene in place of (3-(methoxymethoxy)naphthalen-1-yl trifluoromethanesulfonate in Step D. ES+APCI MS m/z 567.2 $[M+H]^+$.

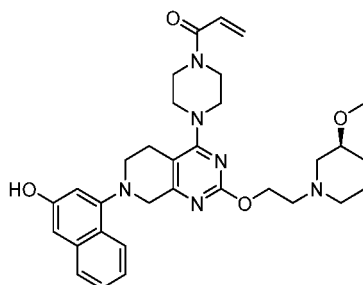
EXAMPLE 97



(R)-1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-(2-(2-methylpiperidin-1-yl)ethoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0465] Synthesized according to the method of **Example 8**, using (R)-2-(2-methylpiperidin-1-yl)ethan-1-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 557.3

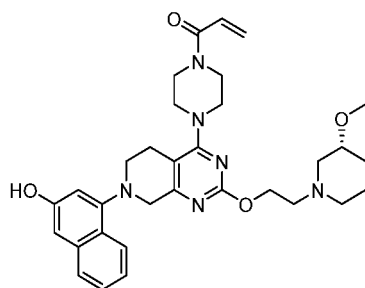
EXAMPLE 98



(S)-1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-(2-(3-methoxypiperidin-1-yl)ethoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0466] Synthesized according to the method of **Example 8**, using (S)-2-(3-methoxypiperidin-1-yl)ethan-1-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 557.3 $[M+H]^+$.

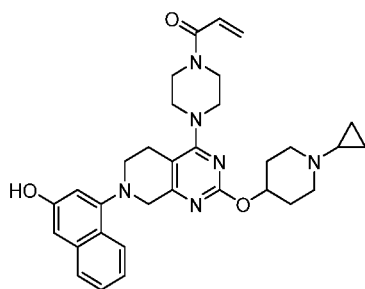
EXAMPLE 99



(R)-1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-(2-(3-methoxypiperidin-1-yl)ethoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0467] Synthesized according to the method of **Example 8**, using (R)-2-(3-methoxypiperidin-1-yl)ethan-1-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 557.3 [M+H]⁺.

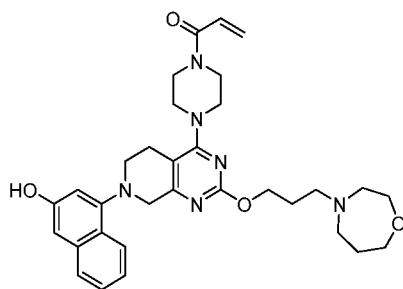
EXAMPLE 100



1-(4-(2-((1-cyclopropylpiperidin-4-yl)oxy))-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0468] Synthesized according to the method of **Example 8**, using (1-cyclopropylpiperidin-4-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 555.3 [M+H]⁺.

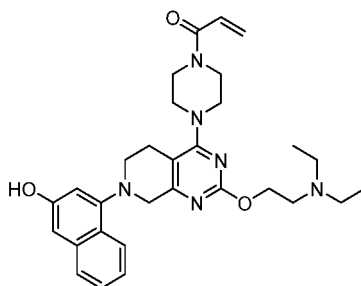
EXAMPLE 101



1-(4-(2-(3-(1,4-oxazepan-4-yl)propoxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0469] Synthesized according to the method of **Example 8**, using (3-(1,4-oxazepan-4-yl)propan-1-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 573.3 [M+H]⁺.

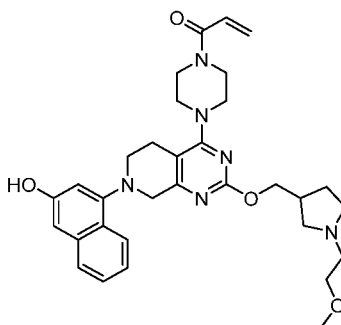
EXAMPLE 102



1-(4-(2-(3-(1,4-oxazepan-4-yl)propoxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0470] Synthesized according to the method of **Example 8**, using 2-(diethylamino)ethan-1-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 531.3 [M+H]⁺.

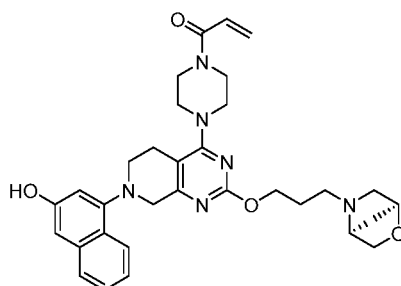
EXAMPLE 103



1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-((1-(2-methoxyethyl)pyrrolidin-3-yl)methoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0471] Synthesized according to the method of **Example 8**, (1-(2-methoxyethyl)pyrrolidin-3-yl)methanol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 573.3 $[M+H]^+$.

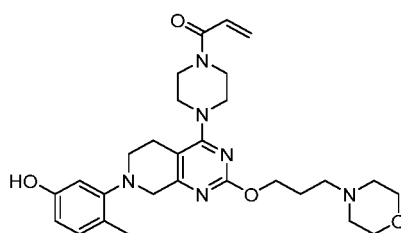
EXAMPLE 104



1-(4-(2-(3-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)propoxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0472] Synthesized according to the method of **Example 8**, using 3-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)propan-1-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 571.3 $[M+H]^+$.

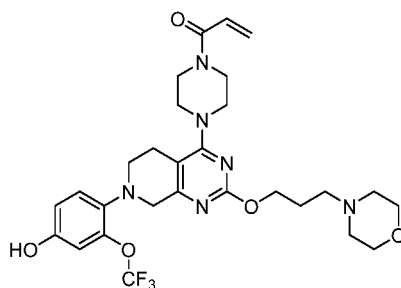
EXAMPLE 105



1-(4-(7-(5-hydroxy-2-methylphenyl)-2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0473] Synthesized according to the method of **Example 8**, using 3-morpholinopropan-1-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B, and using 2-bromo-4-(methoxymethoxy)-1-methylbenzene in place of (3-(methoxymethoxy)naphthalen-1-yl trifluoromethanesulfonate in Step D. ES+APCI MS m/z 523.3 $[M+H]^+$.

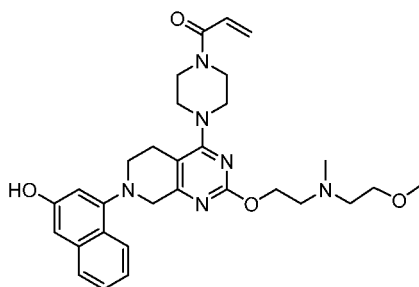
EXAMPLE 106



1-(4-(7-(4-hydroxy-2-(trifluoromethoxy)phenyl)-2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0474] Synthesized according to the method of **Example 8**, using 3-morpholinopropan-1-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B, and using 2-bromo-5-(methoxymethoxy)-1-(trifluoromethoxy)benzene in place of (3-(methoxymethoxy)naphthalen-1-yl trifluoromethanesulfonate in Step D. ES+APCI MS m/z 593.2 [M+H]⁺.

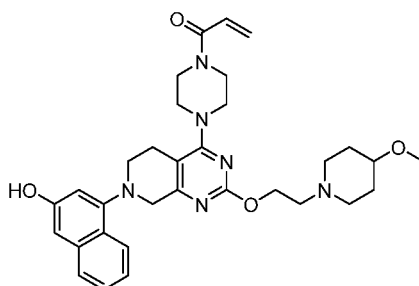
EXAMPLE 107



1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-(2-((2-methoxyethyl)(methyl)amino)ethoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0475] Synthesized according to the method of **Example 8**, using 2-((2-methoxyethyl)(methyl)amino)ethan-1-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 547.3 [M+H]⁺.

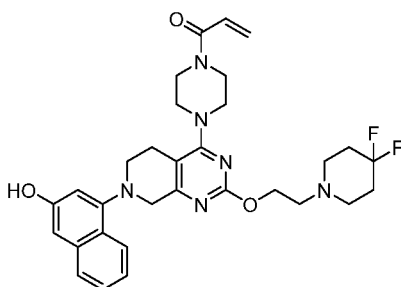
EXAMPLE 108



1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-(2-(4-methoxypiperidin-1-yl)ethoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0476] Synthesized according to the method of **Example 8**, using 2-(4-methoxypiperidin-1-yl)ethan-1-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 573.3 [M+H]⁺.

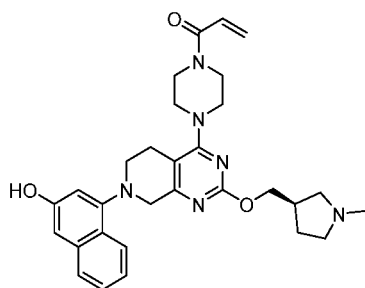
EXAMPLE 109



1-(4-(2-(2-(4,4-difluoropiperidin-1-yl)ethoxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0477] Synthesized according to the method of **Example 8**, using 2-(4,4-difluoropiperidin-1-yl)ethan-1-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 579.2 [M+H]⁺.

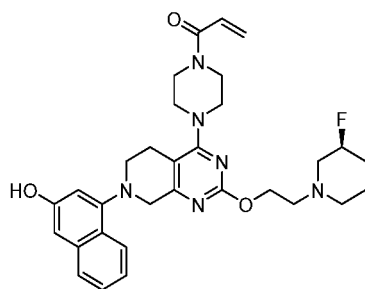
EXAMPLE 110



(R)-1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-((1-methylpyrrolidin-3-yl)methoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0478] Synthesized according to the method of **Example 8**, using (R)-(1-methylpyrrolidin-3-yl)methanol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 529.3 [M+H]⁺.

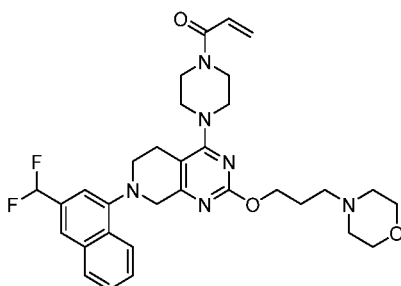
EXAMPLE 111



(S)-1-(4-(2-(2-(3-fluoropiperidin-1-yl)ethoxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0479] Synthesized according to the method of **Example 8**, using (S)-2-(3-fluoropiperidin-1-yl)ethan-1-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 561.3 [M+H]⁺.

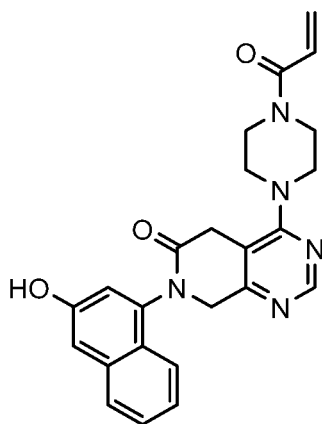
EXAMPLE 112



1-(4-(7-(3-(difluoromethyl)naphthalen-1-yl)-2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0480] Synthesized according to the method of **Example 8**, using 3-morpholinopropan-1-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B, and using 1-bromo-3-(difluoromethyl)naphthalene (0.129 g, 0.503 mmol) in place of (3-(methoxymethoxy)naphthalen-1-yl trifluoromethanesulfonate in Step D. ES+APCI MS m/z 593.2 $[M+H]^+$.

EXAMPLE 113



4-(4-acryloylpiperazin-1-yl)-7-(3-hydroxynaphthalen-1-yl)-7,8-dihydropyrido[3,4-d]pyrimidin-6(5H)-one

[0481] Step A: tert-butyl 4-(6-fluoropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate: To a solution of 4-chloro-6-fluoropyrido[3,4-d]pyrimidine (1.07 g, 5.83 mmol) in DCM (20 mL) was added N-ethyl-N-isopropylpropan-2-amine (2.09 mL, 11.7 mmol) followed by tert-butyl piperazine-1-carboxylate (1.19 g, 6.41 mmol) and the reaction stirred at room temperature for 2 hours. The reaction mixture was washed with brine, dried over $MgSO_4$ and concentrated *in*

vacuo to provide tert-butyl 4-(6-fluoropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate, which was used directly in the next step (1.8 g, 92.6%) **ES+APCI MS** m/z 334.1 [M+H]⁺.

[0482] Step B: tert-butyl 4-(6-(benzyloxy)pyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate:

To a solution of phenylmethanol (0.65 g, 6.0 mmol) in DMA (10 mL) was added sodium hydride (0.24 g, 6.0 mmol) in portions while degassing with nitrogen and the reaction mixture was stirred for 30 minutes at room temperature. To the reaction was added tert-butyl 4-(6-fluoropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (1.0 g, 3.0 mmol) as a solid and the reaction mixture was stirred at room temperature for 3 hours. The reaction was poured into water (300 mL) and the aqueous layer extracted with ethyl acetate. The organic layer was washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The crude material was chromatographed using a gradient of 0 to 100% ethyl acetate/DCM as the eluent to give tert-butyl 4-(6-(benzyloxy)pyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (0.4 g, 0.95 mmol, 32 % yield). **ES+APCI MS** m/z 422.2 [M+H]⁺.

[0483] Step C: tert-butyl 4-(6-oxo-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate:

To a solution of tert-butyl 4-(6-(benzyloxy)pyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (0.40 g, 0.95 mmol) in 95% ethanol (30 mL) purged with nitrogen was added Pd/C (0.10 g, 0.95 mmol). The reaction was evacuated with vacuum and backfilled with hydrogen three times. After the third backfill the reaction mixture was stirred at room temperature for 4 hours. The reaction was again degassed with nitrogen, the slurry filtered through Celite® and the filtrate was concentrated in *vacuo* to give tert-butyl 4-(6-oxo-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (0.4g, 126%). **ES+APCI MS** m/z 334.4 [M+H]⁺.

[0484] Step D: tert-butyl 4-(7-(3-(methoxymethoxy)naphthalen-1-yl)-6-oxo-5,6,7,8-

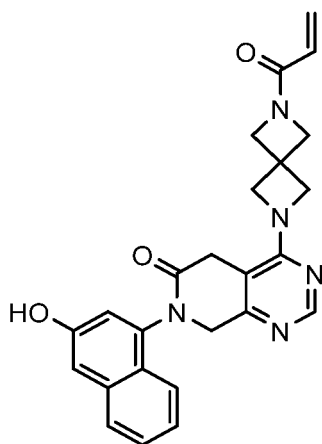
tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate: To a solution of tert-butyl 4-(6-oxo-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (0.28 g, 0.84 mmol) in dioxanes (4 mL) in a sealed tube was added potassium phosphate (0.36 g, 1.7 mmol), N1,N2-dimethylethane-1,2-diamine (0.074 g, 0.84 mmol) and 1-iodo-3-(methoxymethoxy)naphthalene (0.53 g, 1.7 mmol). The reaction sparged with argon for 20 minutes, followed by addition of copper(I) iodide (0.16 g, 0.84 mmol). The reaction vessel sealed and heated to 100 °C overnight. The reaction was diluted with water and the aqueous

layer extracted with ethyl acetate (2 x 150 mL). The organics were washed with brine, dried over MgSO_4 and concentrated in vacuo. The material was chromatographed using a gradient of 0 to 100% ethyl acetate/DCM as the eluent to give tert-butyl 4-(7-(3-(methoxymethoxy)naphthalen-1-yl)-6-oxo-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (0.30 g, 0.58 mmol, 69 % yield) ES+APCI MS m/z 520.2 $[\text{M}+\text{H}]^+$.

[0485] Step E: 7-(3-hydroxynaphthalen-1-yl)-4-(piperazin-1-yl)-7,8-dihydropyrido[3,4-d]pyrimidin-6(5H)-one: To a solution of tert-butyl 4-(7-(3-(methoxymethoxy)naphthalen-1-yl)-6-oxo-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (0.30 g, 0.58 mmol) in methanol (10 mL) was added aqueous hydrogen chloride (0.38 mL, 2.3 mmol) and the reaction stirred over night at 50°C. The reaction was concentrated in vacuo to give 7-(3-hydroxynaphthalen-1-yl)-4-(piperazin-1-yl)-7,8-dihydropyrido[3,4-d]pyrimidin-6(5H)-one as the bis HCl salt (0.26g, 100%). ES+APCI MS m/z 376.1 $[\text{M}+\text{H}]^+$.

[0486] Step F: 4-(4-acryloylpiperazin-1-yl)-7-(3-hydroxynaphthalen-1-yl)-7,8-dihydropyrido[3,4-d]pyrimidin-6(5H)-one: To a slurry of 7-(3-hydroxynaphthalen-1-yl)-4-(piperazin-1-yl)-7,8-dihydropyrido[3,4-d]pyrimidin-6(5H)-one dihydrochloride (0.26 g, 0.58 mmol) in a 1:1 solution of DCM/acetonitrile (10 mL) was added N-ethyl-N-isopropylpropan-2-amine (0.45 g, 3.5 mmol) and acryloyl chloride (0.052 g, 0.58 mmol) and the reaction stirred at room temperature for 1 hour. The reaction was concentrated *in vacuo* and the material purified by reverse preparative HPLC (using a gradient of 5 to 95% ACN/water) to give 4-(4-acryloylpiperazin-1-yl)-7-(3-hydroxynaphthalen-1-yl)-7,8-dihydropyrido[3,4-d]pyrimidin-6(5H)-one (0.038 g, 0.088 mmol, 15 % yield). ES+APCI MS m/z 430.2 $[\text{M}+\text{H}]^+$.

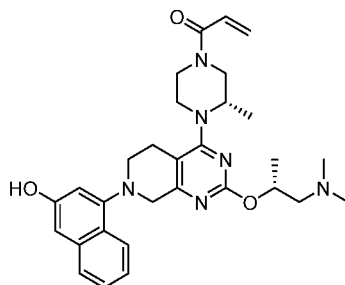
EXAMPLE 114



4-(6-acryloyl-2,6-diazaspiro[3.3]heptan-2-yl)-7-(3-hydroxynaphthalen-1-yl)-7,8-dihydropyrido[3,4-d]pyrimidin-6(5H)-one

[0487] Synthesized according to the method of **Example 8**, using tert-butyl 2,6-diazaspiro[3.3]heptane-2-carboxylate hydrochloride (305 mg, 1.54 mmol) in place of tert-butyl piperazine-1-carboxylate (1.19 g, 6.41 mmol) in Step B. ES+APCI MS m/z 442.2 $[M+H]^+$

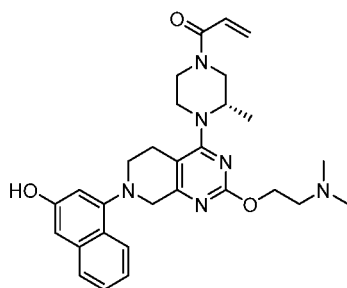
EXAMPLE 115



1-((S)-4-(2-(((R)-1-(dimethylamino)propan-2-yl)oxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)-3-methylpiperazin-1-yl)prop-2-en-1-one

[0488] Synthesized according to the method of **Example 8**, using benzyl (S)-3-methylpiperazine-1-carboxylate (1.155 g, 4.931 mmol) in place of Benzyl 1-piperazinecarboxylate in step A. ES+APCI MS m/z 531.3 $[M+H]^+$.

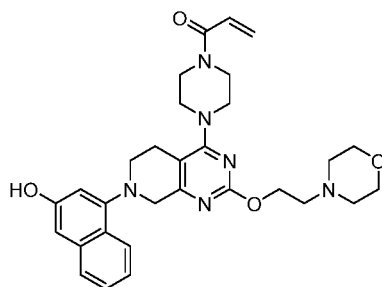
EXAMPLE 116



(S)-1-(4-(2-(2-(dimethylamino)ethoxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)-3-methylpiperazin-1-yl)prop-2-en-1-one

[0489] Synthesized according to the method of **Example 8**, using benzyl (S)-3-methylpiperazine-1-carboxylate (1.155 g, 4.931 mmol) in place of Benzyl 1-piperazinecarboxylate in step A. Also, using 2-(dimethylamino)ethan-1-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 517.3 $[M+H]^+$.

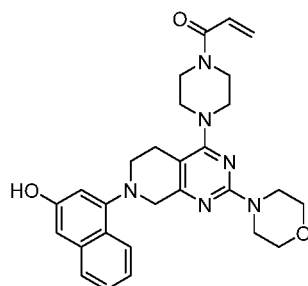
EXAMPLE 117



1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-(2-morpholinoethoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0490] Synthesized according to the method of **Example 8**, using 2-morpholinoethan-1-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 545.2 $[M+H]^+$.

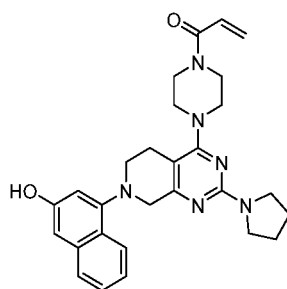
EXAMPLE 118



1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-morpholino-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0491] Synthesized according to the method of **Example 8**, using morpholine in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 501.3 $[M+H]^+$.

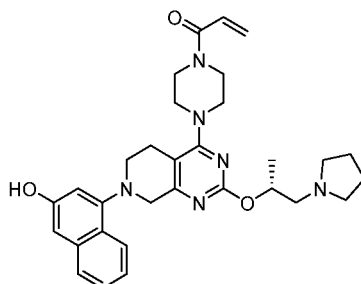
EXAMPLE 119



1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-(pyrrolidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0492] Synthesized according to the method of **Example 8**, using pyrrolidine in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 485.2 $[M+H]^+$.

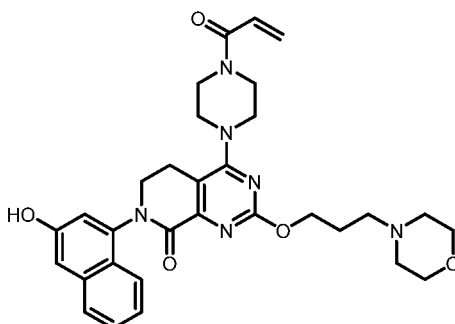
EXAMPLE 120



(R)-1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-((1-(pyrrolidin-1-yl)propan-2-yl)oxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0493] Synthesized according to the method of **Example 8**, using (R)-1-(pyrrolidin-1-yl)propan-2-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 543.4 [M+H]⁺.

EXAMPLE 121



4-(4-acryloylpiperazin-1-yl)-7-(3-hydroxynaphthalen-1-yl)-2-(3-morpholinopropoxy)-6,7-dihydropyrido[3,4-d]pyrimidin-8(5H)-one

[0494] Step A: Tert-butyl 2,4-dichloro-8-oxo-5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate. To a round bottom flask was added tert-Butyl 2,4-dichloro-5,6-dihydropyrido[3,4-d]pyrimidine-7(8H)-carboxylate (1.0 g, 3.29 mmol) and EtOAc (16.4 mL). A solution of sodium periodate (2.11 g, 9.86 mmol) in water (16.4 mL) was added. Ruthenium (III) chloride (0.102 g, 0.493 mmol) was added and the mixture was stirred loosely capped and vigorously stirred for 6 h at ambient temperature. The mixture was partitioned between water and EtOAc and the layers were separated. The aqueous layer was extracted further with EtOAc (2 x 20 mL) and the combined extracts were washed with brine and dried over Na₂SO₄, filtered and concentrated. The crude product was purified via column chromatography (10-30% EtOAc/hexanes, loading with CH₂Cl₂) to afford 0.864 g (82%) of the product as an off-white solid.

[0495] Step B: Tert-butyl 4-(4-((benzyloxy)carbonyl)piperazin-1-yl)-2-chloro-8-oxo-5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate. To a solution of tert-butyl 2,4-dichloro-8-oxo-5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate (0.400 g, 1.26 mmol) in CH₂Cl₂

(5.0 mL) was added N,N-Diisopropylethylamine (0.325 g, 2.51 mmol) followed by benzyl 1-piperazinecarboxylate (0.255 mL, 1.32 mmol) and the reaction stirred at ambient temperature for 1.5 h. The reaction mixture was diluted with CH₂Cl₂ (10 mL) and washed with a 0.5M KHSO₄ solution (5 mL), followed by a saturated aqueous NaHCO₃ solution and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated. The crude product was sonicated in 10 mL MTBE and the resulting solid was isolated by vacuum filtration. The solid was dried in vacuo to provide 0.507 g (80%) of the desired product as an off-white solid which was used directly in the next step. ES+APCI MS m/z 502.1[M+H]⁺.

[0496] Step C: Benzyl 4-(2-chloro-8-oxo-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate. A solution of tert-butyl 4-(4-((benzyloxy)carbonyl)piperazin-1-yl)-2-chloro-8-oxo-5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate (0.255 g, 0.5080 mmol) in CH₂Cl₂ (1.0 mL) was cooled to 0 °C. Trifluoroacetic acid (0.3890 mL, 5.080 mmol) was added and the mixture was warmed to ambient temperature. After 1 hour the mixture was diluted with CH₂Cl₂ and added to a mixture brine (10 mL) and 3.0 M aqueous NaOH (1.7 mL, 5.080 mmol). The layers were combined and adjusted to pH 8 with saturated aqueous NaHCO₃ solution. The layers were separated and the aqueous phase was extracted with 2×10 mL of CH₂Cl₂. The combined organic layers were dried over Na₂SO₄, filtered and concentrated under vacuum. The title compound (0.223 g, quant.) was obtained as a yellow/orange foam. ES+APCI MS m/z 402.1[M+H]⁺.

[0497] Step D: Benzyl 4-(2-(3-morpholinopropoxy)-8-oxo-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate. To a vial was added N-Hydroxypropanylmorpholine (0.687 g, 4.73 mmol) and benzyl 4-(2-chloro-8-oxo-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (0.190 g, 0.473 mmol) followed by dioxane (1.6 mL). Cesium carbonate (0.462 g, 1.42 mmol) was added and the mixture was stirred at 65 °C for 15 hours. The mixture was diluted with CHCl₃ and filtered, and the solid was washed with additional CHCl₃. The filtrate was concentrated in vacuo and was purified by column chromatography (2-10% MeOH/DCM with 1% NH₄OH) to afford 0.061 g (25%) of the desired product as a thick, colorless oil. ES+APCI MS m/z 511.2[M+H]⁺.

[0498] Step E: Benzyl 4-(7-(3-(methoxymethoxy)naphthalen-1-yl)-2-(3-morpholinopropoxy)-8-oxo-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate. To a vial was

added benzyl 4-(2-(3-morpholinopropoxy)-8-oxo-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (0.060 g, 0.12 mmol), N,N'-Dimethylethylenediamine (0.010 g, 0.12 mmol) and 1-iodo-3-(methoxymethoxy)naphthalene (0.074 g, 0.24 mmol) followed by dioxane (0.78 mL) and Potassium phosphate tribasic (0.050 g, 0.24 mmol). The reaction was purged with bubbling Ar for 10 min, then Copper (I) Iodide (0.022 g, 0.12 mmol) was added and the vial was sealed. The mixture was heated to 110 °C and stirred for 16 hours. The mixture was cooled to ambient temperature, diluted with water and extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated. The mixture was purified via column chromatography (2-8% MeOH/DCM) to afford 0.062 g (76%) of the product as a tan foam. ES+APCI MS m/z 697.3[M+H]⁺.

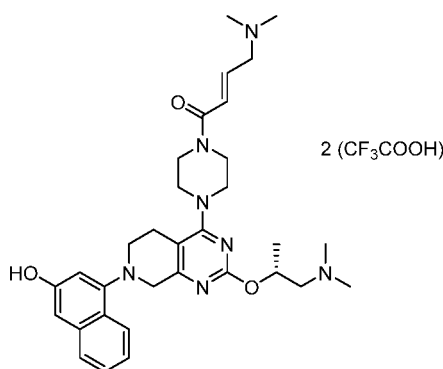
[0499] Step F: 7-(3-(methoxymethoxy)naphthalen-1-yl)-2-(3-morpholinopropoxy)-4-(piperazin-1-yl)-6,7-dihydropyrido[3,4-d]pyrimidin-8(5H)-one. To a solution of benzyl 4-(7-(3-(methoxymethoxy)naphthalen-1-yl)-2-(3-morpholinopropoxy)-8-oxo-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (0.062 g, 0.089 mmol) in EtOH (0.44 mL) and THF (0.44 mL) was added Palladium on Carbon (0.038 g, 0.018 mmol) (Degussa Type, 10 wt%, 50% H₂O) and then an atmosphere of hydrogen was introduced via vacuum followed by balloon pressure. The mixture was stirred at ambient temperature for 1.5 h, then warmed to 45 °C and stirred for 1 hour. The mixture was diluted with EtOAc and filtered through a nylon filter. The filtrate was concentrated in vacuo providing a light tan foam (0.052g) that was dried overnight and resubmitted to the same reaction conditions above. After stirring at ambient temperature for 5 h additional Pd/C (0.050 g) was added and the reaction was stirred at ambient temperature for another 2 h. The mixture was diluted with EtOAc and filtered through a nylon filter. The solid was washed with EtOAc and MeOH and the filtrate was concentrated in vacuo providing 0.029 g (58%) of the desired product as a light tan foam. ES+APCI MS m/z 563.3[M+H]⁺.

[0500] Step G: 4-(4-acryloylpiperazin-1-yl)-7-(3-(methoxymethoxy)naphthalen-1-yl)-2-(3-morpholinopropoxy)-6,7-dihydropyrido[3,4-d]pyrimidin-8(5H)-one. To a solution of 7-(3-(methoxymethoxy)naphthalen-1-yl)-2-(3-morpholinopropoxy)-4-(piperazin-1-yl)-6,7-dihydropyrido[3,4-d]pyrimidin-8(5H)-one (0.028 g, 0.050 mmol) in CH₂Cl₂ (0.50 mL) at -78 °C was added Triethylamine (0.014 mL, 0.100 mmol). Acryloyl chloride (0.55 mL, 0.055 mmol,

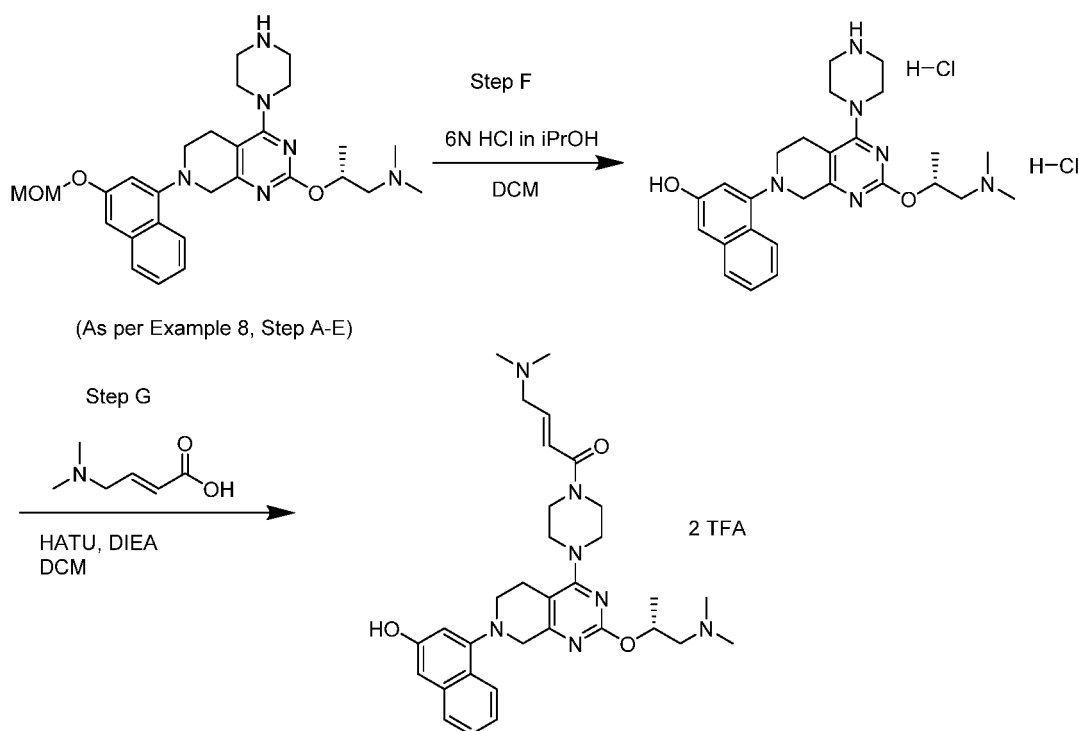
freshly prepared 0.1M CH₂Cl₂) was added and the reaction was then stirred for 0.5 h. The mixture was diluted with CHCl₃ and a saturated aqueous NH₄Cl solution was added. The layers were separated and the aqueous layer was extracted with CHCl₃ (2 x 10 mL). The combined extracts were dried over Na₂SO₄, filtered and concentrated. The crude product was purified via column chromatography (4-6% MeOH/DCM) to afford 0.018 g (59%) to provide the title compound as a solid off-white foam. ES+APCI MS m/z 617.3[M+H]⁺.

[0501] Step H: 4-(4-acryloylpiperazin-1-yl)-7-(3-hydroxynaphthalen-1-yl)-2-(3-morpholinopropoxy)-6,7-dihydropyrido[3,4-d]pyrimidin-8(5H)-one. To a solution of 4-(4-acryloylpiperazin-1-yl)-7-(3-(methoxymethoxy)naphthalen-1-yl)-2-(3-morpholinopropoxy)-6,7-dihydropyrido[3,4-d]pyrimidin-8(5H)-one (0.018 g, 0.0292 mmol) in 1/1 MeOH/THF (0.6 mL) was added HCl (0.0486 mL, 0.292 mmol, 6 N Aqueous). The mixture was stirred at 35 °C for 7 hours. The mixture was diluted with brine and adjusted to pH 8 with a saturated aqueous NaHCO₃ solution. The mixture was extracted with 10% IPA/CHCl₃ (2 x 10 mL) and CHCl₃ (10 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The crude material was purified via column chromatography (6-10% MeOH/DCM) to afford 0.012 g (71%) of the product as an off-white solid. ES+APCI MS m/z 573.3[M+H]⁺.

EXAMPLE 122



(R,E)-4-(dimethylamino)-1-(4-(2-((1-(dimethylamino)propan-2-yl)oxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)but-2-en-1-one bis-trifluoroacetate



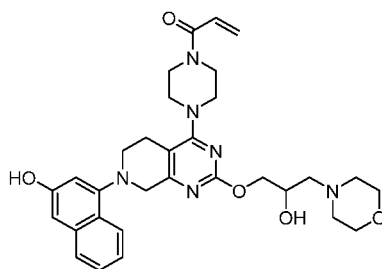
[0502] Steps A-E: (R)-2-((7-(3-(methoxymethoxy)naphthalen-1-yl)-4-(piperazin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-2-yl)oxy)-N,N-dimethylpropan-1-amine was synthesized according to the method of Example 8, Step A through Step E, using (R)-1-(dimethylamino)propan-2-ol in place of (S)-1-(dimethylamino)propan-2-ol in Step B.

[0503] Step F: (R)-4-(2-((1-(Dimethylamino)propan-2-yl)oxy)-4-(piperazin-1-yl)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)naphthalen-2-ol dihydrochloride: To a solution of (R)-2-((7-(3-(methoxymethoxy)naphthalen-1-yl)-4-(piperazin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-2-yl)oxy)-N,N-dimethylpropan-1-amine (75 mg, 0.15 mmol) in DCM (2.9 mL) was added 6N HCl in iPrOH (247 μ l, 1.5 mmol) and the mixture was stirred at ambient temperature for 1h. The reaction mixture was concentrated to dryness to provide (R)-4-(2-((1-(Dimethylamino)propan-2-yl)oxy)-4-(piperazin-1-yl)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)naphthalen-2-ol dihydrochloride which was used directly in the next step. ES+APCI MS m/z 463.2 $[M+H]^+$.

[0504] Step G: (R,E)-4-(Dimethylamino)-1-(4-(2-((1-(dimethylamino)propan-2-yl)oxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)but-2-

en-1-one bis-trifluoroacetate: A solution of (R)-4-(2-((1-(Dimethylamino)propan-2-yl)oxy)-4-(piperazin-1-yl)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)naphthalen-2-ol dihydrochloride (7 mg, 0.01 mmol), HATU (6.2 mg, 0.02 mmol), (2E)-4-(dimethylamino)but-2-enoic acid (2.1 mg, 0.02 mmol), DIEA (6.9 μ l, 0.04 mmol) in DCM (131 μ l) was stirred at ambient temperature for 1h. The residue was filtered and the filtrate was loaded directly onto a Gilson C18 prep HPLC eluting with 5-95% acetonitrile / water with 0.1% TFA additive. The fractions containing the desired product were concentrated to provide (R,E)-4-(Dimethylamino)-1-(4-(2-((1-(dimethylamino)propan-2-yl)oxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)but-2-en-1-one bis-trifluoroacetate. ES+APCI MS m/z 574.2 [M+H]⁺.

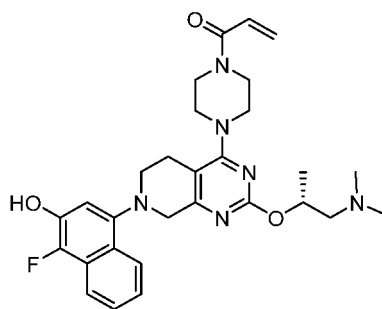
EXAMPLE 123



1-(4-(2-(2-hydroxy-3-morpholinopropoxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0505] Synthesized according to the method of Example 8, using 3-morpholinopropane-1,2-diol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 575.2 [M+H]⁺.

EXAMPLE 124

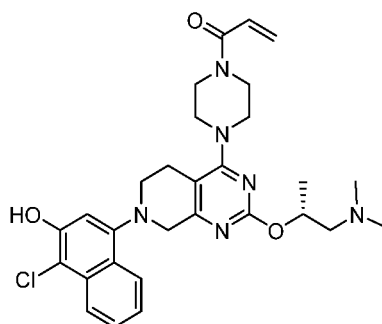


(R)-1-(4-(2-((1-(dimethylamino)propan-2-yl)oxy)-7-(4-fluoro-3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0506] Step A: Benzyl (R)-4-(2-((1-(dimethylamino)propan-2-yl)oxy)-7-(3-(methoxymethoxy)naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (221 mg, 0.345 mmol) was placed in ACN (2 mL) and the mixture was cooled to 0 °C. SelectFluor (183 mg, 0.517 mmol) was added and the reaction was stirred at room temperature for 30 minutes. Water was added and the mixture was extracted with DCM. The organic layers were combined and concentrated. The resulting residue was purified by reverse phase chromatography (5-95% ACN:water with 0.1% TFA) to provide benzyl (R)-4-(2-((1-(dimethylamino)propan-2-yl)oxy)-7-(4-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate trifluoroacetate (48 mg, 0.0729 mmol, 21.1 % yield).

[0507] Step B: (R)-1-(4-(2-((1-(dimethylamino)propan-2-yl)oxy)-7-(4-fluoro-3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one was prepared following Example 33, Steps D-F substituting (R)-4-(2-((1-(dimethylamino)propan-2-yl)oxy)-7-(4-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate trifluoroacetate for benzyl 4-(7-(3-(methoxymethoxy)naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate. ES+APCI MS m/z 535.2 [M+H]⁺.

EXAMPLE 125

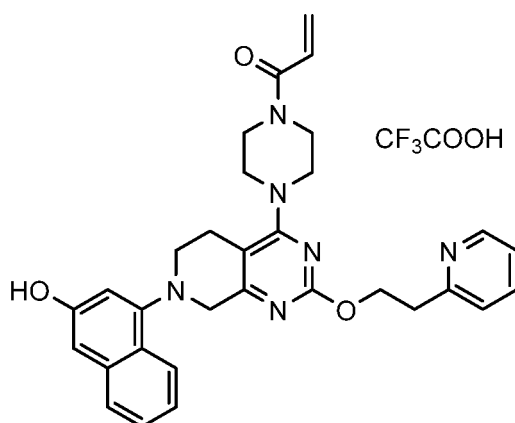


(R)-1-(4-(7-(4-chloro-3-hydroxynaphthalen-1-yl)-2-((1-(dimethylamino)propan-2-yl)oxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

[0508] Step A: Benzyl (R)-4-(2-((1-(dimethylamino)propan-2-yl)oxy)-7-(3-(methoxymethoxy)naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (83 mg, 0.130 mmol) and NCS (21.6 mg, 0.162 mmol) were placed in ACN (2 mL) and stirred at room temperature for 3 hours. Water was added and the mixture was extracted with DCM (3x15 mL). The organic layers were combined and concentrated. The resulting residue was purified by reverse phase chromatography (5-95% ACN:water with 0.1% TFA) to provide benzyl (R)-4-(7-(4-chloro-3-(methoxymethoxy)naphthalen-1-yl)-2-((1-(dimethylamino)propan-2-yl)oxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate trifluoroacetate (17 mg, 0.0252 mmol, 19.4 % yield).

[0509] Step B: (R)-1-(4-(7-(4-chloro-3-hydroxynaphthalen-1-yl)-2-((1-(dimethylamino)propan-2-yl)oxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one was prepared following Example 33, Steps D-F substituting (R)-4-(7-(4-chloro-3-(methoxymethoxy)naphthalen-1-yl)-2-((1-(dimethylamino)propan-2-yl)oxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate trifluoroacetate for benzyl 4-(7-(3-(methoxymethoxy)naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate and using THF as the solvent in Step D. ES+APCI MS m/z 551.2 [M+H]⁺.

EXAMPLE 126



1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-(2-(pyridin-2-yl)ethoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one trifluoroacetate

[0510] Step A: benzyl 4-(7-(3-(methoxymethoxy)naphthalen-1-yl)-2-(2-(pyridin-2-yl)ethoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate: To a slurry of benzyl 4-(2-chloro-7-(3-(methoxymethoxy)naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (0.20 g, 0.35 mmol) in dioxane in a microwave was added N-ethyl-N-isopropylpropan-2-amine (0.45 g, 3.5 mmol), Cs₂CO₃ (0.34 g, 1.0 mmol) and 2-(pyridin-2-yl)ethan-1-ol (0.43 g, 3.5 mmol) and the reaction heated to 15 °C for 1 hr in the microwave. The reaction was diluted with EtOAc and washed with water, brine, dried over MgSO₄ and concentrated in vacuo. The material was chromatographed using a gradient of 0 to 100% EtOAc/DCM as the eluent to give benzyl 4-(7-(3-(methoxymethoxy)naphthalen-1-yl)-2-(2-(pyridin-2-yl)ethoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (0.16 g, 0.24 mmol, 70 % yield).

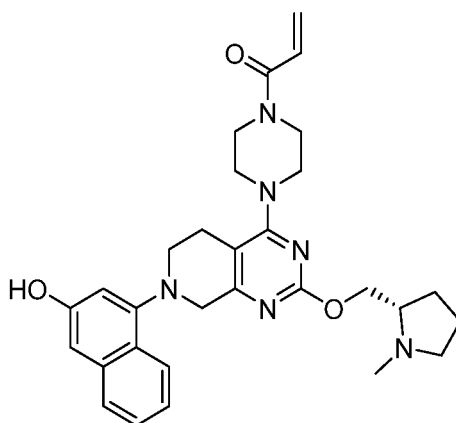
[0511] Step B: 4-(4-(piperazin-1-yl)-2-(2-(pyridin-2-yl)ethoxy)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)naphthalen-2-ol: To the solid benzyl 4-(7-(3-(methoxymethoxy)naphthalen-1-yl)-2-(2-(pyridin-2-yl)ethoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (0.12 g, 0.18 mmol) was added MeOH (20 mL). The solution was degassed with nitrogen 5 minutes, followed by addition of Pd/C (0.058 g, 0.54 mmol). The reaction vessel was evacuated by vacuum and backfilled with H₂. This procedure was performed three times, and after the third backfill the slurry was left to stir under an atmosphere of hydrogen for 1 hr. The reaction was again degassed with nitrogen for 5 minutes.

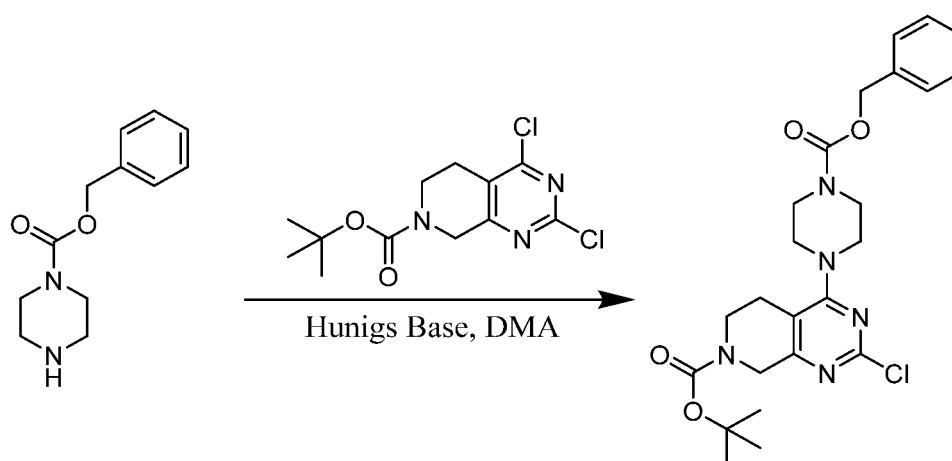
The slurry was next filtered through Celite® and the Celite® was washed with MeOH (100 mL). The combined organic extracts were concentrated and treated with 10 mL of 1:1 TFA/DCM for 2 hrs. The reaction was again concentrated in vacuo to give 4-(4-(piperazin-1-yl)-2-(2-(pyridin-2-yl)ethoxy)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)naphthalen-2-ol (0.096 g, 0.20 mmol, 110 % yield).

[0512] Step C: 1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-(2-(pyridin-2-yl)ethoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one: To a solution of 4-(4-(piperazin-1-yl)-2-(2-(pyridin-2-yl)ethoxy)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)naphthalen-2-ol (0.096 g, 0.20 mmol) in DCM was added Hunig's Base (0.17 mL, 0.99 mmol) and acryloyl chloride (0.018 g, 0.20 mmol) and the reaction stirred for 30 minutes at room temperature. The reaction was concentrated in vacuo and the crude material was purified by reverse preparative HPLC to give 1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-(2-(pyridin-2-yl)ethoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one trifluoroacetate (0.0057 g, 0.011 mmol, 5.3 % yield). **ES+APCI MS** m/z 537.2 [M+H]⁺.

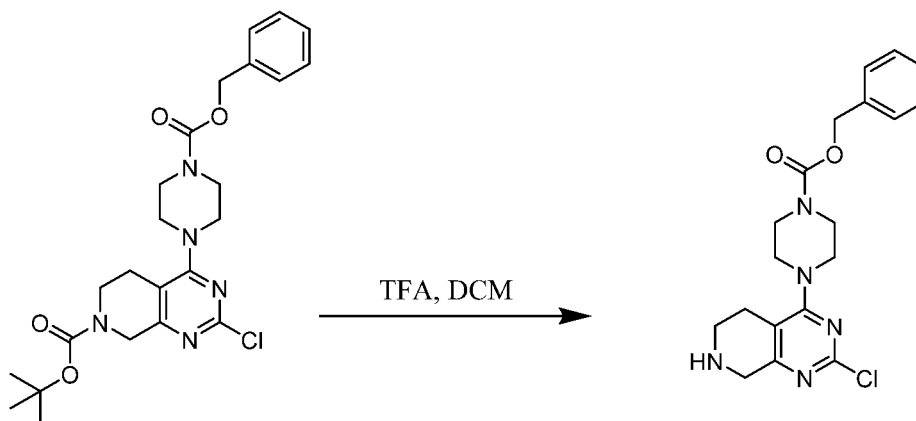
EXAMPLE 127

(S)-7-(3-(methoxymethoxy)naphthalen-1-yl)-2-((1-methylpyrrolidin-2-yl)methoxy)-4-(piperazin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine

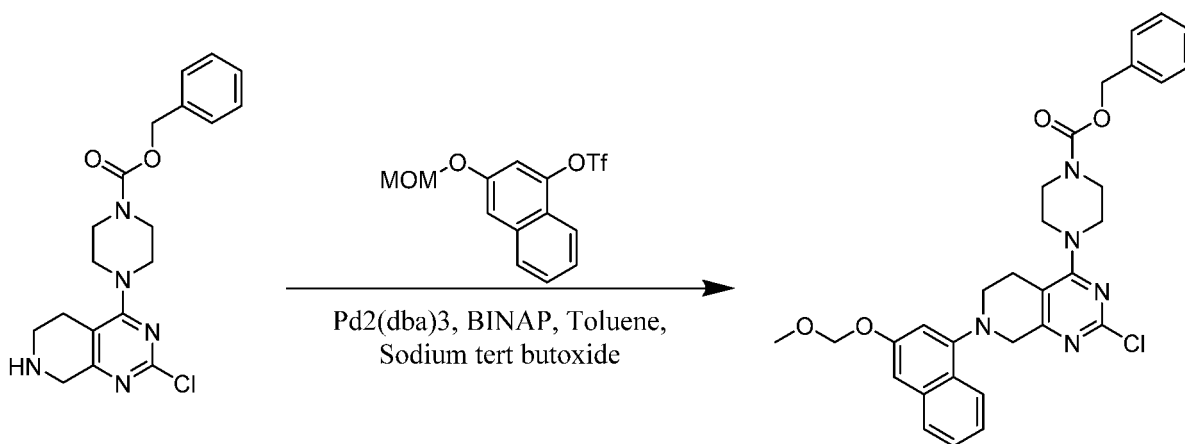




[0513] Step A: tert-butyl 4-(4-((benzyloxy)carbonyl)piperazin-1-yl)-2-chloro-5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate: To a solution of tert-butyl 2,4-dichloro-5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate (8 g, 26.30 mmol) in DMA (263.0 ml, 26.30 mmol) was added benzyl piperazine-1-carboxylate (5.793 g, 26.30 mmol) and N-ethyl-N-isopropylpropan-2-amine (4.721 ml, 26.30 mmol) and the reaction stirred at room temperature for 2 hours. TLC (20% EtOAc/DCM), UV visualization, showed reaction completion. The reaction was next poured into water and extracted into DCM. The organics were next washed with water (2x), brine, dried over MgSO₄ and concentrated in vacuo. The concentrate was loaded onto a 220g RegiSep column and chromatographed on the CombiFlash (0%-10%, EtOAc:DCM). All fractions containing desired product were combined and concentrated to give tert-butyl 4-(4-((benzyloxy)carbonyl)piperazin-1-yl)-2-chloro-5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate (9.768 g, 20.02 mmol, 76.11 % yield) as a white foam. ES+APCI MS m/z 488.2 [M+H]⁺.

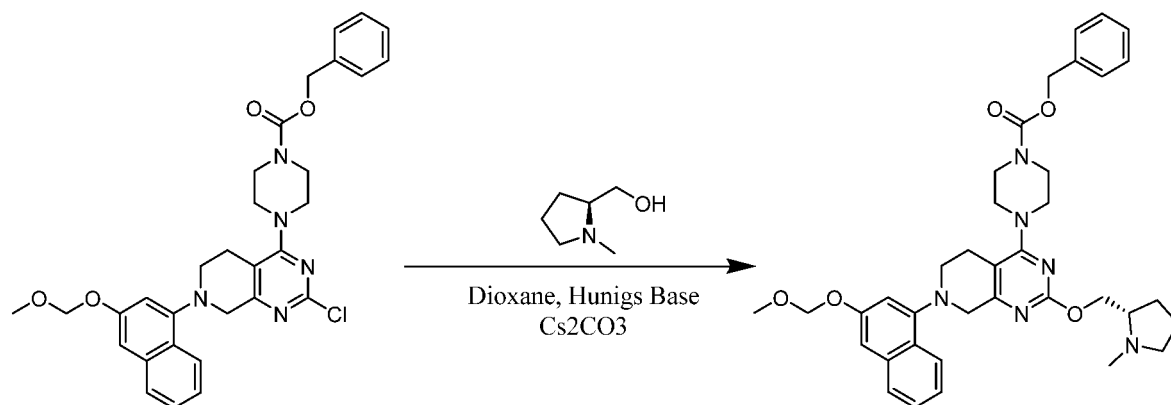


[0514] Step B: benzyl 4-(2-chloro-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate: tert-butyl 4-(4-((benzyloxy)carbonyl)piperazin-1-yl)-2-chloro-5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate (9.768 g, 20.02 mmol) was dissolved in dichloromethane (200.2 ml, 20.02 mmol) and treated with 2,2,2-trifluoroacetic acid (15.33 ml, 200.2 mmol). The reaction mixture stirred at room temp for 4 hours. After completion the reaction was next concentrated in vacuo and taken up in EtOAc and the organics washed with 1M NaOH (2X), brine, dried over MgSO₄ and concentrated in vacuo. benzyl 4-(2-chloro-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (7.406 g, 19.09 mmol, 95.39 % yield) was used crude in the next reaction. ES+APCI MS m/z 388.2 [M+H]⁺.

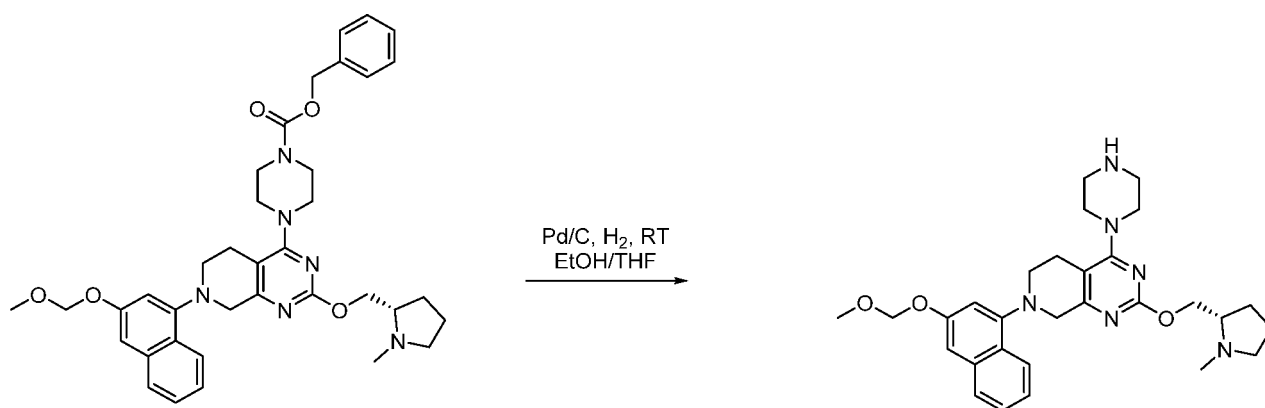


[0515] Step C: benzyl 4-(2-chloro-7-(3-(methoxymethoxy)naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate: To the benzyl 4-(2-chloro-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate, BINAP (0.275 g, 0.442 mmol) and Pd₂(dba)₃ (0.203 g, 0.221 mmol) under argon was added toluene (221 ml, 11.1 mmol) and the reaction bubbled with Ar for 10 minutes followed by heating to 100°C for 10 minutes. The reaction was next cooled to room temperature and benzyl 4-(2-chloro-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (4.29 g, 11.1 mmol) and Sodium Tert-Butoxide (2.13 g, 22.1 mmol) were added to the dark solution as solids. Finally, 3-(methoxymethoxy)naphthalen-1-yl trifluoromethanesulfonate (7.44 g, 22.1 mmol) was added (as the oil) and the reaction heated to 100°C for 1 hour. The reaction was cooled to room temperature and concentrated in vacuo. The concentrate was dissolved with EtOAc and washed with water and brine. The combined organics were dried over Na₂SO₄ and concentrated in vacuo. The residue was then loaded on the CombiFlash and chromatographed

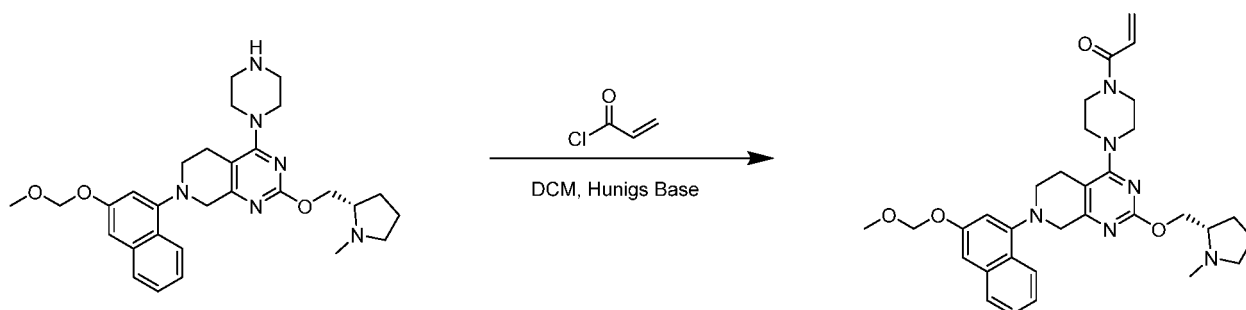
using 0%-->50% Hexane:EtOAc as eluent. Fractions containing clean product were combined and concentrated in vacuo to afford benzyl 4-(2-chloro-7-(3-(methoxymethoxy)naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (2.6 g, 4.53 mmol, 40.9 % yield). ES+APCI MS m/z 574.2 $[M+H]^+$.



[0516] Step D: benzyl (S)-4-(7-(3-(methoxymethoxy)naphthalen-1-yl)-2-((1-methylpyrrolidin-2-yl)methoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate: In a microwave tube benzyl 4-(2-chloro-7-(3-(methoxymethoxy)naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (300 mg, 0.523 mmol) was dissolved in Dioxane (6532 μ l, 0.523 mmol) and treated with cesium carbonate (511 mg, 1.57 mmol), Hunig's base (913 μ l, 5.23 mmol) and N-Methyl-L-prolinol (421 mg, 3.66 mmol). The tube was then capped and microwaved at 170°C for 3 hours. The reaction was filtered through GF/F paper. The filtrate was concentrated in vacuo and the residue loaded onto a 12g RegiSep gold column and chromatographed on the CombiFlash (0%-15%, DCM:MeOH). All fractions containing clean product were combined and concentrated in vacuo to give benzyl (S)-4-(7-(3-(methoxymethoxy)naphthalen-1-yl)-2-((1-methylpyrrolidin-2-yl)methoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (220 mg, 0.337 mmol, 64.5 % yield). ES+APCI MS m/z 653.3 $[M+H]^+$.

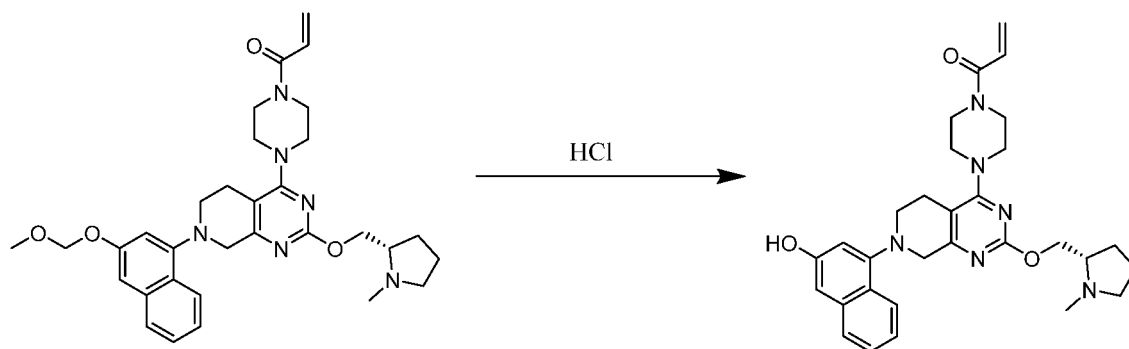


[0517] Step E: (S)-7-(3-(methoxymethoxy)naphthalen-1-yl)-2-((1-methylpyrrolidin-2-yl)methoxy)-4-(piperazin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine: A solution of benzyl (S)-4-(7-(3-(methoxymethoxy)naphthalen-1-yl)-2-((1-methylpyrrolidin-2-yl)methoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (220 mg, 0.337 mmol) in EtOH (3370 μ l, 0.337 mmol) and THF (3370 μ l, 0.337 mmol) was purged with N₂ for 5 minutes. To this solution was added Palladium on carbon (179 mg, 0.0843 mmol) (Degussa Type, 10 wt%, 50% H₂O), and was immediately capped and purged with N₂ for an additional 5 min. The solution then stirred under H₂ introduced via vacuum followed by balloon pressure. The mixture was then stirred at ambient temperature over night. LC/MS showed reaction completion. The mixture was diluted with MeOH and filtered through packed celite. The filtrate was then concentrated in vacuo and (S)-7-(3-(methoxymethoxy)naphthalen-1-yl)-2-((1-methylpyrrolidin-2-yl)methoxy)-4-(piperazin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine (91 mg, 0.175 mmol, 52.1 % yield) was taken forward as the crude. ES+APCI MS m/z 519.3 [M+H]⁺.



[0518] Step F: (S)-1-(4-(7-(3-(methoxymethoxy)naphthalen-1-yl)-2-((1-methylpyrrolidin-2-yl)methoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one: To

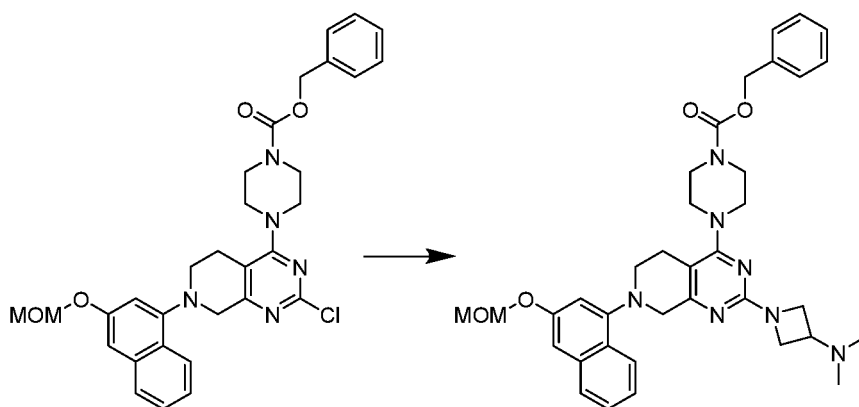
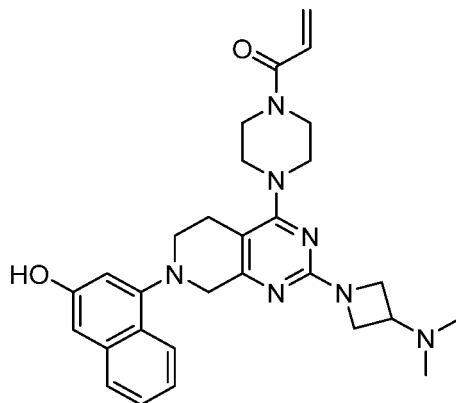
a suspension of (S)-7-(3-(methoxymethoxy)naphthalen-1-yl)-2-((1-methylpyrrolidin-2-yl)methoxy)-4-(piperazin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine (92 mg, 0.18 mmol) in dichloromethane (1774 μ l, 0.18 mmol) at ambient temperature was added Acryloyl Chloride (1774 μ l, 0.18 mmol) followed by Hunig's base (62 μ l, 0.35 mmol). The reaction was then stirred at ambient temperature for 1 hour. The mixture was then concentrated and loaded onto a 4g RegiSep gold column and chromatographed on the CombiFlash (0%-15%, DCM:MeOH). All fractions containing clean product were combined and concentrated in vacuo to give (S)-1-(4-(7-(3-(methoxymethoxy)naphthalen-1-yl)-2-((1-methylpyrrolidin-2-yl)methoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one (74 mg, 0.13 mmol, 73% yield). ES+APCI MS m/z 573.3 $[M+H]^+$.



[0519] Step G: (S)-1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-((1-methylpyrrolidin-2-yl)methoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one: (S)-1-(4-(7-(3-(methoxymethoxy)naphthalen-1-yl)-2-((1-methylpyrrolidin-2-yl)methoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one (74 mg, 0.13 mmol) was dissolved in methanol (4307 μ l, 0.13 mmol) and treated with hydrogen chloride (1077 μ l, 6.5 mmol) (aq). The reaction stirred at 55°C for 1 hour. The reaction mixture was concentrated in vacuo and was resuspended in 1.5mL of MeOH. The suspension was loaded on to the Gilson (prep HPLC), which was eluted with 5-->95% ACN/0.1% TFA in water/0.1% TFA. All fractions containing clean product were combined and lyophilized overnight to give (S)-1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-((1-methylpyrrolidin-2-yl)methoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one (26 mg, 0.049 mmol, 38% yield). ES+APCI MS m/z 529.3 $[M+H]^+$.

EXAMPLE 128

1-(4-(2-(3-(dimethylamino)azetidin-1-yl)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

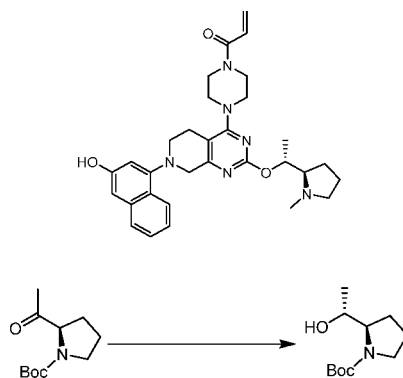


[0520] Step A: benzyl 4-(2-(3-(dimethylamino)azetidin-1-yl)-7-(3-(methoxymethoxy)naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate: To a solution of benzyl 4-(2-chloro-7-(3-(methoxymethoxy)naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (0.20 g, 0.35 mmol) in dioxanes was added N,N-dimethylazetidin-3-amine hydrochloride (0.24 g, 1.7 mmol) and N-ethyl-N-isopropylpropan-2-amine (0.45 g, 3.5 mmol) and the reaction was heated to 80°C for 72 hrs. The reaction was concentrated in vacuo and the residue chromatographed using 0-->20% MeOH/DCM as eluent to give benzyl 4-(2-(3-(dimethylamino)azetidin-1-yl)-7-(3-(methoxymethoxy)naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (0.25g, 105%). ES+APCI MS m/z 638.3 $[M+H]^+$.

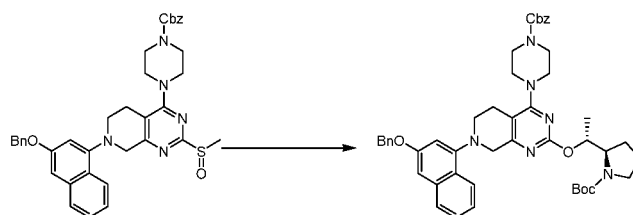
[0521] 1-(4-(2-(3-(dimethylamino)azetidin-1-yl)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one was made according to Example 127 substituting benzyl 4-(2-(3-(dimethylamino)azetidin-1-yl)-7-(3-(methoxymethoxy)naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate for benzyl (S)-4-(7-(3-(methoxymethoxy)naphthalen-1-yl)-2-((1-methylpyrrolidin-2-yl)methoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate in step E. ES+APCI MS m/z 514.2 $[M+H]^+$.

EXAMPLE 129

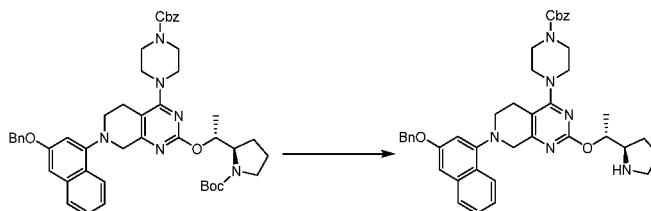
1-[4-[7-(3-hydroxy-1-naphthyl)-2-[(1*R*)-1-[(2*R*)-1-methylpyrrolidin-2-yl]ethoxy]-6,8-dihydro-5*H*-pyrido[3,4-d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one



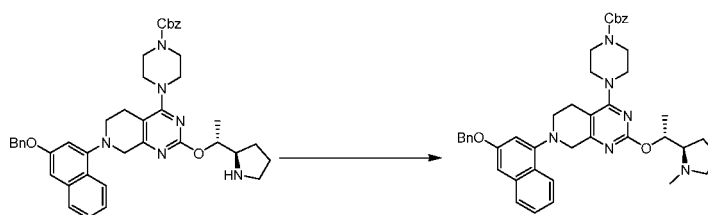
[0522] Step A: *tert*-butyl (2*R*)-2-[(1*R*)-1-hydroxyethyl]pyrrolidine-1-carboxylate: A mixture of $BH_3 \cdot Me_2S$ (10 M, 549 μL) and (3*aS*)-1-methyl-3,3-diphenyl-3*a*,4,5,6-tetrahydropyrrolo[1,2-*c*][1,3,2]oxazaborole (1.00 M, 844 μL), in THF (10 mL) was stirred at 15 °C for 1 hour. To the mixture was added a solution of *tert*-butyl (2*R*)-2-acetylpyrrolidine-1-carboxylate (0.90 g, 4.22 mmol) in THF (10 mL) and the mixture stirred at 15 °C for 1 hour. The mixture was quenched by addition of methanol (2.00 mL) and the reaction concentrated under vacuum. The residue was purified by column chromatography (SiO_2 , petroleum ether/ether acetate = 50/1 - 5/1) to give *tert*-butyl (2*R*)-2-[(1*R*)-1-hydroxyethyl]pyrrolidine-1-carboxylate (0.60 g, 2.79 mmol, 66.0 % yield) as a colorless oil. 1H NMR (400MHz, CD_3OD) δ = 5.18 (br s, 1H), 3.73 (dt, J = 4.8, 8.0 Hz, 1H), 3.70 - 3.43 (m, 2H), 3.28 (td, J = 6.64, 10.8 Hz, 1H), 1.96 (qd, J = 7.2, 12.8 Hz, 1H), 1.89 - 1.68 (m, 2H), 1.62 (br s, J = 6.4 Hz, 1H), 1.47 (s, 9H), 1.15 (d, J = 6.0 Hz, 3H).



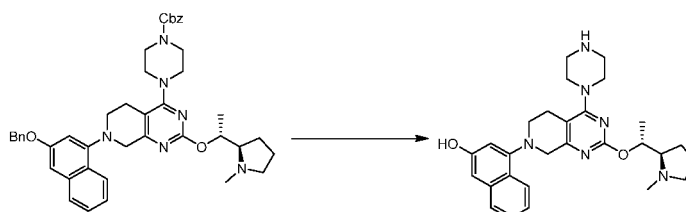
[0523] Step B: benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[(1R)-1-[(2R)-1-tert-butoxycarbonylpyrrolidin-2-yl]ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate: To a solution of benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-methylsulfinyl]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (0.70 g, 1.08 mmol) and *tert*-butyl (2R)-2-[(1R)-1-hydroxyethyl]pyrrolidine-1-carboxylate (349 mg, 1.62 mmol) in THF (10 mL) was added t-BuONa (312 mg, 3.24 mmol) and the mixture stirred at 10 °C for 1 hour. The mixture was diluted with water (10 mL) and the aqueous layer extracted with ethyl acetate (3 × 10 mL). The combined organics were washed brine (20 mL), dried over Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by column chromatography (SiO₂, petroleum ether/ether acetate = 3/1) to give benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[(1R)-1-[(2R)-1-tert-butoxycarbonylpyrrolidin-2-yl]ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (0.35 g, 412 μmol, 38.1 % yield) as a yellow solid. ES+APCI MS *m/z* 799.4 [M+H]⁺.



[0524] Step C: benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[(1R)-1-[(2R)-pyrrolidin-2-yl]ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate: A mixture of benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[(1R)-1-[(2R)-1-*tert*-butoxycarbonylpyrrolidin-2-yl]ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (0.30 g, 375 μmol) and TFA (642 mg, 5.63 mmol, 417 μL) in dichloromethane (0.42 mL) was stirred at 10 °C for 1 hour. The mixture was concentrated under vacuum to give benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[(1R)-1-[(2R)-pyrrolidin-2-yl]ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (305 mg) LCMS [M+1]: ES+APCI MS *m/z* 699.2 [M+H]⁺.

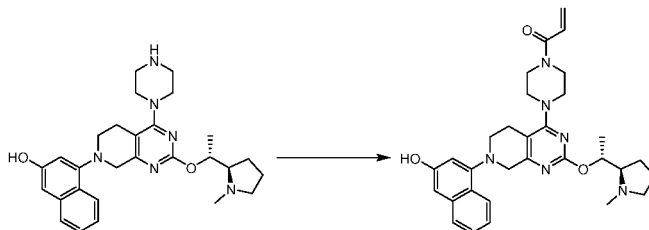


[0525] Step D: benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[(1R)-1-[(2R)-1-methylpyrrolidin-2-yl]ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate: A mixture of benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[(1R)-1-[(2R)-pyrrolidin-2-yl]ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (0.30 g, crude), formaldehyde (210 mg, 1.85 mmol, 192 uL, 37 % water) and AcOH (22.16 mg, 369 umol, 21.1 uL) in methanol (3.00 mL) was stirred at 15 °C for 0.5 hours. To the mixture was added NaBH₃CN (58.0 mg, 923 umol) and the mixture stirred at 15 °C for 48 hours. The mixture was quenched by addition of H₂O (5 mL) at 0 °C, and the aqueous layer extracted with ether acetate (3 × 10 mL). The combined organics were washed with brine (15.0 mL), dried over Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by reverse phase flash [water(0.10 % Formic Acid)/acetonitrile] to give benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[(1R)-1-[(2R)-1-methylpyrrolidin-2-yl]ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (0.10 g, 126 umol) as a yellow oil. ES+APCI MS m/z 713.4 [M+H]⁺.



[0526] Step E: 4-[2-[(1R)-1-[(2R)-1-methylpyrrolidin-2-yl]ethoxy]-4-piperazin-1-yl]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-7-yl]naphthalen-2-ol: Ammonia was bubbled into methanol (3 mL) at -78 °C for 30 minutes. benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[(1R)-1-[(2R)-1-methylpyrrolidin-2-yl]ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (0.09 g, 126 umol) and dry 10% Pd/C (0.10 g) were next added and the mixture stirred at 10 °C for 1 hour under H₂ (15 psi). The reaction was filtered and the filtrate was concentrated under vacuum to give 4-[2-[(1R)-1-[(2R)-1-methylpyrrolidin-2-yl]ethoxy]-4-

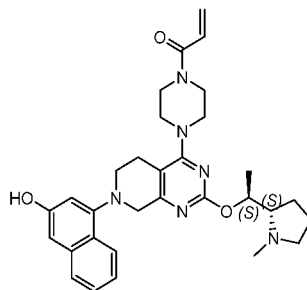
piperazin-1-yl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]naphthalen-2-ol (0.04 g, crude) as a yellow oil. ES+APCI MS *m/z* 489.2 [*M*+*H*]⁺.



[0527] Step F: 1-[4-[7-(3-hydroxy-1-naphthyl)-2-[(1*R*)-1-[(2*R*)-1-methylpyrrolidin-2-yl]ethoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one: To a solution of 4-[2-[(1*R*)-1-[(2*R*)-1-methylpyrrolidin-2-yl]ethoxy]-4-piperazin-1-yl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]naphthalen-2-ol (0.04 g) and Et₃N (124 mg, 1.23 mmol, 171 μ L) in DCM (2.00 mL) at -40 °C was added prop-2-enoyl prop-2-enoate (7.23 mg, 57.3 μ mol) and the reaction stirred at -40 °C for 0.5 h. The mixture was quenched by addition of methanol (0.10 mL) and concentrated under vacuum. The residue was purified by prep-HPLC (column: Phenomenex Synergi C18 150*25*10 μ m; mobile phase: [water (0.225% Formic Acid)-ACN]; B%: 10%-37% over 10 minutes) to give 1-[4-[7-(3-hydroxy-1-naphthyl)-2-[(1*R*)-1-[(2*R*)-1-methylpyrrolidin-2-yl]ethoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one (9.13 mg, 15.5 μ mol) as a yellow solid. ES+APCI MS *m/z* 543.4 [*M*+*H*]⁺.

EXAMPLE 130

1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-((*S*)-1-((*S*)-1-methylpyrrolidin-2-yl)ethoxy))-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

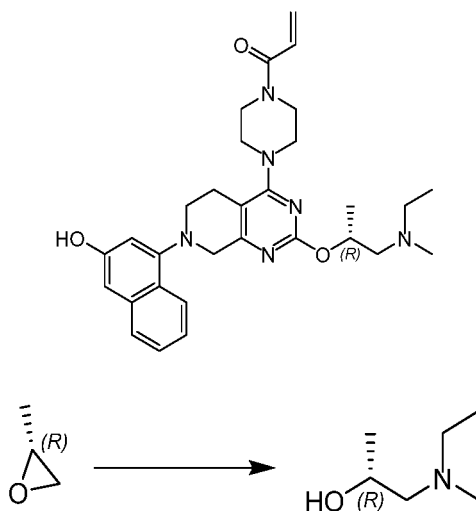


[0528] 1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-((*S*)-1-((*S*)-1-methylpyrrolidin-2-yl)ethoxy))-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one was prepared

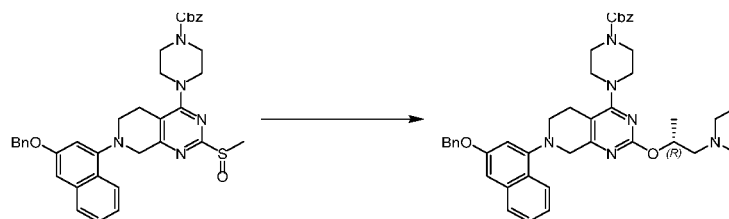
following **Example 129** substituting (3aR)-1-methyl-3,3-diphenyl-3a,4,5,6-tetrahydropyrrolo[1,2-c][1,3,2]oxazaborole for (3aS)-1-methyl-3,3-diphenyl-3a,4,5,6-tetrahydropyrrolo[1,2-c][1,3,2]oxazaborole in Step A while also substituting *tert*-butyl (2*S*)-2-acetylpyrrolidine-1-carboxylate for *tert*-butyl (2*R*)-2-acetylpyrrolidine-1-carboxylate in Step A. ES+APCI MS m/z 543.4 $[M+H]^+$.

EXAMPLE 131

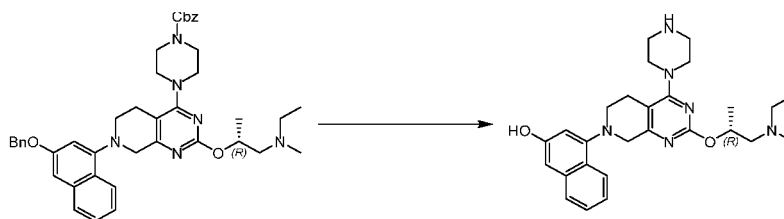
1-[4-[2-[(1*R*)-2-[ethyl(methyl)amino]-1-methyl-ethoxy]-7-(3-hydroxy-1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one



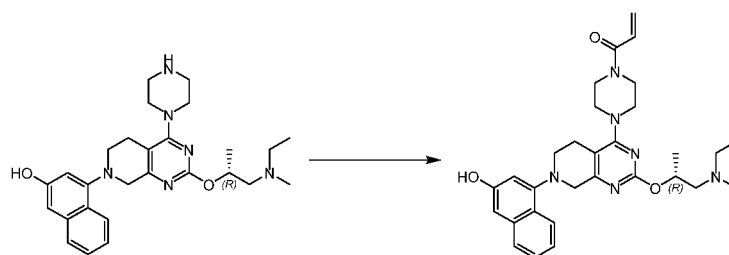
[0529] Step A: (2*R*)-1-[ethyl(methyl)amino]propan-2-ol: (2*R*)-2-methyloxirane (540 mg, 9.31 mmol, 651 μ L) was added to *N*-methylethanamine (500 mg, 8.46 mmol, 725 μ L) in MeOH (10 mL). The resulting solution was stirred at 80 °C for 3 hours in a sealed tube. Upon completion, the mixture was concentrated under vacuum to give (2*R*)-[ethyl(methyl)amino]propan-2-ol (260 mg, crude) as a light yellow oil which was used directly in the next step without further purification.



[0530] Step B: benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[(1*R*)-2-[ethyl(methyl)amino]-1-methyl-ethoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate: To a solution of (2*R*)-1-[ethyl(methyl)amino]propan-2-ol (217 mg, 1.85 mmol) in toluene (20 mL) was added benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-methylsulfinyl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (400 mg, 617 μ mol), Pd₂(dba)₃ (56.6 mg, 61.8 μ mol), BINAP (76.9 mg, 124 μ mol) and NaOtBu (178 mg, 1.85 mmol,) and the mixture degassed with N₂ for 15 minutes and then heated to 90 °C for 16 hours under N₂. Upon completion, the reaction mixture was filtered and the filtrate concentrated under vacuum. The residue was purified by reversed-phase chromatography to give benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[(1*R*)-2-[ethyl(methyl)amino]-1-methyl-ethoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (110 mg, 153 μ mol, 24.8 % yield, 97.5 % purity). ES+APCI MS *m/z* 701.4 [M+H]⁺.



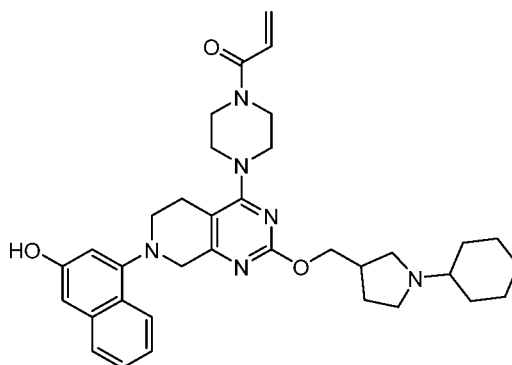
[0531] Step C: 4-[2-[(1*R*)-2-[ethyl(methyl)amino]-1-methyl-ethoxy]-4-piperazin-1-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]naphthalen-2-ol: To a solution of benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[(1*R*)-2-[ethyl(methyl)amino]-1-methyl-ethoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (100 mg, 143 μ mol) in MeOH (3.00 mL) was added HCl/MeOH (4 M, 143 μ L), followed by Pd(OH)₂/C (50 mg) under N₂. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (15 psi) at 40 °C for 4 hours. Upon completion, the reaction mixture was filtered and the filtrate concentrated to give 4-[2-[(1*R*)-2-[ethyl(methyl)amino]-1-methyl-ethoxy]-4-piperazin-1-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]naphthalen-2-ol (76.0 mg, 125 μ mol, 87.5 % yield, 90.3 % purity, 2 HCl) which was used directly in the next step without further purification. ES+APCI MS *m/z* 477.2 [M+H]⁺.

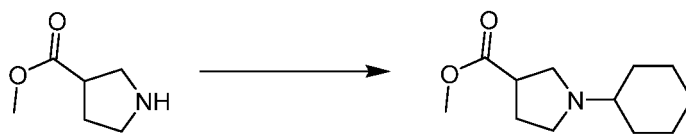


[0532] Step D: 1-[4-[2-[(1*R*)-2-[ethyl(methyl)amino]-1-methyl-ethoxy]-7-(3-hydroxy-1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one: To a solution of 4-[2-[(1*R*)-2-[ethyl(methyl)amino]-1-methyl-ethoxy]-4-piperazin-1-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]naphthalen-2-ol (70 mg, 127 μ mol, 2 HCl) and DIEA (98.8 mg, 764 μ mol, 133 μ L) in DCM (1.50 mL) was added prop-2-enoyl prop-2-enoate (12.9 mg, 102 μ mol) dropwise at -50 °C. The mixture was stirred at -40 to -20 °C for 30 minutes. Upon completion, the mixture was quenched by addition of MeOH (17.0 mg) and concentrated under vacuum. The residue was diluted with water (1 mL) and extracted with DCM (3 $\times$ 6 mL). The organic layers were dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by prep-HPLC (column: Phenomenex Gemini 150*25mm*10 μ m; mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN]; B%: 48%-78%, 10min) to give 1-[4-[2-[(1*R*)-2-[ethyl(methyl)amino]-1-methyl-ethoxy]-7-(3-hydroxy-1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one (9.23 mg, 17.2 μ mol, 13.5 % yield, 98.7 % purity) as a yellow solid. ES+APCI MS *m/z* 531.3 [M+H]⁺.

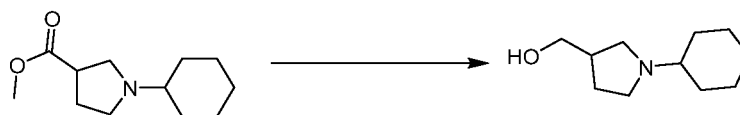
EXAMPLE 132

1-[4-[2-[(1-cyclohexyl)pyrrolidin-3-yl]methoxy]-7-(3-hydroxy-1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one





[0533] Step A: 1-cyclohexylpyrrolidine-3-carboxylate: To a solution of methyl pyrrolidine-3-carboxylate (1.00 g, 6.04 mmol, HCl) and DIEA (780 mg, 6.04 mmol, 1.05 mL) was added cyclohexanone (652 mg, 6.64 mmol, 686 μ L) and HOAc (725 mg, 12.1 mmol, 691 μ L) at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 h. To the reaction mixture was added $\text{NaBH}(\text{OAc})_3$ (3.84 g, 18.12 mmol) in portions at 0°C. The reaction mixture was stirred at 0 to 15°C for 12 hours. Upon completion, the reaction mixture was quenched by addition of water (5 mL) and organics concentrated under vacuum. The aqueous layer was extracted with DCM (10 mL $\times$ 2) and the pH adjusted with sat NaHCO_3 (10 mL) and Na_2CO_3 (2 mL) to pH>8. The organic layers were combined, dried over Na_2SO_4 and concentrated under vacuum. The residue was triturated with MTBE/Petroleum Ether (1:3, 20 mL) and the filtrate concentrated under vacuum to give methyl 1-cyclohexylpyrrolidine-3-carboxylate (1.00 g, 4.73 mmol, 78.4 % yield) as brown oil. ES+APCI MS m/z 212.2 $[\text{M}+\text{H}]^+$.



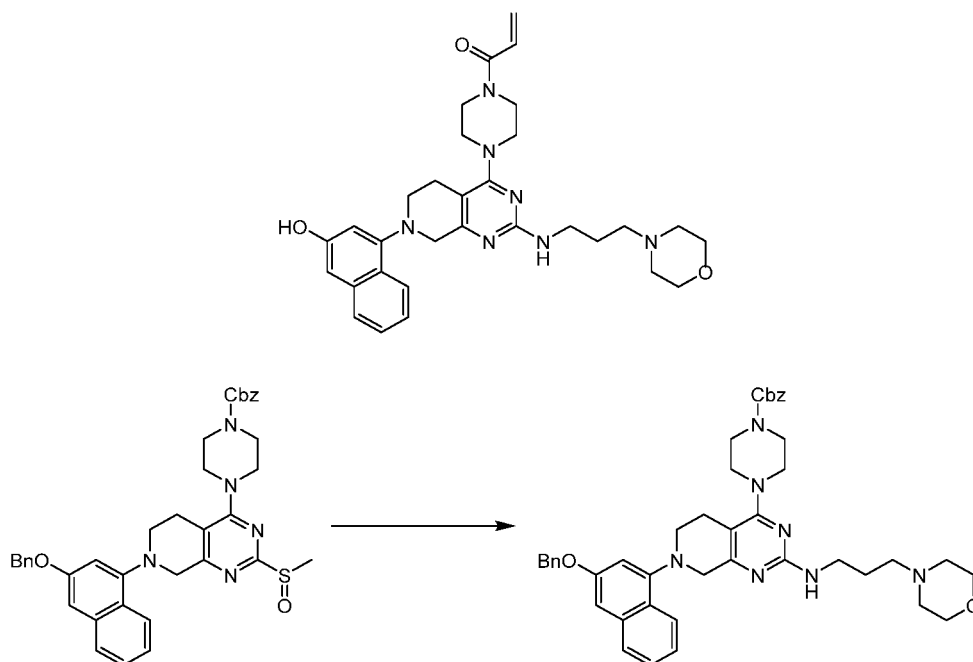
[0534] Step B: (1-cyclohexylpyrrolidin-3-yl)methanol: To a solution of methyl 1-cyclohexylpyrrolidine-3-carboxylate (1.00 g, 4.73 mmol) in THF (20 mL) was added LiAlH_4 (413 mg, 10.9 mmol) at -10 °C. The reaction mixture was stirred at -10 °C for 0.5 hour. The reaction mixture was quenched by addition of saturated Na_2SO_4 (2 mL) and mixture filtered and the filter cake washed with THF (3 $\times$ 50 mL). The combined organics were concentrated under vacuum to give : (1-cyclohexylpyrrolidin-3-yl)methanol (800 mg, 4.36 mmol, 92.3 % yield) as a colorless oil. ^1H NMR (400MHz, CHCl_3 -d) δ = 3.71 (dd, J = 4.1, 10.0 Hz, 1H), 3.53 (dd, J = 4.4, 10.0 Hz, 1H), 2.90 (dt, J = 4.4, 8.8 Hz, 1H), 2.74 (dd, J = 3.2, 8.8 Hz, 1H), 2.53 (dd, J = 6.8, 8.8 Hz, 1H), 2.36 - 2.24 (m, 2H), 2.04 - 1.93 (m, 2H), 1.90 (br s, 2H), 1.78 - 1.64 (m, 3H), 1.61 - 1.52 (m, 1H), 1.33 - 1.12 (m, 5H)

[0535] 1-[4-[2-[(1-cyclohexylpyrrolidin-3-yl)methoxy]-7-(3-hydroxy-1-naphthyl)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one was prepared following

Example 131 substituting (1-cyclohexylpyrrolidin-3-yl)methanol for (2*R*)-1-[ethyl(methyl)amino]propan-2-ol in Step B. ES+APCI MS m/z 597.4 $[M+H]^+$.

EXAMPLE 133

1-[4-[7-(3-hydroxy-1-naphthyl)-2-(3-morpholinopropylamino)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one

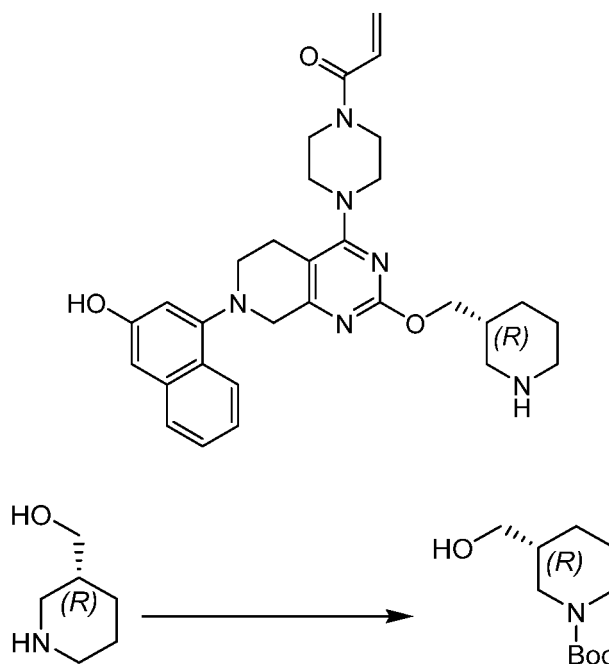


[0536] Step A: benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-(3-morpholinopropylamino)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate: A solution of benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-methylsulfinyl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (400 mg, 617 μmol) and 3-morpholinopropan-1-amine (534 mg, 3.70 mmol, 540 μL) in DMSO (4.00 mL) was heated to 100 °C for 12 hours. Upon completion, the mixture was diluted with water (4 mL) and extracted with EtOAc (3 $\times$ 20 mL). The organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography over Al_2O_3 eluting with Ethyl Acetate/Petroleum Ether (20 $\rightarrow$ 100%) to give benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-(3-morpholinopropylamino)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (245 mg, 320 μmol , 51.8 % yield, 95.0 % purity) as a yellow oil. ES+APCI MS m/z 728.6 $[M+H]^+$.

[0537] 1-[4-[7-(3-hydroxy-1-naphthyl)-2-(3-morpholinopropylamino)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one was prepared following **Example 131** substituting benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-(3-morpholinopropylamino)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate for benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[(1R)-2-[ethyl(methyl)amino]-1-methyl-ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate in Step C. ES+APCI MS m/z 558.6 $[M+H]^+$.

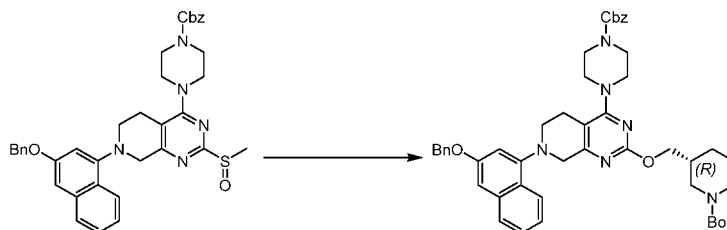
EXAMPLE 134

(R)-1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-(piperidin-3-ylmethoxy))-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

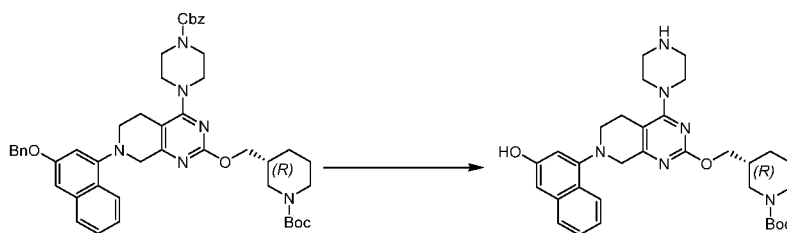


[0538] Step A: tert-butyl (3R)-3-(hydroxymethyl)piperidine-1-carboxylate: TEA (1.76 g, 17.4 mmol, 2.42 mL) was added to a solution of [(3R)-3-piperidyl]methanol (1.0 g, 8.68 mmol) in THF (25.0 mL), followed by the addition of a solution of Boc_2O (1.89 g, 8.68 mmol, 1.99 mL) in THF (5 mL) at 15 °C. The mixture was stirred at 15 °C for 12 hours. The solvent was removed under vacuum and the residue dissolved in ethyl acetate (50 mL) and H_2O (30 mL). The solution was acidified with HCl (6 M) to pH~6 and the layers separated. The organics were washed with brine (3×50 mL) and the combined organics concentrated to dryness to give *tert*-

butyl (3*R*)-3-(hydroxymethyl)piperidine-1-carboxylate (1.68 g, 7.80 mmol, 89.9% yield, 100% purity) as colorless crystals. ¹H NMR (400MHz, chloroform-*d*) δ = 3.73 (br s, 2H), 3.51 (br d, *J* = 6.8 Hz, 2H), 3.05 (br s, 2H), 1.83 - 1.71 (m, 2H), 1.62 (br s, 1H), 1.46 (s, 9H), 1.44 - 1.37 (m, 1H), 1.35 - 1.22 (m, 1H).

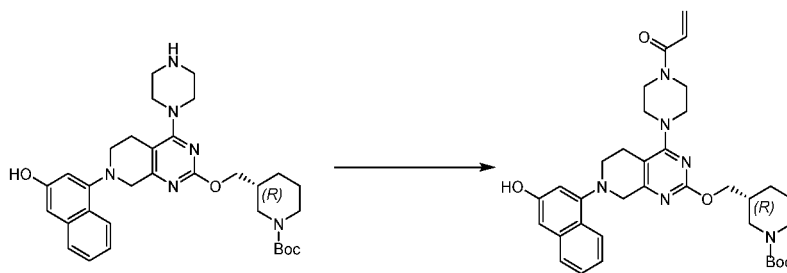


[0539] Step B: benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[[3*R*)-1-*tert*-butoxycarbonyl -3-piperidyl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate: To a solution of *tert*-butyl (3*R*)-3-(hydroxymethyl) piperidine-1-carboxylate (332 mg, 1.54 mmol) in THF (5 mL) was added t-BuONa (223 mg, 2.32 mmol). A solution of benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-methyl sulfinyl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (500 mg, 772 μ mol) in THF (5 mL) was next added and the mixture stirred at 0 °C for 1 hour. The reaction mixture was filtered and concentrated under reduced pressure and the residue purified by column chromatography eluting with Petroleum ether/Ethyl Acetate (10/1 to 3/1) to give benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[[3*R*)-1-*tert*-butoxycarbonyl -3-piperidyl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (510 mg, 628 μ mol, 81.4% yield, 98.4% purity) as a white solid. ES+APCI MS *m/z* 799.4 [M+H]⁺.

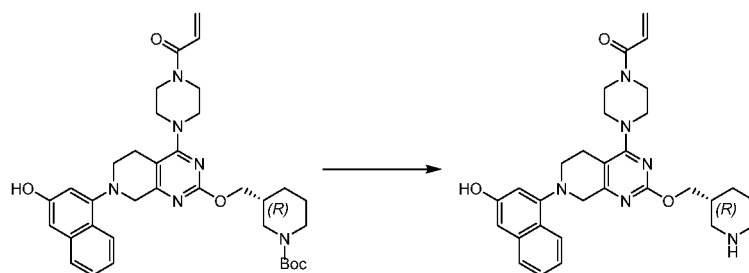


[0540] Step C: *tert*-butyl (3*R*)-3-[[7-(3-hydroxy-1-naphthyl)-4-piperazin-1-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-2-yl]oxymethyl]piperidine-1-carboxylate: A solution of benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[[3*R*)-1-*tert*-butoxycarbonyl-3-piperidyl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (250 mg, 313 μ mol) in MeOH (5 mL)

was purged with NH₃ (10 %, w/w) and then 10% Pd/C (50 mg) was added. The suspension was degassed under vacuum and the mixture stirred under H₂ (15 psi) at 15 °C for 12 hours. The reaction mixture was filtered and concentrated under reduced pressure to dryness to give *tert*-butyl (3*R*)-3-[[7-(3-hydroxy-1-naphthyl)-4-piperazin-1-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-2-yl]oxymethyl]piperidine-1-carboxylate (126 mg, 211 umol, 67.4% yield, 96.2% purity) as a colorless oil. ES+APCI MS *m/z* 575.5 [M+H]⁺.



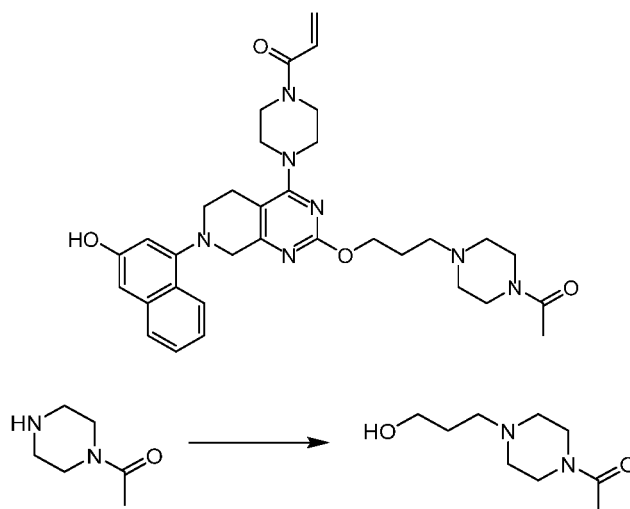
[0541] Step D: *tert*-butyl(3*R*)-3-[[7-(3-hydroxy-1-naphthyl)-4-(4-prop-2-enoyl piperazin-1-yl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-2-yl]oxymethyl]piperidine-1-carboxylate: To a solution of *tert*-butyl (3*R*)-3-[[7-(3-hydroxy-1-naphthyl) -4-piperazin-1-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-2-yl]oxymethyl]piperidine-1-carboxylate (126 mg, 219 umol) and TEA (33.3 mg, 329 umol, 45.8 uL) in DCM (5.0 mL) was added prop-2-enoyl prop-2-enoate (24.9 mg, 197 umol) dropwise at - 40 °C and the reaction stirred for 30 minutes at -40°C. The reaction mixture was quenched by addition MeOH (0.5 mL) and concentrated to dryness. The residue was dissolved into EtOAc (50 mL) and H₂O (20 mL). The resulting solution was acidified with HCl (1 M) to pH~6 and the layers separated. The combined organics were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give *tert*-butyl(3*R*)-3-[[7-(3-hydroxy-1-naphthyl)-4-(4-prop-2-enoyl piperazin-1-yl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-2-yl]oxymethyl]piperidine-1-carboxylate (120 mg, 172 umol, 78.5% yield, 90.2% purity) as a yellow oil, which was used directly for next step without further purification. ES+APCI MS *m/z* 629.6 [M+H]⁺.



[0542] Step E: 1-[4-[7-(3-hydroxy-1-naphthyl)-2-[[*(3R)*-3-piperidyl] methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one: To a solution of *tert*-butyl(*3R*)-3-[[7-(3-hydroxy-1-naphthyl)-4-(4-prop-2-enoyl)piperazin-1-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-2-yl]oxymethyl]piperidine-1-carboxylate (120 mg, 191 μ mol) in DCM (3.0 mL) was added TFA (326 mg, 2.86 mmol, 212 μ L) at 0 °C. The mixture was stirred at 15 °C for 2 hours under N₂ atmosphere. The reaction mixture was basified with NH₃ (30 % in water, three drops) and concentrated to dryness. The residue was purified by prep-HPLC (column: Phenomenex Synergi C18 150*25*10 μ m; mobile phase:[water (0.225% Formic Acid)-ACN]; B%: 5% - 35%, 10 min) to give 1-[4-[7-(3-hydroxy-1-naphthyl)-2-[[*(3R)*-3-piperidyl] methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one (24.5 mg, 38.9 μ mol, 20.4% yield) as a yellow solid. ES+APCI MS m/z 529.4 [M+H]⁺.

EXAMPLE 135

1-[4-[2-[3-(4-acetylpiperazin-1-yl)propoxy]-7-(3-hydroxy-1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one

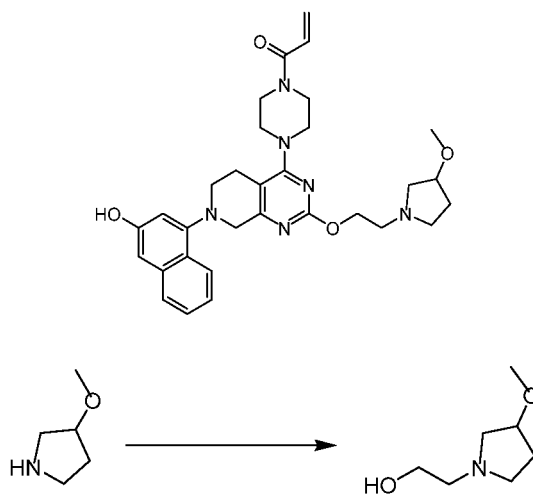


[0543] Step A: 1-[4-(3-hydroxypropyl)piperazin-1-yl]ethanone: To a solution of 1-piperazin-1-ylethanone (2.00 g, 15.6 mmol) and K₂CO₃ (4.31 g, 31.2 mmol) in CH₃CN (50.0 mL) was added 3-bromopropan-1-ol (3.25 g, 23.4 mmol). The mixture was stirred at 80 °C for 5 hours. The solid was filtered and the filtrate was evaporated to give 1-[4-(3-hydroxypropyl)piperazin-1-yl]ethanone (2.00 g, 10.7 mmol, 68.8 % yield) as a colorless oil.

[0544] 1-[4-[2-[3-(4-acetylpiperazin-1-yl)propoxy] -7-(3-hydroxy-1-naphthyl)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one was prepared following **Example 131** substituting 1-[4-(3-hydroxypropyl)piperazin-1-yl]ethanone for benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[(1*R*)-2-[ethyl(methyl)amino]-1-methyl-ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate in Step C. ES+APCI MS *m/z* 600.3 [M+H]⁺.

EXAMPLE 136

1-[4-[7-(3-hydroxy-1-naphthyl)-2-[2-(3-methoxypyrrolidin-1-yl)ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one



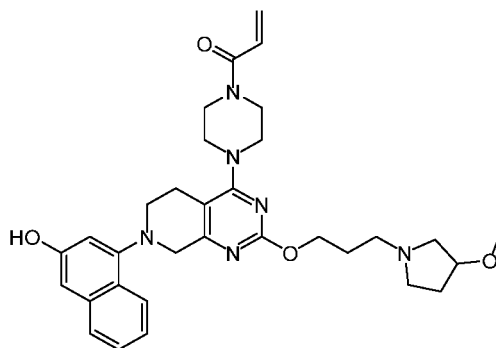
[0545] Step A: 2-(3-methoxypyrrolidin-1-yl)ethanol: To a solution of 3-methoxypyrrolidine (450 mg, 3.27 mmol, HCl) and 2-bromoethanol (408 mg, 3.27 mmol) in CH₃CN (10 mL) was added K₂CO₃ (1.36 g, 9.81 mmol). The mixture was stirred at 80 °C for 3 hours. The solid was filtered and the filtrate was evaporated to give 2-(3-methoxypyrrolidin-1-yl)ethanol (450 mg, 3.10 mmol, 94.8 % yield) as a colorless oil.

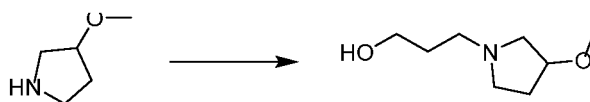
[0546] Step B: benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[2-(3-methoxypyrrolidin-1-yl)ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate: A mixture of benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-methylsulfinyl]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (500 mg, 771 μmol), 2-(3-methoxypyrrolidin-1-yl)ethanol (224 mg, 1.54 mmol), and t-BuONa (222 mg, 2.32 mmol) in toluene (10 mL) was stirred at 20 °C for 1 hour under N₂ atmosphere. The mixture was cooled to 0 °C and HCl(2M) was added until pH~7. The mixture was filtered and filtrate was concentrated in vacuum. The residue was purified by column chromatography using 0→10% MeOH/DCM as eluent to give benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[2-(3-methoxypyrrolidin-1-yl)ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (110 mg, 147.9 μmol , 19.1 % yield) ES+APCI MS m/z 729.2 [M+H]⁺.

[0547] 1-[4-[7-(3-hydroxy-1-naphthyl)-2-[2-(3-methoxypyrrolidin-1-yl)ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one was prepared following **Example 131** substituting benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[2-(3-methoxypyrrolidin-1-yl)ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate for benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[(1R)-2-[ethyl(methyl)amino]-1-methyl-ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate in Step C. ES+APCI MS m/z 559.3 [M+H]⁺.

EXAMPLE 137

1-[4-[7-(3-hydroxy-1-naphthyl)-2-[3-(3-methoxypyrrolidin-1-yl)propoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one



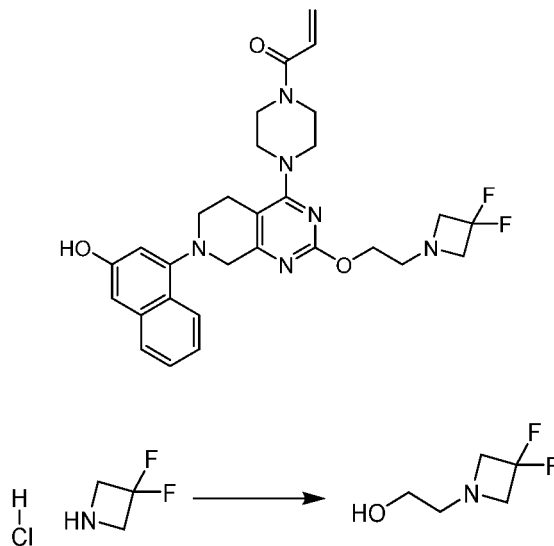


[0548] Step A: (3-methoxypyrrolidin-1-yl)propan-1-ol: To a solution of 3-methoxypyrrolidine (500 mg, 3.63 mmol, HCl) and 3-bromopropan-1-ol (505 mg, 3.63 mmol) in CH₃CN (10 mL) was added K₂CO₃ (1.51 g, 10.9 mmol). The mixture was stirred at 20 °C for 5 hours. The solid was filtered and the filtrate was evaporated to give 3-(3-methoxypyrrolidin-1-yl)propan-1-ol (540 mg, 3.39 mmol, 93.3 % yield).

[0549] 1-[4-[7-(3-hydroxy-1-naphthyl)-2-[3-(3-methoxypyrrolidin-1-yl)propoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one was prepared following **Example 131** substituting (3-methoxypyrrolidin-1-yl)propan-1-ol for (2*R*)-1-[ethyl(methyl)amino]propan-2-ol in Step B. ES+APCI MS *m/z* 573.3 [M+H]⁺.

EXAMPLE 138

1-[4-[2-[2-(3,3-difluoroazetidin-1-yl)ethoxy]-7-(3-hydroxy-1-naphthyl)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one



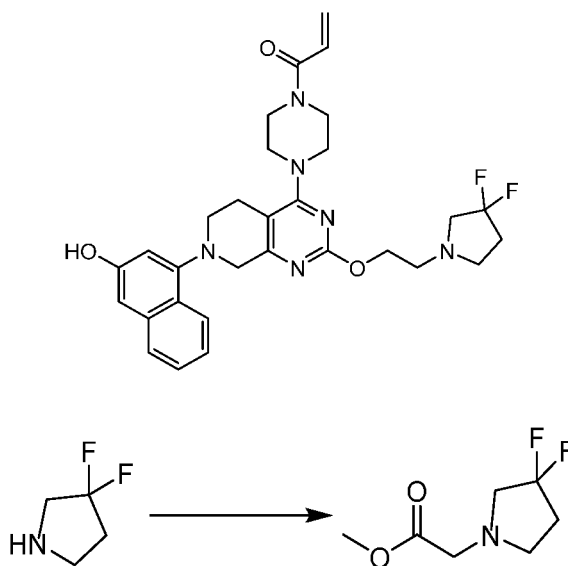
[0550] Step A: 2-(3,3-difluoroazetidin-1-yl)ethanol: To a solution of 3,3-difluoroazetidine (500 mg, 3.86 mmol, **HCl**) and 2-bromoethanol (482 mg, 3.86 mmol, 274 μ L) in CH₃CN (10 mL) was added K₂CO₃ (1.60 g, 11.5 mmol) and the reaction stirred at 80 °C for 16 hours. The

reaction was filtered and the filtrate evaporated to give 2-(3,3-difluoroazetidin-1-yl)ethanol (300 mg, 2.19 mmol, 56.7 % yield).

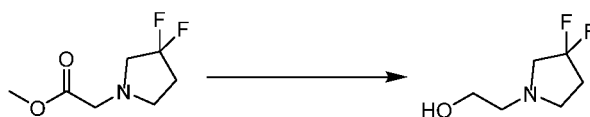
[0551] 1-[4-[2-[2-(3,3-difluoroazetidin-1-yl)ethoxy]-7-(3-hydroxy-1-naphthyl)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one was prepared following **Example 131** substituting give 2-(3,3-difluoroazetidin-1-yl)ethanol for (2*R*)-1-[ethyl(methyl)amino]propan-2-ol in Step B. ES+APCI MS m/z 551.4 $[M+H]^+$.

EXAMPLE 139

1-[4-[2-[2-(3,3-difluoropyrrolidin-1-yl)ethoxy]-7-(3-hydroxy-1-naphthyl)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one



[0552] Step A: Methyl 2-(3,3-difluoropyrrolidin-1-yl)acetate: To a suspension of methyl 2-bromoacetate (1.17 g, 7.67 mmol, 723 μ L) in DCM (10 mL) cooled to 0 °C was added TEA (1.76 g, 17.4 mmol, 2.42 mL) and 3,3-difluoropyrrolidine (1.00 g, 6.97 mmol, HCl) and the reaction mixture stirred at 20 °C for 16 hours. The reaction was filtered and filtrate was evaporated. The residue was purified by column chromatography with 0.5%-->20% MeOH/DCM as eluent to give methyl 2-(3,3-difluoropyrrolidin-1-yl)acetate (580 mg, 3.24 mmol, 46.4 % yield). ^1H NMR (400MHz, chloroform- d) δ = 3.73 (s, 3H), 3.38 (s, 2H), 3.11 (t, J = 13.6 Hz, 2H), 2.92 (t, J = 6.8 Hz, 2H), 2.36-2.26 (m, 2H).



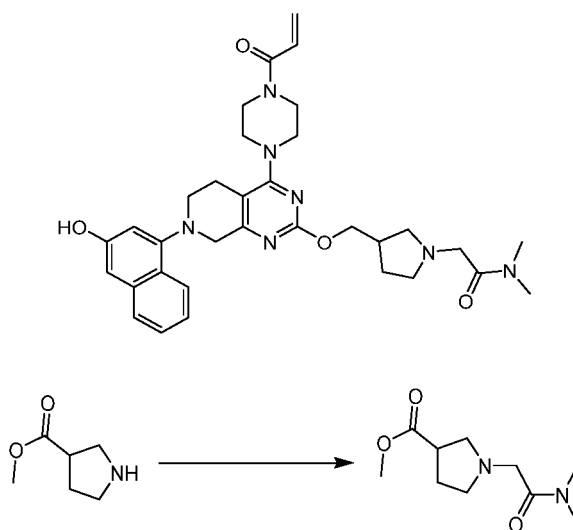
[0553] Step B: 2-(3,3-difluoropyrrolidin-1-yl)ethanol: To a solution of LiAlH₄ (184 mg, 4.86 mmol) in THF (5.0 mL) was added a solution of methyl 2-(3,3-difluoropyrrolidin-1-yl)acetate (580 mg, 3.24 mmol) in THF (5.0 mL) dropwise at 0 °C. The mixture was warmed to 20 °C and stirred for 3 hours. The mixture was quenched by addition of saturated aqueous sodium sulfate solution (1.50 mL). The reaction was filtered and the filtrate was concentrated under vacuum to give 2-(3,3-difluoropyrrolidin-1-yl)ethanol (330 mg, 2.18 mmol, 67.4 % yield) as a colourless oil. ¹H NMR (400MHz, chloroform-d) δ = 3.64 (t, *J* = 5.2 Hz, 2H), 2.97 (t, *J* = 13.2 Hz, 2H), 2.82 (t, *J* = 7.2 Hz, 2H), 2.68 (t, *J* = 5.2 Hz, 2H), 2.49 (br. s, 1H), 2.34-2.24 (m, 2H).

[0554] 1-[4-[2-[2-(3,3-difluoropyrrolidin-1-yl)ethoxy]-7-(3-hydroxy-1-naphthyl)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one was prepared following

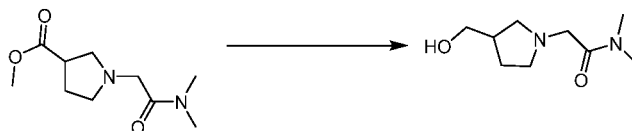
Example 131 substituting 2-(3,3-difluoropyrrolidin-1-yl)ethanol for (2*R*)-1-[ethyl(methyl)amino]propan-2-ol in Step B. ES+APCI MS *m/z* 565.3 [M+H]⁺.

EXAMPLE 140

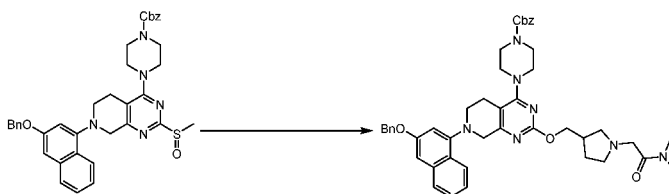
2-[3-[[7-(3-hydroxy-1-naphthyl)-4-(4-prop-2-enoylpiperazin-1-yl)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-2-yl]oxymethyl]pyrrolidin-1-yl]-*N,N*-dimethyl-acetamide



[0555] Step A: methyl 1-[2-(dimethylamino)-2-oxo-ethyl]pyrrolidine-3-carboxylate: A solution of methyl pyrrolidine-3-carboxylate (1.00 g, 6.04 mmol, HCl) and NaHCO₃ (1.01 g, 12.1 mmol, 470 uL) in ACN (200.0 mL) was stirred at 10 °C for 5 minutes. A solution of 2-bromo-*N,N*-dimethyl-acetamide (1.00 g, 6.04 mmol) in ACN (5.00 mL) was next added at 10 °C and the reaction stirred at 10 °C for 6 hours followed by and stirring at 50 °C for 2 hours. The mixture was filtered and and solids washed with DCM (3 × 15 ml). The filtrate was concentrated under vacuum and the residue purified by column chromatography using 0→10% MeOH/DCM as eluent to to give methyl 1-[2-(dimethylamino)-2-oxo-ethyl]pyrrolidine-3-carboxylate (480 mg, 2.02 mmol, 33.4% yield).



[0556] Step B: 2-[3-(hydroxymethyl)pyrrolidin-1-yl]-*N,N*-dimethyl-acetamide: To a solution of methyl 1-[2-(dimethylamino)-2-oxo-ethyl]pyrrolidine-3-carboxylate (500 mg, 2.33 mmol) in THF (10 mL) was added LiAlH₄ (203 mg, 5.36 mmol) at -60 °C and the reaction mixture stirred at -60 °C for 10 minutes. The reaction mixture was quenched by the addition of saturated Na₂SO₄ (0.4 mL) and and the slurry was filtered. The filter cake was washed with THF (3 X 50 mL) and the filtrate concentrated under vacuum to give 2-[3-(hydroxymethyl)pyrrolidin-1-yl]-*N,N*-dimethyl-acetamide (400 mg, 2.15 mmol, 92.2% yield) as a brown oil. ES+APCI MS *m/z* 187.1 [M+H]⁺.



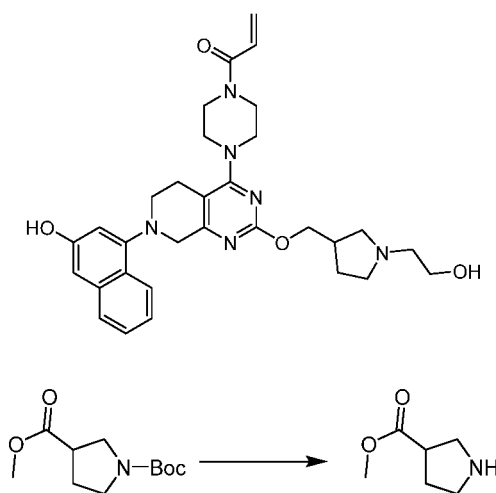
[0557] Step C: benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[[1-[2-(dimethylamino)-2-oxo-ethyl]pyrrolidin-3-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate: A mixture of benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-methylsulfinyl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (500 mg, 772 umol), 2-[3-(hydroxymethyl)pyrrolidin-1-yl]-*N,N*-dimethyl-acetamide (216 mg, 1.16 mmol) and NaOBu-t (148 mg, 1.54 mmol) in toluene (10 mL) was stirred at 15 °C for 15 minutes. The reaction

mixture was purified directly by silica gel chromatography using 20→100% EtOAc/Petroleum Ether to give benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[[1-[2-(dimethylamino)-2-oxo-ethyl]pyrrolidin-3-yl]methoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (310 mg, 395 μ mol, 51.1% yield, 98% purity) as a brown solid. ES+APCI MS m/z 770.4 $[M+H]^+$.

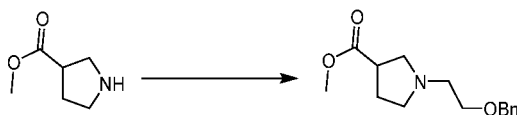
[0558] 2-[3-[[7-(3-hydroxy-1-naphthyl)-4-(4-prop-2-enyl)piperazin-1-yl]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-2-yl]oxymethyl]pyrrolidin-1-yl]-*N,N*-dimethyl-acetamide was prepared following **Example 131** substituting benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[[1-[2-(dimethylamino)-2-oxo-ethyl]pyrrolidin-3-yl]methoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate for benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[(1*R*)-2-[ethyl(methyl)amino]-1-methyl-ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate in Step C. ES+APCI MS m/z 600.3 $[M+H]^+$.

EXAMPLE 141

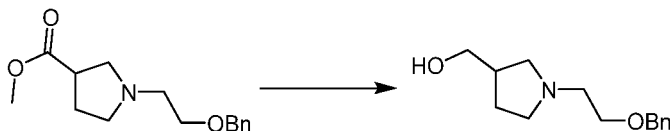
1-[4-[2-[[1-(2-hydroxyethyl)pyrrolidin-3-yl]methoxy]-7-(3-hydroxy-1-naphthyl)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one



[0559] Step A: methyl pyrrolidine-3-carboxylate: To a solution of 1-(tert-butyl) 3-methyl pyrrolidine-1,3-dicarboxylate (10.0 g, 43.6 mmol) in DCM (50 mL) was added HCl/dioxane (4 M, 109 mL) at 0 °C and stirred at 0 °C for 1 hour. The mixture was concentrated under vacuum to give methyl pyrrolidine-3-carboxylate (7.00 g, crude, HCl) as brown oil. ^1H NMR (400MHz, methanol- d_4) δ = 3.77 (s, 3H), 3.56 - 3.53 (m, 2H), 3.41 - 3.37 (m, 3H), 2.40 - 2.24 (m, 2H).



[0560] Step B: methyl 1-(2-benzyloxyethyl)pyrrolidine-3-carboxylate: A solution of methyl pyrrolidine-3-carboxylate (3.0 g, 18.1 mmol, HCl), Cs_2CO_3 (17.7 g, 54.3 mmol) and KI (301 mg, 1.81 mmol) in MeCN (60 mL) was stirred at 15 °C for 5 min. Then a solution of 2-bromoethoxymethylbenzene (4.67 g, 21.7 mmol, 3.43 mL) in ACN (15 mL) was added to the mixture at 15 °C and stirred at 15 °C for 1 hour. The mixture was next warmed to 50 °C and stirred at 50 °C for 12 hours. The reaction mixture was filtered and the filter cake washed with DCM (3 × 30 mL) and the filtrate concentrated under vacuum. The residue was purified by prep-HPLC (column: Phenomenex luna C18 250*50mm*10 um; mobile phase: [water(0.1%TFA)-ACN]; B%: 10ACN%-40ACN%, 30min40%min) to give methyl 1-(2-benzyloxyethyl)pyrrolidine-3-carboxylate (1.48 g, 5.06 mmol, 27.9 % yield, 90.0 % purity) as brown oil. ^1H NMR (400MHz, chloroform- d) δ = 7.36 - 7.28 (m, 5H), 4.56 (s, 2H), 3.70 (s, 3H), 3.61 - 3.58 (t, J =6.0 Hz, 2H), 3.02 - 3.00 (m, 2H), 2.78 - 2.67 (m, 4H), 2.58 - 2.49 (m, 1H), 2.11 - 2.08 (m, 2H)

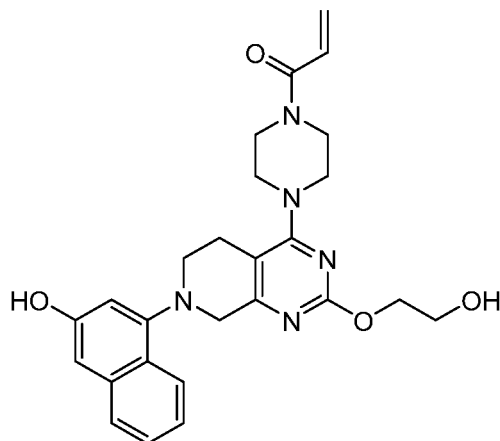


[0561] Step C: (1-(2-(benzyloxy)ethyl)pyrrolidin-3-yl)methanol: To the solution of methyl 1-(2-benzyloxyethyl)pyrrolidine-3-carboxylate (1.38 g, 5.24 mmol) in THF (27 mL) was added LiAlH_4 (457 mg, 12 mmol) at -10 °C and stirred at -10 °C for 0.5 hour. The reaction mixture was quenched by saturated Na_2SO_4 (1 mL) and filtered, the filter cake was washed with THF (5 × 30 mL), the filtrate was concentrated under vacuum to give (1-(2-(benzyloxy)ethyl)pyrrolidin-3-yl)methanol (1.30 g, 3.31 mmol, 63.3% yield, 60.0 % purity) as brown oil. ES+APCI MS m/z 236.1 $[\text{M}+\text{H}]^+$.

[0562] 1-[4-[2-[1-(2-hydroxyethyl)pyrrolidin-3-yl]methoxy]-7-(3-hydroxy-1-naphthyl)-6,8-dihydro-5H-pyrido[3,4- d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one was prepared following **Example 136** substituting (1-(2-(benzyloxy)ethyl)pyrrolidin-3-yl)methanol for 2-(3-methoxypyrrolidin-1-yl)ethanol in Step B. ES+APCI MS m/z 559.3 $[\text{M}+\text{H}]^+$.

EXAMPLE 142

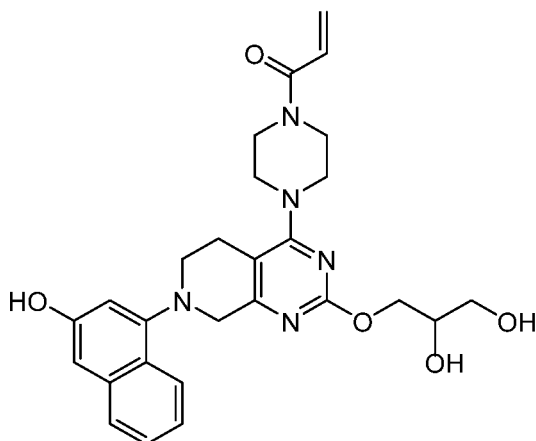
1-[4-[2-(2-hydroxyethoxy)-7-(3-hydroxy-1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-
d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one



[0563] 1-[4-[2-(2-hydroxyethoxy)-7-(3-hydroxy-1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-
d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one was prepared following **Example 136** substituting 2-[*tert*-butyl(dimethyl)silyl]oxyethanol for 2-(3-methoxypyrrolidin-1-yl)ethanol in Step B. ES+APCI MS m/z 476.2 $[M+H]^+$.

EXAMPLE 143

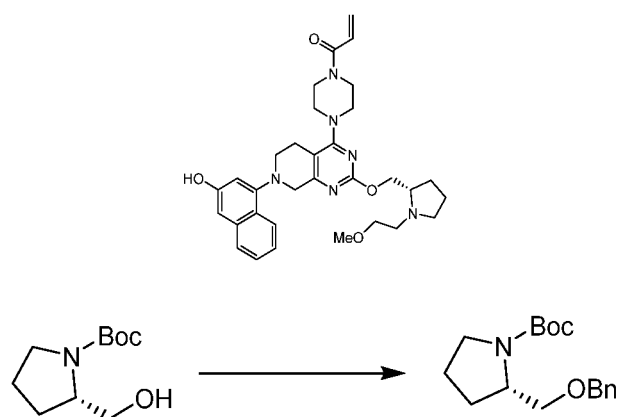
1-[4-[2-(2,3-dihydroxypropoxy)-7-(3-hydroxy-1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-
d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one



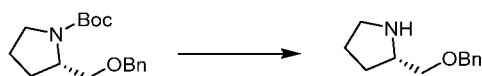
[0564] 1-[4-[2-(2,3-dihydroxypropoxy)-7-(3-hydroxy-1-naphthyl)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one was prepared following **Example 136** substituting (2,2-dimethyl-1,3-dioxolan-4-yl)methanol for 2-(3-methoxypyrrolidin-1-yl)ethanol in Step B. ES+APCI MS m/z 506.3 $[M+H]^+$.

EXAMPLE 144

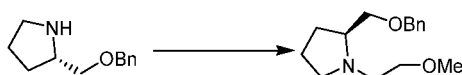
(S)-1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-((1-(2-methoxyethyl)pyrrolidin-2-yl)methoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one



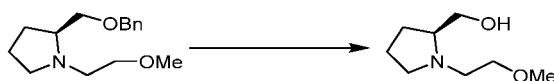
[0565] Step A: tert-butyl (2S)-2-(benzyloxymethyl)pyrrolidine-1-carboxylate: To a slurry of NaH (2.38 g, 59.6 mmol, 60% purity) in THF (50 mL) was added a solution of *tert*-butyl (2S)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (10 g, 49.69 mmol) in THF (50 mL) at 0 °C and the mixture was stirred at 10 °C for 1 hour. Bromomethylbenzene (12.8 g, 74.5 mmol, 8.85 mL) was added dropwise at 0 °C and the mixture was stirred at 10 °C for 16 hours. The mixture was quenched by addition of saturated aqueous ammonia chloride solution (20 mL) and then diluted with ethyl acetate (200 mL) and water (100 mL). The separated organic layer was washed with water (100 mL) and brine (100 mL), dried over sodium sulfate, filtered and concentrated under vacuum. The residue was purified by column chromatography over silica gel (petroleum ether/ethyl acetate 100/1 to 5/1) to give *tert*-butyl (2S)-2-(benzyloxymethyl)pyrrolidine-1-carboxylate (8.2 g, 28.06 mmol, 56.5% yield, 99.7% purity) was obtained as a colorless oil. ES+APCI MS m/z 192.1 $[M+H-Boc]^+$.



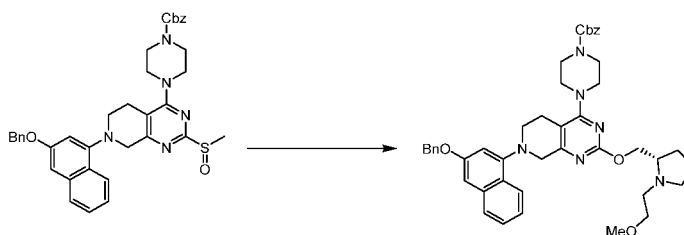
[0566] Step B: (2S)-2-(benzyloxymethyl)pyrrolidine: To a solution of *tert*-butyl (2S)-2-(benzyloxymethyl)pyrrolidine-1-carboxylate (8.2 g, 28.14 mmol) in CH₂Cl₂ (28 mL) was added TFA (43.1 g, 378 mmol, 28.0 mL) dropwise at 0 °C under nitrogen atmosphere. The mixture was stirred at 15 °C for 1 hour. The mixture was concentrated under vacuum. The residue was diluted with dichloromethane (100mL) and then washed with 1M aqueous sodium hydroxide (10 mL) until the aqueous layer reached pH ~ 10. The separated organic layer was washed with brine (2 × 20 mL), dried over sodium sulfate, filtered and concentrated under vacuum to give (2S)-2-(benzyloxymethyl)pyrrolidine (4 g, 20.9 mmol, 74.3% yield) LCMS ES+APCI MS m/z 192.2 [M+H]⁺.



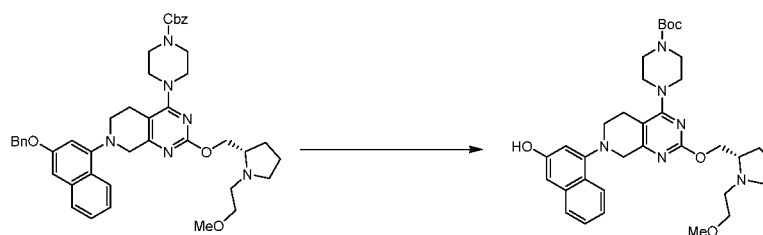
[0567] Step C: (2S)-2-(benzyloxymethyl)-1-(2-methoxyethyl)pyrrolidine: A mixture of 1-bromo-2-methoxy-ethane (0.9 g, 6.48 mmol, 608 uL), (2S)-2-(benzyloxymethyl)pyrrolidine (1.24 g, 6.48 mmol) and K₂CO₃ (2.68 g, 19.4 mmol) in CH₃CN (20 mL) was stirred at 15 °C for 1 hours and then at 78 °C for 12 hours. The mixture was diluted with ethyl acetate (50 mL) and water (50 mL). The separated organic layer was washed with brine (1 × 50 mL), dried over sodium sulfate, filtered and concentrated under vacuum. The residue was purified by column chromatography over silica gel (ethyl acetate/dichloromethane/methanol 1/1/0 to 10/10/2) to give (2S)-2-(benzyloxymethyl)-1-(2-methoxyethyl)pyrrolidine (900 mg, 3.61 mmol, 55.7% yield) as a colorless oil. ES+APCI MS m/z 250.2 [M+H]⁺.



[0568] Step D: (S)-(1-(2-methoxyethyl)pyrrolidin-2-yl)methanol: A solution of (2S)-2-(benzyloxymethyl)-1-(2-methoxyethyl)pyrrolidine (900 mg, 3.61 mmol) in MeOH (20 mL) was added 10% Pd/C (721.88 umol) and the slurry stirred under H₂ (50 psi) at 10 °C for 16 hours. The reaction was filtered and the filtrate concentrated under vacuum to give (S)-(1-(2-methoxyethyl)pyrrolidin-2-yl)methanol (450 mg, 2.83 mmol, 78.30% yield).

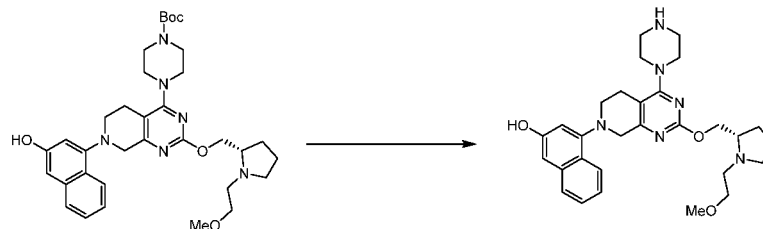


[0569] Step E: Benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[[*(2S)*-1-(2-methoxyethyl)pyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate: A mixture of [*(2S)*-1-(2-methoxyethyl)pyrrolidin-2-yl]methanol (245 mg, 1.54 mmol), benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-methylsulfinyl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (500 mg, 772 μ mol), and *t*-BuONa (223 mg, 2.32 mmol) in THF (5 mL) was stirred at 20 °C for 0.5 hour under N₂ atmosphere. The reaction mixture was poured into H₂O (30 mL) and the aqueous layer extracted with ethyl acetate (3x30 mL). The combined organics were washed with brine (30 mL), dried over anhydrous Na₂SO₄ and concentrated under vacuum to give a residue. The residue was purified by column chromatography (SiO₂, DCM/MeOH = 300/1 to 10:1) to give Benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[[*(2S)*-1-(2-methoxyethyl)pyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (260 mg, 349 μ mol, 45.3 % yield). ES+APCI MS *m/z* 743.4 [M+H]⁺.

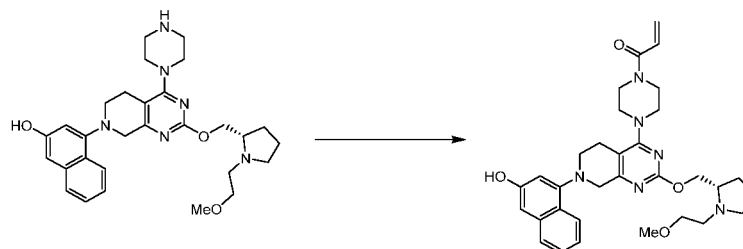


[0570] Step F: *tert*-Butyl 4-[7-(3-hydroxy-1-naphthyl)-2-[[*(2S)*-1-(2-methoxyethyl)pyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate: To a solution of benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[[*(2S)*-1-(2-methoxyethyl)pyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (240 mg, 323 μ mol) and (Boc)₂O (141 mg, 646 μ mol, 148 μ L) in MeOH (150 mL) was added 10% Pd/C (100 mg) under N₂ atmosphere. The suspension was degassed and purged with H₂ 3 times. The mixture was stirred under H₂ (15 PSI) at 40 °C for 12 hours. The reaction mixture was filtered and the filtrate concentrated to give *tert*-Butyl 4-[7-(3-hydroxy-1-naphthyl)-2-[[*(2S)*-1-(2-

methoxyethyl)pyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (215 mg, crude). ES+APCI MS m/z 619.1 $[M+H]^+$.



[0571] Step G: 4-[2-[[*(2S)*-1-(2-methoxyethyl)pyrrolidin-2-yl]methoxy]-4-piperazin-1-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]naphthalen-2-ol: To a solution of *tert*-butyl 4-[7-(3-hydroxy-1-naphthyl)-2-[[*(2S)*-1-(2-methoxyethyl)pyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (215 mg, 347 μ mol) in DCM (500 μ L) was added TFA (594 mg, 5.21 mmol, 385 μ L) and the mixture stirred at 15 $^{\circ}$ C for 1 hour. The mixture was concentrated under vacuum to give 4-[2-[[*(2S)*-1-(2-methoxyethyl)pyrrolidin-2-yl]methoxy]-4-piperazin-1-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]naphthalen-2-ol (219 mg, 346 μ mol). ES+APCI MS m/z 519.4 $[M+H]^+$.

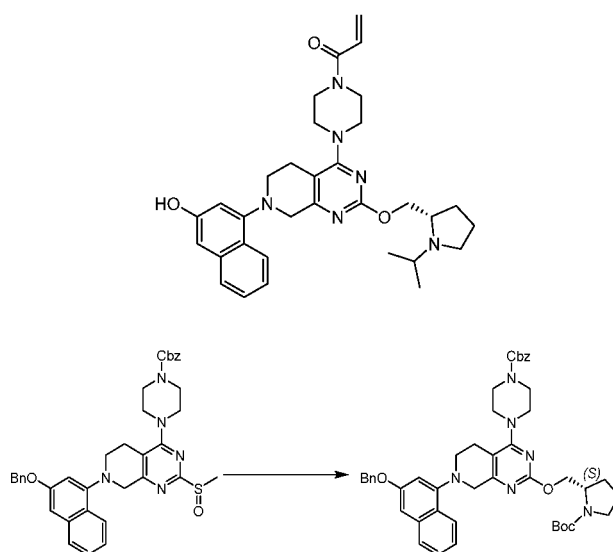


[0572] Step H: 1-[4-[7-(3-hydroxy-1-naphthyl)-2-[[*(2S)*-1-(2-methoxyethyl)pyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one: To a mixture of 4-[2-[[*(2S)*-1-(2-methoxyethyl)pyrrolidin-2-yl]methoxy]-4-piperazin-1-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]naphthalen-2-ol (219 mg, 346 μ mol) and DIEA (447 mg, 3.46 mmol, 603 μ L) in dichloromethane (4.00 mL) cooled to -40 $^{\circ}$ C was added a solution of prop-2-enoyl prop-2-enoate (34.9 mg, 276.92 μ mol) in dichloromethane (1.00 mL) under a nitrogen atmosphere. The mixture was stirred at -40 $^{\circ}$ C for 1 hour. The reaction was quenched by addition of saturated NaHCO_3 (2.00 mL) and the mixture poured into ice-water (20 mL) and extracted with dichloromethane (20 mL $\times$ 2). The combined organics were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by prep-HPLC (column:

Gemini 150*25 5u; mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN]; B%: 32%-62%, 12 min) to give 1-[4-[7-(3-hydroxy-1-naphthyl)-2-[[*(2S)*-1-(2-methoxyethyl)pyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one (27 mg, 46.7 umol). ES+APCI MS *m/z* 573.3 [M+H]⁺.

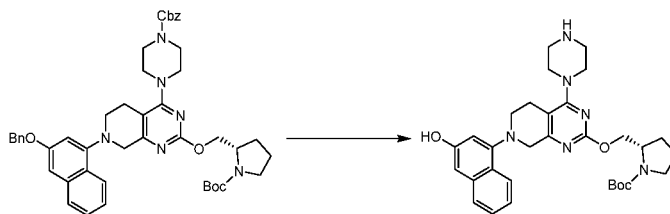
EXAMPLE 145

1-[4-[7-(3-hydroxy-1-naphthyl)-2-[[*(2S)*-1-isopropylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one

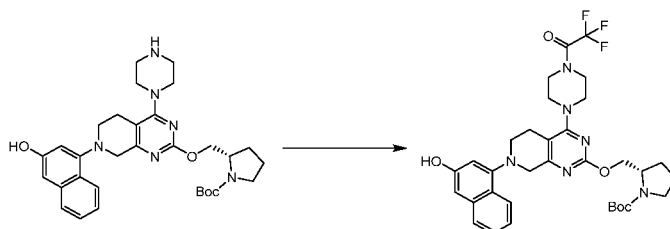


[0573] Step A: Benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[[*(2S)*-1-*tert*-butoxycarbonylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate: To a solution of *tert*-butyl (*2S*)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (1.24 g, 6.17 mmol) and benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-methylsulfinyl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (2 g, 3.09 mmol) in THF (50 mL) was added *t*-BuONa (890 mg, 9.26 mmol) and the reaction stirred at 15 °C for 0.5 hour. The reaction mixture was poured into H₂O (100 mL) and extracted with ethyl acetate (3X100 mL). The combined organics were washed with brine (50 mL), dried over anhydrous Na₂SO₄ and concentrated under vacuum to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 100/1 to 1:1) to give Benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[[*(2S)*-1-*tert*-butoxycarbonylpyrrolidin-2-yl]methoxy]-6,8-dihydro-

5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (1.62 g, 2.02 mmol, 65.5 % yield). ES+APCI MS *m/z* 785.6 [M+H]⁺.

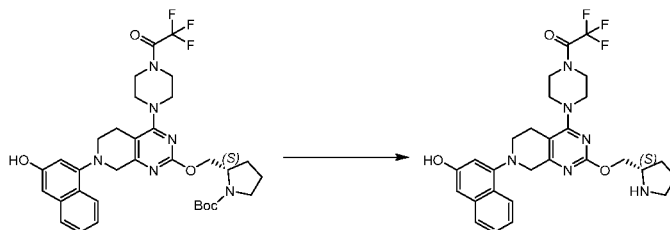


[0574] Step B: (2*S*)-2-[[7-(3-hydroxy-1-naphthyl)-4-piperazin-1-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-2-yl]oxymethyl]pyrrolidine-1-carboxylate: NH₃ was bubbled into MeOH (50 mL) at 15 °C for 30 minutes. To this solution was added benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[[[(2*S*)-1-tert-butoxycarbonyl pyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (1.6 g, 2.04 mmol) followed by dry 10 % Pd/C (500 mg) under N₂. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (15 psi) at 40 °C for 1 hour. The mixture was then filtered and the filtrate concentrated under vacuum to give *tert*-butyl (2*S*)-2-[[7-(3-hydroxy-1-naphthyl)-4-piperazin-1-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-2-yl]oxymethyl]pyrrolidine-1-carboxylate (1.00 g, 1.78 mmol). ES+APCI MS *m/z* 561.5 [M+H]⁺.

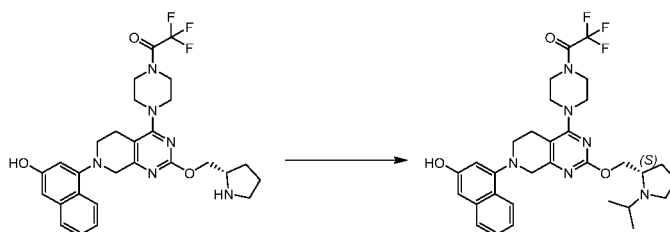


[0575] Step C: *tert*-butyl (2*S*)-2-[[7-(3-hydroxy-1-naphthyl)-4-[4-(2,2,2-trifluoroacetyl)piperazin-1-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-2-yl]oxymethyl]pyrrolidine-1-carboxylate: To a solution of *tert*-butyl (2*S*)-2-[[7-(3-hydroxy-1-naphthyl)-4-piperazin-1-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-2-yl]oxymethyl]pyrrolidine-1-carboxylate (800 mg, 1.43 mmol) in DCM (5.00 mL) at 0 °C was added TFAA (599 mg, 2.85 mmol) and DIEA (737 mg, 5.71 mmol) and the reaction stirred at 0 °C for 0.5 hour. The reaction mixture was poured into H₂O (50 mL) and extracted with ethyl acetate (50 mL×3). The combined organics were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum to give *tert*-butyl (2*S*)-2-[[7-(3-

hydroxy-1-naphthyl)-4-[4-(2,2,2-trifluoroacetyl)piperazin-1-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-2-yl]oxymethyl]pyrrolidine-1-carboxylate (1.5 g, crude). ES+APCI MS m/z 657.5 $[M+H]^+$.

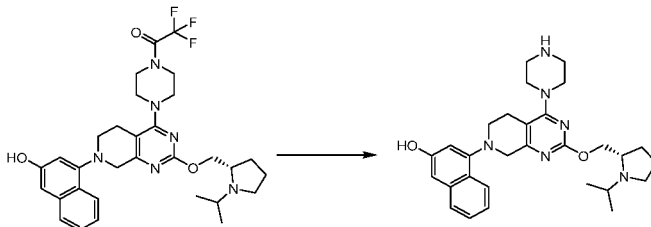


[0576] Step D: 2,2,2-trifluoro-1-[4-[7-(3-hydroxy-1-naphthyl)-2-[(2*S*)-pyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]ethanone: To a solution of *tert*-butyl (2*S*)-2-[[7-(3-hydroxy-1-naphthyl)-4-[4-(2,2,2-trifluoroacetyl)piperazin-1-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-2-yl]oxymethyl]pyrrolidine-1-carboxylate (300 mg, crude) in DCM (500 μ L) was added TFA (521 mg, 4.57 mmol, 338 μ L) and the mixture stirred at 15 $^{\circ}$ C for 1 hour. The mixture was concentrated under vacuum to give 2,2,2-trifluoro-1-[4-[7-(3-hydroxy-1-naphthyl)-2-[(2*S*)-pyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]ethanone (306 mg). ES+APCI MS m/z 557.3 $[M+H]^+$.

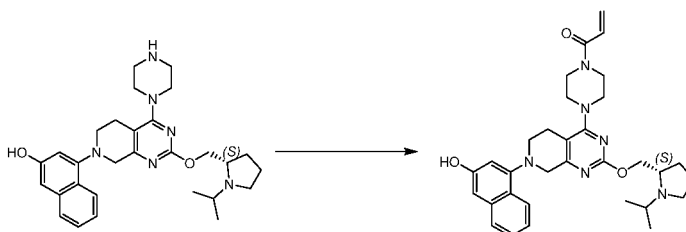


[0577] Step E: 2,2,2-trifluoro-1-[4-[7-(3-hydroxy-1-naphthyl)-2-[(2*S*)-1-isopropylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]ethanone: To a solution of acetone (132 mg, 2.28 mmol, 167 μ L,) and 2,2,2-trifluoro-1-[4-[7-(3-hydroxy-1-naphthyl)-2-[(2*S*)-pyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]ethanone (306 mg, crude, TFA) in MeOH (5.00 mL) was added AcOH (54.8 mg, 912 μ mol, 52.2 μ L) and NaBH_3CN (115 mg, 1.83 mmol) and the mixture stirred at 15 $^{\circ}$ C for 16 hours. The reaction mixture was diluted with H_2O (20 mL) and extracted with ethyl acetate (20 mL $\times$ 3). The combined organics were washed with brine (10 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give 2,2,2-trifluoro-1-[4-[7-(3-

hydroxy-1-naphthyl)-2-[[*(2S)*-1-isopropylpyrrolidin-2-yl] methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]ethanone (300 mg, crude). ES+APCI MS *m/z* 599.5 [*M*+*H*]⁺.



[0578] Step F: 4-[2-[[*(2S)*-1-isopropylpyrrolidin-2-yl]methoxy]-4-piperazin-1-yl]-6,8- dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]naphthalen-2-ol: To a solution of 2,2,2-trifluoro-1-[4-[7-(3-hydroxy-1-naphthyl)-2-[[*(2S)*- 1-isopropylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]ethanone (300 mg, crude) in MeOH (10 mL) was added K₂CO₃ (346 mg, 2.51 mmol) and the mixture stirred at 15 °C for 1 hour. The reaction mixture was filtered and the filtrate concentrated to give 4-[2-[[*(2S)*-1-isopropylpyrrolidin-2-yl]methoxy]-4-piperazin-1-yl]-6,8- dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]naphthalen-2-ol (250 mg). ES+APCI MS *m/z* 503.3 [*M*+*H*]⁺.

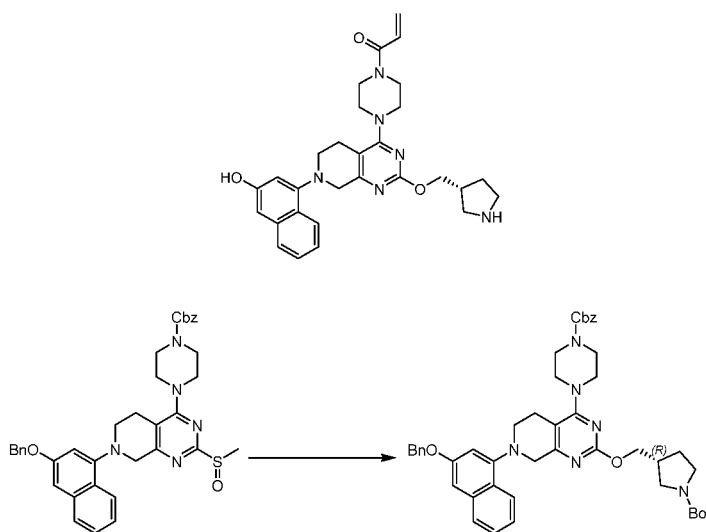


[0579] Step G: 1-[4-[7-(3-hydroxy-1-naphthyl)-2-[[*(2S)*-1-isopropylpyrrolidin-2-yl] methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one: To a mixture of 4-[2-[[*(2S)*-1-isopropylpyrrolidin-2-yl]methoxy]-4- piperazin-1-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]naphthalen-2-ol (250 mg, crude) and DIEA (643 mg, 4.97 mmol, 866 uL) in DCM (5.00 mL) cooled to - 40°C was added a solution of prop-2-enoyl prop-2-enoate (50.2mg, 398 umol) in DCM (1 mL) under nitrogen atmosphere. The mixture was stirred at -40 °C for 1 hour. The reaction was quenched by addition of saturated NaHCO₃ (2.00 mL). The mixture was poured into ice-water (20 mL) and extracted with DCM (20 mL×2). The combined organics were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by prep-HPLC (column: Phenomenex Gemini 150*25mm*10um; mobile phase: [water (0.05%

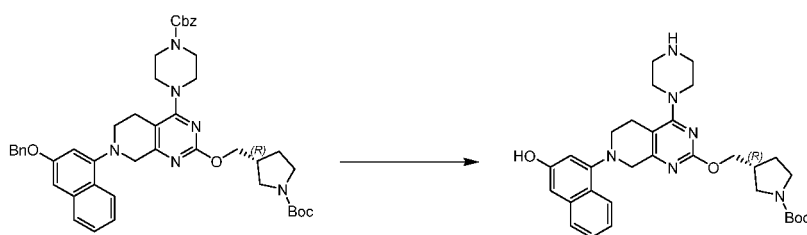
ammonia hydroxide v/v)-ACN]; B%: 52%-78%, 12min). 1-[4-[7-(3-hydroxy-1-naphthyl)-2-[[*(2S)*-1-isopropylpyrrolidin-2-yl] methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one (10 mg, 17.6 μ mol). ES+APCI MS m/z 557.3 $[M+H]^+$.

EXAMPLE 146

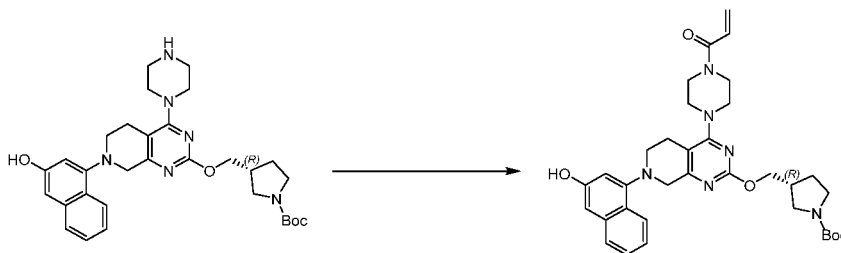
1-[4-[7-(3-hydroxy-1-naphthyl)-2-[[*(3R)*-pyrrolidin-3-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one



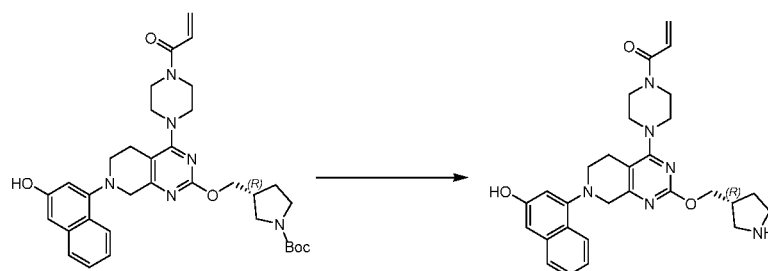
[0580] Step A: benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[[*(3R)*-1-tert-butoxycarbonylpyrrolidin-3-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate: A mixture of benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-methylsulfinyl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (0.50 g, 772 μ mol), *tert*-butyl (*3R*)-3-(hydroxymethyl)pyrrolidine-1-carboxylate (311 mg, 1.54 mmol) and *t*-BuONa (223 mg, 2.32 mmol) in THF (10 mL) was stirred at 20 °C for 1 hour. The mixture was diluted with water (10 mL) and the aqueous layer extracted with ether acetate (3 $\times$ 20 mL). The combined organics were washed with saturated sodium chloride (1 $\times$ 30 mL), dried over Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by column chromatography (SiO₂, petroleum ether/ether acetate = 3/1) to give benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[[*(3R)*-1-tert-butoxycarbonylpyrrolidin-3-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (0.40 g, 499 μ mol). ES+APCI MS m/z 785.2 $[M+H]^+$.



[0581] Step B: *tert*-butyl (3*R*)-3-[[7-(3-hydroxy-1-naphthyl)-4-piperazin-1-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*] pyrimidin-2-yl]oxymethyl]pyrrolidine-1-carboxylate: NH₃ was bubbled into methanol (10 mL) at -78 °C for 30 minutes. Benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[(3*R*)-1-tert-butoxycarbonylpyrrolidin-3-yl] methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (0.25 g, 319 μmol) and 10% Pd/C (0.10 g) were added into the mixture and stirred at 10 °C for 1 hour under H₂ (15 psi). The mixture was filtered and concentrated under vacuum to give *tert*-butyl (3*R*)-3-[[7-(3-hydroxy-1-naphthyl)-4-piperazin-1-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*] pyrimidin-2-yl]oxymethyl]pyrrolidine-1-carboxylate (0.17 g, 303 μmol). ES+APCI MS *m/z* 561.3 [M+H]⁺.



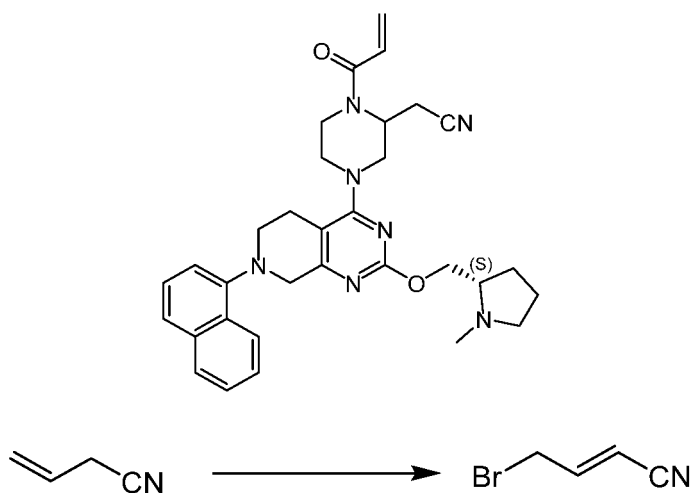
[0582] Step C: *tert*-butyl (3*R*)-3-[[7-(3-hydroxy-1-naphthyl)-4-(4-prop-2-enoylpiperazin-1-yl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-2-yl]oxymethyl]pyrrolidine-1-carboxylate: To a solution of *tert*-butyl (3*R*)-3-[[7-(3-hydroxy-1-naphthyl)-4- piperazin-1-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-2-yl]oxymethyl]pyrrolidine-1-carboxylate (0.17 g, 303 μmol) and Et₃N (153 mg, 1.52 mmol, 211 μL) in dichloromethane (4.00 mL) cooled to -40 °C was added prop-2-enoyl prop-2-enoate (26.8 mg, 212 μmol) and the mixture stirred at -40 °C for 0.5 h. The mixture was quenched by addition of methanol (0.10 mL) and concentrated under vacuum. The residue was purified by column chromatography (Al₂O₃, dichloromethane/methane = 10/1) to give *tert*-butyl (3*R*)-3-[[7-(3-hydroxy-1-naphthyl)-4-(4-prop-2-enoylpiperazin-1-yl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-2-yl]oxymethyl]pyrrolidine-1-carboxylate (0.12 g, 189 μmol). ES+APCI MS *m/z* 615.5 [M+H]⁺.



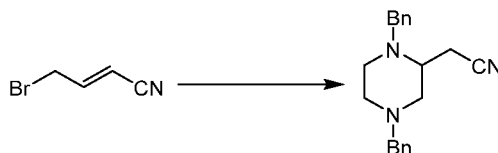
[0583] Step D: 1-[4-[7-(3-hydroxy-1-naphthyl)-2-[[*(3R)*-pyrrolidin-3-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one: A mixture of *tert*-butyl (*(3R)*-3-[[7-(3-hydroxy-1-naphthyl)-4-(4-prop-2-enoylpiperazin-1-yl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-2-yl]oxymethyl]pyrrolidine-1-carboxylate (0.10 g, 163 μ mol) and TFA (278 mg, 2.44 mmol, 181 μ L) in dichloromethane (0.20 mL) was stirred at 10 °C for 1 hour. The mixture was quenched by addition of $\text{NH}_3 \cdot \text{H}_2\text{O}$ and the pH adjusted until the pH = 7. The mixture was purified by prep-HPLC (column: Venusil XBP C8 150*25*10 μ m; mobile phase: [water (0.225% Formic Acid)-ACN]; B%: 15%-45%, 10min) to give 1-[4-[7-(3-hydroxy-1-naphthyl)-2-[[*(3R)*-pyrrolidin-3-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one (22.8 mg, 42.9 μ mol). ES+APCI MS m/z 515.4 $[\text{M}+\text{H}]^+$.

EXAMPLE 147

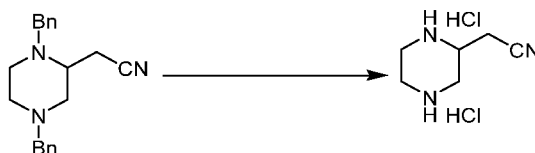
2-[4-[2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-7-(1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile



[0584] Step A: (Z) and (E)-4-bromobut-2-enenitrile: To a solution of but-3-enenitrile (98 g, 1.46 mol, 118 mL) in *tert*-butanol (150 mL) and petroleum ether (575 mL) was added a solution of Br₂ (233 g, 1.46 mol, 75.3 mL) in *tert*-butanol (150 mL) at 15 °C and the reaction stirred for 30 minutes. To the reaction was next added an ethanol solution of sodium ethoxide (100 g, 0.6 mol, 850 mL). The reaction mixture was stirred for 2 hours at the 15 °C. The reaction was next filtered and the filtrate concentrated under vacuum. The residue was purified by column chromatography using 2→20% ethyl acetate/petroleum ether as eluent to give a mixture of (Z) and (E)-4-bromobut-2-enenitrile (141 g, *E/Z* = 2.5/1, crude) as a slight yellow oil. ¹H NMR (400MHz, chloroform-d,) (*E*), δ = 6.79 (td, *J* = 7.2, 16.0 Hz, 1H), 5.63 (d, *J* = 16.0 Hz, 1H), 4.00 (dd, *J* = 1.2, 6.8 Hz, 2H); (*Z*), δ = 6.66 (td, *J* = 8.0, 10.8 Hz, 1H), 5.44 (d, *J* = 10.8 Hz, 1H), 4.16 (dd, *J* = 0.8, 8.0 Hz, 2H).

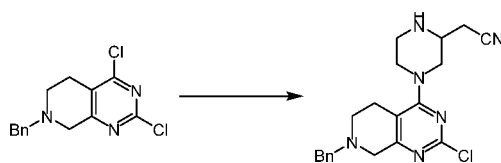


[0585] Step B: 2-(1,4-dibenzylpiperazin-2-yl)acetonitrile: To a mixture of *N,N'*-dibenzylethane-1,2-diamine (115 g, 480 mmol, 113 mL) and TEA (97.0 g, 959 mmol, 133 mL) in toluene (1 L) was added 4-bromobut-2-enenitrile (70 g, crude) dropwise at 0 °C and the reaction stirred at 15 °C for 12 hours. The reaction mixture was filtered and the filtrate concentrated under reduced pressure. The residue was purified by column chromatography using 5→50% EtOAc/Petroleum Ether as eluent to give 2-(1,4-dibenzylpiperazin-2-yl)acetonitrile (82 g, 240 mmol, two steps 37 % yield, 89.3% purity) as a slight yellow semisolid. ES+APCI MS *m/z* 306.3 [*M*+*H*]⁺. ¹H NMR (400MHz, chloroform-d) δ = 7.40 - 7.23 (m, 10H), 3.85 - 3.76 (m, 1H), 3.54 - 3.44 (m, 3H), 3.07 - 2.96 (m, 1H), 2.94 - 2.84 (m, 1H), 2.68 - 2.35 (m, 7H).

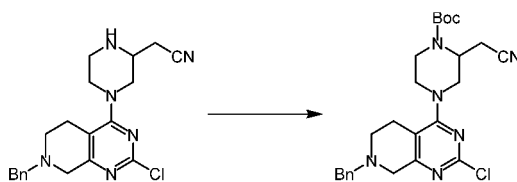


[0586] Step C: 2-piperazin-2-ylacetonitrile: To a solution of 2-(1,4-dibenzylpiperazin-2-yl)acetonitrile (164 g, 536 mmol) in DCE (1500 mL) was added 1-chloroethyl carbonochloridate (306 g, 2.14 mol) dropwise at 0 °C. After addition, the reaction mixture was

heated to 85 °C for approximately 48 hours. The dichloroethane was evaporated and the residue was taken up in MeOH (1500 mL) and heated to 70 °C for 1 hour. The reaction mixture was concentrated under reduced pressure and the solids triturated with MTBE (3X3 L) and the solids dried under reduced pressure to give 2-piperazin-2-ylacetonitrile. The crude product was purified by recrystallization with Ethanol and water (8:1, v:v) to give 2-piperazin-2-ylacetonitrile as an off-white solid (53 g, 428 mmol, 40.0 % yield, 96.4% purity, 2 HCl). ES+APCI MS m/z 126.2 $[M+H]^+$. 1H NMR (400MHz, D₂O) δ = 4.01 - 3.96 (m, 1H), 3.81 - 3.67 (m, 3H), 3.46 - 3.27 (m, 3H), 3.09 (d, J = 6.0 HZ, 2H).

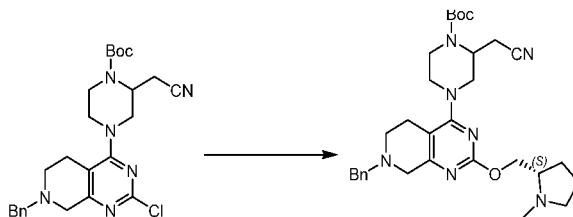


[0587] Step D: 2-[4-(7-benzyl-2-chloro-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl]acetonitrile: To a mixture of 7-benzyl-2,4-dichloro-6,8-dihydro-5H-pyrido[3,4-d]pyrimidine (1.2 g, 4.08 mmol) and 2-piperazin-2-ylacetonitrile (808 mg, 4.08 mmol, 2HCl) in dioxane (24 mL) was added DIEA (2.64 g, 20.4 mmol, 3.55 mL). The reaction mixture was stirred at 50 °C for 3 hours. Upon completion, the reaction mixture was diluted with water (50 mL) and the aqueous layer extracted with EtOAc (3 × 80 mL). The combined organic layers were washed with brine (30 mL), dried over Na₂SO₄ and concentrated under vacuum to give 2-[4-(7-benzyl-2-chloro-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl]acetonitrile (1.56 g, 4.07 mmol, 100% yield) as a brown solid.

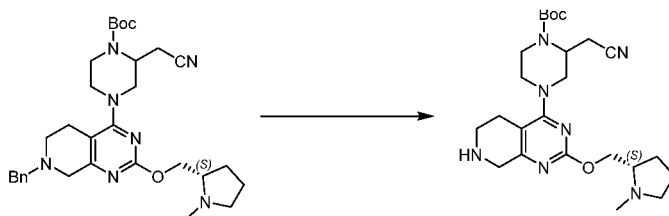


[0588] Step E: tert-butyl 4-(7-benzyl-2-chloro-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl)-2-(cyanomethyl)piperazine-1-carboxylate: To 2-[4-(7-benzyl-2-chloro-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl]acetonitrile (1.56 g, 4.07 mmol) was added (Boc)₂O (9.50 g, 43.5 mmol, 10 mL) and the mixture heated to 50 °C for 2 hours. Upon completion, the reaction mixture was purified by silica gel chromatography using 10→50% EtOAc/Petroleum Ether as eluent to give *tert*-butyl 4-(7-benzyl-2-chloro-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-

4-yl)-2-(cyanomethyl)piperazine-1-carboxylate (1.2 g, 2.44 mmol, 59.9% yield, 98.3% purity) as brown solid. ES+APCI MS m/z 483.3 $[M+H]^+$. 1H NMR (400MHz, CHLOROFORM- d) δ = 7.39 - 7.27 (m, 5H), 4.59 (br s, 1H), 4.06 (br d, J = 13.6 Hz, 2H), 3.90 (br d, J = 11.6 Hz, 1H), 3.74 - 3.49 (m, 4H), 3.29 (dd, J = 4.0, 13.6 Hz, 1H), 3.18 (br s, 1H), 3.10 - 3.00 (m, 1H), 2.85 - 2.55 (m, 6H), 1.53 - 1.45 (m, 9H).

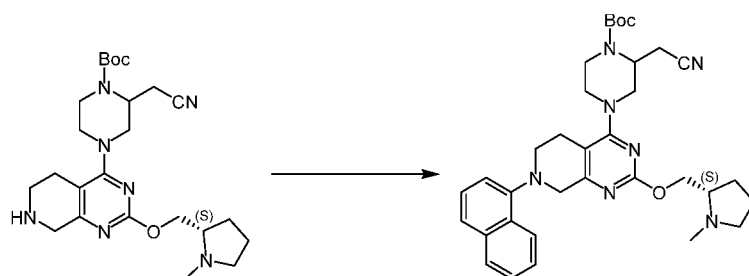


[0589] Step F: *tert*-butyl 4-[7-benzyl-2-[(2*S*)-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl)-2-(cyanomethyl)piperazine-1-carboxylate: To a solution of [(2*S*)-1-methylpyrrolidin-2-yl]methanol (655.74 mg, 5.69 mmol, 676 μ L in THF (25 mL) was added NaH (182 mg, 4.55 mmol, 60% purity) at 0 °C and the reaction mixture stirred at 0 °C for 0.5 h. To the mixture was added *tert*-butyl 4-(7-benzyl-2-chloro-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl)-2-(cyanomethyl) piperazine-1-carboxylate (1.1 g, 2.28 mmol) and the reaction mixture stirred at 70 °C for 12 hours in a sealed tube under N_2 . Upon completion, the reaction mixture was quenched by addition of saturated NH_4Cl (20 mL) and the aqueous layer extracted with EtOAc (2×50 mL). The combined organics were washed with brine (10 mL), dried over Na_2SO_4 , filtered and concentrated under vacuum to give *tert*-butyl 4-[7-benzyl-2-[(2*S*)-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl)-2-(cyanomethyl)piperazine-1-carboxylate (1.1 g, 1.86 mmol, 81.7% yield, 95% purity) as a brown solid. ES+APCI MS m/z 562.4 $[M+H]^+$.



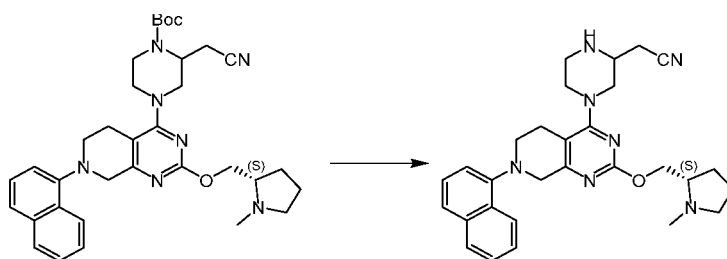
[0590] Step G: *tert*-butyl 2-(cyanomethyl)-4-[2-[(2*S*)-1-methylpyrrolidin-2-yl]methoxy]-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl)piperazine-1-carboxylate: Ammonia was bubbled into MeOH (30 mL) for 5 minutes. To this solution was added *tert*-butyl 4-[7-benzyl-2-

[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-2-(cyanomethyl)piperazine-1-carboxylate (950 mg, 1.69 mmol) and 10% Pd/C (200 mg). The suspension was degassed under vacuum and purged with H₂ several times and the mixture stirred under H₂ (15 psi) at 40°C for 9 hours. Upon completion, the reaction mixture was filtered and concentrated under vacuum. The residue was purified by prep-HPLC (column: Phenomenex Synergi Max-RP 250*50mm*10 um; mobile phase: [water(0.225%Formic Acid)-ACN]; B%: 15%-40%, 30; 58% min) to give *tert*-butyl 2-(cyanomethyl)-4-[2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (400 mg, 830 umol, 49.1% yield, 97.8% purity) was obtained as brown oil. ES+APCI MS *m/z* 472.4 [M+H]⁺. ¹H NMR (400MHz, CHLOROFORM-*d*) δ = 4.59 (br s, 1H), 4.43 - 4.28 (m, 1H), 4.18 - 4.09 (m, 1H), 4.07 - 3.90 (m, 4H), 3.88 - 3.78 (m, 1H), 3.21 (br dd, *J* = 3.2, 13.6 Hz, 2H), 3.16 - 3.05 (m, 2H), 3.03 - 2.90 (m, 2H), 2.82 - 2.55 (m, 4H), 2.48 (s, 3H), 2.33 - 2.22 (m, 1H), 2.11 - 2.00 (m, 1H), 1.91 - 1.62 (m, 4H), 1.51 (s, 9H).

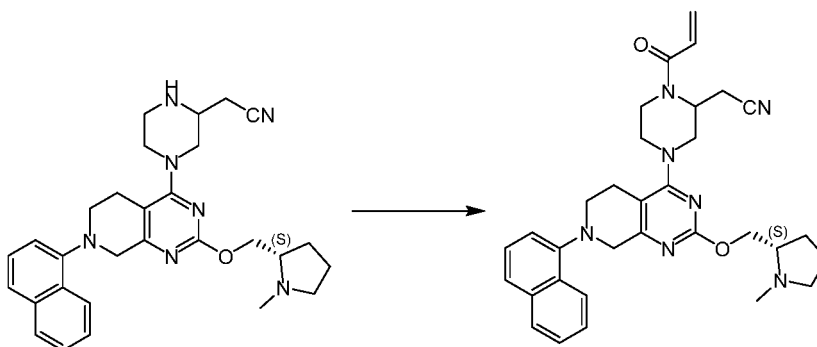


[0591] Step H: *tert*-butyl 2-(cyanomethyl)-4-[2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-7-(1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate: To a solution of *tert*-butyl 2-(cyanomethyl)-4-[2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (150 mg, 318 umol), 1-bromonaphthalene (98.8 mg, 477 umol, 66.3 uL), Cs₂CO₃ (311 mg, 954 umol), and RuPhos (29.7 mg, 63.6 umol) in toluene (3 mL) was added Pd₂(dba)₃ (29.1 mg, 31.8 umol) and the suspension was degassed under vacuum and purged with N₂ 3 times. The reaction mixture was stirred at 100 °C for 12 hours. The mixture was partitioned between water (10 mL) and EtOAc (20 mL) and the layers separated. The aqueous layer was extracted subsequently with EtOAc (3 × 20 mL). The combined organics were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by reverse flash to give *tert*-butyl 2-(cyanomethyl)-4-[2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-7-(1-

naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (70 mg, 111 μ mol, 35.0 % yield, 95.0 % purity) as brown solid. ES+APCI MS m/z 598.6 $[M+H]^+$. 1H NMR (400 MHz, chloroform-*d*) δ = 8.21 - 8.20 (m, 1H), 7.87 - 7.85 (m, 1H), 7.61 - 7.59 (d, J =8.0 Hz, 1H), 7.51 - 7.49 (m, 2H), 7.45 - 7.41 (t, J =7.6 Hz, 1H), 7.15 - 7.13 (d, J =7.2 Hz, 1H), 4.63 (br s, 1H), 4.46 (br s, 1H), 4.33 - 4.28 (m, 4H), 4.10 - 4.07 (m, 2H), 3.97 - 3.94 (br d, J =11.6 Hz, 1H), 3.46 (br s, 1H), 3.31 - 3.27 (br d, J =14.0 Hz, 1H), 3.07 - 3.01 (m, 2H), 2.77 (br s, 3H), 2.55 (br s, 3H), 2.35 (br s, 1H), 1.82 (br s, 7H), 1.52 (s, 9H).



[0592] Step I: 2-[4-[2-[[*(2S)*]-1-methylpyrrolidin-2-yl]methoxy]-7-(1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-2-yl]acetonitrile: To a solution of *tert*-butyl 2-(cyanomethyl)-4-[2-[[*(2S)*]-1-methylpyrrolidin-2-yl]methoxy]-7-(1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (60 mg, 100 μ mol) in DCM (0.1 mL) was added TFA (154 mg, 1.35 mmol, 0.1 mL) at 15 °C and stirred at 15 °C for 1 hour. The reaction mixture was concentrated under vacuum to give 2-[4-[2-[[*(2S)*]-1-methylpyrrolidin-2-yl]methoxy]-7-(1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-2-yl]acetonitrile (50 mg) as brown oil.

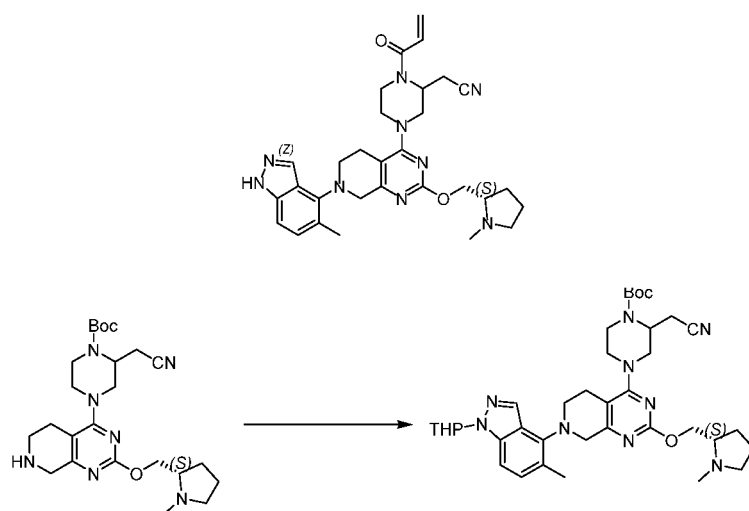


[0593] Step J: 2-[4-[2-[[*(2S)*]-1-methylpyrrolidin-2-yl]methoxy]-7-(1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile: To a solution of 2-[4-

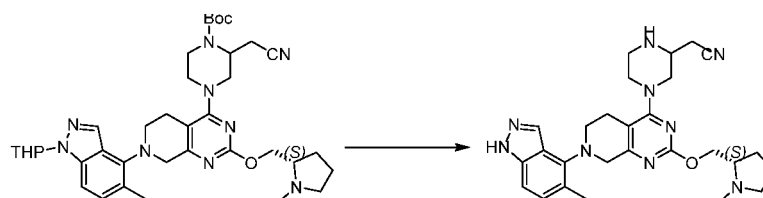
[2-[[[(2S)-1-methylpyrrolidin-2-yl]methoxy]-7-(1-naphthyl)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazin-2-yl]acetonitrile (50 mg, 81.8 μ mol, TFA) and DIEA (106 mg, 817 μ mol, 142 μ L) in DCM (0.2 mL) was added prop-2-enoyl prop-2-enoate (11.3 mg, 89.9 μ mol) at 0 °C and the reaction stirred at 0-15 °C for 1.5 hour. The reaction mixture was concentrated under vacuum. The residue was purified by prep-HPLC (column: Phenomenex Synergi C18 150*30mm*4 μ m; mobile phase: [water(0.225%Formic Acid)-ACN]; B%: 15%-45%, 10.5min) to give 2-[4-[2-[[[(2S)-1-methylpyrrolidin-2-yl]methoxy]-7-(1-naphthyl)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile (9.16 mg, 15.1 μ mol, 18.5 % yield, 98.7 % purity, Formate) as yellow oil. ES+APCI MS m/z 552.5 $[M+H]^+$. 1H NMR (400 MHz, chloroform- d) δ = 8.45 (br s, 1H), 8.22 - 8.19 (m, 1H), 7.87 - 7.85 (m, 1H), 7.62 - 7.60 (d, J =8.0 Hz, 1H), 7.51 - 7.49 (m, 2H), 7.45 - 7.43 (t, J =7.6 Hz, 1H), 7.15 - 7.13 (d, J =7.2 Hz, 1H), 6.60 (br s, 1H), 6.42 - 6.38 (m, 1H), 5.84 - 5.82 (br d, J =10.8 Hz, 1H), 5.08 (br s, 1H), 4.78 - 4.53 (br dd, J =6.8, 11.6 Hz, 2H), 4.42 - 4.40 (m, 1H), 4.27 (br s, 2H), 4.21 - 4.18 (br d, J =14.0 Hz, 1H), 4.12-3.78 (br d, J =12.8 Hz, 2H), 3.68 - 3.07 (m, 7H), 3.05 - 2.84 (m, 3H), 2.77 (d, J =1.6 Hz, 3H), 2.71 - 2.64 (m, 1H), 2.26 - 2.17 (m, 1H), 2.11 - 2.03 (m, 1H), 2.02 - 1.88 (m, 2H).

EXAMPLE 148

2-[4-[7-(5-methyl-1H-indazol-4-yl)-2-[[[(2S)-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile

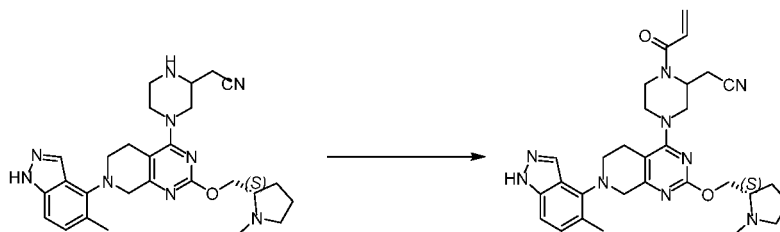


[0594] Step A: *tert*-butyl 2-(cyanomethyl)-4-[2-[[[(2*S*)-1-methylpyrrolidin-2-yl]methoxy]-7-(5-methyl-1-tetrahydropyran-2-yl-indazol-4-yl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate: To a solution of *tert*-butyl 2-(cyanomethyl)-4-[2-[[[(2*S*)-1-methylpyrrolidin-2-yl]methoxy]-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (200 mg, 424 μ mol), 4-bromo-5-methyl-1-tetrahydropyran-2-yl-indazole (188 mg, 636 μ mol), RuPhos (39.6 mg, 84.8 μ mol) and Cs₂CO₃ (414 mg, 1.27 mmol) in toluene (6 mL) was added Pd₂(dba)₃ (38.8 mg, 42.4 μ mol) and the reaction stirred at 100 °C for 12 hours under N₂. Upon completion, the mixture was purified directly by silica gel chromatography (PE: EtOAc=3:1 to 0:1) to give *tert*-butyl 2-(cyanomethyl)-4-[2-[[[(2*S*)-1-methylpyrrolidin-2-yl]methoxy]-7-(5-methyl-1-tetrahydropyran-2-yl-indazol-4-yl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (120 mg, 149 μ mol, 35.1% yield, 85.0% purity) as a brown solid. ES+APCI MS *m/z* 686.6 [M+H]⁺. ¹H NMR (400MHz, CHLOROFORM-*d*) δ = 8.04 (d, *J* = 2.0 Hz, 1H), 7.33 - 7.29 (m, 2H), 5.70 (dd, *J* = 2.4, 9.2 Hz, 1H), 4.62 (br s, 1H), 4.39 (br s, 1H), 4.34 - 4.28 (m, 2H), 4.20 - 4.14 (m, 1H), 4.05 (br d, *J* = 12.0 Hz, 2H), 3.91 (br d, *J* = 12.4 Hz, 1H), 3.81 - 3.72 (m, 1H), 3.53 (br t, *J* = 4.8 Hz, 2H), 3.27 (br d, *J* = 10.8 Hz, 2H), 3.10 (br d, *J* = 6.8 Hz, 1H), 3.06 - 2.96 (m, 1H), 2.90 - 2.65 (m, 5H), 2.59 (br d, *J* = 10.2 Hz, 1H), 2.50 (s, 3H), 2.43 (s, 3H), 2.35 - 2.26 (m, 1H), 2.23 - 2.15 (m, 1H), 2.11 (br s, 2H), 1.90 - 1.65 (m, 7H), 1.54 (s, 9H).



[0595] Step B: 2-[4-[7-(5-methyl-1*H*-indazol-4-yl)-2-[[[(2*S*)-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-2-yl]acetonitrile: To a solution of *tert*-butyl 2-(cyanomethyl)-4-[2-[[[(2*S*)-1-methylpyrrolidin-2-yl]methoxy]-7-(5-methyl-1-tetrahydropyran-2-yl-indazol-4-yl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (150 mg, 219 μ mol) in DCM (0.2 mL) was added TFA (616 mg, 5.40 mmol, 0.4 mL) and the reaction mixture stirred at 15 °C for 12 hours. Upon completion, the solvent was removed under vacuum to give 2-[4-[7-(5-methyl-1*H*-indazol-4-yl)-2-[[[(2*S*)-1-

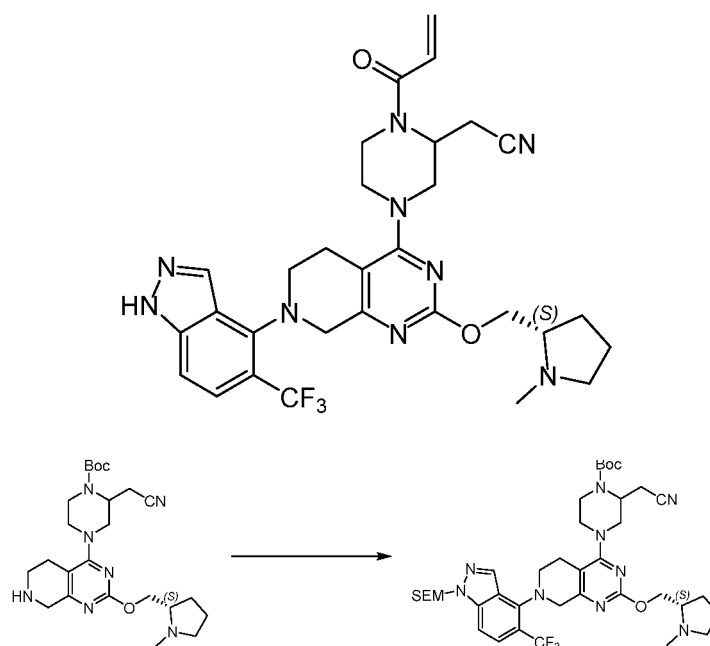
methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-2-yl]acetonitrile (159 mg, 218 μ mol, 99.6% yield, 2TFA) as a red oil.



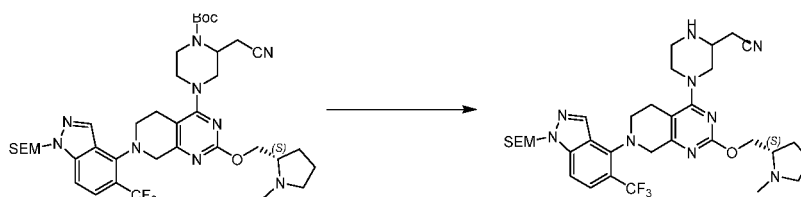
[0596] Step C: 2-[4-[7-(5-methyl-1*H*-indazol-4-yl)-2-[[*(2S)*]-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile: To a solution of 2-[4-[7-(5-methyl-1*H*-indazol-4-yl)-2-[[*(2S)*]-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-2-yl]acetonitrile (159 mg, 218 μ mol, 2TFA) and DIEA (366 mg, 2.83 mmol, 493 μ L) in DCM (4 mL) at -40°C was added prop-2-enoyl prop-2-enoate (24.7 mg, 196 μ mol,) and the reaction mixture was stirred at -20 °C for 1 hour. Upon completion, the reaction mixture was quenched by addition of water (2 mL) and the aqueous layer separated and back extracted with DCM (2 $\times$ 10 mL). The combined organics were concentrated under vacuum and the residue purified by silica gel chromatography (DCM: MeOH=50:1 to 5:1) followed by purification by reverse prep HPCL (column: Phenomenex Synergi C18 150*25*10 μ m; mobile phase: [water(0.225%Formic Acid)-ACN]; B%: 4%-34% over 10 minutes) to give 2-[4-[7-(5-methyl-1*H*-indazol-4-yl)-2-[[*(2S)*]-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile (1.77 mg, 3.10 μ mol). ES+APCI MS *m/z* 556.5 [M+H]⁺. ¹H NMR (400MHz, CHLOROFORM-*d*) δ = 8.00 (s, 1H), 7.18 (br s, 1H), 7.16 - 7.11 (m, 1H), 6.52 (br s, 1H), 6.37 - 6.21 (m, 1H), 5.75 (br d, *J* = 10.4 Hz, 1H), 4.99 (br s, 1H), 4.67 (br dd, *J* = 6.4, 11.6 Hz, 1H), 4.34 (br dd, *J* = 3.9, 11.6 Hz, 1H), 4.24 (s, 2H), 4.11 (br d, *J* = 12.8 Hz, 1H), 3.94 (br s, 1H), 3.57 - 3.40 (m, 4H), 3.29 (br d, *J* = 13.8 Hz, 1H), 3.19 (br s, 1H), 3.02 (br dd, *J* = 12.4, 19.7 Hz, 2H), 2.87 (br dd, *J* = 8.4, 16.4 Hz, 2H), 2.76 - 2.58 (m, 6H), 2.35 (s, 3H), 2.22 - 2.10 (m, 1H), 2.01 (br d, *J* = 8.4 Hz, 1H), 1.89 (br s, 2H).

EXAMPLE 149

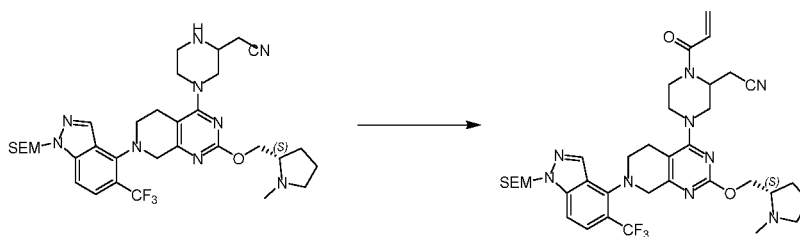
2-[4-[2-[[*(2S)*]-1-methylpyrrolidin-2-yl]methoxy]-7-[5-(trifluoromethyl)-1*H*-indazol-4-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile



[0597] Step A: *tert*-butyl 2-(cyanomethyl)-4-[2-[[[(2*S*)-1-methylpyrrolidin-2-yl] methoxy]-7-[5-(trifluoromethyl)-1-(2-trimethylsilylethoxymethyl)indazol-4-yl]-6,8-dihydro-5*H*-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate: *tert*-butyl 2-(cyanomethyl)-4-[2-[[[(2*S*)-1-methylpyrrolidin-2-yl] methoxy]-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (130 mg, 276 μ mol), 2-[[4-bromo-5-(trifluoromethyl)indazol-1-yl]methoxy]ethyltrimethylsilane (120 mg, 303 μ mol), $\text{Pd}_2(\text{dba})_3$ (50.5 mg, 55.1 μ mol), RuPhos (51.5 mg, 110 μ mol), Cs_2CO_3 (225 mg, 689 μ mol) in toluene (3.00 mL) was de-gassed with N_2 and then heated to 90 $^\circ\text{C}$ for 12 hours under N_2 . Upon completion, the mixture was filtered and the filtrate was concentrated. The residue was purified by prep-TLC (EtOAc/MeOH 8/1) to give *tert*-butyl 2-(cyanomethyl)-4-[2-[[[(2*S*)-1-methylpyrrolidin-2-yl] methoxy]-7-[5-(trifluoromethyl)-1-(2-trimethylsilylethoxymethyl)indazol-4-yl]-6,8-dihydro-5*H*-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (140 mg, 169 μ mol, 61.4 % yield, 95.0 % purity) as a yellow solid. ES+APCI MS m/z 786.3 $[\text{M}+\text{H}]^+$.

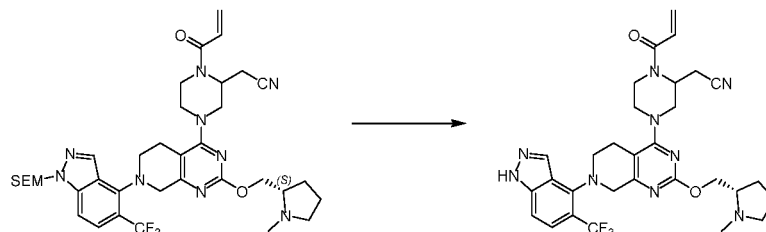


[0598] Step B: 2-[4-[2-[[*(2S)*-1-methylpyrrolidin-2-yl] methoxy]-7-[5-(trifluoromethyl)-1-(2-trimethylsilylethoxymethyl)indazol-4-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-2-yl]acetonitrile: To a solution of *tert*-butyl 2-(cyanomethyl)-4-[2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-7-[5-(trifluoromethyl)-1-(2-trimethylsilylethoxymethyl)indazol-4-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (140 mg, 178 μ mol) in DCM (3.00 mL) was added 2,6-dimethylpyridine (229 mg, 2.14 mmol) and TMSOTf (238 mg, 1.07 mmol) at 0 °C. The mixture was stirred at 15 °C for 2 hours. Upon completion, the mixture was quenched by addition of MeOH (0.5 mL) and concentrated under vacuum to give 2-[4-[2-[[*(2S)*-1-methylpyrrolidin-2-yl] methoxy]-7-[5-(trifluoromethyl)-1-(2-trimethylsilylethoxymethyl)indazol-4-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-2-yl]acetonitrile (200 mg, crude) as a yellow oil which was used directly in the next step without further purification. ES+APCI MS m/z 686.6 $[M+H]^+$.



[0599] Step C: 2-[4-[2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-7-[5-(trifluoromethyl)-1-(2-trimethylsilylethoxymethyl)indazol-4-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile: To a solution of 2-[4-[2-[[*(2S)*-1-methylpyrrolidin-2-yl] methoxy]-7-[5-(trifluoromethyl)-1-(2-trimethylsilylethoxymethyl)indazol-4-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-2-yl]acetonitrile (122 mg, 178 μ mol) and DIEA (138 mg, 1.07 mmol, 186 μ L) in DCM (3.00 mL) was added prop-2-enoyl prop-2-enoate (18.0 mg, 143 μ mol) dropwise at 0 °C. The mixture was stirred at 20 °C for 1.5 hours. Upon completion, the mixture was diluted with water (0.5 mL) and extracted with EtOAc (2 $\times$ 5 mL). The organic layers were dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by prep-TLC (EA/MeOH 10/1) and prep-HPLC (column: Boston pH-lex 150*25 10 μ m; mobile phase: [water(0.1%TFA)-ACN]; B%: 39%-69%, 10min) to give 2-[4-[2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-7-[5-(trifluoromethyl)-1-(2-

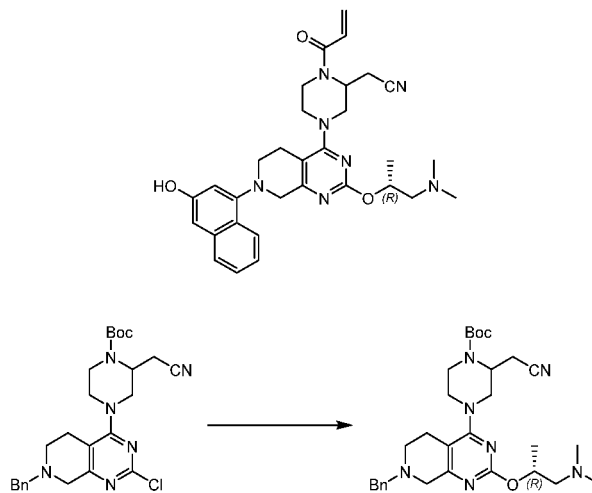
trimethylsilylethoxymethyl)indazol-4-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile (54.0 mg, 43.8 μ mol). ES+APCI MS m/z 740.6 $[M+H]^+$.



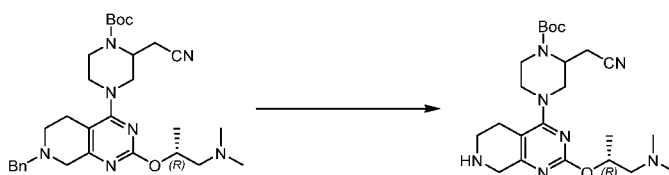
[0600] Step D: 2-[4-[2-[[*(2S)*]-1-methylpyrrolidin-2-yl]methoxy]-7-[5-(trifluoromethyl)-1*H*-indazol-4-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile: To a solution of 2-[4-[2-[[*(2S)*]-1-methylpyrrolidin-2-yl]methoxy]-7-[5-(trifluoromethyl)-1-(2-trimethylsilylethoxymethyl)indazol-4-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile (20 mg, 27.0 μ mol) in DCM (60 μ L) was added TFA (30.8 mg, 270 μ mol). The mixture was stirred at 20 °C for 1 hour. The reaction was not complete so additional TFA (30.8 mg) was added and the reaction stirred at 20 °C for an additional 0.5 hour. Upon completion, the pH of the mixture was adjusted to 8 by addition of saturated aqueous NaHCO_3 (1 mL) and the aqueous layer extracted with EtOAc (2×5 mL). The combined organics were washed with brine (3 mL), dried over Na_2SO_4 and concentrated under vacuum. The residue was diluted with MeOH (0.5 mL) and $\text{NH}_3 \cdot \text{H}_2\text{O}$ (0.5 mL) added and the mixture stirred at 20 °C for 0.5 hour. The mixture was purified by prep-HPLC (column: Phenomenex Synergi C18 150*30mm*4 μ m; mobile phase: [water(0.225%Formic Acid)-ACN]; B%: 15%-45%, 10.5min) to give 2-[4-[2-[[*(2S)*]-1-methylpyrrolidin-2-yl]methoxy]-7-[5-(trifluoromethyl)-1*H*-indazol-4-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile (2.68 mg, 3.99 μ mol) as a white solid. ES+APCI MS m/z 610.5 $[M+H]^+$. ^1H NMR (400 MHz, chloroform-*d*) δ = 8.22 (s, 1H), 7.68 (d, J =9.2 Hz, 1H), 7.45 (d, J =8.8 Hz, 1H), 6.60 (br s, 1H), 6.45 - 6.35 (m, 1H), 5.84 (br d, J =11.2 Hz, 1H), 5.09 (br s, 1H), 4.71 - 4.60 (m, 1H), 4.42 - 4.27 (m, 3H), 4.17 (br d, J =11.2 Hz, 1H), 4.01 (br d, J =12.4 Hz, 2H), 3.78 - 3.31 (m, 5H), 3.23 - 3.03 (m, 2H), 3.02 - 2.75 (m, 4H), 2.71 (s, 3H), 2.66 - 2.57 (m, 1H), 2.27 - 2.12 (m, 1H), 2.10 - 2.03 (m, 3H). ES+APCI MS m/z 610.1 $[M+H]^+$.

EXAMPLE 150

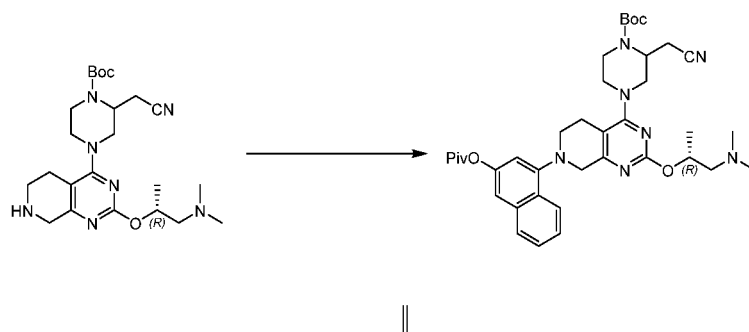
2-(1-acryloyl-4-(2-(((*R*)-1-(dimethylamino)propan-2-yl)oxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl)piperazin-2-yl)acetonitrile



[0601] Step A: *tert*-Butyl 4-[7-benzyl-2-[(1*R*)-2-(dimethylamino)-1-methyl-ethoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-2-(cyanomethyl)piperazine-1-carboxylate: To a mixture of *tert*-butyl 4-(7-benzyl-2-chloro-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl)-2-(cyanomethyl)piperazine-1-carboxylate (500 mg, 1.04 mmol), (2*R*)-1-(dimethylamino)propan-2-ol (214 mg, 2.07 mmol) and sodium *tert*-butoxide (298 mg, 3.11 mmol) in toluene (20 mL) was added BINAP (129 mg, 207 μ mol) and $\text{Pd}_2(\text{dba})_3$ (94.8 mg, 104 μ mol) and the mixture was sparged with nitrogen followed by stirring at 90 °C for 5 hr. The mixture was diluted with ethyl acetate (100 mL) and water (100 mL) and the organic layer was separated and dried over sodium sulfate, filtered and concentrated under vacuum. The residue was purified by reversed phase flash chromatography [water (0.1% Formic Acid water)/acetonitrile]. The desired fractions were collected and neutralized with saturated aqueous sodium carbonate solution (5 mL) and extracted with 10% MeOH/DCM (2 $\times$ 50 mL). The combined organics were dried over sodium sulfate, filtered and concentrated under vacuum to give *tert*-Butyl 4-[7-benzyl-2-[(1*R*)-2-(dimethylamino)-1-methyl-ethoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-2-(cyanomethyl)piperazine-1-carboxylate (300 mg, 480 μ mol) ES+APCI MS m/z 550.4 $[\text{M}+\text{H}]^+$.

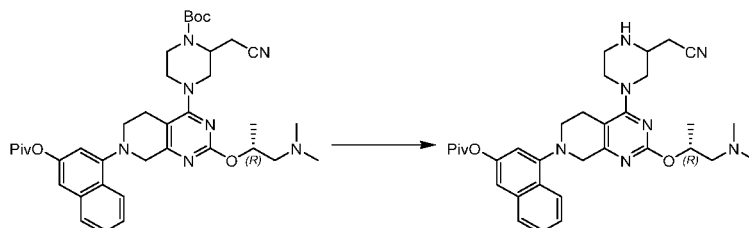


[0602] Step B: *tert*-butyl 2-(cyanomethyl)-4-[2-[(1*R*)-2-(dimethylamino)-1-methyl-ethoxy]-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate: To a solution of *tert*-butyl 4-[7-benzyl-2-[(1*R*)-2-(dimethylamino)-1-methyl-ethoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-2-(cyanomethyl)piperazine-1-carboxylate (1.1 g, 2.00 mmol) in MeOH (10 mL) was added a solution of NH₃ (792 mg, 46.5 mmol) in MeOH (3.96 g, 123.56 mmol, 5 mL), followed by 10% Pd/C (500 mg). The mixture was stirred at 40 °C for 12 hr under H₂ (15 psi). The reaction was filtered and the filtrate was concentrated under reduced pressure to dryness to give *tert*-butyl 2-(cyanomethyl)-4-[2-[(1*R*)-2-(dimethylamino)-1-methyl-ethoxy]-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (756 mg, crude) was obtained as a yellow solid. ES+APCI MS *m/z* 460.3 [M+H]⁺.

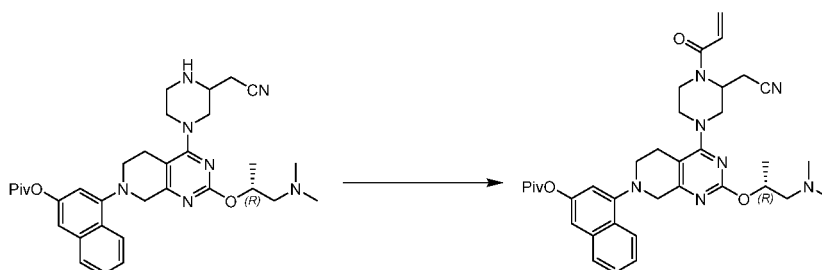


[0603] Step C: *tert*-butyl 2-(cyanomethyl)-4-[2-[(1*R*)-2-(dimethylamino)-1-methyl-ethoxy]-7-[3-(2,2-dimethylpropanoyloxy)-1-naphthyl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate: A mixture of (4-bromo-2-naphthyl) 2,2-dimethylpropanoate (304 mg, 990 μmol), *tert*-butyl 2-(cyanomethyl)-4-[2-[(1*R*)-2-(dimethylamino)-1-methyl-ethoxy]-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (350 mg, 761 μmol), [2-(2-aminoethyl)phenyl]-chloro-palladium, dicyclohexyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane (84.4 mg, 114 μmol) and Cs₂CO₃ (620 mg, 1.90 mmol) in toluene (10 mL) was purged with N₂ 3 times and the mixture stirred at 70 °C for 16 hours under N₂ atmosphere. The reaction mixture was poured into H₂O (50 mL) and extracted with ethyl acetate (50 mL × 3). The combined organics were washed with brine (30 mL), dried over anhydrous Na₂SO₄ and concentrated under vacuum to give a residue. The residue was purified by reversed phase flash [water (0.1 % formic acid)/acetonitrile] to give *tert*-butyl 2-(cyanomethyl)-4-[2-[(1*R*)-2-(dimethylamino)-1-methyl-ethoxy]-7-[3-(2,2-

dimethylpropanoyloxy)-1-naphthyl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (210 mg, 303 μ mol). ES+APCI MS m/z 686.4 $[M+H]^+$.

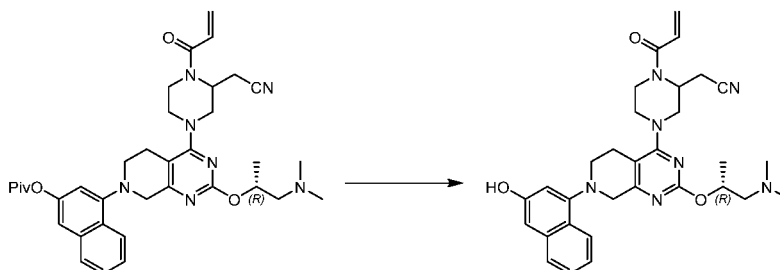


[0604] Step D: [4-[4-[3-(cyanomethyl)piperazin-1-yl]-2-[(1*R*)-2-(dimethylamino)-1-methyl-ethoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]-2-naphthyl] 2,2-dimethylpropanoate: To a solution of *tert*-butyl 2-(cyanomethyl)-4-[2-[(1*R*)-2-(dimethylamino)-1-methyl-ethoxy]-7-[3-(2,2-dimethylpropanoyloxy)-1-naphthyl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (210 mg, 306 μ mol) in dichloromethane (300 μ L) was added TFA (523 mg, 4.59 mmol, 340 μ L) and the mixture stirred at 15 $^{\circ}$ C for 2 hours. The mixture was concentrated under vacuum to give [4-[4-[3-(cyanomethyl)piperazin-1-yl]-2-[(1*R*)-2-(dimethylamino)-1-methyl-ethoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]-2-naphthyl] 2,2-dimethylpropanoate (214 mg, 305 μ mol). ES+APCI MS m/z 586.4 $[M+H]^+$.



[0605] Step E: [4-[4-[3-(cyanomethyl)-4-prop-2-enoyl-piperazin-1-yl]-2-[(1*R*)-2-(dimethylamino)-1-methyl-ethoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]-2-naphthyl] 2,2-dimethylpropanoate: To a mixture of [4-[4-[3-(cyanomethyl)piperazin-1-yl]-2-[(1*R*)-2-(dimethylamino)-1-methyl-ethoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]-2-naphthyl] 2,2-dimethylpropanoate (214 mg, 305 μ mol, TFA) and DIEA (395 mg, 3.06 mmol, 532 μ L) in dichloromethane (5.00 mL) cooled to -40 $^{\circ}$ C was added a solution of prop-2-enoyl prop-2-enoate (38.6 mg, 305 μ mol) in dichloromethane (1.00 mL) under nitrogen atmosphere. The mixture was warmed up to 0 $^{\circ}$ C and stirred for 1 hour. The mixture was concentrated under vacuum to give a residue. The residue was purified by reversed phase flash [water (0.1%

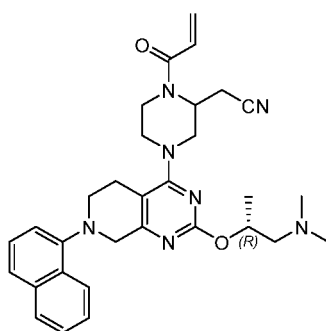
trifluoroacetic acid)\acetonitrile] to give [4-[4-[3-(cyanomethyl)-4-prop-2-enoyl- piperazin-1-yl]-2-[(1*R*)-2-(dimethylamino)-1-methyl-ethoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]-2-naphthyl] 2,2-dimethylpropanoate (100 mg, 156 μ mol). ES+APCI MS m/z 640.7 $[M+H]^+$.



[0606] Step F: 2-[4-[2-[(1*R*)-2-(dimethylamino)-1-methyl-ethoxy]-7-(3-hydroxy-1- naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile: To a solution of [4-[4-[3-(cyanomethyl)-4-prop-2-enoyl-piperazin- 1-yl]-2-[(1*R*)-2-(dimethylamino)-1-methyl-ethoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]-2-naphthyl] 2,2-dimethylpropanoate (90 mg, 141 μ mol) in THF (500 μ L) cooled to 0 °C was added NaOH (2 M, 281.34 μ L) and the mixture stirred at 15 °C for 16 hours. The pH of the mixture was adjusted to 7 by addition of a 20 % with formic acid solution. The aqueous solution was next extracted with dichloromethane (3 $\times$ 10 mL). The combined organics were dried over Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by prep-HPLC (column: Phenomenex Synergi C18 150*25*10 μ m; mobile phase: [water (0.225%Formic Acid)-ACN]; B%: 7%-37%, 10 min) to give 2-[4-[2-[(1*R*)-2-(dimethylamino)-1-methyl-ethoxy]-7-(3-hydroxy-1- naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile (5 mg, 8.82 μ mol, 6.27 % yield, 98 % purity) ES+APCI MS m/z 556.3 $[M+H]^+$. ¹H NMR (400MHz, methanol-*d*₄) δ = 8.54 (br s, 0.6 H), 8.07 (d, J = 8.4 Hz, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.37 (t, J = 7.2 Hz, 1H), 7.30 - 7.21 (m, 1H), 6.91 - 6.72 (m, 3H), 6.29 (br d, J = 16.4 Hz, 1H), 5.84 (br d, J = 11.2 Hz, 1H), 5.48 (br s, 1H), 5.26 - 4.96 (m, 1H), 4.57 (br s, 1H), 4.24 - 4.09 (m, 4H), 3.74 - 3.54 (m, 1H), 3.48 (m, 2H), 3.22 (m, 2H), 3.10 - 2.86 (m, 5H), 2.78 (br d, J = 14.4 Hz, 1H), 2.53 (br s, 6H), 1.37 (dd, J = 2.0, 6.4 Hz, 3H).

EXAMPLE 151

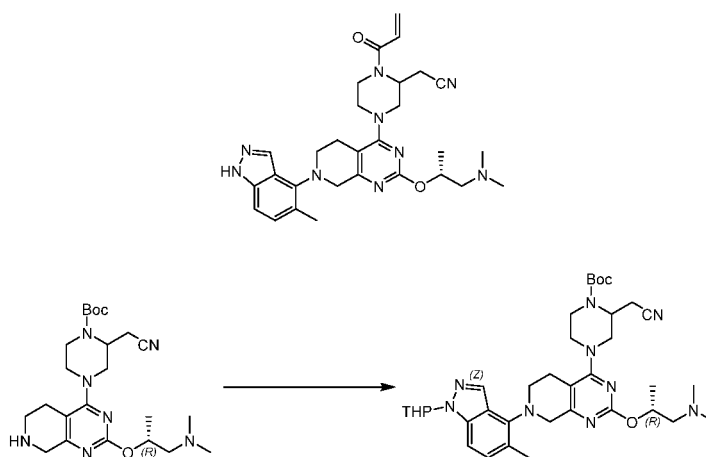
2-(1-acryloyl-4-(2-(((*R*)-1-(dimethylamino)propan-2-yl)oxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl)piperazin-2-yl)acetonitrile



[0607] (2-(1-acryloyl-4-(2-(((*R*)-1-(dimethylamino)propan-2-yl)oxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile was prepared following **Example 150** substituting 1-bromonaphthalene for (4-bromo-2-naphthyl) 2,2-dimethylpropanoate in Step C and omitting Step F. ES+APCI MS m/z 540.3 $[M+H]^+$. 1H NMR (400MHz, methanol- d_4) δ = 8.51 (s, 1H), 8.26 - 8.19 (m, 1H), 7.90 - 7.84 (m, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.53 - 7.47 (m, 2H), 7.46 - 7.39 (m, 1H), 7.25 - 7.18 (m, 1H), 6.82 (br s, 1H), 6.30 (br d, J = 17.2 Hz, 1H), 5.84 (br d, J = 10.4 Hz, 1H), 5.62-5.53 (m, 1H), 5.08 (br s, 1H), 4.70 - 4.39 (m, 1H), 4.26 - 4.11 (m, 4H), 3.94 - 3.59 (m, 1H), 3.48 - 3.34 (m, 2H), 3.28-3.18 (m, 3H), 3.13 - 2.92 (s, 5H), 2.79 - 2.61 (s, 6H), 1.48 (dd, J = 2.0, 6.0 Hz, 3H).

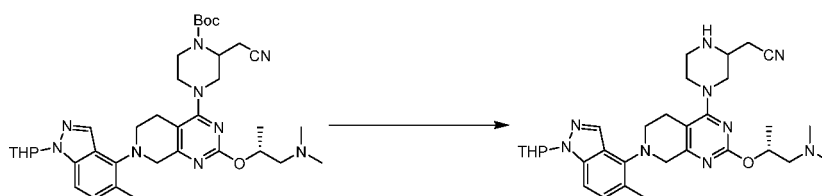
EXAMPLE 152

2-[4-[2-[(1*R*)-2-(dimethylamino)-1-methyl-ethoxy]-7-(5-methyl-1*H*-indazol-4-yl)-6,8-dihydro-5*H*-pyrido[3,4-d]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile



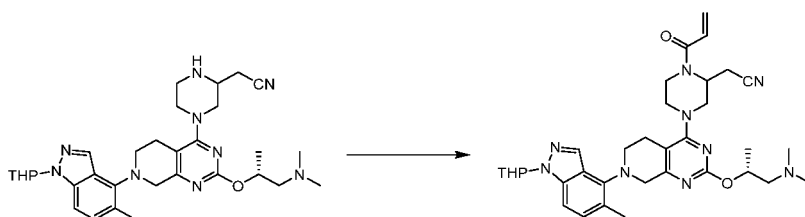
[0608] Step A: *tert*-butyl 2-(cyanomethyl)-4-[2-[(1*R*)-2-(dimethylamino)-1-methyl-ethoxy]-7-(5-methyl-1-tetrahydropyran-2-yl-indazol-4-yl)-6,8-dihydro-5*H*-pyrido[3,4-d]pyrimidin-4-

yl]piperazine-1-carboxylate: A mixture of *tert*-butyl 2-(cyanomethyl)-4-[2-[(1*R*)-2-(dimethylamino)-1-methyl-ethoxy]-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (0.50 g, 1.09 mmol), 4-bromo-5-methyl-1-tetrahydropyran-2-yl-indazole (482 mg, 1.63 mmol), *t*-BuONa (314 mg, 3.26 mmol) and [2-(2-aminoethyl)phenyl]-chloro-palladium;dicyclohexyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane (80.4 mg, 109 μ mol) in toluene (30 mL) was stirred at 70 °C for 10 hours. The mixture was diluted with water (10 mL) and the aqueous layer extracted with ethyl acetate (3 $\times$ 20 mL). The organic layers were washed with saturated sodium chloride solution (30 mL), dried over Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by reverse phase flash [water (Formic Acid, 0.1 %)/acetonitrile] to give *tert*-butyl 2-(cyanomethyl)-4-[2-[(1*R*)-2-(dimethylamino)-1-methyl-ethoxy]-7-(5-methyl-1-tetrahydropyran-2-yl-indazol-4-yl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (0.40 g, 522 μ mol, 48.0 % yield) as a yellow solid. ES+APCI MS *m/z* 674.3 [M+H]⁺. ¹H NMR (400MHz, chloroform-*d*) δ = 8.03 (d, *J* = 1.6 Hz, 1H), 7.31 - 7.27 (m, 2H), 5.68 (dd, *J* = 2.4, 9.6 Hz, 1H), 5.31 (br s, 1H), 4.61 (br s, 1H), 4.28 (s, 2H), 4.08 - 3.94 (m, 3H), 3.86 (br d, *J* = 11.6 Hz, 1H), 3.79 - 3.71 (m, 1H), 3.52 (br t, *J* = 4.8 Hz, 2H), 3.24 (br d, *J* = 12.8 Hz, 2H), 3.04 - 2.91 (m, 1H), 2.87 - 2.67 (m, 5H), 2.65 - 2.47 (m, 2H), 2.41 (s, 3H), 2.32 (br s, 6H), 2.17 (br d, *J* = 4.0 Hz, 1H), 2.09 (br s, 1H), 1.77 (br t, *J* = 10.8 Hz, 3H), 1.52 (s, 9H), 1.36 (d, *J* = 6.0 Hz, 3H).

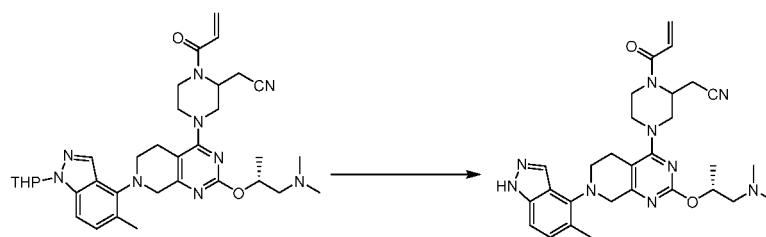


[0609] Step B: 2-[4-[2-[(1*R*)-2-(dimethylamino)-1-methyl-ethoxy]-7-(5-methyl-1-tetrahydropyran-2-yl-indazol-4-yl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-2-yl]acetonitrile: To a solution of *tert*-butyl 2-(cyanomethyl)-4-[2-[(1*R*)-2-(dimethylamino)-1-methyl-ethoxy]-7-(5-methyl-1-tetrahydropyran-2-yl-indazol-4-yl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (0.38 g, 564 μ mol) in dichloromethane (10 mL) was added TMSOTf (752 mg, 3.38 mmol) and 2,6-dimethylpyridine (725 mg, 6.77 mmol) at 0 °C and the mixture stirred at 10 °C for 1 hour. The mixture was quenched by addition of methanol (0.10 mL) and concentrated under vacuum. The residue was purified by reversed phase

chromatography [water (Formic Acid, 0.1 %)/acetonitrile]. The collected fractions were combined and the pH adjusted pH > 7 by addition of saturated sodium bicarbonate solution and the aqueous layer extracted with dichloromethane/methanol (10/1) (3 × 10 mL). The extracts were washed with saturated sodium chloride solution (10 mL), dried over Na₂SO₄, filtered and concentrated under vacuum to give 2-[4-[2-[(1*R*)-2-(dimethylamino)-1-methyl-ethoxy]-7-(5-methyl-1-tetrahydropyran-2-yl-indazol-4-yl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-2-yl]acetonitrile (0.30 g, crude) as a yellow solid. ES+APCI MS *m/z* 574.1 [M+H]⁺.



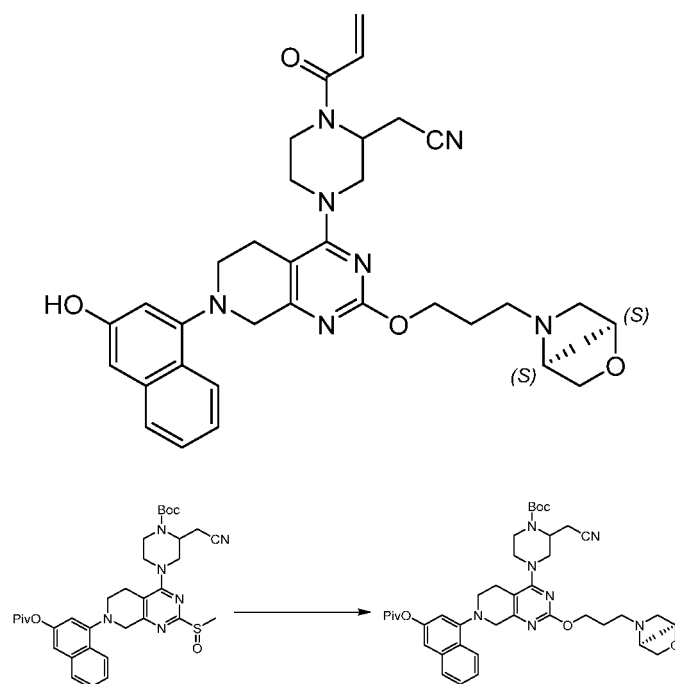
[0610] Step C: 2-[4-[2-[(1*R*)-2-(dimethylamino)-1-methyl-ethoxy]-7-(5-methyl-1-tetrahydropyran-2-yl-indazol-4-yl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile: To a solution of 2-[4-[2-[(1*R*)-2-(dimethylamino)-1-methyl-ethoxy]-7-(5-methyl-1-tetrahydropyran-2-yl-indazol-4-yl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-2-yl]acetonitrile (0.20 g, crude) and TEA (176mg, 1.74 mmol, 243 uL) in dichloromethane (1.00 mL) was added prop-2-enoyl prop-2-enoate (44.0 mg, 349 umol) at 0 °C. and the reaction stirred at 0 °C for 0.5 h. The mixture was quenched by addition of methanol (0.10 mL) and concentrated under vacuum. The residue was purified by reversed phase flash [water (Formic Acid, 0.1 %)/acetonitrile]. The collected fractions were combined and the pH adjusted to pH > 7 by addition of saturated sodium bicarbonate solution and the aqueous layer extracted with dichloromethane/methanol (10/1) (3 × 5.00 mL). The extracts were washed with saturated sodium chloride solution (1 × 10 mL), dried over Na₂SO₄, filtered and concentrated under vacuum to give 2-[4-[2-[(1*R*)-2-(dimethylamino)-1-methyl-ethoxy]-7-(5-methyl-1-tetrahydropyran-2-yl-indazol-4-yl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile (0.10 g, 127 umol, two steps 36.6 % yield) as a yellow solid. ES+APCI MS *m/z* 628.6 [M+H]⁺.



[0611] Step D: 2-[4-[2-[(1*R*)-2-(dimethylamino)-1-methyl-ethoxy]-7-(5-methyl-1*H*-indazol-4-yl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile: A mixture of 2-[4-[2-[(1*R*)-2-(dimethylamino)-1-methyl-ethoxy]-7-(5-methyl-1-tetrahydropyran-2-yl-indazol-4-yl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile (40 mg, 63.7 μ mol,) and TsOH (1.10 mg, 6.37 μ mol) in acetonitrile (3 mL) was stirred at 90 °C for 1 hour. The mixture was quenched by addition of saturated sodium bicarbonate (2 mL) at 0 °C and concentrated under vacuum. The residue was purified by column chromatography (Al_2O_3 , dichloromethane/methanol = 5/1). The collected desired fractions were concentrated under vacuum to give white solid. The residue was purified by prep-HPLC (column: Phenomenex Gemini 150*25mm*10 μ m; mobile phase: [water (10mM NH_4HCO_3)-ACN]; B%: 35%-65%, 3min) and (column: Boston Green ODS 150*30 5 μ ; mobile phase: [water (0.225%Formic Acid)-ACN]; B%: 15%-45%, 10min). The desired fractions were pooled and lyophilized to give 2-[4-[2-[(1*R*)-2-(dimethylamino)-1-methyl-ethoxy]-7-(5-methyl-1*H*-indazol-4-yl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile (2.99 mg, 5.50 μ mol). ES+APCI MS m/z 544.5 $[\text{M}+\text{H}]^+$. ^1H NMR (400MHz, chloroform-*d*) δ = 8.36 (br s, 1H), 8.09 (s, 1H), 7.29 (br s, 1H), 7.24 - 7.20 (m, 1H), 6.62 (br d, J = 13.6 Hz, 1H), 6.47 - 6.24 (m, 1H), 5.83 (br d, J = 10.8 Hz, 1H), 5.50 (br s, 1H), 5.08 (br s, 1H), 4.60 (br s, 1H), 4.31 (s, 2H), 4.12 (br d, J = 14.4 Hz, 1H), 3.99 (br d, J = 10.8 Hz, 1H), 3.55 (br t, J = 5.6 Hz, 2H), 3.42 - 3.29 (m, 1H), 3.10 (br s, 1H), 3.00 - 2.68 (m, 7H), 2.49 (s, 6H), 2.43 (s, 3H), 1.39 (d, J = 6.0 Hz, 3H).

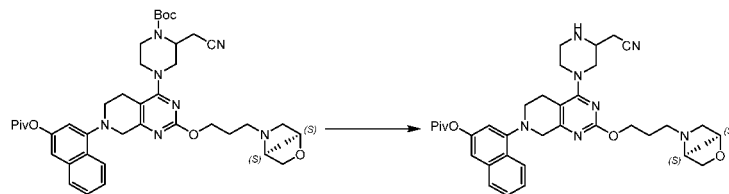
EXAMPLE 153

2-[4-[7-(3-hydroxy-1-naphthyl)-2-[3-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]propoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile

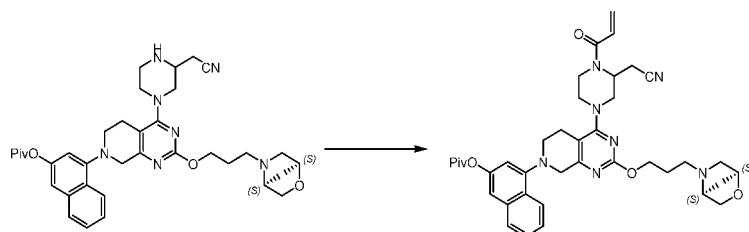


[0612] Step A: *tert*-butyl 2-(cyanomethyl)-4-[7-[3-(2,2-dimethylpropanoyloxy)-1-naphthyl]-2-[3-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]propoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate: To a solution of *tert*-butyl 2-(cyanomethyl)-4-[7-[3-(2,2-dimethylpropanoyloxy)-1-naphthyl]-2-methylsulfonyl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (500 mg, 773 μ mol) and 3-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]propan-1-ol (219 mg, 1.39 mmol) in toluene (10 mL) was added *t*BuONa (111 mg, 1.16 mmol) under N₂. The reaction mixture was stirred at 18 °C for 0.5 hour. Upon completion, the mixture was purified by silica gel chromatography (PE: EtOAc= 3:1 to 0:1 then EA: MeOH=50:1 to 10:1) followed by reversed flash chromatography (50 % to 90 % MeCN in water, base condition) to give *tert*-butyl 2-(cyanomethyl)-4-[7-[3-(2,2-dimethylpropanoyloxy)-1-naphthyl]-2-[3-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]propoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (120 mg, 156 μ mol, 20.5% yield, 97.9% purity) as a brown solid. ¹H NMR (400MHz, CHLOROFORM-*d*) δ = 8.19 - 8.12 (m, 1H), 7.83 - 7.77 (m, 1H), 7.55 - 7.43 (m, 2H), 7.29 (d, *J*=1.6 Hz, 1H), 6.84 (d, *J*=2.0 Hz, 1H), 4.64 (br s, 1H), 4.42 - 4.35 (m, 3H), 4.26 (br d, *J*=5.2 Hz, 2H), 4.12 - 4.03 (m, 3H), 3.96 (br d, *J*=12.8 Hz, 1H), 3.62 (dd, *J*=1.6, 7.6 Hz, 1H), 3.50 (br s, 2H), 3.31 (br d, *J*=13.6 Hz, 3H), 3.11 - 2.97 (m, 2H), 2.94 (br d, *J*=8.8 Hz, 1H), 2.89 - 2.69 (m, 5H), 2.54 (br

d, $J=9.8$ Hz, 1H), 2.00 - 1.92 (m, 2H), 1.90 - 1.83 (m, 1H), 1.73 (br d, $J=10.0$ Hz, 1H), 1.53 (s, 9H), 1.41 (s, 9H)

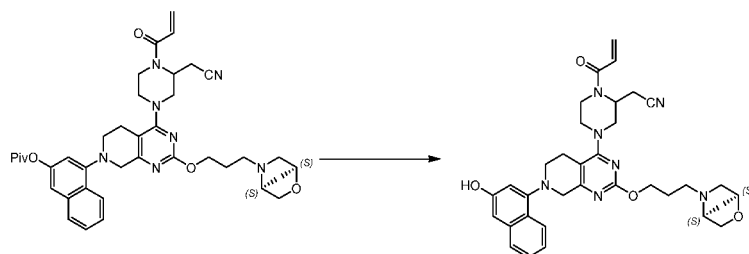


[0613] Step B: 4-[4-[3-(cyanomethyl)piperazin-1-yl]-2-[3-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]propoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]-2-naphthyl] 2,2-dimethylpropanoate: A solution of *tert*-butyl 2-(cyanomethyl)-4-[7-[3-(2,2-dimethylpropanoyloxy)-1-naphthyl]-2-[3-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]propoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (120 mg, 162 μ mol) in TFA (370 mg, 3.24 mmol, 240 μ L) was stirred at 18 °C for 1 hour. Upon completion, the solvent was removed under vacuum to give 4-[4-[3-(cyanomethyl)piperazin-1-yl]-2-[3-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]propoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]-2-naphthyl] 2,2-dimethylpropanoate (140 mg, 161 μ mol, 99.5% yield, 2TFA) as brown oil.



[0614] Step C: [4-[4-[3-(cyanomethyl)-4-prop-2-enoyl-piperazin-1-yl]-2-[3-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]propoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]-2-naphthyl] 2,2-dimethylpropanoate: To a solution of [4-[4-[3-(cyanomethyl)piperazin-1-yl]-2-[3-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]propoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]-2-naphthyl] 2,2-dimethylpropanoate (140 mg, 161 μ mol) and DIEA (167 mg, 1.29 mmol, 225 μ L) in DCM (2 mL) was added prop-2-enoyl prop-2-enoate (30.5 mg, 242 μ mol) at 0°C. The reaction mixture was stirred at 18 °C for 1 hour. Upon completion, the reaction mixture was quenched by addition of water (5 mL) and the aqueous layer extracted with DCM (3 $\times$ 10 mL). The combined organic layers were dried over Na₂SO₄, filtered and

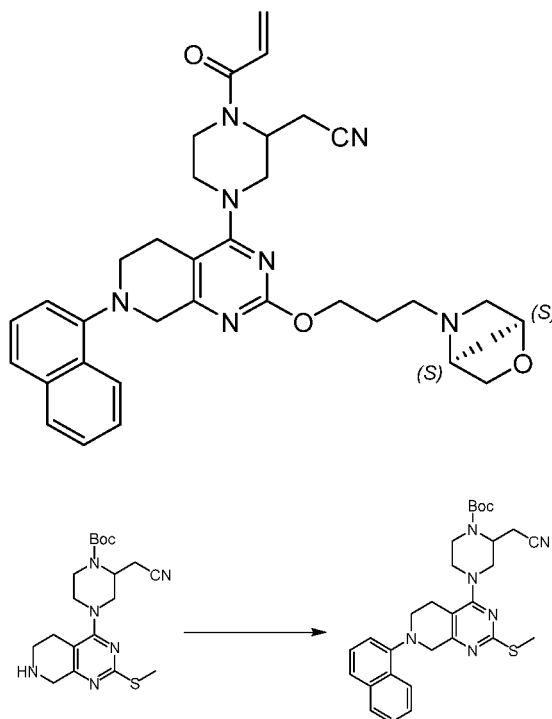
concentrated under vacuum. The residue was purified by reversed flash (Base condition, MeCN/NH₃•H₂O in water: 50 % to 80%) to give [4-[4-[3-(cyanomethyl)-4-prop-2-enoyl-piperazin-1-yl]-2-[3-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]propoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]-2-naphthyl] 2,2-dimethylpropanoate (60 mg, 86.5 μ mol, 53.6% yield). ¹H NMR (400MHz, CHLOROFORM-*d*) δ = 8.22 - 8.13 (m, 1H), 7.84 - 7.78 (m, 1H), 7.56 - 7.45 (m, 2H), 7.31 (d, *J*=2.0 Hz, 1H), 6.86 (d, *J*=2.4 Hz, 1H), 6.62 (br s, 1H), 6.47 - 6.37 (m, 1H), 5.92 - 5.79 (m, 1H), 5.24 - 4.88 (m, 1H), 4.75 (br s, 1H), 4.45 - 4.36 (m, 3H), 4.31 - 4.20 (m, 2H), 4.15 (br d, *J*=13.6 Hz, 1H), 4.10 - 4.01 (m, 2H), 3.64 (dd, *J*=1.6, 7.6 Hz, 2H), 3.51 (br s, 2H), 3.38 (br s, 2H), 3.14 (br s, 1H), 3.08 - 2.73 (m, 7H), 2.56 (br d, *J*=10.0 Hz, 1H), 2.03 - 1.93 (m, 2H), 1.88 (br d, *J*=9.6 Hz, 1H), 1.78 - 1.70 (m, 1H), 1.61 (s, 9H), 1.43 (s, 9H).



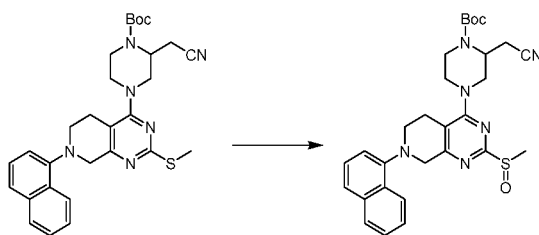
[0615] Step D: 2-[4-[7-(3-hydroxy-1-naphthyl)-2-[3-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]propoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile: To a solution of [4-[4-[3-(cyanomethyl)-4-prop-2-enoyl-piperazin-1-yl]-2-[3-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]propoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]-2-naphthyl] 2,2-dimethylpropanoate (60 mg, 86.5 μ mol) in THF (0.5 mL) was added NaOH (2 M, 600 μ L). The reaction mixture was stirred at 18 °C for 12 hours. Upon completion, the reaction mixture was acidified by addition of 4 drops of HCOOH (20 % in water) and the aqueous layer was extracted with DCM (5 $\times$ 8 mL). The combined organics were dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by prep-HPLC (column: Luna C18 150*25 5 μ ; mobile phase: [water(0.225%Formic Acid)-ACN]; B%: 10%-40%, 10min) to give 2-[4-[7-(3-hydroxy-1-naphthyl)-2-[3-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]propoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile (19.8 mg, 28.3 μ mol, 32.8% yield, 93.8% purity, Formic Acid salt) was obtained as a brown solid. ES+APCI MS *m/z* 610.5 [M+H]⁺.

EXAMPLE 154

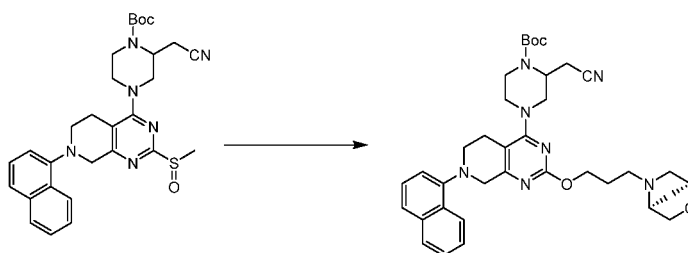
2-[4-[7-(1-naphthyl)-2-[3-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]propoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile



[0616] Step A: *tert*-butyl 2-(cyanomethyl)-4-[2-methylsulfany-7-(1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate: To the solution of *tert*-butyl 2-(cyanomethyl)-4-(2-methylsulfany-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl)piperazine-1-carboxylate (3 g, 7.42 mmol), 1-bromonaphthalene (3.07 g, 14.8 mmol, 2.06 mL) and Cs₂CO₃ (7.25 g, 22.2 mmol) in toluene (60 mL) was added XPhos palladacycle gen 3 (628 mg, 742 μ mol) under N₂ and the suspension was degassed under vacuum and purged with N₂ several times. The mixture was warmed to 70 °C and stirred at 70 °C for 10 hours. The resulting mixture was filtered and the filter cake was washed with EtOAc (3 $\times$ 20 mL). The combined organics were concentrated under reduced pressure to give a residue. The residue was purified by silica gel chromatography (PE: EtOAc from 50:1 to 3:1) to give *tert*-butyl 2-(cyanomethyl)-4-[2-methylsulfany-7-(1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (3.55 g, 6.02 mmol, 81.2% yield, 90.0 % purity) as brown oil. ES+APCI MS *m/z* 531.4 [M+H]⁺.

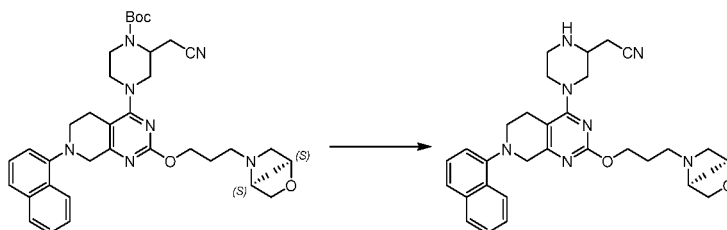


[0617] Step B: *tert*-butyl 2-(cyanomethyl)-4-[2-methylsulfinyl-7-(1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate: To the solution of *tert*-butyl 2-(cyanomethyl)-4-[2-methylsulfanyl-7-(1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (2.95 g, 5.56 mmol) in DCM (60 mL) was added *m*-CPBA (1.13 g, 5.56 mmol, 85.0 % purity) at 0 °C and stirred at 0 °C for 1 hour. The reaction mixture was quenched by addition of saturated Na₂S₂O₃ (20 mL) at 0 °C and layers were separated, and the aqueous layer diluted with water (20 mL) and extracted with EtOAc (60 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by reversed phase flash column (ACN/Water (0.1% Formic Acid) = 100 %) to give *tert*-butyl 2-(cyanomethyl)-4-[2-methylsulfinyl-7-(1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (1.7 g, 2.80 mmol, 50.3 % yield, 90.0 % purity) as brown solid. . ES+APCI MS *m/z* 574.4 [M+H]⁺.

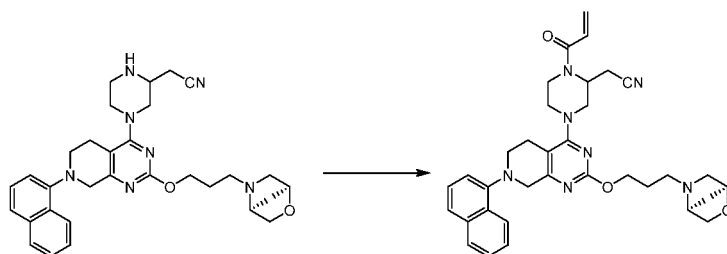


[0618] Step C: *tert*-butyl 2-(cyanomethyl)-4-[7-(1-naphthyl)-2-[3-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]propoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate: To a solution of *tert*-butyl 2-(cyanomethyl)-4-[2-methylsulfinyl-7-(1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (300 mg, 549 μmol,) and 3-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]propan-1-ol (160 mg, 1.02 mmol) in toluene (6 mL) was added *t*BuONa (79.1 mg, 823 μmol). The reaction mixture was stirred at 18 °C for 0.5 hour. Upon completion, the reaction mixture was purified by silica gel chromatography

(PE:EA= 3:1 to 0:1 then EA:MeOH=50:1 to 10:1) to give *tert*-butyl 2-(cyanomethyl)-4-[7-(1-naphthyl)-2-[3-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]propoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (200 mg, 249 μ mol, 45.3% yield, 79.6% purity) was obtained as a brown solid. ES+APCI MS m/z 640.5 $[M+H]^+$.



[0619] Step D: 2-[4-[7-(1-naphthyl)-2-[3-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]propoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-2-yl]acetonitrile: A reaction mixture of *tert*-butyl 2-(cyanomethyl)-4-[7-(1-naphthyl)-2-[3-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]propoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (200 mg, 313 μ mol) in TFA (770 mg, 6.75 mmol, 500 μ L) was stirred at 18 °C for 1 hour. Upon completion the solvent was removed under vacuum to give 2-[4-[7-(1-naphthyl)-2-[3-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]propoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-2-yl]acetonitrile (271 mg, crude) as a brown oil.

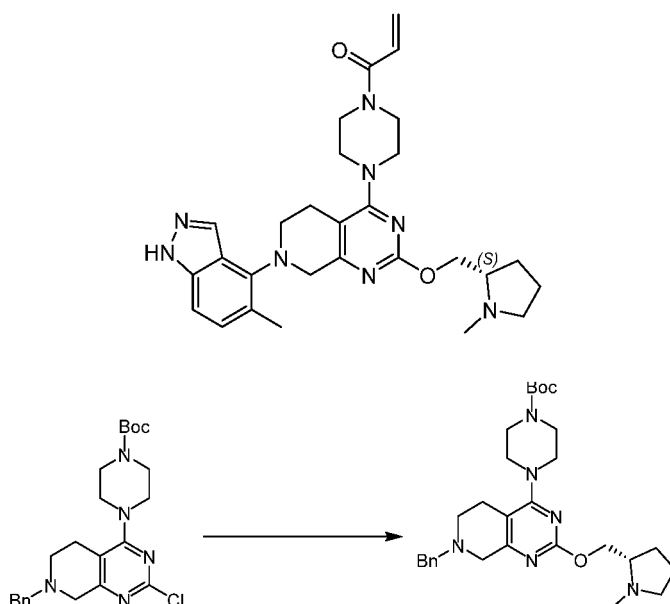


[0620] Step E: 2-[4-[7-(1-naphthyl)-2-[3-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]propoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile: To a solution of 2-[4-[7-(1-naphthyl)-2-[3-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]propoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-2-yl]acetonitrile (271 mg, 502 μ mol) and DIEA (323 mg, 2.50 mmol, 0.435 mL) in DCM (6 mL) was added prop-2-enoyl prop-2-enoate (60 mg, 476 μ mol) at 0 °C and the reaction mixture stirred at 18 °C for 1 hour. Upon completion, the reaction mixture was quenched by addition of a drop of water and purified by silica gel chromatography (PE: EtOAc=3:1 to 0:1) then prep

HPLC (column: Gemini 150*25 5u; mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN]; B%: 33%-63%, 12 min) to give 2-[4-[7-(1-naphthyl)-2-[3-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]propoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile (23.8 mg, 40.0 μ mol, 7.97% yield) as yellow solid. ES+APCI MS m/z 594.5 $[M+H]^+$.

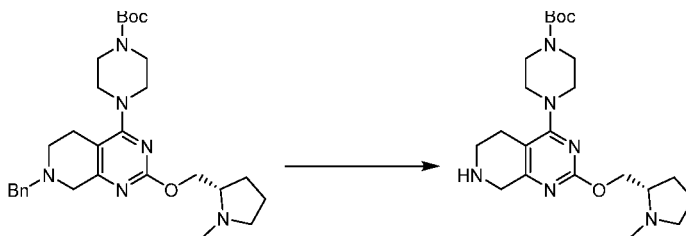
EXAMPLE 155

(*S*)-1-(4-(7-(5-methyl-1*H*-indazol-4-yl)-2-((1-methylpyrrolidin-2-yl)methoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

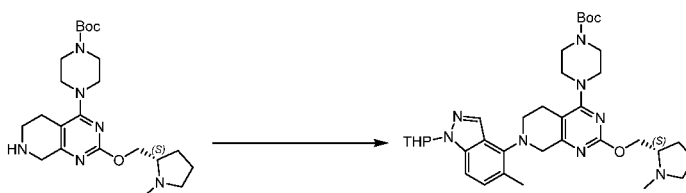


[0621] Step A: *tert*-butyl 4-[7-benzyl-2-[(2*S*)-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate: To a mixture of [(2*S*)-1-methylpyrrolidin-2-yl]methanol (4.15 g, 36.0 mmol, 4.28 mL) in THF (100 mL) was added NaH (2.16 g, 54.06 mmol, 60% purity) in portions at 0 °C. After the mixture was stirred at 0 °C for 1 hour, a solution of *tert*-butyl 4-(7-benzyl-2-chloro-6,8-dihydro-5*H*-pyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (8.0 g, 18.02 mmol) in THF (60 mL) was added and the mixture was stirred at 70 °C for 11 hours. After completion, the reaction mixture was poured into aqueous NH₄Cl (160 mL), and the aqueous layer extracted with EtOAc (2 × 100 mL). The combined organics were dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=3/1 to Ethyl

acetate/Methanol=10:1) to give *tert*-butyl 4-[7-benzyl-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (4.9 g, 8.70 mmol, 48.3% yield, 92.8% purity) as gray solid. ES+APCI MS *m/z* 523.2 [*M*+*H*]⁺

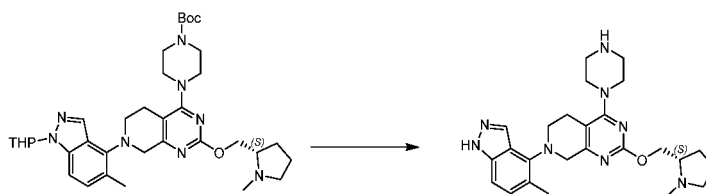


[0622] Step B: *tert*-butyl 4-[2-[[*(2S)*-1-methylpyrrolidin-2-yl] methoxy] -5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate: To a mixture of *tert*-butyl 4-[7-benzyl-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (2.20 g, 4.21 mmol) in MeOH (30 mL) was added Pd(OH)₂/C (700 mg, 10% purity) and the mixture was degassed under vacuum and purged with H₂ several times and the reaction stirred at 40 °C for 12 hours under H₂ (15 Psi). After completion, the reaction mixture was filtered through celite and the filtrate concentrated to give *tert*-butyl 4-[2-[[*(2S)*-1-methylpyrrolidin-2-yl] methoxy] -5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (1.80 g, 4.02 mmol, 95.6% yield, 96.7% purity) as black solid. ES+APCI MS *m/z* 433.1 [*M*+*H*]⁺.

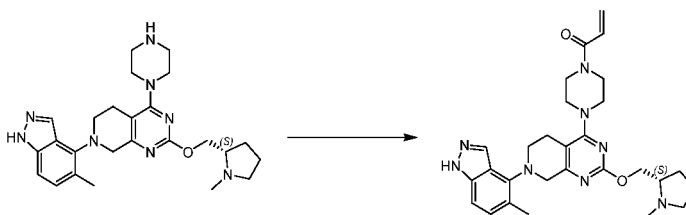


[0623] Step C: *tert*-butyl 4-[2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy] -7-(5-methyl-1-tetrahydropyran-2-yl-indazol-4-yl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate: To a mixture of *tert*-butyl 4-[2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (200 mg, 462 μmol) and 4-bromo-5-methyl-1-tetrahydropyran-2-yl-indazole (204 mg, 694 μmol) in toluene (4 mL) was added Pd₂(dba)₃ (63.5 mg, 69.4 μmol), RuPhos (43.2 mg, 92.5 μmol) and Cs₂CO₃ (301 mg, 925 μmol) and the mixture stirred at 110 °C for 12 hours under N₂. After completion, the reaction

mixture was partitioned between water (10 mL) and EtOAc and the layers separated. The aqueous layer was subsequently extracted with EtOAc (2×10 mL) and the combined organics were dried over Na_2SO_4 , filtered and concentrated. The residue was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate=5/1 to Ethyl acetate/MeOH=10/1) to give *tert*-butyl 4-[2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-7-(5-methyl-1-tetrahydropyran-2-yl-indazol-4-yl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (240 mg, 310 μmol , 67.1% yield, 83.6% purity) as brown oil. ES+APCI MS m/z 647.6 $[\text{M}+\text{H}]^+$.



[0624] Step D: 7-(5-methyl-1*H*-indazol-4-yl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-4-piperazin-1-yl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidine: To a mixture of *tert*-butyl 4-[2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-7-(5-methyl-1-tetrahydropyran-2-yl-indazol-4-yl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (240 mg, 371 μmol) in DCM (1 mL) was added TFA (1.54 g, 13.5 mmol, 1 mL) and the mixture stirred at 15 °C for 1 hour. After completion, the reaction mixture was concentrated to give 7-(5-methyl-1*H*-indazol-4-yl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-4-piperazin-1-yl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidine (250 mg, 309 μmol , 83.4% yield, 85.5% purity, 2TFA) as brown solid which was used for the next step without further purification. ES+APCI MS m/z 463.4 $[\text{M}+\text{H}]^+$.

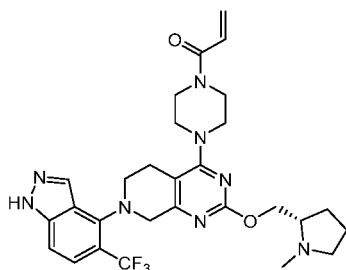


[0625] Step E: 1-[4-[7-(5-methyl-1*H*-indazol-4-yl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one: To a mixture of 7-(5-methyl-1*H*-indazol-4-yl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-4-piperazin-1-yl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidine (250 mg, 362 μmol , 2TFA) in DCM (2 mL) was added DIEA (702 mg, 5.43 mmol, 946 μL) and the mixture cooled to -50 °C. Prop-2-enoyl prop-2-

enoate (36.5 mg, 289 μmol) was added in portions to the reaction at $-50\text{ }^{\circ}\text{C}$ and the mixture stirred at $-50\text{ }^{\circ}\text{C}$ for 30 minutes. After completion, the reaction mixture was quenched by addition of MeOH (1 mL) and the mixture concentrated. The residue was taken up in DCM (10 mL) and the organics washed with H_2O ($2 \times 8\text{ mL}$). The organics were dried over Na_2SO_4 , filtered and concentrated. The residue was purified by prep-HPLC ((Instrument: gx-l; Column: Phenomenex Gemini C18 250*50mm*10 μm ; Condition: water (0.05% ammonia hydroxide v/v)-ACN; Begin B: 32; End B: 62; Gradient Time (min): 12; 100%B Hold Time (min): 2; FlowRate (ml/min): 25) to give 1-[4-[7-(5-methyl-1*H*-indazol-4-yl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one (48.6 mg, 92.9 μmol , 25.7% yield, 98.7% purity) as yellow solid. ES+APCI MS m/z 517.5 $[\text{M}+\text{H}]^+$.

EXAMPLE 156

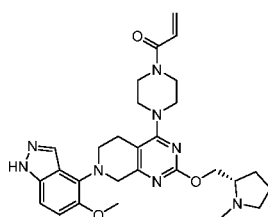
(*S*)-1-(4-(2-((1-methylpyrrolidin-2-yl)methoxy)-7-(5-(trifluoromethyl)-1*H*-indazol-4-yl)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one



[0626] (*S*)-1-(4-(2-((1-methylpyrrolidin-2-yl)methoxy)-7-(5-(trifluoromethyl)-1*H*-indazol-4-yl)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one was prepared following **Example 155** substituting 4-bromo-1-tetrahydropyran-2-yl-5-(trifluoromethyl)indazole (Intermediate 60) for 4-bromo-5-methyl-1-tetrahydropyran-2-yl-indazole in Step C. ES+APCI MS m/z 571.4 $[\text{M}+\text{H}]^+$.

EXAMPLE 157

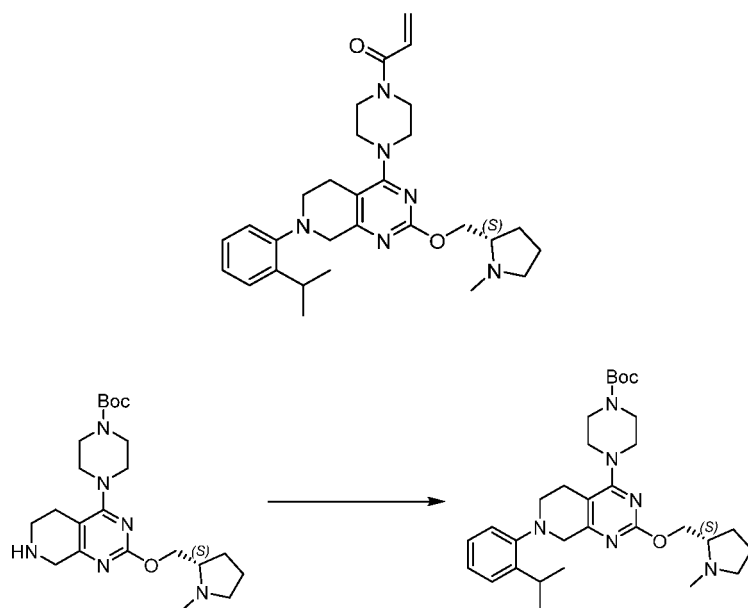
(*S*)-1-(4-(7-(5-methoxy-1*H*-indazol-4-yl)-2-((1-methylpyrrolidin-2-yl)methoxy)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one



[0627] (*S*)-1-(4-(7-(5-methoxy-1*H*-indazol-4-yl)-2-((1-methylpyrrolidin-2-yl)methoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one was prepared following **Example 155** substituting 4-bromo-5-methoxy-1-tetrahydropyran-2-yl-indazole for 4-bromo-5-methyl-1-tetrahydropyran-2-yl-indazole in Step C. ES+APCI MS m/z 533.4 $[M+H]^+$.

EXAMPLE 158

1-[4-[7-(2-isopropylphenyl)-2-[(2*S*)-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one



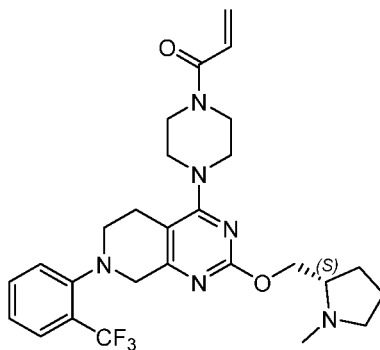
[0628] Step A: *tert*-butyl 4-[7-(2-isopropylphenyl)-2-[(2*S*)-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate: *tert*-butyl 4-[2-[(2*S*)-1-methylpyrrolidin-2-yl]methoxy]-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (200 mg, 462 μ mol), 1-bromo-2-isopropyl-benzene (120 mg, 601 μ mol), Cs_2CO_3 (452 mg, 1.39 mmol) and XPHOS PALLADACYCLE GEN 3 (78.3 mg, 92.5 μ mol) in toluene

(4.00 mL) was de-gassed with N₂ and then heated to 100 °C for 10 hours under N₂. Upon completion, the mixture was filtered and the filtrate was concentrated. The crude product was purified by silica gel chromatography eluted with EtOAc/MeOH= 50/1 to 5/1 to give *tert*-butyl 4-[7-(2-isopropylphenyl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (84.6 mg, 134 μ mol, 28.9 % yield, 87.0 % purity) as a yellow solid. ES+APCI MS m/z 551.2 [M+H]⁺.

[0629] 1-[4-[7-(2-isopropylphenyl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one was prepared following **Example 155** substituting *tert*-butyl 4-[7-(2-isopropylphenyl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate for *tert*-butyl 4-[2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-7-(5-methyl-1-tetrahydropyran-2-yl-indazol-4-yl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate in Step D. ES+APCI MS m/z 505.6 [M+H]⁺.

EXAMPLE 159

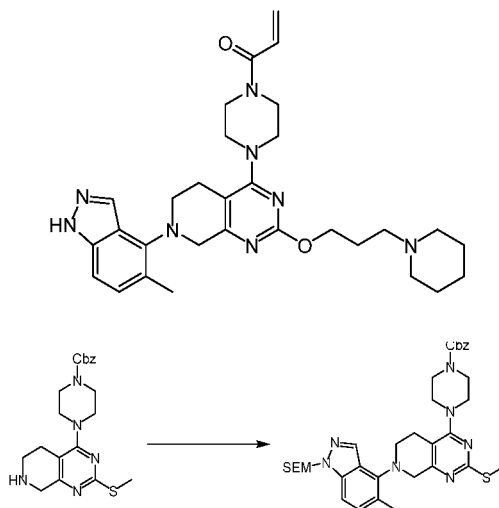
(*S*)-1-(4-(2-((1-methylpyrrolidin-2-yl)methoxy)-7-(2-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one



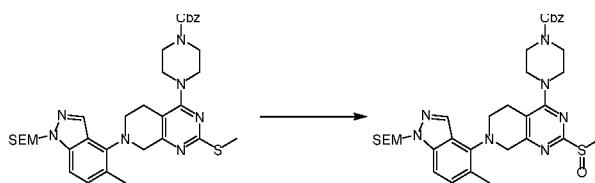
[0630] (*S*)-1-(4-(2-((1-methylpyrrolidin-2-yl)methoxy)-7-(2-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one was prepared following **Example 155** substituting 1-bromo-2-(trifluoromethyl)benzene for 4-bromo-5-methyl-1-tetrahydropyran-2-yl-indazole in Step C. ES+APCI MS m/z 531.5 [M+H]⁺.

EXAMPLE 160

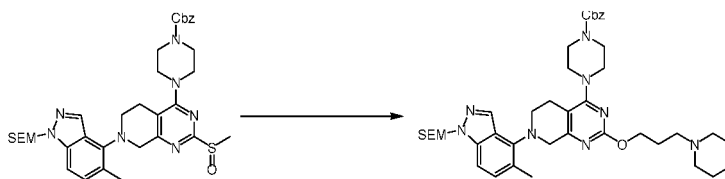
1-(4-(7-(5-methyl-1*H*-indazol-4-yl)-2-(3-(piperidin-1-yl)propoxy)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one



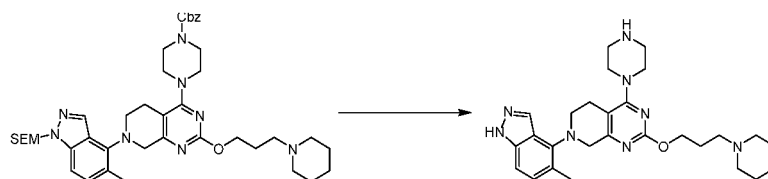
[0631] Step A: Benzyl 4-[2-methylsulfanyl-7-[5-methyl-1-(2-trimethylsilylethoxymethyl)indazol-4-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate: A mixture of benzyl 4-(2-methylsulfanyl-5,6,7,8-tetrahydropyrido[3,4-*d*] pyrimidin-4-yl)piperazine-1-carboxylate (3.15 g, 7.88 mmol), 2-[(4-bromo-5-methyl-indazol-1-yl)methoxy]ethyl-trimethyl-silane (3.50 g, 10.2 mmol), Cs₂CO₃ (6.42 g, 19.70 mmol), Pd₂(dba)₃ (1.08 g, 1.18 mmol) and RuPhos (735 mg, 1.58 mmol) in toluene (50 mL) was degassed and with N₂ 3 times and the mixture stirred at 90 °C for 10 hours under N₂ atmosphere. The reaction mixture was quenched by addition of water (100 mL) and the aqueous layer extracted with ethyl acetate (3 × 100 mL). The combined organics were washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced. The residue was purified by column chromatography using 1→33% EtOAc/Petroleum Ether to give benzyl 4-[2-methylsulfanyl-7-[5-methyl-1-(2-trimethylsilylethoxymethyl)indazol-4-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (2.30 g, 2.93 mmol, 37.1 % yield). ES+APCI MS *m/z* 660.3 [M+H]⁺.



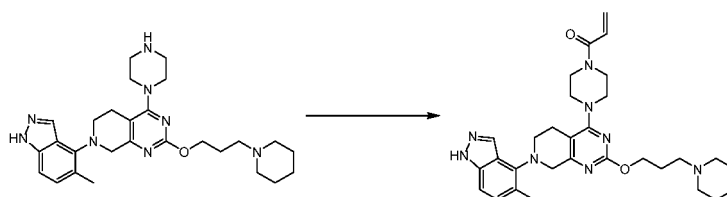
[0632] Step B: benzyl 4-[2-methylsulfinyl-7-[5-methyl-1-(2-trimethylsilyl ethoxymethyl)indazol-4-yl]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate: To a stirred solution of benzyl 4-[2-methylsulfinyl-7-[5-methyl-1-(2-trimethylsilyl ethoxymethyl)indazol-4-yl]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (2.30 g, 3.49 mmol) in DCM (20 mL) was added m-CPBA (601 mg, 3.49 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour under N₂ atmosphere. The reaction mixture was quenched by addition Na₂S₂O₃ (10 mL) at 0 °C, and then diluted with water (100 mL) and the aqueous layer extracted with DCM (200 mL). The combined organics were washed with brine (200 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography using 1→10% MeOH/DCM as eluent to give benzyl 4-[2-methylsulfinyl-7-[5-methyl-1-(2-trimethylsilyl ethoxymethyl)indazol-4-yl]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (2.00 g, 2.84 mmol, 81.4 % yield). ES+APCI MS m/z 676.3 [M+H]⁺.



[0633] Step C: benzyl 4-[7-[5-methyl-1-(2-trimethylsilyl ethoxymethyl)indazol-4-yl]-2-[3-(1-piperidyl)propoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate: To a mixture of benzyl 4-[2-methylsulfinyl-7-[5-methyl-1-(2-trimethylsilyl ethoxymethyl)indazol-4-yl]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (500 mg, 739 μmol) and 3-(1-piperidyl)propan-1-ol (211 mg, 1.48 mmol) in THF (10 mL) was added t-BuONa (213 mg, 2.22 mmol) portion wise and the mixture stirred at 20 °C for 1 hour under N₂ atmosphere. The mixture was cooled to 0 °C and HCl(2M) was added until the pH~7. The mixture was filtered and filtrate was concentrated in vacuo. The residue was purified by reversed phase flash using water 5→95% 0.5% TFA/water/acetonitrile as eluent to give benzyl 4-[7-[5-methyl-1-(2-trimethylsilyl ethoxymethyl)indazol-4-yl]-2-[3-(1-piperidyl)propoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (300 mg, 385. μmol, 52.1 % yield). ES+APCI MS m/z 755.4 [M+H]⁺.



[0634] Step D: 7-(5-methyl-1*H*-indazol-4-yl)-4-(piperazin-1-yl)-2-(3-(piperidin-1-yl)propoxy)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidine: To a solution of benzyl 4-[7-[5-methyl-1-(2-trimethylsilylethoxymethyl) indazol-4-yl]-2-[3-(1-piperidyl)propoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (300 mg, 397 μ mol) in MeOH (20 mL) was added HCl/MeOH (4 M, 1.99 mL) and Pd(OH)₂ (200 mg, 10 % purity) under N₂. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (15 psi) at 25 °C for 1 hour. The reaction mixture was filtered and the filtrate was concentrated to give 7-(5-methyl-1*H*-indazol-4-yl)-4-(piperazin-1-yl)-2-(3-(piperidin-1-yl)propoxy)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidine (250 mg, 360 μ mol, 90.7 % yield).

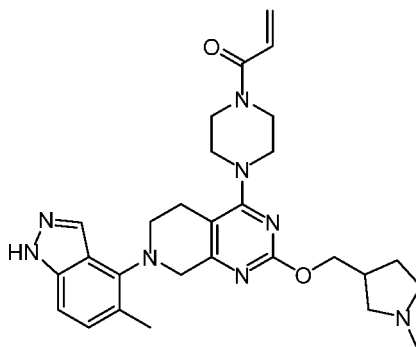


[0635] Step E: 1-[4-[7-(5-methyl-1*H*-indazol-4-yl)-2-[3-(1-piperidyl)propoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one: To a mixture of 7-(5-methyl-1*H*-indazol-4-yl)-4-(piperazin-1-yl)-2-(3-(piperidin-1-yl)propoxy)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidine (250 mg, 360 μ mol, 2HCl) and DIEA (465 mg, 3.60 mmol, 629 μ L) in DCM (8.00 mL) was added a solution of prop-2-enoyl prop-2-enoate (36.3 mg, 288 μ mol) in DCM (2.00 mL) at -40 °C under nitrogen atmosphere and the reaction stirred for 1 hour. The reaction mixture was quenched by addition NaHCO₃ (500 μ L) at -40°C, and then diluted with water (10 mL) and the aqueous layer extracted with DCM (10 mL). The organics were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, DCM/MeOH 1/0 to 5/1) and further purified by prep-HPLC (column: Phenomenex Synergi C18 150*25*10 μ m; mobile phase: [water (0.225% Formic Acid)-ACN]; B%: 8%-28%, 10min) to give 1-[4-[7-(5-methyl-1*H*-indazol-4-yl)-2-[3-(1-piperidyl)propoxy]-

6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one (16.0 mg, 29.1 μ mol, 8.07 % yield). ES+APCI MS m/z 545.3 $[M+H]^+$.

EXAMPLE 161

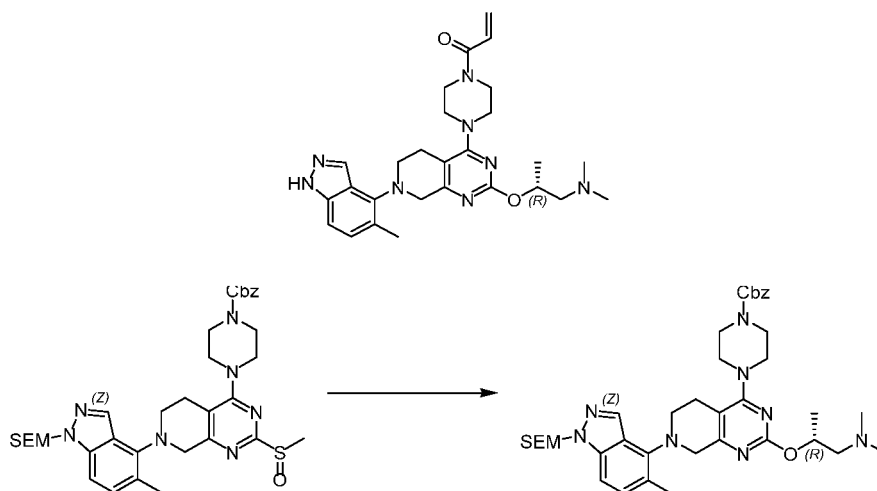
1-[4-[7-(5-methyl-1*H*-indazol-4-yl)-2-[(1-methylpyrrolidin-3-yl)methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one



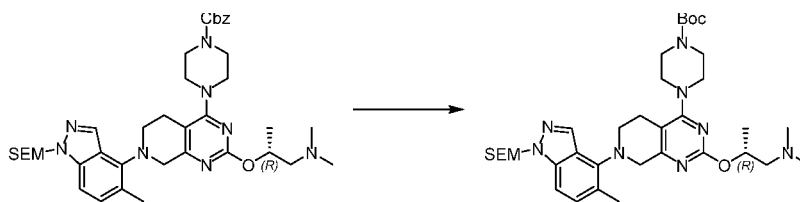
[0636] 1-[4-[7-(5-methyl-1*H*-indazol-4-yl)-2-[(1-methylpyrrolidin-3-yl)methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one was prepared following **Example 160** substituting (1-methylpyrrolidin-3-yl)methanol for 3-(1-piperidyl)propan-1-ol in Step C. ES+APCI MS m/z 517.4 $[M+H]^+$.

EXAMPLE 162

1-[4-[2-[(1*R*)-2-(dimethylamino)-1-methyl-ethoxy]-7-(5-methyl-1*H*-indazol-4-yl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one

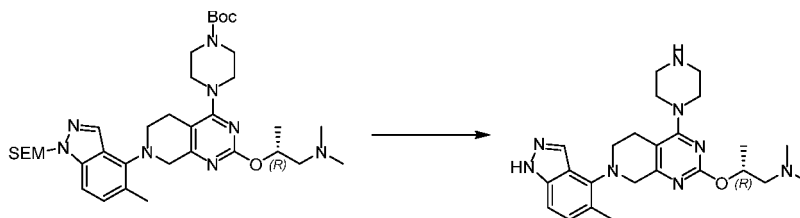


[0637] Step A: benzyl 4-[2-[(1*R*)-2-(dimethylamino)-1-methyl-ethoxy]-7-[5-methyl-1-(2-trimethylsilylethoxymethyl)indazol-4-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate: A mixture of (2*R*)-1-(dimethylamino)propan-2-ol (183 mg, 1.78 mmol) (8.00 mL), benzyl 4-[2-methylsulfinyl-7-[5-methyl-1-(2-trimethylsilylethoxymethyl)indazol-4-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (400 mg, 592 μ mol) and NaOtBu (114 mg, 1.18 mmol) in toluene were stirred at 15 °C for 0.5 hour. The reaction mixture was filtered and the filtrate was concentrated under vacuum. The residue was purified by column chromatography over Al₂O₃ (Petroleum Ether/EthylAcetate 10/1 to 0/1) to give benzyl 4-[2-[(1*R*)-2-(dimethylamino)-1-methyl-ethoxy]-7-[5-methyl-1-(2-trimethylsilylethoxymethyl)indazol-4-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (280 mg, 352 μ mol). ¹H NMR (400 MHz, chloroform-*d*) δ = 8.08 (s, 1H), 7.46 - 7.39 (m, 5H), 7.38 - 7.33 (m, 2H), 5.76 (s, 2H), 5.43 - 5.33 (m, 1H), 5.24 (s, 2H), 4.35 (s, 2H), 3.72 - 3.67 (m, 4H), 3.64 - 3.56 (m, 4H), 3.55 - 3.47 (m, 4H), 2.87 - 2.80 (m, 2H), 2.74 (dd, *J*=6.8, 12.8 Hz, 1H), 2.49 (s, 3H), 2.47 - 2.40 (m, 1H), 2.36 (s, 6H), 1.42 (d, *J*=6.4 Hz, 3H), 0.98 - 0.92 (m, 2H), 0.00 (s, 9H).

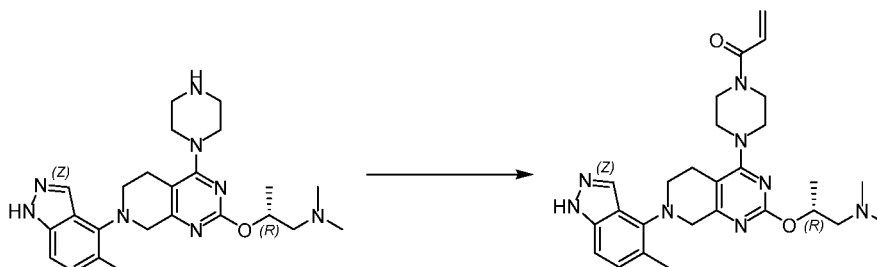


[0638] Step B: *tert*-butyl 4-[2-[(1*R*)-2-(dimethylamino)-1-methyl-ethoxy]-7-[5-methyl-1-(2-trimethylsilylethoxymethyl)indazol-4-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate: To a solution of benzyl 4-[2-[(1*R*)-2-(dimethylamino)-1-methyl-ethoxy]-7-[5-methyl-1-(2-trimethylsilylethoxymethyl)indazol-4-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (200 mg, 280 μ mol) and (Boc)₂O (122 mg, 559 μ mol, 129 μ L) in MeOH (6.00 mL) was added 10% Pd/C (80 mg) under N₂. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (15 psi) at 25 °C for 1 hour and 35 °C for 1 hour. Upon completion, the mixture was filtered and the filtrate concentrated under vacuum to give mixture of *tert*-butyl 4-[2-[(1*R*)-2-(dimethylamino)-1-methyl-ethoxy]-7-[5-methyl-1-(2-trimethylsilylethoxymethyl)indazol-4-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate and (2*R*)-*N,N*-dimethyl-

2-[[7-[5-methyl-1-(2-trimethylsilylethoxymethyl)indazol-4-yl]-4-piperazin-1-yl]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-2-yl]oxy]propan-1-amine as a mixture (110 mg). ES+APCI MS m/z 681.3 $[M+H]^+$.

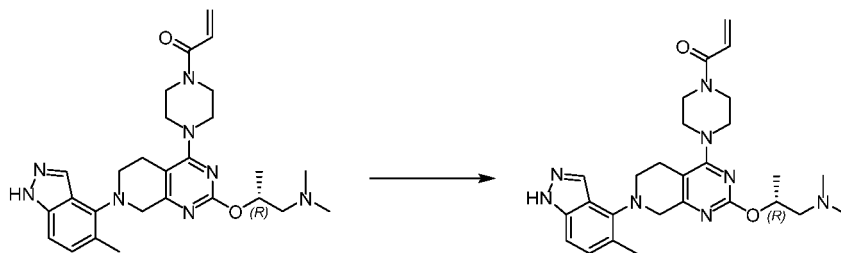


[0639] Step C: (2R)-N,N-dimethyl-2-[[7-(5-methyl-1H-indazol-4-yl)-4-piperazin-1-yl]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-2-yl]oxy]propan-1-amine (TFA) and [4-[2-[(1R)-2-(dimethylamino)-1-methyl-ethoxy]-4-piperazin-1-yl]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-7-yl]-5-methyl-indazol-1-yl]methanol. A solution of 110 mg mixture of *tert*-butyl 4-[2-[(1R)-2-(dimethylamino)-1-methyl-ethoxy]-7-[5-methyl-1-(2-trimethylsilylethoxymethyl)indazol-4-yl]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate and (2R)-N,N-dimethyl-2-[[7-[5-methyl-1-(2-trimethylsilylethoxymethyl)indazol-4-yl]-4-piperazin-1-yl]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-2-yl]oxy]propan-1-amine in TFA (3.08 g, 27.0 mmol) was stirred at 30 °C for 1 hour. Upon completion, the mixture was concentrated under vacuum to give 260 mg mixture of (2R)-N,N-dimethyl-2-[[7-(5-methyl-1H-indazol-4-yl)-4-piperazin-1-yl]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-2-yl]oxy]propan-1-amine and [4-[2-[(1R)-2-(dimethylamino)-1-methyl-ethoxy]-4-piperazin-1-yl]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-7-yl]-5-methyl-indazol-1-yl]methanol. ES+APCI MS m/z 451.3 $[M+H]^+$.



[0640] Step D: 1-[4-[2-[(1R)-2-(dimethylamino)-1-methyl-ethoxy]-7-(5-methyl-1H-indazol-4-yl)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one: To a solution

of 260 mg mixture of (2*R*)-*N,N*-dimethyl-2-[[7-(5-methyl-1*H*-indazol-4-yl)-4-piperazin-1-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-2-yl]oxy]propan-1-amine and [4-[2-[(1*R*)-2-(dimethylamino)-1-methyl-ethoxy]-4-piperazin-1-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]-5-methyl-indazol-1-yl]methanol in DCM (1.00 mL) cooled to - 50 °C was added DIEA (594 mg, 4.59 mmol) followed by prop-2-enoyl prop-2-enoate (18.0 mg, 143 μ mol) dropwise and the mixture was stirred at between -50°C to -40 °C for 30 minutes. Upon completion, the mixture was concentrated under vacuum to give 100 mg mixture of 1-[4-[2-[(1*R*)-2-(dimethylamino)-1-methyl-ethoxy]-7-(5-methyl-1*H*-indazol-4-yl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one and 1-[4-[2-[(1*R*)-2-(dimethylamino)-1-methyl-ethoxy]-7-[1-(hydroxymethyl)-5-methyl-indazol-4-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one. ES+APCI MS m/z 505.4 $[M+H]^+$.

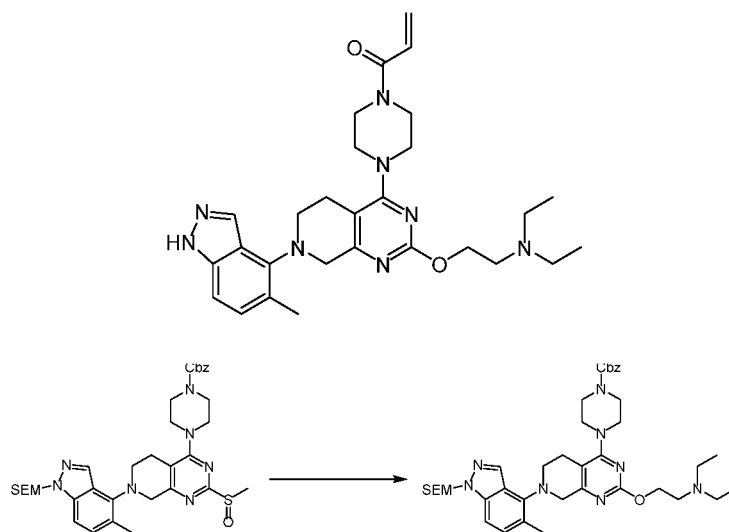


[0641] Step E: 1-[4-[2-[(1*R*)-2-(dimethylamino)-1-methyl-ethoxy]-7-(5-methyl-1*H*-indazol-4-yl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one: A mixture of 100 mg of 1-[4-[2-[(1*R*)-2-(dimethylamino)-1-methyl-ethoxy]-7-(5-methyl-1*H*-indazol-4-yl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one and 1-[4-[2-[(1*R*)-2-(dimethylamino)-1-methyl-ethoxy]-7-[1-(hydroxymethyl)-5-methyl-indazol-4-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one in THF (22 mL) and water (550 μ L) was added NaOH (44.8 mg, 1.12 mmol) and the mixture stirred at 10 °C for 3 hours. Upon completion, the mixture was concentrated under vacuum. The residue was diluted with water (1 mL) and extracted with DCM (3 $\times$ 5 mL). The combined organics were dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by prep-HPLC (column: Phenomenex Synergi C18 150*25*10 μ m; mobile phase: [water(0.225% Formic Acid)-ACN]; B%: 10%-40%, 12min) to give 1-[4-[2-[(1*R*)-2-(dimethylamino)-1-methyl-ethoxy]-7-(5-methyl-1*H*-indazol-4-yl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-

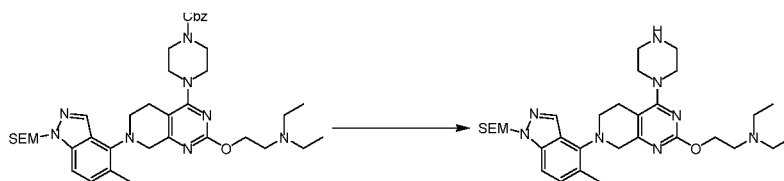
en-1-one (16.2 mg, 29.2 μ mol, 99.0 % purity, Formic Acid Salt) as a off-white solid. ES+APCI MS m/z 505.2 $[M+H]^+$.

EXAMPLE 163

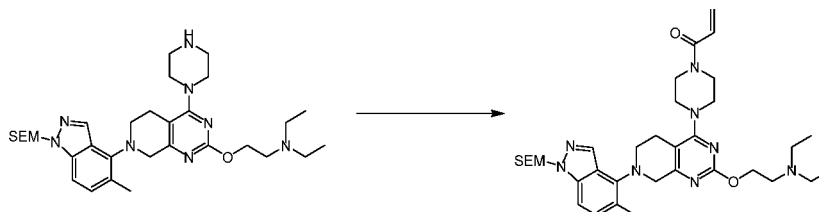
1-(4-(2-(2-(diethylamino)ethoxy)-7-(5-methyl-1*H*-indazol-4-yl)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one



[0642] Step A: benzyl 4-[2-[2-(diethylamino)ethoxy]-7-[5-methyl-1-(2-trimethylsilylethoxymethyl)indazol-4-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate: To a mixture of benzyl 4-[2-methylsulfinyl-7-[5-methyl-1-(2-trimethylsilylethoxymethyl)indazol-4-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (500 mg, 739 μ mol) and 2-(diethylamino)ethanol (173 mg, 1.48 mmol, 197 μ L) in THF (10 mL) was added *t*-BuONa (213 mg, 2.22 mmol), and the mixture stirred at 20 °C for 1 hour under N_2 atmosphere. The mixture was cooled to 0 °C and HCl (2 M) was added until pH~7. The mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography using 0→10% MeOH/DCM as eluent to give impure material which was further purified by reversed phase chromatography to give benzyl 4-[2-[2-(diethylamino)ethoxy]-7-[5-methyl-1-(2-trimethylsilylethoxymethyl)indazol-4-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (220 mg, 295 μ mol, 39.9 % yield). ES+APCI MS m/z 729.3 $[M+H]^+$.

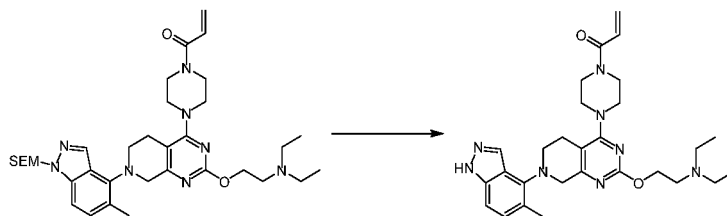


[0643] Step B: *N,N*-diethyl-2-[[7-[5-methyl-1-(2-trimethylsilylethoxymethyl)indazol-4-yl]-4-piperazin-1-yl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-2-yl]oxy]ethanamine: To a solution of benzyl 4-[2-[2-(diethylamino)ethoxy]-7-[5-methyl-1-(2-trimethylsilylethoxymethyl)indazol-4-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (120 mg, 164 μ mol) in MeOH (10 mL) was added Pd(OH)₂ (99.4 mg, 10% purity) and HCl/MeOH (4 M, 823.05 μ L) under N₂. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (15 psi) at 25 °C for 1 hour. The mixture was concentrated in vacuo to give *N,N*-diethyl-2-[[7-[5-methyl-1-(2-trimethylsilylethoxymethyl)indazol-4-yl]-4-piperazin-1-yl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-2-yl]oxy]ethanamine (105 mg, 157.24 μ mol). ES+APCI MS *m/z* 595.4 [M+H]⁺.



[0644] Step C: 1-[4-[2-[2-(diethylamino)ethoxy]-7-[5-methyl-1-(2-trimethylsilylethoxymethyl)indazol-4-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one: To a mixture of *N,N*-diethyl-2-[[7-[5-methyl-1-(2-trimethylsilyl)ethoxymethyl)indazol-4-yl]-4-piperazin-1-yl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-2-yl]oxy]ethanamine (105 mg, 158 μ mol, 2 HCl) and DIEA (204 mg, 1.58 mmol, 276 μ L) in DCM (8 mL) at -40 °C was added a solution of prop-2-enoyl prop-2-enoate (15.9 mg, 126.4 μ mol) in DCM (2 mL) under nitrogen atmosphere and the reaction stirred for 1 hour. The reaction mixture was quenched by addition NaHCO₃ (500 μ L) at -40 °C, and then diluted with water (10 mL). The aqueous layer was extracted with DCM (10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography using 0→20% MeOH/DCM as eluent to give 1-[4-[2-[2-(diethylamino)ethoxy]-7-[5-methyl-1-(2-trimethylsilylethoxymethyl)indazol-4-yl]-6,8-dihydro-

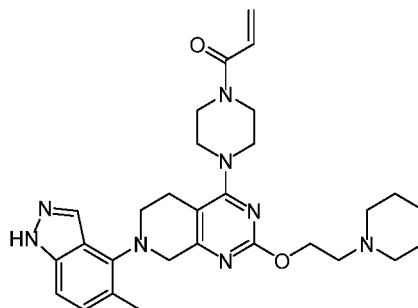
5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one (60.0 mg, 71.2 μ mol, 45.0 % yield). ES+APCI MS m/z 649.3 $[M+H]^+$.

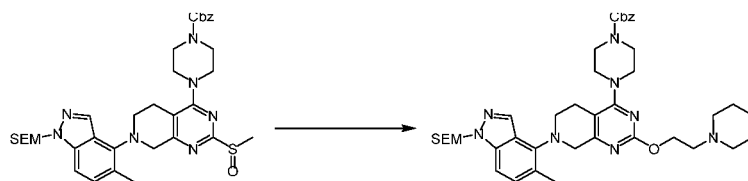


[0645] Step D: 1-[4-[2-[2-(diethylamino)ethoxy]-7- (5-methyl-1*H*-indazol-4-yl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one: To a solution of 1-[4-[2-[2-(diethylamino)ethoxy]-7-[5-methyl-1- (2-trimethylsilylethoxymethyl)indazol-4-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one (50 mg, 77.0 μ mol) in DCM (500 μ L) was added TFA (175 mg, 1.54 mmol, 114 μ L). The mixture was stirred at 15 °C for 16 hours. The reaction mixture was concentrated under vacuum and the residue purified by prep-HPLC (column: Phenomenex Gemini C18 250*50mm*10 μ m; mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN]; B%: 32%-62%, 12min) to give 1-[4-[2-[2-(diethylamino)ethoxy]-7- (5-methyl-1*H*-indazol-4-yl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one (16.0 mg, 30.2 μ mol, 39.2 % yield). ES+APCI MS m/z 519.3 $[M+H]^+$.

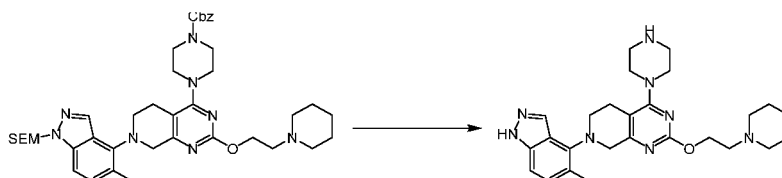
EXAMPLE 164

1-(4-(7-(5-methyl-1*H*-indazol-4-yl)-2-(2-(piperidin-1-yl)ethoxy)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl)piperazin-1-yl)ethanone

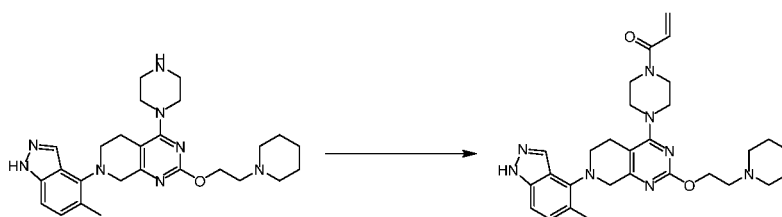




[0646] Step A: benzyl 4-[7-[5-methyl-1-(2-trimethylsilylethoxy methyl)indazol-4-yl]-2-[2-(1-piperidyl)ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate: To a solution of benzyl 4-[2-methylsulfinyl-7-[5-methyl-1-(2-trimethylsilylethoxymethyl)indazol-4-yl]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (500 mg, 739 μmol) and 2-(1-piperidyl)ethanol (191 mg, 1.48 mmol, 197 μL) in toluene (20 mL) was added t-BuONa (213 mg, 2.22 mmol). The mixture was stirred at 20 °C for 1 hour under N_2 atmosphere. The mixture was cooled to 0 °C and HCl (2 M) was added until pH~7. The mixture was filtered and the filtrate concentrated in vacuo. The residue was purified by column chromatography using 0 $\rightarrow$ 10% MeOH/DCM as eluent to give benzyl 4-[7-[5-methyl-1-(2-trimethylsilylethoxy methyl)indazol-4-yl]-2-[2-(1-piperidyl)ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (300 mg, 404 μmol , 54.7 % yield). ES+APCI MS m/z 741.4 $[\text{M}+\text{H}]^+$.



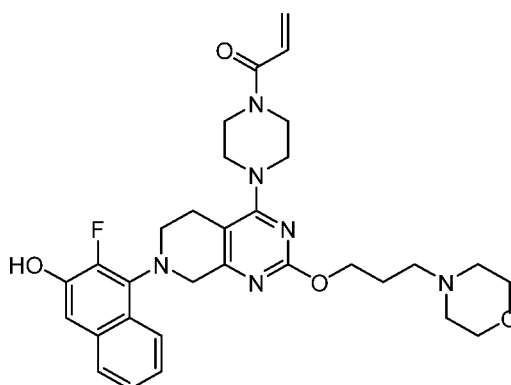
[0647] Step B: 7-(5-methyl-1H-indazol-4-yl)-4-piperazin-1-yl-2-[2-(1-piperidyl)ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidine: A solution of benzyl 4-[7-[5-methyl-1-(2-trimethylsilylethoxymethyl) indazol-4-yl]-2-[2-(1-piperidyl)ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (250 mg, 337 μmol) in TFA (10 mL) was stirred at 80 °C for 1 hour. The reaction mixture was concentrated under vacuum to give 7-(5-methyl-1H-indazol-4-yl)-4-piperazin-1-yl-2-[2-(1-piperidyl)ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidine (200 mg, 283 μmol , 84.1 % yield). ES+APCI MS m/z 477.3 $[\text{M}+\text{H}]^+$.

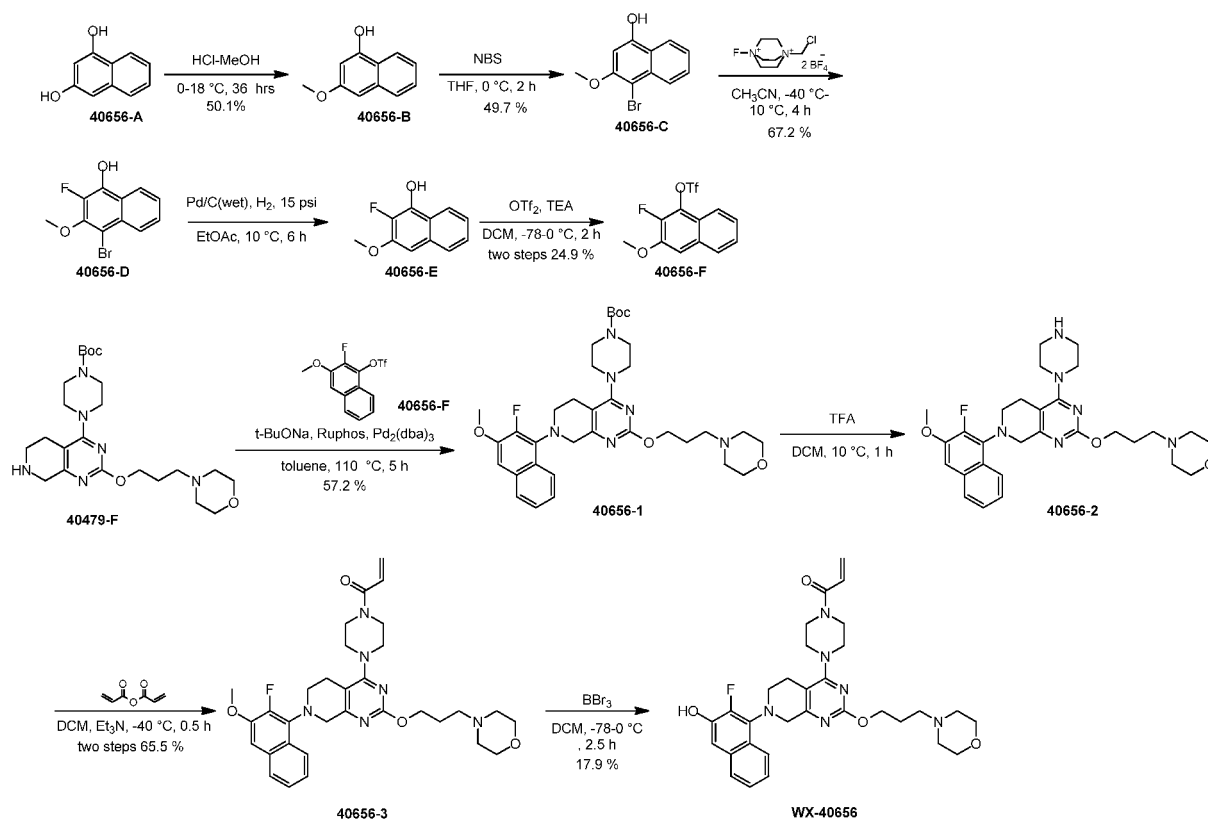


[0648] Step C: 1-[4-[7-(5-methyl-1*H*-indazol-4-yl)-2- [2-(1-piperidyl)ethoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one: To a mixture of 7-(5-methyl-1*H*-indazol-4-yl)-4-piperazin-1-yl-2- [2-(1-piperidyl)ethoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidine (200 mg, 283 μ mol, 2TFA) and DIEA (366 mg, 2.84 mmol, 495 μ L) in DCM (8 mL) at - 40 °C was added a solution of prop-2-enoyl prop-2-enoate (28.6 mg, 227 μ mol) DCM (2 mL) under nitrogen atmosphere and the reaction stirred for 1 hour. The reaction mixture was quenched by addition NaHCO₃ (500 μ L) at - 40°C, and then diluted with water (10 mL) and DCM (10 mL). The separated organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Phenomenex Gemini C18 250*50mm*10 μ m;mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN]; B%: 30% - 60%, 12min). 1-[4-[7-(5-methyl-1*H*-indazol-4-yl)-2- [2-(1-piperidyl)ethoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one (6.00 mg, 11.1 μ mol, 3.94 % yield, 99.0 % purity). ES+APCI MS *m/z* 531.4 [M+H]⁺.

EXAMPLE 165

1-[4-[7-(2-fluoro-3-hydroxy-1-naphthyl)-2-(3-morpholinopropoxy)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one





[0649] Step A: 3-methoxynaphthalen-1-ol: To a solution of naphthalene-1,3-diol (20 g, 125 mmol) in MeOH (150 mL) was added HCl/MeOH (4 M, 250 mL) at 0 °C. The mixture was warmed up to 18 °C and stirred for 36 hours. The mixture was concentrated under vacuum. The residue was purified by column chromatography over silica gel (petroleum ether/ethyl acetate 100/1 to 1/1). The desired fractions were collected and concentrated under vacuum to give 3-methoxynaphthalen-1-ol (11 g, 62.5 mmol, 50.1% yield, 99% purity) as a light yellow solid. ES+APCI MS *m/z* 175.1 [M+H]⁺.

[0650] Step B: 4-bromo-3-methoxy-naphthalen-1-ol: To a solution of 3-methoxynaphthalen-1-ol (0.50 g, 2.87 mmol) in THF (10 mL) was added a solution of NBS (562 mg, 3.16 mmol) in THF (3.00 mL) at 0 °C. After stirring at 0 °C for 2 hours, the mixture was concentrated under vacuum, diluted with H₂O (5 mL), extracted with dichloromethane (3 × 10 mL). The combined extracts were washed with saturated sodium chloride (1 × 20 mL), dried over Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by column chromatography (SiO₂, petroleum ether/ether acetate = 3/1) to give 4-bromo-3-methoxy-naphthalen-1-ol (0.43 g, 1.43 mmol, 49.7 % yield) as a yellow solid. ES+APCI MS *m/z* 253 [M+H]⁺.

[0651] Step C: 4-bromo-2-fluoro-3-methoxy-naphthalen-1-ol: To a solution of 4-bromo-3-methoxy-naphthalen-1-ol (4.00 g, 15.8 mmol) in acetonitrile (20 mL) was added a solution of 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane;ditetrafluoroborate (6.72 g, 19.0 mmol) in acetonitrile (20 mL) at -40 °C. After stirring at -40 °C for 1 hour and 10 °C for 3 hours, the mixture was concentrated under vacuum. The residue was purified by column chromatography (SiO₂, petroleum ether/ether acetate = 3/1) to give 4-bromo-2-fluoro-3-methoxy-naphthalen-1-ol (4.00 g, 10.6 mmol, 67.2 % yield) as a yellow solid. ES+APCI MS m/z 271.0 [M+H]⁺.

[0652] Step D: 2-fluoro-3-methoxy-naphthalen-1-ol: A mixture of 4-bromo-2-fluoro-3-methoxy-naphthalen-1-ol (2.00 g, 7.38 mmol) and 10% Pd/C (0.01 g) in ethyl acetate (20 mL) was stirred at 10 °C for 1 hour under H₂ at 15 psi. The mixture was filtered and concentrated under vacuum to give 2-fluoro-3-methoxy-naphthalen-1-ol (1.60 g, crude) as yellow oil and used into next step without further purification. ES+APCI MS m/z 193.0 [M+H]⁺.

[0653] Step E: (2-fluoro-3-methoxy-1-naphthyl) trifluoromethanesulfonate: To a solution of 2-fluoro-3-methoxy-naphthalen-1-ol (1.60 g, crude) and TEA (1.85 g, 18.3 mmol, 2.55 mL) in dichloromethane (30 mL) was added trifluoromethylsulfonyl trifluoromethanesulfonate (2.35 g, 8.33 mmol, 1.37 mL) at -78 °C for 1 hour. The mixture was quenched with saturated ammonium chloride (30 mL), extracted with ethyl acetate (3 × 20 mL), washed with saturated sodium chloride (1 × 50 mL), dried over Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by column chromatography (SiO₂, petroleum ether/ether acetate = 3/1) to give (2-fluoro-3-methoxy-1-naphthyl) trifluoromethanesulfonate (1.10 g, 2.07 mmol, two steps 24.9 % yield) as a yellow solid. ES+APCI MS m/z 324.9 [M+H]⁺.

[0654] Step F: *tert*-butyl 4-[7-(2-fluoro-3-methoxy-1-naphthyl)-2-(3-morpholinopropoxy)-6,8-dihydro-5H-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate: A mixture of *tert*-butyl 4-[2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (0.40 g, 865 μmol), (2-fluoro-3-methoxy-1-naphthyl) trifluoromethanesulfonate (561 mg, 1.73 mmol), RuPhos (80.7 mg, 173 μmol), Pd₂(dba)₃ (79.2 mg, 86.5 μmol) and *t*-BuONa (249 mg, 2.59 mmol) in toluene (10 mL) was stirred at 110 °C for 5 hours under N₂. The mixture was diluted with water (10 mL), extracted with ether acetate (3 × 10 mL). The extracts were washed with saturated sodium chloride (1 × 20 mL), dried over Na₂SO₄, filtered

and concentrated under vacuum. The residue was purified by reversed phase flash chromatography [water (0.1 % Formic Acid)/acetonitrile] to give *tert*-butyl 4-[7-(2-fluoro-3-methoxy-1-naphthyl)-2-(3-morpholinopropoxy)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (0.35 g, 495 μ mol, 57.2 % yield) as a yellow oil. ES+APCI MS m/z 637.1 $[M+H]^+$.

[0655] Step G: 4-[3-[[7-(2-fluoro-3-methoxy-1-naphthyl)-4-piperazin-1-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-2-yl]oxy]propyl]morpholine: A mixture of *tert*-butyl 4-[7-(2-fluoro-3-methoxy-1-naphthyl)-2-(3-morpholinopropoxy)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (0.40 g, 628 μ mol) and TFA (1.07 g, 9.42 mmol, 698 μ L) in dichloromethane (0.70 mL) was stirred at 10 °C for 1 hour. The mixture was concentrated under vacuum to give 4-[3-[[7-(2-fluoro-3-methoxy-1-naphthyl)-4-piperazin-1-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-2-yl]oxy]propyl]morpholine (0.41 g, crude, TFA) as a yellow oil and used into next step without further purification. ES+APCI MS m/z 537.5 $[M+H]^+$.

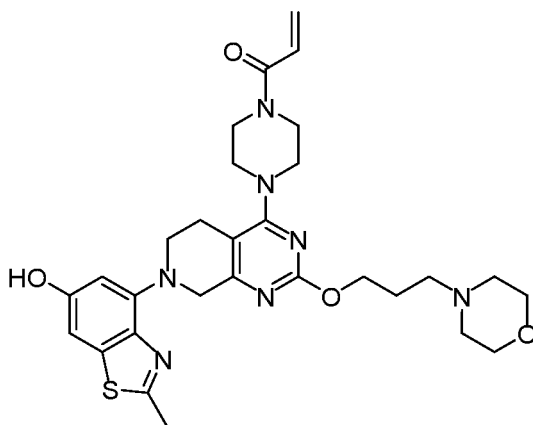
[0656] Step H: 1-[4-[7-(2-fluoro-3-methoxy-1-naphthyl)-2-(3-morpholinopropoxy)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one: To a solution of 4-[3-[[7-(2-fluoro-3-methoxy-1-naphthyl)-4-piperazin-1-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-2-yl]oxy]propyl]morpholine (0.41 g, crude, TFA salt) and TEA (635 mg, 6.27 mmol, 873 μ L) in dichloromethane (5.0 mL) was added prop-2-enoyl prop-2-enoate (79.1 mg, 627 μ mol) at -40 °C. After stirring at -40 °C for 0.5 h, the mixture was quenched with methanol (0.10 mL) and concentrated under vacuum. The residue was purified by column chromatography (Al_2O_3 , dichloromethane/methanol = 10/1) to give 1-[4-[7-(2-fluoro-3-methoxy-1-naphthyl)-2-(3-morpholinopropoxy)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one (0.25 g, 411 μ mol, two steps 65.5 % yield) as a yellow oil. ES+APCI MS m/z 591.0 $[M+H]^+$.

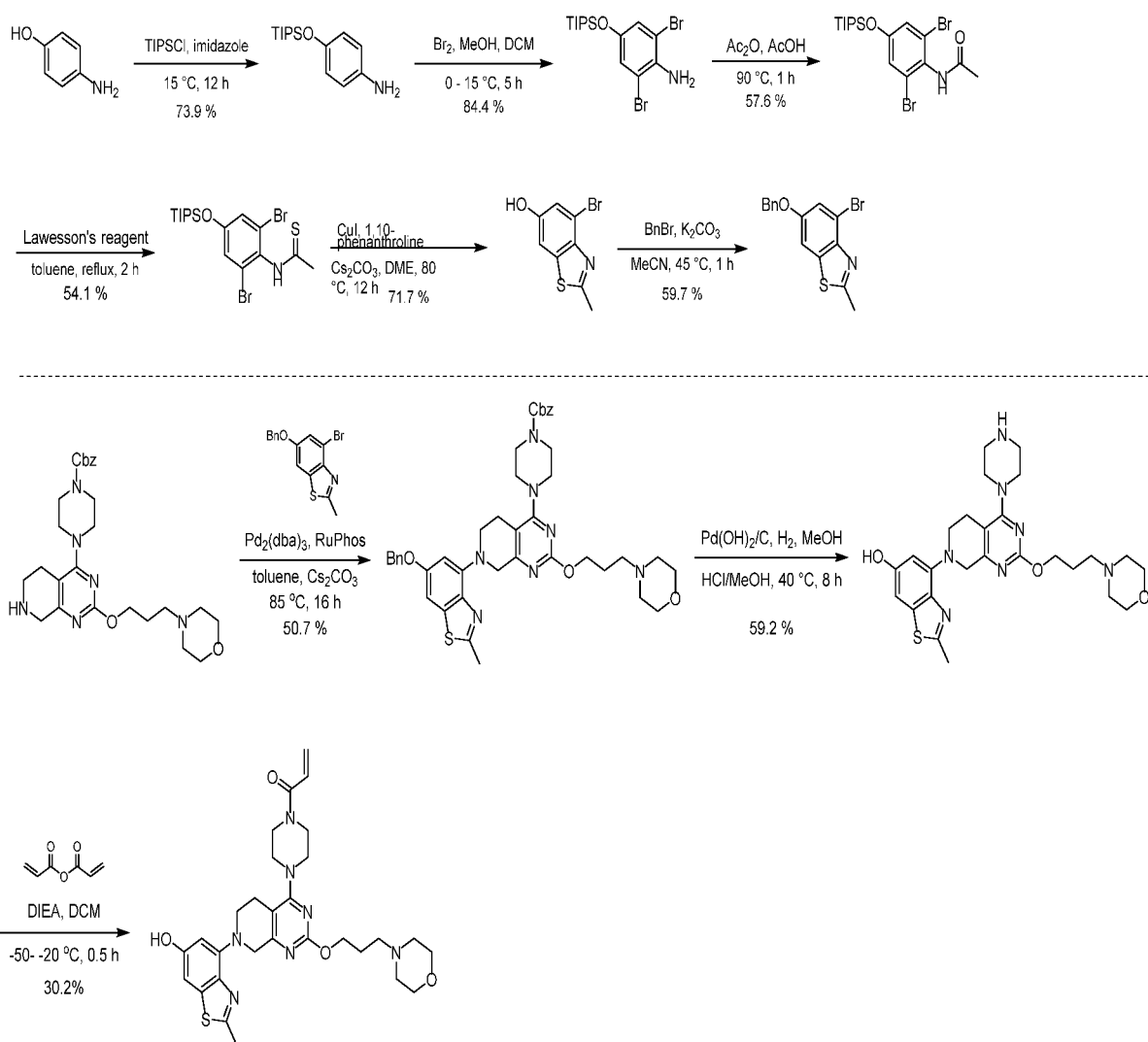
[0657] Step I: 1-[4-[7-(2-fluoro-3-hydroxy-1-naphthyl)-2-(3-morpholinopropoxy)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one: To a solution of 1-[4-[7-(2-fluoro-3-methoxy-1-naphthyl)-2-(3-morpholinopropoxy)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one (0.20 g, 339 μ mol) in dichloromethane (4.00 mL) was added BBr_3 (424 mg, 1.69 mmol, 163 μ L) at -78 °C for 0.5 hour and stirred at 0 °C for 2 hours. The mixture was quenched with saturated sodium bicarbonate (5 mL) at -78 °C and

stirred at 0 °C for 0.5 h. The mixture was extracted with dichloromethane (3×10 mL) and concentrated under vacuum. The residue was purified by prep-HPLC (column: Phenomenex Synergi C18 150*25*10um; mobile phase: [water(0.225% Formic Acid)-ACN]; B%: 13%-45%, 7min) to give 1-[4-[7-(2-fluoro-3-hydroxy-1-naphthyl)-2-(3-morpholinopropoxy)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one (35.2 mg, 60.8 μ mol, 17.9 % yield, 99.4 % purity) as a yellow solid. ES+APCI MS m/z 577.0[M+H]⁺.

EXAMPLE 166

1-[4-[7-(6-hydroxy-2-methyl-1,3-benzothiazol-4-yl)-2-(3-morpholinopropoxy)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one





[0658] Step A: 4-triisopropylsilyloxyaniline: To a solution of 4-aminophenol (5.00 g, 45.8 mmol, 7.14 mL) in DCM (50.0 mL) was added imidazole (4.06 g, 59.6 mmol). TIPSCl (13.3 g, 68.7 mmol, 14.7 mL) was added to the mixture dropwise. The mixture was stirred at 15 °C for 12 hours. Upon completion, the reaction mixture was filtered and the filtrate was concentrated under vacuum. The residue was purified by automated flash chromatography system (PE/EA 100/1 to 3/1) to give 4-triisopropylsilyloxyaniline (9.46 g, 33.9 mmol, 73.9 % yield, 95.0 % purity) as a black oil.

[0659] ^1H NMR (400 MHz, chloroform- d) δ = 6.74 - 6.71 (m, 1H), 6.71 - 6.69 (m, 1H), 6.60 - 6.58 (m, 1H), 6.58 - 6.55 (m, 1H), 3.66 - 2.98 (m, 2H), 1.28 - 1.16 (m, 3H), 1.11 - 1.06 (m, 18H)

[0660] Step B: 2,6-dibromo-4-triisopropylsilyloxy-aniline: To a solution of 4-triisopropylsilyloxyaniline (7.30 g, 27.5 mmol) in DCM (73.0 mL) and MeOH (73.0 mL) was added Br₂ (11.0 g, 68.8 mmol, 3.55 mL) in DCM (5 mL) dropwise at 0 °C. The mixture was stirred at 15 °C for 5 hours. Upon completion, the mixture was diluted with sodium sulfite solution (60 mL) and extracted with DCM (3 × 200 mL). The organic layers were dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by column chromatography (PE/EA 50/1 to 1/1) to give 2,6-dibromo-4-triisopropylsilyloxy-aniline (10.8 g, 23.2 mmol, 84.4 % yield, 90.8 % purity) as a brown oil. ES+APCI MS m/z 423.9[M+H]⁺.

[0661] Step C: N-(2,6-dibromo-4-triisopropylsilyloxy-phenyl)acetamide: To a solution of 2,6-dibromo-4-triisopropylsilyloxy-aniline (10.4 g, 24.6 mmol) and CH₃COOH (52 mL) was added acetic anhydride (10.9 g, 107 mmol, 10 mL). The reaction mixture was stirred at 90 °C for 1 hour. Upon completion, water (100 mL) and DCM (200 mL) were added and layers were separated. The aqueous phase was extracted with DCM (100 mL × 2). The combined extracts were washed with 5 % Na₂CO₃ (80 mL), washed with brine (100 mL), dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by column chromatography (PE/EA 50/1 to 1:1) to give N-(2,6-dibromo-4-triisopropylsilyloxy-phenyl)acetamide (7.32 g, 14.2 mmol, 57.6 % yield, 90.0 % purity) as a brown solid.

[0662] ¹H NMR (400 MHz, chloroform-d) δ = 7.16 (s, 1H), 7.11 (s, 2H), 2.21 (s, 3H), 1.28 - 1.24 (m, 3H), 1.12 - 1.09 (m, 18H).

[0663] Step D: N-(2,6-dibromo-4-triisopropylsilyloxy-phenyl)thioacetamide: To a solution of N-(2,6-dibromo-4-triisopropylsilyloxy-phenyl)acetamide (7.22 g, 15.5 mmol) in toluene (116 mL) was added LAWESSION'S REAGENT (3.14 g, 7.76 mmol). The mixture was heated to 110 °C for 2 hours. Upon completion, the mixture was concentrated under vacuum. The residue was purified by column chromatography (PE/EA 100/1 to 1/1) N-(2,6-dibromo-4-triisopropylsilyloxy-phenyl)thioacetamide (5.41 g, 8.40 mmol, 54.1 % yield, 74.7 % purity) as a yellow oil. ES+APCI MS m/z 481.9[M+H]⁺.

[0664] Step E: 4-bromo-2-methyl-1,3-benzothiazol-6-ol: CuI (94.2 mg, 494 μmol) was added to a solution of N-(2,6-dibromo-4-triisopropylsilyloxy-phenyl)thioacetamide (2.38 g, 4.94 mmol), 1,10-phenanthroline (134 mg, 741 μmol) and Cs₂CO₃ (4.83 g, 14.8 mmol) in DME (48.0 mL).

Then the reaction mixture was stirred at 80 °C for 12 hours under N₂. Upon completion, the reaction mixture was filtered and the filtrate was concentrated. The residue was purified by column chromatography (PE/EA 50/1 to 0/1) to give 4-bromo-2-methyl-1,3-benzothiazol-6-ol (1.33 g, 3.54 mmol, 71.7 % yield, 65.0 % purity) as a brown oil.

[0665] ¹H NMR (400 MHz, DMSO-d₆) δ = 7.33 (d, *J*=2.4 Hz, 1H), 7.14 (d, *J*=2.4 Hz, 1H), 3.40 - 3.33 (m, 1H), 2.72 (s, 3H).

[0666] Step F: 6-benzyloxy-4-bromo-2-methyl-1,3-benzothiazole: To a mixture of 4-bromo-2-methyl-1,3-benzothiazol-6-ol (1.28 g, 5.24 mmol) and K₂CO₃ (2.17 g, 15.72 mmol) in ACN (26.0 mL) was added BnBr (988 mg, 5.76 mmol, 685 uL). The reaction mixture was stirred at 45 °C for 1 hour. Upon completion, the reaction mixture was filtered and the filtrate was concentrated. The residue was purified by column chromatography (PE/EA 200/1 to 10/1) to give 6-benzyloxy-4-bromo-2-methyl-1,3-benzothiazole (1.10 g, 3.13 mmol, 59.7 % yield, 95.0 % purity) as a light yellow solid. ES+APCI MS *m/z* 336.2 [M+H]⁺.

[0667] Step G: benzyl 4-[7-(6-benzyloxy-2-methyl-1,3-benzothiazol-4-yl)-2-(3-morpholinopropoxy)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate: Benzyl 4-[2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (400 mg, 805 umol), 6-benzyloxy-4-bromo-2-methyl-1,3-benzothiazole (323 mg, 967 umol), RuPhos (75.2 mg, 161 umol), Cs₂CO₃ (787 mg, 2.42 mmol) and Pd₂(dba)₃ (73.8 mg, 80.6 umol) in toluene (16 mL) was stirring at 85 °C for 16 hours under N₂. Upon completion, the reaction mixture was filtered and the filtrate was concentrated. The residue was purified by column chromatography over Al₂O₃ (PE/EA 10/1 to 0/1) to give benzyl 4-[7-(6-benzyloxy-2-methyl-1,3-benzothiazol-4-yl)-2-(3-morpholinopropoxy)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (340 mg, 408 umol, 50.7 % yield, 90.0 % purity) as a yellow oil. ES+APCI MS *m/z* 750.5[M+H]⁺.

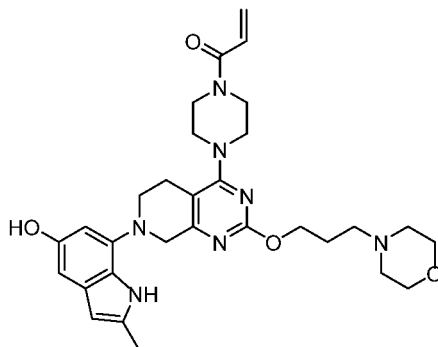
[0668] Step H: 2-methyl-4-[2-(3-morpholinopropoxy)-4-piperazin-1-yl]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-7-yl]-1,3-benzothiazol-6-ol: To a solution of benzyl 4-[7-(6-benzyloxy-2-methyl-1,3-benzothiazol-4-yl)-2-(3-morpholinopropoxy)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (160 mg, 213 umol) in MeOH (4 mL) was added HCl/MeOH (4 M, 533 uL), followed by Pd(OH)₂/C (80 mg, 533 umol) under N₂. The

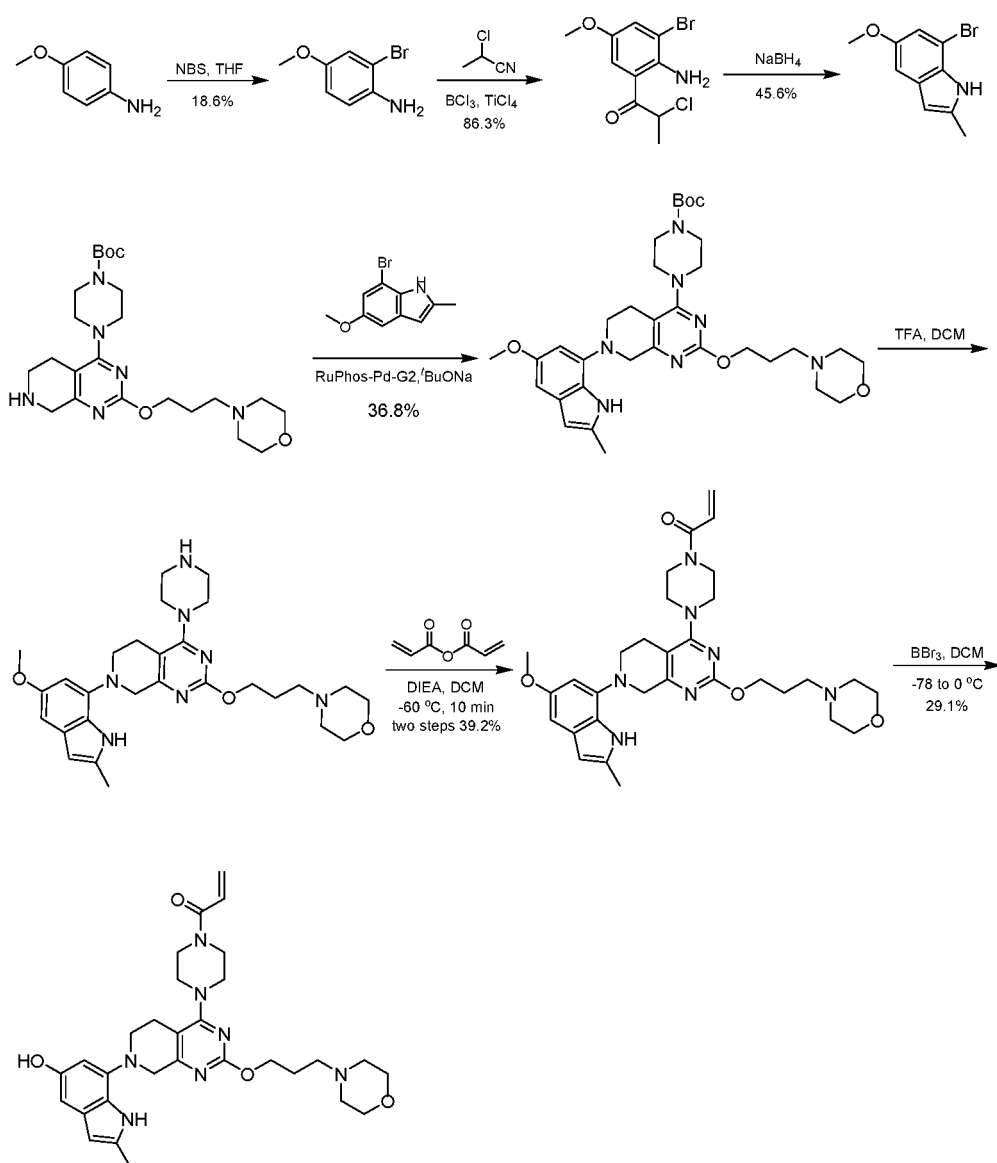
suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (15 psi) at 40 °C for 8 hours. Upon completion, the reaction mixture was filtered and the filtrate was concentrated to give 2-methyl-4-[2-(3-morpholinopropoxy)-4-piperazin-1-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]-1,3-benzothiazol-6-ol (110 mg, 126 umol, 59.2 % yield, 68.7 % purity, 2 HCl) as a yellow solid which was used directly in the next step without further purification. ES+APCI MS *m/z* 526.2[M+H]⁺.

[0669] Step I: 1-[4-[7-(6-hydroxy-2-methyl-1,3-benzothiazol-4-yl)-2-(3-morpholinopropoxy)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one: To a solution of 2-methyl-4-[2-(3-morpholinopropoxy)-4-piperazin-1-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]-1,3-benzothiazol-6-ol (110 mg, 184 umol, 2 HCl) and DIEA (143 mg, 1.10 mmol, 193 uL) in DCM (2.00 mL) was added prop-2-enoyl prop-2-enoate (18.5 mg, 147 umol) dropwise at - 50 °C. The mixture was stirred at -40 - -20 °C for 30 minutes. Upon completion, the mixture was quenched by MeOH (0.5 mL) and concentrated under vacuum. The residue was diluted with water (2 mL) and extracted with DCM (3 × 6 mL). The organic layers were dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by column chromatography over Al₂O₃ (DCM/MeOH 20/1 to 10/1), prep-HPLC (column: Gemini 150*25 5u; mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN]; B%: 21%-51%, 12min) to give 1-[4-[7-(6-hydroxy-2-methyl-1,3-benzothiazol-4-yl)-2-(3-morpholinopropoxy)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one (32.4 mg, 55.4 umol, 30.2 % yield, 99.1 % purity) as a yellow solid. ES+APCI MS *m/z* 580.4[M+H]⁺.

EXAMPLE 167

1-(4-(7-(5-hydroxy-2-methyl-1*H*-indol-7-yl)-2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one





[0670] Step A: 2-bromo-4-methoxyaniline: At $-10\text{ }^\circ\text{C}$, to a solution of 4-methoxyaniline (100 g, 812 mmol) in THF (3 L) was added *N*-bromosuccinimide (152 g, 853 mmol) in three portions and the mixture was stirred at the same temperature for 30 min. The mixture was concentrated under reduced pressure. The residue was purified by column chromatography. (petroleum ether/ethyl acetate 15/1) to give 2-bromo-4-methoxyaniline as red oil (30.58 g, 18.6% yield). ^1H NMR (400 MHz, CDCl_3) δ = 7.01 (d, J =2.4 Hz, 1H), 6.74-6.70 (m, 2H), 3.85-3.74 (m, 2H), 3.73 (s, 3H).

[0671] Step B: 1-(2-amino-3-bromo-5-methoxyphenyl)-2-chloropropan-1-one: To a $0\text{ }^\circ\text{C}$ solution of 2-bromo-4-methoxy-aniline (15.0 g, 74.2 mmol) in 1,1-dichloroethane (220 mL)

was added boron trichloride (1.00 M, 89.1 mL), 2-chloropropanenitrile (9.97 g, 111 mmol) and titanium tetrachloride (16.9 g, 89.1 mmol). The mixture was heated at 85 °C for 24 hours. The mixture was poured into ice and hydrochloric acid (20%, 300 mL) at 0 °C, concentrated and the residue was refluxed for 0.5 hour. This mixture was basified at 0 °C with sodium hydroxide (saturated aqueous, 120 mL) until pH 4 was attained and then extracted with ethyl acetate (300 mL × 2). The combined organic extracts were washed with brine (200 mL), dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate/dichloromethane 50/1/1), to give 1-(2-amino-3-bromo-5-methoxyphenyl)-2-chloropropan-1-one as yellow solid (18.7 g, 86.3% yield). ¹H NMR (400 MHz, CDCl₃) δ = 7.37 (d, *J* = 2.8 Hz, 1H), 7.32 (d, *J* = 2.8 Hz, 1H), 6.60 (brs, 2H), 5.25 (q, *J* = 6.4 Hz, 1H), 3.80 (s, 3H), 1.74 (d, *J* = 6.4 Hz, 3H).

[0672] Step C: 7-bromo-5-methoxy-2-methyl-1*H*-indole: To a solution of 1-(2-amino-3-bromo-5-methoxy-phenyl)-2-chloro-propan-1-one (18.7 g, 64.1 mmol) in dioxane (500 mL) and H₂O (50 mL) was added NaBH₄ (2.67 g, 70.5 mmol) and this mixture stirred at 100 °C for 15 hours. The mixture was cooled, diluted with hydrochloric acid (aq., 0.10 M, 100 mL) and extracted with dichloromethane (300 mL × 2). The organics were washed with brine (200 mL), dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate 25/1) to give 7-bromo-5-methoxy-2-methyl-1*H*-indole as yellow solid (7.01 g, 45.6% yield). ¹H NMR (400 MHz, CDCl₃) δ = 7.91 (brs, 1H), 7.03-6.91 (m, 2H), 6.23 (d, *J* = 1.2 Hz, 1H), 3.84 (s, 3H), 2.46 (s, 3H).

[0673] Step D: *tert*-butyl 4-(7-(5-methoxy-2-methyl-1*H*-indol-7-yl)-2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl)piperazine-1-carboxylate: To a mixture of *tert*-butyl 4-[2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (275 mg, 594 μmol) and 7-bromo-5-methoxy-2-methyl-1*H*-indole (130 mg, 540 μmol) in 2-methyl-2-butanol (15.0 mL) was added ^tBuONa (104 mg, 1.08 mmol) and chloro(2-dicyclohexylphosphino-2',6'-di-*i*-propoxy-1,1'-biphenyl)[2-(2-aminoethylphenyl)]palladium(II) methyl-*t*-butyl ether adduct (44.1 mg, 54.0 μmol). This mixture stirred at 90 °C for 8 hours under a N₂ atmosphere. The mixture was filtered, concentrated under reduced pressure. The residue was purified by prep-TLC (dichloromethane/methanol 10/1), to give *tert*-butyl 4-(7-(5-

methoxy-2-methyl-1*H*-indol-7-yl)-2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl)piperazine-1-carboxylate as yellow oil (131 mg, 36.8 % yield). ES+APCI MS m/z 622.4[M+H]⁺.

[0674] Step E: 4-[3-[[7-(5-methoxy-2-methyl-1*H*-indol-7-yl)-4-piperazin-1-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-2-yl]oxy]propyl]morpholine: To a 0 °C solution of *tert*-butyl 4-[7-(5-methoxy-2-methyl-1*H*-indol-7-yl)-2-(3-morpholinopropoxy)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (131 mg, 211 μ mol) in dichloromethane (10 mL) was added trifluoroacetic acid (2.00 mL) dropwise and the reaction stirred at 15 °C for 3 hours. The mixture was concentrated under reduced pressure, and the residue was used in the next step without further purification. (126 mg crude product). ES+APCI MS m/z 522.4[M+H]⁺.

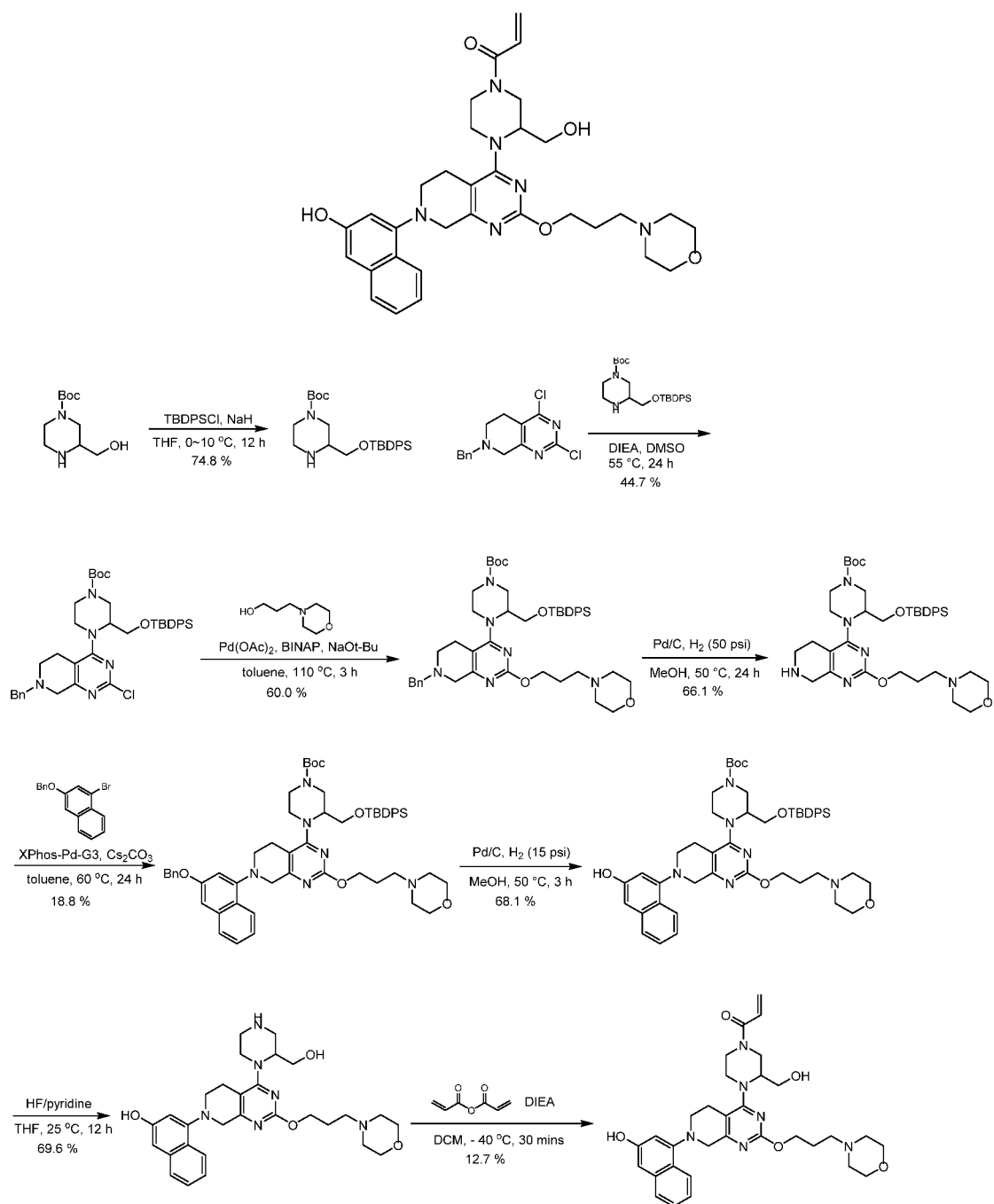
[0675] Step F: 1-(4-(7-(5-methoxy-2-methyl-1*H*-indol-7-yl)-2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one: To a -60 °C solution of 4-[3-[[7-(5-methoxy-2-methyl-1*H*-indol-7-yl)-4-piperazin-1-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-2-yl]oxy]propyl]morpholine (74 mg, 116 μ mol, trifluoroacetic acid salt) in dichloromethane (5 mL) was added diisopropylethylamine (45.1 mg, 349 μ mol, 60.8 μ L) and the mixture stirred at the same temperature for 10 min. The mixture was quenched with citric acid (aq., 1.00 mL), extracted with dichloromethane (10 mL $\times$ 2), washed with brine (15 mL), dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by prep-TLC to give 1-(4-(7-(5-methoxy-2-methyl-1*H*-indol-7-yl)-2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one as yellow solid (31 mg, 39.2 % yield). ES+APCI MS m/z 576.4[M+H]⁺.

[0676] Step G: 1-(4-(7-(5-hydroxy-2-methyl-1*H*-indol-7-yl)-2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one: To a -78 °C solution of 1-[4-[7-(5-methoxy-2-methyl-1*H*-indol-7-yl)-2-(3-morpholinopropoxy)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one (26 mg, 45.2 μ mol) in dichloromethane (5 mL) was added boron tribromide (56.6 mg, 226 μ mol, 21.8 μ L). The reaction was allowed to warm to 0 °C and stirred for 12 hours. The mixture was neutralized with NaHCO₃ (aq., 3 mL) and extracted with dichloromethane (5 mL $\times$ 2), washed with brine (10 mL), dried by anhydrous sodium sulfate, concentrated under vacuum. The residue was purified by prep-HPLC to give 1-(4-(7-(5-hydroxy-2-methyl-1*H*-indol-7-yl)-2-(3-

morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one as yellow solid (8.16 mg, 29.1% yield, 90.3% purity). ES+APCI MS m/z 562.5[M+H]⁺.

EXAMPLE 168

1-(3-(hydroxymethyl)-4-(7-(3-hydroxynaphthalen-1-yl)-2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one



[0677] Step A: *tert*-butyl 3-[[*tert*-butyl(diphenyl)silyl]oxymethyl]piperazine-1-carboxylate: To a solution of *tert*-butyl 3-(hydroxymethyl)piperazine-1-carboxylate (3.50 g, 16.2 mmol) in THF (30 mL) was added NaH (3.24 g, 80.9 mmol, 60.0 % purity) at 0 °C. After stirring for 30 minutes, TBDPSCl (6.67 g, 24.3 mmol, 6.23 mL) was added in one portion. The mixture was warmed to 10 °C and stirred for 12 hours under N₂ atmosphere. The reaction mixture was quenched by addition water at 0 °C, and then extracted with DCM (200 mL). The organic layer was dried with Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate 1/0 to 1/2) to give *tert*-butyl 3-[[*tert*-butyl(diphenyl)silyl]oxymethyl]piperazine-1-carboxylate (6.34 g, 12.1 mmol, 74.8 % yield, 86.8 % purity) as a colorless oil. ES+APCI MS *m/z* 455.3[M+H]⁺.

[0678] Step B: *tert*-butyl 4-(7-benzyl-2-chloro-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl)- 3-[[*tert*-butyl(diphenyl)silyl]oxymethyl]piperazine-1-carboxylate: A mixture of *tert*-butyl 3-[[*tert*-butyl(diphenyl)silyl]oxymethyl] piperazine-1-carboxylate (7.25 g, 13.9 mmol), 7-benzyl-2,4-dichloro-6,8-dihydro -5*H*-pyrido[3,4-*d*]pyrimidine (3.89 g, 13.2 mmol) and DIEA (4.27 g, 33.0 mmol, 5.77 mL) in DMSO (60 mL) was stirred at 55 °C for 24 hours under N₂ atmosphere. The reaction mixture was diluted with ethyl acetate (300 mL) and washed with brine (3 × 150 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate 1/0 to 3/1) to give *tert*-butyl 4-(7-benzyl-2-chloro-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl)- 3-[[*tert*-butyl(diphenyl)silyl]oxymethyl]piperazine-1-carboxylate (4.50 g, 5.91 mmol, 44.7 % yield, 93.5 % purity) as a yellow solid. ES+APCI MS *m/z* 721.3[M+H]⁺.

[0679] Step C: *tert*-butyl 4-[7-benzyl-2-(3-morpholinopropoxy)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-3-[[*tert*-butyl(diphenyl)silyl]oxymethyl]piperazine-1-carboxylate: A mixture of *tert*-butyl 4-(7-benzyl-2-chloro-6,8-dihydro-5*H*-pyrido [3,4-*d*]pyrimidin-4-yl)-3-[[*tert*-butyl(diphenyl)silyl]oxymethyl]piperazine-1-carboxylate (2.00 g, 2.81 mmol), 3-morpholinopropan-1-ol (815 mg, 5.62 mmol), Pd(OAc)₂ (94.6 mg, 422 μmol), BINAP (350 mg, 562 μmol) and *t*-BuONa (674 mg, 7.03 mmol) in toluene (30 mL) was degassed and purged with N₂ for 3 times, and then the mixture was heated to 110 °C and stirred for 3 hours under N₂ atmosphere. After completion, the reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, DCM/MeOH 70/1 to

20/1) to give *tert*-butyl 4-[7-benzyl-2-(3-morpholinopropoxy)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-3-[[*tert*-butyl(diphenyl)silyl]oxymethyl]piperazine-1-carboxylate (1.50 g, 1.69 mmol, 60.0 % yield, 92.3 % purity) as a yellow solid. ES+APCI MS *m/z* 821.4[M+H]⁺.

[0680] Step D: *tert*-butyl 3-[[*tert*-butyl(diphenyl)silyl]oxymethyl]-4-[2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate: To a solution of *tert*-butyl 4-[7-benzyl-2-(3-morpholinopropoxy)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-3-[[*tert*-butyl(diphenyl)silyl]oxymethyl]piperazine-1-carboxylate (1.50 g, 1.83 mmol) in MeOH (20 mL) was added Pd-C (10 %, 1.5 g) under N₂. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (50 psi) at 50 °C for 24 hours. The reaction mixture was filtered and concentrated under reduced pressure to give *tert*-butyl 3-[[*tert*-butyl(diphenyl)silyl]oxymethyl]-4-[2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (988 mg, 1.21 mmol, 66.1 % yield, 89.5 % purity) as a colorless oil, which was used directly for next step without further purification. ES+APCI MS *m/z* 731.5[M+H]⁺.

[0681] Step E: *tert*-butyl 4-[7-(3-benzyloxy-1-naphthyl)-2-(3-morpholinopropoxy)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-3-[[*tert*-butyl(diphenyl)silyl]oxymethyl]piperazine-1-carboxylate: A mixture of *tert*-butyl 3-[[*tert*-butyl(diphenyl)silyl]oxymethyl]-4-[2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (731 mg, 1.00 mmol), 3-benzyloxy-1-bromo-naphthalene (783 mg, 2.50 mmol), [2-(2-aminophenyl)phenyl]palladium(1+);dicyclohexyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane;methanesulfonate (169 mg, 200 μmol), Cs₂CO₃ (815 mg, 2.50 mmol) in toluene (15 mL) was degassed and purged with N₂ 3 times, and then the mixture was stirred at 60 °C for 24 hours under N₂ atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to dryness and purified by column chromatography (SiO₂, DCM/MeOH = 70/1 to 30/1) to give *tert*-butyl 4-[7-(3-benzyloxy-1-naphthyl)-2-(3-morpholinopropoxy)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-3-[[*tert*-butyl(diphenyl)silyl]oxymethyl]piperazine-1-carboxylate (250 mg, 188 μmol, 18.8 % yield, 72.3 % purity) as a yellow solid. ES+APCI MS *m/z* 963.4[M+H]⁺.

[0682] Step F: *tert*-butyl 3-[[*tert*-butyl(diphenyl)silyl]oxymethyl]-4-[7-(3-hydroxy-1-naphthyl)-2-(3-morpholinopropoxy)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-

carboxylate: To a solution of *tert*-butyl 4-[7-(3-benzyloxy-1-naphthyl)-2-(3-morpholinopropoxy)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-3-[[*tert*-butyl(diphenyl)silyl]oxymethyl]piperazine-1-carboxylate (250 mg, 188 μ mol) in MeOH (3 mL) was added 10% Pd/C (0.25 g) under N₂. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (15 psi) at 50 °C for 3 hours. After completion, the reaction mixture was filtered and concentrated under reduced pressure to dryness to give *tert*-butyl 3-[[*tert*-butyl(diphenyl)silyl]oxymethyl]-4-[7-(3-hydroxy-1-naphthyl)-2-(3-morpholinopropoxy)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (180 mg, 128 μ mol, 68.1 % yield, 62.0 % purity) as a dark yellow solid, which was used directly for next step without further purification. ES+APCI MS *m/z* 873.4[M+H]⁺.

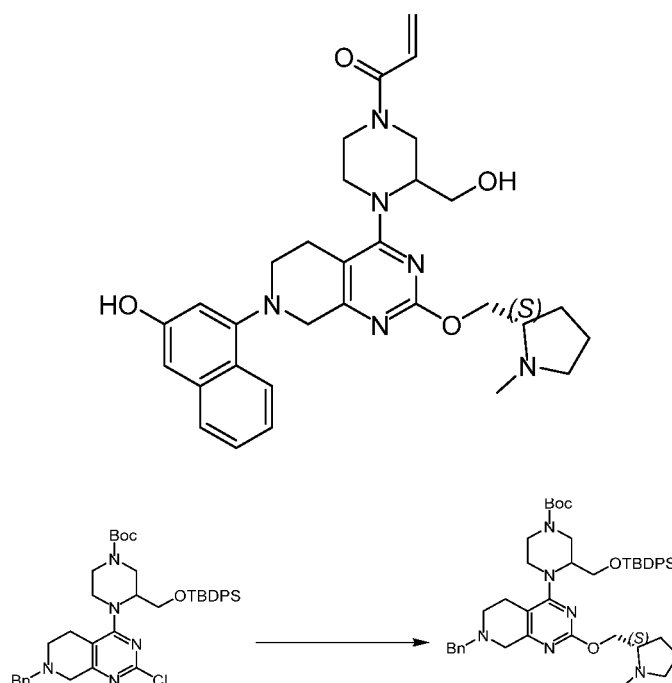
[0683] Step G: 4-[4-[2-(hydroxymethyl)piperazin-1-yl]-2-(3-morpholinopropoxy)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]naphthalen-2-ol: A mixture of *tert*-butyl 3-[[*tert*-butyl(diphenyl)silyl]oxymethyl]-4-[7-(3-hydroxy-1-naphthyl)-2-(3-morpholinopropoxy)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (130 mg, 149 μ mol), pyridine hydrofluoride (123 mg, 744 μ mol, 112 μ L, 60.0 % purity) in THF (1.5 mL) was stirred at 25 °C for 12 hours under N₂ atmosphere. The reaction mixture was concentrated under reduced pressure to dryness. The residue was purified by reverse phase HPLC (TFA condition; MeCN in H₂O; 0 ~ 30 %, flow rate; 40 mL/min). The desired fractions were concentrated under reduced pressure to give 4-[4-[2-(hydroxymethyl)piperazin-1-yl]-2-(3-morpholinopropoxy)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]naphthalen-2-ol (84 mg, 104 μ mol, 69.6 % yield, 94.1 % purity, 2TFA) as a yellow semisolid. ES+APCI MS *m/z* 535.3 [M+H]⁺.

[0684] Step H: 1-[3-(hydroxymethyl)-4-[7-(3-hydroxy-1-naphthyl)-2-(3-morpholinopropoxy)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one: To a mixture of 4-[4-[2-(hydroxymethyl)piperazin-1-yl]-2-(3-morpholinopropoxy)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]naphthalen-2-ol (84.0 mg, 114 μ mol, 2TFA), DIEA (36.9 mg, 285 μ mol, 49.8 μ L) in DCM (3 mL) was added prop-2-enoyl prop-2-enoate (8.63 mg, 68.44 μ mol) drop wise at -40 °C, and then stirred at -40 °C for 0.5 hours under N₂ atmosphere. The reaction mixture was quenched by addition MeOH (0.5 mL) and concentrated under reduced pressure to dryness. The residue was purified by prep-HPLC (column: Venusil XBP C8 150 * 25 * 10 μ m; mobile phase:

[water (0.225 % Formic Acid)-ACN]; B%: 10% - 40%, 10 min). The desired fractions were collected and lyophilized to dryness to give 1-[3-(hydroxymethyl)-4-[7-(3-hydroxy-1-naphthyl)-2-(3-morpholinopropoxy)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one (9.75 mg, 14.5 μ mol, 12.7 % yield, 94.4 % purity, Formic Acid Salt) as a yellow solid. ES+APCI MS m/z 589.3[M+H]⁺.

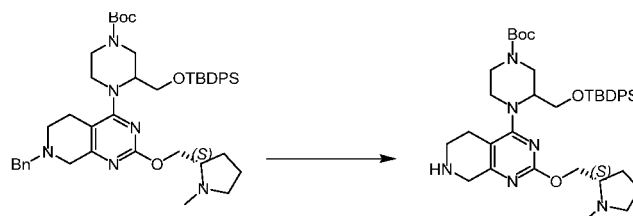
EXAMPLE 169

1-[3-(hydroxymethyl)-4-[7-(3-hydroxy-1-naphthyl)-2-[(2S)-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one

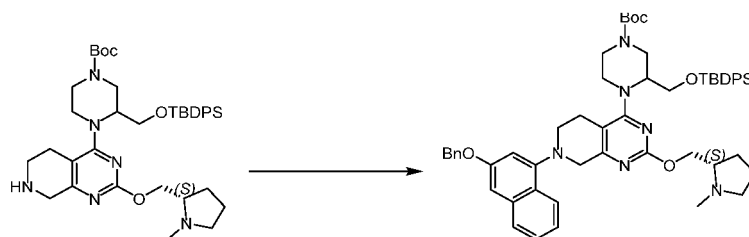


[0685] Step A: *tert*-butyl 4-[7-benzyl-2-[[[(2S)-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]-3-[[*tert*-butyl(diphenyl)silyl]oxymethyl]piperazine-1-carboxylate: To a mixture of *tert*-butyl 4-(7-benzyl-2-chloro-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl)-3-[[*tert*-butyl(diphenyl)silyl]oxymethyl]piperazine-1-carboxylate (495 mg, 694 μ mol), [(2S)-1-methylpyrrolidin-2-yl]methanol (160 mg, 1.39 mmol, 165 μ L) and sodium *tert*-butoxide (200 mg, 2.08 mmol) in toluene (25 mL) was added BINAP (86.5 mg, 139 μ mol) and Pd₂(dba)₃ (63.6 mg, 69.5 μ mol). The mixture was bubbled with nitrogen atmosphere and stirred at 80 °C for 6 h. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (2 $\times$ 15 mL). The combined organic layers were washed with water (2 $\times$ 30 mL),

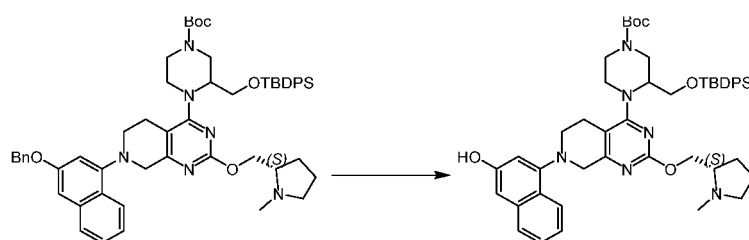
dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 30/1 to 1:1) to give *tert*-butyl 4-[7-benzyl-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-3-[[*tert*-butyl(diphenyl)silyl]oxymethyl]piperazine-1-carboxylate (207 mg, 262 μmol, 37.7 % yield) as a yellow solid. ¹H NMR (400MHz, chloroform-*d*) δ = 7.62 - 7.53 (m, 4H), 7.43 - 7.28 (m, 11H), 4.42 - 4.29 (m, 1H), 4.26 - 3.87 (m, 4H), 3.81 (br d, *J* = 13.2 Hz, 2H), 3.75 - 3.60 (m, 4H), 3.44 (dd, *J* = 1.6, 17.2 Hz, 1H), 3.24 - 3.04 (m, 3H), 2.96 (br s, 1H), 2.75 (br s, 3H), 2.49 (s, 3H), 2.43 - 2.28 (m, 2H), 2.10 - 1.96 (m, 2H), 1.91 - 1.80 (m, 1H), 1.80 - 1.67 (m, 2H), 1.43 (s, 9H), 1.02 - 0.89 (m, 9H).



[0686] Step B: *tert*-butyl 3-[[*tert*-butyl(diphenyl)silyl] oxymethyl]-4-[2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate: NH₃ was bubbled in methanol (30 mL) at -40 °C for 30 minutes. To a solution of *tert*-butyl 4-[7-benzyl-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-3-[[*tert*-butyl(diphenyl)silyl]oxymethyl]piperazine-1-carboxylate (530 mg, 670 μmol) in above mixture was added dry 10% Pd/C(0.30 g) under N₂. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred at 40°C for 10 hours under 15 psi of H₂. The reaction mixture was filtered and concentrated under reduced pressure to give *tert*-butyl 3-[[*tert*-butyl(diphenyl)silyl] oxymethyl]-4-[2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (394 mg, 427 μmol, 63.8 % yield) as a yellow solid. ¹H NMR (400MHz, chloroform-*d*) δ = 7.57 (br t, *J* = 6.0 Hz, 4H), 7.43 - 7.33 (m, 6H), 4.43 (br dd, *J* = 5.2, 10.4 Hz, 1H), 4.32 - 4.00 (m, 4H), 3.99 - 3.89 (m, 2H), 3.88 - 3.65 (m, 4H), 3.27 - 2.89 (m, 6H), 2.81 (br d, *J* = 8.4 Hz, 2H), 2.56 - 2.50 (m, 3H), 2.42 (br d, *J* = 16.8 Hz, 2H), 2.13 - 2.03 (m, 1H), 1.88 (br d, *J* = 6.8 Hz, 1H), 1.79 (br d, *J* = 5.2 Hz, 2H), 1.43 (s, 9H), 0.95 (br s, 9H).

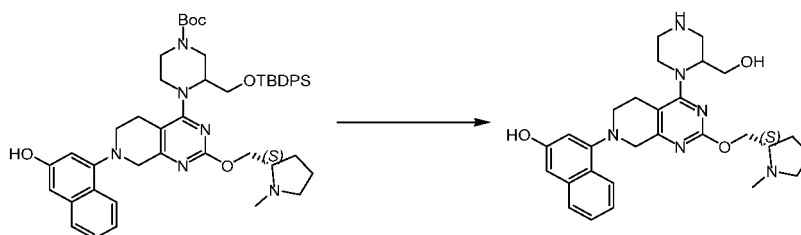


[0687] Step C: *tert*-butyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-3-[[*tert*-butyl(diphenyl)silyl]oxymethyl]piperazine-1-carboxylate: A mixture of *tert*-butyl 3-[[*tert*-butyl(diphenyl)silyl]oxymethyl]-4-[2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (0.16 g, 228 μmol), 3-benzyloxy-1-bromo-naphthalene (143 mg, 457 μmol), [2-(2-aminoethyl)phenyl]-chloro-palladium;dicyclohexyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane (16.9 mg, 22.8 μmol) and *t*-BuONa (43.9 mg, 457 μmol) in toluene (4 mL) was stirred at 70 °C for 12 hours under N_2 . The mixture was diluted with water (5.00 mL) and extracted with ether acetate (3 $\times$ 10 mL). The combined organics were washed with saturated sodium chloride (10 mL), dried over Na_2SO_4 , filtered and concentrated under vacuum. The residue was purified by reversed phase flash [water (formic acid, 0.1 %)/acetonitrile] to give *tert*-butyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-3-[[*tert*-butyl(diphenyl)silyl]oxymethyl]piperazine-1-carboxylate (0.15 g, 157 μmol , 68.9 % yield) as a yellow solid. ES+APCI MS m/z 933.1[M+H]⁺.

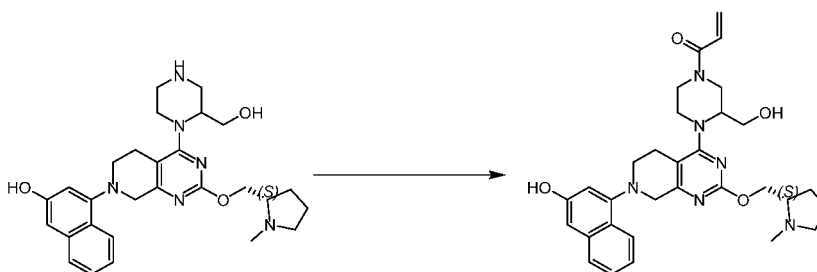


[0688] Step D: *tert*-butyl 3-[[*tert*-butyl(diphenyl)silyl]oxymethyl]-4-[7-(3-hydroxy-1-naphthyl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate: NH_3 was bubbled into methanol (10 mL) at -78 °C for 30 minutes. *tert*-butyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-3-[[*tert*-butyl(diphenyl)silyl]oxymethyl]piperazine-1-carboxylate (0.10 g, 107 μmol) and dry 10% Pd/C (0.01 g) were added and the mixture was

stirred at 10 °C for 1 hour under 15 psi of H₂. The slurry was filtered through a pad of celite and the filtrate concentrated under vacuum to give *tert*-butyl 3-[[*tert*-butyl(diphenyl)silyl]oxymethyl]-4-[7-(3-hydroxy-1-naphthyl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (0.09 g, crude) as a yellow oil and used into next step without further purification. ES+APCI MS *m/z* 843.0 [M+H]⁺.



[0689] Step E: 4-[4-[2-(hydroxymethyl)piperazin-1-yl]-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]naphthalen-2-ol: A mixture of *tert*-butyl 3-[[*tert*-butyl(diphenyl)silyl]oxymethyl]-4-[7-(3-hydroxy-1-naphthyl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (0.04 g, crude) and pyridine;hydrofluoride (118 mg, 712 μ mol, 106 μ L) in dichloromethane (2 mL) was stirred at 0 °C for 1 hour and stirred at 10 °C for 12 hours. The pH of the mixture was adjusted to pH>7 by addition of saturated sodium bicarbonate solution (3.00 mL) and concentrated under vacuum. The residue was purified by column chromatography (Al₂O₃, dichloromethane/methanol = 5/1) to give 4-[4-[2-(hydroxymethyl)piperazin-1-yl]-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]naphthalen-2-ol (0.04 g, crude) as a yellow solid. ES+APCI MS *m/z* 505.2 [M+H]⁺.

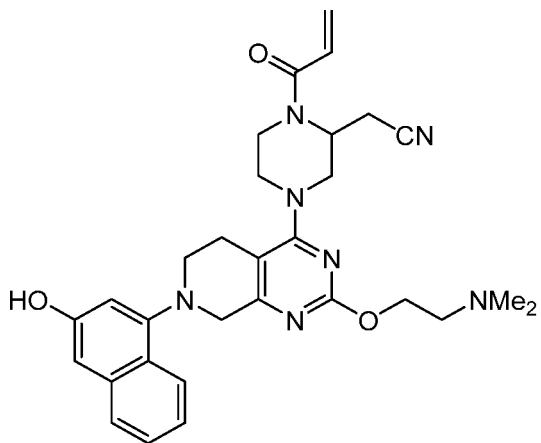


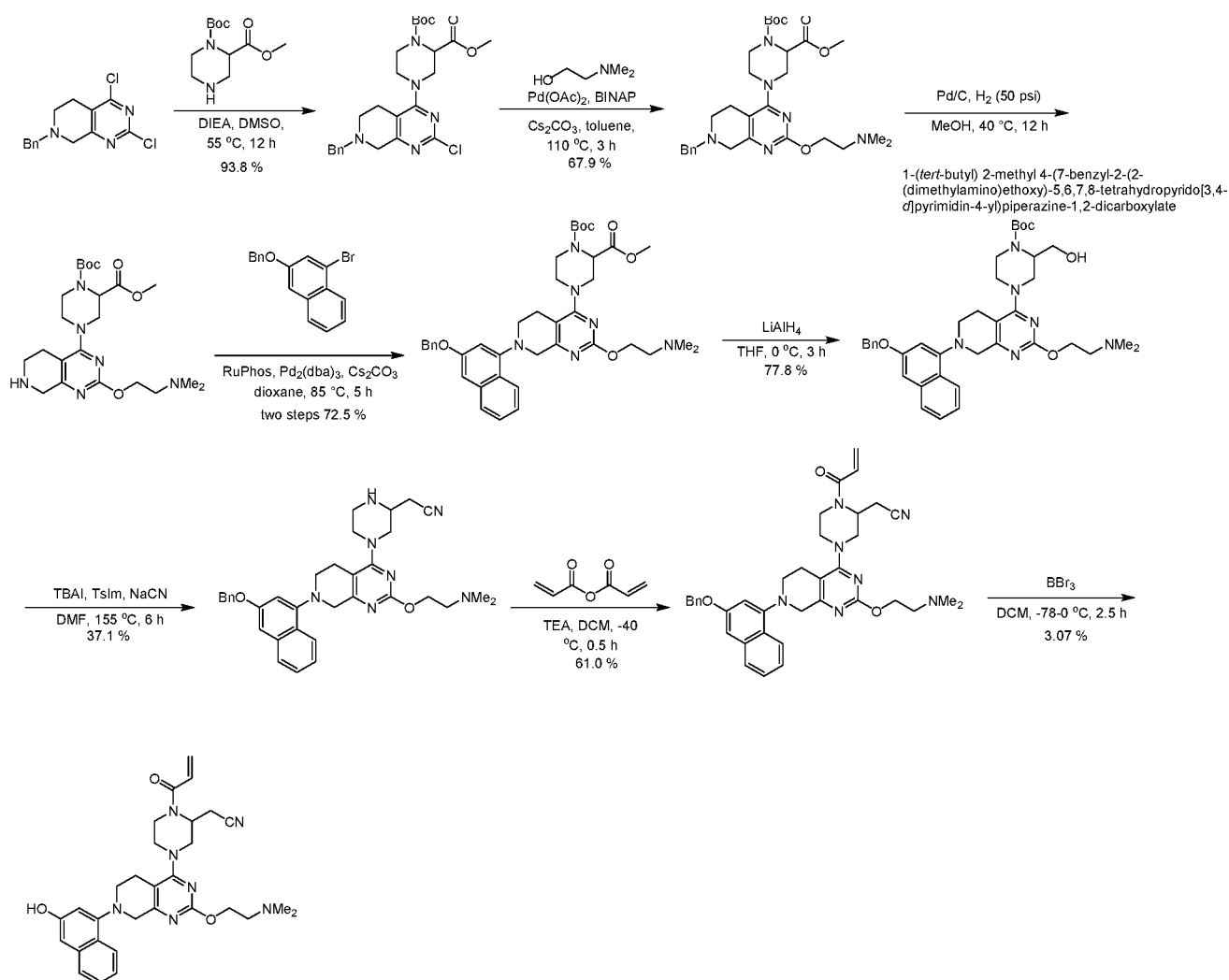
[0690] Step F: 1-[3-(hydroxymethyl)-4-[7-(3-hydroxy-1-naphthyl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one:

To a solution of 4-[4-[2-(hydroxymethyl)piperazin-1-yl]-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]naphthalen-2-ol (0.02 g, crude) and TEA (40.1 mg, 396 μ mol, 55.17 μ L) in dichloromethane (2 mL) was added prop-2-enoyl prop-2-enoate (999 μ g, 7.93 μ mol) at -40 °C, then the mixture was stirred at -40 °C for 0.5 h. The mixture was quenched by addition of methanol (0.10 mL) and concentrated under vacuum. The residue was purified by column chromatography (Al_2O_3 , dichloromethane/methanol = 5/1). The desired fractions were collected and concentrated under vacuum. The residue was purified by prep-HPLC (column: Phenomenex Gemini 150*25mm*10 μ m; mobile phase: [water (10mM NH_4HCO_3)-ACN]; B%: 38%-68%, 3min). The desired fractions were collected and lyophilized to give 1-[3-(hydroxymethyl)-4-[7-(3-hydroxy-1-naphthyl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one (1.08 mg, 1.73 μ mol). ES+APCI MS m/z 559.5 $[\text{M}+\text{H}]^+$.

EXAMPLE 170

2-(1-acryloyl-4-(2-(2-(dimethylamino)ethoxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl)piperazin-2-yl)acetonitrile





[0691] Step A: 1-(*tert*-butyl)2-methyl4-(7-benzyl-2-chloro-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl) piperazine-1,2-dicarboxylate: To a solution of 7-benzyl-2,4-dichloro-6,8-dihydro-5*H*-pyrido [3,4-*d*] pyrimidine (5.00 g, 17.0 mmol) and 1-*tert*-butyl 2-methylpiperazine-1,2- dicarboxylate (4.24 g, 17.3 mmol) in DMSO (80 mL) was added DIEA (5.49 g, 42.5 mmol, 7.42 mL). After stirring at 55 °C for 12 hours, the mixture was diluted with ethyl acetate (100 mL), washed with brine (3 × 150 mL), dried over Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by column chromatography (SiO₂, PE/EA = 3/1) to give 1-*tert*-butyl 2-methyl 4-(7-benzyl-2-chloro-6,8-dihydro-5*H*-pyrido[3,4-*d*] pyrimidin-4-yl)piperazine-1,2-dicarboxylate (8.00 g, 15.9 mmol, 93.8 % yield) as a yellow oil. ES+APCI MS *m/z* 502.1[M+H]⁺.

[0692] Step B: 1-(*tert*-butyl) 2-methyl 4-(7-benzyl-2-(2-(dimethylamino)ethoxy) -5,6,7,8-tetrahydropyrido [3,4-*d*]pyrimidin-4-yl) piperazine-1,2-dicarboxylate: A mixture of 1-*tert*-butyl 2-methyl 4-(7-benzyl-2-chloro-6,8-dihydro- 5*H*-pyrido[3,4-*d*]pyrimidin-4-yl) piperazine-1,2-dicarboxylate (8.00 g, 15.9 mmol), 2-(dimethylamino)ethanol (2.84 g, 31.9 mmol, 3.19 mL), Cs₂CO₃ (13.0 g, 39.8 mmol), Pd(OAc)₂ (537 mg, 2.39 mmol) and BINAP (1.98 g, 3.19 mmol) in toluene (30 mL) was stirred at 110 °C for 3 hours under nitrogen. The mixture was diluted with water (30 mL) and then extracted with ethyl acetate (3 × 50 mL). The extracts were washed with brine (1 × 100 mL), dried over Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by reverse phase HPLC (TFA, 0.1 %) to give 1-*tert*-butyl 2-methyl 4-[7-benzyl-2-[2-(dimethylamino)ethoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1,2-dicarboxylate (6.00 g, 10.8 mmol, 67.9 % yield) as a yellow solid. ES+APCI MS *m/z* 555.3[M+H]⁺.

[0693] Step C: 1-*tert*-butyl 2-methyl 4-[2-[2-(dimethylamino)ethoxy]- 5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1,2-dicarboxylate: A mixture of 1-*tert*-butyl 2-methyl 4-[7-benzyl-2-[2-(dimethylamino)ethoxy]-6,8-dihydro- 5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1,2-dicarboxylate (6.00 g, 10.8 mmol) and 10% Pd/C (600 mg, 10.8 mmol) in MeOH (100 mL) was stirred at 40 °C for 12 hours under H₂ at 50 psi. The mixture was filtered and the filtrate was concentrated under vacuum to give 1-*tert*-butyl 2-methyl 4-[2-[2-(dimethylamino)ethoxy]- 5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1,2-dicarboxylate (4.50 g, crude) was obtained as a yellow solid. ES+APCI MS *m/z* 465.3[M+H]⁺.

[0694] Step D: 1-*tert*-butyl 2-methyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[2-(dimethylamino)ethoxy]-6,8-dihydro-5*H*- pyrido[3,4-*d*]pyrimidin-4-yl]piperazine -1,2-dicarboxylate: A mixture of 1-*tert*-butyl 2-methyl 4-[2-[2-(dimethylamino)ethoxy]- 5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1,2-dicarboxylate (2.90 g, 6.24 mmol), 3-benzyloxy-1-bromo-naphthalene (2.54 g, 8.12 mmol), Pd₂(dba)₃ (857 mg, 936 μmol), RuPhos (728 mg, 1.56 mmol) and Cs₂CO₃ (5.08 g, 15.6 mmol) in 1,4-dioxane (150 mL) was stirred at 85 °C for 5 hours under N₂. The mixture was diluted with water (100 mL), extracted with DCM (1 × 200 mL). The extracts were, washed with brine (1 × 300 mL), dried over Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by reverse phase HPLC (TFA, 0.1 %) to give 1-*tert*-butyl 2-methyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[2-(dimethylamino)ethoxy]-6,8-

dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1,2-dicarboxylate (3.50 g, 5.02 mmol, two steps 72.5 % yield) as a brown solid. ES+APCI MS m/z 697.3 $[M+H]^+$.

[0695] Step E: *tert*-butyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[2-(dimethylamino)ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]-2-(hydroxymethyl)piperazine-1-carboxylate: To a solution of 1-*tert*-butyl 2-methyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[2-(dimethylamino)ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1,2-dicarboxylate (1.00 g, 1.44 mmol) in THF (10 mL) was added $LiAlH_4$ (219 mg, 5.76 mmol) in portions at $-60\text{ }^\circ\text{C}$. After stirring for 2 hours, the mixture was quenched with saturated sodium sulfate solution (0.3 mL), filtered and the filter cake washed with DCM (100 mL). The combined filtrate was concentrated under vacuum to give *tert*-butyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[2-(dimethylamino)ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]-2-(hydroxymethyl)piperazine-1-carboxylate (750 mg, 1.12 mmol, 77.8 % yield) as a yellow solid. ES+APCI MS m/z 669.3 $[M+H]^+$.

[0696] Step F: 2-[4-[7-(3-benzyloxy-1-naphthyl)-2-[2-(dimethylamino)ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazin-2-yl]acetonitrile: A mixture of *tert*-butyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[2-(dimethylamino)ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]-2-(hydroxymethyl)piperazine-1-carboxylate (100 mg, 149 μmol), TBAI (11.1 mg, 29.9 μmol), 1-(*p*-tolylsulfonyl)imidazole (79.9 mg, 359 μmol), NaCN (0.12 g, 2.45 mmol), and TEA (37.8 mg, 374 μmol , 51.8 μL) in DMF was stirred at $155\text{ }^\circ\text{C}$ for 6 hours. The mixture was concentrated under vacuum, diluted with water ($1 \times 5\text{ mL}$) and then extracted with ethyl acetate ($3 \times 10\text{ mL}$). The extracts were washed with brine ($1 \times 20\text{ mL}$), dried over Na_2SO_4 , filtered and concentrated under vacuum. The residue was purified by prep-HPLC column: Phenomenex Gemini C18 250*50mm*10 μm ; mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN]; B%: 50%-70%, 28 MIN) to give 2-[4-[7-(3-benzyloxy-1-naphthyl)-2-[2-(dimethylamino)ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazin-2-yl]acetonitrile (160 mg, 277 μmol , 37.1 % yield) as a yellow solid. ES+APCI MS m/z 578.5 $[M+H]^+$.

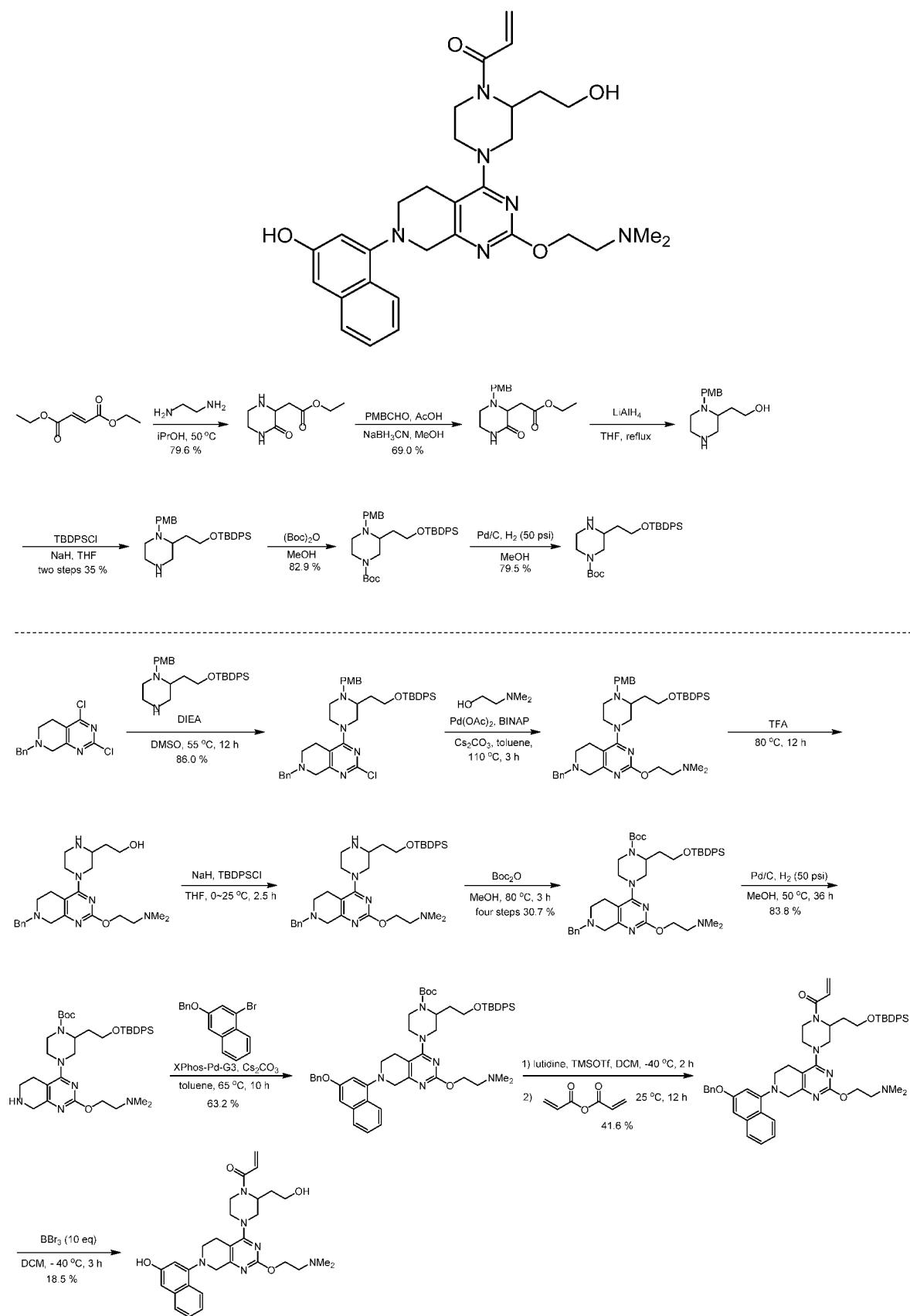
[0697] Step G: 2-[4-[7-(3-benzyloxy-1-naphthyl)-2-[2-(dimethylamino)ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile: To a solution of 2-[4-[7-(3-benzyloxy-1-naphthyl)-2-[2-(dimethylamino)ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazin-2-yl]acetonitrile (60 mg, 104 μmol) and DIEA (67.1 mg, 519 μmol ,

90.7 uL) in DCM (2 mL) was added prop-2-enoyl prop-2-enoate (13.1 mg, 104 umol) at 0 °C. After stirred at 10 °C for 4 hours, the mixture was quenched with MeOH (0.1 mL), then concentrated under vacuum. The residue was purified by column chromatography (SiO₂, DCM/MeOH 10/1) to give 2-[4-[7-(3-benzyloxy-1-naphthyl)-2-[2-(dimethylamino)ethoxy] - 6,8-dihydro-5*H*-pyrido [3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile (40.0 mg, 63.3 umol, 61.0 % yield) as a yellow oil. ES+APCI MS *m/z* 632.3[M+H]⁺.

[0698] Step H: 2-[4-[2-[2-(dimethylamino)ethoxy]-7-(3-hydroxy-1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile: To a solution of 2-[4-[7-(3-benzyloxy-1-naphthyl)-2-[2-(dimethylamino)ethoxy] -6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile (30 mg, 47.5 umol) in DCM (2 mL) was added BBr₃ (35.7 mg, 142 umol, 13.7 uL) at -78 °C under 0.5 h. The mixture was warmed up to 0 °C and stirred for 2 hours. The mixture was concentrated under vacuum and then quenched with saturated sodium bicarbonate solution at -78 - 0 °C. The mixture was purified by column chromatography (Al₂O₃, DCM/MeOH = 5/1), then further purified by prep-HPLC (column: Gemini 150*25 5u;mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN];B%: 30%-60%,12min). The desired fractions were collected and lyophilized to give 2-[4-[2-[2-(dimethylamino)ethoxy]-7-(3-hydroxy-1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile (810 ug, 1.46 umol, 3.07% yield, 97.5% purity) as a yellow solid. ES+APCI MS *m/z* 542.5 [M+H]⁺.

EXAMPLE 171

1-(4-(2-(2-(dimethylamino)ethoxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl)-2-(2-hydroxyethyl)piperazin-1-yl)prop-2-en-1-one



[0699] Step A: Ethyl 2-(3-oxopiperazin-2-yl)acetate: To a solution of diethyl (*E*)-but-2-enedioate (30.2 g, 175 mmol, 28.8 mL) in *i*-PrOH (300 mL) was added ethane-1,2-diamine (11.0 g, 183 mmol, 12.2 mL). After stirring at 25 °C for 12 hours, the reaction mixture was concentrated under reduced pressure to dryness. The crude white solid was washed with MTBE (500 mL) and dried under vacuum to give ethyl 2-(3-oxopiperazin-2-yl)acetate (26.0 g, 140 mmol, 79.6 % yield, 100 % purity) as a white solid. ¹H NMR (400 MHz, Chloroform-*d*) δ = 6.55 (br s, 1H), 4.15 (q, *J* = 6.8 Hz, 2H), 3.80 - 3.72 (m, 1H), 3.47 (dt, *J* = 4.8, 11.2 Hz, 1H), 3.36 - 3.22 (m, 1H), 3.18 - 3.08 (m, 1H), 3.07 - 2.95 (m, 2H), 2.76 - 2.70 (m, 1H), 1.25 (t, *J* = 7.2 Hz, 3H).

[0700] Step B: Ethyl 2-[1-[(4-methoxyphenyl)methyl]-3-oxo-piperazin-2-yl]acetate: To a mixture of ethyl 2-(3-oxopiperazin-2-yl)acetate (23.6 g, 127 mmol) in methanol (400 mL) was added 4-methoxybenzaldehyde (18.9 g, 139 mmol, 16.9 mL) and CH₃COOH (15.2 g, 253 mmol, 14.5 mL) at 0 °C. After stirring at 0 °C for 1 hour, the reaction mixture was cooled to -10 °C. NaBH₃CN (23.9 g, 380 mmol) was added to the mixture in portions and the reaction mixture was warmed up to 15 °C and stirring for another 11 hours. The reaction was quenched by adding water (400 mL) and extracted with DCM (2 × 300 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The residue was re-dissolved with ethyl acetate (300 mL), then washed with 0.5 M HCl solution (2 × 200 mL). The aqueous phase was adjusted to pH 7 ~ 8 with Na₂CO₃ solid, then extracted with DCM (2 × 300 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated to give ethyl 2-[1-[(4-methoxyphenyl)methyl]-3-oxo-piperazin-2-yl]acetate (27.2 g, 87.6 mmol, 69.0 % yield, 98.5 % purity) as colorless oil. ES+APCI MS *m/z* 307.1 [M+H]⁺.

[0701] Step C: 2-[1-[(4-methoxyphenyl)methyl]piperazin-2-yl]ethanol: To a mixture of ethyl 2-[1-[(4-methoxyphenyl)methyl]-3-oxo-piperazin-2-yl]acetate (27.2 g, 88.8 mmol) in THF (500 mL) was added LiAlH₄ (10.1 g, 266 mmol) in portions at 0 °C. After stirring at 0 °C for 1 hour, the reaction mixture was heated to 70 °C and stirred for 11 hours. After completion, the reaction was quenched with sat. Na₂SO₄ aqueous (40 mL), filtered and then concentrated. The product 2-[1-[(4-methoxyphenyl)methyl]piperazin-2-yl]ethanol (20 g, crude) was obtained as yellow oil. ES+APCI MS *m/z* 251.1 [M+H]⁺.

[0702] Step D: *tert*-butyl-[2-[1-[(4-methoxyphenyl)methyl] piperazin-2-yl]ethoxy]- diphenyl-silane: To a mixture of 2-[1-[(4-methoxyphenyl)methyl]piperazin-2-yl]ethanol (20 g, crude) in THF(300 mL) was added NaH (15.9 g, 399 mmol, 60 % purity) at 0 °C in portions, then a solution of TBDPSCl (65.9 g, 239 mmol, 61.6 mL) in THF (100 mL) was added. The mixture was warmed up to 15 °C and stirred for a further 12 hours. After completion, the reaction was poured into NH₄Cl solution (300 mL), and extracted with DCM (2 × 300 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (SiO₂, Petroleum ether: Ethyl acetate 3/1 to Dichloromethane/Methanol 10/1) to give *tert*-butyl-[2-[1-[(4-methoxyphenyl)methyl] piperazin-2-yl]ethoxy]-diphenyl-silane (29.5 g, 59.9 mmol, two steps 35 %, 99.2 % purity) as yellow oil. ES+APCI MS m/z 489.4[M+H]⁺.

[0703] Step E: *tert*-butyl 3-[2-[*tert*-butyl(diphenyl)silyl]oxyethyl]-4-[(4-methoxyphenyl)methyl] piperazine-1-carboxylate: To a mixture of *tert*-butyl-[2-[1-[(4-methoxyphenyl) methyl] piperazin-2-yl]ethoxy]-diphenyl-silane (11.0 g, 22.5 mmol) in MeOH (200 mL) was added TEA (6.83 g, 67.5 mmol, 9.36 mL) and (Boc)₂O (9.82 g, 45.0 mmol, 10.3 mL). After stirring at 15 °C for 3 hours, the reaction was concentrated. The residue was purified by column chromatography (SiO₂, Petroleum ether: Ethyl acetate 1/0 to 5/1) to give *tert*-butyl 3-[2-[*tert*-butyl(diphenyl)silyl]oxyethyl]-4-[(4-methoxyphenyl)methyl] piperazine-1-carboxylate (11.0 g, 18.7 mmol, 82.9 % yield, 100 % purity) as colorless oil. ES+APCI MS m/z 589.4 [M+H]⁺.

[0704] Step F: *tert*-butyl 3-[2-[*tert*-butyl(diphenyl) silyl]oxyethyl]piperazine-1-carboxylate: To a mixture of *tert*-butyl 3-[2-[*tert*-butyl(diphenyl)silyl]oxyethyl]-4- [(4-methoxyphenyl)methyl]piperazine-1-carboxylate (9.00 g, 15.3 mmol) in MeOH (150 mL) was added 10% Pd/C (849 umol). The suspension was degassed under vacuum and purged with H₂ for three times. The mixture was stirred under H₂ (50 Psi) at 40 °C for 18 hours. After completion, the reaction mixture was filtered through a Celite plug and the filtrate was concentrated. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate 10/1 to 3:1) to give *tert*-butyl 3-[2-[*tert*-butyl(diphenyl) silyl]oxyethyl]piperazine-1-carboxylate (5.80 g, 12.2 mmol, 79.5 % yield, 98.2 % purity) as colorless oil. ES+APCI MS m/z 469.4 [M+H]⁺.

[0705] Step G: 2-[4-(7-benzyl-2-chloro-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl)-1-[(4-methoxyphenyl)methyl]piperazin-2-yl]ethoxy-*tert*-butyl-diphenyl-silane: A mixture of 7-benzyl-2,4-dichloro-6,8-dihydro-5*H*-pyrido[3,4-*d*] pyrimidine (4.00 g, 13.6 mmol), *tert*-butyl-[2-[1-[(4-methoxyphenyl)methyl] piperazin-2-yl]ethoxy]-diphenyl-silane (6.98 g, 14.3 mmol) and DIEA (4.39 g, 34.0 mmol, 5.93 mL) in DMSO (80 mL) was degassed and purged with N₂ for 3 times, and the mixture was heated to at 55 °C and stirred for 12 hours under N₂ atmosphere. The reaction mixture was diluted with water (300 mL) and extracted with ethyl acetate (3 × 200 mL). The combined organic layers were washed with brine (3 × 200 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to dryness. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate 1/0 to 3/1) to give 2-[4-(7-benzyl-2-chloro-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl)-1-[(4-methoxyphenyl)methyl]piperazin-2-yl]ethoxy-*tert*-butyl-diphenyl-silane (9.00 g, 11.7 mmol, 86.0 % yield, 97.0 % purity) as a yellow oil. ES+APCI MS *m/z* 746.4[M+H]⁺.

[0706] Step H: 2-[[7-benzyl-4-[3-[2-[*tert*-butyl(diphenyl)silyl]oxyethyl]-4-[(4-methoxyphenyl)methyl]piperazin-1-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-2-yl]oxy]-*N,N*-dimethylethanamine: A mixture of 2-(dimethylamino)ethanol (2.39 g, 26.8 mmol, 2.69 mL), 2-[4-(7-benzyl-2-chloro-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl)-1-[(4-methoxyphenyl)methyl]piperazin-2-yl]ethoxy-*tert*-butyl-diphenyl-silane (8.00 g, 10.7 mmol), Pd(OAc)₂ (361 mg, 1.61 mmol), BINAP (1.34 g, 2.14 mmol) and Cs₂CO₃ (8.73 g, 26.8 mmol) in toluene (100 mL) was degassed and purged with N₂ for 3 times. The mixture was heated to 110 °C and stirred for 3 hours under N₂ atmosphere. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to dryness. The residue was purified by column chromatography (SiO₂, DCM/MeOH 50/1 to 10/1) to give 2-[[7-benzyl-4-[3-[2-[*tert*-butyl(diphenyl)silyl]oxyethyl]-4-[(4-methoxyphenyl)methyl]piperazin-1-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-2-yl]oxy]-*N,N*-dimethylethanamine (6.50 g, crude) as a yellow semisolid. ES+APCI MS *m/z* 799.4 [M+H]⁺.

[0707] Step I: 2-[4-[7-benzyl-2-[2-(dimethyl amino)ethoxy]-6,8-dihydro-5*H*-pyrido [3,4-*d*]pyrimidin-4-yl]piperazin-2-yl]ethanol: 2-[4-[7-benzyl-2-[2-(dimethyl amino)ethoxy]-6,8-dihydro-5*H*-pyrido [3,4-*d*]pyrimidin-4-yl]piperazin-2-yl]ethanol: A solution of 2-[[7-benzyl-4-[3-[2-[*tert*-butyl (diphenyl)silyl]oxyethyl] -4-[(4-methoxyphenyl)methyl]piperazin-1-yl] -6,8-

dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-2-yl]oxy]-*N,N*-dimethyl-ethanamine (6.50 g, crude) in TFA (80 mL) was stirred at 80 °C for 12 hours. The reaction mixture was concentrated under reduced pressure to dryness and the residue was re-dissolved into DCM (300 mL) and washed with water (200 mL). The water phase was collected and basified with saturated NaHCO₃ aqueous to pH ~ 8 and then extracted with DCM (3 × 200 mL). The combined organic phase was dried over Na₂SO₄, filtered and concentrated under reduced pressure to give 2-[4-[7-benzyl-2-[2-(dimethyl amino)ethoxy]-6,8-dihydro-5*H*-pyrido [3,4-*d*]pyrimidin-4-yl]piperazin-2-yl]ethanol (3.00 g, crude) as a yellow semisolid, which was used directly for next step without further purification.

[0708] Step J: 2-[[7-benzyl-4-[3-[2-[*tert*-butyl(diphenyl)silyl]oxyethyl]piperazin-1-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-2-yl]oxy]-*N,N*-dimethyl-ethanamine: A solution of 2-[4-[7-benzyl-2-[2-(dimethylamino)ethoxy]-6,8-dihydro -5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-2-yl]ethanol (3.0 g, crude) in THF (40 mL) was added NaH (1.36 g, 34.1 mmol, 60.0 % purity) at 0 °C. After stirring for 30 minutes, TBDPSCl (2.81 g, 10.2 mmol, 2.63 mL) was added by portions. The mixture was warmed to 25 °C and stirred for another 2 hours under N₂ atmosphere. The reaction mixture was quenched by addition water (30 mL) at 0 °C and extracted into ethyl acetate(3 × 100 mL). The combined organic layers were washed with brine (3 × 100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to dryness to give 2-[[7-benzyl-4-[3-[2-[*tert*-butyl(diphenyl)silyl]oxyethyl]piperazin-1-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-2-yl]oxy]-*N,N*-dimethyl-ethanamine (6.00 g, crude) as a yellow oil, which was used directly for next step without further purification. ES+APCI MS *m/z* 679.4 [M+H]⁺.

[0709] Step K: *tert*-butyl4-[7-benzyl-2-[2-(dimethylamino)ethoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-2-[2-[*tert*-butyl(diphenyl)silyl]oxyethyl]piperazine-1-carboxylate: A mixture of 2-[[7-benzyl-4-[3-[2-[*tert*-butyl(diphenyl)silyl]oxyethyl] piperazin-1-yl]-6,8-dihydro- 5*H*-pyrido[3,4-*d*]pyrimidin-2-yl]oxy]-*N,N*-dimethyl-ethanamine (6.0 g, crude), Boc₂O (18.5 g, 84.8 mmol, 19.5 mL) in MeOH (3 mL) was degassed and purged with N₂ for 3 times. The mixture was heated to 80 °C and stirred for 3 hours under N₂ atmosphere. The reaction mixture was concentrated under reduced pressure to dryness. The residue was purified by column chromatography (SiO₂, DCM /MeOH 1/0 to 10/1) to give *tert*-butyl4-[7-benzyl-2-[2-

(dimethylamino)ethoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-2-[2-*tert*-butyl(diphenyl)silyl]oxyethyl]piperazine-1-carboxylate (3.10 g, 3.28 mmol, four steps 30.7 % yield, 82.2 % purity) as a semisolid. ES+APCI MS *m/z* 779.4 [M+H]⁺.

[0710] Step L: *tert*-butyl2-[2-[*tert*-butyl(diphenyl)silyl]oxyethyl]-4-[2-[2-(dimethylamino)ethoxy]-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate: To a solution of *tert*-butyl4-[7-benzyl-2-[2-(dimethylamino)ethoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-2-[2-[*tert*-butyl(diphenyl)silyl]oxyethyl]piperazine-1-carboxylate (3.10 g, 3.28 mmol, 82.2 % purity) in MeOH (60 mL) was added Pd-C (10 %, 2 g) under N₂. The suspension was degassed under vacuum and purged with H₂ for three times. The mixture was stirred under H₂ (50 psi) at 50 °C for 36 hours. The reaction mixture was filtered and concentrated under reduced pressure to dryness to give *tert*-butyl2-[2-[*tert*-butyl(diphenyl)silyl]oxyethyl]-4-[2-[2-(dimethylamino)ethoxy]-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (2.20 g, 2.75 mmol, 83.8 % yield, 86.0 % purity) as a yellow solid, which was used directly for next step without further purification. ES+APCI MS *m/z* 689.4 [M+H]⁺.

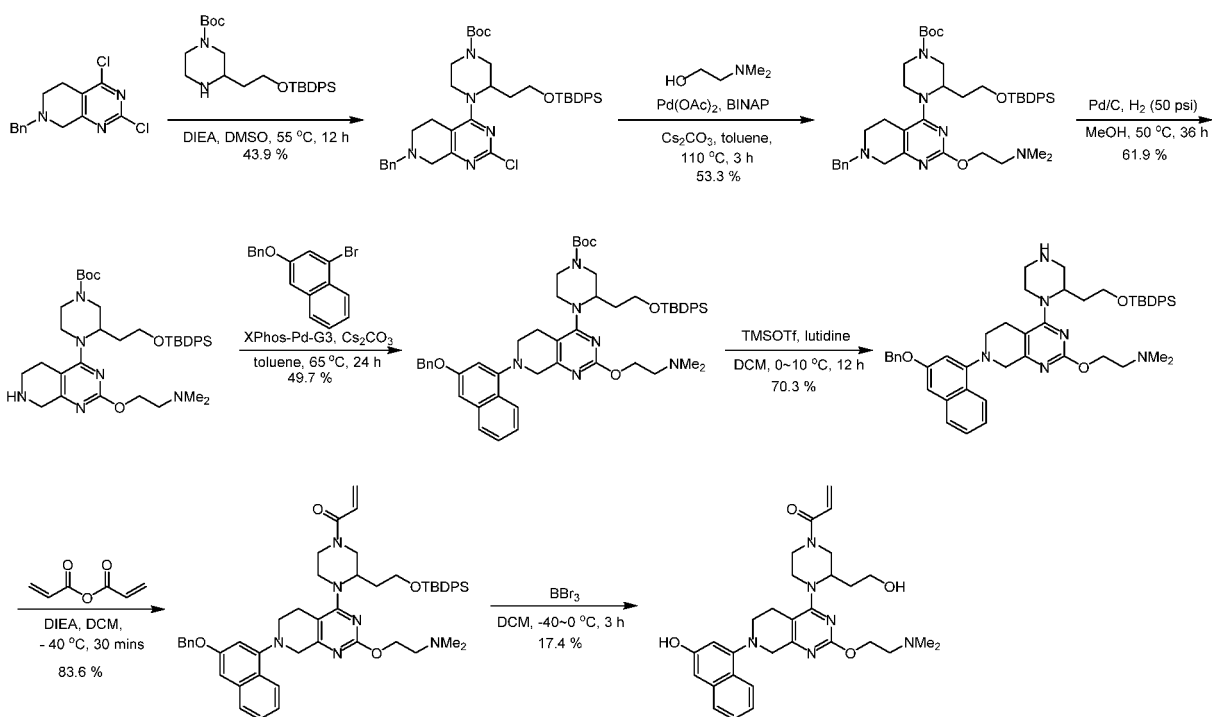
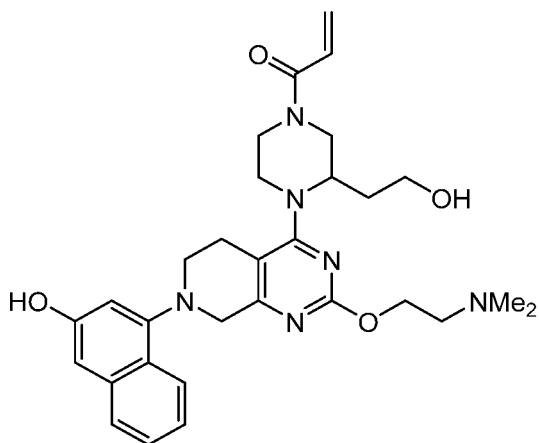
[0711] Step M: *tert*-butyl4-[7-(3-benzyloxy-1-naphthyl)-2-[2-(dimethylamino)ethoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-2-[2-[*tert*-butyl(diphenyl)silyl]oxyethyl]piperazine-1-carboxylate: A mixture of *tert*-butyl2-[2-[*tert*-butyl(diphenyl)silyl]oxyethyl]-4-[2-[2-(dimethylamino)ethoxy]-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (1.85 g, 2.69 mmol), 3-benzyloxy-1-bromo-naphthalene (1.09 g, 3.49 mmol), Cs₂CO₃ (2.19 g, 6.71 mmol), [2-(2-aminophenyl)phenyl]palladium(1+); dicyclohexyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane;methanesulfonate (341 mg, 403 μmol) in toluene (40 mL) was degassed and purged with N₂ for 3 times, and the mixture was stirred at 65 °C for 10 hours under N₂ atmosphere. After completion, the reaction mixture was filtered and concentrated under reduced pressure to dryness. The residue was purified by column chromatography (SiO₂, DCM/MeOH 1/0 to 10 /1) to give *tert*-butyl4-[7-(3-benzyloxy-1-naphthyl)-2-[2-(dimethylamino)ethoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-2-[2-[*tert*-butyl(diphenyl)silyl]oxyethyl]piperazine-1-carboxylate (1.85 g, 1.69 mmol, 63.2 % yield, 84.3 % purity) as a yellow solid. ES+APCI MS *m/z* 922.5 [M+H]⁺.

[0712] Step N: 1-[4-[7-(3-benzyloxy-1-naphthyl)-2-[2-(dimethylamino)ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]-2-[2-[*tert*-butyl(diphenyl)silyl]oxyethyl]piperazin-1-yl]prop-2-en-1-one: To a solution of *tert*-butyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[2-(dimethylamino)ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]-2-[2-[*tert*-butyl(diphenyl)silyl]oxyethyl]piperazine-1-carboxylate (500 mg, 543 μ mol), 2,6-lutidine (700 mg, 6.51 mmol, 759 μ L) in DCM (10 mL) was added TMSOTf (724 mg, 3.26 mmol, 588 μ L). After stirring at 40 °C for 2 hours under N₂ atmosphere, the reaction mixture was cooled to -40 °C and prop-2-enoyl prop-2-enoate (137 mg, 1.09 mmol) was added portionwise. The reaction mixture was warmed to 25 °C and stirred for another 12 hours under N₂ atmosphere. After completion, the reaction mixture was purified directly by column chromatography (SiO₂, DCM/MeOH 30/1 to 10/1) to give 1-[4-[7-(3-benzyloxy-1-naphthyl)-2-[2-(dimethylamino)ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]-2-[2-[*tert*-butyl(diphenyl)silyl]oxyethyl]piperazin-1-yl]prop-2-en-1-one (256 mg, 226 μ mol, 41.6 % yield, 77.2 % purity) as a semisolid. ES+APCI MS m/z 875.5 [M+H]⁺.

[0713] Step O: 1-[4-[2-[2-(dimethylamino)ethoxy]-7-(3-hydroxy-1-naphthyl)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]-2-(2-hydroxyethyl)piperazin-1-yl]prop-2-en-1-one: To a solution of 1-[4-[7-(3-benzyloxy-1-naphthyl)-2-[2-(dimethyl amino)ethoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]-2-[2-[*tert*-butyl(diphenyl)silyl]oxyethyl]piperazin-1-yl]prop-2-en-1-one (133 mg, 152 μ mol) in DCM (5.00 mL) was added BBr₃ (571 mg, 2.28 mmol, 220 μ L) dropwise at -40 °C. The reaction mixture was warmed to 0 °C and stirred for 3 hours. The mixture was concentrated under reduced pressure to dryness. The crude material was washed with MTBE (25 mL) and the solid was collected. The solid was washed with saturated NaHCO₃ solution (0.5 mL) to pH ~ 8 at 0 °C then dissolved in MeOH (3 mL). The mixture was directly purified by prep-HPLC(column: Boston Green ODS 150*30 5 μ ; mobile phase: [water (0.225 % Formic Acid)-ACN]; B %: 15 % - 39 %, 10 min) to give 1-[4-[2-[2-(dimethylamino)ethoxy]-7-(3-hydroxy-1-naphthyl)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]-2-(2-hydroxyethyl)piperazin-1-yl]prop-2-en-1-one (16.7 mg, 28.2 μ mol, 18.5 % yield, 99.9 % purity, Formic Acid Salt) as a yellow solid. ES+APCI MS m/z 547.3 [M+H]⁺.

EXAMPLE 172

1-(4-(2-(2-(dimethylamino)ethoxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)-3-(2-hydroxyethyl)piperazin-1-yl)prop-2-en-1-one



[0714] Step A: *tert*-butyl 4-(7-benzyl-2-chloro-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl)-3-[2-[*tert*-butyl(diphenyl)silyl]oxyethyl]piperazine-1-carboxylate: A mixture of 7-benzyl-2,4-dichloro- 6,8-dihydro-5*H*-pyrido[3,4-*d*] pyrimidine (3.04 g, 10.3 mmol), *tert*-butyl 3-[2-[*tert*-butyl(diphenyl)silyl]oxyethyl] piperazine-1-carboxylate (5.08 g, 10.8 mmol), DIEA (3.34 g, 25.8 mmol, 4.51 mL) in DMSO (60 mL) was degassed and purged with N₂ for 3 times. The

mixture heated to 55 °C and stirred for 16 hours under a N₂ atmosphere. After cooling to room temperature, the reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with brine (3 × 100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to dryness. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate 1/0 to 3/1) to give *tert*-butyl 4-(7-benzyl-2-chloro-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl)-3-[2-[*tert*-butyl(diphenyl)silyl]oxyethyl]piperazine-1-carboxylate (3.50 g, 4.53 mmol, 43.9 % yield, 94.0 % purity) as a yellow semisolid. ES+APCI MS *m/z* 726.4 [M+H]⁺.

[0715] Step B: *tert*-butyl 4-[7-benzyl-2-[2-(dimethylamino)ethoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-3-[2-[*tert*-butyl(diphenyl)silyl]oxyethyl]piperazine-1-carboxylate: A mixture of 2-(dimethylamino)ethanol (1.07 g, 12.1 mmol, 1.21 mL), *tert*-butyl 4-(7-benzyl-2-chloro-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl)-3-[2-[*tert*-butyl(diphenyl)silyl]oxyethyl]piperazine-1-carboxylate (3.50 g, 4.82 mmol), Pd(OAc)₂ (162 mg, 723 μmol), BINAP (600 mg, 964 μmol) and Cs₂CO₃ (3.92 g, 12.1 mmol) in toluene (40 mL) was degassed and purged with N₂ for 3 times. The mixture was heated to 110 °C with stirring for 3 hours under N₂ atmosphere. After cooling to the room temperature, the reaction mixture was filtered and concentrated under reduced pressure to dryness. The residue was purified by column chromatography (SiO₂, DCM/MeOH = 1/0 to 10/1) to give *tert*-butyl 4-[7-benzyl-2-[2-(dimethylamino)ethoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-3-[2-[*tert*-butyl(diphenyl)silyl]oxyethyl]piperazine-1-carboxylate (2.30 g, 2.57 mmol, 53.3 % yield, 87.0 % purity) as a yellow solid. ES+APCI MS *m/z* 779.5 [M+H]⁺.

[0716] Step C: *tert*-butyl 3-[2-[*tert*-butyl(diphenyl)silyl]oxyethyl]-4-[2-[2-(dimethylamino)ethoxy]-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate: To a solution of *tert*-butyl 4-[7-benzyl-2-[2-(dimethylamino)ethoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-3-[2-[*tert*-butyl(diphenyl)silyl]oxyethyl] piperazine-1-carboxylate (2.30 g, 2.95 mmol) in MeOH (40 mL) was added Pd-C(10%, 1.5 g) under N₂. The suspension was degassed under vacuum and purged with H₂ several times. After stirring under H₂ (50 psi) at 50 °C for 36 hours, the reaction mixture was filtered and concentrated under reduced pressure to give *tert*-butyl 3-[2-[*tert*-butyl(diphenyl)silyl]oxyethyl]-4-[2-[2-(dimethylamino)ethoxy]-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-

carboxylate (1.58 g, 1.83 mmol, 61.9 % yield, 79.6 % purity) as a colorless oil, which was used directly for next step without further purification. ES+APCI MS m/z 689.4 $[M+H]^+$.

[0717] Step D: *tert*-butyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[2-(dimethylamino)ethoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-3-[2-[*tert*-butyl(diphenyl)silyl]oxyethyl] piperazine-1-carboxylate: A mixture of *tert*-butyl 3-[2-[*tert*-butyl(diphenyl)silyl]oxyethyl]-4-[2-[2-(dimethylamino)ethoxy]-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl] piperazine-1-carboxylate (1.48 g, 2.15 mmol), 3-benzyloxy-1-bromo-naphthalene (875 mg, 2.80 mmol), Cs_2CO_3 (1.75 g, 5.38 mmol), [2-(2-aminophenyl)phenyl]palladium(1+); dicyclohexyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane; methanesulfonate (273 mg, 323 μ mol) in toluene (30 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 65 °C for 24 hours under N_2 atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to dryness. The residue was purified by column chromatography (Al_2O_3 , DCM/MeOH = 1/0 to 20/1) to give *tert*-butyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[2-(dimethylamino)ethoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-3-[2-[*tert*-butyl(diphenyl)silyl]oxyethyl]piperazine-1-carboxylate (1.20 g, 1.07 mmol, 49.7 % yield, 82.0 % purity) as a yellow solid. ES+APCI MS m/z 921.4 $[M+H]^+$.

[0718] Step E: 2-[[7-(3-benzyloxy-1-naphthyl)-4-[2-[2-[*tert*-butyl(diphenyl)silyl]oxyethyl]piperazin-1-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-2-yl]oxy]-*N,N*-dimethyl-ethanamine: A mixture of *tert*-butyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[2-(dimethyl amino)ethoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-3-[2-[*tert*-butyl(diphenyl)silyl]oxyethyl]piperazine-1-carboxylate (300 mg, 326 μ mol) and 2,6-lutidine (419 mg, 3.91 mmol, 455 μ L) in DCM (10 mL) was added TMSOTf (434 mg, 1.95 mmol, 353 μ L) portionwise at 0 °C. The mixture was warmed to 10 °C and stirred for 12 hours under N_2 atmosphere. The reaction mixture was purified directly by column chromatography (Al_2O_3 , DCM/MeOH 1/0 to 50/1) to give 2-[[7-(3-benzyloxy-1-naphthyl)-4-[2-[2-[*tert*-butyl(diphenyl)silyl]oxyethyl]piperazin-1-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-2-yl]oxy]-*N,N*-dimethyl-ethanamine (210 mg, 229 μ mol, 70.3 % yield, 89.5 % purity) as a yellow semi-solid. ES+APCI MS m/z 821.5 $[M+H]^+$.

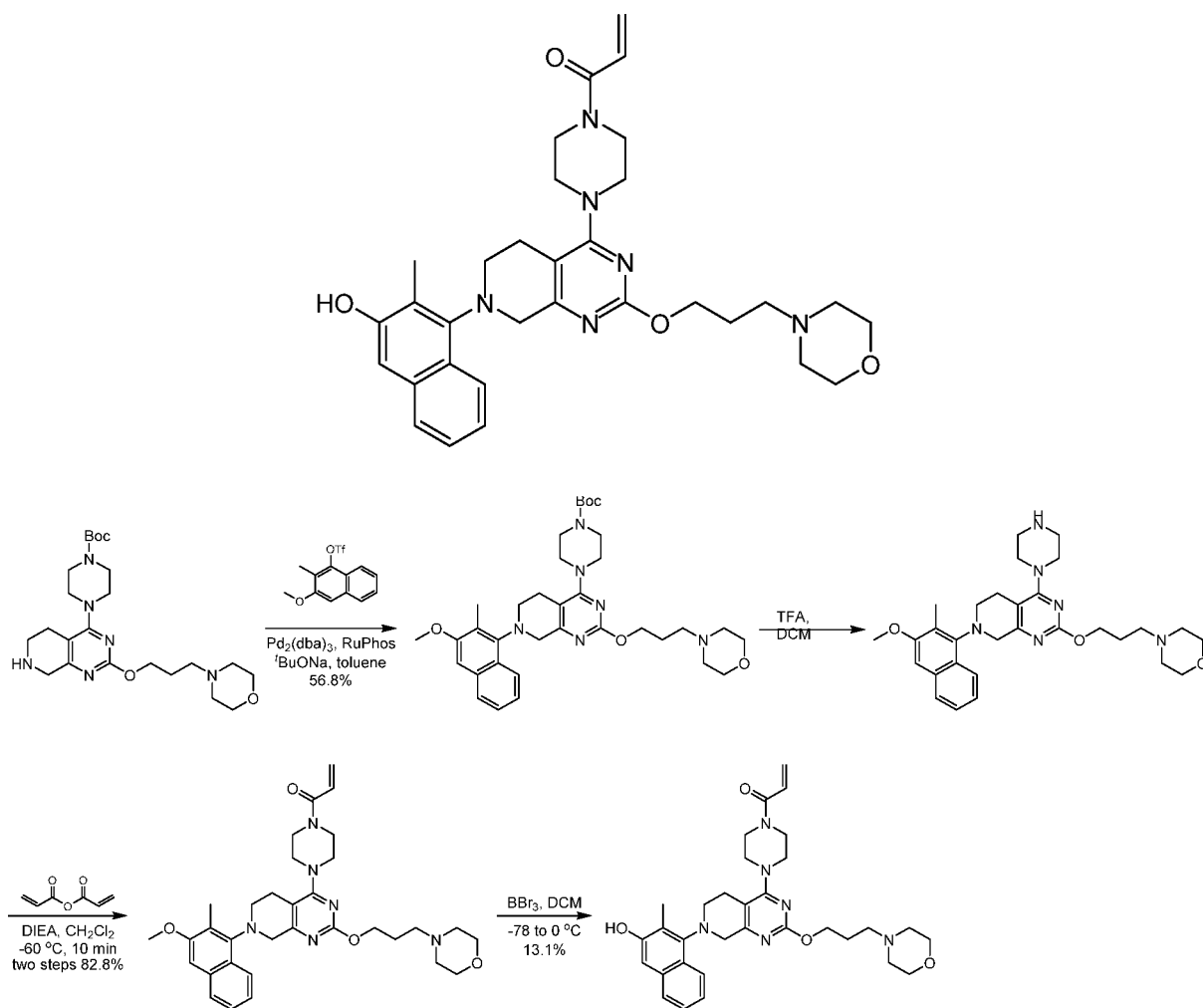
[0719] Step F: 1-[4-[7-(3-benzyloxy-1-naphthyl)-2-[2-(dimethylamino)ethoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-3-[2-[*tert*-butyl(diphenyl)silyl]oxyethyl]piperazin-1-yl]prop-

2-en-1-one: To a mixture of 2-[[7-(3-benzyloxy-1-naphthyl)-4-[2-[2-*tert*-butyl (diphenyl)silyl]oxyethyl]piperazin-1-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-2-yl]oxy]-*N,N*-dimethylethanamine (210 mg, 256 μ mol) and DIEA (49.6 mg, 384 μ mol, 67.0 μ L) in DCM (10 mL) was added prop-2-enoyl prop-2-enoate (33.9 mg, 269 μ mol) portionwise at $-40\text{ }^{\circ}\text{C}$ under nitrogen atmosphere. After stirring for 30 minutes at the same temperature, the reaction mixture was purified directly by column chromatography (Al_2O_3 , DCM/MeOH 1/0 to 50/1) to give 1-[4-[7-(3-benzyloxy-1-naphthyl)-2-[2-(dimethylamino)ethoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-3-[2-[*tert*-butyl(diphenyl)silyl]oxyethyl]piperazin-1-yl]prop-2-en-1-one (221 mg, 214 μ mol, 83.6 % yield, 84.7 % purity) as a slight yellow semi-solid. ES+APCI MS m/z 875.4 $[\text{M}+\text{H}]^+$.

[0720] Step G: 1-[4-[2-[2-(dimethylamino)ethoxy]-7-(3-hydroxy-1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-3-(2-hydroxyethyl)piperazin-1-yl]prop-2-en-1-one: A mixture of 1-[4-[7-(3-benzyloxy-1-naphthyl)-2-[2-(dimethylamino)ethoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-3-[2-[*tert*-butyl(diphenyl)silyl]oxyethyl]piperazin-1-yl]prop-2-en-1-one (221 mg, 253 μ mol) in DCM (10 mL) was added BBr_3 (949 mg, 3.79 mmol, 365 μ L) at $-40\text{ }^{\circ}\text{C}$. The mixture was stirred at $0\text{ }^{\circ}\text{C}$ for 3 hours under N_2 atmosphere. The reaction mixture was concentrated under reduced pressure to dryness. The crude pdt was washed with MTBE (25 mL), saturated NaHCO_3 solution (0.5 mL) to pH ~ 8 at $0\text{ }^{\circ}\text{C}$ and dissolved in MeOH (3 mL). The resulting solution was purified by prep-HPLC (column: Boston Green ODS 150*30 5 μ ; mobile phase: [water (0.225 % Formic Acid) - ACN]; B %: 11 % - 41 %, 10 min) to give 1-[4-[2-[2-(dimethylamino)ethoxy]-7-(3-hydroxy-1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-3-(2-hydroxyethyl)piperazin-1-yl]prop-2-en-1-one (26.7 mg, 44.0 μ mol, 17.4 % yield, 97.8 % purity, Formic Acid Salt) as a yellow solid. ES+APCI MS m/z 547.3 $[\text{M}+\text{H}]^+$.

EXAMPLE 173

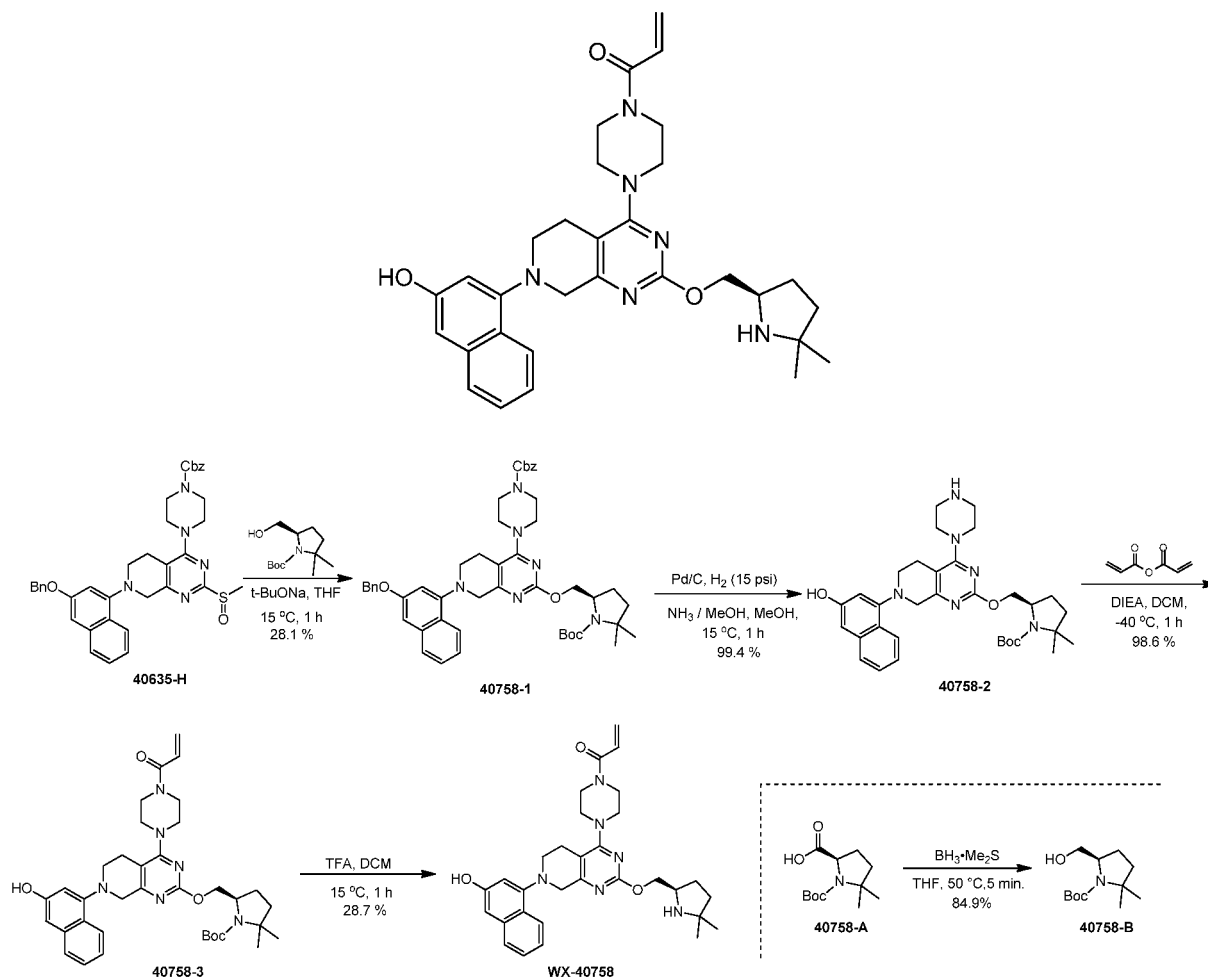
1-(4-(7-(3-hydroxy-2-methylnaphthalen-1-yl)-2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one



[0721] 1-(4-(7-(3-hydroxy-2-methylnaphthalen-1-yl)-2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one was prepared according to the procedure for **Example 165** 1-[4-[7-(2-fluoro-3-hydroxy-1-naphthyl)-2-(3-morpholinopropoxy)-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one substituting (3-methoxy-2-methyl-1-naphthyl) trifluoromethanesulfonate for (2-fluoro-3-methoxy-1-naphthyl) trifluoromethanesulfonate in step F to give the desired product 1-(4-(7-(3-hydroxy-2-methylnaphthalen-1-yl)-2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one as yellow solid (10.4 mg, 13.1% yield, 98.1% purity). ES+APCI MS m/z 573.5 $[\text{M}+\text{H}]^+$.

EXAMPLE 174

(*R*)-1-(4-(2-((5,5-dimethylpyrrolidin-2-yl)methoxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one



[0722] Step A: *tert*-Butyl (5*R*)-5-(hydroxymethyl)-2,2-dimethyl-pyrrolidine-1-carboxylate: To a solution of (2*R*)-1-*tert*-butoxycarbonyl-5,5-dimethyl-pyrrolidine-2-carboxylic acid (500 mg, 2.06 mmol) in anhydrous THF (4 mL) was added $\text{BH}_3 \cdot \text{Me}_2\text{S}$ (2 M, 1.23 mL) dropwise at 15 °C. The reaction was heated at 50 °C for 5 minutes. After cooling in an ice-bath, to the mixture was added Methanol (20 mL). The reaction mixture was concentrated under reduced pressure at 25 °C. *tert*-Butyl (5*R*)-5-(hydroxymethyl)-2,2-dimethyl-pyrrolidine-1-carboxylate (400 mg, 1.74 mmol, 84.9% yield) was obtained as a white solid.

[0723] ^1H NMR (400MHz, methanol- d_4) δ = 3.97 - 3.81 (m, 1H), 3.62 (dd, J = 3.6, 10.8 Hz, 1H), 3.45 - 3.33 (m, 1H), 2.02 - 1.79 (m, 3H), 1.79 - 1.67 (m, 1H), 1.49 - 1.41 (m, 12H), 1.32 (s, 3H).

[0724] Step B: Benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2- [[(2*R*)-1-*tert*-butoxycarbonyl-5,5-dimethyl-pyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate: To a solution of *tert*-butyl (5*R*)-5-(hydroxymethyl)-2,2-dimethyl- pyrrolidine-1-carboxylate (212 mg, 926 μmol) and benzyl 4-[7-(3-benzyloxy-1-naphthyl) -2-methylsulfinyl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (300 mg, 463 μmol ,) in THF (10 mL) was added *t*-BuONa (133 mg, 1.39 mmol). After stirring at 15 °C for 1 hour, the reaction mixture was poured into H₂O (20 mL) and extracted with ethyl acetate (20 mL $\times$ 3). The organic phase was washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by reversed phase flash [water (0.1% formic acid)/acetonitrile]. The desired fractions were collected and concentrated under vacuum. Compound benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2- [[(2*R*)-1-*tert*-butoxycarbonyl-5,5-dimethyl-pyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (110 mg, 129 μmol , 28.1% yield, 96% purity) was obtained as a yellow solid. ES+APCI MS m/z 813.5 [$\text{M}+\text{H}$]⁺.

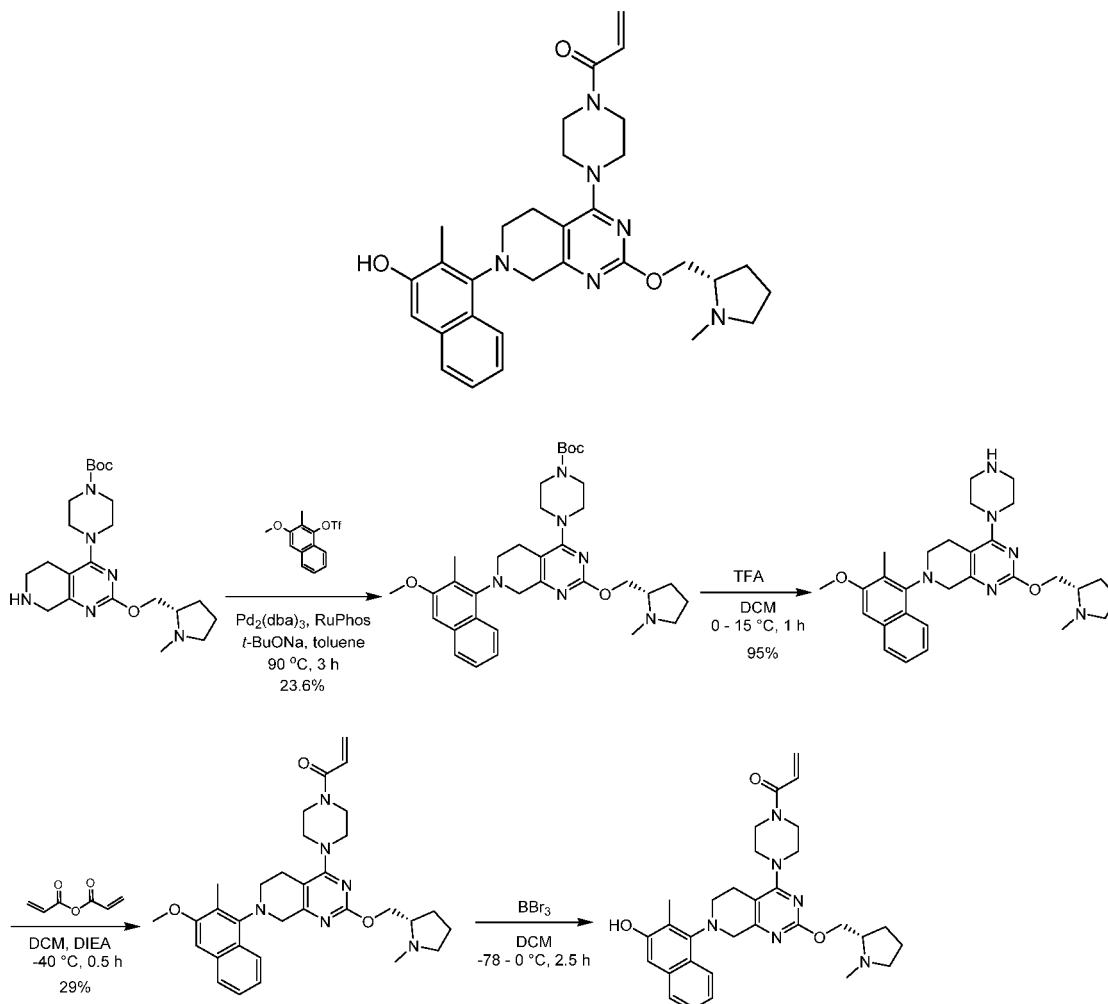
[0725] Step C: *tert*-butyl (5*R*)-5-[[7-(3-hydroxy-1-naphthyl)-4-piperazin-1-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-2-yl]oxymethyl]-2,2-dimethyl-pyrrolidine-1-carboxylate: NH₃ was bubbled into MeOH (30 mL) at - 40 °C for 30 minutes. To a solution of benzyl 4-[7-(3-benzyloxy-1-naphthyl)-2-[[(2*R*)-1-*tert*-butoxycarbonyl-5,5- dimethyl-pyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (200 mg, 246 μmol) in above the mixture (NH₃/MeOH) was added dry Pd-C (10%, 100 mg) under N₂. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (15 psi) at 15 °C for 1 hour. The catalyst was filtered off and the filtrate was concentrated to give the product *tert*-butyl (5*R*)-5-[[7-(3-hydroxy-1-naphthyl)-4-piperazin-1-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-2-yl]oxymethyl]-2,2-dimethyl-pyrrolidine-1-carboxylate (150 mg, 244 μmol , 99.4% yield, 96 % purity) as a yellow solid and directly used next step without purification. ES+APCI MS m/z 589.3 [$\text{M}+\text{H}$]⁺.

[0726] Step D: *tert*-Butyl (5*R*)-5-[[7-(3-hydroxy-1-naphthyl)-4-(4-prop-2-enoylpiperazin-1-yl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-2-yl]oxymethyl]-2,2-dimethyl-pyrrolidine-1-carboxylate: To a mixture of *tert*-butyl (5*R*)-5-[[7-(3-hydroxy-1-naphthyl)-4-piperazin-1-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-2-yl]oxymethyl]-2,2-dimethyl-pyrrolidine-1-carboxylate (130 mg, 221 μ mol) and DIEA (285 mg, 2.21 mmol, 385 μ L) in dichloromethane (3 mL) was added a solution of prop-2-enoyl prop-2-enoate (22.3 mg, 176 μ mol) in dichloromethane (1 mL) at - 40 °C under nitrogen atmosphere. The mixture was stirred at - 40 °C for 1 hour. The reaction was quenched by addition of saturated NaHCO₃ (2 mL) aqueous solution. Then the mixture was poured into water (20 mL) and extracted with dichloromethane (20 mL $\times$ 2). The combined organics was dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO₂, dichloromethane/methanol = 1/0 to 10/1). *tert*-Butyl (5*R*)-5-[[7-(3-hydroxy-1-naphthyl)-4-(4-prop-2-enoylpiperazin-1-yl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-2-yl]oxymethyl]-2,2-dimethyl-pyrrolidine-1-carboxylate (140 mg, 217 μ mol, 98.6 % yield) was obtained as a brown oil. ES+APCI MS *m/z* 643.6 [M+H]⁺.

[0727] Step E: 1-[4-[2-[[[(2*R*)-5,5-dimethylpyrrolidin-2-yl]methoxy]-7-(3-hydroxy-1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one: To a solution of *tert*-butyl (5*R*)-5-[[7-(3-hydroxy-1-naphthyl)-4-(4-prop-2-enoylpiperazin-1-yl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-2-yl]oxymethyl]-2,2-dimethyl-pyrrolidine-1-carboxylate (120 mg, 187 μ mol) in dichloromethane (200 μ L) was added TFA (212 mg, 1.87 mmol, 138 μ L). The mixture was stirred at 15 °C for 1 hour. The reaction mixture was concentrated under vacuum, then diluted with dichloromethane (5 mL) and adjusted PH=7 by addition saturated NaHCO₃ aqueous solution. The mixture was extracted with dichloromethane (10 mL $\times$ 3). The combined organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by prep-HPLC (column: Phenomenex Gemini 150*25mm*10 μ m; mobile phase: [water (0.05 % ammonia hydroxide v/v)-ACN]; B%: 45 %-75 %, 12min). 1-[4-[2-[[[(2*R*)-5,5-dimethylpyrrolidin-2-yl]methoxy]-7-(3-hydroxy-1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one (30 mg, 53.6 μ mol, 28.7 % yield, 97 % purity) was obtained as yellow solid by lyophilization. ES+APCI MS *m/z* 543.5 [M+H]⁺.

EXAMPLE 175

(*S*)-1-(4-(7-(3-hydroxy-2-methylnaphthalen-1-yl)-2-((1-methylpyrrolidin-2-yl)methoxy)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

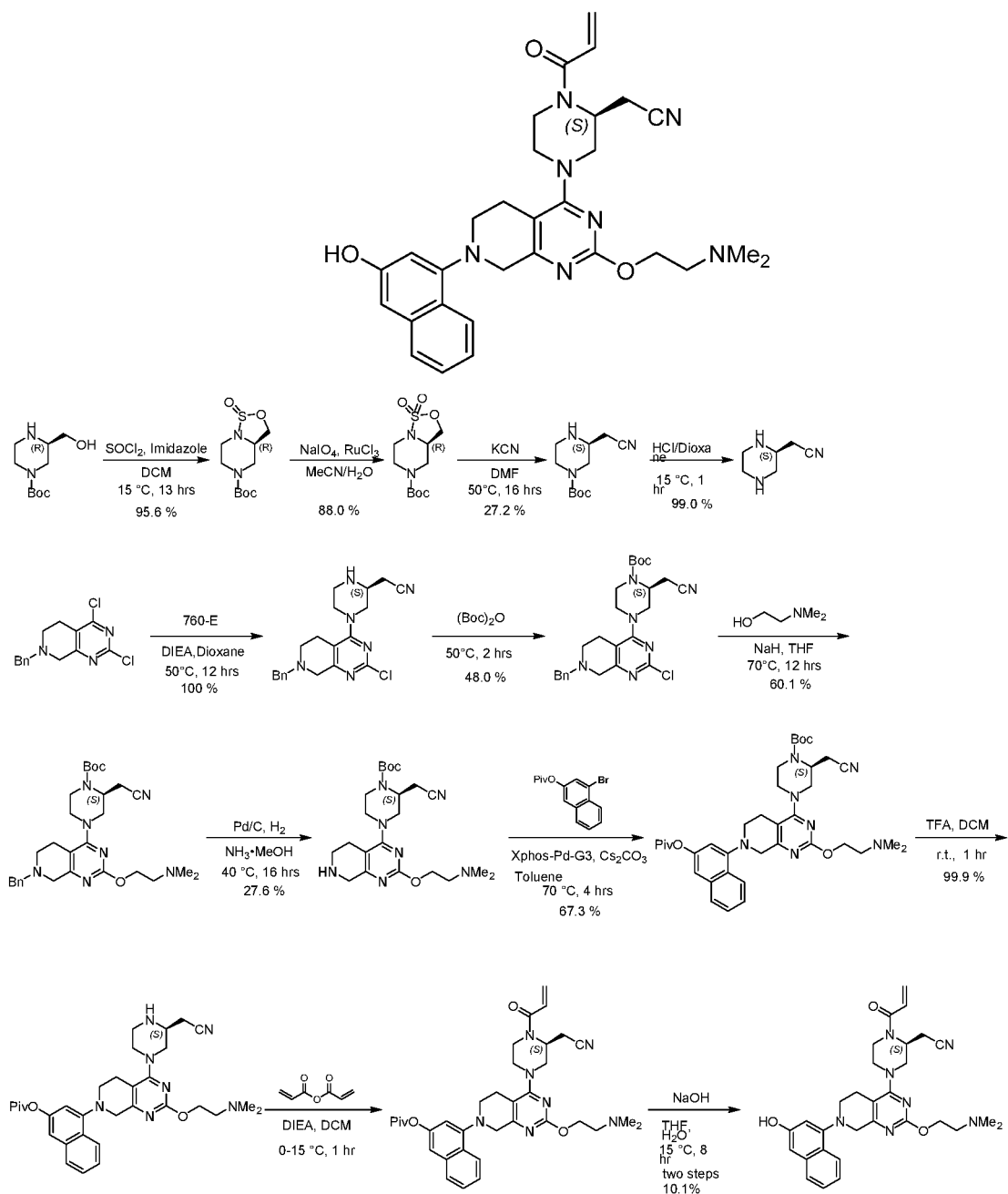


[0728] (*S*)-1-(4-(7-(3-hydroxy-2-methylnaphthalen-1-yl)-2-((1-methylpyrrolidin-2-yl)methoxy)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one was synthesized according to the procedure for Example 165 substituting *tert*-butyl 4-[2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate for *tert*-butyl 4-[7-(2-fluoro-3-methoxy-1-naphthyl)-2-(3-morpholinopropoxy)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate and (2-fluoro-3-methoxy-1-naphthyl) trifluoromethanesulfonate for (3-methoxy-2-methyl-1-naphthyl) trifluoromethanesulfonate in Step F. to give 1-[4-[7-(3-hydroxy-2-methyl-1-naphthyl)-2-[(2*S*)-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one (10.2

mg, 17.3 μ mol, 21.4 % yield, 100 % purity, Formic Acid Salt) as a white solid. ES+APCI MS m/z 543.4 $[M+H]^+$.

EXAMPLE 176

2-[(2*S*)-4-[2-[2-(dimethylamino)ethoxy]-7-(3-hydroxy-1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enyl-piperazin-2-yl]acetonitrile



[0729] Step A: *tert*-butyl (3*R*)-1-oxo-3*a*,4,6,7-tetrahydro-3*H*-oxathiazolo[3,4-*a*]pyrazine-5-carboxylate: To a solution of imidazole (15.7 g, 231 mmol) in DCM (100 mL) was added SOCl₂ (8.25 g, 69.4 mmol, 5.03 mL) at 0 °C. The reaction mixture was stirred at 15 °C for 1 hour. To the mixture was added *tert*-butyl (3*R*)-3-(hydroxymethyl)piperazine-1-carboxylate (5 g, 23.1 mmol) in DCM (100 mL) at -70 °C. The reaction mixture was stirred at 15 °C for 12 hour. Upon completion, the reaction mixture was quenched by saturated NH₄Cl (100 mL) and separated, the aqueous layer was extracted with DCM (40 mL). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated under vacuum to give *tert*-butyl (3*R*)-1-oxo-3*a*,4,6,7-tetrahydro-3*H*-oxathiazolo[3,4-*a*]pyrazine-5-carboxylate (5.8 g, 22.1 mmol, 95.6% yield) as a brown solid.

[0730] Step B: *tert*-butyl (3*R*)-1,1-dioxo-3*a*,4,6,7-tetrahydro-3*H*-oxathiazolo[3,4-*a*]pyrazine-5-carboxylate: To a solution of *tert*-butyl (3*R*)-1-oxo-3*a*,4,6,7-tetrahydro-3*H*-oxathiazolo[3,4-*a*]pyrazine-5-carboxylate (7.5 g, 28.6 mmol) in MeCN (225 mL) was added NaIO₄ (7.95 g, 37.2 mmol, 2.06 mL) in water (75 mL) followed by RuCl₃·H₂O (129 mg, 572 μmol) at 0 °C. The reaction mixture was stirred at 15 °C for 0.5 hour. Upon completion, the reaction mixture was quenched with saturated NH₄Cl (10 mL) and extracted with EtOAc (20 mL). The organic layer was washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by silica gel chromatography (PE: EtOAc=3:1 to 1:1) to give *tert*-butyl (3*R*)-1,1-dioxo-3*a*,4,6,7-tetrahydro-3*H*-oxathiazolo[3,4-*a*]pyrazine-5-carboxylate (7 g, 25.2 mmol, 88.0% yield) as a white solid. ¹H NMR (400MHz, CHLOROFORM-*d*) δ = 4.64 (dd, *J*=6.4, 8.0 Hz, 1H), 4.36 - 3.94 (m, 3H), 3.64 (ddt, *J*=3.6, 6.0, 9.2 Hz, 1H), 3.46 (br d, *J*=11.6 Hz, 1H), 3.13 (br s, 1H), 2.96 (dt, *J*=3.2, 11.2 Hz, 2H), 1.48 (s, 9H)

[0731] Step C: *tert*-butyl (3*S*)-3-(cyanomethyl)piperazine-1-carboxylate: To a solution of *tert*-butyl (3*R*)-1,1-dioxo-3*a*,4,6,7-tetrahydro-3*H*-oxathiazolo[3,4-*a*]pyrazine-5-carboxylate (5 g, 18.0 mmol) in DMF (100 mL) was added KCN (1.04 g, 16.0 mmol, 684.94 μL). The reaction mixture was heated to 50 °C for 16 hours. Upon completion, the reaction mixture was quenched by HCl (2 M, 50 mL) and stirred at 15 °C for 1h. The mixture was basified by NaOH (40 %, 10 mL) and extracted with EtOAc (3 × 100 mL). The organic layer was dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by silica gel chromatography (PE: EtOAc=3:1 to 0:1 then EtOAc: MeOH= 100:1 to 10:1) to give *tert*-butyl (3*S*)-3-

(cyanomethyl)piperazine-1-carboxylate (1.1 g, 4.88 mmol, 27.2% yield) as a brown oil. ¹H NMR (400MHz, CHLOROFORM-d) δ = 4.05 - 3.71 (m, 2H), 3.08 - 2.88 (m, 3H), 2.84 - 2.62 (m, 2H), 2.56 - 2.37 (m, 2H), 1.47 (s, 9H).

[0732] Step D: 2-[(2*S*)-piperazin-2-yl]acetonitrile: A reaction mixture of *tert*-butyl (3*S*)-3-(cyanomethyl)piperazine-1-carboxylate (850 mg, 3.77 mmol) and HCl/dioxane (4 M, 20 mL) was stirred at 15 °C for 1 hour. Upon completion, the solvent was removed under vacuum to give 2-[(2*S*)-piperazin-2-yl]acetonitrile (740 mg, 3.74 mmol, 99.0% yield, 2HCl) as a white solid. ¹H NMR (400MHz, METHANOL-d₄) δ = 4.04 - 3.90 (m, 1H), 3.81 - 3.70 (m, 2H), 3.69 - 3.61 (m, 2H), 3.53 - 3.36 (m, 2H), 3.13 (d, *J*=6.4 Hz, 2H).

[0733] Step E: 2-[(2*S*)-4-(7-benzyl-2-chloro-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl)piperazin-2-yl]acetonitrile: To a mixture of 7-benzyl-2,4-dichloro-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidine (1.3 g, 4.42 mmol) and 2-[(2*S*)-piperazin-2-yl]acetonitrile (1.17 g, 5.91 mmol, 2HCl) in dioxane (25 mL) was added DIEA (2.86 g, 22.1 mmol, 3.85 mL). The reaction mixture was stirred at 50 °C for 12 hours. Upon completion, the reaction mixture was diluted with water (50 mL) and extracted with EtOAc (3 × 80 mL). The combined organic layers were washed with brine (30 mL), dried over Na₂SO₄ and concentrated under vacuum to give 2-[(2*S*)-4-(7-benzyl-2-chloro-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl)piperazin-2-yl]acetonitrile (1.69 g, 4.41 mmol, 100% yield) as a brown solid.

[0734] Step F: *tert*-butyl (2*S*)-4-(7-benzyl-2-chloro-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl)-2-(cyanomethyl)piperazine-1-carboxylate: A reaction mixture of 2-[(2*S*)-4-(7-benzyl-2-chloro-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl)piperazin-2-yl]acetonitrile (1.69 g, 4.41 mmol) and (Boc)₂O (10.3 g, 47.2 mmol, 10.8 mL) was heated to 50 °C for 2 hours. Upon completion, the reaction mixture was purified by silica gel chromatography (PE: EtOAc=10:1 to 1:1) to give *tert*-butyl (2*S*)-4-(7-benzyl-2-chloro-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl)-2-(cyanomethyl)piperazine-1-carboxylate (1.1 g, 2.12 mmol, 48.0% yield, 93% purity) as brown solid. ES+APCI MS *m/z* 483.4 [M+H]⁺.

[0735] Step G: *tert*-butyl (2*S*)-4-[7-benzyl-2-[2-(dimethylamino)ethoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-2-(cyanomethyl)piperazine-1-carboxylate: To a solution of 2-(dimethylamino)ethanol (415 mg, 4.66 mmol, 468 μ L) in THF (20 mL) was added NaH (149

mg, 3.73 mmol, 60% purity) 0 °C. The reaction mixture was stirred at 0 °C for 0.5 h. To the mixture was added *tert*-butyl (2*S*)-4-(7-benzyl-2-chloro-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl)-2-(cyanomethyl)piperazine-1-carboxylate (900 mg, 1.86 mmol). The reaction mixture was stirred at 70 °C for 12 hours at sealed tube under N₂. Upon completion, the reaction mixture was quenched by water (10 mL) and extracted with EtOAc (3 × 40 mL). The combined organic layers were treated with activated carbon and filtered. The filtrate was concentrated under vacuum to give *tert*-butyl (2*S*)-4-[7-benzyl-2-[2-(dimethylamino)ethoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-2-(cyanomethyl)piperazine-1-carboxylate (600 mg, 1.12 mmol, 60.1% yield) as a brown solid.

[0736] Step H: *tert*-butyl (2*S*)-2-(cyanomethyl)-4-[2-[2-(dimethylamino)ethoxy]-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate: NH₃ was bubbled into MeOH (20 mL) for 5 min. To the solution was added *tert*-butyl (2*S*)-4-[7-benzyl-2-[2-(dimethylamino)ethoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-2-(cyanomethyl)piperazine-1-carboxylate (600 mg, 1.12 mmol) and 10% Pd/C (200 mg). The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (15 psi) at 40 °C for 16 hours. Upon completion, the mixture was filtered and the filter cake was washed with MeOH (3 × 30 mL). The filtrate was concentrated under vacuum. The residue was purified by prep-HPLC (column: Phenomenex luna(2) C18 250*50 10u; mobile phase: [water(0.225% Formic Acid)-ACN]; B%: %-%, 30MIN; 60%min) to give *tert*-butyl (2*S*)-2-(cyanomethyl)-4-[2-[2-(dimethylamino)ethoxy]-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (167 mg, 331 umol, 29.6% yield, 88.3% purity) as a colorless oil. ES+APCI MS *m/z* 446.3 [M+H]⁺.

[0737] Step I: *tert*-butyl (2*S*)-2-(cyanomethyl)-4-[2-[2-(dimethylamino)ethoxy]-7-[3-(2,2-dimethylpropanoyloxy)-1-naphthyl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate: To a solution of *tert*-butyl (2*S*)-2-(cyanomethyl)-4-[2-[2-(dimethylamino)ethoxy]-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (180 mg, 404 umol), (4-bromo-2-naphthyl) 2,2-dimethylpropanoate (248 mg, 808 umol) and Cs₂CO₃ (395 mg, 1.21 mmol) in toluene (6 mL) was added XPHOS Palladacycle Gen 3 (34.20 mg, 40.4 umol). The reaction mixture was stirred at 70 °C for 4 hours under N₂. Upon completion, the reaction mixture was purified by silica gel chromatography (PE:EA= 5:1 to 0:1) to give *tert*-butyl (2*S*)-

2-(cyanomethyl)-4-[2-[2-(dimethylamino)ethoxy]-7-[3-(2,2-dimethylpropanoyloxy)-1-naphthyl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (200 mg, 272 μ mol, 67.3% yield, 91.3% purity) as a brown solid. ES+APCI MS m/z 672.0 $[M+H]^+$.

[0738] Step J: [4-[4-[(3*S*)-3-(cyanomethyl)piperazin-1-yl]-2-[2-(dimethylamino)ethoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]-2-naphthyl] 2,2-dimethylpropanoate: To a solution of *tert*-butyl (2*S*)-2-(cyanomethyl)-4-[2-[2-(dimethylamino)ethoxy]-7-[3-(2,2-dimethylpropanoyloxy)-1-naphthyl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (200 mg, 298 μ mol) in DCM (0.3 mL) was added TFA (420 mg, 3.68 mmol, 273 μ L). The reaction mixture was stirred at 15 °C for 1 hour. Upon completion, the reaction mixture was concentrated under vacuum to give [4-[4-[(3*S*)-3-(cyanomethyl)piperazin-1-yl]-2-[2-(dimethylamino)ethoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]-2-naphthyl] 2,2-dimethylpropanoate (238 mg, 298 μ mol, 99.9% yield, 2TFA) as a brown oil.

[0739] Step K: [4-[4-[(3*S*)-3-(cyanomethyl)-4-prop-2-enoyl-piperazin-1-yl]-2-[2-(dimethylamino)ethoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]-2-naphthyl] 2,2-dimethylpropanoate: To a solution of [4-[4-[(3*S*)-3-(cyanomethyl)piperazin-1-yl]-2-[2-(dimethylamino)ethoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]-2-naphthyl] 2,2-dimethylpropanoate (238 mg, 298 μ mol, 2TFA) and DIEA (308 mg, 2.38 mmol, 415 μ L) in DCM (5 mL) was added prop-2-enoyl prop-2-enoate (56.3 mg, 446 μ mol) at 0 °C. The reaction mixture was stirred at 15 °C for 1 hour. Upon completion, the reaction mixture was quenched with a drop of water. The mixture was purified by silica gel chromatography (PE: EtOAc= 1:1 to 0:1 then EtOAc: MeOH= 50:1 to 3:1) to give [4-[4-[(3*S*)-3-(cyanomethyl)-4-prop-2-enoyl-piperazin-1-yl]-2-[2-(dimethylamino)ethoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]-2-naphthyl] 2,2-dimethylpropanoate (300 mg, crude) as a brown oil. ES+APCI MS m/z 626.4 $[M+H]^+$.

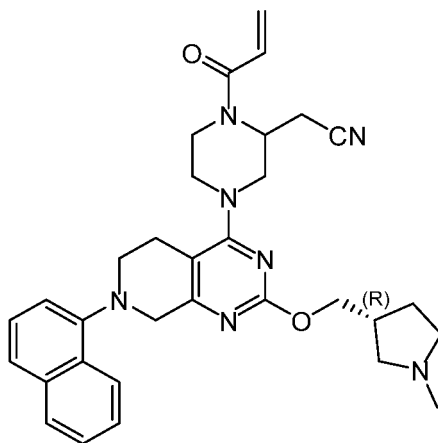
[0740] Step L: 2-[(2*S*)-4-[2-[2-(dimethylamino)ethoxy]-7-(3-hydroxy-1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile: To a solution of [4-[4-[(3*S*)-3-(cyanomethyl)-4-prop-2-enoyl-piperazin-1-yl]-2-[2-(dimethylamino)ethoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]-2-naphthyl] 2,2-dimethylpropanoate (300 mg, 479 μ mol) in THF (3 mL) was added NaOH (2 M, 3 mL) in water. The reaction mixture was stirred at 15 °C for 8 hours. Upon completion, the reaction mixture was acidified by 0.5 mL of formic

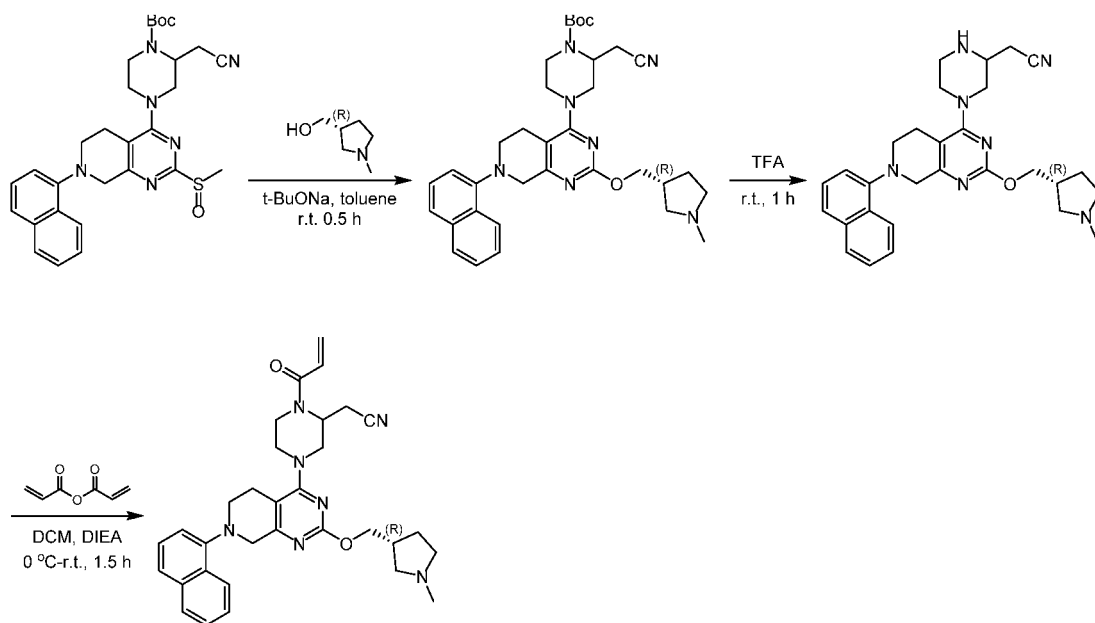
acid (20 % in water) to PH=7 and extracted with DCM (5×10 mL). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated under vacuum.

[0741] The residue was purified by prep-HPLC (column: Boston Green ODS 150*30 5u; mobile phase: [water(0.225% Formic Acid)-ACN]; B%: 25%-49%, 10min) to give 2-[(2*S*)-4-[2-[2-(dimethylamino)ethoxy]-7-(3-hydroxy-1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile (18.3 mg, 30.2 μmol , two steps 10.1% yield, 96.7% purity, Formic Acid Salt) as a yellow solid. ES+APCI MS m/z 542.5 $[\text{M}+\text{H}]^+$.

EXAMPLE 177

2-[4-[2-[[*(3R)*]-1-methylpyrrolidin-3-yl]methoxy]-7-(1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile





[0742] Step A: *tert*-butyl 2-(cyanomethyl)-4-[2-[[*(3R)*-1-methylpyrrolidin-3-yl]methoxy]-7-(1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate: To a solution of *tert*-butyl 2-(cyanomethyl)-4-[2-methylsulfinyl-7-(1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (300 mg, 549 μ mol) and [*(3R)*-1-methylpyrrolidin-3-yl]methanol (126 mg, 1.10 mmol) in toluene (6 mL) was added *t*-BuONa (79.1 mg, 823 μ mol) at 18 °C and the reaction mixture stirred at 18 °C for 0.5 hour. To the mixture was then added EtOAc (20 mL) and water (15 mL), then extracted with EtOAc (3 $\times$ 20 mL). The combined organic layers were washed with brine (20 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by reversed phase flash column (ACN/Water (0.1% Formic Acid) = 42 %) to give *tert*-butyl 2-(cyanomethyl)-4-[2-[[*(3R)*-1-methylpyrrolidin-3-yl]methoxy]-7-(1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (200 mg, 331 μ mol, 60.4 % yield, 99.0 % purity) as yellow solid. ES+APCI MS *m/z* 598.3[M+H]⁺.

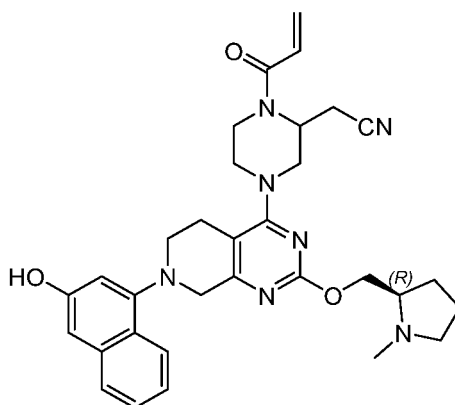
[0743] Step B: 2-[4-[2-[[*(3R)*-1-methylpyrrolidin-3-yl]methoxy]-7-(1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-2-yl]acetonitrile: A mixture of *tert*-butyl 2-(cyanomethyl)-4-[2-[[*(3R)*-1-methylpyrrolidin-3-yl]methoxy]-7-(1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (200 mg, 334 μ mol) and TFA (763 mg, 6.69 mmol, 495 μ L) was stirred at 18 °C for 1 hour. The reaction mixture was concentrated under vacuum to give 2-[4-[2-[[*(3R)*-1-methylpyrrolidin-3-yl]methoxy]-7-(1-naphthyl)-6,8-

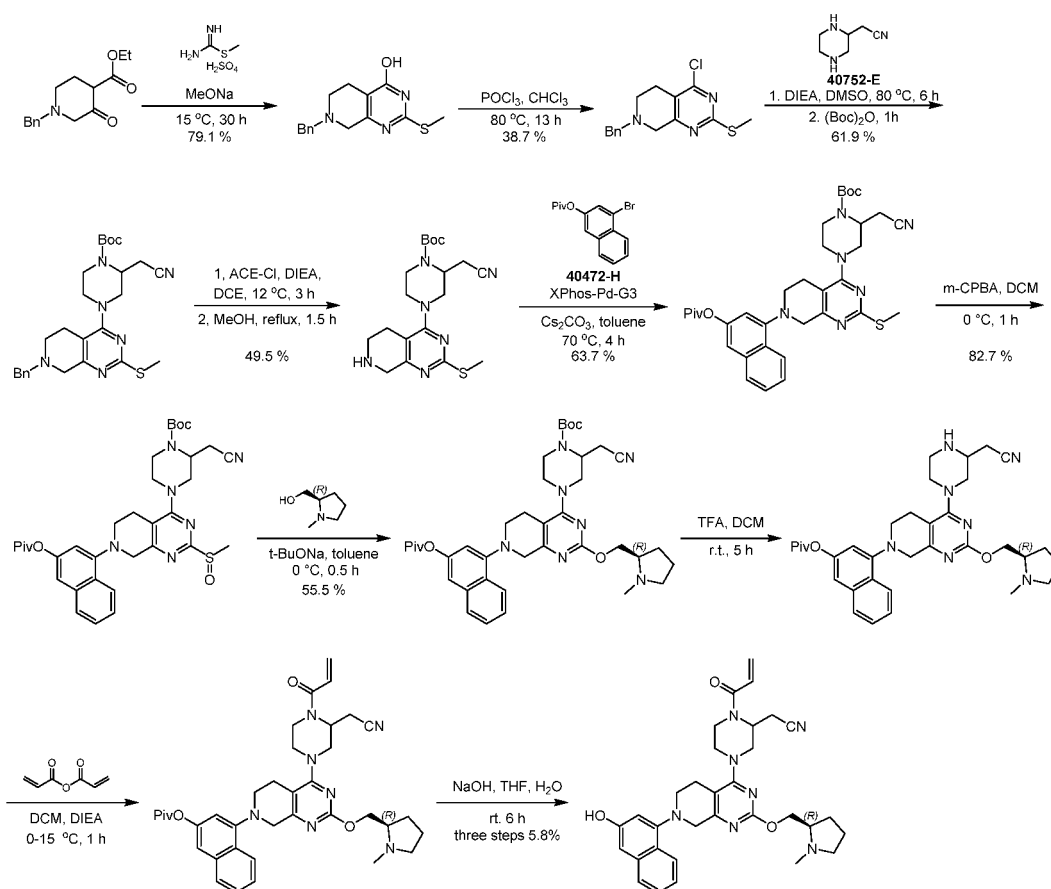
dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-2-yl]acetonitrile (250 mg, crude, 2TFA) as brown oil.

[0744] Step C: 2-[4-[2-[[*(3R)*]-1-methylpyrrolidin-3-yl]methoxy]-7-(1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile: To a solution of 2-[4-[2-[[*(3R)*]-1-methylpyrrolidin-3-yl]methoxy]-7-(1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-2-yl]acetonitrile (250 mg, 344 μ mol, 2TFA) and DIEA (356 mg, 2.76 mmol, 480 μ L) in DCM (5 mL) was added prop-2-enoyl prop-2-enoate (65.2 mg, 517 μ mol) at 0 °C and the mixture was stirred at 18 °C for 1.5 hours. The reaction mixture was quenched with water (3 mL) and then extracted with DCM (3 $\times$ 6 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Phenomenex Gemini 150*25mm*10 μ m; mobile phase: [water(10mM NH₄HCO₃)-ACN]; B%: 30%-60%, 3min) to give 2-[4-[2-[[*(3R)*]-1-methylpyrrolidin-3-yl]methoxy]-7-(1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile (9.98 mg, 17.0 μ mol, 4.94 % yield, 94.1 % purity) as white solid. ES+APCI MS *m/z* 552.5[M+H]⁺.

EXAMPLE 178

2-[4-[7-(3-hydroxy-1-naphthyl)-2-[[*(2R)*]-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile





[0745] Step A: 7-benzyl-2-methylsulfanyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-ol: A suspension of MeOH (1000 mL) and Na (22.0 g, 957 mmol, 22.7 mL) was stirred for 30 min. To this mixture was added ethyl 1-benzyl-3-oxopiperidine-4-carboxylate (50 g, 191 mmol) and 2-methylisothiourea (47.9 g, 344 mmol, 0.5 H_2SO_4) at 15°C . The reaction mixture was stirred at 15°C for 30 hours. The reaction mixture was acidified by HCl (2 M) (300 mL) until pH=6 and concentrated under reduced pressure. The residue was suspended in 200 mL of water and stirred rapidly. The suspension was filtered and the white solid collected and washed with ethyl acetate. 7-benzyl-2-methylsulfanyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-ol (68 g, 151 mmol, 79.1 % yield, 64.0 % purity) was obtained as a white solid.

[0746] Step B: 7-benzyl-4-chloro-2-methylsulfanyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidine: To a solution of 7-benzyl-2-methylsulfanyl-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-ol (50 g, 174 mmol) in CHCl_3 (1000 mL) was added POCl_3 (166 g, 1.08 mol, 100 mL) and the mixture stirred at 80°C for 13 hours. Upon completion, the reaction mixture was concentrated under vacuum. The residue was diluted with EtOAc (500 mL) and basified using saturated Na_2CO_3

(800 mL) to PH=7. The mixture was extracted with ethyl acetate (3 × 400 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (PE: EA from 100:1 to 80:1) to give 7-benzyl-4-chloro-2-methylsulfanyl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidine (21.7 g, 67.4 mmol, 38.7 % yield, 95.0 % purity) as brown oil. ES+APCI MS *m/z* 306.1[M+H]⁺.

[0747] Step C: *tert*-butyl 4-(7-benzyl-2-methylsulfanyl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl)-2-(cyanomethyl)piperazine-1-carboxylate: To a solution of 7-benzyl-4-chloro-2-methylsulfanyl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidine (2.6 g, 8.50 mmol) and 2-piperazin-2-ylacetonitrile (1.68 g, 8.50 mmol, 2HCl) in DMSO (52 mL) was added DIEA (5.49 g, 42.5 mmol, 7.40 mL). The mixture was warmed to 80 °C and stirred at 80 °C for 6 hours. To the mixture was added (Boc)₂O (18.5 g, 85.0 mmol, 19.5 mL) and the mixture stirred at 80 °C for 1 hour. Water (150 mL) was added and the mixture was extracted with ethyl acetate (3 × 200 mL). The combined organic phase was washed with brine (200 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (PE: EA from 10:1 to 0:1) to give *tert*-butyl 4-(7-benzyl-2-methylsulfanyl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl)-2-(cyanomethyl)piperazine-1-carboxylate (2.74 g, 5.26 mmol, 61.9 % yield, 95.0 % purity) as brown solid. ES+APCI MS *m/z* 495.4[M+H]⁺.

[0748] Step D: *tert*-butyl 2-(cyanomethyl)-4-(2-methylsulfanyl-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl)piperazine-1-carboxylate: To a solution of *tert*-butyl 4-(7-benzyl-2-methylsulfanyl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl)-2-(cyanomethyl)piperazine-1-carboxylate (2.51 g, 5.07 mmol) and DIEA (1.97 g, 15.2 mmol, 2.65 mL) in DCE (50 mL) was added 1-chloroethyl carbonochloridate (1.81 g, 12.7 mmol) at 0 °C, and the mixture stirred at 15 °C for 3 hours. The reaction mixture was concentrated under vacuum. The residue was dissolved in MeOH (50 mL) and the reaction mixture was stirred at 70 °C for 1.5 hours. The mixture was concentrated under vacuum. The residue was purified by prep-HPLC (column: Phenomenex Synergi Max-RP 250*50mm*10 um; mobile phase: [water(0.225%FA)-ACN]; B%: 23%-48%, 30; 50%min) to give *tert*-butyl 2-(cyanomethyl)-4-(2-methylsulfanyl-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl)piperazine-1-carboxylate (1.13 g, 2.51 mmol, 49.5 % yield, 90.0 % purity) as pink solid. ES+APCI MS *m/z* 405.3[M+H]⁺.

[0749] Step E: *tert*-butyl 2-(cyanomethyl)-4-[7-[3-(2,2-dimethylpropanoyloxy)-1-naphthyl]-2-methylsulfanyl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate: To a solution of *tert*-butyl 2-(cyanomethyl)-4-(2-methylsulfanyl-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl)piperazine-1-carboxylate (730 mg, 1.80 mmol), (4-bromo-2-naphthyl) 2,2-dimethylpropanoate (832 mg, 2.71 mmol) and Cs₂CO₃ (1.76 g, 5.41 mmol) in toluene (18 mL) was added [2-(2-aminophenyl)phenyl]palladium(1+);dicyclohexyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane-methanesulfonate (153 mg, 180 μ mol), the suspension was degassed under vacuum and purged with N₂ several times. The reaction mixture was stirred at 70 °C for 4 hours. Upon completion, water (20 mL) was added to the mixture. The resulting mixture was extracted with EtOAc (4 $\times$ 20 mL). The combined organic layers were washed with brine (40 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (PE: EtOAc from 30:1 to 0:1) to give *tert*-butyl 2-(cyanomethyl)-4-[7-[3-(2,2-dimethylpropanoyloxy)-1-naphthyl]-2-methylsulfanyl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (740 mg, 1.15 mmol, 63.7 % yield, 98.0 % purity) as brown solid. ES+APCI MS *m/z* 631.5[M+H]⁺.

[0750] Step F: *tert*-butyl 2-(cyanomethyl)-4-[7-[3-(2,2-dimethylpropanoyloxy)-1-naphthyl]-2-methylsulfinyl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate: To a solution of *tert*-butyl 2-(cyanomethyl)-4-[7-[3-(2,2-dimethylpropanoyloxy)-1-naphthyl]-2-methylsulfanyl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (100 mg, 158 μ mol) in DCM (2 mL) was added *m*-CPBA (32.2 mg, 158 μ mol, 85.0 % purity) at 0 °C and the mixture stirred at 0 °C for 1 hours. The reaction mixture was quenched by saturated Na₂S₂O₃ (4 mL) at 0°C and separated, then diluted with water (10 mL) and extracted with ethyl acetate (10 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel chromatography (PE: EA from 10:1 to 0:1) to give *tert*-butyl 2-(cyanomethyl)-4-[7-[3-(2,2-dimethylpropanoyloxy)-1-naphthyl]-2-methylsulfinyl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (90 mg, 125 μ mol, 79.0 % yield, 90.0 % purity) as brown solid. ES+APCI MS *m/z* 647.5[M+H]⁺.

[0751] Step G: *tert*-butyl 2-(cyanomethyl)-4-[7-[3-(2,2-dimethylpropanoyloxy)-1-naphthyl]-2-[[*(2R)*-(1-methylpyrrolidin-2-yl)methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-

yl]piperazine-1-carboxylate: To a solution of *tert*-butyl 2-(cyanomethyl)-4-[7-[3-(2,2-dimethylpropanoyloxy)-1-naphthyl]-2-methylsulfinyl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (560 mg, 866 μ mol), [(2*R*)-1-methylpyrrolidin-2-yl]methanol (199 mg, 1.73 mmol) in toluene (10 mL) was added *t*-BuONa (125 mg, 1.30 mmol) at 0 °C and the mixture was stirred at 0 °C for 0.5 hour. The mixture was partitioned between EtOAc (20 mL) and water (15 mL) and separated. Then the aqueous layer was extracted with EtOAc (3 $\times$ 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by reverse phase flash column to give *tert*-butyl 2-(cyanomethyl)-4-[7-[3-(2,2-dimethylpropanoyloxy)-1-naphthyl]-2-[[[(2*R*)-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (340 mg, 481 μ mol, 55.5 % yield, 98.7 % purity) as brown oil. ES+APCI MS *m/z* 698.4[M+H]⁺.

[0752] Step H: [4-[4-[3-(cyanomethyl)piperazin-1-yl]-2-[[[(2*R*)-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]-2-naphthyl] 2,2-dimethylpropanoate: To a solution of *tert*-butyl 2-(cyanomethyl)-4-[7-[3-(2,2-dimethylpropanoyloxy)-1-naphthyl]-2-[[[(2*R*)-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (140 mg, 201 μ mol) in DCM (0.2 mL) was added TFA (229 mg, 2.01 mmol, 148 μ L) at 15 °C and the mixture was stirred at 15 °C for 5 hours. The reaction mixture was concentrated under vacuum to give [4-[4-[3-(cyanomethyl)piperazin-1-yl]-2-[[[(2*R*)-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]-2-naphthyl] 2,2-dimethylpropanoate (170 mg, crude, 2TFA) as brown oil.

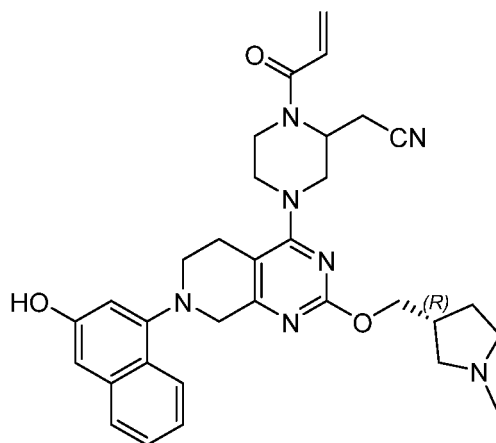
[0753] Step I: [4-[4-[3-(cyanomethyl)-4-prop-2-enoyl-piperazin-1-yl]-2-[[[(2*R*)-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]-2-naphthyl] 2,2-dimethylpropanoate: To a solution of [4-[4-[3-(cyanomethyl)piperazin-1-yl]-2-[[[(2*R*)-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]-2-naphthyl] 2,2-dimethylpropanoate (170 mg, 206 μ mol, 2TFA) and DIEA (213 mg, 1.65 mmol, 287 μ L) in DCM (0.3 mL) was added prop-2-enoyl prop-2-enoate (38.9 mg, 309 μ mol) at 0 °C and this mixture was stirred at 15 °C for 1 hour. The reaction mixture was quenched by water (0.5 mL), then concentrated under vacuum. The residue (DCM: MeOH=10:1) was purified by silica gel chromatography (from PE: EtOAc=2:1 to EtOAc: MeOH=0:1) to give [4-[4-[3-(cyanomethyl)-

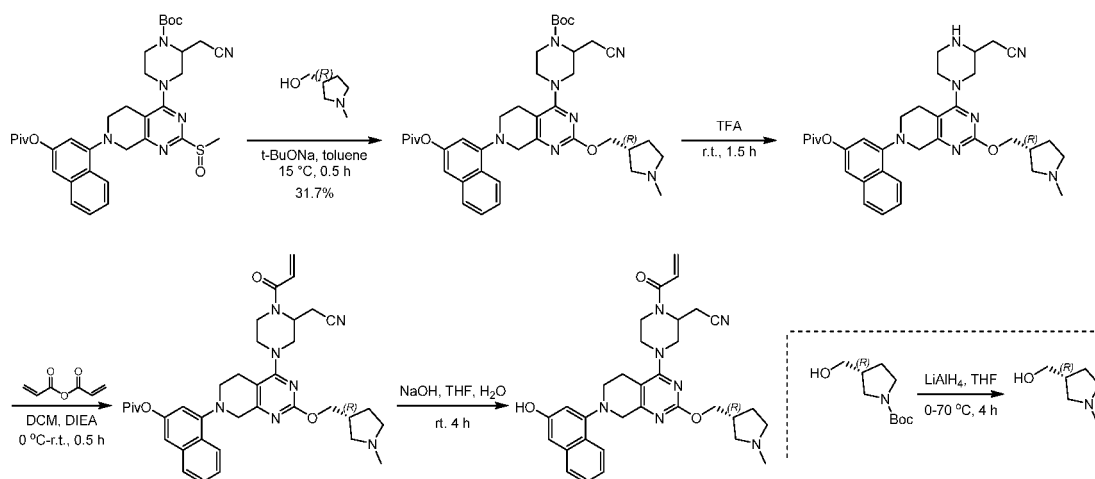
4-prop-2-enoyl-piperazin-1-yl]-2-[[*(2R)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]-2-naphthyl]2,2-dimethylpropanoate (170 mg, 182 μ mol, 88.7 % yield, 70.0 % purity) as brown oil. ES+APCI MS m/z 652.6[M+H]⁺.

[0754] Step J: 2-[4-[7-(3-hydroxy-1-naphthyl)-2-[[*(2R)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile: To a solution of [4-[4-[3-(cyanomethyl)-4-prop-2-enoyl-piperazin-1-yl]-2-[[*(2R)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]-2-naphthyl]2,2-dimethylpropanoate (170 mg, 261 μ mol) in THF (1.5 mL) was added NaOH (2 M, 1.5 mL) and the reaction was stirred at 15 °C for 6 hours. The reaction mixture was neutralized by HCOOH (20 %, 0.1 mL) to pH=7. The resulting mixture was extracted with DCM (3 $\times$ 5 mL), the combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Luna C18 150*25 5 μ ; mobile phase: [water(0.225% Formic Acid)-ACN]; B%: 12%-39%, 10min) to give 2-[4-[7-(3-hydroxy-1-naphthyl)-2-[[*(2R)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile (6.88 mg, 11.6 μ mol, 4.44 % yield, 95.6 % purity) as yellow solid. ES+APCI MS m/z 568.5[M+H]⁺.

EXAMPLE 179

2-[4-[7-(3-hydroxy-1-naphthyl)-2-[[*(3R)*-1-methylpyrrolidin-3-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile





[0755] Step A: [(3*R*)-1-methylpyrrolidin-3-yl]methanol: To the solution of *tert*-butyl (3*R*)-3-(hydroxymethyl)pyrrolidine-1-carboxylate (1 g, 4.97 mmol) in THF (40 mL) was added LiAlH₄ (377 mg, 9.94 mmol) at 0 °C, then the mixture was warmed to 70 °C and stirred at 70 °C for 4 hours. The reaction mixture was quenched by saturated Na₂SO₄ (3 mL) and filtered, the filter cake was washed with THF (5 × 20 mL). The combined organic phase was concentrated under vacuum to give [(3*R*)-1-methylpyrrolidin-3-yl]methanol (820 mg, crude) as yellow oil. ¹H NMR (400 MHz, chloroform-*d*) δ = 3.66 - 3.62 (dd, *J*=4.8, 10.0 Hz, 1H), 3.53 - 3.49 (dd, *J*=5.6, 10.0 Hz, 1H), 3.35 - 3.18 (m, 1H), 2.77 - 2.68 (m, 1H), 2.59 - 2.53 (m, 1H), 2.52 - 2.45 (m, 1H), 2.40 - 2.33 (m, 1H), 2.32 (s, 3H), 2.31 - 2.26 (m, 1H), 2.04 - 1.93 (m, 1H), 1.69 - 1.59 (m, 1H)

[0756] Step B: *tert*-butyl 2-(cyanomethyl)-4-[7-[3-(2,2-dimethylpropanoyloxy)-1-naphthyl]-2-[[[(3*R*)-1-methylpyrrolidin-3-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate: To the solution of *tert*-butyl 2-(cyanomethyl)-4-[7-[3-(2,2-dimethylpropanoyloxy)-1-naphthyl]-2-methylsulfinyl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (500 mg, 773 μmol) and [(3*R*)-1-methylpyrrolidin-3-yl]methanol (178 mg, 1.55 mmol) in toluene (10 mL) was added *t*-BuONa (111 mg, 1.16 mmol) and this mixture stirred at 15 °C for 0.5 hour. To the mixture was added ethyl acetate (20 mL) and water (15 mL), then extracted with ethyl acetate (3 × 20 mL). The combined organic layers were

washed with brine (20 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by reversed phase flash column (ACN/Water (0.1% Formic Acid) = 42 %) to give *tert*-butyl 2-(cyanomethyl)-4-[7-[3-(2,2-dimethylpropanoyloxy)-1-naphthyl]-2-[[*(3R)*-1-methylpyrrolidin-3-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (180 mg, 245 μ mol, 31.7 % yield, 95.0 % purity) as brown solid. ES+APCI MS *m/z* 698.6[M+H]⁺.

[0757] Step C: [4-[4-[3-(cyanomethyl)piperazin-1-yl]-2-[[*(3R)*-1-methylpyrrolidin-3-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]-2-naphthyl] 2,2-dimethylpropanoate: A mixture of *tert*-butyl 2-(cyanomethyl)-4-[7-[3-(2,2-dimethylpropanoyloxy)-1-naphthyl]-2-[[*(3R)*-1-methylpyrrolidin-3-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (180 mg, 258 μ mol) and TFA (588 mg, 5.16 mmol, 382 μ L) was stirred at 20 °C for 1.5 hours. The reaction mixture was concentrated under vacuum to give [4-[4-[3-(cyanomethyl)piperazin-1-yl]-2-[[*(3R)*-1-methylpyrrolidin-3-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]-2-naphthyl] 2,2-dimethylpropanoate (200 mg, crude, 2TFA) as a brown oil.

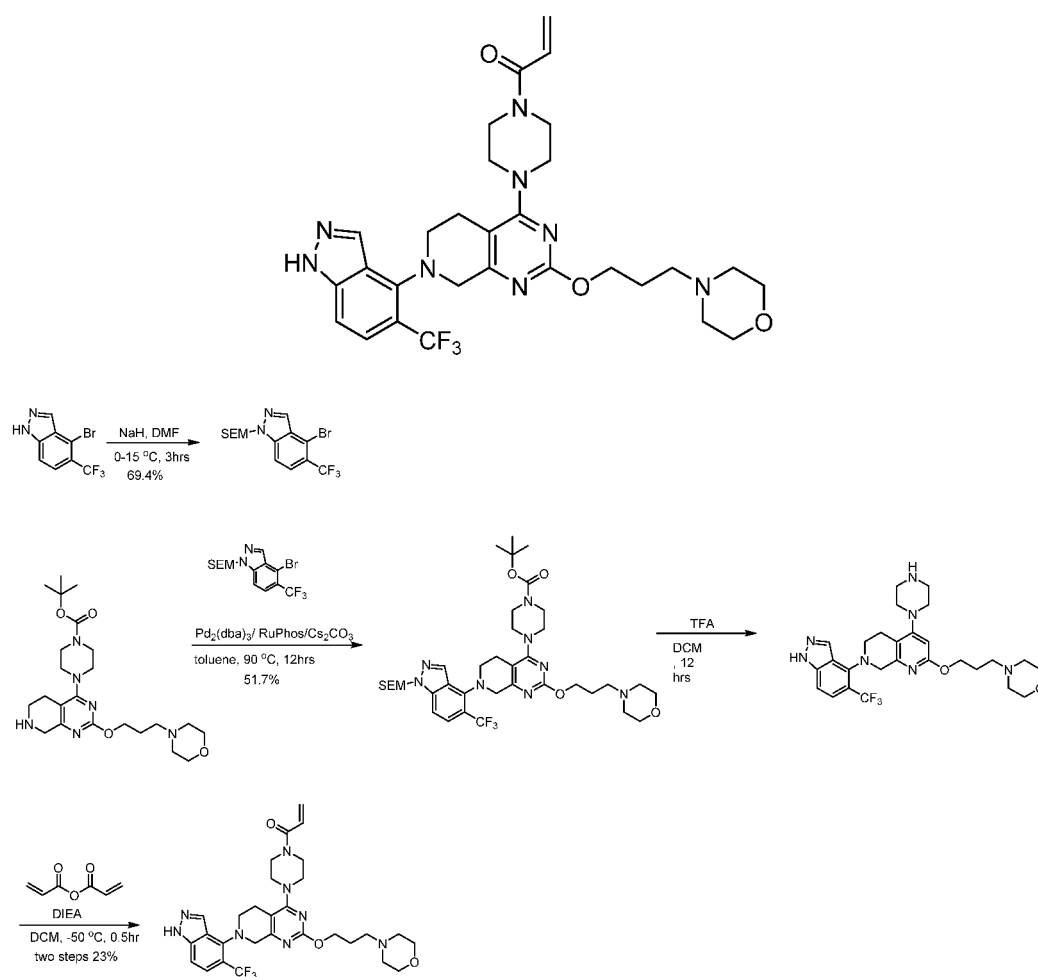
[0758] Step D: [4-[4-[3-(cyanomethyl)-4-prop-2-enoyl-piperazin-1-yl]-2-[[*(3R)*-1-methylpyrrolidin-3-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]-2-naphthyl] 2,2-dimethylpropanoate: To the solution of [4-[4-[3-(cyanomethyl)piperazin-1-yl]-2-[[*(3R)*-1-methylpyrrolidin-3-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]-2-naphthyl] 2,2-dimethylpropanoate (200 mg, 242 μ mol, 2TFA) and DIEA (470 mg, 3.63 mmol, 633 μ L) in DCM (0.6 mL) was added prop-2-enoyl prop-2-enoate (30.5 mg, 242 μ mol) at 0 °C and the reaction stirred at 15 °C for 1 hour. The reaction mixture was concentrated under vacuum. The residue was purified by silica gel chromatography (PE: EA= 2:1~0:1 to DCM: MeOH=50:1~1:1) to give [4-[4-[3-(cyanomethyl)-4-prop-2-enoyl-piperazin-1-yl]-2-[[*(3R)*-1-methylpyrrolidin-3-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]-2-naphthyl] 2,2-dimethylpropanoate (630 mg, crude) as brown oil. ES+APCI MS *m/z* 652.6[M+H]⁺.

[0759] Step E: 2-[4-[7-(3-hydroxy-1-naphthyl)-2-[[*(3R)*-1-methylpyrrolidin-3-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile: To a solution of [4-[4-[3-(cyanomethyl)-4-prop-2-enoyl-piperazin-1-yl]-2-[[*(3R)*-1-methylpyrrolidin-3-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]-2-naphthyl] 2,2-

dimethylpropanoate (630 mg, 966 μmol) in THF (3 mL) was added NaOH (2 M, 3 mL) at 18 °C and the mixture stirred at 18 °C for 2 hours. The reaction mixture was neutralized by HCOOH (20 %, 0.5 mL) to PH=7. The resulting mixture was extracted with DCM (3×5 mL), the combined organic layers were dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Phenomenex Gemini 150*25mm*10 μm ; mobile phase: [water(10mM NH_4HCO_3)-ACN]; B%: 35%-65%, 3min) to give 2-[4-[7-(3-hydroxy-1-naphthyl)-2-[[*(3R)*-1-methylpyrrolidin-3-yl]methoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile (9.4 mg, 15.8 μmol , 1.64 % yield, 95.5 % purity) as yellow solid. ES+APCI MS m/z 568.5[M+H]⁺.

EXAMPLE 180

4-(3-(4-(piperazin-1-yl)-7-(5-(trifluoromethyl)-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-2-yloxy)propyl)morpholine



[0760] Step A. 2-[[4-bromo-5-(trifluoromethyl)indazol-1-yl]methoxy]ethyl-trimethyl-silane: To a solution of 4-bromo-5-(trifluoromethyl)-1H-indazole (650 mg, 2.45 mmol, 1 eq) in DMF (30 mL) was added NaH (117.71 mg, 2.94 mmol, 60% purity, 1.2 eq) at 0 °C. After being stirred at 0 °C for 1 hour, a solution of 2-(chloromethoxy)ethyltrimethyl-silane (531.56 mg, 3.19 mmol, 564.29 μ L, 1.3 eq) in DMF (10 mL) was added dropwise. The mixture was warmed to 15 °C and stirred for 2 hours. The mixture was quenched with saturated aqueous ammonium chloride solution (50.0 mL), diluted with water (100.0 mL) and then extracted with ethyl acetate (3 $\times$ 100.0 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated under vacuum to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 10:1). 2-[[4-bromo-5-(trifluoromethyl)indazol-1-yl]methoxy]ethyl-trimethyl-silane (680 mg, 1.70 mmol, 69.44% yield, 99.0% purity) was obtained as a colorless oil. ES+APCI MS m/z 395.0[M+H]⁺.

[0761] Step B. tert-butyl 4-[2-(3-morpholinopropoxy)-7-[5-(trifluoromethyl)-1-(2-trimethylsilylethoxymethyl)indazol-4-yl]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate: A mixture of 2-[[4-bromo-5-(trifluoromethyl)indazol-1-yl]methoxy]ethyl-trimethyl-silane (444.35 mg, 1.12 mmol, 1.3 eq), tert-butyl 4-[2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (400 mg, 864.71 μ mol, 1 eq), RuPhos (80.70 mg, 172.94 μ mol, 0.2 eq), Pd₂(dba)₃ (118.77 mg, 129.71 μ mol, 0.15 eq), and Cs₂CO₃ (845.21 mg, 2.59 mmol, 3 eq) in toluene (40 mL) was degassed and purged with N₂ 3 times, and the mixture was stirred at 90 °C for 12 hrs under nitrogen. The reaction mixture was concentrated under reduced pressure to remove toluene. The residue was diluted with water 100 mL and extracted with Ethyl acetate 300 mL (100 mL $\times$ 3). The combined organic layers were washed with water 300 mL (100 mL $\times$ 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, DCM: CH₃OH = 30:1 to 20:1). tert-butyl 4-[2-(3-morpholinopropoxy)-7-[5-(trifluoromethyl)-1-(2-trimethylsilylethoxymethyl)indazol-4-yl]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (400 mg, 446.87 μ mol, 51.68% yield, 86.8% purity) was obtained as a yellow solid. ES+APCI MS m/z 773.3[M+H]⁺.

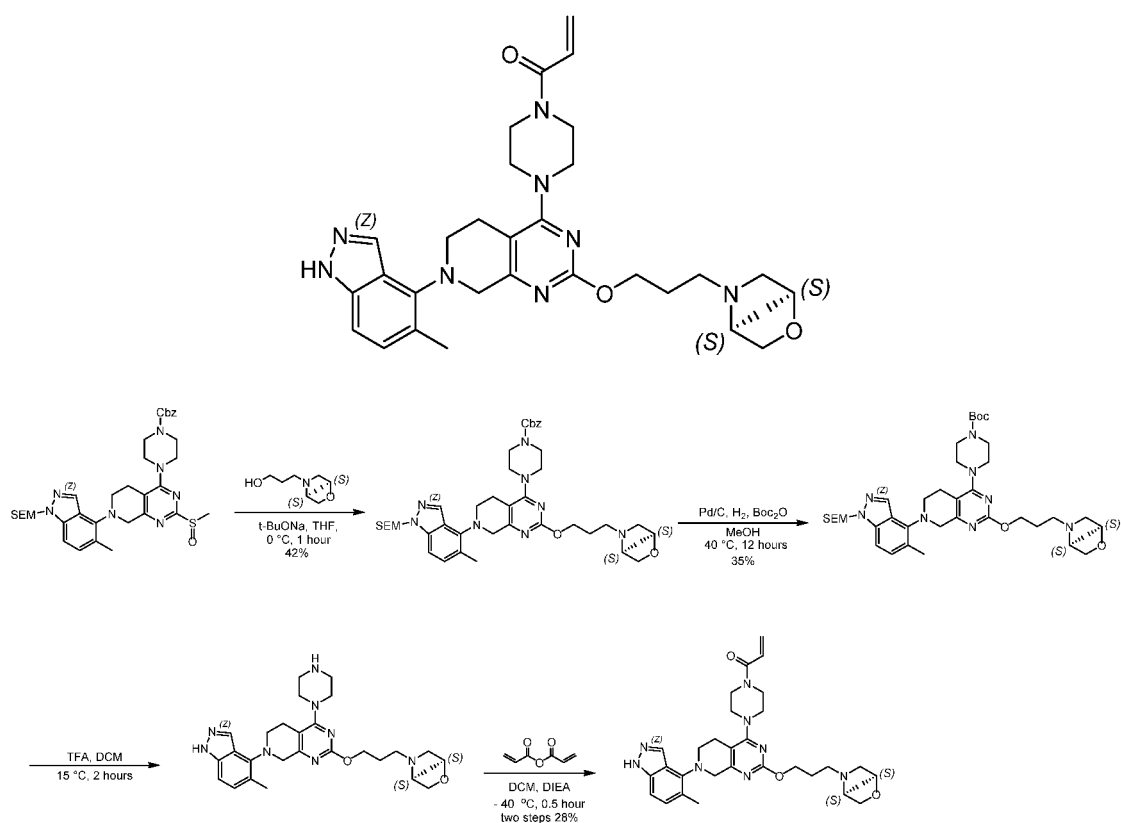
[0762] Step C. 4-[3-[[4-piperazin-1-yl]-7-[5-(trifluoromethyl)-1H-indazol-4-yl]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-2-yl]oxy]propyl]morpholine: To a solution of tert-butyl-4-[2-(3-

morpholinopropoxy)-7-[5-(trifluoromethyl)-1-(2-trimethylsilylethoxymethyl)indazol-4-yl]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (100 mg, 111.72 μ mol, 1 eq) in DCM (2 mL) was added TFA (254.77 mg, 2.23 mmol, 165.43 μ L, 20 eq) at 25°C. The reaction mixture was stirred at 25 °C for 12 hours. The reaction mixture was concentrated in vacuum. 4-[3-[[4-piperazin-1-yl-7-[5-(trifluoromethyl)-1H-indazol-4-yl]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-2-yl]oxy]propyl]morpholine (200 mg, crude, TFA) was obtained as a brown color oil. The crude product was used directly to the next step without further purification. ES+APCI MS m/z 547.5[M+H]⁺.

[0763] Step D. 1-[4-[2-(3-morpholinopropoxy)-7-[5-(trifluoromethyl)-1H-indazol-4-yl]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one: To a solution of 4-[3-[[4-piperazin-1-yl-7-[5-(trifluoromethyl)-1H-indazol-4-yl]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-2-yl]oxy]propyl]morpholine (200 mg, TFA) and DIEA (600 mg, 4.64 mmol, 808.63 μ L) in DCM (2 mL) was added dropwise prop-2-enoyl prop-2-enoate (13 mg, 103.08 μ mol) at - 50 °C. The mixture was stirred at -50°C for 30 min. The mixture was quenched with water and extracted with ethyl acetate (50 mL), the organic layer was washed with water (1 $\times$ 20 mL) and brine (1 $\times$ 20 mL). The separated organic layer was dried over sodium sulfate, filtered and concentrated under vacuum. The residue was purified by prep-HPLC (FA condition) column: Luna C18 150*25 5 μ ; mobile phase: [water(0.225%FA)-ACN]; B%: 15%-36%, 10min]. 1-[4-[2-(3-morpholinopropoxy)-7-[5-(trifluoromethyl)-1H-indazol-4-yl]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one (18.26 mg, 28.12 μ mol, two steps 23%, 99.6% purity, FA) was obtained as a yellow solid. ES+APCI MS m/z 601.4[M+H]⁺.

EXAMPLE 181

1-(4-(2-(3-((1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)propoxy)-7-(5-methyl-1*H*-indazol-4-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one



[0764] Step A. benzyl 4-(2-(3-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)propoxy)-7-(5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate: To a solution of 3-((1S,4S)-2-oxa-5-azabicyclo[2.2.1] heptan-5-yl)propan-1-ol (107 mg, 681 μ mol) in THF (2 mL) was added t-BuONa (98.1 mg, 1.02 mmol) followed by benzyl 4-[2-methylsulfinyl -7-[5-methyl-1-(2-trimethylsilylethoxymethyl)indazol-4-yl]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate (230 mg, 340 μ mol). The mixture was stirred at 0 °C for 1 hour. The mixture was poured into water (10 mL) and extracted with DCM (2x10 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated. The obtained product was purified by prep-HPLC (column: Phenomenex Synergi C18 150*25*10 μ m; mobile phase: [water (0.1%TFA) - ACN]; B%: 25%-55%, 12min) to give benzyl 4-(2-(3-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)propoxy)-7-(5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (110 mg, 143 μ mol, 42.0 % yield) was obtained as yellow solid. ¹H NMR (400 MHz, Chloroform-d) δ 8.08 - 8.01 (m, 1H), 7.45 - 7.43 (m, 4H), 7.37 - 7.31 (m, 3H), 5.76 (s, 2H), 5.24 (s, 2H), 4.76 - 4.63 (m, 1H), 4.60 - 4.45 (m, 3H), 4.42 (s, 2H), 4.36 - 4.24 (m, 1H), 3.96 - 3.83 (m, 2H), 3.79 -

3.65 (m, 8H), 3.64 - 3.53 (m, 6H), 3.12 - 2.92 (m, 1H), 2.90 - 2.77 (m, 2H), 2.48 (s, 3H), 2.44 - 2.41 (m, 1H), 2.36 - 2.12 (m, 3H), 0.98 - 0.93 (m, 2H), 0.01 - -0.03 (m, 9H)

[0765] Step B. *tert*-butyl 4-(2-(3-((1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)propoxy)-7-(5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazol-4-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate: To a solution of benzyl 4-(2-(3-((1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)propoxy)-7-(5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazol-4-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (90 mg, 117 μ mol) and BOC₂O (51.1 mg, 234.1 μ mol, 53.8 μ L) in MeOH (2 mL) was added Pd/C (10 %, 50 mg) under an N₂ atmosphere. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (15 psi) at 40 °C for 12 hours. The mixture was filtered and concentrated. The residue was purified by prep-TLC (SiO₂, DCM/MeOH = 10 : 1) to give *tert*-butyl 4-(2-(3-((1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)propoxy)-7-(5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazol-4-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (30 mg, 40.8 μ mol). ES+APCI MS *m/z* 735.6[M+H]⁺.

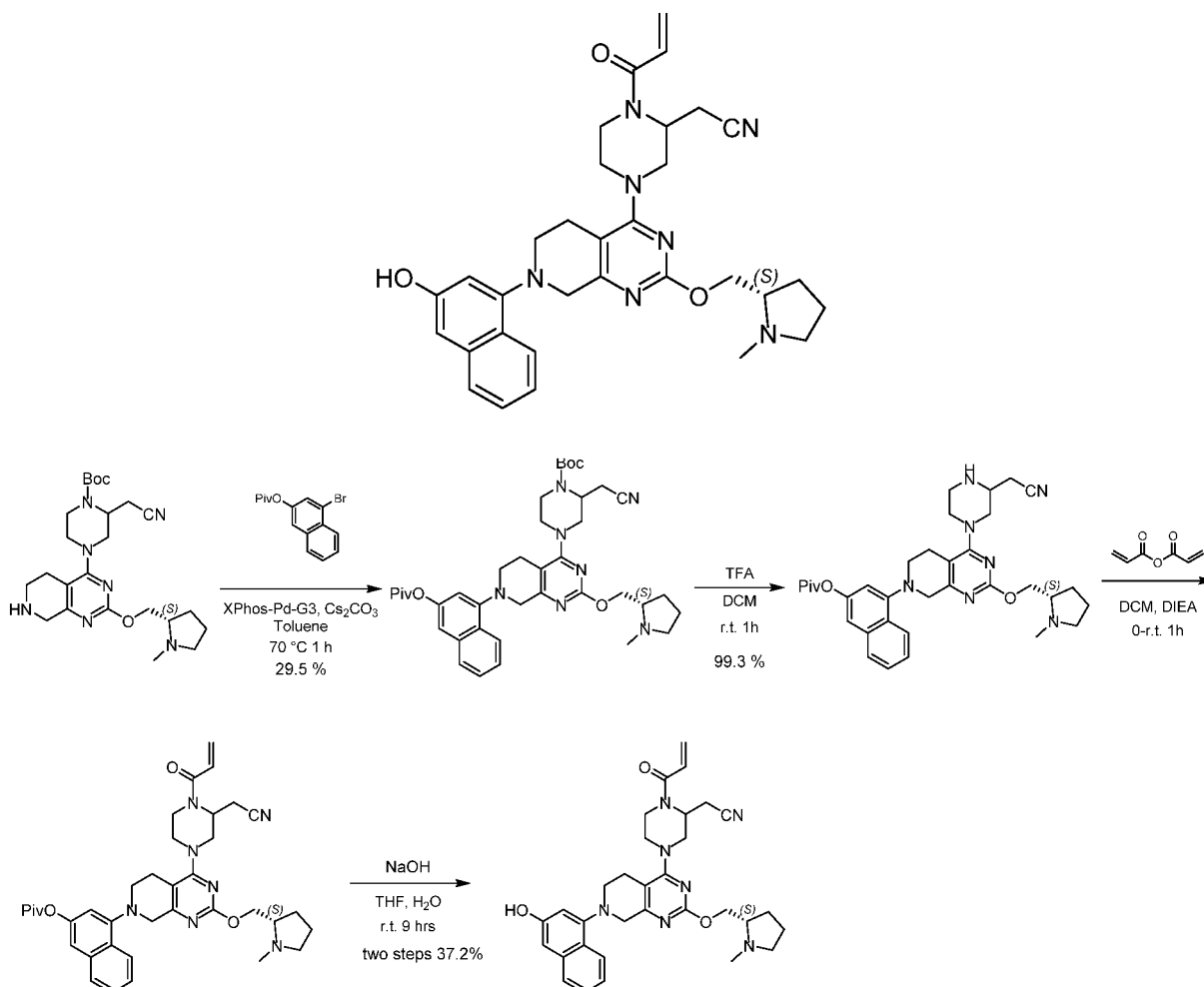
[0766] Step C. (1*S*,4*S*)-5-(3-((7-(5-methyl-1*H*-indazol-4-yl)-4-(piperazin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-2-yl)oxy)propyl)-2-oxa-5-azabicyclo[2.2.1]heptane: To a solution of *tert*-butyl 4-(2-(3-((1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)propoxy)-7-(5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazol-4-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (30 mg, 40.8 μ mol) in DCM (0.5 mL) was added TFA (770 mg, 6.75 mmol) dropwise. The mixture was stirred at 15 °C for 2 hours. The mixture was concentrated under vacuum to give (1*S*,4*S*)-5-(3-((7-(5-methyl-1*H*-indazol-4-yl)-4-(piperazin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-2-yl)oxy)propyl)-2-oxa-5-azabicyclo[2.2.1]heptane (30 mg, crude). ES+APCI MS *m/z* 505.5[M+H]⁺.

[0767] Step D. 1-(4-(2-(3-((1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)propoxy)-7-(5-methyl-1*H*-indazol-4-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one: To a solution of (1*S*,4*S*)-5-(3-((7-(5-methyl-1*H*-indazol-4-yl)-4-(piperazin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-2-yl)oxy)propyl)-2-oxa-5-azabicyclo[2.2.1]heptane (20 mg, 39.6 μ mol, 1 *eq*) and DIEA (30.7 mg, 238 μ mol, 41.4 μ L, 6 *eq*) in DCM (2 mL) was added prop-2-enoyl prop-2-enoate (4.00 mg, 31.7 μ mol, 0.8 *eq*) at -50 °C. The mixture was stirred at -

40 - -20 °C for 0.5 hour. The mixture was concentrated under vacuum. The obtained product was purified by prep-HPLC (column: Phenomenex Gemini 150*25mm*10um; mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN]; B%: 35%-65%, 12min). The product 1-(4-(2-(3-((1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)propoxy)-7-(5-methyl-1*H*-indazol-4-yl)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one (6.48 mg, 11.2 umol, two steps 28.3 % yield, 96.8 % purity) was obtained as white solid. ES+APCI MS *m/z* 559.5[M+H]⁺.

EXAMPLE 182

2-[4-[7-(3-hydroxy-1-naphthyl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile



[0768] Step A: *tert*-butyl 2-(cyanomethyl)-4-[7-[3-(2,2-dimethylpropanoyloxy)-1-naphthyl]-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate. To a mixture of *tert*-butyl 2-(cyanomethyl)-4-[2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (190 mg, 403 μ mol), (4-bromo-2-naphthyl) 2,2-dimethylpropanoate (248 mg, 806 μ mol) and Cs_2CO_3 (394 mg, 1.21 mmol) in toluene (5 mL) was added XPHOS Palladacycle Gen 3 (34.1 mg, 40.29 μ mol) and the reaction mixture stirred at 70 °C for 4 hours under N_2 . Upon completion, the reaction mixture was purified by silica gel chromatography (PE: EA=3:1 to 0:1) to give *tert*-butyl 2-(cyanomethyl)-4-[7-[3-(2,2-dimethylpropanoyloxy)-1-naphthyl]-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (95 mg, 118 μ mol). ES+APCI MS m/z 698.4 $[\text{M}+\text{H}]^+$.

[0769] Step B: [4-[4-[3-(cyanomethyl)piperazin-1-yl]-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]-2-naphthyl] 2,2-dimethylpropanoate. To a solution of *tert*-butyl 2-(cyanomethyl)-4-[7-[3-(2,2-dimethylpropanoyloxy)-1-naphthyl]-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (40 mg, 57.3 μ mol) in DCM (0.1 mL) was added TFA (154 mg, 1.35 mmol) at 15 °C. The reaction mixture was stirred at 15 °C for 1 hour. Upon completion, the solvent was removed under vacuum to give [4-[4-[3-(cyanomethyl)piperazin-1-yl]-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]-2-naphthyl] 2,2-dimethylpropanoate (47 mg, 56.9 μ mol).

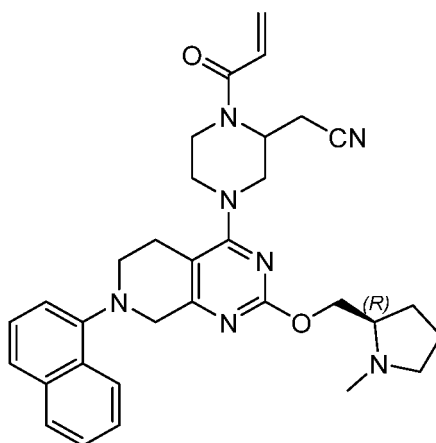
[0770] Step C: [4-[4-[3-(cyanomethyl)-4-prop-2-enoyl-piperazin-1-yl]-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]-2-naphthyl] 2,2-dimethylpropanoate. To a solution of [4-[4-[3-(cyanomethyl)piperazin-1-yl]-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]-2-naphthyl] 2,2-dimethylpropanoate (47 mg, 56.9 μ mol) and DIEA (58.9 mg, 455 μ mol) in DCM (1 mL) was added prop-2-enoyl prop-2-enoate (10.8 mg, 85.4 μ mol) at 0 °C. The reaction mixture was stirred at 15 °C for 1 hour. Upon completion, the reaction mixture was quenched by addition of a drop of water. The residue was purified by silica gel chromatography (PE: EtOAc=3:1 to EtOAc: MeOH=3:1) to give [4-[4-[3-(cyanomethyl)-4-prop-2-enoyl-piperazin-1-yl]-2-[[*(2S)*-1-

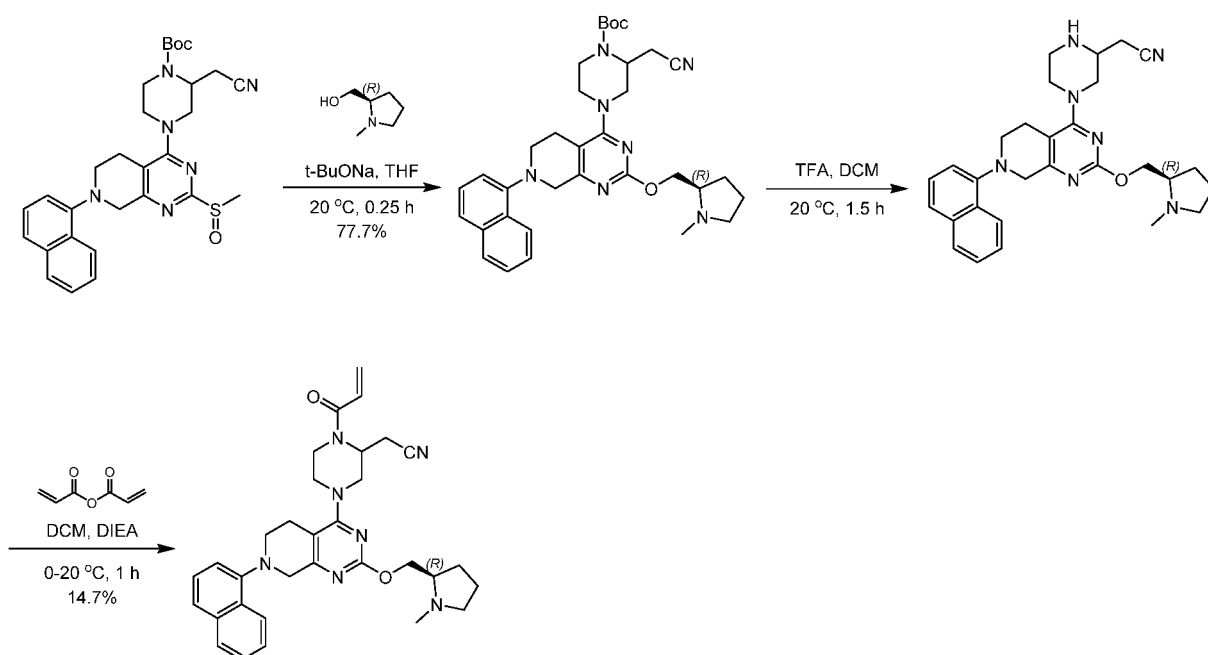
methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]-2-naphthyl] 2,2-dimethylpropanoate (130 mg, crude). ES+APCI MS *m/z* 652.5 [M+H]⁺.

[0771] Step D: 2-[4-[7-(3-hydroxy-1-naphthyl)-2-[[*(2S)*]-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile. To a solution of [4-[4-[3-(cyanomethyl)-4-prop-2-enoyl-piperazin-1-yl]-2-[[*(2S)*]-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-7-yl]-2-naphthyl] 2,2-dimethylpropanoate (250 mg, 384 μ mol) in THF (1.5 mL) was added NaOH (2 M, 1.5 mL) in water. The reaction mixture was stirred at 15 °C for 9 hours. Upon completion, the reaction mixture was acidified by addition of two drops of formic acid (20 % in water) to reach a pH=7 and the aqueous layer extracted with DCM (5 $\times$ 10 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by prep-HPLC(column: Boston Green ODS 150*30 5 μ ;mobile phase: [water(0.225%FA)-ACN];B%: 20%-47%,10min) to give 2-[4-[7-(3-hydroxy-1-naphthyl)-2-[[*(2S)*]-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile (13.1 mg, 21.2 μ mol). ES+APCI MS *m/z* 568.5 [M+H]⁺.

EXAMPLE 183

2-[4-[2-[[*(2R)*]-1-methylpyrrolidin-2-yl]methoxy]-7-(1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile





[0772] Step A: *tert*-butyl 2-(cyanomethyl)-4-[2-[[*(2R)*]-1-methylpyrrolidin-2-yl]methoxy]-7-(1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate. To a solution of *tert*-butyl 2-(cyanomethyl)-4-[2-methylsulfinyl-7-(1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (300 mg, 549 μ mol) and [*(2S)*]-1-methylpyrrolidin-2-yl]methanol (126 mg, 1.10 mmol, 130 μ L) in toluene (6.00 mL) was added *t*-BuONa (105 mg, 1.10 mmol). The mixture was stirred at 20 °C for 0.25 hour. Upon completion, the mixture was filtered and the filtrate was concentrated. The residue was purified by silica gel chromatography (EA/MeOH 50/1 to 10/1) to give *tert*-butyl 2-(cyanomethyl)-4-[2-[[*(2R)*]-1-methylpyrrolidin-2-yl]methoxy]-7-(1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (300 mg, 427 μ mol). ES+APCI MS m/z 598.6 $[M+H]^+$.

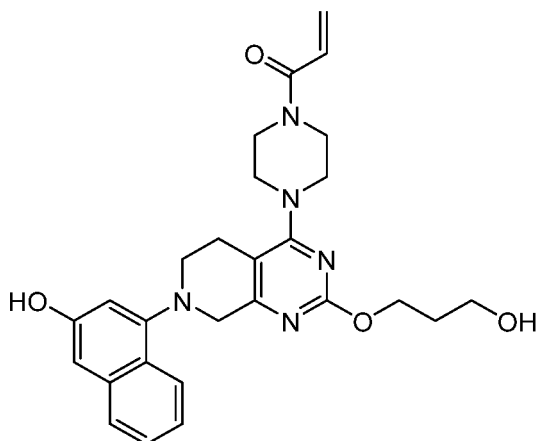
[0773] Step B: 2-[4-[2-[[*(2R)*]-1-methylpyrrolidin-2-yl]methoxy]-7-(1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-2-yl]acetonitrile. To a solution of *tert*-butyl 2-(cyanomethyl)-4-[2-[[*(2R)*]-1-methylpyrrolidin-2-yl]methoxy]-7-(1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (270 mg, 452 μ mol) in DCM (330 μ L) was added TFA (515 mg, 4.52 mmol). The mixture was stirred at 20 °C for 0.5 hour and concentrated under vacuum. Then TFA (334 μ L) was added. The mixture was stirred at 20 °C for 1 hour. Upon completion, the mixture was concentrated under vacuum to give 2-[4-[2-

[[*(2R)*-1-methylpyrrolidin-2-yl]methoxy]-7-(1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-d]pyrimidin-4-yl]piperazin-2-yl]acetonitrile (400 mg, crude). ES+APCI MS m/z 498.4 $[M+H]^+$.

[0774] Step C: 2-[4-[2-[[*(2R)*-1-methylpyrrolidin-2-yl]methoxy]-7-(1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-d]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile. To a solution of 2-[4-[2-[[*(2R)*-1-methylpyrrolidin-2-yl]methoxy]-7-(1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-d]pyrimidin-4-yl]piperazin-2-yl]acetonitrile (276 mg, 451 μ mol) and DIEA (1.46 g, 11.3 mmol) in DCM (4.00 mL) was added prop-2-enoyl prop-2-enoate (51.2 mg, 406 μ mol) dropwise at 0 °C. The mixture was stirred at 20 °C for 1 hour. Upon completion, the mixture was diluted with water (0.5 mL) and extracted with EtOAc (2 $\times$ 10 mL). The combined organic layers were dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by prep-HPLC (column: Phenomenex Gemini 150*25mm*10 μ m; mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN]; B%: 55%-85%, 12min) to give 2-[4-[2-[[*(2R)*-1-methylpyrrolidin-2-yl]methoxy]-7-(1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-d]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile (37.1 mg, 66.3 μ mol). ES+APCI MS m/z 552.4 $[M+H]^+$.

EXAMPLE 184

1-[4-[7-(3-hydroxy-1-naphthyl)-2-(3-hydroxypropoxy)-6,8-dihydro-5*H*-pyrido[3,4-d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one

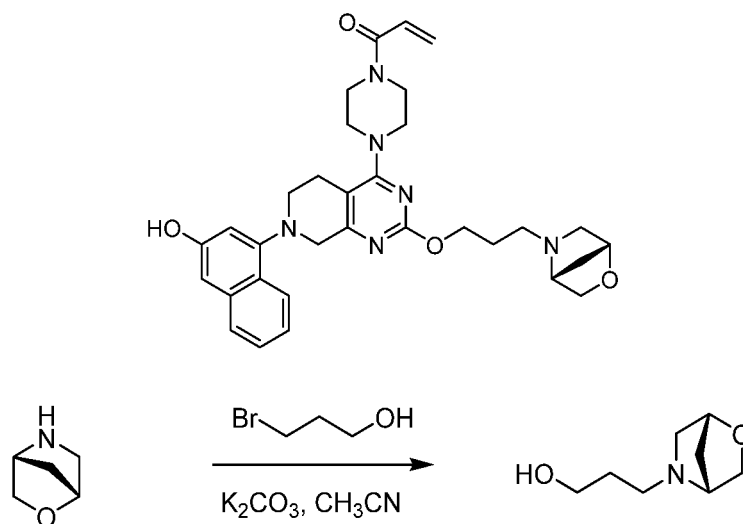


[0775] 1-[4-[7-(3-hydroxy-1-naphthyl)-2-(3-hydroxypropoxy)-6,8-dihydro-5*H*-pyrido[3,4-d]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one was prepared following **Example 136**

substituting 3-[*tert*-butyl(dimethyl)silyl]oxypropan-1-ol for 2-(3-methoxypyrrolidin-1-yl)ethanol in Step B. ES+APCI MS m/z 490.3 $[M+H]^+$.

EXAMPLE 185

1-(4-(2-(3-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)propoxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one



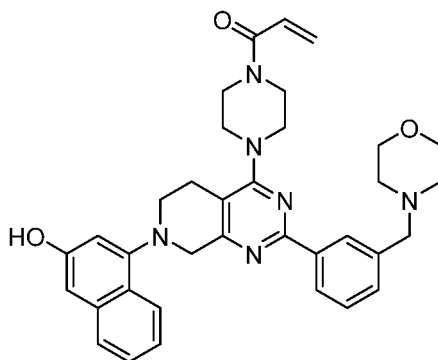
[0776] Step A: 3-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)propan-1-ol: To a vial was added (1R,4R)-2-Oxa-5-azabicyclo[2.2.1]heptane HCl salt (0.250 g, 2.522 mmol), CH₃CN (5.04 mL) and 3-Bromo-1-propanol (0.274 mL, 3.026 mmol). Then K₂CO₃ (1.05 g, 7.57 mmol) was added and the mixture was warmed to 50 °C where it stirred for 16 hours. The mixture was then cooled to ambient temperature, diluted with CH₂Cl₂ and filtered and the solid was washed with CH₂Cl₂. The filtrate was then concentrated and the crude oil was purified via column chromatography (5% MeOH/DCM with 0.2% NH₄OH) to afford the product as a colorless oil.

[0777] Step B: 1-(4-(2-(3-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)propoxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one: Synthesized according to the method of Example 127 using the following procedure in place of that outlined in Step D. To a vial was added 3-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)propan-1-ol (0.171 g, 1.09 mmol) and benzyl 4-(2-chloro-7-(3-(methoxymethoxy)naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-

1-carboxylate (0.125 g, 0.218 mmol) followed by dioxane (0.435 mL). Then Cs₂CO₃ (0.213 g, 0.653 mmol) was added and the mixture was heated to 100 °C for 15 hours. The reaction was diluted with CH₂Cl₂, filtered and the residual solid was washed with CH₂Cl₂. The filtrate was then dried over Na₂SO₄, filtered and concentrated. The crude residue was purified by column chromatography (4% MeOH/DCM with 0.2% NH₄OH) to afford the product as a yellow foam. ES+APCI MS m/z 571.2 [M+H]⁺.

EXAMPLE 186

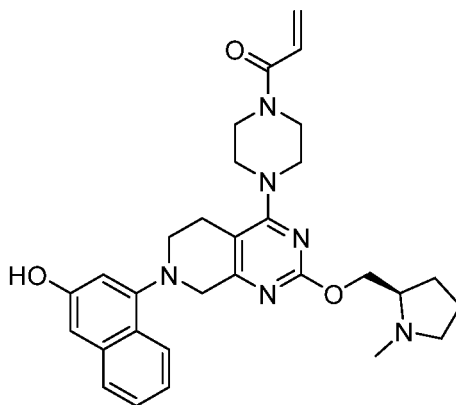
Benzyl 4-(7-(3-(methoxymethoxy)naphthalen-1-yl)-2-(3-(morpholinomethyl)phenyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate



[0778] Benzyl 4-(7-(3-(methoxymethoxy)naphthalen-1-yl)-2-(3-(morpholinomethyl)phenyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate: Synthesized according to the method of Example 127 using the following procedure in place of that outlined in Step D. To a solution of benzyl 4-(2-chloro-7-(3-(methoxymethoxy)naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (0.150 g, 0.261 mmol) and 3-(4-Morpholinomethyl)-phenylboronic acid pinacol ester hydrochloride (0.266 g, 0.784 mmol) in dioxane (2.61 mL) was added Na₂CO₃ (0.523 mL, 1.0452 mmol, 2.0M Aq). The mixture was degassed by argon bubbling for 5 min. Then Tetrakis(triphenylphosphine)palladium (0) (0.030 g, 0.026 mmol) was added and the mixture was heated to 95 °C where it stirred for 7 hours. The reaction was cooled to ambient temperature and then diluted with CH₂Cl₂ and filtered. The solid was washed with CH₂Cl₂. The filtrate was then dried over Na₂SO₄, filtered and concentrated. The crude residue was purified by column chromatography (30-50% EtOAc/DCM) to afford the product as a yellow foam. ES+APCI MS m/z 591.3 [M+H]⁺.

EXAMPLE 187

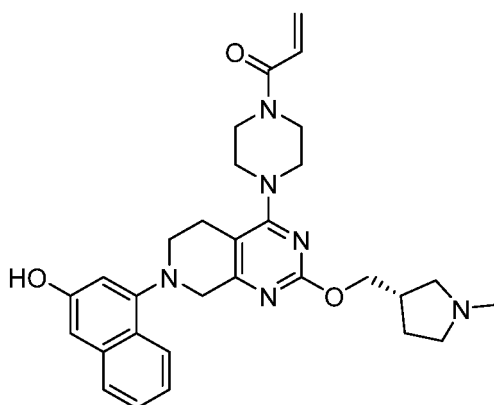
(R)-1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-((1-methylpyrrolidin-2-yl)methoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one



[0779] (R)-1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-((1-methylpyrrolidin-2-yl)methoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one. This compound was prepared following **Example 127** substituting N-Methyl-D-prolinol for N-Methyl-L-prolinol in Step D. ES+APCI MS m/z 529.3 [M+H]⁺.

EXAMPLE 188

(S)-1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-((1-methylpyrrolidin-3-yl)methoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

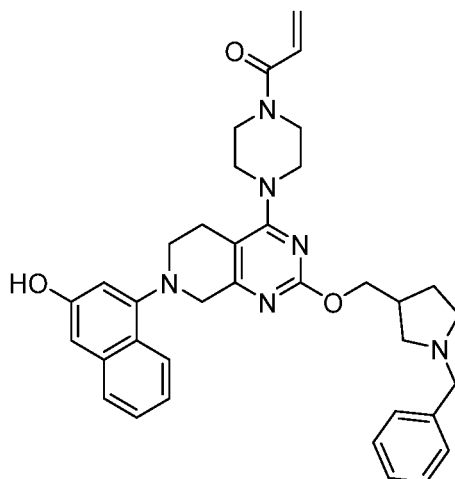


[0780] (S)-1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-((1-methylpyrrolidin-3-yl)methoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one. This compound was

prepared following **Example 127** substituting (3S)-(1-Methyl-pyrrolidin-3-yl)-methanol for N-Methyl-L-prolinol in Step D. ES+APCI MS m/z 529.2 [M+H]⁺.

EXAMPLE 189

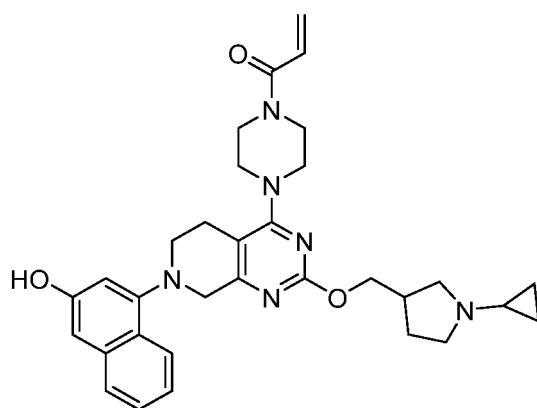
1-(4-(2-((1-benzylpyrrolidin-3-yl)methoxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one



[0781] 1-(4-(2-((1-benzylpyrrolidin-3-yl)methoxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one. This compound was prepared following **Example 127** substituting (1-Benzylpyrrolidin-3-yl)methanol for N-Methyl-L-prolinol in Step D. ES+APCI MS m/z 605.3 [M+H]⁺.

EXAMPLE 190

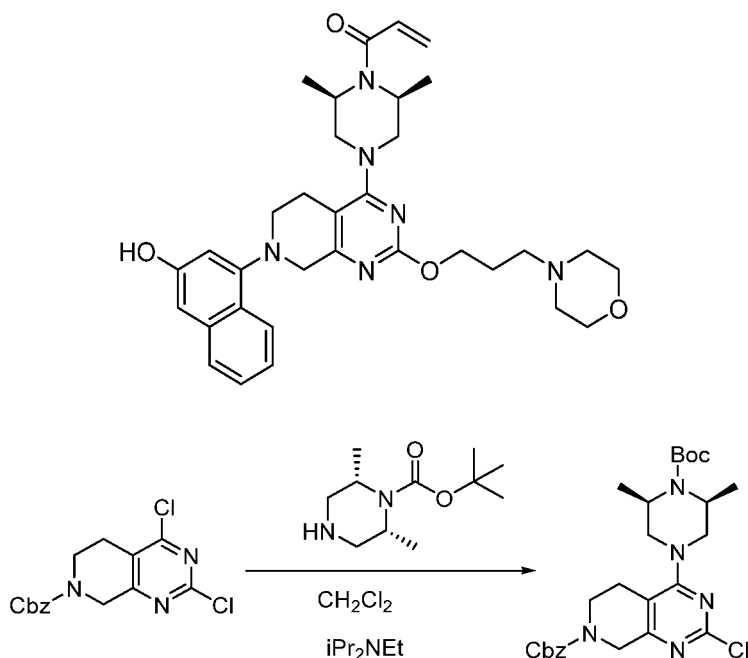
1-(4-(2-((1-cyclopropylpyrrolidin-3-yl)methoxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one



[0782] 1-(4-(2-((1-cyclopropylpyrrolidin-3-yl)methoxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one. This compound was prepared following **Example 127** substituting (1-Cyclopropyl-3-pyrrolidinyl)methanol for N-Methyl-L-prolinol in Step D. ES+APCI MS m/z 555.3 $[M+H]^+$.

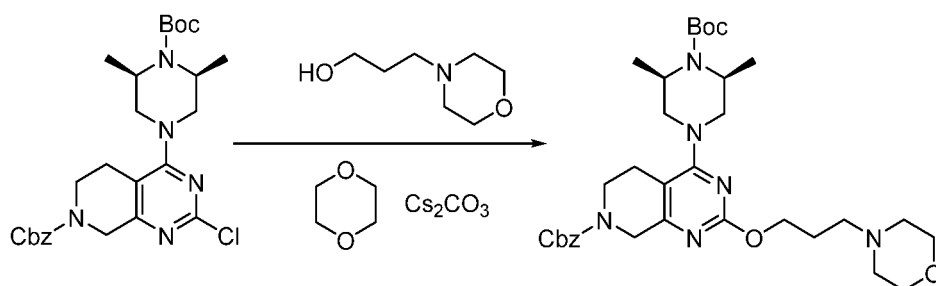
EXAMPLE 191

1-((2S,6R)-4-(7-(3-hydroxynaphthalen-1-yl)-2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)-2,6-dimethylpiperazin-1-yl)prop-2-en-1-one

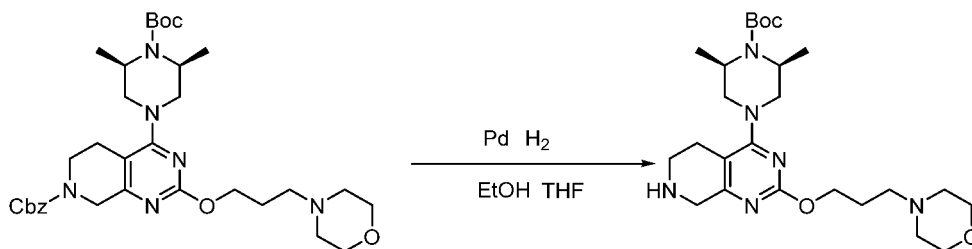


[0783] Step A: Benzyl 4-((3S,5R)-4-(tert-butoxycarbonyl)-3,5-dimethylpiperazin-1-yl)-2-chloro-5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate: A suspension of benzyl 2,4-dichloro-

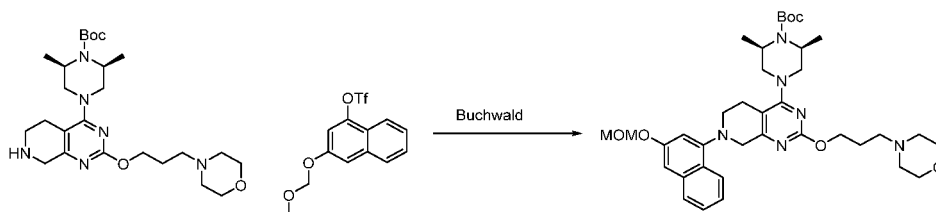
5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate (500 mg, 1.48 mmol), tert-butyl cis-2,6-dimethylpiperazine-1-carboxylate (349 mg, 1.63 mmol) and DIEA (0.26 mL) in *N,N*-dimethylacetamide (1 mL) was stirred at r.t. overnight. The reaction mixture was divided between EtOAc (15 mL) and 1M NaHCO₃ (5 mL) and the layers separated. The organic layer was washed with 2M Na₂CO₃ and brine (2 mL each), dried over Na₂SO₄ and evaporated in vacuo. The residue was chromatographed on silica gel Redisep 24g column using 20 to 50% EtOAc in hexane as eluent to give a colorless solid (0.440 g, 58%). ES+APCI MS *m/z* 516.2 [M+H]⁺.



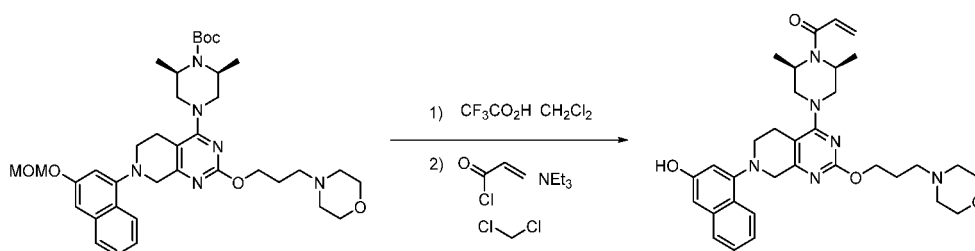
[0784] Step B: Benzyl 4-((3*S*,5*R*)-4-(tert-butoxycarbonyl)-3,5-dimethylpiperazin-1-yl)-2-(3-morpholinopropoxy)-5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate: A mixture of benzyl 4-((3*S*,5*R*)-4-(tert-butoxycarbonyl)-3,5-dimethylpiperazin-1-yl)-2-chloro-5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate (400 mg, 0.775 mmol), 3-morpholinopropan-1-ol (400 mg, 2.33 mmol, 5 eq.), cesium carbonate (1.26 g, 3.88 mmol, 5 eq.) and dioxane (3 mL) in a 4-mL vial was purged with nitrogen. The vial was capped and the mixture stirred at 110°C for 20h, then at 120°C overnight. The reaction was cooled, diluted with EtOAc (10 mL), filtered through Celite and evaporated in vacuo. The product was purified by chromatography on silica, Redisep 40g, using 2 to 10% MeOH/DCM +0.2% NH₄OH as eluent to give a light-yellow amorphous solid (272 mg, 56%).



[0785] Step C: tert-butyl (2S,6R)-2,6-dimethyl-4-(2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate: A mixture of benzyl 4-((3S,5R)-4-(tert-butoxycarbonyl)-3,5-dimethylpiperazin-1-yl)-2-(3-morpholinopropoxy)-5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate (272 mg, 0.095 mmol), palladium on carbon (50 mg, *Degussa Type, 10 wt%, 50% H₂O*), EtOH (5 mL) and THF (5 mL) was purged with hydrogen and stirred under H₂ atmosphere (rubber balloon) for 3 hours. The reaction mixture was diluted with EtOH (3 mL), filtered through Celite and the celite washed with EtOH (2 x 2 mL). The combined organics were evaporated in vacuo and dried under high vacuum over 2 days to give an off-white foam (205 mg, 96%). ES+APCI MS m/z 491.3 [M+H]⁺.



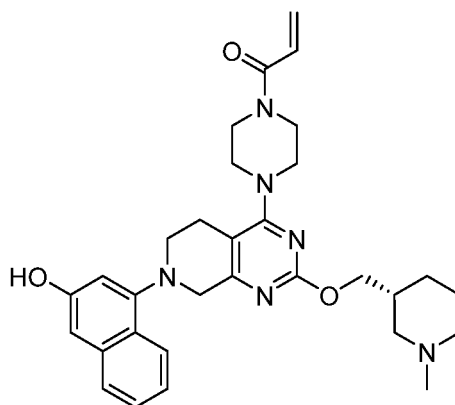
[0786] Step D: tert-butyl (2S,6R)-4-(7-(3-(methoxymethoxy)naphthalen-1-yl)-2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)-2,6-dimethylpiperazine-1-carboxylate: To a stirred suspension of tris(dibenzylideneacetone)dipalladium (0) (19 mg, 0.020 mmol) in dry degassed toluene (0.5 mL) at room temperature under nitrogen was added (+/-)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (24 mg, 0.038 mmol). The mixture was then heated to 100 °C for 15 minutes. The resulted dark mixture was cooled to room temperature and solid sodium-t-butoxide (39 mg, 0.41 mmol) was added, followed by a solution of 3-(methoxymethoxy)naphthalen-1-yl trifluoromethanesulfonate (82 mg, 0.25 mmol) and tert-butyl (2S,6R)-2,6-dimethyl-4-(2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (100 mg, 0.20 mmol) in degassed dry toluene (0.5 mL). The flask was closed and heated with stirring to 100 °C for 30 min. The reaction mixture was cooled and divided between EtOAc (20 mL) and water (10 mL). The organic layer was separated and washed with brine, dried over Na₂SO₄ and evaporated in vacuo. The product was purified by chromatography on silica, Redisep 40g, using 4% MeOH + 0.1% NH₄OH in DCM as eluent to give a colorless solid (87 mg, 63%). ES+APCI MS m/z 684.3 [M+H]⁺.



[0787] Step E: 1-((2S,6R)-4-(7-(3-hydroxynaphthalen-1-yl)-2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)-2,6-dimethylpiperazin-1-yl)prop-2-en-1-one: Tert-butyl (2S,6R)-4-(7-(3-(methoxymethoxy)naphthalen-1-yl)-2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)-2,6-dimethylpiperazine-1-carboxylate (87 mg, 0.129 mmol) was dissolved in 1M TFA/DCM. The reaction mixture turned red-brown, then dark-red. LCMS indicated non-selective deprotection of Boc and MOM. After stirring 30 min at room temperature, 0.2 mL of additional TFA was added and the reaction mixture was left at room temperature for another 30 min. The resulted biphasic mixture was vaporated in vacuo, divided between water (5 mL) and DCM (10 mL) + NEt₃ (0.5 mL) and the organic layer separated. The organic layer was dried over Na₂SO₄ and evaporated in vacuo. The residue was purified by chromatography on silica, Redisep 40g, using 6% MeOH in DCM +0.2% NH₄OH as eluent to give another residue which was repurified on reverse phase, C18, 5-95% MeCN-H₂O +0.1%TFA to give product assumed to be the bis-salt with TFA (1.35 mg, 1.3%). ES+APCI MS m/z 587.3 [M+H]⁺.

EXAMPLE 192

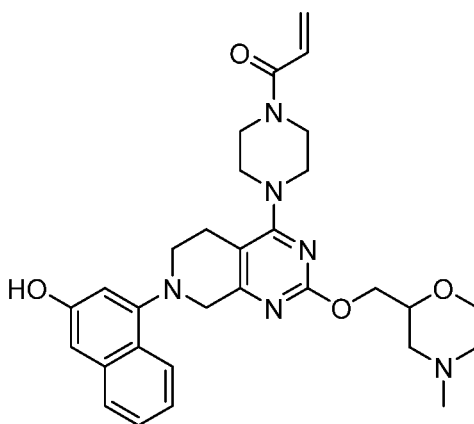
(R)-1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-((1-methylpiperidin-3-yl)methoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one



[0788] (R)-1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-((1-methylpiperidin-3-yl)methoxy))-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one. This compound was prepared following **Example 127** substituting 3-Piperidinemethanol, 1-methyl-, (3R)- for N-Methyl-L-prolinol in Step D. ES+APCI MS m/z 543.3 [M+H]⁺.

EXAMPLE 193

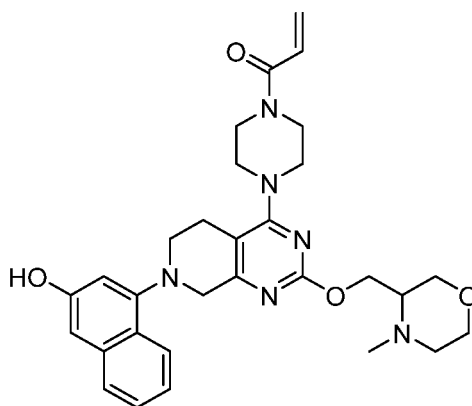
1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-((4-methylmorpholin-2-yl)methoxy))-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one



[0789] 1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-((4-methylmorpholin-2-yl)methoxy))-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one. This compound was prepared following **Example 127** substituting (4-methyl-2-morpholinyl)methanol for N-Methyl-L-prolinol in Step D. ES+APCI MS m/z 545.3 [M+H]⁺.

EXAMPLE 194

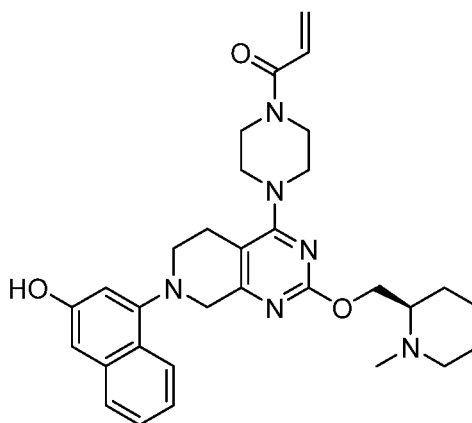
1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-((4-methylmorpholin-3-yl)methoxy))-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one



[0790] 1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-((4-methylmorpholin-3-yl)methoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one. This compound was prepared following **Example 127** substituting 4-Methyl-3-(hydroxymethyl)morpholine for N-Methyl-L-prolinol in Step D. ES+APCI MS m/z 545.2 $[M+H]^+$.

EXAMPLE 195

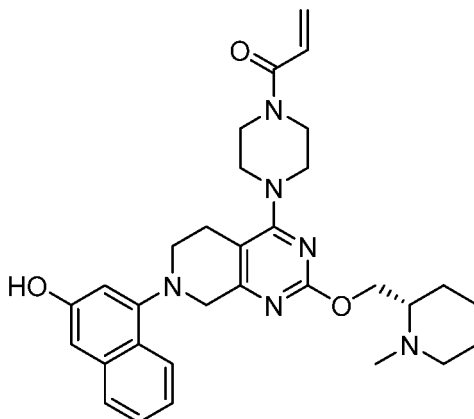
(R)-1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-((1-methylpiperidin-2-yl)methoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one



[0791] (R)-1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-((1-methylpiperidin-2-yl)methoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one. This compound was prepared following **Example 127** substituting (R)-(1-Methylpiperidin-2-yl)methanol for N-Methyl-L-prolinol in Step D. ES+APCI MS m/z 543.3 $[M+H]^+$.

EXAMPLE 196

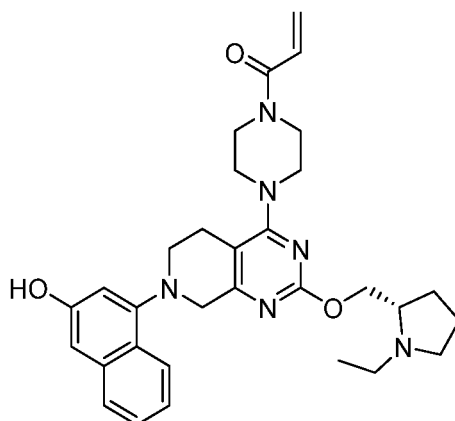
(S)-1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-((1-methylpiperidin-2-yl)methoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one



[0792] (S)-1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-((1-methylpiperidin-2-yl)methoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one. This compound was prepared following **Example 127** substituting (S)-(1-Methylpiperidin-2-yl)methanol for N-Methyl-L-prolinol in Step D. ES+APCI MS m/z 543.2 $[M+H]^+$.

EXAMPLE 197

(S)-1-(4-(2-((1-ethylpyrrolidin-2-yl)methoxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

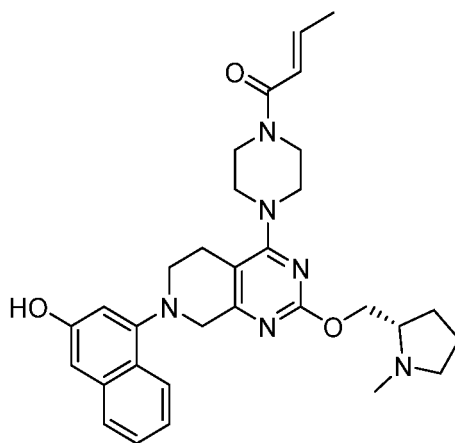


[0793] (S)-1-(4-(2-((1-ethylpyrrolidin-2-yl)methoxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one. This compound was

prepared following **Example 127** substituting [(2S)-1-Ethyl-2-pyrrolidinyl]methanol for N-Methyl-L-prolinol in Step D. ES+APCI MS m/z 543.3 [M+H]⁺.

EXAMPLE 198

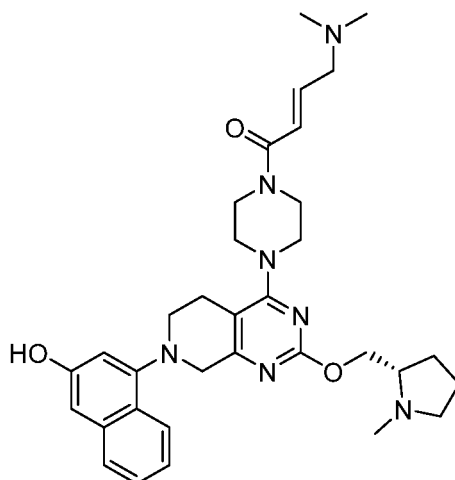
(S,E)-1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-((1-methylpyrrolidin-2-yl)methoxy))-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)but-2-en-1-one



[0794] (S,E)-1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-((1-methylpyrrolidin-2-yl)methoxy))-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)but-2-en-1-one. This compound was prepared following **Example 127** substituting trans-Crotonyl chloride for Acryloyl Chloride in Step F. ES+APCI MS m/z 543.2[M+H]⁺.

EXAMPLE 199

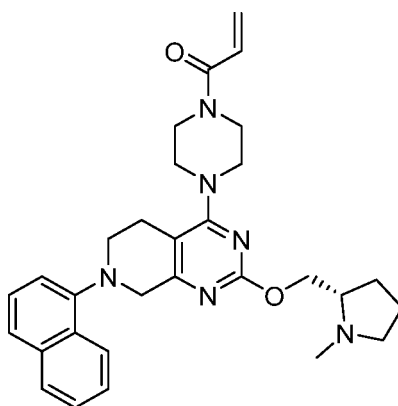
(S,E)-4-(dimethylamino)-1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-((1-methylpyrrolidin-2-yl)methoxy))-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)but-2-en-1-one



[0795] (S,E)-4-(dimethylamino)-1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-((1-methylpyrrolidin-2-yl)methoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)but-2-en-1-one. This compound was prepared following Example 127 substituting the following procedure for step F. 7-(3-(methoxymethoxy)naphthalen-1-yl)-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-4-(piperazin-1-yl)-4a,5,6,7,8,8a-hexahydropyrido[3,4-d]pyrimidine (150 mg, 0.288 mmol) was dissolved in DCM (5 mL) and treated with (2E)-4-(Dimethylamino)but-2-enoic acid (74.4 mg, 0.576 mmol) and Hunig's base (252 μ l, 1.44 mmol). To this mixture was added EDC (55.2 mg, 0.288 mmol) and HOBt (38.9 mg, 0.288 mmol) neat as powders. The reaction mixture was stirred at room temperature for 1 hour and heated to 35°C for an additional 3 hours. The reaction mixture was concentrated in vacuo and purified on the CombiFlash (0%-15% DCM/MeOH w/ 1% NH₄OH modifier). All fractions containing clean desired product were combined and concentrated in vacuo to afford (E)-4-(dimethylamino)-1-(4-(7-(3-(methoxymethoxy)naphthalen-1-yl)-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-4a,5,6,7,8,8a-hexahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)but-2-en-1-one (105 mg, 0.166 mmol, 57.7 % yield). The product followed the rest of Example 127 accordingly to give (S,E)-4-(dimethylamino)-1-(4-(7-(3-hydroxynaphthalen-1-yl)-2-((1-methylpyrrolidin-2-yl)methoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)but-2-en-1-one (14.8 mg, 0.025 mmol, 15.2% yield). ES+APCI MS m/z 586.3[M+H]⁺.

EXAMPLE 200

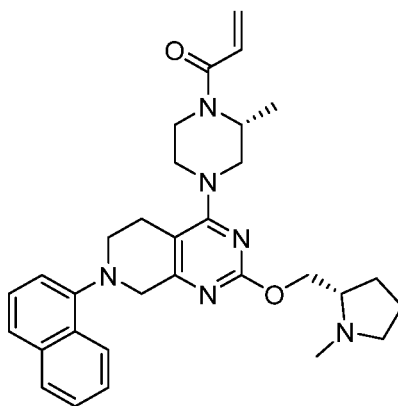
(S)-1-(4-(2-((1-methylpyrrolidin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one



[0796] (S)-1-(4-(2-((1-methylpyrrolidin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one. This compound was prepared following **Example 127** substituting naphthalen-1-yl trifluoromethanesulfonate for 3-(methoxymethoxy)naphthalen-1-yl trifluoromethanesulfonate in Step C and not performing step F. ES+APCI MS m/z 513.3 $[M+H]^+$.

EXAMPLE 201

1-((R)-2-methyl-4-(2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

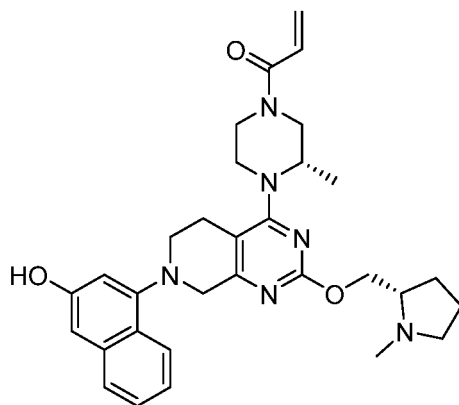


[0797] 1-((R)-2-methyl-4-(2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one. This compound was prepared following **Example 127** substituting (R)-benzyl 2-methylpiperazine-1-carboxylate for benzyl piperazine-1-carboxylate in Step A and substituting naphthalen-1-yl

trifluoromethanesulfonate for 3-(methoxymethoxy)naphthalen-1-yl trifluoromethanesulfonate in Step C and not performing step F. ES+APCI MS m/z 527.3 $[M+H]^+$.

EXAMPLE 202

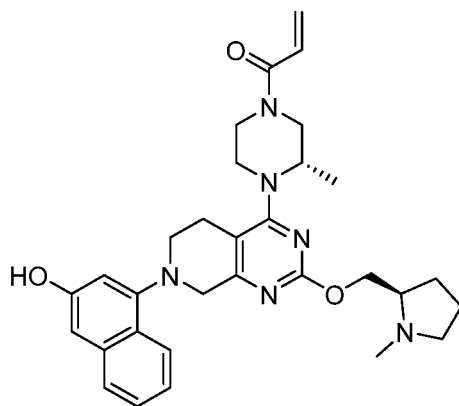
1-((S)-4-(7-(3-hydroxynaphthalen-1-yl)-2-(((S)-1-methylpyrrolidin-2-yl)methoxy))-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)-3-methylpiperazin-1-yl)prop-2-en-1-one



[0798] 1-((S)-4-(7-(3-hydroxynaphthalen-1-yl)-2-(((S)-1-methylpyrrolidin-2-yl)methoxy))-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)-3-methylpiperazin-1-yl)prop-2-en-1-one. This compound was prepared following **Example 127** substituting benzyl (S)-3-methylpiperazine-1-carboxylate for benzyl piperazine-1-carboxylate in Step A. ES+APCI MS m/z 543.3 $[M+H]^+$.

EXAMPLE 203

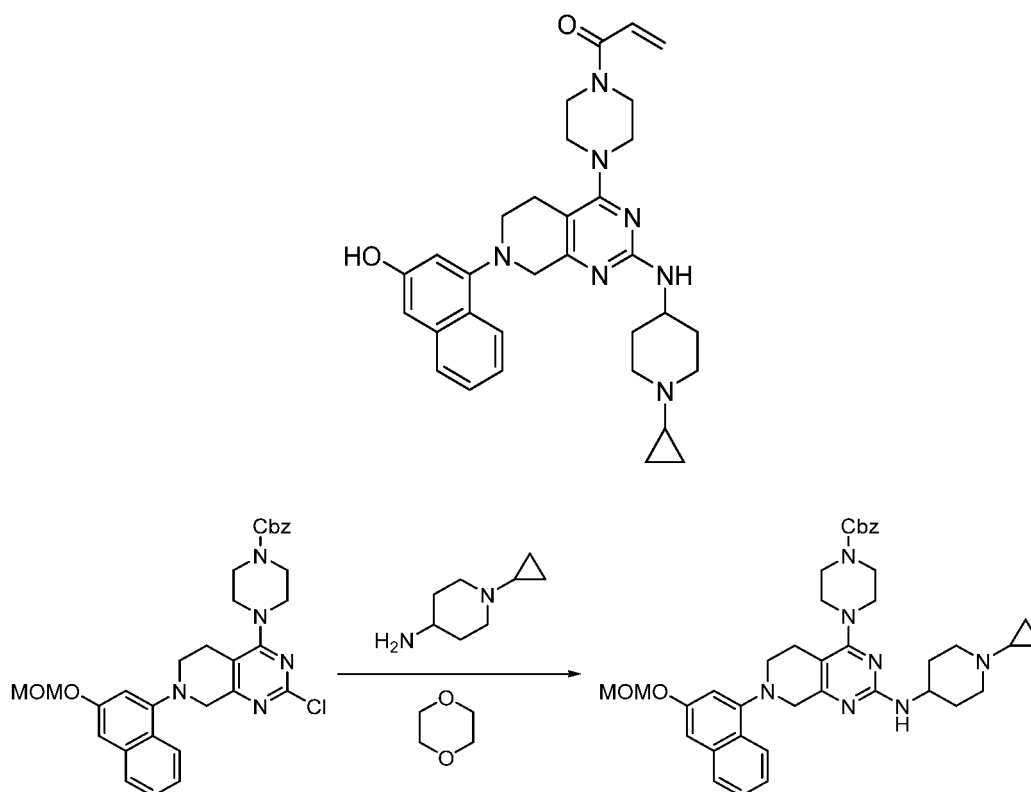
1-((S)-4-(7-(3-hydroxynaphthalen-1-yl)-2-(((R)-1-methylpyrrolidin-2-yl)methoxy))-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)-3-methylpiperazin-1-yl)prop-2-en-1-one



[0799] 1-((S)-4-(7-(3-hydroxynaphthalen-1-yl)-2-(((R)-1-methylpyrrolidin-2-yl)methoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)-3-methylpiperazin-1-yl)prop-2-en-1-one. This compound was prepared following **Example 127** substituting benzyl (S)-3-methylpiperazine-1-carboxylate for benzyl piperazine-1-carboxylate in Step A and substituting N-Methyl-D-prolinol for N-Methyl-L-prolinol in Step D. ES+APCI MS m/z 543.3 $[M+H]^+$.

EXAMPLE 204

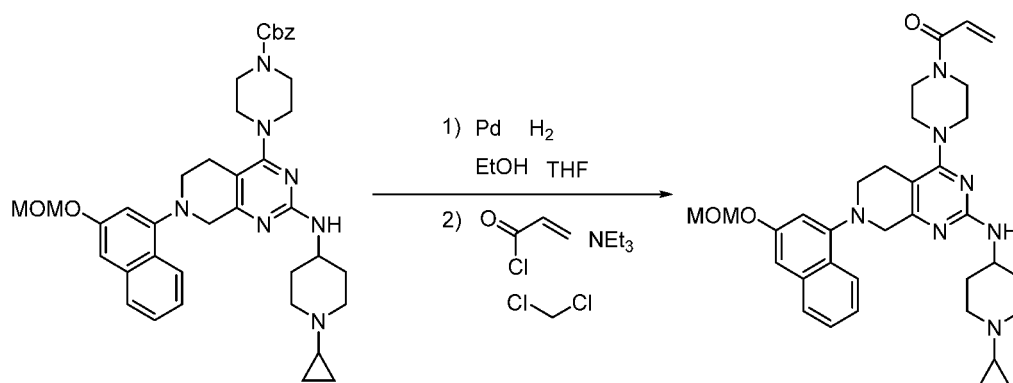
1-(4-(2-((1-cyclopropylpiperidin-4-yl)amino)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one



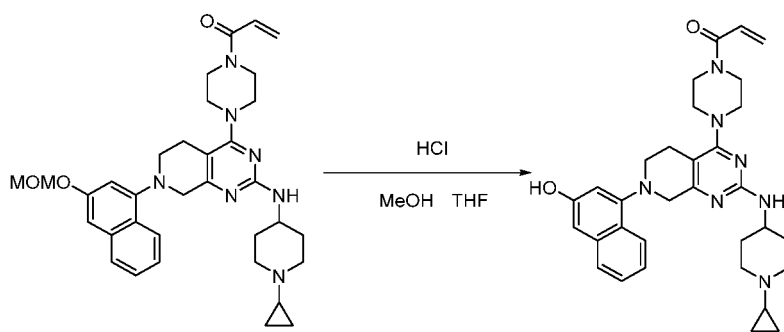
[0800] Step A: Benzyl 4-(2-((1-cyclopropylpiperidin-4-yl)amino)-7-(3-(methoxymethoxy)naphthalen-1-yl))-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate: A mixture of benzyl 4-(2-chloro-7-(3-(methoxymethoxy)naphthalen-1-yl))-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (75 mg, 0.13 mmol), 1-cyclopropylpiperidin-4-amine (55 mg, 0.39 mmol) and dioxane (0.5 mL) was heated to 120°C for 36h. The reaction mixture was cooled to room temperature, divided between EtOAc (10 mL) and water (3 mL) and the layers separated. The organic layer was washed with brine, dried over

Na₂SO₄ and evaporated in vacuo and the residue chromatographed on silica, Redisep 24g, using 6 to 10% MeOH in DCM +0.2% NH₄OH as eluent to give a colorless solid (43 mg, 49%).

ES+APCI MS m/z 678.3 [M+H]⁺.



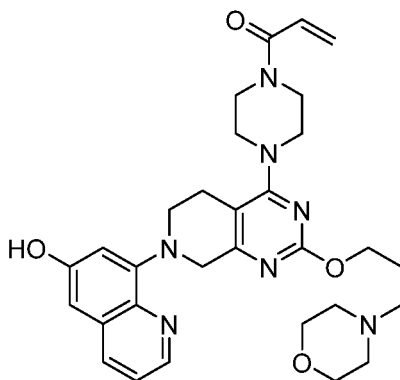
[0801] Step B: 1-(4-(2-((1-cyclopropylpiperidin-4-yl)amino)-7-(3-(methoxymethoxy)naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one: A mixture of benzyl 4-(2-((1-cyclopropylpiperidin-4-yl)amino)-7-(3-(methoxymethoxy)-naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (43 mg, 0.063 mmol), palladium on carbon (20 mg, *Degussa Type, 10 wt%, 50% H₂O*), EtOH (1.5 mL) and THF (1.5 mL) was purged with hydrogen and stirred under H₂ atmosphere (rubber balloon) for 3 hours. The mixture was diluted with EtOH (3 mL), filtered through Celite and the celite washed with EtOH (2 x 2 mL). The combined organics were evaporated in vacuo. The residue was dissolved in DCM (5 mL) and cooled on ice-salt bath with stirring. Triethylamine (0.03 mL) was next added at once, followed by acryloyl chloride (10 µL). After 1 min at -5°C the reaction was quenched with NH₄OH (0.05 mL) and evaporated in vacuo. The residue was stirred 5 min with DCM (5 mL), filtered and chromatographed on silica gel, Redisep 12g, using 6 to 20% MeOH in DCM +0.2% NH₄OH as eluent to give a colorless solid (22 mg, 48%). ES+APCI MS m/z 598.3 [M+H]⁺.

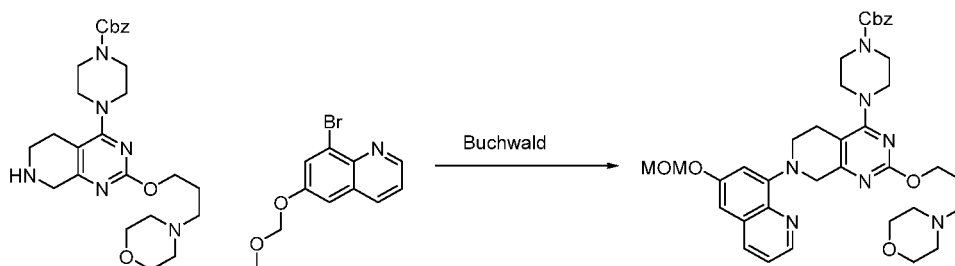


[0802] Step C: 1-(4-(2-((1-cyclopropylpiperidin-4-yl)amino)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one: To a stirred solution of 1-(4-(2-((1-cyclopropylpiperidin-4-yl)amino)-7-(3-(methoxymethoxy)naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one (22 mg, 0.037 mmol) in a mixture of MeOH and THF 1:1 (3 mL) was added 6M aqueous HCl (0.3 mL, 34 eq.) all at once and the resulting solution was heated with stirring at 50°C for 1.5 hours. The reaction mixture was cooled to room temperature, divided between EtOAc (15 mL) and 0.5M Na₂CO₃ (10 mL) and the organic layer separated. The combined organics were washed with brine (3 mL), dried over Na₂SO₄ and evaporated in vacuo. The residue was chromatographed on silica, Redisep 12 g, using 8 to 10% MeOH in DCM + 0.2 % NH₄OH as eluent to give a colorless solid (15 mg, 74%). ES+APCI MS m/z 554.3 [M+H]⁺.

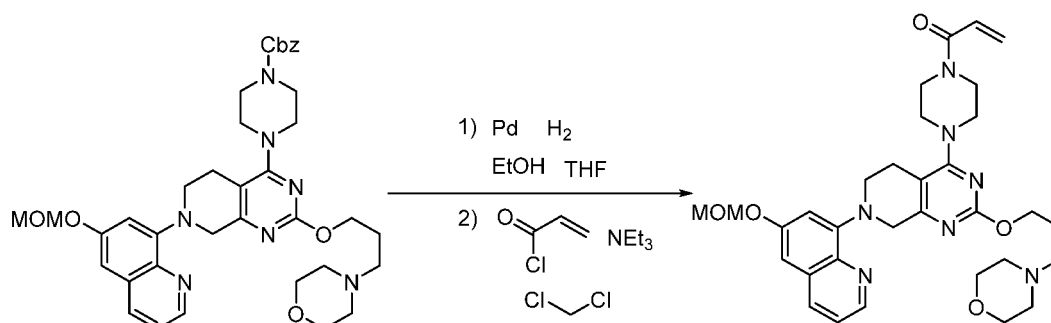
EXAMPLE 205

1-(4-(7-(6-hydroxyquinolin-8-yl)-2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one



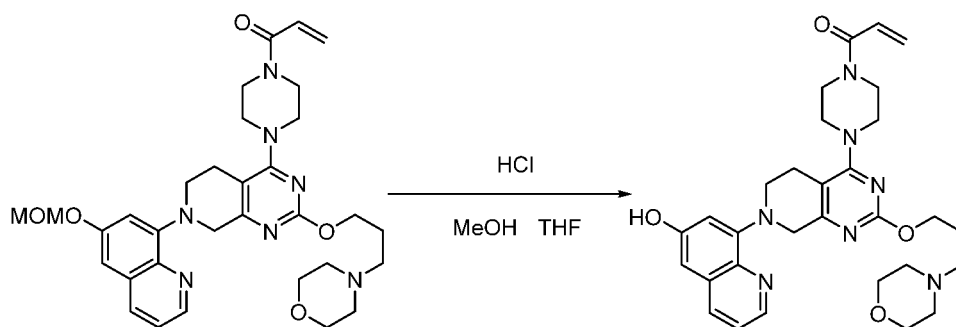


[0803] Step A: Benzyl 4-(7-(6-(methoxymethoxy)quinolin-8-yl)-2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate: To a stirred suspension of tris(dibenzylideneacetone)dipalladium (0) (17 mg, 0.019 mmol) in degassed dry toluene (0.5 mL) under nitrogen at room temperature was added (+/-)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (24 mg, 0.038 mmol) and the mixture was heated to 100 °C for 15 minutes. The dark mixture was cooled to room temperature and solid sodium-*t*-butoxide (36 mg, 0.38 mmol) was then added, followed by a solution of 8-bromo-6-(methoxymethoxy)quinoline (61 mg, 0.23 mmol) and benzyl 4-(2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (94 mg, 0.19 mmol) in degassed dry toluene (0.5 mL). The flask was closed and heated to 100 °C for 1 hour. The reaction mixture was cooled to room temperature, divided between EtOAc (15 mL) and water (5 mL) and the organic layers separated. The organic layer was washed with brine, dried over Na₂SO₄ and evaporated in vacuo. The residue was chromatographed on silica gel, Redisep 24g, using 4 to 10% MeOH in dichloromethane (+0.2% NH₄OH) as eluent to give a yellow solid (28 mg, 22%). ES+APCI MS *m/z* 684.3 [M+H]⁺.



[0804] Step B: 1-(4-(7-(6-(methoxymethoxy)quinolin-8-yl)-2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one: A mixture of benzyl 4-

(7-(6-(methoxymethoxy)quinolin-8-yl)-2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (28 mg, 0.095 mmol), Pd/C (15 mg, *Degussa Type*, 10 wt%, 50% H₂O), EtOH (2 mL) and THF (2 mL) was purged with hydrogen and stirred under H₂ atmosphere (rubber balloon) for 2 hours. The reaction mixture was diluted with EtOH (3 mL), filtered through Celite and the celite washed with EtOH (2 x 2 mL) and the combined organics evaporated in vacuo. The resulted solid was dissolved in DCM (5 mL) and cooled in an ice-salt bath with stirring. Triethylamine (0.04 mL, 3 eq.) was then added at once followed by acryloyl chloride (16 μ L, 2 eq.). After 1 min at -5°C the reaction was quenched with NH₄OH (0.05 mL) and evaporated in vacuo. The mixture was filtered through a cotton plug, chromatographed on silica gel, Redisep 12g, using 6 to 10% MeOH in DCM +0.2% NH₄OH as eluent to give another residue which was repurified on reverse phase, C18, 5 to 95% MeCN, +0.1% HCO₂H to give product which was assumed to be the bis-formate salt as a yellow solid (12 mg, 42%). ES+APCI MS m/z 604.2 [M+H]⁺.

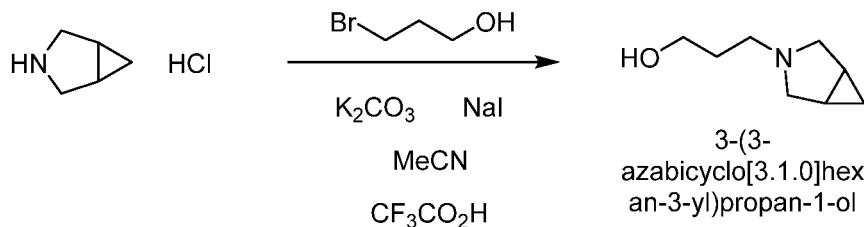
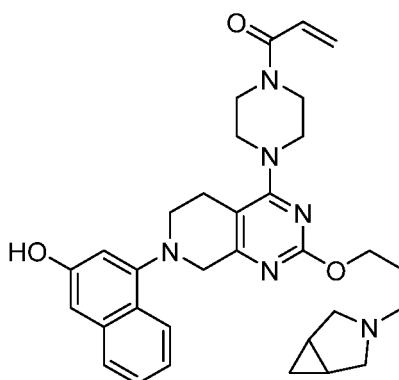


[0805] Step C: 1-(4-(7-(6-hydroxyquinolin-8-yl)-2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-yl)prop-2-en-1-one: To a stirred solution of 1-(4-(7-(6-(methoxymethoxy)quinolin-8-yl)-2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-yl)prop-2-en-1-one (12 mg, 0.017 mmol) in a mixture of MeOH and THF 1:1 (1 mL) was added 6M aqueous HCl (0.1 mL, 35 eq.) at once and the solution was heated with stirring at 50°C for 1.5h. The reaction mixture was cooled to room temperature, divided between EtOAc (15 mL) and 0.5M Na-phosphate buffer with pH 8 (5 mL) and the layers separated. The combined organics were washed with brine (1 mL), dried over Na₂SO₄ and evaporated in vacuo. The product was purified by chromatography on silica, Redisep 12 g, using 7 to 10% MeOH in DCM +0.2 % NH₄OH as eluent to give a residue which was repurified by reverse phase chromatography, C18, 5 to 95% MeOH +0.1%TFA,) to give

product as the tris TFA salt as a colorless solid (4.87 mg, 31%). ES+APCI MS m/z 560.3 $[M+H]^+$.

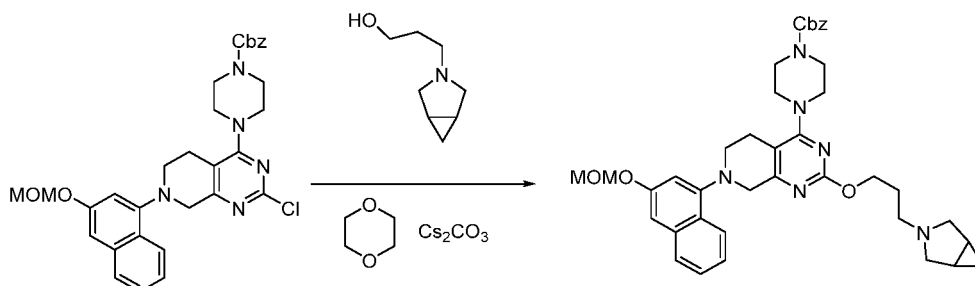
EXAMPLE 206

1-(4-(2-(3-(3-azabicyclo[3.1.0]hexan-3-yl)propoxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

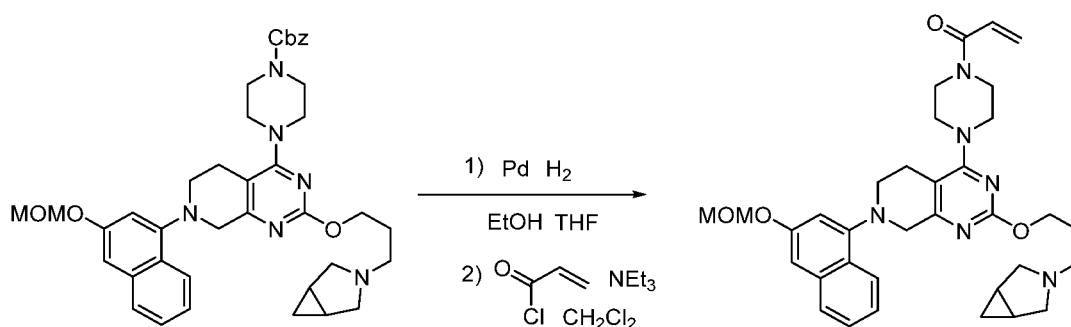


[0806] Step A: 3-(3-azabicyclo[3.1.0]hexan-3-yl)propan-1-ol. A mixture of 3-azabicyclo[3.1.0]hexane hydrochloride (200 mg, 1.67 mmol), 3-bromopropan-1-ol (166 μL , 1.84 mmol, 1.1 eq.), K_2CO_3 (0.69 g, 5.02 mmol, 3 eq.), NaI (251 mg, 1.67 mmol, 1 eq.) and acetonitrile (2 mL) in a 4-mL vial was flushed with N_2 . The vial was capped and stirred at room temperature for 2 days. The mixture was diluted with water (2 mL) and extracted with ether (15 mL). The ether solution was washed with brine, dried over Na_2SO_4 and decanted into a pear-shaped flask and trifluoroacetic acid (128 μL , 1 eq) added and the mixture was concentrated to ~ 5 mL. The upper etherial layer was decanted and discarded, the residual oily liquid was dried under vacuum overnight. The oily liquid was diluted with water (0.5 mL) then ether (10 mL) was added with stirring followed by 50% NaOH (0.2 mL, 2.5 mmol, 2 eq.). The layers were

separated, the organic solution was dried over KOH and carefully concentrated under nitrogen to yield crude 3-(3-azabicyclo[3.1.0]hexan-3-yl)propan-1-ol as colorless oil. Used on the next stage without further purification.

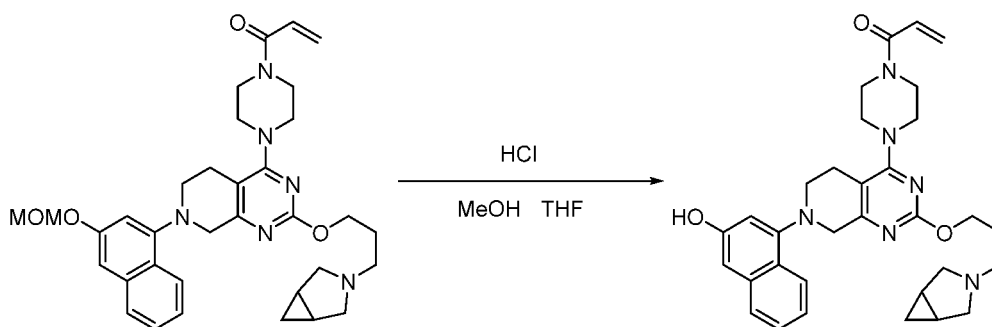


[0807] Step B: Benzyl 4-(2-(3-(3-azabicyclo[3.1.0]hexan-3-yl)propoxy)-7-(3-(methoxymethoxy)-naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate: A mixture of benzyl 4-(2-chloro-7-(3-(methoxymethoxy)naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (75 mg, 0.13 mmol), crude 3-(3-azabicyclo[3.1.0]hexan-3-yl)propan-1-ol (55 mg, 0.39 mmol, 3 eq.), Cs₂CO₃ (213 mg, 0.65 mmol, 5 eq.) and dioxane (0.5 mL) in a 1.7-mL vial was purged with nitrogen. The vial was capped and stirred at 120°C over the weekend. The reaction mixture was cooled, divided between EtOAc (15 mL) and water (5 mL) and the layers separated. The organic layer was washed with brine, dried over Na₂SO₄, evaporated in vacuo and the residue chromatographed on silica gel, Redisep 24g, using 4 to 10% MeOH + 1% NH₄OH as eluent to give product. ES+APCI MS m/z 679.3 [M+H]⁺.



[0808] Step C: 1-(4-(2-(3-(3-azabicyclo[3.1.0]hexan-3-yl)propoxy)-7-(3-(methoxymethoxy)naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-

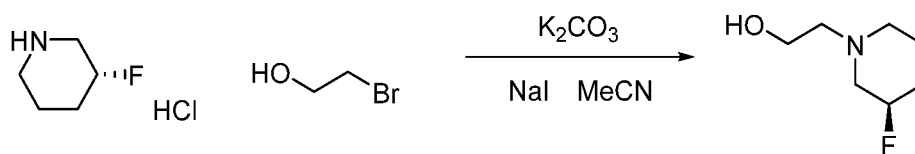
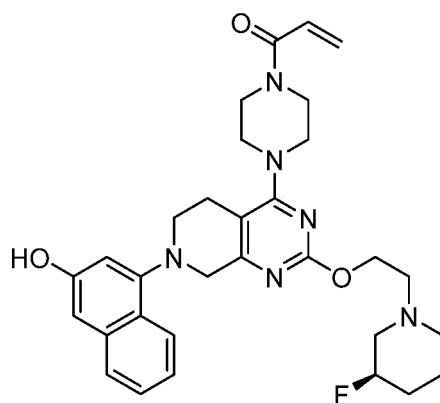
yl)prop-2-en-1-one: A mixture of benzyl 4-(2-(3-(3-azabicyclo[3.1.0]hexan-3-yl)propoxy)-7-(3-(methoxymethoxy)-naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (49 mg, 0.072 mmol), palladium on carbon (12 mg, *Degussa Type*, 10 wt%, 50% H_2O), EtOH (1.5 mL) and THF (1.5 mL) was purged with hydrogen and stirred under H_2 atmosphere (rubber balloon) for 3 hours. The reaction mixture was diluted with EtOH (3 mL), filtered through Celite and the celite washed with EtOH (2 x 2 mL). The combined organics were evaporated in vacuo. The resulted colorless solid was dissolved in DCM (5 mL), cooled in an ice-salt bath with stirring and triethylamine (0.04 mL, 3 eq.) was added at once followed by addition of acryloyl chloride (16 μ L, 2 eq.). After 1 min at -5°C the reaction was quenched with NH_4OH (0.05 mL) and evaporated in vacuo. The crude product was dissolved in DCM (5 mL), filtered through a cotton plug and chromatographed on silica gel, Redisep 12g, using 6 to 10% MeOH in DCM +0.2% NH_4OH as eluent to give a colorless solid (30 mg, 69%). ES+APCI MS m/z 599.3 $[M+H]^+$.



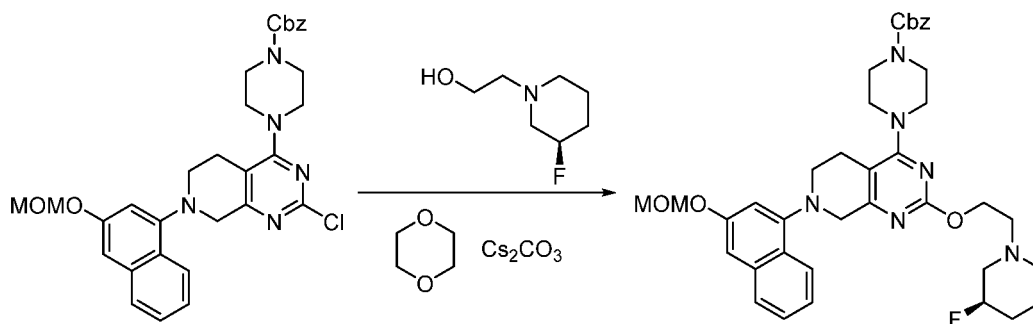
[0809] Step D: 1-(4-(2-(3-(3-azabicyclo[3.1.0]hexan-3-yl)propoxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one: To a stirred solution of 1-(4-(2-(3-(3-azabicyclo[3.1.0]hexan-3-yl)propoxy)-7-(3-(methoxymethoxy)naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one (30 mg, 0.050 mmol) in a mixture of MeOH and THF 1:1 (3 mL) was added 6M aqueous HCl (0.3 mL, 36 eq.) and the solution was heated with stirring at 50°C for 1.5 h. The reaction mixture was cooled to room temperature, divided between EtOAc (20 mL) and 0.5M Na_2CO_3 (5 mL) and the layers separated. The organic layer was washed with brine (1 mL), dried over Na_2SO_4 and evaporated in vacuo. The residue was chromatographed on silica, Redisep 12 g, using 6% MeOH in DCM +0.2 % NH_4OH as eluent to give a colorless solid (20.62 mg, 74%). ES+APCI MS m/z 555.4 $[M+H]^+$.

EXAMPLE 207

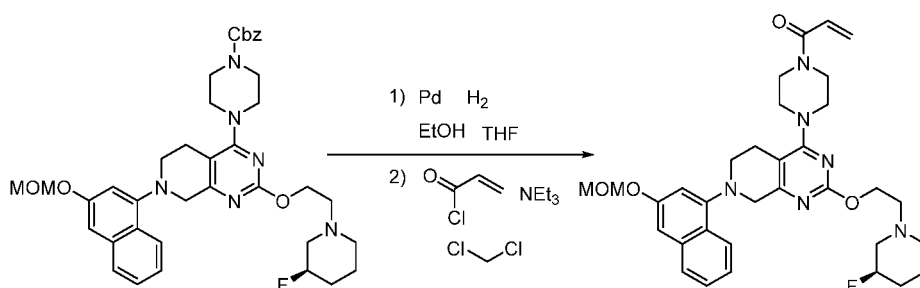
(R)-1-(4-(2-(2-(3-fluoropiperidin-1-yl)ethoxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one



[0810] Step A: (R)-2-(3-fluoropiperidin-1-yl)ethan-1-ol. A mixture of R-3-fluoropiperidine hydrochloride (209 mg, 1.50 mmol), 2-bromoethan-1-ol (117 μ L, 1.65 mmol, 1.1 eq.), K_2CO_3 (0.62 g, 4.5 mmol, 3 eq.), sodium iodide (225 mg, 1.5 mmol, 1 eq.) and acetonitrile (2 mL) in a 4-mL vial was flushed with N_2 . The vial was capped and stirred at room temperature for 2 days. The resulted suspension was diluted with water (2 mL) and extracted with ether (15 mL). The ether solution was washed with brine, dried over Na_2SO_4 and decanted into a pear-shaped flask and trifluoroacetic acid (115 μ L, 1 eq) was added and the mixture was concentrated to $\sim$ 5 mL. The upper ethereal layer was decanted, the residual oily liquid was dried under vacuum overnight. The oily liquid was diluted with water (0.5 mL) and ether (10 mL) with stirring, followed by addition of 50% NaOH (0.2 mL, 2.5 mmol, 2 eq.). The layers were separated, the organic solution was dried over KOH, filtered and carefully concentrated under nitrogen to yield crude amino alcohol as a colorless oil (120 mg, 54%).

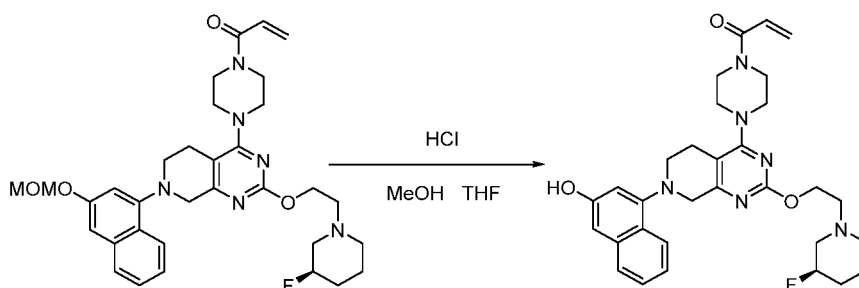


[0811] Step B: Benzyl (R)-4-(2-(2-(3-fluoropiperidin-1-yl)ethoxy)-7-(3-(methoxymethoxy)naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate: A mixture of benzyl 4-(2-chloro-7-(3-(methoxymethoxy)naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (75 mg, 0.13 mmol), crude (R)-2-(3-fluoropiperidin-1-yl)ethan-1-ol (58 mg, 0.39 mmol), Cs₂CO₃ (213 mg, 0.65 mmol), and dioxane (0.5 mL) in a 1.7-mL vial was purged with nitrogen. The vial was capped and stirred at 110°C for 48 hours. The reaction mixture was cooled, diluted with EtOAc (1 mL), filtered through Celite and the celite washed with EtOAc (2 x 2 mL) and the combined organics evaporated in vacuo. The residue was chromatographed on silica, Redisep 24g, using 6 %MeOH in DCM +0.2% NH₄OH as eluent to give a colorless solid (30 mg, 34%). ES+APCI MS m/z 685.4 [M+H]⁺.



[0812] Step C: (R)-1-(4-(2-(2-(3-fluoropiperidin-1-yl)ethoxy)-7-(3-(methoxymethoxy)naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one: A mixture of benzyl (R)-4-(2-(2-(3-fluoropiperidin-1-yl)ethoxy)-7-(3-(methoxymethoxy)naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (30 mg, 0.044 mmol), palladium on carbon (10 mg, *Degussa Type*, 10 wt%, 50% H₂O), EtOH (1.5 mL) and THF (1.5 mL) was purged with hydrogen and stirred under H₂ atmosphere (rubber balloon) for 2 hours. The reaction mixture was diluted with EtOH (3 mL),

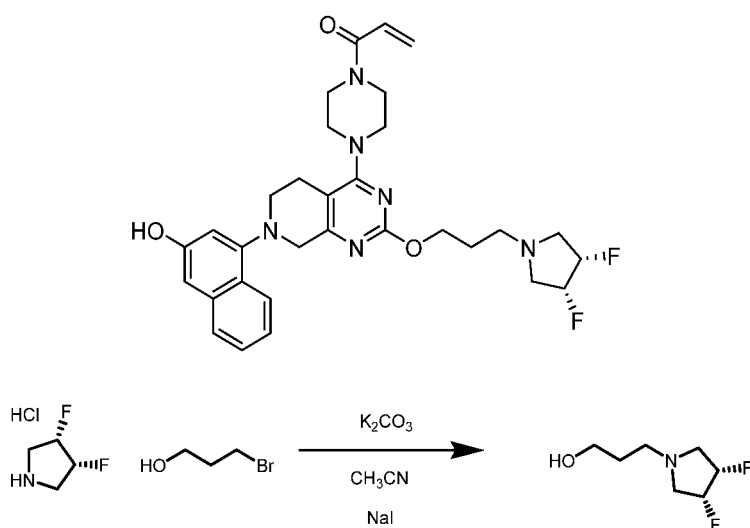
filtered through Celite and the celite washed with EtOH (2 x 2 mL). The combined organics were evaporated in vacuo. The residue was dissolved in DCM (3 mL) and cooled in an ice-salt bath with stirring. Triethylamine (0.02 mL, 3 eq.) was next added at once followed by addition of acryloyl chloride (7 μ L, 2 eq.). After 1 min at -10°C the reaction was quenched with NH₄OH (0.03 mL) and evaporated in vacuo. The residue was dissolved in DCM (5 mL), filtered, and chromatographed on silica gel, Redisep 12g, using 6 to 10% MeOH in DCM +0.2% NH₄OH in DCM as eluent to give a colorless solid (22 mg, 83%). ES+APCI MS m/z 605.3 [M+H]⁺.



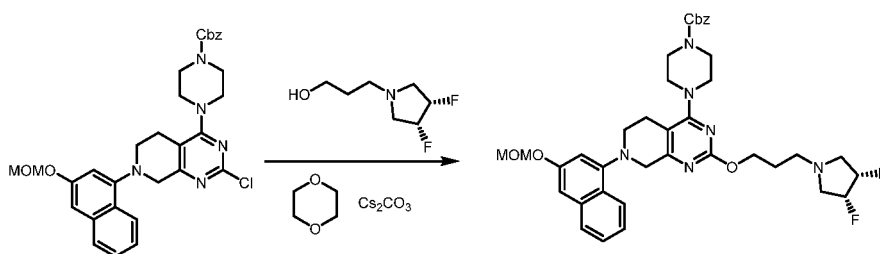
[0813] Step D: (R)-1-(4-(2-(2-(3-fluoropiperidin-1-yl)ethoxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one: To a stirred solution of (R)-1-(4-(2-(2-(3-fluoropiperidin-1-yl)ethoxy)-7-(3-(methoxymethoxy)naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one (22 mg, 0.036 mmol) in a mixture of MeOH and THF 1:1 (3 mL) was added 6M aqueous HCl (0.3 mL) and the solution was heated with stirring at 50°C for 1.5h. The reaction mixture was cooled to room temperature, divided between EtOAc (20 mL) and 0.5M Na₂CO₃ (5 mL) and the layers separated. The organic layer was washed with brine (1 mL), dried over Na₂SO₄ and evaporated in vacuo. The residue was chromatographed on silica gel, Redisep 12 g, using 6% MeOH in DCM +0.2 % NH₄OH as eluent to give a colorless solid (16.86 mg, 83%). ES+APCI MS m/z 561.2 [M+H]⁺.

EXAMPLE 208

1-(4-(2-(3-((3R,4S)-3,4-difluoropyrrolidin-1-yl)propoxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

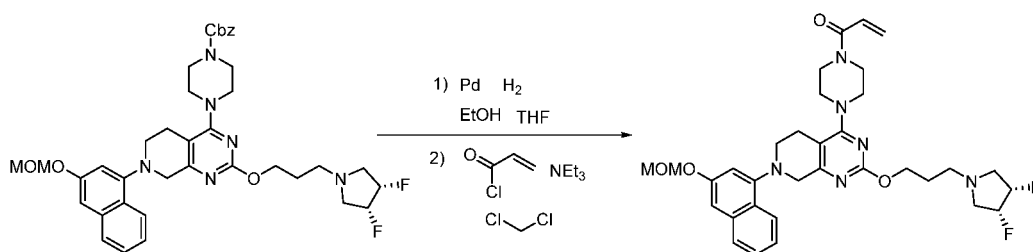


[0814] Step A: 3-((3R,4S)-3,4-difluoropyrrolidin-1-yl)propan-1-ol. A mixture of (3R,4S)-3,4-difluoropyrrolidine hydrochloride (200 mg, 1.39 mmol), 3-bromopropan-1-ol (126 μ L, 1.39 mmol, 1.0 eq.), potassium carbonate (577 mg, 4.18 mmol, 3 eq.), sodium iodide (209 mg, 1.39 mmol, 1 eq.) and acetonitrile (2 mL) in a 7-mL vial was flushed with N_2 . The vial was capped and the reaction mixture was stirred at room temperature for 2 days. The mixture was diluted with water (2 mL) and extracted with ether (15 mL). The ether solution was washed with brine, dried over Na_2SO_4 and decanted into a pear-shaped flask. Trifluoroacetic acid (107 μ L, 1 eq) was next added and the mixture was evaporated and dried in vacuo. The residue was diluted with water (0.5 mL) and washed with ether (5 mL). To the aqueous layer was added diethyl ether (15 mL) followed by 10M NaOH (0.2 mL, 5 mmol) and the mixture was stirred for 1 hour. The organic layer was separated and dried over solid KOH, filtered through a cotton plug and evaporated under N_2 to give a colorless oil (80 mg, 35%) which was used crude in the next reaction.

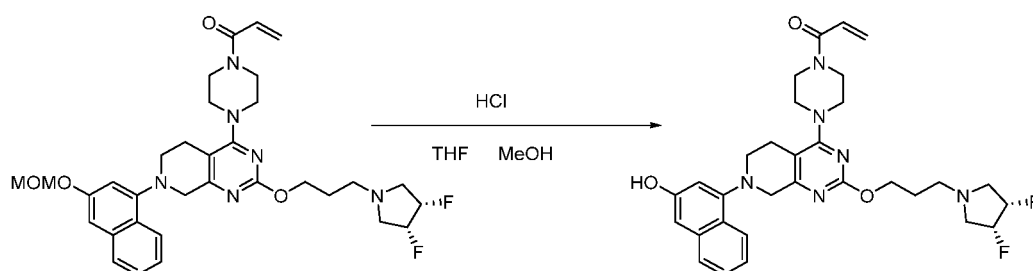


[0815] Step B: Benzyl 4-(2-(3-((3R,4S)-3,4-difluoropyrrolidin-1-yl)propoxy)-7-(3-(methoxymethoxy)naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-

1-carboxylate: A mixture of benzyl 4-(2-chloro-7-(3-(methoxymethoxy)naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (75 mg, 0.13 mmol), crude 2-(4,4-difluoropiperidin-1-yl)ethan-1-ol (65 mg, 0.39 mmol), cesium carbonate (213 mg, 0.65 mmol, 5 eq.) and dioxane (0.5 mL) in a 1.7-mL vial was purged with nitrogen. The vial was capped and stirred at 110°C over the weekend. The reaction mixture was cooled to room temperature and divided between EtOAc (15 mL) and water (5 mL) and the layers separated. The organic layer was washed with brine, dried over Na₂SO₄ and evaporated in vacuo. The product was purified by chromatography on silica, Redisep 24g, using 3% MeOH in DCM as eluent to give a colorless solid (46 mg, 50%). ES+APCI MS m/z 703.3 [M+H]⁺.



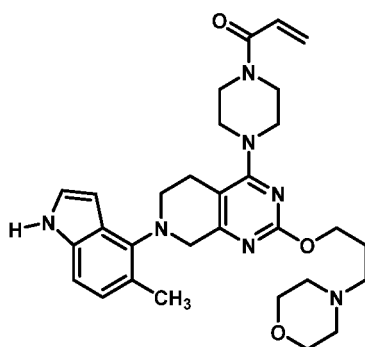
[0816] Step C: 1-(4-(2-(3-((3R,4S)-3,4-difluoropyrrolidin-1-yl)propoxy))-7-(3-(methoxymethoxy)naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one: A mixture of benzyl 4-(2-(3-((3R,4S)-3,4-difluoropyrrolidin-1-yl)propoxy))-7-(3-(methoxymethoxy)naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (46 mg, 0.065 mmol), palladium on carbon (15 mg, *Degussa Type*, 10 wt%, 50% H₂O), EtOH (1 mL) and THF (1 mL) was purged with hydrogen and stirred under H₂ atmosphere (rubber balloon) for 3 hours. The reaction mixture was diluted with EtOH (3 mL), filtered through Celite and the celite washed with EtOH (2 x 2 mL). The combined organics were evaporated in vacuo. The residue was dissolved in DCM (3 mL) and cooled in an ice-salt bath with stirring. Triethylamine (0.02 mL) was next added followed by addition of acryloyl chloride (7 µL, 2 eq.). After 1 min at -10°C the reaction was quenched with NH₄OH (0.03 mL) and evaporated in vacuo. The residue was dissolved in DCM (3 mL), filtered and purified by chromatography on silica gel, Redisep 12g, using 5 % MeOH in DCM as eluent to give a colorless solid (29 mg, 71%). ES+APCI MS m/z 623.3 [M+H]⁺.

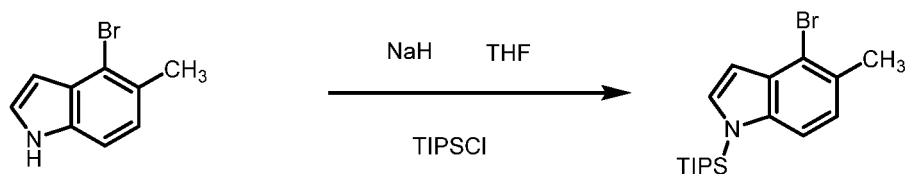


[0817] Step D: 1-(4-(2-(3-((3R,4S)-3,4-difluoropyrrolidin-1-yl)propoxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one: To a stirred solution of 1-(4-(2-(3-((3R,4S)-3,4-difluoropyrrolidin-1-yl)propoxy)-7-(3-(methoxymethoxy)naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one (29 mg, 0.047 mmol) in a mixture of MeOH and THF 1:1 (2 mL) was added 6M aqueous HCl (0.2 mL) and the solution was heated with stirring at 50°C for 1.5h. The reaction mixture was cooled to room temperature, divided between EtOAc (15 mL) and 0.5M Na₂CO₃ (10 mL) and the layers separated. The organic layer was washed with brine (3 mL), dried over Na₂SO₄ and evaporated in vacuo. The residue was purified by chromatography on silica, Redisep 12 g, using 5% MeOH in DCM as eluent to give a colorless solid (12.87 mg, 48%). ES+APCI MS m/z 579.2 [M+H]⁺.

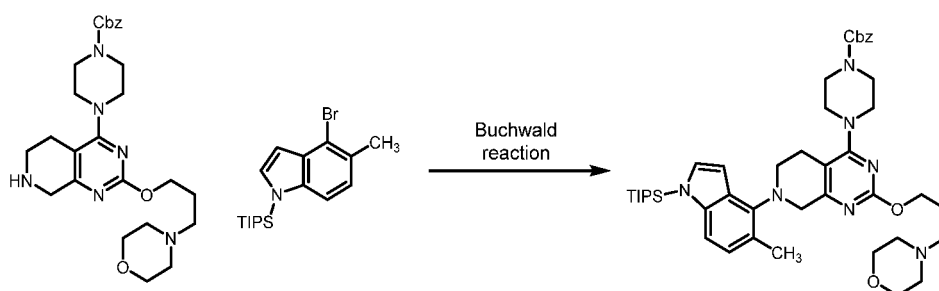
EXAMPLE 209

1-(4-(7-(5-methyl-1H-indol-4-yl)-2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one



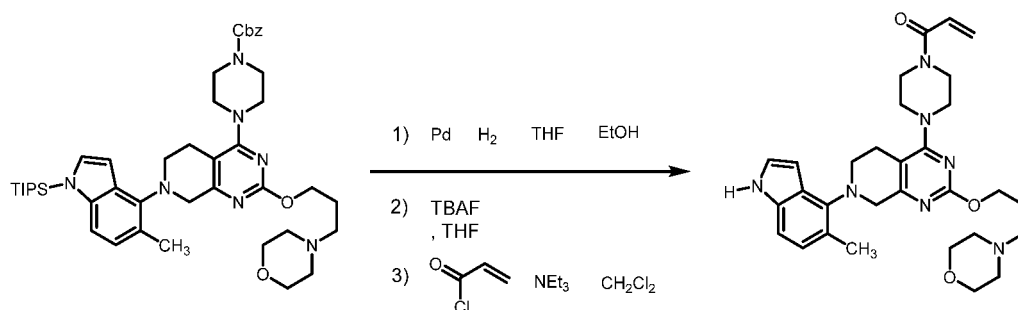


[0818] Step A: 4-bromo-5-methyl-1-(triisopropylsilyl)-1H-indole: A solution of 4-bromo-5-methyl-1H-indole (100 mg, 0.476 mmol) in dry THF (2 mL) under nitrogen was cooled with stirring in an ice-salt bath. Sodium hydride (23 mg 60% in oil, 0.57 mg, 1.2 eq.) was added and the mixture was stirred for 30 min at -5°C , then 1 h at room temperature (gas evolution ceased). Chlorotriisopropylsilane (0.10 mL, 0.48 mmol, 1 eq.) was next added and the reaction mixture was stirred at r.t. for 2 hours. The reaction was divided between EtOAc (15 mL) and water (10 mL) and the layers separated. The organic layer was washed with water (5 mL), brine (5 mL), dried over Na_2SO_4 and evaporated in vacuo. The residue was purified on silica gel using hexanes as eluent to give product. (107 mg, 63%).



[0819] Step B: Benzyl 4-(7-(5-methyl-1-(triisopropylsilyl)-1H-indol-4-yl)-2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate: A stirred mixture of tris(dibenzylideneacetone)dipalladium (0) (17 mg, 0.019 mmol) and (+/-)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (24 mg, 0.038 mmol) in dry degassed toluene (0.5 mL) under nitrogen was heated to 100°C for 15 minutes. The mixture was cooled to room temperature and solid sodium-*t*-butoxide (37 mg, 0.38 mmol) added followed by addition of a solution of 4-bromo-5-methyl-1-(triisopropylsilyl)-1H-indole (90 mg, 0.25 mmol) and benzyl 4-(2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (94 mg, 0.19 mmol) in dry degassed toluene (0.5 mL). The reaction flask was closed and heated to 100°C overnight. The reaction mixture was cooled to room temperature, divided between EtOAc (15 mL) and water (5 mL) and the layers separated. The organic layer was washed with brine, dried over Na_2SO_4 and evaporated in vacuo. The product was purified by

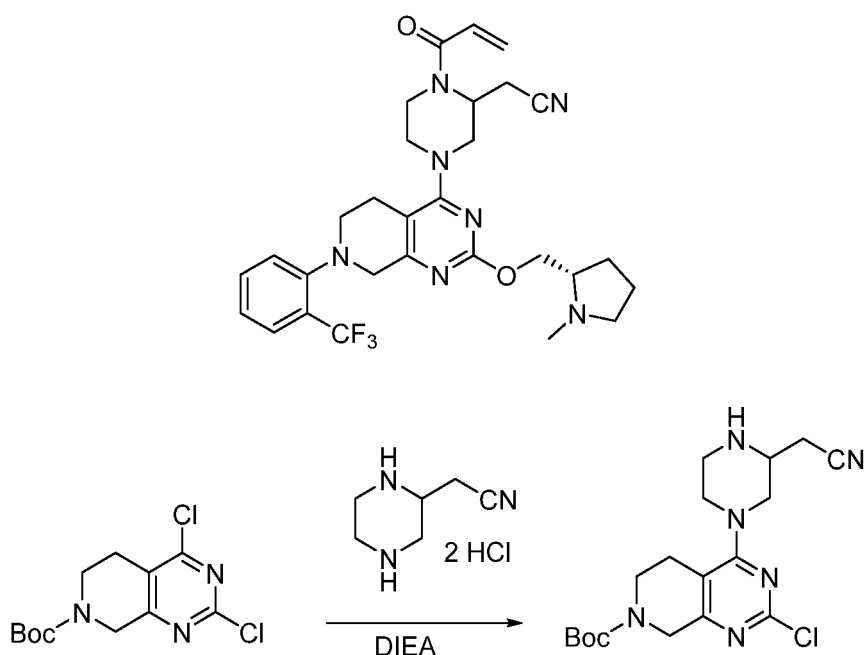
chromatography on silica gel, Redisep 24g, using 3 to 5% MeOH in dichloromethane as eluent to give a light-yellow solid (28 mg, 19%). ES+APCI MS m/z 782.3 $[M]^+$.



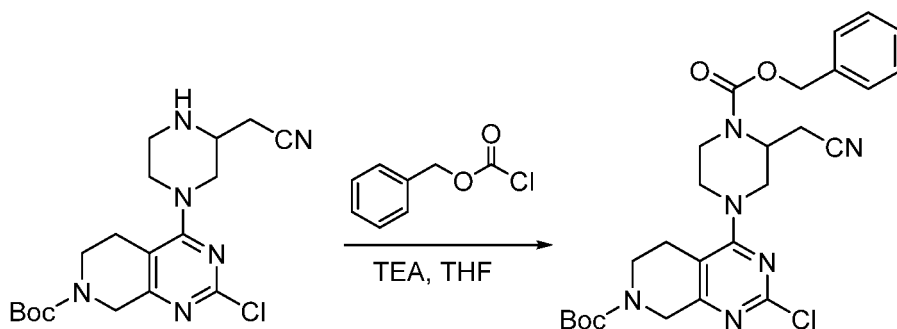
[0820] Step C: 1-(4-(7-(5-methyl-1H-indol-4-yl)-2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one: A mixture of benzyl 4-(7-(5-methyl-1-(triisopropylsilyl)-1H-indol-4-yl)-2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (46 mg, 0.065 mmol), palladium on carbon (35 mg, *Degussa Type*, 10 wt%, 50% H_2O) in EtOH (1 mL) and THF (1 mL) was purged with hydrogen and stirred under H_2 atmosphere (rubber balloon) overnight. The reaction mixture was diluted with dioxane (3 mL), filtered through celite and the celite washed with dioxane (2 x 2 mL). The combined organics were evaporated in vacuo and dried under high vacuum. The residue was dissolved in THF (1 mL) under N_2 , then 1M tetra-*n*-butylammonium fluoride in THF (0.07 mL, 2 eq.) was added with stirring and the solution stirred at 0°C for 15 minutes. The reaction mixture was divided between ether (15 mL) and water (5 mL) and the layers separated. The organic layer was washed with water (3 mL), brine (3 mL), dried over Na_2SO_4 and evaporated under nitrogen. The crude product was dissolved in DCM (3 mL) and cooled in an ice-salt-dry ice bath (-20°C) with stirring. Triethylamine (10 μ L, 2 eq.) was next added followed by acryloyl chloride (2 μ L, 0.75 eq.). After 10 min at -20°C the reaction was quenched with NH_4OH (0.03 mL). and evaporated in vacuo. The product was purified by chromatography on silica gel column using 5 % MeOH/DCM + 0.1% NH_4OH as eluent to give a colorless solid (3.69 mg, 19%). ES+APCI MS m/z 546.3 $[M+H]^+$.

EXAMPLE 210

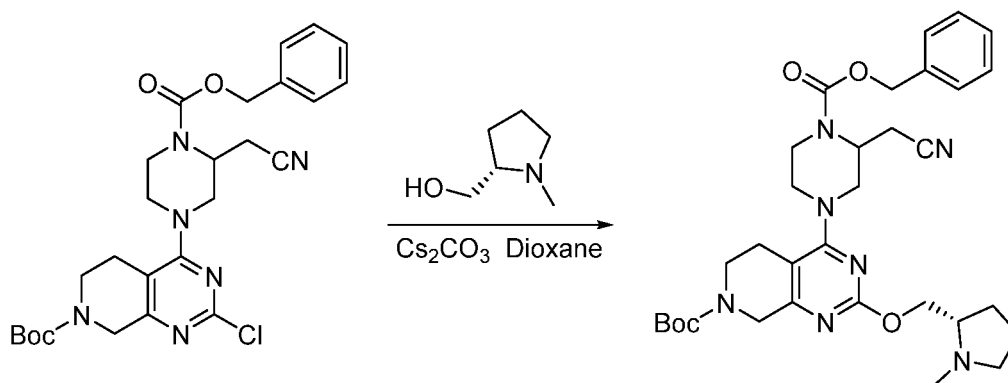
2-(1-acryloyl-4-(2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-7-(2-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile



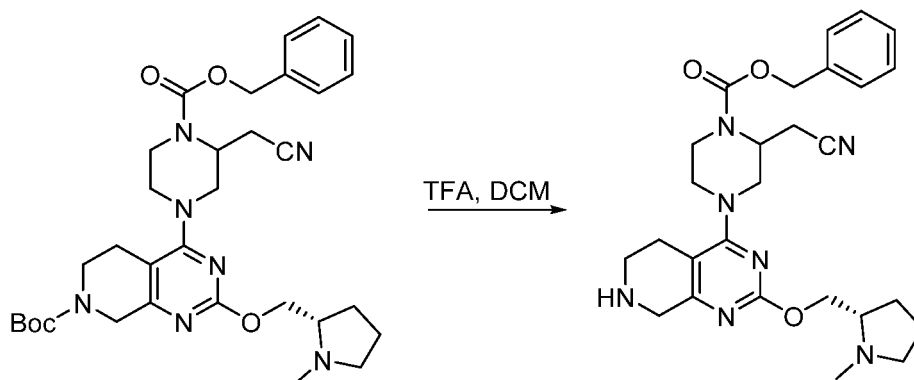
[0821] Step A: tert-butyl 2-chloro-4-(3-(cyanomethyl)piperazin-1-yl)-5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate: tert-butyl 2,4-dichloro-5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate (8.00 g, 26.3 mmol), Hunig's base (22.9 ml, 132 mmol) and 2-(piperazin-2-yl)acetonitrile dihydrochloride (5.21 g, 26.3 mmol) were placed in DMA (75 mL) and stirred at room temperature for 20 minutes. Water was added to the reaction and the mixture was extracted with EtOAc (3x100 mL). The extracts were combined and washed with water (3x 50 mL), dried with sodium sulfate, filtered and concentrated to provide crude material that was used as is. ES+APCI MS m/z 393.3 $[M+H]^+$.



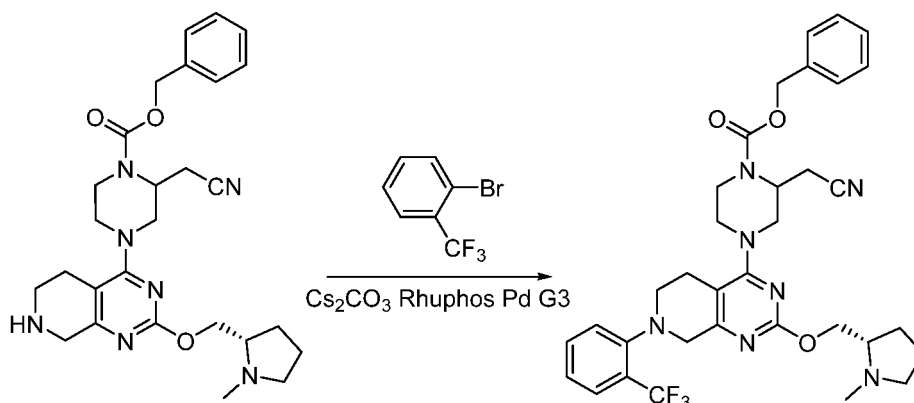
[0822] Step B: tert-butyl 4-(4-((benzyloxy)carbonyl)-3-(cyanomethyl)piperazin-1-yl)-2-chloro-5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate: tert-butyl 2-chloro-4-(3-(cyanomethyl)piperazin-1-yl)-5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate (10.5 g, 26.7 mmol) and TEA (5.6 ml, 40.1 mmol) were placed in THF (100 mL) and cooled to 0°C. Benzyl carbonochloridate (5.7 ml, 40.1 mmol) was added and the reaction was stirred at 0°C for 30 minutes. Water was added to the reaction and the mixture was extracted with DCM (3x 50 mL) and the extracts were combined and concentrated. The residue was purified by silica gel (0-60% EtOAc in hexane as eluent) to provide tert-butyl 4-(4-((benzyloxy)carbonyl)-3-(cyanomethyl)piperazin-1-yl)-2-chloro-5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate (12.9 g, 24.5 mmol, 92 % yield). ES+APCI MS m/z 527.1 [M+H]⁺.



[0823] Step C: tert-butyl 4-(4-((benzyloxy)carbonyl)-3-(cyanomethyl)piperazin-1-yl)-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate: In a sealed tube tert-butyl 4-(4-((benzyloxy)carbonyl)-3-(cyanomethyl)piperazin-1-yl)-2-chloro-5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate (1.50 g, 2.85 mmol) was dissolved in dioxane (1.42 ml, 2.85 mmol) and treated with milled cesium carbonate (1.85 g, 5.69 mmol) and (2S)-1-Ethyl-2-pyrrolidinyl]methanol (1.64 g, 14.2 mmol). The tube was then capped and heated to 90°C for 24hr. The reaction was cooled to room temperature and water was added. The mixture was extracted with DCM (3x 25 mL), and the combined organics concentrated in vacuo. The residue was purified by silica gel (0-12% MeOH in DCM w/0.2% NH₄OH as eluent) to give tert-butyl 4-(4-((benzyloxy)carbonyl)-3-(cyanomethyl)piperazin-1-yl)-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate (831 mg, 1.37 mmol, 48 % yield). ES+APCI MS m/z 606.2 [M+H]⁺.

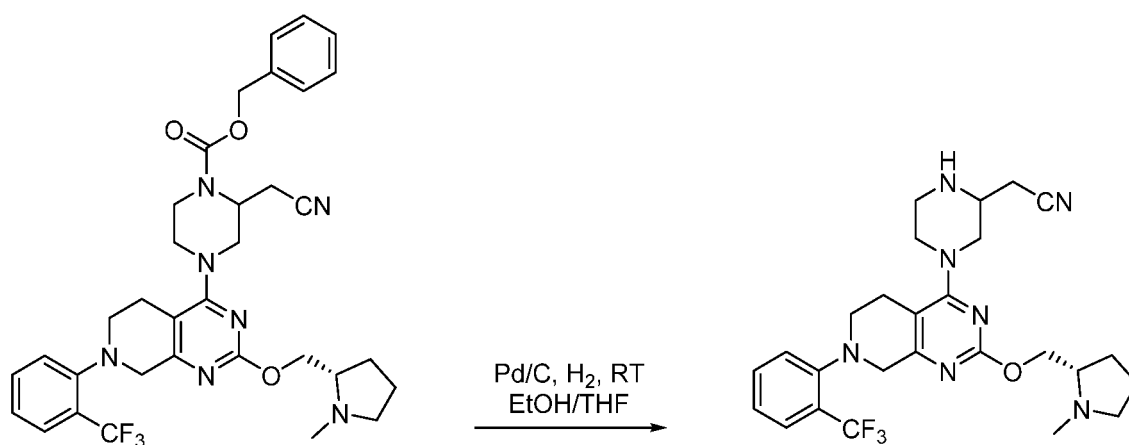


[0824] Step D: benzyl 2-(cyanomethyl)-4-(2-(((S)-1-methylpyrrolidin-2-yl)methoxy))-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate: tert-butyl 4-(4-((benzyloxy)carbonyl)-3-(cyanomethyl)piperazin-1-yl)-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate (831 mg, 1.37 mmol) was placed in DCM (15 mL) and TFA (2114 μ L, 27.4 mmol) was added and the reaction was stirred at rt for 1hr. The reaction was concentrated. Saturated bicarbonate was added and the mixture was extracted with DCM (3x25 mL). The extracts were combined, dried with sodium sulfate, filtered and concentrated to give benzyl 2-(cyanomethyl)-4-(2-(((S)-1-methylpyrrolidin-2-yl)methoxy))-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (665 mg, 1.32 mmol, 96 % yield) which was used as is. ES+APCI MS m/z 506.2 $[M+H]^+$.

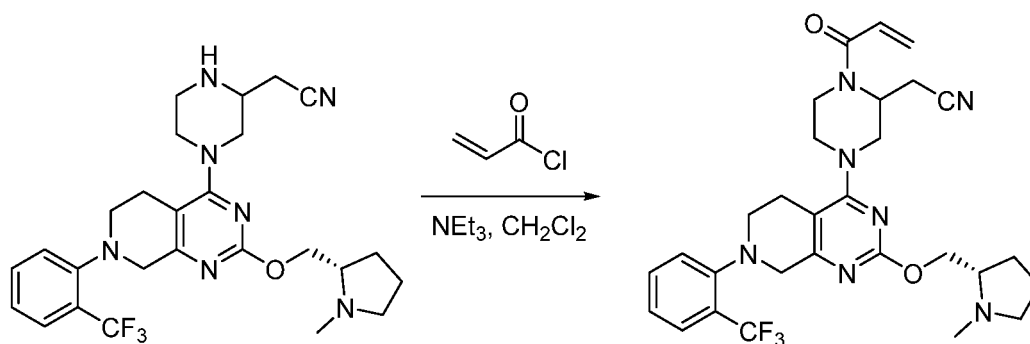


[0825] Step E: benzyl 2-(cyanomethyl)-4-(2-(((S)-1-methylpyrrolidin-2-yl)methoxy))-7-(2-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate: To a vial was added cesium carbonate (103 mg, 0.316 mmol), benzyl 2-(cyanomethyl)-4-(2-(((S)-1-methylpyrrolidin-2-yl)methoxy))-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (80 mg, 0.158 mmol), Rhuphos Pd G3 (13.2 mg,

0.016 mmol), 1-bromo-2-(trifluoromethyl)benzene (53.4 mg, 0.237 mmol) and 1,4-dioxane (1582 μ L, 0.158 mmol) and the vial was degassed with Ar, sealed then heated to 70°C for 24 hours. Water and saturated NH₄Cl were added to the reaction and the mixture was extracted with DCM. The organic layer concentrated in vacuo. The resulting residue was purified by silica gel (0-12% MeOH in DCM w/0.2% NH₄OH as eluent) to provide benzyl 2-(cyanomethyl)-4-(2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-7-(2-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (20.5 mg, 0.032 mmol, 20 % yield). ES+APCI MS m/z 650.3 [M+H]⁺.



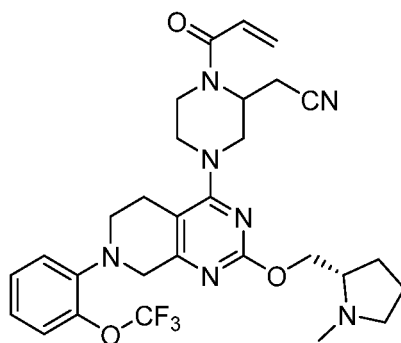
[0826] Step F: 2-(4-(2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-7-(2-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile: To a solution of benzyl 2-(cyanomethyl)-4-(2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-7-(2-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (20.5 mg, 0.032 mmol) in EtOH (316 μ L, 0.0316 mmol) and THF (316 μ L, 0.032 mmol) was added palladium (16.8 mg, 0.008 mmol) (Degussa Type, 10 wt%, 50% H₂O) and then an atmosphere of H₂ was introduced via vacuum followed by balloon pressure and was stirred for 2 hours. The mixture was then diluted with MeOH and filtered through GF/F paper. The filtrate was then concentrated to provide desired product which was used as is. ES+APCI MS m/z 516.2 [M+H]⁺.



[0827] Step G: 2-(1-acryloyl-4-(2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-7-(2-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile: 2-(4-(2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-7-(2-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile (16.3 mg, 0.032 mmol) and triethylamine (13.2 μ L, 0.095 mmol) were placed in CH₂Cl₂ (316 μ L, 0.032 mmol) and cooled to 0°C. Acryloyl chloride (632 μ L, 0.063 mmol) was added (freshly prepared 0.1M solution in DCM) and the reaction was stirred for 1 hour at 0°C. The mixture was concentrated and the resulting residue was purified by reverse phase chromatography (0-50% ACN:water w/ 0.1%TFA) to provide desired product (18.9 mg, 0.027 mmol, 87 % yield). ES+APCI MS m/z 570.3 [M+H]⁺.

EXAMPLE 211

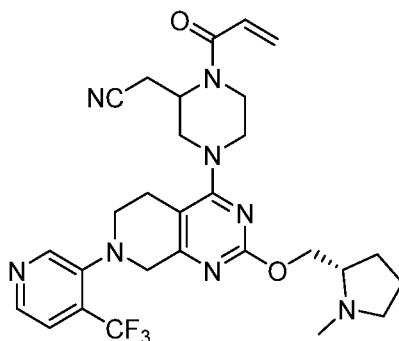
2-(1-acryloyl-4-(2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-7-(2-(trifluoromethoxy)phenyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile



[0828] Synthesized according to **Example 210**, Steps E-G using 1-bromo-2-(trifluoromethoxy)benzene in place of 1-bromo-2-(trifluoromethyl)benzene in Step E. ES+APCI MS m/z 586.3 [M+H]⁺.

EXAMPLE 212

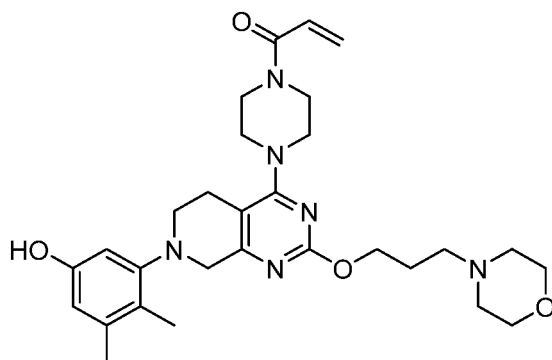
2-(1-acryloyl-4-(2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-7-(4-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile

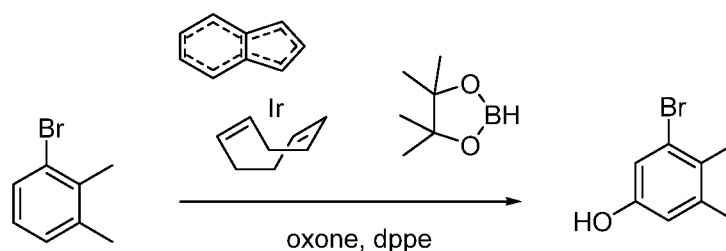


[0829] Synthesized according **Example 210**, Steps E-G using 3-bromo-4-(trifluoromethyl)pyridine in place of 1-bromo-2-(trifluoromethyl)benzene in Step E. ES+APCI MS m/z 571.3 [M+H]⁺.

EXAMPLE 213

1-(4-(7-(5-hydroxy-2,3-dimethylphenyl)-2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one





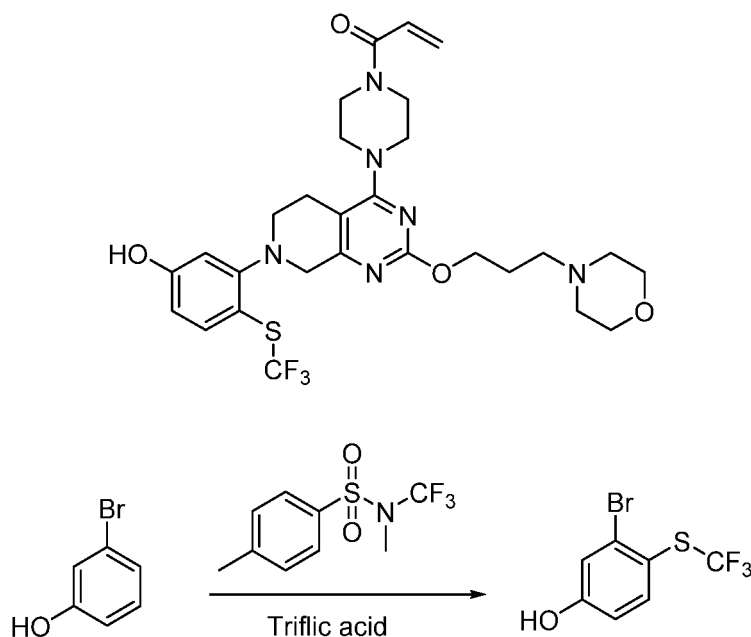
[0830] Step A: 3-bromo-4,5-dimethylphenol: In a sealed tube DPPE (0.431 g, 1.08 mmol), 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.73 g, 13.5 mmol), (1,5-Cyclooctadiene)-eta5-indenyl)iridium(I) (0.449 g, 1.08 mmol) and 1-bromo-2,3-dimethylbenzene (1.00 g, 5.40 mmol) were placed in cyclohexane (6 mL) and was heated to 100°C for 50hr. The reaction was concentrated down and brought up in acetone (5 mL) and oxzone (3.32 g, 5.40 mmol) was added and stirred for 10 min. The reaction was quenched with saturated NaHSO₃ and was extracted with DCM (3x20 ml). The extracts were washed with brine, water and concentrated. The residue was passed through a plug of silica eluting with DCM to provide 3-bromo-4,5-dimethylphenol (238 mg, 1.18 mmol, 22 % yield).

[0831] Step B: 1-bromo-5-(methoxymethoxy)-2,3-dimethylbenzene: Was prepared according to the preparation for Intermediate 3 substituting the 3-bromo-4,5-dimethylphenol for 2-bromo-3-fluorophenol.

[0832] Step C: 1-(4-(7-(5-hydroxy-2,3-dimethylphenyl)-2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one 2,2,2-trifluoroacetate: was prepared according to Example 1 Steps C-F substituting Intermediate 25 for benzyl 4-(5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate and 1-bromo-5-(methoxymethoxy)-2,3-dimethylbenzene for 1-bromo-3-(methoxymethoxy)naphthalene in Step C. ES+APCI MS m/z 537.3 [M+H]⁺.

EXAMPLE 214

1-(4-(7-(5-hydroxy-2-((trifluoromethyl)thio)phenyl)-2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one



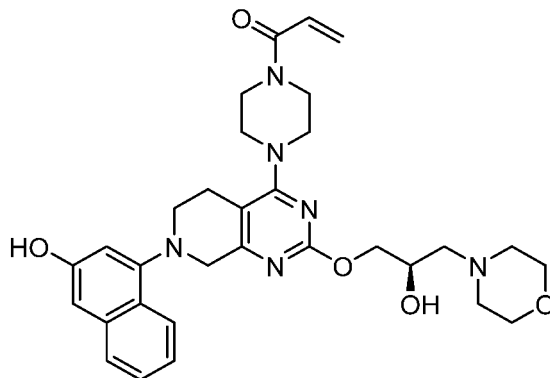
[0833] Step A: 3-bromo-4-((trifluoromethyl)thio)phenol: In a sealed tube 3-bromophenol (575 mg, 3.32 mmol) and N,4-dimethyl-N-(trifluoromethyl)benzenesulfonamide (1010 mg, 3.99 mmol) were placed in dry DCE (6 mL). Triflic acid (295 μ L, 3.32 mmol) was added slowly and the reaction was then heated to 80°C for 18 hours. The reaction was cooled and the solvent was removed under vacuum and the resulting residue was purified by silica gel (0-20% EtOAc in hexanes) to provide 3-bromo-4-((trifluoromethyl)thio)phenol (650 mg, 2.38 mmol, 72 % yield)

[0834] Step B: (2-bromo-4-(methoxymethoxy)phenyl)(trifluoromethyl)sulfane: Was prepared according to the preparation for Intermediate 3 substituting the 3-bromo-4-((trifluoromethyl)thio)phenol for 2-bromo-3-fluorophenol.

[0835] Step C: 1-(4-(7-(5-hydroxy-2-((trifluoromethyl)thio)phenyl)-2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one: Synthesized according to Example 1 Step C-F substituting Intermediate 25 for benzyl 4-(5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate and (2-bromo-4-(methoxymethoxy)phenyl)(trifluoromethyl)sulfane for 1-bromo-3-(methoxymethoxy)naphthalene in Step C. ES+APCI MS m/z 609.2 $[M+H]^+$.

EXAMPLE 215

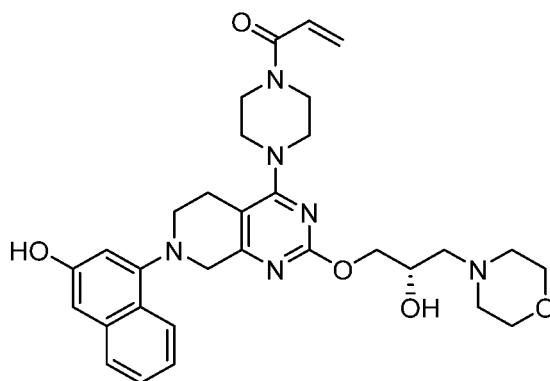
(R)-1-(4-(2-(2-hydroxy-3-morpholinopropoxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one



[0836] Title compound was obtained by SFC chiral resolution of **Example 123** using a Phenomenex OZ-H column (4.6mm x250mm, 5u) and eluting with 40-60% MeOH:IPA:DEA (80:20:1) at 4mL/min. Collecting the first eluting peak provided the desired compound where the stereochemistry was arbitrarily assigned. ES+APCI MS m/z 575.2 [M+H]⁺.

EXAMPLE 216

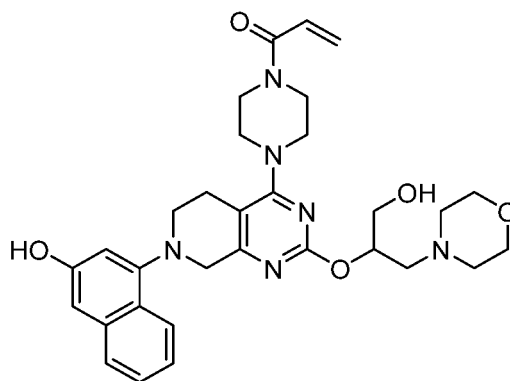
(S)-1-(4-(2-(2-hydroxy-3-morpholinopropoxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one



[0837] Title compound was obtained by SFC chiral resolution of **Example 123** using a Phenomenex OZ-H column (4.6mm x250mm, 5u) and eluting with 40-60% MeOH:IPA:DEA (80:20:1) at 4mL/min. Collecting the second eluting peak provided the desired compound where the stereochemistry was arbitrarily assigned. ES+APCI MS m/z 575.2 [M+H]⁺.

EXAMPLE 217

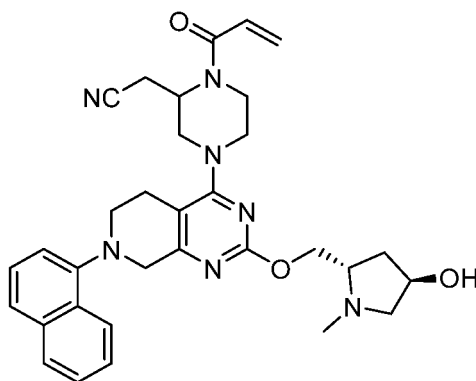
1-(4-(2-((1-hydroxy-3-morpholinopropan-2-yl)oxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one



[0838] Synthesized according to the method of **Example 8**, using 3-morpholinopropane-1,2-diol in place of (S)-1-(dimethylamino)propan-2-ol in Step B. ES+APCI MS m/z 575.2 $[M+H]^+$.

EXAMPLE 218

2-(1-acryloyl-4-(2-(((2S,4R)-4-hydroxy-1-methylpyrrolidin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile



[0839] Step A: benzyl 4-(2-(((2S,4R)-1-(tert-butoxycarbonyl)-4-((tert-butyl)dimethylsilyl)oxy)pyrrolidin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)-2-(cyanomethyl)piperazine-1-carboxylate: In a sealed vial, a solution of benzyl 4-(2-chloro-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-

d]pyrimidin-4-yl)-2-(cyanomethyl)piperazine-1-carboxylate (150 mg, 0.27 mmol) in dioxane (2712 μ L, 0.27 mmol) was sparged with argon and (2S,4R)-4-{[tert-Butyl(dimethyl)silyl]oxy}-2-(hydroxymethyl)pyrrolidine-1-carboxylate (270 mg, 0.81 mmol), Cs₂CO₃ (265 mg, 0.81 mmol), Rhuphos Pd G3 (22.7 mg, 0.027 mmol) were sequentially added under argon and sparged for an additional 5 min. The reaction mixture was capped and heated at 100°C for 2hr. Water was added and the mixture was extracted with DCM (3x15 mL). The extracts were combined and concentrated and the resulting residue was purified by silica gel (0-40 % EtOAc in hexanes) to provide benzyl 4-(2-(((2S,4R)-1-(tert-butoxycarbonyl)-4-((tert-butyl)dimethylsilyl)oxy)pyrrolidin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)-2-(cyanomethyl)piperazine-1-carboxylate (113 mg, 0.13 mmol, 49 % yield).

[0840] Step B: tert-butyl (2S,4R)-4-((tert-butyl)dimethylsilyl)oxy)-2-(((4-(3-(cyanomethyl)piperazin-1-yl)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-2-yl)oxy)methyl)pyrrolidine-1-carboxylate: To a solution of benzyl 4-(2-(((2S,4R)-1-(tert-butoxycarbonyl)-4-((tert-butyl)dimethylsilyl)oxy)pyrrolidin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)-2-(cyanomethyl)piperazine-1-carboxylate (113 mg, 0.133 mmol) in EtOH (1.3 mL, 0.133 mmol) and THF (1.3 mL, 0.133 mmol) was added palladium (70.9 mg, 0.033 mmol) (Degussa Type, 10 wt%, 50% H₂O) and then an atmosphere of H₂ was introduced via vacuum followed by balloon pressure. The mixture was then stirred at ambient temperature for 2 hours. The mixture was then diluted with 1:1 MeOH and THF and filtered through GF/F paper. The filtrate was then concentrated to provide crude product which was used as is.

[0841] Step C: tert-butyl (2S,4R)-2-(((4-(4-acryloyl-3-(cyanomethyl)piperazin-1-yl)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-2-yl)oxy)methyl)-4-((tert-butyl)dimethylsilyl)oxy)pyrrolidine-1-carboxylate: tert-butyl (2S,4R)-4-((tert-butyl)dimethylsilyl)oxy)-2-(((4-(3-(cyanomethyl)piperazin-1-yl)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-2-yl)oxy)methyl)pyrrolidine-1-carboxylate (95 mg, 0.13 mmol) and triethylamine (56 μ L, 0.40 mmol) were placed in CH₂Cl₂ (1331 μ L, 0.13 mmol) and cooled to 0°C. Acryloyl chloride (2661 μ L, 0.27 mmol) (freshly prepared 0.1M solution in DCM) was added and the reaction was stirred for 30 min at 0°C. Water was added to the

reaction and the mixture was extracted with DCM (3x15 mL). The extracts were combined and concentrated to provide crude material which was used as is.

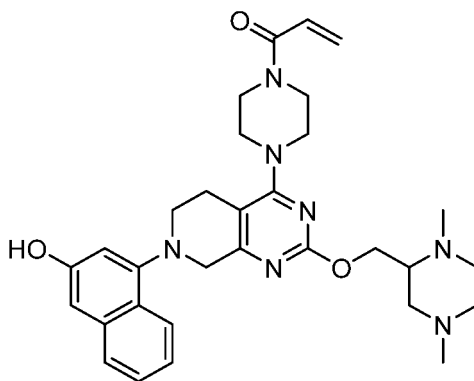
[0842] Step D: 2-(1-acryloyl-4-(2-(((2S,4R)-4-((tert-butyldimethylsilyl)oxy)pyrrolidin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile. tert-butyl (2S,4R)-2-(((4-(4-acryloyl-3-(cyanomethyl)piperazin-1-yl)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-2-yl)oxy)methyl)-4-((tert-butyldimethylsilyl)oxy)pyrrolidine-1-carboxylate (92 mg, 0.12 mmol) was placed in DCM (3 mL) and TFA (92 μ L, 1.2 mmol) was added and the reaction was stirred at room temperature for 2 hours. Saturated bicarbonate was added to the reaction and the mixture was extracted with DCM (3x15 mL). The extracts were combined, dried with sodium sulfate, filtered and concentrated to give crude material that was used as is.

[0843] Step E: 2-(1-acryloyl-4-(2-(((2S,4R)-4-((tert-butyldimethylsilyl)oxy)-1-methylpyrrolidin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile: 2-(1-acryloyl-4-(2-(((2S,4R)-4-((tert-butyldimethylsilyl)oxy)pyrrolidin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile (80 mg, 0.12 mmol), formaldehyde (45.0 μ L, 0.60 mmol) and Na(OAc)₃BH (50.8 mg, 0.24 mmol) were placed in THF (2 mL) and stirred for 2 hrs. Saturated bicarbonate was added and the mixture was extracted with 10% MeOH in DCM (3x15 mL). The extracts were combined, dried with sodium sulfate, and concentrated to provide crude material which was used as is.

[0844] Step F: 2-(1-acryloyl-4-(2-(((2S,4R)-4-hydroxy-1-methylpyrrolidin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile 2,2,2-trifluoroacetate: 2-(1-acryloyl-4-(2-(((2S,4R)-4-((tert-butyldimethylsilyl)oxy)-1-methylpyrrolidin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile (81 mg, 0.119 mmol) was placed in DCM (5 mL) and HCl (594 μ L, 2.38 mmol) was added and the reaction was stirred for 1 hr. The reaction was concentrated and the material was purified by reverse phase chromatography (0-50% ACN:water with 0.1% TFA) to provide 2-(1-acryloyl-4-(2-(((2S,4R)-4-hydroxy-1-methylpyrrolidin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile (38.9 mg, 0.057 mmol, 48 % yield). ES+APCI MS m/z 568.3 [M+H]⁺.

EXAMPLE 219

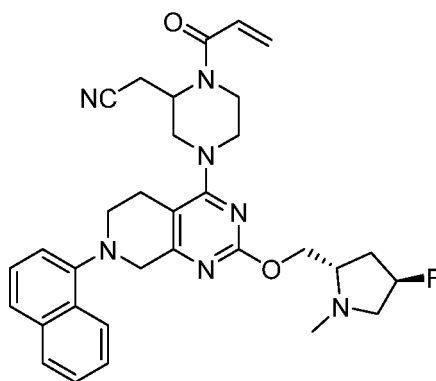
1-(4-(2-((1,4-dimethylpiperazin-2-yl)methoxy)-7-(3-hydroxynaphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

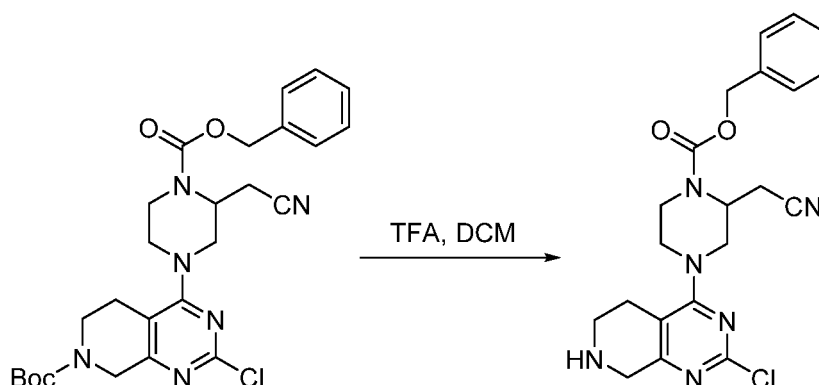


[0845] Title compound was prepared the same as **Example 127**, substituting (1,4-Dimethyl-2-piperazinyl)methanol in place of N-Methyl-L-prolinol in Step D. ES+APCI MS m/z 558.3 $[M+H]^+$.

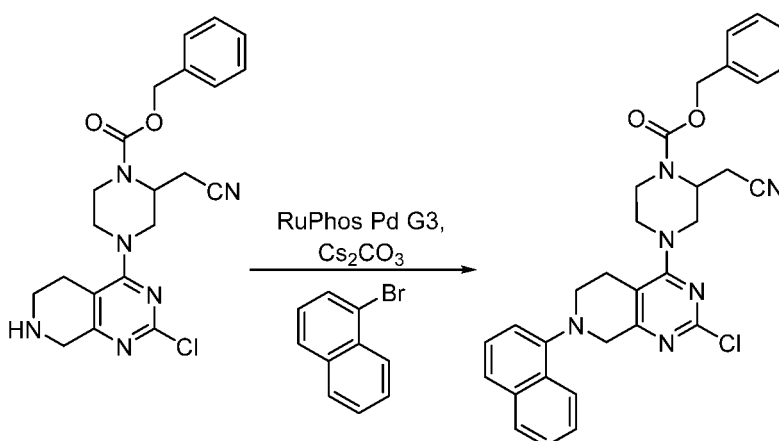
EXAMPLE 220

2-(1-acryloyl-4-(2-(((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile



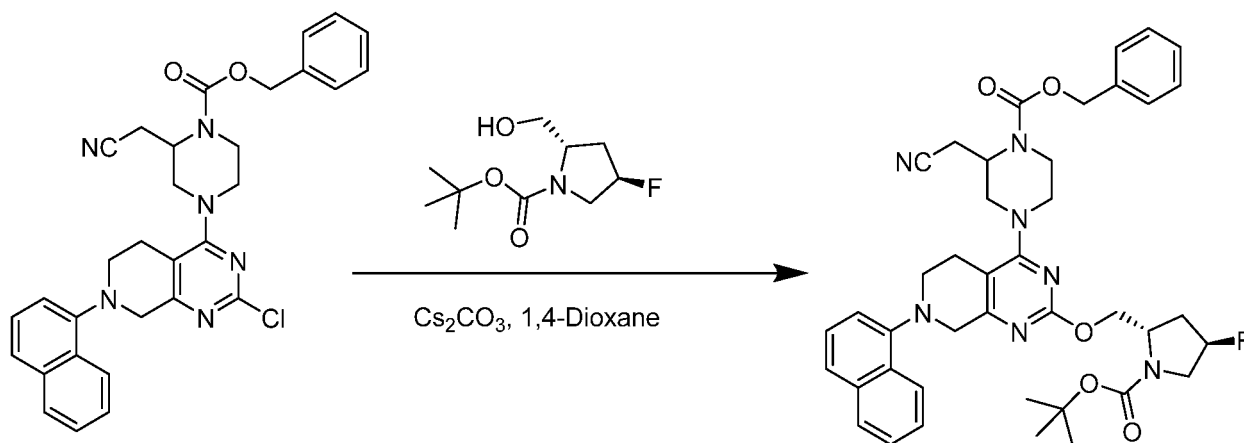


[0846] Step A: benzyl 4-(2-chloro-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)-2-(cyanomethyl)piperazine-1-carboxylate: To a solution of tert-butyl 4-(4-((benzyloxy)carbonyl)-3-(cyanomethyl)piperazin-1-yl)-2-chloro-5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate (4.00 g, 7.59 mmol) in DCM (25.3 ml, 7.59 mmol) was added trifluoroacetic acid (17.4 ml, 227.7 mmol) and the reaction was stirred at room temperature for 3 hours. The reaction was concentrated to a thick oil. Saturated bicarbonate was added slowly and the mixture was extracted with 10% MeOH in DCM (3x 50 mL). The extracts were combined, dried with sodium sulfate and concentrated to provide the desired product (3.24 g, 7.6 mmol, 100 % yield) which was used as is. ES+APCI MS m/z 506.2 $[M]^+$.

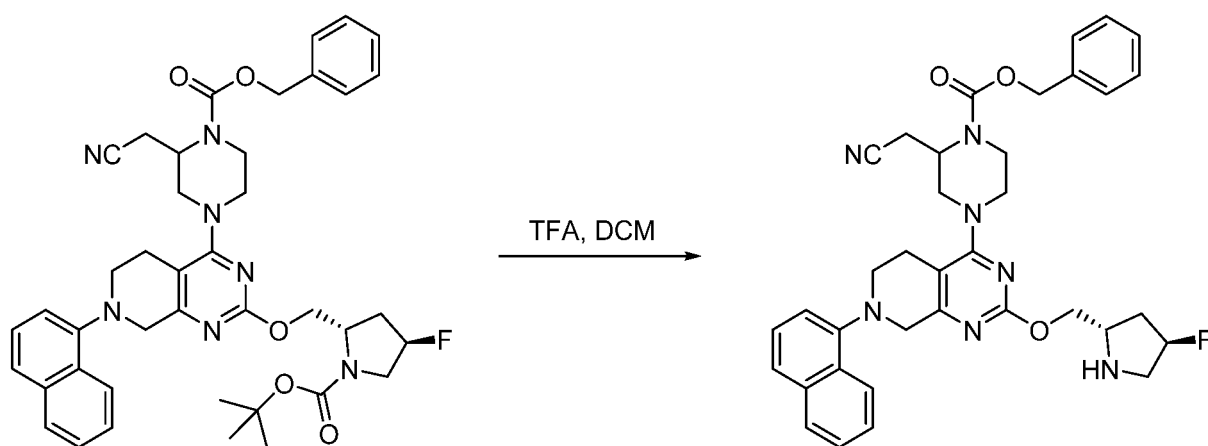


[0847] Step B: benzyl 4-(2-chloro-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)-2-(cyanomethyl)piperazine-1-carboxylate: To a round bottomed flask was added cesium carbonate (8.01 g, 24.6 mmol), benzyl 4-(2-chloro-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)-2-(cyanomethyl)piperazine-1-carboxylate (3.5 g, 8.2 mmol), 1-bromonaphthalene (4.6 ml, 32.8 mmol) and RuPhos Pd G3 (1.0 g, 1.23 mmol). After evacuating

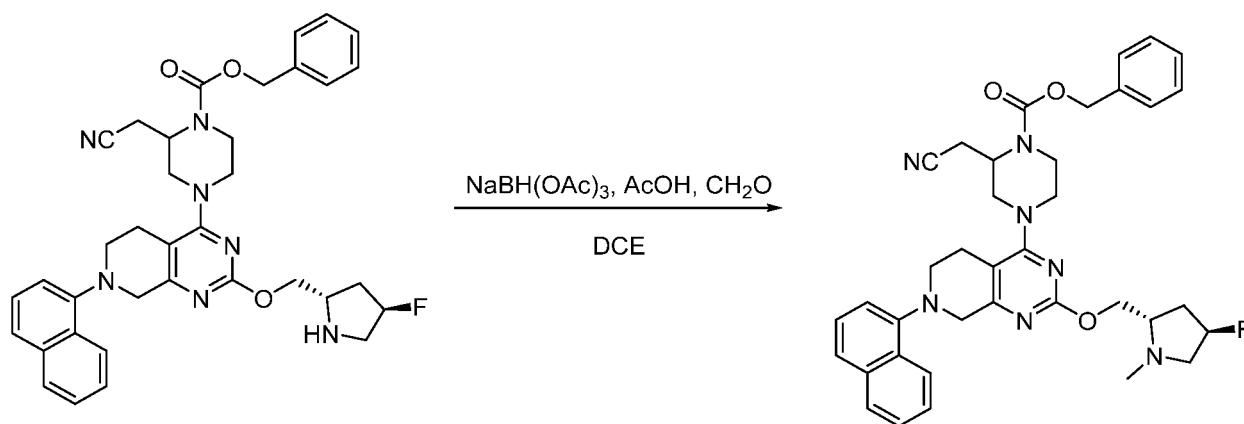
the flask, 1,4-dioxane (82.0 ml, 8.20 mmol) was added through a septum under argon flow. Argon was bubbled through the mixture for 5 minutes and then the mixture was heated to 70°C overnight. The reaction was cooled and water was added and extracted with ethyl acetate and the organics concentrated in vacuo. The yellow solids were dissolved in minimal DCM and purified by silica chromatography (25-60% EtOAc in hexanes) to provide benzyl 4-(2-chloro-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)-2-(cyanomethyl)piperazine-1-carboxylate (2.0 g, 3.6 mmol, 44.1 % yield). ES+APCI MS m/z 553.2 $[M]^+$.



[0848] Step C: benzyl 4-(2-(((2S,4R)-1-(tert-butoxycarbonyl)-4-fluoropyrrolidin-2-yl)methoxy))-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)-2-(cyanomethyl)piperazine-1-carboxylate: In a vial benzyl 4-(2-chloro-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)-2-(cyanomethyl)piperazine-1-carboxylate (120 mg, 0.22 mmol) was dissolved in dioxane (108 μ L, 0.217 mmol) and treated with cesium carbonate (141 mg, 0.434 mmol), and (2S,4R)-1-(tert-Butoxycarbonyl)-4-fluoro-2-hydroxymethylpyrrolidine (47.6 mg, 0.217 mmol). The tube was then capped and heated to 90°C for 12 hours. The reaction was filtered through GF/F paper and concentrated. The residue was purified by silica chromatography (0-6% MeOH in DCM). ES+APCI MS m/z 736.3 $[M+H]^+$.

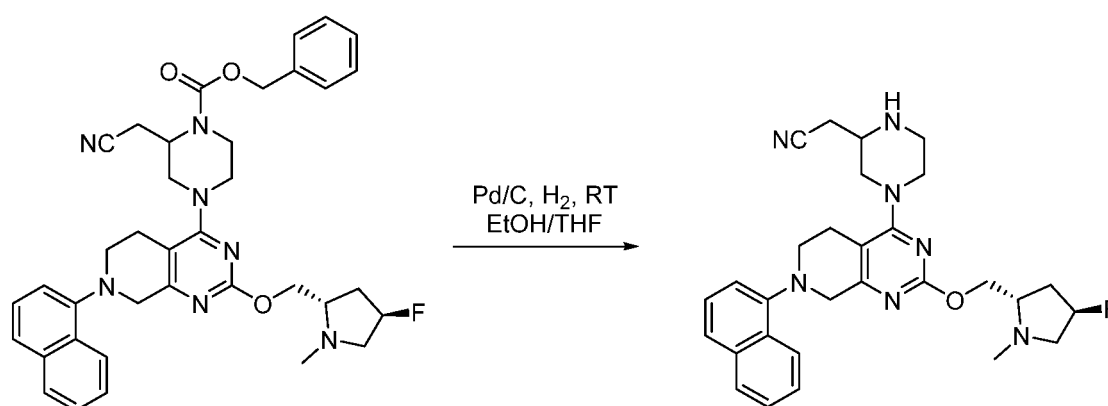


[0849] Step D: benzyl 2-(cyanomethyl)-4-(2-(((2S,4R)-4-fluoropyrrolidin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate: To a solution of benzyl 4-(2-(((2S,4R)-1-(tert-butoxycarbonyl)-4-fluoropyrrolidin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)-2-(cyanomethyl)piperazine-1-carboxylate (125 mg, 0.170 mmol) in DCM (170 μ L, 0.170 mmol) was added trifluoroacetic acid (195 μ L, 2.55 mmol) and the reaction stirred at RT for 2 hr. The organics were washed with sodium bicarbonate and the aqueous layer was back extracted with DCM. The combined organic layers were concentrated and used without further purification. ES+APCI MS m/z 636.3 $[M+H]^+$.

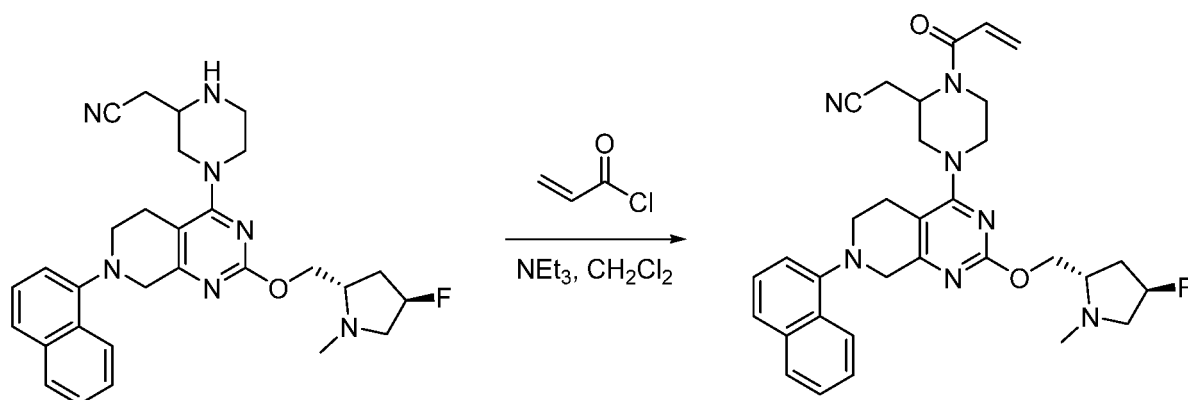


[0850] Step E: benzyl 2-(cyanomethyl)-4-(2-(((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate: To a solution of benzyl 2-(cyanomethyl)-4-(2-(((2S,4R)-4-fluoropyrrolidin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-

carboxylate (105 mg, 0.1652 mmol) in DCE (3303 μ L, 0.1652 mmol) was added formaldehyde (124.1 μ L, 1.652 mmol) (37% in water) followed by sodium triacetoxyborohydride (175.0 mg, 0.8258 mmol). The mixture was stirred vigorously at RT for 2.5h. The mixture was treated with saturated sodium bicarbonate (30 mL), stirred for 10 min then extracted with DCM (3 x 10 mL). The combined organic phases were dried over sodium sulfate, filtered and concentrated and used as is in the next reaction. ES+APCI MS m/z 650.3 $[M+H]^+$.



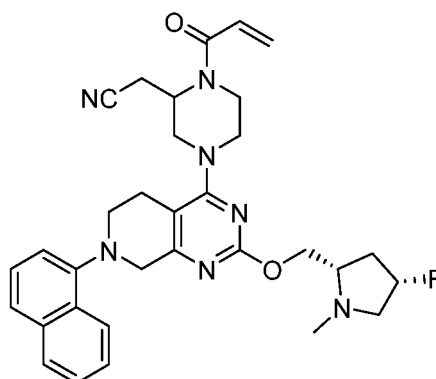
[0851] Step F: 2-(4-(2-(((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)methoxy))-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile: To a solution of benzyl 2-(cyanomethyl)-4-(2-(((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)methoxy))-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (85 mg, 0.13 mmol) in EtOH (1308 μ L, 0.13 mmol) and THF (1308 μ L, 0.13 mmol) was added palladium (70 mg, 0.033 mmol) (Degussa Type, 10 wt%, 50% H₂O) and then an atmosphere of H₂ was introduced via vacuum followed by balloon pressure. The mixture was then stirred at ambient temperature overnight. The mixture was then diluted with MeOH and filtered through GF/F paper. The filtrate was then concentrated to provide 2-(4-(2-(((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)methoxy))-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile. ES+APCI MS m/z 516.3 $[M+H]^+$.



[0852] Step G: 2-(1-acryloyl-4-(2-(((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile : To a suspension of 2-(4-(2-(((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile (65 mg, 0.126 mmol) in DCM (1261 μ L, 0.126 mmol) at 0°C was added acryloyl chloride (2521 μ L, 0.252 mmol) (freshly prepared 0.1M solution in DCM) followed by triethylamine (35.1 μ L, 0.252 mmol). The reaction was then stirred at 0°C for 45 minutes. The reaction was concentrated and purified by reverse phase chromatography (0-50% CAN:water with 0.1% TFA) to provide the title compound. ES+APCI MS m/z 570.3 $[M+H]^+$.

EXAMPLE 221

2-(1-acryloyl-4-(2-(((2S,4S)-4-fluoro-1-methylpyrrolidin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile

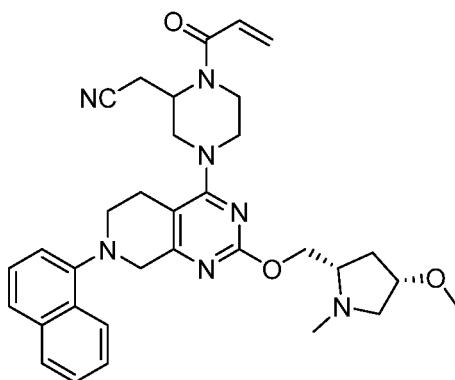


[0853] Synthesized according to the method of **Example 220**, Step C-G, using tert-butyl (2S,4S)-4-fluoro-2-(hydroxymethyl)pyrrolidine-1-carboxylate in place of tert-butyl (2S,4R)-4-

fluoro-2-(hydroxymethyl)pyrrolidine-1-carboxylate in Step C. ES+APCI MS m/z 570.3 $[M+H]^+$.

EXAMPLE 222

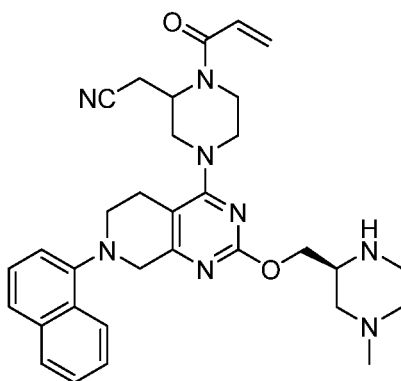
2-(1-acryloyl-4-(2-(((2S,4S)-4-methoxy-1-methylpyrrolidin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile



[0854] Title compound was prepared following **Example 220** (Steps C-G), substituting tert-butyl (2S,4S)-2-(hydroxymethyl)-4-methoxypyrrolidine-1-carboxylate for (2S,4R)-1-(tert-Butoxycarbonyl)-4-fluoro-2-hydroxymethylpyrrolidine in Step C. ES+APCI MS m/z 582.3 $[M+H]^+$.

EXAMPLE 223

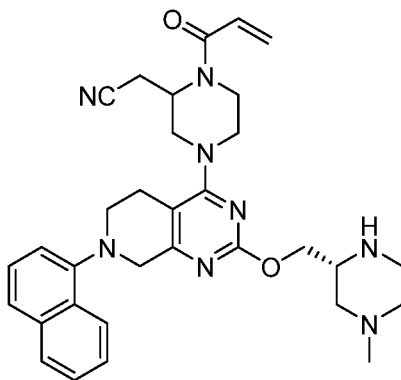
2-(1-acryloyl-4-(2-(((S)-4-methylpiperazin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile



[0855] Steps A-F: 2-(1-acryloyl-4-(2-(((S)-4-methylpiperazin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile: Title compound was prepared following **Example 220** (Steps C-G), substituting tert-butyl (S)-2-(hydroxymethyl)-4-methylpiperazine-1-carboxylate for (2S,4R)-1-(tert-Butoxycarbonyl)-4-fluoro-2-hydroxymethylpyrrolidine in Step C. ES+APCI MS m/z 567.3 [M+H]⁺.

EXAMPLE 224

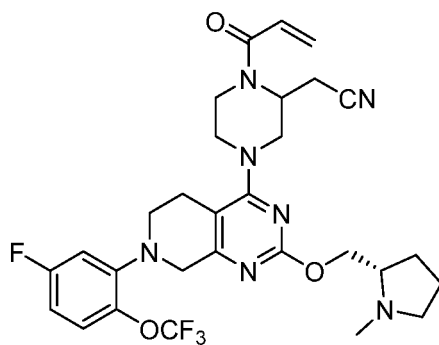
2-(1-acryloyl-4-(2-(((R)-4-methylpiperazin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile



[0856] Title compound was prepared following **Example 220** (Steps C-G), substituting tert-butyl (R)-2-(hydroxymethyl)-4-methylpiperazine-1-carboxylate for tert-butyl (S)-2-(hydroxymethyl)-4-methylpiperazine-1-carboxylate in Step C. ES+APCI MS m/z 567.3 [M+H]⁺.

EXAMPLE 225

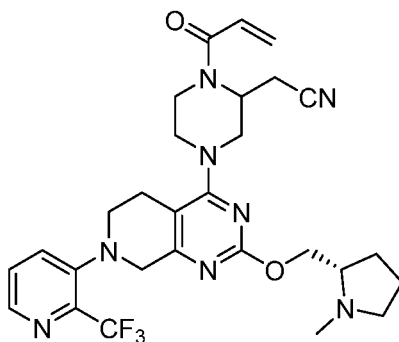
2-(1-acryloyl-4-(7-(5-fluoro-2-(trifluoromethoxy)phenyl)-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile



[0857] Title compound was prepared as in **Example 210** Steps E-G, substituting 2-bromo-4-fluoro-1-(trifluoromethoxy)benzene for 1-bromo-2-(trifluoromethyl)benzene in step E. ES+APCI MS m/z 604.3 $[M+H]^+$.

EXAMPLE 226

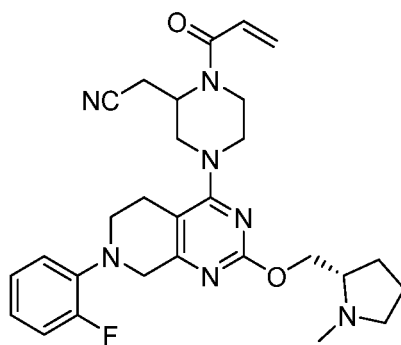
2-(1-acryloyl-4-(2-(((S)-1-methylpyrrolidin-2-yl)methoxy))-7-(2-(trifluoromethyl)pyridin-3-yl))-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile



[0858] Title compound was prepared as in **Example 210** Steps E-G, substituting 3-bromo-2-(trifluoromethyl)pyridine for 1-bromo-2-(trifluoromethyl)benzene in Step E. ES+APCI MS m/z 571.3 $[M+H]^+$.

EXAMPLE 227

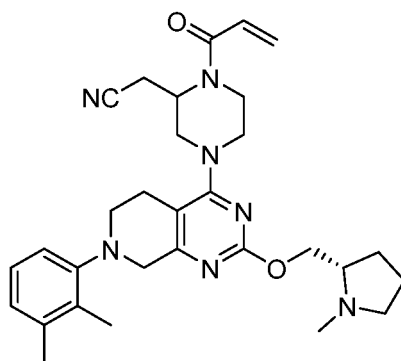
2-(1-acryloyl-4-(7-(2-fluorophenyl)-2-(((S)-1-methylpyrrolidin-2-yl)methoxy))-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile



[0859] Title compound was prepared as in **Example 210** Steps E-G, substituting 1-bromo-2-fluorobenzene for 1-bromo-2-(trifluoromethyl)benzene in step E. ES+APCI MS m/z 520.3 [M+H]⁺.

EXAMPLE 228

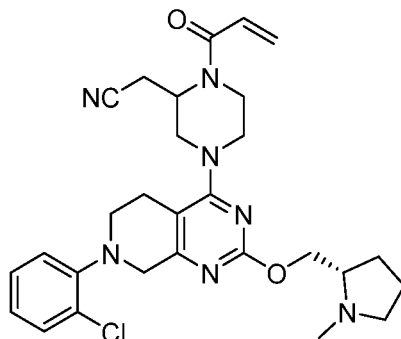
2-(1-acryloyl-4-(7-(2,3-dimethylphenyl)-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile



[0860] Title compound was prepared as in **Example 210** Steps E-G, substituting 1-bromo-2,3-dimethylbenzene for 1-bromo-2-(trifluoromethyl)benzene in Step E. ES+APCI MS m/z 530.3 [M+H]⁺.

EXAMPLE 229

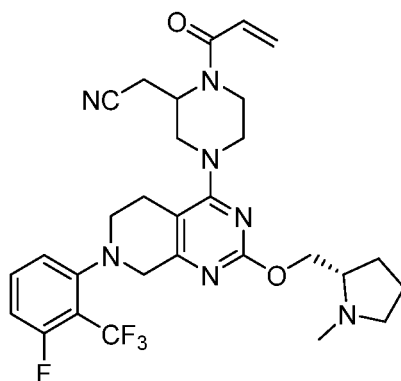
2-(1-acryloyl-4-(7-(2-chlorophenyl)-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile



[0861] Title compound was prepared as in **Example 210** Steps E-G, substituting 1-bromo-2-chlorobenzene for 1-bromo-2-(trifluoromethyl)benzene in step E. ES+APCI MS m/z 536.2 $[M]^+$.

EXAMPLE 230

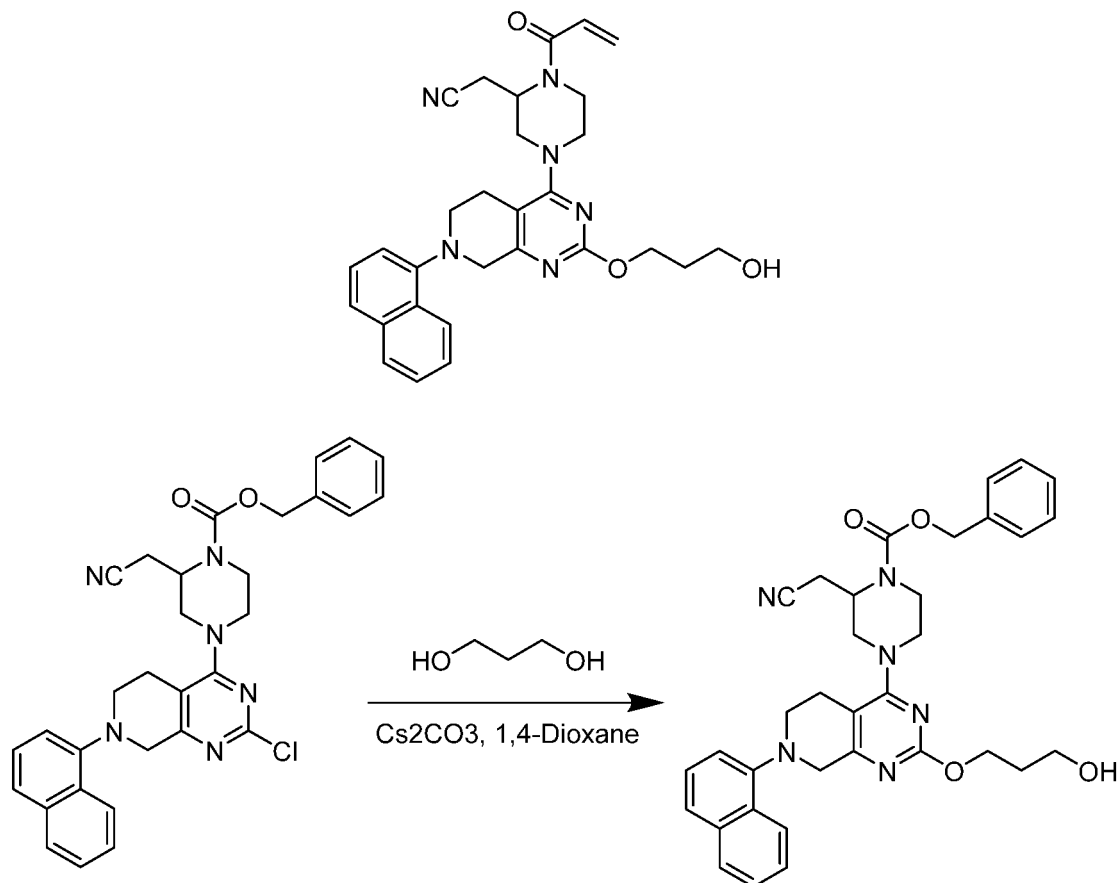
2-(1-acryloyl-4-(7-(3-fluoro-2-(trifluoromethyl)phenyl)-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile



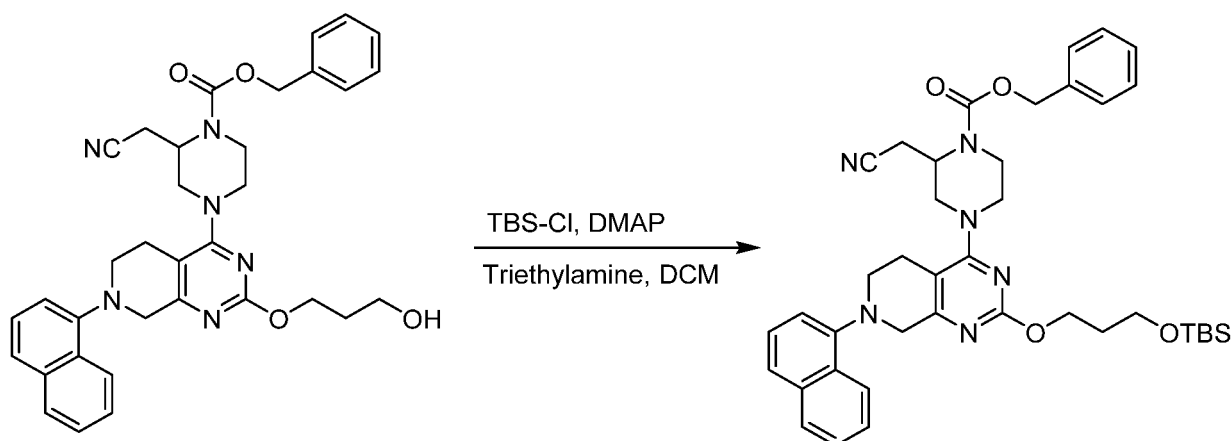
[0862] Title compound was prepared as in **Example 210** Steps E-G, substituting 1-bromo-3-fluoro-2-(trifluoromethyl)benzene for 1-bromo-2-(trifluoromethyl)benzene in Step E. ES+APCI MS m/z 588.3 $[M+H]^+$.

EXAMPLE 231

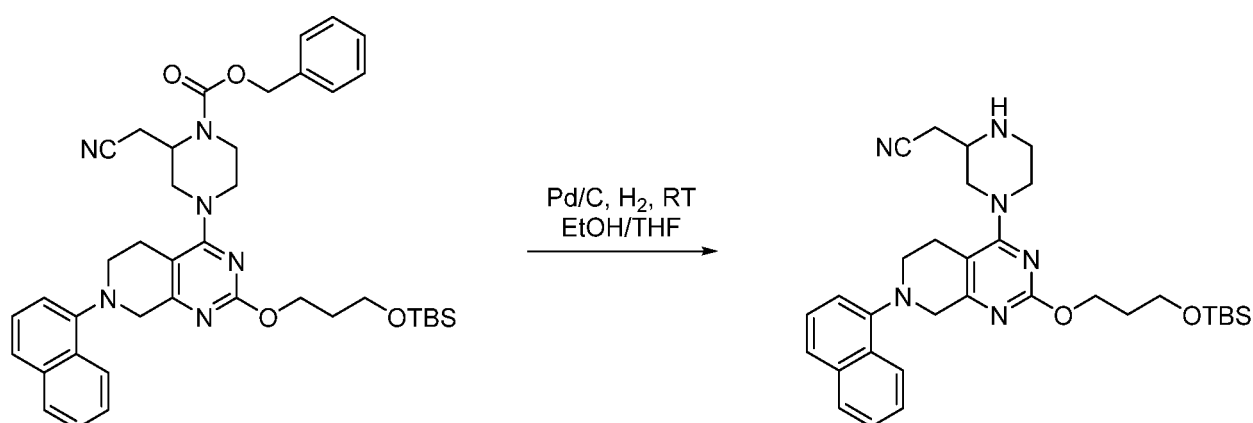
2-(1-acryloyl-4-(2-(3-hydroxypropoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile



[0863] Step A: benzyl 2-(cyanomethyl)-4-(2-(3-hydroxypropoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate: Title compound was prepared as in Example 220 Step C, substituting propane-1,3-diol for (2S,4R)-1-(tert-Butoxycarbonyl)-4-fluoro-2-hydroxymethylpyrrolidine. ES+APCI MS m/z 593.3 [M+H]⁺.

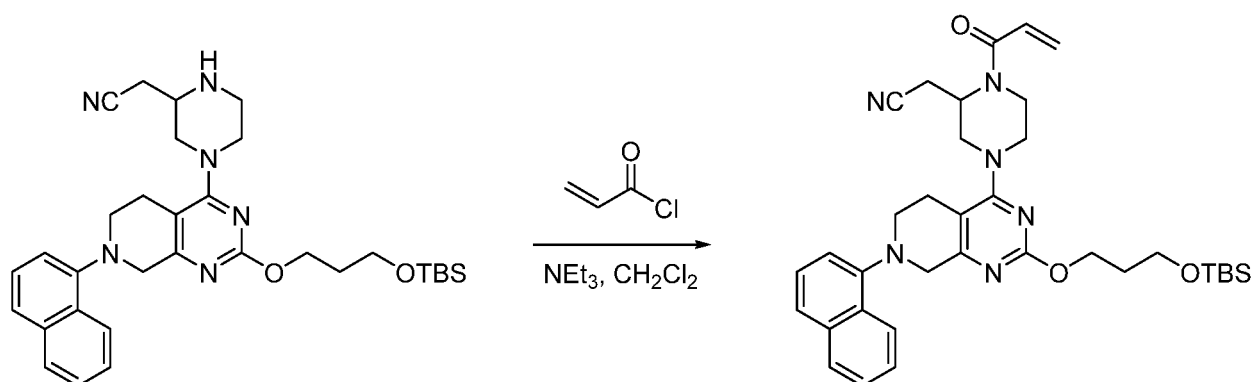


[0864] Step B: benzyl 4-(2-(3-((tert-butyldimethylsilyl)oxy)propoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)-2-(cyanomethyl)piperazine-1-carboxylate: To a vial was added benzyl 2-(cyanomethyl)-4-(2-(3-hydroxypropoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (77.6 mg, 0.131 mmol), which was dissolved in DCM (655 μ L, 0.131 mmol). The mixture was cooled to 0 °C and then triethylamine (36.5 μ L, 0.262 mmol) was added followed by 4-(dimethylamino)-pyridine (4.80 mg, 0.04 mmol). Then tert-butyldimethylsilyl chloride (29.6 mg, 0.196 mmol) was added and the mixture was stirred overnight while warming to room temperature. The reaction mixture was poured onto a saturated brine solution (5ml) and the mixture extracted twice with EtOAc (10 mL). The organic phases were dried over sodium sulfate, filtered and concentrated. The crude reaction product was used as is. ES+APCI MS m/z 707.4 $[M+H]^+$.

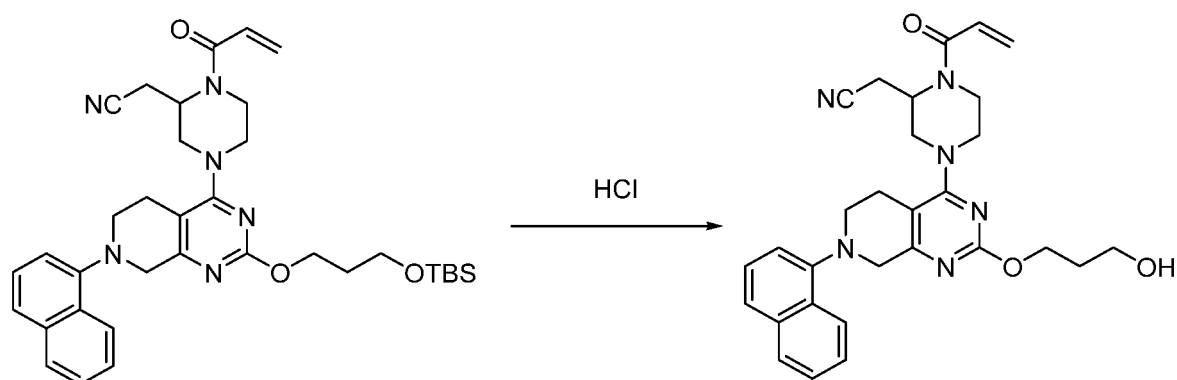


[0865] Step C: 2-(4-(2-(3-((tert-butyldimethylsilyl)oxy)propoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile: To a solution of benzyl 4-(2-

(3-((tert-butyldimethylsilyl)oxy)propoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)-2-(cyanomethyl)piperazine-1-carboxylate (106 mg, 0.150 mmol) in EtOH (1499 μ L, 0.150 mmol) and THF (1499 μ L, 0.150 mmol) was added palladium (79.8 mg, 0.0375 mmol) (Degussa Type, 10 wt%, 50% H₂O) and then an atmosphere of H₂ was introduced via vacuum followed by balloon pressure. The mixture was then stirred at ambient temperature overnight. The mixture was then diluted with MeOH and filtered through GF/F paper. The filtrate was then concentrated to a colorless solid that was used without further purification. ES+APCI MS m/z 573.3 [M+H]⁺.



[0866] Step D: 2-(1-acryloyl-4-(2-(3-((tert-butyldimethylsilyl)oxy)propoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile: To a suspension of 2-(4-(2-(3-((tert-butyldimethylsilyl)oxy)propoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile (75 mg, 0.131 mmol) in DCM (1309 μ L, 0.131 mmol) at -78°C was added acryloyl chloride (2619 μ L, 0.262 mmol) (freshly prepared 0.1M solution in DCM) followed by triethylamine (36.5 μ L, 0.262 mmol). The reaction was then stirred at 0°C for 30 minutes. The reaction was concentrated and used crude in the next reaction. ES+APCI MS m/z 627.4 [M+H]⁺.

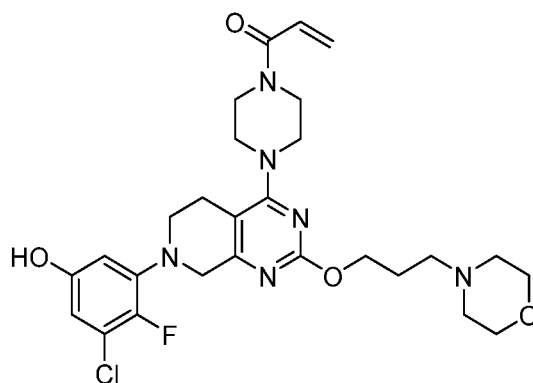


[0867] Step E: 2-(1-acryloyl-4-(2-(3-hydroxypropoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile: To a solution of 2-(1-acryloyl-4-(2-(3-((tert-butyldimethylsilyl)oxy)propoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile (90 mg, 0.14 mmol) in DCM (1436 μ L, 0.14 mmol) was added hydrochloric acid (4.0 M in 1,4-dioxane) (359 μ L, 1.4 mmol) at 0°C. The reaction was stirred for 30 min at which point it was quenched with saturated sodium bicarbonate and extracted into 10% IPA in CHCl₃ (3x15 ml). The combined organic layers were concentrated and the residue was purified by reverse phase chromatography (0-95% ACN:H₂O with 0.1TFA). ES+APCI MS m/z 513.2 [M+H]⁺.

[0868]

EXAMPLE 232

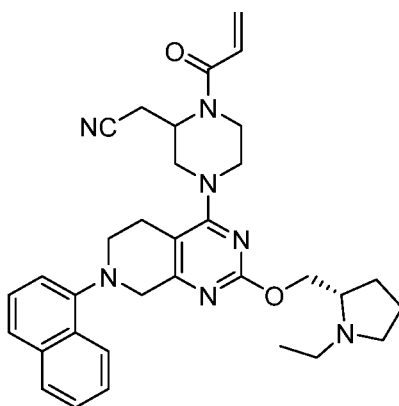
1-(4-(7-(3-chloro-2-fluoro-5-hydroxyphenyl)-2-(3-morpholinopropoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one



[0869] The title compound was prepared according to **Example 1** Step C-F substituting Intermediate 25 for benzyl 4-(5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate and 1-bromo-3-chloro-2-fluoro-5-(methoxymethoxy)benzene for 1-bromo-3-(methoxymethoxy)naphthalene in Step C. ES+APCI MS m/z 561.2 $[M]^+$.

EXAMPLE 233

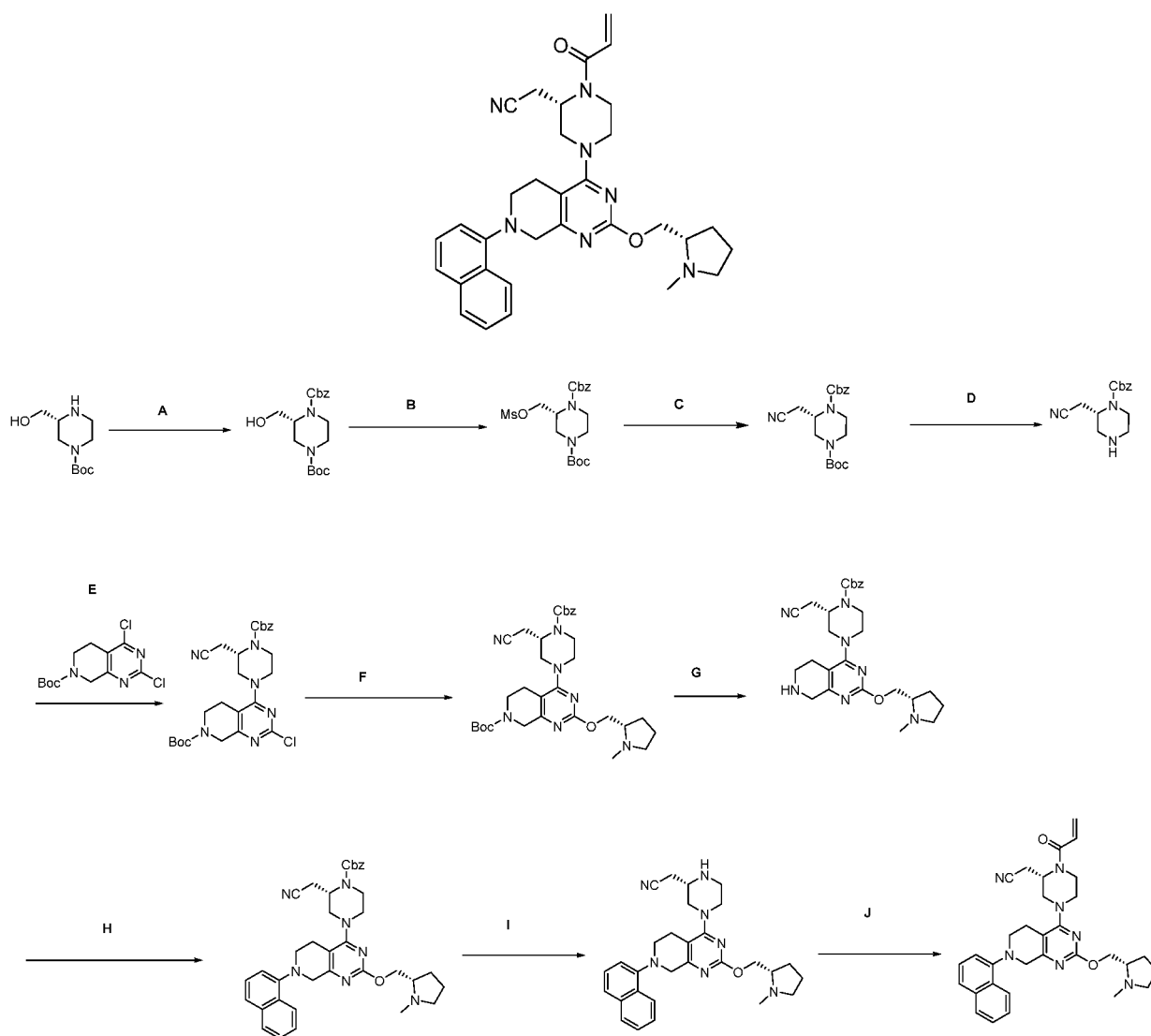
2-(1-acryloyl-4-(2-(((S)-1-ethylpyrrolidin-2-yl)methoxy))-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile



[0870] 2-(1-acryloyl-4-(2-(((S)-1-ethylpyrrolidin-2-yl)methoxy))-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile. This compound was prepared following **Example 147** substituting (S)-(1-ethylpyrrolidin-2-yl)methanol for N-Methyl-L-prolinol for [(2S)-1-methylpyrrolidin-2-yl]methanol in Step F. ES+APCI MS m/z 566.3 $[M+H]^+$.

EXAMPLE 234

2-((S)-1-acryloyl-4-(2-(((S)-1-methylpyrrolidin-2-yl)methoxy))-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile



[0871] Step A: 1-Benzyl 4-(tert-butyl) (R)-2-(hydroxymethyl)piperazine-1,4-dicarboxylate: To a stirred biphasic solution of (R)-1-Boc-3-hydroxymethylpiperazine (5.00 g, 23.1 mmol) and NaHCO_3 (5.83 g, 69.4 mmol) in ethyl acetate (46.2 ml) and water (46.2 ml) at 0°C was added benzyl chloroformate (4.95 ml, 34.7 mmol) dropwise. The reaction mixture was stirred at ambient temperature overnight. The reaction mixture was diluted with EtOAc (50.0 ml) and the organic layer was separated, dried (Na_2SO_4) and concentrated. The crude product was purified by flash chromatography eluting with 10-50% EtOAc/hexanes gradient to afford the title compound (7.62 g, 21.7 mmol, 94.1%). ESI MS m/z 251.1 $[\text{M}-\text{Boc}+\text{H}]^+$.

[0872] Step B. 1-Benzyl 4-(tert-butyl) (R)-2-(((methylsulfonyl)oxy)methyl)piperazine-1,4-dicarboxylate: To a solution of 1-benzyl 4-(tert-butyl) (R)-2-(hydroxymethyl)piperazine-1,4-

dicarboxylate (1.69 g, 4.83 mmol) and triethylamine (1.01 ml, 7.25 mmol) in CH₂Cl₂ (32.2 ml) at 0°C was added dropwise MsCl (0.561 ml, 7.25 mmol) neat and the resulting mixture was stirred at RT for 10 min. The reaction mixture was poured into a separatory funnel, diluted with ethyl acetate, then washed sequentially with 1N HCl, water, NaHCO₃ (sat.), and brine to afford the title compound (1.9 g, ~100%, used as crude material in next step). **ESI MS** m/z 329.1 [M-Boc+H]⁺.

[0873] Step C. 1-Benzyl 4-(tert-butyl) (S)-2-(cyanomethyl)piperazine-1,4-dicarboxylate: A solution of 1-benzyl 4-(tert-butyl) (R)-2-(((methylsulfonyl)oxy)methyl)piperazine-1,4-dicarboxylate (2.10 g, 4.90 mmol), sodium cyanide (0.480 g, 9.80 mmol) in DMA (49.0 ml) was heated at 55°C for 1 day. The reaction was followed by HPLC (15 min method). The mixture was partitioned between EtOAc/brine, and the organic layer was washed with brine (3x), dried over MgSO₄ and concentrated. The residue was purified by flash chromatography eluting with 0-100% EtOAc/hexanes gradient to afford the title compound (1.40 g, 3.90 mmol, 79.5%). Aqueous layers were basified and disposed of in cyanide waste stream. **ESI MS** m/z 260.1 [M-Boc+H]⁺.

[0874] Step D. Benzyl (S)-2-(cyanomethyl)piperazine-1-carboxylate hydrochloride: 1-Benzyl 4-(tert-butyl) (S)-2-(cyanomethyl)piperazine-1,4-dicarboxylate (5.32 g, 14.8 mmol) was placed in CH₂Cl₂ (25 mL) and HCl (4.0 N in dioxane, 18.5 ml, 74.0 mmol) was added and the reaction was stirred at ambient temperature for 1d. The reaction mixture was concentrated to afford the title compound (4.3 g, 99%). **ESI MS** m/z 260.1 [M+H]⁺.

[0875] Step E. tert-Butyl (S)-4-(4-((benzyloxy)carbonyl)-3-(cyanomethyl)piperazin-1-yl)-2-chloro-5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate: A solution of benzyl (S)-2-(cyanomethyl)piperazine-1-carboxylate (1.01 g, 3.89 mmol), tert-butyl 2,4-dichloro-5,6-dihydropyrido[3,4-d]pyrimidine-7(8H)-carboxylate (1.18 g, 3.89 mmol) and DIEA (1.36 ml, 7.79 mmol) in DMSO (19.5 ml) was heated at 50 °C for 1 day. The reaction mixture was partitioned between ethyl acetate and brine and the organics separated. The organic phase was washed with brine (3x), dried over MgSO₄ and concentrated to afford the title compound (1.63 g, 3.09 mmol, 79.4%). **ESI MS** m/z 527.2 [M+H]⁺.

[0876] Step F. tert-butyl 4-(((S)-4-((benzyloxy)carbonyl)-3-(cyanomethyl)piperazin-1-yl)-2-(((S)-1-methylpyrrolidin-2-yl)methoxy))-5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate: In 250 mL heavy-wall round bottom flask with a PTFE screw cap was added a solution of tert-butyl (S)-4-(4-((benzyloxy)carbonyl)-3-(cyanomethyl)piperazin-1-yl)-2-chloro-5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate (1.64 g, 3.11 mmol) in dioxane (31.1 ml) and the mixture was sparged with argon. To the mixture was added sequentially (S)-(1-methylpyrrolidin-2-yl)methanol (1.08 g, 9.34 mmol), Cs₂CO₃ (3.04 g, 9.34 mmol) and Ruphos-Pd Gen3 catalyst (0.260 g, 0.311 mmol) under argon and sparged for an additional 5 min. The reaction mixture was capped and heated at 100°C for 1 day. The reaction mixture was diluted with ethyl acetate and the organics washed with brine (2x). The organic layer was dried over MgSO₄ and concentrated to give a residue that was purified by flash chromatography eluting with 0-20% (MeOH + 2% NH₄OH) in DCM to afford the title compound (1.42 g, 2.34 mmol, 75.3%). ESI MS m/z 606.3 [M+H]⁺.

[0877] Step G. Benzyl (S)-2-(cyanomethyl)-4-(2-(((S)-1-methylpyrrolidin-2-yl)methoxy))-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate bis-trifluoroacetate salt: A solution of tert-butyl 4-(((S)-4-((benzyloxy)carbonyl)-3-(cyanomethyl)piperazin-1-yl)-2-(((S)-1-methylpyrrolidin-2-yl)methoxy))-5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate (38 mg, 0.063 mmol) in CH₂Cl₂ (627 µl) and TFA (242 µl, 3.1 mmol) was stirred at room temperature for 1 day. The reaction mixture was concentrated and used as bis-TFA salt in the next reaction (46 mg, 0.063 mmol, 100%). ESI MS m/z 506.3 [M+H]⁺.

[0878] Step H. Benzyl (S)-2-(cyanomethyl)-4-(2-(((S)-1-methylpyrrolidin-2-yl)methoxy))-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate: A suspension of benzyl (S)-2-(cyanomethyl)-4-(2-(((S)-1-methylpyrrolidin-2-yl)methoxy))-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate bistrifluoroacetate salt (46 mg, 0.063 mmol), 1-bromonaphthalene (39.3 mg, 0.190 mmol) and Cs₂CO₃ (61.9 mg, 0.190 mmol) in dioxane (633 µl) was sparged with argon for 5 min. To this mixture was added Ruphos Pd Gen 3 (5.29 mg, 0.006 mmol) and the resulting suspension was sparged for an additional 1 minute with argon. The vial was capped and heated at 100°C for 2h. The reaction mixture was partitioned between EtOAc and water and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were dried over MgSO₄ and concentrated. The residue was purified by

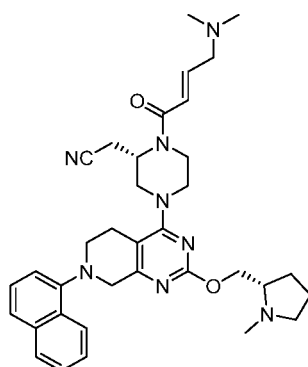
flash chromatography eluting with 5% MeOH/1%NH₄OH/CH₂Cl₂ isocratic to afford the title compound (31.9 mg, 0.050 mmol, 79.8%). **ESI MS** m/z 632.3 [M+H]⁺.

[0879] Step I. 2-((S)-4-(2-(((S)-1-Methylpyrrolidin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile: To a solution of benzyl (S)-2-(cyanomethyl)-4-(2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (31 mg, 0.049 mmol) in methanol (981 μ l) and THF (981 μ l) sparged with nitrogen was added Pd/C (10.4 mg, 0.00491 mmol) and the mixture was stirred under balloon pressure atmosphere of H₂ for 1 day. The reaction mixture was filtered through a PTFE syringe filter (25mm) and the filtrate was concentrated to afford the title compound (23.4 mg, 0.047 mmol, 95.8%). **ESI MS** m/z 498.3 [M+H]⁺.

[0880] Step J. 2-((S)-1-Acryloyl-4-(2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile: To a solution of 2-(((S)-4-(2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile (23.4 mg, 0.047 mmol) in CH₂Cl₂ (470 μ l) was added DIEA (41.1 μ l, 0.235 mmol) then acryloyl chloride (12 μ l, 0.141 mmol). The resulting mixture was stirred at ambient temperature for 15 minutes. The reaction mixture was partitioned between EtOAc and 2N K₂CO₃ and brine. The aqueous layer was extracted with EtOAc (2x). The combined organic layers were dried over MgSO₄ and concentrated. The residue was purified by flash chromatography eluting with 5% MeOH / 1% NH₄OH in CH₂Cl₂ to afford the title compound (19.2 mg, 0.035 mmol, 74.0%). **ESI MS** m/z 552.3 [M+H]⁺.

EXAMPLE 235

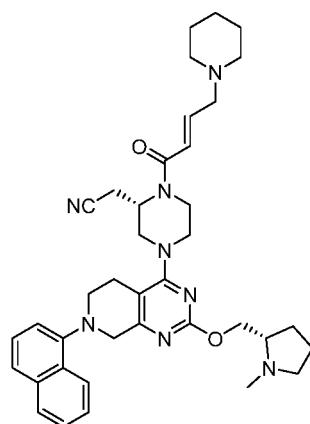
2-((S)-1-((E)-4-(dimethylamino)but-2-enoyl)-4-(2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile



[0881] Step A. 2-((S)-1-((E)-4-(dimethylamino)but-2-enoyl)-4-(2-(((S)-1-methylpyrrolidin-2-yl)methoxy))-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile: To a solution of 2-((S)-4-(2-(((S)-1-methylpyrrolidin-2-yl)methoxy))-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile (25 mg, 0.0502 mmol) from **Example 234** Step I, (2E)-4-(dimethylamino)but-2-enoic acid (13.0 mg, 0.100 mmol), DIEA (43.9 μ l, 0.251 mmol) in CH_2Cl_2 (502 μ l) was added HATU (28.7 mg, 0.0754 mmol) and the resulting mixture was stirred at ambient temperature for 1 hour. The reaction mixture was partitioned between EtOAc and brine. The aqueous layer was extracted with EtOAc (2x). The combined organic layers were dried over MgSO_4 and concentrated. The residue was purified by preparative-C18 eluting with 5-95% ACN/ H_2O + 0.1% TFA. The desired fractions were partitioned between EA/2M K_2CO_3 . The aqueous was extracted with EtOAc (2x). The combined organic layers were dried over MgSO_4 and concentrated to afford the title compound (19.0 mg, 0.031 mmol, 62.1%). **ESI MS** m/z 609.4 $[\text{M}+\text{H}]^+$.

EXAMPLE 236

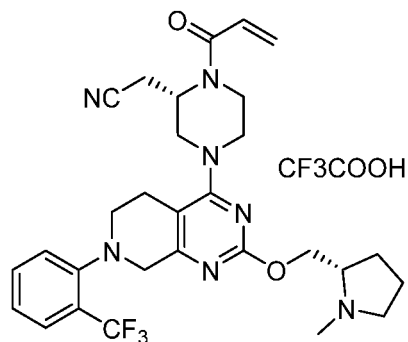
2-((S)-4-(2-(((S)-1-methylpyrrolidin-2-yl)methoxy))-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)-1-(E-4-(piperidin-1-yl)but-2-enoyl)piperazin-2-yl)acetonitrile



[0882] Step A. 2-((S)-4-(2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)-1-(E-4-(piperidin-1-yl)but-2-enoyl)piperazin-2-yl)acetonitrile was prepared according to **Example 235**, substituting (2E)-4-(1-piperidinyl)-2-butenic acid HCl salt, to afford the title compound (30 mg, 0.046 mmol, 92.0%). **ESI MS** m/z 649.3 $[M+H]^+$.

EXAMPLE 237

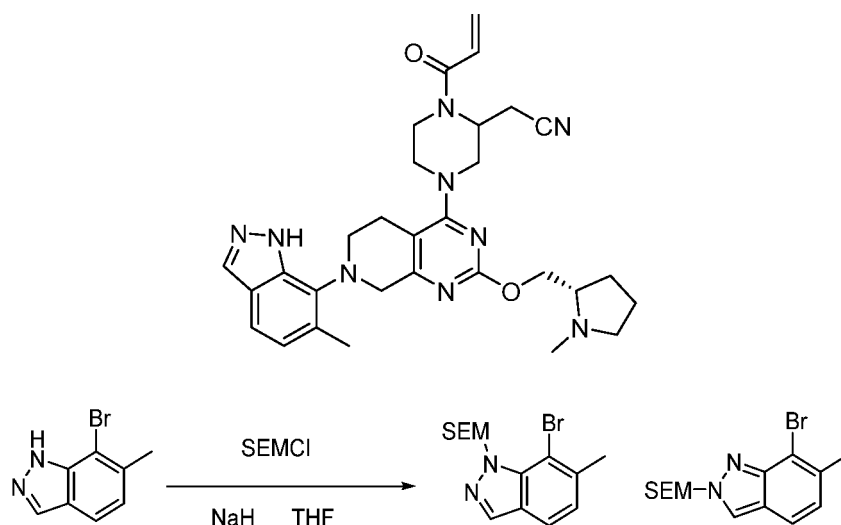
2-((S)-1-acryloyl-4-(2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-7-(2-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile 2,2,2-trifluoroacetate



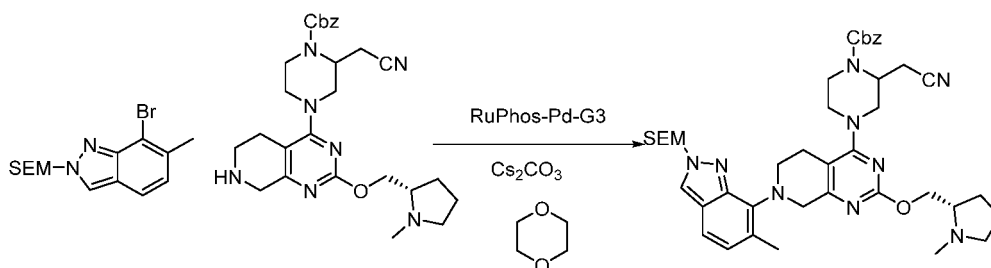
[0883] Synthesized according to **Example 234** substituting 1-bromo-2-(trifluoromethyl)benzene for 1-bromonaphthalene. **ES+APCI MS** m/z 570.3 $[M+H]^+$.

EXAMPLE 238

2-(1-acryloyl-4-(7-(6-methyl-1H-indazol-7-yl)-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile

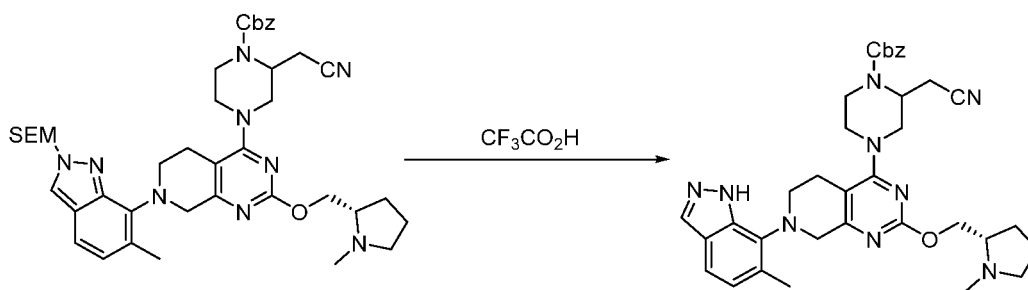


[0884] Step A: 7-bromo-6-methyl-2-((2-(trimethylsilyl)ethoxy)methyl)-2H-indazole. A solution of 7-bromo-6-methyl-1H-indazole (200 mg, 0.948 mmol) in tetrahydrofuran (2 ml, 0.948 mmol) was cooled with stirring in an ice bath. Sodium hydride (45.5 mg, 1.14 mmol) was added portionwise to the mixture and the reaction was stirred at 0°C for 1 hour. (2-(chloromethoxy)ethyl)trimethylsilane (0.201 ml, 1.14 mmol) was next added and the reaction stirred for 2 hours while warming to room temperature. The mixture was divided between EtOAc (20 mL) and water (10 mL) and the layers separated. The organic layer was washed with water (2 x 10 mL), brine (10 mL), dried over Na₂SO₄ and evaporated in vacuo. The product was purified by chromatography on silica gel using 20 to 40% EtOAc/hexanes as eluent to give 7-bromo-6-methyl-2-((2-(trimethylsilyl)ethoxy)methyl)-2H-indazole (46 mg, 14%) along with isomer 7-bromo-6-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole (214 mg, 66%). ES+APCI MS *m/z* 341.1 [M]⁺.

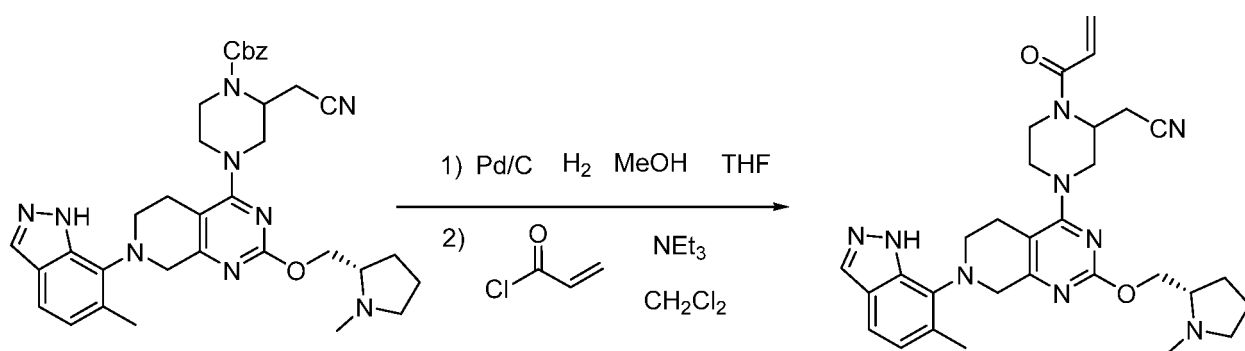


[0885] Step B: Benzyl 2-(cyanomethyl)-4-(7-(6-methyl-2-((2-(trimethylsilyl)ethoxy)methyl)-2H-indazol-7-yl)-2-(((S)-1-methylpyrrolidin-2-yl)methoxy))-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate: A mixture of benzyl 2-(cyanomethyl)-4-(2-(((S)-1-

methylpyrrolidin-2-yl)methoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (50 mg, 0.099 mmol), 7-bromo-6-methyl-2-((2-(trimethylsilyl)ethoxy)methyl)-2H-indazole (46 mg, 0.13 mmol), Cs₂CO₃ (97 mg, 0.30 mmol), Ruphos Pd G3 (83 mg, 0.099 mmol) and dioxane (1 mL) was purged with nitrogen and stirred at 70°C for 6 hours. The reaction mixture was cooled to room temperature and divided between EtOAc (20 mL) and water (10 mL) and the layers separated. The organic layer was washed with water (5 mL), brine (5 mL), dried over Na₂SO₄ and evaporated in vacuo. The product was purified by chromatography on silica gel, Redisep 24g, using 2 to 20% MeOH/DCM as eluent to give a colorless solid (50 mg, 66%). ES+APCI MS m/z 766.4 [M]⁺.



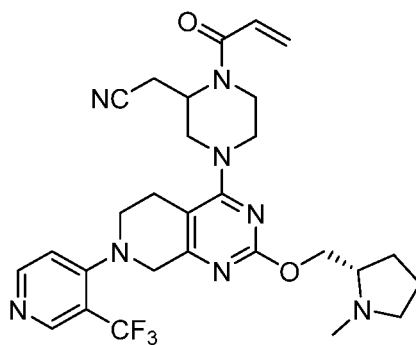
[0886] Step C: Benzyl 2-(cyanomethyl)-4-(7-(6-methyl-1H-indazol-7-yl)-2-(((S)-1-methylpyrrolidin-2-yl)methoxy))-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate: Neat benzyl 2-(cyanomethyl)-4-(7-(6-methyl-2-((2-(trimethylsilyl)ethoxy)methyl)-2H-indazol-7-yl)-2-(((S)-1-methylpyrrolidin-2-yl)methoxy))-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (10 mg, 0.0131 mmol) (10 mg, 0.0131 mmol) was dissolved in trifluoroacetic acid (1 mL, 13.1 mmol) and the yellow-brown solution was stirred at room temperature for 1.5 hours. The reaction mixture was poured into ethyl acetate (20 mL) and the organics washed carefully with 2M Na₂CO₃ (10 mL, 20 mmol), water (2 x 3 mL), brine (5 mL), dried over Na₂SO₄ and evaporated in vacuo to give a yellowish solid (8 mg, 96%). ES+APCI MS m/z 636.3 [M+H]⁺.



[0887] Step D: 2-(1-acryloyl-4-(7-(6-methyl-1H-indazol-7-yl)-2-(((S)-1-methylpyrrolidin-2-yl)methoxy))-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile: A stirred mixture of benzyl 2-(cyanomethyl)-4-(7-(6-methyl-1H-indazol-7-yl)-2-(((S)-1-methylpyrrolidin-2-yl)methoxy))-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (16 mg, 0.02517 mmol), methanol (1.5 mL, 0.02517 mmol), tetrahydrofuran (1.815 mg, 0.02517 mmol) and palladium on carbon (10 mg, 5%, *Degussa type E101 NO/W*) was degassed and stirred under hydrogen atmosphere for 1 hour. The mixture was filtered through Celite (2 mL) and the celite washed with THF (3 x 3 mL). The combined organics were concentrated in vacuo to ~0.5 mL, dissolved in DCM (5 mL), cooled to -30°C with stirring in an EtOH-H₂O-CO₂ bath. Triethylamine (0.02 mL, 5 eq.) was next added followed by acryloyl chloride (0.006134 mL, 0.07550 mmol) and the reaction mixture was stirred 1 min at -30°C. The reaction was quenched with NH₄OH (0.03 mL) and concentrated in vacuo. The residue was divided between 1M NaHCO₃ (3 mL) and EtOAc (15 mL) and the layers separated. The organic layer was washed with water (3 mL), brine (3 mL), dried over Na₂SO₄ and evaporated in vacuo. The product was purified by chromatography on silica gel, Redisep 12g, using 10 to 20% MeOH/DCM + 0.2% NH₄OH as eluent to give a colorless solid (5.96 mg, 43%). ES+APCI MS m/z 556.3 [M+H]⁺.

EXAMPLE 239

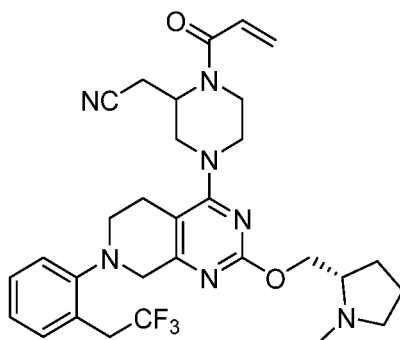
2-(1-acryloyl-4-(2-(((S)-1-methylpyrrolidin-2-yl)methoxy))-7-(3-(trifluoromethyl)pyridin-4-yl))-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile



[0888] Synthesized according to **Example 210**, Steps E-G using 4-Bromo-3-(trifluoromethyl)pyridine hydrobromide in place of 1-bromo-2-(trifluoromethyl)benzene in Step E. ES+APCI MS m/z 571.3 $[M+H]^+$.

EXAMPLE 240

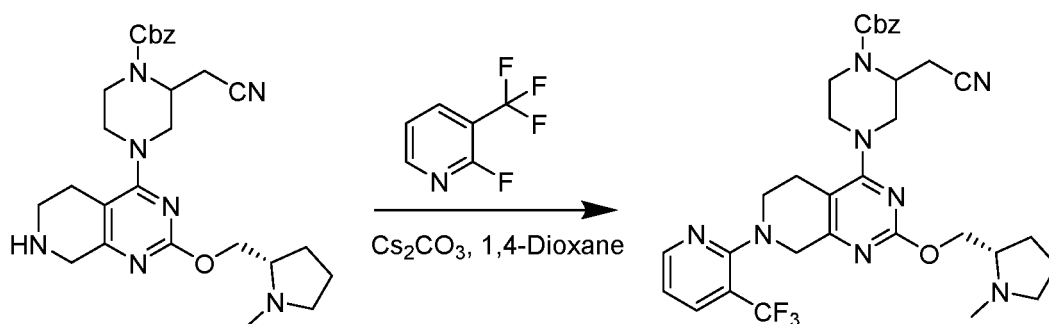
2-(1-acryloyl-4-(2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-7-(2-(2,2,2-trifluoroethyl)phenyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile



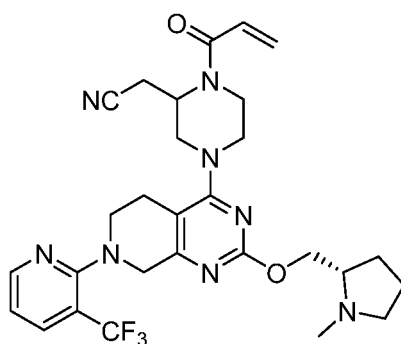
[0889] Synthesized according to **Example 210**, Steps E-G using 1-bromo-2-(2,2,2-trifluoroethyl)benzene in place of 1-bromo-2-(trifluoromethyl)benzene in Step E. ES+APCI MS m/z 584.3 $[M+H]^+$.

EXAMPLE 241

benzyl 2-(cyanomethyl)-4-(2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-7-(3-(trifluoromethyl)pyridin-2-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate



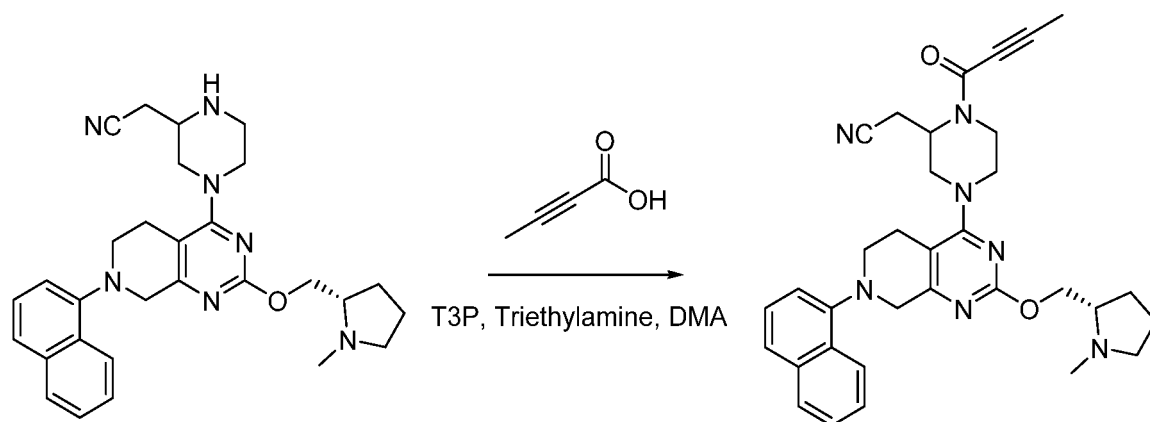
[0890] Step A: In a vial, benzyl 2-(cyanomethyl)-4-(2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (100 mg, 0.198 mmol) was dissolved in dioxane (98.9 μ l, 0.198 mmol) and treated with cesium carbonate (129 mg, 0.396 mmol), and 2-Fluoro-3-(trifluoromethyl)pyridine (163 mg, 0.989 mmol). The tube was then capped and heated to 90°C for 12hr. Reaction was filtered through GF/F paper and concentrated. The residue was purified by silica chromatography (0-12% MeOH in DCM).



[0891] Step B: Synthesized according to **Example 210**, Steps F-G using benzyl 2-(cyanomethyl)-4-(2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-7-(3-(trifluoromethyl)pyridin-2-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate in place of benzyl 2-(cyanomethyl)-4-(2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-7-(2-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate in Step F. ES+APCI MS m/z 571.3 $[M+H]^+$.

EXAMPLE 242

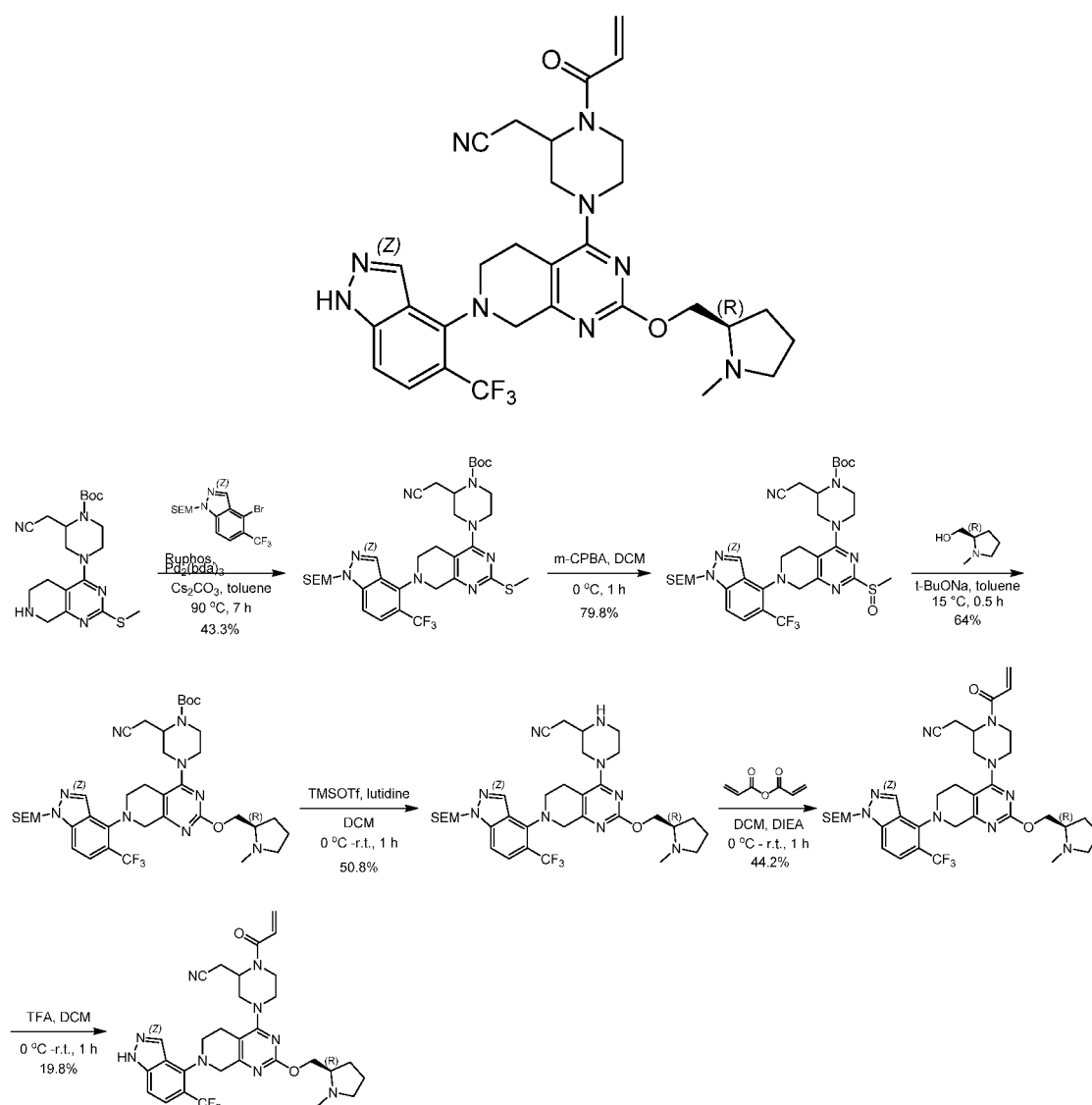
2-(1-(but-2-ynoyl)-4-(2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile



[0892] At 0°C, to a 25 mL RBF containing N,N-dimethylformamide (603 μ L, 0.06 mmol) was added 2-(4-(2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile (30 mg, 0.06 mmol) and triethylamine (12.2 mg, 0.12 mmol). The reaction mixture was vigorously stirred while 2-Butynoic acid (6.08 mg, 0.07 mmol) was added in one portion. Next, 1-Propanephosphonic acid cyclic anhydride (26.9 μ L, 0.09 mmol) was added to the stirring mixture. The reaction was allowed to stir for 2h at 0°C. Water was added and the reaction extracted with EtOAc (2x 25 mL). The organic layers were washed with saturated LiCl, NaCl, and water (10 mL each wash). Dried and concentrated to a solid that was purified by reverse phase prep HPLC (5-95% ACN:H₂O, with 0.1% TFA) to provide the title compound.

EXAMPLE 243

2-[4-[2-[[2-(2R)-1-methylpyrrolidin-2-yl]methoxy]-7-[5-(trifluoromethyl)-1H-indazol-4-yl]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile



[0893] Step A: *tert*-butyl 2-(cyanomethyl)-4-[2-methylsulfanylmethyl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl piperazine-1-carboxylate: To a solution of *tert*-butyl 2-(cyanomethyl)-4-(2-methylsulfanylmethyl)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl piperazine-1-carboxylate (1.05 g, 2.60 mmol), 2-[[4-bromo-5-(trifluoromethyl)indazol-1-yl]methoxy]ethyl-trimethyl-silane (1.13 g, 2.86 mmol), RuPhos (484 mg, 1.04 mmol) and Cs₂CO₃ (2.11 g, 6.49 mmol) in toluene (20 mL) was added Pd₂(dba)₃ (475 mg, 519 μmol) under N₂, the suspension was degassed under vacuum and purged with N₂ several times. The mixture was warmed to 90 °C and stirred at 90 °C for 7 hours. The reaction mixture was filtered and the filter cake was washed with EtOAc (3 × 20 mL). The combined organic layers were concentrated under vacuum. The residue was purified by silica gel

chromatography (PE: EA from 30:1 to 4:1) and then by reversed phase flash column (ACN: 100%) to give *tert*-butyl 2-(cyanomethyl)-4-[2-methylsulfanyl-7-[5-(trifluoromethyl)-1-(2-trimethylsilylethoxymethyl)indazol-4-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (850 mg, 1.12 mmol, 43.3 % yield, 95.0 % purity) as a yellow solid. ESI MS *m/z* 719.5 [M+H]⁺.

[0894] Step B: *tert*-butyl 2-(cyanomethyl)-4-[2-methylsulfinyl-7-[5-(trifluoromethyl)-1-(2-trimethylsilylethoxymethyl)indazol-4-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate: To a solution of *tert*-butyl 2-(cyanomethyl)-4-[2-methylsulfanyl-7-[5-(trifluoromethyl)-1-(2-trimethylsilylethoxymethyl)indazol-4-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (850 mg, 1.18 mmol) in DCM (17 mL) was added *m*-CPBA (240 mg, 1.18 mmol, 85.0 % purity) at 0 °C and stirred at 0 °C for 1 hour. The reaction mixture was quenched by saturated Na₂S₂O₃ (15 mL) at 0 °C and separated, then diluted with water (10 mL) and extracted with EtOAc (30 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by reversed phase flash column (ACN/Water (0.1% FA) = 80 %) to give *tert*-butyl 2-(cyanomethyl)-4-[2-methylsulfinyl-7-[5-(trifluoromethyl)-1-(2-trimethylsilylethoxymethyl)indazol-4-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (730 mg, 944 μmol, 79.8 % yield, 95.0 % purity) as yellow solid. ESI MS *m/z* 735.5 [M+H]⁺.

[0895] Step C: *tert*-butyl 2-(cyanomethyl)-4-[2-[(2*R*)-1-methylpyrrolidin-2-yl]methoxy]-7-[5-(trifluoromethyl)-1-(2-trimethylsilylethoxymethyl)indazol-4-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate: To a solution of *tert*-butyl 2-(cyanomethyl)-4-[2-methylsulfinyl-7-[5-(trifluoromethyl)-1-(2-trimethylsilylethoxymethyl)indazol-4-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (300 mg, 408 μmol) and [(2*R*)-1-methylpyrrolidin-2-yl]methanol (94.0 mg, 816 μmol) in toluene (6 mL) was added *t*-BuONa (58.8 mg, 612 μmol) at 15 °C and stirred at 15 °C for 0.5 hour. To the mixture was added EtOAc (15 mL) and water (5 mL), then extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by reversed phase flash column (ACN/Water (0.1% FA) = 54 %) to give *tert*-butyl 2-(cyanomethyl)-4-[2-[(2*R*)-1-methylpyrrolidin-2-yl]methoxy]-7-[5-(trifluoromethyl)-

1-(2-trimethylsilylethoxymethyl)indazol-4-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (216 mg, 261 μ mol, 64.0 % yield, 95.0 % purity) as brown solid. ESI MS m/z 786.6[M+H]⁺.

[0896] Step D: 2-[4-[2-[[*(2R)*-1-methylpyrrolidin-2-yl]methoxy]-7-[5-(trifluoromethyl)-1-(2-trimethylsilylethoxymethyl)indazol-4-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-2-yl]acetonitrile: To a solution of *tert*-butyl 2-(cyanomethyl)-4-[2-[[*(2R)*-1-methylpyrrolidin-2-yl]methoxy]-7-[5-(trifluoromethyl)-1-(2-trimethylsilylethoxymethyl)indazol-4-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (190 mg, 242 μ mol) and 2,6-dimethylpyridine (311 mg, 2.90 mmol, 338 μ L) in DCM (4 mL) was added TMSOTf (645 mg, 2.90 mmol, 524 μ L) at 0 °C and stirred at 20 °C for 1 hour. The reaction mixture was quenched by MeOH (1 mL), then concentrated under vacuum. The residue was purified by reversed phase flash column (ACN/Water (0.1% FA) =40 %). 2-[4-[2-[[*(2R)*-1-methylpyrrolidin-2-yl]methoxy]-7-[5-(trifluoromethyl)-1-(2-trimethylsilylethoxymethyl)indazol-4-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-2-yl]acetonitrile (85 mg, 123 μ mol, 50.8 % yield, 99.0 % purity) was obtained as a white solid. ESI MS m/z 686.5 [M+H]⁺.

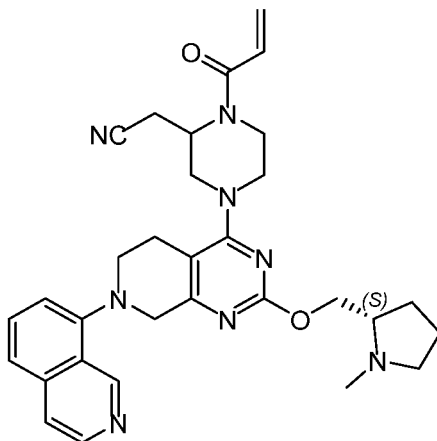
[0897] Step E: 2-[4-[2-[[*(2R)*-1-methylpyrrolidin-2-yl]methoxy]-7-[5-(trifluoromethyl)-1-(2-trimethylsilylethoxymethyl)indazol-4-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile To a solution of 2-[4-[2-[[*(2R)*-1-methylpyrrolidin-2-yl]methoxy]-7-[5-(trifluoromethyl)-1-(2-trimethylsilylethoxymethyl)indazol-4-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-2-yl]acetonitrile (85.0 mg, 124 μ mol), DIEA (96.1 mg, 744 μ mol, 130 μ L) in DCM (2 mL) was added prop-2-enoyl prop-2-enoate (23.4 mg, 186 μ mol) at 0 °C and the mixture stirred at 20 °C for 1 hour. The reaction mixture was quenched by water (2 mL). The resulting mixture was extracted with DCM (3 $\times$ 5 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by reversed phase flash column (ACN/Water (0.1% FA) =48 %) to give 2-[4-[2-[[*(2R)*-1-methylpyrrolidin-2-yl]methoxy]-7-[5-(trifluoromethyl)-1-(2-trimethylsilylethoxymethyl)indazol-4-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile (45 mg, 54.7 μ mol, 44.2 % yield, 90.0 % purity) as white solid. ¹H NMR (400 MHz, chloroform-*d*) δ = 8.16 (s, 1H), 7.71 (d, *J*=8.8 Hz, 1H), 7.52 (d, *J*=8.8 Hz, 1H), 6.59 (br s, 1H), 6.45 - 6.36 (m, 1H), 5.84 (br d, *J*=10.4 Hz, 1H), 5.76 (s, 2H), 5.12 (s,

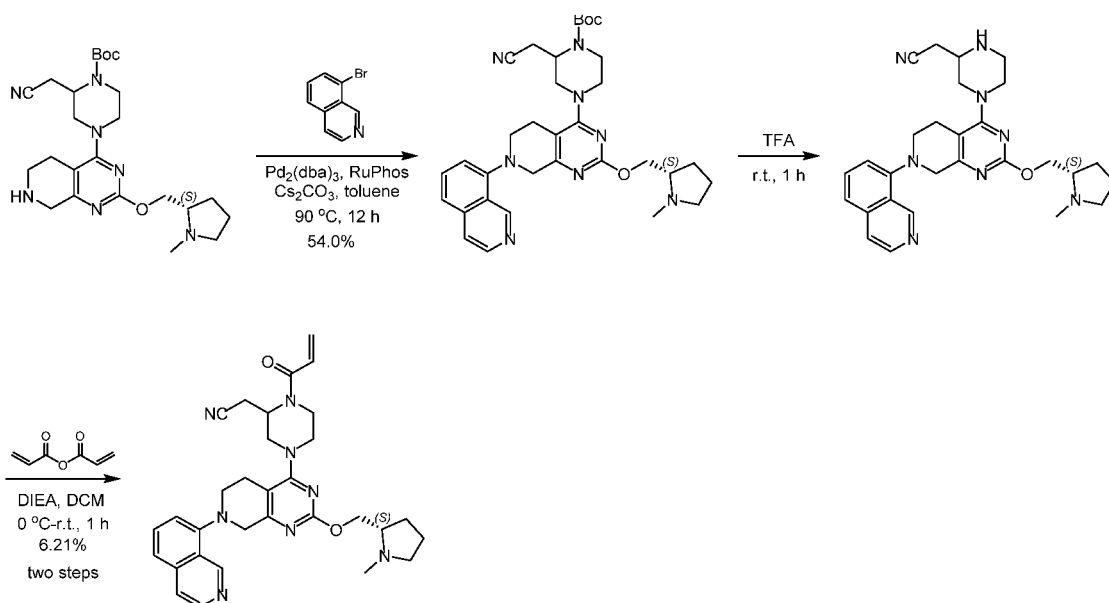
1H), 4.44 - 4.28 (m, 3H), 4.21 - 4.08 (m, 2H), 3.98 (br d, $J=12.0$ Hz, 1H), 3.63 - 3.54 (m, 2H), 3.48 - 3.39 (m, 2H), 3.32 (br s, 1H), 3.10 (br s, 2H), 2.99 - 2.86 (m, 2H), 2.80 (br s, 2H), 2.73 - 2.58 (m, 2H), 2.49 (s, 3H), 2.28 (br s, 1H), 2.05 (br s, 1H), 1.77 (br s, 4H), 0.94 - 0.88 (m, 2H), - 0.04 (s, 9H).

[0898] Step F: 2-[4-[2-[[*(2R)*-1-methylpyrrolidin-2-yl]methoxy]-7-[5-(trifluoromethyl)-1*H*-indazol-4-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile To a solution of 2-[4-[2-[[*(2R)*-1-methylpyrrolidin-2-yl]methoxy]-7-[5-(trifluoromethyl)-1-(2-trimethylsilylethoxymethyl)indazol-4-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile (45 mg, 60.8 μ mol) in DCM (0.15 mL) was added TFA (208 mg, 1.82 mmol, 135 μ L) and the mixture stirred at 20 °C for 1 hour. The reaction mixture was basified by saturated NaHCO_3 (2 mL) to pH=8. The resulting mixture was extracted with DCM: MeOH (10:1) (3×5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered and concentrated under vacuum. The residue was purified by prep-HPLC (column: Phenomenex Synergi C18 150*30mm*4 μ m; mobile phase: [water(0.225%FA)-ACN]; B%: 10%-40%, 10.5min) to give 2-[4-[2-[[*(2R)*-1-methylpyrrolidin-2-yl]methoxy]-7-[5-(trifluoromethyl)-1*H*-indazol-4-yl]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile (8.2 mg, 12.0 μ mol, 19.8 % yield, 96.2 % purity, FA) as yellow oil. ESI MS m/z 610.4 $[\text{M}+\text{H}]^+$.

EXAMPLE 244

2-[4-[7-(8-isoquinolyl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile





[0899] Step A: *tert*-butyl 2-(cyanomethyl)-4-[7-(8-isoquinolyl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate: To a solution of *tert*-butyl 2-(cyanomethyl)-4-[2-[(1-methylpyrrolidin-2-yl)methoxy]-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (210 mg, 445 μ mol), 8-bromoisoquinoline (185 mg, 891 μ mol), RuPhos (41.6 mg, 89.1 μ mol) and Cs_2CO_3 (435 mg, 1.34 mmol) in toluene (4.5 mL) was added $\text{Pd}_2(\text{dba})_3$ (40.8 mg, 44.5 μ mol) under N_2 . The suspension was degassed under vacuum and purged with N_2 several times. The mixture was stirred under N_2 at 90 °C for 12 hours. The mixture was filtered and the filter cake was washed with EtOAc (3×10 mL). The combined organic layers were concentrated under vacuum. The residue was purified by reversed phase flash column (ACN/Water (0.1% FA) = 20 %) to give *tert*-butyl 2-(cyanomethyl)-4-[7-(8-isoquinolyl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (160 mg, 240 μ mol, 54.0 % yield, 90.0 % purity) as brown solid. ESI MS m/z 599.4 $[\text{M}+\text{H}]^+$.

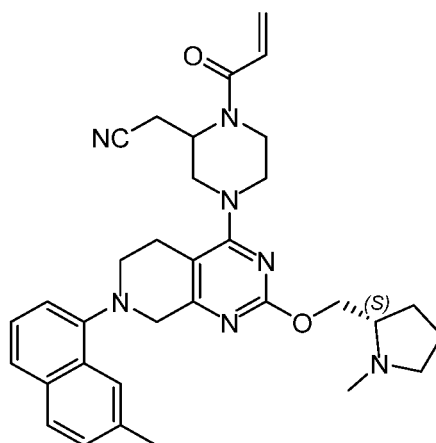
[0900] Step B: 2-[4-[7-(8-isoquinolyl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-2-yl]acetonitrile: A solution of *tert*-butyl 2-(cyanomethyl)-4-[7-(8-isoquinolyl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (190 mg, 317 μ mol) and TFA (724 mg, 6.35 mmol, 470 μ L) was stirred at 20 °C for 1 hour. The reaction mixture was concentrated under vacuum to give 2-[4-[7-(8-isoquinolyl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-

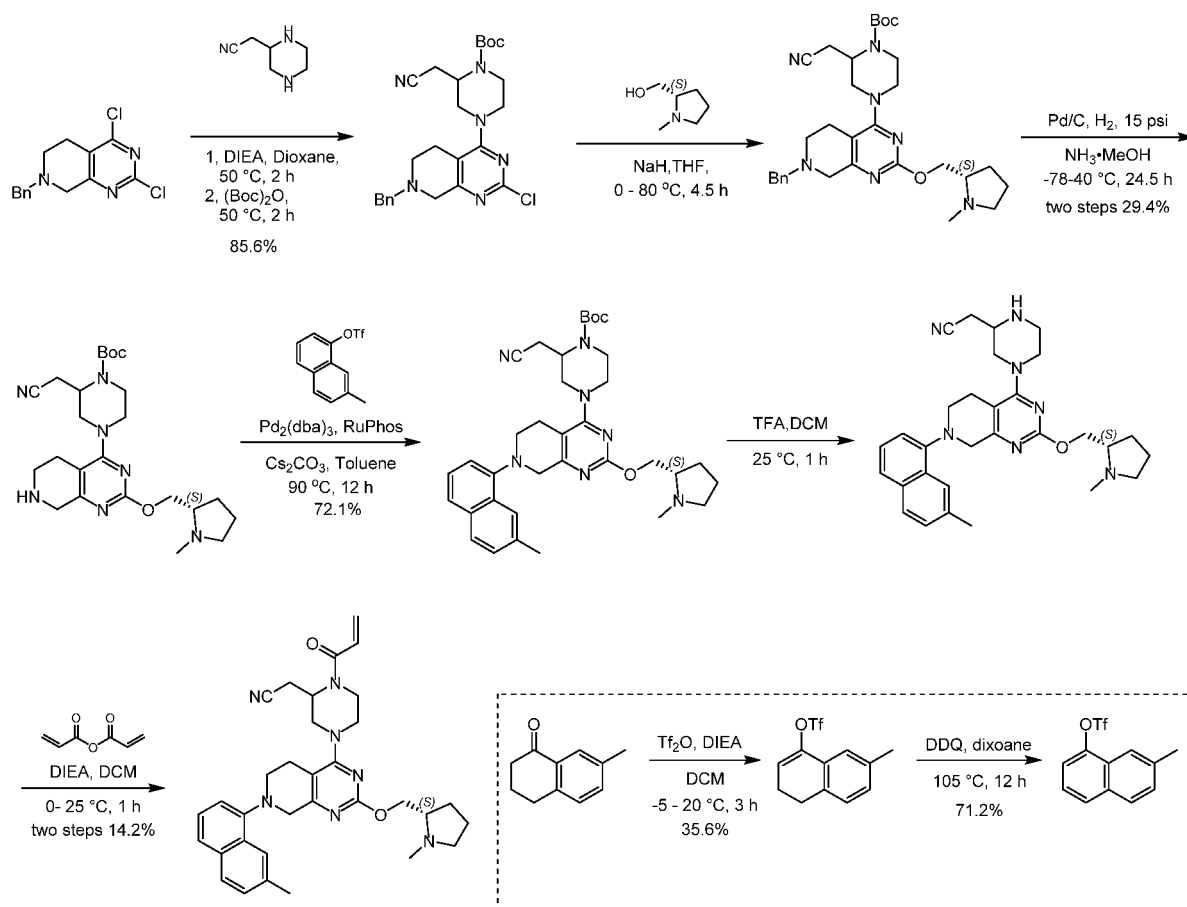
5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-2-yl]acetonitrile (230 mg, crude, 2TFA) as a brown oil.

[0901] Step C: 2-[4-[7-(8-isoquinolyl)-2-[[*(2S)*]-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile: To a solution of 2-[4-[7-(8-isoquinolyl)-2-[[*(2S)*]-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-2-yl]acetonitrile (230 mg, 316 μmol , 2TFA) and DIEA (409 mg, 3.17 mmol, 551 μL) in DCM (5 mL) was added prop-2-enoyl prop-2-enoate (47.9 mg, 380 μmol) at 0 °C, then the mixture was stirred at 20 °C for 1 hour. Water (5 mL) was added to the mixture. The resulting mixture was extracted with DCM (3 $\times$ 5 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by prep-HPLC (column: Phenomenex Synergi C18 150*25*10 μm ; mobile phase: [water(0.225%FA)-ACN];B%: 1%-20%,10min) to give 2-[4-[7-(8-isoquinolyl)-2-[[*(2S)*]-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile (12.5 mg, 19.7 μmol , 6.23 % yield, 94.5 % purity, FA) as yellow solid. ESI MS m/z 553.2 [M+H]⁺.

EXAMPLE 245

2-[4-[7-(7-methyl-1-naphthyl)-2-[[*(2S)*]-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile





[0902] Step A: (7-methyl-3,4-dihydronaphthalen-1-yl) trifluoromethanesulfonate: To a solution of 7-methyltetralin-1-one (2.00 g, 12.5 mmol) and DIPEA (4.84 g, 37.5 mmol, 6.52 mL) in DCM (30 mL) was added Tf₂O (5.28 g, 18.7 mmol, 3.09 mL) dropwise at -5 °C. The mixture was stirred at 20 °C for 3 hours. Upon completion, the mixture was concentrated under vacuum. The residue was purified by silica gel chromatography (PE/EA 1/0 to 100/1) to give (7-methyl-3,4-dihydronaphthalen-1-yl) trifluoromethanesulfonate (1.53 g, 4.45 mmol, 35.6 % yield, 85.0 % purity) as a yellow oil. ¹H NMR (400 MHz, chloroform-d) δ = 7.17 (s, 1H), 7.11 - 7.05 (m, 2H), 6.01 (t, *J* = 4.8 Hz, 1H), 2.83 (t, *J* = 8.0 Hz, 2H), 2.50 (dt, *J* = 4.8, 8.0 Hz, 2H), 2.36 (s, 3H).

[0903] Step B: (7-methyl-1-naphthyl) trifluoromethanesulfonate: A mixture of (7-methyl-3,4-dihydronaphthalen-1-yl)trifluoro methanesulfonate (1.40 g, 4.79 mmol) and DDQ (2.17 g, 9.58 mmol) in dioxane (28 mL) was stirred at 105 °C for 12 hours. Upon completion, the mixture was concentrated under vacuum. The residue was purified by silica gel chromatography (PE/EA 1/0 to 100/1) to give (7-methyl-1-naphthyl) trifluoromethanesulfonate (1.10 g, 3.41 mmol, 71.2 %

yield, 90.0 % purity) as a yellow oil. ^1H NMR (400 MHz, chloroform- d) δ = 7.87 - 7.79 (m, 3H), 7.49 - 7.38 (m, 3H), 2.59 (s, 3H).

[0904] Step C: *tert*-butyl 4-(7-benzyl-2-chloro-6,8-dihydro-5*H*-pyrido[3,4-*d*] pyrimidin-4-yl)-2-(cyanomethyl)piperazine-1-carboxylate: A mixture of 7-benzyl-2,4-dichloro-6,8-dihydro-5*H*-pyrido [3,4-*d*]pyrimidine (10 g, 34.0 mmol), 2-piperazin-2-ylacetonitrile (10.1 g, 51.0 mmol, 2 HCl) and DIEA (17.6 g, 136 mmol, 23.7 mL) in dioxane (100 mL) was stirred at 50 °C for 2 hours. Boc_2O (14.8 g, 68.0 mmol, 15.6 mL) was added and the mixture was stirred at 50 °C for 2 hours. The mixture was concentrated under vacuum and the residue was diluted with ethyl acetate (500 mL). The separated organic layer was washed with water (1×300 mL), brine (1×200 mL), dried over sodium sulfate, filtered and concentrated under vacuum. The residue was triturated with ethyl acetate (100 mL). The precipitate was filtered and the filtered cake was washed with ethyl acetate (50 mL) and dried under vacuum to give a gray solid. The filtrate was concentrated under vacuum. The residue was purified by column chromatography over silica gel (petroleum ether/ethyl acetate 100/1 to 1/2). The desired fractions were collected and concentrated under vacuum to give solid then combined with above solid to give *tert*-butyl 4-(7-benzyl-2-chloro-6,8-dihydro-5*H*-pyrido[3,4-*d*] pyrimidin-4-yl)-2-(cyanomethyl)piperazine-1-carboxylate (15 g, 29.10 mmol, 85.6% yield, 93.7% purity) as yellow solid. ESI MS m/z 483.1 $[\text{M}+\text{H}]^+$.

[0905] Step D: 4-[7-benzyl-2-[(1-methylpyrrolidin-2-yl)methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*] pyrimidin-4-yl]-2-(cyanomethyl)piperazine-1-carboxylate: To a solution of [(2*S*)-1-methylpyrrolidin-2-yl]methanol (1.19 g, 10.4 mmol, 1.23 mL, 2.5 eq) in THF (30.0 mL) was added NaH (331 mg, 8.28 mmol, 60 % purity in mineral oil, 2.00 eq) at 0 °C and the mixture was stirred at 0 °C for 0.5 h. *tert*-Butyl 4-(7-benzyl-2-chloro-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl)-2-(cyanomethyl)piperazine-1-carboxylate (2.00 g, 4.14 mmol, 1.00 eq) was added into the mixture and the mixture was stirred at 80 °C for 4 hours. The mixture was poured into ice water (100 mL) and extracted with ether acetate (3×150 mL). The organic layers were washed with saturated sodium chloride solution (1×200 mL), dried over Na_2SO_4 , filtered and concentrated under vacuum to give *tert*-butyl 4-[7-benzyl-2-[(1-methylpyrrolidin-2-yl)methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*] pyrimidin-4-yl]-2-(cyanomethyl)piperazine-1-carboxylate (2.86 g, crude) as a

black oil which was used in the next step without further purification. ESI MS m/z 562.3 $[M+H]^+$.

[0906] Step E: *tert*-butyl 2-(cyanomethyl)-4-[2-[(1-methylpyrrolidin-2-yl)methoxy]-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate: NH_3 was bubbled into methanol (70.0 mL) at $-78^\circ C$ for 30 minutes. *tert*-Butyl 4-[7-benzyl-2-[(1-methylpyrrolidin-2-yl)methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-2-(cyanomethyl)piperazine-1-carboxylate (2.00 g, crude) and Pd/C (0.20 g, 10% purity) were added into the mixture. The mixture was stirred at $40^\circ C$ for 24 hours under H_2 at 15 psi. The mixture was filtered and concentrated under vacuum. The residue was purified by reverse phase flash [water (FA, 0.1 %)/acetonitrile]. The desired fractions were adjusted to $pH > 7$ by saturated sodium bicarbonate solution (5.00 mL) and the aqueous layer extracted with ether acetate (3×100 mL). The combined organic layers were washed with brine (1×100 mL), dried over Na_2SO_4 , filtered and concentrated under vacuum to give *tert*-butyl 2-(cyanomethyl)-4-[2-[(1-methylpyrrolidin-2-yl)methoxy]-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (0.40 g, 845 μmol , two steps 29.4% yield) as a yellow solid. ESI MS m/z 472.2 $[M+H]^+$.

[0907] Step F: *tert*-butyl 2-(cyanomethyl)-4-[2-[(1-methylpyrrolidin-2-yl)methoxy]-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate: A solution of *tert*-butyl 2-(cyanomethyl)-4-[2-[(1-methylpyrrolidin-2-yl)methoxy]-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (185 mg, 392 μmol), (7-methyl-1-naphthyl) trifluoromethanesulfonate (159 mg, 549 μmol), $Pd_2(dba)_3$ (35.9 mg, 39.2 μmol), RuPhos (36.6 mg, 78.5 μmol) and Cs_2CO_3 (320 mg, 981 μmol) in toluene (30 mL) was de-gassed with N_2 and then heated to $90^\circ C$ for 12 hours under N_2 . Upon completion, the mixture was filtered and the filtrate was concentrated under vacuum. The residue was purified by reversed-phase flash [water(0.1% $NH_3 \cdot H_2O$)/acetonitrile] to give *tert*-butyl 2-(cyanomethyl)-4-[7-(7-methyl-1-naphthyl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (180 mg, 283 μmol , 72.1 % yield, 96.1 % purity) as a yellow solid. ESI MS m/z 612.6 $[M+H]^+$.

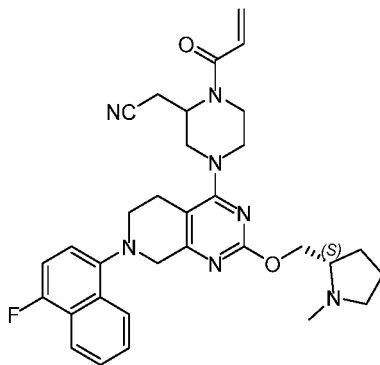
[0908] Step G: 2-[4-[7-(7-methyl-1-naphthyl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-2-yl]acetonitrile: A solution of *tert*-butyl 2-(cyanomethyl)-4-[7-(7-methyl-1-naphthyl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-

dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (180 mg, 294 μmol) in TFA (671 mg, 5.88 mmol, 436 μL) was stirred at 20 °C for 1 hour. Upon completion the mixture was concentrated under vacuum to give 2-[4-[7-(7-methyl-1-naphthyl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-2-yl]acetonitrile (0.37 g, crude, TFA) as a yellow oil which was used directly in the next step without further purification.

[0909] Step H: 2-[4-[7-(7-methyl-1-naphthyl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile: To a solution of 2-[4-[7-(7-methyl-1-naphthyl)-2-[[*(2S)*-1-methyl pyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-2-yl]acetonitrile (189 mg, crude, TFA) and DIEA (976 mg, 7.55 mmol, 1.32 mL) in DCM (4 mL) was added prop-2-enoyl prop-2-enoate (38.1 mg, 302 μmol) dropwise at 0 °C. The mixture was stirred at 25 °C for 1 hour. Upon completion, the reaction was quenched with MeOH (0.5 mL), diluted with water (1 mL) and extracted with DCM (3 $\times$ 5 mL). The organic layers were dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by prep-HPLC (column: Phenomenex Synergi C18 150*30mm*4 μm ; mobile phase: [water(0.225%FA) - ACN]; B%: 15% - 45%, 10.5 min) to give 2-[4-[7-(7-methyl-1-naphthyl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile (13.2 mg, 21.3 μmol , two steps 14.2% yield, 98.4% purity, FA) as a yellow solid. ESI MS m/z 566.5 [M+H]⁺.

EXAMPLE 246

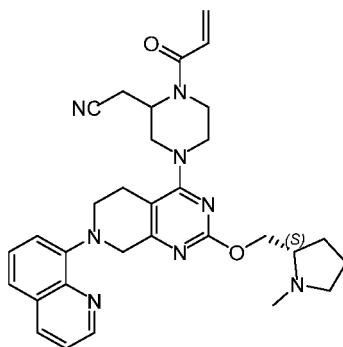
2-[4-[7-(4-fluoro-1-naphthyl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile.



[0910] Synthesized according to the method for **Example 147** substituting 1-bromo-4-fluoronaphthalene for 1-bromonaphthalene in step H. ESI MS m/z 570.5 $[M+H]^+$.

EXAMPLE 247

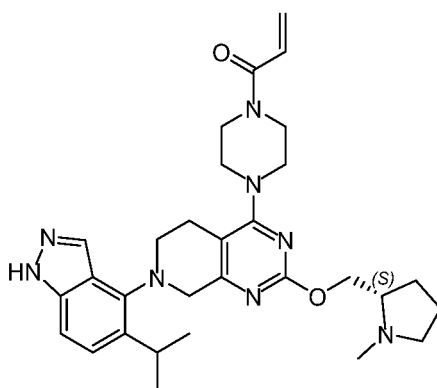
2-(1-acryloyl-4-(2-(((*S*)-1-methylpyrrolidin-2-yl)methoxy)-7-(quinolin-8-yl)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl)piperazin-2-yl)acetonitrile

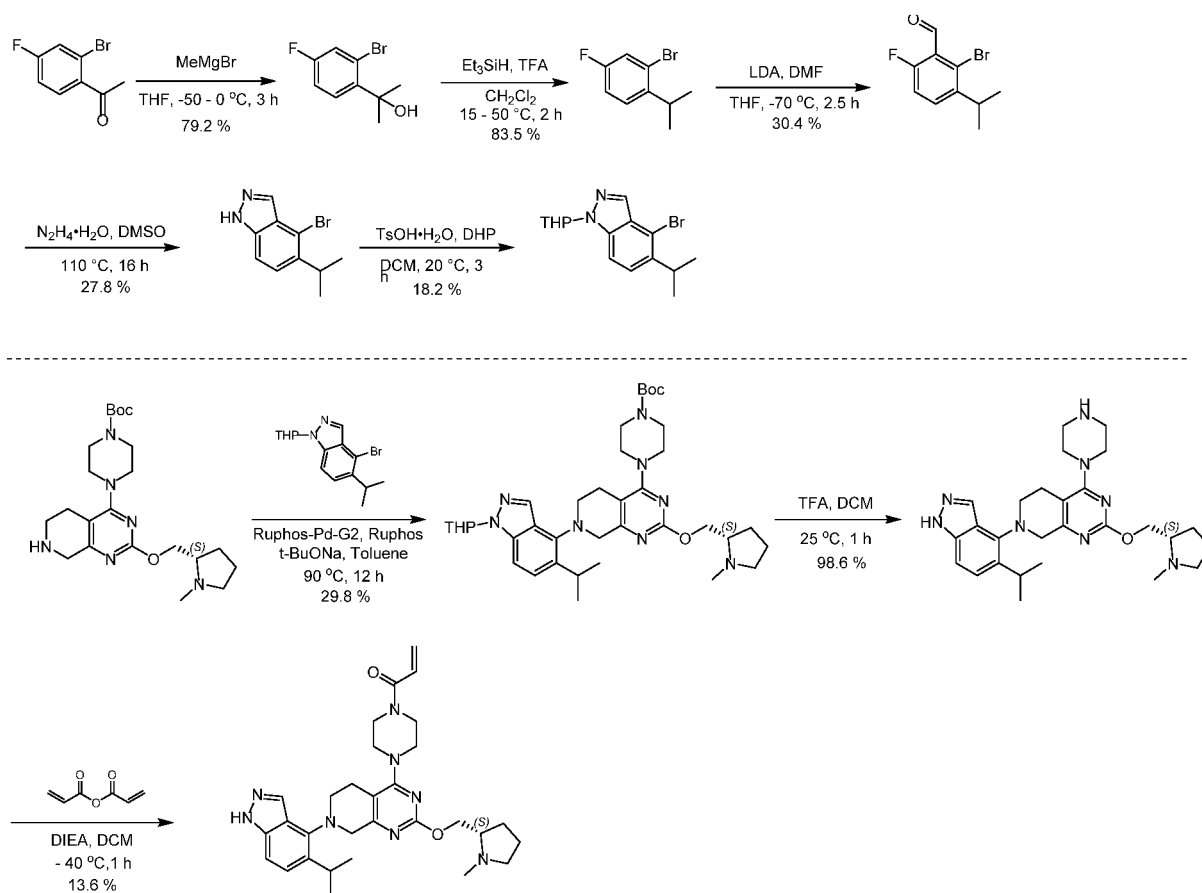


[0911] Synthesized according to the method for **Example 147** substituting 8-bromoquinoline for 1-bromonaphthalene in Step H. ESI MS m/z 553.2 $[M+H]^+$.

EXAMPLE 248

(*S*)-1-(4-(7-(5-isopropyl-1*H*-indazol-4-yl)-2-((1-methylpyrrolidin-2-yl)methoxy)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one





[0912] Step A: 2-(2-bromo-4-fluoro-phenyl)propan-2-ol: To a solution of 1-(2-bromo-4-fluoro-phenyl)ethanone (10 g, 46.1 mmol) in THF (100 mL) was added MeMgBr (in ether) (3 M, 46.08 mL) at - 50 °C. The mixture was warmed up to 0 °C and stirred for 3 hours. The mixture was quenched with saturated aqueous ammonium chloride solution (10 mL) at - 50 °C. The mixture was warmed up to 15 °C and was then diluted with ethyl acetate (500 mL). The separated organic layer was washed with water (1 × 500 mL) and brine (1 × 500 mL), dried over sodium sulfate, filtered and concentrated under vacuum to give 2-(2-bromo-4-fluoro-phenyl)propan-2-ol (10 g, 36.5 mmol, 79.2% yield, 85% purity) as a colorless oil.

[0913] Step B: 2-bromo-4-fluoro-1-isopropyl-benzene: To a solution of 2-(2-bromo-4-fluoro-phenyl)propan-2-ol (9 g, 38.6 mmol) in dichloromethane (100 mL) was added Et₃SiH (8.98 g, 77.2 mmol, 12.3 mL) and TFA (65.1 g, 571 mmol, 42.3 mL). The mixture was stirred at 15 °C for 1 hour and then heated to 50 °C for 1 hour. The reaction mixture was concentrated under vacuum and then diluted with ethyl acetate (100 mL). The aqueous layer pH was adjusted to pH = 7 by addition of saturated NaHCO₃ aqueous solution and extracted with ethyl acetate (50 mL ×

3). The combined organic phase was washed with brine (30 mL), dried with anhydrous Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by silica gel chromatography (Petroleum ether/Ethyl acetate = 1/0 to 100/1). The desired fractions were collected and concentrated under vacuum. 2-bromo-4-fluoro-1-isopropyl-benzene (7 g, 32.2 mmol, 83.5 % yield) was obtained as colorless oil. ¹H NMR (400MHz, chloroform-d) δ = 7.36-7.27 (m, 2H), 7.09 - 7.02 (m, 1H), 3.46-3.31 (m, 1H), 1.28 (d, J = 6.8 Hz, 6H).

[0914] Step C: 2-bromo-6-fluoro-3-isopropyl-benzaldehyde: To a mixture of 2-bromo-4-fluoro-1-isopropyl-benzene (7 g, 32.2 mmol in THF (100 mL) was added LDA (2 M in toluene, 24.2 mL) at - 70 °C under nitrogen atmosphere. The mixture was stirred for 0.5 hour, and then DMF (7.07 g, 96.7 mmol, 7.44 mL) was added. The mixture was stirred at - 70 °C for 2 hours. The reaction was quenched with water (100 mL) and extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, PE\EA = 1\0 to 10\1). The desired fractions were collected and concentrated under vacuum to give 2-bromo-6-fluoro-3-isopropyl-benzaldehyde (2.4 g, 9.79 mmol, 30.4 % yield) as a yellow oil. ¹H NMR (400MHz, chloroform-d) δ = 10.41 (s, 1H), 7.48 (dd, J = 5.6, 8.8 Hz, 1H), 7.13(t, J = 9.2, 1H), 3.57 - 3.46 (m, 1H), 1.26 (d, J = 7.2 Hz, 6H).

[0915] Step D: 4-bromo-5-isopropyl-1H-indazole: 2-bromo-6-fluoro-3-isopropyl-benzaldehyde (2.4 g, 9.79 mmol) in DMSO (3 mL) was added N₂H₄•H₂O (15.4 g, 302 mmol, 15 mL, 98% purity) and the mixture was heated to 110 °C and stirred for 16 hours. The reaction mixture was poured into H₂O (10 mL) and extracted with ethyl acetate (20 mL × 3). The organic phase was washed with brine (10 mL), dried over anhydrous Na₂SO₄ and concentrated under vacuum to give the residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 1/0 to 5/1) to give 4-bromo-5-isopropyl-1H-indazole (650 mg, 2.72 mmol, 27.8 % yield) as a yellow solid. ¹H NMR (400MHz, chloroform-d) δ = 10.24 (br s, 1H), 8.08 (d, J = 0.8 Hz, 1H), 7.43 (d, J = 8.8 Hz, 1H), 7.34 (d, J = 8.8 Hz, 1H), 3.56 (td, J = 6.8, 13.6 Hz, 1H), 1.29 (d, J = 6.8 Hz, 6H).

[0916] Step E: 4-bromo-5-isopropyl-1-tetrahydropyran-2-yl-indazole: To a solution of 3,4-dihydro-2H-pyran (457 mg, 5.44 mmol, 497 μ L, 2 eq) in dichloromethane (15 mL) was added TsOH•H₂O (51.7 mg, 271 μ mol) and 4-bromo-5-isopropyl-1H-indazole (650 mg, 2.72 mmol).

The mixture was stirred at 20 °C for 3 hours. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL × 2). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 1/0 to 5/1) and further purified by reversed phase flash [water (0.1% formic acid)/acetonitrile] to give 4-bromo-5-isopropyl-1-tetrahydropyran-2-yl-indazole (170 mg, 494 umol, 18.2% yield, 94% purity) as a yellow oil. ESI MS *m/z* 323.0 [M+H]⁺.

[0917] Step F: *tert*-butyl 4-[7-(5-isopropyl-1-tetrahydropyran-2-yl-indazol-4-yl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate: A mixture of 4-bromo-5-isopropyl-1-tetrahydropyran-2-yl-indazole (136 mg, 420 umol), *tert*-butyl 4-[2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (140 mg, 323 umol), RuPhos (15.1 mg, 32.4 umol), RuPhos-Pd-G2 (25.1 mg, 32.4 umol) and *t*-BuONa (77.7 mg, 809 umol) in toluene (3 mL) was degassed and purged with N₂ 3 times and the mixture was stirred at 90 °C for 12 hours under N₂ atmosphere. The mixture was diluted with ethyl acetate (20 mL) and washed with water (20 mL). The organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, DCM/MeOH = 100/1 to 10/1) and the desired fractions were collected and concentrated under vacuum to give *tert*-butyl 4-[7-(5-isopropyl-1-tetrahydropyran-2-yl-indazol-4-yl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (70 mg, 96.5 umol, 29.8% yield, 93% purity) as a yellow solid. ESI MS *m/z* 675.3 [M+H]⁺.

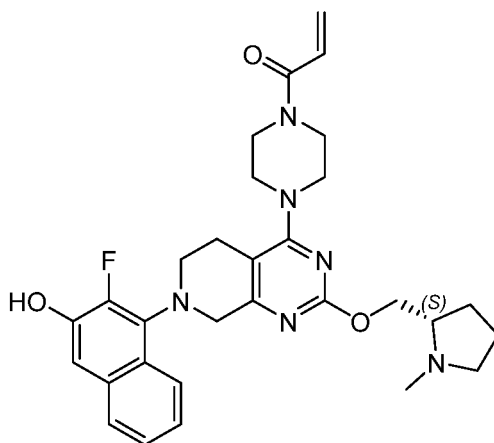
[0918] Step G: 7-(5-isopropyl-1*H*-indazol-4-yl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-4-piperazin-1-yl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidine: To a solution of *tert*-butyl 4-[7-(5-isopropyl-1-tetrahydropyran-2-yl-indazol-4-yl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (40 mg, 59.3 umol) in dichloromethane (100 uL) was added TFA (101 mg, 889 umol, 65.8 uL). The mixture was stirred at 25 °C for 1 hour. The mixture was concentrated under vacuum to give 7-(5-isopropyl-1*H*-indazol-4-yl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-4-piperazin-1-yl-6,8-dihydro-5*H*-

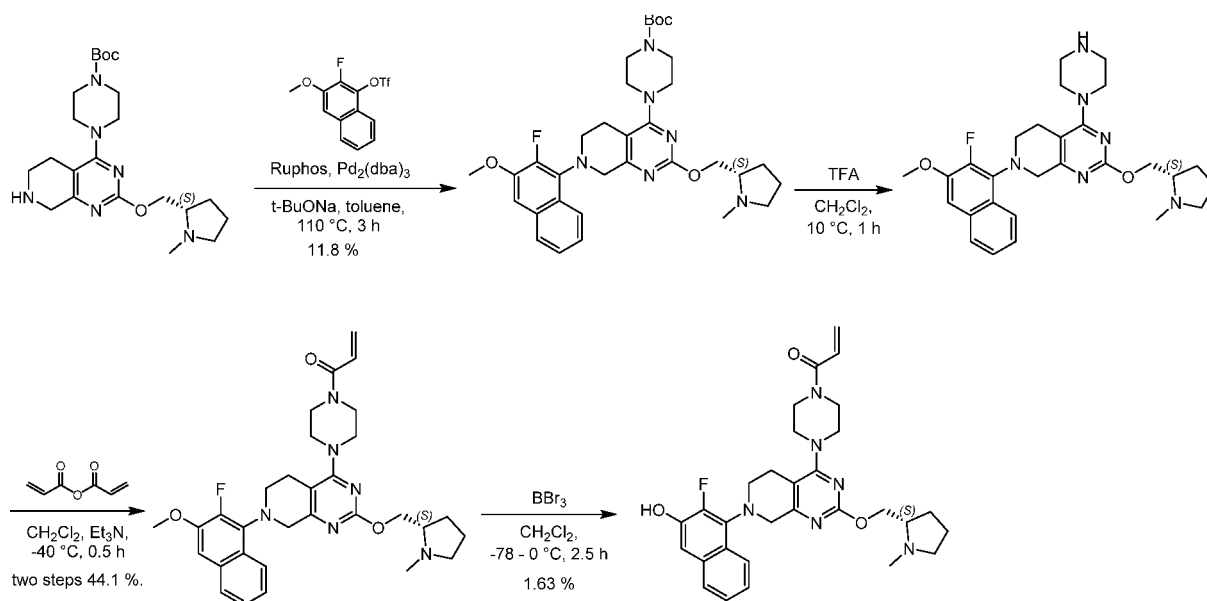
pyrido[3,4-*d*]pyrimidine (42 mg, 58.4 μ mol, 98.6% yield, 2 TFA) as a brown oil which was used in next step directly without purification. ESI MS m/z 491.4 $[M+H]^+$.

[0919] Step H: 1-[4-[7-(5-isopropyl-1*H*-indazol-4-yl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one: To a mixture of 7-(5-isopropyl-1*H*-indazol-4-yl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-4-piperazin-1-yl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidine (42 mg, 58.4 μ mol) and DIEA (75.5 mg, 584 μ mol, 102 μ L) in dichloromethane (2 mL) was added a solution of prop-2-enoyl prop-2-enoate (7.37 mg, 58.4 μ mol, 1 *eq*) in dichloromethane (1 mL) at -40 °C under nitrogen atmosphere. The mixture was stirred at -40 °C for 1 hour. The reaction was quenched by adding saturated NaHCO₃ (2 mL) aqueous solution. Then the mixture was poured into water (20 mL) and extracted with dichloromethane (20 mL $\times$ 2). The combined organics were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by prep-HPLC (column: Luna C18 150*25 5 μ ; mobile phase: [water (0.225%FA) - ACN]; B%: 5% - 38%, 10 min) to give 1-[4-[7-(5-isopropyl-1*H*-indazol-4-yl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one (4.5 mg, 7.93 μ mol, 13.6% yield, 96% purity) as a yellow solid. ESI MS m/z 545.2 $[M+H]^+$.

EXAMPLE 249

1-[4-[7-(2-fluoro-3-hydroxy-1-naphthyl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one





[0920] Step A: *tert*-butyl 4-[7-(2-fluoro-3-methoxy-1-naphthyl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate: A mixture of *tert*-butyl 4-[2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (0.50 g, 1.16 mmol), (2-fluoro-3-methoxy-1-naphthyl) trifluoromethanesulfonate (562 mg, 1.73 mmol), RuPhos (108 mg, 231 μ mol), Pd₂(dba)₃ (106 mg, 116 μ mol) and *t*-BuONa (333 mg, 3.47 mmol) in toluene (7 mL) was stirred at 110 °C for 3 hours under nitrogen atmosphere. The mixture was cooled and the pH of the aqueous layer adjusted to 7 by addition of saturated sodium bicarbonate solution and the aqueous layer extracted with ether acetate (3 $\times$ 20 mL). The combined organic layers were washed with saturated sodium chloride solution, dried over Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by column chromatography (SiO₂, dichloromethane/methanol = 10/1) and the mixture was concentrated to give *tert*-butyl 4-[7-(2-fluoro-3-methoxy-1-naphthyl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (0.20 g, 274 μ mol, 11.8 % yield,) as a yellow solid. ESI MS *m/z* 607.0 [M+H]⁺.

[0921] Step B: 7-(2-fluoro-3-methoxy-1-naphthyl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl] methoxy]-4-piperazin-1-yl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidine: A mixture *tert*-butyl 4-[7-(2-fluoro-3-methoxy-1-naphthyl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (0.20 g, 330 μ mol) and TFA (564 mg, 4.94 mmol,

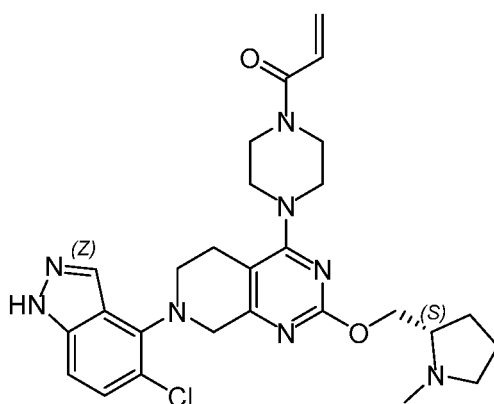
366 uL) in dichloromethane (0.4 mL) was stirred at 10 °C for 1 hour. The mixture was concentrated under vacuum to give 7-(2-fluoro-3-methoxy-1-naphthyl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-4-piperazin-1-yl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidine (205 mg, crude) as a yellow oil which was used in the next step without further purification. ESI MS *m/z* 507.0 [M+H]⁺.

[0922] Step C: 1-[4-[7-(2-fluoro-3-methoxy-1-naphthyl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one: To a solution of 7-(2-fluoro-3-methoxy-1-naphthyl)-2-[[*(2S)*-1-methyl pyrrolidin-2-yl]methoxy]-4-piperazin-1-yl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidine (0.20 g, crude) and TEA (399 mg, 3.95 mmol, 549 uL) in dichloromethane (5mL) was added prop-2-enoyl prop-2-enoate (49.8 mg, 394 umol) at -40 °C, then stirred at -40 °C for 0.5 h. The mixture was quenched with methanol (0.10 mL) and concentrated under vacuum. The residue was purified by reversed phase flash [water (0.1 % TFA)/acetonitrile]. The aqueous layer pH was to 7 by addition of saturated sodium bicarbonate solution and the aqueous layer extracted with dichloromethane/methanol (10/1) (3 × 10mL). The combined organic layers were washed with saturated sodium chloride (1 × 5mL), dried over Na₂SO₄, filtered and concentrated under vacuum to give 1-[4-[7-(2-fluoro-3-methoxy-1-naphthyl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one (0.10 g, 174 umol, 44.1 % yield) as a yellow oil. ESI MS *m/z* 561.5 [M+H]⁺.

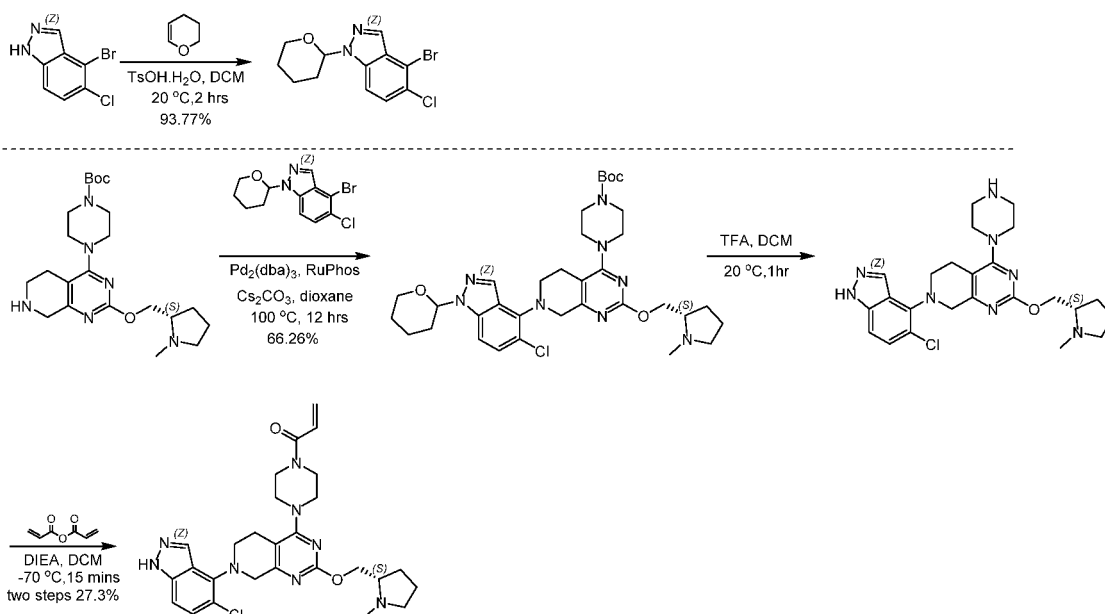
[0923] Step D: 1-[4-[7-(2-fluoro-3-hydroxy-1-naphthyl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one: To a solution of 1-[4-[7-(2-fluoro-3-methoxy-1-naphthyl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one (0.10 g, 174 umol) in dichloromethane (3mL) was added BBr₃ (223 mg, 892 umol, 85.9 uL) at -78 °C. The mixture was stirred at -78 °C for 0.5 h and 0 °C for 2 hours. The mixture was concentrated under vacuum, diluted with dichloromethane (3mL) and water and the aqueous layer pH adjusted to > 7 by addition of saturated sodium bicarbonate solution at -78 - 0 °C. The aqueous layer was next extracted with dichloromethane (3 × 5.00 mL). The combined organics were concentrated under vacuum. The residue was purified by column chromatography (Al₂O₃, dichloromethane/methanol = 10/1) and the mixture was concentrated under vacuum. The residue

was purified by prep-HPLC (column: Phenomenex Gemini 150*25mm*10um; mobile phase: [water (10mM NH₄HCO₃) - ACN]; B%: 30% - 60%, 3 min) and further purified by prep-HPLC (column: Luna C18 150*25 5u; mobile phase: [water (0.225% FA) - ACN]; B%: 20% - 50%, 10 min). The desired fractions were collected and lyophilized to give 1-[4-[7-(2-fluoro-3-hydroxy-1-naphthyl)-2-[[[(2*S*)-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one (1.59 mg, 2.91 umol, 1.63 % yield, 100 % purity, FA) as a yellow solid. ESI MS *m/z* 547.2[M+H]⁺.

EXAMPLE 250



1-[4-[7-(5-chloro-1*H*-indazol-4-yl)-2-[[[(2*S*)-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one



Step A: 4-bromo-5-chloro-1-tetrahydropyran-2-yl-indazole: To a solution of 4-bromo-5-chloro-1*H*-indazole (100 mg, 432.0 μ mol) in DCM (3 mL) was added TsOH·H₂O (8.22 mg, 43.2 μ mol) and 3,4-dihydro-2*H*-pyran (72.7 mg, 864 μ mol, 79.0 μ L). The mixture was stirred at 20°C for 2 hours. The reaction was washed by water (20 mL) and the aqueous layer extracted with ethyl acetate (20 mL x 2). The combined organics were dried with Na₂SO₄ and the solvent removed under vacuum. The residue was purified by column chromatography (SiO₂, **Petroleum ether/Ethyl acetate = 10:1**) to give 4-bromo-5-chloro-1-tetrahydropyran-2-yl-indazole (270 mg, 810 μ mol, 93.8% yield) as a white solid. ESI MS m/z 547.2[M+H]⁺.

[0924] Step B: tert-butyl-4-[7-(5-chloro-1-tetrahydropyran-2-yl-indazol-4-yl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate: A mixture of tert-butyl 4-[2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (123 mg, 284.4 μ mol), 4-bromo-5-chloro-1-tetrahydropyran-2-yl-indazole (135 mg, 427 μ mol), Pd₂(dba)₃ (26.0 mg, 28.4 μ mol), RuPhos (20.0 mg, 42.9 μ mol) and Cs₂CO₃ (278 mg, 853 μ mol) in dioxane (10 mL) was degassed and purged with N₂ and then the mixture was stirred at 100 °C for 12 hrs under N₂ atmosphere. The reaction was quenched by adding water (20 mL). The mixture was extracted with ethyl acetate (20 mL x 3). The combined organics were dried with Na₂SO₄ and the solvent was concentrated under vacuum. The residue was purified by column chromatography (SiO₂, **Ethyl acetate/MeOH=10/1**) to give tert-butyl-4-[7-(5-chloro-1-tetrahydropyran-2-yl-indazol-4-yl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (130.0 mg, 188.4 μ mol, 66.3% yield) as a white solid. ESI MS m/z 668.2[M+H]⁺.

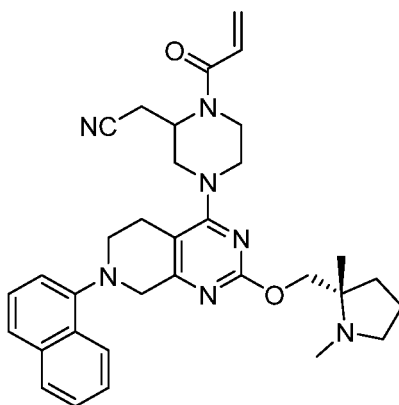
[0925] Step C: 7-(5-chloro-1*H*-indazol-4-yl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-4-piperazin-1-yl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidine: To a solution of tert-butyl 4-[7-(5-chloro-1-tetrahydropyran-2-yl-indazol-4-yl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (50.0 mg, 74.9 μ mol) in DCM (2 mL) was added TFA (1.95 mL). The mixture was stirred at 20°C for 1 hr. The organic solvent was removed under vacuum to give 7-(5-chloro-1*H*-indazol-4-yl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-4-piperazin-1-yl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidine (40.0 mg, crude, 2TFA)

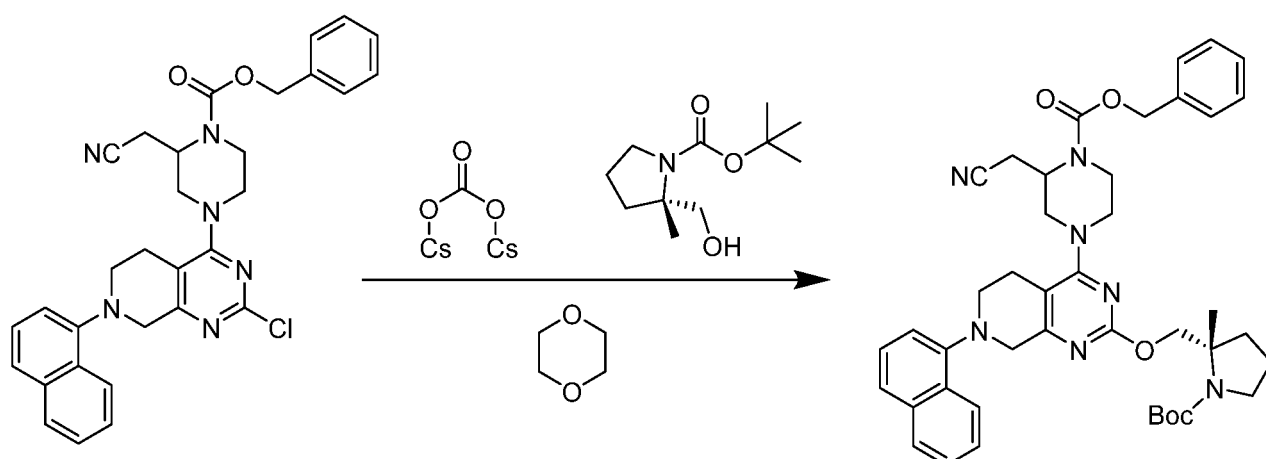
as a yellow oil which was used directly in the next step without further purification. ESI MS m/z 483.4 $[M+H]^+$.

[0926] Step D: 1-[4-[7-(5-chloro-1*H*-indazol-4-yl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one: To a solution of 7-(5-chloro-1*H*-indazol-4-yl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-4-piperazin-1-yl-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidine (40.0 mg, 2TFA) and DIEA (50 mg, 387 μ mol, 67.4 μ L) in DCM (3mL) was added dropwise acrylic anhydride (9.0 mg, 71.4 μ mol) under N_2 atmosphere. The mixture was stirred at -70 °C for 15 mins. The reaction was quenched by adding water (10 mL). The mixture was extracted with ethyl acetate (10 mL x 3). The organic layer was dried with Na_2SO_4 and the solvent removed under vacuum. The residue was purified by prep-HPLC (column: Luna C18 150*25 5 μ ; mobile phase: [water (0.225%FA)-ACN];B%: 10%-37%,10 mins) and lyophilized to give 1-[4-[7-(5-chloro-1*H*-indazol-4-yl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-1-yl]prop-2-en-1-one (11.9 mg, 20.8 μ mol, two steps 27.3%,100% e.e.) as a yellow solid. ESI MS m/z 537.2 $[M+H]^+$.

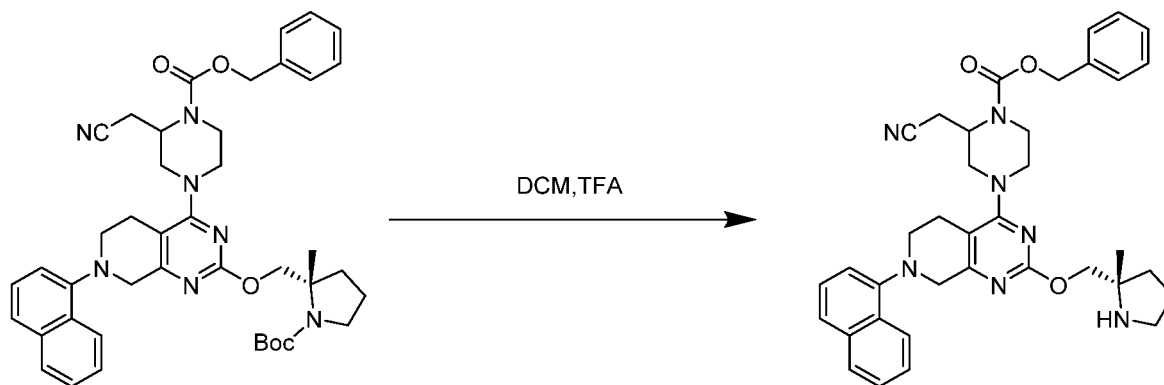
EXAMPLE 251

2-(1-acryloyl-4-(2-(((*S*)-1,2-dimethylpyrrolidin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl)piperazin-2-yl)acetonitrile

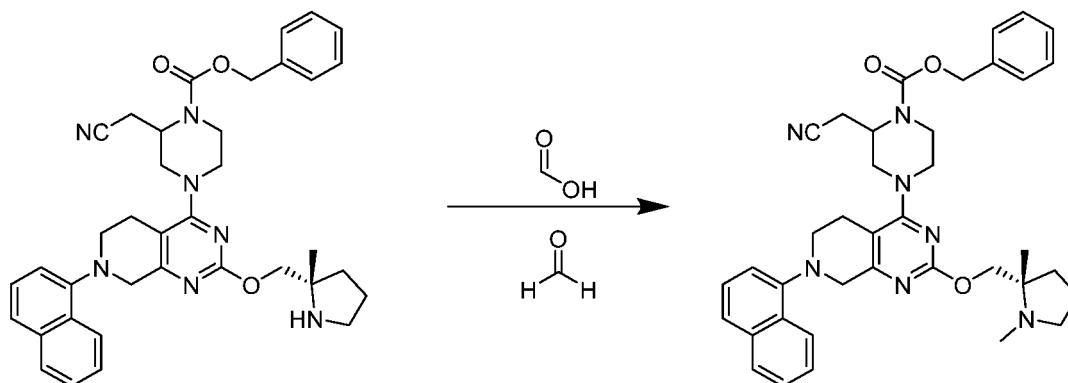




[0927] Step A: benzyl 4-(2-(((S)-1-(tert-butoxycarbonyl)-2-methylpyrrolidin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)-2-(cyanomethyl)piperazine-1-carboxylate. In a microwave tube benzyl 4-(2-chloro-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)-2-(cyanomethyl)piperazine-1-carboxylate (200 mg, 0.362 mmol) was dissolved in dioxane (181 μ l, 0.362 mmol) and treated with cesium carbonate (236 mg, 0.723 mmol) and (S)-tert-butyl 2-(hydroxymethyl)-2-methylpyrrolidine-1-carboxylate (389 mg, 1.81 mmol). The tube was then capped and heated to 90°C for 2 hours. LC/MS showed reaction completion. The reaction was cooled to room temperature and filtered through GF/F paper. The filtrate was concentrated in vacuo and chromatographed on the CombiFlash (0%-10% DCM:MeOH). All fractions containing clean product were combined and concentrated to give benzyl 4-(2-(((S)-1-(tert-butoxycarbonyl)-2-methylpyrrolidin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)-2-(cyanomethyl)piperazine-1-carboxylate (264 mg, 0.361 mmol, 99.7 % yield). ES+APCI MS m/z 732.4 $[M+H]^+$.

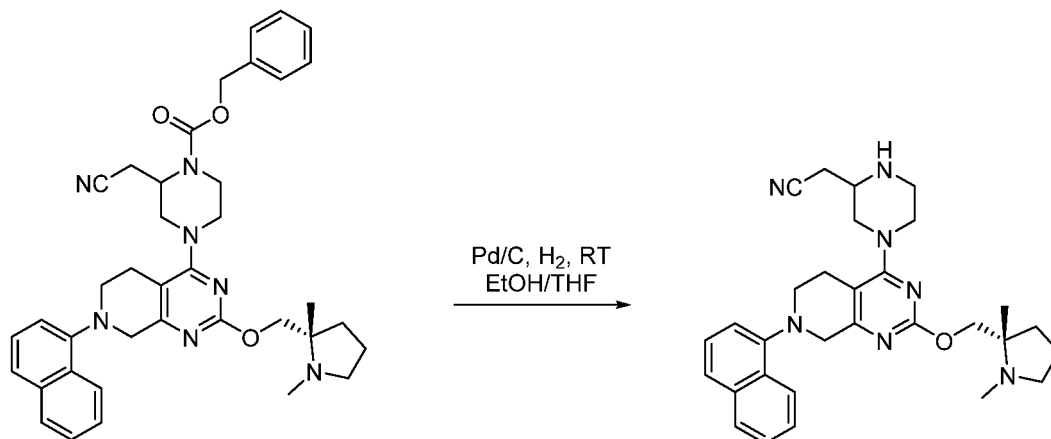


[0928] Step B: benzyl 2-(cyanomethyl)-4-(2-(((S)-2-methylpyrrolidin-2-yl)methoxy))-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate. benzyl 4-(2-(((S)-1-(tert-butoxycarbonyl)-2-methylpyrrolidin-2-yl)methoxy))-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)-2-(cyanomethyl)piperazine-1-carboxylate (264 mg, 0.361 mmol) was dissolved in dichloromethane (3607 μ l, 0.361 mmol) and treated with TFA (556 μ l, 7.21 mmol). The reaction stirred at room temperature for 1 hour. LC/MS showed reaction completion. The reaction was concentrated in vacuo and treated with saturated bicarb. The aqueous layer was extracted with DCM (2X) and the combined organics dried over Na₂SO₄ and concentrated in vacuo to give benzyl 2-(cyanomethyl)-4-(2-(((S)-2-methylpyrrolidin-2-yl)methoxy))-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (210 mg, 0.332 mmol, 92.2 % yield). ES+APCI MS m/z 632.3 [M+H]⁺.

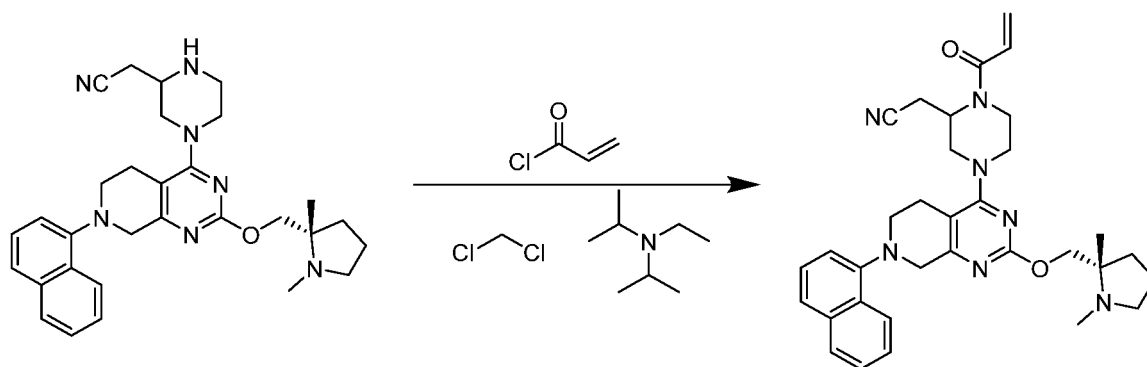


[0929] Step C: benzyl 2-(cyanomethyl)-4-(2-(((S)-1,2-dimethylpyrrolidin-2-yl)methoxy))-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate. benzyl 2-(cyanomethyl)-4-(2-(((S)-2-methylpyrrolidin-2-yl)methoxy))-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (105 mg, 0.1662 mmol) was dissolved in formic acid (94.05 μ l, 2.493 mmol) and treated with Formaldehyde (1868 μ l, 24.93 mmol). The reaction mixture stirred at 85°C for 1 hour. LC/MS showed reaction completion. The reaction was cooled to room temperature and treated with saturated bicarb and the mixture was extracted with DCM (2X) and the organics combined and dried over Na₂SO₄. The combined organics were concentrated in vacuo and chromatographed on the CombiFlash (0%-10% DCM:MeOH). All fractions containing clean product were combined and concentrated in vacuo to give benzyl 2-(cyanomethyl)-4-(2-(((S)-1,2-dimethylpyrrolidin-2-yl)methoxy))-7-

(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (75 mg, 0.1161 mmol, 69.88 % yield). ES+APCI MS m/z 646.4 $[M+H]^+$.

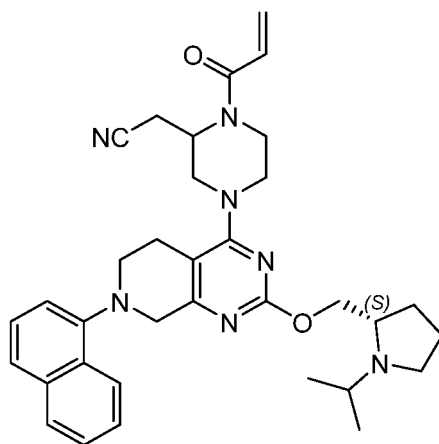


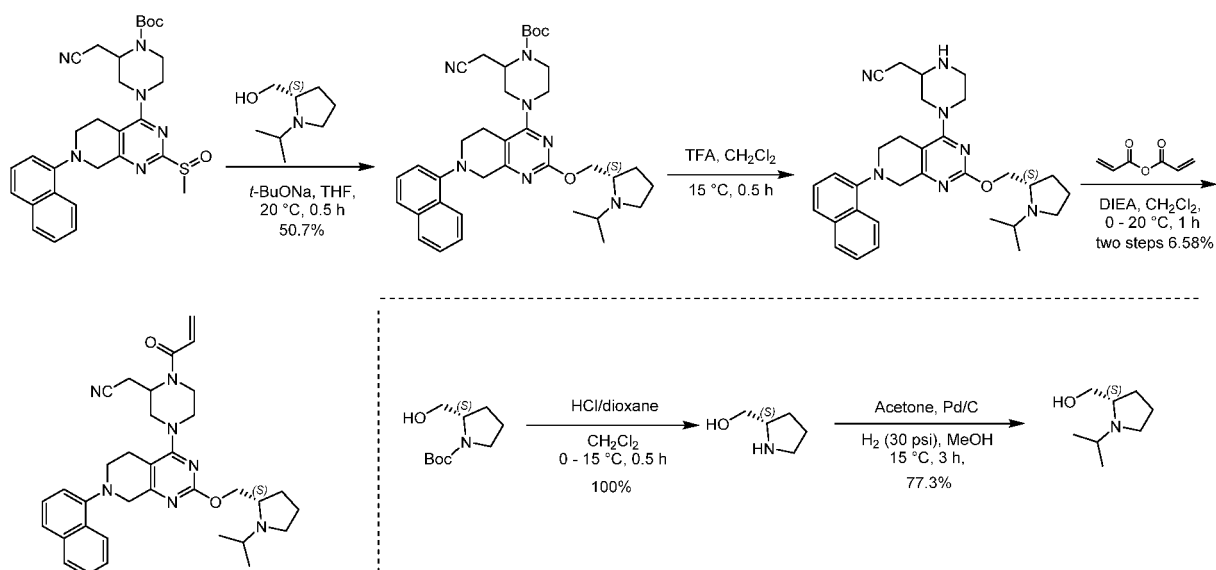
[0930] Step D: 2-(4-(2-(((S)-1,2-dimethylpyrrolidin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile. A solution of benzyl 2-(cyanomethyl)-4-(2-(((S)-1,2-dimethylpyrrolidin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (117 mg, 0.181 mmol) in EtOH (1812 μ l, 0.181 mmol) and THF (1812 μ l, 0.181 mmol) was purged with N_2 for 5 minutes. To this solution was added Palladium (96.4 mg, 0.0453 mmol) (Degussa Type, 10 wt%, 50% H_2O), and was immediately capped and purged with N_2 for an additional 5 min. The solution was then stirred under H_2 atmosphere for 1 hour. LC/MS showed clean desired product. The mixture was diluted with MeOH and filtered through packed celite. The filtrate was then concentrated in vacuo to provide 2-(4-(2-(((S)-1,2-dimethylpyrrolidin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile (88 mg, 0.172 mmol, 94.9 % yield). ES+APCI MS m/z 512.3 $[M+H]^+$.



Step E: 2-(1-acryloyl-4-(2-(((S)-1,2-dimethylpyrrolidin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile. To a suspension of 2-(4-(2-(((S)-1,2-dimethylpyrrolidin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile (88 mg, 0.17 mmol) in dichloromethane (1720 μ l, 0.17 mmol) at ambient temperature was added Acryloyl Chloride (14 μ l, 0.17 mmol) followed by Hunig's base (60 μ l, 0.34 mmol). The reaction was then stirred at ambient temperature for 30 minutes. LC/MS showed reaction completion. The reaction mixture was concentrated in vacuo. The concentrate was resuspended in a 60:40 mixture of ACN:H₂O and purified on the Gilson (prep HPLC) using 5-->95% ACN/0.1% TFA in water/0.1% TFA as eluent. Fractions containing product were combined and free based with saturated bicarb and the organics extracted with DCM. The organics were dried over MgSO₄ and concentrated in vacuo to give 2-(1-acryloyl-4-(2-(((S)-1,2-dimethylpyrrolidin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile (14 mg, 0.025 mmol, 14 % yield). ES+APCI MS m/z 566.3 [M+H]⁺.EXAMPLE 252

tert-butyl 2-(cyanomethyl)-4-[2-[[[(2S)-1-isopropylpyrrolidin-2-yl]methoxy]-7-(1-naphthyl)-6,8-dihydro-5H-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate





[0931] Step A: (S)-pyrrolidin-2-ylmethanol: To a solution of (S)-*tert*-butyl 2-(hydroxymethyl)pyrrolidine-1-carboxylate (2 g, 9.94 mmol) in CH₂Cl₂ (40 mL) was added HCl (4 M in dioxane, 49.69 mL) at 0 °C under a nitrogen atmosphere. After stirring at 15 °C for 30 min, the mixture was concentrated under vacuum. (S)-pyrrolidin-2-ylmethanol (1.37 g, 9.96 mmol, 100% yield, HCl) was obtained as a yellow solid.

[0932] Step B: [(2S)-1-isopropylpyrrolidin-2-yl] methanol: A mixture of [(2S)-pyrrolidin-2-yl]methanol (750 mg, 7.41 mmol, 724 uL) and acetone (4.31 g, 74.2 mmol, 5.46 mL) in MeOH (20 mL) was hydrogenated under H₂ (30 psi) with Pd/C (100 mg, 7.41 mmol, 10% purity) at 15 °C for 3 hours. The mixture was filtered and concentrated under vacuum. [(2S)-1-isopropylpyrrolidin-2-yl]methanol (0.821 g, 5.73 mmol, 77.3% yield) was obtained as a yellow oil. ¹H NMR (400MHz, methanol-d₄) δ = 3.54 (dd, *J* = 4.0, 10.8 Hz, 1H), 3.40 - 3.35 (m, 1H), 2.99 - 2.86 (m, 3H), 2.60 - 2.50 (m, 1H), 1.94 - 1.82 (m, 1H), 1.82 - 1.66 (m, 3H), 1.15 (d, *J* = 6.4 Hz, 3H), 1.08 (d, *J* = 6.4 Hz, 3H).

[0933] Step C: *tert*-butyl 2-(cyanomethyl)-4-[2-[[[(2S)-1-isopropylpyrrolidin-2-yl] methoxy]-7-(1-naphthyl)-6,8-dihydro-5H-pyrido[3,4-*d*]pyrimidin-4-yl] piperazine-1-carboxylate: To a mixture of *tert*-butyl 2-(cyanomethyl)-4-[2-methylsulfinyl- 7-(1-naphthyl)-6,8-dihydro-5H-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (300 mg, 549 umol) and [(2S)-1-isopropylpyrrolidin-2-yl]methanol (157 mg, 1.10 mmol) in THF (5 mL) was added *t*-BuONa (158 mg, 1.65 mmol). After stirring at 20 °C for 0.5 hour, the reaction mixture was neutralized

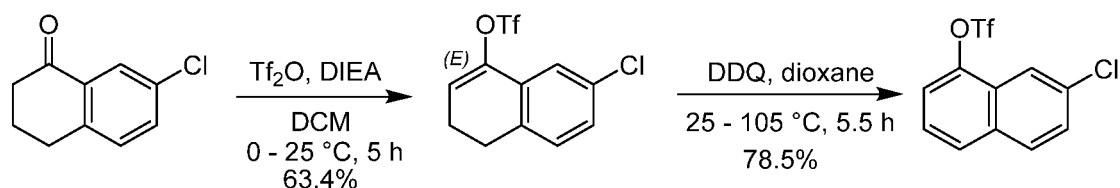
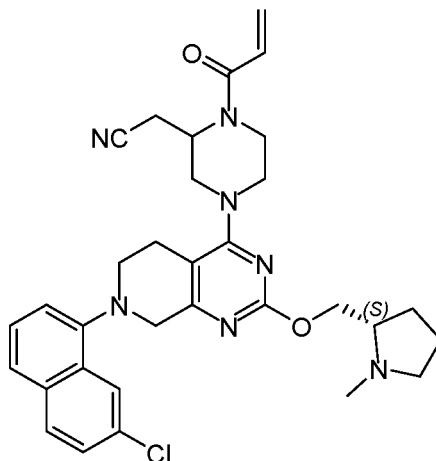
with HCl (1 M) to pH = 7 while holding the solution temperature to 0°C, and then the mixture was concentrated under reduced pressure. The residue was purified by reversed phase flash [water (0.1% TFA)/acetonitrile]. The desired fractions were collected and neutralized with saturated NaHCO₃ solution and extracted with ethyl acetate (200mL). The organic layer was dried over sodium sulfate, filtered and concentrated under vacuum. *tert*-butyl 2-(cyanomethyl)-4-[2-[[*(2S)*-1-isopropylpyrrolidin-2-yl]methoxy]-7-(1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (174 mg, 278 umol, 50.7% yield, 100% purity) was obtained as a yellow oil. ESI MS *m/z* 626.2 [M+H]⁺.

[0934] Step D: 2-[4-[2-[[*(2S)*-1-isopropylpyrrolidin-2-yl] methoxy]-7-(1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-2-yl]acetonitrile: To a solution of *tert*-butyl 2-(cyanomethyl)-4-[2-[[*(2S)*-1-isopropyl pyrrolidin-2-yl]methoxy]-7-(1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazine-1-carboxylate (174 mg, 278 umol) in CH₂Cl₂ (5 mL) was added TFA (7.70 g, 67.5 mmol, 5.00 mL) at 0 °C under nitrogen atmosphere. After stirring at 15 °C for 0.5 h, the mixture was concentrated under vacuum. 2-[4-[2-[[*(2S)*-1-isopropylpyrrolidin-2-yl] methoxy]-7-(1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-2-yl]acetonitrile (178 mg, crude, TFA) was obtained as a yellow oil. ESI MS *m/z* 526.1 [M+H]⁺.

[0935] Step E: 2-[4-[2-[[*(2S)*-1-isopropylpyrrolidin- 2-yl]methoxy]-7-(1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile: To a mixture of 2-[4-[2-[[*(2S)*-1-isopropylpyrrolidin-2-yl]methoxy]- 7-(1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-2-yl]acetonitrile (178 mg, crude, TFA salt) and DIEA (360 mg, 2.78 mmol, 485 uL) in CH₂Cl₂ (5 mL) was added prop-2-enoyl prop-2-enoate (28.1 mg, 223 umol) at 0 °C. The mixture was stirred at 20 °C for 1 hour. The reaction mixture was quenched with NaHCO₃ saturated solution (5 mL) at 0 °C, and then extracted with CH₂Cl₂ (2 × 25 mL). The combined organic layers were washed with brine (1 × 50 mL), dried over sodium sulfate, filtered and concentrated under vacuum. The residue was purified by prep-HPLC (column: Boston Green ODS 150*30 5u; mobile phase: [water (0.225%FA) - ACN]; B%: 27% - 54%, 10 min). 2-[4-[2-[[*(2S)*-1-isopropylpyrrolidin- 2-yl]methoxy]-7-(1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile (11.7 mg, 18.3 umol, two steps 6.58% yield, 97.9% purity, FA) was obtained as a brown solid. ESI MS *m/z* 580.2 [M+H]⁺.

EXAMPLE 253

2-(1-acryloyl-4-(7-(7-chloronaphthalen-1-yl)-2-(((*S*)-1-methylpyrrolidin-2-yl)methoxy))-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl)piperazin-2-yl)acetonitrile



[0936] Step A: (7-chloro-3,4-dihydronaphthalen-1-yl) trifluoromethanesulfonate: To a mixture of 7-chlorotetralin-1-one (2 g, 11.1 mmol, 1 eq) and DIEA (4.29 g, 33.2 mmol, 5.79 mL) in DCM (35 mL) was added Tf_2O (4.69 g, 16.6 mmol, 2.74 mL) in one portion at 0 °C under N_2 . The mixture was stirred at 25 °C for 5 hours. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate = 200/1 to 50/1). (7-chloro-3,4-dihydronaphthalen-1-yl) trifluoromethanesulfonate (2.25 g, 7.02 mmol, 63.4% yield, 97.6 % purity) was obtained as a colorless oil. ^1H NMR (400MHz, chloroform-*d*) δ = 7.32 (d, J = 2.0 Hz, 1H), 7.24 (dd, J = 2.0, 8.0 Hz, 1H), 7.12 (d, J = 8.0 Hz, 1H), 6.10 (t, J = 4.8 Hz, 1H), 2.88 - 2.80 (m, 2H), 2.53 (dt, J = 4.8, 8.0 Hz, 2H).

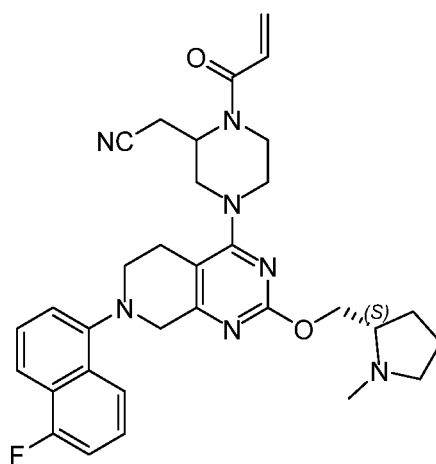
[0937] Step B: (7-chloro-1-naphthyl) trifluoromethanesulfonate: To a mixture of (7-chloro-3,4-dihydronaphthalen-1-yl) trifluoromethanesulfonate (1.57 g, 5.02 mmol) in dioxane (35 mL) was

added DDQ (2.28 g, 10.0 mmol) in one portion under N₂. The mixture was stirred at 25 °C for 30 min, then heated to 105 °C and stirred for 5 hours. The reaction mixture was concentrated under reduced pressure to remove 1,4-dioxane. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 200/1 to 50/1). (7-chloro-1-naphthyl) trifluoromethanesulfonate (1.24 g, 3.94 mmol, 78.5 % yield, 98.7 % purity) was obtained as a colorless oil. ¹H NMR (400MHz, chloroform-d) δ = 8.05 (d, *J* = 2.0 Hz, 1H), 7.87 - 7.83 (m, 2H), 7.57 - 7.47 (m, 3H).

[0938] Title compound was prepared as in **Example 210** Steps E-G, substituting (7-chloro-1-naphthyl) trifluoromethanesulfonate for 1-bromo-2-(trifluoromethyl)benzene in step E and also substituting prop-2-enoyl prop-2-enoate for acryloyl chloride in step G. ESI MS *m/z* 586.1 [M+H]⁺.

EXAMPLE 254

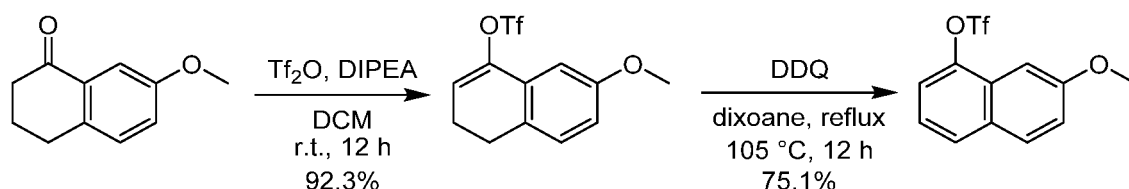
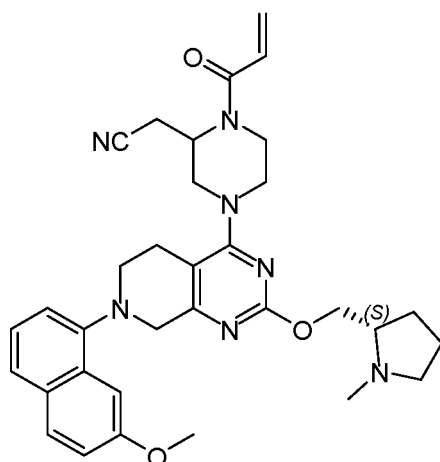
2-[4-[7-(5-fluoro-1-naphthyl)-2-[(2*S*)-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile



[0939] Title compound was prepared as in **Example 210** Steps E-G, substituting 1-bromo-5-fluoronaphthalene for 1-bromo-2-(trifluoromethyl)benzene in step E and also substituting prop-2-enoyl prop-2-enoate for acryloyl chloride in step G. ESI MS *m/z* 570.3 [M+H]⁺.

EXAMPLE 255

2-[4-[7-(7-methoxy-1-naphthyl)-2-[(2*S*)-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile



[0940] Step A: (7-methoxy-3,4-dihydronaphthalen-1-yl) trifluoromethanesulfonate: To the solution of 7-methoxytetralin-1-one (1 g, 5.67 mmol) and DIEA (2.20 g, 17.0 mmol, 2.97 mL) in DCM (15 mL) was added Tf_2O (2.40 g, 8.51 mmol, 1.40 mL) dropwise, then the mixture was stirred at 20 °C for 12 hours. The reaction mixture was concentrated under vacuum. The residue was purified by silica gel chromatography (PE: EtOAc from 1:0 to 100:1) to give (7-methoxy-3,4-dihydronaphthalen-1-yl) trifluoromethanesulfonate (1.7 g, 5.24 mmol, 92.3 % yield, 95.0 % purity) as yellow oil. ^1H NMR (400 MHz, chloroform- d) δ = 7.06 (d, J =8.4 Hz, 1H), 6.75 (dd, J =2.4, 8.4 Hz, 1H), 6.66 (d, J =2.4 Hz, 1H), 6.45 (s, 1H), 3.80 (s, 3H), 3.04 - 2.96 (m, 2H), 2.68 (t, J =8.4 Hz, 2H).

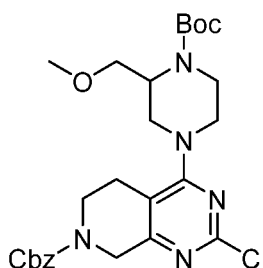
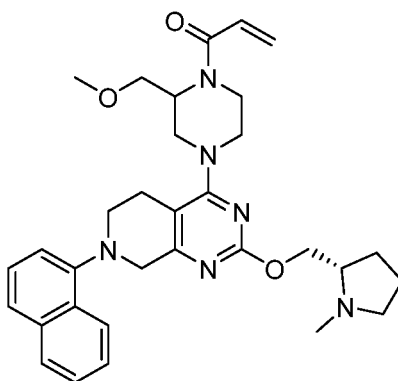
[0941] Step 2: (7-methoxy-1-naphthyl) trifluoromethanesulfonate: A mixture of (7-methoxy-3,4-dihydronaphthalen-1-yl) trifluoromethanesulfonate (1.7 g, 5.51 mmol) and DDQ (2.50 g, 11.0 mmol) in dioxane (30 mL) was stirred at 105 °C for 12 hours. The reaction mixture was concentrated under vacuum. The residue was purified by silica gel chromatography (PE: EtOAc from 1:0 to 50:1) to give (7-methoxy-1-naphthyl) trifluoromethanesulfonate (1.41 g, 4.14 mmol, 75.1 % yield, 90.0 % purity) as a colourless oil. ^1H NMR (400 MHz, chloroform- d) δ = 7.84 (d,

$J=9.2$ Hz, 1H), 7.78 (d, $J=8.8$ Hz, 1H), 7.65 (d, $J=2.4$ Hz, 1H), 7.24 - 7.21 (m, 2H), 7.15 (d, $J=2.4$ Hz, 1H), 3.94 (s, 3H).

[0942] Title compound was prepared as in **Example 210** Steps E-G, substituting (7-methoxy-1-naphthyl) trifluoromethanesulfonate for 1-bromo-2-(trifluoromethyl)benzene in step E and also substituting prop-2-enoyl prop-2-enoate for acryloyl chloride in step G. ESI MS m/z 582.4 $[M+H]^+$.

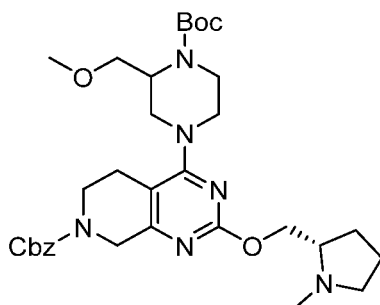
EXAMPLE 256

1-(2-(methoxymethyl)-4-(2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one

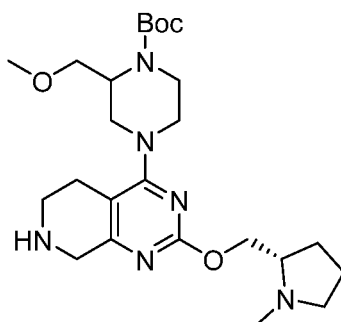


[0943] Step A: benzyl 4-(4-(tert-butoxycarbonyl)-3-(methoxymethyl)piperazin-1-yl)-2-chloro-5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate: A solution of tert-butyl 2-(methoxymethyl)piperazine-1-carboxylate (0.715 g, 3.10 mmol) in N,N-dimethylacetamide (3 ml) was cooled on an ice bath with stirring and solid benzyl 2,4-dichloro-5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate (1.00 g, 2.96 mmol) was added in small portions, followed by

DIPEA (0.57 mL, 3.25 mmol, 1.1 eq.). The resulting solution was allowed to warm up to r.t. over 1 hour, and then divided between water (15 mL) and MTBE (50 mL). The organic layer was washed with water (2 x 10 mL), brine (10 mL), dried over Na₂SO₄ and evaporated in vacuo to give a yellow solid (1.54 g, 98%). ES+APCI MS m/z 532.3, [M+H]⁺.

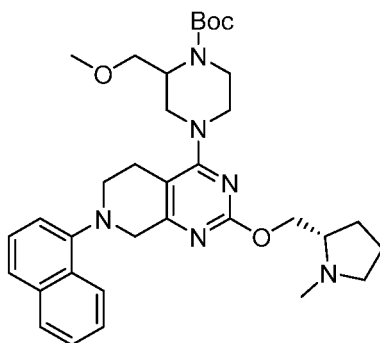


[0944] Step B: benzyl 4-(4-(tert-butoxycarbonyl)-3-(methoxymethyl)piperazin-1-yl)-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate: A mixture of crude benzyl 4-(4-(tert-butoxycarbonyl)-3-(methoxymethyl)piperazin-1-yl)-2-chloro-5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate (500 mg, 0.940 mmol), (S)-(1-methylpyrrolidin-2-yl)methanol (216 mg, 1.88 mmol), Cs₂CO₃ (612 mg, 1.88 mmol) and dioxane (0.5 mL) was flushed with nitrogen. The vial was capped and stirred at 120°C overnight. The reaction mixture was cooled, divided between EtOAc (20 mL) and water (10 mL), the organic layer was washed with water and brine (5 mL each), dried over Na₂SO₄ and evaporated in vacuo. The compound was purified by silica gel chromatography, Redisep 40g, eluting with 4 to 10% MeOH/DCM +0.2%NH₄OH to give a yellow solid (197 mg, 34%). ES+APCI MS m/z 611.4 [M+H]⁺.

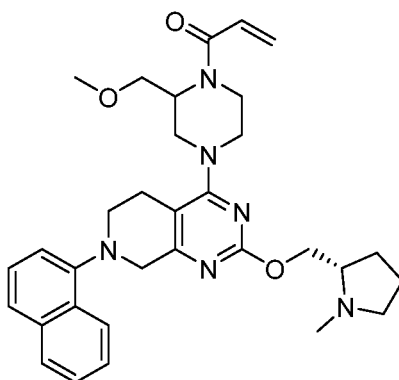


[0945] Step C: tert-butyl 2-(methoxymethyl)-4-(2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate: A mixture of benzyl 4-

(4-(tert-butoxycarbonyl)-3-(methoxymethyl)piperazin-1-yl)-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate (197 mg, 0.323 mmol), methanol (10 mL) and palladium on carbon (10 mg, 5%, *Degussa type E101 NO/W*) was degassed and stirred under hydrogen atmosphere (balloon) for 1 hour. The reaction mixture was filtered through Celite (2 mL), washed with MeOH (3 x 3 mL), evaporated in vacuo, and dried by evaporation with toluene in vacuo and under high vacuum to give a colorless solid (150 mg, 98%). ES+APCI MS m/z 477.2 $[M+H]^+$.



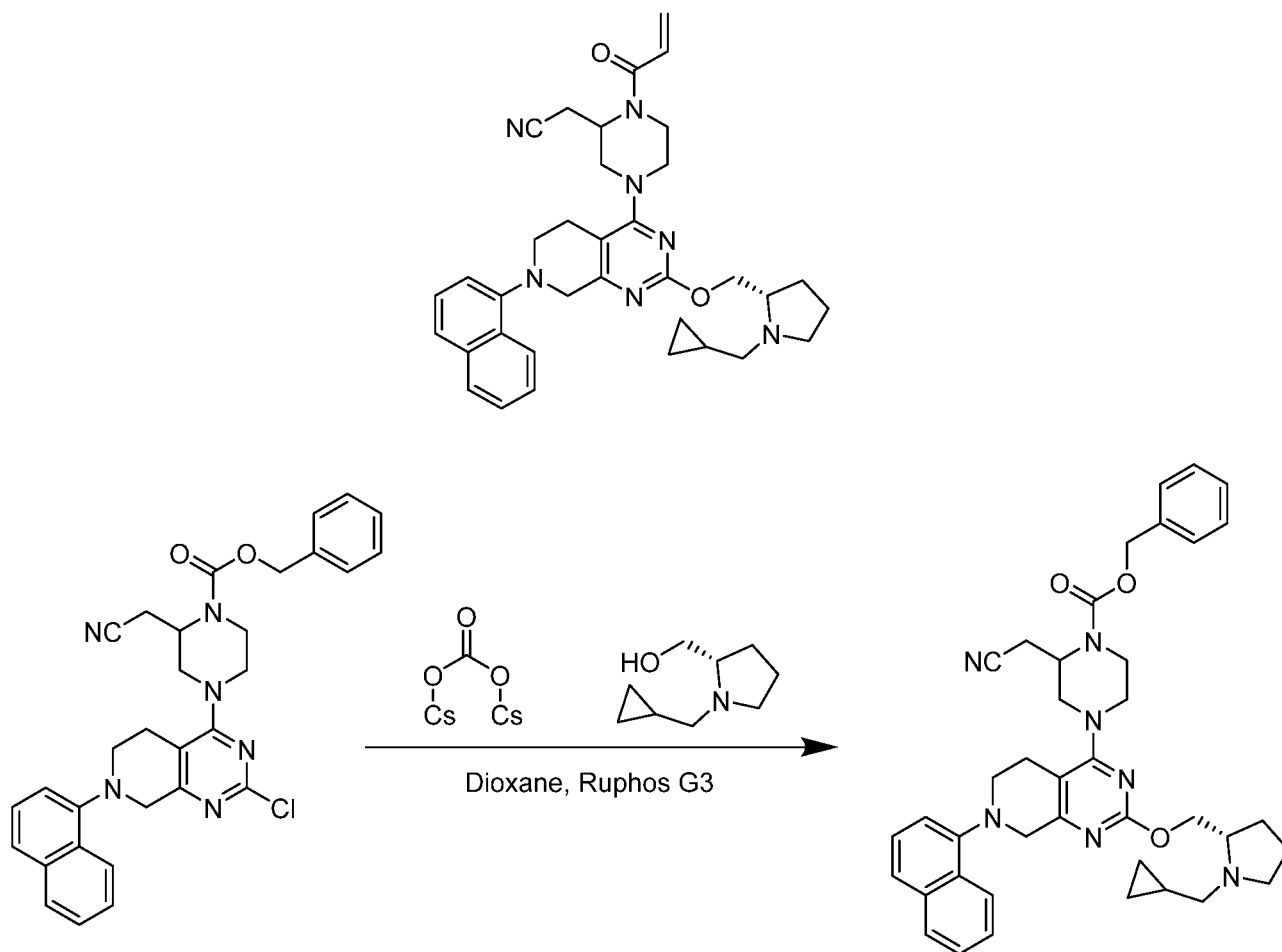
[0946] Step D: tert-butyl 2-(methoxymethyl)-4-(2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate: A mixture of tert-butyl 2-(methoxymethyl)-4-(2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-5,6,7,8-tetrahydropyrido-[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (150 mg, 0.315 mmol), Cs_2CO_3 (308 mg, 0.944 mmol), dioxane (1 mL), 1-iodonaphthalene (0.0689 mL, 0.472 mmol) and methanesulfonato(2-dicyclohexylphosphino-2',6'-di-*i*-propoxy-1,1'-biphenyl)(2-amino-1,1'-biphenyl-2-yl)palladium(II) (26.3 mg, 0.0315 mmol) (RuPhos-Pd-G3) was purged with nitrogen, the flask was capped and stirred at 70°C overnight. The reaction mixture was cooled, divided between EtOAc (15 mL) and water (5 mL), the organic layer was washed with water and brine (5 mL each), dried over Na_2SO_4 and evaporated in vacuo. The compound was purified by silica gel chromatography, Redisep 40g, using 4 to 10% MeOH +0.5% NH_4OH as eluent to give a colorless solid, 131 mg. ES+APCI MS m/z 603.3 $[M+H]^+$.



[0947] Step E: 1-(2-(methoxymethyl)-4-(2-(((S)-1-methylpyrrolidin-2-yl)methoxy))-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-1-yl)prop-2-en-1-one. Tert-butyl 2-(methoxymethyl)-4-(2-(((S)-1-methylpyrrolidin-2-yl)methoxy))-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (130 mg, 0.2157 mmol) was dissolved in 1M trifluoroacetic acid in DCM, and the resulted solution was allowed to stay at r.t. for 1h. The reaction mixture was divided between 2M Na₂CO₃ (5 mL) and DCM (15 mL), and the organic layer was evaporated in vacuo. The solid residue was dissolved in DCM (5 mL), cooled on ice-EtOH-CO₂ bath with stirring to -30°C and triethylamine (0.09 ml, 0.64 mmol) was added, followed by acryloyl chloride (0.035 ml, 0.43 mmol). After 1 min at -30°C the reaction mixture was quenched with NH₄OH (0.05 mL) and evaporated in vacuo and dried under high vacuum. The residue was dissolved in DCM (5 mL), filtered through a cotton plug and purified by silica gel chromatography, Redisep 40g, eluting with 5 to 10% MeOH/DCM +0.25% NH₄OH to give a colorless solid (19.6 mg, 16%). ES+APCI MS m/z 557.3, [M+H]⁺.

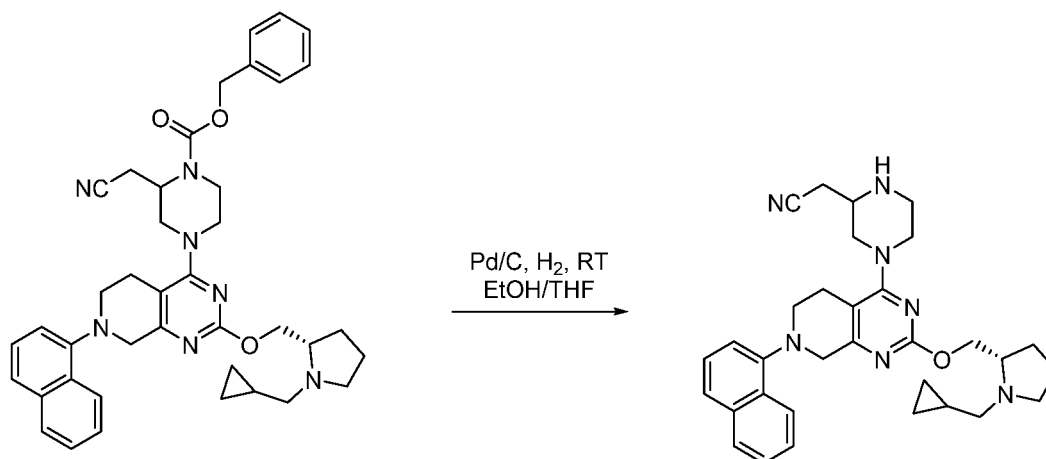
EXAMPLE 257

2-(1-acryloyl-4-(2-(((S)-1-(cyclopropylmethyl)pyrrolidin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile

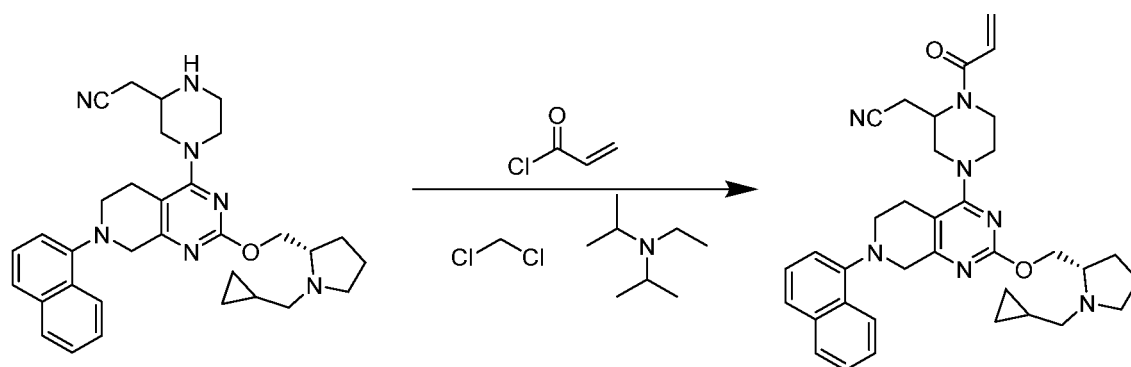


[0948] Step A: benzyl 2-(cyanomethyl)-4-(2-(((S)-1-(cyclopropylmethyl)pyrrolidin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate: In a conical bottom vial, a solution of benzyl 4-(2-chloro-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)-2-(cyanomethyl)piperazine-1-carboxylate (200 mg, 0.362 mmol) in dioxane (3616 μ l, 0.362 mmol) was sparged with Argon for 5 minutes. (S)-1-(cyclopropylmethyl)pyrrolidin-2-yl)methanol (168 mg, 1.08 mmol), Cs₂CO₃ (353 mg, 1.08 mmol), Rhuphos Pd G3 (30.2 mg, 0.0362 mmol) were sequentially added under Argon and sparged for an additional 5 minutes. The reaction mixture was capped and heated at 100°C for 1 hour. LC/MS showed reaction completion. EtOAc was added and washed with brine (2x). The combined organics were dried over Na₂SO₄ and concentrated in vacuo. The concentrate was

purified by flash chromatography eluting with 0-20% DCM/MeOH + 2% NH₄OH. All fractions containing clean desired product were combined and concentrated to give benzyl 2-(cyanomethyl)-4-(2-(((S)-1-(cyclopropylmethyl)pyrrolidin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (90 mg, 0.134 mmol, 37.0 % yield). ES+APCI MS *m/z* 672.4 [M+H]⁺.



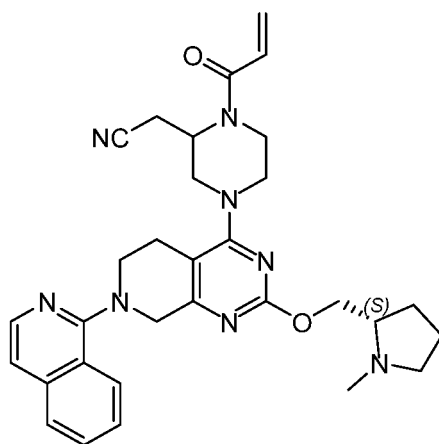
[0949] Step B: 2-(4-(2-(((S)-1-(cyclopropylmethyl)pyrrolidin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile: A solution of benzyl 2-(cyanomethyl)-4-(2-(((S)-1-(cyclopropylmethyl)pyrrolidin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate (90 mg, 0.13 mmol) in EtOH (1340 μ l, 0.13 mmol) and THF (1340 μ l, 0.13 mmol) was purged with N₂ for 5 min. To this solution was added Palladium (36 mg, 0.033 mmol) (Degussa Type, 10 wt%, 50% H₂O), and was immediately capped and purged with N₂ for an additional 5 min. The solution was then stirred under H₂ introduced via vacuum followed by balloon pressure. The mixture was then stirred at ambient temperature for 1 hour. LC/MS showed desired product. The mixture was diluted with MeOH and filtered through packed celite. The filtrate was then concentrated in vacuo to provide 2-(4-(2-(((S)-1-(cyclopropylmethyl)pyrrolidin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile (71 mg, 0.13 mmol, 99 % yield). ES+APCI MS *m/z* 538.3 [M+H]⁺.



[0950] Step C: 2-(1-acryloyl-4-(2-(((S)-1-(cyclopropylmethyl)pyrrolidin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile: To a suspension of 2-(4-(2-(((S)-1-(cyclopropylmethyl)pyrrolidin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile (71 mg, 0.132 mmol) in dichloromethane (1320 μ l, 0.132 mmol) at ambient temperature was added Acryloyl Chloride (10.7 μ l, 0.132 mmol) followed by Hunig's base (46.1 μ l, 0.264 mmol). The reaction was then stirred at ambient temperature for 1 hour. LC/MS showed reaction completion. The reaction mixture was concentrated in vacuo. The concentrate was resuspended in a 60:40 mixture of ACN:H₂O and purified on the Gilson (prep HPLC) eluting with 5-->95% ACN/0.1% TFA in water/0.1% TFA. Fractions containing product were combined and free based with saturated bicarb and the organics extracted with DCM. The organics were dried over MgSO₄ and concentrated in vacuo to give 2-(1-acryloyl-4-(2-(((S)-1-(cyclopropylmethyl)pyrrolidin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile (15.7 mg, 0.0265 mmol, 20.1 % yield). ES+APCI MS m/z 592.4[M+H]⁺.

EXAMPLE 258

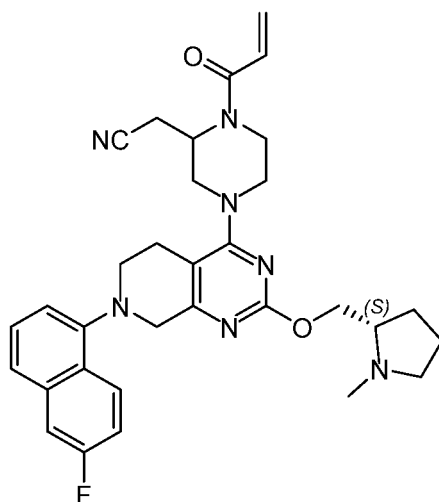
2-[4-[7-(1-isoquinolyl)-2-[[[(2*S*)-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-d]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile

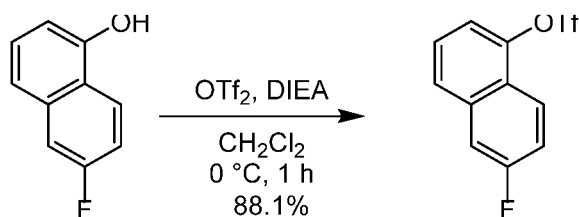


[0951] Title compound was prepared as in **Example 210** Steps E-G, substituting 1-bromoisoquinoline for 1-bromo-2-(trifluoromethyl)benzene in step E and also substituting prop-2-enoyl prop-2-enoate for acryloyl chloride in step G. ESI MS m/z 553.3 $[M+H]^+$.

EXAMPLE 259

2-[4-[7-(6-fluoro-1-naphthyl)-2-[[*(2S)*]-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5H-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile



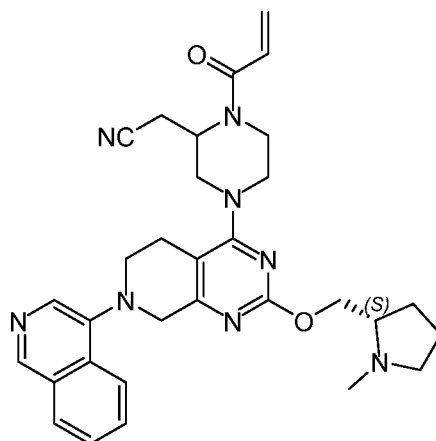


[0952] Step A: (6-fluoro-1-naphthyl) trifluoromethanesulfonate: To a solution of 6-fluoronaphthalen-1-ol (0.10 g, 617 μ mol) and DIEA (159 mg, 1.23 mmol, 215 μ L) in dichloromethane (3 mL) was added trifluoromethylsulfonyl trifluoromethanesulfonate (191 mg, 678 μ mol, 112 μ L,) at 0 °C. After stirred at 0 °C for 1 hour, the mixture was diluted with water (5 mL) and extracted with dichloromethane (3 $\times$ 5 mL). The organic layers were washed with brine (1 $\times$ 5 mL), dried over Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 3/1) to give (6-fluoro-1-naphthyl) trifluoromethanesulfonate (0.17 g, 543 μ mol, 88.1 % yield) as a colourless oil. ¹H NMR (400MHz, chloroform-d) δ = 8.10 (dd, J = 5.2, 8.8 Hz, 1H), 7.83 (d, J = 8.4 Hz, 1H), 7.58 - 7.50 (m, 2H), 7.48 - 7.40 (m, 2H).

[0953] Title compound was prepared as in **Example 210** Steps E-G, substituting 1(6-fluoro-1-naphthyl) trifluoromethanesulfonate for 1-bromo-2-(trifluoromethyl)benzene in step E and also substituting prop-2-enoyl prop-2-enoate for acryloyl chloride in step G. ESI MS m/z 570.3 [M+H]⁺.

EXAMPLE 260

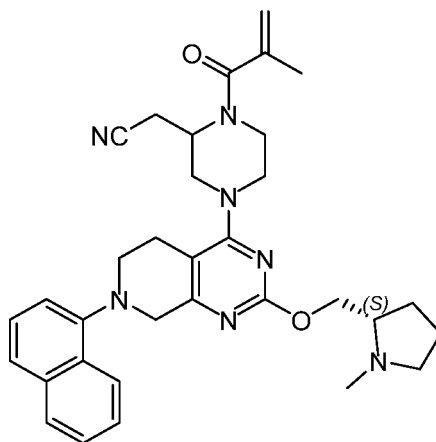
2-[4-[7-(4-isoquinolyl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile



[0954] Title compound was prepared as in **Example 210** Steps E-G, substituting 4-bromoisoquinoline for 1-bromo-2-(trifluoromethyl)benzene in step E and also substituting prop-2-enoyl prop-2-enoate for acryloyl chloride in step G. ESI MS m/z 553.1 $[M+H]^+$.

EXAMPLE 261

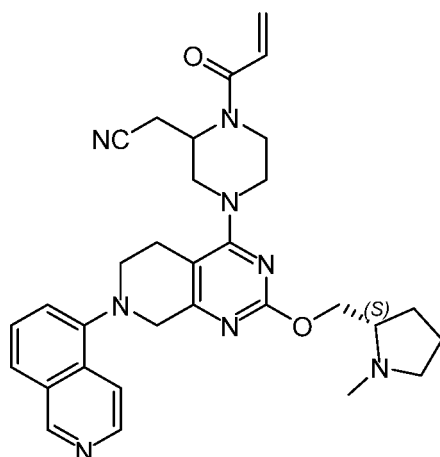
2-[1-(2-methylprop-2-enoyl)-4-[2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-7-(1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-2-yl]acetonitrile



[0955] Title compound was prepared as in **Example 210** Steps E-G, substituting 1-bromonaphthalene for 1-bromo-2-(trifluoromethyl)benzene in step E and also substituting 2-methylprop-2-enoyl chloride for acryloyl chloride in step G. ESI MS m/z 566.4 $[M+H]^+$.

EXAMPLE 262

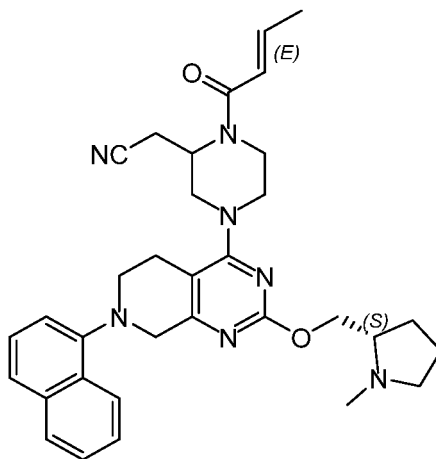
2-[4-[7-(5-isoquinolyl)-2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile



[0956] Title compound was prepared as in **Example 210** Steps E-G, substituting 5-bromoisquinoline for 1-bromo-2-(trifluoromethyl)benzene in step E and also substituting prop-2-enoyl prop-2-enoate for acryloyl chloride in step G. ESI MS m/z 553.4 $[M+H]^+$.

EXAMPLE 263

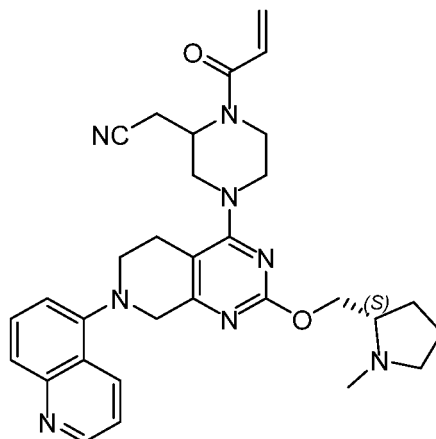
2-[1-[(*E*)-but-2-enoyl]-4-[2-[(2*S*)-1-methylpyrrolidin-2-yl]methoxy]-7-(1-naphthyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]piperazin-2-yl]acetonitrile



[0957] Title compound was prepared as in **Example 210** Steps E-G, substituting 1-bromonaphthalene for 1-bromo-2-(trifluoromethyl)benzene in step E and (*E*)-but-2-enoyl chloride for acryloyl chloride in step G. ESI MS m/z 566.4 $[M+H]^+$.

EXAMPLE 264

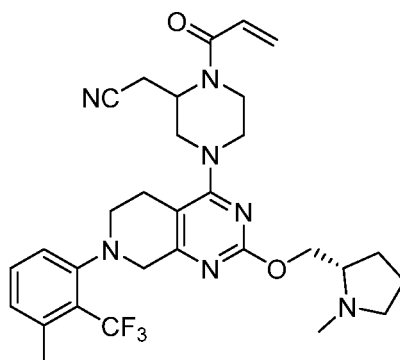
2-[4-[2-[[*(2S)*-1-methylpyrrolidin-2-yl]methoxy]-7-(5-quinolyl)-6,8-dihydro-5*H*-pyrido[3,4-*d*]pyrimidin-4-yl]-1-prop-2-enoyl-piperazin-2-yl]acetonitrile



[0958] Title compound was prepared as in **Example 210** Steps E-G, substituting 5-bromoquinoline for 1-bromo-2-(trifluoromethyl)benzene in step E and also substituting prop-2-enoyl prop-2-enoate for acryloyl chloride in step G. ESI MS m/z 553.4 $[M+H]^+$.

EXAMPLE 265

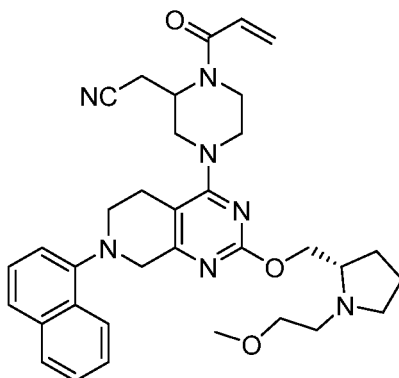
2-(1-acryloyl-4-(7-(3-methyl-2-(trifluoromethyl)phenyl)-2-(((*S*)-1-methylpyrrolidin-2-yl)methoxy)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl)piperazin-2-yl)acetonitrile



[0959] Title compound was synthesized according to Example 210, Steps E-G using 1-bromo-3-methyl-2-(trifluoromethyl)benzene for 1-bromonaphthalene in Step E ES+APCI MS m/z 584.3 $[M+H]^+$.

EXAMPLE 266

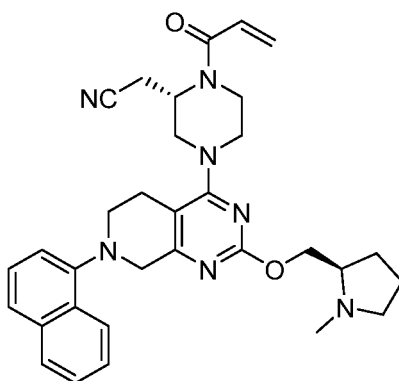
2-(1-acryloyl-4-(2-(((S)-1-(2-methoxyethyl)pyrrolidin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile



[0960] Title compound was synthesized according to Example 147, Steps F-J, using (S)-(1-(2-methoxyethyl)pyrrolidin-2-yl)methanol in place of (S)-(1-methylpyrrolidin-2-yl)methanol in Step F. ES+APCI MS m/z 596.3 [M+H]⁺.

EXAMPLE 267

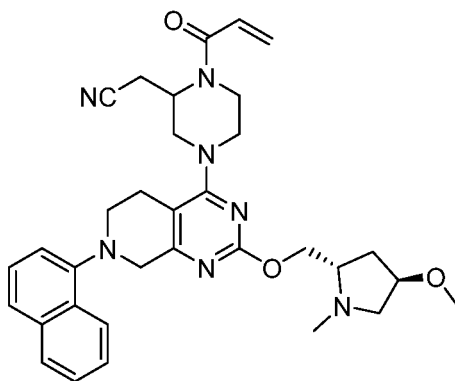
2-(((S)-1-acryloyl-4-(2-(((R)-1-methylpyrrolidin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile



[0961] Title compound was synthesized according to Example 234 using (R)-(1-methylpyrrolidin-2-yl)methanol in place of (S)-(1-methylpyrrolidin-2-yl)methanol in Step F. ES+APCI MS m/z 552.3 [M+H]⁺.

EXAMPLE 268

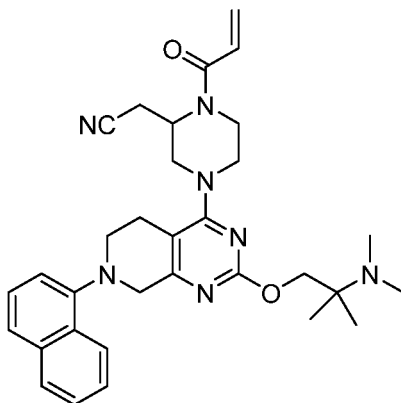
2-(1-acryloyl-4-(2-(((2S,4R)-4-methoxy-1-methylpyrrolidin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile



[0962] Title compound was synthesized according to **Example 220**, (Steps C-G), using tert-butyl (2S,4R)-2-(hydroxymethyl)-4-methoxypyrrolidine-1-carboxylate in place of (2S,4R)-1-(tert-Butoxycarbonyl)-4-fluoro-2-hydroxymethylpyrrolidine in Step C. ES+APCI MS m/z 582.3 $[M+H]^+$.

EXAMPLE 269

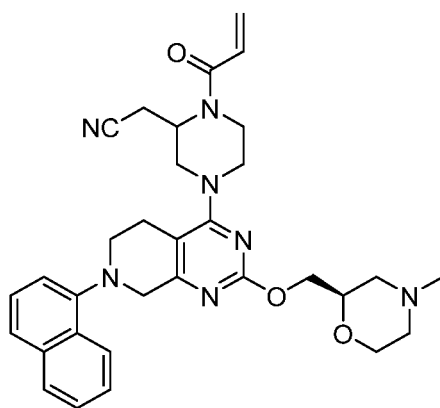
2-(1-acryloyl-4-(2-(2-(dimethylamino)-2-methylpropoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile



[0963] The title compound was synthesized following **Example 147** substituting 2-Dimethylamino-2-methyl-1-propanol for (S)-(1-(cyclopropylmethyl)pyrrolidin-2-yl)methanol in Step F. ES+APCI MS m/z 554.4 $[M+H]^+$.

EXAMPLE 270

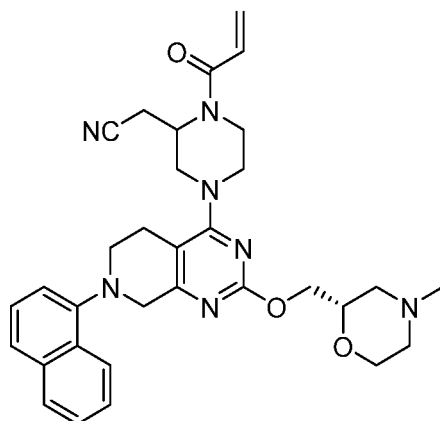
2-(1-acryloyl-4-(2-(((R)-4-methylmorpholin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile



[0964] Title compound was synthesized according to **Example 147**, Steps F-J, using (R)-N-Boc-2-hydroxymethylmorpholine in place of (S)-(1-methylpyrrolidin-2-yl)methanol in Step F. ES+APCI MS m/z 568.3 $[M+H]^+$.

EXAMPLE 271

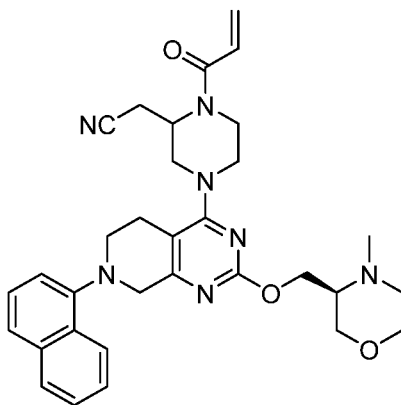
2-(1-acryloyl-4-(2-(((S)-4-methylmorpholin-2-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile



[0965] Title compound was synthesized according to **Example 147**, Steps F-J, using (S)-N-Boc-2-hydroxymethylmorpholine in place of (S)-(1-methylpyrrolidin-2-yl)methanol in Step F. ES+APCI MS m/z 568.3 $[M+H]^+$.

EXAMPLE 272

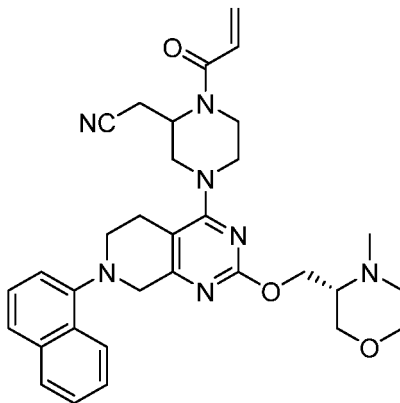
2-(1-acryloyl-4-(2-(((S)-4-methylmorpholin-3-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile



[0966] Title compound was synthesized according to **Example 147**, Steps F-J, using tert-butyl (R)-3-(hydroxymethyl)morpholine-4-carboxylate in place of (S)-(1-methylpyrrolidin-2-yl)methanol in Step F. ES+APCI MS m/z 568.3 $[M+H]^+$.

EXAMPLE 273

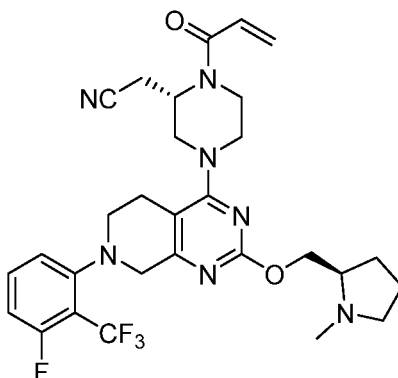
2-(1-acryloyl-4-(2-(((R)-4-methylmorpholin-3-yl)methoxy)-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile



[0967] Title compound was synthesized according to **Example 147**, Steps F-J, using tert-butyl (S)-3-(hydroxymethyl)morpholine-4-carboxylate in place of (S)-(1-methylpyrrolidin-2-yl)methanol in Step F. ES+APCI MS m/z 568.3 $[M+H]^+$.

EXAMPLE 274

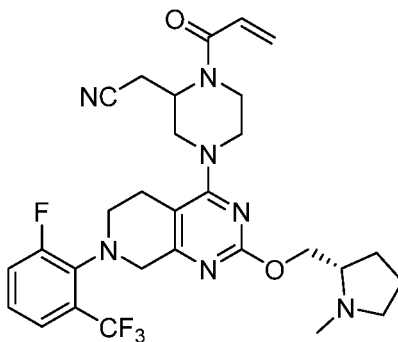
2-((S)-1-acryloyl-4-(7-(3-fluoro-2-(trifluoromethyl)phenyl)-2-(((R)-1-methylpyrrolidin-2-yl)methoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile



[0968] Title compound was synthesized according to **Example 234**, Steps G-J using (R)-(1-methylpyrrolidin-2-yl)methanol in place of (S)-(1-methylpyrrolidin-2-yl)methanol in Step F and 1-bromo-3-fluoro-2-(trifluoromethyl)benzene for 1-bromonaphthalene in Step H. ES+APCI MS m/z 588.3 $[M+H]^+$.

EXAMPLE 275

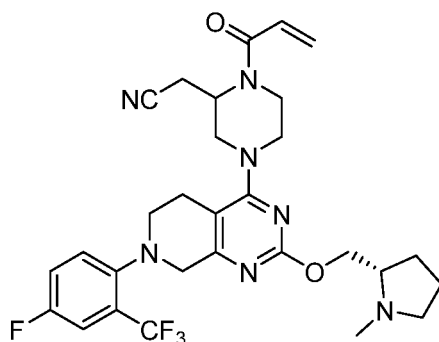
2-(1-acryloyl-4-(7-(2-fluoro-6-(trifluoromethyl)phenyl)-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile



[0969] Title compound was synthesized according to **Example 210**, Steps E-G using 2-bromo-1-fluoro-3-(trifluoromethyl)benzene for 1-bromonaphthalene in Step E. ES+APCI MS m/z 588.3 $[M+H]^+$.

EXAMPLE 276

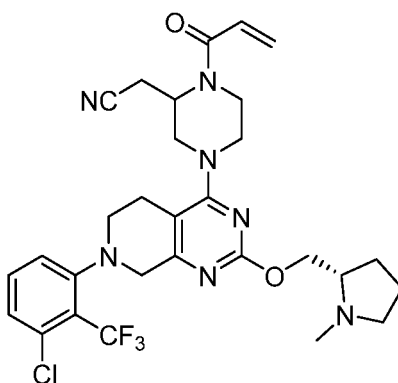
2-(1-acryloyl-4-(7-(4-fluoro-2-(trifluoromethyl)phenyl)-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile



[0970] Title compound was synthesized according to **Example 210**, Steps E-G using 1-bromo-4-fluoro-2-(trifluoromethyl)benzene for 1-bromonaphthalene in Step E. ES+APCI MS m/z 588.3 $[M+H]^+$.

EXAMPLE 277

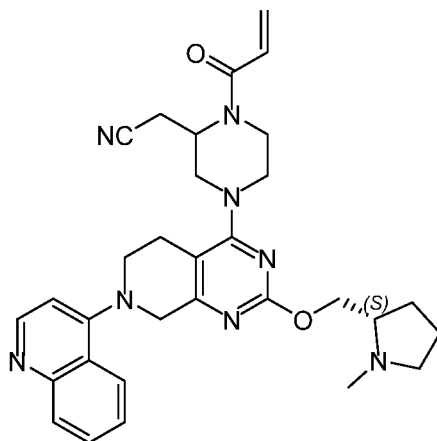
2-(1-acryloyl-4-(7-(3-chloro-2-(trifluoromethyl)phenyl)-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile



[0971] Title compound was synthesized according to **Example 210**, Steps E-G using 1-bromo-3-chloro-2-(trifluoromethyl)benzene for 1-bromonaphthalene in Step E and THF in place EtOH/THF in Step F. ES+APCI MS m/z 604.3 $[M+H]^+$.

EXAMPLE 278

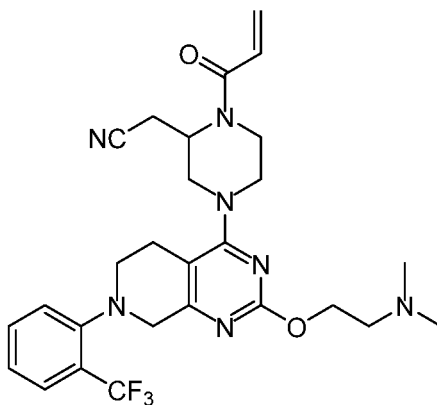
2-(1-acryloyl-4-(2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-7-(quinolin-4-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile



[0972] Title compound was prepared as in **Example 210** Steps E-G, substituting 4-bromoquinoline for 1-bromo-2-(trifluoromethyl)benzene in step E and also substituting prop-2-enoyl prop-2-enoate for acryloyl chloride in step G.

EXAMPLE 279

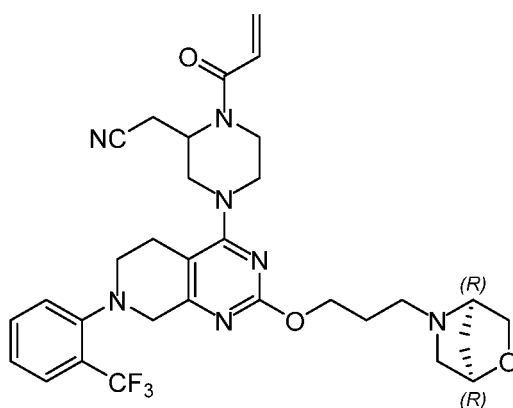
2-(1-acryloyl-4-(2-(2-(dimethylamino)ethoxy)-7-(2-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile



[0973] Title compound was prepared as in **Example 210**, substituting N, N-dimethyl-ethanolamine for (2S)-1-Ethyl-2-pyrrolidinyl]methanol in step C and also substituting prop-2-enoyl prop-2-enoate for acryloyl chloride in step G.

EXAMPLE 280

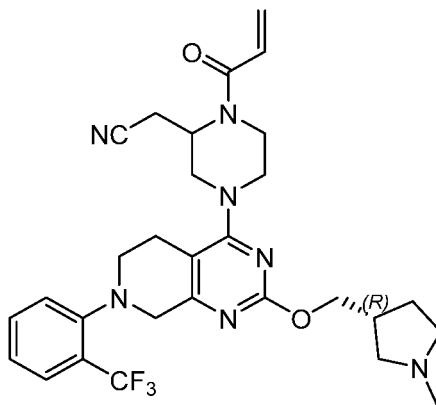
2-(4-(2-(3-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)propoxy)-7-(2-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)-1-acryloylpiperazin-2-yl)acetonitrile



[0974] Title compound was prepared as in **Example 210**, substituting 3-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)propan-1-ol for (2S)-1-Ethyl-2-pyrrolidinyl]methanol in step C and also substituting prop-2-enoyl prop-2-enoate for acryloyl chloride in step G.

EXAMPLE 281

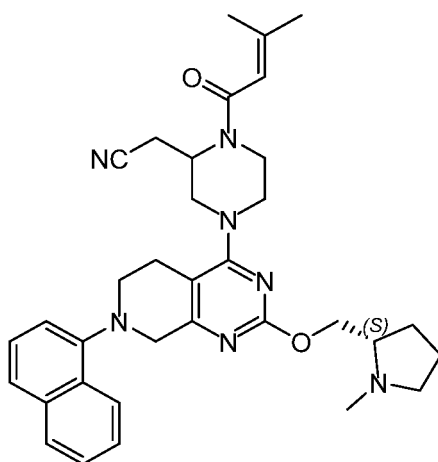
2-(1-acryloyl-4-(2-(((R)-1-methylpyrrolidin-3-yl)methoxy)-7-(2-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile



[0975] Title compound was prepared as in **Example 210**, substituting (R)-(1-methylpyrrolidin-3-yl)methanol for (2S)-1-Ethyl-2-pyrrolidinyl]methanol in step C and also substituting prop-2-enoyl prop-2-enoate for acryloyl chloride in step G.

EXAMPLE 282

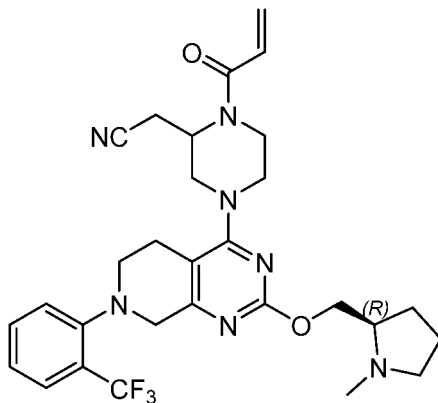
2-(1-(3-methylbut-2-enoyl)-4-(2-(((S)-1-methylpyrrolidin-2-yl)methoxy))-7-(naphthalen-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile



[0976] Title compound was prepared as in **Example 210**, substituting 1-bromonaphthalene for 1-bromo-2-(trifluoromethyl)benzene in step E and 3-methylbut-2-enoyl chloride for acryloyl chloride in step G.

EXAMPLE 283

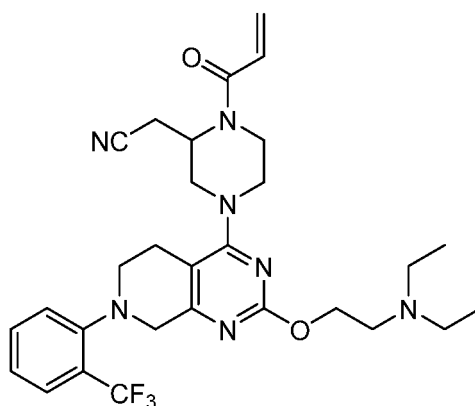
2-(1-acryloyl-4-(2-(((R)-1-methylpyrrolidin-2-yl)methoxy))-7-(2-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile



[0977] Title compound was prepared as in **Example 210**, substituting (2R)-1-Ethyl-2-pyrrolidinyl]methanol for (2S)-1-Ethyl-2-pyrrolidinyl]methanol in step C and also substituting prop-2-enoyl prop-2-enoate for acryloyl chloride in step G.

EXAMPLE 284

2-(1-acryloyl-4-(2-(2-(diethylamino)ethoxy)-7-(2-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)piperazin-2-yl)acetonitrile



[0978] Title compound was prepared as in **Example 210**, substituting N, N-diethyl-ethanolamine for (2S)-1-Ethyl-2-pyrrolidinyl]methanol in step C and also substituting prop-2-enoyl prop-2-enoate for acryloyl chloride in step G.

EXAMPLE A

KRas G12C Modification Assay

[0979] This Example illustrates that exemplary compounds of the present invention covalently bind to KRas G12C using a LCMS assay to detect a covalent adduct of the exemplary compound and KRAS G12C.

[0980] The protein concentration of GDP-loaded K-Ras (1-169) G12C, C51S,C80L,C118S and GTP-loaded K-Ras (1-169) G12C,C51S,C80L,C118S,Q61H was adjusted to 2 μ M in K-Ras Assay Buffer (25 mM HEPES, 150 mM NaCl, 5 mM MgCl₂, and 10 mM Octyl β -glucopyranoside at pH 7.5). A 10 μ L aliquot of each protein solution was then transferred to a 384 well microtiter plate. Initial compound stocks were generated at fifty times their desired final assay concentration in DMSO.

[0981] Exemplary compounds of Formula (I) were diluted 25-fold into K-Ras Assay Buffer to a final of two times their final concentration. A 10 μ L aliquot of each diluted compound solution was then added to each of the protein solutions in the microtiter plate to initiate reaction. Typical final compound concentrations were 3.0, 5.0 and 25.0 μ M. At each time point, the reactions were quenched with 20 μ L of a 25 mM acetic acid solution. Usual assay endpoints were 15, 180 and 1440 minutes. Once all reactions were quenched, the plates were heat sealed and the samples were injected into a LC/MS system for data acquisition.

[0982] Data collection took place on an Agilent 6520 Q-TOF Accurate Mass Spectrometer. Samples were injected in their liquid phase onto a C-3 reverse phase column to remove assay buffer and prepare the samples for mass spectrometer. The proteins were eluted from the column using an acetonitrile gradient and fed directly into the mass analyzer. Initial raw data analysis took place in Agilent MassHunter software immediately post data acquisition.

[0983] Raw data analysis of the intact protein was exclusively a deconvolution of the multiple charge states of each protein in solution using a maximum entropy deconvolution provided in Mass Hunter. To minimize complexity, only the data over limited mass ranges were considered for analysis, with a minimum of one Dalton mass step intervals. The heights of all masses identified during raw data analysis were exported to be further analyzed in Spotfire® data analysis software.

[0984] Final data analysis was a multistep process in the Spotfire® data analysis software package. Briefly, each protein mass was calculated as a percent of the total signal of that sample, that percentage was then normalized to the percentage of signal of the protein in the absence of reactive compounds. Those normalized signals were reported as normalized percent of control (POC). An increased POC value indicates a compound that displays a higher degree of modification at a given condition compared to other compounds under the same conditions. The results for exemplary compounds of Formula (I) tested at 5 μ M concentration for 3 hours are shown in Table 1. Key: "A" $\leq$ 25% POC; "B" $>$ 25% POC - $\leq$ 50% POC; "C" $>$ 50% POC and ND = not determined.

Table 1

Inhibition of KRas G12C Activity by Exemplary Compounds of Formula (I)

Example No.	POC	Example No.	POC
1	B	140	C
2	A	141	C
3	A	142	C
4	A	143	C
5	A	144	C
6	B	145	C
7	A	146	B
8	B	147	C
9	C	148	C
10	C	149	B
11	C	150	C
12	C	151	B
13	C	152	C
14	C	153	C
15	C	154	C
16	C	155	C
17	B	156	C
18	C	157	C
19	C	158	C
20	C	159	C
21	C	160	C
22	C	161	C
23	C	162	B
24	A	163	C
25	A	164	C
26	C	165	C
27	C	166	B
28	C	167	B
29	C	168	C
30	A	169	C
31	B	170	C
32	C	171	C
33	B	172	C
34	A	173	C
35	C	174	C
36	C	175	C
37	C	176	C
38	C	177	C
39	C	178	C
40	C	179	C
41	A	180	C
42	A	181	C
43	C	182	C
44	C	183	C

45	A	184	C
46	A	185	C
47	C	186	B
48	C	187	C
49	B	188	C
50	C	189	C
51	A	190	C
52	C	191	C
53	C	192	C
54	A	193	C
55	C	194	C
56	C	195	C
57	C	196	C
58	C	197	C
59	C	198	C
60	C	199	C
61	C	200	C
62	C	201	B
63	C	202	C
64	C	203	C
65	C	204	C
66	C	205	C
67	C	206	C
68	A	207	C
69	A	208	C
70	C	209	C
71	A	210	C
72	C	211	C
73	C	212	C
74	C	213	C
75	C	214	C
76	C	215	C
77	C	216	C
78	C	217	C
79	A	218	C
80	C	219	C
81	C	220	C
82	C	221	C
83	C	222	C
84	A	223	C
85	C	224	C
86	A	225	C
87	A	226	C
88	C	227	A
89	C	228	C

90	C	229	C
91	A	230	C
92	C	231	C
93	C	232	C
94	A	233	C
95	A	234	C
96	A	235	C
97	C	236	C
98	C	237	C
99	C	238	C
100	C	239	C
101	C	240	C
102	C	241	C
103	C	242	C
104	C	243	C
105	B	244	C
106	A	245	C
107	C	246	C
108	C	247	C
109	C	248	C
110	C	249	C
111	C	250	C
112	A	251	C
113	C	252	ND
114	B	253	ND
115	C	254	ND
116	C	255	ND
117	C	256	C
118	A	257	C
119	B	258	C
120	C	259	C
121	C	260	C
122	C	261	A
123	A	262	A
124	C	263	C
125	A	264	C
126	C	265	C
127	C	266	C
128	C	267	C
129	C	268	C
130	C	269	C
131	C	270	C
132	C	271	C
133	C	272	C
134	C	273	C

135	C	274	C
136	C	275	C
137	C	276	C
138	C	277	C
139	C		

EXAMPLE B

Inhibition of KRas G12C-dependent Cell Growth

[0985] This Example illustrates that exemplary compounds of the present invention inhibit the growth of tumor cell lines that express KRas G12C.

[0986] The cellular inhibition of KRAs G12C by exemplary compounds of the present invention was determined by measuring the amount of a downstream marker of KRas activity, phosphorylated ERK ("Phospho-ERK").

[0987] NCI-H358 cells (ATCC CRL-5807) express KRas G12C and were grown in RPMI medium supplemented with 10% fetal bovine serum, penicillin/streptomycin and 10 mM HEPES. Cells were plated in poly-D-Lysine coated 96-well plates at a concentration of 50,000 cells/well and allowed to attach for 8-12 hours. Diluted compounds were then added at a final concentration of 0.5 % DMSO. After 3 hours, the medium was removed, 150 μ L of 4% formaldehyde was added and the plates were incubated for 20 minutes. The plates were washed with PBS, and permeabilized using 150 μ L of ice cold 100% methanol for 10 minutes. Non-specific antibody binding to the plates was blocked using 100 μ L Licor Blocking Buffer (Li-Cor Biotechnology, Lincoln NE) for 1 hour at room temperature. Positive control samples and samples lacking cells were parallel processed with test samples as standards.

[0988] The amount Phospho-ERK was determined using an antibody specific for the phosphorylated form of ERK and compared to the amount of GAPDH. Primary antibodies used for detection were added as follows: Phospho-ERK (Cell Signaling cs9101) diluted 1:500 and GAPDH (Millipore MAB374) diluted 1:5000 in Licor block + 0.05% Tween 20. The plates were incubated for 2 hours at room temperature. The plates were washed with PBS + 0.05% Tween 20.

[0989] Secondary antibodies used to visualize primary antibodies were added as follows: Anti-rabbit-680 diluted 1:1000 and Anti-mouse-800 diluted 1:1000 in Licor Block + 0.05% Tween 20 and incubated for 1 hour at room temperature. The plates were washed with PBS + 0.05% Tween 20. A 100 μ L aliquot of PBS was added to each well and the plates were read on a LICOR AERIUS plate reader.

[0990] The pERK(Thr202/Tyr204) signal was normalized with the GAPDH signal and percent of DMSO control values were calculated. IC₅₀ values were generated using a 4 parameter fit of the dose response curve. The results for exemplary compounds of Formula (I) are shown in Table 2. Key: "A" $\geq 0.001 - \leq 1$ μ M; "B" > 1 μ M and ND = not determined.

Table 2

Inhibition of KRas G12C-mediated Cell Proliferation by Exemplary Compounds

Example No.	IC ₅₀	Example No.	IC ₅₀
1	B	140	B
2	B	141	B
3	B	142	B
4	B	143	B
5	B	144	A
6	B	145	A
7	B	146	B
8	B	147	A
9	B	148	A
10	B	149	A
11	A	150	A
12	B	151	B
13	B	152	A
14	B	153	A
15	B	154	A
16	B	155	A
17	B	156	A
18	B	157	B
19	A	158	B
20	B	159	B
21	A	160	B
22	B	161	B
23	B	162	B
24	B	163	B
25	B	164	B
26	B	165	B

27	A	166	B
28	A	167	B
29	B	168	B
30	B	169	A
31	B	170	A
32	A	171	B
33	B	172	B
34	B	173	B
35	B	174	B
36	B	175	A
37	B	176	A
38	A	177	A
39	A	178	A
40	A	179	A
41	B	180	A
42	B	181	B
43	B	182	A
44	B	183	A
45	B	184	B
46	B	185	A
47	B	186	B
48	B	187	A
49	B	188	A
50	B	189	B
51	B	190	A
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53	B	192	A
54	B	193	A
55	A	194	B
56	A	195	B
57	B	196	A
58	B	197	A
59	B	198	B
60	B	199	B
61	B	200	B
62	B	201	B
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64	A	203	A
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66	B	205	B
67	A	206	A
68	B	207	B
69	B	208	B
70	B	209	B
71	B	210	A

72	A	211	A
73	B	212	A
74	A	213	B
75	A	214	B
76	B	215	B
77	A	216	B
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80	B	219	B
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83	B	222	A
84	B	223	A
85	B	224	A
86	B	225	A
87	B	226	A
88	A	227	A
89	A	228	A
90	A	229	A
91	B	230	A
92	A	231	A
93	B	232	B
94	B	233	A
95	B	234	A
96	B	235	A
97	A	236	A
98	B	237	A
99	B	238	A
100	B	239	B
101	A	240	B
102	A	241	B
103	A	242	A
104	A	243	A
105	B	244	A
106	B	245	A
107	B	246	A
108	A	247	B
109	B	248	B
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113	B	252	ND
114	B	253	ND
115	A	254	ND
116	A	255	ND

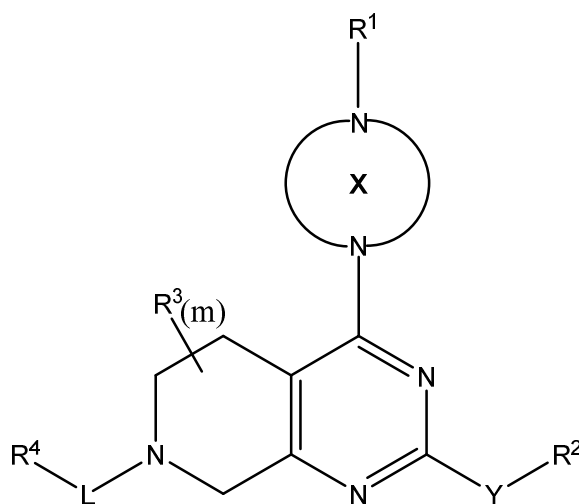
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124	B	263	A
125	B	264	B
126	B	265	A
127	A	266	A
128	B	267	A
129	A	268	A
130	A	269	A
131	A	270	A
132	A	271	A
133	B	272	A
134	B	273	B
135	A	274	A
136	B	275	A
137	B	276	A
138	B	277	A
139	B		

[0991] While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice within the art to which the invention pertains and as may be applied to the essential features hereinbefore set forth, and as follows in the scope of the appended claims.

CLAIMS

WE CLAIM:

1. A compound of formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof:

wherein:

X is a 4-12 membered saturated or partially saturated monocyclic, bridged or spirocyclic ring, wherein the saturated or partially saturated monocyclic ring is optionally substituted with one or more R⁸;

Y is a bond, O, S or NR⁵;

R¹ is $-\text{C}(\text{O})\text{C}(\text{R}^{\text{A}}) \text{-----} \text{C}(\text{R}^{\text{B}})_p$ or $-\text{SO}_2\text{C}(\text{R}^{\text{A}}) \text{-----} \text{C}(\text{R}^{\text{B}})_p$;

R² is hydrogen, alkyl, hydroxyalkyl, dihydroxyalkyl, alkylaminylalkyl, dialkylaminylalkyl, -Z-NR⁵R¹⁰, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, or heteroarylalkyl, wherein each of the Z, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl may be optionally substituted with one or more R⁹;

Z is C1 – C4 alkylene;

each R³ is independently C1 – C3 alkyl, oxo, or haloalkyl;

L is a bond, -C(O)-, or C1 – C3 alkylene;

R⁴ is hydrogen, cycloalkyl, heterocyclyl, aryl, aralkyl or heteroaryl, wherein each of the cycloalkyl, heterocyclyl, aryl, aralkyl and heteroaryl may be optionally substituted with one or more R⁶ or R⁷;

each R⁵ is independently hydrogen or C1 – C3 alkyl;

R⁶ is cycloalkyl, heterocyclyl, heterocyclalkyl, aryl, or heteroaryl, wherein each of the cycloalkyl, heterocyclyl, aryl, or heteroaryl may be optionally substituted with one or more R⁷;

each R⁷ is independently halogen, hydroxyl, C1 – C6 alkyl, cycloalkyl, alkoxy, haloalkyl, amino, cyano, heteroalkyl, hydroxyalkyl or Q-haloalkyl, wherein Q is O or S;

R⁸ is oxo, C1 – C3 alkyl, C2 – C4 alkynyl, heteroalkyl, cyano, -C(O)OR⁵, -C(O)N(R⁵)₂, -N(R⁵)₂, wherein the C1 – C3 alkyl may be optionally substituted with cyano, halogen, -OR⁵, -N(R⁵)₂, or heteroaryl;

each R⁹ is independently hydrogen, oxo, acyl, hydroxyl, hydroxyalkyl, cyano, halogen, C1 – C6 alkyl, aralkyl, haloalkyl, heteroalkyl, cycloalkyl, heterocyclalkyl, alkoxy, dialkylaminyl, dialkylamidalkyl, or dialkylaminylalkyl, wherein the C1 – C6 alkyl may be optionally substituted with cycloalkyl;

each R¹⁰ is independently hydrogen, acyl, C1 – C3 alkyl, heteroalkyl or hydroxyalkyl;

R^A is absent, hydrogen, or C1 – C3 alkyl;

each R^B is independently hydrogen, C1 – C3 alkyl, alkylaminylalkyl, dialkylaminylalkyl or heterocyclalkyl;

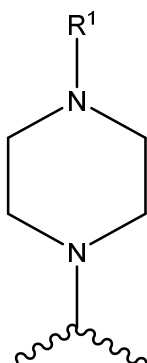
m is zero or an integer between 1 and 2;

p is one or two; and wherein,

when $\equiv$ is a triple bond then R^A is absent, R^B is present and p equals one,

or when $=$ is a double bond then R^A is present, R^B is present and p equals two, or R^A, R^B and the carbon atoms to which they are attached form a 5-8 membered partially saturated cycloalkyl optionally substituted with one or more R⁷.

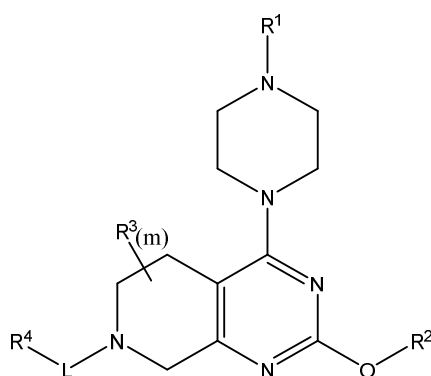
2. The compound of claim 1, wherein R¹-X is:



wherein the piperazinyl ring is optionally substituted with R⁸.

3. The compound of claim 2, wherein R¹ is $-\text{C}(\text{O})\text{C}(\text{R}^{\text{A}}) \text{---} \text{C}(\text{R}^{\text{B}})_p$, wherein --- is a triple bond R^A is absent, p is one and R^B is C1 – C3 alkyl, or --- is a double bond, R^A is hydrogen or C1 – C3 alkyl, p is two and each R^B is independently hydrogen, C1 – C3 alkyl, dialkylaminylalkyl or heterocyclalkyl.
4. The compound of claim 1, wherein R¹ is $-\text{C}(\text{O})\text{CH}=\text{CH}_2$.
5. The compound of according to claim 1, wherein Y is O.
6. The compound of claim 1, wherein R² is heterocyclalkyl.
7. The compound of claim 6, wherein the heterocycl of the heterocyclalkyl is independently azetidiny, methylazetidiny, difluoroazetidiny, tetrahydropyran, pyrrolidiny, methylpyrrolidiny, diethylpyrrolidiny, isopropylpyrrolidiny, cycloalkylalkylpyrrolidiny, hydroxypyrrolidiny, fluoropyrrolidiny, difluoropyrrolidiny, methoxyethylpyrrolidiny, (N-methyl)methoxypyrrolidiny, piperazinyl, dimethylaminylpyrrolidiny, morpholinyl, methylmorpholinyl, 1,4-oxazepanyl, piperdiny, methylpiperidiny acylpiperdiny, cyanopiperdiny, cycloalkylpiperdiny, halopiperdiny, dihalopiperdiny, fluoropiperdiny, difluoropiperdiny, alkoxy piperdiny, pyrrolidonyl, piperidinonyl, thiomorpholinyl-1,1-dioxide, 3-azabicyclo[3.1.0]hexanyl, oxa-5-azabicyclo[2.2.1]heptan-5-yl, or azabicyclo[2.2.1]heptan-2-yl.
8. The compound of claim 1, wherein R² is $-\text{ZNR}^5\text{R}^{10}$.

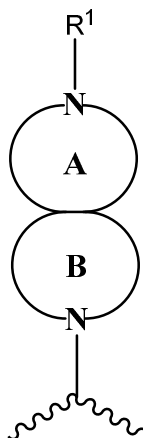
9. The compound according to claim 1, wherein R^4 is aryl optionally substituted with one or more R^7 .
10. The compound of claim 9, wherein the aryl is selected from the group consisting of phenyl and naphthyl optionally substituted with one or more R^7 .
11. The compound according to any one of claims 2-10, wherein R^4 is heteroaryl.
12. The compound of claim 11, wherein the heteroaryl is pyridinyl, indolyl, indazolyl, quinolinyl, isoquinolinyl or benzo[d]thiazolyl.
13. The compound according to claim 1, wherein R^4 is aralkyl optionally substituted with one or more R^7 .
14. The compound according to claim 1, wherein L is a bond.
15. The compound according to claim 1, wherein R^8 is heteroalkyl, C2-C4 alkynyl, or C1 – C3alkyl optionally substituted with $-OR^5$, cyano or heteroaryl.
16. The compound of claim 13, wherein R^8 is C1 – C3 alkyl substituted with $-OR^5$.
17. The compound of claim 13, wherein R^8 is oxazolylmethyl.
18. The compound of claim 1, wherein the compound is of Formula I-B:



Formula I-B

where the piperazinyl ring is optionally substituted with R^8 , and R^1 , R^3 , R^4 , R^9 , L and m are as defined in claim 1.

19. The compound of claim 16, wherein R^2 is heterocyclylalkyl.
20. The compound of claim 17, wherein the heterocyclyl portion of the heterocyclylalkyl of R^2 is pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, 1,4-oxazepanyl, thiomorpholinyl-1,1-dioxide, 3-azabicyclo[3.1.0]hexanyl, 2-oxa-5-azabicyclo[2.2.1]heptan-5-yl, or azabicyclo[2.2.1]heptan-2-yl, each optionally substituted with one or more R^9 .
21. The compound of claim 13, wherein R^8 is heteroalkyl, C2-C4 alkynyl, or C1 – C3alkyl optionally substituted with $-OR^5$, cyano or heteroaryl.
22. The compound according to any one of claims 18-21, wherein L is a bond and R^4 is aryl or heteroaryl, each optionally substituted with one or more R^6 or R^7 .
23. The compound of claim 1, wherein R^1 -X is:

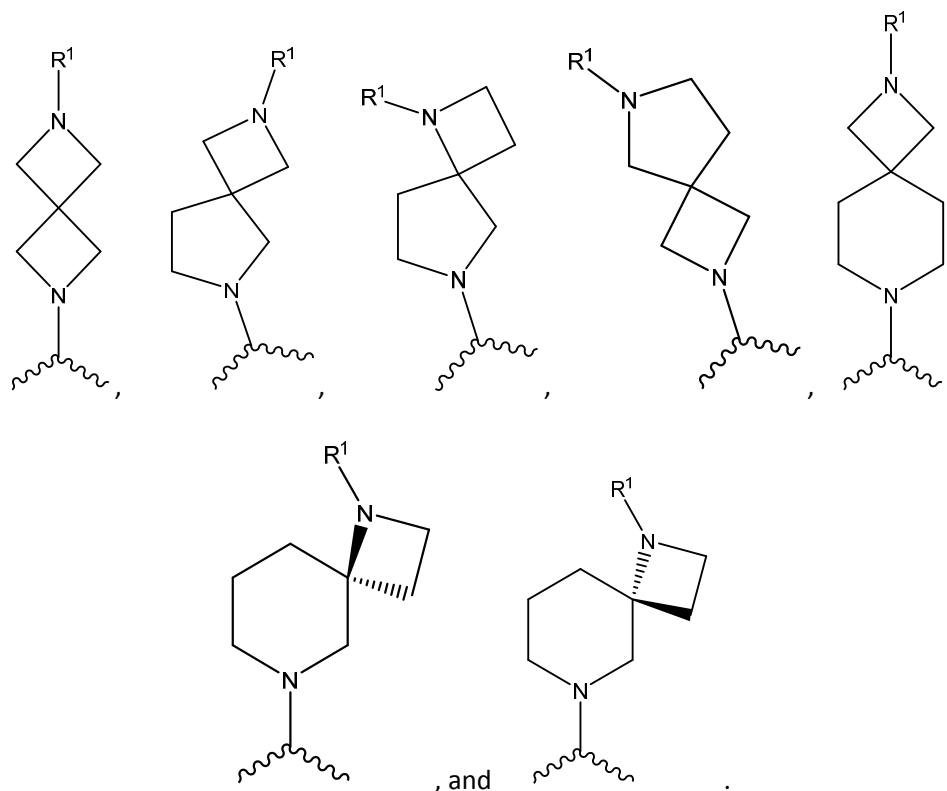


wherein A and B are a spirocyclic ring system, wherein A and B are the same or different and independently represent a 4-6 membered saturated ring system optionally substituted with one or more R^8 .

24. The compound according to claim 18, wherein R^4 is aryl optionally substituted with one or more R^7 .
25. The compound of claim 22, wherein the aryl is selected from the group consisting of phenyl and naphthyl optionally substituted with one or more R^7 .

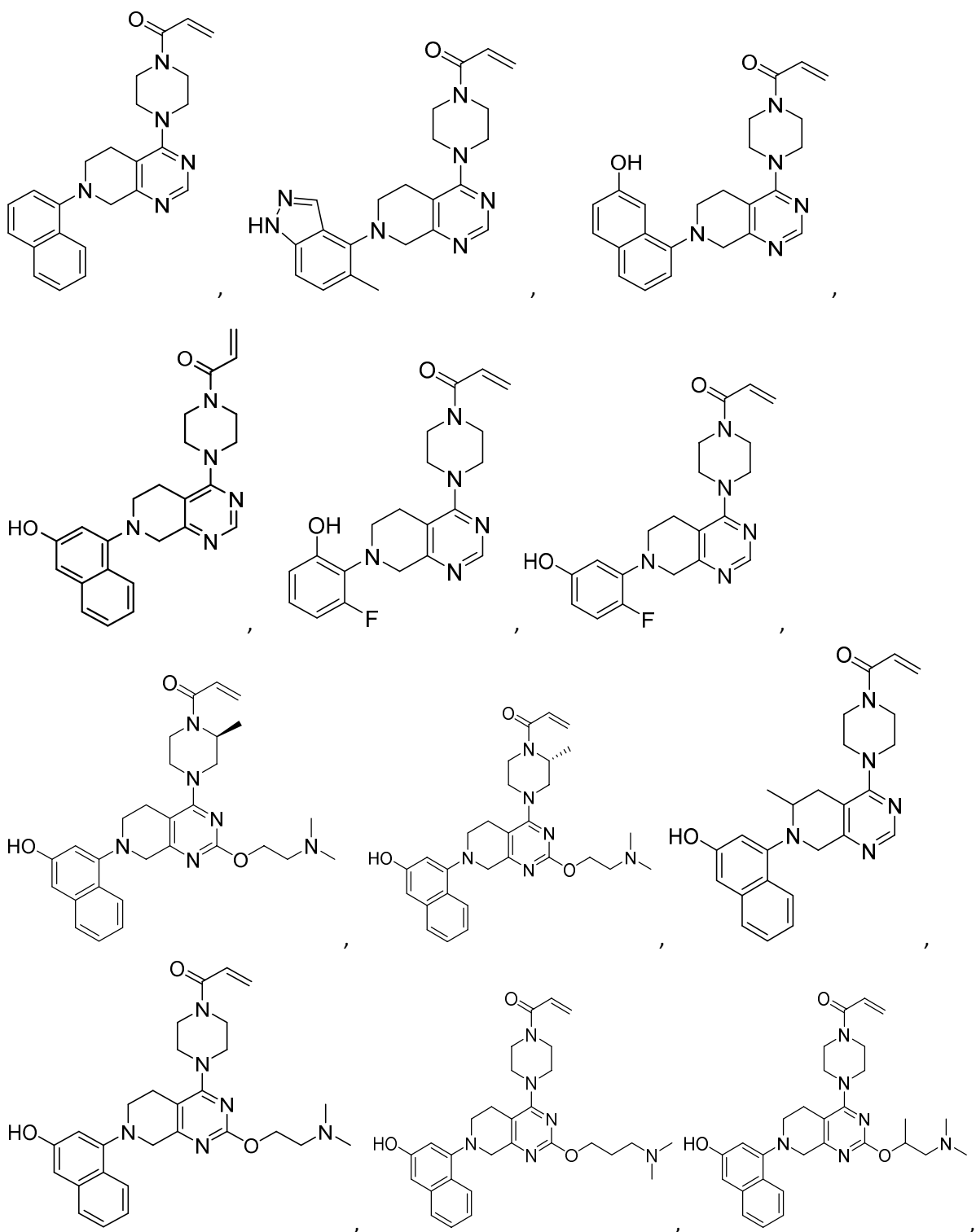
26. The compound according to claim 21, wherein L is a bond.

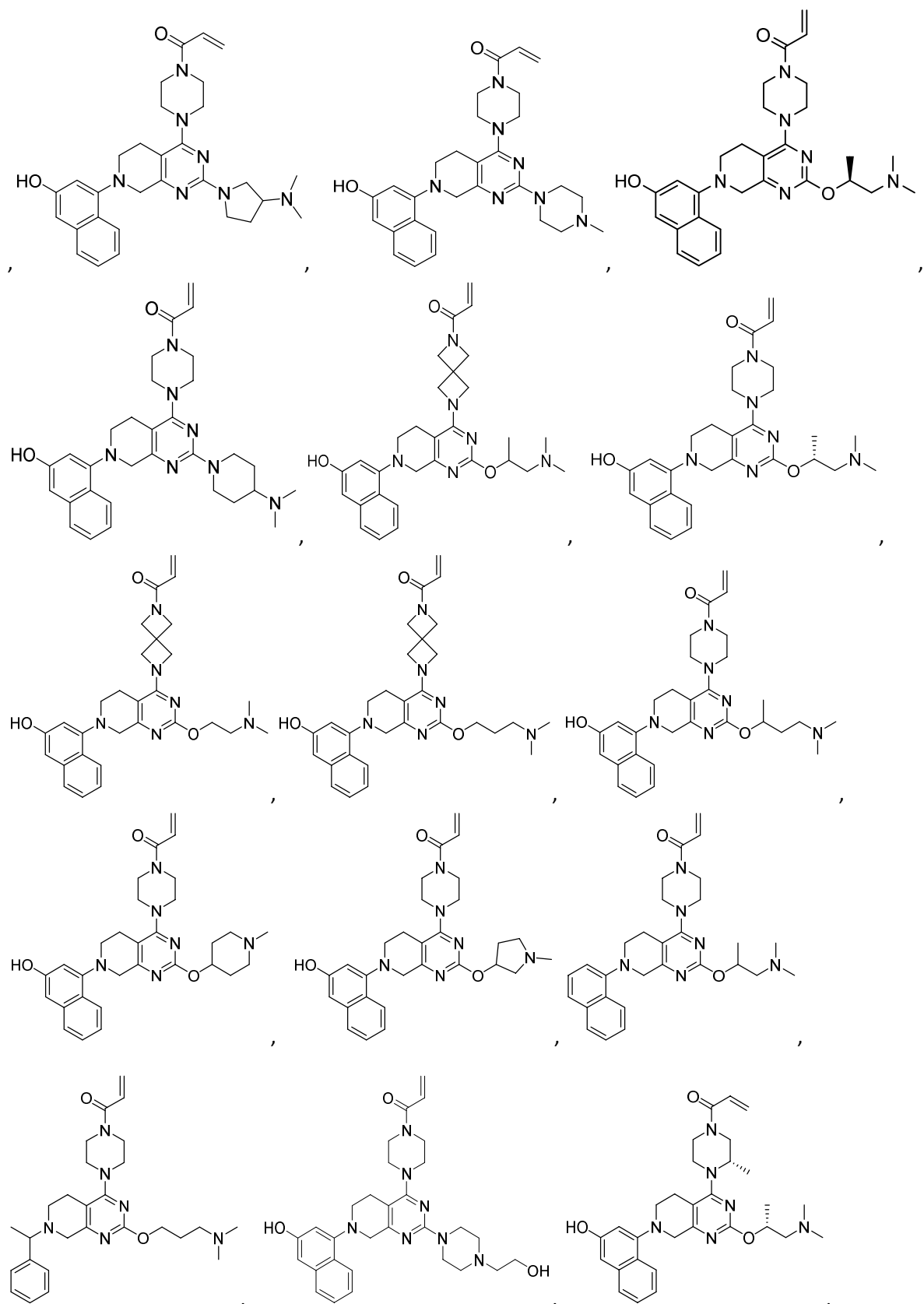
27. The compound according to claim 23, wherein the spirocyclic ring system formed by A and B are selected from the group consisting of:

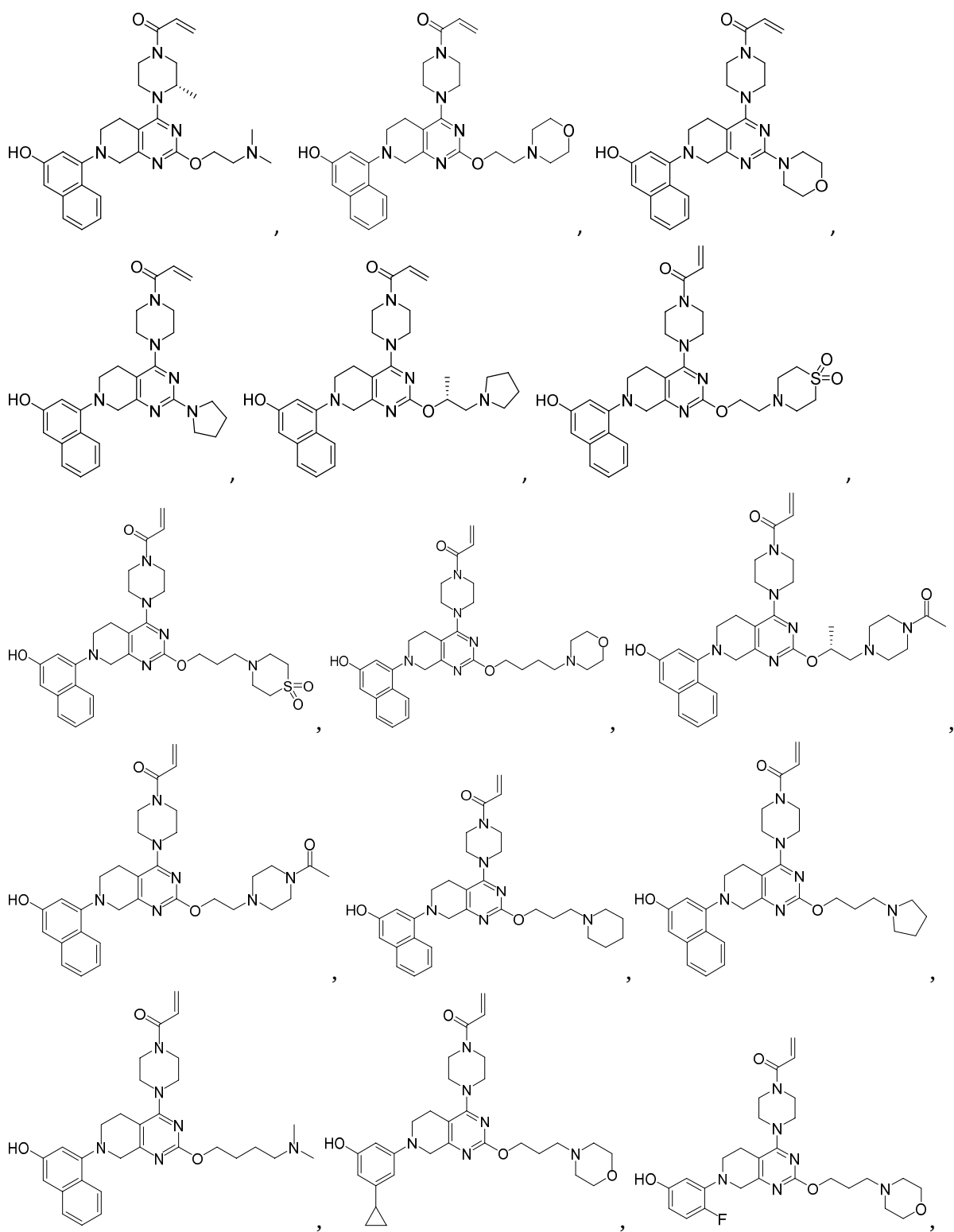


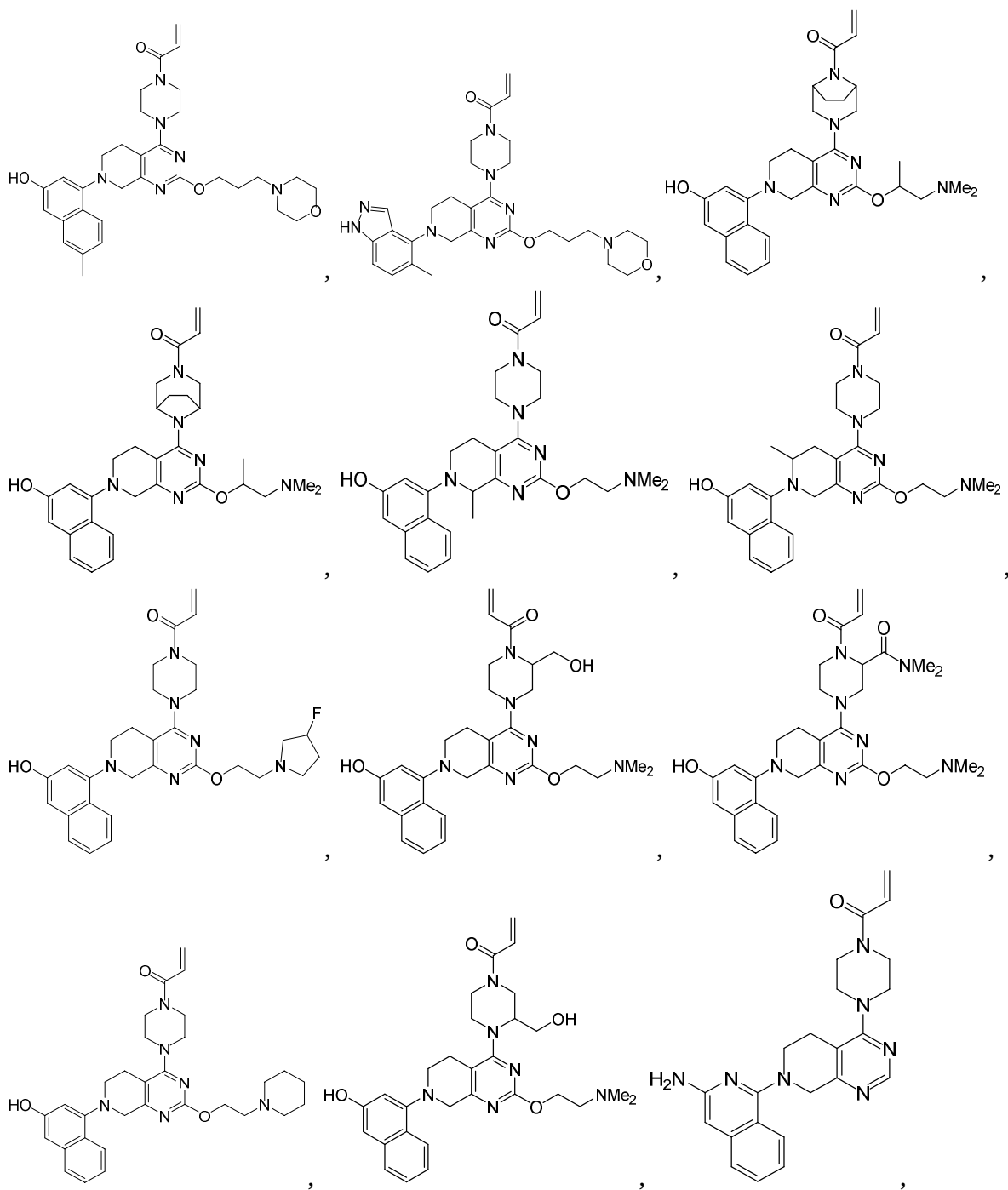
28. The compound of claim 1, wherein R^4 is phenyl or naphthyl.

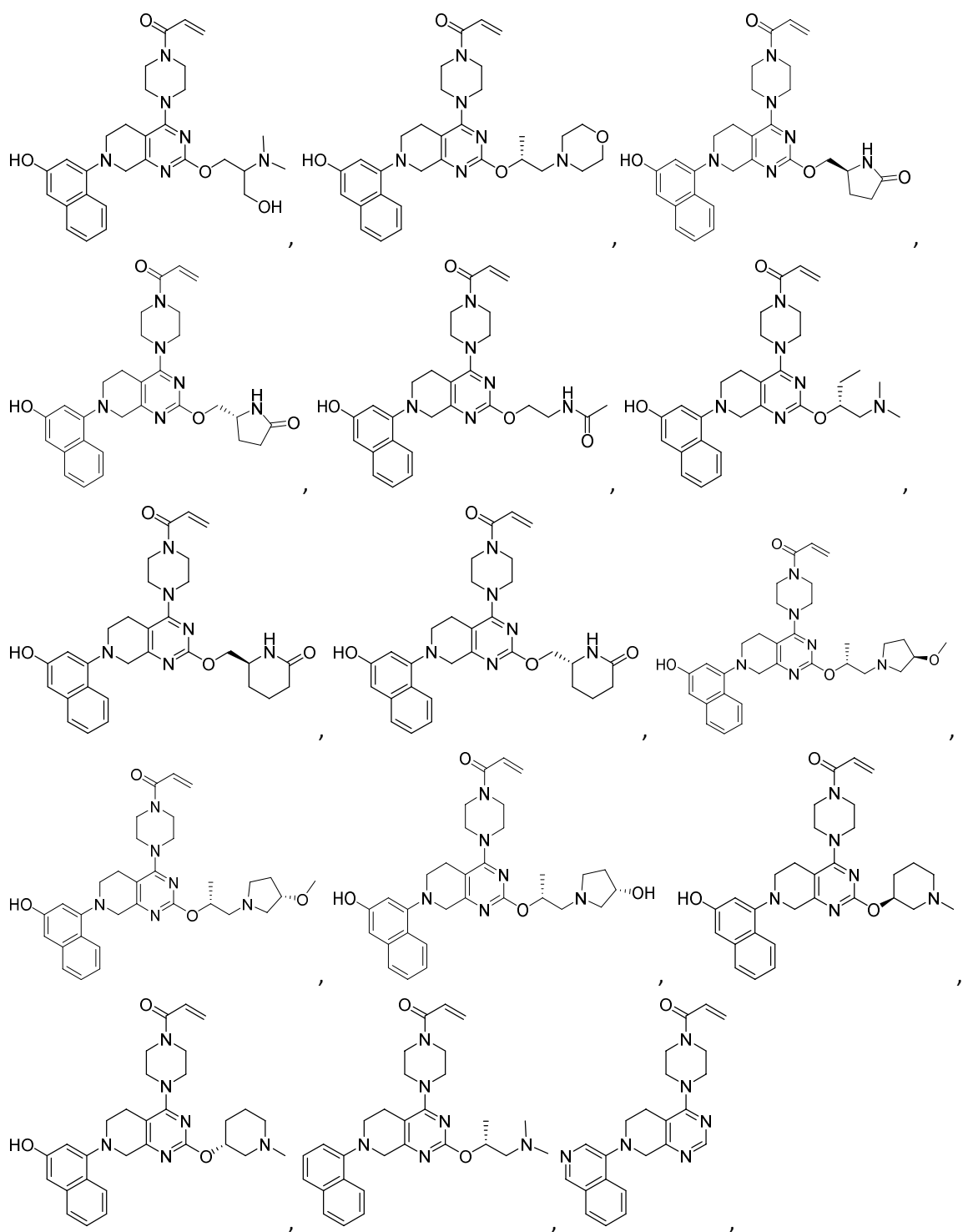
29. The compound of claim 1, wherein the compound is selected from the group consisting of:

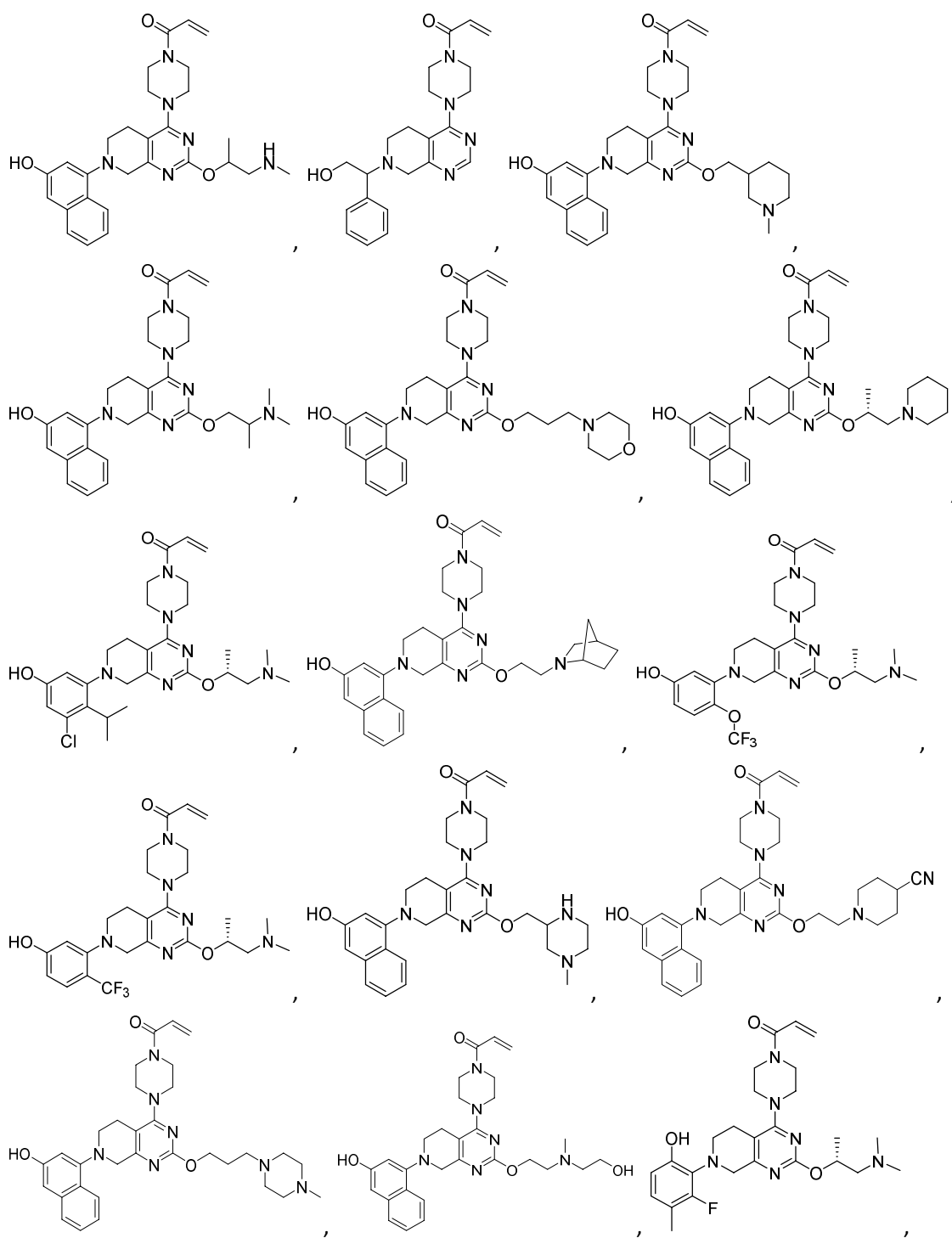


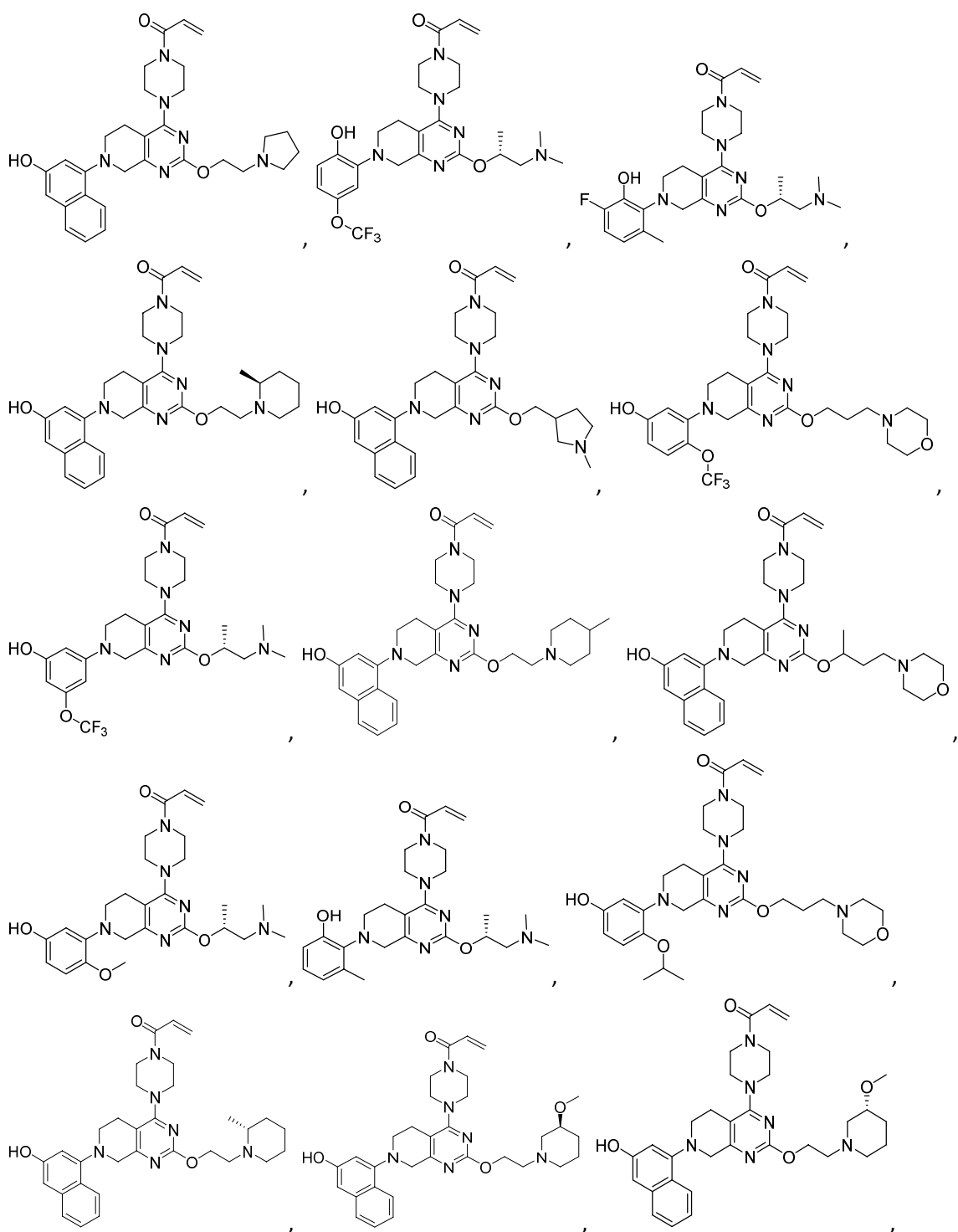




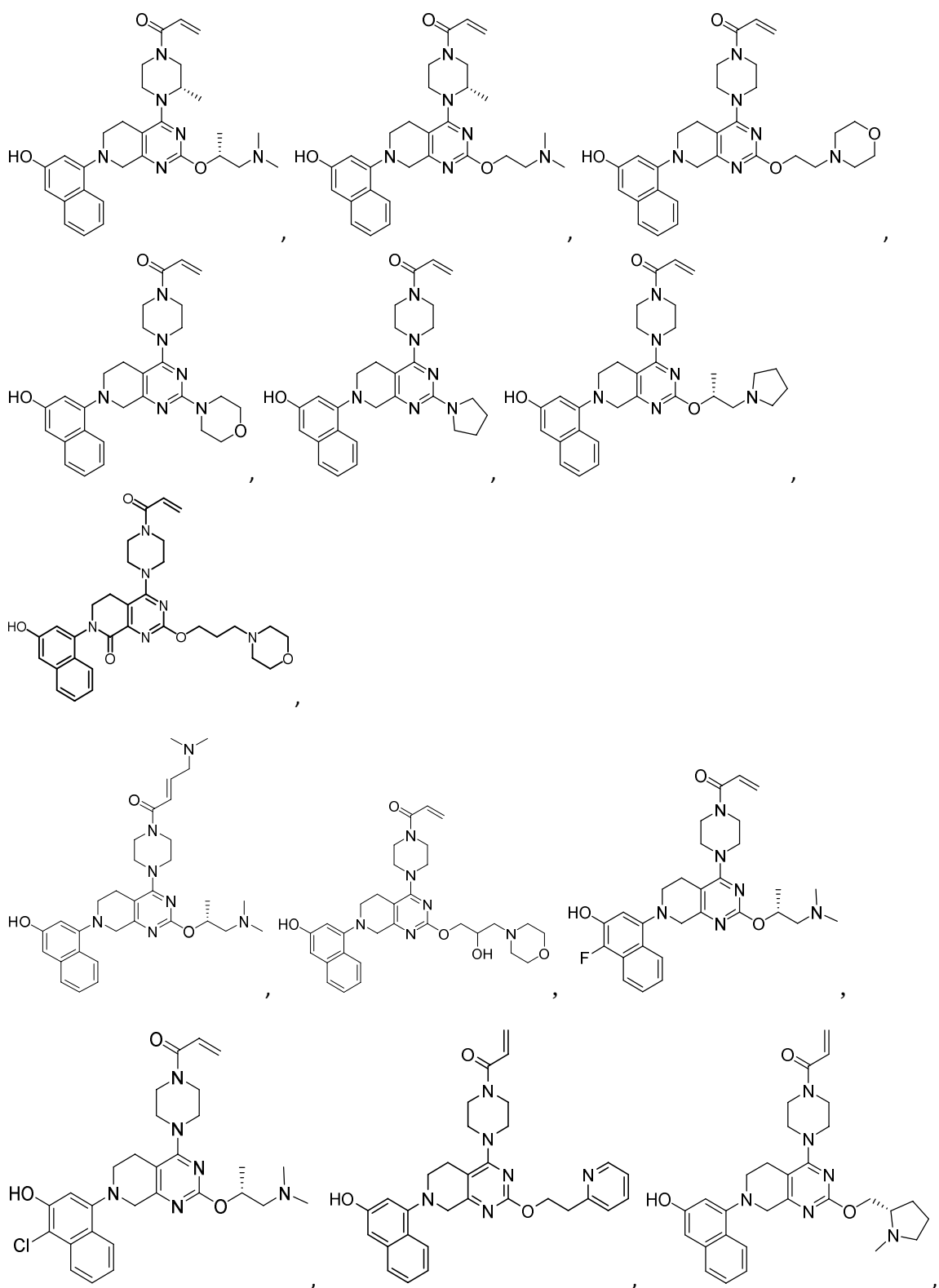


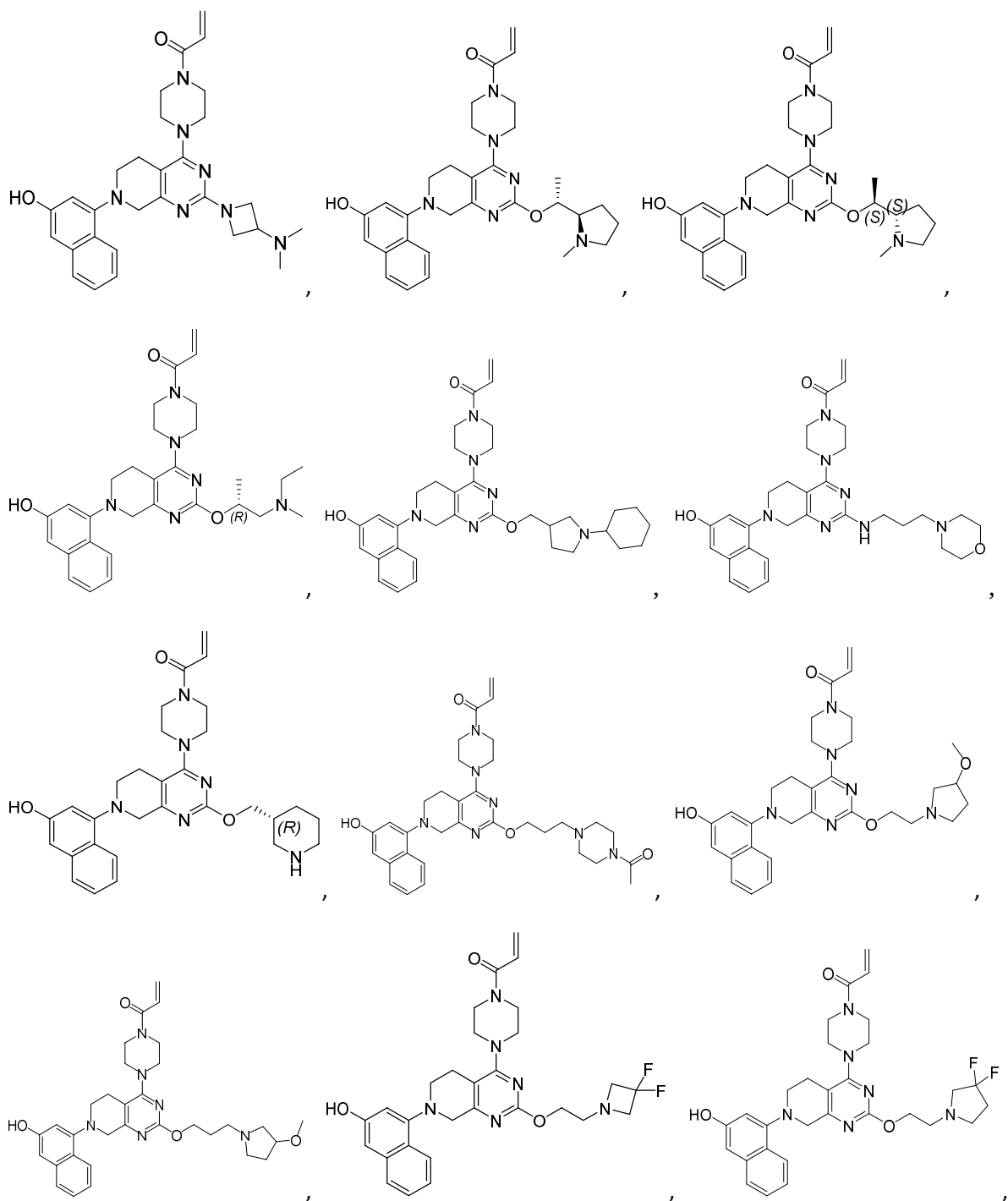


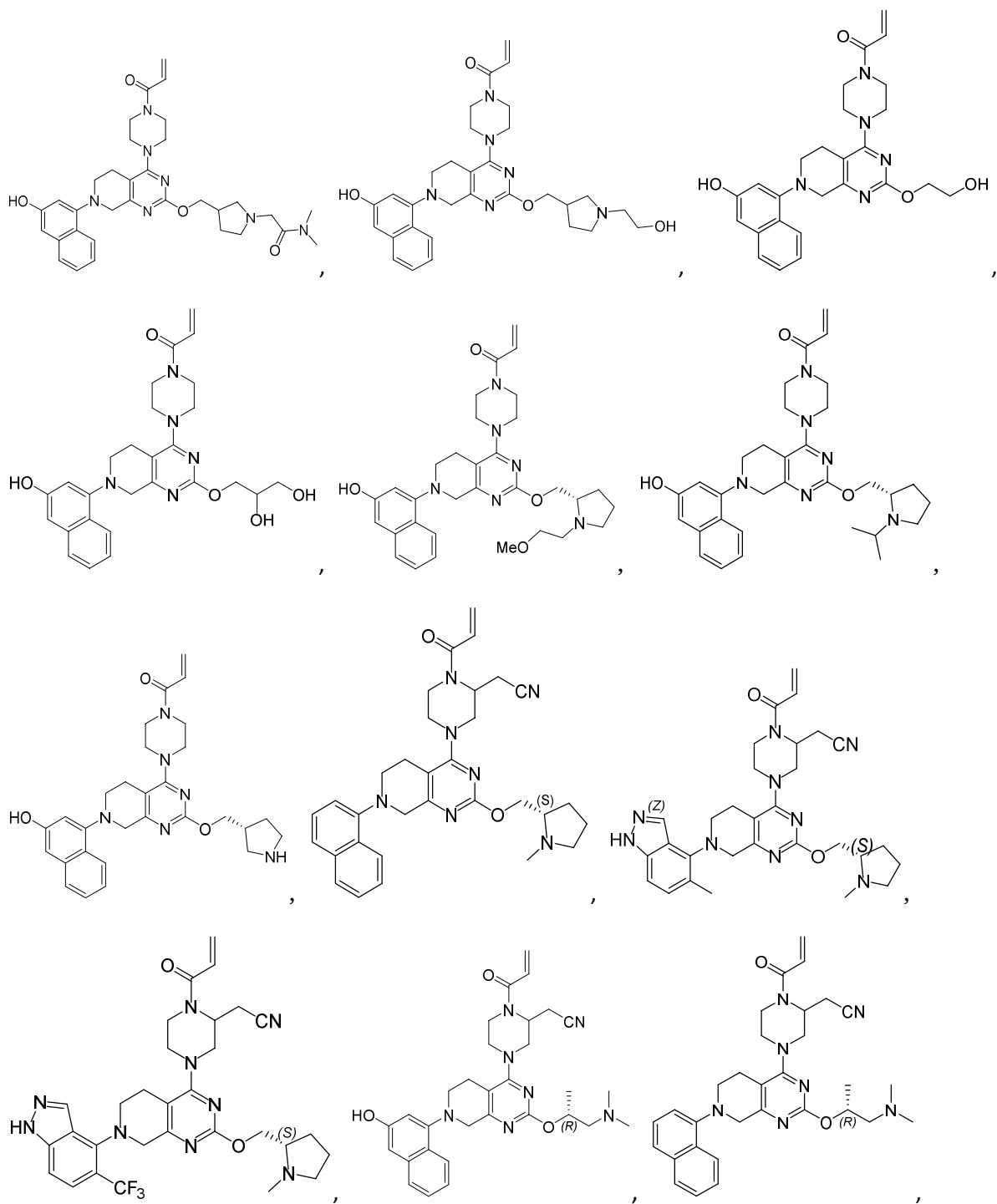


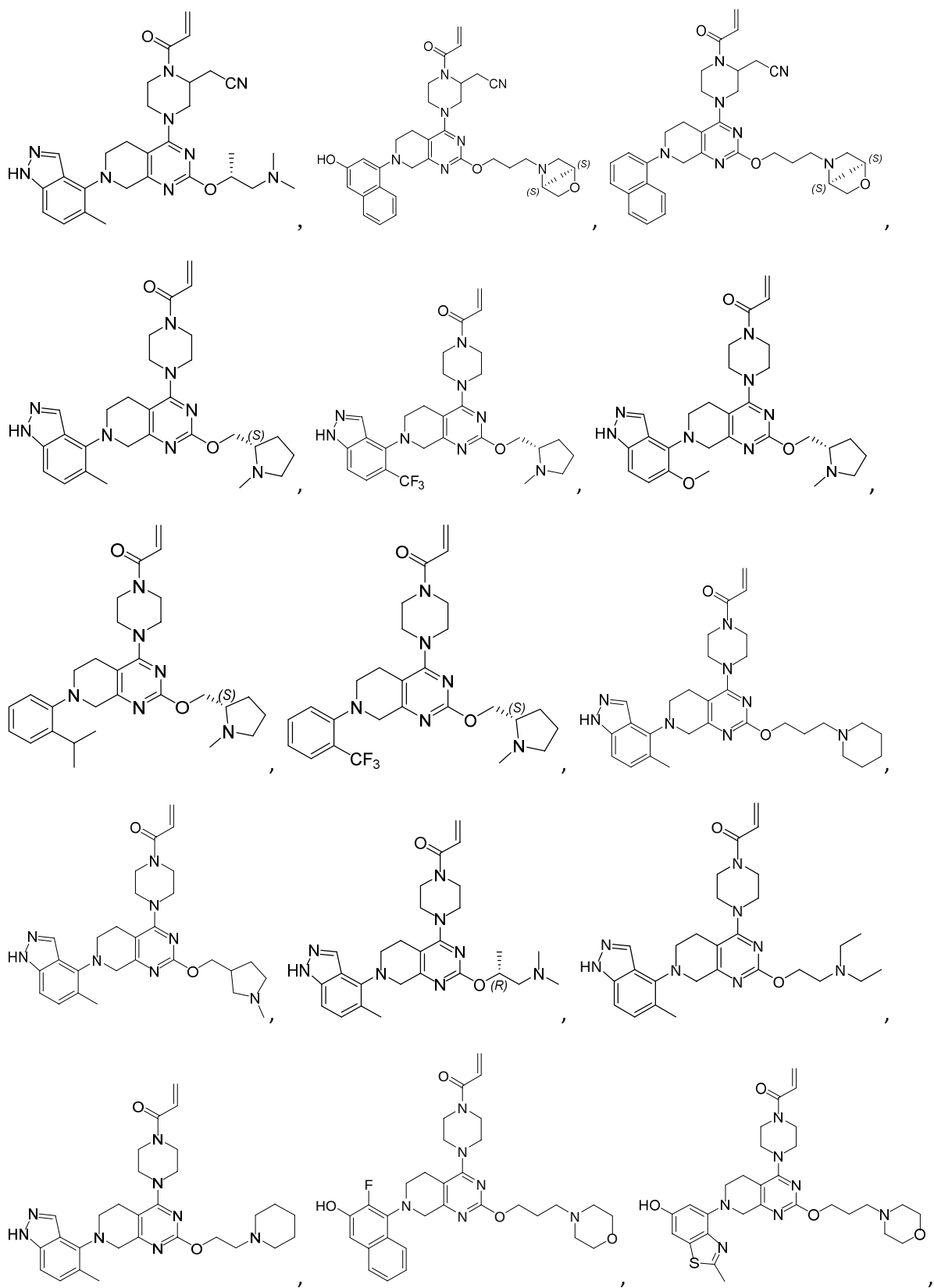


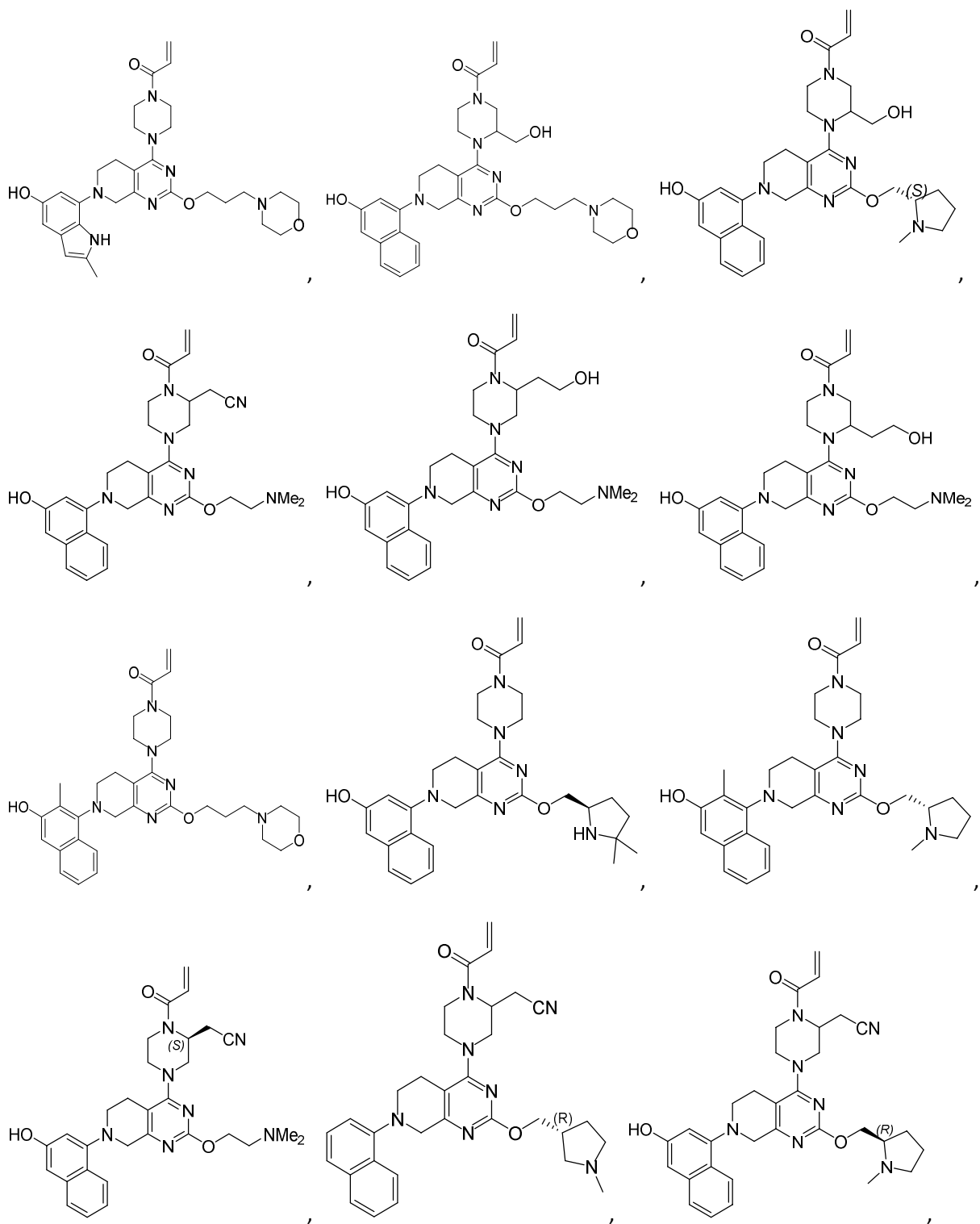


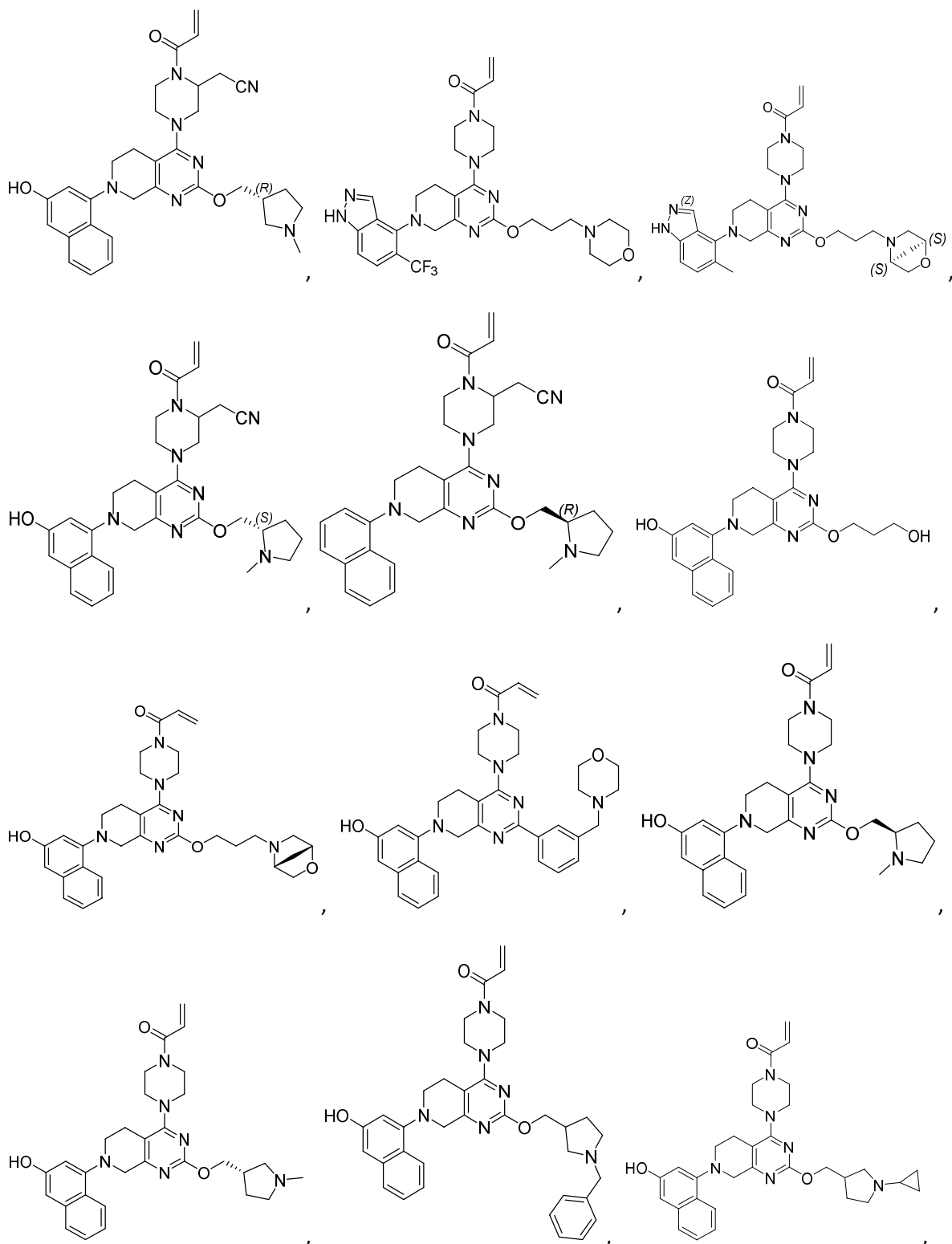


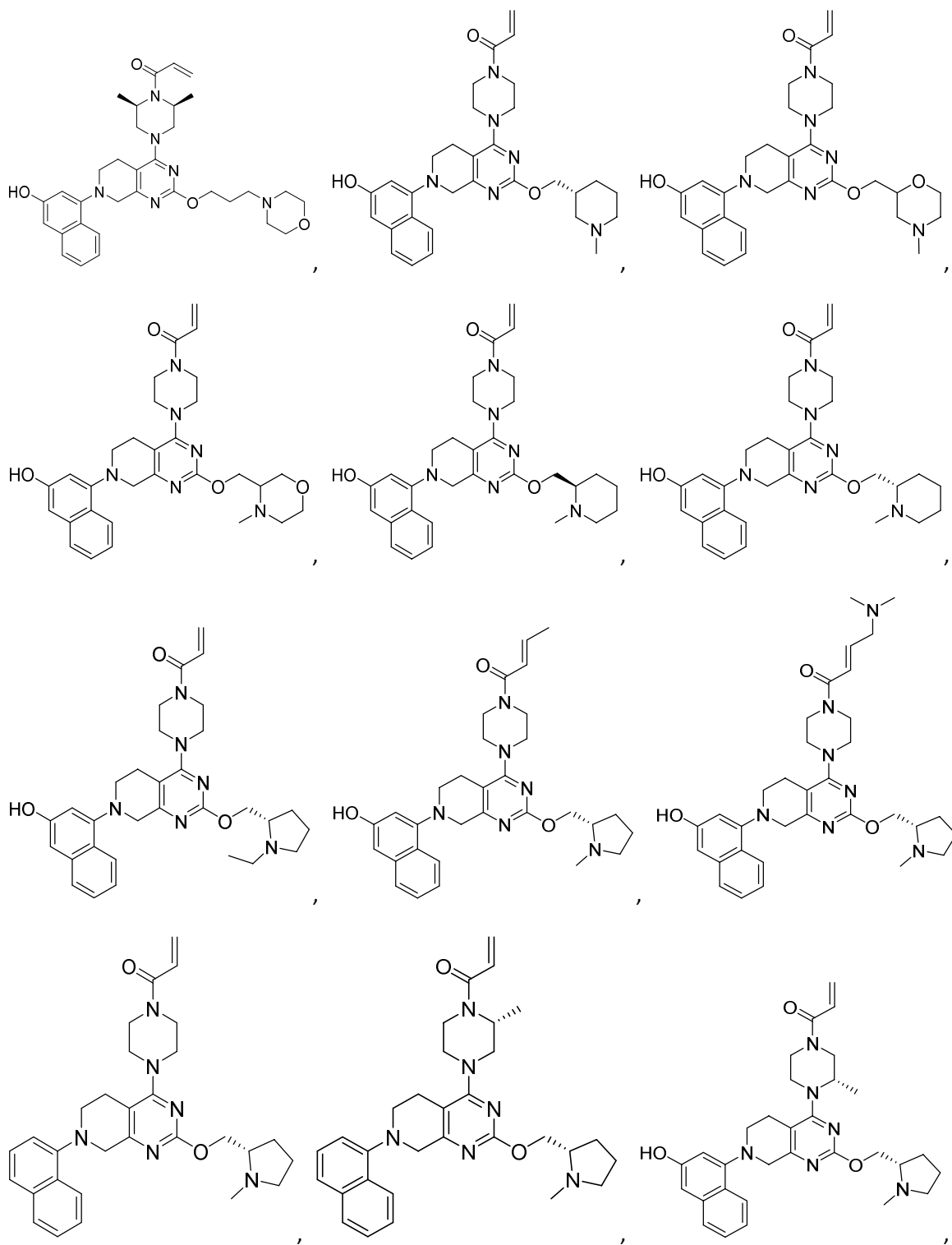




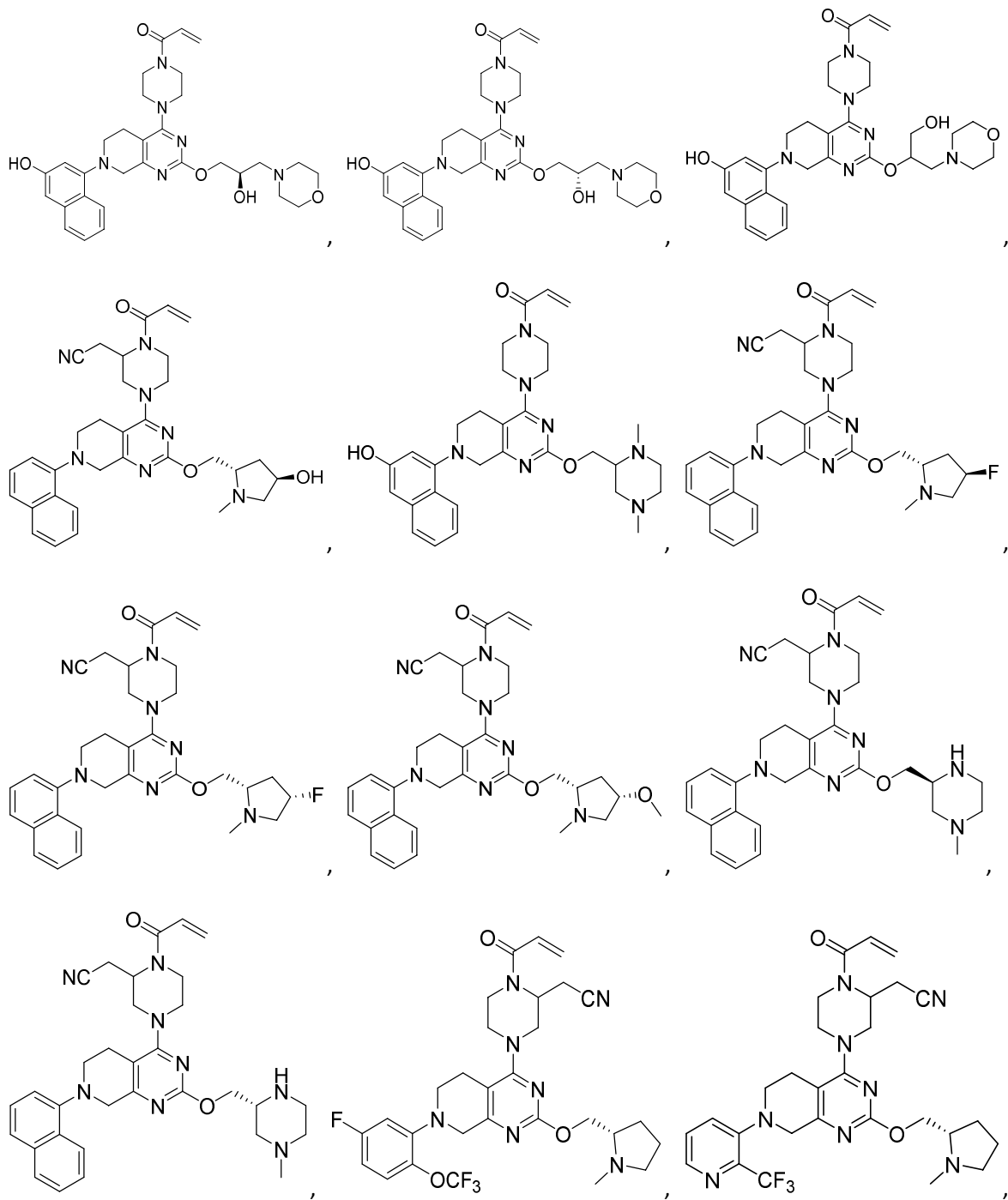


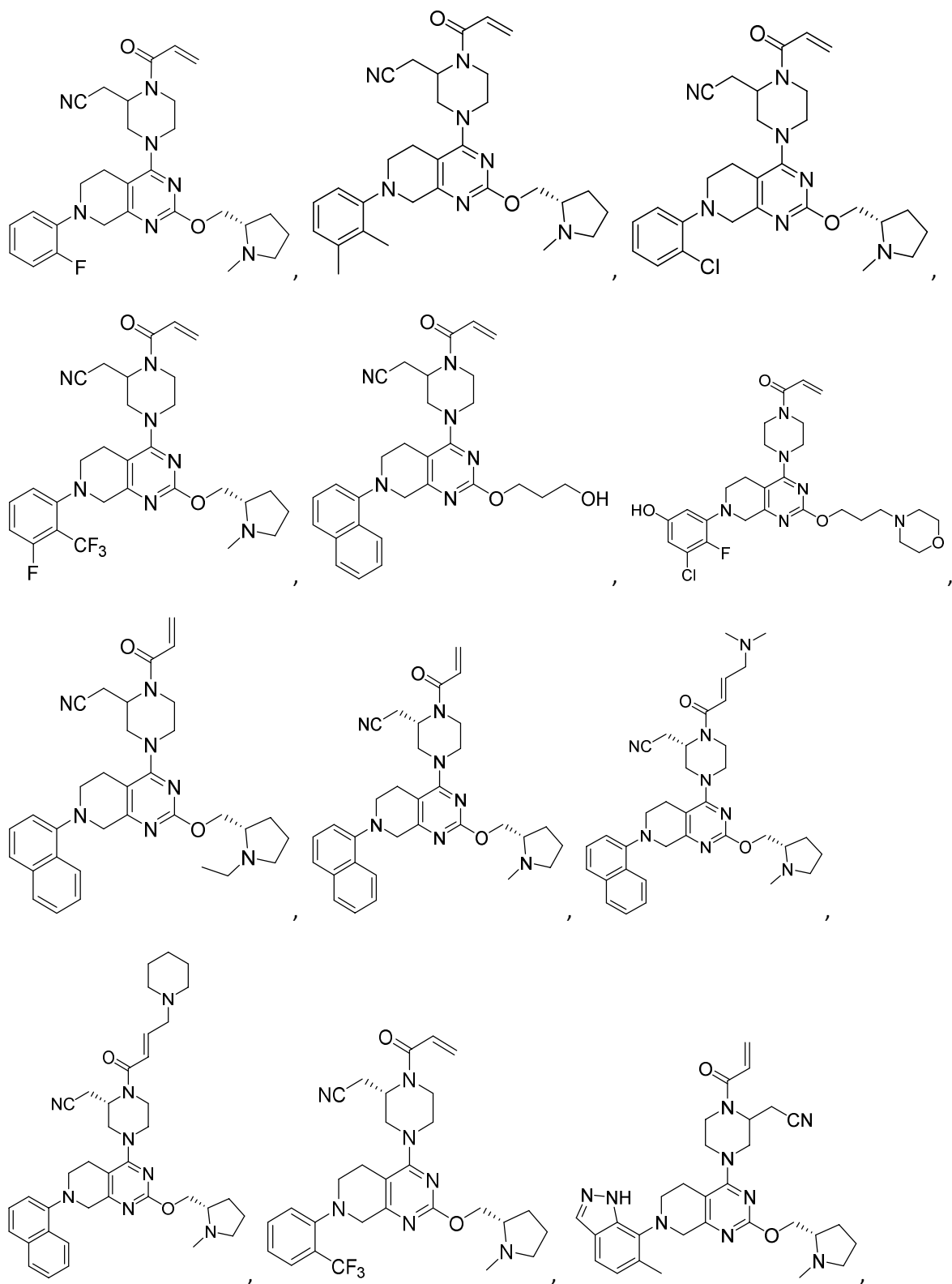


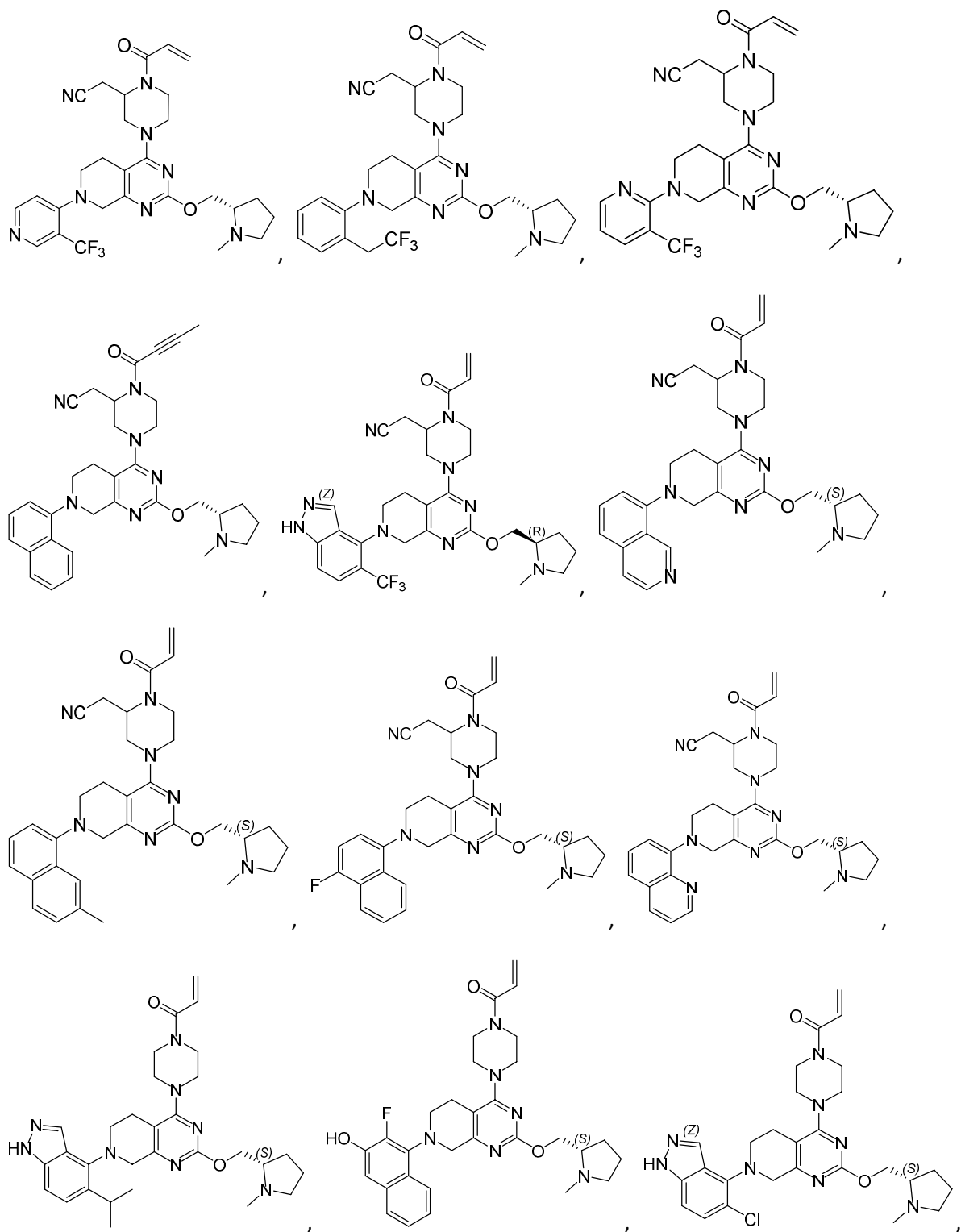


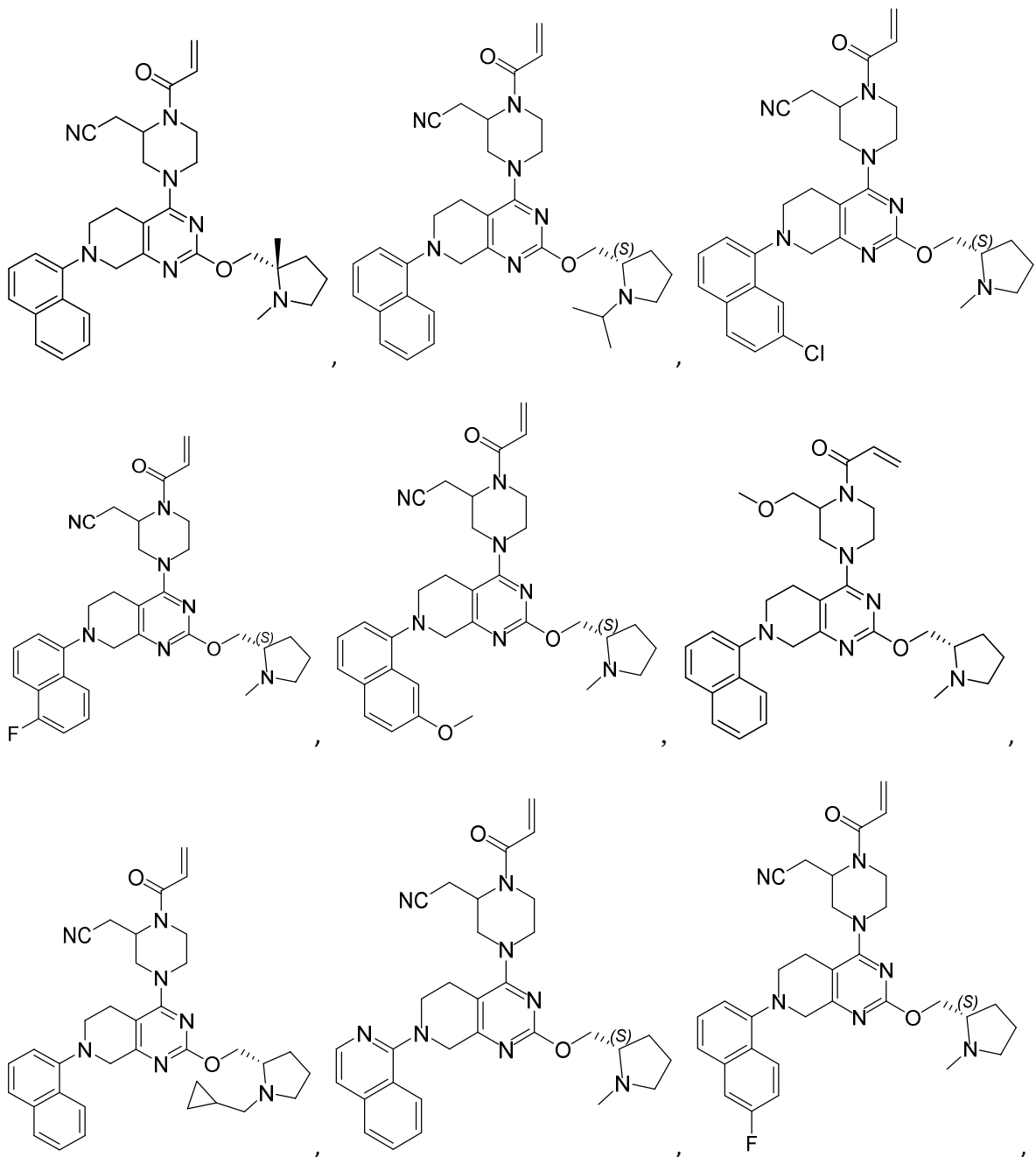


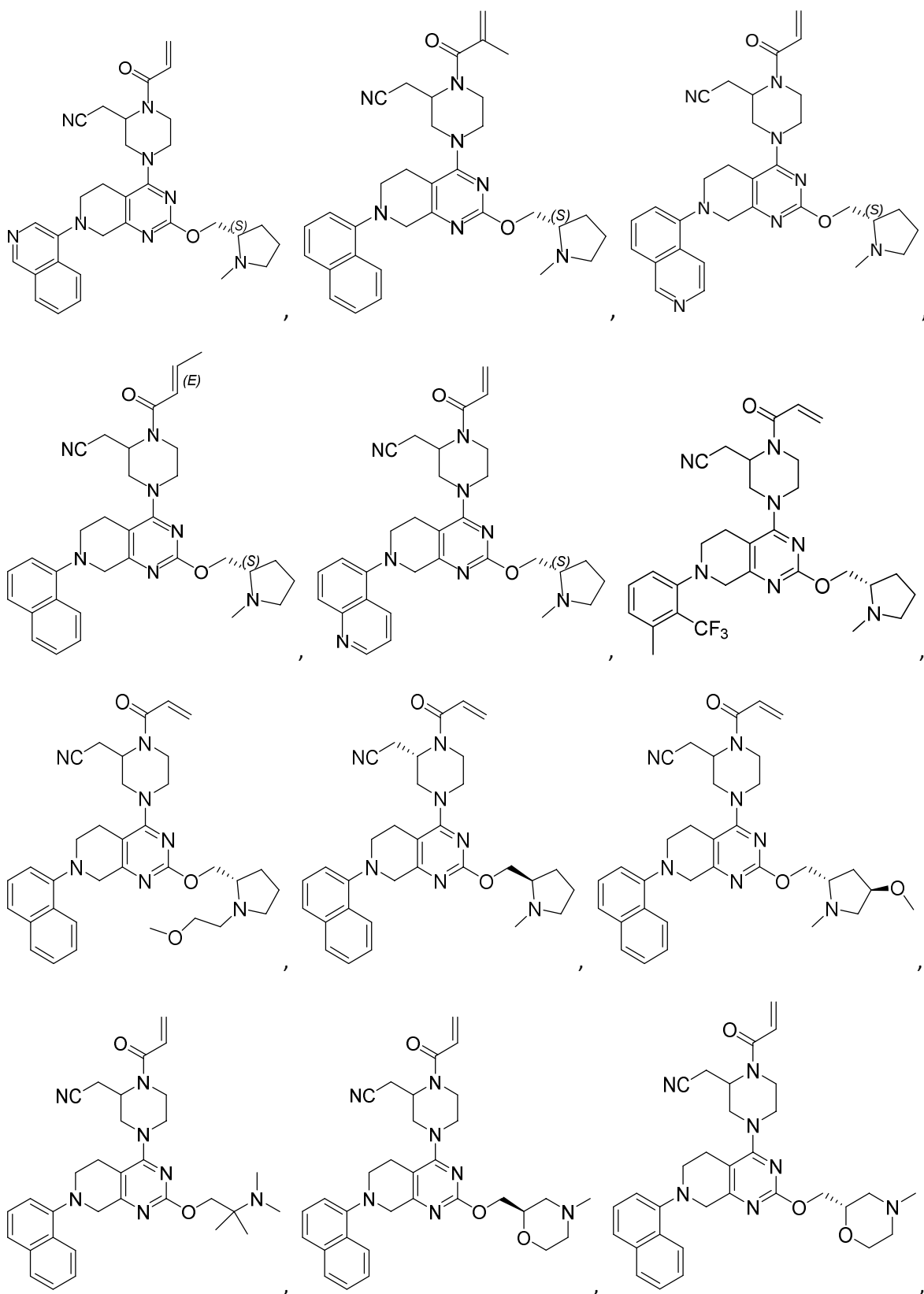


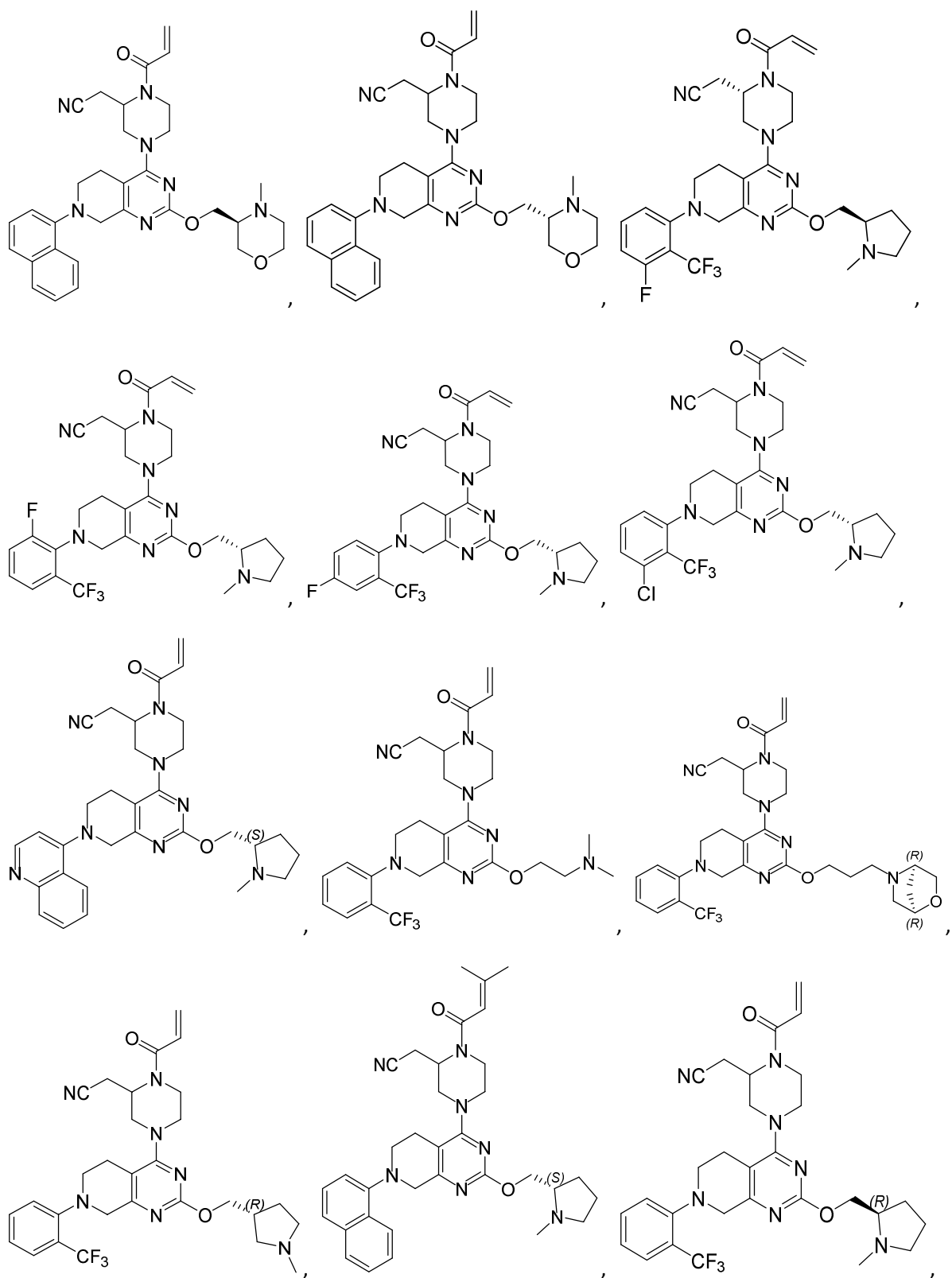


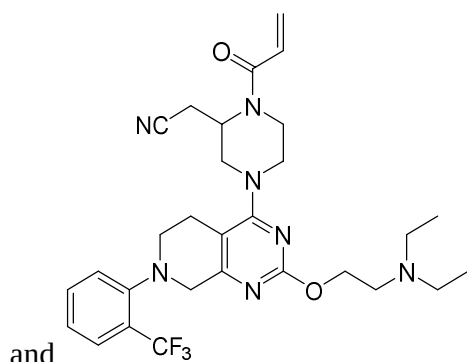












30. A pharmaceutical composition, comprising a therapeutically effective amount of a compound according to claim 1, and a pharmaceutically acceptable excipient.

31. An *in vitro* method for inhibiting KRas G12C activity in a cell, comprising contacting the cell in which inhibition of KRas G12C activity is desired with an effective amount of a compound according to claim 1, pharmaceutically acceptable salts thereof or pharmaceutical compositions containing the compound of Formula (I) or Formula I-B, or pharmaceutically acceptable salt thereof.

32. Use of a compound according to claim 1 or a pharmaceutically acceptable salt thereof, alone or combined with a pharmaceutically acceptable carrier, excipient or diluents, in the manufacture of a medicament for the treatment of cancer, wherein the cancer is a KRas G12C-associated cancer, wherein a therapeutically effective amount is to be administered to a patient in need thereof.

33. The use of claim 32, wherein the cancer is selected from the group consisting of Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma,

lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor (nephroblastoma), lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Biliary tract: gall bladder carcinoma, ampullary carcinoma, cholangiocarcinoma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochondroma (osteochondrogenous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma (pinealoma), glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma (serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma), granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia (acute and chronic), acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma (malignant lymphoma); Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and Adrenal glands: neuroblastoma.

34. The use of claim 32, wherein the cancer is non-small cell lung cancer.

35. Use of a compound according to claim 1 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of cancer in a patient in need thereof, wherein the cancer is associated with a KRas G12C mutation (e.g., a KRas G12C-associated cancer); and wherein a therapeutically effective amount of the compound or a pharmaceutically acceptable salt thereof is to be administered.